PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia

August 18, 2015

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted **to pCODR by Gilead Sciences** compared Idelalisib and Rituximab combination therapy to Chlorambucil for patients with relapsed or refractory Chronic Lymphocytic Leukemia (CLL). Idelalisib is administered orally, Rituximab is administered intravenously, and Chlorambucil is administered orally.

According to the pCODR Clinical Guidance Panel (CGP) the comparison to Chlorambucil is appropriate in the case of Ontario, and may be less appropriate in the case of other provinces where Rituximab plus Chlorambucil is the standard of care for many patients. The clinical study by Furman et al. 2014 (Study 116), compared Idelalisib+Rituximab to Rituximab alone. This is not the standard of care in Canada. Given that there is no uniform standard of care for relapsed/refractory CLL across Canada, Chlorambucil is one of the appropriate comparators.

The comparison is made for relapsed and refractory patients, whereas the clinical data are based on a study of early relapsed and refractory patients (<24 months). The clinical data speak to a smaller group of patients with a worse prognosis, the economic data speaks to the larger group of patients with relapsed and refractory CLL.

Patients considered the oral administration of Idelalisib and indicated that oral agents are preferred to therapies that require travel to a health care site (e.g. hospital) and chair time. Although there is a preference for an orally administered agent, Idelalisib is indicated in combination with intravenously administered Rituximab. The economic analysis includes utility values that were provided by patients during the clinical trial, however the utility values do not capture patient preferences for oral versus intravenous medications. Moreover, the utility values were from the randomized controlled trial which compared Idelalisib+Rituximab with Rituximab, while the economic report uses a comparator of Chlorambucil.

The **Provincial Advisory Group (PAG)** considered drug wastage to be a potential problem. PAG noted there are two tablet strengths of Idelalisib available and PAG has some concerns with drug wastage if dose reductions require change in tablet strength prior to the previously dispensed strength being all used. The economic analysis addresses the issue of drug wastage in the analysis.

Idelalisib costs $85.35 per 150 mg tablet. At the recommended dose of 150 mg twice daily, the cost of Idelalisib per 28 day cycle is $4,779.60. Idelalisib is given in combination with Rituximab. Rituximab costs $453.10 for a 100 mg vial, and $2,265.50 for a 500 mg vial. The recommended dose of Rituximab is an infusion of 375 mg/m^2 on day 1 of cycle 1, followed by 500 mg/m^2 every 2 weeks for 4 cycles and then every 4 weeks for 3 doses, for a total of 8 infusions. The average cost of Rituximab per 28 day cycle is 4974.66. The average total cost of Idelalisib in combination with Rituximab per 28 day cycle is $9754.26. Chlorambucil costs $1.468 per 2 mg tablet.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio is between $156,969 and $264,124 per quality-adjusted life year (QALY)

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect, which incorporate patients' experiences of quality of life (ΔE). The EGP's best estimate of:

- The extra cost of Idelalisib+Rituximab as compared to Chlorambucil is $122,203.67. The primary driver of this extra cost is the direct drug cost. A less impactful driver of the cost difference is the management of side-effects, which is more costly under the Idelalisib+Rituximab treatment.
- The extra clinical effect of Idelalisib+Rituximab as compared to Chlorambucil is 1.12 life years and 0.77 QALYs gained. This is an average across the patients included in the economic model.
- A driver of both costs and clinical benefits in the economic model is the assumption of the time-horizon. The EGP reanalysis is based on a 5 year time horizon.

The EGP based these estimates on the model submitted by Gilead Sciences and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- The time-horizon is shortened to 5 years, which according to the CGP is clinically a more reasonable assumption for all relapsed/refractory CLL patients, the ICER increases to $156,969 per QALY.
- The time-horizon is shortened to 3 years, which according to the CGP is a clinically reasonable assumption for patients in Study 116 (patients with early relapsed/refractory CLL), the ICER increases to $264,124/QALY.
- If the patients are assumed to have the same average body surface area as the patients who participated in the pivotal clinical trial ($1.9m^2$), the ICER increases to $161,438/QALY. The main analysis is based on the assumption that patients have the same average body surface area as the general population which is estimated at $1.8m^2$.

The EGP's estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Gilead Sciences, when Idelalisib with Rituximab is compared with Chlorambucil:

- The extra cost of Idelalisib+Rituximab is $129,249 (ΔC). Costs considered in the analysis included costs of treatment, pre-medication, adverse event management, follow-up and palliative care.
- The extra clinical effect of Idelalisib+Rituximab is 1.59 life years gained or 1.12 QALY (ΔE). The clinical effect considered in the analysis was based on progression-free survival, overall survival, and health state utilities.

The Submitter estimated that the incremental cost-effectiveness ratio was $115,233 per QALY gained.

1.3 Summary of Economic Guidance Panel Evaluation

The EGP's estimates the incremental cost-effectiveness ratio to be $156,969 and $264,124 per QALY gained. The Submitter's estimates the incremental cost-effectiveness ratio to be $115,233 per QALY gained. This is a difference of $41,736 and $148,891 per QALY.

The main reason for the difference in estimated cost-effectiveness ratios is the assumption of the time horizon in the economic model. The economic model uses data from the clinical trial which has a short follow-up period. Thus there is high degree of uncertainty in estimates based on a longer time horizon. Moreover the CGP and EGP concluded that the submitted time horizon is not a reasonable clinical assumption for this patient group given their relatively poor prognosis. The EGP's estimated ICER also differs from the Submitter's estimate because the EGP considered wastage in the calculation of costs of Rituximab.

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

The factors most relevant to patients as expressed by the submissions of the patient advocacy groups were: (i) the convenience of Idelalisib as an oral agent (as compared to an IV therapy); and (ii) the high toxicity of Idelalisib. The issue of convenience is less relevant when Idelalisib is taken in combination with Rituximab, since Rituximab is an IV therapy. The issue of toxicity is incorporated into the economic model on the costs side, where the management of adverse events is higher under Idelalisib+Rituximab than under Chlorambucil. Toxicity is also indirectly captured in the utility scores. However, no on-treatment-utility scores were available for Chlorambucil. The manufacturer used the utility scores from the control arm (Rituximab) of the pivotal trial in their economic model. The EGP reanalysis assigned the same on-treatment-utility values for Idelalisib+Rituximab and Chlorambucil.

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

The model structure is adequate, given the available information and modeling techniques**.**

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?

A key assumption is Chlorambucil as the comparator therapy. This assumption is necessary, because there is no uniform standard of care across Canada. The assumption is more appropriate in the context of Ontario than other provinces. There is no alternate assumption that would be more appropriate in the context of Canada as a whole, although Chlorambucil+Rituximab and Ibrutinib also are appropriate comparators.

A key assumption was that the increased clinical benefit found in the clinical trial for Idelalisib versus the comparator Rituximab was the same as the increased clinical benefit used in the economic model for the comparator Chlorambucil. This may not be appropriate, because the trial compared Idelalisib+Rituximab to Rituximab, whereas the economic model compares Idelalisib+Rituximab to Chlorambucil. This assumption did not have substantive impact on the ICER.

A key assumption, as discussed above, is the submitted time-horizon. This assumption was changed by the EGP in the re-estimation, time horizon had a substantive impact on the ICER.

Assumptions of the body surface area were assessed by the EGP. Re-estimations by the EGP showed that these did not have a substantive impact on the ICER.

The submitter assumed that there was no wastage in dispensing of drugs. The EGP assumed that there was full wastage. The reality is likely that there is some, not full wastage. The assumption did not have substantive impact on the ICER.

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?

Clinical effect data from a key clinical trial were used and this is what the EGP would have chosen. The clinical trial compared Idelalisib and Rituximab to Rituximab alone. In the economic analysis, Chlorambucil is the comparator. This is based on an absence of standard therapy in Canada for relapsed/refractory CLL. The EGP agreed that this is a reasonable assumption, although clinical data on Chlorambucil would have been preferred. Clinical data undergo a series of estimations to arrive at the clinical benefit used in the economic analysis. The EGP would have made some different assumptions, for example a shorter time horizon, drug wastage, and equivalent utility values. Cost estimations were generally accepted by EGP.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The BIA estimates how many patients with relapsed or refractory CLL are using the available therapies. The source of these estimates is confidential, therefore the EGP is not able to assess validity. BIA estimates assume that patients are smaller than what is assumed in the economic report. The EGP re-estimated the BIA using the same size assumption as used in the cost-effectiveness analysis. This Submitter's assumption underestimates the budget impact by approximately $100,000 per year.

A key driver of the BIA is the assumption that new expenditures on Idelalisib are offset by lower expenditures on Ibrutinib. This results in a relatively low budget impact. A change in this assumption, and comparison to a situation where Chlorambucil (the comparator used in the economic analysis) is the main comparator, substantially (4 to 5 fold) increases the budget impact, and removes the savings projected in year 3.

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

The BIA considers Ibrutinib as the main comparator and not Chlorambucil or Chlorambucil+Rituximab. Therefore, the BIA and the CEA models are inconsistent – the CEA model assumes Chlorambucil to be the main comparator, the BIA assumes Ibrutinib to be the main comparator. As Ibrutinib is expensive, the BIA is favourable primarily due to the assumption that expenditures on Idelalisib replace expenditures on Ibrutinib, with relatively low budget impact. The BIA does not consider the costs of implementation (new therapy management and monitoring of its associated adverse events) that are flagged as important by the Provincial Advisory Group.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?
Economic research of cost-effectiveness must rely on available clinical data. If clinical data were available comparing Idelalisib+Rituximab to Chlorambucil, then a cost-effectiveness analysis comparing these two therapies should be re-estimated. The choice of economic model could be better supported with statistical tests.

Is there economic research that could be conducted in the future that would provide valuable information related to Idelalisib for relapsed/refractory CLL?

There are no published economic studies on the cost-effectiveness of Idelalisib in CLL.

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 Hematology 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 Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia. A full assessment of the clinical evidence of Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia 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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