CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

BRENTUXIMAB VEDOTIN (ADCETRIS)

(Seattle Genetics, Inc.)

Indication: For the treatment of previously untreated patients with Stage IV Hodgkin lymphoma, in combination with doxorubicin, vinblastine, and dacarbazine.

Version: Final
Publication Date: December 3, 2020
Report Length: 17 Pages

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

CADTH

List of Tables

Abbreviations

ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
AE	adverse event
AIC	Akaike information criterion
ASCT	autologous stem cell transplant
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BIC	Bayesian information criterion
BV	brentuximab vedotin
BV+AVD	brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine
CDR	CADTH Common Drug Review
CGP	Clinical Guidance Panel
DHAP	dexamethasone, cytarabine, cisplatin
GCSF	granulocyte-colony stimulating factor
GDP	gemcitabine, dexamethasone, cisplatin
HL	Hodgkin lymphoma
ICER	incremental cost-effectiveness ratio
IRF	independent review facility
kg	kilogram
LY	life-year
mPFS	modified PFS
mg	milligram
NOC	Notice of Compliance
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
QALY	quality-adjusted life-year

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Brentuximab vedotin (Adcetris), 50 mg lyophilized powder for intravenous infusion following reconstitution
Submitted price	Brentuximab vedotin, 50 mg, intravenous infusion: $4,840 per vial
Indication	For the treatment of previously untreated patients with Stage IV Hodgkin lymphoma, in combination with doxorubicin, vinblastine, and dacarbazine
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	May 2, 2019
Reimbursement request	As per indication
Sponsor	Seattle Genetics Inc.
Submission history	Previously reviewed: Yes Indication: Hodgkin lymphoma at high risk of relapse or progression post-ASCT Recommendation date: February 21, 2018 Recommendation: Recommended with clinical criteria

ASCT = autologous stem cell transplantation; NOC = Notice of Compliance

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov cohort model
Target population	Patients with previously untreated Stage IV Hodgkin lymphoma
Treatment	Brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (BV+AVD)
Comparator	Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (65 years)
Key data source	ECHELON-1 trial
Submitted results for base case	ICER = $62,258 per QALY (0.96 incremental QALYs; $59,981 incremental cost)
Key limitations	• Comparative treatment efficacy was based on the modified progression-free survival (mPFS) as assessed by investigators, which is at greater risk of bias compared to the same outcome as assessed by an independent review facility. This potentially overestimates the magnitude of clinical benefit with BV+AVD compared with ABVD. • Monthly costs of chemotherapy following frontline failure (i.e., failure on first treatment) were likely overestimated, as the costs were inappropriately sourced and implemented within the model. • The impact of pulmonary toxicity on mortality in patients on ABVD was overestimated due to it's assumed duration. The sponsor assumed that the risk of mortality with pulmonary toxicity would endure for a patient's lifetime, while the CGP noted this was likely to be for a far shorter duration (five years at most). • The rate of use and efficacy of brentuximab vedotin following autologous stem-cell transplant, when brentuximab vedotin has been administered as part of the initial frontline therapy, are uncertain. • The sponsor overestimated the proportion of patients on ABVD receiving granulocyte-colony stimulating factor (GCSF) prophylaxis, thereby overestimating the costs associated with ABVD. • The sponsor did not consider BV+AVD or ABVD within the context of PET-adaptive approaches. The cost-effectiveness of BV+AVD in the context of PET-adaptation, which is standard clinical practice in Canada, is unknown.
CADTH reanalysis results	• CADTH conducted a reanalysis which included: use of mPFS as assessed by the independent review facility data to inform treatment efficacy; updating the chemotherapy costs associated with frontline treatment failure; adjusting the duration of the impact of pulmonary toxicity on mortality with ABVD; and, altering the proportion of patients on ABVD receiving GCSF prophylaxis. • Based on CADTH reanalyses, the ICER was $134,059 per QALY gained. The probability that BV+AVD was the cost-effective option at willingness-to-pay threshold of $50,000 per QALY gained was 5%. • Uncertainty remains with the cost-effectiveness of BV+AVD due to limitations related to the efficacy and costs of subsequent therapies that could not be addressed, as noted above. Specifically, there is limited evidence on the use and efficacy of BV following autologous stem-cell transplant (i.e., BV consolidation) after BV has been used as part of frontline therapy, as well as limitations with the manner in which the costs of chemotherapy after frontline failure were implemented within the model. • A price reduction of at least 53% for brentuximab vedotin would be required for BV+AVD to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained, though uncertainty remains with how large a price reduction would be required given the uncertainty that remains with the model.

BV+AVD = brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine; CGP = Clinical Guidance Panel; GCSF = granulocyte-colony stimulating factor; ICER = incremental cost-effectiveness ratio; LY = life-year; mPFS = modified progression free survival; PET = positron emission tomography; QALY= quality-adjusted life-year

Conclusions

CADTH undertook reanalyses of the sponsor's economic submission to address some of the identified limitations, which included: the use of treatment efficacy data (i.e., mPFS) for BV+AVD and ABVD as measured by an independent review facility instead of the investigator assessed mPFS; correcting the monthly chemotherapy costs for patients in whom frontline therapy failed; adjusting the duration of the effect of pulmonary toxicity on mortality risk with ABVD; and, updating the proportion of patients on ABVD receiving GCSF prophylaxis to better reflect the pivotal ECHELON-1 trial and Canadian clinical practice. Based on CADTH re-analyses, the ICER for BV+AVD compared to ABVD was $134,059 per QALY gained.

The CADTH base case indicates that BV+AVD is not cost-effective at the submitted price for BV, though the true ICER and necessary price reduction remain uncertain due to limitations with key model drivers. The rate of use and efficacy of brentuximab vedotin following autologous stem-cell transplant, when brentuximab vedotin has been administered as part of the initial frontline therapy, is unknown, while issues remained with the implementation and costing of chemotherapy in subsequent lines of therapy that could not be addressed with certainty. CADTH conducted scenario analyses which demonstrated that the results are sensitive to the assumptions around the efficacy and rate of use of BV consolidation following an autologous stem cell transplant when BV is part of the frontline regimen, as well as to the costs of chemotherapy following frontline failure. As a result of this remaining uncertainty, the potential price reduction necessary for BV+AVD to be cost-effective remains uncertain. Using the CADTH base case, a price reduction of at least 53% in the price of brentuximab vedotin would be required for BV+AVD to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained, with the magnitude of the required price reduction potentially greater due to the uncertainty with the estimate.

Due to the exclusion of PET-adaptive approaches within the sponsor's submission, the generalizability of these results to the use of BV+AVD and ABVD within PET-adaptation is uncertain, and as a result, the cost-effectiveness of BV+AVD within the likely context of its use in Canadian clinical practice remains unknown.

Based on the sponsor's submitted budget impact analysis, the total incremental cost is estimated to be $8,388,816 over the first three years. CADTH reanalyses suggest that the estimated budget impact of introducing BV+AVD to the market was underestimated in the sponsor's budget impact analysis. The estimated incremental cost from introducing BV+AVD to the market in the CADTH re-analysis was $47,433,529 over three years. Due to the exclusion of PET-adaptive approaches within the sponsor's submission, the budget impact of BV+AVD in settings where ABVD is used in the PET-adaptive context remains unknown. The inclusion of PET-adaptive approaches would likely be associated with a different estimated market uptake of BV+AVD and the budget impact is highly sensitive to this parameter.

Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 5: Submitted BIA and CADTH Appraisal

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

References

1. Adcetris® (brentuximab vendotin): lyophilized powder for recostitution with 10.5 mL of sterile water for injection, USP 50 mg [product monograph]. Bothell (WA): Seattle Genetics, Inc; 2020 Nov 22.

2. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med.* 2018;378(4):331-344.

3. Pharmacoeconomic evaluation. In: pan-Canadian Oncology Drug Review sponsor submission: Adcetris® (brentuximab vedotin), 50 mg lyophilized powder for reconstitution, in combination with doxorubicin, vinblastine, and dacarbazine (AVD). Seattle Genetics, Inc. Bothell (WA): Seattle Genetics, Inc; 2020 Apr 2.

4. pan-Canadian Oncology Drug Review sponsor submission: Adcetris® (brentuximab vedotin), 50 mg lyophilized powder for reconstitution, in combination with doxorubicin, vinblastine, and dacarbazine (AVD). Seattle Genetics, Inc. Bothell (WA): Seattle Genetics, Inc.; 2020 Apr 2.

5. Morschhauser F, Brice P, Ferme C, et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: results of the prospective multicenter H96 trial by the GELA/SFGM study group. *J Clin Oncol.* 2008;26(36):5980-5987.

6. Gerrie AS, Power MM, Shepherd JD, et al. Chemoresistance can be overcome with high-dose chemotherapy and autologous stem-cell transplantation for relapsed and refractory Hodgkin lymphoma. *Ann Oncol.* 2014;25(11):2218-2223.

7. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;385(9980):1853-1862.

8. Bonthapally V, Yang H, Ayyagari R, et al. Brentuximab vedotin compared with other therapies in relapsed/refractory Hodgkin lymphoma post autologous stem cell transplant: median overall survival meta-analysis. *Curr Med Res Opin.* 2015;31(7):1377-1389.

9. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. *J Clin Oncol.* 2003;21(18):3431-3439.

10. Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol.* 2005;23(30):7614-7620.

11. Ramsey SD, Nademanee A, Masszi T, et al. Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma. *Br J Haematol.* 2016;175(5):860-867.

12. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leuk Lymphoma.* 2015;56(6):1839-1845.

13. Ontario Ministry of Health Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2019; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2020 Jul 2.

14. Cancer Care Ontario. Drug formulary. Funded evidence-informed regimens. 2020; https://www.cancercareontario.ca/en/drugformulary/regimens?f%5B0%5D=field_type_of_cancer%3A626. Accessed 2020 Apr 28.

15. Ontario Case Costing Initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2018: https://www.ontario.ca/data/ontario-case-costing-initiative-occi. Accessed 2020 Jul 2.

16. Interprovincial Health Insurance Agreements Coordinating Committee (IHIACC). Interprovincial billing rates for designated high cost transplants effective for discharges on or after April 1, 2019. Toronto (ON): Ministry of Health and Long-Term Care; 2019 Mar 5: http://www.health.gov.on.ca/en/pro/programs/ohip/bulletins/na_85/high_cost.pdf Accessed 2020 Sep 1.

17. Cheung MC, Hay AE, Crump M, et al. Gemcitabine/dexamethasone/cisplatin vs cytarabine/dexamethasone/cisplatin for relapsed or refractory aggressive-histology lymphoma: cost-utility analysis of NCIC CTG LY.12. *J Natl Cancer Inst.* 2015;107(7).

18. Walker H, Anderson M, Farahati F, et al. Resource use and costs of end-of-life/palliative care: Ontario adult cancer patients dying during 2002 and 2003. *J Palliat Care.* 2011;27(2):79-88.

19. Bank of Canada. Inflation calculator. 2019; https://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 2020 Jul 2.

20. Merli F, Luminari S, Gobbi PG, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. *J Clin Oncol.* 2016;34(11):1175-1181.

21. DeltaPA. Ottawa (ON): IQVIA; 2019: https://www.iqvia.com/. Accessed 2020 Jul 2.

22. Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics. Toronto (ON): Canadian Cancer Society; 2019: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2019-EN.pdf?la=en. Accessed 2020 Sep 1.

23. Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics: a 2018 special report on cancer incidence by stage. Toronto (ON): Canadian Cancer Society; 2018: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2018-EN.pdf?la=en. Accessed 2020 Sep 1.