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CADTH Reimbursement Recommendation

Durvalumab (Imfinzi)

Indication: First-line treatment of adult patients with ES-SCLC in combination with etoposide and either carboplatin or cisplatin

Sponsor: AstraZeneca Canada Inc.

Final Recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Imfinzi?

CADTH recommends that Imfinzi should be reimbursed by public drug plans for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) if certain conditions are met.

What Are the Conditions for Reimbursement?

Imfinzi should only be reimbursed if it is prescribed and monitored by clinicians who have been trained in oncology and immunotherapy, and if the price of Imfinzi is reduced.

Which Patients Are Eligible for Coverage?

Imfinzi should only be covered to treat adult patients who have not received previous treatment for ES-SCLC.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Imfinzi combined with etoposide and platinum-based chemotherapy improved survival compared with etoposide-platinum chemotherapy alone and has manageable side effects, which are outcomes identified as important to patients.
- Based on public list prices, Imfinzi combined with etoposide-platinum chemotherapy is not considered cost-effective at a willingness to pay of $50,000 per QALY for the indicated population, relative to etoposide-platinum chemotherapy alone. Economic evidence suggests that an 88% price reduction is needed to ensure Imfinzi is cost-effective at a $50,000 per QALY threshold.
- Based on public list prices, the estimated 3-year budget impact of Imfinzi when used in combination with etoposide-platinum chemotherapy is $283 million.

Additional Information

What Is ES-SCLC?

In Canada, SCLC accounts for 12% to 15% of lung cancer cases, and 7% of patients diagnosed with SCLC are expected to be alive in 5 years. Approximately two-thirds of SCLC cases are classified as ES-SCLC, which is characterized by widespread tumour involvement in the lungs, metastases, and a poor prognosis.

Unmet Needs in ES-SCLC

There are very few treatment options for ES-SCLC. Although most patients respond to first-line treatment with chemotherapy, most patients with ES-SCLC relapse within months. Many patients are not well enough to receive second-line chemotherapy after relapse, and those who are do not experience much benefit.

How Much Does Imfinzi Cost?

Treatment with Imfinzi when used in combination with etoposide-platinum chemotherapy is expected to cost approximately $12,588 to $12,783 per 21-day cycle for the first 4 cycles and $11,733 per 28-day cycle of Imfinzi alone thereafter.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that durvalumab in combination with etoposide and platinum (EP) chemotherapy (cisplatin or carboplatin) should be reimbursed for the treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (CASPIAN, N = 805) in adult patients with ES-SCLC, demonstrated that the addition of durvalumab to EP chemotherapy resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) compared with EP alone. Median OS was 13.0 (95% CI, 11.5 to 14.8) months in the durvalumab plus EP arm compared with 10.3 (95% CI, 9.3 to 11.2) months in the EP arm (HR = 0.73; 95% CI, 0.59 to 0.91; P = 0.0047). Patients identified a need for a treatment with manageable side effects that prolongs survival, and durvalumab meets this need. Further, the results of the symptom analysis suggested that adding durvalumab to EP chemotherapy may be associated with less appetite loss compared with EP chemotherapy alone. Patient and clinician input to pERC recognized that ES-SCLC is an aggressive disease with a poor prognosis and that current treatment options for ES-SCLC are limited.

Using the sponsor-submitted price for durvalumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for durvalumab in combination with EP was $441,635 per quality-adjusted life-year (QALY) compared with EP alone. At this ICER, durvalumab is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for the first-line treatment of patients with ES-SCLC. A reduction in price of at least 88% is required for durvalumab to be considered cost-effective at a $50,000 per QALY threshold when added to EP.

Table 1: Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Patient must not have received previous treatment for ES-SCLC.	Evidence from the CASPIAN study demonstrates that durvalumab + EP prolongs survival when used as a first-line treatment in adult patients with ES-SCLC; this is aligned with the Health Canada indication.
2. Patient must have good performance status upon treatment initiation with durvalumab.	CASPIAN excluded patients who had an ECOG PS > 1 at baseline.
Discontinuation	
1. Reimbursement of durvalumab should be discontinued for disease progression based on RECIST criteria or unacceptable toxicity, as detected by clinical assessment with every treatment cycle or imaging every 2 to 3 months.	In the CASPIAN study, treatment with durvalumab was discontinued if a patient experienced disease progression, or intolerable or serious adverse events. This is aligned with clinical practice.

Reimbursement Condition	Reason
Prescribing	
1. Treatment should be prescribed and monitored by clinicians who have been trained in oncology and immunotherapy.	To ensure that durvalumab is prescribed only for appropriate patients.
2. Treatment with durvalumab could be provided at any outpatient or inpatient chemotherapy unit at a Canadian cancer centre or hospital.	To optimize toxicity management.
Pricing	
1. Reduction in price.	Durvalumab + EP is more costly than EP alone. The ICER for durvalumab in combination with EP was $441,635 per QALY compared with EP alone. A price reduction of at least 88% for durvalumab is necessary for durvalumab + EP to be considered cost-effective at a $50,000 per QALY threshold.

ECOG PS = Eastern Cooperative Oncology Group Performance Status; EP = etoposide and platinum; ES = extensive stage; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SCLC = small cell lung cancer.

Implementation Guidance

1. pERC discussed that enrolment in the CASPIAN study was limited to patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, which does not reflect the Canadian ES-SCLC patient population. There is currently no evidence to confirm whether the addition of durvalumab would benefit patients with an ECOG PS greater than 1. However, the clinical experts noted that patients with an ECOG PS of 2 can experience treatment benefit and that ECOG PS often improves after the treatment cycle in patients with ES-SCLC. Therefore, it could be reasonable to offer durvalumab to patients with an ECOG PS of 2. The clinical experts confirmed that patients with ECOG PS of 3 or 4 would have difficulty tolerating chemotherapy and that treatment with durvalumab may not be appropriate in these patients.
2. Durvalumab is intended to be administered in combination with EP. Patients would only receive alternative chemotherapy in the first-line setting if they were unable to access EP chemotherapy. Durvalumab should be administered as per the CASPIAN trial and the product monograph. For patients who have already initiated EP chemotherapy in the first-line setting, pERC agreed with clinical expert input that durvalumab should not be added to chemotherapy or offered to patients who recently completed EP chemotherapy.
3. As per the Health Canada–recommended dosing for durvalumab, the recommended dosage is 1,500 mg in combination with etoposide and either carboplatin or cisplatin every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as monotherapy until disease progression or unacceptable toxicity. For patients weighing less than 30 kg, dosage should be based on weight and be equivalent to 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg. However, there is no evidence to support weight-based dosing or to inform the appropriate dose cap of durvalumab in patients with ES-SCLC because this was not evaluated in the CASPIAN trial. Public plans will need to consider the potential budget impact of weight-based dosing.
4. pERC discussed that patients with ES-SCLC frequently develop brain metastases, and patients may be treated with prophylactic cranial irradiation (PCI). According to the clinical experts, the gains in OS from these treatments are modest and selection of patients that

are most likely to benefit from PCI remains challenging. In the CASPIAN trial, prophylactic cranial irradiation was only permitted for patients randomized to the EP chemotherapy alone group, therefore, there is no evidence demonstrating the effect of PCI in addition to durvalumab in patients with ES-SCLC.

5. In the CASPIAN trial, patients were treated with durvalumab until they experienced progressive disease (PD). pERC agreed with clinical expert input that if durvalumab was discontinued due to an adverse event (AE), it would be reasonable to restart durvalumab after the AE had resolved because AEs are often transient in nature.
6. CADTH reanalyses estimated the incremental budget impact of reimbursing durvalumab to be $283,353,601 over 3 years, which the Committee considered substantial and a potential barrier to implementation. The budget impact analysis did not restrict the eligible patient population by ECOG status.

Discussion Points

- Delaying disease progression and improving quality of life (QoL) were identified as outcomes of importance to patients. pERC discussed that in the CASPIAN study, progression-free survival (PFS) results were generally supportive of the OS results and suggest that the addition of durvalumab may be beneficial for PFS over EP chemotherapy alone. However, it was not possible to formally test PFS for statistical significance within the multiple testing procedure at either the interim or final analysis. pERC also discussed that the results of the CASPIAN trial for time to deterioration in health-related quality of life (HRQoL) appeared to suggest that durvalumab plus EP may have a beneficial effect, but that there is uncertainty associated with this finding due to lack of control for multiplicity and differences in completion rates of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and QLQ-LC13 between treatment arms.

Background

Durvalumab has a Health Canada indication for the first-line treatment of adult patients with ES-SCLC in combination with etoposide and either carboplatin or cisplatin. Durvalumab is a humanized monoclonal antibody that selectively blocks the interaction of programmed death-ligand 1 (PD-L1) with programmed cell death protein-1 (PD-1) and cluster of differentiation 80 (CD80). It is available as a single-use vial and is administered as an IV infusion over 60 minutes. The Health Canada–recommended dosage for patients weighing more than 30 kg is 1,500 mg IV in combination with etoposide and either carboplatin or cisplatin every 3 weeks for 4 cycles, followed by 1,500 mg IV every 4 weeks as monotherapy until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized controlled trial in adult patients with ES-SCLC
- patient perspectives gathered by 2 patient groups: Lung Cancer Canada and Lung Health Foundation
- 2 clinical specialists with expertise diagnosing and treating patients with ES-SCLC
- input from 2 clinician groups: Lung Cancer Canada and the Ontario Health Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Patient Input

Two patient advocacy groups, Lung Cancer Canada and Lung Health Foundation, provided input for this submission. Patient perspectives were obtained from environmental scans, interviews with patients and their families and/or caregivers, and online surveys. The following is a summary of key input from the perspective of the patient groups:

- A diagnosis of lung cancer and the subsequent treatment has a major impact on the life of the patient and their families. More than half of patient respondents from the Lung Health Foundation reported current issues with work, day-to-day chores, and socialization. Caregivers reported that they may need to take time off work to provide care, which affects work productivity and finances and can cause mental stress. The emotional and physical toll during and after treatment may affect caregivers' ability to fulfill their roles in the family and at work and affect their ability to participate in activities they enjoy.
- There are poor survival outcomes for ES-SCLC, and a lack of treatment options with manageable side effects. Treatment of SCLC has not changed in the last 30 years, representing a significant unmet need. Some patients reported having experience with immunotherapy, but none had experience specifically with durvalumab. Patients reported that immunotherapy is a form of treatment that has allowed many patients to hope for improved outcomes and has been shown to improve QoL with more manageable side effects. Patients report feeling better within days of their first treatment with other forms of immunotherapy. Since lung cancer patients, and SCLC patients in particular have a high symptom burden, this is an important benefit of this form of treatment.
- Key outcomes identified as important to patients include the following: controlling the cancer and stopping or delaying progression with manageable side effects, improving symptoms, delaying deterioration, extending survival with a good QoL, and providing longer-lasting and durable treatment.

Drug Plan Input

In response to the Drug Plan's questions about administering durvalumab to patients in Canada, the clinical experts consulted by CADTH indicated that they would administer

durvalumab according to the pivotal CASPIAN trial design and the product monograph. In response to questions about when to stop maintenance therapy with durvalumab, the clinical experts indicated that clinicians would like to continue durvalumab maintenance therapy until a patient experiences disease progression, intolerable or serious AEs, or the patient wishes to stop treatment. The clinical experts indicated that it would be unlikely that patients would have difficulty tolerating 4 cycles of EP therapy when initiating treatment with durvalumab. If durvalumab was temporarily stopped due to an immune-mediated AE, the clinical experts felt that it would be reasonable to restart durvalumab after the event had resolved. The clinical experts are not aware of evidence to support weight-based dosing of durvalumab in ES-SCLC.

Clinical Evidence

Clinical Trials

The systematic review included 1 open-label, phase III, randomized controlled trial of durvalumab as a first-line treatment regimen in adult patients with ES-SCLC. The CASPIAN trial randomized a total of 805 patients in a 1:1:1 ratio to 3 treatment arms: durvalumab with tremelimumab in combination with etoposide and either carboplatin or cisplatin, durvalumab in combination with etoposide and either carboplatin or cisplatin, and etoposide and either carboplatin or cisplatin alone. In the experimental treatment arms, patients received durvalumab, with or without tremelimumab, administered concurrently with first-line EP chemotherapy every 3 weeks for 4 cycles. After chemotherapy was completed, durvalumab was administered every 4 weeks as monotherapy until PD. In the control arm, patients received 4 to 6 cycles of EP every 3 weeks and PCI at the investigator's discretion. The type of platinum-based chemotherapy (cisplatin or carboplatin) used was the investigator's choice.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the Committee discussed the following: OS, PFS, duration of response, objective response rate, HRQoL, and change in symptoms. The primary outcome in the CASPIAN trial was OS, and PFS was the key secondary outcome; however, PFS was not formally tested for statistical significance. HRQoL and symptoms were assessed by the EORTC QLQ-C30 and EORTC QLQ-L13 scales. The EORTC QLQ C30 is a questionnaire for evaluating the QoL of patients with cancer participating in clinical trials that consists of 5 functional scales, 3 symptom scales, and 6 single items. This instrument also includes global health status and overall QoL. A higher score on a functional scale corresponds to higher level of function, while a higher score in the symptom scale corresponds to higher burden of symptoms. The QLQ-LC13 is a lung cancer–specific module that consists of lung cancer–related symptoms and treatment side effects.

Efficacy

The CASPIAN trial met its primary end point of OS at the pre-specified interim analysis. Median OS was 13.0 (95% CI, 11.5 to 14.8) months in the durvalumab plus EP arm compared with 10.3 (95% CI, 9.3 to 11.2) months in the EP arm (HR = 0.73; 95% CI, 0.59 to 0.91; P = 0.0047). As of the final analysis, median OS was 12.9 (95% CI, 11.3 to 14.7) months in the durvalumab plus EP arm compared with 10.5 (95% CI, 9.3 to 11.2) months in the EP arm.

As of the interim analysis, median PFS was 5.1 (95% CI, 4.7 to 6.2) months in the durvalumab plus EP arm and 5.4 (95% CI, 4.8 to 6.2) months in the EP arm. As of the final analysis, median PFS was 5.1 (95% CI, 4.7 to 6.2) months in the durvalumab plus EP arm and 5.4 (95% CI, 4.8 to 6.2) months in the EP arm. It was not possible to formally test PFS for statistical significance within the multiple testing procedure at either the interim or final analysis.

The unconfirmed ORR was 79.5% and 70.6% in the durvalumab plus EP and EP arms, respectively (OR = 1.61; 95% CI, 1.086 to 2.401). The confirmed ORR was 67.9% and 58.0% in the durvalumab plus EP and EP arms, respectively (OR = 1.53; 95% CI, 1.078 to 2.185). Duration of response was calculated post hoc in the subset of patients who had a confirmed response.

Median time to deterioration in global health status/QoL was 8.4 (95% CI, 7.3 to 11.5) months in the durvalumab plus EP arm compared with 7.2 (95% CI, 6.3 to 9.0) months in the EP arm. The mixed model for repeated measures analysis of EORTC QLQ-C30 and EORTC QLQ-LC13 key symptoms from baseline to PD or 12 months showed a statistically significant difference in appetite loss in favour of durvalumab plus EP. The adjusted mean change from baseline in appetite loss score was −12.7 points in the durvalumab + EP arm, which was greater than the minimal important difference; the estimated difference between treatment arms was −4.5 points (95% CI, −9.04 to −0.04; P = 0.009). No statistically significant differences between treatment arms were observed for the symptoms of fatigue, cough, dyspnea, and chest pain.

Harms (Safety)

A total of 260 (98.1%) patients in the durvalumab plus EP arm and 258 (97.0%) patients in the EP arm experienced an AE. The most commonly reported AEs in the durvalumab plus EP arm and the EP arm were neutropenia (41.9% and 46.6%, respectively), anemia (38.5% and 47.0%, respectively), nausea (33.6% and 33.5%, respectively), and alopecia (31.7% and 34.2%, respectively). Adverse events led to discontinuation of study treatment in 10.2% of patients in the durvalumab plus EP arm and 9.4% of patients in the EP arm. A greater percentage of patients in the EP arm experienced a serious AE compared with the durvalumab plus EP arm (36.5% versus 32.1%, respectively). The most commonly reported serious AEs in the durvalumab plus EP arm and the EP arm were febrile neutropenia (4.5% and 4.5%, respectively), anemia (1.9% and 4.5%, respectively), pneumonia (2.3% and 3.4%, respectively), and thrombocytopenia (0.4% and 3.4%, respectively). As of the final analysis, 78.4% of patients in the durvalumab plus EP arm and 85.9% of patients in the EP arm had died, with most deaths being attributed to ES-SCLC.

Immune-related AEs were more frequent in the durvalumab plus EP arm compared with the EP arm (53.2% versus 39.1%, respectively), although the clinical experts consulted by CADTH reported that the immune-related AE profile was expected and consistent with other immune checkpoint inhibitors. The most commonly reported immune-related AEs in the durvalumab plus EP arm were endocrine (28.3%) and dermatitis/rash (19.2%). The most commonly reported immune-related AEs in the EP arm were diarrhea/colitis (11.7%) and dermatitis/rash (9.4%). Infusion-related and hypersensitivity and/or anaphylactic reactions were uncommon, and the incidence of infections was similar in both groups. In the durvalumab plus EP arm, 35.1% of patients experienced an infection compared with 30.8% of patients in the EP arm.

Economic Evidence

Cost and Cost-Effectiveness

At the submitted price of $938.67 per 2.4 mL vial or $3,911.11 per 10 mL vial of durvalumab, the cost of durvalumab + EP per 21-day cycle during the initial 4 cycles of therapy is $12,588 to $12,783 per patient, depending on whether carboplatin or cisplatin is selected, while the cost per 28-day cycle of durvalumab alone after this to disease progression is $11,733 per patient.

The sponsor submitted a cost-utility analysis based on a 3-state partitioned survival model assessing durvalumab plus EP compared with EP alone in adult patients with histologically or cytologically documented ES-SCLC caused by multiple lung nodules that were too extensive or a tumour or nodal volume that was too large to be encompassed in a tolerable radiation plan. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer. The proportions of patients who were progression-free, experienced progression, or who had died at any given time over the 10-year time horizon were derived from non–mutually exclusive survival curves. The clinical efficacy of durvalumab plus EP was informed using landmark PFS and OS data observed over 24 months in the CASPIAN trial.

The following key limitations were identified:

- The CASPIAN trial excluded patients with an ECOG PS greater than 1, which limits the generalizability of the results to the population of patients expected to be seen in clinical practice and potentially leads to survival estimates that are not aligned with expectations in the full population who would receive durvalumab.
- The extrapolation of the treatment effect beyond the 2 available years of observed data is uncertain and may overestimate survival benefits associated with durvalumab in the extrapolation period.
- The sponsor's implementation of time-to-death health utilities incorporated time-to-death categorizations that did not align with time points typically corresponding to key changes in patients' QoL and included utility weights for all time-to-death categories that were higher than expected considering the severity of ES-SCLC. As a result, incremental QALYs may be overestimated.
- The use of subsequent chemotherapies was underestimated, although this only had a minor impact on the results.

CADTH reanalyses incorporated health state–specific utility values to address the likely overestimation of accrued QALYs in the sponsor's base case via the sponsor's time-to-death approach to health utilities and revised the proportion of patients receiving subsequent chemotherapy to be consistent with the values reported in the CASPIAN trial. The CADTH base case aligns with the results reported by the sponsor. Durvalumab plus EP is not considered cost-effective at a WTP threshold of $50,000 per QALY, with an ICER of $441,635 per QALY gained compared with EP alone. A price reduction of 88% would be required for durvalumab to be considered cost-effective at a WTP threshold of $50,000 per QALY gained.

Important identified limitations could not be addressed by CADTH. Uncertainty remains about the generalizability of the results to the patient population most likely to be treated with durvalumab plus EP in clinical practice due to the exclusion of patients with an ECOG PS greater than 1 from the trial; the cost-effectiveness in patients with a higher ECOG PS (worse

functioning) is uncertain. There is also uncertainty in the extrapolation of OS and PFS curves over the 10-year time horizon from the approximately 2 years of observed data because more than 65% of incremental QALYs gained in the model were accrued during the extrapolated period of the model for which there is no observed data. A series of scenario analyses were conducted exploring some areas of uncertainty in the submitted model; none of these scenarios was associated with an ICER approaching $50,000 per QALY gained.

Budget Impact

The sponsor estimated the incremental budget impact of reimbursing durvalumab to be $176,157,498 over 3 years. CADTH identified limitations with the submitted budget impact analysis and performed a reanalysis, which estimated the incremental budget impact of reimbursing durvalumab to be $283,353,601 over 3 years. The model was most sensitive to the proportion of patients receiving first-line therapy and to the price of durvalumab.

Members of the pCODR Expert Review Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: May 14, 2021

Regrets: None

Conflicts of Interest: None