pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Brentuximab (Adcetris) for Hodgkin Lymphoma – Resubmission

March 7, 2019

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by SeattleGenetics** compared brentuximab vedotin (BV) to current standard of care for patients with Hodgkin Lymphoma (HL) after failure of at least two multi-agent chemotherapy regimens and who are not autologous stem cell transplant candidates. This patient population aligns with the pCODR requested reimbursement criteria.

It is important to note that the pCODR requested reimbursement criteria defined above do not align perfectly with the inclusion/exclusion criteria of the phase IV trial by Walewski et al. (2018)[1] [C25007 trial], which informs key data inputs for the economic model of this pCODR review.

The pCODR requested reimbursement criteria are for the broader ASCT ineligible patient population, however, the majority of patients in the phase IV trial[1] were a subgroup of ASCT ineligible patients who had the potential to receive ASCT if they responded to further treatment. It is important to note that there are two distinct subgroups of ASCT ineligible patients with different treatment goals:

- The first subgroup includes patients who are ASCT ineligible due to lack of response to salvage therapy prior to ASCT but have the potential to become ASCT eligible if they respond to further treatment. In these patients, BV could be a bridge to ASCT.
- The second subgroup includes patients who are ASCT ineligible due to fragility, old age, or comorbidities. These patients will never be eligible to receive a transplant but may benefit from BV treatment due to favourable efficacy and toxicity and not as a bridge to ASCT.

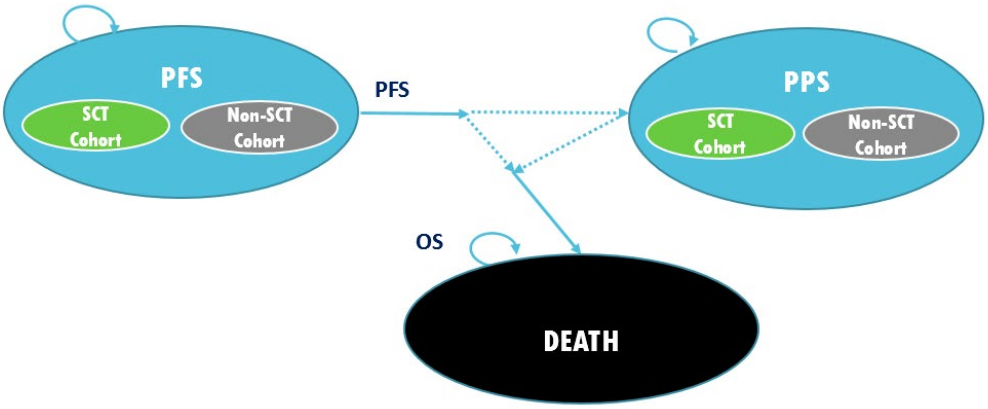
While the number of patients in the C25007 trial by Walewski et al al.[1], who were ASCT ineligible due to fragility, old age, or comorbidities could not be confirmed by the Submitter, the Clinical Guidance Panel (CGP) suggested that based on the small number of patients over the age of 65 in the trial (n=5/60), it is likely that most patients in the trial belonged to the first subgroup, i.e. those who were transplant ineligible due to chemotherapy resistance or high-risk refractory disease to first-line chemotherapy and therefore had the potential to receive ASCT if they responded to subsequent treatment.

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

Table 1. Submitted Economic Model

Funding Request	*Economic model matches funding request and NOC.*
Patient Population Modelled	1. *Funding request: Adults with HL after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates.* 2. *Phase IV trial publication[1]: Adults with relapsed/refractory HL with a history of ≥ 1 prior systemic chemotherapy regimen and considered unsuitable for SCT/multi-agent chemotherapy at the time of study entry.*
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival*
Comparator	*Single-agent chemotherapy (Gemcitabine)*
Year of costs	*2018*
Time Horizon	*70 years (3-week cycle length)*
Perspective	*Government*
Cost of brentuximab vedotin*	*Brentuximab costs $4,840.00 per 50 mg vial. At the recommended dose of 1.8mg/kg intravenously, every 3 weeks, brentuximab vedotin costs:* • *$691.43 per day* • *$19,360.00 per 28-day course* • *Total of 126 mg used (3 vials) once per 21-day cycle for average body weight of 70 kg.*
Cost of gemcitabine*	*Gemcitabine costs $270.00 per 1,000 mg. At the recommended dose of 1000mg/m^2, 3 times (days 1, 8, 15) per 28 day course, gemcitabine costs:* • *$49.18 per day* • *$1,377.00 per 28-day course*
Model Structure	*The model comprised three health states: pre-progression, post-progression and death. See Figure 2 below.*
Key Data Sources	*Phase IV trial* C25007 trial) – *Walewski et al.*[1] *Reyal et al.*[2] *for post-SCT survival Bröckelmann et al.*[3] *for non-SCT survival*
** Price Source: Drug prices taken from the submission materials provided by Seattle Genetics, Inc. According to the pharmacoeconomic report price information for brentuximab vedotin and gemcitabine was based on previous pCODR recommendations (pERC Adcetris Final Recommendation[15] and pERC Pembrolizumab* Final Recommendation[16], respectively).* *All calculations in this table are based on BSA of 1.7m^2 or weight of 70kg. Note that in the submitted model a weight of 76.30 kg and BSA of 1.90/m^2 were used.*	

Figure 1. Model diagram of partitioned-survival approach



1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

- Relevant issues identified included:
  - The CGP agreed that there *is* a net clinical benefit to brentuximab vedotin compared with chemotherapy for the treatment of HL patients after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates.
  - The comparison of brentuximab vedotin to gemcitabine is appropriate for the requested patient population given the absence of randomized phase III data.
  - Although limited by the non-comparative design of this phase IV trial by Walewski et al.[1] and the misalignment of the trial population with the reimbursement criteria, it appears that the response rates and PFS are acceptable evidence of efficacy, compared to the paucity of other agents or regimens available, such as single agent gemcitabine, miniBEAM or other chemotherapy options, which have comparable or less efficacy, with significantly larger toxicity profiles and resource use for inpatient admissions, transfusion, and growth factor support.
  - Responsiveness to treatment, converting a patient from transplant ineligibility to eligible for ASCT, which is a curative measure in this young patient population, is a meaningful endpoint. Whether these patients benefit from long-term overall survival benefit remains to be determined.
  - Brentuximab vedotin represents an important addition to the limited therapy options available for these young patients who are considered incurable at this disease time point.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered that brentuximab vedotin provides a clear unmet need for those with relapsed or refractory HL through two different treatment goals: as a bridge to ASCT for those currently ineligible and as therapy for those who will never be eligible for ASCT given its favourable toxicity. Registered clinicians considered that brentuximab vedotin has favorable toxicity and improved efficacy when compared to current alternatives, and has the potential to cure patients, many of which are young.

Summary of patient input relevant to the economic analysis
Patients considered side effects and toxicity of great concern with their previous treatments. Patients also reported that treatment-related fatigue and other treatment aspects impacting their quality of life negatively. One side effect related to brentuximab vedotin that was noted as important for patients was peripheral neuropathy; the cost of treating this, along with the decrement in quality of life were included in the economic analysis.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for brentuximab vedotin which are relevant to the economic analysis:

- PAG noted brentuximab vedotin is an additional line of therapy.

- The maximum dose of brentuximab vedotin is 180mg for relapsed classical HL. This is in line with the dosages in the phase IV trial: 1.8mg/kg, capped at 100 kg.

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

    - The pCODR Clinical Guidance Panel (CGP) noted that other treatment options for this patient population have side effects; the CGP does not expect extra resource use (through visits or costs) with brentuximab vedotin, and treatment with brentuximab vedotin may in fact decrease resource use.

- PAG is also seeking confirmation of the treatment duration as the trial was up to 16 cycles or until disease progression or unacceptable toxicities.

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

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	5.38	1.97	N/A
Progression free	0.05	0.05	
Post-progression - no SCT	0.25	0.25	
Progression free - post SCT	2.79	1.15	
Post-progression - post SCT	2.30	0.51	
ΔE (QALY)	3.31	1.30	N/A
Progression free	0.02	0.02	
Post-progression - no SCT	0.08	0.08	
Progression free - post SCT	2.48	1.03	
Post-progression - post SCT	0.73	0.16	
ΔC ($)	$111,878	$107,708	N/A
ICER estimate ($/QALY)	$33,767	$82,973	N/A

The main assumptions and limitations with the submitted economic evaluation were:

- *Data sources for economic model:* There is no head-to-head clinical trial data to inform this economic analysis for either progression-free survival, overall survival or the proportion of patients who go on to stem cell transplant. The evidence used to inform the economic model is based on descriptive data analyses with no formal hypothesis testing. From a study design perspective, phase IV studies (that which informs PFS in this economic model) are not meant to provide estimates of efficacy of treatment options. As phase IV trials are post-marketing trials that evaluate drugs in the real word setting, they do not receive the same level of scrutiny as phase I – III, with respect to design, analysis and reporting. Finally, a full critical appraisal of the C25007 trial[1] was not possible, as the trial protocol and statistical analysis plan were not available to pCODR due to a data sharing agreement. This was also the case for additional information requested.
- *Lack of direct comparative effectiveness:* The data for PFS and response rates for single-agent chemotherapy came from the prospective phase IV study (Walewski et al. 2018)[1], specifically the efficacy for the most recent prior therapy received by patients before enrolling into this phase IV study[1]. A pre-specified analysis was performed comparing PFS from the most recent treatment prior to study entry with PFS following brentuximab vedotin treatment. Response rates were taken directly from the Walewski et al. paper[1] with no further analyses conducted. The results of these analyses should be viewed cautiously, as the submitter could not provide comprehensive information on the methods used to generate the results and collect this data.
- *Time horizon:* In the submitted base case, the time horizon was 70 years. The CGP noted that this was unreasonable for this patient population. Firstly, for patients in the SCT cohort, patients will always have a higher mortality rate than the general Canadian population as they have increased morbidity. Secondly, previous submissions[23, 25] in this population have used a time horizon of 15 years. Finally, the data from the trial has a relatively short follow-up and it is unreasonable to extrapolate this data to 70 years.
- *Data source for patients receiving SCT in the single-agent chemotherapy arm:* There is no data to support the percentage of patients post single agent chemotherapy who receive a stem cell transplant. The submitter stated that feedback from clinicians varied, therefore, they assumed that all patients who achieved a complete or partial response would proceed to SCT, which was 25%. The CGP felt that this assumption was high, especially if the salvage treatment was to be gemcitabine; these estimates are also higher than what was reported in the NICE publication[27] (34% for BV and 5.3% for single-agent chemotherapy). Specifically, the CGP were doubtful that 1 in 4 patients would respond to 3rd line treatment and thus go on to receive a SCT.
- *Data source for patients receiving SCT in the brentuximab vedotin arm:* In the phase IV study, patients who likely had chemosensitivity proceeded to receive a stem cell transplantation, as per the criteria of the treating centre. Though the response rate was equal to 47% (28/60), only 10/60 patients went to ASCT straight off BV. Though this input was not an assumption per se, and was based on data from the phase IV study, there are limitations. The first is that the sample size is relatively small and therefore may not be generalizable. The second is that the CGP identified that clinical practice across Canada varies and the trial flow (any patient with a response proceeds to SCT) would not necessarily be reflective of clinical practice at all centers across Canada. Thirdly, of the 28 patients who proceeded to stem cell transplant, 6 had received only one line of therapy, whereas the funding request is for 2 or greater lines of therapy. The CGP noted that it is difficult to know if the outcome of brentuximab vedotin would be different for those having received just one line of therapy vs. 2 or more. Efficacy estimates were not estimated for the patient subgroup who failed ≥ 2 multi-agent chemotherapy regimens, but are available for trial patients who received > 1 prior therapies (n=49; 82%) and 1 prior therapy (n=11/ 18%). In these patient subgroups, the ORR by IRF estimates were similar to the overall ITT estimate. Fourthly, the submitter reported that 10/28 patients who went on to SCT did so immediately after BV. The other

18 patients proceeded to SCT after receiving other subsequent therapy following BV. Information regarding types of subsequent therapies was requested, but not provided by the submitter.

- *Overall survival data for patients who do not receive SCT:* Overall survival in the model was not taken from the phase IV trial[1] where data on PFS was taken; there were limited data options available to inform this input. For the brentuximab vedotin arm, it was based on a published study[3]. The CGP felt that this study was an appropriate proxy. For the single-agent chemotherapy arm, there was no data available, and therefore, median overall survival was based on an assumption from key opinion leaders. Though the CGP felt that the assumed median overall survival of 12 months was reasonable, it is an assumption and not based on published data.
- *Overall survival data for patients who receive SCT:* The source of data for overall survival for patients who received SCT was taken from a retrospective study[2] of patients who underwent allogeneic SCT. The economic model assumes that all SCTs are autologous, and are costed as such. The CGP confirmed that in clinical practice, allogeneic SCT is rarely used. The outcomes with autologous SCT are likely to be better than allogeneic, though the CGP indicated that for consistency reasons it would have been better to use a source of data reflective of clinical practice, if this data were available with a reasonable sample size. Using data from the allogeneic SCT population underestimates survival compared to autologous SCT. However, as these survival estimates are being used in both treatment arms, the impact on the ICER of this assumption is likely to be minimal. A further limitation with this input in the economic model is that overall survival was assumed to be the same for both treatment arms (BV and single agent chemotherapy). This is likely a conservative estimate as the CGP indicated that patients who received BV prior to transplant are likely to have better outcomes.
- *Parametric curve for patients who receive SCT:* In the submitted base case, the curve used to project overall survival for patients who received a SCT was the Gompertz curve. This curve was not the best fitting curve. The best fitting curve was the generalized gamma curve. The Gompertz curve has a very flat tail – meaning that patients do not continue to die off at a rate that is expected in clinical practice. The Gamma curve declines slightly over time. The CGP confirmed that this makes more sense clinically.
- *Source of data for utilities:* Utilities were not collected in this patient population. Utilities were taken from a vignette study[5]. Vignette studies are when a scenario is described to a member of the public and they are to rate their quality of life based on the description. Therefore, utilities from vignette studies are not measured in the population with the disease under study. Further, this vignette study was based on health states for relapsed / refractory systemic anaplastic large-cell lymphoma patients. These patients are often much sicker than those with Hodgkin lymphoma. Despite these limitations, the CGP supported the utility values used in the economic model.
- *Stem cell transplantation:* The cost for stem cell transplantation did not include the cost of post-transplant care. The CGP indicated that these costs can be significant and are of considerable duration.
- *Subsequent treatment following progression after SCT:* In the submitted economic model, patients could progress following the receipt of an SCT. However, no subsequent treatments and their related costs were included for this group of patients.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- Time horizon: In the submitted base case, the submitter used a time horizon of 70 years. Despite the young median age of these patients, a time horizon of 70 years is unrealistic. The CGP indicated that these patients have a higher mortality than the general Canadian population, and are not likely to live a long life. Further, as noted in

the limitations section above, the overall survival data for patients in either the SCT or non-SCT cohort is not taken from a phase III trial in the same population. In order to provide a conservative cost-effectiveness estimate, and to align with previous pCODR reviews[23, 25], the EGP elected to use a 15 year time horizon in their reanalysis. This limits the amount of extrapolation needed.

- Parametric curve chosen for post-SCT overall survival: The EGP elected to choose the best fitting curve for post-SCT overall survival. No rationale was provided for selecting the Gompertz. Further, the Gompertz curve had a very flat tail. This flattening of overall survival was identified by the CGP as unrealistic given that in this patient population, even following SCT, patients are at increased risk of mortality. The generalized gamma curve did experience a decline in survival over time that was greater than the Gompertz curve, and was identified as best fit.
- No upper bound: The EGP elected to not place an upper bound on their reanalysis. This decision was based on several factors. First, there is no head-to-head clinical data to inform the economic model. In the absence of comparative effectiveness estimates, several assumptions needed to be made (see Table 22), which introduce uncertainty into the results. Further, the primary source of data to inform the response rate and the proportion of patients receiving SCT was based on a phase IV study[1] which did not exactly match the funding request (see Table 22). The limitations in the data used to inform the submitted economic model hinder the ability to estimate a range for the ICER, therefore, no upper bound was examined.

Table 3. EGP reanalysis estimates

	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICER
Submitted base case	$111,878	3.31	5.38	$33,767	--
EGP's Reanalysis for the Best Case Estimate					
LOWER BOUND					
Time horizon - 15 years	$106,798	1.46	2.32	$73,060	$39,293
Parametric curve - post-SCT overall survival (generalized gamma)	$110,871	2.74	4.10	$40,506	$6,739
Best estimate of above 2 parameters	**$107,708**	**1.30**	**1.97**	**$82,973**	**$49,206**
UPPER BOUND					
No upper bound					

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- the number of HL patients who fail (relapse or refractory) after frontline therapy. Increasing the number of HL patients who fail (relapse or refractory) after frontline therapy to 30%, increases the submitted 3-year incremental budget impact of brentuximab vedotin by about 87%.

- the number of patients who get ASCT. Decreasing the number of patients who are ASCT eligible to 70% increases the 3-year incremental budget impact by about 50%.

Key limitations of the BIA model include the assumption that the number of patients not eligible for ASCT is 20%. The CGP stated that the proportion of patients who are likely to get ASCT would be around 70%. This is a cost driver in the BIA.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for brentuximab when compared to single-agent chemotherapy is:

- A minimum of $82,973/QALY with no upper bound.
- It is difficult to estimate where the best estimate would lie, given the lack of comparative effectiveness data.
- The extra cost of brentuximab vedotin is at least $107,708 (ΔC). *The main factors that influence ΔC include the time horizon and the proportion of patients receiving SCT.*
- The extra clinical effect of vedotin is at least 1.30 (ΔE). *The main factors that influence ΔE include the proportion of patients receiving SCT and the time horizon.*

Overall conclusions of the submitted model:

- *The data supporting this conclusion are from non-randomized studies.*
- *The EGP recognizes the challenges for decisions-makers when no upper bound is provided. However, the lack of an upper bound is a reflection of the uncertainty in the data.*
- *Though there is consensus from the CGP that there is net clinical benefit with the addition of brentuximab vedotin for this patient population, it is not possible to determine the upper bound given the uncertainty in the data assumptions used in the economic model.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lymphoma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of brentuximab vedotin for Hodgkin Lymphoma. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic 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 Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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