Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

Reimbursement Recommendation

Confidential Draft

Durvalumab (Imfinzi)

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

Sponsor: AstraZeneca Canada Inc.

Recommendation: Reimburse with Conditions

Publication Date: May 2025

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

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Recommendation

The CDA-AMC pCODR Expert Review Committee (pERC) recommends that durvalumab be reimbursed, as monotherapy, for the treatment of adult patients with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy (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 (ADRIATIC, N = 730) in adult patients 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 OS, when compared with placebo. The median OS was 55.9 months (95% CI: 37.3, not reached) in the durvalumab group compared to 33.4 months (95% CI: 25.5, 39.9) in the placebo group (stratified hazard ratio [HR] = 0.73; 95% CI, 0. 0.57, 0.93; p = 0.0104). The median PFS was 16.6 months (95% CI: 10.2, 28.2) in the durvalumab group versus 9.2 months (95% CI: 7.4, 12.9) in the placebo group (HR = 0.76; 95% CI: 0.61, 0.95; p = 0.0161). In the ADRIATIC trial, immune-mediated adverse events 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 of 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 symptom and no determinant in health-related quality of life (HRQoL) in terms of global health status or functional scales. However, 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 (ICER) for durvalumab was $79,547 per quality-adjusted life-year (QALY) gained compared with active surveillance. At this ICER, durvalumab is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for adult patients 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) patients 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 concurrent 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 two months after completion of concurrent CRT in select cases where a delay in starting consolidation therapy is necessary (e.g., due to side effects from concurrent CRT).
2. Patients must have 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 more than 1 may be treated at the discretion of the treating physician
Discontinuation		
3. Treatment with durvalumab should be discontinued upon the 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 = chemoradiation therapy; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

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 frequently 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. pERC agreed with the clinical experts that patients who receive sequential CRT typically cannot tolerate concurrent CRT and would be considered a different patient population. pERC noted that the efficacy and safety of durvalumab in patients who receive sequential CRT is unknown based on the submitted evidence. Therefore, there is currently insufficient evidence to support the use of durvalumab in settings other than after definitive concurrent CRT.

- **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 adverse events, 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 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 endpoints. 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 predominantly white or of Asian ethnicity, with Black and other racial groups 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 Canadian practice setting. 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 and accounting for 23% of all cancer-related deaths in 2024. Small-cell lung cancer (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 five 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 adult patients with limited-stage small cell lung cancer whose disease has not progressed following platinum-based chemoradiation therapy. 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 intravenous infusion. The dosage recommended in the product monograph is 1500 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 (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.
- input from two clinical specialists with expertise diagnosing and treating patients with small-cell lung cancer.
- 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 (CCSN), Lung Cancer Canada (LCC), and the Lung Health Foundation (LHF). The information was gathered through an online survey conducted from August to November 2024. LCC also conducted three interviews with patients with small-cell lung cancer who had direct experience with durvalumab in November 2024. There was 1 respondent to this survey who was a patient with NSCLC 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 having cough, difficulty fighting infection, fatigue, reduced appetite, weight loss, nausea, waking up in the night or early morning because of breathing problems, feeling cold, 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 three interviewees with SCLC reported their experience with disease as having cough and 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 one 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 now his energy has recovered significantly, and the third interviewee only had 2 treatments of durvalumab in 2021 before he had to stop it since he had no appetite, was vomiting constantly, had diarrhea, and lost almost 48-50 pounds. According to the input, one of the patients noted that she was relying on her pension and if she had to pay for durvalumab, she 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 the only option, which frequently leads to disease recurrence with poor survival outcomes (median OS of 25–30 months and five-year survival rate of 29–34%). 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 response to CRT would derive the most benefit. The inclusion of medically operable Stage I/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 2–3 months. Important outcomes include progression-free survival, overall survival, and symptom management. A clinically meaningful response was defined as measurable improvements in survival (e.g., at least two additional months of PFS or OS) and symptom stabilization or improvement. The experts emphasized the importance of long-term survival data, such as five-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, nephritis, and significant deterioration in patient quality of life. One clinical expert suggested that treatment could continue when radiologic progression is observed early after chemoradiation or within a timeframe compatible with durvalumab-mediated pseudoprogression. This was based on the clinician's clinical experience where post-treatment imaging may show apparent tumor enlargement due to treatment effects, such as radiation-induced inflammation or transient mediastinal mass enlargement. In such cases, a follow-up CT scan after two 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 centers equipped to manage severe immune-related adverse events, 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 Lung Cancer Canada Medical Advisory Committee (LCC MAC) including contribution of 27 clinicians, and Ontario Health-Cancer Care Ontario (OH-CCO) Lung Cancer Drug Advisory Committee including contribution of 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 overall survival. The clinician input from 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 the mentioned 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, 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 0-1 (or ECOG 2 patients in the real-world setting) post chemotherapy and radiation would be suitable candidates. According to the OH-CCO's Lung Cancer Drug Advisory Committee input, the outcomes to determine whether a patient is responding to treatment in clinical practice included overall survival and disease progression based on signs, symptoms, radiology and laboratory tests. Chest imaging (CT or CXR) should be done every 3 to 6 months, and imaging of abdomen, bones, brain, and pelvis should be done on a symptom derived basis. OH-CCO's 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 prior to each new cycle for treatment. Both clinician groups noted that disease progression and intolerable treatment-related adverse effects are the main reasons for discontinuation of durvalumab. Based on the clinician groups' input, durvalumab after chemoradiation can be administered as an outpatient 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 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(s) 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 to a maximum of 24 months.	*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 in the 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 who remain stable for two years on durvalumab and experience disease progression afterward, a disease-free

Drug program implementation questions	Clinical expert response
	interval of six months may be considered appropriate before starting immunotherapy in ES-SCLC.
Considerations for discontinuation of therapy	
Treatment interruptions For patients who stop for reasons other than disease progression, can durvalumab be restarted if the disease progresses while 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 two 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.
Considerations for prescribing of therapy	
Dosing, schedule/frequency, dose intensity If therapy is funded/implemented, most 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).	*Comment from the drug plans to inform pERC deliberations.*
Generalizability	
Populations of interest matching the indication but with insufficient data Should patients with ECOG Performance Status of 2 or greater be eligible? Should patients with either mixed SCLC and NSCLC, or patients 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 non-small cell lung cancer (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 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 chemoradiation 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 an 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

Drug program implementation questions	Clinical expert response
	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(s) under review Can patients who have recently finished concurrent chemoradiotherapy be allowed to switch over to durvalumab?	The clinical experts consulted for this review suggested that patients who have recently finished concurrent chemoradiotherapy may switch to durvalumab; however, the timing is important. • The ADRIATIC trial protocol allowed for initiation within 42 days after completion of concurrent chemoradiotherapy. Subgroup analyses suggest a potential trend towards 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 the clinical experts who noted clinical practice may allow for treatment initiation of durvalumab up to two months post-chemoradiotherapy in select cases.
Care provision issues	
Drug preparation, storage, administration or dispensing Preparation of durvalumab is familiar to many jurisdictions due to its use in other indications.	*Comment from the drug plans to inform pERC deliberations.*
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability Feasibility of adoption (budget impact) – as this will become the new standard of care.	*Comment from the drug plans to inform pERC deliberations.*

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, with 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 endpoints of OS and PFS. Secondary outcomes included HRQoL and safety. Additional efficacy endpoints included duration of response (DoR) and time to death or distant metastasis (TTDM). Efficacy and safety data were evaluated at multiple pre-specified interim analyses.

Baseline characteristics were generally balanced between the treatment groups. The mean age was 62 years, and all patients had a WHO/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 hazard ratio (HR) for OS was 0.73 (95% CI: 0.569, 0.928; p = 0.01042) favoring durvalumab, representing a 27% reduction in the risk of death. Median OS was 55.9 months (95% CI: 37.3, not reached [NR]) in the durvalumab group compared to 33.4 months (95% CI: 25.5, 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, 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, 28.2) in the durvalumab group versus 9.2 months (95% CI: 7.4, 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 TTDM between treatment with durvalumab and placebo (HR: [redacted]) at this interim analysis.

Patient-reported outcomes (PROs) assessed using the EORTC QLQ-C30 questionnaire revealed no clinically meaningful differences between treatment groups in global health status/quality of life (GHS/QoL) scores or functional scales. Chest pain was the only symptom that showed improvement with durvalumab treatment compared to placebo (odds ratio (OR): 2.28; p = 0.0308).

Harms Results

Treatment-emergent adverse events (TEAEs) were reported for 94.3% of patients in the durvalumab group and 88.3% 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 adverse events (imAEs) 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: 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 (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 potential unblinding likely occurred due to imbalances in imAEs in the durvalumab group. This could introduce bias in subjective outcomes like HRQoL, but not in objective endpoints like OS.

A total of [redacted] patients ([redacted]) had at least one 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]] vs. [redacted] patients in the placebo arm [redacted] primarily due to [redacted]. Another common deviation was [redacted] ([redacted] patients [redacted]] in the durvalumab arm vs. [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 RECIST v1.1 criteria and assessed by BICR, 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 tumor assessments at their last evaluable visit) and comparing investigator-assessed PFS with BICR results, both of which yielded consistent hazard ratio (HR) estimates. A Cox model adjusting for stratification factors also confirmed the robustness for OS. While these analyses reinforced the reliability of findings, moderate imprecision was noted due to variations in censoring assumptions.

External validity

The ADRIATIC trial population and interventions are largely generalizable to Canadian practice but with some limitations. The trial excluded patients with medically operable Stage I/II disease, which does not reflect routine Canadian practice where surgery may be considered in select cases. The trial population was approximately 50% White and 48% Asian, with Black and other racial groups underrepresented, potentially limiting generalizability to the racially diverse Canadian population. The median age of 62 years also reflects a younger-than-expected population compared to real-world Canadian cases, according to the clinical experts consulted by CDA-AMC. In addition, patients with ECOG performance status 0 or 1 represented a relatively healthy subset of LS-SCLC patients, and as such, generalizability to patients with ECOG 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 the 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, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CDA-AMC's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

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

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

The reference points for the certainty of evidence assessment for OS, PFS, any immune-related TEAEs 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 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 Versus 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.
Health – Related Quality of Life – full analysis set							
Global health status/QoL: Average over 24 months*	418 (1 RCT)	NA	[redacted]	[redacted] to	[redacted] to [redacted]	Low [d]	Due to the limited certainty of evidence, the effect of durvalumab on health-related quality of life remains uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Durvalumab	Difference		
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 [redacted] 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.

First interim analysis data-cutoff date of January 15, 2024.
CI = Confidence Interval; DOR = Duration of Response; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire 30-item; EORTC QLQ-LC13 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer-13; NA = Not Applicable; NR = Not Reported; OS = Overall Survival; PFS = Progression-Free Survival; RCT = Randomized Controlled Trial; SAE = Serious Adverse Event; TTDM = Time to Death or Distant Metastasis.
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] 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 confidence intervals, 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 confidence intervals, which include 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 confidence intervals.
[d] Despite no meaningful change in HRQoL, clinical experts emphasized that this was acceptable because the comparator was placebo and maintenance of HRQoL was viewed positively. However, rated down 2 for imprecision due to wide confidence intervals, which include 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 confidence intervals, which include large effect estimates. Source: 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 materials 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

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult patients with LS-SCLC who did not experience disease progression following platinum-based chemoradiation therapy
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 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, and 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 clinical expert feedback received for this review, survival is approximately one year after progression. However, the merging of OS and PFS curves results in a likely overestimation of PFS for active surveillance and 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.

Component	Description
	• 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 the Weibull distribution to extrapolate the OS for patients under active surveillance, adopting the exponential distribution to model the OS for patients on durvalumab, and excluding adverse events not likely to be related to treatment with durvalumab. • In the CDA-AMC base case, durvalumab is associated with an ICER of $79,547 per QALY gained compared with active surveillance (incr. costs: $121,169; incr. 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.

Adverse event = AE; ICER = incremental cost-effectiveness ratio; incr. = incremental; 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 the eligibility to medically inoperable patients 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. The impact of durvalumab on subsequent therapy costs was uncertain.

CADTH 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 and 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 adult patients with LS-SCLC who 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