Canadian Journal of Health Technologies

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

August 2025 Volume 5 Issue 8

Drugs Health Technologies Health Systems

Reimbursement Review

Nivolumab: Supplemental Material

Requester: Public drug programs
Therapeutic area: Classic Hodgkin lymphoma

Table of Contents

List of Tables

List of Figures

Abbreviations

AE	adverse event
AVD	doxorubicin (Adriamycin), vinblastine, and dacarbazine
Bv	brentuximab
N	nivolumab
RCT	randomized controlled trial

Background Appendices

Appendix 1: Characteristics of Different Treatment Regimens

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

Table 1: Key Characteristics of Nivolumab + AVD and Comparators

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
Nivolumab + AVD (doxorubicin, vinblastine, and dacarbazine)	Nivolumab: PD-1 inhibitor AVD: Antineoplastic agents	No Health Canada indication for cHL	IV infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles. • Nivolumab: 240 mg in adults and 3 mg/kg of body weight in children 12 to < 18 years of age (capped at 240 mg) • Doxorubicin: 25 mg/m^2 of body-surface area • Vinblastine: 6 mg/m^2 of body-surface area • Dacarbazine: 375 mg/m^2 of body-surface area	Immune-related toxicities, fatigue, diarrhea, rash
Comparators				
ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)	Combination of drugs used in chemotherapy (for treatment of cHL)	No Health Canada indication for cHL	IV	Various systemic toxicities, secondary malignancy
BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)	Combination of drugs used in chemotherapy (for treatment of cHL)	No Health Canada indication for cHL	IV; prednisone (oral)	Various systemic toxicities, secondary malignancy
Bv-AVEPC (doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide)	Combination of brentuximab vedotin and drugs used in chemotherapy (for treatment of pediatric patients with high-risk cHL)	No Health Canada indication for cHL	IV; prednisone (oral)	Various systemic toxicities, secondary malignancy
ABVEPC (doxorubicin, bleomycin, vincristine,	Combination of brentuximab vedotin and drugs used in chemotherapy	No Health Canada indication for cHL	IV; prednisone (oral)	Various systemic toxicities, secondary malignancy

Treatment	Mechanism of action	Indication[a]	Recommended dosage and route of administration	Serious adverse effects or safety issues
etoposide, prednisone, cyclophosphamide)	(for treatment of pediatric patients with high-risk cHL)			

cHL = classic Hodgkin's lymphoma; PD-1 = Programmed death receptor 1.

[a]Health Canada–approved indication.

Clinical Review Appendices

Appendix 2: Methods of the Clinical Review

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

Search Strategy

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.

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 were nivolumab and Hodgkin lymphoma. 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).

Search filters were applied to limit retrieval to any types of clinical trials or observational studies. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results.

The initial search was completed on December 13, 2024. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee on May 15, 2025.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A 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.

A focused literature search for indirect treatment comparisons (ITCs) dealing with Hodgkin lymphoma was run in MEDLINE on December 13, 2024.

Retrieval was not limited by publication date or by language.

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: December 13, 2024

Alerts: Bi-weekly search updates until project completion

Search filters applied: randomized controlled trials; controlled clinical trials

Limits:

- Publication date limit: 1996-none
- Language limit: none
- Conference abstracts: excluded

Table 2: 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/
2. (nivolumab* or opdivo* or xdivane* or MDX-1106 or MDX1106 or BMS-936558 or BMS936558 or BMS-986298 or BMS986298 or ONO-4538 or ONO4538 or ba-1104 or ba1104 or cmab-819 or cmab819 or ly-01015 or ly01015 or pbp-2101 or pbp2101 or GTPL-7335 or GTPL7335 or 31YO63LBSN).ti,ab,kf,ot,rn,nm.
3. or/1-2
4. Hodgkin Disease/
5. (Hodgkin* or reed sternberg*).ti,ab,kf.
6. ((lymphoma* or lymphogranuloma* or granuloma*) adj5 malign*).ti,ab,kf.
7. ((nodular lymphocyte* or nodular sclerosing or lymphocyte depletion* or mixed cellularity or lymphocyte-rich*) adj5 lymphoma*).ti,ab,kf.
8. (classical HL or classical HD).ti,ab,kf.
9. (lymphocyt* adj3 (HD or HL)).ti,ab,kf.
10. or/4-9
11. 3 and 10
12. 11 use medall
13. *nivolumab/
14. (nivolumab* or opdivo* or xdivane* or MDX-1106 or MDX1106 or BMS-936558 or BMS936558 or BMS-986298 or BMS986298 or ONO-4538 or ONO4538 or ba-1104 or ba1104 or cmab-819 or cmab819 or ly-01015 or ly01015 or pbp-2101 or pbp2101 or GTPL-7335 or GTPL7335).ti,ab,kf,dq.
15. or/13-14
16. exp Hodgkin disease/
17. (Hodgkin* or reed sternberg*).ti,ab,kf,dq.
18. ((lymphoma* or lymphogranuloma* or granuloma*) adj5 malign*).ti,ab,kf,dq.
19. ((nodular lymphocyte* or nodular sclerosing or lymphocyte depletion* or mixed cellularity or lymphocyte-rich*) adj5 lymphoma*).ti,ab,kf,dq.
20. (classical HL or classical HD).ti,ab,kf,dq.

21. (lymphocyt* adj3 (HD or HL)).ti,ab,kf,dq.
22. or/16-21
23. 15 and 22
24. 23 use oemezd
25. 24 not (conference abstract or conference review).pt.
26. 12 or 25
27. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
28. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
29. Multicenter Study.pt.
30. Clinical Studies as Topic/
31. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp “Clinical Trial (topic)”/
32. Multicenter Study/ or Multicenter Studies as Topic/ or “Multicenter Study (topic)”/
33. Randomization/
34. Random Allocation/
35. Double-Blind Method/
36. Double Blind Procedure/
37. Double-Blind Studies/
38. Single-Blind Method/
39. Single Blind Procedure/
40. Single-Blind Studies/
41. Placebos/
42. Placebo/
43. Control Groups/
44. Control Group/
45. Cross-Over Studies/ or Crossover Procedure/
46. (random* or sham or placebo*).ti,ab,hw,kf.
47. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
48. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
49. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
50. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
51. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.

52. (phase adj6 (study or studies or trial*)).ti,ab,hw,kf.
53. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
54. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
55. allocated.ti,ab,hw.
56. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
57. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
58. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
59. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
60. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
61. trial.ti,kf.
62. or/27-61
63. exp animals/
64. exp animal experimentation/
65. exp models animal/
66. exp animal experiment/
67. nonhuman/
68. exp vertebrate/
69. or/63-68
70. exp humans/
71. exp human experiment/
72. or/70-71
73. 69 not 72
74. 62 not 73
75. 26 and 74
76. remove duplicates from 75

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 | Hodgkin Lymphoma AND Nivolumab]

WHO ICTRP

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

[Search terms -- nivolumab AND hodgkin*]

Health Canada's Clinical Trials Database

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

[Search terms -- Hodgkin AND nivolumab]

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 AND Hodgkin]

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 AND Hodgkin]

Grey Literature

Search dates: December 3, 2024 – December 5, 2024

Keywords: [nivolumab, opdivo, xdivane, Hodgkin lymphoma]

Limits: Publication years: none

Relevant websites from the following sections of the grey literature checklist Grey Matters: A 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

Study Selection and Data Extraction

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.

Critical Appraisal

Critical appraisal of the included studies was guided by the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0).[1]

Appendix 3: Included and Excluded Studies

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

Table 3: Included Studies

Reference	Study Design and Description
Herrera AF. et al. Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma. New England Journal of Medicine 2024, 391(15):1379-1389.	A phase 3 RCT assessed the efficacy and safety of nivolumab plus chemotherapy with doxorubicin, vinblastine, and dacarbazine (N + AVD), as compared with brentuximab plus AVD (Bv + AVD), in patients with newly diagnosed classic Hodgkin's lymphoma. Supplementary Appendix: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2405888/suppl_file/nejmoa2405888_appendix.pdf

AVD = doxorubicin (adriamycin), vinblastine, and dacarbazine; Bv = brentuximab; RCT = randomized controlled trial.

Table 4: Excluded Studies

Study	Study Design and Reason for Exclusion
Ansell SM. Immunotherapy of Hodgkin Lymphoma: Mobilizing the Patient's Immune Response. Cancer J. 2018, 24(5):249-253.	Review
Bröckelmann PJ. Treatment approaches for older Hodgkin lymphoma patients. Curr Opin Oncol. 2024, 36(5):353-359.	Review
Bröckelmann PJ. et al. Efficacy of Nivolumab and AVD in Early-Stage Unfavourable Classic Hodgkin Lymphoma: The Randomized Phase 2 German Hodgkin Study Group NIVAHL Trial. JAMA Oncol. 2020, 6(6):872-880.	Randomized controlled trial; irrelevant comparator
Bröckelmann PJ. et al. Hodgkin Lymphoma in Adults. Dtsch Arztebl Int. 2018, 115(31-32):535-540.	Review
Cashen AF. The evolving role of checkpoint inhibitors in the treatment of Hodgkin lymphoma. Front Oncol. 2024,14:1392653.	Review
Friedberg JW. Brentuximab vedotin with dacarbazine or nivolumab as frontline cHL therapy for older patients ineligible for chemotherapy. Blood. 2024,143(9):786-795.	Review
Goldkuhle, M., et al. Nivolumab for adults with Hodgkin's lymphoma (a rapid review using the software RobotReviewer). Cochrane Database of Systematic Reviews 2018 7:CD012556.	Systematic review
Hanel W. et al. Management of classical Hodgkin lymphoma: a look at up to date evidence and current treatment approaches. Exp Hematol Oncol. 2022, 11(1):108.	Review
Lee HJ. et al. Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine for Advanced-Stage Classical Hodgkin Lymphoma. Blood 2024, 02:02	Randomized controlled trial; irrelevant intervention
Lehner B. et al. Advanced stage Hodgkin's lymphoma 2024-Update on first line treatment. Memo - Magazine of European Medical Oncology 2024, 17(3):172-174	Review

Study	Study Design and Reason for Exclusion
Lei H. et al. Clinical characteristics, diagnosis, treatment, and prognosis of nivolumab induced gastritis. Invest New Drugs 2024, 42(1):53-59.	Retrospective study of case reports, case series, and clinical studies.
McKenna M. et al. The Management of older patients with Hodgkin lymphoma: implications of S1826. Seminars in Hematology 2024, 61(4):236-244.	Review
Oncale MB. et al. Harnessing the immune system through programmed death-1 blockade in the management of Hodgkin lymphoma. Blood and Lymphatic Cancer: Targets and Therapy 2023 7(no pagination)	Review
Vassilakopoulos TP. et al. Incorporating Monoclonal Antibodies into the First-Line Treatment of Classical Hodgkin Lymphoma. Int J Mol Sci. 2023, 24(17):13187.	Review
Voltin CA. et al. Early Response to First-Line Anti-PD-1 Treatment in Hodgkin Lymphoma: A PET-Based Analysis from the Prospective, Randomized Phase II NIVAHL Trial. Clinical Cancer Research 2021 27(2):402-407.	Randomized controlled trial; no comparative results

Table 5: Eligibility Criteria

Inclusion criteria	Exclusion criteria
• 12 years and older • Histologically confirmed newly diagnosed, previously untreated stage III or IV cHL (nodular sclerosing, mixed cellularity, lymphocyte-rich, or lymphocyte-depleted, or not otherwise specified). Nodular lymphocyte predominant Hodgkin lymphoma is not eligible • Bidimensionally measurable disease (at least 1 lesion with longest diameter ≥ 1.5 cm). • A whole body or limited whole body PET-CT scan performed within 42 days before registration. PET-CT is preferred over CT, MRI or MRI-PET • A performance status corresponding to Zubrod scores of 0, 1 or 2. Use Lansky for patients ≤ 17 years of age • Adequate renal function, cardiac function, and hepatic function • Patients with known HIV infection must be receiving anti-retroviral therapy and have an undetectable or unquantifiable viral load at their most recent viral load test within 6 months before registration. • Patients with peripheral neuropathy must have < grade 2 at date of registration • One formalin-fixed paraffin embedded (FFPE) diagnostic tumour block or at least 1 diagnostic, 4 to 5 micron, hematoxylin and eosin (H&E) slide collected before registration and available for submission. • No second prior malignancy is allowed except for adequately treated basal (or squamous cell) skin cancer, any in situ cancer or other cancer for which the patient has been disease free for 2 years. • Females of childbearing potential having a negative pregnancy test within 28 days before registration.	• Received any prior chemotherapy, radiation, or antibody-based treatment for classical Hodgkin lymphoma. Steroid pre-treatment is permitted • Prior solid organ transplant • Prior allogeneic stem cell transplantation • Received a live vaccine within 30 days before planned day 1 of protocol therapy. • Active hepatitis B (HBV) or hepatitis C virus (HCV) at date of registration • Central nervous system lymphoma • A diagnosis of inherited or acquired immunodeficiency • History of or active interstitial pneumonitis or interstitial lung disease. • A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days before registration • Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, immunosuppressive drugs, or corticosteroids with doses higher than prednisone 10 mg or equivalent).

cHL = classic Hodgkin lymphoma.

Appendix 4: Treatment Plan

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

General Overview

The therapy duration was 6 × 28-day cycles, with study treatment administered on Days 1 and 15 of each cycle.

Pre-medication, Concomitant Therapy, and Supportive Care

Pre-medications such as antiemetics and steroids were allowed per institutional practice. The use of G-CSF was required for patients receiving Bv + AVD, but was optional for patients receiving N + AVD.

Permitted concomitant medications included dexrazoxane (use in concomitant with doxorubicin as a cardiac protectant), and topical, inhalational and ophthalmic steroids.

Prohibited concomitant medications included any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for those subjects planned to receive radiation), immunosuppressive agents (except to treat a drug-related AE), systemic corticosteroids (except as pre-medications, antiemetics, for prophylaxis, or treatment of non-autoimmune conditions for brief course), replacement therapy, and ritonavir or HIV therapy that uses pharmacologic boosters.

Supportive care included medications for treatment of hypersensitivity reactions, such as epinephrine, antihistamines, and steroids, and prophylactic antiemetics administration for nausea and/or vomiting. Suspected Progressive Multifocal Leukoencephalopathy, suspected immunoreaction to nivolumab and cardiac conditions were monitored.

PET-CT response assessment

Primary response assessment by PET-CT occurred 4 to 8 weeks after Cycle 6, Day 15 or at time of end-of-treatment in event that protocol treatment is discontinued early (for any reason), whichever occurs first.

Responses were assessed based on the local radiology review according to the 2014 Lugano classification using the 5-point Deauville score.

Indications for radiotherapy

The indication for radiotherapy was based on the end-of-treatment imaging evaluation performed upon completion of 6 cycles of systemic therapy (4 to 8 weeks after Cycle 6, Day 15). It is delivered when patients had 1 to 2 sites initially involved with HL that achieve only a partial response.

Criteria for radiotherapy:

- Residual nodal mass ≥ 2.5cm in axial diameter, or residual extranodal lesion > 1cm in axial diameter (e.g., lung nodule or splenic nodule), and
- Deauville score = 4 or 5, and
- ≥ 30% reduction in maximal transverse diameter compared to pretreatment imaging.

Radiotherapy dose was 3000 to 3600 cGy in fractions of 150 to 180 cGy per day. The treatment was given 5 days per week, total elapsed treatment time was approximately 4 weeks.

Dose modifications due to toxicities

Dose interruption or delay is permitted at the discretion of the treating investigator if toxicity is attributable to any single agent.

The dose of nivolumab should not be modified; the entire dose is held until the patient meets criteria for nivolumab re-initiation and then the patient should resume full dose.Treatment with nivolumab is interrupted with grade 2 treatment-related AEs including myocarditis; nephritis; diarrhea (immune-related enterocolitis); endocrinopathy (hypophysitis, adrenal insufficiency, Type 1 diabetes); pneumonitis, broncho-spasm, pulmonary toxicity or interstitial lung disease; neurologic (encephalitis, encephalopathy; seizure, Guillain-Barre syndrome, myelitis, excludes peripheral neuropathy); skin rash; amylase or lipase, associated with GI symptoms. Nivolumab should be permanently discontinued with grade 4 of those treatment-related AEs.

Dose delay or dose modification is allowed for toxicities related to brentuximab therapy. Treatment-related AEs that requires dose modifications of brentuximab include anaphylaxis (discontinue at any grade), peripheral neuropathy (dose reduction with grade 2; treatment delay with grade 3; discontinue with grade 4), pneumonitis (discontinue with grade 3 to 4), progressive multifocal leukoencephalopathy (discontinue with any grade), abnormal liver function (dose reduction or discontinue with grade 3 to 4), febrile neutropenia, sepsis, infections or infestations (dose reduction or discontinue with grade 3 to 4), thrombocytopenia (delay treatment for grade 4), and non-hematologic events (dose reduction or discontinue with grade 3 to 4).

Appendix 5: Critical Appraisal of Included Publication

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

Table 6: Risk of Bias Assessment of Clinical Study Using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2)[1]

Questions	Comments	Response
Domain 1: Risk of bias arising from randomization process		
1.1 Was the allocation sequence random?	Patients were randomized using a randomized dynamic balancing algorithm.	PY
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Method allocation concealment could not be found in the study protocol, published article, clinical trial registry, or in the supplementary appendix of the trial.	PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No imbalances in patient baseline characteristics were apparent as reported in the publication article.	N
Risk-of-bias judgement	The allocation sequence was likely adequately concealed and there were no apparent differences in characteristics of the patients at baseline in both intervention groups.	Low risk of bias

Questions	Comments	Response
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1 Were participants aware of their assigned intervention during the trial?	As this study was open-labelled, participants were aware of the intervention during the trial.	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Physicians and carers who delivered the interventions must be aware of participants' assigned intervention during the trial.	Y
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	There were no apparent deviations from the intended interventions. Pre-medication, concomitant therapy, and supportive care guidelines were clearly described in the protocol. Major protocol deviation was low and balanced between intervention groups.	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All prespecified outcomes were analyzed using the modified intention-to-treat (mITT) population. This excluded patients who were found to not meet eligibility criteria, which is appropriate.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA
Risk-of-bias judgement	Patients, physicians and carers might be aware of the assigned intervention during the trial. However, there were no apparent deviations from the intended intervention.	Low risk of bias
Domain 3: Risk of bias due to missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	All prespecified primary and secondary outcomes were analyzed for all patients in the mITT population.	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA

Questions	Comments	Response
Risk-of-bias judgement	Outcome data were available nearly all, randomized participants. Nearly all randomized patients were included in the efficacy and safety analysis (mITT population).	Low risk of bias
Domain 4: Risk of bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	The methods of measuring the outcomes were appropriate and clearly described in the protocol of the trial.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Methods of outcome measurement and thresholds were similar between intervention groups.	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	It appeared that the outcomes were assessed by the investigators.	PY
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	The efficacy and safety outcomes might likely be influenced by the knowledge of intervention received (open-label).	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
Risk-of-bias judgement	The methods of measuring the outcomes were appropriate. The measurements or ascertainment of the outcomes did not differ between intervention groups. The assessment of the outcomes could have been influenced by knowledge of the intervention received.	Some concerns
Domain 5: Risk of bias in selection of the reported result		
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Data that produced the results in the published report were analyzed in accordance with a pre-specified analysis plan reported in details in the protocol of the trial.	Y
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results from multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	Efficacy outcomes such as PFS, EFS, and OS were assessed followed their pre-defined analyses and performed interim analyses as described in the protocol.	N
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results from multiple eligible analyses of the data?	The protocol was generally followed.	N

Questions	Comments	Response
Risk-of-bias judgement	The data were analysed in accordance with a pre-specified plan. The results being assessed were unlikely to have been selected.	Low risk of bias

N = no; NA = not applicable; PN = probably no; PY = probably yes; Y = yes.

Appendix 6: Summary of Clinical Outcomes

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

Table 7: Per Protocol End-of-Treatment Radiation in Modified Intention-to-Treat Analysis Set

End-of-Treatment Radiotherapy	N + AVD n (%)	Bv + AVD n (%)	Total n (%)
Eligible patients	487 (100)	483 (100)	970 (100)
Planned use of protocol-specified radiotherapy	286 (59)	287 (59)	573 (59)
Received protocol-specified radiotherapy	3 (0.6)	4 (0.8)	7 (0.7)

AVD = doxorubicin (adriamycin), vinblastine, dacarbazine; Bv = brentuximab vedotin; N = nivolumab.

Source: Supplementary Appendix of Herrera et al. (2024)[2] From The New England Journal of Medicine, Herrera AF, LeBlanc M, Castellino SM, et al, Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma, Volume No. 391, Page No. 1379-1389. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

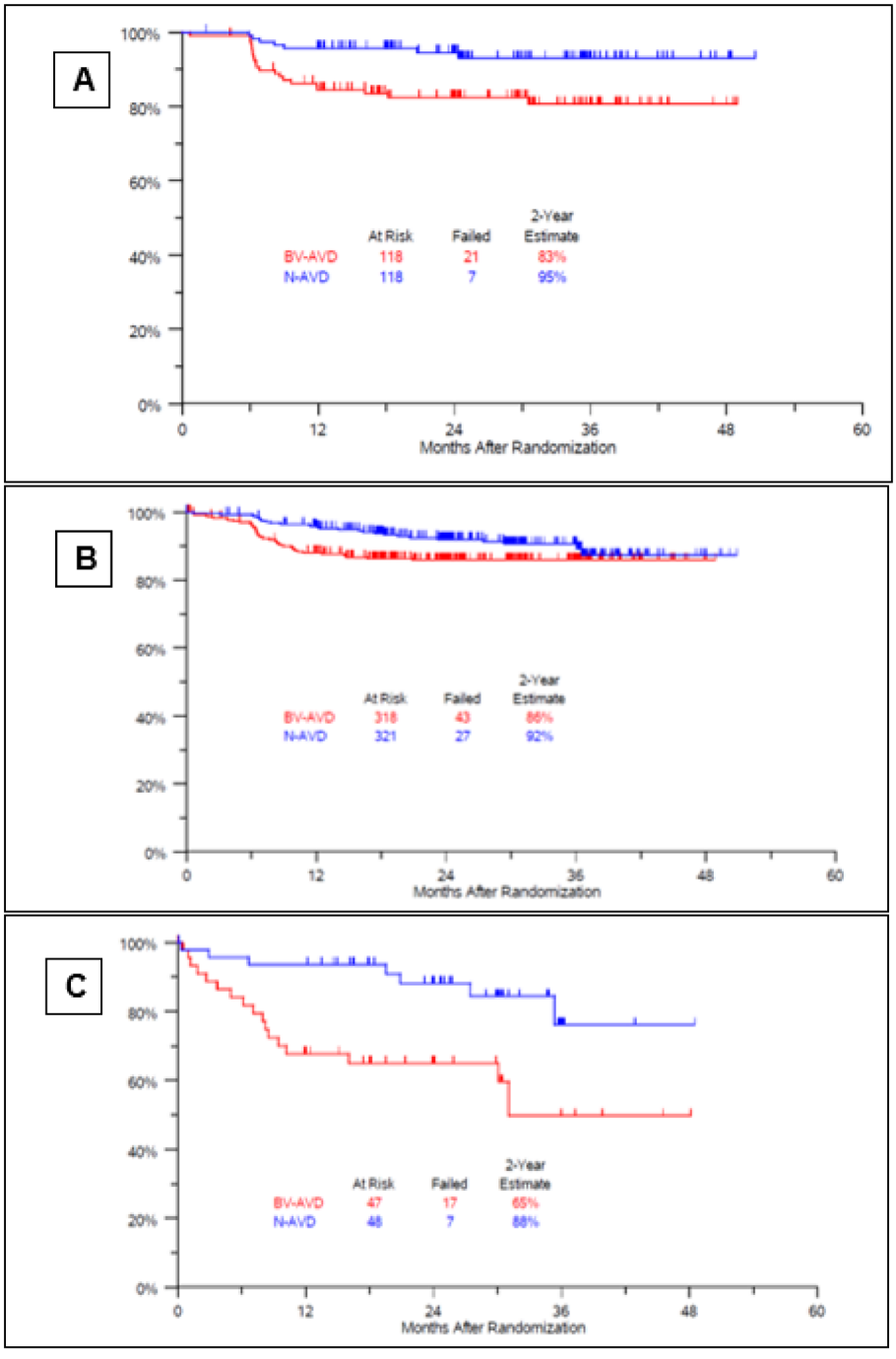
Table 8: Types of Event Free Survival Events in Modified Intention-to-Treat Analysis Set

Type of EFS Event	N + AVD n (%)	Bv + AVD n (%)
Eligible patients	487 (100)	483 (100)
Non-protocol chemotherapy before progression	10 (2.1)	7 (1.4)
Non-protocol radiation before progression	3 (0.6)	5 (1.0)
Progression/Relapse	32 (6.6)	67 (13.9)
Death without progression	7 (1.4)	12 (2.5)
Total EFS events	52 (10.7)	91 (18.8)

AVD = doxorubicin (adriamycin), vinblastine, dacarbazine; Bv = brentuximab vedotin; EFS = event-free survival; N = nivolumab.

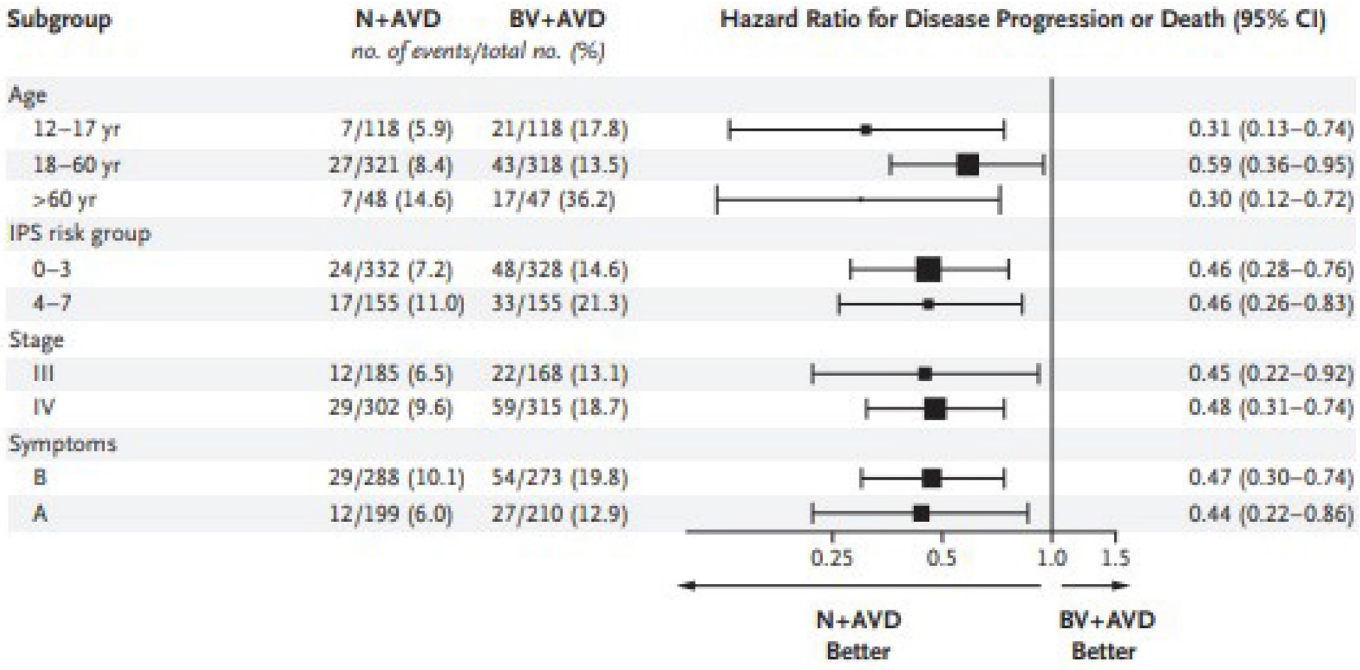
Source: Supplementary Appendix of Herrera et al. (2024)[2] From The New England Journal of Medicine, Herrera AF, LeBlanc M, Castellino SM, et al, Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma, Volume No. 391, Page No. 1379-1389. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure 1: Progression Free Survival by Age Subgroup in the mITT Analysis Set



Source: Supplementary Appendix of Herrera et al. (2024)[2] From The New England Journal of Medicine, Herrera AF, LeBlanc M, Castellino SM, et al, Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma, Volume No. 391, Page No. 1379-1389. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure 2: Subgroup Analysis of Progression Free Survival (mITT population)



Source: Herrera et al. (2024)[2] From The New England Journal of Medicine, Herrera AF, LeBlanc M, Castellino SM, et al, Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma, Volume No. 391, Page No. 1379-1389. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Appendix 7: Summary of Safety Outcomes

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

Table 9: Adverse Events of Any Grade in Modified Intention-to-Treat Analysis Set

Event	N + AVD n (%)	Bv + AVD n (%)
Eligible patients	482 (100)	476 (100)
Nausea	312 (65)	331 (70)
Fatigue	228 (47)	242 (51)
Neutrophil count decreased	272 (56)	160 (34)
Anemia	190 (39)	217 (46)
Peripheral sensory neuropathy	139 (29)	266 (56)
Constipation	193 (40)	204 (43)
ALT increased	160 (33)	201 (42)
White-cells decreased	197 (41)	128 (27)
Vomiting	134 (28)	157 (33)
AST increased	125 (26)	160 (34)

Event	N + AVD n (%)	Bv + AVD n (%)
Diarrhea	100 (21)	129 (27)
Alopecia	103 (21)	124 (26)
Lymphocyte count decreased	103 (21)	109 (23)
Mucositis, oral	107 (22)	100 (21)
Anorexia	61 (13)	106 (22)
Abdominal pain	58 (12)	107 (22)
Headache	69 (14)	75 (16)
Platelet count decreased	52 (11)	86 (18)
Bone pain	40 (8)	96 (20)
Alkaline phosphatase increased	54 (11)	81 (17)
Fever	62 (13)	61 (13)
Arthralgia	64 (13)	58 (12)
Hyperglycemia	57 (12)	63 (13)
Maculopapular rash	54 (11)	58 (12)
Myalgia	52 (11)	57 (12)
Dyspnea	42 (9)	58 (12)
Weight loss	25 (5)	71 (15)
Dysgeusia	35 (7)	59 (12)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AVD = doxorubicin (adriamycin), vinblastine, dacarbazine; Bv = brentuximab vedotin; mITT = modified intention-to-treat; N = nivolumab.

Source: Herrera et al. (2024)[2] From The New England Journal of Medicine, Herrera AF, LeBlanc M, Castellino SM, et al, Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma, Volume No. 391, Page No. 1379-1389. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 10: Adverse Events of Grade 3 or Higher in Modified Intention-to-Treat Analysis Set

Event	N + AVD n (%)	Bv + AVD n (%)
Eligible patients	482 (100)	476 (100)
Neutrophil count decreased	232 (48)	126 (26)
White blood cell decreased	73 (15)	61 (13)
Anemia	29 (6)	43 (9)
Lymphocyte count decreased	30 (6)	41 (9)
Febrile neutropenia	28 (6)	33 (7)
ALT increased	22 (5)	23 (5)
Peripheral sensory neuropathy	5 (1)	39 (8)
AST increased	12 (2)	14 (3)

Event	N + AVD n (%)	Bv + AVD n (%)
Platelet count decreased	9 (2)	16 (3)
Sepsis	8 (2)	16 (3)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AVD = doxorubicin (adriamycin), vinblastine, dacarbazine; Bv = brentuximab vedotin; mITT = modified intention-to-treat; N = nivolumab.

Source: Supplementary Appendix of Herrera et al. (2024)[2] From The New England Journal of Medicine, Herrera AF, LeBlanc M, Castellino SM, et al, Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma, Volume No. 391, Page No. 1379-1389. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 11: Possible Immune-Related Adverse Events of Any Grade in Modified Intention-to-Treat Analysis Set

	N + AVD n (%)					Bv + AVD n (%)				
	Grade					Grade				
Adverse Events	1	2	3	4	5	1	2	3	4	5
Adrenal insufficiency	0	1	1	0	0	0	0	0	0	0
ALT increased	112	26	18	4	0	144	34	23	0	0
Arthralgia	46	16	2	0	0	43	9	6	0	0
Arthritis	1	3	0	0	0	0	0	0	0	0
AST increased	102	11	9	3	0	130	16	13	1	0
Blood bilirubin increased	7	1	3	0	0	5	6	3	0	0
Diarrhea	68	24	8	0	0	93	27	9	0	0
Enterocolitis	0	1	1	0	0	0	1	0	0	0
Esophagitis	1	0	1	0	0	1	2	0	0	0
Guillain-Barre syndrome	0	0	0	0	0	0	0	0	1	0
Hyperthyroidism	11	2	0	0	0	0	0	0	0	0
Hypothyroidism	13	21	1	0	0	2	1	0	0	0
Lipase increased	1	0	1	0	0	0	1	0	0	0
Myositis	1	0	1	0	0	0	0	0	0	0
Pancreatitis	0	1	3	0	0	0	0	1	0	0
Pneumonitis	1	7	3	0	0	1	4	7	2	1
Rash acneiform	16	1	0	0	0	11	1	0	0	0
Rash maculo-papular	43	7	4	0	0	44	14	0	0	0
Seizure	1	0	1	0	0	0	1	0	0	0
Serum amylase increased	1	0	0	0	0	0	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AVD = doxorubicin (driamycin), vinblastine, dacarbazine; Bv = brentuximab vedotin; mITT = modified intention-to-treat; N = nivolumab.

Source: Modified from Supplementary Appendix of Herrera et al. (2024)[2] From The New England Journal of Medicine, Herrera AF, LeBlanc M, Castellino SM, et al, Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma, Volume No. 391, Page No. 1379-1389. Copyright © 2024 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Appendix 8: Cost Comparison Table

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

The comparators presented in Table 12 and Table 13 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses for N + AVD were based on S1826 trial[2] and validated by clinical experts. If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. The price for nivolumab was based on a previous CADTH review.[3] Pricing for comparator products was based on publicly available list prices.

In the adult patient population, the recommended dose of nivolumab for adults is 240 mg on days 1 and 15 of each 28 day cycle for up to 6 cycles (Table 12). At $782.22 and $1,955.56 per 40 mg and 100 mg vial, respectively, the treatment acquisition cost of nivolumab is $335.24 daily, or $9,387 per patient per 28-day cycle. The 28-day cycle cost for N + AVD was $11,611 per patient. The incremental savings associated with N + AVD compared with Bv + AVD is $9,973 per patient per 28-day cycle. Compared with ABVD and BEACOPP, at public list prices, nivolumab + AVD is associated with incremental costs of $7,709 and $3,956 per patient per 28-day cycle, respectively. Results may differ by jurisdiction depending on individual list prices for the drugs under review compared to those presented in Table 12.

Table 12: Canada's Drug Agency Cost Comparison Table for Frontline Regimens for the Treatment of Advance Stage Hodgkin Lymphoma

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	28-day cycle cost
N + AVD						
Nivolumab	10 mg / mL	Sterile solution for injection 40 mg vial 100 mg vial	 782.2200[a] 1,955.5600[a]	240 mg on days 1 and 15 of each 28-day cycle for up to 6 cycles	335.24	9,387
Dacarbazine (generic)	600 mg / 100 mL vial	IV	251.8200	375 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	35.97	1,007
Doxorubicin (generic)	10 mg / 5 mL 50 mg / 25 mL vial 200 mg / 100 mL	IV	50.0000 255.0000 770.0000	25 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	18.21	510
Vinblastine (generic)	10 mg / 10 mL vial	IV	176.7900	6 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	25.26	707
N + AVD					**414.68**	**11,611**

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	28-day cycle cost
BV + AVD						
Brentuximab vedotin (Adcetris)	50 mg / vial	IV	4,840.0000	1.2 mg/kg on days 1 and 15 for each 28-day cycle of up to 6 cycles	691.43	19,360
Dacarbazine (generic)	600 mg / 100 mL vial	IV	251.8200	375 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	35.97	1,007
Doxorubicin (generic)	10 mg / 5 mL 50 mg / 25 mL vial 200 mg / 100 mL	IV	50.0000 255.0000 770.0000	25 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	18.21	510
Vinblastine (generic)	10 mg / 10 mL vial	IV	176.7900	6 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	25.26	707
BV + AVD					**770.87**	**21,584**
ABVD						
Bleomycin (generic)	15 units / 10mL vial	IV	419.4000	10 units/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	59.91	1,678
Dacarbazine (generic)	600 mg / 100 mL vial	IV	251.8200	375 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	35.97	1,007
Doxorubicin (generic)	10 mg / 5 mL 50 mg / 25 mL vial 200 mg / 100 mL	IV	50.0000 255.0000 770.0000	25 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	18.21	510
Vinblastine (generic)	10 mg / 10 mL vial	IV	176.7900	6 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	25.26	707
ABVD					**139.35**	**3,902**
BEACOPP						
Cyclophosphamide (generic)	500 mg vial 1000 mg vial 2000 mg vial	IV	107.8100 195.4200 359.4000	1250 mg/m^2 on day 1 of each 21-day cycle for up to 8 cycles	22.25	622.95

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	28-day cycle cost
Doxorubicin (generic)	10 mg / 5 mL 50 mg / 25 mL vial 200 mg / 100 mL	IV	50.0000 255.0000 770.0000	35 mg/m^2 on day 1 of each 21-day cycle for up to 8 cycles	16.90	473
Etoposide (generic)	100 mg / 5mL 200 mg / 10 mL 500 mg / 25 mL 1,000 mg / 50 mL	IV	75.0000 150.0000 375.0000 750.0000	200 mg/m^2 on days 1 to 3 of each 21-day cycle for up to 8 cycles	42.86	1,200
Procarbazine (generic)	50 mg	PO	81.3959[b]	100 mg/m^2 daily on days 1 to 7 of each 21-day cycle for up to 8 cycles	108.53	3,039
Vincristine (generic)	1 mg/mL	IV	30.6000[b]	1.4 mg/m^2 on day 8 (max of 2mg) of each 21-day cycle for up to 8 cycles	2.91	82
Bleomycin (generic)	15 units / 10mL vial	IV	419.4000	10 units/m^2 on day 8 of each 21-day cycle for up to 8 cycles	79.89	2,237
BEACOPP					**273.34**	**7,653**

ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine; BV+AVD = brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; N = nivolumab.

[a]Price from CADTH review of nivolumab.[3]

[b]Price obtained from Ontario Drug Benefit Formulary (accessed March 2025).[4]

Note: Costs assume a mean patient weight of 75.06 kg and BSA = 1.88 m^2 consistent with a previous CADTH review.[5]

Note: All prices are from the Delta PA database (accessed March 2025),[6] unless otherwise indicated, and do not include dispensing fees.

In the pediatric patient population, the recommended dose of nivolumab for pediatric patients is 3 mg / kg (capped at 240 mg) on days 1 and 15 of each 28 day cycle for up to 6 cycles (Table 13). At $782.22 and $1,955.56 per 40 mg and 100 mg vial, respectively, the treatment acquisition cost of nivolumab is $279.36 daily, or $7,822 per patient per 28-day cycle (Table 13). The 28-day cycle cost for N + AVD was $9,189 per patient. The incremental savings associated with N + AVD compared with Bv + AVEPC is $11,950 per patient per 28-day cycle. Compared with ABVE-PC, at public list prices, nivolumab + AVD is associated with incremental costs of $6,169 per 28-day cycle. Results may differ by jurisdiction depending on individual list prices for the drugs under review compared to those presented in Table 13.

Table 13: Canada's Drug Agency Cost Comparison Table for Frontline Regimens for the Treatment of Previously Untreated High-Risk Hodgkin Lymphoma in the Pediatric Population

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	28-day cycle cost
Nivolumab	10 mg / mL 40 mg vial 100 mg vial	Sterile solution for injection	782.2200[a] 1,955.5600[a]	3 mg/kg (capped at 240 mg) on days 1 and 15 of each 28 day cycle for up to 6 cycles	279.36	7,822
Dacarbazine (generic)	600 mg / 100 mL vial	IV	251.8200	375 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	17.99	504
Doxorubicin (generic)	10 mg / 5 mL 50 mg / 25 mL vial 200 mg / 100 mL	IV	50.0000 255.0000 770.0000	25 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	18.21	510
Vinblastine (generic)	10 mg / 10 mL vial	IV	176.7900	6 mg/m^2 on days 1 and 15 of each 28-day cycle for up to 6 cycles	12.63	354
N + AVD					**328.19**	**9,189**
BV + AVEPC						
Brentuximab vedotin (Adcetris)	50 mg / vial	IV	4,840.0000	1.8 mg/kg for each 21-day cycle of up to 5 cycles	691.43[b]	19,360[b]
Doxorubicin (generic)	10 mg / 5 mL 50 mg / 25 mL vial 200 mg / 100 mL	IV	50.0000 255.0000 770.0000	25 mg/m^2 on days 1 and 2 of each 21-day cycle for up to 5 cycles	19.05	533
Vincristine (generic)	1 mg / mL	IV	30.6000[c]	1.4 mg/m^2 on day 1 of each 21-day cycle for up to 5 cycles	4.37	122
Etoposide (generic)	100 mg / 5mL 200 mg / 10 mL 500 mg / 25 mL 1,000 mg / 50 mL	IV	75.0000 150.0000 375.0000 750.0000	125 mg/m^2 on days 1 to 3 of each 21-day cycle for up to 5 cycles	21.43	600
Prednisone (generic)	5 mg 50 mg	Tab	0.0220[c] 0.1735[c]	20 mg/m^2 twice daily on days 1 to 7 of each 21-day cycle for up to 5 cycles	0.10	3

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	28-day cycle cost
Cyclophosphamide (generic)	500 mg vial 1000 mg vial 2000 mg vial	IV	107.8100 195.4200 359.4000	600 mg/m^2 on day 1 and 2 of each 21-day cycle for up to 5 cycles	18.61	521
BV + AVEPC					**754.99**	**21,140**
ABVE-PC						
Doxorubicin (generic)	10 mg / 5 mL 50 mg / 25 mL vial 200 mg / 100 mL	IV	50.0000 255.0000 770.0000	25 mg/m^2 on days 1 and 2 of each 21-day cycle for up to 5 cycles	19.05	533
Bleomycin (Generic)	15 units / 10 mL vial	IV	419.4000	5 mg/m^2 on day 1 and 10 mg/m^2 on day 8 of each 21-day cycle for up to 5 cycles	39.94	1,118
Etoposide (generic)	100 mg / 5mL 200 mg / 10 mL 500 mg / 25 mL 1,000 mg / 50 mL	IV	75.0000 150.0000 375.0000 750.0000	125 mg/m^2 on days 1 to 3 of each 21-day cycle for up to 5 cycles	21.43	600
Prednisone (generic)	5 mg 50 mg	Tab	0.0220[c] 0.1735[c]	20 mg/m^2 twice daily on days 1 to 7 of each 21-day cycle for up to 5 cycles	0.10	3
Cyclophosphamide (generic)	500 mg vial 1000 mg vial 2000 mg vial	IV	107.8100 195.4200 359.4000	600 mg/m^2 on day 1 and 2 of each 21-day cycle for up to 5 cycles	18.61	521
Vincristine (generic)	1 mg / mL vial	IV	30.6000[c]	1.4 mg/m^2 on days 1 and 8 of each 21-day cycle for up to 5 cycles	8.74	245
ABVE-PC					**107.88**	**3,021**

ABVE-PC = doxorubicin, bleomycin, etoposide, prednisone, vincristine, cyclophosphamide; BV + AVPE = brentuximab, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide; N = nivolumab; Tab = tablet.

Note: Costs assume a mean patient weight of 58.5 kg and BSA = 1.6 m^2 consistent with a previous HL review.[7]

Note: All prices are from the Delta PA database (accessed March 2025),[6] unless otherwise indicated, and do not include dispensing fees.

[a]Price from CADTH review of nivolumab.[3]

[b]Daily and 28-day cycle costs represents costs for patients with weights ranging from 55.7 kg to 83 kg. For patients weighing 0 to 55.6 kg, daily and 28-day cycle costs would be $460.95 and $12,910, respectively.

[c]Price obtained from Ontario Drug Benefit Formulary (accessed March 2025).[4]

References

1. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi: 10.1136/bmj.l4898 PubMed
2. Herrera AF, LeBlanc M, Castellino SM, et al. Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma. *N Engl J Med*. 2024;391(15):1379-1389. doi: 10.1056/NEJMoa2405888 PubMed
3. CADTH. Reimbursement Review: nivolumab (Opdivo) in combination with ipilimumab (Yervoy). *Can J Health Technol*. 2021;1(9). doi: 10.51731/cjht.2021.168
4. Ontario Ministry of Health, Ontario Ministry of Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2024. Accessed March 26, 2025. https://www.formulary.health.gov.on.ca/formulary/
5. Canada's Drug Agency. Reimbursement review: brentuximab vedotin (Adcetris). *Can J Health Technol*. 2024;4(12). doi: 10.51731/cjht.2024.104
6. IQVIA. *DeltaPA*. 2023. Accessed March 26, 2025. https://www.iqvia.com/
7. CADTH. Reimbursement review: pembrolizumab (Keytruda). *Can J Health Technol*. 2021;1(12). doi: 10.51731/cjht.2021.225

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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