CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Dabrafenib-Trametinib for Melanoma Adjuvant Therapy

May 3, 2019

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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List of Abbreviations

AE(s)	Adverse event(s)
AJCC	American Joint Committee on Cancer
CI	Confidence Interval
CrI	Credible interval
CT	Computed tomography
DFS	Disease-free survival
DMFS	Distant metastasis-free survival
ECOG	Eastern Cooperative Oncology Group
EQ-5D-3L	EuroQol-5D-3L
FFR	Freedom from relapse
HR	Hazard ratio
HRQOL	Health-related quality of life
IFN	Interferon
IPSOR	International Society of Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IVRS	Interactive voice response system
KM	Kaplan-Meier
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PE	Pharmacoeconomic
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT(s)	Randomized controlled trial(s)
RFS	Relapse-free survival
SAE(s)	Serious adverse event(s)
STE	Surrogate threshold effect
VAS	Visual analogue scale

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding dabrafenib and trametinib in combination for the adjuvant treatment of BRAF-mutated melanoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding adjuvant dabrafenib-trametinib for BRAF-mutated melanoma conducted by the Melanoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on adjuvant dabrafenib-trametinib for BRAF-mutated melanoma, a summary of submitted Provincial Advisory Group Input on adjuvant dabrafenib-trametinib for BRAF-mutated melanoma, and a summary of submitted Registered Clinician Input on adjuvant dabrafenib-trametinib for BRAF-mutated melanoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) as adjuvant treatment for patients with BRAF-mutated melanoma with regional lymph node involvement who have undergone resection.

On September 21, 2018, a Notice of Compliance (NOC) was issued by Health Canada for the following indication: 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. The requested reimbursement criteria are the same as the approved Health Canada indication.

According to the Product Monograph, dabrafenib is a small molecule inhibitor of RAF kinases, including BRAF; and trametinib is a small molecule inhibitor of mitogen-activated extracellular signal-regulated kinase 1 and 2 (MEK1 and MEK2). MEK1 and MEK2 are components of the MAPK pathway (including RAS/RAF/MEK/ERK). Dabrafenib and trametinib provide concomitant inhibition of the pathway at the level of the RAF and MEK kinases, respectively. The combination of dabrafenib with trametinib is synergistic in BRAF V600 mutation-positive melanoma cell lines and delayed the emergence of resistance in BRAF V600 mutation-positive melanoma xenografts.

The recommended dose of dabrafenib is 150 mg given orally twice daily (two 75 mg capsules corresponding to a total daily dose of 300 mg) with 2 mg of trametinib given orally once daily. The planned duration of treatment should be 12 months, unless disease recurrence or unacceptable toxicity occurs.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

COMBI-AD[1] is a randomized, double-blind, placebo-controlled, multicentre phase III international trial, globally distributed across 26 countries, that evaluates whether the

combination of dabrafenib and trametinib improves relapse-free survival (RFS), overall survival (OS), distant metastasis–free survival (DMFS), and freedom from relapse (FFR) in patients with stage III melanoma with BRAF V600E or V600K mutations after complete surgical resection. The trial design was developed jointly by GlaxoSmithKline and the academic authors and was funded by GlaxoSmithKline and Novartis.

Eligible patients were randomized in a 1:1 ratio to receive oral dabrafenib plus trametinib (combination therapy, n=438) or two matched placebo tablets (n=432). As the trial was conducted prior to the release of the American Joint Committee on Cancer (AJCC) 8th edition staging system, patient classification and stratification were based on the AJCC 7th edition system, which included only three prognostic stage III groupings (IIIA to IIIC) in comparison to the four groupings (IIIA to IIID) that are included in the 8th edition. Patients were also stratified according to their 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. For more details on the eligibility criteria used in the trial refer to Table 4 in Section 6 of this report.

There were a total of 870 patients, ≥18 years of age, 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 randomized into the study. More patients in the dabrafenib and trametinib group had either stage IIIA or IIIC disease, while more patients in the placebo group had stage IIIB disease. All the patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease and most patients had an ECOG performance status of 0. BRAF V600 mutation status was confirmed in the primary tumour or lymph node tissue by a central reference laboratory.

Overall, there were no major concerns with the conduct of COMBI-AD trial. However, some limitations and potential sources of bias of the COMBI-AD trial were noted by the pCODR Methods Team. Among these, was some imbalance between the two groups with respect to the types of therapy that were administered after recurrence, which could have an effect on OS outcomes. Additionally, differences in adverse events (AEs) leading to dose interruptions, reductions and discontinuations observed between treatment groups had the potential to unmask patients in the dabrafenib plus trametinib group. The extent to which spontaneous unblinding of patients and investigators occurred is unknown, but the possible influence of this on patient-reported outcomes should be considered. Finally, the sponsors GlaxoSmithKline and Novartis funded the trial and were involved in all aspects of its conduct, including design of the study, data collection, performing data analysis, and interpreting results. The extent to which the Sponsor's involvement may have influenced the results and reporting of the trial is unknown.

PRIMARY OUTCOME
Relapse-free Survival (RFS)

As of the primary analysis data cut-off date of June 30th, 2017, disease recurrence had been reported in 37% (163/438) of patients in the dabrafenib plus trametinib group and in 57% (247/432) of patients in the placebo group. The combination of dabrafenib and trametinib demonstrated superiority over placebo for the primary outcome of investigator-assessed RFS with an estimated hazard ratio (HR) of 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). 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, 12.7to 22.1) in the placebo group

(Table 1). Three- and four-year RFS rates were 59% (95% CI, 55% to 64%) and 54% (95% CI, 49% to 59%) in the dabrafenib plus trametinib group, and 40% (95% CI, 35% to 45%) and 38% (95% CI, 34% to 44%) in the placebo group, respectively. An updated analysis of RFS at the April 30, 2018 data cut-off date resulted in a median patient follow-up of 44 months in the dabrafenib plus trametinib group and 42 months in the placebo group. The estimated HR was 0.49 (95% CI, 0.40 to 0.59), which was consistent with the primary analysis.

Secondary Outcomes

Overall Survival (OS)

As of the first data cut-off date of June 30th, 2017, 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 was melanoma (in 54 patients [12%] and 77 patients [18%], respectively). The estimated rate of OS was 97% at one year, 91% at two years, and 86% at three years in the dabrafenib plus trametinib group, as compared with rates of 94%, 83%, and 77%, respectively, in the placebo group. 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. Median OS was not reached in either group; however, the OS data are still immature due to the low number of events observed. The second interim OS analysis is planned when approximately 299 deaths have occurred (i.e., 50% of the targeted 597 events required for the final OS analysis).[1,2]

Distant metastases-free survival (DMFS)

Based on the primary analysis data cut-off of June 30th, 2017, the estimated HR for DMFS was 0.51 (95% CI, 0.40 to 0.65), indicating a 49% reduction in the risk of developing distant metastases or death when patients were treated with dabrafenib plus trametinib. The updated analysis of DMFS from the 30th April 30th, 2018 data cut-off yielded an HR of 0.53 (95% CI, 0.42 to 0.67). The Kaplan-Meier estimated DMFS rates at four years were 67% (95% CI, 62 to 72%) in the dabrafenib plus trametinib group and 56% (95% CI, 51 to 62%) in the placebo group.

Freedom from Relapse (FFR)

In the FFR analysis, at the first data cut-off of June 30th, 2017, local or distant recurrence or a new primary melanoma were counted as events, and patients who died of causes other than melanoma or treatment-related toxicity were censored. Among the 412 disease or treatment-related relapses or deaths, 165 (38%) events (163 relapse, two deaths) occurred in the dabrafenib plus trametinib group, and 247 (57%) events (247 relapse, 0 deaths) occurred in the placebo group. The estimated HR for FFR was 0.47 (95% CI, 0.39 to 0.57).

Harms Outcomes

A total of 435 patients in the dabrafenib plus trametinib group and 432 patients in the placebo group were included in the safety analysis at the first data cut-off of June 30th, 2017. A total of 97% and 88% of patients reported at least one AE in the combination therapy and placebo groups, respectively. While the majority of AEs were of grade 1 or 2 in severity, grade 3 or 4 AEs occurred in 41% of patients in the dabrafenib plus trametinib group and 14% in the placebo group. The top three most common AEs that occurred in

patients in the dabrafenib plus trametinib 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%). Serious adverse events (SAEs) occurred in 155 patients (36%) in the dabrafenib plus trametinib group in addition to one fatality due to pneumonia. There were 44 patients (10%) in the placebo group reporting SAEs.

Exploratory Outcome

HRQOL - EuroQol EQ-5D-3L[3]

Health-related quality life (HRQOL) was assessed by the EQ-5D-3L (utility score and visual analogue scale [VAS]) every three months as an exploratory outcome in the COMBI-AD trial. A change from baseline of 0.08 points in the utility score or 7 points in the VAS, were considered minimally important differences. Analysis of the intent-to-treat (ITT) population from the first data cut-off of June 30th, 2018 showed that, during the treatment phase (0-12 months), there were no meaningful changes in the adjusted EQ-5D-3L utility scores or EQ-5D adjusted mean VAS scores between treatment groups, and changes from baseline were minimal for all assessments throughout the study period. An assessment of change from baseline in adjusted mean VAS scores for patients who did or did not experience AEs in the dabrafenib and trametinib treatment group was undertaken. There were no AEs associated with a clinically meaningful decrease in HRQOL during treatment and during the follow-up phase. VAS scores improved over time for patients who experienced each of the most common AEs such as pyrexia, nausea, headache, diarrhea, arthalgia and rash; further, 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 (> 12 months), with adjusted mean VAS scores in both treatment groups showing an upward trend, with no clinically meaningful differences between groups.

Table 1: Highlights of Key Outcomes in the COMBI-AD trial.

Key Efficacy Outcomes	Dabrafenib +Trametinib (n=438)	Placebo (n=432)
Primary Outcome		
RFS (Data cut-off April 30, 2018)		
Number of events (%)	174 (40%)	253 (59%)
Local/regional relapse only	56 (13)	110 (25)
Distant relapse only	102 (23)	130 (30)
Concurrent local & distant relapse	9 (2)	6 (1)
Secondary primary melanoma	9 (2)	8 (2)
Died (event)	3 (<1)	1 (<1)
Median RFS (months)	NE (46.9-NE)	16.6 (12.7-22.1)
HR (95% CI)	0.49 (0.40-0.59)	
p-value (2-sided)	p=NR	
Kaplan-Meier estimate (95% CI)		
1-year RFS rate	0.88 (0.85-0.91)	0.56 (0.51-0.61)
2-year RFS rate	0.67 (0.62-0.72)	0.44 (0.40-0.49)
3-year RFS rate	0.59 (0.55-0.64)	0.40 (0.35-0.45)
4-year RFS rate	0.54 (0.49-0.59)	0.38 (0.34-0.44)
Key Secondary Outcomes		
OS (Data cut-off June 30, 2017)		

Key Efficacy Outcomes	Dabrafenib +Trametinib (n=438)	Placebo (n=432)
Number of events (%)	60 (14%)	93 (22%)
Median OS (months)	NE (NE-NE)	NE (NE-NE)
HR (95% CI)	0.57 (0.42-0.79)	
p-value (2-sided)	$p=6 \times 10^{-4}$	
DMFS (Data cut-off April 30, 2018)		
Number of events (%)	110 (25%)	152 (35%)
Median DMFS (months)	NE (NE-NE)	NE (41.2-NE)
HR (95% CI)	0.53 (0.42-0.67)	
p-value (2-sided)	P=NR	
FFR (Data cut-off June 30, 2017)		
Number of events (%)	165 (38%)	247 (57%)
Median time (months)	NE (44.5-NE)	16.6 (12.7-22.3)
HR (95% CI)	0.47 (0.39-0.57)	
p-value (2-sided)	p<0.001	
Abbreviations: RFS = relapse free survival; OS = overall survival; DMFS=distant metastasis-free survival; FFR = freedom from relapse; HR = hazard ratio; CI = confidence interval; NE – not estimable; NR = not reported.		

Sources: Hauschild 2018,[4] Long 2017,[1] EMA report.[2]

1.2.2 Additional Evidence

Patient Advocacy Group Input

Two patient advocacy groups, Melanoma Network of Canada (MNC) and the Save Your Skin Foundation (SYSF), provided input on dabrafenib and trametinib (Tafinlar and Mekinist) in combination as adjuvant therapy for patients with BRAF-mutated melanoma with lymph node involvement who have undergone resection. For a summary of this input, refer to Section 3.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified clinical and economic factors that could impact the implementation of dabrafenib plus trametinib as adjuvant treatment for BRAF-mutated melanoma. For a summary of this input, refer to Section 4.

Registered Clinician Input

Two registered clinician submissions were received by pCODR that provided input on dabrafenib-trametinib as adjuvant treatment for BRAF-mutated melanoma; one joint submission from Cancer Care Ontario providing the perspective of four oncologists, and one individual input from an oncologist working at the Ottawa Hospital Cancer Centre, for a total of five clinicians providing input. For a summary of this input, please refer to Section 5.

Summary of Supplemental Questions

The following supplemental question was identified during the development of the review protocol as relevant to the pCODR review of dabrafenib plus trametinib:

- Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA)[5] comparing dabrafenib in combination with trametinib to relevant comparators in patients with high-risk (IIB-C and IIIA-C) melanoma with BRAF mutation positive status.

In the absence of randomized controlled trials (RCTs) directly comparing the combination of dabrafenib and trametinib to other relevant treatment comparators, a NMA was provided by the Manufacturer that indirectly compared the combination to other pharmacological interventions for patients with high-risk radically resected, BRAF mutation positive melanoma. The pCODR Methods Team focused their review and critical appraisal to the NMA conducted in the subgroup of BRAF-positive patients (target population), which was carried out using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[6]

Results of the NMA found that dabrafenib plus trametinib had significantly better RFS compared to observation or placebo and ipilimumab, and was comparable in RFS to nivolumab, pembrolizumab and vemurafenib. High-dose interferon (IFN) was not included as a comparator in the subgroup analysis because it could not be connected in the network of trials. The quality assessment performed identified concerns with the overall relevance and credibility of the NMA. The main limitations include 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) and the use of a fixed-effects analysis which, although appropriate given the small number of trials included in the network, produces treatment effect estimates that do not take this heterogeneity into account. Additional limitations include potential bias introduced through differences in RFS/ DFS definitions and patient follow-up time across the trials in the network, and the fact other important outcomes including OS, HRQOL and safety were not/could not be assessed. Considering these limitations, the conclusions drawn from the NMA should be interpreted with caution. For the complete review and critical appraisal of the NMA, refer to section 7.1.

Comparison with Other Literature

The pCODR CGP and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence; an assessment of the limitations and sources of bias associated with the COMBI-AD trial can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of factors that may affect the generalizability of evidence from the COMBI-AD trial.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(COMBI-AD trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="2">Population</td><td>Histologic type of disease</td><td>The COMBI-AD trial limited its inclusion criteria to patients with cutaneous melanoma.</td><td>Are the trial results generalizable to other types of melanoma (i.e., mucosal, ocular)?</td><td>The CGP felt the data from the COMBI-AD trial could not reliably be generalizable to patients with non-cutaneous melanoma, particularly because the study specifically excluded patients with non-cutaneous melanoma. The issue is not of significant impact, as BRAF mutations are uncommon in non-cutaneous melanoma.</td></tr>
<tr><td>Performance status</td><td>COMBI-AD trial limited eligibility by performance status, specifying patients were required to have an ECOG status of 0 or 1.
<table>
<tr><th>Characteristic</th><th>Dabrafenib + Trametinib (n=438)</th><th>Placebo (n=432)</th></tr>
<tr><td colspan="3">ECOG Performance Status – no. (%)</td></tr>
<tr><td>0</td><td>405 (92)</td><td>390 (90)</td></tr>
<tr><td>1</td><td>33 (8)</td><td>41 (9)</td></tr>
<tr><td>Unknown</td><td>3 (1)</td><td>1 (<1)</td></tr>
</table></td><td>Do the results apply to patients with ECOG PS >1?</td><td>The CGP felt the results of the COMBI-AD trial could be extrapolated to those with greater disability, for example patients with a performance status of ECOG 2. This position was taken based on clinical experience in the treatment of patients with metastatic melanoma, where safety and efficacy has been shown in patients with relatively poor performance status. The decision for treatment with dabrafenib/trametinib following complete resection of stage III melanoma should rely upon clinical judgment, taking in to account all patient factors (including performance status and patient co-morbidities) in the consideration of treatment benefit versus risk.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(COMBI-AD trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>BRAF V600 mutations</td><td>Inclusion criteria specified patients had to have a BRAF V600E or V600K mutation determined by a central laboratory.

<table><tr><th>Characteristic</th><th>Dabrafenib + Trametinib (n=438)</th><th>Placebo (n=432)</th></tr><tr><td colspan="3">BRAF mutation status – no. (%)</td></tr><tr><td>V600E</td><td>397 (91)</td><td>395 (91)</td></tr><tr><td>V600K</td><td>41 (9)</td><td>37 (9)</td></tr></table></td><td>Are the trial results generalizable to other types of BRAF V600 mutations (i.e., V600R, V600E2 or V600D)?</td><td>Substitution of glutamic acid (E) or lysine (K) for valine (V) at the 600 codon are the two most common oncogenic BRAF V600 mutations, and the COMBI-AD clinical trial restricted enrolment to these two subgroups of patients. However, patients with non-V600E/K BRAF mutations may respond to dabrafenib-trametinib treatment, as shown in the metastatic treatment setting. The CGP felt it would be reasonable to consider extrapolating the results from the COMBI-AD trial to patients with non-V600E/K BRAF mutations.</td></tr>
<tr><td></td><td>Stage</td><td>COMBI-AD included only patients with completely resected stage IIIA (limited to lymph node metastasis of >1mm), IIIB, and IIIC.<table><tr><th>Characteristic</th><th>Dabrafenib + Trametinib (n=438)</th><th>Placebo (n=432)</th></tr><tr><td colspan="3">Disease Stage – no. (%)</td></tr><tr><td>IIIA</td><td>83 (19)</td><td>71 (16)</td></tr><tr><td>IIIB</td><td>169 (39)</td><td>187 (43)</td></tr><tr><td>IIIC</td><td>181 (41)</td><td>166 (38)</td></tr><tr><td>III unspecified</td><td>5 (1)</td><td>8 (2)</td></tr></table></td><td>Are the trial results also generalizable to patients with completely resected stage IIB/C with T4 lesions (high-risk node negative) and completely resected stage IV disease, since these patients are also offered adjuvant treatment?</td><td>The AJCC (8th ed.) staging classification indicates patients with high-risk stage II lesions may have a prognosis equal to or worse than those with stage III melanoma. In recognition of this fact, clinical trials are currently underway to evaluate adjuvant systemic therapy for the treatment of patients with high-risk, stage II disease. However, at this time the CGP felt the available evidence to support the use of dabrafenib-trametinib could not be extended to those with resected stage II melanoma lesions, as these patients were not included in the COMBI-AD clinical trial.

Patients with resected stage IV disease represent a distinct classification of patients, and were ineligible for enrolment to the COMBI-AD clinical trial. In the absence of clinical data, the CGP was unable to comment on the treatment of these patients with dabrafenib/trametinib as adjuvant therapy following surgery.</td></tr>
<tr><td></td><td>Staging system</td><td>COMBI-AD was initiated before the release of the AJCC 8th edition and, as such, stage grouping</td><td>Are the trial results generalizable to</td><td>The patient population under study in the COMBI-AD clinical trial encompassed</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(COMBI-AD trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>was based on AJCC 7th edition. The difference between the 7th and 8th editions reflects an updated analysis that “weighted” patient factors with respect to prognosis, as well as the addition of a new stage IIID category.</td><td>AJCC 8th edition stage IIIA-D patients?</td><td>patients with stage IIIA-C, although patients with stage IIIA disease required a minimum focus of 1 mm of nodal disease. The transition from the 7th to the 8th edition should not be very impactful, as the 8th edition captures the clinical trial population within stages IIIA through IIID, and therefore there should be little confusion between classification systems with respect to stage of disease and eligibility for treatment.</td></tr>
<tr><td></td><td>In-transit metastases</td><td>In the trial 12% and 8% of patients in the dabrafenib-trametinib and placebo groups, respectively, had in-transit metastases.
<table><tr><th>Characteristic</th><th>Dabrafenib + Trametinib (n=438)</th><th>Placebo (n=432)</th></tr><tr><td colspan="3">In-transit metastases – no. (%)</td></tr><tr><td>Yes</td><td>51 (12)</td><td>36 (8)</td></tr><tr><td>No</td><td>387 (88)</td><td>395 (91)</td></tr><tr><td>Unknown</td><td>0</td><td>1 (<1)</td></tr></table></td><td>Are the trial results also generalizable to patients with unresected in-transit metastases?</td><td>The CGP felt the results of the COMBI-AD trial are generalizable to patients with resected in-transit metastases, however patients with unresectable/unresected in-transit metastatic disease should be considered metastatic, and therefore should not be considered for adjuvant systemic therapy.</td></tr>
<tr><td></td><td>Age</td><td>The trial limited eligibility to patients ≥18 years of age.</td><td>Are the trial results generalizable to pediatric patients with BRAF V600 mutation positive melanoma?</td><td>Pediatric melanoma is fortunately rare. For the pediatric patient with resected, BRAF v600 mutation positive melanoma the CGP felt the results of the COMBI-AD trial were generalizable.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(COMBI-AD trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Organ dysfunction</td><td>The trial limited eligibility to patients with adequate organ function.</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results and affect generalizability to patients with any existing organ dysfunction?</td><td>The CGP did not feel the clinical trial exclusion criteria significantly limited the interpretation of the clinical trial results. The exclusion criteria pertaining to organ dysfunction were primarily included for patient safety reasons, and clinicians should take in to account clinically significant organ dysfunction when considering therapy with dabrafenib/trametinib as adjuvant treatment to surgery.</td></tr>
<tr><td></td><td>Lymphadenectomy</td><td>All trial patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual disease within 12 weeks before randomization.
<table><tr><th>Characteristic</th><th>Dabrafenib + Trametinib (n=438)</th><th>Placebo (n=432)</th></tr><tr><td colspan="3">Type of lymph node involvement – no. (%)</td></tr><tr><td>Microscopic</td><td>152 (35)</td><td>157 (36)</td></tr><tr><td>Macroscopic</td><td>158 (36)</td><td>161 (37)</td></tr><tr><td>Unknown</td><td>128 (29)</td><td>114 (26)</td></tr></table></td><td>Are the trial results generalizable to patients who have not undergone completion lymph-adenectomy?</td><td>The CGP felt completion lymph node dissection for patients with micrometastatic lymph node involvement detected on sentinel lymph node biopsy should not be a requirement for consideration of treatment with dabrafenib-trametinib as adjuvant therapy to surgery.

This is based on recent clinical trials which have established observation within this patient population as a viable treatment strategy, as melanoma-specific survival was not improved with reflexive completion lymph node dissection. Notably, more recent clinical trials investigating systemic therapy as adjuvant to surgical treatment have not mandated reflexive completion lymph node dissection in the case of patients with micrometastatic disease detected on sentinel lymph node biopsy.</td></tr>
<tr><td></td><td>Prior adjuvant therapy</td><td>The trial restricted inclusion to patients who had not undergone previous radiotherapy.</td><td>Are the trial results generalizable to patients who had prior adjuvant radiotherapy?</td><td>The CGP felt the results of the COMBI-AD trial could be generalized to patients treated with radiation therapy as adjuvant to surgery.</td></tr>
<tr><td></td><td></td><td>The trial restricted inclusion to patients who had not undergone previous systemic anticancer treatment.</td><td>Are the trial results generalizable to</td><td>Patients previously treated with IFN as adjuvant to surgery were not permitted enrolment to the COMBI-AD clinical trial.</td></tr>
</table>

Domain	Factor	Evidence (COMBI-AD trial)[1]	Generalizability Question	CGP Assessment of Generalizability
			patients who have prior IFN therapy?	However, under rare circumstances clinicians may wish to transition a patient from receiving adjuvant IFN to treatment with dabrafenib-trametinib as adjuvant to surgery; in addition, clinicians may wish to offer a relapsed patient dabrafenib-trametinib as adjuvant to surgery despite the fact treatment with IFN as adjuvant to surgery may previously have been used. While no supporting clinical data exists, in practice the decision may be reasonable. For patients currently receiving adjuvant IFN who wish to transition to adjuvant dabrafenib/trametinib, factors such as duration of IFN therapy and tolerance to IFN therapy will be relevant.
Comparator	Standard of care	COMBI-AD compared the combination of dabrafenib and trametinib to placebo.	Are the results of the trial applicable given other adjuvant treatment regimens (i.e., IFN) are available in the Canadian setting?	Despite meta-analyses which support a modest improvement in patient survival with the use of IFN as adjuvant treatment to surgery,[7] the regimen is uncommonly prescribed in practice. Chief among the reasons for non-utilization is the toxicity associated with the regimen and the resulting negative impact on patient preference. Further, the clinical trials which previously demonstrated the benefit to treatment with IFN following surgery were primarily conducted in the era predating both targeted and immune checkpoint inhibitor therapy, calling in to question the relevance of the data in the current treatment era. Therefore, the CGP felt placebo was the most appropriate comparator considering that in Canadian practice most patients decline treatment with IFN, instead choosing watchful waiting/observation.

Domain	Factor	Evidence (COMBI-AD trial)[1]	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Assessment of key Outcomes	Disease assessments included clinical examination and imaging by means of CT, MRI or both.	Are the key outcomes assessed differently in the trial compared with clinical practice in Canada?	The CGP felt the assessment of key outcomes within the COMBI-AD clinical trial was appropriate, and felt the study design was comparable to current Canadian clinical practice.
Abbreviations: AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; RFS = relapse-free survival; DMFS = distant metastasis-free survival; OS = overall survival.				

1.2.4 Interpretation

Melanoma is the most commonly diagnosed cancer in individuals between the ages of 20 and 29 years, impacting otherwise healthy individuals with active family, career and social lives, thus adding to the stress of a diagnosis with cancer. Despite recent advancements in treatment, a diagnosis with malignant melanoma still portends a guarded prognosis, prompting the evaluation of effective palliative therapies within the adjuvant treatment setting. For the approximately 40% of melanoma patients with metastatic BRAF V600-mutated disease, therapy directed against this target represents highly efficacious treatment. As was the case for patients with metastatic disease, utilizing BRAF-directed targeted therapy as adjuvant treatment to surgery has improved patient outcomes.

In the COMBI-AD trial,[1] patients were randomized to receive the combination of dabrafenib with trametinib versus treatment with matched placebos, with RFS as the primary endpoint and OS and safety included as secondary endpoints. To be eligible for this international, multi-centre clinical trial, adult patients (≥18 years of age) must have undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (according to the criteria of the AJCC 7th edition)[8] with BRAF V600E or V600K mutations. None of the patients had undergone previous systemic anticancer treatment or radiotherapy for melanoma. All the patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an ECOG performance status of 0 or 1. As reported in 2017, with a median follow-up of 2.8 years, the estimated three-year rate of RFS was 58% in the combination-therapy group and 39% in the placebo group (HR=0.47; 95% CI, 0.39 to 0.58; p<0.001). The three-year OS rate was 86% in the combination-therapy group and 77% in the placebo group (HR=0.57; 95% CI, 0.42 to 0.79; p=0.0006). With an additional 10 months of follow-up, three- and four-year RFS rates were 59% (95% CI, 55% to 64%) and 54% (95% CI, 49% to 59%) in the dabrafenib plus trametinib group and 40% (95% CI, 35% to 45%) and 38% (95% CI, 34% to 44%) in the placebo group, respectively (HR=0.49; 95% CI, 0.40 to 0.59).[4] DMFS also favoured dabrafenib plus trametinib (HR=0.53; 95% CI, 0.42 to 0.67). While the OS data were not statistically significant according to a pre-specified interim analysis threshold, a strong trend towards improvement with treatment with dabrafenib plus trametinib was demonstrated. A benefit with respect to relapse or death across all subgroups studied was seen with the exception of the 10% of patients included with V600K BRAF mutations, although a strong trend favouring the active treatment group was observed even in this small subset of patients. Importantly, the HR for RFS was 0.50 or less in each of stage IIIA, IIIB and IIIC disease. In addition to demonstrating improvement in RFS, the tolerability of treatment in this patient population was similar to that seen in the metastatic setting, with 41% of patients experiencing a grade 3 or 4 toxicity (versus 14% of placebo-treated patients), and 26% of patients experiencing an AE leading to treatment discontinuation. The most commonly reported toxicities stemmed from the so-called pyrexic syndrome, which included fever, chills, headache, fatigue and nausea.

Historically, in the Canadian landscape only IFN has been available to patients following curative-intent surgery for melanoma. 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 at high-risk for systemic recurrence. A NMA[5] that indirectly compared dabrafenib plus trametinib was provided with this submission that indirectly suggests probable superiority of dabrafenib-trametinib versus IFN as adjuvant to surgery; while the analysis has several limitations (notably the fact that patients independent of BRAF status, and with stage II disease were included in the analysis), it nonetheless supports the use of dabrafenib and

trametinib in favour of IFN. The CGP felt the results of this NMA, while helpful, were not essential to the evaluation of dabrafenib-trametinib as adjuvant to surgery, as observation (and not IFN) is currently the most relevant comparator in Canada. Further, while not compared directly against IFN as adjuvant treatment to surgery, the CGP felt the toxicities associated with the use of dabrafenib and trametinib in the COMBI-AD trial indicate dabrafenib-trametinib to be the safer, better tolerated treatment option between the two. This statement is derived from clinical experience, and was agreed upon by all members of the CGP. The most prevalent toxicities reported in conjunction with the use of dabrafenib-trametinib included drug-related fever, fatigue, nausea, headache and chills; a constellation of AEs that often occur in parallel in clinical practice and commonly recognized as the pyrexic syndrome. However, these toxicities were rarely serious and algorithms for their management have been developed which, when followed properly, generally lead to resolution of the toxicity and resumption of treatment.[9] Furthermore, approximately one-quarter of dabrafenib-trametinib treated patients experienced an AE which led to drug discontinuation, and the median duration of exposure to dabrafenib-trametinib was similar to that of placebo (11.0 versus 10.0 months, respectively). In clinical practice, completion of a full year of IFN as adjuvant treatment following surgical resection of disease is uncommon. The CGP considered the demonstrated safety/tolerability profile of dabrafenib-trametinib against their historical experience with IFN, and concluded that the adoption of dabrafenib-trametinib as adjuvant treatment following surgery likely represents an improvement over IFN in this regard.

Following the issuing of the pERC initial recommendation for dabrafenib in combination with trametinib as adjuvant therapy to surgery for patients with resected malignant melanoma and lymph node involvement, feedback was received from registered clinicians and the PAG. The feedback centred on intolerance to first selected adjuvant therapy and disease staging. The registered clinicians commented that BRAF-mutated patients should be offered the opportunity to switch adjuvant therapy (targeted therapy to immunotherapy and vice versa) if they experience intolerance. The PAG also raised the issue of intolerance, specifically inquiring whether BRAF-mutated patients 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 (e.g., a combined one year of adjuvant therapy). In terms of staging, the registered clinicians disagreed that eligibility for adjuvant dabrafenib-trametinib in stage IIIA disease should be restricted to patients with lymph node metastases measuring >1 mm. They noted that excluding patients with lymph node metastases measuring <1 mm will make it complex to provide clinical care in certain situations (e.g., a single foci metastasis <1 mm versus multi focal metastases <1 mm). The PAG noted that jurisdictions may experience implementation issues related to staging, with dabrafenib-trametinib recommended for completely resected stage IIIA-D BRAF-mutated melanoma and nivolumab recommended for completely resected stage IIIB/C/D and stage IV melanoma (all according to the AJCC 8th edition staging system). The CGP's responses to the stakeholder feedback follow the CGP's Conclusions summarized below.

1.3 Conclusions

The CGP concluded that there is a net clinical benefit to dabrafenib plus trametinib in the adjuvant treatment of patients with completely resected Stage IIIA to IIID melanoma (AJCC 8th edition) based on the COMBI-AD trial which demonstrated a significant improvement in RFS (primary outcome) in favour of dabrafenib plus trametinib compared with placebo, and a compelling trend in OS favouring the combination despite OS not yet meeting the pre-specified threshold for statistical significance at the first interim analysis. The clinical

need for improved adjuvant treatment options is clearly represented within the commentary of Patient Advocacy Groups submitting input for review. A theme common among patient voices is the anxiety that surrounds a diagnosis with malignant melanoma. Patients spoke on the stress and strain the diagnosis and treatments placed on their work, social and family lives. The uncertainty following a diagnosis with melanoma, particularly in those for whom only post-surgical observation was appropriate, represents a significant negative impact on well-being, and it is reasonable to hope that access to a tolerable and efficacious adjuvant therapy such as dabrafenib-trametinib may in part alleviate this burden.

The CGP also considered that:

- Selection of placebo as comparator against dabrafenib-trametinib: the decision to compare dabrafenib-trametinib against placebo has raised question as to whether this was the appropriate or optimal comparator. However, scrutiny of this decision suggests the choice was a pragmatic one. Despite meta-analyses which support a modest improvement in patient survival with the use of IFN as adjuvant treatment to surgery[7] the regimen is uncommonly prescribed in practice. Chief among the reasons for non-utilization is the toxicity associated with the regimen and the resulting negative impact on patient preference. Further, the clinical trials which previously demonstrated the benefit to treatment with IFN following surgery were primarily conducted in the era predating both targeted and immune checkpoint inhibitor therapy, calling in to question the relevance of the data in the current treatment era. Likewise, the use of high-dose IFN as the comparator to orally administered dabrafenib-trametinib would have precluded a blinded study design, significantly increasing the risk of bias within the study, as IFN is dosed on a daily schedule through the first four weeks, followed by subcutaneous injections three times per week.
- Choice of RFS as the clinical trial primary outcome: the choice of RFS as the primary endpoint was a pragmatic one, as access to treatment for relapsed patients has improved the survival of a patient with metastatic melanoma from months to years; upon relapse, patients have access to immune checkpoint inhibitors and in the case of patients with BRAF-mutated melanoma, highly efficacious targeted therapy. And for the population of patients with metastatic disease treated with immunotherapy in some cases deep and durable tumour responses following treatment with immune checkpoint inhibitors may last years. Ideally, when recommending a systemic therapy as adjuvant treatment to surgery an improvement in OS would be demonstrated, but the reality (fortunate for patients living with metastatic melanoma) is that effective treatments in the metastatic setting creates a scenario where sample size would have to be unacceptably large or follow-up unacceptably long to detect this difference.
- Selection of optimal systemic therapy as adjuvant treatment to surgery for patients with BRAF-mutated melanoma: while patients without actionable BRAF mutations should not be considered for treatment with BRAF-directed therapy, patients with BRAF-mutated melanoma may benefit from non-BRAF-directed therapies such as immune checkpoint inhibitor therapy. At the present time, there are no data to guide clinicians in choosing between BRAF-targeted or non-BRAF-targeted adjuvant therapy for the patient with resected BRAF-mutated melanoma.
- Sequencing of currently available adjuvant therapies: patients previously treated with IFN as adjuvant to surgery were *not* permitted enrolment to the COMBI-AD trial. However, under rare circumstances clinicians may wish to transition a patient

from receiving adjuvant IFN to treatment with dabrafenib-trametinib as adjuvant to surgery. While no supporting clinical data exists, in practice the decision may be reasonable. In practice, this situation is likely to be very infrequent (as IFN is not routinely prescribed in Canada at the present time), but as guidance the CGP recommend that clinicians contemplating a change from IFN to dabrafenib-trametinib consider patient factors such as time from diagnosis, age, and performance status. The CGP suggested clinicians may also wish to look to the COMBI-AD inclusion/exclusion criteria as guidance when contemplating this change in adjuvant systemic therapy. IFN is the only systemic therapy available to patients as adjuvant treatment to surgery at the time of writing, but in the future, the situation is likely to arise where patients with BRAF-mutated melanoma relapse following treatment with immune checkpoint inhibitor therapy used as adjuvant to surgery who are then surgically rendered free of disease; there is 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.[10] For this reason, the use of dabrafenib-trametinib as adjuvant treatment to surgery could be considered in patients where previous adjuvant therapy with immune checkpoint inhibitor therapy has failed. Given the rarity of this clinical scenario, quality evidence to support this practice will not likely be forthcoming.

- Impact of utilization of dabrafenib-trametinib as adjuvant treatment to surgery on subsequent treatment decision-making in the metastatic (relapsed) setting: no data are currently available to guide treatment decision-making in this context. A review of post-protocol treatments in the COMBI-AD trial reveals that patients treated with dabrafenib-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. Clinicians will likely wish to consider all of these options for the relapsed patient following treatment with adjuvant dabrafenib-trametinib, taking into account factors such as time-to-relapse and patient performance status.
- Time between surgery and initiation of dabrafenib-trametinib as adjuvant treatment to surgery: to have been considered for enrolment within COMBI-AD patients must have been surgically rendered free of macroscopic disease within 12 weeks of randomization. This is an acceptable benchmark for consideration for the use of dabrafenib-trametinib as adjuvant treatment to surgery in practice, and aligns with general principles of oncologic management.
- Degree of metastatic lymph node involvement: the COMBI-AD clinical trial enrolled patients with completely resected stage IIIA through IIIC disease.[8] However, patients with stage IIIA disease were only eligible for screening if they had a focus of nodal disease >1 mm. In the time since the trial was designed and conducted, an updated melanoma staging classification system has been adopted.[11] The revised AJCC 8th edition staging classification captures the clinical trial population within stages IIIA through IIID, therefore there should be little confusion between classification systems with respect to stage of disease and eligibility for treatment. In pragmatic fashion, Health Canada has granted approval for the use of dabrafenib-trametinib as adjuvant treatment to surgery for patients with completely resected melanoma with lymph node involvement, a basis that simplifies the scenario in the clinic and honors the oncologic principle of systemic therapy as adjuvant to surgery. The CGP felt the inclusion criteria of the COMBI-AD trial reasonably identified a high-risk patient population warranting treatment with

dabrafenib-trametinib as adjuvant treatment following surgery, and further agreed with limiting treatment to patients with stage IIIA disease to those with a focus of disease >1 mm.

- Requirement for completion lymphadenectomy following positive sentinel lymph node biopsy: in the time since the COMBI-AD clinical trial was designed and conducted, evidence has emerged which suggests futility in reflexively performing completion lymphadenectomy following the detection of micrometastatic lymph node disease.[12] As a result, clinical practice has recently changed, and it is now appropriate to defer completion lymphadenectomy in favour of surveillance of the affected lymph node basin following a positive sentinel lymph node biopsy. The CGP considered whether this change in practice was germane to the interpretation of the results of the COMBI-AD trial, but ultimately concluded the results from this study were applicable within the current surgical landscape. Therefore, the CGP felt it was reasonable to extend treatment with dabrafenib-trametinib as an adjuvant therapy following surgery to patients who would otherwise fit within the clinical trial's inclusion criteria, irrespective of whether completion lymphadenectomy was performed.
- Patients treated with radiation as adjuvant therapy to surgery: in the COMBI-AD trial patients were not permitted to receive radiation as adjuvant therapy prior to enrolment. However, as discussed above, radiation as adjuvant therapy to surgical resection of melanoma confers an advantage in terms of loco-regional control, although this benefit does not translate to improvement in patient survival.[13] Nonetheless, the situation may arise where clinicians may wish to consider radiation and systemic therapy as adjuvant treatment to surgery. The CGP felt the decision to pursue radiation therapy as adjuvant to surgery should not disqualify a patient for consideration for dabrafenib-trametinib as adjuvant treatment to surgery.

The CGP discussed the stakeholder feedback received following the release of the pERC's initial recommendation, and provided the following remarks:

- **Regarding the ability of a patient with BRAF-mutated melanoma to change from therapy with adjuvant dabrafenib-trametinib to immunotherapy in situations where treatment with dabrafenib-trametinib was not tolerated, or vice versa.** The CGP is cognizant that patients may be intolerant of that regimen which was first selected as adjuvant therapy, and clinicians and patients alike may reasonably wish to continue systemic treatment as adjuvant therapy to surgery by selecting an alternate agent. Within the initial Clinical Guidance Report, this specific scenario was not referenced, however the CGP recognizes this is a scenario that is common in clinic, and applies to the general oncology population, including patients with malignant melanoma. The CGP discussed this scenario, and are in agreement with the clinician group providing feedback that patients who are unable to tolerate therapy with one class of adjuvant treatment should be allowed the option to resume treatment with an alternate agent. The CGP further discussed a number of issues related to this topic. Recognizing there does not currently exist evidence to guide treatment decision making for this scenario, the CGP felt, in general, clinicians may wish to consider a total duration of treatment of one year, irrespective of the duration of therapy already administered at the time of transition from one class of therapy to another. Further, the CGP discussed the fact that in the COMBI-AD trial, only two-thirds of patients completed the full year of protocol-directed adjuvant therapy and among those who discontinued treatment prematurely the majority did so for treatment-related toxicity. This is mentioned

to raise the point that patients may not need to complete a full year of therapy to derive the reported benefit within the COMBI-AD trial, and clinicians and patients may wish to therefore consider the duration of therapy received when contemplating a change to a new treatment. For instance, the CGP discussed a scenario where a patient having already received the majority of their treatment with dabrafenib-trametinib as adjuvant therapy following surgery presents with treatment-limiting toxicity (i.e., >6 of the 12 months of planned therapy), and in this instance the CGP felt a careful deliberation by the treating physician would be required regarding whether any additional adjuvant therapy was in fact required. Conversely, should the scenario arise where a patient develops treatment-limiting toxicity within the early period of treatment (i.e., <3 of the 12 months of planned therapy) the CGP felt it reasonable to contemplate a switch to a novel class of adjuvant systemic therapy.

- **Regarding the restriction of treatment within the stage IIIA patient population to those with a minimum focus of metastatic disease of 1 mm.** The COMBI-AD trial allowed for the use of dabrafenib-trametinib as adjuvant treatment to surgery for patients with completely resected stage IIIA - IIIC (AJCC 7th edition) disease, but excluded those patients with IIIA disease if the focus of disease within the lymph node measured <1 mm. The CGP considered a number of factors with respect to the feedback received regarding this issue, and ultimately agreed that limiting treatment of stage IIIA patients to only those with a focus of disease greater than 1 mm may create complexities in practice which are unnecessary. The CGP considered a number of factors in choosing to agree with the feedback provided, including:
    - Absence of limiting criteria within the stage III population within Health Canada's Notice of Compliance. The CGP noted that Health Canada's Notice of Compliance allows for the treatment of patients with stage III resected melanoma and lymph node involvement, without excluding the minority of patients with nodal metastases measuring < 1 mm who were excluded from the COMBI-AD trial.
    - Predicted restrictions (or lack thereof) regarding the use of alternate therapies as adjuvant treatment to surgery. The CGP is aware that treatments other than dabrafenib-trametinib have demonstrated efficacy as adjuvant therapy to surgery for patients with melanoma with nodal involvement. Specifically, immune checkpoint inhibitors will likely soon be available for this indication, and have been the focus of recent pCODR deliberations. Up to this point, Health Canada has seen fit to approve nivolumab, pembrolizumab and dabrafenib-trametinib for use as adjuvant treatment to surgery for patients with resected melanoma with nodal involvement. Recognizing this, the CGP felt it important to recommend a scenario where each of these regimens is equally available to patients with stage III disease. An exception to this opinion exists where (resected) stage IV disease exists, as the CGP felt this was a distinct population of patients from the stage III population, and only the CheckMate 238 clinical trial (nivolumab) allowed for recruitment of these patients. But where patients with resected stage III disease are concerned, the CGP felt it was reasonable to recommend access to each of the three regimens without further recommending subset(s) of patients be excluded.
    - Desire to honor the oncologic principle behind the use of systemic therapy as adjuvant treatment to surgery. The CGP discussed the fact that the

exclusion of patients with stage IIIA disease without a focus of at least 1 mm of micrometastatic nodal disease was not made for clinical nor biological reasons, but was instead a decision made in the interest of identifying a study population for which an adjuvant clinical trial could reasonably be powered to detect a clinical benefit. The CGP felt that patients with resected stage IIIA disease without a minimum focus of disease of 1 mm should not be deprived of the potential for benefit inherent to the use of dabrafenib-trametinib as adjuvant treatment to surgery, particularly because no evidence exists that would refute this potential benefit to this patient population.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Melanoma CGP. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Malignant melanoma is a relatively uncommon but aggressive skin cancer with an estimated incidence in Canada of 7 200 cases per year.[14] Approximately 1 in 50 Canadians will be diagnosed with a malignant melanoma in their lifetime. While the disease may be uncommon, melanoma is the most commonly diagnosed cancer in individuals between the ages of 20 and 29, creating a disproportionate societal impact. Unfortunately, the incidence of melanoma in Canada continues to rise, despite efforts of patient advocacy groups and public awareness campaigns to educate the public regarding risk factor modification, specifically avoidance of ultraviolet radiation. Most diagnoses of melanoma represent early stage disease and are cured with surgery alone, however a proportion of patients will present with locally advanced cancers which, while also amenable to surgery, portend a high risk of relapse and death. Prognosis varies within the subset of patients presenting with nodal involvement, but for those at highest risk for relapse (stage IIID, AJCC 8th edition)[11] the five- and ten-year disease-specific survival rate is 32% and 24%, respectively.

For patients with metastatic melanoma, effective systemic treatment strategies prior to the era of targeted and immunotherapies did not exist. More recently, targeted inhibition of the mitogen-activated protein kinase (MAPK) signaling pathway has emerged as an extremely effective palliative therapy that has also improved the survival of patients with melanoma that harbors a mutation in the BRAF gene. In approximately 40% of the total patient population, mutations occurring at the BRAF V600 codon result in constitutive activation of the MAPK signalling cascade, leading to dysregulated cellular proliferation and metastatic spread of disease. For those patients with BRAF-mutant melanoma, agents such as dabrafenib and vemurafenib (now commonly prescribed in combination with the MEK inhibitors trametinib and cobimetinib, respectively) represent highly effective palliative therapy.[15,16]

As an alternative to targeted therapy (or for the majority of melanoma patients with non-mutated or wild-type BRAF disease) immune checkpoint inhibitors have similarly impacted patient survival. Ipilimumab, an inhibitor of cytotoxic T-Lymphocyte antigen-4 (CTLA-4) was the first immunotherapy to improve the survival of patients with metastatic melanoma,[17] followed by similar successes with agents such as nivolumab[18] and pembrolizumab.[19] The latter study demonstrated targeting the Programmed Death-1 (PD-1) checkpoint molecule was superior to CTLA-4 inhibition, however more recent data suggests there may be further gain from dual blockade of CTLA-4 and PD-1, extending the three-year survival for patients with metastatic melanoma to nearly 60%.[20]

With these improvements in patient survival, it should not be surprising that attempts have been made to reduce the risk of relapse and death in patients with locally advanced, non-metastatic melanoma. Both targeted and immunotherapies have been tested in the adjuvant setting, and both strategies have yielded improved patient outcomes. In the COMBI-AD trial, combined dabrafenib and trametinib improved RFS at three years when compared against matched placebos (HR for relapse or death was 0.47) and a trend towards improved OS was also observed.[21] Similarly, when compared against placebo, ipilimumab improved patient survival for patients with resected stage III melanoma (five-year survival was increased by 11% from 54.4% to 65.4%, HR for death was 0.72).[22] More

recently, when compared against ipilimumab, treatment with nivolumab following complete resection of stage III or IV melanoma improved RFS at one year (70.5% versus 60.8%, HR for relapse or death was 0.65).[23] An adjuvant clinical trial comparing dual blockade of CTLA-4 and PD-1 against nivolumab is ongoing (NCT03068455).[24] And finally, the use of pembrolizumab as adjuvant to surgery for patients with resected stage III melanoma has resulted in significantly longer recurrence-free survival when compared against treatment with placebo.[25]

2.2 Accepted Clinical Practice

For patients presenting with resected stage III or IV melanoma, current adjuvant treatment options are limited, particularly with respect to systemic therapy. 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 at high-risk for systemic recurrence, within 56 days of surgery (product monograph). In practice, however, IFN is infrequently prescribed. The approval for the use of adjuvant high-dose IFN came at a time when no efficacious treatments were available for patients with recurrent disease, a clinical scenario which fortunately has changed for the better with the introduction of targeted and immunotherapies. Furthermore, IFN as adjuvant to surgical treatment for patients with melanoma has been well studied, and meta-analyses support the use of the treatment in a relatively small proportion of patients. As an example, a recent Cochrane meta-analysis examining 10,499 patients across 18 RCTs identified a benefit from the use of adjuvant IFN with respect to DFS and OS, reporting a HR for the latter of 0.91.[7] The same meta-analysis reported a number needed to treat (NNT) of 35 to prevent one death from melanoma recurrence, and when the significant toxicity of the treatment regimen is considered the actual benefit to the patient population is further diminished, particularly when one recognizes the data utilized within the meta-analysis predates the use of checkpoint inhibitor therapy; although unproven, it seems plausible that the durable immunotherapy responses observed in patients with metastatic disease could further diminish the small gains seen with the use of IFN. Attempts have been made to identify a subset of patients for whom the use of adjuvant IFN may confer a greater benefit; although not supported by the previously referenced Cochrane meta-analysis, more recent studies suggest patients with ulcerated primary melanomas may derive greater benefit versus the unselected patient population.[26] If confirmed, the use of ulceration as a predictive biomarker could in theory reduce the NNT to confer a benefit from IFN, although it is worth noting the aforementioned clinical trial utilized pegylated IFN-alpha, a treatment not currently approved in Canada as an adjuvant to surgery.

Given the relatively modest benefit observed after treatment with adjuvant IFN, in practice most patients decline this treatment option, instead choosing observation alone. Although not rooted in evidence, the option of active surveillance is routinely offered to patients with resected melanoma. This is a relevant point, as active surveillance is not without an associated cost. Practice will differ between Canadian cancer centres, but most will offer a variant of a schedule of assessments that includes clinical assessments performed on a 3-6 month basis as well as periodic re-staging imaging studies, although the benefit from diagnostic imaging has not yet been conclusively proven. In a subset of patients with resected nodal disease (or in patients with resected in-transit metastatic disease) radiation therapy may be considered as an adjuvant to surgical resection, although neither RFS nor OS is improved with this strategy.[13]

2.3 Evidence-Based Considerations for a Funding Population

High quality RCTs support the use of targeted or immunotherapy as adjuvant treatment following surgical resection of stage III malignant melanoma. CTLA-4 directed therapy has been compared against placebo in patients with resected stage III melanoma.[22] After patients had undergone complete resection of stage III cutaneous melanoma, they were randomly assigned to receive ipilimumab at a dose of 10 mg per kilogram (475 patients) or placebo (476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred. Recurrence-free survival was the primary end point. Secondary end points included OS, DMFS, and safety. At a median follow-up of 5.3 years, the 5-year rate of recurrence-free survival was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (HR for recurrence or death 0.76). The rate of overall survival at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group (HR for death 0.72). Despite the fact that more patients in the placebo arm received post-protocol treatment with both CTLA-4, PD-1 and BRAF-directed therapies at the time of relapse, the survival advantage to adjuvant ipilimumab was preserved, suggesting this treatment strategy is unlikely to be negated by a potential salvage effect of reserving the use of immune checkpoint inhibitors for the time of relapse. Subgroup analyses demonstrated the benefit to treatment with ipilimumab as adjuvant to surgery was greatest in those patients at highest risk for disease relapse (stage IIIC patients, specifically those with four or more lymph nodes positive for metastatic melanoma) and again, patients with ulcerated primary melanomas seemed to derive proportionally greater benefit (HR for death 0.64). Treatment with ipilimumab at a dose of 10 mg/kg resulted in nearly half of patients experiencing a grade 3-5 immune-related AE (42.7% versus 2.7% in the placebo group). In the ipilimumab group of treated patients, five patients died from a drug-related cause: three patients died of intestinal perforation (colitis), while one patient each died from myocarditis and multi-organ failure secondary to Guillain Barré syndrome. An approval from Health Canada for the use of ipilimumab as adjuvant therapy to surgery was not sought.

More recently, the CheckMate 238 RCT compared adjuvant CTLA-4 -directed therapy against inhibition of PD-1.[23] In this randomized, double-blind, phase III trial 906 patients (≥15 years of age) who had undergone complete resection of stage IIIB, IIIC, or IV melanoma received an intravenous infusion of either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks (453 patients) or ipilimumab at a dose of 10 mg per kilogram every 3 weeks for four doses and then every 12 weeks (453 patients). The patients were treated for a period of up to one year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The primary end point was recurrence-free survival in the intention-to-treat population. This was a positive study; with a minimum follow-up of 18 months, the 12-month rate of recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group (HR for disease recurrence or death was 0.65). Importantly, treatment with nivolumab as adjuvant to surgery was significantly safer versus treatment with ipilimumab. Treatment-related grade 3 or 4 AEs were reported in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group; treatment was discontinued because of any AE in 9.7% and 42.6% of the patients, respectively. Two deaths (0.4%) related to toxic effects were reported in the ipilimumab group more than 100 days after treatment. The utility of tumoral PD-L1 staining as a predictive biomarker was studied but failed to identify a subset of patients with preferential benefit from the use of adjuvant nivolumab. Nivolumab was superior to ipilimumab in both patients with PD-L1 expression greater than and less than 5%. The 12-month rate of recurrence-free survival was greater in patients with PD-L1 expression greater than 5%, however the gain was consistent whether

treatment was with nivolumab or ipilimumab, suggesting PD-L1 expression may offer better prognostic versus predictive insight. For the most part, subgroup analyses tended to favour treatment with nivolumab as opposed to ipilimumab; of particular importance, both patients with BRAF-mutant and wild-type melanoma derived preferential benefit from treatment with nivolumab. Of the adjuvant RCTs cited in this review, the CheckMate 238 study was unique in that patients with completely resected stage IV disease (including patients with resected CNS metastases) were eligible for enrolment, and also allowed for treatment of non-cutaneous melanoma (mucosal and acral-lentiginous melanoma patients were permitted to enroll, however patients with ocular melanoma were excluded). The HR for relapse or death was statistically non-significant within each of these subgroups, however this may be due to the fact small numbers of patients from these subgroups were enrolled. Nivolumab has approval from Health Canada as adjuvant therapy to surgery and a conditional initial pERC recommendation.

The Keynote-054 RCT enrolled patients who were 18 years of age or older and had histologically confirmed cutaneous melanoma with metastasis to regional lymph nodes.[25] To be eligible, patients must have presented with either stage IIIA melanoma (patients with stage N1a melanoma had to have at least one micrometastasis measuring >1 mm in greatest diameter), stage IIIB or stage IIIC disease with no in-transit metastases as defined by the AJCC 7th edition.[8] A complete regional lymphadenectomy was required to have been performed within 13 weeks before the start of treatment. Exclusion criteria included an ECOG performance status score of more than 1 (scores range from 0 to 5, with higher numbers indicating greater disability), autoimmune disease, uncontrolled infections, use of systemic glucocorticoids, and previous systemic therapy for melanoma. Patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of 200 mg of pembrolizumab or placebo every three weeks for a total of 18 doses, or until disease recurrence, unacceptable toxic effects, a major protocol violation, or withdrawal of consent occurred. With a primary endpoint of RFS and with a median follow-up of 15 months, the one-year rate of RFS in patients who received pembrolizumab was 75.4%, versus 61% in the placebo-treated group (HR for relapse or death was 0.54). The benefit in RFS was seen in patients with both BRAF-mutated and -wildtype disease, and while all subgroup analyses indicated a trend that favoured treatment with pembrolizumab, a clear benefit from treatment was observed in patients with stage IIIB and C disease, patients with PD-L1 positive tumours and patients with ulcerated primary lesions. The rate of grade 3 or greater toxicities was roughly doubled in pembrolizumab-treated patients (31.6% versus 18.5%), with an overall toxicity profile in the adjuvant setting similar to that seen in patients with metastatic disease. A cooperative group study is currently underway which will compare pembrolizumab against IFN-alpha as adjuvant treatment to surgery.[27]

Finally, in the COMBI-AD trial, which is the focus of this review, patients were randomized to receive the combination of dabrafenib with trametinib versus treatment with matched placebos, with RFS as the primary endpoint and OS and safety included as secondary endpoints. To be eligible for this international, multi-centre clinical trial, adult patients (≥18 years of age) must have undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (according to the criteria of the AJCC 7th edition) with BRAF V600E or V600K mutations. None of the patients had undergone previous systemic anticancer treatment or radiotherapy for melanoma. All the patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional node disease within 12 weeks before randomization, had recovered from definitive surgery, and had an ECOG performance status of 0 or 1.

The evidence seems clear that for cutaneous melanoma patients surgically rendered free of macroscopic disease, clinical benefit may be derived from the use of targeted therapy as adjuvant treatment to surgery. In most studies, the available evidence reveals a benefit with respect to RFS, although one study comparing ipilimumab against a matched placebo as adjuvant treatment to surgery also supports an advantage in terms of overall patient survival. Not coincidentally, that clinical trial also offers the longest duration of follow-up. The majority of evidence for treatment exists within the stage III patient population, with just one RCT (the CheckMate-238 trial comparing nivolumab against ipilimumab) allowing for treatment of patients with completely resected stage IV disease. There exists inter-trial heterogeneity between the populations of patients with stage III disease, with some but not all studies allowing for the treatment of patients with stage IIIA melanoma, and in two of the cited studies patients with stage IIIA disease must have had a minimum focus of nodal disease of 1 mm. None of the included studies were powered for subgroup analyses which might otherwise have indicated a preferential benefit within the unselected stage III patient population. Likewise, with the exception of the COMBI-AD trial, which only allowed for treatment of patients with BRAF-mutated melanoma, none of the included immunotherapy studies identified a preferential benefit to treatment in either BRAF-mutated or -wildtype melanoma.

2.4 Other Patient Populations in Whom the Drug May Be Used

The introduction of systemic therapy as adjuvant treatment to surgery for patients with melanoma will benefit the majority of patients with resected lymph node metastases. The populations included within the clinical trials described above were mostly comprised of adult patients with cutaneous melanoma. With respect to the proportion of patients who present with resected BRAF-mutated melanoma, in the future it may be necessary for clinicians and patients to choose between a targeted treatment option or an immunotherapy treatment. When specifically considering BRAF-targeted therapy as an adjuvant treatment option, the patient population in whom treatment may be considered will in large part define itself by the presence of an actionable BRAF V600 mutation, and in the majority of cases the inclusion criteria defined by the COMBI-AD trial will define the patient population appropriate for treatment. Exceptions to this statement may include:

- Patient age: the COMBI-AD trial limited enrolment to patients 18 years of age or older. Melanoma in the pediatric population is rare, but not unheard of. Because of the rarity of the diagnosis within the pediatric population, clinical trials examining the efficacy and safety of dabrafenib plus trametinib as adjuvant treatment following surgery in patients with melanoma younger than 18 years will not likely be forthcoming. Therefore, the CGP felt it was reasonable to extrapolate the benefit seen within the COMBI-AD clinical trial to patients younger than 18 years of age, and felt the decision to utilize dabrafenib-trametinib as adjuvant treatment following surgery in patients younger than 18 years of age could be considered.
- Extrapolation of potential treatment benefit to patients with performance status >1: only those patients with a performance status of ECOG 0 or 1 were permitted enrolment to the COMBI-AD trial. The CGP felt the results of the COMBI-AD trial could be extrapolated to those with greater disability, for example patients with a performance status of ECOG 2. This position was taken based on clinical experience in the treatment of patients with metastatic melanoma, where safety and efficacy has been shown in patients with relatively poor performance status.[15] The decision for treatment with dabrafenib-trametinib following complete resection of stage III melanoma should rely upon clinical judgment, taking in to account all patient

factors (including performance status and medical comorbidities) in the consideration of treatment benefit versus risk.

- Extrapolation of submitted evidence for consideration of the use of dabrafenib-trametinib as adjuvant treatment to surgery for patients with non-cutaneous melanoma: enrolment to the COMBI-AD trial was restricted to patients with completely resected, stage III cutaneous melanoma harboring either a BRAF V600E or V600K mutation. Patients with non-cutaneous melanoma subtypes such as mucosal or ocular melanoma were ineligible for enrolment. Therefore, the CGP felt the use of dabrafenib-trametinib as adjuvant treatment to surgical resection should be limited to those patients presenting with BRAF-mutated cutaneous melanoma. The impact of this position on patients with non-cutaneous melanoma will not be significant, as BRAF mutations are not typically found in ocular melanoma, and are relatively rare in mucosal disease.
- Extrapolation of potential treatment benefit to patients with non-V600E or K mutations: substitution of glutamic acid (E) or lysine (K) for valine (V) at the 600 codon are the two most common oncogenic BRAF V600 mutations, and the COMBI-AD trial restricted enrolment to these two subgroups of patients. However, patients with non-V600E/K BRAF mutations may respond to dabrafenib-trametinib treatment, as shown in the metastatic treatment setting. There will likely be a desire on the part of clinicians and patients to access dabrafenib-trametinib as adjuvant treatment following surgery, and the CGP felt it would be reasonable to consider extrapolating the results from the COMBI-AD trial to patients with non-V600E/K BRAF mutations.
- Extrapolation of potential treatment benefit to patients with stage IIB/C with T4 lesions: the AJCC 8th edition staging classification indicates patients with high-risk stage II lesions may in fact have a prognosis equal to or worse than those with stage III melanoma. In recognition of this fact, clinical trials are currently underway to evaluate a potential benefit for adjuvant systemic therapy for the treatment of patients with high-risk, stage II disease. However, at this time the CGP felt the available evidence to support the use of dabrafenib-trametinib could not be extended to those with resected stage II melanoma lesions, as these patients were not included in the COMBI-AD trial.
- Patients with resected stage IV disease: patients with resected stage IV disease represent a distinct classification of patients, and were ineligible for enrolment to the COMBI-AD trial. In the absence of clinical data, the CGP was unable to comment on the treatment of these patients with dabrafenib-trametinib as adjuvant therapy following surgery.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient input regarding dabrafenib and trametinib (Tafinlar and Mekinist) in combination as adjuvant therapy for patients with BRAF mutated melanoma with lymph node involvement (who have undergone resection) was provided by two patient advocacy groups: Melanoma Network of Canada (MNC) and the Save Your Skin Foundation (SYSF). Their methods and input are summarized below.

MNC gathered data by way of an online survey. The survey link was emailed to their database of Canadian patients and any patients and caregivers, regardless of stage, were asked to participate. Social media was also used to promote the survey. The latter was made available from August 1, 2018 to September 30, 2018. MNC received responses from a total of 208 individual patients and 115 caregivers. In the patient sample, 130 were female and 78 were male; 125 were stage 0 to III, 55 were stage IV and the remaining 28 did not know their stage. Sixty-six percent of respondents were from Ontario, 12% Alberta, 7% BC, 6% Quebec, and the remainder from the other provinces. The age of the respondents ranged from 18 to more than 70; 67% were older than 50 years of age. Twenty-one patients were in the adjuvant therapy clinical trial and 28 indicated they had been on treatment for metastatic disease.

SYSF obtained information on patient experience through surveys and one-on-one conversations. A total of 63 patients provided input for this submission; 95% of patients were surveyed and 5% participated in one-on-one conversations. All individuals recounting their experience with cancer (100%) were either stage III (55%) or IV (32%) melanoma patients, and all 15% of patients reporting experience with the treatment under review had undergone such treatment. Over 80% of interviewees were female (81%; males 19%), and their age ranged from 18 years to over 60 years. Over 50% of patients were employed (62% working full- or part-time) and 16% were retired. Patients from all provinces were interviewed and 20% of those interviewed did not live in Canada (being from the USA and Australia).

From a patient perspective, resected stage III melanoma was mostly associated with impaired mental health due to the chronic, traumatic fear of recurrence, as well as physical impacts of cancer surgery such as scarring and lymphedema. Patient groups explained that there are currently no viable therapies to prevent recurrence, which occurs in about 60% of individuals, which strongly heightens the level of worry and despair. These perspectives were shared by caregivers.

Experience with adjuvant IFN alpha, a treatment that is not widely applied, led to significant side effects and treatment discontinuation in almost all patients surveyed. Watchful waiting after surgery was met with disappointment and fear by patients. Experience with the drug combination under review through clinical trials was associated with a range of side effects such as fever, joint pain, fatigue and rash. There was a widespread feeling of optimism among all who took the drug combination, and some reported disease control.

Patient groups expressed a preference for earlier (adjuvant) treatment compared with the risk of disease progression, and did not consider side effects a barrier. Patient groups maintained that early and equitable access to affordable cancer drugs was important to patient and caregiver well-being.

Please see below for a summary of specific input received from MNC and SYSF. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Melanoma

MNC stressed that melanoma is a cancer that has been historically difficult to treat if it spreads and that there are currently no adjuvant therapies for patients at high risk of recurrence (stage III). Traditionally, some patients were offered IFN alpha, but this treatment had lasting side effects with little if any benefits, and is no longer being offered in most of Canada. Patients have to rely on limited access to clinical trials at major treatment centres. Overall, MNC emphasized that there is an unmet need in providing effective adjuvant therapy for stage III melanoma patients.

According to MNC, the physical impacts of surgery, mobility issues for many, scarring and lymphedema, are compounded by significant emotional distress when patients are told that they are at high risk for recurrence. These effects in turn impact the daily lives of patients including their ability to work and function. MNC and SYSF report that 40-60% of these patients will experience disease progression.

Survey results from both MNC and SYSF on patient experience with melanoma are summarized in Table 1.

Table 1: Patient experiences with melanoma.

	MNC (n=208)	SYSF (n=63)
Fear and/or anxiety	73%	88%
Fatigue	59%	65%
Financial loss or job loss	31%	31%
Scarring and disfigurement	74%	71%
Pain	43%	50%
Weight loss or weight gain	NR	48%
Disrupted sleep	42%	48%
Nausea or vomiting	NR	31%
Negative impact to family or social life	39%	39%
Depression	48%	50%
Negative impact on sexuality	29%	NR
Loss of/ gain of appetite	NR	29%
Lymphedema	28%	27%
PTSD	NR	23%
Cognitive Impairment	NR	23%
Damage to organ	NR	21%
Breathing problems	NR	6%
Mobility Issues	21%	19%
Headaches	NR	31%
No effects	NR	6%

NR = not reported; PTSD = post-traumatic stress disorder

Overall, a majority of patients report mental health challenges including fear, anxiety and depression. Pain, scarring, fatigue and disrupted sleep are also prominently reported by patients. Both MNC and SYSF provided common comments collected from patients or caregivers. Many relate to a looming fear of disease progression:

- *"The fear of the disease progressing is always at the back of my mind. The mental stress is always there; Couldn't work. Skin grafts wouldn't heal. Family life in tatters. Depressed."*
- *"I am 5 years post diagnosis of Stage 2c melanoma and I still worry it will come back."*
- *"I have/had post-traumatic stress from diagnosis and treatment including nightmares, avoiding triggers like hospitals, hypervigilance, emotional numbness."*
- *"Cancer affects all the aspects of your life. It kills your personality and your dreams before killing your body. I am and will never be the same person."*

Other comments emphasized the physical impairment of melanoma and associated treatments:

- *"I had to stop athletic activities before diagnosis due to the fatigue the melanoma was causing me. Pain was manageable, surgery was difficult[…]"*
- *"Lymphedema is an ongoing issue for pain and swelling. Fatigue slows [me] down at work and with my kids"*
- *"Inability to walk for a month after excision/skin graft -general exhaustion limiting daily activities […]".*

Finally, impacts on daily living, and professional and familial relationships were mentioned:

- *"Have had issues with relationships with those close to me due to frustration and anger since being diagnosed."*
- *"Impact on family planning and unsure if we can have another child", "Limited outdoor activities in the daytime, increased costs for protective sun gear (sunscreen, UV clothing, etc.)."*
- *"It brings out some nasty emotions and beliefs about cancer, so I've had to adjust my standards for what type of people I'm willing to have in my life."*

Only 10% of patients interviewed by SYSF found that they were limited due to disease or treatment and were unable to work, while 90% were able to manage ongoing symptoms and other issues with "side effect management", support, etc.

3.1.2 Patients' Experiences with Current Therapy for Melanoma

MNC indicated that there is no current available treatment for stage III melanoma other than surgery or localized injection to control spread in certain cases, since IFN alpha is no longer being offered and is neither sufficiently effective nor safe. Of note, 38% of patients interviewed by SYSF had experience with IFN. In addition, 15% had experience with Opdivo (nivolumab) and 6% with another experimental treatment. Thirty-eight percent of the SYSF patients were in the "wait and watch for progression" category.

The experiences from patients responding to SYSF who underwent IFN therapy are presented in Table 2 below.

Table 2: SYSF patient experiences with IFN-alpha.

Severe fatigue	100%
Nausea and vomiting	90%
Hair loss or thinning	90%
Depression	90%
Weight loss	95%
Flu like symptoms	100%
Did not complete treatment due to side effects	90%
Side effects could not be managed	100%
Side effects were not worth the result (i.e., stage IV recurrence)	95%

Patients interviewed by SYSF shared their impressions regarding watchful waiting after stage III melanoma surgery. Many expressed their disappointment at the unavailability of viable treatment options and the reassurance that such therapies would bring:

- *"Having a treatment option would have given me Peace of Mind."*
- *"It would have meant the world to me to be offered treatment. It would have been a game changer!"*
- *"It would have been important to have a drug therapy as I wanted to do everything possible to fight".*

3.1.3 Impact of Melanoma and Current Therapy on Caregivers

MNC indicated that extreme levels of stress are experienced by caregivers due to the lack of availability of treatment options in the adjuvant setting beyond surgery. Many concerns from caregivers mirrored that of their partners in many respects: fatigue due to increased responsibilities of care and time off work for appointments and home care, impacts to the financial state of the household due to lost income, increased costs associated with treatment, uncertainty about the future and fear of losing a loved one, negative impact on family and work.

SYSF provided excerpts of caregiver comments. As reported by MNC, many highlight the significant impact that melanoma diagnosis and care of their loved one has on their relationship, finances, professional life, and overall physical and mental well-being. For example:

- *"Just knowing how much time I have left, planning for my stage 4, hard on relationship and a financial worry!"*
- *"The entire family is still in shock! We do not know what to do and where to seek help. The doctor told us that the only drug that would help the cancer not advance to stage IV is not approved […]".*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Experiences To Date with Dabrafenib and Trametinib

Twenty-one of the patients responding to MNC indicated they were on adjuvant therapy for stage III melanoma and 28 were on treatment for metastatic disease. For metastatic patients, prior surveys conducted and submitted by MNC to pCODR indicate that the dabrafenib-trametinib combination is well tolerated by most patients. Side effects for these drugs are different and often significantly less than IFN while having a superior impact on quality of life.

Of the 15% of patients interviewed by SYSF who received dabrafenib-trametinib all had received the drug combination through a clinical trial. The proportion of these patients who had stage III versus stage IV melanoma was not provided in the submission. Eighty-five percent of the patients experienced at least one side effect. All patients said the benefits of the treatment outweighed the side effects and that they were thankful to be part of the clinical trial, and a large majority (93%) said side effects were manageable.

Side effects from dabrafenib-trametinib combination therapy are summarized in Table 3 below.

Table 3: Side effects from dabrafenib-trametinib therapy.

	MNC (n=49)	SYSF(n=unknown)
Mild fever	67% (any fever)	10%
Severe fever with chills and dizziness		10%
Mild transient blurred vision	Not reported	2%
Muscle and joint pain	56%	3%
Fatigue	89%	15%
Mild skin rash	56% (any skin rash)	5%
Severe skin rash		2%

Of all patients surveyed by MNC who took the combination, 33% indicated slowed disease progression, 22% indicated complete cancer elimination, 17% said there was no impact, 11% indicated it created lingering health issues, and 16% indicated the effect was unknown as there was no indication of disease and they were hopeful treatment would prevent recurrence.

Patients provided specific comments to MNC about the drugs under review. Patients indicated the treatment side effects were worth it, and were hopeful that the treatment would help control the disease:

- *"If the treatment eventually works, then it is worth it to deal with the side effects."*
- *"I got too sick but having the ability to have access to a treatment gave me hope and therefore kept my spirits up. Gave me hope."*

Meanwhile, others experienced ongoing disease control:

- *"I am alive and completely free of disease now for seven years. I am not without ongoing side effects – joint pain and lingering fatigue – but hell, I am alive, I just celebrated my 54th birthday, my daughter is getting married and I am able to look at life ahead of me."*

MNC reported on the experience of caregivers regarding access to the new therapy. Many felt relieved and fortunate with the opportunity to try the drug and not having to pay out of pocket or running out of options. Many indicated that the drug therapy did not cause any issues for them or the family other than frequent appointments. A few were concerned with the side effects and interruptions in the treatment schedule due to these, and whether that would impact outcomes. One caregiver reported on fulfilled hope of remission as follows:

- *"I felt like we had hope. And when the drugs started to work after only a week or two, and you could visibly see the tumours shrinking, I was scared to be hopeful, but he is in remission now and you would never know he is a stage IV patient. Miracles happen."*

Most (78%) patients and caregivers did not have issues with accessing treatment in the context of clinical trials. A small number indicated it took several weeks to have the BRAF test to be approved to start treatment. Some patients ended up paying out of pocket for the drugs. Compared with IV drugs, patients on the oral therapy had less frequent requirements to travel to see the doctor, making it easier on them from a time, effort, financial, and stress standpoint.

3.2.2 Patient Expectations for Dabrafenib and Trametinib

SYSF provided a list of symptoms that surveyed patients believed should be controlled by therapy: mental health such as fear, anxiety, depression, outlook (73%); fatigue (48%); pain (40%); scarring and disfigurement (21%); lymphedema (23%). In additional, these patients consistently mentioned longer survival, disease control and possible eradication, with minimal and manageable side effects, as desirable outcomes of the new therapy. As one patient commented:

- *"Treatments that work, work quickly, that have minimal side effects and are cost manageable."*

Another patient summed up her expectations with this statement:

- *"The ability to overcome the cancer earlier at stage 3 would enable me to continue to take care of my children and grandchildren and my husband and work, pay taxes and be a contributing member of society instead of being a burden to the system. It would mean saving a human life. It would mean ability to see grandchildren growing up. It would mean hope for the future and an end of despair."*

According to patients consulted by MNC, the current burden of side effects is manageable and worthwhile compared with dying of the disease. They suggested that improvements in identifying those who would benefit most from therapy would be ideal. Patients expect the options to become available (i.e., covered) quickly without undue delay. Both MNC and SYSF submitted that early treatment when patients are healthier would be more efficient from a clinical and financial perspective than waiting for the disease to worsen and

spread. MNC did not see a trade-off since there are no alternatives to the new therapies, which afford improvements in quality of life. According to MNC, the significant difference in side effect profile is illustrated by the fact that many advanced stage patients who are on targeted therapies can continue working.

3.3 Companion Diagnostic Test

The companion diagnostic tool used to determine treatment with dabrafenib and trametinib is the BRAF mutation test. According to MNC, when the first drugs were launched, there were significant delays in being able to access this test, but this is believed to have been rectified in most centres. However, MNC still hears from patients that it can take several weeks to receive the test results, which delays treatment further. There is hope for standards imposed to ensure that access to treatment is not delayed, to avoid potential progression of disease and increased anxiety for patients.

3.4 Additional Information

MNC underscored the dire situation of melanoma patients having no viable solution for adjuvant therapy. For the organization, delays to access to therapy due to bureaucratic processes unnaturally push patients to high levels of desperation and are thus unacceptable. Until such times as the diagnostic testing allows for clearer understanding of the best approach and therapy for each individual patient, MNC believes it is unconscionable to be waiting and delaying treatment and access, a situation that may be costing lives.

SYSF pointed out that 80% of interviewed patients were not able to receive the drug therapy but wished that could have – 91% of patients interviewed said they would take a drug therapy in the early stages of melanoma if offered. Hopes are high and anxiety was magnified when patients could not access the drug. SYSF emphasized the unappreciated mental health cost of passive or ineffective care while one waits for disease progression. SYSF and patients are concerned with disparities and inequalities in the system, as they know that new treatments may not be accessible even after a long wait and the promise of survival. Patients are also aware that the provincial process is slow and that with a disease that has over a 60% change of reoccurrence, time is of the essence.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Sequencing with current therapies

Economic factors:

- Additional resources to administer, monitor and treat adverse events

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that currently, high dose IFN alfa is available in all provinces. For those intolerant to or unwilling to undergo IFN alfa therapy, they may receive observation. BRAF/MEK inhibitors (e.g., vemurafenib, cobimetinib), are used for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. PAG also noted that immunotherapies (e.g., pembrolizumab, nivolumab) may also be available for advanced melanoma irrespective of BRAF status.

PAG noted that the comparator in the COMBI-AD trial was placebo, PAG is seeking information on data comparing dabrafenib trametinib with IFN alfa.

4.2 Eligible Patient Population

The COMBI-AD trial excluded patients with ECOG PS of 2 as well as patients with known mucosal or ocular melanoma or the presence of unresectable in-transit metastases. PAG is seeking guidance on whether dabrafenib trametinib would be limited to patients with ECOG PS of 0-1 and cutaneous melanoma (e.g., not mucosal, ocular or acral melanoma).

PAG noted that adjuvant treatment is offered to 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. PAG is seeking guidance on the use of adjuvant dabrafenib trametinib in these patient subpopulations.

PAG is seeking guidance for use of adjuvant dabrafenib trametinib for patients who would have been eligible at the time of diagnosis, but who are currently being treated with IFN alfa or on observation. PAG is seeking guidance on, if recommended these patients transition to dabrafenib trametinib therapy, what would be the appropriate treatment duration (e.g., one year of dabrafenib trametinib or combined one year of IFN alfa plus dabrafenib trametinib).

If recommended for reimbursement, PAG noted that patients awaiting BRAF testing results who test BRAF positive would need to be addressed on a time-limited basis.

4.3 Implementation Factors

PAG noted that both dabrafenib and trametinib are oral drugs that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

PAG 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 1 year may be required in this patient population to deliver adjuvant dabrafenib trametinib therapy, as IFN alfa is not well tolerated, and based on experience, many patients do not complete 1 year of IFN alfa therapy and some patients decline IFN alfa therapy.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate treatment options in the adjuvant and metastatic setting for patients with a BRAF V600 mutation,

- What is the optimal sequencing of adjuvant dabrafenib trametinib treatment with available metastatic treatment including BRAF/MEK inhibitors (either alone or in combination) and immunotherapies (e.g., ipilimumab, nivolumab and pembrolizumab)?
- What would be the appropriate timeframe (i.e., relapse free period) from completion of adjuvant dabrafenib trametinib therapy and initiation of metastatic treatment?
- If appropriate, what is the optimal time period between completion of dabrafenib trametinib in the adjuvant setting and dabrafenib trametinib in the metastatic setting?
- PAG noted that adjuvant treatment with nivolumab may be available. What would be the best treatment for BRAF mutation positive patients in the adjuvant setting?
- For patients who receive nivolumab for adjuvant melanoma and cannot tolerate nivolumab, would dabrafenib trametinib be considered for these patients?

4.5 Companion Diagnostic Testing

PAG noted that currently BRAF testing is routinely conducted for metastatic melanoma only. The additional testing costs in this setting as well as turnaround time for test results would be barriers to implementation. PAG is also seeking clarity on whether the BRAF mutation status evolves over the natural history of melanoma and whether repeated samples are warranted (e.g., patients test negative for BRAF in stage III or earlier disease and whether testing would be repeated once the patient develops metastatic disease).

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were received by pCODR: one joint submission from Cancer Care Ontario providing the perspective of four oncologists, and one individual input from an oncologist working at the Ottawa Hospital Cancer Centre, for a total of five clinicians providing input.

The oncologists who reached out for this drug review generally agreed that the combination of dabrafenib and trametinib would provide a much awaited and beneficial adjuvant option for BRAF V600 positive stage III melanoma patients.[i] They also suggested that use of the drug (as adjuvant therapy) in stage IIC patients may occur. According to the oncologists, the only currently available adjuvant treatment, high dose IFN, is mostly ineffective and not tolerable. Patients who relapse despite treatment may be subsequently treated with oral targeted therapies or immunotherapy. BRAF mutation testing would need to be expanded to include high-risk non-metastatic patients.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for Melanoma

The oncologists providing input indicated that the only currently available adjuvant treatment for stage III melanoma consists of high dose IFN alpha, which has significant toxicity and very modest if any benefit. Absolute benefits (in terms of metastatic relapse) is only about 3-4% and toxicity is substantial (fever, flu like symptoms, myelosuppression, liver toxicity, depression – the latter having previously caused some deaths) while overall survival benefit is not seen. In recent times, most stage IIC-IIIC patients have preferred observation alone, with risks of relapse of 40-60%.

For patients with private insurance or the means to pay for therapy, recently approved drugs can be given. For the melanoma patient population with a BRAF V600 mutation (~40%), adjuvant oral combined targeted therapy with dabrafenib-trametinib is used.

5.2 Eligible Patient Population

Oncologists providing input clarified that the patient population eligible to receive the drug would have stage IIIA (>1mm in sentinel node), IIIB, or IIIC melanoma, with all clinical and radiological evidence of disease excised. Patients of all ECOG performance status categories should be included. Clinicians pointed out that this patient population is relatively small compared with other cancers. While melanoma is increasing in frequency, the target population is smaller and the duration of treatment (one year) is well defined. BRAF mutation is present in approximately 40-50% of the melanoma patient population.

Clinicians indicated that the risk of metastatic relapse for stage IIC patients is higher than for stage IIIA. Therefore, they suggest that some indication drift to include stage IIC patients (if otherwise eligible) could be expected.

5.3 Relevance to Clinical Practice

Clinicians submitting input agreed that dabrafenib-trametinib should be used in patients with stage IIIA-C as in the reference clinical trial. They considered the therapy very important as stage IV disease is still a palliative situation; avoiding progression to this stage would be a highly valuable endpoint. They suggest that oncologists should also consider the treatment for stage IIC

[i] After clinician input was received, the approved Health Canada indication included a wording revision (underlined text was added): 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.

patients given the relatively high risk of relapse. From a clinical perspective, benefits include a dramatic lowering in the risk of metastatic relapse at two and three years, seemingly holding up over time, whereas harms include short-term toxicities while on treatment (pyrexia, fatigue, rash, GI side effects, and laboratory abnormalities). Oncologists should now be adept at monitoring for and treating these side effects (with supportive medications, drug holidays, rechallenging, and dose modifications) based on their experience using these drugs for metastatic disease patients.

According to the clinicians submitting input, the only current option is high dose IFN, a treatment with minimal clinical benefit, poor tolerability and several adverse events. The dabrafenib-trametinib combination is far superior to IFN in their opinion — it is better tolerated and has a meaningful clinical benefit. As for adjuvant nivolumab, clinicians indicated that there is no head-to-head comparative data comparing it to oral dabrafenib-trametinib for BRAF V600 mutation positive patients, although the latter combination demonstrates the best risk reduction and the least risk of long-term toxicities.

Clinicians believe that all patients identified in the trial should be eligible to receive this drug. The only significant contraindications mentioned by the clinicians would be hypersensitivity reaction or severe adverse events.

5.4 Sequencing and Priority of Treatments with Dabrafenib and Trametinib

The oncologists providing input indicated that the question of sequencing is not really applicable to this adjuvant indication. Patients who relapse with metastases despite treatment would potentially be candidates for systemic drug therapy for metastatic disease with oral targeted drugs (if V600 mutations are present) if recurring after a lengthy treatment-free interval (> 12 months), or pembrolizumab, or combination immunotherapy with ipilimumab (or newer CTLA4 variants) and nivolumab.

In terms of priority, clinicians surmise that the new drugs will replace both high dose IFN and observation alone (in patients who are eligible). The impact on metastatic treatment cannot be clearly ascertained for patients who have received the same or similar agents in the adjuvant setting. Determining the absolute impact will require long-term follow-up.

5.5 Companion Diagnostic Testing

The oncologists providing input noted that BRAF testing (V600E and V600K mutations) will be required on all high-risk patients (not just metastatic patients) and cautioned that this is not uniformly available. They also mentioned that a relatively modest volume of imaging and blood tests may be further required for patients on treatment.

5.6 Additional Information

Clinicians maintained that the need for adjuvant treatments is urgent. Practice-changing “level I evidence” supporting this treatment has been available for about one year and current patients are not able to access it.

5.7 Implementation Questions

5.7.1 In regards to the previous question on sequencing and priority, please include considerations

for use of BRAF/MEK inhibitors, single agent PD-1 immunotherapy (nivolumab or pembrolizumab), and combination immunotherapy (nivolumab + ipilimumab) for both clinical scenarios of relapse during or after adjuvant dabrafenib trametinib.

According to responding clinicians, physician choice depends on the patient's ability to tolerate therapy and their BRAF status. If a BRAF mutation is identified, then the choice is dependent on clinical evidence to determine what the patient will tolerate and respond to best. Clinicians mentioned that a typical patient who has progressed on dabrafenib-trametinib would receive nivolumab plus ipilimumab (if appropriate – approximately 30% of patients) or single-agent pembrolizumab or nivolumab (70% of patients). The choice will depend on the time after exposure to dabrafenib-trametinib. Some patients progress on dabrafenib-trametinib with metastatic disease within weeks of stopping the drug (perhaps due to toxicity), and then have had their disease controlled upon restarting the drugs. This palliative benefit should not be withheld according to the clinician's input. Clinicians may be more inclined to give first-line immunotherapy for a patient who progressed less than 6 months after adjuvant dabrafenib-trametinib, but there should still be an option to provide patients with the targeted therapy option for second-line.

5.7.2 For those patients who relapse with metastatic disease after completing adjuvant dabrafenib-trametinib, what time interval (i.e., relapse-free period) after completion of adjuvant therapy and the start of a metastatic option would be reasonable?

Clinicians providing input suggest between six and 12 months unless immunotherapy is not an option (e.g., solid organ transplant), and then no restriction should be given. They note that this group of patients includes, 1) patients who developed resistance of disease on therapy, and 2) patients with undiagnosed metastatic disease that was suppressed on therapy that then grew off therapy. Further studies will be needed to clarify the time interval.

5.7.3 Nivolumab for the treatment of adjuvant melanoma is currently under review at pCODR, and may become an available treatment option in the future. In what clinical scenarios would nivolumab or dabrafenib-trametinib be the preferred treatment for adjuvant melanoma with a BRAF V600 mutation? Please comment on the preference considering patient preference, efficacy, safety, and administration.

According to responding clinicians, BRAF mutation positive patients who rapidly progress would want dabrafenib-trametinib. If the patient cannot tolerate one of the therapies, then one would use the other. Compared to single agent nivolumab, the combination BRAF/MEK therapy would probably be better tolerated. Clinicians also noted that patients wanting oral drugs may prefer oral treatment as well. Clinicians would prefer to put patients that are somehow immunosuppressed on dabrafenib-trametinib as opposed to immunotherapy. The decision would also depend on history of autoimmune diseases and other comorbidities like heart disease (a consideration for BRAF/MEK therapy). Patient and physician choice in regards to tolerability of therapy and convenience come into play as well. According to oncologists responding to this question, the published data does not give a clear direction for which therapy to recommend to patients. They remarked that choice of metastatic treatment should not be used based on what was used in adjuvant treatment.

5.7.4 For patients that test negative for BRAF in stage III or earlier disease, are there situations where the test would be repeated once the patient develops metastatic disease (e.g., does the mutation status evolve over the natural history of melanoma and thus repeated samples are warranted)?

Clinicians noted that the status can change on occasion (or new mutations may develop) but testing is typically not repeated if initially positive, although retesting may be indicated for a

metastatic deposit when the primary melanoma was negative. The clinicians mentioned that there is a discrepancy between primary and metastatic results in about 10% of cases. There are no clear guidelines on when to repeat the test. However, since patients with a history of melanoma are at risk for second melanomas, a metastatic lesion could represent an unknown primary, so testing is sometimes requested.

Clinicians explained that some patients with multiple primaries may test negative on one primary, but the metastatic lesion might be from a different primary and thus test differently. The data surrounding this issue is evolving and different information may quickly become available.

6 SYSTEMACTIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) as adjuvant treatment compared to standard therapy (INF or observation with best supportive care) in BRAF-mutated melanoma patients with lymph node involvement who have undergone resection.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA) comparing dabrafenib in combination with trametinib to relevant comparators in patients with high-risk (IIB-C and IIIA-C) melanoma with BRAF mutation positive status.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Selection Criteria.

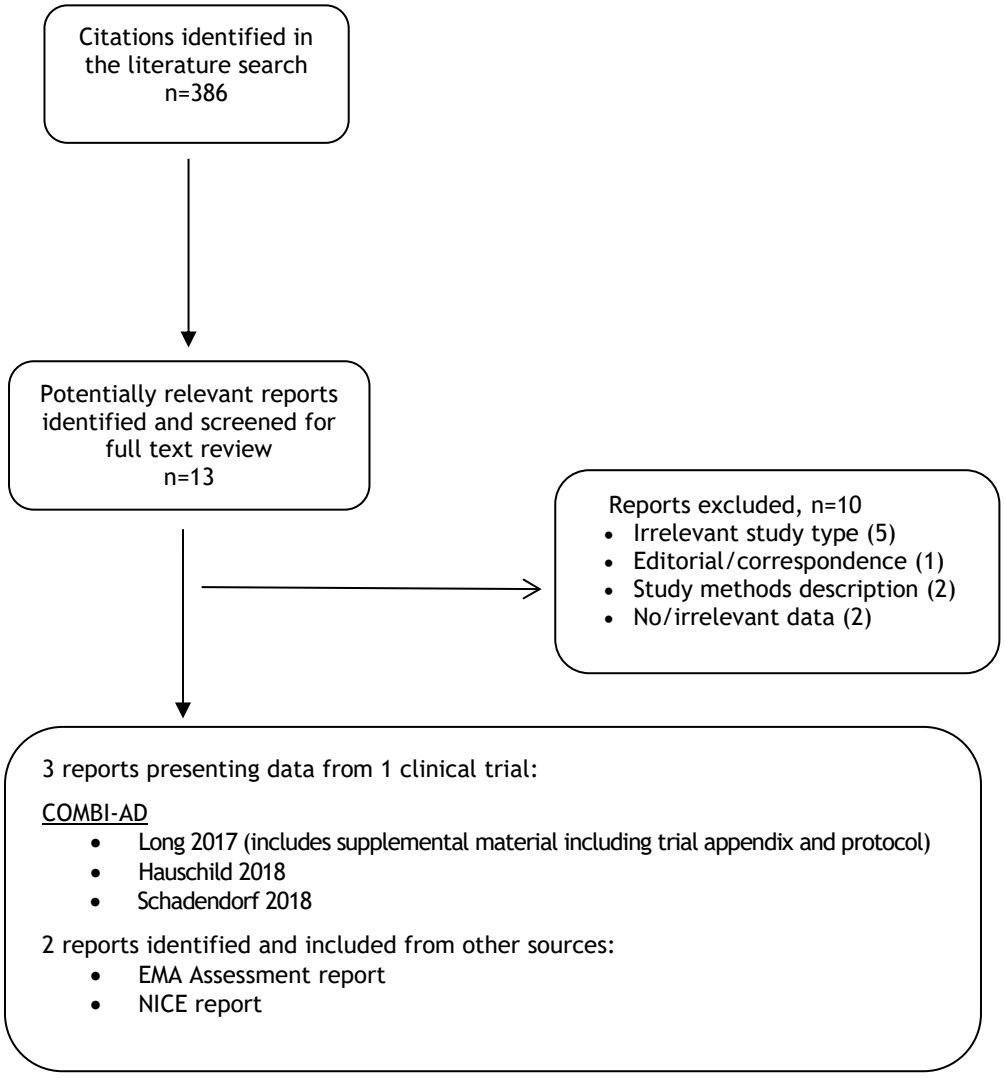
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes**
Published and unpublished RCTs. In the absence of RCTs, fully published non-comparative clinical trials investigating efficacy and safety of dabrafenib and trametinib combination therapy should be included.	Patients with melanoma with lymph node involvement and BRAF V600 mutations who have undergone resection.	Dabrafenib in combination with trametinib in the adjuvant setting	All appropriate adjuvant treatment regimens, including but not limited to: • Dabrafenib • Trametinib • IFN-a • Pegylated IFN-a • Observation with BSC • Encorafenib +/- binimetinib • Nivolumab • Pembrolizumab • Ipilimumab • Vemurafenib +/- cobimetinib • Conventional chemotherapy	Efficacy • **RFS** • **OS** • DMFS • FFR • **HRQOL** Safety • AEs • TRAEs • SAEs • DAEs
Abbreviations: RCT(s) = randomized controlled trial(s); IFN-a = IFN-alpha; BSC = best supportive care; RFS = relapse-free survival; OS = overall survival; DMFS = distant metastasis-free survival; FFR = freedom from relapse; HRQOL = health-related quality of life; AE = adverse events; TRAE = treatment-related adverse events; SAE = serious adverse events; DAE = discontinuation due to adverse events. *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). **Bold outcomes were identified as important by patients' input.				

6.3 Results

6.3.1 Literature Search Results

Of the 386 potentially relevant reports identified, one trial with data presented in three reports was included in the pCODR systematic review.[1,3,4] A total of 10 reports reviewed in full text were excluded; the reasons for their exclusion included irrelevant study type,[28-30] editorial/correspondence,[31] a description of study methods,[32,33] or no/irrelevant data.[34,35] Two additional reports [2,36] identified from other sources were also included as they reported data/information on the included COMBI-AD trial (Figure 1).

Figure 1: PRISMA Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to the COMBI-AD trial were also obtained through requests to the Submitter by pCODR[5]

6.3.2 Summary of Included Studies

One clinical trial was identified that met the eligibility criteria and is included in this systematic review (refer to Table 4). COMBI-AD is a randomized, international, multicentre phase III trial that evaluated the efficacy and safety of the combination of dabrafenib and trametinib versus placebo in the adjuvant treatment of adult (≥ 18 years) patients with BRAF V600E or V600K mutated melanoma with lymph node involvement and who had undergone resection. Quality characteristics of the COMBI-AD trial are reported in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
COMBI-AD[1] NCT01682083 BRF115532 Randomized, double-blind, placebo-controlled, Phase III study 870 randomized; 867 received study treatment (dabrafenib plus trametinib n=435; placebo n=432) 169 sites in 26 countries from Europe, North and South America, Asia and Oceania Patient Enrolment Dates: January 2013 to December 2014 Data cut-off dates: Primary analysis - June 30, 2017 Updated analysis - April 30, 2018 for RFS and DMFS[4] Estimated study completion date: November 30, 2030 Funding: Novartis Note: the trial was initiated by GlaxoSmithKline in 2013; however, dabrafenib and trametinib were acquired by Novartis in March 2015, resulting in study sponsorship being transferred to Novartis.	<u>Key Inclusion Criteria:</u> • Age ≥18 years or older • Completely resected histologically confirmed high-risk stage IIIa (LN metastasis more than 1 mm), IIIb or IIIc cutaneous melanoma • V600E/K mutation positive determined by a central laboratory • Patients presenting with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma are eligible • Surgically rendered free of disease no more than 12 weeks before randomization • Recovered from definitive surgery (e.g. no uncontrolled wound infections or indwelling drains) • ECOG performance status of 0-1 • Adequate hematologic, hepatic, renal and cardiac function* <u>Key Exclusion Criteria:</u> • Known mucosal or ocular melanoma or the presence of unresectable in-transit metastases • Evidence of distant metastatic disease • Prior systemic anti-cancer treatment and radiotherapy for melanoma; prior surgery for melanoma was allowed • History of another malignancy or concurrent malignancy including prior malignant melanoma;	<u>Intervention:</u> Dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 12 months <u>Comparator:</u> Matching placebo	<u>Primary:</u> RFS by investigator assessment <u>Secondary:</u> OS DMFS FFR Safety <u>Exploratory:</u> HRQOL

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	exceptions to this include: patients who have been disease-free for 5 years or patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma, for example, cervical cancer in situ, atypical melanocytic hyperplasia or melanoma in situ, multiple primary melanomas, or other malignancies for which the patient has been disease free for > 5 years • History or current evidence of cardiovascular risk • History or current evidence of retinal vein occlusion or central serous retinopathy		

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LN = lymph node; RFS = relapse free survival; OS = overall survival; DMFS=distant metastasis-free survival; FFR = freedom from relapse; HRQOL = health-related quality of life.

* Adequate organ function includes: hematologic - absolute neutrophil count ≥1.2 × 10^9/L, hemoglobin ≥9 g/dL, platelet count ≥100 × 10^9/L, prothrombin time/international normalized ratio and partial thromboplastin time ≤1.5 × upper limit of normal; hepatic - albumin ≥2.5 g/dL, total bilirubin ≤1.5 × upper limit of normal, aspartate aminotransferase and alanine aminotransferase ≤2.5 × upper limit of normal; renal - ≥1 of the following: serum creatinine ≤1.5 mg/dL or creatinine clearance ≥50 mL/min; and cardiac - left ventricular ejection fraction ≥ lower limit of normal by echocardiography.

Table 5: Select quality characteristics of the COMBI-AD trial.[1]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
COMBI-AD	Dabrafenib + Trametinib vs. placebo	RFS	To enable the observation of 467 total events, an estimated total of 852 patients (426 in each arm) were to be enrolled. However, due to a lower than projected rate of RFS events, the protocol was amended (version 7) in May 2017, revising the primary RFS analysis from being an event driven outcome to a follow-up driven outcome. This analysis was performed at the pre-defined cut-off date of June 30, 2017, which corresponded to a median of 3.3 years of patient follow-up and approximately 410 events. This yielded more than 90% power to detect the original target HR of 0.71 (corresponding to a median RFS of 15 months and 21 months in the placebo and combination groups, respectively). The final OS analysis will be performed when approximately 597 deaths are observed, which will provide 80% power to detect a HR of 0.793 (corresponding to median OS times of 48 and 60.5 months in the placebo and combination groups, respectively).	Dabrafenib + Trametinib (435) Placebo (432)	IVRS	Yes	Double -blind	Yes	**No**	No	Yes

Abbreviations: RFS = relapse-free survival; HR = hazard ratio; IVRS = interactive voice system; OS = overall survival; vs. = versus; ITT = intention to treat.

a) Trials

COMBI-AD[1] is a randomized, double-blind, placebo-controlled, multicentre phase III international trial, globally distributed across 26 countries, that evaluates whether the combination of dabrafenib and trametinib improves outcomes in patients with stage III melanoma with BRAF V600E or V600K mutations after complete surgical resection. The trial design was developed jointly by GlaxoSmithKline and the academic authors and was funded by GlaxoSmithKline and Novartis. Data were collected by investigators at individual study sites and were subsequently transferred to and analyzed by the Sponsor (GlaxoSmithKline and Novartis after March 2, 2015). The vast majority of the authors declared having a consulting or advisory role with the manufacturer.

The key eligibility criteria used in the trial are summarized in Table 4. Eligible patients were randomized in a 1:1 ratio to receive oral dabrafenib plus trametinib (combination therapy, n=438) or two matched placebo tablets (n=432). As the trial was conducted prior to the release of the American Joint Committee on Cancer (AJCC) 8th edition staging system, patient classification and stratification were based on the AJCC 7th edition system, which included only three prognostic stage III groupings (IIIA to IIIC) in comparison to the four groupings (IIIA to IIID) that are included in the 8th edition. Patients were also stratified according to their 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.

Outcomes

The primary efficacy outcome of the COMBI-AD trial was RFS, which was defined as the time from randomization to disease recurrence or death from any cause. The types of recurrence considered an event included loco-regional, distant metastases, and new primary melanoma. Malignancies (including any new primary cancer from another histology, non-melanoma skin cancers including squamous cell carcinoma, or keratoacanthoma or basal cell carcinoma), excluding new primary melanomas, were not considered as melanoma recurrence events. Instead, these treatment-emergent malignancies, with the exception of basal cell carcinoma, were required to be reported as a SAE. Tumour tissue samples of any new primary cancers (including melanoma) were submitted for biomarker characterization. The analysis of RFS was based on the ITT population.[2] Any death occurring without prior documentation of tumour recurrence was considered an event (and not censored in the statistical analysis).

The key secondary efficacy outcome was OS, defined as the interval from randomization to the date of death, irrespective of the cause of death. Other secondary outcomes included DMFS, defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurred first; and FFR, defined as the interval from randomization to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death.

Patient reported health outcomes were assessed at baseline and at various time points throughout the trial. Changes in HRQOL from baseline were assessed and compared between treatment groups using the EuroQol-5D-3L (EQ-5D-3L) questionnaire. Safety was assessed by monitoring and recording potential AEs of the treatment using the CTCAE version 4.0 at each study visit.

Disease Assessment

BRAF V600 mutation status was confirmed in the primary tumour or lymph node tissue by a central reference laboratory using the bioMérieux BRAF THxID IUO assay. Patients underwent imaging every three months for the first 24 months, and every six months after month 24. Follow-up for disease recurrence continued until the first recurrence was observed, and thereafter patients were followed for survival; patients remained on study for follow-up assessments every three months until month 24, and then every 6 months thereafter. Follow-up assessments included updates on anti-cancer treatments received and responses to those treatments, as well as OS and HRQOL. Patients who had not died but were no longer being followed for disease recurrence or survival were considered to have discontinued from the study. All disease-recurrence analyses were based on investigator assessment.[1]

Radiological efficacy assessments were primarily performed by contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis (magnetic resonance imaging [MRI] was also acceptable if scanning sequences were optimized for disease type). A contrast-enhanced MRI scan of the brain (contrast- enhanced CT was allowed only if MRI was contraindicated or unavailable) was required for all patients at baseline, and subsequent scans were performed only as clinically indicated. Whenever possible, the same diagnostic method, including use of contrast when applicable, was used throughout the study. For cases of disease recurrence, patients were managed per institutional practice.[1]

Statistical Data Analyses

During the trial, the study protocol was amended (Amendment 07) to allow for the primary analysis of RFS to be performed using a data cut-off date at approximately 2.5 years after the last patient randomized received their first dose of study drug which also corresponds to a projected median follow up of 3.3 years for all patients. The amendment also included an additional interim OS analysis (see below for further details).[1]

The cut-off date for the primary analysis of efficacy (RFS), safety and HRQOL was June 30, 2017.[4] An additional data cut-off date of April 30, 2018 provided an extra 10 months of follow-up for RFS and its subgroup analyses, as well as for DMFS, although these were not pre-planned analyses (post-hoc). All analyses, with the exception of safety outcomes, were assessed in the intention-to-treat (ITT) population. Patients with no event by the time of the analysis cut-off date were censored at the date of the last efficacy assessment (i.e., either radiological or non-radiological). Patients lost to follow-up, prior to disease recurrence were censored.[2] Patients who started subsequent anti-cancer therapy prior to disease recurrence were censored at the date of last efficacy assessment (either radiological or non-radiological) before the initiation of subsequent anti-cancer therapy. Safety analyses included all patients who had received at least one dose of a trial drug. The Kaplan–Meier method was used to estimate RFS, OS, DMFS and FFR and a stratified log-rank test was used to compare the two trial groups. HRs with corresponding 95% CIs were calculated with the use of the Pike estimator for all time-to-event outcomes.[1]

To assess homogeneity and consistency of the treatment effect across pre-defined patient subsets, subgroup analyses of the primary outcome were performed. Assessment of RFS in subgroups on the basis of mutation status, baseline disease

stage (per AJCC 7th edition), gender, age at screening, race, geographical region, and nodal tumour burden were pre-specified exploratory analyses at the June 30, 2017 data cut-off date. Evaluation of RFS on the basis of AJCC 8th edition disease stage at baseline and tumour ulceration status was performed as post-hoc subgroup analyses at the April 30, 2018 data cut-off date.

OS assessment was based on a three-look Lan-DeMets group sequential design with two interim analyses and a final analysis. The first planned interim analysis of OS was performed at the time of the primary analysis of RFS. A protocol amendment (#7) added an additional OS interim analysis to be performed when approximately 299 deaths have occurred (50% information fraction of the originally targeted 597 deaths, projected to occur in December 2019) in order to provide early efficacy information on survival. The rationale for the additional interim analysis was the low event rate. The thresholds for statistical significance were determined based on the observed information fraction and pre-defined O'Brien-Fleming type of stopping boundary. In order to control the overall type-I error rate for multiple testing of outcomes, a hierarchical approach was undertaken. As such, OS was to be formally statistically tested only if RFS, the primary efficacy outcome, was statistically significant.

HRQOL assessed by the EQ-5D-3L (utility score and visual analogue scale [VAS]) and was an exploratory outcome in the COMBI-AD trial. The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. The EQ VAS records the respondent's self-rated health on a vertical VAS where outcomes are labelled 'best imaginable health state' and 'worst imaginable health state'. A mixed-model, repeated-measures analysis was used to assess differences in mean scores.[3]

b) Populations

There were a total of 870 patients, ≥18 years of age, who had undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (according to the criteria of the AJCC, seventh edition) with BRAF V600E or V600K mutations randomized into the study. Patients with known mucosal or ocular melanoma or the presence of unresectable in-transit metastases were excluded. Overall, baseline characteristics appeared well balanced between the groups (Table 6); slight differences were observed for disease stage and in-transit metastases. More patients in the dabrafenib and trametinib group had either stage IIIA or IIIC disease, while more patients in the placebo group had stage IIIB disease. There was a 4% difference between the groups in the proportion of patients with in-transit metastases, with more patients in the dabrafenib and trametinib group having clinically evident cutaneous or subcutaneous metastases identified at a distance of more than 2 cm from the primary melanoma in the region between the primary melanoma and the first echelon of regional lymph nodes.

The median age was 50 years in the dabrafenib and trametinib treatment group and 51 years in the placebo group. The majority of patients were males (56% in dabrafenib plus trametinib and 55% in placebo),[37] had an ECOG status of 0 (92% in the dabrafenib plus trametinib and 90% in placebo), and BRAF V600E mutations (91% of patients in each group). All trial patients had undergone completion lymphadenectomy with no clinical or radiographic evidence of residual regional

node disease. Most patients had stage IIIB or IIIC disease and nodal involvement of one positive node (dabrafenib plus trametinib 40%; placebo 42%). Micro and macro-metastatic disease was observed in similar proportions in both treatment groups and tumour ulceration, which is an established adverse prognostic factor, was present in 41% of patients in both treatment groups. Two to three positive nodes were seen in 36% and 35% of patients in the dabrafenib plus trametinib and placebo groups, respectively. A total of 17% of all patients had four or greater positive nodes.

Table 6: Baseline characteristics of included patients in the COMBI-AD trial.

Characteristic	Dabrafenib plus Trametinib (N=438)	Placebo (N=432)
Median age (range) — yr	50 (18–89)	51 (20–85)
Sex — no. (%)		
Male	195 (45)	193 (45)
Female	243 (55)	239 (55)
BRAF mutation status — no. (%)		
V600E	397 (91)	395 (91)
V600K†	41 (9)	37 (9)
ECOG performance status — no. (%)		
0	402 (92)	390 (90)
1	33 (8)	41 (9)
Unknown	3 (1)	1 (<1)
Disease stage — no. (%)		
IIIA	83 (19)	71 (16)
IIIB	169 (39)	187 (43)
IIIC	181 (41)	166 (38)
III unspecified	5 (1)	8 (2)
No. of positive lymph nodes — no. (%)		
1	177 (40)	183 (42)
2 or 3	158 (36)	150 (35)
≥4	73 (17)	72 (17)
Unknown	30 (7)	27 (6)
Type of lymph-node involvement — no. (%)		
Microscopic	152 (35)	157 (36)
Macroscopic	158 (36)	161 (37)
Unknown	128 (29)	114 (26)
Primary-tumor ulceration — no. (%)		
Yes	179 (41)	177 (41)
No	253 (58)	249 (58)
Unknown	6 (1)	6 (1)
In-transit metastases — no. (%)‡		
Yes	51 (12)	36 (8)
No	387 (88)	395 (91)
Unknown	0	1 (<1)

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group.
† One patient who had both a *BRAF* V600E mutation and a *BRAF* V600K mutation is included in the V600K subgroup.
‡ In-transit metastases are clinically evident cutaneous or subcutaneous metastases identified at a distance of more than 2 cm from the primary melanoma in the region between the primary melanoma and the first echelon of regional lymph nodes.

Source: From the New England Journal of Medicine, Long GV et al., Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma, 377, 1813-23. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Note: An official errata is pending for the Long et. al. (NEJM 2017) publication due to reported reversed percentages for gender.

c) Interventions

Patients were randomized to receive either oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily or two matched placebo tablets. Matching placebo capsules/tablets contained the same inactive ingredients and film coatings as the dabrafenib and trametinib study treatment. Patients in both groups were to continue receiving blinded treatment for 12 months in the absence of disease recurrence, unacceptable toxic effects, withdrawal of consent, or death. Dose modifications or interruptions were permitted during the trial for non-hematologic adverse events of grade 2 or higher that could not be managed with routine supportive care or for patients who were unable to tolerate the protocol-specified dosing scheme. Concomitant medications, such as warfarin and proton pump inhibitors, were permitted but with caution.[1]

If a dose adjustment was required, doses of both treatments were reduced simultaneously, with the exception of dose reductions for pyrexia, hypertension, or valvular toxicity (reduce and/or interrupt dabrafenib dose only); and dose reductions for visual changes (including retinal vein occlusion and central serous retinopathy), left ventricular ejection fraction reduction, rash, or pneumonitis (reduce and/or interrupt trametinib dose only). For dabrafenib, the dose was reduced to 100 mg on first reduction and 75 mg on second reduction; however, the dose was not reduced to <75 mg. Trametinib was reduced to 1.5 mg on first reduction and 1 mg on second reduction; however, the dose was not reduced to <1 mg.[1]

The median daily dose of dabrafenib (283.9 mg; range, 88.5 to 300.0) and trametinib (2.0 mg; range, 0.6 to 2.0) was similar to the intended daily dose (300 mg and 2 mg, respectively). The median duration of exposure to trial drug was 11.0 months for both dabrafenib and trametinib and 10.0 months for both placebo tablets.[1]

Subsequent Therapy

A summary of post-treatment anti-cancer therapies is presented in Table 7, based on the safety analysis set, which includes all patients who received at least one dose of randomized treatment. A higher proportion of patients in the placebo group (42%) compared to the treatment group (28%) received post-treatment systemic anti-cancer therapy, which is primarily due to a higher number of disease relapses in the placebo group. Median time from disease recurrence to start of subsequent anti-cancer therapy was similar between the two groups (7.1 weeks for dabrafenib plus trametinib and 7.3 weeks for placebo). The most common systemic therapies received after recurrence were small-molecule targeted therapy (in 14% of the patients receiving dabrafenib plus trametinib and 32% receiving placebo), immunotherapy against PD-1 or PDL-1 (16% in each group), and anti–CTLA-4 immunotherapy (12% and 16%, respectively).

d) Patient Disposition

At the time of the updated cut-off date of April 30, 2018, all patients (870 randomized - 438 patients in the dabrafenib plus trametinib group and 432 patients in the placebo group) were off treatment and in the follow-up phase.[4] A total of three patients, all in the dabrafenib plus trametinib group, did not receive

treatment because consent was withdrawn. The median patient follow-up was 44 months in the combination group and 42 months in the placebo group.

In the dabrafenib plus trametinib group, 272 patients (63%) completed the scheduled dabrafenib treatment and 277 (64%) completed the scheduled trametinib treatment. In the placebo group, 227 (53%) completed all scheduled matched placebo treatments (Table 8). Accordingly, premature study treatment discontinuations were higher in the placebo group (47% for both matching placebos) compared to the dabrafenib plus trametinib group (37% and 36%, respectively). Based on data from the first data cut-off of June 30, 2017, the main reason for treatment discontinuation was disease recurrence in the placebo group (41%) compared to the dabrafenib plus trametinib group (5%). However, the proportion of patients who discontinued due to AEs was greater in the dabrafenib plus trametinib group compared to placebo; discontinuation due to AEs was 25% for dabrafenib and 24% for trametinib, versus 3% in the placebo group. Discontinuation due to patient/proxy decision was 6% in the dabrafenib plus trametinib group and 3% in the placebo group.[1,4]

Protocol deviations were observed in both treatment groups. A total of 407 patients (93%) and 393 patients (91%) in the dabrafenib plus trametinib group and placebo group, respectively, had protocol deviations.[2] In the combination group, most of the protocol deviations were pertaining to assessments and/or procedures (385 patients; 88%) and visit windows (267 patients; 61%).[2] Deviations with respect to eligibility criteria were reported in 53 patients (12%).[5] In the placebo group, most of the protocol deviations also pertained to assessments and/or procedures (356 patients; 82%) and visit windows (258 patients; 60%).[2] Deviations with respect to eligibility criteria were reported in 49 patients (11%).[2]

Table 7: Subsequent therapy after melanoma recurrence (safety population; June 30th, 2017 data cut-off date).

Type of Therapy	Dabrafenib plus Trametinib (N=435)	Placebo (N=432)
	no. (%)	
Any anticancer therapy	148 (34)	217 (50)
Surgery	78 (18)	131 (30)
Radiotherapy	60 (14)	72 (17)
Any systemic therapy†	120 (28)	183 (42)
Small-molecule targeted therapy	63 (14)	137 (32)
Any BRAF inhibitor	63 (14)	137 (32)
Dabrafenib	44 (10)	86 (20)
Vemurafenib	29 (7)	59 (14)
Encorafenib	0	16 (4)
Any MEK inhibitor	47 (11)	77 (18)
Trametinib	28 (6)	48 (11)
Cobimetinib	20 (5)	18 (4)
Binimetinib	2 (<1)	15 (3)
Immunotherapy	89 (20)	103 (24)
Anti–PD-1 or PD-L1	71 (16)	68 (16)
Anti–CTLA-4	53 (12)	68 (16)
Interferon	6 (1)	11 (3)
T-VEC	0	1 (<1)
Biologic therapy	1 (<1)	1 (<1)
Chemotherapy	20 (5)	23 (5)
Investigational treatment	6 (1)	19 (4)
Other systemic therapy	2 (<1)	0

* Percentages are based on the safety population rather than on the number of patients who had disease recurrence (163 who received combination therapy with dabrafenib plus trametinib and 247 who received placebo). Patients could have had more than one type of therapy. Data regarding therapy after recurrence were available only if such information was provided to the investigator by the time of the data cutoff and were not available for patients who withdrew from the trial or died shortly after recurrence. CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed death 1, PD-L1 programmed death ligand 1, and T-VEC talimogene laherparepvec.

† The median time from disease recurrence to the initiation of systemic therapy was 7.1 weeks (range, 0 to 136) in the combination-therapy group and 7.3 weeks (range, 0 to 78) in the placebo group.

Source: From the New England Journal of Medicine, Long GV et al., Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma, 377, 1813-23. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Table 8: Patient disposition in the COMBI-AD trial (April 30, 2018 data cut-off date).

Variable	Dabrafenib (n = 435)	Trametinib (n = 435)	Placebo to Match Dabrafenib (n = 432)	Placebo to Match Trametinib (n = 432)
Patients treated, No. (%)				
Treatment ongoing as of data cutoff	0	0	0	0
End of treatment	435 (100)	435 (100)	432 (100)	432 (100)
Treatment status, No. (%)				
Completed scheduled treatments	272 (63)	277 (64)	227 (53)	227 (53)
Prematurely discontinued treatment	163 (37)	158 (36)	205 (47)	205 (47)
Patient status, No. (%)				
Died	75 (17)	75 (17)	103 (24)	103 (24)
In follow-up	313 (71)	313 (71)	264 (61)	264 (61)
Withdrawn from study	50 (11)	50 (11)	65 (15)	65 (15)
Reason for study withdrawal, No. (%)				
Lost to follow-up	11 (3)	11 (3)	19 (4)	19 (4)
Investigator discretion	5 (1)	5 (1)	4 (< 1)	4 (< 1)
Withdrew consent	34 (8)	34 (8)	42 (10)	42 (10)

Source: Hauschild A et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant stage III melanoma. *J Clin Oncol*. 2018. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6286159/pdf/JCO.18.01219.pdf Used under Creative Commons license (CC BY-NC-ND 4.0) (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH doesn't own this work and permission should be sought from the copyright owner.[4]

e) Limitations/Sources of Bias

Overall, there were no major concerns with the conduct of the COMBI-AD trial. The randomization method, allocation concealment and sample size were adequate. The efficacy analysis was conducted according to the ITT principal, regardless of whether randomized treatment was administered. Furthermore, the study protocol was approved by institutional review boards or independent ethics committees at each study centre and the trial was conducted in accordance with Good Clinical Practice guidelines.

The following limitations and potential sources of bias of the COMBI-AD trial were noted by the pCODR Methods Team:

- The results of the subgroup analyses of RFS across the pre-defined patient subsets were consistent with those of the overall population; however, it should be noted that the trial was not powered to detect differences in treatment effect within patient subgroups, thus the interpretation of these results is challenging due to a lack of statistical power. Moreover, results interpreted as statistically significant (based on reported confidence intervals) should be viewed with some caution due to the small number of patients included in some subgroups, and the lack of adjustment for multiple comparisons.
- There was some imbalance between the two groups with respect to the types of therapy that were administered after recurrence which could have an effect on OS outcomes. This may affect the overarching findings, diminishing the benefits observed with dabrafenib and trametinib combination therapy.
- Although COMBI-AD was a double-blind study, disease assessment included clinical examination and imaging. While it is common for adjuvant therapy RCTs to assign such imaging exams to an Independent Review Committee masked to treatment assignments, it appears as though these were investigator assessed. The extent to which the investigator's assessment may have influenced the results and reporting of the trial is unknown.

- The differences in AEs leading to dose interruptions, reductions and discontinuations observed between treatment groups had the potential to unmask patients in the dabrafenib plus trametinib group. The extent to which spontaneous unblinding of patients and investigators occurred is unknown, but the possible influence on disease assessment and patient-reported outcomes should be considered.
- Selection bias over time should be considered when interpreting results of the HRQOL assessment, as the long-term responders tend to be healthier patients.
- The sponsors GlaxoSmithKline and Novartis funded the trial and were involved in all aspects of its conduct including design of the study, data collection, performing data analysis, and interpreting results. The extent to which the Sponsor's involvement may have influenced the results and reporting of the trial is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

PRIMARY OUTCOME
Relapse-free Survival (RFS)

As of the primary analysis data cut-off date of June 30, 2017, disease recurrence had been reported in 37% (163/438) of patients in the dabrafenib plus trametinib group and in 57% (247/432) of patients in the placebo group. Types of recurrence considered as an event were loco-regional, distant metastases, and second primary melanoma.[1] The combination of dabrafenib and trametinib demonstrated superiority over placebo for the primary outcome of investigator-assessed RFS with an estimated HR of 0.47 (95% 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). Investigator-assessed 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 (Table 9). The majority of RFS events in both groups were distant recurrences (22% in the combination therapy group and 29% in the placebo group). More patients in the placebo group had loco-regional recurrences (25%) compared to the dabrafenib plus trametinib group (12%).

Three- and four-year RFS rates were 59% (95% CI, 55% to 64%) and 54% (95% CI, 49% to 59%) in the dabrafenib plus trametinib group and 40% (95% CI, 35% to 45%) and 38% (95% CI, 34% to 44%) in the placebo group, respectively. Few RFS events occurred after three years of follow-up in both treatment groups and the Kaplan-Meier estimates of RFS rates from year one through to year four consistently favoured the combination of dabrafenib plus trametinib (Table 10).

The updated analysis of RFS performed at the April 30, 2018 data cut-off date resulted in a median patient follow-up of 44 months in the dabrafenib plus trametinib group and 42 months in the placebo group. The estimated HR was 0.49 (95% CI 0.40 to 0.59), which is consistent with the primary analysis results.

Table 9: Summary of RFS results in the COMBI-AD trial.

	Primary analysis (data cut off 30-Jun-2017)		Updated Analysis (data cut off 30-Apr-2018)	
Category	Dabrafenib + Trametinib N=438	Placebo N=432	Dabrafenib + Trametinib N=438	Placebo N=432
Number of patients				
Relapsed (event)	163 (37%)	247 (57%)	174 (40%)	253 (59%)
Died (event)	3 (<1%)	1 (<1%)	3 (<1%)*	1 (<1%)*
Censored, follow-up ended#	43 (10%)	35 (8%)	45 (10%)	39 (9%)
Censored, follow-up ongoing#	229 (52%)	149 (34%)	216 (49%)	139 (32%)
Percentiles (95% CI) (months)				
25th percentile	17.9 (16.6, 21.4)	5.3 (3.3, 5.6)	17.9 (16.6, 21.4)	5.3 (3.3, 5.6)
Median	NE (44.5, NE)	16.6 (12.7, 22.1)	NE (46.9, NE)	16.6 (12.7, 22.1)
75th percentile	NE (NE, NE)	NE (NE, NE)	NE (NE , NE)	57.9 (57.9, NE)
Hazard ratio (95% CI) vs. placebo	0.47 (0.39, 0.58)		0.49 (0.40, 0.59)	

Hazard ratio is obtained from the stratified Pike estimator. Hazard Ratio is model adjusted for randomized strata: Disease Stage and BRAF mutation status.
NE: Not estimable.
* Includes 2 subjects whose deaths secondary to melanoma before documented disease recurrence.
# Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from study by the time of data cut-off. Patients censored with follow-up ended are the remaining censored patients

Source: Reproduced from: European Medicines Agency. Assessment report: Mekinist (trametinib) and Tafinlar (dabrafenib). (European public assessment report); 2018. [Table 16].[2]

Subgroup Analyses of RFS

All subgroup analyses showed HRs <1 in favour of the combination treatment group, including for known prognostic factors such as disease stage, nodal status and ulceration according to lymph node involvement. The subgroup analysis results for the primary analysis data cut-off date (June 30, 2017) are presented in a forest plot in Figure 2.

Updated subgroup analyses from the April 30, 2018 data cut-off also showed a reduction in the risk of relapse or death in patients with baseline micrometastases (HR=0.49; 95% CI, 0.34 to 0.70) compared with treatment with placebo. Similar results were seen for patients with baseline macrometastases (HR=0.43; 95% CI, 0.31 to 0.58). HRs for subgroups based on the number of nodal metastases (one, two-three, or four or greater nodal metastases) ranged from 0.40 to 0.53, consistently showing a benefit for the combination therapy over placebo. Across all baseline factors, consistent benefit favouring dabrafenib plus trametinib versus placebo was observed.

Multivariate Cox Regression

To better estimate the effects of prognostic characteristics on RFS and their impact on the treatment effect, a pre-planned stratified multivariate Cox model was fitted based on data from the June 30th, 2017 data cut-off date. Prognostic characteristics of gender (male, female), tumour staging and ulceration, nodal stage, presence or absence of in-transit disease, and melanoma subtype (superficial spreading, nodular and other) were included in

the model for RFS as covariates. The HR for treatment effect after adjusting for these covariates was 0.43 (95% CI, 0.35 to 0.53).[2]

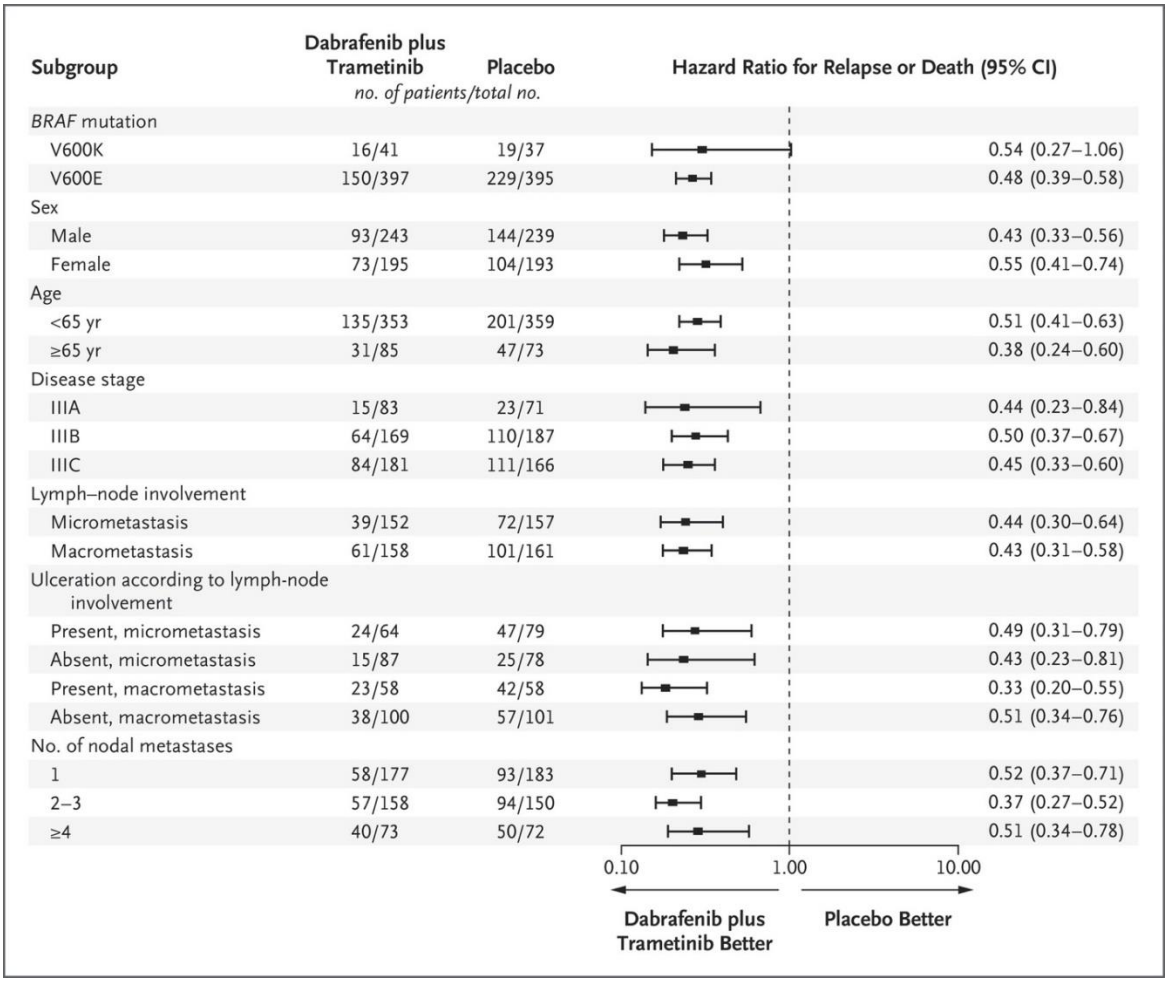


Figure 2: Forest plot of hazard ratios for RFS (relapse or death) according to pre-specified patient subgroups in the COMBI-AD trial. (Data cut-off date of June 30, 2017).

Source: From the New England Journal of Medicine, Long GV et al., Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma, 377, 1813-23. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Post-hoc Analyses of RFS Data

RFS on the basis of disease stage (AJCC 7th and 8th editions)

Disease stage on the basis of AJCC 7th edition—stage IIIA, IIIB, and IIIC—was a stratification factor in the trial and the basis for a subgroup analysis at the updated analysis (April 30th 2018 data cut-off date). On the basis of disease stage per AJCC 7th edition, dabrafenib plus trametinib improved RFS compared with placebo in stage IIIB and IIIC patient subgroups but not for IIIA patients (stage IIIA: HR=0.58; 95% CI, 0.32 to 1.06; stage IIIB: HR=0.49; 95% CI, 0.37 to 0.66; stage IIIC: HR=0.46; 95% CI, 0.34 to 0.61) (Table 10).[4] A combination of those patients at highest risk of disease relapse, staged IIIB and IIIC, demonstrated a 52% reduction in the risk of relapse or death that favoured the dabrafenib plus trametinib group (HR=0.48; 95% CI, 0.39 to 0.59). The post-hoc analysis of RFS by stage groupings according to AJCC 8th edition found dabrafenib plus trametinib improved RFS across all AJCC 8th edition stage subgroups compared with placebo (stage IIIA: HR=0.63; 95% CI, 0.26 to 1.56; stage IIIB: HR=0.48; 95% CI, 0.34 to 0.67; stage IIIC: HR=0.50; 95% CI, 0.38 to 0.64; stage IIID: HR=0.34; 95% CI, 0.14 to 0.79) (Table 10).[4]

RFS on the basis tumour ulceration[4]

RFS based on baseline tumour ulceration status, ulcerated and non-ulcerated, was assessed at the 30th April 2018 data cut-off date and showed a similar treatment benefit that favoured dabrafenib plus trametinib compared with placebo regardless of status,. The HR for RFS was 0.53 (95% CI, 0.41 to 0.69) in patients without baseline tumor ulceration and 0.45 (95% CI, 0.34 to 0.60) among patients with baseline tumor ulceration.[4]

Cure-Rate Model

A mixed Weibull cure-rate model was used to estimate long-term relapse–free fractions of patients in each treatment group. Cure-rate models represent a statistical modeling approach used to model time-to-event data in situations in which it is reasonable to assume that a subset of patients will remain event-free long-term and are therefore cured. Based on the 30th April 2018 data cut-off date, the estimated fraction of patients who may never experience relapse was 54% (95% CI, 49% to 59%) in the dabrafenib plus trametinib group compared with 37% (95% CI, 32% to 42%) in the placebo group.[4]

Table 10: RFS rates from the COMBI-AD trial by AJCC edition.

RFS Rate, %	AJCC 7th Edition			AJCC 8th Edition		
	Dabrafenib + Trametinib	Placebo	HR (95% CI)	Dabrafenib + Trametinib	Placebo	HR (95% CI)
Stage IIIA						
1-year	97	79	0.58 (0.32-1.06)	98	84	0.63 (0.26-1.56)
2-year	84	69		89	75	
3-year	80	62		84	71	
4-year	69	62		75	71	
Stage IIIB						
1-year	87	59	0.49 (0.37- 0.66)	89	58	0.48 (0.34-0.67)
2-year	66	44		70	47	
3-year	58	39		64	43	
4-year	56	37		60	40	
Stage IIIC						
1-year	86	42	0.46 (0.34 -0.61)	87	52	0.50 (0.38-0.64)
2-year	61	34		62	39	
3-year	51	31		52	33	
4-year	46	30		47	33	
Stage IIIB/C or IIID	**Stage IIIB/C**			**Stage IIID**		
1-year	86	51	0.48 (0.39-0.59)	76	24	0.34 (0.14-0.79)
2-year	63	39		52	18	
3-year	54	35		43	18	
4-year	51	34		43	18	

Abbreviations: CI – confidence interval; HR - hazard ratio; RFS – relapse-free survival.

Source: Hauschild 2018.[4]

Secondary Outcomes

Overall Survival (OS)

In keeping with the hierarchical statistical testing specified in the statistical analysis plan, since the primary outcome was statistically significant, the key secondary outcome of OS was formally tested with an interim OS analysis. As of the first data cut-off date, 30th June 2017, 153 deaths had occurred, 60 (14%) in the dabrafenib plus trametinib group and 93 (22%) in the placebo group.[1] 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 was melanoma (in 54 patients [12%] and 77 [18%], respectively). All other deaths (five in the combination therapy group and 15 in the placebo group), had an unknown or "other" cause listed; among these patients, melanoma had recurred before death in five patients in the combination therapy group and 15 in the placebo group.[1]

The estimated rate of OS was 97% at one year, 91% at two years, and 86% at three years in the dabrafenib plus trametinib group, as compared with rates of 94%, 83%, and 77%, respectively, in the placebo group. 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. Median OS was not reached in either group; however, the OS data are still immature due to the low number of events observed (i.e., 331 patients [76%] in the combination therapy group and 277 [64%] patients in the placebo arm were censored, with follow-up

ongoing).[2] The second interim OS analysis is planned when approximately 299 deaths have occurred (i.e., 50% of the targeted 597 events required for the final OS analysis).[1,2]

Distant metastases-free survival (DMFS)

Based on the primary analysis data cut-off of June 30, 2017, the estimated HR for DMFS was 0.51 (95% CI, 0.40 to 0.65), indicating a 49% reduction in the risk of developing distant metastases or death when patients were treated with dabrafenib plus trametinib.[1] The DMFS event analysis included 106 relapses and four deaths in the dabrafenib plus trametinib group and 150 relapses and two deaths in the placebo group. Due to the low event rates, the median DMFS was not reached in either treatment group.[2] The percentage of patients who were censored with no additional follow-up was similar between the dabrafenib plus trametinib group (23%) and the placebo group (30%). The Kaplan-Meier (KM) estimated DMFS rate at three years was 71% (95% CI, 66 to 76%) in dabrafenib plus trametinib arm and 57% (95% CI, 52 to 63%) in the placebo group.

The updated analysis of DMFS in the ITT population from the 30th April 2018 data cut-off yielded an HR of 0.53 (95% CI, 0.42 to 0.67).[4] The DMFS event analysis included 114 relapses and four deaths in the dabrafenib plus trametinib arm and 153 relapses and two deaths in the placebo group.[2] The KIM estimated DMFS rates at four years were 67% (95% CI, 62 to 72%) in the dabrafenib plus trametinib group and 56% (95% CI, 51 to 62%) in the placebo group.

Freedom from Relapse (FFR)

In the FFR analysis, at first the data cut-off of 30th June, 2017, local or distant recurrence or a new primary melanoma were counted as events, and patients who died of causes other than melanoma or treatment-related toxicity were censored. The FFR event analysis included a total of 412 disease or treatment-related relapses or deaths. Among these, 165 (38%) events (163 relapses, two deaths) occurred in the dabrafenib plus trametinib group, and 247 (57%) events (247 relapse, 0 deaths) occurred in the placebo group. The estimated HR for FFR was 0.47 (95% CI, 0.39 to 0.57). Median FFR was 16.6 (95% CI, 12.7 to 22.3) months in the placebo group and was not reached (44.5-NR) in the dabrafenib plus trametinib group. The percentage of patients who were censored with no additional follow-up available was similar between the dabrafenib plus trametinib (10%) and placebo (8%) groups. [1,2]

Table 11: Summary of key efficacy outcomes in the COMBI-AD trial.

Key Efficacy Outcomes	Dabrafenib +Trametinib (n=438)	Placebo (n=432)
Primary Outcome		
RFS (Data cut-off April 30, 2018)		
Number of events (%)	174 (40%)	253 (59%)
Local/regional relapse only	56 (13)	110 (25)
Distant relapse only	102 (23)	130 (30)
Concurrent local & distant relapse	9 (2)	6 (1)
Secondary primary melanoma	9 (2)	8 (2)
Died (event)	3 (<1)	1 (<1)
Median RFS (months)	NE (46.9-NE)	16.6 (12.7-22.1)
HR (95% CI)	0.49 (0.40-0.59)	
p-value (2-sided)	p=NR	
Kaplan-Meier estimate (95% CI)		
1-year RFS rate	0.88 (0.85-0.91)	0.56 (0.51-0.61)
2-year RFS rate	0.67 (0.62-0.72)	0.44 (0.40-0.49)
3-year RFS rate	0.59 (0.55-0.64)	0.40 (0.35-0.45)
4-year RFS rate	0.54 (0.49-0.59)	0.38 (0.34-0.44)
Key Secondary Outcomes		
OS (Data cut-off June 30, 2017)		
Number of events (%)	60 (14%)	93 (22%)
Median OS (months)	NE (NE-NE)	NE (NE-NE)
HR (95% CI)	0.57 (0.42-0.79)	
p-value (2-sided)	$p=6 \times 10^{-4}$	
Kaplan-Meier estimate (95% CI)		
1-year OS rate	0.97 (0.95-0.99)	0.94 (0.92-0.96)
2-year OS rate	0.91 (0.88-0.94)	0.83 (0.79-0.86)
3-year OS rate	0.86 (0.82-0.89)	0.77 (0.72-0.81)
DMFS (Data cut-off April 30, 2018)		
Number of events (%)	110 (25%)	152 (35%)
Median DMFS (months)	NE (NE-NE)	NE (41.2-NE)
HR (95% CI)	0.53 (0.42-0.67)	
p-value (2-sided)	p=NR	
Kaplan-Meier estimate (95% CI)		
1-year DMFS rate	0.91 (0.88-0.94)	0.70 (0.66-0.75)
2-year DMFS rate	0.77 (0.73-0.82)	0.60 (0.55-0.66)
3-year DMFS rate	0.71 (0.67-0.76)	0.57 (0.52-0.62)
4-year DMFS rate	0.67 (0.62-0.72)	0.56 (0.51-0.62)
FFR (Data cut-off June 30, 2017)		
Number of events (%)	165 (38%)	247 (57%)
Median time (months)	NE (44.5-NE)	16.6 (12.7-22.3)
HR (95% CI)	0.47 (0.39-0.57)	
p-value (2-sided)	p<0.001	
Kaplan-Meier estimate (95% CI)		
1-year FFR rate	0.88 (NR)	0.56 (NR)

Key Efficacy Outcomes	Dabrafenib +Trametinib (n=438)	Placebo (n=432)
2-year FFR rate	0.67 (NR)	0.44 (NR)
3-year FFR rate	0.59 (NR)	0.39 (NR)
Abbreviations: RFS = relapse free survival; OS = overall survival; DMFS=distant metastasis-free survival; FFR = freedom from relapse; HR = hazard ratio; CI = confidence interval; NE – not estimable; NR = not reported.		

Sources: Hauschild 2018,[4] Long 2017,[1] EMA report.[2]

Harms Outcomes

A total of 435 patients in the dabrafenib plus trametinib group and 432 patients in the placebo group were included in the safety analysis at the first data cut-off of June 30, 2017 (Table 12). A total of 97% and 88% of patients reported at least one AE in the combination therapy and placebo groups, respectively (Table 12). While the majority of AEs were of grade 1 or 2 in severity, grade 3 or 4 AEs occurred in 41% of patients in the dabrafenib plus trametinib group and 14% in the placebo group. The top three most common AEs that occurred in patients in the dabrafenib plus trametinib 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 occurred in 155 patients (36%) in the dabrafenib plus trametinib group in addition to one fatality due to pneumonia. There were 44 patients (10%) in the placebo group reporting SAEs. Among patients treated with dabrafenib plus trametinib, a new primary melanoma was reported in 11 patients (3%) and in 10 (2%) patients in the placebo group. Cutaneous squamous-cell carcinoma or keratoacanthoma was reported in 2% of patients in both treatment groups; basal-cell carcinoma was reported in 19 (4%) of the patients receiving dabrafenib plus trametinib and 14 (3%) of patients receiving placebo. Non-cutaneous cancers were reported in 10 (2%) and four patients (1%), respectively.[1]

A greater proportion of patients in the combination therapy group compared with placebo experienced AEs leading to dose interruptions (66% vs 15%), dose reductions (38% vs 3%) and discontinued study treatment (26% versus 3%).[1] In the combination therapy group, any dose interruptions of 14 days or more were observed in 53% of patients for dabrafenib and 45% of patients for trametinib, while in the placebo arm, most patients had dose interruptions of seven days or less (70% for the two placebos).[2] The median duration of dose interruptions was longer in the dabrafenib plus trametinib group (16.5 days and 13.0 days, respectively) than in the placebo group (4.0 days). A higher proportion of patients in the combination therapy group had three or more dose interruptions (52% dabrafenib, 28% trametinib) compared to placebo (21% and 9%, respectively).[2]

Dose escalations occurred at a similar frequency in the dabrafenib plus trametinib group (4% for both) and in the placebo group (2% and 5%, respectively). The most common reason for dose escalation was following resolution of AEs or due to patient non-compliance.

As of the updated data cut-off date of April 30, 2018, there were 178 deaths of which 75 (17%) were in the dabrafenib plus trametinib group and 103 (24%) were in the placebo group.[4]

Table 12: Adverse events (safety population; June 30th, 2017 data cut-off date).

Adverse Event	Dabrafenib plus Trametinib (N=435)		Placebo (N=432)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	422 (97)	180 (41)	380 (88)	61 (14)
Pyrexia	273 (63)	23 (5)	47 (11)	2 (<1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (<1)
Nausea	172 (40)	4 (1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhea	144 (33)	4 (1)	65 (15)	1 (<1)
Vomiting	122 (28)	4 (1)	43 (10)	0
Arthralgia	120 (28)	4 (1)	61 (14)	0
Rash	106 (24)	0	47 (11)	1 (<1)
Cough	73 (17)	0	33 (8)	0
Myalgia	70 (16)	1 (<1)	40 (9)	0
Elevated alanine aminotransferase	67 (15)	16 (4)	6 (1)	1 (<1)
Influenza-like illness	67 (15)	2 (<1)	29 (7)	0
Elevated aspartate aminotransferase	63 (14)	16 (4)	7 (2)	1 (<1)
Pain in limb	60 (14)	2 (<1)	38 (9)	0
Asthenia	58 (13)	2 (<1)	42 (10)	1 (<1)
Peripheral edema	58 (13)	1 (<1)	19 (4)	0
Dry skin	55 (13)	0	32 (7)	0
Dermatitis acneiform	54 (12)	2 (<1)	10 (2)	0
Constipation	51 (12)	0	27 (6)	0
Hypertension	49 (11)	25 (6)	35 (8)	8 (2)
Decreased appetite	48 (11)	2 (<1)	25 (6)	0
Erythema	48 (11)	0	14 (3)	0
Adverse event leading to dose interruption	289 (66)	NA	65 (15)	NA
Adverse event leading to dose reduction	167 (38)	NA	11 (3)	NA
Adverse event leading to discontinuation of study regimen	114 (26)	NA	12 (3)	NA

* Listed are adverse events that were reported in more than 10% of the patients who received combination therapy with dabrafenib plus trametinib. NA denotes not applicable.

Source: From the New England Journal of Medicine, Long GV et al., Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma, 377, 1813-23. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Exploratory Outcome

HRQOL - *EuroQol EQ-5D-3L*

In the adjuvant setting, where the disease has been completely resected, no disease-related symptoms are expected to occur. As such, HRQOL was assessed by the EQ-5D-3L (utility score and visual analogue scale [VAS]) every three months as an exploratory outcome in the COMBI-AD trial. A change from baseline of 0.08 points in the utility score or 7 points in the VAS, were considered minimal clinically

important differences. Completion rates for the EQ-5D-3L questionnaire, as a percentage of available patients at the time of assessment, were high through month 36. By month 36, the number of available patients with non-missing scores dropped to 186 (42%) in the dabrafenib plus trametinib group and 132 (31%) in the placebo group. Baseline utility and VAS scores were similar between the two treatment groups.[3]

Analysis of the ITT population from the first data cut-off date of June 30th, 2018 showed that, during the treatment phase (0-12 months), there were no meaningful changes in the adjusted EQ-5D-3L utility scores or EQ-5D-3L adjusted mean VAS scores between treatment groups, and changes from baseline were minimal for all assessments throughout the study period. Furthermore, because AEs can influence patient perception of HRQOL, an assessment of change from baseline in adjusted mean VAS scores for patients who did or did not experience AEs in the dabrafenib and trametinib treatment group was undertaken. There were no AEs associated with a clinically meaningful decrease in HRQOL during treatment and during the follow-up phase VAS scores improved over time for patients who experienced each of the most common AEs such as pyrexia, nausea, headache, diarrhea, arthalgia and rash; further, no clinically meaningful changes from baseline VAS were observed in patients in the combination therapy group who discontinued treatment early.[3]

Similar results were observed during the long-term follow-up phase (> 12 months), with adjusted mean VAS scores in both treatment groups showing an upward trend, with no clinically meaningful differences between groups. The proportion of patients reporting problems on the EQ-5D-3L usual activities, pain/discomfort, and anxiety/depression dimensions showed a decrease over time in both groups. Disease recurrence was associated with a reduction in both mean VAS and utility scores. In the absence of disease-related symptoms in the adjuvant setting, the fact that comparable scores were observed over time across both groups suggested that the combination of dabrafenib plus trametinib did not incur additional burden or negatively impact HRQOL during treatment or long-term follow-up.[3]

As was noted in the NICE technology report[36] the initially high reporting rates for the EQ-5D-3L tended to decline to month 24, which coincides with a decline in the number of patients remaining in the trial. It is during this period that the mean reported HRQOL values show some tendency to increase. Whether this reflects reporting bias or genuine improvements in HRQOL cannot be determined. However, it is noteworthy that the mean EQ-5D-3L evolves in a similar manner in both groups, despite reporting rates in the placebo arm declining more precipitously than in the dabrafenib plus trametinib arm.[36]

6.4 Ongoing Trials

No ongoing trials were identified that met the selection criteria of this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of dabrafenib plus trametinib:

- Critical appraisal of the Manufacturer's submitted network meta-analysis (NMA)[5] comparing dabrafenib in combination with trametinib to relevant comparators in patients with high-risk (IIB-C and IIIA-C) melanoma with BRAF mutation positive status.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of the Manufacturer's Submitted NMA

7.1.1 Rationale and Objective

There are no randomized trials that directly compare the efficacy of dabrafenib plus trametinib to other competing adjuvant treatment regimens in patients with high-risk radically resected, BRAF mutation positive melanoma (target population). Therefore, the Manufacturer had a NMA conducted to examine the comparative efficacy of dabrafenib plus trametinib against relevant comparators that included the following: placebo, watchful waiting, nivolumab, pembrolizumab, ipilimumab, vemurafenib, chemotherapy, IFNs, LGX818 or any other treatment listed as an eligible intervention.

The objective of this section is to summarize and critically appraise the methods and results of the performed NMA, in patients with high-risk (IIB-C and IIIA-C) melanoma with BRAF mutation positive status, in order to inform the pCODR clinical and economic evaluations of dabrafenib plus trametinib.

7.1.2 Findings

Objective of NMA

The objective of the Manufacturer-submitted analysis was two-fold:

1. To estimate the relationship between RFS/disease-free survival (DFS), and OS with respect to the treatment effects observed in patients with radically resected, BRAF V600E/K mutation-positive, high-risk cutaneous melanoma; and
2. Estimate the relative treatment effects in terms of RFS, DFS, and (predicted) OS between competing interventions, including dabrafenib plus trametinib, for the adjuvant treatment of radically resected, BRAF V600E/K mutation-positive, high-risk cutaneous melanoma.

Systematic Review

The evidence informing the NMA was identified through a systematic review that defined the study population as patients with *radically resected, high-risk cutaneous melanoma independent of the BRAF mutation status*. It was anticipated that very few RCTs would exist in the target population (*radically resected, BRAF V600E/K mutation-positive, high-risk cutaneous melanoma);* hence, an assumption was made on the premise that the target population is a subset of the broader study population and that any effects observed in the study population will apply to the target population.

The methods used for the systematic review followed PRISMA guidelines for reporting and appeared comprehensive. Details were provided on the inclusion criteria used for the review, the specific evidence sources searched (i.e., data bases, conference proceedings, hand searches), the

literature search strategies performed, the methods used for trial selection (i.e., independent reviewers, with discrepancies adjudicated by a third reviewer) and data extraction (i.e., prospectively determined data fields). Included trials were assessed for quality (risk of bias) using the Cochrane risk of bias instrument and the results of these assessments were provided.

An update to the evidence base was conducted in July 2018 to include additional follow-up data from two trials (COMBI-AD and Checkmate-238); a comprehensive literature search was not conducted but conference proceedings were also searched for three conferences over the past two publication years.

Scope of Meta-analyses

Meta-analysis for surrogacy: The meta-analysis aimed to estimate the relationship of RFS/DFS and OS HRs in high-risk radically resected BRAF-mutation positive cutaneous melanoma (target population). As previously mentioned, the assumption was made that the relationship between HRs for RFS/DFS and OS was not affected by BRAF status, and therefore the findings were applicable to the BRAF mutation-positive subgroup. A meta-analysis on the relationship of RFS/DFS and OS HRs was performed on: 1) the overall group of trials independent of BRAF mutation status; and 2) a subgroup of trials reporting on stage III.

NMA for comparative efficacy: The overall NMA included patients with high-risk radically resected cutaneous melanoma independent of BRAF mutation status given that the evidence base in the target population was limited. The high-risk cutaneous melanoma was defined *a priori* as per AJCC-7 stage IIB, IIC, IIIA, IIIB, or IIIC cutaneous melanoma. Competing interventions considered included watchful waiting, nivolumab, pembrolizumab, ipilimumab, vemurafenib, chemotherapy, IFNs, and LGX818.

Both the meta-analysis for surrogacy and the NMA were updated to include the additional follow-up data from the COMBI-AD and Checkmate-238 trials.

Systematic Review Results

The original literature search, which was current to July 27, 2017, identified 18 trials that reported on RFS and OS data, and were included in the RFS/OS surrogacy analysis. An updated literature search was performed in May 2018 to include data from the Keynote-054 trial, and again in July 2018 to include 40-month follow-up RFS data from the COMBI-AD trial and 24-month data from Checkmate-238 for RFS and DMFS. Overall, 22 trials were included in the NMA of high-risk melanoma independent of BRAF mutation status, eight trials for the stage III subgroup analysis, and four trials in BRAF-positive patients.

Study Quality

Overall, the trials were considered to have a low-risk of bias based on the assessment using the Cochrane Collaboration's Risk of Bias tool. Randomization was often carried out in a proper manner, with the exception of some trials, where it was not clear how randomization was conducted. Treatment allocation concealment was adequate amongst all of the trials. Similarly, care providers, outcome assessors, and participants were blinded in the majority of trials. Similar low-risk biases were observed in the remaining categories. The only sources of high-risk of bias came from incomplete outcome data, lack of blinding and selective reporting in less than five trials.

Feasibility of Meta-analysis and Assessment of Heterogeneity

Meta-analysis for surrogacy: Meta-analysis was deemed feasible since the outcomes of interest were defined similarly in the included trials, and data were available for RFS and OS outcomes.

Overall, baseline characteristics were well distributed across the 18 trials and the interventions reported in the studies were separated into four categories: targeted therapies, IFNs, chemotherapy, and mixed treatments (immunotherapy and chemotherapy).

NMA for comparative efficacy: In order to gauge the appropriateness of proceeding with an NMA, the feasibility assessment included: 1) a determination of whether the RCT evidence for the interventions of interest formed one evidence network for each population and outcome of interest; and 2) an assessment of the distribution of treatment, outcomes, study and patient characteristics that may affect treatment effects across direct comparisons (i.e. effect modifiers) of the evidence networks.

In order to address the heterogeneity between studies in terms of disease stage and BRAF mutation status; the following sub-group analyses were planned:

i. Stage III (AJCC-7th edition) resectable melanoma independent of BRAF mutation status; and
ii. High-risk (AJCC-7th edition IIB-C and IIIA-C) BRAF mutation positive resectable melanoma.

For the purposes of this review, the network of trials in BRAF mutation positive patients (target population) is the main evidence network of interest, and the focus of the critical appraisal.

Meta-analysis Methodology

Meta-analysis for surrogacy: Overall, the meta-analyses performed to estimate the relationship between RFS/DFS and OS, including underlying statistical assumptions and the statistical programs used, were well reported. The relationship between RFS and OS was assessed using a linear regression of log HRs, where the dependent variable was OS and the independent variable was RFS. As this was done in a frequentist framework, no priors were required. In order to determine whether the models were robust, cross-validation was conducted using the leave-one-out analysis. For every trial included in the meta-analysis, a given trial was removed and a new regression model was fitted with the remaining trials, thereby predicting the OS of the removed trial from its observed RFS using the regression model and comparing the predicted OS with its observed value. The meta-analysis results were presented graphically and using correlation coefficient r; additionally, the surrogate threshold effect (STE), defined as the minimum RFS treatment effect for which the predicted OS would be different from zero, was also presented.

NMA for comparative efficacy: Where results of the RCTs identified in the systematic review formed part of one evidence network and were deemed sufficiently similar for each population of interest, they were synthesized by means of a Bayesian NMA by outcome of interest. The NMA for RFS/DFS, OS, and DMFS, assuming proportional (constant) hazards between treatments, was performed using a regression model with a contrast-based normal likelihood for the log HR of each trial in the network. Normal non-informative prior distributions were used for all parameters (mean 0; variance of 10,000). Relative treatment effects were expressed as HRs with 95% credible intervals (CrI), which reflect a 95% probability that the estimate is contained with the specified range.

An additional time-varying HR analysis was also conducted to estimate comparative efficacy between treatments. The justification for using this approach was not specified; however, follow-up with the Submitter confirmed that this method was used to assess the validity of the proportional/constant hazards assumption, and to determine which analysis (constant versus varying) provided the best fit to the available data. The Submitter concluded that the results obtained with the time-varying HR NMA should be interpreted with caution, as the fractional polynomial model had limited utility in capturing the shape of the dabrafenib-trametinib RFS curve, which led to misleading results. The Submitter explained this could partly be attributed to the immature RFS data, as the median RFS has not yet been reached in the combination therapy

group in the COMBI-AD trial. The conclusion of the Submitter's proportional hazards assumption assessment was not reported.

While both fixed- and random-effects models were considered, the fixed-effects model was considered the best-fit given the limited number of available trials (in the subgroups of interest) to estimate between-study heterogeneity. Tabular and graphical summaries were provided of estimates of treatment effect versus each comparator in the network (HRs with corresponding 95% CrI) for each outcome.

Meta-analysis Results

Meta-analysis for surrogacy: HRs for RFS and OS were available for 18 trials overall, of which seven trials had HRs estimated from KM curves, five trials reported HRs for the stage III subgroup, two trials focused on the targeted therapies, and one trial included BRAF mutation-positive patients. The limited number of trials available for meta-analysis yielded unreliable results in the stage III subgroup, and precluded a meta-analysis in the BRAF positive subgroup.

The slope of the relationship between log HRs of RFS and OS was 0.89 and the correlation coefficient r was 0.74, which suggested RFS was highly predictive of OS. This relationship was consistent regardless of the inclusion of the COMBI-AD trial data. The correlation of RFS and OS was considered positive and strong (>0.64 in all scenarios) and, overall, the results were held valid using a leave-one-out cross validation method. The latest updated analysis including longer follow-up data (COMBI-AD and Checkmate-238) produced consistent results with a slope of 0.91 and a correlation coefficient r of 0.74. The STE for RFS was estimated to be 0.912, which is interpreted as an RFS HR of 0.912 or less is required to predict a positive treatment effect on OS. Of note, the STE estimate obtained in this analysis is higher than other published data (STE=0.77) validating RFS as a surrogate for OS in this patient population (treated with IFNs).[38]

NMA for comparative efficacy: The network of evidence is presented in Figure 3 and a summary of baseline characteristics of patients in the included trials is presented in Table 13.

Four trials reported RFS/DFS HRs in the BRAF V600E/K positive population:

- COMBI-AD compared dabrafenib and trametinib combination to placebo and included stage III BRAF V600E/K positive patients.
- BRIM-8 compared vemurafenib to placebo and included stage II and III BRAF V600E/K positive patients.
- Checkmate-238 compared nivolumab to ipilimumab and included stage III and IV patients, with 42% of patients being BRAF positive (type not specified).
- Keynote-054 compared pembrolizumab to placebo and included stage III patients of which 43% were BRAF V600E/K mutation positive.

In addition to these four trials, the EORTC 18071 trial, which does not report on BRAF status, was required to connect dabrafenib plus trametinib to nivolumab.

The posterior distributions of estimated relative treatment effects between the compared interventions obtained with the Bayesian analyses are summarized by their median and 95% CrIs

(constructed from the 2.5th and 97.5th percentiles) and are presented in Table 14. Overall survival and safety outcomes were not available for the BRAF positive subgroup analysis.

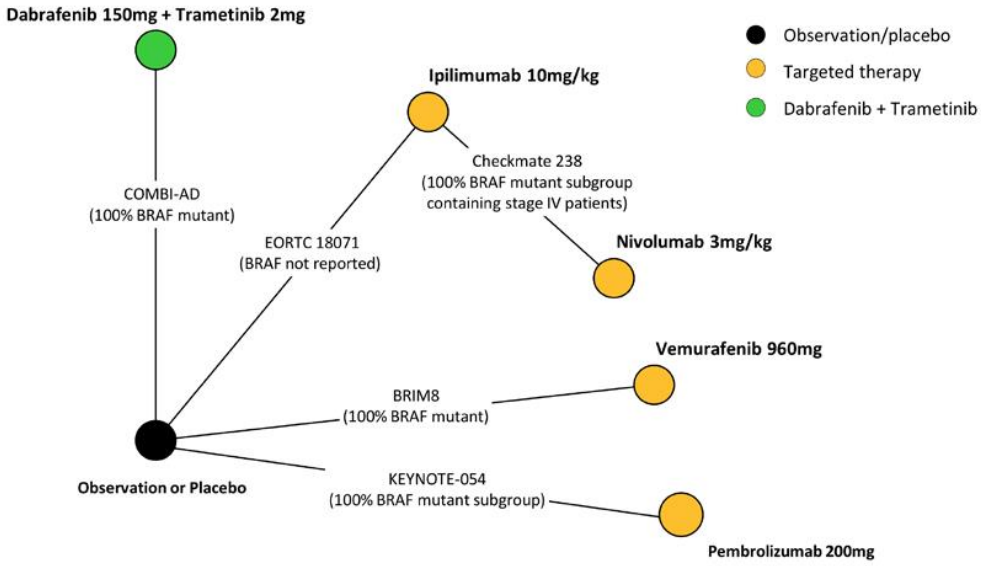


Figure 3: High-risk (AJCC-7 IIB-C and IIIA-C) melanoma BRAF mutation positive status – network of randomized controlled trials for RFS/DFS; subgroup analysis.[5]

Table 13: Summary of individual trials included in the Manufacturer's submitted NMA for efficacy in high-risk melanoma - BRAF mutation positive subgroup analysis.

Trial	Treatment (n)	Age	Male %	Stage III a-c %	Stage IV %	BRAF mutation %	Clinically detectable nodal metastases %	Disease relapse %	Survival Hazard Ratio (95% CI)		
									OS	RFS/DFS	DMFS
COMBI-AD	Dabrafenib 150mg + Trametinib 2mg (438)	50.0	44.5	100	0	100	36.1	37.2	0.57 (0.42-0.79)	0.47* (0.39-0.58)	0.51 (0.40-0.65)
	Placebo (432)	51.0	44.7	100		100	37.3	57.2			
EORTC 18071	Ipilimumab 10mg/kg (475)	50.7	62.3	100	-	-	55.8	55.6	0.72 (0.58- 0.88)	0.76 (0.64- 0.89)	0.76 (0.64- 0.92)
	Observation/placebo (476)	51.5	61.6	100			59.5	67.9			
Checkmate - 238	Ipilimumab 10mg/kg (453)	54.0	59.4	80.8	19.2	42.8	47.2	45.5	NR	0.65** (0.51- 0.82)	0.73** (0.55- 0.95)
	Nivolumab 3mg/kg (453)	56.0	57.0	81.0	18.1	41.3	48.3	34.0			
BRIM8	Vemurafenib 960mg (250)	52.5	54.4	94.0	-	100	NR	38.8	NR	0.80 (0.54- 1.18)	0.91 (0.57- 1.44)
	Observation/placebo (248)	49.4	59.3	95.2		100		50.4			
KEYNOTE-054	Pembrolizumab 200mg (514)	54	63	100	-	40.9	63.6	21.2	NR	0.54 (0.36-0.83)***	NR
	Observation/placebo (505)	54	60.2	100		45.7	68.1	35.4			

Notes:
*Updated analysis included 40-month data from the COMBI-AD trial and resulted in a RFS/DFS HR of 0.49 (95% CI, 0.40-0.59).
** Updated analysis included 24-month data from the Checkmate-238 trial and resulted in a RFS/DFS HR of 0.68 (95% CI, 0.54-0.85) and a DMFS HR of 0.76 (95% CI, 0.59-0.98).
*** Source of KM and HR data is the supplementary appendix of the KEYNOTE-054 trial.

RFS

RFS data were reported in BRAF mutant positive (V600E/K) patients in four trials; of these, COMBI-AD and BRIM-8 were 100% BRAF V600E/K positive populations while Keynote-054 and Checkmate-238 studies reported on 42% and 43% BRAF-positive patients, respectively. In order to create a network of evidence that contained dabrafenib plus trametinib and nivolumab, two allowances (sources of heterogeneity) were implemented:

- The Checkmate-238 nivolumab trial reported RFS for the BRAF mutation positive subgroup. However, this subgroup contained stage IV patients, which is not a stage of interest.
- In order to connect dabrafenib plus trametinib to nivolumab, the EORTC 18071 trial was required, which does not report on BRAF status.

Table 14 depicts the results of the constant HR NMA for RFS; the HRs are displayed as treatments listed in rows comparing treatments listed in columns.

Based on the assumptions noted above, the results from the constant HR RFS NMA in BRAF-positive high-risk melanoma were in line with the overall primary analysis results[ii] where dabrafenib plus trametinib performed significantly better than placebo (HR=0.47; 95% CrI, 0.38 to 0.57) and ipilimumab (HR=0.62; 95% CrI, 0.48 to 0.80), and was comparable to nivolumab (HR=0.86; 95% CrI, 0.57 to 1.30), vemurafenib (HR=0.72; 95% CrI, 0.52 to 1.00) and pembrolizumab (HR=0.87; 95% CrI, 0.60 to 1.27).

Table 14: High-risk (AJCC-7 IIB-C and IIIA-C) melanoma BRAF mutation positive status – hazard ratios estimated from fixed-effects NMA for RFS/DFS; subgroup analysis.

Observation or Placebo	**2.13 (1.75, 2.60)**	**1.83 (1.27, 2.63)**	**1.54 (1.18, 2.01)**	**1.32 (1.12, 1.55)**	**1.85 (1.35, 2.55)**
0.47 (0.38, 0.57)	**Dabrafenib+ Trametinib**	0.86 (0.57, 1.30)	0.72 (0.52, 1.00)	**0.62 (0.48, 0.80)**	0.87 (0.60, 1.27)
0.55 (0.38, 0.79)	1.17 (0.77, 1.77)	**Nivolumab**	0.84 (0.53, 1.32)	**0.72 (0.52, 1.00)**	1.01 (0.63, 1.64)
0.65 (0.50, 0.85)	1.39 (1.00, 1.93)	1.19 (0.76, 1.87)	**Vemurafenib**	0.86 (0.63, 1.17)	1.20 (0.80, 1.83)
0.76 (0.64, 0.90)	**1.62 (1.25, 2.10)**	**1.39 (1.00, 1.92)**	1.17 (0.85, 1.59)	**Ipilimumab**	1.41 (0.99, 2.01)
0.54 (0.39, 0.74)	1.15 (0.79, 1.68)	0.99 (0.61, 1.59)	0.83 (0.55, 1.25)	0.71 (0.50, 1.01)	**Pembrolizumab**
Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 9.34; Deviance: 4.34					

Results from the updated analysis incorporating longer follow-up RFS data (COMBI-AD and Checkmate-238) were consistent with the initial analysis results [dabrafenib plus trametinib versus: placebo (HR=0.49; 95% CrI, 0.40 to 0.59), ipilimumab (HR=0.64; 95% CrI, 0.50 to 0.83), nivolumab (HR=0.88; 95% CrI, 0.59 to 1.31), vemurafenib (HR=0.75; 95% CrI, 0.54 to 1.05) and pembrolizumab (HR 0.91; 95% CrI, 0.57 to 1.44)].

[ii] The overall primary analysis results (RFS; stage IIB-C and IIIA-C, independent of BRAF mutation status; fixed effects model) for the comparison of dabrafenib-trametinib versus the following comparators: placebo (HR=0.48; 95% CrI, 0.39-0.59), ipilimumab (HR=0.63; 95% CrI, 0.49-0.82), nivolumab (HR=0.98; 95% CrI, 0.69-1.39) vemurafenib (HR=0.73; 95% CrI, 0.53-1.01), and pembrolizumab (HR=0.84; 95% CrI, 0.63-1.13).

Conclusion of the NMA

The authors of the NMA concluded that RFS can be regarded as a robust surrogate for OS in high-risk resectable cutaneous melanoma and believe that the results can be safely interpolated to BRAF positive high-risk melanoma in the adjuvant setting. While the authors noted direct head-to-head trials are needed to confirm the results, they believe the NMA results suggest that dabrafenib plus trametinib significantly prolongs survival outcomes in high-risk resectable cutaneous melanoma compared to IFNs, ipilimumab, while the combination is comparable to nivolumab, pembrolizumab, and vemurafenib.

Critical Appraisal of NMA

The quality of the manufacturer-submitted NMA was assessed according to the 2014 ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.[6] The questionnaire items were scored with yes/no/not reported or applicable and discussed in a narrative summary. A summary of the quality assessment is provided in Table 16.

Overall, the relevance of the NMA was considered questionable, as the patients in the included trials did not completely align with the target population of interest to this review: radically resected, BRAF V600E/K mutation-positive, high-risk cutaneous melanoma. The reporting of the methods used to conduct both the systematic review and meta-analyses were, for the most part, clear and comprehensive. There are concerns, however, in terms of credibility (i.e., internal validity, interpretation, and conflict of interest), which are summarized below:

- There were systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact treatment effects) across the different treatment comparisons in the network. The Checkmate-238 trial included stage IV disease in the subgroup of BRAF positive patients; and EORTC 18071 did not report BRAF mutation type. There were also a higher percentage of patients with nodal metastases in Keynote-054 and patients with disease relapse in EORTC 18071. The extent to which these patient characteristics and any associated change in prognosis may have influenced study outcomes is unknown. Further, consideration should also be given to possible diminished benefits observed with dabrafenib and trametinib combination therapy.
- Given the allowances made in order to form a network of trials in the BRAF mutation positive subgroup (inclusion of Checkmate-238 with stage IV patients and EORTC 18071 which doesn't report on BRAF status) the results should be interpreted with caution, as the subgroup doesn't completely align with the target population of this review.
- A comprehensive update of the literature was not conducted to identify studies published after the initial July 2017 literature search. While new (Keynote-054) and updated results (COMBI-AD, Checkmate-238) from a few individual trials published after this date were included, others may have been missed. The risk for publication bias, which was not assessed, warrants caution when interpreting the comparative efficacy results obtained.
- Investigator-assessed RFS and DFS were the primary outcomes of the NMA and they have the potential to be biased in favour of whichever treatment the investigator feels is superior.
- The definitions of RFS and DFS used in each of the included studies were not provided. If these outcomes were defined differently across the included trials, the uncertainty around the estimates of the indirect comparisons would increase, and consequently, this would affect RFS and DFS estimates.
- As an alternative to the constant HR, which is a univariate treatment effect measure, a multivariate treatment effect measure that describes how the relative treatment effect (e.g. HR) develops over time can be used. The authors noted that a time-varying HR fractional polynomial model was employed to verify the proportional hazards assumption

but that it had limited utility in capturing the shape of the dabrafenib plus trametinib KM curves for RFS in the COMBI-AD trial, and therefore they considered the results of this analysis to be unreliable. However, it was not reported or confirmed by the Submitter whether or not the proportional hazards assumption was actually violated in the constant HR analysis; therefore, the possibility of non-proportional hazards and its impact on the results obtained cannot be eliminated.

- While subgroup analyses can be used to assess the impact of potential treatment effect modifiers, they are limited by the amount of information available regarding the patient characteristics of the subgroups and have limited power. Accordingly, a fixed effects model, which assumes no heterogeneity, was used for the analysis given the limited number of trials available in the BRAF mutation positive subgroup. Although an appropriate approach, heterogeneity among the trials was indeed present, and this variation must be acknowledged when interpreting the results, as it affects the reliability of the comparative treatment effect estimates obtained.
- The differences in the included trials' duration of follow-up may have also affected the treatment effects observed in each trial thus violating the similarity assumption and confounding these comparisons.
- The submitted NMA did not explore the comparative safety or HRQOL between dabrafenib plus trametinib and other therapies in the BRAF mutation positive subgroup, which presumably would be important especially when a combination therapy is compared to a single-agent therapy.
- The submitted NMA was performed by an external consultancy group hired and funded by the manufacturer. Therefore, the results should be viewed considering this potential conflict of interest and lack of peer-review.

Table 16: ISPOR Questionnaire[6] to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis.[†]

ISPOR Questions[†]	Details and Comments[‡]
1. Is the population relevant?	**Yes, in part**. The patients included in the four trials that were part of the subgroup analysis mostly align with the target population of interest: radically resected, BRAF V600E/K mutation-positive, high-risk cutaneous melanoma. However, the EORTC 18071 trial included patients independent of BRAF mutation and Checkmate-238 included stage IV patients. Not all patients in CheckMate-238 or Keynote-054 were BRAF positive.
2. Are any critical interventions missing?	No. The NMA included all the relevant treatment comparators at appropriate doses, schedules and modes of administration
3. Are any relevant outcomes missing?	**Yes**. OS, AEs and HRQOL were not considered in the BRAF positive subgroup analysis.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes, in part**. The original systematic review appeared comprehensive in terms of approach used to search for evidence. However, updates to the original SLR did not include comprehensive searches and therefore trials published subsequently could have been missed.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes. The included trials formed a connected network comprising of single trial connections with no closed loop.
7. Is it apparent that poor quality studies were included thereby leading to bias?	No. The included trials were assessed for risk of bias using the Cochrane Collaboration's Risk of Bias tool and the results of the assessments were provided. The overall quality of the trials was judged as good (low risk of bias).
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	No.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes**. Differences between the trials in both patient and disease characteristics existed. Checkmate-238 included stage IV disease in the subgroup of BRAF positive patients and EORTC 18071 did not report BRAF mutation type (included an all-comer population). There was also a higher percentage of patients with nodal metastases in Keynote-054 and patients with disease relapse in EORTC 18071.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes. To account for the heterogeneity, subgroup analyses were planned and undertaken.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in	Not applicable (no closed loop).

ISPOR Questions†	Details and Comments‡
treatment effects (i.e. consistency) evaluated or discussed?	
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable (no closed loop).
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	Yes. A fixed effects model was chosen given the limited number of trials available to estimate the between-study heterogeneity.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable (fixed effects analysis).
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Yes. In order to address the heterogeneity between studies in terms of disease stage and BRAF mutation status; the following sub-group analyses were planned: i. Stage III (AJCC-7th edition) resectable melanoma independent of BRAF mutation status; and ii. High-risk (AJCC-7th edition IIB-C and IIIA-C) BRAF mutation positive resectable melanoma.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes. Hazard ratios from the individual studies are reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Not applicable as there were no direct comparisons.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No. Ranking of therapies by highest probability of being the most efficacious was not provided despite having the network meta-analysis fitted within a Bayesian framework.
23. Is the impact of important patient characteristics on treatment effects reported?	Yes, however the list of important patient characteristics was not comprehensive enough to conclude the full impact on treatment effects.
24. Are the conclusions fair and balanced?	**Unclear**. There is a level of uncertainty in the reported results and conclusions of the BRAF mutation positive subgroup due to concerns over differences in patient characteristics and other factors (heterogeneity) between trial treatment groups.

ISPOR Questions†	Details and Comments‡
25. Were there any potential conflicts of interest?	**Yes**. The report was solicited by and prepared for the manufacturer.
26. If yes, were steps taken to address these?	**No**. COI was not reported within the report. Furthermore, the publication was not peer-reviewed.

† Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report.

‡Bolded comments are considered a weakness of the NMA.

7.1.3 Summary

In the absence of RCTs directly comparing the combination of dabrafenib and trametinib to other relevant treatment comparators, a NMA was provided by the Manufacturer that indirectly compared the combination to other pharmacological interventions for patients with high-risk radically resected, BRAF mutation positive melanoma. The pCODR Methods Team focused their review and critical appraisal to the NMA conducted in the subgroup of BRAF-positive patients (target population), which was carried out using the ISPOR Task Force Indirect Comparison/Network Meta-analysis Study Questionnaire.

Results of the NMA found that dabrafenib plus trametinib had significantly better RFS compared to observation or placebo and ipilimumab, and was comparable in RFS to nivolumab, pembrolizumab and vemurafenib. High-dose IFN was not included as a comparator in the subgroup analysis because it could not be connected in the network of trials. The quality assessment performed identified concerns with the overall relevance and credibility of the NMA. The main limitations include 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) and the use of a fixed-effects analysis which, although appropriate given the small number of trials included in the network, produces treatment effect estimates that do not take this heterogeneity into account. Additional limitations include potential bias introduced through differences in RFS/DFS definitions and patient follow-up time across the trials in the network, and the fact other important outcomes including OS, HRQOL and safety were not/could not be assessed. Considering these limitations, the conclusions drawn from the NMA should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

The pCODR CGP and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Melanoma CGP is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the CGP was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** August 2018**, Embase** 1974 to 2018 October 1**, Ovid MEDLINE(R) ALL** 1946 to October 01, 2018

#	Searches	Results
1	(dabrafenib* or tafinlar* or gsk 2118436 or gsk2118436 or gsk 2118436a or gsk2118436a or gsk 2118436b or gsk2118436b or QGP4HA4G1B).ti,ab,ot,kf,kw,hw,nm.	4222
2	(trametinib* or mekinist* or gsk 1120212 or gsk1120212 or gsk 1120212b or gsk1120212b or jtp 74057 or jtp74057 or 33E86K87QN).ti,ab,ot,kf,kw,hw,nm.	4558
3	1 and 2	2559
4	exp Melanoma/ or exp skin neoplasms/ or (melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or (skin adj2 (cancer* or neoplasm* or tumor* or tumour*))).ti,ab,kf,kw.	528882
5	3 and 4	2085
6	5 use cctr	110
7	5 use medall	362
8	*dabrafenib/ or (dabrafenib* or tafinlar* or gsk 2118436 or gsk2118436 or gsk 2118436a or gsk2118436a or gsk 2118436b or gsk2118436b).ti,ab,kw,dq.	2535
9	*trametinib/ or (trametinib* or mekinist* or gsk 1120212 or gsk1120212 or gsk 1120212b or gsk1120212b or jtp 74057 or jtp74057).ti,ab,kw,dq.	2750
10	8 and 9	1387
11	exp melanoma/ or exp skin tumor/ or (melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or (skin adj2 (cancer* or neoplasm* or tumor* or tumour*))).ti,ab,kw,dq.	462566
12	10 and 11	1183
13	12 use oemezd	751
14	13 not (conference abstract or conference review).pt.	425
15	13 and (conference abstract or conference review).pt.	326
16	limit 15 to yr="2013 -Current"	300
17	7 or 14	787
18	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1102463
19	Randomized Controlled Trial/	983438
20	exp Randomized Controlled Trials as Topic/	277593
21	"Randomized Controlled Trial (topic)"/	149193
22	Controlled Clinical Trial/	550704
23	exp Controlled Clinical Trials as Topic/	288751
24	"Controlled Clinical Trial (topic)"/	9561
25	Randomization/	175449

26	Random Allocation/	192277
27	Double-Blind Method/	394113
28	Double Blind Procedure/	153174
29	Double-Blind Studies/	258391
30	Single-Blind Method/	74541
31	Single Blind Procedure/	32455
32	Single-Blind Studies/	76488
33	Placebos/	324449
34	Placebo/	323483
35	Control Groups/	111321
36	Control Group/	111229
37	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3944316
38	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	772069
39	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2912
40	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2570993
41	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	93429
42	allocated.ti,ab,hw.	174143
43	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	112388
44	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24260
45	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	924
46	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	10768
47	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	16956
48	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	125102
49	or/18-48	5646787
50	17 and 49	217
51	6 or 50	327
52	remove duplicates from 51	242
53	16 and 49	101
54	52 or 53	343
55	limit 54 to english language	323

2. **Literature search via PubMed**
A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#11	Search #8 AND #9 Filters: English	26
#10	Search #8 AND #9	26
#9	Search publisher[sb]	530390
#8	Search #6 AND #7	326
#7	Search Melanoma[mh] or skin neoplasms[mh] or melanoma*[tiab] or melanotic[tiab] or melanocarcinoma*[tiab] or melanomalignoma*[tiab] or naevocarcinoma*[tiab] or nevocarcinoma*[tiab] or pigmentary cancer*[tiab] or skin cancer*[tiab] or skin neoplasm*[tiab] OR skin tumor*[tiab] OR skin tumour*[tiab]	208825
#6	Search #4 AND #5	397
#5	Search trametinib*[tiab] OR mekinist*[tiab] OR gsk 1120212[tiab] OR gsk1120212[tiab] OR gsk 1120212b[tiab] OR gsk1120212b[tiab] OR jtp 74057[tiab] OR jtp74057[tiab] OR 33E86K87QN[tiab]	739
#4	Search dabrafenib*[tiab] OR tafinlar*[tiab] OR gsk 2118436[tiab] OR gsk2118436[tiab] OR gsk 2118436a[tiab] OR gsk2118436a[tiab] OR gsk 2118436b[tiab] OR gsk2118436b[tiab] OR QGP4HA4G1B[tiab]	744

3. Cochrane Central Register of Controlled Trials (Central)
Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Tafinlar (dabrafenib) and Mekinist (trametinib), melanoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Tafinlar (dabrafenib) and Mekinist (trametinib), melanoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search: afinlar (dabrafenib) and Mekinist (trametinib), melanoma

– last 5 years

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946-) via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) via OVID; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Tafinlar (dabrafenib) and Mekinist (trametinib) and melanoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of January 30, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the CGP and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR CGP wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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