CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (previously untreated)

November 3, 2016

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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 Janssen** compared ibrutinib to chlorambucil for patients with untreated chronic lymphocytic leukemia or small lymphocytic lymphoma who are not eligible for fludarabine-based therapy.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*Previously untreated CLL patients who are not appropriate for fludarabine-based treatments.*
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned survival model*
Comparator	*Chlorambucil*
Year of costs	*2015*
Time Horizon	*15 years*
Perspective	*Government*
Cost of ibrutinib	*Ibrutinib costs $90.65 per 140 mg capsule* *At the recommended dose of 420 mg once daily, ibrutinib costs:* • *$271.95 per day* • *$7614.60 per 28-day course*
Cost of chlorambucil*	*Chlorambucil costs $1.43 per 2 mg tablet* *At a dose of 0.5 mg/kg iv on days 1 and 15 of each 28 day cycle, chlorambucil costs:* • *$1.79 per day* • *$50.22 per 28-day course*
Model Structure	*A partitioned survival model that included three health states (progression-free, post-progression, and dead) was used. All patients enter the progression free health state. The difference between the overall survival and progression-free survival curves inform the post-progression state.*
Key Data Sources	*RESONATE-2 trial*[1] *Chart review & expert opinion*
* *Price Source: IMS Brogan accessed June 7, 2016*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, though it is not ideal because not many patients are on ibrutinib; many patients who are eligible move to fludarabine. At the time of trial design, this comparator was the most likely to be used; there are now other treatments. The Submitter considered an indirect comparison versus obinutuzumab + chlorambucil, however, differences between the two trials identified (RESONATE-2 and CLL-11) in the dosage of chlorambucil, and variability in the study population led to their conclusion that an indirect comparison is not appropriate.

- Relevant issues identified by the CGP included:
  - *There is net clinical benefit with ibrutinib for patients with previously untreated CLL.*
  - The choice of comparator was appropriate at the time the study was designed.
  - Patients with the del(17p13.1) mutation should be eligible for treatment with ibrutinib

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered:

- CLL is a common malignancy and given the aging Canadian demographics, more incident cases are expected
- Longer progression free survival likely to mean significantly longer time until another line of therapy required.
- Lack of infusion reactions, less cytopenias, less expected resource utilization (e.g. hospital admissions, frequent visits for blood transfusion support).
- The oral route will require enhanced patient education (re toxicity reporting), team education (nursing, pharmacist) and compliance monitoring.
- Concerns about rare but concerning toxicities of bleeding (rarely grade 3-4) and atrial fibrillation.
- Adverse events and progression free survival were modeled in the economic analysis.

Summary of patient input relevant to the economic analysis
Patients considered side effects, chance to live longer, achieve a remission and have an improved quality of life. Each of these factors were considered in the economic analysis.

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 ibrutinib, which are relevant to the economic analysis:

Enablers

- Flat, once, daily dose of ibrutinib.
- Oral route of administration.

Barriers

- High cost of ibrutinib.
- Long duration of treatment, which is unknown given the lack of data.
- Large prevalent number of patients potentially eligible for treatment.

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
ICER estimate ($/QALY)	$101,405	$141,616	$233,945
ΔE (QALY)	2.87	1.76	0.77
Progression-free	2.04	1.82	0.73
Post-progression	0.84	0.05	0.03
ΔE (LY)	3.74	1.72	0.51
Progression-free	2.43	2.16	0.94
Post-progression	1.31	-0.45	-0.43
ΔC ($)	$291,214	$249,509	$178,941

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

- The assumed ongoing benefit of ibrutinib. Given the relatively short duration of the clinical trial (median follow-up for PFS was 18.4 months), the model assumed that there would be an increased long term benefit for those on ibrutinib, despite a lack of data from the trial to support this. In order to model long-term benefit, the model relied on extrapolation. Both the length and the type of extrapolation introduce uncertainty into the estimates.
- The submitted base case shows incremental gains in QALYs in the post-progression health state. According to the CGP, there is no biological plausibility for this benefit.

1.4 Detailed Highlights of the EGP Reanalysis

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

Lower bound

- The EGP used a time horizon of 10 years, instead of 15 years used in the base case, based on input from the CGP. The CGP considered 10-years as an appropriate time horizon by considering the life expectancy of patients with CLL from start of treatment and median age at time of diagnosis. Further, a time horizon of ten years is consistent with other CLL drugs reviewed by pCODR.
- Overall survival hazard ratio = 0.44 (95% CI: 0.212 - 0.917). Given the absence of long term follow up data, the submitter used data from the Ladyzinki chlorambucil curves and applied the HR for ibrutinib to the curves for the period of extrapolation (after the end of the trial) in the submitted base case. Given that data were available from a collective dataset of patients within the RESONATE-2 trial and those that went onto the non-randomized, observational, extension follow-up, the EGP used the HR: 0.44 (95% CI: 0.212 - 0.917) at the 28 month analysis from this collective dataset to inform the OS curve following the end of the trial period.

Upper bound

- Hazard ratio equal to 1 at 26 months (trial end date) for both PFS and OS, given the short follow-up, as a conservative exploratory analysis. Further, this analysis explores a reduction in the post-progression gains seen with ibrutinib; the CGP confirmed there is no reason that patients on ibrutinib, after progression, would continue to have QALY gains. The EGP considered feedback from the submitter regarding the use of a HR equal to 1 for OS and PFS following the trial period. Given the short follow up period for the trial data, the EGP used estimates that best captured the uncertainty in the data to

model long term results. The EGP did not consider it appropriate to use 3 year updated Phase 1/2b trial results of 31 patients to model survival over 10 years. The EGP also noted that using a HR equal to 1 at trial end date was the best approach with the submitted model, in order to reduce the post-progression gain in QALY's observed in the base case results. While the EGP acknowledges using a HR equal to 1 after the trial period is conservative and that it is unlikely that treatment benefit would end at the end of the trial, given the limitations in the available evidence and modeling of post-progression benefit, it was considered appropriate to use this approach to estimate an upper bound of the reanalysis estimates.

- No utility increment for ibrutinib, based on CGP feedback that these drugs are similar, and therefore patients would experience similar quality of life on these drugs. The EGP wanted to include the possibility that there was no utility difference between ibrutinib and chlorambucil and explored this in the upper bound.
- Include idelalisib as a subsequent treatment option for 50% of ibrutinib patients. Though there is no standard of care in subsequent treatments across Canada, the CGP indicated that idelalisib is a possibility, and could be administered in patients. As a conservative estimate, it was assumed that 50% of patients would receive idelalisib. The EGP considered feedback from the submitter regarding the assumption in the reanalysis that 50% of patients would receive idelalisib as a subsequent therapy. Given the recommendation for reimbursement of idelalisib in this subsequent line of treatment, the EGP and CGP agreed that it is reasonable to consider the impact of this treatment with the assumption that it would be used in 50% of patients. Additionally, the EGP agreed that there is no rationale to consider that exploring the uncertainty in the long term benefit of ibrutinib and exploring the potential for 50% of patients to be treated with idelalisib in subsequent treatments are mutually exclusive. Regardless of the benefit a patient would gain through ibrutinib, upon progression, patients would move to a subsequent treatment. The EGP presented a conservative estimate in the upper bound exploring the inputs that created the largest uncertainty in the ICER.

Table 3. EGP Reanalysis Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline ICUR
Submitted base case	**$291,213**	**2.87**	**$101,405**	**----**
EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
Time horizon - 10 years	$273,534	2.44	$111,955	$10,550
Overall survival hazard ratio 0.44 at trial end	$255,206	1.88	$135,882	$34,477
Best case estimate of above two parameters	**$249,509**	**1.76**	**$141,616**	**$40,211**
UPPER BOUND				
Hazard ratio = 1 at trial end (PFS & OS)	$140,365	0.84	$167,587	$66,182
No utility increment for ibrutinib (ie: utilities are the same for both groups)	$291,213	2.73	$106,558	$5,153
Idelalisib included as a subsequent treatment for 50% of ibrutinib patients	$336,974	2.92	$115,590	$14,185
Best case estimate of above five parameters	**$178,941**	**0.77**	**$233,945**	**$132,540**

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- Number of patients with CLL (20% more patients increases the incremental costs by 20%),
- Patient adherence (20% increase in patient adherence increases the incremental the costs by 25%),
- Market share (20% increase in the market share increases the incremental costs by 20%),
- number of patients eligible for reimbursement (increasing the number of patients eligible for reimbursement form 67% to 100% increases the incremental costs by 50%), and
- Cost of ibrutinib (20% increase in cost of ibrutinib increases the incremental costs by 16%).

Key limitations of the BIA model include not including the long-term treatment duration. Patients who are on ibrutinib may be on it for many years; these down-stream costs were not captured. These parameters were not able to be modified and explored by the EGP.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for ibrutinib when compared to chlorambucil is:

- Between $141,616/QALY and $233,945/QALY
- The extra cost of ibrutinib is between $178,941 and $249,509. *The main factors that influence incremental costs are the overall and progression-free survival estimates, the cost of ibrutinib and the type of subsequent treatment included.*
- The extra clinical effect of ibrutinib is between 0.77 and 1.76 (ΔE). *The main factors that influence incremental effectiveness are the time horizon, the duration of treatment effect, and overall survival estimates.*

Overall conclusions of the submitted model:

- *This model attempts to project the long-term benefits of ibrutinib as a first-line therapy. Given the short duration of the trial, the model relied heavily on extrapolating immature overall survival data that was not a primary end-point in the clinical trial, using extrapolation methods that may not replicate clinical practice (ie maintenance of hazard ratio, and linear decrease).*
- *If one accepts that the overall survival benefit would not last beyond the trial, then the ICER is more likely to be towards the upper bound of the range (~$200,000/QALY).*
- *Though the EGP provided re-analysis estimates, there remains a significant amount of uncertainty in the OS of ibrutinib compared with chlorambucil due to the relatively short trial follow-up. Therefore, the ICER could be higher or lower depending on the true overall survival benefit for ibrutinib compared with chlorambucil.*

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 Leukemia 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 ibrutinib (Imbruvica) for chronic lymphocytic leukemia/small lymphocytic leukemia. A full assessment of the clinical evidence of ibrutinib (Imbruvica) for chronic lymphocytic leukemia/small lymphocytic 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.

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