CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Venetoclax (Venclexta) for Chronic Lymphocytic Leukemia

December 1, 2016

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by AbbVie** compared venetoclax monotherapy to ibrutinib for patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy (second and subsequent line treatment), and who have del(17p) mutation.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*Aligns with funding request and trial data*
Type of Analysis	*CEA & CUA*
Type of Model	*Partitioned-survival*
Comparator	*Ibrutinib*
Year of costs	*2016*
Time Horizon	*5-years*
Perspective	*Canadian health care system (government)*
Cost of venetoclax	Venetoclax costs $6.80 per 10 mg, $33.99 per 50 mg and $67.99 per 100mg The recommended ramp up dose for venetoclax includes: • Week 1: 2 x 10 mg daily • Week 2: 1 x 50 mg daily • Week 3: 1 x 100 mg daily • Week 4: 2 x 100 mg daily All subsequent doses are: • Week 5 & onward: 4 x 100 mg daily At the recommended ramp-up and subsequent doses, venetoclax costs: • $62.89 per day and $1,760.88 per 28-day course for first cycle (ramp up) • $271.95 per day and $7,614.60 per 28-day course for subsequent cycles
Cost of ibrutinib ** Price Source: IMS Brogan accessed [Date]*	Ibrutinib costs $90.65 per 140mg capsule At the recommended dose of 420mg per day, ibrutinib costs: • *$271.95* per day and $7,614.60 per 28 day cycle.
Model Structure	*Disease pathway separated into: progression-free survival (PFS), post-progression survival (PPS) and death. Area under the curve survival analyses used to estimate the proportion of patients in each of the health states over time.*
Key Data Sources	*M13-982 single-arm phase II trial (venetoclax data)* *RESONATE-17 (ibrutinib data)*
**Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The Clinical Guidance Panel also considers that idelalisib and rituximab may be a clinically relevant comparator for this patient population, though it may not currently be funded in all provinces. The Submitter included this comparison in modifications to the main economic analysis, though it shares many of the same limitations to the main economic analysis due to the source and quality of the data inputs. In patients who have already been treated with ibrutinib or idelalisib plus rituximab (resistant or intolerant), a few of whom were included in the clinical trial from which the data are based, the CGP agreed that there is currently no standard of care and choice of treatment will largely depend on what patients may have received in the past. This patient population was not addressed specifically in the economic model.

Relevant issues identified by the CGP for this submission included:

- *In patients who would receive ibrutinib or idelalisib plus rituximab, there remains uncertainty around the magnitude and direction of the incremental clinical benefit given the absence of comparative clinical trials between venetoclax and these two available treatment options.*
- *Inputs for efficacy were derived from an indirect comparison.*
    - *Limited information was available on the methodology and results of this indirect comparison and thus only a limited critical appraisal was done. These data are also pending peer-review and publication.*
    - *For the matched adjusted indirect comparison, not all important variables were considered for matching as these data were only available for a small number of patients in the M13-982 trial.*
    - *Overall, although the point estimates of the analyses suggest that venetoclax is more effective than ibrutinib in terms of progression-free survival and overall survival, great caution should be used in drawing conclusions based on these data and a careful examination of the 95% confidence intervals should be considered.*
- *In the sub-population of patients who have already received and failed ibrutinib or idelalisib plus rituximab, the CGP agreed that venetoclax is more likely to be effective than currently available treatment options. However, there is uncertainty as to the magnitude of benefit given the absence of comparative trials for this sub-population which was included in the M13-982 trial.*
- *Adverse events and health related quality of life appear favourable compared to control.*
- *Sufficient resources need to be available to appropriately manage and monitor the risk of tumour lysis syndrome.*
- *Venetoclax should be administered as monotherapy and continued indefinitely until intolerable toxicity or disease progression. Given that the M13-982 trial had not reached maturation, treatment duration is uncertain and greatly impacts the economic model.*

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

- Venetoclax is superior to any other available therapy for patients who have failed a kinase inhibitor (ibrutinib or idelalisib), including patients with and without del(17p).
- For patients with del(17p) who have not previously been treated with a kinase inhibitor, it is unclear if this drug is superior or equivalent to the novel kinase inhibitors (ibrutinib and idelalisib).
- No companion diagnostic test is required prior to starting treatment with venetoclax. However, CT scanning would be required to measure the largest lymph node size for determining tumour lysis syndrome risk and that CT scanning is not currently a routine test in CLL and would be a specific and special consideration for venetoclax.

- The toxicities with venetoclax are also generally very manageable for experienced hematologists (the most common being neutropenia and/or infections).

Summary of patient input relevant to the economic analysis
Patients with CLL value the availability of new therapies that produce quick, favourable outcomes with relatively mild side effects and increased quality of life, compared to existing treatments. The economic analysis incorporated these as survival, adverse events and quality of life.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the below factors (enablers or barriers) important to consider if implementing a funding recommendation for venetoclax, which are relevant to the economic analysis.

Enablers to implementation:
- Venetoclax is a once daily dosing with oral administration.

Barriers to implementation:
- Lack of phase 3 comparative data
- Monitoring for and treatment of adverse effects, such as tumour lysis syndrome and neutropenia.
- Clarity of treatment population.
- Cost, however, if venetoclax is recommended only for patients with 17p deletion CLL, the budget impact would be smaller.

1.3 Submitted and EGP Reanalysis Estimates

The main assumptions and limitations with the submitted economic evaluation were:
- *The assumption that venetoclax was more effective than ibrutinib, based on an indirect comparison and results that indicated lack of statistical significance in either PFS or OS in these two groups.*
- *Treatment duration from the M13-982 study was not reported, and therefore was estimated based on the PFS curve from the trial. Actual mean and median treatment duration are not known for venetoclax. Further, it was assumed that treatment duration would differ between ibrutinib and venetoclax.*
- *Though the funding request was vague enough to include patients that have previously been treated with ibrutinib or idelalisib (population from M13-982),* the submitted economic analysis did not specifically address this group of patients (resistant or intolerant to ibrutinib or idelalisib plus rituximab)
    - In order to use the current economic model to determine the cost effectiveness of venetoclax in patients following failure of either ibrutinib or idelalisib plus rituximab, an assumption must be made that the incremental cost and benefit of venetoclax in this population is the same as patients who have failed treatment options other than ibrutinib or idelalisib plus rituximab. The EGP cautions that there is considerable uncertainty in this assumption. Given the high amount of uncertainty in the analysis for the overall population, the EGP did not consider conducting separate analyses for this subgroup due to the even greater uncertainty that would be introduced by accepting this assumption.

1.4 Detailed Highlights of the EGP Reanalysis

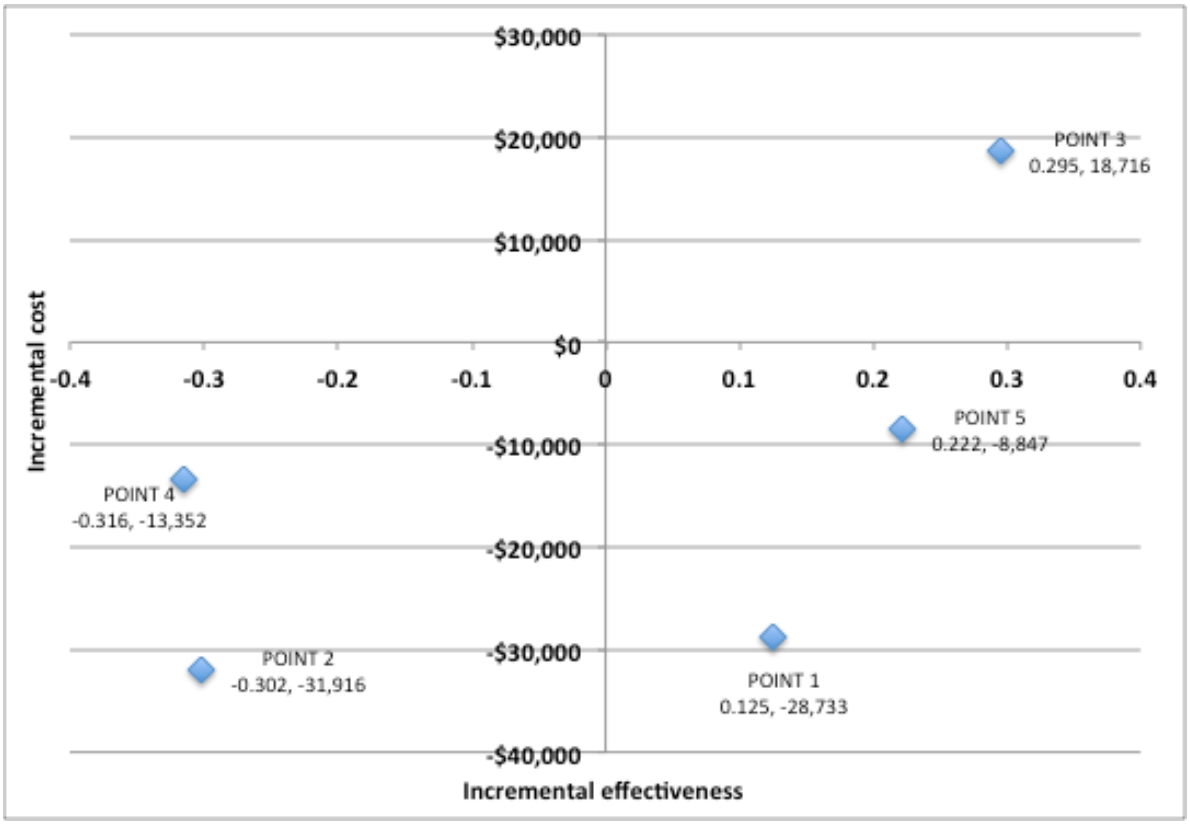
The EGP made the following changes to the economic model:

- In the base case analysis, the submitter assumed, based on the match adjusted indirect comparison that PFS and OS differed in favour of venetoclax. However, the 95% CI indicated that there was no statistically significant difference in PFS or OS between the two treatment strategies. Additionally, limited information was available for this indirect comparison, given that the full report was deemed non-disclosable by the submitter pending a peer reviewed publication. Based on the CGP, given the absence of direct comparative evidence it is not possible to determine whether there is a difference in efficacy or what the magnitude of any difference may be between venetoclax and available alternative regimens for key outcomes such as PFS, OS, or quality of life.
- In the base case analysis, as the trial had not reached maturity with a direct measurement of mean/median treatment duration, the submitter assumed modeled treatment duration for venetoclax based on the PFS curve. The CGP, however, did not support a difference in treatment duration between the two treatment strategies and the EGP chose to have an equal treatment duration of 30 months for both treatments, which is based on trial data for the treatment duration of ibrutinib.

Table 2. EGP Reanalysis Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Figure 13
Submitted base case	**-$28,733**	**0.125**	**-$230,058**	**Point 1**
EGP's Reanalysis for the Best Case Estimate – One way analyses				
PFS – HR, 95% lower CI	-$93,220	-0.302	$308,555	-----
PFS – HR, 95% upper CI	$39,523	0.295	$133,915	-----
OS – HR, 95% lower CI	-$32,751	-0.316	$103,586	-----
OS – HR, 95% upper CI	-$27,847	0.222	-$125,374 (Dominant)	-----
Equal treatment duration of 30 months	-$9,333	0.125	-$74,726	-----
EGP's Reanalysis for the Best Case Estimate – Two way analyses				
PFS – HR, 95% lower CI & equal treatment duration of 30 months	-$31,916	-0.302	$105,642	Point 2
PFS – HR, 95% upper CI & equal treatment duration of 30 months	$18,716	0.295	$63,413	Point 3
OS – HR, 95% lower CI & equal treatment duration of 30 months	-$13,352	-0.316	$42,228	Point 4
OS – HR, 95% upper CI & equal treatment duration of 30 months	-$8,447	0.222	-$38,031	Point 5

Figure 1. Submitted and EGP Reanalysis Estimates



1.5 Evaluation of Submitted Budget Impact Analysis

Factors that influence the budget impact analysis include the number of patients with CLL who would be eligible for venetoclax, cost of drug and market share. The EGP however noted that any change made to an input had a linear impact on the BIA and it was therefore difficult to determine which input had the greatest impact.

Key limitations of the BIA model include incorrect pricing in subsequent years for BIA pricing, the assumption that only 80% of patients would be able to access venetoclax through the reimbursement plan and the lack of trial data to support treatment duration.

1.6 Conclusions

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

- Not possible to determine.
- This is due to considerable uncertainty in the comparative effectiveness between the two treatment options and uncertainty in costs that range from cost savings to increased costs.
- Should the assumptions of resource use hold, the cost savings of venetoclax is between -$31,916 and -$8,447. Treatment duration is also a determinant of cost.
- The uncertainty in the estimates of comparative effectiveness are high, given the MAIC. Using the results of the submitted analysis, the extra clinical effect of venetoclax when examining the 95% CI is between -0.316 and 0.295 (ΔE). The hazard ratio for PFS and OS are key determinants of effectiveness.

Overall conclusions of the submitted model:

- The lack of certainty in the comparative effectiveness inputs for PFS and OS are the greatest limitation of this economic model.
- Depending on where the effectiveness inputs lie for PFS or OS, the ICER could be more or less effectiveness, or more or less costly.

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 venetoclax (Venclexta) for chronic lymphocytic leukemia. A full assessment of the clinical evidence of venetoclax (Venclexta) 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.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.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this 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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