PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Brentuximab Vedotin (Adcetris) for Hodgkin Lymphoma

August 29, 2013

INQUIRIES

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

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3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Brentuximab Vedotin for Hodgkin Lymphoma patients
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Seattle Genetics Inc.

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees __X_ agrees in part ____ disagree

Seattle Genetics Inc. agrees in part with the initial recommendation related to the statements made in the pERC initial recommendation:

Summary of the feedback:

- We support the pERC initial recommendations for brentuximab vedotin funding in HL patients who have relapsed following autologous stem cell transplantation (ASCT)
- We do not agree with pERC initial recommendation not to fund Brentuximab Vedotin in HL patients who are not candidates for ASCT and who have relapsed disease following at least two prior multi-agent therapies.
- We believe that there is sufficient evidence to determine a clinical benefit in this patient population and we respectfully ask pERC to review the information supplied in this feedback report and approve funding for this patient population in their final recommendation
- This patient population is small yet has a high unmet need for an effective treatment to manage their disease

pERC Initial Recommendation: *"pERC did not recommend funding brentuximab in patients with Hodgkin Lymphoma who are not ASCT candidates 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." (Page 1, paragraph 2 of the initial pERC recommendation)*

Throughout the pCODR submission process, including the Check-In meeting, and subsequent requests for additional information, the issue regarding data for patients not eligible for ASCT was not brought to our attention. If pCODR had brought this question to Seattle Genetics, we would have highlighted and submitted information to satisfy this concern. For this reason, we have provided our rationale and highlighted study data for this patient subset to address pERC's concern over the "insufficient evidence to determine if there was

a clinical benefit in this population".

- **Significant unmet need in patients who are not candidates for ASCT**

The regulatory authorities in their approval of ADCETRIS in Canada, the United States and the European Union, all recognize the significant lack of treatment options for relapsed HL patients who have failed additional lines of therapy and are not ASCT candidates. Data submitted to these regulatory agencies (highlighted below) was compelling enough to gain approval for this indication. Very few viable treatment options exist for these patients who are in need of some form of effective treatment to manage their disease. Brentuximab vedotin in this patient population has been shown in several studies to provide a range of response rates effectively equivalent to those observed in the pivotal trial. This data is summarized below. Single agent brentuximab vedotin is a viable option to help control refractory disease and achieve prolonged disease free intervals. Elimination of funding for this patient population leaves little alternative for these patients other than supportive and palliative care.

1. Forero-Torres A, Fanale M, Advani R, Bartlett N, et al. Brentuximab Vedotin in Transplant-Naïve Patients with Relapsed or Refractory Hodgkin Lymphoma: Analysis of Two Phase I studies. The Oncologist 2012; 17:000-000

This report included 20 transplant-naïve patients who were enrolled in two Phase I multicenter studies. As described in this report, transplant-naïve patients who were enrolled in the phase I trials of brentuximab vedotin had an ORR of 30% with a CR rate of 10%. Although the response rate observed in this case series is lower than that seen in the pivotal trial of brentuximab vedotin (ORR of 75% with a CR rate of 34%), the activity is still notable considering the majority of patients enrolled in the phase I trials were transplant naïve due to chemorefractory disease and patients received a range of doses. Furthermore, patients who received single-agent brentuximab vedotin achieved objective responses without the characteristic toxicity of combination chemotherapy regimens. References for this patient data from the phase I studies was included in the pCODR submission in the efficacy and safety and studies synopses (SGN035-0001 and SGN035-002).

2. Sasse S, Rothe A, Goergen H, et al. Brentuximab vedotin (SGN-35) in patients with transplant-naive relapsed/refractory Hodgkin lymphoma [epub ahead of print: 10.3109/10428194.2013.775434]. Leuk Lymphoma. Mar 27 2013.

This retrospective analysis evaluated 14 patients with primary refractory or relapsed HL who had received ADCETRIS as a single-agent in a Named Patient Program (NPP) and who had not received prior high-dose chemotherapy plus ASCT due to refractory disease (n=9), comorbidity (n=4), and unknown (n=1). The ORR was 71% (10/14), which included 5 CRs. A total of 5 of the 9 patients with refractory disease and all 4 patients with comorbidity responded. A consolidating ASCT or alloSCT was performed in 5 patients. The median PFS was 9 months and the median OS has not been reached.

3. Gibb A, Jones C, Bloor A, et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK centre. Haematologica 2012 [Epub ahead of print]

The data presented demonstrated that brentuximab vedotin was effective with an overall response rate of 72% with complete response rate of 17% in a population of heavily pre-

treated relapsed/refractory HL patients, very similar to the 75% and 34% reported in the pivotal phase II trial in HL where all patients had received a prior auto transplant.

- **pCODR Clinical Guidance Report conflicts with pERC's Initial Funding Recommendation**

  Based on pCODR's Clinical Guidance report, two sections in the document state that brentuximab vedotin be considered as an appropriate treatment option for this subset of patients. Section 3.2 *Accepted Clinical Practice* (page 14, paragraph 5) and Section 3.4 *Other Patient Populations in Whom the Drug May be Used* (page 15, paragraph 3).

- **The predicted patient population for HL patients not eligible for ASCT is small**

  In Canada, a total of 940 new cases of HL were estimated to occur in 2012. Assuming that 75 -80% of these cases are cured with upfront treatment, approximately 180 patients will have relapsed/refractory disease. Approximately 20% of these patients could be deemed transplant ineligible due to age and co-morbidities (36 patients) and another 15-20% will not have adequate response to second and third-line salvage therapies (36 patients). Thus the potential population for which funding could be considered is much less than 100 patients annually, approximately 70-75 patients. A decision to fund the transplant ineligible population would add only a small number of patients who could stand to benefit greatly.

  As stated in pCODR's Clinical Guidance Report: "As an enabler, PAG noted that the HL patient population with refractory/resistant disease is small and as such implementing a funding decision will have a small budgetary impact". (Page 19, paragraph 7).

We believe that funding brentuximab for these patients will provide an option for patients with significant unmet need with a small budgetary impact. Seattle Genetics respectfully requests that pCODR issue a positive decision in their final recommendation

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.	__X__ Do not support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.	Recommendation should be reconsidered by pERC.

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.