pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Obinutuzumab (Gazyva) for Follicular Lymphoma

June 2, 2017

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

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
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Hoffman-La Roche compared obinutuzumab + bendamustine followed by obinutuzumab maintenance (GB) to bendamustine alone for patients with follicular lymphoma who were refractory to rituximab or a rituximab containing regimen as a its primary analysis.[1]

In a secondary analysis GB was compared to potentially relevant treatment options in Canada in the same population based on indirect evidence

Table 1. Submitted Economic Model	
The funding request was for obinutuzumab plus chemotherapy followed by maintenance obinutuzumab for up to two years for treatment for patients with follicular lymphoma who relapsed or are refractory to a rituximab containing regimen.	The primary analysis of the economic model was based on the comparators and evidence of follicular lymphoma patients from the GADOLIN trial. The GADOLIN trial compared obinutuzumab plus bendamustine followed by maintenance obinutuzumab. Bendamustine is one type of chemotherapy that obinutuzumab could be combined with. The trial included patients that were refractory (defined as progressing during or within 6 months of stopping treatment) to a rituximab containing regimen. The trial did not include patients that relapsed after a rituximab containing regimen.
Type of Analysis	Cost Utility Analysis, Cost-effectiveness analysis
Type of Model	3 health state Markov model
Comparator	obinutuzumab plus bendamustine followed by obinutuzumab maintenance (GB) vs. bendamustine alone
Year of costs	*2016*
Time Horizon	*25 years*
Perspective	*Government*
Cost of GB (obinutuzumab plus bendamustine followed by obinutuzumab maintenance up to 2 years)	Obinutuzumab costs $5,381.01 per 1000 mg Bendamustine costs: $312.50 per 25 mg vial $1250.00 per 100mg vial Based on the GADOLIN protocol dose of Cycle 1 (28 days per cycle): obinutuzumab 1000mg X 3 bendamustine 90mg/m^2 X 2 Cycles 2-6 (28 days per cycle) obinutuzumab 1000mg X 1 bendamustine 90mg/m^2 X 2 Maintenance (every 2 months) obinutuzumab 1000mg X 1 The cost of GB is* • $20,463 per 28-day course (cycle 1) • $9,701 per 28 day course (cycles 2-6)

Table 1. Submitted Economic Model	
	• $5381 every two months (maintenance up to 2 years) *assumes bsa=1.92 and vial sharing
Cost of bendamustine alone	Bendamustine costs: $312.50 per 25 mg vial $1250.00 per 100mg vial Based on the GADOLIN protocol dose of Cycles 1 -6 (28 day cycles): bendamustine 120mg/m^2 X 2 The cost of bendamustine alone is* $5,760 per 28 day course (cycles 1-6) *assumes bsa=1.92 and vial sharing
Model Structure	The model was comprised of 3 health states: 1) Alive no progression; 2) Alive post progression; 3) Dead. The following determine the proportion of patient that would be in each of the health states every month. • Progression free survival • Mortality rates while progression free • Post progression survival
Key Data Sources	GADOLIN, a phase 3 RCT trial which compared GB to bendamustine alone in indolent non-Hodgkins lymphoma patients who were refractory to rituximab or a rituximab regimen. Data from follicular lymphoma patients from GADOLIN (81% of subjects) used to estimate: • Progression free survival • Mortality while progression free • Post progression survival • Adverse Event rates • Subsequent treatments LymphoCare registry, a database of 2,728 follicular lymphoma patients from U.S centers. Registry is maintained by Hoffman La Roche • Indirect measures of relative effect for GB vs. potentially relevant treatment options in Canada used in secondary analysis *IMS Brogan* • *Unit costs of all medications*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison to obinutuzumab plus bendamustine followed by maintenance obinutuzumab compared to bendamustine alone is appropriate.

Relevant issues brought up by the CGP included:

- The GADOLIN study began enrolling patients in 2010. Since that time, bendamustine has moved to an earlier treatment line than is reflected by the GADOLIN study. This limits generalizability
- While there was some evidence of improvements in overall survival for the patients taking obinutuzumab plus bendamustine, relative to bendamustine monotherapy, the magnitude of difference in median survival benefit is unclear based on the most recent data cut-off because the data are not mature (April 1, 2016).
- Given the limitations with internal validity and external validity of the indirect comparison, no conclusions can be drawn with regards to the relative efficacy of GB and other potentially relevant treatment options in Canada (secondary analysis comparator).

Summary of patient input relevant to the economic analysis

Patients considered the following aspects highly important for a new drug to control their follicular lymphoma: prolonging their life, offer disease control, bring about a remission and improve quality of life. The economic evaluation model formally considered both the impact of treatment on length of life and quality of life as the primary outcome of the economic evaluation was quality adjusted life years. Patients who had experience with obinutuzumab said they experienced less side effects with it than they had with other FL treatments. The impact of serious adverse events on quality of life for was incorporated in the model.

Summary Provincial advisory group input relevant to the economic analysis

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for obinutuzumab plus chemotherapy followed by maintenance obinutuzumab which are relevant to the economic analysis:

- PAG noted that obinutuzumab has flat dosing dose and that vial sizes provide doses without wastage. PAG stated that this would be an enabler to implementation. The economic analysis does not address this issue.
- Obinutuzumab is an intravenous medication that requires infusion over 4 hours. In cycle 1, three doses are required, followed by monthly doses for cycles 2 to 6 and maintenance dose of every 2 months until disease progression or for two years. PAG is concerned that these are barriers as there would be chemotherapy chair utilization and increased nursing resources. The economic analysis does adequately address this as it includes the cost of nursing time and chair time associated with both obinutuzumab and bendamustine IV infusions during both initiation and maintenance periods.
- There would be increased costs associated with monitoring infusion reactions and other adverse events. This is addressed in the economic evaluation as it includes physician fees

associated with chemotherapy monitoring along with the costs associated with treating grade 3 or higher adverse events.

- The number of patients eligible for treatment is unknown and PAG noted that there could be a large incremental budget impact. The budget impact analysis does address this by estimating the number of refractory and relapsed patients that would be eligible for treatment and the increased drug costs associated with funding this treatment.

- In some jurisdictions, the administration of obinutuzumab is restricted to treatment centres with the experience and resources to manage infusion related reactions. This is not addressed in the economic evaluation.

- PAG identified that first dose of obinutuzumab in cycle 1 can be given divided over day 1 and 2 to reduce risk of infusion reaction. This would not require an extra visit as patients would already be returning for a dose of bendamustine. The economic analysis does not address this issue.

1.3 Submitted and EGP Reanalysis Estimates

The main cost drivers of the manufacturer's model were drug acquisition costs and drug administration costs. Other inputs to the model that affected estimates of costs were subsequent treatment costs and the costs of adverse events. The main drivers of the clinical outcomes of the model (QALYs, Life Years) were: 1) progression free survival estimates over time; 2) post-progression survival estimates over time; 3) the time horizon used in the model and 4) the utility values assigned to patients over the duration of the model time horizon. In the secondary analysis the hazard ratio from the indirect comparison was also a key driver for estimating outcomes. Other model variables that impacted clinical outcomes predicted by the model included adverse event rates and disutility values for adverse event rates.

Overall, the assumptions made in the model and related input variables were mostly reasonable and appropriate. Most of the key model variables were based on data from the GADOLIN trial which compared GB to bendamustine in indolent non-Hodgkin's lymphoma patients who were refractory to rituximab or a rituximab containing regimen. Model inputs were based on data on follicular lymphoma patients from this trial (81% of all GADOLIN subjects). However, there were a few concerns and limitations of the model which are listed below in order of importance.

- **Overall survival**: Differences in overall survival were not modelled on direct evidence of overall survival but indirectly based on combining progression free survival data with post progression survival data from the GADOLIN trial. This leads to uncertainty around the incremental overall survival predictions made in the model. The manufacturer stated that overall survival data from the GADOLIN trial was not used because the data was not mature enough.

- **Time Horizon:** The time horizon of the manufacturer's model is 25 years. A long time horizon may be justified due to the indolent nature of follicular lymphoma. However PFS and PPS estimates used in the model are based on extrapolated estimates from GADOLIN which had a limited time horizon. The longer data is extrapolated out over time the more susceptible it is to overestimate of projected benefits. This is particularly true when overall survival is

estimated indirectly by combining progression free survival and post progression survival projections. Therefore a shorter time horizon of 10 years was used in the reanalysis.

- **Post progression survival curve**: The choice of models to use to estimate long term PFS and PPS required a lot of judgement by the submitter. For PFS, the Weibull model was chosen despite having one of the worst goodness of fit (AIC) because it gave one of the more conservative estimates of incremental PFS and had more conservative tails compared to other models. For post progressive survival, the Weibull model was chosen because it had more conservative tails then other models despite having the worst goodness of fit. The Weibull model also provided the largest estimate of incremental overall survival amongst the tested models. The lognormal model had the best goodness of fit and resulted in the second most conservative estimate of incremental overall survival. Therefore in the EGP reanalysis, the lognormal model was used to estimate post progression survival.

- **Drug wastage**: The base case model assumes vial sharing for obinutuzumab and bendamustine. However, there is likely to be some drug wastage. Because there is a set dosage for obinutuzumab which matches it vial size (1000mg), the assumption of vial wastage will have no effect on the cost of this medication. However, it will affect the cost of treatment with bendamustine as the dosage varies with patient body surface area. Therefore in the EGP reanalysis drug wastage was assumed.

- **Small calculation errors**: In the manufacturers submitted electronic version of the model there was a small error in the calculation of drug acquisition costs. In the EGP reanalysis, this error was corrected.

- **Secondary analysis**: There is uncertainty associated with the hazard ratio derived from the indirect comparison of obinutuzumab and bendamustine with potentially relevant treatment options in Canada, given the limitations with internal validity and external validity. The hazard ratio was a key driver for estimating outcomes. Scenario analyses using the upper and lower bounds of the confidence interval generated ICERs ranging from $58,943/QALY to $103,326/QALY.

Table 2 provides a summary of the cost effectiveness results from manufacturer's analysis and from the EGP reanalysis

Table 2. Submitted and EGP Estimates[1]		
Primary analysis GB vs. Benda		
Estimates	Submitted	EGP Reanalysis
ICER estimate ($/QALY)	$62,833	$84,510
ΔE (QALY)	1.20	0.89
ΔE (LY)	1.39	0.93
ΔC ($)	$75,229	$74,957
Secondary analysis GB vs. Potentially relevant treatment options in Canada		
Estimates	Submitted	EGP Reanalysis
ICER estimate ($/QALY)	$65,213	$84,441
ΔE (QALY)	1.72	1.34
ΔE (LY)	1.99	1.42
ΔC ($)	$112,347	$112,998

1.4 Detailed Highlights of the EGP Reanalysis

The following changes were conducted in the EGP reanalysis:

- The time horizon of the model was changed from 25 years to 10 years
- Post progression survival curve was based on the lognormal distribution instead of the Weibull distribution
- Drug wastage was assumed in the model
- Minor calculation errors in the model were corrected

The results of the EGP reanalyses for the primary economic analysis is provided in Table 3

Table 3 cost-effectiveness results from EGP reanalysis: Primary analysis GB vs. Bendamustine

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1. Base case	$75,229	1.20	$62,833	
2. Correction to calculation error related to drug costs	$74,715	1.20	$62,403	-$430
3. Change time horizon from 25 years to 10 years	$75,526	0.95	$79,098	$16,265
4. Change distribution used for post progression survival to lognormal	$74,957	0.89	$84,510	$7,066
5. Assume drug wastage	$74,716	1.20	$62,405	-$428
6. Best Estimate of cost effectiveness (includes changes in 2,3, 4 and 5)	$74,957	0.89	$84,510	$21,677

The results of the EGP reanalyses for the secondary economic analysis are provided in Table 4.

Table 4 cost-effectiveness results from EGP reanalysis: Secondary Analysis GB vs. Potentially relevant treatment option in Canada

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY From base case
1. Base case	$112,347	1.72	$65,213	
2. Correction to calculation error related to drug costs	$113,004	1.72	$65,594	$381
3. Change time horizon from 25 years to 10 years	$112,674	1.46	$77,322	$12,109
4.Change distribution used for post progression survival to lognormal	$112,448	1.54	$72,921	$7,708
5. Assume drug wastage	$112,752	1.72	$65,448	$235
6. Best Estimate of cost effectiveness (includes changes in 2,3, 4 and 5)	$112,998	1.34	$84,441	$19,228

1.5 Evaluation of Submitted Budget Impact Analysis

The overall approach and assumptions of the BIA appears to be reasonable and appropriate. The factors that influenced the BIA the most was assumed future market share of obinutuzumab and the number of people that would be eligible for obinutuzumab in the next 3 years.

1.6 Conclusions

- The EGP's best estimate of the incremental cost per QALY of GB compared to Benda is $84,510/ QALY. The EGP's best estimate of the incremental cost per QALY of GB compared to a potentially relevant treatment option in Canada is $84,441/ QALY.

- The EGP's best estimate of the incremental cost of GB compared to Benda is $74,957. The EGP's best estimate of the incremental cost of GB compared to a potentially relevant treatment option in Canada is $112,998. Incremental cost is most affected by acquisition costs of medication and administration costs of medications.

- The EGP's best estimate of the incremental QALY's gained of GB compared to Benda is 0.89. The EGP's best estimate of the incremental QALY's gained GB compared to a potentially relevant treatment option in Canada is 1.34. Incremental QALYs were most impacted by progression free survival estimates, post progression survival estimates and model time horizon.

Overall, the approach taken and the assumptions made in the submitted model were reasonable and appropriate. Because overall survival data from the GADOLIN trial were immature, they were not used to estimate overall survival in the model. Instead the model indirectly estimated overall survival by combining progression free survival data and post-progression survival data from the GADOLIN trial. A few of the model variables values were changed to derive the EGP best estimate of cost effectiveness. First, the time horizon was shortened from 25 years 10 years to reduce possible overestimates of overall survival extrapolations. To extrapolate post-progression survival a lognormal model was used in the EGP analysis as it provided the best fit to the trial data. Finally, the EGP changed the assumption around drug wastage in the model to assume that there would be drug wastage.

Responses to comments by submitter and PAG after initial recommendation

The submitter raised concerns about pERC's statement in the initial recommendation that assuming the same post progression mortality for the G-Benda and the Benda arms favoured obinutuzumab. As the submitter points out, the model does include the option of having separate post-progression survival curves for the two treatment arms based on post-progression survival data from the GADOLIN trial. Assuming independent post-progression survival curves does indeed result in a more favorable cost-effectiveness for G-Benda ($42,953/QALY) compared to the basecase ($53,800/QALY). However, this does not alleviate the main concern for both the EGP and pERC around the overall survival estimates. This concern was that the model did not use OS data directly from GADOLIN but modeled it indirectly by combining PFS and post-progression survival data from the trial.

The submitter also raised concerns about the 10 year time horizon the EGP submitted to pERC. The submitter felt that this chosen time horizon was arbitrary and noted that the CADTH guidelines suggest that the time horizon should correspond to the time when survival is zero. The EGP acknowledges that the 10 year time horizon chosen was somewhat arbitrary however the EGP still feels that there is too much potential for inaccurate estimates of incremental benefits being made when extrapolating the GADOLIN trial to 25 years, due to the relatively short median duration of follow-up in the trial. Therefore the EGP continues to recommend using a 10 year time horizon instead of the 25 year time horizon used by the submitter.

The submitter did not agree with the EGP's decision to use a lognormal model for post-progression survival instead of the submitters' choice (Weibull model). The submitter noted that the EGP choose the lognormal model due to it having the best statistical fit and resulting in the most conservative estimate of overall survival amongst the various PPS models tested. The submitter noted that statistical fit was not the only criterion to base the choice of statistical model on and the Weibull model provided more clinical plausibility in terms of predicting long term survival. The EGP acknowledges that more than one criteria should be considered when choosing amongst statistical models. However, there remains subjectivity on which criteria receive the most weight. The EGP continues to recommend using the lognormal model for the estimates of post progression survival.

PAG had requested that the EGP address the uncertainty in cost effectiveness due to the approach the submitter took in estimating overall survival including providing a best estimate of cost-effectiveness. Unfortunately, this would require having access to the raw trial data in order to estimate overall survival curves using OS data from the GADOLIN trial. Since we do not have access to this data, the EGP is not able to provide a best estimate of cost-effectiveness incorporating OS data from the GADOLIN trial.

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/ Myeloma 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 and follicular lymphoma. A full assessment of the clinical evidence of [drug name and indication] 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.

REFERENCES

1. pan-Canadian Oncology Drug Review manufacturer submission: Gazyva® (obinutuzumab), 1000 mg IV. Company: Hoffmann-La Roche Limited. Mississauga (ON): Hoffmann-La Roche Limited; 2016 Nov 4.

2. Wild D, Walker M, Pettengell R, Lewis G. PCN62 utility elicitation in patients with follicular lymphoma. Value Health. 2006;9(6):A294.