CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Sponsor)

Brentuximab Vedotin (Adcetris) for Primary Cutaneous Anaplastic Large Cell Lymphoma or CD30-Expressing Mycosis Fungoides

December 3, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	**ADCETRIS® (brentuximab vedotin)** Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides
Eligible Stakeholder Role	Manufacturer
Organization Providing Feedback	Seagen Canada Inc.

** CADTH may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by CADTH.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the initial recommendation:

☐ Agrees ☒ Agrees in part ☐ Disagrees

Seagen Canada is pleased with pERC's initial recommendation to reimburse ADCETRIS for the treatment of primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides.

Seagen Canada agrees that there is a net clinical benefit for ADCETRIS, based on a clinically meaningful improvement in objective response and progression-free survival, a manageable toxicity profile, and no detriment in quality of life.

Seagen Canada, however, disagrees with the pharmacoeconomic assessment for ADCETRIS (referred to as BV in the text below) based on the following points:

1. Limitations with the data informing post-alloSCT outcomes

Response: Over the entire disease progression, patients may require several types of treatment and repeated courses of therapy to provide disease control and improve quality of life. For patients with multiple relapses progressing on systemic therapy, allogenic hematopoietic cell transplantation (alloSCT) may be considered as the only curative therapy. Input from five (5) Canadian clinicians on the development of the economic model confirmed that the model structure reflected the clinical pathway for patients with CTCL. Although it was noted that a small proportion of patients (less than 5%) are currently receiving alloSCT in real-world practice, these clinicians also acknowledged that up to 10% of patients would be eligible to receive alloSCT following BV due to the significantly improved response rates observed in the BV arm in the ALCANZA trial. It was noted in the CADTH PE report that the efficacy outcomes associated with alloSCT included in the model represented the more severe patient population. However, this is likely to underestimate the long-term outcomes associated with alloSCT compared to the ALCANZA ITT population, representing a conservative approach to modelling the outcomes of BV. In the model, patients are eligible for alloSCT if they have complete or partial response to treatment, with the same proportion of eligible patients going on to receive alloSCT in each treatment arm. In the submitted base case, 15% of complete or partial responders received alloSCT, leading to 9.76% of BV and 3.1% of physician's choice (PC) patients. We request that CADTH consider 5% of complete or partial responders to receive alloSCT, leading to 3.25% of BV

and 1.03% of PC patients receiving alloSCT. This is well below the ranges deemed plausible by clinicians and leads to 2.14% of all patients receiving alloSCT, only slightly more than 1.6% observed in ALCANZA. The introduction of BV may allow more patients to receive the potentially curative intervention and provide the opportunity to consolidate treatment response to achieve durable remission.

To address the limitation on post-alloSCT outcomes, we are not aware of any available data associated with alloSCT outcomes in the CTCL population specific to Canada. Thus, the best available UK data were utilized and confirmed by Canadian clinicians as appropriate. We acknowledge that there is missing information on subsequent therapies post-alloSCT relapse from the UK data, which may create uncertainty in the economic analysis. However, Canadian clinicians' advice indicated that patients would receive the same subsequent therapies whether patients progressed following active therapy (BV or PC) or alloSCT. Thus, subsequent therapies included in the model such as gemcitabine, and CHOP were deemed to be appropriate for modelling all progressing patients, whether their prior treatment included or excluded alloSCT.

2. Plausibility of the clinical pathway following disease progression - BV as subsequent therapy

Response: In the ALCANZA trial, some patients in both the BV and PC arms were treated with BV after progression. Twelve BV patients underwent retreatment (18.75%), and 33 PC patients had BV as crossover treatment (51.56%), which rounded to 19% and 52%, respectively, that were applied in the ALCANZA economic model. With the potential for retreatment to provide disease control, it is clinically appropriate to include some proportion (vs 0%) of BV re-treatment in the clinical pathway, as confirmed by input from Canadian clinicians and by the Clinical Guidance Panel (CGP), which noted that patients who are chemo-sensitive to BV could be re-treated with BV if their response duration was reasonable (i.e. 12 months) and also noted that if a patient completed 16 cycles of BV, responded well to BV, and had a durable response for at least 6 months, re-treatment with BV may be considered if disease occurs after the 48-week treatment course. We request that CADTH consider a 50% adjustment to the re-treatment rates observed from the ALCANZA trial (9.38% and 25.78% for BV and PC respectively) to incorporate the potential real-world impact on patient outcomes.

3. Uncertainty in overall survival in the absence of alloSCT

Response: The ALCANZA trial did not show a statistically significant difference in OS between the two treatment arms. However, as reflected in the CADTH PE report, the "clinical experts consulted by CADTH suggested that the current evidence does not support the assumption of no OS gain as implemented within the model". We explored this assumption by replicating CADTH's base case and exploring alternate OS assumptions: 1) separate OS curves for BV and PC based on ALCANZA; and 2) separate OS curves up to a specified time point then assuming equal mortality risk. Although OS was not statistically different between BV and PC arms, parametric curves have been fit to each treatment arm separately.

All the parametric curve fits show substantial and sustained differences in OS between BV and PC. Log-normal was selected to model BV OS, as this is the same curve used for PC and there was no robust statistical evidence to prefer any of the parametric curves (with the exception of excluding generalized gamma). Results showed a nearly 4-year improvement in life years for BV over PC, with an incremental cost of $331,087 and incremental QALYs of 2.99, giving an ICER of $110,764. We believe this may represent an optimistic assessment of BV's survival

benefit and thus, evaluated an alternative scenario below.

Equal mortality risk after a specific time point

An increase in LYs of 4 years is unlikely to be clinically plausible, and as such, we explored alternative assumptions which cap the OS benefit seen by BV at a certain point in time. After this specified timepoint, patients on BV have the same mortality risk as those on PC. Both curves used log-normal fits. Although the data are immature, and therefore the amount of OS benefit is uncertain, we have explored multiple time points for this analysis, to show best and worst-case scenarios. We believe that assuming equal mortality risk after 2 years is a reasonable assumption.

As seen in the scenario where the hazard of death for patients treated with BV switches to that of the PC arm, treatment with BV after 2 years is associated with an incremental LY gain of 0.74 (approximately 9 months). We request that CADTH model BV and PC OS separately, with BV having equal mortality risk to PC after 2 years. This analysis, using the CADTH base case, produces an ICER of $267,884. If we consider that the PFS data from ALCANZA show approximately a 13.2 month improvement in PFS for patients treated with BV (median PFS was 16.7 months in the BV arm vs 3.5 months with PC arm), a scenario which yields approximately 1.1 LYs suggests that all of the PFS benefit observed in the study translates to OS benefit, which is likely to represent the top end of the plausible range.

4. Stepped analysis

We have recreated the stepped analysis CADTH presented, using our requested adjustments to CADTH's base case. All analysis includes CADTH's assumption on equal end-stage care of 6 months, revised frequencies of resource use, and 100% drug dose intensity.

Summary of the Stepped Analysis

Stepped analysis	Treatment	Total costs	Total QALYs	ICER
Reanalysis 1: 5% of PR/SD patients receive alloSCT*	PC	$631,543	6.55	**$575,385**
	BV	$694,967	6.66	
Reanalysis 2: 50% of observed re-treated patients are re-treated with BV as subsequent therapy**	PC	$584,407	6.60	**$339,473**
	BV	$657,062	6.81	
Reanalysis 3: OS benefit for 2 years	PC	$623,763	6.60	**$114,645**
	BV	$705,130	7.31	
Reanalysis 1 + 2 + 3	PC	$591,356	6.55	**$197,899**
	BV	$718,304	7.19	

*3.25% of BV and 1.03% of PC patients receive alloSCT

**9.38% of BV and 25.78% of PC patients are re-treated with BV as subsequent therapy

b) Please provide editorial feedback on the initial recommendation to aid in clarity. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the stakeholder would support this initial recommendation proceeding to final recommendation ("early conversion"), which would occur two business days after the end of the feedback deadline date.

☐ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

☒ Do not support conversion to final recommendation.

Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a final recommendation, please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the stakeholder during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a resubmission.

Additionally, if the eligible stakeholder supports early conversion to a final recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

Template for Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

1 About Stakeholder Feedback

CADTH invites eligible stakeholders to provide feedback and comments on the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) initial recommendation.

As part of the CADTH's pan-Canadian Oncology Drug Review (pCODR) process, pERC makes an initial recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. The initial recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 business days within which to provide their feedback on the initial recommendation. It should be noted that the initial recommendation may or may not change following a review of the feedback from stakeholders.

CADTH welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The stakeholder feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the initial recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part, or disagree with the initial recommendation, and to provide a rationale for their response. Please note that if a stakeholder agrees, agrees in part or disagrees with the initial recommendation, they can still support the recommendation proceeding to a final recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a final recommendation ("early conversion")?**

   An efficient review process is one of the key guiding principles for CADTH's pCODR process. If all eligible stakeholders support the initial recommendation proceeding to a final recommendation and that the criteria for early conversion as set out in the *Procedures for the CADTH Pan-Canadian Oncology Drug Review* are met, the final recommendation will be posted on the CADTH website two business days after the end of the feedback deadline date. This is called an "early conversion" of an initial recommendation to a final recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the initial recommendation proceeding to a final recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the initial recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the initial recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with pERC, and may not require reconsideration at a subsequent pERC meeting.

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

2 Instructions for Providing Feedback

- The following stakeholders are eligible to submit feedback on the initial recommendation:
    - The sponsor and/or the manufacturer of the drug under review;
    - Patient groups who have provided input on the drug submission;
    - Registered clinician(s) who have provided input on the drug submission; and
    - CADTH's Provincial Advisory Group (PAG)
- 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.
- The template for providing stakeholder is located in section 3 of this document.
- The template must be completed in English. The stakeholder 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.
- Feedback on the initial recommendation should not exceed three 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 provided to the pERC for their consideration.
- 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, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.
- References may be provided separately; however, these cannot be related to new evidence.
- CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback must be disclosable and will be posted on the CADTH website.
- The template must be filed with CADTH as a Microsoft Word document by the posted deadline.
- If you have any questions about the feedback process, please e-mail requests@cadth.ca