

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

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

pERC Final Recommendation

This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Brentuximab Vedotin (Adcetris)

Submitted Funding Request:

For Hodgkin lymphoma patients after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior therapies in patients who are not ASCT candidates

Submitted By:
Seattle Genetics, Inc.

Manufactured By:
Seattle Genetics, Inc.

NOC Date:
February 1, 2013

Submission Date:
March 14, 2013

Initial Recommendation:
July 5, 2013

Final Recommendation:
August 29, 2013

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding brentuximab vedotin (Adcetris) in patients with Hodgkin lymphoma, conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients with Hodgkin lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status of 0 or 1. pERC made this recommendation because the Committee considered that there may be a net clinical benefit of brentuximab based on a meaningful proportion of patients experiencing a durable complete response. pERC also considered that the patient population to whom this recommendation applies is small and has no other effective therapeutic options; also, a randomized controlled trial was not thought to be feasible. However, pERC acknowledged that because of the non-randomized, non-comparative phase two study design, there was considerable uncertainty around the magnitude of the benefit and in the cost-effectiveness of brentuximab. This led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, brentuximab could not be considered cost-effective at the submitted price.

pERC did not recommend funding brentuximab in patients with Hodgkin lymphoma who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent chemotherapies. This patient population was not included in the non-randomized non-comparative phase two study, therefore, pERC considered there was insufficient evidence to determine if there was a clinical benefit in this patient population.

**POTENTIAL NEXT STEPS
FOR STAKEHOLDERS**

Pricing Arrangements to Improve Cost-Effectiveness

Given that pERC was satisfied that there may be a net clinical benefit of brentuximab vedotin in patients with Hodgkin lymphoma who have relapsed disease following autologous stem cell transplant, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of brentuximab to an acceptable level. pERC noted that the cost per cycle of brentuximab was extremely high and that drug price was a key driver of the incremental cost-effectiveness estimates. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a substantial reduction in drug price would likely be required in order to improve cost-effectiveness.

Collecting Evidence to Reduce Uncertainty in Cost-Effectiveness

Given the considerable uncertainty in the magnitude of clinical benefit of brentuximab vedotin in patients with Hodgkin lymphoma who have relapsed disease following autologous stem cell transplant, pERC concluded that any additional prospective evidence that could be collected to decrease the uncertainty in the incremental effect would be of benefit in understanding the true cost-effectiveness of brentuximab.

Collecting Prospective Evidence in Non-ASCT Patients

While pERC noted that there was insufficient evidence to recommend funding brentuximab in patients who are not candidates for autologous stem cell transplant (ASCT) and who have relapsed disease following at least two prior multi-agent chemotherapies, pERC strongly emphasized that prospective data collection on the efficacy of brentuximab in this setting would help define the potential clinical benefit in this population.

SUMMARY OF pERC DELIBERATIONS

pERC noted that standard treatment for patients with Hodgkin lymphoma that relapses after autologous stem cell transplant (ASCT) can include chemotherapy or radiation, administered with palliative intent for symptom management. It was noted that the median survival of patients who relapse after ASCT is approximately two years. One non-randomized study was included in the pCODR systematic review, Study SG035-0003 (Younes 2012), which evaluated brentuximab in 102 patients with Hodgkin lymphoma who had relapsed after, or were refractory to high-dose ASCT. pERC considered that this was a heavily pre-treated patient population (median 3.5 prior chemotherapies) with no alternative treatment options and for whom there was an important need for new therapeutic options. Also, the study population was relatively young with a median age of 31 years and there is a therapeutic need for effective options in this population. pERC also discussed that Hodgkin lymphoma is a relatively uncommon malignancy and that the number of patients with Hodgkin lymphoma who relapse after ASCT is small. Considering these factors, pERC concluded that the size of Study SG035-0003 was relatively large for this clinical setting but agreed with the pCODR Clinical Guidance Panel that it would likely not be feasible to conduct a randomized controlled trial in this patient population in a reasonable timeframe.

[pERC's Deliberative Framework](#) for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of Study SG035-0003 and determined that there may be a net clinical benefit of treatment with brentuximab. pERC noted that a substantial proportion of patients (34%) experienced a complete response, which is an important and meaningful outcome in Hodgkin lymphoma. In addition, it was noted that the median duration of complete response was 20.5 months, which pERC considered evidence of a durable response. pERC also reviewed safety evidence for brentuximab from Study SG035-0003 and considered that it was challenging to assess the safety of brentuximab in the absence of comparative data. However, given that these patients do not have other effective therapeutic options but would likely be exposed to toxic or ineffective chemotherapies, pERC concluded that brentuximab's toxicity profile appeared reasonable and manageable in this setting. The most common adverse event was neutropenia, which pERC noted may incur an additional cost to care. pERC also noted that one of the most common adverse events that was observed was peripheral neuropathy, which is at least partially reversible after stopping treatment. pERC discussed the limitations of relying on non-randomized, non-comparative evidence and concluded that there was considerable uncertainty surrounding the clinical benefit of brentuximab. However, pERC agreed with the pCODR Clinical Guidance Panel that there may be a net clinical benefit of treatment with brentuximab in patients who have relapsed following ASCT. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group about the uncertainties associated with non-randomized non-comparative evidence. pERC acknowledged these uncertainties but considered that in exceptional circumstances, as with brentuximab for patients who have relapsed following ASCT, this level of evidence can be acceptable. pERC further reiterated that a meaningful proportion of patients receiving brentuximab in the single-arm phase two study had experienced a durable complete response, which led pERC to conclude that there may be a net clinical benefit of brentuximab in patients who have relapsed following ASCT. pERC also considered it important to note that equipoise no longer exists for brentuximab in this population and a randomized controlled trial is likely not feasible now.

pERC noted that patients who are not candidates for ASCT and who had failed at least two prior therapies were not included in Study SG035-0003. Therefore, pERC considered that there was insufficient evidence to determine if there was a clinical benefit of brentuximab in this population. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer and the patient advocacy group regarding the need for brentuximab in patients who are not candidates for ASCT and who have failed at least two multi-agent chemotherapies. pERC also noted three additional studies the manufacturer identified that provided data on the use of brentuximab in patients who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent chemotherapies. pERC discussed that these studies had been identified in the literature search for the

pCODR systematic review but were excluded from the review because they were retrospective case series. pERC confirmed that the inclusion and exclusion criteria of the systematic review were appropriate as retrospective case series constitute lower quality data. pERC acknowledged the pCODR Clinical Guidance Panel's position that brentuximab would likely be an effective treatment option in this patient population, however, pERC considered there was insufficient evidence to be able to make a recommendation to fund brentuximab in this population. While pERC considered that there was insufficient evidence to recommend funding brentuximab in patients who are not candidates for autologous stem cell transplant (ASCT) and who have relapsed following at least two prior multi-agent chemotherapies, pERC considered that prospective data collection on the efficacy of brentuximab in this setting would help define the potential clinical benefit in this population.

pERC discussed input on brentuximab from one patient advocacy group and considered that brentuximab aligned with patient values. Although patient advocacy group input indicated that patients valued improvements in quality of life, Study SG035-0003 did not measure quality of life. pERC considered that this was a population with limited treatment options who valued new effective treatments, and providing brentuximab as a treatment would align with this value. pERC discussed that patient input indicated that patients were willing to tolerate side effects associated with new treatments if they offered improved efficacy. pERC had noted that the toxicity profile of brentuximab appeared reasonable in this setting. It was also noted that Hodgkin lymphoma often affects a relatively young population and the patient advocacy group input indicated that this young population places considerable value on extending their years of life. Therefore pERC considered that providing brentuximab as a treatment for this population would align with patient values.

pERC deliberated upon the cost-effectiveness of brentuximab compared with chemotherapy, radiotherapy and allogeneic stem cell transplant. It was noted that due to the limitations of relying on non-randomized evidence from Study SG035-0003, there was substantial uncertainty in the magnitude of the clinical benefit associated with brentuximab. This made it challenging to estimate the incremental effect of treatment with brentuximab and, therefore, the resulting incremental cost-effectiveness estimates for brentuximab. Given that the median survival of Hodgkin lymphoma patients who relapse after ASCT is approximately two years, pERC considered that the manufacturer had substantially overestimated the incremental effect of brentuximab and that it was extremely unlikely that brentuximab provides an additional year of life (i.e. 0.99 life years gained) to patients with Hodgkin lymphoma who have relapsed following ASCT. This considerable uncertainty in the magnitude of clinical benefit of brentuximab led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, brentuximab could not be considered cost-effective at the submitted price.

pERC further noted that the price of brentuximab was a key driver of cost-effectiveness and that the cost per 28-day cycle of brentuximab was \$16,262.40. pERC considered this absolute cost to be extremely high relative to other new high cost cancer drug treatments and that it is above and beyond typical costs. The Committee noted that in order to improve the cost-effectiveness of brentuximab and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would likely be required. pERC also considered that any further prospective evidence regarding clinical efficacy that could be collected to decrease the uncertainty in the incremental effect would be of benefit in understanding the true cost-effectiveness of brentuximab.

pERC discussed the feasibility of adoption and noted that due to the small number of patients with Hodgkin lymphoma that relapse following ASCT, vial sharing would be unlikely and therefore drug wastage will be an issue with brentuximab.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy groups (Lymphoma Foundation Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Lymphoma Foundation Canada)
- the Submitter (Seattle Genetics, Inc.)

The pERC Initial Recommendation was to fund brentuximab for patients with Hodgkin lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status of 0 or 1, conditional on the cost-effectiveness being improved to an acceptable level. pERC did not recommend funding brentuximab in patients with Hodgkin lymphoma who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent chemotherapies. This patient population was not included in the non-randomized non-comparative phase two study, therefore, pERC considered there was insufficient evidence to determine if there was a clinical benefit in this population. Feedback on the pERC Initial Recommendation indicated that the manufacturer and patient advocacy group agreed in part with the initial recommendation and pCODR's Provincial Advisory Group disagreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated 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.

Studies included: one single-arm study

The pCODR systematic review included one non-randomized single-arm phase two clinical trial, the SG035-0003 study (Younes 2012), which evaluated brentuximab in patients with Hodgkin lymphoma who had relapsed after, or were refractory to high-dose ASCT (N=102). Brentuximab, at a dose of 1.8 mg/kg, was administered intravenously once every 3 weeks for up to 16 cycles or until disease progression or unacceptable toxicity.

No randomized controlled trials were identified that met the eligibility criteria of this systematic review. pERC discussed that Hodgkin lymphoma is a relatively uncommon malignancy and that the number of patients with Hodgkin lymphoma that relapse after ASCT is small. pERC also discussed that the rate at which patients were recruited to Study SG035-0003 was relatively rapid (approximately 7 months) but that this could be expected in a clinical setting where there are no alternative treatment options and there is a prevalent population requiring treatment. pERC noted that conducting a randomized controlled trial of brentuximab in an incident population would require an extended period of time. Considering these factors, pERC concluded that the size of Study SG035-0003 was relatively large for this clinical setting and agreed with the pCODR Clinical Guidance Panel that it may not be feasible, now, to conduct a randomized controlled trial in this patient population in a reasonable timeframe. Upon reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the manufacturer identifying three additional studies that provided data on the use of brentuximab in patients who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent chemotherapies. pERC discussed that these studies had been identified in the literature search for the pCODR systematic review but were excluded from the review because they were retrospective case series. pERC confirmed that the inclusion and exclusion criteria of the systematic review were appropriate as retrospective case series constitute lower quality data.

Patient populations: young, heavily pre-treated patients who relapsed following ASCT

Study SG035-0003 included patients with Hodgkin lymphoma who had relapsed after, or who were refractory to, high-dose ASCT and who had an ECOG performance status of 0 or 1. Patients who had previously received allogeneic stem cell transplant were ineligible for the study.

pERC considered that the study population was relatively young with a median age of 31 years (range, 15 to 77 years). pERC also discussed that the patients included in Study SG035-0003 were heavily pre-treated: 66% had received prior radiation therapy and the median number of prior chemotherapy regimens was 3.5 (range 1 to 13).

pERC noted that patients who are not candidates for ASCT and who had failed at least two prior therapies were not included in Study SG035-0003. Therefore, pERC considered that there was insufficient evidence to determine if there were a clinical benefit of brentuximab in this population. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer and the patient advocacy group regarding the need for brentuximab in patients who are not candidates for ASCT and who have failed at least two multi-agent chemotherapies. pERC acknowledged the pCODR Clinical Guidance Panel's position that brentuximab would likely be an effective treatment option in this patient population; however, pERC considered that there was insufficient evidence to be able to make a recommendation to fund brentuximab in this population. While pERC considered that there was insufficient evidence to recommend funding brentuximab in patients who are not candidates for autologous stem cell transplant (ASCT) and who relapse following at least two prior multi-agent chemotherapies, pERC considered that prospective data collection on the efficacy of brentuximab in this setting would help define the potential clinical benefit in this population.

Key efficacy results: meaningful and durable complete response rate, no quality of life data

Key efficacy outcomes deliberated upon by pERC included objective response rate, the primary outcome of Study SG035-0003, complete response, duration of response, progression-free survival and overall survival.

Objective response rate, as assessed by an independent review committee, was 75% (95% confidence interval [CI], 64.9% to 82.6%) while the complete response rate was 34% (95% CI, 25.2% to 44.4%). pERC discussed these results and considered complete response to be an important outcome in Hodgkin lymphoma, noting that the proportion of patients who experienced a complete response was substantial. pERC also noted that the Clinical Guidance Panel considered that these response rates were comparable to results reported in previous studies of single agent and multi-agent chemotherapies that are currently used. 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), which pERC considered evidence of a durable response. pERC considered the meaningful and durable complete response rates an indication that there may be a clinical benefit associated with brentuximab in this population. pERC discussed the limitations of relying on non-randomized evidence and agreed that there was considerable uncertainty surrounding the clinical benefit of brentuximab and its exact magnitude. However, pERC generally agreed with the pCODR Clinical Guidance Panel that there may be a net clinical benefit of treatment with brentuximab in patients who have relapsed following ASCT.

At the time of the primary analysis (median follow-up of 18.5 months), median progression-free survival was estimated to be 5.6 months (95% CI 5.0 to 9.0 months) and median overall survival was estimated to be 22.4 months (95% CI 21.7 months to not estimable). The estimated 12 month overall survival rate was 89% (95%CI 83% to 95%). An updated survival analysis (median follow-up of 29.5 months) estimated the 24-month overall survival rate to be 65% (95% CI, 55% to 74%).

Quality of life was not measured in Study SG035-0003 although it was an outcome patient advocacy group input indicated was important.

Safety: toxicity profile reasonable in this setting, peripheral neuropathy manageable

pERC discussed the safety of brentuximab based on adverse events reported in Study SG035-0003. The most common grade 3 or 4 adverse events included neutropenia (20%), peripheral sensory neuropathy (8%), fatigue (2%), pyrexia (2%), diarrhea (1%), and peripheral motor neuropathy (1%). pERC considered that it was challenging to assess the safety of brentuximab in the absence of randomized comparative data. However, given that these patients do not have other effective therapeutic options and would be otherwise exposed to toxic chemotherapies, pERC considered that brentuximab's toxicity profile appeared reasonable and manageable in this setting. The most common adverse event was neutropenia, which pERC noted may incur an additional cost to care. pERC also discussed that one of the most common adverse events that was observed was peripheral neuropathy, which is reversible after stopping treatment.

pERC noted that three cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with relapsed Hodgkin lymphoma who had received brentuximab but pERC considered this to be a rare adverse event. pERC discussed that patient advocacy group input indicated that patients would be willing to tolerate significant side effects in an effective treatment and that the risk of PML would likely be acceptable in this patient population with relapsed Hodgkin lymphoma that currently has no effective treatment options.

Limitations: uncertainty in clinical benefit due to lack of randomized comparative data

pERC discussed the limitations of non-randomized, non-comparative studies and considered that, although the SG035-0003 trial was appropriately conducted, the conclusions that can be drawn from non-randomized, non-comparative data are not as robust as those that can be drawn from randomized controlled trials. pERC considered that, given the lack of randomized comparative studies, there is considerable uncertainty surrounding the clinical benefit of brentuximab, including the precise magnitude of that potential clinical benefit. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group about the uncertainties associated with non-randomized non-comparative evidence. pERC acknowledged these uncertainties but considered that in exceptional circumstances, as with brentuximab for patients who have relapsed following ASCT, this level of evidence can be acceptable. pERC further reiterated that a meaningful proportion of patients receiving brentuximab in the single-arm phase two study had experienced a durable complete response, which led pERC to conclude that there may be a net clinical benefit of brentuximab in patients who have relapsed following ASCT. pERC also considered it important to note that equipoise no longer exists for brentuximab in this population and a randomized controlled trial is likely not feasible.

Need: important need in a population with no alternative treatment options

pERC discussed that Hodgkin lymphoma is a relatively uncommon malignancy which is considered highly curable using treatment modalities including chemotherapy, radiation and transplantation. For the small proportion of patients who relapse following ASCT, the median survival is about two years. pERC discussed that currently, there are no agents with regulatory approval in Canada for the treatment of relapsed Hodgkin lymphoma and because this lymphoma subtype is uncommon, there have been relatively few studies conducted evaluating new agents in this patient population. It was noted that chemotherapies currently used in these patients are associated with increasing toxicity and decreasing effectiveness over time and patients also require treatments to manage symptoms or complications. Patients included in Study SG035-0003 had received a median of 3.5 prior chemotherapies. Therefore, pERC considered that this was a heavily pre-treated patient population with no alternative effective treatment options for whom there was an important need for new therapeutic options. Also, the study population was relatively young with a median age of 31 years and there is a therapeutic need for effective options in this population.

PATIENT-BASED VALUES

Values of patients with Hodgkin lymphoma: young patients who value extending life and choice of effective treatment options

Patient advocacy group input highlighted that patients with relapsed or refractory Hodgkin lymphoma have limited treatment options and that there is a significant unmet need for safe and effective treatments. pERC noted that patients want additional drug therapies for the treatment of Hodgkin lymphoma and being able to choose amongst therapies is an important consideration. Patient input also highlighted that many patients with Hodgkin lymphoma are young adults who place a high value on extending their life, especially when there are many patients with Hodgkin lymphoma who do not relapse and whose disease is cured. pERC noted that the Study SG035-0003 population was relatively young with a median age of 31 years. Therefore pERC considered that providing brentuximab as a treatment for this population would align with these patient values.

Patient values on treatment: disease control, tolerable side effects, improved quality of life

pERC discussed patient advocacy group input indicating 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. Most patients indicate they 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. Although Study SG035-0003 did not measure or report quality of life data, pERC discussed that a meaningful and durable complete response rate was observed and that the

toxicity profile of brentuximab appeared reasonable relative to the toxicities associated with chemotherapies, to which this population would otherwise be exposed. pERC discussed that there were 3 reports of PML in patients with relapsed Hodgkin lymphoma who had received brentuximab but considered that this would likely be an acceptable risk for patients who did not have other alternative therapeutic options. Therefore pERC considered that providing brentuximab as a treatment for this population would align with these patient values.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility

The economic analysis submitted by Seattle Genetics Inc. compared brentuximab vedotin to chemotherapy, with or without radiotherapy, as well as intent to provide allogeneic stem cell transplant for patients with Hodgkin lymphoma that had relapsed following ASCT.

Basis of the economic model: clinical and economic inputs

Costs included drug acquisition and administration costs (incorporating wastage), costs of managing and treating adverse events and downstream costs associated with allogeneic stem cell transplant and disease progression, where appropriate.

Key clinical effects included progression-free survival and overall survival data based on the non-randomized study SG035-0003 and observational registry data. Literature-based utilities associated with complete response, stable or progressive disease, and utility decrements from adverse events were also considered.

Drug costs: high absolute drug cost, wastage due to limited potential for vial sharing

At the list price, brentuximab costs \$4,840.00 per 50 mg vial. At the recommended dose of 1.8mg/kg and assuming no wastage, the average daily cost for a 70 kg patient is \$580.80 and the average cost per 28-day course is \$16,262.40. Assuming wastage of the excess brentuximab, the average daily cost for a 70 kg patient is \$691.43 and the average cost per 28-day course is \$19,360.

pERC considered this absolute cost of \$16,262.40 per 28 days to be extremely high relative to other new high cost cancer drug treatments and that it is above and beyond typical costs. The price of brentuximab is a key driver of its cost-effectiveness, therefore, pERC considered that a substantial reduction in the price of brentuximab would be required for it to be considered cost-effective.

pERC noted input from pCODR's Provincial Advisory Group on the potential for wastage because only 50 mg vials are available and the drug has only 24 hour stability following reconstitution. pERC noted that due to the small number of patients with Hodgkin lymphoma who relapse following ASCT, vial sharing would be unlikely and therefore drug wastage will be an issue with brentuximab for provinces to manage.

Cost-effectiveness estimates: substantial uncertainty in the incremental effect and resulting estimates of cost effectiveness due to limitations of non-randomized data

pERC deliberated upon the cost-effectiveness of brentuximab compared with chemotherapy, radiotherapy and intent to provide allogeneic stem cell transplant. It was noted that due to the limitations of the non-randomized evidence from Study SG035-0003, there was substantial uncertainty in the magnitude of the clinical benefit associated with brentuximab. This made it challenging to estimate the incremental effect of treatment with brentuximab and the resulting incremental cost-effectiveness estimates for brentuximab.

pERC noted that the pCODR Economic Guidance Panel's estimates of cost-effectiveness started at \$135,684 per quality adjusted life year (QALY) but were likely substantially higher since these analyses were based on non-comparative data and the Panel was not confident in the incremental effect estimates that were obtained from these data. The manufacturer's estimates of the cost-effectiveness of brentuximab compared to chemotherapy with or without radiotherapy were \$111,752 per QALY or \$130,349 per life year and were based on incremental effect estimates of 1.16 QALYs and 0.99 life years gained, respectively. Given that the median survival of Hodgkin lymphoma patients who relapse after ASCT is approximately two years, pERC considered that the manufacturer had substantially overestimated

the incremental effect of brentuximab and that it was extremely unlikely that brentuximab provides another additional year of life (i.e. 0.99 life years) to patients with Hodgkin lymphoma who have relapsed following ASCT. This considerable uncertainty in the magnitude of clinical benefit of brentuximab led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, brentuximab could not be considered cost-effective at the submitted price.

pERC further noted that the price of brentuximab was a key driver of cost-effectiveness and that the absolute cost of brentuximab was extremely high relative to other cancer drug treatments. The Committee noted that in order to improve the cost-effectiveness of brentuximab and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would likely be required. pERC also considered that any real-world clinical evidence that could be prospectively collected to decrease the uncertainty in the incremental clinical effect would be of benefit in understanding the true cost-effectiveness of brentuximab.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: potential drug wastage, increased chair time and costs associated with managing neutropenia

pERC considered input from pCODR's Provincial Advisory Group on the feasibility of implementing a recommendation and concluded that several factors would be important to consider.

pERC discussed a number of issues related to the cost of brentuximab and subsequent budget impact. pERC noted that due to the small number of patients with Hodgkin lymphoma who had relapsed following ASCT, the budget impact could be small. However, because of the small patient population, vial sharing would be unlikely and therefore drug wastage will be an issue with brentuximab. pERC also noted that while each intravenous infusion requires only 30 minutes of chair time, overall, there would be an increase in the chair time required due to the number of treatment cycles relative to other chemotherapy protocols for patients with Hodgkin lymphoma. pERC also noted that in Study SG035-0003, 20% of patients reported grade 3 or 4 neutropenia, and that the treatment and management of febrile neutropenia would incur additional costs.

pERC also noted that patients who are not candidates for ASCT but failed at least two prior therapies were not included in Study SG035-0003. Therefore, pERC considered that there was insufficient evidence to determine if there was a clinical benefit of brentuximab in this population.

pERC also discussed input from pCODR's Provincial Advisory Group on the potential need for CD30 testing in patients with relapsed Hodgkin lymphoma. pERC considered that CD30 testing via immunohistochemistry would likely have been conducted upfront for these patients.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> Chimeric monoclonal antibody that targets CD30 50 mg single-use vial The recommended dose is 1.8mg/kg
Cancer Treated	<ul style="list-style-type: none"> Hodgkin lymphoma, relapsed
Burden of Illness	<ul style="list-style-type: none"> Uncommon malignancy that typically presents in a younger patient population Approximately 900 new cases of Hodgkin lymphoma in Canada each year with 160 Canadians dying annually
Current Standard Treatment	<ul style="list-style-type: none"> 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 radiotherapy.
Limitations of Current Therapy	<ul style="list-style-type: none"> Short duration of disease control. 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.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
 Dr. Maureen Trudeau, Oncologist (Vice-Chair)
 Dr. Chaim Bell, Economist
 Dr. Scott Berry, Oncologist
 Bryson Brown, Patient Member
 Mario de Lemos, Pharmacist
 Dr. Sunil Desai, Oncologist
 Mike Doyle, Economist

Dr. Bill Evans, Oncologist
 Dr. Allan Grill, Family Physician
 Dr. Paul Hoskins, Oncologist
 Danica Lister, Pharmacist
 Carole McMahon, Patient Member Alternate
 Jo Nanson, Patient Member
 Dr. Peter Venner, Oncologist
 Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Chaim Bell and Dr. Sunil Desai who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the final recommendation except:

- Mario de Lemos and Dr. Scott Berry who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of brentuximab Vedotin (Adcetris) for HL, through their declarations, no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

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