pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Brentuximab (Adcetris) for Hodgkin Lymphoma - Resubmission

March 7, 2019

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding brentuximab vedotin (Adcetris) for Hodgkin lymphoma (HL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding brentuximab vedotin (Adcetris) for Hodgkin lymphoma (HL) conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on brentuximab vedotin (Adcetris) for Hodgkin lymphoma (HL), a summary of submitted Provincial Advisory Group Input on brentuximab vedotin (Adcetris) for Hodgkin lymphoma (HL), and a summary of submitted Registered Clinician Input on brentuximab vedotin (Adcetris) for Hodgkin lymphoma (HL), and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of brentuximab vedotin (Adcetris) for the treatment of adult patients (≥ 18 years) with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not autologous stem cell transplant (ASCT) candidates.

Health Canada has issued conditional marketing authorization for brentuximab vedotin for the treatment of patients with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates. This marketing authorizations is conditional, pending the results of studies to verify its clinical benefit. Note that the Health Canada indication differs slightly from the pCODR reimbursement criteria, in that it does not specify 'adults patients (≥18 years)' in its indication.

It is important to highlight that the pCODR requested reimbursement criteria do not exactly align with the patient population in the phase IV C25007 trial. Please find further details in section 1.2.1.

Brentuximab vedotin is an antibody-drug conjugate, which selectively targets tumor cells expressing the CD30 antigen, a defining marker of HL. The Health Canada recommended dose is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg. In the absence of disease progression or unacceptable toxicity, patients who achieve stable disease or better should continue to receive brentuximab vedotin for a minimum of 8 cycles and up to a maximum of 16 cycles. Treatment beyond 16 cycles should be administered only when agreed to by the patient and their health care professional after consideration of the risks associated with prolonged treatment.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One clinical trial was identified that met the selection criteria of the pCODR systematic review. Clinical trial C25007 by Walewski et al 2018[1] is an ongoing, single group, multicentre phase IV trial evaluating the efficacy of brentuximab vedotin in patients with CD30-positive relapsed/refractory (R/R) HL who were not candidates for either stem cell transplant (SCT) or multiagent chemotherapy.

It is important to highlight that the pCODR requested reimbursement criteria do not exactly align with the patient population in the C25007 trial. Whereas the pCODR requested reimbursement criteria are for the broader ASCT ineligible patient population, the majority of patients in the phase IV trial represent the subgroup of ASCT ineligible patients who have the potential to receive ASCT if they respond to further treatment. It is important to note that there are two distinct subgroups of ASCT ineligible patients with different treatment goals:

- One subgroup includes patients who are ASCT ineligible due to lack of response to salvage therapy prior to ASCT but have the potential to become ASCT eligible if they respond to further treatment. In those patients, brentuximab vedotin could be a bridge to ASCT.
- The other subgroup includes patients who are ASCT ineligible due to fragility, old age, or comorbidities. These patients will never receive a transplant but may benefit from brentuximab vedotin due to favourable efficacy and toxicity. This subgroup forms a minority of ASCT ineligible patients, estimated to be less than 5% by the pCODR Clinical Guidance Panel (CGP).

While the number of patients in the C25007 trial who were ASCT ineligible due to fragility, old age, or comorbidities could not be confirmed by the Submitter, it has been suggested by the CGP that based on the small number of patients over the age of 65 in the trial (n=5/60), it is likely that most patients in the trial belong to the first subgroup, i.e. those who were transplant ineligible due to chemotherapy resistance or high-risk refractory disease to first-line chemotherapy and therefore had the potential to receive ASCT if they responded to subsequent treatment.

In their feedback on the initial recommendation, the submitter noted that the statement that *"the requested reimbursement criteria included patients who were ASCT ineligible because of: 1) lack of response to salvage prior to ASCT or 2) advanced age or comorbidities"* (initial recommendation; page 3) is unclear as it may incorrectly imply that the requested reimbursement criteria included older patients with HL who failed one line of multi-agent chemotherapy regimen. In response to the submitter's feedback, the pCODR Methods Team acknowledged that the statement does not specify "after failure of at least two-multi-agent chemotherapy regimens". However, the pCODR Methods Team noted that whether or not the results of the C25007 trial can be generalised to older patients after failure of one multi-agent chemotherapy regimen, has been addressed by the pCODR Clinical Guidance Panel (CGP) in the CGR in the Generalizability Table 1.2 (page 11) and in the CGP Conclusions (page 22).

Furthermore, while the pCODR requested reimbursement criteria specify that patients should have received at least two multiagent chemotherapy regimens, the C25007 trial included patients who had failed ≥ *1* multi-agent chemotherapy regimen(s). The percentage of patients in the trial who had failed ≥ 2 multi-agent regimens was 50% (n=30).

Trial C25007[1]

C25007 was designed to fulfill a requirement of the conditional marketing authorisation of brentuximab vedotin in the European Union, and was conducted at 18 centres in seven countries (the Czech Republic, Germany, Malaysia, Poland, Spain, Thailand and Turkey). Seattle Genetics and Takeda are jointly developing brentuximab vedotin; under the terms of the collaboration agreement, Seattle Genetics has US and Canadian commercialization rights, and Takeda has rights to commercialize the drug in the rest of the world.

Patients included in the trial met the following key criteria:

- Age ≥ 18 years
- Histologically confirmed CD30-positive R/R classical HL
- ≥ 1 prior systemic chemotherapy regimen(s)
- Considered unsuitable for SCT or multiagent chemotherapy based on the following criteria:
    - Progressive disease (PD) during frontline multiagent chemotherapy
    - PD within 90 days of complete response (CR) or unconfirmed CR after multiagent front-line chemotherapy and/or radiotherapy
    - Relapse after ≥ 2 prior chemotherapy regimens, which included pre-SCT salvage treatments
- ECOG performance status of 0-1
- Patients with previous brentuximab vedotin exposure, or who had undergone an ASCT or allogeneic SCT were excluded from the trial.

Outcomes

The primary outcome of C25007 was overall response rate (ORR) assessed by independent review facility (IRF). Secondary outcomes of interest included duration of response (DOR), progression-free survival by IRF (PFS by IRF), overall survival (OS), the proportion of patients proceeding to SCT (ASCT or allogeneic SCT)[3] following treatment with brentuximab vedotin, CR rate, duration of CR, and safety. Quality of life was not assessed.

Disease Assessment and Statistical Analyses

Tumour response was determined according to International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma and was assessed at baseline, and at cycles 2, 4, 7, 10, 13, and 16 by CT scan of the chest, neck, abdomen; PET scans were performed at baseline and cycles 4 and 7. Patients were assessed for PFS and OS every three months until 18 months after treatment with brentuximab vedotin; after 18 months, patients were followed for OS every six months until death or end of study. Safety was assessed throughout the treatment period until 30 days after the last dose of brentuximab vedotin.

The statistical analyses performed of the trial data were descriptive with no formal hypothesis testing performed. For the primary outcome, ORR by IRF, two-sided 95% confidence intervals (CI) were calculated for the overall patient population, and exploratory subgroup analyses were performed to estimate ORR by IRF by sex, race, weight (≤ 100 kg versus > 100 kg), number of prior regimens (1 versus > 1), baseline ECOG performance score (0 versus 1), and B symptoms (present versus absent). Time-to-event outcomes were estimated using Kaplan Meier (KM) methods. A pre-specified correlational 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. All efficacy analyses were performed by intention-to-treat (ITT); and safety analyses included all patients who had received at least one dose of brentuximab vedotin.

Population

The trial enrolled a total of 60 patients between March 2014 and March 2015. The baseline characteristics of trial patients were considered by the trial authors as representative of patients with R/R HL deemed unsuitable for SCT or multiagent chemotherapy. The median age of patients was 32 years (range, 18-75), with 92% of patients under the age of 65. The majority of patients were male (60%), of white race (70%), and had an ECOG performance status of 1 (55%). Extranodal and bone marrow involvement were present in 37% and 7% of patients, respectively. Patients had received a median of two prior therapies (range, 1-7) and 82% of patients had received > 1 prior therapy. In 67% of trial patients (n=40), PD was the best response to last prior therapy.

Patients were considered ineligible for SCT or multiagent chemotherapy at trial entry due to the following reasons: PD during frontline multiagent chemotherapy (32%; n=19); PD within 90 days of CR or unconfirmed CR after treatment with multiagent chemotherapy and/or radiation therapy (18%; n=11); and relapse after ≥ 2 prior chemotherapy regimens in (50%; n=30). Based on the low percentage of patients over the age of 65 in the trial, the pCODR CGP suggested that it is likely that most patients were ASCT ineligible due to chemotherapy resistance or high-risk refractory disease to first-line chemotherapy, rather than due to fragility, old age or comorbidities.

Intervention

Trial patients received brentuximab vedotin at a dose of 1.8 mg /kg intravenously once every three weeks for up to a maximum of 16 cycles, or until PD or unacceptable toxicity. For patients who proceeded to SCT, it is unknown if patients received brentuximab vedotin as consolidation treatment post-transplant. Patients in the trial received a median of seven treatment cycles of brentuximab vedotin (range, 1-16); and 13% (n=8) of patients completed the maximum number of 16 cycles.

In terms of subsequent therapy after treatment with brentuximab vedotin, 70% (n=42) of patients in the trial received subsequent treatment. Among these patients, 47% (n=28) received a SCT. The Submitter was unable to verify the non-transplant subsequent therapies received by patients in the trial.

Patient Disposition

All patients received treatment with brentuximab vedotin and eventually discontinued treatment with the study drug. 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 study drug due to treatment-emergent adverse events (TEAEs; 5%), symptomatic deterioration (5%), and other reasons (7%).

The trial is ongoing with 60% (n=36) of patients remaining in long-term follow-up; most patients who discontinued from follow-up did so due to death (20%), with fewer patients discontinuing due to PD (5%), patient withdrawal (5%), withdrawal of informed consent (3%), and other reasons (7%).[4]

Summary of Outcomes

The median follow-up time upon which the primary efficacy analysis (ORR by IRF) results are based was not reported. The Submitter confirmed a data cut-off date of May 24, 2016, however, they were unable to provide the median follow-up time. Details regarding the timing of PFS and OS outcome analyses (whether they were pre-specified and event driven) were also requested but could not be confirmed. Requests were also made to obtain efficacy results in the trial patients who had received ≥ 2 prior systemic therapies (target population of requested reimbursement criteria), but they could not be provided due to a data sharing agreement between Seattle Genetics and Takeda.[5]

A summary of key outcomes from the C25007 trial is available in Table 1.1.

Table 1.1: Key outcomes in patients treated with brentuximab vedotin monotherapy in trial C25007.[1]

Key Outcomes	Brentuximab vedotin Monotherapy (n=60)	
Efficacy		
DBL	May 24, 2016	
Median follow-up	Not available	
	IRF Assessment	Investigator Assessment
ORR, n (%; 95% CI)	30 (50; 37-63)	29 (48; 35-62)
Best clinical response n, (%; 95% CI)		
CR	7 (12; 5-23)	9 (15; 7-27)
PR	23 (38; 26-52)	20 (33; 22-47)
SD	18 (30; 19-43)	25 (42; 29-55)
PD	8 (13; 6-25)	2 (3;<1-12)
NE	4 (7; 2-16)	4 (7; 2-16)
Median DOR, in months (95% CI)	4.6 (3.4-7.9)	5.3 (3.6-NE)
Median duration of CR, in months (95% CI)	6.1 (2.1-NE)	7.6 (2.1-NE)
Median duration of PR, in months (95% CI)	3.7 (2.4-7.9)	3.8 (3.5-6.4)
PFS		
Median follow-up, in months	6.9	
No. of PFS events	39	Not reported
Median PFS, in months	4.8 (3.0-5.3)	5.0 (4.8-6.2)[3]
OS		
Median follow-up, in months	16.6	
No. deaths	12	
OS rate at one year, % (95% CI)	86 (74.0-93.4)	
OS rate at two years, % (95% CI)	74 (58.0-84.6)[3]	
Proportion of patients receiving SCT after brentuximab vedotin		
Received SCT, n	28 (47)	
Received SCT immediately post-brentuximab vedotin	10 (17)	
Received subsequent therapy post-brentuximab vedotin and prior to SCT	18 (30)	
Harms		
TEAE, n (%) - all grade / grade 3-4	52 (87) / 21 (35)	
Drug-related TEAE	41 (68) / 11 (18)	
Peripheral neuropathy SMQ	21 (35) / 3 (3)	
SAE	11 (18)	
Drug-related SAE	3 (5)	
TEAE resulting in dose modification	15 (25)	
TEAE resulting in treatment discontinuation	3 (5)	

Abbreviations: DBL - database lock; DOR - duration of response; CI - confidence interval; CR - complete response; NE- not estimable; ORR - objective response rate; PD - progressive disease; PR - partial response; OS - overall survival; PFS - progression-free survival; SAE - serious adverse event; SCT - stem cell transplant; SD - stable disease; SMQ - standardized MedDRA Queries; TEAE - treatment emergent adverse events.

Efficacy

The efficacy of brentuximab vedotin was evaluated in the ITT population and various patient subgroups that did not, however, include the patient population that aligns with the requested reimbursement criteria for this pCODR review, which is patients with R/R HL who have received 2 or more prior therapies. In the C25007 trial, these patients comprised 50% of trial patients (n=30). Efficacy estimates are available for trial patients who received > 1 prior therapies (82%; n=49) and 1 prior therapy (18%; n=11). Please refer to Table 9 for the primary efficacy results by patient subgroup.

Primary Outcome – ORR by IRF

At the data-cut-off date, the ORR by IRF in the ITT patient population was 50% (n=30; 95% CI, 37-63%); CR (n=7) and PR (n=23) were observed in 12% and 38% of patients, respectively. ORR by investigator assessment showed a similar result to assessment by IRF (Table 1.1). ORR by IRF ranged from 20% to 61% across pre-specified subgroups.

DOR by IRF

Among patients who achieved an ORR, CR and PR, the median durations of these responses were 4.6 months (95%, 3.4-7.9), 6.1 months (95% CI, 2.1-not estimable), and 3.7 months (95% CI, 2.4-7.9), respectively. The estimates of these outcomes by investigator assessment were generally similar to DOR by IRF and are available in Table 1.1.

PFS by IRF

After a median follow-up time of 6.9 months, 39 PFS events (PD or death) were observed in the ITT population; the median PFS by IRF was 4.8 months (95% CI, 3.0-5.3). Median PFS by investigator assessment was similar to the IRF estimate (Table 1.1).

PFS Correlation Analysis

The median 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 HR for this comparison was 0.66 (95% CI, 0.45-0.98; p=0.037), which suggested a 34% improvement in PFS with brentuximab vedotin compared to prior therapy.

OS

After a median follow-up of 16.6 months, a total of 12 deaths were observed in the ITT trial population; at this time median OS had not been reached, and the OS rate at one year was 86%.

Proportion of Patients Proceeding to ASCT after Brentuximab vedotin

Of the 60 patients who were deemed unsuitable for SCT or multiagent chemotherapy at trial entry, 47% (n=28) went on to receive a SCT. All 28 patients received ASCT, with one patient also receiving allogeneic SCT.[3] Considering the 28 patients who proceeded to SCT, 21% (n=6) had received one prior therapy and a median of six cycles (range, 4-6) of brentuximab vedotin; and the remaining 22 patients (79%) had received more than one prior therapy and a median of seven cycles (range, 4-16) of brentuximab vedotin.

SCT occurred immediately after treatment with brentuximab vedotin in 17% (n=10) of trial patients. Patient proportions for the number and types of prior therapies received by these patients, as well as the median number of cycles of brentuximab vedotin received, could not be obtained by the Submitter.[4]

SCT 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) [other reasons included completed maximum number of brentuximab vedotin cycles (n=1), AE (n=1), and symptomatic deterioration (n=1)] and then received subsequent therapy prior to SCT. The median number of cycles of brentuximab vedotin and the subsequent therapies received by these patients was not reported.

Harms

Adverse event (AE) data are reported in terms of the all grade treatment emergent adverse events (TEAE) occurring in ≥ 10% of patients, and grade 3-4 TEAE occurring in ≥ 2 patients. Peripheral neuropathy was evaluated using Standardized MedDRA Queries (SMQ) that included the following preferred terms: peripheral sensory neuropathy, peripheral neuropathy, polyneuropathy, paresthesia, and autonomic neuropathy.

TEAEs

The incidence of all grade TEAE in the trial was 87%, with grade 3-4 TEAE occurring in 35% of patients; of these, 68% and 18% were deemed related to study drug. Serious adverse events (SAE) occurred in 18% of patients, and 5% of these were deemed drug-related.

The most common all grade TEAE occurring in patients were peripheral neuropathy (35%), pyrexia (18%), diarrhea (10%) and neutropenia (10%). The most common grade 3-4 TEAE were neutropenia, anemia (n=3 each), pyrexia and back pain (n=2 each). Infusion-related TEAE occurred in 7% of patients. The Submitter could not confirm if any patients in the trial experienced febrile neutropenia.[4]

TEAE resulted in dose modification in 25% of patients and treatment discontinuation in 5% of patients.

Resolution of Peripheral Neuropathy

Of the 35% (n=21) who experienced peripheral neuropathy while on study (grade 1: 22%; grade 2: 10%; grade 3: 3%), symptoms were considered related to study drug in 32% of patients (n=19). The median time to onset of peripheral neuropathy was 9.4 weeks (range, 0.6-39.1). At the end of treatment/last follow-up, 57% (n=12/21) of patients experienced complete resolution of peripheral neuropathy symptoms, and 43% (9/21) experienced no resolution of symptoms (grade 1: 24%, grade 2: 14%, and grade 3: 5%).

Deaths

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 study drug.

Limitations and Sources of Bias

Critical appraisal of the C25007 trial was primarily based on reporting in the trial publication by Walewski et al 2018.[1] Valuable information sources, including the trial protocol and SAP, were not made available to pCODR; and the Submitter was unable to provide responses to most requests for additional information due to a data sharing agreement between Seattle Genetics and Takeda.[4] Consequently, a complete critical appraisal is challenging when important trial information is not available. Based on the data available to the pCODR Methods Team, the following limitations related to the C25007 trial were noted:

- The C25007 trial is an open-label, single group phase IV trial with no active treatment or placebo control group. The evidence obtained from this trial should be considered in light of the limitations associated with phase IV trial design. Phase IV trials are post-marketing trials that evaluate drugs in real world settings, often conducted by the manufacturer to fulfill additional evidence requirements related to drug safety and long-term effects, and in special patient groups. Unlike pre-marketing trials (phase 1-3), phase IV trials do not receive the same level of scrutiny and appraisal from drug regulatory agencies, with respect to design, analysis and reporting. As such, potential

threats to the internal validity of these trials may not be identified and considered in the interpretation of results. Further, these trials often employ a non-comparative trial design (see below), and are frequently underpowered to provide reliable estimates of treatment effect.[6,7]

- It is difficult to draw conclusions on the efficacy of brentuximab vedotin in R/R HL in the absence of a direct comparison to standard of care treatment (single-agent chemotherapy, BSC). The available evidence is based on descriptive data analyses with no formal hypothesis testing; and therefore, in the absence of inferential statistical approaches, the phase IV trial data cannot provide a definitive estimate of efficacy. While the authors performed a pre-specified correlation analysis to compare the PFS estimate obtained with brentuximab vedotin to the PFS patients experienced on their most recent prior therapy, the results of this analysis should be viewed cautiously, as no details were provided on the methods that informed this analysis. Similar methodology, such as Von Hoff's PFS ratio,[8] can lead to biased estimates due to several factors, such as differences in PD and censoring definitions, and the exclusion of patients who die before progression and are lost to follow-up. The robustness of this analysis cannot be determined based on available information.
- Making a judgement on efficacy is also made difficult by the fact that the trial was small (n=60), and the patient population does not completely align with the target population of this review. The number of patients who were ineligible for SCT/multiagent chemotherapy based on ≥ 2 prior therapies was 50% of trial patients (n=30). Efficacy was not estimated for this patient subgroup, but was estimated for trial patients who received > 1 prior therapies (n=49; 82%). In this patient group, the ORR by IRF estimate (51%; n=25/49) was similar to the overall ITT estimate (50%; n=30/60).
- One finding of the trial was the 28 patients (47%) at trial entry who were unsuitable for SCT or multiagent chemotherapy, who then proceeded to SCT. Upon closer examination, only 10 (17%) of these patients proceeded to SCT directly following treatment with brentuximab vedotin. The majority of patients (n=15/28) developed PD while receiving brentuximab vedotin, and proceeded to SCT after receiving other subsequent therapy. Therefore, in this latter group of patients, caution is advised in attributing the ability to proceed to SCT to brentuximab vedotin.
- The primary outcome of the trial was ORR by IRF. This is a surrogate outcome that may not translate to benefits in PFS and OS. PFS and OS were assessed in the trial but cannot be used to confirm the ORR clinical benefit due to the single group trial design. Further, estimates of OS are confounded by the subsequent therapies received by patients after treatment with brentuximab vedotin.
- Data on patient-reported QOL, an important outcome, was not collected in the trial; as such, the impact of brentuximab vedotin on the QOL of patients in the trial is uncertain.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient group, Lymphoma Canada (LC), provided input from patients with Hodgkin Lymphoma (HL).

From a patient's perspective, fatigue or lack of energy and enlarged lymph nodes were the most commonly reported symptoms related to HL affecting quality of life. Specifically, fatigue was highlighted by LC as being a symptom greatly impacting patients. Respondents also indicated experiencing great emotional and mental distress due to their condition; patients felt anxiety and worry negatively impacting their quality of life. In addition In terms of other aspects of life affected by their disease, the majority of respondents (61%, 51/83) 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 (93%) indicated having received at least one line of conventional chemotherapy; ABVD (81%) 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). Respondents indicated that the following treatment-related factors significantly negatively impacted their quality of life: treatment-related fatigue, the ability to tolerate treatment, infusion reaction, infusion time, and number of clinic visits.

Of patients with experience with brentuximab vedotin (n=14), all experienced at least one side effect while receiving brentuximab vedotin. The most common side effects experienced were fatigue and peripheral neuropathy. Respondents indicated a strong willingness to tolerate significant side effects for a chance of remission or cure. Based on patient's responses, brentuximab vedotin did not seem to have a significant positive or negative impact on aspects of quality of life, such as work, family, friendships, intimate relations, activities or travel. Regardless, over half of respondents indicated that they experienced a positive impact on their health and well-being due to brentuximab vedotin.

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

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarification on subtypes of HL eligible for treatment
- Maximum dose recommended
- Appropriate sequencing with immunotherapy for patients with classical HL subtype

Economic factors:

- Additional line of therapy

Registered Clinician Input

Two separate clinician inputs were provided regarding brentuximab vedotin for HL after failure of at least two multi-agent chemotherapy regimens in adult patients (≥ 18 years) who are not ASCT candidates. Both clinicians indicated having experience prescribing brentuximab vedotin.

Both clinicians expressed the large need for more treatment options for patients with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates. One of the clinicians highlighted that there are two subgroups within ASCT ineligible patients that have different treatment goals: 1) patients who are ASCT ineligible due to a lack of response to salvage therapy prior to ASCT, and 2) patients who are ASCT ineligible due to age. For patients in the first category, 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 category, brentuximab vedotin would be the preferred therapy over other available options due to favourable efficacy and toxicity. Further, both clinicians suggested that while for patients in the first category brentuximab vedotin is appropriate for use in the third-line, it may also be appropriate in the second-line for patients in the second category. One clinician pointed out that as some Canadian provinces have restricted reimbursement of brentuximab vedotin to patients that have undergone ASCT, clinicians were able to prescribe brentuximab vedotin to their patients via compassionate access programs, private funding, and clinical trials. CD30 expression testing was noted to already be part of the pathological assessment for HL, therefore no additional companion diagnostic testing would be required.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence for brentuximab vedotin for HL

Domain	Factor	Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]	Generalizability Question	CGP Assessment of Generalizability
Population	Transplant ineligible	Patients included in the trial had to be ineligible for SCT or multiagent chemotherapy at trial entry due to the following reasons: 1) PD during front-line multiagent chemotherapy (32%; n=19); 2) PD within 90 days of	Does the reason for transplant ineligibility limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the	There are two distinct subgroups of ASCT ineligible patients with different treatment goals. One subgroup includes patients who are ASCT ineligible due to lack of response to salvage therapy prior to ASCT but have the potential to become

Domain	Factor	Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]	Generalizability Question	CGP Assessment of Generalizability
		CR or unconfirmed CR after treatment with multiagent chemotherapy and/or radiation therapy (18%; n=11); 3) Relapse after ≥ 2 prior chemotherapy regimens in (50%; n=30). The specific reasons patients were deemed unsuitable for SCT or multiagent chemotherapy at trial entry (e.g., advanced age and comorbidities, chemotherapy resistance) were not reported in the trial publication and could not be confirmed by the Submitter. Based on the low percentage of patients over the age of 65 in the trial (n=5 out of 60), the CGP suggested that likely most patients were ASCT ineligible due lack of chemoresponsive disease or high-risk refractory disease to first-line chemotherapy.	factor, etc.)?	ASCT eligible if they respond to further treatment. In those patients brentuximab vedotin could be a bridge to ASCT. The other subgroup includes patients who are ASCT ineligible due to fragility, old age, or comorbidities. These patients will never receive a transplant but may benefit from brentuximab vedotin due to favourable efficacy and toxicity. The latter subgroup forms a minority of ASCT ineligible patients (< 5 %). The phase IV trial is evaluating patients who were ineligible for ASCT at study entry due to lack of chemoresponsive disease or high-risk refractory disease to first-line chemotherapy, but could become ASCT candidates if they responded to brentuximab vedotin, and as such, demonstrated chemoresponsiveness as per the criteria required by individual centres. There were five patients over the age of 65, which could be the age cut-off for ASCT at some centres, and therefore, may have been ineligible for age-related reasons. The ASCT ineligible criteria used in the trial are similar to what is used in Canadian centres to determine transplant ineligibility. It is likely that mostly criteria (3) applies (relapse after 2 or more chemotherapy regimens), as that

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td></td><td></td><td>would be the most common criteria used to determine this.

It is considered reasonable, from a clinical perspective, to generalize the trial results to the subgroup of ASCT ineligible patients, who will never be eligible for salvage chemotherapy and ASCT, after failure of one line of multiagent chemotherapy. A second-line multiagent chemotherapy regimen is often not feasible or desirable for these patients.</td></tr>
<tr><td></td><td>Stage of disease</td><td>Patients included in the trial had R/R classical HL. The trial did not limit eligibility by stage of disease; the proportions of patients entered into the trial by stage at diagnosis were as follows:

<table><tr><th>Ann Arbor stage at diagnosis</th><th>n (%)</th></tr><tr><td>I</td><td>3 (5)</td></tr><tr><td>II</td><td>21 (35)</td></tr><tr><td>III</td><td>16 (27)</td></tr><tr><td>IV</td><td>18 (30)</td></tr><tr><td>Other</td><td>2 (3)</td></tr></table>
No subgroup analyses (for the primary outcome) were conducted by stage of disease at diagnosis.</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>One would expect to see similar stage breakdown in Canadian patients, and as such results are generalizable to our population.</td></tr>
<tr><td></td><td>Subtypes of HL</td><td>Patients included in the trial had classical HL.</td><td>Are the results of the treatment generalizable to an alternative subtypes of HL (e.g., nodular lymphocyte predominant HL)?</td><td>The results are generalizable to all subtypes of classical HL, but would not be generalizable to nodular lymphocyte predominant HL as it is not CD30+ and such patients were not included in any of the brentuximab vedotin</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td></td><td></td><td>studies.</td></tr>
<tr><td></td><td>Performance status</td><td>The trial limited eligibility to ECOG performance status of 0-1. The proportions of patients entered into the trial by performance status category were as follows:

<table><tr><th>ECOG Performance Status</th><th>n (%)</th></tr><tr><td>0</td><td>27 (45)</td></tr><tr><td>1</td><td>33 (55)</td></tr></table>
Subgroup analyses were conducted by performance status and were pre-specified; the results of these analyses were as follows:

<table><tr><th>ECOG PS</th><th>ORR (CR+PR) by IRF n/N (%; 95% CI)</th></tr><tr><td>0</td><td>14/27 (52; 32-71)</td></tr><tr><td>1</td><td>16/33 (48; 31-66)</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Performance status of Canadian patients would be expected to be the same as the patients enrolled in the phase IV trial (i.e. ECOG PS 0-1).</td></tr>
<tr><td></td><td>Age</td><td>The trial limited eligibility to adult patients (≥18 years of age); the median age of patients in the trial was 32 years (range, 18-75). There were five patients (8%) who were aged ≥ 65 years.

No subgroup analyses were conducted by age.</td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>The age eligibility was restricted to adult patients 18 or older, however brentuximab vedotin has been successfully tested in previous landmark trials in ages 12 and above, thus it is reasonable to conclude that the results would apply similarly to a younger age population if applicable in specific clinical settings and provinces where patients aged 15 and above may be considered adults.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td>The trial limited eligibility to patients with adequate hematological, hepatic and renal organ function.</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of</td><td>Safety in patients with significant liver and renal dysfunction has not yet been established; most</td></tr>
</table>

Domain	Factor	Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]	Generalizability Question	CGP Assessment of Generalizability
			the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	patients who proceed to ASCT would not have significant organ dysfunction.
	Ethnicity or demographics	70% (n=42) of trial patients were white, and 30% (n=18) were Asian.	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	There is no reason to believe that the results would be different in the Canadian population of patients with HL who are ineligible for transplant.
Intervention	Treatment intent	The intent of treatment in the trial was curative and palliative.	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	The results would be generalizable to both palliative and curative treatment intents, although most patients when starting off treatment as transplant ineligible would be considered as being treated with palliative intent. However, there are a small proportion of long-term survivors on brentuximab vedotin for R/R disease post-ASCT who could be considered cured.
	Line of therapy	The trial limited eligibility to patients who had received ≥ 1 prior systemic chemotherapy regimen(s). The proportions of patients entered into the trial by prior therapies were as follows: No. prior | n (%)	Are the results of the trial generalizable to other lines of therapy?	It is common practice in Canada to consider a patient transplant ineligible after failure of 2 or more lines of prior systemic therapy, if previously transplant eligible. It is likely in clinical practice, patients would have had up to at maximum

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>therapies</td><td></td></tr>
<tr><td>1</td><td>11 (18)</td></tr>
<tr><td>>1</td><td>49 (82)</td></tr>
</table>

Subgroup analyses were conducted by number of prior therapies and were pre-specified; the results of these analyses were as follows:
<table>
<tr><th>No. prior therapies</th><th>ORR (CR+PR) by IRF n/N (%; 95% CI)</th></tr>
<tr><td>1</td><td>5/11 (45; 17-77)</td></tr>
<tr><td>>1</td><td>25/49 (51; 36-66)</td></tr>
</table>
</td><td></td><td>3-4 prior lines of therapy, as not many other options are available. It is unclear how that would impact the outcomes of transplant. Though if chemosensitivity is demonstrated with brentuximab vedotin, patients would be expected to derive benefit from transplant if felt appropriate. Although the results could be generalized to those with 1 prior therapy (n = 11 out of 60 patients), it would not be common practice in Canada to consider such patients transplant ineligible unless age or comorbidities were the reasons for transplant ineligibility. It is considered reasonable from a clinical perspective, that for older patients, who are not eligible for salvage chemotherapy and ASCT, brentuximab vedotin would be a reasonable treatment choice after failure of 1 line of multi-agent chemotherapy. It is difficult to know if the outcome of brentuximab vedotin would be different for those having received just one line of therapy vs. 2 or more, but the subgroup analysis presented here would suggest not, at least in this high-risk HL population.</td></tr>
<tr><td></td><td>Administration of intervention</td><td>Brentuximab vedotin was administered at a dose of 1.8 mg/kg IV once every 3 weeks for up to 16 cycles or until PD or</td><td>Is the intervention administered differently (e.g., dose or schedule) in clinical practice</td><td>Brentuximab vedotin is given in the trial at 1.8 mg/kg (and capped at 100kg). This reflects standard dose and</td></tr>
</table>

Domain	Factor	Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]	Generalizability Question	CGP Assessment of Generalizability
		unacceptable toxicity. The actual dose received by patients was determined by individual patient weight but was capped at 100 kg.	than in the trial?	schedule as used in Canada.
Comparator	Standard of care	Was the comparator in the trial a standard of care in Canada?	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	The phase IV trial was a single group study with no comparator. In the Canadian context, single-agent (or combination therapy) may be used in patients with HL after failure of at least two multiagent chemotherapy regimens who are not ASCT candidates. The results from this phase IV study compares favourably to currently available therapies, such as single agent gemcitabine. Although other multiagent regimens are tried, there is no evidence to support that they are better or have different outcomes than single-agent gemcitabine, as they all have poor outcomes in this setting. In the economic model the comparator data are based on the efficacy outcomes (PFS and response rates) of the last prior therapy received by patients before enrolment into the study. In the absence of comparative data this is an appropriate approximation. Primary therapies in this setting are fairly standardized.
Outcomes	Appropriateness of primary and secondary outcomes	The primary outcome of the trial was ORR by IRF. The secondary outcomes were DOR, PFS, CR rate, duration of CR, OS, and percentage of patients proceeding to SCT after	Were the primary and secondary outcomes appropriate for the trial design?	In this young patient population, where being transplant ineligible essentially means non-curable, any treatment options that lead to a clinical response are

Domain	Factor	Evidence from the phase IV C25007 trial by Walewski et al, 2018[1]	Generalizability Question	CGP Assessment of Generalizability
		brentuximab vedotin.		meaningful. There are no data to prove ORR is a surrogate for OS, however, it could be inferred that it might be, especially in patients who based on their ORR become transplant eligible and can go on to receive a SCT. A transplant is considered curative, and as such, it could be inferred from transplant data in HL that ORR would be an important step towards prolonged survival in this population. The safety profile is very favourable.
Notes: ASCT - autologous stem cell transplant; CR - complete response; DOR - duration of response; ECOG - Eastern Cooperative Oncology Group; HL - Hodgkin lymphoma; IRF - independent review facility; ORR - overall response rate; OS - overall survival; PD - progressive disease; PFS - progression-free survival; R/R - relapsed/refractory; SCT- stem cell transplant.				

1.2.4 Interpretation

Burden of Illness and Need

Hodgkin lymphoma (HL) is an uncommon but distinct lymphoma subtype that typically presents in young adults but that can also be seen in children, adolescents, and in patients over the age of 60 years. HL accounts for approximately 8-10% of all diagnoses of lymphoma. The median age at diagnosis in most reported series is 35-40 years and approximately 15% 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. Despite the excellent complete remission rates with current doxorubicin, vinblastine, bleomycin, dacarbazine (ABVD) chemotherapy (>95% for localized and >80% for advanced stage disease), relapse is experienced by up to 10-15% of patients with early stage disease and up to 30% of those with advanced disease. For patients who have relapsed or who have refractory disease, the best chances of cure are with autologous stem cell transplantation (ASCT), however, only patients who are chemosensitive will be eligible. Up to 20-30% of patients with HL are not eligible for ASCT because they fail more than 2 lines of multi-agent chemotherapy. A minority of patients (<5%) is not eligible for ASCT because of age or comorbidities. At that point, management is mostly aimed at palliation and symptom control with chemotherapy or radiotherapy. Given the young age of most of these patients, brentuximab vedotin adds to the armamentarium of palliative treatment/management strategies in young patients who are otherwise deemed incurable. Practice patterns of what is required for transplant eligibility can be centre specific, but if chemosensitivity is a criteria, response to brentuximab may convert some transplant ineligible patients to transplant eligibility.

Brentuximab Vedotin is an anti-CD30 antibody-drug conjugate that is now approved for the treatment of patients with HL after failure of ASCT or at least two prior multi-agent chemotherapy regimens.[9] In a large phase II trial in heavily pretreated patients (median number of prior regimens 3.5, range 1-11), the response rate to brentuximab vedotin at a dose of 1.8 mg/kg every 3 weeks was 75% and complete response rate 34%; median progression-free survival was 6 months and median duration of complete response 20.5 months.[10] In most provinces, brentuximab vedotin has become the treatment of choice as initial therapy for relapse after ASCT because of its favourable toxicity profile (grade 3 neutropenia 14%, grade 4 6%; other grade 3-4 events $\leq$ 2%).

Effectiveness

Overall Response Rate

In a phase IV, multicentre study, brentuximab vedotin was given to 60 patients with a history of ≥1 prior systemic chemotherapy regimen, considered unsuitable for ASCT/multi-agent chemotherapy. The pCODR requested reimbursement criteria do not exactly align with the patient population in the phase IV C25007 trial. The pCODR requested reimbursement criteria are for the broader ASCT ineligible patient population, addressing two subgroups: 1) patients who are ASCT ineligible due to lack of response to salvage therapy prior to ASCT but have the potential to become ASCT eligible if they respond to further treatment and 2) patients who are ASCT ineligible due to fragility, old age or comorbidities; these patient will never receive a transplant. While the number of patients in the C25007 trial who were ASCT ineligible due to fragility, old age, or comorbidities could not be confirmed by the submitter, it has been suggested by the pCODR Clinical Guidance Panel (CGP) that based on the small number of patients (n = 5 out of 60) over the age of 65 in the trial, it is likely that most patients in the trial belong to the first subgroup, i.e. those who were transplant ineligible due to chemotherapy resistance or high-risk refractory disease to first line chemotherapy. Furthermore, while the pCODR requested reimbursement criteria specify that patients should have received at last two multi-agent chemotherapy regimens, the C25007 trial included patients who had failed ≥1 multi-agent chemotherapy regimen(s). The percentage of patients in the trial who had failed ≥ 2 multi-agent regimens was 50% (n=30). It is difficult to know if the outcome of brentuximab vedotin would be different for those having received just one line of therapy vs. 2 or more. Efficacy estimates were not estimated for the patient subgroup who failed ≥ 2 multi-agent chemotherapy regimens, but are available for trial patients who received > 1 prior therapies (n=49; 82%) and 1 prior therapy (n=11; 18%). In these patient subgroups, the ORR by IRF estimates (51%; n=25/49 for the former and 45%; n =5/11 for the letter) were similar to the overall ITT estimate (50%; n=30/60).

Given the small numbers and the data submitted, the data on all 60 patients is considered for this review.

The patient characteristics were as expected for a relapsed/refractory Hodgkin lymphoma population, with only 5 patients (8%) being 65 or older. The median number of prior therapies was 2 (1-7) and most patients (67%) had progressive disease as the best response to their last prior therapy.

The overall response rate (ORR) by independent review was the primary endpoint, and the ORR was 50% with a CR rate of 12%. The investigator-assess ORR was similar, with an ORR of 49% and CR rate of 15%. The median duration of response was 4.6 months and the median duration of CR was 6.1 months per independent review and 7.6 months

for investigator assessed. Median time to response was 6 weeks and to best response 11.2 weeks.

Anti-tumour activity was similar across subgroups, as much as can be concluded from these small numbers of patients.

Progression Free Survival

The median follow-up provided is short, but the median PFS has been reached at 4.8 months. No breakdown by subgroup was provided.

Overall Survival

With a median follow-up of 16.6 months, 12 deaths were reported, for an estimated 1 year OS rate of 86% and a median OS not reached, which is not unexpected in this population, with early follow-up.

Other Secondary Endpoints

A very meaningful endpoint in this disease and population is proportion of patients who were able to receive stem cell transplantation as this would mean a potentially curable treatment option for young patients who were otherwise felt to be palliative. Of the 60 patients who were not eligible for SCT at the start, 28 went on to receive ASCT after a median of 7 cycles of brentuximab vedotin. However, only 10 discontinued brentuximab vedotin to immediately go on to SCT. The other 18 discontinued due to other reasons, mostly progression (15 patients), and received other treatments that allowed them to go on to SCT. No further details were publicly reported and the submitter was not able to add information. However, this likely reflects individual centre practices as to the chemosensitivity criteria they use to consider someone transplant eligible. Most centres likely have the PR or 'close to PR' criteria for chemosensitivity (some patients may be transplanted based on 'close to stable disease' criteria, but that is case-by-case specific). This also likely applies more to the patients who had brentuximab vedotin after 1 line of therapy, where further treatment was given with brentuximab vedotin progression. Overall, given common Canadian practice of considering a patient transplant eligible if chemosensitivity is demonstrated through a least a partial response to therapy, the proportion of patients who would be able to have a transplant based on this data is close to 50% (i.e., 28 out of 60 patients went on to receive ASCT), and thus in line with what was observed [i.e, ORR by IRF in the ITT patient population was 50% (n=30; 95% CI, 37-63%)]. While it is estimated that 50% of patients relapse after transplant, those who do not relapse after around 5 years are considered potentially cured.

While there was no control arm in this study, and recognizing the limitations of cross-study comparisons, the ORR rate reported by this phase IV trial of brentuximab vedotin was comparable or even superior to publications of other salvage regimens used after failing 2 prior chemotherapy regimens.[11-14] A commonly used 2nd salvage regimen is miniBEAM, which has a much more significant toxicity profile, leading to toxicity complications which could preclude further treatments, and impair ability to collect stem cells. It is not really possible to determine the effect of brentuximab vedotin on PFS and OS, as the heterogeneity of this series was much higher than other published series with other regimens, thus there is a lack of a true direct comparator. Given the

small number of patients with HL, it is unrealistic to expect a randomized clinical trial to be undertaken in this population.

Health-related Quality of Life

This was not assessed in this study.

Safety

Brentuximab vedotin is associated with a low rate of serious (grade 3 or 4) toxicities (in 18% of patients) and the toxicities of this study were very similar to those previously reported when used post-ASCT. The most common grade 3 and above adverse events were anemia, neutropenia (3 patients each), back pain and pyrexia (2 patients each). Three patients (5%) discontinued to treatment-related adverse events of peripheral neuropathy, polyneuropathy and septic shock (1 patient each). One patient died due to septic shock, which was considered treatment related. 35% of patients (21 patients) experienced peripheral neuropathy, but only 3% was grade 3. 57% of patients experienced resolution of the neuropathy after end of treatment.

PAG Clinical Scenario Question

Several questions have been raised regarding the applicability of these results to certain clinical scenarios:

1) PAG is seeking guidance on the use of brentuximab vedotin in third line as a bridge to transplant in patients who would potentially be eligible for ASCT and who have not had adequate response to two lines of therapy.

   Given the young age of most of these patients, brentuximab vedotin adds to the armamentarium of palliative treatment/management strategies in young patients who are otherwise deemed incurable. Presently, in most Canadian practices, patients failing to respond to salvage chemotherapy (generally partial response or better) would be considered ineligible for stem cell transplant due to lack of demonstration of chemosensitive disease. Practice patterns of what is required for transplant eligibility can be centre specific, but if chemosensitivity is a criteria of such a centre, response to brentuximab may convert some transplant ineligible patients to transplant eligibility and this would be appropriate. This phase IV trial did evaluate a population as described above and demonstrates that in centres that do require this chemosensitivity, generally accepted as some response (mostly partial response or better), it can be done as occurred in this study.

2) If a patient were to be deemed transplant ineligible after two lines of therapy because of refractory disease but then responded to third line brentuximab vedotin, would the patient then be eligible for transplant (provided age and comorbidities are good)?
   Yes, they would as described above.

3) PAG identified that the 30 minute infusion is an enabler to implementation. However, resources may be required to monitor and treat infusion-related reactions and adverse events (e.g. peripheral neuropathy).

Any other treatments options also have side effects, comparing them, we would not expect extra visits or costs, and likely less.

4) PAG is seeking guidance on the appropriate sequencing of brentuximab vedotin with immunotherapies (i.e., nivolumab, pembrolizumab) in patients with classical HL. How would you sequence brentuximab vedotin with pembrolizumab or nivolumab?

   The data[15,16] mostly supports patients first receiving brentuximab vedotin, and then being eligible for immunotherapy.

1.3 Conclusion:

The Clinical Guidance Panel concluded that there *is* a net clinical benefit to brentuximab vedotin, compared with chemotherapy, for the treatment of HL patients after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates. From the results of the phase IV trial presented by the submitter, although limited by the non-comparative design and the misalignment of the trial population with the reimbursement criteria, it appears that the response rates and PFS are acceptable evidence of efficacy, compared to the paucity of other agents or regimens available, such as single agent gemcitabine, miniBEAM or other chemotherapy options, which have comparable or less efficacy, with significantly larger toxicity profiles and resource use for inpatient admissions, transfusion, and growth factor support. From larger phase II and III trials post-ASCT, we know the drug has a high degree of efficacy with durable responses and acceptable and predictable toxicity in HL patients. Brentuximab vedotin represents an important addition to the limited therapy options available for these young patients who are considered incurable at this disease time point. More effective and less toxic therapies which lead to a clinical response and potentially improved survival rates are urgently required in this population. A very meaningful endpoint in the provided phase IV study was the proportion of patients who were able to receive stem cell transplantation (n = 28 out of 60). It remains unclear whether patients, previously ineligible to ASCT, but who end-up proceeding to ASCT after treatment with brentuximab vedotin, experience long term survival benefit. It is considered reasonable from a clinical perspective, that for older patients, who are not eligible for salvage chemotherapy and ASCT, brentuximab vedotin would be a reasonable treatment choice after failure of 1 line of multi-agent chemotherapy.

In making this conclusion, the Clinical Guidance Panel considered that:

- Without direct comparison to other available agents or combinations, the incremental benefit to patients with HL is difficult to measure.
- Brentuximab vedotin represents an important addition to the limited therapy options available for these young patients who are considered incurable at this disease timepoint.
- Responsiveness to treatment, converting a patient from transplant ineligibility to eligible for ASCT, which is a curative measure in this young patient population, is a meaningful endpoint. Whether these patients benefit from long-term overall survival benefit remains to be determined.
- Uncertainty remains as to the ideal time to consider stopping brentuximab if there is a response and proceeding on to ASCT, and whether to finish off the course of 16 doses post-ASCT.
- There are no known predictive markers for response to brentuximab

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Classical Hodgkin lymphoma (HL) is an uncommon but distinct lymphoma subtype that typically presents in young adults, but is seen in both children and adolescents, and those over the age of 60 years. It is characterized by the presence of CD30+ Reid-Sternberg cells. HL accounts for approximately 8-10% of all diagnoses of lymphoma. The median age at diagnosis in most reported series is 35-40 years and approximately 15% are older than 60 years. There are approximately 900 new cases of Hodgkin lymphoma in Canada each year and approximately 160 Canadians will die annually from this disease.[17]

2.2 Accepted Clinical Practice

Approximately two thirds of patients with HL will present with localized disease (stage I and II according to the Ann Arbor classification), and are generally treated with combination chemotherapy and involved field radiation (IFRT). Those who present with advanced stage disease (stage III and IV) and some with stage I and II who present with bulky masses and constitutional ("B") symptoms are usually managed with combination chemotherapy alone. In Canada, the standard regimen is ABVD with or without radiotherapy, depending on risk factors such a stage and bulk of disease. For patients with high risk disease as classified by the Hasenclever IPS score, escBEACOPP is occasionally given. Despite the excellent complete remission rates with current doxorubicin, vinblastine, bleomycin, dacarbazine (ABVD) chemotherapy (>95% for localized and >80% for advanced stage disease), relapse is experienced by up to 10-15% of patients with early and 30% of those with advanced disease.[18,19]

The best chance of cure in patients with relapsed or refractory disease remains with autologous stem cell transplantation (ASCT) however 50% of relapsed patients and 60-70% of refractory patients do still develop progression post-ASCT.[20] Furthermore, ASCT is felt to mostly be effective in patients who have chemosensitive disease. Unfortunately, up to 40% of relapsed/refractory patients are not chemosensitive, thus become transplant-ineligible and do not have good treatment options. Furthermore, ASCT is not considered appropriate treatment for older patients (those older than 70 years), especially those with significant medical co-morbidities, or for those of all ages with progressive disease following salvage chemotherapy. For these latter patients, treatment is palliative and directed at controlling the growth of lymphoma and its symptoms.[21]

Treatment of patients who are not eligible for ASCT due to age and comorbidities has generally been palliative in intent, for relief of symptoms and employs single agent chemotherapy. The most common drugs used are vinblastine, gemcitabine or vinorelbine, which are given every other week (vinblastine) or weekly intravenously for 3 weeks out of 4 each month, unless hematologic toxicity mandates a shorter cycle of 2 doses every 3 weeks (vinorelbine, gemcitabine).[22,23] Combination regimens such as COPP (cyclophosphamide, vincristine, procarbazine, prednisone) can be used if patients have good performance status and bone marrow reserve. Involved field radiation is beneficial for those with localized relapse outside of a previous radiation field, but there are few long-term survivors. Long term disease control is achieved in 25-30% of patients, and patients with B symptoms, response duration to initial therapy of less than 12 months, advanced stage at relapse (III/IV), and poor performance status are predictors of worse outcomes with salvage radiotherapy.[24,25]

In patients deemed transplant ineligible due to lack of chemosensitivity, (generally accepted as some response, mostly partial response or better), treating physicians may try a second-line salvage in an attempt to still demonstrate chemosensitivity, which may convert a patient back

to transplant eligibility. There have been publications on delivering second-line salvage in attempts to still demonstrate chemosensitivity, and it has been shown to be of limited success. An older series in patients with DHAP failure, 8/11 responded to miniBEAM and were able to proceed to ASCT.[26] An updated series from Princess Margaret Cancer Centre in Toronto reviewed the experience of second salvage with miniBEAM in patients with an inadequate response to GDP, defined as PD, residual functional imaging abnormalities or presence of disease >5cm. Of 19 patients, 32% had a response, thus allowing them to proceed to ASCT. The 5yr PFS after ASCT was disappointing at 11%.[13] There is not much data examining the outcomes with novel agent containing regimens in patients not eligible for ASCT due to an inadequate response to 1st salvage. A retrospective study by Sasse et al (2013) of 14 relapsed/refractory HL patients who had not received high-dose chemotherapy (HDCT) and ASCT due to reasons including refractory disease and comorbidity reported an ORR of 71% (CR rate of 36%) following treatment with brentuximab vedotin. A recent phase 1/2 study examined the combination of bendamustine and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma with a median of 3.5 prior lines of therapy. In the phase 2 component, 16 out of 37 patients had not undergone ASCT, and 12/16 (75%) had a response (PR or CR).[27] Second salvage regimens such as miniBEAM are very toxic, requiring multiday inpatient administration, high need for transfusion support while recovering counts, granulocyte-colony stimulating factor (GCSF) support and high risk of febrile neutropenia and serious infections and risk of inability to then collect stem cells due to marrow toxicity. Comparably, brentuximab vedotin has a much more favourable toxicity and resource utilization profile. More effective and less toxic therapies which lead to a clinical response and improve survival rates are urgently required in this population.

Brentuximab vedotin could potentially be an appropriate treatment option for patients who have relapsed after primary chemotherapy and who are not considered appropriate candidates for ASCT on the basis of age or comorbidities. Such patients were not included in the phase II study reported by Younes et al.[10] In addition the submitter could not confirm if these patients were included in the phase IV trial (C25007), which provides the evidence for this review. However, it would be quite appropriate for such patients to be treated with brentuximab vedotin because of its favorable toxicity profile and significant activity in more heavily pre-treated, younger patients.

2.3 Evidence-Based Considerations for a Funding Population

There are approximately 900 new cases of HL in Canada per year, and we would anticipate about 15-20% to relapse post-first line therapy, thus about 180 patients. The response rate to 1st salvage, which is mostly GDP, is 70-80%. Thus up to 30% of patients with relapse HL will fail 2 lines of multi-agent therapy, thus fitting the criteria for this submission, which could be up to 54 patients per year. These patients would fit the criteria of half of the patients in this phase IV trial, which provides the evidence for this review. It is anticipated that those responding to brentuximab vedotin would proceed on to ASCT, as most patients would be of an age where they would be eligible. The median number of cycles of brentuximab vedotin prior to transplant was 7, although in our practice, we would generally plan for 4 cycles, and if there was a response, go on to ASCT. Very few patients in the phase IV study set (5 over the age of 65) and in our practice, where we use a cut-off age of 70 for ASCT, would get this treatment and not go on to transplant. For this older population, as 2nd line multi-agent chemo regimen is not often feasible or desirable, however.

Brentuximab vedotin targets CD30, a surface membrane protein expressed on the majority of HL Reid-Sternberg cells at diagnosis and at relapse. It would be expected that patients who are considered candidates for brentuximab vedotin would have pathological confirmation of the presence of CD30 on initial biopsy or one taken at any time after disease recurrence.

2.4 Other Patient Populations in Whom the Drug May Be Used

There is no evidence for the use of brentuximab vedotin in nodular LP Hodgkin lymphoma, which is not generally a CD30+ disease. Studies of brentuximab vedotin in other lymphoma subtypes such as CD30 positive diffuse large B cell and peripheral T cell lymphoma are underway and will likely be the subject of other submissions. The benefit of re-treatment with brentuximab vedotin if previous exposure or continuation post-ASCT as maintenance to complete a 16 week treatment course is the subject of ongoing investigation.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient group, Lymphoma Canada (LC), provided input from patients with Hodgkin Lymphoma (HL). Two surveys regarding HL were conducted by LC and sent to both patients and caregivers, with responses collected between June 5, 2017 and June 30, 2017. LC also sent an additional survey to patients who had direct experience with brentuximab-vedotin; responses were collected between July 26, 2017 and August 10, 2017. These surveys were conducted for a previous pCODR drug review conducted in 2017 for patients with relapsed/refractory HL treated with brentuximab vedotin. LC decided to use information from this previous pCODR submission as they believed that results of a more recent survey would not have differed significantly enough to warrant unnecessarily burdening patients with repeated questions for input. Patients and caregivers registered in the LC database were sent the surveys via links through email; links were also made available through social media platforms (LC Twitter, Facebook accounts, and other HL-dedicated social media pages and groups), through HL patient forums, and international lymphoma organization's own contacts. The surveys contained multiple choice, rating and open-ended questions.

A total of 112 respondents provided input through LC's three surveys, comprising 15 caregivers and 97 patients. Demographic information was not available from all respondents. However, of patients with available demographic information, 51% (40/78) resided within Canada (Table 1), 70% (52/74) were female, and 55% (41/74) were between 20 and 39 years of age (Table 2). Of the 97 patients included in this submission, 14 reported having experience with brentuximab vedotin. Thirteen of these patients provided their demographic information, and indicated that most were younger than 40 years of age (77%), and female (69%).

Table 1: Respondents by Country

Respondents, n=112	CAN	USA	UK	EU	Other	Skipped	Total
Patients WITH brentuximab vedotin experience	3	6	2	2	0	2	15
Patients WITHOUT brentuximab vedotin experience	37	5	10	6	7	17	82
Caregivers	5	2	4	1	0	3	15

Table 2: Gender and age of survey respondents

Respondents, n=112	Age Range (years)					Gender		
	< 20	20-39	40-59	≥ 60	Did not answer	Female	Male	Did not answer
Total Patients	3	41	21	9	23	42	22	23
Patients WITH brentuximab vedotin experience	1	9	3	0	2	9	4	2
Patients WITHOUT brentuximab vedotin experience	2	32	18	9	21	43	18	21
Caregivers	0	2	7	3	3	9	3	3

From a patient's perspective, fatigue or lack of energy and enlarged lymph nodes were the most commonly reported symptoms related to HL affecting quality of life. Specifically, fatigue was highlighted by LC as being a symptom greatly impacting patients. Respondents also indicated experiencing great emotional and mental distress due to their condition; patients

felt anxiety and worry negatively impacting their quality of life. In addition In terms of other aspects of life affected by their disease, the majority of respondents (61%, 51/83) 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 (93%) indicated having received at least one line of conventional chemotherapy; brentuximab vedotin (81%) 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). Respondents indicated that the following treatment-related factors significantly negatively impacted their quality of life: treatment-related fatigue, the ability to tolerate treatment, infusion reaction, infusion time, and number of clinic visits.

Of patients with experience with brentuximab vedotin (n=14), all experienced at least one side effect while receiving brentuximab vedotin. The most common side effects experienced were fatigue and peripheral neuropathy. Respondents indicated a strong willingness to tolerate significant side effects for a chance of remission or cure. Based on patient's responses, brentuximab vedotin did not seem to have a significant positive or negative impact on aspects of quality of life, such as work, family, friendships, intimate relations, activities or travel. Regardless, over half of respondents indicated that they experienced a positive impact on their health and well-being due to brentuximab vedotin.

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

Please see below for a summary of specific input from LC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Hodgkin Lymphoma

LC stated that the majority of patients (74%, 71/96) indicated having been diagnosed with HL when they were a teenager or young adult (between 13 and 39 years of age). LC asked patients to indicate aspects of HL that most commonly affected their quality of life at diagnosis; fatigue or lack of energy (72%), enlarged lymph nodes (67%), drenching night sweats (43%), itching (42%), and persistent cough (40%) were mentioned to be the most commonly reported aspects affecting quality of life by patients. LC also mentioned that other symptoms noted by respondents to negatively affect quality of life in greater than 10% of patients were unexplained weight loss, loss of appetite, trouble breathing, fever and chills and chest pain. Ongoing fatigue, for example constant, lasting fatigue or waves of fatigue, were also mentioned by LC as being reported by many respondents (63%, 49/78).

When asked about how HL impacted respondent's current quality of life, 48% of respondents (42/88) indicated anxiety and worry as being greatly impacted due to the disease. Overall, respondents highlighted symptoms related to mental and emotional distress as being symptoms that negatively impact their current quality of life due to HL (Table 3).

Table 3: Effect of HL on current quality of life of patients (Total responses = 88)		
Symptom or problem related to HL	# of respondents	% of respondents
Anxiety/worry	42	48%
Problems concentrating	32	37%
Loss of sexual desire	29	33%
Stress of diagnosis	25	29%
Difficulty sleeping	25	29%
Memory loss	25	29%
Depression	20	23%
None of these	10	11%

LC provided the following quotes by patients, which highlight how fatigue and lack of energy impacted aspects of patient's work and education, as well as the long lasting emotional toll of having HL:

- *"I experience more fatigue than I used to and although I'm able to work, I'm exhausted at the end of the day. Exercise is difficult to do on a weekday."* Female, 21-39, USA
- *"I immediately lost my job, as I work in an environment not safe for someone with a compromised immune system. I had to give up my study at uni, and both devastated me. I was very fit, but now if I try to exercise at the same level I become exhausted very easily. It's very hard."* Female, 21-39, Australia
- *"I almost feel like I suffer from ptsd from this experience. I went into remission for about a year and then had a recurrent. I'm always worried it might come back. If I smell alcohol swabs - like they use before taking blood or administering chemo - my mind goes right back to treatment days - and that's more than 25 years ago."* Female, 50-59, Canada

Respondents were asked by LC to indicate the aspects of their lives that had been negatively impacted by HL. Out of 83 respondents, the majority of individuals (61%, 51/83) indicated that HL negatively impacted their ability to work. Other aspects of life that were reported to be negatively impacted due to HL are included in Table 4. A small proportion of respondents (13%, 11/83) indicated they did not experience any of the negative impacts (listed in Table 4) due to their condition, which might indicate that a minority of patients experience very little side effects due to HL and can maintain relatively good quality of life.

Table 4: Effect of HL on day-to-day life of patients (Total responses = 83)		
Aspect of life NEGATIVELY impacted by HL	# of respondents	% of respondents
Ability to work	51	61%
Personal Image	39	47%
Family obligations	38	46%
Intimate relations	31	37%
Friendships	30	36%
Ability to attend school	13	16%
None of these	11	13%

3.1.2 Patients' Experiences with Current Therapy for Hodgkin Lymphoma

All 97 patients reported that they were either currently receiving treatment, or had received treatment in the past. Seventy-three patients provided responses as to what therapy they had received or were currently on: 93% (n=68) reported being treated with at least one line of conventional chemotherapy, 38% (n=28) reported receiving two or more lines of chemotherapy, and 16% (n=12) reported receiving at least three or more lines of therapy. Patients reported

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) as being the most common conventional therapy regimen received (81%); other chemotherapy regimens reported by patients can be found in Table 6. Other common therapies reported by patients included radiation (50%), autologous stem cell transplant (26%), and others (Table 5).

Table 5: Current or Previously Received Treatments by Patients	
Regimen	% (n=73)
Chemotherapy	
ABVD	81%
GDP	10%
BEACOPP	8%
MOPP/COPP	5%
Radiation	50%
Autologous stem cell transplant	26%
Surgery	10%
Allogenic stem cell transplant	4%
Nivolumab	1%
CAR-T therapy	1%
ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine GDP: gemcitabine, dexamethasone, cisplatin BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone MOPP/COPP: mechlorethamine/cyclophosphamide, vincristine, procarbazine, prednisone	

Fifty of the 76 patients (66%) indicated they were in remission following their most recent line of therapy; 30% (n=23) of patients reported being in remission for greater than five years, and 15% (n=11) reported previously having relapsed after one or more lines of therapy. LC asked patients to indicate on a scale from 1 to 10 (10 indicating 'strongly agree') how much they agree with the following statement, "My most recent therapy could manage my Hodgkin lymphoma symptoms." A large proportion of respondents (72%) provided a rating of greater than or equal to 7, indicating that many patients considered their most recent treatment to adequately manage most, if not all, of their HL symptoms.

However, many patients reported concerns related to the side effects experienced due to their previous treatments. The most commonly reported side effects included fatigue (95%), hair loss (91%), nausea or vomiting (88%), mouth sores (69%), and peripheral neuropathy (53%) (Table 6). The side effects reported to be most difficult to tolerate included nausea or vomiting (50%, 25/50), fatigue (46%, 23/50), and hair loss (22%, 11/50). LC indicated that patients also reported experiencing long-term treatment-related side effects lasting greater than two years, or having appeared more than two years after the end of their treatment; the more commonly reported symptoms included fatigue (65%, 43/66), "chemo-brain" (59%, 39/66), peripheral neuropathy (32%, 21/66), loss of menstrual periods (23%, 15/66), thyroid dysfunction (18%, 12/66), sterility (15%, 10/66) and lung damage (14%, 9/66).

Table 6: Side effects of current HL therapies (Total responses = 74)		
Side effect	# of respondents	% of respondents
Fatigue	70	95%
Hair loss	67	91%
Nausea/vomiting	65	88%
Mouth sores	51	69%
Peripheral neuropathy	39	53%

Table 6: Side effects of current HL therapies (Total responses = 74)		
Side effect	# of respondents	% of respondents
Low platelets	36	49%
Anemia and/or neutropenia	34	46%
Diarrhea	33	45%
Skin rashes/severe itching	29	39%
Loss of menstrual periods	26	35%
Breathing difficulties	23	31%
Infections	23	31%
Back pain	22	30%
Cough	20	27%
Irregular heartbeat	15	20%
Bowel obstruction	12	16%
Viral reactivation (e.g. shingles)	9	12%

LC asked patients to rate how different aspects of their treatment experience impacted their quality of life, on a scale from 1 to 10 (10 indicating the greatest impact on quality of life, while it was not reported what 1 indicated). Treatment-related fatigue, the ability to tolerate treatment, infusion reaction, infusion time, and number of clinic visits were rated by a majority of patients to be significantly negatively impactful on their quality of life. Treatment-related fatigue was given a score of 7 to 10 by 80% of patients with a weighted average of 7.5 (Table 7).

Table 7: Negative impact of specific aspects of treatment (Total responses = 74)				
Aspect of treatment	Weighted average	Rating = 7-10 (significant impact), n (%)	Rating = Not applicable	Total number of responses
Treatment-related fatigue	7.5	59 (80%)	0 (0%)	74
Ability to tolerate treatment	6.6	44 (59%)	(0%)	74
Infusion reaction	6.3	39 (55%)	6 (9%)	71
Infusion time	6.3	40 (54%)	5 (7%)	74
Number of clinic visits	6.2	43 (59%)	0 (0%)	73
Number of infections	4.3	16 (22%)	7 (10%)	73
Frequency of infections	4.0	11 (15%)	8 (11%)	74

LC also asked patients to rate how different aspects of previous treatments impacted their daily living on a scale from 1 to 10 (10 indicating a significant impact on patients' daily living, while it was not reported what 1 indicated). The ability to work or travel, and engage in activities, intimate relations, family obligations and friendships were all aspects of daily living that greater than 50% of patients reported being significantly impacted (each of these aspects receiving a score of 7 to 10 by patients). It should be noted that while nearly two thirds of patients indicated that they were not currently in school, 72% of patients that were in school

rated their ability to attend school being significantly impacted (score of 7 to 10); the weighted average of ratings among patients who indicated their education was impacted was 8.86, indicating a significant negative impact, similar to patients ability to attend work or travel (Table 8).

Table 8: Negative impact of previous treatments on quality of life (Total responses = 74)

Aspect of life	Weighted average	Rating = 7-10 (significant impact), n (%)	Rating = Not applicable	Total number of responses
Ability to attend school	8.86	18 (24%)	49 (66%)	74
Ability to work	7.89	51 (69%)	10 (14%)	74
Travel	7.47	55 (75%)	5 (7%)	73
Activities	7.35	56 (76%)	1 (1%)	74
Intimate relations	7.08	48 (68%)	4 (5%)	71
Family obligations	6.14	41 (55%)	2 (3%)	74
Friendships	5.76	40 (54%)	0 (0%)	74

LC provided quotes from three female patients; the following quotes convey the challenges they faced with previously received therapies and how it impacted different aspects of their lives.

- *"The chemotherapy I received before and with my bone marrow transplant put me into premature menopause (i'm in my 20s) and that has negatively affected my intimate relations."* Female, 21-39, USA
- *"My short term memory from chemo is very bad on some days, which affects me at work and home. I'm constantly tired, I work full time and have 4 children. One of whom I was pregnant with when diagnosed."* Female, 21-39, UK
- *"I was unable to finish the first semester of nursing school at the time. I was unable to help coach basketball because of low self esteem from hair loss and fatigue. Did not really want to go places and visit friends because of hair loss."* Female, under 20, USA

LC inquired as to how patients were accessing their treatment. The majority (79%, n=59/74) of patients reported being able to access their treatment in their own community. Fifteen patients indicated being unable to access their treatment in their own community; of these, 73% reported living in a community without a cancer centre, 20% reported their treatment being unavailable in their province, and 7% indicated their treatment being unavailable in their country. An absence from work or school was the most commonly reported aspect of life that patients reported experiencing as a financial impact due to their treatment (69%, n=58/70). Two patients commented on the financial burden and the impact of treatments on their occupations:

- *"Medications cost me over $80,000 over the 7 years to help deal with side-effects of chemo. I am now on long-term disability, because I cannot work."* Female, 20-39, Canada
- *"Absence from work caused me to get into debt, first and second time."* Female, 50-59, UK

Parking, cost of medications and travel to and from appointments were other financial burdens also reported by 40%, 30% and 29% of patients, respectively.

3.1.3 Impact of Hodgkin Lymphoma and Current Therapy on Caregivers

LC asked caregivers to rate on a scale from 1 to 10 (10 indicating 'significant negative effect', while it was not reported what 1 indicated) how caring for someone with HL had negatively impacted their day-to-day activities and quality of life; all caregivers provided a response to this question. The majority of caregivers indicated that their ability to concentrate, contribute financially to their household, travel, attend to household chores, and volunteer were significantly impacted by having to care for someone with HL (Table 9).

Table 9: Effects of caregiving on quality of life (Total responses = 15)

Daily activity	# of respondents who rated ≥ 7
Ability to concentrate	10 (67%)
Contribute financially to household	9 (60%)
Travel	9 (60%)
Attend to household chores	8 (53%)
Volunteer	8 (53%)
Spend time with family and friends	7 (47%)
Exercise	5 (33%)
Fulfill family obligations	4 (27%)

The quotes below were provided by LC from caregivers. The quotes provide give an indication of how caring for someone with HL can impact social and family lives, and the toll the condition can have on both the patient and their caregiver.

- *"My 20 year old son was diagnosed with hl. This last year has been a nightmare. Family, friends don't call or even know what to say. We are left alone, while everyone's life continues."* Female, 40-59, USA
- *"I was pregnant with twins while caring for my man and we did what we had to do and we stuck together. It was hard to be away from our older kids when he was receiving treatments but nurses in oncology dept. are angels."* Female, over 60, Canada
- *"I've become a caregiver. Scheduling my daughters appointments, managing her medicine. Taken over her care. She was in between jobs at diagnosis and her prospects for a new job has significantly decreased. We support her financially now."* Female, over 60, Canada

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for & Experiences with Brentuximab vedotin

A total of 14 patients reported having experience with brentuximab vedotin, 13 of whom provided their demographic information: 77% (n=10) were younger than 40 years of age and 69% (n=9) were female. Six respondents (43%) received brentuximab vedotin as consolidation/maintenance therapy following autologous-stem cell transplant (ASCT), seven (50%) received brentuximab vedotin alone or in combination with other drugs, and one (7%) received it as consolidation therapy prior to an ASCT. All 14 patients indicated receiving a minimum of two prior lines of systemic therapy; eight patients (57%) indicated receiving four or more lines of therapy. A list of previous therapies is included in Table 10. At the time of completing LC's survey, three patients (21%) indicated having completed the full course of treatment with brentuximab vedotin, three (21%) were still undergoing treatment, one (7%)

stopped treatment early due to intolerable side effects, and seven patients (50%) did not complete the full course of treatment as their HL had not responded to brentuximab vedotin.

Table 10: Previous Therapies Received by Patients	
Therapy	n (%)
ABVD	11 (79)
GDP	5 (36)
Nivolumab	4 (29)
BEACOPP	2 (14)
GVD	2 (14)
ESHAP	2 (14)
Bendamustine	2 (14)
COPP	1 (7)
DHAP	1 (7)
Stanford V	1 (7)
ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; GDP: gemcitabine, dexamethasone, cisplatin; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GVD: gemcitabine, vinorelbine, pegylated liposomal doxorubicin; ESHAP: etoposide, methyl-prednisone, cytosine arabinoside, cisplatin; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; DHAP: dexamethasone, cytarabine, cisplatin; Stanford V: doxorubicin, vinblastine, chlormethine, vincristine, bleomycin, etoposide, prednisone	

All respondents indicated having experienced one or more side effects while receiving brentuximab vedotin treatment. Fatigue and peripheral neuropathy were the most commonly reported side effects by respondents (Table 11). LC also mentioned that peripheral neuropathy was reported as a significant concern for 29% (n=4/14) of respondents. When asked to rate how willing they were to tolerate side effects of brentuximab vedotin on a scale of 1 (indicating not willing to tolerate side effects) to 10 (indicating they "will tolerate significant side effects"), 86% of respondents (n=12/14) provided a rating of seven or greater; overall, most patients indicated a high willingness to tolerate significant side effects if they had a chance of remission or cure.

Table 11: Side Effects Experienced with Brentuximab Vedotin (Total responses = 14)	
Side effect	Number of responses
Fatigue	10 (71%)
Peripheral neuropathy	8 (57%)
Nausea/vomiting	5 (36%)
Diarrhea	4 (29%)
Muscle or joint pain	4 (29%)
Itching	3 (21%)
Constipation	3 (21%)
Low blood counts	2 (14%)
Rash	2 (14%)
Cough	2 (14%)
Headache	2 (14%)
Other	2 (14%)
Fever	1 (7%)
Upper respiratory infection	1 (7%)
Infusion reactions	1 (7%)

Based on respondent's experiences with brentuximab vedotin, LC asked patients whether they would take the drug again if their doctor recommended it as their best choice. The majority of respondents (79%, n=11/14) indicated that they would take brentuximab vedotin again if it was recommended by their physician as their best choice in treatment.

Patients were asked to rate how brentuximab vedotin treatment affected different aspects of their quality of life on a scale from 1 (indicating a significant negative impact) to 10 (indicating a significant positive impact). While the majority of respondents indicated 'not applicable' to brentuximab vedotin affecting aspects of their schooling, a weighted average of 9.15 was recorded for the three respondents who were in school at the time of completing LC's survey. Other recorded aspects of life were given weighted averages between 5.79 and 6.57, indicating that brentuximab vedotin had a minimal impact on the quality of these aspects of life (Table 12).

Table 12: Impact of Brentuximab Vedotin on aspects of life (Total responses = 14)

Aspect of life	Negative impact (rating = 1-4)	Positive impact (rating = 7-10)	Minimal impact (rating = 5-6)	Not applicable	Total responses	Weighted average
Work	4 (29%)	3 (21%)	4 (29%)	3 (21%)	14	6.29
School	1 (7%)	2 (14%)	0 (0%)	10 (79%)	13	9.15
Family	1 (7%)	4 (29%)	8 (57%)	1 (7%)	14	6.21
Friendships	1 (7%)	5 (36%)	6 (43%)	2 (14%)	14	6.57
Intimate relations	4 (29%)	5 (36%)	4 (29%)	1 (7%)	14	6.07
Activities	3 (21%)	5 (36%)	5 (36%)	1 (7%)	14	5.79
Travel	3 (21%)	6 (43%)	3 (21%)	2 (14%)	14	6.29

Many respondents (57%, 8/14) indicated that brentuximab vedotin treatment had positively impacted their health and well-being. Treatment failure was the most commonly reported reason (4/14) indicated by respondents as to why brentuximab vedotin did not have a positive impact on their health and well-being; one patient indicated having experienced significant side effects, and another patient did not provide a reason as to why brentuximab vedotin did not positively impact their life. The following quotes were provided by LC from patient respondents who had a positive experience while on brentuximab vedotin treatment:

- *"Changed it for the better. I am now in remission and have never been so that has overall helped me mentally and has bettered my wellbeing."* Respondent, no demographic data reported
- *"I am very happy with the outcome of the treatment I received. Obviously I would like to be able to feel my toes right now but I'm hopeful those nerves will come back. I had no problem living my life the way I wanted to."* Female, 20-39, Canada
- *"…it has helped me to stay cancer free for 3 years and counting!"* Female, 20-39, USA
- *"I am a healthy person now, I feel good and that part I am most thankful for. I'm thankful for the drug…"* Female, 20-39, Canada

3.3 Additional Information

LC asked respondents questions identifying needs in relation to treatments for HL. Choice of therapy, effectiveness of therapy, and minimal side effects were identified by patients as being important when considering a new treatment.

Respondents rated the importance of having a choice of therapy to take on a scale from 1 (indicating "not important") to 10 (indicating "very important"). The majority of respondents (82%, 70/85) provided a rating of seven or greater with a weighted average of 8.5, indicating that respondents felt very strongly about having greater treatment choices for their condition. When asked to indicate what respondents considered to be the most important aspects of a new drug or treatment, "effectiveness" was the most common response (70%, 31/44). "Minimal side effects" or "less side effects than current treatments" was also very important to respondents (57%, n=25).

LC asked respondents to indicate whether they would be willing to take a drug with known, potentially serious side effects if it was recommended by their physician as their best choice. Of those without experience with brentuximab vedotin (n=76), very few respondents indicated "no" (3%, n=2)); 43% (n=33) indicated that they did not know, and 55% (n=42) indicated that they would. Of those with experience with brentuximab vedotin (n=14), the majority (79%, n=11) indicated that they would take a drug with potentially significant side effects if their doctor recommended it to them; the remaining patients (21%, n=3) indicated that they did not know, and no patients indicated "no".

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarification on subtypes of HL eligible for treatment
- Maximum dose recommended
- Appropriate sequencing with immunotherapy for patients with classical HL subtype

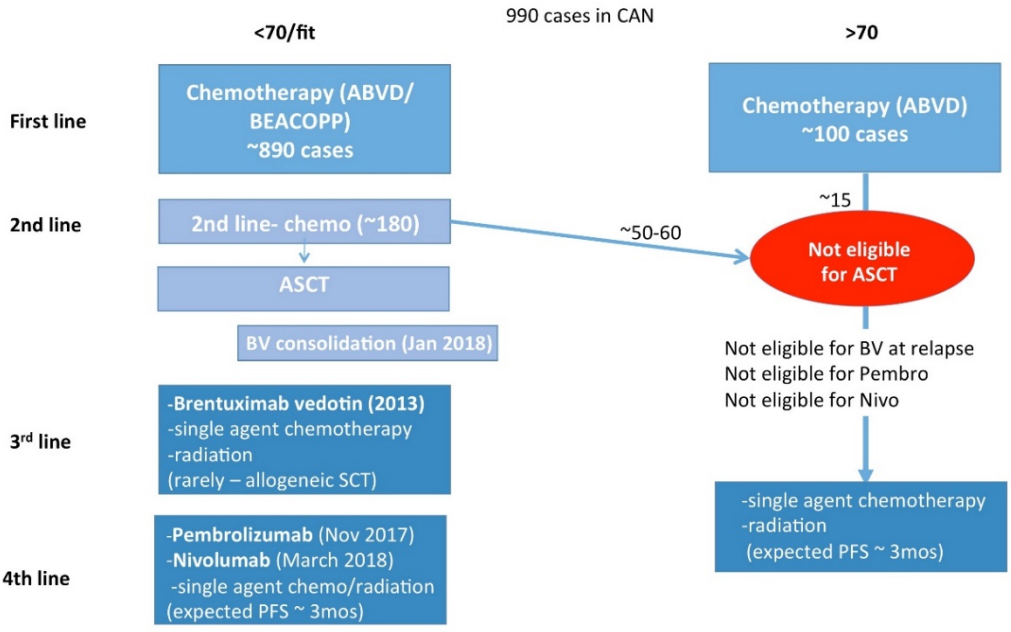
Economic factors:

- Additional line of therapy

Please see below for more details.

4.1 Currently Funded Treatments

For patients who have already been treated with two lines of therapy and are not eligible for transplant, the treatment options are clinical trials and palliative, single agent chemotherapy or best supportive care.



4.2 Eligible Patient Population

PAG is seeking information on the use of brentuximab vedotin for various subtypes of Hodgkin's lymphoma (e.g., classical HL and nodular lymphocyte predominant HL).

PAG is seeking guidance on the use of brentuximab vedotin in third line as a bridge to transplant in patients who would potentially be eligible for ASCT and who have not had adequate response to two lines of therapy.

4.3 Implementation Factors

PAG noted that the maximum dose of brentuximab vedotin recommended is 180mg for relapsed classical HL. PAG is seeking guidance on the recommended dose, as the trial used 1.8mg/kg, without reference to a cap of 180mg. PAG is also seeking confirmation of the treatment duration as the trial was up to 16 cycles or until disease progression or unacceptable toxicities.

PAG identified that the 30 minute infusion is an enabler to implementation. However, resources may be required to monitor and treat infusion-related reactions and adverse events (e.g. peripheral neuropathy).

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate sequencing of brentuximab vedotin with immunotherapies (i.e., nivolumab, pembrolizumab) in patients with classical HL.

4.5 Companion Diagnostic Testing

None required.

4.6 Additional Information

No additional information provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two separate clinician inputs were provided regarding brentuximab vedotin for HL after failure of at least two multi-agent chemotherapy regimens in adult patients (≥ 18 years) who are not ASCT candidates. Both clinicians indicated having experience prescribing brentuximab vedotin.

Both clinicians expressed the large need for more treatment options for patients with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates. One of the clinicians highlighted that there are two subgroups within ASCT ineligible patients that have different treatment goals: 1) patients who are ASCT ineligible due to a lack of response to salvage therapy prior to ASCT, and 2) patients who are ASCT ineligible due to age. For patients in the first category, 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 category, brentuximab vedotin would be the preferred therapy over other available options due to favourable efficacy and toxicity. Further, both clinicians suggested that while for patients in the first category brentuximab vedotin is appropriate for use in the third-line, it may also be appropriate in the second-line for patients in the second category. One clinician pointed out that as some Canadian provinces have restricted reimbursement of brentuximab vedotin to patients that have undergone ASCT, clinicians were able to prescribe brentuximab vedotin to their patients via compassionate access programs, private funding, and clinical trials. CD30 expression testing was noted to already be part of the pathological assessment for HL, therefore no additional companion diagnostic testing would be required. Please see below for details from the clinician inputs.

5.1 Current Treatment(s) for Hodgkin Lymphoma

Both clinicians indicated radiation and chemotherapy as being the main forms of treatment for patients with HL who are ineligible for ASCT. The clinicians listed the following available treatments in this setting: mini-BEAM chemotherapy (BCNU [carmustine], etoposide, Ara-C [cytarabine], and melphalan), COPP chemotherapy (cyclophosphamide, vincristine sulfate, procarbazine hydrochloride, and prednisone) or single-agent chemotherapy (i.e., vinblastine, gemcitabine), and radiation therapy. One of the clinicians also stated that patients may access anti-PD1 antibodies, such as nivolumab or pembrolizumab, or brentuximab vedotin via clinical trials.

5.2 Eligible Patient Population

Both clinicians stated that there is currently a large unmet need for patients with HL who are ASCT ineligible. One of the clinicians stated that the inclusion/exclusion criteria from trial C25007 seem reasonable. Both clinicians also stated that while brentuximab vedotin is appropriate as a third-line therapy, it may also be appropriate in the second-line.

One of the clinicians stated that patients with relapsed or refractory HL are potentially curable, and that therapies used as current standards of care were defined by usually small, phase 2 clinical trials or institutional studies.

One of the clinicians highlighted that there are two subgroups within ASCT ineligible patients that have different treatment goals: 1) patients who are ASCT ineligible due to a lack of response to salvage therapy prior to ASCT, and 2) patients who are ASCT ineligible due to age. For patients in the first category, 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 category, brentuximab vedotin would be the preferred therapy over other available options due to favourable efficacy and toxicity.

One clinician noted that while there are currently no prospective clinical trials employing large datasets in the ASCT ineligible disease setting, there are data available to highlight the favorable outcomes of brentuximab vedotin. These results are further supported by accumulated clinical experience in this setting. Given improved efficacy and favourable toxicity, brentuximab vedotin was stated to be the preferred option over alternatives, such as systemic single- or multi-agent chemotherapies. The clinician also stated that radiotherapy may also be considered for patients who are potentially ASCT eligible if the radiation field does not lead to excessive transplant-related toxicity.

5.3 Relevance to Clinical Practice

Both clinicians were supportive of using brentuximab vedotin as a third-line therapy for transplant ineligible patients. One of the clinicians stated that for those patients, who are ASCT ineligible due to chemoresistant disease, the goal of treatment is to induce a response to treatment with reasonable toxicity to proceed to SCT. The clinician posited that, compared to chemotherapy, brentuximab vedotin may induce a response to treatment more effectively. For patients with widespread disease, potentially limiting the use of radiation therapy, the clinician stated that brentuximab vedotin may be a viable third-line therapy to induce remission and allow for patients to become eligible for ASCT. Furthermore, the clinician indicated that for patients who are ASCT ineligible due to age or presence of comorbidities, brentuximab vedotin may be an appealing option due to its high response rate and favourable toxicity profile compared to chemotherapy.

One of the clinicians noted that the PFS and OS from trial C25007 were reasonable considering brentuximab vedotin was used as a third-line treatment option for transplant ineligible patients. The same clinician stated that the retrospective nature of the phase IV trial should be considered; however, it should be noted that the trial had a prospective design and the intent of the registered clinician's statement could not be verified. The clinician stated that patients who progress appear to have a short, or poor, prognosis, and that toxicities due to brentuximab vedotin are comparable to other chemotherapies already in this treatment space. It should be noted that input provided by the other clinician indicated a preference for the toxicity profile of brentuximab vedotin compared to other combination regimens, but mentioned a similar toxicity profile compared to other IV monotherapies. Through their own anecdotal experience, the clinician mentioned that no additional safety signals were identified; in addition, they were unable to identify further safety concerns in the literature.

One of the clinicians noted that brentuximab vedotin is an essential component of therapy for patients with relapsed or refractory HL. It has been used for several years and is no longer a new therapy. Some Canadian provinces have restricted reimbursement of brentuximab vedotin to patients who have already undergone ASCT, as per the pivotal phase II trial. Also, it was mentioned that brentuximab vedotin has become standard of care in multiple countries, and that in Canada it has been used by clinicians dependent upon availability, including through alternative funding mechanisms, such as compassionate access programs, private payer, clinical trials, etc. One clinician mentioned using brentuximab vedotin or brentuximab vedotin-based therapies for the present indication under review, through the availability of clinical trials, compassionate access programs, and private funding of treatment.

5.4 Sequencing and Priority Treatments

The current indication for brentuximab vedotin is for third-line treatment following a minimum of two multi-agent chemotherapy regimens (for example, ABVD). As there is currently no standard therapy, one clinician thought that brentuximab vedotin could likely become another treatment option in the third-line.

The other clinician provided two different sequencing patterns depending on whether patients were ASCT ineligible due to a lack of treatment response, or due to age or presence of comorbidities. For patients who are ASCT ineligible due to lack of treatment response, ABVD currently remains the standard first-line treatment, followed by GDP (gemcitabine, dexamethasone, and cisplatin) as second-line therapy. Brentuximab vedotin would then follow as third-line therapy, replacing treatments such as mini-BEAM which have additional costs and are frequently given as an inpatient treatment regimen. For patients who are ASCT ineligible due to age or comorbidity, ABVD-based treatments should remain the first-line treatment; patients may be given other treatments if ABVD is contraindicated. Second-line therapies could be radiation, if the disease is localized, or brentuximab vedotin. Brentuximab vedotin could then also be third-line therapy in patients who are fit enough to receive intravenous systemic therapy.

5.5 Companion Diagnostic Testing

Testing for CD30 expression is routinely tested as part of the pathological assessment of HL.

5.6 Additional Information

One of the clinicians stated that the majority of the patients in the relapsed or refractory HL setting are young, potentially curable, and have experienced significant treatment-related toxicities. When standard second-line treatment fails, brentuximab vedotin can be another important component to a curative treatment approach. Among older patients, where the toxicity profile of treatment is an important driver of treatment choice, the clinician stated that the favourable toxicity:efficacy ratio associated with brentuximab vedotin could potentially induce long-term remission or result in cure.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of brentuximab vedotin (Adcetris) in adult patients with Hodgkin lymphoma (HL) after failure of at least two prior multiagent chemotherapy regimens who are not candidates for autologous stem cell transplantation (ASCT).

Note: A Supplemental Question relevant to the pCODR review and to the Provincial Advisory Group was not identified while developing the review protocol.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel (CGP) and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3. Trial Selection Criteria.

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs • In the absence of RCT data, fully published clinical trials investigating the efficacy of brentuximab vedotin were included	• Adult patients (≥ 18 years) with HL who have failed treatment with at least two prior multi-agent chemotherapy regimens and are not candidates for ASCT	• Brentuximab vedotin monotherapy	• Single-agent chemotherapy including gemcitabine, vinorelbine, vinblastine, lomustine, bleomycin, or bendamustine • Multi-agent chemotherapy with gemcitabine, vinorelbine, pegylated liposomal doxorubicin • Immunotherapy with nivolumab or pembrolizumab • Radiation therapy alone • BSC	• OS • Response rate (CR and PR) • PFS • Duration of response • Proportion of patients proceeding to ASCT • HRQOL • Safety
Abbreviations: ASCT -autologous stem cell transplantation; BSC - best supportive care; CR -complete response; HL - Hodgkin Lymphoma; iv - intravenous; OS - overall survival; PFS - progression-free survival; PR - partial response; HRQOL - health-related quality of life; RCT - randomized controlled trial.				

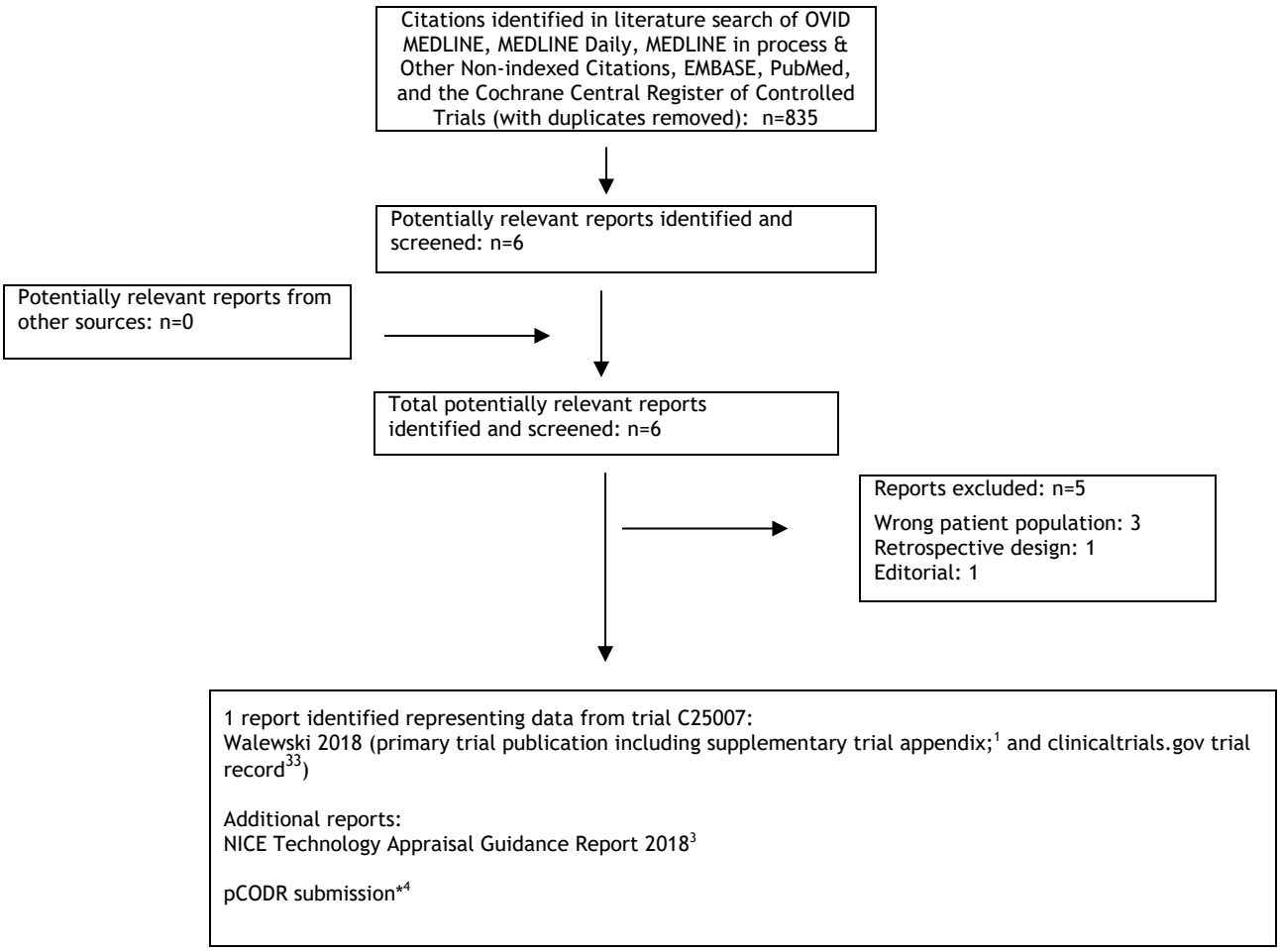
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 835 potentially relevant reports identified, one report[1] was included in the pCODR systematic review and six reports were excluded. Six reports were excluded upon full text review because they included the wrong patient population,[28-30] were retrospective in design[31] or were editorial in nature.[32]

Figure 1. PRISMA Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to trial C25007 were also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

One clinical trial, C25007 by Walewski et al 2018,[1] was identified that met the selection criteria of the pCODR systematic review.

It is important to highlight that the pCODR requested reimbursement criteria do not exactly align with the patient population in the phase IV C25007 trial. Whereas the pCODR requested reimbursement criteria are for the broader ASCT ineligible patient population, the majority of patients in the phase IV trial represent the subgroup of ASCT ineligible patients who have the potential to receive ASCT if they respond to further treatment. It is important to note that there are two distinct subgroups of ASCT ineligible patients with different treatment goals:

- One subgroup includes patients who are ASCT ineligible due to lack of response to salvage therapy prior to ASCT but have the potential to become ASCT eligible if they respond to further treatment. In those patients, brentuximab vedotin could be a bridge to ASCT.
- The other subgroup includes patients who are ASCT ineligible due to fragility, old age, or comorbidities. These patients will never receive a transplant but may benefit from brentuximab vedotin due to favourable efficacy and toxicity. This subgroup forms a minority of ASCT ineligible patients, estimated to be less than 5% by the pCODR Clinical Guidance Panel (CGP).

While the number of patients in the C25007 trial who were ASCT ineligible due to fragility, old age, or comorbidities could not be confirmed by the submitter, it has been suggested by the pCODR Clinical Guidance Panel (CGP) that based on the small number of patients over the age of 65 in the trial (n= 5/60), it is likely that most patients in the trial belong to the first subgroup, i.e. those who were transplant ineligible due to chemotherapy resistance or high-risk refractory disease to first-line chemotherapy and therefore had the potential to receive ASCT if they responded to subsequent treatment.

In their feedback on the initial recommendation, the submitter noted that the statement that *"the requested reimbursement criteria included patients who were ASCT ineligible because of: 1) lack of response to salvage prior to ASCT or 2) advanced age or comorbidities"* (initial recommendation; page 3) is unclear as it may incorrectly imply that the requested reimbursement criteria included older patients with HL who failed one line of multi-agent chemotherapy regimen. In response to the submitter's feedback, the pCODR Methods Team acknowledged that the statement does not specify "after failure of at least two-multi-agent chemotherapy regimens". However, the pCODR Methods Team noted that whether or not the results of the C25007 trial can be generalised to older patients after failure of one multi-agent chemotherapy regimen, has been addressed by the pCODR Clinical Guidance Panel (CGP) in the CGR in the Generalizability Table 1.2 (page 11) and in the CGP Conclusions (page 22).

Furthermore, while the pCODR requested reimbursement criteria specify that patients should have received at least two multi-agent chemotherapy regimens, the C25007 trial included patients who had failed ≥ *1* multi-agent chemotherapy regimen(s). The percentage of patients in the trial who had failed ≥ 2 multi-agent regimens was 50% (n=30).

Key characteristics of the C25007 trial, including design, eligibility criteria and outcomes of interest, are summarized in Table 4. Specific aspects of trial quality, including sample size, statistical considerations, and efficacy analyses are summarized in Table 5.

In their feedback on the initial recommendation, PAG noted that there is additional real world evidence on the use of brentuximab vedotin in patients who are not transplant eligible, referring to the clinical paper by Pellegrini et al. (2017) "*Italian real life experience with brentuximab vedotin: results of a large observational study on 234 relapsed/refractory Hodgkin's lymphoma*'. In response to PAG's feedback, the pCODR Methods Team noted that, while the observational study by Pellegrini et al. (2017) was identified by the pCODR systematic literature search that was conducted as part of the evidence assessment for this submission, it was excluded based on its retrospective design, which did not meet the selection criteria of this pCODR review (refer to Table 3).
Given the limitations in the evidence from this retrospective observational study, the pCODR Methods Team noted that the results should be interpreted with caution. Specifically, the following limitations were noted:

- The publication by Pellegrini et al (2017) reports limited information on the design and conduct of the study; therefore, the pCODR Methods Team was unable to conduct a rigorous evaluation of the observational study.
- The results reported by Pellegrini et al are based on descriptive data analyses. In the absence of pre-specified formal hypothesis testing, the retrospective real-world data reported in this study cannot provide a definitive estimate of efficacy (or its magnitude), and therefore, should be viewed as an exploratory treatment effectiveness study.
- The entire study patient population (n=234) does not completely align with the target population of this pCODR review. The number of patients who were ineligible for SCT based on ≥ 2 prior therapies and chemorefractory disease was small, about 7% of trial patients (n=16). Reporting of efficacy results for this patient subgroup was limited to response, with no indication of how many patients obtained CRs and/or PRs; it was reported that of the 16 patients, 8/16 had a response to brentuximab vedotin and 8/16 underwent ASCT.
- It was not reported if the subgroup of 8 patients who proceeded to ASCT did so directly, following treatment with brentuximab vedotin, or if these patients proceeded to ASCT after receiving other subsequent therapy.

In their feedback on the initial recommendation, the submitter noted that other jurisdictions (Australia and the UK) have made positive funding decisions for brentuximab vedotin on the basis of similar clinical evidence submitted to pCODR as well as real world evidence on the use of brentuximab vedotin in patients who are not transplant eligible. The submitter provided to pCODR 10 articles on real world evidence data for brentuximab vedotin in patients with relapsed/refractory HL (7 out of the 10 articles had been provided as part of the original submission materials to pCODR). In response to the submitter's feedback, the pCODR Methods Team noted that none of the 10 articles on real world evidence meet the selection criteria of the pCODR systematic literature search (refer to Table 3). For a summary of the 10 articles see Table 4 below.

Table 4: Real world evidence provided by submitter in their feedback on the initial recommendation

References Provided by Submitter	**Identified by pCODR SLR; and Reason for Exclusion** (underlined)	**Not identified by pCODR SLR; description of study**
Angelopoulou et al, Hematological Oncology, 2018	• Retrospective study; describes experience of patients (n=95) treated in 20 centres in Greece; a subset of	

	patients (n=25) treated without prior SCT	
Zinzani et al, Haematologica, 2013	• Retrospective study: describes experience of patients (n=65) who were treated through Named Patient Program (NPP; Italian patients may overlap with Pellegrini et al study); a subset of patients (n=5) treated without prior SCT	
Zinzani et al, Critical Reviews in Oncology/Hematology, 2015	• Retrospective pooled analysis of NPP patient data identified by SLR; of patients included with HL (n=207) a subset had not received prior SCT (27%)	
Forero-Torres et al, The Oncologist, 2012	• Retrospective pooled analysis of patients treated in two phase 1 studies, who were ASCT ineligible (n=20)	
Sasse et al, Leukemia & Lymphoma, 2013	--	• Retrospective study of patients who were treated in NPP (Germany) who had not received prior ASCT (n=14)
Gibb et al, Haematologica, 2013	• Retrospective study; describes experience of patients (n=18 HL) treated in NPP (UK); a subset of patients had not received prior ASCT (n=12)	
Onishi et al, Hematological Oncology, 2015	--	• Retrospective study evaluates whether BV normalizes FDG PET imaging prior to high-dose therapy and ASCT (n=15); reports number of patients proceeding to ASCT
Zinzani et al, The Oncologist, 2015	• Retrospective study; describes outcomes of ASCT ineligible patients (n=30) treated in Italian centres between 2011 and 2014	
Eyre et al, British Journal of Hematology, 2017	• Retrospective study; describes outcomes of ASCT ineligible patients (n=99) treated at UK centres between 2011 and 2016	
Brockelmann et al, European Journal of Haematology, 2017	• Retrospective study; describes outcomes of ASCT ineligible patients (n=136) diagnosed/treated at centres in UK and Germany between 2008 and 2014.	

6.3.2.1 Detailed Trial Characteristics

Table 5: Summary of trial characteristics of the included phase IV C25007 trial.[1]

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
C25007 (NCT01990534) Phase IV,[a] single-arm, multicentred n=60 18 centres in seven countries including Czech Republic, Germany, Malaysia, Poland, Spain, Thailand, and Turkey Patient enrolment dates: March 2014 to March 2015 Data cut-off date: May 24, 2016[33] Final Analysis Date: March 2020[33] Funded by Seattle Genetics/Millennium Pharmaceuticals, Inc. /Takeda Pharmaceuticals	<u>Key Inclusion Criteria:</u> • Age ≥18 years • Histologically confirmed CD30-positive relapsed/refractory classical HL • ≥1 prior systemic chemotherapy regimen • Deemed unsuitable for SCT/multi-agent chemotherapy at time of study entry based on the following criteria: o PD during front-line multi-agent chemotherapy o PD within 90 days of CR or unconfirmed CR after treatment with multi-agent chemotherapy and/or radiotherapy o Relapse after ≥2 prior chemotherapy regimens (including pre-SCT salvage treatments) • ECOG PS 0-1 • Measureable disease ≥1.5 cm by CT scan • Adequate hematological, hepatic and renal function <u>Key Exclusion Criteria:</u> • Previous brentuximab vedotin treatment • Previous ASCT/allogeneic SCT	<u>Intervention:</u> • Brentuximab vedotin 1.8 mg/kg IV once every 3 weeks for up to 16 cycles or until PD or unacceptable toxicity o Patients with a CR, PR or SD received a minimum of 8 cycles o Patients with an objective response (CR or PR) and who became suitable for an SCT could discontinue receiving brentuximab vedotin after four cycles and proceed to SCT.	<u>Primary:</u> • ORR by IRF <u>Secondary:</u> • DOR • CR rate, duration of CR • PFS by IRF • OS • Proportion of patients proceeding to SCT following brentuximab vedotin • Safety <u>Tertiary/Exploratory:</u> • Time-to-response (CR or PR) • Time-to-best response • Time-to-CR • TTP • B symptom resolution rate
Abbreviations: ASCT - autologous stem cell transplant; CR - complete response; CT - computed tomography; DOR - duration of response; ECOG - Eastern Cooperative Oncology Group; HL - Hodgkin lymphoma; IRF - independent review facility; ORR - overall response rate; OS - overall survival; PR - partial response; PS - performance status; SCT - stem cell transplant; SD - stable disease; TTP - time-to-progression.			
Notes: [a] - Study was conducted as part of a post-authorisation requirement that accompanied the conditional marketing authorization in the European Union. [b] - Actual dose administered was determined on the basis of patients' weight, but capped at 100 kg.			

a) Trial

C25007 is a single group, multicentre phase IV trial evaluating the efficacy of brentuximab vedotin in patients with CD30-positive relapsed/refractory (R/R) HL who were not candidates for either stem cell transplant (SCT) or multiagent chemotherapy. The type of transplant for which patients were unsuitable, i.e. ASCT or allogeneic, was not indicated in the trial publication and could not be

confirmed by the Submitter.[4] The trial was designed to fulfill a requirement of the conditional marketing authorisation of brentuximab vedotin in the European Union. The trial was conducted at 18 centres in seven countries including the Czech Republic, Germany, Malaysia, Poland, Spain, Thailand and Turkey. Canadian patients were not included.

During the pCODR review of brentuximab vedotin for R/R HL, the pCODR Methods Team identified multiple questions regarding the C25007 trial that required either clarification or additional information from the Submitter. For the majority of questions posed, the Submitter indicated they were unable to provide a response owing to a data sharing agreement in place between Seattle Genetics and Takeda Pharmaceuticals, which prohibits the sharing of the C25007 trial data.[4] The agreement also precluded pCODR from obtaining key documents including the trial protocol and statistical analysis plan (SAP). Consequently, there are multiple areas in the pCODR CGR where information is unknown or data were unavailable.

Funding

Seattle Genetics and Takeda are jointly developing brentuximab vedotin; under the terms of the collaboration agreement, Seattle Genetics has US and Canadian commercialization rights, and Takeda has rights to commercialize the drug in the rest of the world. The trial publication did not indicate the party responsible (trial authors, Submitter) for trial conduct and oversight, including data analysis, interpretation, and trial publication. The majority of trial authors reported potential conflicts of interest related to the drug under study, by either being employed by or having received research funding, honoraria, and consultancy fees from the drug manufacturer and/or its subsidiary.

Eligibility Criteria

The C25007 trial included patients who met the following key criteria:

- Age ≥ 18 years
- Histologically confirmed CD30-positive relapsed/refractory classical HL
- ≥ 1 prior systemic chemotherapy regimen(s)
- Considered unsuitable for SCT or multiagent chemotherapy based on the following criteria:
    - Progressive disease (PD) during frontline multi-agent chemotherapy
    - PD within 90 days of CR or unconfirmed CR after multiagent frontline chemotherapy and/or radiotherapy
    - Relapse after ≥ 2 prior chemotherapy regimens, which included pre-SCT salvage treatments
    - ECOG performance status of 0-1
- Patient with previous brentuximab vedotin exposure, or who had undergone an ASCT or allogeneic SCT were excluded from the trial.

For a more comprehensive list of the eligibility criteria used in the trial refer to Table 4.

Table 6: Select quality characteristics of trial C25007.[1]

Trial Quality Characteristics	C25007
Treatment	• Brentuximab vedotin monotherapy • Non-comparative (single group)
Primary outcome	• ORR by IRF
Required sample size	• A sample size of 60 patients was determined to enable estimation of the activity of brentuximab vedotin (in terms of ORR) with reasonable narrow 95% CI
Randomization method	• Not applicable
Allocation concealment (yes/no)	• No
Blinding	• Open label • IRF outcome assessment
ITT analysis (yes/no)	• Yes
Efficacy analyses	• Data cut-off date: May 24, 2016 • Descriptive with no formal hypothesis testing • For primary outcome (ORR by IRF), two-sided 95% CI were calculated and exploratory subgroup analyses were performed by sex, race, weight (≤100 kg versus >100 kg), number of prior regimens (1 versus >1), baseline ECOG PS, and baseline B symptoms (yes/no) • Pre-specified correlated analysis that compared PFS from most recent treatment prior to study entry versus PFS by investigator assessment with brentuximab vedotin
Final analysis (yes/no)	• No • Final analysis expected March 2020[33]
Early termination (yes/no)	• No
Ethics approval (yes/no)	• Yes

Abbreviations: ECOG - Eastern Cooperative Oncology Group; IRF -independent review facility; CI - confidence interval; DBL - data base lock; ITT - intent-to-treat; ORR - overall response rate; PS - performance status.

The primary outcome of trial C25007 was overall response rate assessed by independent review facility (ORR by IRF).

Secondary outcomes of interest included duration of response (DOR), progression-free survival by IRF (PFS by IRF), overall survival (OS), the proportion of patients proceeding to SCT (ASCT or allogeneic SCT[3]) following treatment with brentuximab vedotin, complete response (CR) rate, duration of CR, and safety. Quality of life outcomes were not assessed in the trial. Tertiary outcomes included time-to-response [CR or partial response (PR)], time-to-best response, time-to-CR, time-to-progression (TTP), and B symptom resolution rate.

Disease Assessment

Tumour response was assessed at baseline, and at cycles 2, 4, 7, 10, 13, and 16 by CT scan of the chest, neck, abdomen; and PET scans were performed at baseline and cycles 4 and 7. Tumour response assessed by IRF and by investigator were determined according to International Working Group Revised Response Criteria for Malignant Lymphoma.

Patients were assessed for PFS and OS every three months until 18 months after treatment with brentuximab vedotin; after 18 months, patients were followed for OS every six months until death or end of study.

Safety was assessed throughout the treatment period until 30 days after the last dose of brentuximab vedotin. Treatment emergent adverse events (TEAEs) were evaluated according to NCIC Common Criteria for AEs version 4.03 and tabulated using MedDRA preferred terms. Peripheral neuropathy was evaluated using Standardized MedDRA Queries (SMQ) that included the following preferred terms: peripheral sensory neuropathy, peripheral neuropathy, polyneuropathy, paresthesia, and autonomic neuropathy.

Statistical Analyses

The statistical analyses performed of the trial data were described in the trial publication as descriptive, with no formal hypothesis testing performed. As previously noted, the Submitter was unable to provide pCODR with the SAP of the trial.

For the primary outcome, ORR by IRF, two-sided 95% confidence intervals (CI) were calculated for the overall patient population, and exploratory subgroup analyses were performed to estimate ORR by IRF by sex, race, weight (≤ 100 kg versus > 100 kg), number of prior regimens (1 versus > 1), baseline ECOG performance score (0 versus 1), and B symptoms (present versus absent).

Time-to-event outcomes (PFS by IRF, OS, DOR, duration of CR, time-to-response, TTP) were estimated using Kaplan Meier (KM) methods. In addition to estimating PFS, a pre-specified correlational analysis was performed to compare the PFS of patients from their most recent treatment prior to study entry versus PFS by investigator assessment with brentuximab vedotin. KM methods were used to assess PFS distribution on prior therapy; and the hazard ratio (HR) and 95% CI were estimated using a Cox proportional hazards model. Details of the methodology used for the correlational analysis were not reported.

All efficacy analyses were performed by intention-to-treat (ITT); and safety analyses included all patients who had received at least one dose of brentuximab vedotin.

b) Populations

The trial enrolled a total of 60 patients from Europe and Asia between March 2014 and March 2015. The baseline demographics and clinical/disease characteristics of patients are summarized in Table 6.

The baseline characteristics of trial patients were reported as representative of patients with R/R HL deemed unsuitable for SCT or multi-agent chemotherapy. The median age of patients was 32 years (range, 18-75), with 92% of patient under the age of 65. 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%). The percentage of

patients who presented with bulky disease was not reported. Extranodal and bone marrow involvement were present in 37% and 7% of patients, respectively.

At baseline, patients had received a median of two prior therapies (range, 1-7); 82% of patients had received > 1 prior therapy. While a comprehensive list of all types of prior therapies received by patients prior to trial entry could not be provided by the Submitter, common prior therapies received by patients included the following chemotherapy regimens: doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD, 93%), ifosfmide, 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.[4] In 67% of trial patients (n=40), PD was the best response to last prior therapy. The median time from initial diagnosis to first dose of brentuximab vedotin was 15.9 months (range, 0-312.0).

Patients were considered ineligible for SCT or multiagent chemotherapy at trial entry due to the following: PD during frontline multiagent chemotherapy (32%; n=19); PD within 90 days of CR or unconfirmed CR after treatment with multiagent chemotherapy and/or radiation therapy (18%; n=11); and relapse after ≥ 2 prior chemotherapy regimens in (50%; n=30).

While the number of patients in the C25007 trial who were ASCT ineligible due to fragility, old age, or comorbidities was not reported in the trial publication and could not be confirmed by the Submitter, it has been suggested by the pCODR CGP that based on the small number of patients over the age of 65 in the trial (n= 5/60), it is likely that most patients were transplant ineligible due to chemotherapy resistance or high-risk refractory disease to first-line chemotherapy, and therefore, had the potential to receive ASCT if they responded to subsequent treatment.

Table 7: Baseline patient demographics and disease characteristics in trial C25007.

Table I. Summary of study population demographics and baseline disease characteristics.

Characteristics	Brentuximab vedotin (N = 60)
Median age, years (range)	32 (18–75)
Male, *n* (%)	36 (60)
Age, *n* (%)	
<65 years	55 (92)
≥65 years	5 (8)
Race, *n* (%)	
White	42 (70)
Asian	18 (30)
Ann Arbor stage at initial diagnosis, *n* (%)	
I	3 (5)
II	21 (35)
III	16 (27)
IV	18 (30)
Other	2 (3)
ECOG PS, *n* (%)	
0	27 (45)
1	33 (55)
B symptoms, *n* (%)	22 (37)
Extranodal involvement, *n* (%)	22 (37)
Bone marrow involvement, *n* (%)	4 (7)
Prior radiation, *n* (%)	25 (42)
Median number of prior therapies, *n* (range)	2 (1–7)
Best response to last prior therapy, *n* (%)	
CR	6 (10)
PR	9 (15)
SD	4 (7)
PD	40 (67)
Unknown	1 (2)
Median time from initial diagnosis to first dose of brentuximab vedotin, months (range)	15·9 (0–312)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PR, partial response; SD, stable disease.

Source: British Journal of Haematology. Prospective study of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma patients who are not suitable for stem cell transplant or multi-agent chemotherapy. Walewski et al., 183(3):400-410. Table I. Reprinted with permission from British Society for Haematology.

c) *Interventions*

Trial patients received brentuximab vedotin at a dose of 1.8 mg /kg intravenously once every three weeks for up to a maximum of 16 cycles, or until PD or unacceptable toxicity. The actual dose received by patients was determined by individual patient weight but was capped at 100 kg. Patients who achieved a CR, PR or stable disease (SD) 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. For patients who proceeded to SCT, it is unknown to pCODR and could not be confirmed by the Submitter, if these patients received brentuximab vedotin as consolidation treatment post-transplant.[4]

The median duration of treatment exposure was not specified, but it was reported that patients in the trial received a median of seven treatment cycles of brentuximab vedotin (range, 1-16); and 13% (n=8) of patients completed the maximum number of 16 cycles. The median relative dose intensity of brentuximab vedotin was 100% (range, 66.8-108%).

No information was reported on the concomitant medications used by patients in the trial.

In terms of subsequent therapy after treatment with brentuximab vedotin, 70% (n=42) of patients in the trial received subsequent treatment. Among these patients, 47% (n=28) received a SCT; 17% (n=10) of patients received SCT immediately after brentuximab vedotin, and 30% (n=18) received other therapy (not specified) after brentuximab vedotin prior to SCT. In 23% of patients (n=14) subsequent therapy that was not SCT (unspecified) was received. A separate public source (NICE technical appraisal document) reported that all patients in the C25007 trial received ASCT (with one patient receiving both ASCT and allogeneic SCT).[3] The Submitter was unable to verify the specific non-transplant subsequent therapies received by patients in the trial.[4]

d) *Patient Disposition*

A summary of the disposition of patients through the C25007 trial is provided in Table 7.

A total of 70 patients were assessed for trial eligibility; and 10 patients were excluded for not meeting specific eligibility criteria (Table 7). All patients received treatment with brentuximab vedotin and all patients eventually discontinued treatment with the study drug. 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 study drug due to treatment-emergent adverse events (TEAEs;5%), symptomatic deterioration (5%), and other reasons (7%).

The trial is ongoing with 60% (n=36) of patients remaining in long-term follow-up; most patients who discontinued from follow-up did so due to death (20%), with fewer patients discontinuing due to PD (5%), patient withdrawal (5%), withdrawal of informed consent (3%), and other reasons (7%).[4]

Major protocol violations occurred in 3% (n=2) of patients. One patient was identified as having received prior ASCT, and the other patient did not meet specified laboratory values at the time of the first dose of brentuximab vedotin.

The ITT and safety analyses were both based on the 60 patients enrolled into the trial.

Table 8: Patient disposition in trial C25007.[4]

	Patient Disposition	ADCETRIS N (%)
Enrollment	Assessed for eligibility	70
	Excluded (did not meet following eligibility criteria): Bidimensional measurable disease for malignant Lymphoma Confirmed diagnosis of relapsed/refractory classical Hodgkin Lymphoma Recovery to Grade 1 or lower from toxicity prior to therapy Specified clinical laboratory values during screening History of at least 1 prior chemotherapeutic regimen	 10 4 2 1 1 1 1
Allocation	Allocated to intervention	60
	Did not receive allocated intervention	0
	Received allocated intervention	60 (100)
Follow-up	Excluded from long term follow up Death Progressive disease Protocol violation Withdrawal of informed consent Symptomatic deterioration Withdrawal by subject Reason not specific	24 (40) 12 (20) 3 (5) 1 (2) 2 (3) 1 (2) 3 (5) 2 (3)
	Remain in long term follow up (ongoing in study)	36 (60)
	Completed 16 cycles of therapy	8 (13)
	Reasons for study drug discontinuation Progressive disease Initiation of stem cell transplant Completed 16 cycles of therapy per protocol Treatment emergent adverse event Symptomatic deterioration Patient withdrawal Protocol violation	60 (100) 33 (55) 9 (15) 8 (13) 3 (5) 3 (5) 3 (5) 1 (2)
Analysis*	Intent-to-treat (ITT) analysis set	60 (100)
	Per-protocol	58 (97)
	Safety population	60 (100)

e) Limitations/Sources of Bias

Critical appraisal of trial C25007 was primarily based on reporting in the trial publication by Walewski et al 2018.[1] Valuable information sources, including the trial protocol and SAP, were not made available to pCODR; and the Submitter was unable to provide responses to most requests for additional information due to a data sharing agreement between Seattle Genetics and Takeda.[4] Consequently, a complete critical appraisal is challenging when important trial

information is not available. Based on the data available to the pCODR Methods Team, the following limitations related to the C25007 trial were noted:

- C25007 is an ongoing, open-label, single group phase IV trial with no active treatment or placebo control group. The evidence obtained from this trial should be considered in light of the limitations associated with phase IV trial design. Phase IV trials are post-marketing trials that evaluate drugs in real world settings, often conducted by the manufacturer to fulfill additional evidence requirements related to drug safety and long-term effects, and in special patient groups. Unlike pre-marketing trials (phase I-III), phase IV trials do not receive the same level of scrutiny and appraisal from drug regulatory agencies, with respect to design, analysis and reporting. As such, potential threats to the internal validity of these trials may not be identified and considered in the interpretation of results. Further, these trials often employ a non-comparative trial design (see below), and are frequently underpowered to provide reliable estimates of treatment effect.[6,7]
- It is difficult to draw conclusions on the efficacy of brentuximab vedotin in R/R HL in the absence of a direct comparison to standard of care treatment (single-agent chemotherapy, BSC). The available evidence is based on descriptive data analyses with no formal hypothesis testing; and therefore, in the absence of inferential statistical approaches, the phase IV trial data cannot provide a definitive estimate of efficacy. While the authors performed a pre-specified correlation analysis to compare the PFS estimate obtained with brentuximab vedotin to the PFS patients experienced on their most recent prior therapy, the results of this analysis should be viewed cautiously, as no details were provided on the methods that informed this analysis. Similar methodology, such as Von Hoff's PFS ratio,[8] can lead to biased estimates due to several factors, such as differences in PD and censoring definitions, and the exclusion of patients who die before progression and are lost to follow-up. The robustness of this analysis cannot be determined based on available information.
- Making a judgement on efficacy is also made difficult by the fact that the trial was small (n=60), and the patient population does not completely align with the target population of this review. The number of patients who were ineligible for SCT/multiagent chemotherapy based on ≥ 2 prior therapies was 50% of trial patients (n=30). Efficacy was not estimated for this patient subgroup, but was estimated for trial patients who received > 1 prior therapies (n=49; 82%). In this patient group, the ORR by IRF estimate (51%; n=25/49) was similar to the overall ITT estimate (50%; n=30/60).
- One finding of the trial was the 28 patients (47%) at trial entry who were unsuitable for SCT or multiagent chemotherapy, who then proceeded to SCT. Upon closer examination, only 10 (17%) of these patients proceeded to SCT directly following treatment with brentuximab vedotin. The majority of patients (n=15/28) developed PD while receiving brentuximab vedotin, and proceeded to SCT after receiving other subsequent therapy. Therefore, in this latter group of patients, caution is advised in attributing the ability to proceed to SCT to brentuximab vedotin.

- The primary outcome of the trial was ORR by IRF. This is a surrogate outcome that may not translate to benefits in PFS and OS. PFS and OS were assessed in the trial but cannot be used to confirm the ORR clinical benefit due to the single group trial design. Further, estimates of OS are confounded by the subsequent therapies received by patients after treatment with brentuximab vedotin.
- Data on patient-reported QOL, an important outcome, was not collected in the trial; as such, the impact of brentuximab vedotin on the QOL of patients in the trial is uncertain.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The median follow-up time upon which the primary efficacy analysis (ORR by IRF) results of C25007 are based was not reported in the trial publication by Walewski et al 2018.[1] The Submitter confirmed a data cut-off date of May 24, 2016, however, they were unable to provide the median follow-up time. Further, details regarding the timing of PFS and OS outcome analyses (whether they were pre-specified and event driven) were requested but could also not be confirmed.[4] Requests were also made to obtain efficacy results in the trial patients who had received ≥ 2 prior systemic therapies (target population; as well as other subgroups of interest), but they could not be provided due to the aforementioned data sharing agreement.[4]

Efficacy Outcomes

The efficacy of brentuximab vedotin was evaluated in the ITT population and various patient subgroups that did, however, not include the patient population that aligns with the requested reimbursement criteria for this pCODR review, which is patients with R/R HL who have received 2 or more prior therapies. In the C25007 trial, these patients comprised 50% of trial patients (n=30). Efficacy estimates are available for trial patients who received > 1 prior therapies (82%; n=49) and 1 prior therapy (18%; n=11). Please refer to Table 9 for the primary efficacy results by patient subgroup.

The efficacy outcomes of the C25007 trial are summarized in Table 8. For the results of tertiary/exploratory trial outcomes, which include time-to-response (CR or PR), time-to-best response, time-to-CR, TTP, and B symptom resolution rate, please refer to Table 8.

Primary Outcome – ORR by IRF

At the data-cut-off date, the ORR by IRF in the ITT patient population was 50% (n=30; 95% CI, 37-63%); CR (n=7) and PR (n=23) were observed in 12% and 38% of patients, respectively. ORR by investigator assessment showed a similar result to assessment by IRF (Table 9). Results of the pre-specified exploratory subgroup analyses are available in Table 9; the ORR by IRF ranged from 20% to 61% across subgroups. Specific ORRs should be considered with their sample size, which ranged from 5 to 55 patients.

DOR by IRF

Among patients who achieved an ORR, CR and PR, the median durations of these responses were 4.6 months (95%, 3.4-7.9), 6.1 months (95% CI, 2.1-not estimable), and 3.7 months (95% CI, 2.4-7.9), respectively. The estimates of these outcomes by investigator assessment, which were generally similar to DOR by IRF, are available in Table 8.

PFS by IRF

For the analysis of PFS, the date of PD was based on the time of first documentation of PD regardless of protocol violations, discontinuations of study treatment, or initiation of subsequent anticancer therapy.

After a median follow-up time of 6.9 months, 39 PFS events (PD or death) were observed in the ITT population; the median PFS by IRF was 4.8 months (95% CI, 3.0-5.3). The Kaplan Meier curve for PFS by IRF is presented in Figure 2 (A). Median PFS by investigator assessment was similar to the IRF estimate (Table 8).

PFS Correlation Analysis

The median 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 HR for this comparison was 0.66 (95% CI, 0.45-0.98; p=0.037), which suggested a 34% improvement in PFS with brentuximab vedotin compared to prior therapy.

OS

After a median follow-up of 16.6 months, a total of 12 deaths were observed in the ITT trial population; at this time median OS had not been reached, and the OS rate at one year was 86%. The Kaplan Meier curve for OS is presented in Figure 2 (B).

Proportion of Patients Proceeding to ASCT after brentuximab vedotin

Of the 60 patients who were deemed unsuitable for SCT or multiagent chemotherapy at trial entry, 47% (n=28) went on to receive a SCT. All 28 patients received ASCT, with one patient also receiving allogeneic SCT.[3] Considering the 28 patients who proceeded to SCT, 21% (n=6) had received one prior therapy and a median of six cycles (range, 4-6) of brentuximab vedotin; and the remaining 22 patients (79%) had received more than one prior therapy and a median of seven cycles (range, 4-16) of brentuximab vedotin.

SCT occurred immediately after treatment with brentuximab vedotin in 17% (n=10) of trial patients. Patient proportions for the number and types of prior therapies received by these patients, as well as the median number of cycles of brentuximab vedotin received, could not be obtained by the Submitter.[4]

SCT 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) [other reasons included completed maximum number of brentuximab vedotin cycles (n=1), AE (n=1), and symptomatic deterioration (n=1)] and then received subsequent therapy prior to SCT. The median number of cycles of brentuximab vedotin and the subsequent therapies received by these patients was not reported.

Table 9: Efficacy outcomes in patients treated with brentuximab vedotin monotherapy in trial C25007.[1]

Efficacy Outcomes	Brentuximab vedotin Monotherapy (n=60)	
DBL	May 23, 2016	
Median follow-up	Not available	
	IRF Assessment	Investigator Assessment
ORR, n (%; 95% CI)	30 (50; 37-63)	29 (48; 35-62)
Best clinical response n, (%; 95% CI)		
CR	7 (12; 5-23)	9 (15; 7-27)
PR	23 (38; 26-52)	20 (33; 22-47)
SD	18 (30; 19-43)	25 (42; 29-55)
PD	8 (13; 6-25)	2 (3;<1-12)
NE	4 (7; 2-16)	4 (7; 2-16)
Median DOR, in months (95% CI)	4.6 (3.4-7.9)	5.3 (3.6-NE)
Median duration of CR, in months (95% CI)	6.1 (2.1-NE)	7.6 (2.1-NE)
Median duration of PR, in months (95% CI)	3.7 (2.4-7.9)	3.8 (3.5-6.4)
Median TTR, in weeks (range)		
TTR (CR + PR)	6.0 (5-39)	6.1 (5-53)
Time-to-best response	11.2 (5-60)	11.8 (5-53)
Time-to-CR	12 (6-60)	12.1 (11-29)
Time-to-PR	6.0 (5-39)	9.1 (5-53)
PFS		
Median follow-up, in months	6.9	
No. of PFS events	39	Not reported
Median PFS, in months	4.8 (3.0-5.3)	5.0 (4.8-6.2)[3]
OS		
Median follow-up, in months	16.6	
No. deaths	12	
OS rate at one year, % (95% CI)	86 (74.0-93.4)	
OS rate at two years, % (95% CI)	74 (58.0-84.6)[3]	
Proportion of patients receiving SCT after brentuximab vedotin		
Received SCT, n	28 (47)	
Received SCT immediately post-brentuximab vedotin	10 (17)	
Received subsequent therapy post-brentuximab vedotin and prior to SCT	18 (30)	
Patients with B symptoms at baseline, n (%)	22 (37)	
B symptom resolution rate, % (range)	91 (71-99)	
Median time-to-resolution of symptoms in weeks after initiation of brentuximab vedotin (range)	3.1 (3.0-6.1)	

Abbreviations: DBL - database lock; DOR - duration of response; CI - confidence interval; CR - complete response; NE- not estimable; ORR - objective response rate; PD - progressive disease; PR - partial response; OS - overall survival; PFS - progression-free survival; SCT - stem cell transplant; SD - stable disease; TTR - time-to-response.

Table 10: Subgroup analysis of ORR by IRF in trial C25007.

Table III. Subgroup analysis of ORR by IRF in the ITT population.

Characteristic	ORR per IRF (CR + PR), *n*/*N* (%)	95% CI
Sex		
Male	16/36 (44)	28–62
Female	14/24 (58)	37–78
Race		
White	19/42 (45)	30–61
Asian	11/18 (61)	36–83
Weight (kg)		
≤100	29/55 (53)	39–66
>100	1/5 (20)	<1–72
Prior regimen		
1	5/11 (45)	17–77
>1	25/49 (51)	36–66
ECOG PS		
0	14/27 (52)	32–71
1	16/33 (48)	31–66
B symptoms at baseline		
Present	7/22 (32)	14–55
Absent	23/38 (61)	43–76

CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRF, independent review facility; ITT, intent-to-treat; ORR, overall response rate; PR, partial response.

Source: British Journal of Haematology. Prospective study of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma patients who are not suitable for stem cell transplant or multi-agent chemotherapy. Walewski et al., 183(3):400-410. Table II. Reprinted with permission from British Society for Haematology.

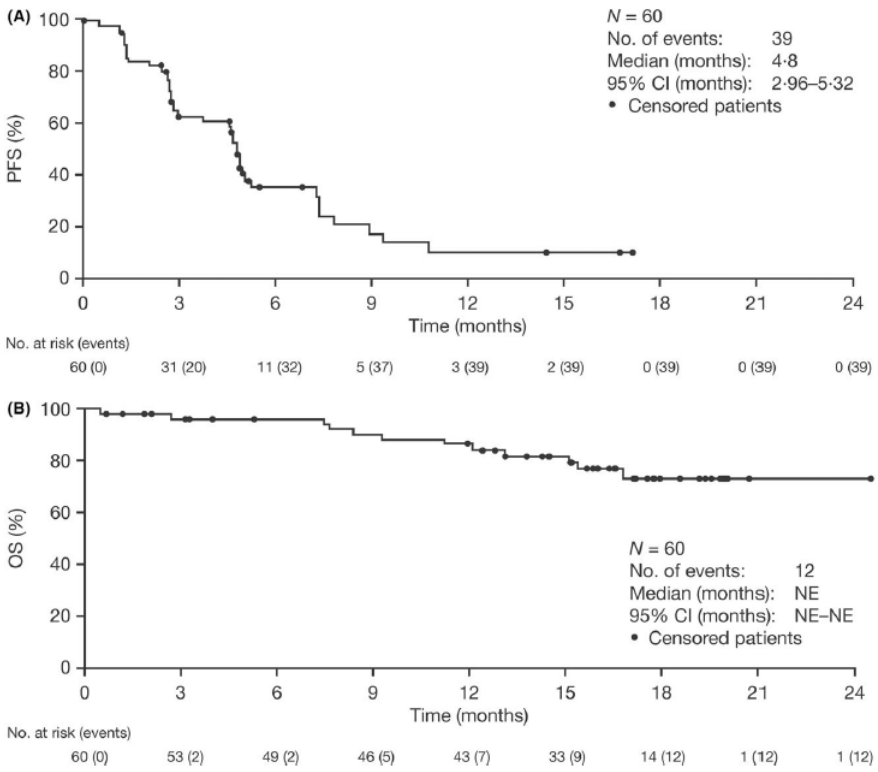


Fig 2. PFS by (A) independent review facility and (B) OS in the intent-to-treat population. CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Figure 2: Kaplan-Meier curves of PFS by IRF (A) and OS (B) in trial C25007.

Source: British Journal of Haematology. Prospective study of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma patients who are not suitable for stem cell transplant or multi-agent chemotherapy. Walewski et al., 183(3):400-410. Figure 2. Reprinted with permission from British Society for Haematology.

Harms Outcomes

The safety population includes all trial patients (n=60). Safety outcomes observed in the trial are summarized in Table 10; adverse event (AE) data are reported in terms of the all grade TEAE occurring in ≥ 10% of patients, and grade 3-4 TEAE occurring in ≥ 2 patients.

Adverse Events

The incidence of all grade TEAE in the trial was 87%, with grade 3-4 TEAE occurring in 35% of patients; of these, 68% and 18% were deemed related to study drug. Serious AEs (SAE) occurred in 18% of patients, and 5% of these were deemed drug-related.

The most common all grade TEAE occurring in patients were peripheral neuropathy (35%), pyrexia (18%), diarrhea (10%) and neutropenia (10%). The most common grade 3-4 TEAE were neutropenia, anemia (n=3 each), pyrexia and back pain (n=2 each). Infusion-related TEAE occurred in 7% of patients. The Submitter could not confirm if any patients in the trial experienced febrile neutropenia.[4]

TEAE resulted in dose modification in 25% of patients and treatment discontinuation in 5% of patients.

Resolution of Peripheral Neuropathy

Of the 35% (n=21) who experienced peripheral neuropathy while on study (grade 1: 22%; grade 2: 10%; grade 3: 3%), symptoms were considered related to study drug in 32% of patients (n=19). The median time to onset of peripheral neuropathy was 9.4 weeks (range, 0.6-39.1). At the end of treatment/last follow-up, 57% (n=12/21) of patients experienced complete resolution of peripheral neuropathy symptoms, and 43% (9/21) experienced no resolution of symptoms (grade 1: 24%, grade 2: 14%, and grade 3: 5%).

Deaths

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 study drug. The pCODR Methods team inquired if any patient deaths occurred before or after receipt of SCT, however, the Submitter was only able to confirm the single death reported in the trial publication.[4]

Table 11: Safety outcomes in patients treated with brentuximab vedotin monotherapy in trial C25007.[1]

Adverse events, n (%)	Brentuximab vedotin (n=60)	
	All grade[a]	Grade 3-4[b]
Any TEAE	52 (87)	21 (35)
Drug related TEAE	41 (68)	11 (18)
Peripheral neuropathy SMQ	21 (35)	3 (3)[c]
Pyrexia	NR (18)	2 (NR)
Diarrhea	NR (10)	NR
Neutropenia	NR (10)	3 (NR)
Anemia	NR	3 (NR)
Back pain	NR	2 (NR)
SAE	11 (18)	
Drug-related SAE	3 (5)	
TEAE resulting in dose modification	15 (25)	
TEAE resulting in treatment discontinuation	3 (5)	
Infusion-related TEAE	4 (7)	
On study death	1 (2)	
Abbreviations: AE(s) - adverse events; brentuximab vedotin - brentuximab vedotin; NR - not reported; SMQ - standardized MedDRA Queries; TEAE - treatment emergent adverse event.		
Notes: [a] - Occurring in ≥ 10% of patients. [b] - Occurring in ≥ 2 patients. [c] - Grade 3 only.		

6.4 Ongoing Trials

One ongoing trial was identified that met the selection criteria of the pCODR review. KEYNOTE-204 is a phase III trial evaluating brentuximab vedotin compared to the PD-1 inhibitor pembrolizumab in patients with R/R HL.[34,35] The trial is enrolling patients who (1) have failed to achieve a response or progressed after ASCT and have not received prior treatment with brentuximab vedotin, and (2) are not ASCT candidates due to chemorestistance, advanced age or comorbidities, and have received ≥ 2 prior multiagent chemotherapy regimens that did not include brentuximab vedotin.

Table 12: Ongoing trials of brentuximab vedotin monotherapy that include adult patients with HL after failure of at least two prior multi-agent chemotherapy regimens who are not candidates for ASCT.[34,35]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
KEYNOTE-204 (NCT02684292) Phase 3, open label RCT with 1:1 randomization Estimated enrollment: 300 27 centres in 5 countries Study start date: May 23, 2016 Estimated DBL for primary outcome: December 30, 2018 Estimated study completion date: July 31, 2020 Funding: Merck Sharp & Dohme Corp.	<u>Key Inclusion Criteria:</u> • ≥18 years of age • Relapse or refractory classical HL • Has responded to brentuximab vedotin or brentuximab vedotin-containing regiments if previously treated with brentuximab vedotin • Measurable disease • ECOG performance status of 0 or 1 • Able to provide an evaluable core excisional lymph node biopsy at trial screening • Adequate organ function <u>Key Exclusion Criteria:</u> • Prior mAb, targeted small molecule therapy, chemotherapy, radiation therapy including investigational agents within 4 weeks prior to first dose of study drug or has not recovered from AEs due to these agents • Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, CTLA-4 antibody, or OX-40, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. • Prior allogeneic SCT with last five years • Diagnosis of immunosuppression or is receiving systemic steroid therapy within 7 days prior to first dose of study drug • Known active CNS metastases and/or carcinomatous meningitis • Active autoimmune disease that has required systemic treatment in the past 2 years	Pembrolizumab 200 mg intravenously on day 1 of each 3-week cycle up to 35 cycles. *versus* Brentuximab vedotin 1.8 mg/kg intravenously on day 1 of each 3-week cycle for up to 35 cycles.	<u>Primary:</u> • PFS by BICR according to IWG criteria • OS <u>Secondary:</u> • ORR • CR • DOR

Abbreviations: BICR - blinded independent central review; CNS - central nervous system; CR - complete response; CTLA-4 - cytotoxic T-lymphocyte-associated protein 4; DBL - database lock; DOR - duration of response; ECOG - Eastern Cooperative Oncology Group; HL - Hodgkin Lymphoma; IWG - International Working Group Revised Response Criteria for Malignant Lymphoma; mAB - monoclonal antibody; ORR - objective response rate; OS - overall survival; OX-40 - tumour necrosis factor receptor superfamily, member 4; PD-1 - programmed cell death-1; PD-L1/2 - programmed cell death ligand 1 or 2; PFS - progression-free survival; SCT - stem cell transplant.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified during the pCODR review.

8 COMPARISON WITH OTHER LITERATURE

No comparison to other literature was undertaken for the pCODR review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on brentuximab vedotin for Hodgkin lymphoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lymphoma Clinical Guidance Panel is comprised of three medical oncologist.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2018, Embase 1974 to 2018 September 13, Ovid MEDLINE(R) ALL 1946 to September 13, 2018

Line #	Searches	Results
1	(Brentuximab* or Adcetris* or adtsetrys* or SGN-35 or SGN35 or 7XL5ISS668 or cAC10-vcMMAE).ti,ab,ot,kf,kw,hw,rn,nm.	3817
2	Hodgkin Disease/ or (Hodgkin* or reed Sternberg*).ti,ab,kw,kf.	176126
3	((lymphoma* or lymphogranuloma* or granuloma*) adj3 malign*).ti,ab,kw,kf.	42212
4	1 and (2 or 3)	2422
5	4 use medall	464
6	4 use cctr	169
7	*Brentuximab vedotin/ or (brentuximab* or adcetris* or adtsetrys* or SGN-35 or SGN35 or 7XL5ISS668 or cAC10-vcMMAE).ti,ab,kw,dq.	2707
8	exp Hodgkin Disease/ or (Hodgkin* or reed Sternberg*).ti,ab,kw,dq.	176086
9	((lymphoma* or lymphogranuloma* or granuloma*) adj3 malign*).ti,ab,kw,dq.	42165
10	7 and (8 or 9)	1855
11	10 use oemezd	1256
12	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.	1102105
13	(Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	849873
14	Multicenter Study.pt.	317656
15	Clinical Studies as Topic/	151206
16	exp Clinical Trial/ or exp Clinical Trials as Topic/ or exp "Clinical Trial (topic)"/	2669573
17	Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/	473772
18	Randomization/	175064
19	Random Allocation/	191892
20	Double-Blind Method/	392941
21	Double Blind Procedure/	152423
22	Double-Blind Studies/	257372
23	Single-Blind Method/	74258
24	Single Blind Procedure/	32242
25	Single-Blind Studies/	76205
26	Placebos/	323255
27	Placebo/	322308
28	Control Groups/	111323
29	Control Group/	111231

30	Cross-Over Studies/ or Crossover Procedure/	133929
31	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3932245
32	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	770493
33	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2900
34	(control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf,kw.	8818985
35	(clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	6030493
36	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	93069
37	(phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	460933
38	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	182563
39	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	680105
40	allocated.ti,ab,hw.	173513
41	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	111946
42	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24121
43	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	913
44	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	10675
45	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	16817
46	trial.ti,kf,kw.	857539
47	or/12-46	13736391
48	exp animals/	45346560
49	exp animal experimentation/	2269284
50	exp models animal/	1691137
51	exp animal experiment/	2269284
52	nonhuman/	5518926
53	exp vertebrate/	44116004
54	animal.po.	0
55	or/48-54	47047680
56	exp humans/	36561733
57	exp human experiment/	412143
58	human.po.	0
59	or/56-58	36563169
60	55 not 59	10485423
61	47 not 60	11063236
62	5 and 61	235
63	11 and 61	873
64	63 not conference abstract.pt.	407
65	6 or 62 or 64	811
66	remove duplicates from 65	579

67	limit 66 to english language	547
68	limit 67 to yr="2012 -Current"	499
69	63 and conference abstract.pt.	466
70	limit 69 to english language	466
71	limit 70 to yr="2013 -Current"	400
72	68 or 71	899

2. Literature search via PubMed
A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search #3 AND publisher[sb] Filters: Publication date from 2012/01/01; English	13
#3	Search #1 AND #2	474
#2	Search Hodgkin Disease[mh] OR Hodgkin*[tiab] OR reed Sternberg*[tiab] OR ((lymphoma*[tiab] OR lymphogranuloma*[tiab] OR granuloma*[tiab]) AND malign*[tiab])	105335
#1	Search Brentuximab vedotin[Supplementary Concept] OR brentuximab*[tiab] OR Adcetris*[tiab] OR adtsetrys*[tiab] OR SGN-35[tiab] OR SGN35[tiab] OR 7XL6ISS668[rn] OR cAC10-vcMMAE[tiab]	756

3. Cochrane Central Register of Controlled Trials (Central)
Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Adcetris/brentuximab, Hodgkin lymphoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Adcetris/brentuximab, Hodgkin lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search: Adcetris/brentuximab, Hodgkin lymphoma – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-13Sept2018) with in-process records & daily updates via Ovid; Embase (1974-13Sept2018) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Adcetris, brentuximab and Hodgkin lymphoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents with a publication date of January 1, 2012-September 13, 2018.

The search is considered up to date as of November 29, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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