CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Atezolizumab (Tecentriq)

Indication: As monotherapy for adjuvant treatment following resection and platinum-based chemotherapy for patients with non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TCs).

Sponsor: Hoffmann-La Roche Ltd.

Recommendation: Reimburse with Conditions

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Single Technology

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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 be reimbursed as monotherapy for the adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to IIIA (American Joint Committee on Cancer [7th edition]) non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TCs) and do not have epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (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 of 0.47, 95% confidence interval 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 the ability to maintain 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 and delays disease recurrence.

Using the sponsor submitted price for atezolizumab, the incremental cost-effectiveness ratio (ICER) for atezolizumab was $68,858 per quality-adjusted life-year (QALY) compared with active surveillance. At this ICER, atezolizumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adult patients with completely resected stage II to IIIA NSCLC who received platinum-based chemotherapy and whose tumors have PD-L1 expression on ≥ 50% 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 IIIA NSCLC whose tumours have PD-L1 expression on ≥50% of TCs and have do not have EGFR or ALK mutations	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 fully resected stage II to IIIA patients who had a primary tumour > 5 cm regardless of nodal status or who were node positive regardless of primary tumour size. Based on clinical expert opinion, patients with the common EGFR 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 ALK fusion; thus, there may be limited, if any, benefit for a resected ALK-positive patient from adjuvant immunotherapy.	Based on clinical expert opinion, Stage IIIB patients 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, initiation of atezolizumab should be within 3 to 8 weeks from the completion of chemotherapy, and up to 12 weeks for patients who had received platinum-chemotherapy but where atezolizumab was not accessible, is reasonable on a time-limited need.
2. Patients must have 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.	—
Prescribing		

Reimbursement Condition	Reason	Implementation Guidance
6. 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		
7. A reduction in price	In the reimbursement request population considering a patient population without an EGFR or ALK 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		
8. Access to PD-L1 testing	PD-L1 testing is needed to identify patients whose tumours have PD-L1 expression on ≥50% of TCs.	—

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life-year; TCs = tumour cells.

Discussion Points

- pERC acknowledged that the critical appraisal was limited by the Health Canada decision to amend the notice of compliance from the original overall population to include only a subset of the population and as a result, the IMpower010 study was not powered for the HC indication under review. However, DFS in patients with PD-L1 ≥ 50% was a pre-specified secondary endpoint. pERC deliberated on the value of DFS as a primary endpoint in the adjuvant setting and noted that 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 <50% and acknowledged that while the overall population of the IMpower010 study included stage IB disease and those with PD-L1 expression <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 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 HRQoL. HRQoL was not measured in the IMpower010 study; therefore, pERC was unable to draw any conclusions pertaining to the potential benefit of atezolizumab on HRQoL

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

Background

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer deaths in Canada, with non-small cell lung cancer (NSCLC) accounting for approximately 88% of lung cancer cases. Approximately half of NSCLC cases in Canada are stage I-III at diagnosis, and one-third of NSCLC patients have operable disease. Early-stage NSCLC (i.e., Stages I-IIIA per the AJCC 7th edition) is often asymptomatic. When patients do present with symptoms, these are usually non-specific 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 computerized tomography (CT), positron emission tomography, and/or magnetic resonance imaging scans, bronchoscopy with or without EBUS 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 has been approved by Health Canada on 14 January 2022 as monotherapy for adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with Stage II to IIIA (according to the AJCC 7th edition) NSCLC whose tumours have PD-L1 expression on $\geq$ 50% of tumour cells (TC). Atezolizumab is a Fc-engineered humanized IgG1 monoclonal antibody. It is available as IV infusion and the dosage recommended in the product monograph is 840 mg every 2 weeks, 1200 mg every 3 weeks or 1680 mg every 4 weeks.

Sources of Information Used by the Committee

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

- A review of 1 on-going phase III randomized trial in patients with Stage IB to Stage IIIA NSCLC (as per the UICC/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
- Two of 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 input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Patient input was provided by two groups: Lung Cancer Canada (LCC) and the Lung Health Foundation. LCC is a national charity and 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 Ontario Lung Association, is charity that provides education, programs and services for patients and health care providers, as well as invests in research and policy improvement in lung health. LCC collected the thoughts and experiences from 9 patients NSCLC and small cell lung cancer (SCLC) and from 1 caregiver (Canada, US, UK, and Australia) in December 2021 via phone interviews and environmental scans. LHF conducted phone interviews

with 3 patients (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 [were] less human” due to poor prognosis of lung cancer. These feeling 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, the psychosocial effects such as anxiety, distress, depression, and some of the harsh side effects from chemotherapy, radiation, 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: 1. delayed disease progression and increased long-term remission to ultimately improved survivorship; 2. minimal side effects from treatments; 3. maintenance of independence and functionality (to minimize burden on caregivers and loved ones); and 4. full and worthwhile quality of life. Respondents from both surveys emphasized a lack of treatment options for patients with PD-L1 positive, driver mutation-negative 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 metastatic stage) with durable efficacy to maintain stable disease and increase chance of cure.

Clinician input

Input from clinical experts consulted by CADTH

Based on input from the clinical experts consulted by CADTH, 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 pre-existing therapy, 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 tumors greater than 5 centimeters (cm) in size, or node positive tumours regardless of size of primary tumour with a PD-L1 tumour score of $\geq$ 50%. According to the clinical experts, the only way to know if adjuvant therapy is successful is to follow a NSCLC patient after completion of all curative intent therapy to disease relapse. The majority of disease relapse, as cited by the clinical expert, occurs within 5 years after completion of therapy. The clinical experts recommended that treatment with atezolizumab should be discontinued in the events of dangerous or intolerable adverse events, 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 by 3 clinicians on behalf of Cancer Care Ontario Drug Advisory Committee (OH-CCO DAC) and 17 physicians treating lung cancer across Canada via Lung Cancer Canada (LCC).

OH-CCO Lung and Thoracic DAC indicated the need for therapy with increased cure and overall survival rates. Both groups stated that patients with stage II to III (UICC/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 post-operative 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 PD-L1 positive patients, are suited for atezolizumab. LCC suggests that patients with stage II to IIIA resected lung cancer (UICC/AJCC 7th edition) with a tumour PD-L1 positive (≥ 1%) determined by immunohistochemistry after at least 1 cycle of adjuvant therapy regardless stage or nodal status are suitable for atezolizumab.

OH-CCO Lung and Thoracic DAC considered disease-free survival a clinically meaningful outcome measure. LCC emphasized that recurrent disease (disease-free survival) should be considered a critical outcome on its own (besides overall survival, which is the gold standard) given the high patient, healthcare and social level 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 endpoints reported in the trial can reasonably be expected to correlate with overall survival (OS). Also, both clinical groups believed other strategies (e.g., a short course with only 3 doses of neoadjuvant immunotherapy with chemotherapy) are expected to be less expensive compared to 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 3 randomized study comparing atezolizumab 1200 mg IV every 3 weeks x 16 cycles (or 1 year) to best supportive care (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?	pERC agreed with the clinical experts that the eligible population would include fully resected patients who had a primary tumour > 5 cm regardless of nodal status or who were 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. pERC discussed the main differences in the 7th and 8th edition noted by the clinical experts that are relevant to the indication: • In the 7th edition, T2 tumours were defined as measuring between >3-7 cm. They were further subdivided into T2a >3cm-5 cm and T2b >5-7 cm. If a tumour was T2a N0 (node negative), it was stage IB. If a tumour was T2bN0, it was stage IIA. Adjuvant chemotherapy is offered to patients who are node negative with tumours 4 cm or greater, thus some stage IB patients by the 7th edition qualified for adjuvant chemotherapy, while others did not. Likewise some stage IB patients by the 7th edition were eligible for enrollment in IMpower010. In the 8th edition, T2a has been redefined to >3-4 cm, T2b is now >4-5cm and tumours >5-7 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 IMpower010 which used the 7th edition as stage IB with tumours that were between 4-5 cm and were node negative, would now be considered stage IIA under the 8th edition. These IB 7th edition patients were not included in the analysis of stage II and III patients from IMpower010 on which this submission is based, and hence, in writing the indication using the current 8th edition, it would be stage II or III node positive or node negative primary tumour > 5 cm. The data for the IB 7th edition patients from IMpower010 is still immature, however, it is possible that the indication for adjuvant atezolizumab would be extended to include those with tumours 4 to 5cm who are node negative.

Implementation Issues	Response
	• 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 to 7cm), N2 or T3N2 disease were considered stage IIIA, and would have been enrolled in IMpower010 if they had been fully resected and received adjuvant chemotherapy. In the 8th edition, as per above, those with primary tumours > 5 to 7 are now T3, and those who are 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 T4 in the 8th edition, and those who are 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 are resectable, and would have been considered stage IIIA in the 7th edition, and thus eligible for enrollment in IMpower010. These patients should not be excluded from receiving adjuvant atezolizumab because their staging in the 8th edition is stage IIIB, as long as they were successfully resected and given appropriate adjuvant chemotherapy. pERC agreed with the clinical experts that the eligible population based on the 8th edition would be fully resected stage II to IIIA patients who had a primary tumour > 5 cm regardless of nodal status or who were node positive regardless of primary tumour size. Stage IIIB patients 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.
All patients on IMpower010 received prior cisplatin-based doublet chemotherapy.	pERC noted that the clinical experts highlighted that guidelines and mature trial evidence do not support the use of non-cisplatin doublet chemotherapy as adjuvant chemotherapy and that there were no non-cisplatin-based regimens studied in the IMpower010 study.
Patients on IMpower010 received a median 4 cycles (range of 1-4) of cisplatin-based chemotherapy. Is there a minimum number of cycles of chemotherapy required in order to be eligible for atezolizumab?	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. The clinical experts stated that given the propensity for adjuvant cisplatin-based chemotherapy to be toxic, and those toxicities can be 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.
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?	Yes. pERC acknowledged the clinical experts' input that if the data on retreatment with immunotherapy on relapse after adjuvant atezolizumab from IMpower010.
Patients on IMpower010 were enrolled between 4 to 12 weeks of surgical resection and initiated chemotherapy thereafter. Within 3 to 8 weeks of completing chemotherapy, patients were randomized to atezolizumab.	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.

Implementation Issues	Response
In clinical practice, when should chemotherapy be initiated after surgical resection? When should atezolizumab be initiated after chemotherapy?	
Considerations for prescribing of therapy	
Would alternate dosing – i.e., 1680 mg IV every 4 weeks be reasonable to offer?	pERC agreed with the clinical experts that alternative dosing is reasonable.
Generalizability	
Can the trial results be extended to patients with ECOG >1?	pERC acknowledged the response from the clinical experts: Yes. The clinical experts explained that if a patient was 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. Lastly, the clinical experts highlighted that they would not offer atezolizumab to patients if the ECOG PS was 3 to 4.
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)	pERC acknowledged the time-limited need at the initial onset of reimbursement of atezolizumab and agreed with the clinical experts. The clinical experts recommended that for patients being initiated to atezolizumab, it is required that they are started on the treatment within 3 to 8 weeks from the completion of chemotherapy. However, clinical experts highlighted that it may be reasonable to accept up to 12 weeks for patients who had received platinum-chemotherapy but when atezolizumab was not accessible; the clinical experts noted this would be infrequent and at the initial onset of reimbursement of atezolizumab.
Funding algorithm (oncology only)	
Jurisdictions highlighted that NSCLC is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products	pERC acknowledged the statement from the jurisdictions.
Care provision issues	
PD-L1 testing would need to be in place to confirm patient eligibility.	pERC acknowledged that PD-L1 testing is required.

AJCC = American Joint Committee on Cancer; BSC =best supportive care; IV = intravenous; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death 1; PD-L1 = programmed death-ligand 1; PS = performance status

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

One on-going phase III, global, multicentre, open-label, randomized study was included in the review. The IMpower010 trial compared the efficacy and safety of atezolizumab versus best supportive care (BSC) in patients with Stage IB to Stage IIIA NSCLC (as per the UICC/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 disease-free survival (DFS) as assessed by the investigator. Secondary efficacy outcomes included overall survival (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 (IHC) assay in patients with Stage II-IIIA NSCLC as defined by the UICC/AJCC 7th edition. The IMpower010 study consisted of 2 phases: an enrollment phase and a randomized phase. In the enrollment phase, patients who had undergone completed resection of their NSCLC were screened, and if eligible, were enrolled to receive one 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 (26 February 2016) to the clinical data cut-off date of 21 January 2021 for the protocol-specified interim analysis for DFS.

At baseline, there were 229 patients with stage II to IIIA NSCLS and PD-L1 expression on ≥ 50% of TC. 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 0), and reported to have previously used tobacco (69.9%). At diagnosis, most patients were diagnosed at Stage IIIA (48.0%) and with non-squamous histology (59.8%). Among the 137 patients with non-squamous histology, 94.2% were identified as having 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 IIIA NSCLC with PD-L1 expression on ≥ 50% of TC (as per indication under review) unless otherwise specified.

Overall survival

Among the subpopulation of patients with stage II to IIIA disease and PD-L1 expression on ≥ 50% of TC, 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 groups, 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 group 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 IIIA disease and PD-L1 expression on ≥ 50% of TC, 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 group 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 IIIA NSCLC and PD-L1 expression on ≥ 50% of TC who experienced a protocol defined disease recurrence (BSC, 50; atezolizumab, 25), locoregional disease recurrence was experienced by a 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 to the atezolizumab arm. Central nervous system (CNS) 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 IIIA NSCLC and PD-L1 expression on ≥ 50% of TC, 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 (BSC: 9.8% vs. atezolizumab: 14.2%); nasopharyngitis (BSC: 12.5% vs. atezolizumab: 8.8%), arthralgia (BSC: 5.4% vs 13.3%), pruritis (BSC: 2.7% vs. atezolizumab: 11.5%), and anemia (BSC: 8.0% vs. atezolizumab: 7.1%). 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 IIIA NSCLC and PD-L1 expression on ≥ 50% of TC, at least 1 Grade 3-4 AE was reported in 11.6% and 20.4% of patients randomized to BSC and atezolizumab, respectively. The most commonly reported Grade 3-4 AEs were neutrophil count decreased (1.8%) in patients who received BSC; and alanine aminotransferase increased (1.8%) and hepatic function abnormal (2.7%) in patients who received atezolizumab. No Grade 5 AEs were reported.

Serious adverse events

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

Dose interruptions due to adverse events

Among patients with stage II to IIIA NSCLC and PD-L1 expression on ≥ 50% of TC, 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 IIIA NSCLC and PD-L1 expression on ≥ 50% of TC, 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 aspartate aminotransferase increased (1.4%).

Mortality

There were no treatment related death data in the subpopulation of patients with stage II to IIIA NSCLS and PD-L1 expression on ≥ 50% of TC.

Among the overall safety population, the proportion of patients who died were similar in the BSC (18.2%) and atezolizumab (19.2%) treatment group. Of these deaths, 95.1% occurred more than 30 days from last study treatment or safety visit. Treatment related deaths due to adverse events 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 IIIA NSCLC and PD-L1 expression on ≥ 50% of TC, reported immune-mediated reactions related to endocrinopathies included hypothyroidism (atezolizumab, 14.2%; BSC, 0%) and hyperthyroidism (atezolizumab, 4.4%l 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 3-4 rash. Immune-mediated colitis (Grade 3-4) 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 3-4. 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 3-4 immune-mediated hepatitis.

Data related to infusion-related reactions were not reported for the subpopulation of patients with stage II to IIIA NSCLS and PD-L1 expression on ≥ 50% of TC.

Critical Appraisal

The critical appraisal of the IMpower010 study by CADTH was limited by the decision made by Health Canada to amend the NOC from original indication population to include only the subset of the population of patients with stage II to IIIA NSCLC whose tumour had a PD-L1 expression on ≥ 50% of TC. Randomization was stratified by sex (female vs. male), tumor histology (squamous vs. non-squamous), extent of disease (Stage IB vs. Stage II vs. Stage IIIA based on the UICC/AJCC 7th edition) and PD-L1 expression status (TC2/3 and any IC vs. TC0/1 and IC2/3 vs TC0/1 and IC0/1 using the SP142 IHC 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 that PD-L1 tumor 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 endpoints 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 ≥ 50% TC at the time of the interim analysis was due uncertainty with the clinical benefit of atezolizumab in the PD-L1 1% to 49% TC Stage II-IIIA population; HC noted that the improvement in DFS was mainly driven by PD-L1 ≥ 50% TC subgroup. Likewise, the European Medicines Agency also considered the PD-L1 ≥ 50% TC subgroup the most relevant for labelling at the time of the interim analysis.

Although DFS in patients with PD-L1 expression on ≥ 50% TC was a pre-specified secondary endpoint, 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 endpoints. 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% of TCs and Stage II-IIIA, 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 ITT 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 health-related quality of life, 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	• Adult patients with completely resected stage II-IIIA NSCLC who received platinum-based chemotherapy whose tumors have PD-L1 expression on ≥ 50% of TCs (according to Health Canada indication). • Adult patients with completely resected stage II-IIIA NSCLC who received platinum-based chemotherapy whose tumors have PD-L1 expression on ≥ 50% of TCs and do not have EGFR/ALK mutations (aligned with reimbursement request).
Treatment	Atezolizumab
Submitted Price	Atezolizumab, 1200 mg/20 mL (60 mg/mL): $6,776.00 per 1200mg 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 versus active surveillance following complete resection and adjuvant platinum-based chemotherapy in stage IB-IIIA NSCLC.
Key limitations	• As OS data in the Impower010 trial were immature, it is unknown whether atezolizumab confers an OS benefit compared to active surveillance. Further there is uncertainty associated with the DFS findings from the pivotal trial in the subpopulation of patients with PDL1 expression ≥ 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 locoregional (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 two, 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 LR patients 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.
CADTH reanalysis results	• 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, as well as the distribution of recurrence type.

NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand-1; TC = tumor cells; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY= quality-adjusted life-year; inc. = incremental; OS = overall survival; LR = locoregional recurrence; 1L MR = first-line metastatic recurrence; KM = Kaplan Meier.

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 three-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 three 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).

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 13, 2022

Regrets: Two expert committee members did not attend

Conflicts of Interest: None