Canada's Drug Agency
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Drugs Health Technologies Health Systems

Reimbursement Review

Nivolumab Plus Ipilimumab (Opdivo-Yervoy)

Requester: Public drug programs
Therapeutic area: Melanoma

Key Messages

What Is Resectable Stage III Melanoma?

- Resectable stage III melanoma is invasive melanoma that has spread from the site where it began to nearby lymph nodes or to surrounding tissue and can be removed by surgery.
- Patients with stage III melanoma have a high risk of recurrence after surgery alone and systemic therapy decreases this risk and improves relapse-free survival.

What Are the Treatment Goals and Current Treatment Options for Resectable Stage III Melanoma?

- The goal of therapy for patients with stage III melanoma is cure.

What is Nivolumab Plus Ipilimumab and Why Did We Conduct This Review?

- Nivolumab plus ipilimumab is a combined immunotherapy treatment that activates the immune system against cancer. This combination therapy is used in advanced melanoma and has recently been studied to treat patients with earlier stages of melanoma. Early results from a clinical trial in patients with stage III melanoma indicate that this treatment can be effective in these patients.
- At the request of the participating drug programs, we reviewed nivolumab plus ipilimumab to inform a recommendation on whether it should be reimbursed for patients with resectable, macroscopic stage IIII melanoma.

How Did We Evaluate Nivolumab Plus Ipilimumab?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of nivolumab plus ipilimumab versus other treatments used in Canada for the treatment of patients with resectable stage III melanoma. Preoperative pembrolizumab, nivolumab, dabrafenib plus trametinib, and preoperative and postoperative pembrolizumab were considered relevant comparators.
- The clinical evidence was identified through a systematic search for available studies. We consulted 2 clinical specialists with expertise in the diagnosis and management of melanoma as part of the review process. The review was also informed by 2 patient group submissions, clinicians, and the pharmaceutical industry in response to our call for input, and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation.

Key Messages

What Did We Find?

Clinical Evidence

- We reviewed 1 trial (the NADINA trial) comparing neoadjuvant (preoperative) nivolumab plus ipilimumab with adjuvant (postoperative) nivolumab only in patients who underwent surgery for resectable, macroscopic stage III melanoma.
- The evidence from the NADINA trial suggests that patients with resectable, macroscopic stage III melanoma who are treated with neoadjuvant nivolumab plus ipilimumab may have better event-free survival (EFS) without progression to unresectable melanoma or disease recurrence) compared to patients treated with adjuvant nivolumab only. Data on overall survival (OS) and health-related quality of life (HRQoL) are not yet available but are planned to be analyzed 3 years following the last patient enrolled.

Economic Evidence

- Reimbursing neoadjuvant nivolumab plus ipilimumab, followed by surgical resection, and response-driven adjuvant treatment (dabrafenib plus trametinib [if *BRAF* mutation positive] or nivolumab [if *BRAF* wild type]) for the treatment of adult patients with resectable, macroscopic stage III melanoma is expected to decrease costs to the public drug programs if patients have a major pathological response and increase costs if patients do not respond or have a partial response compared with adjuvant therapy (i.e., nivolumab or dabrafenib plus trametinib).
- Neoadjuvant nivolumab plus ipilimumab, followed by surgical resection, and response-driven adjuvant treatment is expected to decrease costs to the public drug programs compared with pembrolizumab (neoadjuvant plus adjuvant and adjuvant), but increase costs for patients with a positive *BRAF* mutation receiving adjuvant dabrafenib plus trametinib. Conclusions about decreased drug cost are based on public list prices and may not hold if negotiated prices are used for nivolumab, ipilimumab, or comparator therapies.

Table of Contents

List of Tables

List of Figures

Abbreviations

AE	adverse event
CI	confidence interval
DMFS	distant metastasis-free survival
EFS	event-free survival
HR	hazard ratio
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention to treat
OS	overall survival
RFS	recurrence-free survival
SAE	serious adverse event

Background and Review Methods

Introduction

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Nivolumab (Opdivo): 10 mg nivolumab/mL, 40 mg and 100 mg vials, for injection Ipilimumab (Yervoy): 5 mg ipilimumab/mL, 10 mL and 40 mL vials, for injection
Health Canada indication	Not applicable
Mechanism of action	Nivolumab is a fully human IgG4 antibody targeting the immune checkpoint PD-1. Ipilimumab is a fully humanized IgG1 monoclonal antibody that blocks CTLA-4 thereby removing an inhibitory signal from reducing the activity of T lymphocytes.
Recommended dosage	Nivolumab: 240 mg every 3 weeks[a] Ipilimumab: 80 mg every 3 weeks
Data protection status	Nivolumab: ended March 25, 2024 Ipilimumab: ended August 1, 2020
Information on the CDA-AMC review	
Requestor	Provincial Advisory Group
Indication under consideration for reimbursement	In the neoadjuvant setting for resectable stage III melanoma
Clinical review focus	Population: adult patients with resectable, macroscopic stage III melanoma Intervention: neoadjuvant ipilimumab (2 cycles at a dose of 80 mg) plus nivolumab (at a dose of 240 mg every 3 weeks), followed by surgical resection, and response-driven adjuvant treatment (dabrafenib + trametinib [if *BRAF* mutation positive] or nivolumab [if *BRAF* wild type] and radiotherapy) Comparators: • Adjuvant treatment (no neoadjuvant treatment): nivolumab, pembrolizumab, dabrafenib + trametinib • Neoadjuvant + adjuvant pembrolizumab Outcomes: • Efficacy: tumour response (i.e., pathologic response), event-free survival, recurrence-free survival, distant metastasis-free survival, overall survival, health-related quality of life • Safety: AEs, serious AEs, discontinuation due to AEs, death from AEs, immune-related AEs

AE = adverse event; CDA-AMC = Canada's Drug Agency.

[a]Not based on Health Canada indication (based on clinical trial and expert input). Weight-based dosing may be used for nivolumab: 2 mg/kg up to 240 mg every 3 weeks in the neoadjuvant setting and 6 mg/kg every 4 weeks in the adjuvant setting.

Objective

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of nivolumab plus ipilimumab in the neoadjuvant treatment of patients with resectable, macroscopic stage III melanoma. The focus will be placed on comparing nivolumab plus ipilimumab to

relevant comparators and identifying gaps in the current evidence. The Economic Review consists of a cost comparison for nivolumab plus ipilimumab compared with relevant comparators. The comparators considered relevant to the reviews were adjuvant nivolumab, adjuvant pembrolizumab, adjuvant dabrafenib plus trametinib, and neoadjuvant-adjuvant pembrolizumab.

Review Methods

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from patient groups, clinician groups, the public drug programs that participate in the Non-Sponsored Reimbursement Review process, and the pharmaceutical industry.

Calls for patient group, clinician group, and industry input are issued for each Non-Sponsored Reimbursement Review. The full submissions received are available in the consolidated input document. Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient and clinician group input and industry input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are posted on the Canada's Drug Agency website.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two oncologists with expertise in the diagnosis and management of melanoma participated as part of the review team, with representation from Ontario.

Submitted Input From Patient Groups, Clinician Groups, and Industry

Two patient groups, Save Your Skin Foundation and Melanoma Canada, provided input for this review with information collected via online surveys. Save Your Skin Foundation collected information from 45 respondents: 16 were patients with stage III melanoma, with 8 indicating that it could be resected and 2 were unsure. None of the respondents had experience with the drug under review. Melanoma Canada's input was based on 141 individual patient responses and a further 11 caregiver responses. Twenty-three respondents indicated that they had stage III melanoma and 22 reported having been on treatment with neoadjuvant-adjuvant nivolumab and ipilimumab.

A letter of support was provided by 6 oncologists practising in Alberta, Ontario, Saskatchewan, New Brunswick, and British Columbia. Further input by clinician groups was submitted by the Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee.

Bristol Myers Squibb Canada also provided input for this review.

Disease Background

Melanoma is the deadliest form of skin cancer and is the seventh most diagnosed cancer in Canada. In 2024, an estimated 11,300 people in Canada will be diagnosed with melanoma, a 17% increase from 2023,[1] and an estimated 1,300 people in Canada will die from the disease.[1] Clinical stage III melanoma, defined as resectable (Response Evaluation Criteria in Solid Tumours [RECIST] measurable nodal disease with or without in-transit metastases), represents about 15% of new melanoma diagnoses every year with additional cases presenting as recurrent nodal disease following prior treatment of a primary melanoma.[2] The standard of care for patients with resectable, clinical stage III melanoma is surgical resection, consisting of therapeutic lymph node dissection and/or resection of in-transit disease, and consideration of adjuvant systemic therapy and occasionally adjuvant radiation. Patients with stage III melanoma represent a high-risk patient population and have high rates of regional recurrence and progression to metastatic disease after surgery and adjuvant therapy highlighting the need for more effective treatment strategies.[2]

Current Management

Treatment Goals

The clinical experts consulted for this review indicated that the goal of therapy for patients with stage III melanoma is cure (i.e., no relapse with long-term survival). The patient group also emphasized the importance of access to treatment as soon as possible after diagnosis to maximize chances of a cure for patients diagnosed with stage III melanoma.

Current Treatment Options

The clinical experts consulted for this review indicated that the current treatment options for patients with macroscopic stage III melanoma include surgery (i.e., a wide local excision and a sentinel lymph node biopsy) followed by adjuvant therapy (usually with either pembrolizumab, nivolumab, or *BRAF* or *MEK* inhibitors with dabrafenib and trametinib). An alternative adjuvant immunotherapy to pembrolizumab is adjuvant treatment with nivolumab for 1 year. Therefore, patients may be treated with either adjuvant pembrolizumab or adjuvant nivolumab for a total of 1 year; pembrolizumab could also be used before surgery. An alternative approach made available in Canada during the COVID-19 pandemic involves 3 doses of neoadjuvant pembrolizumab, followed by surgery and adjuvant pembrolizumab to complete 1 year of treatment.

The Formulary Management Expert Committee (FMEC) reviewed the neoadjuvant-adjuvant use of pembrolizumab in patients with resectable stage III or stage IV melanoma and issued a positive recommendation. This is currently the only neoadjuvant-adjuvant treatment in this setting in Canada.[3]

Key characteristics of nivolumab and ipilimumab are summarized with other treatments available for resectable stage III melanoma in Table 1 in the Supplemental Material.

Unmet Needs and Existing Challenges

The clinical experts explained that adjuvant treatments to date have demonstrated improvement in disease-free intervals and likely OS although this has yet to be fully realized. Available treatments are associated

with high toxicity and often with long-term adverse effects. Approximately one-half of patients experience relapse with primary treatment for whom few to no treatment options are available and subsequently die relatively rapidly from their melanoma. Therefore, an important unmet need for patients is to have additional treatment options that improve OS with reduced toxicity. There are continued high treatment failure rates with adjuvant therapy. There is growing biological and clinical evidence to support the use of neoadjuvant immunotherapy in patients who have existing melanoma at the primary and regional sites. Several phase II studies have demonstrated the benefits of using neoadjuvant versus adjuvant therapy alone in patients with stage III melanoma.[2] While adjuvant therapies have come a long way, according to the clinical experts there is a pathophysiological understanding that the neoadjuvant approach would work better than an adjuvant approach, by tackling the tumour and allowing an immune response earlier in the disease process.

The input from the patient group also advocated for access to neoadjuvant treatment by allowing treatment initiation promptly upon diagnosis. The input noted that surgical delays remain an issue across Canada and delays in starting treatment allow for disease progression, often at a significant rate. In addition, the stress and anxiety that patients and families incur waiting for treatment impact quality of life and often health outcomes.

Clinical Review

Methods

Eligibility Criteria

We included studies that adhered to the a priori eligibility criteria, detailed in Table 3 in the Supplemental Material. Eligible studies included published and unpublished phase III and IV randomized controlled trials, relevant to patients with resectable stage III melanoma being treated with neoadjuvant nivolumab plus ipilimumab. Relevant comparators included drugs used in clinical practice in Canada to treat patients described in the indication under review and those included in the Economic Review. These included adjuvant nivolumab, pembrolizumab, and dabrafenib-trametinib, and neoadjuvant-adjuvant pembrolizumab.

We selected outcomes for review considering clinical expert input, and patient and clinician group input. Selected outcomes are those considered relevant to expert committee deliberations. These included tumour response, EFS, recurrence-free survival (RFS), distant metastasis-free survival (DMFS), OS, and HRQoL, as well as adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, deaths due to AEs, and immune-related AEs.

We included indirect treatment comparisons (ITCs) that adhered to the previously mentioned selection criteria, except for the study design criteria.

Search Strategy

An information specialist conducted a peer reviewed literature search of key bibliographic databases, trial registries, and grey literature sources. The initial search was completed on July 31, 2024, with alerts

maintained until the Formulary Management Expert Committee (FMEC) meeting on November 21, 2024. Refer to Appendix 2 in the Supplemental Material for detailed search strategies.

Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report.

Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical experts, and patient and clinician groups, with input from a methodologist. Critical appraisal of the included studies was guided by version 2 of the Cochrane risk of bias tool for randomized trials.[4]

Clinical Evidence

From the search for primary studies, we identified 575 unique records via the searches of databases and registers, of which we excluded 574 by title and abstract. In total, we included 1 report of 1 study in the systematic review. We also included 2 newly published conference abstracts reporting updated results of the included study that we were alerted to by the clinical experts.[5,6]

From the search for ITCs, we identified 289 unique records via the searches of databases and registers. No ITCs relevant to the report were identified.

Systematic Review

Description of Study

The NADINA trial is an ongoing, open-label, multicentre, international (Australia, Europe, and US), randomized phase III trial. There were no study sites in Canada. Sources of support included the Netherlands Cancer Institute and the manufacturer, Bristol Myers Squibb. The primary objective was to compare EFS of neoadjuvant ipilimumab plus nivolumab (followed by adjuvant nivolumab or dabrafenib plus trametinib in patients not achieving pathologic response) versus adjuvant nivolumab. Patients with resectable, macroscopic stage III melanoma were enrolled between July 2021 and December 2023 and were randomized in a 1:1 ratio to receive either neoadjuvant or adjuvant immune checkpoint inhibition. Randomization was stratified by *BRAF* status, continent, and the presence or absence of in-transit metastases. Detailed eligibility criteria and intervention details are in Table 2.

Patients in the neoadjuvant arm received 2 cycles of neoadjuvant nivolumab plus ipilimumab followed by a therapeutic lymph node dissection and, if applicable, resection of the in-transit metastases. Adjuvant therapy was based on patient response to neoadjuvant treatment: patients who had a locally assessed major pathological response (≤ 10% residual viable tumour) did not receive any adjuvant treatment, and patients who had a pathological partial response (11% to 50% residual viable tumour) or a pathological nonresponse (> 50% residual viable tumour) received adjuvant dabrafenib plus trametinib if the melanoma had a *BRAF* mutation or received adjuvant nivolumab if the melanoma was *BRAF* wild type. Patients in the adjuvant arm

underwent a therapeutic lymph node dissection followed by adjuvant nivolumab. Adjuvant radiotherapy was allowed in both arms except for patients who had a major pathological response after neoadjuvant treatment.

The primary end point was EFS, defined as the time from randomization to the occurrence of progression to unresectable melanoma before surgery, disease recurrence, or death. The key secondary end point was OS defined as time between randomization and date of death. Additional secondary end points included RFS, DMFS, pathological response, safety, and HRQoL. RFS was defined as time between the date of surgery and the date of melanoma recurrence, treatment-related death or melanoma-related death, whichever occurs first. DMFS was defined as the time between the date of randomization and the date of first distant metastasis, treatment-related death, or melanoma-related death, whichever occurs first. Pathological response was conducted according to the International Neoadjuvant Melanoma Consortium criteria and the retrospective central review was performed at the Netherlands Cancer Institute or the Melanoma Institute of Australia. AEs were scored with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

One interim analysis was planned for when 60 EFS events had accrued. Secondary to a protocol amendment, the interim analysis was rescheduled to be performed after the inclusion of 420 patients. The final analysis of OS is planned to occur 3 years after the final patient was enrolled. Efficacy results were presented for the intention-to-treat (ITT) population, whereas safety results were presented for all patients who started treatment.

Table 2: Key Eligibility Criteria and Intervention Details for the Included Study

Detail	NADINA trial
Key inclusion criteria	• At least 16 years of age • WHO performance status of 0 or 1 • Cytologically or histologically confirmed resectable stage III melanoma of cutaneous or unknown primary origin with 1 or more macroscopic lymph node metastases (clinically detectable), that can be biopsied and a maximum of 3 additional resectable in-transit metastases. • No other malignancies, except adequately treated and with a cancer-related life expectancy of more than 5 years • No prior immunotherapy targeting CTLA-4, PD-1, PD-L1, or LAG-3 • No prior targeted therapy targeting *BRAF* and/or *MEK*
Exclusion criteria	• Distantly metastasized melanoma • Uveal, ocular, or mucosal melanoma • In-transit metastases only (without cytologically or histologically proven lymph node involvement) • Active autoimmune disease or a documented history of autoimmune disease, or history of a syndrome that required systemic steroids or immunosuppressive medications • Prior radiotherapy targeting the affected lymph node region(s) • Acute or chronic hepatitis B or C virus; history of HIV or AIDS
Intervention	Two cycles of neoadjuvant ipilimumab (at a dose of 80 mg) plus nivolumab (at a dose of 240 mg) every 3 weeks, followed by a therapeutic lymph node dissection and resection of the in-transit metastases in week 6, if needed. Patients who had a locally assessed major pathological response did not receive any adjuvant

Detail	NADINA trial
	treatment, and patients who had a pathological partial response or a pathological nonresponse received adjuvant dabrafenib (at a dose of 150 mg twice daily) plus trametinib (at a dose of 2 mg once daily) for 46 weeks if the melanoma had a *BRAF* V600E or V600K mutation or received an additional 11 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks if the melanoma was *BRAF* wild type.
Comparator	Therapeutic lymph node dissection in week 0 followed by 12 cycles of adjuvant nivolumab every 4 weeks starting between week 6 and 12.

Source: Blank et al. (2024)[7]

Results

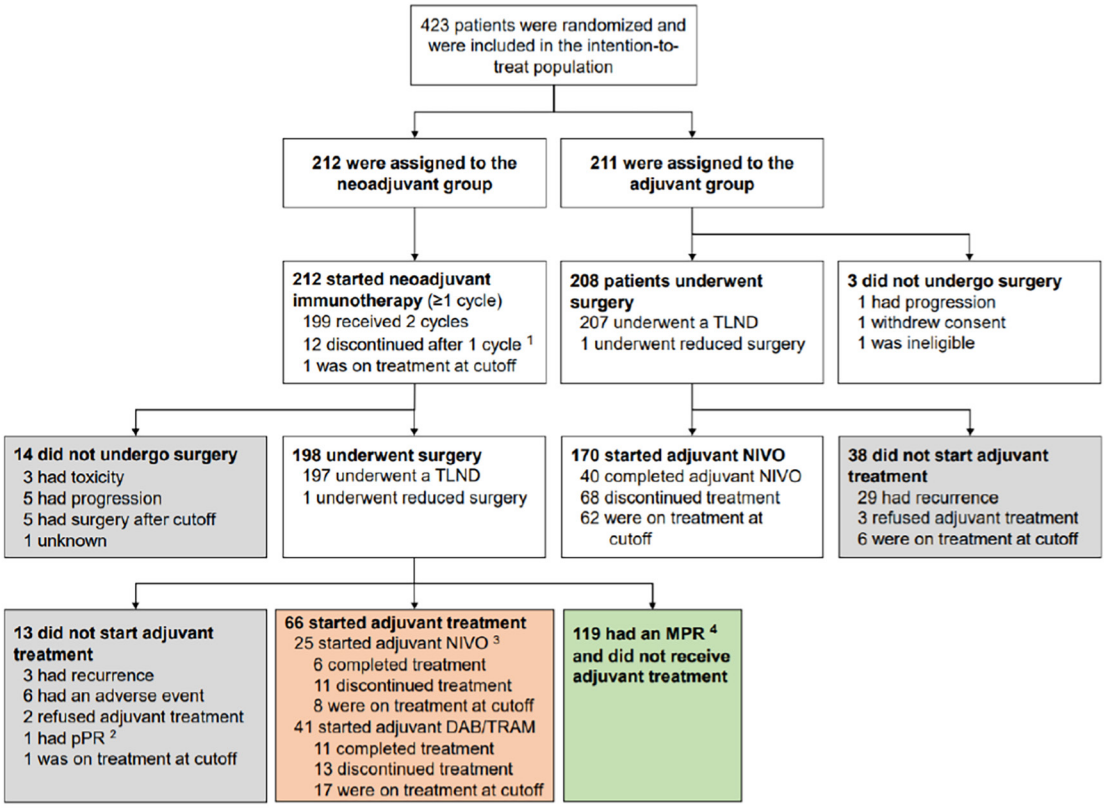
Patient Disposition

Patient disposition is shown in Figure 1. A total of 485 patients were screened and 423 underwent randomization; 212 were randomized to the neoadjuvant arm and 211 were randomized to the adjuvant arm.

In the neoadjuvant arm, all of the patients started systemic therapy, and 198 patients (93.4%) underwent surgery. A total of 197 patients underwent a therapeutic lymph node dissection, and 1 patient had an index lymph node procedure. Surgery was not performed on patients because of toxic effects (n = 3), progression (n = 5), and an unknown reason (n = 1). For 5 patients, surgery was planned for after the data cut-off date. Of the 78 patients in the neoadjuvant arm who were intended to receive adjuvant therapy because of the lack of major pathological response, 65 (83.3%) started systemic adjuvant treatment. As of the data cut-off date, 137 (64.6%) patients in the neoadjuvant arm had completed treatment, 31 patients (14.6%) were still on treatment, and 44 (20.8%) had discontinued treatment. Among those who had discontinued treatment, 5 had progression before surgery, 12 had recurrence, 19 had an AE, and 8 refused further treatment (1 of whom was lost to follow-up).

In the adjuvant arm, 3 patients did not undergo surgery and thus did not start treatment according to the protocol. There were 207 therapeutic lymph node dissections, and 1 selective lymph node dissection performed. There were 170 of 208 patients (81.7%) who started treatment with nivolumab. As of the data cut-off date, 40 patients had completed treatment (1 of whom was lost to follow-up), 68 patients were still on treatment, and 100 had discontinued treatment. Among those who had discontinued treatment, 62 had progression or recurrence, 29 had an AE, 6 refused further treatment (4 of whom were lost to follow-up), 1 was based on physician's choice, 1 died due to toxicity, and 1 died due to another reason.

Figure 1: Patient Disposition



DAB/TRAM = dabrafenib plus trametinib; MPR = major pathological response; NIVO = nivolumab; pPR = pathological partial response; TLND = therapeutic lymph node dissection.

[1] Eight of 12 patients did undergo surgery despite receiving 1 neoadjuvant cycle only.

[2] One patient had a pPR and was treated according to protocol version 3.0, according to which patients with pPR did not receive adjuvant treatment.

[3] One patient received adjuvant treatment despite having an MPR as assessed by the local pathologist.

[4] MPR was assessed by the local pathologist. After central review, 1 of 120 patients had a non-MPR instead of an MPR and did not receive adjuvant treatment. Four of 74 patients had an MPR instead of non-MPR, but did receive adjuvant treatment. TLND denotes therapeutic lymph node dissection, NIVO nivolumab, pPR pathological partial response (11% to 50% residual viable tumour), DAB/TRAM, dabrafenib plus trametinib, MPR major pathological response (≤ 10% residual viable tumour).

Source: From the *New England Journal of Medicine*, Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma, Volume 2 No. 2. Copyright (2024) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[7]

Baseline Characteristics

The characteristics of the patients at baseline were balanced between the 2 treatment arms for most characteristics. The median age was 60 years (range, 22 to 84) in the neoadjuvant arm, and 59 years (range, 19 to 87) in the adjuvant arm. Also, 33.5% and 36.0% of the patients in the neoadjuvant and adjuvant arms, respectively, were female. Ninety percent of patients in both arms had a WHO performance status of 0 (Table 3).

Efficacy

At the time of the preplanned interim analysis (data cut-off date: January 12, 2024), the median duration of follow-up was 10.6 months (interquartile range, 5.2 to 16.8) in the neoadjuvant arm and 9.9 months (interquartile range, 4.6 to 16.8) in the adjuvant arm.[7]

At the updated analysis (data cut-off date: July 12, 2024), the median follow-up was 15.4 months. The results of this analysis were presented as a conference abstract and included updated results for EFS, as well as first results reported for DMFS and RFS.[8]

Pathologic Response

All 212 patients in the neoadjuvant arm received at least 1 dose of neoadjuvant treatment and could be assessed for pathological response.

At the time of the preplanned interim analysis, in the neoadjuvant arm 47.2% of patients had a pathological complete response and 11.8% had a pathological near-complete response (1 to 10% residual viable tumour) as determined by central review, leading to a major pathological response of 59.0%. Eight percent of patients had a pathological partial response and 26.4% had a pathological nonresponse, and 2.4% had progression before surgery. Response data were unavailable for 9 patients (4.2%), 5 of whom underwent surgery after the cut-off date, 3 of whom had not undergone surgery due to toxic effects, and 1 who had not undergone surgery for an unknown reason. Confidence intervals (CIs) were not reported for any of the response estimates.

At the updated analysis, 60.8% (129 of 212 patients) had major pathological response, 8% had a pathological partial response, and 27.4% had a pathological nonresponse.

Table 3: Baseline Characteristics

Characteristic	Neoadjuvant (N = 212)	Adjuvant (N = 211)
Sex, n (%)		
Female	71 (33.5)	76 (36.0)
Male	141 (66.5)	135 (64.0)
Median age, year (range)	60 (22 to 84)	59 (19 to 87)
Continent, n (%)		
Australia	71 (33.5)	71 (33.6)
Europe	141 (66.5)	139 (65.9)
North America	0	1 (0.5)
Median weight, kg[a] (range)	85.1 (52.0 to 144.0)	83.1 (49.0 to 151.0)
Median body mass index (range)[a]	27.6 (19.1 to 52.3)	26.9 (19.1 to 42.0)
WHO performance status score, n (%)[b]		
0	192 (90.6)	192 (91.0)
1	20 (9.4)	19 (9.0)
Tumour stage, n (%)[c]		
T1	25 (11.8)	36 (17.1)
T2	41 (19.3)	39 (18.5)

Characteristic	Neoadjuvant (N = 212)	Adjuvant (N = 211)
T3	41 (19.3)	49 (23.2)
T4	52 (24.5)	46 (21.8)
Tx	7 (3.3)	6 (2.8)
Melanoma of unknown primary origin, n (%)	46 (21.7)	35 (16.6)
Ulceration, n (%)		
Yes	71 (33.5)	57 (27.0)
No	85 (40.1)	102 (48.3)
Melanoma of unknown primary origin, n (%)	46 (21.7)	35 (16.6)
Unknown	10 (4.7)	17 (8.1)
In-transit metastases, n (%)		
Yes	22 (10.4)	25 (11.8)
No	190 (89.6)	186 (88.2)
Short-axis diameter of largest lymph node, n (%)[d]		
< 15 mm	67 (31.6)	74 (35.1)
15 to 30 mm	115 (54.2)	102 (48.3)
31 to 50 mm	24 (11.3)	29 (13.7)
> 50 mm	4 (1.9)	4 (1.9)
No lymph node reported on CT scan	2 (0.9)	2 (0.9)
Median sum of diameters of lymph nodes, mm^2 (range)	25 (15 to 74)	25 (15 to 82)
Location or locations of affected lymph nodes, n of N (%)[e]		
Neck	55 of 211 (26.1)	57 of 211 (27.0)
Axilla	86 of 211 (40.8)	86 of 211 (40.8)
Groin	66 of 211 (31.3)	66 of 211 (31.3)
Axilla and neck	3 of 211 (1.4)	0
Other	1 of 211 (0.5)	2 of 211 (0.9)
No. of lymph nodes positive for disease on PET, n of N (%)[f]		
1	126 of 200 (63.0)	122 of 205 (59.5)
2 or 3	52 of 200 (26.0)	64 of 205 (31.2)
> 3	17 of 200 (8.5)	12 of 205 (5.9)
0	5 of 200 (2.5)	7 of 205 (3.4)
BRAF mutation status, n (%)		
V600E	95 (44.8)	87 (41.2)
V600K	17 (8.0)	25 (11.8)
Other *BRAF* mutation	5 (2.4)	4 (1.9)

Characteristic	Neoadjuvant (N = 212)	Adjuvant (N = 211)
Wild type	95 (44.8)	95 (45.0)
LDH level, n (%)		
< ULN	196 (92.5)	192 (91.0)
1 to 1.5 × ULN	16 (7.5)	19 (9.0)
Previous surgical treatment to nodal basin, n (%)		
Sentinel node procedure	75 (35.4)	78 (37.0)
Lymph node dissection	1 (0.5)	1 (0.5)
Both procedures	0	3 (1.4)
None	136 (64.2)	129 (61.1)

LDH = lactate dehydrogenase; RECIST = Response Evaluation Criteria in Solid Tumours; ULN = upper limit of normal.

Note: Data shown are for the intention-to-treat population, which included all patients who had undergone randomization. Percentages may not total 100 because of rounding.

[a]The weight and body mass index (the weight in kg divided by the square of the height in metres) are missing for 1 patient in the neoadjuvant group and 5 patients in the adjuvant group.

[b]WHO performance status scores range from 0 to 5, with higher numbers indicating greater disability.

[c]The stages are defined according to the eighth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.

[d]The sums of the diameters of the lymph nodes that were longer than 15 mm at the shortest axis were measured on the baseline CT scan, in accordance with RECIST. Data were missing for 68 patients in the neoadjuvant group and 76 patients in the adjuvant group.

[e]The locations of lymph nodes are based on the baseline CT scan. Data were missing for 3 patients in the neoadjuvant group and 5 patients in the adjuvant group and were thus determined on the basis of surgical information for 2 patients in the neoadjuvant group and 5 patients in the adjuvant group.

[f]Patients were eligible for inclusion in the trial if they had a pathologically proven lymph node that could be assessed with the use of RECIST, was positive for disease according to PET, or was palpable at baseline.

Source: From the *New England Journal of Medicine*, Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma, Volume 2 No.2. Copyright (2024) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[7]

Event-Free Survival

At the time of data cut-off for the preplanned interim analysis, a total of 100 events (progression, recurrence, or death from melanoma or treatment) had occurred in the ITT population: 28 were in the neoadjuvant arm (progression before surgery = 5 and recurrence of melanoma = 23) and 72 in the adjuvant arm (progression before surgery = 2, recurrence of melanoma = 69, and death due to treatment-related toxicity = 1).

The EFS at 12 months was 83.7% (99.9% CI, 73.8 to 94.8) in the neoadjuvant arm and 57.2% (99.9% CI, 45.1 to 72.7) in the adjuvant arm. The between-group difference in estimated EFS probability was not reported. The adjusted hazard ratio (HR) for progression, recurrence, or death was 0.32 (99.9% CI, 0.15 to 0.66; P < 0.0001). Results of the Kolmogorov-type supremum test suggested a violation of the proportional hazards assumption, which was attributed by the investigators to the wider separation of the curves in the first months after randomization. The adjusted difference in restricted mean survival time was 8.00 months (99.9% CI, 4.94 to 11.05; P < 0.001), at a restriction time of 27.8 months (Figure 2). According to the authors, results of the piecewise hazard function to address nonproportionality and of a sensitivity analysis for competing risks yielded similar results to those for the main analysis. Given the results of the interim analysis, this analysis became the final analysis for EFS.

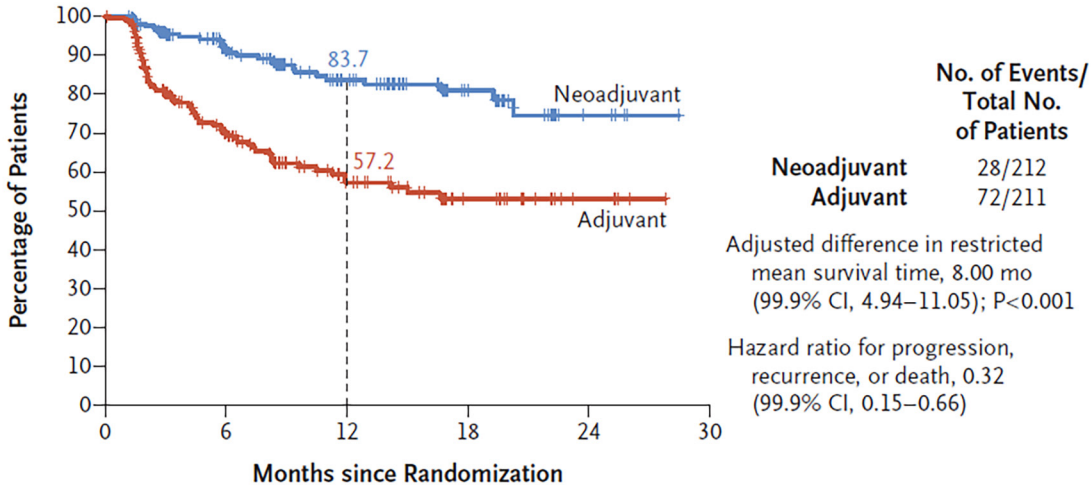
At the updated analysis, the estimated EFS at 18 months was 80.8% versus 53.9% in the neoadjuvant and adjuvant groups, respectively (adjusted HR = 0.32; 95% CI, 0.22 to 0.48; P < 0.001).[8] CIs were not reported for the probabilities of EFS at 18 months, nor was the estimated between-group difference (Figure 3).

Distant Metastasis-Free Survival

Results for DMFS were not reported at the time of the preplanned interim analysis.

In the updated analysis, the estimated DMFS at 18 months was 85.7% versus 62.4% in the neoadjuvant and adjuvant arms, respectively (adjusted HR = 0.37; 95% CI, 0.24 to 0.57; P < 0.001). CIs were not reported for the probabilities of DMFS at 18 months, nor was the estimated between-group difference.

Figure 2: Event-Free Survival



No. at Risk (no. censored)

Neoadjuvant	212 (0)	126 (71)	77 (111)	34 (152)	5 (179)
Adjuvant	211 (0)	100 (57)	53 (89)	23 (116)	6 (133)

Source: From the *New England Journal of Medicine*, Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma, Volume 2 No.2. Copyright (2024) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[7]

Recurrence-Free Survival

Results for RFS were not reported at the time of the preplanned interim analysis.

In the updated analysis, at 18-months follow-up the estimated RFS rates were 89.4% (95% CI, 82.3 to 97.0) versus 64.1% (95% CI, 54.3 to 75.7) among patients with stage IIIB disease in the neoadjuvant versus adjuvant groups, respectively. Among patients with stage IIIC disease, the estimated RFS was 78.0% (95% CI, 68.8 to 88.4) in the neoadjuvant group and 43.6% (95% CI, 33.5 to 56.8) in the adjuvant group. The stage IIID subgroup was too small for analysis (11 versus 8 patients). Between-group differences and CIs were not reported for any subgroup. The estimated overall effect was also not reported.

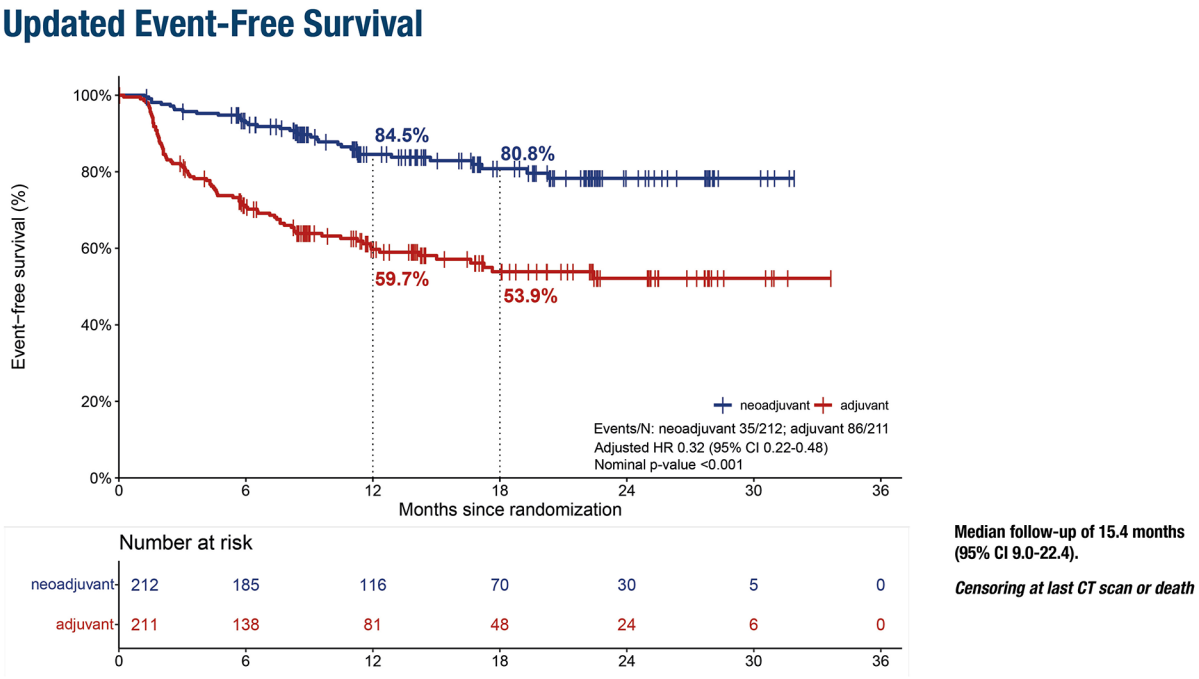
Overall Survival

Results for OS were not reported.

Health-Related Quality of Life

Results for HRQoL were not reported.

Figure 3: Updated Event-Free Survival (18 Months of Follow-Up)



Source: *ESMO Daily Reporter* (September 14, 2024) 2024; Long-term survival benefits reported with neoadjuvant immunotherapy combinations in stage III melanoma [conference news release]. Copyright European Society for Medical Oncology. All rights reserved.[5]

Harms

Detailed results for harms at the time of the first interim analysis are available in the Blank et al. (2024) supplementary appendix (tables S7 to S11).

- Nearly all patients (96% and 93%) were reported to have 1 or more AEs in the neoadjuvant and adjuvant groups, respectively.
- Common AEs (reported in 20% or more patients in either group) in the neoadjuvant versus adjuvant groups were: aspartate transaminase increased (22% versus 12%), pruritis (20% versus 14%), alanine transaminase increased (24% versus 12%), diarrhea (22% versus 16%), wound infection (19% versus 24%), seroma (25% versus 31%), rash (41% versus 21%), and fatigue (34% versus 29%).

- SAEs were reported in 36.3% of the patients in the neoadjuvant arm and 24.0% of those in the adjuvant arm. Details of these SAEs were not reported. Deaths due to treatment-emergent AEs were not explicitly reported; however, 1 patient in the adjuvant arm died from pneumonitis caused by nivolumab. No treatment-related deaths occurred in the neoadjuvant arm.
- AEs of grade 3 or higher were reported in 47.2% of patients in the neoadjuvant arm and in 34.1% in the adjuvant arm. Few grade 3 or higher AEs occurred in more than 3% of patients in either group, except for wound infection (6% versus 8%), alanine transaminase increased (5% versus 2%), aspartate transaminase increased (5% versus 2%), diarrhea (5% versus 8%), and hyperglycemia (4% versus 2%).
- In the neoadjuvant arm, 23.1% of patients had an AE of grade 3 or higher that was related to systemic treatment within the first 12 weeks and thus considered related to neoadjuvant treatment.
- Nine percent of patients in the neoadjuvant arm and 14% in the adjuvant arm discontinued treatment due to AEs.
- The percentage of patients with immune-related AEs was not reported.

Table 4: Adverse Events

Events	Neoadjuvant (N = 212)	Adjuvant (N = 208)
Any adverse event, n (%)	204 (96.2)	194 (93.3)
Any grade ≥ 3 adverse event, n (%)	100 (47.2)	71 (34.1)
Serious adverse event, n (%)	77 (36.3)	49 (23.6)
Surgery-related adverse event, n of N (%)	120 of 198 (60.6)	151 of 208 (72.6)
Surgery-related grade ≥ 3 adverse event, n of N (%)	28 of 198 (14.1)	30 of 208 (14.4)
Adverse event related to systemic treatment, n of N (%)	181 of 212 (85.4)	123 of 170 (72.4)
Grade ≥ 3 adverse event related to systemic treatment, n of N (%)	63 of 212 (29.7)	25 of 170 (14.7)
Discontinuation of treatment due to adverse event, n (%)	19 (9.0)	30 (14.4)
Death due to treatment-related adverse event, n (%)	0	1 (0.5)

Note: Included are adverse events that were reported between randomization and 100 days after the last trial treatment. The safety population included all patients who started trial treatment. Surgery-related adverse events were assessed in all patients who underwent surgery. Adverse events related to systemic treatment were assessed in all patients who received at least 1 dose of systemic treatment. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Source: From the *New England Journal of Medicine*, Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma, Volume 2 No. 2. Copyright (2024) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[7]

Critical Appraisal

Internal Validity

In the NADINA trial, randomization seems to be effective as baseline characteristics between the 2 treatment arms were balanced at baseline for the reported demographic and disease characteristics. The trial was open-label; the lack of blinding increases risk of bias due to deviations from the intended interventions (e.g., different supportive care) because the patients and investigators were aware of the treatments received. However, given that the primary outcome assessment was confirmed by retrospective central review, the

risk of bias in the measurement of the outcome is relatively low. Pathological response was assessed using established international criteria. The trial followed a prespecified analysis plan, and patients were analyzed in their randomized treatment group, regardless of the treatment received postrandomization (ITT analysis), which is appropriate for informing the effect of assignment to the interventions. All reported outcomes were appropriate for this setting. Cure and long-term survival were identified in this review as a goal of treatment. Results for OS from the NADINA trial are not yet available and will be analyzed 3 years after the last patient was enrolled. Further, HRQoL was measured in the trial but results were not reported. As such, the effect of neoadjuvant compared with adjuvant therapy on OS and HRQoL among patients with resectable stage III melanoma is unknown. The statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary end points or in subgroups, thus for statistically significant results there is an increased risk that the null hypothesis was erroneously rejected. The proportional hazards assumption was appropriately verified for EFS at the time of the preplanned interim analysis. As the assumption appeared violated, the difference in restricted mean survival time between the treatment arms with adjustment for the stratification factors at randomization was provided. Further, the investigators reported that results of a piecewise hazard function provided results similar to those for the main analysis; however, the results were not reported thus the Canada's Drug Agency review team could not verify the accuracy of the statement. For EFS and other time to event end points (i.e., DMFS and RFS) reported at the time of the updated analysis, results of testing for the proportional hazards assumption were not reported. Further, Kaplan-Meier plots were not provided, which would have facilitated visual inspection of the Kaplan-Meier curves to assess the plausibility of this assumption. As such, it is not clear whether the proportional hazards assumption was plausible for these end points and the reported HRs need to be interpreted considering this uncertainty.

Interpretation of the NADINA trial results was limited by incomplete reporting. For example, although the probabilities of EFS, DMFS, and RFS at clinically relevant time points were reported for each group, estimated between-group differences with CIs were not reported, precluding judgments about the precision of the differences. Results for RFS were reported for subgroups of patients based on disease stage; however, the overall estimated effect (for all randomized patients) was not reported. The subgroup analysis was not prespecified, as such, there is a risk of selective reporting. There was no formal statistical testing for subgroup differences. The randomization was not stratified by disease stage; thus, the subgroups may not be prognostically comparable and randomization within each subgroup may not hold.

To date, the results reported from the NADINA trial are based on interim analyses; as such, reported beneficial effects may be overestimated.[9] Follow-up remains short and results for some key secondary analyses including OS have not yet been reported. The first interim analysis became the final analysis for EFS given the positive results for this outcome. It is uncertain if end points like pathological response, EFS, DMFS, and RFS are valid surrogates for OS. Since EFS is a surrogate end point, it needs to be validated for each unique tumour type, treatment, and stage of disease. Similarly, pathological response has often been used as a surrogate end point in trials of neoadjuvant therapies but while there is evidence that patients with major pathological response have high relapse-free rates, the relationship between pathological response

with OS among patients with resectable stage III melanoma who receive neoadjuvant treatment remains uncertain.

External Validity

The NADINA trial's inclusion criteria were clinically relevant and based on clinical expert input, generalizable to the patient population in Canada. However, the trial excluded patients with mucosal melanoma and those with more than 3 in-transit metastases. According to the clinical experts, these patients would be treated in practice. The trial regimens were also generalizable to the clinical setting in Canada both in dose and duration of treatment. The comparator of the trial which was adjuvant nivolumab is one of the current treatment options used for resectable stage III melanoma in Canada. However, there is no comparative evidence available for the other comparators (i.e., adjuvant pembrolizumab, adjuvant dabrafenib plus trametinib and neoadjuvant-adjuvant pembrolizumab) that are current treatment options in this setting.

With regards to outcomes measured in the NADINA trial, OS and prevention of relapse are the most important outcomes in this setting where treatment is intended to be curative. The clinical experts noted that pathological response was an important outcome that is used in clinical practice, and this was measured in the trial and determined subsequent treatment. However, the input by the Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee noted that the use of pathological major response to guide postsurgical adjuvant therapy would be challenging as this in-depth pathological assessment after neoadjuvant therapy required to determine the next steps in treatment is not standard. If discontinuation of adjuvant therapy is considered, proper pathological assessment will be needed. This will require additional resources for pathology to provide this needed information.

Discussion

Efficacy

the NADINA trial demonstrated a statistically significant improvement in EFS when patients received neoadjuvant immunotherapy with nivolumab plus ipilimumab followed by response-driven adjuvant therapy, compared to adjuvant treatment with nivolumab alone. The clinical experts and the clinician input indicated that these results are clinically meaningful. However, it should be noted that between-group differences with CIs for the probability of EFS at clinically relevant follow-up times were not reported thus the precision of the estimated effects is unknown (i.e., whether the CIs included the potential for little to no difference between groups). There also remains uncertainty as to whether EFS is a valid surrogate for OS in this patient population (and if so, what effect size for EFS would be needed to predict a clinically significant OS benefit). Patients treated with neoadjuvant nivolumab plus ipilimumab only received adjuvant treatment with nivolumab if they had a pathologic partial or nonresponse; if a major pathological response was observed at the time of surgical resection (and following just 2 infusions of neoadjuvant immunotherapy), patients underwent surveillance without further active therapy. More than one-half of patients received only neoadjuvant therapy. To date, the results of the trial reported suggest that for most patients, neoadjuvant systemic therapy (without resumption of treatment postoperatively) may be sufficient.

The results of the NADINA trial are based on interim analysis except for the primary end point of EFS; final results for secondary end points including OS and HRQoL are not yet available. It is uncertain if the benefits of neoadjuvant and response-driven adjuvant immunotherapy observed with EFS and pathological response rates will translate to similar benefits for OS. The clinical experts noted that the ideal initial surrogate response is the response of the nodal disease to the neoadjuvant treatment (i.e., tumour response), which evaluates response early during treatment, and can translate into long-term outcomes including disease-free survival and OS.[10] The evaluation of tumour response is critical and helps inform subsequent treatment decisions (e.g., patients who are unable to achieve a complete response with neoadjuvant therapy may then proceed with surgery). The clinical experts emphasized that both clinical and importantly, pathological response to treatment, are important outcomes in the setting of neoadjuvant treatment of resectable melanoma.

Neoadjuvant-adjuvant pembrolizumab was recently reviewed (nonsponsored review) with a positive reimbursement recommendation for the treatment of adult patients with stage III or stage IV melanoma.[3] which is currently the only neoadjuvant-adjuvant treatment option in this setting (although not yet fully implemented). There are no studies comparing neoadjuvant nivolumab plus ipilimumab followed by response-driven adjuvant nivolumab to neoadjuvant-adjuvant pembrolizumab in stage III melanoma. The clinical experts indicated that although there are no comparative studies, in clinical practice these neoadjuvant-adjuvant regimens are considered similar but not equivalent, and that there is a place in therapy for both treatment options. In the metastatic setting, combination immunotherapy with a CTLA-4 and a PD-1 inhibitor is considered more effective compared to PD-1 inhibitor monotherapy (nivolumab or pembrolizumab), thus this combination therapy would be prioritized for patients with stage III melanoma.[2] However, for patients who may not tolerate the higher toxicity of combination immunotherapy with nivolumab plus ipilimumab, neoadjuvant-adjuvant pembrolizumab would be preferred.

Harms

In the NADINA trial the combination of nivolumab and ipilimumab in the neoadjuvant arm was associated with a higher rate of AEs compared with nivolumab monotherapy in the adjuvant arm. These AE rates are consistent with previously published randomized controlled trial data for ipilimumab and combination ipilimumab and nivolumab.[11] The clinical experts explained that the AEs for combination nivolumab plus ipilimumab are well-established in patients with metastatic disease. Patients would be monitored at least every 3 weeks, and more frequently if they experienced AEs that are severe or necessitate management before the 3-week assessment.

Conclusion

The evidence from 1 randomized phase III trial comparing neoadjuvant with adjuvant immunotherapy in resectable stage III melanoma suggests that 2 cycles of neoadjuvant nivolumab plus ipilimumab and response-driven adjuvant treatment may result in longer EFS than adjuvant treatment with nivolumab alone. Longer follow-up is needed to confirm that this benefit extends to long-term outcomes including OS. There is a lack of direct or indirect comparative evidence for neoadjuvant-adjuvant pembrolizumab. The clinicians and clinical experts support a change in practice from adjuvant to neoadjuvant immunotherapy. The shift in

treatment paradigm would incorporate a shorter course of combined treatment with 2 cycles of nivolumab plus ipilimumab before surgery followed by response-driven adjuvant treatment, instead of the current standard of care of 12 cycles of adjuvant treatment for all patients.

Economic Review

The Economic Review consisted of a cost comparison for neoadjuvant nivolumab plus ipilimumab, followed by surgical resection, and response-driven adjuvant treatment (dabrafenib plus trametinib [if *BRAF* mutation positive] or nivolumab [if *BRAF* wild type]) and radiotherapy compared with comparators for the treatment of adult patients with stage III resectable melanoma.

Based on sponsor-submitted prices from previous CADTH reviews,[12] neoadjuvant nivolumab plus ipilimumab is expected to have a per patient cost of $21,724 per 28-day cycle (Table 4 in the Supplemental Material). When used as recommended, neoadjuvant nivolumab plus ipilimumab, followed by surgical resection, and response-driven adjuvant treatment (dabrafenib plus trametinib [if *BRAF* positive] or nivolumab [if *BRAF* wild type]) is expected to cost from $43,449 to $250,661 per patient for the treatment course (2 cycles). Comparators include adjuvant nivolumab, adjuvant dabrafenib plus trametinib, neoadjuvant plus adjuvant pembrolizumab, and adjuvant pembrolizumab. The treatment course cost of comparators ranges from $112,640 to $234,240 per patient. Neoadjuvant nivolumab plus ipilimumab may reduce costs for patients who have a major pathological response to neoadjuvant therapy because these patients would not require adjuvant therapy (i.e., nivolumab or dabrafenib plus trametinib). However, for patients who do not respond or have a partial response to neoadjuvant therapy, treatment costs are expected to be higher than adjuvant therapy (i.e., nivolumab or dabrafenib plus trametinib). The impact of neoadjuvant nivolumab plus ipilimumab on overall treatment costs is uncertain because potential cost savings in patients who do respond to treatment may be offset by higher costs in partial or for patients who do not respond to treatment. The amount of net change in treatment costs depends on factors like relative OS rates, efficacy and costs of subsequent therapies, and other elements beyond the scope of this report. As such, the reimbursement of neoadjuvant nivolumab plus ipilimumab for the treatment of adult patients with stage III resectable melanoma may increase or decrease overall treatment costs, depending on downstream changes in health care resource utilization and efficacy.

Neoadjuvant nivolumab plus ipilimumab is expected to be less costly than pembrolizumab (neoadjuvant plus adjuvant and adjuvant), except for patients with a positive *BRAF* mutation receiving adjuvant dabrafenib plus trametinib. The overall economic impact of reimbursing neoadjuvant nivolumab plus ipilimumab on overall treatment costs compared with pembrolizumab (neoadjuvant plus adjuvant and adjuvant) is uncertain due to a lack of direct or indirect clinical evidence comparison of these treatments.

Additional items for consideration are provided, as follows:

- Based on the Clinical Review conclusions, neoadjuvant nivolumab plus ipilimumab provides a clinically meaningful benefit on EFS compared with adjuvant nivolumab. Longer follow-up is needed to confirm that this EFS benefit extends to OS. A higher proportion of patients using neoadjuvant

nivolumab plus ipilimumab had AEs in the NADINA trial; however, combination therapy is known to be associated with higher toxicity. There were no studies comparing neoadjuvant nivolumab plus ipilimumab with adjuvant dabrafenib plus trametinib for patients with a positive *BRAF* mutation status. Moreover, no literature was identified comparing neoadjuvant nivolumab plus ipilimumab followed by response-driven adjuvant nivolumab and dabrafenib plus trametinib to neoadjuvant plus adjuvant or adjuvant only pembrolizumab among patients with stage III melanoma. Therefore, the comparative efficacy of these treatments is unknown.

- Feedback from drug plans indicated that nivolumab dosing would be weight based to a cap (i.e., 3 mg/kg up to 240 mg every 3 weeks). However, clinical expert feedback was that neoadjuvant nivolumab dosing as per the NADINA trial (i.e., 2 cycles of a fixed dose of 240 mg every 3 weeks) would likely be used in clinical practice. The clinical experts did not have any concerns with implementing weight-based dosing in the adjuvant setting.
- Clinical expert feedback highlighted the need for a standardized assessment of response to neoadjuvant therapy because the initiation of adjuvant treatment is driven by a patient's response to neoadjuvant therapy. Without a clear treatment response criterion, patients with a treatment response may end up receiving adjuvant therapy, potentially leading to unnecessary additional treatment. This may decrease estimated cost savings for patients with a major pathological response to neoadjuvant therapy.
- According to clinical expert input, neoadjuvant nivolumab plus ipilimumab is expected to be associated with improved health outcomes in terms of EFS, potentially reducing costs of subsequent therapies for patients with major pathological response. Patients who do not respond or have partial response to neoadjuvant treatment are unlikely to experience changes in subsequent therapy costs due to the inherent characteristics of their disease. Neoadjuvant nivolumab plus ipilimumab is also associated with a higher, yet manageable, toxicity profile compared with adjuvant nivolumab. Costs related to AEs, subsequent therapy, and disease management were not considered as part of the cost comparison. To consider this alongside the health care resource implications associated with comparative clinical benefits, a cost-effectiveness analysis comparing neoadjuvant nivolumab plus ipilimumab with standard adjuvant treatment (nivolumab and dabrafenib plus trametinib) would be required.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on October 22, 2024.

Conclusion

Results of the cost comparison demonstrate that neoadjuvant nivolumab plus ipilimumab is expected to be less costly than adjuvant nivolumab and dabrafenib plus trametinib for patients with a major pathological response and more costly for patients with a partial or no major response to neoadjuvant therapy. The reimbursement of neoadjuvant nivolumab plus ipilimumab for the treatment of adult patients with stage III resectable melanoma may increase or decrease overall drug acquisition costs, depending on treatment response. Compared with pembrolizumab (neoadjuvant plus adjuvant or adjuvant only), neoadjuvant

nivolumab plus ipilimumab is expected to be less costly, except for patients with a positive *BRAF* mutation treated with adjuvant dabrafenib plus trametinib. The impact of reimbursing neoadjuvant nivolumab plus ipilimumab on overall treatment costs compared with pembrolizumab (neoadjuvant plus adjuvant and adjuvant) is uncertain due to a lack of direct or indirect clinical evidence comparison of these treatments.

If patients have a major pathological response to neoadjuvant therapy, neoadjuvant nivolumab plus ipilimumab is associated with decreased drug acquisition costs and higher EFS compared with adjuvant nivolumab. As such, neoadjuvant nivolumab plus ipilimumab may represent a cost-effective treatment option in this group of patients. If patients have a partial or no major pathological response, given that neoadjuvant nivolumab plus ipilimumab is associated with increased drug acquisition costs and potentially higher EFS compared with adjuvant nivolumab, additional information is needed to estimate the magnitude of change in overall treatment costs and benefits among all patients. For the subgroup of patients with stage III resectable melanoma and a positive *BRAF* mutation, neoadjuvant nivolumab plus ipilimumab is expected to be less costly than *BRAF*-targeted therapies for patients with a major pathological response and more costly for patients with a partial or no major response to neoadjuvant therapy.

Based on the Clinical Review conclusions, neoadjuvant nivolumab plus ipilimumab is expected to provide a clinically meaningful EFS benefit compared with adjuvant nivolumab. Longer follow-up is needed to confirm that this benefit extends to OS. There were no studies identified in the literature to estimate the comparative efficacy of neoadjuvant nivolumab plus ipilimumab with other comparators, including *BRAF*-targeted therapies and neoadjuvant plus adjuvant or adjuvant only pembrolizumab. The overall cost impact of neoadjuvant nivolumab plus ipilimumab compared to these treatments is highly influenced by differences in efficacy, and further analysis is needed to quantify the economic implications of adopting this approach to treatment.

References

1. Brenner DR, Gillis J, Demers AA, et al. Projected estimates of cancer in Canada in 2024. *CMAJ.* 2024;196(18):E615-E623. PubMed
2. Hieken TJ, Kreidieh F, Aedo-Lopez V, Block MS, McArthur GA, Amaria RN. Neoadjuvant Immunotherapy in Melanoma: The Paradigm Shift. *Am Soc Clin Oncol Educ Book.* 2023;43:e390614. PubMed
3. CADTH. CADTH reimbursement review: Pembrolizumab (clinical and pharmacoeconomic report). Ottawa: CADTH; 2024: https://www.cda-amc.ca/sites/default/files/DRR/2024/PX0346_%20Clinical_and_Pharmacoeconomic_Combined_Report.pdf. Accessed October 17, 2024.
4. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898. PubMed
5. Long-term survival benefits reported with neoadjuvant immunotherapy combinations in stage III melanoma [conference news release]. *ESMO Daily reporter (September 14, 2024)* 2024; https://dailyreporter.esmo.org/esmo-congress-2024/congress-highlights/long-term-survival-benefits-reported-with-neoadjuvant-immunotherapy-combinations-in-stage-iii-melanoma. Accessed October 17, 2024.
6. Lucas MW, Lijnsvelt J, Pulleman S, et al. The NADINA trial: A multicenter, randomised, phase 3 trial comparing the efficacy of neoadjuvant ipilimumab plus nivolumab with standard adjuvant nivolumab in macroscopic resectable stage III melanoma. *J Clin Oncol.* 2022;40(16 Supplement 1):TPS9605.
7. Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma. *N Engl J Med.* 2024;02:02.
8. Lucas MW, Menzies AM, Lopez-Yurda M, et al. LBA42 - Distant metastasis-free survival of neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in resectable, macroscopic stage III melanoma: The NADINA trial. Barcelona: ESMO Congress 2024: https://cslide.ctimeetingtech.com/esmo2024/attendee/confcal/show/session/45. Accessed October 17, 2024.
9. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA.* 2010;303(12):1180-1187. PubMed
10. Rawson RV, Adhikari C, Bierman C, et al. Pathological response and tumour bed histopathological features correlate with survival following neoadjuvant immunotherapy in stage III melanoma. *Ann Oncol.* 2021;32(6):766-777. PubMed
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. PubMed
12. Drug Reimbursement Review pharmacoeconomic report: Nivolumab (Opdivo) for Stage IIB or IIC melanoma, adjuvant. Ottawa (ON): CADTH; 2024: https://www.cda-amc.ca/sites/default/files/DRR/2024/PC0339-Opdivo-Melanoma-Combined-Report.pdf. Accessed October 17, 2024.

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