pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Brentuximab (Adcetris) for systemic Anaplastic Large Cell Lymphoma

December 5, 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 for patients with relapsed/refractory systemic anaplastic large cell lymphoma (sALCL). 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 appropriate. Some patients can receive subsequent stem cell transplant (SCT) following chemotherapy, and this is explored in the analysis as well.

Patients considered the following factors important in the review of brentuximab: availability and choice in 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.

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 maximum cycle cap, and potential for significant wastage.

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 $130,498 / QALY gained, but could be higher, when brentuximab is compared with chemotherapy +/- radiotherapy.

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 $132,182 (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 SCT and progression, where appropriate.
- The extra clinical effect of brentuximab is 1.018 QALYs, but because the clinical data are based on phase II results, include small patient numbers and 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 in such a rare indication and without direct comparison to the other available agents, the benefit to patients with relapsed sALCL 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 particularly, additional SCT 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 outcomes from a phase II, single arm trial of brentuximab and a retrospective study of patients using chemotherapy +/- radiotherapy for recurrence in a combination of similar, rare lymphomas (peripheral T-cell lymphomas or PTCL, of which sALCL is a subtype), excluding any patients who received subsequent stem cell transplant (SCT). In addition, it was assumed that half of all patients with response to therapy would receive subsequent SCT (43% in brentuximab and 28% in chemotherapy group), and separate survival data from PTCL patients who received subsequent SCT were incorporated in both treatment groups as weighted averages. The rate of SCT for brentuximab in the submitted model is higher than observed: 28% of patients actually received subsequent SCT in the brentuximab clinical trial (Pro et al 2012). As well, the submitted model assumes the brentuximab clinical trial data only reflected those patients without subsequent SCT. The weighted average approach in the submitted model may overestimate the early survival benefits for the cohort (see Section 2.2.2 Figure 1).

Patient-level data were not available for either treatment arm, so curves were fitted to data points from digitalized Kaplan-Meier curves available from the published literature.

These uncertainties, 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. After modifying the model to better account for treatment costs and shortening the time horizon (the best estimate described above), the EGP created scenarios to explore the uncertainties in the clinical effectiveness data. The reanalysis conducted by the EGP using the submitted model showed that when:

- Using equal rates of subsequent SCT (28% each) in the brentuximab and chemotherapy groups, the extra cost decreased to $116,541, the extra clinical effect decreased to 0.783 QALYs, and the ICER increased to $148,843 / QALY gained.
- Assuming SCT outcomes are already fully reflected in the brentuximab clinical trial data (i.e. adding SCT costs for 28% of patients but not additional survival benefits) and comparing to the chemotherapy group with 28% receiving subsequent SCT, the extra clinical effect decreased to 0.339 QALYs, and the ICER increased to $343,731 / QALY gained.
- Assuming no costs or survival benefits from subsequent SCT in both groups, the extra cost decreased to $117,219, and the ICER decreased to $115,621 / QALY gained.
- Different parametric distributions are fitted to brentuximab and chemotherapy survival data in the model, the extra clinical effect of brentuximab ranged from 0.806 to 0.990 QALYs, and the ICER was increased in all cases (Table 10 Reanalysis 8, ICERs $134,240 - $164,257 / QALY gained).

These scenarios 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:

- The extra cost of brentuximab was $94,637 (ΔC). Costs considered in the analysis included drug acquisition costs, administration, management and treatment of adverse events, and downstream treatment with SCT and for progression where appropriate. Drug costs **did not** include wastage in the submitted model.
- The extra clinical effect of brentuximab was 1.17 quality-adjusted life years (QALYs) gained (ΔE), or 1.45 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 $81,055 / QALY gained and $65,249 / LY gained.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The EGP used a shortened time horizon of 15 years (compared to 40 years in the submitted analysis), more appropriately accounted for total drug costs in the model, and examined the impact of the survival curve estimations and use of subsequent SCT in the treatment groups.

There is limited clinical evidence in this patient population, due to the rarity of sALCL. Survival in both treatment groups were based on curves fitted to the data points from digitalized Kaplan Meier curves from the single arm brentuximab trial and observational registry data of 153 patients with relapsed or refractory peripheral T-cell lymphomas (PTCL), of which sALCL is a subtype. Both studies had limited sample size and were non-comparative. It is not clear why patient-level data from the clinical trial were not available to the model developers. Without any estimate of individual patient data, only few parametric survival distributions can be fitted to the PFS or OS data to assess the impact of extrapolating beyond the available data. In addition, the use of subsequent SCT was incorporated using separate survival data and the assumptions about the parametric survival distribution and the rates in each group have a large impact on the results. The time horizon was shortened to mitigate any long-term impact of extrapolating based on poor quality data, but this method has shortcomings. 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. Progressive multifocal leukoencephalopathy (PML), a severe adverse event associated with brentuximab, has not been observed in this patient population and appropriately is not included in the model.

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 to address the impact of the new drug on progression and death in late stage cancer, except the method for accruing drug costs in the model resulted in underestimation. The EGP made modifications to address this limitation.

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 model included SCT as subsequent therapy for half of those with response to therapy, a rate that was higher than observed in brentuximab trial. In addition, there is uncertainty in the SCT inputs, particularly with respect to whether the brentuximab clinical outcomes are already representative of subsequent SCT in the cohort.

The submitter chose one type of parametric distribution to model all survival data, when other approaches were also feasible or better fitting. The submitter also assumed 40 year time horizon. Modifying these variables led to increases in the ICER.

Lastly, the submitter assumed no wastage, and drug acquisition costs realized in the model were underestimated. Both were addressed in the EGP's reanalysis.

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 EGP is not able to fully evaluate the SCT survival data incorporated into both treatment arms, as these data are unpublished and provided by the study author in the form of a Kaplan-Meier curve only. More importantly, the use of additional data to model subsequent SCT outcomes is uncertain in this context. As 28% of patients received subsequent SCT during the phase II clinical trial for brentuximab, the trial data already captures some impact of subsequent SCT in OS and PFS, insofar as the follow-up time has allowed. Additionally, the median PFS remained unchanged when patients were censored at the time of SCT. The submitter argues that this suggests the clinical outcomes from the trial are representative of outcomes for patients who received no subsequent transplant. Another possible interpretation would be that subsequent SCT does not necessarily translate into large improvement in outcomes, and the model output curve that includes added survival benefits for subsequent SCT is possibly not realistic. The percentages used (half of all responders) were also higher than observed. The EGP considered alternate scenarios in re-analysis.

Otherwise, it is important to emphasize that because the clinical data were non-comparative and patient level data were not available for either treatment arm, the survival estimates and incremental benefits are uncertain. The patient-level data from the phase II clinical trial for brentuximab could have been made available to the model developers. Though non-comparative and based on a small sample size, the phase II clinical trial for brentuximab was the largest study of its kind in relapsed or refractory

sALCL. Due to the absence of non-comparative studies in this population, and limited clinical data in general, the EGP would have used similar 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 likely overestimates the number of patients with relapsed sALCL estimated in Canada. The CGP estimates the eligible patient population to be <100 patients per year, and anecdotally describe the disease as extremely rare (few cases observed over many years). The model uses 9 cycles, when the mean cycles (8.2) should be used. There is also a possibility that the mean cycles will increase. In the clinical trial, the doses were capped at 16, and only a few patients received the full 16 cycles in the clinical trial. However, there may be impetus to use more than 16 cycles for those with good response to therapy. There is an on-going clinical trial examining extended treatment beyond 16 cycles for responders in this indication. Lastly, the market uptake estimates seem low, given the clinical interest. On balance, the total budget impact is likely to be equal to or lower than the submitted estimate.

1.5 Future Research

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

The submitted model would benefit from using individual patient-level data for brentuximab, or estimates of such for both treatment groups using established methods, assessment of goodness of fit and use of additional 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 further information about subsequent stem cell transplant, and ideally, comparative clinical trial data for sALCL.

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 Final 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 systemic anaplastic large cell lymphoma. A full assessment of the clinical evidence of brentuximab vedotin (Adcetris) for systemic anaplastic large cell lymphoma 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 information redacted from 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.

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