CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Durvalumab (Imfinzi)

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

Recommendation: Reimburse with Conditions

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Single Technology

CADTH

DURVALUMAB (IMFINZI — ASTRAZENECA CANADA INC.)

Therapeutic Area: Extensive-stage small cell lung cancer

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that durvalumab 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 etoposide + carboplatin or cisplatin (EP) resulted in a statistically significant and clinically meaningful improvement in OS compared with EP alone. Median OS was 13.0 (95% CI: 11.5, 14.8) months in the durvalumab + EP arm compared with 10.3 (95% CI: 9.3, 11.2) months in the EP arm (HR, 0.73; 95% CI: 0.59, 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 may be associated with less appetite loss compared to EP 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 CASPIAN demonstrates that durvalumab 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.
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/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.

Implementation Guidance

1. pERC discussed that enrollment in the CASPIAN study was limited to patients with 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 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 alterative 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.
3. As per the Health Canada recommended dosing for durvalumab, the recommended dose is 1500 mg in combination with etoposide and either carboplatin or cisplatin every 3 weeks for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy until disease progression or unacceptable toxicity. Weight-based dosing should be considered for patients weighing less than 30 kg 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 as 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 alone group, therefore, there is no evidence demonstrating the effect of prophylactic cranial irradiation in addition to durvalumab in patients with ES-SCLC.
5. In the CASPIAN trial, patients were treated with durvalumab until they experienced progressive disease. pERC agreed with clinical expert input that if durvalumab was discontinued due to an AE, it would be reasonable to restart durvalumab after the AE had resolved as AEs are often transient in nature.
6. CADTH reanalyses estimated the incremental budget impact of reimbursing durvalumab to be $283,353,601 over three years, which the committee considered substantial and a potential barrier to implementation. The BIA did not restrict the eligible patient population by ECOG status.

Discussion Points

- Delaying disease progression and improving quality of life were identified as outcomes of importance to patients. pERC discussed that in the CASPIAN study, PFS results were generally supportive of the OS results and suggest that the addition of durvalumab may be beneficial for PFS over EP 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 HRQoL appear to suggest that durvalumab + EP may have a beneficial effect, but that there is uncertainty associated with this finding due lack of control for multiplicity and differences in completion rates of the 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 dose in patients weighing more than 30 kg is 1500 mg IV in combination with etoposide and either carboplatin or cisplatin every 3 weeks for 4 cycles, followed by 1500 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 one 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
- Two clinical specialists with expertise diagnosing and treating patients with ES-SCLC
- Input from 2 clinician groups, including 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 LHF 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 the 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 for 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 quality of life 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, and delaying deterioration, extending survival with a good quality of life, 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 generally indicated that they would administer durvalumab according to the pivotal CASPIAN trial design and the product monograph. In response to questions regarding when to stop maintenance therapy with durvalumab, the clinical experts indicated that the clinicians would like to continue durvalumab maintenance therapy until a patient experiences disease progression, intolerable or serious adverse events, 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 adverse event, 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 one 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: (i) durvalumab with tremelimumab in combination with etoposide and either carboplatin or cisplatin, (ii) durvalumab in combination with etoposide and either carboplatin or cisplatin, and (iii) 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 progressive disease (PD). In the control arm, patients received 4 to 6 cycles of EP every 3 weeks and prophylactic cranial irradiation 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: overall survival (OS), progression-free survival (PFS), duration of response, objective response rate, health-related quality of life, and change in symptoms. The primary outcome in the CASPIAN trial was overall survival (OS) and PFS was the key secondary outcome, however, PFS was not formally tested for statistical significance. Health-related quality of life and symptoms were assessed by the EORTC QLQ-C30 and EORTC QLQ-L13 scales. The EORTC QLQ C30 is a questionnaire for evaluating the quality of life of patients with cancer participating in clinical trials, which consists of five functional scales, three symptom scales, and six single items. This instrument also includes global health status and overall quality of life (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 endpoint of OS at the prespecified interim analysis. Median OS was 13.0 (95% CI: 11.5, 14.8) months in the durvalumab + EP arm compared to 10.3 (95% CI: 9.3, 11.2) months the EP arm (HR, 0.73; 95% CI: 0.59, 0.91; P = 0.0047). As of the final analysis, median OS was 12.9 (95% CI: 11.3, 14.7) months in the durvalumab + EP arm compared to 10.5 (95% CI: 9.3, 11.2) months in the EP arm.

As of the interim analysis, median PFS was 5.1 (95% CI: 4.7, 6.2) months in the durvalumab + EP arm and 5.4 (95% CI: 4.8, 6.2) months in the EP arm. As of the final analysis, median PFS was 5.1 (95% CI: 4.7, 6.2) months in the durvalumab + EP arm and 5.4 (95% CI: 4.8, 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 + EP and EP arms, respectively (OR: 1.61; 95% CI: 1.086, 2.401). The confirmed ORR was 67.9% and 58.0% in the durvalumab + EP and EP arms, respectively (OR: 1.53; 95% CI: 1.078, 2.185). Duration of response was calculated post-hoc in the subset of patients that had a confirmed response.

Median time to deterioration in global health status/QoL was 8.4 (95% CI: 7.3, 11.5) months in the durvalumab + EP arm compared to 7.2 (95% CI: 6.3, 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 + EP. The adjusted mean change from baseline in appetite loss score was -12.7 points in the durvalumab + EP arm, which is greater than the minimal important difference, and the estimated difference between treatment arms -4.5 points (95% CI: -9.04, -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 + EP arm and 258 (97.0%) patients in the EP arm experienced an AE. The most commonly reported AEs in the durvalumab + EP and EP arms 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 + EP arm and 9.4% of patients in the EP arm. A greater percentage of patients in the EP arm experienced a SAE compared to the durvalumab + EP arm (36.5% versus 32.1%, respectively). The most commonly reported SAEs in the durvalumab + EP and EP arms 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 durvalumab + EP arm and 85.9% of patients in EP arm had died, with most deaths being attributed to ES-SCLC.

Immune-related AEs were more frequent in the durvalumab + EP arm compared to 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 + 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/anaphylactic reactions were uncommon, and the incidence of infections was similar in both groups. In the durvalumab + EP arm, 35.1% of patients experienced an infection compared to 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 or $3,911.11 per 10 mL vial of durvalumab, the cost of durvalumab + EP per 21-day cycle during the initial four 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 thereafter until disease progression is $11,733 per patient.

The sponsor submitted a cost-utility analysis based on a three-state partitioned survival model assessing durvalumab + EP compared to EP alone in adult patients with histologically or cytologically documented ES-SCLC due to multiple lung nodules that are too extensive or had a tumour/nodal volume that is too large to be encompassed in a tolerable radiation plan. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded healthcare 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 + EP was informed using landmark progression-free survival and overall survival observed over 24 months in the CASPIAN trial.

The following key limitations were identified:

- The CASPIAN trial excluded patients with an ECOG performance status greater than 1, limiting the generalizability of the results to the population of patients expected to be seen in clinical practice and potentially leading to survival estimates not aligned with expectations in the full population who would receive durvalumab.
- The extrapolation of the treatment effect beyond the two 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 timepoints typically corresponding to key changes in patients' quality of life 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, though 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 a 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 + EP is not considered cost effective at a willingness to pay threshold of $50,000 per QALY, with an ICER of $441,635 per QALY gained compared to EP alone. A price reduction of 88% would be required for durvalumab to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY gained.

Important identified limitations could not be addressed by CADTH. Uncertainty remains with the generalizability of the results to the patient population most likely to be treated with durvalumab + EP in clinical practice due to the exclusion of patients with an ECOG performance status greater than 1 from the trial; the cost-effectiveness in patients with a higher ECOG performance status (worse functioning) is uncertain. There is also uncertainty in the extrapolation of overall and progression-free survival curves over the 10-year time horizon from the approximately two years of observed data, as 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 three-years. CADTH identified limitations with the submitted budget impact analysis and undertook reanalyses which estimated the incremental budget impact of reimbursing durvalumab to be $283,353,601 over three years. The model was most sensitive to the proportion of patients receiving first line therapy, as well as to the price of durvalumab.

pERC Members

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.

May 14, 2021 Meeting

Regrets

None

Conflicts of Interest

None

CADTH

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