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

CDA-AMC REIMBURSEMENT REVIEW

Patient/Clinician/Industry Input

nivolumab ipilimumab

(non-sponsored review)

Indication: Indicated in neoadjuvant setting for resectable stage III melanoma.

Jan 3, 2025

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. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: **nivolumab ipilimumab**
Indication: Indicated in neoadjuvant setting for resectable stage III melanoma.
Name of Patient Group: Melanoma Canada
Author of Submission: Annette Cyr

1. About Your Patient Group

Melanoma Canada advocates for and supports Canadians living with melanoma and skin cancer with helpful resources, education, psychosocial support services, and more. We are a national patient support organization, founded in 2009 and we advocate on behalf of patients to ensure timely and effective diagnosis and treatments are available to all patients across Canada.

www.melanomacanada.ca

2. Information Gathering

Data was gathered for this submission by way of an on-line survey. We used social media links and communications to our registered network of patients to solicit responses to our survey.

Demographics: A total of 141 individual patient responses and a further 11 caregiver responses. Of the total responses for patients, 95 were female and 46 were male. The survey was open to all patients and caregivers, regardless of stage. 27 respondents were stage IV, 23 stage III, 4 Stage II, 15 stage 1 and the remainder were in-situ 0 or did not know their staging. We had 5 respondents from outside Canada, 93 of respondents from Ontario, 6 Nova Scotia, 15 BC, 15 Alberta, 7 Quebec, 6 Sask, 1 Manitoba and 1 from Newfoundland. It was a very wide representation across the country. 22 patients indicated they had been on treatment with neo-adjuvant nivolumab and ipilimumab. The majority of respondents to the survey were over 50 years of age. Ages of respondents are indicated in Table 1.

Table 1: Age Distribution of Respondents

Answer Choices	Responses
18 to 30 years	0.65%
31 to 40 years	1.96%
41 to 50 years	7.84%
51 to 60 years	21.57%
61 to 70 years	43.14%
71 years or greater	24.84%

3. Disease Experience

In many prior surveys, we have asked patients about the effect of the diagnosis of melanoma on their day-to-day life and quality of life. Commonly, the most significant impacts reported are 1 – Scarring and Disfigurement; 2. Fear or Anxiety; 3. Disrupted Sleep as well as pain, fatigue, and depression. See Table 2 below:

Table 2: Impact of Diagnosis of Melanoma on Quality of Life for Patients

Answer Choices	Responses	
Pain	32.11%	35
Scarring or disfigurement	67.89%	74
Mobility issues (unable to walk or impaired movement)	17.43%	19
Gastrointestinal issues	10.09%	11
Headaches	10.09%	11
Peripheral neuropathy (nerve pain or damage)	15.60%	17
Disrupted sleep	37.61%	41
Appetite loss or weight gain	22.02%	24
Fear or anxiety	60.55%	66
Fatigue	33.94%	37
Depression	32.11%	35
Post traumatic stress	11.01%	12
Nausea or vomiting	2.75%	3
Damage to organs, such a lungs, liver, brain	10.09%	11
Negative Impact to family or social life	24.77%	27
Financial loss or job loss	11.93%	13
Impact on sexuality	16.51%	18
None - there has been no impact	7.34%	8
Other (please explain)		16
	Answered	**109**

Patients provided the following comments on the impact on their quality of life from the disease itself:

- The fatigue physically limited me and therefore I couldn't function as normal. Burden fell on my husband. Extremely anxious and that made me uncomfortable and hard on my family.
- Time off work, limited physical activities, require more rest.
- My nodal melanoma was painful, ulcerated and bleeding from June-Sept. 2021, which made it necessary to keep a dressing on it at all times. I was fearful and had anxiety as I awaited my surgical oncology referral from May 2021.
- Surgery was on my upper arm, definitely impacted daily activity including work (typing). Serious anxiety and fears since diagnosis and surgery.
- Sleep difficulties. Anxiety. Emotional trauma from scar disfigurement. Social phobia, mild degree.
- My husband died of colon cancer in 2000. At the time our sons were 10, 14 and 18 years old. When I was diagnosed with melanoma in 2019, they were concerned that their remaining parent had also been diagnosed with cancer.
- I have lost some flexibility in the leg that I had two surgeries on. I have scars. I now wear a lymphedema compression stocking, have fittings, and pay for this every 6 month.
- Loss of mobility, can no longer ride my bike, swelling and stiffness due to lymphoma, loss of independence.
- The fatigue means I've decreased my workdays to 2 per week and have reduced my levels of physical activity. Dealing with depression has reduced my desire to be social and is thus leading to loneliness and isolation.
- Nerve pain constantly, deep tissue pain, weakness, hiding disfigured surgical site

- Crippling fear and depression, constant thoughts of death and dying of cancer and not being around for my kids, worries for the future, obsession with my skin and all lesions on it.
- Caused permanent damage to my leg and nerves which impacts ability to walk and stand for long periods due to swelling. I have had long term psychological impact – PTSD
- Anxiety and emotional impacts for sure. I was warned at the start that this journey would be a roller coaster of emotions, uncertainty, and fear. My medical team was always great but there is the uncertainty of how much time I had left and my determination not to waste the time or my energy on frivolous things or people.
- I am anxious about reoccurrence. This anxiety seems to preoccupy many of my thoughts and causes me stress.
- I have had to deal with ongoing scarring issues which affect my identity and the mobility of my shoulder. I have to "hide "from the sun and gave up many enjoyable outdoor activities. We moved from our island and now I live mostly indoors.
- At the very onset of being diagnosed this event significantly impacted my relationship with my spouse. My view of life changed drastically at the time and my spouse appears to be unable to relate to the anxieties and fear I was feeling as various times. There has been improvements over the past month after having received some good news indicating the cancer has not spread to my lymph nodes.
- I tire very easy and due to my steroid of hydrocortisone I have troubles sleeping
- I was very concerned about my life expectancy - made it difficult to find joy in life thinking that my life could end within 12 months
- Worry about summer weather, going on vacation, always trying to stay out of the sun. Not being able to do things with my children because of sun concerns. Worrying about their getting melanoma in the future.
- I find it very hard to walk due to my arterial blockages in both legs , and being limited to carrying no more than 20 lbs , I find it very hard to do groceries , after going through Chemo treatments I am required to go for blood work one a Month for my Cancer D R , I also go for blood work once monthly for My family D R due to My thyroid and diabetic Disease.
- As I waited for my specialist appointment from May to Sept. 2021, I had to keep a dressing on the lesion on my calf all last summer, due to ulcerating and how awful it looked. I also didn't swim at all because I got infection and irritated skin around the lesion. It was painful and I had trouble sleeping due to anxiety and discomfort. After both surgeries, I had mobility issues.
- I am 11 years from original diagnosis. During the critical treatment time and the following follow up years, fear and anxiety were a real presence. With the progression of time and positive follow ups, that has gradually disappeared. A part of the fear and anxiety is that there were no real post-surgical options for me at that time. It was only watch and wait. I would have truly valued some choices post surgery that improved the odds.
- Lymphedema (swelling) of affected arm and hand causes ongoing pain and discomfort
- Having a difficult time with appetite, feelings of nausea, and not able to do much because of these problems. Loss of sleep is also significant.
- Having had 2 episodes of melanoma - 25 years apart, I am in constant fear of recurrence. Since my husband had also had melanoma, we fear for our children as well.
- Surgery on wrist limits mobility to some extent effecting golf swing; lifting items; gardening and painting. Scarring on forehead from surgery/skin graft effects self image
- I do not go outside, therefore no gardening, outside physical activities, picnics, which I used to do prior to the melanomas
- symptoms (from the disease and long-term treatments impacted me in terms of not being able to work fulltime; disease made me modify my daily routine by modifying the time of day I would go outside (fear of the sun), but now am less fearful and use clothing, sunscreen, etc to limit sun exposure

- It impacts how I am treated at work. It limits my sports severely. It robs me of sleep (I get 4 hrs max per night). It limits my walking, enjoyment of outings. I have to sit frequently (it was on my ankle). Anxiety improves with each passing year.
- I have shortness of breath which has led to mobility issues. I have lymphedema in my arm and neck. I have lost mobility in my arm; can't lift it and I can't hold things n my hand. I work from home due to my mobility issues. On medication for nerve damage.
- The cancer has impacted my emotional well being. I have post traumatic stress. I have permanent visible scaring. Financial and career impact was huge.

Caregivers commented on the amount of time and additional costs of taking their family member to appointments and receiving outside care (home care). The time off work for the caregiver is often problematic, and in the case where the patient is working and has to be off work, potentially permanently - affects the financial existence and well-being of many families. As can be seen in the comments above, the emotional impact the disease can be devastating for the entire family. A couple mentioned that it has permanently put them on social assistance and food banks as the loss of income was significant.

We also need to be aware that there is a growing community of seniors that do not have a care giver in the household or family to rely upon. The impact of this disease is felt to an even greater degree by this group and managing appointments, self care, understanding the diagnosis, and dealing with surgical issues can be overwhelming for this more isolated demographic.

4. Experiences With Currently Available Treatments

This combination therapy has been approved for usage for some time now for resectable stage III melanoma. Even though there are well documented side effects associated with this therapy, it has been proven safe and effective and is tolerated by most patients in treating melanoma for years now. This submission is aimed at supporting providing the neoadjuvant use of this drug therapy. While this combination therapy is currently in use for treatment after surgery, studies have indicated improved outcomes with starting the therapy before surgery. Surgical delays remain an issue across Canada and delays in starting treatment allow for disease progression, often at a significant rate. As well, the stress and anxiety patients and families incur waiting for treatment impact quality of life and often health outcomes as well.

The Formulary Management Expert Committee (FMEC) has approved the neoadjuvant-adjuvant use of pembrolizumab (August 2024) as it showed at least similar efficacy to adjuvant pembrolizumab in patients with resectable stage III or stage IV melanoma. This is the only neo-adjuvant therapy approved so far. FMEC also considered that neoadjuvant pembrolizumab meets patients' unmet needs by allowing treatment initiation promptly upon diagnosis, while patients are awaiting surgical resection. We would hope this would be the same outcome for the ipi-nivo combination therapy, as this would allow for better outcome potential for patients.

5. Improved Outcomes

A total of 22 patients indicated that they had received neo-adjuvant treatment with the combination therapy, although we suspect a few might have confused the timing of the therapy with post-surgical treatment with the combination therapy. However, patients and their caregivers both indicate the need to start treatment as soon as possible to prevent further progression of disease. Treatment started in advance of surgery could potentially eliminate the need for surgery or could create less negative side effects from surgery. Often there are delays in starting drug therapy after surgery, while waiting for healing and dealing with infections from surgery. If patients have the option to start therapy earlier, possibly removing the need for surgery or lessening the impact of surgery because tumours have shrunk or disappeared, this will be seen as a significant improvement in the treatment landscape and improving quality of life.

6. Experience With Drug Under Review

For patients treated with this combination therapy, in the neoadjuvant setting or otherwise, the following comments were made when asked what their experience with the treatment has been and the response overall:

- Surgery was for the primary cancer was in Oct 2021. Immunotherapy (nivo/ipi) was for the metastasis acral melanoma in lungs and lymph nodes (stage 4) in Oct 2022. Surgery was not an option. After 3 treatments, I had no evidence of disease (Feb 2023). Eliminated the cancer - presently cancer free.

- I was stage III when I started treatment. It was the ipi+nivo combo that saved my life. Eliminated the cancer - presently cancer free.
- This treatment is helping to contain my melanoma as mine is anal and cannot be operated on.
- Only able to do 2 rounds of combo treatment, which sent my liver levels too high. Had to stop treatment for 2 months and took high dosages of Prednisone before resuming on ipilimumab only for 15 months, before surgery.
- Had treatment but no surgery. Cancer had metastasized to lungs. But, has completely eliminated my cancer, so there was no need for surgery.
- Seeing as though my tumor was on my lower back and I could feel and see it, I had the treatment before surgery and mentally to start it was horrible but once the tumor disappeared by week 7, I was super happy.
- Immunotherapy only - no surgery required as cancer disappeared.
- I started treatment for Melanoma located on my right shoulder/upper back AND at T3 with a combined treatment of these drugs, then transitioned to single dose of nivolumab. I am on treatment #31 now. These treatments have resulted in a finding of no cancer in the shoulder. The T3 site remains active, and later scans located a small site in my lower left lung, which is no longer present on the latest scans. Although surgery is not in the plan yet, my results seen thus far would make it imperative to start the treatment at the earliest possible moment.
- I had surgery which caused my in situation to rapidly become stage 4. My tumour regrew to larger than prior to surgery and then we got approval for this novo/ illi treatment. Wish I had never had the surgery because the drug treatment resolved the initial tumour and all other incidence of disease, (bone lung liver) after the series of 54 treatments I show no signs of the disease. Treatment started in 2018 complete in 2021 and still no signs of disease recurrence. Was on a drug trial.

For those that responded, there was overwhelmingly positive results. Interestingly, several patients indicated no further need for surgery as the drug therapy eliminated the cancer. This has an extremely positive impact on quality of life for patients and also a significant savings for the health care system.

All patients and caregivers were also asked about the potential benefits they would want, if the combination therapy was offered in the neoadjuvant setting. Comments that give the perspective on treatment include:

- I am currently in this very situation, waiting, waiting, waiting after a stage 4 lung recurrence. So, it would mean the world to be on treatment while I wait!
- Speedy treatment, to stop the spread of a melanoma, is essential to prevent further damage. Therefore, starting immunotherapy at diagnosis, makes absolute sense. Why wait until after surgery? Treating melanoma is all about timing. The earlier one can take control of the disease the better. I would prefer to go that route.
- Knowing the stress that this disease caused at time of diagnosis and EVERY SINGLE TIME I notice something new on my skin it would be good knowing that I wasn't having to wait for treatment. When you feel so helpless probably one of the biggest comforts is doing something right away to give yourself, hopefully, a better outcome. As we all know, as soon as you get that diagnosis you just want it out of your body and every day is one day too many.
- I would appreciate being able to access immunotherapy prior to surgery because sometimes one has to wait a long time for surgery. Access to immunotherapy while waiting for surgery may mean the melanoma has less chance to further develop and spread.
- It would be life saving. The science and trials are there to confirm it.
- It would mean potentially stopping spread of disease sooner. Less stress and anxiety waiting to get a surgery date. Being on top of this disease is important. If you can stop it early enough, there is a better chance of survival.
- Having the option to have treatment sooner would be a good option to have. I would appreciate having the option to choose this route of care

- Anything that reduces recurrence risk should be used. This is good for the patient and in the end costs the healthcare system less.
- The chance to go on the offense against cancer would be a huge benefit psychologically and improved outcomes speak for themselves
- *I have Merkel Cell Carcinoma. Was staged 3b [macro] at Dana Farber Cancer Institute and treated there this past winter. DFCI pioneered the use of neoadjuvant immunotherapy for MCC and it is now the gold standard in many jurisdictions. I had a month of Nivolumab before wide resection and in the time the primary shrank from 3.5cm to 4.0 mm viable material. I came home at the end of February completely disease free First 3 month checkup continue to show zero cancer. I would not consider any other therapy and want dearly to help bring neoadjuvant therapy to all Canadian patients.*
- After having such a high success from it, I'd recommend doing it before to see if it will work. Now I didn't need any surgery after but I chose too anyway to be sure it was cleaned up. So I still got cut up.
- The metastasis might have been smaller by the time of surgery. So not as invasive.
- Now that I am stage IV Melanoma and know more about immunotherapy treatments, and currently in 2nd round of IPI+NIVO of my treatment for my Stage IV, I would suggest it.
- Received the drugs after and with long wait for surgery it spread to other sites and crossed to other side - drugs could have started a few months earlier
- It would mean life over death, an improved quality of life, better mental health and less burden on the medical system.

We had one patient indicate that they had severe side effects from the drug combination that resulted in delays for surgery. However, this was the only negative comment. All others were very supportive of the need to start treatment as early as possible to increase the probability for a more positive outcome in the treatment of this disease.

7. Companion Diagnostic Test

There is no companion diagnostic test required.

8. Anything Else?

As can be seen in the responses from patients, there is unanimous support for neoadjuvant therapy. Given a stage III diagnosis, there is an absolute need to start therapy as soon as possible and to have that option. Delays in treatment create significant mental health issues and also lead to more advance disease. We are in support of bringing this treatment to the neoadjuvant setting. It is a win for patients, doctors and the medical system.

Appendix: Patient Group Conflict of Interest Declaration

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

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

   No

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

   No.

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

Table 1: Financial Disclosures

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

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bristol Myers Squibb				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
Patient Group: Melanoma Canada
Date: August 22, 2024

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Neoadjuvant Nivolumab-Ipilimumab for Resectable Stage III Melanoma
Indication: Indicated in neoadjuvant setting for resectable stage III 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.

2. Information Gathering

Over the past month and a half, we conducted a comprehensive online survey to gather insights from a diverse cohort of patients and caregivers within our SYSF Community. As a national organization, we ensured the survey's accessibility by offering it in both English and French. The survey was disseminated across multiple social media platforms and newsletters, with the primary objective of assessing whether neoadjuvant nivolumab-ipilimumab should be publicly reimbursed for resectable stage III melanoma.

We successfully collected a total of (45) individual responses, comprising (38) English-speaking and (7) French-speaking participants. The respondent pool was varied: (32) identified as patients, (6) as caregivers, (3) as healthcare providers, and (3) as others.

To ensure the relevance of our data, respondents were asked to identify the stage of melanoma they or their patients had been diagnosed with. The responses were as follows:

- (7) Stage 0 / in situ
- (6) Stage I
- (3) Stage II
- (16) Stage III
- (13) Stage IV
- (3) Unsure

Among those diagnosed with stage III melanoma, we further inquired whether their melanoma was considered resectable. Of these respondents, (8) confirmed it was resectable, (3) stated it was not, and (2) were unsure.

Subsequently, we asked those with resectable stage III melanoma whether they had received neoadjuvant therapy. The responses revealed that only (1) respondent had undergone this therapy, while (9) had not. This outcome aligns with the current limited availability of this treatment within Canada, where the majority of our survey participants reside.

Although the sole participant who had received the drug under review opted to skip the follow-up questions, we asked all respondents with stage III resectable melanoma how important they believed it was to have access to neoadjuvant therapy with nivolumab-ipilimumab. The responses were as follows:

- (11) "Yes"
- (0) "No"
- (3) "Unsure" and in need of further information

These findings underscore the critical necessity for this treatment option to be made available within Canada. Demographically, the respondents were predominantly female (33), with (12) males. They represented various regions, including:

- (18) from British Columbia (BC)
- (7) from Alberta (AB)
- (0) from Saskatchewan (SK)
- (1) from Manitoba (MB)
- (9) from Ontario (ON)
- (7) from Quebec (QC)
- (1) from New Brunswick (NB)
- (1) from Nova Scotia (NS)
- (1) from Australia
- (1) from the USA
- (2) preferred not to disclose their location

The age distribution of the respondents was as follows:

- (2) aged 18-29
- (8) aged 30-49
- (4) aged 50-59
- (18) aged 60-69
- (11) aged 70-79
- (1) aged 80-89
- (1) aged 90+
- (2) preferred not to disclose their age

Despite the current unavailability of this treatment in Canada, our survey results strongly indicate the need for it. Many respondents who did not have access to neoadjuvant therapy expressed that they would have seriously considered it had it been an option.

Through this survey, we have integrated a wealth of perspectives from patients, healthcare providers, and caregivers, all of whom have firsthand experience with melanoma. The results emphasize the importance of advancing discussions on the reimbursement of this drug, as it would provide patients with a more comprehensive array of treatment options for their cancer journey.

3. Disease Experience

Based on the insights gathered from (45) individual responses, several key themes emerged regarding the patient and caregiver experience with melanoma. These perspectives provide a comprehensive understanding of how this illness impacts day-to-day life and quality of life.

Physical Challenges:A significant number of respondents (28) emphasized the profound physical challenges associated with melanoma, including pain, fatigue, and side effects from treatment. These symptoms often disrupt daily routines and diminish overall well-being.

Emotional Impact: The emotional toll of melanoma was highlighted by (32) respondents, who reported experiencing anxiety, depression, and stress. The psychological burden of living with this diagnosis, especially the fear of recurrence, cannot be overstated.

Impact on Daily Life:A total of (22) participants noted that melanoma severely affects their ability to work and perform daily activities. This disruption to normal life routines is a constant reminder of the disease's pervasive influence.

Access to Care:(19) respondents pointed out challenges related to accessing care, including long wait times, distance to healthcare facilities, and the availability of treatments. These factors significantly affect their ability to manage the disease effectively.

Financial Impact: The financial burden was mentioned by (16) respondents, who discussed the high cost of treatment, loss of income, and travel expenses. The economic strain adds another layer of stress to the already challenging experience of dealing with melanoma.

Social Impact:(16) participants described the social impact of melanoma, including changes in relationships and feelings of isolation. The disease often alters social dynamics, leading to a sense of disconnection from friends and family.

Support from Healthcare Providers: Support from healthcare providers was mentioned by (16) respondents, who stressed the importance of communication, compassion, and availability. The quality of interaction with healthcare professionals plays a critical role in their treatment experience.

Support from Family and Friends:(15) respondents highlighted the emotional support and caregiving assistance they received from family and friends, which is crucial in managing the disease's challenges.

Experience with Clinical Trials:(10) respondents shared their experiences with clinical trials, noting the significance of participation and the outcomes they encountered.

Experience with Specific Treatments:(6) respondents provided insights into their experiences with specific treatments, including surgery, chemotherapy, and immunotherapy.

When asked about ongoing symptoms, the most frequently mentioned were fatigue (8), fear of recurrence (3), various forms of pain (4), and lymphedema (2).

These symptoms illustrate the persistent physical and mental challenges faced by patients.

Respondents also described how melanoma has impacted their daily lives:

- *"Loss of ability to work (temporary), lasting psychological impact of being out in the sun, 1 year of treatment with physical side effects, ongoing need to follow-up."*
- *"Mental health, relationships, physical health/weight gain, side effects from immunotherapy requiring additional medication."*
- *"Low energy during treatments. Now that treatments are complete, things seem to be back to 'normal'."*
- *"I had to move to another location to receive treatments. Ironically, the emotional component brought our family even closer together, despite us already being close."*
- *"I had to stop work immediately for the initial surgeries, then chemo, and then learning to live again."*
- *"The diagnosis made me face my worst fear. The nivolumab treatments were very hard for me—I was left devastated."*
- *"Anxiety that it is going to come back. Concern over what treatment is available if it does."*
- *"Mental stress due to wearing compression garments."*
- *"Stopped working. Spend a lot more time on physical and mental health/wellness activities. Socially, I'm less connected. Difficulty planning beyond the short term."*

These responses highlight the multifaceted impact of melanoma on mental health, energy levels, relationships, and the ability to work. They provide a glimpse into the realities faced by those living with this disease.

When asked about maintaining quality of life, participants reiterated the profound physical and emotional toll of melanoma. They emphasized that the disease creates a "before and after" effect, altering their lifestyle and how they navigate their daily lives. Some respondents find the transition manageable, while others struggle with the ongoing adjustments.

Additional quotes from patients include:

- *"I need to be confident that if I have another melanoma recurrence, I can re-enter the medical system and see my oncologist in a timely manner."*
- *"I don't know how to answer this as it impacted every aspect of his life."*
- *"I think more concentration on a healthy lifestyle, including monitoring my intake of healthy foods and medication."*
- *"Quality of life, monitoring, continuing being NED, and new resources."*

- *"If I 'overdo' physical activity or recreational activities like cycling or skiing, it can cause fatigue, taking 4 days to recover."*
- *"Knowing it is recurring in my body makes me aware that melanoma is in my system."*
- *"Stress and concerns with the ability to carry out daily tasks like dog walking. Time out in the sun is stressful, even with sunscreen and protective clothing."*
- *"Limitations I never had before because of surgery on my leg; now every issue, pain, etc., makes me think cancer is back."*
- *"Effects on my self-esteem. Limits my ability to travel, wear a bathing suit, shorts, etc."*
- *"Significant change personally and to my family. I'm fortunate to be alive with treatment, but there has been an impact."*

These insights vividly demonstrate that a melanoma diagnosis is a life-altering event. The effects are far-reaching, impacting every facet of a patient's life, from physical health to emotional well-being and social relationships. The constant fear of recurrence and the ongoing struggle with daily tasks underline the critical need for more accessible and effective treatments across all stages of the disease. Recognizing these experiences is vital when considering the introduction of new treatments, as the impact of melanoma extends far beyond the disease itself, touching every aspect of a patient's life.

4. Experiences With Currently Available Treatments

The survey responses provide valuable insights into the experiences of those affected by melanoma, offering a clear picture of how patients and caregivers are managing their illnesses with currently available treatments. The respondents' diagnosis ranged across various stages of melanoma:

- (7) In situ (Stage 0)
- (6) Stage I
- (3) Stage II
- (15) Stage III
- (13) Stage IV
- (3) Unsure

Experiences With Specific Treatments:

When discussing their treatment experiences, the respondents provided detailed feedback on the various therapies they have undergone:

Surgery: (23) respondents underwent surgery, often as the initial treatment for melanoma. While surgery is effective in removing the primary tumor, it is associated with significant recovery time and sometimes permanent scarring.

Interferon: (3) respondents were treated with interferon, which, while offering some benefit, was noted for its challenging side effects, including severe fatigue and flu-like symptoms.

Immunotherapy: Several forms of immunotherapy were used by respondents:

- (7) received nivolumab.
- (5) received a combination of ipilimumab and nivolumab.
- (6) received pembrolizumab.
- (3) received a form of immunotherapy not specifically mentioned.

Immunotherapy, though promising in extending survival, was frequently associated with severe side effects such as colitis, skin rashes, and endocrine disorders. The side effects required careful management and, in some cases, additional medications.

Targeted Therapy: Respondents also mentioned targeted therapies:

- (1) received dabrafenib/trametinib.
- (1) received encorafenib/binimetinib.
- (1) received vemurafenib/cobimetinib.

These therapies were effective for those with specific genetic mutations but also brought challenges such as skin issues, joint pain, and fatigue.

Chemotherapy: Chemotherapy was used by a smaller subset:

- (1) received dacarbazine, temozolomide.
- (1) received carboplatin.
- (1) received interferon alpha-2b.

While chemotherapy was less commonly used, it was generally reported as harsh, with significant side effects such as nausea and severe fatigue.

Radiation Therapy: (5) respondents underwent radiation therapy, which was effective in targeting specific areas but often caused pain and fatigue.

Ongoing Symptoms:

The survey also highlighted ongoing symptoms that continue to affect participants, even after treatment:

Fatigue: Reported by (8) respondents, fatigue is one of the most persistent and debilitating symptoms, affecting daily life and overall well-being.

Pain: (5) respondents reported ongoing pain, often related to nerve damage or surgery.

Anxiety: (4) respondents mentioned anxiety, particularly related to the fear of recurrence.

Other Symptoms: Respondents also experienced a variety of other symptoms, including vision problems (2), hearing loss (1), early menopause (1), colitis (2), memory issues (2), nerve damage (1), and gastrointestinal issues such as difficulty swallowing (2).

Patient Experiences and Reflections:

When asked to reflect on how melanoma and its treatment have impacted their lives, respondents provided the following insights:

Emotional Support: "Although my family tried to understand, I never got the emotional help I needed from them. I sought out professional emotional help, and that helped me keep it together during the hard times."

Lifestyle Adjustments: "All of the above and having to look at how I managed my old life."

Physical Limitations: "Treatment attacked my muscles, and I could not walk or talk for 8 months. I was on the strongest steroids."

Social Isolation: "Stopped working. I spend a lot more time on physical and mental health/wellness activities. Socially, I'm less connected. Difficulty planning beyond the short term."

Lasting Psychological Impact: "Loss of ability to work (temporary), lasting psychological impact of being out in the sun, 1 year of treatment with physical side effects, ongoing need to follow-up."

Trust in the System: "I rely on faith and trust in the system to ensure that I am monitored to catch any metastases early. I am thankful for my therapy because I know that it has kept me alive."

Physical and Mental Stress: "Knowing it is recurring in my body makes me aware that melanoma is in my system."

Relocation for Treatment: "I had to move to another location from where I live to receive treatments. The emotional component ironically brought our family even closer together than we were prior, even though we were already a close family."

Physical and Emotional Concerns: "Limitation that I never had before, because of surgery on my leg, and now every issue, pain, etc., makes me think cancer is back."

Desire for Less Invasive Options: "I don't think melanoma can be controlled, but it is important to offer less invasive surgeries and most effective adjuvant or neo-adjuvant support to ensure that there is no residual cancer."

Mixed Feelings on Treatment Necessity: "I could have been 'cured' with surgery alone. I had no evidence of disease on imaging prior to initiating treatment and continue to have no evidence of disease."

Challenges in Accessing Treatment:

Respondents also shared their challenges in accessing treatments:

Financial Challenges: (2) respondents faced financial challenges, including the cost of treatment and insurance issues.

Travel-Related Challenges: (1) respondent experienced difficulties related to travel, such as the distance to the clinic and transportation issues.

Time-Related Challenges: (3) respondents reported challenges related to time, such as taking time off work and scheduling conflicts.

Logistical Challenges: (2) respondents noted logistical challenges in managing appointments and coordinating care.

No Challenges: (7) respondents indicated that they did not face any challenges in accessing treatment.

Patient Quote on Treatment Challenges:

- *"It has taken me almost 3 years to recover from the nivolumab treatments -- they can be very tough on one's body. Mentally, it has left me a shadow of who I used to be."*

The experiences shared by respondents underscore the significant challenges in managing melanoma with currently available treatments. While some therapies provide hope and extend survival, the associated side effects, ongoing symptoms, and emotional toll are considerable. Access to care, financial burdens, and the impact on daily life further complicate the journey for both patients and caregivers. These insights emphasize the critical need for continued advancements in melanoma treatment, particularly those that improve quality of life and reduce the physical and emotional burden on those affected.

Given these challenges, the introduction of neoadjuvant nivolumab-ipilimumab for resectable stage III melanoma offers a promising option. This therapy not only addresses the high anxiety and fear of recurrence that many patients experience but also shows potential in minimizing side effects and reducing the need for surgery. Additionally, the promising survival rates associated with this treatment make a compelling case for its public reimbursement, providing patients with an essential and potentially life-saving option in their cancer care.

5. Improved Outcomes

When considering improved outcomes for melanoma treatments, it's essential to recognize the diverse experiences and needs of patients and caregivers. Participants expressed that living with melanoma, especially in later stages, involves constant concern over recurrence and progression. Having access to a treatment option that offers promising results and addresses these concerns is vital.

Key Patient and Caregiver Priorities:

Participants highlighted several crucial aspects that they believe are necessary to maintain or improve their quality of life:

- *"Ability to access treatment"*

- *"Monitoring (scans) and support from Doctors and support group Save Your Skin. It is important to stay on top of this disease."*
- *"Early intervention for toxicities"*
- *"Easier access to treatments"*
- *"Better surgical options than what I was afforded."*

Desires for New Treatments:

When asked what they hope new treatments could offer, respondents emphasized the following:

- *"Effectiveness #1 priority. Fewer side effects, especially permanent ones. Shorter overall duration of therapy. Logistical simplification of medication administration - targeted therapy required fasting for a couple hours before and after taking the medication (which was twice a day, 12 hours apart), which was actually quite difficult for me. One of the medications also required refrigeration which was cumbersome, especially in the summer and when traveling."*
- *"Ask questions as many as you can before the treatment. Understand the side effects and later stage of the treatment plan."*
- *"Availability My husband qualified for a trial so costs were covered. This saved his life."*
- *"Early detection and screening."*
- *"Access to timely treatment(s) with good results and minimal side-effects."*
- *"I would very much have preferred the neoadjuvant treatment, and I have heard of new trials for an individualised vaccine-style treatment that I would be very interested in if I had to do another round of treatments."*
- *"I guess the thing that worries me personally is what if my melanoma comes back what medications I would receive."*
- *"Better efficacy, less toxicity."*
- *"To find something that will kill the cancer but not hurt our body in the process."*
- *"Access for all to all treatments."*
- *"Effective, fully funded, time-limited treatments with limited or no adverse effects, and certainly with no long-term effects (e.g., significant immune responses)."*

These responses underscore the urgent need for effective treatments that offer fewer toxicities and side effects—qualities that neoadjuvant therapy could potentially provide. Participants also expressed a strong desire for treatments that are accessible, timely, and financially supported.

Impact on Quality of Life:

We also asked how the availability of neoadjuvant therapy might impact daily life and quality of life:

- (31) respondents, representing 92%, indicated that improvements in treatment could significantly enhance their quality of life and that of their caregivers.
- When specifically asked if access to neoadjuvant nivolumab-ipilimumab would be important, (11) participants affirmed the importance, with (2) requesting more information and (1) stating no.
- Additionally, (25) respondents, averaging 78%, anticipated a positive change in their daily lives and overall well-being if neoadjuvant therapy were available.

Acceptable Trade-offs:

When asked about trade-offs in choosing a new therapy like neoadjuvant therapy, (19) participants shared their considerations:

- *"Side effects, quality of life versus longevity."*
- *"I'd look for the same effectiveness/success rate and minimal side-effects."*
- *"Would want to know ahead of time regarding side effects if any."*
- *"There is a higher risk of upfront toxicity. Most patients would trade that for the higher cure rates, decrease risk of metastasis."*
- *"I would consider just about any trade off. Having Lymphoedema has ruined my life and made me have to give up many things that I have enjoyed. It has also ruined my self-esteem, personal self-worth and made a huge hole in my bank account."*
- *"Age. Quality of life. Other new potential health conditions."*
- *"I would weigh expected outcomes, particularly overall survival, against likely side effects. I am particularly concerned about longer-term side effects that might change the quality of my life by causing other health problems (e.g., arthritis, thyroid problems, diabetes) and would lead to having to take additional treatments, e.g., thyroid medications, steroids."*

These results indicate a strong preference among patients and caregivers for treatments that improve survival rates while minimizing side effects and maintaining quality of life. Neoadjuvant nivolumab-ipilimumab offers a promising option in this regard. It is evident that public reimbursement for this treatment could significantly impact the lives of those with resectable stage III melanoma, offering them a vital tool in managing their disease and potentially improving their overall outcomes.

6. Experience With Drug Under Review

When we surveyed our community regarding their experiences with neoadjuvant nivolumab-ipilimumab, we anticipated limited data, as this therapy is not currently available in Canada. However, this does not diminish the importance of evaluating its potential for public reimbursement, especially for resectable stage III melanoma.

Access to the Drug:

Given the unavailability of neoadjuvant nivolumab-ipilimumab in Canada, the majority of our respondents had no direct experience with this therapy. Of the respondents with resectable stage III melanoma:

- (8) indicated their melanoma was resectable,
- (3) indicated it was not, and
- (2) were unsure.

When asked if they had received neoadjuvant treatment:

- (1) respondent had received it,
- (10) had not.

Unfortunately, the sole respondent who had received neoadjuvant therapy chose not to provide detailed follow-up information. This lack of firsthand experience among our participants reflects the broader issue of limited access to innovative therapies in Canada, highlighting the need for public reimbursement to make such treatments available.

Comparison to Previous Therapies:

Although specific experiences with neoadjuvant nivolumab-ipilimumab were not shared, respondents did express concerns with existing treatment options. Many patients voiced dissatisfaction with the side effects, the complexity of administration, and the lack of effective options, particularly for those with later-stage melanoma. For example:

- *"Better surgical options than what I was afforded."*
- *"Effectiveness #1 priority. Fewer side effects, especially permanent ones."*

These responses suggest that neoadjuvant nivolumab-ipilimumab, which has shown promise in clinical trials for improving outcomes and reducing the need for extensive surgery, could address some of these unmet needs. The therapy's potential to offer better efficacy with fewer side effects could significantly improve patients' quality of life compared to their current options.

Benefits and Disadvantages:

While we could not gather specific patient feedback on the benefits and disadvantages of neoadjuvant nivolumab-ipilimumab, the broader literature and clinical studies suggest several potential advantages:

- **Improved survival rates:** Neoadjuvant therapy has been associated with better long-term outcomes in clinical trials, offering hope for increased survival.
- **Reduced need for surgery:** By shrinking tumors before surgery, this therapy could make less invasive procedures possible, reducing recovery times and surgical complications.

- **Management of side effects:** While all cancer treatments come with potential side effects, the goal of neoadjuvant therapy is to balance efficacy with tolerability, potentially offering a better overall quality of life.

Although direct patient experiences with neoadjuvant nivolumab-ipilimumab are limited due to its current unavailability in Canada, the potential benefits highlighted by clinical research and the expressed needs of patients strongly support the case for public reimbursement. This therapy offers a promising option for improving outcomes in resectable stage III melanoma and should be made accessible to all who could benefit from it.

7. Companion Diagnostic Test

Our survey did not specifically address companion diagnostic testing for neoadjuvant nivolumab-ipilimumab, as this therapy is not yet available in Canada. However, it is important to consider the broader implications of companion diagnostics if this therapy becomes available.

Access to Testing: If a companion diagnostic test is required for neoadjuvant nivolumab-ipilimumab, timely access will be crucial. Delays in testing can cause significant anxiety and stress for patients and caregivers. One participant emphasized the importance of timely and effective treatments:

- *"If this has been clinically proven to improve care and prevent further surgeries or treatments…DO IT. In the long run, it will save money and improve patient outcomes."*

This reflects a sentiment that any necessary diagnostics should be easily accessible to facilitate the timely introduction of effective therapies.

Cost of Testing: The cost of companion diagnostic testing is a critical issue. Without public funding, out-of-pocket expenses could be a barrier to accessing this therapy. As highlighted by one participant:

- *"Hugely cost-saving. Very impressive efficacy. This is a no-brainer, and approval and pCODR recommendations need to be expedited."*

This underscores the need for both the treatment and diagnostic tests to be covered by the public healthcare system to ensure equitable access for all patients.

Patient and Caregiver Feelings About Testing: The emotional impact of waiting for test results and making treatment decisions based on those results is significant. Clear communication from healthcare providers about the purpose, timing, and implications of the test is essential to alleviate anxiety and support patients' well-being.

While specific experiences with companion diagnostics for neoadjuvant nivolumab-ipilimumab were not collected, the need for accessible, affordable, and patient-friendly testing is evident. Public reimbursement for both the therapy and any required diagnostics aligns with patient priorities for timely and effective care.

8. Anything Else?

The survey findings highlight the profound impact of melanoma, regardless of stage, on multiple aspects of patients' lives. A consistent theme among respondents is the fear of recurrence and the critical need for treatment options that align with their lifestyle and concerns. Several participants provided additional insights that they believe CADTH should consider:

- **Early Treatment Benefits:** Respondents expressed that if earlier treatment could reduce the spread of disease or shorten treatment duration, it would be highly beneficial, both for patient outcomes and healthcare costs. However, they also noted that the nature of surgery might affect the suitability of early treatment, particularly when considering recovery from surgery alongside the side effects of immunotherapy. One participant shared, *"If earlier treatment led to reduced spread of disease it would be beneficial to have it available. If earlier treatment led to a reduction in length of treatment - beneficial for patients and reduces cost to healthcare."*

- **Access to Treatment:** There was a strong belief among participants that every patient should have access to any treatment that could potentially benefit them. *"I believe every patient should have access to any treatment that may benefit them,"* emphasized one respondent, reflecting a sentiment echoed by many.

- **Patient and Oncologist Considerations:** Participants stressed the need to consider the time commitment required from both patients and oncologists when choosing between neoadjuvant and adjuvant therapies. The combination of these treatments should be carefully evaluated to ensure they meet the needs of both parties.

- **Future Options:** Concerns were raised about what alternatives exist if the combination of drugs stops working. Patients want to be informed about all possible options to manage their condition.

- **Neoadjuvant Therapy Appeal:** The theoretical appeal of neoadjuvant therapy was also noted, with participants expressing that it feels proactive, helping to boost the immune system and alleviate stress during the waiting period before surgery. This aligns with the desire to have treatment options that enhance the overall treatment experience. One participant mentioned, *"In theory, neo-adjuvant treatment is appealing because it feels like something is being done to boost the immune system during the time before surgery takes place."*

- **Quality of Life:** One respondent, speaking in French, emphasized the importance of quality of life during treatment, especially in comparison to chemotherapy.

This feedback underscores the need to advance discussions on reimbursements for neoadjuvant therapy, ensuring that if the treatment works, it is made available to all patients. Many participants have experienced challenges with recurrence, and the idea of not having access to potentially life-saving treatments is a significant concern.

We also received a letter from a patient in Australia who wanted to share their thoughts and experience with neoadjuvant nivolumab-ipilimumab. Their insights further highlight the importance of making this treatment accessible to those who could benefit from it.

Ultimately, it is crucial that patients have decision-making power in their treatment and care. Many healthcare professionals believe that when patients feel in control, their mental health and treatment outcomes improve. Offering neoadjuvant therapy as part of the range of available options for stage III melanoma patients could help address concerns about side effects, recurrence, and surgery scars, potentially leading to better survival outcomes.

The insights gathered show that a melanoma diagnosis is a life-changing event, with effects that extend beyond physical health to impact emotional well-being and social relationships. Ensuring access to advanced treatment options like neoadjuvant nivolumab-ipilimumab is not just a medical necessity but a critical factor in improving the overall quality of life for patients.

Patient Perspectives and International Insights:

9 Brian Street
Bentleigh East
Victoria, Australia 3165

To Whom It May Concern,

I am writing to express my strong support for the availability of neoadjuvant therapy in the treatment of melanoma. My personal experience with this innovative treatment approach has been nothing short of life-changing, and I believe it holds the potential to offer the same hope and improved outcomes to many others facing similar battles.

At 37 years old, while 37 weeks pregnant with my second daughter, I was diagnosed with primary melanoma on my neck. The timing could not have been more challenging, as what should have been one of the happiest periods of my life quickly became overshadowed by fear and uncertainty. After giving birth, I underwent a wide local excision. Just a few months later, when my daughter was only 3.5 months old, I discovered a lump near my scar. A biopsy confirmed my worst fear: the melanoma had metastasised.

It was at this point that we were offered the opportunity to participate in the Nadina trial. After careful consideration, we decided to proceed, and I was randomised to the neoadjuvant arm of the study. I received two doses of Nivolumab and Ipilimumab before undergoing a neck lymph node dissection. The results of the surgery brought us incredible news: I had achieved a complete pathological response.

The impact of this treatment extended far beyond the medical results. For my family and me, it meant that I spent significantly less time undergoing treatment, which allowed us to regain a sense of peace much sooner than we had anticipated. I was able to return to work and resume contributing to our family's economic stability, which was crucial during this tumultuous time. The emotional and physical toll of a cancer diagnosis, especially during a period meant to be filled with joy, cannot be overstated. I feel incredibly fortunate to have been given the chance to undergo a treatment that not only saved my life but also allowed me to resume my role as a mother, wife, and professional more quickly.

I wholeheartedly believe that neoadjuvant therapy is a game changer in the fight against melanoma. I urge you to consider the profound benefits it offers not just to patients but to their families and broader communities. It is my sincere hope that others who may find themselves in the same position I was in will be given the opportunity to access this life-saving treatment option.

Thank you for your attention to this important matter.

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.

We did not receive any help at this time.

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.

We did not receive any help at this time.

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
BMS				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 and Founder
Patient Group: Save Your Skin Foundation
Date: **August 23, 2024**

August 26, 2024

RE: Clinician Statement regarding neoadjuvant ipilimumab in combination with nivolumab immunotherapy for the treatment of patients with locally advanced (M0), resectable malignant melanoma

To whom it may concern:

The undersigned physicians are submitting this letter in support of the application for treatment with neoadjuvant ipilimumab in combination with nivolumab immunotherapy for patients with locally advanced, resectable malignant melanoma.

The results from the NADINA trial were presented at the annual general meeting of the American Society of Clinical Oncology in June of this year, and simultaneously published within the New England Journal of Medicine (N Engl J Med 2023;388:813-823). The NADINA trial is a randomized, phase III clinical trial which assigned patients with resectable, macroscopic stage III melanoma to two cycles of neoadjuvant ipilimumab plus nivolumab followed by surgery, or surgery followed by 12 cycles of adjuvant nivolumab. Only patients in the neoadjuvant group with a partial response or nonresponse received adjuvant treatment. The primary end point was event-free survival.

The results of the NADINA trial have been favorably received by the Canadian community of medical oncologists. The study was sufficiently robust, enrolling 423 patients and the results were clinically meaningful. The study was designed to test the hypothesis that neoadjuvant (or pre-operative) treatment with immunotherapy would improve patient outcomes, and was predicated on earlier, successful clinical trials investigating neoadjuvant immunotherapy for patients with melanoma. Indeed, the NADINA trial was successful, demonstrating a statistically and clinically significant improvement in event-free survival when patients received neoadjuvant immunotherapy, as opposed to receiving treatment with adjuvant (post-operative) immunotherapy alone (hazard ratio for progression, recurrence, or death, 0.32; 99.9% CI, 0.15 to 0.66).

Furthermore, the NADINA clinical trial utilized a highly pragmatic study design. Patients treated with neoadjuvant ipilimumab in combination with nivolumab only received adjuvant (post-operative) treatment with nivolumab if they demonstrated a pathologic partial or nonresponse; in other words, if a major pathological response was observed at the time of surgical resection (and following just two infusions of neoadjuvant immunotherapy) patients underwent surveillance without further active therapy. More than one-half of patients only received neoadjuvant therapy, thus the results of the intent-to-treat analysis described above suggest for most patients pre-operative systemic therapy (without resumption of treatment post-operatively) may be sufficient. Given the strain the Canadian cancer care system is currently

under, not only do these results suggest a less involved course of treatment for patients, but they also indicate a significant savings in resources, including direct and indirect costs of therapy.

The undersigned physicians represent a cross-section of medical oncologists from across the country. Given the improvement in treatment outcomes seen with neoadjuvant in combination with nivolumab and considering the anticipated reduction in both direct and indirect healthcare resource utilization, we support the application to include this treatment option within our formulary of reimbursed therapies.

Sincerely,

[redacted]

John Walker, MD PhD FRCPC
Medical Oncologist & Associate Professor
Division Director, Medical Oncology
Cross Cancer Institute
[redacted]

[redacted]

Dr. Tahir Abbas, FRCP
Medical Oncologist
Saskatoon Cancer Centre
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Head of Medical Oncology and Interim
Program Medical Director Oncology Program
Systemic Lead Skin Cancer
Queen's University
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[redacted]

Caroline Hamm, MD
Medical Oncologist
Melanoma specialist
[redacted]

CADTH

CADTH Reimbursement Review
Clinician Group Input Template
CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PX0371-000
Generic Drug Name (Brand Name): nivolumab-ipilimumab
Indication: Indicated in neoadjuvant setting for resectable stage III melanoma.
Name of Clinician Group: OH (CCO) Skin Cancer Drug Advisory Committee
Author of Submission: Dr. Francis Wright, Dr. Marcus Butler, Dr. Teresa Petrella, 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 by email and videoconference.

3. Current Treatments and Treatment Goals

Standard treatment for patients with clinically detected stage III or IV melanoma has been surgical resection and a year of adjuvant therapy. However, these patients are at very high risk for treatment failure. Phase 2 studies have demonstrated improved survival with a neoadjuvant approach where patients receive neoadjuvant pembrolizumab followed by surgical resection and then completion of 1 year of therapy (18 pembrolizumab doses). We anticipate a neoadjuvant approach will become standard of care (see recent positive draft CADTH recommendation) as these studies have demonstrated improved survival outcomes.

Recent investigations have looked at potentially downstaging the amount of adjuvant therapy if patients have received neoadjuvant therapy and have had a major pathologic response (≤10% residual viable tumor).

In the NADINA trial, patients with clinical stage III resectable melanoma were randomized to either: 2 doses of ipilimumab (low dose) and nivolumab, surgery, and further adjuvant therapy if they did not have a major pathologic response OR surgery and a year of adjuvant therapy. The primary outcome was event free survival.

Please note in the NADINA trial includes patients with cutaneous or acral melanoma, or melanoma of unknown primary, and the assumption is there would be a similar response for patients with mucosal melanoma.

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.

High treatment failure rate with adjuvant therapy alone. Now we have multiple clinical trials demonstrating superiority in efficacy with the neoadjuvant approach (i.e. NADINA, OpACIN-neo). While we have highly effective therapies for patients who relapse with metastatic disease, more than half patients either do not respond to therapy or develop resistant disease. Moreover, in the metastatic setting therapies such as combination immunotherapy at the standard doses have high toxicity rates. One advantage for the NADINA treatment regimen is that 2 doses of combination therapy with lower ipilimumab doses is associated with less toxicity than the doses used for combination therapy in the metastatic unresectable setting.

The neoadjuvant approach has a higher event-free survival than the adjuvant approach.

5. Place in Therapy

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

This treatment, the combination of both ipilimumab and nivolumab, would be used in the setting of neoadjuvant therapy for resectable patients and is a change in the treatment paradigm (single agent immunotherapy likely to be approved soon). Of note, in NADINA, patients with pathological major or complete responses (59%) were able to discontinue therapy and did not receive adjuvant therapy. This is also a treatment paradigm change. In patients who harbored a BRAF mutation and no major path response, adjuvant treatment was given with targeted therapy, dabrafenib and trametinib. This is also a shift in the current treatment paradigm. For patient with WT BRAF, non-pathological major response, adjuvant nivolumab was given. .

The Drug Advisory Committee suggested that

In patients with a BRAF mutation and who have a pathological partial response (11 to 50% residual viable tumor) or a pathological nonresponse (>50% residual viable tumor), the subsequent adjuvant treatment would be at the discretion of the treating clinician given it is a changing landscape.

There should be consistency in using flat dosing in the neoadjuvant setting, as this is different than the dosing in the metastatic setting.

The DAC felt strongly that no change in lines of therapy for the metastatic patient population should made and the doses in NADINA incorporate a low dose of ipilimumab. This should not impact access to post neoadjuvant to adjuvant first line therapy in the metastatic i.e. full dose ipilimumab-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?

This would be appropriate for patients with clinically or radiologically detected stage III resectable melanoma. We can consider extrapolating to resectable stage IV given the SWOG neoadjuvant pembrolizumab data. All patient who would be suitable for immunotherapy should be considered. It is possible that patient who are deemed resectable at the start of neoadjuvant therapy become unresectable. These patients should be eligible for first line metastatic treatment. Of note, recently CADTH has offered a positive recommendation that patients progressing on nivolumab or pembrolizumab should have access to standard dose ipilimumab+nivolumab. Patients who progress or become unresectable post low dose ipilimumab+nivolumab would possibly benefit from standard dose ipilimumab+nivolumab.

One major issue is the use of pathological major response to guide post-surgery adjuvant therapy. This in depth pathological assessment after neoadjuvant therapy required to determine the next steps in treatment is not standard. If discontinuation of adjuvant therapy is considered, proper pathological assessment will be needed. This will require additional resources for pathology to provide this needed information.

The Skin DAC strongly feels that this treatment is beneficial and if operationally rolled out it would be cost saving and would avoid toxicity with patients but requires an operational plan.

Patients should be re-staged before going for surgery.

Patients require a needle biopsy prior to initiation of treatment.

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?

A multidisciplinary approach must be taken when giving neoadjuvant ipilimumab-nivolumab.

Pathological assessment of response should follow the International Neoadjuvant Melanoma Consortium pathological assessment criteria as mentioned in the NADINA trial. This may require more resourcing in pathology.

Treatment response should be assessed every 3 to 6 months as per the surveillance guidelines.

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

Toxicity and disease progression.

Decision to withhold adjuvant therapy must be based on properly conducted pathologic review.

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]?

Medical oncology, surgical oncology radiology, and expertise in dermatopathology and assessment of pathological immunological response are needed.

6. Additional Information

If patients receive ipilimumab-nivolumab in the neoadjuvant setting, patients can still benefit from access in the metastatic setting and should be eligible in the metastatic setting. The doses are different in the metastatic setting versus in the neoadjuvant setting. Patients shouldn't be precluded from getting ipilimumab-nivolumab in the metastatic setting.

The Skin DAC prefers to keep flat dosing, as per the trial.

Time from detection of nodes to starting of neoadjuvant therapy in melanoma should be a QI indicator.

There needs to be timely access to radiology for diagnosis as well as proper pathology assessment which may required additional resources.

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. Frances Wright
Position: Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee lead
Date: 18-08-2024

☒ **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. Teresa Petrella
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 16-08-2024

☒ 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**
BMS	X			

Add company name				
Add or remove rows as required				

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

Declaration for Clinician 3

Name: Dr. Marcus Butler
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 16-08-2024

☒ 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 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**
BMS	X			
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 4

Name: Dr. Xinni Song
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 16-08-2024

☒ 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 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**
BMS	X			
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 5

Name: Dr. Tara Baetz
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 16-08-2024

☒ 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 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**
BMS	X			
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 6

Name: Dr. Elaine McWhirter
Position: Member, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
Date: 16-08-2024

☒ 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 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**
BMS	X			
Add company name				
Add or remove rows as required				

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

CADTH

CADTH Non-Sponsored Reimbursement Review

Industry Input

CADTH Project Number: PX0371
Generic Drug Name: nivolumab and ipilimumab
Indication: Neoadjuvant nivolumab plus ipilimumab for Resectable Stage III Melanoma
Name of Organization: Bristol Myers Squibb Canada
Author of Submission: Bristol Myers Squibb Canada

1. Does the proposed project scope accurately reflect the treatment landscape?

The proposed project scope overall accurately reflects the treatment landscape.

However, the population criteria (Table III) should be adjusted to patients with “resectable, macroscopic stage III melanoma” in alignment with the NADINA trial.

In addition, the intervention criteria (Table III) would be clearer if it specified that the adjuvant treatment following neo-adjuvant treatment with nivolumab plus ipilimumab is response-driven rather than “+/-“ as currently indicated.

Finally, for the comparators criteria (Table III) it should be noted that adjuvant nivolumab is 12 cycles (Q4W) or 24 cycles (Q2W). The same comment applies for pembrolizumab with 16 cycles (Q3W) or 8 cycles (Q6W) in the adjuvant setting, and 3 neo-adjuvant cycles (Q3W) followed by 15 adjuvant cycles (Q3W) when used per SWOG1801 protocol.

2. Are you aware of relevant published studies that you would like considered in the clinical review?

Following their recent release, the results of the NADINA phase 3 study have been described as practice changing for the management of patients with resectable macroscopic stage III melanoma.[1] Exploration into the use of neoadjuvant combination PD1+CTLA4 immune checkpoint inhibition began in 2015 with the phase 2 OpACIN study. OpACIN determined there was increased biological/immunological benefit to the administration of combination nivolumab+ipilimumab in the neoadjuvant/peri-operative setting as opposed to all drug being given in the adjuvant setting, post-surgical resection.[2] The biological rationale for these data suggests that neoadjuvant therapy induces a broader immune response than adjuvant therapy characterized by the activation of many different T cell clones. Immune activation depends on exposure to a broad range of tumor antigens, when drug is administered prior to surgical resection while the tumor and its full antigen profile are still present (neoadjuvant therapy) this can result in increased immune detection and subsequent tumor destruction.[3] Investigators next set their sights on determining the optimal dose scheduling of nivolumab +

ipilimumab in the neoadjuvant setting with the phase 2 OpACIN-Neo study. OpACIN-Neo tested two combination doses of nivolumab 1mg/kg + ipilimumab 3mg/kg or nivolumab 3mg/kg + ipilimumab 1mg/kg each administered Q3W or a sequential approach with ipilimumab 3mg/kg Q3W for two doses followed by two doses of nivolumab 3mg/kg Q2W.[4] The OpACIN-Neo study determined that the optimal dose to further explore in the neoadjuvant setting would be two doses of nivolumab 3mg/kg + ipilimumab 1mg/kg given Q3W, as this dose resulted in pathological complete response (pCR) of 57%, a near pCR (near-pCR, 10% or less viable tumor cells in resected tissue) of 7%, combined for a 64% major pathological response (MPR), and only 20% of patients experiencing a grade 3-4 immune-related adverse event. These investigators then explored response-driven therapeutic escalation/de-escalation in the phase 2 PRADO study.[5] Utilizing the previously determined two pre-operative/neoadjuvant Q3W doses of nivolumab 3mg/kg + ipilimumab 1mg/kg patients achieving an MPR in their index lymph node (ILN, the largest lymph node metastasis at baseline), therapeutic lymph node dissection (TLND) and adjuvant therapy were omitted. Patients with pathologic partial response (pPR; >10 to ≤50% viable tumor) underwent TLND only, whereas patients with pathologic non-response (pNR; >50% viable tumor) underwent TLND and adjuvant systemic therapy ± synchronous radiotherapy. 61% of the 99 patients participating in the PRADO study achieved an MPR (pCR = 49%, near-pCR = 12%) and did not undergo a TLND or adjuvant therapy. Of these patients 93% and 98% had not experienced a disease relapse or development of distant metastasis respectively at 24 months. The safety profile in PRADO was very similar to that observed in the OpACIN-Neo arm of the same dose posology, with 22% of patients experiencing a grade 3-4 immune-related adverse event.

With such a plethora of evidence suggesting two doses of Q3W neoadjuvant nivolumab 3mg/kg + ipilimumab 1mg/kg results in an MPR in approximately 60% of patients, these patients may not require TLND or any additional adjuvant therapy, and the therapy is associated with approximately 20% grade 3-4 immune-related adverse events the investigators then decided to test this regimen in a phase 3 trial. The randomized phase 3 NADINA study tested this neoadjuvant regimen against the current standard care of adjuvant anti–PD-1 with a primary endpoint of event-free survival (EFS). Following neoadjuvant systemic therapy patients in the neoadjuvant group underwent a TLND. Patients who achieved an MPR did not receive any adjuvant treatment, and patients who had a pathological partial response (11 to 50% residual viable tumor) or a pathological nonresponse (>50% residual viable tumor) received adjuvant dabrafenib (at a dose of 150 mg twice daily) plus trametinib (at a dose of 2 mg once daily) for 46 weeks if the melanoma had a BRAF V600E or V600K mutation or received an additional 11 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks if the melanoma was BRAF wild type. It should also be noted that in the NADINA study a flat-fixed dose of 240mg of nivolumab + 80mg of ipilimumab were used, which correlates to nivolumab 3mg/kg + ipilimumab 1mg/kg in an 80kg patient. Patients were randomized 1:1 to 6 weeks of neoadjuvant nivolumab + ipilimumab vs 12 months of adjuvant nivolumab ± radiotherapy. With a median duration of follow-up of 10.6m in the neoadjuvant group, and 9.9m in the adjuvant group the study met its primary endpoint of EFS with 12 month EFS estimates of 83.7% (73.8-94.8) and 57.2% (45.1- 72.7), respectively, adjusted difference in restricted mean survival time was 8.00 months (4.94-11.05; P<0.001), and an overall adjusted hazard ratio of 0.32 (0.15- 0.66).[1] As determined by central review, 47.2% of the patients had a pCR and 11.8% had a near-pCR, resulting in an MPR of 59%. These patients did not receive adjuvant therapy following TLND and had a 12m recurrence-free survival (RFS) probability greater than 94%. Adverse events of grade 3 or higher that were related to systemic

treatment occurred in 29.7% of the patients in the neoadjuvant group and in 14.7% of the patients in the adjuvant group.

Though the NADINA study has limited follow up, similarities in the data to the phase 2 PRADO and OPACIN-Neo studies should be noted. In 2023 Blank et al reported longer follow up of data compiled from the phase 2 OPACIN-Neo and PRADO studies. Patients who achieved an MPR and did not receive systemic adjuvant therapy but underwent a TLND (similar to NADINA) had 36m landmark RFS and DMFS of 96% and 98% respectively. Similarly, patients with an MPR who did not receive adjuvant systemic therapy or a TLND had 36m landmark RFS and DMFS of 93% and 98% respectively. This data suggests that 2 neoadjuvant/pre-operative doses of combination nivolumab + ipilimumab provides long-term benefit to patients who achieve an MPR in the absence of both systemic adjuvant therapy, with or without a TLND.[6]

In conclusion the randomized phase 3 NADINA study confirms that for patients with clinically detectable stage III melanoma neoadjuvant nivolumab + ipilimumab should be considered the new standard of care.

3. Do you have additional comments that you feel are pertinent to this review?

It should be noted that the introduction of nivolumab+ ipilimumab in a neoadjuvant setting has the potential to lead to significant savings by reducing the pool of patients receiving adjuvant therapy post-surgery given the unique response-driven adjuvant treatment approach. It also has the potential to increase the curative fraction which will eventually reduce the pool of resectable/metastatic patients.

Regimen		**Cost per course ($)**
Nivolumab	Nivolumab	$112,676
Pembrolizumab	Pembrolizumab	$158,414
Dabrafenib plus trametinib	Dabrafenib	$290,645
	Trametinib	
SWOG1801	Pembrolizumab	$132,000
NADINA	Nivolumab	<u>Patients with major pathological response:</u> $12,518 <u>BRAFwt patients without major pathological response:</u> $115,791
	Ipilimumab	
	Dabrafenib	<u>BRAFmt patients without major pathological response:</u> $136,966
	Trametinib	

Cost calculation assumptions used:

- List prices used for all drugs

- Weight-based dosing used aligned with current reimbursement criteria in Canada or study protocols (for NADINA and SWOG1801) for nivolumab and pembrolizumab. An average weight of 81.33 kg is used based on the CheckMate 238 trial data.

-Time on treatment from pivotal trial when available, i.e. CheckMate 238 for adjuvant nivolumab, Keynote 054 for adjuvant pembrolizumab and COMBI-AD for adjuvant dabrafenib-trametinib.

- Full treatment course assumed for NADINA and SWOG1801

References

1. Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma. *New England Journal of Medicine*. 0(0)doi:doi:10.1056/NEJMoa2402604
2. Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nature Medicine*. 2018/11/01 2018;24(11):1655-1661. doi:10.1038/s41591-018-0198-0
3. Versluis JM, Long GV, Blank CU. Learning from clinical trials of neoadjuvant checkpoint blockade. *Nature Medicine*. 2020/04/01 2020;26(4):475-484. doi:10.1038/s41591-020-0829-0
4. Rozeman EA, Menzies AM, van Akkooi AC, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. *The Lancet Oncology*. 2019;20(7):948-960.
5. Reijers ILM, Menzies AM, van Akkooi ACJ, et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. *Nature Medicine*. 2022/06/01 2022;28(6):1178-1188. doi:10.1038/s41591-022-01851-x
6. Reijers ILM, Menzies AM, Versluis JM, et al. The impact of response-directed surgery and adjuvant therapy on long-term survival after neoadjuvant ipilimumab plus nivolumab in stage III melanoma: Three-year data of PRADO and OpACIN-neo. *Journal of Clinical Oncology*. 2023;41(16_suppl):101-101. doi:10.1200/JCO.2023.41.16_suppl.101