pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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 Funding Request:
For the treatment of adult patients (≥ 18 years) with Hodgkin lymphoma after failure of at least two multi-agent chemotherapy regimens in patients who are not autologous stem cell transplant candidates.

Submitted by:
Seattle Genetics, Inc.

Manufactured by:
Seattle Genetics, Inc.

NOC Date:
January 2, 2013

Submission Date:
August 27, 2018

Initial Recommendation Issued:
January 4, 2019

Approximate per Patient Drug Costs	Brentuximab vedotin costs: $4,840.00 per 50 mg vial • At the recommended dose of 1.8mg/kg intravenously, every 3 weeks, brentuximab vedotin costs: $19,360.00 per 28-day cycle.

pERC RECOMMENDATION

pERC does not recommend reimbursement of brentuximab vedotin for the treatment of adult patients (≥ 18 years) with Hodgkin lymphoma (HL) after failure of at least two multi-agent chemotherapy regimens in patients who are not candidates for autologous stem cell transplant (ASCT).

The Committee made this recommendation because it was unable to conclude that there is a net clinical benefit of brentuximab vedotin compared with single-agent chemotherapy given the limitations in the evidence from the available phase IV clinical trial. While pERC noted that there is a significant need for more effective treatment options in this setting and that brentuximab vedotin produces anti-tumour activity, the Committee concluded that there was considerable uncertainty in the evidence available on outcomes important to decision-making, such as rates of subsequent ASCT, overall survival (OS), and progression-free survival (PFS). Furthermore, the Committee was unable to determine how brentuximab vedotin compares with current treatment options given the lack of robust comparative data on outcomes important to decision-making.

	pERC agreed that brentuximab vedotin aligned with patient values as it offers an additional treatment option, produces anti-tumour activity, and has manageable side effects. However, the Committee was unable to make conclusions on the magnitude of the benefit of brentuximab vedotin, nor was it able to determine brentuximab vedotin's impact on patients' quality of life (QoL) as it was not measured in the available trial. The Committee concluded that brentuximab vedotin, at the submitted price, was likely not cost-effective compared with single-agent chemotherapy due to the uncertainty in the available clinical data.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC noted that new clinical data comparing brentuximab vedotin with currently available treatments in Canada for patients with HL who have failed at least two prior therapies and are not candidates for ASCT could form the basis of a resubmission to pCODR if comparative efficacy data important to decision-making such as PFS, OS, and QoL are available. **Access to Brentuximab Vedotin for ASCT Ineligible Patients** pERC noted that reimbursement of brentuximab vedotin for patients who are not candidates for ASCT is not uniform across Canada and results in a significant treatment gap for ASCT ineligible patients in most provinces.

SUMMARY OF pERC DELIBERATIONS

Hodgkin lymphoma (HL) accounts for approximately 8% to 10% of all diagnoses of lymphoma. The median age at diagnosis in most reported series is 35 to 40 years and approximately 15% of patients with HL are older than 60 years. There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease. In patients with relapsed or refractory disease, the best chance of cure remains with ASCT. However, ASCT is not considered appropriate treatment for patients who have chemo-resistant disease, progressive disease following salvage chemotherapy, or are at an advanced age (older than 70 years), especially those with significant medical comorbidities. Treatment of patients who are not eligible for ASCT is mostly aimed at palliation and symptom control with chemotherapy or radiotherapy. pERC discussed at length the unmet need for more effective and less toxic therapies in this population.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of a single-arm, multi-centre, phase IV clinical trial evaluating the efficacy of brentuximab vedotin in patients with CD30-positive relapsed/refractory HL who were not candidates for either stem cell transplant (SCT) or multi-agent chemotherapy. pERC noted that the trial population did not exactly align with the requested reimbursement criteria because the trial included patients who had failed one or more prior multi-agent chemotherapy regimens, and the requested reimbursement population was specifically for patients who had failed two or more prior therapies. The Committee noted that the latter subgroup comprised half of the trial population and that, despite a request to the submitter, no efficacy results were available for this patient subgroup. Furthermore, pERC noted that the requested reimbursement criteria included patients who were ASCT ineligible because of: (1) lack of response to salvage therapy prior to ASCT, or (2) advanced age or comorbidities. However, as the number of patients in the trial who belonged to the latter subgroup could not be confirmed by the submitter, pERC agreed with the pCODR Clinical Guidance Panel (CGP) that, based on the small number of patients over the age of 65 in the trial, it is likely that most patients belonged to the former subgroup (i.e., those who were transplant ineligible due to lack of response to salvage therapy prior to ASCT). While pERC acknowledged that an objective tumour response was observed with brentuximab vedotin, it also noted the limitations of using phase IV trials as the basis of the clinical evidence that informs pERC deliberations. Specifically, the Committee was concerned about the limited evidence submitted, given the descriptive data analyses with no formal hypothesis testing, the small sample size, and the lack of data on the subgroup of patients with two or more prior therapies. Furthermore, pERC noted uncertainty around the rates of subsequent ASCT as a significant number of patients developed progressive disease (PD) while receiving brentuximab vedotin, and proceeded to ASCT after receiving other subsequent therapy. pERC considered that this phase IV trial was exclusively conducted in trial centres across the European Union, where practice patterns may be different as to the chemosensitivity criteria they use to consider someone transplant eligible, as well as the sequencing of brentuximab vedotin with other chemotherapy regimens. In addition, pERC was unable to determine how brentuximab vedotin compared with current treatment options given the lack of robust direct or indirect comparative data on efficacy outcomes important to decision-making, such as rates of subsequent ASCT, OS, and PFS. pERC discussed that the submitted trial cannot provide a definitive estimate of efficacy and that it was unsure about whether the results observed in this phase IV trial will translate into more rigorously conducted clinical trials or into real-world clinical practice.

pERC noted that the impact of brentuximab vedotin on patients' QoL is unknown as it was not measured in the trial. pERC further considered the safety profile observed with brentuximab vedotin, noting that the single-arm, non-randomized design of the phase IV trial made interpreting the safety events attributable to brentuximab vedotin challenging given that all patients received the same treatment. The most common all-grade treatment-emergent adverse events were peripheral neuropathy, pyrexia, diarrhea, and neutropenia. At the end of treatment, more than half of the patients experienced complete resolution of peripheral neuropathy symptoms. Overall, pERC agreed with the CGP and the registered

clinicians that the toxicity observed in the phase IV study compared favourably to currently available chemotherapy options in patients with HL who have failed two or more lines of prior therapy, and that brentuximab vedotin can be given safely, and that toxicities can be mitigated with careful dose modifications.

In deliberating on the evidence for this patient population, pERC recognized the significant need for treatment options in this setting as these young patients, who are ASCT-ineligible, are considered incurable with no reasonable treatment options remaining. Therapies that lead to treatment responses can provide a bridge to transplant, which is the last curative measure in this setting. However, given the high level of uncertainty in the results from the available phase IV trial, the Committee could not confidently conclude that brentuximab vedotin addresses the need for more effective treatment options in this setting.

Overall, pERC was unable to conclude that there is a net clinical benefit of brentuximab vedotin compared with single-agent chemotherapy given the limitations in the evidence from the available phase IV clinical trial. While pERC acknowledged the CGP's positive conclusion, the significant need for more effective treatment options in this setting, and that brentuximab vedotin produces anti-tumour activity, the Committee concluded that there was considerable uncertainty in the evidence available on outcomes important to decision-making, such as rates of subsequent ASCT, OS, and PFS. Furthermore, the Committee was unable to determine how brentuximab vedotin compares with current treatment options given the lack of robust comparative data on efficacy outcomes important to decision-making.

pERC deliberated on input from one patient advocacy group. pERC noted that the majority of patients with experience using brentuximab vedotin reported a positive impact on their health and well-being. Patient respondents indicated a strong willingness to tolerate significant side effects for a chance of remission or cure. The most common side effects experienced were fatigue and peripheral neuropathy. pERC considered that patients value having access to more effective therapies that offer them more choices with minimal side effects. pERC agreed that brentuximab vedotin aligned with patient values as it offers an additional treatment option, produces anti-tumour activity, and has manageable side effects; however, the Committee was unable to determine the magnitude of the benefit compared with other currently available treatment options.

pERC deliberated the cost-effectiveness of brentuximab vedotin in patients with HL after failure of at least two multi-agent chemotherapy regimens and who are not ASCT candidates, and concluded that brentuximab vedotin is likely not cost-effective when compared with gemcitabine at the submitted price. pERC noted that the pCODR Economic Guidance Panel (EGP) reanalysis of cost-effectiveness presented an incremental cost-effectiveness ratio (ICER) as the lower bound with no upper bound, given the uncertainty in the evidence from the available non-comparative phase IV trial. pERC also noted that the submitted base-case ICER was lower than the EGP's lower-bound ICER estimate. This was primarily due to two factors:

- A shorter time horizon: the time horizon was shortened to address uncertainty in survival estimates based on extrapolation of short-term trial data and to maintain consistency with other pCODR reviews.
- Different parametric curve chosen for post-SCT survival: the EGP elected to choose the generalized gamma curve, which demonstrated a decline in survival over time that aligned with the CGP's opinion that this patient population is at increased risk of mortality, even following SCT.

pERC discussed several additional limitations in the submitted analyses, particularly the lack of comparative effectiveness data and the resulting uncertainty in relative efficacy between brentuximab vedotin and gemcitabine. pERC noted that in the absence of comparative efficacy data, the submitter provided a naive indirect treatment comparison, incorporating efficacy outcomes for the most recent prior therapy received by patients before enrolling in the submitted phase IV clinical trial. Although this comparison suggested that brentuximab vedotin is associated with improved efficacy as compared with gemcitabine, these results should be interpreted with caution as the submitter could not provide comprehensive information on the methods used to generate the results and collect this data. Further, pERC noted that, while patients were allowed to progress to other treatments following the receipt of a transplant, no subsequent treatments and their costs were included in the model. Hence, estimates of survival would include any potential benefit received from these treatments, without accounting for their

cost. Overall, pERC agreed with the EGP's reanalyses and the limitations identified in the submitted economic model. Consequently, pERC concluded that brentuximab vedotin was likely not cost-effective at the submitted price compared with gemcitabine.

pERC considered the feasibility of implementing a reimbursement recommendation for brentuximab vedotin in patients with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates. pERC discussed the Provincial Advisory Group's request for clarity on sequencing of treatments, and whether the results of the phase IV trial could be generalized to certain HL subgroups not included in the submitted trial. pERC also considered that brentuximab vedotin is a high-cost regimen and that the submitted Canada-wide budget impact was likely underestimated. A key limitation of the budget impact analysis model included the assumption that the number of patients eligible to get ASCT would be 80%. The CGP stated that this number would more likely be around 70%. pERC noted that decreasing the number of patients who are ASCT eligible to 70% increases the incremental budget impact by about 50%. Further, increasing the number of patients with HL who fail (relapse or refractory) after front-line therapy to 30% increases the submitted three-year incremental budget impact of brentuximab vedotin by about 87%. Overall, the Committee concluded that the budget impact is likely underestimated.

CONTEXT OF THE RESUBMISSION

On March 14, 2013, the CADTH pan-Canadian Oncology Drug Review (pCODR) received a submission for brentuximab vedotin (Adcetris) for patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior therapies in patients who are not ASCT candidates. The pCODR Expert Review Committee (pERC) Final Recommendation was issued on August 29, 2013.

- The pERC Final Recommendation was to:
  - Fund brentuximab vedotin in patients with HL who have relapsed disease following ASCT
  - Not fund brentuximab vedotin in patients with HL who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent chemotherapies.
- The resubmission made by the submitter provided new information on brentuximab vedotin for patients with HL who are not candidates for ASCT and have failed at least two prior multi-agent chemotherapies. The new information included:
  - New efficacy and safety data from an ongoing phase IV clinical trial
  - A revised economic evaluation based on the new data.

EVIDENCE IN BRIEF

pERC deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis (BIA)
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group: Lymphoma Canada (LC)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of brentuximab vedotin (Adcetris) for the treatment of adult patients with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates.

Studies included: One small phase IV clinical trial

The pCODR systematic review included one ongoing, single-group, multi-centre, phase IV trial (C25007), that evaluated the efficacy and safety of brentuximab vedotin in patients with CD30-positive relapsed/refractory (R/R) HL who were not candidates for either stem cell transplant (SCT) or multi-agent chemotherapy. C25007 was designed to fulfill a requirement of the conditional marketing authorization of brentuximab vedotin in the European Union.

The trial population did not exactly align with the requested reimbursement criteria because the trial included patients who had failed one or more prior multi-agent chemotherapy regimens, and the requested reimbursement population was specifically for patients who had failed two or more prior therapies. The latter subgroup comprised half of the trial population and, despite a request to the submitter, no efficacy results were available for this patient subgroup. The requested reimbursement criteria included patients who are ASCT ineligible because of: (1) lack of response to salvage therapy prior to ASCT, or (2) advanced age or comorbidities. However, as the number of patients in the trial who belonged to the latter subgroup could not be confirmed by the submitter, the pCODR Clinical Guidance Panel (CGP) suggested that, based on the small number of patients over the age of 65 in the trial, it is likely that most patients belonged to the former subgroup (i.e., those who were transplant ineligible due to lack of response to salvage therapy prior to ASCT).

Patient populations: Median age 32 years; 82% of patients received more than one prior therapy

The key eligibility criteria of the trial specified that patients be at least 18 years old with histologically confirmed CD30-positive R/R classical HL and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Eligible patients had received one or more prior systemic chemotherapy regimen(s) and were considered unsuitable for SCT or multi-agent chemotherapy based on the following criteria:

- Progressive disease (PD) during front-line multi-agent chemotherapy
- PD within 90 days of complete response (CR) or unconfirmed CR after multi-agent front-line chemotherapy and/or radiotherapy
- Relapse after two or more prior chemotherapy regimens, which included pre-SCT salvage treatments.

Patients with previous brentuximab vedotin exposure, or those who had undergone an ASCT or allogeneic SCT were excluded from the trial.

C25007 enrolled a total of 60 patients from 18 centres in Europe and Asia. Patients received brentuximab vedotin at a dosage of 1.8 mg/kg intravenously once every three weeks for up to a maximum of 16 cycles, or until PD or unacceptable toxicity. Patients who achieved a CR, partial response, or stable disease received a minimum of eight treatment cycles; and patients who achieved an ORR and became suitable for SCT could discontinue brentuximab vedotin after four cycles, and then proceed to SCT. The submitter could not confirm if patients who proceeded to SCT received brentuximab vedotin as consolidation treatment post-transplant. Patients in the trial received a median of seven treatment cycles of brentuximab vedotin (range, 1 to 16); and 13% (n = 8) of patients completed the maximum number of 16 cycles.

The median age of trial patients was 32 years (range, 18 to 75), with 92% of patients under the age of 65 years. The majority of patients were male (60%), of white race (70%), and had an ECOG performance status of 1 (55%). Most patients had an Ann Arbor disease stage of II (35%), III (27%), or IV (30%). Extranodal and bone marrow involvement were present in 37% and 7% of patients, respectively. Patients received a median of two prior therapies (range, 1 to 7) and 82% of patients had received more than one prior therapy. While a complete list of all the types of prior therapies received by patients prior to trial entry could not be provided by the submitter, common prior chemotherapies received by patients in the trial included doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD, 93%); ifosfamide, carboplatin, and etoposide (ICE, 43%); and dexamethasone, cytarabine, and cisplatin (DHAP, 22%). In terms of non-systemic prior therapy, 42% of trial patients had received radiation therapy and 15% had received a surgical procedure related to treatment for HL. In 67% of trial patients (n = 40) PD was the best response to last prior therapy.

Patients were considered ineligible for SCT or multi-agent chemotherapy at trial entry due to PD during front-line multi-agent chemotherapy in 32% of patients (n = 19); PD within 90 days of CR, or unconfirmed CR after treatment with multi-agent chemotherapy and/or radiation therapy in 18% of patients (n = 11); and relapse after two or more prior chemotherapy regimens in 50% of patients (n = 30).

All patients received brentuximab vedotin and eventually discontinued treatment. The primary reason for study drug discontinuation was PD (55%), followed by initiation of SCT (15%), and completion of the maximum 16 cycles (13%). A smaller percentage of patients discontinued the study drug due to treatment-emergent adverse events (TEAEs; 5%), symptomatic deterioration (5%), and other reasons (7%). Subsequent therapy after treatment with brentuximab vedotin was received by 70% (n = 42) of trial patients. The trial is ongoing with 60% (n = 36) of patients remaining in long-term follow-up.

Key efficacy results: Objective response rate and ASCT post-brentuximab vedotin: magnitude of comparative benefit uncertain

The efficacy of brentuximab vedotin was evaluated in the intent-to-treat (ITT) patient population and various patient subgroups that did not, however, include the patient population that aligns with the requested reimbursement criteria for this pCODR review. A request was made to the submitter to obtain efficacy results in the trial patients who had received two or more prior systemic therapies (target

population of requested reimbursement criteria), but they could not be provided to pCODR due to a data-sharing agreement between Seattle Genetics and Takeda.
The key efficacy outcome deliberated by pERC was ORR assessed by independent review facility (IRF), which was the primary outcome of the trial; the key secondary outcomes included the proportion of patients proceeding to SCT (ASCT or allogeneic SCT) following treatment with brentuximab vedotin, progression-free survival by IRF (PFS by IRF), and overall survival (OS). In addition to estimating PFS, a pre-specified correlation analysis was also performed to compare the PFS of patients from their most recent treatment prior to study entry versus PFS by investigator assessment with brentuximab vedotin. Details of the specific methodology used for this analysis were requested but could not be provided by the submitter.

Tumour response was determined according to the International Working Group Revised Response Criteria for Malignant Lymphoma and was assessed at baseline and at cycles 2, 4, 7, 10, 13, and 16. The statistical analyses performed of the trial data were descriptive in nature with no formal hypothesis testing. Exploratory subgroup analyses were performed to estimate ORR by IRF by sex, race, weight (≤ 100 kg versus > 100 kg), number of prior regimens (one versus more than one), baseline ECOG performance score (0 versus 1), and B symptoms (present versus absent).

The median follow-up time upon which the primary efficacy analysis results are based was not reported and could not be confirmed by the submitter. At the data cut-off date (May 24, 2016), the ORR by IRF in the ITT patient population was 50% (n = 30; 95% confidence interval [CI], 37% to 63%); CR (n = 7) and PR (n = 23) were observed in 12% and 38% of patients, respectively. ORR by IRF ranged from 20% to 61% across the aforementioned pre-specified patient subgroups. The ORR by IRF estimate in trial patients who received one or more prior therapies was 51% (n = 25/49).

Of the 60 patients who were deemed unsuitable for SCT or multi-agent chemotherapy at trial entry, 47% (n = 28) went on to receive a SCT. All 28 patients received ASCT, with one patient also receiving an allogeneic SCT. Of the 28 patients who proceeded to SCT, 21% (n = 6) had received one prior therapy and a median of six cycles (range, 4 to 6) of brentuximab vedotin; and the remaining 79% (n = 22) had received more than one prior therapy and a median of seven cycles (range, 4 to 16) of brentuximab vedotin. ASCT occurred immediately after treatment with brentuximab vedotin in 17% (n = 10) of trial patients; information on the number of prior therapies received by these patients as well as the median number of cycles of brentuximab vedotin received was requested but could not be confirmed by the submitter. ASCT followed subsequent treatment after brentuximab vedotin in 30% (n = 18) of trial patients; most of these patients had discontinued brentuximab vedotin due to PD (n = 15) and then received subsequent therapy prior to ASCT. The median number of cycles of brentuximab vedotin and the subsequent therapies received by these patients were also requested but could not be confirmed by the submitter.

After a median follow-up time of 6.9 months, 39 PFS events (PD or death) were observed in the ITT population and the median PFS by IRF was 4.8 months (95% CI, 3.0 to 5.3). For the PFS correlational analysis, the median investigator-assessed PFS of trial patients based on their most recent prior therapy was estimated at 4.1 months (95% CI, not reported) versus 5.0 months (95% CI, not reported) for brentuximab vedotin. The estimated hazard ratio for this comparison was 0.66 (95% CI, 0.45 to 0.98; *P* = 0.037), which suggested a 34% improvement in PFS with brentuximab vedotin compared with prior therapy. After a median follow-up of 16.6 months, a total of 12 deaths (20%) were observed in the ITT population; median OS had not been reached and the OS rate at one year was 86%.

Patient-reported outcomes: quality of life not assessed

Patient-reported quality of life (QoL) was not assessed in trial C25007.

Safety: Manageable side effects

The analysis of safety included all trial patients and was reported based on the incidence of all-grade TEAEs occurring in ≥ 10% of patients, and grade 3 to 4 TEAEs occurring in ≥ 2% patients. The incidence of all-grade TEAEs in the trial was 87%, with grade 3 to 4 TEAEs occurring in 35% of patients; of these, 68% and 18%, respectively, were deemed related to study drug. Serious adverse events (AEs) occurred in 18% of patients, and 5% of these were deemed drug-related. The most common all-grade TEAEs were peripheral neuropathy (35%), pyrexia (18%), diarrhea (10%), and neutropenia (10%). The most common grade 3 to 4 TEAEs were neutropenia, anemia (n = 3 each), pyrexia, and back pain (n = 2 each). Infusion-related TEAEs occurred in 7% of patients. The submitter could not confirm if any patients in the trial

experienced febrile neutropenia. TEAEs resulted in dose modification in 25% of patients and treatment discontinuation in 5% of patients. One on-study death was reported in the trial; this patient experienced septic shock within 30 days of the last dose of brentuximab vedotin, which was considered to be related to the study drug.

Peripheral neuropathy was experienced by 35% (n = 21) of trial patients (grade 1: 22%; grade 2: 10%; grade 3: 3%), and symptoms were considered related to the study drug in 32% of patients. The median time-to-onset of peripheral neuropathy was 9.4 weeks (range, 0.6 to 39.1). At the end of treatment/last follow-up, 57% of these patients experienced complete resolution of peripheral neuropathy symptoms and 43% experienced no resolution of symptoms (grade 1: 24%; grade 2: 14%; and grade 3: 5%).

Limitations: No direct comparative data to standard care option (single-agent gemcitabine)

The data for PFS and response rates for single-agent chemotherapy came from the C25007 trial, specifically the efficacy for the most recent prior therapy received by patients before enrolling into this phase IV study. A pre-specified analysis was performed comparing PFS from the most recent treatment prior to study entry with PFS following brentuximab vedotin treatment. Response rates were taken directly from the C25007 trial with no further analyses conducted. The results of these analyses should be viewed cautiously as the submitter could not provide comprehensive information on the methods used to generate the results and collect this data.

Need and burden of illness: Limited treatment options for young patients

There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease. Despite the excellent complete remission rates with current ABVD chemotherapy (> 95% for localized and > 80% for advanced stage disease), relapse is experienced by up to 10% to 15% of patients with early stage disease and up to 30% of those with advanced disease. For patients who have R/R disease, the best chances of cure are with ASCT; however, only patients whose disease is chemosensitive will be eligible. Approximately 20% to 30% of patients with HL are not eligible for ASCT because they fail two or more lines of multi-agent chemotherapy. A minority of these patients (< 5%) is not eligible for ASCT based on age or comorbidities. At that point, management is mostly aimed at palliation and symptom control with chemotherapy or radiotherapy. Given the young age of the majority of ASCT ineligible patients, brentuximab vedotin adds to the limited palliative treatment and management strategies available for young patients who are otherwise deemed incurable.

Registered clinician input: Unmet need for additional treatment options

The two registered clinicians providing input for this recommendation expressed that there is a large unmet need for additional treatment options for patients with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not candidates for ASCT. One clinician highlighted the two subgroups of patients within the ASCT ineligible patient population who have different treatment goals: patients who are ASCT ineligible due to a lack of response to salvage therapy prior to ASCT, and patients who are ASCT ineligible due to age and comorbidities. For patients in the first subgroup, the clinician suggested that ASCT may serve as a cure and that brentuximab vedotin could serve as a bridge to definitive treatment. For patients in the second subgroup, brentuximab vedotin would be the preferred therapy over other available options due to favourable efficacy and toxicity. Both clinicians suggested that for patients in the first category brentuximab vedotin is appropriate to use in the third line, but it may also be appropriate as a second-line option for patients in the second subgroup. It was noted by one clinician that because some Canadian provinces have restricted the reimbursement of brentuximab vedotin to patients who have undergone ASCT, some clinicians are only able to prescribe brentuximab vedotin to their patients via compassionate access programs, private funding, and clinical trials.

PATIENT-BASED VALUES

Values of patients with Hodgkin lymphoma: Choice of therapy, effectiveness of therapy, and minimal side effects

From a patient's perspective, fatigue or lack of energy and enlarged lymph nodes were the most commonly reported symptoms related to HL affecting QoL, and fatigue was specifically highlighted by LC as being a symptom greatly impacting patients. Patients also indicated experiencing great emotional and mental distress due to their condition, and patients felt anxiety and worry negatively impacted their QoL. The majority of patients indicated that HL negatively impacted their ability to work. All patients reported either currently receiving a treatment or having received a prior treatment in the past. Most patients indicated having received at least one line of conventional chemotherapy, with ABVD being the most commonly

reported chemotherapy regimen. Patients reported experiencing significant side effects related to previous treatments (e.g., nausea, vomiting, fatigue, hair loss) as well as long-term treatment-related side effects lasting more than two years (e.g., fatigue, "chemo-brain," peripheral neuropathy, loss of menstrual periods, thyroid dysfunction, sterility, and lung damage). Patients indicated that treatment-related factors, including treatment-related fatigue, the ability to tolerate treatment, infusion reactions, infusion time, and number of clinic visits, significantly negatively impacted their QoL.

LC noted that choice of therapy, effectiveness of therapy, and minimal side effects were identified by patients as being important when considering a new treatment.

Patient values on treatment: Overall positive impact on health and well-being, most common side effects fatigue and peripheral neuropathy

Of the patients in the LC sample with experience with brentuximab vedotin (n = 14), all patients experienced at least one side effect while receiving brentuximab vedotin. The most common side effects were fatigue and peripheral neuropathy. Patients indicated a strong willingness to tolerate significant side effects for a chance of remission or cure. Based on patients' responses, brentuximab vedotin had a minimal or positive impact on aspects of QoL, such as work, family, friendships, intimate relations, activities, or travel. Regardless, more than half of patients indicated that they experienced a positive impact on their health and well-being due to brentuximab vedotin.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis and one cost-effectiveness analysis of brentuximab vedotin compared with current standard of care (single-agent gemcitabine chemotherapy) for patients with HL after failure of at least two multi-agent chemotherapy regimens who are not candidates for ASCT.

Basis of the economic model: Clinical and economic inputs

The clinical outcomes considered in the submitted model included response rate, percentage of patients proceeding to SCT, PFS, and OS (pre- and post-ASCT), and AEs.

The submitted model considered costs for drug acquisition, drug administration, drug wastage, medical resource use, SCT (excluding post-transplant costs), AEs, and palliative/terminal care.

Drug costs: High drug cost

The unit cost of brentuximab vedotin is $4,840.00 per 50 mg vial. At the recommended dose of 1.8 mg/kg intravenously, every three weeks, brentuximab vedotin costs $691.43 per day and $19,360.00 per 28-day course. This assumes a total of 126 mg used (three vials) once per 21-day cycle for an average body weight of 70 kg.

The unit cost of single-agent gemcitabine is $270.00 per 1,000 mg. At the recommended dose of 1,000 mg/m^2 three times per 28-day course, gemcitabine costs $49.18 per day and $1,377.00 per 28-day course.

Cost-effectiveness estimates: Likely not cost-effective; upper bound not estimable due to uncertainty in data sources and assumptions

pERC deliberated the cost-effectiveness of brentuximab vedotin compared with single-agent gemcitabine chemotherapy. The EGP's reanalyses of cost-effectiveness presented incremental cost-effectiveness ratio (ICER) as lower bound with no upper bound, given the uncertainty around the clinical comparative efficacy of treatments. The submitted base-case ICER ($33,797 per quality adjusted life-year) was lower than the EGP's lower-bound ICER estimate ($82,973 per quality adjusted life-year). This was primarily due to two factors:

- A shorter time horizon: the time horizon was shortened to address uncertainty in survival estimates based on extrapolation of short-term trial data and to maintain consistency with other pCODR reviews.
- Different parametric curve chosen for post-SCT survival (generalized gamma instead of Gompertz): the EGP elected to choose the generalized gamma curve that demonstrated a decline

in survival over time that aligned with the CGP's opinion that this patient population is at increased risk of mortality, even following SCT.

The EGP identified several additional limitations in the submitted analysis:

- The lack of comparative effectiveness data and the resulting uncertainty in relative efficacy between brentuximab vedotin and gemcitabine. In the absence of comparative efficacy data, the submitter provided a naive indirect treatment comparison, incorporating efficacy outcomes for the most recent prior therapy received by patients before enrolling in the submitted phase IV clinical trial. Although this comparison suggested that brentuximab vedotin is associated with improved efficacy as compared with gemcitabine, these results should be interpreted with caution as the submitter could not provide comprehensive information on the methods used to generate the results and collect this data.
- Patients were allowed to progress following the receipt of a transplant; however, no subsequent treatments and their costs were included in the model. Therefore, estimates of survival would include any potential benefit received from these treatments, without accounting for their cost.
- The main evidence used to inform the economic model was based on the C25007 trial, which is a phase IV post-marketing trial that employed descriptive data analyses with no formal hypothesis testing. From a study design perspective, phase IV trials are not meant to provide estimates of treatment efficacy.
- Trial data important to the critical appraisal and clinical interpretation of the trial (trial protocol, statistical analysis plan, and additional information requests) could not be obtained because of a data-sharing agreement between Seattle Genetics and Takeda.
- Uncertainty in the proportion of patients receiving SCT after brentuximab vedotin: The low percentage of patients who proceeded to SCT immediately following brentuximab vedotin, variation in treatment practices (systemic therapies offered and patient eligibility thresholds for proceeding to SCT), and the possibility that outcomes may vary depending on the number of prior therapies received.
- Uncertainty in the data to inform OS: In the absence of robust data sources, OS data in the model was based on retrospective chart reviews or expert opinion.
- The costs associated with post-transplant care, which can be significant and of considerable duration, and the subsequent treatments used post-SCT were not included in the submitted model.

The EGP noted that it was difficult to know where the best estimate of the ICER lies in the absence of comparative data. According to the EGP's reanalysis, the factors that most influence the incremental effectiveness of brentuximab vedotin include the time horizon and the proportion of patients proceeding to SCT. The EGP estimated that the incremental cost of brentuximab vedotin is at least $107,708, with the main cost drivers in the model being the time horizon and the proportion of patients receiving SCT.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact is likely underestimated

pERC deliberated on the feasibility of implementing a reimbursement recommendation for brentuximab vedotin for patients with R/R HL who have failed at least two multi-agent chemotherapy regimens and are not candidates for ASCT. Factors raised by PAG included sequencing of treatments and whether the results of the phase IV trial could be generalized to certain HL patient subgroups not included in the submitted trial.

pERC also considered the submitted BIA, noting that brentuximab vedotin is a high-cost regimen and that the submitted Canada-wide budget impact was likely underestimated. A key limitation of the BIA model included the assumption that the number of patients eligible to get ASCT would be 80%. The CGP stated that this number would more likely be around 70%. Decreasing the number of patients who are ASCT eligible to 70% increases the incremental budget impact by about 50%. Increasing the number of HL patients who fail (relapse or refractory) after front-line therapy to 30% increases the submitted three-year incremental budget impact of brentuximab vedotin by about 87%.

DRUG AND CONDITION INFORMATION

Drug Information	• Brentuximab vedotin is an antibody-drug conjugate. • Brentuximab vedotin is administered at a dose of 1.8 mg/kg as an intravenous infusion over 30 minutes every 3 weeks.
Cancer Treated	• Relapsed or refractory Hodgkin lymphoma (HL).
Burden of Illness	• There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease. In patients with relapsed or refractory disease, the best chance of cure remains with autologous stem cell transplantation (ASCT). However, up to 40% of relapsed/refractory patients are transplant ineligible and do not have good treatment options.
Current Standard Treatment	• Palliation and symptom control with chemotherapy or radiotherapy.
Limitations of Current Therapy	• Patients who are ASCT ineligible have a very poor prognosis, and the treatment is palliative with chemotherapy and best supportive care.

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 Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Economist

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

- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pERC 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 brentuximab vedotin for Hodgkin lymphoma, through their declarations, no member had a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, no member was 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

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.

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