pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Brentuximab (Adcetris) for systemic Anaplastic Large Cell Lymphoma

December 5, 2013

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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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 systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

Brentuximab vedotin (Adcetris) is a chimeric monoclonal antibody that targets the cell membrane protein CD30 and is linked to the cytotoxic monomethyl auristatin E.[1] 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 SG035-0004 study (N=58), met the inclusion criteria for this review.[2] No randomized trials were identified that met the eligibility criteria of this systematic review. Given the single-arm design, the trial provides no comparative evidence regarding the efficacy of brentuximab in relation to any other treatment for relapsed or refractory sALCL. The study has potential limitations with respect to its single-arm design and small sample size; however, it was a well-designed and conducted non-comparative study. 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.[2]

The SG035-0004 study enrolled 58 patients who had relapsed (29 patients, 50%) after their most recently received therapy or were refractory (29 patients, 50%) to their most recently received therapy. Patients were 55% male, had a median age of 52 years (range, 14 to 76 years), CD30-positive as documented by central pathology review and had an ECOG Performance status 0 or 1.[2] The median number of prior chemotherapy regimens per patient was two (range, 1-6). Twenty-six patients (45%) had prior radiation therapy and 15 patients (26%) had prior ASCT.[2] Fourteen of 58 patients discontinued treatment due to an investigator's decision, and of those13 patients proceeded to autologous or allogeneic stem cell transplant.[3]

Patients who had previous allogeneic stem cell transplantation were excluded from the study.

Efficacy

The primary outcome of the study was objective response rate (ORR). Secondary outcomes included complete response, duration of response, progression-free survival, overall survival and adverse events. The primary endpoint, objective response rate, was 86% of 58 patients (95% confidence interval [CI], 74.6% to 93.9%) and the secondary endpoint, complete response rate, was 57% (95% CI, 43.2% to 69.8%).[2]

The median duration of objective response was 12.6 months (95% CI, 5.7 months to not estimable) and in the updated analysis (April 2012), was 13.2 months (range, 0.1 months to 27.7+ months).[4]

The median duration of complete response was 13.2 months (95% CI, 10.8 months to not estimable) and In the updated analysis (April 2012), was 14.6 months (no range or confidence intervals were reported).[4]

Harms

Sixty percent of patients experienced a Grade 3 or higher adverse event.[2] The most common Grade 3 or 4 adverse events were peripheral sensory neuropathy (12%), neutropenia (21%), and thrombocytopenia (14%). Adverse events of any grade that occurred in more than 20% of patients included, peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhea (29%), rash (24%), constipation (22%), and neutropenia (21%).[2]

Adverse events led to treatment discontinuation in 14 patients (24%), with peripheral sensory neuropathy as the reason for six patients. Of note, no patients in the study experienced progressive multifocal leukoencephalopathy (PML).[5]

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

Anaplastic large cell lymphoma (ALCL) represents a distinct subset of T-cell non-Hodgkin lymphomas accounting for approximately 3% of adult NHL diagnoses. Systemic ALCL is an aggressive malignancy with a median age at onset of 34 years and 65% of patients present with advanced (stage III or IV) disease.

Treatment options for patients with sALCL that has relapsed after, or was refractory to, multi-agent chemotherapy, vary depending on certain patient characteristics. In patients with relapsed chemotherapy-sensitive disease who are transplant-eligible, high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) is generally, the recommended treatment option. Treatment options for patients who have relapsed after HDT-ASCT or who are not eligible for HDT-ASCT are generally limited to non-curative approaches including gemcitabine-dexamethasone-cisplatin (GDP) or dexamethasone-high dose AraC-cisplatin (DHAP). Single-agent alkylator-based regimens may be used in older, unfit patients. There is a need for new treatment options with reduced toxicity to treat this group of patients.

Effectiveness

While the SG035-0004 study has obvious limitations in relation to the small number of patients treated and the lack of a comparator arm, it remains the largest study of its kind in relapsed or refractory sALCL. The response rates, overall response rate of 86% with 57% of patients achieving a complete response, was accepted as a meaningful outcome in this

context and compares favourably to those seen in other second-line strategies for this disease.

Despite the limitations associated with the single-arm design of the study, this is the largest study of its kind in relapsed or refractory sALCL and it is not reasonable to expect large randomized studies to be carried out in this condition. It is also notable that only three patients received the maximum number of cycles (16) offered to patient on this trial; thus limiting our ability to make accurate estimates of the incidence and severity of adverse effects associated with prolonged exposure to brentuximab vedotin.

Safety

The rate of adverse events in patients with relapsed or refractory sALCL treated with brentuximab vedotin compares favourably with those rates expected with other treatment strategies. Brentuximab vedotin is also associated with a low rate of treatment discontinuation for toxicity. Hematological adverse events were uncommon, with grade 4 neutropenia and thrombocytopenia seen in just 9% and 5% of patients, respectively. The most common non-hematological adverse effect was peripheral neuropathy, with only 14% of patients experienced grade 3 peripheral neuropathy and only six patients cited peripheral neuropathy as the primary reason to discontinue treatment. Improvement or resolution of neuropathy was seen in the majority of patient on discontinuation.

While progressive multifocal leukoencephalopathy was noted in patients treated with brentuximab vedotin for Hodgkin lymphoma it has not been observed in patients treated for the present indication.

1.3 Conclusions

The Lymphoma Clinical Guidance Panel concluded that there is net clinical benefit to the treatment of relapsed or refractory systemic anaplastic large cell lymphoma with brentuximab vedotin. This conclusion is based on a single-arm clinical trial that enrolled a meaningful number of patients given the condition is uncommon. Evidence in favour of this conclusion includes a high rate of clinically meaningful responses among previously treated patients and low rates of grade 3 or 4 adverse events.

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

- The conclusions of a previous pCODR assessment of a single-arm phase II clinical trial, Study SG035-0003, of brentuximab vedotin in Hodgkin lymphoma indicated that there may be net clinical benefit in that entity. However, the Clinical Guidance Panel felt that a stronger recommendation should be made in the case of relapsed sALCL, despite the smaller number of patients studied with this condition, because of the more aggressive clinical course of relapsed sALCL and the relative paucity of effective, non-toxic palliative strategies for this disease.
- The current study only supports the use of brentuximab vedotin for a maximum of 48 weeks

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 sALCL. 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.

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

Anaplastic large cell lymphoma (ALCL) represents a distinct subset of T-cell non-Hodgkin lymphomas accounting for approximately 3% of adult NHL diagnoses. Histologically ALCL is a T-cell lymphoma with large neoplastic cells with pleomorphic, often horseshoe-shaped nuclei and abundant eosinophilic cytoplasm. It is differentiated from other anaplastic malignancies by the expression of CD30. Systemic ALCL is an aggressive malignancy with a median age at onset of 34 years. Males outnumber females by 1.5:1 and 65% of patients present with advanced (stage III or IV) disease. B-symptoms, particularly fevers, are common, as is extra nodal (primarily bone and soft tissue) involvement.

Treatment options for patients with sALCL that has relapsed after, or was refractory to, multi-agent chemotherapy, vary depending on certain patient characertistics. In patients with relapsed chemotherapy-sensitive disease who are transplant-eligible, high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) is generally, the recommended treatment option. Treatment options for patients who have relapsed after HDT-ASCT or who are not eligible for HDT-ASCT are generally limited to non-curative approaches including gemcitabine-dexamethasone-cisplatin (GDP) or dexamethasone-high dose AraC-cisplatin (DHAP). Single-agent alkylator-based regimens may be used in older, unfit patients. There is a need for new treatment options with reduced toxicity to treat this group of patients.

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.[1] The targeted nature of brentuximab allows for the delivery of the cyotoxic component of the agent directly into cells expressing CD30,[1] which is typically expressed in sALCL and in Hodgkin lymphoma Reed-Sternberg cells.[6-8]

Brentuximab has a Health Canada approval for use in the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one multi-agent chemotherapy regimen.[9] Brentuximab was also approved by the U.S. Food and Drug Administration (FDA) on August 19, 2011, for the treatment of sALCL after failure of at least one prior multi-agent chemotherapy regimen.[10]

A submission to pCODR was made in March 2013 to request funding for brentuximab vedotin (Adcetris) for the second-line treatment of patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen.[11]

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 systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

See Table 3 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 SG035-0004 study, met the inclusion criteria.[2,4,12-15] The study was conducted in 22 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.

Patients with sALCL that had relapsed after, or were refactory to, at least one prior therapy of curative intent were enrolled into the SG035-0004 study.[2] Patients who had previously received an allogeneic stem cell transplantation were ineligible. 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.[2]

Table 1. Summary of Trial characteristics of the SG035-0004 Study.[2]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00866047 Open-label phase II trial 22 sites in the U.S.A., Canada, and Europe Patient accrual: June 2009 through May 2010 Data cut-off (analysis): January 14, 2011 Enrolled: n=58 Funded by: Seattle Genetics, Bothell, WA, U.S.A.	Diagnosis of relapsed or refractory sALCL after failure of at least one prior therapy with curative intent. CD30-positive disease and histology by central pathology review. Patients had measurable disease by CT (>1.5cm) and fluorodeoxyglucose-avid disease by PET. ECOG Performance status 0 or 1. **Exclusion criteria:** 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.	**Primary** ORR* **Secondary** DoR* CRR* PFS* OS AE's

Abbreviations: AE's = adverse events; **CRR**= complete response rate; **CT** = computed tomography; **DoR** = duration of response; **i.v.** = intravenously; **ECOG** = Eastern Cooperative Oncology Group; **ORR** = objective response rate; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **sALCL**=systemic anaplastic large cell lymphoma.

* Response-based outcomes were assessed using the Revised Response Criteria for Malignant Lymphoma[16] by an independent review facility.

The investigators planned to enrol a total of 55 patients.[5] The primary outcome of the study was objective response rate. Secondary outcomes included complete response rate, duration of response, progression-free survival, overall survival, and adverse events. Outcomes based on assessments of response were assessed using the Revised Response Criteria for Malignant Lymphoma[16] by an independent review facility.[2] Duration of response, progression-free survival and overall survival were estimated using the Kaplan-Meier method.[2]

A total of 58 patients were enrolled. Fifty-seven percent of patients were male. The median age was 52 years (range, 14 to 76 years).[2] The median number of prior chemotherapy regimens per patient was two (range, 1-6). Twenty-six patients (45%) had prior radiation therapy and 15 patients (26%) had prior ASCT.[2] Pro et al reported that 29 patients (50%) were refractory to their most recently received therapy, defined as either a best response of partial remission, stable disease, or progressive disease if a patient had only one prior therapy, or as a best response of stable disease or progressive disease if a patient had more than one prior therapy. The remaining 29 patients (50%) were relapsed after their most recently received therapy, defined as either a best response of complete remission if a patient had only one prior therapy, or as a best response of complete or partial remission if a patient had more than one prior therapy.[2] Fourteen of 58 patients discontinued treatment due to an investigator's decision, and of those13 patients proceeded to autologous or allogeneic stem cell transplant.[3]

All 58 patients were included in the final analysis (data cut-off: January 2011).[2] At the time of the analysis 49 patients had discontinued treatment and nine were still continuing

treatment.[3] Reasons for discontinuation included, adverse events (n=14), investigator decision (n=14), disease progression (n=13), or patient's decision (n=5), and three patients completed all 16 cycles of treatment.[3] At the December 2012 American Society of Hematology (ASH) annual meeting, Pro et al[4] reported the results of an updated analysis with a data cut-off in April 2012.

The SG035-0004 study was a well conducted and designed single-arm trial investigating the use of brentuximab in patients with relapsed or refractory sALCL who had received at least one prior therapy of curative intent. The study has potential limitations with respect to its single-arm design and small sample size, which make it difficult to estimate the true incidence and severity of adverse events that are due to brentuximab and to reliably estimate time to event outcomes such as progression-free survival, duration of response, and overall survival. Given the single-arm design, the trial provides no comparative evidence regarding the efficacy of brentuximab in relation to any other treatment for relapsed or refractory sALCL.

A summary of the efficacy and key adverse events can be found in Table 2. The objective response rate was 86% (95% confidence interval [CI], 74.6% to 93.9%) of 58 patients and the complete response rate was 57% (95% CI, 43.2% to 69.8%).[2] The median duration of objective response was 12.6 months (95% CI, 5.7 months to not estimable) and the median duration of complete response was 13.2 months (95% CI, 10.8 months to not estimable). In the updated analysis (April 2012), the estimated median duration of objective response was 13.2 months (range, 0.1 months to 27.7+ months).[4] The estimated median duration of complete response was not reached in the updated analysis.[4]

At the time of the final analysis in January 2011, 18 patients had died and the median overall survival had not been reached with a range of 14.6 months to not estimable.[2] The median follow-up was not reported. The estimated 12-month survival rate was 70%.[2] At the updated analysis in April 2012, 21 patients had died and the median overall survival was still not yet reached, with a 12-month survival rate of 71% (95% CI, 57% to 80%).[4,5]

A summary of the Grade 3 or 4 adverse events experienced by at least two patients in the trial can be found in Table 2. Sixty percent of patients experienced a Grade 3 or higher adverse event.[2] The most common Grade 3 or 4 adverse events were peripheral sensory neuropathy (12%), neutropenia (21%), and thrombocytopenia (14%). Adverse events of any grade that occurred in more than 20% of patients included, peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhea (29%), rash (24%), constipation (22%), and neutropenia (21%).[2]

A total of 31 patients (53%) experienced peripheral neuropathy of any grade. Of those, 41% experienced peripheral sensory neuropathy, 7% paresthesia, 5% neuralgia, 5% peripheral motor neuropathy, and 2% each, burning sensation and polyneuropathy.[2] Eight patients (14%) experienced a Grade 3 peripheral neuropathy but none experienced one of Grade 4.

Table 2. Key efficacy outcomes and adverse events reported in the single-arm SG035-0004 study.[2] N=58

Efficacy	ORR (%)	CRR (%)	Duration of OR (Mdn, mos)	Duration of CR (Mdn, mos)	PFS (Mdn, mos)	OS (Mdn, mos)		Follow-up (Mdn, mos)
						Jan 2011[A]	Apr 2012[B]	
Estimate	86	57	12.6	13.2	13.3	NYR	NYR	22.8[C]
95% CI	74.6-93.9	43.2-69.8	5.7-NE	10.8-NE	6.9 to NE	-	-	
Adverse events	**Peripheral sensory neuropathy**	**Neutropenia**	**Thrombo-cytopenia**	**Fatigue**	**Diarrhea**	**Vomiting**	**Pain in extremity**	**Weight decreased**
Any Grade (%)	41	21	14	38	29	17	12	14
Grade 3/4 (%)	12	21	14	5	3	3	3	3

Abbreviations: CR(R)=compete response (rate); **Mdn**=median; **mos**=months; **NE**=not estimable; **NYR**=not yet reached; **OR(R)**=objective response (rate); **OS**=overall survival; **PFS**-progression-free survival.
[A]Final analysis conducted in January 2011 at which point 18 patients had died.
[B]Updated analysis conducted in April 2012, at which point 21 patients had died.
[C]Median follow-up reported at updated analysis conducted in April 2012. The length of follow-up was not reported for the final analysis conducted in January 2011.

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 sALCL 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. Patients are 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. There is a significant unmet need for less toxic and effective treatment for sALCL.

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 brentuximab is a "first-in-class", targeted therapy for the treatment of relapsed/refractory sALCL. PAG also noted that the sALCL patient population with refractory/resistant disease is very small and as such implementing a funding decision will have a small budgetary impact. Both factors were seen as enablers to implementation.

PAG is uncertain as to how the drug will be assessed in determining its placement in a line of therapy in relapsed/refractory sALCL patients as the pivotal study presented is a single arm Phase 2 trial and does not have a comparator arm. PAG noted a possibility for indication creep as the disease is uncommon with a prognosis that is generally poor and the potential to fail. PAG also noted a significant possibility for drug wastage, given the limited drug stability after reconstitution and small patient population which reduces the possibility for vial sharing.

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

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 SG035-0004 study did not report any occurrences of PML. Of note, 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.[5] The EPAR also reported that in total, three confirmed cases of PML have occurred out of approximately 2000 patients treated with brentuximab.[5]

The product monograph provided by the manufacturer (Seattle Genetics, Inc.) provides several warnings and precautions including, but not limited to:[9]

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

Anaplastic large cell lymphoma is an uncommon subtype of non-Hodgkin lymphoma, with an estimated incidence of 230 new cases per year across Canada. Of these patients, approximately 66% may be cured with conventional chemotherapy or salvage autologous stem cell transplantation at first relapse. As a result it is estimated that fewer than 100 patients per year would require treatment with novel agents for relapsed or refractory disease in Canada. Given it is relatively uncommon and affects such a small number of patients it is not likely that meaningful randomized studies will be carried out in this condition.

Patients with relapsed or refractory sALCL have few effective treatment options. Patients with localized relapse may benefit from radiotherapy for symptomatic control. Those with more systemic relapses may be treated with combination or single-agent chemotherapy depending on performance status and disease burden. Such treatment is likely to result in remissions of limited duration at the expense of toxicities such as neutropenic infection, peripheral neuropathy and reduced quality of life. Patient advocacy groups indicate an urgent need for less toxic treatments for patients with this condition.

Efficacy

In a single-arm phase II study patients (n=58) with systemic anaplastic large cell lymphoma relapsed after or refractory to at least one line of chemotherapy were treated with brentuximab vedotin every three weeks for a maximum of 16 cycles or until disease progression. Other characteristics of the group were CD30-positivity documented by central pathology review and ECOG performance status of 0 – 1. The overall response rate was 86%, with 57% of patients achieving a complete response. Responses lasted approximately 13 months. While this study has obvious limitations in relation to the small number of patients treated and the lack of a comparator arm, it remains the largest study of its kind in relapsed or refractory sALCL. Response rates compare favourably to those seen in other second-line strategies for this disease.

Safety

Brentuximab vedotin is associated with a low rate of treatment discontinuation for toxicity. Hematological adverse events were uncommon, with grade 4 neutropenia and thrombocytopenia seen in just 9% and 5% of patients, respectively. The most common non-hematological adverse effect seen in patients treated with brentuximab vedotin was peripheral neuropathy, which occurred in approximately half of patients. Only 14% of patients experienced grade 3 peripheral neuropathy and only six patients cited peripheral neuropathy as the primary reason to discontinue treatment with brentuximab vedotin. Improvement or resolution of neuropathy was seen in the majority of patient on discontinuation. While progressive multifocal leukoencephalopathy was noted in patients treated with brentuximab vedotin for Hodgkin lymphoma it has not been observed in patients treated for the present indication.

The rate of adverse events in patients with relapsed or refractory sALCL treated with brentuximab vedotin compares favourably with those rates expected with other treatment strategies.

Limitations

The current study enrolled pre-treated patients (median number of prior regimens 2 (range 1 – 6)). The effect of offering this agent to less heavily pre-treated patients (who would be expected to experience fewer adverse effects) is unknown. Only three patients received the maximum number (16) of cycles offered to patient on this trial; this limits our ability to make accurate estimates of the incidence and severity of adverse effects associated with prolonged exposure to brentuximab vedotin. The current study supports the use of brentuximab vedotin for a maximum of 48 weeks. Strategies using this agent for longer periods of time are under investigation and further recommendations will have to await publication of these results. Brentuximab vedotin may be useful as a bridge to allogeneic stem cell transplantation for highly selected, transplant eligible patients. Its role in this setting has not been determined but allografting has been used as a strategy for patients with chemosensitive relapsed lymphoma.

The single-arm design of the study reported by Pro et al.[2] makes it impossible to determine the relative efficacy of brentuximab vedotin compared with other treatment strategies. The small number of patients enrolled also makes accurate estimates of time to event endpoints such as overall- and progression-free survival difficult. Nonetheless, this is the largest study of its kind in relapsed or refractory sALCL and it is not reasonable to expect large randomized studies to be carried out in this condition and response rate was accepted as a meaningful outcome in this context.

2.3 Conclusions

The Lymphoma Clinical Guidance Panel concluded that there is net clinical benefit to the treatment of relapsed or refractory systemic anaplastic large cell lymphoma with brentuximab vedotin. This conclusion is based on a single-arm clinical trial that enrolled a meaningful number of patients given the condition is uncommon. Evidence in favour of this conclusion includes a high rate of clinically meaningful responses among previously treated patients and low rates of grade 3 or 4 adverse events.

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

- The conclusions of a previous pCODR assessment of a single-arm phase II clinical trial, Study SG035-0003, of brentuximab vedotin in Hodgkin lymphoma indicated that there may be net clinical benefit in that entity. However, the Clinical Guidance Panel felt that a stronger recommendation should be made in the case of relapsed sALCL, despite the smaller number of patients studied with this condition, because of the more aggressive clinical course of relapsed sALCL and the relative paucity of effective, non-toxic palliative strategies for this disease.
- The current study only supports the use of brentuximab vedotin for a maximum of 48 weeks

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

Anaplastic large cell lymphoma (ALCL) represents a distinct subset of T-cell non-Hodgkin lymphomas accounting for approximately 3% of adult NHL diagnoses. No particular risk factors have been recognized for this disease and it does not appear to be associated with infection with any of the viruses commonly described in association with the development of lymphoma in humans, such as Epstein-Barr virus, HHV-8 and the human T-cell retroviruses. It does not appear to be more common in immunocompromised individuals, although its occurrence in this population is associated with an aggressive clinical course and poor overall survival.

Histologically ALCL is a T-cell lymphoma with large neoplastic cells with pleomorphic, often horseshoe-shaped nuclei and abundant eosinophilic cytoplasm. It is differentiated from other anaplastic malignancies by the expression of CD30. Two distinct subtypes of ALCL have been described based on primary site of involvement and the expression of ALK, the product of the hallmark cytogenetic abnormality t(2;5). Primary cutaneous ALCL is generally ALK-negative and has an indolent clinical course. Systemic ALCL is an aggressive malignancy with a median age at onset of 34 years. Males outnumber females by 1.5:1 and 65% of patients present with advanced (stage III or IV) disease. B-symptoms, particularly fevers, are common, as is extra nodal (primarily bone and soft tissue) involvement.

3.2 Accepted Clinical Practice

Prognostic factors in systemic ALCL appear to be broadly similar to those of other aggressive lymphomas, and include factors such as age, stage at presentation, and tumour markers such as lactate dehydrogenase and ß2-microglobulin. The IPI is commonly used for prognostication in systemic ALCL,[17] although the GELA group has reported that overall and progression-free survival may be predicted more accurately by using a two-factor system consisting of age and ß2-microglobulin. Good-risk patients (age < 40 and ß2-microglobulin < 3 mg/L) experience 8-year OS and PFS 84% and 76% while in the high risk group (age > 40 and ß2-microglobulin > 3 mg/mL) these are only 22% and 13%.[18] In general, the prognosis of patients with systemic ALCL is better than it is for any other subset of T-cell lymphoma.[19]

Due to its relative rarity and recent description systemic ALCL has not been studied separately from other aggressive non-Hodgkin lymphomas. Its distinct clinical course has also excluded patients with this disease from clinical trials of novel agents in T-cell lymphoma. The inferior outcome of T-cell compared with B-cell non-Hodgkin lymphoma was described by the GELA group in the LNH-87 trial. The complete response (CR) rate for B-cell lymphomas was 63% versus 54% for T-cell lymphomas (p=0.004).[20] The CR rate among 146 systemic ALCL patients reported in this study was 75%, with a 5-year overall survival (OS) of 66%.[21] While the regimens tested in the LNH-87 trial contained anthracycline many were distinctly not CHOP-like and included mBACOD, ACVB and high-dose CVB and autologous stem cell transplantation. Excellent results have been reported with CHOP and similar regimens, with CR rates between 55-79% and 5-year OS between 44-61%.[22-24] Reiser et al. describe a median overall survival of 11.5 years in a cohort of 19 patients with systemic ALCL treated with CHOP chemotherapy.[24]

High-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) is generally recommended for transplant-eligible patients with relapsed, chemo sensitive systemic ALCL. This recommendation is based on logical inference from the Parma trial, in which patients with aggressive non-Hodgkin lymphoma were randomized between high-dose therapy and conventional salvage.[25] Patients in the high-dose arm enjoyed considerably higher OS and PFS. The results of second-line HDT-ASCT in peripheral T-cell lymphoma have been described in several retrospective series. Three-year failure-free survival ranges between 32-50% and OS is generally poor after progression.[26-30] Studies reporting histology have consistently noted better outcomes from HDT-ASCT for patients with systemic ALCL compared with other subtypes of T-cell lymphoma. Blystad et al. described the outcome of HDT-ASCT for patients with relapsed peripheral T-cell lymphomas in a single-center report from Norway.[30] In this report 3-year OS for patients with systemic ALCL was 79% compared with 44% among patients with non-ALK+ systemic ALCL peripheral T-cell lymphoma.[30] Another single center report from Vanderbilt University describes 86% 3-year OS for systemic ALCL vs. 47% OS for non-ALCL T-cell lymphomas.[28]

The treatment of patients with systemic ALCL who have relapsed after HDT-ASCT or who are not eligible for intensive treatment due to comorbidity, failure to mobilize stem cells or advanced age remains unsatisfactory. At present such patients are treated with a variety of non-curative approaches, including salvage regimens such as gemcitabine-dexamethasone-cisplatin (GDP) or dexamethasone-high-dose AraC-cisplatin (DHAP). Single-agent alkylator-based regimens may be recommended for older, unfit individuals. The identification of novel agents with reduced toxicity would be especially beneficial in this group of patients.

3.3 Evidence-Based Considerations for a Funding Population

The SG035-0004 study enrolled patients with sALCL that had relapsed after, or were refractory to, at least one prior therapy with curative intent. Patients had to have CD30-positive disease by central pathology review and an ECOG performance status of 0 or 1. Anaplastic large cell lymphoma is an uncommon subtype of non-Hodgkin lymphoma, with an estimated incidence of 230 new cases per year across Canada. Of these patients, approximately 66% may be cured with conventional chemotherapy or salvage autologous stem cell transplantation at first relapse. As a result it is estimated that fewer than 100 patients per year would require treatment with novel agents for relapsed or refractory disease in Canada. No supplemental diagnostic or pathology tests will be required as immunohistochemical staining to prove CD30 positivity is standard and is required to confirm a diagnosis of sALCL.

3.4 Other Patient Populations in Whom the Drug May Be Used

The SG035-0004 study enrolled patients with sALCL that had relapsed after, or were refractory to, at least one prior therapy with curative intent. Patients had to have CD30-positive disease by central pathology review and an ECOG performance status of 0 or 1. It has not been used in first line, although clinical trials testing up-front combinations of brentuximab vedotin in peripheral T-cell lymphomas are ongoing. Brentuximab vedotin may be useful as a bridge to allogeneic stem cell transplantation for highly selected, transplant eligible patients. Its role in this setting has not been determined but allografting has been used as a strategy for patients with chemosensitive relapsed lymphoma.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group provided input on brentuximab for systemic Anaplastic Large Cell Lymphoma (sALCL) and their input is summarized below:

- Lymphoma Foundation Canada

The Lymphoma Foundation Canada conducted one-on-one interviews with patients with direct experience with brentuximab to gather information about patient and caregiver experiences. Information was also collected from oncologists and from reading literature about the drug under review and about sALCL. The patient advocacy group indicated they were unable to conduct interviews, surveys or focus groups with patients with sALCL as the patient base is limited.

From a patient perspective, additional drug therapies for the treatment of sALCL 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. Patients are 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. There is a significant unmet need for less toxic and effective treatment for sALCL.

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 sALCL

Anaplastic large cell lymphoma (ALCL) is an uncommon form of non-Hodgkin lymphoma. ALCL occurs in two forms: systemic ALCL which can affect all organs in the body and is aggressive; and primary cutaneous ALCL which is confined to the skin and tends to be slow-growing. A common early sign of patients diagnosed with sALCL is the painless enlargement of one or more lymph nodes in the neck, armpit or groin, or less often, a swollen lymph node near the ears, the elbow or in the throat near the tonsils. As there are about 600 lymph nodes in the body, other parts of the body commonly affected include bones, skin, bone marrow, lungs and the liver. Night sweats, fevers and unexplained weight loss may also be present in patients with sALCL.

The Lymphoma Foundation Canada was unable to interview patients with sALCL as the patient base is limited. Depending on the location of the swollen lymph nodes some patients experience pain in the area of the swollen lymph node. Many patients experience severe night sweats. The anxiety caused by these symptoms is cause for great concern for patients. It is important for patients to receive a definitive diagnosis in as short a time as possible.

4.1.1 Patients' Experiences with Current Therapy for SALCL

Input from the Lymphoma Foundation Canada indicates that systemic ALCL in the first-line setting is treated with the chemotherapy regimen CHOP (cyclophosphamide, doxorubin, vincristine and prednisone) and that second –line therapy may include DHAP (dexamethasome, (cytarabine, cisplatin); ICE (ifosfamide, carboplastin, etoposide); ESHAP

(etoposide, methylprednisolone, high-dose cytarabine and cisplatin); or GDP (gemcitabine, vinorelbine, liposomal doxorubicin.

The Lymphoma Foundation Canada indicates that 40-65 % of patients with ALCL experience a relapse and that when patients do relapse there are currently no other therapies available. Current therapies are very toxic and depending on a patient's age, staging and performance status the side effects can be difficult to tolerate. Patients are willing to try any new medication if it can provide a cure or put their cancer into remission.

4.1.2 Impact of sALCL and Current Therapy on Caregivers

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

Caregivers face daily stress and worry about the wellbeing of the patient. Fear of dying are issues that both the patient and caregiver experience. Caregivers need to know the "right" way to deal with death, 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 may be required to stop working, yet still incur the costs associated with travel and drugs not funded by public or private plans. There is also the issue of the health and age of the caregiver and how their quality of life is affected.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Brentuximab

The Lymphoma Foundation Canada was unable to interview patients with ALCL due to the small patient base who have this type of cancer. However, as with all relapsed cancer patients, the patient advocacy group is certain that patients want treatment options that will control their disease and extend their life, while also allowing them to enjoy a good quality of life and a possibility for a cure. Many cancer patients are willing to incur side effects if it will increase their likelihood for survival.

Patient advocacy group input indicates that is it very important for patients and physicians to have a choice in deciding which drug therapy the patient should receive. 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. Patients are willing to incur side effects to increase the likelihood of survival.

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 systemic anaplastic large cell lymphoma (sALCL). 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).

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 brentuximab is a "first-in-class", targeted therapy for the treatment of relapsed/refractory sALCL. PAG also noted that the sALCL patient population with refractory/resistant disease is very small and as such implementing a funding decision will have a small budgetary impact. Both factors were seen as enablers to implementation.

PAG is uncertain as to how the drug will be assessed in determining its placement in a line of therapy in relapsed/refractory sALCL patients as the pivotal study presented is a single arm Phase 2 trial and does not have a comparator arm. PAG noted a possibility for indication creep as the disease is uncommon with a prognosis that is generally poor and the potential to fail. PAG also noted a significant possibility for drug wastage, given the limited drug stability after reconstitution and small patient population which reduces the possibility for vial sharing.

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

5.1 Factors Related to Comparators

PAG members indicated that in patients whose disease has relapsed or is resistant to standard initial therapy, further therapeutic options include salvage combination chemotherapy or non-curative single agent chemotherapy and autologous stem cell transplant (ASCT). If a patient fails salvage chemotherapy and ASCT, PAG members indicate that further therapy is limited and consists of palliation. 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 the therapy of relapsed/refractory sALCL patients.

5.2 Factors Related to Patient Population

PAG noted a possibility for indication creep as the disease is uncommon, with a generally poor prognosis and potential to fail.

As an enabler, PAG noted that the number of patients with refractory/resistant sALCL is small. This means that implementing a funding decision will have a small budgetary impact.

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

5.3 Factors Related to Accessibility

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 patients with of relapsed/refractory is small. This presents a barrier to accessibility for patients.

PAG noted that similar to the accessibility of current salvage chemotherapy protocols, brentuximab will likely only 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.

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 sALCL 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 sALCL 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 and may require additional pharmacy resources.

PAG noted that although brentuximab will require chemotherapy chair time for 30min IV infusions, the protocol requires less time that other more aggressive chemotherapies currently available for patients with sALCL, 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 sALCL. 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

As an enabler, PAG noted that brentuximab is a first in class targeted therapy for the treatment of sALCL in relapsed/refractory patients.

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 systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

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

Note: No Supplemental Questions relevant to the pCODR review and 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† 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 sALCL who have failed treatment after at least one prior multi-agent chemotherapy regimen.	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.	In fit patients: ASCT In patients not fit for ASCT: Best supportive care	**OS** **PFS** **Response rate (CR and PR)** **Duration of response** **QOL** **Adverse events**

Abbreviations: ASCT=autologous stem cell transplantation; **CR**=complete response; **i.v.**=intravenously; **OS**=overall survival;

PFS=progression-free survival; **PR**=partial response; **QOL**=quality of life; **RCT**=randomized controlled trial; **sALCL**=systemic anaplastic large cell lymphoma.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
† 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 8) 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 September 5, 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 – clinicatrials.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:

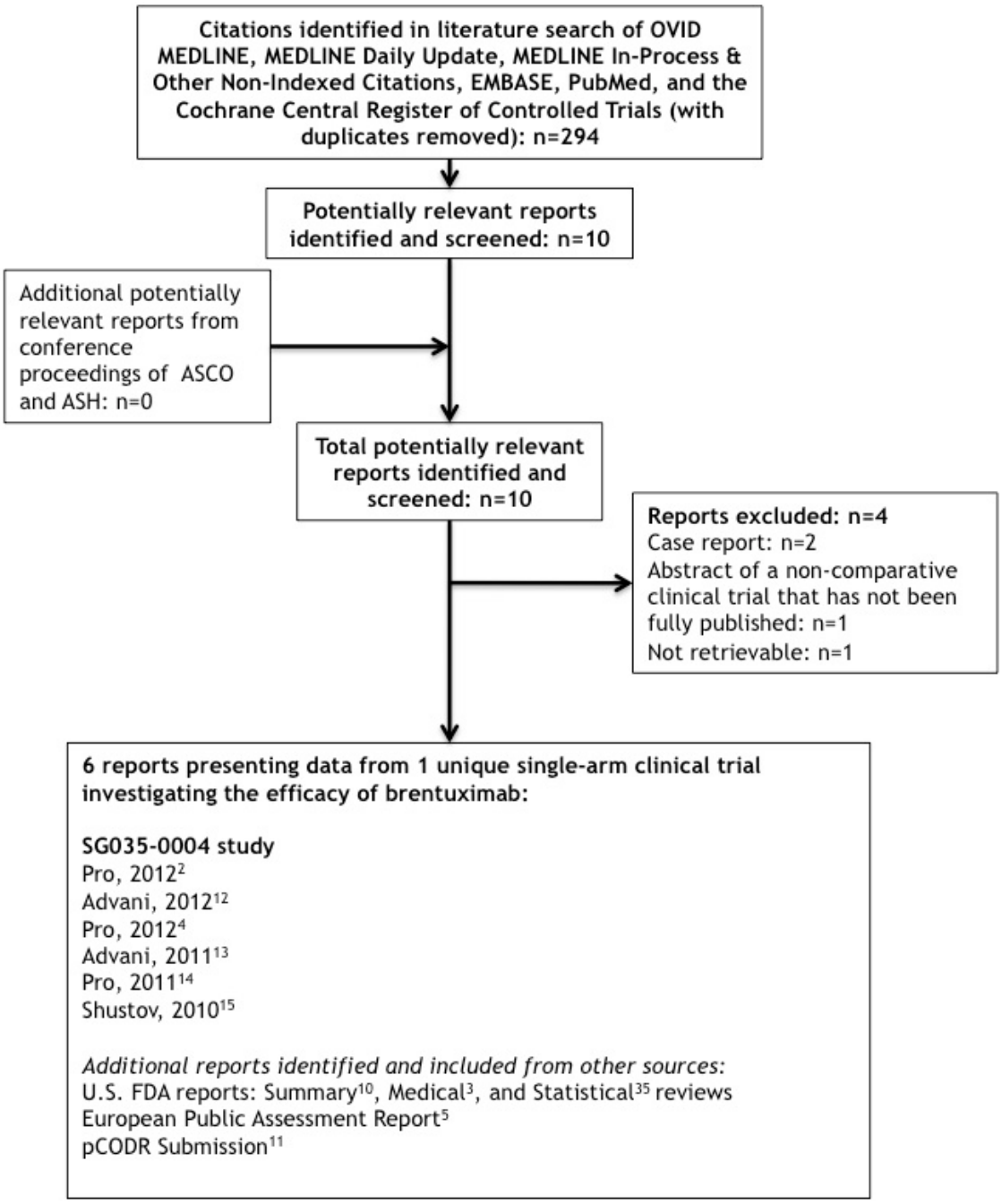
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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 294 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 294 citations, 10 potentially relevant reports were retrieved for full text review. Six reports were included in the pCODR systematic review [2,4,12-15] and four reports were excluded. Studies were excluded because two were case reports [31,32], one citation was not retrievable[33], and one was an abstract of a single-arm clinical trial that has not yet been fully published.[34] The latter study was included in Section 6.4 *Ongoing Trials*. In addition, the United States Food and Drug Administration's (U.S. FDA) Summary[10], Medical[3] and Statistical Reviews[35] and the European Medicines Agency's European Public Assessment Report (EPAR)[5] on brentuximab were also included as was the submission by the manufacturer to pCODR.[11]

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 SG035-0004 study, met the inclusion criteria for this review. Select characteristics of that trial, reported in a full publication by Pro et al[2], can be found in Table 2. The trial was conducted at 22 centres in the U.S.A., Canada, and Europe. The study was funded by Seattle Genetics, Bothell, WA, U.S.A.

The primary outcome of the study was objective response rate (ORR) as determined by an independent review facility.[2] A total of 55 patients were planned to be enrolled in order to rule out an ORR of 20% or smaller, if the true ORR was at least 50%.[35] 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 according to the Revised Response Criteria for Malignant Lymphoma[16] by an independent review facility.[2] Response was assessed by computed tomography (CT) at cycles 2, 4, 7, 10, 13, and 16 and by positron-emission tomography (PET) at cycles 4 and 7. Follow-up visits were conducted every 12 months after discontinuation of study treatment until disease progression for those patients who discontinued study treatment with stable disease or better.[2]

Response rates were calculated and included the two-sided 95% exact confidence interval (CI). Median duration of response, progression-free survival, and overall survival and their 95% CI were estimated using the methods of Kaplan and Meier.[2]

Given the single-arm design of this study, no statistical comparisons were planned or reported.

b) Populations

The SG035-0004 study enrolled patients with sALCL that had relapsed after, or were refractory to, at least one prior therapy with curative intent. Patients had to have CD30-positive disease by central pathology review and an ECOG performance status of 0 or 1. Table 2 provides further details regarding the trial's inclusion and exclusion criteria.

A total of 58 patients were enrolled into the study of whom 33 were male (57%) and 25 were female (43%).[2] Forty-eight patients ((83%) were White, seven (12%) were Black or African American, one (2%) was Asian, and two (3%) were classified as 'Other'.[2] The median age was 52 years with a range of 14 years to 76 years.[2] While all 58 patients were CD30-positive by central review[3], only 56 patients (97%) had a pathologic diagnosis of sALCL by central assessment[2]; one patient had Hodgkin lymphoma and one had a CD30-positive lymphoproliferative disorder.[3] At baseline, 15 patients (26%) had malignant cutaneous lesions. The median number of prior chemotherapy regimens per patient was two, with a range of 1-6. Twenty-six patients (45%) had prior radiation therapy and 15 patients (26%) had prior autologous stem cell transplantation.[2] Thirteen patients (22%) had no response to any prior treatment and 36 patients (62%) were primary refractory to first-line therapy (defined as no complete remission or relapse within 3 months of first-line therapy). Forty-two patients (72%) had anaplastic lymphoma kinase (ALK)-negative disease.

Half of the patients (n=29) in the SG035-0004 study were refractory to their most recently received therapy (defined as a best response of partial remission, stable disease, or progressive disease if a patient had only one prior therapy, or a best response of stable disease or progressive disease to the most recent therapy if a patient had more than one prior therapy). The other half of the patients (n=29) relapsed after their most recently received therapy (defined as a best response of complete remission if a patient had only one prior therapy, or a best response of complete or partial remission to the most recent therapy if a patient had more than one prior therapy).[2] Of note, the U.S. FDA Medical Review noted that the investigators' definition of refractory disease is not commonly accepted and therefore the FDA reviewer re-analyzed the refractory disease status of the 29 patients that the investigator classified as having refractory disease.[3] The reviewer reclassified 15 patients as having relapsed disease, 11 patients with primary refractory disease, one as unknown, and two patients remained classified as refractory. The reviewer concluded that the trial included 44 patients (76%) with relapsed sALCL, 11 patients (19%) with primary refractory sALCL, and two patients (3%) who were refractory to their last line of treatment.[3]

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.[2]

All patients received at least one dose of the study drug.[2] The median number of cycles per patient was seven (range, 1-16 cycles).[2] Three patients received the maximum number of cycles: 16.[3]

d) Patient Disposition

All 58 enrolled patients were included in the final analysis.[2] The U.S. FDA Medical Review[3] reported details regarding patient disposition in the SG035-0004 study. At the time of the analysis, nine patients were continuing treatment and 49 patients had discontinued treatment.[3] Of the 49 patients who discontinued treatment 14 patients (29%) were due to adverse events, 14 patients (29%) were due to investigator decision, 13 patients (27%) were due to disease progression, and five patients (10%) were due to the patient's decision, and three patients completed all 16 cycles of treatment.[3] Of the 14 patients who discontinued due to an investigator's decision, 13 patients proceeded to autologous or allogeneic stem cell transplant.[3]

e) Limitations/Sources of Bias

The SG035-0004 study was a well designed and conducted single-arm trial investigating the use of brentuximab in patients with relapsed or refractory sALCL who had received at least one prior therapy of curative intent. The study has potential limitations with respect to its single-arm design and small sample size, which make it difficult to estimate the true incidence and severity of adverse events that are due to brentuximab and to reliably estimate time to event outcomes such as progression-free survival, duration of response, and overall survival. Given the single-arm design, the trial provides no comparative evidence regarding the efficacy of brentuximab in relation to any other treatment for relapsed or refractory sALCL.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

A total of 58 patients were included in the intent-to-treat efficacy analysis and the safety analysis.[2] That analysis had a data cut-off of January 2011. An updated analysis was reported at the annual American Society of Hematology meeting in December of 2012.[4] That analysis had a

data cut-off of April 2012 and all patients had discontinued treatment by that point with a median follow-up time (from first study dose) of 22.8 months (range, 0.8 months to 32.2 months).[4]

Efficacy Outcomes

Response and Duration of Response

The ORR was 86% (95% CI, 74.6% to 93.9%) in 58 patients and the CRR was 57% (95% CI, 43.2% to 69.8%).[2]

The median duration of objective response was 12.6 months (95% CI, 5.7 months to not estimable).[2] For the 33 patients who had a complete response, the median duration of that response was 13.2 months (95% CI, 10.8 months to not estimable).[2]

In the updated analysis, the estimated median duration of objective response by the Kaplan-Meier method was 13.2 months (range, 0.1 months to 27.7+ months).[4] The estimated median duration of response for patients who obtained a complete response was not reached (range, 0.7 months to 27.7+ months).[4]

Progression-free Survival

The estimated median progression-free survival was 13.3 months (95% CI, 6.9 months to not estimable) and greater than the magnitude that was reported for the most recent prior treatment (HR=0.48, P=0.001).[2] In the updated analysis, the estimated median progression-free survival was 14.6 months (95% CI, 6.9months to 20.6 months).[4]

Overall Survival

At the January 2011 analysis, 18 patients had died and the median overall survival had not been reached with a range of 14.6 months to not estimable. The estimated 12-month survival rate was 70%.[2]

At the April 2012 updated analysis, median overall survival had not been reached.[4] The European Public Assessment Report indicated that at the time of that analysis, 21 patients had died and the estimated 12-month survival rate was 71% (95% CI, 57% to 80%).[5]

Harms Outcomes

Table 4 provides a summary of the adverse events (any grade, Grade 3, or Grade 4) that occurred in more than 10% of patients in the SG035-0004 study.[2]

Adverse events of any grade that occurred in more than 20% of patients included peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhea (29%), rash (24%), constipation (22%), and neutropenia (21%).[2] Sixty percent of patients experienced a Grade 3 or higher adverse event.[2] The most common Grade 3 adverse events were peripheral sensory neuropathy (12%), neutropenia (12%) and thrombocytopenia (9%).[2] Grade 4 neutropenia and thrombocytopenia occurred in 9% and 5% of patients, respectively.[2] In addition, Grade 4 fatigue and pain in extremity occurred in 2% of patients, each.[2] Grade 3 or higher anemia was experienced by 7% of patients.

A total of 31 patients (53%) experienced peripheral neuropathy of any grade. Of those, 41% experienced peripheral sensory neuropathy, 7% paresthesia, 5% neuralgia, 5% peripheral motor neuropathy, and 2% each, burning sensation and polyneuropathy.[2] Eight patients (14%) experienced Grade 3 peripheral neuropathy and no patients experienced a Grade 4 peripheral neuropathy.[2] The median time to onset of peripheral neuropathy of

any grade was 13.3 weeks and 28.4 weeks for Grade 3 events. Improvement or resolution of neuropathy occurred in 25 of 31 patients (81%), with complete resolution in 15 patients (48%).[2] The median time to improvement or resolution was 9.9 weeks (range, 0.3 weeks to 32.9 weeks).[2]

Six patients died within 30 days of the last dose of brentuximab; however none of those deaths were attributed to brentuximab. Adverse events led to treatment discontinuation in 14 patients (24%), with peripheral sensory neuropathy as the reason in six patients. Of note, no patients in the study experienced progressive multifocal leukoencephalopathy (PML).[5]

Table 4. Adverse Events That Occurred in More Than 10% of all Patients (n=58) in the SG035-0004 Study.[2]

Adverse event	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)
Peripheral sensory neuropathy	24 (41)	7 (12)	0
Nausea	23 (40)	1 (2)	0
Fatigue	22 (38)	2 (3)	1 (2)
Pyrexia	20 (34)	1 (2)	0
Diarrhea	17 (29)	2 (3)	0
Rash	14 (24)	0	0
Constipation	13 (22)	1 (2)	0
Neutropenia	12 (21)	7 (12)	5 (9)
Headache	11 (19)	1 (2)	0
Pruritus	11 (19)	0	0
Cough	10 (17)	0	0
Dyspnea	10 (17)	1 (2)	0
Upper respiratory tract infection	10 (17)	0	0
Vomiting	10 (17)	2 (3)	0
Decreased appetite	9 (16)	1 (2)	0
Dizziness	9 (16)	0	0
Insomnia	9 (16)	0	0
Myalgia	9 (16)	1 (2)	0
Alopecia	8 (14)	0	0
Chills	8 (14)	0	0
Muscle spasms	8 (14)	1 (2)	0

Thrombocytopenia	8 (14)	5 (9)	3 (5)
Weight decreased	8 (14)	2 (3)	0
Edema, peripheral	7 (12)	0	0
Pain in extremity	7 (12)	1 (2)	1 (2)

Notes: N=number of patients.

6.4 Ongoing Trials

No ongoing RCTs were identified that investigated the use of brentuximab monotherapy and three single-arm clinical trials (NCT00947856[34,36], NCT01703949[37], and NCT01909934[38]) that met the eligibility criteria of this review were identified. Details of the identified ongoing trials can be found in Tables 5-7.

Table 5. Study NCT00947856: Treatment with SGN-35 in patients with CD30-positive hematologic malignancies who have previously participated in an SGN-35 study.[34,36]

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

Table 6. Study NCT01703949: A Pilot Study of Weekly Brentuximab Vedotin in Patients With CD30+ Malignancies Refractory to Every ≥3 Week Brentuximab Vedotin.[37]

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

Table 6. Study NCT01703949: A Pilot Study of Weekly Brentuximab Vedotin in Patients With CD30+ Malignancies Refractory to Every ≥3 Week Brentuximab Vedotin.[37]			
Trial Design	**Inclusion Criteria**	**Interventions and Comparators**	**Outcomes**
20. Sponsor: Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium. Collaborator: National Cancer Institute.	enough to be expected to be able to complete 2 cycles of chemotherapy on study. Expected survival if untreated >90 days. <u>Exclusion:</u> Prior transplant within 100 days. Radioimmunotherapy within 12 weeks. Eastern Cooperative Oncology Group (ECOG) performance status: >2. HIV or hepatitis B positive.		

Table 7. Study NCT01909934: A phase 4, open-label, single-arm study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma.[38]			
Trial Design	**Inclusion Criteria**	**Interventions and Comparators**	**Outcomes**
Study NCT01909934 Single-arm phase 4 trial. Start date: September 2013. Estimate study completion date: May 2020. Estimated enrolment: 45. Sponsor: Millennium Pharmaceuticals, Inc.	Relapsed or refractory sALCL who have previously received at least 1 multi-agent chemotherapy regimen. Bidimensional measurable disease. Eastern Cooperative Oncology Group (ECOG) performance status: 0 or 1. <u>Exclusion:</u> Previous treatment with brentuximab vedotin. Previous treatment with allogeneic stem cell transplantation. Patients with	Brentuximab vedotin i.v. over 30 minutes, on day 1 of each 3 week cycle, up to a maximum of 16 cycles.	<u>Primary outcomes:</u> Objective response rate by independent review <u>Secondary outcomes:</u> Duration of response Progression-free survival Complete response rate Overall survival

Table 7. Study NCT01909934: A phase 4, open-label, single-arm study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma.[38]			
Trial Design	**Inclusion Criteria**	**Interventions and Comparators**	**Outcomes**
	cerebral/meningeal disease. HIV-positive patients. Hepatitis B surface antigen-positive. Known or suspected hepatitis C infection.		

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified for this review.

8 ABOUT THIS DOCUMENT

This Final 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 sALCL. 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).

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

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). 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

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: brentuximab, adcetris, SGN-35

Select International Agencies:

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

European Medicines Agency (EMA):
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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