Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

pembrolizumab (Keytruda)

(Merck Canada Inc.)

Indication: Keytruda (pembrolizumab) is indicated for the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum containing chemotherapy as neoadjuvant treatment, and the continued as monotherapy as adjuvant treatment

September 27, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC 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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CDA-AMC does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Pembrolizumab

Indication: Keytruda (pembrolizumab) is indicated for the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum containing chemotherapy as neoadjuvant treatment, and the continued as monotherapy as adjuvant treatment.

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

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

1. About Your Patient Group

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

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/

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 Lung Health Foundation (previously named the Ontario Lung Association) is registered with the CADTH and pCODR. The Lung Health Foundation (Ontario Lung Association) 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. The Foundation provides programs and services to patients and health-care providers, invests in lung research and advocates for improved policies in lung health. It is run by a board of directors and has approximately 46 employees, supported by thousands of dedicated volunteers. www.lunghealth.ca

2. Information Gathering

Together, the Canadian Cancer Survivor Network (CCSN), Lung Cancer Canada (LCC), and Lung Health Foundation (LHF) all worked to produce a survey to be circulated amongst all three of their networks. The survey was disseminated through the three organizations' social media

platforms, as well as CCSN's monthly newsletter. The survey was conducted from August 1, 2024, to September 16, 2024, to obtain responses. All respondents to the survey are from Canada. From looking at the demographic data, it was identified that there was one (1) caregiver and three (3) patients who had responded to having experience with this indication. All four (4) respondents to the survey have had experience with pembrolizumab.

3. Disease Experience

Respondents were asked to identify what type of lung cancer that they had been diagnosed with. All respondents answered with the following:

- Small Cell Lung Cancer (SCLC): 1
- Non-Small Cell Lung Cancer (NSCLC): 3

Respondents were asked to identify the stage of their lung cancer. All respondents answered with the following levels of disease:

- Stage 1b: 1
- Stage 3c: 1
- Stage 4, Metastatic: 2

Current treatments that were identified include:

- Radiation: 1
- Surgical Therapy: 1
- Immunotherapy: 1
- Clinical Trial: 1

Respondents were asked to identify the symptoms or problems that they experience with lung cancer that affect their quality of life. The following issues were highlighted by the individuals' responses:

- Cough: 1
- Shortness of breath: 2
- Chest tightness: 1
- Wheezing: 1
- Fatigue: 2
- Nausea: 1

When asked about the activities that they or the person that they care for are unable to do on a regular basis due to their lung disease or condition, the respondents highlighted these key areas:

- Work: 1
- Leisure activities and hobbies: 2
- Housework: 1
- Sports and physical activities: 3
- Travel: 1

When asked about the negative impacts that they or their loved one has experienced due to the lung disease or condition, the respondents answered with the following examples:

- Waking up in the night or early morning because of breathing problems: 1
- Being short-tempered, impatient with others:1
- Being unable to do daily activities because of shortness of breath: 1
- Being unable to do daily activities because of fatigue: 1
- Managing symptoms: 1
- Emotional well-being: 1
- Family relationships: 1
- Financial cost burden: 1

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

- Trouble breathing: 2
- Wheezing: 1
- Fatigue: 1
- Trouble swallowing: 1
- Loss of quality of life: 1

Respondents were asked how they or their loved ones currently cope with their condition. Individuals gave these responses:

- Seek support from friends, family and/or peers with lung disease or conditions: 1
- Problem solve different approaches to engaging in activities of daily living: 2
- Avoid discussing or thinking about my situation: 1
- Focus on distractions: 1
- Other: 1 (Had a stent put in)

4. Experiences With Currently Available Treatments

Respondents were asked to list the medications that they are currently taking. Individuals shared the following treatments:

- “Pemetrex, carboplatin, Keytruda in 2020. Then clinical trial drug velretinib March 2021 to 2024. Now on antibody drug by AbbVie telisotuzumab vedotin (Teliso-V) given by infusion”
- “Carbo and pemetrexed. This chemo combo was highly effective and well tolerated.”
- “Prednisone (ongoing), Dexamethasone (2023), Apixaban (ongoing).”

Respondents were asked to identify the benefits of the medications that they had listed. These benefits included:

- Reduced fatigue: 1
- Reduced cough: 2
- Reduced shortness of breath: 1

- Improved appetite/weight gain: 1
- Increased energy: 1
- Increased ability to fight infections: 1
- Reduced pain: 2
- Reduced nausea: 1
- Increased mood: 1
- Increased participation in daily activities: 1
- Ability to exercise: 1
- Other: 2 (1 Dexamethasone prior to brain metastasis treatment. Prednisone after radiation. Apixaban for blood clots. 1 It decreased the nodes that were pressing on his esophagus preventing him from passing food.)

When asked about the side effects that were experienced while taking these medications, the respondents shared these details:

- No side effects: 1
- Fatigue: 1
- Low energy: 1
- Other: 2 (1 Increased edema of the eyes and feet and nails falling out, 1 Weight gain from prednisone.)

Respondents were asked if they have had issues accessing their current therapies. They gave these responses:

- Limited availability in my community: 1
- Travel costs associated with accessing therapy/treatment: 1
- I haven't had any issues accessing therapy: 2
- Other: 1 (There are no approved targeted therapies available to me in Canada. My oncologist went to the pharmaceutical company in US for antibody treatment..for free!! CADTH have denied tepotinib and capmatanib for use in Canada..Quebec approved capmatanib recently.. shameful it's only available in Quebec!!!)

When asked if they were talking to a friend about how they were managing while taking their current treatments and what would they tell them, the respondents had these comments to share:

- "I'm managing very well!! Thankful for my oncologist securing me antibody treatment from the US for free.. I feel Health Canada is too far behind other countries when it comes to approving targeted therapies!! Especially when these targeted therapies are available in the US for multiple years!!"
- "Symptoms were well managed. my father had no side effects from the chemo."
- "I have had positive results (reduction in cancer) so all side effects have been well worth that."

When asked if any of their needs in their current or previously administered treatments were not being met, the respondents shared these insights:

- “Edema is an issue.”
- “Being able to go back to previous treatments that worked before progression occurred.”
- “All good at the moment.”

5. Improved Outcomes

When asked about the considerations that they would make when choosing a new medication, the respondents shared these points:

- Reduced cost: 3
- Reduction in symptoms: 1
- Improved symptom management: 2
- Improved quality of life: 3
- Improved energy: 1
- Other: 1 (Manages cancer even if it cannot be cured, keeping it stable.)

6. Experience With Drug Under Review

Pembrolizumab has been a standard of care treatment within the lung cancer treatment paradigm for several years, and having its indications expanded for early-stage II-IIIB NSCLC patients is very widely welcome. The innovation of having pembrolizumab available as a peri-adjuvant treatment, first in combination with chemotherapy, then as adjuvant monotherapy is a novel indication that has many benefits for patients, including being able to manage disease at numerous points during their course of treatment. Patients who are lucky to have their disease diagnosed at early stages where it is operable generally have very full lives, many with children and busy careers, so having a good quality of life is extremely important to them. As highlighted through the survey results, the treatment was successful in managing their disease, and the KeyNote 671 clinical trial results also highlight the incredibly drastic improvement in EFS at 47.2 months vs 18.3 months in comparison to standard-of-care chemotherapy. The extra 29 months that patients on the pembrolizumab arm gained is incredibly valuable to them, being able to spend quality time with loved ones, go back to work and hobbies, and live full lives.

The adverse events experienced while taking pembrolizumab reported by the respondents are as follows:

- Fatigue: 2
- Infection: 1
- Diarrhea: 1
- Changes in appearance (including hair loss): 1
- Other: 2 (1 Colitis but it occurred towards the end when progression happened, 1 Hypothyroidism, rheumatoid arthritis)

When asked if the adverse effects were manageable, one respondent said no and three said yes. One of the respondents added that they were able to manage their symptoms with prescription medications.

When asked if they have had any issues accessing pembrolizumab, the respondents highlighted three key points:

- Limited availability in my community: 1
- I did not have any/enough information about clinical trials or how to access them: 1
- I haven't had any issues accessing therapy: 1

Respondents were asked to rate pembrolizumab on a scale of 1-10. The ratings were as follows:

- 1 - I strongly prefer other therapies to Pembrolizumab (Keytruda) / Other treatments were so much better than Pembrolizumab (Keytruda)
- 4
- 6
- 9 - I strongly prefer Pembrolizumab (Keytruda) over other therapies / Pembrolizumab (Keytruda) was so much better than others

When asked if they were talking to a friend about how they were managing while taking pembrolizumab and what would they tell them, the respondents had these comments to share:

- "I managed okay but keytruda didn't work for me because my PDL-1 is too low!"
- "Even though my father developed colitis at 21 months of use, keytruda saved his life. And he was able to go to work and do all of the things he loved."
- "This is the only ongoing treatment that I have received. It seems to be working well with fairly manageable side effects."

7. Companion Diagnostic Test

N/A

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

CCSN, LCC, and LHF are aware of the limitations of this submission given the small number of respondents. Even with a small number of responses, it is shown that there have been benefits to the respondents with the experience with pembrolizumab. For someone to be able to receive the treatment and then be able to return to work is an accomplishment that not only supports the patient but their family and community as well. I think it is important to note that this indication's approach can provide an option for clinicians and patients to work together to decide what works best for the patient based on their individual case.

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 a 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 - Lung Cancer Canada (2023)			X	
Merck - Lung Cancer Canada (2024)				X

Merck - Lung Health Foundation (2023)			X	
Merck - Lung Health Foundation (2024)				X
Merck - CCSN (2023)				X
Merck - CCSN (2024)			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: Lindsay Timm
Position: Community Engagement Manager
Patient Group: Canadian Cancer Survivor Network
Date: **Sep 26, 2024**

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0385-000
Generic Drug Name (Brand Name): pembrolizumab (Keytruda)
Indication: indicated for the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment.
Name of Clinician Group: OH (CCO) Lung Cancer Drug Advisory Committee
Author of Submission: Dr. Donna Maziak, Dr. Peter Ellis

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 email.

3. Current Treatments and Treatment Goals

Current treatment options include neoadjuvant platinum-based chemotherapy plus nivolumab for patients with resectable stage II and III NSCLC (8th ed TNM). These patients have no access to adjuvant immunotherapy.

Patients with resected stage II/III NSCLC and high PD-L1 expression, who did not receive neoadjuvant chemoimmunotherapy are eligible to receive adjuvant chemotherapy followed by one year of adjuvant atezolizumab.

The treatment goal is curative and to improve overall survival.

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.

There is currently no access to immunotherapy in the adjuvant setting in patients who received neoadjuvant chemoimmunotherapy. Neoadjuvant chemoimmunotherapy and neoadjuvant plus adjuvant (perioperative) approaches have both demonstrated improvements in event free survival. There are no data comparing neoadjuvant IO strategies to perioperative IO strategies. Therefore, there is uncertainty whether there is additional survival benefit from the addition of adjuvant IO to neoadjuvant chemo immunotherapy. However, perioperative immunotherapy could offer patients improved therapy.

Currently, immunotherapy in the adjuvant setting is only available to those with PDL-1>50%.

5. Place in Therapy

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

Perioperative chemoimmunotherapy with pembrolizumab would represent an alternative treatment approach to neoadjuvant chemoimmunotherapy with nivolumab.

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 with resectable stage II/III disease (8th edition TNM) and no contraindication to immunotherapy. As well as patients with no EGFR or ALK mutations.

There is no clear indication as to who would be more suitable to this treatment than 3 cycles of neoadjuvant immunotherapy.

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?

These are patients who have undergone curative resection for stage II/III (8th edition TNM) NSCLC. The standard is to have a CT chest scan performed within 2 months prior to surgery. Standard of care follow up post surgical resection would be CT imaging 3-6 months post surgery, then every 6 months for 2 years, then yearly thereafter. For patients receiving adjuvant immunotherapy, patients should be imaged every 3-6 months in the initial year on therapy.

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

Severe adverse events, disease recurrence 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

N/A

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: Dr. Donna Maziak
Position: Lead, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 25-08-2024

☒ **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. Peter Ellis
Position: Member, OH (CCO) Lung Cancer Drug Advisory Committee
Date: 25-08-2024

☒ 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	X			
Add company name				
Add or remove rows as required				

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

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0385-000
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Indication: Keytruda (pembrolizumab) is indicated for the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment. Staging is from AJCC Eighth edition
Name of Clinician Group: Lung Cancer Canada – Medical Advisory Committee
Author of Submission: Dr. Geoffrey Liu (lead), Dr. Silvana Spadafora, Dr.David Stewart, Dr. Biniam Kidane, Dr. Ron Burkes, Dr. Barbara Melosky, Dr. Vishal Navani, Dr. Rosalyn Juergens, Dr. Shaqil Kassam, Dr. Stephanie Snow, Dr. Christian Finley, Dr. Kevin Jao, Dr. Michela Febbraro, Dr. Alison Wallace, Dr. Nicole Bouchard, Dr. Lacey Pitre, Dr. Jeffrey Rothenstein, Dr. Nathalie Daaboul, Dr. Randeep Sangha, Dr. Paul Wheatley-Price, Dr. Quincy Chu, Dr. Catherine Labbé, Dr. Sunil Yadav

1. About Your Clinician Group

Lung Cancer Canada (LCC) is a national charity with the purpose of increasing awareness about lung cancer, providing support and education to lung cancer patients and their families, to support research and to advocate for access to the best care for all lung cancer patients in all provinces and territories.

Through the LCC Medical Advisory Committee (MAC), we provide clinician input for submissions of new lung cancer drugs to the HTA process for many years. The LCC MAC consists of clinicians and key opinion leaders in the field of lung cancer across the country.

www.lungcancercanada.ca

2. Information Gathering

The information provided in this submission is from publicly available sources, primarily published manuscripts and conference presentations, together with clinical experience of members from the MAC. This submission is entirely independent of the manufacturer (Merck).

3. Current Treatments and Treatment Goals

According to the Canadian Cancer Society annual report, lung cancer is the most commonly diagnosed cancer and the most common cause of cancer death in Canada. In 2024, 32,100 Canadians will be diagnosed and 20,700 will die from lung cancer. About 80-85% are non-small cell lung cancer (NSCLC, with only 20-30% are deemed to have early-stage cancers, namely stage I-

IIIA, which are potentially resectable. But only a portion of these patients will be considered as operable due to comorbidity, lung function and patient wishes.

The goals of any treatment in the early-stage resectable patients are:

1. The ultimate goal of all neoadjuvant and adjuvant therapy is an increase in chance of cure, as measured by overall survival (OS) or OS rates, post resection: West et al. also reported the median OS and 5-year OS for the entire population being 76.6 months and 57.5%, respectively. The median OS and 5-years OS by stage were correspondingly 97.9 months and 66% in stage IB, 75.5 months and 55.6% in stage II, and 66.2 months and 54% in stage IIIA.

2. A secondary critical goal is the reduction of the chance of recurrence measured by disease-free survival (DFS): with surgery alone, the 5-year DFS for stages IB, II and III according to AJCC 7th and 8th edition were 62%, 50% and 34%, respectively. Due to changes in staging categorization for the 8th edition, the 8th edition and new 9th edition staging would have a 5-year DFS of 30-60% for stages II-IIIB (T3-4N2), the staging categories included in the current proposed indication. Almost all the patients who have disease recurrence will be deemed incurable. Thus, prevention of recurrence of NSCLC is key to improve their overall survival [Rajaram et al. Thoracic Oncology 2024;165(5):1260-1370]. West et al. [Lung Cancer 2023;24(3):260-268] reported the use of adjuvant chemotherapy and outcome in this patient population using the SEER database. Forty-one percent of patients received adjuvant chemotherapy among those patients with stage IB (>4cm)-IIIA by AJCC 7th edition and specifically, only 21.6% in stage IB, 42.6% in stage II and 53% in stage III. The median DFS in the overall population was a sobering 24.8 months and the 5-year DFS rate was 29.3%. The corresponding median DFS and 5-year DFS for stage IB, stage II and stage IIIA were 40.9 months and 38.9%, 24.4 months and 29.1% and 13.8 months and 21.5%, respectively. DFS data for the 8th edition is similar for Stages II-IIIB (T3-4N2)[Taber et al, Innov Surg Sci. 2020 Aug 12;5(1-2):1-9.] and DFS data for the new 9th edition is still forthcoming, but not expected to be significantly better, as the 9th edition database was in the era of neoaduvant or adjuvant chemotherapy but without immunotherapy.

3. Surgery is still considered as the most important treatment in early-stage NSCLC. Neoadjuvant and perioperative treatments should enhance the chance of cure and DFS, while not increasing surgical complication rates, or reduce surgical resectability.

4. Toxicity and quality-of-life: toxicities should be tolerable while quality of life should be reasonable for patients, both short and long term.

Therefore, with the current OS and DFS data, there is significant room for further improvement.

Recently, with the adaptation of precision medicine, the current Canadian treatment algorithm for patients with resectable Stage IB-IIIA NSCLC, the standard of care will be determined by the presence or absence of actionable mutation, PDL-1 status and stage.

1. For those with EGFR mutation, the standard of care is based on the results of ADAURA [4, 5] demonstrating 3 years of adjuvant osimertinib statistically and clinically improvement the median DFS (NR versus 28.1 months; HR= 0.20, p<0.001) and median OS (HR=0.49, p=0.001) over placebo, regardless of stage and prior cisplatin-based adjuvant chemotherapy. The 2-year DFS in those who had received osimertinib and placebo were 89%, 87%, 91%, 88% and 53%, 73%, 56% and 32% for all patients, stage IB, stage II and Stage IIIA patients, respectively. The 5-year OS for osimertinib-arm and placebo were 88%, 94%, 85%, 85% and 78%, 88%, 78%, 67% for all patients, stage IB, stage II and stage IIIA patients, respectively. The treatment will include:

a. An anatomical resection such as a lobectomy, bi-lobectomy, and pneumonectomy, and systemic therapy according to stage of disease:

i. For those who have stage IB (3-4 cm) by AJCC 7th edition, patients will receive 3 years of adjuvant Osimertinib.

ii. For those who have stage IIA (4-5 cm) by AJCC 7th edition, patients may receive 4 cycles of adjuvant cisplatin-based chemotherapy and will have 3 years of adjuvant Osimertinib.

iii. For those who have Stage IIB-IIIA by AJCC 7th edition, patients will receive 4 cycles of adjuvant cisplatin-based chemotherapy and 3 years of adjuvant Osimertinib.

2. For those with ALK translocation, the standard of care will soon be based on the results of ALINA, demonstrating a strongly statistically and clinically important improvement in median DFS (NR versus 44.4 months; HR=0.24, p<0.0001) over 4 cycles of cisplatin-based adjuvant chemotherapy, regardless of stage. The corresponding 2-year DFS for all patients, stage IB, stage II and stage IIIA for alectinib-treated and chemotherapy-treated patients were 93.6% ,92.3%, 95.6%, 92.7% and 63.7%, 71.6%, 66.3%, 60.7%, respectively. There have not been enough events for the overall survival analysis. The treatment will include:

a. An anatomical resection such as lobectomy, bi-lobectomy, and pneumonectomy and systemic therapy of alectinib for 2 years in those with stage IB (≥4 cm)-Stage IIIA by AJCC 7th edition. The value of 4 cycles of adjuvant chemotherapy prior to alectinib has not been established.

3. For those with no EGFR and ALK gene aberration, the standard of care includes

a. An anatomical resection such as a lobectomy, bi-lobectomy, and pneumonectomy and

ii. For those with Stage IB > 4 cm by AJCC 6th edition, adjuvant platinum-based chemotherapy can be offered with an absolute improvement of 5-year OS rate of 5% (HR=0.92). Note that in the 8th and 9th edition of staging, many of these tumours are now considered Stage IIA,

iii. For those with stage IIA-IIIA by AJCC 6th edition, adjuvant platinum-based chemotherapy will be offered with an absolute improvement of 5-year OS rate of 10% (HR=0.83). Note that in the 8th and 9th edition of staging, many of these tumours are now considered Stage IIA-IIIB (T3-4 N2).

and

b. some form of neoadjuvant or adjuvant systemic therapy.

In terms of adjuvant therapy, there are two options, based on PDL-1 status.

1. IMPOWER 010, there was a statistically and clinically important improvement in the median DFS for stage II-IIIA patients by AJCC 7th edition with PDL-1 ≥1% and any PDL-1 after adjuvant atezolizumab (NR versus 35.3 months; HR=0.66, p=0.0039 and 42.3 months versus 35.3 months; HR=0.79, p=0.02, respectively) across all major subgroups. Specifically, the HR were 0.71 and 0.68, 0.77 and 0.88, 0.62 and 0.81 for those with stage IIA, IIB and IIIA disease with PDL-1 ≥1 and any PDL-1, respectively. The OS is still immature with a HR of 0.77 and 0.99 for those of stage II-IIIA and PDL-1 ≥ 1% and any PDL-1, respectively, favouring atezolizumab. Currently, only those patients with stage II-IIIA by AJCC 7th edition and PDL-1 ≥ 50% who have received at least 1 cycle of cisplatin-based adjuvant chemotherapy, based on subgroup analysis, the median DFS was improved with HR=0.43 (NR versus 35.7%), atezolizumab at 1200 mg every 3 weeks for 17 cycles after adjuvant chemotherapy is considered the standard of care.

2. KEYNOTE091/PEARL, stage IB >4 cm to stage IIIA by AJCC 7th edition patients of any PDL-1 level treatment with pembrolizumab at 200 mg every 3 weeks for 1 year had improvement of median DFS (53.6 months versus 42 months; HR 0.74, p=0.0014) while for those with PDL-1 ≥50%, the median DFS was not reached in either arm with HR 0.82 (p=0.14) and the overall survival for all patients is immature with a HR 0.87 (p=0.17). While there was no benefit of pembrolizumab in those patients received no prior adjuvant chemotherapy with a HR of 1.25, benefit of pembrolizumab was observed in those who had prior adjuvant chemotherapy with HR 0.73. The benefit was observed regardless of stage (HR=0.76 in stage IB, HR=0.70 in stage II and HR=0.92 in stage III). Thus, current Health Canada indication and available Patient Access Program allows only stage IB-IIIA patients who have received at least 1 cycle of cisplatin-based adjuvant chemotherapy at any PDL-1 level to receive 1 year of pembrolizumab at 200 mg every 3 weeks. Reimbursement is currently being considered in patients with stage IB >4cm-stage IIIA and PDL-1 <50% in resected stage IB > 4cm to stage IIIA by AJCC 7th edition who have at least 1 cycle of adjuvant cisplatin-based chemotherapy.

In terms of neoadjuvant therapy, the rationale for neoadjuvant immunotherapy was based on that the presence of tumour during neoadjuvant therapy, there may be a stronger antitumour T-cell response due to increased tumour burden and antigen presentation [Uprety D et al. J Thorac oncol 2020;15:1281-97 and Liu et al. Cancer Discov 2016;6:1382-99; Cascone Cancer Res 2018;78:1719]. The addition of chemotherapy to immunotherapy, may further stimulate the immune system by inducing immunogenic tumour cell death and increase antigen presentation to dendritic cells, directly stimulating T-cell response and inhibiting immunosuppressive mechanisms [Chaft J et al. Nat Rev Clinic Oncol 2021;18:547-57; bracci et al. Cell Death Differ 2014; 21:15-25; Wang Z et al.

Oncoimmunology 2017;6:e1331807]. Thus, neoadjuvant chemotherapy and PD(L)1 inhibitors will improve the outcome of early-stage NSCLC.

One alternative is neoadjuvant platinum-based chemotherapy and nivolumab at 360 mg every 3 weeks in resectable stage IB (>4cm)-IIIA NSCLC by AJCC 7th edition of 3 cycles, followed by anatomical resection with an optional cycle of adjuvant platinum-based chemotherapy based on CHECKMATE 816 study. The initial results showed a statistically significant improvement in the pathological complete response (pCR) of 24% versus 2.2% (OR=13.94, p<0.0001) and median event-free survival (EFS) at 31.6 months as compared to 20.8 months (HR=0.63, p=0.0052) and all subgroups including stage, PDL-1 level, and histology benefited with the combination. Specifically, there was an improvement of median EFS in stage IB-II (NR versus NR; HR=0.87) and stage IIIA (32 months versus 16 months; HR=0.54). The overall survival was still immature and there was an improvement for the combination with HR=0.57 (p=0.0079), though not statistically significant yet. In 2024, the 4-year follow-up data continued to show an improvement of median EFS (43.8 months versus 18.4 months, HR=0.66) with 4-year EFS at 49% versus 38% and a trend towards improvement in median OS (HR=0.71, p=0.0451) and a 4-years OS of 71% versus 58%.

At this time, it is still unclear if adjuvant chemotherapy, followed by adjuvant immunotherapy or neoadjuvant chemotherapy and immunotherapy or perioperative chemotherapy and immunotherapy is superior. This will be answered in ongoing and future clinical trials. A peri-operative or neoadjuvant approach involving chemo-immunotherapy with a statistically significant OS benefit when compared to neoadjuvant/perioperative chemotherapy alone would achieve a current unmet need.

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

As stated above, there is no direct comparison in DFS/EFS of adjuvant chemotherapy followed by immunotherapy, neoadjuvant chemotherapy and immunotherapy and perioperative chemotherapy and immunotherapy, followed by immunotherapy.

Related to this submission, the most appropriate comparator will be neoadjuvant chemotherapy and nivolumab as per CHECKMATE816 as both studies included similar early-staged NSCLC patients as compared to the patients enrolled in IMPOWER 010 and KEYNOTE091/PEARL trials. The most significant treatment gaps are the role of adjuvant immunotherapy after neoadjuvant therapy and if there is a role who are the patients to get the adjuvant immunotherapy after initial neoadjuvant chemotherapy and immunotherapy. The gap in knowledge is especially clinically relevant in those with no pathological complete response (pCR). It is not uncommon that such cases are being brought to Multidisciplinary Rounds (MDT).

In the CHECKMATE816 trial's ASCO 2024 update, the median EFS with nivolumab plus chemotherapy (n = 179) was 43.8 months (95% CI, 30.6-not reached [NR]) vs 18.4 months (95% CI, 14.0-26.7) with chemotherapy alone (n = 179), with a hazard ratio of 0.66 (95% CI, 0.49-0.90). In the exploratory analysis of CHECKMATE 816, the median EFS in patients who did not have pCR, the outcome in patients treated with neoadjuvant chemotherapy and nivolumab was comparable to those with neoadjuvant chemotherapy (26.6 months versus 18.4 months).

Similar exploratory analysis was performed in KEYNOTE671, perioperative chemotherapy and pembrolizumab followed by pembrolizumab versus perioperative chemotherapy/placebo, followed by placebo study in this setting, those with neoadjuvant chemotherapy and pembrolizumab and adjuvant pembrolizumab and with or without pCR, may have better outcome than chemotherapy/placebo (HR=0.39 and 95% CI 0.09-1.22 and HR 0.69 and 95% CI 0.55-0.85).

Although there was a recent exploratory subgroup landmark analysis presented at ESMO 2024 (Garassino et al) of the KEYNOTE 671 trial suggested that receiving the adjuvant pembrolizumab provided additional clinical benefit post-resection, these exploratory analyses of a post-randomization factor has to be interpreted with caution and cannot determine the relative contributions of the individual treatment phases (neoadjuvant vs adjuvant), which would require a study design involving neoadjuvant chemotherapy-immunotherapy, surgery, and then randomization to receive or not receive adjuvant immunotherapy. There is such a study being developed by the European Thoracic Oncology Platform (ETOP); however, results from that trial will take upwards of a decade to generate results. In the meantime, the International Association to Study Lung Cancer (IASLC) consensus guidelines (Spicer et al, J Thor Oncol, in press) recommends individualization of choice by physicians and patients on the currently available options.

Note that CHECKMATE 816 was not powered to report OS as a primary endpoint, and one ultimate key unmet need is a demonstration of improved OS or OS benefit with any neoadjuvant/perioperative immunotherapy trial.

KEYNOTE 671 is able to meet the following treatment goals:

1. KEYNOTE 671 has not only EFS benefit but also OS benefit that is statistically and clinically significant (Spicer et al, ESMO, 2023 presentation; Spicer et al, Ann Oncol, Sept, 2024 published online). With a median time from randomization to the 10 July 2023 data cut-off of 36.6 mo (range, 18.8-62.0), the KEYNOTE 671 trial reported 254 (31.9%) deaths. OS was significantly improved in the perioperative chemo-pembrolizumab arm (HR 0.72 [95% CI 0.56-0.93]; *P* = 0.00517) when compared to the neoadjuvant chemotherapy only arm. Median OS was not reached (NR) (95% CI NR-NR) in the pembrolizumab arm vs 52.4 mo (95% CI 45.7-NR) in the neoadjuvant chemotherapy only arm; 36-mo OS rates were 71.3% vs 64.0%. EFS continued to be improved in the pembrolizumab-containing experimental arm (HR 0.59 [95% CI 0.48-0.72]; median [95% CI] 47.2 mo [32.9-NR] vs 18.3 mo [14.8-22.1] for the chemotherapy only arm; 36-mo rate, 54.3% vs 35.4%).

2. In the updated analysis presented at ESMO 2023, treatment-related adverse events (AEs) were grade ≥3 in 45.2% of pts in the pembrolizumab arm vs 37.8% in the chemotherapy arm. These AEs did lead to discontinuation of all treatment in 20.2% vs 9.3%, and led to death in 1.0% vs 0.8% (no new treatment-related deaths since the first interim analysis). Thus, the toxicity of this regimen is clinically acceptable and tolerable, despite a higher rate of discontinuation with the addition of peri-operative pembrolizumab.

3. From a quality of life (QoL) perspective, Garassino et al (ASCO Annual Conference, 2024) reported that perioperative pembrolizumab did not decrease Health related (HR) QoL compared to neoadjuvant chemotherapy in the KEYNOTE 671 trial. HRQoL decreased during the neoadjuvant phase in both arms, but returned to approximately baseline levels during the adjuvant phase in both treatment groups. Perioperative pembrolizumab meets the criteria of not detrimentally affecting QoL.

4. Perioperative pembrolizumab (with neoadjuvant chemo) did not affect the choice of surgical procedure, delay surgery, or prolong the duration of the surgical hospital stay (Nadal et al, ESTS 2024) in the KEYNOTE 671 trial. In fact when compared to neoadjuvant chemotherapy, the addition of perioperative pembrolizumab was associated with a higher percentage of R0 resections, a numerically higher percentage of lymph node downstaging, and post-surgical mortality rates. Perioperative pembrolizumab meets the criteria of not worsening surgical outcomes, given the central nature of surgery in effecting early stage lung cancer cures.

5. Place in Therapy

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

Based on the discussion in Sections 3 and 4, perioperative platinum-based chemotherapy and pembrolizumab (KEYNOTE 671) should be available as the alternative option to neoadjuvant chemotherapy and nivolumab as in CHECKMATE 816 for patients with stage IIA-IIIB (T3-4N2) tumours by AJCC 8th edition (stage IIA-IIIB T3-N2a/b if 9th edition), resectable NSCLC patients who are candidates for neoadjuvant therapy. KEYNOTE 671 does have the advantage of having not only demonstrating an EFS benefit, but also an OS benefit of 7.3% improvement at 3 years at a median of 3 years of follow-up with the addition of perioperative pembrolizumab.

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?

The NSCLC patients who are best suited for KEYNOTE 671 are those with:

1. Stage II-IIIB (the IIIB consisting of T3-4 N2 8th edition or T3-4 N2a/b 9th edition) disease per standard Canadian staging techniques, but preferably with PET/CT of the chest/abdomen +/- pelvis, brain imaging, and mediastinal sampling, where appropriate.

2. Deemed a surgical candidate with adequate lung function before surgical resection

3. Lacking any significant comorbidity that will increase the surgical morbidity and mortality to the point of deeming patient inoperable

4. Deemed by thoracic surgeons to be a candidate for a complete or R0 resection at the time of commencement of the KEYnote 671 neoadjuvant treatment plan

5. No contraindication to platinum-based chemotherapy and immunotherapy

6. No EGFR mutation or ALK rearranged tumours;

7. Any PDL-1 status

Of note, reimbursement of molecular testing for EGFR, ALK and PDL-1 in this setting is still not universal across the country. Additional funding may be needed for those provinces that does not have provincial reimbursement yet.

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?

During the pre-operative period, the response evaluation by CT scan chest/abdomen +/- pelvis during and after neoadjuvant therapy. PET scan may be performed as per the oncology team discretion. Scans should be reviewed by thoracic surgeons to ensure resectability.

During the adjuvant period, a post-operative CT scan chest/abdomen +/- pelvis can be done as a baseline, followed by CT scan every 3-4 cycles during treatment to determine if patients have recurrence of disease.

During the post-treatment period, CT scan surveillance will continue as per provincial guidelines.

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

During the pre-operative period, treatment will discontinue if there is clinical or radiological evidence of progression, clinically important chemotherapy and/or immune-related toxicity that are deemed unsafe to continue and patient wishes.

During the adjuvant period, treatment will discontinue if there is clinical or radiological evidence of recurrence, clinically important immune-related toxicity that is deemed unsafe to continue, patient wishes and a maximum total of 13 cycles of pembrolizumab q3w is given. Where provincially allowed, the equivalent of double-dosed pembrolizumab at q6w will also be allowed.

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]?

Chemotherapy and pembrolizumab as per KEYNOTE 671 trial can be delivered in the outpatient setting in both the academic and non-academic oncology clinics under the supervision of medical oncologists.

The diagnosis of NSCLC is performed through pulmonary physicians/respirologists/thoracic surgeons via EBUS/bronchoscopic biopsy or radiologist via percutaneous CT guided biopsy.

The histological and molecular diagnostics are completed through accredited pathology services in each hospital.

The surgery is performed by thoracic surgeons associated with a cancer centre or with appropriate experience.

As radiation was allowed if there were microscopic positive margins, gross residual disease, or extracapsular nodal extension at the time of surgery, radiation can be performed at any accredited Canadian radiation oncology centre. Radiation was also allowed in patients who did not end up undergoing surgical resection.

6. Additional Information

Although the KEYNOTE 671 trial utilized cisplatin-gemcitabine (squamous) and cisplatin-pemetrexed (non-squamous) regimens for uniformity of analysis, multiple trials in the advanced/metastatic setting have found similar results for all platinum-based doublet chemotherapeutic regimens. There should be no restriction on the choice of platinum-doublet used in clinical practice, when combined with perioperative immunotherapy, except the standard use of pemetrexed only in the non-squamous histology setting.

Further, as with the CHECKMATE 816 trial and all perioperative chemo-immunotherapy trials, approximately 20% of patients may not undergo surgical resection after starting the KEYNOTE 671 chemo-immunotherapy regimen, due to patient or tumour-related issues that arise during the course of neoadjuvant therapy. Under those circumstances, and similar to our request for CHECKMATE 816, the option to switch to a chemoradiation approach followed by durvalumab for unresectable NSCLC, per PACIFIC trial protocol, should be made available to this small subset of patients.

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.

   No

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.**

New or Updated Declaration for Clinician 1	
Name	*Dr. Geoffrey Liu*
Position	*Medical Oncologist, Princess Margaret Cancer Center*
Date	Sept 27, 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.	
	Check Appropriate Dollar Range

Company	$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: Sept 27, 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 2

Company	Check appropriate dollar range*			
	$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.

New or Updated Declaration for Clinician 3	
Name	Michela Febbraro
Position	Medical Oncologist, Algoma District Cancer Program
Date	Sept 27, 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 4	
Name	*Biniam Kidane*
Position	*Associate Professor, Dept of Surgery, University of Manitoba*
Date	Sept 27, 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 5	
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	Sept 27, 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 6

Name: NATHALIE DAABOUL
Position: Hematologist-Oncologist, Université de Sherbrooke
Date: Sept 27, 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 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**

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 7	
Name	*Ronald Burkes*
Position	*Medical Oncologist Mount Sinai Hospital*
Date	Sept 27, 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 8

Name: Silvana Spadafora
Position: Medical Oncologist, Algoma District Cancer Program
Date: Sept 27, 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 8

Company	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		X		
Merck		X		
Novartis		X		

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

Conflict of Interest Declaration for Clinician 9

Name: Dr. Kevin Jao
Position: Medical Oncologist, Hôpital Sacré-Cœur, Montreal
Date: Sept 27, 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 10

Name: Dr Catherine Labbé
Position: Head of Respiratory Medicine Service, Université de Laval
Date: Sept 27, 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 10: Conflict of Interest Declaration for Clinician 10

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			
Astra Zeneca		X		
Brystol-Myers Squibb	X			
Jazz Pharmaceuticals	X			
LEO Pharma	X			
Merck	X			
Pfizer	X			
Roche	X			
Sanofi Genzyme	X			

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

Declaration for Clinician 11

Name: Dr. Rosalyn Juergens
Position: Chair, LCC Medical Advisory Committee; Medical Oncologist, Juravinski Cancer Center
Date: Sept 27, 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

Company	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	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 Sept 27, 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

Company	Check appropriate dollar range*			
	$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	Sept 27, 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 Sunil Yadav
Position: Medical Oncologist, Saskatoon Cancer Centre
Date: Sept 27, 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 14: Conflict of Interest Declaration for Clinician 14

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 15

Name: Dr. Barbara Melosky
Position: Medical Oncologist, BC Cancer
Date: Sept 27, 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 15

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

Novartis	Advisory Board	☒	☐	☐	☐
Roche	Advisory Board	☒	☐	☐	☐
Merck	Advisory Board	☒	☐	☐	☐

New or Updated Declaration for Clinician 16	
Name	*David J. Stewart*
Position	Professor of Medicine, University of Ottawa and The Ottawa Hospital
Date	Sept 27, 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 17

Name: Dr. Shaqil Kassam
Position: Medical Oncologist, Southlake Regional Hospital
Date: Sept 27, 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	**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 18

Name: Stephanie Snow
Position: Professor Dalhousie University, Medical Oncologist QEII Health Sciences Centre, Halifax, NS
Date: Sept 27, 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 18

	Check appropriate dollar range*			
Company	**$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			

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

Declaration for Clinician 19

Name: Dr Nicole Bouchard
Position: Respirologist, Sherbrooke University Hospital
Date: Sept 27, 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 19

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 20

Name: Dr Randeep Sangha
Position: Medical Oncologist, Cross Cancer Institute
Date: Sept 27, 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 20: Conflict of Interest Declaration for Clinician 20

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 21

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

Date: Sept 27, 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 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
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			

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

Declaration for Clinician 22

Name: Dr Jeffrey Rothenstein
Position: Medical Oncologist, Lakeridge Health
Date: Sept 27, 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 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
Roche	x			

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

New or Updated Declaration for Clinician 23	
Name	*Christian Finley*
Position	*Thoracic Surgeon, St. Joseph's Healthcare Hamilton*
Date	Sept 27, 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	☐	☐	☐	☐