CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

Pembrolizumab

Non-Sponsored

Indication: Neoadjuvant treatment of adult patients with Stage III or Stage IV melanoma

January 8, 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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CADTH

CADTH Reimbursement Review

Name of Drug: Pembrolizumab

Indication: Project **PX0346-000 for Neoadjuvant treatment of adult patients with Stage III or Stage IV melanoma**

Name of Patient Group: Melanoma Canada

Author of Submission: Annette Cyr

1. About Your Patient Group

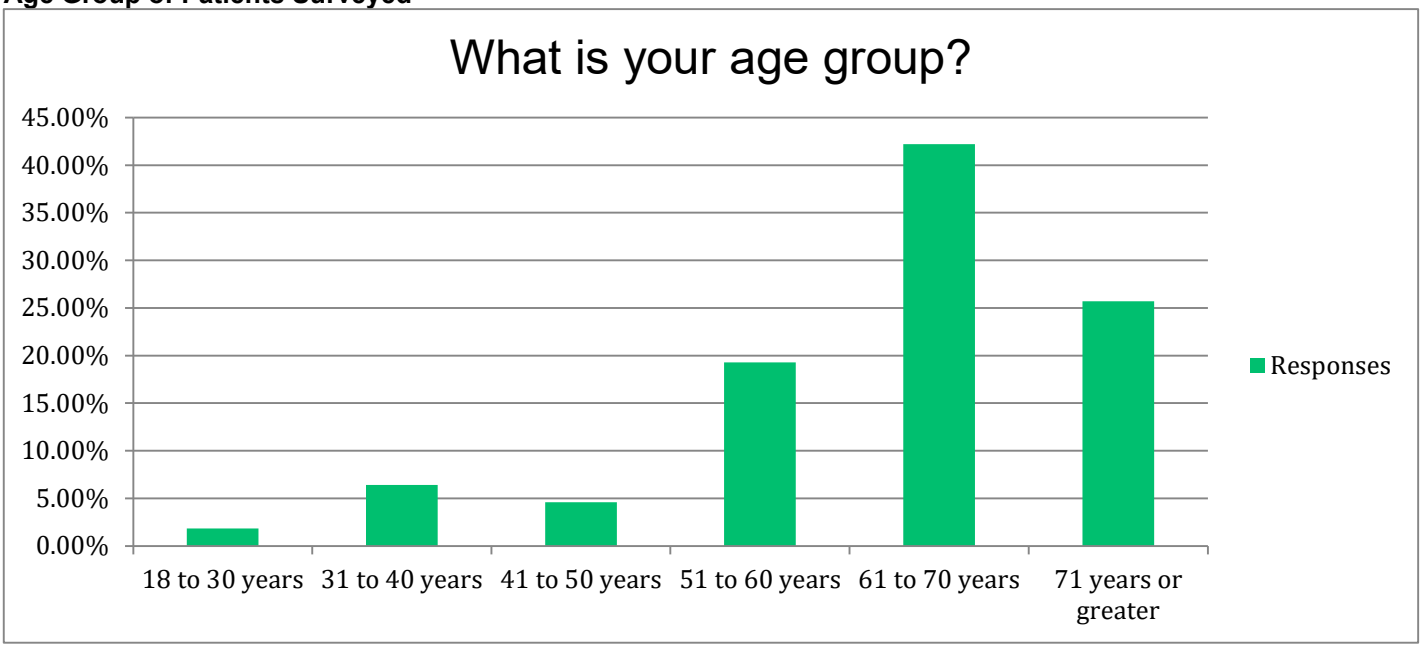
Melanoma Canada (formerly Melanoma Network of Canada) was founded in 2009 to provide information resources, support and prevention initiatives for melanoma and skin cancers. We advocate on behalf of patients to ensure timely and effective diagnosis and treatments are available to all patients across Canada.

2. Information Gathering

Data was gathered for this submission by way of an on-line survey. The survey link was emailed to our database of patients as well as posted online in social media venues. Patients and caregivers, regardless of stage or familiarity with the drug therapy in question, were asked to participate. The survey was made available Dec.12th, 2023 to Jan 3rd, 2024.

Demographics: We received a total of 109 individual patient responses. Of the total responses for patients, 79 were female and 30 were male. The survey was open to all patients, regardless of stage or whether or not they had been on the combination drug therapy. We had 21 patients that were stage 0; stage I – 5; stage II – 7; stage III – 19; stage IV – 27 and a further 30 did not know their stage. 72 respondents were from Ontario, 9 Alberta, 10 BC, 6 Quebec, 2 from Manitoba and the remainder from other provinces.

Age Group of Patients Surveyed



3. Disease Experience

Pain, Scarring, lymphedema, fatigue, anxiety, fear and depression are common impacts of a diagnosis of melanoma that affect the quality of life for patients and their families. With these types of issues continuing to be reported year over year there is a need to address not only improved drug therapy, but earlier diagnosis and treatment to avoid the health, emotional and financial impacts of advanced disease. Depending on several factors including mitotic rate, Melanoma can progress more rapidly than other types of cancer. In addition, patients often experience significant delays in scheduling of surgery. This is even more common at present. Delays in diagnosis, accessing a dermatologist and then access to timely surgery all contribute to heightened risk for spread of disease while waiting for treatment. Both caregivers and patients agree that there is a continuing need to address this gap and improve on timely and effective treatment. It is critical to look for ways to improve the treatment pathway and experience for patients. By allowing access to treatment in a neo-adjuvant setting, patients may have the opportunity to slow progression of disease, prevent a recurrence after surgery or eliminate the disease entirely. There was significant commentary from patients which provides insight into the impact of the disease:

Disease Experience: Impact of Melanoma on Patients

Answer Choices	Responses	
Pain	25.21%	30
Scarring or disfigurement	57.98%	69
Edema or fluid retention	10.92%	13
Lymphedema	21.01%	25
Mobility issues (unable to walk or impaired movement)	11.76%	14
Gastrointestinal issues	9.24%	11
Breathing problems	4.20%	5
Headaches	11.76%	14
Peripheral neuropathy (nerve pain or damage)	10.92%	13
Disrupted sleep	30.25%	36
Appetite loss or weight gain	15.13%	18
Fear or anxiety	57.98%	69
Fatigue	36.13%	43
Depression	26.89%	32
Post traumatic stress	14.29%	17
Cognitive impairment	2.52%	3
Nausea or vomiting	2.52%	3
Damage to organs, such a lungs, liver, brain	6.72%	8
Negative impact to family or social life	25.21%	30
Financial loss or job loss	11.76%	14
Impact on sexuality	9.24%	11
None - there has been no impact	8.40%	10

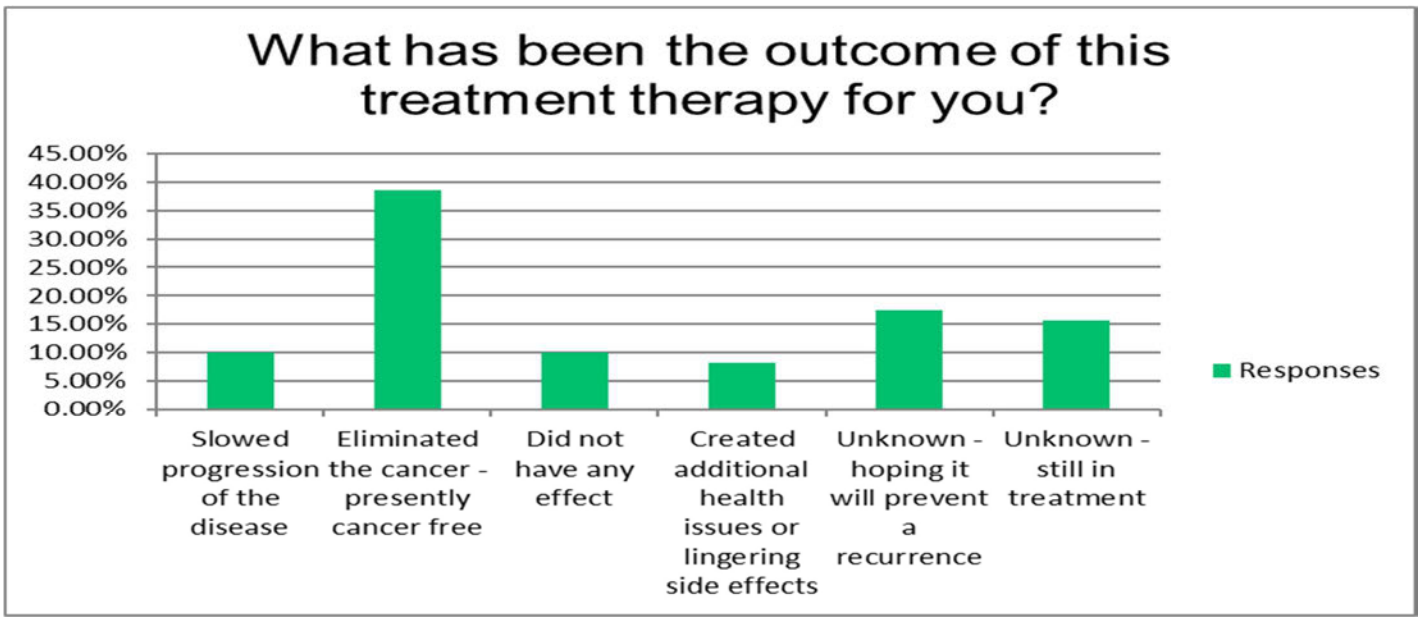
4. Experiences With Currently Available Treatments

We asked patients to indicate their experience with treatments and the outcomes thus far. The majority of the respondents have not had the opportunity to be placed on neoadjuvant pembrolizumab, as this is a new approach in Canada.

Drug Therapies Provided to Patients

Which drug therapy are you or have you been treated with, if any?		
Answer Choices	Responses	
Dabrafenib (Tafinlar) & trametinib (Mekinist) - combination therapy in the form of daily pills	4.59%	5
Vemurafenib (Zelboraf) & cobimetinib (Cotellic) - combination therapy in the form of daily pills	0.92%	1
Braftovi (Encorafenib) & Mektovi (Binimetinib) - combination therapy in the form of daily pills	0.92%	1
Trametinib (Mekinist) as a monotherapy	0.00%	0
Relatlimab & Nivolumab (Opdualag) - IV combination therapy	0.00%	0
Vemurafenib (Zelboraf) as a monotherapy	0.00%	0
Dabrafenib (Tafinlar) as a monotherapy	0.00%	0
Nivolumab (Opdivo) monotherapy administered in clinic by intravenous	10.09%	11
Nivolumab (Opdivo) in combination with ipilimumab (Yervoy)	11.01%	12
Ipilimumab (Yervoy) monotherapy administered in clinic by intravenous	0.92%	1
Pembrolizumab (Keytruda) monotherapy administered in clinic by intravenous	24.77%	27
Interleukin-2 (Aldesleukin, Proleukin) - injections into unresectable tumours	0.00%	0
Interferon alfa -2b (Intron A)	4.59%	5
Dacarbazine (DTIC) - chemotherapy	0.00%	0
None of the above	28.44%	31
Other (please specify)	13.76%	15
	Answered	**109**

Results of the Drug Therapies Reported by Patients



5. Improved Outcomes

Patients and caregivers would like to have access to treatment in a more timely and effective manner. Delays in scheduling surgery are a frequent occurrence in most provinces and territories. To have the option of neo-adjuvant treatment that can improve patient outcomes for reduced spread of disease, or potentially eliminating recurrence or eliminating cancer altogether is something that will improve the lives of patient for the healthcare and their mental well-being. There should also be a positive impact on the cost to our healthcare system, with a reduction in the cases of advanced disease. Improvements that can be made to positively impact health and healthcare should be implemented without hesitation.

6. Experience With Drug Under Review

While we were unable to connect with any patients that had been treated in the neo-adjuvant setting. However, we asked patients to tell us what impact they feel they would see by having access to neo-adjuvant treatment. Responses from patients are included below:

- It would be beneficial especially since you have to wait quite a few months for surgery. It could help in feeling like something was happening and also possibly would catch rogue cancer cells
- Would be helpful to start as soon as possible. Pembro was extremely effective in shrinking the lesions in my liver - even after just 6 or 7 infusions. I had to stop early due to side effects but the treatment I did receive means I am still NED 5 years later.
- It definitely should have been offered prior to treatment. My melanoma was diagnosed by biopsy of a lymph node early June. I did not have surgery until the end of July and treatment didn't start until mid-September. Melanoma can metastasize in less than 6 weeks. Having treatment prior to treatment would definitely give me a better chance to survive
- It would help with peace of mind.
- This drug could mean the difference between seeing my child grow up. Patients should have every opportunity to receive treatment as soon as possible that could prolong their life. This should not be up for debate, this should be approved immediately.
- It would mean a lot. Fear of recurrence is always lurking.
- It would mean greater chance for positive outcomes so that hope for recovery would still be strong instead of a patient becoming depressed, anxious which can lead to many other health issues.
- Would have preferred to have some form of treatment that might slow the cancer while waiting for 4 months to have surgery which in the end was cancelled as cancer had spread.
- I had surgery before the pembrolizumab. There was a significant wait period (almost three months) between the two. Having some doses of pembrolizumab before the surgery may have prevented the relapse, I had subsequent to the 12-month treatment period.
- I would appreciate having the opportunity to have my system bolstered with an immunotherapy to make me stronger for the surgery and help make my recovery faster and more effective. It could be life saving.
- It would add more reassurance of a successful recovery and reduce reoccurrence of cancer
- Reducing the spread is of utmost importance.
- I started the Prembrolizumab in a clinical trial and because more cancer showed up while on the trial it had to be aborted, then more surgery. If I stayed on it I may have not had to have the extra surgery. 6 months later I had more cancer and started another trial of Prembro and the cancer disappeared after 8 months. Because I was on a trial I continued with the treatment for a total of 2 years.
- I am in this boat currently.After three surgeries and the recovery of each- yet to still find out you have melanoma. Pretreatment would be beneficial I feel.
- Not knowing weighed on my mind - if something helps with future spreading, I'd probably go for it.
- It would be incredible! To have this medication available would give a better chance at living longer. And to have a much lower risk of recurrence would mean looking g forward to living longer and healthier with less fear. Looking forward to the future and just living life stress free!! How amazing!!
- Earlier access gives a better chance of good outcomes.
- If the evidence supports this, I would value it. However, I had significant side effects from my immunotherapy (Nivolumab) so I wonder if I had received it prior to surgery if it would have complicated my recovery

- My original surgery was in 1984 when there was no treatment. The immunotherapy may have stopped the disease from spreading which of course would be wonderful.
- Depends on the risk balance of side effects. To date the cancer has not been detected elsewhere, if it did spread to other organs that would be a game changer.
- I am at higher risk having a three generational family history of melanoma. If there is a way to reduce the spread of the disease earlier, I think that is incredibly important.
- This would have been a great treatment option for me when I had surgery earlier this year, potentially stopping additional mets.
- Knowing that I would be able to start treatment right away before surgery would have provided me with additional peace of mind while I waited for surgery. I was very lucky and was able to get in fairly quickly for the surgery, but I know many people wait for an extensive period time. Any additional treatment that could prevent spread or recurrence is meaningful to melanoma patients. I am currently receiving Keytruda infusion every 6 weeks (one year total). This was after a WLE and lymph node dissection.
- If it would mean that it would assist in stopping the disease and prolong my life it would be something that would be most appreciated!!
- Perhaps it would mean a smaller plastic surgery site after wide excision, and eliminate the cancer.
- It would be life changing to use this treatment. I want access to it before my surgery as well as post surgery
- It is a wonder drug. I had only a bit of diarrhea for 2 weeks during my 1 1/2 years of treatment - and no sign of recurrence in past 4 1/2 years after stage 4 metastatic melanoma (scalp tumour spread to ileum and jejunum). The earlier the better please!
- It would mean a better chance at survival if I'm reading everything correctly.
- Very Important to have an alternate choice like pembrolizumab before a surgery if needed. All options should be available for my Treatment. Immunotherapy drugs are a life saver. If I was diagnosed 20 years ago before these drugs were available, I most likely would not be here right now.
- Anything that would potentially stop the spread and give me the chance to continue to live is a benefit. To be able to get this treatment before surgery sounds like a big improvement. Hoping it gets approved. Waiting until surgery and recovering from that then waiting to start therapy is too long - the disease can get a further hold while waiting. The sooner treatment starts the better and it is better for our mental well being as well.
- This would mean a lot to me. I'm a mom with young children (1yr old and 7yr old) and need to do everything possible to prolong my life and maintain quality of life so I can care for my children.
- I expect it would have made an immense difference. From all appearances the cancer had not spread as I waited for surgery so treatment before surgery may well have prevented the spread that did occur as I waited for surgery and waited to recover from surgery.

7. Companion Diagnostic Test

There is no companion diagnostic, other than the normal process of identifying whether a patient is BRAF positive or negative. The neoadjuvant treatment protocol with pembrolizumab does not require a new companion diagnostic test.

8. Anything Else?

Diagnostic delays as well as surgical delays in Canada are common unfortunately. This has been exasperated by the lack of treatment during COVID years and the system is still backlogged for surgery. Even without these delays, the time to get surgery scheduled for melanoma patients is generally longer than other more common cancers. The data from clinical trials demonstrates that by permitting neo-adjuvant treatment with pembrolizumab or other immunotherapy for melanoma, health outcomes are improved. There is a definite need to continue to adopt the best practices that contribute to improved health outcomes. This new process will provide improve health outcomes and improve the lives of our patient community.

Appendix: Patient Group Conflict of Interest Declaration

CADTH

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				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: Annette Cyr
Position: Volunteer, Honorary Chair & Founder – Melanoma Canada
Patient Group: Melanoma Canada
Date: January 8, 2024

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: **Pembrolizumab for Neoadjuvant Treatment of Stage III or IV Melanoma**
Indication: **A for treatment of Stage III or IV Melanoma**
Name of Patient Group: **Save Your Skin Foundation**
Author of Submission: **Kathy Barnard**

1. About Your Patient Group

Save Your Skin Foundation (SYSF) is a national patient-led not-for-profit group dedicated to the fight against non-melanoma skin cancers, melanoma and ocular melanoma through nationwide education, advocacy, and awareness initiatives. SYSF provides a community of oncology patient and caregiver support throughout the entire continuum of care, from prevention and diagnosis to survivorship.

Website: https://saveyourskin.ca/

2. Information Gathering

We obtained valuable insights by conducting an extensive online survey, accessible in both English and French. This survey was widely shared on various social media platforms and newsletters, targeting all stages of melanoma. The primary objective was to address the question of whether pembrolizumab should be publicly reimbursed for neoadjuvant treatment for those in stages Stage III or IV melanoma.

Engaging with (36) individuals representing diverse melanoma stages ((35) English-speaking; (1) French-speaking), our data indicates that (11) participants were diagnosed with Stage III, while (18) were diagnosed with Stage IV, making them eligible for Pembrolizumab for neoadjuvant treatment. Notably, the remaining individuals were diagnosed at the following stages: (3) at 0/in situ, (4) at stage I, (1) at stage II, (8) with unresectable conditions, and (16) with metastatic melanoma. This comprehensive month-long data collection, exclusive to patients and caregivers, underscores the pressing need for neoadjuvant treatment in melanoma care.

Between both the English and French surveys, responses were received from (22) females and (14) males, distributed across various age groups: 30-49 (1), 50-59 (10), 60-69 (12), and 70-79 (10). The respondents were geographically diverse, with participants from British Columbia (10), Alberta (3), Manitoba (5), Ontario (11), Quebec (0), Nova Scotia (1), Saskatchewan (1), USA (4), France (1), and one individual who chose not to disclose their location.

Common themes emerged in participants' experiences with melanoma and their treatments. The results underscore the validity of Pembrolizumab for neoadjuvant treatment and consistently highlight the crucial need for diverse treatment options. Notably, almost all respondents highlighted scarring and disfigurement from surgery and/or radiation being the first line of treatment they received. In some cases, these physical changes rendered participants insecure or made them uneasy about leaving home.

In our survey, we inquired about the usage of Pembrolizumab as a treatment for stage III or IV melanoma in both the adjuvant and neoadjuvant settings. Of the respondents, (17) confirmed having received the drug, while (18) reported not having undergone this treatment. Specifically regarding neoadjuvant administration, (5) responded affirmatively, with (1) utilizing compassionate access, (3) being uncertain, and one participant choosing not to respond.

Participants were asked to provide a hypothetical response to the possibility of receiving a neoadjuvant care protocol, wherein systemic therapy (immunotherapy or targeted therapy) is administered before surgical resection. The question asked whether this option, available only to those with stages III or IV melanoma, would be of interest. Of the respondents, (28) expressed positive interest, while (7) were uncertain.

In conclusion, our survey offers insight into the collective perspectives of stage III and stage IV melanoma patients, along with insights from individuals at all stages of melanoma. These findings reinforce the relevance of the drug in the current treatment landscape and underscore the critical importance of providing patients with a comprehensive array of options for their cancer journey.

To complement the survey data, we will incorporate a wealth of perspectives gathered from patients in this survey and accompanying letters.

3. Disease Experience

Listed are the symptoms and their frequencies among the patients:

These points, derived from an analysis of over 36 quotes, represent the most commonly mentioned aspects highlighted by the majority of respondents. Quotes elaborating on these points will be showcased below.

- Scarring and Disfigurement
- Mental health decline
- Emotional toll on their support system and themselves
- Physical pain
- Fear and anxiety
- Blurry or poor vision
- Depression/suicidal thoughts
- Issues concentrating
- Financial strain

All surveyed patients reported a variety of emotions, with one recurrent theme being scarring and disfigurement. Upon reviewing all the quotes and individuals' experiences with the disease, many expressed concerns about surgery being the initial line of defense or the primary treatment approach. The enduring impact of scarring and disfigurement on emotional and mental well-being was evident, as it serves as a constant, visible reminder of one's cancer journey. While achieving a cancer-free status is the ultimate objective, having persistent reminders of the disease in prominent places raises concerns for those who participated in the survey.

Inquiring about their sentiments regarding melanoma and its influence on their daily lives, a consistent pattern emerged throughout the survey. Participants frequently expressed concern about the unknown, whether it be the fear of the disease spreading or uncertainties surrounding survival rates. This apprehension often led to significant lifestyle alterations, with many respondents having to discontinue work or temporarily halt retirement plans. Overall, their perspectives on life underwent substantial changes, as the diagnosis became a central aspect of their daily existence. Many highlighted that their lives now revolve around managing and addressing this new reality, representing a profound shift for individuals who were cancer-free before.

Patient Quotes:

"The treatments and their side effects were worse than the cancer itself."

"It has more of a mental-emotional toll on my wife."

"A very scary, emotional 14-year rollercoaster."

"Being diagnosed with stage 4 Melanoma has been emotionally devastating. In one day, I went from looking forward to my retirement years to facing an uncertain future with the strong possibility of not surviving the year. This roller coaster of emotions continues with each diagnostic test and each debilitating side effect."

"This is the third cancer I have been diagnosed with, so I'm suffering from the stress of facing my own mortality."

"Crushing depression and suicidal thoughts. Considering MAID."

"2 foot surgeries (2 skin grafts) left with disfigurement. Depression. Unable to work due to cancer-related fatigue and side effects from cancer-related treatments. Financial strain from out-of-pocket cancer-related travel: less income on LTD. Stress related to several reoccurrences and ongoing care needed."

"Not good. Stress, anxiety, some loss of coordination, possible loss of hearing in one ear. Too many things to mention. Pembroke, however, was very tolerable for me."

"Disfigurement; loss of self-confidence; self-conscious about looks; medication to treat pneumonitis caused by immunotherapy created so many side-effects that I needed a walker, etc."

"The treatments and their side effects were worse than the cancer itself. I had to stop working once started on the immunotherapy of Opdivo and Yervoy due to the potential serious side effects."

“Completely changed my life and my outlook on life. Eleven surgeries, brain surgery when I was 6 months pregnant, a few radiation treatments, blood transfusions and iron infusions. So vulnerable and terrified but trying to stay positive at the same time.”

“Huge impact. I have young kids. They have had to suffer with me away and injured and now recovering after treatment.”

“My life revolves around meditation times and documenting and traveling to doctor appointments.”

“I have had to slow my pace considerably and allow time for naps to rejuvenate. It is difficult to watch others do the work while I sit back and rest. I have been unable to carry on with tasks because of extreme dizziness, extreme fatigue, and constant headaches. I have struggled with poor memory so am dependent on others in this area as well. I am afraid of being in the sun.”

“Social isolation due to increased risk of infection related to lowered immunity. Financial stressors. Fatigue exacerbated from long-distance travel to out-of-town appointments.”

“I am disfigured; self-conscious and embarrassed about my looks. I am immunocompromised because of medication I need to take to protect me from getting pneumonitis again.”

“Full-time impact for two years, until I was treated with 5 infusions of pembrolizumab in a Phase 1 clinical trial. Afterwards, no impact beyond filling out surveys. (Complete cure.)”

“It changed it completely. I value each day, don't put off things I want to do, and prioritize family. I try to give back more. I feel privileged to be here. I received Pembro as part of the trial by the company. It was not yet available to the general public. I feel if I had had access to Pembro when I was first diagnosed as a follow to the surgery it may not have metastasized. I was 'followed' for 2 years and the metastases [were] discovered by chance.”

4. Experiences With Currently Available Treatments

The survey results reveal that a majority of respondents have not received treatment Pembrolizumab for Neoadjuvant Treatment of Stage III or IV Melanoma, with the following breakdown:

- (17) confirmed having received the drug in the non-neoadjuvant setting
- (18) reported not having undergone this treatment at all.

The remaining respondents were asked about the alternative treatments they have undergone, and their responses included:

- Radiation (7)
- Surgery or incisions (9)
- Mekinist and Tafinlar (1)
- Opdivo and Yervoy (1)
- Encorafenib/Binimetinib (1)
- Immunotherapy (6)
- Chemotherapy or Oral Chemotherapy (2)
- Clinical Trials (3)

Diagnosis years of survey respondents:

- 1995 (1)
- 2000 (1)
- 2005 (3)
- 2011 (2)
- 2012 (3)
- 2013 (2)
- 2015 (3)
- 2017 (1)
- 2018 (4)
- 2019 (3)
- 2020 (3)
- 2021 (3)
- 2022 (7)
- 2023 (3)

When inquiring about the treatments received, we specifically asked if respondents had undergone Pembrolizumab for their melanoma diagnoses, *specifically in the adjuvant setting* :

- (11) responded that they did receive Pembrolizumab as a treatment.
- (5) received it at stage III.
- (5) received it at stage IV.
- (7) received it at the Metastatic stage.

When asked how they received Pembrolizumab, their responses included:

- (1) clinical trial.
- (1) private payer.
- (2) not sure.
- (7) selected other.

Regarding the completion of the full course of treatment:

- (5) responded yes.
- (2) still in treatment.
- (1) responded no.

Exploring their experiences with Pembrolizumab in the adjuvant setting, respondents reported:

- (9) fatigue.
- (1) Cognitive impairment.
- (3) Nausea and/or vomiting.
- (3) Skin rash.
- (1) Damage to organs.
- (1) Gastrointestinal issues.
- (1) Breathing problems.
- (1) headaches.
- (2) weight loss or weight gain.
- (2) loss or gain of appetite.
- (9) selected other.

The average rating for the manageability of side effects was 3.8 our of 5, with a 5 indicating "completely manageable.". 54.55% (6) participants labelled the side effects as "mostly manageable" and 27.27% (3) as "completely manageable."

When asked if the benefits of the treatment outweigh the experience of side effects, they responded:

- (7) yes.
- (2) unsure.
- (1) not applicable.
- (1) selected other.

While all respondents stated they did not face hardships in receiving the treatment, one comment highlighted a significant financial burden:

"Traveled 2 hours each way for the first couple of treatments. $6000 out of pocket for fees not covered by my private health insurance, $210 clinic fee every 3 weeks. No provincial coverage because I wasn't advanced enough."

For all respondents, receiving this treatment was deemed extremely important to their support system and loved ones:

"Lifesaving important!!! Beyond important!!!"

"If I didn't receive this treatment (in 2020), I wouldn't be here today."

Further asked all respondents if they have any scarring or lasting effects related to their first-line of treatment of radiation or surgery, and they responded:

- Yes (29)
- No (4)
- Not Applicable (3)

Those that responded "yes" shared what these effects entailed for them:

"Three scars and swelling of the left leg, caused by lymphedema, and no feeling in the thigh."

"Deformed, skin sensitivity at surgery site."

"Four scars from excisions of lesions and some skin discoloration and absence of body hair from radiation therapy."

"Complete amputation of my right thumb. Learning to adapt has had significant challenges."

"Lost my mobility following spinal cord compression."
"Scars, bald spots on scalp, neck surgery left numbness and discomfort."

"I have a scar from a stage zero wide local excision on my back, and I have a disfigured ear from surgical excision of a stage two melanoma with a skin graft that failed."

"Scars, possible cognitive decline."

"Melanoma was on my face, so I am disfigured from surgery and radiation and feel embarrassed and self-conscious."

“Scar from donor site for skin graft, groin deficit from lymph node removal, abdominal scar from tumor removal from pelvis. The initial site of removal of the lesion on my heel has had the most lasting effect because I lost part of my heel, and sometimes it is hard to find footwear. As well, the skin of the foot and the grafted skin are of different textures, so callous control is paramount.”

“I have a large discolored "divot" in my left calf. It is painful at times, and I am self-conscious about it. I also have pain in my left thigh below the site where the lymph nodes were removed. I have lymphedema in my left leg for which I wear a custom compression stocking.”

These responses indicate that while adjuvant immunotherapy may be effective in mitigating late-stage melanoma, it can come at a great cost to the patient, who might have lasting debilitating or appearance-altering side effects. Care plans that minimize these effects are valuable options for maintaining patients’ physiological and mental wellness in their lives after cancer, which is the ultimate goal of cancer care.Commonly, when people think of cancer treatments, they envision a sequence involving chemotherapy, followed by surgery, and then additional treatment. However, in the realm of melanoma, the approach varies significantly, varying from case to case. Having alternatives to surgery, such as treatment options before surgery, can significantly benefit patients and enhance their quality of life. The experiences shared by respondents above highlight the considerable challenges and changes faced by those who undergo adjuvant treatment.

5. Improved Outcomes

When queried with the aforementioned hypothetical scenario regarding neoadjuvant treatment protocol, (28) respondents expressed keen interest, while (7) remained uncertain.

The magnitude of affirmative responses demonstrates that participants were overwhelmingly interested in the neoadjuvant treatment format for those in stage III and stage IV melanoma. To gain deeper insights, respondents were encouraged to provide additional details, and their responses are as follows:

"If a drug could have shrunk the tumor, so less radiation could have been used, it would have been ideal. Potentially saving some vision."

"Surgical excision appears to be highly effective. I would want to understand the advantages of this therapy instead."

"I wasn't able to have surgical resection, but if I was, and there was a treatment, I'd need to get more information on benefits of receiving treatment before surgery vs afterward."

"Yes. Knowing what I know now, I would have liked to have had the option."

"Yes. As soon as I knew, I would have started on anything to prevent or slow down mets. My diagnosis was a long time ago, and only two options were available. I certainly would have considered a third option, but

knowing what I know now, I probably would have made the same decision, as my choice was a proven cure. However, after my cancer metastasized, I would like more choices."

"My cancer was non-resectable, but if it were, this protocol would have been preferable to me. I think it may have decreased the extent of surgery."

"Definitely. A means to 'cure' or treat my Stage II tumor without surgery is a no-brainer."

"It might have saved me from needing surgery since I responded so well to Keytruda. On the flip side, my lung tumor was used for the clinical trial, so I would not have been able to be part of that trial without having the surgery."

"Yes. If the bilateral neck dissection could have been avoided. It has been 7 years but still causes daily discomfort."

"Yes, Data shows improved results."

"Yes, of course, anything to reduce the risk of metastasis, and to shrink or cure metastasis."

"Would not have to go through surgery."

"When I was first diagnosed with melanoma on my face, I asked for immunotherapy as I had already undergone a number of skin grafts and was told that radiation would shrink the skin grafts. The radio oncologist told me that I did not qualify for immunotherapy and had no choice but to undergo radiation on my face. I am now disfigured because of it and the cancer spread to my lung. At that point, I qualified for immunotherapy but unfortunately, it attacked my lungs and gave me pneumonitis. To this day, I think that if I had received immunotherapy from the beginning, I would not be disfigured and the cancer would not have spread to my lungs. I think immunotherapy would have been successful on me if it had been done from the beginning when my body was still strong."

"Yes, my husband would have preferred immunotherapy instead of whole brain radiation at the time of his metastatic stage IV melanoma diagnosis. Unfortunately, pembrolizumab was not available as a treatment option in early 2013."

"Systemic treatment would perhaps lessen the likelihood of mets occurring or helping if it had already spread and was lying in wait."

"The pembrolizumab treatment shrank my many tumors to nothing within 12 weeks. If immunotherapy showed promise to be that effective, why would I opt for surgery, which rarely prevents subsequent metastasis?"

"If there was a possibility that the size of the tumor would have been decreased, perhaps my surgery would have been less invasive. The melanoma might not have metastasized to the lymph nodes, and I wouldn't have required immunotherapy."

When questioned about the potential availability of this outcome and how opting for it could have altered aspects of their lives, a consistent trend emerged:

- The prospect of their cancer not metastasizing.
- Minimal or non-existing scarring.
- Reduced anxiety and depression.

In conclusion, the overwhelming interest expressed by (28) respondents in hypothetically receiving neoadjuvant treatment underscores its potential significance for individuals with stages III or IV melanoma. The desire for alternatives to traditional approaches, as highlighted by respondents' detailed considerations, emphasizes the importance of expanding treatment options to enhance outcomes and address the unique needs of patients. The consistent theme of desiring a reduced risk of metastasis, minimized scarring, and alleviated anxiety and depression further emphasizes the potential benefits and importance of exploring neoadjuvant treatment options in melanoma care.

6. Experience With Drug Under Review

In our survey, we asked the same suite of questions to respondents who received Pembrolizumab in the neoadjuvant setting as the adjuvant setting (above). Below are the exclusive results of those who indicated receiving Pembrolizumab in the neoadjuvant setting:

Out of the (36) patients who responded to the survey:

- (6) had received Pembrolizumab in the neoadjuvant setting.
- (3) of those respondents received it at Stage III.
- (3) received it when their cancer was metastatic.

Regarding how they received the drug under review, the respondents stated:

- (1) compassionate access.
- (3) selected other.
- (2) skipped the question.

In response to completing the full course of treatment:

- (3) responded yes.
- (1) responded still in treatment.
- (1) said no and commented it was due to side effects.
- (1) skipped the question.

When asked about side effects experienced during treatment, they reported:

- (5) Fatigue.
- (1) Cognitive impairment.
- (1) Skin rash.
- (3) Gastrointestinal issues.
- (1) Breathing problems.
- (1) Headaches.
- (1) Arthritis flare-up.

However, when asked to provide an average rating, they scored 3.3 out of 5 regarding the manageability of side effects, with a 5 indicating "completely manageable."

Regarding whether the benefits of the treatment outweigh the experience of side effects, respondents said:

- (4) yes.
- (1) responded other, while the remainder skipped the question.

None of the respondents had issues accessing the treatment in the neoadjuvant setting. When asked if it was important to their loved ones and support system that they received the treatment, they all responded Yes. Highlighted responses include:

"Absolutely Critical."

"Cannot be measured. I believe it saved my life and certainly gave me more than the 5 years my other oncologist predicted in 2013."

7. Companion Diagnostic Test

Within the survey seeking responses to the drug combination in question, we did not include companion diagnostics testing. To address this topic, we will share some of the quotations below from our submission survey for the Nivolumab + Relatlimab review (November 2023). This quotations demonstrate that companion diagnostics testing is not consistently offered to patients, despite the benefits it can offer in the age of precision medicine.

"I don't know if I had companion diagnostic testing."

"Was not offered"

"Do not know what this testing is"

"Grateful that it was available to me."

8. Anything Else?

In our extensive survey of (36) individuals representing various stages of melanoma, we have uncovered compelling evidence supporting the urgent need for public reimbursement of Pembrolizumab for neoadjuvant treatment in stage III or IV melanoma patients. Engaging with a diverse group of respondents, we have observed a shared sentiment regarding the challenges associated with current treatments, such as scarring and disfigurement from surgery, mental health decline, and the emotional toll on both patients and their support systems.

Our data reflects a strong interest, expressed by (28) respondents, in exploring neoadjuvant treatment options. This aligns with the broader theme of seeking alternatives to traditional approaches, as highlighted by patients' detailed considerations. The overwhelming desire for reduced metastasis risk, minimized scarring and alleviated anxiety and depression emphasizes the potential benefits of introducing neoadjuvant treatment into melanoma care.

Patient testimonials underscore the profound impact of melanoma on their lives, with scarring, emotional distress, and fear of the unknown featuring prominently. As advocates for patients, we acknowledge the transformative impact that innovative treatments, like Pembrolizumab, can have on survival rates. However, it is equally essential to address the challenges faced by patients without access to these advancements.

In conclusion, our survey findings strongly advocate for the public reimbursement of Pembrolizumab for neoadjuvant treatment in stage III or IV melanoma. This approach not only aligns with patients' preferences and desires but also addresses the gaps in the current treatment landscape. As we continue to champion patient-centric care, we believe that integrating neoadjuvant options will not only enhance the quality of life for melanoma patients but also contribute to more favourable outcomes in their cancer journey.

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.

   YES. The following patient groups helped share this survey with their members to spread our reach.

   Supporter:

   - Canadian Skin Patient Alliance (CSPA)

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 the 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				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: Kathleen Barnard
Position: President
Patient Group: Save Your Skin Foundation
Date: January 8th, 2024

Provincial Health Services Authority

Dec 22, 2023

CADTH
865 Carling Ave., Suite 600
Ottawa, ON
Canada
K1S 5S8

Dear CADTH

CADTH Project Number: PX0346-000
Generic Drug Name: Pembrolizumab
Indication: Neoadjuvant treatment of adult patients with Stage III or Stage IV melanoma.
Name of Clinician Group: We represent melanoma experts in medical oncology and dermatology from across Canada. We are not an official clinician group.
Author of Submission: Vanessa Bernstein, MD, FRCP(C), Medical Oncologist BC Cancer

About the Clinician Group

This is a multiprovincial expert physician letter of support for the application of neoadjuvant pembrolizumab that is currently under your consideration. We are not a formal clinician group, but rather a group of recognized expert medical oncologists and dermatologists in the treatment of advanced melanoma. We are all members of the Canadian Cancer Clinical Trials (CCTG) Melanoma Disease Site Committee. While this letter is supported by the CCTG, it is being submitted independent of them.

Information Gathering

The letter was drafted by Dr Vanessa Bernstein, who is a medical oncologist at BC Cancer with specialty in treating advanced skin cancers. She is also the current chair of the BC Cancer Skin Tumor Group. Dr Bernstein drafted this letter using information obtained from Statistics Canada, published references of the KEYNOTE 054 trial (Eggermont *et. al.* N Engl J Med 2018; 378:1789-1801 and Eggermont *et. al.* Lancet Oncol 2021; 22(5): 643-654) and the Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma Trial (Dr S Patel *et. al.* N Engl J Med 2023; 388:813-823). This letter was then sent to the other supporting physicians for review and comments. The final letter was then submitted to the supporting physicians to endorse and complete their conflict of interest statements. The letter and all the signatures were sent to Kathleen Barnard of Save Your Skin to be included in their submission.

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[redacted]

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Letter of Support of Treatment

Melanoma accounts for approximately 3.8% of all new cancer diagnoses in Canada, making it the 8th most common cancer in Canadian adults, with an estimated 9700 new cases in 2023. In addition, the Canadian incidence rate has been steadily increasing by about 2% annually since 1984. While the incidence rates and mortality are still highest in older individuals, melanoma is the 4th most common cancer in Canadians aged 15-49 years. Approximately 7% of new melanoma patients will be diagnosed with stage III disease. According to the AJCC Version 8 TNM staging for melanoma, patients with stage IIIB have a 10-year melanoma specific survival (MSS) of 77%, while those with stage IIIC and IIID have a 10-year MSS of 60% and 24%, respectively.

Since 2011 advances in immunotherapy and targeted therapy have significantly improved outcomes, including overall survival, in patients with unresectable stage III or stage IV melanoma. These agents were then trialed in the adjuvant setting in patients with completely resected stage III or stage IV melanoma to see if they could improve relapse free and overall survival, and the results were practice changing.

In May 2018 the first results of Keynote 054 were published in the New England Journal of Medicine (NEJM). This was a phase III, randomized, blinded, placebo-controlled trial of adjuvant pembrolizumab 200 mg iv q 3 weeks for 18 doses (52 weeks) (N=514) vs placebo (N=505) in 1019 patients with completely resected stage III cutaneous melanoma. The baseline patient characteristics were well balanced. With a median follow up of 15 months, pembrolizumab was associated with a significantly longer RFS than placebo in the overall intention to treat population. One-year RFS was 75.4% vs 61% (HR for recurrence of death 0.57, $p<0.001$) in favor of pembrolizumab. Forest plot analysis of different subgroups reported similar benefits for pembrolizumab regardless of stage, microscopic or macroscopic nodal involvement, BRAF status, sex and age. The rate of distant recurrence, either alone or in combination with locoregional relapse, was15.2% for patients in the pembrolizumab arm as compared to 27.3% in the placebo arm. The 18-month cumulative incidence of distant metastasis being the first site of recurrence was 16.7% for pembrolizumab vs 29.7% for placebo, HR 0.53 (99% CI 0.37-0.76). Adverse events of grade 3-4 related to the trial regimen were reported in 14.7% of patients on the pembrolizumab arm vs 3.4% on the placebo. 13.8% of patients randomized to pembrolizumab stopped treatment due to an adverse event.

Five-year update results of Keynote 054 were published in NEJM Evidence in Sept 2022. In the overall intention-to-treat population, pembrolizumab was still associated with longer recurrence-free survival than placebo. 5-year rate of

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recurrence-free survival was 55.4% vs. 38.3%, in favor of pembrolizumab (hazard ratio for recurrence or death 0.61 [95% CI, 0.51 to 0.72]). There was also an improvement in 5-year distant metastasis-free survival, 60.6% vs. 44.5% (hazard ratio for distant metastasis or death, 0.62 [95% CI, 0.52 to 0.75]). Currently Canadian patients with completely resected stage III-IV melanoma can receive 1 year of funded adjuvant pembrolizumab after surgery.

In March 2023, a phase II trial of Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma Trial was published in the NEJM. In this trial patients with clinically detectable and measurable stage IIIB to IVC melanoma that was amenable to surgical resection were randomized to three doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (neoadjuvant–adjuvant group) or to surgery followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year or until disease recurred or unacceptable toxic effects developed (adjuvant-only group). The primary end point was event-free survival (EFS) in the intention-to-treat population. Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. Safety was also evaluated. At a median follow-up of 14.7 months, the neoadjuvant–adjuvant group (N=154) had significantly longer EFS than the adjuvant-only group (N=159) (P=0.004). In a landmark analysis, EFS at 2 years was 72% (95% confidence interval [CI], 64 to 80) in the neoadjuvant–adjuvant group and 49% (95% CI, 41 to 59) in the adjuvant-only group. The percentage of patients with treatment-related adverse events of grades 3 or higher during therapy was 12% in the neoadjuvant–adjuvant group and 14% in the adjuvant-only group. 11% of patients in the neoadjuvant group did not proceed to the adjuvant therapy portion. 14% of patients randomized to adjuvant therapy did not receive it after surgery.

As medical experts treating patients with advanced melanoma, we strongly believe that it is better for patients presenting with operable stage III-IV melanoma (*i.e.,* patients with clinically detectable nodal disease or resectable limited metastatic disease) to have the opportunity to be treated with 3 cycles of neoadjuvant pembrolizumab followed by surgery and 15 cycles of adjuvant pembrolizumab, rather than having to undergo surgery first followed by 18 cycles of adjuvant pembrolizumab. The cost of 18 cycles of pembrolizumab should be the same regardless of when the cycles are administered and the results as outlined above are clearly superior, with no increased toxicity. In addition, there is corroborative translational data providing the biological rationale for superiority of preoperative administration, and its ability to induce a stronger

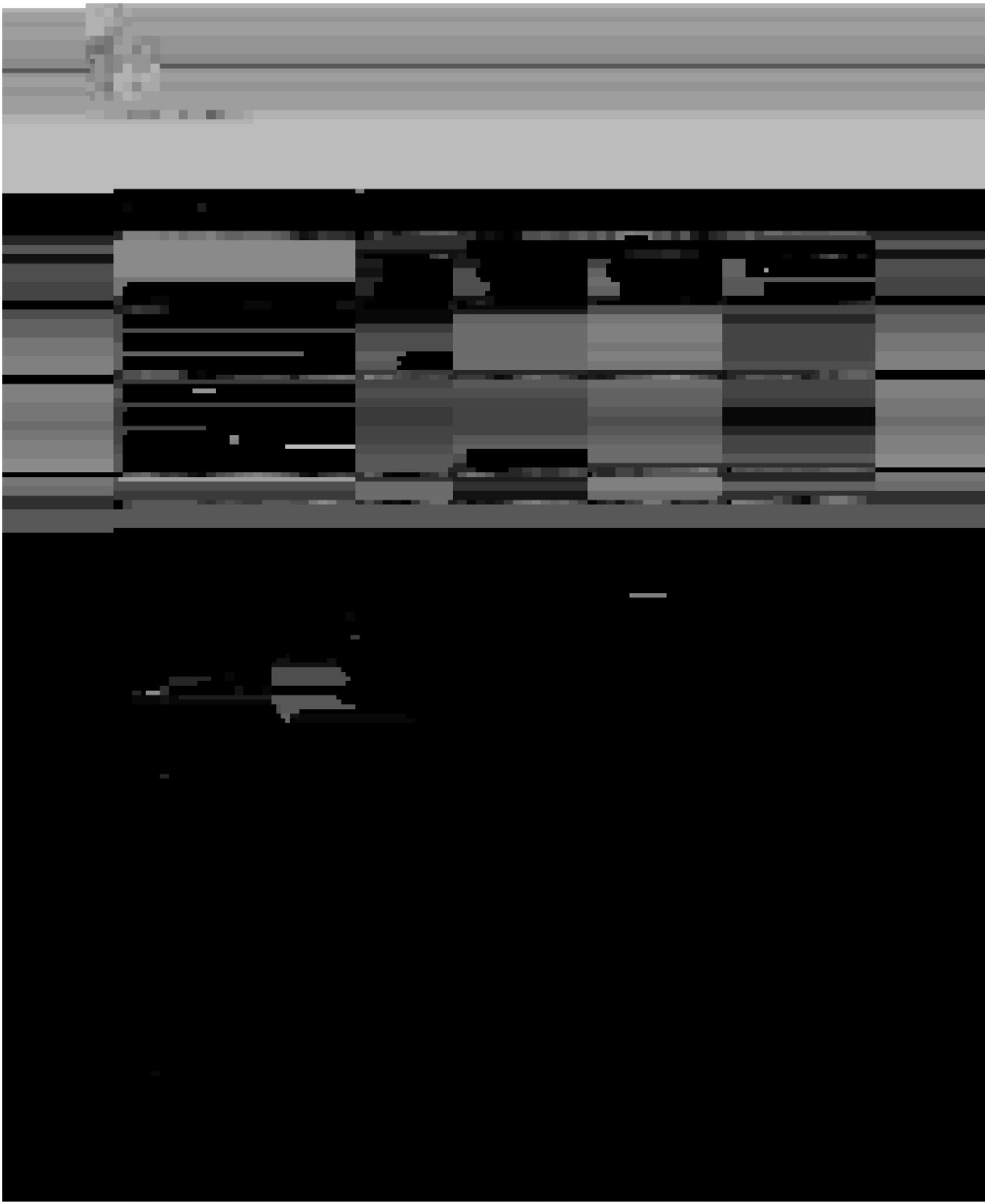
and broader antitumor immune response, as compared to post operative administration. There is also clinical trial data supporting the prognostic value of the pathologic response and its predictive value, allowing for the potential to tailor treatment for patients with complete versus incomplete response. Although the latter findings require a definitive phase III trial, a definitive trial testing this question can only be considered if neoadjuvant therapy is considered standard therapy. The potential benefits in cost savings, limiting toxicity and inconvenience to patients are tremendous from this future research.

Taken together, these data support the use of Pembrolizumab for Neoadjuvant Treatment of Stage III or IV Melanoma. A significant improvement in treatment efficacy is observed with an associated cost that is very reasonable, and treatment appears safe for this subset of patients. Accordingly, we strongly support the listing of Pembrolizumab for Neoadjuvant Treatment of Stage III or IV Melanoma for the Canadian patient population outlined in this statement.

Each appended page to this letter reports the necessary relevant conflict-of-interest disclosure for each signatory, and all the signatories endorse the position stated within this letter.

Sincerely,

- Dr. Vanessa Bernstein, Medical Oncologist, BC Cancer – Vancouver Island Cancer Centre, Chair, BC Cancer Skin Tumor Group
- Dr. Kerry Savage, Medical Oncologist, BC Cancer
- Dr. Joel Claveau, CHU de Québec, Quebec City, Quebec
- Dr. Alison Weppler, Medical Oncologist, BC Cancer, Vancouver
- Dr. Tina Cheng, Medical Oncologist, University of Calgary Cumming School of Medicine, Calgary, Alberta
- Dr. Xini Song, Medical Oncology, Ottawa Hospital Cancer Center, Ottawa, Ontario
- Dr. John Walker MD PhD FRCPC, Division Director, Medical Oncology, Cross Cancer Institute, Edmonton, Alberta
- Dr. Ralph Wong, Medical Oncologist, Cancer Care Manitoba
- Dr. Robyn Marfarlane, Medical Oncologist, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia
- Dr. Wilson H. Miller Jr, Medical Oncologist
- Dr. Janet Dancey, MD, FRCPC (medical oncology), Director, Canadian Cancer Trials Group
- Dr. Jose Monpon, Medical Oncologist



BC CANCER
Provincial Health Services Authority

Conflict of Interest Declaration of the Additional Supporting Authors

Declaration for Clinician

Name: Kerry Savage

Position: Medical Oncologist, BC Cancer

Date: January 7, 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

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS research funds				x
Merck, Seagen, Janssen, Abbvie	x			

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

Thank you for your consideration of this program and our letter of support of CADTH Project Number: PX0346-000

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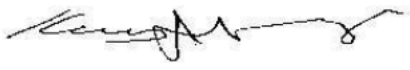

Clinician Signature

Clinician Name Kerry Savage

Position Medical Oncologist, BC Cancer

Date January 7, 2024

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[redacted]

Conflict of Interest Declaration of the Additional Supporting Authors

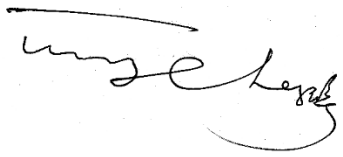
Name:	**Dr Tina Cheng**
Position:	**Medical Oncologist**
Institution:	**University of Calgary Cumming School of Medicine**
Date:	**December 27, 2023**

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 Physician

Company	**Check appropriate dollar range**			
	$0 - $5000	**$5001 - $10 000**	**$10 001 - $50 000**	**In excess of $50 000**
Sanofi	X			
Pfizer	X			

Thank you for your consideration of this program and our letter of support of **CADTH project number PX0347-000.**



Associate Professor
Division of Medical Oncology
Department of Oncology
University of Calgary Cumming School of Medicine
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Conflict of Interest Declaration of the Additional Supporting Authors

Declaration for Clinician

Name: Xinni Song

Position: medical oncology – Ottawa Hospital Cancer Center.

Date: Jan 7, 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 _____

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 (AD board)	X			

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

Thank you for your consideration of this program and our letter of support of CADTH Project Number: PX0346-000

.

Clinician Signature _____

Clinician Name Xinni Song

Position medical oncology

Date Jan 7, 2024.

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Conflict of Interest Declaration of the Additional Supporting Authors

Declaration for Clinician: John Walker

Name:	**John Walker MD PhD FRCPC**
Position:	**Associate Professor, University of Alberta**
Institution:	**Cross Cancer Institute, Edmonton, AB**
Date:	**December 27, 2023**

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 Physician: John Walker

Company	**Check appropriate dollar range**			
	$0 - $5000	**$5001 - $10 000**	**$10 001 - $50 000**	**In excess of $50 000**
Merck (advisory board)	X			

Thank you for your consideration of this program and our letter of support of **CADTH project number PX0346-000.**

John Walker MD PhD FRCPC
Division director, Medical Oncology
Associate Professor of Oncology
Cross Cancer Institute
Edmonton, AB

BC CANCER
Provincial Health Services Authority

Conflict of Interest Declaration of the Additional Supporting Authors

Declaration for Clinician

Name: Ralph Wong

Position: Medical Oncologist, Cancercare Manitoba

Date: December 29, 2023

☒ 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 _____

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	X			
Merck	X			
BMS	X			

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

Thank you for your consideration of this program and our letter of support of CADTH
Project Number: PX0346-000

Clinician Signature _____

Clinician Name Ralph Wong

Position Medical Oncologist, Cancercare Manitoba

Date December 29, 2023

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BC CANCER

Provincial Health Services Authority

Conflict of Interest Declaration of the Additional Supporting Authors

Declaration for Clinician

Name: Robyn MacFarlane

Position: Medical Oncologist QEII Health Sciences Centre, Chair of the provincial Melanoma Cancer Site Team, Nova Scotia

Date: Jan 3, 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 Robyn MacFarlane

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 → honoraria/ consultancy 2022-2023	X			

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

Thank you for your consideration of this program and our letter of support of CADTH Project Number: PX0346-000

Clinician Signature

Clinician Name Robyn MacFarlane

Position

Date Jan 3/2024.

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[redacted]

Dr. Robyn MacFarlane, PMB# 014061
Medical Oncology, 4th floor, Bethune Building
Queen Elizabeth II Health Sciences Centre
1276 South Park Street
Halifax NS B3H 2Y9

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Conflict of Interest Declaration of the Additional Supporting Authors

Declaration for Clinician

Name: Wilson H. Miller Jr

Position: Medical Oncologist

Date: January 8, 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 _____

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 Consulting	X			
Merck Clinical trial payments to Jewish General Hospital				X

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

Thank you for your consideration of this program and our letter of support of CADTH Project Number: PX0346-000

Clinician Signature_____

Clinician Name: Wilson H. Miller Jr.

Position: Medical Oncologist

Date: January 8, 2024

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BC CANCER
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Conflict of Interest Declaration of the Additional Supporting Authors

Declaration for Clinician

Name: Janet Dancey, MD, FRCPC (medical oncology)

Position: Director, Canadian Cancer Trials Group,

Date: January 8th, 2024

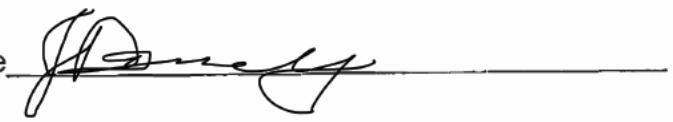
☐ X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
My institution receives research funds to support clinical trials I conduct as investigator

Table 1: Conflict of Interest Declaration for Clinician: Janet Dancey

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
BristolMyersSquibb				X
Seagen				X

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

Thank you for your consideration of this program and our letter of support of CADTH Project Number: PX0346-000

Clinician Signature 

Clinician Name

Position Director, Canadian Cancer Trials Group

Date January 8th, 2024

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www.bccancer.bc.ca

CSPA Canadian Skin Patient Alliance

Unite.
Educate.
Empower.

January 8th, 2024

Canadian Agency For Drugs And Technologies In Health (CADTH)
865 Carling Avenue, Suite 600
Ottawa, ON K1S 5S8
Canada

Dear CADTH Drug Review Committee,

Subject: Endorsement for Public Reimbursement of Pembrolizumab in Neoadjuvant Treatment for Stage III or IV Melanoma

The Canadian Skin Patient Alliance (CSPA) remains steadfast in its commitment to advancing healthcare access, fostering patient well-being, and promoting informed decision-making throughout Canada. It is with great enthusiasm that we extend our support to the CADTH submission titled "Pembrolizumab for Neoadjuvant Treatment of Stage III or IV Melanoma," a commendable initiative led by the Save Your Skin Foundation.

Acknowledging the pivotal role played by CADTH in evaluating pharmaceutical treatments for efficacy, safety, and cost-effectiveness, we underscore the nature of incorporating the patient's perspective in this critical process. This integration is crucial for tailoring treatments to meet the distinctive needs of patients.

Our organization advocates for patient-centric approaches to healthcare decision-making, championing the endeavours of Save Your Skin Foundation in collecting and presenting patient viewpoints to CADTH. By doing so, we anticipate that decision-makers will be better equipped to provide recommendations that prioritize patient well-being, potentially fostering the expansion of treatment options and facilitating easier access to transformative therapies, including Pembrolizumab for Neoadjuvant Treatment of Stage III or IV Melanoma.

In essence, we wish to express our unwavering endorsement for the CADTH submission titled "Neoadjuvant Treatment of Adult Patients with Stage III or Stage IV Melanoma and Experiences with Pembrolizumab (KEYTRUDA®)," spearheaded by the dedicated efforts of Save Your Skin Foundation. We firmly believe that our organizations share a mutual commitment to patient-centered healthcare, and this survey marks a significant stride toward realizing this collective objective.

Central to our support is the conviction that Pembrolizumab should be publicly reimbursed for neoadjuvant treatment of Stage III or IV melanoma, based on its potential to significantly enhance patient outcomes and contribute to the advancement of melanoma care.

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Ottawa, Ontario K1G 4L3
[redacted]
www.canadianskin.ca

Unite.
Educate.
Empower.

We respectfully implore CADTH to carefully consider the insights gleaned from this comprehensive survey during the evaluation of Pembrolizumab for Neoadjuvant Treatment in Stage III or IV Melanoma. Your dedicated attention to this matter is sincerely appreciated. For any inquiries or additional information, please do not hesitate to contact us.

Sincerely,

Canadian Skin Patient Alliance (CSPA)
Canadianskin.ca | [redacted]

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www.canadianskin.ca

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PX0346
Generic Drug Name (Brand Name): Pembrolizumab
Indication: Neoadjuvant treatment of adult patients with Stage III or Stage IV melanoma
Name of Clinician Group: Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Author of Submission: Dr. Frances Wright, Dr. Teresa Petrella, Dr. Marcus Butler, Dr. Xinni Song, Dr. Tara Baetz, Dr. Elaine McWhirter

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 in a videocall and finalized by email.

3. Current Treatments and Treatment Goals

There are no approved or funded neoadjuvant-adjuvant treatments in this setting of clinically detected Stage IIIB/C/D or Stage IV resectable melanoma.

Currently the only treatment options for stage III melanoma patients are anti-PD1 medications such as pembrolizumab or nivolumab, and targeted therapy for BRAF mutated melanoma, after surgical treatment. This is the first drug approved to start before surgery in melanoma (neoadjuvant). Following surgery these patients have ongoing pembrolizumab to complete a total of one year of treatment.

The goal of using neoadjuvant-adjuvant pembrolizumab is to prolong event-free survival, as per the result of the S1801 study, in comparison to standard post-surgical adjuvant therapy alone.

Neoadjuvant-adjuvant Pembrolizumab will be used for curative intent.

The same number of total doses will be used in the neoadjuvant-adjuvant setting as in the post-surgical adjuvant setting.

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.

Implementing neoadjuvant to adjuvant pembrolizumab reduces the occurrence of treatment failure and the development of non-resectable metastatic disease.

5. Place in Therapy

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

The total number of pembrolizumab cycles (17 cycles) remains consistent in both scenarios; however, 3 cycles are given prior to surgery and the remaining cycles are administered post-surgery in the neoadjuvant-adjuvant protocol.

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 best suited are those with resectable stage IIIB, resectable stage IIIC, resectable stage IIID, and resectable stage 4 disease. Eligible patients would have clinical or radiologic detection of lymph node involvement or resectable Stage IV disease.

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?

Outcomes that would determine if a patient is responding include a lack of disease recurrence, improved relapse-free survival, improved overall survival and cure.

Treatment response should be assessed as per the OH-CCO guideline 8-7 v2 “Surveillance of patients with Stage I, II, III or resectable IV melanoma who were treated with curative intent.” In addition to this, the DAC suggests conducting imaging before initiating immunotherapy then repeating after completing 3 cycles of immunotherapy. This approach allows clinicians to assess when a patient is suitable for surgery.

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

Presence of toxicity or lack of clinical benefit is considered when deciding to discontinue treatment.

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]?

An outpatient setting with multidisciplinary care including a medical oncologist and surgical oncologist.

6. Additional Information

A dedicated dermatopathology assessment of surgical specimens when the patient has been treated with neoadjuvant therapy is necessary for best clinical care.

The use of neoadjuvant pembrolizumab for resectable stage 3B to stage 4 melanoma is recommended in the updated August 2023 ASCO guidelines and NCCN guidelines. This Pharmaceutical Benefits Advisory Committee Australia has also recommended to fund neoadjuvant pembrolizumab in resectable stage IIIB-D melanoma.

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 each clinician 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. Frances Wright
Position: Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee lead
Date: 08-01-2024

☒ **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				

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

Declaration for Clinician 2

Name: Dr. Teresa Petrella
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 13-12-2023

☒ 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			

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

Declaration for Clinician 3

Name: Dr. Marcus Butler
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 21-12-2023

☒ 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*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	X			

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

Declaration for Clinician 4

Name: Dr. Xinni Song
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 13-12-2023

☒ 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			

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

Declaration for Clinician 5

Name: Dr. Tara Baetz
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 15-12-2023

☒ 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**
Merck	X			

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

Declaration for Clinician 6

Name: Dr. Elaine McWhirter
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 05-01-2023

☒ 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 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			

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