CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Clinical Guidance Report

# Dabrafenib (Tafinlar) and Trametinib (Mekinist) for Non-Small Cell Lung Cancer

November 2, 2017

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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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# 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 (Tafinlar) plus trametinib (Mekinist). 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 dabrafenib (Tafinlar) plus trametinib (Mekinist) for BRAF V600 mutation positive NSCLC conducted by the lung 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 dabrafenib (Tafinlar) plus trametinib (Mekinist) for BRAF V600 mutation positive NSCLC, a summary of submitted Provincial Advisory Group Input on dabrafenib (Tafinlar) plus trametinib (Mekinist) for BRAF V600 mutation positive NSCLC, and a summary of submitted Registered Clinician Input on dabrafenib (Tafinlar) plus trametinib (Mekinist) for BRAF V600 mutation positive NSCLC, and are provided in Sections 2, 3, 4, and 5 respectively.

## 1.1 Introduction

The objective of this review is to evaluate the effectiveness and safety of dabrafenib (Tafinlar) in combination with trametinib (Mekinist) for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600 mutation (BRAF V600) mutation who have been previously treated with chemotherapy. This is similar to the Health Canada market authorization which is approved for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600 mutation whose disease has progressed following systemic therapy.

Dabrafenib is a targeted oral BRAF inhibitor. Trametinib is a targeted oral inhibitor of the mitogen-activated protein kinase (MAPK) pathway. The recommended doses are dabrafenib, 150 mg orally twice daily, and trametinib, 2 mg orally once daily.

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

One trial, BRF113928 (Cohort B) met the inclusion criteria for this review.[1] BRF113928 (Cohort B) is a Phase 2, open-label, single-arm, multi-centre study. This trial was conducted across 30 centres in nine countries across North America, Europe and Asia. This trial evaluated the combination of dabrafenib and trametinib in adults with BRAF V600E-mutant Stage IV NSCLC who were previously treated with chemotherapy.[1] The inclusion criteria were:

- Aged ≥ 18 years
- Histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC
- Documented tumour progression after at least 1 platinum-based chemotherapy regimen
- No more than 3 previous systemic treatments for metastatic NSCLC
- Measurable disease (RECIST 1.1)

- ECOG ≤ 2
- Adequate organ function
- Estimated life expectancy ≥ 3 months

The primary outcome was investigator-assessed (IA) overall response rate (ORR), a composite outcome. ORR was defined as the proportion of patients with a confirmed complete or partial response according to RECIST version 1.1.[1] Secondary outcomes were progression-free survival (PFS) based on IA disease response, duration of response, overall survival (OS), safety and tolerability. Health related quality of life was not measured in the study.

Patients (n=57) were enrolled between December 20, 2013 and January 14, 2015. All patients received at least one dose of dabrafenib plus trametinib. Data cut-off for the published study was October 7, 2015 (median follow up time 11.6 months (IQR 8.8 – 15.2)).[1] Following a request for additional information through the Checkpoint meeting (June 12, 2017), the submitter provided updated outcomes data (data cut-off August 8, 2016; median follow up time 16.6 months, IQR not provided).[2] These data were based on results presented at ASCO on June 3, 2017. Please see Table 1 for a summary of key outcomes. Note, where data are presented from the published trial,[1] independent review committee (IRC) outcomes are presented rather than IA outcomes.

**[Table 1]: Highlights of Key Outcomes**

| | | **BRF113928 (Cohort B)[1]** |
|---|---|---|
| **Efficacy Outcomes** | **Data cut/Follow up** | **Dabrafenib plus trametinib (n=57)** |
| **Primary outcome** | | |
| **Overall response rate, % (95% CI)** | October 7, 2015 data cut (11.6 months follow up)[1] | **36, 63.2% (49.3, 75.6)** |
| **Overall response rate, n, % (95% CI)** | August 8, 2016 data cut[2] | **36, 63.2% (49.3, 75.6)** |
| Other Key Endpoints | | |
| Overall survival (months), median (95% CI) | October 7, 2015 data cut (11.6 months follow up) | Not mature (23-57, 40% of patients died) |
| Overall survival (months), median (95% CI) | August 8, 2016 data cut[2] | 18.2 (14.3; NE) |
| Progression-free survival, median (95% CI) | October 7, 2015 data cut (11.6 months follow up)[1] | 8.6 (5.2, 19.1) |
| Progression-free survival, median (95% CI) | August 8, 2016 data cut [2] | 8.6 (5.2; 16.8) |
| **HrQoL**[1, 2] | | HrQoL was not evaluated. |
| **Harms Outcomes**[1] | | |
| Grade 3 and 4, n (%)* | | 28 (49%) |
| Pyrexia (any grade), n (%) | | 26 (46%) |
| AE (any grade), n (%) | | 56 (98%) |
| WDAE, n (%) | | 7 (12%) |

**AE** = adverse event, **CI** = confidence interval, **HRQoL** = health-related quality of life, **NE** = not estimable, **NR** = not reported, **SD** = standard deviation, **WDAE** = withdrawal due to adverse event
Note: Where data are presented from the published trial,[1] Independent Review Committee outcomes are presented rather than IA outcomes.
* proportion of patients reporting grade ≥3 is not reported (only have grades 3 & 4 combined)

Limitations / Sources of Bias

Trial design:

- The most significant limitation of this trial is that the results for dabrafenib plus trametinib are from a small, single-arm, Phase 2 trial (BRF113928 (Cohort B)).[1] Such a trial is typically used to determine whether or not to go forward to a definitive Phase 3 trial. The lack of a comparator, small sample size, short duration of follow-up and use of a surrogate endpoint (ORR), limit the conclusions that can be drawn regarding the efficacy (eg, OS, PFS and ORR (the primary outcome)) and safety of dabrafenib plus trametinib compared with appropriate comparators (e.g., XYZ) in patients with BRAF V600E-mutant Stage IV NSCLC who were previously treated with chemotherapy.

- Ideally, in the design of a non-randomised study, data based on a currently approved therapy (e.g., docetaxel, nivolumab) would be used to help determine the null hypothesis for the primary outcome. There is implicit reference to a historical comparator in the design of BRF113928 (Cohort B), i.e. "The null hypothesis was that the overall response was not clinically meaningful (≤ 30%) and the alternative hypothesis was that 55% or more of second-line to fourth-line patients with BRAF V600E-mutant NSCLC would achieve an overall response with dabrafenib plus trametinib".[1] The submitter suggests a 30% expected response based on Cohort A of the BRF113928 trial using dabrafenib monotherapy.[3] However, dabrafenib monotherapy is not used to treat NSCLC in Canada and, as such, is not a relevant historical comparator. At Checkpoint (June 13, 2017), the submitter confirmed again that response rate to dabrafenib monotherapy (30%) was used to determine the null hypothesis (response rate ≤30%) that would be suitable for "further clinical development" (REF Checkpoint Response June 13, 2017). The submitter indicated in their response to Checkpoint follow-up questions that: "As the Committee noted, dabrafenib monotherapy is not approved in Canada and Novartis agrees that it is not a comparable 2$^{nd}$ line treatment".[4] Lack of information regarding ORR (as well as OS and PFS) using a relevant comparator makes it difficult to determine the relative efficacy of dabrafenib plus trametinib as 2$^{nd}$ line and beyond treatment in BRAF V600E-mutant Stage IV NSCLC patients.

- To establish the comparative efficacy of dabrafenib plus trametinib, the submitters provide evidence for an indirect comparison using matching adjusted indirect comparison (MAIC) and network meta-analysis.[5] Due to the single-arm nature of BRF113928 (Cohort B), using MAIC methodology, a pseudo trial was created to link BRF113928 (Cohort B) to the network. Using indirect comparison to establish comparative treatment efficacy and safety has major limitations and these are addressed in Section 7.

Choice of outcome:

- The primary outcome for this study was ORR. Currently, there is no evidence to support ORR as a surrogate for OS in BRAF V600E-mutant Stage IV NSCLC. Based on the IRC assessment, no patients experienced a complete response and ORR was driven exclusively by partial response.

Analysis of results:

- There is no mention of blinding of the outcome adjudicators (i.e., those responsible for radiological disease assessment by CT scans based on RECIST version 1.1,). If the assessors are aware that the patients had undergone experimental therapy they may be biased towards a "positive outcome", thus there is a potential for misclassification

bias with respect to the RECIST version 1.1 criteria. The evaluation of tumour size by IA is even more prone to be bias compared with the IRC due to investigator-bias. At Checkpoint (June 12, 2017), the submitter confirmed that the IA was not blinded.[2] They note that the IRC was blinded to investigator assessment results.[2]
- Investigator bias is likely present as all IA outcomes (primary and all secondary) favour treatment to a greater degree than IRC assessed outcomes.

### 1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

***Patient Advocacy Group Input***

From a patient perspective, lung cancer impacts many aspects of day-to-day life. Specifically, both The Ontario Lung Association (OLA) and Lung Cancer Canada (LCC) reported that it affects the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, emotional well-being and may cause financial hardship. It was reported by both patient and caregiver respondents that high symptom burden of lung cancer is difficult to manage. LCC indicated that symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burdens for lung cancer patients is fatigue or lack of energy. OLA noted that symptoms are not fixed or consistent, but rather change frequently, which can be difficult to manage.

For the vast majority of this patient population, the current standard of care will be chemotherapy, viewed as a necessary, but feared treatment. The infusions themselves presented challenges beyond travel time and hospital visits; some respondents reported feeling sick even before the infusion was completed and that significant recovery time was needed after each chemotherapy infusion.

Key treatment outcomes that respondents would most like to address are: to stop or slow the progression of the disease, to reduce or eliminate side effects (e.g., reduce pain, fatigue, cough and shortness of breath, inability to fight infection, burning of skin and impact to mood), and to improve appetite and energy. Respondents would also like the ability to have treatments at home, so it would remove the need for the patient or the caregiver to take time off of work. For respondents who have experience with dabrafenib-trametinib, they have indicated that the response to this treatment was positive. While some respondents had no side effects, others experienced high to severe side effects from this treatment. The vast majority of these cases were resolved with dosing adjustments.

***Provincial Advisory Group (PAG) Input***

Input was obtained from six provinces (Ministries of Health and/or cancer agencies) and the federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation of dabrafenib/trametinib combination therapy:

Clinical factors:
- Place in therapy of dabrafenib/trametinib and sequencing with currently available treatments for NSCLC
- Comparison with other treatments
- BRAF testing not currently routinely done for NSCLC

Economic factors:

- High cost of combination therapy
- Cost of BRAF testing in all patients with NSCLC who have failed first-line platinum therapy to identify the 1-2% with BRAF mutation (the number of patients to be tested and the number of patients with BRAF mutation).

### *Registered Clinician Input*

Two clinician inputs were provided from two groups: Medical Advisory Committee Lung Cancer Canada and from a provincial tumour group advisory committee.

The clinicians providing input noted that there is a very small number of patients with BRAF V600E mutation positive NSCLC who could benefit from treatment with dabrafenib/trametinib. The clinicians providing input identified that the optimal algorithm for BRAF mutation testing would be upfront next generation sequencing so the result is available after progression on platinum doublet. There is a difference in opinion on where dabrafenib/trametinib would fit in sequence of therapies.

### *Summary of Supplemental Questions*

Summary of the manufacturer-submitted indirect comparison of dabrafenib plus trametinib with other second-line treatments for patients with advanced NSCLC who have been previously treated with chemotherapy.

See Section 7 for further details on supplemental questions.

The submitter provided an indirect comparison of efficacy outcomes for dabrafenib and trametinib combination therapy in the treatment of previously treated advanced or metastatic NSCLC.[5] Indirect comparisons were achieved using "matching adjusted indirect comparison" (MAIC) and network meta-analysis (NMA).

A systematic review was conducted to identify trials meeting the inclusion criteria. One trial of dabrafenib plus trametinib was identified (BRF113928 (Cohort B)).[1] Nine additional RCTs were identified. Of these, 8 reported OS, 6 reported PFS and 9 reported ORR. Due the single-arm nature of BRF113928 (Cohort B), MAIC methodology was used to create a pseudo trial to link BRF113928 (Cohort B) to the network. Two pseudo trials were created using aggregate level data from Checkmate 057 (docetaxel vs. nivolumab).[6] The two pseudo trials were dabrafenib plus trametinib compared with docetaxel and, dabrafenib plus trametinib compared with nivolumab.

Prior to matching, patients enrolled in BRF113928 (Cohort B) were similar to patients enrolled in Checkmate 057 on baseline characteristics. Matching using MAIC did not meaningfully improve the comparability of the majority of baseline characteristics. As a result, OS, PFS and ORR did not meaningfully change pre-matching to post-matching. This suggests that similar patients were enrolled in both of these trials. The results of the NMA suggest that dabrafenib plus trametinib is superior to other treatments in terms of OS, PFS and ORR.

However, there are limitations in this indirect comparison. As there is currently no head-to-head trial comparing dabrafenib plus trametinib versus other currently approved treatments (e.g., docetaxel, nivolumab), MAIC was used to create a pseudo trial using data from Checkmate 057. The absence of a common comparator arm is a critical limitation as validation of the matching is not possible.[7] There may be important, unmeasured cross-trial differences that account for the observed superior efficacy (OR, PFS, ORR) of dabrafenib plus trametinib compared with other therapies identified in the systematic review. In particular, dabrafenib plus trametinib is the only trial that exclusively enrolled

patients with BRAF V600E-mutant Stage IV NSCLC previously treated with chemotherapy. All other trials were conducted in unselected (for mutation) populations. Ideally, to fairly compare BRF113928 (Cohort B) to Checkmate057, BRF113928 (Cohort B) trial inclusion and exclusion criteria (including BRAF V600E mutation status) would be applied to Checkmate 057 and the OS, PFS and ORR reported for this subgroup. In the absence of this evidence, there is substantial uncertainty when interpreting outcomes (OS, PFS, ORR) across trials.

### *Comparison with Other Literature*

See Section 8 for further details on the comparison with other literature section.

Natural history of BRAF V600E Stage IV NSCLC

Two studies were reviewed to obtain evidence regarding the natural history of patients with BRAF V600E-mutant Stage IV NSCLC previously treated with chemotherapy.[8,9] Both studies provide data for OS, PFS and ORR. However, due to the non-protocolized assessment of tumour response, PFS and ORR are not comparable to BRF113928. However, OS is less likely to be biased across studies. Barlesi 2016 provides data on 132 BRAF V600E NSCLC patients who received 2$^{nd}$-line therapy.[8] OS was 13.8 months (95% CI 8.5, 21.9). Davis 2016 provides data on 8 BRAF V600E NSCLC patients who received 2$^{nd}$-line therapy.[9] OS was 12.5 months (95% CI 1.9, 46.3).[9] The current data from BRF113928 (Cohort B) includes 57 patients. OS, provided at Checkpoint, was 18.2 months (95% CI 14.3, Not Estimable).[2] However, any differences observed between studies should be interpreted with caution as the populations may be different. Ideally, the BRF113928 (Cohort B) inclusion and exclusion criteria would be applied to Barlesi 2016 and Davis 2016. This may result in a healthier population who may be more responsive to treatment (regardless of type) which may result in improved OS, PFS, and ORR. At Checkpoint, the submitter was asked if BRF113928 (Cohort B) inclusion and exclusion criteria could be applied to Davis 2016. The submitter replied:[4]

"Because of the relative scarcity of these patients and consequently the small size of this data set, it is not possible for us to specifically focus on patients who would precisely meet the eligibility criteria of Study BRF113928 Cohort B."

Overall response rate as a surrogate endpoint for overall survival

There are limited data regarding the utility of ORR as a surrogate endpoint for OS among patients with advanced NSCLC with BRAF V600 mutation. Efficacy of dabrafenib plus trametinib using ORR as a surrogate for OS should be interpreted with caution.

## 1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

**[Table 2]: Assessment of generalizability of evidence for dabrafenib plus trametinib in BRAF V600E-mutant NSCLC**

| Domain | Factor | Evidence | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| **Population** | Driver mutation status | The requested funding population is for patients with the BRAF V600 mutation.<br><br>All patients in the trial had V600E mutation and data was not available on any patients with the V600K mutation. | Are the trial results generalizable to patient who have the BRAF V600 K mutation? | The CGP do not generalize the current data to patients with the BRAF V600K mutation as there is no evidence to support the effectiveness of dabrafenib plus trametinib in this population. |
| | ECOG performance status | Few patients in the trial had an ECOG PS of 2. The majority of patients in the trial had an ECOG PS of 0 (30%) or 1 (61%). A small minority had PS 2 (9%). | Are the overall trial results generalizable to patient an ECOG PS of 2 or greater? | Despite the limitations of the data, this therapy should be considered as second-line therapy in good performance status patients (ECOG 0-2). |
| | Brain metastasis | Treated or asymptomatic brain metastases<br><br>October 7, 2015 data cut: 1 (2%)<br>Investigator assessment, August 8, 2016 data cut [2]: 2 (4%)<br>Independent review committee, August 8, 2016 data cut [2]: 5 (9%) | Are the trial results generalizable to patient metastasis to the brain? | A recent report by Davies et al, in patients with metastatic melanoma, reported an intracranial ORR of 58% for the combination of dabrafenib and trametinib. The high level of activity in CNS metastases in melanoma suggests that these drugs do penetrate the CNS to levels sufficient to result in objective response, and support the use of dabrafenib and trametinib in patients with BRAF mutated NSCLC and who have stable/treated brain metastases. |

### 1.2.4 Interpretation

The discovery of molecular oncogenic drivers in advanced non-squamous NSCLC has revolutionized the approach to the treatment of this disease. In an unselected population of patients with advanced NSCLC, 30-40% of patients might be expected to show an objective response to platinum-based chemotherapy. The median PFS is generally 6-7 months and median OS approximately 12 months, with expected two year survival of 20%. In molecularly defined subgroups of NSCLC, including patients with tumors harbouring *EGFR* mutations and *ALK* translocations, the likelihood of tumor response to molecularly targeted therapy is almost doubled (60-70%), with substantial improvements in PFS (10-16 months).[20, 21, 22, 23, 31, 32] While the natural history of these tumors may be more favourable, the median survival is approximately 2 to 2.5 years with 5 year survival figures of 20%. Molecularly targeted therapies have become the preferred initial therapy in these diseases.

In the second-line setting, docetaxel has been shown to improve median overall survival from 4.6 to 7.5 months with an improvement in one year survival of 37% versus 11%. ORR is only 7.1% though.[49] More recently anti PD-1 antibodies, nivolumab and pembrolizumab, were shown to be superior to docetaxel.[6, 25, 26] Approximately 20% of patients have an objective response to therapy, with a gain in median survival of about three months in all trials. One year survival estimates range from 42-51%.

However, there remains a significant need to identify new therapeutic targets to advance treatment options in those patients who are *EGFR* wild type (WT), or *ALK* negative. The identification of less common molecular abnormalities in this population of patients with advanced non-squamous NSCLC, including *BRAF* mutations, represents the initial step in advancing therapeutic options.

*BRAF* mutations are rare mutations occurring in non-squamous NSCLC, accounting for approximately 2% of lung adenocarcinomas. In Canada, this represent between 250 and 380 patients annually, of whom about a half have V600E mutations. The available data from a single arm phase II trial demonstrate high efficacy from combination therapy with a *BRAF* inhibitor, dabrafenib, in combination with a *MEK* inhibitor, trametinib. The ORR among 57 patients with previously treated, advanced *BRAF V600E* positive NSCLC was high (63.2%) with nearly 80% of patients demonstrating disease control. Median PFS was also longer than expected in this group of previously treated NSCLC patients (9.7 months). The median duration of response was 9 months. Data were immature to comment on overall survival. These data suggest much greater clinical benefit than what would be expected from standard second-line therapies, although this represents a select group of patients.

The observed toxicity profile of combination therapy with dabrafenib and trametinib is different to that expected from second-line chemotherapy or immunotherapy. Almost all patients experienced some adverse events (AE) on treatment. Common AEs included pyrexia, nausea, vomiting, diarrhea, asthenia and anorexia. Nearly half of patients experienced at least one grade 3 or 4 AE, including neutropenia, hyponatremia and anemia. Dose reductions were required in 35% of patients and 12% discontinued treatment because of an AE. In the absence of randomized comparisons, it is difficult to estimate the difference in toxicity. However with such high activity, dabrafenib plus trametinib would likely yield better patient outcomes than docetaxel which has significant toxicity. The toxicities associated with it do seem to be managed by appropriate dose reductions.

These data all support dabrafenib and trametinib as an active combination therapy for patients with *BRAF V600E* mutated NSCLC. The efficacy of dabrafenib and trametinib is

less clear in NSCLC patients with other *BRAF* mutations. The phase II data with dabrafenib and trametinib appear similar to phase II data for EGFR and ALK inhibitors with respect to outcomes. The Phase II data with EGFR/ALK inhibitors were remarkably consistent with the results in terms of ORR and PFS observed in subsequent phase III trials comparing an EGFR/ALK inhibitor with standard chemotherapy treatments. There are no randomized clinical trials underway or planned to compare dabrafenib and trametinib with second-line therapies such as nivolumab, pembrolizumab, or docetaxel, so it is unlikely that higher level evidence will be available to evaluate this combination. The current trial took 13 months to recruit 57 patients from 30 centres in nine countries. The Phase II trial of dabrafenib and trametinib was of reasonable size to be confident of the ORR and PFS. The ORR and PFS for docetaxel and Nivolumab in the second line setting are well established and clearly significantly lower than dabrafenib and trametinib Given the uncommon frequency of *BRAF* mutations and the impressive ORR and PFS seen in the phase II trial, many experts would question the ethics of randomized trials of dabrafenib and trametinib compared with chemotherapy in *BRAF* mutated NSCLC in the second line setting. The principle that active targeted therapy for NSCLC with defined driver mutations results in better outcomes than non-specific therapy with cytotoxic agents has been well established with EGFR and ALK .

There are limitations to the existing data for dabrafenib and trametinib. Firstly, information on the natural history of *BRAF* mutated NSCLC is poor quality. There is only one single arm phase II trial evaluating the efficacy and safety of dabrafenib plus trametinib. Survival data are immature and it is unclear what the magnitude of benefit on overall survival is for the combination treatment in comparison to other established second-line therapies in NSCLC. The manufacturer provided a matched adjusted indirect comparison (MAIC) and network meta-analysis (NMA). However, these comparisons were inherently flawed due to major selection bias. They compare data from a highly select group of patients with a population of patients unselected for molecular characteristics. Neither old data from trials of docetaxel, or more recent data from trials of immune checkpoint inhibitors have information on *BRAF* mutation status to understand the expected ORR, PFS, or OS for *BRAF* mutated NSCLC treated with existing standard second-line therapies. However, there is no plausible rationale to expect that the outcomes for patients with *BRAF* mutated tumors would be substantially better than for unselected patients treated with docetaxel or immunotherapy. The efficacy of docetaxel or immunotherapy in these patients would certainly not be expected to approach the efficacy data observed in the trial by Planchard et al, which does show major activity of dabrafenib and trametinib. Notably, based on estimated gains in QALY's for dabrafenib plus trametinib when compared to appropriate comparators, the submitter has indicated that the incremental benefit with dabrafenib plus trametinib would be 4-5 months when compared to immunotherapies and nearly 9 months when compared to chemotherapies. Although the CGP agree that dabrafenib-trametinib is effective, there is uncertainty concerning the magnitude of overall survival benefit.

There is a paucity of data in BRAF mutated NSCLC regarding dabrafenib therapy alone. The publication by Planchard et al, make reference to an ORR of 33% from dabrafenib alone, although the scope of the current review is evaluating combination therapy with dabrafenib plus trametinib. The ORR from combination dabrafenib and trametinib in NSCLC is almost double. This comparison is weak evidence. However, *BRAF* mutations also occur in patients with melanoma. In randomized trials of dabrafenib and trametinib versus either dabrafenib, or another *BRAF* inhibitor in patients with *BRAF*-mutated melanoma, vemurafenib, demonstrated superior OS for the combination therapy in comparison to single agent BRAF therapy. It seems reasonable to extrapolate the findings of these trials in melanoma, to combination *BRAF* and *MEK* inhibition in *BRAF* mutated NSCLC.

Some questions exist concerning the ability to generalize the observed data for dabrafenib and trametinib to patients with brain metastases. The trial by Planchard et al, allowed patients with stable or treated brain metastases. However, only one patient (although based on additional information received from the submitter during the review, according to investigator assessment, there were 2 patients with brain metastasis and 5 according to the independent review committee assessment) with brain metastases was included. A recent report by Davies et al, in patients with metastatic melanoma, reported an intracranial ORR of 58% for the combination of dabrafenib and trametinib. The high level of activity in CNS metastases in melanoma suggests that these drugs do penetrate the CNS to levels sufficient to result in objective response, and support the use of dabrafenib and trametinib in patients with *BRAF* mutated NSCLC who have stable/treated brain metastases.

In summary, the available data for the combination of dabrafenib and trametinib in *BRAF* mutated NSCLC shows evidence of significant efficacy. The observed ORR and PFS are more than double that expected from standard second-line therapies and represent an additional treatment option in this group of NSCLC patients. Despite the limitations of the data, this therapy should be considered as second-line therapy in good performance status patients (ECOG 0-2) with *BRAF V600E* mutated NSCLC. Based on available data, combination therapy with dabrafenib and trametinib would insert into the existing NSCLC treatment algorithm following first-line chemotherapy and before immune checkpoint inhibitors such as nivolumab or pembrolizumab. In most patients that would be following platinum-based chemotherapy.

## 1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall benefit with the use of dabrafenib plus trametinib in patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation who have been previously treated with chemotherapy. This conclusion was based on a single uncontrolled phase II trial with 57 participants which demonstrated high efficacy. The ORR was 63.2% and median investigator assessed PFS was 9.7 months. The median duration of response was 9 months. These data suggest much greater clinical benefit than what would be expected from standard second-line therapies, although representing a select group of patients.

In making this conclusion the CGP also considered:

- Both pembrolizumab and nivolumab have been shown to be superior to docetaxel as second line therapy. For patients not candidates for immunotherapy, docetaxel would still be a treatment option. Pemetrexed is a second line chemotherapy option for patients with non-squamous NSCLC who have not receive platinum pemetrexed-maintenance pemetrexed.
- The lack of data from randomized trials, or an appropriate control group of *BRAF* positive NSCLC patients, make it unclear what the magnitude of benefit is on overall survival and other clinically relevant outcomes for the combination treatment. Indirect comparison of matched data from other trials of second-line therapy are inherently subject to bias, to make these comparisons difficult to interpret. Nevertheless, there are no randomized trials ongoing, or planned to compare dabrafenib and trametinib with current second-line therapies in *BRAF* mutated NSCLC.
- Overall survival data were immature in the trial. Based on the estimated gains in QALY's for dabrafenib plus trametinib when compared to appropriate comparators, the submitter assumes a 4 to 5 month advantage in survival compared to immunotherapies and nearly 9 months advantage compared to chemotherapies. Although the CGP agree

that dabrafenib-trametinib is effective, there is uncertainty concerning the magnitude of overall survival benefit.

- *BRAF* mutated NSCLC represents an uncommon subtype of non-squamous NSCLC. There is a lack of data regarding the effectiveness of existing therapies for NSCLC specifically in patients with *BRAF* mutations. Given the poor outcome of advanced and metastatic NSCLC, there is a need for improved treatment options.
- Moderate levels of toxicity were observed from the combination therapy. Common side effects observed included pyrexia, nausea, vomiting, diarrhea, asthenia and anorexia. Nearly half of patients experienced at least one grade 3 or 4 AE, including neutropenia, hyponatremia and anemia. Dose reductions were required in 35% of patients and 12% discontinued treatment because of an AE.
- *BRAF* mutations also occur in patients with melanoma. Randomized trials of dabrafenib and trametinib versus either dabrafenib, or another *BRAF* inhibitor, vemurafenib, demonstrate superior OS for the combination therapy in comparison to single agent BRAF therapy. It seems reasonable to extrapolate the findings of these trials in melanoma, to combination *BRAF* and *MEK* inhibition in *BRAF* mutated NSCLC.
- Dabrafenib and trametinib would insert into the existing NSCLC treatment algorithm in patients with good performance status (ECOG 0-2), following first-line chemotherapy and before immune checkpoint inhibitors such as nivolumab or pembrolizumab. In most patients that would be following platinum-based chemotherapy. The CGP however does not support generalizing the available the evidence to include patients with the BRAF V600K mutation.
- As BRAF is a relatively simple and established test it is available throughout Canada. Molecular analysis is already routinely performed on lung samples for EGFR testing therefore BRAF analysis would need to be added. With funding for the test this should not be an obstacle (as stated in the document).

The Clinical Guidance Panel (CGP) considered the pERC initial recommendation and feedback received from stakeholders. The CGP disagree with pERC's conclusions related to the feasibility of an RCT noting that there will not be a randomized trial in this subgroup of patients in the future. The CGP noted that the evidence presented in the trial represents the evolution in evidence for precision medicine in lung and other cancers. The CGP also note that the current decision disadvantages Canadians in being able to access personalized medicine and potential treatment options that advance outcomes.

# 2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lung Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

## 2.1 Description of the Condition

Lung cancer represents the second most common cause of cancer among both men and women in Canada, but the largest cause of death from cancer. In 2016, there were approximately 28,400 new cases of lung cancer and 20,800 deaths from lung cancer.[10] About 85% of these cases would be classified as Non-Small Cell Lung Cancer (NSCLC). Approximately 50% of NSCLC patients have stage IV disease at the time of presentation, with another 25-30% presenting with locally advanced stage III disease.[11] Only 20-25% of patients present with early stage disease amenable to surgical resection. The incidence of NSCLC rises with age and the median age at diagnosis is 70 years. Given the high proportion of patients presenting with advanced stage, it is not surprising that the expected five year survival is only 18%.[10]

## 2.2 Accepted Clinical Practice

Historically, the approach to treatment of patients with advanced and metastatic NSCLC was straight forward. These treatment algorithms were applied to all patients regardless of histologic subtype of NSCLC. First-line therapy included four to six cycles of a platinum agent (cisplatin or carboplatin) in combination with docetaxel, paclitaxel, gemcitabine or vinorelbine.[12] Upon disease progression, patients well enough for consideration of further therapy could be treated with docetaxel,[13] pemetrexed[14] and/ or erlotinib.[15] However, analysis of Ontario provincial data from the Institute of Clinical Evaluative Sciences (ICES) suggest that only one in four patients with advanced NSCLC receive any systemic therapy and only one in three of these patients receive second-line treatment.[16]

Treatment algorithms for advanced NSCLC have become increasingly complex in the last decade. Histologic subtype is an important factor in selecting treatment for patients with NSCLC. Data in both the first-line, maintenance and second-line settings demonstrated that histologic subtype was predictive of response and improved overall survival to pemetrexed chemotherapy. In the first-line, maintenance and second-line settings, patients with non-squamous histology receiving pemetrexed had superior overall survival when treated with pemetrexed.[14,17,18] As a result of these data, histology is now routinely used in the selection of chemotherapy drugs for patients with advanced NSCLC.

More recently, data from multiple studies have emerged demonstrating the importance of molecular profiling of lung adenocarcinomas. One representative study from the Lung Cancer Mutation Consortium (LCMC) undertook molecular profiling of 1007 lung adenocarcinomas.[19] Oncogenic drivers were found in 64% of cases. Commonly observed gene mutations included *KRAS* (25%), *EGFR* (17%) and *ALK* (8%). Mutations occurring in 1-2% of patients included *ERBB2*, *BRAF*, *MET*, *NRAS*, *MEK* and *ROS1*. Therapeutic options for several of these oncogenic driver mutations have demonstrated superior efficacy to standard chemotherapies and have dramatically changed the treatment paradigms for advanced NSCLC. Oral targeted therapies directed at the tyrosine kinase domain of the *EGFR*, *ALK* and *ROS1* genes have all shown high objective response rates and improved progression free survival (PFS) and have been incorporated into treatment algorithms. Molecular profiling of lung adenocarcinomas for *EGFR* mutations and *ALK* translocations is now routinely performed at the time of initial lung cancer diagnosis. Molecularly targeted therapies such as gefitinib,[20,21] afatanib[22,23] and crizotinib[24] are now the preferred initial therapy in patients with these molecular abnormalities.

The most recent significant change in lung cancer treatment options involves the use of immune checkpoint inhibitors. Monoclonal antibodies against the Programmed Death-1 (PD-1) receptor (nivolumab and pembrolizumab),[6,25,26] or its ligand (PD-L1, atezolizumab)[27,28] have all demonstrated higher response rates and improved overall survival in comparison to second-line chemotherapy with docetaxel. Conflicting information exists about the predictive value of tumor expression of PD-L1. Only pembrolizumab therapy is limited to patients with tumors expressing PD-L1. In the first-line setting, pembrolizumab has been shown to be superior to platinum-based chemotherapy among patients with tumors with high PD-L1 expression (50% or more of cells).[29] In addition, the combination of pembrolizumab with standard carboplatin and pemetrexed chemotherapy improved response rates, PFS and overall survival in a randomized phase II trial.[30] These data require confirmation in a phase III trial before being implemented into practice.

Therefore we have moved from an algorithm for advanced NSCLC applicable to all patients to current treatment algorithms that are dependent on histological subtype, molecular profile and potentially tumor expression of PD-L1.

*EGFR* mutated and *ALK* translocated NSCLC

Current treatment algorithms for the 17% of NSCLC patients with tumors harboring an activating mutation of the *EGFR* gene include gefitinib,[20,21] erlotinib,[31,32] or afatinib[22,23] as first-line therapy. Multiple studies demonstrate significant improvements in overall response rate (ORR) and PFS, in comparison to current best chemotherapy options for patients with non-squamous NSCLC. Response rates of 60-80% in combination of median PFS of 10-16 months can be expected in contrast to a 30-40% ORR and 6-7 month PFS from chemotherapy. A randomized trial comparing gefitinib and afatinib found a modest advantage in PFS in favor of afatinib, but significantly increased toxicity and no difference in overall survival.[33] At the time of progression approximately 50% of these patients develop a resistance mutation, T790M. These patients would receive osimertinib, a third generation EGFR TKI, as second-line therapy.[34] Third-line therapy, in patients well enough to receive further therapy at the time of next progression, would include a platinum agent in combination with pemetrexed, with or without maintenance pemetrexed.[35] Forth-line therapy and beyond may include docetaxel, or a PD-1 inhibitor such as nivolumab or pembrolizumab (in PD-L1 positive tumors).

A similar algorithm exists for NSCLC patients with tumors harboring an *ALK* translocation, with molecularly targeted therapies preferred as first and second-line treatment. Crizotinib is the preferred initial therapy based on randomized data demonstrating superior ORR and PFS compared with cisplatin and pemetrexed plus maintenance pemetrexed.[24] Single arm phase II trials of the second generation ALK inhibitors, ceritinib[36,37] and alectinib,[38] both demonstrate response rates of approximately 40-60% with favourable PFS data of 6-7 months in the second-line setting. Both agents are now approved by Health Canada as second-line therapy but not yet publically funded. Nevertheless they would be preferred second-line therapy in patients with *ALK* positive NSCLC. Recent data suggest that alectinib has superior efficacy than crizotinib, but this has yet to impact on clinical practice.[39] Similar to patients with *EGFR* mutations, third-line therapy and beyond include a platinum-agent plus pemetrexed and maintenance pemetrexed, docetaxel and a PD-1 inhibitor.

Challenges exist in determining appropriate treatment algorithms for patients with rare targetable mutations. *ROS1* translocations occur in about 1% of lung adenocarcinomas. Conducting randomized trials in these rare subtypes is challenging. However, many similarities exist between *ROS1* and *ALK*. Crizotinib has been approved by Health Canada in *ROS1* NSCLC based on high ORR and PFS in phase I/II trials and similar data exist for ceritinib.[40,41] Crizotinib would be the preferred first-line therapy for patients with *ROS1* NSCLC, although lack of provincial funding limits this in many provinces across Canada.

Squamous NSCLC

Currently there are no approved targeted agents in Canada for patients with squamous NSCLC. First-line therapy in Canada is generally a platinum-agent plus gemcitabine, but could also include carboplatin plus paclitaxel, or cisplatin plus vinorelbine.[42] There are no approved maintenance therapies in squamous NSCLC. Second-line therapy would be a PD-1 inhibitor nivolumab,[25] or pembrolizumab (in PD-L1 positive tumors).[26] Docetaxel may be offered as third-line therapy[13] and erlotinib remains a fourth-line option in this patient population,[15] although few patients would likely receive this.

Non-squamous NSCLC without a targetable mutation

Several options exist for first-line treatment of NSCLC with tumors that do not have targetable molecular abnormalities. Data support the use of carboplatin, paclitaxel plus bevacizumab.[43] However, the lack of provincial funding for bevacizumab, plus the conflicting data on overall survival, limit the use of this combination. The most common treatment approach for this patient group would be a platinum-agent in combination with pemetrexed followed by maintenance pemetrexed.[35] Other platinum combinations might be considered, although the use of gemcitabine is not recommended.[42] Maintenance pemetrexed remains an option in patients treated with first-line non pemetrexed based therapy.[17] Nivolumab or pembrolizumab (in PD-L1 positive tumors) would be recommended as second-line therapy. For patients not candidates for immunotherapy, docetaxel would still be a treatment option. Pemetrexed is also a second line chemotherapy option for patients with non-squamous NSCLC who have not receive platinum pemetrexed-maintenance pemetrexed. Otherwise, docetaxel or pemetrexed (if not previously used) would be considered as third-line therapy and erlotinib remains a fourth-line option.

New directions

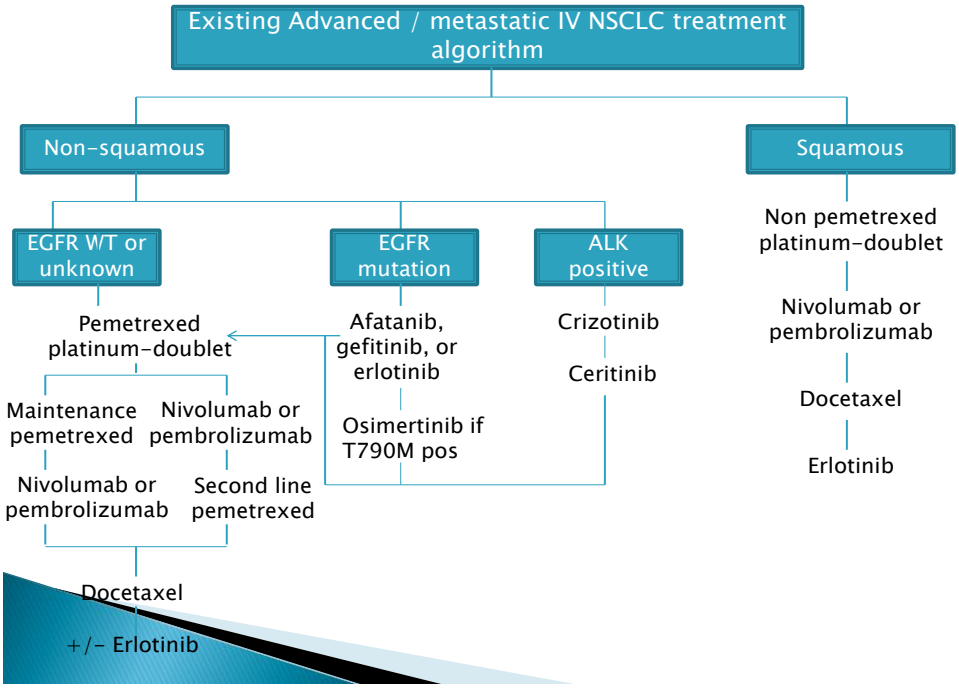
The field of immuno-oncology in NSCLC is rapidly evolving. PD-1 and PD-L1 inhibitors have demonstrated improved overall survival in comparison to second-line therapy with docetaxel. Data is also emerging in the first-line setting. Pembrolizumab has demonstrated higher ORR and longer overall survival compared to platinum-based chemotherapy among NSCLC patients with tumors with high PD-L1 expression (PD-L1 in > 50% of cells).[29] In addition, a randomized phase II trial demonstrated significant improvement in ORR from the addition of pembrolizumab to carboplatin and pemetrexed chemotherapy. These data have already modified practice in the US and will likely change practice in Canada over the next year.

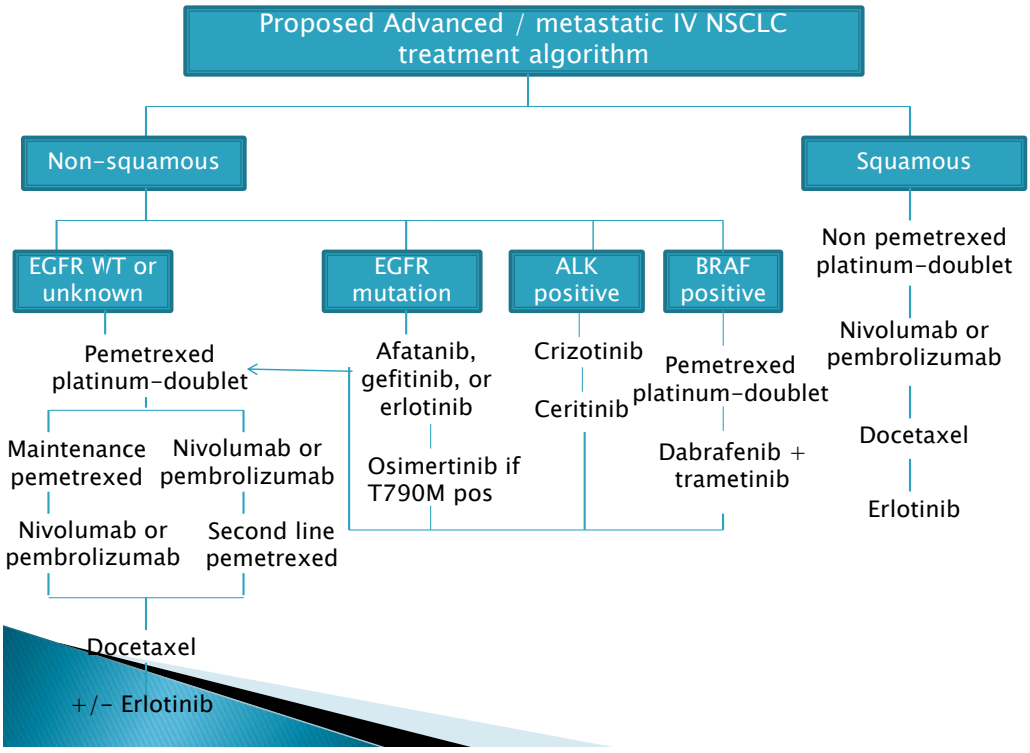
Therefore treating algorithms for NSCLC are changing rapidly on multiple fronts, based on molecular profiling and tumor expression of PD-L1. Many of the molecularly defined subgroups of NSCLC occur in only 1% or 2% of cases and represent uncommon or rare diseases. This creates challenges in understanding the place in therapy for new treatments for these rare diseases. The efficacy of established lung cancer therapies was derived in unselected NSCLC patient populations. New data using targeted therapies is derived from molecularly selected subsets of NSCLC and it is unclear whether these molecularly defined subgroups respond differently to established therapy. This is the context in which to evaluate new data for molecularly targeted therapies in NSCLC patients with tumors harboring a *BRAF* mutation. These patients would represent small proportions of patients in existing clinical trials. However, there are no data on treatment efficacy of established therapies in specific *BRAF* populations. Therefore there is a need to consider data for *BRAF* targeted therapies in the context of the lessons learned from other activating molecular abnormalities in NSCLC such as *EGFR*, *ALK* and *ROS1*, as well as other *BRAF* dependent malignancies such as melanoma.

Dabrafenib and trametinib are molecularly targeted therapies for patients with *BRAF V600E* mutations. Based on data from the LCMC above, *BRAF* mutations occur in approximately 2% of NSCLC adenocarcinomas and are considered oncogenic drivers. They generally occur independent of other common oncogenic drivers, including *EGFR* mutations and *ALK* translocations. Dabrafenib and trametinib were evaluated in a single arm, multicentre phase II trial. Eligible patients included patients with *BRAF V600E* mutations, who had received no more than three prior treatments for advanced NSCLC (including platinum-based therapy), ECOG performance status 0-2 and good organ function. Patients with small asymptomatic or stable treated brain metastases were allowed. These patients had all received standard first-line platinum-based therapy and many (67%) were receiving dabrafenib and trametinib as second-line treatment. The expected response rate to standard second-line chemotherapy is approximately 8-10%, with expected median PFS of 3-4 months and median overall survival of 7-8 months.[14] The observed response rate for dabrafenib and trametinib was 63.2% with a median PFS of 9.7 months. Responses were observed rapidly after initiation of therapy and the median duration of response was 10.6 months. These efficacy parameters are all substantially better than the expected efficacy from second-line chemotherapy with docetaxel or pemetrexed. They are reflective of the efficacy observed with targeted therapies in other molecularly defined subgroups of NSCLC such as *EGFR* mutations and *ALK* and *ROS1* translocations. The toxicity profile of dabrafenib and trametinib is different to that expected from chemotherapy, with common side effects of pyrexia, nausea, vomiting, diarrhea and asthenia.

The efficacy of dabrafenib and trametinib is very reflective of data observed from single arm phase II trials of EGFR and ALK inhibitors, which accurately predicted efficacy in phase III randomized trials. Based on available data, dabrafenib and trametinib would be used as second-line therapy for patients with *BRAF V600E* mutation positive NSCLC tumors, although there will be an existing cohort of patients with *BRAF* mutations who have already received second-line therapy. It would represent an incremental treatment option in this group of patients displacing nivolumab or pembrolizumab to third-line therapy and docetaxel to fourth-line therapy. Erlotinib would unlikely be used in this patient population unless there was a co-existing *EGFR* mutation.

| Patients with *BRAF V600E* positive NSCLC | | |
|---|---|---|
| Line of Therapy | Current | Proposed |
| 1st-Line | Platinum-agent plus pemetrexed | Platinum-agent plus pemetrexed |
| Maintenance | Pemetrexed | Pemetrexed |
| 2nd-Line | Nivolumab or pembrolizumab | Dabrafenib plus trametinib |
| 3rd -Line | Docetaxel | Nivolumab or pembrolizumab |
| 4th -Line | Erlotinib | Docetaxel |



## 2.3 Evidence-Based Considerations for a Funding Population

There are approximately 28,800 new cases of lung cancer annually in Canada.

| | |
|---|---|
| Proportion of NSCLC (85%) | 24,480 |
| Proportion with locally advanced or metastatic disease (75%) | 18,360 |
| Proportion with adenocarcinoma (70%) | 12,852 |
| Proportion with *BRAF* mutation (2-3%) | 257 - 386 |
| Proportion with *BRAF V600E* mutation (58%) | 149 – 224 |

Based on the above assumptions, it is estimated that there are between 149 and 224 new cases of advanced or metastatic *BRAF V600E* NSCLC annually in Canada. Patients being considered for therapy with dabrafenib and trametinib would have previously received platinum-based chemotherapy in either the adjuvant and/or metastatic setting. They would have an ECOG performance status of 0-2 and good organ function. Patients with asymptomatic or treated brain metastases would be considered for treatment. Not all patients with advanced and metastatic NSCLC are referred for, or receive treatment and not all patients have tissue available for molecular testing. All these factors will reduce the number of *BRAF V600E* positive patients who actually receive therapy with dabrafenib and trametinib.

NSCLC tumor samples are currently not routinely tested for *BRAF* mutations. However, *BRAF* testing is routinely performed for patients with metastatic melanoma. Therefore, there is existing experience within pathology laboratories to conduct *BRAF* mutation testing and this is not expected to be a barrier. There will be a need to fund *BRAF* testing in conjunction with drug funding. BRAF testing can be included in an initial panel when molecular analysis is performed on a lung sample, or performed after other molecular analysis and initial chemotherapy has failed. If BRAF testing is to be done following other molecular analysis, residual DNA from testing should be stored so that BRAF analysis can be done on the residual material. There may be some patients who do not have adequate tumor tissue available for testing who require repeat biopsy to obtain tissue. Greater efficiencies will be made through the use of platform molecular testing of lung cancer samples, but this is currently not uniformly available across the country.

The expected population of patients eligible for therapy with dabrafenib and trametinib would be adult men and women with advanced and metastatic NSCLC. Evidence-based funding criteria for dabrafenib and trametinib would include:

- Metastatic *BRAF V600E* positive NSCLC
- Prior platinum-based therapy for metastatic disease unless relapse within 12 months of adjuvant therapy
- ECOG performance status 0-2
- If brain metastases present should be asymptomatic or stable post treatment.

## 2.4 Other Patient Populations in Whom the Drug May Be Used

The population of patients to be treated with dabrafenib and trametinib should be fairly obvious. There would be no reason to offer dabrafenib and trametinib to NSCLC patients without *BRAF* mutations. There is some potential that treatment may be offered off label to patients with non *V600E BRAF* mutations. It is also likely that oncologists will extrapolate the existing data to patients with poor performance status (ECOG 3 and 4). There may be value in setting up a prospective register of patients with poor performance status who receive treatment with dabrafenib and trametinib.

# 3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Input on Dabrafenib (Tafinlar) and Trametinib (Mekinist) for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation and who have been previously treated with chemotherapy was provided by two patient advocacy groups: Lung Cancer Canada (LCC), and The Ontario Lung Association (OLA). Their input is summarized below.

OLA conducted two recent phone interviews with patient respondents living with COPD and lung cancer within a six month period, as well they gathered information from twelve respondents (eight patients with lung cancer and four family members) who completed phone interviews approximately 1 year ago. A certified respiratory educator also provided input that was used within the OLA submission. OLA reported that there were no patients within this evidence group submission that have experience with dabrafenib and trametinib for NSCLC.

LCC conducted a national survey of lung cancer patients and caregivers in August 2015. There were 91 patient and 72 caregiver respondents who completed the survey. All of the patient respondents who completed the survey have or have had lung cancer, and all of the caregiver respondents are currently caring for, or have previously cared for patients with lung cancer. To provide context around lung cancer treatments and patients and caregiver needs, LCC included individual interviews from recent LCC submissions that were submitted to the pCODR program; these included submissions for crizotinib (first line), ceritinib (second line), osimertinib and alectinib. A total of 68 patient and 49 caregiver respondents were gathered from these previous submissions.

To gather information on patients with experience with the BRAF+ gene mutation based on the notification issued in April 2017, LCC conducted appeals across social media, the internet, international lung cancer patient groups, Canadian oncologists and US clinical trial oncologist. LCC had a difficult time finding patients and caregivers with this experience because this particular genetic mutation is so rare. LCC conducted five one-on-one interviews with patients with BRAF+ experience. Only three Canadian patients were found, so the search was broadened to include the US where two additional patients were found. One of the US patients had tried the dabrafenib-trametinib combo. LCC also conducted an environmental scan of online forums to gather patient and caregiver feedback regarding dabrafenib and trametinib and the BRAF+ gene mutation in general. From this, the comments from four patient and nine caregiver respondents were included.

In summary, the perspectives of nine patients and nine caregivers, all with BRAF+ experience, are captured in the LCC submission. Through both one-on-one interviews and environmental scans LCC captured the perspectives of 11 patients and caregivers who had experience with the dabrafenib and trametinib combination therapy (one husband and wife, caregiver and patient, respectively, from Quebec were interviewed together. Their experience has been counted only once for this total), four tried dabrafenib as monotherapy, one tried trametinib as monotherapy and two were currently on other treatments (one patient who tried trametinib as monotherapy was intolerant and is currently on off-label Zelboraf).

Below is a chart supplied by LCC that illustrates those whose experiences where included in their submission.

| Tafinlar/Mekinist | | | | | Rx | | | |
|---|---|---|---|---|---|---|---|---|
| Type | Age | Location | Gender | Status | Combo | Tafinlar | Mekinist | Other |
| 1 on 1 | 32 | ON | F | Patient | | | | Keytruda |
| 1 on 1 | 64 | NY | F | Patient | | | * | Zelboraf |

| Tafinlar/Mekinist | | | | | Rx | | | |
|---|---|---|---|---|---|---|---|---|
| Type | Age | Location | Gender | Status | Combo | Tafinlar | Mekinist | Other |
| 1 on 1 | 73 | ON | M | Patient | | * | | |
| 1 on 1 | 67 | NH | M | Patient | * | | | |
| Env. Scan | | | | Caregiver | * | | | |
| Env. Scan | | | F | Caregiver | | * | | |
| Env. Scan | | | F | Caregiver | | * | | |
| Env. Scan | 42 | | F | Patient | * | | | |
| Env. Scan | | | | Patient | * | | | |
| 1 on 1 | 71 | QC | M | Caregiver | * | | | |
| 1 on 1 | 71 | QC | F | Patient | * | | | |
| Env. Scan | | | M | Patient | * | | | |
| Env. Scan | | | F | Caregiver | * | | | |
| Env. Scan | | | F | Caregiver | * | | | |
| Env. Scan | | | | Patient | * | | | |
| Env. Scan | | | F | Caregiver | * | | | |
| Env. Scan | | | | Caregiver | * | | | |
| Env. Scan | | | F | Caregiver | | * | | |

From a patient perspective, lung cancer impacts many aspects of day-to-day life. Specifically, both OLA and LCC reported that it affects the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, emotional well-being and may cause financial hardship. It was reported by both patient and caregiver respondents that high symptom burden of lung cancer is difficult to manage. LCC indicated that symptoms may include: loss of appetite, cough, pain, and shortness of breath. Moreover, one of the most common symptom burdens for lung cancer patients is fatigue or lack of energy. OLA noted that symptoms are not fixed or consistent, but rather change frequently, which can be difficult to manage.

For the vast majority of this patient population, the current standard of care will be chemotherapy. According to LCC, chemotherapy is viewed as a necessary, but feared treatment. The infusions themselves presented challenges beyond travel time and hospital visits; some respondents reported feeling sick even before the infusion was completed and that significant recovery time was needed after each chemotherapy infusion.

Respondents who do not have experience with the drug under review reported that key treatment outcomes that respondents would most like to address are: to stop or slow the progression of the disease, to reduce or eliminate side effects (e.g., reduce pain, fatigue, cough and shortness of breath, inability to fight infection, burning of skin and impact to mood), and to improve appetite and energy. Respondents would also like the ability to have treatments at home, so it would remove the need for the patient or the caregiver to take time off of work.

For respondents who have experience with dabrafenib-trametinib, they have indicated that the response to this treatment was positive. LCC reported that four of those respondents stated: '*no evidence of disease*'. While some respondents had no side effects, others experienced high to severe side effects from this treatment. In a couple of cases, the side effects were so severe that hospitalization was required. One respondent on combination therapy reported that he needed to stop treatment altogether due to severe side effects. However, the vast majority of these cases were resolved with dosing adjustments. After adjustments, side effects were reported to be none/low by 8 of the 11 respondents on combination therapy.

Please see below for a summary of specific input received from LCC and OLA. 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 Advanced Non-Small Cell Lung Cancer with a BRAF V600 Mutation

Both LCC and OLA reported that lung cancer impacts many aspects of day-to-day life for people living with it. Specifically, it affects: the respondents' ability to work, travel, socialize and participate in leisure and physical activities. It also affects their relationships with family and friends, independence, emotional well-being and their financial situation. LCC also found that, in a survey of Canadian patients with advanced lung cancer, it was reported that two-thirds of respondents feel their symptoms interfered with daily activities; anxiety or worry is common, reported as "frequent" or "constant" in 27%. Rates of depression in advanced lung cancer patients varied between 16-50%, which is seen to be consistently higher than other cancer sites.

For some, it was reported that it strips them of their ability to do anything on their own. One respondent stated: "*this disease has affected all parts of my life. I am not able to go outside on cold days, I am no longer able to drive, and must use volunteer drivers to get to my appointments, I am dependent on my neighbours to get my mail each day and take my weekly trash out. I have lost a significant amount of weight and am tired, weak and without energy. I am no longer able to do the activities I enjoy. It is very hard to be positive and hopeful.*"

OLA also reported similar symptoms and problems that patients experience as a result of lung cancer, which include: pain (could be very intense at times), shortness of breath, cough, weakness, fatigue and being bed-ridden. OLA indicated that symptoms are not fixed or consistent, but rather change frequently, which can also be difficult to manage.

Similarly, LCC noted that lung cancer patients experience the highest burden of symptoms. Based on a literature search conducted by LCC, these can include fatigue, loss of appetite, cough, pain, shortness of breath and blood in sputum were found to have significant impact on the quality of life predictors.

In addition, LCC found that financial hardship was experienced by 41% of respondents in the Canadian study. Approximately 69% of respondents believed their illness imposed a significant hardship on those close to them.

LCC reported that about 2% of NSCLC patients are BRAF+ and 1% have the BRAF V600 mutation. In conjunction with lung cancer's 17% five-year survival rate, LCC found that this posed a significant challenge when trying to find patient and caregivers who are willing to share their experiences.

OLA found that many of the people interviewed spoke about issues of timeliness and heightened anxiety during this interval. One respondent stated "*I waited six months to see the specialist and by then he said he couldn't do anything. It was too late.*" Another respondent shared a similar concern, stating "*It took a year to finally make the diagnosis.*" OLA also noted that many of the respondents stated that they had little information about the disease (either cancer in general or lung cancer specifically), its treatment options, and the eventual prognosis in terms that would apply to them.

### 3.1.2 Patients' Experiences with Current Therapy for Advanced Non-Small Cell Lung Cancer with a BRAF V600 Mutation

LCC reported that for any NSCLC patient that tests negative for the ALK or EGFR biomarkers, their first line of therapy will be chemotherapy, even for those that test positive for BRAF. According to LCC, chemotherapy can put a patient's life on hold. One respondent stated: "*Chemo kicks the crap out of your body and mind. You feel absolutely horrible. [For a] half year of your life you feel like hell for a week, every three weeks. It's not for wimps!*"

Respondents interviewed by OLA reported using the following treatments: Spiriva, Seebri, Advair, Symbicort, Daxas, Prednisone, Ventolin, Atrovent, Serevent, Onbrez, Tudorza and Ventolin (as needed). One patient is also undergoing radiation and chemotherapy, and the other patient only had radiation.

According to OLA, current treatments provide some relief for the following symptoms: fatigue, shortness of breath, cough, appetite loss and low energy, but side effects such as: palpitations, dry mouth, mouth sores, vision and urinary problems and impact on mood need to be better managed. For one respondent it was reported that the radiation has left them with an extremely sore and painful throat. One respondent stated: "*I have been burned from my treatments from front to back. I now struggle to swallow, but must eat to re-gain weight and energy. I have also lost the feeling in the tips of my fingers and toes. This makes it difficult for me to pick up items, especially money / change when paying for something.*" Another OLA respondent indicated that "*whenever I try to swallow food, it feels like I am swallowing knives*".

All of the BRAF+ patients included in LCC submission were reported to be at stage 4 NSCLC. It was reported that all respondents received chemotherapy before receiving any kind of targeted therapy including, in most cases, dabrafenib and trametinib combination therapy. According to LCC respondents, the burden of chemotherapy was felt during all stages of the treatment. Moreover, the burden of chemotherapy extends beyond the patient; for example, many caregivers must take time off from work to care for the patient receiving treatment.

Below are the key points reported by LCC to help illustrate the burden of chemotherapy felt by respondents during the different stages of the treatment:

1. Diagnosis: Chemotherapy carried a psychological burden even before receiving the first dose. Those that did not have to go through chemotherapy expressed it as a "*relief*". One respondent stated: "*When I was first diagnosed, the fear of traditional chemotherapy and radiation was overwhelming.*" Patients used words such as "*cytotoxic killer*" and "*poison*" to describe chemotherapy.

2. Infusion: The infusions themselves presented challenges beyond travel time and hospital visits. Some respondents reported feeling sick even before the infusion was completed.

3. Recovery: Significant recovery time was needed after each chemotherapy infusion. For respondents, this meant "*two bad weeks and one good week.*" It was also reported that walking and activity were difficult. One respondent stated: "*I was so sick on infusion chemo. I wasn't functional*," In addition to being sick and tired, this respondent also noted that he would have mood swings and get irritated easily. His wife relied on him to drive her to work, but the chemotherapy significantly impacted the family. Other respondents found that chemotherapy took away precious time that they could spend with loved ones due to the side effects. Even when the more acute side effects subsided, their susceptibility to infections due to low white blood counts made spending time with friends

and family difficult. One respondent stated that the social element is very important to helping her stay positive.

4. Lasting effects of chemotherapy: One respondent that was on chemotherapy felt that you never recover and that it can leave them "*too tired to do anything. There's no point in going out*." Another BRAF+ respondent described her current treatment as, "*much more manageable than chemotherapy which was terrible. I was so sick I wanted to die. I felt 'metallic' all the time*." She reported that it took her a full year to go back to feeling 75% normal, before diagnosis.

5. "Looking sick": LCC reported that not only did respondents feel sick on chemotherapy, they also looked sick. On chemotherapy, they tended to stay at home and some experienced hair loss. In contrast, LCC reported that respondents felt and looked well on the oral therapies. Respondents and their families felt that "*No one could tell I [they] had cancer*."

OLA reported that respondents would like their treatments to provide enough help that they will experience improved independence and require less assistance from others. The desire for: fewer medical appointments and less financial cost burden. As an example of this cost burden, OLA noted that due to the weight loss and need for good nutrition; one patient respondent was instructed to buy certain foods (such as Ensure – a nutritional supplement) which can be expensive for those living on a fixed income or pension. Training for general practitioners (GPs) was also mentioned as a need, as these patients felt their GPs needed to know more about lung diseases so there would not be unnecessary delays in diagnosis and treatment.

### 3.1.3 Impact of Advanced Non-Small Cell Lung Cancer with a BRAF V600 Mutation and Current Therapy on Caregivers

According to both LCC and OLA, caregivers of patients living with lung cancer experience many of the same negative impacts on their lives as the patients themselves. Caregiver respondents also indicated that caring for patients has affected their work, finances, relationships with family and friends, physical and leisure activities, independence, and ability to travel and socialize. LCC found that when asked what feelings were associated with the lung cancer experience, anxious/stressed was the number one response with 50% of respondents. It was also found that 42% of patient respondents reported having these feelings of anxiety, while 61% of caregiver respondents who reported feeling the same. OLA highlighted an overarching theme was the emotional toll of watching patients with lung cancer suffer in pain, and knowing there is little you can do to alleviate the discomfort and pain.

To help illustrate the experiences of caregivers, below are some of the key responses reported by LCC:

1) The stigma unique to lung cancer places an additional emotional burden on caregivers. In the Faces of Lung Cancer Report (FOLCR), caregivers seemed to feel the stigma more acutely than patients. In addition to this, 38% of responding caregivers felt that they had to advocate more strongly for their family members because of a lung cancer diagnosis.

2) Lung cancer is further handicapped by late diagnosis. Across Canada, most lung cancer is diagnosed in Stage IV (Statistics Canada, Canadian Cancer Registry) – LCC believes this is potentially when the physical and emotional demands of caregiving are at their peak. The FOLCR indicated that 82% of caregivers said their caregiving experience was somewhat to very stressful. The most common source of stress for caregivers was dealing with the caregivers declining health.

3) Lung cancer carries a significant economic toll on household finances. Work and relationships often gave way to the challenge of providing care. LCC reported that 59% of caregivers reduced the number of hours they worked and a further 8% quit their jobs. Moreover, 50% of caregivers reported a negative impact on their household financial situation. With patients also reducing their number of working hours or being unable to continue with work, this trend threatens to have a significant impact on the economy by taking not one but two members out of the workforce.

LCC also noted that the high cost of lung cancer drugs that have Health Canada approval for efficacy but have not yet been approved for funding or refused funding, places an extremely stressful burden on patients and caregivers. LCC states that patients either have to pay "insane" prices out of pocket, be fortunate enough to have the right type of insurance or simply decide to go without the lifesaving drug.

4) High symptom burden of lung cancer is difficult to manage for both patients and caregivers. LCC indicated that one of the most common symptom burden for lung cancer patients is fatigue or lack of energy. This finding is aligned with the ones that caregivers and patients in the FOLCR found hardest to manage, and had the highest impact on quality of life. Fatigue was also the top treatment side-effect that both patients (68%) and caregivers (43%) found most difficult to manage. This was followed by pain, concentration or memory issues and nausea – each with a combined patient and caregiver rating of 31%.

5) Testing required so that lung cancer doesn't turn into a waiting game. According to LCC, lung cancer doesn't wait for anybody, but lung cancer care can be a waiting game. By far the biggest stressor for caregivers is fear. The anxiety felt with a loved one's disease was the feeling, more than any other, that was most associated with their lung cancer experience (50%) and this was reported by more caregivers (61%) than the patients themselves (42%) in the FOLCR. "It is emotional insanity to make people wait!" says one respondent, a BRAF+ patient. The fear and anxiety with lung cancer itself is enough. By adding wait times, such as for multiple biopsies and testing, that fear and anxiety is compounded. LLC states that lung cancer patients already have limited time as it is and testing for genetic markers such as BRAF needs to be put into place and implemented as early as possible so that patients and caregivers know that they have options and what those options are.

6) BRAF+ treatment offers hope. LCC found that caregivers express relief when they learn what it means for their loved one to be BRAF+. To know that there are treatments available that are specifically designed to target and treat this particular form of cancer offers a great deal of hope. Upon learning that her husband has the BRAF V600e mutation and that there are clinical trials available that utilize targeted therapy, a respondent expressed her eagerness to access this type of treatment by stating, "There are trials near our home, but they were all closed…We'd travel ANYWHERE." Another caregiver respondent described it as a "miracle." His wife had 3 biopsies before BRAF was found and said, "We always felt left out, you've got to keep testing. A marker gives you something to aim for. Without it, you're shooting in the dark." This patient is now on dabrafenib-trametinib.

## 3.2 Information about the Drug Being Reviewed

### 3.2.1 Patient Expectations for and Experiences To Date with Dabrafenib-Trametinib

OLA reported that key treatment outcomes with the drug under review that respondents would most like to address are: to stop or slow the progression of the disease, to reduce pain, fatigue, cough and shortness of breath, and to improve appetite and energy.

Respondents would expect the drug under review to reduce or eliminate the following current side effects: pain, fatigue, nausea, shortness of breath, appetite loss, low energy, inability to fight infection, burning of skin and impact to mood. They would also like there to be less or no cost burden associated with new treatments. Respondents were focused on the issues of understanding the treatment options and what those options actually meant for them. Several stated the need for clear communication about these topics as an important aspect of their decision-making and coping.

On a practical level, respondents would like the ability to have treatments at home, so it would remove the need for the patient or the caregiver to take time off of work. In their view, this would also lead to less disruption of the daily routine.

**Patient Experiences with Dabrafenib-Trametinib.**

None of the respondents from OLA had experience with dabrafenib-trametinib combination for NSCLC.

According to LCC, all 9 of the respondents represented in this section were BRAF positive.

LCC found dabrafenib and trametinib to be effective at treating the disease. They noted that many of the patient and caregiver respondents were very pleased with their results. Seven respondents stated that the response to this treatment was positive with four of those respondents reporting what every person with lung cancer wants to hear: '*no evidence of disease*'.

One caregiver respondent said, "*My husband was on his death bed when he started this combo. His last PET scan stated 'marked response with no evidence of lung disease present.' Nothing lit up!*" Another respondent that was interviewed stated that he thought he was going to die within six months. He had previously been treated with chemotherapy but upon receiving combination therapy from a clinical trial, he reported that he "*felt a difference after five days and after nine days it was day and night (compared with chemotherapy). I felt so much better! I can't think of any side effects*." He has been on therapy for 2.5 years and was declared NED within 24 weeks of receiving the treatment.

LCC reported that side effects varied greatly between patient respondents. While some patient respondents experienced no side effects, others experienced high to severe side effects from this treatment. LCC found the most commonly reported side effects of all the 18 respondents were: flu and fever-like symptoms (n=6), nausea (n=5), fatigue (n=5), chills (n=4) and rash (n=3). Vision problems and hypersensitivity to the sun were also reported in one case each. In terms of magnitude, patients and caregivers reported side effects as: none/low (n=4), medium (n=2) or high/severe (n=8).

In a couple of cases, the side effects were so severe that hospitalization was required. One patient respondent on combination therapy reported that he needed to stop treatment altogether due to severe side effects. One caregiver respondent was dismayed since the treatment had been working very well at first, "*My wife stopped Tafinlar/Mekinist 4 days ago (due to) chills, severe tremors, high temp., nausea and vomiting. Just hate to stop the only treatment that showed such a dramatic decrease in tumours*." This respondent went on to say that his wife resumed dabrafenib and trametinb after only a few days off of treatment. She received a second dose reduction and she is now "*eating well, her weight is back and she feels good. We are now into month ten!*" After adjustments, side effects were reported to be none/low by 8 of the 11 patients and caregiver respondents on combination therapy. LCC concluded that on the whole, the dabrafenib-trametinib combination therapy is a highly tolerated drug.

LCC indicated that dose reductions appeared to resolve side effect issues. Of the eight respondents who were on combination therapy and reported high/severe side effects, the vast majority of these cases were resolved with dosing adjustments. Six of these respondents reported receiving dosing adjustments. Five of those six reported their side effects were reduced to a manageable level or completely to zero and a return of energy and a continuation of their life. One respondent stated that "*In the beginning there were a lot of med(ical) adjustments due to high fevers and chill (sic) but I haven't had that in a while now. Most every day is great*." According to LCC, patients and caregivers were able to get their life back with this treatment. LCC noted that it is important to remember that three of these patients report no side effects at all and four have reported no evidence of disease.

LCC noted that side effects of treatment are not the only challenge faced by lung cancer patients. Symptoms of the disease itself can represent a significant encumbrance. One patient said he went from feeling tired, shortness of breath and coughing 200-500 times per day prior to receiving treatment, to feeling great with no coughing, symptoms or side effects. One respondent stated: "*After nine days it was 'night and day'*". For another, within two weeks of starting dabrafenib-trametinib her breathing was better and her coughing stopped. "*The results were dramatic*," she said. Another respondent said he found a return of the same energy levels he had before being diagnosed. LCC submits that targeted therapy not only offers an improvement in disease response with fewer side effects than chemotherapy, but also alleviates the heavy symptom burden of lung cancer.

Respondents felt that getting their lives back is a priority. According to LCC, one important factor in the lives of patients is the ability to go back to work. Feeling useful and contributing to society gives patients a sense of self-worth. Conversely, when they are unable to return to work due to symptoms or side effects, it leaves patients feeling empty. Moreover, there is a huge economic toll on patients and their families if they are no longer able to earn their normal salary, 58% of respondents reported often lowering their hours at work or quitting, [FOLCR, 2015]. One respondent said he feels optimistic, grateful and positive. "*I still work. I'm a family person and I can enjoy going on vacation now. It worked for me and I might not be here now*."

LCC found that there is a feeling of positivity and gratitude when patients discover they have the BRAF+ gene mutation as they report that it gives them hope. Hope in the form of options. When a target is identified, they know that there are more treatment options available to them and this comes with a big sense of relief. A respondent on dabrafenib-trametinib therapy said "*I feel good! It was a miracle to find some mutation to help me through this*." Another respondent reported that her doctors were "*very excited when she was BRAF+, they told me it was my luckiest day!*" Although she is currently receiving Zelboraf off-label (she lives in the US), she stated that she is "*optimistic about future treatments*" including dabrafenib and trametinib.

## 3.3 Additional Information

OLA indicated that a biopsy is often required for an accurate diagnosis of lung cancer and described it being as "incredibly painful". One patient respondent had to have this procedure done three times, as the technician was not skilled and had difficulty reaching the tumour.

LCC believes that testing for the BRAF genetic marker should not be a barrier to treatment. LCC noted that the testing for BRAF is already in place for melanoma, as such, there is no new setup or technology needed and no additional burden required on the healthcare system. The fact that any patient who is ALK negative and EGFR negative will immediately go on chemotherapy, allows time to implement the BRAF test during chemotherapy and therefore would not represent a delay in treatment. LCC submits that once panel testing is the standard

of care, this will no longer be an issue. BRAF+ patients should have access to the same additional treatment options afforded to those with other genetic markers.

According to LCC, there is no reason to withhold dabrafenib-trametinib while decisions are pending for other treatments because targeted therapies work much better compared to chemotherapy. Where optimal sequencing is a concern for the dabrafenib-trametinib combination treatment, LCC is of the opinion that sequencing has already been established by a previous pCODR recommendation. pCODR issued a positive recommendation for pembrolizumab to be used after failure on chemotherapy.

> "Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should have disease progression on authorized therapy for these aberrations and cytotoxic chemotherapy prior to receiving pembrolizumab." [Pembrolizumab (Keytruda) Non-Small Cell Lung Cancer - pERC Final Recommendation, 2016]

LCC considers that, after failing on chemotherapy, the sequence of treatments should exhaust any existing targets first and then move on to immunotherapy. Since dabrafenib and trametinib are targeted therapies, it stands that this combination treatment should be placed in the same sequence, following chemotherapy and preceding immunotherapy.

LCC notes that targeted therapies do not just offer marginal life benefits. Patient testimony and clinical data support that patients on these therapies live longer and live well. Without public funding, these patients face an impossible choice, accept a less effective standard of care, or take from savings that may have been set aside for the family's future.

LCC submits that targeted therapy has changed the paradigm for the evaluation of efficacy. In the case of dabrafenib and trametinib, LCC asserts that there will be no phase III data as no further studies are planned due to the low numbers and difficulty in finding BRAF+ patients. In fact, one BC physician has been testing for an entire year and has only found one BRAF+ patient. Nevertheless, LCC believes that those lung cancer patients who are BRAF+, and their families, should be accorded the same opportunities as others and should not be penalized because treatment development has evolved at a pace faster than governing and regulatory bodies can adapt to.

LCC recognizes that funding and overall burden on the public health system is a concern. All stakeholders including the manufacturer must work together to find solutions. As one caregiver states, "*I'm disappointed that it costs so much. I understand that money spent to produce and market these drugs is high, but the cost is insane*." LCC submits that cost is an issue that must be globally addressed. However despite the cost, LCC is of the opinion that funding this patient population will not be overly burdensome on the healthcare budget for of the following reasons: (1) BRAF+ lung cancer patients are only 2% of the overall lung cancer population; and (2) not every BRAF+ positive lung cancer patient will survive progression on first-line chemotherapy.

# 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. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

**Overall Summary**

Input was obtained from six provinces (Ministries of Health and/or cancer agencies) and the federal drug plan participating in pCODR. PAG identified the following as factors that could impact the implementation of dabrafenib/trametinib combination therapy:

Clinical factors:

- Place in therapy of dabrafenib/trametinib and sequencing with currently available treatments for NSCLC
- Comparison with other treatments
- BRAF testing not currently routinely done for NSCLC

Economic factors:

- High cost of combination therapy
- Cost of BRAF testing in all patients with NSCLC who have failed first-line platinum therapy to identify the 1-2% with BRAF mutation (the number of patients to be tested and the number of patients with BRAF mutation).

Please see below for more details.

## 4.1 Factors Related to Comparators

Although there are multiple treatments available for NSCLC, PAG noted that there is no treatment specifically targeting BRAF V600 mutation. However, PAG is seeking information comparing and sequencing dabrafenib/trametinib to existing treatments.

## 4.2 Factors Related to Patient Population

PAG noted that the number of previously treated patients with BRAF mutation NSCLC would be relatively small. PAG is seeking information on whether patients previously treated with non-platinum based chemotherapy, such as single agent docetaxel, would be eligible for treatment with dabrafenib/trametinib, if they have BRAF mutation.

Dabrafenib/trametinib is indicated for BRAF V600 mutation. PAG is seeking information on whether other variants of BRAF mutation exists in lung cancer and whether dabrafenib/trametinib would be effective in these other variants.

PAG indicated that there may be requests for use of dabrafenib/trametinib in first line for patients whose BRAF status is known upfront, especially for patients where chemotherapy may be difficult to deliver. PAG noted the Health Canada approved indication includes all patients with BRAF mutation and that the phase 2 trial included a cohort with a very small number of patients using dabrafenib/trametinib first line. However, the funding request for this review is for patients who have been previously treated with at least one line of prior chemotherapy and PAG noted that first-line use would be out of scope of this review. PAG also noted that mesothelioma and other types of lung cancer would be out of scope.

PAG is seeking guidance on the place in therapy and sequencing of existing treatments, including other oral targeted therapies (if an EGFR or ALK mutation can co-exist with BRAF) , PD-1 inhibitors and chemotherapy, with dabrafenib/trametinib. PAG is seeking information on whether dabrafenib/trametinib would be used in third-line after second-line treatment with PD-1 inhibitors or whether dabrafenib/trametinib would be used second-line followed by PD-1 inhibitors in third-line.

## 4.3 Factors Related to Dosing

PAG has concerns with patient compliance due to pill burden and dose confusion. The dose of dabrafenib is two capsules twice daily and the dose of trametinib is one tablet once daily. There are some concerns that patients may confuse the number of tablets versus the number of capsules and the frequency of the tablets versus the frequency of the capsules. These are issues for implementation, with increased patient education requirements.

## 4.4 Factors Related to Implementation Costs

PAG indicated that BRAF testing is not currently done for patients with NSCLC. PAG is seeking guidance on whether BRAF mutation testing should be done at diagnosis when ALK mutation, EGFR mutation and PD-L1 testing is done or after failure of chemotherapy. In addition to time for test results, PAG has concerns that an adequate tissue sample may not be obtained for all the tests to be conducted upon diagnosis. If BRAF mutation is done after failure of chemotherapy, patients may need another biopsy. PAG noted that it is a large number of patients to be tested to find 1-2% of patients with BRAF V600 mutation. PAG has concerns regarding the cost of testing and that the health system may not have adequate laboratory resources to accommodate the large number of additional patients with lung cancer to be tested for BRAF mutation.

## 4.5 Factors Related to Health System

PAG noted that pyrexia is a potential adverse event frequently associated with dabrafenib/trametinib and PAG indicates that resources for monitoring and managing patients for pyrexia and other similar adverse events will be required.

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 and chemotherapy chair time is not required. 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.

With two different drugs, two dispensing fees, two co-payments and varying deductibles would be applied in provinces where oral drugs are funded through its pharmacare program.

## 4.6 Factors Related to Manufacturer

The high cost of combination therapy and lack of comparative data demonstrating cost effectiveness are barriers to implementation.

# 5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided from two groups: Medical Advisory Committee Lung Cancer Canada and from a provincial tumour group advisory committee.

The clinicians providing input noted that there is a very small number of patients with BRAF V600E mutation positive NSCLC who could benefit from treatment with dabrafenib/trametinib. The clinicians providing input identified that the optimal algorithm for BRAF mutation testing would be upfront next generation sequencing so the result is available after progression on platinum doublet. There is a difference in opinion on where dabrafenib/trametinib would fit in sequence of therapies.

Please see below for a summary of specific input received from the registered clinician(s).

## 5.1 Current Treatment(s) for NSCLC

The clinicians in both groups identified that the current treatment for metastatic NSCLC is immunotherapy or chemotherapy (e.g. pemetrexed or docetaxel).

## 5.2 Eligible Patient Population

The clinicians providing input noted that the BRAF V600E mutation is very rare in lung cancer. Patients who do not have the BRAF V600E mutation would be out of scope and would not be eligible for treatment with dabrafenib/trametinib. This treatment should only be given to patients with BRAF V600 mutations with adequate performance status (ECOG 0, 1 or 2) as per the study.

One group of clinicians estimated that 28,400 Canadians will be diagnosed with lung cancer this year and 20,800 will die of the disease. From published series, they estimate that between 1-4% of metastatic NSCLC patients will have a BRAF mutations and half of those will be V600 mutations that are relevant to this application. If you presume that all 20,800 patients who die of the disease have metastatic disease given the median survival of stage IV lung cancer is about 12 months (with treatment), then 415 patients will have V600 mutations. This does not account for the fact that less than half of patients with metastatic lung cancer receive any treatment and less than half of those patients receive second line therapy or beyond. A more realistic estimate would be around 100 patients per year with the above information.

## 5.3 Identify Key Benefits and Harms with Dabrafenib plus Trametinib

The clinicians providing input identified several benefits of dabrafenib/trametinib combination:

- The response rate of dabrafenib/trametinib is 63.2% in comparison to 12% for docetaxel and 19% for nivolumab.
- The duration of response of dabrafenib/trametinib is nine months in comparison to 5.6 months for docetaxel. Nivolumab has a potentially longer duration of response at 17.2 months (from the pivotal trial of nivolumab vs docetaxel in non-squamous NSCLC – Borghaei, NEJM October 2015).

The risks of harm from dabrafenib/trametinib combination are the side effects of the agents. Serious adverse events were reported in 32 (56%) of 57 patients in the most robust clinical trial available on the combination in NSCLC. Side effects included pyrexia in nine

(16%), anaemia in three (5%), confusional state in two (4%), decreased appetite in two (4%), haemoptysis in two (4%), hypercalcaemia in two (4%), nausea in two (4%), and cutaneous squamous cell carcinoma in two (4%). The most common grade 3–4 adverse events were neutropenia in five patients (9%), hyponatraemia in four (7%), and anaemia in three (5%). No new toxicity signals were seen in patients with NSCLC in comparison to the larger cohort of melanoma that has been treated with dabrafenib/trametinib. Docetaxel has a similar rate of serious adverse events (56% in the Borghaei paper). Fewer serious adverse events are reported with nivolumab (10% in the Borghaei paper).

## 5.4 Advantages of Dabrafenib plus Trametinib Over Current Treatments

The combination of dabrafenib/trametinib appears clinically superior to historical standard treatment with docetaxel based on response rate and duration of response. This combination is personalized therapy for this small subgroup of NSCLC patients. Similar benefits have been observed in other molecularly defined subgroups of lung cancer, such as those with EGFR mutations as well as ALK and ROS1 translocations.

These patients may still benefit from immunotherapy. However, it is unclear whether dabrafenib/trametinib combination is superior to immunotherapy in the second-line setting in this population. There is no data to date on the efficacy of immunotherapy in patients with BRAF mutation, specifically since this population is so small and BRAF testing is not routine at this time, given there is not an approved drug for BRAF mutated NSCLC. The clinicians providing input indicated that most patients with BRAF mutations are current or former smokers and that same population has a greater chance of benefit from immunotherapy in the pivotal trials.

There is an unmet need for this patient population. In two small case series looking at the natural history of BRAF mutant NSCLC (Paik JCO 2011; Litvak, JTO 2014), these patients have a better overall survival than the average patient with lung cancer and are generally candidates for several lines of therapy. In the most recent of these series, half of the patients were alive at three years and half of the patients were able to have access to BRAF inhibitors on clinical trial.

Another benefit of dabrafenib/trametinib is that they are both oral agents and can be taken at home, whereas nivolumab and docetaxel require intravenous administration in a cancer clinic.

## 5.5 Sequencing and Priority of Treatments with Dabrafenib plus Trametinib

With the currently available treatments, one group of clinicians would sequence the use of BRAF inhibitors after failure of platinum doublet. The trial allowed any number of prior therapies and similar benefit was demonstrated whether patients had only one prior therapy or 2 or more prior therapies. This treatment combination would not replace a current treatment, but rather add a new line of therapy similar to what is seen with EGFR and ALK aberrant patients

Another group of clinicians felt that dabrafenib/trametinib, as a novel combination, would shift current treatments downstream. However, there is no evidence on optimal sequencing and the small population of BRAF mutated NSCLC patients will never be able to generate evidence. The clinicians in this group input would offer dabrafenib/trametinib as third-line or last line of therapy after platinum doublet and immunotherapy. They viewed dabrafenib/trametinib as a “nice-to-have”, rather than a “must-have”.

## 5.6 Companion Diagnostic Testing

BRAF mutation testing is already currently accredited in many labs across the country for use in melanoma and in Alberta for colorectal cancer. The same test can be validated and expanded for use in lung cancer as patients will need to be BRAF V600E positive to derive benefit from this combination.

Most next generation sequencing panels also include BRAF mutation testing which is an advantage over single analyte testing in NSCLC given the other known driver mutations. Multiplex testing with next generation sequencing would significantly decrease the cost of testing for BRAF. All patients with adenocarcinoma of the lung are already getting epidermal growth factor receptor testing either by single analyte testing (ex: RT PCR) or through next generation sequencing at the discretion of the laboratory. Use of next generation sequencing to determine both EGFR and BRAF testing will be an improvement over single analyte testing in that no additional tumour sample will be required over what is already needed for EGFR (lung cancer patients often have small biopsy samples) and no additional work to pathology outside of the reporting.

The optimal algorithm for testing would be upfront next generation sequencing so the result is available after progression on platinum doublet. Patients who have already had their initial molecular diagnostic testing completed will need to be tested separately for BRAF as this recommendation is implemented since the test is not currently being performed on NSCLC patients.

## 5.7 Additional Information

This drug combination for use in BRAF mutated NSCLC is an extension of much more extensive research done in melanoma. BRAF mutations in melanoma comprise nearly 50% of all metastatic melanoma patients. The safety and efficacy of the combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) have been well established through multiple randomized clinical trials. BRAF mutations in NSCLC are less common as described above. Because these mutations in lung cancer are rare, no future randomized trials versus chemotherapy are planned due to feasibility issues. Just to do this one single arm trial of 56 patients it took 13 months across 30 centres in 9 countries on 3 continents. The response rate in the randomized phase 3 trial of dabrafenib and trametinib in melanoma with BRAF V600 mutations was 64% with a median duration of response of 13.8 months in previously untreated patients. The response rate in the single arm phase 2 trial in NSCLC of dabrafenib and trametinb was 63.2% with a median duration of response of 9 months in previously treated patients. This data suggests that dabrafenib and trametinib has similar efficacy in BRAF mutated patients with both lung cancer and melanoma with V600 BRAF mutations. Only 2 patients in the trial were previously untreated. Both of them had an objective response (1 CR and 1 PR) with a longer duration than what was seen in the previously treated cohort but obviously the sample size here is very small. The adverse event profile was similar between lung and melanoma patients and the combination was tolerable in both groups.

# 6 SYSTEMATIC REVIEW

## 6.1 Objectives

To evaluate the efficacy and safety of dabrafenib and trametinib in combination for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600 mutation (BRAF V600) mutation who have been previously treated with chemotherapy.

Supplemental Questions and Comparison with Other Literature 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 and section 8. Section 7, the supplemental question concerns the critical appraisal of a manufacturer-submitted indirect comparison assessing the relative efficacy of dabrafenib plus trametinib in patients with advanced NSCLC with BRAF V600 compared with other selected 2nd line treatments in unselected patients with NSCLC. Section 8 provides 1) a literature review regarding the natural history of NSCLC among those with BRAF V600 mutation and 2) addresses overall response rate (ORR) as a surrogate for overall survival in previously treated patients BRAF V600-mutant, Stage IV NSCLC.

## 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 or unpublished RCTs<br><br>In the absence of RCTs, fully published non-comparative clinical trials evaluating dabrafenib plus trametinib** | Adult patients with advanced non-small cell lung cancer (NSCLC) with BRAF V600 mutation who have been previously treated with chemotherapy | Dabrafenib and trametinib in combination | Patients receiving 2nd line therapy: docetaxel, pemetrexed, immunotherapy agents (e.g., nivolumab and pembrolizumab) | 1. Overall survival (All-cause mortality)<br>2. Progression free survival<br>3. Quality of life<br>4. Overall response rate<br>5. Grade 3 and 4 adverse events<br>6. Withdrawal due to adverse effects<br>7. Other adverse effects<br>**8. Pyrexia** |
| RCT: Randomized control trial<br>* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).<br>**Dose escalation trials were excluded but mixed design clinical trials (i.e., trials with a dose escalation phase followed by an efficacy-determining phase in which the intervention is administered at the same dose and schedule to all patients) were included if data were reported separately for the two phases of the trial. | | | | |

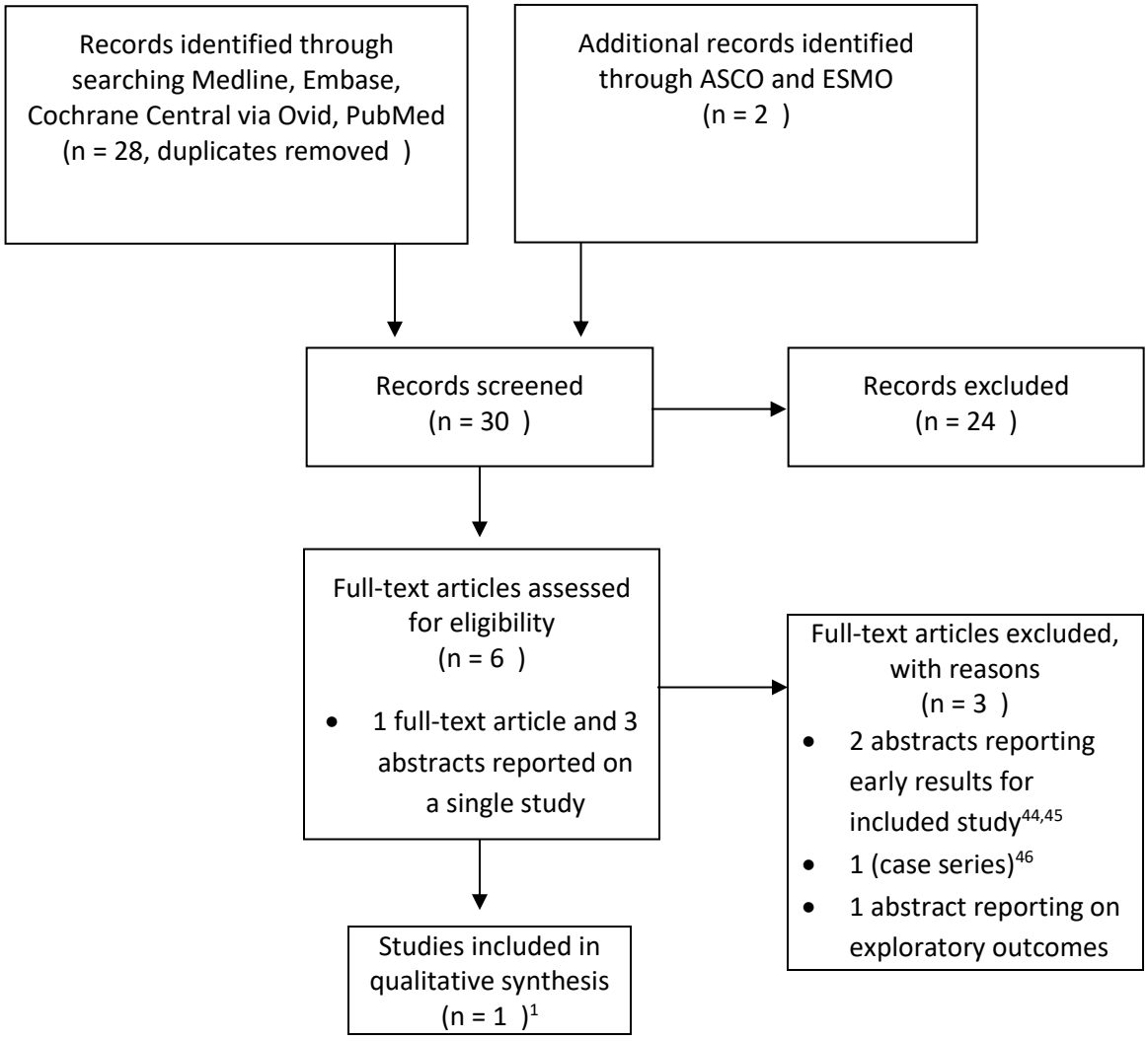
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

## 6.3 Results

### 6.3.1 Literature Search Results

Among the 4 potentially relevant records identified by the search, 1 study was included in the pCODR systematic review[1] and 3 records were excluded. Two records were excluded because they were abstracts reporting early and final results of the included trial[44,45] and 1 study was excluded because of study design (case series).[46] The search is considered up to date as of July 4, 2017.

**Figure 1. Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies**




*Note: Additional data related to study BRF113928 were also obtained through requests to the Submitter by pCODR [Checkpoint Meeting [2]]*

### 6.3.2 Summary of Included Studies

One Phase 2, open-label, single-arm trial was identified that met the inclusion criteria of this review. This trial, BRF113928 (Cohort B), evaluated the combination of dabrafenib and trametinib in adults with BRAF V600E-mutant Stage IV NSCLC who were previously treated with chemotherapy.[1] Key characteristics of the trial are summarized in Table 4 and specific aspects of the trial quality are detailed 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 |
|---|---|---|---|
| BRF113928 (Cohort B) (NCT01336634)[1]<br><br>Single group, open-label, Phase 2 clinical trial<br><br>N treated=57<br><br>30 centres and 9 countries (North America, Europe & Asia)<br><br>Patient Enrolment Dates: December 20, 2013 – January 14, 2015<br><br>Data cut-off: October 7, 2015<br><br>Final Analysis Date: not reported<br><br>Funded by GlaxoSmithKline. Studied products were later acquired by Novartis. | Key Inclusion Criteria:<br>• Aged ≥ 18 years<br>• Histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC<br>• Documented tumour progression after at least 1 platinum-based chemotherapy regimen<br>• No more than 3 previous systemic treatments for metastatic NSCLC<br>• Measurable disease (RECIST 1.1)<br>• ECOG ≤ 2<br>• Adequate organ function<br>• Estimated life expectancy ≥ 3 months<br><br>Key Exclusion Criteria:<br>• Treatment with BRAF or MEK inhibitor<br>• Received anticancer treatment within 14 days before start of study<br>• Received investigational anticancer drug within 14 days or 5 half-lives of start of therapy<br>• Active GI disease<br>• Hepatitis B or C<br>• Brain metastases unless asymptomatic, untreated, and measured less than 1 cm OR if treated were clinically & radiographically stable 3 weeks after local therapy | Intervention:<br>Oral dabrafenib (150 mg 2x/ day) plus oral trametinib (2mg 1x/day) in continuous 21-day cycles until disease progression, unacceptable adverse events, withdrawal or death | Primary:<br>OR (proportion of pts with a confirmed complete response or partial response according to RECIST 1.1)<br><br>Secondary:<br>• PFS<br>• DOR<br>• OS<br>• Safety & tolerability<br>• pharmacokinetic<br><br>Tertiary ("Exploratory"):<br>• Molecular mechanisms of sensitivity<br>• Resistance to dabrafenib plus trametinib<br>• Relationship between exposure and response<br>• Assessment of cell free DNA to ID BRAF mutation<br>• Investigation of relationship between genetic variations & efficacy, safety and pharmacokinetics<br><br>**NOTE: all outcomes were investigator assessed. Independent review committee assessment was completed as a sensitivity analysis.** |
| **Abbreviations:** BRAF - v-Raf murine sarcoma viral oncogene homolog B; DOR – duration of response; ECOG – Eastern Cooperative Oncology Group; IRC – independent review committee; MEK – MAP (Mitogen-Activated Protein) Kinase / ERK (Extracellular Signal-Regulated Kinase) Kinase; NSCLC – non-small cell lung cancer; OR - overall response; OS – overall survival; PFS – progression free survival; RECIST – Response Evaluation Criteria in Solid Tumors | | | |

**Table 5: Select quality characteristics of included studies of dabrafenib plus trametinib in patients with stage IV NSCLC**

| Study | BRF113928 (Cohort B)[1] |
|---|---|
| Treatment vs. comparator | Dabrafenib plus trametinib<br><br>No comparator |
| Primary outcome | OR |
| Required sample size | Two-stage Green-Dahlberg design was used to assess clinical response to enable early stopping for futility if sufficient clinical activity was not shown. An interim analysis was planned after 20 patients had ≥2 post-baseline scans or withdrew from the study before a response was assessed.<br><br>The null hypothesis was that the overall response was not clinically meaningful (≤30%) and the alternative hypothesis was that 55% or more of patients would achieve an overall response.<br><br>The trial could be terminated for futility after 20 patients were enrolled if a confirmed response was not noted in ≥6 of 20 patients after stage 1 and ≥18 of 40 patients after both stages.<br><br>40 patients (20 in each stage) were required to provide 92.2% power and a type I error of 0.032. |
| Sample size | 57 |
| Randomization method | NA |
| Allocation concealment | NA |
| Blinding | No (confirmed at Checkpoint on June 12, 2017[2]) |
| ITT analysis | No[a] |
| Final analysis | Yes |
| Early termination | No |
| Ethics approval | Yes |
| Abbrevations: ITT- intention to treat; NA – not applicable; OR – overall response; | |
| Notes: [a]All results presented in the published study include only those patients who received ≥1 dose of dabrafenib plus trametinib | |

### *a) Trials*

One trial, BRF113928 (Cohort B)[1] met the inclusion criteria for this review. BRF 113928 consists of 3 separate single-arm, Phase 2 trials conducted in patients with BRAF V600E-mutant stage IV NSCLC: Cohort A, Cohort B and Cohort C.[3] Patient enrolled in Cohort A had received at least 1 previous line of treatment and were treated with dabrafenib monotherapy.[3] Patients enrolled in Cohort B had received at least 1 previous line of treatment and were treated with dabrafenib plus trametinib.[3] Patients enrolled in Cohort C were treatment naïve and were treated with dabrafenib plus trametinib.[3]

This trial, Cohort B, is a single-arm, Phase 2, open-label, multi-centred study. This trial was conducted in 30 centres in nine countries across North America, Europe and Asia. This trial evaluated the combination of dabrafenib and trametinib in adults with advanced NSCLC with BRAF V600E mutation who were previously treated with chemotherapy. The following inclusion criteria were applied:

- Aged ≥ 18 years
- Histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC
- Documented tumour progression after at least 1 platinum-based chemotherapy regimen
- No more than 3 previous systemic treatments for metastatic NSCLC
- Measurable disease (RECIST 1.1)

- ECOG ≤ 2
- Adequate organ function
- Estimated life expectancy ≥ 3 months

Role of the sponsor
GlaxoSmithKline (GSK) funded this trial. The study was designed by the academic authors in conjunction with representatives of GSK.[1] The data were collected by GSK and analysed in collaboration with the authors.[1] Editorial support was provided by ArticulateScience and funded by GSK. As of March 2, 2015 dabrafenib and trametinib were acquired by Novartis.

Outcomes
The published trial indicated that all outcomes were investigator-assessed (IA). An independent review committee (IRC) assessment was performed as a sensitivity analysis.

The primary outcome was IA overall response rate (ORR). Overall response was defined as the proportion of patients with a confirmed complete response or partial response according to RECIST version 1.1 criteria. Radiological disease assessment by CT scans based on RECIST version 1.1 were done at baseline, at week 6, every 6 weeks until week 36, and then every 12 weeks, and the responses were confirmed by repeat assessment 4-7 weeks after initial response.[1]

Secondary outcomes were:
- Progression-free survival (PFS). PFS is defined as the interval between the first dose of study drug and the earliest date of disease progression or death due to any cause.[47]
- Duration of response (DOR). DOR is based on the investigator-assessed confirmed response was defined as the time from first documented evidence of complete or partial response until the time of first documented disease progression or death due to any cause, whichever occurs earlier.[47]
- Overall survival (OS). OS was defined as the time from first dose of study drug until death due to any cause.[47]
- Safety and tolerability
- Pharmacokinetic assessment

Exploratory outcomes:
- Molecular mechanisms of sensitivity and resistance
- Relationship between exposure and response
- Assessment of cell free DNA to identify BRAF mutation
- Relationship between genetic variations and efficacy, safety and pharmacokinetics

### *b) Populations*

There were 59 patients enrolled in Cohort B of this trial. Two treatment-naïve patients were excluded in the analysis as they were enrolled due to an accidental protocol violation. These two patients are reported separately. Thus, 57 patients were included in the final analysis.

The median age of patients was 64 (IQR 58-71), 86% (49/57) identified their ethnicity as White, 91% (52/57) had ECOG status of 0 or 1, 11% (6/57) were current smokers and 67% (38/57) were previously treated with only 1 chemotherapy regimen. Please see Table 7 for further details on baseline characteristics.

### c) *Interventions*

Dose

Patients were treated with oral dabrafenib (150 mg twice per day) plus oral trametinib (2 mg once per day) in continuous 21-day cycles until disease progression, unacceptable adverse events, withdrawal of consent or, death.[1] Information provided via the Registered Clinician Input indicates that oral route of administration is preferable for patients.

Progressive disease and continuation of treatment

Patients with progressive disease (RECIST v1.1) were allowed to continue treatment if they had a confirmed partial or complete response (RECIST v1.1) or, had stable disease ≥ 12 weeks, had no clinical signs or symptoms of disease progression, no grade 4 or SAEs during previous 4 weeks of treatment and the investigator believe the patient was clinically benefiting from therapy.[1] Approval to continue treatment had to be provided by the GlaxoSmithKline Medical Monitor. There was no information available on whether or not any patients received treatment beyond progression.

Dose modification

Dose modifications or interruptions were used to manage intolerable grade 2 or worse adverse events.[1] But for specific adverse events, dabrafenib and trametinib were reduced simultaneously. Dabrafenib was reduced to 100 mg on first reduction, 75 mg on second reduction and 50 mg on third reduction; dose should not be reduced to < 50 mg. Trametinib was reduced to 1.5 mg on first reduction and 1 mg on second reduction; dose should not be reduced to < 1 mg.[47]

Adverse events led to permanent discontinuation in seven patients (12%), dose interruption or delay in 35 (61%) and dose reduction in 20 (35%).[1]

Concomitant medications

Use of concomitant medications was not reported in the trial publication[1] or in Appendix I.[47] At Checkpoint, the submitter provided the following information:

"In the Combination Second-Line Plus Population, all subjects (100%) received at least one concomitant medication while on study treatment. Medications received by ≥ 20% of subjects were paracetamol (67%), amoxicillin (26%), prednisone (30%), and folic acid (21%)."[2]

Duration of treatment

Median duration of treatment for both dabrafenib and trametinib was 10.6 months (IQR 4.2-12.2). Thirty three (58%) of 57 patients received at least 80% of the planned dose of dabrafenib and 43 (75%) of 57 patients received at least 80% of the planned dose of trametinib. The study authors report that 17 (30%) of 57 patients received more than 12 months of treatment. However, upon reviewing Figure 3, Appendix 1, it is noted that 15 patients received more than 12 months of treatment and 2 patients received up to 12 months of treatment.[47]

### d) *Patient Disposition*

**Table 6. Patient disposition**

| Item | Dabrafenib plus trametinib |
|---|---|
| Total enrolled | 57[a] |
| Received ≥1 dose | 57[a] |
| Total withdrawal from treatment | 36 |
| Due to disease progression | 28 |

| Item | Dabrafenib plus trametinib |
|---|---|
| Due to adverse event | 7 |
| At patient's request | 1 |
| Protocol violation | Not reported |
| Lost to follow-up | 0 |
| Patients missing data | Not reported |
| Population for efficacy | 57 |
| Population for safety | 57 |
| Note: [a]59 enrolled, 2 excluded due to protocol deviation (were treatment naïve). | |

Analysis populations

All enrolled patients who received ≥ 1 dose of dabrafenib plus trametinib (n=57) were included in all analyses. It is unclear how many patients were enrolled and received 0 doses of the study treatment.

Withdrawals

Patients who discontinued the study drugs were followed up for subsequent treatments and survival every 12 weeks until death or study completion.[1] At the cut-off date (October 7, 2015), 36/57 (63%) patients discontinued treatment (28 due to disease progression, 7 due to adverse events, 1 at patient's request). At database lock, 21 patients (37%) were still on study treatment.

Missing data

Methods for handling missing data were not included in trial publication or in the Appendix. At Checkpoint, the submitter indicated that no imputation was done for missing data[2] and provided the following additional information:

- For the assessment of "best response", 5 patients by IA (6 patients by IRC) did not have sufficient information (either two post-baseline with 12 weeks of follow-up or progression within the first 12 weeks) to assess best response. They were included in the denominator for OR.[2]

- For the assessment of PFS, 3 patients by IA (4 patients by IRC) were censored due to missing at least two scheduled assessments. For the assessment of OS, 2 patients were censored due to loss to follow-up.[2]

Related Issues

Two treatment naïve patients were enrolled in error and were analysed separately.

### *e) Limitations/Sources of Bias*

Please refer to Table 5 for a summary of quality-related features of BRF113928 (Cohort B).

Trial design:

- The most significant limitation of this trial is that the results are based on a small, single-arm, Phase 2 trial (BRF113928 (Cohort B)).[1] Such a trial is typically used to determine whether or not to go forward to a definitive Phase 3 trial. The lack of a comparator, small sample size, short duration of follow-up and use of a surrogate endpoint (ORR), limit the conclusions that can be drawn regarding the efficacy (eg, OS, PFS and ORR (the primary outcome)) and safety of dabrafenib plus trametinib in

patients with BRAF V600E-mutant Stage IV NSCLC who were previously treated with chemotherapy compared with appropriate comparators.

- Ideally, in the design of a non-randomised study, data based on a currently approved therapy (e.g., docetaxel, nivolumab) would be used to help determine the null hypothesis for the primary outcome. There is implicit reference to a historical comparator in the design of BRF113928 (Cohort B), i.e. "The null hypothesis was that the overall response was not clinically meaningful (≤ 30%) and the alternative hypothesis was that 55% or more of second-line to fourth-line patients with BRAF V600E-mutant NSCLC would achieve an overall response with dabrafenib plus trametinib". However, the investigators do not justify their choice of response rates in the published trial. The submitter suggests a 30% expected response was chosen based on Cohort A of the BRF113928 trial using dabrafenib monotherapy.[3] However, dabrafenib monotherapy is not used for the treatment of NSCLC in the Canadian setting and, as such, is not a relevant historical comparator. At Checkpoint (June 12, 2017), the submitter further confirmed that response rate to dabrafenib monotherapy (30%) was used to determine the null hypothesis (response rate ≤30%) that would be suitable for "further clinical development."[2] The submitter indicated in their response to Checkpoint follow-up questions that: "As the Committee noted, dabrafenib monotherapy is not approved in Canada and Novartis agrees that it is not a comparable 2nd line treatment."[4] Lack of information regarding ORR (as well as OS and PFS) using a relevant comparator makes it difficult to determine the relative efficacy of dabrafenib plus trametinib as 2nd line and beyond treatment in BRAF V600E-mutant Stage IV NSCLC patients.

Choice of outcome:

- The primary outcome for this study was ORR. Currently, there is no evidence to support ORR as a surrogate for OS in the treatment of patients with BRAF V600E-mutant Stage IV NSCLC. Based on the IRC assessment, no patients experienced a complete response and ORR was driven exclusively by partial response.

Analysis of results:

- There is no mention of blinding of the outcome adjudicators (i.e., those responsible for radiological disease assessment by CT scans based on RECIST versions 1.1,). If the assessors are aware that the patients had undergone experimental therapy they may be biased towards a "positive outcome", thus there is a potential for misclassification bias with respect to the RECIST version 1.1 criteria. The evaluation of tumour size by IA is even more prone to be bias compared with the IRC due to investigator-bias. At Checkpoint (June 12, 2017), the submitter confirmed that the IA was not blinded.[2] They note that the IRC was blinded to investigator assessment results.[2]
- Investigator bias is likely present as all IA outcomes (primary and all secondary) favour treatment to a greater degree than IRC assessed outcomes.

Other:

- The published study provides data for only those patients who received ≥ 1 dose of the study medications. Information regarding the number of patients who enrolled and received 0 doses would provide an estimate of the proportion of the treatment-eligible population that might receive the combination treatment.

*Table 7. Baseline characteristics[1] Planchard*

| | Patients receiving dabrafenib plus trametinib as second-line or later treatment (n=57) |
|---|---|
| Age (years) | 64 (58-71) |
| Sex | |
| Male | 29 (51%) |
| Female | 28 (49%) |
| Ethnic origin | |
| White | 49 (86%) |
| Black | 2 (4%) |
| Asian | 4 (7%) |
| Mixed | 1 (2%) |
| Missing | 1 (2%) |
| ECOG | |
| 0 | 17 (30%) |
| 1 | 35 (61%) |
| 2 | 5 (9%) |
| Histology at initial diagnosis | |
| Adenocarcinoma | 56 (98%) |
| Large cell | 1 (2%) |
| History of tobacco use | |
| Never smoker | 16 (28%) |
| Current smoker | 6 (11%) |
| Former smoker | 35 (61%) |
| Smoking history | |
| ≤30 pack-years | 22 (54%) |
| >30 pack-years | 19 (46%) |
| Number of previous systemic regimens for metastatic disease | |
| 1 | 38 (67%) |
| ≥2 | 19 (33%) |
| Treated or asymptomatic brain metastases | |
| Published trial | 1 (2%) |
| IA, Checkpoint June 12, 2017[2] | 2 (4%) |
| IRC, Checkpoint June 12, 2017[2] | 5 (9%) |
| Data are median (IQR) or n(%). ECOG – Eastern Cooperative Oncology Group | |

### 6.3.2.2 Detailed Outcome Data and Summary of Outcomes

#### *Efficacy Outcomes*

Analysis of efficacy outcomes included all patients treated with a least one dose of dabrafenib plus trametinib (n=57). It is unclear from the published study report (Planchard 2016) the number of patients who were enrolled and received 0 doses of dabrafenib plus trametinib. Lack of comparator makes it difficult to assess the comparative efficacy of dabrafenib plus trametinib. Key outcomes are summarized in Table 8.

Overall survival (OS)

OS was a secondary outcome. At 6 months, 10 (18%) of 57 patients had died. At data cut-off (October 7, 2015, 11.6 months of follow-up), 23 of 57 (40%) patients had died. OS was not reported in the published trial and the study authors note that the "median overall survival data

are immature". Within the submission, the submitter reported that the preliminary median OS was 17.6 months (95% CI 14.3, Not Estimable).[3]

Updated overall survival data were reported at the June 3, 2017 ASCO meeting. Median OS was 18.2 months (95% CI 14.3, Not estimable).[2]

Progression-free survival (PFS)

PFS was a secondary outcome. PFS was defined as the interval between the first dose of study drug and the earliest date of disease progression or death due to any cause.[47] The median follow-up was 11.6 months (IQR 8.8-15.2).

PFS as assessed by IA was 9.7 months (95% CI 6.9-19.6). PFS as assessed by IRC was 8.6 months (95% CI 5.2-19.1).

At data cut-off, 32 (56%) of 57 patients had died or progressed.

Based on the June 3, 2017 poster presented at ASCO (data cut-off August 8, 2016). Independent Review Committee median PFS was 8.6 months (95% CI 5.2, 16.8). Investigator assessed median PFS was 10.2 months (95% CI 6.9-16.7)[2]

Overall response (OR)

IA assessed OR was the primary outcome for this study. OR is a composite outcome and is defined as the proportion of patients with a confirmed complete response or partial response according to RECIST version 1.1.[1] The median follow-up was 11.6 months (IQR 8.8-15.2).

OR as assessed by IA occurred in 36 / 57 patients (63.2%, 95% CI 49.3-75.6). There were 2/57 (4%) complete responses and 34/57 (60%) partial responses.

OR as assessed by IRC occurred in 36 / 57 patients (63.2%, 95% CI 49.3-75.6). There were 0 complete responses and 36/57 partial responses.

Based on the June 3, 2017 poster presented at ASCO (data cut-off August 8, 2016), independent Review Committee ORR was 63.2% (95% CI 49.3, 75.6). Investigator assessed OR was 66.7% (95% CI 52.9-78.6) [2]

### *Quality of Life*

A measure of Quality of Life (QoL) was not reported in the main trial results.[1] QoL was not listed as an outcome in the trial registration at "ClinicalTrials.gov".

At Checkpoint, the submitter provided the following: "Quality of Life (QoL) measures are critical to properly assessing the benefit of any novel therapy from a patient's perspective, particularly in the context of a comparison to standard therapy.

At the time the BRF113928 study was initiated in 2011, due to the rarity of BRAF-positive NSCLC, it was planned as an exploratory single-arm, open-label trial. The value of QoL assessment in such trials is debatable, as there is no opportunity for comparative assessments. Consequently, QoL data were not collected as part of the BRF113928 program."[2]

### *Harms Outcomes*

Analysis of safety outcomes included all patients treated with a least one dose of dabrafenib plus trametinib (n=57). Patients were assessed for safety at least once every 3 weeks. Adverse events, laboratory values and vital signed were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Lack of comparator makes it difficult to assess the

comparative safety of dabrafenib plus trametinib with existing 2nd line treatments. Harms outcomes are summarized in Table 9.

The median duration of treatment for both dabrafenib and trametinib was 10.6 months (IQR 4.2-12.2). 17 (30%) of 57 patients received ≥12 months of treatment. The median duration of follow-up was 11.6 months (IQR 8.8-15.2). Overall, 98% (56/57) of patients experienced at least 1 adverse event and 56% (32/57) of patients experienced at least 1 serious adverse event.[1]

Based on the June 3, 2017 poster presented at ASCO no new safety signals were observed other than what is reported below.

Grade 3, 4 and 5 adverse events

28 (49%) patients experienced at least one grade 3-4 adverse event. The most common (≥5%) were (n, %): neutropenia (5, 9%), hyponatremia (4, 7%), anaemia (3, 5%). There were a total of 4 grade 5 adverse events: 1 respiratory distress, 1 neoplasm progression, 1 retroperitoneal haemorrhage, 1 subarachnoid haemorrhage.[1]

Withdrawal due to adverse effects

Adverse events led to permanent discontinuation in 7 (12%) patients, dose interruption or delay in 35 (61%) and dose reduction in 20 (35%).

Pyrexia

Pyrexia was identified as an important adverse event by patients and PAG. Among the 57 enrolled patients, 25 (44%) experienced at least one grade1-2 event, 1 (2%) experienced a grade 3 event and no patients experienced a grade 4-5 event.

The study protocol also required that grade 2 or worse pyrexia be reported as a protocol specified serious adverse event (SAE), regardless of whether or not they met the standard definition of serious adverse events.[1] Definition of a "serious adverse event" was not provided by the study authors. However, the study authors use the terminology "standard definition of serious adverse events". This is taken to mean the FDA definition (e.g., death, life threatening, hospitalization etc.). Among the 57 patients enrolled, 9 (16%) experienced pyrexia that was classified as a SAE.

**Table 8. Highlights of Key Outcomes**

| | | **BRF113928 (Cohort B)[1]** |
|---|---|---|
| **Efficacy Outcomes** | **Data cut/Follow up** | **Dabrafenib plus trametinib (n=57)** |
| **Primary outcome** | | |
| **Overall response rate, % (95% CI)** | October 7, 2015 data cut (11.6 months follow up)[1] | **36, 63.2% (49.3, 75.6)** |
| **Overall response rate, n, % (95% CI)** | August 8, 2016 data cut[2] | **36, 63.2% (49.3, 75.6)** |
| Other Key Endpoints | | |
| Overall survival (months), median (95% CI) | October 7, 2015 data cut (11.6 months follow up) | Not mature (23-57, 40% of patients died) |
| Overall survival (months), median (95% CI) | August 8, 2016 data cut[2] | 18.2 (14.3; NE) |
| Progression-free survival, median (95% CI) | October 7, 2015 data cut (11.6 months follow up)[1] | 8.6 (5.2, 19.1) |
| Progression-free survival, median (95% CI) | August 8, 2016 data cut [2] | 8.6 (5.2; 16.8) |
| **HrQoL**[1, 2] | | HrQoL was not evaluated. |
| **Harms Outcomes**[1] | | |
| Grade 3 and 4, n (%)* | | 28 (49%) |
| Pyrexia (any grade), n (%) | | 26 (46%) |
| AE (any grade), n (%) | | 56 (98%) |
| WDAE, n (%) | | 7 (12%) |

**AE** = adverse event, **CI** = confidence interval, **HRQoL** = health-related quality of life, **NE** = not estimable, **NR** = not reported, **SD** = standard deviation, **WDAE** = withdrawal due to adverse event
Note: Where data are presented from the published trial,[1] Independent Review Committee outcomes are presented rather than IA outcomes.
* proportion of patients reporting grade ≥3 is not reported (only have grades 3 & 4 combined)

**Table 9**. Adverse events occurring in ≥10% of enrolled patients receiving at least one dose of study medications (n=57) (please see published BRF113928 (Cohort B) trial Table 3 for a complete list of reported AEs).[1] Data are n (%).

| Adverse event | Any grade | Grade 3 & 4 |
|---|---|---|
| Pyrexia | 26 (46%) | 1 (2%) |
| Nausea | 23 (40%) | 0 |
| Vomiting | 20 (35%) | 0 |
| Diarrhea | 19 (33%) | 1 (2%) |
| Decreased appetite | 17 (30%) | 0 |
| Asthenia | 18 (32%) | 2 (4%) |
| Dry skin | 15 (26%) | 1 (2%) |
| Peripheral oedema | 13 (23%) | 0 |
| Chills | 13 (23%) | 1 (2%) |
| Cough | 12 (21%) | 0 |
| Rash | 12 (21%) | 1 (2%) |
| Arthralgia | 11 (19%) | 0 |
| Neutropenia | 11 (19%) | 5 (9%) |
| Constipation | 10 (18%) | 0 |
| Fatigue | 10 (18%) | 1 (2%) |
| Dyspnea | 10 (18%) | 2 (4%) |
| Anaemia | 10 (18%) | 3 (5%) |
| Blood alkaline phosphatase increased | 9 (16%) | 0 |
| Pruritus | 9 (16%) | 1 (2%) |
| Dizziness | 8 (14%) | 0 |
| Weight decreased | 8 (14%) | 1 (2%) |
| Upper abdominal pain | 7 (12%) | 0 |
| Hypotension | 7 (12%) | 0 |
| Chest pain | 6 (11%) | 0 |
| Dysgeusia | 6 (11%) | 0 |
| Headache | 6 (11%) | 0 |
| Muscle spasms | 6 (11%) | 0 |
| Myalgia | 6 (11%) | 0 |
| Productive cough | 6 (11%) | 0 |
| Vertigo | 6 (11%) | 0 |

## 6.4 Ongoing Trials

One on-going trial was identified in ClinicalTrials.gov. This study is unlikely to provide any additional information regarding comparative efficacy and safety as it is also a Phase II study with no comparator.

**[Table 9]: Ongoing trials of dabrafenib plus trametinib in patients with advance NSCLC with BRAF V600E mutation**

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| Study<br>Efficacy and safety of dabrafenib and trametinib combination therapy in | Key Inclusion Criteria:<br><br>Histologically- or cytologically-confirmed diagnosis of NSCLC stage IV (according to AJCC Staging 7th Edition) | Dabrafenib plus trametinib<br><br>No comparator | Primary:<br>Overall response<br><br>Secondary: |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| any-line Japanese patients with BRAF V600E Stage IV NSCLC (NCT02672358 )<br><br>Characteristics<br>Phase II, open label, single-arm study<br><br>N treated=10 (enrolment ongoing)<br><br>Number of centres and number of countries:<br>Not reported<br><br>Patient Enrolment Dates:<br>October 2017 - ?March 2020<br><br>Data cut-off: NA<br><br>Final Analysis Date: NA<br><br>Funding | Presence of a BRAF V600E mutation in lung cancer tissue. BRAF V600E mutation tested by local laboratory (e.g. study center laboratory, local laboratory company) with proper quality control and license to operation by local health authority is allowed.<br><br>Measurable disease according to RECIST v1.1.<br><br><br>Key Exclusion Criteria:<br><br>Previous treatment with a BRAF inhibitor (including but not limited to dabrafenib, vemurafenib, encorafenib, and XL281/BMS-908662) or MEK inhibitor (including but not limited to trametinib, cobimetinib, binimetinib, AZD6244, and RDEA119) prior to start of study treatment<br><br>Patients with brain metastases are excluded if their brain metastases are:<br><br>Symptomatic OR<br><br>Treated (surgery, radiation therapy) but not clinically and radiographically stable 3 weeks after local therapy (as assessed by contrast enhanced magnetic resonance imaging [MRI] or computed tomography [CT]), OR<br><br>Asymptomatic and untreated but >1 cm in the longest dimension<br><br>History of malignancy with confirmed activating RAS mutation at any time.<br><br>History of interstitial lung disease or pneumonitis<br><br>A history or current evidence of retinal vein occlusion (RVO)<br><br>Current evidence of unstable aneurysm or one that needs treatment | | • Duration of response<br><br>• Disease control<br><br>• Progression free survival<br><br>• Overall survival<br><br>Tertiary: |
| Study: NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma NCT02465060<br><br>Characteristics<br>Phase II, open label, non-randomized, parallel assignment<br><br>Estimated enrolment=6452<br><br>Number of centres and number of countries:<br>Puerto Rico, United States<br><br>Patient Enrolment Dates: | **The study has 30 parallel arms from various solid tumors, lymphoma and multiple myeloma. One of these arms targets the patient's population of interest.**<br><br>Key Inclusions Criteria<br><br>18 Years and older (Adult, Senior)<br><br>Patients must have histologically documented solid tumors or histologically confirmed diagnosis of lymphoma or multiple myeloma requiring therapy and meet one of the following criteria:<br>• Patients must have progressed following at least one line of standard systemic therapy and there must not be other approval/standard therapy available that has been shown to prolong overall survival (i.e. in a randomized trial against another standard treatment or by comparison to historical controls); patients who cannot receive other standard therapy that has been shown to prolong overall survival due to medical issues will be eligible, if other eligibility criteria are met; if the patient is currently receiving therapy, the clinician must have assessed that the current therapy is no | Experimental: Subprotocol H (BRAF V600E/R/K/D mutation) Patients with BRAF V600E/R/K/D mutation receive dabrafenib PO BID and trametinib PO QD on days 1-28. Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity. | Primary outcome<br>Objective response rate (ORR)<br><br>Secondary outcomes<br>OS<br>PFS<br>Time to progression |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Trial Outcomes |
|---|---|---|---|
| Not reported but currently recruiting<br><br>Estimated primary completion: June 30, 2022 (Final data collection date for primary outcome measure)<br><br>Study sponsor: National Cancer Institute (NCI) | longer benefitting the patient prior to enrolling on MATCH, regardless of whether it is considered standard OR<br>• Patients for whose disease no standard treatment exists that has been shown to prolong overall survival<br><br>NOTE: No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer; in situ cervical cancer; adequately treated stage I or II cancer from which the patient is currently in complete remission; any other cancer from which the patient has been disease-free for 5 years<br><br>Patients must have measurable disease<br><br>Patients with brain metastases or primary brain tumors must have completed treatment, surgery or radiation therapy >= 4 weeks prior to start of treatment | | |

# 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 in advanced NSCLC with BRAF V600E mutation who have been previously treated with chemotherapy.

- Summary of the manufacturer-submitted indirect comparison of dabrafenib plus trametinib with other second-line treatments for patients with advanced NSCLC who have been previously treated with chemotherapy.

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

## 7.1 Summary of the manufacturer-submitted indirect comparison of dabrafenib plus trametinib with other second-line treatments for patients with advanced NSCLC who have been previously treated with chemotherapy[5]

### 7.1.1 Objective

To summarize and critically appraise the manufacturer-submitted indirect comparison of dabrafenib plus trametinib with other second-line treatments for patients with advanced NSCLC who have been previously treated with chemotherapy.[5]

### 7.1.2 Findings

Overview of Methods

As there are no RCTs comparing dabrafenib plus trametinib to existing 2nd line therapies in patients with advanced NSCLC, an indirect comparison was required.[5] The indirect comparison reported in the manufacturer-submitted study used two approaches: matching-adjusted indirect comparison (MAIC) and network meta-analysis (NMA). Together, these approaches provide evidence of comparative effectiveness between dabrafenib plus trametinib and comparators identified based on treatment practice and in the systematic review.

A systematic review was conducted to identify comparators of interest. The following databases were searched: EMBASE (OvidSP), MEDLINE (OvidSP), MEDLINE In-Process (OvidSP), Cochrane Central Register of Controlled Trials (OvidSP), ASCO, ESMO, ELCC, WCLC and ClinicalTrials.gov. The PICOS are summarized in Table 1.

As discussed in Section 6, there is only one study of dabrafenib plus trametinib conducted among patients with advanced NSCLC who have been previously treated with chemotherapy.[1] Due to the single-arm design of BRF113928 (Cohort B), a pseudo trial was created to compare dabrafenib plus trametinib with data from an in-network study (i.e., a study identified in the systematic review and included in the NMA). The in-network study chosen was CheckMate057, an RCT comparing docetaxel to nivolumab in second-line treatment for patients with advanced NSCLC.[6] MAIC was used to create two pseudo trials—dabrafenib plus trametinib compared with docetaxel and, dabrafenib plus trametinib compared with nivolumab. The pseudo trial comparing dabrafenib plus trametinib to nivolumab provides the link to the network which is anchored on docetaxel (see Figure 1)

Evidence networks were created for overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and disease control rate (DCR). Separate NMA models were fit for each outcome measure. Fractional polynomial models were used for time-to-event outcomes (OS, PFS).

The generalized linear models framework (as described in the NICE guidelines[48]) was used for response rate outcomes (ORR, DCR).

**Table 1. PICOS for included studies[5]**

| | |
|---|---|
| Patient | Adults (>= 18 yrs); advanced or metastatic (stage IIIb or IV) NSCLC; failed first-line therapy |
| Interventions | Intervention included at least one of the following: Dabrafenib (monotherapy), dabrafenib + trametinib, nivolumab (monotherapy), nintedanib + docetaxel, docetaxel (monotherapy only if not combined with nintedanib), pemetrexed (monotherapy only), pembrolizumab (monotherapy only), erlotinib (monotherapy or combo therapy), bevacizumab ( mono or combo therapy), best supportive car / standard palliative care |
| Comparators | Not explicitly stated |
| Outcomes | Response rate, duration of response, overall survival, time to progression, time to treatment failure, progression-free survival |
| Study design | All clinical trials |
| Notes:<br>The MeSH terms were not provided.<br>There are discrepancies between the Methods (6.2 in the submitted documents) and appendix with detailed search strategy. Detailed search strategy also includes dabrafenib monotherapy, 6.2 indicates that RCT is included if at least two of the treatments were included. | |

Results

*MAIC*

Two pseudo trials were created using MAIC: dabrafenib plus trametinib compared with docetaxel and, dabrafenib plus trametinib compared with nivolumab. Data for docetaxel and nivolumab were obtained from CheckMate 057[6] and individual-level patient data was available for BRF113928 (Cohort B). In the manufacturer-submitted indirect comparison, the MAIC comparing dabrafenib plus trametinib and nivolumab was used to link to the network. The pseudo trial comparing dabrafenib plus trametinib to docetaxel was used to perform a sensitivity analysis.

The MAIC did not meaningfully improve the comparability of baseline characteristics (e.g., age, sex, smoking status, ECOG status, number of prior systemic regimes) between dabrafenib plus trametinib and nivolumab / docetaxel (see Table 3). However, the MAIC did improve the baseline comparability of proportion of patients who received ≥2 prior systemic regimens for metastatic disease. The lack of meaningfully improved comparability of baseline characteristics is likely because both studies enrolled similar populations (but for BRAF V600E mutation status), as the comparability of baseline characteristics prior to matching was reasonable (see Table 3). The results suggest that, after matching, dabrafenib plus trametinib has improved efficacy in terms of OS (19.2 months vs. 9.3 months, p=0.054), PFS (9.8 months vs. 2.2 months, p=0.001) and ORR (66% vs. 19%, p<0.001) compared with nivolumab.[5] Results are similar for docetaxel.[5]

NMA

Please see Table 2 for trials included in the NMA as identified by the systematic review. Evidence network figures were presented for each efficacy outcome (please see Figure 1 for OS). Note there is an error in the OS network figure; the study connecting nivolumab and docetaxel is Borghaei 2015 (not Shepherd 2005).

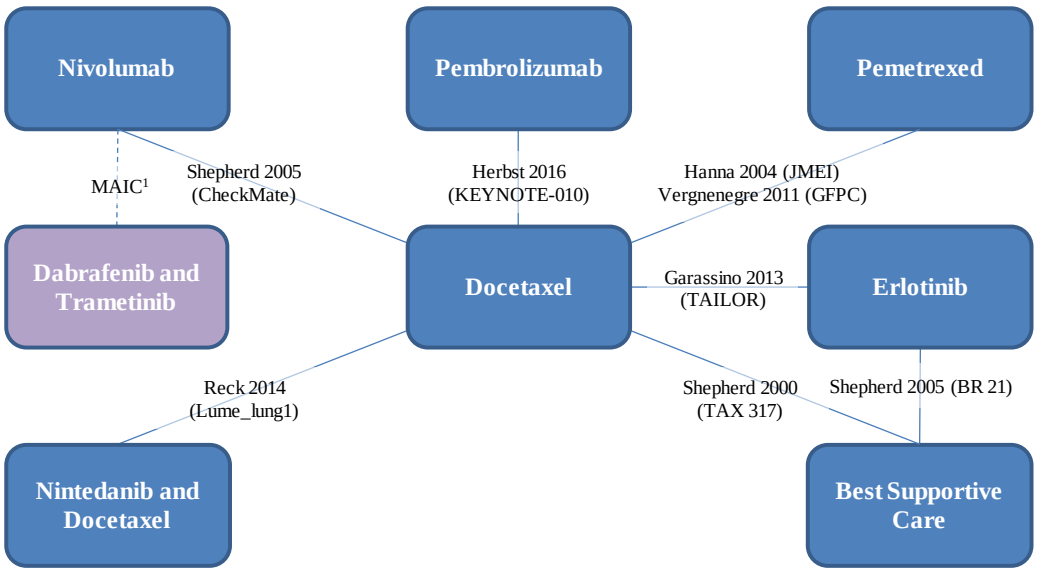
Fractional polynomials were used to compare OS and PFS across trials. For both OS and PFS, dabrafenib plus trametinib was associated with better overall survival over time compared with all

other interventions. For ORR, using docetaxel as the reference, both the fixed effect model and random effects model indicated that, compared with all other treatments, dabrafenib plus trametinib demonstrated the greatest odds of achieving ORR (13.2, 95% CrI (5.5, 33.0). A critical appraisal applying ISPOR criteria is provided in Table 4.

**Table 2. "Table 7.1: Trials identified the systematic literature review for inclusion in selected analyses[5]"**

| Trial acronym | MAIC vs. Docetaxel | MAIC vs. Nivolumab | Binomial NMA | | Fractional Polynomial NMA | |
|---|---|---|---|---|---|---|
| | | | ORR | DCR | PFS | OS |
| BRF113928 (Cohort B) | x | x | x | x | x | x |
| CheckMate 057 | x | x | x | x | x | x |
| TAX317 | | | x | x | | x |
| GFPC 05-06 | | | x | x | | x |
| NCT00095199 | | | x | x | | |
| JMEI | | | x | x | x | x |
| BR 21 | | | x | | x | x |
| TAILOR | | | x | x | x | x |
| Keynote-010 | | | x | | x | x |
| LUME-Lung 1 | | | x | x | x | x |

**Figure 1. "Figure 7.6: Evidence network for OS[5]"**




**Note:**

[1] The dabrafenib and trametinib combination therapy was linked to the network via a matching-adjusted indirect comparison (MAIC) versus nivolumab. Patients baseline characteristics in BRF113928 (the dabrafenib and trametinib trial) Cohort B were matched to those reported in CheckMate 057.

### 7.1.3 Summary

MAIC limitations

As there are no head-to-head RCTs comparing dabrafenib plus trametinib to existing 2nd-line treatments, a pseudo trial was created. This pseudo trial compared dabrafenib plus trametinib[1] to nivolumab (CheckMate 057).[6] The absence of a common comparator arm is a critical limitation as validation of the matching is not possible.[7]

Matching did not meaningfully change the OS, PFS and OR in the dabrafenib plus trametinib trial from before-matching to after-matching. This is likely because the patients enrolled in these trials, but for BRAF V600E mutation status, were quite similar in terms of baseline characteristics.

The results from the manufacturer-submitted indirect comparison suggest that dabrafenib and trametinib may be an effective 2nd line (and beyond) treatment among patients with advanced NSCLC with BRAF V600E mutation. However, there may be imbalances on important, unmeasured prognostic factors between the patients enrolled in BRF113928 (Cohort B) and CheckMate 057. In particular, dabrafenib plus trametinib is the only trial that exclusively enrolled patients with BRAF V600E-mutant Stage IV NSCLC previously treated with chemotherapy. Checkmate 057 (and all other trials identified in the systematic review) were conducted in unselected (for mutation) populations. Ideally, the report would have provided information regarding the outcomes (i.e., OS, PFS, OR) for patients enrolled in CheckMate 057 (docetaxel vs nivolumab) who were eligible for the trial of dabrafenib plus trametinib (i.e., BRAF V600E mutation positive and who met all trial inclusion and exclusion criteria). Without this information it is difficult to assess the relative efficacy of dabrafenib plus trametinib compared with docetaxel and nivolumab in patients with previously treated BRAF V600E-mutated Stage IV NSCLC.

NMA limitations

The results from the NMA are dependent on linking BRF113928 (Cohort B) to the network using MAIC (i.e., two pseudo trials created using aggregate data from Checkmate 057 (docetaxel vs. nivolumab)[6]). Thus, the NMA is limited by the concerns raised in the MAIC (see above).

Table 3. "Table 7.4: Comparison of baseline characteristics of dabrafenib plus trametinib and nivolumab[5]"

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | Dabrafenib plus trametinib N=57 | Nivolumab N=292 | p-value | Dabrafenib plus trametinib ESS = 34 | Nivolumab N=292 | p-value |
| Age < 65 years | 50.9 | 63.0 | 0.086 | 63.0 | 63.0 | 1.000 |
| Male | 50.9 | 51.7 | 0.908 | 51.7 | 51.7 | 1.000 |
| Race – White | 87.7 | 91.4 | 0.373 | 91.4 | 91.4 | 1.000 |
| Current or former smoker | 71.9 | 79.1 | 0.232 | 79.1 | 79.1 | 1.000 |
| Adenocarcinoma | 98.2 | 93.5 | 0.158 | 93.5 | 93.5 | 1.000 |
| ECOG performance status >=1 | 70.2 | 71.2 | 0.872 | 71.2 | 71.2 | 1.000 |
| Number of prior systemic regimens for metastatic disease >=2 | 33.3 | 12.3 | <0.001 | 12.3 | 12.3 | 1.000 |
| Prior anti-cancer radiotherapy | 28.1 | 47.6 | 0.007 | 47.6 | 47.6 | 1.000 |

| | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | Dabrafenib plus trametinib N=57 | Nivolumab N=292 | p-value | Dabrafenib plus trametinib ESS = 34 | Nivolumab N=292 | p-value |
| Prior anti-cancer maintenance therapy | 35.1 | 41.8 | 0.347 | 41.8 | 41.8 | 1.000 |
| Complete or partial response to the most recent prior anti-cancer therapy | 28.1 | 25.0 | 0.627 | 25.0 | 25.0 | 1.000 |

Table 4. ISPOR Critical Appraisal of NMA

| Item | Comments |
|---|---|
| **Relevance** | |
| 1. Is the population relevant | No. Eight of the nine trials included in the NMA to examine OS and PFS were conducted in unselected patients (i.e., not BRAF V600E positive). Only one trial tested the efficacy of dabrafenib plus trametinib patients with Stage IV NSCLC with BRAF V600E mutation who have failed first line treatment (Planchard 2016). This study was not an RCT and was linked to the network using MAIC methodology to create a pseudo trial. CheckMate 057 (docetaxel v. nivolumab) was used to link BRF113928 (Cohort B) to the network. |
| 2. Are any relevant interventions missing? | No |
| 3. Are any relevant outcomes missing? | No. However, median follow up for PFS and OS was only 11.6 months in BRF113928 (Cohort B). |
| 4. Is the context (settings and circumstances) applicable? | Yes |
| **Credibility** | |
| Evidence base used for the indirect comparison or network meta-analysis | |
| 1. Did the researchers attempt to identify and include all relevant RCTs? | Yes |
| 2. Do the trials for the interventions of interest form one connected network of RCTs? | Yes. However, BRF113928 (Cohort B) was connected to the network using MAIC methodology to create a pseudo trial as BRF113928 (Cohort B) was a Phase II, single-arm trial. Both treatment arms in CheckMate 057 (docetaxel v. nivolumab) were used as comparators. That is, a pseudo trial was created to compared dabrafenib plus trametinib v. docetaxel and, dabrafenib plus trametinib v. nivolumab. |
| 3. Is it apparent that poor quality studies were included, thereby leading to bias? | No |
| 4. Is it likely that bias was induced by selective reporting of outcomes in the studies? | No |
| 5. Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that have an impact on the treatment effects) across the different treatment comparison in the network? | Yes. The NMA provides evidence about the comparative efficacy of dabrafenib plus trametinib with other 2nd line treatments in Stage IV / advanced NSCLC among patients with BRAF V600E mutation. However, only one study (BRF113928 (Cohort B)) exclusively enrolled patients with |

| Item | Comments |
|---|---|
| **Relevance** | |
| | BRAF V600E mutation. All other trials included unselected patients with respect to mutation status. |
| 6. 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 before comparing individual study results? | In the "Overview of Study Methods" sections:<br>"As no data are currently available from head-to-head randomized trials of dabrafenib + trametinib combination therapy versus other treatments available for the treatment of advanced or metastatic NSCLC patient, the present study relied on indirect comparisons."<br><br>In section 8.2 "Study strengths and limitations" the report states:<br>"Systematic cross-trial differences in tumor genetics; in particular, dabrafenib + trametinib was targeted on NSCLC patients with BRAF V600E mutations, while other comparators have not been studied specifically on the BRAF V600E mutant NSCLC patients" |
| Analysis | |
| 7. Were statistical methods used that preserve within-study randomization? (No naïve comparisons) | Yes |
| 8. If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed? | The only closed-loop was for docetaxel-erlotinib-best supportive care. This comparison was not the focus of the NMA and was not discussed. |
| 9. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis? | n/a |
| 10. 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? | MAIC methodology was used to create a pseudo trial comparing dabrafenib plus trametinib combination (BRF 113928) and docetaxel (CheckMate057)and, comparing dabrafenib plus trametinib combination (BRF113928) and nivolumab (CheckMate057). MAIC methodology imposed balance on baseline characteristics between BRF113928 and CheckMate057. |
| 11. Was a valid rationale provided for the use of random-effects or fixed-effect models? | In the binomial NMA (ORR, DCR), both random-effects and fixed-effect models were used. No rationale was provided for using both. |
| 12. If a random-effects model was used, were assumptions about heterogeneity explored or discussed? | No |
| 13. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with prespecified covariates performed? | No |
| 14. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison | Yes |
| 15. Are the individual study results reported? | No. Individual study results were only reported for BRF113928 and CheckMate057. The individual study results |

| Item | Comments |
|---|---|
| **Relevance** | |
| | for the remaining 8 studies in the binomial NMA (ORR, DCR) and 7 studies in the fractional polynomial NMA (PFS, OS). |
| 16. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis? | No |
| 17. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty? | No |
| 18. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome? | Yes, however it appears that the estimated ORR and DCR are ranked only by the OR and the uncertainty as measured by the 95% CrI, is not taken under consideration. |
| 19. Is the effect of important patient characteristics on treatment effects reported? | No. |
| Interpretation | |
| 20. Are the conclusions fair and balanced? | The report provides a discussion of "strengths and limitations". The impact on OS and PFS of all comparator trials including a population unselected for BRAF V600E warrants further discussion. |
| Conflict of interest | |
| 21. Were there any potential conflicts of interest? | None were declared |
| 22. If yes, were steps taken to address these? | See #21. |

# 8 COMPARISON WITH OTHER LITERATURE

The following comparison with other literature was identified during development of the review protocol as relevant to the pCODR review of dabrafenib plus trametinib in advanced NSCLC with BRAF V600E mutation who have been previously treated with chemotherapy.

- Natural history of NSCLC among patients with BRAF V600E mutation.
- ORR as a surrogate outcome for OS in NSCLC patients with BRAF V600E

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

## 8.1 Natural history of NSCLC in patients with BRAF V600E mutation

*Overview of studies*

Two studies describing the natural history of advanced NSCLC in patients receiving 2nd line (and beyond) therapy are included.[8,9] Please see Table 1 for study details.

French Cooperative Thoracic Intergroup (IFCT)[8]

In France, all consecutive patients with NSCLC were routinely screened for molecular alternations during a 1-year period (April 2012 – April 2013) at one of 28 certified molecular genetics centres. The database was locked on July 23, 2014. Among 17 664 patients, 18 679 molecular analyses were conducted for 6 genes (EGFR, KRAS, BRAF (exon 15 = V600E), HER2, PIK3CA, ALK). There were 262 (1%) molecular analyses that tested positive for BRAF V600E. This study provide OS (n=132), PFS (n=71) and ORR (n=59 ) for BRAF V600E patients who received second-line treatment. The design and outcomes are summarized in Table 1 and Table 2 respectively.

Real-world treatment patterns, natural history and burden of illness in NSCLC with BRAF V600[9]

In this historical cohort study, NSCLC BRAF V600 mutation-positive patients were identified in two academic oncology clinics. Database lock was June 17, 2016 and the last index date for inclusion was December 17, 2015 (to provide a minimum 6 months of follow up). The start date for the sampling frame is not stated. There were 26 patients included in this study and 15 patients received 2nd-line therapy. This study provides natural history (i.e., not receiving targeted therapy: BRAF inhibitor (dabrafenib or vemurafenib) or MEK inhibitor (trametinib)) for OS (n=8), PFS (n=10) and ORR (n=10). The design and outcomes are summarized in Table 1 and Table 2 respectively.

**Table 1. Studies reporting the natural history of NSCLC among those with BRAF V600E mutation compared with dabrafenib plus trametinib (BRF113928 (Cohort B))**

| Study name | BRF113928 (Cohort B)[1] | Barlesi Lancet 2016[8] | Davis 2016[9] |
|---|---|---|---|
| Population | Adults, advanced NSCLC with BRAF V600E receiving dabrafenib plus trametinib in 2nd-line (and beyond) treatment | All consecutive patients with NSCLC who were routinely screened for molecular alternations during a 1-year period at one of 28 certified molecular genetics centres in France<br>Prescription of routine molecular screening is mandatory for advanced non-squamous NSCLC was solely the | Patients with a confirmed diagnosis of metastatic NSCLC and BRAF V600 mutation |

| Study name | BRF113928 (Cohort B)[1] | Barlesi Lancet 2016[8] | Davis 2016[9] |
|---|---|---|---|
| | | responsibility of the treating physician. | |
| Study design | Phase II, open-label, non-comparator | Population based cohort | Historical cohort<br>2 academic oncology centers<br>Last index date for inclusion: Dec 17, 2015 (to allow for a minimum 6 months f/up)<br>Sampling frame: start date unknown; data base lock: June 17, 2016. |
| Key inclusion criteria | • Histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC<br>• Documented tumour progression after at least 1 platinum-based chemotherapy regimen<br>• No more than 3 previous systemic treatments for metastatic NSCLC<br>• Measurable disease (RECIST 1.1)<br>• ECOG ≤ 2<br>• Adequate organ function<br>• Estimated life expectancy ≥ 3 months | | Patients not enrolled in a BRAF inhibitor clinical trial. However, off-label treatment with a BRAF inhibitor was permitted (i.e., in routine practice). |
| Number enrolled with BRAF V600E mutation and receiving 2nd line (and beyond) treatment | 57 | 132 | 8<br>Note: may only be BRAF rather than BRAF V600E. Unclear from report. |
| Available 2nd-line (and beyond) treatment | Dabrafenib plus trametinib | Taxane, pemetrexed, erlotinib, crizotinib, trial, BSC | Pemetrexed, carboplatin + pemetrexed, vinorelbine, docetaxel, other (not specified). |

Summary & limitations

Please see Table 2 for a summary of key outcomes (OS, PFS, ORR). As demographic data specific to patients receiving 2nd line treatment was not reported in either study, it is difficult to compare the study populations. Ideally, to fairly compare the outcomes between BRF113928 (Cohort B) and, Barlesi 2016 and Davis 2016, all inclusion and exclusion criteria from BRF113928 (Cohort B) should be applied to the patients in these studies. Selection of patients included in Barlesi 2016 and Davis 2016 in this manner may result in a healthier population which may result in improved OS, PFS and OR.

At Checkpoint, the submitter was asked to provide data from Davis 2016 that were limited to those patients who met the eligibility criteria for BRF113928 (Cohort B). The submitter provided the following response:

"Because of the relative scarcity of these patients and consequently the small size of this data set, it is not possible for us to specifically focus on patients who would precisely meet the eligibility criteria of Study BRF113928 Cohort B.[4]"

Given the potential lack of comparability of the patients enrolled in BRF113928 (Cohort B) and, Barlesi 2016 and Davis 2016, there is a substantial uncertainty regarding any observed differences in OS, PFS and ORR. These data should be interpreted with caution.

At Checkpoint, the submitter provided updated OS, PFS and ORR for BRF113928 (Cohort B) (see Table 2). This update is based on data presented at ASCO on June 3, 2017.

**Table 2. Outcomes: OS, PFS and ORR**

| Study name | BRF113928 (Cohort B)[1] | Barlesi Lancet 2016[8] | Davis 2016[9] |
|---|---|---|---|
| OS (months)<br>(n, median, 95% CI) | August 8, 2016 data cut[2]:<br>57, 18.2 (14.3, NE) | 132, 13.8 (8.5 – 21.9) | 8, 12.5 (1.9, 46.3) |
| 6-month OS<br>(n, %, 95% CI) | October 7, 2015 data cut (11.6 months follow up)<br>57, 82%, (NR) | 132, 68%, (59.5 – 76.2) | 8, 50%, (NR) |
| 12-month OS<br>(n, %, 95% CI) | NR | 132, 52% (42.4 – 61.6) | 8, 18.8%, (NR) |
| PFS (months) *<br>(n, median, 95% CI) | October 7, 2015 data cut (11.6 months follow up)<br>57, 8.6 (5.2 – 19.1)<br><br>August 8, 2016 data cut[2]:<br>57, 8.6 (5.2, 16.8) | 71, 3.1 (1.4 – 6.1) | 10, 3.3, (0.5, 8.5) |
| 6-month PFS<br>(n, %, 95% CI) | October 7, 2015 data cut (11.6 months follow up)<br>57, 65% (51 - 76) | 71, 41% (28.7 – 53.9) | 10, 30.0%, NR |
| 12-month PFS<br>(n, %, 95% CI) | NR | 71, 18% (6.2 - 30.1) | 10, 20%, NR |
| ORR*<br>(n, %, 95% CI) | October 7, 2015 data cut (11.6 months follow up)<br>57, 63.2% (49.3 – 75.6)<br><br>August 8, 2016 data cut[2]:<br>57, 63.2% (49.3, 75.6) | 59, 8% (95% CI 5.8 – 9.6) | 10, 0 |

### 8.2 Overall response rate (ORR) as a surrogate for overall survival (OS)

Currently, there is no evidence supporting ORR as a surrogate for OS among patients with advanced NSCLC with BRAF V600 mutation. Efficacy of dabrafenib plus trametinib using ORR as a surrogate for OS should be interpreted with caution.

# 9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel 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 (Tafinlar) plus trametinib (Mekinist) for BRAF V600 mutation positive NSCLC. 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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

# APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

## Literature Search Methods

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-present) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017 April 06) via Ovid; The Cochrane Central Register of Controlled Trials (March 2017) 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, Mekinist, trametinib and non-small cell lung cancer.

No filters were applied to limit retrieval by study type. 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 July 4, 2017

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) and the European Society for Medical Oncology (ESMO) 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.

### 1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2017**, Embase** 1974 to 2017 April 06**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

| # | Searches | Results |
|---|---|---|
| 1 | (dabrafenib or Tafinlar* or GSK 2118436* or GSK2118436* or QGP4HA4G1B or 1195765-45-7).ti,ab,ot,kf,kw,hw,rn,nm. | 3171 |
| 2 | (trametinib or Mekinist* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057 or 33E86K87QN or 871700-17-3).ti,ab,ot,kf,kw,hw,rn,nm. | 3161 |
| 3 | 1 and 2 | 1819 |
| 4 | 3 use pmez | 300 |
| 5 | 3 use cctr | 50 |
| 6 | 4 or 5 | 350 |
| 7 | Carcinoma, Non-Small-Cell Lung/ or NSCLC.ti,ab,kf,kw. | 108661 |

| | | |
|---|---|---|
| 8 | (exp Adenocarcinoma/ or Carcinoma, Large Cell/ or exp Carcinoma, Squamous Cell/ or Carcinoma, Adenosquamous/ or Carcinoma/) and (lung* or pulmonary or bronchial).ti,ab,kf,kw. | 97532 |
| 9 | ((non-small cell or nonsmall cell or large cell or squamous or bronchoalveolar or bronchiolo alveolar) and (neoplasm* or cancer* or carcinoma* or tumor* or tumour* or adenocarcinoma*) and (lung* or pulmonary or bronchial)).ti,ab,kf,kw. | 167698 |
| 10 | 7 or 8 or 9 | 239778 |
| 11 | 6 and 10 | 11 |
| 12 | *dabrafenib/ or (dabrafenib or Tafinlar* or GSK 2118436* or GSK2118436).ti,ab,kw. | 1807 |
| 13 | *tametinib/ or (trametinib or Mekinist* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057).ti,ab,kw. | 1739 |
| 14 | 12 and 13 | 879 |
| 15 | Non small cell lung cancer/ or NSCLC.ti,ab,kw. | 117751 |
| 16 | (exp Adenocarcinoma/ or Large cell carcinoma/ or exp Squamous cell carcinoma/ or Carcinoma/) and (lung* or pulmonary or bronchial).ti,ab,kw. | 97173 |
| 17 | ((non-small cell or nonsmall cell or large cell or squamous or bronchoalveolar or bronchiolo alveolar) and (neoplasm* or cancer* or carcinoma* or tumor* or tumour* or adenocarcinoma*) and (lung* or pulmonary or bronchial)).ti,ab,kw. | 167200 |
| 18 | 15 or 16 or 17 | 242998 |
| 19 | 14 and 18 | 35 |
| 20 | 19 use oemezd | 26 |
| 21 | 20 and conference abstract.pt. | 12 |
| 22 | limit 21 to yr="2012 -Current" | 10 |
| 23 | (11 or 20) not 21 | 25 |
| 24 | 22 or 23 | 35 |

**2. Literature search via PubMed**

A limited PubMed search was performed to capture records not found in MEDLINE.

| Search | Query | Items found |
|---|---|---|
| #9 | Search #8 AND publisher[sb] Filters: English | 2 |
| #8 | Search #7 AND #2 AND #3 Filters: English | 8 |
| #7 | Search #4 OR #5 OR #6 Filters: English | 90049 |
| #6 | Search (non-small cell[tiab] OR nonsmall cell[tiab] OR large cell[tiab] OR squamous[tiab] OR bronchoalveolar[tiab] OR bronchiolo-alveolar[tiab] OR bronchioloalveolar[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR malignan*[tiab]) AND (lung*[tiab] OR pulmonary[tiab] OR bronchial[tiab]) Filters: English | 57168 |

| | | |
|---|---|---|
| #5 | Search (Adenocarcinoma[mh] OR Carcinoma, Large Cell[mh] OR Carcinoma, Squamous Cell[mh] OR Carcinoma, Adenosquamous[mh] OR Carcinoma[mh:noexp]) AND (lung*[tiab] OR pulmonary[tiab] OR bronchial[tiab]) Filters: English | 38894 |
| #4 | Search Carcinoma, Non-Small-Cell Lung[mh] OR NSCLC[tiab] Filters: English | 43431 |
| #3 | Search trametinib[supplementary concept] OR trametinib[tiab] OR Mekinist*[tiab] OR GSK 1120212*[tiab] OR GSK1120212*[tiab] OR JTP 74057[tiab] OR JTP74057[tiab] OR 33E86K87QN[rn] OR 871700-17-3[rn] Filters: English | 510 |
| #2 | Search dabrafenib[supplementary concept] OR dabrafenib[tiab] OR Tafinlar*[tiab] OR GSK 2118436*[tiab] OR GSK2118436*[tiab] OR QGP4HA4G1B[rn] OR 1195765-45-7[rn] Filters: English | 563 |

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 + Mekinist/trametinib + lung cancer

**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 + Mekinist/trametinib + lung cancer

**Conference abstracts:**

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

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search: Tafinlar/dabrafenib + Mekinist/trametinib + lung cancer
- last 5 years

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