

CADTH Reimbursement Recommendation

Atezolizumab (Tecentriq)

Indication: As monotherapy for adjuvant treatment following resection and platinum-based chemotherapy for patients with non–small cell lung cancer whose tumours have programmed death-ligand 1 expression on 50% or more of tumour cells.

Sponsor: Hoffmann-La Roche Ltd.

Final recommendation: Reimburse with conditions

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What Is the CADTH Reimbursement Recommendation for Tecentriq?

CADTH recommends that Tecentriq be reimbursed by public drug plans after surgery and chemotherapy for the treatment of patients with stage II to stage IIIA non–small cell lung cancer (NSCLC) whose tumour is positive for programmed death-ligand 1 (PD-L1) in at least 50% of tumour cells (TCs) and does not have an abnormal *EGFR* or *ALK* gene if certain conditions are met.

Which Patients Are Eligible for Coverage?

Tecentriq should only be covered to treat adult patients (18 years or older) with stage II to stage IIIA NSCLC whose tumour is positive for PD-L1 in at least 50% of TCs and does not have an abnormal *EGFR* or *ALK* gene.

What Are the Conditions for Reimbursement?

Tecentriq should only be used alone after surgery and chemotherapy. Tecentriq should only be reimbursed if it is prescribed by a specialist and if the patient is in relatively good health (i.e., has a good performance status, as determined by a specialist). Tecentriq should not be reimbursed if the patient is not a candidate for surgery or chemotherapy. The cost of Tecentriq must be lowered to be cost-effective and affordable.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Tecentriq lowered the chances of cancer returning compared to best supportive care.
- Based on CADTH's assessment of the health economic evidence, Tecentriq does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, it is estimated that Tecentriq will cost the public drug plans approximately \$59 million over the next 3 years.

Additional Information

What is Early-Stage NSCLC?

NSCLC is the most common type of lung cancer. In those with NSCLC, unusual growth of cells takes place inside the lungs or lining of the airways and forms into tumours. Cancer that is stage I, II, or IIIA is considered early stage, meaning the tumour has not spread to other parts of the body.

Unmet Needs in NSCLC

The intention of surgery for early-stage NSCLC is to cure patients. However, it is possible for cancer to return for some patients who have had surgery; therefore, there is a need for treatment options that can prevent cancer from returning.

How Much Does Tecentriq Cost?

Treatment with Tecentriq is expected to cost approximately \$9,035 per 28-day cycle.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that atezolizumab be reimbursed as monotherapy for adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to IIIA (per the American Joint Committee on Cancer [AJCC], 7th edition) NSCLC whose tumours have PD-L1 expression on 50% or more of TCs and do not have *EGFR* or *ALK* genomic tumour aberrations only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, open-label, randomized study (IMpower010) demonstrated a clinically meaningful disease-free survival (DFS) benefit (DFS hazard ratio [HR] = 0.47; 95% confidence interval [CI], 0.29 to 0.75; P value = 0.0012) with atezolizumab versus best supportive care (BSC) in patients with stage II to stage IIIA NSCLC following complete resection and adjuvant cisplatin-based chemotherapy. Atezolizumab addresses an unmet need for this patient population with poor prognosis and high risk of disease recurrence.

Patients expressed a need for an additional treatment option that has manageable side effects, delays disease progression, improves survivorship, and maintains quality of life. Patients highlighted the importance of maintaining their independence and functionality to minimize the burden on caregivers and loved ones. Given the totality of the evidence, pERC concluded that atezolizumab met some of the needs identified by patients in terms of an additional treatment option that delays disease recurrence.

Using the sponsor-submitted price for atezolizumab, the incremental cost-effectiveness ratio for atezolizumab was \$68,858 per quality-adjusted life-year (QALY) compared with active surveillance. At this incremental cost-effectiveness ratio, atezolizumab is not cost-effective at a \$50,000 per QALY willingness-to-pay threshold for adult patients with completely resected stage II to stage IIIA NSCLC who received platinum-based chemotherapy and whose tumours have PD-L1 expression on 50% or more of TCs and do not have *EGFR* or *ALK* mutations. A reduction in price is required for atezolizumab to be considered cost-effective at a \$50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with atezolizumab should be initiated only as monotherapy for adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to stage IIIA NSCLC	pERC acknowledged that while the Health Canada-approved indication is according to the American Joint Committee on Cancer, 7th edition, the 8th edition staging system is currently used in Canadian clinical practice. Based on clinical expert opinion, the eligible population based on the 8th edition would be patients with fully	Based on clinical expert opinion, patients with stage IIIB cancer who are stage T3N2 or T4N2 on the basis of a primary tumour > 7 cm or diaphragm involvement and have been fully resected should also be eligible. Based on clinical expert opinion, chemotherapy should be initiated within

Reimbursement condition	Reason	Implementation guidance
whose tumours have PD-L1 expression on \geq 50% of TCs and have do not have <i>EGFR</i> or <i>ALK</i> mutations.	resected stage II to stage IIIA cancer who had a primary tumour > 5 cm regardless of nodal status or who's tumours were node positive regardless of primary tumour size. Based on clinical expert opinion, patients with the common <i>EGFR</i> mutations (exon 19 del and exon 21 L858R) should not be offered adjuvant atezolizumab in favour of adjuvant osimertinib. The clinical experts also noted that immune checkpoint inhibitors do not have significant activity in the advanced setting in patients with <i>ALK</i> fusion; thus, there may be limited, if any, benefit from adjuvant immunotherapy for a patient with a resected <i>ALK</i> -positive tumour.	12 weeks of surgical resection. Starting atezolizumab within 3 to 8 weeks from the completion of chemotherapy is reasonable in the real world. It is reasonable on a time-limited basis to offer atezolizumab to patients who had received platinum-chemotherapy up to 12 weeks but where atezolizumab was not accessible.
2. Patients must have a good performance status.	Based on clinical expert opinion, if a patient is robust enough to receive chemotherapy and had an ECOG PS of 2, they would be robust enough to receive atezolizumab.	—
3. Patients are ineligible for atezolizumab if they are: 3.1. not eligible for surgical resection 3.2. not eligible for initiation of cisplatin-based adjuvant chemotherapy.	As per IMpower010 study criteria.	Based on clinical expert opinion, patients who become ineligible for cisplatin after 1 cycle due to toxicities should be eligible to receive atezolizumab.
Renewal		
4. Atezolizumab should be renewed for patients who tolerate treatment and have no evidence of disease recurrence.	As per IMpower010 study and clinical experts.	—
5. Patients should be assessed for evidence of disease recurrence based on standard care.	As per clinical expert opinion.	—
Discontinuation		
6. Treatment with atezolizumab should be discontinued on the occurrence of any of the following: 6.1. disease recurrence 6.2. unacceptable toxicity 6.3. treatment up to 48 weeks.	As per IMpower010 study.	If treatment is withheld due to toxicity, then maximum duration will be 16 cycles.

Reimbursement condition	Reason	Implementation guidance
Prescribing		
7. Atezolizumab should be prescribed by clinicians with expertise in managing NSCLC.	To ensure that atezolizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
8. A reduction in price	In the reimbursement request population considering a patient population without an <i>EGFR</i> or <i>ALK</i> mutation, the ICER for atezolizumab is \$68,858 per QALY when compared with active surveillance. A price reduction of 24% would be required for atezolizumab to achieve an ICER of \$50,000 per QALY compared to active surveillance.	—
Feasibility of adoption		
9. Access to PD-L1 testing	PD-L1 testing is needed to identify patients whose tumours have PD-L1 expression on $\geq 50\%$ of TCs.	—

ECOG PS = Eastern Cooperative Oncology Group performance status; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life-year; TC = tumour cell.

Discussion Points

- pERC acknowledged that the critical appraisal was limited by Health Canada's decision to amend the Notice of Compliance from the original overall population to include only a subset of the population; as a result, the IMpower010 study was not powered for the Health Canada indication under review. However, DFS in patients with PD-L1 of 50% or greater was a prespecified secondary end point. pERC deliberated on the value of DFS as a primary end point in the adjuvant setting and noted that overall survival (OS) data were immature. pERC agreed with the clinical experts that the results of the IMpower010 study led to a clinically meaningful benefit in DFS.
- pERC discussed the extension of eligibility to those with stage IB disease and those with PD-L1 expression lower than 50% and acknowledged that while the overall population of the IMpower010 study included those with stage IB disease and those with PD-L1 expression lower than 50%, given the Health Canada-approved indication, these subgroups are out of scope for this review. Hence, pERC did not recommend reimbursement of atezolizumab for these subgroups. pERC also noted that the IMpower010 study is ongoing and anticipates that as data mature for these subgroups, this may lead to a future expanded Health Canada indication (i.e., for those with stage IB disease and those with PD-L1 expression < 50%).
- The patient groups' input to CADTH highlighted that patients need a treatment that maintains their health-related quality of life (HRQoL). HRQoL was not measured in the

IMpower010 study; therefore, pERC was unable to draw any conclusions around the potential benefit of atezolizumab on HRQoL.

- pERC discussed the toxicity profile of atezolizumab and noted the discontinuation rate due to adverse events (AEs) (19% of patients treated with atezolizumab), which were mainly due to pneumonitis (1.4%), hypothyroidism (1.4%), or aspartate aminotransferase (AST) increase (1.4%). pERC felt that these AEs were expected and manageable.

Background

Lung cancer is 1 of the most commonly diagnosed cancers and is the leading cause of cancer deaths in Canada, with NSCLC accounting for approximately 88% of lung cancer cases. Approximately half of NSCLC cases in Canada are stage I to III at diagnosis, and one-third of patients with NSCLC have operable disease. Early-stage NSCLC (i.e., stages I to IIIA per the AJCC, 7th edition) is often asymptomatic. When patients do present with symptoms, these are usually nonspecific and difficult to directly attribute to lung cancer. The most common symptoms include fatigue, cough, chest or shoulder pain, hemoptysis, weight loss, dyspnea, hoarseness, bone pain, and fever. Diagnostic procedures include imaging with CT, PET, and/or MRI scans, bronchoscopy with or without endobronchial ultrasound, and tissue biopsy. Pathologic testing of biomarkers on lung biopsy specimens assists in determining treatment options and risk stratification. The 5-year net survival for lung cancer is 22%. The high mortality rate associated with lung cancer reflects both its high incidence rate and its low survival rate.

The primary goal of treatment for patients with stage IB to IIIA NSCLC (per the AJCC, 7th edition; the equivalent stages using the AJCC, 8th edition, are stages IIA to IIIB) is to cure and prolong life. The secondary goal of treatment is to delay disease relapse, thereby allowing patients a longer period of time living disease-free. Attaining these treatment goals primarily involves surgical resection of the tumour, followed by adjuvant cisplatin-based doublet chemotherapy.

Atezolizumab was approved by Health Canada on January 14, 2022, as monotherapy for adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to stage IIIA (according to the AJCC, 7th edition) NSCLC whose tumours have PD-L1 expression on 50% or more of TCs. Atezolizumab is an Fc-engineered humanized immunoglobulin G1 monoclonal antibody. It is available as IV infusion and the dosage recommended in the product monograph is 840 mg every 2 weeks, 1,200 mg every 3 weeks, or 1,680 mg every 4 weeks.

Sources of Information Used by the Committee

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

- a review of 1 ongoing phase III randomized trial in patients with stage IB to stage IIIA NSCLC (as per the Union Internationale Contre le Cancer [UICC] or AJCC staging system, 7th edition) following complete resection and adjuvant cisplatin-based chemotherapy

- patient perspectives gathered by patient groups, Lung Cancer Canada (LCC) and the Lung Health Foundation
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- input from 2 clinician groups, including Ontario Health-Cancer Care Ontario Drug Advisory Committee (OH-CCO DAC) and LCC
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of the input provided by the patient groups that responded to CADTH's call for patient input and from the clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Patient input was provided by 2 groups: LCC and the Lung Health Foundation. LCC is a national charity, a member of the Global Lung Cancer Coalition, and serves as a resource for lung cancer education, patient support, research, and advocacy. The Lung Health Foundation, formerly known as the Ontario Lung Association, is charity that provides education, and programs and services for patients and health care providers, as well as invests in research and policy improvement in lung health. LCC collected thoughts and experiences from 9 patients with NSCLC and small cell lung cancer, and from 1 caregiver (this included patients from Canada, the US, the UK, and Australia) in December 2021 via phone interviews and environmental scans. The Lung Health Foundation conducted phone interviews with 3 patients (1 each from Ontario, Manitoba, and Quebec) from September to October 2021, as well as with a registered nurse and a certified respiratory educator.

Patient respondents from both surveys reported difficulty with coping with their diagnosis and noted that they felt like there was "no hope, no light and [they were] less human" due to the poor prognosis of lung cancer. These feelings were amplified when the cancer was detected late. Patient respondents also reported that cancer-related symptoms were hard to manage. While the physical symptoms of shortness of breath, cough, and fatigue were reported to be mild, psychosocial effects such as anxiety, distress, depression, and some of the harsh side effects from chemotherapy, radiation, and surgery (e.g., nausea, vomiting, neuropathy, lung injury) were harder to manage. Similarly, the psychosocial burden placed on family members and caregivers impacted their emotional well-being, ability to travel and socialize, and work life.

Patient respondents deemed the following outcomes as important: delayed disease progression and increased long-term remission to ultimately improved survivorship; minimal side effects from treatments; maintenance of independence and functionality (to minimize burden on caregivers and loved ones); and full and worthwhile quality of life. Respondents from both surveys emphasized a lack of treatment options for patients with positive PD-L1 driver mutation lung cancer to reduce a risk of recurrence after post-surgery chemotherapy. Patients emphasized wanting a choice in therapy that works in the early stages of disease

(as opposed to the metastatic stage) with durable efficacy to maintain stable disease and increase chance of cure.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH indicated that despite the current standard of care with adjuvant chemotherapy, many patients who have undergone surgical resection and adjuvant chemotherapy experience disease relapse. In the majority of these cases, the disease is often incurable. The survival benefit that accompanies adjuvant chemotherapy is modest, representing an unmet need for other effective treatments for this patient population. If adopted, atezolizumab would be an additional therapy, and not a replacement for preexisting therapies (i.e., atezolizumab would be given in addition to adjuvant chemotherapy and not instead of). Also, if adopted, atezolizumab would be offered to patients with resected NSCLC with tumours greater than 5 cm in size, or node positive tumours, regardless of size of primary tumour, with a PD-L1 tumour score of 50% or greater. According to the clinical experts, the only way to know if adjuvant therapy is successful is to follow a patient with NSCLC after completion of all curative intent therapy to disease relapse. The majority of disease relapse, as cited by the clinical experts, occurs within 5 years of completion of therapy. The clinical experts recommended that treatment with atezolizumab be discontinued in the events of dangerous or intolerable AEs, disease relapse, or patient choice to stop therapy. Atezolizumab may be administered at any outpatient cancer systemic therapy infusion unit where immunotherapy checkpoint inhibitors are already administered.

Clinician Group Input

Input was received from 3 clinicians on behalf of OH-CCO DAC and 17 physicians treating lung cancer across Canada via LCC.

OH-CCO Lung and Thoracic DAC indicated the need for therapy with increased cure and OS rates. Both groups stated that patients with stage II to stage III (per UICC or AJCC, 8th edition) lung cancer have the greatest unmet need. Both clinician groups indicated that atezolizumab would supplement and/or be added to the current postoperative management of resected NSCLC after at least 1 dose of adjuvant (platinum doublet) chemotherapy, and not be a replacement for current therapies. OH-CCO Lung and Thoracic DAC indicated that patients with higher PD-L1 (> 50%), or all patients who are PD-L1 positive, are suited for atezolizumab. LCC suggests that patients with stage II to stage IIIA resected lung cancer (per UICC or AJCC, 7th edition) with a tumour positive for PD-L1 ($\geq 1\%$), as determined by immunohistochemistry after at least 1 cycle of adjuvant therapy, regardless of stage or nodal status, are suitable for atezolizumab.

OH-CCO Lung and Thoracic DAC considered DFS a clinically meaningful outcome measure. LCC emphasized that recurrent disease (DFS) should be considered a critical outcome on its own (besides OS, which is the gold standard) given the high patient, health care, and social ramifications associated with recurrence. Both groups indicated discontinuation of therapy at disease progression and toxicity. As for the treatment settings, hospital (outpatient clinic) and any oncology settings where infusions are performed were considered appropriate prescribing settings for atezolizumab by OH-CCO Lung and Thoracic DAC and LCC, respectively. OH-CCO Lung and Thoracic DAC agreed that the end points reported in the trial can reasonably be expected to correlate with OS. Also, both clinical groups believed

other strategies (e.g., a short course with only 3 doses of neoadjuvant immunotherapy with chemotherapy) would be less expensive than a full-year course of adjuvant immunotherapy.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. 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 submission was based on the IMpower010 study, which is a phase III randomized study comparing atezolizumab 1,200 mg IV every 3 weeks for 16 cycles (or 1 year) to BSC.	pERC noted that the comparison in the IMpower010 study was atezolizumab to BSC.
Considerations for initiation of therapy	
Can pERC clarify the eligible patient population based on the AJCC, 8th edition, staging system?	<p>pERC agreed with the clinical experts that the eligible population would include patients with fully resected tumours, who had a primary tumour > 5 cm regardless of nodal status or who's disease was node positive, regardless of primary tumour size. While pERC acknowledged that the Health Canada indication for atezolizumab considered the 7th edition staging system, pERC recognized that the 8th edition staging system is currently used in Canadian clinical practice.</p> <p>pERC discussed the main differences between the 7th and 8th edition noted by the clinical experts that are relevant to the indication:</p> <ul style="list-style-type: none"> • In the 7th edition, T2 tumours were defined as measuring between > 3 cm and 7 cm. They were further subdivided into T2a > 3 cm to 5 cm and T2b > 5 cm to 7 cm. If a tumour was T2aN0 (node negative), it was stage IB. If a tumour was T2bN0, it was stage IIA. Adjuvant chemotherapy is offered to patients with node negative disease with tumours 4 cm or greater; thus, some patients with stage IB disease, per the 7th edition, qualified for adjuvant chemotherapy, while others did not. Likewise, some patients with stage IB disease, per the 7th edition, were eligible for enrolment in the IMpower010 study. In the 8th edition, a T2a tumour has been redefined to > 3 cm to 4 cm, T2b is now > 4 cm to 5 cm, and tumours > 5 cm to 7 cm are now T3. The overall staging for these groups has also shifted; in the 8th edition, T2aN0 remains stage IB, but T2bN0 is now stage IIA, and T3N0 is now stage IIB. The key difference is that those cancers included in the IMpower010 study, which used the 7th edition as stage IB with tumours that were between 4 cm and 5 cm and were node negative, would now be considered stage IIA under the 8th edition. These patients with IB per the 7th edition were not included in the analysis of patients with stage II and III from the IMpower010 study on which this submission is based; hence, in writing the indication using the current 8th edition, it would be a stage II or III node positive or node negative primary tumour > 5 cm. The data for patients with IB per the 7th edition from the IMpower010 study is still immature; however,

Implementation issues	Response
	<p>it is possible that the indication for adjuvant atezolizumab would be extended to include those with tumours 4 cm to 5 cm with node negative disease.</p> <ul style="list-style-type: none"> • Patients with N2 nodal disease limited to a single nodal station are generally considered surgical candidates as long as there is no local invasion that would render a complete surgical resection unfeasible. In the 7th edition, patients with T2B (> 5 cm to 7 cm), N2, or T3N2 disease were considered stage IIIA, and would have been enrolled in the IMpower010 study if the tumours had been fully resected and the patient had received adjuvant chemotherapy. In the 8th edition, as was previously noted, those with primary tumours > 5 cm to 7 cm now have T3 disease, and those who are classified as T3N2 have been upstaged from stage IIIA to IIIB. Further, tumours that were T3 in the 7th edition on the basis of a primary tumour > 7 cm or invasion of the diaphragm are now classified as T4 in the 8th edition, and those who with T4N2 have been upstaged from stage IIIA to IIIB. Ultimately, this means that there are some patients with stage IIIB disease by the 8th edition who have tumours that are resectable, would have been considered stage IIIA in the 7th edition, and are thus eligible for enrolment in the IMpower010 study. These patients should not be excluded from receiving adjuvant atezolizumab because their staging in the 8th edition is stage IIIB, as long as their tumours were successfully resected and they were given appropriate adjuvant chemotherapy. <p>pERC agreed with the clinical experts that the eligible population based on the 8th edition would be patients with fully resected stage II to IIIA tumours who had a primary tumour > 5 cm regardless of nodal status or who's cancer is node positive, regardless of primary tumour size. Patients with stage IIIB disease classified as stage T3N2 or T4N2 on the basis of a primary tumour > 7 cm or diaphragm involvement with fully resected tumours should also be eligible.</p>
<p>All patients in the IMpower010 study received prior cisplatin-based doublet chemotherapy.</p>	<p>pERC noted that the clinical experts highlighted that guidelines and mature trial evidence do not support the use of non-platinum containing doublet chemotherapy as adjuvant chemotherapy and that there were no non-cisplatin-based regimens studied in the IMpower010 study.</p>
<p>Patients in the IMpower010 study received a median 4 cycles (range of 1 to 4) of cisplatin-based chemotherapy.</p> <p>Is there a minimum number of cycles of chemotherapy required to be eligible for atezolizumab?</p>	<p>pERC agreed with the clinical experts that patients who become ineligible for cisplatin after 1 cycle due to toxicities should be eligible to receive atezolizumab.</p> <p>The clinical experts stated that given the propensity for adjuvant cisplatin-based chemotherapy to be toxic, and those toxicities being permanent and serious in some patients, any amount of chemotherapy would be acceptable. This is also reflective of the trial design. There is a group of patients who become ineligible for cisplatin after 1 cycle due to toxicities (examples include renal toxicity and ototoxicity). This group of patients should be eligible to receive atezolizumab.</p>
<p>Can pERC confirm that patients can be re-treated with downstream PD-1 or PD-L1 inhibitors provided that disease recurrence occurs more than 6 months from the last dose of adjuvant atezolizumab?</p>	<p>Yes and pERC acknowledged the clinical experts' input.</p>

Implementation issues	Response
<p>Patients in the IMpower010 study were enrolled between 4 to 12 weeks after surgical resection and initiated chemotherapy thereafter. Within 3 to 8 weeks of completing chemotherapy, patients were randomized to atezolizumab.</p> <p>In clinical practice, when should chemotherapy be initiated after surgical resection? When should atezolizumab be initiated after chemotherapy?</p>	<p>pERC agreed with the clinical experts that chemotherapy should be initiated within 12 weeks of surgical resection. Starting atezolizumab within 3 to 8 weeks from the completion of chemotherapy is reasonable in the real world.</p>
Considerations for prescribing of therapy	
<p>Would alternate dosing (i.e., 1,680 mg IV every 4 weeks) be reasonable to offer?</p>	<p>pERC agreed with the clinical experts that alternative dosing is reasonable.</p>
Generalizability	
<p>Can the trial results be extended to patients with ECOG PS > 1?</p>	<p>pERC acknowledged the response from the clinical experts: Yes. The clinical experts explained that if a patient were robust enough to receive chemotherapy and had an ECOG PS of 2, they would be robust enough to receive atezolizumab. The clinical experts further described with an extrapolation from the metastatic setting that patients with an ECOG PS of 2 can benefit from immunotherapy. Finally, the clinical experts highlighted that they would not offer atezolizumab to patients if their ECOG PS was 3 to 4.</p>
<p>Should atezolizumab be offered to patients who had received platinum-chemotherapy when atezolizumab was not accessible, provided all other trial criteria are met (i.e., a time-limited need)?</p>	<p>pERC acknowledged the time-limited need at the initial onset of reimbursement of atezolizumab and agreed with the clinical experts.</p> <p>The clinical experts stated that chemotherapy should be initiated within 12 weeks of surgical resection. Starting atezolizumab within 3 to 8 weeks from the completion of chemotherapy is reasonable in the real world. According to the clinical experts, it may be reasonable to accept up to 12 weeks for patients who had received platinum-chemotherapy when atezolizumab was not accessible on a time-limited need; the clinical experts noted this would be infrequent and at the initial onset of reimbursement of atezolizumab.</p>
Funding algorithm (oncology only)	
<p>Jurisdictions highlighted that NSCLC is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.</p>	<p>pERC acknowledged the statement from the jurisdictions.</p>
Care provision issues	
<p>PD-L1 testing would need to be in place to confirm patient eligibility.</p>	<p>pERC acknowledged that PD-L1 testing is required.</p>

AJCC = American Joint Committee on Cancer; BSC = best supportive care; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLC = non-small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PD-1 = programmed cell death 1; PD-L1 = programmed death-ligand 1.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One ongoing phase III, global, multicentre, open-label, randomized study was included in the review. The IMpower010 trial compared the efficacy and safety of atezolizumab versus BSC in patients with stage IB to stage IIIA NSCLC (as per the UICC and AJCC staging system, 7th edition) following complete resection and adjuvant cisplatin-based chemotherapy. A total of 1,005 patients were randomized across 204 sites in 21 countries in North America (including 2 sites in Canada), Europe, Asia, and Australia.

The primary efficacy outcome was DFS as assessed by the investigator. Secondary efficacy outcomes included OS, 3-year and 5-year DFS rates, and DFS in the PD-L1 subpopulations defined as 50% or higher TC expression by SP263 immunohistochemistry assay in patients with stage II to stage IIIA NSCLC as defined by the UICC and AJCC, 7th edition. The IMpower010 study consisted of 2 phases: an enrolment phase and a randomized phase. In the enrolment phase, patients who had undergone completed resection of their NSCLC were screened, and if eligible, were enrolled to receive 1 of 4 cisplatin-based chemotherapy regimens (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed), based on investigator choice. Patients who were still deemed eligible to continue with the study after up to 4 cycles of cisplatin-based chemotherapy proceeded to the randomization phase in which patients were randomized in a 1:1 ratio to receive atezolizumab or BSC. The clinical report provided to CADTH presented the analysis of study data collected from the date of the first patient randomized (February 26, 2016) to the clinical data cut-off date of January 21, 2021, for the protocol-specified interim analysis for DFS.

At baseline, there were 229 patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or greater of TCs. The indication population had a median age of 62 (range = 36 to 84) years, were predominantly male (72.9%) and White (70.3%), had high functional performance (57.2% with an Eastern Cooperative Oncology Group [ECOG] performance score of 0), and reported to have previously used tobacco (69.9%). At diagnosis, most patients were diagnosed at stage IIIA (48.0%) and with nonsquamous histology (59.8%). Among the 137 patients with nonsquamous histology, 94.2% were identified as having the adenocarcinoma subtype. *EGFR* or *ALK* mutation was detected in 8.7% of patients. Most patients underwent prior lobectomy (74.2%) and mediastinal lymph node dissection (81.7%).

Efficacy Results

Efficacy results are presented using the subpopulation of patients who had stage II to stage IIIA NSCLC with PD-L1 expression on 50% or more of TCs (per indication under review) unless otherwise specified.

Overall Survival

Among the subpopulation of patients with stage II to stage IIIA disease and PD-L1 expression on 50% or more of TCs, the observed deaths at the time of the interim analysis (median = 32.2 [range, 0 to 58.8] months follow-up) were 22.8% and 9.6% in the BSC and atezolizumab treatment arms, respectively. The stratified HR was 0.40 (95% CI, 0.20 to 0.81) in favour of atezolizumab. The median OS could not be estimated in either treatment arm due to the low rate of death events at the time of the planned interim analysis. At year 3, 90.85% of patients

in the atezolizumab treatment arm were event-free compared to 76.67% of those randomized to receive BSC, representing a difference in proportion of 14.27% (95% CI, 4.19 to 24.35%).

Disease-Free Survival

Among the subpopulation of patients with stage II to stage IIIA disease and PD-L1 expression on 50% or more of TCs, 45.6% of patients in the BSC treatment arm experienced a disease recurrence or death compared to 24.3% in the atezolizumab arm. The stratified HR for DFS was 0.47 (95% CI, 0.29 to 0.75). At year 3, 73.79% of patients in the atezolizumab arm were event-free compared to 48.61% of those randomized to receive BSC, representing a difference in event-free rate of 25.18% (95% CI, 11.01 to 39.36%).

Type of Recurrence

Of those patients with stage II to stage IIA NSCLC and PD-L1 expression on 50% or more of TCs who experienced a protocol defined disease recurrence (BSC = 50; atezolizumab = 25), locoregional disease recurrence was experienced by 60% of patients in the atezolizumab treatment arm compared to 34% in the BSC arm. Distant only disease recurrence was experienced by 42% of patients in the BSC arm compared 24% in the atezolizumab arm. Central nervous system only disease recurrence was experienced by 14% of patients in the BSC arm compared to 4% in the atezolizumab arm. A combined locoregional plus distant disease recurrence was similar between the treatment arms (BSC = 18%; atezolizumab = 16%).

Harms Results

Adverse Events

Among patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs, 94.7% of patients who received atezolizumab compared to 69.6% who received BSC reported at least 1 AE. The top 5 reported AEs were cough (9.8% for BSC versus 14.2% for atezolizumab); nasopharyngitis (12.5% for BSC versus 8.8% for atezolizumab), arthralgia (5.4% for BSC versus 13.3% for atezolizumab), pruritis (2.7% for BSC versus 11.5% for atezolizumab), and anemia (8.0% for BSC versus 7.1% for atezolizumab). The following AEs had a difference of at least 5% between the treatment arms, with a greater proportion in the atezolizumab arm: arthralgia, asthenia, blood creatine increased, diarrhea, rash, pruritus, and pyrexia.

Adverse Events by Grade

Among patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs, at least 1 grade 3 to 4 AE was reported in 11.6% and 20.4% of patients randomized to BSC and atezolizumab, respectively. The most commonly reported grade 3 to 4 AEs were decreased neutrophil count (1.8%) in patients who received BSC; and increased alanine aminotransferase (1.8%) and abnormal hepatic function (2.7%) in patients who received atezolizumab. No grade 5 AEs were reported.

Serious Adverse Events

Among patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs, 15% of patients who received atezolizumab reported at least 1 serious AE compared to 5.4% who received BSC. The most commonly reported serious AE was pyrexia (1.8%).

Dose Interruptions Due to Adverse Events

Among patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs, 29.2% of patients who received atezolizumab had at least 1 dose interruption due to an AE. Reasons for the dose interruptions included hyperthyroidism (3.5%), pneumonia (2.7%), upper respiratory tract infection (1.8%), pyrexia (1.8%), rash (1.8%), and oropharyngeal pain (1.8%).

Discontinuation of Treatment Due to Adverse Events

Among patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs, 18.6% of patients who received atezolizumab stopped treatment due to an AE. Reasons for the discontinuation were not available for this subpopulation.

Among the overall safety population, 18.2% of patients who received atezolizumab stopped treatment due to an AE. The most common events leading to treatment discontinuation were pneumonitis (1.4%), hypothyroidism (1.4%), and increased AST (1.4%).

Mortality

There were no treatment-related death data in the subpopulation of patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs.

Among the overall safety population, the proportion of patients who died were similar in the BSC (18.2%) and atezolizumab (19.2%) treatment arms. Of these deaths, 95.1% occurred more than 30 days from last study treatment or safety visit. Treatment-related deaths due to AEs occurred in 0.6% and 1.6% of patients in the BSC and atezolizumab arms, respectively. The majority of deaths were due to disease progression.

Notable Harms

Among the subpopulation of patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs, reported immune-mediated reactions related to endocrinopathies included hypothyroidism (atezolizumab = 14.2%; BSC = 0%) and hyperthyroidism (atezolizumab = 4.4%; BSC = 1.8%). Overall immune-mediated rashes were reported by 1.8% and 18.6% of patients who received BSC and atezolizumab, respectively. One person who received atezolizumab experienced a grade 3 to 4 rash. Immune-mediated colitis (grade 3 to 4) was reported by 1 person who received atezolizumab. Immune-related pneumonitis was reported by 5.3% of patients who received atezolizumab, of which 1 was graded at 3 to 4. Immune-mediated hepatitis was reported by 4.5% and 13.3% of patients who received BSC and atezolizumab, respectively. Among patients who received atezolizumab, 5.3% experienced grade 3 to 4 immune-mediated hepatitis.

Data related to infusion-related reactions were not reported for the subpopulation of patients with stage II to stage IIIA NSCLC and PD-L1 expression on 50% or more of TCs.

Critical Appraisal

The critical appraisal of the IMpower010 study by CADTH was limited by the decision made by Health Canada to amend the Notice of Compliance from the original indication population to include only the subset of the population of patients with stage II to stage IIIA NSCLC whose tumour had a PD-L1 expression on 50% or more of TCs. Randomization was stratified by sex (female versus male), tumour histology (squamous versus nonsquamous), extent of disease (stage IB versus stage II versus stage IIIA, based on the UICC and AJCC, 7th edition) and PD-L1 expression status (TC2 or TC3 and any tumor-infiltrating immune

cell [IC]; IC versus TC0 or TC1 and IC2 or IC3 versus TC0 or TC1 and IC0 or IC1 using the SP142 immunohistochemistry assay). The choice of stratification factors was considered to be reasonable, and as noted in the Health Canada report, stage of disease is a known prognostic factor for NSCLC, and PD-L1 tumour performance status is a predictive factor for immunotherapy efficacy in the setting of incurable NSCLC. The enrolled subpopulation of patients that met the Health Canada indication only accounted for 22.8% of the total randomized population and was not a defined subpopulation among the primary end points for the analysis in the IMpower010 trial design. As such, the IMpower010 trial was not powered for the Health Canada indication under review. Of note, Health Canada's decision to amend the indication to PD-L1 expression on 50% or more of TCs at the time of the interim analysis was due to uncertainty with the clinical benefit of atezolizumab in the PD-L1 1% to 49% TCs stage II to stage IIIA population; Health Canada noted that the improvement in DFS was mainly driven by the PD-L1 expression on 50% or more of TCs subgroup. Likewise, the European Medicines Agency also considered the PD-L1 expression on 50% or more of TCs subgroup the most relevant for labelling at the time of the interim analysis.

Although DFS in patients with PD-L1 expression on 50% or more of TCs was a prespecified secondary end point, it was absent from the statistical testing hierarchy. Thus, the statistical analyses of the efficacy outcomes were conducted with no control for multiplicity, which increases the risk of false-positive conclusions. Several subgroup analyses were performed to examine the consistency of the treatment effect observed for the primary and key secondary efficacy end points. However, proper interpretation of all subgroups was not possible due to lack of sample size considerations and their absence from the statistical testing hierarchy. Moreover, data for OS were immature, and while clinical experts believe it is plausible that the findings for DFS will translate to OS, there remains uncertainty whether the findings for DFS will translate to OS.

Among the subgroup of patients with PD-L1 expression on 50% or more of TCs and stage II to stage IIIA disease, there were some minor imbalances across groups but these did not universally favour either group and may be considered reasonable given the small sample size. Additionally, minor differences in characteristics between this subgroup and the intention-to-treat population were not expected to confound the efficacy analyses.

The demographic characteristics of the study population were considered by the clinical expert to be generally reflective of the relevant population with NSCLC in Canada. The clinical experts considered the results of the IMpower010 multinational, multicentre study to be generalizable to the Canadian setting. The clinical experts did highlight a few notable differences in disease characteristics (i.e., larger proportion of patients with squamous lung cancer) and treatment regimen (i.e., cisplatin doublets containing gemcitabine and docetaxel are not commonly used in Canadian lung cancer practice in the adjuvant setting) between the trial population and the Canadian NSCLC population. Patient-important outcomes, such as HRQoL, were not reported.

Indirect Comparisons

No indirect treatment comparisons were included in the sponsor's submission to CADTH or identified in the literature search.

Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH or identified in the literature search.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	<ul style="list-style-type: none"> • Adult patients with completely resected stage II to stage IIIA NSCLC who received platinum-based chemotherapy and whose tumours have PD-L1 expression on $\geq 50\%$ of TCs (according to the Health Canada indication). • Adult patients with completely resected stage II to stage IIIA NSCLC who received platinum-based chemotherapy and whose tumours have PD-L1 expression on $\geq 50\%$ of TCs and do not have <i>EGFR</i> or <i>ALK</i> mutations (aligned with reimbursement request).
Treatment	Atezolizumab, 1,200 mg every 3 weeks for up to 1 year
Submitted price	Atezolizumab, 1,200 mg/20 mL (60 mg/mL): \$6,776.00 per 1,200 mg vial
Treatment cost	The 28-cycle cost of atezolizumab adjuvant therapy is estimated to be \$9,035, and the annual cost \$98,673 (18 cycles).
Comparator	Active surveillance, consisting of no active treatment
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (39 years)
Key data source	IMpower010, a global, randomized, phase III trial evaluating atezolizumab vs. active surveillance following complete resection and adjuvant platinum-based chemotherapy in patients with stage IB to stage IIIA NSCLC.
Key limitations	<ul style="list-style-type: none"> • As OS data in the IMpower010 trial were immature, it is unknown whether atezolizumab confers an OS benefit compared to active surveillance. Furthermore, there is uncertainty associated with the DFS findings from the pivotal trial in the subpopulation of patients with PD-L1 expression $\geq 50\%$. The impact of atezolizumab adjuvant therapy on long-term DFS and its subsequent impact on OS is also highly uncertain. • Difference in the distribution of LR and metastatic recurrence for atezolizumab in comparison with active surveillance is uncertain. Few events were reported in the trial, and testing for statistical significance was not possible. Additionally, how the distribution might change beyond the trial period is unknown and could not be assessed. • The time to establish cure in the sponsor's base case, which monotonically increased after year 2, is faster than could be reasonably expected in clinical practice. Cure for patients in the LR state was not explicitly modelled in the sponsor's base case, despite 80% of patients with LR accessing treatment with curative intent. • Adverse events were only assumed to occur in the first month of treatment with atezolizumab. • Subsequent treatments in the LR setting were not aligned with Canadian clinical practice.

Component	Description
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH conducted reanalyses by applying the following changes: altering the parametric survival extrapolation of DFS, allowing for more plausible gains in DFS and OS, using pooled trial data to inform the type of first event recurrence, and adjusting the time to establish cure so that the proportion of patients who may be considered cured starts to increase at month 60, attaining its maximum at month 84. • In the reimbursement request population, deemed most reflective of the anticipated place in therapy for atezolizumab, the ICER for atezolizumab relative to active surveillance is \$68,858 per QALY. A price reduction of 24% would be necessary to achieve cost-effectiveness at a WTP threshold of \$50,000 per QALY. • Results from scenario analyses indicated that the cost-effectiveness of atezolizumab in the adjuvant setting was most sensitive to assumptions regarding long-term DFS, the number of cycles of therapy, and as the distribution of recurrence type.

DFS = disease-free-survival; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; LY = life-year; NSCLC = non-small cell lung cancer; OS = overall survival; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life-year; TC = tumour cell; WTP = willingness to pay.

Budget Impact

CADTH identified the following limitations in the sponsor’s base case: the proportion of patients that would undergo PD-L1 biomarker testing is underestimated; the projected market share of adjuvant atezolizumab is underestimated; and there is uncertainty with the estimation of atezolizumab’s treatment duration, as it is not reflective of the product monograph. CADTH performed reanalyses, in line with clinician expert opinion, by assuming that 99% of patients who undergo surgical resection receive PD-L1 biomarker testing and increasing the projected market share of atezolizumab to 80%, 90%, and 100% in years 1, 2, and 3, respectively. Based on the CADTH reanalyses, the budget impact from the introduction of atezolizumab adjuvant therapy in the reimbursement request population is expected to be \$17,525,096 in year 1, \$19,914,406 in year 2, and \$22,351,822 in year 3, with a 3-year total of \$59,791,324. If atezolizumab were available at a 24% price reduction, the expected budget impact would decrease to \$45,583,434 over 3 years. CADTH performed scenario analyses whereby patients in the new drug scenario on atezolizumab received 18 cycles of adjuvant atezolizumab to reflect the potential full-year treatment duration, as per atezolizumab’s product monograph. This led to an increase in the estimated budget impact (\$67,191,267).

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 13, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None