



## pan-Canadian Oncology Drug Review Final Clinical Guidance Report

### Brentuximab Vedotin (Adcetris) for Hodgkin Lymphoma

August 29, 2013

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## **FUNDING**

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# 1 GUIDANCE IN BRIEF

## 1.1 Background

The purpose of this review is to evaluate the safety and efficacy of brentuximab vedotin (Adcetris) monotherapy, compared to appropriate comparators, in patients with Hodgkin lymphoma (HL):

- after failure of autologous stem cell transplant (ASCT) or
- after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT.

Brentuximab has Health Canada approval for use in patients with HL after failure of ASCT or after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates.

Brentuximab vedotin (Adcetris) is a chimeric monoclonal antibody that targets the cell membrane protein CD30 and is linked to the cytotoxic monomethyl auristatin E.<sup>1</sup> The recommended dose of brentuximab is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks.

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

One single-arm phase II clinical trial, the SG035-0003 study (N=102), met the inclusion criteria for this review.<sup>2</sup> No randomized trials were identified that met the eligibility criteria of this systematic review. As the trial had only a single arm, it provides no comparative evidence regarding the efficacy of brentuximab in relation to any other treatment. It should be noted that single-arm clinical trials, in general, have limitations with respect to the conclusions that can be drawn from them. However, SG035-003 study was a well-designed and conducted non-comparative trial.

Study SG035-0003 enrolled a total of 102 patients with HL that had relapsed after, or were refractory to, high-dose chemotherapy and ASCT and had an ECOG status 0 or 1.<sup>2</sup> Patients were 47% male and had a median age of 31 years (range, 15 to 77 years). Prior radiation therapy was received by 66% of patients and the median number of prior chemotherapy regimens was 3.5 (range 1 to 13). The study intervention was brentuximab vedotin (brentuximab) 1.8 mg/kg intravenously over 30 minutes, once every 3 weeks for up to 16 cycles or until disease progression or unacceptable toxicity.<sup>2</sup>

Patients who had previously received allogeneic stem cell transplant were ineligible.

Study SG035-0003 included only patients who had relapsed after, or were refractory to high-dose chemotherapy and ASCT and provided no direct evidence regarding the efficacy of brentuximab in patients who have failed at least two prior multi-agent standard-dose chemotherapy regimens.<sup>2</sup>

### *Efficacy*

The primary outcome of the study was objective response rate as assessed using the Revised Response Criteria for Malignant Lymphoma<sup>3</sup> by an independent review facility.<sup>2</sup>

Secondary outcomes included complete response, duration of response, progression-free survival, overall survival and adverse events.

The primary outcome, objective response rate, was 75% (95% confidence interval [CI], 64.9% to 82.6%) of 102 patients and the complete response rate, a secondary outcome, was 34% (95% CI, 25.2% to 44.4%).<sup>2</sup> Of the 76 patients who had an objective response the median duration of objective response was 6.7 months (95% CI, 3.6 to 14.8 months) and of the 35 patients that had a complete response, the median duration of complete response was 20.5 months (95% CI 10.8 to not estimable).<sup>2</sup>

At the time of the primary analysis (median follow-up of 18.5 months), 31 patients were alive and free of documented progressive disease, with an estimated median progression-free survival of 5.6 months (95% CI 5.0 to 9.0 months).<sup>2</sup>

The estimated median overall survival was 22.4 months (95% CI 21.7 months to not estimable) with a total of 28 deaths. The estimated 12-month overall survival rate was 89% (95% CI, 83% to 95%). Chen et al reported, in abstract form only, an updated analysis conducted in July 2012.<sup>4</sup> After a median follow-up of 29.5 months, 42 patients had died and the estimated 24-month overall survival rate was 65% (95% CI, 55% to 74%).<sup>4</sup>

Although quality of life was noted as an important outcome by patient advocacy groups, it was not an outcome studied in the SG035-0004 trial.

### *Harms*

Grade 3 or higher adverse events were reported in 55% of patients and included neutropenia (20%), peripheral sensory neuropathy (8%), fatigue (2%), pyrexia (2%), diarrhea (1%), and peripheral motor neuropathy (1%).<sup>2</sup> The most commonly occurring adverse events of any Grade included peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%), and diarrhea (18%). Peripheral neuropathy was the most commonly reported adverse event of any grade. The median time to onset of peripheral neuropathy was 12.4 weeks.<sup>2</sup> Resolution or improvement (of one grade or more) was seen in 80% of patients.<sup>2</sup> Complete resolution of peripheral neuropathy occurred in 50% of patients.<sup>2</sup> A total of 20 patients (20%) discontinued treatment due to an adverse event, the most common of which was peripheral sensory neuropathy (6 patients) and peripheral motor neuropathy (3 patients).<sup>2</sup>

Two patients in study SG035-0003 experienced progressive multifocal leukoencephalopathy (PML), which resulted in the death of one of them.<sup>5</sup>

### **1.2.2 Additional Evidence**

pCODR received input on brentuximab from one patient advocacy group (Lymphoma Foundation Canada). Provincial Advisory Group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

No supplemental issues were identified during the development of the review.

## 1.2.3 Interpretation and Guidance

### Burden of Illness and Need

Hodgkin lymphoma (HL) is relatively uncommon malignancy which is considered highly curable using current combined modality therapy or combination chemotherapy. Second-line therapy for those who experience relapse cures about 50% of patients who undergo autologous stem cell transplantation (ASCT). ASCT is less effective in patients with HL who experience early relapse following primary therapy, a partial response to second-line or salvage therapy pre-transplant, and those with extensive stage disease at progression. The median survival of patients with HL that relapses after ASCT is two years and patients often require episodic treatment to manage symptoms or complications. For those who are not candidates for ASCT, additional chemotherapy or radiation is administered with palliative intent. In both of these circumstances, currently available chemotherapy is associated with increasing toxicity and decreasing effectiveness over time.

Currently, there are no agents approved for the treatment of relapsed HL. Because this lymphoma subtype is uncommon, there have been relatively few studies conducted evaluating novel agents in this patient population.

### Effectiveness

While there was no control arm in this study, and recognizing that cross-study comparisons pose numerous methodological limitations, the response rate in the study reported by Younes, et al<sup>2</sup>, compares favorably to publications of current single agent treatments<sup>6-8</sup>. The response rate and progression-free survival demonstrated with brentuximab are comparable to combination therapy with GVD, while having a reduced toxicity profile. It is not possible to determine the effect of brentuximab vedotin on overall survival in patients with multiply relapsed HL because of a lack of a direct comparator. Given the small number of patients with HL, it is unrealistic to expect randomized clinical trials to be undertaken in this population.

In a subpopulation of patients (10-15%) with relapse after ASCT<sup>9,10</sup>, reduced intensity conditioning (RIC) allogeneic stem cell transplantation may be considered for those who relapse later (more than one year after ASCT), who are without co-morbidities and who have had a response to additional chemotherapy.<sup>11</sup> Brentuximab vedotin also appears to compare favorably with RIC allogeneic stem cell transplantation, since transplant is associated with a 15-20% risk of treatment-related mortality<sup>12</sup>, and similar median progression-free survival reported in a number of series of 6-8 months.<sup>13</sup>

### Safety

Brentuximab vedotin is associated with a low rate of serious (grade 3 or 4) toxicities. Grade 3 adverse events included neutropenia (14%), peripheral sensory neuropathy (8%), fatigue (2%), pyrexia (2%), diarrhea (1%), and peripheral motor neuropathy (1%). In addition, Grade 4 neutropenia occurred in 6% of patients.<sup>2</sup>

A small number of cases for progressive multifocal leukoencephalopathy (PML) have been reported among patients receiving brentuximab vedotin. The true incidence of this neurological complication is unknown, but appears to be rare. PML has previously been reported in the literature in patients receiving combination chemotherapy for HL, including ASCT, and has been reported rarely with more frequently used agents for treatment of lymphoma such as Rituximab. Additional follow-up in patients receiving

brentuximab vedotin is necessary to determine whether the incidence of PML is higher than might be expected in the relapsed HL population.

### 1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net clinical benefit to the use of brentuximab vedotin for the treatment of HL following relapse after ASCT, or after two lines of systemic therapy for those not candidates for ASCT. This is based on a large phase II trial which shows a high degree of efficacy, an important number of patients with durable complete responses, and acceptable and predictable toxicity. While patients with relapsed HL who have not undergone ASCT were not part of this study population, it is considered reasonable from a clinical perspective for such patients also to receive brentuximab vedotin, in light of the high response rate seen in Study SG035-0003 and the paucity of agents available to these patients.

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 treatment options for patients with relapsed HL.
- Uncertainty remains as to the benefit of brentuximab vedotin treatment beyond 48 weeks (16 cycles), and its use earlier in the course of relapsed HL (for example: prior to ASCT, after progression on ABVD or other primary therapy for those not proceeding to ASCT, or as maintenance therapy after ASCT).



## 2 CLINICAL GUIDANCE

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's Lymphoma. 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 pCODR website, [www.pcodr.ca](http://www.pcodr.ca).

This Clinical Guidance is based on: a systematic review of the literature regarding brentuximab vedotin (Adcetris) conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; 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. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on brentuximab vedotin (Adcetris) and a summary of submitted Provincial Advisory Group Input on brentuximab vedotin (Adcetris) are provided in Sections 3, 4 and 5 respectively.

### 2.1 Context for the Clinical Guidance

#### 2.1.1 Introduction

Hodgkin lymphoma (HL) is an uncommon but distinct pathological entity that typically presents in young adults, but is seen in both children and adolescents, and those 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. There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease.

Patients who experience disease progression after ASCT or are not candidates for ASCT following treatment with multi-agent chemotherapy are generally treated with single-agent chemotherapy (such as gemcitabine, vinblastine, or vinorelbine), multi-agent chemotherapy, or with involved field radiation. The goal of treatment in patients who are not candidates for ASCT is generally palliation and directed at controlling the growth of lymphoma and its symptoms.<sup>14</sup> Similarly, for patients with progressive HL after ASCT, the prospects of long term remission with subsequent therapy are very limited and the duration of disease control (as measured by progression-free survival) is very short with currently available therapies.

Brentuximab vedotin (Adcetris; brentuximab) is a chimeric monoclonal antibody that targets the cell membrane protein CD30 and is linked to the cytotoxic monomethyl auristatin E.<sup>1</sup> The targeted nature of brentuximab allows for the delivery of the cytotoxic component of the agent directly into cells expressing CD30<sup>1</sup>, which is typically expressed in HL Reed-Sternberg cells and in systemic anaplastic large cell lymphoma.<sup>15-17</sup>

Brentuximab has a Health Canada approval for use in the treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates. Brentuximab was also approved by the U.S. Food and Drug Administration (FDA) on August 19, 2011, for the treatment of HL that has relapsed or progressed following ASCT on the basis of a high complete response

rate, favourable toxicity profile, and limited treatment options in this patient population.<sup>18</sup>

A submission to pCODR was made in March 2013 requesting funding for brentuximab vedotin (Adcetris) for the treatment of patients with HL after failure of ASCT or after disease progression following at least two prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT.<sup>19</sup>

## 2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of brentuximab vedotin (brentuximab; Adcetris) monotherapy, compared to appropriate comparators, in patients with HL, after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT. See Table 1 in Section 6.2.1 for outcomes of interest and appropriate comparators.

## 2.1.3 Highlights of Evidence in the Systematic Review

*This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.*

No randomized trials were identified that met the eligibility criteria of this review. One single-arm phase II clinical trial, the SG035-0003 study, met the inclusion criteria for this review.<sup>2,4,20,21</sup> The study was conducted in 25 centres in the U.S., Canada, and Europe and it was funded by Seattle Genetics, Bothell, WA. Table 1 provides select characteristics of the trial.

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00848926 Open-label phase II trial  25 sites in U.S.A., Canada, and Europe  Patient accrual: February 2009 through August 2009 Data cut-off (primary analysis): August 2010 Subsequent data cut-off to assess duration of response and resolution of peripheral neuropathy: March 2011  Enrolled: n=102	Diagnosis of relapsed or refractory HL after high-dose chemotherapy and ASCT. Histologically documented CD30-positive Hodgkin's Reed-Sternberg cells by central pathology review. Aged 12 years or older. Measurable disease $\geq 1.5$ cm by CT Fluorodeoxyglucose-avid disease by PET ECOG Performance status 0 or 1  <u>Exclusion criteria:</u> Previous allogeneic stem cell transplantation	Brentuximab vedotin 1.8 mg/kg i.v. over 30 minutes, once every 3 weeks for up to 16 cycles, disease progression, or unacceptable toxicity.  NO comparator—single-arm study.	<u>Primary</u> ORR*  <u>Secondary</u> DoR* CRR* PFS* OS AE's

Table 1. Summary of Trial characteristics of the SG035-0003 Study. <sup>2</sup>			
Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Funded by Seattle Genetics, Bothell, WA, U.S.A.			
<p><b>Abbreviations:</b> AE's = adverse events; ASCT = autologous stem cell transplantation; CRR= complete response rate; CT = computed tomography; DoR = duration of response; i.v. = intravenously; ECOG = Eastern Cooperative Oncology Group; HL = Hodgkin Lymphoma; ORR = objective response rate; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival.</p> <p>* Response-based outcomes were assessed using the Revised Response Criteria for Malignant Lymphoma<sup>3</sup> by an independent review facility.</p>			

The planned enrolment of this phase II trial was 100 patients. The primary outcome of the study was objective response rate and secondary outcomes included complete response, duration of response, progression-free survival, overall survival and adverse events. Response outcomes were assessed using the Revised Response Criteria for Malignant Lymphoma<sup>3</sup> by an independent review facility.<sup>2</sup> Duration of response, progression-free survival and overall survival were estimated using the Kaplan-Meier Method.<sup>2</sup>

A total of 102 patients were enrolled. Forty-seven percent of 102 patients were male. The median age was 31 years (range, 15 to 77 years). Prior radiation therapy was received by 66% of patients and the median number of prior chemotherapy regimens was 3.5 (range 1 to 13).

All 102 enrolled patients were included in the final analysis with a data cut-off of August 2010.<sup>2</sup> Reasons for treatment discontinuation included: completion of all treatment cycles (18% of 102 patients), progressive disease (48%), adverse events (21%), to pursue more aggressive therapy (9%), not wanting to continue with study treatment (3%), and having stable disease (1%).<sup>22</sup> At the time of the final analysis, 28 patients had died.<sup>2</sup>

The SG035-0003 study was a single-arm trial and as such, the results of the trial provide no comparative evidence regarding the efficacy of brentuximab in relation to any other treatment. In addition, the study included only patients who had relapsed after, or were refractory to high-dose chemotherapy and ASCT. The SG03-0003 study provides no direct evidence regarding the efficacy of brentuximab in patients who have failed at least two prior multi-agent standard-dose chemotherapy regimens.<sup>2</sup>

A summary of the efficacy outcomes and key adverse events can be found in Table 2. The objective response rate was 75% (95% confidence interval [CI], 64.9% to 82.6%) of 102 patients and the complete response rate was 34% (95% CI, 25.2% to 44.4%).<sup>2</sup> The median duration of objective response was 6.7 months (95% CI, 3.6 to 14.8 months) and the median duration of complete response was 20.5 months (95% CI 10.8 to not estimable).<sup>2</sup>

Efficacy	ORR (%)	CRR (%)	Duration of ORR (Mdn, mos)	Duration of CRR (Mdn, mos)	PFS (Mdn, mos)	OS (Mdn, mos)	Follow-up (Mdn, mos)
Estimate	75	34	6.7	20.5	5.6	22.4	18.5
95% CI	64.9-82.6	25.2-44.4	3.6-14.8	10.8-NE	5.0 to 9.0	21.7-NE	
Adverse events	Peripheral sensory neuropathy	Neutropenia	Fatigue	Pyrexia	Diarrhea	Peripheral motor neuropathy	Nausea
Brentuximab-related events, any Grade (%)	42	19	34	14	18	11	35
Any Grade 3/4 (%)	8	20	2	2	1	1	0

Abbreviations: CRR=complete response rate; Mdn=median; mos=months; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

At the time of the primary analysis (median follow-up of 18.5 months), 31 patients were alive and free of documented progressive disease, with an estimated median progression-free survival of 5.6 months (95% CI 5.0 to 9.0 months).<sup>2</sup> The estimated median overall survival was 22.4 months (95% CI 21.7 months to not estimable) with a total of 28 deaths. The estimated 12-month overall survival rate was 89% (95% CI, 83% to 95%). Chen et al<sup>4</sup> reported, in abstract form only, an updated analysis conducted in July 2012. After a median follow-up of 29.5 months, 42 patients had died and the estimated 24-month overall survival rate was 65% (95% CI, 55% to 74%).<sup>4</sup>

A summary of the Grade 3 or 4 adverse events experienced by patients in the trial can be found in Table 2. The European Medicines Agency EPAR reported that 98% of 102 patients experienced any grade treatment-emergent adverse event.<sup>5</sup> Younes et al<sup>2</sup> reported that 94 patients (92%) experienced a treatment-related adverse event and that a total of 56 patients (55%) experienced a Grade 3 or higher adverse event.

The following grade 3 or higher adverse events were reported: neutropenia (20%), peripheral sensory neuropathy (8%), fatigue (2%), pyrexia (2%), diarrhea (1%), and peripheral motor neuropathy (1%).<sup>2</sup> The most commonly occurring adverse events of any Grade included: peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%), and diarrhea (18%). Please see Table 4 in Section 6.3.2.2 for additional adverse event data.

Peripheral neuropathy was the most commonly reported adverse event. Fifty-six patients (55%) experienced any grade, 20% experienced Grade 2, and 8% experienced a Grade 3 event. The median time to onset of peripheral neuropathy was 12.4 weeks.<sup>2</sup> Resolution or improvement (of one grade or more) was seen in 80% of patients, with a median time to improvement or resolution of 13.2 weeks.<sup>2</sup> Complete resolution of peripheral neuropathy occurred in 50% of patients.<sup>2</sup>

Two patients in this study experienced progressive multifocal leukoencephalopathy (PML), which resulted in the death of one of them.<sup>5</sup>

#### 2.1.4 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.

#### 2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

#### 2.1.6 Other Considerations

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

##### ***Patient Advocacy Group Input***

From a patient perspective, additional drug therapies for the treatment of Hodgkin Lymphoma (HL) which enable the patient to have a choice in their therapy, is an important aspect when consideration is given to treatment. In addition, patients want treatment options that will control their disease and extend their life, while also allowing them to enjoy a good quality of life. Most patients indicate they would be willing to tolerate the side effects of a new therapy, even significant side effects, if the therapy is able to control their disease and there is an improvement in their quality of life for a substantial length of time afterwards. Many patients with HL are young adults. Patients with relapsed or refractory HL have limited treatment options. There is a significant unmet need for a safe and effective treatment.

##### ***PAG Input***

Input on the brentuximab vedotin (Adcetris) review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG noted that HL is generally diagnosed in young patients in their twenties and thirties and as such the availability of a “first-in-class” targeted therapy for the treatment of HL is an enabler. PAG also noted that the HL patient population with refractory/resistant disease is small and as such implementing a funding decision will have a small budgetary impact.

PAG is uncertain as to how the drug will be assessed in determining its placement in a line of therapy in relapsed/refractory HL patients as the pivotal study presented is a single arm Phase 2 trial and does not have a comparator arm. PAG also noted a possibility for indication creep into earlier lines of therapy and a significant possibility for drug wastage.

PAG noted the US FDA warnings regarding risk of a life threatening adverse effect, progressive multifocal leukoencephalopathy (PML), which presents as a barrier to implementation.

### *Other*

Although quality of life was noted as an important outcome by patient advocacy groups, it was not an outcome studied in the SG035-0004 trial.

The Provincial Advisory Group noted that the U.S. FDA provides a warning for progressive multifocal leukoencephalopathy (PML) in patients taking brentuximab (see, product monograph warnings, below). The European Medicines Agency (EMA) European Public Assessment Report (EPAR) for brentuximab reported that, two patients included in the Hodgkin lymphoma pivotal trial of brentuximab (SG-35-0003) suffered from PML, resulting in the death of one of them.<sup>5</sup> The EPAR also reported that in total, three confirmed cases of PML have occurred out of approximately 2000 patients treated with brentuximab.<sup>5</sup>

The product monograph provided by the manufacturer (Seattle Genetics, Inc.) provides several warnings and precautions including, but not limited to:<sup>23</sup>

#### *Progressive multifocal leukoencephalopathy - Serious Warnings and Precautions*

Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in Adcetris-treated patients. Contributing factors may include prior therapies and underlying disease that may cause immunosuppression. Healthcare professionals should monitor patients on Adcetris for any new sign or symptom that may be suggestive of PML. Further treatment with Adcetris should be withheld immediately at the first sign or symptom suggestive of PML.

## 2.2 Interpretation and Guidance

### **Burden of Illness and Need**

Hodgkin lymphoma (HL) is relatively uncommon malignancy which is considered highly curable using current combined modality therapy or combination chemotherapy. Second-line therapy for those who experience relapse cures about 50% of patients who undergo autologous stem cell transplantation (ASCT). ASCT is less effective in patients with HL who experience early relapse following primary therapy, a partial response to second-line or salvage therapy pre-transplant, and those with extensive stage disease at progression. The median survival of patients with HL that relapses after ASCT is two years and patients often require episodic treatment to manage symptoms or complications. For those who are not candidates for ASCT, additional chemotherapy or radiation is administered with palliative intent. In both of these circumstances, currently available chemotherapy is associated with increasing toxicity and decreasing effectiveness over time.

Currently, there are no agents approved for the treatment of relapsed HL. Because this lymphoma subtype is uncommon, there have been relatively few studies conducted evaluating novel agents in this patient population.

## Effectiveness

In a single- arm phase II trial (N=102), brentuximab vedotin administered intravenously every three weeks resulted in a response rate of 75% and progression free survival of approximately six months.<sup>2</sup> Although only 102 patients were included, this is one of the largest phase II studies of any therapy that has been conducted in relapsed HL, which is notable given that relapsed HL is uncommon. In addition, although complete response rate is not a validated surrogate for overall survival, it is commonly considered a very important treatment goal. In the palliative setting, active treatment that reduces disease burden and symptoms (the component of response) and duration of disease control (PFS being the best measure of this) are reasonable treatment goals. While there was no control arm in this study, and recognizing that cross-study comparisons pose numerous methodological limitations, the response rate in the study reported by Younes, et al<sup>2</sup>, compares favorably to publications of current single agent treatments<sup>6-8</sup>, and resulted in a response rate and progression-free survival comparable to combination therapy with GVD, with much less toxicity. It is not possible to determine the effect of brentuximab vedotin on overall survival in patients with multiply relapsed HL because of a lack of a direct comparator.

In a subpopulation of patients (less than 10-15% at most centers in Canada) with relapse after ASCT<sup>9,10</sup>, reduced intensity conditioning (RIC) allogeneic stem cell transplantation may be considered for those who relapse later (more than one year after ASCT), who are without co-morbidities and who have had a response to additional chemotherapy.<sup>11</sup> Compared to RIC allogeneic stem cell transplantation, brentuximab vedotin also compares favorably, since such transplants are associated with a 15-20% risk of treatment-related mortality<sup>12</sup>, and similar median progression-free survival reported in a number of series of 6-8 months.<sup>13</sup>

## Safety

Brentuximab vedotin is associated with a low rate of serious (grade 3 or 4) toxicities. In a population of patients who have received prior myelosuppressive chemotherapy, the incidence of hematologic toxicity was low, and rate of significant neutropenia was acceptable. Because of the mechanism of action of the cytotoxic MMAE, a molecule that targets intracellular tubulin, neurological toxicity consisting of peripheral neuropathy was anticipated. This was the most common troublesome side effect for patients, occurring in about 50%. However, this was an uncommon cause of treatment discontinuation in the phase II study described above. Recently, a small number of cases have been reported to develop progressive multifocal leukoencephalopathy (PML) among patients receiving brentuximab vedotin. The true incidence of this neurological complication is unknown, but it appears to be rare. PML has previously been reported in the literature in patients receiving combination chemotherapy for HL, including ASCT, and has been reported rarely with more frequently used agents for treatment of lymphoma such as rituximab. Additional follow-up in patients receiving brentuximab vedotin is necessary to determine whether the incidence of PML is higher than might be expected in the relapsed HL population.

## Limitations

In the study by Younes, et al., patients received brentuximab vedotin for up to 16 cycles.<sup>2</sup> There are no published data at present to support or discourage the use of brentuximab vedotin for periods of time for more than 16 cycles, although anecdotally patients have

tolerated treatment beyond 16 cycles. More prolonged treatment may increase the risk or severity of neuropathy.

The current published data were derived in a population of patients who have relapsed following ASCT, and had received a median of four prior systemic therapy regimens. It is not known whether similar results would have been achieved in a different patient population; that is, those treated earlier in the course of disease (immediately after relapse following ASCT) or in those who had not undergone ASCT. There are no direct comparisons of brentuximab vedotin to other agents and given the small number of patients with HL, it is unrealistic to expect that randomized clinical trials to be undertaken. This necessitates having to rely on non-comparative data with regard to evaluating the effectiveness of this agent. While the rarity of relapsed HL has made evaluation of novel therapies a challenge, at the same time a small number of patients in Canada who might receive this drug annually is quite small, and the burden on the health care system will be relatively minor compared to other more common forms of cancer.

## 2.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net clinical benefit to the use of brentuximab vedotin for the treatment of HL following relapse after ASCT, or after two lines of systemic therapy for those not candidates for ASCT. This is based on a large phase II trial which shows a high degree of efficacy, an important number of patients with durable complete responses, and acceptable and predictable toxicity. While patients with relapsed HL who have not undergone ASCT were not part of this study population, it is considered reasonable from a clinical perspective for such patients also to receive brentuximab vedotin, in light of the high response rate seen in Study SG035-0003 and the paucity of agents available to these patients.

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 treatment options for patients with relapsed HL.
- Uncertainty remains as to the benefit of brentuximab vedotin treatment beyond 48 weeks (16 cycles), and its use earlier in the course of relapsed HL (for example: prior to ASCT, after progression on ABVD or other primary therapy for those not proceeding to ASCT, or as maintenance therapy after ASCT).



### 3 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.

#### 3.1 Description of the Condition

Hodgkin lymphoma (HL) is an uncommon but distinct pathological entity that typically presents in young adults, but is seen in both children and adolescents, and those 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. There are approximately 900 new cases of Hodgkin lymphoma in Canada each year and approximately 160 Canadians will die annually from this disease.

#### 3.2 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. Those who present with advanced stage disease (stage III and IV) and those who present with constitutional ("B") symptoms are usually managed with combination chemotherapy alone.<sup>24</sup> In Canada, the standard regimen is ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for 6 or 8 cycles; a minority of patients with large tumour masses at presentation (areas of bulky disease >10 cm) may also receive involved field radiation. Despite the excellent complete remission rates with modern chemotherapy approaches (>95% for localized and >80% for advanced stage disease), relapse is experienced by 10-15% of patients with early and 30% of those with advanced disease.

Patients who experience treatment failure (disease progression on or relapse after primary therapy) are usually candidates for second-line (sometimes called salvage) chemotherapy followed by autologous stem cell transplantation (ASCT). The outcomes of this second treatment are most favourable in those with a long early remission and those with a complete response to second line chemotherapy. Approximately 50% of those undergoing ASCT will be alive and relapse-free five years after treatment and are generally considered cured. ASCT is not considered appropriate treatment for older patients (those older than 65 years), especially those with significant medical co-morbidities, or for those with progressive disease following salvage chemotherapy. For these latter patients, treatment is palliative and directed at controlling the growth of lymphoma and its symptoms.<sup>14</sup> Similarly, for those who experience disease progression following ASCT, the prospects of long term remission with additional therapy are very limited, and while chemotherapy and occasionally involved field radiation may result in objective responses in a minority of patients, the duration of disease control (as measured by progression free survival ) is very short with currently available therapies. The median survival following relapse after ASCT is approximately 2 years, and is shorter for patients who relapse within 6 months of transplant and for those transplanted with disease that was refractory to primary therapy.<sup>25</sup>

In some centres, for young patients who have relapsed after ASCT with a long disease-free interval (more than one year), and a good response to additional salvage therapy, reduced intensity allogeneic stem cell transplantation from an HLA-matched sibling donor or unrelated matched donor is sometimes used. While some centres have reported good short-term results with this strategy, these results have not been reproducible, and many centres consider that allogeneic transplantation post-ASCT is still investigational

A retrospective comparison of reduced intensity conditioning (RIC) using alemtuzumab compared to historical controls who were responsive to additional chemotherapy and who remained alive 12 months after relapse reported improved survival at 5 years post-ASCT favouring patients who

underwent allogeneic transplant: 65% vs 15%.<sup>11</sup> Among patients who were considered potential candidates for allogeneic transplant who underwent HLA typing after relapse following ASCT, a significantly better outcome was observed for patients with a compatible donor compared to those without a potential donor: progression-free survival at 2 years was 39% vs 14% and overall survival 66% vs 42%, respectively.<sup>13</sup> In this study, among patients actually receiving reduced intensity transplantation, median PFS was 7 months, median overall survival 28 months, and at 2 years PFS was 31% and overall survival 41%.

In a recent phase II evaluation of reduced intensity allogeneic transplantation for HL reported from the EBMT, 78 of 92 patients treated with salvage chemotherapy responded and underwent transplantation from sibling or matched unrelated donors. Non-relapse mortality was 15% at one year, PFS was 47% and 18% at one and four years, and overall survival was 48% and 24%.<sup>12</sup> Similarly, in a recent registry study from France of 191 patients (prior ASCT in 92%), non-relapse mortality at 3 years post-transplant was 16%, PFS 39%, probability of relapse 46% and overall survival 63%. Patients with early relapse within 6-12 months after ASCT, and those with HL that is resistant to additional chemotherapy prior to transplant have a very low likelihood of durable benefit from reduced intensity allogeneic transplantation.<sup>9,10</sup> Overall, allogeneic transplantation considered appropriate therapy for approximately 10-15% of patients who relapse after ASCT.

Treatment of such patients generally consists of single agent chemotherapy, since re-treatment with ABVD is precluded by the risk of cardiac toxicity from cumulative doxorubicin treatment and pulmonary toxicity from bleomycin. 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).<sup>6-8</sup> Reported response rates range from 20-40% and progression-free survival from 6-8 months.<sup>14</sup> Combination regimens, such as, gemcitabine, vinorelbine and liposomal doxorubicin (GVD), have shown significant activity in patients who have relapsed after or who were not eligible for ASCT, with response rates that appear higher than that achieved with single agents above, but progression-free survival was only 8 months, and the hematologic toxicity of combination therapy was significant.<sup>26</sup> Due to restrictions on reimbursement in many provinces, this regimen is not generally available in Canada, and other combination regimens such as COPP (cyclophosphamide, vincristine, procarbazine, prednisone) are used if patients have good performance status and bone marrow reserve. Involved field radiation is suitable for those with localized relapse outside of a previous radiation field, but there are few long-term survivors.<sup>27</sup>

Brentuximab Vedotin is approved for the treatment of patients with HL after failure of ASCT or at least two prior multi-agent chemotherapy regimens. In light of its favourable toxicity profile and high response rate in heavily pretreated patients (median number of prior regimens 3.5, range 1-11), BV would likely become the treatment of choice as initial therapy for relapse after ASCT.

It would be anticipated that BV could be considered an appropriate treatment option for patients who have relapsed after primary chemotherapy who are not considered appropriate candidates for ASCT on the basis of age or co-morbidities. While such patients were not included in the phase II study reported by Younes et al<sup>2</sup>, it would be clinically appropriate for such patients to be treated with BV because of its toxicity profile and significant activity in more heavily pre-treated, younger patients.

### 3.3 Evidence-Based Considerations for a Funding Population

Based on the number of patients dying in Canada per year from HL, 160, and assuming that approximately 80% of patients dying would have undergone ASCT prior to death (using age as a criterion for transplant eligibility, only 20% of diagnoses are made in patients over age 65), then each year approximately 100-120 patients who have relapsed after ASCT would be eligible for treatment with brentuximab vedotin. The patient population studied by Younes, et al<sup>2</sup>, had all previously undergone ASCT and had received a median of 3.5 prior chemotherapy regimens. Since nearly all patients experienced some disease regression following treatment with BV and 75% achieved a response, despite being heavily pretreated, it would be anticipated that this therapy would be used in all patients who have experienced relapse after ASCT. Furthermore, since the response rate observed appears to exceed that reported with single agents and is similar to that reported by Bartlett, et al<sup>26</sup>, with the combination of gemcitabine, vinorelbine and liposomal doxorubicin, which has significant hematologic toxicity, it is likely that BV will be used preferentially as initial treatment at the time of relapse post ASCT for those requiring systemic chemotherapy.

BV 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 BV would have pathological confirmation of the presence of CD30 on initial biopsy or one taken at any time after disease recurrence.

### 3.4 Other Patient Populations in Whom the Drug May Be Used

It would be anticipated that BV could be considered an appropriate treatment option for patients who have relapsed after primary chemotherapy who are not considered appropriate candidates for ASCT on the basis of age or co-morbidities. While such patients were not included in the phase II study reported by Younes et al<sup>2</sup>, it would be clinically appropriate for such patients to be treated with BV because of its toxicity profile and significant activity in more heavily pre-treated, younger patients. The use of BV inALCL will be discussed in another document. Studies of BV in other lymphoma subtypes such as CD30 positive diffuse large B cell and peripheral T cell lymphoma are underway but results of those studies are not yet available. A clinical trial of the addition of BV as maintenance therapy after ASCT is being carried out, as are phase II studies of BV as part of salvage chemotherapy approaches prior to ASCT in order to assess tolerability and ability to improve response rate prior to transplant for HL.

## 4 SUMMARY OF PATIENT ADVOCACY GROUP

The following patient advocacy group provided input on brentuximab for Hodgkin Lymphoma (HL) and their input is summarized below:

- Lymphoma Foundation Canada

The Lymphoma Foundation Canada conducted one-on-one interviews with 9 patients and 1 caregiver to gather information about patient and caregiver experiences with Hodgkin Lymphoma (HL). Information was also collected from oncologists and from literature about the drug under review.

From a patient perspective, additional drug therapies for the treatment of Hodgkin Lymphoma (HL) which enable the patient to have a choice in their therapy, is an important aspect when consideration is given to treatment. In addition, patients want treatment options that will control their disease and extend their life, while also allowing them to enjoy a good quality of life. Most patients indicate they would be willing to tolerate the side effects of a new therapy, even significant side effects, if the therapy is able to control their disease and there is an improvement in their quality of life for a substantial length of time afterwards. Many patients with HL are young adults. Patients with relapsed or refractory HL have limited treatment options. There is a significant unmet need for a safe and effective treatment.

Please see below for a summary of specific input received from the patient advocacy group.

### 4.1 Condition and Current Therapy Information

#### 4.1.1 Experiences patients have with Hodgkin Lymphoma

Patients with HL may initially present with a number of symptoms that interfere with their quality of life and daily activities, including the ability to work or attend school. Symptoms may include: enlarged lymph nodes, flu like symptoms, shortness of breath, drenching night sweats, unexplained pain, fatigue, and weight loss. Fatigue is often debilitating for many patients. Every patient is different and therefore symptoms can vary.

The symptoms of HL may not be easily recognized by physicians until further investigation is undertaken. There are many patients that have flu and cold like symptoms for months before investigation is initiated and a diagnosis is confirmed. Patients seek a cure for their disease.

#### 4.1.2 Patients' Experiences with Current Therapy for HL

Currently, HL is considered to be among the most curable of all cancers. Patient advocacy group input indicates that the optimal first-line therapy for advanced stage HL is controversial, with the trade-off of exposing patients to more toxic chemotherapy regimens versus having a higher percentage of patients relapse. Despite the advances in HL treatment, there are patients that relapse or have refractory disease. For these patients the treatment options are limited and there remains a significant unmet need for a safe and effective treatment.

Input from the Lymphoma Foundation Canada indicates that although the therapy for advanced-stage HL has improved, up to 10% of patients with advanced-stage HL will not achieve complete remission and 20-30% of responding patients will subsequently relapse

after treatment. Salvage chemotherapy followed by autologous stem cell transplantation (ASCT) is the treatment of choice in patients with relapsed HL or if the disease is refractory to initial chemotherapy. Unfortunately, lack of response to salvage chemotherapy is not uncommon, and clinicians are left with limited treatment options for relapsed or refractory HL patients. Input from the Lymphoma Foundation Canada noted that there is no evidence that supports that one regimen is superior to another, although some regimens do show a better Overall Response Rate.

Young adult HL patients report their lives are affected in many ways, including, but not limited to: the time it takes to obtain a diagnosis; cost of time off from work or school; need to move home during treatment to receive needed care; loss of friends and potential impact on their fertility. Patients cite the cancer has a significant impact on their self esteem.

#### **4.1.3 Impact of Hodgkin Lymphoma and Current Therapy on Caregivers**

Patient advocacy group input indicates that the impact of HL on caregivers and families is significant. Caregivers often experience physical, emotional, financial, and time impacts.

Many HL patients are young adults and often it is a parent who is the caregiver. Patients may need to move home for care as their independence is compromised. Fear of infertility and death are issues that both the patient and caregiver experience. Caregivers face daily stress and worry about the wellbeing of the patient. Caregivers need to know the "right" way to deal with a young adult, as well as, how to cope with the fear of losing their loved one.

Caregivers must also be knowledgeable with the side effects of treatment and how to support the patient through the side effects. Nausea and fatigue must be managed and this is not easy for the caregiver.

Many caregivers are still working and one parent may be required to stop working, yet still incur the costs associated with travel and drugs not covered by public or private insurance.

## **4.2 Information about the Drug Being Reviewed**

### **4.2.1 Patient Expectations for and Experiences To Date with Brentuximab**

Four (4) patients interviewed by the Lymphoma Foundation Canada had direct experience with brentuximab. These patients experienced a decrease in their tumours over a short time period. This was evidenced on their CT scans. These patients expressed they were beginning to feel well and felt they were getting better. All patients had already exhausted all treatment options. Some patients were able to return to work or school after their treatment with brentuximab. Neuropathy was the most common side effect, but patients were willing to tolerate this side effect of the therapy.

Some patients interviewed had accessed brentuximab through a clinical trial in the US at no cost, one (1) patient had to pay for the drug through funds raised by a family fundraiser. Two (2) patients died before they could take brentuximab for any duration of time.

### 4.3 Additional Information

The Lymphoma Foundation Canada states that although the questions on the *pCODR Patient Advocacy Group Input on a Drug Review* template are clear, they are not relevant when a patient is dying. Patients are willing to incur any risk to try and stay alive, especially young adult patients. Patient advocacy group input on pCODR drug reviews is very important to the Lymphoma Foundation Canada and require a great deal of time. However, LFC expressed that the system is not transparent and they could not determine the impact it has on funding decisions.

Not all provinces in Canada have a system in place for special access when NOC is granted and a funding policy has not been made as of yet. The Lymphoma Foundation Canada states that access must be provided because patients are dying due to processes.

## 5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for brentuximab vedotin (Adcetris) for Hodgkin's lymphoma (HL). 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 ([www.pcodr.ca](http://www.pcodr.ca)).

### Overall Summary

Input on the brentuximab vedotin (Adcetris) review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG noted that HL is generally diagnosed in young patients in their twenties and thirties and as such the availability of a "first-in-class" targeted therapy for the treatment of HL is an enabler. PAG also noted that the HL patient population with refractory/resistant disease is small and as such implementing a funding decision will have a small budgetary impact.

PAG is uncertain as to how the drug will be assessed in determining its placement in a line of therapy in relapsed/refractory HL patients as the pivotal study presented is a single arm Phase 2 trial and does not have a comparator arm. PAG also noted a possibility for indication creep into earlier lines of therapy. PAG noted a significant possibility for drug wastage.

PAG noted the US FDA warnings regarding risk of a life-threatening adverse effect, progressive multifocal leukoencephalopathy (PML), which presents as a barrier to implementation.

### 5.1 Factors Related to Comparators

PAG members indicated that in patients who have relapsed disease or disease resistant to standard initial therapy, further therapeutic options are limited and consists of palliative chemotherapy. Although brentuximab may potentially offer a therapeutic option in patients that fail initial therapy, PAG members indicate that the pivotal study presented is a single arm Phase 2 trial and does not have a comparator arm. As a result, PAG is uncertain as to how the drug will be assessed in determining its placement in a line of therapy in relapsed/refractory HL patients.

### 5.2 Factors Related to Patient Population

PAG noted a possibility for indication creep into earlier lines of therapy as current treatments have toxicities associated with them. PAG noted that a clear definition of "failed therapy" and "ASCT ineligibility" may be required to avoid indication creep into earlier lines of therapy. PAG also noted that indication creep may be possible in patients that are ASCT eligible and who have a partial response to salvage chemotherapy but are unable to achieve adequate depth of response. In these cases, brentuximab may be requested to bring patients into adequate pre-transplant responsiveness.

As an enabler, PAG noted that the HL patient population with refractory/resistant disease is small. This means that implementing a funding decision will have a small budgetary impact.

### 5.3 Factors Related to Accessibility

PAG noted that patients may require growth factor support to maintain high dose therapy with brentuximab. This supportive therapy is not covered in all jurisdictions and may pose additional costs to the patient presenting as a barrier to implementation. PAG noted that some chemotherapy clinics may choose not to administer brentuximab due to the possibility of drug wastage, as the drug has a 24hr stability following reconstitution and the number of relapsed/refractory patients is small. This presents a barrier to accessibility for patients.

PAG noted that, similar to the accessibility of current salvage chemotherapy protocols, brentuximab is likely only going to be available in tertiary centers and so implementation of brentuximab would not change current treatment practices. PAG also noted that some jurisdictions have compassionate access programs (CAP) that may allow for case-by-case accessibility of brentuximab to patients that have failed currently available lines of therapy.

PAG would like clarity from the Lymphoma Guidance Clinical Panel as to whether there is a need for CD30 testing to identify eligibility for treatment among relapse/refractory HL patients or whether this is part of diagnostic work-up.

### 5.4 Factors Related to Dosing

PAG noted that treatment is recommended up to a maximum of 16 cycles, disease progression or unacceptable toxicity. PAG requested further clarity on the 16 cycle limit especially in patients with relapsed/refractory HL who tolerate the drug well as there may be interest from treating physicians to continue treatment.

PAG noted that the availability of a ceiling dose for patients 100kg or over to be an enabler to implementation as it will enhance treatment precision for patients.

### 5.5 Factors Related to Implementation Costs

PAG noted that drug wastage may become a significant barrier as only 50mg vials are available and patients may require up to four vials (180mg = 1.8mg/kg IV for 100kg patient) per treatment cycle. In addition, PAG noted that the drug has 24hr stability after reconstitution and as the number of relapsed/refractory HL patients is few, it is unlikely that vial sharing can be instituted to avoid drug wastage. PAG also noted that the drug requires refrigeration for storage which may require additional pharmacy resources.

PAG noted that although brentuximab will require chemotherapy chair time for 30min IV infusions, the protocol requires less time than other more aggressive chemotherapies currently available for patients with HL, which presents as an enabler to implementation. Although IV infusion requires 30 minutes, the number of cycles of treatment is much more than other chemotherapy protocols for HL. PAG noted that infusion reactions are possible with brentuximab, especially in the 24 hrs after infusion, which may require patients to stay within close proximity of hospital. This presents a barrier to implementation as it may incur additional costs for patients.



## 5.6 Other Factors

PAG noted that HL is generally diagnosed in young patients in their twenties and thirties and as such the availability of a “first-in-class” targeted therapy for the treatment of HL is an enabler.

PAG noted that the drug monograph in Lexicomp indicates a contraindication with bleiomyacin, normally part of a combination therapy in earlier lines of therapy for HL patients. As such PAG would like clarity as to the current indication and whether it will be part of monotherapy or part of a combination therapy. If the indication is in combination with other drugs, PAG noted this to be a potential barrier to implementation as it may indicate a possibility for combination use with other drugs used in previous lines of therapy for HL.

PAG noted the US FDA warnings regarding risk of progressive multifocal leukoencephalopathy (PML), a potentially life-threatening adverse-effect, as a barrier to implementation. PAG requested more information on this AE as it will require monitoring

## 6 SYSTEMATIC REVIEW

### 6.1 Objectives

To evaluate the effect of brentuximab vedotin (brentuximab; Adcetris) monotherapy, compared to appropriate comparators, in patients with Hodgkin lymphoma (HL), after failure of autologous stem cell transplantation (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT.

See Table 3 in Section 6.2.1. for outcomes of interest and appropriate comparators.

Note: No Supplemental Questions relevant to this pCODR review or to the Provincial Advisory Group were identified.

### 6.2 Methods

#### 6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel 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.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT.  In the absence of RCT data, fully published clinical trials investigating the efficacy of brentuximab were to be included. Exclude reports of trials with only a dose-escalation design. Reports of trials with a mixed design <sup>†</sup> were to be included only if separate data were reported for the cohort of patients who were included in the efficacy-determining phase of the study.	Patients with HL who have failed treatment with ASCT or after treatment with at least two prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT.	Brentuximab monotherapy 1.8 kg/mg i.v. over 30 minutes every 3 weeks for a minimum of 8 cycles up to a maximum of 16 cycles, disease progression, or unacceptable toxicity.	Single-agent chemotherapy with: gemcitabine, vinorelbine, or vinblastine.  <i>OR</i> Multi-agent chemotherapy with gemcitabine, vinorelbine, pegylated liposomal doxorubicin  <i>OR</i> Radiation therapy alone	<b>OS</b> <b>PFS</b> Response rate (CR and PR) Duration of response <b>QOL</b> Adverse events
Abbreviations: ASCT=autologous stem cell transplantation; CR=complete response; i.v.=intravenously; OS=overall survival; PFS=progression-free survival; PR=partial response;				

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
QOL=quality of life; RCT=randomized controlled trial.				

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

<sup>†</sup>A mixed design was defined as a trial with a dose-escalation phase followed by an efficacy-determining phase in which the study intervention was administered at the same dose and schedule to all patients (generally the maximum tolerated dose determined in the dose-escalation phase).

## 6.2.2 Literature Search Methods

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- ) with in-process records & daily updates via Ovid; EMBASE (1980- ) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 5) 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 concept was brentuximab (Adcetris).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of June 6, 2013.

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 - clinictrials.gov and Ontario Institute for Cancer Research - Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were limited to the last five years. 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 information as required by the pCODR Review Team.

## 6.2.3 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. Two members 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.

## 6.2.4 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.

### 6.2.5 Data Analysis

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

### 6.2.6 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 overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

## 6.3 Results

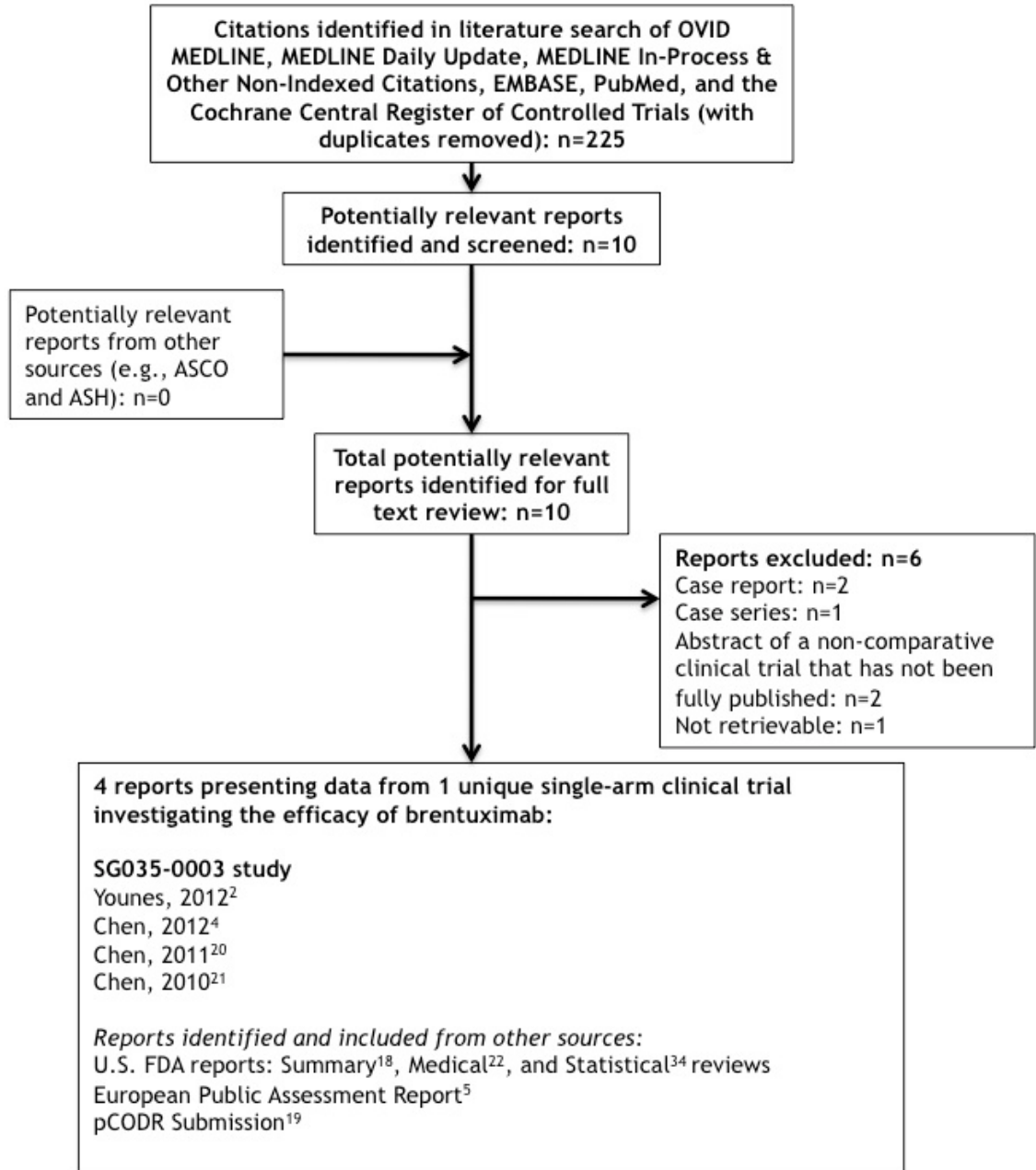
### 6.3.1 Literature Search Results

A total of 225 unique citations were identified through searches of MEDLINE (OVID), MEDLINE Daily Update (OVID), MEDLINE In-Process & Other Non-Indexed Citations (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials, and PubMed (Figure 1). No additional abstracts were identified through searches of the annual conferences of ASCO or ASH. Of those 225 citations, ten potentially relevant reports were retrieved for full text review. Four studies were included in the pCODR systematic review<sup>2,4,20,21</sup> and six studies were excluded. Studies were excluded because they were case reports<sup>28,29</sup>, retrospective case series<sup>30</sup>, not retrievable<sup>31</sup>, or they were abstracts of single-arm clinical trials that have not been fully published.<sup>32,33</sup> The latter two studies were included in Section 6.4 *Ongoing Trials*. In addition, the United States Food and Drug Administration's (U.S. FDA) Summary<sup>18</sup>, Medical<sup>22</sup> and Statistical<sup>34</sup> Reviews and the European Medicines Agency's European Public Assessment Report (EPAR)<sup>5</sup> on brentuximab were also included as was the submission by the manufacturer to pCODR.<sup>19</sup>

The submitter commented on pERC's Initial Recommendation that three studies they felt should be included in this systematic review were excluded. Although these studies were identified in the literature search, they were excluded during title and abstract screening phase as all three were retrospective case series.<sup>35-37</sup>

Retrospective case series were not included in this systematic review as they are generally considered low quality evidence that is susceptible to many forms of bias, including, but not limited to, incomplete data collection and selection bias. In addition, the inclusion of studies in this systematic review was based on a pre-specified protocol in order to prevent bias in the selection of studies for inclusion. Choosing to include studies that do not meet the pre-specified eligibility criteria of the systematic review has the potential to bias the results in the direction that is of interest to the author while also negating the reason for having eligibility criteria.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies.



## 6.3.2 Summary of Included Studies

### 6.3.2.1 Detailed Trial Characteristics

#### a) *Trials*

No randomized trials were identified that met the inclusion criteria for this review. One single-arm phase II clinical trial, the SG035-0003 study, met the inclusion criteria for this review. Select characteristics of that trial, reported in a full publication by Younes et al<sup>2</sup>, can be found in Table 1. The trial was conducted at 25 sites in the U.S., Canada, and Europe. The study was funded by Seattle Genetics, Bothell, WA.

The primary outcome of the study was objective response rate (ORR) as determined by an independent review facility.<sup>2</sup> A total of 100 patients were planned to be enrolled, allowing a 29% ORR to exclude an ORR  $\leq$ 20% with 95% confidence. Secondary outcomes included complete response rate (CRR), duration of response, progression-free survival, overall survival, and adverse events. Outcomes based on response assessment (i.e., ORR, CRR, duration of response, and progression-free survival) were assessed using the Revised Response Criteria for Malignant Lymphoma<sup>3</sup> by an independent review facility. Response was assessed by CT scans at cycles 2, 4, 7, 10, 13, and 16 and by PET scan at cycles 4 and 7. After discontinuation of study treatment, follow-up assessments were conducted every 12 weeks until patient death or study closure. Patients who discontinued study treatment and who had stable disease or better also received CT scans every 12 weeks until disease progression. Progression-free survival was defined as the time from the start of study treatment to the date of the first documented objective tumour progression or death from any cause. Overall survival was defined as the time from the start of study treatment to the date of death from any cause.

Duration of response, progression-free survival, and overall survival were estimated using the Kaplan-Meier method.<sup>2</sup>

#### b) *Populations*

The SG035-0003 study enrolled patients with HL that had relapsed after, or were refractory to, high-dose chemotherapy and ASCT.<sup>2</sup> In addition, patients had to have CD30-positive Hodgkin's Reed Sternberg cells by central pathology review as well as an ECOG performance status of 0 or 1. Table 1 provides further details regarding the trial's inclusion criteria. Of note, patients who had received prior allogeneic stem cell transplantation were not eligible for enrolment.

A total of 102 patients were enrolled into the study.<sup>2</sup> A total of 48 patients (47%) were male. The median age was 31 years (range, 15 to 77 years). Eighty-nine patients (87%) were white. Sixty-seven patients (66%) had received prior radiation therapy and the median number of prior chemotherapy regimens was 3.5 (range 1-13). Ninety-one patients (89%) received one prior ASCT and 11 patients (11%) received two prior ASCTs. Seventy-two patients (71%) had primary refractory disease (failure to obtain a complete remission with front-line therapy or relapse within three months of front-line therapy). With respect to patients' most recent prior therapy, 59 patients (58%) had relapsed disease (best response of CR or PR) and 43 patients (42%) had refractory disease (best response of stable or progressive disease). The median time to relapse after the last ASCT was 6.7 months (range 0-131 months) and 72 patients (71%) relapsed within one year of receiving ASCT.

### ***c) Interventions***

The study intervention was brentuximab vedotin (brentuximab) 1.8 mg/kg i.v. over 30 minutes, once every 3 weeks for up to 16 cycles or until disease progression or unacceptable toxicity.<sup>2</sup>

The median duration of treatment with brentuximab was 27 weeks (range, 3-56 weeks).<sup>22</sup> A median of 9 cycles were administered per patient (range, 1-16 cycles).<sup>2</sup> The mean number of cycles was 10, and the median relative dose intensity was 96%.<sup>2</sup>

### ***d) Patient Disposition***

All 102 enrolled patients were included in the final analysis.<sup>2</sup> The U.S. FDA Medical Review<sup>22</sup> provided details regarding patient disposition that were not reported in the primary publication by Younes et al.<sup>2</sup> Reasons for treatment discontinuation, as reclassified by the FDA, were as follows: 18 patients (18%) due to completing all 16 cycles of treatment, 49 patients (48%) due to progressive disease, 21 patients (21%) due to adverse events, nine patients (9%) to pursue more aggressive therapy (eight of whom received an allogeneic stem cell transplant before any evidence of tumour progression), three patients (3%) did not want to continue with study treatment, and one patient (1%) due to stable disease.<sup>2,22</sup> At the date of the data cut-off, a total of 28 patients had died.<sup>2</sup>

### ***e) Limitations/Sources of Bias***

The SG035-003 study was a well-designed and conducted non-comparative trial. There were no biases or potential limitations in the design or conduct of this specific trial that would have had an impact on the trial's results. However, it should be noted that single-arm clinical trials, in general, have limitations with respect to the conclusions that can be drawn from them. As the trial had only a single arm, it provides no comparative evidence regarding the efficacy of brentuximab in relation to any other treatment.

In addition, the SG035-003 study included only patients who had relapsed after, or were refractory to high-dose chemotherapy and ASCT. The Health Canada indication<sup>19</sup> also includes patients who have failed at least two prior multi-agent chemotherapy regimens. The SG035-003 study did not include this group of patients and therefore does not provide direct evidence regarding the efficacy of brentuximab in patients who have failed at least two prior multi-agent chemotherapy regimens.<sup>2</sup>

## **6.3.2.2 Detailed Outcome Data and Summary of Outcomes**

A total of 102 patients were included in the intent-to-treat efficacy analysis and the safety analysis.<sup>2</sup>



## Efficacy Outcomes

### *Response and Duration of Response*

The ORR was 75% (95% confidence interval [CI], 64.9%-82.6%) of 102 patients and the CRR was 34% (95% CI, 25.2%-44.4%).<sup>2</sup>

For the 76 patients who had an objective response, the median duration of objective response was 6.7 months (95% CI, 3.6-14.8 months).<sup>2</sup> For the 35 patients who had a complete response, the median duration of complete response was 20.5 months (95% CI, 10.8 months to not estimable).<sup>2</sup>

### *Progression-free Survival*

Younes et al<sup>2</sup> reported that at the time of the primary analysis, a total of 31 patients were alive and free of documented progressive disease, with an estimated median progression-free survival of 5.6 months (95% CI, 5.0-9.0 months). After a median follow-up of 18.5 months (range, 1.8 months to 23.5 months), a total of 28 patients had died.<sup>2</sup>

### *Overall Survival*

The estimated median overall survival was 22.4 months (95% CI, 21.7 months to not estimable) and the estimated overall survival at 12 months was 89% (95% CI, 83%-95%).<sup>2</sup>

Chen et al<sup>4</sup> reported, in abstract form, an analysis of long-term follow-up for patients in the SG035-0003 study, conducted in July 2012. After a median follow-up of 29.5 months (range 1.8-36.9 months), 42 patients had died and the estimated 24-month overall survival rate was 65% (95% CI, 55%-74%).<sup>4</sup>

## Harms Outcomes

Table 4 summarizes the adverse events that occurred in all 102 patients in the SG035-0003 study as reported by Younes et al.<sup>2</sup> Drug-related adverse events of any Grade that occurred in more than 15% of patients, as reported by Younes et al<sup>2</sup>, were peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%), and diarrhea (18%; Table 4). Of the commonly reported drug-related adverse events of any Grade (see Table 4), Younes et al<sup>2</sup> reported the following Grade 3 adverse events: neutropenia (14%), peripheral sensory neuropathy (8%), fatigue (2%), pyrexia (2%), diarrhea (1%), and peripheral motor neuropathy (1%). In addition, Grade 4 neutropenia occurred in 6% of patients.<sup>2</sup> No cases of febrile neutropenia were reported.<sup>2</sup>

The European Medicines Agency's EPAR reported that 98% of the 102 patients experienced any treatment-emergent adverse event.<sup>5</sup> A total of 56 patients (55%) experienced any Grade 3 or higher adverse event.<sup>2</sup> Treatment-related adverse events of any Grade occurred in 94 patients (92%).<sup>5</sup> Serious adverse events occurred in 25 patients (25%) and treatment-related serious adverse events occurred in 14 patients (14%).<sup>5</sup> A total of 20 patients (20%) discontinued treatment due to an adverse event, the most common of which was peripheral sensory neuropathy (6 patients) and peripheral motor neuropathy (3 patients).<sup>2</sup> No deaths were reported within 30 days from the last administration of brentuximab.<sup>2</sup>

Younes et al<sup>2</sup> reported that peripheral neuropathy of any grade occurred in 56 patients (55%), Grade 2 in 20% of patients, Grade 3 in 8% of patients, and no patient experienced Grade 4 peripheral neuropathy. The median time to onset of any peripheral neuropathy was 12.4 weeks.<sup>2</sup> Resolution or improvement (of one grade or more) was seen in 80% of patients, with a median time to improvement or resolution of 13.2 weeks.<sup>2</sup> Complete resolution of peripheral neuropathy occurred in 50% of patients.<sup>2</sup>

Of note, the EMA EPAR reported that two patients in the SG035-0003 study experienced progressive multifocal leukoencephalopathy (PML), which resulted in the death of one of them.<sup>5</sup>

Table 4. Incidence of brentuximab-related adverse events of any Grade that occurred in 10% or more of patients and incidence of Grade 3 or 4 adverse events as reported in the Younes et al study.<sup>2</sup>

Adverse event	Brentuximab-Related Events of Any Grade No. of patients (%)	Any Grade 3 Events* No. of patients (%)	Any Grade 4 Events* No. of patients (%)
Peripheral sensory neuropathy	43 (42)	8 (8)	0
Nausea	36 (35)	0	0
Fatigue	35 (34)	2 (2)	0
Neutropenia	19 (19)	14 (14)	6 (6)
Diarrhea	18 (18)	1 (1)	0
Pyrexia	14 (14)	2 (2)	0
Vomiting	13 (13)	0	0
Arthralgia	12 (12)	0	0
Pruritis	12 (12)	0	0
Myalgia	11 (11)	0	0
Peripheral motor neuropathy	11 (11)	1 (1)	0
Alopecia	10 (10)	0	0

\*Any adverse events includes those adverse events that may or may not be related to the study intervention.

## 6.4 Ongoing Trials

One ongoing RCT (NCT01100502) and three single-arm clinical trials (NCT00947856; Erdem et al<sup>33</sup>, NCT01703949) that met the eligibility criteria of this review were identified. Details of the identified ongoing trials can be found in Tables 4-7.

**Table 4. Study NCT01100502: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of SGN-35 and Best Supportive Care (BSC) Versus Placebo and BSC in the Treatment of Patients at High Risk of Residual Hodgkin Lymphoma Following Autologous Stem Cell Transplant (AETHERA Trial).**<sup>38</sup>

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
<p><b>Study NCT01100502</b></p> <p>Double-blind, placebo-controlled, randomized phase III trial.</p> <p>Start date: April 2010. Estimated final data collection for primary analysis: January 2014. Estimated study completion date: April 2016.</p> <p>Estimated enrolment: 329.</p> <p>Sponsor: Seattle Genetics, Inc. Collaborator: Millennium Pharmaceuticals, Inc.</p>	<p>Patients with HL who have received ASCT in the previous 30-45 days and at high risk of residual HL post-ASCT.</p> <p>Histologically confirmed HL.</p> <p>ECOG PS 0 or 1.</p>	<p><u>Two arms:</u></p> <p>Brentuximab vedotin 1.8 mg/kg i.v., once every 3 weeks.</p> <p><i>OR</i></p> <p>Placebo i.v., once every 3 weeks.</p>	<p><u>Primary outcomes:</u></p> <p>Progression-free survival</p> <p><u>Secondary outcomes:</u></p> <p>Overall survival Adverse events</p>

**Table 5. Study NCT00947856: Treatment with SGN-35 in patients with CD30-positive hematologic malignancies who have previously participated in an SGN-35 study.**<sup>32,39</sup>

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
<p><b>Study NCT00947856</b></p> <p>Single-arm phase II trial.</p> <p>Start date: July 2009. Estimate study completion date: March 2013.</p> <p>Estimated enrolment: 111.</p>	<p>Participated in previous SGN-35 study and achieved an objective response with prior brentuximab vedotin and experienced relapse after discontinuing treatment.</p> <p>CD30-positive hematologic</p>	<p>Brentuximab vedotin 1.8 mg/kg i.v., once every 3 weeks.</p>	<p><u>Primary outcomes:</u></p> <p>Adverse events (incidence)</p> <p>Best clinical response</p> <p><u>Secondary outcomes:</u></p> <p>Duration of response Progression-free survival Overall survival</p>

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Note: Bartlett et al reported that a total of 14 patients with HL were enrolled in the study.  Sponsor: Seattle Genetics, Inc. Collaborator: Millennium Pharmaceuticals, Inc.	malignancy.		

**Table 6. Erdem et al study: Brentuximab vedotin (SGN-35) in Hodgkin's lymphoma patients relapsed after autologous peripheral blood stem-cell transplantation.<sup>33</sup>**

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
<b>Erdem et al study</b> Single-arm phase II trial.  Start date: Unknown. Estimate study completion date: Unknown.  Estimated enrolment: Unknown.  Sponsor: Unknown.	Patients with HL relapsed after autologous peripheral blood stem cell transplantation.	Brentuximab vedotin 1.8 mg/kg i.v. over 30 minutes, once every 3 weeks for up to 10 cycles.	<u>Primary outcomes:</u> Objective response rate Toxicity  <u>Secondary outcomes:</u> NR

**Table 7. Study NCT01703949: A Pilot Study of Weekly Brentuximab Vedotin in Patients With CD30+ Malignancies Refractory to Every ≥3 Week Brentuximab Vedotin.<sup>40</sup>**

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
<b>Study NCT01703949</b> Single-arm phase II trial.  Start date: March 2013. Estimate study completion date: March 2015.  Estimated enrolment: 20.	Relapsed or refractory CD30+ lymphoma that has either achieved <PR to brentuximab (minimum of 2 cycles) or progressed while receiving brentuximab.  Patients must be fit enough to be expected to be able to complete 2 cycles of chemotherapy on study.	Brentuximab vedotin 1.2 mg/kg i.v. over 30 minutes, on days 1,8,15, every 4 weeks, for up to 4 cycles.	<u>Primary outcomes:</u> Response rate  <u>Secondary outcomes:</u> Adverse events Correlate response with CD30 density

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
<p>Sponsor: Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium. Collaborator: National Cancer Institute.</p>	<p>Expected survival if untreated &gt;90 days.</p> <p><u>Exclusion:</u> Prior transplant within 100 days.</p> <p>Radioimmunotherapy within 12 weeks.</p> <p>ECOG performance status: &gt;2.</p> <p>HIV or hepatitis B positive.</p>		

## 7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified in this review.

## 8 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 (Adcetris) for Hodgkin's 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 pCODR website ([www.pcodr.ca](http://www.pcodr.ca)).

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.

The Lymphoma Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website ([www.pcodr.ca](http://www.pcodr.ca)). 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

### 1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. (brentuximab: or adcetris: or sgn-35: or cac10-vcmmae:).ti,ab,sh,hw,ot,rn,nm.
2. 914088-09-8.rn,nm.
3. 1 or 2

Ovid EMBASE

1. exp \*brentuximab vedotin/
2. (brentuximab: or adcetris: or sgn-35: or cac10-vcmmae:).ti,ab.
3. 1 or 2

### 2. Literature Search via PubMed

PubMed

1. brentuximab\* or adcetris\* or SGN-35\* or cac10-vcmmae\*
2. publisher[sb]
3. 1 and 2

### 3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Search terms: (brentuximab\* or adcetris\* or SGN-35\* or cac10-vcmmae\*) in Cochrane Central Register of Controlled Trials.

### 4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov  
[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Ontario Institute for Cancer. Ontario Cancer trials  
[www.ontariocancertrials.ca](http://www.ontariocancertrials.ca)

Search terms: brentuximab, adcetris, SGN-35

Select International Agencies:

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

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

Search terms: brentuximab, adcetris

**Conference Abstracts:**

**American Society of Clinical Oncology (ASCO)**

via the *Journal of Clinical Oncology* search portal: <http://jco.ascopubs.org/search>

Search terms: brentuximab, adcetris, SGN-35

**American Society of Hematology (ASH)**

via the *Blood* search portal: <http://bloodjournal.hematologylibrary.org/search>

Search terms: brentuximab, adcetris, SGN-35

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