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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Brentuximab (Adcetris) for Hodgkin Lymphoma – Resubmission

February 21, 2018

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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 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Seattle Genetics** compared brentuximab vedotin to best supportive care for patients with Hodgkin's Lymphoma (HL) who received an autologous stem cell transplant (ASCT) in the previous 30-45 days and are considered to be at increased risk of relapse or progression.

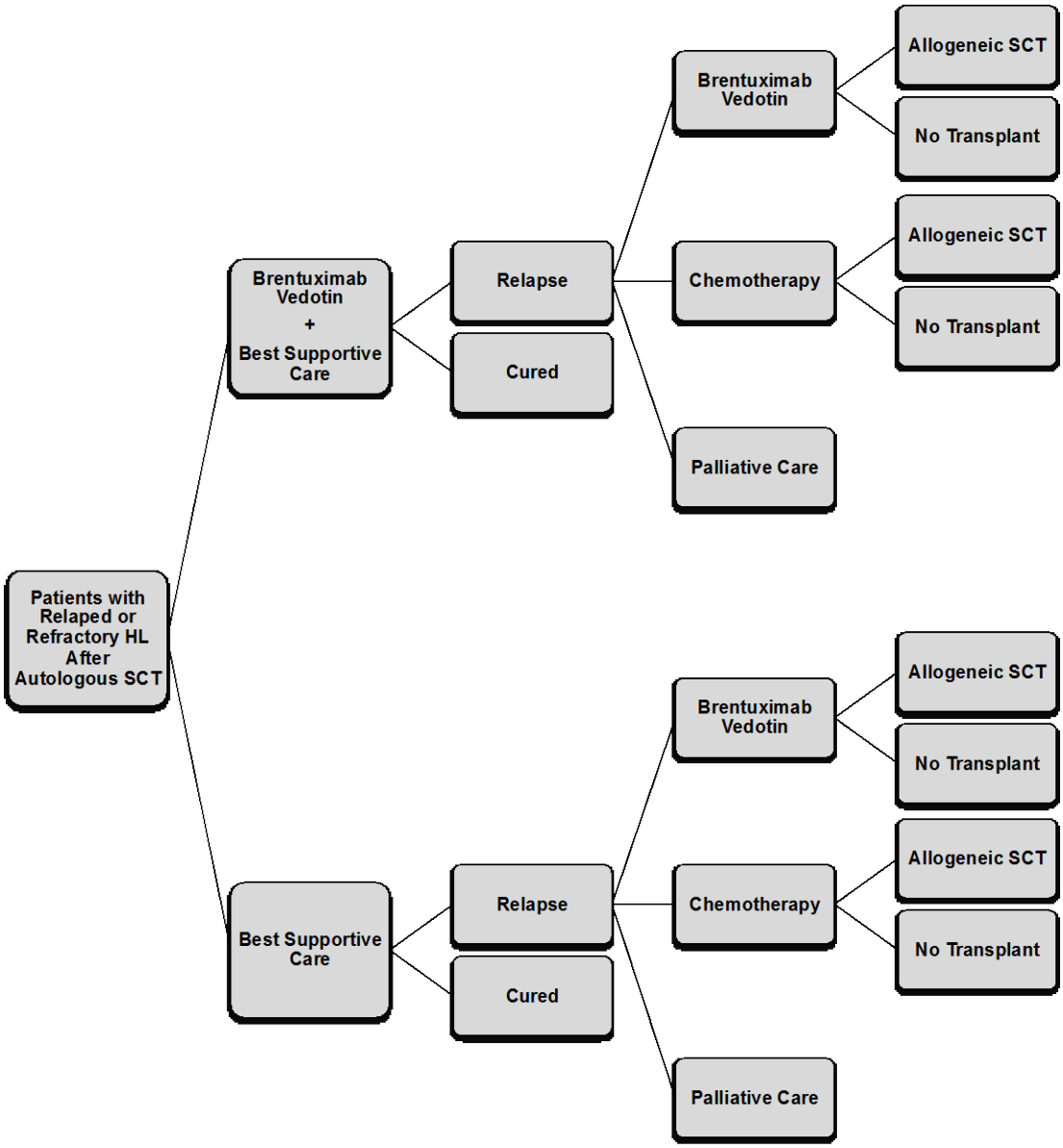
Increased risk of post-ASCT relapse or progression was defined as: 1) failure to achieve complete remission after frontline therapy, 2) relapsed HL occurring <12 months following frontline therapy, or 3) relapsed HL at greater or equal to 12 months with extranodal involvement.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*Matches that of the AETHERA trial.*
Type of Analysis	*CUA / CEA*
Type of Model	*Partitioned-survival curve*
Comparator	*Best supportive care*
Year of costs	*2016*
Time Horizon	*Lifetime*
Perspective	*Government*
Cost of brentuximab vedotin*	*Brentuximab vedotin costs $4,840.00 per 50mg vial* • *At the recommended dose of 1.8 mg/kg intravenously, every 3 weeks, brentuximab vedotin costs:* o *$691.43 per day* o *$19,360.00 per 28-day cycle* *Total of 126 mg used (using a total of 3 vials) once per 21-day cycle for average body weight of 70 kg.*
Cost of best supportive care	*Costs of best supportive care were not explicitly included in the model because both arms would receive BSC.*
Model Structure	*Partitioned survival model with three health states: pre-relapse, post-relapse and death.* *See Figure 1 for more details*
Key Data Sources	*AETHERA trial*[3] *Peer-reviewed literature* *Government sources (life tables & costs)*
Key Assumptions	*Gains in progression-free survival translate to gains in overall survival.* *Patients who do not relapse during the 5*

	years post-transplant are cured.
** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA– accessed on January 5, 2018. All calculations are based on 70kg and BSA = 1.7m^2*	

Figure 1. Simplified schematic of decision tree, as taken from the pCODR submission



1.2 Clinical Considerations

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

- Relevant issues identified by the CGP included:
  - There is a net clinical benefit to brentuximab vedotin consolidation treatment following ASCT for relapsed or refractor HL patients at high risk for disease progression.
  - The follow-up of the AETHERA trial, the source of clinical effectiveness data for the economic model, was short and has yet to observe a difference in overall survival. This may be due to the use of brentuximab vedotin in the control arm following disease progression.

- Progression-free survival as an end-point is clinically relevant when the improvement is of the magnitude observed in the AETHERA[3] trial.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians noted that the funding of brentuximab vedotin for this indication would only affect a very small number of patients. The registered clinicians found the magnitude of progression-free survival gain encouraging. The increase in adverse events was identified as a key harm, though the most typical side effects of peripheral neuropathy and hematologic toxicity could be managed with dose modifications or dose delays. These factors have been incorporated into the economic analysis.

Summary of patient input relevant to the economic analysis
Patients considered symptom management that affect quality of life, adverse events and toxicity associated with treatments, and disease remission as important. Patients expressed that they seek individualized treatment options that will offer disease control and remission, with fewer side effects than current options. These factors were incorporated into the economic model through survival and averse events.

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:

Enablers
- Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients.
- Brentuximab vedotin is already used for other indications and health care professionals are familiar with its preparation, administration and monitoring for adverse events.
- Additional chemotherapy chair time is not required for monitoring post-infusion reactions and the infusion does not require intense nursing resources.
- The administration schedule of every three weeks only slightly increases the frequency of clinic visits as these patients are already regularly seen in clinic for follow-up and observation.

Barriers
- Large incremental cost per patient.
- In some areas patients would need to travel far distances to an outpatient chemotherapy center to receive brentuximab vedotin intravenously.
- Potential for drug wastage.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	4.30	0.93	0.59
Pre-progression	5.36	1.74	1.40
Post-progression	-1.06	-0.81	-0.81
ΔE (QALY)	4.33	1.19	0.89

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
Pre-progression	4.75	1.52	1.22
Post-progression	-0.42	-0.33	-0.33
ΔC ($)	$113,900	$125,510	$123,999
ICER estimate ($/QALY)	**$26,303**	**$105,383**	**$139,286**

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

- The assessment of the outcome in the economic model was by investigator; the trial protocol specific assessment of outcomes by independent review.
- The submitter used progression-free survival as a proxy for overall survival. The degree to which PFS predicts OS is unknown.
- The model is not equipped to modify the cure rates of each treatment arm independently.

1.4 Detailed Highlights of the EGP Reanalysis

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

- Use of independently-assessed instead of investigator-assessed outcome: As per the study protocol, the EGP elected to use the independent assessment of PFS, which was done at 3 years, with a hazard ratio of 0.58.
- Time horizon of 15 years: The CGP felt that the chosen baseline time horizon of 65 years was inappropriate for this patient population. The long-term survival is derived from a modeled extrapolation of the Kaplan-Meier progression-free survival curves. At a longer time horizon, such as the submitted base case of 65 years, there is increasing uncertainty in the survival estimates in both arms due to extrapolation. The long-duration of the time horizon chosen by the submitter possibly leads to an overestimation of the benefit of brentuximab vedotin. Though a 20-year time horizon would be expected to capture all of the deaths in this population of freshly transplanted HL patients, the structural limitations of the economic inputs in the model that are non-modifiable (limited trial data of 30 months extrapolated to long time horizons, along with no observed difference in overall survival) led to the EGP examining an upper bound with a 15 year time horizon. The time horizon had a significant impact on the ICER.
- Treatment duration: The median number of cycles in the AETHERA clinical trial was 15. The planned duration with brentuximab vedotin is 16 cycles. The CGP indicated that most patients would not discontinue treatment due to toxicity. In order to align with a real-world setting, the EGP chose a treatment duration based on the product monograph of 16 cycles.

Table 3. EGP Reanalysis Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	**$113,900**	**4.33**	**$26,303**	**----**
EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
Independent assessment of	$72,851	2.23	$32,717	$6,414

outcomes, HR 0.58				
Time horizon - 20 years	$107,633	2.32	$46,423	$20,120
Treatment duration - 16 cycles	$172,252	4.33	$39,822	$13,519
Best case estimate of above three parameters	*$125,510*	*1.19*	*$105,383*	*$79,080*
UPPER BOUND				
Independent assessment of outcomes, HR 0.58	$72,851	2.23	$32,717	$6,414
Time horizon - 15 years	$106,970	1.73	$61,201	$34,898
Treatment duration - 16 cycles	$172,252	4.33	$39,822	$13,519
Best case estimate of above four parameters	*$123,999*	*0.89*	*$139,286*	*$112,983*

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- The change in the number of HL patients who relapse or are refractory after frontline therapy.
- Increasing the treatment duration.
- Market share.

Key limitations of the BIA model include treatment duration: the BIA base case assumes 12 cycles, whereas the median treatment duration in the AETHERA trial was 15 cycles, and number of recommended cycles can be as high as 16. This parameter could be modified by the EGP and has a large impact on the 3-year budget impact. The BIA is also very sensitive to changes in the number of HL patients who relapse or are refractory after frontline therapy.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for brentuximab vedotin when compared to standard of care is:

- Between $105,383/QALY and $139,286/QALY
- The extra cost of brentuximab vedotin is between $125,510 and $123,999 (ΔC). The main factors that influence ΔC include treatment duration and subsequent treatment options. The EGP took a conservative approach and included 16 cycles of treatment duration in its reanalysis as the median number of treatment cycles in the clinical trial was 15.
- The extra clinical effect of brentuximab vedotin is between 0.89 and 1.19 (ΔE). The main factors that influence ΔE include the time horizon and the assessment of progression-free survival (investigator vs independently assessed). The EGP incorporated these into their reanalysis based on feedback from the CGP.

Overall conclusions of the submitted model:

- *The model structure made it difficult to directly assess overall survival. The CGP felt that the model overestimated the incremental difference in QALY benefits between the two groups (Δ 4.33). Modifying the time horizon and using independent assessment for the ascertainment of outcomes (as per protocol) impacted the incremental QALYs significantly.*

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 Tumour Group 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 (Adcetris) for Hodgkin Lymphoma (HL) (post-ASCT consolidation). 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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