CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

pembrolizumab (Keytruda)

(Merck Canada)

Indication: Keytruda as monotherapy is indicated for the adjuvant treatment of adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy.

July 26, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Pembrolizumab (Keytruda)

Indication: Keytruda as monotherapy for the adjuvant treatment of adult patients with Stage IB (T2a 4 cm), II, or IIIA NSCLC, and with PD-L1 tumor proportion score (TPS) 50% who have undergone complete resection and platinum-based chemotherapy.

Name of Patient Group: Joint Submission by Lung Health Foundation, Lung Cancer Canada and the Canadian Cancer Survivor Network

Author of Submission: Riley Sanders - Lung Health Foundation, Winky Yau – Lung Cancer Canada, Lindsay Timm - Canadian Cancer Survivor Network

1. About Your Patient Group

This patient input submission is jointly submitted by Lung Health Foundation (LHF), Lung Cancer Canada (LCC), and the Canadian Cancer Survivor Network (CCSN).

The Lung Health Foundation (www.lunghealth.ca) legally known as the Ontario Lung Association, is registered with the CADTH and pCODR, and stands as a cornerstone of trust and reliability in the Canadian healthcare and public health systems. Lung Health Foundation is a registered charity that assists and empowers people living with or caring for others with lung disease. It is a recognized leader, voice and primary resource in the prevention and control of respiratory illness, tobacco cessation and prevention, and its effects on lung health. We are governed by a dedicated board of directors and supported by a team of approximately 40 employees alongside thousands of passionate volunteers. Together, we work tirelessly to improve the lung health of Canadians, driving positive change and fostering a brighter, healthier future for all.

Lung Cancer Canada is a registered national charitable organization that serves as Canada's leading resource for lung cancer education, patient support, research and advocacy. Lung Cancer Canada is a member of the Global Lung Cancer Coalition and is the only national organization in Canada focused exclusively on lung cancer. Lung Cancer Canada is registered with CADTH. https://www.lungcancercanada.ca/

The Canadian Cancer Survivor Network (CCSN) is a national network of patients, families, survivors, friends, community partners, funders, and sponsors who have come together to take action to promote the very best standard of care, whether it be early diagnosis, timely treatment and follow-up care, support for cancer patients, or issues related to survivorship or quality of end-of-life care. https://survivornet.ca/

2. Information Gathering

The information provided from the Lung Health Foundation in this submission builds from our robust experience working directly with people living with lung cancer through our patient and caregiver support programs, lung cancer patient advisory group, our lung cancer patient advocates as well as information obtained from interviews with 3 people living with lung cancer and an online survey completed by 33 people who identified as living with lung cancer.

The first interview was conducted with a male patient in his 50's who resides in Ottawa, ON, the second interview was conducted with a female patient in her 30's who resides in Vancouver, BC, and the third interview was conducted with a male in his 60's who resides in Toronto, ON. All the 33 online respondents to the survey are from Canada and all respondents identified as patients. These respondents completed the survey between June 2023 - June 2024. Alchemer was the online survey tool utilized for the collection of this data.

In Section 6, *Experience with Drug under Review*, information was gathered from 3 patients who were interviewed for previous submissions who had experience with pembrolizumab, mainly in the advanced/metastatic NSCLC setting. 2 patients, [redacted] and [redacted] are female, and [redacted] identifies as male. All 3 are Canadian.

3. Disease Experience

The respondents had varying experiences with their lung cancer diagnosis, but several consistent themes did arise. First, the theme of it being difficult to get an accurate and timely diagnosis was evident among this group. "It's hard to get a diagnosis at an early stage." One of the interviewees reported that what led him to the emergency department, and eventual lung cancer diagnosis, was severe numbness in his right hand. While there, he mentioned his cough that wouldn't go away. It was discovered he had a brain tumor (secondary), and after that the primary source was discovered, lung cancer. Another interviewee stated: "It's hard to get a diagnosis at an early age. I wish, at least after the brutal news, we could have easy access to affordable medications. Maybe it's too late for me, but not too late for others." And a third respondent shared: "During the few months before my lung cancer diagnosis, I had a poor quality of life. I was unable to have full conversations without being abruptly interrupted by coughing fits. During remote work virtual meetings, I often had to be on mute and found it difficult to speak. I had to ask other teammates to carry on conversations for me. In the evenings, my cough would be worse, and I could only communicate with my partner via writing at times. The symptoms did not allow me to work, exercise and socialize like I had before. Once diagnosed, on the right therapy and on the right dosage, I have been able to resume my regular life activities such as working, exercise, traveling, sleeping, and spending time with family and friends. My treatment is taken orally which offers me a convenient way to receive treatment that I can take anywhere. Living with lung cancer is difficult in many ways. What truly makes it a manageable disease is having access to effective, convenient and affordable/covered therapies."

A second theme was the symptoms and challenges these patients experienced because of their lung cancer. At the top of the list was fatigue (53%), followed by shortness of breath (50%), cough (23%), and pain (20%). Chest tightness, wheezing, weight loss, diminished appetite, low mood / depressive periods and challenges with physical and emotional intimacy were also noted by some respondents.

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A third theme was how lung cancer negatively affected their day-to-day life. The inability to work was at the top of this list (48%), followed by the inability to participate in physical activities (33%), do housework (21%), use stairs (22%), or partake in hobbies (21%).

As a result of living with lung cancer almost all respondents indicated it had negative impacts on their emotional well-being. Some (44%) feel isolated and struggle to manage their symptoms. Others indicated they feel guilty for the burden they are putting on their family members / friends. One respondent stated his daughter attends all medical appointments with him so that is time-consuming for her and causes her to miss work. Another respondent stated the real-life impact of living with lung cancer is hard. “I used to be extremely outgoing. Now with my shortness of breath, I never know how I am going to be feeling from one day to the next. I don't make long term plans as my breathing is unpredictable.”

When asked if there was an aspect of their disease that is most important to them to control, the respondents gave these responses:

- “Improved energy levels and less fatigue”
- “Shortness of breath”
- “Managing pain and side effects from treatments”
- “Simply maintaining a quality of life”
- “More resources and support”

4. Experiences With Currently Available Treatments

The treatments tried by the respondent’s included surgery, radiation, chemotherapy, targeted therapy and immunotherapy. The medications tried included Alectinib, Lorlatinib, Maxolone, Gefitinib, Entrectnib, Tagrisso and Alunbrig. Some patients are participating in clinical trials. The benefits experienced with the treatments were: reduced cough, reduced shortness of breath, increased participation in daily activities, ability to exercise, prolonged life, delayed disease progression and a reduction in the severity of other disease-related symptoms. Patients on oral drugs also value the flexibility the drugs provide in allowing them to work and travel without restrictions. “These drugs are expensive but do work. I have a life and, when metastasis develops, I hope the next treatment option is approved and funded. What lung cancer needs is more public education to promote awareness and to reduce the association with smoking. This will help to lead to more funding and support for the development of a broad-based screening test to catch it early, in stage 1 not 4. Anyone with lungs can get lung cancer.” Another respondent stated: “Each time meds are changed there is a fear that I will not be able to get the new drug. All have been via compassionate care programs. Cost is prohibitive in most cases. Provincial and or federal coverage is a must.”

Some patients reported struggling with lingering side effects. Respondents who received surgery reported deconditioning and chronic fatigue. Some of the side effects reported from radiation were fatigue, skin changes, hair loss and tissue scarring. With medications, the side effects reported included extreme itching that affects sleep, brain fog, fatigue, nausea, vomiting, mood changes, diminished appetite, weight loss, hair loss, anemia, and neuropathy. Side effects from chemotherapy severely impacted the patients’ quality of life, ability to work and in some cases, the ability to perform activities of daily living.

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When asked about challenges with access to treatment, the respondents reported that they struggled with the cost associated with some treatments. They also found it challenging to navigate the healthcare system and in some cases, they were not clear where to go for information and support. Patients on targeted therapy also worry about access to the next line of treatment if or when their current treatment stops working. “I have ALK+ NSCLC diagnosed in 2021. I am a non-smoker. I have been through chemo and radiation but only saw real improvement in my cancer with Alectinib. However, no medication lasts forever and I don't know what will happen when I have progression as the next drug, Lorlatinib, is not readily available in all provinces.”

5. Improved Outcomes

Key treatment outcomes for this group of lung cancer patients included stopping or slowing the progression of the disease with minimal side effects. Regarding side effects, one responded stated that, “I hope for little to no side effects, particularly when it comes to energy levels, and ability to focus. Being able to work, contribute to my community and be with friends & family is important to me. This requires the right energy levels and focus.”

Patients would also like to see medications that are effective for advanced disease. Due to the poor outcomes associated with advanced disease, patients describe feeling very anxious about any sign or prospect of disease progression. “ALK-positive affects mainly non-smokers and is treated with inhibitors. These are very expensive but work for years. I have been on Alectinib for 4 years. The next drug when this one stops working is called Lorlatinib and can also be used as 1st line treatment. Alectinib is provincially funded in Ontario but no 2nd line drugs are. These are lifesaving. It is very stressful knowing a 2nd line drug is available but is cost prohibitive.”

When choosing therapy, patients are also interested in the efficacy of the medication. One respondent commented that they would be more receptive to side effects if there was strong evidence that the medication would stop or slow down the progression of their lung cancer.

There is a need for increased treatment options that not only treats their disease successfully but also delays its progression.

6. Experience With Drug Under Review

Pembrolizumab has been available in Canada for a number of years now for the treatment of NSCLC in addition to other cancer types, and to expand its accessibility for this indication in early-stage lung cancer is a key step moving forward in the treatment paradigm. Currently for resected Stage IB-IIIA NSCLC patients with PDL1 < 50%, there is no indication for adjuvant immunotherapy, which defines an unmet need that the approval of pembrolizumab can address. Currently available treatments are also inadequate in achieving high rates of cure and also preventing recurrence in the early-stage resected NSCLC patient population.

In previous CADTH submissions for pembrolizumab, it has been presented that patients on treatment are able to maintain a high quality of life level. Pembrolizumab has been seen to be effective at reducing tumour size and controlling symptoms, Patients are able to be independent as side effects are highly manageable and patients are able to engage in life, perform tasks and even work without caregiver assistance. This means that caregivers do not have to

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take time off work to care for their loved one or take them to treatments, thus minimizing the financial impact of the treatment. Patients are able to maintain a high level of functionality and this positively impacts the mental health of patients and their families.

[redacted] had always been very active throughout her life, played numerous different sports each week and worked out nearly everyday. One day in April 2022, the sudden onset of severe back and chest pain brought her to the hospital as she thought she'd been having a heart attack, but instead, was shocked to hear she had lung cancer. She had no symptoms of the disease or any indication she'd been unwell, so when doctors initially thought the disease was localized, she had surgery to remove the tumour but were shocked to see she had numerous tiny lesions in her chest across both lungs, meaning she had stage 4 lung cancer and was positive for the EGFR Exon 20 mutation.

[redacted] started first-line treatment after surgery with pembrolizumab in combination with chemotherapy for 19 months between June 2022 until January 2024. She recalls that although constipation and nausea were the only consistent side effects during this treatment, it didn't stop her from being able to carry on with her activities of daily living, while also staying active and excersizing nearly as often as she did prior to her diagnosis. [redacted] says with pembrolizumab, she felt she was in this *"weird middle ground where I'd never felt 100% myself any day, but still strong enough to push it all down and carry on with my activities*". When she progressed at the beginning of 2024, she then started second-line amivantamab in February 2024, which she is still on currently. [redacted] says that she has been "incredibly grateful" her treatments like pembrolizumab have allowed her to maintain an excellent quality of life, and even continues to play tennis and pickleball each week throughout treatment.

[redacted] was first diagnosed with lung cancer in spring of 2016 at stage 1, which was successfully removed with surgery and remained disease-free for 3 years without active treatments, going back to work as a school superintendent. In May 2018 shortly after retiring, his routine scans showed there were now 11 new nodules in his lungs. He had a wedge resection which confirmed his disease had metastasized into both lungs and was now stage 4 NSCLC. Further biomarker testing showed he had a high PDL1 expression, so he started immunotherapy treatment with pembrolizumab in March 2021, which he was on fornearly 3 years until the start of 2024.

[redacted] recalls he had minimal side effects from pembrolizumab, all of which were manageable. He experienced some diarrhea, his eczema and diabetes got worse, had sore muscles, felt tired, and liver enzymes got worse. He had to see a dermatologist and endocrinologist to manage the liver and skin issues (and continues to do so today in mid-2024), but he says all the side effects were managed well and did not impede his ability to go about his day-to-day life. He even started an annual fundraising walk/run for lung cancer in the midst of treatment, which has been incredibly fulfilling for him and says he is grateful to have maintained a great quality of life thanks to pembrolizumab.

[redacted] was diagnosed with stage 4 NSCLC in August 2017, and testing showed she had PDL-1 expression and KRAS mutation as well. She had 2 large brain tumours which were removed surgically and then treated with whole brain radiation, She was then treated with pembrolizumab in November, which were effective in shrinking the tumours, and [redacted] remained on it for 3 years until being taken off in October 2020, as the tumours were considered inactive. Unfortunately by December 2020, the tumours became active in the lymph nodes, abdominal area and chest, and she was put back on Keytruda on a double dose, which were successful again as some new tumours have disappeared and some others shrunk, and after just two months one of her tumours have shrunk from 3.5 to 1.1cm. She recalls minimal side effects from the therapy as well. [redacted] says, "My healthcare team is happy with how Keytruda has worked for me. I hope it treats all my tumours and I never have to go on treatment again. I look forward to being told by my doctors that I am NED."

7. Companion Diagnostic Test

N/A

8. Anything Else?

There is an unmet need for lung cancer therapies that will prolong progression-free survival and improve health-related quality of life for patients. Our patients consistently raise quality of life as a critical consideration when balancing benefits and risks when they are working with their physicians to select their treatment options. Lung Health Foundation, Lung Cancer Canada and the Canadian Cancer Survivor Network all strongly urge the Canada Drug Agency to recognize the gap and barrier in adequate treatment options that are specific to these patients who deserve treatments that will work and increase the accessibility of these treatments for patients across Canada.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck Canada (LHF)				X
Merck Canada (LCC)				X
Merck Canada (CCSN)				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jess Rogers
Position: Vice President Programs, Research, and Public Affairs
Patient Group: Lung Health Foundation (Legal name: Ontario Lung Association)
Date: July 26, 2024

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0369-000
Generic Drug Name (Brand Name): Pembrolizumab
Indication: Keytruda as monotherapy for the adjuvant treatment of adult patients with Stage IB (T2a 4 cm), II, or IIIA NSCLC, and with PD-L1 tumor proportion score (TPS) < 50% who have undergone complete resection and platinum-based chemotherapy.
Name of Clinician Group: Lung Cancer Canada – Clinician Group
Author of Submission: Dr. Geoffrey Liu (lead), Dr. Paul Wheatley-Price, Dr. Michela Febbraro, Dr. Alison Wallace, Dr. Jeffrey Rothenstein, Dr. Nathalie Daaboul, Dr. Shaqil Kassam, Dr. Nicole Bouchard, Dr. Nicholas Meti, Dr. Cheryl Ho, Dr. Mark Vincent, Dr. Sunil Yadav, Dr. Callista Phillips, Dr. David Dawe, Dr. Randeep Sangha, Dr. Stephanie Snow, Dr. Vishal Navani, Dr. Silvana Spadafora, Dr. Mahmoud Abdelsalam, Dr. Kevin Jao, Dr. Biniam Kidane, Dr. Stephen Lam, Dr. Parneet Cheema, Dr. Quincy Chu, Dr. Ron Burkes, Dr. Rosalyn Juergens, Dr. David Stewart, Dr. Natasha Leighl, Dr. Lacey Pitre, Dr. Christian Finley, Dr. Shantanu Banerji, Dr. Sara Taylor, Dr. Susanna Cheng, Dr. Wociech Morzycki, Dr. Dorothy Lo

1. About Your Clinician Group

Lung Cancer Canada is a national charitable organization that serves as Canada's leading resource for lung cancer education, patient support, research and advocacy. Based in Toronto, Ontario, Lung Cancer Canada has a wide reach that includes both regional and pan-Canadian initiatives. Lung Cancer Canada is a member of the Global Lung Cancer Coalition and is the only organization in Canada focused exclusively on lung cancer.

2. Information Gathering

Information gathered for this submission was based on relevant published clinical data and expert evidence-based review amongst lung cancer medical oncologists across Canada. The key sources of data relevant to this new indication are below.

Manuscript: O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, Esteban E, Isla D, Martinez-Marti A, Faehling M, Tsuboi M, Lee JS, Nakagawa K, Yang J, Samkari A, Keller SM, Mauer M, Jha N, Stahel R, Besse B, Peters S; EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol. 2022 Oct;23(10):1274-1286. doi: 10.1016/S1470-2045(22)00518-6. Epub 2022 Sep 12. PMID: 36108662.

ESMO 2022 Virtual Plenary Presentation: L. Paz-Ares, M. O'Brien, M. Mauer, U. Dafni, K. Oselin, L. Havel, E. Esteban, D. Isla, A. Martinez-Marti, M. Faehling, M. Tsuboi, J.S. Lee, K. Nakagawa, J. Yang, S.M. Keller, N. Jha, S. Marreaud, R. Stahel, S. Peters, B. Besse on behalf of the PEARLS/KEYNOTE-091 Investigators. Pembrolizumab Versus Placebo For Early-Stage NSCLC Following CompleteResection and Adjuvant Chemotherapy When Indicated: Randomized, Triple-Blind, Phase 3 EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Study.. Ann Oncol 33 (4): 451-453.

ASCO 2022 Oral Presentation: M O'Brien, L Paz-Ares, N Jha, U Dafni, K Oselin, L Havel, E Estaban, D Isla, A Martinez-Marti, M Faehling, M Tsuboi, JS Lee, K Nakagawa, J Yang, SM Kewller, M Mauer, S Marreaud, R Stahel, B Besse, S Peters. EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 study of pembrolizumab versus placebo for completely resected early-stage non-small cell lung cancer (NSCLC): Outcomes in subgroups related to surgery, disease burden, and adjuvant chemotherapy use. J Clin Oncol 40 (16 suppl): Abstr 8612

ESMO 2022: Mini Oral Abstract Presentation: S. Peters, B. Besse, S. Marreaud, U. Dafni, K. Oselin, L. Havel, E. Esteban Gonzalez, D. Isla, A. Martinez-Marti, M. Faehling, M. Tsuboi, J-S. Lee, K. Nakagawa, J. Yang, S.M. Keller, M.E. Mauer, N. Jha, R.A. Stahel, L. Paz-Ares, M.E.R. O'Brien. 930MO PD-L1 expression and outcomes of pembrolizumab and placebo in completely resected stage IB-IIIA NSCLC: Subgroup analysis of PEARLS/KEYNOTE-091. Ann Oncol 33 (supp1):S971-S972.

ASCO 2023 Oral Presentation: K Oselin, BY Shim, M Okada, M Bryl, L Bonanno, G Demurag, I Colantonio, M Kimmich, U Janzic, J Vansteenkiste, R Bernabe Caro, A Scherz, A Curioni-Fontecedro, M Fruh, M Wollner, J Yang, N Shar iati, S Marreaud, S Peters, M O'Brien. Pembrolizumab vs placebo for early-stage non–small-cell lung cancer after resection and adjuvant therapy: Subgroup analysis of Patients Who Received Adjuvant Chemotherapyt in the Phase 3 PEARLS/KEYNOTE-091 Study. J Clin Oncol 41(16): Abstr 8520

ESMO Immuno-Oncology Congress 2023: Mini Oral Abstract Presentation: B. Besse, L. Havel, S. Peters, S.I. Marreaud, N. Jha, K. Oselin, E. Esteban Gonzalez, M.D. Isla Casado, A. Martinez-Marti, M. Faehling, J. Lee, Y. Luo, S.M. Keller, U. Dafni, M.E. Mauer, R. Stahel, M.E.R. O'Brien, M. Tsuboi, L. Paz-Ares. 120MO - Adjuvant Pembrolizumab versus Placebo for Early-Stage NSCLC After Resection and Optional Chemotherapy: Updated Results From PEARLS/KEYNOTE-091. https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress-2023/adjuvant-pembrolizumab-versus-placebo-for-early-stage-nsclc-after-resection-and-optional-chemotherapy-updated-results-from-pearls-keynote-091

3. Current Treatments and Treatment Goals

In Canada, the treatment for Stages IB-IIIA non-small cell lung cancer (NSCLC) is stage dependent. Canadian practice is aligned with practices from around the world, as evidenced from data from both the IASLC Dataset and North American-based National Cancer Database. Complete resection is the primary goal, whenever this is possible, with the ultimate goal of a cure. Chemotherapy, immunotherapy, radiation, and targeted agents play roles in subsets of resected Stage IB-IIIA NSCLCs to improve outcomes and cure

rates. These are defined typically as 5-year Disease-free and Overall Survival rates, which can also be expressed in measures of median overall and disease-free survival.

There are two differing approaches to supplement surgical resection: adjuvant therapy and neoadjuvant therapy. There is no consensus on which approach should be adopted for any specific patient. The decision to choose one approach over the other is now dependent on a variety of factors, including stage, nodal status and location, ease of resectability, PDL1 TPS biomarker status, and even surgeon/multidisciplinary team and patient preferences. This is because there are no head-to-head studies of neoadjuvant vs adjuvant approaches, and there will likely be no such studies forthcoming, as treatment decisions in this context tend to be complex, focusing on tumour, surgical and medical/comorbidity considerations simultaneously. Recently, perioperative (combined neoadjuvant and adjuvant) chemo-immunotherapy approaches are also being considered for approval and funding in Canada through the recent publications of the Keynote 671 (pembrolizumab), Checkmate 77T (nivolumab), and AEGEAN (durvalumab) trials.

Neoadjuvant Chemo-immunotherapy: With neoadjuvant therapy, the CheckMate 816 trial regimen has been CDA-approved and funded, whereby patients with Stage IB-IIIA are treated with nivolumab and platinum doublet chemotherapy for three cycles, followed by surgical resection. The goal is cure. A subset of patients (~20%) will be found to unresectable after chemo-immunotherapy, and this group may undergo chemoradiation for salvage curative therapy (PACIFIC regimen).

Adjuvant Chemotherapy +/- Radiation: For stage IB NSCLC, the primary goal is cure. To achieve this goal, the standard treatment is complete surgical resection (R0). Thereafter, a minority of fit patients are offered adjuvant platinum-doublet chemotherapy, particularly those with pathological findings consistent with high risk of relapse such as larger T-sizes and nodal disease. In a small fraction of cases, surgical resection leads to an incomplete resection, and adjuvant radiation is potentially offered in this context. In medically inoperable patients, sometimes localized radiation (external beam or stereotactic body radiation) is given in lieu of an operation, with or without concurrent or sequential chemotherapy.

For stage II NSCLC, the primary goal is cure (i.e., to improve 5-year overall survival). To achieve this goal the standard treatment is complete surgical resection (R0). Thereafter, fit patients are offered adjuvant platinum-doublet chemotherapy. In a small fraction of cases, surgical resection leads to an incomplete resection, and adjuvant radiation is potentially offered in this context, which would be given sequentially to adjuvant chemotherapy.

For stage IIIA NSCLC, the primary goal is cure. To achieve this goal, the standard treatment depends on whether the primary tumour is considered resectable or not, balancing benefits and risks, including peri-operative risks, the ultimate chance of cure, the number of lobes that will be resected (e.g. lobectomy vs pneumonectomy), and the long-term residual effects of the operation (e.g. expected residual pulmonary reserve and function after a resection). If surgery is considered reasonable, the next step would depend on whether mediastinal lymph nodes are known to be involved with cancer. If not (T4N0 or T3 or T4N1), medically eligible patients will start with surgery and then proceed to adjuvant platinum-based chemotherapy.

Adjuvant platinum-doublet chemotherapy given after resection of stage IB-IIIA NSCLC patients typically consists of four cycles of treatment, with each cycle lasting 21-28 days, for a total of 12 -16 weeks of therapy. Specific platinum-doublet chemotherapy with the best evidence of efficacy has been with the

combination of cisplatin and vinorelbine, but other platinum-doublet combinations such as cisplatin and pemetrexed have been increasingly used over the recent years.

Neoadjuvant Chemoradiation: For those Stage IIIA patients with N2 mediastinal lymph nodes involved, neoadjuvant chemotherapy concurrent with radiation, followed by complete surgical resection is sometimes offered in lieu of neoadjuvant chemo-immunotherapy, especially if the nodal disease is non-bulky and limited in extent. In some Stage IIIA resectable patients, chemoradiation is considered an acceptable approach, with 2-3 cycles of platinum-doublet chemotherapy administered concurrently (rarely sequentially) with 50-70 Gy of external beam radiation spread over multiple fractions of 1.8-2.0 Gy over 5-7 weeks. This is followed by surgical resection. The goal is cure. In a small fraction of cases, surgical resection leads to an incomplete resection, and adjuvant radiation is potentially offered in this context, but sequentially (and not concurrent) with any adjuvant chemotherapy. Another small subset of patients may be found to be unresectable after neoadjuvant chemotherapy, and this group may then undergo durvalumab maintenance therapy, as these patients have transitioned into the unresectable setting based on the PACIFIC trial data.

Definitive chemoradiation for unresectable Stage III disease: If surgery is not considered reasonable, definitive chemotherapy concurrent with radiation is given, followed by consideration of a year of durvalumab (PACIFIC trial regimen).

Adjuvant Immunotherapy: The IMpower trial assessed the role of adjuvant atezolizumab in patients receiving adjuvant chemotherapy. The primary outcome for this study was disease free survival of patients with stage II-IIIA resected lung cancer (UICC 7th edition) with a tumour that is determined to be PDL1 positive (≥1%) by immunohistochemistry, after at least 1 cycle of adjuvant therapy. In this scenario, the stratified HR was 0.66 (95% CI: 0.50-0.88) favouring adjuvant atezolizumab. However, Dr. Wakelee provided the first OS data at the 2022 World Conference on Lung Cancer on the Stage II-IIIA patients by PDL1-status. The importance of the PDL1 biomarker was most pronounced in patients with PD-L1 expression of at least 50% (HR = 0.43). Patients with PDL1 expression between 1% and 49% had a hazard ratio of 0.95, whereas those with PDL1–negative tumors had a hazard ratio of 1.36. This led to the Health Canada decision to approve only use of adjuvant atezolizumab in patients with PDL1 >= 50%. The final DFS data was reported in a 2023 ASCO poster (LBA8035): in patients with tumours with PDL1 TPS 1-49%, the HR was 0.91 (0.65, 1.27), whereas in the patients who had developed resected Stage II-IIIA tumours with PDL1 TPS >= 50% had a HR of 0.48 (0.32-0.72), virtually identical to the interim OS HRs.

Currently for resected Stage IB-IIIA NSCLC patients with PDL1 < 50%, there is no indication for adjuvant immunotherapy, which defines an unmet need.

Staging Edition Considerations: The current staging system we use globally is the 8th edition of the Union of International Cancer Control (UICC) staging system. This trial was conducted using the 7th edition of the UICC staging system. Discussion above referenced the standard practice for the 7th edition which was used in the trial. Relevant differences include: stage IB cancers that are considered high risk for relapse (tumour size 4-5 cm) are now considered stage II tumours. Adjuvant chemotherapy is not required for patients with stage I cancers in the 8th edition system (< 4 cm, node negative). Stage III has now been divided into stage IIIA, IIIB and IIIC. Stage IIIC by definition are unresectable. A subset of patients with stage IIIA and B will be

resected and offered adjuvant platinum based chemotherapy, or chemo-immunotherapy (if PDL1 TPS is >= 50%) as described above. These patients previously were all typed as IIIA in the 7th edition staging.

EGFR-mutated and ALK-rearranged resected NSCLCs: Osimertinib is CDA-approved and funded after tumour resection in patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. This population is a specific subgroup of NSCLC with a sensitizing mutation in the tyrosine kinase domain of EGFR and comprises 10-15% of adenocarcinomas. ADAURA trial of single agent adjuvant osimertinib for 3 years, with an OS HR of 0.49 (0.34-0.70) and DFS HR of 0.27 (0.21-0.34) for Stage IB-IIIA resected tumours.

Similarly the ALINA trial was performed in patients with Anaplastic Lymphoma kinase (ALK)-gene rearranged tumours who were completely resected Stage IB-IIIA. Patients were randomized to 2 years of alectinib monotherapy vs standard adjuvant platinum-doublet chemotherapy. This trial demonstrated a DFS HR of 0.24 (0.13 to 0.43) favouring monotherapy alectinib over adjuvant chemotherapy. Adjuvant electinib treatment was recently approved by Health Canada and is undergoing CDA review.

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4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The most important goal that an ideal treatment would have for any adjuvant therapy in early stage non-small cell lung cancer is ***to prolong cancer-free life and life itself*** (i.e., recurrence-free survival and overall survival).

UNMET NEED 1: Current therapies are inadequate to achieve high rates of cure in early stage resected IB-IIIA NSCLC patients, based on 5-year overall survival rates.

The outcomes of such patients remain poor even with the best current treatments, falling far below the outcomes of other cancer disease sites. Unlike metastatic disease (where there has been significant progress), the clinical impact of improving outcomes in early stage NSCLC is far greater, with patients having longer cancer-free intervals and being considered true cancer survivors (i.e. cured).

Lung cancer five-year survival, even amongst the early stages, has significantly worse outcomes than in other common cancers. **Figure 1** below illustrates how much of a gap there is between lung cancer and other common cancers, such as breast, colon and prostate cancers. In **Figure 1**, for the localized and extended (i.e. non-metastatic) stages of common cancers, such as breast, colorectal, and prostate cancer, the five-year survival times sit above 75%. In contrast, the results are significantly worse in lung cancer (30-55% five-year survival for Stages I-III lung cancer). Similar results are echoed in **Figure 2**, which demonstrate that regardless of whether one uses the 7th or 8th edition of the AJCC/UICC lung cancer staging system, the 5-year overall survival rates are between 36% (Stage IIIA) and 66-68% (Stage IB). All of these results presented are in the contemporary era where adjuvant chemotherapy has been widely adopted.

There has been progress in the patients who have resected Stage IB-IIIA NSCLCs who have PDL1 >= 50% through the IMpower trial (see Section 3 above), and these improvements will likely be measurable after the 9th/10th AJCC/UICC current and future staging data are analysed.

However, the last time there had been improvements in NSCLC adjuvant therapy in the patients with PDL1 < 50% was through the incorporation of adjuvant chemotherapy in Stages IB-IIIA resected NSCLC. Following an earlier large meta-analysis, the publication of the LACE collaborative pooled analysis of multiple trials (IALT, NCIC CTG BR.10, BLT, ALPI, ANITA), showed absolute survival improvements ranging from 8.8-15%. However, it has been two decades since the large-scale introduction of adjuvant chemotherapy into clinical practice across in Canada. There is a dire need to improve survival outcomes in our Stage IA-IIIB patients with PDL1 < 50% further, especially in the setting where long-term cancer-free survival and potential cure rates are involved.

UNMET NEED 2: Current therapies are inadequate to prevent recurrences in early stage resected IB-IIIA NSCLC patients, based on disease-free survival rates.

Improving lung cancer disease-free survival is an equally important unmet need, as it has biologic and clinical association with overall survival in early stage NSCLC patients. Further, in Section 5.3.1, recurrences and disease-free survival are discussed in detail as to why these are legitimate and key clinical outcomes in their own right, with significant patient, healthcare and societal impacts.

Recurrences after resection of an initial early-stage NSCLC are primarily through distant spread or metastases. This metastatic disease is generally incurable (there are only rare instances of regional or oligometastatic recurrences where treatment may yield long term survival); looking at the survival curves of *de novo* stage IV cancers (see **Figure 2** below) is evidence of the poor outcomes that occur once metastatic disease has been diagnosed. Clinically, these findings demonstrate that, to impact on NSCLC overall survival, one needs to reduce disease recurrence substantially in early-stage NSCLCs.

Further, disease-free and overall survival mirrored each other the last time there was an effective adjuvant therapy for stage IB-IIIA resected NSCLC: in the LACE collaborative, the overall survival benefit of adjuvant chemotherapy was HR = 0.89 (95% CI, 0.82 to 0.96; P = .005) whilst for recurrence-free survival, the results were similar, HR = 0.84 (95% CI, 0.78 to 0.91; P < .001). DFS and OS mirrored each other in the IMpower trial of adjuvant atezolizumab in patients with Stage II-IIIA completely resected tumours who had PDL1 TPS >= 50%, where the final DFS HR was reported as 0.48, which the second interim OS HR was reported as 0.43.

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Which patients have the greatest unmet need for an intervention such as the drug under review?

Patients with NSCLC as mentioned above carry a worse prognosis stage for stage when compared to other curatively treated solid tumours. The risk of relapse jumps dramatically with each increase in stage. Currently, the only group where we recommend surgery alone are those patients with tumours less than 4 cm based on the data of platinum doublet chemotherapy (i.e., mostly Stage IA patients). Once you reach stage II in the 8th edition of staging (4 cm or greater in size, which were partially previously included in some Stage IB categories before) OR any lymph node involvement (stage II in the 7th staging edition), the survival plummets to 60%. If you have a larger tumour or ipsilateral regional lymph node involvement which defines stage III the 5-year survival only ranges from 26-36%. Therapies that improve the outcomes in this group are a huge unmet need.

This is not a niche population. According to the Canadian Cancer Society's 2024 annual report, 32,100 people are estimated to be diagnosed with lung cancer this year, and 20,700 will die this year. According to the CCS 2020 Special Report in Lung Cancer, 49% of newly diagnosed lung cancer patients have stage I-III disease, 21% stage 1, 8% stage II and 20% stage III. Even if only one third of these patients are resected and of high enough stage to qualify for adjuvant chemotherapy, and PDL1 < 50% comprised 60% of these cases, that is still over 3000 Canadians who may benefit annually from this additional treatment.

Based on the data from other trials of immunotherapy in lung cancer and this new PEARLS/KN-091 data, we agree that pembrolizumab does address an unmet need.

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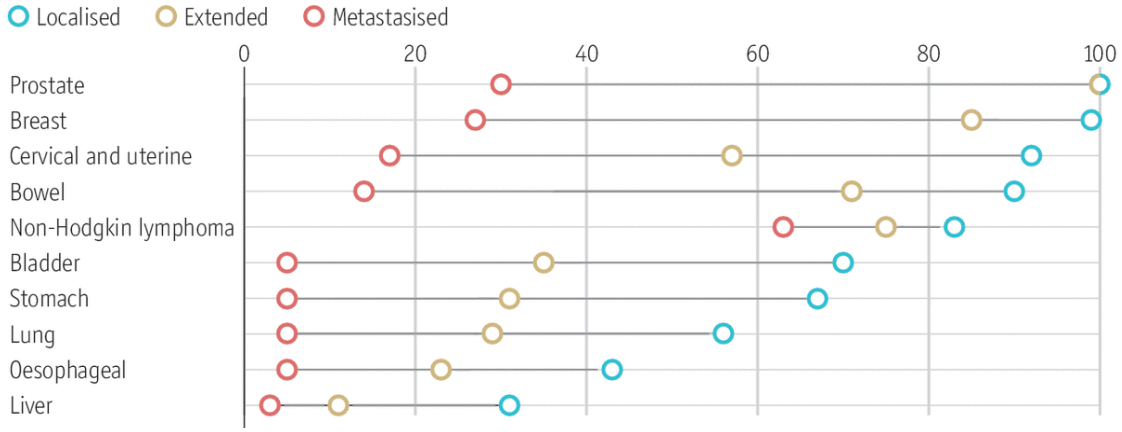
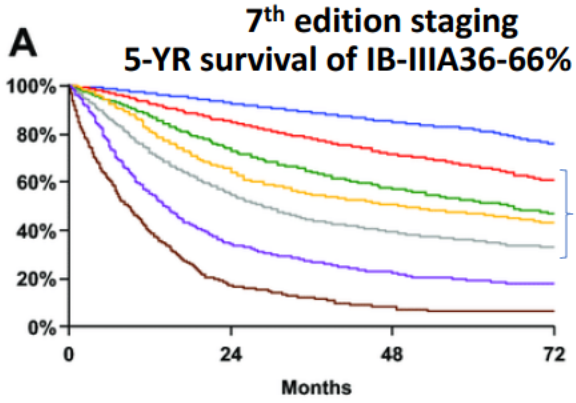
FIGURES FOR THIS SECTION

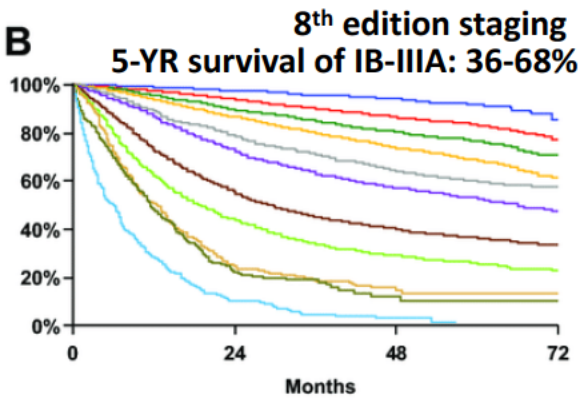
United States SEER data (2016) on five-year survival rates of various cancers, by disease stage at diagnosis. Stage I = localized; Stage II-III = Extended



Adapted from the Technology Quarterly section of The Economist on September 16th 2017

Figure 1. The relative poor outcomes, shown as 5-year overall survival rates, as demonstrated in Stage IB-IIIA lung cancer patients (represented by localized [blue, Stage I] and extended [yellow, stage II-III] open circles), when compared to other common cancers, such as prostate, breast, and colorectal cancer.





7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Overall survival by clinical stage according to the seventh edition (A) and the eighth edition (B) groupings using the entire database available for the eighth edition. MST, median survival time. Survival is weighted by type of database submission: registry versus other.

Nicholson, Andrew & Chansky, Kari & Crowley, John & Beyruti, Ricardo & Kubota, Kaoru & Turrisi, Andrew & Eberhardt, Wilfried & Meerbeeck, Jan & Rami-Porta, Ramon. (2015). The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology. 11. 10.1016/j.jtho.2015.10.008.

Figure 2. Overall survival is poor in Stage IB (red), IIA (green), IIB (yellow), and IIIA (grey) NSCLC patients, regardless of whether one is using the seventh or eighth edition of non-small cell lung cancer staging, ranging from 36% through 68%.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

5.1.1 Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Pembrolizumab is the second immunotherapy that has been shown in a randomized clinical trial to improve outcomes in the post surgical setting, but the first to show improved survival outcomes in the subgroup of patients with Stage IB-IIIA NSCLC resected tumours that have PDL1 < 50%.

5.1.2. Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Based on the PEARLS/KN-091 results, pembrolizumab should be added to the current post-operative management of resected Stage IB-IIIA (7th ed.) tumours with PDL1 < 50% as a second adjuvant treatment. Similar to the atezolizumab IMpower trial, benefit was seen in the 85% of patients in the PEARLS/KN-091 trial who received at least 1 cycle of platinum doublet chemotherapy. Adjuvant platinum doublet chemotherapy should remain as the first post-operative treatment initiated. Pembrolizumab should not be considered a replacement for chemotherapy.

5.1.3 Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Immunotherapy, including pembrolizumab, has been studied extensively in the metastatic lung cancer space both as monotherapy and in combination with chemotherapy. This treatment approach is highly effective. PD-1/L1 inhibitors are the first class of drugs that has led to a dramatic improvement in overall survival in the metastatic setting. Immunotherapy is now considered a new pillar of cancer treatment based on these trials. One of the benefits of immunotherapy is the durability of its benefit. These drugs work to block self tolerance allowing a patient's own immune system an opportunity to eliminate any identified cancer cells. The other benefit of this class is the tolerability. In the process of blocking self tolerance, patients can manifest autoimmune phenomena that might have previously been suppressed. Fortunately, most autoimmune side effects can be readily managed with steroids or other immunosuppressants. The management of these side effects is now part of the expertise of oncologists as these agents are being used across many tumour types.

5.1.4 Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

No, this drug advances clinical care in its own right. It does not replace an existing treatment, but rather is a novel adjuvant therapeutic strategy that is added to adjuvant chemotherapy in patients with Stage IB-IIIA resected NSCLC tumours that are PDL1 < 50%.

5.1.5 Is the drug under review expected to cause a shift in the current treatment paradigm?

Yes, this will be the first drug used adjuvantly in the Stage IB-IIIA post-resection space in patients with tumours with PDL1 < 50%. There are no alternative drugs to use in this space.

5.1.6 Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

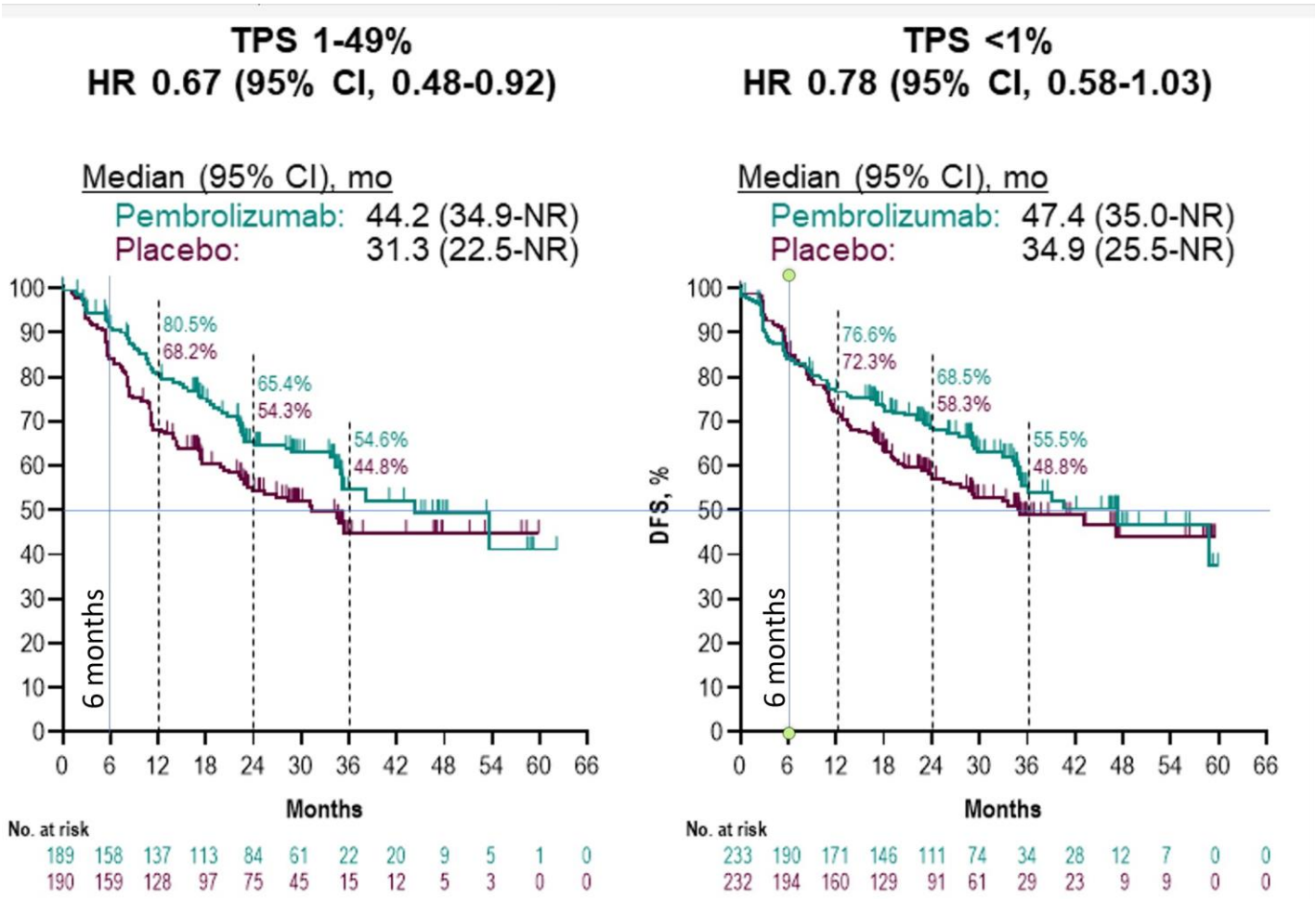
This question is not designed for the current submission. Adjuvant chemotherapy should be administered independently of consideration of pembrolizumab. Other ongoing trials involving similar patient populations have not had their results reported, and would need to be adjudicated separately once the results become available.

5.1.7 How would this drug affect the sequencing of therapies for the target condition?

Re-using a drug in the metastatic setting after use in the adjuvant setting is a consideration.

Data are not available as to when and if to reuse immunotherapy in the recurrent/advanced/metastatic setting, when pembrolizumab was used in the adjuvant setting. PEARLS/KN-091 did not mandate how patients should be treated at disease recurrence. We await future data on the rates of use of immunotherapy in the post-recurrence setting of the PEARLS/KN-091 trial, as well as the proportions of relapses that are locoregional vs distant, as treatment of recurrent/metastatic disease with immunotherapy partly depends on these factors. However, when relapses are historically more than 6 months after completion of prior immunotherapy treatment, we generally allow rechallenge with immunotherapy presuming there is no contraindication. In the subset of patients with PDL1 TPS 1-49%, fewer than 10% of patients had disease recurrence earlier than 6 months, and for PDL1 < 1%, that proportion was <20% (see figure below). Therefore, because relapses on the pembrolizumab arm were generally much later than 6 months, first line metastatic treatments including immunotherapy should be allowed. A similar paradigm has been followed for unresectable stage III patients treated with consolidation durvalumab.

Figure: Kaplan Meier curves by PDL1 TPS scores. Adapted from Peters et al, ESMO 2022 presentation



5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

5.2.1 Which patients are most likely to respond to treatment with drug under review?

The dual primary outcomes for this study were disease free survival of patients with stage II-IIIA resected lung cancer (UICC 7th edition) patients and in the subset with a tumour that is determined to be PD-L1 positive (≥1%) by immunohistochemistry, In this scenario, the final DFS HR was 0.76 (95% CI: 0.63, 0.91; p=0.0014) for all patients and HR of 0.83 (0.59-1.16; P=0.13) for those with PDL1 TPS >= 50%, demonstrating that the main benefit occurred in patients with PDL1 < 50%.

Those who received any adjuvant chemotherapy benefited, with HR of 0.80 (0.67-0.96). When evaluating the 86% (1010 of 1178) of patients who received any adjuvant chemotherapy, a consistent picture in the forest plots emerges: in all subcategories, the HRs favoured pembrolizumab adjuvant therapy. This subpopulation also mirrored the IMpower 010 trial of adjuvant atezolizumab, which required at least one cycle of adjuvant chemotherapy to be eligible for that study.

When this study was initiated, there was no place for adjuvant immunotherapy for Stage IB-IIIA resected NSCLCs in any setting. However, by the time this study reported results, the IMpower 010 trial of adjuvant atezolizumab had already reported out and in Canada, atezolizumab has since been approved in the patients who had complete resections of their Stage II-IIIA NSCLC tumours with PDL1 TPS >=50%. It happened to be that the best performing subgroups in the current PEARLS/KN-91 trial were in the opposing cohorts, i.e. patients with Stage IB-IIIA resected tumours that were PDL1 < 50%, where the HR was 0.67 for PDL1 TPS 1-49% and the HR was 0.69 for PDL1 TPS < 1%.

5.2.2 Which patients are most in need of an intervention? Would this differ based on any disease characteristics such as stage?

Immunotherapy is part of the upfront current treatment landscape across all stages from IB-IV in non-targetable NSCLC. As indicated before, Stage IA patients have relatively good survival outcomes and cure rates that adjuvant therapy of any type (chemotherapy, radiation, targeted, immunotherapy) has not been established as being beneficial. The table below shows that there is upfront treatment in the neoadjuvant, adjuvant, definitive chemoradiation, and front-line metastatic therapies in NSCLC across all of the remaining stages (IB-IV) EXCEPT for those with resected Stage IB-IIIA NSCLC tumours that were PDL1 TPS < 50%. PEARLS/KN-091 would fill that need. There is no specific biological reason why all other stages and PDL1 statuses benefit clinically from immunotherapy as part of its upfront management but not this one subpopulation of patients.

Table: Non-chemotherapy management of NSCLC: Targeted and Immunotherapy: Note that PEARLS/KN-91 would address a relatively large lung cancer subpopulation in current need of improved interventions beyond chemotherapy and surgery. Shaded boxes show the central role of immunotherapy in the upfront treatment of NSCLCs across all stages, except for those who are resected Stage IB-IIIA patients with tumours that have PDL1 < 50%. PEARLS/KN-091 would fill that gap.

	PDL1 < 50%	PDL1 >=50%	EGFR (15-20% of NSCLC)	ALK (2-3% of NSCLC)
Neoadjuvant Stage IB-IIIA	CM816	CM816	Trial ongoing	Not established
Resected Stage (IB) II-IIIA	PEARLS/KN-091	IM power 010 (Stage II-IIIA)	ADAURA	ALINA
Unresectable Stage III	PACIFIC	PACIFIC	LAURA	Trial ongoing
Incurable Stage IIIB/IV	Multiple	Multiple	Multiple	Multiple

5.2.3 How would patients best suited for treatment with the drug under review be identified? Are there any issues related to diagnosis? Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)? Is there a companion biomarker test required?

Patients will be identified based on a combination of stage and PD-L1 status. As these tumours are all resected, accurate staging and diagnosis will be determined by the pathologist and reported as part of the histologic description on the pathology report.

PD-L1 testing is routinely offered across the country and is generally done reflexively for all stages and histologic subtypes of NSCLC. In this study, the PD-L1 testing was done with the 22C3 assay, which is one of the Canadian standards. Historically, specific companion diagnostics have not been required by provincial funders. Generally, a validated test is required. Extensive work has already been undertaken to validate PD-L1 testing across the country. Individual institutions have been allowed to choose to use a commercial test or to create a local test that would be validated. The International Association for the Study of Lung Cancer alongside the American Society of Clinical Oncology and the American Association for Cancer Research conducted a project comparing and contrasting the commercially developed assays for determination of PD-L1. The results of this work have shown that the S22C3 and 28-8 assays generally used for clinical determination of PD-L1 provide consistent results with each other. One of the leaders of the Blueprint project is Dr. Ming Tsao, a highly respected Canadian pathologist who was instrumental in the validation of PD-L1 testing across Canada when PD-L1 testing was first being refined. Based on the Blueprint data, we do not feel a new assay needs to be created to identify patients for this treatment. The previously validated test used by the local lab will be sufficient.

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5.2.4 Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

We anticipate that this question was designed for submissions related to the advanced/metastatic setting, and not relevant for this submission involving adjuvant therapy.

“Response to therapy” is not an appropriate outcome in this population. If the purpose of this question is to address which patients are most likely to benefit, then the follow eligibility criteria reflect the subset of patients most likely to benefit from adjuvant pembrolizumab:

As stated above, patients meeting the main eligibility with several additional criteria are most likely to benefit:

1. Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7 (or equivalent by AJCC v8)
2. Complete surgical resection with negative margins (R0) with no evidence of disease post-resection
3. ECOG PS 0 or 1
4. Received at least one cycle of adjuvant chemotherapy
5. PDL1 TPS by local Canadian testing < 50%
6. Individuals who have no clear contraindication to immunotherapy.

Eligibility points 1 through 3 were part of the original study eligibility,

For Eligibility point 4, the issue of requiring the use of adjuvant therapy has been addressed in Section 5.2.1, where subgroup data becomes consistently in favour of pembrolizumab, when restricted to patients treated with at least one cycle of adjuvant chemotherapy.

For Eligibility point 5, although patients who have PDL1 >=50% were included into the PEARLS/KN-91 trial, as clinicians we simply would not treat such patients with pembrolizumab, per PEARLS/KN-91 based on the subgroup data. We would consider that in this subgroup, the results of the funded adjuvant atezolizumab per IMpower 010 trial in the PDL1 TPS >= 50% would dominate over the current PEARLS/KN-91 trial data, especially when the HR is above 1.0. In contrast, atezolizumab was not approved by Health Canada for use in the PDL1 TPS < 50% subgroup of resected Stage IB-IIIA patients because its HRs are either close to 1 (PDL1 TPS 1 -49%) or well above 1 (PDL1 TPS < 1%). Therefore the major unmet need remains in the PDL1 < 50% subgroup.

For Eligibility point 6, patients least suitable for treatment are those patients who have a contraindication to immunotherapy treatment, such as organ transplant. Risks and benefits would need to be discussed with patients who have prior or active autoimmune disease as their risk of side effects is generally higher than for those patients without that history. Active autoimmune disease would be considered a relative contraindication.

Several additional factors are addressed below:

Patients with PD-L1 positive, EGFR mutated lung cancers were included in PEARLS/KN-091 trial, comprising a small 6.5% (66/1010) of the chemo-adjuvantly treated patients, and had a DFS HR of 0.39 (0.20-0.76). This contrasts with the mature data from the large ADAURA trial of single agent adjuvant osimertinib for 3 years, with an OS HR of 0.49 (0.34-0.70) and DFS HR of 0.27 (0.21-0.34). In the situation of a patient with a resected NSCLC with a sensitizing EGFR mutation and PD-L1 expression identified, clinicians would have to choose between adjuvant sequential chemotherapy and immunotherapy, based on the PEARLS/KN-091 trial or adjuvant osimertinib. We recommend that risks and benefits of each of these therapies be reviewed with the patient and a choice be made for the best treatment for that individual patient.

One group that may not benefit are patients with ALK translocations. Even in the metastatic setting, the data on the benefits of immunotherapy in ALK+ NSCLC is sparse and most clinicians do not recommend its use unless other treatment options have been exhausted. As ALK data in PEARLS/KN-091 was even sparser than that of EGFR mutations (n=14; 1% of the entire study sample), little can be said of its benefit or lack thereof in this population. However, with the ALINA trial demonstrating a DFS HR of 0.24 (0.13 to 0.43) with monotherapy alectinib vs adjuvant chemotherapy, it would be highly unlikely that any clinicians would choose an adjuvant chemotherapy-pembrolizumab approach used in PEARLS/KN-091, over adjuvant alectinib, should both be made available.

One last bit of data to consider is the choice of adjuvant chemotherapy. In the presentation by Dr. O'Brien at ASCO Annual Meeting in 2022, one of the patient groups that benefited less from adjuvant pembrolizumab were those who were treated with adjuvant carboplatin and paclitaxel (11% of the total study population). This was an exploratory analysis with relatively small numbers of patients and thus should be interpreted with caution. No such restriction should be placed on the specific type of adjuvant chemotherapy, based on this exploratory analysis.

All grade adverse events, Grade 3-5 toxicities, immune-related and treatment emergent adverse events, and permanent discontinuations, were similar in the experimental immunotherapy arms of IMpower 010 (adjuvant atezolizumab) and PEARLS/KN-091 (adjuvant pembrolizumab), with no new safety signals than were reported for the multi-disease site, widely used pembrolizumab. The routine cautions and contraindications, both relative and absolute, as described in clinical practice for the use of pembrolizumab, should suffice.

References:

Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohé C, Wang J, Goldman JW, Lu S, Su WC, de Marinis F, Shepherd FA, Lee KH, Le NT, Dechaphunkul A, Kowalski D, Poole L, Bolanos A, Rukazenkov Y, Wu YL; ADAURA Investigators. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. N Engl J Med. 2023 Jul 13;389(2):137-147. doi: 10.1056/NEJMoa2304594. Epub 2023 Jun 4. PMID: 37272535.

Herbst RS, Wu YL, John T, Grohe C, Majem M, Wang J, Kato T, Goldman JW, Laktionov K, Kim SW, Yu CJ, Vu HV, Lu S, Lee KY, Mukhametshina G, Akewanlop C, de Marinis F, Bonanno L, Domine M, Shepherd FA, Urban D, Huang X, Bolanos A, Stachowiak M, Tsuboi M. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol. 2023 Apr 1;41(10):1830-1840. doi: 10.1200/JCO.22.02186. Epub 2023 Jan 31. Erratum in: J Clin Oncol. 2023 Aug 1;41(22):3877. doi: 10.1200/JCO.23.00658. PMID: 36720083; PMCID: PMC10082285.

Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, Lee JS, Zhong W, Horinouchi H, Mao W, Hochmair M, de Marinis F, Migliorino MR, Bondarenko I, Lu S, Wang Q, Ochi Lohmann T, Xu T, Cardona A, Ruf T, Noe J, Solomon BJ; ALINA Investigators. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2024 Apr 11;390(14):1265-1276. doi: 10.1056/NEJMoa2310532. PMID: 38598794.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

5.3.1 Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

In clinical practice, we describe benefit of treatment in several ways, in terms of 5-year cure rates, the median time increase in being disease-free, and in overall survival.

The primary outcome in this trial to determine whether pembrolizumab has worked is whether disease recurrence has occurred, (disease-free survival) and ultimately, cure rates, as measured by 5-year OS and Kaplan Meier curves for OS. Typically, most recurrences of Stage IB-IIIA NSCLC patients occur within 2-3 years while OS typically requires a greater number of years of follow-up.

In the setting of early-stage NSCLC, there has been growing clinician recognition of the enormous negative impact of recurrent disease on patients, independent of overall survival. Recurrent disease can occur across a multitude of organ systems. For example, bone metastases and CNS metastases are often symptomatic, requiring local therapies such as radiation to manage symptoms. Lung metastases and pleural disease can lead to shortness of breath and requiring such procedures as thoracenteses. Reducing the rate of recurrence or delaying recurrences impacts patients greatly, independent of the treatment's ultimate impact on overall survival.

The costs to patient health, quality of life, utilization of health care resources, economic loss of productivity, and overall costs to the society are substantial when a patient relapses especially those with metastatic disease. Delaying or reducing disease recurrence thus has enormous benefit from each of these perspectives.

One main feature of immunotherapy as noted in the metastatic setting is that the benefits are durable. For example, in the Keynote 024 trial of pembrolizumab, we now know that 33% of patients with highly PD-L1 positive NSCLCs (TPS ≥50%) treated with immunotherapy will be 5 year survivors). This type of statistic is unheard of from either chemotherapy or targeted therapy. We have also seen from the PACIFIC trial that the outcome of disease free survival translated into a clear overall survival benefit of 10% at 5 years. Based on the durability of response in the metastatic setting as well as the clear relationship between disease free survival and overall survival in the curative intent unresectable stage III setting, we anticipate a similar durability to the benefit in the adjuvant setting and overall survival benefit in the post-surgical setting.

Thus, in summary, outcomes used in current practice (recurrences or disease-free survival, and overall survival) are aligned with the IMpower010 primary and secondary clinical outcomes. In an older era, disease-free survival may only have been seen as a surrogate for overall survival; however, in our contemporary era, our clinician group sees recurrent disease as its own critical outcome, with substantial patient-level, health-care level, and societal-level ramifications. Disease free survival is already an acceptable outcome in other disease sites (e.g. breast, melanoma), partly because of such impact. The same standard should be applied to adjuvant NSCLC therapy.

References:

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leal TA, Riess JW, Jensen E, Zhao B, Pietanza MC, Brahmer JR. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021 Jul 20;39(21):2339-2349. doi: 10.1200/JCO.21.00174. Epub 2021 Apr 19. PMID: 33872070; PMCID: PMC8280089.

David R. Spigel, Corinne Faivre-Finn, Jhanelle Elaine Gray, David Vicente, David Planchard, Luis G. Paz-Ares, Johan F. Vansteenkiste, Marina Chiara Garassino, Rina Hui, Xavier Quantin, Andreas Rimner, Yi-Long Wu, Mustafa Ozguroglu, Ki Hyeong Lee, Terufumi Kato, Maike de Wit, Euan Macpherson, Michael Newton, Piruntha Thiyagarajah, and Scott Joseph Antonia. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. Journal of Clinical Oncology 2021 39:15_suppl, 8511-8511.

5.3.2 What would be considered a clinically meaningful response to treatment?

As per previous comments, we have rephrased the first question to “What would be considered a clinically meaningful benefit of treatment”.

The comparisons for adjuvant therapy in NSCLC are:

(i) Adjuvant chemotherapy, which has been accepted and funded in Canada and globally. Based on this standard, novel therapeutic strategies with a disease-free survival benefit of a hazard ratio of 0.84 or lower (Pignon et al) would be considered a clinical meaningful improvement in outcome.

(ii) Adjuvant atezolizumab in the patient population who have PDL1 TPS >= 50%. IMpower010’s DFS benefit has a HR of 0.48, which met this standard, and led to CDA funding recommendation.

(iii) Adjuvant pembrolizumab in the patient populations who are PDL1 TPS 1-49% or <1% and who received adjuvant chemotherapy in the PEARLS/KN-091 trial had DFS HRs of 0.67 (0.48-0.94; TPS 1-49%) and 0.69 (0.51-0.94; TPS < 1%). Based on the chemotherapy standard, PEARLS/KN-091 results also meet this standard.

The gold standard is overall survival. The overall survival data from this trial are not mature but the current HR is 0.87 (amongst all PDL1 levels and with/without adjuvant chemotherapy) which shows that the data are trending toward a benefit with this additional secondary outcome. We anticipate that even eventual data are mature, the subgroups of patients with PDL1 < 50% who received adjuvant chemotherapy will enrich for those benefiting and further improve the OS HR.

See section 5.2 and Section 3 (UNMET NEED #2) for additional rationale for why clinicians accept DFS as a primary outcome for clinical purposes.

5.3.3 Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

As for the magnitude of benefit, for the PDL1 TPS 1-49% subgroup, the median DFS improves from 31.3 to 44.2 months, a median increase of 12.9 months; for the PDL1 TPS < 1% subgroup, the median DFS improves from 34.9 to 47.4 months, a median increase of 12.5 months (see figure in Section 5.1.6). There will be no question that clinicians will consider that a median DFS increase of over a year will be a major advance for patients. Further, given the similarities in the trial population and our clinical populations, there will likely be little variation across populations across Canada.

References:

Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008 Jul 20;26(21):3552-9. doi: 10.1200/JCO.2007.13.9030. Epub 2008 May 27. PMID: 18506026.

ASCO 2024: HA Wakelee, NK Altorki, C Zhoiu, T Csoszi, IO Vynnychenko, O Goloborodko, A Rittmeyer, M Reck, A Martinez-Marti, H, Kenmotsu, YM Chen, A Chella, S Sugawara, C Fu, M Bellinger, Y Deng, MK Srivastava, E Bennett, BJmGitlitz, E Felip. IMpower010: Final disease-free survival (DFS) and second overall survival (OS) interim results after ≥5 years of follow up of a phase III study of adjuvant atezolizumab vs best supportive care in resected stage IB-IIIA non-small cell lung cancer (NSCLC). J Clin Oncol 42 (supp 17): Abstr LBA8035

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment should continue for 18 cycles (1 year) or until side effects dictate that treatment should be discontinued or disease progression is detected. In the PEARLS/KEYNOTE-091 study, 52% of patients completed the full course of pembrolizumab treatment, 23% of participants discontinued drug due to adverse events and 12% discontinued due to disease progression.

Given that adjuvant pembrolizumab is administered over a one-year period, there will need to be periodic follow-up for toxicity of the drug and periodic follow-up for recurrent disease.

Follow-up intervals for assessment of pembrolizumab are generally each cycle (every 3 weeks) with laboratory and clinical assessments.

Time intervals between imaging will also vary. Initially, imaging scans at 3-4 month intervals would be common-place, but, imaging as sparse as 6+ months intervals may occur especially in the lower stage patients.

These follow-up and imaging time intervals, in part, reflect the wide range of follow-up practices across Canada and globally, where there has been no consensus. However, resected Stage IB-IIIA NSCLC patients generally are followed-up for at least 5-years post-operatively by at least one oncologist (typically surgical or medical oncologist) in most settings.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Pembrolizumab can be given in any oncology setting where infusions are performed. Pembrolizumab is a well-known drug to oncologists.

6. Additional Information

N/A

7. Conflict of Interest Declarations

CADTH

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   <Enter Response Here>

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   <Enter Response Here>

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

New or Updated Declaration for Clinician 1	
Name	*Dr. Geoffrey Liu*
Position	*Medical Oncologist*
Date	*July 26, 2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pfizer	☐	☒	☐	☐
Novartis	☒	☐	☐	☐
Anheart	☒	☐	☐	☐
Takeda	X			
AstraZeneca		X		
Jazz	X			

Roche	X			
Johnson & Johnson	X			
EMD Seron	X			
Merck	X			

Declaration for Clinician 2

Name: Quincy Chu
Position: Medical Oncologist, Cross Cancer Institute, Edmonton, AB
Date: *July 26, 2024*

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie	X			
Amgen	X			
AnHeart	X			
Astellas	X			
Astra Zeneca		X		
Boehringer Ingelheim	X			
BMS	X			
Daichii Sankyo	X			
Eli Lilly	X			
GSK	X			
Janssen	X			
Meck	X			
Novartis	X			
Ocellaris	X			
Pfizer	X			
Roche		X		
Takeda	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Mahmoud Abdelsalam
Position: Medical Oncologist, Horizon Health Network
Date: *July 26, 2024*

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 3

Company	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BMS	Advisory role, Honoraria and travel grants	☐	☒	☐	☐

* Place an X in the appropriate dollar range cells for each company.

New or Updated Declaration for Clinician 4	
Name	Michela Febbraro
Position	Medical Oncologist, Algoma District Cancer Program
Date	*July 26, 2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca	☐	☒	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Biniam Kidane*
Position	*Associate Professor, Dept of Surgery, University of Manitoba*
Date	*July 26, 2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca	☐	☐	☒	☐
Merck	☒	☐	☐	☐
Roche	☐	☒	☐	☐
Bristol Myers Squibb	☒	☐	☐	☐
Medtronic	☒	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	*Dr. Alison Wallace*
Position	*Assistant Professor Department of Surgery, Division of Thoracic Surgery and Department of Pathology, Dalhousie University. Thoracic Surgeon QEII HSC, Halifax. NS.*
Date	*July 26, 2024*
-☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Confli-ct of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck	☒	☐	☐	☐
Bristol Myers Squibb	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐

Declaration for Clinician 7

Name: NATHALIE DAABOUL
Position: Hematologist-Oncologist, Université de Sherbrooke
Date: *July 26, 2024*

x I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Amgen	x			
AstraZeneca	x			
BMS	x			
Eisai	x			
Jazz	x			
Merck	x			
Novartis	x			
Pfizer	x			
Sanofi	x			
Takeda	x			
Taiho	x			

* Place an X in the appropriate dollar range cells for each company.

New or Updated Declaration for Clinician 8	
Name	*Ronald Burkes*
Position	*Medical Oncologist Mount Sinai Hospital*
Date	*July 26, 2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AZ / Pfizer	☒	☐	☐	☐
Merck / Taiho / Takeda / Amgen	☒	☐	☐	☐

Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 9

Name: Silvana Spadafora
Position: Medical Oncologist, Algoma District Cancer Program
Date: *July 26, 2024*

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astra Zeneca		X		
Merck		X		
Novartis		X		

* Place an X in the appropriate dollar range cells for each company.

Conflict of Interest Declaration for Clinician 10

Name: Dr. Kevin Jao
Position: Medical Oncologist, Hôpital Sacré-Cœur, Montreal
Date: *July 26, 2024*

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Bristol-Myers Squibb	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bristol-Myers Squibb	Advisory Role	☒	☐	☐	☐

Declaration for Clinician 11

Name: Dr. Rosalyn Juergens
Position: Chair, LCC Medical Advisory Committee; Medical Oncologist, Juravinski Cancer Center
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bristol Myers Squibb	x			
Astra Zeneca		x		
Merck Sharp and Dohme	x			
Roche	x			

Declaration for Clinician 12

Name: Dr. Paul Wheatley-Price
Position: Medical Oncologist, The Ottawa Hospital. Associate Professor, Department of Medicine, University of Ottawa
Date July 26, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sanofi	X			
Astra Zeneca	X			
Jazz Pharmaceuticals	X			
Amgen	X			
Janssen	X			
Novartis	X			
Merck	X			
BMS	X			
Roche	X			
EMD Serono	X			
Pfizer	X			
Bayer	X			
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

New or Updated Declaration for Clinician 13	
Name	*Vishal Navani*
Position	*Medical Oncologist, University of Calgary*
Date	July 26, 2024
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Janssen	☐	☐	☒	☐
Consulting - Novotech Pty, Pfizer, Sanofi, Astra Zeneca, EMD Serono, Oncology Education, Sanofi, Janssen, Roche, MSD, Bristol Meyers Squibb, Takeda	☐	☐	☒	☐
Speaking – Ipsen, Astra Zeneca, MSD, Bristol Meyers Squibb	☐	☐	☒	☐
Research – Astra Zeneca (Inst), Janssen (Inst)			X	
Travel – EMD Serono, Pfizer, Sanofi			X	

Declaration for Clinician 14

Name: Dr Randeep Sangha
Position: Medical Oncologist, Cross Cancer Institute
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 9: Conflict of Interest Declaration for Clinician 14

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 15

Name: Dr Sunil Yadav
Position: Medical Oncologist, Saskatoon Cancer Centre
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 12: Conflict of Interest Declaration for Clinician 15

Bristol-Myers Squibb	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	
Bristol-Myers Squibb	Advisory Board	☒	☐	☐	
Astra Zeneca	Advisory Board and Speaking	☒	☐	☐	☐
Merck	Advisory Board and Speaking	☐	☐	☒	☐
Roche	Advisory Board and Speaking	☐	☒	☐	☐
Takeda	Advisory Board and Speaking	☒	☐	☐	☐

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 16

Name: Dr. Shaqil Kassam
Position: Medical Oncologist, Southlake Regional Hospital
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 16

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Roche	x			
Merck	x			
BMS	x			
Takeda	x			
Novartis	x			
Ipsen	x			
Sanofi	x			
Pfizer	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 17

Name: Dr Nicole Bouchard
Position: Respirologist, Sherbrooke University Hospital
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 17

Company	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	Advisory Role/Conference	☒	☐	☐	☐
Bristol-Myers Squibb	Advisory Role/Research	☒	☐	☐	☐
Merck	Advisory Role /Research/Conference	☒	☐	☐	☐
Bayer	Advisory Role	☒	☐	☐	☐
Pfizer	Conference/Research	☒	☐	☐	☐
Roche	Advisory Role	☒	☐	☐	☐

Declaration for Clinician 18

Name: Dr. David Dawe
Position: Medical Oncologist, CancerCare Manitoba
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 8: Conflict of Interest Declaration for Clinician 18

Name of Organization	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
AstraZeneca	Advisory boards	☒	☐	☐	☐
Merck	Advisory Boards	☒	☐	☐	☐
AstraZeneca	Research Grant	☐	☐	☒	☐
Boehringer-Ingelheim	Honoraria	☒	☐	☐	☐

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 19

Name: Stephanie Snow
Position: Professor Dalhousie University, Medical Oncologist QEII Health Sciences Centre, Halifax, NS
Date: July 26, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 19

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca			X	
Astellas	X			
BMS		X		
Taiho	X			
Roche			X	
Merck		X		
GSK	X			
Janssen	X			
Pfizer	X			
Sanofi	X			
Knight	X			

Lilly	X			
Takeda	X			

Declaration for Clinician 20

Name: Dr. Parneet Cheema
Position: Medical Director of Cancer Care, William Osler Health System
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 20

Company	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bristol Myers Squibb	Advisory board/Honoraria	☒	☐	☐	☐
Merck	Advisory board/Honoraria	☒	☐	☐	☐
Astrazeneca	Advisory board/Honoraria	☒	☐	☐	☐
Roche	Advisory board/Honoraria	☒	☐	☐	☐
Novartis	Advisory board/Honoraria	☒	☐	☐	☐
		☐	☐	☐	☐

Declaration for Clinician 21

Name: Dr Jeffrey Rothenstein
Position: Medical Oncologist, Lakeridge Health
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 21

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Roche	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 22

Name: Callista Phillips
Position: Medical Oncologist and Clinical Lead, Oncology Clinic, Joseph Brant Hospital
Date: July 26, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 22

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X			
Bayer	X			
Roche	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 23

Name: Dr. Cheryl Ho
Position: Medical Oncologist, BC Cancer
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 23

Company	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	Advisory role	☒	☐	☐	☐
Roche	Advisory role, travel, research grants	☐	☐	☐	☒

Declaration for Clinician 24

Name: Dr. Stephen Lam
Position: Medical Oncologist, BC Cancer
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 24

No COI to declare

Declaration for Clinician 25

Name: Susanna Cheng
Position: Medical Oncologist, Sunnybrook Hospital; Associate Professor, University of Toronto
Date: July 26, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 25

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Merck	X			
BMS	X			
AstraZeneca	X			
Janssen	X			
Roche	X			
Amgen	X			

Declaration for Clinician 26

Name: Dr. Mark Vincent
Position: Medical Oncologist, London Regional Cancer Centre
Date: July 26, 2024
☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 26

Company	Nature or description of activities or interests	Check Appropriate Dollar Range			
		$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
			☐	☐	☐

Declaration for Clinician 27

Name: Dorothy Lo
Position: Medical oncologist
Date: July 26, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 27

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	X			
BMS	x			
Sanofi	x			
Novartis	x			
astellas		x		
Eisai	x			
Astra Zeneca	x			

Declaration for Clinician 28

Name: Dr. Natasha Leighl
Position: Medical Oncologist, Princess Margaret Cancer Center
Date: July 26, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 28

Company	**Nature or description of activities or interests**	**Check Appropriate Dollar Range**			
		$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
		☐	☐	☐	☐
		☐	☐	☐	☐

Declaration for Clinician 29

New or Updated Declaration for Clinician 29	
Name	*David J. Stewart*
Position	Professor of Medicine, University of Ottawa and The Ottawa Hospital
Date	*July 26, 2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.	
Company	**Check Appropriate Dollar Range**

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck Canada 2021, 2023	☒	☐	☐	☐
AstraZeneca Canada 2021, 2023	☒	☐	☐	☐
Abbvie Canada 2021, 2022, 2023	☒	☐	☐	☐
Canadian Agency for Drugs and Technologies in Health 2021	x			
Amgen Canada 2022	x			

Declaration for Clinician 30

Name: Lacey Pitre
Position: Medical Oncologist, Systemic Therapy Lead - Northeast Region, CCO/Ontario Health
Date: July 26, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 30

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis Ribbon Program 2018	X			
MERCK Oncology Speaker's honoraria 2017	X			
EMD Serono Speaker's honoraria 2018	X			
MERCK Oncology Speaker's honoraria 2021	X			
Astra Zeneca Speaker's honoraria 2021	X			
Astra Zeneca Speaker's honoraria 2022	X			
Fuse Health Advisory Board 2017	X			
Novartis Advisory Board 2018	X			
Astella's Oncology Advisory Board 2016	X			

Declaration for Clinician 31

Name: Dr. Wojciech Morczycki
Position: Medical Oncologist, QEII Health Sciences Centre
Date: July 26, 2024
☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 31

Company	**Check Appropriate Dollar Range**

	Nature or description of activities or interests	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
			☐	☐	☐

Declaration for Clinician 32

New or Updated Declaration for Clinician 32	
Name	*Christian Finley*
Position	*Thoracic Surgeon, St. Joseph's Healthcare Hamilton*
Date	*July 26, 2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astrazeneca	☐	☒	☐	☐
Roche	☐	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 33

New or Updated Declaration for Clinician 33	
Name	*Shantanu Banerji*
Position	*Medical Oncologist, Manitoba CancerCare*
Date	*July 26, 2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astrazeneca	☐	☒	☐	☐
Roche	☐	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 34

New or Updated Declaration for Clinician 34	
Name	Sara Taylor
Position	*Medical Oncologist, BC Cancer*
Date	*July 26,2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astrazeneca	☐	☒	☐	☐
Roche	☐	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 35

New or Updated Declaration for Clinician 35	
Name	Nicholas Meti
Position	*Medical Oncologist, St Mary's Hospital Centre*
Date	*July 26,2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astrazeneca	☐	☒	☐	☐
Roche	☐	☒	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0369-000
Generic Drug Name (Brand Name): pembrolizumab
Indication: Keytruda as monotherapy for the adjuvant treatment of adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC, and with PD-L1 tumor proportion score (TPS) < 50% who have undergone complete resection and platinum-based chemotherapy.
Name of Clinician Group: OH (CCO) Lung Cancer Drug Advisory Committee
Author of Submission: Dr. Donna Maziak

1. About Your Clinician Group

OH(CCO)'s Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered by a videocall and finalized through email.

3. Current Treatments and Treatment Goals

The current treatment in patients with stage IB (T2a >/- 4 cm), II, or IIIA NSCLC (PDL1 <50% and no EGFR/ALK alterations) who have undergone complete surgical resection upfront and platinum-based chemotherapy (up to 4 cycles) includes active surveillance. Only patients with PDL1 high (>50%) have the option of adjuvant Atezolizumab x 1 year.

The goals are to improve survival and delay recurrence. These patients are treated with curative intent, although there are significant risks of recurrence.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Despite adjuvant chemotherapy in this group, 50% will die. Currently, patients with PDL-1<50% have no access to adjuvant immunotherapy.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

This is given after adjuvant chemotherapy for this patient population. There is no other therapy available after chemotherapy. There are competing treatment strategies for this population of patients. These include neoadjuvant or perioperative chemoimmunotherapy, adjuvant chemotherapy, and adjuvant immunotherapy. Currently, patients who are PD-L1 <50% who do not receive neoadjuvant

chemoimmunotherapy are not eligible for adjuvant immunotherapy. The request for reimbursement for pembrolizumab would fill a gap in existing care for these patients.

In the trial, patients were permitted to receive pembrolizumab even without chemotherapy and this should be considered for patients that are chemo-ineligible.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients have undergone complete surgical resection, no contraindications to immunotherapy, meet stage PDL-1 criteria.

Patients least suitable for treatment are those who are unable to tolerate or receive immunotherapy safely.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

It is not possible in the adjuvant setting to tell if a patient is responding, or not. It is only possible to tell when a treatment is not working when there is recurrence or death.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Disease recurrence, severe adverse events, or completion of therapy.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Patients should be treated in an outpatient setting under the supervision of a medical oncologist, or pulmonologist experienced in the management of thoracic malignancies.

6. Additional Information

It is unclear why this drug is limited to PDL-1 <50% when the data supports the use of pembrolizumab in all levels of PDL-1 scores.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH (CCO) provided a secretariat function to the group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Donna Maziak
Position: Lead, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 18-06-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Andrew Robinson
Position: Member, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 18-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Stephanie Brule
Position: Member, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 18-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Merck	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Peter Ellis
Position: Member, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 12-07-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Merck	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Natash Leighl

Position: Member, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 18-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Mihaela Mates
Position: Member, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 15-07-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.