Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Nivolumab Plus Ipilimumab

Reimbursement request: 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

Final recommendation: Reimburse with conditions

Summary of Recommendation

The Formulary Management Expert Committee (FMEC) recommends that nivolumab plus ipilimumab should be publicly reimbursed for the first-line treatment of advanced melanoma in patients who progress during or within 6 months of adjuvant PD-1 therapy.

FMEC determined that there is no evidence to determine the appropriate time frame from progression on adjuvant therapy to initiation of treatment in the metastatic setting. FMEC acknowledged the absence of data comparing nivolumab plus ipilimumab to ipilimumab monotherapy in the patient population of interest; however, FMEC also noted that future studies examining this question are unlikely to be conducted.

FMEC considered that nivolumab plus ipilimumab in patients who progress during or within 6 months of adjuvant PD-1 therapy meets patients' unmet needs for earlier access to a treatment option.

Therapeutic Landscape

What Is Advanced Melanoma and How Is it Treated?

Melanoma, the deadliest form of skin cancer, arises from a malignant transformation of melanocytes, which synthesize melanin, a photoprotective pigment. Advanced melanoma refers to tumours that are inoperable or have metastasized or spread to other sites in the body. Immune checkpoint inhibitor immunotherapy, including anti-PD (L)-1 (nivolumab, pembrolizumab, atezolizumab), and anti-CTLA-4 (ipilimumab), are the most widely used standard of care therapies for patients with melanoma. However, many patients develop resistance to these agents and eventually experience progression on front-line therapies with limited options in the following lines of treatment.

Why Did We Conduct This Review?

Current treatment options for patients whom anti–PD-1 therapies are limited, particularly for those who do not have a *BRAF* mutation and are not suitable for *BRAF-MEK* targeted therapy. Based on the Provisional Funding Algorithm, patients who progress on anti–PD-1 therapy in the adjuvant setting are only eligible for a combination of ipilimumab and nivolumab if they progress more than 6 months from prior anti–PD-1 treatment. Following a request from publicly funded drug plans, we reviewed the available evidence on the efficacy and safety of first-line treatment with ipilimumab and nivolumab combination therapy in patients who progress during or within 6 months of anti–PD-1 treatment.

Person With Lived Experience

A person with lived experience from Ontario presented her experience living with melanoma after a diagnosis in 2017. A spot on her heel led to a biopsy, and further testing showed it had spread to her lymph nodes. She then participated in a clinical trial of nivolumab plus ipilimumab, with good results, despite ending treatment early due to side effects of reduced cortisone levels and mouth and skin sores. By 2022, multiple treatment options were trialled with limited success and significant side effects until her new oncologist suggested she return to nivolumab and ipilimumab.

Due to limitations in medical coverage, she was required to pay for her treatment out of pocket and navigate exceptional access programs while continuing to work and support her family. She expressed concerns about the financial strain that prolonged treatments have on patients, given the significant out of pocket costs to access nivolumab plus ipilimumab. After 11 treatments, she reported minimal side effects and a substantial tumour reduction.

"The last thing a person needs when their health is failing is to be consumed by financial stress and uncertainty."

Input From Community Partners

What Did We Hear From Patients?

Advanced melanoma has a significant impact on patients' lives as patients navigate the challenges of late-stage diagnosis with limited treatment options. Timely access, flexible options, and individualized treatments can mitigate the health, emotional, and financial impacts. Many of the patients who reported receiving nivolumab plus ipilimumab were willing to endure its side effects if the combination was effective in delaying disease progression or eliminating the cancer entirely. Patient groups advocated for funding the combination therapy in a second-line setting following the progression on anti–PD-1 therapy to alleviate financial strain, offer alternative options, and potentially improve health outcomes and quality of life.

What Did We Hear From Clinicians?

Clinician groups highlighted that combination treatment with nivolumab plus ipilimumab for patients who relapse during or within 6 months of anti–PD-1 therapy, regardless of prior treatment in the adjuvant or metastatic setting and regardless of *BRAF* mutation status, aligns with international guidelines and clinical practice. Furthermore, clinician groups and clinical experts consulted for the review noted that funding ipilimumab and nivolumab combination in the second-line setting would allow patients who might not tolerate combination therapy well or those with low-volume disease to start with single-drug anti–PD-1 therapy and only receive combination therapy if they progress.

What Did We Hear From the Pharmaceutical Industry?

Industry supported the research protocol but emphasized that conducting randomized clinical trials comparing nivolumab and ipilimumab combination with ipilimumab monotherapy is deemed unethical in the context of available data to date demonstrating superior efficacy of dual immune checkpoint blockade with nivolumab and ipilimumab and therefore, cannot be expected to take place in the future.

What Did We Hear From Public Drug Programs?

Public drug plans inquired about treatment eligibility of ipilimumab and nivolumab combination in both the first- and second-line unresectable or metastatic settings for patients who have progressed during or within 6 months of anti–PD-1 adjuvant therapy; for patients with *BRAF* mutation; and for patients who had received anti–PD-1 monotherapy as first-line treatment for unresectable or metastatic melanoma and progressed during or within 6 months of completing treatment; and the possibility of a time-limited opportunity to add nivolumab for 4 cycles for patients currently on ipilimumab monotherapy (after progression).

Refer to the Stakeholder Input section of the clinical and pharmacoeconomic report.

Deliberation

The FMEC concluded unanimously that nivolumab plus ipilimumab should be publicly reimbursed for the first-line treatment of advanced melanoma in patients who progress during or within 6 months of adjuvant PD-1 therapy.

Decision Summary

Why Did We Make This Recommendation?

- A total of 5 studies were included in this review: 2 phase II randomized controlled trials and 3 observational studies comparing ipilimumab plus nivolumab with ipilimumab monotherapy after anti–PD-1 progression in patients with advanced melanoma. All the studies included patients with advanced melanoma with prior anti-PD-1 therapy either in the adjuvant or the advanced setting, and none of the studies provided precise information on the time of progression from anti–PD-1 treatment to the initiation of ipilimumab plus nivolumab. These studies were not designed to compare the efficacy outcomes of ipilimumab plus nivolumab with ipilimumab monotherapy in the patient population under review.
- FMEC recognized that the restriction for limiting the use of nivolumab plus ipilimumab in the first-line metastatic setting to patients who never had prior anti–PD-1 adjuvant therapy or completed adjuvant anti–PD-1 therapy at least more than 6 months before relapse was not included in the initial pERC recommendations for adjuvant nivolumab or combination nivolumab plus ipilimumab (for previously untreated patients with advanced melanoma).
- FMEC acknowledged that there is no evidence to determine the appropriate time frame from progression on adjuvant therapy to initiation of treatment in the metastatic setting. FMEC also noted that it is highly unlikely that new studies comparing patients who progress within 6 months or after 6 months of adjuvant treatment would ever be conducted.
- FMEC recognized that there is an unmet need for patients who relapse early and currently do not have access to dual therapy that has previously been shown to have significantly better clinical efficacy compared to monotherapy in previously untreated advanced melanoma.

- FMEC concluded that it is reasonable for nivolumab plus ipilimumab to be publicly reimbursed for advanced melanoma in patients who progress during or within 6 months of adjuvant PD-1 therapy.
- FMEC acknowledged the stakeholder input about the need for access to a combination of nivolumab plus ipilimumab in second and subsequent lines of therapy for advanced melanoma. Although this indication was deemed out of scope for the current review, it would be further explored if requested by drug plans.

Feedback on Draft Recommendation

Melanoma Canada, Save Your Skin Foundation, BC Cancer Skin and Melanoma Tumour Group, Ontario Health Skin Cancer Drug Advisory Committee, Bristol Myers Squibb Canada, and the Provincial Advisory Group provided feedback on the draft recommendation. Although these partners agreed with the committee's recommendation, they all highlighted the need to review nivolumab and ipilimumab for second and subsequent lines of therapy in advanced melanoma. Second-line treatment was not the focus of this review. Review of nivolumab plus ipilimumab for other lines of treatment in advanced melanoma may be considered in the future.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and 2 medical oncologists from Alberta and Ontario. 1 expert committee member did not attend.

Meeting date: May 10, 2024

Conflicts of interest: None

Special thanks: Canada's Drug Agency extends our special thanks to the individual who presented directly to FMEC on behalf of people with lived experience, as well as the patient organizations representing the community of those living with Melanoma, notably The Save Your Skin Foundation, which includes Kathleen Barnard, Jasmine MacGowan, and Donna Barton.

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