Canada's Drug and
Health Technology Agency

Reimbursement Recommendation

Nivolumab-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

Draft 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 & How is it Treated?

Melanoma, the deadliest form of skin cancer, arises from a malignant transformation of melanocytes, the cells that synthesize melanin, a photoprotective pigment. Advanced melanoma refers to tumours that are inoperable or that 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 next lines of treatment.

Why Did We Conduct This Review?

Current treatment options for patients who fail anti-PD-1 therapy are limited, particularly for those who do not have a BRAF mutation and are not suitable for BRAF/MEK targeted therapy. Based on the current Provincial Funding Algorithm, patients who progress on anti-PD-1 therapy in the adjuvant setting, are only eligible for combination 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. [OBJ][OBJ].

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 lead to a biopsy, and further testing showed it had spread to her lymph nodes. She then participated in a clinical trial of Nivolumab and 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 trialed 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 and Ipilimumab. 11 treatments later, she reported minimal side effects and a substantial reduction in her tumours.

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

Stakeholder Feedback

What Did We Hear From Patients?

Advanced melanoma has 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 second line setting following 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 and 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 agent 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 a) both the first- and second-line unresectable/metastatic settings for patients who have progressed during or within 6 months of anti-PD-1 adjuvant therapy; b) for patients with BRAF mutation; and c) for patients who had received anti-PD-1 monotherapy as first line treatment for unresectable/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 Stakeholder Input section of the clinical and pharmacoeconomic report.

Deliberation

With a unanimous vote, the Formulary Management Expert Committee (FMEC) concluded 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 as part of this review: two phase 2 randomized controlled trials and 3 observational studies comparing ipilimumab plus nivolumab with ipilimumab monotherapy after anti-PD1 progression in patients with advanced melanoma. All the studies included patients with advanced melanoma with prior anti-PD1 therapy either in the adjuvant or the advanced setting, and none of the studies provided precise information on the time of progression on anti-PD1 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 either.

- 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-PD1 adjuvant therapy or completed adjuvant anti-PD1 therapy at least more than 6 months before relapse was not included in any prior CADTH recommendation issued by a committee.

- 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 on the need to have access to combination nivolumab and 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

<to be updated after the stakeholder feedback period.>

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, Dr. Teresa Petrella (guest specialist), and Dr. Michael Smylie (guest specialist). 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 include Kathleen Barnard, Jasmine MacGowan, and Donna Barton.

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