CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

# Obinutuzumab (Gazyva) for Follicular Lymphoma

November 1, 2018

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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.

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# 1 ECONOMIC GUIDANCE IN BRIEF

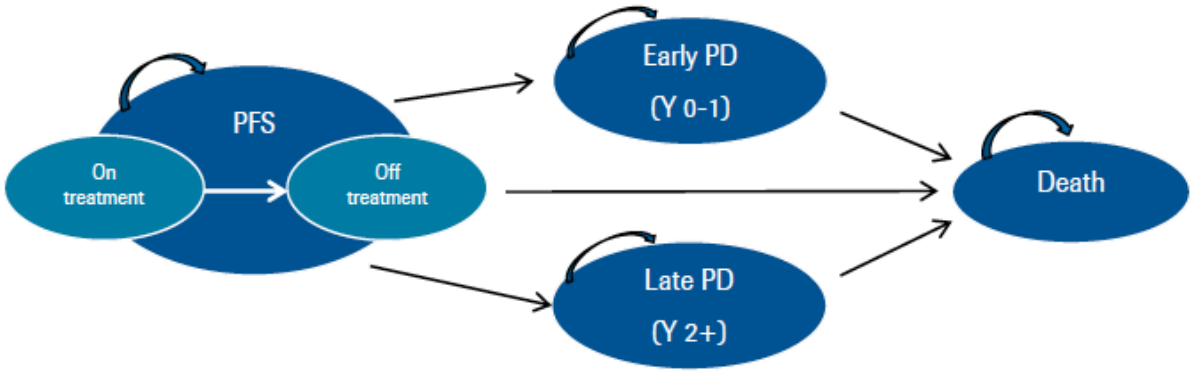
## 1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by** Hoffmann-La Roche compared obinutuzumab in combination with chemotherapy followed by obinutuzumab monotherapy to rituximab plus chemotherapy followed by rituximab monotherapy for patients with previously untreated follicular lymphoma.

*Table 1. Submitted Economic Model*

| | |
|---|---|
| Patient Population Modelled | Patients with previously untreated follicular lymphoma. |
| Type of Analysis | CUA / CEA |
| Type of Model | Partitioned-survival analysis |
| Intervention | Induction obinutuzumab plus chemotherapy followed by maintenance obinutuzumab monotherapy |
| Comparator | Induction rituximab plus chemotherapy followed by maintenance rituximab monotherapy |
| Year of costs | 2017 |
| Time Horizon | 40 years |
| Perspective | Government |
| Cost of obinutuzumab<br>*Fixed dose administered by IV* | • $5,429 per 1000 mg vial<br>• Fixed dose<br>• Total regimen cost of induction treatment with bendamustine plus obinutuzumab is $68,510.<br>• Total maintenance cost of obinutuzumab every two months for two years is $65,153. |
| Cost of rituximab<br>*Dosing of mg/m$^2$ based on an average BSA of1.86* | • $2,352.59 per 500 mg vial<br>• Dosing based on mg/m$^2$<br>• Total regimen cost of induction treatment with bendamustine plus rituximab is $42,794.<br>• Total maintenance cost of rituximab every three months for two years is $23,108. |
| Model Structure | Survival-based decision analytic Markov model with four mutually exclusive health states: progression-free survival (PFS), early progressive disease (early PD), late progressive disease (late PD) and death. PFS was further sub-divided into PFS on treatment and PFS off treatment. Overall survival derived from PFS and post-progression survival. Model displayed in Figure 1. |
| Key Data Sources | Phase III GALLIUM trial (progression-free survival)[1]<br>Phase III PRIMA trial (post-progression survival)[2] |

*Figure 1. Model structure*




## 1.2 Clinical Considerations

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate.

- Relevant issues identified included:
- There may be a net clinical benefit when obinutuzumab is combined with chemotherapy for the treatment of previously untreated follicular lymphoma. There is a small benefit with obinutuzumab but whether this benefit is clinically meaningful is difficult to determine.
- Adverse event profiles are similar between obinutuzumab and rituximab. However, there appears to be a higher rate of secondary malignancies in patients treated with obinutuzumab.
- Progression-free survival is a relevant endpoint in follicular lymphoma.
- The benefits of obinutuzumab are seen regardless of the chemotherapy backbone it is combined with.

**Summary of registered clinician input relevant to the economic analysis**
Two clinicians with experience with obinutuzumab provided input. Registered clinicians considered that that obinutuzumab meets current clinical needs for patients with follicular lymphoma, and that it may provide patients with a treatment option that will prolong time between treatments, compared to rituximab, for patients who will need to be eventually retreated. Registered clinicians identified that obinutuzumab resulted in greater toxicity and infusion reactions when compared to rituximab.

**Summary of patient input relevant to the economic analysis**
Patients considered longer survival and longer remission as most important for new treatment when compared to current therapies. Improvement in quality of life and fewer side effects were also considered important. The most commonly reported disease symptoms affecting quality of life were fatigue, enlarged lymph nodes and drenching night sweats. Other impacts on quality of life include anxiety or worry, and the ability to work. The most common side effects experienced with obinutuzumab included fatigue, neutropenia and infection. Patients were interested in controlling symptoms like fatigue. Quality of life was incorporated into the economic analysis, along with adverse events. There is currently no long term evidence from the GALLIUM trial demonstrating an overall survival benefit.

**Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis**
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for obinutuzumab which are relevant to the economic analysis:

Enablers:

- The dose of obinutuzumab is 1000 mg (flat dose) and the vials are available as 1000 mg. There is no drug wastage.

Barriers:

- Additional resources and chemotherapy chair time are required for the administration of obinutuzumab. Obinutuzumab is administered on days 1, 8 and 15, which requires more chemotherapy visits compared to cycle 1 of rituximab. In addition, obinutuzumab is infused over approximately four hours after cycle 1, whereas rituximab can be infused over 90 minutes after cycle 1; rituximab subcutaneous injection is available after cycle 1 and the administration time is 5 minutes.
- Obinutuzumab maintenance is administered every two months while rituximab maintenance is usually administered every three months.
- Additional resources may be required to monitor and treat adverse events, which appear to be more frequent with obinutuzumab.

## 1.3 Submitted and EGP Reanalysis Estimates

*Table 2. Submitted and EGP Reanalysis Estimates*

| Estimates (range/point) | Submitted | EGP Reanalysis Lower Bound | EGP Reanalysis Upper Bound |
|---|---|---|---|
| ΔE (LY) | 0.96 | 0.87 | 0.62 |
| Progression-free | 1.42 | 1.40 | 0.88 |
| Post-progression | -0.46 | -0.53 | -0.26 |
| ΔE (QALY) | 0.80 | 0.73 | 0.52 |
| Progression-free | 1.16 | 1.15 | 0.72 |
| Post-progression | -0.36 | -0.42 | -0.20 |
| ΔC ($) | $39,697 | $55,457 | $69,067 |
| ICER estimate ($/QALY) | $49,562 | $76,261 | $133,801 |

**The main assumptions and limitations with the submitted economic evaluation were:**

- *Absence of long-term data:* The GALLIUM trial was stopped early for benefit, however, median overall survival was not reached. In order to model overall survival, the submitter used data from the PRIMA trial, which examined rituximab maintenance after first-line treatment in patients with follicular lymphoma receiving an induction rituximab plus chemotherapy regimen. Using the data from the PRIMA trial may underestimate the benefit of obinutuzumab, however, the magnitude of any benefit associated with obinutuzumab is unknown given the lack of long-term data for this population with the intervention under study.
- *Treatment administration of obinutuzumab in the maintenance setting:* The CGP identified that the treatment administration of obinutuzumab in the maintenance setting may be similar to the rituximab administration schedule (i.e., maintenance every 3 months) and not that of the submitted base case (i.e., maintenance every 2 months). Though this may impact

the ICER, this ultimately depends on the assumption that the effect of obinutuzumab is maintained regardless of the maintenance schedule.

- *Subsequent treatments:* Subsequent treatments were not taken from the GALLIUM trial. Subsequent treatments included only one course of therapy, with a fixed duration for both treatment arms. The CGP indicated that patients in the Canadian setting, following obinutuzumab combined with chemotherapy followed by obinutuzumab monotherapy, patients are more likely to receive bendamustine than CVP or CHOP, which are less relevant. The CGP also indicated that SCT would most likely be divided between autologous and allogeneic stem cell transplants depending on the transplant centre.

## 1.4 Detailed Highlights of the EGP Reanalysis

**The EGP made the following changes to the submitted economic model:**

- Time horizon: The submitted time horizon was 40 years. The CGP stated that a time horizon of this length is not clinically plausible for this patient population given the median age of the patients in the trial was 60 years. The EGP chose a time horizon of 30 years to better align with expert opinion of the CGP for this patient population.
- Proportion of rituximab administered subcutaneously: In the submitted base case, it was assumed that 0% of rituximab would be administered subcutaneously. Despite the first dose being given intravenously as a standard of care, the CGP stated that some provinces in Canada do administer rituximab subcutaneously. Based on the expert opinion of the CGP, the EGP estimated the use of rituximab SC as 50%.
- Frequency of maintenance therapy: In the submitted base case, it was assumed that maintenance would be given every two months in the comparator arm for rituximab plus chemotherapy. Currently in the Canadian setting, maintenance therapy of rituximab is given every 3 months. The EGP changed this for the best estimate in order to align with clinical practice.
- Rituximab IV price: A biosimilar of rituximab is expected to be available on the market in the future (expected 2019 - 2021). The EGP, in their upper bound, considered the price of the biosimilar -- a discount of 35%.
- Duration of treatment effect: Given the immaturity of the data from the GALLIUM trial and the use of indirect data from the PRIMA trial to inform post-progression survival, the EGP elected to truncate the treatment effect to 5 years. Five years was chosen as this was the duration of follow-up in the GALLIUM trial.

Following the posting of the pERC Initial Recommendation, the EGP provided further clarification on the following issues that were raised in feedback from the submitter on the pERC Initial Recommendation.

In the absence of mature OS data to provide a full picture of the long term effects of treatment with obinutuzumab, the EGP elected to truncate the duration of treatment effect of obinutuzumab to 5 years in the reanalysis. This was done as a means of exploring uncertainty in the ongoing benefit of obinutuzumab (due to the extrapolation of long term estimates from data with a shorter follow-up period) and the impact of this benefit on overall survival, given the use of indirect data from the PRIMA trial to inform post-progression survival, which may not reflect the course of a patient being treated with obinutuzumab therapy. The EGP chose 5 years as it corresponds to the duration of follow up in the GALLIUM trial. In truncating the treatment effect at 5 years, the EGP assumed no incremental treatment effect of obinutuzumab beyond the GALLIUM trial follow-up of 5 years. The EGP noted that this analysis could represent the worst case scenario and therefore included it as part of their upper bound ICER estimate and that this is an appropriate approach to demonstrate the impact of unknown long term treatment effect on overall survival, and the ICER.

The submitted base case assumed that maintenance treatment of rituximab plus chemotherapy would be administered every two months in the comparator arm, as per the GALLIUM trial. In the EGPs reanalysis, the EGP changed the frequency of maintenance therapy of rituximab to every 3 months to reflect current Canadian clinical practice. The submitter provided feedback noting that this approach biases the results in favour of rituximab by reducing the incremental cost between the two treatments, while assuming the same magnitude of clinical benefit for rituximab plus chemotherapy with a lower dose. The EGP and CGP re-affirm the inclusion of administration of maintenance therapy of rituximab every 3 months to reflect standard of care in Canadian clinical practice.

*Table 3. EGP reanalysis for best case estimates*

| Baseline (Submitter's best case) | $39,697 | 0.80 | 0.96 | $49,562 | -- |
|---|---|---|---|---|---|
| Description of Reanalysis | ΔC | ΔE QALYs | ΔE LYs | ICUR (QALY) | Δ from baseline submitted ICER |
| LOWER BOUND | | | | | |
| *Time horizon - 30 years* | $39,599 | 0.73 | 0.87 | $54,455 | $4,893 |
| *Rituximab administered SC for 50% of patients* | $46,517 | 0.80 | 0.95 | $58,114 | $8,552 |
| *Frequency of maintenance therapy of rituximab - every 3 months* | $50,099 | 0.80 | 0.95 | $62,590 | $13,028 |
| Best case estimate of above 3 parameters | $55,457 ($50,808, $59,888) | 0.73 (0.27, 1.19) | 0.87 (0.31 - 1.42) | $76,261 | $26,699 |
| UPPER BOUND | | | | | |
| *Biosimilar rituximab (discount of 35%)* | $56,061 | 0.80 | 0.95 | $70,037 | $20,475 |
| *Duration of treatment effect truncated at 5 years* | $40,526 | 0.57 | 0.68 | $70,799 | $21,237 |
| Best case estimate of above 4 parameters | $69,067 ($64,589, $73,257) | 0.52 (0.19, 0.85) | 0.62 (0.23, 1.00) | $133,801 | $84,239 |

## 1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis for Ontario include (noting that the following estimates assume no wastage):

- R-chemo maintenance frequency every 3 months instead of every 2 months increases the budget impact by ~18%.
- Increasing the size of eligible FL population by 10% increases the 3-year budget impact by ~10%.
- Assuming the biosimilar cost for all rituximab products at a 35% discount increases the 3-year budget impact by ~36%.
- Market share of obinutuzumab.

Key limitations of the BIA model include the inability to assess the budget impact for all of Canada, though it is possible to estimate province by province. It is possible to explore the administration of rituximab sub-cutaneously with the increased use of the subcutaneous formulation. The BIA, however, does not contain administration costs and therefore currently underestimates incremental budget impact of obinutuzumab because it does not directly consider cost of administration.

## 1.6 Conclusions

**The EGP's best estimate of ΔC and ΔE for obinutuzumab plus chemotherapy when compared to rituximab plus chemotherapy is:**

- Between $76,261/QALY and $133,801/QALY
- The true estimate of the ICER is dependant on the duration of treatment effect. If one believes that the duration of treatment effect is 9 years, the ICER would be towards the lower range. If one believes the duration of treatment effect is 5 years, the ICER would be towards the upper range.
- The extra cost of obinutuzumab is between $55,457 and $69,067 (ΔC). *The main factors that influence ΔC include the proportion of rituximab that is administered sub-cutaenously, the price of rituximab IV and the frequency of maintenance therapy.*
- The extra clinical effect of obinutuzumab is between 0.52 and 0.73 (ΔE). *The main factors that influence ΔE include the duration of treatment effect and the time horizon.*

**Overall conclusions of the submitted model:**

- *The submitted model was transparent and easy to manipulate.*
- *Several of the limitations were unable to be assessed in scenario analyses, including immaturity of clinical data, incorporation of second malignancies and administration of obinutuzumab ever three months in the maintenance setting.*

# 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 obinutuzumab for FL (previously untreated). A full assessment of the clinical evidence of obinutuzumab for FL (previously untreated) 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 information redacted from this publicly available Guidance Report.

A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

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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