CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Atezolizumab (Tecentriq)
Indication: in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

Sponsor: Hoffmann-La Roche Ltd.

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	August 2022
Report Length:	15 Pages

Single Technology

CADTH

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.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that atezolizumab in combination with a platinum-based chemotherapy and etoposide be reimbursed for the first-line 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, double-blind, randomized placebo-controlled trial (IMpower133, N=403) in adult patients with chemotherapy-naïve ES-SCLC demonstrated that the addition of atezolizumab to carboplatin and etoposide resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) compared with placebo plus carboplatin and etoposide. The median OS was 12.3 months (95% confidence interval [CI], 10.8 to 15.8) in the atezolizumab arm and 10.3 months (95% CI, 9.3 to 11.3) in the placebo arm (stratified hazard ratio [HR] = 0.75; 95% CI 0.60 to 0.95; p=0.015). The median progression-free survival (PFS) was 5.2 (95% CI, 4.4 to 5.6) months in the atezolizumab arm and 4.3 (95% CI, 4.2 to 4.5) months in the placebo arm (stratified HR = 0.77; 95% CI, 0.62 to 0.96; p=0.017). The sponsor-submitted indirect treatment comparisons (ITC) suggested no statistically significant differences between atezolizumab and durvalumab in terms of PFS and OS, when these regimens were used in combination with a platinum-based chemotherapy and etoposide.

Patients identified a need for effective treatment options with manageable side effects that offer delayed disease progression and prolonged survival, and can maintain patients' independence and quality of life. pERC concluded that atezolizumab plus carboplatin and etoposide met these needs identified by patients because it provides an additional treatment option with manageable adverse effects, improved OS and PFS, and no deterioration in quality of life.

Using the sponsor submitted price for atezolizumab and publicly listed price for durvalumab, atezolizumab combination therapy was less costly compared with durvalumab combination therapy and considered similarly effective.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. Patient must not have received previous treatment for ES-SCLC.	Evidence from the IMpower133 trial demonstrated that atezolizumab plus carboplatin and etoposide can prolong survival when used as a first-line treatment in adult patients with ES-SCLC.	—
2. Patient must have good performance status upon treatment initiation with atezolizumab.	The IMpower133 trial included patients with an ECOG PS of 0 or 1.	Based on clinical expert input, selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.
Discontinuation		
3. Reimbursement of atezolizumab 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 IMpower133 trial, treatment with atezolizumab was discontinued if a patient experienced disease progression, or intolerable or serious adverse events. Patients who are unable to complete treatment with atezolizumab due to unacceptable toxicity would likely not be able to receive further treatment with atezolizumab.	Efficacy assessments in the IMpower133 trial were performed every 6 weeks for the first 48 weeks and every 9 weeks thereafter. According to the clinical expert input, in clinical practice, response to treatment would typically be assessed every 3 months. pERC agreed that follow-up intervals and imaging assessments may be prolonged at the discretion of the treating physician.
4. If one component of the combination therapy with atezolizumab plus carboplatin and etoposide is discontinued permanently because of tolerability concerns, the patient can continue with other components at the discretion of the treating physician, until disease progression.	This condition reflects the treatment discontinuation criteria used in the IMpower133 trial.	—
Prescribing		
5. Treatment should be prescribed and monitored by clinicians who have been trained in oncology and immunotherapy.	To ensure that atezolizumab is prescribed only for appropriate patients.	—
6. Treatment with atezolizumab could be provided at any outpatient or inpatient chemotherapy unit at a Canadian cancer centre/hospital.	To optimize toxicity management.	—
7. Atezolizumab should be prescribed in combination with a platinum-based chemotherapy and etoposide for eligible patients.	In the IMpower133 trial, atezolizumab was prescribed in combination with carboplatin and etoposide. pERC did not review any evidence to suggest an additional benefit of atezolizumab as monotherapy or in combination with other treatments.	pERC agreed with the clinical experts that carboplatin and cisplatin can be considered interchangeable for the first-line treatment of adult patients with ES-SCLC.

Reimbursement Condition	Reason	Implementation Guidance
Pricing		
8. Atezolizumab should provide cost savings for drug programs relative to the cost of treatment with durvalumab for the treatment of ES-SCLC in combination with platinum-based chemotherapy and etoposide.	At its submitted price, atezolizumab was cost saving in comparison with durvalumab when both are considered in combination with platinum-based chemotherapy and etoposide. This analysis considered publicly available list prices and did not consider potential confidential negotiated prices. The price of atezolizumab should be negotiated to ensure suggested cost savings are maintained.	—

CT = computerized tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small cell lung cancer; PAG = Provincial Advisory Group; RECIST = Response Evaluation Criteria in Solid Tumours criteria

Discussion Points

- The clinical experts consulted by CADTH noted that prolonging survival and improving quality of life are the most important goals of treatment in the first-line setting. The current standard first-line treatment for patients with newly diagnosed ES-SCLC consists of chemotherapy with a platinum agent (cisplatin or carboplatin) with etoposide. The clinical experts noted that although patients may show initial response to first-line chemotherapy with a platinum agent (cisplatin or carboplatin) and etoposide, response to treatment is not generally durable and most patients will ultimately relapse within the first year after treatment completion. Therefore, first-line treatment options that increase expected survival are highly desired by patients and clinicians. pERC acknowledged that ES-SCLC is an aggressive disease with poor outcomes and agreed that patients with ES-SCLC have an unmet need for better first-line therapies with more durable response that can prolong survival and preserve quality of life.
- pERC deliberated on the updated OS analysis results from the IMpower133 trial and noted that first-line treatment with atezolizumab plus carboplatin and etoposide resulted in survival benefit in patients with ES-SCLC, after a median follow up period of 22.9 months. pERC discussed that the net gain of 2 months in median OS observed with the addition of atezolizumab to carboplatin and etoposide was modest; however, the committee agreed with the clinical experts consulted by CADTH that the improved OS reported in the trial was clinically meaningful in the first-line setting where patients experience rapid tumor growth, fast clinical deterioration, and have poor survival prognosis.
- Patients expressed a need for effective treatments with manageable side effects that can control symptoms, delay disease progression, and prolong survival. Additionally, patients seek therapies that will help improve their quality of life while enabling them to maintain independence and functionality to minimize the burden on their caregivers and loved ones. pERC noted that atezolizumab plus carboplatin and etoposide align with the needs identified by patients because it provides an additional treatment option with manageable adverse effects, improved OS and PFS, and no deterioration in quality of life.
- pERC discussed the results of the sponsor-submitted ITC that provided comparative efficacy estimates between atezolizumab and durvalumab for the first-line treatment of ES-SCLC. Durvalumab is the only other immunotherapy agent approved (but not currently funded by the drug plans) in Canada that can be considered an alternative treatment option in combination with etoposide and carboplatin or cisplatin chemotherapy for the first-line treatment of ES-SCLC. Results of the submitted ITC showed no statistically significant differences between atezolizumab and durvalumab in terms of OS and PFS, when these regimens were used in combination with a platinum-based chemotherapy and etoposide. However, pERC acknowledged that the interpretation of ITC results was limited by the heterogeneity between the included studies and wide credible intervals around the reported point estimates of comparative treatment effect. pERC further compared the study characteristics and key outcome results of the IMpower133 trial with those of the CASPIAN trial (which informed the pERC recommendation of durvalumab for first-line ES-SCLC) and concluded that the efficacy and safety results reported for atezolizumab and durvalumab were comparable. Considering input from patients and clinician groups, pERC agreed that atezolizumab would offer an alternative treatment option to allow for a choice of therapy for patients who may not be able tolerate or access durvalumab.
- pERC discussed the sponsor's submitted cost-minimization analysis comparing atezolizumab with durvalumab. pERC found the sponsor's assumption of comparable efficacy and safety underpinning the submitted analysis to be appropriate and the cost savings with atezolizumab suggested by the sponsor's submission to be substantial. pERC noted that the submitted analysis only took into account publicly available list prices and that the confidential price of durvalumab should be considered to ensure the cost savings suggested by the sponsor are realized with atezolizumab.

Background

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in Canada.[1] An estimated 29,600 Canadians were diagnosed with lung cancer in 2021, representing approximately 13% of all new cancer cases, and an estimated 21,000 Canadians died from lung cancer. Small cell lung cancer (SCLC) accounts for about 15% of cases and is distinguished from NSCLC by its rapid growth, early development of metastatic disease and initial responsiveness to platinum-based chemotherapy. Extensive stage (ES) disease is defined as disease that cannot be classified as limited, including malignant pleural or pericardial effusions, contralateral hilar or supraclavicular lymph nodes, and hematogenous metastases. Approximately two-thirds of patients with SCLC have ES disease at diagnosis, which is associated with particularly poor prognosis. ES-SCLC has a median survival of 7 to 10 months, and a 1-year overall survival (OS) rate of 40% (with treatment). Until recently, standard first-line treatment of patients with ES-SCLC was a platinum agent (cisplatin or carboplatin) and etoposide chemotherapy. Recently, immune checkpoint inhibitors added to platinum and etoposide chemotherapy have demonstrated benefit in this setting. Two immune checkpoint inhibitors, durvalumab and atezolizumab are approved in Canada, in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of patients with ES-SCLC. However, neither is currently publicly funded. Durvalumab received a CADTH recommendation to reimburse in July 2021, but the health technology assessment process is not yet complete and price negotiations are ongoing with the pan-Canadian Pharmaceutical Alliance (pCPA).

Atezolizumab in combination with carboplatin and etoposide has been approved by Health Canada for the first-line treatment of adult patients with ES-SCLC. Atezolizumab (Tecentriq) is an engineered humanized immunoglobulin (IgG1) monoclonal antibody targeting PD-L1 and provides a dual blockade of interactions between PD-L1 and PD-1 and B7.1 receptors, whereby restoring tumour-specific T-cell immunity. Atezolizumab for injection is supplied as a concentrate for solution for infusion, 60 mg/mL, 1200 mg/20 mL and 840 mg/14mL single use vials. During the induction phase, the recommended dose of atezolizumab is 1200 mg administered by IV infusion followed by carboplatin, and then etoposide administered by IV infusion on day 1. Etoposide is administered by IV infusion on days 2 and 3. This regimen is administered every 3 weeks for 4 cycles. The induction phase is followed by a maintenance phase without chemotherapy in which 1200 mg atezolizumab is administered by IV infusion every 3 weeks. Patients are treated with atezolizumab until loss of clinical benefit or unacceptable toxicity.

Submission History

Atezolizumab in combination with a platinum-based chemotherapy and etoposide was previously reviewed by CADTH for the treatment of ES-SCLC and received a recommendation of 'Do Not Reimburse' (pERC Final recommendation, January 30, 2020).

The previous CADTH review of atezolizumab included 1 ongoing multinational (IMpower133), phase III, double-blind, randomized, placebo-controlled trial (N = 403) evaluating the efficacy and safety of atezolizumab in combination with carboplatin plus etoposide compared with carboplatin and etoposide plus placebo as a first line treatment for ES-SCLC. pERC made a negative recommendation because it was unable to conclude that there was a clinically meaningful net benefit with atezolizumab on combination with a platinum-based chemotherapy ad etoposide compared with carboplatin and etoposide plus placebo in this patient population. While pERC noted that there was an unmet need for additional effective treatments in this setting, atezolizumab in combination with a platinum-based chemotherapy and etoposide had a very modest OS and PFS benefit compared with platinum-based chemotherapy and etoposide alone.

The current review is based on the resubmission of data from the IMpower133 trial (including the updated OS analysis at the January 24, 2019, data-cut), and a network meta-analysis conducted to indirectly compare the efficacy and safety of atezolizumab with durvalumab in the patient population under review. Durvalumab, in combination with etoposide and platinum chemotherapy, received a recent CADTH recommendation of 'Reimburse With Conditions' for the first-line treatment of adult patients ES-SCLC (pERC Final recommendation, 27 July, 2021).

Sources of Information Used by the Committee

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

- A review of 1 clinical trial in adult patients with ES-SCLC.
- A review of 1 sponsor-submitted indirect treatment comparison (ITC) and 9 published ITCs retrieved from literature.
- Patient perspectives gathered by 1 patient group: the Lung Canada Cancer (LCC).
- Input from 2 clinician groups, including Ontario Health (Cancer Care Ontario) Drug Advisory Committee and the Lung Canada Cancer (LCC).
- Input from public drug plans that participate in the CADTH review process.
- Input from 2 clinical specialists with expertise diagnosing and treating patients with ES-SCLC.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

The patient and caregiver input received for this review was collected by the Lung Canada Cancer (LCC) from interviews with patients with SCLC and their caregiver gathered from December 2021 to February 2022, as well as information from previous LCC submissions. Six respondents with SCLC had experience with atezolizumab (in combination with chemotherapy or as a single treatment), four of whom had ES disease. Five patients had access to atezolizumab through clinical trial, and one through a compassionate access program. Four of these respondents resided in Ontario, one resided in British Columbia, and one resided in Quebec. Respondents indicated that a diagnosis of SCLC and the subsequent treatment had a major impact on the lives of patients and their family members. They reported that they expect the following key outcomes to be improved from any new drug or treatment: disease symptoms relieve, manageable side effects, improved quality of life, maintaining independence and functionality, greater access across jurisdictions, maintaining disease stability, longer periods of remission, and prolonged survival. Patients with SCLC patient have a very high unmet need, as there have been no new treatment options for SCLC in the last 30 years until the last 12 months, when durvalumab was approved for treatment of ES-SCLC. Six respondents who received or continue to receive atezolizumab indicated that this drug has had promising and durable treatment results with tolerable side effects. They also mentioned that atezolizumab helped them regain independence, functionality, and livelihood, which reduced the burden on their caregivers and loved ones.

Clinician input

Input from clinical experts consulted by CADTH

The clinical experts consulted by CADTH noted that ES-SCLC has a relatively short median OS (10 months). Although patients typically have initial response rates, most patients relapse within 6 months with poor prognosis. Given most patients' poor performance status and poor response to subsequent therapies, first-line treatment options that increase survival are highly desired. The combination of immunotherapy and chemotherapy is widely accepted as the new standard of care for the management of ES-SCLC. The addition of durvalumab, or atezolizumab to a platinum agent and etoposide would be the most appropriate initial therapy for ES-SCLC. The clinical experts consulted also indicated that there is no specific subgroup of patients best suited for treatment with atezolizumab + carboplatin + etoposide and all patients with ES-SCLC should be treated with combination immunotherapy and chemotherapy in the first-line setting irrespective of symptoms, as ES-SCLC is an aggressive disease and requires prompt treatment. Response to treatment is typically assessed every 3 cycles while on chemotherapy using radiographic imaging with a CT scan, and every 3 months thereafter.

Clinician group input

Clinician input was received from Ontario Health (Cancer Care Ontario) Drug Advisory Committee and from LCC. The clinician groups noted that patients with ES-SCLC have a high unmet need for more effective therapies since most patients progress in a

short period of time despite high response rate to initial therapy. Atezolizumab would be used as initial systemic therapy in patients with ES-SCLC in combination with 4 cycles of platinum and etoposide, followed by maintenance atezolizumab until disease progression. Atezolizumab will be an alternative option to durvalumab (if durvalumab is indeed added to the provincial/territorial public formularies across Canada following negotiations with the pCPA in the first-line treatment of patients with ES-SCLS. It would fit into the current treatment paradigm only as an agent to be started concurrently with first-line platinum and etoposide chemotherapy, with the intention of continuing until disease progression, intolerance, or a patient's choice to discontinue therapy. Patients with symptomatic brain metastases would need to receive treatment for their brain metastases prior to starting systemic therapy. The clinician groups believed that no specific subgroups of patients are more likely to benefit from the addition of atezolizumab to platinum-based chemotherapy and etoposide, therefore they felt the treatment should be considered for any patient with ES-SCLC and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or better.

Drug Program Input

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

Table 2. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant comparators	
The current funded standard of care is platinum-based chemotherapy plus etoposide. Durvalumab is not funded at this time.	pERC acknowledged the drug plans' input.
In some jurisdictions cisplatin + etoposide is used rather than the platinum-based regimen used in the IMpower133 trial, i.e., carboplatin + etoposide. Is it reasonable to consider combination therapy with platinum-based chemotherapy + etoposide for the implementation of atezolizumab?	pERC agreed with the clinical experts that carboplatin and cisplatin can be considered interchangeable in the first-line treatment of adult patients with ES-SCLC. The results of the IMpower133 trial with respect to the efficacy of atezolizumab plus carboplatin and etoposide can be generalized to atezolizumab plus cisplatin and etoposide.
Considerations for initiation of therapy	
IMpower133 required patients to have an ECOG PS of 0 or 1. PAG is asking if the drug combination under review would be offered to patients with an ECOG PS of 2?	pERC agreed with the clinical experts, that patients with an ECOG PS of 2 can be considered for combination therapy with atezolizumab, especially if the poor performance status is disease-related. The clinical experts indicated that this would be consistent with guideline recommendations for the treatment of patients with lung cancer.
Is there evidence to treat patients requiring radiation for local symptomatic control, prophylactic cranial irradiation, or whole brain radiation with atezolizumab?	pERC agreed with the clinical experts that radiation therapy should not be a barrier to accessing atezolizumab therapy. Patients could have received prior radiation therapy before entering the IMpower133 trial.
If the patient's disease progresses during a treatment break of atezolizumab maintenance, can atezolizumab be restarted or should the patient be re-treated with atezolizumab + platinum + etoposide, followed by atezolizumab maintenance?	Retreatment was not part of the planned therapy in the IMpower133 trial. pERC noted that there was insufficient evidence to support retreatment with atezolizumab.
Considerations for discontinuation of therapy	
Should patients be treated with atezolizumab until disease progression or until loss of clinical benefit? in clinical practice, what would be the stopping rules for atezolizumab (e.g., usual immunotherapy is l0% increase in total tumor burden confirmed with a second	The IMpower133 trial allowed treatment until disease progression but did allow treatment to continue in patients who had ongoing symptomatic or clinical benefit. The clinical experts believed that it would be most appropriate to allow treatment until disease progression or loss of treatment benefit. pERC agreed with the clinical experts that patients with ongoing benefit and evidence of disease progression

Implementation Issues	Response
CT scan 6 to 8 weeks following the last scan if progression is suspected)?	according to RECIST should be allowed to continue treatment until the next disease reassessment. If there is further progression, treatment should be discontinued.
Considerations for prescribing of therapy	
In ES-SCLC, atezolizumab is in the same therapeutic space as durvalumab. Consider alignment of the prescribing criteria.	pERC acknowledged the drug plans' input.
Generalizability of trial populations to the broader populations in the jurisdictions	
Would PERC support use of atezolizumab in the second- line setting as monotherapy or in combination with topotecan following progression on platinum-based chemotherapy?	The clinical experts believed that atezolizumab would not be suited in second-line since there are randomized clinical trial data showing atezolizumab is inferior to topotecan, and that they were aware of no evidence to support the use of combination therapy in second-line. pERC considered this question to be out of the scope of the current review.
Current patients receiving platinum-based chemotherapy (cisplatin/carboplatin with etoposide) without progression, could they have atezolizumab added?	pERC agreed with the clinical experts consulted by CADTH that patients who are receiving platinum and etoposide chemotherapy, and have not completed chemotherapy, should be allowed to receive add-on atezolizumab.

CT = computerized tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small cell lung cancer; PAG = Provincial Advisory Group

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

IMpower133 is a randomized, multicentre, double-blind, placebo-controlled phase III study designed to evaluate the efficacy and safety of treatment with atezolizumab + carboplatin and etoposide compared with treatment with placebo + carboplatin and etoposide in patients with chemotherapy-naïve ES-SCLC. The trial was conducted in 106 sites across 21 countries (none in Canada). The co-primary endpoints were investigator-assessed progression-free survival (PFS) and OS. The key secondary endpoints were investigator-assessed objective response rate (ORR), and investigator-assessed duration of response (DOR). Patient reported outcomes (PROs) included health-related quality of life (HRQoL). The clinical cut-off date for the primary analysis (primary PFS analysis and interim OS analysis) was April 24, 2018. The clinical cut-off date for the updated analysis (final analysis of OS) was January 24, 2019. Overall, mean age was 63.7 years (standard deviation [SD]=8.9); 64.8% were male and 79.9% were White. Patients had to have an ECOG PS of 0 or 1 and approximately 64% of the patients in both treatment arms had an ECOG PS of 1. Of 526 patients screened, 403 patients were randomized, 201 patients to the atezolizumab arm, and 202 patients to the placebo arm. The median duration of follow-up was 13.9 months at the data cut-off date April 24, 2018 (PFS analysis, interim OS analysis) and 22.9 months at the data cut-off date of January 24, 2019 (final OS analysis).

Efficacy Results

Progression-Free Survival

At the data cut-off date for PFS analysis (April 24, 2018), the median PFS was 5.2 (95% confidence interval [CI], 4.4 to 5.6) months in the atezolizumab arm and 4.3 (95% CI, 4.2 to 4.5) months in the placebo arm. The stratified hazard ratio (HR) for disease progression or death was 0.77 (95% CI, 0.62 to 0.96; P = 0.0170).

Overall Survival

At the time of the OS interim analysis (data cut-off date April 24, 2018), patients had a median survival follow-up time of 13.9 months. Median OS was 12.3 months (95% CI, 10.8 to 15.9) in the atezolizumab arm and 10.3 months (95% CI, 9.3 to 11.3) in the placebo arm. The stratified HR for death was 0.70 (95% CI, 0.54 to 0.91; P = 0.007).

At the final OS analysis (data cut-off date January 24, 2019), the median survival follow-up time was 22.9 months. The median OS was 12.3 months (95% CI, 10.8 to 15.8) in the atezolizumab arm and 10.3 months (95% CI, 9.3 to 11.3) in the placebo arm. The stratified HR for death was 0.75 (95% CI, 0.60 to 0.95; P = 0.015). The 2-year event-free rates were 22.0% in the atezolizumab arm, and 16.8% in the placebo arm.

Objective Response Rate

Investigator-assessed confirmed ORR was 60.2% in the atezolizumab arm, and 64.4% in the placebo arm; 2.5% and 1.0% of patients in the atezolizumab and placebo arms respectively, had a complete response. At the updated analysis, the confirmed investigator-assessed ORR was 60.2% (95% CI, 53.1 to 67.0) in the atezolizumab arm and 64.4% (95% CI, 57.3 to 71.0) in the placebo arm; 3.5% and 1.0% of patients in the atezolizumab and placebo arms, respectively, had a complete response.

Duration of Response

The median DOR (confirmed) was 4.2 months (range, 1.4 to 19.5), in the atezolizumab arm, and 3.9 months (range, 2.0 to 16.1) in the placebo arm. At data cut off (April 24, 2018) 14.9% of patients in the atezolizumab arm and 5.4% of patients in the placebo arm had ongoing response. At the updated analysis, the median DOR was 4.2 months (95% CI: 4.1 to 4.5) in the atezolizumab arm and 3.9 months (95% CI: 3.1 to 4.2) in the placebo arm.

Harms Results

The majority of patients in both treatment arms; 100% in the atezolizumab arm and 96.4% in the placebo arm, experienced at least one adverse event (AE) of any grade. In the atezolizumab arm, the most common AE of any grade by preferred term experienced by ≥10% of patients were anemia (43.4%), nausea (37.9%), and neutropenia (37.4%). In the chemotherapy arm, the most common AEs of any grade by preferred term experienced by ≥10% of patients were anemia (35.2%), neutropenia (35.2%) and alopecia (34.7%).

Grade 3 or 4 AEs occurred in 67.7% of patients in the atezolizumab arm and 63.3%% of patients in the chemotherapy arm. The most common grade 3 or 4 AEs reported in ≥5% of patients in any treatment arm in the atezolizumab and placebo arms were neutropenia (22.7% versus 25.0%), decreased neutrophil count (15.7% versus 16.8%), anaemia (15.7% versus 13.3%), thrombocytopenia (10.1% versus 8.7%), and hyponatraemia (4.5% versus 6.6%).

In the atezolizumab arm, 37.4% of patients had at least 1 serious AE (SAE). In the chemotherapy arm 34.7% of patients experienced at least 1 SAE. The most common SAEs experienced by at least 1% of patients in either atezolizumab or chemotherapy arm were: pneumonia (4.5% versus 3.6%), neutropenia (3.5% versus 4.1%), febrile neutropenia (2.5% versus 4.6%), and thrombocytopenia (2.5% versus 2.0%).

Withdrawal from any study treatment due to AEs were reported for 12.1% of patients in the atezolizumab arm and 3.1% of patients in the chemotherapy arm. In the atezolizumab arm 11.6% of patients experienced AEs leading to discontinuation of atezolizumab, and in the placebo arm, 2.6% of patients had AEs leading to discontinuation of placebo. The main reasons for permanently discontinuing atezolizumab in 21 patients in the atezolizumab arm were infusion-related reactions and gastrointestinal disorders.

Grade 5 fatal AEs occurred in 4 patients (2.0%, including pneumonia, respiratory failure, death and neutropenia) in the atezolizumab arm, and 11 patients (5.6%, including pneumonia, pulmonary sepsis, sepsis, septic shock, acute respiratory failure, haemoptysis, cardiopulmonary failure, pericardial effusion and general physical health deterioration) in the placebo arm. The only grade 5 AE (by preferred term) that occurred in more than 1 patient was pneumonia (1 patient in the atezolizumab arm and 3 patients in the placebo arm). Of the grade 5 events, 3 events in each arm were considered related to at least one component of study treatment. In the atezolizumab arm, a grade 5 ‘death’ was considered related to all study treatment, there was also one grade 5 pneumonia and one case of grade 5 neutropenia that were both considered related to both carboplatin and etoposide. In the placebo arm, a grade 5

septic shock was considered related to all study treatment, a grade 5 pneumonia was considered related to placebo, and a grade 5 cardiopulmonary failure was considered related to carboplatin.

Immune-related AEs were reported for 41.4% of patients in the atezolizumab arm and 24.5% of patients in the placebo arm. Rash (both treatment arms) and hypothyroidism (atezolizumab arm) were the most common (≥10% incidence) and most differentially reported (≥ 5% difference between treatment arms) immune-related AEs during treatment. Immune-related infusion-related reaction events were experienced by 5.6% of patients (n=11) in the atezolizumab arm, and 5.1% of patients (n=10) in the placebo arm. The majority of these events were grade 1 or 2 (atezolizumab arm: n=7 [3.5%]; placebo arm n=9 [4.6%]). Four patients (2.0%) in the atezolizumab arm and 1 patient (0.5%) in the placebo arm had grade 3 or 4 infusion-related reactions.

Critical Appraisal

The baseline demographic and disease characteristics across treatment arms were roughly balanced between the two treatment arms. Response outcomes (ORR and DOR) were assessed by investigators per RECIST v1.1. While the trial was double-blinded and the investigators were blinded to treatment assignment, risk of bias cannot be ruled out. For example, nearly half of the patients in the atezolizumab arm experienced immune-related AEs or other events. These events may have possibly made the investigator aware of the patient's treatment assignment. Therefore, for all investigator-assessed outcomes there may be a degree of subjectivity which could have biased the results. In addition, although the proportion of patients receiving concomitant and supportive care for symptom control were largely similar in the two treatment arms, which may have led to comparable PROs including QoL outcomes as observed in the trial, this may not mean that the two trial regimens truly have comparable safety and impact on QoL. Interim and final analyses were planned a priori and adequately described. The interim analysis applied Lan-DeMets alpha spending function with the O'Brien-Fleming stopping boundary, which is deemed conservative in controlling type I error in claiming a treatment effect based on interim analysis. The updated final analysis results of OS were consistent with the interim analysis results.

The patient population in the IMpower133 study generally reflects patients in clinical practice in this setting. However, there were some patient groups that were not represented including those with ECOG PS of 2 and patients with active untreated metastases. The proportion of patients with brain metastases (9%) was lower than that observed in clinical practice (10-20%), but this is likely due to the specific inclusion requirements for these patients (e.g., only supratentorial and cerebellar metastases, and no ongoing requirement for corticosteroids as therapy for CNS disease). Due to the small number of patients in some subgroups, including brain metastases at baseline, subgroup analyses failed to demonstrate similar effects in patients with brain metastases as in patients free of brain metastases. The comparator in the IMpower133 trial (carboplatin and etoposide) is relevant to the Canadian context as platinum (carboplatin or cisplatin) and etoposide chemotherapy is the current standard of care.

Indirect Comparisons

Description of studies

One sponsor-submitted indirect treatment comparison (ITC) and 9 published ITCs retrieved from literature were summarized and appraised for this CADTH review.

The sponsor-submitted ITC provided estimates of PFS, OS, ORR and incidence of SAEs between atezolizumab+ carboplatin + etoposide and competing interventions platinum doublet therapies and immunotherapies used for the first-line treatment of ES-SCLC. The results of comparisons between atezolizumab + carboplatin + etoposide versus etoposide + carboplatin, etoposide + cisplatin, and durvalumab + etoposide + carboplatin (or cisplatin) were considered relevant for the purpose of this CADTH review.

The sponsor's base-case analysis for each outcome included adjusted or stratified HRs reported across the trials in the relevant evidence network. Additional scenario analyses were conducted to investigate the choice of platinum agent for the analyses of PFS and OS, and to explore the effect of one study with outlier ECOG PS data on OS.

Efficacy Results

This section will focus on the findings of the sponsor-submitted network meta-analysis (NMA).[14]

PFS

The results of the base-case analysis showed that atezolizumab+ carboplatin + etoposide was associated with longer PFS compared to carboplatin (or cisplatin) + etoposide [redacted]. Similar findings were observed in the scenario analyses that included [redacted]

or considered [redacted].

The results of the base-case analysis for comparison of atezolizumab+ carboplatin+ etoposide with durvalumab + carboplatin or cisplatin + etoposide showed no statistically significant difference in PFS based on CrI which included the null, and the point estimate that was close to the null value [redacted]. Similar findings were observed in the scenario analyses that included unadjusted or unstratified HRs [redacted].

OS

The results of base-case analysis suggested that atezolizumab + carboplatin + etoposide may be associated with improvement in OS, when compared with etoposide + carboplatin or cisplatin [redacted]. Similar findings were obtained in the other three scenario analyses that included unadjusted or unstratified HRs [redacted]; investigated the robustness of the results to exclusion of a study with outlier ECOG PS data (i.e., Hermes 2008 study) [redacted]; or considered etoposide and cisplatin as distinct nodes [redacted].

The results of the base-case analysis for comparison of atezolizumab+ carboplatin+ etoposide with durvalumab + carboplatin or cisplatin + etoposide showed no statistically significant difference in OS based on the CrI which included the null, and the point estimate that was close to the null value [redacted]. Similar findings were obtained in the other three scenario analyses that included unadjusted or unstratified HRs [redacted]; investigated the robustness of the results to exclusion the Hermes 2008 study [redacted]; or considered etoposide and cisplatin as distinct nodes [redacted].

Objective response rate

The comparison of atezolizumab+ carboplatin + etoposide with durvalumab + carboplatin or cisplatin + etoposide showed that atezolizumab+ etoposide+ carboplatin was associated with a lower odds of ORR [redacted]. The OR for the comparison of atezolizumab + carboplatin + etoposide against etoposide + carboplatin or cisplatin [redacted] and the OR for the comparison of atezolizumab + carboplatin + etoposide with etoposide + cisplatin was [redacted].

Harms Results

SAEs

Two studies were used to inform the evidence network for SAEs. The OR observed in the comparison of atezolizumab + carboplatin+ etoposide with durvalumab+ carboplatin or cisplatin+ etoposide [redacted] and in the comparison of atezolizumab +carboplatin+ etoposide with etoposide + cisplatin [redacted]. No statistically significant difference was observed based on the CrIs which included the null value, and the point estimates that were close to the null value (i.e., OR = 1).

Critical Appraisal

The sponsor's systematic review methods for identifying and assessing studies included in the network were considered appropriate for identifying relevant studies. The PICO criteria (i.e., population, interventions, comparisons, outcomes) were pre-specified, and articles were reviewed by 2 independent reviewers while a second analyst extracted data. All relevant comparators identified in the CADTH review protocol that were considered relevant to the Canadian practice context were presented in the sponsor's NMA. Outcomes presented in the trials included in the network analysis were considered relevant and clinically meaningful by the clinician experts consulted during the CADTH review. The population studied in all eight trials was considered relevant for the reimbursement request. Most studies included untreated patients with extensive stage small lung cell cancer. One study (Skarlos 1994) recruited a

different population in the trial but had a subgroup of patients with ES-SCLC. Information from the subgroup analysis was used to inform the network. Quality assessments were conducted using the validated seven-criteria checklist provided by the NICE single technology appraisal (STA) user guide.

A generalized linear regression model (GLM) with a binomial likelihood, logit link model was used which was considered appropriate for the types of outcomes assessed in the network. The sponsor explored both FE and RE models in their base case scenarios and results from the FE model were presented. The sponsor provided a justified rationale for using the FE model over the RE model based on the model fit criteria including a judgement on the similarities of studies included in terms of effect modifiers.

The transitivity assumption was assessed by evaluating potential effect modifiers. There was considerable heterogeneity across trials, particularly in terms of ECOG PS. The Hermes 2008 trial enrolled <53% of patients with an ECOG PS of 0 or 1 in both treatment arms versus 100% in the CASPIAN, ECOG-ACRIN EA5161, IMpower133, and KEYNOTE-604 trial. In the Okamoto 2007 trial, patients with an ECOG PS of 0 to 2 were included in those aged ≥70 years and an ECOG PS of 3 for patients aged <70 years. There was inconsistency in the reporting of number and type of metastatic sites across the trials. Heterogeneity in the use of subsequent anticancer therapy administered to patients in the second line and higher recruited in the studies was identified as a potential source of bias affecting OS assessment which may also affect the generalizability of the findings of the NMA to Canadian setting. There was also variability observed in the dosing of etoposide plus carboplatin or cisplatin across the trials which may impact the findings of the ITC.

According to the sponsor's ITC report, a meta-regression analysis was not possible investigate inter-trial heterogeneity due to insufficient studies (i.e., the presence of several single study connections between interventions). Scenario analyses related to certain characteristics of interest were included in the sponsor's NMA report to address heterogeneity across the trials included in the network (e.g., removal of the Hermes 2008 trial which was an outlier with smallest proportion of patients with ECOG PS <2 from the OS base case analysis). According to the clinical expert consulted, ECOG PS, metastatic sites (liver and brain, were the most significant effect modifiers in treatment of ES-SCLC patients. The sponsor acknowledged that additional scenario or subgroup analyses were feasible for PFS and OS; however, because relevant subgroup data are not currently available from the trials of the evidence networks investigation immunotherapies (i.e., CASPIAN, ECOG-ACRIN EA5161, and KEYNOTE-6040 ongoing trials), all possible subgroup analyses were not included in the sponsor's report. Therefore, the NMA results should be interpreted with caution due to limitations that may arise from between-study differences in some covariates; and lack of sufficient evidence to minimize heterogeneity and inconsistency (e.g., by performing meta-regression analysis).

Other Relevant Evidence

No other relevant evidence was identified.

Conclusions

Based on clinical data from the IMpower133 study, atezolizumab in combination with carboplatin and etoposide demonstrated a statistically significant benefit compared to placebo in combination with carboplatin and etoposide in the first-line treatment of patients with ES-SCLC. The updated OS analysis with a median of 22.9 months of follow-up showed consistent results with those reported at the interim OS analysis and suggests maintained clinical benefit for atezolizumab in combination with carboplatin and etoposide. Although the net gain of about 1 month in median PFS and 2 months in median OS observed with the addition of atezolizumab to carboplatin and etoposide is modest, it was considered by the clinical experts consulted by CADTH to be clinically meaningful in this setting where patients experience rapid tumor growth, fast clinical deterioration and have poor prognosis. The toxicity profile of atezolizumab was consistent with its immune-mediated mechanism of action with no new safety concerns. Based on the results of the sponsor-submitted ITC, atezolizumab appears to demonstrate comparable benefit in terms of improving PFS and OS as durvalumab, the only other immunotherapy agent approved (but not currently funded by the drug plans in Canada) for the first-line treatment of ES-SCLC in Canada. However, no firm conclusions could be drawn due to small number of studies per comparison leading to lower precision of effect estimates.

Economic Evidence

Table 3. Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with extensive-stage small-cell lung cancer (ES-SCLC) who were chemotherapy-naïve for their ES disease
Treatments	• Atezolizumab in combination with carboplatin and etoposide (Health Canada indication) • Atezolizumab in combination with any platinum-based chemotherapy and etoposide (scenario analysis aligned with reimbursement request)
Submitted Price	$6,776.00 per 1200 mg vial
Treatment Cost	The cost for atezolizumab is $9,035 per 28-day.
Comparator	Durvalumab in combination with platinum-based chemotherapy and etoposide
Perspective	Canadian publicly funded health care payer
Time horizon	One year
Key data source	A sponsor commissioned indirect treatment comparison to establish equivalent comparative efficacy and safety of atezolizumab in combination with carboplatin and etoposide in comparison with durvalumab in combination with platinum-based chemotherapy and etoposide.
Costs considered	Drug acquisition costs, drug administration costs, monitoring costs
Submitted results	• Health Canada indication: Atezolizumab in combination with carboplatin and etoposide was associated with incremental cost savings of $25,967 per patient annually in comparison with durvalumab in combination with platinum-based chemotherapy and etoposide. • Similar cost savings were observed in the scenario assessing the sponsor's reimbursement request.
Key limitations	• In the absence of direct evidence comparing atezolizumab and durvalumab, both in combination with a platinum-based chemotherapy and etoposide, a sponsor-commissioned NMA was submitted, which showed no clinically meaningful difference in the survival benefit observed between atezolizumab and durvalumab. However, the CADTH clinical review noted the credible intervals were wide, which introduces some uncertainty in the conclusions that may be drawn.
CADTH reanalysis results	• CADTH did not undertake a base case re-analysis and accepted the sponsor's base case results. • Under an assumption of equal efficacy and safety, atezolizumab in combination with carboplatin and etoposide is associated with cost savings of $25,967 per patient in comparison with durvalumab in combination with platinum-based chemotherapy and etoposide. Similar cost savings were observed in the sponsor's reimbursement request scenario analysis ($25,938). • These results depend on the availability of durvalumab and the publicly available list price for durvalumab.

Budget Impact

CADTH identified two key limitations with the sponsor's analysis: 1) The sponsor's assumption that clinical trials have a market share was inappropriate; 2) there was uncertainty in the proportion of patients assumed to be treated. In a CADTH reanalysis, the market share of clinical trials was redistributed over immunotherapies based on feedback from clinical experts. Based on the CADTH reanalysis, the three-year budget impact to the public drug plans of introducing atezolizumab in combination with carboplatin-based chemotherapy and etoposide, followed by atezolizumab monotherapy for first line treatment of adult patients with ES-SCLC was cost-savings of $32,622,953 (Year 1: $9,331,270; Year 2: $11,150,989; Year 3: $12,140,694). Similar results were estimated in analyses aligned with the sponsor's reimbursement request.

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting Date: July 12, 2022

Regrets

One expert committee member did not attend.

Conflicts of Interest

None