pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Idelalisib (Zydelig) for Follicular Lymphoma

September 29, 2016

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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 **Gilead Sciences Canada, Inc.** compared Zydelig® (idelalisib) monotherapy with Best Supportive Care (BSC). A secondary comparator, last line of previous therapy (LLPT), was also considered for the treatment of patients with follicular lymphoma (FL) who have received at least two prior systemic therapies and are refractory to both rituximab and an alkylating agent.

Table 1. Submitted Economic Model

Funding Request	Gilead Sciences Canada Inc. is requesting Zydelig to be listed for the treatment of patients with FL who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent. This aligns with the patient population that the economic model is built on.
Type of Analysis	Cost effectiveness and cost utility analysis
Type of Model	Partitioned-survival model
Comparator	Base-case analysis was performed for BSC. A secondary comparator was, LLPT.
Time Horizon	30 years
Perspective	Publicly funded health care system in Canada
Cost of idelalisib	Idelalisib costs $85.35 per 150 mg tablet At the recommended dose of 150 mg BID, idelalisib costs: • $170.70 per day • $4779.60 per 28-day cycle
Cost of BSC	No drug acquisition cost. (*Based on Quebec AQPP or Ontario Drug Benefit)*
Cost of LLPT	Fludarabine costs $38.33 per 10mg. Monthly cost is $1,303. (Fludarabine was used as a proxy for LLPT in base case) (*Based on Quebec AQPP or Ontario Drug Benefit)*
Model Structure	The model was comprised of 3 health states: pre-progression, progression (or post-progression), and death. Transitions between these health states were driven by the DELTA study including 72 FL patients, but the base-case survival benefits were based on parametric models. For the BSC and LLPT
Key Data Sources	The efficacy and safety parameters were based on the DELTA trial. Fully parametrical models were used to extrapolate survival beyond the trial period. To form a comparator arm, the non-responders from DELTA were considered as a proxy for BSC. In the secondary analysis, the LLPT information collected at study entry into the DELTA study, was used to inform the potential efficacy of a comparator arm.
LLPT: last line of prior therapy, BSC: best supportive care, BID: twice daily, FL: follicular lymphoma	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison between idelalisib group and BSC is appropriate. Based on the available clinical evidence, the CGP concluded that there may be a net overall clinical benefit to idelalisib in the treatment of follicular lymphoma. The panel agreed that idelalisib use should be restricted to patients having two or more prior lines of therapy, refractory to alkylators (both bendamustine and cyclophosphamide), and rituximab, and when other treatment options have been exhausted.

The EGP and CGP could not identify an appropriate methodology to derive data for a realistic BSC arm in the economic model. The submitter had derived a BSC comparator from the non-responders (patients treated with idelalisib in the DELTA trial who did not respond). The CGP considered the use of these data to be inappropriate because follicular lymphoma that is refractory to alkylators and rituximab but sensitive to idelalisib cannot reasonably be considered to be the same as follicular lymphoma that is refractory to alkylators, rituximab and idelalisib. Therefore the two populations would inherently be different and inappropriate to compare.

Given the absence of alternative data to use for the BSC arm, the EGP used the submitted results (non-responders as BSC arm) noting the limitation associated with the use of these data. The Submitter also included a second analysis, comparing idelalisib to last line of previous therapy (LLPT). Given that the CGP concluded that idelalisib may be used in patients that no longer have a treatment option, the EGP did not focus on this analysis.

Relevant issues identified included:

1) Limitations and biases of a phase II study with no comparator arm;
2) No other studies addressing other treatment options in this specific patient group;
3) No other studies of this patient population with a comparator arm:
4) Use of the non-responders group as comparator arm (BSC arm). This limitation could not be addressed in the EGP's re-analysis estimates as there was no alternative data available to use for the BSC arm. The EGP provided sensitivity analysis by varying the E with BSC to illustrate the impact of this input on the ICER.

The analyses performed using these assumptions and with the limitations noted resulted in an incremental difference in benefit between the idelalisib group and BSC that favors idelalisib. However, as the non-responders may not be representative of patients receiving BSC in the real-world setting, the incremental benefit may be unrealistically high compared to a "true" BSC population.

Summary of patient input relevant to the economic analysis

Lymphoma Canada (LC) conducted online surveys and interviews of FL patients and caregivers.

- the physical and emotional impact of living with WM was varied. Most respondents reported that the impact of WM on their quality of life was moderate; however, there was a sizeable minority who reported that their quality of life was significantly impacted due to symptoms of WM.
- symptoms having the most impact were tiredness/lack of energy, tingling or numbness in feet or legs, weakness, shortness of breath, joint or muscle pain, swollen lymph nodes, heavy night sweats, and frequent infections.
- Desire for new treatment that results in remission, control disease symptoms, allows for longer survival, improves quality of life, and improves blood counts.
- Fewer side effects with ibrutinib than other therapies, significant improvement in symptoms management with using ibrutinib. Tope symptoms controlled by ibrutinib include weakness, tiredness or lack of energy and shortness of breath.

- there are very few treatment options for FL patients who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent. As an oral therapy, idelalisib could reduce drug administration costs associated (no chemo chair time) and reduce the need to travel for patients and caregivers. Furthermore, some patients treated with idelalisib may be eligible for a potentially curative allogeneic transplant. Idelalisib may also help some transplant patients bridge to a donor lymphocyte infusion.

Patients considered they have an improved quality of life while on idelalisib with very few side effects. This was adequately considered in the economic analysis by a utility value of 0.81 in progression-free survival state.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

Input was obtained from all the provinces participating in pCODR. PAG identified the following as factors that could impact the implementation of idelalisib for follicular lymphoma (FL):

Clinical factors:

- Clarity of the recommended population and definition of refractory to rituximab
- Safety and risks of treatment given the recent alert issued by the Food and Drug Administration in the U.S. and the stopping of several ongoing trials
- Lack of comparative data and long-term data

Economic factors:

- Large prevalent patient population
- Duration of treatment until disease progression or unacceptable toxicities

Please note that these factors were not considered in the EGP re-analysis, as there cannot be integrated into the submitted economic model.

1.3 Submitted and EGP Reanalysis Estimates

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

In summary, the key assumption that has the most impact on the results of the economic evaluation is the magnitude of benefit between idelalisib and the BSC arm. The EGP was, however, unable to modify this input in the model given that an alternative data source was not available. Additionally, the method of extrapolation for survival benefit and the different treatment pathways between groups had impacts on the ICER. The model provided by the submitter did allow an opportunity to change the survival estimation method, but did not allow for different treatment pathways. The EGP performed several re-analyses and these results are presented in Table 2.

The following re-analyses have been performed by varying components of the model that were significant drivers of either the incremental effect or the incremental cost, such as survival, utilities and cost. The EGP, however, noted that the magnitude of benefit between idelalisib and BSC was an input that could not be altered and likely had the largest impact on the ICER.

1. Changing the survival assumptions in the economic evaluation (parametric curves, and KM curve with tail). EGP noted that there is no description provided for what the submitter referred to as "the KM with tail" by which was meant using the KM data from the trial and then using a parametric curve to extrapolate over the remainder of the time horizon. The method of extrapolating the survival data from the end of the trial data to the time horizon had a large impact on the ICER.

2. EGP noted that in the submitted model, utility values had been obtained from the literature and not from the trial. The EGP performed re-analyses to reflect uncertainty related to the utility values. The use of alternative utility values from the literature, however, had only a small impact on the ICER.
3. The EGP noted that the cost of relapse-related management was overestimated; several re-analyses have been performed to account for the uncertainty related to the use of allogeneic, and autologous stem cell transplantation, respectively. The use of alternative costs associated with relapse-related management, however, had only a small impact on the ICER.
4. The proportion of patients experiencing different types of AE was derived from the overall population of 125 patients. The EGP conducted re-analyses to account for the occurrence of AEs in the FL population (72 patients). The use of the FL population to determine the proportion of patients experiencing AE's, however, had only a small impact on the ICER.

Table 2. Submitted and EGP Reanalysis Estimates

Estimates	Submitted	EGP Reanalysis: lower and upper bounds
ICER estimate ($/QALY), range/point	$130,435 and $143,299	**$128,643** and **$244,164**
ΔE (QALY), range/point	0.367 and 0.312	0.187 and 0.366
ΔE (LY), range/point	0.475 and 0.403	0.175 and 0.431
ΔC ($), range/point	$47,863 and $44,738	$45,754 and $48,023

Within this range, the best estimate would likely be $231,019/QALY, corresponding to the scenario of survival benefits estimated by KM with extrapolated tail. The EGP note that the ICER is possibly higher as the magnitude of benefit between idelalisib and BSC remains unknown. The data used to estimate the benefit in the submitted model and EGP's reanalysis estimates likely overestimate the ΔE with idelalisib given that responders and non-responders are inherently different populations that are not comparable.

Table 3: Detailed Description of EGP Reanalysis				
	ΔC	ΔE	ICER	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$47,863	0.367	$130,435	--
LOWER BOUND				
AEs in FL patients (N=72); Idelalisib vs BSC	$48,023	0.366	$131,049	$614
10% allogeneic, and 10% autologous stem cell transplantation; Idelalisib vs BSC	$47,205	0.367	$128,643	-$1,792
Time horizon 10- or 20- years; Idelalisib vs BSC	$47,863	0.367	$130,435	$0
Best case estimate of above 3 parameters	$47,365	0.366	$129,254	-$1,181
UPPER BOUND				
Survival benefits estimates: KM curve with tail; Idelalisib vs BSC	$45,768	0.198	$231,019	$100,584
Utility values: Disutilities : all values set to -0.6; Idelalisib vs BSC	$47,863	0.356	$134,275	$3,840
Time horizon 5 years; Idelalisib vs BSC	$47,776	0.364	$131,167	$732
Best case estimate of above 3 parameters	$45,754	0.187	$244,164	$113,729

1.4 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include estimation of the eligible population, market share and duration of idelalisib treatment. It was possible to modify these parameters and various alternative parameters were explored by the EGP. In particular, the EGP felt that the initial

market share considered by the submitter was very low: 5% of eligible patients in Year 1, 33% in Year 2, and 57% in Year 3. Increasing the proportion of patients eligible for provincial coverage and increasing the number of patients receiving idelalisib increases significantly the budget impact. The estimated 3-year BIA was estimated at: $6.5M, $7.0M and $8.1M when increasing the number of eligible patients to 20% (from 5% in the submitted model) and when increasing the number of patients covered by ODB to 100% (was 80% in the submitted model), and when both of these increases occur simultaneous, respectively. The submitted 3-year BIA was $5.5M.

1.5 Conclusions

The EGP's best estimate of ΔC and ΔE for Idelalisib when compared to BSC (non-responders in idelalisib group) is:

- Between $128,643/QALY and $244,164/QALY. The EGP further notes that this range is uncertain given that the magnitude of benefit between idelalisib and BSC is unknown and cannot reasonably be estimated. The EGP anticipates that this is likely to have the biggest impact on the ICER.
- Within the provided range, the best estimate would likely be $231,019/QALY, corresponding to the scenario of survival benefits estimated by using the KM data from the trial and using a parametric curve to extrapolate over the remainder of the time horizon.
- The extra cost of idelalisib is between $45,754 and $48,023. The factor that influences this cost is the length of time spent in each state (progression free state vs post-progression state) which varies with the extrapolation method (full parametric versus KM with parametric tail).
- The extra clinical effect of idelalisib is between 0.187 QALY and 0.366 QALY. The factor that influences the effectiveness is the extrapolation method used (full parametric versus KM with extrapolation on the tail of the curve).

Overall conclusions of the submitted model:

Though the submitted model included many appropriate assumptions, there were some assumptions that were not consistent with Canadian clinical practice, including assumptions around the post-progression treatments for FL and the AEs in the FL population. However, these had minor impacts on the ICER. The main factor driving the economic model was the choice of comparator group. The CGP and EGP considered the comparator chosen by the submitter as inappropriate. Using the non-responders as the BSC group resulted in an incremental difference in benefit between the idelalisib and BSC groups favoring idelalisib. However, the CPG and EGP agreed that the non-responders are not likely representative of patients receiving BSC in the clinical setting, and are likely to have poorer outcomes compared to a true BSC group of patients in this clinical setting i.e., Patients having failed two or more prior lines of therapy, refractory to alkylators (both bendamustine and cyclophosphamide), and rituximab, and when other treatment options have been exhausted. The EGP performed re-analyses with reduced incremental effectiveness. The EGPs best estimate of the incremental cost utility was $231,019. The EGP acknowledges that there is a high level of uncertainty in reaching this estimate due to uncertainty in the magnitude of benefit of idelalisib compared with a true BSC group.

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 idelalisib (Zydelig) for follicular lymphoma. A full assessment of the clinical evidence of idelalisib (Zydelig) for follicular 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.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. Boland A, Bagust A, Hockenhull J, Davis H, Chu P, Dickson R. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma. Health Technol Assess. 2009;13 Suppl 2:41-8.

2. Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, et al. Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation. Health Technol Assess. 2002;6(3):1-85.

3. Wirt DP, Giles FJ, Oken MM, Solal-Celigny P, Beck JR. Cost-Effectiveness of interferon alfa-2b added to chemotherapy for high-tumor-burden follicular non-Hodgkin's lymphoma. Leuk Lymphoma. 2001;40(5-6):565-79.

4. Soini EJ, Martikainen JA, Vihervaara V, Mustonen K, Nousiainen T. Economic evaluation of sequential treatments for follicular non-hodgkin lymphoma. Clin Ther. 2012;34(4):915-25 e2.