pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Brentuximab vedotin (Adcetris)

Submitted Reimbursement Request: For the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or cluster of differentiation (CD)30-expressing mycosis fungoides (MF) who have had prior systemic therapy

Submitted by: Seattle Genetics, Inc.

Manufactured by: Seattle Genetics, Inc.

NOC Date: December 21, 2018

Submission Date: March 30, 2020

Initial Recommendation Issued: October 1, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	At the recommended dose of 1.8 mg/kg every three weeks, brentuximab vedotin (BV) costs $14,520 per cycle (21 days) and $19,360 per month (28 days).

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions***
☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of BV for adult patients with CD30-positive pcALCL or MF who have had prior systemic therapy, if the following condition is met:

- cost-effectiveness improved to an acceptable level.

Eligible patients should have good performance status with confirmation of CD30-positivity (defined as having ≥ 10% CD30-positive malignant cells or lymphoid infiltrate). Patients with MF must have received at least one prior systemic therapy and patients with pcALCL must have received at least one prior systematic therapy or prior radiation therapy. Treatment with BV should continue for a maximum of 16 cycles (48 weeks of treatment) or until unacceptable toxicity or disease progression, whichever occurs first.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of BV compared to physician's choice (PC; methotrexate or bexarotene), based on a statistically significant and clinically meaningful improvement in objective response lasting at least four months (ORR4), progression-free survival (PFS), a manageable toxicity profile, as well as a statistically significant lower burden of symptoms, no observed detriment to quality of life (QoL), and a need for treatment options that lead to long-term response.

	pERC agreed that BV aligns with patient values in that it offers an additional treatment choice, a lower burden of symptoms, no observed detriment to QoL, and has manageable side effects. The Committee concluded that, based on the sponsor's economic analysis and at the submitted price, BV is not considered cost-effective compared with PC (methotrexate or bexarotene). pERC noted that the results of the analysis were driven by the high cost of BV, and that uncertainty remained due to limitations with the sponsor's submitted model, concluding that a price reduction would be required for BV to be cost-effective compared with PC. pERC also concluded that the budget impact is underestimated and the uptake of BV at the submitted price would be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing arrangements to improve cost-effectiveness and reduce the budget impact** Given that pERC was satisfied that, compared with PC (methotrexate or bexarotene), there is a net clinical benefit of BV for the treatment of patients with MF or pcALCL who have received prior systemic therapy, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of BV to an acceptable level and reduce the budget impact. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

MF and pcALCL are subtypes of cutaneous T-cell lymphomas (CTCL), accounting for approximately 80% to 85% of all CTCLs. Diagnosis of CTCL often includes a combination of assessments, which include skin biopsies and clinical, histopathological, and immunohistochemistry data. MF is characterized by skin patches, plaques, and tumours with lymph node involvement at early stage disease, but can involve lymph nodes, blood, and visceral organs in more advanced stages. Sézary syndrome is characterized as a related variant of MF. pcALCL is characterized by solitary or grouped large, ulcerating tumours. The disease-specific five-year survival is estimated to be 88% for patients with MF and 95% for patients with pcALCL. pERC agreed with the Clinical Guidance Panel (CGP) and the registered clinician that there is currently no standard of care for patients with MF or pcALCL, and that available treatments may vary across jurisdictions and clinical practice. The goal of treatment for patients is to provide local disease control, increase survival, lengthen remission, reduce symptoms, and improve QoL. Allogeneic stem cell transplant (alloSCT) is the only curative treatment option for patients with adequate organ function. Patients with early stage MF are treated with skin-directed therapies (topical steroids, local radiotherapy, UV light); for advance stage disease, retinoids, interferon, and systemic therapies are offered. For patients with pcALCL, surgery and radiotherapy are offered as initial treatments for those in the early stage of disease; for patients with advanced disease, systemic therapies (e.g., methotrexate, interferon, single-agent chemotherapy) are offered. Multi-agent chemotherapy is usually reserved for those with extensive disease who have failed single-agent therapy. Current treatment options provide limited durable response and poor outcomes, and patients may receive several types of treatments and repeated courses to obtain disease control. The proportions of patients achieving an objective response for many monotherapies are approximately 20% to 35% that last approximately four to six months. Overall, pERC concluded that there is unmet need for effective treatment options to achieve disease control, achieve long-term response, and improve QoL in patients with pcALCL and MF.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated one open-label, multi-centre, phase III, randomized controlled trial (ALCANZA) comparing BV to PC, either methotrexate or bexarotene, among adult patients with CD30-positive MF or pcALCL who had received at least one prior systemic therapy, or radiotherapy for patients with pcALCL. pERC noted that a phase III trial for this relatively rare disease with a heterogenous population of CTCLs was commendable given that therapies previously evaluated in CTCL were based on non-randomized trial evidence. pERC acknowledged that the sponsor conducted a randomized comparative trial that included different subtypes of CTCL. Although a comparison to other available therapies was not available, pERC considered it noteworthy that the trial compared BV to active treatment. In addition, pERC acknowledged that the number of approved treatments in this setting is limited, and that control arms of clinical trials may not reflect treatment agents available to patients; however, pERC agreed with the CGP that methotrexate and bexarotene were appropriate comparators, even though access to the latter is limited. pERC discussed that the primary end point of the trial was ORR4, defined as the proportion of patients achieving an objective response lasting at least four months as assessed by independent review facility (IRF). pERC noted that ORR4 was a composite endpoint comprising a global response score based on several variables, including a skin evaluation (Modified Severity Weighted Assessment Tool [mSWAT)] per investigator, nodal and visceral radiographic assessment per IRF, and, for patients with MF, Sézary cell blood count per IRF. pERC noted that there was a statistically significant and clinically meaningful improvement in ORR4 in favour of BV compared to PC. pERC acknowledged that ORR4 was considered an acceptable end point by the CGP and was reflective of usual patient assessments for pcALCL and MF in clinical practice. In addition, pERC considered that a response duration of at least four months was acceptable considering the importance of a durable and longer response in this patient population. pERC also acknowledged the statistically significant and clinically meaningful improvement in PFS in favour of BV compared to PC, and discussed the results of OS, which demonstrated a trend in favour of treatment with BV compared to PC, but noted that OS analyses were considered exploratory and should be

interpreted with caution. pERC acknowledged that there was considerable uncertainty around the magnitude of OS benefit with BV based on the trial results.

pERC discussed the safety profile of BV and noted that, in general, the incidence of grade 3 or higher adverse events (AEs), treatment-related grade 3 or higher AEs, and serious AEs was similar across both treatment groups in the ALCANZA trial. However, pERC noted that a higher proportion of patients discontinued treatment due to an AE in the BV group compared to the PC group. Overall, pERC concluded that BV has a manageable toxicity profile and that AEs could be managed with supportive care and dose modifications.

pERC discussed the QoL results reported in the ALCANZA trial, and noted that the analysis of patient-reported outcomes using the symptom domain of the Skindex-29 questionnaire was a key secondary end point that showed a statistically significantly greater reduction in symptom burden in the BV group as compared to the PC group. pERC discussed that there is no validated minimal important difference (MID) method applicable to the Skindex-29 questionnaire and that the sponsor conducted its own analysis to determine a MID to interpret the Skindex-29 symptom results. Although the reduction in symptom burden was statistically significant, pERC was uncertain if this reduction could be considered clinically meaningful. pERC also noted that other QoL measures, such as the emotional and function domains of the Skindex-29, the Functional Assessment of Cancer Therapy–General (FACT-G), and the EuroQol 5-Dimensions (EQ-5D) assessments, showed no substantial differences between the treatment groups. Overall, pERC concluded that QoL was similar between the two groups and treatment with BV did not appear to have a detrimental effect on QoL compared with PC. pERC acknowledged the limitations in the QoL analyses and noted that they should be interpreted with caution.

Overall, pERC was satisfied that compared with PC, there is a net clinical benefit of BV in patients with CD30-positive pcALCL or MF who have had prior systemic therapy based on a statistically significant and clinically meaningful improvement in ORR4, PFS, a manageable toxicity profile, an observed lower symptom burden, no observed detriment to QoL, and a need for treatment options that lead to long-term response.

pERC deliberated one patient advocacy group input provided jointly by Lymphoma Canada (LC) and the Canadian Skin Patient Alliance (CSPA) concerning BV. pERC discussed the large burden on QoL due to symptoms of pcALCL and MF as well as side effects of current treatments. In particular, pERC acknowledged that patients experience great difficulty with symptoms related to lymphoma involvement of their skin, noting the physical burden and emotional toll patients face due to the visual appearance of skin lesions associated with this condition. pERC considered that the appearance of skin and itching skin were the most commonly reported symptoms to negatively impact QoL. Feelings of stress, anxiety and worry, and apprehension about body image were significant concerns related to patient's conditions, and led to lower self-esteem, withdrawal from social interactions and a sense of isolation. pERC also discussed the unmet need in this setting, noting that CTCL is a long-term chronic disease without a standard of care, and that current treatments do little to provide patients with durable responses. pERC discussed that patients value additional treatment options (as they must endure their condition for lengthy periods of time and receive multiple therapies), longer survival, better QoL, longer remission, and fewer side effects. pERC considered that there appears to be a reduced burden of symptoms with BV and agreed with the CGP that a greater reduction of skin symptoms may improve a patient's QoL. Overall, pERC concluded that BV aligns with patient values in that it offers an additional treatment options, with fewer side effects, lower burden of symptoms, and no observed detriment to QoL.

pERC deliberated the cost-effectiveness of BV compared with a blended comparator referred to as PC, which comprised methotrexate or bexarotene. pERC discussed the limitations of the submitted model described by the Economic Guidance Panel and noted that substantial uncertainty remained due to key limitations that could not be addressed. One such concern was associated with the use of a blended 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 compared to relevant comparators is unknown. CADTH was also unable to address the uncertainty related to the sponsor's assumptions of equal efficacy in terms of OS between BV and PC in patients who did not receive alloSCT. Although this assumption may seem conservative, the modelling of no OS benefit alongside a PFS benefit for treatment with BV meant that, after disease progression, patients taking BV died more quickly than those taking PC. Consequently, patients receiving BV had less time on subsequent therapies and less time in the highly resource-intensive end-stage care phase compared with patients taking PC. As such, patients receiving BV accrued lower health care costs compared with those on PC. Furthermore, BV was associated with 0.06 incremental

QALYs compared with PC, BV however, was associated with 0.34 fewer QALYs during the trial period and 0.40 additional QALYS during the extrapolated period (i.e. -0.34 + 0.40 = 0.06), casting further uncertainty on the clinical effectiveness and cost-effectiveness of BV. A price reduction of at least 72% is required for BV to be considered cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained, compared with PC.

pERC also discussed the budget impact analysis and noted that the factors with the greatest influence on the estimated budget impact were the estimated number of patients with CTCL, the estimated market uptake, and the average weight used to model the total cost of BV per patient. pERC noted that the Economic Guidance Panel considered the number of patients with CTCL and the market uptake calculated by the sponsor to be underestimated, and that the use of alternative estimates provided by the clinical experts consulted for this review produced a higher overall budget impact when compared to the sponsor's estimate. pERC anticipates that the estimate remains uncertain due to potential variability in the actual number of patients with CTCL and the expected uptake of BV.

The Committee deliberated the input from PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- one joint input from two patient advocacy groups: LC and the CSPA
- input from one registered clinician
- input from PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of BV (Adcetris) for adult patients with CD30-expressing pcALCL or MF who have had prior systemic therapy.

Studies included: One open-label, multicenter, phase III trial

The pCODR systematic review included one open-label, multicenter, phase III RCT (ALCANZA). A total of 131 patients were randomized 1:1 to receive BV (n = 66) or PC (n = 65), either methotrexate or bexarotene, among patients with CD30+ CTCL. Patients randomized to the BV group were given treatment at a dose of 1.8mg/kg through an IV infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or a maximum of 16 cycles (48 weeks). Patients randomized to the PC group received either methotrexate at 5mg to 50 mg orally every week for a maximum of 48 weeks, or bexarotene at 300 mg/m^2 orally daily for a maximum duration of 48 weeks. Crossover or treatment beyond progression were not permitted.

The trial enrolled patients from 52 academic centres across 13 countries. Eligible patients included adults aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 2 or greater, and histologically confirmed CD30+ MF who received at least one prior systemic therapy or with CD30+ pcALCL who received at least one previous systemic therapy or radiation therapy. Status of CD30 positivity was determined through one or more biopsy samples with 10% or more CD30+ malignant cells or lymphoid infiltrate, as assessed by central laboratory review. Two or more skin biopsy samples were taken from separate lesions for patients with MF, and one or more samples were taken from patients with pcALCL. Patients who had previously progressed on methotrexate and bexarotene were not eligible for enrolment. Other exclusion criteria for patients included the presence of coexisting diseases, or receipt of previous BV or systemic therapy with vitamin A at a dose of greater than 5,000 mcg per day within three weeks of the first dose of study drug. The intention-to-treat population consisted of 128 patients with 64 patients in each of the BV and PC treatment groups. The safety population consisted of all 131 patients. Efficacy data were presented for the ALCANZA trial at the primary (median follow-up = 22.9 months), updated (median follow-up = 33.9 months), and final analyses (median follow-up = 45.9 months) dates corresponding to the data cut-off dates of May 31, 2016, August 16, 2017, and September 28, 2018, respectively.

Patient populations: Mostly balanced baseline characteristics; 76% of patients had MF, 24% of patients had pCALCL; median of four prior therapies

In the ALCANZA trial, baseline characteristics of patients were generally balanced between the two treatment groups. The median age was 62 years (range = 51 to 70) and 59 years (range = 48 to 67) in the BV and PC groups, respectively. There were 33 males (52%) and 37 males (58%) in the BV and PC groups, respectively. Most patients had an ECOG PS of 0 (67% in the BV group and 72% in the PC group) or 1 (28% and 25%) and were White (88% and 83%). The median number of prior therapies for patients was similar between the two treatment groups, with a median of 4 and 3.5 prior therapies for the BV and PC groups, respectively. Patients diagnosed with MF comprised 76% of the intention-to-treat population (75% in the BV group and 77% in the PC group), with patients with pcALCL comprising 24% (25% in the BV group and 23% in the PC group); however, the proportion of patients with stage IVA2 MF in the PC group was greater than that of patients in the BV group (16% and 4%, respectively), and the proportion of patients with IVB

MF was greater in the BV group than in the PC group (15% and 0%, respectively). Furthermore, the disease stage of patients with pcALCL also varied across treatment groups as there was greater presence of extracutaneous pcALCL in the BV group (44%) compared to the PC group (27%). Time since progression on last therapy was also longer for patients in the BV group (2.4 months; range = 1.4 to 7.9) compared to the PC group (1.3 month; range = 0.9 to 3.7).

Key efficacy results: Statistically significant and clinically meaningful improvement in ORR4, and PFS in favour of BV

The key efficacy outcome of the ALCANZA trial was ORR4, the proportion of patients who achieved an objective response (complete response or partial response) for a duration of four months or more, as determined by an IRF. ORR4 is a composite end point whereby objective response was determined via a global response score consisting of the following components: an mSWAT assessment by investigator; nodal and visceral radiographic assessments by IRF; and detection of Sézary cells (for patients with MF only) by IRF. Other key secondary efficacy end points of the trial included complete response and PFS.

At the primary data analysis (data cut-off: May 31, 2016), 36 patients (56%) in the BV group and eight patients (13%) in the PC group achieved ORR4, resulting in a statistically significant and clinically meaningful improvement in patients receiving BV over PC (between group difference = 43.8%; 95% confidence interval [CI] = 29.1 to 58.4; P < 0.001); this improvement was observed across patients with MF or pcALCL in both treatment groups. The improvement in patients observed through ORR4 was consistent at the updated (data cut-off: August 16, 2017) and final (data cut-off: September 16, 2018) analyses of the ALCANZA trial; there were 39 patients (61%) versus five patients (8%) achieving ORR4 at the updated analysis (data cut-off: August 16, 2017) in the BV and PC groups, respectively, and 35 patients (55%) versus eight patients (13%) achieving ORR4 at the final analysis (data cut-off: September 28, 2018) in the BV and PC groups, respectively.

At the primary data cut-off date, 86 patients (67%) experienced a PFS event; progressive disease per IRF was observed in 74 patients (58%) comprised of 30 patients (47%) in the BV group and 44 patients (69%) in the PC group, while death occurred in 12 patients with six deaths (9%) in each of the BV and PC groups. At the final analysis with a median PFS follow-up of 36.8 months (95% CI, 31.7 to 40.2), the median PFS according to IRF was 16.7 months in the BV group compared to 3.5 months in the PC group (hazard ratio = 0.378; 95% CI, 0.247 to 0.577; P < 0.001).

The median OS was 48.4 months in the BV group (95% CI, 41.0 to 51.7), and 42.9 months in the PC group (95% CI, 38.6 to 49.4). Based on the exploratory analysis of OS, treatment with BV was favoured over treatment with PC (hazard ratio = 0.745; 95% CI, 0.421 to 1.318; P = 0.310).

Patient-reported outcomes: Statistically significant difference in symptom domain of Skindex-29 favouring BV; no observed difference between treatment groups

Health-related QoL was assessed by the symptom domain of the Skindex-29 questionnaire, a key secondary end point of the ALCANZA trial. Other measures of health-related QoL also included the emotional and functional domains of the Skindex-29, the FACT-5, and the EQ-5D questionnaires. Compliance was stated to be high in all questionnaires.

The symptom domain of the Skindex-29, a key secondary end point, showed a statistically significant difference between treatment groups of –19.0 (95% CI, 26.7 to –11.4); this difference crossed the pre-specified minimally important difference calculated by the sponsor favouring treatment with BV. While both the emotional and functional domains of the SKindex-29 indicated that skin disease may be less burdensome to patients receiving BV compared to PC, neither showed substantial change over time. For the emotional domain of the Skindex-29, the mean change from baseline to end of treatment was –14.43 (standard deviation [SD] = 20.901) for the BV group compared to –1.84 (SD = 18.555) for the PC group. For the functional domain, the mean change from baseline to end of treatment was –11.10 (SD = 25.312) for the BV group and –1.22 (SD = 22.448) in the PC group. No meaningful differences were observed in patients through the FACT-G and EQ-5D questionnaires. Mean FACT-G total score changes from baseline to the end of treatment were 0.15 (SD = 16.388) for patients in the BV group compared to –2.29 (SD = 17.171) for patients in the PC group. Mean EQ-5D changes from baseline to end of treatment in EQ-5D US time trade-offs were 0.02 and –0.02 in the BV and PC groups, respectively. The mean changes from baseline to the end of treatment in EQ-5D UK time trade-offs were 0.03 and –0.04, in the BV and PC groups, respectively. The MID was not reached for either the FACT-G or EQ-5D questionnaires.

Limitations: Lack of evidence comparing BV to other currently available therapies

Due to the lack of defined standard treatments for patients with pcALCL or MF, no indirct treatment comparisons or network meta-analysis were provided by the sponsor comparing BV to other available treatments. Therefore, the CADTH Review Team was unable to determine the comparative efficacy and safety of BV against other treatments, aside from methotrexate or bexarotene, that may be available to patients. While the CGP acknowledged that methotrexate and bexarotene are treatments for patients with pcALCL or MF, other treatments are also currently available (e.g., interferon-alphas; cyclophosphamide, doxorubicin hydrochloride, vincristine sulphate, and prednisone [CHOP]; and cyclophosphamide, epirubicin, vincristine, and prednisone [CEOP]); the comparative efficacy and safety of BV in relation to these other treatments is unknown.

Other limitations identified by pERC included the open-label nature of the study, which introduced bias related to lack of blinding that potentially favoured treatment with BV compared to PC; the lack of blinding may also have affected patients' reporting of QoL outcomes given that they were aware of their treatment allocation, and may have biased their reporting toward BV; that OS was an exploratory end point which the ALCANZA trial was not powered to detect differences between groups; that analyses of many subgroups for primary and secondary end points were not controlled for multiplicity; that no validated methods for calculation of an MID for QoL outcomes existed for the Skindex-29; and that the sponsor's own calculation of an MID, while stated to be in accordance with European Medicines Agency guidelines, may be biased toward detection of meaningful improvement where none may exist. Furthermore, the use of a composite end point (ORR4) may have led to an overestimation of the clinical benefit and resulted in misinterpretation of the results. For complete analysis of ORR4, an analysis of each component of the composite end point should be conducted.

Safety: Similar frequencies of AEs for the BV and PC treatment groups

The safety data reported for the ALCANZA trial were based on the primary analysis (data cut-off: May 31, 2016) and a median follow-up of 22.9 months. There were 66 patients in the BV group and 62 patients in the PC group that received treatment and were included in the safety population. Overall, the occurrences of AEs were similar across both treatment groups; 63 patients (95%) in the BV group and 56 patients (90%) in the PC group reported at least one AE of any grade. Grade 3 or higher AEs were also similar between treatment groups, with 27 patients (41%) reporting grade 3 or higher AEs in the BV group compared to 29 patients (47%) in the PC group. The proportion of grade 3 or higher AEs related to treatment was the same across both treatment groups, with 19 patients (29%) and 18 patients (29%) in the BV and PC groups, respectively. The occurrence of grade 3 or higher AEs (41% versus 47%), drug-related grade 3 or higher AEs (29% versus 29%), and serious AEs (29% versus 29%) were similar in the BV and PC groups, respectively. A higher proportion of patients in the BV group discontinued treatment due to an AE as compared to patients in the PC group (16 patients [24%] and five patients [8%], respectively).

In the BV group (n = 66), the most frequently reported grade 3 treatment-emergent AEs were peripheral sensory neuropathy in three patients (5%) and fatigue in three patients (5%). No grade 4 treatment-emergent AEs occurred in the BV group. Of the patients that received methotrexate in the PC group (n = 25), the most frequently reported grade 3 treatment-emergent AEs were fatigue, pyrexia, and skin infection, which occurred in one patient (4%) each. There were no grade 4 treatment-emergent AEs reported for patients who received methotrexate in the PC group. Of the patients that received bexarotene in the PC group (n = 37), the most frequently reported grade 3 treatment-emergent AE was hypertriglyceridemia, which occurred in five patients (14%). Similarly, of patients who received methotrexate in the PC group, the most frequently reported grade 4 treatment-emergent AE was hypertriglyceridemia, which occurred in three patients (8%).

Deaths were similar between both treatment groups, with 16 deaths (24%) and 14 deaths (23%) having occurred in the BV and PC groups, respectively. There were four patients in the BV group that experienced on-treatment deaths; three were unrelated to study drug and caused by, one each of, sepsis, disease progression, and pulmonary embolism. Multiple organ dysfunction occurred in one patient with $T_{3b}N_0M_1$ pcALCL who experienced tumour lysis (on sites of visceral lymphoma involvement) caused by BV.

Need and burden of illness: Need for additional treatment options with durable responses

CTCLs are a heterogenous group of non-Hodgkin lymphomas. MF and pcALCL account for 80% to 85% of CTCLs, requiring skin biopsies and a combination of clinical, histopathological, and immunohistochemistry data for diagnosis. Due to the chronic nature of MF and pcALCL, patients undergo many treatments that

often do not result in durable responses for patients. In addition to requiring multiple therapies, patients also require repeated courses of therapies to achieve disease control, which can be taxing and negatively impact QoL. Patients with MF and pcALCL experience significant morbidity both due to their condition and treatments. Therefore, there is a significant unmet need for additional treatment options that can also provide durable responses for patients with CTCL.

Registered clinician input: BV expected to be used frequently in clinical practice due to lack of current standard of care

One registered clinician input was provided on behalf of one individual oncologist from Ontario. Various treatments were stated to be currently available to patients through public funding or compassionate access. However, no direct comparator was identified by the clinician as no available treatment options are considered standard of care. The registered clinician agreed that the eligibility criteria from the ALCANZA trial were applicable to clinical practice. Due to the lack of defined standard treatments for patients, the clinician expected that BV would be used very frequently in practice. After failure of an initial therapy, BV was suggested as a possible treatment in the second line. When asked how BV would be sequenced relative to alloSCT, the clinician acknowledged that this indication would be rare; therefore, not many patients are expected to receive a sequence of treatments with BV and alloSCT. Re-treatment with BV was considered reasonable so long as a patient's response to BV was initially durable (i.e., 12 months). As patients are often first reviewed by expert hematopathologists or dermatopathologists, no companion diagnostic testing was stated to be needed. However, pERC noted that, per the ALCANZA trial, CD30 testing is required to be performed in patients with MF and pcALCL to determine eligibility for BV. Morphological and clinical assessments were stated to be used as tools to monitor response to therapy.

PATIENT-BASED VALUES

Experience of patients with MF or pcALCL: Physical and psychological toll of visible symptoms on skin

One joint input was provided by LC and CSPA for the review BV for pcALCL or MF. LC and CSPA conducted an anonymous online survey that was sent via email to respondents registered in the LC database and made available between March 30, 2020, and April 20, 2020. In total, 86 patient respondents provided input through the survey; of note, there were no caregiver respondents. Most respondents were diagnosed with MF (96%). Many of the respondents indicated experiencing delays in obtaining a diagnosis for their condition, with some waiting over a year for their diagnosis after first showing symptoms. Appearance of skin and itchy skin were the most commonly reported symptoms to negatively impact QoL. Feelings of stress, anxiety and worry, and apprehension about body image were significant concerns which led to loss of self-esteem, withdrawal from social interactions and a sense of isolation. The number of clinic visits and treatment-related fatigue were aspects of daily living respondents felt were significantly impacted due to current treatment. Almost one-third of patients reported difficulty in accessing treatment, mainly due to treatments being unavailable in their local cancer centre or due to living in a community without a local cancer centre.

Patient values, experience on or expectations for treatment: Additional treatment options, longer survival, fewer side effects, improved QoL

Overall, patients reported that having additional treatment options was highly valued. Especially among patients with advanced disease and prior experience with systemic therapies, additional treatment options are considered to be extremely important. In addition, longer survival, better QoL, longer remission, and fewer side effects were important considerations for new treatment options for cutaneous lymphoma. LC and CSPA highlighted an unmet need for patients related to the chronic nature of cutaneous lymphomas, which can affect patients over extended periods of time.

ECONOMIC EVALUATION

The recommended dose of BV is 1.8 mg per kg up to a maximum of 180 mg. BV should be administered and monitored by a health care provider as an IV infusion over 30 minutes every three weeks for a maximum of 16 cycles (21 day cycles), until disease progression, or until the patient experiences unacceptable toxicity. BV is supplied as 50 mg vials of lyophilized powder for IV infusion following

reconstitution. The drug acquisition cost of BV is $4,840 per 50 mg vial. Assuming a mean body weight of 82 kg and without taking into account vial wastage, the cost of BV is estimated to be $14,520 per 21-day cycle and $232,320 per treatment course (16 cycles).

The sponsor submitted a cost-utility analysis comparing BV and a blended comparator of PC (methotrexate and bexarotene) in adults with pcALCL or CD30-expressing MF who have had prior systemic therapy. The sponsor modelled the costs and QALYs over a lifetime time horizon (45 years) from a public health care payer perspective. The partitioned survival model was characterized by five health states: pre-progression for patients who did not receive alloSCT and remained progression-free; pre-progression after alloSCT for those who received alloSCT and remained progression-free; progressed disease for patients who did not receive alloSCT and relapsed; progressed disease for patients who relapsed after alloSCT; and death.

All patients in the pre-progression state were either on or off treatment based on time to discontinuation data from the ALCANZA trial and were assumed to have not yet received alloSCT. PFS without alloSCT was based on parametric functions that were independently fit to data from each treatment group in the ALCANZA trial, according to goodness of fit statistics, expert opinion, and visual fit. These patients could relapse and transition to the progressed disease health state or transition to the death health state. The sponsor assumed there was no difference in overall survival (OS) between patients taking BV or PC who did not receive alloSCT and applied OS data from the PC arm in the ALCANZA trial for both treatment groups within the model using a fitted log-normal model. Fixed proportions of patients in the pre-progression health state who responded to BV (10%) and PC (3%), as defined by the ALCANZA trial's global response scores, received alloSCT at 18 weeks (i.e., after six cycles of BV or PC treatment) and transitioned to the health state characterized by PFS following alloSCT. The patients who received alloSCT remained progression-free in this state or transitioned to the death state, as determined by Gompertz and log-normal distributions, respectively, that were fit to unpublished data. If patients who received alloSCT relapsed, they transitioned to the progressed disease health state for patients who received alloSCT. Finally, the mean time spent in both of the progressed disease health states for transplant and non-transplant patients was apportioned into three periods: subsequent therapy, no subsequent therapy (remaining time), and end-stage disease management.

CADTH identified the following key limitations with the sponsor's economic analysis:

- The modelled comparator, PC, is a blended comparator of methotrexate and bexarotene, which does not reflect Canadian practice given that bexarotene is rarely prescribed. Further, other relevant comparators (e.g., interferon-alphas) were not considered.
- The data used to model the effects of supplementary alloSCT were obtained from patients who were substantially different to the modelled population of 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 the dose recommendations outlined in 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. The implication of assuming no OS benefit for BV in patients 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 reanalyses excluded alloSCT from the treatment pathway and BV as a subsequent therapy; revised the length of end-stage care to be the same for patients in either treatment group; and revised resource use frequencies and relative dosing intensities. CADTH was unable to address the limitations associated with the PC comparator (i.e., the combination of methotrexate and the rarely prescribed bexarotene) and the exclusion of other relevant comparators (e.g., interferon-alphas). CADTH was also unable to address the uncertainty related to the sponsor's assumption of equal efficacy in terms of OS between BV and PC in patients who did not receive alloSCT. In the CADTH base case, for patients who did not receive alloSCT, the incremental cost-effectiveness ratio for BV compared with PC was $2,094,685 per QALY gained. The probability that BV was cost-effective at a WTP threshold of $50,000 per QALY gained was 0%. A price reduction of at least 72% is required for BV to be considered cost-effective at a WTP threshold of $50,000 per QALY gained, compared with PC.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Submitted budget impact analysis is underestimated

CADTH identified limitations associated with the sponsor's method of deriving the number of patients with CTCL, the assumed mean weight for patients with pcALCL or CD30-expressing MF, and the market uptake for BV, which did not align with feedback provided by the clinical experts consulted by CADTH, resulting in an underestimated budget impact for BV. CADTH addressed these concerns as reanalyses in which the total budget impact following the introduction of BV was $34,475,075 over three years. This estimate remains uncertain due to potential variability in the actual number of patients with CTCL and the expected uptake of BV.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Winson Cheung and Dr. Marianne Taylor who were not present for the meeting
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of BV (Adcetris) for adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy, through their declarations, no members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC recommendation
Currently funded treatments	
PAG noted that there is no current standard therapy and no curative treatment (with the exception of allogeneic stem cell transplant) for pcALCL or MF. Generally, patients with early stage disease tend to be prescribed skin-directed therapies such as surgery or local radiotherapy followed by maintenance with low-dose methotrexate. Patients with more advanced disease are commonly treated with systemic therapies such as CHOP or CEOP. Relapsed patients or patients with aggressive disease or extracutaneous involvement can be given isotretinoin or alitretinoin, interferon, bexarotene, alemtuzumab, or single-agent chemotherapy (gemcitabine, liposomal doxorubicin, etoposide); funding of these drugs varies across provinces. Patients may require several types of treatment and repeated courses of therapy to obtain disease control. The ALCANZA trial compared BV to PC of methotrexate or bexarotene. PAG is seeking comparison between BV and retinoids, interferon, gemcitabine, liposomal doxorubicin, and etoposide.	The ALCANZA trial compared BV to PC of methotrexate and bexarotene. An indirect treatment comparison to other available drugs for patients with MF or pcALCL was not included in the submission and therefore the relative efficacy of BV compared to retinoids, interferon, gemcitabine, liposomal doxorubicin, and etoposide is unknown.
Eligible patient population	
PAG is seeking guidance on generalizability of treatment with BV to the following patient groups: • Patients with an ECOG PS greater than 2	• Patients with ECOG PS >2 were excluded from the ALCANZA trial. pERC agreed with the CGP that it would be appropriate to treat patients with ECOG PS greater than 2 with BV at the discretion of the treating physician. Poor performance status may be due to the underlying disease and treating physicians may decide to offer BV to these patients.
• Patients with cardiac symptoms	• pERC agreed with the CGP that patients with stable cardiac disease should be eligible for BV, as the risk of cardiac toxicity with brentuximab is <5%.
• Patients with Sézary syndrome showing CD30 positivity or other subtypes of CD30+ cutaneous T-cell lymphoma	• Patients with Sézary syndrome showing CD30 positivity or other subtypes of CD30+ cutaneous T-cell lymphoma were excluded from the ALCANZA trial. Therefore, pERC agreed with the CGP that these patients would not be eligible for treatment with BV.

• Patients who progressed on both previous methotrexate and bexarotene, but who would be eligible for other systemic therapies	• Patients who have progressed on both methotrexate and bexarotene should be eligible for BV. These patients were excluded from the ALCANZA trial because they may have been randomized to the PC arm of methotrexate and bexarotene. pERC agreed with the CGP that patients with prior treatment with methotrexate and bexarotene should be eligible for BV.
• Patients with CNS involvement and PML symptoms	• While the risk of CNS relapse in patients with MF is extremely low, patients with CNS involvement and PML symptoms were excluded from the ALCANZA study. Therefore, pERC agreed with the CGP that BV should not be offered to patients with CNS involvement and PML symptoms.
• Patients with T-cell lymphoma transformed from MF who otherwise meet eligibility criteria	• Patients with transformed MF were eligible to enrol in the ALCANZA trial. Patients were deemed to have LCT if any single biopsy showed the presence of large cells with nuclei ≥4 times larger than those of normal lymphocytes present in >25% of total dermal infiltrate or forming microscopic nodules. Patients with MF were evaluated for LCT status (n = 48 in each arm) and were included in the response-by-LCT analyses. Therefore, pERC agreed that patients with transformed MF would be eligible for treatment with BV.
• Previously untreated patients and patients who are not progressing but cannot tolerate a first-line systemic therapy	• Patients previously untreated for pCALCL and MF would not be eligible for treatment with BV. pERC agreed with the CGP that patients should initiate treatment with BV if they progress on a current therapy or are intolerant to a current therapy.
If recommended for reimbursement, PAG noted that patients who have already initiated second-line systemic therapy would need to be addressed on a time-limited basis. PAG seeks guidance on whether to switch these patients to BV or rather wait for disease progression. In addition, PAG noted a potential for indication creep with BV for patients with CD30+ Sézary syndrome and for first-line treatment of pcALCL and MF. There is also potential for use in earlier stages of MF.	• pERC agreed with the CGP that the preference is not to switch patients who have already initiated second-line systemic therapy with no disease progression. pERC agreed that it is appropriate to switch a patient to BV if a patient experiences disease progression on current treatment or has poor tolerance to a current treatment.
Implementation factors	
The recommended dose of BV is 1.8 mg/kg every 3 weeks. BV is given until disease progression, unacceptable toxicity, or a maximum of 16 cycles (48 weeks). PAG is seeking a clear definition of disease progression for the development of discontinuation criteria.	pERC agreed with the CGP that BV should be discontinued as per the ALCANZA trial. BV should be discontinued for patients who meet the following criteria: • completed 16 cycles of BV therapy or 48 weeks of reference therapy • experienced progressive disease or unacceptable toxicity
Additional resources (e.g., nursing and clinic visits) are required to monitor and treat infusion-related reactions and adverse events (e.g., diarrhea, neutropenia/febrile neutropenia, and peripheral neuropathy) as well as monitor complete blood count. The cost of supportive therapy (e.g., G-CSF) also needs to be considered in	In the ALCANZA trial, the use of platelet and/or RBC transfusions or supportive growth factors was allowed when applicable and the use of colony-stimulating factors for the treatment of neutropenia was permitted during therapy according to institutional practice. pERC noted the use of G-CSF in clinical practice is physician dependent and that criteria vary across provinces.

implementation as it will likely be required as primary prophylaxis.	
Available vial size and wastage.	pERC noted the high cost and potential for drug wastage associated with BV. BV is priced per vial, and there are only 50 mg vials available. pERC noted that BV has a 24-hour stability upon reconstitution and vial sharing may be unlikely due to the small patient population. pERC agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, including advocating for the availability of a smaller vial size.
Sequencing and priority of treatment	
PAG is seeking to confirm the eligible patient population and line of therapy with BV, and the possible sequencing of treatments, including the scenarios below:	
• Eligibility to BV upon progression on maintenance with low-dose methotrexate or other systemic therapies following skin-directed therapy.	• pERC agreed with the CGP that patients would be eligible to receive BV upon progression on maintenance with low-dose methotrexate or other systemic therapies following skin-directed therapy.
• Priority relative to all second-line and beyond systemic therapies including single- and multi-agent chemotherapy, retinoids, and interferon therapy.	• pERC noted that patients with MF who received at least one prior systemic therapy or patients with pcALCL who received prior radiation therapy or at least one prior systemic therapy would be eligible for BV.
• Optimal sequencing with other systemic therapies and number of therapies that should be tried before a patient becomes eligible to BV.	• pERC concluded that the optimal sequencing of therapies is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognized that provinces will need to address this issue upon implementation of a reimbursement recommendation for BV and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
• Sequencing with allogeneic stem cell transplant.	• The number of patients who went on to receive allogeneic stem cell transplant in the ALCANZA trial was very low. In the BV group, one patient (1.6%) received allogeneic stem cell transplant following study treatment. pERC agreed with the CGP that it may be reasonable to offer allogeneic stem cell transplant following treatment with brentuximab if a patient achieved a complete response.
• Evidence of benefit from giving BV in combination with other systemic therapies.	• pERC noted that there is no evidence from the ALCANZA trial to combine BV with other systemic therapies for patients with pcALCL or MF or for patients who have progressed to Sézary syndrome.
• Optimal stage of disease for treatment with BV.	• Disease stages included in the ALCANZA trial for pcALCL and MF would be eligible for treatment with BV. pERC agreed with the CGP that the trial population in terms of stage of disease at presentation is reflective of patients in Canadian clinical practice. Therefore, the stage of disease does not limit the interpretation of the trial results in the Canadian context.

• Timing and appropriateness of re-treatment with BV if disease recurs after the 48-week treatment course.	• pERC was uncertain of an appropriate time frame for re-treatment with BV as there is insufficient evidence to guide re-treatment with BV. pERC noted that the registered clinician input stated that similar to other lymphomas, patients who are chemo-sensitive to BV could be re-treated with BV if their response duration was reasonable (i.e. 12 months). The CGP noted that if a patient completed 16 cycles of BV therapy, responded well to BV, and had a durable response for at least 6 months, re-treatment with BV may be considered if disease occurs after the 48-week treatment course.

BV = brentuximab vedotin; CD = cluster of differentiation; CEOP = cyclophosphamide, epirubicin, vincristine, and prednisone; CGP = Clinical Guidance Panel; CHOP = cyclophosphamide, doxorubicin hydrochloride, vincristine sulphate, and prednisone; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony-stimulating factor; LCT = large cell transformation; MF = mycosis fungoides; mSWAT = Modified Severity Weighted Assessment Tool; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PC = physician's choice; pcALCL = primary cutaneous anaplastic large cell lymphoma; PML = progressive multifocal leukoencephalopathy; PS = performance status; RBC = red blood cell.