pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Brentuximab Vedotin (Adcetris) for Hodgkin Lymphoma

August 29, 2013
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted to pCODR by Seattle Genetics Inc. compared brentuximab vedotin to chemotherapy +/- radiotherapy as well as intent to allogeneic stem cell transplant (alloSCT) for patients with post-ASCT recurrent Hodgkin Lymphoma. Brentuximab is administered intravenously and the included chemotherapies are a mixture of orally and intravenously administered.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is somewhat appropriate. The Clinical Guidance Panel considered that alloSCT is only appropriate in a subset of carefully selected patients, as is second autologous stem cell transplant (ASCT). The Submitter did not include second ASCT in modifications to the main economic analysis and considered alloSCT-eligible patients separately from alloSCT-ineligible patients instead of the target population as a whole. The CGP considered that the mixed treatment group may be a more clinically relevant comparator. The EGP used this approach for the re-analysis.

Patient advocacy group input considered the following factors important in the review of brentuximab: availability of treatment options, improved disease control and survival, and quality of life impact of treatment and adverse events. These factors are addressed in the economic model. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The Provincial Advisory Group (PAG) considered that several factors would be important to consider if implementing a funding recommendation for brentuximab, and which are relevant to the economic analysis. They identified as enablers the small patient population, but were concerned about the limited evidence for effectiveness to guide place in therapy, the possibility of indication creep, the rationale for the maximum dose cap, and potential for significant wastage. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

At the list price, brentuximab costs $4,840.00 per 50mg vial. At the recommended dose of 1.8mg/kg, the average cost, for a 70kg patient, per day in a 28-day course is $580.80 and the average cost per 28-day course is $16,262.40. The cost of brentuximab provided is assuming no wastage.

1.2 Summary of Results

The EGP’s best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $135,684 / QALY gained, but could be higher when brentuximab is compared with chemotherapy +/- RT and alloSCT.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP’s best estimate of:

- The extra cost of brentuximab is $127,187 (ΔC). This estimate includes drug acquisition and administration costs, includes wastage, and also includes administration, management and treatment of adverse events and downstream costs associated with alloSCT and progression, where appropriate.
• The extra clinical effect of brentuximab is 0.94 QALY, but because the clinical data are non-comparative, the EGP is not confident in this estimate (ΔE). This concern was also expressed by the Clinical Guidance Panel, which acknowledged that without direct comparison to the other available agents the benefit to patients with HL is difficult to measure. In the economic analysis, this issue is compounded by the extrapolation of the clinical effect. The economic results are influenced by the time horizon (15 years in this re-analysis compared to 40 years in the submitted model) and the ways in which the non-comparative clinical data for brentuximab and for chemotherapy +/- radiotherapy and alloSCT outcomes are incorporated into the model.

The EGP based these estimates on the model submitted by Seattle Genetics and reanalyses conducted by the EGP. The submitted model is based on a phase II, single arm trial of brentuximab and estimates of progression-free survival (PFS) and overall survival (OS) using current therapies from observational studies. It included OS for brentuximab with 18.5 months median follow-up, with considerable censoring near the end of data collection. To compensate for the uncertainty in the tail end of the data, the submitter only used OS data from the trial only until 20% of patients were censored. An updated analysis with 29.5 months median follow-up was presented as a poster at ASH 2012 but these data were not included in the model. This uncertainty, combined with the absence of comparative data in this population, produces a wide range in possible incremental benefit, and therefore also in the estimates of the incremental cost-effectiveness ratio. The reanalysis conducted by the EGP using the submitted model showed that when:

• Parametric survival curves fitted to brentuximab PFS are used during the trial or for the extrapolated period in the model, the extra clinical effect of brentuximab ranged from 0.46 to 0.89 QALYs, and the ICER was increased in all cases (Table 10 Reanalyses 6-7, ICERS $162,867 - $231,164 / QALY gained).

• The full follow-up (with 65% censoring) was used for brentuximab OS or using the comparator hazard with some catch-up (HR >1) to extrapolate beyond the trial also increased the ICER (Table 10 Reanalysis 8, ICERS $152,298 - $182,776 / QALY gained).

These reanalyses highlight the uncertainty in the clinical effectiveness data used in the model.

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Seattle Genetics, when brentuximab is compared with chemotherapy +/- radiotherapy only:

• The extra cost of brentuximab was $129,728 (ΔC). Costs considered in the analysis included drug acquisition costs, administration, management and treatment of adverse events.

• The extra clinical effect of brentuximab was 1.16 quality-adjusted life years (QALYs) gained (ΔE), or 0.99 life years (LYs) gained. The clinical effect considered in the analysis was based on non-comparative phase II and observational registry PFS and OS data, and the utility of complete response, stable or progressive disease, along with the utility decrements from adverse events.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) for brentuximab compared to chemotherapy +/-radiotherapy was $111,752 / QALY gained and $130,349 / LY gained.
1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of \( \Delta C \), \( \Delta E \) and the ICER differ from the Submitter’s, what are the key reasons?

The EGP compared brentuximab to the total post-ASCT recurrent HL population and used a shortened time horizon of 15 years (compared to 40 years in the submitted analysis). The comparators were based on digitalized Kaplan Meier curves from observational registry data and no parametric survival curves were fitted to the comparator PFS or OS data to assess the impact of extrapolating beyond the available data. Additionally, no age-specific mortality was included as a competing risk for death. Thus, the time horizon was shortened to mitigate any long-term impact of extrapolating based on poor quality data. Because the data are non-comparative, the EGP is not confident in the results.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Yes, the model captured the impact on quality of life of improved disease control, survival benefit and the impact of major adverse events. The utilities used to quantify quality of life impact were elicited in a separate study (i.e. not from clinical trial or specific to brentuximab treatment), but was specific to the population under review. The estimate of incremental survival benefit with brentuximab is uncertain. The only major adverse event missing is progressive multifocal leukoencephalopathy (PML), which is very severe but also quite rare.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

The model structure was adequate once the two comparators were combined to represent the post-ASCT recurrent HL population eligible for brentuximab.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The Submitter assumed a patient’s alloSCT-eligibility would influence the choice to treat with brentuximab, which is not supported by the CGP, as alloSCT-eligibility is partially dependent on chemotherapy response. Thus, the choice of chemotherapy is the relevant decision, and subsequent alloSCT is relevant to downstream costs and benefits in certain patients. The Submitter also made assumptions with respect to the extrapolation of survival data that could be construed as selective, particularly the use of immature OS data when longer and more complete follow-up is available from the 003 trial, and only until 20% of patients are censored (follow-up from the initial data cut has 65% censored).

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

The Submitter used progression-free survival estimates from the most recent prior therapy used by patients in the brentuximab clinical trial, however these data are limited in that the progression was assessed retrospectively, not measured with the same rigour as while...
on trial therapy. Also, there is no information on the chemotherapies used and these patients may underestimate PFS in the broader post-ASCT recurrent HL population.

For alloSCT PFS and comparator OS estimates, the data used were from observational registries, which were chosen because they were larger studies and in the case of Martinez et al 2010, allowed for some case-mix adjustment to improve the comparison. The CGP felt that these data sources were reasonable and when the EGP assessed the external validity, the survival estimates generated in the model (e.g. median OS) were similar to other estimates in the literature. However, it is important to emphasize that because the clinical data were non-comparative and long-term follow-up were not available for brentuximab (median follow-up 18.5 months), the overall survival estimates and incremental benefits are uncertain. The EGP requested access to the overall survival data from an updated analysis (median follow-up 29.5 months) but to date, these data have not been provided in the model. Additionally, the model did not include options to vary or use fitted curves for the PFS of the comparator groups, or the OS of any group, and the parametric curves fitted to the brentuximab PFS data all increased the ICER. Due to the absence of comparative studies in this population, the EGP would have used similar data (except with the updated brentuximab survival results and additional review for relevant chemotherapy PFS data), but the approach must be interpreted with caution.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact is influenced by the number of patients eligible for treatment, number of cycles, comparator costs and market uptake. The total budget impact is also impacted by wastage, which is included in the analysis.

What are the key limitations in the submitted budget impact analysis?

The BIA model only accounts for HL patients who are post-ASCT recurrent, while the drug is also indicated for HL patients ineligible for ASCT who have received 2 prior lines of therapy. The manufacturer acknowledges that the 88 patients estimated in Canada is likely an underestimate. The CGP estimates the eligible patient population to be 100-150 patients per year. The BIA model also uses median cycles (9), when the mean cycles (9.66) should be used. There is a chance that the mean cycles will increase, as in the trial the doses were capped at 16, but a treatment extension trial is currently underway for patients who respond well to therapy. The comparator costs in the model included bendamustine, which is not currently available in Canada for treatment of HL. Including this expensive therapy in the comparator group decreases the incremental cost of using brentuximab. Lastly, the market uptake estimates seem low, given the clinical interest in a drug that produces good response with a favourable toxicity profile compared to current options. The potential combined impact of these factors is substantial.
1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The submitted model would benefit from using longer OS follow-up presented at ASH by Chen et al 2012, validation of the PFS data for the comparator arm, and assessment of goodness of fit for parametric survival curves.

Is there economic research that could be conducted in the future that would provide valuable information related to brentuximab for post-ASCT recurrent HL?

The submitted model would benefit from comparative clinical trial data in the post-ASCT recurrent HL population.
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 (Adcetris) for HL. A full assessment of the clinical evidence of brentuximab vedotin (Adcetris) for HL 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.pcodr.ca).

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 this publicly available Guidance Report.

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.pcodr.ca). 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.
REFERENCES


