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Reimbursement Recommendation

Durvalumab (Imfinzi)

Indication: As monotherapy, for the treatment of adult patients with limited-stage small cell lung cancer whose disease has not progressed following platinum-based chemoradiation therapy

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Canada's Drug Agency Reimbursement Recommendation for Imfinzi?

Canada's Drug Agency (CDA-AMC) recommends that Imfinzi be reimbursed by public drug plans for the treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiotherapy (CRT), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Imfinzi should only be covered to treat adults with LS-SCLC (stage I to III) who have not experienced disease progression after receiving platinum-based CRT. Patients must have completed 4 cycles of CRT and must be in relatively good health (as measured by performance status).

What Are the Conditions for Reimbursement?

Imfinzi should only be reimbursed if it is prescribed as monotherapy, by a clinician with expertise in treating lung cancer and immunotherapy, and if the cost of Imfinzi is reduced. Treatment should be stopped if the cancer gets worse, its side effects become too severe, or after 24 months of therapy.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that treatment with Imfinzi prolongs survival and delays disease progression in people with LS-SCLC when compared to placebo.
- Imfinzi may meet some of the needs identified as important to patients as it offers a novel treatment option that may improve survival and it may delay disease progression without worsening the patient's overall quality of life.
- Based on the CDA-AMC assessment of the health economic evidence, Imfinzi does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Imfinzi is estimated to cost the public drug plans approximately $133 million over the next 3 years.

Additional Information

What Is LS-SCLC?

Small cell lung cancer (SCLC) is an aggressive type of lung cancer that accounts for 12% of lung cancers in Canada. LS-SCLC is a form of SCLC in which the disease is limited to the chest and local lymph nodes.

Summary

Unmet Needs in LS-SCLC

Most patients with LS-SCLC experience disease recurrence after completing initial treatment, and long-term survival remains low. There is a need for new treatment options that can improve survival outcomes, delay disease progression, and lower the risk of the disease spreading to other parts of the body. Patients also value treatments that maintain or improve quality of life and have fewer side effects.

How Much Does Imfinzi Cost?

Treatment with Imfinzi is expected to cost approximately $11,733 per patient per 28-day cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that durvalumab be reimbursed, as monotherapy, for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based CRT only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, placebo-controlled, randomized controlled trial (RCT) (ADRIATIC; N = 730) in adults with LS-SCLC who did not experience disease progression after definitive, platinum-based, concurrent CRT demonstrated that consolidation therapy with durvalumab following CRT resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) when compared with placebo. The median OS was 55.9 months (95% confidence interval [CI], 37.3 to not reached) in the durvalumab group compared to 33.4 months (95% CI, 25.5 to 39.9) in the placebo group (stratified hazard ratio [HR] = 0.73; 95% CI, 0. 0.57 to 0.93; P = 0.0104). The median progression-free survival (PFS) was 16.6 months (95% CI, 10.2 to 28.2) in the durvalumab group versus 9.2 months (95% CI, 7.4 to 12.9) in the placebo group (HR = 0.76; 95% CI, 0.61 to 0.95; P = 0.0161). In the ADRIATIC trial, immune-mediated adverse events (AEs) occurred more frequently in the durvalumab group. However, pERC agreed with the clinical experts that the safety profile of durvalumab was consistent with known toxicities of immune checkpoint inhibitors and can be managed with appropriate monitoring and care.

Patients identified a need for treatments with more limited side effects that prolong survival, prevent or delay disease progression, and improve quality of life. pERC concluded that durvalumab meets some patients' needs as it offers a treatment option that may delay disease progression and improve survival when compared to placebo. Evidence from the ADRIATIC trial suggested that, compared to placebo, consolidation therapy with durvalumab may result in improvement in chest pain symptoms and no determinant in health-related quality of life (HRQoL) in terms of global health status or functional scales. However, the results for HRQoL were uncertain due to high attrition rates.

Using the sponsor-submitted price for durvalumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for durvalumab was $79,547 per quality-adjusted life-year (QALY) gained compared with active surveillance. At this incremental cost-effectiveness ratio, durvalumab is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for adults with LS-SCLC who did not experience disease progression following platinum-based CRT. A price reduction is required for durvalumab to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with durvalumab should be reimbursed when initiated in adult (≥ 18 years) who have all the following: 1.1. histologically or cytologically documented LS-SCLC (stage I to III SCLC, as defined by the AJCC classification, eighth edition) 1.2. completed 4 cycles of an appropriate first-line platinum-based CRT within the past 42 days 1.3. no disease progression following platinum-based CRT.	Evidence from the ADRIATIC trial demonstrated statistically significant and clinically meaningful OS and PFS benefits in patients who fulfilled the characteristics listed in this condition.	pERC agreed with the clinical experts that, in clinical practice, durvalumab treatment may be initiated up to 2 months after completion of CRT in select cases where a delay in starting consolidation therapy is necessary (e.g., due to side effects from CRT).
2. Patients must have a good performance status.	The ADRIATIC trial included patients with an ECOG Performance Status of 0 or 1.	pERC agreed with the clinical experts that patients with an ECOG Performance Status of more than 1 may be treated at the discretion of the treating physician.
Discontinuation		
3. Treatment with durvalumab should be discontinued upon occurrence of any of the following: 3.1. clinical or radiological disease progression 3.2. unacceptable toxicity 3.3. completion of 24 months of active treatment.	Patients in the ADRIATIC trial discontinued treatment upon progression or unacceptable toxicity, consistent with clinical practice. Patients in the ADRIATIC trial were treated with durvalumab for a maximum of 24 months.	—
Prescribing		
4. Durvalumab should be prescribed and monitored by clinicians with expertise in treating lung cancer and immunotherapy.	This condition is to ensure that durvalumab is prescribed for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
5. A reduction in price.	The ICER for durvalumab is $79,547 per QALY gained when compared with active surveillance. A price reduction of 34% would be required for durvalumab to achieve an ICER of $50,000 per QALY gained compared to active surveillance.	—

Reimbursement condition	Reason	Implementation guidance
Feasibility of adoption		
6. The economic feasibility of adoption of durvalumab must be addressed.	At the submitted price, the incremental budget impact of durvalumab is expected to be greater than $40 million in years 2 and 3.	—

AJCC = American Joint Committee on Cancer; CRT = chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; LS-SCLC = limited-stage small cell lung cancer; OS = overall survival; pERC = pan-Canadian Oncology Drug Review Expert Committee; PFS = progression-free survival; QALY = quality-adjusted life-year; SCLC = small cell lung cancer.

Discussion Points

- **Unmet needs**: pERC acknowledged that LS-SCLC remains an area of high unmet medical need due to the limited survival benefits of current standard of care. The clinical experts consulted for this review noted that, after completing concurrent CRT, patients are left with surveillance as the only option, which leads to disease recurrence in nearly 90% of patients with poor survival outcomes. pERC noted that the clinical experts and patients highlighted the need for novel therapeutic approaches to improve outcomes and reduce progression to metastatic disease.
- **Relevant comparators:** The clinical experts indicated that there are no approved systemic consolidation therapies available in Canada for patients with LS-SCLC following CRT, and that the current standard of care for these patients is surveillance. pERC agreed that placebo is an appropriate comparator in this treatment space given the current lack of an adjuvant therapy after definitive CRT for the patient population under review.
- **Sequentially administered CRT:** pERC discussed the possibility of using durvalumab consolidation therapy after radiation and chemotherapy when they are not given concurrently. The clinical experts consulted for this review noted that the current standard of care for the patient population of interest before receiving durvalumab is concurrent CRT, and sequential CRT is typically an option for patients who cannot tolerate concurrent CRT. However, pERC considered that a small proportion of patients who are otherwise eligible for concurrent CRT may be treated with sequential therapy based on patient choice or logistical or administrative considerations. Acknowledging that the efficacy and safety of durvalumab in patients who receive sequential CRT is unknown based on the submitted evidence, pERC agreed that patients who are treated with sequential CRT may be considered for consolidation therapy with durvalumab at the treating physician's discretion.
- **Adverse effects:** pERC noted that, in the ADRIATIC trial, treatment with durvalumab was associated with a higher frequency of immune-mediated events and treatment-related discontinuations. The clinical experts consulted for this review noted that the increase in immune-related AEs, such as thyroid dysfunction and dermatitis, aligns with the toxicity profile of immune checkpoint inhibitors. The clinical experts indicated that while these risks are expected, they can be managed with appropriate monitoring and supportive care. pERC agreed with the clinical experts that the potential for serious

immune-mediated toxicities underscores the need for careful patient selection and access to specialized care, particularly in community settings where close monitoring may be challenging.

- **HRQoL:** pERC discussed the patient-reported outcome results from the ADRIATIC trial and noted that, although both the durvalumab and placebo groups experienced declines in functioning over time, no statistically significant between-group differences were reported in global health status and most symptom end points. However, the committee noted that the HRQoL results were uncertain due to a notable amount of missing data and the exploratory nature of some patient-reported outcomes analyses.
- **Generalizability of the pivotal trial results**: pERC discussed that the ADRIATIC trial population was reported to be those who were predominantly white or of Asian ethnicity, with those who were Black and from other racial groups were underrepresented. The committee noted that this can potentially limit generalizability to the racially diverse population in Canada. The clinical expert consulted for this review believed that the pivotal trial population was largely generalizable to clinical practice in Canada; however, inclusion of relatively younger and healthier subset of patients with LS-SCLC in the trial could limit the generalizability of results to less fit patients commonly encountered in the practice setting in Canada. pERC agreed that the demographic differences and exclusion of patients with significant comorbidities should be considered when interpreting the study results.

Background

Lung cancer is the most common and deadliest cancer in Canada, with an estimated 32,100 new cases accounting for 23% of all cancer-related deaths in 2024. SCLC, the most aggressive form of lung cancer, represents 12% of all lung cancer cases. Approximately one-third of SCLC cases are classified as LS-SCLC, in which the disease is confined to the thorax and regional lymph nodes. Without treatment, patients with LS-SCLC have a life expectancy of 10 to 12 weeks. Even with the current standard of care — platinum-based CRT using cisplatin or carboplatin combined with etoposide — median survival is only 12 to 16 months. Although prophylactic cranial irradiation (PCI) may be used in responders to reduce brain metastases, nearly 90% of patients relapse, and only up to 25% survive 5 years. LS-SCLC is considered a rare and aggressive cancer with high unmet need, and long-term survival outcomes remain poor despite decades of clinical research.

Durvalumab has been approved by Health Canada, as monotherapy, for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based CRT. Durvalumab is a fully human monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80. It is available as a 50 mg/mL solution for IV infusion. The dosage recommended in the product monograph is 1,500 mg every 4 weeks. Therapy should continue for 24 months or until disease progression or unacceptable toxicity. Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 20 mg/kg every 4 weeks until weight increases to greater than 30 kg.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized, double-blind, placebo-controlled trial (ADRIATIC) in patients with LS-SCLC; no long-term extension studies, indirect treatment comparisons, or studies addressing gaps in the systematic review evidence were submitted
- a joint submission of patients' perspectives by 3 patient groups: the Canadian Cancer Survivor Network, Lung Cancer Canada (LCC), and the Lung Health Foundation
- input from the public drug plans and cancer agencies that participate in the reimbursement review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with SCLC
- input from 2 clinician groups: the Ontario Health – Cancer Care Ontario (OH-CCO) Lung Cancer Drug Advisory Committee and the Lung Cancer Canada Medical Advisory Committee (LCC MAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received a joint submission from the Canadian Cancer Survivor Network, LCC, and the Lung Health Foundation. The information was gathered through an online survey conducted from August to November 2024. LCC also conducted 3 interviews with patients with SCLC who had direct experience with durvalumab in November 2024. There was 1 respondent to this survey who was a patient with non-SCLC who had experience with durvalumab. The patient group submitting input believed that, in the absence of input from patients with LS-SCLC, the information obtained from these patients would still be valuable to include in the submission.

Based on the submitted input, the survey respondent explained their experience with the disease as including a cough, difficulty fighting infection, fatigue, reduced appetite, weight loss, nausea, waking up in the night or early morning because of breathing problems, feeling cold, impact on emotional well-being, and excessive time spent attending medical appointments. According to the input, the important outcomes reported by the survey respondent included reduced cost, improved quality of life, and improved energy level.

The patient group input noted that the 3 interviewees with SCLC reported their experience with the disease as having a cough; some of the side effects of currently available treatments experienced by patients included difficulties swallowing and eating, stomach pain, voice loss, hair loss, nausea, problems with day-to-day activities, tiredness, and hearing problems. Regarding experience with the drug under review, the input noted that 1 of the patients had no side effects after receiving 2 treatments, the second interviewee (who has received 2 treatments of durvalumab through the compassionate access program) reported feeling more

nauseous after the treatments but that their energy has now recovered significantly, and the third interviewee only had 2 treatments of durvalumab in 2021 before they had to stop it as they had no appetite, were vomiting constantly, had diarrhea, and lost almost 48 to 50 pounds. According to the input, 1 of the patients noted that they were relying on their pension and if they had to pay for durvalumab, they wouldn't have been able to afford it.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts emphasized that LS-SCLC remains an area of high unmet medical need due to the limited survival benefits of current standard treatments. After completing concurrent CRT, patients are left with surveillance as their only option, which frequently leads to disease recurrence with poor survival outcomes (median OS of 25 to 30 months and 5-year survival rate of 29% to 34%). The experts highlighted the need for therapies that reduce the risk of recurrence or disease progression, particularly given the rapid progression associated with relapses.

The clinical experts indicated that durvalumab would be used as a consolidation therapy for patients who have completed CRT and whose disease has not progressed. They noted that durvalumab would be added as a consolidation therapy rather than replacing CRT, and they agreed that this represents a significant addition to the treatment paradigm for LS-SCLC, potentially shifting standard practice.

The experts identified patients with LS-SCLC who achieve complete or partial response or stable disease after CRT as the most suitable candidates for durvalumab. They noted that patients with good Eastern Cooperative Oncology Group (ECOG) Performance Status (0 or 1), minimal comorbidities, and a positive disease response to CRT would derive the most benefit. The inclusion of medically operable stage I or II cases was considered reasonable based on clinical practice in Canada.

The clinical experts indicated that response to durvalumab should be assessed using imaging and clinical evaluation every 2 to 3 months. Important outcomes include PFS, OS, and symptom management. A clinically meaningful response was defined as measurable improvements in survival (e.g., at least 2 additional months of PFS or OS) and symptom stabilization or improvement. The experts emphasized the importance of long-term survival data, such as 5-year OS rates, to understand the drug's long-term impact.

The clinical experts outlined factors for discontinuing durvalumab, including evidence of disease progression; development of intolerable or potentially life threatening immune-related toxicities such as pneumonitis, colitis, hepatitis, myocarditis, and/or nephritis; and significant deterioration in patient quality of life. One clinical expert suggested that treatment could continue when radiologic progression is observed early after CRT or within a time frame compatible with durvalumab-mediated pseudoprogression. This was based on the clinician's clinical experience, in which post-treatment imaging may show apparent tumour enlargement due to treatment effects, such as radiation-induced inflammation or transient mediastinal mass enlargement. In such cases, a follow-up CT scan after 2 months may help determine true progression before discontinuing treatment, provided the patient's overall condition remains stable and symptoms do not worsen.

The clinical experts noted that durvalumab should be prescribed by oncologists experienced in managing systemic cancer therapies and checkpoint inhibitor–related toxicities. They highlighted that initial treatments should be administered in centres equipped to manage severe immune-related AEs, with subsequent cycles transitioning to outpatient settings under the supervision of trained oncology practitioners.

Clinician Group Input

CDA-AMC received 2 clinician group input submissions from LCC MAC, with contributions from 27 clinicians, and the OH-CCO Lung Cancer Drug Advisory Committee, with contributions from 5 clinicians. Both clinician groups agreed that the current standard treatment for LS-SCLC is 4 cycles of cytotoxic platinum–based (cisplatin or carboplatin) and etoposide chemotherapy combined with concurrent or sequential radiation, and the treatment goal is to prevent or delay disease recurrence and improve OS. The clinician input from the OH-CCO Lung Cancer Drug Advisory Committee anticipated that durvalumab would be used after standard systemic therapy with platinum-based chemotherapy and etoposide, as well as radiation treatments. In settings where the cancer recurs while on durvalumab, the use of more durvalumab in the metastatic setting would not occur. It was noted that the mechanism of action of durvalumab is different than that of chemotherapy or radiation therapy; therefore, it would not replace either of these therapies. LCC MAC added that platinum-etoposide combined with either durvalumab or atezolizumab followed by maintenance immunotherapy as monotherapy is the standard of care in Canada for patients with ES-SCLC with good performance status and no contraindications to therapy.

OH-CCO's Lung Cancer Drug Advisory Committee believed that patients with LS-SCLC who have completed chemotherapy and radiation therapy and who have not had significant pneumonitis, disease progression, or autoimmune disease, would be most suitable for treatment with durvalumab. Patients with poor disease-related performance status and those who have radiation pneumonitis would not be suitable. LCC MAC added that patients who have shown disease stabilization or shrinkage after standard concurrent treatment with cytotoxic platinum-etoposide chemotherapy and thoracic radiation, and those with an ECOG Performance Status of 0 to 1 (or patients with an ECOG Performance Status of 2 in the real-world setting) after chemotherapy and radiation, would be suitable candidates.

According to the OH-CCO Lung Cancer Drug Advisory Committee input, the outcomes to determine whether a patient is responding to treatment in clinical practice included OS and disease progression based on signs, symptoms, and radiology and laboratory tests. Chest imaging (CT or X-ray) should be done every 3 to 6 months, and imaging of abdomen, bones, brain, and pelvis should be done on a symptom-derived basis. The OH-CCO Lung Cancer Drug Advisory Committee added that improved survival is clinically meaningful if the absolute number is greater than 5%, or a median of greater than 6 months. LCC MAC noted that quality of life is another important outcome. LCC MAC added that in addition to assessment every 3 to 4 months, patients who are on durvalumab will also be assessed clinically every 4 weeks before each new cycle for treatment. Both clinician groups noted that disease progression and intolerable treatment-related AEs are the main reasons for discontinuation of durvalumab.

Based on the clinician groups' input, durvalumab after chemoradiation can be administered to outpatients in a systemic therapy treatment unit and can be performed in the community oncology setting. Treatment

most often would be given in a specialized cancer hospital by health care professionals with chemotherapy and immunotherapy experience. Treatment should be under the supervision of the appropriate oncology care team.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs (refer to Table 2).

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 In the ADRIATIC trial, the comparator to durvalumab was placebo. The current standard of care in Canada is active surveillance, so the choice of placebo was an appropriate comparator. Patients in both groups were treated for a maximum of 24 months.	This was a comment from the drug plans to inform pERC deliberations.
Considerations for initiation of therapy	
Eligibility to re-treatment Are patients who are treated with durvalumab in the LS-SCLC setting eligible for downstream immunotherapy for ES-SCLC? What would be an appropriate disease-free interval?	The clinical experts noted that re-treatment eligibility depends on the timing of disease progression. More specifically: • For disease progression during durvalumab treatment for LS-SCLC, downstream immunotherapy is not recommended as it is unlikely to provide additional benefit. • For patients whose disease remains stable for 2 years on durvalumab and who experience disease progression afterward, a disease-free interval of 6 months may be considered appropriate before starting immunotherapy for ES-SCLC. pERC agreed with the clinical experts.
Considerations for discontinuation of therapy	
Treatment interruptions For patients who stop for reasons other than disease progression, can durvalumab be restarted if their disease progresses while they are off therapy?	pERC agreed with the clinical experts that, for patients who stop durvalumab treatment due to reasons unrelated to disease progression (e.g., adverse events or unrelated medical interventions), treatment can be resumed following interruption, or after toxicity resolves to acceptable levels, to complete the planned 2 years if no disease progression occurs during the interruption. The clinical experts noted that, if disease progression occurs during the interruption, re-treatment with durvalumab alone would not be appropriate. In such cases, treatment should follow the extensive-stage paradigm, which currently involves combination chemotherapy. pERC agreed with the clinical experts.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
Dosing, schedule and/or frequency, dose intensity If therapy is funded and implemented, most jurisdictions are likely to implement the 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 was a comment from the drug plans to inform pERC deliberations. pERC acknowledged that weight-based dosing for durvalumab may be used by jurisdictions upon implementation of a reimbursement recommendation for durvalumab.
Generalizability	
Populations of interest matching the indication but with insufficient data Should patients with an ECOG Performance Status of 2 or greater be eligible? Should patients with either mixed SCLC and NSCLC, or those with brain metastases, be eligible?	**ECOG Performance Status** The clinical experts suggested patients with an ECOG Performance Status of 2 should be considered eligible for treatment as there is supporting data from similar settings, including NSCLC (e.g., the PACIFIC trial). Eligibility for those with an ECOG Performance Status of 3 is uncertain and warrants further expert input. pERC agreed that patients with an ECOG Performance Status of more than 1 may be treated at the discretion of the treating physician. **Mixed SCLC and NSCLC** Patients with mixed SCLC and NSCLC were excluded from the ADRIATIC trial. The clinical experts suggested that these patients should be considered eligible to receive durvalumab as the SCLC component of their condition is more aggressive. They also noted that results from the PACIFIC trial suggested benefit for consolidation therapy with durvalumab after CRT in patients with NSCLC. pERC agreed with the clinical experts. **Brain metastases** pERC discussed that patients with brain metastases would typically be considered to have extensive-stage disease. However, pERC agreed with the clinical experts that, overall, patients with brain metastases may be eligible to receive durvalumab if the metastases are stable, treated, and not causing clinical problems. The clinical experts indicated that modern approaches, such as stereotactic body radiation therapy, often allow for treatment with curative intent in this context. However, patients with progressing or uncontrolled brain metastases are not considered eligible.
Patients on active treatment with a time-limited opportunity to switch to the drug under review Can patients who have recently finished concurrent CRT be allowed to switch over to durvalumab?	The clinical experts consulted for this review suggested that patients who have recently finished concurrent CRT may switch to durvalumab; however, the timing is important. • The ADRIATIC trial protocol allowed for initiation within 42 days after completion of concurrent CRT. Subgroup analyses suggest a potential trend toward greater benefit with earlier initiation of durvalumab, though the analyses were exploratory and not powered to demonstrate definitive differences. • Clinical experts supported maintaining the 42-day initiation window outlined in the ADRIATIC trial. They noted that while earlier initiation may provide greater benefit, some flexibility may be needed due to real-world factors such as patient recovery, side effects, and scheduling. pERC agreed with

Drug program implementation questions	Clinical expert response
	the clinical experts who noted clinical practice may allow for treatment initiation of durvalumab up to 2 months after CRT in select cases.
Care provision issues	
Drug preparation, storage, administration, or dispensing Durvalumab preparation is familiar to many jurisdictions due to its use in other indications.	This was a comment from the drug plans to inform pERC deliberations.
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability The public drug programs expressed concern about feasibility of adoption (budget impact) as this will become the new standard of care.	This was a comment from the drug plans to inform pERC deliberations.

CRT = chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; ES-SCLC = extensive-stage small cell lung cancer; LS-SCLC = limited-stage small cell lung cancer; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Committee; SCLC = small cell lung cancer.

Clinical Evidence

Description of Studies

One trial, ADRIATIC (N = 730), was included in the sponsor's submission. The objective of the ADRIATIC trial was to evaluate the efficacy and safety of durvalumab consolidation therapy compared with placebo in patients with LS-SCLC following concurrent CRT. This was a randomized, double-blind, placebo-controlled, phase III trial. Participants included adults who had completed CRT without disease progression and had an ECOG Performance Status score of 0 or 1. Patients were excluded if they had prior immune checkpoint inhibitor therapy, active autoimmune diseases, or uncontrolled comorbidities.

The Health Canada indication and reimbursement request aligned with the trial population. Outcomes relevant to the CDA-AMC review included the dual primary end points of OS and PFS. Secondary outcomes included HRQoL and safety. Additional efficacy end points included duration of response and time to death or distant metastasis. Efficacy and safety data were evaluated at multiple prespecified interim analyses.

Baseline characteristics were generally balanced between the treatment groups. The mean age was 62 years, and all patients had a WHO or ECOG Performance Status of 0 or 1. The trial population consisted of 50% white, 48% Asian, and 2% other racial groups. A total of 90.8% of patients had a history of smoking and common comorbidities included [redacted] and [redacted]. Prior treatments included platinum-based chemotherapy with concurrent radiotherapy. Overall, 53.8% of patients received PCI.

Efficacy Results

At the data cut-off (January 15, 2024), the HR for OS was 0.73 (95% CI, 0.569 to 0.928; P = 0.01042) favouring durvalumab, representing a 27% reduction in the risk of death. Median OS was 55.9 months (95% CI, 37.3 to not reached) in the durvalumab group compared to 33.4 months (95% CI, 25.5 to 39.9) in the placebo group. Survival probabilities at 24 and 36 months were higher in the durvalumab group (68.0% and 56.5%, respectively) than in the placebo group (58.5% and 47.6%, respectively).

Durvalumab also significantly improved PFS, with an HR of 0.76 (95% CI, 0.606 to 0.950; P = 0.01608), translating to a 24% reduction in the risk of progression or death. The median PFS was 16.6 months (95% CI, 10.2 to 28.2) in the durvalumab group versus 9.2 months (95% CI, 7.4 to 12.9) in the placebo group. At the 24-month landmark analysis, 46.2% of patients in the durvalumab group were progression free, compared to 34.2% in the placebo group.

There was no difference in time to death or distant metastasis between treatment with durvalumab and placebo (HR = [redacted]) at this interim analysis.

Patient-reported outcomes assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) questionnaire revealed no clinically meaningful differences between treatment groups in global health status/quality of life scores or functional scales. Chest pain was the only symptom that showed improvement with durvalumab treatment compared to placebo (odds ratio = 2.28; P = 0.0308).

Harms Results

Treatment-emergent AEs were reported for 94.3% of patients in the durvalumab group and 88.3% of patients in the placebo group. Serious adverse events (SAEs) were reported for 29.7% and 24.2% of the durvalumab and placebo groups, respectively. The most commonly reported SAEs in the durvalumab group included radiation pneumonitis (5.0%), pneumonia (4.6%), and pneumonitis (3.1%).

Immune-mediated AEs occurred more frequently in the durvalumab group (32.1% versus 10.2% in the placebo group). Moreover, the following AEs accrued more frequently in the durvalumab group than the placebo group: hypothyroidism (16.0% versus 3.8%), hyperthyroidism (10.3% versus 1.5%), and rash (10.7% versus 6.0%). Discontinuation due to AEs was also higher in the durvalumab group than in the placebo group (16.4% versus 10.6%), with the primary reasons being radiation pneumonitis (3.8%) and pneumonitis (3.1%).

AEs resulting in death occurred in 2.7% of patients in the durvalumab group and 1.9% in the placebo group. Deaths in the durvalumab group were primarily attributed to pneumonia (0.8%), bacterial pneumonia (0.8%), cardiac failure (0.4%), encephalopathy (0.4%), and pneumonitis (0.4%).

Critical Appraisal

Internal Validity

In the phase III ADRIATIC trial, randomization and allocation concealment procedures were appropriately conducted using clinically relevant stratification factors (disease stage and receipt of PCI), with allocation managed through an interactive response system. Blinding was maintained with placebo infusions, though unblinding likely occurred due to imbalances in immune-mediated AEs in the durvalumab group. This could introduce bias in subjective outcomes like HRQoL, but not in objective end points like OS.

A total of [redacted] patients ([redacted]) had at least 1 protocol deviation, with [redacted] patients ([redacted]) in the durvalumab group and [redacted] patients ([redacted]) in the placebo group. The most frequently reported protocol deviations included deviation from key eligibility criteria ([redacted] patients in the durvalumab group [redacted] versus [redacted] patients in the placebo arm [redacted] primarily due to [redacted]. Another common deviation was [redacted] ([redacted] patients [redacted] in the durvalumab arm versus [redacted] patients [redacted] in the placebo arm). These protocol deviations were not considered to be major by the review team and, therefore, were not expected to have a major impact on the interpretability of the trial data.

The trial's hierarchical testing strategy for OS and PFS controlled for multiplicity. The primary outcomes were measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and assessed by blinded independent central review, reducing the potential for information (or measurement) bias. Sensitivity analyses were conducted to test the robustness of OS and PFS results, addressing potential biases from missing data, censoring rules, and assessment methods. These included alternative censoring rules (e.g., censoring patients with missed tumour assessments at their last evaluable visit) and comparing investigator-assessed PFS with blinded independent central review results, both of which yielded consistent HR estimates. A Cox model adjusting for stratification factors also confirmed the robustness for OS. While these analyses reinforced the reliability of the findings, moderate imprecision was noted due to variations in censoring assumptions.

External Validity

The ADRIATIC trial population and interventions are largely generalizable to practice in Canada, with some limitations. The trial excluded patients with medically operable stage I or II disease, which does not reflect routine practice in Canada, where surgery may be considered in select cases. The trial population was approximately 50% white and 48% Asian, with Black people and other racial groups underrepresented, potentially limiting generalizability to the racially diverse population in Canada. The median age of 62 years also reflects a younger-than-expected population compared to real-world cases in Canada, according to the clinical experts consulted by CDA-AMC. In addition, patients with an ECOG Performance Status of 0 or 1 represented a relatively healthy subset of patients with LS-SCLC and, as such, generalizability to

patients with an ECOG Performance Status of 2 may be limited. The clinical experts noted that the dosing schedule of durvalumab used in the ADRIATIC trial is consistent with what would be used in clinical practice in Canada; however, the requirement for close monitoring during early cycles may pose challenges to implementation of the drug for the condition under review in community settings. The review team considered placebo as an appropriate comparator in this treatment space, given the current lack of a standard of care for LS-SCLC. While survival benefits were clinically meaningful, long-term follow-up beyond 36 months may be necessary to fully evaluate the generalizability of OS results from the ADRIATIC trial.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform the CDA-AMC expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

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

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for OS, PFS, any immune-related treatment-emergent AEs, and any infusion-related reactions were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. The reference point for the certainty of the evidence assessment for EORTC QLQ-C30 and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13) global health status scores were set according to the presence or absence of an important effect based on a threshold suggested by the sponsor that was informed by the literature.

The selection of outcomes for GRADE assessment 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 expert committee members:

- survival outcomes (OS and PFS)
- HRQoL outcome (EORTC QLQ-C30 and EORTC QLQ-LC13 global health status)
- notable harms (SAEs and pneumonitis).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for durvalumab versus placebo.

Table 3: Summary of Findings for Durvalumab vs. Placebo for Patients With Limited-Stage Small Cell Lung Cancer — ADRIATIC Trial

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Durvalumab	Difference		
OS (full analysis set)							
Probability of survival at 24 months Median follow-up for all patients: 37.2 months	530 (1 RCT)	NA	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted])	[redacted] per 1,000 ([redacted] to [redacted])	Moderate[a]	Durvalumab likely results in a clinically important increase in the probability of survival at 24 months compared to placebo.
Probability of survival at 36 months Median follow-up for all patients: 37.2 months	530 (1 RCT)	NA	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted])	[redacted] per 1,000 ([redacted] to [redacted])	Moderate[b]	Durvalumab likely results in a clinically important increase in the probability of survival at 36 months compared to placebo.
PFS (full analysis set)							
Probability of PFS at 18 months Median follow-up: 27.4 months (durvalumab) and 27.7 months (placebo)	530 (1 RCT)	NA	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted])	[redacted] per 1,000 ([redacted] to [redacted])	Moderate[c]	Durvalumab likely results in a clinically important improvement in PFS at 18 months compared to placebo.
Probability of PFS at 24 months Median follow-up: 27.4 months (durvalumab) and 27.7 months (placebo)	530 (1 RCT)	NA	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted])	[redacted] per 1,000 ([redacted] to [redacted])	Moderate[c]	Durvalumab likely results in a clinically important improvement in PFS at 24 months compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Durvalumab	Difference		
HRQoL (full analysis set)							
Global health status/ Quality of Life: Average over 24 months[a]	418 (1 RCT)	NA	[redacted]	[redacted] to [redacted]	[redacted] to [redacted]	Low[d]	Due to the limited certainty of evidence, the effect of durvalumab on health-related quality of life remains uncertain.
Harms (safety analysis set)							
SAEs Median follow-up: 27.4 months (durvalumab) and 27.7 months (placebo)	527 (1 RCT)	NA	[redacted] per 1,000	[redacted] per 1,000 to [redacted])	[redacted] per 1,000 ([redacted] to [redacted])	Moderate[e]	Durvalumab likely increases the risk of SAEs compared to placebo, notably radiation pneumonitis and pneumonia.
Pneumonitis Median follow-up: 27.4 months (durvalumab) and 27.7 months (placebo)	530 (1 RCT)	NA	[redacted] per 1,000	[redacted] per 1,000 ([redacted] to [redacted])	[redacted] per 1,000([redacted] to [redacted])	Moderate[e]	Durvalumab likely increases the risk of pneumonitis compared to placebo.

CI = confidence interval; HRQoL = health-related quality of life; NA = not applicable; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

Notes: 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 following footnotes. First interim analysis data cut-off date of January 15, 2024.

[a]A between-group absolute risk difference of 5% (30 fewer or more events per 1,000 patients) at 24 and 36 months was clinically important according to the clinical experts. The point estimate exceeded the threshold. Rated down 1 level for imprecision due to wide CIs, which include large effect estimates.

[b]A between-group absolute risk difference of 5% (30 fewer or more events per 1,000 patients) at 24 and 36 months was clinically important according to the clinical experts. The point estimate exceeded the threshold. Rated down 1 level for imprecision due to wide CIs, which include a null value.

[c]A between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) at 18 and 24 months was clinically important according to the clinical experts. The point estimate exceeded the threshold. Rated down 1 level for imprecision due to wide CIs.

[d]Despite no meaningful change in HRQoL, the clinical experts emphasized that this was acceptable because the comparator was placebo and maintenance of HRQoL was viewed positively. However, rated down 2 levels for imprecision due to wide CIs, which include a null value, and there is uncertainty based on the loss to follow-up at later times.

[e]Rated down 1 level for imprecision due to wide CIs, which include large effect estimates.

Sources: Details included in the table are from the ADRIATIC Clinical Study Report, Section 12, and additional information provided in the sponsor's submission (data cut-off: January 15, 2024).

Long-Term Extension Studies

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

Indirect Comparisons

No indirect treatment comparisons were submitted by the sponsor.

Studies Addressing Gaps in the Evidence From the Systematic Review

No additional studies 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 PSM
Target population	Adults with LS-SCLC who did not experience disease progression following platinum-based chemoradiotherapy
Treatment	Durvalumab
Dose regimen	1,500 mg every 4 weeks for 24 months or until disease progression or unacceptable toxicity
Submitted price	Durvalumab: $938.67 per 120 mg/2.4 mL single-use vial for IV infusion Durvalumab: $3,911.11 per 500 mg/10 mL single-use vial for IV infusion
Submitted treatment cost	$11,733 per 28-day cycle
Comparator	Active surveillance
Perspective	Publicly funded health care payer in Canada
Outcomes	QALYs, LYs
Time horizon	Lifetime (38 years)
Key data source	ADRIATIC trial informed PFS, OS, TTD, and health state utility values
Key limitations	• The long-term extrapolation of OS for patients on active surveillance lacks face validity. According to the clinical expert feedback received for this review, the proportion of patients alive beyond the trial follow-up was likely overestimated. • The impact of durvalumab on long-term OS is highly uncertain due to concerns with the generalizability of the ADRIATIC trial results to the patient population commonly encountered in clinical practice in Canada, as well as lack of validated long-term comparative evidence. Approximately 57% of incremental LYs gained by patients treated with durvalumab were accrued through extrapolation beyond the time frame of the ADRIATIC trial (maximum follow-up: 60.2 months). • The modelled PFS lacks face validity. According to the clinical expert feedback received for this review, survival is approximately 1 year after progression. However, the merging of OS and PFS curves likely results in an overestimation of PFS for active surveillance and

Component	Description
	durvalumab. • The sponsor's modelled impact of AEs suggests that patients on active surveillance experience greater disutility associated with AEs compared with durvalumab, which lacks face validity. These included AEs likely to be associated with prior radiation or smoking history, rather than those likely to be related to immunotherapy. • The sponsor's approach to modelling subsequent therapy did not account for the timing of disease progression, which the clinical expert input noted would influence the choice of subsequent therapy and, as a result, the costs. The cost offset estimated for treatment with durvalumab is derived from the reduced cost of subsequent therapy, which is uncertain. • The sponsor adopted poor modelling practices, such as extensive use of IFERROR statements.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by making changes to the following model parameters: adopting a Weibull distribution to extrapolate OS for patients under active surveillance, adopting an exponential distribution to model OS for patients on durvalumab, and excluding AEs not likely to be related to durvalumab treatment. • In the CDA-AMC base case, durvalumab is associated with an ICER of $79,547 per QALY gained compared with active surveillance (incremental costs: $121,169; incremental QALYs: 1.52). A price reduction of 34% is required for durvalumab to be considered cost-effective relative to active surveillance at a WTP threshold of $50,000 per QALY gained. • The cost-effectiveness of durvalumab is sensitive to the modelled impact of AEs and subsequent therapy. When assumed that patients on active surveillance have no AEs, the ICER for durvalumab increased to $90,744 per QALY gained compared to active surveillance. When subsequent therapy costs were excluded, the ICER for durvalumab increased to $105,319 per QALY gained compared to active surveillance.

AE = adverse event; CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; LS-SCLC = limited-stage small cell lung cancer; LY = life-year; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; TTD = time to treatment discontinuation; WTP = willingness to pay.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: restricting eligibility to patients who are medically inoperable did not reflect anticipated clinical practice, the market uptake of durvalumab was underestimated, the treatment duration may also have been underestimated for patients initiating in year 3 of the budget impact model, and the impact of durvalumab on subsequent therapy costs was uncertain.

CDA-AMC corrected the sponsor's base case by aligning the mean weight with the cost-utility analysis and trial data. CDA-AMC reanalyses included increasing the proportion of patients deemed medically inoperable, as well as the market share for durvalumab. Based on the CDA-AMC base case, the 3-year budget impact is expected to be $133,319,319 (year 1: $39,053,199; year 2: $44,425,786; year 3: $49,840,333) should the public drug plans reimburse durvalumab for the treatment of adults with LS-SCLC whose disease did not progress following platinum-based CRT. The 3-year total budgetary impact increased to $157,658,840 when subsequent therapy costs were excluded.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Phillip Blanchette, Dr. Kelvin Chan, 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 Villeneuve, and Danica Wasney.

Meeting date: April 9, 2025

Regrets: None

Conflicts of interest: None

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Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.