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

January 2025

Drugs Health Technologies Health Systems

Reimbursement Review

Nivolumab Plus Ipilimumab (Opdivo-Yervoy): Supplemental Material

Requester: Public drug programs
Therapeutic area: Melanoma

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Appendix 1: Treatment Characteristics

Please note that this appendix has not been copy-edited.

Table 1: Key Characteristics of Treatments

Treatment	Mechanism of action	Health Canada Indication
Nivolumab	Fully human, anti-programmed death-1 (PD-1) checkpoint inhibitor that selectively blocks the interaction of the PD-1 receptor with PD ligands 1 and 2	**Unresectable or metastatic melanoma** • As monotherapy or in combination with ipilimumab, for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma • Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor **Adjuvant treatment of melanoma** • As monotherapy for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases • As monotherapy for the adjuvant treatment of adult patients with Stage IIIB or IIC melanoma following complete resection.
Ipilimumab	Fully humanized IgG1 monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4) thereby removing an inhibitory signal from reducing the activity of T-lymphocytes.	• Unresectable or metastatic melanoma, as a single agent • Unresectable or metastatic melanoma in adults who have not received prior systemic therapy for unresectable or metastatic melanoma, when used in combination with nivolumab
Pembrolizumab	A highly selective IgG4-kappa humanized monoclonal antibody against PD-1 receptors.	• For the treatment of adult patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. • For the treatment of adult patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor. • For the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC or III melanoma following complete resection.
Dabrafenib	An inhibitor of RAF kinases, including BRAF. It acts on BRAF mutations which result in a constitutively active MAPK pathway (including RAS, RAF, MEK and ERK) and stimulated cell growth.	In combination with trametinib, is indicated for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of lymph node(s), following complete resection.
Trametinib	MEK-targeted kinase inhibitor-inhibits growth of BRAF-mutated cells by blocking the downstream cell signalling by MEK1 and MEK2.	In combination with dabrafenib for the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of lymph node(s), following complete resection.

Clinical Review Appendices

Appendix 2: Methods of the Systematic Review

Please note that this appendix has not been copy-edited.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Adult patients with stage III resectable 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 plus trametinib [if BRAF positive] or nivolumab [if BRAF wild type] and radiotherapy)
Comparator	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 • HRQoL Safety: • Adverse events • SAEs • Discontinuation due to AEs • Death from AEs Notable AEs: immune-related AEs
Study design	Published and unpublished Phase 3 and 4 RCTs

AE = adverse event; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event.

Search Strategy

Strategy for Primary Studies (Systematic Review)

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[1] Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS

framework and research questions. The main search concepts nivolumab ipilimumab and melanoma The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

The search was limited to randomized controlled trials or controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on July 31, 2024. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee meeting on November 21, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

Strategy for Indirect Treatment Comparisons

A focused literature search for indirect treatment comparisons (ITCs) dealing with nivolumab ipilimumab and melanoma was run in MEDLINE on August 20, 2024. No limits were applied.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: July 31, 2024

Alerts: Biweekly search updates until project completion

Search filters applied: Randomized controlled trials or controlled clinical trials filter was applied to limit the retrieval by study type.

Limits:

- Publication date limit: none
- Language limit: none

- Conference abstracts: excluded

Table 3: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.rn	Registry number
.nm	Name of substance word (MEDLINE)

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy

1. Nivolumab/ or (opdivo* or nivolumab* or nivo or bms 936558 or bms936558 or cmab 819 or cmab819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or HSDB 8256 or HSDB8256 or GTPL 7335 or GTPL7335 or xdivane* or ba 1104 or ba1104 or "ly 01015" or ly01015 or pbp 2101 or pbp2101 or bms 986213 or bms986213 or bms 986298 or bms986298 or 31YO63LBSN).ti,ab,kf,ot,hw,rn,nm.
2. Ipilimumab/ or (yervoy* or ipilimumab* or IPI or strentarga* or anti ctla 4* or anti ctla4* or antictla4* or mdx ctla 4 or mdx ctla4 or mdxctla 4 or mdxctla4 or "mdx 010" or mdx010 or mdx 101 or mdx101 or bms 734016 or bms734016 or moab ctla 4 or moabctla 4 or moab ctla4 or moabctla4 or cs 1002 or cs1002 or ibi 310 or ibi310 or 6T8C155666).ti,ab,kf,ot,hw,rn,nm.
3. exp melanoma/ or exp skin neoplasms/ or (melanoma* or melanocarcinoma* or melano-carcinoma* or melanoblastoma* or melano-blastoma* or melanomalignoma* or melano-malignoma* or melanosarcoma* or melano-sarcoma* or naevocarcinoma* or naevo-carcinoma*or nevocarcinoma*

or nevo-carcinoma* or pigmentary cancer* or dermatoma or melanocytic maligan* or melanotic carcinoma*).ti,ab,kf.

4. ((skin or cutaneous or dermal or dermis or epidermal or epidermis) adj3 (cancer* or neoplas* or tumor* or tumour* or malignan* or sarcoma* or carcinoma* or blastoma*)).ti,ab,kf.
5. 3 or 4
6. 1 and 2 and 5
7. 6 use medall
8. *nivolumab/ or (opdivo* or nivolumab* or nivo or bms 936558 or bms936558 or cmab 819 or cmab819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or HSDB 8256 or HSDB8256 or GTPL 7335 or GTPL7335 or xdivane* or ba 1104 or ba1104 or “ly 01015” or ly01015 or pbp 2101 or pbp2101 or bms 986213 or bms986213 or bms 986298 or bms986298).ti,ab,kf,dq.
9. *ipilimumab/ or (yervoy* or ipilimumab* or IPI or strentarga* or anti ctla 4* or anti ctla4* or antictla4* or mdx ctla 4 or mdx ctla4 or mdxctla 4 or mdxctla4 or “mdx 010” or mdx010 or mdx 101 or mdx101 or bms 734016 or bms734016 or moab ctla 4 or moabctla 4 or moab ctla4 or moabctla4 or cs 1002 or cs1002 or ibi 310 or ibi310).ti,ab,kf,dq.
10. exp melanoma/ or exp skin tumor/ or (melanoma* or melanocarcinoma* or melano-carcinoma* or melanoblastoma* or melano-blastoma* or melanomalignoma* or melano-malignoma* or melanosarcoma* or melano-sarcoma* or naevocarcinoma* or naevo-carcinoma*or nevocarcinoma* or nevo-carcinoma* or pigmentary cancer* or dermatoma or melanocytic maligan* or melanotic carcinoma*).ti,ab,kf,dq.
11. ((skin or cutaneous or dermal or dermis or epidermal or epidermis) adj3 (cancer* or neoplas* or tumor* or tumour* or malignan* or sarcoma* or carcinoma* or blastoma*)).ti,ab,kf,dq.
12. 10 or 11
13. 8 and 9 and 12
14. 13 use oemezd
15. 14 not (conference review or conference abstract).pt.
16. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
17. Randomized Controlled Trial/
18. exp Randomized Controlled Trials as Topic/
19. “Randomized Controlled Trial (topic)”/
20. Controlled Clinical Trial/
21. exp Controlled Clinical Trials as Topic/
22. “Controlled Clinical Trial (topic)”/
23. Randomization/
24. Random Allocation/

25. Double-Blind Method/
26. Double Blind Procedure/
27. Double-Blind Studies/
28. Single-Blind Method/
29. Single Blind Procedure/
30. Single-Blind Studies/
31. Placebos/
32. Placebo/
33. Control Groups/
34. Control Group/
35. (random* or sham or placebo*).ti,ab,hw,kf.
36. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
37. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
38. (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
39. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
40. allocated.ti,ab,hw.
41. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
42. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
43. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
44. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
45. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
46. (phase adj3 (III or “3”) adj3 (study or studies or trial*)).ti,hw,kf.
47. or/16-46
48. 7 and 47
49. 15 and 47
50. 48 or 49
51. remove duplicates from 50
52. nadina.ti,ab,kf.
53. 47 and 52
54. 51 or 53

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | nivolumab ipilimumab AND melanoma]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- nivolumab ipilimumab AND melanoma]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- nivolumab ipilimumab AND melanoma]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- nivolumab ipilimumab AND melanoma]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- nivolumab ipilimumab AND melanoma]

Grey Literature

Search dates: July 19 to 31, 2024

Keywords: nivolumab ipilimumab AND melanoma

Limits: none

Relevant websites from the following sections of the grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews

- Clinical Trials Registries
- Databases (free)
- Internet Search

Economic Review Appendices

Appendix 3: Cost Comparison Table

Please note that this appendix has not been copy-edited.

The comparators presented in Table 4 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on the NADINA trial and SWOG S1801 trial,[2,3] and validated by clinical experts. If discrepancies in dosing between the trials and Canadian clinical practice exist, the dose specified by clinical experts was used. Pricing for comparator products was based on sponsor submitted prices from a previous CADTH review and Ontario Exceptional Access Program Formulary.[4,5]

Table 4: CDA-AMC Cost Comparison Table for pediatric patients with adult patients with stage III resectable melanoma

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost	Average cost per 28-days
Nivolumab (Opdivo)	10 mg/mL	Sterile solution for injection 40 mg vial 100 mg vial	$782.2200[a] $1,955.5600[a]	Neoadjuvant Fixed dose: 240 mg every 3 weeks[b] Weight-based dose: 3 mg/kg every 3 weeks[b] Adjuvant 6 mg/kg up to 480 mg every 4 weeks[b]	Neoadjuvant: $223.49 Adjuvant: $335.24	Neoadjuvant: $6,258 Adjuvant: $9,387
Ipilimumab (Yervoy)	5 mg/mL	IV infusion Solution 50 mg vial[c]	$5,800.0000[a]	80 mg every 3 weeks[b]	$552.38	$15,467
Neoadjuvant nivolumab plus ipilimumab					$1,034.50	$21,724
Neoadjuvant nivolumab plus ipilimumab (2 cycles) plus no adjuvant treatment followed by surgical resection, if major pathological response[b]					$1,034.50	$43,449
Neoadjuvant nivolumab plus ipilimumab (2 cycles) plus adjuvant nivolumab (11 cycles) followed by surgical resection, if no or partial pathological response and BRAF wild-type[b]					$419.15	$146,702
Neoadjuvant nivolumab plus ipilimumab (2 cycles) plus dabrafenib plus trametinib (46 weeks) followed by surgical resection, if no or partial pathological response and BRAF V600E or V600K mutation[b]					$688.63	$250,661
BRAF targeted therapies						
Dabrafenib (Tafinlar)	50 mg 75 mg	Capsule	$50.32550 $75.34730	150 mg twice daily	$301.39	$8,439

Treatment	Strength / concentration	Form	Price	Recommended dosage	Average daily cost	Average cost per 28-days
Trametinib (Mekinist)	0.5 mg 2 mg	Tablet	$86.4933 $342.1270	2 mg daily	$342.13	$9,580
Dabrafenib plus trametinib (52 weeks) followed by surgical resection[b,d]					$643.52	$234,240
Immunotherapy						
Nivolumab	10 mg/mL	Sterile solution for injection 40 mg vial 100 mg vial	$782.2200[a] $1,955.5600[a]	Adjuvant 6 mg/kg up to 480 mg every 4 weeks	$335.24	$9,387
Adjuvant nivolumab (12 cycles) followed by surgical resection[b]					$335.24	$112,640
Pembrolizumab	25 mg/mL	4 mL vial Solution for IV infusion	4,400.0000[a]	2 mg/kg up to 200 mg every 3 weeks[f]	$419.05	$11,733
Neoadjuvant and adjuvant pembrolizumab (neoadjuvant – 3 cycles; adjuvant – 15 cycles)[e]					$558.73	$211,200
Adjuvant pembrolizumab only (adjuvant – 17 to 18 cycles)[e,f]					$558.73	$199,467 to $211,200

Note: All prices are from the Ontario Exceptional Access Program Formulary (accessed October 7, 2024),[4] unless otherwise indicated, and do not include dispensing fees. For treatments using weight-based dosing, CADTH assumed a weight of 75 kg. All costs include wastage of unused medication in vials. If vial sharing and weight-based dosing is assumed, the average cost per 28-day cycle is $5,5867 for neoadjuvant nivolumab, $8,800 for adjuvant nivolumab and $8,800 for pembrolizumab treatment.

Note: According to clinical expert input, adjuvant radiotherapy may be allowed at the discretion of physician's assessment of local recurrence.

[a]CADTH review of nivolumab.[5]

[b]Dosing is based on the NADINA trial,[2] and validated by clinical experts.

[c]Ipilimumab is available in 200 mg strength (40 mL vial) in the product monograph but there is no cost available for this strength.[6]

[d]According to clinical expert input, patients with BRAF wild-type status may receive adjuvant BRAF targeted therapies or immunotherapy at the discretion of clinician.

[e]Dosing is based on the SWOG S1801 trial.[3]

[f]According to clinical expert feedback, patients may be given 17 to 18 cycles of adjuvant pembrolizumab.

The recommended dose of neoadjuvant nivolumab plus ipilimumab is 240 mg every 3 weeks (Table 1). At $782 and $1,956 per 40 mg and 100 mg vials of nivolumab, respectively, and $5,800 per 50 mg vial of ipilimumab, the treatment acquisition cost of neoadjuvant nivolumab plus ipilimumab is $1,034.50 daily, or $21,724 per patient per cycle. When used as recommended, neoadjuvant nivolumab plus ipilimumab, followed by surgical resection, and response-driven adjuvant treatment (dabrafenib plus trametinib [if BRAF mutation positive] or nivolumab [if BRAF mutation wild-type]) is expected to cost from $43,449 to $250,661 per patient. Neoadjuvant nivolumab plus ipilimumab is less costly by $69,191 and $190,791 per patient compared with adjuvant nivolumab and dabrafenib plus trametinib, respectively, if major pathological response to neoadjuvant treatment is present. However, neoadjuvant nivolumab plus ipilimumab is expected to cost more by $34,062 and $16,421 compared with adjuvant nivolumab and dabrafenib plus trametinib, respectively, for patients with partial or no major pathological response. Compared with pembrolizumab (neoadjuvant plus adjuvant or adjuvant only), neoadjuvant nivolumab plus ipilimumab is expected to cost less by $167,751 for patients with a major pathological response. For patients with partial or no major response to neoadjuvant therapy, neoadjuvant nivolumab plus ipilimumab is expected to cost less by $64,498 per patient for patients with BRAF mutation wild-type and more by $39,461 per patient for patients with BRAF mutation positive, compared with pembrolizumab (neoadjuvant plus adjuvant or adjuvant only).

Results may differ by jurisdiction depending on individual list prices for the drugs under review compared to those presented in Table 4.

References

1. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol.* 2016;75:40-46. PubMed
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6. Yervoy (Ipilimumab): 5 mg/mL and 10 mL and 40 mL vials [product monograph]. Montreal (Quebec): Bristol-Myers Squibb Canada; 2023: https://www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf. Accessed October 17, 2024.

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