Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Cemiplimab (Libtayo)

Indication: Cemiplimab in combination with platinum-based chemotherapy for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) whose tumors have no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or c-ROS oncogene 1 (ROS1) aberrations and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC.

Sponsor: sanofi-aventis Canada Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that cemiplimab in combination with platinum-based chemotherapy (cemiplimab + PBC) be reimbursed for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) whose tumors have no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or c-ROS oncogene 1 (ROS1) aberrations and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, placebo-controlled trial (EMPOWER-Lung 3; N = 466) demonstrated that cemiplimab + PBC resulted in added clinical benefit in adult patients with advanced NSCLC whose tumors had no EGFR, ALK, or ROS1 aberrations, and who were not candidates for surgical resection or definitive chemoradiation or had metastatic disease. The EMPOWER-Lung 3 trial demonstrated that, compared with placebo + PBC, cemiplimab + PBC resulted in a statistically significant and clinically meaningful improvement in median overall survival (OS) at 16.4-month median follow-up time (21.9 versus 13.0 months; hazard ratio [HR] = 0.71; 95% confidence interval [CI]: 0.53 to 0.93; P = 0.0140). 2-year OS rates at the final analysis with a 28.4-month median follow-up time were 42.7% (95% CI: 36.9 to 48.4) and 27.2% (95% CI: 20.1 to 34.9) for the cemiplimab + PBC and placebo + PBC groups, respectively. Cemiplimab + PBC also demonstrated statistically significant improvements in progression-free survival (PFS) (HR = 0.56; 95%CI, 0.44 to 0.70; P <0.0001) and objective response rate (odds ratio [OR]: 2.7; 95% CI, 1.72 to 4.19; P <0.0001), compared with placebo + PBC. pERC considered the safety profile of cemiplimab + PBC to be manageable and consistent with the known safety profiles of cemiplimab and PBC.

pERC reviewed the results of a sponsor-submitted indirect treatment comparison (ITC) comparing cemiplimab + PBC to current treatment options, pembrolizumab + PBC and nivolumab + ipilimumab + PBC. Due to limitations of the ITC, pERC was unable to draw definitive conclusions on the relative efficacy of cemiplimab + PBC compared to other combination therapies.

Patients identified a need for effective treatment options that delay disease progression, improve quality of life, have fewer side effects and the potential for cure, and improved patient access. pERC concluded that, compared with placebo + PBC, cemiplimab + PBC met some of the patients' needs as it delays disease progression, prolongs survival, and offers an additional treatment option. pERC noted that the fixed dose of cemiplimab + PBC may improve patient accessibility in rural and remote regions by avoiding the need for vial sharing associated with weight-based dosing with other immunotherapy combinations. Although patients expressed an unmet need for treatments that improve quality of life, no definitive conclusion could be reached regarding the effects of cemiplimab + PBC on health-related quality of life (HRQoL) due to a significant decline in the number of patients available to provide assessments over time and the descriptive nature of the analyses.

At the sponsor submitted price for cemiplimab + PBC and publicly listed price for all other comparators, cemiplimab + PBC was more costly than pembrolizumab + PBC when assumed to be similarly effective based on the economic evaluation. As there is no evidence to suggest that cemiplimab + PBC is more effective than pembrolizumab + PBC and nivolumab + ipilimumab + PBC, the total drug cost of cemiplimab + PBC should not exceed the total drug cost of the least costly immunotherapy over the duration of treatment.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with cemiplimab + PBC should be reimbursed in adult patients with NSCLC who meet the following criteria: 1.1 Stage IIIB or IIIC NSCLC and not suitable for curative surgery or definitive chemoradiation, or stage IV NSCLC 1.2 No prior systemic treatment.	Evidence from the EMPOWER-Lung 3 trial demonstrated that treatment with cemiplimab + PBC resulted in a clinical benefit in patients with these characteristics.	pERC noted that patients who progress at least 6 months after their last dose of adjuvant or neoadjuvant platinum doublet chemotherapy and PD-1 or PD-L1 inhibitor should be eligible to receive cemiplimab + PBC, in line with the EMPOWER-Lung 3 trial criteria.
2. Patients should have good performance status.	Patients with an ECOG performance status 0 or 1 were included in the EMPOWER-Lung 3 trial.	Treating patients with an ECOG performance status of 2 may be at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1 Tumours with EGFR, ALK, or ROS1 aberrations 3.2 Active or untreated brain metastases 3.3 Prior neoadjuvant or adjuvant anti-PD-1 or anti-PD-L1 therapy within 6 months of treatment start or any prior anti-PD-1 or anti-PD-L1 therapy in the advanced disease setting.	There is no evidence to support a benefit of cemiplimab + PBC treatment in patients with these characteristics as they were excluded from the EMPOWER-Lung 3 trial.	—
Renewal		
4. Reimbursement of cemiplimab should be renewed for patients who demonstrate a continued response to treatment defined as absence of disease progression. 4.1 Assessment for renewal should be based on clinical and radiographic evaluation every 3 to 4 months.	In clinical practice, treatment response is evaluated clinically at each visit, and radiologically approximately every 3 to 4 months. This is aligned with the frequency of radiographic evaluation in the EMPOWER-Lung 3 trial, which was performed every 9 weeks (3 cycles) until disease progression.	—
5. Cemiplimab treatment should be reimbursed for a maximum of 108 weeks.	There is insufficient evidence to demonstrate a benefit of cemiplimab in patients treated beyond 108 weeks. Patients in the cemiplimab group of the EMPOWER-Lung 3 received cemiplimab for up to 108 weeks (36 treatment cycles).	—
Prescribing		
6. Treatment with cemiplimab + PBC should be prescribed by clinicians with expertise and experience in treating NSCLC. The treatment should be	This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
supervised and delivered in outpatient specialized oncology clinics with expertise in systemic therapy delivery and management of immunotherapy-related side effects.		
7. Cemiplimab + PBC should only be reimbursed when administered in combination.	There is no data supporting the efficacy and safety of Cemiplimab + PBC when used in combination with additional anticancer drugs, or when either component is initially used as monotherapy.	Cemiplimab can continue as monotherapy after 4 cycles of PBC.
Pricing		
8. Cemiplimab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly immunotherapy reimbursed for first line treatment of adult patients with NSCLC whose tumors have no EGFR, ALK, or ROS1 aberrations and • who have locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or • metastatic NSCLC	There is no clinical evidence to justify a cost premium for cemiplimab over the least costly immunotherapy reimbursed for the indicated population	—

ALK = anaplastic lymphoma kinase; ECOG = Eastern Co-operative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PBC = platinum-based chemotherapy; PD-L1 = Programmed death-ligand 1; ROS1 = c-ROS oncogene 1

Discussion Points

- pERC noted that other combination therapies, such as pembrolizumab + PBC or nivolumab + ipilimumab + PBC, are currently available for the requested patient population. pERC discussed the results of a sponsor-submitted ITC comparing cemiplimab + PBC with pembrolizumab + PBC and nivolumab + ipilimumab + PBC. pERC acknowledged several limitations with the submitted network meta-analysis (NMA), notably the small number of studies and heterogeneity across study designs and populations. Due to the limitations in the NMA, pERC could not draw definitive conclusions on the relative efficacy and safety of cemiplimab + PBC versus other combination therapies.
- pERC noted that patients with NSCLC identified a need for alternative treatment options with fewer side effects. Comparative safety from the EMPOWER-Lung 3 trial indicated that GRADE ≥3 and serious adverse events (AEs) were more common in patients treated with cemiplimab + PBC compared with placebo + PBC. pERC heard from the clinical experts that a higher proportion of AEs was expected in the cemiplimab + PBC group, given that a combination therapy was being evaluated in comparison to chemotherapy only. pERC could not draw conclusions regarding the safety of cemiplimab + PBC compared to other combination therapies due to limitations of the submitted indirect evidence. However, pERC acknowledged clinical expert input that the safety profile of cemiplimab + PBC appeared consistent with and as manageable as other currently available combinations of immunotherapy and PBC.
- pERC discussed input from patient and clinician groups highlighting potential advantages with the fixed dose of cemiplimab + PBC versus weight-based dosing, which is used for alternative combination therapies by some jurisdictions. According to stakeholder input, weight-based dosing may require vial sharing and patients to travel to larger hospitals for infusions, which may pose financial, emotional, and mental burdens to patients. A fixed dosing option, such as cemiplimab + PBC, may help to close an equity gap by avoiding the need for vial sharing and allowing treatment to be administered in community settings closer to patients' homes, thereby reducing barriers to treatment access. pERC agreed that cemiplimab + PBC may improve patient accessibility in rural and remote regions by avoiding the need for vial sharing.

Background

Lung and bronchus cancer is the most commonly diagnosed cancer in Canada (excluding non-melanoma skin cancers). In 2022 an estimated 30,000 Canadians were diagnosed with lung and bronchus cancer, representing approximately 13% of all new cancer cases, and 20,700 Canadians died from lung cancer, representing 24% of all cancer deaths in 2022. The risk factors include tobacco smoking, second-hand smoke, radon, asbestos, and other environmental exposures, with symptoms like cough, shortness of breath, and chest pain. Lung cancer is primarily divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC found in almost 80% of lung cancer cases. The prognosis largely depends on the stage at diagnosis, with half of the cases being diagnosed at Stage IV.

Early-stage NSCLC (Stages I, II, some IIIA) typically involves surgical resection, often combined with chemotherapy and/or radiation. Advanced stages (IIIB/IIIC, IV) are treated with systemic therapies like immunotherapy, chemotherapy, or both, depending on factors like PD-L1 expression and the presence of specific genetic alterations. Platinum-based chemotherapy, once the mainstay, is now often combined with or replaced by targeted therapies and immunotherapies, especially for tumors without oncogenic alterations. In Canada, treatment strategies include targeted therapy for actionable genetic alterations, with immunotherapy and chemotherapy used in various combinations based on PD-L1 expression and other factors.

The heterogeneity of NSCLC, with its various subtypes and molecular profiles, means that some patients may not respond to available treatments or may develop a lack of response over time, leading to disease progression. The current mortality rate in NSCLC remains high, and thus there is a need for therapies that can offer a more durable response and ultimately improve survival rates. The toxicity associated with systemic therapies for NSCLC is a significant concern. Adverse effects can range from mild to severe and life-threatening. Therefore, there is a need for treatments that extend survival while minimizing treatment-related toxicity.

Cemiplimab for injection, 350 mg/ 7 mL (50 mg/mL), single-use vial for IV infusion is indicated in combination with platinum- based chemotherapy for the first - line treatment of adult patients with NSCLC whose tumors have no EGFR, ALK or ROS1 aberrations and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III trial randomized controlled trial (RCT) in patients with advanced NSCLC and 1 sponsor-submitted ITC
- patients' perspectives gathered by 3 patient groups, Canadian Cancer Survivor Network (CCSN), Lung Cancer Canada (LCC), and Lung Health Foundation (LHF)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- input from 2 clinician groups, Lung Cancer Canada (LCC) - Medical Advisory Committee (MAC), Ontario Health-Cancer Care Ontario (OH-CCO) Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Three patient groups provided input to CADTH: CCSN (9 patients, 1 caregiver), LLC (4 patients), and LHF (15 patients, 1 caregiver). Input was gathered through surveys and discussions, focusing on experiences with lung cancer treatments, including cemiplimab. The disease significantly impacts patients' and families' daily lives, causing physical and emotional strain. Key outcomes important to patients include symptom management, quality of life, and delay in disease progression. The CCSN emphasized the challenges

faced by patients and caregivers, including managing side effects and emotional burdens, with most patients reporting satisfactory access to existing treatments. LCC noted positive experiences with cemiplimab, particularly in symptom management and ease of use. The LHF reported on the significant impact of symptoms on patients' lives, the effectiveness of current treatments in symptom relief, and the desire for earlier biomarker testing. All groups underscored the need for treatments that effectively delay disease progression with minimal side effects.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to clinical experts consulted by CADTH, unmet needs in NSCLC include improving survival and quality of life while minimizing treatment toxicity. Cemiplimab, combined with platinum-based chemotherapy, is seen as an alternative to existing first-line therapies for advanced or metastatic NSCLC patients without specific driver mutations and with varying PD-L1 expression levels. The experts identified the most benefit for patients with high disease burden and least suitability for those with significant comorbidities or poor performance status. Response to treatment should be assessed clinically and radiologically, focusing on tumor shrinkage and quality of life. Discontinuation of treatment can be considered upon disease progression, unacceptable toxicity, or after 2 years of treatment. Treatment with cemiplimab is managed by a Medical Oncologist in outpatient settings.

Clinician Group Input

CADTH received input from 2 clinician groups, LCC – MAC, and OH-CCO Lung Cancer Drug Advisory Committee. In total 2 clinicians from LCC - MAC and 12 clinicians from OH-CCO Lung Cancer Drug Advisory Committee provided input to the submissions. Clinician groups agreed that the first line of treatment is chemotherapy and immunotherapy, or pembrolizumab alone in patients with a PDL1 status >50%. For patients not eligible for immunotherapy, platinum doublet chemotherapy remains an option. There was agreement among all clinicians that improvements in PFS, OS and quality of life are treatment goals. LCC - MAC noted the benefits of cemiplimab having a flat dose of 350mg, without a weight-based option. This clinician group felt that this would provide significant advantages in delivering treatment closer to home for many patients with lung cancer because vial sharing would not be required. Both clinician groups agreed that in terms of place in therapy, cemiplimab in combination with platinum-based chemotherapy would be an alternative first line treatment.

Regarding the patient's eligibility criteria, other than incurable NSCLC, first line therapy, and no EGFR/ALK/ROS1 alterations; the clinical expert consulted by CADTH noted any PDL1 expression and ECOG 0-2; while LCC - MAC added that patients in rural areas will benefit more from cemiplimab because no vial sharing would be required.

Clinical and radiological assessments were noted as the best ways to determine whether a patient is responding to the treatment. Disease progression, toxicity, patient preference, and certain adverse events were factors to be considered when deciding to discontinue treatment.

It was agreed that outpatient clinics under supervision of a medical oncologist are the appropriate setting for treatment with cemiplimab in combination with platinum-based chemotherapy. LCC – MAC added that in many jurisdictions across Canada, particularly in more remote or rural communities, medical oncologists work in partnership with General Practitioners in Oncology (GPOs) to co-manage patients.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 2 for details.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
EMPOWER-Lung 3 compared cemiplimab + PBC vs. PBC alone in advanced NSCLC patients with no EGFR/ALK/ROS-1 driver mutations, irrespective of the PD-L1 status. More appropriate comparators include single agent pembrolizumab (if PD-L1 ≥ 50%), ipilimumab-nivolumab-chemotherapy, pembrolizumab-pemetrexed-platinum (non-squamous only), pembrolizumab-non-pemetrexed platinum (squamous). How does cemiplimab + PBC compare to the above immunotherapy +/- chemotherapy regimens?	No direct evidence from a clinical trial currently exists to compare cemiplimab + PBC to other immunotherapies given as monotherapy or in combination with chemotherapy. The clinical experts consulted by CADTH anticipated that the 2-year overall survival and progression-free survival with cemiplimab + PBC are likely comparable to other immunotherapies in combination with chemotherapy. Furthermore, the clinical experts consulted by CADTH anticipated the toxicity profile of cemiplimab + chemotherapy to be similar to that of pembrolizumab + chemotherapy. pERC acknowledged the clinical experts' response and noted that there is insufficient evidence to draw definitive conclusions on the relative efficacy and safety of cemiplimab + PBC versus other combination therapies.
Considerations for initiation of therapy	
The trial included never smokers, patients with treated brain metastases, and ECOG PS of 0 or 1. Should cemiplimab + PBC be considered for patients with ECOG PS of greater than 1?	pERC agreed with the clinical expert that patients with ECOG 2 are likely to benefit from cemiplimab + PBC and should be considered.
Are patients who had previous adjuvant or neoadjuvant immunotherapy eligible for cemiplimab + PBC and if so, is there a minimum disease-free interval that must be met?	The clinical experts noted that patients with NSCLC who have previously received adjuvant or neoadjuvant immunotherapy may be considered for subsequent treatment with cemiplimab + PBC. The optimal disease-free interval remains a subject of clinical judgment in the absence of robust evidence. The decision should be individualized, taking into account the duration and type of prior immunotherapy, the patient's disease course, and the potential benefits and risks of re-treatment with immunotherapy-chemotherapy combinations. pERC noted that patients who progress at least 6 months after their last dose of adjuvant or neoadjuvant platinum doublet chemotherapy and PD-1 or PD-L1 inhibitor should be eligible to receive cemiplimab + PBC, in line with the EMPOWER-Lung 3 trial criteria.
If a patient receives 108 weeks of cemiplimab and subsequently relapses, is there evidence to support re-treatment and if so, would there be a maximum duration?	pERC agreed with the clinical experts suggesting to align retreatment eligibility of cemiplimab + PBC with other reimbursed combinations of immunotherapy and chemotherapy combinations. pERC noted that patients who completed 2 years of cemiplimab treatment and progressed after the end of treatment should be eligible for retreatment for up to 17 cycles (1 year).
Considerations for discontinuation of therapy	
If a patient discontinues treatment before the completion of 108 weeks due to toxicity, but without relapse, could the patient restart and be treated to a maximum of 108 weeks?	Patients were allowed to resume therapy after resolution of toxicity in EMPOWER-Lung 3. pERC agreed with the clinical experts that these trial criteria were applicable to clinical practice.
Considerations for prescribing of therapy	
Although CADTH had issued a positive recommendation, single agent cemiplimab remains unfunded since a national agreement could not be	Comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
reached. The CADTH assessment needs to account for the initiation of this regimen as a combination regimen.	
Funding algorithm (oncology only)	
Cemiplimab + PBC would be an alternative treatment option to existing immunotherapy +/- chemotherapy regimens that are already funded. Under what conditions would cemiplimab + PBC be preferred over pembrolizumab +/- chemotherapy, or nivolumab-ipilimumab plus chemotherapy?	pERC agreed with the clinical experts that cemiplimab + PBC may be a valuable addition to the treatment landscape but may not drastically change the current standard of care. Cemiplimab + PBC may expand the options available to patients who are not suitable candidates for other treatments and have not progressed on other PD-1 or PD-L1 therapies in the advanced setting.
System and economic issues	
In certain jurisdictions that do not fund drug wastage, cemiplimab may be a preferred option given the flat dosing. The cost of cemiplimab + PBC should not exceed the drug program cost of existing funded immunotherapy-chemotherapy regimens.	Comment from the drug programs to inform pERC deliberations.
Confidential prices are in place for pembrolizumab, ipilimumab-nivolumab.	Comment from the drug programs to inform pERC deliberations.

ALK = anaplastic lymphoma kinase; ECOG PS = Eastern Co-operative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PBC = platinum-based chemotherapy; PD-L1 = Programmed death-ligand 1; ROS1 = c-ROS oncogene 1

Clinical Evidence

Description of Studies

One pivotal phase 3, randomized controlled trial was included in the systematic review: EMPOWER-Lung 3 Part 2. EMPOWER-Lung 3 is a two-part, phase 3 clinical trial evaluating the efficacy and safety of cemiplimab in combination with PBC versus placebo plus PBC in patients with advanced NSCLC regardless of PD-L1 expression levels. EMPOWER-Lung 3 did not include Canadian sites and maintained separate protocols for Parts 1 and 2. Part 2 of the study compared cemiplimab + PBC to placebo + PBC across different PD-L1 expression levels and is the focus of this report. Two data cut-off dates were reported for EMPOWER-Lung 3 Part 2: the first on June 14, 2021 (pre-specified second interim analysis) after a median follow-up of 16.4 months, and the second on June 14, 2022 (pre-specified final analysis) after approximately 28.4 months of follow-up. Since the efficacy boundary was crossed at the second interim analysis, no alpha was assigned to the pre-specified final analysis for OS. The Independent Data Monitoring Committee (IDMC) recommended unblinding the study after the first data cut-off date when statistical significance for OS was achieved. The primary objective of Part 2 was to assess OS differences between the cemiplimab + PBC and placebo + PBC groups in first-line treatment of advanced NSCLC. Secondary objectives included PFS and objective response rate (ORR).

Patients were randomized in a 2:1 ratio to receive histology-specific platinum-doublet chemotherapy with cemiplimab or placebo, stratified by histology and PD-L1 expression levels. Treatment continued for up to 108 weeks or until disease progression or unacceptable toxicity, with mandatory pemetrexed maintenance for non-squamous histology. The study design instituted caps on enrollment based on PD-L1 expression and histology. Eligible participants were adults with advanced squamous or non-squamous NSCLC, with no prior systemic treatment for metastatic disease. Patients with certain genetic aberrations were excluded, as targeted therapies are the standard of care for those conditions. Enrollment was open to patients with adequately treated brain metastases, controlled viral infections, and without significant autoimmune diseases. The main intervention was cemiplimab or placebo, administered intravenously in combination with PBC every three weeks for four cycles. The primary outcome, OS, was defined as the time from randomization to death from any cause. PFS, a key secondary outcome, was the time to disease progression or death, assessed by an Independent Review Committee using RECIST 1.1 criteria. ORR was the proportion of patients with a confirmed complete or partial response, reported as a key secondary outcome. The study also utilized the EORTC QLQ-C30 and QLQ-LC13 questionnaires to measure health related quality of life (HRQoL) as other secondary outcomes.

Efficacy Results

At the secondary interim analysis (June 14, 2021, data cut-off date), cemiplimab +PBC showed statistically significant improvements in OS, PFS, and ORR for patients with advanced NSCLC compared to placebo + PBC. Results at the subsequent data cut-off date, June 14, 2022, including the final OS analyses, were consistent with the those seen at the previous data cut-off date.

At the June 14, 2022 data cut-off date, cemiplimab +PBC showed improvements in OS and PFS for patients with advanced NSCLC compared to placebo + PBC. Median OS was longer in the cemiplimab + PBC group (21.1 months with a 95% CI of 15.9 to 23.5) versus the placebo + PBC group (12.9 months with a 95% CI of 10.6 to 15.7) with a stratified hazard ratio (HR) of 0.645 (95% CI, 0.507 to 0.820; P = 0.0003) in favour of the cemiplimab + PBC group. Survival probabilities at 12-months and 24-months were 66.4% and 42.7%, respectively, in the cemiplimab + PBC, and were 53.9% and 27.2%, respectively, in the placebo + PBC group. The median PFS was 8.2 months with a 95% CI of 6.4 to 9.0 in the cemiplimab + PBC group compared to 5.5 months with a 95% CI of 4.3 to 6.2 in the placebo + PBC group. PFS probabilities at 12-months and 24-months PFS rates were 38.7% and 19.7%, respectively, in the cemiplimab + PBC group and 16.1% and 3.6%, respectively, in the placebo + PBC group. The ORR was higher in the cemiplimab + PBC group (43.6% with a 95% CI of 38.0 to 49.3) versus the placebo + PBC group (22.1% with a 95% CI of 15.8 to 29.5).

Harms Results

Safety results from the EMPOWER-Lung 3 trial Part 2 at the June 14, 2022, data cut-off date, indicated that, overall, the safety profile of the combination treatment appeared consistent with the known safety profiles of cemiplimab and that of PBC. Similar proportions of patients in both treatment groups experienced adverse events (96.5% in the cemiplimab + PBC, and 94.8% in placebo + PBC). The most frequent AEs (cemiplimab + PBC versus placebo + PBC) included anemia (45.8% versus 39.9%), alopecia (37.2% versus 43.8%), nausea (25.3% versus 16.3%), hyperglycemia (18.3% versus 11.8%), and increased ALT levels (17.6% versus 15.0%). A total of 48.7% of patients in the cemiplimab + PBC group and 32.7% of patients in the placebo + PBC group experienced at least 1 ≥ grade 3 TEAE. The most common TEAEs ≥ grade 3 experienced by ≥2% of patients within the cemiplimab + PBC group (cemiplimab + PBC versus placebo + PBC) included anemia (10.9% versus 6.5%), neutropenia (6.4% versus 5.9%), white blood cell count decreased (3.2% versus 2.0%), and thrombocytopenia (3.2% versus 1.3%). Numerically, a higher proportion of serious adverse events (SAEs) were reported in the cemiplimab + PBC group (30.1%) than in placebo + PBC (24.2%), with comparable rates for the most commonly reported SAEs (cemiplimab + PBC versus placebo + PBC): pneumonia (2.9% versus 2.0%), anemia (2.9% versus 1.3%), febrile neutropenia (1.3% versus 2.6%), and death (8.7% versus 9.2%). Adverse events of special interest (AESIs) were reported in [redacted] of patients in the cemiplimab + PBC group and [redacted] in the placebo + PBC group as of the June 14, 2022 data cut-off. The most frequent AESI was [redacted], occurring in [redacted] of patients in the cemiplimab + PBC group and [redacted] in the placebo + PBC group. A total of [redacted] patients ([redacted]) died due to treatment-related TEAEs in the cemiplimab + PBC group and [redacted] patient ([redacted]) died due to treatment-related TEAEs in the placebo + PBC group.

Critical Appraisal

The EMPOWER-Lung 3 Part 2 study was a double-blind, placebo-controlled phase 3 RCT. The study's randomization was facilitated by an interactive web response system, stratified by histology and PD-L1 expression level. The study employed appropriate methods for time-to-event analysis, including the Kaplan-Meier method and Cox proportional hazard model.

Limitations in the EMPOWER-Lung 3 Part 2 study included the higher percentage of subsequent anti-cancer therapies received by patients in the placebo + PBC group compared to the cemiplimab + PBC group which may have introduced a confounding variable, potentially affecting OS results. Further, since the study was concluded at the secondary interim analysis, data between the interim analysis cut-off date of June 2021 and the final analysis with a data cut-off date of June, 2022, were collected from an unblinded period of the study, potentially introducing biases in subjective outcomes such as HRQoL and harms. In addition, the high rate of missing patient-reported outcomes data over time, especially in the placebo group, makes interpretation of patient reported outcomes over time challenging and results remain inconclusive.

Clinical experts noted that the study's inclusion criteria and patient characteristics align with typical oncology trials and Canadian clinical practice and suggested that baseline demographic and tumor characteristics were generally consistent with an expected population of NSCLC patients seen in their practices. A limitation to generalizability was the trial's comparator (placebo + PBC) which

does not reflect current Canadian practice, where patients typically receive immunotherapy. No trial sites were located in Canada, excluding the representation of Canadian healthcare settings in the trial. The overall low rates of subsequent therapies in both groups reduces generalizability of the results to the Canadian practice.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

Description of Study

The indirect treatment comparison (ITC) submitted by the sponsor aimed to assess the comparative efficacy of cemiplimab +PBC versus other Health Canada-approved therapies for first-line treatment for patients who have locally advanced or metastatic NSCLC patients. Outcomes of interest included OS, PFS, ORR, and certain harms. A systematic literature review (SLR) was conducted, with searches updated until March 2022, to identify RCTs for inclusion in a NMA. The SLR focused on trials from 2010 onwards. The review process included independent reviewers and a PRISMA flow diagram documenting study selection. The feasibility of an NMA was assessed, considering the connectedness of evidence, similarity of comparators, and distribution of baseline characteristics. Bayesian NMA was performed using both fixed and random-effects models, with a fixed-effect model considered the default base-case.

Efficacy Results

The SLR identified 11 relevant RCTs, with five unique RCTs included in the NMA for any PD-L1 expression and any histology. The evidence network allowed for comparisons of cemiplimab + PBC with pembrolizumab + PBC, nivolumab + ipilimumab + PBC, and investigator choice (IC) chemotherapy.

Cemiplimab + PBC showed favorable OS (HR at 24 months = 0.66, 95% credible interval [CrI], 0.51 to 0.87), PFS (HR at 24 months = 0.61, 95%CrI, 0.48 to 0.78), and ORR (OR at 24 months = 2.76, 95%CrI, 1.79 to 4.37) compared to IC chemotherapy. This is consistent with the direct evidence established in EMPOWER-Lung 3 Part 2. Comparisons against other immunotherapy combinations is much less robust and cannot inform on the comparative efficacy of cemiplimab + PBC against other immunotherapy combinations. Results for indirect comparison of cemiplimab + PBC against pembrolizumab + PBC included a HR at 24 months for OS of 0.88 (95%CrI, 0.65 to 1.21), a HR at 24 months for PFS of 0.87 (95%CrI, 0.66 to 1.15), and an OR of 0.89 (95%CrI, 0.54 to 1.49) for ORR. Results for indirect comparison of cemiplimab + PBC against nivolumab + ipilimumab + PBC included a HR at 24 months for OS of 0.85 (95%CrI, 0.61 to 1.19), a HR at 24 months for PFS of 0.91 (95%CrI, 0.68 to 1.24), and an OR of 1.53 (95%CrI, 0.89 to 2.67) for ORR.

Harms Results

Due to the limited evidence base and small number of events, harms results are not reported.

Critical Appraisal

The sponsor submitted ITC was performed through a SLR, which systematically identified all the trials in the network, according to prespecified criteria.

However, there was a lack of reporting on the result of the quality assessment, even though it was stated that Cochrane risk of bias tool was used, and it was unknown how studies with high-risk of bias were handled, if applicable. Several limitations due to the sparse network might have contributed to high uncertainty in the results obtained. The small number of included studies in the network with Bayesian fixed-effect model mandated several untested assumptions, including the clinical homogeneity assumption. However, a significant concern is whether this assumption would have been held; given there was significant heterogeneity across patient populations, highly varied subsequent therapies, differences in the level of PD-L1 expressions, histology, metastasis sites and status, chemotherapy, and maintenance therapy across the included studies.

Considering the limitations related to sparse network and clinical heterogeneity across the included trials, it is not possible to conclude that cemiplimab + PBC has similar effect as other immunotherapies in combination with PBC on OS, PFS, and ORR. Considering the consistency of the direction of the indirect results of cemiplimab + PBC versus chemotherapy in the ITC with the direct and existing evidence in the form of EMPOWER-Lung 3 Part 2, the indirect results can be considered supportive of the findings in the EMPOWER-Lung 3 Part 2 trial.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for EORTC QLQ-C30 based on a threshold identified in the literature for this review. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for OS, PFS, ORR, and harms.

Table 3 presents the GRADE summary of findings for cemiplimab + PBC versus placebo + PBC in patients with NSCLC.

Table 3: Summary Of Findings For Cemiplimab + PBC Versus Placebo + PBC For Patients With advanced NSCLC Whose Tumors Have No EGFR, ALK, Or ROS1 Aberrations

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + PBC	Cemiplimab + PBC	Difference		
Overall Survival							
Overall survival, Median follow-up: 28.42 months	466 (1 RCT)	OS events (i.e., deaths) at data cut-off (June 14, 2022): • Cemiplimab + PBC: 57.7 per 100 persons • Placebo + PBC: 72.1 per 100 persons • Hazard Ratio = 0.645 (95% CI, 0.507 to 0.820) Median OS at data cut-off (June 14, 2022): • Cemiplimab + PBC: 21.1 months (95% CI, 15.9 to 23.5) • Placebo + PBC: 12.9 months (95% CI, 10.6 to 15.7)				High[a]	Cemiplimab + PBC results in an increase in overall survival compared to PBC alone.
Progression Free Survival							
Progression Free Survival, Median follow-up: 28.42 months	466 (1 RCT)	PFS events (i.e., disease progression or death) at data cut-off (June 14, 2022): • Cemiplimab + PBC: 75.0 per 100 persons • Placebo + PBC: 86.4 per 100 persons • Hazard Ratio = 0.549 (95%CI 0.441, 0.683) Median PFS at last data cut-off (June 14, 2022): • Cemiplimab + PBC: 8.2 months (95%CI 6.4, 9.0) • Placebo + PBC: 5.5 months (95%CI 4.3, 6.2)				High[a]	Cemiplimab + PBC results in an increase in progression free survival compared to PBC alone.
Response							
Objective response rate Follow-up: Up to 108 weeks	466 (1 RCT)	2.82 (1.80 to 4.41)	22.1 per 100	43.6 per 100 (38.0 to 49.3)	21.51 more per 100 (12.96 to 30.07 more)	High[b]	Cemiplimab + PBC results in an increase in the number of people achieving an objective response rate compared to PBC alone. The clinical importance of the increase is uncertain.
Health-related Quality of Life							
EORTC QLQ-C30 – Global Health	466 (1 RCT)	NA	1.08 more points	1.69 more points (0.20 to 3.19)	0.61 more points (–2.23	Low[c]	Cemiplimab + PBC may result in a little-to-no clinically important difference in change in

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + PBC	Cemiplimab + PBC	Difference		
Status/QoL (100 [best] to 0 [worst])* Follow-up: Up to Cycle 21					fewer to 3.45 more)		EORTC QLQ-C30 when compared to PBC alone.
Harms							
Patients with any treatment emergent adverse events of special interest Follow-up: on-treatment period	466 (1 RCT)	NR	3.3 per 100	3.8 per 100	0.58 (-2.96 to 4.11)	Low[d]	Cemiplimab + PBC may result in little-to-no difference in treatment emergent adverse events of special interest when compared with PBC alone.

CI = Confidence Interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; NE = Not Estimated, NR = Not Reported; OS = Overall Survival; PBC = Platinum-Based Chemotherapy; PFS = Progression Free Survival; QoL = quality of life; RCT = Randomized Controlled Trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the HR using the null as the threshold. The clinical expert consulted by CADTH noted that the HR results are clinically meaningful. This observation is consistent with the decision by the trial data and safety monitoring board to terminate the study early due to demonstrated efficacy.

[b] No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. Did not rate down for imprecision; a between-group difference of larger than the null and a confidence interval that excludes the null suggest benefit compared to PBC as judged by the CADTH review team.

[c] Rated down 2 levels for very serious risk of bias due to missing data. Data were available for [redacted] of patients [redacted] in the placebo + PBC group and [redacted] in the cemiplimab + PBC group. Did not rate down for imprecision. Based on literature a 10-point change from the baseline in total score was clinically important, the point estimate and entire confidence interval suggest little-to-no difference.

[d] Rated down 2 levels for very serious concerns about imprecision due to very small number of events.

* Results based on data collected for secondary interim analysis with data cut-off date of June 14, 2021

Source: Source: Study EMPOWER-Lung 3 Part 2 Clinical Study Report.

Details included in the table are from the sponsor's Summary of Clinical Evidence

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	First-line treatment of adult patients with NSCLC whose tumors have no EGFR, ALK, or ROS1 aberrations, who have • locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or • metastatic NSCLC
Treatment	Cemiplimab in combination with platinum-based chemotherapy (cemiplimab + PBC)
Dose regime	350 mg every 3 weeks, until progression or unacceptable toxicity
Submitted price	Cemiplimab 350 mg: $8,200 per vial[a]
Submitted treatment cost	Cemiplimab + PBC = $183,025 per patient annually, if patients remain on treatment for a full year

Comparators	Pembrolizumab in combination with platinum-based chemotherapy (pembrolizumab + PBC)
	• Nivolumab in combination with ipilimumab and platinum-based chemotherapy (nivolumab + ipilimumab + PBC)
	• Platinum-based chemotherapy (PBC alone), consisting of:
	  ○ pemetrexed plus cisplatin
	  ○ pemetrexed plus carboplatin,
	  ○ paclitaxel plus carboplatin, or
	  ○ paclitaxel plus cisplatin

Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (30 years)
Key data sources	Phase 3 R2810-ONC-16113 (EMPOWER-Lung 3) trial for the efficacy of cemiplimab + PBC and PBC alone; Sponsor-submitted network meta-analysis (NMA) including EMPOWER-Lung 3, Checkmate-9LA, KEYNOTE-189, KEYNOTE 407 and KEYNOTE-021G trials, for the efficacy of the other comparators
Key limitations	• In EMPOWER-Lung 3, patients receiving PBC alone do not reflect Canadian clinical practice, as current practice would emphasize the use of immunotherapy along with PBC. Furthermore, there was a lower proportion of patients receiving subsequent therapy potentially resulting in lower survival than anticipated over the trial period. As such, the survival benefit for cemiplimab + PBC may be overestimated. • The long-term extrapolation of overall survival for PBC alone lacks face validity. Based on the clinical experts consulted by CADTH, overall survival appears to be overestimated for an undertreated population (receiving low rates of subsequent therapy). • CADTH's clinical review highlighted several methodological limitations with the sponsor-submitted NMA, in particular concerns with clinical heterogeneity. Thus, no firm conclusions could be drawn on the comparative efficacy and safety between cemiplimab plus PBC versus pembrolizumab + PBC and nivolumab + ipilimumab + PBC. • The treatment costs of pembrolizumab and nivolumab are overestimated as the sponsor adopted a fixed dosing for pembrolizumab and nivolumab but weight-based dosing is typically used in clinical practice. Additionally, the costs of subsequent therapy disproportionately inflate the cost of the PBC alone arm as it was applied to 100% of patients in the progression state. • Pembrolizumab monotherapy is excluded as a comparator from the submission but is a relevant treatment option for a subset of the indicated population (i.e., those expressing PD-L1 in ≥ 50% of tumour cells). • The sponsor's assumption of sustained relative treatment effect is uncertain due to the lack of long-term data.

Component	Description
	• The model structure has important limitations for the decision problem because it accounts for the costs of subsequent therapies over a lifetime time horizon but has limited flexibility to capture changes to clinical outcomes (i.e., response) in later lines of therapy.

CADTH reanalysis results	• CADTH incorporated the following changes to address some of the key identified limitations: using a generalized gamma distribution to extrapolate OS of patients treated with PBC alone; using the EMPOWER-Lung 3 trial data to model the comparative efficacy of cemiplimab + PBC versus PBC; assuming equal efficacy of all immunotherapies used in first-line treatment versus PBC alone (assuming the same relative effect observed in the EMPOWER-Lung 3 trial); applying weight-based dosing for pembrolizumab and nivolumab and aligning the proportion of patients receiving subsequent therapy costs with the trial. CADTH could not incorporate the efficacy of subsequent therapies, nor include the comparison with pembrolizumab monotherapy for patients with PD-L1≥ 50%.
	• In the CADTH base case, PBC alone, pembrolizumab + PBC and nivolumab + ipilimumab + PBC remained on the cost-effectiveness frontier. Cemiplimab + PBC is dominated by pembrolizumab + PBC - associated with similar QALYs gained but higher total costs (cemiplimab + PBC: $194,203 vs. pembrolizumab + PBC: $166,127).
	  ○ Assuming similar efficacy across immunotherapies, a price reduction of at least 20% is required for cemiplimab + PBC to be similar in terms of total costs to immunotherapy (pembrolizumab + PBC).
	  ○ For the small number of patients for whom PBC alone is the relevant comparator, a price reduction of at least 71% is required for cemiplimab + PBC to become cost-effective as a first-line treatment at a WTP of $50,000 per QALY gained.
	  ○ Higher price reductions may be warranted due to the remaining uncertainty of the relative treatment effect versus PBC alone and negotiated prices of comparators by public plans.
	• The results were driven by the alternative assumptions for the OS extrapolation of PBC alone, comparative efficacy across immunotherapy arms and dosing assumptions for the other immunotherapies (weight-base versus fixed dosing). Results from scenario analysis showed that when fixed based dosing was adopted (i.e., maximum dosing was assumed), the ICER for cemiplimab + PBC compared to PBC alone was $171,113 per QALY gained (no longer dominated by pembrolizumab + PBC).

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = Network meta-analysis; NSCLC = Non-small cell lung cancer; PBC = platinum-based chemotherapy; PSM = partitioned survival model; QALY= quality-adjusted life-year; ROS1 = C-ros oncogene; vs. = versus

[a] The sponsor has confirmed that the 250 mg vial is being discontinued in Canada.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the sponsor's approach to modelling treatment duration was misaligned with the pharmacoeconomic model; the dosing of pembrolizumab and nivolumab did not reflect clinical practice (fixed dosing vs. weight-based dosing); and the market share of cemiplimab and pembrolizumab monotherapy was overestimated. The proportion of patients with a driver mutation was also uncertain.

CADTH reanalysis adjusted the market shares for cemiplimab and pembrolizumab monotherapy as well as adopted treatment costs for PBC alone and all immunotherapy arms estimated from the CADTH base case of the CUA (which reflected mean treatment duration, weight-based dosing for pembrolizumab and nivolumab, and aligned distribution of PBC components and subsequent therapies across treatment arms with the clinical trial). In the CADTH base case, the 3-year budget impact of reimbursing cemiplimab + PBC is expected to be $5,279,805 ($1,029,683 in year 1, $2,015,034 in year 2, and $2,235,088 in year 3). The incremental budget impact was sensitive to assumptions on the dosing of pembrolizumab and market shares captured from nivolumab + ipilimumab + PBC.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, 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: March 13, 2024

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None