## CADTH REIMBURSEMENT REVIEW

# Patient and Clinician Group Input

### Nivolumab and Ipilimumab

Non-Sponsored

**Indication**: In combination, for the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma when patients progress during or within 6 months of adjuvant PD-1 therapy

**January 08, 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
# Patient Input Template

Name of Drug: Ipilimumab & Nivolumab
Indication: Project : **PX0347-000 In combination, for the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma when patients progress during or within 6 months of adjuvant PD-1 therapy.**
Name of Patient Group: Melanoma Canada
Author of Submission: Annette Cyr

## 1. About Your Patient Group

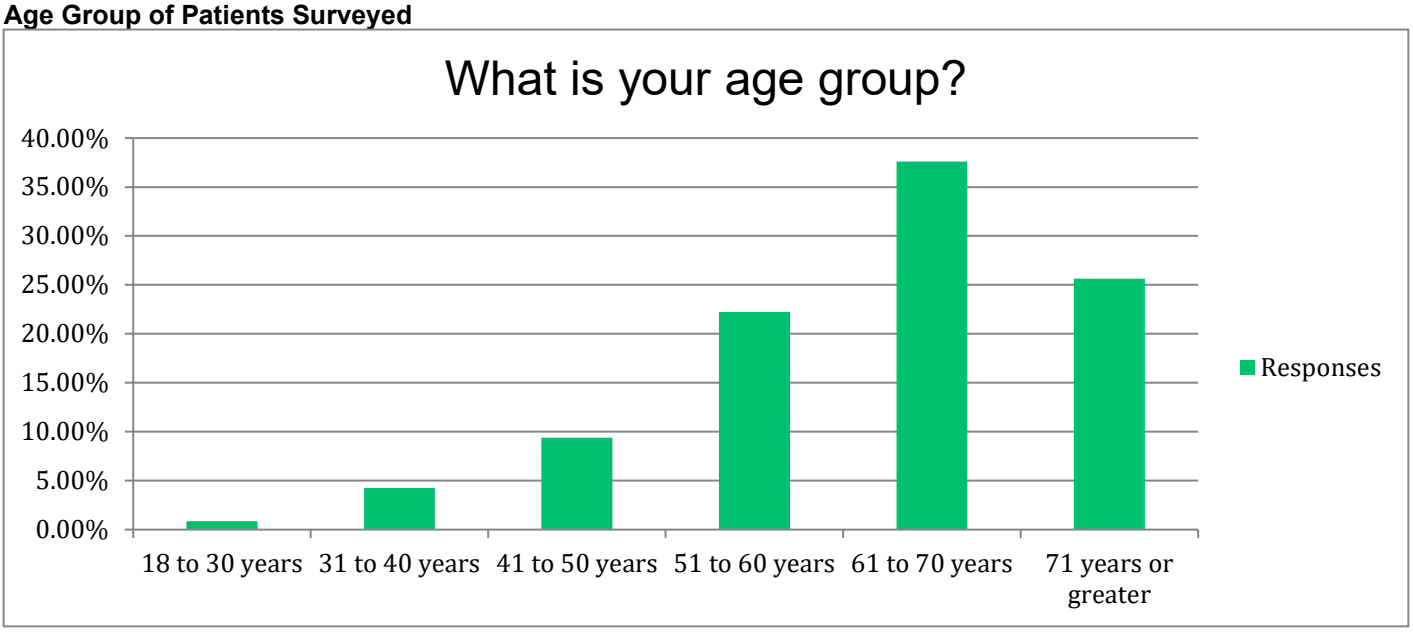
Melanoma Canada (formerly Melanoma Network of Canada) was founded in 2009 to provide information resources, support and prevention initiatives for melanoma and skin cancers. We advocate on behalf of patients to ensure timely and effective diagnosis and treatments are available to all patients across 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 117 individual patient responses. Of the total responses for patients, 82 were female and 35 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 20 patients that were stage 0; stage I – 9; stage II – 6; stage III – 20; stage IV – 35 and a further 16 did not know their stage. 70 respondents were from Ontario, 17 Alberta, 13 BC, 7 Quebec, 2 from the US, 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. These are ongoing issues reported year after year. As such, there is a need to address not only improved drug therapies, but the need for flexibility in addressing timely access, flexibility in options and flexibility in offering more individualized treatment to avoid the health, emotional and financial impacts of advanced disease. Both caregivers and patients agree that there is a continuing need to address this gap and improve timely and effective treatment. It is critical to look for ways to improve the treatment pathway and experience for patients. Patients have commented in past surveys on 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 |

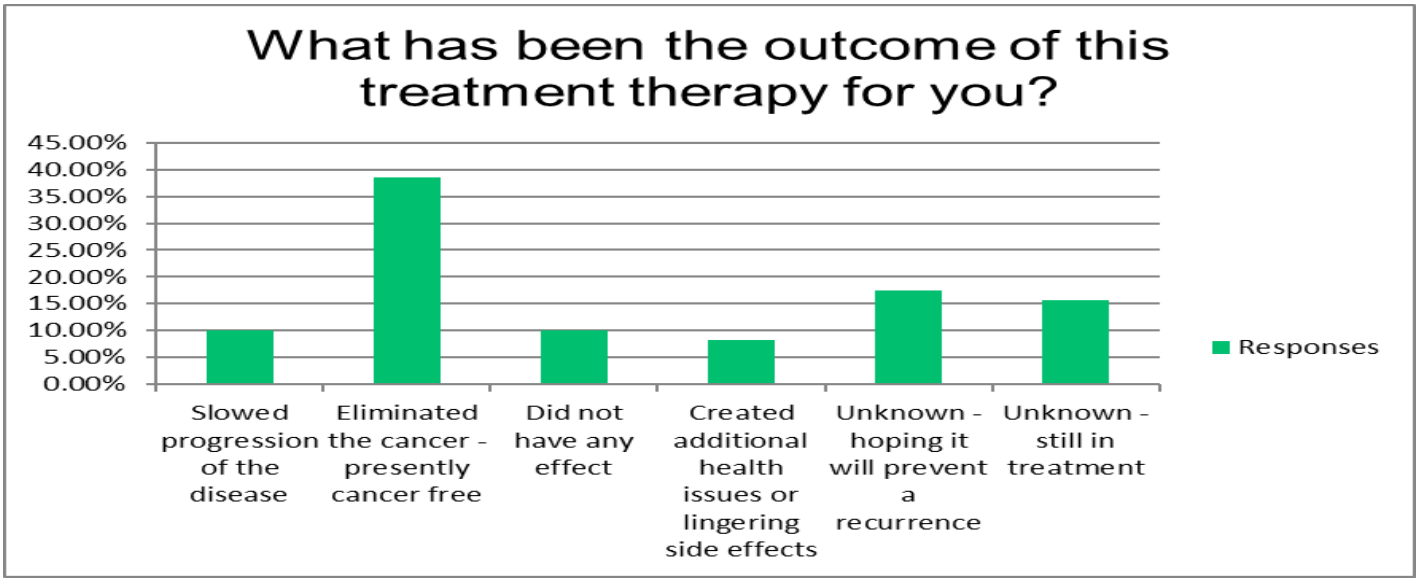
## 4. Experiences With Currently Available Treatments

We asked patients to indicate which drug therapies, if any, they had been prescribed**.** We also asked what the outcome of treatment was for them. The following tables include the responses:

**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

Currently, if a patient receives a monotherapy to treat advanced melanoma and experiences progression of disease, there is no effective alternative treatment option. In effect, they are at the end of the line for treatment options. Patients with unresectable stage III or IV melanoma with disease progression on prior PD-1/PD-L1 inhibition must have the option of trying treatment with a combination therapy to halt disease progression. Nivolumab plus ipilimumab is an appropriate next-line treatment in patients without response to anti–PD-1 alone. Clinical trial data results have indicated that certain subgroups of patients appear to have done particularly well with the combination therapy including patients with stage IV disease, patients with no prior adjuvant therapy, and patients who received less than 6 months of anti–PD-1 therapy prior to combination therapy treatment.

Patients were asked "*What considerations regarding quality or quantity of life might you have if the immunotherapy you are receiving stopped working and you were offered another combination therapy? Would another option be important to you if it could delay spread of disease or potentially eliminate the cancer?".*

102 of the 117 respondents indicated that they would absolutely want another alternative if they had disease progression and would definitely consider the combination therapy. 8 indicated they would not consider the alternative therapy if the side effects were going to be bad, because of age and/or other pre-existing conditions. The remainder were trying other options. The concerns were mainly expressed in management of side effects but given the alternatives and the gravity of the disease, most would accept significant levels of side effects to avoid dying of the disease.

To have the option of an additional line of 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 patients and their mental well-being. Adding the accessibility of this alternative combination therapy after progression on monotherapy will save lives and positively impact health and well-being of patients and their families. It should be implemented without hesitation.

One of the most significant takeaways from our patient input is that the availability of additional treatments is incredibly important. When asked how important another option would be to patients if they could delay the spread of disease or eliminate cancer, most respondents fervently expressed the importance of having options available to them. Most respondents said that they would look at any and all options available to them and most said they would be more than willing to try alternatives if their original therapy had to be stopped. Many also stated that having options available to them would also improve their mental health and ability to cope. Even for respondents who indicated they were diagnosed in early stages, and therefore did not require or receive systemic treatment, they highlighted the importance of having hope and the availability of additional treatment options. Those respondents said they would "certainly consider all options available if recommended" and that "all hope is very important". Comments included:

- "I would have **no hesitation** in trying another therapy should the current therapy stopped working. I am **less concerned about dealing with other side effects** than having melanoma progress. I am retired so no consideration regarding employment income and I have support from my husband and daughters to draw upon."
- "Yes, very much. I would be **willing to try other options** to delay spread of melanoma and hopefully eliminate it."
- "100%. This has been a game changer and has **given me hope**, I would definitely consider another combo therapy if available."
- "If my immunotherapy stopped working, I would need another option, **or my mental health would suffer** significantly."
- "I would consider treatment. **Always**."
- "It would be incredibly important. I may be 71 **but I'm a young and active 71**. I want to live to see my **grandchildren get married**. Even though I've been diagnosed with stage 3 melanoma I'm still very active. I'm terrified that my initial treatment doesn't work, and **I don't have the option of further treatment**."
- "Since I had to stop using pembrolizumab due to side effects, an alternative would definitely be intriguing if my cancer would return."
- "If there is an opportunity to delay the spread and potentially eliminate the cancer would be a significant impact to my life."
- "Another option would be of utmost significance in my life. Stopping the spread of disease or eliminating it would be of **utmost priority to me**."
- "[I'd] **do anything** to get better."
- "My [worse side effects are] better than no treatment".
- "I will take any evidence-based therapy that will slow/stop the progression of this disease".
- "Another option would be very important. I want durable remission".
- "My [outlook] would be [to] keep going [and] stop this disease from progressing. I would opt in for another treatment immediately."

- "Any option is better than none as long as it improves the quality of my remaining life."
- "Knowing there are options is very important."
- "I would welcome and accept any option that my care team recommends if it adds to quantity of life."
- "Absolutely, have any or all options available at the time of treatment to save or extend a patient's life."
- "Absolutely 100%, [having] this option would be my life. Currently on surveillance after Opdivo, [and] if I had this option I feel I **might have a chance at extending my life**. I feel any day now I will progress and there will be ZERO treatment (immunotherapy) offered. **I am scared to death** to be honest".
- "There are **very few options** for patients like me with brain metastasis. Being able to combine immunotherapies has proven to be absolutely lifesaving. Being able to choose to use them independently in any order would also save lives. Just another tool in the toolkit. I would hate **to die due to lack of approval** for a drug that is already on the drug benefit list is able to be provided to patients like me".
- "I'm a single mother of a 1yr old and 7yr old. They need me to be available as an active caregiver with energy to support them daily with all their physical and emotional needs. They also need me to have a long life as they are still so young! **They need a mom**. If my treatment stopped working, I would need another option. **Dying is not an option for me."**
- "I would want my loved one to have access and choice for all therapies especially if one was not working any longer. It would **be extremely cruel to deny the hope and possibility** of another treatment."
- "I would honestly have no considerations. I **would want whatever possible** to delay spread or potentially eliminate."
- "If the immunotherapy stopped working it would be **crucial to have another combination**. My husband received two combination doses and then became ill with myositis. He has not been able to resume treatment with no other available combination. The **risk of suffering similar side effects would be acceptable** as we feel it is less risky than the alternative."
- "Not only am I a melanoma patient/survivor - 3 times - I am also my husband's caregiver. It would be a last resort for me to take any therapy that made me ill for a long period of time (Interferon-A made me feel sick for 1 year). But **my husband depends on me**, so I need to get rid of the melanoma. Having options would be extremely important."
- "Would always **be willing to try other options**. Options are a very important part of a patient's cancer journey."

## 6. Experience With Drug Under Review

The optimal use of immunotherapy is not well defined in melanoma. 6 patients who completed the survey indicated they had received the ipi/nivo combination therapy, after experiencing disease progression with a monotherapy within six months of start of treatment. Comments and outcomes for the 6 patients include:

- I was able to continue working, only had to take a few sick during the whole treatment.
- I had no side effects, none, and complete response.
- Zero side effects and it didn't work.
- While serious I view the side effects as a trade off as this combination therapy helped to slow spread.
- Worth it because even only the 2 combined treatments 8 months apart seems to have had an impact on the size of the tumours. Subsequent clinical trial treatments of Encorafenib and Binimetinib have been successful in inhibiting further growth.
- Couldn't continue with the treatment due to lots of complications.

All but one of the six patients indicated difficulty in accessing this additional treatment. One indicated he paid out of pocket and accessed it privately. Most expressed significant delays, causing disease progression and extreme anxiety and distress for themselves and their families. As this is currently not approved for usage in this manner, it was difficult to gather greater insights from more patients. However, patients commented that it is essential to have the option to try the combination therapy, as a last and viable option at present to halt progression and ultimately or potentially death. Based on responses, we can see the importance of effective treatment options that can provide a good quality of life and longer survival. Most patients feel very strongly about having the ability to receive treatment and that prolonging life, despite potential side effects, was the main objective of receiving treatment. Based on comments, many patients expressed their goal was the do anything to get better, and this is also demonstrated in how many patients expressed their willingness to tolerate the side effects of treatment and its impact on their quality of life, if it was effective in delaying the progression or eliminating the cancer entirely.

One respondent noted how another "option would be essential" to them and that they would "choose a treatment with more significant side effects [over] stopping treatments altogether". We cannot express enough how important it is to patients to have treatment *options.* Some of the more significant sources of emotional distress we hear from patients is being taken off treatment and given no alternatives. This significantly impacts quality of life, as the mental health impacts are significant. There continue to be gaps in available treatment options that have profound effects on all aspects of a patient's life. Many respondents did not respond to

current therapies and are often left with no treatment plan. The impact this has on mental and physical health cannot be underestimated.

Melanoma and skin cancer rates continue to rise, and the availability of effective, safe, and reliable treatment options is not only important for those in later stages, but those diagnosed in early stages as well. Those diagnosed earlier stated the importance of knowing there were treatment options available, given the likelihood of recurrence in melanoma patients.

## 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 treatment protocol does not require a new companion diagnostic test.

## 8. Anything Else?

Patients with unresectable stage III or IV melanoma with disease progression on prior PD-1/PD-L1 inhibition must have the option of trying treatment with a combination therapy to halt disease progression. As we must know by now, the growing field of immunotherapy treatment for cancer is evolving and we are growing our knowledge of the best and most efficacious means to use these therapies. More and more there will be a need for more individualized treatment and also the flexibility to allow our physicians to make the best determination of treatment path for their patients.

Using this combination therapy treatment, even after progression on a monotherapy, we know that a significant percentage of patients will have a complete response or it may further delay disease progression, resulting in improved longer life which aligns with the health outcomes patients and their families are seeking. Melanoma affects all genders, races and age groups. Melanoma is one of the few cancers that is experiencing a statistically significant increase in rates of occurrence annually. Patients need options to have a chance at life and to continue to contribute to their families and to society. There is a definite need to continue to adopt the best practices that contribute to improved health outcomes. This new avenue of possible treatment will provide better health outcomes and improve the lives for patients and their families.

## 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 & Founder – Melanoma Canada**
**Patient Group: Melanoma Canada**
**Date**: January 8, 2024

CADTH

# Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: **Nivolumab and Ipilimumab for Advanced Melanoma**
Indication: **A treatment for advanced melanoma in patients who progress during or within 6 months of adjuvant PD-1 therapy**
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 through an extensive online survey available in both English and French. This survey was broadly disseminated across diverse social media platforms and newsletters, reaching individuals at all stages of melanoma. The primary aim was to investigate whether public reimbursement should be extended to nivolumab and ipilimumab for advanced melanoma patients experiencing progression during or within six months of adjuvant PD-1 therapy.

Engaging with (59) individuals across diverse melanoma stages ((57) English-speaking; (2) French-speaking), our data reveals that (8) participants were diagnosed with Ocular/Uveal melanoma, (12) with melanoma, (2) at 0/in situ, (4) at stage I, (4) at stage II, (8) at stage III, (34) at stage IV, (9) with unresectable conditions, and (29) with metastatic melanoma. This comprehensive data collection, exclusive to patients and caregivers, highlights the urgent demand for the Nivolumab and Ipilimumab combination to address the needs of individuals facing advanced melanoma.

Between both the English and French surveys, responses were collected from (38) females and (21) males, spanning various age groups: 18-29 (1), 30-49 (10), 50-59 (20), 60-69 (14), and 70-79 (14). The participants demonstrated geographical diversity, hailing from regions such as British Columbia (22), Alberta (6), Manitoba (3), Ontario (13), Quebec (3), Nova Scotia (1), Newfoundland & Labrador (1), Saskatchewan (1), USA (7), UK (2), Ireland (1), with (4) individuals opting not to disclose their location.

Common themes surfaced in participants' accounts of their diagnoses and treatments. The findings underscore the relevance of Nivolumab and Ipilimumab for Advanced Melanomas, emphasizing the shared understanding within the melanoma community regarding the imperative need for diverse treatment options.

Significantly, nearly all respondents highlighted the profound physical and mental toll their diagnoses brought upon them.

In our survey, we explored patient responses to Nivolumab and Ipilimumab, delving into when respondents received this treatment and at which stage of their diagnosis. Eighteen (18) respondents initiated Nivolumab plus Ipilimumab as their primary treatment, (9) adopted it as a subsequent treatment option, while (4) underwent a more intricate treatment approach. Regarding the mode of treatment reception, (5) participated in clinical trials, (2) accessed it through compassionate means, (2) utilized private payment, (3) were uncertain, and (19) provided other responses.

It is crucial to emphasize that when respondents were asked whether, if they hadn't received the Nivolumab + Ipilimumab combination, it would be important for them to have access to it, the majority responded affirmatively, with only (2) respondents explicitly stating otherwise (these participants reiterated that they had received Nivolumab).

In conclusion, our survey illuminates both individual and collective perspectives of individuals diagnosed with melanoma and ocular/uveal melanoma across various stages of their condition, with a significant portion being in the advanced stages. These findings underscore the significance of the drug and highlight the critical importance of offering patients a comprehensive range of options for their cancer journey.

To enrich the survey data, we will integrate a wealth of perspectives gleaned from patients in this survey and the accompanying letters.

## 3. Disease Experience

Derived from an analysis of over 59 responses, these key points encapsulate the most frequently mentioned aspects emphasized by the majority of respondents. The quotes will provide additional insight into these critical elements.

- Mental health decline
- Emotional toll on their support system and themselves
- Physical pain
- Fear and anxiety
- Blurry or poor vision
- Depression
- Constant worry of recurrence or spreading
- Issues concentrating
- Financial strain

Upon delving into the emotions expressed by all respondents, a prevalent theme emerges – the profound physical and emotional toll experienced by those grappling with late-stage diagnoses. Several respondents explicitly point out the trauma associated with being diagnosed at an advanced stage and how it significantly

impacts their daily lives. A sense of desperation becomes palpable when reviewing their comments, as they navigate the challenges of late-stage cancer with limited options available due to various factors.

The responses demonstrate that an aggressive melanoma or ocular melanoma diagnosis is a life-altering event that holistically impacts the patient. The quotations below demonstrate the physiological, mental, and financial affects of receiving cancer care, particularly that is not always covered by insurance or offered close to home. In addition to the burdens of having to travel or pay for treatment costs out-of-pocket, we see here that the physical, emotional, and fiscal repercussions of having cancer bleed into patients' relationships and ability to maintain their preferred lifestyle, compromising their support systems. The struggle with cancer is not limited to the disease alone, but every facet of life, a struggle which is exacerbated by treatment access barriers.

In light of these revelations, it becomes imperative to acknowledge the profound impact of late-stage diagnoses on individuals' well-being and the pressing need for more accessible and effective treatment options. These voices underscore the urgency of addressing the unique challenges faced by those in advanced stages of melanoma, emphasizing the importance of comprehensive and compassionate care.

**Patient Quotes:**

*"Life-changing in every way."*

*"Periods of sadness daily because of uncertainty regarding mets, financially has been difficult as I opted to go to the States for treatment because I felt I could not be seen soon enough to my liking here in Canada at PMHCC."*

*"All of the above, left a lot of mobility in my left arm due to surgery and radiation. Had to travel for 2 of the 4 treatments at my cost. The mental and emotional toll during diagnosis and beyond treatment have been huge."*

*"Physical (2 surgeries and skin grafts) Financial (now on LTD) and struggling with the cost of travel for treatments / medical appts + now having to pay for my monthly extended health benefits at $560 a month Struggle with depression."*

*"Devastating! My mom was diagnosed with Stage 3 in April 2018, and she went through surgery on May 31st. She was told that the chances that it would come up back were very high unless she took nivolumab treatment. However, she was not eligible because BC healthcare plan covered nivolumab only at Stage 4. We were devastated. We searched around the world to buy the drugs from Turkey, India, we tried to fundraise among friends and family. Eventually, by the help of Save Your Skin, the owners of the company provided the drug at free of charge. It was a life-saving. My mom took only 3 doses and the effect on her body was very substantial. We had to stop after 3 doses, but that was sufficient so she lived cancer-free since then. During the past five years, we were fortunate to have her. She took care of our sick dad and saw*

*the birth of 3 new grandchildren. There was a five years given to us as a present and enjoyed it fully. She is now getting ready to see her 4th grandchild in Canada (10th in total), signed up for yoga, eats super healthy. Our kids love her more than they love their own parents for sure."*

*"I already have PTSD from when my husband had unresectable Stage IV metastatic Colorectal cancer in 2009 at age 30 and we advocated for bevacizumab in Alberta. I am numb. Planning for the worst. Can't work. Can't talk to him about this. He is overwhelmed and has PTSD from it too."*

*"Being 27 and knowing you are going to die young."*

*"Physical toll due to the 17 years of battling it and many many surgeries to many parts of my body, financial because of the cost of the drug, emotional because it is so uncertain even to this day if the cancer will progress even more, family toll as my children have to be told every 2 years that my cancer has metastasized to different parts and then endure seeing me with the aftermath of surgeries and recovery. They also suffer from the length of my journey."*

*"Side effects of surgery lymphoedema in both my leg & upper arm."*

*"Metastatic disease has fewer treatment options in Canada vs other countries."*

*"The continued appointments out of province take me away from my family is emotionally stressful."*

*"Physically and emotionally, it has been a rollercoaster. But once given an opportunity to enter a clinical trial allowed me to feel a lot more positive. As well being aware if I had a relapse and the cancer came back I feel much more comfortable the drugs would help me again."*

*"This has been the worst rollercoaster experience in my life. I feel that this has thrown me into limbo where I don't feel like I can make plans for the future. In 1 year, I don't know if I will be cured or dead.... or somewhere in between. I've had to reduce work, so finances have been a struggle. Emotionally, and mentally I am walking on eggshells."*

*"Initial partial paralysis which resolved due to treatment. Relationship with my fiancee fell apart. Forced to retire early due to illness and ongoing treatments."*

*"Had to go off work for a year, disrupted my entire life. Still does. Physically and emotionally draining for myself and my family. Sparks my depression."*

*"After I had to stop the Ipi/Nivo because of side effects and was told there wasn't anything more that could be done possibly a clinical trial. I was not HLA+, Tebe was not an option for me. Waited 6 months to get into a clinical trial in Toronto. I fly into Toronto once a month since Oct 31/22 to present. Treatment would be much*

*better in Edmonton or closer to home where I have more support. It has been very expensive traveling back and forth from Edmonton to Toronto."*

*"Physically, I was stripped of energy. Mentally, I suffered from brain fog and confusion. Emotionally, I find it hard to explain the toll it takes on both yourself and your relationships when you find out you only have 9 months to live. Financially, I closed my small business and haven't been able to work again due to the side effects of the drugs."*

*"Emotionally, it is hard knowing I will not have the life, experiences, and time with my husband, daughters and grandkids that I was looking forward to in retirement."*

When respondents were asked about aspects of melanoma or ocular/uveal melanoma that they feel are more important for them to control than others to maintain their quality of life, their responses highlighted concern about having additional treatment options in case of failure or recurrence. One respondent stressed, *"Access to further treatment in a timely manner, if I require it later, is a huge concern. In Canada, options are limited."* This illuminates the anxiety surrounding timely access to treatments, particularly given the restricted choices within the Canadian healthcare system.

Another participant emphasized the importance of diverse treatment options, stating, *"Treatment options so that when something stops working or doesn't work, we Canadians can have options."* This sentiment echoes the need for a variety of treatments, ensuring patients have alternatives when faced with the ineffectiveness of a particular therapy.

The significance of advancements in immunotherapy was underscored by a respondent who articulated, *"Advances in immunotherapy are critical for prolonging survival."* This perspective emphasizes the pivotal role that ongoing innovations in immunotherapy play in extending the survival rates of individuals grappling with melanoma.

One respondent vividly expressed the fear of being denied access to life-saving drugs stating, *"The fear of not being allowed to take a life-saving drug like the ipi/nevo combo. Had I not been fortunate to raise the funds to pay for this drug (thanks to Save Your Skin), then I would probably not be alive."* This poignant account highlights the life-altering impact of access to specific medications and underscores the vital role that financial considerations can play in treatment options.

These responses collectively highlight the pressing need for diverse, timely, and accessible treatment options for individuals battling late-stage melanoma. The challenges presented by limited options, especially in the Canadian context, underscore the urgency of addressing these access issues to ensure improved outcomes and quality of life for patients.

## 4. Experiences With Currently Available Treatments

**Respondents Diagnoses:**

- (8) Ocular/Uveal melanoma
- (12) Melanoma
- (2) 0/In situ
- (4) Stage I
- (4) Stage II
- (8) Stage III
- (34) Stage IV
- (9) Unresectable conditions
- (29) Metastatic melanoma

**A majority of respondents have undergone Nivolumab and Ipilimumab as treatment. However, their received treatments for melanoma or ocular/uveal melanoma include:**

- (21) Immunotherapy
- (12) Radiation
- (25) Surgery
- (4) Incisions/skin grafts
- (4) Targeted Therapy
- (2) Enucleation
- (2) Chemotherapy
- (1) Avastin injections
- (1) Prednisolone eye drops
- (3) Clinical trials

**It's important to note the years of diagnosis for these respondents:**

- (1) 2003
- (1) 2005
- (1) 2006
- (2) 2007
- (2) 2011
- (5) 2012
- (2) 2014
- (6) 2015
- (3) 2016
- (4) 2017
- (6) 2018

- (3) 2019
- (11) 2020
- (5) 2021
- (10) 2022
- (7) 2023

**In regards to their experience with melanoma or ocular/uveal melanoma, respondents mentioned:**

- (10) Emotional toll
- (8) Mental strain
- (15) Physical challenges
- (4) Financial struggles
- (3) Uncertainty regarding diagnosis
- (2) Concerns about treatment access
- (3) Impact on family and relationships
- (4) Work-related disruptions
- (3) Fear of recurrence
- (3) Traumatic experience
- (3) Anxiety and depression
- (2) Side effects of treatments
- (2) Impact on lifestyle and plans
- (2) Sleep disturbances
- (2) Concerns about spreading
- (2) Impact on appearance
- (2) Challenges with access to treatments
- (2) Survivor guilt
- (2) Adverse effects of treatments
- (1) Coping with physical limitations
- (1) Coping with mobility issues
- (1) Coping with vision impairment
- (1) Coping with disruptions in work and retirement plans
- (1) Coping with changes in self-identity

**When asked about the impact of melanoma or ocular/uveal melanoma on their daily lives, respondents mentioned:**

- (15) Physical side effects
- (13) Mental and emotional impact
- (9) Lifestyle changes
- (6) Impact on relationships and social life
- (5) Financial impact

- (4) Impact on daily life
- (4) Coping mechanisms
- (4) Impact on work and career
- (2) Changes in perception and self-awareness
- (2) Impact on daily tasks and functionality

**While facing numerous challenges, respondents shared personal experiences:**

*"I cannot drive anymore as it went to the brain. I spend most days in bed. I'm so tired I've gained weight. The physical appearance is difficult, and most friends ghost you; that's very hard."*

*"Mentally, it can be a lot as stressful if it spreads."*

*"My life ended."*

*"I am reluctant to be seen in public because of the tumor on my face. Pain management is a consuming fact of life. I have no sense of smell. Food is no longer interesting. Swelling in my eye makes reading difficult. Many of my former activities have been curtailed due to dizziness when crouching or bending over."*

*"Intense fear that you will not be around to support and live life with your family."*

*"Stress, stress, stress - going to Toronto for treatments is particularly difficult."*

*"Constant worry, fear, and stress. Also, because I am (currently) stage 2a, I am not eligible for immunotherapy, and therefore do not have an oncologist to whom I can address my concerns."*

*"Loss of vision. I travel weekly 900 km for treatment. It's insane."*

*"There's virtually no part of my life that melanoma hasn't ripped into. Probably one of the surprising and not positive effects of being diagnosed at stage 4 is that the program melanoma 2.0 is running in the back of my mind constantly. Thinking about clinical studies, diet, parsing out extra scraps of meaning from every word that comes out of the oncologist's mouth, complementary care, worrying, worrying about worrying. The only way the program ends is with cure or death; otherwise, there is only brief respite through distraction."*

*"It's always on my mind. Changed the way I live because I love going outside on sunny days. Now I limit my time in the sun. It's been expensive buying sun protection clothing and better sunscreens."*

*"Other than the exceedingly ugly melanoma staring at everyone I meet and the negative side-effects on my scalp and hair, I look like and feel the absolute picture of health. Mentally, I am the tiniest fraction of the confident active person I used to be."*

Respondents encompassed a diverse array of melanoma diagnoses, with prominent cases of Ocular/Uveal melanoma, melanoma across various stages, and metastatic conditions. Nivolumab + Ipilimumab emerged as a prevalent treatment, alongside immunotherapy, radiation, surgery, and participation in clinical trials. Diagnoses spanned from 2003 to 2023, revealing the prolonged impact of melanoma in some cases. The emotional toll, mental strain, and physical challenges were underscored by numerous respondents, echoing concerns about financial struggles, work disruptions, and fears of recurrence. Beyond statistical insights, the personal narratives painted vivid pictures of life-altering consequences: from the emotional toll and physical limitations to the drastic impact on relationships, daily life, and self-identity.

## 5. Improved Outcomes

When considering improved outcomes, it is crucial to emphasize the diverse experiences of all respondents. It's important to recognize that for some patients, Nivolumab + Ipilimumab for advanced melanoma might be their only lifeline, highlighting the critical role of available treatments. Many respondents express a understanding of this reality, leading to heightened levels of anxiety, depression, stress, and an overwhelming sense of uncertainty and shaping their expectations from the medical system. The provided quotes shed light on these aspects of their melanoma or ocular/uveal melanoma journeys, offering insights that they deem important for others to understand. These narratives reflect a shared desire to assert control over their lives and maintain quality of life, while facing the challenges posed by their diagnosis.

*“There's very little that I can control with regards to this disease. I am working hard a cutting a fine balance between doing everything within my control to have a good outcome, and realizing that the outcome is beyond my control..... I wish we had better data, especially with regards [to] melanoma patients on their 3rd or 4th line of treatment.”*

*“I had no control over anything, it felt like. I was at the mercy of the medical system, the cancer clinic, my oncologist, the drug company, etc. The only thing I could do myself was feed my body properly and do what I could to keep my mental health up.”*

**When inquiring about their preferences for new treatments in the market, respondents shared the following. Many of these responses reiterated the desire for care options in the case of failure or recurrence**

*“Affordable. I was a test study and the combination would have been a financial burden if I didn’t qualify. “*

*“Ipi/nivo approval for reoccurrence and approval of opdualag”*

*“All. Things the US has. All options like immunoembolization, immatics trial, trisalus, TIL, liver directed therapies like delcath”*

*“Continuing research into all of the available evidence on new options”*

*“More treatments with less impactful complications.”*

*“a cancer vaccine is a real possibility to not only vanquish this round of melanoma, but prevent recurrences.”*

*“I would ask that all our existing drugs that have been used to help people get to the remissionstage are kept available. Unfortunately some people think if a new drug becomes available people want to bring it on board but than they eliminate some of the existing drugs. Some of those drugs eliminated have saved lives. I hope and pray that the new drugs will help evenmore people but I hope we do not eliminate the existing ones.”*

*“More treatment options if first treatment protocol doesn't work.”*

*“Protocol is that treatment stops after 2 years Would like to see some sort of on going maintenance to prevent recurrence”*

*“Potential other options should there be a reoccurrence.”*

**We asked respondents to share their insights on how the quality of life for themselves or their support system would have changed if the described improvements were offered by an available treatment. Here are their responses:**

*“huge - constant uncertainty is wildly stressful”*

*“I would be less stressed knowing that there are more options available.”*

*“I wouldn't be using my life savings for treatment...and I would have more time at home with my family.”*

It's crucial to acknowledge that, for some respondents, there were trade-offs that either they or their support system had to consider when selecting a therapy that could impact what they perceive as improved outcomes.

One respondent noted, *“There wasn’t much selection in treatment options when I was diagnosed; once my cancer metastasized, my only option was ipi/novo.”*

Another shared, *“The immunotherapy was the only choice, as otherwise I had been given 1-2 months to live. I was, and still am, extremely thankful that it was available, and that the oncology clinic got me on it very quickly.”*

A participant mentioned, *“For me, there was only one option.”*

Explaining their situation, one respondent stated, *“There really weren't other viable options. I chose Opdivo first to avoid some other more serious side effects of the Yervoy.”*

A challenging decision was described by a respondent: *“I was told that I could not have the immunotherapy in 2018 unless I moved away from my children and husband from Whistler to live in Vancouver closer to the hospital. I was given the ultimatum to choose one or the other. I chose my family. As such, I did not receive*

*proper treatment until too late. I might have not had so many tumors if I had the drug earlier. But my children were young, and I felt they were my priority."*

Reflecting on the limited options, another respondent shared, *"When I was first diagnosed with melanoma (on my face) which could not be totally removed, I was told that my only option was radiation. I am now disfigured for life."*

Summing up the lack of alternatives, one respondent expressed, *"No other options at the time of treatment. This may provide those possibilities."*

**Finally, we asked respondents if, in the case of not having received the Nivolumab + Ipilimumab combination, it would be important to them to have access to it. This question encompasses everything that has been stated above, and the respondents had this to say:**

*"Yes, it's my understanding that it's a very promising treatment, and I would certainly want the option."*

*"Absolutely, I would want it. It looks like a brilliant track to get rid of my stage four for the minute; it's just sad it's gone to my brain."*

*"Receiving one type of immunotherapy for a certain period of time can also limit or block your access to other types. Some of these rules seem arbitrary; made with the goal of saving money for the province, with limited concern for people's lives."*

*"Extremely important to have treatment options available."*

*"Yes, and possibly less chances of recurrence."*

*"Absolutely important, the drugs I'm on at present are only partially working. I may need these drugs in the future."*

*"Yes I believe it is critical that people have access to this combination. If I wasn't given that opportunity I know for a fact I wouldn't be on this earth. It has saved my life."*

*"Yes, yes and yes.... since we don't know why one person responds and another doesn't, it is really important to have all options for saving people's lives!"*

*"Absolutely. I would like to see it available to all cancer patients where it has a reasonable chance of helping them."*

*"ABSOLUTELY yes!!!! It has been life saving to me and my neighbour in Whistler also had melanoma and he is cancer free for over 5 years after taking Ippi."*

## 6. Experience With Drug Under Review

**We inquired from respondents whether they have undergone Nivolumab + Ipilimumab treatment for stage III or IV melanoma or stage IV ocular/uveal melanoma, with the following breakdown:**

- (31) confirmed having received the drug
- (26) reported not having undergone this treatment at all.
- (2) skipped the question

**Regarding the cancer stage at which they received this treatment, applicable respondents mentioned:**

- (2) Ocular/uveal melanoma
- (12) Melanoma
- (3) Stage III
- (26) Stage IV
- (6) Unresectable
- (22) Metastatic

**When asked if these respondents received Nivolumab + Ipilimumab as a first or second-line treatment:**

- (18) First line
- (9) Subsequent treatment option
- (4) Responded other

**Respondents' methods of obtaining this treatment included:**

- (5) Clinical trial
- (2) Compassionate access
- (2) Private payer
- (3) Not sure
- (19) Responded other

**Regarding completion of the full course of treatment:**

- (11) Yes
- (3) Still in treatment
- (15) No

Respondents who did not complete the full course cited severe complications like pneumonia, colitis, hepatitis, kidney issues, and potentially life-threatening side effects.

**Side effects experienced during treatment:**

- (23) Fatigue
- (3) Cognitive impairment
- (9) Fever
- (7) Nausea and/or vomiting
- (19) Skin rash
- (9) Damage to organs
- (6) Gastrointestinal issues
- (4) Breathing problems
- (8) Headaches
- (11) Weight loss or weight gain
- (5) Loss or gain of appetite
- (14) Other

A notable comment was, “It attacked my Petrucci gland; I had diabetes, jaundice, hepatitis, vitiligo, liver failure, shingles, pneumonia.”

**When asked if the side effects were manageable, the average rating was 3.0 out of 5, with a 5 indicating “completely manageable.”. Respondents on whether the experienced side effects outweigh the benefits:**

- (22) Yes
- (2) No
- (2) Unsure
- (3) Not applicable
- (2) Other

It's crucial to highlight that some respondents faced challenges accessing treatment due to travel distances and personal expenses.

**Regarding the importance of receiving this treatment to their support system:**

*“Crucially, as it was a life or death situation.”*

*“It meant everything.”*

*“Extremely important as it kept me alive when the initial prognosis was dire.”*

*"Life-saving - can't put a price on it. I am alive only because of this treatment."*

*"Very important - life-saving"*

**When asked to elaborate further and share insights with decision-makers:**

*"We were very grateful to have had it as it appeared to slow my tumor growth for at least 7 months."*

*"Complete response in 3 months, been NED for 3 years. Lucky to be approved for ipi/nivo again."*

*"Hope it becomes more available; it saved my life."*

*"Improving testing and tracking of patients through immunotherapies is essential to determine who will benefit without unnecessary risks."*

*"Wish access to the drug was faster; there should not be a monetary barrier to a life-saving drug. This drug has slowed the process of death by melanoma for me."*

## 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."*

*"Great. I knew they would do everything possible for me and I wanted holistic, comprehensive testing"*

*"Fine, it was important."*

## 8. Anything Else?

The survey findings resoundingly emphasize that for a significant number of individuals dealing with advanced melanoma, particularly those experiencing progression during or within six months of adjuvant PD-1 therapy, Nivolumab + Ipilimumab stands out as not just a treatment option but as a potential lifeline. The compelling narratives shared by respondents underscore the pivotal role of this combination, suggesting that its exclusion from public reimbursement could starkly limit patients' access to crucial life-saving interventions, potentially compromising their chances of survival and overall well-being. This is particularly true for ocular melanoma patients, who face a rare and potentially debilitating disease with only one or two care options.

The resounding call is for decision-makers to acknowledge the unique and often irreplaceable position that Nivolumab + Ipilimumab holds in the landscape of advanced melanoma treatment, highlighting the pressing need for their public reimbursement to ensure equitable accessibility for all individuals facing these challenging diagnoses.

In light of the survey's comprehensive insights into the experiences of those with melanoma and ocular melanoma, there is a compelling case for decision-makers to prioritize the public reimbursement of Nivolumab + Ipilimumab. The narratives showcase that the patient experience of melanoma or ocular melanoma is incredibly challenging, and public reimbursement of this combination would take financial pressure off of some patients, while also offering the assurance of another option in the case of failure or recurrence. This latter point was highlighted repeatedly by respondents in different contexts throughout the survey.

The urgency is clear from these patient perspectives: securing public reimbursement for these therapies is essential to address the unique challenges posed by advanced melanoma and ocular melanoma, offering affected individuals a fighting chance and a pathway to an improved quality of life.

## 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 |
|---|---|---|---|---|
| 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
Patient Group: Save Your Skin Foundation
Date: January 8th, 2024

Canadian Agency for Drugs and Technologies in Health (CADTH)
865 Carling Ave., Suite 600
Ottawa, ON Canada K1S 5S8

**December 12, 2023**

**Name of Drug:** Nivolumab (Opdivo®) + Ipilimumab (Yervoy®) for Stage III and IV Melanoma
**Indication:** A treatment for advanced melanoma in Stages III and IV when patients progress during or within 6 months of Adjuvant PD-1 Therapy
**Policy Question:** Should Nivolumab (Opdivo®) + Ipilimumab (Yervoy®) be publicly reimbursed for advanced melanoma [and ocular/uveal melanoma] in patients who progress during or within 6 months of adjuvant PD-1 therapy?
**Name of Patient Group Affiliation:** Save Your Skin Foundation

To the CADTH Reimbursement Review Committee,

My name is Joan Denroche and I am a patient and survivor with Stage 4 melanoma. I am aware that CADTH is currently doing an evaluation of Nivolumab (Opdivo®) + Ipilimumab (Yervoy® ) for continued public reimbursement approval in Canada. I believe it is critical that melanoma patients have this combination as an option for care. Having as many treatment options for adjuvant, metastatic melanoma and ocular melanoma is imperative, as every patient is different, and every patient deserves to have multiple options. The possibility of access to Nivolumab (Opdivo®) + Ipilimumab (Yervoy®) could mean the difference between life and death for those who, without this combination, would have very limited options.

**I would like to tell you about my experience with melanoma and why I believe this treatment option should be reimbursed in Canada…**

My journey with melanoma started in 2007 when a small pimple did not go away. When a doctor finally relented to have it biopsied I was told that I had less than 6 months to live. My children were 5 and 7 years old and I was a single mother.

I had 4 surgeries to try to get a clear edge. The surgeries were not successful and I was told to get my estate in order. I begged a Mohs surgeon to try to help me resect this tumor without the cut and paste attempt as the past surgeries. He finally agreed but it was an 11 hour surgery all while I was awake. It had a huge toll on my but also the surgeon. I can not imagine how expensive it was for the health care system. My success of overcoming melanoma was short lived.

I was cancer free for 2 years until I was diagnosed with cervical cancer. This turned into a blessing in disguise as I was scanned and a lung tumor from metastatic cancer was found. Again I went through cervical cancer surgery and then less than a year later, a lung resection. Many more surgeries – more time in hospitals. It was only at this time that I was assigned an

oncologist. She offered me an immunotherapy trial drug but I was informed that I had to leave my family and live in Vancouver. This was an impossible decision both emotionally and financially. If you are told you have limited time to live the choice to live alone in an apartment while your children and husband were hours away; it was unfathomable. I chose my family. As such I had more mets develop and therefore more surgeries.

I started Nevo when I was found with a non- resectable met in my other lung. After this I changed oncologists and I was allowed to go on Nevo trial but I had to have someone drive me to and from Vancouver 1.5 hours each way. I had to leave my children but at least it was only for the day. Had I been on Nevo earlier I think I would not have had the mets. It was the barrier of the forced move that meant that I was untreated.

I was treated with Nevo for 3 years when a scan of my brain was done and there was a brain met. I had brain surgery and also radiation. Then I was offered the combination but the problem was that since I had been on Nevo there was no trial option for me so I had to come up with 80,000 dollars. Thankfully Save Your Skin guided me through this challenge and I was able to come up with the funds to pay for the series of treatments. I believe that the treatments DEFINITELY slowed the progress of my melanoma and has allowed me to survive for 17 years when I was originally given 6 months. I truly believe that if others were given the drugs early then there would be less cost on the medical system as there would be less need for expensive and personally expensive surgeries.

I am a contributing member of society and have been allowed to be with my children all through their developing years, which is invaluable. My hope is that all people with diagnosed with any form of melanoma is given the opportunity to access *the Nivolumab (Opdivo®) + Ipilimumab (Yervoy) combination.* Had I not been able to raise the funds for the combo drug I know that I would have been a very costly patient in the health care system as I would have many more mets and surgeries.

Please help people survive and live their lives to the fullest. These drugs allow this. Today I am still living with cancer but I have hope and believe that I still have a future.

Thank you for your consideration.

Best,
**Joan Denroche**
[redacted]

John Walker MD PhD FRCPC
Division director, Medical Oncology
Associate Professor of Oncology
Cross Cancer Institute
Edmonton, AB
T6G 1Z2

Canadian Agency for Drugs and Technologies in Health (CADTH)
865 Carling Avenue, Suite 600
Ottawa, ON
K1S 5S8

December 27, 2023

**Subject: Clinician Statement regarding Nivolumab + Ipilimumab in the treatment of metastatic melanoma in patients who have recurred while receiving or within 6 months of completing adjuvant anti-PD-1 therapy**

**CADTH project number:** PX0347-000
**Indication:** In combination, for the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma when patients progress during or within 6 months of adjuvant PD-1 therapy.
**Name of clinician group:** A national consortium of medical experts experienced in the treatment of malignant melanoma.
**Author of submission:** John Walker, MD PhD FRCPC.

Dear colleagues:

We are providing this letter of support for the approval of first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma when patients progress during or within 6 months of completing adjuvant PD-1 therapy.

We are a consortium of expert-physicians with extensive experience in the treatment of patients with malignant melanoma. While we are not a formal physician group, collectively we represent a physician cohort responsible for the treatment of most Canadians with malignant melanoma. Included among the undersigned are authors of the pivotal registration clinical trials which have transformed the treatment landscape for patients with advanced malignant melanoma. This statement is provided within the context of our expertise as medical oncologists with the requisite Canadian qualifications, including Royal College of Physicians and Surgeons of Canada (adult medicine, medical oncology) certification.

There is a serious and pressing unmet need for Canadian patients with metastatic melanoma who prove resistant to currently available therapies, specifically treatment with nivolumab or pembrolizumab in the adjuvant setting. Although the treatment landscape for these patients has changed dramatically over the past decade, the number of available therapies remains few, and for the roughly one-half of patients who progress during or shortly after anti-PD1 therapies, often only supportive care is available. Melanoma is the most common cancer in young adults aged 20-29, thus it is our limited access to effective therapies that results in our inadequate treatment of these patients rather than patient fitness.

Currently the combination of nivolumab plus ipilimumab is not available after melanoma recurrence while receiving (or within 6 months of completing) adjuvant therapy with the immune checkpoint inhibitors nivolumab or pembrolizumab. This limitation is not supported by clinical grounds nor currently available data. The original trials of nivolumab combined with ipilimumab were conducted in a time period where adjuvant therapy was not available, thus limiting the extrapolation of data to patients who were treated with immunotherapy in the adjuvant setting.

There is both prospective and retrospective data (references below) that demonstrate efficacy and long-term durable cancer control with nivolumab in combination with ipilimumab in a significant subset of patients who progress on or soon after adjuvant anti-PD1 therapy. An additional reference demonstrates the lower response rate of ipilimumab monotherapy within this patient population. ***Importantly, in contrast to most other advanced cancers the durable responses observed following treatment with ipilimumab in combination with nivolumab represent a potential cure, even in the setting of advanced disease.***

References for consideration:

1. ILLUMINATE 301: A randomized phase 3 study of tilsotolimod in combination with ipilimumab compared with ipilimumab alone in patients with advanced melanoma following progression on or after anti-PD-1 therapy. Journal of Clinical Oncology 37, no. 15_suppl. ClinicalTrials.gov Identifier: NCT03445533.
2. VanderWalde A, Moon J, Bellasea S, et al. Ipilimumab plus nivolumab versus ipilimumab alone in patients with metastatic or unresectable melanoma that did not respond to anti-PD-1 therapy. Presented at: 2022 AACR Annual Meeting; April 8-13, 2022; New Orleans, LA. Abstract CT013.
3. Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD 1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. The Lancet Oncology 2021.
4. Data from the Opdivo Melanoma Continuation Program (OMCP) in Australia from November 2022 to June 2022.

At present, the only standard-of-care immunotherapy treatment available in Canada for patients who recur on or within 6 months of receiving adjuvant treatment with nivolumab or pembrolizumab is ipilimumab monotherapy. A recent large, prospective, randomized clinical trial (reference 1) demonstrated an objective response rate of just 8.6% with this approach to treatment. Conversely, a recent prospective randomized clinical trial (reference 2) and a large

multicentre retrospective analysis (reference 3) show improved outcomes with combination nivolumab plus



ipilimumab versus ipilimumab alone. In this prospective clinical trial which included patients progressing post adjuvant PD1 therapy, a response rate of 28% in patients treated with nivolumab in combination with ipilimumab was observed, versus just 9% in the ipilimumab-treated cohort. Six month progression-free survival between the two treatment arms also varied significantly: of in patients who had progressed on or after PD1-directed therapy 34% of combination-treated patients were alive and progression-free at this benchmark, versus just 13% of the ipilimumab treated cohort. In the retrospective analysis by Pires da Silva (reference #3) which also included patients progressing post adjuvant therapy, overall response rate was 13/36 (36%) with combination ipilimumab plus nivolumab compared to an overall response rate of 1/8 (13%) to ipilimumab alone. While these patients who progressed on or after adjuvant therapy represent a subgroup of the larger cohort of patients progressing on anti-PD1 therapy in the metastatic setting, the results are consistent across all populations. Lastly, the Australian prospective clinical experience with the OMCP (reference 4), provides data on 42 patients who progressed on or within 6 months after anti-PD1 therapy in the adjuvant setting. The Overall Response Rate was 47.6%, which is a clinically meaningful improvement over the historical experience of ipilimumab in this setting (ORR ~<10%). Further, the twelve-month progression-free and overall survival of 43%
and 44%, respectively, illustrates the clinical significance of offering these patients combined immunotherapy treatment following failure of PD-1 -directed monotherapies.

Given this impressive data, it should be noted that in providing access to ipilimumab monotherapy and not the combination of ipilimumab plus nivolumab, practice patterns in Canada have become discordant with almost all comparable jurisdictions, including the United States, Europe and Australia.

It is important to note that in the Australian OMCP, the incremental cost of adding nivolumab to ipilimumab comprised an average of 3 doses of nivolumab (1 mg/kg per dose every 21 days) in the induction phase and an average of 3 doses of nivolumab (480 mg every 28 days) in the maintenance phase. The incremental cost increase associated with utilizing ipilimumab in combination with nivolumab in the post-PD1 patient population only includes the cost of nivolumab, as current Canadian reimbursement guidelines permit the use of ipilimumab in this setting. We suggest that treatment with ipilimumab in combination with nivolumab for patients who progress during or shortly after treatment with nivolumab is highly cost-effective when the clinically significant improvement in efficacy is considered.

Of note, there was no unexpected additional toxicity when ipilimumab in combination with nivolumab following progression of disease on PD-1 monotherapy was examined. As such, in Australia, the United States, and the European Union, the combination of ipilimumab and nivolumab is now considered the standard-of-care for patients who recur on or soon after adjuvant PD1, and in the majority of non-Canadian centers the combination is standard-of-care for those that progress with first-line PD1 in the metastatic setting, as well.

Taken together, these data support the use of ipilimumab in combination with nivolumab after progression on or soon after treatment with anti-PD1 therapy. 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 ipilimumab in combination with nivolumab for the Canadian patient population outlined in this statement.

Such as monitoring social media metrics



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 Matthew Anaka, Cross Cancer Institute, Edmonton, Alberta
Dr Vanessa Bernstein, British Columbia Cancer Agency, Victoria, British Columbia
Dr Parneet Cheema, William Osler Health System, Brampton, Ontario
Dr Tina Cheng, Tom Baker Cancer Center, Calgary, Alberta
Dr Khashayar Esfahani, McGill University, Montreal, Quebec
Dr Caroline Hamm, Windsor Regional Hospital, Windsor, Ontario
Dr Marco Iafolla, William Osler Health System, Toronto, Ontario
Dr Robyn Macfarlane, QEII Health Sciences Center, Halifax, Nova Scotia
Dr Catalin Mihalciooiu, Cedars Cancer Center, Montreal, Quebec
Dr Wilson Miller, Jewish General Hospital, Montreal, Quebec
Dr Jose Monzon, Tom Baker Cancer Center, Calgary, Alberta
Dr Sudha Rajagopal, Peel Regional Cancer Center, Mississauga, Ontario
Dr Kerry Savage, British Columbia Cancer Agency, Vancouver, British Columbia
Dr Eve St-Hilaire, Dr Léon Richard Oncology Center, Moncton, New Brunswick
Dr John Walker, Cross Cancer Institute, Edmonton, Alberta
Dr Alison Weppler, British Columbia Cancer Agency, Vancouver, British Columbia
Dr Ralph Wong, CancerCare Manitoba, Winnipeg, Manitoba
Dr Joel Claveau, CHU de Québec, Quebec city, Quebec
Dr Michael Humphreys, BC Cancer Medical Oncologist, Vernon, BC

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Matthew Anaka**
**Position: Medical Oncologist**
**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

| **Company** | **Check appropriate dollar range** | | | |
|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| Not applicable. I have no relevant conflicts of interest to disclose. | | | | |

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

Matthew Anaka MD PhD FRCPC
Assistant Professor of Oncology
Cross Cancer Institute
Edmonton, AB

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Vanessa Bernstein**
**Position: Medical Oncologist**
**Institution: BCCA Victoria**
**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

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|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS honoraria/consultancy | X | | | |
| BMS– unrestricted educational grants to BC Cancer Skin Tumor Group retreats | | X | | |

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

Vanessa Bernstein, MSc, MD, FRCPC
Clinical Associate Professor
Division of Medical Oncology
University of British Columbia
Chair BC Cancer Skin Tumor Group
[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Parneet Cheema**
**Position: Medical Oncologist**
**Institution: CCO Brampton**
**Date: December 27, 2023**

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| | | | | |
| | | | | |
| | | | | |

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

Dr. Parneet Cheema, MD, MBiotech, FRCPC
Assistant Professor, University of Toronto
Director of Cancer Care | Medical oncologist
William Osler Health System
Brampton, Ontario
[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**

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| | **$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.**

**Dr Tina Cheng**
Associate Professor
Division of Medical Oncology
Department of Oncology
University of Calgary Cumming School of Medicine
1331-29 Street NW
Calgary, Alberta T2N 4N2
[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Khashayar Esfahani Position: Medical Oncologist**
**Institution: McGill University**
**Date: December 27, 2023**

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|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS | X | | | |
| | | | | |
| | | | | |

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

Khashayar Esfahani, M.D. M.Sc.
Assistant professor of Oncology
McGill University
Canada
[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Caroline Hamm**
**Position: Medical Oncologist**
**Institution: Medical Oncology Windsor Regional Hospital**
**Date: December 27, 2023**

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Table 1: Conflict of Interest Declaration for Physician

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|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| Nothing to disclose. | | | | |

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

**Caroline Hamm, MD**
Medical Oncologist
Melanoma specialist
[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Marco Iafolla**
**Position: Medical Oncologist**
**Institution: William Osler Health System Date: December 27, 2023**

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Table 1: Conflict of Interest Declaration for Physician

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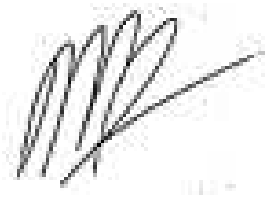
|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| Novartis | X | | | |
| Bayer | X | | | |
| Canadian Urologic Association | X | | | |
| CompassMD | X | | | |
| Ipsen | X | | | |
| MD Analytics | X | | | |
| Merck | X | | | |
| Sanofi | X | | | |
| Save Your Skin | X | | | |
| Sermo Team | X | | | |

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



Dr Marco Iafolla, MD, MSc, FRCPC
Assistant Professor, University of Toronto
Medical Oncologist
Genitourinary and Cutaneous Site Lead
William Osler Health System

[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Robyn Macfarlane**
**Position: Medical Oncologist**
**Institution: QEII Health Sciences Center 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

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|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS | X (speakers fees/honoraria – advisory board) | | | |
| | | | | |
| | | | | |

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

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Catalin Mihalcioiu**
**Position: Medical Oncologist**
**Institution: Cedars Cancer Center**
**Date: December 27, 2023**

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Table 1: Conflict of Interest Declaration for Physician

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| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS (consulting) | X | | | |
| | | | | |
| | | | | |

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

**Dr Catalin Mihalcioiu**
Assistant Professor of Oncology and Medicine
McGill University Health Centre
Cedars Cancer Centre
1001 Decarie Boulevard
Montreal, Quebec H4A 3J1

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Wilson Miller**
**Position: Medical Oncologist**
**Institution: Jewish General Hospital, McGill University**
**Date: December 27, 2023**

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Table 1: Conflict of Interest Declaration for Physician

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|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS (consulting) | X | | | |
| BMS (clinical trial payments to the Jewish General Hospital | | | | X |
| | | | | |

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

**Dr Wilson Miller, MD FRCPC**

# Conflict of Interest Declaration of the Additional Supporting Authors

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

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| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS consulting | X | | | |
| | | | | |
| | | | | |

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

Jose G. Monzon
Ph.D., M.D., F.R.C.P.C.
Medical Oncologist
Medical Leader, Clinical Research Unit
Tom Baker Cancer Centre
[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Sudha Rajagopal**
**Position: Medical Oncologist**
**Institution: Peel Regional Cancer Center 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.

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| BMS | X | | | |
| | | | | |
| | | | | |

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

**Sudha Rajagopal MD, FRCPC**
Medical Oncolgist
Skin Site Group Lead
Peel Regional Cancer Center
University of Toronto
THP, Mississauga, Ontario
[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Kerry Savage**
**Position: Medical Oncologist**
**Institution: Medical Oncology Vancouver BCCA Date: December 27, 2023**

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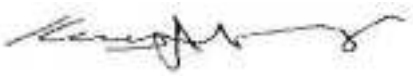
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS Research funds | | | | X |
| Merck, Seagen, Janssen, Abbvie | X | | | |
| | | | | |

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



Kerry Savage, MD MSc
Medical Oncologist, BC Cancer
Professor of Medicine, UBC
Systemic therapy lead, Skin Tumor Group
[redacted]

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Eve St-Hilaire**
**Position: Medical Oncologist**
**Institution: Dr Leon Richard Oncology Center Date: December 27, 2023**

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| BMS | X | | | |
| | | | | |
| | | | | |

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

**Dr Eve St-Hilaire, MD FRCPC**

# Conflict of Interest Declaration of the Additional Supporting Authors

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

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|---|---|---|---|---|
| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| Bristol-Myers Squibb | X (advisory board) | | | X (research funds) |
| | | | | |
| | | | | |

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

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

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Alison Weppler, MD Position: Site Lead Skin and Melanoma Team**
**Institution: BCCA - Vancouver**
**Date: January 4, 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.

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| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| Bristol-Myers Squibb (advisory board); 2022/23 | X | | | |
| | | | | |
| | | | | |

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

Dr. Alison Weppler, MD MPH FRCPC
Assistant Clinical Professor, University of British Columbia
Site Lead Skin and Melanoma Team
BC Cancer – Vancouver
Vancouver, BC

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Dr Ralph Wong**
**Position: Medical Oncologist**
**Institution: Medical Oncology Vancouver BCCA Date: December 27, 2023**

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| BMS | Advisory Board | | | |
| | | | | |

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

Ralph Wong MD
Medical Oncologist
CancerCare Manitoba
Winnipeg

# Conflict of Interest Declaration of the Additional Supporting Authors

**Name: Joel Claveau, MD, CSPQ, FRCPC**
**Position: Dermato-Oncologist**
**Institution: Melanoma Clinic, CHU, Quebec City, QC Date: December 27, 2023**

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| | **$0 - $5000** | **$5001 - $10 000** | **$10 001 - $50 000** | **In excess of $50 000** |
| BMS | X | | | |
| Merk | | X | | |
| Novartis<br>Pfizer | | X<br>X | | |

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

Joel Claveau, MD, CSPQ, FRCPC
Dermato-Oncologist
CHU de Québec, Quebec city, QC, Canada

# Conflict of Interest Declaration of the Additional Supporting Authors

| | |
|---|---|
| **Name:** | **Dr. Michael Humphreys** |
| **Position:** | **Medical Oncologist** |
| **Institution:** | **BC Cancer** |
| **Date:** | **January 8, 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 Physician

| Company | Check appropriate dollar range | | | |
|---|---|---|---|---|
| | $0 - $5000 | $5001 - $10 000 | $10 001 - $50 000 | In excess of $50 000 |
| Bristol-Myers Squibb (advisory board/speaking engagements 2022 | X | | | |
| Bristol-Myers Squibb (advisory board/speaking engagements 2023 | X | | | |
| | | | | |

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

Dr. Michael Humphreys
BC Cancer Medical Oncologist
Clinical Instructor, UBC
McMurtry and Baerg Cancer Center
Vernon Jubilee Hospital, Vernon, BC
[redacted]

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 of Patient Perspectives on Nivolumab (Opdivo®) + Ipilimumab (Yervoy®) for Stage III and IV Melanoma and Ocular/Uveal

The Canadian Skin Patient Alliance (CSPA) is committed to advancing healthcare access, patient well-being, and informed decision-making in Canada. We lend our robust support to the CADTH submission titled "Nivolumab and Ipilimumab for Advanced Melanoma When Patients Progress During or Within 6 Months of Adjuvant PD-1 Therapy" spearheaded by Save Your Skin Foundation.

Recognizing CADTH's pivotal role in assessing pharmaceutical treatments for efficacy, safety, and cost-effectiveness, we emphasize the paramount importance of incorporating the patient's perspective. This inclusion is vital for aligning treatments with the distinctive needs of patients.

Our organization strongly advocates for patient-centric approaches to healthcare decision-making, supporting the commendable initiatives of Save Your Skin Foundation in gathering and presenting patient perspectives to CADTH. This collaborative effort aims to empower decision-makers with a more comprehensive understanding, enabling them to offer well-informed recommendations that prioritize patient well-being. The potential outcome includes the broadening of treatment options and streamlining access to therapies like Nivolumab and Ipilimumab for individuals with advanced melanoma. We strongly urge the consideration of these therapies for public reimbursement, especially for patients who experience progression during or within 6 months of adjuvant PD-1 therapy.

In summary, we express our unwavering support for the CADTH submission, "Patient Opinions on Nivolumab (Opdivo®) + Ipilimumab (Yervoy®) for Stage III and IV Melanoma and Ocular/Uveal," led by Save Your Skin Foundation. We believe that both our organizations share a common commitment to patient-centered healthcare, and this survey signifies a significant stride toward achieving this objective.

We respectfully urge CADTH to consider the insights garnered in this survey during the evaluation of Nivolumab (Opdivo®) + Ipilimumab (Yervoy®) for Stage III and IV Melanoma and Ocular/Uveal. Thank you for your dedicated attention to this crucial matter. For further inquiries

G303-851 Industrial Ave
Ottawa, Ontario K1G 4L3
[redacted]
www.canadianskin.ca

Unite.
Educate.
Empower.

or additional information, please feel free to contact us. We eagerly anticipate ongoing collaboration for improved healthcare outcomes in Canada.

Sincerely,

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

CADTH

# CADTH Reimbursement Review

## Clinician Group Input

CADTH Project Number: PX0347
Generic Drug Name (Brand Name): Nivolumab and ipilimumab
Indication: In combination, for the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma when patients progress during or within 6 months of adjuvant PD-1 therapy
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 by a videocall and finalized by email.

### 3. Current Treatments and Treatment Goals

The Skin DAC is asking to expand the scope and indication to give nivolumab/ipilimumab when patients progress during or within 6 months of PD-1 therapy regardless of BRAF mutation status and regardless of whether PD-1 therapy was given in adjuvant or metastatic setting.

The current treatments available for this new indication are ipilimumab monotherapy and BRAF targeted therapy (if BRAF mutated).

The treatment goals are to delay disease progression, improve quality of life, improve response rate and overall survival.

### 4. Treatment Gaps (unmet needs)

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

Ipilimumab monotherapy has a lower response rate while the combination of nivolumab-ipilimumab shows a higher response rate as per the S1616 study.

There are limited treatment options for patients without a BRAF mutation and for patients that have progressed post-BRAF targeted therapy.

### 5. Place in Therapy

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

Nivolumab-ipilimumab would be indicated for patients who relapse during or within 6 months of PD-1 therapy regardless if adjuvant or metastatic, and regardless of BRAF mutation status.

### 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 metastatic or recurrent disease that have failed monotherapy.

### 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?

Indicators of treatment response include clinical stabilization, radiographic response and improvement in quality of life.

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

Factors to consider when deciding to discontinue treatment include toxicity, clinical deterioration, and disease progression.

### 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]?

Outpatient setting under the advisement of a medical oncologist.

## 6. Additional Information

The skin DAC strongly believe this is an unmet need. This treatment is considered standard in other countries (i.e., US, Australia).

The NCCN guidelines do not exclude the use of ipilimumab-nivolumab in patients who have progressed on or within 6 months of PD-1 therapy.

## 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:** 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 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** |
| BMS | 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: 14-12-2023

☒ 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 |
| BMS | 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 |
| BMS | 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: 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 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 | | | |

* 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: 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 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 | | | |

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

**Post Adjuvant PD1 inhibitor**

This is area of unmet need. Patient who progressed within 6 months of finishing adjuvant immunotherapy, and are BRAF mutation negative, have very limited option. There is data supporting improved outcome in patient receiving doublet treatment (continuation of nivolumab with addition of ipilimumab) in this situation. As number of such patients would be low, it would not pose significant burden on the budgeting. As a medical oncologist treating melanoma, I would strongly advocate for approval of combination regimen in this situation.

**Anti-PD-1 monotherapy in the metastatic setting**

Other group of patients who are in similar situation are those who are progressing on PD-1 monotherapy. Again there is good clinical data to support using doublet immunotherapy (i.e. Continuation of nivolumab with addition 4 cycles of ipilimumab) in this situation. Majority of patients who are fit and able to tolerate doublet immunotherapy upfront would receive that but certain patients who are of at low risk (i.e. Low burden of disease), older age group, and with some comorbidity are treated with single agent immunotherapy to spare them from toxicity of doublet treatment. However when the progress on single agent treatment, sadly we are not allowed to add CTLA 4 inhibitor to existing PDL1 inhibitor. This is also a unmet need and doublet treatment should be allowed in this situation.

CADTH

# CADTH Non-Sponsored Reimbursement Review

## Industry Input

CADTH Project Number: PX0347-000
Generic Drug Name: nivolumab and ipilimumab
Indication: In combination, for the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma when patients progress during or within 6 months of adjuvant PD-1 therapy.
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 scope of this project focusing on the use of nivolumab + ipilimumab does align with Canadian physicians, patients and patient advocacy groups needs.

Adjuvant anti-PD-1 therapy following the resection of stage IIB/C, III & IV melanoma is the current standard of care in Canada. However, Canada is currently a unique country worldwide where the access to nivolumab + ipilimumab upon progression on or within the 6 months following an anti-PD1 in the adjuvant setting is restricted, since Australia recently lifted this restriction.[1] The current treatment algorithm limits the use of subsequent first-line anti-PD1 containing regimens including the nivolumab + ipilimumab combination, leaving ipilimumab monotherapy as the only approved treatment option for Canadian patients whose melanoma does not harbor a BRAF-mutation (aka BRAF wild type), as combination targeted therapy is available as an option for those with BRAF-mutated disease. The justification or rationale for the 6-month wash-out period used by CADTH jurisdictions is based on a November 2019 CADTH "Optimal Use 360 Report" on "Dosing and Timing of Immuno-Oncology Drugs".[2] This report was produced outside of the drug reimbursement reviews conducted by CADTH. As such, it is not based on the usual systematic review of scientific evidence, but rather based largely on a consultation process with local experts to help better understand appropriate use in clinical practice. Of note, nivolumab + ipilimumab is currently approved by Health Canada regardless of prior adjuvant or neoadjuvant therapy.[3]

Since the publication of this report in November 2019, the clinical practice has evolved significantly, and physicians worldwide are able to prescribe nivolumab - ipilimumab for the first line treatment of melanoma in the metastatic setting regardless of the timing relative to the last dose of anti-PD1 received as adjuvant treatment. This allows patients to benefit from the superior efficacy associated with dual immunotherapy.

Anti-PD1-based regimens, including nivolumab + ipilimumab, nivolumab monotherapy and pembrolizumab monotherapy are used by the majority of advanced/metastatic melanoma patients in a first-line setting.[4]

However, they are unavailable to the Canadian patients who unfortunately progress to unresectable/metastatic disease on or within 6 months from their last dose of anti-PD1 therapy received in the adjuvant treatment

setting. These so-called “rapid progressors” represent one of the most significant treatment gaps that currently exists in the Canadian melanoma treatment landscape. The majority of patients who progress rapidly on adjuvant anti-PD-1 therapy go on to receive ipilimumab monotherapy, which has been shown to provide less clinical benefit compared to the combination of nivolumab + ipilimumab in anti-PD-1 refractory patients.[2,5-7] Moreover, the unmet need for rapid progressors patients has been extensively highlighted by Canadian physicians and patient advocacy groups in multiple forums such as the Canadian Melanoma Conferences.

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

Several published studies relevant to the clinical review are presented below. It should be noted that specific studies and/or datasets in the post adjuvant anti-PD1 setting are limited, and we rely heavily on data from patients treated with anti-PD-(L)1 in the metastatic setting. Randomized clinical trials of nivolumab + ipilimumab vs ipilimumab are no longer considered an ethical clinical undertaking in the context of the data available to date and therefore cannot be expected to take place in the future.

***da Silva et al (2021)[6]***

This is a multicenter, retrospective, cohort study completed at 15 melanoma centers in Australia, Europe and the USA. The study included adults (≥18 years) with unresectable Stage III or IV metastatic melanoma who were resistant to anti-PD-(L)1 (innate or acquired resistance) and who then received either ipilimumab monotherapy or ipilimumab plus anti-PD-1 (PEMBRO or NIVO) between 1 February 2011 to 6th February 2020. Patients who received ipilimumab previously were excluded, but other previous use of systemic treatments (BRAF and MEK inhibitors, other ICI and chemotherapy) were allowed. No other inclusion or exclusion criteria were used in the patient selection for the study. Progressive disease with anti-PD-(L)1 was defined according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) according to the doctor’s best estimate, but no confirmatory scans were done. The study endpoints were ORR, PFS, OS and safety of ipilimumab compared with ipilimumab + anti-PD-1. This study included 355 patients with metastatic melanoma, resistant to anti-PD-(L)1, who had been treated with ipilimumab monotherapy (n=162 [46%]) or ipilimumab plus anti-PD-1 (n=193 [54%], of note n=192 [99%] were treated with the Health Canada approved nivolumab 1mg/kg + ipilimumab 3mg/kg dosing). The objective response rate (ORR) for the entire patient population was higher with ipilimumab plus anti-PD-1 (60 [31%] of 193 patients) than with ipilimumab monotherapy (21 [13%] of 162 patients; p<0·0001; table 2). In addition, a subgroup analysis looking at only patients who progressed on prior anti-PD-(L)1 in the adjuvant setting (n=44, n=36 treated with ipilimumab + anti-PD-1, n=8 ipilimumab) showed a higher ORR in the combination patients vs ipilimumab monotherapy, 36% vs 13% [odds ratio = 0·25 (0·03–2·270]. In the entire patient population overall survival was also significantly longer in the ipilimumab plus anti-PD-1 group (median 20·4 months [95% CI 12·7–34·8]) than in the ipilimumab monotherapy group (8·8 months [6·1–11·3]; hazard ratio [HR] 0·50 [0·38–0·66], p<0·0001. 1-year overall survival, analyzed post hoc, was 58% (95% CI 51–66) in the ipilimumab plus anti-PD-1 group (73 deaths) versus 38% (31–48) in the ipilimumab group (89 deaths).

PFS was also longer in the ipilimumab plus anti-PD-1 group (median 3·0 months [95% CI 2·6–3·6]) than in the ipilimumab group (2·6 months [2·4–2·9]; HR 0·69 [95% CI 0·55–0·87], p=0·0019). 1-year progression-free survival, analyzed post hoc, was 24% (95% CI 19–32) in the ipilimumab plus anti-PD-1 group (140 disease progression events) versus 12% (8–19) in the ipilimumab group (139 disease progression events). No subgroup analysis for OS and PFS were performed on the patients who progressed on prior anti-PD-(L)1 in the adjuvant setting.

***VanderWalde et al (2023) [SWOG S1616 (NCT03033576)]***[7]

The Southwest Oncology Group (SWOG) Cancer Research Network clinical trial S1616 is a randomized phase 2 study to address the scientific and clinical question of whether CTLA-4 blockade, alone or in combination with continued PD-1 blockade, could reverse resistance to previous anti-PD-1therapy. All patients had advanced melanoma with primary resistance to anti-PD-1 or anti-PD-L1 inhibitors, defined as tumors having no objective clinical response (complete or partial response) without intervening therapy for advanced disease, or with recurrence) to the prior use of anti-PD-1 or anti-PD-L1 blocking agents while on adjuvant anti-PD-1 therapy. The clinical trial was designed to test the hypothesis that combination nivolumab plus ipilimumab is superior to single-agent ipilimumab in terms of progression-free survival (PFS) in this anti-PD-1 or anti-PD-L1-experienced population, with the analysis of changes in intratumor infiltration by CD8 T cells as a secondary endpoint. The S1616 clinical trial utilized a 3:1 randomization (nivolumab plus ipilimumab vs ipilimumab monotherapy) and was open at 39 academic sites across the United States. Of note, S1616 was not powered to detect differences in overall survivor (OS), and survival data were collected as a secondary endpoint. The clinical trial met its primary endpoint of PFS with the combination of nivolumab plus ipilimumab having a statistically significantly benefit compared to ipilimumab therapy alone (hazard ratio (HR) = 0.63, 90% CI = 0.41–0.97 P = 0.04, prespecified one-sided α = 0.1). The 6-month PFS estimates were 34% (90% CI = 25–43%) and 13% (4–27%) for the combination therapy versus ipilimumab-alone groups, respectively. Objective response rate (ORR) (defined as a complete response (CR) or partial response (PR) to therapy as per RECIST v.1.1) were also reported. The ORR was 28% (90% CI = 19–38%) in the combination therapy group and 9% (90% CI = 2–25%) in the ipilimumab-alone group (P = 0.05, one-sided Fisher exact test). Because this was not the primary endpoint, no threshold for significance was prespecified and P values should be interpreted qualitatively. Eight patients (12%) receiving combination therapy achieved a CR and 11 (16%) a PR. No patients on ipilimumab alone achieved a CR, and two (9%) achieved a PR. S1616 was not powered to detect differences in overall survivor (OS), and survival data were collected as a secondary endpoint; there was no significant difference between the two groups as of the last data lock of 3 November 2022 (HR = 0.83, 90% CI = 0.50–1.39, P = 0.28). Toxicities observed in the study are consistent with the known toxicities of these regimens. Additionally, it should be noted that no subgroup analysis was performed specifically on the patients who progressed on prior anti-PD-1 or anti-PD-L1 in the adjuvant setting. However, as the entire patient population of the study had not received prior benefit from their previous therapy it can be extrapolated that biologically these patients disease is more similar to those who progress in the adjuvant setting vs other post anti-PD-(L)1 datasets.

***Opdivo Melanoma Continuation Program (OMCP)[8]***

The OMCP is a patient access program that opened November 2020 at 62 institutions throughout Australia. The OMCP allowed patients who progressed on or within 6 months of adjuvant nivolumab for resected stage III-IV melanoma to continue treatment with nivolumab while adding in ipilimumab at the approved dosing (nivolumab 1mg/kg + ipilimumab 3mg/kg Q3W for four doses followed by nivolumab maintenance). The PBAC evaluation report included real-world evidence on patients treated in this program, which was provided by participating physicians who chose to contribute.[8]

Table 1 provides a summary of efficacy results specifically from the Da Silva et al, OMCP and CheckMate 067.

**Table 1: Unanchored side-by-side comparison of efficacy outcomes with ipilimumab + PD-1 inhibitor treatment from patients in da Silva et al (2021), the OMCP and CheckMate 067[8]**

| | da Silva et al (2021) (n=36) | OMCP data (n=42)* | CheckMate 067 (n=314) |
|---|---|---|---|
| **Response, %** | | | |
| ORR (CR + PR) | 36% | 47.6% | 57.6% |
| CR | NR | 16.7% | 17.2% |
| PR | NR | 31.0% | 41.7% |
| SD | NR | 7.1% | 11.5% |
| PD | NR | 45.2% | 23.6% |
| NR | NR | 0 | 6.1% |
| **Progression-free survival** | | | |
| 12-month PFS, % | 47% | 47.9% | 50% |
| **Overall survival** | | | |
| 12-month OS, % | 75% | 63.8% | 73% |

Source: PBAC evaluation report, Table 8, p.15

CR = complete response; NR = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

* Outcome data was available for 42 patients in the OMCP.

NOTE: SWOG1616 data is excluded from table as there was no subgroup analysis performed specifically on the post- adjuvant PD-1 patient population

To date, all evidence reinforces the superior positive clinical outcomes seen with the utilization of nivolumab + ipilimumab in the post-PD-1 setting relative to ipilimumab monotherapy. It should be noted that the ORRs of ipilimumab monotherapy fall within a similar historical range of that seen in its clinical development, ranging from 10-19% (10-13).[9-12]

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

Currently in Canada patients are faced with the reality of choosing adjuvant therapy with an anti-PD-1 antibody (nivolumab/pembrolizumab), in a potentially curative setting at the risk of not having access to nivolumab + ipilimumab should they progress to unresectable/metastatic disease within a certain timeframe or forego adjuvant treatment to retain access to nivolumab + ipilimumab should they need it for advanced disease.

Until recently this issue only impacted patients with resected stage III-IV disease but has now expanded in those with resected stage IIB/IIC disease and pending a positive CADTH review of pembrolizumab for the neoadjuvant treatment of adult patients with Stage III or Stage IV melanoma, patients who progress after this therapy could fall into the same Canadian treatment gap.

It should be of note that one additional data set excluded from this document is Owen et al (2020)[13]. Though it looked specifically at patients who progressed on adjuvant anti-PD1 therapy it did not separate out efficacy data for nivolumab plus ipilimumab vs ipilimumab alone, reporting an ORR of 26% for patients treated with ipilimumab (±anti-PD1). Without separation of efficacy outcomes by treatment this dataset did not address the question at hand. Looking forward, no further randomized clinical trials can be expected to occur exploring ipilimumab vs nivolumab + ipilimumab in a melanoma patient population that are refractory to anti-PD-1 therapy. The collection of evidence to date supporting the benefit nivolumab + ipilimumab over ipilimumab monotherapy in this space is thought to make randomization to such a study unethical due to a lack of clinical equipoise.

According to Canadian experts and evidence from phase III adjuvant anti-PD1 trials, an estimated 25% of patients receiving an anti-PD1 in the adjuvant setting will experience disease recurrence on or within 6 months. Bristol Myers Squibb estimates that approximately 200 Canadians will fall in this category annually. As these patients are for the most part currently receiving ipilimumab, the budget impact of extending funding to the combination of nivolumab + ipilimumab is expected to be limited.[14]

Given the high unmet need and lack of effective treatment options in rapid progressor patients, the expansion of the current nivolumab + ipilimumab listing conditions to allow patients who experienced disease progression either while receiving or within 6 months of completing adjuvant treatment with an anti-PD1 based therapy to receive nivolumab + ipilimumab in the metastatic setting should be implemented to provide Canadian melanoma patients with the best long-term efficacy outcomes.[2]

## References


1. care AMDoHaa. Affordable treatment for recurrent melanoma. 2023.
2. CADTH. *Dosing and Timing of Immuno-Oncology Drugs.* November 2019 2019.
3. PBAC. *PHARMACEUTICAL BENEFITS ADVISORY COMMITTEE (PBAC) MEETING OUTCOMES NOVEMBER 2022 PBAC MEETING.* 2022.
4. CADTH. CADTH Reimbursement Review: Provisional Funding Algorithm: Melanoma. 2023; https://www.cadth.ca/melanoma. Accessed 07 February, 2023.
5. Squibb BM. *Internal BMS market share data 1L melanoma, 2023.* 2023 2023.
6. Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. *Lancet Oncol.* 2021;22(6):836-847.
7. VanderWalde A, Bellasea SL, Kendra KL, et al. Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma: a randomized phase 2 trial. *Nat Med.* 2023;29(9):2278-2285.
8. PBAC. PBAC nivolumab + ipilimumab Public Summary Document (PSD) November 2022 PBAC Meeting 2023; https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-11/nivolumab-%20Opdivo-PSD-November-2022. Accessed November 30, 2023.
9. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* 2011;364(26):2517-2526.
10. Lipson EJ, Sharfman WH, Drake CG, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. *Clin Cancer Res.* 2013;19(2):462-468.
11. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015;373(1):23-34.
12. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723.
13. Owen CN, Shoushtari AN, Chauhan D, et al. Management of early melanoma recurrence despite adjuvant anti-PD-1 antibody therapy☆. *Annals of Oncology.* 2020;31(8):1075-1082.
14. Canada BMS. *Budget Impact Analysis - Financial impact of the expansion of the current nivolumab+ipilimumab listing to allow patients who experienced disease recurrence either while receiving or within 6 months of completing adjuvant treatment with an anti-PD1 based therapy to receive nivolumab+ipilimumab in the metastatic setting* 2023.