PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Economic Guidance Report

Obinutuzumab (Gazyva) for Chronic Lymphocytic Leukemia

January 27, 2015

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

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

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Hoffmann-La Roche** compared obinutuzumab plus chlorambucil to chlorambucil monotherapy for patients with previously untreated chronic lymphocytic leukemia where fludarabine-based therapy is considered inappropriate. Obinutuzumab is administered intravenously and chlorambucil is administered orally.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, although, there are other comparators for the treatment of CLL that are equally appropriate (for example, rituximab plus chlorambucil, bendamustine). The submitter provided a comparison of obinutuzumab plus chlorambucil versus rituximab plus chlorambucil as a modification to the main economic analysis. The submitter also provided an indirect comparison with bendamustine; however, with input with CGP, this indirect comparison was deemed inappropriate due to differences in population.

Patients considered the following factors important in the review of obinutuzumab, which are relevant to the economic analysis: long remission, less toxicity, and improved quality of life. These were accounted for in the economic model as survival, adverse events and quality of life estimates.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for obinutuzumab and which are relevant to the economic analysis.

Enablers to the implementation of obinutuzumab include:

- Flat dosing, no wastage concerns;
- Short number of treatments.

Barriers to the implementation of obinutuzumab include:

- Four hour infusion time;
- Monitoring of infusion related reactions;
- Indication creep into the relapsed/refractory setting;
- Administration costs of obinutuzumab.

The majority of these factors have been considered in the economic model through resource utilization and administration costs. The impact of indication creep into the relapsed/refractory setting was not examined.

Obinutuzumab costs $5,275.50 per 1,000mg vial. At the recommended dose of 1,000 mg on days 1/2, day 8, day 15, followed by 1,000mg on day 1 of cycles 2-6, this results in a cost of $42,204.00 per episode of care. 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 on day 1 of cycles 2 – 6. Chlorambucil costs $1.39 per 2 mg tablet. Bendamustine costs $312.50 and $1,250.00 per 25mg/vial and 100mg/vials. At the recommended dose of 100mg/m2 IV on days 1 & 2 every 28 days, bendamustine costs $151.79 per day and $4,250.00 per 28 day cycle. Note that obinutuzumab is administered as a flat dose and wastage is not anticipated as per feedback from the Provincial Advisory Group. As such, the model did not contain a wastage parameter. The cost of obinutuzumab is based on a list price submitted by the manufacturer.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ICER) (ΔC / ΔE) is between $32,369 and $49,823 when obinutuzumab plus chlorambucil is compared with chlorambucil monotherapy.

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 obinutuzumab plus chlorambucil is between $29,240 and $29,958. The factors that most influence the costs is the cost of obinutuzumab.
- the extra clinical effect of obinutuzumab plus chlorambucil is between 0.587 and 0.926 (ΔE). The factors that most influence the effectiveness of obinutuzumab is overall survival.

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

- Overall survival was based on the hazard ratio from the clinical trial (instead of 1 minus cumulative deaths), the extra cost of obinutuzumab plus chlorambucil is $29,958 ($\Delta C_1$) and the extra clinical effect of obinutuzumab is 0.926 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $32,369 (from $30,844). Using the hazard ratio from the trial for overall survival and setting the hazard ratio to 1 after the end of the clinical trial, minimizes any post-progression survival.
- Overall survival was based on the upper 95% confidence interval of the hazard ratio, the extra cost of obinutuzumab plus chlorambucil is $29,240 ($\Delta C_2$) and the extra clinical effect of obinutuzumab is 0.587 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $49,823 (from $30,844). Using the upper confidence interval limit allowed exploration of some of the uncertainty around the immaturity of the clinical trial data.

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is $68,021 when obinutuzumab plus chlorambucil is compared with rituximab plus chlorambucil.

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 obinutuzumab plus chlorambucil is $16,068 (ΔC). The factors that most influence the costs is the cost of obinutuzumab.
- the extra clinical effect of obinutuzumab plus chlorambucil 0.236 (ΔE). The factors that most influence the effectiveness of obinutuzumab is overall survival.

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

- Overall survival was set to 1.0, given that the 95% confidence intervals cross 1.0 (indicating no difference in overall survival between the two treatment arms), the extra cost and the extra effectiveness are $16,068 and 0.236, respectively, which increases the incremental cost-effectiveness ratio to $68,021 (from $29,868). Setting the hazard ratio to 1.0 allowed exploration of the lack of overall survival benefit between these two treatments.

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Roche, when obinutuzumab plus chlorambucil is compared with chlorambucil monotherapy:

- the extra cost of obinutuzumab plus chlorambucil is $30,065 (ΔC). Costs considered in the analysis included drug costs, administration costs, supportive care, subsequent treatment costs and adverse event costs.
- the extra clinical effect of obinutuzumab plus chlorambucil is 0.975 quality-adjusted life years (ΔE) or 1.038 life years. The clinical effect considered in the analysis was based on progression-free survival, overall survival, adverse events, and utilities.

So, the submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $30,844 per quality-adjusted life year or $28,957 per life year gained.

According to the economic analysis that was submitted by Roche, when obinutuzumab plus chlorambucil is compared with rituximab plus chlorambucil:

- the extra cost of obinutuzumab plus chlorambucil is $16,757 (ΔC). Costs considered in the analysis included drug costs, administration costs, supportive care, subsequent treatment costs and adverse event costs.
- the extra clinical effect of obinutuzumab plus chlorambucil is 0.561 quality-adjusted life years (ΔE) or 0.546 life years. The clinical effect considered in the analysis was based on progression-free survival, overall survival, adverse events, and utilities.

So, the submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $29,868 per quality-adjusted life year or $30,712 per life year 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?

For obinutuzumab plus chlorambucil versus chlorambucil monotherapy, the EGP wanted to explore the upper 95% confidence interval for the hazard ratio for overall survival as these data did not come from the main clinical trial as the data are still immature. Further, manipulating overall survival had a large impact on the ICER. For obinutuzumab plus chlorambucil versus rituximab plus chlorambucil, the EGP wanted to explore no benefit in overall survival between the two treatments as the 95% confidence interval crossed 1.0.

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

Yes, factors important to patients were adequately addressed in the economic analysis. These factors included survival, quality of life and side effects.

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

Yes, a limitation of this study design is that it is not a standard Markov model, but rather two independent survival curves (one relating to overall survival and the other one to progression-free survival) – a partitioned survival model. This becomes a limitation when one considers the possibility of a carry-over effect from the treatment of obinutuzumab-chlorambucil. Despite stopping treatment, some gains in survival are seen. If this were a traditional Markov model, the design would allow the independently assessment of the impact of these survival estimates (exploration of the upper and lower confidence limits of hazard ratios) on the ICER, which the EGP was unable to do. The economic model provided was, however, fairly transparent and allowed for the manipulation of many factors relevant to the economic analysis.

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 assumptions that had the greatest impact on the results were overall survival, time horizon and post-progression survival. In order to account for the uncertainty that overall survival may have on the results, the upper 95% confidence limit was explored, as overall survival data from the clinical trial was still immature and therefore death was calculated from progression-free survival deaths and progressed health states deaths. However, progressed health states deaths were not taken from the main clinical trial. In accordance with the CGP, the EGP felt a time horizon of 10 years was reasonable, given the survival of CLL patients. Post-progression survival was a cost driver, and the EGP examined an equal weekly rate of death for both comparators, which did not have a large impact on the ICER (survival equal between the two treatment arms). As post-progression survival data did not come from the main clinical trial, there is uncertainty around this parameter.

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?

Yes. The majority of the clinical effect estimates came from one clinical trial (with the exception of post-progression survival). Ideally, all estimates would have come from that clinical trial. The type and proportion of subsequent treatment was determined by expert opinion; the EGP, with input from the CGP, determined that this assumption was reasonable and alternate assumptions were examined in a scenario analysis.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact analysis was most sensitive to an increase in price of the drug, the proportion of patients seeking treatment and the proportion of patients ineligible for fludarabine-based therapies.

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

As new agents are entering this therapeutic area, market shares have the potential to change rapidly, including agents that are not currently in use. Not all current scenarios of treatment of first line CLL may be reflected in this budget impact analysis.

1.5 Future Research

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

Providing an economic evaluation with mature clinical trial data would limit the reliance on assumptions, and decrease the uncertainty with these assumptions.

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

Collecting utilities alongside the clinical trial would increase the validity of the assumptions.

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 Obinutuzumab (Gazyva) for Chronic Lymphocytic Leukemia. A full assessment of the clinical evidence of Obinutuzumab (Gazyva) 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.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 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.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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