

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

BRENTUXIMAB VEDOTIN (ADCETRIS)

(Seattle Genetics, Inc.)

Indication: Adult patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have had prior systemic therapy

Version: Final
Publication Date: December 3, 2020
Report Length: 16 Pages

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

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.

Table of Contents

| | |
|--|----|
| List of Tables | 4 |
| Abbreviations | 5 |
| Executive Summary | 6 |
| Conclusions | 8 |
| Stakeholder Input Relevant to the Economic Review | 9 |
| Economic Review | 10 |
| Appendix 1: Cost Comparison Table | 11 |
| Appendix 2: Submission Quality | 12 |
| Appendix 3: Additional Information on the Submitted Economic Evaluation | 13 |
| Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation | 14 |
| Appendix 5: Submitted BIA and CADTH Appraisal | 15 |

List of Tables

| | |
|--|---|
| Table 1: Submitted for Review..... | 6 |
| Table 2: Summary of Economic Evaluation..... | 7 |

Abbreviations

| | |
|----------------|---|
| AIC | Akaike information criterion |
| alloSCT | allogeneic stem cell transplantation |
| ASCT | autologous stem cell transplant |
| BIC | Bayesian information criterion |
| BV | brentuximab vedotin |
| CDR | CADTH Common Drug Review |
| ICER | incremental cost-effectiveness ratio |
| ITT | intention-to-treat |
| KM | Kaplan-Meier |
| LY | life-year |
| MF | mycosis fungoides |
| mg | milligram |
| NOC | Notice of Compliance |
| OS | overall survival |
| PC | physician's choice |
| pcALCL | primary cutaneous anaplastic large cell lymphoma |
| PFS | progression-free survival |
| PROCLIP | Prospective Cutaneous Lymphoma International Prognostic Index |
| QALY | quality-adjusted life-year |
| TOT | time off treatment |
| USP | United States Pharmacopeia |

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), lyophilized powder for reconstitution with 10.5 mL of sterile water for injection, USP 50 mg |
| Submitted price | Brentuximab vedotin, 50 mg, lyophilized powder: \$4,840 per 50 mg vial |
| Indication | Adult patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have had prior systemic therapy. |
| Health Canada approval status | NOC |
| Health Canada review pathway | Standard |
| NOC date | December 21, 2018 |
| Reimbursement request | As per indication |
| Sponsor | Seattle Genetics, Inc. |
| Submission history | Previously reviewed: Yes Indication: Hodgkin's Lymphoma at high risk of relapse or progression post-ASCT Recommendation date: February 21, 2018 Recommendation: Recommended with clinical criteria; a substantial reduction in drug price would likely be required. |

ASCT = autologous stem cell transplant; NOC = Notice of Compliance; USP = United States Pharmacopeia

Table 2: Summary of Economic Evaluation

| Component | Description |
|--|---|
| Type of economic evaluation | Cost-utility analysis Partitioned survival model |
| Target population | Adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have had prior systemic therapy. |
| Treatment | Brentuximab vedotin (BV) |
| Comparator | Physician's choice (PC), methotrexate or bexarotene |
| Perspective | Canadian publicly funded health care payer |
| Outcomes | QALYs, LYs |
| Time horizon | Lifetime (45 years) |
| Key data source | ALCANZA study |
| Submitted results for base case | ICER = \$20,637 per QALY gained (incremental cost = \$6,025; incremental QALYs = 0.29) |
| Key limitations | <ul style="list-style-type: none"> The modeled comparator, physician's choice, is a blended comparator of methotrexate and bexarotene, which does not reflect Canadian practice since bexarotene is rarely prescribed. Further, other relevant comparators (e.g., interferon-alphas) were not considered. Data used to model the effects of supplementary alloSCT were obtained from patients who were substantially different to the modeled population as per the ALCANZA trial. According to the clinical expert consulted by CADTH, key features of the treatment pathway following relapsed disease are not reflective of expected clinical practice. These included the use of BV as a subsequent therapy for relapsed patients (particularly among those who did not receive alloSCT) and the different durations of end-stage care for different treatment comparators. Although the sponsor accounted for vial wastage using a method of moments approach, the sponsor also applied the relative dose intensity observed within ALCANZA for BV (95% of the recommended dose per kg) which decreased the number of BV vials required. According to the clinical expert consulted by CADTH, this approach underestimated the drug acquisition cost of BV as the quantity of BV vials dispensed within practice would likely be made according to dose recommendations outlined within the product monograph. The sponsor incorporated expert-elicited frequencies of resource use that did not align with Canadian clinical practice based on feedback from the clinical expert. The sponsor assumed that no OS benefit was associated with BV compared with PC in patients who did not receive alloSCT given the immaturity of OS data in ALCANZA.^a The implication of assuming no OS benefit for BV in patients that who do not receive alloSCT is that patients receiving BV die more quickly upon progression compared with PC and incur lower health care costs associated with progression than if the length of post-progression survival was equal between patients receiving BV and PC. This was not expected to reflect clinical practice according to the clinical experts consulted by CADTH. |
| CADTH reanalysis results | <p>CADTH as part of its reanalysis, revised the proportion of treatment responders that received alloSCT within the treatment pathway and BV as a subsequent therapy; revised the length of end-stage care to be the same for all patients; and, revised resource use frequencies and relative dosing intensities. CADTH was unable to address the other identified limitations in reanalyses.</p> <p>ICER: \$1,266,378 per QALY gained (\$96,492 incremental costs, 0.08 incremental QALYs) compared with a blended comparator of methotrexate and bexarotene.</p> <ul style="list-style-type: none"> CADTH noted that the results in the indicated population warrant careful interpretation as BV was associated with 0.37 fewer QALYs than PC during the trial period and 0.45 additional QALYs than PC during the extrapolated period (i.e., 590% of the total 0.08 incremental QALYs were accrued during the extrapolation period). A price reduction of 64% is required for BV to be considered cost-effective at a WTP threshold of \$50,000 per QALY gained. |

| Component | Description |
|-----------|--|
| | <ul style="list-style-type: none"> The cost-effectiveness of BV relative to individual treatments such as methotrexate or bexarotene, or excluded comparators (e.g., interferon-alphas) is unknown. |

alloSCT = allogeneic stem cell transplant; BV = brentuximab vedotin; ICER = incremental cost-effectiveness ratio; LY = life-year; MF = mycosis fungoides; PC = physician's choice; pcALCL = primary cutaneous anaplastic large cell lymphoma; QALY= quality-adjusted life-year; WTP = willingness-to-pay

^a Although the sponsor assumed that no OS benefit was associated with BV compared with PC in patients who did not receive alloSCT, the total expected survival reported for these patients in Table 3 (sponsor's base case results) differed. For example, total life-years accrued in the pre-progression and post-progression health states for those who did not receive alloSCT was 8.13 for BV (1.89+6.04+0.20) and 8.71 for PC (0.65+7.64+0.42). The reason for this difference was that a greater proportion of patients on BV than PC were modeled to receive alloSCT (BV = 10%; PC = 3%), which was assumed to be associated with a survival benefit.

Conclusions

To address identified limitations with the sponsor's economic model, CADTH: adjusted the proportions who received alloSCT in the treatment pathway; modified the proportion of treatment responders who received BV as a subsequent therapy; revised the length of end-stage care to be the same for all patients; and, revised resource use frequencies and relative dosing intensities. In the CADTH base case, the ICER for BV compared with a blended comparator of methotrexate and bexarotene (i.e. Physician's Choice (PC)) was \$1,266,378 per QALY gained. The probability that BV was cost-effective at a willingness-to-pay (WTP) threshold of \$50,000 per QALY gained was 0%. A price reduction of at least 64% is required for BV to be considered cost-effective at a WTP threshold of \$50,000 per QALY gained, compared with PC.

The application of sponsor-submitted proportions of partial and complete responders who should receive alloSCT in separate scenario analyses resulted in ICERs of \$357,664 per QALY gained (15% of responders receive alloSCT) and \$819,127 per QALY gained (5% of responders receive alloSCT), further suggesting that BV compared with PC was not cost-effective at WTP thresholds of \$50,000 or \$100,000 per QALY gained.

CADTH was unable to address limitations associated with the PC comparator (i.e., the combination of methotrexate and the rarely prescribed bexarotene, as opposed to modelling each treatment individually) and the exclusion of other relevant comparators (e.g., interferon-alphas). As such the cost-effectiveness of BV relative to these comparators is unknown. Furthermore, the majority of BV's incremental benefit (590% of the total 0.08 incremental QALYs) was accrued beyond the trial period for which data was available, casting further uncertainty on the clinical and cost-effectiveness of BV.

Based on the sponsor's submitted budget impact analysis, the total incremental cost was estimated to be \$10,569,101 over the first three years. CADTH's reanalysis suggests that the estimated budget impact of introducing BV to the market was underestimated in the sponsor's budget impact analysis. The total incremental cost of introducing BV to the market in the CADTH re-analysis is estimated \$34,475,075 over three years.

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. Patient input. In: pan-Canadian Oncology Drug Review sponsor submission: Adcetris® (brentuximab vedotin), 50 mg lyophilized powder for injection in pcALCL or CD30-expressing MF. Bothell (WA): Seattle Genetics; 2020.
2. Clinician input. In: pan-Canadian Oncology Drug Review sponsor submission: Adcetris® (brentuximab vedotin), 50 mg lyophilized powder for injection in pcALCL or CD30-expressing MF. Bothell (WA): Seattle Genetics; 2020.
3. PAG input. In: pan-Canadian Oncology Drug Review sponsor submission: Adcetris® (brentuximab vedotin), 50 mg lyophilized powder for injection in pcALCL or CD30-expressing MF. Bothell (WA): Seattle Genetics; 2020.
4. Updated pharmacoeconomic evaluation. In: Additional information provided by Seattle Genetics in response to pCODR checkpoint meeting questions. 2020 Jun 11.
5. Notice of Compliance: Adcetris (brentuximab vedotin). Ottawa (ON): Health Canada; 2018 Dec 21.
6. P^rAdcetris® (brentuximab vedotin): lyophilized powder for reconstitution with 10.5 mL of sterile water for injection, USP 50 mg [product monograph]. Bothell (WA): Seattle Genetics; 2019 Nov 22.
7. Adcetris® (brentuximab vedotin) reimbursement submission clinical summary. In: pan-Canadian Oncology Drug Review sponsor submission: Adcetris® (brentuximab vedotin), 50 mg lyophilized powder for injection in pcALCL or CD30-expressing MF. Bothell (WA): Seattle Genetics; 2020 Mar 30.
8. Morris S. Reduced intensity allogeneic stem cell transplantation for advanced stage mycosis fungoides and Sezary syndrome. A series of 53 patients from the UK [abstract]. *Eur J Cancer*. 2018;101:S36.
9. Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma. *NICE Technology appraisal guidance*. London (UK): National Institute for Health and Care Excellence; 2019: <https://www.nice.org.uk/Guidance/TA577>. Accessed 2020 Jun 22.
10. van Agthoven M, Vellenga E, Fibbe WE, Kingma T, Uyl-de Groot CA. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. A prospective randomised trial. *Eur J Cancer*. 2001;37(14):1781-1789.
11. 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.
12. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2019; <https://www.formulary.health.gov.on.ca/formulary/>. Accessed 2019 Nov 30
13. Liste de médicaments. Montreal (QC): Association québécoise des pharmaciens propriétaires; 2020: <https://www.monpharmacien.ca/espace-pharmaciens/connexion/?redirect=https%3A%2F%2Fwww.monpharmacien.ca%2Fespace-pharmaciens%2F#list>. Accessed 2020 Jun 22.
14. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective March 1, 2016. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physerv/sob_master20181115.pdf. Accessed 2020 Feb 28.
15. Pharmacist in Canada. Ottawa (ON): Government of Canada: <https://www.jobbank.gc.ca/marketreport/wages-occupation/18196/ca>. Accessed 2020 Jun 22.
16. Nurse in Canada. Ottawa (ON): Government of Canada: <https://www.jobbank.gc.ca/marketreport/wages-occupation/696/ca>. Accessed 2020 Jun 22.
17. Pettigrew M, Kavan P, Surprenant L, Lim HJ. Comparative net cost impact of the utilization of panitumumab versus cetuximab for the treatment of patients with metastatic colorectal cancer in Canada. *J Med Econ*. 2016;19(2):135-147.
18. 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 2019 Oct 22.
19. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-Cell lymphoma and lymphomatoid papulosis. *J Clin Oncol*. 2015;33(32):3759-3765.
20. Morris S, Scarisbrick J, Frew J, et al. The results of low-dose total skin electron beam radiation therapy (TSEB) in patients with mycosis fungoides from the UK cutaneous lymphoma group. *Int J Radiat Oncol Biol Phys*. 2017;99(3):627-633.
21. de Oliveira C, Pataky R, Bremner KE, et al. Phase-specific and lifetime costs of cancer care in Ontario, Canada. *BMC Cancer*. 2016;16(1):809.
22. Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous T-cell lymphoma. *JAMA Dermatol*. 2013;149(11):1295-1299.