CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Rituximab (Rituxan) for Acute Lymphoblastic Leukemia

June 29, 2017

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Cancer Care Manitoba with support from Hoffmann-La Roche Limited** compared rituximab plus chemotherapy backbone to chemotherapy backbone for patients with Philadelphia chromosome negative (Ph-), CD20 positive (CD20+), B-cell precursor acute lymphoblastic leukemia (ALL).

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Funding request matches economic model.
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival*
Comparator	*Hyper-CVAD—used more in the older population* *Dana Farber—used more in the younger population*
Year of costs	*2016*
Time Horizon	*15 years*
Perspective	*Canadian publicly funded health care system*
Cost of rituximab[#]	Rituximab costs $4.71 per mg When combined with Hyper-CVAD, rituximab is dosed as 2 infusions during induction, 2 infusions during re-induction (if needed), 6 infusions during consolidation, 2 infusions during intensification and 6 infusions during first-year maintenance at 375 mg/m^2 for a total of 16-18 infusions. For 16 infusions, rituximab costs: • 131.49 per day • $3681.62 per 28-day course For 18 infusions, rituximab costs: • $147.92 per day • $4141.82 per 28-day course Based on the cost used in the economic model, rituximab costs $6,548.86 per cycle. A 50mL (10mg/mL) vial costs $2,331.61
Cost of Hyper-CVAD[#]	Hyper-CVAD consists of multiple agents. Based the Sunnybrook Hospital protocol and cost data from Quintile IMS Delta PA, the cost of Hyper-CVAD is $173.80 per day and $6316.72 per 28 days.
Cost of Dana Farber[#]	The Dana Farber protocol consists of multiple agents. Based the Sunnybrook Hospital protocol and cost data from Quintile IMS Delta PA, the cost of the Dana Farber regimen is $247.28 per day and $6923.92 per 28 days.
Model Structure	*The model was composed of four main health states: event-free survival (EFS), relapsed/resistant, cured and death. Patients were considered cured after spending 60 months in the EFS state.*
Key Data Sources	*GRAALL-R*(1)

Foot Notes: All cost calculations for IV drugs are based on a BSA=1.7m^2; weight = 70kg
Acronyms: Hyper: hyper fractionated; CVAD: Course A-cyclophosphamide, doxorubicin, vincristine, dexamethasone + Course B - methotrexate, cytarabine as per Sunnybrook Hospital protocol
[#]Price Soucre: Quintile IMS Delta PA accessed on June 5, 2017

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), a comparison to Hyper-CVAD or Dana Farber is appropriate, as these are the current regimens used to treat ALL in Canada. The pivotal trial informing the clinical input of this economic model was based on the use of comparators that are inappropriate in the Canadian setting. Additionally, the trial was not designed to detect a significant differences for key clinical outcomes such as overall survival and quality of life. Canadian comparators include Dana Farber and/or Hyper-CVAD. The effectiveness inputs in the clinical model are based on the GRALL-2005-R trial (which uses comparators not available in Canada) and cost inputs from Dana Farber and/or Hyper-CVAD.

- Relevant issues identified in the CGP conclusions included:
  - *Overall, no net clinical benefit*
    - *There is a lack of overall survival advantage. Although OS is considered to be an important outcome for ALL, the trial was not powered to detect a difference in OS.*
    - *There is a lack of appropriate and meaningful quality of life data therefore there is an absence of information on whether or not there is a quality of life benefit in this population.*
    - *Though event free survival (EFS) was statistically significantly in the trial, with an improvement in favour of the rituximab group, EFS is not a clinically meaningful outcome in previously untreated ALL and evidence based on this outcome is not used to make treatment decisions, including treatment practice changes, in ALL.*
    - *It is difficult to generalize the results of GRAAL-2005-R trial to the Canadian setting as the comparator used in the trial was inappropriate in the Canadian setting.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered the current treatment is a modified Dana Farber chemotherapy protocol. The benefit of rituximab is in prolonging EFS with no increase in toxicity.

Summary of patient input relevant to the economic analysis
No patient advocacy input was received by pCODR. Through a literature search, references were identified where patients experience with ALL and rituximab were identified. **Patients** considered adverse events related to treatment and disease and quality of life as important, which are 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 rituximab which are relevant to the economic analysis:

<u>Enablers</u>

- Small number of patients who would be eligible for the drug.
- Possibility of vial sharing when administered in outpatient chemotherapy clinics.

<u>Barriers</u>

- Increased risk of wastage when rituximab is used in hospital during induction phase as vial sharing may not be possible.
- High per patient treatment costs as patients receive a total of 16 to 18 doses of rituximab.
- Increase in resources for patients during both the induction, consolidation, intensification phases (in hospital) and during the maintenance and coordination phases (outpatient).

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (LY)	1.33	0.10	0.04
Event-free	0.541	0.489	0.00
Relapsed/resistant	-0.052	-1.259	0.035
Cure	0.839	0.865	0.00
ΔE (QALY)	1.16	0.69	0.01
Event-free	0.462	0.418	0.00
Relapsed/resistant	-0.029	-0.473	0.011
Cure	0.722	0.744	0.00
ΔC ($)	$45,259	$32,299	$44,372
ICER estimate ($/QALY)	$39,181	$46,894	$4,193,972

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

- *Trial data efficacy not based in Canada and not reflective of Canadian comparators: The trial was conducted in centers in Europe, and no Canadian centers were included. The CGP felt that the trial results could not be generalized to the Canadian setting as there were chemotherapy regimens used in the trial that are not considered to be standard of care in Canada. As the trial was done in a different treatment setting, with different comparators, efficacy results are not generalizable to the Canadian population.*
- *Assumptions based on expert opinion: Expert opinion is subject to bias, and may not be generalizable. Inputs that relied on expert opinion include the proportion of patients receiving second and third line treatment, the proportion receiving stem-cell transplant, treatment duration of the standard of care, assumptions around the use of utilities from the literature, and some resources/costs that are applied to both treatment arms.*
- *Utility values: Utility values were not collected in the trial but were derived from a study conducted in the UK in a relapsed or refractory ALL population. Several limitations were identified with the generalizability of the utility values. First, the data is based on a relapsed or refractory population, Further, the study reported that the mean EQ-5D score from the study was different from values reported in previous studies that have reported higher mean EQ-5D values in the UK general population. The study authors also reported that they did not test for any significant differences in demographics between the study population and the general population in the UK. This could indicate bias in the study and questions the validity of the results. The EGP varied this input, however, due to lack of other available data, it is unknown what the utility of patients with ALL in the relapsed/resistant state in Canada would be. In the current model, improvement in the EFS state in QALYs is included, but the absolute value of the incremental difference in EFS QALYs is unknown, given the data source.*
- *Efficacy: The CGP concluded there is no net clinical benefit in adding rituximab to the standard of care. This was based on the absence of demonstrated overall survival benefit and lack of quality of life data addressing the impact of adding rituximab to standard treatment options. To align with this conclusion, the EGP altered treatment effect for overall survival to be zero starting at time 0. The CGP agreed that there was improvement in event free survival, as less patients in the rituximab group experience relapse. The CGP, however, felt that EFS is not a clinically meaningful outcome. Further, they are uncertain of the impact on a patient's quality of life of being in the relapse free state, as quality of life was not measured directly in the clinical trial.*

- *Event-free survival not a meaningful end point in ALL for adults: The primary outcome of the GRAALL-2005-R trial was EFS. The CGP noted that EFS is not a validated surrogate outcomes for OS for patients with ALL. The CGP felt that the improvement in EFS was not sufficient to warrant a change in practice by adding rituximab to chemotherapy. The CGP highlighted that to date, no changes in practice for treating patients with ALL have been supported without robust OS benefit and/or quality of life improvement. The model structure reflects the clinical trial, but neither reflect clinical practice.*

1.4 Detailed Highlights of the EGP Reanalysis

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

- *Net clinical benefit—overall survival: the CGP stated that there is no net clinical benefit with the addition of rituximab. Given that statement and the lack of conclusive evidence based on the trial (hazard ratio confidence intervals for overall survival crossing 1), the EGP elected to assume no clinical benefit in the rituximab group. This was modified in the economic model by setting the "no net treatment" effect parameter to 0 months—that is, at no point in the economic model was there a net treatment benefit with the addition of rituximab.*
- *Net clinical benefit—event-free survival: Trial duration was 4 years and during this time, EFS was significantly different between the two groups, though the trial was powered to detect a difference in EFS at two years only. The CGP concluded, however, that EFS is not a clinically meaningful outcome for patients. Meaningful outcomes in patients with ALL would constitute improvements in OS (not a primary end point in the trial) and/or quality of life (not collected in the trial). As the CGP stated that EFS is not a clinically meaningful endpoint in ALL, and to align with the design of the trial, the EGP considered 2 years follow-up in EFS as a lower bound estimate, and no EFS benefit as an upper bound estimate.*
- *Discounting: at the time of this report, CADTH has published new guidelines on economic modeling which suggest using a discount rate of 1.5% for both costs and effectiveness. This was applied in the base case to align with the recommendations.*

Table 3. Detailed Description of EGP Reanalysis

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	$45,259	1.16	$39,181	-----
EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
Discounting - 1.5%	$46,115	1.45	$31,794	$7,387
Overall survival - no net benefit	$33,799	0.42	$81,123	$41,942
Event-free survival- no benefit after 24 months	$47,193	1.02	$46,476	$7,295
Best case estimate of above parameters	$32,299	0.69	$46,894	$7,713
UPPER BOUND				
Discounting - 1.5%	$46,115	1.45	$31,794	$7,387
Overall survival - no net benefit	$33,799	0.42	$81,123	$41,942
Event-free survival- no net benefit	$58,014	0.47	$122,793	$83,612
Best case estimate of above parameters	$44,372	0.01	$4,193,972	$4,190,061

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- The number of doses administered: increasing the number of doses from 10 cycles to 16 cycles increases the BIA by about 39%.
- Age distribution of population: increasing the number of adult patients from 33% to 42% increases the BIA by about 21%.
- The proportion of Ph-Negative patients: increasing the proportion of Ph-Negative patients from 75% to 85% increases the BIA by about 12%.

Beyond the assumptions listed in the table above, there were no other key limitations of the BIA model that were identified.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for rituximab plus chemotherapy backbone when compared to chemotherapy backbone is:

- Between $46,894/QALY and $4,193,972/QALY
- If there truly is no net clinical benefit – that is, no survival advantage of rituximab in either the event-free state or the overall survival state-- the best estimate would likely be towards the upper end of the range.
- If a net benefit in event-free survival is to be believed, resulting in a greater proportion of cured at 5 years in the rituximab group, the best estimate is likely towards the lower end of the range.
- The extra cost of rituximab is between $32,299 and $44,372 (ΔC). *The factors that most impact ΔC are the duration of treatment effect for overall and event-free survival and rituximab compliance.*
- The extra clinical effect of rituximab is between 0.01 and 0.69 (ΔE). *The factors that influence ΔE are the duration of treatment effect for overall and event-free survival and the time horizon.*

Overall conclusions of the submitted model:

- Overall, the model structure is somewhat reasonable as it is based on the clinical inputs from the clinical trial. However, limitations render the interpretation of some of the scenarios difficult. In the instance of the lower bound, there is a loss of QALYs in the relapsed/resistant state in the RTX+SOC arm, due to the fact that this state is based on the difference between overall survival and event-free survival. As we were unable to remove the benefit in the SOC arm, an incremental loss of QALYs was observed.

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 on rituximab for acute lymphoblastic leukemia (ALL). 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 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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