CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Tepotinib (Tepmetko)

Indication: For the treatment of adult patients with locally advanced unresectable metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) tyrosine kinase receptor exon 14 skipping alterations.

Sponsor: EMD Serono Canada, a division of EMD Inc.

Recommendation: Do Not Reimburse

Version:	1.0
Publication Date:	March 2022
Report Length:	12 Pages

Single Technology

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines*.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TEPOTINIB (TEPMETKO — EMD SERONO CANADA)

Therapeutic Area: Locally advanced or metastatic non-small cell lung cancer

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that tepotinib not be reimbursed for the treatment of adult patients with locally advanced unresectable or metastatic NSCLC harbouring *MET* tyrosine kinase receptor exon 14 skipping alterations.

Rationale for the Recommendation

One phase II, open-label study (VISION; N=151 in pivotal Cohort A), evaluated the efficacy and safety of tepotinib in adult patients with locally advanced or metastatic NSCLC harbouring a *MET*ex14 skipping mutation; however, whether treatment with tepotinib results in added clinical benefit versus any relevant treatment comparators is unknown due to the single-arm design of this descriptive study and the complete lack of statistical testing. Further, pERC noted the uncertainty regarding the HRQoL data from the VISION trial due to decreased sample sizes at later treatment cycles, open-label administration of tepotinib, and absence of a comparator arm. As a result, the effect of tepotinib on HRQoL remains unknown. Indirect evidence submitted by the sponsor that compared the VISION Cohort A to patients treated with other available therapies were limited by important methodological issues and several sources of bias that precluded pERC from concluding that treatment with tepotinib resulted in added clinical benefit in progression-free survival (PFS) or overall survival (OS) relative to chemotherapy or immunotherapy. Additionally, tepotinib was not compared to a combination of chemotherapy and immunotherapy, and there was no comparative evidence on health-related quality of life or harms. Given the totality of the evidence, pERC concluded there is a high degree of uncertainty regarding the clinical significance of the treatment benefit with tepotinib in patients with locally advanced or metastatic NSCLC harbouring a *MET*ex14 skipping mutation relative to standard of care therapies for NSCLC.

Patients identified a need for treatments that stop or slow the progression of disease, prolong life, promote independence, improve symptoms and quality of life, and have minimal side effects. pERC noted that there is insufficient evidence that tepotinib meets these therapeutic needs because no definitive conclusion could be reached regarding the effects of tepotinib on these outcomes compared to standard of care therapies; however, pERC does recognize there is a need for new oral, targeted therapy options for these patients.

Discussion Points

- pERC recognized the need for an effective targeted treatment option for patients with NSCLC harbouring *MET*ex14 skipping alterations. However, pERC concluded that the available evidence did not demonstrate that tepotinib meets these needs. pERC also discussed the need for new treatments with fewer or more manageable adverse effects than current standard of care. Since there was no evidence on the relative safety of tepotinib compared to standard of care therapies, pERC concluded that it remains unknown whether tepotinib addresses this patient need. Although the oral formulation of tepotinib may lead to increased patient independence and avoid IV administration procedures, there was insufficient evidence to demonstrate that this would translate into benefits to patients such as improved health-related quality of life.
- Current standard of care for the treatment of NSCLC with *MET*ex14 skipping alterations is immunotherapy with or without chemotherapy. pERC noted the absence of a direct comparison of tepotinib to a relevant treatment comparator and the important limitations of the indirect evidence. Limitations associated with the ITC submitted by the sponsor include a significant risk of bias in study selection, limited reporting of methods employed in the indirect treatment comparisons, important differences in study design that could not be accounted for in the analyses, differences in definitions and assessments of study endpoints, incomplete assessment of heterogeneity, and the lack of adjustment for all important potential confounders in the analyses . In view of the substantial uncertainty in the ITC results, pERC could not draw any conclusions pertaining to the efficacy of tepotinib compared to chemotherapy or immunotherapy in patients with advanced NSCLC harbouring METex14 skipping alterations. In addition, important outcomes (i.e., duration of response, ORR, HRQoL, harms) were not assessed and tepotinib was not compared to the combination of chemotherapy and immunotherapy in the indirect evidence analyses, which represent significant gaps in the evidence. The potential benefits and safety of tepotinib compared with other standard of care therapies remain unknown.
- pERC discussed the prevalence of the condition under review. *MET*ex14 skipping alterations occur in approximately 3% of NSCLC cases, which is not substantially lower than ALK alterations. pERC noted that drugs targeting the latter are associated with much more robust evidence from phase 3 trials.

Background

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths in Canada. Survival from lung cancer of all stages and histologies is poor, with an overall 5-year net survival of 19%. Lung cancer is classified into non-small cell lung cancer (NSCLC) or small cell lung cancer, with NSCLC accounting for approximately 88% of cases in Canada. The symptoms of advanced/metastatic NSCLC can be variable and often depend on the site of metastasis. At presentation, the most common signs and symptoms of NSCLC include persistent cough, shortness of breath, chest pain, wheezing, and hemoptysis. In advanced patients with distant metastasis, symptoms may include bone pain, headache, neurological or psychiatric abnormalities, paraplegia, hepatomegaly, and pathological fractures.

The mesenchymal-epithelial transition (MET) receptor tyrosine kinase is an oncogenic driver of NSCLC. Mutations that result in loss of exon 14 in the *MET* gene, called *MET* exon 14 (*MET*ex14) skipping alterations, lead to dysregulation and inappropriate signaling. *MET*ex14 skipping alterations occur in approximately 3% of NSCLC cases. Currently, patients in Canada with advanced (i.e., stage IV and stage IIIB not amenable to curative treatment approaches) NSCLC harbouring METex14 skipping mutations are usually treated per guidelines for advanced NSCLC without driver mutations. In the first-line setting, current treatments include immunotherapy with or without chemotherapy. In the second- or later-line setting, single agent chemotherapy, single agent immunotherapy, or platinum-based chemotherapy doublets may be used.

Tepotinib has been approved by Health Canada indication for the treatment of adult patients with locally advanced unresectable or metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) tyrosine kinase receptor exon 14 skipping alterations. Tepotinib is a MET receptor tyrosine kinase inhibitor. It is available as tablets and the dosage recommended in the product monograph is 450 mg once daily.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 phase II, single-arm clinical study in patients with advanced (locally advanced or metastatic) NSCLC
- Patients' perspectives gathered by 2 patient groups, the Lung Health Foundation (LHF) and Lung Cancer Canada (LCC)
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Input from two clinical specialists with expertise diagnosing and treating patients with NSCLC
- Input from 3 clinician groups, including Northeast Cancer Centre – Thoracic Cancer Clinicians, Ontario Health – Cancer Care Ontario's (OH-COO) Lung and Thoracic Cancers Drug Advisory Committee, and LCC Medical Advisory Committee
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient input

CADTH received input from 2 patient advocacy groups: the Lung Health Foundation (LHF) and Lung Cancer Canada (LCC). The LHF collected information from an online survey with 13 patients and 1 caregiver, and phone interviews with 2 patients. LCC collected data from phone and video interviews with 4 patients and 1 caregiver. Patients' experiences with lung cancer varied from no symptoms to having the disease negatively impact their ability to perform instrumental activities of daily living. The most frequently reported symptoms were shortness of breath, fatigue, and depression. Other notable concerns were anxiety and stigma related to their diagnosis that prevented them from fully engaging with their families and participating in social activities.

Patients indicated that they want treatments that stop or slow the progression of disease, prolong life, improve symptoms and quality of life, and have minimal side effects. The patients expressed that it is important to maintain independence and functionality. Patients reported that they struggled to navigate the healthcare system and access biomarker testing for *MET* mutations in Canada. The patients indicated that they want the equal access to biomarker testing across Canada at the time of diagnosis or early in treatment.

Clinician input

Input from clinical experts consulted by CADTH

CADTH received input from 2 clinical specialists with expertise in the diagnosis and management of NSCLC. The clinical experts reported that retrospective studies have indicated patients with *MET*ex14 alterations have a poor prognosis and there appears to be less benefit with immunotherapy in these patients. Moreover, the clinical experts noted that patients with *MET*ex14 skipping mutations tend to be an elderly population that often experience increased side effects with chemotherapy, thus better-tolerated treatments are needed. The clinical experts noted that there is currently no targeted treatment for *MET*ex14 mutated NSCLC that is publicly funded. The clinical experts indicated that the goals of treatment in locally advanced (not amenable to curative treatment)/metastatic NSCLC are to improve overall survival (OS), progression-free survival (PFS), and response rate, as well as maintain quality of life. In addition, the clinical experts thought that new treatment options should minimize adverse events (AEs).

The clinical experts indicated that tepotinib would preferentially be used in the first-line setting for patients with *MET*ex14 skipping alterations because it is a targeted therapy. If patients received tepotinib or another MET receptor tyrosine kinase inhibitor as first-line treatment, later lines of therapy would consist of chemotherapy, immunotherapy, or chemotherapy plus immunotherapy based on established provincial funding algorithms. If tepotinib was not used as first-line therapy, it would be used as second- or later-line therapy.

The clinical experts thought tepotinib should be used in patients with locally advanced or metastatic NSCLC harbouring a *MET*ex14 skipping mutation who meet the eligibility criteria used in the VISION trial. Patients with *MET*ex14 mutated NSCLC would be identified by molecular biomarker testing using tumour tissue biopsy or liquid biopsy followed by next-generation sequencing (NGS)

or panel testing. The clinical experts noted that it would be ideal for this testing to be done at the time of diagnosis of advanced NSCLC. The clinical experts would also consider using tepotinib in patients with an ECOG PS of ≥2 that otherwise met the VISION trial eligibility criteria.

The clinical experts reported that, in standard practice, response to treatment is assessed using computed tomography (CT)/bone scans every 2-4 months as clinically indicated. In addition, if patients presented with disease-related symptoms prior to starting treatment, clinical assessments were conducted on regular intervals (e.g., every 3 months) to assess symptom control. The clinical experts reported that a clinically meaningful response to treatment would be improved survival and maintenance or improvement in quality of life. The clinical experts indicated that treatment with tepotinib would be discontinued if a patient experienced disease progression or intolerable treatment-related side effects.

Clinician group input

CADTH received input from 3 clinician groups with a total of 21 clinicians: Northeast Cancer Centre – Thoracic Cancer Clinicians, Ontario Health – Cancer Care Ontario's (OH-CCO) Lung and Thoracic Cancers Drug Advisory Committee, and LCC Medical Advisory Committee. The clinician groups generally agreed with the input provided by the clinical experts consulted by CADTH. The clinician groups indicated that there is an unmet need for targeted therapy and improved outcomes in patients with advanced NSCLC harbouring *MET*ex14 skipping alterations. They thought that tepotinib would be preferentially offered as first-line therapy and offered as a subsequent therapy to those who had already received other treatments.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for tepotinib:

- The drug programs noted that the VISION trial eligibility included patients with ECOG PS of 0 or 1 and asked whether patients with ECOG PS ≥2 should be eligible for tepotinib if reimbursed.
- The drug programs noted that patients currently receiving alternate first-line or subsequent lines of therapy would have a time-limited opportunity to switch to tepotinib at the time of public funding if reimbursed.
- The drug programs noted that in patients with advanced NSCLC with driver mutations (e.g., *EGFR, ALK, ROS, BRAF*) who receive targeted treatment in the first-line setting, chemotherapy is required prior to accessing immunotherapy, in alignment with previous pERC recommendations. If tepotinib were reimbursed, the drug programs indicated that jurisdictions would use the same sequencing principles for therapies used after tepotinib, regardless of programmed death-ligand 1 (PD-L1) tumour proportion score (TPS).
- The drug programs noted that, if it was reimbursed, tepotinib may change place in therapy of drugs reimbursed in subsequent lines.
- The drug programs noted that METex14 skipping alteration testing may not be routinely available in some jurisdictions and would need to be implemented if reimbursed.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

One ongoing, phase II, single-arm, open-label, multicentre trial (VISION) was included in the CADTH systematic review. The primary objective of the VISION study was to assess the efficacy of tepotinib in patients with advanced (locally advanced or metastatic) NSCLC, as per objective response (confirmed complete response [CR] or partial response [PR]) determined according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, based on independent review in patients that tested positive for *MET*ex14 skipping alterations or *MET* amplification. There were 3 cohorts in the VISION study (Cohorts A, B, and C). Patients were selected for each cohort based on defined *MET* alterations or *MET* amplification identified in tumor tissue and/or in circulating tumor

DNA (ctDNA) derived from plasma (i.e., liquid biopsy). Patients with METex14 skipping alterations were enrolled into Cohort A and Cohort C under the same eligibility criteria and underwent the same study procedures. Cohort A was the pivotal cohort; Cohort C was a confirmatory cohort added as a protocol amendment to extend and confirm the existing results for Cohort A, and to expand the *MET*ex14 population in the study. After accrual for Cohort A was complete, enrollment at sites was shifted from Cohort A to Cohort C (Cohort A: N=151; Cohort A+C: N=254). Cohort B does not align with the Health Canada indication or reimbursement request, therefore data will not be presented for Cohort B in this review. All patients received 500 mg tepotinib hydrochloride hydrate containing 450 mg tepotinib orally once daily in 21-day cycles. Treatment was continued until disease progression, death, an AE leading to discontinuation, or withdrawal of consent. The primary outcome was objective response rate (ORR) by independent review committee (IRC) assessment. Secondary outcomes included OS; PFS by IRC; PFS by investigator; ORR by investigator; duration of response (DOR) by IRC; DOR by investigator; change from baseline and time-to-deterioration (TTD) by 10 points in European Quality of Life Five Dimension Five Level (EQ-5D-5L) visual analog score (VAS), European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (global health status/quality of life [QoL] score), and EORTC Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13) (coughing, dyspnea, and chest pain symptom scales); and safety. Data were analyzed descriptively; no statistical testing was performed.

The mean age of study patients in Cohort A and Cohort A+C was 73 years. Most patients were White (70.9% in Cohort A, 67.1% in Cohort A+C), had an ECOG PS of 1 (73.5% in Cohort A, 72.2% in Cohort A+C), adenocarcinoma histology type (86.8% in Cohort A, 81.2% in Cohort A+C), and stage IV disease at study entry (74.8% in Cohort A, 64.3% in Cohort A+C). Approximately half of the patients in Cohort A and Cohort A+C had received prior anticancer drug therapy for advanced or metastatic disease (54.3% and 51.0%, respectively). The most common types of prior anticancer therapies were cytotoxic therapy (49.7% in Cohort A, 44.3% in Cohort A+C) and immunotherapy (25.8% in Cohort A, 25.9% in Cohort A+C). Most patients had not had prior anticancer surgery (68.9% in Cohort A, 67.5% in Cohort A+C). Per IRC assessment, 9.9% of patients in Cohort A and 12.2% of patients in Cohort A+C had brain metastases at baseline.

Efficacy Results

Data from an interim analysis of VISION (data cutoff date of July 1, 2020) for the pivotal Cohort A and pooled Cohort A+C (i.e., entire *MET*ex14 skipping population) are reported below. The results of key efficacy outcomes in the modified intention-to-treat (mITT) population are summarized in Table 2.

Overall Survival

Median OS was 17.6 (95% confidence interval [CI]: 15.0, 21.0) months in Cohort A and 19.1 (95% CI: 15.3, 22.1) months in Cohort A+C.

Progression-Free Survival

Median PFS by IRC was 8.9 (95% CI: 8.2, 11.0) months in Cohort A and 9.5 (95% CI: 8.2, 11.2) months in Cohort A+C.

Objective Response Rate

The ORR by IRC was the primary endpoint in the VISION trial. The ORR by IRC was 45.0% (95% CI: 36.9, 53.3) in Cohort A and 46.4% (95% CI: 39.8, 53.2) in Cohort A+C. All observed responses by IRC assessment were PR.

Duration of Response

Median DOR by IRC was 11.1 (95% CI: 8.4, 18.5) months in Cohort A and 11.1 (95% CI: 9.5, 18.5) months in Cohort A+C.

Health-Related Quality of Life / Patient-Reported Outcomes

[redacted]

[redacted]

Harms Results

Adverse Events

In Cohort A, 99.3% of patients experienced at least 1 treatment-emergent AE. The most frequently reported AE was peripheral edema (75.0%). Grade ≥3 peripheral edema was reported in 18 (11.8%) patients in Cohort A. Other frequently reported AEs in Cohort A included nausea (35.5%), diarrhea (31.6%), hypoalbuminemia (29.6%), and increased blood creatinine (28.9%). In Cohort A+C, 96.5% of patients experienced at least 1 treatment-emergent AE. The most frequently reported AE was peripheral edema (60.0%). Grade ≥3 peripheral edema was reported in 20 (7.8%) patients. Other frequently reported treatment-emergent AEs in Cohort A+C were nausea (26.3%), diarrhea (26.3%), increased blood creatinine (25.1%), and hypoalbuminemia (23.1%).

Serious Adverse Events

In Cohort A, 55.9% of patients experienced at least 1 SAE as of the July 1, 2020 data cutoff date. The most frequently reported SAEs were pleural effusion (8.6%), disease progression (6.6%), and pneumonia (6.6%). In Cohort A+C, 45.1% of patients experienced at least 1 SAE. The most frequently reported SAEs were pleural effusion (6.7%), disease progression (4.7%), and pneumonia (4.7%).

Withdrawals Due to Adverse Events

In Cohort A, a total of 42 (27.6%) of patients permanently discontinued study treatment due to an AE. The most frequently reported AEs leading to treatment discontinuation were peripheral edema (4.6%), pleural effusion (3.3%), and general physical health deterioration (2.6%). In Cohort A+C, 20.4% of patients permanently discontinued study treatment due to an AE. The most frequently reported AEs leading to treatment discontinuation were peripheral edema (3.5%) and pleural effusion (2.0%).

Mortality

In Cohort A, 50.0% patients had died as of the July 1, 2020 data cutoff date. Causes of death were reported to be disease progression in 39.5% of patients and an AE in 7.9% of patients. In Cohort A+C, 33.7% of patient had died. Causes of death were reported to be disease progression in 25.9% of patients and an AE in 5.9% of patients.

Notable Harms

The most frequently reported hepatotoxicity-related AEs in Cohort A and Cohort A+C were increased ALT (11.8% and 11.4%, respectively), increased AST (8.6% and 7.5%, respectively), increased blood ALP (7.2% and 7.8%, respectively), and increased GGT (5.9% and 5.5%, respectively). The most frequently reported renal toxicity-related AE in Cohort A and Cohort A+C was increase in blood creatinine (28.9% and 25.1%, respectively). A total of 2 patients experienced interstitial lung disease and 6 patients experienced pneumonitis in Cohort A. As of the data cutoff date, 75.0% of patients in Cohort A and 60.0% of patients in Cohort A+C experienced peripheral edema.

Critical Appraisal

For the primary endpoint and most secondary endpoints, an IRC was appropriately used. The primary limitations of the VISION trial were the absence of a comparator group, no statistical testing, and open-label administration of tepotinib. The time-to-event analyses were appropriate, although the data are difficult to interpret in a single-arm trial without a control group. Open-label administration of tepotinib may have impacted subjectively measured outcomes, such as health-related quality of life (HRQoL)/patient-reported outcomes (PROs), response, and AEs, although the direction of the potential bias is unknown. In addition, there is uncertainty in the HRQoL/PRO data due to reduced samples sizes contributing to the analysis at later treatment cycles, which is likely to overestimate treatment effects. Due to the absence of a comparator group and statistical hypothesis testing, no definitive conclusions can be drawn on the efficacy of tepotinib based on the VISION trial.

The treatment regimen used in the VISION trial aligns with Health Canada recommended dose. The VISION trial was an international, multicentre study but there were no sites in Canada. The clinical experts consulted by CADTH indicated that the eligibility criteria used in the VISION trial were appropriate and commonly used in NSCLC trials. The VISION trial restricted enrollment to patients with an ECOG PS of 0 or 1, and patients with NSCLC in Canada often have an ECOF PS of ≥ 2. The VISION trial used liquid biopsy and/or tumour tissue biopsy to determine study patients' *MET*ex14 skipping alteration status and the clinical experts indicated that both methods could be used in Canada.

Indirect Comparisons

Description of studies

The sponsor-submitted indirect treatment comparison (ITC) consisted of 2 parts: (i) an indirect comparison of individual patient data from the VISION trial to pooled real-world data (RWD) using propensity scoring, and (ii) an indirect comparison of individual patient data from the VISION trial to retrospective observational studies using an unanchored matching adjusted indirect comparison (MAIC).[15] In the indirect comparison using propensity scoring, tepotinib data from the VISION trial were compared to chemotherapy (without immunotherapy) and immunotherapy as monotherapy using a dataset derived from 4 real-world evidence (RWE) cohort studies and a database. For the indirect comparison using an unanchored MAIC, the VISION trial was compared to 3 retrospective observational studies including patients that were treated with chemotherapy or immunotherapy. The relative efficacy of tepotinib to immunotherapy in combination with chemotherapy in NSCLC patients harbouring *MET*ex14 skipping alterations was not assessed. Efficacy was assessed in terms of PFS and OS. Safety outcomes were not assessed.

Efficacy Results

Overall, the authors of the ITC concluded that patients treated with tepotinib had a greater PFS time compared to patients treated with chemotherapy or immunotherapy. The authors also concluded that tepotinib conferred a benefit in OS compared to chemotherapy or immunotherapy, albeit of smaller magnitude than PFS. For the indirect comparisons of VISION to pooled RWD using propensity scoring, the Cox proportional HR for OS was 0.91 (95% CI: 0.62-1.35) in favour of tepotinib for the chemotherapy group and 0.91 (95% CI: 0.59-1.42) in favour of tepotinib for the immunotherapy group. For PFS, the Cox proportional HR was 0.49 (95% CI: 0.35-0.69) in favour of tepotinib for the chemotherapy group and 0.59 (95% CI: 0.39-0.90) in favour of tepotinib for the immunotherapy group. No HRs or other statistics were reported for the MAIC; the MAIC results were comprised of Kaplan-Meier curves for visual comparison.

Harms Results

Harms outcomes were not assessed in the sponsor-submitted ITC.

Critical Appraisal

The description of the methods used in the ITC analyses lacked important details, which creates uncertainty in the data. The methods used to identify relevant studies and the criteria used for study selection were unclear. The sponsor submitted a systematic literature review that identified 2 of the 3 studies included in the MAIC; the third study included in the MAIC and the 4 RWD sources included in the indirect comparison using propensity scoring were not identified in this systematic literature review, thus it remains unclear how these studies were identified and selected for inclusion in the indirect comparisons. No a priori protocol for selecting

studies for inclusion in the indirect comparisons specifically was reported. Furthermore, it is unclear why other studies that were identified in the sponsor's systematic literature review were not included in the ITC. The quality of the RWD sources was not assessed by the authors of the ITC and therefore not considered in the ITC analysis. The quality of 2 studies included in the MAIC was determined to be low, and the quality of the third study was not assessed. Any potential risks of bias of the included data sources (i.e., methodological limitations) were not assessed and not reported. A limited assessment of heterogeneity was reported. Key gaps in the evidence provided by the ITC were that no safety outcomes were assessed and chemotherapy in combination with immunotherapy was not included as a comparator.

Overall, substantial bias is expected in the results given the inherent limitations of the study design and the results observed in the indirect treatment analyses are unlikely to be valid. The true effect may be substantially different than the results observed in the ITC. A number of key limitations related to the selection and assessment of studies and patients, as well as the methods used that could potentially bias the results were identified. First, fundamental differences in study design between the VISION trial, RWD sources, and retrospective observational studies were noted, as were concerns over differences in the definition, assessment, and timing of the clinical endpoints. These differences could not be accounted for in the indirect comparisons. Second, there was limited assessment and reporting of clinically important heterogeneity, and the statistical analyses completed are unlikely to have accounted for all major differences. The generation of propensity scores and the unanchored MAIC did not include all important potential confounders/effect modifiers and prognostic factors. In the unanchored MAIC, a large reduction in ESS was observed, which suggests there was likely significant heterogeneity between the VISION study and comparator studies. The results for comparisons with major reductions of ESS are not reliable. In addition, the indirect comparisons may have been biased by the differential distribution of invalid or missing data between the VISION clinical trial and retrospective datasets. Given these issues, there is substantial concern for the risk of bias in the sponsor-submitted ITCs and no conclusions can be drawn from the data.

Regarding external validity, the majority of patient data were from sites in the US. It is likely that a number of important differences between the US and Canada exist with regard to the management of these patients, including differences in treatments available, health insurance coverage, and overall healthcare system structures, which would be expected to impact treatment eligibility and thus outcomes. In addition, the multiple studies included patients enrolled over a decade ago and these patients are unlikely to be representative of contemporary patients where better therapies and supportive care is available, which would be expected to bias the study results in favor of tepotinib.

Other Relevant Evidence

No long-term extension studies or additional relevant studies were included in the sponsor's submission to CADTH.

Economic Evidence

Cost and Cost-Effectiveness

	Description
Type of economic evaluation Component	Cost-utility analysis (CUA) Partitioned survival model (PSM)
Target population(s)	Adult patients with locally advanced unresectable or metastatic NSCLC harbouring *MET* tyrosine kinase receptor exon 14 skipping alterations
Treatment	Tepotinib
Submitted price	Tepotinib, 225mg, tablet: $153.96
Treatment cost	$8,622 per 28 days at a dose of 450 mg once daily
Comparators	Line-agnostic population • Immunotherapy (pembrolizumab, nivolumab, atezolizumab) First line (1L) population • Immunotherapy + PDC (pembrolizumab + pemetrexed + carboplatin/cisplatin) Second line or later (2L+) population • Chemotherapy (pemetrexed + carboplatin/cisplatin, docetaxel)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs; LYs

	Description
Time horizon	Lifetime (10 years)
Key data source	• VISION phase II clinical trial was used to inform efficacy and safety inputs for tepotinib • Sponsor indirect treatment comparisons (ITCs) were used to inform efficacy of immunotherapy, immunotherapy + PDC, and chemotherapy
Key limitations	• The VISION trial is a phase II, single-arm trial. Due to the absence of direct comparative evidence and lack of robust indirect comparative evidence, no definitive conclusions can be drawn regarding the comparative clinical efficacy of tepotinib. • The sponsor used line-agnostic efficacy data and compared this to immunotherapy in the line-agnostic base case analysis. Given there is considerable heterogeneity across different lines of therapy in terms of comparators and prognosis, there is a large amount of uncertainty in the line-agnostic base case analysis. Therefore, the CADTH base case focused on the cost-effectiveness of each line individually as provided by the sponsor, since the 1L and 2L+ analyses used line-specific efficacy data. • Relevant comparators were omitted, such as chemotherapy and immunotherapy as a monotherapy in the 1L analysis. • *MET*ex14 testing costs were excluded in the sponsor's base case. It is uncertain to what extent *MET*ex14 testing will be available across jurisdictions and some jurisdictions may need to implement testing. Since *MET*ex14 skipping alterations are rare, many tests would need to be administered to identify each patient and thus the testing costs per patient may be significantly underestimated. • The sponsor's cost/resource use assumptions underestimated tepotinib costs and overestimated comparator costs.
CADTH reanalysis results	• Given the challenges with interpreting the clinical evidence from the single arm VISION trial and limitations associated with the comparative clinical evidence, the cost-effectiveness of tepotinib is highly uncertain. • The CADTH exploratory reanalysis attempts to provide more plausible estimates of the cost-effectiveness of tepotinib, though is still grounded in highly uncertain clinical evidence. • In CADTH's exploratory reanalysis for the 1L population, tepotinib was dominated (i.e., more costly and less effective) by immunotherapy alone, regardless of whether testing costs were included. When the costs of PDC were added to immunotherapy, immunotherapy plus PDC was more costly and more effective then tepotinib, ICER for immunotherapy + PDC vs. tepotinib was $45,487 per QALY (incremental costs: $30,482; incremental QALYs: 0.6701). • In CADTH's exploratory analysis for the 2L+ population, the ICER for tepotinib vs. chemotherapy was $836,523 per QALY under the assumption that additional testing costs are incurred by the public payer through implementing *MET*ex14 testing. Excluding *MET*ex14 testing costs decreased the ICER to $551,240 per QALY. Since the true testing costs are uncertain, the ICER is expected to be between this upper and lower limit.

Budget Impact

The sponsor estimated the budget impact of tepotinib over three years. Several key limitations were identified related to treatment duration assumptions; pembrolizumab dosage; tepotinib market capture assumptions; comparator market shares; *MET*ex14 testing assumptions; and comparator drug costs. While the sponsor's results suggested that the introduction of tepotinib would lead to a budgetary savings of $16,965,241 over a 3-year time horizon, CADTH reanalyses estimated a budget impact of $1,073,988 in year 1, $4,302,036 in year 2, $8,122,224 in year 3, with a 3-year budget impact of at least $13,498,247. When testing costs were corrected and included, the 3-year budget impact increased substantially to $69,931,737. CADTH noted these resulted were associated with substantial uncertainty.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: February 9, 2022

Regrets

None

Conflicts of Interest

None