pan-Canadian Oncology Drug Review

Final Economic Guidance Report

Erratum: This is a revised Final Economic Guidance Report which supersedes the Final Economic Guidance Report for this drug and indication dated April 1, 2016. The revision does not impact the Final Clinical Guidance Report or the Final pERC Recommendation. The clarification added to the report describes an error within the structure of the model that had no impact on the presented re-analysis estimates.

Blinatumomab (Blincyto) for Acute Lymphoblastic Leukemia

November 11, 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 Amgen Canada Inc.** compared blinatumomab to currently available treatments (referred to herewith by the EGP as the "comparator") for patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (R/R Ph(-) ALL).

Submitted Economic Model	
Funding Request	*The patient population in the economic model is the same as the patient population in the funding request: blinatumomab for the treatment of patients with R/R Ph(-) ALL. Population modeled is based on the study population from Study MT103-211*
Type of Analysis	*CUA, along with a CEA*
Type of Model	*Partitioned-survival*
Comparator	*Based on the CGP input, there is no single accepted standard of care for the patient population in this economic analysis. The salvage regimen, hyper-CVAD, was however chosen as a relevant comparator for the purposes of the economic evaluation. The submitter noted that no major efficacy difference is expected between different salvage regimens*
Year of costs	*2015*
Time Horizon	*50 years*
Perspective	*Government health payer*
Cost of blinatumomab*	• $2,978.27 per vial (38.5mcg/vial) • Recommended dose in cycle 1 is 9 mcg/day for week 1 (first 7 days). • Subsequent cycles increased to 28 mcg/day starting week 2 through week 4 of first cycle. All subsequent cycles also dosed at 28 mcg/day through entire 4 week cycle. • At the recommended dose, blinatumomab costs $1187.76-$1443.32 per day and $39,601.96-$46,977.25 per 28 day cycle
Cost of comparator	• At the recommended dose, Hyper-CVAD costs $126.29 per day and $3536.19 per 28 day cycle. • The submitter noted that the cost of Hyper-CVAD and other chemotherapy regimens were assumed to be equal.
Model Structure	The model was comprised of three health states: remission (complete remission; complete remission with partial haematological recovery; complete remission by study group), progressive disease and death. Patients who survive for 60 months in the treatment phase were assumed to be cured and enter the ongoing phase.
Key Data Sources	*Non head-to-head clinical trial data (study MT103-211) Comparator data taken from historical comparator with statistical adjustment to make baseline patient characteristics between study MT103-211 and this historical cohort somewhat similar.*

Submitted Economic Model
Acronyms: Hyper: hyper fractionated; CVAD: Course A-cyclophosphamide, doxorubicin, vincristine, dexamethasone + Course B - methotrexate, cytarabine as per Sunnybrook Hospital protocol. **Cost calculations for blinatumomab based on 48 hour infusion only.*

1.2 Clinical Considerations

Following the identification, by the submitter, of an error within the structure of the submitted economic model, the following clarification was added to the report to outline that this structural error did not have an impact on the re-analysis estimates provided by the EGP:

> **Based on CGP input, the number of days patients would spend in hospital was not reflected appropriately in the submitted base case analysis. To account for the additional number of days patients are expected to spend in hospital, the EGP used the model input for inpatient admissions as a proxy for the number of days spent in hospital (changing it from 1 to 1.5 in the EGP's reanalysis). The EGP had requested the submitter to provide a new model that allowed for alterations to be made to the number of days spent in hospital through the Checkpoint meeting; however, no such model was made available.**
>
> **The error identified by the submitter clarified that the use of in-patient admission as a proxy for number of days spent in hospital results in an inflation of the cost associated with inpatient admission beyond the 1.5 cycles entered as the re-analysis estimate. Despite this, the intent of the EGP's re-analysis was not to simply reflect an increase in the in-patient admission from 1 to 1.5 cycles but to account for an increase in the cost associated with the number of days spent in hospital. Therefore, by taking into account CGP input and the expected costs with length of stay, the EGP's re-analysis resulted in an ICER estimate of $291,027/QALY, an ICER which reflected the intent of the EGP's re-analysis.**

According to the pCODR Clinical Guidance Panel (CGP), a comparison to combination chemotherapy (eg. Hyper-CVAD) is appropriate, however there were limitations in the data available for the patient population in the comparator. The comparator arm in the economic analysis was informed from a historical cohort (retrospective chart review) and weighted analysis was used to produce a cohort of patients that are similar to those in the blinatumomab arm (patients enrolled in the MT103-211 study).

- *The CGP noted that the historical comparator is one of the largest cohorts of ALL patients described so far.* Relevant issues *were however identified for this historical comparator. Despite these limitations, conservative estimates of comparative efficacy can be drawn using these data however caution should be exercised in interpreting these results. Issues identified in the data included:*
  - *Date range of included study population: the generalizability of the study cohort included in the historical comparator may be limited given that treatment strategies have evolved since the 1990s. Estimating effectiveness based on out-dated regimens may limit the generalizability of the results and increase uncertainty.*
  - *The timeframe of the historical and blinatumomab cohorts are different.*
  - *There were also imbalances in important baseline characteristics (prior HSCT, bone marrow blasts at diagnosis and prior lines of therapy) that may have compromised the comparability of efficacy outcomes between the two cohorts.*

- *The data has been extensively manipulated statistically in order to account for the imbalances in the baseline characteristics.*

Summary of patient input relevant to the economic analysis
Input was received from patients for the review of blinatumomab but no patients had direct experience with blinatumomab. In terms of experience with ALL, patients considered better control of symptoms, better control of side effects, and to stop progression of the disease as factors that are important to consider with treatment. Adverse events were not considered in the economic model. However, the submitter felt that this was a conservative approach since it is assumed that adverse events are no worse with blinatumomab, than with the historical comparator treatment arm.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
At the time the input was made, PAG considered the following factors important to consider if implementing a funding recommendation for blinatumomab which are relevant to the economic analysis. Enablers included:

- Very small patient population.
  - This has been addressed in the budget impact analysis.

Barriers included:

- Complex and highly resource intensive preparation and administration. Infusion bags may be changed as often as every 24 or 48 hours. Feedback received from PAG indicated that although blinatumomab can be stable and administered up to a 96 hour infusion period, infusion pumps currently available in various jurisdictions may not last up to 96 hours due to their battery lifespan. As a result, infusion pumps for blinatumomab in clinical practice may need to be over 48 hours to ensure continuous infusion of treatment to patients.
- Rigorous monitoring for toxicities.
- Access to treatment an issue since hospitalization required for administration in the first two cycles and proximity to tertiary care centres required.
- High cost of drug.
  - All of the above factors were addressed in the economic analysis.

1.3 Submitted and EGP Reanalysis Estimates

Estimates	Submitted	EGP Reanalysis
ICER estimate ($/QALY), range/point	$91,202	$291,027 - not estimable
ΔE (QALY), range/point	1.21	0.65 - not estimable
ΔE (LY), range/point	1.42	0.77 - not estimable
ΔC ($), range/point	$110,269	$188,963 - not estimable

Based on the pCODR Economic Guidance Panel's (EGP's) assessment of the submitted economic evaluation, cost drivers in the model include the number of cycles of blinatumomab, number of inpatient admissions/cycle, and cost of drugs. Effect drivers include the estimates of clinical benefit, time horizon, utilities after 60 months, and time spent in progressive disease for non-responders. The main assumptions and limitations, in no order of importance with the submitted economic evaluation were:

- *Source of data for the comparator may not be generalizable to today's population of patients. Further, important differences were observed in baseline characteristics between the two cohorts such as proportion of patients having had prior transplant and blast count at diagnosis, factors that may impact on prognosis of patient. Therefore the comparability of results between the two cohorts was uncertain. Additionally, the definition of primary outcome differed*

throughout the study and treatment regimens considered may not be similar to today's clinical practice.

- *Lack of head-to-head clinical trial data which impacted the ability to estimate the time spent in health states for the comparator arm, the use of subsequent treatments and adverse events due to lack of data.*
- *Number of days spent in hospital per treatment is not modifiable in the submitted model. Only the number of inpatient admissions per cycle of treatment was modifiable. Inpatient admissions are associated with high costs. This input was modified by the EGP as a proxy for assessing the high resource intensive nature of blinatumomab therapy.*
- *Proportion of patients who receive HSCT was not modifiable in the submitted model. The inability to modify this parameter introduces uncertainty into the model as HSCT impacts both costs and effects of a given treatment regimen.*
- *Adverse events were not modeled and were assumed to be the same between blinatumomab and currently available therapies (ie. Hyper-CVAD). The submitter noted that inpatient admission costs accounted for AE management.*
- *Given the size of the vials (38.5 mcg) and the recommended daily dose of 28 mcg, some wastage may be expected and varies on the infusion period chosen. Both reconstituted vial (24 hours- fridge) and admixture (96 hours- room temperature; 10 days fridge) have limited stability. It is notable that the 96 hour infusion may not be feasible in Canadian jurisdictions.*
    - *As the daily dose for most of the treatment cycles requires 28ug (with the exception of week 1 in cycle 1) it is expected that 32.5ug are required to account for the dose administered to the patient and the drug required for the admixing. Therefore in this instance 16% of the vial will be wasted.*
    - *In the instance a 9ug/day dose is given (cycle 1, week 1), and assuming the 48 hour infusion is used (based on PAG feedback on availability of infusion pumps), it is expected that 21.25ug will be required accounting for the dose given to the patient and drug required for admixing. In this instance, 45% of the vial is wasted.*
- *The ability to explore wastage was not built into the economic model. The EGP attempted to explore the impact of wastage on the ICER* through alternate means *by conducting an analysis where 55 vials of blinatumomab are used (compared to 46 in the base case). This resulted in an increase of $22,169 in the ICER. This analysis was not included in the EGP`s re-analysis estimate and was done to illustrate the impact of wastage on the ICER.*

EGP Reanalysis

Baseline (Submitter's best case)	**$110,269**	**1.21**	**1.42**	**$91,202**	--
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICER (QALY)	Δ from baseline submitted ICER
Lower bound					
Time horizon after 5 years- 5 years (akin to 10 years)	$109,599	0.65	0.77	$168,796	$77,594
Number of inpatient admissions / cycle—1.5	$189,633	1.21	1.42	$156,842	$65,640
Best case estimate of the above two parameters	**$188,963**	**0.65**	**0.77**	**$291,027**	**$199,825**
Upper bound					
Not estimable	-------	------		-------	-------

Best case estimate of the above four parameters	not estimable	not estimable	not estimable	not estimable	not estimable

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

- Time horizon akin to 10 years: The CGP noted that it is unreasonable to assume a lifetime horizon of 86 years after diagnosis. Though the submitter had chosen this lifetime horizon, once a patient is "cured" through stem cell transplantation, mortality is equal to those of their peers in the general Canadian population. Continuing to accrue benefit beyond this time is unreasonable. Only those being cured by stem cell transplantation, in either group, would be surviving at 10 years.
- Number of inpatient admissions: Inpatient admissions were a cost driver of the model. Given that the EGP was unable to modify the length of stay of each inpatient admission to examine the impact on the magnitude of the ICER, the number of inpatient admissions was modified as a proxy for assessing the high resource intensive nature of blinatumomab therapy. The CGP noted that there was a very high likelihood that patients receiving this drug would receive most of it in a hospital setting. Additionally feedback from the Provincial Advisory Group indicated that blinatumomab is a resource intensive therapy to administer.
- *As part of the EGP's re-analysis estimates, the upper end of the ICER was undefined. The EGP based this on input from the Clinical Guidance Panel, where it was agreed that there is sufficient uncertainty in the comparative efficacy results obtained through the historical comparator data. While the CGP agreed the data was reasonable to use in the economic evaluation, they noted that the results should be interpreted with caution. The CGP therefore supported an approach providing a range that only includes a lower estimate of the ICER without attempting to assess an upper limit.*

1.4 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include are the cost of blinatumomab, the market share of blinatumomab and the average number of vials of blinatumomab per patient.

Key limitations of the BIA model include the lack of inclusion of drug administration costs. These parameters could not be modified and explored by the EGP.

1.5 Conclusions

The EGP's best estimate of ΔC and ΔE for blinatumomab when compared to the historical comparator regimen (hyper-CVAD) is:

- Between $291,027/QALY and unknown
- It is difficult to estimate where the best estimate would likely be, given the data provided. Input from the CGP noted that the estimates of comparative efficacy derived through the historical data should be interpreted with caution. Additionally, the EGP was unable to modify various important model parameters that were noted to potentially have an impact on the clinical effectiveness estimates.
- Given these limitations, the EGP therefore expects that the true ICER is unlikely to be close to the lower bound of the re-analysis range of estimates.

Overall conclusions of the submitted model:

- *The utilisation of a historical comparator limited the data available for the economic model.*
- *If one accepts the data from the historical comparator to be comparable to the MT 103-211 Study and relevant, then the ICER may be towards the lower end of the range $291,027/QALY, though*

this should still be interpreted with caution as there was no direct comparison between the two groups and important inputs were not able to be modified to examine their impact on the ICER.

- *If the data from the historical comparator is not comparable to the MT 103-211 Study and does not provide adequate comparative efficacy data, it is unlikely that the ICER is towards the lower end of the range and it is difficult to estimate how high the ICER is likely to go.*

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 blinatumomab (Blincyto) for ALL. A full assessment of the clinical evidence of blinatumomab (Blincyto) for ALL 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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