CADTH

CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

Dabrafenib (Tafinlar) in Combination with Trametinib (Mekinist)

(Novartis Pharmaceuticals Inc.)

Indication: Dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600 mutation

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Abbreviations

AE	adverse event
ALK	anaplastic lymphoma kinase
ASCO	American Society for Clinical Oncology
BOR	best overall response
BRAF	v-Raf murine sarcoma viral oncogene homolog B
CCO	Cancer Care Ontario
CGP	Clinical Guidance Panel
CI	confidence interval
CR	complete response
DCR	disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	epidermal growth factor receptor
ELCC	European Lung Cancer Congress
EMR	electronic medical record
ESMO	European Society for Medical Oncology
HR	hazard ratio
HRQoL	health related quality of life
ICES	Institute of Clinical Evaluative Sciences
IRC	independent review committee
IQR	interquartile range
ITC	indirect treatment comparison
ITT	intention-to-treat
KM	Kaplan Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LCC	Lung Cancer Canada
MAIC	matching adjusted indirect comparison
MAPK	mitogen-activated protein kinase
MEK	MAP (Mitogen-Activated Protein) Kinase/ERK (Extracellular Signal-Regulated Kinase) Kinase
NE	not estimable
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PAG	Provincial Advisory Group
PCR	polymerase chain reaction

pCODR	pan-Canadian oncology drug review
PD-1	programmed death-1
PD-L1	programmed death- ligand 1
pERC	pCODR Expert Review Committee
PFS	progression free survival
PH	proportional hazards
PK	pharmacokinetic
PR	partial response
PSWA	propensity score weighted analysis
QoL	quality of life
RAF	rapidly accelerated fibrosarcoma
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ros oncogene 1
RWE	real world evidence
SAE	serious adverse event
SD	standard deviation
SLR	systematic literature review
SMD	standardized mean difference
SOC	standard of care
STK11	serine/threonine kinase 11
TTD	time to treatment discontinuation
TTP	time to tumor progression
ULN	upper limit of normal
WCLC	World Congress on Lung Cancer
WDAE	withdrawal due to adverse event

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®) in combination with trametinib (Mekinist®) in previously untreated patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF (v-Raf murine sarcoma viral oncogene homolog B) V600 mutation. 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 conducted by the Clinical Guidance Panel (CGP) and the CADTH 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, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of the systematic review is to evaluate the efficacy and safety of dabrafenib (Tafinlar®) in combination with trametinib (Mekinist®) for the treatment of adult patients with metastatic NSCLC with a BRAF V600 mutation who have not received any prior anti-cancer therapy for metastatic disease.

The reimbursement request under review by CADTH is for dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600 mutation and who have not received any prior anti-cancer therapy for metastatic disease. The reimbursement request is different from the Health Canada indication. The approved Health Canada indication is dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600 mutation.[1,2] A validated test is required to identify BRAF V600 mutation status of NSCLC tumours.

Dabrafenib is a small molecule inhibitor of rapidly accelerated fibrosarcoma (RAF) kinases, including BRAF. Oncogenic mutations in BRAF lead to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway and may promote tumour cell growth.[1,2] Dabrafenib and trametinib provide concomitant inhibition of the pathway and the combination was synergistic in V600E-mutated NSCLC cell lines.[1,2]

Dabrafenib is administered at a dose of 150 mg (two 75 mg capsules) given orally twice daily (corresponding to a total daily dose of 300 mg) with 2 mg of trametinib given orally once daily; and treatment should continue until disease progression or the development of unacceptable toxicity.[1,2]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One trial met the inclusion criteria of the CADTH systematic review. Study BRF113928 (Cohort C) is the pivotal trial that was included as evidence in the CADTH submission.[3] BRF113928 is a phase 2, open label, single arm, multicentre study conducted in 19 centres in eight countries (North America, Europe, Asia). Cohort C of the trial evaluated the combination of dabrafenib and trametinib in previously untreated adult patients with BRAF V600E-mutant stage IV NSCLC. Patients enrolled in Cohort C of the trial met the following key inclusion criteria:

- Aged ≥ 18 years
- Histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2
- Estimated life expectancy of greater than or equal to three months

- No previous BRAF or MEK inhibitor therapy
- No brain metastases unless asymptomatic, untreated, or measuring less than 1cm (or if treated, were clinically or radiographically stable three weeks after local therapy)

Eligible patients were treated with oral dabrafenib (150 mg twice per day) plus oral trametinib (2 mg once per day) until disease progression, unacceptable toxicity, consent withdrawal, or death. Treatment beyond progression was allowed in patients who had a confirmed response (RECIST version 1.1) or stable disease for at least 12 weeks during study treatment and were judged by the investigator to be clinically benefitting from the study treatment. The median patient daily dose was 269.2 mg (interquartile range [IQR], 211 to 298) for dabrafenib and 1.9 mg (IQR, 1.6 to 2.0) for trametinib. The median durations of treatment exposure to dabrafenib and trametinib were 9.0 months (IQR, 3.14 to 20.53) and 9.5 months (IQR, 3.2 to 19.3), respectively. The majority of trial patients had a median duration of exposure to dabrafenib and trametinib that was greater than 12 months; 39% of patients received dabrafenib and 42% of patients received trametinib for at least 12 months. Radiologically detected disease per RECIST version 1.1 was evaluated with CT at baseline, at week six, every six weeks until week 36, and every 12 weeks thereafter. Responses were confirmed by repeat assessments performed four to seven weeks after an initial response. An independent review committee (IRC) also reviewed RECIST scans. For patients who discontinued treatment, follow-up for subsequent treatment and survival was done every 12 weeks until death or study completion. Adverse events (AEs), laboratory values and vital signs were evaluated at least every three weeks.

The primary outcome was investigator-assessed overall response rate (ORR), defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) according to RECIST version 1.1. Secondary outcomes were ORR by IRC assessment, progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety. Health-related quality of life (HRQoL) was not evaluated in the trial. The analyses of efficacy were performed by intention to treat (ITT) and the analyses of safety were performed in patients treated with at least one dose of dabrafenib plus trametinib. The analyses of time-to-event outcomes (i.e., DOR, PFS, and OS) were considered descriptive since no formal hypotheses or statistical testing was performed. The trial was considered complete when a minimum of 70% of patients had died (or were no longer being followed), or when five years have passed since patients' first dose, whichever comes first. The data cut-off date for the primary efficacy analysis was April 28, 2017; and an updated analysis was performed with a data cut-off date of June 22, 2019 (785 days from the first efficacy analyses). The median duration of follow up was 15.9 months at the time of the primary efficacy analysis[3] and 16.3 months at the time of the updated efficacy analysis.[4]

A total of 36 patients were enrolled in Cohort C between April 16, 2014 and December 28, 2016. The median age of patients was 67 years, and most patients were female (61%; n=22) and of White race (83%; n=30). The median time from diagnosis was 2.05 months. At baseline, most patients had an ECOG PS of 1 (61%; n=22). For the majority of patients (89%; n=32) histology at initial diagnosis was determined as non-squamous adenocarcinoma. At the primary efficacy analysis data cut-off date, 19 patients (53%) were still alive, 11 (31%) were still on study treatment, and 17 (47%) had died. Among the 25 patients (69%) who had discontinued treatment by the data cut-off date, 14 patients had discontinued due to disease progression and eight had discontinued due to AEs.

Outcomes

A summary of the key outcomes in Cohort C of Study BRF113928, based on the primary analysis, is presented in Table 1.

Efficacy

At the primary analysis, the investigator-assessed ORR was 63.9% based on 23 patients who had a confirmed response; this included two patients (6%) who achieved a CR and 21 patients (58%) who achieved a PR. There were 27 patients (75.0%) who achieved disease control (23 with a confirmed response and four considered to have stable disease).[3] At the time of the updated efficacy analysis, the ORR was maintained (63.9%; 95% CI, 46.2 to 79.2).[4] The median DOR by investigator assessment was 10.4 months (95% CI, 8.3 to 17.9) at the primary analysis and 10.2 months (95% CI, 8.3 to 15.2) at the updated analysis.[4]

At the primary analysis, the median investigator-assessed PFS was 10.9 months (95% CI, 7.0 to 16.6) and PFS at six months was 72% (95% CI, 53 to 84). At this analysis, 19 patients (53%) remained alive and 17 (47%) patients had died; the median OS was 24.6 months (95% CI, 12.3 to not estimable [NE]) and two-year OS was 51% (95% CI, 33 to 67). At the updated analysis, median PFS

was 10.8 months (95% CI, 7.0 to 14.5) and the median OS was 17.3 months (95% CI, 12.3 to 40.2).[4] OS at 12, 24 and 36 months was 74% (95% CI, 55 to 85), 49% (95% CI, 32 to 65), and 40% (95% CI, 24 to 56), respectively.[4]

Harms

All patients had at least one AE of any grade. The most commonly reported AEs were pyrexia (64%, n=23), nausea (56%, n=20), diarrhea (36%, n=13), fatigue (36%, n=13), peripheral oedema (36%, n=13), decreased appetite (33%, n=12), dry skin (33%, n=12), and vomiting (33%, n=12). Serious AEs (SAEs) occurring in more than two patients included alanine aminotransferase increase (14%, n=5), pyrexia (11%, n=4), aspartate aminotransferase increase (8%, n=3), and ejection fraction decrease (8%, n=3). One patient died from a SAE (cardiorespiratory arrest), which was considered unrelated to the study treatment. A total of 22% (n=8) of patients discontinued treatment due to AEs.

Table 1: Highlights of Key Outcomes in Cohort C of Study BRF113928

Key Outcomes*	BRF113928 (Cohort C) Dabrafenib + trametinib (N=36)
Efficacy	
ORR, n (%; 95% CI)	23 (64%; 46–79)
CR, n (%)	2 (6%)
PR	21 (58%)
Stable disease	4 (11%)
Progressive disease	5 (14%)
DOR, median (95% CI)	10.4 (8.3–17.9)
PFS in months, median (95% CI)	10.9 (7.0–16.6)
6-month PFS in months, % (95% CI)	72 (53 to 84)
OS in months, median (95% CI)	24.6 (12.3–NE)
2-year OS in months, % (95% CI)	51 (33–67)
Harms	
AE (any grade), n (%)	36 (100)
AE (Grade 3 or 4), n (%)	25 (69)
Pyrexia	4 (11)
Alanine aminotransferase increase	4 (11)
Hypertension	4 (11)
vomiting	3 (8)
WDAE, n (%)	8 (22)

AE = adverse event, CI = confidence interval, CR = complete response; DOR = duration of response; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; WDAE = withdrawal due to adverse event.

* Based on primary analysis data cut-off date of April 28, 2017.

Source: Planchard et al, 2017[3]

Key limitations

The most significant limitation of Study BRF113928 is that it is a single arm trial with no placebo or control group(s). The lack of a comparator, the small sample size, and short duration of follow-up limit the conclusions that can be drawn regarding the efficacy and

safety of dabrafenib plus trametinib compared to currently available treatments for previously untreated patients with BRAF V600E-mutant stage IV NSCLC. In addition, ORR was the primary endpoint, and it is unknown whether a clinically meaningful ORR translates into clinical benefits in terms of PFS and OS. Although the CGP noted that in clinical practice response rate is often related to survival, there is currently no strong empirical evidence to support ORR as a surrogate for OS in BRAF V600E-mutant stage IV NSCLC. In Cohort C of Study BRF113928, ORR was largely driven by PRs with only two out of 36 patients achieving CR. Moreover, the descriptive analyses of secondary time-to-event outcomes (i.e., DOR, PFS and OS) in this trial with a small sample size further limits interpretation of the efficacy results. Another important limitation is the lack of HRQoL measures, which are important for capturing the benefits of novel therapies from a patient's perspective to confirm whether improvements in survival outcomes are accompanied by improved quality of life (QoL) for patients.

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

One patient group input was provided by Lung Cancer Canada (LCC) for the review of dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600E mutation. LCC gathered patient and caregiver input through surveys, patient and caregiver interviews and an environmental scan of social media. The data were accessed from September to October 2020. LCC also consulted previous LCC submissions for NSCLC patients treated with chemotherapy, immunotherapy and a combination of both treatments. From the patient perspective, symptoms of advanced NSCLC that most affected patients' QoL were cough, shortness of breath and fatigue. The disease can cause a significant physical, emotional and financial burden on patients and their caregivers. LCC identified a high unmet need for Canadian patients with advanced NSCLC with BRAF mutations, as currently no targeted therapies exist for this small groups of patients. Current treatments include chemotherapy, immunotherapy and a combination of both immunotherapy and chemotherapy. Patients noted that chemotherapy was associated with side effects such as nausea, vomiting and fatigue, and many patients eventually progress on the treatment. Patients reported a much favourable preference for immunotherapy and the combination of chemotherapy and immunotherapy; however, LCC noted that in the long-term, immunotherapy has been documented to have poor efficacy for patients with targeted mutations. Additionally, immunotherapy can be burdensome for patients as it can require multiple hospital visits, thus necessitating the need for an oral option like dabrafenib in combination with trametinib. Four patients and 2 caregivers reported having experience with dabrafenib and trametinib, all of whom reported an overall favourable experience with the drug. Patients reported that the drug combination helped reduce the size of the tumour and control their symptoms. Most patients reported very minimal side-effects that were manageable. Patients noted that the drug had allowed them to return to their normal activities and regain their independence. However, a concern reported by 1 patient was the high cost of the drug combination which would have made the drug inaccessible without insurance and a special access program. Patients expressed strong hopes for this combination to be accessible to all Canadian patients with advanced NSCLC with the BRAF V600E mutation. Overall, patients value prolonged survival, better symptom control, and manageable side effects with an improved quality of life. Given the high unmet need and favourable patient experiences, LCC highly supports the reimbursement of dabrafenib and trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600E mutation.

Provincial Advisory Group (PAG) Input

The PAG 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 CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

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

Clinical factors:

- Clinical eligibility criteria
- Definition of disease progression

Economic factors:

- BRAF testing
- Large NSCLC population

Registered Clinician Input

A total of two registered clinician inputs were provided for the review of dabrafenib and trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600E mutation, who have not received any prior anti-cancer therapy for metastatic disease: one joint input submission on behalf of three clinicians from the Ontario Health (Cancer Care Ontario) Lung Cancer Advisory Committee (CCO) and one joint input submission on behalf of 15 clinicians from LCC. Overall, both groups of clinicians were supportive of the use of dabrafenib and trametinib for metastatic NSCLC patients with the BRAF V600E mutation. Particularly, the clinicians from CCO noted that this drug is a great option for elderly and comorbid patients as it is well tolerated. The clinicians were pleased with the oral nature of the drug combination, especially during the current COVID-19 pandemic as it eliminates the need for patients to travel to the cancer centre or infusion site. Clinicians from CCO recommended the use of dabrafenib and trametinib in the second line setting for patients with the BRAF V600E mutation after first-line treatment with immunotherapy or the combination of chemotherapy and immunotherapy. Contrarily, the clinicians from LCC recommended the use of this drug combination in the first-line setting for patients with the BRAF V600E mutation. The clinicians from LCC explained that the use of first-line immunotherapy has not been well documented in patients with driver mutations and the use of targeted inhibitors early on in the treatment process provides a greater chance for long term survival and an improved QoL. The clinicians from LCC stated that immunotherapy with platinum doublets is a good option in the second line setting and docetaxel is an option in the third line setting. Overall, both groups of clinicians emphasized that dabrafenib and trametinib would address a high unmet need for NSCLC patients with the BRAF V600E mutation as it is a rare mutation for which there are currently no available targeted therapies.

Summary of Supplemental Questions

A supplemental question relevant to the pCODR review and to the PAG was identified while developing the review protocol and is outlined in section 7:

- Critical Appraisal of a Sponsor-submitted Propensity Score Weighted Analysis (PSWA) Comparing Clinical Outcomes in Patients Treated with Dabrafenib and Trametinib in Study BRF113928 (Cohort C) versus a Real-world, Retrospective Cohort of Patients Treated with Standard of Care Treatments for BRAF-mutated Advanced NSCLC

Due to a lack of direct evidence comparing dabrafenib and trametinib combination therapy to other existing treatments for patients with previously untreated BRAF-mutated advanced NSCLC, the sponsor conducted an indirect treatment comparison (ITC) to estimate the comparative efficacy of dabrafenib and trametinib to relevant comparators for the treatment of patients with previously untreated BRAF-mutated advanced NSCLC. A PSWA was conducted that used data from Cohort C of Study BRF113928 (index trial) of first-line dabrafenib and trametinib and real-world evidence (RWE) obtained from the Flatiron Enhanced Data Mart (EDM) database.

Two RWE Cohorts were derived from the Flatiron EDM database: RWE Cohort 1 included patients treated with first-line PD(L)1 plus chemotherapy regimens (i.e., pembrolizumab plus platinum doublet chemotherapy) and RWE Cohort 2 included patients treated with first-line chemotherapy regimens (i.e., platinum-based chemotherapy). After adjusting for differences in baseline characteristics between Cohort C from Study BRF113928 and the RWE Cohorts, the PSWA results showed that the HR for OS favoured dabrafenib and trametinib over first-line platinum-based chemotherapy (HR=0.51; 95% CI, 0.29 to 0.92; p=0.03); and for the comparison of dabrafenib and trametinib versus first-line pembrolizumab plus platinum-doublet chemotherapy, the HR for OS was not statistically significant (HR=0.57; 95% CI, 0.28 to 1.17; p=0.13).

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

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

See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence 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 from Cohort C of Study BRF113928

Domain	Factor	Evidence from Cohort C of Study BRF113928[3]	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS	1 of 36 (3%) patients in the trial had an ECOG performance score ≥ 2	Are the overall trial results generalizable to patients with ECOG score ≥ 2?	As Cohort C only included one patient with an ECOG PS of ≥2, there are insufficient data from the study to judge the impact of dabrafenib and trametinib in patients with a poor PS. With chemotherapy in NSCLC, it is known that in patients with a poor PS, the degree of clinical benefit is lower and the risk of death from toxicity is higher when compared to patients who have a good PS. Despite this, patients with a poor PS have a 50% probability of experiencing symptomatic improvement with chemotherapy.[5] Further, it is known that targeted therapies may result in very rapid PS improvement and symptomatic improvement in patients with the relevant target. Therefore, the CGP recommends that the clinical decision to offer dabrafenib and trametinib in patients with a PS ≥ 2 be considered on an individual basis.
Outcomes	Appropriateness of primary and secondary outcomes	• Primary: investigator-assessed ORR • Secondary: ORR by IRC assessment, DOR, PFS, OS, and safety	Were the primary and secondary outcomes appropriate for the trial design?	The CGP believe that the primary and secondary outcomes of Study BRF113928 were appropriate given the design of the trial (i.e., non-randomized phase 2 trial). While ORR has been questioned as a surrogate for OS, ORR correlates strongly with OS for both chemotherapy and targeted agents in various malignancies.[6] As well, crossover in clinical trials and the use of subsequent treatments affect the reliability of OS gain (but not PFS or ORR) as an indicator of drug benefit.
Setting	Trial centres (Netherlands, France, Norway, Germany, Spain, United Kingdom, Republic of Korea, United States)	There were no study centres in Canada.	Do trial results apply to patients in Canada? Do any known differences exist in terms of clinical practice between the countries listed and Canada?	The CGP believes that there would be no clinical practice, demographic, or pharmacogenetic basis to expect a difference in outcome in Canada compared to the countries in which Study BRF113928 was conducted.

CGP = clinical guidance panel; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC – independent review committee; NSCLC – non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

1.2.4 Interpretation

Dabrafenib and trametinib are molecularly targeted therapies for patients with BRAF V600E mutations. Published data[7] indicate that BRAF V600E mutations occur in approximately 2% of NSCLC adenocarcinomas and are considered oncogenic drivers. They generally occur independently of other common oncogenic drivers, including EGFR mutations and ALK translocations. Currently, patients with a BRAF V600 driver mutation have no targeted therapies available to them. Thus, there remains a significant unmet need for therapies that will advance treatment options in these patients. Dabrafenib and trametinib were evaluated in a single arm, multicentre phase 2 trial of treatment-naïve NSCLC patients with BRAF V600E mutations.[3] In Cohort C of Study BRF113928, eligible patients included those with BRAF V600E mutations who had received no prior systemic treatment for advanced NSCLC, had an ECOG PS of 0 to 2, and good organ function. The ORR of 64%, which was the primary endpoint of the trial, is substantially higher than the usual response rates of 20% to 40% that have been observed with chemotherapy and is similar to the response rates seen with therapies targeting EGFR mutations and ALK and ROS1 translocations. Similarly, the median PFS of 10.9 months that was observed in Cohort C is also higher than the usual median PFS of four to seven months with chemotherapy in unselected NSCLC patients and is similar to the median PFS observed with agents targeting EGFR mutations and ALK and ROS1 translocations. The median OS of 24.6 months observed in Cohort C is superior to the usual median OS of 11 to 12 months that is generally expected with chemotherapy and was again similar to that of agents targeting EGFR mutations and ALK and ROS1 translocations. The efficacy outcomes of dabrafenib and trametinib from Cohort C also appear improved when compared to the published results for pembrolizumab combined with chemotherapy in unselected patients with metastatic NSCLC (response rate 48%, median PFS 8.8 months, median OS 22 months).[8,9] These observations are made with the caveat that cross-trial comparisons do not account for important differences in patient populations and trial conduct. However, it is reassuring that the outcomes of Cohort C are similar to those of other effective targeted therapies in appropriately selected NSCLC patients, and to outcomes for this combination in BRAF-mutant melanoma.

Because BRAF mutations are very uncommon in NSCLC, it would be challenging to conduct a randomized trial comparing dabrafenib and trametinib to chemotherapy with or without pembrolizumab. No NSCLC trials have been completed comparing targeted therapies to chemoimmunotherapy in untreated patients, but each of response rate, PFS and OS were numerically superior with the dabrafenib and trametinib combination when compared with published data for chemotherapy with or without pembrolizumab.[8,9] Hence, the probability would be low that dabrafenib and trametinib would be substantially inferior to chemoimmunotherapy if a randomized comparison were to be conducted; and based on grade 3-5 toxicity rates in the published data,[3,9] it would not be expected to be more toxic, although the major types of toxicity that are seen with the combination are different than those seen with chemotherapy and chemoimmunotherapy. Dabrafenib and trametinib have also not been directly compared to chemotherapy; however, when such randomized comparisons have been conducted with other similarly effective targeted therapies, they have consistently demonstrated the superior efficacy and favourable toxicity profile of the targeted therapy in NSCLC[10,11] and other relevant malignancies.[12]

The sponsor submitted an ITC in the form of a PSWA that compared data from Cohort C of Study BRF113928 to an external control group of BRAF-mutant patients whose data were obtained from a RWE database (Flatiron EDM).[13] Compared to Flatiron BRAF-mutant patients treated with chemotherapy, the dabrafenib and trametinib combination had a favourable, statistically significant PFS and OS HR. Compared to Flatiron BRAF-mutant patients treated with pembrolizumab plus chemotherapy, the dabrafenib-trametinib combination again had favourable PFS and OS HRs, although not statistically significant. Overall, the results from the ITC suggest that the dabrafenib and trametinib is superior to chemotherapy and is at least as good as pembrolizumab plus chemotherapy. However, in addition to the PSWA not being randomized, other limitations were identified by the CADTH Methods Team that introduce uncertainty in the comparative estimates that were obtained by the analysis. The main limitations of the PSWA included the potential for residual confounding due to differences in baseline characteristics and missing data, differences in the definitions of PFS and the manner in which progression data were obtained between Study BRF113928 the RWE control groups, as well as small sample size and violation of the proportional hazard assumption for some analyses.

Despite the lack of direct comparisons or robust ITCs, the efficacy of dabrafenib and trametinib is reflective of data observed from single arm phase 2 trials of EGFR and ALK inhibitors, which accurately predicted efficacy in phase 3 randomized trials. While the number of previously untreated NSCLC patients who received dabrafenib and trametinib in Cohort C of Study BRF113928 was small, the response rate, PFS and OS results are reassuringly similar to those observed with other effective targeted therapies (e.g., EGFR,

ALK, and ROS1 inhibitors) in NSCLC patients with the appropriate target, and are also in keeping with the high level of activity seen with this combination in BRAF-mutant melanoma patients.[14]

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. This toxicity is generally controlled effectively by supportive therapies and dose reductions, as needed. With respect to tolerability, the proportion of patients developing grade 3-5 toxicity with the combination as first-line NSCLC therapy[3] was similar to the proportion developing grade 3-5 toxicity with chemotherapy alone or chemotherapy combined with pembrolizumab,[8,9] and similar proportions of patients required dose reductions or therapy discontinuation for toxicity. For other targeted therapies, experience tells us that toxicity can often be managed very effectively with dose reductions, while efficacy is maintained. QoL was not assessed in Study BRF113928, however, there is an extensive clinical experience that therapies that cause tumour regression will generally also improve many cancer symptoms.

Given the similarity of results, one might ask whether it might be reasonable to stick with chemoimmunotherapy instead of giving access to dabrafenib and trametinib. However, it is important to note that the important question is not whether to treat with one therapy versus the other, but rather which should be given first. Since metastatic NSCLC will not be cured by either option, tumour progression will eventually occur, and a patient would potentially benefit from the other modality of therapy after progression on the first. Therapies targeting EGFR, ALK, and ROS1 are also active when given as second-line therapy after chemotherapy, as is the dabrafenib-trametinib combination.[3] The general consensus in oncology is that it is best to start with an effective targeted therapy first due to its efficacy, its favourable toxicity profile and convenience of administration, and to then move to chemotherapy following progression on the targeted therapy, as needed. Since EGFR-mutant and ALK-mutant tumours are relatively resistant to immunotherapy (unlike tumours with mutations in BRAF, KRAS and TP53), there is little information on sequencing targeted therapies before versus after chemoimmunotherapy, but the toxicity profile and convenience would argue in favour of giving the targeted therapy first, even if sequence had no net impact on therapy efficacy.

The median OS with untreated metastatic NSCLC is about four months[15] and is approximately 11 to 12 months with chemotherapy.[8,9] Since the combination of dabrafenib and trametinib is associated with an OS of about 24 months,[3] the use of this combination could potentially translate into an average of 1.7 life-years saved in patients who were not treated with other systemic therapies but could be treated with this combination, and an average of one life-year saved for patients who receive this therapy instead of chemotherapy. In addition to the potentially meaningful prolongation of life expectancy with the targeted combination, there are also several other patient, caregiver or health care system burdens that this therapy could reduce by delaying (or avoiding) the need for intravenous therapies:

- Reducing patient travel to a cancer centre for treatment
- Reducing chair time in chemotherapy treatment units, and reducing pharmacy time in mixing the intravenous therapy
- Avoiding hospital admissions for febrile neutropenia
- Reducing patient anxiety about therapy, since patients and their families typically fear oral therapies less than intravenous cancer therapies, while also finding them more convenient
- More effective therapies reduce the burden on the health care system by reducing cancer symptoms, and thereby keeping patients out of emergency rooms and inpatient beds

Following the posting of the pERC Initial Recommendation, the CGP reviewed and discussed the feedback that was received from eligible stakeholder groups. The patient advocacy group (LCC), registered clinician groups (CCO and LCC), as well as the sponsor, all agreed with the pERC Initial Recommendation to conditionally reimburse dabrafenib and trametinib (upon cost-effectiveness being improved and feasibility of adoption [budget impact] being addressed) and supported early conversion to a Final Recommendation, while the PAG disagreed with the Initial Recommendation and did not support early conversion. PAG sought clarity on the following issues:

- the rationale for issuing an Initial Recommendation based on a small cohort of patients.
- the unmet need for dabrafenib and trametinib compared to currently available therapies.
- appropriateness of accepting ORR for outcomes important to decision making.

- Whether more clinical data are forthcoming as it was noted that previous NSCLC submissions that used ORR as the main clinical outcome did not receive a positive recommendation (in those situations more clinical data were forthcoming).

The CGP has responded to PAG's comments below.

Rationale of an Initial Recommendation based on a small cohort of patients: A single small study is an unreliable predictor of benefit in some situations but is more reliable in other situations. If a drug represents a new class of agents where there is no prior evidence to inform on clinical efficacy and safety, then an initial small study has the potential to indicate an unreliable magnitude of clinical benefit. In this situation, it is reasonable to require additional evidence in larger patient numbers before issuing a recommendation for reimbursement. However, if there is prior relevant evidence, it increases the confidence with which one may make a recommendation.[16]

In the case of dabrafenib and trametinib in NSCLC, there is additional relevant evidence that supports the use of this regimen either as first-line therapy or as a later line of therapy in patients with BRAF V600 mutant NSCLC, a point also raised by both clinician groups providing feedback on the Initial Recommendation. Specifically:

- The degree of benefit seen in previously treated BRAF mutant NSCLC patients who have received this regimen[17] was almost as high as the benefit in untreated patients;[3] and the degree of benefit in the Flatiron cohort was similarly high (RWE data submitted by sponsor). False positive results across all 3 treatment settings would be much less likely than in a single setting. Further, the degree of benefit of the combination in BRAF V600E mutant melanoma was comparable to that observed in NSCLC.[14]

- Across a range of mutation types, mutations that drive tumour cell growth have proven to be valid therapy targets for small ATP-mimetic molecules that have high binding affinity for the ATP binding pocket of the mutated protein. These small molecules may be less effective when targeting gene amplification (e.g., HER-2) or protein over-expression (e.g., estrogen receptor in breast cancer), and they are relatively ineffective if the binding affinity for the mutated protein is low (e.g., with some EGFR inhibitors vs EGFR exon 20 insertions). However, they are highly effective when targeting a mutated protein with reasonably high binding affinity (e.g., EGFR inhibitors in EGFR exon 19 deletions and L858R point mutations[18,19] and inhibitors of mutated fusion genes such as ALK,[20] ROS1,[21] RET,[22] NTRK[23] in NSCLC; BRAF V600E in melanoma;[14] and cKIT in gastrointestinal stromal tumours[24]). In each case, the degree of activity is very similar to that observed with the dabrafenib and trametinib combination in NSCLC. Further, if given after chemotherapy as second- or third-line therapy, these other agents have consistently proven to be highly effective in the same way that dabrafenib and trametinib was highly effective in previously treated patients.

- For these other effective small molecules that have been compared to chemotherapy as first line treatment in patients with relevant mutations, they have consistently proven superior to chemotherapy. Hence, in patients with the relevant target, they are of substantial value whether given as first-line therapy or as second-line therapy. They are most effective given first-line, but it is highly important that if patients do not have access to them as first-line therapy, they then at least have access to them as a later line of therapy.

The unmet need compared to currently available therapies: The unmet need is that almost all patients with metastatic lung cancer die of their disease. Lung cancer is the second leading cause of death in Canada after heart disease. Being treated with any available chemotherapy or chemoimmunotherapy regimen does not alter this prognosis. Consequently, almost all patients with metastatic BRAF V600 mutant NSCLC will ultimately need this therapy either before chemo(immunotherapy) or after it. There are distinct advantages to giving targeted therapies as first-line therapy, as outlined in this report**.** Most therapies that give high response rates also give prolongation of life expectancy and improvement in symptoms.

The appropriateness of accepting response rate as an outcome: While response is a very important indicator of drug benefit, response rate was not the only outcome that should be considered. The CGP also considered PFS and OS from the original publications of this combination as first-line therapy (PFS 14.6 months, OS 24.6 months)[3] or in previously treated patients (PFS 9.7 months, 6-month OS rate 82%),[17] as well as the submitted RWE data from the Flatiron database. Again, the PFS and OS outcomes reported were very similar to those seen for this combination in melanoma (PFS 11.1 months, OS 25.9 months)[14] and for other effective targeted therapies in NSCLC.

More clinical data forthcoming: The CGP has not seen any indication at recent international meetings that any major trials are underway in this patient population. In a search of Clinicaltrials.gov, there is one retrospective evaluation that is underway,[25] as well as one phase 2 non-randomized trial in Asia.[26] There was no indication of when the results of these studies would be available, and these studies will have the same limitations as the data already available.

With respect to waiting for more clinical data, the CGP disagrees with this suggestion. Unlike a completely new class of therapy with no evidence base, the similarity in mechanism of action and outcome for this therapy compared to a range of other effective targeted therapies supports the reliability of the submitted and published data, limited as it may be. Waiting for further data that may or may not come simply means that patients who need this therapy will continue to not have access. As it is, there is a delay in Canada, with thousands of life-years lost between the time new cancer therapies are demonstrated to be effective and the time that provincial governments fund them.[27]

The CGP also provided their response to the CCO clinician group's comments on the appropriateness of a time limited switch in therapy to dabrafenib and trametinib for patients currently on other first-line treatments for NSCLC in the absence of disease progression (refer to Table 3 below).

1.3 Conclusions

The CGP concluded that there is a net overall clinical benefit with the use of dabrafenib and trametinib in previously untreated patients with metastatic NSCLC with BRAF V600 mutations. Based on the phase 2 data from Cohort C of Study BRF113928,[3] the combination demonstrated efficacy in terms of ORR, PFS and OS. These data appear comparable to efficacy data of other targeted therapies in relevant NSCLC populations (e.g., with EGFR, ALK and ROS1 mutations), and roughly similar to the efficacy of the combination in BRAF-mutant metastatic melanoma.[14] Small patient numbers and the lack of direct randomized comparisons limit the ability to compare the combination to chemoimmunotherapy and chemotherapy regimens. Although cross-trial comparisons must be interpreted cautiously, the available data from Cohort C of Study BRF113928 suggest dabrafenib and trametinib provides greater clinical benefit than what would be expected from standard first-line therapies while acknowledging that the clinical benefit associated with standard therapies is based on unselected patients with metastatic NSCLC. Accordingly, the CGP believe dabrafenib and trametinib should be made available as first-line treatment for patients with metastatic NSCLC who have a BRAF V600 driver mutation.

Several questions were raised by the PAG, if dabrafenib and trametinib were to be recommended for reimbursement, specifically with respect to the eligible patient population, implementation factors, and sequencing of available treatments. The CGP's responses to these questions are summarized in Table 3. For the CGP's assessment of generalizability (external validity of the evidence from Study BRF113928 [Cohort C] related to specific factors), refer to Table 2 in Section 1 of this report.

Table 3: CADTH Clinical Guidance Panel Response to PAG Implementation Questions

PAG Implementation Questions	CGP Response
Eligible Patient Population	
In view of the characteristics of the patient population and exclusion criteria in the BRF113928 phase II trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with dabrafenib in combination with trametinib:	
• Patients with tumours harboring V600 mutations other than V600E (e.g., V600K, V600R, V600D)	There are little data on the efficacy of dabrafenib and trametinib in NSCLC patients with BRAF mutations other than V600E. The combination is active in NSCLC cell lines with a wide range of both V600 and non-V600 BRAF mutations, including non-V600 mutations with either active or impaired kinase activity,[28] although it has been questioned whether clinically achievable drug concentrations would be sufficient to

PAG Implementation Questions	CGP Response
	inhibit non-V600 mutations. In melanoma, the combination appears to be active and superior to single agent BRAF inhibitor in patients with BRAF V600K mutations (although the number of patients with the V600K variant is relatively small),[29,30] and BRAF inhibitor monotherapy has demonstrated responses in melanoma patients with BRAF V600R mutations.[31] Overall, the CGP believe it is likely that the combination would be active in NSCLC patients with a range of BRAF V600 mutations (as in the case for melanoma), and therefore all patients with tumours harboring V600 mutations should be eligible for treatment with dabrafenib and trametinib.
• Patients with active unstable brain metastases	There are limited data on the use of dabrafenib and trametinib in patients with BRAF-mutant NSCLC and brain metastases since patients with brain metastases are often excluded from clinical trials. Because of blood-brain barrier disruption in brain tumours, systemic therapies have been found to reach high concentrations in brain tumours despite only low concentrations in the normal central nervous system, and response rates to systemic therapies of previously untreated brain metastases from lung cancer are only slightly lower than those for extracranial tumour deposits.[32] Several targeted agents in NSCLC (e.g., crizotinib) have demonstrated efficacy among patients with brain metastases;[33] and other clinical trial data show that the survival of NSCLC patients with brain metastases is no worse than the survival of NSCLC stage M1c patients with metastases to other extrathoracic sites such as liver, bone, and adrenal glands.[34-36] Therefore, the CGP believes there is no reason to expect that the combination of dabrafenib and trametinib would be ineffective in BRAF-mutated NSCLC. As Study BRF113928 permitted the inclusion of patients with treated or asymptomatic brain metastases, the CGP support the use of dabrafenib and trametinib in this group of patients.
If dabrafenib in combination with trametinib were recommended for reimbursement, PAG noted that BRAF V600 patients currently on first-line chemotherapy or immunotherapy and who have not progressed may need to be addressed on a time-limited basis and seeks advice on switching these patients to dabrafenib and trametinib.	The CGP believes that patients currently on first-line chemotherapy or immunotherapy who have not progressed should be permitted to switch to dabrafenib and trametinib. The CGP would also consider delaying the switch until there is evidence of tumour progression on the prior therapy based on data from Cohort B of the BRF113928 trial. Response rate and PFS were almost as good for second-line therapy with dabrafenib and trametinib as for first-line therapy (OS data were immature).[3] • The CGP agrees with the CCO registered clinician group that switching patients who are on an effective treatment (i.e., not progressing) is not entirely appropriate, as they may lose access to this treatment again in the future and lose benefit. However, a switch to dabrafenib and trametinib should be permitted in patients without progressive disease when side effects from toxicities impair quality of life since the combination therapy is usually well tolerated. As noted above, the CGP would also consider a switch when there is evidence of tumour

PAG Implementation Questions	CGP Response
	progression on prior therapy based on data from Cohort B of the BRF113928 trial.
Implementation Factors	
For both dabrafenib and trametinib, treatment should be continued until disease progression or unacceptable toxicity. PAG seeks a clear definition of disease progression for development of discontinuation criteria.	In general, RECIST criteria can be used as a general guideline for therapy continuation. However, the RECIST criteria were designed to guide efficacy assessments in the highly controlled environment of clinical trials and thus have limitations for decision making in routine clinical practice. For example, it is well recognized that a patient on a targeted therapy may have “oligoprogression”, with worsening of just one or two tumour deposits with ongoing control of other tumour sites and with benefit from radiation or surgery for the local progression while continuing the targeted therapy.[37] Further, it is very frequent to see development of new lesions due to inflammatory changes on scan that are interpreted as being new tumour deposits but that disappear on short term follow-up. Therefore, the decision to discontinue treatment should be made by the oncologist and patient that takes into consideration multiple factors that is guided by but not limited to RECIST criteria.
Sequencing and Priority of Treatments	
PAG is seeking to confirm the place in therapy of dabrafenib and trametinib and sequencing with other therapies for NSCLC including the scenarios below:	
• Discontinuation of either drug in case of toxicity and continuation of the other for the remainder of the therapy.	Both drugs individually can potentially have therapeutic benefit;[38] as such, the CGP believe it is reasonable to continue one drug if the other has to be discontinued. This should be a clinical decision by the oncologist in discussion with the patient.
• Is it common for patients to receive targeted therapy (EGFR/ALK) adjuvantly and also have BRAF mutation and be treated with dabrafenib and trametinib in the metastatic setting?	Currently, targeted therapies are used almost exclusively in patients with the relevant target. Adjuvant osimertinib is likely to be used increasingly in patients with resected EGFR mutant NSCLC.[38] It is possible but unlikely that a BRAF mutation would be found at recurrence after or during adjuvant osimertinib; and it is highly unlikely that an EGFR or ALK therapy would be used in the adjuvant setting at all if the relevant mutation was not present. It is possible that a very small proportion of patients would develop a new primary lung cancer that had a BRAF mutation after receiving adjuvant osimertinib for a resected EGFR-mutant NSCLC. Accordingly, very few patients would be candidates to go from one to another of these therapies, and extremely few (if any) would be candidates for both.
• Use of targeted BRAF therapy to induce a response, then switch to immunotherapy as "maintenance". If this were to occur, there may be a desire to use BRAF targeted therapy at the time of disease progression. Therefore, could BRAF targeted	There are currently no situations in lung cancer where a targeted therapy is used as induction followed by a switch to immunotherapy maintenance. This approach might possibly be tested in a clinical trial in the future, but it would not be in keeping with usual practices, where targeted therapies are typically continued until tumour progression. If a targeted therapy was stopped in the absence of tumour progression

PAG Implementation Questions	CGP Response
therapy be re-started at the time of disease progression?	and a different form of therapy was initiated as maintenance, then it would generally likely be appropriate to restart the targeted therapy at eventual progression. There are extensive data across several oncology therapy types and several malignancies indicating that patients will often benefit from rechallenge with a drug that was previously effective, particularly if the drug had initially been discontinued prior to tumour progression.[39]
• Alternative therapy options for patients with a BRAF V600 mutation who are unable to tolerate dabrafenib and trametinib including immunotherapies. Is there evidence to inform whether immunotherapies are effective in BRAF V600 mutants?	To date, data are limited but suggest that immune checkpoint inhibitors may be effective in some NSCLC patients with BRAF mutations. In 43 NSCLC patients with BRAF mutations, the response rate with immune checkpoint inhibitors was 24%, which is similar to the response rate in NSCLC patients with KRAS mutations (response rate 26%) and higher than the response rate with EGFR mutations (12%) or ALK fusion genes (0%).[40] Since neither targeted therapies nor immunotherapy nor chemotherapy cure metastatic NSCLC, it is likely that most patients who do not have contraindications to the therapies would eventually be candidates for all of them sequentially. The rapidly improving life expectancy of patients with metastatic NSCLC is the result of both improving access to effective new therapies and sequencing of these effective therapies.
• Availability of single-agent immunotherapy in subsequent lines. PAG seeks confirmation that patients should first complete chemotherapy prior to being eligible for immune checkpoint inhibitors.	There are insufficient data to inform sequencing of treatments. However, the CGP's suggested approach would be for patients to receive chemoimmunotherapy (or chemotherapy alone if they had a contraindication to immunotherapy) after progression on dabrafenib and trametinib, although it would be reasonable for patients with tumours with high PD(L)1 expression to be treated with pembrolizumab alone.
Companion Diagnostic Testing	
BRAF testing is not routinely performed for patients with NSCLC and would need to be implemented. PAG is seeking clarity on whether BRAF testing would be required in all patients and the appropriate timing of BRAF testing (e.g., upfront or when progressed with metastatic disease). With the multiple testing of targets required for lung cancer, PAG is seeking clarity on whether this would be performed on one tissue sample. Due to the high prevalence of NSCLC, the impact on lab budgets may be significant.	Molecular testing is currently considered to be the standard of care for management of non-squamous NSCLC patients with incurable disease. In some centres, this is only done if a patient is confirmed to be incurable, while in others there is "reflex" testing on all patients at diagnosis since a high proportion eventually develop metastatic disease and a reflex testing approach at diagnosis may be most cost effective in the long run. Because of the number of targets that are now relevant, an increasing number of centres are in the process of rapidly moving to NGS for mutation analysis. For example, BRAF testing is currently required for patients with metastatic melanoma and colorectal cancer, and it is generally most efficient to use the same NGS testing platform for all solid tumour types. NGS generally reports on BRAF mutations at no increased cost over and above testing for the other relevant NGS mutations. Hence, there should generally be no net budgetary impact. For most patients, all molecular testing can be done on a single biopsy sample.

ALK = anaplastic lymphoma kinase; BRAF = v-Raf murine sarcoma viral oncogene homolog B; CGP = Clinical Guidance Panel; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; NGS = next generation sequencing; OS = overall survival; PAG = Provincial Advisory Group; PD(L)1= Programmed cell death protein (ligand) 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

2 Background Clinical Information

2.1 Description of the Condition

Lung cancer is the second most common cancer in women and the third most common cancer in men in Canada.[41,42] In the overall population (men and women combined), it is the most common cancer, with approximately 29,800 new cases in Canada in 2020.[41,42] With approximately 21,200 lung cancer deaths in Canada, it is by far the most common cause of cancer death, accounting for approximately 25% of all Canadian cancer deaths. This is more deaths than those caused by cancers of the breast, colon and prostate combined.[42] Lung cancer is the second overall leading cause of death in Canada after heart disease, accounting for approximately 7.4% of all deaths in Canada, which places it ahead of other common causes of death such as stroke, chronic obstructive lung disease, diabetes, accidents, infections, etc.

NSCLC accounts for about 88% of all lung cancer cases.[41] 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.[41] 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 and the high proportion of early stage patients who suffer incurable recurrences despite surgery or high dose radiotherapy, it is not surprising that the expected relative five-year survival is only 18%.[41]

Overall, of the approximately 21,200 Canadians who died of lung cancer in 2020, an estimated 18,656 had NSCLC. Since approximately 3.5% of NSCLCs have BRAF mutations, with a BRAF V600E mutation in 2%,[7] it can be estimated that the deaths of approximately 373 Canadians were caused by a NSCLC with a BRAF V600E mutation in 2020.

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.[43] Upon disease progression, patients well enough for consideration of further therapy could be treated with docetaxel,[44] pemetrexed,[45] and/ or erlotinib.[46] 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 the patients treated with first-line therapy subsequently go on to receive second-line treatment.[47]

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 OS when treated with pemetrexed.[45,48,49] 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.[50] Oncogenic drivers were found in 64% of cases. Commonly observed gene mutations included KRAS (25%), EGFR (17%) and ALK (8%). Mutations occurring in 1% to 2% of patients included ERBB2, BRAF, MET, NRAS, MEK and ROS1.[50] In other similar series, BRAF V600E mutations were found in 2% of NSCLCs.[7] 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 PFS and have been incorporated into treatment algorithms. Molecular profiling of lung adenocarcinomas for EGFR mutations and ALK and ROS1 translocations is now routinely performed at the time of initial lung cancer diagnosis. Molecularly targeted therapies such as gefitinib,[10,51] afatanib,[52,53] and crizotinib[20] rapidly became the preferred initial therapy (rather than chemotherapy) in patients with these molecular abnormalities, and newer, more

effective therapies like osimertinib[54] and alectinib[55] have now replaced these older targeted therapies in patients with the relevant mutations.

While mutations were initially assessed one at a time, there has been a rapid move to using methods such as next generation sequencing (NGS) to assess multiple mutations (e.g., EGFR, KRAS, BRAF) simultaneously.[56] This is the preferred method of assessment since each tumour specimen then only needs to be handled once, physicians do not have to wait for results on one biomarker before another biomarker is assessed (as is the case with older methods such as PCR), and the same laboratory platform can be used to assess multiple different types of malignancies that have different molecular drivers. Currently, an increasingly high proportion of Canadian centres have routine NGS access to inform on the BRAF status of their NSCLC patient but are unable to easily access a relevant targeted therapy if a BRAF V600E mutation is found, despite there being a strong consensus among clinicians that this would be the optimal therapeutic approach.

Another 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),[57-59] or its ligand (PD-L1, atezolizumab)[60,61] have all demonstrated higher response rates and improved OS in comparison to second-line chemotherapy with docetaxel. In the first-line setting, pembrolizumab is superior to chemotherapy in patients whose NSCLCs express PD-L1 in more than 50% of their cells,[62] and in metastatic NSCLC, pembrolizumab combined with chemotherapy is superior to chemotherapy alone (platinum-pemetrexed in non-squamous NSCLC and carboplatin-paclitaxel in squamous cell lung cancer), irrespective of degree of PD-L1 expression.[8,9,63,64] In NSCLC patients without a targetable mutation, chemotherapy combined with pembrolizumab is now the front-line treatment of choice in patients who have no immunotherapy contraindication (such as a major autoimmune disease), irrespective of tumour cell PD-L1 expression, and pembrolizumab alone is an option in patients in whom ≥50% of the tumour cells express PD-L1.

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 tumours harboring an activating mutation of the EGFR gene have rapidly moved from chemotherapy to first- and second-generation EGFR inhibitors, and now to the third-generation EGFR inhibitor osimertinib.[54] Multiple studies demonstrate significant improvements in ORR and PFS, in comparison to current best chemotherapy options for patients with EGFR-mutant NSCLC. Response rates of 60% to 80%, a median PFS of 10 to 16 months and median OS of about two years were achieved with first- and second-generation EGFR inhibitors in contrast to a 30% to 40% ORR, a 4-7-month median PFS and a median OS of approximately 1 year from chemotherapy. Front-line osimertinib was significantly superior to earlier EGFR inhibitors, with an ORR of 80%, PFS of 19 months, and median OS of more than three years.[18,54] Osimertinib is also more effective than chemotherapy against NSCLCs that progress on other EGFR inhibitors as a result of development of a T790M mutation.[65]

Subsequent therapy, in patients well enough to receive further therapy at the time of progression on osimertinib would include a platinum agent in combination with pemetrexed, with or without maintenance pemetrexed.[66] Forth-line therapy and beyond may include docetaxel, or a PD-1 inhibitor such as nivolumab or pembrolizumab, although PD-1 inhibitors are less effective in patients with EGFR mutations compared to patients without these mutations.[67]

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 was demonstrated to be superior to chemotherapy in patients with an ALK translocation,[20] and newer ALK inhibitors such as alectinib result in a significantly better outcome than crizotinib.[55] Hence, as first-line treatment for patients with NSCLC with an ALK translocation, the current usual approach is to start with alectinib, and to switch to another ALK inhibitor such as brigatinib or lorlatinib (if available through private insurance or on a compassionate release basis), and to then consider subsequent salvage therapy with a platinum-agent plus pemetrexed. A PD-1 inhibitor may be considered, but as with EGFR mutations (and unlike tumours with KRAS, BRAF or TP53 mutations), tumours with ALK translocations are relatively resistant to immune checkpoint inhibitors.[68]

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[69] and similar data exist for ceritinib.[70] Crizotinib is now funded in Ontario as the preferred first-line therapy for patients with ROS1 NSCLC.

Squamous NSCLC

Currently there are no approved targeted agents in Canada for patients with squamous NSCLC. Pembrolizumab combined with carboplatin plus paclitaxel has recently been demonstrated to be superior to chemotherapy alone, irrespective of level of PDL-1 expression,[63,64] and this is currently considered the first-line therapy of choice in patients with metastatic squamous cell carcinoma of lung who do not have a contraindication to immunotherapy. In patients with a contraindication to immunotherapy, first-line therapy is typically a platinum agent combined with gemcitabine, paclitaxel, or vinorelbine.[71] There are no approved maintenance therapies in squamous NSCLC apart from continuing pembrolizumab after completion of four cycles of combined chemotherapy-immunotherapy. For patients who did not receive immunotherapy as part of first-line therapy and have no contraindications to immunotherapy, second-line therapy would be a PD-1 inhibitor such as nivolumab or pembrolizumab.[58,59] Docetaxel may be offered as third-line therapy.[44]

Non-squamous NSCLC without a targetable mutation

Several options exist for first-line treatment of patients with non-squamous NSCLCs that do not have targetable molecular abnormalities, although, as discussed previously, the treatment of choice is pembrolizumab combined with a platinum and pemetrexed in patients who do not have a contraindication to immunotherapy,[8,9] with the option of pembrolizumab alone if the tumor has high PD-L1 expression.[62] While data support the use of carboplatin, paclitaxel plus bevacizumab,[72] this is not funded in most provinces, and hence is not commonly used.

In non-squamous NSCLC patients without a targetable mutation but with a contraindication to immunotherapy, the most common treatment approach would be a platinum-agent in combination with pemetrexed followed by maintenance pemetrexed.[66] Other platinum combinations might be considered, although the use of gemcitabine is not recommended.[71] Maintenance pemetrexed remains an option in patients treated with first-line non pemetrexed based therapy.[48]

Nivolumab or pembrolizumab would be recommended as second-line therapy for patients who did not receive pembrolizumab as part of front-line therapy. For patients not candidates for immunotherapy, docetaxel would still be a treatment option.

For patients treated with pembrolizumab alone as front-line therapy, second-line therapy would generally be a platinum plus pemetrexed followed by pemetrexed maintenance, with a subsequent option being docetaxel.

New directions

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 previously 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 in some cases, 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 tumours 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. Published data[7] indicate that BRAF V600E mutations occur in approximately 2% of NSCLC adenocarcinomas and are considered oncogenic drivers. They generally occur independently of other common oncogenic drivers, including EGFR mutations and ALK translocations. Dabrafenib

and trametinib were evaluated in a single arm, multicentre phase II trial of treatment-naïve NSCLC patients with BRAF V600E mutations.[3] In Study BRF113928 (Cohort C), the response rate with the combination of dabrafenib and trametinib was 64%, median PFS was 10.9 months, and median OS was 24.6 months.

Dabrafenib plus trametinib is also highly active in BRAF mutant patients who have previously received chemotherapy.[17] Hence, it would be reasonable to use it as either first-line therapy or as second-line therapy in NSCLC patients with BRAF V600E mutations. However, there is a general consensus that effective targeted therapies should usually be used in the first-line setting because of the convenience to patients, the reduced burden on cancer centre chemotherapy treatment units and pharmacists, the favourable toxicity profile (e.g., the reduced risk of requiring hospital admission for treatment of complications such as febrile neutropenia) and the rapidity of symptomatic improvement, with symptoms often improving within days of therapy initiation. In the United States, NCCN guidelines suggest that NSCLC patients with BRAF V600E mutations be treated with dabrafenib-trametinib first, with other systemic therapy options offered at the time of progression, but with it being a reasonable option to instead use other systemic therapy first and to switch to dabrafenib plus trametinib at progression.[73] Either way, it is very important that BRAF V600E mutant patients have access to this therapy at some point during the course of their illness.

Patients with BRAF V600 positive NSCLC		
Line of Therapy	Current	Proposed
1st-Line	Platinum-agent plus pemetrexed +/- pembrolizumab (with pemetrexed +/- pembrolizumab maintenance)*	Dabrafenib + trametinib
2nd-Line	Nivolumab or pembrolizumab if pembrolizumab not used 1st line	Platinum-agent plus pemetrexed + pembrolizumab (with pemetrexed +/- pembrolizumab maintenance)*
3rd -Line	Docetaxel	Docetaxel

* some patients with high PDL-1 expression would be treated with pembrolizumab alone, then chemotherapy on progression instead of receiving combined chemoimmunotherapy, and patients with a major autoimmune disease that constitutes a contraindication to immunotherapy would receive chemotherapy alone.

Approximately 373 Canadians annually would be potential candidates for this therapy. In a recent analysis, less than 25% of Ontario patients with advanced NSCLC had received systemic therapy.[47] Many deteriorate or die too rapidly while undergoing diagnostic and staging tests for them to even make it to systemic therapy. In some, rapid deterioration results in their performance status being too poor for an oncologist to offer them systemic therapy. Some elect not to proceed to systemic therapy due to its potential toxicity. If only 25% of BRAF V600E patients made it to therapy, then this would reduce the potential annual Canadian dabrafenib-trametinib population to only 93 patients. However, there has been an increasing effort to markedly shorten the time from symptom onset to therapy initiation,[74] and this will probably increase the proportion of NSCLC patients who receive therapy. Similarly, the move to "reflex" molecular testing and NGS will speed access to information on mutation status, and this would be expected to reduce the number of patients deteriorating and dying before they can make it to treatment. Finally, patients are typically more likely to agree to a targeted therapy (like dabrafenib-trametinib) than to chemotherapy, and this will increase the proportion of patients who are treated. Despite all this, not all patients will be treated. It would be reasonable to estimate that with streamlined diagnostic approaches, up to 60% of BRAF V600E mutant patients (approximately 224 patients annually) would receive this therapy if it were funded.

3 Summary of Patient Advocacy Group Input

One patient group input was provided by Lung Cancer Canada (LCC) for the review of dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600E mutation. LCC gathered patient and caregiver input through surveys, patient and caregiver interviews and an environmental scan of social media. The data was accessed from September to October 2020. Table 4 lists the demographic characteristics of the survey respondents.

Table 4: Demographic Characteristics of Survey Respondents

Gender	Age	Patient/Caregiver	Year of Diagnosis	Location	Source of Input
Female	70	Patient	2018	Canada	Interview
Female	67	Patient	2017	N/A	Environmental Scan
Female	48	Caregiver	2016	N/A	Environmental Scan
Male	74	Patient	2020	Canada	Interview
Female	N/A	Caregiver	2020	Canada	Interview
Female	79	Patient	2020	Canada	Interview

LCC also consulted previous LCC submissions for NSCLC patients treated with chemotherapy, immunotherapy and a combination of both treatments.

From the patient perspective, symptoms of advanced NSCLC that most affected their quality of life were cough, shortness of breath and fatigue. The disease can cause a significant physical, emotional and financial burden on patients and their caregivers. LCC identified a high unmet need for Canadian patients with advanced NSCLC with BRAF mutations, as currently no targeted therapies exist for this small groups of patients. Current treatments include chemotherapy, immunotherapy and a combination of both immunotherapy and chemotherapy. Patients noted that chemotherapy was associated with side effects such as nausea, vomiting and fatigue, and many patients eventually progress on the treatment. Patients reported a much favourable preference for immunotherapy and the combination of chemotherapy and immunotherapy; however, LCC noted that in the long-term, immunotherapy has been documented to have poor efficacy for patients with targeted mutations. Additionally, immunotherapy can be burdensome for patients as it can require multiple hospital visits, thus necessitating the need for an oral option like dabrafenib in combination with trametinib. Four patients reported having experience with dabrafenib and trametinib, all of whom reported an overall favourable experience with the drug. Patients reported that the drug combination helped reduce the size of the tumour and control their symptoms. Most patients reported very minimal side-effects that were manageable. Patients noted that the drug had allowed them to return to their normal activities and regain their independence. However, a concern reported by 1 patient was the high cost of the drug combination which would have made the drug inaccessible without insurance and a special access program. Patients expressed strong hopes for this combination to be accessible to all Canadian patients with advanced NSCLC with the BRAF V600E mutation. Overall, patients value prolonged survival, better symptom control, and manageable side effects with an improved quality of life. Given the high unmet need and favourable patient experiences, LCC highly supports the reimbursement of dabrafenib and trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600E mutation.

Please see below for a summary of specific input received from the patient groups. Of note, 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 Patients Experiences

LCC commented on the current landscape of treatments for advanced lung cancer. Latest research has enabled more personalized approaches to lung cancer that have led to the development of targeted treatments for biomarker mutations. These new treatments have resulted in improved outcomes for patients, particularly those who have mutations such as EGFR, ALK and ROS1. However,

no targeted therapies for BRAF mutations are funded in Canada which puts these patients at a significant disadvantage compared to other patients with advanced NSCLC who are on targeted therapies. LCC noted that a disparity also exists at the global level as many countries have implemented dabrafenib and trametinib as the standard of care for patients with BRAF mutations. LCC noted that this is particularly troublesome for Canada as lung cancer is the leading cause of cancer deaths in Canada. Approximately 21,000 Canadians die every from lung cancer. In 2020, it was estimated that 29,800 Canadians would be diagnosed with lung cancer, representing 13% of all new cancer cases. The estimated 5-year survival rate is 19% and in advanced cases, the rate is much lower.

LCC consistently emphasized the need for new treatment options that improve survival and allow for an improved quality of life for patients with the BRAF V600E mutation. One female patient developed a cough, shortness of breath and had to be placed on oxygen. The patient reported that upon diagnosis, she was not eligible for traditional forms of therapy and was very worried about her survival and the impact on her loved ones.

3.1.2 Patients' Experiences with Current Therapy

LCC reiterated that currently there is no specific therapy available to NSCLC patients with the BRAF V600E mutation in Canada, which puts Canadian patients at a significant disadvantage. The current standard of treatment is chemotherapy, immunotherapy and a combination of chemotherapy and immunotherapy. LCC shared some patient experiences with these treatments described in previous LCC patient input submissions.

1. Chemotherapy: In previous LCC patient input submissions, patients have noted that chemotherapy helps to shrink tumours and allows them to somewhat continue their daily activities. One caregiver noted that his wife was able to go bowling, golfing and riding with him. However, many patients eventually progress on chemotherapy. One caregiver stated that their spouse was is remission for 11 months but progressed and had to be treated with more aggressive chemotherapy. Another caregiver stated that her spouse responded well to chemotherapy initially, with a tumour reduction from 8 cm to 4 cm, but eventually progressed and needed more chemotherapy. Patients often complain of various side effects of chemotherapy, such as nausea, vomiting and fatigue with various degrees of severity. One patient in a previous submission reported that although her hair fell out and she felt sick, chemotherapy was overall manageable. Another caregiver reported that chemotherapy was slowly bringing his mother back to life and there were no side-effects. Another patient described chemotherapy as "awful" and reported being bedridden for 2 months. Patients on higher doses of chemotherapy often describe the process as dreadful when going to the hospital for treatments and reported feeling sick during the infusion. Chemotherapy has also been reported to lower patients' immunity, which affects their ability to go out, return to work and socialize.

2. Immunotherapy: Compared to chemotherapy, patients have reported a more favourable experience with immunotherapy. Patients interviewed in previous LCC patient input submissions noted that immunotherapy made them feel better within days of their first treatment. One patient reported that his cough went away after immunotherapy and he was able to live a relatively normal life. The majority of patients from previous submissions described the side effects from immunotherapy as mild and manageable. There were a few noted cases of side-effects that had to be managed by over the counter or prescription drugs; however, most of these patients reported that managing these side effects was easy, and they were able to continue with their normal daily living. LC noted that immunotherapy is typically only recommended for patients whose tumours have a high (≥50%) PD-L1 expression. It was also noted that treatments with immunotherapy can be burdensome to patients and caregivers, as it requires multiple trips to the hospital for intravenous infusions.

3. Chemotherapy and Immunotherapy Combination Therapy: The experiences described below were received from a previous LCC patient input submission for pembrolizumab and chemotherapy. Patients on this therapy reported improved symptoms and a reduction of tumour size. One patient reported the combination to be life changing as surgery and radiation were not viable options for her due to the location of the tumour. The patient was very pleased as the cancer remained stable. Other patients reported significant improvements in their overall health due to reduced symptoms such as resolved pleural effusion, tumour shrinkage and stable metastasizes. Patients reported being able to go back to their daily activities such as work, gardening and playing with grandchildren. One patient received immunotherapy in the first-line setting, but as the cancer progressed, the patient was switched to chemotherapy in combination with immunotherapy. The patient noted that within a week, his breathing and coughing had improved, and his months long suffering of pleural effusion had resolved. His tumour also reduced in size by 30 to 40% and metastasizes were no longer visible on scans.

3.1.3 Impact on Caregivers

The significant burden of the disease on caregivers often results in stress, anxiety and depression. Caregiving is often comprised of a wide range of intensive duties such as providing medical care, as well as financial, informational and emotional support and assisting with daily activities. The physical and emotional toll of caregiving can affect their ability to properly care for their loved ones and even fulfill their duties outside of caregiving such as work. LCC noted that for many patients on chemotherapy, many caregivers reported loss of productivity due to absence from work. Contrarily, for patients on targeted therapies, the side effects were more manageable and thus the demands on caregivers were relatively less as many patients were able to go to appointments by themselves. One caregiver had been caring for her spouse for 11 years through 4 different types of cancer. The caregiver accompanied her spouse on hospital visits and performed multiple caregiving duties at home. The caregiver noted that an oral medication would significantly ease the burden of caregiving as it would eliminate the need for multiple hospital visits. LCC asserted that an effective treatment for advanced NCSLC patients with driver mutations would also be of great value to caregivers as it would lessen their burden and enable them to fulfill their caregiving duties with ease as well as continue with their own personal obligations such as work.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Reflecting on patient and caregiver experiences, LCC observed that patients expect improved symptom control from new therapies, along with manageable side effects, as current therapies are often associated with debilitating side effects. An overall improved quality of life is highly desirable by patients as many patients continuously emphasized the ability to regain their independence and continue enjoying their social lives. Patients also value delayed progression of the disease as well as prolonged survival.

3.2.2 Patient Experiences to Date

A total of 4 patients reported having experience with dabrafenib and trametinib, all of whom reported an overall favourable experience with the drug. The experiences of each patient are described below.

One patient had been experiencing cough, fatigue and shortness of breath and had to be placed on oxygen She was diagnosed with stage 4 BRAF V600E positive NSCLC in December 2018. She was too weak to be treated with chemotherapy and radiation therapy and was placed on dabrafenib and trametinib. The patient reported that she started feeling better once she started the treatment; her breathing had improved, and she no longer needed oxygen therapy as of March 2020. Side effects reported by this patient were minor stomach upset and nausea. The treatment cleared all the tumours in her lung. The patient was very grateful for this treatment combination and commented, “I don’t believe I would be here if it wasn’t for the treatment. It is a miracle.” She is able to look after herself now, has improved energy levels and continues with her daily chores, and has even been well enough to go camping.

Another patient was diagnosed in January 2020 when his tests revealed that he had advanced lung cancer which has spread to the brain, bones, liver and lymph nodes. The patient started treatment in May and was placed on a hydromorphone pump for the pain. The patient’s daughter said the family was unsure which treatments were available and after he came home from the hospital, they thought he was coming home to pass away. The patient and his family were very pleased when they heard of a treatment that could prolong survival. The only side effects of the treatment experienced by this patient were slight hair loss, nausea and fatigue. When initially discharged from the hospital, the patient had difficulty getting out of bed and had to use a walker to get around. The patient is now more active and able to move around without any assistance. His daughter stated that his mental health has also improved a lot. The patient commented, “It is a miracle drug. Having the right mutation and right treatment saved my life.” The patient believes that every patient with the BRAF V600E mutation should have regular access to this treatment. The patient’s daughter had to stop working to care for her father but will be back to work now that her father is doing much better.

One patient reported some significant side effects when she started treatment with dabrafenib and trametinib including high fever, fatigue, malaise, low platelets, hair thinning, dry skin, joint pain and headaches. The patient’s physicians helped lessen the side effects through a dose reduction. Even with a dose reduction, the drug still proved effective at managing her disease as her follow-up PET scans showed no signs of new disease. The patient reported that her overall health has remained stable and commented that she will continue with the treatment and that she is very grateful to be alive.

Another patient was a previous smoker who smoked for 50 years and quit approximately 9 years ago. She was diagnosed with advanced NSCLC with the BRAF V600E mutation in March 2020 and was placed on dabrafenib and trametinib. The patient reported that her tumours have shrunk significantly since starting treatment and she no longer has breathing difficulties. She experienced slight thinning of her hair as well as slight nausea and dizziness which did not last more than a week. The patient reported that the treatment has enabled her to regain her independence such as driving and completing her regular chores around her house. She calls the drug "magic pills" and commented, "it's unbelievable how well I am." However, the patient was disappointed with the high cost of the drug combination. Even with an insurance coverage of 80%, the remaining out of pocket costs amounted to $800 every 28 days, which the patient found difficult to afford. Luckily, the patient was able to cover the remaining amount of $800 through a special access program. The patient commented, "I am on an old age income and would not have been able to afford the medication without the program."

3.3 Companion Diagnostic Testing

LCC commented that testing for the BRAF mutation is routinely conducted in provinces and should be a standard of care for NSCLC patients across the country.

3.4 Additional Information

Throughout the patient input submission, LCC consistently emphasized a high unmet need in Canada for patients with advanced NSCLC with the BRAF V600E mutation. LCC noted that the previous submission for this drug combination was not recommended by pERC for patients with this mutation due to uncertainty regarding a clinical benefit that improved OS and provided these patients with a good quality of life. pERC had felt that a randomized phase III trial is possible for this group of patients and that immunotherapy is an effective option. LCC disagrees and explained that a phase III trial is difficult to implement due to the small population of patients with the BRAF V600E mutation. Immunotherapy has demonstrated poor efficacy for patients with driver mutations and therefore LCC asserted that it wouldn't be a good option for this group of patients either. Targeted treatments are needed to treat patients with matching biomarker mutations, as research has shown that targeted treatments are associated with higher response rates and an increased survival. LCC consistently highlighted that dabrafenib and trametinib is also already a standard of care in many countries and therefore LCC highly encourages pERC to reconsider the reimbursement of the drug for this funding request. This treatment was approved by the Federal Drug Administration in 2017 and has proved to be efficacious by keeping patients out of the hospital and improving their overall quality of life. LCC believes that Canadian patients with the BRAF V600E mutation deserve to have the same options available to their global counterparts. LCC also emphasized that the oral nature of the drug would significantly lessen the burden on not just patients and caregivers, but also the health system as it would eliminate the need for excessive hospital resources to deliver intravenous therapies. An oral treatment is especially needed during the current COVID-19 pandemic, as it would reduce the risk of exposure of this vulnerable population by eliminating the need for hospital visits. LCC hopes that the costs of the drug can be negotiated to ensure that all patients can have access to the drug.

4 Summary of Provincial Advisory Group (PAG) Input

The PAG 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 CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

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

Clinical factors:

- Clinical eligibility criteria
- Definition of disease progression

Economic factors:

- BRAF testing
- Large NSCLC population

Please see below for more details.

4.1 Currently Funded Treatments

There is no specific first-line therapy for BRAF V600-mutated NSCLC. The standard first-line treatment for patients with NSCLC is histology-specific platinum doublet chemotherapy. Pembrolizumab monotherapy is available for patients whose tumours have high (≥50%) PD-L1 expression. For patients with any level of PD-L1 expression, pembrolizumab in combination with chemotherapy is also available. PAG noted that nivolumab-ipilimumab in combination with chemotherapy for first-line NSCLC is currently under review at pCODR. Targeted therapies are available for NSCLC with known activating mutations or genetic aberrations in ALK and EGFR genes.

PAG noted that cohort C of the phase II BRF113928 trial did not include a comparator arm against treatment with dabrafenib and trametinib. PAG seeks comparison of dabrafenib in combination with trametinib versus standard chemotherapy (e.g., platinum chemotherapy) and immunotherapy regimens (e.g., pembrolizumab).

4.2 Eligible Patient Population

The reimbursement request of dabrafenib in combination with trametinib is for treatment of patients with metastatic NSCLC with a BRAF V600 mutation and who have not received any prior anti-cancer therapy for metastatic disease. In view of the characteristics of the patient population and exclusion criteria in the BRF113928 phase II trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with dabrafenib in combination with trametinib:

- Patients with tumours harboring V600 mutations other than V600E (e.g., V600K, V600R, V600D)
- Patients with active unstable brain metastases

If dabrafenib in combination with trametinib were recommended for reimbursement, PAG noted that BRAF V600 patients currently on first-line chemotherapy or immunotherapy and who have not progressed would need to be addressed on a time-limited basis.

PAG noted that dabrafenib in combination with trametinib previously received a negative reimbursement by pERC for the treatment of patients with advanced NSCLC with BRAF V600 mutation who have been previously treated with chemotherapy. Therefore, there is potential indication creep of dabrafenib in combination with trametinib for use in second or subsequent lines. There is also potential indication creep to use as adjuvant therapy and use in BRAF wild-type tumours.

4.3 Implementation Factors

The recommended dose of dabrafenib is 150 mg (two 75 mg capsules) given twice per day plus oral trametinib 2 mg once per day. Dabrafenib is available as 50 mg and 75 mg capsules, while trametinib is offered as 0.5 mg and 2 mg tablets. For both dabrafenib and trametinib, treatment should be continued until disease progression or unacceptable toxicity. PAG seeks a clear definition of disease progression for development of discontinuation criteria.

PAG identified the oral route of administration of dabrafenib and trametinib, in which patients could easily use in the community, as an enabler. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. Furthermore, multiple strengths of dabrafenib and trametinib facilitate dose adjustment. PAG highlighted that resources would be needed to prepare and dispense drugs at the pharmacy, and that there would be increased clinic visits to monitor patients for adverse events as well as blood work required throughout the duration of therapy. In addition, PAG has concerns related to drug-drug interactions with the combination treatment of dabrafenib and trametinib and associated side effects.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the place in therapy of dabrafenib and trametinib and sequencing with other therapies for NSCLC including the scenarios below:

- Discontinuation of either drugs in case of toxicity and continuation of the other for the remainder of the therapy
- Is it common for patients to receive targeted therapy (EGFR/ALK) adjuvantly and also have BRAF mutation and be treated with dabrafenib and trametinib in the metastatic setting?
- Use of targeted BRAF therapy to induce a response, then switch to immunotherapy as "maintenance". If this were to occur, there may be a desire to use BRAF targeted therapy at the time of disease progression. Therefore, could BRAF targeted therapy be re-started at the time of disease progression?
- Alternative therapy options for patients with a BRAF V600 mutation who are unable to tolerate dabrafenib and trametinib including immunotherapies. Is there evidence to inform whether immunotherapies are effective in BRAF V600 mutants?

4.5 Companion Diagnostic Testing

BRAF testing is not routinely performed for patients with NSCLC and would need to be implemented. PAG is seeking clarity on whether BRAF testing would be required in all patients and the appropriate timing of BRAF testing (e.g. upfront or when progressed with metastatic disease). With the multiple testing of targets required for lung cancer, PAG is seeking clarity on whether this would be performed on one tissue sample. Due to the high prevalence of NSCLC, the impact on lab budgets may be significant.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided for the review of combination dabrafenib and trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600E mutation who have not received any prior anti-cancer therapy for metastatic disease: 1 joint input submission on behalf of 3 clinicians from the Ontario Health (Cancer Care Ontario) Lung Cancer Advisory Committee (CCO) and one joint input submission on behalf of 15 clinicians from Lung Cancer Canada (LCC). Overall, both groups of clinicians were supportive of the use of dabrafenib and trametinib for metastatic NSCLC patients with the BRAF V600E mutation. Particularly, the clinicians from CCO noted that this drug is a great option for elderly and comorbid patients as it is well tolerated. The clinicians were pleased with the oral nature of the drug combination, especially during the current COVID-19 pandemic as it eliminates the need for patients to travel to the cancer centre or infusion site. Clinicians from CCO recommended the use of dabrafenib and trametinib in the second-line setting for patients with the BRAF V600E mutation after first-line treatment with immunotherapy or the combination of chemotherapy and immunotherapy. Contrarily, the clinicians from LCC recommended the use of this drug combination in the first-line setting for patients with the BRAF V600E mutation. The clinicians from LCC explained that the use of first-line immunotherapy has not been well documented in patients with driver mutations and the use of targeted inhibitors early on in the treatment process provides a greater chance for long term survival and an improved quality of life. The clinicians from LCC stated that immunotherapy with platinum doublets is a good option in the second line setting and docetaxel is an option in the third-line setting. Overall, both groups of clinicians emphasized that dabrafenib and trametinib would address a high unmet need for NSCLC patients with the BRAF V600E mutation as it is a rare mutation for which there are currently no available targeted therapies.

Please see below for details from the clinician inputs.

5.1 Current Treatment(s)

The clinicians from CCO noted that the current treatments for patients with metastatic NSCLC with a BRAF V600 mutation is chemotherapy plus immunotherapy or immunotherapy alone for patients who have PD-L1 if > 50%.

The clinicians from LCC noted that the preferred standard treatment in the firs- line setting for patients with NSCLC is histology-specific platinum doublet chemotherapy in combination with pembrolizumab, which can only be given to patients who have an ECOG performance status of 0 or 1. The KEYNOTE-189 and KEYNOTE-407 trials excluded patients with EGFR or ALK mutations because targeted therapies exist for those tumours. The clinicians explained that targeted inhibitors should be used first to treat patients as they are very efficacious and well tolerated. Other non-targeted options should only be considered if these targeted therapies no longer provide any clinical benefit. The clinicians emphasized that currently there are no targeted therapies available to patients with the BRAF V600E mutation in Canada. Dabrafenib and trametinib is an effective option for these patients as they inhibit the growth of BRAF V600E mutant cells. Dabrafenib inhibits the MAPK pathway in BRAF mutated cells, and trametinib is an oral small molecule kinase inhibitor of two MAPK pathway constituents, mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). The LCC clinician group also highlighted that based on recent publications (Oshima et al, JAMA Oncol, 2018; Lin et al, J Thorac Oncol, 2019; Uchida et al, Thorac Oncol, 2019; Ribas et al, Nat Med, 2019) there is increasing concerns related to toxicity and sequence of TKIs and PD-(L)1 regimens; specifically, there are a number of reports of increased toxicity with concurrent administration and/or PD-(L)1 followed immediately by a TKI. Thus, they indicated use of a TKI first, followed by a PD-(L)1 regimen in patients with an actionable mutation is felt to be safe with the opposite sequence unsafe.

5.2 Eligible Patient Population

Both groups of clinicians stated that this drug combination is ideal for patients with advanced NSCLC with the BRAF V600E mutation and emphasized that there is an unmet need for this patient population. The clinicians from LCC explained that the further classification of lung cancer by driver molecular pathogenesis has led to the development of specific targeted therapies. Historical treatment such as chemotherapy and immunotherapy have not been studied well enough for many of these molecularly defined diseases and therefore the clinicians are not confident of their use. Both groups of clinicians agreed that the exclusion and inclusion criteria of the clinical trial are applicable to clinical practice. The clinicians from LCC further commented that the applicability of the inclusion criteria means that patients with the following characteristics would be eligible for the drug: previously untreated patients with histologically or cytologically confirmed NSCLC, stage IV disease, presence of BRAF V600E mutations, ECOG performance

status ≤ 2, life expectancy > 3 months, adequate haematology and chemistry laboratory results. The clinicians were pleased with the wide inclusion criteria as this would enable elderly, comorbid or sicker patients to receive an efficacious treatment. Since patients with an ECOG performance status of 2 are eligible to receive this combination, the clinicians noted that this indicates that the drug is well tolerated and provides a greater quality of life. The clinicians from LCC also emphasized that the oral nature of the drug is very important during the COVID-19 pandemic since the medication can be taken at home without the need for patients to travel to the cancer centre or infusion site to receive infusion chemotherapy. The clinicians from LCC stated that there are no additional subgroups for whom they would use the treatment for, whereas the clinicians from CCO stated that they would consider using the treatment in the first-line setting for patients who are averse to chemotherapy.

5.3 Relevance to Clinical Practice

The clinicians from CCO noted that in clinical practice, they would use the drug combination in the second-line setting for patients with the BRAF V600E mutation. The clinicians stated that the combination would have better efficacy and similar tolerability compared to docetaxel, which is the standard of care for this group of patients after chemotherapy or immunotherapy. The clinicians believe that dabrafenib and trametinib should be available as a treatment option for at least one line of therapy for patients with BRAF V600E NSCLC. The favourable data in the phase II trial showed an effective response rate and duration of response in the first- or second-line setting which confirms that it is a very active treatment that can tremendously benefit patients. The clinicians acknowledged that although only phase II data are available, a phase III trial in this rare group of patients would be neither feasible nor ethical.

The clinicians from LCC stated that they would use this treatment in the first-line setting for patients with advanced NSCLC with the BRAF V600E mutation. The clinicians explained that the use of first-line immunotherapy in patients with driver mutations such as ALK or EFGR is not advised because these patients were excluded form the phase III trials since immunotherapy is not expected to demonstrate any efficacy in this patient population. The clinicians believe that this should also be applied to the BRAF V600E mutation as it is a driver mutation. The clinicians reiterated that this drug combination can be given to patients with an ECOG status of 2 which makes it a great option for elderly or comorbid patients.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians from CCO stated that this treatment would be used after first-line treatment with immunotherapy or the combination of chemotherapy and immunotherapy.

The clinicians from LCC noted that treatment in the first-line setting for patients with an ECOG PS of less than 2 would be dabrafenib and trametinib, and that treatment would continue until a lack of clinical benefit is observed. Treatment in the second-line setting would be immunotherapy with a platinum doublet if the patient has an adequate ECOG PS of less than 1. Treatment in the third-line setting would be docetaxel. The clinicians commented that immediate inhibition of the BRAF V600E driver mutation would help ensure the best chance of survival and a good quality of life. The clinicians believe that as with other driver mutations such as EGFR, platinum doublets in the second-line therapy can also be very effective for patients with BRAF V600E driver mutation.

The clinicians from LCC further advised that although immunotherapy plus chemotherapy can be a good second-line option for patients with a good ECOG performance status, the role of immunotherapy and chemotherapy has not been thoroughly studied in NSCLC patients with BRAF mutations. As mentioned above, although patients with BRAF V600E mutations in the KEYNOTE-189 trials were not excluded, there were very few patients enrolled in the trial as it is a rare mutation. Furthermore, the clinicians noted that currently CADTH is reviewing nivolumab-ipilimumab in combination with chemotherapy for first-line treatment of NSCLC in patients with both squamous and non-squamous histology and independent of PD-L1 expression levels. In the CheckMate 9LA trial, patients with the EGFR and ALK mutations were excluded, only 15% of patients were smokers and 30% were squamous histology, which makes the probability of inclusion of patients with the BRAF V600E mutations very low. Additionally, CADTH is also reviewing atezolizumab as monotherapy for the first-line treatment of patients with metastatic NSCLC whose tumours have high PD-(L)1 expression as determined by a validated test and who do not have EGFR or ALK genomic tumour aberrations. Lung cancers with tumours that are being driven by driver mutations do not benefit from single checkmate inhibitors and the clinicians reason that this concept can be similarly applied to tumours driven by the BRAF V600E mutations.

5.4.1 Is there evidence or is it reasonable to continue dabrafenib with trametinib for patients who experience a single or isolated site of disease progression that can be treated "locally" (e.g., a localized treatment modality like RT or RFA)?

Both groups of clinicians agreed that it is reasonable to continue treatment with dabrafenib and trametinib for patients who experience a single or isolated site of disease progression that can be treated locally. The clinicians from LCC further commented that this is how patients with other driver mutations such as an EGFR mutation are usually treated in their practice. The goal of targeted therapy is to keep patients on inhibitors as long as a clinical benefit is observed to help ensure the best chance of survival and a good quality of life

5.4.2 What evidence is there to inform treatment upon progression of dabrafenib and trametinib in patients with BRAF mutation positive NSCLC?

The clinicians from CCO stated that this depends on the line of treatment that patients are currently receiving. If dabrafenib and trametinib is given in the second-line setting after chemotherapy/immunotherapy, then docetaxel would be prescribed post progression. If dabrafenib and trametinib are given after immunotherapy alone, then chemotherapy would be given in the third-line setting. The clinicians from LCC reiterated that platinum doublets are an effective therapy option in the second-line setting for other driver mutations such as EGFR or ALK and the same can be expected for patients with the BRAF V600E driver mutation. For patients with a good performance status, immunotherapy plus chemotherapy can be an effective second-line option.

5.4.3 Does PD-L1 status have any influence on the preferred treatment sequence?

The clinicians from CCO noted that patients with PD-(L)1 expression may have received pembrolizumab in the first-line setting. Therefore, patients with a BRAF V600E mutations could use either dabrafenib and trametinib or standard platinum doublet as it is unclear if one option is better than the other. Patients with a PD-(L)1 expression of less than 50% are likely to receive chemotherapy and pembrolizumab in the first-line setting and therefore, dabrafenib and trametinib would be received as second-line therapy.

The clinicians from LCC explained that many NSCLC patients with the BRAF V600E mutation are non-smokers, for whom single checkpoint inhibitors are not efficacious regardless of their PD-(L)1 status. The clinicians cited a recent study (Mazieres et al, Ann Oncol, 2019) that showed smoking status affects the benefit of immunotherapy in PD-1 expressing patients with the BRAF V600E but not PD-(L)1. As mentioned above, the clinician group noted that the role of immunotherapy in driver mutations is still unclear and debatable based on lessons learned from trying to treat patients with other mutation-driven lung cancers such as EGFR and ALK.

5.5 Companion Diagnostic Testing

Both groups of clinicians noted that testing for the BRAF 600VE mutations is routinely being conducted. The clinicians from LCC noted that patients with advanced NSCLC are recommended to take part in the panel testing for advanced NSCLC of non squamous histology. The turnaround time between testing and receiving results is approximately 2 to 4 weeks, which the clinicians believe is a reasonable time frame for initiating first-line therapy with dabrafenib and trametinib. For patients with minimal testing, the minimal molecular testing requirements should include EGFR, ALK, ROS, BRAF and PD-(L)1.

5.6 Implementation Questions

None to report.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

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

A supplemental question relevant to the pCODR review and to the PAG was identified while developing the review protocol and is outlined in section 7:

- Critical Appraisal of a Sponsor-submitted PSWA Comparing Clinical Outcomes in Patients Treated with Dabrafenib and Trametinib in Study BRF113928 (Cohort C) versus a Real-world, Retrospective Cohort of Patients Treated with Standard of Care Treatments for BRAF-mutated Advanced 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 CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 5. 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 CADTH Methods Team are provided in Appendix A.

Table 5: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCTs, fully published clinical trials evaluating dabrafenib plus trametinib should be included.	Adult patients with advanced or metastatic (stage IIIb or IV) NSCLC with BRAF V600 mutation who have not received prior systemic anti-cancer therapy for metastatic disease	Dabrafenib and trametinib in combination	• Pembrolizumab monotherapy • Platinum doublet chemotherapy ± pembrolizumab • Atezolizumab + bevacizumab + carboplatin + paclitaxel • Atezolizumab + nab-paclitaxel + carboplatin	• **OS** • PFS • ORR • DoR • **HRQoL** • AEs

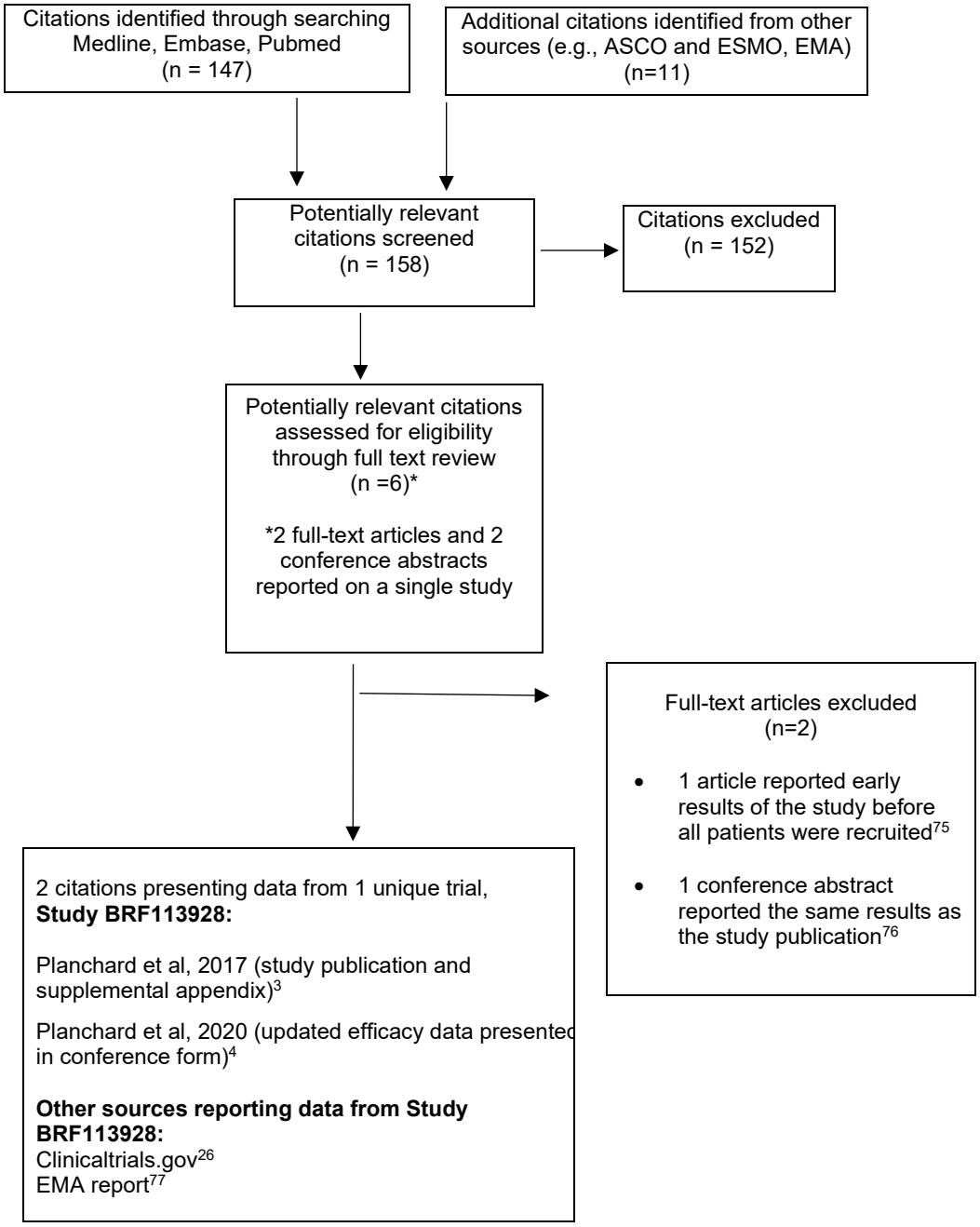
AE = adverse event; BRAF = v-Raf murine sarcoma viral oncogene homolog B; DoR = duration of response; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized control trial.
*Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 158 potentially relevant citations that were identified by the literature search and screened for eligibility, 152 citations were excluded based on abstract screening, and four citations that reported on the same trial (Study BRF113928) underwent full text review (Figure 1). Of the four citations, two were excluded: one citation was the first published article of Study BRF113928 trial where recruitment of patients into Cohort C (previously untreated patients) was ongoing,[75] the other citation was a conference abstract reporting the same data as the study publication of BRF113928.[76] Two other sources of data related to Study BRF113928 were also identified and included an EMA report[77] and one clinical trial record.[26]

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to Study BRF113928 were also obtained through requests to the Sponsor by CADTH.[78]

6.3.2 Summary of Included Studies

One clinical trial was identified that met the selection criteria of the review. Study BRF113928 (also referred to as DRB436E2201) is a phase 2 clinical trial that sequentially enrolled three separate patient cohorts: Cohort A enrolled patients who had received at least one previous line of treatment and were treated with dabrafenib monotherapy; Cohort B enrolled patients who had received at least one previous line of therapy and were treated with combination dabrafenib and trametinib; and Cohort C, the cohort relevant to this review, enrolled previously untreated patients and were treated with the combination of dabrafenib and trametinib. Key characteristics of the three cohorts of Study BRF113928 are presented in Table 6.

Table 6. Key Characteristics of Cohorts in Study BRF113928:

	Cohort A	Cohort B	Cohort C
Study design			
Location	51 sites in 11 countries (Europe, Asia, United Kingdom and United States)		
Description	Dabrafenib monotherapy in treatment-experienced patients	Dabrafenib + trametinib combination therapy in treatment-experienced patients	Dabrafenib + trametinib combination therapy in treatment-Naive patients
N	84	57	36
Population	Adult patients (≥ 18 years) with histologically or cytologically confirmed diagnosis of Stage IV NSCLC and *BRAF* V600E-positive mutation (centrally confirmed after enrolment).		
	Relapsed or progressed after ≥1 prior line of platinum-based chemotherapy (i.e., dabrafenib had to be ≥ 2nd line)	Relapsed or progressed after ≥ 1 prior line of platinum-based chemotherapy but not > 3 prior anti-cancer treatments (i.e., dabrafenib +trametinib had to be 2nd line or beyond treatment)	No prior systemic anti- cancer therapies for metastatic disease (i.e., dabrafenib + trametinib was the 1st line treatment for metastatic disease)
Intervention	Dabrafenib 150 mg twice daily	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily
Primary Endpoint	ORR by Investigator assessment according to RECIST 1.1		
Secondary Endpoints and Other Analyses	• PFS • DOR • OS • PK analyses • Safety and tolerability		
Data cut-off	April 30, 2014 (primary analysis) November 21,2014 (updated efficacy analysis)	August 8, 2016 June 22, 2019	August 8, 2016 (safety analysis) April 28, 2017 (primary analysis) June 22, 2019 (updated analysis)
Crossover	Patients could crossover to dabrafenib + trametinib combination therapy within 4 weeks of disease progression	No	No
Median follow-up	10.7 months	16.6 months	15.9 months 16.3 months
Status	On-going; active but not recruiting		

BRAF = v-Raf murine sarcoma viral oncogene homolog B; DOR = duration of response; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic.

Source: CADTH Submission[13]

6.3.2.1 Detailed Trial Characteristics

a) Trial

As previously noted, Study BRF113928 sequentially enrolled three cohorts of patients with stage IV metastatic BRAF V600E-mutant NSCLC. Cohort C enrolled patients who had not received any prior anti-cancer treatment for metastatic disease; these patients were treated with combination dabrafenib and trametinib and are the focus of this review.[3] Key characteristics of Cohort C of Study BRF113928 are summarized in Table 7.

BRF113928 is an ongoing multicentre, non-randomized, open label phase 2 study conducted in 19 centres in eight countries across North America, Europe, and Asia. There were no Canadian patients enrolled in the trial.[3] Patients were enrolled into Cohort C based on the following key eligibility criteria:

- Aged ≥ 18 years
- Histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC
- Measurable disease (RECIST version 1.1)
- ECOG PS less than or equal to 2
- Estimated life expectancy greater than or equal to three months

Patients were required to have been tested for EGFR and ALK mutations in lung cancer tissue. Patients who tested positive for these mutations were not excluded; and patients who tested positive for these mutations and received EGFR or ALK inhibitor therapy were also not excluded. BRAF V600E mutational status for purposes of enrolment was determined by each study site using local testing methods in laboratories approved by the Clinical Laboratory Improvement Amendments (or its equivalent for study centres outside the US). The trial excluded patients who had received prior treatment with a BRAF or MEK inhibitor, presence of brain metastases unless asymptomatic, untreated, and measured less than 1cm, or if treated, were clinically or radiographically stable three weeks after local therapy, were pregnant, had confirmed hepatitis B or C virus infection, cardiovascular risk, a history of interstitial lung disease, pneumonitis, and history or current evidence of retinal vain occlusion.

Table 7: Key Characteristics of Cohort C in Study BRF113928

Trial Design	Inclusion and Exclusion Criteria	Intervention and Comparator	Outcomes*
BRF113928 - Cohort C (DRB436E2201; NCT1336634) Single group, non-randomized, open-label, phase 2 clinical trial N treated= 36 19 centres in 8 countries (North America, Europe, Asia) Patient Enrolment Dates: April 16, 2014 – December 28, 2015 Data cut-off dates: • Primary efficacy and safety analysis - April 28, 2017 • Updated efficacy and safety analysis - June 22, 2019 Funding: • GlaxoSmithKline	Key inclusion criteria: • Aged ≥ 18 years • Histologically or cytologically confirmed stage IV BRAF V600E-mutant NSCLC • Measurable disease (RECIST 1.1) • ECOG PS ≤ 2 • Estimated life expectancy ≥ 3 months • Laboratory assessment ○ Haematology (absolute neutrophil count ≥ $1.5x10^9$ cells per L, haemoglobin ≥ 90g/L, platelet count ≥ $100x10^9$ per L, prothrombin time/international normalised ratio and partial thromboplastin time of ≤ 1.5xULN ○ Hepatic (total bilirubin ≤ 1.5xULN, aspartate aminotransferase and alanine aminotransferase ≤ 2.5xULN	Intervention: Oral dabrafenib (150 mg twice per day) plus oral trametinib (2 mg once per day) in continuous 21-day cycles until disease progression, unacceptable AEs, consent withdrawal, or death. No comparator	Primary: • Investigator-assessed ORR, defined as the proportion of patients with a confirmed CR or PR according to RECIST 1.1 Secondary: • IRC-assessed ORR • DOR • PFS • OS • AEs • Pharmacokinetics

Trial Design	Inclusion and Exclusion Criteria	Intervention and Comparator	Outcomes*
• Novartis acquired dabrafenib and trametinib March 2, 2015	○ Renal (at lease one of the following: serum creatinine ≤ 1.5 mg/dL [132.6 µmol/L] or creatinine clearance of ≥ mL/min) ○ Cardiac function (left ventricular ejection fraction of at least the lower limit of normal by echocardiography) Key exclusion criteria: • Previous treatment with BRAF or MEK inhibitors • Brain metastases unless asymptomatic, untreated, and measured <1 cm, OR if treated were clinically and radiographically stable 3 weeks after local therapy • Pregnancy • Hepatitis B or C • History of interstitial lung disease or pneumonitis • History of or current evidence of retinal vein occlusion		

AE = adverse event; BRAF = v-Raf murine sarcoma viral oncogene homolog B; CR = complete response; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC = independent review committee; MEK = MAP (Mitogen-Activated Protein) Kinase/ERK (Extracellular Signal-Regulated Kinase) Kinase; NSCLC = non-small cell lung cancer; ORR = overall response rate; PFS = progression-free survival; PR = partial response; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limit of normal.

*All outcomes were investigator assessed. Assessments by an independent review committee were used in sensitivity analyses.
Source: Planchard et al. 2017[3]

Role of the Sponsor

The trial was funded by the sponsor, GlaxoSmithKline (GSK) and was designed and conducted by representatives of GSK in collaboration with the academic authors. The sponsor had an active role in data collection, analysis and interpretation, and preparation of the trial manuscript. Editorial assistance was provided by ArticulateScience and was funded by GSK. Dabrafenib and trametinib were acquired by Novartis as of March 2, 2015.

Disease and Response Assessment

Radiologically detected disease per RECIST version 1.1 was evaluated with CT at baseline, at week six, every six weeks until week 36, and every 12 weeks thereafter. Responses were confirmed by repeat assessments four to seven weeks after an initial response. An IRC also reviewed RECIST scans. For patients who discontinued treatment, follow-up for subsequent treatment and survival was done every 12 weeks until death or study completion. AEs, laboratory values and vital signs were evaluated at least every three weeks.

Study Outcomes

Efficacy Outcomes

All efficacy outcomes were evaluated based on investigator assessment. Outcome assessments were also performed by an IRC as secondary endpoints and for the purpose of sensitivity analyses.

Primary Endpoint

The primary endpoint of the trial was investigator-assessed ORR. ORR was defined as the proportion of patients who achieved a confirmed CR or PR according to RECIST version 1.1 criteria. Patients with either no post-baseline CT scan or those who discontinued after less than 12 weeks without documented progression were considered non-evaluable.[3] Patients with non-evaluable or missing best overall response (BOR) were treated as non-responders.[13] The BOR was the best confirmed response recorded from treatment initiation until disease progression, start of new anti-cancer therapy, or death, whichever occurred first. No subgroup analyses of the primary outcome were planned or performed.

Secondary Endpoints

The following secondary endpoints were assessed in the trial:

- ORR by IRC assessment
- PFS, defined as the interval between the first dose of study drug and the earliest date of disease progression or death due to any cause
- Duration of response (DOR), 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 occurred first, assessed by investigator and independent reviewer
- Overall survival (OS), defined as the time from first dose of study drug to death from any cause
- Safety, which included monitoring and recording of all AEs and SAEs, clinical laboratory tests (e.g., hematology standard chemistry, serum pregnancy, etc.), vital signs, electrocardiogram, echocardiogram, physical examination, dermatological and ophthalmic examinations
- Pharmacokinetic assessment

Statistical Analyses

The sample size for each cohort was planned in order to achieve statistical power of 90% or greater and alpha levels of less than 0.05 for investigator-assessed ORR in each cohort.[77] The null hypothesis was that the response rate of combination therapy was less than or equal to the response rate of platinum-based chemotherapy for first-line treatment of metastatic NSCLC (i.e., ≤ 30%). The alternative hypothesis was that the response rate of combined dabrafenib and trametinib would be higher than that of platinum chemotherapy.[13] The planned sample size consideration was based on a targeted response of at least 60% and the incorporation of an exact binomial test corresponded to the planned enrollment of 25 patients, a type I error of 0.044, and power of 92.2% for the one-stage binomial design (i.e., H0: ORR ≤ 30%, H1: ORR ≥ 60%).

The efficacy analyses of ORR, PFS, DOR and OS were based on the ITT population (defined as all patients who had not received any prior anti-cancer therapy for metastatic disease; this included 34 patients recruited into Cohort C plus two patients from Cohort B who were receiving the combination as first-line treatment due to protocol deviations and who met the eligibility criteria).[13] The analyses of secondary efficacy outcomes were based on the first-line BRAF V600E centrally confirmed population.[13] The study was considered complete when a minimum of 70% of patients had died (or were no longer being followed), or when five years have passed since the patients' first dose, whichever comes first. The final analysis would focus on OS and selected safety data analysis.[13] No interim analyses were planned. The data cut-off date for primary efficacy analyses was April 28, 2017.[3] An updated analysis was performed with a data cut-off date of June 22, 2019 (785 days from first efficacy analyses),[4] which was not prespecified in the study protocol.[13]

All primary efficacy analyses were prespecified. The analysis of time-to-event outcomes (i.e., DOR, PFS, and OS) were considered descriptive since no formal hypotheses or statistical testing were performed. An exact 95% CI was calculated for the ORR using the Clopper-Pearson method. ORR by IRC was analyzed using the same method as the primary endpoint of ORR. Kaplan-Meier (KM) methods were used to descriptively summarize DOR, PFS, and OS. For the analysis of PFS, if the patient received subsequent anti-cancer therapy prior to the date of documented progression or death, PFS was censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the patient did not have a documented date of progression or death, PFS was censored at the date of the last adequate assessment. For the analysis of OS,

the last date of known contact was used for patients who have not died at the time of analysis (i.e. patients were considered censored).[13]

All patients who received at least one dose of study treatment were included in the analysis of safety.[13] AEs, laboratory values and vital signs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). The safety analysis was based on a data cut-off date of August 8, 2016.

b) Populations

A total of 36 patients were enrolled in Cohort C of Study BRF113928. The characteristics of patients in Cohort C at baseline are presented in Table 8. The median age of patients was 67 years (IQR, 62 to 74), and most patients were female (61%; n= 22), and of White race (83%; n=30). Most patients were former smokers (58%; n=21), among whom the median time smoked was 30 years (IQR, 10 to 40) and the median pack-years smoked was 18 (IQR, 5 to 34). The median time from diagnosis was 2.05 months.[13] All but one patient (who was enrolled due to a protocol deviation and had stage III cancer) had stage IV cancer at screening.[77] Histology at initial diagnosis was determined as non-squamous adenocarcinoma in the majority of patients (89%; n=32); and histological grade could not be assessed for half (50%; n=18) of the trial population.[13] At baseline, most patients had an ECOG performance status of 1 (61%; n=22). Tumour samples were available for 92% of patients (n=33), of which 78% (n=28) met specifications for the Oncomine™ assay. Of these, 82% of patients (n=23) were confirmed to have a *BRAF* V600E mutation.[13] Two patients had brain metastases at baseline that were non-target lesions. In Cohort C, 34 (94%) patients received prior anticancer therapy including surgery and other adjuvant treatments. Overall, 33 (92%) patients received surgery for lung cancer and 10 (28%) patients received prior radiotherapy. The most commonly reported anticancer agents in the adjuvant setting were: cisplatin (14%) and carboplatin (8%), pemetrexed disodium (6%), vinorelbine (6%), and vinorelbine detartrate (6%).[13]

Table 8: Baseline Characteristics of Patients Enrolled in Cohort C of Study BRF113928

Characteristic	Cohort C (N=36) Combination First-Line Population
Age, years Mean (SD) Median (min, max) < 65 years, n (%) > 65 years, n (%)	67.8 (11.00) 67.0 (44 to 91) 14 (39) 22 (61)
Sex, n (%) Male Female	 22 (61) 14 (39)
Race, n (%) White Black or African American Asian Other Missing	 30 (83) 1 (3) 3 (8) 1 (3) 1 (3)
Smoking history, n (%) Never smoked Current smoker Former smoker	 10 (28) 5 (14) 21 (58)
No. of years smoked n Median (min, max)	 25 30.0 (2 to 70)
Smoking pack years ≤ 30 pack-years > 30 pack-years	 17 (47) 7 (19)
ECOG PS, n (%) 0 1 2	 13 (36) 22 (61) 1 (3)
Histology, n (%) Adenocarcinoma Adenosquamous carcinoma[a] Adenosquamous carcinoma[b] Bronchioloalveolar Large cell carcinoma NSCLC not otherwise specified	 32 (89) 1 (3) 1 (3) 0 (0) 1 (3) 1 (3)
Stage at screening, n (%) IIIA IV	 1 (3) 35 (97)
Time since diagnosis (months)n Median (min, max)	 32 2.05 (1.0 to 63.2)
Time since last progression (months) n Median (min, max)	 12 1.7 (0.1 to 7.4)

ECOG PS = European Cooperative Oncology Group performance status; NSCLC = non-small cell lung cancer; SD = standard deviation
[a] Predominantly adenocarcinoma
[b] Predominantly squamous cell carcinoma

Source: CADTH Submission[13]

Note: In the Clinical Summary[13] the percentage of males is reported as 61%; and in the study publication[3] the percentage of females is reported as 61%.

c) Interventions

Patients were treated with oral dabrafenib (150 mg twice per day) plus oral trametinib (2 mg once per day) until disease progression, unacceptable AEs, consent withdrawal, or death. The median patient daily dose was 269.2 mg (IQR, 211 to 298) for dabrafenib and 1.9 mg (IQR, 1.6 to 2.0) for trametinib. Treatment beyond disease progression was allowed in patients who had a confirmed response (RECIST version 1.1) or stable disease for at least 12 weeks during study treatment and were considered by the study investigator to be clinically benefitting from the study treatment.

Dose Modification

Dose modifications of dabrafenib and trametinib were permitted in the trial to manage intolerable AEs of grade 2 or higher. Treatment doses of both drugs were reduced simultaneously, except in the case of uveitis in which only the dose of dabrafenib was reduced; and in the cases of retinal vein occlusion, retinal pigment epithelial detachment, left ventricular ejection fraction reduction, pneumonitis, or interstitial lung disease, in which only the dose of trametinib was reduced. Dabrafenib was reduced to a dose of 100 mg, then 75 mg, and to a minimum of 50 mg on the first, second, and third dose reductions, respectively. Trametinib was reduced to a dose of 1.5 mg on the first reduction and a minimum of 1 mg on the second reduction. Dose reductions of dabrafenib were required for 17 patients (47%); 11 (65%) of these patients required one dose reduction, and three patients (18%) each required two and three or more dose reductions. Dose reductions of trametinib occurred in ten (28%) of patients; four (40%) of these patients required one dose reduction and six (60%) required two dose reductions.

Treatment Exposure

At the time of the primary analysis, the median durations of exposure to dabrafenib and trametinib were 9.0 months (IQR, 3.14 to 20.53) and 9.5 months (IQR, 3.2 to 19.3), respectively. The majority of trial patients had a median duration of exposure to dabrafenib and trametinib that was greater than 12 months; (Table 9) 39% of patients (n=14) received dabrafenib and 42% (n=15) of patients received trametinib for a duration of 12 months or greater.

Table 9. Dabrafenib and Trametinib Exposure

	Dabrafenib (N=36)	Trametinib (N=36)
Median duration of exposure (IQR), months	9·0 (3·14–20·53)	9·5 (3·15–19·29)
Duration of exposure category, n (%)		
<3 months	9 (25)	9 (25)
3–6 months	7 (19)	6 (17)
>6–12 months	6 (17)	6 (17)
>12 months	14 (39)	15 (42)
Median patient daily dose (IQR), mg	269·2 (211–298)	1·9 (1·6–2·0)

Source: Reprinted from Planchard et al. Lancet Oncol. 18(10):1307-1316, Copyright 2017 with permission from Elsevier.[3]

d) Patient Disposition

The disposition of patients in Cohort C of Study BRF113928 is summarized in Table 10. Of the 36 patients, 11 (31%) remained on the study treatment at the primary analysis data cut-off date (April 28, 2017), 19 (53%) were alive, and 17 (47%) had died. Among the 25 patients (69%) who had discontinued treatment by the data cut-off date, 14 patients had discontinued due to disease progression, eight due to AEs, one at patient's request and two at the investigator's discretion. There was a total of three patients who were lost to follow up after discontinuing treatment. At the updated analysis cut-off date (June 22, 2019), four patients (11%) remained on the study treatment, and three patients (8%) had withdrawn from the study. Fourteen patients (39%) were alive and 22 (61%) had died.[13]

At least one protocol deviation was reported in 33 patients (92%), of which the majority were related to assessments or procedures (83%; particularly missed assessments or procedures: 78%).[13] Five patients had deviations in eligibility criteria that included the two

patients from Cohort B who were enrolled in Cohort C as protocol deviations. The other eligibility criteria deviations related to issues in obtaining confirmation of BRAF mutation in two patients and multiple reasons in one patient (i.e., systolic blood pressure higher than 140 mmHg on screening and day 1, stage III disease, and not tested for an ALK rearrangement at baseline).[13]

Subsequent Anti-cancer Therapies

After discontinuing treatment with dabrafenib and trametinib, nine (36%) received at least one subsequent therapy. Subsequent anticancer therapies included chemotherapy (n=6), biological therapy (n=4), radiotherapy (n=4), small molecule targeted therapy (n=2), surgery (n=1), and immunotherapy (n=1). The median time from study treatment discontinuation to start of subsequent anti-cancer therapy was 43 days (range, 13.5 to 113). The sponsor indicated that data on treatment beyond progression, and duration of treatment were not captured.[78]

Table 10. Patient Disposition in Study BRF113928

Patient Disposition*	N (%)
Total enrolled	36
Discontinued treatment	25 (69)
Disease progression	14 (39)
Adverse events	8 (22)
Patient decision	1 (3)
Investigator discretion	2 (6)
Lost to follow-up	3 (8) [a]
Protocol deviation	33 (92) [b]
Patients missing data	4 (11) [c]
Population analyzed for efficacy	36 (100)
Population analyzed for safety	36 (100)

[a]One patient lost to follow-up, two patients withdrew consent (all after discontinuing treatment).
[b] Five patients had deviations in eligibility criteria.
[c] Patients not evaluable for best overall response (missing two post-baseline scans).[78]
* Based on primary analysis data cut-off date of April 28, 2017.

Source: Planchard et al, 2017[3]

Missing data

Other than four patients who were not evaluable for BOR (i.e., missing two post-baseline scans to have valid BOR assessment based on RECIST 1.1 criteria), there were no missing patient data for key outcomes. These four patients were assumed to be non-responders and were included in the denominator when calculating percentages.[78]

e) Limitations/Sources of Bias

The submission to CADTH was based on data from Study BRF113928, which was an open-label phase 2 trial with no placebo or control group. The CADTH Methods Team acknowledges the challenges in implementing a large trial with appropriate control groups given the rarity of BRAF V600E-mutated NSCLC, the variability of treatments used in different settings, and the variability of routine genetic testing. Nonetheless, without a robust trial design, and in the absence of a direct comparison to currently available treatment options, determining the magnitude of clinical benefit associated with combination dabrafenib and trametinib in previously untreated patients with BRAF V600E mutant stage IV NSCLC is difficult. The following are notable limitations of Study BRF113928 that forms the evidence base for this submission:

- The primary endpoint of the trial was ORR. ORR as a surrogate outcome may not translate into clinical benefits in terms of PFS and OS. There is no strong evidence to support ORR as a surrogate endpoint for OS in the treatment of patients with BRAF V600E-mutant stage IV NSCLC. In Cohort C of the trial, it appears that ORR was largely driven by

PRs (only two out of 36 patients achieved CR). A recent study evaluating the evidence on surrogate measures in cancer trials, using breast cancer as an example, classified ORR as 'a not strongly correlated surrogate for OS.[79]

- The descriptive analyses of time-to-event outcomes (i.e., DOR, PFS and OS) in a study of such small sample size with no comparator groups limit meaningful interpretation of these outcomes.

- The OS estimates will be confounded by the use of subsequent anti-cancer therapies received by patients after discontinuing combination treatment with dabrafenib and trametinib.

- Data on HRQoL, an important patient outcome, were not collected. At the Checkpoint meeting, the sponsor indicated HRQoL data would be challenging to obtain and interpret in the study due to the small sample size and the lack of a comparator arm. The sponsor cited a recent pCODR recommendation for crizotinib, where it was stated that HRQoL data in single arm phase 2 trial is challenging to interpret given the lack of direct comparative estimates as all patients in the trial received the same treatment.[78] Measurement of HRQoL is important for capturing the benefits of novel therapies from a patient's perspective to confirm whether improvements in survival outcomes are accompanied by improved QoL for patients.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Results of efficacy analyses based on the primary analysis data cutoff date (April 28, 2017) and the updated analysis data cut-off date (June 22, 2019) are presented in Table 11. The median duration of follow up was 15.9 months at the time of the primary analysis[3] and 16.3 months at the time of the updated efficacy analysis.[4]

Table 11. Efficacy Outcomes in the BRF113928 Trial

Efficacy Outcomes	Primary Analysis April 28, 2017[3]	Updated Analysis June 22, 2019[4]
ORR, n % (95% CI)	23 63.9 (46.2–79.2)	23 63.9 (46.2–79.2)
DOR, median (95% CI)	10.4 (8.3–17.9)	10.2 (8.3–15.2)
PFS (months), median (95% CI)	10.9 (7.0–16.6)	10.8 (7.0–14.5)
OS (months), median (95% CI)	24.6 (12.3–NE)	17.3 (12.3–40.2)

DOR = duration of response; CI = confidence interval; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Sources: Planchard et al. 2017;[3] CADTH Submission[13]

Efficacy Outcomes

Primary endpoint

Overall Response Rate

A summary of ORR as assessed by investigator and IRC is presented in Table 12. At the primary analysis, the investigator-assessed ORR was 63.9% based on 23 patients who had a confirmed response; this included two patients (6%) who achieved a CR and 21 patients (58%) who achieved a PR. There were 27 patients (75%) who achieved disease control (23 with a confirmed response and four considered to have stable disease).[3] The ORR was maintained at the updated efficacy analysis (63.9%; 95% CI, 46.2 to 79.2).[4] Investigator assessed and IRC assessed ORR estimates were concordant.

Secondary Endpoints

Duration of Response

The median DOR by investigator assessment was 10.4 months (95% CI, 8.3 to 17.9) and was 15.2 months (95% CI, 7.8 to 23.5) based on IRC assessment. The difference between investigator assessed and IRC assessed DOR was due to censored observations for the assessment by IRC. The IRC did not assess the last scans for five patients who were assessed by the study investigators as having progressive disease; these patients were reported to have had DOR values close to the median. At the updated analysis, the median DOR by investigator assessment was 10.2 months (95% CI, 8.3–15.2) and the DOR by IRC assessment was not reported.[4]

Progression-free Survival

At the time of the primary analysis, 24 patients (67%) had progressed or died. The median investigator assessed PFS was 10.9 months (95% CI, 7.0 to 16.6) and PFS at 6 months was 72% (95% CI, 53 to 84). The median IRC assessed PFS was 14.6 months (95% CI 7.0 to 22.1). At the updated efficacy analysis, median PFS by investigator assessment was 10.8 months (95% CI, 7.0 to 14.5).[4] The difference in estimates between investigator and IRC-assessed PFS was also attributed to censoring in the IRC assessment.

Overall Survival

At the time of the primary analysis, 19 patients (53%) remained alive and 17 (47%) had died; the median OS was 24.6 months (95% CI, 12.3 to NE). The two-year OS was 51% (95% CI, 33 to 67). At the updated efficacy analysis, the median OS was 17.3 months

(95% CI, 12.3 to 40.2); and OS at 12, 24 and 36 months was 74% (95% CI, 55 to 85), 49% (95% CI, 32 to 65), and 40% (95% CI, 24 to 56), respectively.[4]

Table 12. Overall Response as Assessed by Investigator and IRC

	Investigator assessed (n=36)	Independent review committee assessed (n=36)
Overall response (complete and partial responses)	23 (64%; 46–79)	23 (64%; 46–79)
Disease control (complete responses, partial responses, and stable disease)	27 (75%; 58–88)	26 (72%; 55–86)
Complete response	2 (6%)	2 (6%)
Partial response	21 (58%)	21 (58%)
Stable disease	4 (11%)	3 (8%)
Progressive disease	5 (14%)	7 (19%)
Not evaluable	4 (11%)	3 (8%)

Data are n (%; 95% CI) or n (%).

Source: Reprinted from Planchard et al. Lancet Oncol. 18(10):1307-1316, Copyright 2017 with permission from Elsevier.[3]

Adverse Events

A summary of the AEs and SAEs in Study BRF113928 is available in Table 13 and Table 14, respectively.

All patients had at least one AE of any grade. At the time of the primary analysis (April 28, 2017), this was most commonly (> 30% of patients) reported to be pyrexia (64%, n=23), nausea (56%, n=20), diarrhea (36%, n=13), fatigue (36%, n=13), peripheral oedema (36%, n=13), decreased appetite (33%, n=12), dry skin (33%, n=12), and vomiting (33%, n=12). Grade 3 and 4 AEs were reported in 69% (n=25) of patients; the most common (> two patients) grade 3 and 4 events were pyrexia (11%, n=4), alanine aminotransferase increase (11%, n=4), hypertension (11%, n=4), and vomiting (8%, n=3). SAEs occurring in more than two patients included alanine aminotransferase increase (14%, n=5), pyrexia (11%, n=4), aspartate aminotransferase increase (8%, n=3), and ejection fraction decrease (8%, n=3). SAEs occurred in the majority of patients,[13] of which alanine aminotransferase increase (14%; n=5) and pyrexia (11%; n=4) were the most common. One patient died from a SAE (cardiorespiratory arrest), which was considered unrelated to the study treatment. AEs led to permanent treatment discontinuation in 22% (n=8) of patients, dose interruption or delay in 75% (n=27) of patients, and dose reduction in 39% (n=14) of patients.

Table 13. Summary of AEs in All Treated Patients in Cohort C of Study BRF113928

AE Category	Study BRF113928 Cohort C (N=36)
Data cut-off	August 8, 2016*
Any AE, n (%) AE related to study treatment AE leading to permanent DC AE leading to dose reduction AE leading to dose interruption	36 (100) 32 (89) 7 (19) 11 (31) 25 (69)
Any SAE, n (%) SAE related to study treatment Fatal SAE Fatal SAE related to study treatment	21 (58) 16 (44) 1 (3) 0 (0)

AE = adverse event; DC = discontinuation of study treatment; SAE = serious adverse event.
*The median duration of treatment for both dabrafenib and trametinib was 8.21 months (range, 0.3 to 27.8) at the data cut-off date of August 8, 2016.

Source: CADTH Submission[13]

Table 14. Serious Adverse Events in Study BRF113928

Serious adverse event, n (%)	Previously untreated *BRAF* V600E–mutant NSCLC (N=36)
Alanine aminotransferase increased	5 (14)
Pyrexia	4 (11)
Aspartate aminotransferase increased	3 (8)
Ejection fraction decreased	3 (8)
Hypotension	2 (6)
Pulmonary embolism	2 (6)
Vomiting	2 (6)
Abdominal pain	1 (3)
Asthenia	1 (3)
Blood alkaline phosphatase increased	1 (3)
Blood creatinine increased	1 (3)
Cardiac arrest	1 (3)
Chills	1 (3)
Cystitis	1 (3)
Dehydration	1 (3)
Detachment of retinal pigment epithelium	1 (3)
Diarrhoea	1 (3)
Dyspnoea	1 (3)
Gastric haemorrhage	1 (3)
Gastrointestinal pain	1 (3)
Gastrointestinal toxicity	1 (3)
Hypophosphataemia	1 (3)
Ileus	1 (3)
Lymphocyte count decreased	1 (3)
Multiple injuries	1 (3)
Myalgia	1 (3)
Peripheral sensory neuropathy	1 (3)
Pneumonitis	1 (3)
Rash maculo-papular	1 (3)
Renal artery thrombosis	1 (3)
Respiratory arrest	1 (3)
Retinal dystrophy	1 (3)
Splenic thrombosis	1 (3)
Squamous cell carcinoma	1 (3)
Systemic inflammatory response syndrome	1 (3)
Vertigo positional	1 (3)
White blood cell count decreased	1 (3)

Source: Reprinted from Planchard et al. Lancet Oncol. 18(10):1307-1316, Copyright 2017 with permission from Elsevier.[3]

6.4 Ongoing Trials

One ongoing trial was identified through ClinicalTrials.gov (Table 15). This trial is similar in design to Study BRF113928 (i.e., non-comparative phase 2 trial) and evaluates dabrafenib and trametinib in previous untreated patients with BRAF V600E mutated NSCLC but is being carried out in a Chinese population.

Table 15. Ongoing Trials of Dabrafenib and Trametinib in Previously Untreated Patients with BRAF V600-mutated NSCLC

Trial design	Inclusion criteria	Intervention and comparator	Key trial outcomes
Study of Dabrafenib in Combination With Trametinib in Chinese Patients With *BRAF* V600E Mutant Metastatic NSCLC (NCT04452877)[26] Open label Single arm Status: recruiting Estimated enrollment: 20 patients Estimated completion date: June 27, 2023 Data cut-off: NA Final analysis date: NA Funding: Novartis Pharmaceuticals	<u>Key Inclusion Criteria</u>: • Histologically or cytologically confirmed diagnosis of Stage IV NSCLC (according to AJCC 8th edition) that is *BRAF* V600E mutation-positive by local test result from a qualified assay (NMPA and/or MOH-approved) • Previously treated or untreated for metastatic NSCLC • Measurable disease per RECIST v1.1 • Anticipated life expectancy of at least three months • ECOG performance status ≤ 2. <u>Key Exclusion Criteria</u>: • Brain or leptomeningeal metastases if: symptomatic or treated but not clinically and radiographically stable three weeks after local therapy or asymptomatic and untreated but > 1 cm in the longest dimension • Previous treatment with a BRAF inhibitor or a MEK inhibitor • All prior anti-cancer treatment-related toxicities must be Grade 2 or less according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.03; NCI, 2009) at the time of enrollment • Prior anti-cancer treatment within the last two weeks, and prior treatment with immune checkpoint inhibitors within four weeks preceding the first dose of the study	Dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) in combination No comparators	<u>Primary</u> • ORR (central independent review assessed by RECIST v1.1) <u>Secondary</u> • ORR (investigator assessed by RECIST v1.1) • PFS (investigator assessed by RECIST v1.1) • DOR (investigator assessed by RECIST v1.1) • OS (investigator assessed by RECIST v1.1)

AJCC = American Joint Committee on Cancer; BRAF = v-Raf murine sarcoma viral oncogene homolog B; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; MEK = mitogen-activated protein kinase kinase enzymes; MOH = Ministry of Health; NA = not available; NMPA = National Medical products Administration; NSCLC = non-small cell lung cancer; ORR =overall response rate; OS – overall survival; PFS – progression-free survival.

7 Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of dabrafenib and trametinib in combination for the treatment of adult patients with metastatic NSCLC with a BRAF V600 mutation who have not received any prior anti-cancer therapy for metastatic disease:

- Critical Appraisal of a Sponsor-submitted PSWA Comparing Clinical Outcomes in Patients Treated with Dabrafenib and Trametinib in Study BRF113928 (Cohort C) versus a Real-world, Retrospective Cohort of Patients Treated with Standard of Care Treatments for BRAF-mutated Advanced NSCLC

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

7.1 Critical Appraisal of a Sponsor-submitted PSWA Comparing Clinical Outcomes in Patients Treated with Dabrafenib and Trametinib in Study BRF113928 (Cohort C) versus a Real-world, Retrospective Cohort of Patients Treated with Standard of Care Treatments for BRAF-mutated Advanced NSCLC

7.1.1 Objective

The objective of this section is to summarize and critically appraise a sponsor-submitted ITC.[13,80] Due to a lack of direct comparative evidence (i.e., due to single arm design of Study BRF1133928), the sponsor performed a PSWA)[13,80] that compared clinical outcomes among patients treated with dabrafenib and trametinib in Study BRF113928 (Cohort C)[3] (labeled as DRB436E2201 in the PSWA report) versus a real-world, retrospective cohort of patients treated with standard of care (SOC) treatments for BRAF-mutated advanced NSCLC.[13,80] PSWAs were performed to compare the outcomes of patients treated with dabrafenib plus trametinib as either first- or second-line therapy. However, to align with the submitted reimbursement request, this summary and critical appraisal was focused to the comparisons of first-line (1L) treatments for BRAF-mutated advanced NSCLC.

Of note, on February 16, 2021, the sponsor submitted to CADTH an additional report summarizing the results of a retrospective comparison of clinical outcomes (i.e., real-world data versus real-world data comparison) among patients treated with dabrafenib and trametinib versus SOC treatments for BRAF V600-mutated metastatic NSCLC that included pembrolizumab monotherapy. The sponsor indicated that the analysis summarized in the additional report was performed to confirm the findings of the PSWA. Based on the date the additional report was submitted to CADTH, the sponsor was informed and consented to there being insufficient time for CADTH to perform a review and critical appraisal within the regular review timelines;[13] therefore it was not included in this report.

7.1.2 Findings

As part of the submission, the sponsor submitted the PSWA as an unpublished report that was considered non-disclosable.[13] Therefore, reporting of the PSWA is primarily based on a published conference poster[80] and disclosable submission documents (Clinical Summary, Systematic Literature Review [SLR] and ITC Feasibility Reports).[13,80]

Description of Sponsor-Submitted PSWA

Objectives

The primary objective of the PSWA was to evaluate the efficacy of dabrafenib plus trametinib combination therapy (i.e., the index cohort, Study BRF113928 - Cohort C) compared to SOC treatments. Real word evidence (RWE) on patients treated with SOC treatments were obtained from the Flatiron EDM database. The Flatiron EDM is a longitudinal, de-identified database derived from electronic health records (EHR) containing patient-level structured data as well as unstructured data curated via technology-enabled abstraction.[80] At the time of conducting the PSWA, data were derived from approximately 280 cancer clinics (approximately 800 sites of care).[80] The PSWA focused on the following SOC comparator treatments for first-line treatment:

- 1L PD-(L)1 plus Chemotherapy RWE Cohort 1
- 1L Chemotherapy RWE Cohort 2

Systematic Literature Review

The sponsor conducted a SLR to identify clinical evidence as first-line treatment for patients with BRAF-mutated advanced NSCLC. The details with respect to eligible populations, interventions, comparators, outcomes, and study designs included in the SLR are presented in **Error! Reference source not found.**. The choice of comparator treatments was based on recent guidelines (i.e. ASCO,[81] ESMO,[82] and NCCN[83]) for the treatment of EGFR- and ALK-negative NSCLC. The comparison with first-line platinum-based chemotherapy was included to address the current change in SOC from platinum-based chemotherapy to pembrolizumab as monotherapy (PD-L1) or in combination with platinum-based chemotherapy in first-line NSCLC. The databases of MEDLINE (including MEDLINE In-Process), EMBASE, Cochrane Library as well as conferences including American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Lung Cancer Congress (ELCC) and World Conference on Lung Cancer (WCLC) over the past three years were searched to identify relevant publications.[13] The SLR identified four publications of the index trial Study BRF113928, and 12 retrospective observational studies that included relevant comparators in the BRAF-mutated NSCLC population.

Table 16: PICOS of the Systematic Review

PICOS	Details
Population	• Studies including patients with advanced NSCLC who have BRAF mutation • Studies including patients with advanced NSCLC and report outcomes in subgroups of patients with BRAF mutation • Patients in the first-line or the later-line (second-line or above) settings, or when outcomes are reported by line of therapy
Interventions and Comparators	Studies reporting one or more of specifically the following treatment regimens were included: • Dabrafenib + trametinib • Pembrolizumab + platinum (cisplatin or carboplatin) + pemetrexed • Pemetrexed + platinum (cisplatin or carboplatin) • Platinum doublet (cisplatin or carboplatin in combination with gemcitabine, vinorelbine, docetaxel or paclitaxel) • Docetaxel monotherapy • Pemetrexed monotherapy • Erlotinib monotherapy • Pembrolizumab monotherapy • Nivolumab monotherapy • Atezolizumab monotherapy • Grouped chemo- or immunotherapies
Outcomes	Studies reporting at least one of the following outcomes: • Overall survival (e.g., hazard ratio, median, Kaplan-Meier curves, landmark survival rates, etc.) • Progression-free survival (PFS) - Disease control rate (DCR) • Overall response rate (ORR) - Duration of response (DOR) • Time to tumor progression (TTP) • Overall treatment discontinuation and discontinuation due to efficacy and safety reasons, respectively • Overall grade 3/4 adverse events (AEs) • Health-related quality of life (HRQoL)

PICOS	Details

Study Design	• Clinical trials, including:
	  ○ Randomized controlled trials
	  ○ Non-randomized clinical trials
	  ○ Uncontrolled single armed clinical studies
	  ○ Observational studies, including:
	  ○ Cohort study (including registry studies, electronic medical record (EMR) studies, chart review studies, and administrative database (e.g., claims) studies)
	• Trial extension study
	• Pooled analysis of multiple trials/observational studies

Language Restriction	English articles

AE = adverse event; BRAF = v-Raf murine sarcoma viral oncogene homolog B; DCR = disease control rate; DOR = duration of response; EMR = electronic medical record; HRQoL = health-related quality of life; NSCLC = non small cell lung cancer; ORR = overall response rate; PFS = progression-free survival; PICOS = population, intervention, comparator outcome and study design; TTP = time to progression.

Source: CADTH Submission[13]

Feasibility Assessment

The feasibility of performing an ITC was assessed with consideration given to several factors that included study design, patient characteristics, and data availability for efficacy outcomes. Since baseline characteristics were not reported for patients in the RWE Cohorts who received the regimens of interest, the authors concluded that it was not feasible to conduct a traditional ITC or matching-adjusted indirect comparison (MAIC). Therefore, a PSWA was chosen to assess the comparative efficacy of dabrafenib plus trametinib versus relevant comparators using an external control group.[13,80]

Methods of the Sponsor-Submitted PSWA

The main characteristics of the first-line dabrafenib and trametinib cohort (1L DAB plus TRAM Cohort C) and comparator RWE Cohorts selected for the PSWA are presented in Table 17. Patients in the 1L DAB plus TRAM Cohort C had a confirmed BRAF V600E mutation. As previously noted, the comparator RWE Cohorts were from the Flatiron EDM. It was noted that patients from Flatiron EDM had a BRAF mutation with or without V600E mutation due to the fact that the Flatiron EDM has incomplete data on the specific subtypes of BRAF mutation.[13,80]

The effectiveness of dabrafenib and trametinib in the first-line setting was assessed using PSWAs relative to two different comparators: carboplatin plus pembrolizumab plus pemetrexed as first-line of therapy (1L PD(L)1 plus Chemotherapy RWE Cohort 1) ; and platinum-based chemotherapy (carboplatin plus pemetrexed; carboplatin plus paclitaxel; carboplatin plus nab-paclitaxel [protein-bound]; cisplatin plus pemetrexed; or cisplatin plus etoposide) as first-line of therapy (1L Chemotherapy RWE Cohort 2).

The outcomes reported in each PSWA included OS, PFS and TTD (Table 17).

Table 17: Key Characteristics of Cohorts included in the PSWA

Study cohorts	Population	Intervention (Exposure)	Outcomes
DAB plus TRAM Cohort C (i.e., index trial, index cohort)			
BRF113928 Cohort C A single-arm, phase 2 clinical trial	Patients with Stage IV BRAF V600E-mutated NSCLC.	**1L DAB plus TRAM Cohort C** as first-line of therapy	OS PFS TTD
IPD from Flatiron database (i.e., RWE comparator cohorts)			
IPD from a real-world, retrospective cohort (the Flatiron EDM, database)	Matched population as the index cohort Unclear status of the BRAF V600-mutation subtype (V600E)	**1L PD(L)1 plus Chemotherapy RWE Cohort 1** Defined as carboplatin + pembrolizumab + pemetrexed as first-line of therapy	OS PFS TTD
		1L Chemotherapy RWE Cohort 2 Defined as platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) as first-line of therapy	OS PFS TTD

1L= first-line; DAB plus TRAM = dabrafenib plus trametinib; IPD = individual patient data; PD-1= Programmed cell death protein 1; PD-(L)1 = Programmed death ligand 1;; OS = Overall survival; PFS = progression free survival; RWE = real world evidence; TTD = Time to treatment discontinuation.

Source: CADTH Submission[13] Kanakamedala et al. poster, ISPOR 2020[80]

Selection Criteria and Selection Process

The prespecified selection criteria for the comparator RWE Cohorts 1 and 2 are presented in Table 18. To be selected from the Flatiron EDM database, patients had to fulfill the eligibility criteria from Cohort C of Study BRF113928 (i.e., the index trial/cohort). The criteria were applied to the Flatiron EDM following implementation of the data rules described in Table 18. Exclusion criteria for the RWE Cohorts 1 and 2 from the Flatiron database were the exclusion criteria from Study BRF113928 which are also listed in Table 18. In addition, patients from the Flatiron EDM database were also excluded from the PSWAs according to the following criteria:

- Received BRAF inhibitor therapies (i.e., dabrafenib, vemurafenib, encorafenib) or MEK inhibitor therapies (i.e., trametinib, cobimetinib, binimetinib) at any time.
- Received anti-cancer therapy within 14 days prior to the index date (explained below).
- Evidence of pregnancy at any time

Table 18: Inclusion/Exclusion Criteria for Selecting Patients from Flatiron EDM Database

Eligibility Criteria - Matched to Cohort C of Study BRF113928	
Progression data	Progression data were available.
Age	Aged ≥ 18 years at index date.
BRAF-mutation	Presence of a BRAF-mutation in lung cancer tissue. The BRAF mutation must have been known within 60 days after the index date or any time prior to the index date. (This 60-day rule was recommended by Flatiron in order to account for immortal time bias. There was incomplete data in Flatiron EDM on the sub-types of BRAF mutations. Therefore, the real-world cohorts of patients consisted of BRAF-mutated patients with or without V600E subtypes.)
ECOG performance status	ECOG status of 0-2 within 30 days prior to or 7 days after index date.[a] The closest test date to index date was considered for patients with multiple tests. (If there were two test dates (before and after index date) –equidistant to the index date, the test date occurring prior to the index date was considered. If multiple test results were observed on the test date that was closest to the index date, the result with a higher ECOG score was considered. Patients with a missing ECOG score during this timeframe were included in the study.)
Organ function	Adequate organ function at index date within 30 days prior to or 7 days after index date.[a] (Adequate organ function was defined as shown below. If patients had multiple results for the same test within this timeframe, the closest test date was chosen; similar logic detailed above for ECOG test selection was applied. Patients with missing laboratory test results during this timeframe were included. • Absolute neutrophil count ≥ 1.5 x 109/L • Hemoglobin ≥ 9 g/dL • Platelet count ≥ 100 × 109/L • Prothrombin time/INR ≥ 1.5 × ULN • Total bilirubin ≤ 1.5 × ULN • Alanine amino transferase (ALT) ≤ 2.5 × ULN • Serum creatinine ≤ 1.5mg/dL or creatinine clearance ≥ 50 mL/min
NSCLC diagnosis date	At least one visit within 90 days after metastatic NSCLC diagnosis date.
Exclusion Criteria from Cohort C of Study BRF113928	
• Patients who received BRAF-inhibitor therapies (dabrafenib, vemurafenib, encorafenib) or mitogen activated protein kinase kinase (MEK) inhibitor therapies (trametinib, cobimetinib, binimetinib) at any time.	
• Received anti-cancer therapy within 14 days prior to the index date.	

Eligibility Criteria - Matched to Cohort C of Study BRF113928
• Evidence of pregnancy at any time

ALT = alanine amino transferase; BRAF = v-Raf murine sarcoma viral oncogene homolog B; ECOG = Eastern Cooperative Oncology Group; INR = international normalized ratio; MEK = mitogen-activated protein kinase kinase enzymes; NSCLC = non-small cell lung cancer; ULN = upper limit of normal.
[a] Index date was the start date of the index cohort (i.e. BRF113928 trial - Cohort C)
Source: CADTH Submission[13]

The start date of the 1L DAB plus TRAM Cohort C was considered the index date. All clinical trial data were retrieved from the Study BRF113928 (Cohort C) database hosted on the Novartis server (cut-off date: June 22, 2019). All comparator real-world data for RWE Cohorts 1 and 2 were retrieved from the Flatiron EDM for the period from January 1, 2011 to February 29, 2020.[13,80]

No explicit power calculation was planned or performed for the PSWA. Before weighting, 36, 34 and 64 patients were included in the 1L DAB plus TRAM Cohort C, 1L PD(L)1 plus Chemotherapy RWE Cohort 1, and 1L Chemotherapy RWE Cohort 2, respectively; after weighting, the sample sizes were 36, 28, and 37, respectively.[13,80]

Patient characteristics and demographics at baseline were collected for the 1L DAB plus TRAM Cohort C and the comparator cohorts (RWE Cohort 1 and RWE Cohort 2) and these were assessed pre- and post- patient selecting (Table 19).

Table 19: Key Characteristics used for Selecting Patients from the Flatiron EDM Database in the PSWA

Sex (n, %)	Male, female
Age group at index (n, %)	• 18 – 44 • 45 – 54 • 55 – 64 • 65 – 74 • 75 and older
Race (n, %)	• White • Black or African America • Asian • Other
ECOG status (n, %)	0, 1, 2, missing
Cancer stage at initial diagnosis (n, %)	Only available in Flatiron database and was reported for real-world cohort C. (Stage I, Stage II, Stage III, Stage IV)
Cancer stage at index date (n, %)	Only available in BRF113928 trial (Cohort C) and was reported for BRF113928 trial cohort C. (stage III, stage IV)
Smoking status	Former or current smoker, non-smoker

ECOG = Eastern Cooperative Oncology Group; PSWA = propensity score weighted analysis
Source: CADTH Submission[13]

The attrition of patients assigned to the RWE Cohorts 1 and 2 are presented in Table 20. Of the 61,094 patients in the Flatiron EDM database, 2,366 patients (4%) started with 1L PD(L)1 plus Chemotherapy (RWE Cohort 1); 59 of these patients (2%) had evidence of a positive BRAF mutation; and a total of 34 patients met the remaining criteria and were included in the pre-weighted 1L PD(L)1 plus Chemotherapy RWE Cohort 1. Of the 61,094 patients in the Flatiron EDM database, 16,181 patients (26%) started with 1L

Chemotherapy (RWE Cohort 2); 165 of these patients (1%) had evidence of a positive BRAF mutation; and a total of 64 patients met the remaining criteria and were included in the pre-weighted 1L Chemotherapy RWE Cohort 2.

Table 20: Attrition from Real-World Cohorts 1 and 2

Inclusion and Exclusion Criteria	1L PD(L)1 plus Chemotherapy RWE Cohort 1	1L Chemotherapy RWE Cohort 2
Inclusion		
Total N in Flatiron database, n (%)	61,094	61,094
Initiated selected regimens: Index date is the start date of the treatment, n (%)	2,366 (4)	16,181 (26)
Evidence of positive BRAF mutation, n (%)	59 (2)	165 (1)
BRAF test result was within 60 days of chemotherapy start date, n (%)	54 (92)	110 (67%)
Eligible for progression analysis, n (%)	54 (100)	110 (100)
Age ≥ 18 at index, n (%)	54 (100)	110 (100)
ECOG=0,1 or 2 within 30 days prior to index or 7 days after index date, n (%)	53 (98)	109 (99)
With adequate organ function 30 days prior to and 7 days after index date (satisfy all criterion below). Patients with a missing test result are assumed to have had a normal result, n (%)[b]	38 (72)	67 (61)
At least one visit within 90 days after metastatic NSCLC diagnosis date, n (%)	38 (100)	67 (100)
Exclusion		
Had BRAF-inhibitor or MEK inhibitors any time in the database, n (%)	35 (92)	64 (96)
Had EGFR mutation or ALK re-arrangement test with a positive result but did not utilize EGFR/ALK inhibitor; patients with a negative result are not excluded, n (%)	35 (100)	64 (100)
Had evidence of pregnancy at any time in the database, n (%)	35 (100)	64 (100)
Had patient with negative follow up in PFS and OS analysis, n (%)	34 (97)	64 (100)

ALT = Alanine amino transferase; BRAF = v-Raf murine sarcoma viral oncogene homolog B; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; MEK = mitogen-activated protein kinase; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; RWE = real-world evidence; 1L PD(L)1 plus chemotherapy RWE Cohort 1 = first-line "pembrolizumab + carboplatin +pemetrexed" combination therapy; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide);

[a.] Percentage of patients from previous step.

[b.] Absolute neutrophil count ≥ 1.5 x 109/L; Hemoglobin ≥ 9 g/dL; Platelet count ≥ 100 x 109/L; Prothrombin time/INR ≥ 1.5 x ULN; Total bilirubin ≤ 1.5 x ULN; ALT ≤ 2.5 x ULN; Serum creatinine ≤ 1.5mg/dL or creatinine clearance ≥ 50 mL/min).

Source: CADTH Submission[13]

Propensity Score Development

A weighting by inverse odds methodology was used to balance observable baseline prognostic characteristics between the 1L DAB plus TRAM Cohort C and the RWE Cohorts 1 and 2 according to the methods by Li et al 2018[84] and Westreich et al 2017.[85] The odds were computed through a propensity score model, which estimated the log odds of being in the 1L DAB plus TRAM Cohort C versus RWE Cohorts 1 and 2, conditional on covariates that were considered. The propensity scores were applied in the statistical analysis for estimating treatment effect by weight.[13] The covariates considered for deriving the weighted real-world populations are presented in. To assess covariate balance, the distributions of baseline covariates along with standardized mean difference (SMD) pre- and post-weighting were summarized. A SMD of less than 0.25 was considered as balanced. In addition, propensity score and weight distribution plots were reported to assess model fit and stability.

Table 21: Covariates Considered for the Propensity Score Model

Propensity score model covariates	
1	Age group
2	Gender
3	ECOG score [a]
4	History of smoking
5	Race

[a] All patients from the DAB+TRAM cohort had ECOG score. Missing ECOG scores in two comparator cohorts was inputted as ECOG 1
Source: CADTH Submission[13]

Statistical Methods of PSWA

A KM analysis was used to estimate and compare the OS and PFS between 1L DAB plus TRAM Cohort C and RWE Cohorts 1 and 2. The median OS and PFS, and 95% CIs were reported. Statistical differences in in OS and PFS between the 1L DAB plus TRAM Cohort C and RWE Cohorts 1 and 2 were examined using p-values from an adjusted log-rank test. A Cox PH model was fit for PFS and OS to estimate the HR for death and progression in 1L DAB plus TRAM Cohort C versus 1L PD(L)1 plus Chemotherapy RWE Cohort 1 and versus 1L Chemotherapy RWE Cohort 2. A KM analysis was also used to estimate TTD. The PH assumption was assessed by testing the significance of time dependent covariates, Kolmogorov-type supremum proportional test, and graphical check.[13,80]

Results of the PSWA

Patient Characteristics

Pre-weighted and post-weighted patient characteristics are presented in Table 22.

After weighting, there was a higher percentage of females in the 1L DAB plus TRAM Cohort C compared to the 1L PD(L)1 plus Chemotherapy RWE Cohort 1 and the 1L Chemotherapy RWE Cohort 2 (61% vs. 45% and 58%, respectively). The mean age of patients was 67.8 years (range from 44 to 91) in the 1L DAB plus TRAM Cohort C; 68 years (range from 46 to 83) in the 1L PD(L)1 plus Chemotherapy RWE Cohort 1, and 68 years (range from 47 to 82) in the 1L Chemotherapy RWE Cohort 2.[13,80] The majority of patients were white (83% vs. 85% and 86%) and were former or current smokers (72% vs. 90% and 70%). Most patients had an ECOG PS of 1 at baseline (61% vs. 58% and 60%) and had stage IV cancer at the index date (97% vs. 100% and 100%). The distributions of other characteristics were generally similar to the pre-weighted population (Table 22).[13,80]

Table 22: Baseline Characteristics of Included Cohorts in PSWA

Parameter	1L Dabrafenib + trametinib trial cohort	1L chemotherapy RW cohort		1L PD(L)1 + chemotherapy RW cohort	
		Pre-weighting	Post-weighting	Pre-weighting	Post-weighting
Sample size	**N=36**	**N=64**	**N=37**	**N=34**	**N=27.8**
Sex (%)					
Female	61.1	54.7	57.5	41.2	45.1
Male	38.9	45.3	42.5	58.8	54.9
Age at index					
Mean (SD)	67.8 (11.0)	66.5 (9.1)	68.0 (7.0)	69.4 (8.1)	68.0 (8.0)
Age group at index (%)					
Under 54	8.3	6.3	8.8	2.9	6.6
55 to 64	30.6	42.2	25.9	23.5	21.8
>=65	61.1	51.6	65.3	73.6	71.6
Race (%)					
White	83.3	76.6	85.5	79.4	84.5
Other	16.7	23.5	14.5	20.6	15.5
ECOG at Baseline (%)					
0	36.1	25.0	37.1	29.4	38.4
1	61.1	64.1	59.9	47.1	58.3
2	2.8	10.9	2.9	23.5	3.2
Stage at initial diagnosis (%)					
I	NA	7.8	7.8	8.8	11.5
II	NA	7.8	8.3	2.9	0.5
III	NA	26.6	19.8	2.9	2.5
IV	NA	56.3	63.5	82.4	79.7
Missing	100	1.6	0.7	2.9	5.7

ECOG = Eastern Cooperative Oncology Group; PD(L)1= Programmed cell death protein (ligand) 1; OS = overall survival; PFS = progression-free survival; RW = real world; SD = standard deviation; 1L DAB +TRAM = first-line dabrafenib plus trametinib; 1L PD(L)1 plus Chemotherapy RW Cohort = first-line “pembrolizumab+ carboplatin +pemetrexed" combination therapy RW Cohort; 1L Chemotherapy RW Cohort = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) RW Cohort.

Source: Kanakamedala et al. poster, ISPOR 2020[80]

Efficacy Outcomes

Pre-weighted and post-weighted efficacy results are presented in Table 23, Table 24, Figure 2, Figure 3, Figure 4, and Figure 5 below.

Overall Survival

1L DAB plus TRAM Cohort C versus 1L PD(L)1 plus Chemotherapy RWE Cohort 1:

After weighting, the PSWA results showed that there was no statistically significant difference in OS when 1L DAB plus TRAM Cohort C was compared with the 1L PD(L)1 plus Chemotherapy RWE Cohort 1 (HR =0.57; 95% CI, 0.28 to 1.17; p=0.13); The median OS was 17.3 months (95% CI,14.6 to NR) in 1L DAB plus TRAM Cohort C versus 18.0 months (95% CI, 5.1 to not reached) in the 1L PD(L)1 plus Chemotherapy RWE Cohort 1. The difference in median OS was not statistically significant for the comparison of 1L DAB plus TRAM Cohort C versus first-line PD(L)1 plus Chemotherapy RWE Cohort 1 (p=0.15).

1L DAB plus TRAM Cohort C versus 1L Chemotherapy RWE Cohort 2:

After weighting, when compared to the 1L Chemotherapy RWE Cohort 2, the HR for death was statistically significant in favour of the 1L DAB+ plus TRAM Cohort C (HR = 0.51; 95% CI, 0.29 to 0.92; p=0.03). The median OS was 9.7 months (95% CI, 6.4 to 19.6) in the 1L Chemotherapy RWE Cohort 2. The difference in median OS was statistically significant for the comparison of 1L DAB+ plus TRAM Cohort C versus 1L Chemotherapy RWE Cohort 2 p=0.01).

Table 23: Cox Proportional Hazard Model of Treatment Effect for PFS and OS

Treatment Effect	Pre-weighted		Post-weighted	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
1L DAB + TRAM Cohort C versus 1L PD(L)1 plus Chemotherapy RWE Cohort 1				
PFS	0.94 (0.53, 1.68)[a]	0.84[a]	0.96 (0.51, 1.81)[a]	0.90[a]
OS	0.56 (0.29, 1.1)	0.09	0.57 (0.28, 1.17)	0.13
1L DAB + TRAM Cohort C versus 1L Chemotherapy RWE Cohort 2				
PFS	0.75 (0.48, 1.18) [b]	0.22[b]	0.58 (0.35, 0.97) [a]	0.04[a]
OS	0.65 (0.39, 1.1)	0.11	0.51 (0.29, 0.92)	0.03

CI = confidence interval; HR – hazard ratio; OS = overall survival; PD(L)1= Programmed cell death protein (ligand) 1; PFS = progression-free survival; RWE = real-world evidence;1L DAB +TRAM Cohort C= first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 plus Chemotherapy RWE Cohort 1 = first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy RWE Cohort 1; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) Cohort 2.

[a] The PFS results did not violate proportional hazards assumption based on statistical tests but cross over was observed based on visual inspection of the curves.

[b] The results violated this assumption and should not be considered.

Source: CADTH Submission[13] Kanakamedala et al. poster, ISPOR 2020[80]

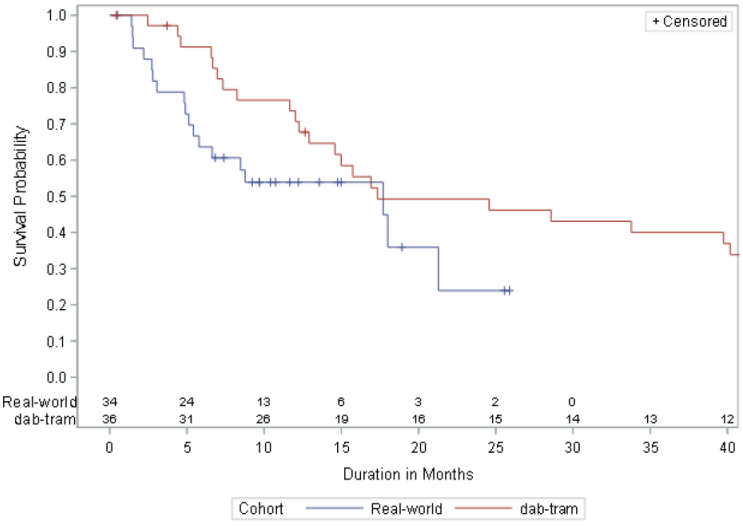
Table 24: Pre-weighted (unadjusted) and Post-weighted (adjusted) Median OS

	1L DAB+TRAM Cohort C		1L PD(L)1 plus Chemotherapy RWE Cohort 1		1L Chemotherapy RWE Cohort 2	
	Pre-weighted (unadjusted)	Post-weighted (adjusted)	Pre-weighted (unadjusted)	Post-weighted (adjusted)	Pre-weighted (unadjusted)	Post-weighted (adjusted)
Total number of patients	36	36	34	27.8	64	36.9
Kaplan-Meier statistics (months)						
Median (95% CI)	17.3 (12.3, 40.2)	17.3 (14.6, NR)	17.7 (5.4, 21.3)	18.0 (5.1, NR)	14.5 (9.2, 19.6)	9.7 (6.4, 19.6)
P value			*DAB+TRAM Cohort C vs. 1L PD(L)1 + Chemotherapy RWE Cohort 1* 0.09	*DAB+TRAM Cohort C vs. 1L PD(L)1 + Chemotherapy RWE Cohort 1* 0.15	*DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2* 0.11	*DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2* 0.01
Mean (SE)	24.0 (2.6)	24.0 (2.6)	12.9 (1.5)	13.1 (1.9)	22.2 (2.9)	18.5 (3.1)

CI = confidence interval; NR = not reached; OS = overall survival; PD(L)1= Programmed cell death protein (ligand) 1; RWE = real-world evidence; SE = standard error; 1L DAB +TRAM Cohort C= first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 plus Chemotherapy RWE Cohort 1= first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy Cohort 1; 1L Chemotherapy RWE Cohort 2= first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) RWE Cohort 2.

Source: CADTH Submission[13] Kanakamedala et al. poster, ISPOR 2020[80]

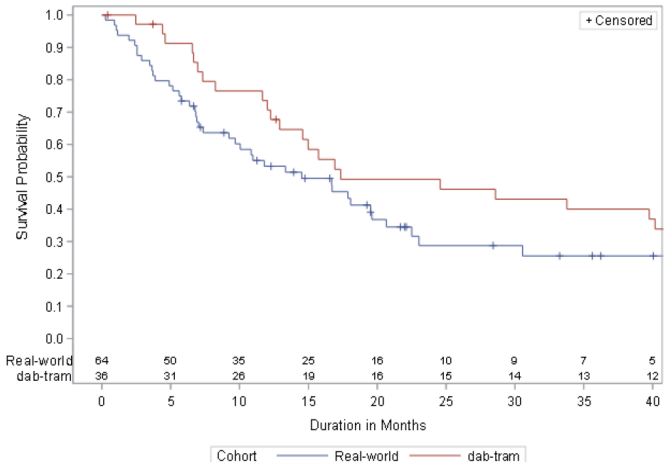
Figure 2: Pre-weighted (unadjusted) KM Curves of OS for 1L DAB+TRAM Cohort C vs. 1L PD(L)1 plus Chemotherapy RWE Cohort 1



KM – Kaplan Meier; OS = overall survival; PD(L)1= Programmed cell death protein (ligand) 1; RWE = real world evidence; 1L DAB +TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 plus Chemotherapy RWE Cohort 1= first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy RWE Cohort 1.

Source: CADTH submission[13]

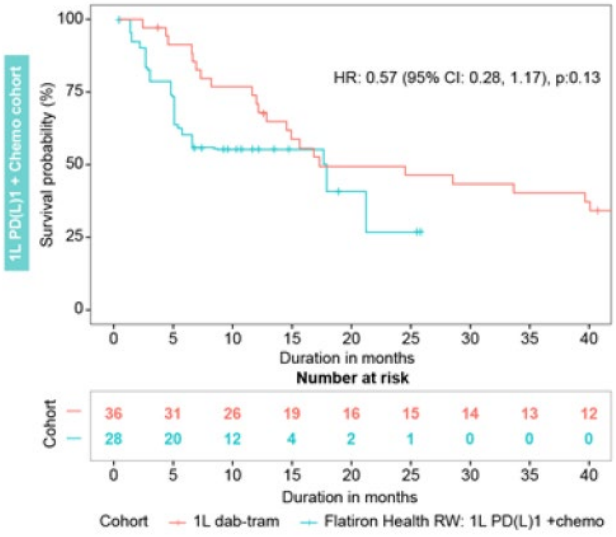
Figure 3: Pre-weighted (unadjusted) KM Curves of OS for 1L DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2



KM – Kaplan Meier; OS = overall survival; RWE = real-world evidence; 1L DAB +TRAM Cohort C= first-line dabrafenib plus trametinib Cohort C; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) Cohort 2.

Source: CADTH submission[13]

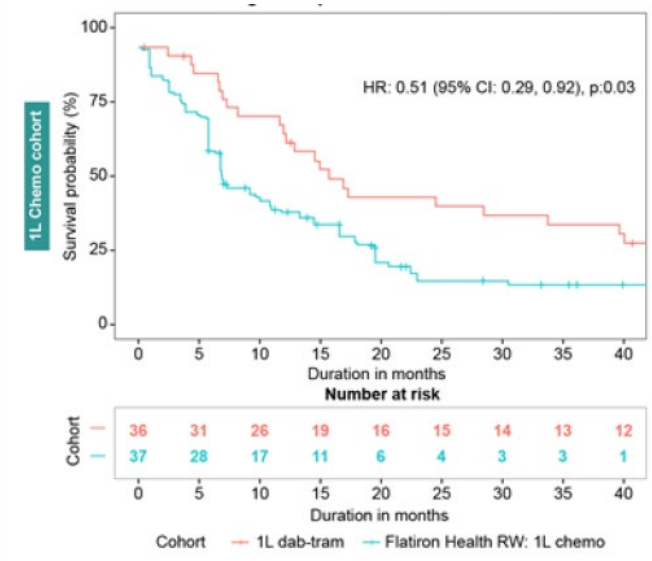
Figure 4: Post weighted (adjusted) KM Curves of OS (post weighted) for 1L DAB+TRAM Cohort C vs. 1L PD(L)1 plus Chemotherapy RWE Cohort 1



KM = Kaplan Meier; OS = overall survival; PD(L)1= Programmed cell death protein (ligand) 1; RWE = real-world evidence; 1L DAB +TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 plus Chemotherapy RWE Cohort 1 = first-line “pembrolizumab+ carboplatin +pemetrexed" combination therapy Cohort 1.

Source: Kanakamedala et al. poster, ISPOR 2020[80]

Figure 5: Post-weighted (adjusted) KM Curves of OS for 1L DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2



OS = overall survival; RWE – real-world evidence; 1L DAB +TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) Cohort 2.

Source: Kanakamedala et al. poster, ISPOR 2020[80]

Progression Free Survival

Pre-weighted and post-weighted PFS results are presented in Table 23, Table 25, Figure 6, Figure 7, Figure 8 and Figure 9.

1L DAB plus TRAM Cohort C versus 1L PD(L)1 plus Chemotherapy RWE Cohort 1:

After weighting, the PSWA results showed there was no statistically significant difference in PFS when 1L DAB plus TRAM Cohort C was compared with the 1L PD(L)1 plus Chemotherapy RWE Cohort 1 (HR = 0.96; 95% CI, 0.51 to 1.81; p=0.90). The authors indicated that the results for the 1L PD(L)1 plus Chemotherapy RWE Cohort 1 did not violate the PH assumption; however, crossover was observed on visual inspection of the curves; therefore, these results should be interpreted with caution.

After weighting, the median PFS was 10.2 months (95% CI, 7.0 to 14.5) in the 1L DAB plus TRAM Cohort C versus 11.3 months (95% CI, 3.7 to not reached) in the 1L PD(L)1 plus Chemotherapy RWE Cohort 1. The difference in median PFS was not statistically significant for 1L PD(L)1 plus Chemotherapy RWE Cohort 1 versus 1L DAB plus TRAM Cohort C (p=0.91).

1L DAB plus TRAM Cohort C versus 1L Chemotherapy RWE Cohort 2:

After weighting, when compared to the 1L Chemotherapy RWE Cohort 2, the HR for progression or death was statistically significant in favour of 1L DAB plus TRAM Cohort C (HR = 0.58; 95% CI, 0.35 to 0.97; p=0.04). The authors indicated that the results for 1L Chemotherapy RWE Cohort 2 did not violate the PH assumption; however, crossover was observed on visual inspection of the curves; therefore, these results should be interpreted with caution.

After weighting, the median PFS was 10.2 months (95% CI, 7.0 to 14.5) in 1L DAB plus TRAM Cohort C while the median PFS was 4.2 months (95% CI: 3.0 to 5.8) in 1L Chemotherapy RWE Cohort 2. The difference in PFS was statistically significant for the comparison of 1L DAB plus TRAM Cohort C versus 1L Chemotherapy RWE Cohort 2 (p=0.03).

Table 25: Pre-weighted (unadjusted) and Post-weighted (adjusted) PFS

	DAB+TRAM Cohort C		1L PD(L)1 plus Chemotherapy RWE Cohort 1		1L Chemotherapy RWE Cohort 2	
	Pre-weighted (unadjusted)	Post-weighted (adjusted)	Pre-weighted (unadjusted)	Post-weighted (adjusted)	Pre-weighted (unadjusted)	Post-weighted (adjusted)
Total number of patients	36	36	34	27.8	64	36.9
Kaplan-Meier statistics (months)						
Median (CI)	10.2 (5.5, 13.8)	10.2 (7.0, 14.5)	5.4 (3.7, 18.0)	11.3 (3.7, NR)	4.5 (3.5, 5.8)	4.2 (3.0, 5.8)
P value			*DAB+TRAM Cohort C vs. 1L PD(L)1 + Chemotherapy RWE Cohort 1* 0.84	*DAB+TRAM Cohort C vs. 1L PD(L)1 + Chemotherapy RWE Cohort* 0.91	*DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2* 0.22	*DAB+TRAM Cohort C vs. 1L Chemo RWE Cohort 2* 0.03
Mean (SE)	11.5 (1.5)	11.5 (1.5)	9.5 (1.3)	9.7 (1.6)	13.6 (2.6)	10.4 (2.8)

CI = confidence interval; NR = not reached; PD(L)1= Programmed cell death protein (ligand) 1; PFS = progression-free survival; SE = standard error; RWE = real-world evidence; 1L DAB +TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C;1L PD(L)1 plus Chemotherapy RWE Cohort 1 = first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy RWE Cohort 1; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) RWE Cohort 2.

Source CADTH submission[13,80]

Figure 6: Pre-weighted (unadjusted) KM Curves of PFS for 1L DAB+TRAM Cohort C vs. 1L PD(L)1 plus Chemotherapy RWE Cohort 1

KM – Kaplan Meier; PFS = progression free survival; RWE = real world evidence; 1L DAB +TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 plus Chemotherapy RWE Cohort 1 = first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy RWE Cohort 1;

Source CADTH Submission[13]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

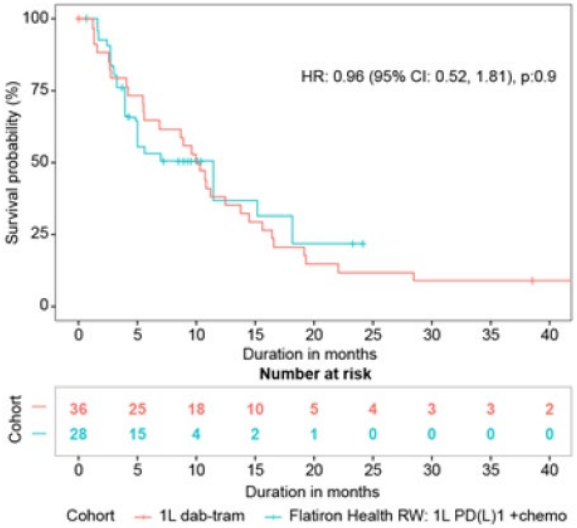
Figure 7: Pre-weighted (unadjusted) KM Curves of PFS for 1L DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2

KM = Kaplan Meier; PFS = progression free survival; RWE = real-world evidence; 1L DAB +TRAM Cohort C = dabrafenib plus trametinib Cohort C; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide).

Source: CADTH Submission[13]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

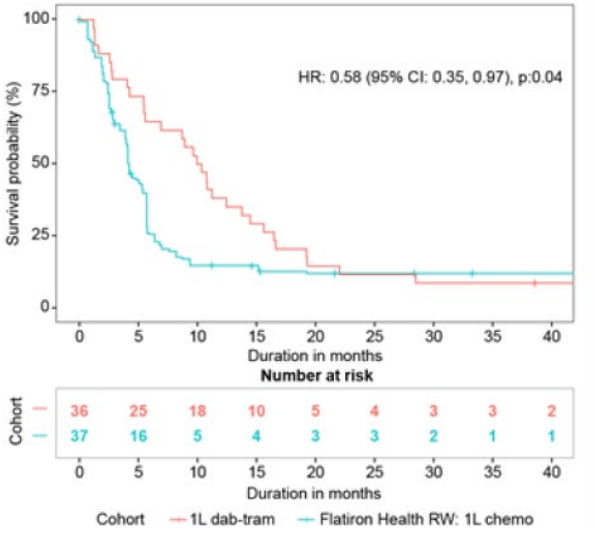
Figure 8: Post-weighted (adjusted) KM Curves of PFS for 1L DAB+TRAM Cohort C vs. 1L PD(L)1 plus Chemotherapy RWE Cohort 1



KM = Kaplan Meier; PD(L)1= Programmed cell death protein (ligand) 1; PFS = progression-free survival; RWE – real-world evidence; 1L DAB plus TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 plus chemo RWE cohort 1 = first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy; =;

Source: Kanakamedala et al. poster, ISPOR 2020[80]

Figure 9: Post-weighted (adjusted) KM Curves of PFS for 1L DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2



KM = Kaplan Meier; PFS = progression-free survival; RWE – real-world evidence; 1L DAB plus TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) RWE Cohort 2.

Source: Kanakamedala et al. poster, ISPOR 2020[80]

Time to Treatment Discontinuation

The pre-weighted median TTD results are presented in Table 26, Figure 10 and Figure 11.

[redacted]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

No post-weighted assessments for TTD were planned or performed in the PSWA; and no rationale was provided in the PSWA report for why only pre-weighted TTD results were reported.[13]

Table 26: Pre-weighted (unadjusted) Estimated TTD

	1L DAB+TRAM Cohort C	1L PD(L)1 plus Chemotherapy RWE Cohort 1	P-Value	1L Chemotherapy RWE Cohort 2	P-Value
Total number of patients					
Kaplan-Meier statistics (months)					
Median (CI)					
Mean (SE)					

CI = confidence interval; NR = not reached; PD(L)1= Programmed cell death protein (ligand) 1; PFS = progression-free survival; RWE = real-world evidence; SE = standard error; TTD = time to treatment discontinuation; 1L DAB +TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 + Chemotherapy RWE Cohort 1 = first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy Cohort 1; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) Cohort 2.

Source: CADTH Submission[13]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Figure 10: Pre-weighed (unadjusted) KM Curves of TTD for 1L DAB+TRAM Cohort C vs. 1L PD(L)1 plus Chemotherapy RWE Cohort 1

TTD = time to treatment discontinuation; PD(L)1= Programmed cell death protein (ligand) 1; RWE = real-world evidence; 1L DAB+TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L PD(L)1 plus Chemotherapy RWE Cohort 1 = first-line "pembrolizumab+ carboplatin +pemetrexed" combination therapy Cohort 1,;.

Source: CADTH Submission[13]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Figure 11: Pre-weighted (unadjusted) KM Curves of TTD for 1L DAB+TRAM Cohort C vs. 1L Chemotherapy RWE Cohort 2

TTD = time to treatment discontinuation; RWE = real-world evidence; 1L DAB+TRAM Cohort C = first-line dabrafenib plus trametinib Cohort C; 1L Chemotherapy RWE Cohort 2 = first-line platinum-based chemotherapy (carboplatin + pemetrexed; carboplatin + paclitaxel; carboplatin + nab-paclitaxel [protein-bound]; cisplatin + pemetrexed; or cisplatin + etoposide) RWE Cohort 2.

Source: CADTH submission[13]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Critical Appraisal of the Sponsor-submitted PSWA

Although the methods on the propensity score model, calculation, and application in the statistical analysis were well described, the CADTH Methods Team identified several limitations that potentially limit the interpretation of the results of the PSWA.

Not all inclusion and exclusion criteria of the 1L DAB+TRAM Cohort C index cohort were feasible to apply to the RWE Cohorts (Flatiron EDM data). Certain prognostic factors captured in the 1L DAB+TRAM Cohort C, – such as presence of brain metastasis, were not feasible for inclusion in both RWE Cohorts in the PSWA analysis since the Flatiron EDM database did not capture such data. In addition, all patients in the 1L DAB+TRAM Cohort C had a BRAF V600E-mutationwhile the RWE Cohorts had a BRAF mutation with or without V600E. It is uncertain how these potential differences may impact the PSWA results.

In the RWE Cohorts, there were a proportion of patients with missing ECOG values who were included in the analysis. Patients with missing ECOG status at baseline were imputed with a value of 1, which could have biased the results. For example, if patients in the RWE Cohorts had an ECOG greater than 2 but their data were missing, these patients would be considered more unwell than those patients in the 1L DAB+TRAM Cohort C, which would bias the results in favour of dabrafenib plus trametinib treatment. Conversely, the patients included in the 1L DAB+TRAM Cohort C all had stage 4 disease, while the patients in the RWE Cohorts were stages 1 to 4. In this case, results may be biased against dabrafenib plus trametinib treatment.

The RWE Cohorts came from a real-world database (Flatiron EDM) and the 1L DAB+TRAM Cohort C was from a phase 2 single arm trial (Study BRF113928 - Cohort C); therefore, the propensity score method may not address differences related to the conditions under which the data were collected (i.e., a highly controlled clinical trial setting versus a routine healthcare setting). Furthermore, in the RWE Cohorts, the progression data were obtained from the EHR of patients. Progression events were defined as distinct episodes in which the clinician concluded that there had been growth or worsening in the disease of interest. While these episodes were clinically meaningful, the data collected were conceptually different from that in the phase 2 trial, in which progression data (i.e., tumour response by imaging) were evaluated at scheduled timepoints and based on objective RECIST criteria. This difference in definitions of disease progression between the index cohort and the RWE cohorts could impact the results of PFS, although the direction of any bias would be unclear.

No explicit power calculation was planned or performed for the PSWA. The sample sizes in the index cohort and the RWE Cohorts were relatively small, therefore the uncertainty in the estimates (i.e., wide confidence intervals) is presumably related to the sample sizes. In addition, some statistics showed violation of the PH assumption or no PH violation existed but crossing of the curves was observed by visual inspection. Altogether, it is challenging to interpret the statistical significance of the results reported in the PSWA considering these violations and observations.

There also may be inherent limitations of non-interventional real-world data (i.e., Flatiron EDM database). The comparator cohort dataset may have missing, inaccurately entered, or incomplete data, although quality assurance and quality control activities were taken to reduce data issues and increase completeness.

There was no post-weighted analysis for TTD and therefore the pre-weighed results of TTD should be interpreted with caution.

No evidence was identified that compared dabrafenib plus trametinib to pembrolizumab monotherapy, which is also a SOC treatment for some patients with previously untreated BRAF-mutated advanced NSCLC.

7.1.3 Summary

Due to a lack of direct evidence comparing dabrafenib and trametinib combination therapy to other existing treatments for patients with previously untreated BRAF-mutated advanced NSCLC, the sponsor conducted an ITC to estimate the comparative efficacy of dabrafenib and trametinib to relevant comparators for the treatment of patients with previously untreated BRAF-mutated advanced NSCLC. A PSWA was conducted that used data from Cohort C of Study BRF113928 (index trial) of first-line dabrafenib and trametinib and RWE obtained from the Flatiron EDM database.

Two RWE Cohorts were derived from the Flatiron EDM database: RWE Cohort 1 included first-line PD(L)1 plus chemotherapy regimens (i.e., pembrolizumab plus platinum doublet chemotherapy) and RWE Cohort 2 included first-line chemotherapy regimens (i.e., platinum-based chemotherapy). After adjusting for differences in baseline characteristics between Cohort C from Study BRF113928 and the RWE Cohorts, the PSWA results showed that the HR for OS favoured dabrafenib and trametinib over first-line platinum-based chemotherapy (HR=0.51; 95% CI, 0.29 to 0.92; p=0.03); and for the comparison of dabrafenib and trametinib versus first-line pembrolizumab plus platinum-doublet chemotherapy, the HR for OS was not statistically significant (HR=0.57; 95% CI, 0.28 to 1.17, p=0.13).

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

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

8 Comparison with Other Literature

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

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Lung Cancer Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on dabrafenib (Tafinlar®) in combination with trametinib (Mekinist®) in previously untreated patients with metastatic NSCLC with a BRAF V600 mutation. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH 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 Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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.

Appendix 1: Literature Search Strategy and Detailed Methodology

Literature Search Methods

1. Literature search via Ovid platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2020, Embase 1974 to 2020 November 02, Ovid MEDLINE(R) ALL 1946 to November 02, 2020
Search Strategy:

#	Searches	Results
1	(dabrafenib* or tafinlar* or gsk 2118436 or gsk2118436 or gsk 2118436a or gsk2118436a or gsk 2118436b or gsk2118436b or QGP4HA4G1B or B6DC89I63E).ti,ab,ot,kf,kw,hw,nm,rn.	6226
2	(trametinib* or mekinist* or gsk 1120212 or gsk1120212 or gsk 1120212b or gsk1120212b or jtp 74057 or jtp74057 or 33E86K87QN or BSB9VJ5TUT).ti,ab,ot,kf,kw,hw,nm,rn.	7179
3	1 and 2	4060
4	(DABRATRAM* or DABR TRAM* or DAB TRAM*).ti,ab,ot,kf,kw,hw,nm,rn.	27
5	3 or 4	4061
6	exp Adenocarcinoma of Lung/	48837
7	Carcinoma, Non-Small-Cell Lung/	82903
8	(exp Lung/ or exp Lung neoplasms/) and (Carcinoma, Large Cell/ or Adenocarcinoma/)	53533
9	(NSCLC* or LCLC* or mNSCLC* or mLCLC*).ti,ab,kf,kw.	140821
10	((non small cell* or nonsmall cell* or large cell or undifferentiated) adj5 (lung* or bronch* or pulmonar*) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplas*)).ti,ab,kf,kw.	193241
11	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kf,kw.	57012
12	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplas* or tumor* or tumour*)).ti,ab,kf,kw.	3696
13	or/6-12	303163
14	5 and 13	433
15	14 use medall	61
16	limit 15 to english language	60
17	14 use cctr	11
18	*dabrafenib/ or (dabrafenib* or tafinlar* or gsk 2118436 or gsk2118436 or gsk 2118436a or gsk2118436a or gsk 2118436b or gsk2118436b).ti,ab,kw,dq.	3716
19	*trametinib/ or (trametinib* or mekinist* or gsk 1120212 or gsk1120212 or gsk 1120212b or gsk1120212b or jtp 74057 or jtp74057).ti,ab,kw,dq.	4349
20	18 and 19	2259
21	(DABRATRAM* or DABR TRAM* or DAB TRAM*).ti,ab,kw,dq.	27
22	20 or 21	2260
23	Non small cell lung cancer/ or Large cell lung carcinoma/ or Lung adenocarcinoma/	163543
24	(NSCLC* or LCLC* or mNSCLC* or mLCLC*).ti,ab,kw,dq.	140615
25	((non small* cell or nonsmall cell* or large cell or undifferentiated) adj5 (lung* or bronch* or pulmonar*) adj5 (cancer* or tumor* or tumour* or carcinoma* or neoplas*)).ti,ab,kw,dq.	192287
26	((bronchial or pulmonary or lung) adj3 (adenocarcinoma* or adeno-carcinoma*)).ti,ab,kw,dq.	57179
27	((bronchioloalveolar or bronchiolo alveolar) adj3 (carcinoma* or cancer* or neoplas* or tumor* or tumour*)).ti,ab,kw,dq.	3687
28	or/23-27	284448
29	22 and 28	215
30	29 use oemezd	149
31	limit 30 to english language	147

32	31 not conference abstract.pt.	76
33	16 or 17 or 32	147
34	remove duplicates from 33	93
35	31 and conference abstract.pt.	71
36	limit 35 to yr="2015 -Current"	66
37	34 or 36	164

2. Cochrane Central Register of Controlled Trials (CENTRAL)
(searched via Ovid)

3. Grey literature search via:

Clinical trials registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

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

Health Canada's Clinical Trials Database
https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trials Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: dabrafenib+trametinib, non-small cell lung cancer

Select international agencies including:

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

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

Search: dabrafenib+trametinib, non-small cell lung cancer

Conference abstracts:

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

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

Search: dabrafenib+trametinib, non-small cell lung cancer-last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[86]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. 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 February 18, 2021.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[87] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trials registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the European Clinical Trials Registry), 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. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. Additional limitations and sources of bias were identified by the CADTH Review Team.

Data Analysis

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

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

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

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