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) in combination with Trametinib (Mekinist)

Submitted Reimbursement Request:
Dabrafenib in combination with trametinib, for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of lymph node(s), following complete resection.

Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: September 21, 2018	**Submission Date:** September 21, 2018
Initial Recommendation: March 7, 2019	**Final Recommendation:** May 3, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	• Dabrafenib costs $66.34 per 75 mg capsule, and trametinib costs $304.17 per 2 mg tablet. • At the recommended daily dose of 300 mg for dabrafenib and 2 mg for trametinib, the combination of dabrafenib plus trametinib costs $569.17 per day and $14,929 per 30-day treatment cycle (adjusted for relative dose intensity).

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 to reimburse dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the adjuvant treatment of patients with stage IIIA (limited to lymph node metastases of > 1 mm) to stage IIID (8th edition of the American Joint Committee on Cancer [AJCC] staging system) BRAF-mutated (all BRAF V600 mutations) cutaneous melanoma. Disease must be completely resected including in-transit metastases; however, presence of regional lymph nodes with micrometastases after sentinel lymph node biopsy alone is allowed. Patients must have good performance status. Reimbursement is only recommended if the following conditions are met:

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

Treatment with dabrafenib plus trametinib should continue until disease recurrence, unacceptable toxicity, or up to a maximum of 12 months.

pERC made this recommendation because it was confident that there is a net clinical benefit of dabrafenib plus trametinib based on a statistically significant and clinically meaningful improvement in relapse-free survival compared with placebo (observation), and a manageable toxicity profile with no detriment to quality of life. pERC agreed that dabrafenib plus trametinib aligns with patient values because it fulfills a need for effective

	treatment options that provide disease control with manageable side effects. pERC concluded that considering the uncertainty related to the overall survival benefit, dabrafenib plus trametinib may not be cost-effective compared with observation at the submitted price. Furthermore, pERC had concerns that the budget impact was underestimated since the market share of dabrafenib plus trametinib was underestimated and only considered drug costs. Other costs associated with the management of melanoma (e.g., BRAF testing, drug administration, management of adverse events, medical visits/hospitalizations) were not included. Therefore, the actual budget impact is likely greater than estimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of dabrafenib plus trametinib for the adjuvant treatment of patients with BRAF-mutated stage IIIA-D cutaneous melanoma (8th edition AJCC), jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability. **No Evidence for Optimal Sequencing** pERC acknowledged that there is no direct comparative evidence investigating the efficacy and safety or the appropriate sequence of adjuvant therapies for patients with BRAF-mutated stage IIIA-D cutaneous melanoma. Further, the optimal sequencing of subsequent therapies for patients with BRAF-mutated metastatic melanoma after disease progression with adjuvant dabrafenib plus trametinib is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for dabrafenib plus trametinib, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value. **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

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7,200 cases per year. The incidence of melanoma in Canada continues to rise and it is the most commonly diagnosed cancer in individuals between the ages of 20 and 29 years. A proportion of patients will present with locally advanced cancers that, while amenable to surgery, signify a high risk of relapse and death, with a five- and 10-year disease-specific survival rate of 32% and 24%, respectively, for patients with high-risk disease (stage IIID according to the 8th edition of the AJCC staging system). In Canada, high-dose interferon-alpha (IFN) is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but are at high-risk for systemic recurrence. In practice, however, IFN is infrequently prescribed due to its substantial toxicity profile and uncertain efficacy, with most patients declining IFN treatment, and instead choosing observation alone (also referred to as watchful waiting). Although a number of immunotherapies and targeted agents are being studied in this setting, for patients presenting with resected stage III melanoma, adjuvant treatment options are currently limited, particularly with respect to systemic therapy. pERC acknowledged that there is a significant need for effective curative treatment options in the adjuvant setting for patients with resected stage III melanoma.

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

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

pERC deliberated on the results of one randomized controlled trial (RCT), COMBI-AD, which evaluated the safety and efficacy of the combination of dabrafenib plus trametinib compared with matched placebos in the adjuvant treatment of patients with completely resected stage III (AJCC 7th edition) BRAF-mutated (V600 E or K) cutaneous melanoma. The COMBI-AD trial demonstrated a statistically significant and clinically meaningful improvement in relapse-free survival (RFS) in favour of dabrafenib plus trametinib compared with placebo. While overall survival (OS) data showed a trend toward improvement with dabrafenib plus trametinib, the difference was not statistically significant according to the predefined statistical threshold used at the first interim analysis. pERC also deliberated on the toxicity profile of dabrafenib plus trametinib and noted that grades 3 or 4 adverse events (AEs), serious adverse events (SAEs), and AEs leading to dose interruption, dose reduction, and treatment discontinuation were all increased in the dabrafenib plus trametinib group compared with the placebo group. pERC noted it was surprising that, despite the increased toxicity in the combination therapy group, no difference in quality of life (QoL) between the groups was observed. pERC noted that QoL was an exploratory end point of the trial, and commented that the QoL results may be a reflection of multiple factors including the use of the EQ-5D-3L to assess QoL, which is more a measure of daily functioning than QoL, established AE management strategies for dabrafenib-trametinib, and attrition of sicker patients over the course of the trial. Overall, pERC agreed with the pCODR Clinical Guidance Panel (CGP) that dabrafenib plus trametinib had a manageable toxicity profile, especially when indirectly compared with the toxicity profile of high-dose IFN. pERC concluded that there is a net clinical benefit of dabrafenib plus trametinib based on the clinically meaningful result in RFS, no observed detriment to QoL, a manageable toxicity profile, and the need for more effective and tolerable treatment options.

pERC discussed the use of placebo as the comparator in the COMBI-AD trial, noting that high-dose IFN is currently the only funded treatment option in Canada. pERC acknowledged, however, that for the majority of stage III patients IFN does not provide a meaningful clinical benefit and is associated with substantial toxicity, leading most patients to opt for a treatment strategy of observation. Based on this practice pattern, pERC considered placebo an appropriate comparator in the COMBI-AD trial. pERC commented that an indirect treatment comparison and network meta-analysis (NMA) was provided by the submitter but it did not include IFN as a comparator in the BRAF-mutated patient subgroup analysis because it could not be connected in the network. The NMA included other comparators of interest (nivolumab and pembrolizumab), but pERC agreed with the pCODR Methods Team that, considering the limitations of the NMA, which included important differences in treatment effect modifiers across the comparisons in the network, its relevance and credibility for providing reliable comparative estimates of efficacy were uncertain.

pERC highlighted that the COMBI-AD trial restricted enrolment to patients with BRAF-mutated stage IIIA-C cutaneous melanoma based on the 7th edition of the AJCC staging system, and required patients with stage IIIA disease to have nodal metastases > 1 mm. In the time since the trial was conducted clinical practice has adopted the AJCC 8th edition classification system, and pERC noted that the 8th edition captures the entire COMBI-AD trial population within stages IIIA through IIID. During reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from registered clinicians who disagreed that eligibility for adjuvant dabrafenib-trametinib in stage IIIA disease should be restricted to patients with lymph node metastases measuring >1 mm. The clinicians noted that excluding patients with lymph node metastases measuring <1 mm will increase the complexity of providing clinical care in certain situations (e.g., a single foci metastasis <1 mm versus multi focal metastases <1 mm). pERC considered the factors identified by the CGP in support of offering adjuvant dabrafenib-trametinib to all stage III patients, which included alignment with the Health Canada indication, which does not specify a minimum focus of nodal disease for any recently approved adjuvant therapy (dabrafenib-trametinib, nivolumab, and pembrolizumab), and the absence of evidence to refute clinical benefit. However, pERC highlighted the low risk of relapse among patients with stage IIIA disease (10-year survival rate of 88% according to AJCC 8th edition), and noted that patients with nodal micrometastases measuring < 1 mm have an even lower risk of relapse. Therefore, considering the good prognosis associated with stage IIIA disease, pERC reiterated that adjuvant dabrafenib plus trametinib be offered to stage IIIA patients based on the eligibility criteria of the COMBI-AD trial, which specified lymph node metastases measure > 1 mm.

pERC discussed the generalizability of the COMBI-AD trial results to subgroups of patients at high-risk of relapse who were not included in the trial, and acknowledged that the AJCC 8th edition indicates patients with stage IIB/C disease and T4 lesions, who were excluded from COMBI-AD, may actually have a worse prognosis than stage III patients. The CGP indicated that clinical trials are under way to evaluate the efficacy and safety of adjuvant systemic treatment in stage IIC patients, and pERC agreed with the CGP's judgment that the decision to use adjuvant dabrafenib plus trametinib after resection in these patients should await the results of these clinical trials. The COMBI-AD trial also did not enrol patients with resected stage IV disease, and as such, was in agreement with the CGP that the use of adjuvant dabrafenib plus trametinib should not be used in this group of patients in the absence of clinical trial data.

pERC also discussed the CGP's assessments regarding other generalizability issues that were identified. The COMBI-AD trial required completion lymphadenectomy for all patients with micrometastatic lymph node involvement detected on a sentinel lymph node biopsy. However, recent evidence has changed this practice and established observation as an acceptable treatment approach, as survival was not improved with complete lymph node dissection. pERC agreed with the CGP that the results of the COMBI-AD trial are generalizable to patients who do not have complete lymph node dissection for micrometastatic nodal involvement, and indicated this practice should not be a requirement for adjuvant treatment with dabrafenib plus trametinib. The COMBI-AD trial enrolled patients with the most common BRAF V600 mutations, E or K, but pERC was in agreement with the CGP that patients with other less common V600 mutations (e.g., V600 D, V600 R) may also derive benefit from adjuvant dabrafenib plus trametinib based on demonstrated clinical benefit in patients with non-V600 E/K mutations treated with the combination in the metastatic setting. pERC therefore concluded that patients with other BRAF non-V600 E/K mutations should be eligible for treatment with dabrafenib plus trametinib. Finally, pERC noted that the COMBI-AD trial only enrolled patients with an ECOG performance status of 0 to 1 and agreed that adjuvant dabrafenib plus trametinib should be offered to patients with a good performance status.

pERC deliberated on input received from two patient advocacy groups and noted that patients with stage III melanoma value access to a variety of effective treatment options that stop disease progression and increase survival, have manageable side effects, and are affordable. The patient input indicated that lack of effective treatment options after surgery is a source of extreme stress and anxiety for patients and their caregivers. Patients treated with IFN indicated they experienced significant side effects that they considered unmanageable. pERC discussed the toxicity profile associated with IFN and acknowledged that most patients find it very difficult to tolerate and are unable to complete the full course of treatment. pERC noted that patients who had experience with dabrafenib plus trametinib indicated the combination was associated with different and fewer AEs compared with IFN, and overall was well tolerated. pERC also considered that many advanced stage patients reported that they continued to work while on treatment with dabrafenib and trametinib. Based on the results of the COMBI-AD trial, which demonstrated a statistically significant improvement in RFS, a trend toward improvement in OS, a manageable toxicity

profile, and no detriment to QoL, pERC concluded that dabrafenib plus trametinib aligned with patient values.

pERC deliberated on the cost-effectiveness of dabrafenib plus trametinib compared with placebo (observation), and concluded that, at the submitted price and based on the submitted economic analysis, dabrafenib plus trametinib may not be cost-effective. pERC reached this conclusion based on the uncertainty that resulted from modelling OS indirectly from RFS curves. pERC discussed that the OS trial data were immature (i.e., the OS curves were from an interim analysis with a small number of events) and noted that differences in the actual versus modelled survival curves suggested the submitter's indirect estimation of OS may overestimate the survival benefit of dabrafenib plus trametinib. The Economic Guidance Panel (EGP)'s reanalysis to obtain a more clinically plausible estimate of the survival difference between the two treatment strategies had the most substantial impact on the incremental cost-utility ratio (ICUR). Furthermore, assumptions about the time horizon also impacted the cost-effectiveness estimates. A time horizon of 35 years was used in the submitted model; however, the CGP viewed 25 years to be a more realistic clinical scenario, which increased the ICUR. pERC agreed with the CGP that a shorter time horizon was more clinically appropriate; however, the Committee discussed that a much shorter time horizon of 10 years was used in the recent pCODR review of nivolumab for stage III melanoma. pERC considered the key differences between the nivolumab and dabrafenib plus trametinib cost-effectiveness analyses identified by the EGP that included the length of follow-up for the OS data and differences in the patient populations (stage of disease) between the two trials. The longer OS data of approximately four years provided by the COMBI-AD trial, compared with approximately two years of data provided by the CheckMate 238 trial (nivolumab), and the inclusion of only stage III patients in the COMBI-AD trial makes extrapolations out to 25 years in the current submission clinically plausible. pERC agreed with the EGP that when the 10-year survival estimates (AJCC 8th edition) of patients with stage III melanoma are considered, which vary between 24% and 88% depending on the patient subgroup, that the use of a 10-year time horizon would likely underestimate the benefits of dabrafenib plus trametinib. Overall, based on the EGP's reanalysis estimates using a 25-year time horizon, and considering the uncertainty related to the OS benefit and the submitted price, pERC concluded that dabrafenib plus trametinib may not be cost-effective. Upon reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the submitter stating disagreement with pERC's conclusion that dabrafenib plus trametinib may not be cost-effective given that both the submitter's base case and the EGP's best estimate of the ICUR were below $100,000. In response to this feedback, pERC reiterated that the uncertainty introduced into the economic evaluation by modelling OS indirectly from RFS trial data precludes a conclusion that dabrafenib-trametinib is cost-effective at the submitted price.

pERC considered the feasibility of implementing a reimbursement recommendation for dabrafenib plus trametinib for the adjuvant treatment of resected stage IIIA-D BRAF-mutated melanoma (AJCC 8th edition). pERC noted that the EGP considered that the budget impact analysis (BIA) was underestimated as it only considered drug costs and that other costs associated with the management of melanoma were omitted (e.g., BRAF testing, drug administration, management of AEs, medical/hospital visits). Additionally, pERC believed the BIA underestimated the market share for dabrafenib plus trametinib and overestimated the use of observation and IFN. pERC noted that immunotherapies including nivolumab and pembrolizumab, which currently are not funded but have either recently completed or are undergoing pCODR review, were not included in the BIA. pERC anticipates that the majority of BRAF-mutated patients will receive dabrafenib plus trametinib in the adjuvant setting. Consequently, the population of patients eligible for dabrafenib plus trametinib may be greater than what is estimated in the submitter's BIA. Given the potentially substantial budget impact of dabrafenib plus trametinib the provinces should consider taking steps to limit the budget impact.

pERC acknowledged that there are a number of immunotherapies being evaluated in the adjuvant setting. pERC agreed with the CGP's assessment that there is no direct evidence from RCTs to inform the sequencing of dabrafenib plus trametinib relative to adjuvant immunotherapies in patients with BRAF-mutated melanoma who are candidates for surgery. In the absence of direct evidence, pERC commented that treatment choice will likely be influenced by toxicity profiles, patient preference for treatment administration (oral versus intravenous), schedules (frequency), and what is provincially funded. During the reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from registered clinicians, who requested the recommendation address the need to switch adjuvant therapy (targeted therapy to immunotherapy and vice versa) if patients experience intolerance. pERC noted that PAG also raised the issue of intolerance, specifically inquiring whether patients with BRAF mutations intolerant to adjuvant nivolumab could be considered for treatment with dabrafenib-trametinib; and if so, what the appropriate duration of adjuvant therapy would be in this situation. pERC agreed with the

CGP that patients who are unable to tolerate one class of adjuvant treatment should be allowed the option to resume treatment with an alternate agent in the absence of disease progression, and that the total duration of adjuvant therapy should not exceed one year. pERC noted, however, that the choice to switch to a novel adjuvant therapy after intolerance should be made after careful deliberation by the physician and patient that takes into account the duration of the first selected adjuvant therapy.

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 (Melanoma Network Canada [MNC] and Save Your Skin Foundation [SYSF])
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one clinician group, Cancer Care Ontario Skin Drug Advisory Committee
- PAG
- the submitter, Novartis Pharmaceuticals Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of dabrafenib (Tafinlar) in combination with trametinib (Mekinist), conditional on cost-effectiveness being improved to an acceptable level and feasibility of adoption being addressed (budget impact). Feedback on the pERC Initial Recommendation indicated that PAG agreed with the Initial Recommendation, and the registered clinician group and the submitter agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of dabrafenib plus trametinib (Tafinlar and Mekinist) for the adjuvant treatment of patients with BRAF V600 mutated melanoma and the involvement of lymph nodes following complete resection, for up to a maximum of 12 months.

Studies included: One randomized phase III placebo-controlled trial

The pCODR systematic review included one randomized, double-blind, placebo-controlled, international phase III trial that evaluated the safety and efficacy of combination dabrafenib plus trametinib in patients with BRAF-mutated stage III melanoma after complete surgical resection. Eligible patients ≥ 18 years of age were randomized in a 1:1 ratio to receive oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg daily (n = 438) or two matched placebo tablets (n = 432). Patients were stratified according to disease stage (AJCC 7th edition stages IIIA-C) and BRAF mutation status (V600E or V600K). Patients in both groups were treated for 12 months or until disease recurrence, unacceptable toxicity, withdrawal of consent, or death. The trial is ongoing with an estimated completion date of November 30, 2030.

Patient populations: Stage III A-C (AJCC 7th edition) completely resected BRAF-mutated cutaneous melanoma

Key eligibility criteria included patients who had undergone complete resection of histologically confirmed stage IIIA (limited to lymph node metastasis of > 1 mm), IIIB, or IIIC cutaneous melanoma (AJCC 7th edition) with BRAF V600E or V600K mutations and an ECOG performance status of 0 or 1. All patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease. Patients were rendered surgically free of disease no more than 12 weeks before randomization. Patients with known mucosal or ocular melanoma or the presence of unresectable in-transit metastases were excluded from the trial.

The median age of patients in the trial was approximately 50 years (range, 18 to 89 years). The majority of patients were male (55%), had an ECOG status of 0 (91%), BRAF V600E mutations (91%), and stage IIIB or IIIC disease and nodal involvement of one positive node (40% to 42%). Micrometastatic (36%) and macro-metastatic (37%) lymph node involvement, tumour ulceration (41%), number of positive lymph nodes (1: 40%; 2 or 3: 35%; ≥ 4: 17%), and in-transit metastases (10%) were observed in similar proportions of patients in each treatment group.

Overall, study treatment discontinuations were higher in the placebo group (47% for both matching placebos) compared with the dabrafenib plus trametinib treatment group (37% and 36%, respectively). The main reason for treatment discontinuations was disease recurrence in the placebo group (41%, compared with 5% with dabrafenib plus trametinib) and AEs in the dabrafenib plus trametinib group (25% for dabrafenib and 24% for trametinib, versus 3% in the placebo group). More patients in the placebo group (42%, versus 28% of patients with dabrafenib plus trametinib) received post-treatment systemic anti-cancer therapy. The most common systemic therapies received after recurrence were small-molecule targeted therapy (14% of the patients receiving dabrafenib plus trametinib and 32% of those receiving placebo), immunotherapy against PD-1 or PD-L1 (16% in each group), and anti–CTLA-4 immunotherapy (12% and 16%, respectively).

Key efficacy results: Statistically significant improvement in RFS

The key efficacy outcome deliberated on by pERC was the primary outcome of investigator assessed RFS. Key secondary efficacy end points included OS, distant metastases-free survival (DMFS), freedom from relapse (FFR), QoL, and safety. The median follow-up time at the primary analysis data cut-off date of June 30, 2017, was 3.3 years. An updated analysis of RFS at the April 30, 2018 data cut-off date provided an additional 10 months of follow-up time (for RFS and DMFS).

At the primary analysis date, the combination of dabrafenib and trametinib demonstrated superiority over placebo for the primary outcome of RFS; the hazard ratio (HR) for relapse or death was 0.47 (95% confidence interval [CI], 0.39 to 0.58) in favour of the dabrafenib plus trametinib treatment group. This result was highly statistically significant with $P < 0.001$ (stratified Log-rank test, two-sided). The median RFS was not reached in the combination therapy group (95% CI, 44.5 months to not reached) and was 16.6 months (95% CI, 12.7 to 22.1) in the placebo group. The updated analysis of RFS was consistent with the primary analysis; the estimated HR was 0.49 (95% CI, 0.40 to 0.59).

At the primary analysis cut-off date (first interim OS analysis) a total of 153 deaths had occurred, 60 (14%) in the dabrafenib plus trametinib group and 93 (22%) in the placebo group. These data are still immature and represent 26% (information fraction) of the total targeted 597 deaths required for the final OS analysis. The most common cause of death in both treatment groups was melanoma. The estimated HR for OS was 0.57 (95% CI, 0.42 to 0.79; stratified Log-rank test $P = 0.0006$, two-sided). As the two-sided threshold for statistical significance at the first interim analysis was $P = 0.000019$, based on the observed information fraction and predefined stopping boundary, this result was not considered statistically significant. The second interim analysis of OS is planned for when approximately 299 deaths have occurred (i.e., 50% of the targeted 597 events required for the final OS analysis).

Secondary outcomes including DMFS and FFR also favoured treatment with dabrafenib plus trametinib compared with placebo.

Patient-reported outcomes: No meaningful differences in QoL between dabrafenib plus trametinib and placebo as assessed by the EQ-5D-3L

Health-related QoL was an exploratory outcome of the trial and was measured using the EQ-5D-3L (utility score and visual analogue scale [VAS]) every three months. The EQ-5D-3L descriptive utility score comprises the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, while the VAS records the respondent's self-rated health (best and worse imaginable health state) on a vertical scale. A change from baseline of 0.08 points in the utility score or 7.0 points in the VAS was considered minimally important differences. Completion rates for the EQ-5D-3L questionnaire were high through month 36 but declined thereafter to 42% in the dabrafenib plus trametinib group and 31% in the placebo group. Baseline utility and VAS scores were similar between the two treatment groups. At the primary analysis data cut-off date, the QoL data showed that during the treatment phase (0 to 12 months), there were no meaningful changes in EQ-5D-3L utility scores or mean VAS scores between the treatment groups. Further, there were no AEs associated with a clinically meaningful decrease in QoL during treatment. VAS scores improved over time for patients who experienced each of the most common AEs such as pyrexia, nausea, headache, diarrhea, arthralgia and rash; and no clinically meaningful changes from baseline VAS were observed in patients in the combination therapy group who discontinued treatment early. Similar results were observed during the long-term follow-up phase of the trial (> 12 months).

Safety: Manageable toxicity profile; higher frequency of grade 3-4 AEs, SAEs, dose interruptions and reductions, and treatment discontinuations in the dabrafenib plus trametinib group

The majority of patients in the trial experienced AEs (97% and 88% of patients in the dabrafenib plus trametinib and placebo groups, respectively), most of which were grade 1 or 2 in severity. Grade 3 or 4 AEs of any cause occurred in more patients in the dabrafenib plus trametinib group at 41%, compared with14% in the placebo group. The three most common AEs occurring in the combination treatment group were pyrexia (any grade, 63%; grade 3 or 4, 5%), fatigue (any grade, 47%; grade 3 or 4, 4%), and nausea (any grade, 40%; grade 3 or 4, < 1%). SAEs were also higher with combined treatment and occurred in 36% of patients, including one fatal SAE due to pneumonia, compared with 10% of patients in the placebo group. Compared with placebo, a greater proportion of patients treated with dabrafenib plus trametinib experienced AEs leading to dose interruptions (66% versus 15%), dose reductions (38% versus 3%), and discontinued study treatment (26% versus 3%). The median duration of dose interruptions was also longer in the dabrafenib plus trametinib group (16.5 days and 13.0 days, respectively) compared with placebo (4.0 days).

Need and burden of illness: Unmet need for stage III patients at high-risk of relapse after surgery

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7,200 cases per year. The incidence of melanoma in Canada continues to rise and it is the most commonly diagnosed cancer in individuals between the ages of 20 and 29 years. A proportion of patients will present with locally advanced cancers that, while amenable to surgery, signify a high risk of relapse and death, with a five- and 10-year disease-specific survival rate of 32% and 24%, respectively, for patients with high-risk disease (stage IIID according to the 8th edition of the AJCC staging system). In Canada, high-dose IFN is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but are at high-risk for systemic recurrence. In practice, however, IFN is infrequently prescribed due to its substantial toxicity profile, with most patients declining IFN treatment, and instead choosing observation alone (also referred to as watchful waiting). Although a number of immunotherapies and targeted agents are being studied in this setting, for patients presenting with resected stage III melanoma, adjuvant treatment options are currently limited, particularly with respect to systemic therapy. Therefore, there is a significant need for effective curative treatment options in the adjuvant setting for patients with resected stage III melanoma.

Registered clinician input: Unmet need for a treatment option

Input from a total of five registered clinicians was received, one joint submission comprising input from four oncologists and one individual oncologist submission. The clinicians unanimously agreed that the combination of dabrafenib plus trametinib is superior to currently available treatment options and commented that the combination would provide a much awaited and beneficial adjuvant treatment option for BRAF V600 mutation positive stage III melanoma patients. The clinicians referenced the clinical benefit observed in the COMBI-AD trial with dabrafenib plus trametinib, citing it provides a meaningful clinical benefit by dramatically reducing the risk of metastatic relapse at two and three years, and that the benefit appears to be sustained over time. They noted that harms of dabrafenib plus trametinib include short-term toxicities while on treatment including pyrexia, fatigue, rash, gastrointestinal side effects, and laboratory abnormalities; and the only significant contradictions to treatment would be hypersensitivity reaction or SAEs. Clinicians suggested patients of all performance statuses be considered for adjuvant treatment with dabrafenib plus trametinib. They also suggested that an indication drift to stage IIC patients may occur as the risk for relapse is higher in these patients. Clinicians indicated most patients opt for a treatment strategy of observation alone. High-dose IFN was cited as the only currently funded treatment option in this patient population but the clinicians considered it to be mostly ineffective in terms of clinical benefit and intolerable due to substantial toxicity that includes fever, flu-like symptoms, myelosuppression, liver toxicity, and depression. They suggested patients who relapse despite treatment with IFN may be subsequently treated with oral targeted therapies or immunotherapy. They also indicated that BRAF mutation testing would need to be expanded to include patients who were high risk and non-metastatic.

PATIENT-BASED VALUES

Experience of patients with stage III melanoma: fear and anxiety about lack of effective treatments

Patient input was received from two patient advocacy groups: MNC and SYSF. Patients with melanoma indicated they value access to a variety of effective treatment options that stop disease progression and increase survival, have manageable side effects, and are also affordable. The patient input indicated that lack of effective treatment options after surgery is a source of extreme stress and anxiety for patients and their caregivers, as they expressed stage III melanoma is associated with a chronic, traumatic fear of recurrence. Other side effects associated with the disease include the physical impact of surgery including scarring, mobility issues, and lymphedema. These impairments had an impact on patients' daily functioning and ability to work. Patients who had experience with IFN, the only currently funded treatment option for stage III disease, said they experienced significant side effects that they considered unmanageable. In most patients these side effects led to treatment discontinuation.

Patient values on treatment: Earlier access to effective treatments; willingness to tolerate side effects for disease control and improved survival

Patients with melanoma expressed a strong desire for earlier (adjuvant) treatments compared with the risk of disease progression and expressed a willingness to tolerate side effects for disease control and longer survival. Patients who had experience with dabrafenib plus trametinib indicated the combination was associated with different and fewer AEs compared with IFN, and overall was well tolerated. This tolerability was supported by a report that many patients continued to work while on treatment with dabrafenib and trametinib. Patients reported side effects that included fever, joint pain, fatigue and rash. The majority of patients said the benefits outweighed side effects, with over half reporting disease control.

ECONOMIC EVALUATION

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

The pCODR EGP assessed the cost-effectiveness (clinical effects measured as life-years gained) and cost-utility analyses (clinical effects measured by quality-adjusted life-years [QALYs] gained) comparing dabrafenib plus trametinib with watchful observation (placebo). The submitter also provided a comparison of dabrafenib plus trametinib to high-dose IFN; however, due to its substantial toxicity, which limits its use in clinical practice, the EGP only presented reanalysis estimates for the comparison between dabrafenib plus trametinib and observation.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were RFS, OS, and utilities. OS data from the COMBI-AD trial are considered immature; therefore, OS data were estimated indirectly and modelled from RFS curves from the trial.

The costs considered in the analysis included those related to BRAF testing, drug treatment and administration, disease management (monitoring and follow-up in the adjuvant and metastatic settings), subsequent treatments, treatment-related AEs, and end of life care.

Drug costs: Treatment cost of dabrafenib plus trametinib and comparators

Dabrafenib costs $66.34 per 75 mg capsule, and trametinib costs $304.17 per 2 mg tablet. At the recommended daily dose of 300 mg for dabrafenib and 2 mg for trametinib, the combination of dabrafenib plus trametinib costs $569.17 per day and $14,929 per 30-day treatment cycle adjusted for a relative dose intensity of 84% for dabrafenib and 90.5% for trametinib.

There were no costs associated with observation as a treatment strategy.

High-dose IFN induction costs $125.82 for 10 international units (IU) per vial. At the recommended daily dose of 20 IU/m^2, induction has a total cost of $10,970.25 per 28-day cycle based on 20 days of use, administration fees of $2,061 and a relative dose intensity of 91%. High-dose IFN maintenance costs $125.82 for 10 IU per vial. At the recommended daily dose of 10 IU/m^2, maintenance has a total cost of

$3,623.77 per 28-day cycle based on 12 days of use, drug administration fees of $1,237.00 and a relative dose intensity of 81.5%.

Clinical effect estimates: Uncertainty in the OS benefit of dabrafenib plus trametinib

The cost-effectiveness estimates of dabrafenib plus trametinib compared with placebo (observation) were derived from the COMBI-AD trial. At the primary analysis data cut-off date, OS data were considered immature due to a low event rate; therefore, RFS data were used to indirectly model OS. The RFS curves were extrapolated beyond the trial horizon of 51 months (maximum follow-up time in the trial) to the end of a 35-year time horizon. The EGP noted that the validation of the modelling of OS demonstrated that the log-logistic unrestricted cure model was not a good fit, where the trial data showed the OS curves were converging toward the end of the trial (based on a limited number of patients at risk) while the modelled curves were diverging. The EGP considered this the main limitation of the submitted evaluation as it makes the estimation of OS highly uncertain and at risk of overestimating the benefits of dabrafenib plus trametinib. The submitter's base-case ICUR was lower than the EGP's reanalysis ICUR. The difference was primarily due to reducing the incremental OS benefit of dabrafenib plus trametinib compared with placebo by modelling a more conservative estimate of the survival difference between the two treatment strategies, which had the most substantial impact on the ICUR; as well as reducing the time horizon to 25 years, as the 35-year horizon was considered too long given the uncertainty in the OS benefit and that it was deemed overly optimistic by the CGP.

Cost-effectiveness estimates: Dabrafenib plus trametinib may not be cost-effective

The EGP's ICUR estimate ($85,850 per QALY) was higher than the submitter's estimate ($33,068 per QALY). The EGP's best estimate ICUR was based on varying the HR (+25%) applied to the RFS curve (log-logistic unrestricted cure model) for the dabrafenib plus trametinib treatment group, reducing the time horizon to 25 years, varying the HR (±25%) applied to RFS curves to estimate the probability of progression after local recurrence, and including the costs for dispensing oral drugs.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Submitted budget impact is underestimated

PAG identified that the oral route of administration of dabrafenib and trametinib is an enabler to implementation; however, they noted that in some jurisdictions oral medications are not funded in the same mechanism as intravenous cancer medications, which may limit accessibility of treatment for patients and cause financial burden on patients and their families in the form of co-payments and deductibles. Patients also expressed concerns about affordability. PAG also identified that additional resources may be required to monitor and treat side effects (e.g., pyrexia) but noted that cancer clinics already have experience with dabrafenib and trametinib. PAG noted that additional clinic visits and bloodwork throughout the first year of treatment may be required to deliver adjuvant dabrafenib and trametinib therapy in comparison with IFN and observation treatment strategies.

Considering there are a number of other immunotherapies being studied in the adjuvant treatment setting, PAG requested guidance on the best adjuvant treatment for BRAF-mutated patients if adjuvant nivolumab or pembrolizumab become funded. There is no direct evidence from RCTs to inform the sequencing of dabrafenib plus trametinib relative to adjuvant immunotherapies in patients with BRAF-mutated melanoma who are candidates for surgery. The results of the submitter's NMA found that dabrafenib plus trametinib had significantly better RFS compared with ipilimumab, and was comparable in RFS to nivolumab, pembrolizumab and vemurafenib. However, the pCODR Methods Team concluded that the results from these indirect treatment comparisons should be interpreted with caution. There were concerns with the overall relevance and credibility of NMA primarily due to systematic differences in treatment effect modifiers across the different treatment comparisons in the network (e.g., inclusion of stage IV patients; and patients whose BRAF status was unknown).

The EGP considered the submitted BIA was underestimated since it only included the acquisition cost of drugs, while other costs associated with the management of melanoma were omitted (e.g., BRAF testing, drug administration, management of AEs, medical/hospital visits). The most influential factors in the BIA were the percentage of newly diagnosed patients with stage III melanoma, the annual incidence of melanoma, the proportion of stage III patients who were successfully resected, and the proportion of patients who tested BRAF-positive. The EGP also noted that the BIA results were sensitive to treatment duration, market share, and relative dose intensity.

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 Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
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. Winson Cheung, who was excluded from voting due to a conflict of interest
- Cameron Lane, who was excluded from voting due to a conflict of interest.

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

- Dr. Christine Kennedy, who was not present for the meeting
- Dr. Winson Cheung, who was excluded from voting due to a conflict of interest
- Cameron Lane, who was excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of the 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 (Tafinlar) plus trametinib (Mekinist) for the adjuvant treatment of BRAF-mutated stage III melanoma, through their declarations, two members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, both of these members were excluded from voting. For the Final Recommendation, two members had a real, potential, or perceived conflict, and based on application of the pCODR Conflict of Interest Guidelines, both of these members were 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*.

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

PAG Implementation Questions	pERC Recommendation
• PAG is seeking information on data comparing dabrafenib plus trametinib with IFN	• pERC agreed with the conclusion of the CGP that observation is the most appropriate comparator in this treatment setting considering that in Canadian practice most patients decline treatment with IFN and instead choose observation. The CGP noted the main reason for non-utilization is the toxicity associated with IFN and the resulting negative impact on patient preference. Further, they point out that clinical trials that previously demonstrated a benefit to treatment with IFN following surgery were primarily conducted in the era predating both targeted and immune checkpoint inhibitor therapy, which calls into question the relevance of the data in the current treatment era.
• PAG is seeking guidance on whether adjuvant dabrafenib plus trametinib would be limited to the following patients: – Patients with an ECOG performance status of 0 to 1 – Patients with cutaneous melanoma (e.g., not mucosal, ocular or acral melanoma) • PAG is seeking guidance on whether adjuvant dabrafenib plus trametinib would be offered to the following patients: – Patients with completely resected stage IV disease as well as resected stage IIB/C disease with T4 lesions (high-risk node negative) who are fit and motivated for treatment – Patients who would have been eligible at the time of diagnosis, but are currently being treated with IFN or on observation. If it is recommended that these patients transition to dabrafenib plus trametinib, PAG is seeking guidance on what the appropriate treatment duration would be (e.g., one year of dabrafenib plus trametinib or combined one year of IFN plus dabrafenib-trametinib)	• pERC noted that the COMBI-AD trial only enrolled patients with an ECOG performance status of 0 to 1 and agreed that adjuvant treatment with dabrafenib plus trametinib should be offered to patients with a good performance status. • pERC agreed with the CGP that the data from the COMBI-AD trial could not reliably be generalized to patients with non-cutaneous melanoma because the trial specifically excluded patients with non-cutaneous melanoma. The CGP noted that BRAF mutations are uncommon in non-cutaneous melanoma. • pERC agreed with the CGP's judgment that the decision to use adjuvant dabrafenib plus trametinib after resection in patients with stage IIB/C disease and T4 lesions should await the results of ongoing clinical trials. pERC acknowledged that this group of patients may have a worse prognosis than some stage III patients; however, patients with stage IIB/C disease and T4 lesions were excluded from the COMBI-AD trial. The trial also did not enrol patients with resected stage IV disease, and as such, pERC was in agreement with the CGP that adjuvant dabrafenib plus trametinib after surgery should not be used in these patients in the absence of clinical trial data. • pERC agreed that there may be rare circumstances when clinicians may wish to transition a patient from receiving adjuvant IFN to treatment with dabrafenib plus trametinib as adjuvant treatment to surgery. Patients previously treated with IFN were not enrolled in the COMBI-AD trial. While no supporting clinical data exists to inform this situation, pERC agreed with the CGP that in practice the decision may be reasonable. For patients currently receiving adjuvant IFN who wish to transition to adjuvant dabrafenib and trametinib, the CGP advised that clinicians may want to consider the COMBI-AD eligibility criteria as guidance when contemplating a change in adjuvant systemic therapy. The CGP also indicated factors such as duration of IFN therapy and tolerance to IFN therapy, as well as patient factors such as time from diagnosis, age, and performance status are also relevant when considering a change in adjuvant systemic therapy.

• PAG is seeking guidance on the optimal sequencing of adjuvant dabrafenib-trametinib with available metastatic treatment including BRAF/MEK inhibitors (either alone or in combination) and immunotherapies (e.g., ipilimumab, nivolumab and pembrolizumab)? • PAG wanted to know the appropriate time frame (i.e., relapse-free period) from completion of adjuvant dabrafenib plus trametinib and initiation of metastatic treatment?	• pERC noted there are no clinical data available to guide treatment decision-making in this situation, and therefore the optimal time frame or relapse-free period from completion of adjuvant dabrafenib-trametinib and initiation of specific metastatic treatments is unknown. The post-protocol treatments administered in the COMBI-AD trial show that patients treated with dabrafenib plus trametinib as adjuvant treatment to surgery received BRAF-targeted agents (in the case of patients with BRAF-mutated melanoma), anti-CTLA-4 immune checkpoint inhibitor therapy, anti-PD-1 immune checkpoint inhibitor therapy, chemotherapy or experimental agents upon relapse. The CGP noted clinicians will likely wish to consider all of these options for the relapsed patient following treatment with adjuvant dabrafenib plus trametinib, taking into account factors such as time-to-relapse and patient performance status.
• PAG wanted to know what would be the best adjuvant treatment for BRAF mutation positive patients if adjuvant nivolumab (or pembrolizumab) becomes funded? • For patients who receive nivolumab/immunotherapy for adjuvant melanoma and cannot tolerate it, PAG wanted to know whether dabrafenib plus trametinib would be considered for these patients?	• pERC agreed with the CGP that patients without actionable BRAF mutations should not be considered for treatment with BRAF-directed therapy but that patients with BRAF-mutated melanoma may benefit from immune checkpoint inhibitor therapy. At the present time, there are no data to guide clinicians in choosing between BRAF-targeted or adjuvant immunotherapy for the patient with resected BRAF-mutated melanoma. pERC noted that in the absence of a direct evidence treatment choice, treatment will likely be influenced by toxicity profiles, patient preference for treatment administrations (oral versus intravenous), schedules (frequency), and what is provincially funded. • pERC agreed with the CGP that patients who are unable to tolerate one class of adjuvant treatment should be allowed the option to resume treatment with an alternate agent in the absence of disease progression, and that the total duration of adjuvant therapy should not exceed one year. pERC noted, however, that the choice to switch to a novel adjuvant therapy after intolerance should be made after careful deliberation by the physician and patient that takes into account the duration of the first selected adjuvant therapy. • pERC noted that the CGP anticipates the situation will arise where patients with BRAF-mutated melanoma will relapse following treatment with immunotherapy, used as adjuvant to surgery who are then surgically rendered free of disease. There are currently no data to inform treatment decision-making in this scenario, but it is known that BRAF-targeted therapy in the second-line following progression of disease after treatment with PD-1-directed immunotherapy is efficacious. For this reason, pERC agreed with the CGP that the use of dabrafenib plus trametinib as adjuvant treatment to surgery could be considered in patients where previous adjuvant therapy with immunotherapy failed.

CGP = Clinical Guidance Panel; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.