CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Venetoclax (Venclexta) Rituximab for Chronic Lymphocytic Leukemia

May 31, 2019

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: info@pcodr.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 Abbvie** compared venetoclax in combination with rituximab (VEN+R) to 1) bendamustine in combination with rituximab (BR), 2) ibrutinib (IBR), and 3) idelalisib plus rituximab (IDE+R), for patients with relapsed / refractory (R/R) chronic lymphocytic leukemia (CLL).

Table 1. Submitted Economic Model

Funding Request	VENCLEXTA (venetoclax) in combination with rituximab (VEN+R) is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, irrespective of their 17p deletion status. This funding request aligns with the population modelled in the economic model.
Type of Analysis	CUA / CEA
Type of Model	Partitioned-survival
Comparator	Bendamustine plus rituximab (BR) Ibrutinib (IBR) Idelalisib plus rituximab (IDE+R)
Year of costs	2018
Time Horizon	10 years; cycle length of 28 days
Discounting	Costs and benefits discounted at 1.5%
Perspective	Government
Cost of venetoclax*	Venetoclax (oral) costs $0.68 per mg ($6.79 per 10 mg, $33.99 per 50 mg, and $67.98 per 100 mg). Dosing schedule: First 5 - week dose ramp up and subsequent daily maintenance dose: week 1: 20 mg; week 2: 50 mg; week 3: 100 mg; week 4: 200 mg; week 5 onward: 400 mg up to 24 months. Cost per 28 - day cycle: • First cycle (ramp up cycle): $1,760.80 • Subsequent cycles: $7, 614.60
Cost of rituximab*	Rituximab (IV) costs 4.75 per mg ($453.10 per 100 mg vial and $2,265.50 per 500 vial). Dosing schedule: 375mg/m^2 day 1 cycle 1; 500 mg/m^2 day 1 cycle 2 to 6. <u>Cost per 28 - day cycle:</u> • First cycle: $3,058.40 • Subsequent cycles: $4,077.90

Cost of bendamustine*	Bendamustine (IV) costs $12.50 per mg ($1,250 per 100 mg). Dosing schedule: 70mg/m^2 day 1 & 2 (per cycle) 28 day cycle; 6 cycles. Cost per 28 - day cycle: $3,375.00
Cost of ibrutinib*	Ibrutinib (oral) costs: $0.67 per mg ($92.19 per 140 mg tablet). Dosing schedule: 420 mg daily. Cost per 28 – day cycle: $7,744.00
Cost of idelalisib*	Idelalisib (oral) costs: $0.57 per mg ($85.35 per 150 mg tablet. Dosing schedule: 150 mg twice daily. Cost per 28 – day cycle: $4,779.60
Model Structure	*The model was comprised of three health states: progression-free survival, post-progression survival and death.* *The patient population within each health state over time are estimated using extrapolated survival curves.*
Key Data Sources	*Phase 3 MURANO RCT*[1] *(comparison to BR)* *Indirect treatment comparison*[2] *for comparisons to IBR and IDE+R*
** Drug costs in this table are based on costing information provided by the submitter, Abbvie Canada, and used in the economic model.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of venetoclax in combination with rituximab (VEN+R) to the various comparators included in this economic model (bendamustine in combination with rituximab (BR), idelalisib in combination with rituximab (IDE+R), and single-agent ibrutinib (IBR)) is appropriate.

- Relevant issues identified included:
  - There is a net clinical benefit to venetoclax in combination with rituximab when compared to bendamustine in combination with rituximab, based on the single high quality randomized controlled trial (MURANO) [1] which showed a clinically meaningful and statistically significant improvement in PFS. A clinically meaningful improvement was also observed for the MRD negative rate.
  - Venetoclax-rituximab demonstrated an acceptable degree of treatment-related toxicity
  - Currently there is no clearly defined standard of care.
  - Bendamustine-rituximab represents a frequent second-line regimen, however, this option is not available in all provinces due to funding limitations. Increasingly, B cell receptor (BCR) pathway inhibitors—ibrutinib and much less frequently idelalisib—are becoming the most common second-line treatments in Canada. IDE+R is less commonly used than single agent IBR because of greater toxicity with the combination, and relative ease of administration of the single agent.
  - Venetoclax-rituximab represents an important new treatment option for patients needing second- or third-line therapy for CLL, because of the prolonged PFS observed with this regimen with a finite duration of therapy.
  - The treatment landscape for CLL and the optimal sequencing of agents is continually evolving and the optimum sequencing is unknown. Recent evidence shows a benefit of receiving ibrutinib as a first-line therapy for patients with CLL; should ibrutinib be adopted in clinical practice in first line, it is likely less frequently used in second line therapy.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered that this is an appropriate new treatment for this patient population. Other relevant inputs included:

- The most relevant comparator for the specific indication is ibrutinib. A head to head clinical trial of venetoclax in combination with rituximab to ibrutinib is not available.
- Clinicians have a positive experience with venetoclax-rituximab and view the time-limited treatment of two years as more attractive to patients and payers, although IV administration of rituximab remains a challenge.
- The fewer contraindications of venetoclax-rituximab compared with ibrutinib also make it an attractive option for patients with cardiovascular conditions.
- Sequencing of alternative therapies before and after venetoclax-rituximab remains theoretical with little supporting data, but most clinicians would prefer venetoclax-rituximab as first-line/second-line and use ibrutinib after venetoclax-rituximab has failed.

Summary of patient input relevant to the economic analysis
Patients considered a choice of therapy for their incurable CLL as very important. Patients seek individualized choice in treatment that will offer disease control and improve quality of life, while offering ease of use relative to other treatments. Patients' priority for a new therapy were increased effectiveness or remission and decreased toxicity.
Most patients saw a reduction in commonly reported symptoms with CLL. The majority of patients experienced improvement in lymph node size, lymphocyte counts, and fatigue.

Treatment with VEN+R led to various side effects; most commonly reported were neutropenia, fatigue, and diarrhea. The majority of respondents indicated that they were willing to tolerate potentially serious or significant side effects. Overall, treatment did not have a significant negative impact on quality of life and daily living, although patients noted that clinician visits and infusions were burdensome. In that regard, patient groups remarked that the potential availability of subcutaneous rituximab would reduce the need for visits to the clinic.

- *Adverse events, quality of life, effectiveness and the effect of subcutaneous rituximab were considered in the economic model.*

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 venetoclax in combination with rituximab which are relevant to the economic analysis:

- PAG noted that the comparator in the MURANO trial[1] was BR, PAG is seeking information on data comparing VEN+R with IBR and IDE+R.
    - *The economic model explores the comparative effectiveness of VEN+R compared with IBR and IDE+R based on effectiveness estimates derived from an indirect treatment comparison (ITC)* [2].

- PAG also noted that additional pharmacy and nursing resources and chair time will be required to prepare and administer the additional rituximab. PAG noted that additional chair time as well as wastage could be reduced with implementation of subcutaneous rituximab for cycles 2 to 6.
    - *The economic model explores the impact of subcutaneous rituximab as scenario analysis (25%, 50% and 75% subcutaneous rituximab administration).*

- PAG noted that prior to initiating therapy with VEN+R, patients should be assessed for risk of tumour lysis syndrome (TLS). Prophylactic intravenous hydration and anti-hyperuricemics are required prior to first dose of venetoclax to reduce risk of TLS and regular monitoring of blood chemistries after the first dose is required. The initiation of treatment may require hospitalization to monitor and treat TLS. Rasburicase may be required to treat TLS which would be additional costs associated with VEN+R therapy.

    a. *The costs of TLS prophylaxis were modelled as once-off cost taking into account patient's risk of TLS occurring. The CGP noted that a once-off cost (and not a continuous cost) seemed reasonable. CGP further noted that the proportion of patients who would require hospitalization for hydration or monitoring (based on high-risk features of bulky adenopathy and elevated lymphocyte count) is hard to predict in general practice, but likely to be less than half of patients. In the Murano trial*[1]*, 28% of patients were at high risk of TLS and 55% at medium risk; therefore about 1 in 4 patients would need admission for hydration and monitoring, but this is usually brief (one or two days for the first admission, one day for the second admission if needed); it is not possible to estimate the proportion who would require rasburicase but in clinical experience it is low.*

- PAG noted that pharmacy resources and weekly clinic visits would be required with VEN+R. Venetoclax is associated with drug-drug interactions and neutropenia. These adverse events would require additional health care resources compared to other second-line therapy options.

    b. *The economic evaluation did not address the consequences of the different frequency of clinical visits between interventions. The CGP noted that beyond the first month of therapy, the frequency of visits to clinic would not be expected to*

be different between those who receive VEN+R versus those receiving BR (in the latter case, it is 3 visits/month for assessment and treatment, not counting visits to manage toxicities). While the incidence of neutropenia is slightly higher, febrile neutropenia was lower with venetoclax, and persistent neutropenia would be managed with dose reduction, as it would for bendamustine. There are significant toxicities associated with idelalisib (pneumonitis, enteritis) that require monitoring, dose adjustment and treatment. Drug interactions are possible with many new targeted agents; patient and practitioner awareness of this will be required and reinforced during clinic assessments, but should not consume additional resources.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates, VEN+R versus BR

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (QALY)	1.463	0.559	Not estimable
Progression-free	2.510	1.450	
Post-progression	-1.046	-0.891	
Adverse event disutility	0.000	0.000	
ΔC ($)	$162,129	$164,949	Not estimable
ICER estimate ($/QALY)	$111,047 / QALY	$295,079 / QALY	---

Table 3. Submitted and EGP Reanalysis Estimates, VEN+R versus IDE+R

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (QALY)	2.553	1.092	Not estimable
Progression-free	2.560	1.480	
Post-progression	-0.004	-0.385	
Adverse event disutility	0.003	0.003	
ΔC ($)	$71,745	$71,362	Not estimable
ICER estimate ($/QALY)	$28,102/QALY	$65,350/QALY	---

Table 4. Submitted and EGP Reanalysis Estimates, VEN+R versus IBR

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (QALY)	1.004	0.315	Not estimable
Progression-free	0.444	0.190	
Post-progression	0.565	0.129	
Adverse event disutility	0.004	0.004	
ΔC ($)	-$261,857	-$141,398	Not estimable
ICER estimate ($/QALY)	Dominated by VEN+R	Dominated by VEN+R	---

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

- *Comparative effectiveness data:* CADTH guidelines state that all relevant comparators need to be included in a cost-effectiveness analysis. For the indication under review, these comparators included BR, IDE+R and IBR. For the IDE+R and IBR, there is no direct comparative effectiveness data available. The CGP noted that IBR is becoming the most commonly used treatment in the second-line setting in Canada. Given the lack of direct comparative effectiveness data, a matched indirect treatment comparison[2] was completed. Challenges are the unanchored effect estimates, the relatively small sample size from MURANO[1], the lack of individual patient data, and overlapping confidence intervals, which introduce uncertainty into the comparative effectiveness. The CGP further expressed that the magnitude of benefit of VEN+R compared to IBR would not be as large in clinical practice; they expressed that they were expecting the two treatments to have similar efficacy. The critique of the submitted ITC[2] by the pCODR Methods Team concluded that the results of the ITC[2] should be interpreted with caution given that the assumptions of the unanchored ITC[2] are difficult to meet resulting in an unknown amount of bias in the unanchored estimate, and PFS and OS data is immature (see section 7 in the CGR). In conclusion, despite the fact that VEN+R remains cheaper than IBR, and remains more effective in the various scenario analyses performed by the EGP, caution should be used in interpreting the incremental efficacy of VEN+R over IBR.
- *Time horizon:* The submitted base case used a time horizon of 10 years. Previous pCODR reviews in this setting (including for the comparators IBR[28] and IDE+R[29]) used a time horizon of 5 years. Further, the submitted base case model did not incorporate subsequent treatments, which many patients would go on to receive for this indication. In order to be consistent, a time horizon of 5 years was used in the EGP re-analysis.
- *Duration of treatment effect:* In the submitted base case, the submitter assumed that the duration of treatment effect for VEN+R would continue indefinitely over the 10-year time horizon. In reality, it is unlikely that any benefit from treatment would extend indefinitely once a patient progresses on VEN+R. The submitter provided two options to explore truncating the duration of treatment effect. The first was to set the hazard ratio of VEN+R to that of a given comparator at 24 months; this option is not possible when conduction a sequential analysis as multiple comparators are included. The second option was to increase the hazards of VEN+R for both PFS. The EGP explored increasing the PFS and OS hazard ratio by 5% commencing at 24 months. Increasing the hazards decreases the effect of VEN+R. This was incorporated into the EGP re-analysis.

1.4 Detailed Highlights of the EGP Reanalysis

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

Hypothetical lower bound

- Use of Model 2: The submitted base case economic model (Model 3) was a joint model that relied on the proportional hazards assumption for VEN+R versus BR as well as between PFS and OS for VEN+R. For the latter, the proportional hazards assumption was violated. The EGP elected to use Model 2, which does not leverage PFS to predict OS. Model 2 included treatment as a covariate, assuming proportionality of hazards between VEN+R and BR, but ***not*** between OS and PFS.
- Treatment waning VEN+R: The EGP elected to incorporate a treatment waning effect as it is unlikely that the benefit derived from being on treatment with VEN+R would extend following discontinuation of treatment at 24 months. The EGP elected to choose

5% increase per year in both PFS and OS hazards as a conservative estimate. The EGP recognizes that the 5% is an arbitrary choice, however, CADTH guidelines state that diminishing treatment effect should be explored.

- Time horizon 5 years: The submitted base case used a time horizon of 10 years. Previous pCODR reviews in this setting (including the comparators IBR and IDE+R) used a time horizon of 5 years. In order to be consistent, a time horizon of 5 years was used in the EGP re-analysis.

Table 5. **Hypothetical lower bound EGP Reanalysis Estimates (probabilistic, 5,000 iterations)**

Description	Costs (95% CI)	QALYs (95% CI)	ICUR vs BR	Sequential analysis*
BR	$67,454 ($63,640, $72,714)	2.61 (2.24, 3.01)	----	-----
IDE+R	$161,041 ($117,630, $212,433)	2.08 (1.19, 2.88)	Dominated by BR**	Dominated by BR
VEN+R	$232,403 ($226,795, $237,881)	3.17 (2.56, 3.67)	$295,079/QALY	$65,350/QALY
IBR	$373,801 ($319,564, $418,593)	2.89 (2.17, 3.47)	$1,094,096/QALY	Dominated by VEN+R***

*Sequential analysis are ICERs that are calculated versus the last non-dominated treatment
**IDE+R costs more and is less effective than BR.
***IBR costs more and is less effective than VEN+R.

<u>Upper bound not estimable</u>

- Given the limitations outlined by the Methods team in the critique of the ITC[2], the magnitude of uncertainty and bias, the effectiveness estimates between VEN+R and IBR are unknown. This is also highlighted in the economic model by overlapping 95% confidence intervals for QALYs gained. Further, the CGP expressed that IBR is the most relevant comparator, but did not support the incremental magnitude in benefit that the model predicted between VEN+R and BR. The EGP elected to not place an upper bound on any of the comparisons included in order to reflect this uncertainty. It is difficult to conclude with any certainty if there is a benefit in survival between VEN+R and IBR, and the magnitude of this benefit. By not placing an upper bound, the EGP acknowledges that it is unclear how high the ICER could go. Given that the effectiveness between VEN+R and IBR may be similar, the ICER comparing these two treatments would reach infinity.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the proportion of patients actively treated, the market share of venetoclax and the cost of rituximab (biosimilar and/or subcutaneous).

The sequencing of treatments for this group of patients is rapidly evolving. Should ibrutinib be used to treat patients in the first-line, given its efficacy reported in recent studies, the market share of venetoclax plus rituximab in the second line may likely increase. This would most likely result in a net incremental increase in costs as opposed to a cost savings in the 3rd year.

1.6 Conclusions

In the absence of head-to-head direct evidence, it is difficult to draw firm conclusions around the treatment effect of VEN+R versus IBR, identified as the most relevant comparator for this treatment indication. The comparative effectiveness of VEN+R versus IBR remains uncertain given overlapping confidence intervals among other limitations. The impact of this uncertainty on the ICER is difficult to quantify, and may potentially have a large impact on the ICER. The EGP acknowledges, however, that the results of the MURANO trial[1] (VEN+R versus BR) demonstrated statistically significant PFS and showed a consistently higher improvement in OS rate with VEN+R.

Overall conclusions of the submitted model:

- *IBR was identified as the most relevant comparator, however, it is difficult to conclude the magnitude in incremental effectiveness of VEN+R versus IBR, if any. VEN+R in all scenarios remained cheaper than IBR. If you believe that VEN+R has similarly efficacy to IBR, the ICER is difficult to estimate given a small magnitude of incremental effectiveness.*
- *Though many assumptions were made in the submitted base case model, the submitter provided options to explore alternates to most of these assumptions.*

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) in combination with rituximab for CLL. 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. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107-1120.
2. UPDATED Indirect treatment comparison of venetoclax + rituximab versus other treatments in patients with relapsed / refractory chronic lymphocytic leukemia. In: pan-Canadian Oncology Drug Review manufacturer submission: Venclexta (venetoclax), 10 mg, 50 mg, and 100 mg film-coated tablets for oral administration, in combination with rituximab. Company: AbbVie Corporation. Saint-Laurent (QC): AbbVie Corporation; 2018 Sep 25.
3. Statistics Canada. Life Tables, Canada, Provinces and Territories 2009 to 2011. 2017.
4. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-1108.
5. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. n engl j med. 2014;37011370:997-1007.
6. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213-223
7. National Institute for Health and Care Excellence (NICE). TA359: Idelalisib for treating chronic lymphocytic leukaemia. In:2015.
8. Dretzke J, Barton P, Kaambwa B, et al. Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia. Health technology assessment (Winchester, England). 2010;14(Suppl. 2):19-26.
9. National Institute for Health and Care Excellence (NICE). Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. 2015.
10. National Institute for Health and Care Excellence (NICE). TA344: Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. In:2015.
11. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health and quality of life outcomes. 2010;8:50-50.
12. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. The European journal of health economics : HEPAC : health economics in prevention and care. 2013;14:749-759.
13. National Institute of Health and Care Excellence (NICE). TA306 Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. 2014.
14. National Institute for Health and Care Excellence (NICE). TA359: Idelalisib for treating chronic lymphocytic leukaemia. In:2015.
15. Canadian Hospice Palliative Care Association. Cost Effectiveness of Palliative Care: A Review of the Literature (December 2012). http://www.hpcintegration.ca/resources/discussion-papers/economic-review.aspx. Published 2012. Accessed Aug 1, 2018.
16. Abbvie Canada. Confidential price information for Venetoclax. In:2018.
17. IMS Brogan. IMS DeltaPA®: The ideal tool for monitoring Canadian prescription drug list prices. http://imsbrogancapabilities.com/pdf/delta-pa-en.pdf. Published 2017. Accessed May 1, 2017.
18. Tam VC, Ko YJ, Mittmann N, et al. Cost-effectiveness of systemic therapies for metastatic pancreatic cancer. Current oncology (Toronto, Ont). 2013;20:e90-e106.
19. Statistics Canada. Consumer Price Index, health and personal care, by province (monthly). Government of Canada. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/cpis13a-eng.htm. Published 2018. Accessed Aug 1, 2018.
20. Indeed. Pharmacy Technician Salaries in Canada. https://ca.indeed.com/salaries/Pharmacy-Technician-Salaries. Published 2018. Accessed.
21. Registered Nurses Association of Ontario. Dollars and Sense: What are nurses paid? Ontario Ministry of Health. http://careersinnursing.ca/new-grads-and-job-seekers/find-nursing-job/dollars-and-sense-what-are-nurses-paid. Published 2018. Accessed.

22. Ontario Ministry of Health and Long-term Care. Schedule of Benefits for Laboratory Services. http://www.health.gov.on.ca/en/pro/programs/ohip/sob/. Published 2017. Accessed Aug 1, 2018.
23. Ontario Ministry of Health and Long-Term Care. Schedule of Benefits for Physician Services under the Health Insurance Act. http://www.health.gov.on.ca/en/pro/programs/ohip/sob/. Published 2016. Accessed Aug 1, 2018.
24. Mittmann N, Hassan S, Seung SJ, et al. Health care resource utilization in the management of chronic lymphocytic leukemia at an Ontario cancer centre. Value in Health. 2014;17(A79):464.
25. Statistics Canada. Consumer Price Index, health and personal care, by province (monthly). Government of Canada. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/cpis13a-eng.htm. Published 2018. Accessed Aug 1, 2018.
26. Lachaine J, Mathurin K, Martinho-Lemay M. Costs associated with the management of relapsed/refractory chronic lymphocytic leukemia: A literature review. Commissioned report for AbbVie Canada. 2016:1-20.
27. Lathia N, Mittmann N, DeAngelis C, et al. Evaluation of direct medical costs of hospitalization for febrile neutropenia. Cancer. 2010;116(3):742-748.
28. pan-Canadian Oncology Drug Review (pCODR) final economic guidance report: Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. Ottawa (ON): CADTH; 2015: https://www.cadth.ca/sites/default/files/pcodr/pcodr-ibrutinib-cll-sll-fn-egr.pdf. Accessed 2019 March 14.
29. pan-Canadian Oncology Drug Review (pCODR) final economic guidance report: Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia. Ottawa (ON): CADTH; 2015: https://www.cadth.ca/sites/default/files/pcodr/pcodr_idelalisib_zydelig_cll_fn_egr.pdf. Accessed 2019 March 14.