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

January 2025

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Nivolumab and Ipilimumab

Reimbursement request: For resectable macroscopic stage III melanoma in the neoadjuvant setting

Requester: Public drug programs

Final recommendation: Reimburse with conditions

Summary

The Formulary Management Expert Committee (FMEC) recommends nivolumab plus ipilimumab be reimbursed for the neoadjuvant treatment of resectable, macroscopic, stage III melanoma, provided certain conditions are met.

FMEC reviewed data from the phase III NADINA trial, identified by Canada's Drug Agency (CDA-AMC)'s systematic review of literature. The NADINA trial compared neoadjuvant nivolumab plus ipilimumab followed by surgery and response-driven adjuvant treatment to surgery followed by adjuvant nivolumab in patients with resectable, macroscopic, stage III melanoma. FMEC also considered input received from external partners, including Save Your Skin Foundation, Melanoma Canada, Ontario Health (Cancer Care Ontario)'s Skin Cancer Drug Advisory Committee, Bristol Myers Squibb Canada, and public drug programs.

FMEC concluded that the results of the NADINA trial published to date suggest patients who are treated with neoadjuvant nivolumab plus ipilimumab followed by response-driven adjuvant therapy have better event-free survival compared to patients treated with adjuvant nivolumab only.

The expected relative drug cost of neoadjuvant nivolumab plus ipilimumab, followed by response-driven adjuvant treatment, is highly dependent on the rate of major pathological response and the choice of adjuvant therapy in patients who do not experience a treatment response.

Therapeutic Landscape

What Is Resectable Stage III Melanoma?

Melanoma, the deadliest form of skin cancer, is the seventh most diagnosed cancer in Canada. In 2024, it was estimated that 11,300 people in Canada would be diagnosed with melanoma and that 1,300 people in Canada would die from it. Melanoma arises from a malignant transformation of melanocytes, which synthesize melanin, a photoprotective pigment. Resectable, macroscopic, stage III melanoma is an invasive melanoma that has spread from the site where it began to nearby lymph nodes or to surrounding tissue, is palpable or measurable on imaging, and can be removed by surgery. The risk of recurrence after surgery alone is high, and systemic therapy decreases this risk.

What Are the Current Treatment Options?

In the neoadjuvant setting, the main treatment goal is to achieve cure. The current treatment options for patients with resectable macroscopic stage III melanoma include surgery followed by adjuvant therapy, usually with either pembrolizumab, nivolumab, or *BRAF*/MEK inhibitors (dabrafenib and trametinib). Recently, neoadjuvant treatment with pembrolizumab, followed by surgery and adjuvant pembrolizumab, has become a treatment option.

Why Did We Conduct This Review?

Available treatments may not be effective and are often associated with long-term adverse effects. With approximately half of patients experiencing relapse with primary treatment, an important unmet need for patients is additional treatment options that improve outcomes with reduced toxicity. There is growing biological and clinical evidence to support the use of neoadjuvant immunotherapy in patients with melanoma.

Given the emergence of new evidence for the use of nivolumab plus ipilimumab in the neoadjuvant setting of melanoma, public drug programs requested this Reimbursement Review. Nivolumab plus ipilimumab was eligible for a Nonsponsored Reimbursement Review given that data protection has expired for both drugs.

Input From Partners

- Two patient groups, **Save Your Skin Foundation** and **Melanoma Canada**, submitted input for this review. Although most patients had no experience with this treatment, given the unavailability of neoadjuvant nivolumab plus ipilimumab in Canada, patients advocated for neoadjuvant immunotherapy with nivolumab plus ipilimumab to offer additional treatment options and enable prompt initiation of treatment that may improve chances of a cure.
- **Ontario Health (Cancer Care Ontario)'s Skin Cancer Drug Advisory Committee** provided input; clinicians indicated that a neoadjuvant approach to the treatment of resectable stage III melanoma would enable an immune response earlier in the disease process. Neoadjuvant nivolumab plus ipilimumab would be a shift in the treatment paradigm, supplanting the current approach of surgery and adjuvant treatment.

- **Bristol Myers Squibb Canada**, a manufacturer of both nivolumab and ipilimumab, provided a discussion of the NADINA trial and the biological rationale for neoadjuvant therapy — which is believed to induce a broader immune activation when the drug is administered before surgical resection while the tumour and its full antigen profile are still present — compared to adjuvant therapy only.
- **Public drug plans** inquired about patient eligibility, including those excluded from the NADINA trial as well as eligibility for neoadjuvant-adjuvant nivolumab plus ipilimumab compared to another neoadjuvant-adjuvant regimen (pembrolizumab).

►Refer to the main report and supplemental material for this review.

Person With Lived Experience

A person with lived experience with neoadjuvant and adjuvant pembrolizumab (a comparator for this Reimbursement Review) shared his journey living with stage III resectable melanoma. Diagnosed in 2019, he underwent 3 treatments with pembrolizumab before surgery, which was deemed successful after removing 54 lymph nodes, and tests showed no remaining cancer. He continued treatment after his surgery for 1 year. He described managing fatigue and minor side effects while continuing to work full-time over the course of his treatment. He emphasized the importance of his medical team's guidance in choosing the treatment and stressed the value of treatment options in improving outcomes and quality of life for patients and their families.

Deliberation

The committee deliberated using the following 5 domains of value:

- **Clinical value** is the value that patients derive from a health technology in terms of its effect on their health and health-related quality of life. The determination of the clinical value of a health technology requires the measurement of its clinical benefits and harms and an assessment of the impact of these effects on patients. Clinical benefits and harms are assessed against relevant comparators.
- **Unmet clinical need** is the morbidity and/or mortality arising from a condition or symptom that is not addressed effectively by available treatments.
- **Distinct social and ethical considerations** include the social and ethical implications of health technologies not already assessed in the other domains, and how they affect patients, caregivers, populations, and the organization of health systems. These include nonclinical needs — social, psychological, and logistical factors affecting the appropriateness, accessibility, and acceptability of

the technology beyond its direct clinical outcomes — as well as broader ethical considerations in the design, evaluation, and implementation of these technologies.

- **Economic considerations** include economic evidence to inform the financial, human, or other resource implications associated with the technology under review, and whether it is worthwhile to allocate resources to the technology under review given its expected clinical benefits. Considerations may include the potential resource or cost impacts of the technology under review versus the relevant comparator(s).
- **Impacts on health systems** include 2 distinct but interrelated components: organizational feasibility of adoption (the ease with which the health technology can be implemented in the health system while realizing its clinical value) and economic feasibility of adoption (which examines how the adoption of a health technology will economically impact the payer or budget holder).

Decision Summary

Table 1: Summary of Deliberation

Domain	Discussion point(s)
Clinical value	• **FMEC concluded that there is uncertainty with the clinical value of nivolumab plus ipilimumab in the neoadjuvant treatment of stage III melanoma.** • Based on the NADINA trial, FMEC noted that there is uncertainty regarding whether the new treatment offers comparable clinical value, given that surrogate outcomes measured have not been validated against overall survival (e.g., event-free survival and complete pathological response) and that between-group differences and confidence intervals were not reported. There is also a lack of evidence comparing nivolumab plus ipilimumab in the neoadjuvant setting with the current comparator of neoadjuvant and adjuvant pembrolizumab. • The clinical experts emphasized that neoadjuvant therapies show efficacy in a very specific patient population (i.e., those with macroscopic disease, but not those with no palpable or clinical disease detected). The immune response from treatment in the neoadjuvant setting is greater, as the tumour has not been surgically removed yet. • FMEC discussed the input from 2 patient groups and highlighted that patients place high value on timely and affordable access to neoadjuvant treatments that offer improved survival and maintain quality of life with minimal short-term and long-term adverse reactions. Patients also accept short-term adverse effects or toxicities for treatment effectiveness to prevent recurrence.
Unmet clinical need	• **FMEC concluded that reimbursement would address a clinical unmet need.** • FMEC noted that advanced melanoma is 1 of the most common cancers in young individuals and advanced disease has a high risk of relapse and mortality. Given recent reported increases in incidence, there is a clinical need arising from the condition. • FMEC discussed the input from patient groups and highlighted that prompt treatment that improves survival rates while minimizing side effects and maintaining quality of life is important. In addition, neoadjuvant treatment may be valued by patients if it prevents surgery or lessens the impact of surgery, and if it minimizes anxiety while waiting for treatment.

Domain	Discussion point(s)
Distinct social and ethical considerations	• FMEC noted that patients report anxiety and concern about timely access to treatment, and fear not controlling the disease early on. The treatments are injectables in the neoadjuvant phase and require more frequent monitoring, with some patients in general describing challenges with commutes to receive treatments or access care for toxicity from treatments. • FMEC also highlighted that the uncertainty of long-term benefits from neoadjuvant treatment and the lack of data with respect to overall survival would need to be communicated to people with this condition, as they would be consenting to fewer cycles of treatment. The guest clinical specialist highlighted that the lack of long-term benefit is not unique to the treatment space in melanoma and that it applies to other tumour settings. The main concern is the lack of overall survival data at this time.
Economic considerations	• The expected treatment cost of neoadjuvant nivolumab plus ipilimumab, followed by response-driven adjuvant treatment (dabrafenib plus trametinib [if *BRAF* mutation positive] or nivolumab [if *BRAF* wild-type]), may be higher or lower than that of adjuvant therapy (i.e., nivolumab or dabrafenib plus trametinib), depending on treatment response. The expected treatment cost of neoadjuvant nivolumab plus ipilimumab is lower than that of pembrolizumab (neoadjuvant plus adjuvant or adjuvant only), except for *BRAF* mutation positive patients treated with adjuvant dabrafenib plus trametinib. • FMEC discussed that, at the system level, cost savings derived from patients who develop a major pathological response and require only neoadjuvant treatment may be offset by increased drug costs for patients with partial or no major pathological response. The net impact of neoadjuvant nivolumab plus ipilimumab on overall costs is unknown.
Impacts on health systems	• FMEC noted that nivolumab plus ipilimumab is expected to result in more frequent adverse events and frequent monitoring would be required every 3 weeks. This would be for only 2 cycles. • Training and competency in assessment of pathological response by pathologists or pathology technologists following neoadjuvant therapy would be needed to determine whether adjuvant treatment is required. The clinical experts emphasized the need to accurately distinguish between major and complete pathological responses. However, FMEC noted that patients with major response should be treated similarly to those with complete pathological response. The challenge is to ensure that major response is accurately determined, which may be addressed by additional training for pathologists and pathology technologists. • Decreased chair time (e.g., nursing) in patients who experience a response to neoadjuvant treatment would be expected, as these patients would not require adjuvant treatment. This would translate into a decrease in postoperative hospital pharmacy resources for parenteral drug preparation (adjuvant treatment options are oral for *BRAF*-positive disease as compared to injectables for neoadjuvant treatment options).

FMEC = Formulary Management Expert Committee.

Full Recommendation

With a vote of 8 to 0, FMEC recommends that nivolumab plus ipilimumab for the neoadjuvant treatment of resectable stage III melanoma be reimbursed, if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Nivolumab plus ipilimumab should be reimbursed for the neoadjuvant treatment of resectable stage III melanoma if the following conditions are met: 1.1. patients are aged at least 16 years 1.2. patients have cytologically or histologically confirmed resectable stage III melanoma of cutaneous or unknown primary origin with 1 or more macroscopic lymph node metastases that can be biopsied, or any number of resectable in-transit metastases 1.3. patients have good performance status.	The initiation criteria reflect the key inclusion criteria from the NADINA trial.	In the NADINA trial, macroscopic (clinically detectable) lymph nodes are defined as any of the following: • a palpable node, confirmed as melanoma by pathology • a nonpalpable but enlarged lymph node according to RECIST 1.1 (at least 15 mm in short axis), confirmed as melanoma by pathology • a PET scan positive lymph node of any size confirmed as melanoma by pathology.
Discontinuation and renewal		
2. Nivolumab plus ipilimumab should be discontinued if there is disease recurrence during treatment or intolerable adverse events. 3. Nivolumab plus ipilimumab should be discontinued after 2 cycles of neoadjuvant ipilimumab plus nivolumab every 3 weeks.	Consistent with patients enrolled in the NADINA trial.	Further adjuvant treatment should be guided by pathological response and disease mutation status. Per the NADINA trial, patients who experienced a major pathological response did not receive additional adjuvant treatment. Patients without a major pathological response were considered for additional adjuvant treatment: Patients with *BRAF* mutation were considered for dabrafenib-trametinib adjuvant therapy for 46 weeks. Patients with *BRAF* wild-type were considered for 11 cycles of adjuvant nivolumab (480 mg) every 4 weeks. Patients with contraindications or intolerance to dabrafenib plus trametinib can be considered for adjuvant treatment with nivolumab or pembrolizumab (based on CDA-AMC clinical expert opinion). Note that, currently, there may be a lack of standardization on how pathology results are reported across institutions, leading to variable access to treatments. Additional resources may be required to support training

Reimbursement condition	Reason	Implementation guidance
		for pathologists and pathology technicians. These additional resources will likely be accompanied by additional costs to the health care system.
Prescribing		
4. Prescribing should be limited to clinicians with expertise in the diagnosis and management of melanoma.	This will ensure that treatment is prescribed for appropriate patients and adverse events are optimally managed.	—
Cost		
5. A reduction in price may be required.	Based on publicly available prices, neoadjuvant nivolumab plus ipilimumab, followed by response-driven adjuvant treatment (dabrafenib plus trametinib [if *BRAF* mutation positive] or nivolumab [if *BRAF* wild-type]), may increase or decrease drug costs compared with adjuvant nivolumab, depending on initial treatment response. These cost-variations reflect uncertainties related to differences in long-term efficacy. Given these uncertainties, a price reduction may be required. A cost-effectiveness analysis would be needed to determine the extent of price reduction. There is also a lack of direct and indirect comparative evidence relative to adjuvant dabrafenib plus trametinib and pembrolizumab (neoadjuvant plus adjuvant and adjuvant). As such, the cost-effectiveness of neoadjuvant nivolumab plus ipilimumab relative to these treatments is unknown.	In addition to the uncertainty around the rate of major pathological response and the choice of adjuvant therapy among those who do not experience a response to treatment, the relative economic impact of nivolumab plus ipilimumab versus other comparators is particularly sensitive to the negotiated price for nivolumab, ipilimumab, and all other comparator treatments.

CDA-AMC = Canada's Drug Agency.

Feedback on Draft Recommendation

One patient group (Melanoma Canada), 1 clinician group (Ontario Health Skin Cancer Drug Advisory Committee), Bristol Myers Squibb Canada, and the public drug programs provided feedback on the draft recommendation. The patient group agreed and strongly supported the recommendation. The clinician group suggested that patients with *BRAF* mutations should have the option to be treated with adjuvant nivolumab in case of contraindications or intolerance to dabrafenib plus trametinib and those who are *BRAF* wild-type should have the option for adjuvant pembrolizumab instead of nivolumab. The clinical experts and FMEC had discussed these treatment options during deliberations and the recommendation was updated accordingly

to reflect this point. Bristol Myers Squibb Canada commented on treatment options for patients who do not have a major pathological response and progress to metastatic disease. Downstream treatment options are outside the scope of the current review and will be addressed in a future provisional funding algorithm.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and 2 guest specialists from Ontario.

Meeting date: November 21, 2024

Conflicts of interest: None

Special thanks: CDA-AMC extends our special thanks to the individuals who presented directly to FMEC on behalf of patients with lived experience, and to patient organizations representing the community of those living with melanoma, including the Save Your Skin Foundation, and particularly Kathleen Barnard, Dwayne Conrad, Wendy Conrad, and Jasmine MacGowan.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journeys with FMEC.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca