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 pCODR Expert Review Committee (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 Funding Request:
In combination for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600 mutation who have been previously treated with chemotherapy

Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: May 9, 2017	**Submission Date:** March 31, 2017
Initial Recommendation: August 31, 2017	**Final Recommendation:** November 2, 2017

Drug Costs	
Submitted list price Dabrafenib: $65.23 per 75 mg capsule Trametinib: $298.70 per 2 mg tablet	**Dabrafenib plus trametinib regimen costs:** $15,669.70 per 28-day course

pERC RECOMMENDATION

pERC does not recommend reimbursement of dabrafenib (Tafinlar) plus trametinib (Mekinist) in patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation and who have been previously treated with chemotherapy.

pERC made this recommendation because the Committee was not confident of the net clinical benefit of dabrafenib plus trametinib due to limitations in the evidence from available clinical trials. While pERC was confident that dabrafenib plus trametinib produces a tumour response, the Committee was unable to determine how it compares with other treatment options (such as immunotherapy and chemotherapy) with regard to outcomes important to decision-making, such as overall survival (OS), progression-free survival (PFS), and quality of life (QoL). Given the availability of new treatment options with demonstrated OS and PFS benefit, pERC was uncertain whether dabrafenib plus trametinib addressed an unmet need. Despite the uncertainty in the net overall clinical effect, pERC noted that dabrafenib plus trametinib partially aligned with patient values, as it is an oral option, has a manageable toxicity profile, and demonstrates tumour activity.

pERC concluded that, at the submitted price, dabrafenib plus trametinib was not cost-effective compared with available treatment options. The Committee also noted that there was considerable uncertainty in the cost-effectiveness estimates because of a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps identified.

SUMMARY OF pERC DELIBERATIONS

Lung cancer is the leading cause of cancer-related deaths worldwide, with the majority of patients presenting with non-curable disease. In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer, with a five-year survival rate of 18%. NSCLC accounts for 85% of all lung cancers. BRAF mutations, which occur in non-squamous NSCLC, account for approximately 2% of lung adenocarcinomas. In Canada, this represents between 250 and 380 patients annually, of whom about one-half have the V600E mutation subtype. Treatment decisions for advanced or metastatic NSCLC are typically dependent on the presence or absence, and type of, driver mutation status of patients in the first-line setting. Targeted therapies are currently available for anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR) mutation–positive disease; however, there remains a need to identify new therapeutic targets to advance treatment options in those patients who are BRAF V600 mutation–positive. Although the identification of less common molecular abnormalities in this population of patients represents the initial step in advancing therapeutic options, pERC agreed that patients with BRAF V600 mutations currently have treatment options following treatment with systemic chemotherapy.

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

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

pERC deliberated upon the results of one non-randomized, non-comparative study evaluating the efficacy and safety of dabrafenib plus trametinib (study BRF113928). The Committee was not satisfied that the available evidence demonstrated a net overall clinical benefit of treatment with this intervention. pERC noted that an objective tumour response was observed with dabrafenib plus trametinib; however, on its own this was not considered to be sufficient evidence of clinical effectiveness. Additionally, investigator-assessed, complete responses were observed in only 4% of patients, with the remainder reporting only partial responses. pERC acknowledged that the current evidence suggests that there is antitumour activity with dabrafenib plus trametinib; however, the magnitude of effect compared with available therapies was uncertain given the lack of comparative data and long-term outcomes important to patients, such as OS, PFS, and QoL. In addition, pERC noted that nearly half of patients in the trial experienced a grade 3 or grade 4 adverse event (AE), and all grades pyrexia were experienced by nearly half of patients. The Committee noted that these toxicities were managed with dose modifications. pERC was unable to deliberate on the impact of dabrafenib plus trametinib on patients' QoL, as these data were not collected in the trial.

pERC noted input from the Clinical Guidance Panel (CGP) and registered clinicians indicating the following: (1) The response rates achieved in the BRF113928 trial are similar to those observed with randomized trials using dabrafenib plus trametinib in other indications (e.g., metastatic melanoma); thus, the data suggest similar efficacy in BRAF-mutated patients across these patient populations. (2) The outcomes with active targeted therapy for NSCLC with defined driver mutations are better compared with non-specific therapy with cytotoxic agents as established with EGFR-specific and ALK-specific therapies. While pERC agreed that the mechanism of action is a reasonable rationale in determining the potential for benefit for dabrafenib plus trametinib, it cannot be used to extrapolate for important outcomes such as OS and PFS across indications and driver mutations. Trials have demonstrated variability of outcomes among indications where the target mechanism of action is similar. Therefore, pERC agreed that more robust direct or indirect clinical evidence is required to address the comparative efficacy and safety of dabrafenib plus trametinib in a setting where treatment options have been approved for reimbursement based on randomized controlled trials (RCTs) that have demonstrated OS and PFS benefit. pERC further considered the feasibility of conducting an RCT in this setting. Although pERC acknowledged that the incidence of BRAF V600 mutation–positive NSCLC is low, the incidence and prevalence of lung cancer is high, and conducting a multi-centre RCT with appropriate comparators would be feasible. pERC noted that objective response rate is an uncertain surrogate for OS in most solid tumours, and that the BRF113928 trial did not provide any comparative evidence on OS, which has been a standard outcome in lung cancer studies. pERC also considered indirect evidence provided through a match-adjusted indirect comparison (MAIC) and network meta-analysis (NMA). The Committee agreed that the biggest limitation of this evidence was related to the absence of matching based on BRAF V600 mutation status. Given that

BRAF mutation status is considered to be an effect modifier, a comparison between such selected and unselected patients is subject to bias. Therefore, there is considerable uncertainty in the results of this indirect analysis. Overall, pERC stated that it has accepted evidence from non-comparative studies in previous submissions for reasons that are context (drug and disease)-specific; however, in this instance — given the absence of a clear advantage over available treatment options, the feasibility of conducting a randomized trial in this disease setting, the short trial follow-up, and a lack of complete responses to treatment in a meaningful proportion of patients — the Committee was unable to draw a conclusion on the comparative effectiveness of dabrafenib plus trametinib.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from the submitter, registered clinician groups, and a patient advocacy group arguing that there is an unmet need for treatment options in this patient population. The Committee recognized that patients have a continued need for more effective treatment options, particularly for therapies targeting specific mutations. However, based on the uncertainty in the evidence available from the BRF113928 trial and the availability of treatment options that have demonstrated clinically meaningful improvements in OS (i.e., immunotherapies), pERC was unable to conclude that dabrafenib plus trametinib addressed an unmet need. pERC reiterated that the RCTs demonstrating the efficacy and safety of immunotherapies in advanced NSCLC did not exclude patients with BRAF V600E mutation disease and therefore these therapies are currently available for use in this population.

pERC had a robust discussion about stakeholder feedback about the feasibility of an RCT. pERC disagreed that the rarity of BRAF V600E mutation–positive advanced NSCLC would make it difficult to conduct an RCT. pERC noted that lung cancer is the most common cancer worldwide, and therefore an international multi-center RCT could have recruited a sufficient number of patients to collect sufficient evidence to inform a recommendation for reimbursement. However, pERC agreed that an RCT for this combination may not be conducted but noted that in instances such as this where the available evidence is not robust, it would be very useful if the submitter was to provide other evidence to demonstrate comparative effectiveness. pERC agreed on the importance of having, at a minimum (1) historical (i.e., retrospective) data on the outcomes of currently available treatments for patients with BRAF 600E mutation-positive metastatic NSCLC previously treated with chemotherapy. These outcomes should be appropriately matched with outcome data for treatment with dabrafenib plus trametinib in order to assess the comparative efficacy and safety of immunotherapy treatments and dabrafenib plus trametinib; (2) more substantive data to demonstrate the surrogacy of response rate for OS in lung cancer regardless of treatment as well as those who have received dabrafenib plus trametinib and; (3) data on whether or not BRAF V600E mutation is an effect modifier or prognostic factor in this disease setting. pERC expressed concern about making a recommendation on reimbursement solely based on non-randomized evidence of objective response supported only by evidence based on the use of various targeted agents in other indications and/or mutation status. pERC noted that although some trials of targeted agents have demonstrated that response rates can subsequently be translated into PFS and OS benefit, there are also examples of positive outcomes in non-randomized phase 2 trials that did not translate into benefits in later phase III randomized trial.

The committee further noted feedback indicating that the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines have supported the use of targeted agents ahead of immunotherapies in the population under review. Upon further investigation, pERC noted that the ASCO guideline did not support such sequencing of agents but indicated that the available evidence came from small trials that were subject to selection bias, and concluded that there was insufficient evidence to determine which agent may be more effective. pERC noted that the NCCN guideline supported the use of dabrafenib plus trametinib in this population ahead of immunotherapies and went further to expand the use of these targeted agents in first line treatment. pERC noted that the ASCO recommendation to use dabrafenib plus trametinib was consensus-based and supported by low quality evidence, while the NCCN guideline was unclear as to how the recommendation was reached and upon what evidence it was based. Overall, pERC maintained its conclusion that there is insufficient evidence to choose dabrafenib plus trametinib over treatment options (immunotherapies) that have demonstrated clinically meaningful OS benefits through randomized controlled trials.

pERC discussed input from a patient advocacy group on dabrafenib plus trametinib. It was noted that both agents in the combination treatment are oral, which would be easier for patients to take and would not require as much personal and caregiver time and resources (e.g., trips to the hospital) as receiving intravenous agents. pERC also acknowledged that patients expressed a need for alternative treatment options specific to their genotype and a preference to avoid receiving treatment with chemotherapy and

radiation therapy, because both have the potential for detrimental side effects and deterioration of QoL. pERC agreed that dabrafenib plus trametinib aligns with these patient values. However, pERC noted that the considerable uncertainty in the clinical effect estimates of dabrafenib plus trametinib compared with appropriate treatment options does not align with patient values. pERC highlighted that immunotherapies (nivolumab and pembrolizumab) with demonstrated OS and PFS benefit are now available to patients; however, pERC does agree that there is a continued need for more effective treatment options. Overall, pERC concluded that dabrafenib plus trametinib partially aligned with patient values.

Upon reconsideration of the initial recommendation, pERC noted feedback from a patient advocacy group that treatment with dabrafenib plus trametinib completely aligns with patient values. Although the patient group argued that the treatment was effective, pERC was not satisfied that the available evidence demonstrated a net overall clinical benefit, and therefore it could not agree that the treatment aligns fully with patient values for more effective treatment. In addition, the patient group commented that the Committee prioritizes immunotherapies over targeted agents. pERC discussed this feedback and reiterated that it strives to ensure that its decision-making is based on rigorous evidence. In this case, the Committee was not confident that the evidence was sufficient to support a decision for the reimbursement of dabrafenib plus trametinib ahead of treatment options (e.g., immunotherapies) that have demonstrated clinically meaningful OS improvements through randomized controlled trials. pERC also considered feedback indicating that evidence about the impact of dabrafenib plus trametinib on patients' quality of life was available through the patient group submission. pERC noted that patient input provides a tremendous aid in helping the committee to understand the lived experience of patients, including their experience with the treatment under review, compared to clinical trial evidence. However, the Committee stressed that it cannot use information from the patient input as a substitute for clinical trial evidence. Although patient input is carefully considered, pERC agreed that each component of its deliberative framework must be addressed based on the appropriate evidence available.

pERC deliberated upon the cost-effectiveness of dabrafenib plus trametinib. Due to the considerable limitations in the available non-randomized data of dabrafenib plus trametinib, the lack of robust direct or indirect comparative effectiveness estimates for PFS and OS, and the high cost of this combination treatment, pERC concluded that dabrafenib plus trametinib is not cost-effective. Given the limitations identified with the indirect data used to inform the clinical effect estimates, pERC agreed that the pCODR Economic Guidance Panel (EGP) estimates are highly uncertain. pERC also highlighted that the high degree of uncertainty with respect to the estimates of extra clinical effect of dabrafenib plus trametinib is not fully captured in the EGP's estimates, as there was no alternative source of data the EGP could use in the reanalysis estimates. pERC also highlighted that the incremental cost-effectiveness ratio (ICER) was primarily driven by the cost of dabrafenib plus trametinib, and that a substantial decrease in the cost of this combination therapy at the submitted price would be necessary to make the treatment cost-effective. Overall, based on the identified limitations in the clinical evidence and on the high drug cost, pERC agreed that dabrafenib plus trametinib is not cost-effective.

pERC discussed the feasibility of implementing a reimbursement recommendation for dabrafenib plus trametinib for the treatment of patients with advanced NSCLC with a BRAF V600 mutation and who have been previously treated with chemotherapy. As a fully oral option, pERC noted that dabrafenib and trametinib can be administered to patients more easily than intravenous therapies in both rural and urban settings. However, costs associated with treatment would be increased for some patients, as the two different drugs would have two dispensing fees, two co-payments, and varying deductibles applied in provinces where oral drugs are funded through pharmacare programs. Barriers to implementation were also identified related to compliance due to pill burden and dose confusion. Despite enablers to implementation, pERC agreed that dabrafenib plus trametinib should not be reimbursed due to the uncertainty in the clinical trial evidence.

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 manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy groups: Lung Cancer Canada and the Ontario Lung Association
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group: Lung Cancer Canada
- two clinician groups: Cancer Care Ontario and Lung Cancer Canada
- the PAG
- the submitter: Novartis Pharmaceuticals Canada Inc.

The pERC Initial Recommendation was to not recommend reimbursement of dabrafenib (Tafinlar) plus trametinib (Mekinist) in patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation and who have been previously treated with chemotherapy. Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy group, and registered clinician group disagreed with the Initial Recommendation, while PAG agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) as compared to an appropriate comparator for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600 mutation who have been previously treated with chemotherapy.

Studies included: One non-comparative study

The pCODR systematic review included one trial, BRF113928, which met the inclusion criteria for this review. While the BRF113928 trial had three cohorts, only cohort B was included in the pCODR systematic review. (Cohort A had received at least one previous line of treatment and was treated with dabrafenib monotherapy; cohort B had received at least one previous line of treatment and was treated with dabrafenib plus trametinib; and cohort C consisted of treatment-naive patients treated with dabrafenib plus trametinib.)

BRF113928 is a phase II, open-label, single-arm, multi-centre study conducted across 30 centres in nine countries across North America, Europe, and Asia. This trial evaluated the combination of dabrafenib and trametinib in adults with BRAF V600E-mutant stage IV NSCLC who were previously treated with chemotherapy. Key inclusion criteria included that patients be aged 18 years or over, have histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC, have documented tumour progression after at least one platinum-based chemotherapy regimen, have received no more than three previous systemic treatments for metastatic NSCLC, and have an Eastern Cooperative Oncology Stats (ECOG) Performance Status (PS) of ≤ 2.

Patient populations: Small patient population

There were 59 patients enrolled in cohort B of the BRF113928 trial. Two treatment-naive patients were excluded from the analysis as they were enrolled due to a protocol violation; therefore, only 57 patients were included in the final analysis. The median age of patients was 64 (range: 58 to 71), 52 of 57 (91%) of whom had an ECOG status of 0 or 1; the majority were current (11%, 6 of 57) or former (67%, 38 of 57) smokers. About half of the enrolled patients were male (51%, 29 of 57). Most patients had one previous systemic therapy for metastatic disease (67%, 38 of 57). Five patients in the trial had treated or asymptomatic brain metastasis.

Key efficacy results: Uncertainty in clinical effect estimates

The key efficacy outcomes deliberated on by pERC were overall response (OR), the primary outcome of the trial, as well as OS and PFS, which were secondary outcomes. In the trial, OR as assessed by investigator assessment (IA) occurred in 36 of 57 patients (63.2%, 95% confidence interval [CI], 49.3 to 75.6). OR as assessed by independent review committee (IRC) was the same. Based on the June 3, 2017, poster presented at the ASCO (16.2 months follow-up), OR assessed by investigators was 66.7% (95% CI, 52.9 to 78.6). OR assessed by IRC was 63.2% (95% CI, 49.3 to 75.6). pERC considered that the objective tumour response observed with dabrafenib plus trametinib was not sufficient evidence of effectiveness. Additionally, investigator-assessed complete response rates were low, occurring in two patients (according to IA) and none (based on the IRC). The majority of responses were partial responses (34 of 57 based on IA and 36 of 57 based on IRC). The current evidence suggests that there is antitumour activity with dabrafenib plus trametinib; however, the magnitude of effect compared with available therapies was uncertain.

PFS as assessed by IA was 9.7 months (95% CI, 6.9 to 19.6). PFS as assessed by IRC was 8.6 months. A June 3, 2017, poster presentation at ASCO reported IRC-assessed median PFS of 10.2 months (95% CI, 6.9 to 16.7). At six months, 10 of 57 (18%) patients had died and medians were not yet reached for OS. Updated OS data (June 3, 2017 ASCO meeting, 16.2 months follow-up) reported median OS of 18.2 months (95% CI, 14.3 to not estimable), with 33 deaths reported. Overall, the Committee was not satisfied that the available evidence demonstrated a net overall clinical benefit of treatment with this intervention. pERC acknowledged that the current evidence suggests that there is antitumour activity with dabrafenib plus trametinib; however, the magnitude of effect compared with available therapies was uncertain, given the lack of comparative data and long-term outcome data on outcomes important to patients, such as OS and PFS.

pERC noted input from the Clinical Guidance Panel (CGP) indicating that the response rates achieved in the BRF113928 trial are similar to those observed with randomized trials using dabrafenib plus trametinib in other indications (e.g., metastatic melanoma); thus, there is a suggestion that similar efficacy may be achieved in BRAF-mutated patients across these indications. pERC also noted the CGP's discussion that outcomes with active targeted therapy for NSCLC with defined driver mutations are better compared with non-specific therapy with cytotoxic agents, as established with epidermal growth factor receptor (EGFR)- and anaplastic lymphoma (ALK)-specific therapies. However, pERC agreed that, while mechanism of action is a reasonable rationale in determining the potential for benefit, it cannot be used to extrapolate on important outcomes such as OS and PFS across indications and driver mutations. Trials have demonstrated variability of outcomes among indications where the target mechanism of action is similar. Therefore, pERC agreed that more robust direct or indirect clinical evidence is required to speak to the comparative efficacy and safety of dabrafenib plus trametinib in a setting where treatment options have been approved for reimbursement based on RCTs that have demonstrated OS and PFS benefit.

pERC further considered the feasibility of conducting an RCT in this setting. Although pERC acknowledged that the incidence of BRAF V600 mutation–positive NSCLC is low, the incidence and prevalence of lung cancer is high, and conducting a multi-centre RCT with appropriate comparators would be feasible. pERC noted that objective response rate is an uncertain surrogate for OS in most solid tumours and that the BRF113928 trial did not provide any comparative evidence on OS, which has been a standard outcome in lung cancer studies. pERC noted that it has accepted evidence from non-comparative studies in previous submissions for reasons that are context (drug and disease)-specific; however, in this instance — given the absence of a clear advantage over available treatment options, the feasibility of conducting a randomized trial in this disease setting, the short trial follow-up, and a lack of complete responses to treatment in a meaningful proportion of patients — the Committee was unable to draw a conclusion on the comparative effectiveness of dabrafenib plus trametinib. Upon reconsideration of the Initial Recommendation, pERC noted further comments provided by the CGP indicating that the shift toward personalized medicine will require that lower levels of evidence be reviewed for reimbursement decision-making purposes. pERC reiterated its concern with the expectation that a recommendation for reimbursement be made solely on a rationale related to the mechanism of action of an agent. The BRF113928 trial demonstrated improvements in objective response; however, the surrogacy of this outcome has not been established for OS. The only supportive evidence for the efficacy of this combination treatment is based on extrapolating data observed with other targeted agents in other indications and/or mutation status. Although trials have demonstrated that response rates with targeted agents have subsequently translated into PFS and OS benefits, a sufficient number of trials have also demonstrated a lack of such association from non-

randomized phase II trials to phase III trials. Overall, the Committee agreed that without more robust evidence, it is difficult to establish that dabrafenib plus trametinib is effective in this patient population.

Patient-reported outcomes: No information on quality of life

pERC was unable to deliberate on the impact of dabrafenib plus trametinib of patients' QoL, as these data were not collected in the trial. Based on patient input, NSCLC affects many aspects of patients' day-to-day lives, including on relationships with family and friends, and patients' and caregivers' emotional well-being. Patients also described the high symptom burden of the disease.

Safety: Increased but manageable toxicity profile

pERC discussed the toxicity profile observed in the BRF113928 trial and noted that nearly half of the patients (49%) in the trial experienced a grade 3 or grade 4 adverse event (AE). The most common (≥ 5%) grade 3 or grade 4 AEs were neutropenia (9%), hyponatremia (7%), and anemia (5%). There were four grade 5 AEs (one each of respiratory distress, neoplasm progression, retroperitoneal hemorrhage, and subarachnoid hemorrhage). The median duration of treatment for both dabrafenib and trametinib was 10.6 months. Pyrexia was identified as an important AE by patients and PAG. Among the 57 enrolled patients, 25 (44%) experienced at least one grade 1 or grade 2 event and 1 (2%) experienced a grade 3 event. No patients experienced grade 4 or grade 5 events. pERC noted that toxicities were manageable with dose modifications.

Comparator information: Comparison between selected BRAF V600 mutation-positive and unselected patients

Given the absence of comparative trials, the submitter provided two pseudo trials, which were created using a match-adjusted indirect comparison (MAIC). Through this method, dabrafenib plus trametinib was compared with nivolumab and docetaxel. The MAIC did not meaningfully change the comparability of most baseline characteristics. The pCODR Methods team's critical appraisal indicated that this lack of change in the comparability of baseline characteristics may be due to a reasonable comparability of baseline characteristics prior to matching. However, patients were not matched based on BRAF mutation status, as the data were not available for the group of patients treated with nivolumab. pERC agreed this was the biggest limitation to the evidence, as BRAF mutation status is considered to be an effect modifier. Given that a comparison between selected BRAF mutation–positive and unselected patients may introduce systematic error due to confounding, bias is introduced into the analysis and there is considerable uncertainty in the results of this indirect analysis. The results of the MAIC suggest that dabrafenib plus trametinib improved OS (19.2 months versus 9.3 months, $P = 0.054$), PFS (9.8 months versus 2.2 months, $P = 0.001$), and overall response rate (ORR) (66% versus 19%, $P < 0.001$) in favour of the dabrafenib plus trametinib group compared with nivolumab. Results were similar for docetaxel.

The submitter used the MAIC comparing dabrafenib plus trametinib to nivolumab to link the dabrafenib plus trametinib trial into a network meta-analysis (NMA). Using this methodology, dabrafenib plus trametinib was compared indirectly to a number of relevant comparators (nivolumab, pembrolizumab, pemetrexed, and docetaxel). Based on this analysis, dabrafenib plus trametinib was associated with better OS and PFS and the greatest odds of achieving ORR. Given that the results from the NMA are dependent on linking BRF113928 to the network using MAIC, pERC agreed that the results of the NMA are limited by the concerns in the MAIC.

Need and burden of illness: Patients with BRAF mutation

Lung cancer is the leading cause of cancer-related deaths worldwide, with the majority of patients presenting with non-curable disease. In Canada, an estimated 28,400 new cases and 20,800 deaths occurred in 2016 from lung cancer. NSCLC accounts for 85% of all lung cancers. Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 25% to 30% presenting with locally advanced stage III disease. Only 20% to 25% of patients present with early-stage disease amenable to surgical resection. The incidence of NSCLC rises with age; the median age at diagnosis is 70 years. Given the high proportion of patients presenting with an advanced stage, it is not surprising that the expected five-year survival rate is 18%. BRAF mutations, which occur in non-squamous NSCLC, are low, accounting for approximately 2% of lung adenocarcinomas. In Canada, this represents between 250 and 380 patients annually, of whom about half have the V600E mutation. Treatment decision-making for advanced or metastatic NSCLC is typically dependent on the presence or absence, and type of, driver mutation status of patients in the first-line setting. In patients without a driver mutation, treatments in the second-line setting include immunotherapies (nivolumab or pembrolizumab). Patients with the ALK or EGFR driver mutation receive targeted therapy up front, second-line platinum-based chemotherapy,

third-line immunotherapy (nivolumab or pembrolizumab), and fourth-line single-agent chemotherapy. Although targeted therapies are currently available, there remains a need to identify new therapeutic targets to advance treatment options for those patients who are EGFR wild-type or ALK-negative (e.g., BRAF V600 mutation–positive). Although the identification of less common molecular abnormalities in this population of patients, including BRAF mutations, represents the initial step in advancing therapeutic options, pERC agreed that patients with BRAF V600 mutations currently have treatment options following treatment with systemic chemotherapy. Upon reconsideration of the Initial Recommendation, pERC noted feedback from the submitter, registered clinician groups, and a patient advocacy group arguing that there is an unmet need for further treatment options in this patient population. The Committee recognized that patients have a continued need for more effective treatment options, particularly therapies targeting specific mutations; however, based on the uncertainty in the evidence available from the BRF113928 trial and the availability of treatment options that have demonstrated clinically meaningful OS benefit (i.e., immunotherapies), pERC was unable to conclude that dabrafenib plus trametinib addressed an unmet need. pERC reiterated that the RCTs demonstrating the efficacy and safety of immunotherapies in advanced NSCLC did not exclude patients with BRAF V600E mutation disease and therefore these therapies are currently available for use in this population.

Registered clinician input: Variable opinion on comparative efficacy against immunotherapies

Clinicians providing input indicated that there is an unmet need that can be filled with dabrafenib plus trametinib. Based on data on the natural history of BRAF NSCLC, these patients have a better OS than the average patient with lung cancer and are generally candidates for several lines of therapy. Clinicians identified that dabrafenib plus trametinib offers benefit in terms of response rate and appears to be superior to historical outcomes seen with docetaxel. Benefits have been observed in other molecularly defined subgroups of lung cancer, such as those with EGFR mutations as well as ALK and ROS1 translocations. However, the response rates observed with nivolumab are longer than those in the BRF113928 trial, and there is a lack of clarity on whether dabrafenib plus trametinib is superior to immunotherapies. There was a difference in opinion related to where dabrafenib plus trametinib would be used in the treatment course of patients. One group of registered clinicians indicated that dabrafenib plus trametinib would be used after failure of a platinum doublet. Another group indicated that dabrafenib plus trametinib would be offered as third-line or last-line of therapy after platinum doublet and immunotherapy. They viewed dabrafenib plus trametinib as a “nice-to-have” rather than a “must-have” treatment. Furthermore, clinicians indicated that most patients with BRAF mutations are current or former smokers, and this population has a greater chance of benefit from immunotherapy in the pivotal trials. pERC discussed these inputs from registered clinicians and agreed that, in the absence of robust comparative effectiveness data, the Committee could not conclude that dabrafenib plus trametinib offered a benefit over currently available treatment options like nivolumab and pembrolizumab.

Registered clinician input stated that the BRF113928 trial is an addition to the more extensive research conducted in BRAF mutation–positive melanoma. The input highlights that the safety and efficacy of this combination therapy have been well established through multiple RCTs. However, the current data suggest that dabrafenib plus trametinib has similar efficacy in BRAF-mutated patients with both lung cancer and melanoma with V600 BRAF mutations. Clinicians also indicated that the AE profile was similar between lung and melanoma patients, and the combination was tolerable in both groups. Given the small number of patients with BRAF mutation–positive NSCLC, registered clinicians do not anticipate that RCTs will be conducted in this setting. pERC considered these inputs from registered clinicians and discussed that mechanism of action as a reasonable rationale in determining the potential for benefit; however, using it to extrapolate for important outcomes such as OS and PFS across indications is inappropriate. pERC reiterated that trials have demonstrated variability of outcomes among different indications where the intervention and target mechanism of action have been similar. pERC agreed that more robust direct or indirect clinical evidence is required to speak to the comparative efficacy and safety of dabrafenib plus trametinib in a setting where treatment options have been approved for reimbursement based on RCTs that have demonstrated OS and PFS benefit. pERC further considered that the incidence of BRAF V600 mutation–positive NSCLC is low; however, the incidence and prevalence of lung cancer is high, and conducting a multi-centre RCT with appropriate comparators may have been feasible. Overall, given the uncertainty in the available evidence, the Committee was unable to draw a conclusion on the comparative effectiveness of dabrafenib plus trametinib.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from registered clinician groups related to the effectiveness of dabrafenib plus trametinib. pERC reiterated that effectiveness in other indications cannot on its own be sufficient evidence for effectiveness in patients with BRAF V600E-

positive NSCLC, particularly in a setting where RCTs have demonstrated OS benefit with current treatment options (i.e., immunotherapies). The submitter indicated in the feedback that a study has suggested that objective response may be a surrogate for OS; however, there is conflicting evidence on this surrogacy, as other studies suggest the opposite. pERC agreed that an RCT would have been feasible based on the incidence of lung cancer worldwide had the sponsors conducted an international multi-centre RCT. However, pERC agreed that an RCT for this combination may not be conducted but noted that in instances such as this where the available evidence is not robust, it would be very useful if the submitter was to provide other evidence to demonstrate comparative effectiveness. pERC agreed on the importance of having, at a minimum (1) historical (i.e., retrospective) data on the outcomes of currently available treatments for patients with BRAF 600E mutation-positive metastatic NSCLC previously treated with chemotherapy. These outcomes should be appropriately matched with outcome data for treatment with dabrafenib plus trametinib in order to assess the comparative efficacy and safety of immunotherapy treatments and dabrafenib plus trametinib; (2) more substantive data to demonstrate the surrogacy of response rate for OS regardless of treatment as well as those who have received dabrafenib plus trametinib and; (3) data on whether or not BRAF V600E mutation is an effect modifier or prognostic factor in this disease setting. pERC also noted that there were some differences in the perspectives provided by registered clinicians in the initial input and the feedback documents with regards to the importance of dabrafenib plus trametinib as a potential treatment option. pERC commented that it is important for registered clinicians to make their perspectives clear at the input stage to aid the committee to better understand the minority vs majority opinion related to the drug under review.

PATIENT-BASED VALUES

Values of patients with BRAF V600 mutation–positive NSCLC: Disease and treatment side effect management

Input from the patient advocacy group indicated that lung cancer is a devastating illness that has a tremendous negative impact on the daily lives of patients and caregivers. Symptoms most frequently experienced by patients include pain (very intense at times), shortness of breath, cough, weakness, fatigue, and being bedridden. These symptoms are not fixed or consistent, but change frequently, which can also be difficult to manage. Fatigue, loss of appetite, cough, pain, shortness of breath, and blood in sputum are known to be significant predictors of QoL. Patients living with lung cancer reported that the disease had an impact on many aspects of their day-to-day lives, including their ability to work, travel, socialize, and participate in leisure and physical activities. Patients' relationships with family and friends, independence, emotional well-being, and financial situations are also affected. Patients noted that frequent or constant anxiety or worry is common. Based on patient input, depression rates in advanced lung cancer patients vary from 16% to 50% and are consistently higher than for patients with other cancer sites. Given the absence of data from the BRF113928 trial, pERC was unable to determine the impact of dabrafenib plus trametinib on QoL, an important patient value.

pERC noted the tremendous burden on patients and their caregivers. Caring for patients affects work, finances, relationships with family and friends, physical and leisure activities, independence, and ability to travel and socialize. Caregivers reported difficulty in managing the high symptom burden of lung cancer, both for patients and caregivers. Caregivers experience stigma unique to lung cancer, which places an additional emotional burden on them. The time required for patients to be tested to confirm diagnosis is associated with tremendous fear and anxiety for caregivers. Thus, caregivers and patients value the availability of testing as early as possible. Caregivers describe the availability of a BRAF-specific treatment as providing relief and offering a great deal of hope.

Patient values on treatment: Improve efficacy, reduce side effects, and provide oral treatment option

Patients indicated that current treatments provide some relief for the following symptoms: fatigue, shortness of breath, cough, appetite loss, and low energy; however, they also indicate that side effects such as palpitations, dry mouth, mouth sores, vision problems, urinary problems, and impact on mood need to be better managed. Patients providing input did not speak to any experiences with treatment using immunotherapies. However, they did describe the burden of chemotherapy, which is felt during all stages of the treatment. Patients desire treatments that will improve their independence and reduce the need for assistance from others by requiring fewer medical appointments and reduced financial burden. Patients also indicated that unnecessary delays in their diagnosis could be avoided if their general practitioners were better equipped to recognize lung cancer symptoms earlier.

Patients would like new treatments that stop or slow the progression of the disease, reduce pain, fatigue, cough, and shortness of breath, and improve appetite and energy. Patients expect dabrafenib plus trametinib to reduce or eliminate the following side effects: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin, and impact on mood. Patients also desire the ability to have treatments at home and expect a reduction in the costs associated with treatment. In the absence of comparative effectiveness data, pERC was unable to determine whether dabrafenib plus trametinib offered benefits to patients above those observed with currently available treatment options that have demonstrated OS and PFS benefits in randomized trials. pERC acknowledged that the oral route of administration would provide ease of administration for patients; however, the costs associated with treatment would be increased for some patients, as the two different drugs would have two dispensing fees, two co-payments, and varying deductibles applied in provinces where oral drugs are funded through pharmacare programs.

Among patients providing input, nine had experience with dabrafenib plus trametinib. Seven stated that their response to this treatment was positive. pERC noted that side effects varied greatly between patients, with some experiencing no side effects and others experiencing high to severe side effects from this treatment. One patient went from feeling tired, having shortness of breath, and coughing 200 to 500 times per day to feeling great, with no coughing, symptoms, or side effects after taking the treatment under consideration. The most commonly reported side effects were flu and fever-like symptoms (n = 6), nausea (n = 5), fatigue (n = 5), chills (n = 4), and rash (n = 3). Vision problems and hypersensitivity to the sun were also reported in one case each. In two cases, the side effects were so severe that hospitalization was required.

Overall, pERC considered that the oral route of administration, demonstrated tumour activity, and increased but manageable toxicity profile of dabrafenib plus trametinib were aspects that aligned with patient values. However, considerable uncertainty remained in the clinical effect estimates of dabrafenib plus trametinib compared with alternative treatment options, which does not align with patient values. pERC highlighted that there is a continued need for more effective treatment options for patients; however, given the availability of immunotherapies (nivolumab and pembrolizumab), pERC agreed that patients do have other treatment options. Overall, pERC agreed that dabrafenib plus trametinib partially aligned with patient values.

Upon reconsideration of the initial recommendation, pERC noted feedback from a patient advocacy group that treatment with dabrafenib plus trametinib completely aligns with patient values. Although the patient group argued that the treatment was effective, pERC was not satisfied that the available evidence demonstrated a net overall clinical benefit, and therefore it could not agree that the treatment aligns fully with patient values for more effective treatment. In addition, the patient group commented that the committee prioritizes immunotherapies over targeted agents. pERC discussed this feedback and re-iterated that it strives to ensure its decision making is based on rigorous evidence. In this case, the Committee was not confident that the evidence was sufficient to support a decision for the reimbursement of dabrafenib plus trametinib ahead of effective treatment options (ie., immunotherapies) that have demonstrated clinically meaningful OS benefit through randomized controlled trials. pERC also considered feedback indicating that evidence about the impact of dabrafenib plus trametinib on patients' quality of life was available through the patient group submission. pERC noted that patient input provides a tremendous aid to the committee in understanding the lived experience of patients, including experiences related to the treatment under review, compared to clinical trial evidence. However, the Committee stressed that it cannot use information from the patient input as a substitute for clinical trial evidence. Although patient input is carefully considered, pERC agreed that each component of its deliberative framework must be addressed based on the appropriate evidence available.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing dabrafenib plus trametinib in patients with BRAF V600 mutation–positive NSCLC who have previously been treated with chemotherapy to each of the following treatment regimens: docetaxel, pemetrexed, nivolumab, and pembrolizumab. Erlotinib and best supportive care were also used as

comparators in the submitted economic analysis, but the pCODR CGP did not consider these to be appropriate comparators.

Basis of the economic model: Non-comparative trial, high drug cost
Costs considered in the analysis included costs related to the drug, administration, subsequent treatment, follow-up, AE management, and terminal care.

The clinical effects considered in the analysis were based on an NMA and MAIC. Limitations were identified in the comparability of patients in the BRF113928 trial and corresponding trials used to generate evidence for the appropriate comparators — mainly the comparison of selected BRAF V600 mutation-positive patients with unselected patients in all other trials. Without robust direct or indirect comparative effectiveness data, the magnitude and direction of the impact of key factors of economic models, such as survival, utilities, or treatment duration, are unknown. In the absence of other sources of data, the pCODR EGP used data generated through the NMA/MAIC.

Drug costs: High cost of combination therapy
Dabrafenib costs $65.23 per 75 mg capsule. At the recommended dose of 150 mg twice daily, dabrafenib costs $260.93 per day and $7,306.10 per 28-day course. Trametinib costs $298.70 per 2 mg tablet. At the recommended dose of 2 mg once daily, trametinib costs $298.70 per day and $8,363.60 per 28-day course.

Cost-effectiveness estimates: Considerable uncertainty in estimates for clinical effectiveness
pERC deliberated upon the cost-effectiveness of dabrafenib plus trametinib. Due to the considerable limitations in the available clinical data of dabrafenib plus trametinib from a non-randomized study, the lack of robust direct or indirect comparative effectiveness estimates for PFS and OS, and the high cost of this combination treatment, pERC concluded that dabrafenib plus trametinib is not cost-effective. In the absence of more robust direct or indirect sources of data, the pCODR EGP used the submitted estimates for efficacy, which were based on an MAIC/NMA. Given the limitations identified with this analysis, pERC agreed that the EGP's estimates are highly uncertain. The EGP captured this uncertainty by providing a lower estimate and no limit to the upper bound of the reanalysis estimate. pERC also highlighted that the incremental cost-effectiveness ratio (ICER) was primarily driven by the cost of dabrafenib plus trametinib, and that a substantial decrease in the cost of this combination therapy from the submitted price would be necessary to make treatment cost-effective. The Committee agreed with the EGP's overall conclusion that, given the lack of robust direct or indirect comparative estimates for PFS and OS, there is a high degree of uncertainty with respect to the estimates of extra clinical effect of dabrafenib plus trametinib, and that this considerable uncertainty is not fully captured in the EGP's estimates. Additional factors that most influence the incremental effectiveness include the duration of treatment and the inclusion of BRAF testing. Overall, based on the identified limitations in the clinical evidence and high drug cost, pERC agreed that dabrafenib plus trametinib is not cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High cost and lack of comparator
pERC discussed the feasibility of implementing a reimbursement recommendation for dabrafenib plus trametinib for the treatment of patients with advanced NSCLC with a BRAF V600 mutation and who have been previously treated with chemotherapy. As a fully oral option, pERC noted that dabrafenib plus trametinib can be administered to patients more easily than intravenous therapies in both rural and urban settings. However, costs associated with treatment would be increased for some patients, as the two different drugs would have two dispensing fees, two co-payments, and varying deductibles applied in provinces where oral drugs are funded through pharmacare programs. Barriers to implementation were also identified related to compliance due to pill burden and dose confusion. Despite enablers to implementation, pERC agreed that dabrafenib plus trametinib should not be reimbursed due to the uncertainty in the clinical trial evidence.

In making a recommendation not to reimburse, pERC acknowledged the continued need for additional treatment options in this patient population. pERC also acknowledged that treatment options with demonstrated OS and PFS benefits have recently been made available in this setting. pERC weighed the strength of the evidence in the BRF113928 trial, and stressed that the Committee's recommendations must be equitable, transparent, timely, and accountable to patients, health care funders, and the public to ensure that effective treatment options are considered for public funding. Conversely, pERC also

recognizes that these recommendations must be rigorous, consistent, and evidence-based. Therefore, based on considerable uncertainty in the evidence provided within the BRF113928 trial, the availability of treatment options in this setting, and the ever-increasing demand for limited public resources to fund effective treatments, pERC was not ready to recommend reimbursement of dabrafenib plus trametinib.

DRUG AND CONDITION INFORMATION

Drug Information	• Dabrafenib is a BRAF V600 inhibitor; trametinib is a mitogen-activated protein kinase (MEK) inhibitor • Dabrafenib is available in 50 mg and 75 mg capsules; trametinib is available in 0.5 mg and 2 mg tablets • The recommended doses are dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily, until disease progression
Cancer Treated	• BRAF V600 mutation–positive metastatic non–small cell lung cancer
Burden of Illness	• Approximately 2% of lung adenocarcinomas (250 to 380 patients annually) • With current therapies, one-year survival estimates range from 42% to 51% with second-line therapy
Current Standard Treatment	• Nivolumab • Pembrolizumab • Docetaxel • Pemetrexed
Limitations of Current Therapy	• Lack of targeted therapies for BRAF V600 mutation–positive population • Intravenous administration of current therapies

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:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

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

- Jo Nanson, Anil Abraham Joy, Danica Wasney, and Kelvin Chan, who were not present for the meeting

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)	Dr. Winson Cheung, Oncologist
Dr. Catherine Moltzan, Oncologist (Co-Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Avram Denburg, Pediatric Oncologist	Leela John, Pharmacist
Dr. Kelvin Chan, Oncologist	Valerie McDonald, Patient Member
Lauren Flay Charbonneau, Pharmacist	Carole McMahon, Patient Member
Dr. Matthew Cheung, Oncologist	Cam Lane, Patient Member Alternate
Dr. Craig Earle, Oncologist	Dr. Marianne Taylor, Oncologist
Dr. Christine Kennedy, Family Physician	Mike Doyle, Health Economist

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

- Kelvin Chan and Lauren Flay Charbonneau, who were not present for the meeting.
- Cam Lane, who did not vote due to his role as a patient member alternate.
- Mike Doyle who didn't vote due to a conflict of interest.

Avoidance of conflicts of interest

All members of the pCODR pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of dabrafenib plus trametinib for BRAF V600–positive non–small cell lung cancer, through their declarations, six members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting. For the Final Recommendation, six members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members 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 pCODR 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 pERC 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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