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CADTH Reimbursement Recommendation

Cemiplimab (Libtayo)

Indication: First-line treatment of adult patients with non–small cell lung cancer (NSCLC) expressing PD-L1 (Tumour Proportion Score [TPS] ≥ 50%), as determined by a validated test, with no EGFR, ALK, or ROS1 aberrations, who have locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC

Sponsor: Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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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.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Libtayo?

CADTH recommends that Libtayo should be reimbursed by public drug plans for the first-line treatment of adult patients with non–small cell lung cancer (NSCLC) expressing programmed death ligand 1 (PD-L1) with a Tumour Proportion Score (TPS) of 50% or greater, as determined by a validated test, with no epidermal growth factor receptor *(EGFR),* anaplastic lymphoma kinase (*ALK*) translocation, or *c-Ros oncogene 1 (ROS*-1) aberrations, who have locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC if certain conditions are met.

Which Patients Are Eligible for Coverage?

Libtayo should only be covered to treat patients who have metastatic NSCLC or locally advanced NSCLC that cannot be treated with surgery or chemoradiation, whose tumours have high levels of PD-L1 protein, whose tumours do not have abnormal *EGFR*, *ALK*, or *ROS1* genes, and who have no prior systemic treatment for advanced or metastatic NSCLC.

What Are the Conditions for Reimbursement?

Libtayo should be prescribed by clinicians with expertise and experience in treating NSCLC and treatment should be supervised and delivered in outpatient specialized oncology clinics. The price of Libtayo should be negotiated so that it does not exceed the cost of treatment with pembrolizumab.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Libtayo improved survival compared with platinum-doublet chemotherapy.
- Libtayo meets patient needs of improving survival and having manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Libtayo does not represent good value to the health care system at the public list price. The Committee determined that there is not enough evidence justify a greater cost for Libtayo compared with pembrolizumab over the duration of treatment.
- Based on public list prices, Libtayo is estimated to cost the public drug plans approximately $13 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is NSCLC?

Lung cancer is the most diagnosed cancer and the leading cause of cancer deaths in Canada. It is estimated that in 2021, 29,600 Canadians were diagnosed with lung cancer and 21,000 Canadians died from lung cancer. Approximately 19% of patients in Canada diagnosed with lung cancer survive for at least 5 years. NSCLC accounts for approximately 85% of lung cancer cases in Canada.

Unmet Needs in NSCLC

Not all patients have a response to currently available first-line treatments for NSCLC and most patients will experience disease progression.

How Much Does NSCLC Cost?

Treatment with Libtayo is expected to cost approximately $11,956 per patient per month.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that cemiplimab be reimbursed for the first-line treatment of adult patients with non–small cell lung cancer (NSCLC) expressing programmed death ligand 1 (PD-L1) with a Tumour Proportion Score (TPS) of 50% or greater, as determined by a validated test, with no *EGFR*, *ALK*, or *ROS1* aberrations, who have locally advanced NSCLC who 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

Evidence from a phase III, open-label randomized controlled trial (RCT) demonstrated that treatment with cemiplimab monotherapy resulted in added clinical benefit over platinum-based doublet chemotherapy in patients with stage IIIB, stage IIIC, or stage IV NSCLC who were not candidates for treatment with definitive chemoradiotherapy, whose tumours expressed PD-L1 in at least 50% of tumour cells, with no *EGFR*, *ALK*, or *ROS1* aberrations, and who had received no prior systemic treatment for their advanced disease. The EMPOWER-Lung 1 trial (N = 710) demonstrated that treatment with cemiplimab monotherapy was associated with a statistically significant and clinically meaningful improvement in overall survival (OS) compared with investigator's choice of platinum-based doublet chemotherapy (hazard ratio [HR] = 0.68; 95% confidence interval [CI], 0.53 to 0.87; P = 0.0022). The progression-free survival (PFS), objective response rate (ORR) and duration of response (DOR) results were supportive of the OS results. Conclusions regarding health-related quality of life (HRQoL) outcomes could not be drawn from the EMPOWER-Lung 1 trial due to the open-label nature of the trial, lack of statistical testing, and limited sample sizes at later time points, but the results suggested that HRQoL may be maintained or improved with cemiplimab monotherapy and not worse with cemiplimab versus chemotherapy. The adverse event (AE) results from the EMPOWER-Lung 1 trial indicated that cemiplimab was generally well tolerated and pERC considered the AEs to be manageable. Overall, cemiplimab monotherapy meets some of the needs identified by patients as it prolongs survival versus chemotherapy, likely does not have a detrimental effect on HRQoL versus chemotherapy, has a manageable side effect profile, and may provide improved access to immunotherapy in rural communities.

pERC agreed with the clinical experts that on an individual patient basis, chemotherapy alone is not a relevant comparator for cemiplimab because patients typically only receive chemotherapy in the first-line setting if they are ineligible for immunotherapy. Conclusions around comparative efficacy and safety from an indirect treatment comparison (ITC) of cemiplimab monotherapy with [redacted] submitted by the sponsor could not be drawn due to substantial heterogeneity between trial populations. Based on the EMPOWER-Lung 1 trial results and the similarity in mechanism of action between cemiplimab and pembrolizumab, pERC agreed with the clinical experts and patients that cemiplimab monotherapy is most likely similar to pembrolizumab monotherapy in terms of efficacy and safety.

At the sponsor-submitted price for cemiplimab and publicly listed price for pembrolizumab, cemiplimab was more costly than pembrolizumab and considered similarly effective based on the economic evaluation. As cemiplimab is considered similarly effective as

pembrolizumab, the total drug cost of cemiplimab should not exceed the total drug cost of pembrolizumab over the duration of treatment.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with cemiplimab should only be reimbursed in adult patients with all of the following: 1.1. Previously untreated stage IV NSCLC, or stage IIIB or IIIC NSCLC not amenable to curative therapy 1.2. PD-L1 strongly positive tumours (TPS ≥ 50%) 1.3. Good performance status	Patients in the EMPOWER-Lung 1 trial had these characteristics, with the exception that only patients with an ECOG performance status of 0 or 1 were eligible.	pERC noted that patients who progress at least 6 months after their last dose of adjuvant or neoadjuvant chemotherapy or immunotherapy should be eligible to receive cemiplimab. pERC agreed with the clinical experts that patients with an ECOG performance status of up to 2 may be considered for eligibility based on data showing efficacy of other treatments such as chemotherapy in these patients.
2. Patients should not have any of the following: 2.1. Tumours with *EGFR*, *ALK*, or *ROS1* aberrations 2.2. A contraindication to immunotherapy 2.3. Uncontrolled and symptomatic CNS metastases	There is no evidence to support a benefit of cemiplimab treatment in patients with these characteristics as they were excluded from the EMPOWER-Lung 1 trial.	Although never smokers were excluded from the EMPOWER-Lung 1 trial, pERC noted that they should not be excluded from treatment with cemiplimab. pERC noted that CNS imaging should not be mandated unless patients have symptomatic CNS metastases.
Renewal		
3. Reimbursement of cemiplimab should be renewed for patients who demonstrate a continued response to treatment defined as absence of disease progression. 3.1. 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 1 trial, which was performed every 9 weeks (3 cycles) until disease progression.	—
4. Cemiplimab treatment should be reimbursed for a maximum of 108 weeks.	There is no evidence to demonstrate a benefit of cemiplimab in patients treated beyond 108 weeks. Patients in the cemiplimab arm of the EMPOWER-Lung 1 received cemiplimab monotherapy for up to 108 weeks (36 treatment cycles).	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). pERC also noted that patients who discontinue treatment before completion due to toxicity can restart treatment as long as the toxicity has resolved.

Reimbursement condition	Reason	Implementation guidance
Prescribing		
5. Treatment should be prescribed by clinicians with expertise and experience in treating NSCLC. The treatment should be supervised and delivered in outpatient specialized oncology clinics with expertise in systemic therapy delivery and management of immunotherapy-related side effects.	This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. Cemiplimab should be negotiated so that it does not exceed the drug program cost of treatment with pembrolizumab.	No evidence was reviewed that supports a clinical benefit for cemiplimab compared to pembrolizumab for this indication.	—
Feasibility of adoption		
7. The feasibility of adoption of cemiplimab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer; PD-L1 = programmed death ligand 1; RECIST = Response Evaluation Criteria in Solid Tumours.

Discussion Points

- Patients expected that the use of a fixed dose for cemiplimab treatment would allow for greater flexibility in administering treatment outside of large centres and that cemiplimab may provide an advantage over pembrolizumab, for which a weight-based dose is used up to the fixed-dose amount. In this regard, pERC discussed that it was unclear whether there is an unmet need in terms of the availability of immunotherapy at smaller centres for this patient population given the arrangements currently in place for providing pembrolizumab at these centres.
- Although pERC was unsure whether any unmet needs in this patient population were addressed with cemiplimab monotherapy, pERC discussed that cemiplimab monotherapy would provide an additional treatment option that could possibly reduce drug wastage should a fixed dose be used.
- pERC noted that the addition of chemotherapy to cemiplimab at disease progression should not be funded as there is insufficient evidence to recommend this practice.
- As cemiplimab monotherapy is likely similar to pembrolizumab monotherapy in terms of mechanism of action, efficacy, and safety, pERC considered that patients experiencing hypersensitivity to 1 of these should be able to switch to the other. Occurrence of hypersensitivity to cemiplimab or pembrolizumab is expected to be rare.

Background

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in Canada. Tobacco smoking, including exposure to second-hand smoke, remains the main cause of lung cancer. The most common symptoms of lung cancer are cough, dyspnea, hemoptysis, and chest pain, and systemic symptoms such as fatigue and weight loss. NSCLC is the most common histological type which accounts for 85% of patients. The overall survival (OS) for patients with NSCLC varies with disease stage. The estimated 5-year survival is 13 to 36% for patients with stage III disease, and only 10% for those with stage IV disease. At the time of diagnosis, the majority of patients with NSCLC are found to have advanced or metastatic disease. For these patients, the goal of treatment is not curative and is focused on improving symptoms and quality of life, delaying disease progression, and extending OS. Treatment decisions are guided by patient-related and disease-related characteristics, including age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumour stage, and presence of driver gene alterations, including epidermal growth factor receptor *(EGFR*) exon 19 deletion and exon 21 L858R mutation, anaplastic lymphoma kinase (*ALK*) translocation, and *c-Ros oncogene 1 (ROS*-1) rearrangement. However, gene alterations are detected in a small fraction of patients. Until recently, patients with advanced or metastatic NSCLC without targetable driver mutations were treated with combination chemotherapy regimens, but chemotherapy regimens alone have been widely replaced with programmed cell death 1 (PD1) and PD-L1 checkpoint immunotherapy treatments (as monotherapy or in combination with chemotherapy) in this setting. Pembrolizumab is the only currently funded immunotherapy used as monotherapy in this setting.

Cemiplimab has been approved by Health Canada for the first-line treatment of adult patients with NSCLC expressing PD-L1 in at least 50% of tumour cells (TPS of 50% or greater), as determined by a validated test, with no *EGFR*, *ALK*, or *ROS1* aberrations, who have locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC. Cemiplimab is a PD-1 immune checkpoint inhibitor and is supplied as a concentrate solution (50 mg/mL) for dilution as 250 mg/5mL and 350 mg/7 mL. The recommended dose of cemiplimab is 350 mg administered as an IV infusion over 30 minutes every 3 weeks.

Sources of Information Used by the Committee

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

- A review of 1 RCT in patients with untreated advanced or metastatic NSCLC whose tumours express PD-L1 in at least 50% of tumour cells and have no *EGFR*, *ALK*, or *ROS1* aberrations.
- One sponsor-submitted ITC which evaluated the comparative efficacy and safety of cemiplimab [redacted] for the treatment of patients with NSCLC with at least 50% PD-L1 expression, and 2 published ITCs identified in the literature.
- Patients' perspectives gathered by 2 patient groups: the Lung Health Foundation (known as the Ontario Lung Association) and Lung Cancer Canada (LCC).
- Input from public drug plans and cancer agencies that participate in the CADTH review process.

- Two clinical specialists with expertise diagnosing and treating patients with NSCLC.
- Input from 1 clinician group, the Ontario Health (Cancer Care Ontario) Lung and Thoracic Cancer Drug Advisory Committee.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Most respondents from the Lung Health Foundation input stated that they experienced some symptoms as a result of their lung cancer, including shortness of breath (64%), fatigue (57%), depression (25%), cough (21%), difficulty fighting infection (21%) and chest tightness (14%). Some respondents indicated that the psychosocial effects of having a disease with a poor prognosis was more debilitating than the physical symptoms. Side effects of currently available treatments reported among participants included: fatigue, nausea, vomiting, mood changes, diminished appetite, weight loss, hair loss, anemia, and neuropathy. Respondents reported that they expect the following key outcomes to be improved from any new drug or treatment: stopping or delaying disease progression with minimal side effects, access to treatments that are effective for advanced disease, and the ability to maintain some quality of life while on treatment. The LCC input evaluated respondents' treatment preferences, with the assumption that patients will have the option to be treated closer to home at local community hospitals with cemiplimab due to its fixed-dosing model. If given the choice between 2 equally efficacious treatment options, 91% of respondents would choose a therapy closer to home as it would provide benefits such as decreased travel time, savings on travel costs, and increased time with family and caregivers. A total of 97% of LCC respondents believed that having access to an additional treatment option closer to home would improve their HRQoL.

Clinician Input

Input From Clinical Experts Consulted By CADTH

The clinical experts consulted by CADTH noted that pembrolizumab is currently the only funded standard of care monotherapy used for the first-line treatment of advanced or metastatic NSCLC in patients with no EGFR, ALK or ROS1 aberrations and with PD-L1 positive tumours (TPS of 50% or greater). Cemiplimab monotherapy in PD-L1 positive (TPS of 50% or greater) NSCLC appears to be another treatment option with a similar mechanism of action in this setting. However, longer follow-up is needed to confirm that efficacy is maintained and similar to other available options. The clinical experts consulted by CADTH indicated that the only predictive marker of response to PD-1 or PD-L1 inhibitors as monotherapy is PD-L1 testing, which is routinely done in all newly diagnosed patients with advanced or metastatic NSCLC. Clinical response (symptom assessment) and radiological surveillance are used to determine whether a patient is responding to treatment in clinical practice. Improvement in survival and quality of life (i.e., less symptoms, higher functional status, or stabilization of symptoms) would be considered a clinically meaningful response to treatment. Treatment response is evaluated clinically at each visit, and radiologically, approximately every 3 to 4 months.

Clinician Group Input

The clinician group noted that the most important goals of any treatment for NSCLC is to improve OS and PFS. Monotherapy immunotherapy also has the additional benefit of avoiding chemotherapy. Patients most likely to benefit from cemiplimab are those with advanced or metastatic NSCLC and tumours having high levels of PD-L1 expression at least 50%. Cemiplimab would be used as monotherapy in first line for these patients and would be an alternative to pembrolizumab monotherapy, pembrolizumab plus platinum-doublet chemotherapy, or the combination of nivolumab-ipilimumab and 2 cycles of platinum-based chemotherapy. It would not be used as an additional therapy to currently available treatment options. In terms of response to treatment, the clinician group noted that the most meaningful response to treatment is the absence of disease progression followed by improvement in disease-related symptoms, which are assessed every 3 months in clinical practice. Disease progression or intolerable side effects were indicated as the primary reasons to discontinue therapy. The clinician group also noted that treatment continuation beyond progression should remain an option as some patients may benefit from continuing treatment beyond RECIST defined progression.

Drug Program Input

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The EMPOWER-Lung 1 trial comparator was platinum-doublet chemotherapy. This is likely not the most relevant comparator anymore. Should the relevant comparator be pembrolizumab alone or in combination with chemotherapy? How about nivolumab plus ipilimumab in combination with chemotherapy (not yet funded, but has a positive CADTH recommendation)?	According to the clinical experts, the most relevant comparator is pembrolizumab alone. On an individual level, the choice would be between cemiplimab monotherapy and pembrolizumab monotherapy. If a patient and/or clinician were to choose a treatment other than pembrolizumab monotherapy, there would be no compelling reason for them to consider cemiplimab monotherapy over that treatment. pERC agreed with the clinical experts.
Considerations for initiation of therapy	
There was about a 70% crossover rate from the chemotherapy alone arm to receive cemiplimab. Should subsequent line treatment be made available on a time-limited basis for patients who would not have had the chance to receive cemiplimab in the first line? And if so, would this only be extended to patients who received chemotherapy alone?	The clinical experts indicated that, in clinical practice, most patients receive immunotherapy alone or in combination with chemotherapy in the first-line setting. Patients who have not received immunotherapy in first-line should be considered to receive it second line (unless contraindicated). Available second-line options are pembrolizumab, nivolumab and atezolizumab. Second-line single drug immunotherapy is readily available in all provinces for patients who progress on chemotherapy. The EMPOWER-Lung 1 data should not be extended to the second-line setting. pERC agreed with the clinical experts and considered that patients who have not received first-line immunotherapy, including those who received chemotherapy alone, should not be eligible for cemiplimab treatment in the second-line setting as it is indicated for the first-line setting only and there is no evidence to support its use in subsequent lines.

Implementation issues	Response
In the EMPOWER-Lung 1 trial, at time of progression, patients were permitted to continue cemiplimab with the addition of histology-specific chemotherapy for up to 4 cycles. In clinical practice, should cemiplimab be continued beyond progressive disease as per the EMPOWER-Lung 1 trial?	The clinical experts noted that, in clinical practice, patients may continue immunotherapy for clinical benefit beyond disease progression. Adding chemotherapy to immunotherapy at disease progression remains investigational. Based on the small number of patients from the EMPOWER-Lung 1 trial that had chemotherapy added to immunotherapy, no definitive conclusions can be derived. At present, the addition of chemotherapy to immunotherapy at disease progression is not funded. pERC agreed with the clinical experts, noting that there is no evidence to support the addition of chemotherapy to immunotherapy at disease progression.
Patients who were never smokers were not eligible for the EMPOWER-Lung 1 trial. Should they be excluded if funded?	The clinical experts noted that never smokers should not be excluded from treatment with cemiplimab. However, since they were excluded from the EMPOWER-Lung 1 trial, there is a lack of evidence on cemiplimab treatment outcomes for this population. pERC agreed with the clinical experts that never smokers should not be excluded from treatment with cemiplimab.
Are patients who had previous adjuvant or neoadjuvant chemotherapy eligible to receive cemiplimab as was allowed in the EMPOWER-Lung 1 trial?	The clinical experts indicated that patients who had previous adjuvant or neoadjuvant chemotherapy or immunotherapy should be eligible to receive cemiplimab. In the EMPOWER-Lung 1 trial, patients had to be 6 months post adjuvant/neo adjuvant chemotherapy to be eligible to participate. pERC agreed with the clinical experts and considered that patients who received previous adjuvant or neoadjuvant chemotherapy should be eligible to receive cemiplimab. In addition, patients who progress at least 6 months after their last dose of immunotherapy should be eligible to receive cemiplimab.
If a patient receives 108 weeks of treatment and subsequently relapses, should they be eligible for retreatment and if so, would there be a maximum duration?	According to the clinical experts, patients should be eligible for retreatment for 17 cycles (1 year) if extrapolating from the KEYNOTE-024 trial that allowed retreatment for patients who stopped immune therapy early (before 2 years) because of complete response or for patients who completed 2 years of immune therapy and subsequently progressed. pERC agreed with the clinical experts that patients who completed 2 years of cemiplimab treatment and subsequently progressed and patients who discontinued cemiplimab after less than 2 years due to complete response should be eligible for retreatment for up to 17 cycles (1 year).
If a patient discontinues treatment before the completion of 108 weeks due to toxicity, but without relapse, could they restart and be treated to a maximum of 108 weeks?	pERC agreed with the clinical experts that patients who discontinue treatment before completion due to toxicity can restart treatment as long as the toxicity has resolved.
Considerations for prescribing of therapy	
In the EMPOWER-Lung 1 trial, the dose is 350 mg IV over 30 minutes every 3 weeks until progressive disease or 108 weeks (36 treatments – approximately 2 years). Is the 3 mg/kg IV over 30 minutes every 2 weeks dosing option for patients with low body weight currently available	The clinical experts noted that there is limited evidence to inform on alternative dosages other than that used in the EMPOWER trial. Ideally, the fixed dose used in the clinical trial should be used. The weight-based dosing would be based on extrapolation from other

Implementation issues	Response
for advanced cutaneous squamous cell carcinoma also recommended for patients with NSCLC?	disease settings. pERC agreed with the clinical experts.
Consider alignment with prescribing criteria for pembrolizumab and nivolumab/ipilimumab.	pERC considered this statement in their deliberations.
Generalizability	
In the EMPOWER trial, patients had an ECOG-PS of 0 or 1. Can patients with ECOG-PS > 1 be considered eligible?	pERC agreed with the clinical experts that patients with ECOG-PS up to 2 may be considered for eligibility based on data showing efficacy of other treatments such as chemotherapy in these patients.
Should treatment be funded for patients who have had pembrolizumab or nivolumab plus ipilimumab in combination with chemotherapy and wish to switch to cemiplimab on a time-limited basis?	According to the clinical experts, switching is not generally necessary. If patients did not progress on pembrolizumab or nivolumab plus ipilimumab, there is no benefit in switching to cemiplimab. pERC agreed with the clinical experts and did not consider it necessary to fund cemiplimab treatment for patients who have not progressed on pembrolizumab or nivolumab plus ipilimumab.
Funding algorithm	
PAG would like to note that other immune checkpoint inhibitors will not be funded in patients that experience disease progression while receiving cemiplimab.	pERC considered this statement in their deliberations.
Under what conditions would cemiplimab use be preferred over pembrolizumab, or nivolumab plus ipilimumab in combination with chemotherapy?	The clinical experts indicated that with similar efficacy and toxicity profiles, the choice of first-line immunotherapy as monotherapy will be based on access and physician choice. Similarly, the decision of first-line monotherapy vs. immunotherapy-chemotherapy combination will be based on access, toxicity considerations, and volume of disease (ultimately physician choice) in the absence of evidence-based comparison data. Longer-term follow-up data supports the use of pembrolizumab over cemiplimab. If funding allowed cemiplimab to continue with the addition of 4 cycles of chemotherapy at the time of progression, this would make it appealing to clinicians. pERC agreed with the clinical experts' response, except that they noted that the addition of 4 cycles of chemotherapy to cemiplimab at the time of disease progression should not be funded given the lack of evidence for this approach.
Care provision issues	
Pembrolizumab is currently reimbursed for this indication and nivolumab plus ipilimumab in combination with chemotherapy is currently undergoing price negotiations.	pERC considered this statement in their deliberations.

ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer; PS = performance status.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The EMPOWER-Lung 1 study is an ongoing randomized, multi-centre, open-label, phase III study of cemiplimab monotherapy versus platinum-based doublet chemotherapy in patients with stage IIIB, stage IIIC, or stage IV NSCLC who were not candidates for treatment with definitive chemoradiotherapy, whose tumours expressed PD-L1 in at least 50% of tumour cells, with no *EGFR*, *ALK*, or *ROS1* aberrations, and who had received no prior systemic treatment for their advanced disease. Never smokers were ineligible for the study. The primary end points were OS and PFS, and the key secondary end point was ORR. Patient-reported outcomes included HRQoL. Overall, mean age was 63 years (standard deviation [SD]: 8.4), and 85% of patients were men. A non-squamous histology was observed in 56% of patients and the disease stage at screening was metastatic (stage IV) in 84% of patients. Patients had to have an ECOG PS of 0 or 1 and approximately 73% of the patients in both treatment arms had an ECOG PS of 1. All patients were current or former smokers as never smokers were excluded from the trial. Of 3,662 patients screened, 710 were randomized, 356 patients to the cemiplimab monotherapy arm and 354 patients to the chemotherapy arm. The mean duration of follow-up was 14.04 months (SD = 7.5) overall and in both treatment arms.

Efficacy Results

Due to issues with PD-L1 testing identified during the sponsor's monitoring, samples from 235 patients tested before August 2018 had to be retested. Of these patients, 56 patients were found to have PD-L1 of less than 50% on retest. Consequently, a PD-L1 of at least a 50% population was pre-specified to include only patients with PD-L1 of at least 50% on retesting and those who were tested after August 2018 and were unaffected by testing irregularities. The PD-L1 of 50% or greater population consisted of 563 patients (n = 283 for cemiplimab and n = 280 for chemotherapy). Efficacy end points were assessed in the intention-to-treat (ITT) population (n = 710) as well as in the PD-L1 of 50% or greater population. Results for OS, ORR, PFS, and DOR in the PD-L1 of 50% or greater population were consistent with those in the ITT population.

Overall Survival

As of the data cut-off date (March 1, 2020), the median OS was 22.1 months (95% confidence interval [CI] lower bound = 17.7 months) in the cemiplimab arm versus 14.3 months (95% CI, 11.7 to 19.2 months) in the chemotherapy arm (P = 0.0022); the hazard ratio (HR) between groups was 0.676 (95% CI, 0.52 to 0.87).

Health-Related Quality of Life

Mean baseline scores for the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) global health status (GHS) scale were similar between patients in the cemiplimab and chemotherapy treatment arms. Mean change in score from baseline of greater than 5 points for the GHS was observed in the cemiplimab arm by cycle 2 (mean change [SD] 5.16 [20.49]), above 9 points by cycle 6 (9.38 [23.359]) and above 10 points by cycle 18 (10.53 [25.71]). It stayed above 10 points, with wide variation thereafter, to cycle 30. Mean change for GHS score in the chemotherapy arm was below 3 until cycle 12 and ranged from −8.33 (24.40) at cycle 18 to 5.56 (12.73) at cycle 21.

The mean GHS scores numerically favoured cemiplimab post-baseline up to cycle 6 and there were no consistent or notable differences between the arms at later time points.

Objective Response Rate

Complete response or partial response was observed in 36.5% of patients in the cemiplimab arm and 20.6% of patients in the chemotherapy arm. The odds ratio for comparison of cemiplimab to chemotherapy was 2.21 (95% CI, 1.58 to 3.10; P < 0.0001).

Progression-Free Survival

The median PFS was 6.2 months (95% CI, 4.5 to 8.3 months) in the cemiplimab arm versus 5.6 months (95% CI, 4.5 to 6.1 months) in the chemotherapy arm (P < 0.0001); the HR between groups was 0.593 (95% CI, 0.491 to 0.718).

Duration of Response

The Kaplan–Meier estimate of median DOR was 21.0 months (lower bound of 95% CI = 14.9 months) for cemiplimab and 6.0 months (95% CI, 4.3 to 6.4 months) for chemotherapy.

Harms Results

As of the data cut-off date, 88.2% of patients in the cemiplimab arm and 94.2% of patients in the chemotherapy arm had experienced at least 1 treatment-emergent adverse event (TEAE). In the cemiplimab arm, the most common TEAEs of any grade by preferred term experienced by at least 10% of patients were anemia (14.6%), decreased appetite (11.8%), and fatigue (10.1%). In the chemotherapy arm, the most common TEAEs of any grade by preferred term experienced by at least 10% of patients were anemia (50.0%), nausea (28.4%), alopecia (24.0%), decreased appetite (18.4%), neutropenia (18.4%), fatigue (17.0%), constipation (15.2%), thrombocytopenia (15.2%), vomiting (14.3%), neutrophil count decreased (12.3%), peripheral neuropathy (10.8%), pneumonia (10.8%), and platelet count decreased (10.5%).

Grade 3 to 4 TEAEs occurred in 28% of patients in the cemiplimab arm and 39% of patients in the chemotherapy arm. Discontinuation of study treatment due to AEs was reported for 6.5% of patients in the cemiplimab arm and 4.1% of patients in the chemotherapy arm. Serious TEAEs were reported for 28.2% of patients in the cemiplimab arm and 27.5% of patients in the chemotherapy arm.

TEAEs that led to death occurred in 9.6% of patients treated with cemiplimab and 9.1% of patients treated with chemotherapy. In 9 (3%) patients treated with cemiplimab, the events leading to death were considered related to treatment, and included autoimmune myocarditis, cardiac failure, cardiopulmonary failure, respiratory failure, septic shock, cardiorespiratory arrest, nephritis, and tumour hyperprogression (n = 1 each).

In the cemiplimab arm, 17.5% of patients experienced at least 1 treatment-emergent immune-related AE, and in the chemotherapy arm, 2.3% of patients experienced at least 1 treatment-emergent immune-related AE. Most of these events were less than grade 3, with 3.7% of patients in the cemiplimab arm and 0.3% of patients in the chemotherapy arm experiencing an immune-related AE that was grade 3 or higher. Grade 4 and 5 immune-related AEs were only reported in the cemiplimab arm, occurring in 0.8% and 0.3% of patients, respectively.

Critical Appraisal

The EMPOWER-Lung 1 trial was an open-label trial, and although patient blinding would not have been possible given the differences in the 2 study treatment regimens, detection

and performance bias that may result from lack of blinding of patients and investigators to assigned study treatments cannot be ruled out, especially for subjective patient-reported outcomes. Issues with PD-L1 testing were discovered when over 50% of the planned population had been recruited, necessitating retesting of the 235 randomized patients at that point, but not all of them had remaining tissue samples (38%) and not all of the retested samples proved to have PD-L1 of 50% or greater (24%). As a result, analyses were also conducted in the population with confirmed PD-L1 TPS of 50% or greater. The ITT population represents a truly randomized sample but includes some patients who did not in fact meet the inclusion criteria of the trial; the PD-L1 of 50% or greater population is not strictly a randomized sample and serves as supportive data, as it may be more clinically relevant. The findings across these 2 populations were largely similar. Amendments to the protocol were made to allow patients who progressed on cemiplimab monotherapy to continue cemiplimab treatment with the addition of 4 cycles of histology-specific chemotherapy until further progression was observed. Similarly, patients in the chemotherapy arm were allowed to cross over to cemiplimab after initial disease progression on chemotherapy. This crossover was not accounted for in the main OS analysis and may have biased the findings in favour of chemotherapy (i.e., underestimated the effect of cemiplimab). Sensitivity analyses were conducted to account for the crossover effect, and these were consistent with the primary analyses.

The EMPOWER-Lung 1 trial included a heterogenous population of patients with NSCLC and a wide range of clinical presentations were well-represented. However, a few patient groups were not included, notably never smokers and patients who were immunocompromised, or had a history of autoimmune diseases, and those with ECOG PS of 2 or higher. Therefore, generalizability of results to these patient groups may be limited. In addition, about 44% of patients presented with squamous histology, which is higher than what is expected in clinical practice (about 30%). The most important limitation of the evidence in terms of generalizability is the relevance of chemotherapy as a comparator in Canadian clinical practice, where the standard of care for the treatment of patients with advanced or metastatic high PD-L1 expressing NSCLC and without oncogenic alterations includes immune checkpoint inhibitors. Pembrolizumab, with or without chemotherapy, is funded and is widely used for this indication. Therefore, the benefit of cemiplimab compared to chemotherapy in terms of improved survival in this patient population is limited in informing treatment choice in Canadian clinical practice.

Indirect Comparisons

Description of Studies

[redacted]

Identified in the literature search were 2 additional published ITCs, 1 of which included a comparison of cemiplimab against pembrolizumab plus chemotherapy. However, due to serious limitations in the published ITCs, conclusions could not be drawn based on the findings and the results are not included in this summary.

Efficacy Results

[redacted]

[redacted]

Harms Results

[redacted]

Critical Appraisal

Few inferences can be made from the results of the network meta-analysis (NMA) because of important limitations with the included studies and the methods and assumptions made in the NMA. The key limitation related to the choice of relevant comparators did not include [redacted], a comparator considered to be relevant in the Canadian treatment landscape for patients with NSCLC expressing PD-L1 50% or greater, though the most relevant comparator, [redacted], was captured. Therefore, the relevance of the systematic literature review and NMA to the Canadian context is unclear. The outcomes assessed were appropriate, though other important outcomes such as HRQoL were deemed not possible to analyze due to differences in study reporting. Moreover, several potential sources of heterogeneity exist across the trials that limit their comparison, including substantial heterogeneity across trial populations, such as tumour histology and smoking status. The available trials formed networks with no closed loops; therefore, it was not possible to validate the transitivity assumption of NMA and check for consistency of results between direct and indirect comparisons. Random-effects models were attempted and determined not to be feasible to include as the base-case analysis due to the small number of included studies.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost utility analysis Partitioned survival model
Target populations	Adult patients with non–small cell lung cancer (NSCLC) expressing PD-L1 (Tumour Proportion Score [TPS] ≥ 50%), as determined by a validated test, with no EGFR, ALK or ROS1 aberrations, who have: • locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or • metastatic NSCLC.
Treatment	Cemiplimab
Submitted price	$8,200 per 350 mg vial
Treatment cost	At the submitted price of $8,200 per 350 mg dose, administered intravenously every 3 weeks until progression, the monthly cycle cost of cemiplimab is $11,955.56.

Component	Description
Comparators	• Pembrolizumab • Chemotherapy
Perspective	Canadian publicly funded health care payer
Outcomes	Quality-adjusted life-years (QALYs), life-years (LYs)
Time horizon	Lifetime (30 years)
Key data sources	Phase III R2810-ONC-1624 trial and sponsor's conducted NMA (KEYNOTE-024 trial)
Submitted results	• The ICER for cemiplimab was $26,521 per QALY when compared to chemotherapy (incremental costs = $56,408; incremental QALYs = 2.13). • Pembrolizumab was extendedly dominated through chemotherapy and cemiplimab (i.e., higher ICER than cemiplimab when compared with chemotherapy).
Key limitations	• There was high uncertainty in the results from the NMA used to inform the relative efficacy of cemiplimab and pembrolizumab. The networks were sparse and there was a high degree of heterogeneity in baseline characteristics across included trials. • The sponsor inappropriately included chemotherapy as a comparator. Clinical experts consulted by CADTH advised that chemotherapy is not an appropriate comparator for cemiplimab. Patients are expected to be treated with chemotherapy only if they are ineligible for immunotherapy in the first-line setting. • The OS and PFS extrapolation for cemiplimab and pembrolizumab lacked clinical validity. The PFS and OS for pembrolizumab predicted from the sponsor's model were substantially lower than those reported in the KEYNOTE-024 trial. • The treatment dosage for pembrolizumab and subsequent treatment regimens did not reflect the standard of care in Canada. • Health utility values applied for pre-progression and post-progression health states did not align with clinical expectations. The health utility value applied in the sponsor's model for pre-progression health state was higher than the age-specific general population utility norm, and the utility value for progressed patients did not adequately capture the expected negative impact of cancer progression on health-related quality of life.
CADTH reanalysis results	• CADTH performed reanalysis by applying the following changes: excluding chemotherapy as a comparator; assuming equal OS and PFS for cemiplimab and pembrolizumab; using an alternative model to extrapolate PFS; applying weight-based dosing with vial sharing for pembrolizumab; applying the same incidence rates of adverse events for cemiplimab and pembrolizumab; applying alternate health state utility values; and revising subsequent treatment regimens based on clinical expert opinion. • Results from CADTH base case showed that cemiplimab resulted in higher costs by $125,981 ($266,281 vs. $140,300) and equal QALYs compared to pembrolizumab. The probability of cemiplimab being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 was 0%. A minimum price reduction of 61% is required for cemiplimab to provide cost-savings when compared with pembrolizumab. • Results from scenario analysis showed that when a treatment stopping rule of 2 years was applied to cemiplimab to align with the R2810-ONC-1624 trial and funding criteria for pembrolizumab, cemiplimab had higher costs by $27,090 ($167,390 vs. $140,300) and equal QALYs compared to pembrolizumab. Thus, the cost difference between cemiplimab and pembrolizumab is reduced when a treatment stopping rule of 2 years is applied to cemiplimab. A minimum price reduction of 25% is required for cemiplimab to provide cost-savings when compared with pembrolizumab in this scenario.

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life year; NSCLC = non–small cell lung cancer; NOC = notice of compliance; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALYs = quality-adjusted life-years; TPS = Tumour Proportion Score; WTP = willingness to pay.

Budget Impact

The sponsor estimated the budget impact of cemiplimab over 3 years. CADTH identified the following key limitations with the sponsor's analysis: treatment cost of pembrolizumab is overestimated, treatment duration adopted in the budget impact analysis is misaligned with the cost-utility analysis (CUA), and the number of patients eligible for cemiplimab is uncertain. CADTH reanalysis included applying weight-based dosing with vial sharing for pembrolizumab, aligning treatment duration estimates with the CUA, and revising the eligible population.

The sponsor's results suggested that the reimbursement of cemiplimab would lead to a budgetary savings of $7,343,746 over a 3-year time horizon. In the CADTH base case, the budget impact of reimbursing cemiplimab is expected to be $2,341,491 in year 1, $5,563,150 in year 2, and $6,012,679 in year 3, with a 3-year total of $13,917,320. If a treatment stopping rule of 2 years is applied for cemiplimab to align with the R2810-ONC-1624 trial and funding criteria for pembrolizumab, the estimated budget impact decreases to $3,136,771.

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: April 13, 2022

Regrets: Two members did not attend.

Conflicts of interest: None