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Reimbursement Recommendation

Durvalumab (Imfinzi) and Tremelimumab (Imjudo)

Indication: In combination with platinum-based chemotherapy for the first-line treatment of adult patients with metastatic non–small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumour aberrations.

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Imfinzi and Imjudo in Combination With Platinum-Based Chemotherapy?

Canada's Drug Agency (CDA-AMC) recommends that Imfinzi in combination with Imjudo and platinum-based chemotherapy should be reimbursed by public drug plans for the first-line treatment of adult patients with metastatic non–small cell lung cancer (NSCLC) with no sensitizing *EGFR* mutations or *ALK* genomic tumour aberrations if certain conditions are met.

Which Patients Are Eligible for Coverage?

Imfinzi and Imjudo, in combination with platinum-based chemotherapy should only be covered to treat adult patients with NSCLC who have stage IV NSCLC with tumours that lack sensitizing *EGFR* mutations or *ALK* genomic tumour aberrations and have not previously been treated with chemotherapy or other systemic therapy for metastatic disease. Patients must not have untreated or progressive brain metastases.

What Are the Conditions for Reimbursement?

Imfinzi and Imjudo, in combination with platinum-based chemotherapy should only be reimbursed if prescribed by a clinician with expertise and experience in treating NSCLC, and if the cost of Imfinzi and Imjudo, in combination with platinum-based chemotherapy does not exceed the total cost of treatment with the least costly immune checkpoint inhibitors (ICIs) plus a platinum-based chemotherapy regimen reimbursed for the same indication.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial showed that after a median of 12.5 months follow-up, patients treated with Imfinzi and Imjudo, along with standard of care (SOC) chemotherapy had significantly better overall survival (OS) and progression-free survival (PFS) compared to those who received SOC chemotherapy alone.
- Based on the CDA-AMC assessment of health economic evidence, Imfinzi and Imjudo do not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Imfinzi and Imjudo compared with other ICIs plus platinum-based chemotherapy regimens reimbursed for the same indication over the duration of treatment.

Summary

- Patients expressed a need for new treatments that extend life, offer a cure, maintain quality of life (QoL), and have fewer side effects. The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) found that Imfinzi and Imjudo, combined with SOC chemotherapy, met some of these needs by improving OS and PFS compared to SOC chemotherapy alone, and provides an additional treatment option.
- pERC observed that severe adverse events (AEs) were more frequent with Imfinzi and Imjudo combined with SOC chemotherapy compared to SOC chemotherapy alone. However, these AEs were consistent with the known and manageable safety profiles of the drugs involved.
- Based on public list prices, Imfinzi and Imjudo are estimated to cost the public drug plans approximately $11.5 million over the next 3 years.

Additional Information

What Is Metastatic NSCLC?

Lung cancer is the leading cause of cancer-related death in Canada. NSCLC makes up about 89% of cases. Metastatic NSCLC is when NSCLC spreads to other parts of the body. Nearly one-half of patients (48.4%) with NSCLC have metastases at diagnosis. Changes in *EGFR* and *ALK* genes cause mutations in about 25% of patients with NSCLC, meaning around 74.5% do not have these mutations.

Unmet Needs in Metastatic NSCLC

The main unmet needs in treating metastatic NSCLC are treatments that prolong life or cure the disease, improve QoL, and have better tolerability with lower rates of immune-related AEs.

How Much Does Imfinzi and Imjudo Cost?

Treatment with Imfinzi and Imjudo plus platinum-based chemotherapy is expected to cost $22,010, per 21-day cycle in the initial treatment stage (up to week 12), $15,387 per 21-day cycle in the initial maintenance phase (week 13 to 16), and $8,952 per 21-day cycle in the subsequent maintenance phase (after week 16).

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that durvalumab, in combination with tremelimumab and platinum-based chemotherapy, be reimbursed for the first-line treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) genomic tumour aberrations only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, open-label, global study (POSEIDON) (N = 1,013), demonstrated that durvalumab and tremelimumab plus SOC chemotherapy results in added clinical benefit for first-line treatment of adult patients with metastatic NSCLC with no sensitizing *EGFR* mutations or *ALK* genomic tumour aberrations, compared to SOC chemotherapy alone. Specifically, after a median follow-up of 12.5 months (range, 0.0 to 44.5 months), the median OS was 14.0 months with durvalumab and tremelimumab plus SOC chemotherapy versus 11.7 months with SOC chemotherapy alone (hazard ratio [HR] = 0.77; 95% confidence interval [CI], 0.650 to 0.916). Similarly, after a median follow-up of 10.3 months (range, 0.0 to 23.1 months) in censored patients, the median PFS was 6.2 months with durvalumab and tremelimumab plus SOC versus 4.8 months with SOC chemotherapy alone (HR = 0.72; 95% CI, 0.600 to 0.860). The between-group differences were statistically significant in favour of durvalumab and tremelimumab plus SOC chemotherapy for both OS and PFS. The survival benefit was maintained after a median follow-up of 63.4 months (range, 0.0 to 73.9 months) in censored patients, with a 5-year OS probability of 15.7% with durvalumab and tremelimumab plus SOC chemotherapy versus 6.8% with SOC chemotherapy alone (HR for median OS at 5 years = 0.76; 95% CI, 0.642 to 0.893).

pERC noted that although the overall incidence of AEs in the POSEIDON trial was similar between treatment arms, the reported grade 3 or 4 AEs of special interest or AEs of potential interest, as well as grade 3 or 4 immune-mediated AEs, were higher with durvalumab and tremelimumab plus SOC chemotherapy than SOC chemotherapy alone. However, pERC determined that the AEs were consistent with the known and manageable safety profile of durvalumab, tremelimumab, and SOC chemotherapy.

Patients identified a need for access to new treatment options that prolong life, provide a cure, maintain QoL, delay the onset of disease symptoms, and have reduced side effects. pERC concluded that, compared with SOC chemotherapy alone, durvalumab and tremelimumab plus SOC chemotherapy met some of the patients' needs as demonstrated in improved OS and PFS results, and offers an additional treatment option. However, pERC found inconclusive evidence on the effects of durvalumab and tremelimumab plus SOC chemotherapy on patient's QoL. This was due to decreased patient survey completion over time, the subjectivity of the patient-reported outcomes in a nonblinded comparative trial, and the inability to determine the statistical significance of the results.

At the sponsor-submitted price for durvalumab and tremelimumab plus platinum-based chemotherapy (defined by the sponsor as nab-paclitaxel or gemcitabine or pemetrexed or paclitaxel, combined with

cisplatin or carboplatin), and publicly listed prices for platinum-based chemotherapy alone, cemiplimab plus platinum-based chemotherapy, pembrolizumab plus platinum-based chemotherapy, and nivolumab and ipilimumab plus platinum-based chemotherapy, treatment with durvalumab and tremelimumab plus platinum-based chemotherapy was more costly than all other comparator regimens. As there is uncertainty regarding the comparative effectiveness of durvalumab and tremelimumab plus platinum-based chemotherapy compared to currently available ICIs plus platinum-based chemotherapy regimens, the total drug cost of durvalumab and tremelimumab plus platinum-based chemotherapy should not exceed the total drug cost of currently available ICIs plus platinum-based chemotherapy regimens.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with durvalumab and tremelimumab, in combination with platinum-based chemotherapy, should be reimbursed in adult patients with NSCLC who meet all of the following criteria: • have stage IV NSCLC • have had no prior treatment with chemotherapy or other systemic therapy for metastatic disease • have tumours that lack sensitizing *EGFR* mutations or *ALK* genomic tumour aberrations.	Evidence from the POSEIDON trial demonstrated that treatment with durvalumab and tremelimumab plus platinum-based chemotherapy likely resulted in a clinical benefit in patients with these characteristics.	pERC agreed with the clinical experts that patients with unresectable locally advanced NSCLC of any stage should be considered if the disease is not amenable to any curative intent option.
2. Patients must not have untreated or progressive CNS or leptomeningeal metastases.	The POSEIDON trial excluded such patients, and there is no evidence regarding the safety and efficacy of durvalumab and tremelimumab plus platinum-based chemotherapy treatment in patients with these characteristics.	—
3. Patients should have a performance status of 0 to 1.	The POSEIDON trial enrolled patients with a WHO or ECOG performance status of 0 or 1.	The clinical experts stated that patients with an ECOG PS of 2 (but not those with an ECOG PS of 3 or 4) could be considered for treatment with durvalumab and tremelimumab plus chemotherapy if the perceived benefits exceed predicted risks. pERC noted that selecting suitable patients may not be solely based on ECOG status; therefore, clinicians may consider using durvalumab and tremelimumab plus platinum-based chemotherapy for patients with an ECOG PS of greater than 1 based on their professional discretion.

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
4. Treatment with durvalumab and tremelimumab, in combination with platinum-based chemotherapy, should be discontinued upon occurrence of clinical and/or radiologic evidence of progressive lung cancer.	In the POSEIDON trial, treatment with durvalumab and tremelimumab combination therapy, durvalumab monotherapy, or SOC chemotherapy was discontinued upon clinical progression or radiological progressive disease, and there are no data to support continued treatment with durvalumab beyond progression.	Clinical experts stated that appropriate discontinuation criteria for durvalumab and tremelimumab would comprise clear widespread progression that is not pseudoprogression and is not oligoprogression amenable to local therapies delivered with the intent of controlling all areas of significant progression.
5. Patients experiencing unresolved or intolerable toxicity from durvalumab, or tremelimumab, or chemotherapy may discontinue the offending therapy and continue with the remaining components of the regimen.	In the POSEIDON trial, treatment with durvalumab and tremelimumab combination therapy, durvalumab monotherapy, or SOC chemotherapy was discontinued if AEs met discontinuation criteria.	According to the clinical experts, a continuation of treatment with durvalumab and tremelimumab after discontinuation of chemotherapy due to chemotherapy-related AEs aligns with current clinical practice.
Prescribing		
6. Durvalumab and tremelimumab in combination with platinum-based chemotherapy should be prescribed by clinicians with expertise and experience in treating NSCLC. The treatment may be supervised and delivered in outpatient specialized oncology clinics with expertise in delivering systemic therapy and managing immunotherapy-related side effects.	This condition is meant to ensure that durvalumab and tremelimumab are prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
7. Durvalumab and tremelimumab should only be reimbursed when started with platinum-based chemotherapy. Durvalumab may be given with pemetrexed for maintenance therapy.	The efficacy and safety evidence from the POSEIDON trial was based on using durvalumab and tremelimumab in combination with platinum-based chemotherapy.	pERC agreed with the clinical experts that patients should receive a minimum of 1 chemotherapy cycle to be eligible for continued treatment with durvalumab and tremelimumab per the POSEIDON trial. In the POSEIDON trial, patients with nonsquamous NSCLC who had received pemetrexed plus carboplatin or cisplatin during the chemotherapy stage and who had not progressed after 4 cycles were eligible to receive maintenance therapy with pemetrexed and with durvalumab maintenance therapy.
Pricing		
8. The total cost of durvalumab and tremelimumab plus platinum-based chemotherapy[a] should be negotiated so that it does	The findings of the indirect evidence suggested a similar clinical benefit in OS and PFS when comparing durvalumab	—

Reimbursement condition	Reason	Implementation guidance
not exceed the total cost of treatment with the least costly immune checkpoint inhibitors plus platinum-based chemotherapy regimen reimbursed for the same indication.	and tremelimumab plus platinum-based chemotherapy to these comparators.	
Feasibility of adoption		
9. The feasibility of adoption of durvalumab and tremelimumab plus platinum-based chemotherapy 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 the CDA-AMC estimate.	—

AE = adverse event; CDA-AMC = Canada's Drug Agency; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; PS = performance status; SOC = standard of care.

[a]The sponsor defined platinum-based chemotherapy as nab-paclitaxel or gemcitabine or pemetrexed or paclitaxel, combined with cisplatin or carboplatin.

Discussion Points

- **Quality of main evidence**: pERC noted that in addition to the statistically significant differences in the OS and PFS resulting in favour of durvalumab and tremelimumab plus platinum-based chemotherapy compared to platinum-based chemotherapy alone in the POSEIDON trial, a Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment indicated with moderate certainty that the gains were likely clinically meaningful.
- **Relevant comparators:** pERC noted that the POSEIDON trial compared durvalumab and tremelimumab plus platinum-based chemotherapy to platinum-based chemotherapy alone. pERC considered that other combination therapies that would be relevant comparators to durvalumab and tremelimumab plus platinum-based chemotherapy for the requested indication include pembrolizumab plus platinum-based chemotherapy; nivolumab and ipilimumab plus platinum-based chemotherapy or cemiplimab plus platinum-based chemotherapy, although cemiplimab plus platinum-based chemotherapy is not currently reimbursed for this indication.
- **Indirect evidence:** pERC discussed the results of a sponsor-submitted indirect treatment comparisons (ITCs) that compared durvalumab and tremelimumab plus platinum-based chemotherapy with other combination therapies and determined that the limitations of the matching-adjusted indirect comparisons (MAICs), including not considering all potential effect modifiers in the adjustments and the reduced effective sample size, precluded drawing definitive conclusions about the relative efficacy of durvalumab and tremelimumab plus platinum-based chemotherapy versus the comparators used in the analyses.
- **Tumours with low or negative PD-L1 expression**: pERC noted that the clinical experts identified a need for additional treatment options for patients with low or negative tumoural PD-L1 expression,

including the need for treatment options with a more favourable toxicity profile. The committee observed that the POSEIDON trial included patients with any tumoural PD-L1 expression, and subgroup analyses indicated that OS and PFS outcomes were consistent across the PD-L1 expression subgroups. However, the analyses involved a small number of patients, and no adjustments were made for multiple testing, thus precluding the ability to draw a definitive conclusion from the results.

- **Options for less responsive mutations:** pERC noted that the clinical experts identified a need for subgroups of patients with mutations associated with a lower chance of responding to immuno-oncology therapy or with a generally poor prognosis, such as *KRAS*, *STK11*, and *KEAP* mutations. Post hoc exploratory subgroup analyses of OS in *KRAS* and *STK11* mutation subgroups performed in patients with a nonsquamous histology in the POSEIDON trial showed an OS benefit of durvalumab and tremelimumab plus SOC chemotherapy compared to SOC chemotherapy alone, but the number of patients was small. pERC acknowledged that the clinical experts identified that the current evidence is hypothesis-generating and that testing for these mutations is not routinely performed or may not be accessible in practice.
- **Duration of ICIs in the economic evaluation:** pERC noted that in contrast with other ICI regimens with a stopping rule implemented at approximately 2 years, durvalumab may be used until disease progression. pERC observed that despite the differences in maximum treatment duration, the current evidence was insufficient to support the sponsor's claim that the OS and PFS benefits for durvalumab and tremelimumab plus platinum-based chemotherapy would persist for a more extended period than other ICIs plus platinum-based chemotherapy regimens. As a result, the committee concluded that there is no robust evidence to support a greater total cost of treatment with durvalumab and tremelimumab plus platinum-based chemotherapy compared with currently available ICIs plus platinum-based chemotherapy regimens.

Background

Lung cancer is the leading cause of cancer-related death in Canada; it is heterogenous in nature, comprised of several different disease subtypes, categorized by histology, staging, and mutation driver status. NSCLC is the most common type, representing approximately 89% of all lung cancer diagnoses in Canada. NSCLC can be categorized into histologic subtypes: squamous cell carcinoma (17% to 27% of NSCLC cases) and nonsquamous cell carcinoma (73% to 83% of NSCLC cases). At early stages, NSCLC may be asymptomatic, with symptoms only developing when the cancer has become more advanced and is no longer amenable to curative intent therapy. Sometimes presenting symptoms can be nonspecific (common manifestations include cough, chest pain, hemoptysis, fatigue, weight loss, dyspnea, hoarseness, and recurring infections with bronchitis and pneumonia), contributing to delays in diagnosis. Screening programs for NSCLC are being established throughout Canada, but many patients who would qualify for NSCLC screening live in jurisdictions where it is not yet available. Although *EGFR* mutations and *ALK* aberrations

have been identified as oncogenic driver mutations, which collectively occur in approximately 25% of patients, an estimated 74.5% of patients with NSCLC do not have *EGFR* mutations or *ALK* aberrations.

Nearly one-half (48.4%) of NSCLC cases are metastatic (stage IV). For the majority of patients with metastatic NSCLC whose tumours lack actionable genomic alterations, treatment is selected based on tumour histology (squamous or nonsquamous); PD-L1 expression (which is predictive of response to ICIs); and patient symptom burden (as measured by the Eastern Cooperative Oncology Group Performance Status [ECOG PS]), comorbidities, and preferences. In recent years, new treatment options include ICI-based therapies (either as monotherapy or in combination with chemotherapy), which are now the standard first-line treatment for metastatic NSCLC without targetable genomic alterations. For patients with any or unknown tumoural PD-L1 expression, first-line options include pembrolizumab plus platinum-based chemotherapy, nivolumab and ipilimumab plus platinum-based chemotherapy, or cemiplimab plus platinum-based chemotherapy. Monotherapy with pembrolizumab or cemiplimab may be selected as first-line treatment for patients with high PD-L1 expression (PD-L1 expression on ≥ 50% of tumour cells). Of note, cemiplimab (with or without platinum-based chemotherapy) is not currently funded in Canada. Platinum-based chemotherapy alone is also a potential first-line treatment option; however, clinical experts consulted by CDA-AMC noted that this would be reserved for patients with significant contraindications to immunotherapy for whom the perceived risks of ICI-based treatment outweigh any potential benefits. Clinical experts indicated that immuno-oncology treatment is considered the backbone of therapy for the first-line treatment of metastatic NSCLC without targetable oncogenic aberrations. The goals of therapy for patients with metastatic NSCLC, as identified by clinical experts, include prolonging survival, extending the time before disease progression, decreasing cancer-related symptoms, and maintaining or improving QoL.

Durvalumab and tremelimumab, in combination with platinum-based chemotherapy, have been approved by Health Canada for the first-line treatment of patients with metastatic NSCLC with no sensitizing *EGFR* mutations or *ALK* genomic tumour aberrations. Durvalumab (an engineered monoclonal antibody) and tremelimumab (a selective, fully human immunoglobulin G2 antibody) are antineoplastic agents. Durvalumab is available as a 50 mg/mL concentrate for IV infusion and tremelimumab is available as a 20 mg/mL concentrate for IV infusion. According to the product monograph, the recommended dosing for durvalumab in combination with tremelimumab and platinum-based chemotherapy differs based on the patient's body weight. The recommended dose during chemotherapy is either durvalumab 1,500 mg in combination with tremelimumab 75 mg and platinum-based chemotherapy (body weight ≥ 30 kg) or durvalumab 20 mg/kg in combination with tremelimumab 1 mg/kg and platinum-based chemotherapy (body weight < 30 kg) every 3 weeks (21 days) for 4 cycles. After platinum-based chemotherapy, the recommended dose of durvalumab is 1,500 mg (body weight ≥ 30 kg) or 20 mg/kg (body weight < 30 kg) every 4 weeks and histology-based pemetrexed maintenance therapy every 4 weeks. A fifth dose of tremelimumab is to be given at week 16 alongside durvalumab dose 6.

Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized, open-label study in patients with metastatic NSCLC with tumours without activating *EGFR* mutations and *ALK* fusions; and 1 sponsor-submitted ITC
- patients' perspectives gathered by 3 patient groups (from 1 joint patient group submission), the Canadian Cancer Survivor Network (CCSN), Lung Cancer Canada (LCC), and the Lung Health Foundation (LHF)
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- input from 2 clinician group(s), the LCC-Medical Advisory Committee (MAC) and the Ontario Health-Cancer Care Ontario (OH-CCO) Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

A joint patient group submission was received from the CCSN, LCC, and the LHF. The CCSN is a national network of patients, families, survivors, friends, community partners, funders, and sponsors who have come together to promote the very best SOC, including early diagnosis, timely treatment and follow-up care, support for cancer patients, or issues related to survivorship or quality of end-of-life care. The LCC is a registered national charitable organization that serves as Canada's leading resource for lung cancer education, patient support, research, and advocacy. The LHF is a registered charity that assists and empowers people living with or caring for others with lung disease. It is a recognized leader, voice, and primary resource in the prevention and control of respiratory illness, tobacco cessation and prevention, and its effects on lung health.

The CCSN, LCC, and LHF collectively worked to produce a survey to be circulated among all 3 of their networks. The survey was disseminated through the 3 organization's social media platforms, as well as CCSN's monthly newsletter to gather responses from August 1, 2024, to the date of writing of the patient group submission. LCC also conducted 1 interview on October 8, 2024, with a patient who was a part of the POSEIDON trial.

Respondents from a previous survey and submission on durvalumab in combination with chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery indicated for the treatment of patients with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known *EGFR* or *ALK* rearrangements shared their experiences with lung cancer and durvalumab. The following symptoms were experienced with lung cancer affecting their QoL: fatigue, pain in chest, shoulder, back or arms, shortness

of breath, infections, pneumonia and/or bronchitis, weight loss, appetite loss, hair loss, or teeth loss. Chemotherapy, immunotherapy, targeted therapy, radiation, surgical therapy, and participation in clinical trials were identified as current treatment options by respondents. The respondents highlighted that these regimens were generally well tolerated; however, they noted several side effects (e.g., joint and muscle pain, fatigue, diarrhea, neuropathy, weight loss, anemia, nausea, vomiting, constipation, migraines, change in vision and hearing, and forgetfulness). One respondent mentioned that they were doing well until their CT scan showed disease progression.

Fatigue was noted as the main side effect with durvalumab by the respondents. In comparison to other therapies, at least 2 respondents indicated that symptom management was much better with durvalumab; however, there was little to no difference for side effects, ease of use, and disease progression.

Respondents noted several unmet needs such as better mental health support, availability of immunotherapy for a longer duration, issues with accessing counselling, and travel costs associated with therapy. The respondents highlighted the following outcomes as important: disease management, prolonged life, a cure, QoL, delayed onset of symptoms, easy to use medication, reduction in side effects, and access to new options for treatment.

The patient who took part in the POSEIDON trial mentioned that diagnosis took a while before they could get started on treatments. The physician who treated the patient confirmed that the patient received durvalumab and tremelimumab in combination with platinum-based chemotherapy. The patient started with first-line chemotherapy and received durvalumab simultaneously. While on chemotherapy, the patient received appropriate care and dealt with minimal side effects including mild diarrhea, bone pain, itching, and tiredness especially on the days of chemotherapy. While on durvalumab, the patient noted temporary side effects such as occasional diarrhea, itching, and hot flashes. The patient highlighted the ability to carry out regular activities during treatment.

Clinician Input

Input From Clinical Experts Consulted for This Review

Clinical experts consulted by CDA-AMC identified goals of first-line treatment of metastatic NSCLC are to improve survival, extend the time before disease progression, decrease cancer-related symptoms, and to improve QoL. Clinical experts acknowledged that currently available first-line treatment options for metastatic NSCLC have been associated with a survival benefit compared to chemotherapy alone but noted that there remains an unmet need for patients with low or negative PD-L1 expression, including options that have lower rates of immune-related AEs. Clinical experts recognized that there is significant unmet need for subgroups of patients with mutations associated with a lower chance of responding to immuno-oncology therapy or with a generally poor prognosis, such as *KRAS*, *STK11*, and *KEAP* mutations. Clinical experts identified that durvalumab and tremelimumab plus platinum-based chemotherapy would be used as a standalone treatment for patients with previously untreated metastatic NSCLC not harbouring a targetable oncogenic aberration with an associated SOC first-line targeted therapy option (e.g., *EGFR* mutation or *ALK* rearrangement) and that this regimen would not be expected to cause a shift in the current treatment paradigm but would be

an additional first-line option combining immuno-oncology treatment and chemotherapy. Clinical experts expressed that patients ideally suited for this treatment would have previously untreated metastatic NSCLC, good ECOG PS (0 or 1), no actionable oncogenic mutations or translocations (including *EGFR* mutations and *ALK* rearrangements), any tumoural PD-L1 expression, no significant comorbidities, and the ability to report adverse effects as soon as possible. Clinical experts expressed that, in practice, the durvalumab and tremelimumab plus platinum-based chemotherapy regimen is anticipated to be used mostly in patients with PD-L1 of less than 50% but highlighted that patients with any PD-L1 status were included in the POSEIDON trial; therefore, approval and funding should be per the trial outcomes. Clinical experts also noted that durvalumab and tremelimumab plus platinum-based chemotherapy may be an option for patients with tumours that have biomarkers that may predict a poor or no response to currently available ICI-based therapies (e.g., those that do not express PD-L1 or have *KRAS*, *STK11*, or *KEAP* mutations). Clinical experts stated that the treatment strategy would be based on an informed decision by the patients in consultation with a medical oncologist and response to treatment would be determined through clinical and radiological assessments. Treatment and monitoring would be administered locally for patients who live close to regional cancer clinics and at community oncology networks for patients living in remote settings, where specially trained family physicians or internists would oversee day-to-day treatment. Clinical experts acknowledged that it would be appropriate for any systemic therapy unit and lung cancer treatment team currently administering other combinations of immuno-oncology therapy and chemotherapy to deliver treatment with durvalumab and tremelimumab plus platinum-based chemotherapy. According to clinical experts, discontinuation of first-line treatment for metastatic NSCLC would occur when there is disease progression, unacceptable toxicity, or when the patient chooses to stop treatment. One clinical expert also noted that discontinuation of treatment may occur when there is suspicion of progression and risk of rapid clinical deterioration if treatment is continued. According to clinical experts, as is the case with any immunotherapy-containing regimen, early identification and management of immune-related AEs is paramount to reduce the risk of treatment-related morbidity or mortality. Subspecialist consultation may be required to effectively manage immune toxicity.

Clinician Group Input

Two clinician groups, the LCC-MAC and the OH-CCO Lung Cancer Drug Advisory Committee provided input for this submission. The LCC-MAC, is a national charity providing support and education, supporting research, and providing clinician input for submissions of new lung cancer drugs to the health technology assessment process for many years. The OH-CCO Lung Cancer Drug Advisory Committee provides evidence-based clinical and health system guidance on drug-related issues to support the mandate of CCO including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program.

A total of 19 clinicians from the LCC-MAC and 5 clinicians from the OH-CCO Lung Cancer Drug Advisory Committee provided input for this submission. The submission from LCC-MAC was informed by data and information from publicly available sources, primarily published manuscripts, and conference presentations, together with clinical experience of the LCC-MAC members. Information from OH-CCO was gathered via teleconference meeting and emails.

The OH-CCO clinician group highlighted that the treatment combination of durvalumab with tremelimumab and platinum-based chemotherapy would serve as a first-line treatment. The LCC-MAC noted that most thoracic oncologists in Canada had experience with using the treatment combination through clinical trials. They also highlighted that the treatment combination would not replace other regimens that were already approved or funded but would serve as an alternative. Chemotherapy and immunotherapy options were noted as appropriate comparators to the treatment combination by LCC-MAC.

In terms of unmet needs, both clinician groups agreed there is a need for treatments with better tolerability. The OH-CCO noted the following additional unmet needs: not all patients responded to available treatments, patients become refractory to current treatment options, and a need for treatments and formulations that improve compliance and convenience.

The clinician groups highlighted similar treatment goals as indicated by the clinical experts, in addition to tumour shrinkage. The LCC-MAC clinician group further noted that an important outcome for immunotherapy combinations is survival with the goal of improving the number of patients with durable benefits of treatment, as manifested by increases in PFS and OS at 5 years.

The clinician groups noted that those best suited for treatment combination included patients without actionable driver mutations with any PD-L1 status and those with *KRAS*, *STK11* and *KEAP* mutations not currently actionable in the first-line setting. The OH-CCO additionally noted that patients with stage 4 or incurable NSCLC, considering first-line therapy would be suitable candidates for treatment.

Both groups highlighted the need for clinical assessment of symptoms and imaging (e.g., CT scans and chest X-rays) to monitor response to treatment. The OH-CCO clinician group advised treatment response assessment every 6 weeks initially, and then less often. However, the LCC-MAC suggested that scans be done every 3 months with symptom assessments every 3 to 4 weeks depending on if a patient receives chemotherapy or single-agent immunotherapy during the maintenance phase.

The clinician groups agreed disease progression is a factor when discontinuing treatment. The LCC-MAC indicated that immunotherapy may be interrupted or discontinued due to immune-related AEs, most low-grade toxicities were manageable with symptom management, topical or oral steroids, and potential treatment interruption. The OH-CCO additionally highlighted intolerable side effects and patient withdrawals when considering treatment discontinuation. The LCC-MAC indicated the initial patient assessment should be done by a medical oncologist. Both clinician groups highlighted that the treatment combination should be administered in facilities with expertise in managing cytotoxic anticancer therapies.

Drug Program Input

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

- relevant comparators
- considerations for initiation of therapy

- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues
- potential need for a provisional funding algorithm.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Issues with the choice of comparator in the submitted trial(s) In addition to PBC, relevant comparators include pembrolizumab-PBC, single-agent pembrolizumab (if PD-L1 > 50%), ipilimumab-nivolumab-PBC, cemiplimab-PBC. How does durvalumab-tremelimumab compare to other immunotherapy+/−PBC regimens?	Clinical experts noted that the POSEIDON trial included patients with any PD-L1 status, and patients with PD-L1 low or negative disease may benefit the most from adding tremelimumab (a CTLA-4 inhibitor) to the therapy. One clinical expert noted that the combination may also benefit patients with very aggressive or high burden disease. According to clinical experts, the regimen that is most similar to durvalumab and tremelimumab plus chemotherapy is nivolumab and ipilimumab plus chemotherapy. The rates and severity of immune-mediated AEs between durvalumab and tremelimumab plus chemotherapy and nivolumab and ipilimumab plus chemotherapy are likely very similar. pERC noted that there are no data to support a difference in efficacy or toxicity outcomes, and the choice of regimen should be at the discretion of the treating oncologist or health care provider and the patient.
Considerations for initiation of therapy	
Prior therapies required for eligibility The trial allowed patients who received prior adjuvant or neoadjuvant PBC or PBC with definitive chemotherapy radiation, provided disease progression occurred ≥ 12 months from the last treatment dose. What if the disease-free interval was ≥ 6 months? What is the minimum number of chemotherapy cycles the patient must have to be eligible for continued durvalumab-tremelimumab?	According to the clinical experts, patients should receive a minimum of 1 chemotherapy cycle to be eligible for continued treatment with durvalumab and tremelimumab since the pivotal trial was in combination with chemotherapy. Discontinuation of chemotherapy in the event of a chemotherapy-related AE and continuation with durvalumab and tremelimumab would align with current clinical practice. One clinical expert stated that patients may be treated with ICIs in the first-line setting for metastatic NSCLC when there is at least a 6-month interval from prior exposure to ICI. pERC agreed with the clinical expert that it may be appropriate to commence therapy if the interval since completing prior neoadjuvant or adjuvant chemotherapy is 6 months or more.
Eligibility to re-treatment In the trial, patients who completed 5 cycles of durvalumab-tremelimumab combination therapy with clinical benefit but had subsequent radiological	According to the clinical experts, appropriate re-treatment criteria for durvalumab and tremelimumab should be according to the POSEIDON clinical trial and at the discretion of the attending clinician. Re-treatment with tremelimumab following progression would be expected to be very uncommon in clinical practice.

Drug program implementation questions	Clinical expert response
progression during durvalumab maintenance could be re-treated with an additional 4 cycles of tremelimumab alongside durvalumab. What are the appropriate re-treatment criteria for durvalumab + tremelimumab? If patients discontinue therapy for reasons other than toxicity, progressive disease, or loss of clinical benefit, should patients be eligible for re-treatment? If yes, what re-treatment protocol and duration would be appropriate?	The clinical experts stated that reasons for discontinuing therapy other than toxicity, progressive disease, or loss of clinical benefit would comprise patient choice and unforeseeable circumstances (e.g., a pandemic). In these cases, eligibility for re-treatment with durvalumab would need to be determined and individualized on a case-by-case basis. pERC considered continuation of treatment after a break to be reasonable. The decision to use the entire combination or its single components to continue treatment would be at the treating clinician's discretion.
Consistency with initiation criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space There are several other therapies in this treatment space previously reviewed by CDA-AMC, including pembrolizumab + PBC, ipilimumab + nivolumab + PBC, and cemiplimab + PBC.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for continuation or renewal of therapy	
Consistency with renewal criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space	This is a comment from the drug programs to inform pERC deliberations.
Considerations for discontinuation of therapy	
Definition of loss of response, absence of clinical benefit, or disease progression In the trial, patients who experienced radiological disease progression during durvalumab maintenance could continue with treatment if they continued to derive benefit and met the trial criteria. What are the appropriate discontinuation criteria for durvalumab + tremelimumab?	Clinical experts stated that appropriate discontinuation criteria for durvalumab and tremelimumab would comprise clear widespread progression that is not pseudoprogression and is not oligoprogression amenable to local therapies delivered with the intent of controlling all areas of significant progression. The clinical expert explained that pseudoprogression is less common in treating advanced NSCLC than tumours in other sites but still occurs in approximately 5% of cases. It was further stated that in case radiographic evidence of progression on ICI is observed in a patient who is clinically well, it is common to continue ICI but with repeat imaging after a few weeks to clarify a true progression as opposed to pseudoprogression. pERC agreed with the clinical experts.
Consistency with discontinuation criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space	This is a comment from the drug programs to inform pERC deliberations.
Considerations for prescribing therapy	
Dosing, schedule or frequency, dose intensity In the POSEIDON trial, the study arm received tremelimumab 75 mg and durvalumab 1,500 mg flat dosing. If therapy is funded or implemented, jurisdictions are likely to implement a weight-based durvalumab dose used for other funded indications (e.g., 20 mg/kg up to a maximum of 1,500 mg per dose).	This is a comment from the drug programs to inform pERC deliberations. pERC stated that the dosing of durvalumab and tremelimumab should align with that used in the POSEIDON trial, which is also recommended in the approved product monograph and includes weight-based dosing.

Drug program implementation questions	Clinical expert response
Consistency with prescribing criteria associated with other drugs reviewed by CDA-AMC in the same therapeutic space	This is a comment from the drug programs to inform pERC deliberations.
Generalizability	
Populations of interest matching the indication but with insufficient data Should the following patients be considered: • unresectable locally advanced stage IIIB NSCLC • NSCLC tumours with exon 20 insertions • patients who are not able to take PBCs • ECOG PS > 1.	According to clinical experts, patients with unresectable locally advanced NSCLC of any stage should be considered if the disease is not amenable to any curative intent options. Clinical experts stated that, based on the PAPILLON study, the preferred first-line treatment option for patients with metastatic NSCLC whose tumours have an exon 20 insertion mutation is chemotherapy and amivantamab. Immunotherapy-based treatments in this subgroup would not be recommended as immunotherapy is known to have little to no activity in patients whose tumours harbour an *EGFR* driver mutation. According to clinical experts, for patients judged to be at high risk for adverse events from PBC, there is insufficient evidence to consider the POSEIDON protocol (durvalumab and tremelimumab plus chemotherapy). However, for patients with previously untreated advanced NSCLC whose tumours are PD-L1 > 50%, it is very common to prescribe pembrolizumab alone (especially if pembrolizumab plus chemotherapy is felt to be too toxic due to age or comorbidities). Clinical experts stated that patients with an ECOG PS of 2 (but not with an ECOG PS of 3 or 4) could be considered for treatment with durvalumab and tremelimumab plus chemotherapy if the perceived benefits exceed predicted risks. pERC noted that the chemotherapy-amivantamab combination is not currently publicly funded in jurisdictions in Canada. pERC noted that selecting suitable patients may not be solely based on ECOG status; therefore, using durvalumab and tremelimumab plus PBC for patients with an ECOG PS of greater than 1 based on their professional discretion. pERC could not comment on the use of durvalumab and tremelimumab in patients with unresectable locally advanced stage III NSCLC and on those who are not able to receive PBC as the committee did not review any evidence in that regard.
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review Should patients currently on other chemotherapy +/− immuno-oncology treatments be allowed to switch to durvalumab-tremelimumab?	One clinical expert stated that switching from another immuno-oncology treatment to durvalumab and tremelimumab plus chemotherapy would only make sense if there was previous toxicity. Another clinical expert noted that patients should only be allowed to switch to durvalumab and tremelimumab if there is a very serious infusion reaction. pERC noted that switching should be allowed only in severe infusion reactions.
Funding algorithm	
Request an initiation of a rapid provisional funding algorithm Note that if the final reimbursement recommendation for this drug under review is “do not reimburse,” the project will be suspended indefinitely.	This is a comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products	This is a comment from the drug programs to inform pERC deliberations.
Other aspects: Under what clinical circumstances will durvalumab-tremelimumab be preferred over other immuno-oncology +/− PBC regimens?	According to clinical experts, durvalumab and tremelimumab would typically be used in patients with tumoural PD-L1 < 50%. (Note: this statement is only intended as information regarding how durvalumab and tremelimumab may be used in clinical practice; it is not a statement that durvalumab and tremelimumab would necessarily be preferred over other immuno-oncology +/− PBC regimens in this population). The clinical experts also noted that, as the POSEIDON trial included patients with all PD-L1 expression, durvalumab and tremelimumab plus chemotherapy should not be restricted to tumoural PD-L1 < 50%. One clinical expert also commented that durvalumab and tremelimumab plus chemotherapy might also be used in patients with rapidly progressive disease and high tumour burden. The clinical experts stated that post hoc analyses suggested that durvalumab and tremelimumab may be active for patients with *STK11*, *KRAS*, and *KEAP* mutations; therefore, this regimen may be preferred in patients with these mutations. pERC noted that these analyses were unplanned, performed in a small subset of the trial participants, and without sufficient power for the evidence to support a recommendation.
Care provision issues	
Drug preparation, storage, administration, or dispensing Preparation of both durvalumab and tremelimumab is familiar to many jurisdictions due to their use in other indication(s).	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
Presence of confidential negotiated prices for comparators Confidential pricing exists for pembrolizumab, ipilimumab, and nivolumab.	This is a comment from the drug programs to inform pERC deliberations.

AE = adverse event; CDA-AMC = Canada's Drug Agency; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICI = immune checkpoint inhibitor; PBC = platinum-based chemotherapy; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; NSCLC = non–small cell lung cancer.

Clinical Evidence

Systematic Review

Description of Studies

One phase III, randomized, open-label, global study (POSEIDON) assessed the efficacy and safety of durvalumab with or without tremelimumab for the first-line treatment in patients (total N = 1,013) with metastatic NSCLC with tumours without activating *EGFR* mutations and *ALK* fusions. Patients were randomized 1:1:1 to 1 of 3 study arms: durvalumab and tremelimumab plus SOC chemotherapy; durvalumab plus SOC chemotherapy; or SOC chemotherapy alone. Randomization was stratified according to PD-L1

tumour expression status (tumour cell ≥ 50% versus < 50%), disease stage (IVA versus IVB), and histology (nonsquamous versus squamous). The primary objective of the POSEIDON trial was to assess efficacy of durvalumab plus SOC chemotherapy compared to SOC chemotherapy alone in terms of dual primary end points of PFS and OS. The key secondary objectives were to assess the efficacy of durvalumab and tremelimumab plus SOC chemotherapy compared to SOC chemotherapy alone in terms of PFS (assessed by blinded independent central review [BICR] using Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) and OS. Other secondary end points included objective response rate (ORR) and health-related quality of life (HRQoL), as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and 13-item lung cancer Quality of Life Questionnaire (EORTC QLQ-LC13), for the comparison of durvalumab and tremelimumab plus SOC chemotherapy versus SOC chemotherapy alone. Results from the comparison of durvalumab and tremelimumab plus SOC chemotherapy versus SOC chemotherapy alone are presented in this report, and include results from the prespecified main analyses of the POSEIDON trial, hereinafter referred to as the final analysis (data cut-off: July 24, 2019 for PFS and other RECIST-related end points; data cut-off: March 12, 2021, for OS and safety data), and a 5-year OS analysis update (data cut-off: August 24, 2023). The primary end points are based on the evaluation of durvalumab plus SOC chemotherapy versus SOC chemotherapy alone, which is outside the scope of the Health Canada indication and the sponsor's reimbursement request; therefore, the primary end points are not the focus of this CDA-AMC review.

Patients eligible for participation in the POSEIDON study were aged 18 years or older with stage IV NSCLC not amenable to curative surgery or radiation with tumours that lacked activating *EGFR* mutations and *ALK* fusions. Across all study arms, the median age of patients was 64 years, and the majority of patients were male (76.0%), white (55.9%), either current or former smokers (78%), and had an ECOG status of 1 (66.5%). The included patients had not received prior chemotherapy or any other systemic therapy for metastatic NSCLC, including prior exposure to immune-mediated therapy. Participants were required to have a WHO or an ECOG PS of 0 or 1. Patients with active or prior documented autoimmune or inflammatory disorders (with some exceptions) were not eligible for the trial.

Efficacy Results

As of March 12, 2021, the median OS in the durvalumab and tremelimumab plus SOC chemotherapy group was 14.0 months (95% CI, 11.7 to 16.1 months) compared with 11.7 months (95% CI, 10.5 to 13.1 months) in the SOC chemotherapy alone group, with an HR of 0.77 (95% CI, 0.650 to 0.916; P = 0.00304). For the OS final analysis results, the median follow-up was 13.63 months in the durvalumab and tremelimumab plus SOC chemotherapy group and 11.17 months in the SOC chemotherapy alone group. At the 5-year OS analysis data cut-off, the median OS in the durvalumab and tremelimumab plus SOC chemotherapy group was 14.0 months (95% CI, 11.7 to 16.1 months) versus 11.6 months (95% CI, 10.5 to 13.1 months) in the SOC chemotherapy alone group, with an HR of 0.76 (95% CI, 0.642 to 0.893). For the 5-year OS analysis results, the median follow-up was 13.63 months in the durvalumab and tremelimumab plus SOC chemotherapy group and 11.10 months in the SOC chemotherapy alone group. The difference in median OS was statistically significant in favour of durvalumab and tremelimumab plus SOC chemotherapy at the final analysis time point (statistical significance could not be determined for the 5-year time point results because

these estimates were not alpha controlled). Results for longer-term survival probability also demonstrated improvement for durvalumab and tremelimumab plus SOC chemotherapy versus SOC chemotherapy alone at 36 months (25.3% versus 13.3%), 48 months (20.9% versus 8.5%), and 60 months (15.7% versus 6.8%). Clinical experts consulted by CDA-AMC considered the differences in median OS at both time points and the differences in survival probabilities at 36, 48, and 60 months to be clinically meaningful.

As of July 24, 2019, the median PFS assessed by BICR in the durvalumab and tremelimumab plus SOC chemotherapy arm was 6.2 months (95% CI, 5.0 to 6.5 months) compared with 4.8 months (95% CI, 4.6 to 5.8 months) in the SOC chemotherapy alone arm, with an HR of 0.72 (95% CI, 0.600 to 0.860; 2-sided P = 0.00031). The difference was statistically significant in favour of durvalumab and tremelimumab plus SOC chemotherapy. The PFS rate at 12 months for patients in the durvalumab and tremelimumab plus SOC chemotherapy arm was 26.6% and for patients in the SOC chemotherapy alone arm was 13.1%. For the PFS results, the median follow-up for censored patients was 11.9 months in the durvalumab and tremelimumab plus SOC chemotherapy group and 5.5 months in the SOC chemotherapy alone group. Clinical experts considered the differences in median PFS and in PFS rate at 12 months to be clinically meaningful.

In terms of other secondary end points, ORR for durvalumab and tremelimumab plus SOC chemotherapy was 46.3% compared with 33.4% for SOC chemotherapy alone, with an odds ratio of 1.72 (95% CI, 1.260 to 2.367; nominal P < 0.001). The statistical significance of this result could not be determined because the ORR end point was not included in the hierarchical statistical analysis plan; however, clinical experts considered the difference between groups to be clinically meaningful. The median follow-up for censored patients was 11.9 months in the durvalumab and tremelimumab plus SOC chemotherapy group and 5.5 months in the SOC chemotherapy alone group. In the assessment of HRQoL, time to deterioration in the EORTC QLQ-C30 global health status scale and quality of life scale was 8.3 months (95% CI, 6.4 to 10.2 months) in the durvalumab and tremelimumab plus SOC chemotherapy arm compared with 5.6 months (95% CI, 4.4 to 7.5 months) in the SOC chemotherapy alone arm. As per ORR, statistical significance of this result could not be determined; however, clinical experts considered the difference between groups to be clinically meaningful. The median duration of follow-up was 13.63 months in the durvalumab and tremelimumab plus SOC chemotherapy group and 11.17 months in the SOC chemotherapy alone group.

There were no published between-group minimum important difference values provided by the sponsor for OS, PFS, ORR, and time to deterioration in the EORTC QLQ-C30 global health status scale and quality of life scale in the first-line treatment of metastatic NSCLC; as such, the thresholds used to judge the target of certainty in the GRADE assessment (Table 3) is based on input from clinical experts consulted by CDA-AMC.

Harms Results

Similar proportions of patients experienced at least 1 AE in the durvalumab and tremelimumab plus SOC chemotherapy arm (97.3%) and the SOC chemotherapy alone arm (96.1%), with the most commonly reported AEs being anemia (49.7% versus 48.9%), nausea (41.5% versus 36.6%), neutropenia (30.0% versus 23.4%), decreased appetite (28.2% versus 24.6%), fatigue (24.5% versus 22.2%), diarrhea (21.5% versus 15.3%), rash (19.4% versus 6.6%), and constipation (19.1% versus 23.7%). Serious AEs were

reported in a higher percentage of patients in the durvalumab and tremelimumab plus SOC chemotherapy arm (44.2%) than in the SOC chemotherapy alone arm (35.1%), as were AEs leading to discontinuation of any study treatment (22.1% versus 15.3%). AEs leading to death were reported in 12.4% of patients in the durvalumab and tremelimumab plus SOC chemotherapy arm and 9.0% of patients in the SOC chemotherapy alone arm.

AEs of special interest (AESIs) or AEs of potential interest (AEPIs) were reported in a higher percentage of patients in the durvalumab and tremelimumab plus SOC chemotherapy arm than in the SOC chemotherapy alone arm ([redacted]), including grade 3 or 4 AESIs or AEPIs ([redacted]) and AESIs or AEPIs that led to study treatment discontinuation ([redacted]). AESIs or AEPIs with an outcome of death were reported in [redacted] patients in the durvalumab and tremelimumab plus SOC chemotherapy arm and [redacted] patient in the SOC chemotherapy alone arm.

The percentage of patients experiencing select AEs and AESIs (identified by clinical experts as AEs of greatest clinical importance) in the durvalumab and tremelimumab plus SOC chemotherapy and SOC chemotherapy alone groups are as follows: neutropenia ([redacted]), pneumonitis ([redacted]), hepatitis ([redacted]), colitis ([redacted]), type I diabetes mellitus (0.3% versus no patients), and myocarditis (0.3% versus no patients).

For the safety analysis, the median follow-up was 13.63 months in the durvalumab and tremelimumab plus SOC chemotherapy arm and 11.17 months in the SOC chemotherapy alone arm.

Critical Appraisal

POSEIDON was a phase III, randomized, open-label, comparative study. Methods of randomization and treatment allocation were adequate. Reported baseline characteristics were generally balanced across the study arms and clinical experts consulted by CDA-AMC did not identify any considerable differences between durvalumab and tremelimumab plus SOC chemotherapy and SOC chemotherapy alone treatment arms that would be expected to impact the interpretation of results. The prespecified sample size was achieved and actual screening failures did not exceed the expected number. The POSEIDON trial was powered for the dual primary end points and power calculations were provided for all end points included in the multiple testing procedure, which included key secondary end points of OS and PFS for the comparison between durvalumab and tremelimumab plus SOC chemotherapy and SOC chemotherapy alone. The study used an open-label design due to differences in administration schedule and duration of study treatments. Of the efficacy end points of interest for this review, OS is an objective end point and PFS, ORR, best objective response, and duration of response were assessed by BICR according to RECIST 1.1 criteria, which helped to mitigate potential bias. Patient-reported efficacy assessments (i.e., HRQoL end points) and reporting of AEs have the potential to be influenced by knowledge of the treatment assignment by patients and clinicians. Other limitations related to internal validity include the potential impact of disproportionate treatment discontinuation between study arms, higher treatment exposure to SOC chemotherapy and overall higher study treatment exposure in the durvalumab and tremelimumab plus SOC chemotherapy arm, and the possible confounding effect of subsequently received anticancer treatments on survival. Greater study treatment exposure (particularly to SOC chemotherapy) in the durvalumab and tremelimumab plus SOC

chemotherapy group may have biased efficacy results in favour of this treatment regimen whereas the higher proportion of patients in the SOC arm who received subsequent systemic anticancer therapy may have diluted the survival benefit observed with the combination treatment compared to SOC chemotherapy alone. Additionally, nonkey secondary end points were not controlled for multiplicity. Overall adherence rates to the patient-reported outcome scales generally decreased over time and were lower in the SOC chemotherapy arm. The missing data presents a challenge in evaluating effects on HRQoL.

Clinical experts consulted by CDA-AMC commented that the POSEIDON trial used standard inclusion and exclusion criteria that would be expected in a study of first-line treatment of patients with metastatic NSCLC. However, the clinical experts identified differences between the POSEIDON trial participants and patients who would receive first-line immuno-oncology therapy plus SOC chemotherapy for metastatic NSCLC in clinical practice in Canada. For example, patients in practice would typically be older, have relative contraindications to immunotherapy (i.e., quiescent inflammatory or autoimmune conditions that would not result in significant morbidity if reactivated), would include patients with an ECOG PS of 2, and those who had received immunotherapy for earlier stage cancer. Also, the POSEIDON trial did not include any sites located in Canada; however, clinical experts noted that, overall, they did not have concerns regarding the generalizability of the study findings to patients seen in clinical practice. The main efficacy and harms outcomes assessed in the POSEIDON trial align with outcomes of importance identified by patients and clinicians.

An important limitation of the POSEIDON trial is that durvalumab and tremelimumab plus SOC chemotherapy was compared to SOC chemotherapy alone. At the time the trial was conducted, platinum-based chemotherapy was the standard of therapy for the indicated population; however, current first-line treatment of metastatic NSCLC without targetable genomic alterations consists of immuno-oncology treatment (on its own or in combination with chemotherapy). Concerning subsequent anticancer treatments received in the POSEIDON trial, clinical experts commented that rechallenging of patients with immunotherapy and the low rate of patients who received immunotherapy following first-line chemotherapy in the POSEIDON trial are not reflective of practice in Canada.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment (Table 3) was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with the expert committee members:

- OS (median and probability of survival at 36, 48, and 60 months)
- PFS (median and PFS rate at 12 months)
- ORR
- HRQoL (time to deterioration in EORTC QLQ-C30 global health status scale and quality of life scale)
- AEs (AESIs or AEPIs).

Table 3: Summary of Findings for Durvalumab and Tremelimumab Plus SOC Chemotherapy Versus SOC Chemotherapy for Patients with Metastatic NSCLC With No Sensitizing *EGFR* Mutations or *ALK* Genomic Tumour Aberrations

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			CT	D + T + CT	Difference		
Overall survival							
OS, median (final analysis[a]) Median follow-up (months): D + T + CT: 13.63 CT: 11.17	N = 675 (1 RCT)	**HR = 0.77** (95% CI, 0.650 to 0.916)	11.7 months (95% CI, 10.5 to 13.1)	14.0 months (95% CI, 11.7 to 16.1)	**2.3 more months** [redacted]	Moderate[b]	The combination of durvalumab and tremelimumab plus SOC chemotherapy likely results in a clinically important increase in OS when compared with SOC chemotherapy alone.
OS, median (5-year OS update[c,d]) Median follow-up (months): D + T + CT: 13.63 CT: 11.10	N = 675 (1 RCT)	**HR = 0.76** (95% CI, 0.642 to 0.893)	11.6 months (95% CI, 10.5 to 13.1)	14.0 months (95% CI, 11.7 to16.1)	**2.4 more months** [redacted]	Moderate[e]	The combination of durvalumab and tremelimumab plus SOC chemotherapy likely results in a clinically important increase in OS when compared with SOC chemotherapy alone.
Probability of survival at 36 months (final analysis[a]) Median follow-up (months): D + T + CT: 13.63 CT: 11.17	N = 675 (1 RCT)	NA	13.3 per 100 people (95% CI, 9.8 to 17.4 per 100)	25.3 per 100 people (95% CI, 20.8 to 30.2 per 100)	**12 more per 100 people** [redacted]	High[f]	The combination of durvalumab and tremelimumab plus SOC chemotherapy results in a clinically important increase in the probability of survival at 36 months when compared with SOC chemotherapy alone.
Probability of survival at 48 months (5-year OS update[c,d]) Median follow-up (months): D + T + CT: 13.63 CT: 11.10	N = 675 (1 RCT)	NA	8.5 per 100 people (95% CI, 5.8 to 11.9 per 100)	20.9 per 100 people (95% CI, 16.7 to 25.4 per 100)	**12.4 more per 100 people** [redacted]	High[g]	The combination of durvalumab and tremelimumab plus SOC chemotherapy results in a clinically important increase in the probability of survival at 48 months when compared with SOC chemotherapy alone.

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			CT	D + T + CT	Difference		
Probability of survival at 60 months (5-year OS update[c,d]) Median follow-up (months): D + T + CT: 13.63 CT: 11.10	N = 675 (1 RCT)	NA	6.8 per 100 people (95% CI, 4.4 to 10.0 per 100)	15.7 per 100 people (95% CI, 12.0 to 19.9 per 100 people)	**8.9 more per 100 people** (	High[g]	The combination of durvalumab and tremelimumab plus SOC chemotherapy results in a clinically important increase in the probability of survival at 60 months when compared with SOC chemotherapy alone.
Progression-free survival per RECIST 1.1 by BICR							
PFS,[h] median Median follow-up for censored patients (months): D + T + CT: 11.9 CT: 5.5	N = 675 (1 RCT)	**HR = 0.72** (95% CI, 0.600 to 0.860)	4.8 months (95% CI, 4.6 to 5.8)	6.2 months (95% CI, 5.0 to 6.5)	**1.4 more months**	Moderate[i]	The combination of durvalumab and tremelimumab plus SOC chemotherapy likely results in a clinically important increase in PFS when compared with SOC chemotherapy alone.
PFS rate at 12 months[h,j] Median follow-up for censored patients (months): D + T + CT: 11.9 CT: 5.5	N = 675 (1 RCT)	NA	13.1 per 100 people (95% CI, 9.3 to 17.6 per 100)	26.6 per 100 people (95% CI, 21.7 to 31.7 per 100)	**13.5 more per 100 people** (	High[f]	The combination of durvalumab and tremelimumab plus SOC chemotherapy results in a clinically important increase in the PFS rate at 12 months when compared with SOC chemotherapy alone.
Objective response rate							
ORR[j] (unconfirmed responses) Median follow-up for censored patients (months): D + T + CT: 11.9 CT: 5.5	N = 667 (1 RCT)	**OR = 1.72** (95% CI, 1.260 to 2.367)	33.4 per 100 people (	46.3 per 100 people (	**12.8 more per 100 people** (	Moderate[k]	The combination of durvalumab and tremelimumab plus SOC chemotherapy likely results in a clinically important increase in ORR when compared with SOC chemotherapy alone.

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			CT	D + T + CT	Difference		
HRQoL							
Time to deterioration (median) in EORTC QLQ-C30 global health status scale and quality of life scale[a,j] Median follow-up (months): D + T + CT: 13.63 CT: 11.17	N = 637 (1 RCT)	**HR = 0.78** (95% CI, 0.631 to 0.961)	5.6 months (95% CI, 4.4 to 7.5 months)	8.3 months (95% CI, 6.4 to 10.2 months)	**2.7 more months** [redacted]	Very low[l]	The evidence is very uncertain about the effect of the combination of durvalumab and tremelimumab plus SOC chemotherapy on time to deterioration in EORTC QLQ-C30 global health status scale and quality of life scalewhen compared with chemotherapy SOC alone.
Harms							
AESIs or AEPIs Median follow-up (months): D + T + CT: 13.63 CT: 11.17	N = 663 (1 RCT)	NA	AESIs or AEPIs were reported in [redacted] patients in the D + T + CT arm and [redacted] patients in the CT arm. Grade 3 or 4 AESIs or AEPIs were reported in [redacted] patients in the D + T + CT arm and [redacted] patients in the CT arm.			High[m]	The combination durvalumab and tremelimumab plus SOC chemotherapy results in higher incidence of AESIs or AEPIs (including those that are grade 3 or 4) when compared with SOC chemotherapy alone.

AE = adverse event; AEPI = adverse event of potential interest; AESI = adverse event of special interest; BICR = blinded independent central review; CI = confidence interval; CT = standard of care chemotherapy; D = durvalumab; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR = hazard ratio; HRQoL = health-related quality of life; MID = minimum important difference; NA = not applicable; NSCLC = non–small cell lung cancer; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; RCT = randomized controlled trial; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; SOC = standard of care; t = tremelimumab

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]Final analysis data cut-off March 12, 2021.

[b]Rated down 1 level for serious imprecision. No MID from the literature was provided therefore the target of certainty appraisal was the MID of 2 to 3 months based on clinical expert input; CI for difference between groups includes the possibility of trivial effects and no difference.

[c]Five-year OS update data cut-off August 24, 2023.

[d]Five-year estimates and CIs are not alpha controlled.

[e]Rated down 1 level for serious imprecision. No MID from the literature was provided therefore the target of certainty appraisal was the MID of 2.5 months based on clinical expert input; CI for difference between groups includes the possibility of trivial effects and no difference.

[f]No MID from the literature was provided therefore the target of certainty appraisal was the MID of 5 to 10 per 100 people based on clinical expert input; CI for difference between groups included potential for important benefit.

[g]No MID from the literature was provided therefore the target of certainty appraisal was the MID of 5 per 100 people based on clinical expert input; CI for difference between groups included potential for important benefit.

[h]Final analysis data cut-off July 24, 2019.

[i]Rated down 1 level for serious imprecision. No MID from the literature was provided therefore the target of certainty appraisal was the MID of 1 to 2 months based on clinical expert input; CI for difference between groups includes the possibility of trivial effects and no difference.

[j]Secondary efficacy end point not adjusted for multiplicity (considered supportive evidence).

[k]Rated down 1 level for serious imprecision. No MID from the literature was provided therefore the target of certainty appraisal was the MID of 10 per 100 people based on clinical expert input; CI for difference between groups includes the possibility of trivial effects.

[l]Rated down 2 levels for serious risk of bias due to knowledge of treatment assignment having the potential to impact reporting or recording of HRQoL outcomes and due to missing data (adherence rates fell below 60% after 88 weeks in the durvalumab and tremelimumab plus chemotherapy arm and after 24 weeks in the chemotherapy alone arm). Rated down 1 level for serious imprecision. No MID from the literature was provided therefore the target of certainty appraisal was the MID of 1.5 months based on clinical expert input; CI for difference between groups includes the possibility of trivial effects and no difference.

[m]No statistical tests were performed. The difference in effects between groups was considered certain based on input from clinical experts.

Sources: Sponsor's Summary of Clinical Evidence, sponsor's data on file. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

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

Indirect Comparisons

Description of Studies

The sponsor conducted ITCs to estimate the relative efficacy of durvalumab and tremelimumab plus platinum-based chemotherapy versus other approved ICIs plus platinum-based chemotherapy combinations among patients with metastatic NSCLC that lack *EGFR* mutations and *ALK* aberrations.

Efficacy Results

Based on the sponsor-submitted MAICs, overall, the efficacy, in terms of OS and PFS, appeared comparable when durvalumab and tremelimumab plus platinum-based chemotherapy was compared with relevant comparators for the first-line treatment of patients with metastatic NSCLC with no sensitizing *EGFR* mutations or *ALK* genomic tumour aberrations.

Durvalumab and tremelimumab plus platinum-based chemotherapy versus pembrolizumab plus chemotherapy: the OS HR (95% CI) was [redacted] and the PFS HR (95% CI) was [redacted] in the nonsquamous population. The OS HR (95% CI) was [redacted], and the PFS HR (95% CI) was [redacted] in the squamous population.

Durvalumab and tremelimumab plus platinum-based chemotherapy versus nivolumab plus ipilimumab plus chemotherapy: the OS HR (95% CI) was [redacted] and the PFS HR (95% CI) was [redacted] in the squamous and nonsquamous population (intention-to-treat population). The OS HR (95% CI) was [redacted] and the PFS HR (95% CI) was [redacted] in the nonsquamous population. The OS HR (95% CI) was [redacted], and the PFS HR (95% CI) was [redacted] in the squamous population.

Durvalumab and tremelimumab plus platinum-based chemotherapy versus cemiplimab plus chemotherapy: the OS HR (95% CI) was [redacted], and the PFS HR (95% CI) was [redacted] in the squamous and nonsquamous population (intention-to-treat population). The OS HR (95% CI) was [redacted], and the PFS HR (95% CI) was [redacted] in the nonsquamous population. The OS HR (95% CI) was [redacted], and the PFS HR (95% CI) was [redacted] in the squamous population.

Harms Results

The sponsor-submitted ITCs did not report harms outcomes.

Critical Appraisal

Overall, the MAICs were conducted according to accepted methodological guidance. The potential key limitations of the MAICs were that not all the important effect modifiers (such as PD-L1 status, sex, age, ECOG PS, presence of brain metastases, disease stage, and type of chemotherapy) were adjusted in the analysis, likely leading to residual heterogeneity between studies. In addition, the MAIC method reduced the effective sample size (up to 40% reduction). Imprecision, observed in the effect point estimates, as

indicated by wide 95% CIs, precluded conclusions about the comparative effectiveness of durvalumab and tremelimumab plus chemotherapy versus other comparators in terms of OS and PFS.

Studies Addressing Gaps in the Evidence from the Systematic Review

No studies addressing gaps in the systematic review evidence were submitted by the sponsor.

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	Adult patients with metastatic NSCLC that lack activating *EGFR* mutations and *ALK* fusions who have not received prior therapy for metastatic disease
Treatment	Durvalumab and tremelimumab in combination with platinum-based chemotherapy (PBC)
Dose regimen[a]	• During chemotherapy: Durvalumab 1,500 mg in combination with tremelimumab 75 mg and platinum-based chemotherapy every 3 weeks (21 days) for 4 cycles. • After platinum-based chemotherapy: Durvalumab 1,500 mg every 4 weeks and histology-based pemetrexed maintenance therapy every 4 weeks. • A fifth dose of tremelimumab should be given at week 16 alongside durvalumab dose 6. • Durvalumab should be taken until disease progression. Tremelimumab should be taken for up to 5 doses or until disease progression, whichever occurs first. • Durvalumab and tremelimumab are administered by IV infusion.
Submitted price	Durvalumab (120 mg/2.4 mL vial): $938.67 Durvalumab (500 mg/10 mL vial): $3,911.11 Tremelimumab (25 mg/1.25 mL vial): $2,859.97 Tremelimumab (300 mg/15 mL vial): $34,319.58
Submitted treatment cost[b]	$22,010, per 21-day cycle in the initial treatment stage (up to week 12), $15,387 per 21-day cycle in the initial maintenance phase (week 13 to 16), and $8,952 per 21-day cycle in the subsequent maintenance phase (beyond week 16).
Comparators	• PBC alone • NIVO + IPI + PBC • PEMBRO + PBC • CEMI + PBC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)

Component	Description
Key data sources	Efficacy inputs for durvalumab + tremelimumab + PBC and PBC were informed by the POSEIDON trial (NCT03164616). Efficacy inputs for NIVO + IPI + PBC, PEMBRO + PBC, and CEMI + PBC were derived from sponsor-submitted anchored MAICs. Efficacy for NIVO + IPI + PBC was informed by the CHECKMATE-9LA study; efficacy for PEMBRO + PBC was informed by the KEYNOTE-407 study (SCC population) and the KEYNOTE-189 study (NSCC population), and efficacy for CEMI + PBC was informed by EMPOWER-Lung3.
Key limitations	• The sponsor-submitted MAICs indicated that OS and PFS were comparable for durvalumab + tremelimumab + PBC relative to PEMBRO + PBC, NIVO + IPI + PBC, and CEMI + PBC. However, there were key limitations with the MAICs such that the CDA-AMC Clinical Review reported that no conclusions could be drawn whether durvalumab + tremelimumab + PBC was favoured over other comparators, or vice versa. • The sponsor assumed OS and PFS benefit for immuno-oncology therapy + PBC comparator regimens was capped at 5 years as the comparator immuno-oncology therapies are limited to a maximum 2-year treatment duration, while durvalumab + tremelimumab + PBC can be used until progression. There is long-term data to suggest there is a maintenance of response for immuno-oncology therapy + PBC regimens beyond treatment discontinuation. Clinical expert feedback agreed that there was no robust evidence to suggest durvalumab + tremelimumab + PBC would be associated with a long-term treatment benefit over NIVO + IPI + PBC, CEMI + PBC, or PEMBRO + PBC. • The sponsor used different initial treatment response assumptions to compare durvalumab + tremelimumab + PBC to PEMBRO + PBC than other treatment comparators, which was inappropriate as it did not accurately capture the comparative effects of durvalumab + tremelimumab + PBC vs. PEMBRO + PBC. The sponsor's approach biased the results in favour of durvalumab + tremelimumab + PBC. Other programming issues were identified when removing the cap to OS and PFS benefit for the immuno-oncology therapy + PBC comparator regimens which led to results that did not meet face validity. • Additional limitations were identified relating to modelling of extrapolated OS and PFS for durvalumab + tremelimumab + PBC and PBC, modelling of time to treatment discontinuation, utility values, comparators, and patient histology. Given the limitations identified, the total cost of treatment with each immuno-oncology therapy + PBC regimen (including durvalumab + tremelimumab) is uncertain.
CDA-AMC reanalysis results	• There is uncertainty regarding the comparative effectiveness of durvalumab + tremelimumab + PBC compared to currently available immuno-oncology therapy + PBC regimens, although the sponsor-submitted indirect evidence suggests durvalumab + tremelimumab + PBC is associated with similar survival outcomes. As such, there is insufficient clinical and economic evidence to justify a price premium for durvalumab + tremelimumab + PBC compared to currently available immuno-oncology therapy + PBC treatment options.

CDA-AMC = Canada's Drug Agency; CEMI = cemiplimab; IPI = ipilimumab; LY = life-year; MAIC = matching-adjusted indirect comparisons; NSCC = non-squamous cell carcinoma; NIVO = nivolumab; NSCLC = metastatic non–small cell lung cancer; OS = overall survival; PBC = platinum-based chemotherapy; SCC = squamous cell carcinoma; PEMBRO = pembrolizumab; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; vs. = versus.

[a]For patients weighing less than 30 kg the initial dosing is as follows: during chemotherapy, patients receive durvalumab 20 mg/kg in combination with tremelimumab 1 mg/kg and PBC every 3 weeks (21 days) for 4 cycles; after PBC, patients receive durvalumab 20 mg/kg every 4 weeks and histology-based pemetrexed maintenance therapy every 4 weeks.

[b]Submitted treatment cost included the combined cost of durvalumab with tremelimumab, in combination with PBC.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: derivation of the eligible population does not align with currently available and published literature in Canada, market shares in the reference scenario are overestimated for cemiplimab plus platinum-based chemotherapy and do not align with clinical expectations, market uptake for durvalumab and tremelimumab plus platinum-based

chemotherapy is overestimated, and the price of drugs paid by public drug plans is uncertain. CDA-AMC reanalysis included updating lung cancer incidence to the Canadian Cancer Society values, removing the decline in cases over the time horizon, and including recurrent cases from the previous 5 years to estimate the total eligible population.

CDA-AMC reanalysis suggests that reimbursing durvalumab and tremelimumab plus platinum-based chemotherapy for the first-line treatment of patients with metastatic NSCLC, with no sensitizing *EGFR* mutation or *ALK* genomic tumour aberrations would be associated with an incremental cost of $3,027,745 in year 1, $3,839,776 in year 2, $4,640,589 in year 3, for a 3-year budgetary impact of $11,508,110.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan (Vice Chair), Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villneuve, and Danica Wasney.

Meeting date: March 05, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.