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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Blinatumomab (Blincyto) for Philadelphia chromosome positive Acute Lymphoblastic Leukemia

April 4, 2019

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Amgen Canada compared blinatumomab (BLINCYTO) with standard of care (SOC) for the treatment of adults with Philadelphia positive (Ph+) relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (BCP-ALL) in the Canadian setting.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	The patient population for funding request is the same as the one in the economic model: adults with Philadelphia positive (Ph+) relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (BCP-ALL)
Type of Analysis	*CEA, CUA*
Type of Model	*Partitioned-survival*
Comparator	*Standard of care (SOC) comprised of a tyrosine kinase inhibitor (TKI) (i.e., ponatinib), chemotherapy (i.e., hyper-CVAD) or TKI+ chemotherapy combination*
Year of costs	*2018*
Time Horizon	*30-years (lifetime)*
Perspective	*Publicly funded health care payer*
Cost of Blinatumomab	Blinatumomab costs $2,978 per 38.5µg vial • Recommended dose in cycle 1 is 9µg/day for 1st week of cycle 1. • Subsequent cycles increased to 28µg/day starting week 2 through week 4 of first cycle. All subsequent cycles (cycles 2-5) dosed at 28µg/day through entire 4-week cycle. When cost calculations are based on 6-week cycles (42 days; i.e., four weeks of treatment, followed by a two-week treatment-free period), blinatumomab costs: • $71,472 per 42-day cycle (cycle 1)* • $83,384 per 42-day cycle (cycle 2-5) *assumes that 3 vials can be shared and will be used for days 1-7 of cycle 1 and that one 38.5µg vial will be used for all other treatment days (28 vials for 28 days of infusion)
Cost of standard of care (SOC)	Hyper-CVAD (multi-drug chemotherapy) • 3,375.66 per 42-day cycle • $2250.44 per 28-day course *Source*: Association québécoise des pharmaciens propriétaires

	Ponatinib • 45 mg/day (1 tablet) • $331.48/day • $ 9281.44 per 28-day course *Source*: Ontario MOHLTC Exceptional access program
Model Structure	A probabilistic partitioned survival model was constructed with five health states: i) initial (pre-response), ii) response iii) relapsed/refractory (R/R), iv) cured and v) dead (Figure 1). All patients started from the initial (pre-response) state where they stay for 12 weeks (unless they die) at which point patients were defined as having a response or relapsed/refractory. Those who responded were at risk of relapse for the first 3 years of therapy. If no relapse occurred at 3 years, patients were considered cured. Patients in R/R state had a risk of ALL-mortality during the first 3 years after which they entered cured state with a subsequent risk of non-ALL mortality.
Key Data Sources	• *Key clinical information (relapse-free survival, overall survival) for blinatumomab came from the ALCANTARA trial (single-arm, open-label, multicenter).*[1] • *Clinical information for the standard of care comparator came from a historical control study.** • *Utilities came from the TOWER study.*[2] • *Recourse utilization (medications, hospitalization, salvage therapy) came from different sources while unit costs reflected the Canadian healthcare setting.*

*After the posting of the initial EGR, the Submitter noted errors in the propensity score analysis submitted to pCODR and therefore requested the correct errors. The review team confirmed that the corrections in the Clinical Guidance Report did not impact the interpretation of the results; and that the Economic Guidance Report and EGP's best case estimates were not impacted by the corrections.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), there is a net clinical benefit from treatment with blinatumomab in patients with Ph+ B-ALL who have been treated with at least two prior TKIs and have relapsed or refractory disease with an ECOG of ≤ 2. The SOC therapy (chemotherapy, TKI or their combination) that was compared to blinatumomab in economic analysis was considered appropriate by CGP. The outcomes of ALCANTARA trial have been considered appropriate and the adverse event profile appropriate.

As noted by CGP, another potentially relevant comparator could have been inotuzumab ozogamacin (InO). However, the Submitter did not include this comparison in modifications to the main economic analysis. Patients treated with InO can still receive blinatumomab if they meet the required eligibility criteria.

The CGP also noted that considering the experience from the TOWER study, a maintenance therapy would be reasonable in this patient population. Since no maintenance therapy was given in the ALCANTARA trial (no blinatumomab use after the 5th cycle and no information on its costs and benefits beyond the 5th cycle), the EGP was unable to perform reanalysis that will consider maintenance therapy.

Summary of registered clinician input relevant to the economic analysis

- Registered clinicians mentioned blinatumomab as an important novel therapy to address a significant medical need in the defined patient population in the funding request. It was mentioned that blinatumomab infusion would require hospitalization but it is also the case with standard therapy in this population.
- Blinatumomab will potentially allow more patients to proceed with their first or second transplant therapy after they achieve remission.

Summary of patient input relevant to the economic analysis

- Both patients and caregivers stressed the significant physical and emotional burden ALL can cause. Patients reported no difficulty in access to ALL care. All patients reported experiencing some side effects (e.g., fatigue, pain, nausea) of ALL treatment most of which subside after remission. Only few patients and caregivers had prior experience with blinatumomab; they rated the experience with the drug positively.
- All patients also mentioned increased susceptibility to infections after remission sometimes requiring hospitalization. In the economic model, all no ALL related costs were assumed after 3-year survival although an assumption was made that the overall survival of these patients will be twice worse than that of sex and gender matched Canadians.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

- PAG considered the potential drug wastage due to insufficient amount of stabilizer as an important barrier that needs to be considered in economic analysis if implementing a funding recommendation for Blinatumomab. As per submitter response, each vial of blinatumomab is packaged with a 10 mL IV solution stabilizer (IVSS) and only 5.5mL of stabilizer is needed for each infusion bag. The blinatumomab dose can be prepared in a 24, 48, 72 and 96-hour bag. The bags can be prepared in advance and refrigerated for up to 10 days. When preparing multi-day (e.g., 48, 96 hrs) infusion bags the requirement of IVSS is still 5.5mL/bag and therefore, over time there will be IVSS left over amounts in centres preventing blinatumomab wastage. The EGP noted that a recent article showed how multi-day infusion bags efficiently save both IVSS wastage and blinatumomab wastage.[3] One vial of blinatumomab contains 38.5µg of the drug while the recommended

daily dose is 28µg. To minimize wastage, the leftover amount of blinatumomab from a vial can be used for the next multi-day infusion bag that will be prepared in advance.

- Another concern by PAG relevant to economic analysis was the duration of blinatumomab treatment after the 5th cycle. The submitter confirmed that there was no maintenance phase after the 5th cycle in the ALCANTARA trial.
- Health care professionals' familiarity with blinatumomab was considered an enabler to implementation.

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)	1.24	0.67	0.67
Initial	0.01	0.01	0.01
Response	0.14	0.14	0.14
Relapsed/refractory	0.19	0.19	0.19
Cured	0.90	0.33	0.33
ΔE (QALY)	1.00	0.55	0.55
Progression-free	0.02	0.02	0.02
Initial	0.12	0.12	0.12
Response	0.14	0.14	0.14
Relapsed/refractory	0.71	0.27	0.27
ΔC ($)	**67,981**	104,685	113,389
ICER estimate ($/QALY)	68,185	190,084	205,889

Based on pCODR EGP assessment, the main assumptions and limitations of the submitted economic evaluations were:

- This was a partitioned survival model with 5 states which limits the ability to test the results under different hazard ratios for overall and relapse free survival. Limited choices were available to test the results under different parametric distributions for OS and RFS other than lognormal or log-logistic distributions.
- Data on clinical benefits came from an open-label, one-arm ALCANTARA trial[1] while the standard of care arm was created using a historical comparator study. The indirect comparison introduces the major uncertainty in relative effectiveness of blinatumomab over SOC. The ALCANTARA study included a more contemporary cohort (enrollment from 2014 to 2015) than the historical cohort (enrollment from 2006 to 2018), and the study populations differed in important prognostic factors in unadjusted baseline comparisons. Although the submitter used propensity score method to create comparable groups, the difference in enrolment years may potentially confound the results towards an overestimation of blinatumomab effectiveness.
- Another model limitation was the selection of the 30-year (lifetime) time horizon by the submitter. This was considered clinically not plausible by the CGP panel. In addition, the extrapolation of survival data was based on a highly censored data. In ALCANTARA trial only 18% of patients were alive at 24 months. The CGP recommended using a 10-year time horizon which was also consistent with the prior pCODR EGP evaluation for blinatumomab for Ph- ALL patients.
- Quality of life was not evaluated in the ALCANTARA trial. Estimates form the TOWER study were used instead.[2] The model did not assign equal '*initial*' state utility values to both arms but rather used values for the 1st 12-week period (before assessment of response) received from a GEE model results in TOWER study.
- Data on resource utilization (e.g., inpatient stay, use of salvage therapy, use of SOC) did not come directly from the ALCANTARA or historical comparator study and was largely assigned based on literature or assumptions. AE costs (and effects on QoL) were not considered in the model and it was assumed that since most of these events occur early in the treatment in-hospital costs will capture these AEs. The submitter noted that blinatumomab has a better AE profile than the SOC therapy as per TOWER study and this was likely a conservative approach.
- Inpatient hospitalization is generally costly and is one of the important cost drivers in economic evaluation studies. In the model, the submitter assumed that the patients in blinatumomab arm will be hospitalized for the first 9 days in cycle 1 and first two days in cycle 2. While having treatment administration in an outpatient setting is a benefit offered by blinatumomab

it is likely that in many Canadian jurisdictions access to outpatient cancer services may be limited, and patients may stay in the hospital for a longer duration. Patients in SOC arm receiving chemotherapy were however assumed to be hospitalized for the full period of receiving the therapy. This was considered not reasonable by the CGP and was further tested by EGP.

- After inpatient stay, patients in blinatumomab arm were assumed to receive the remaining course of treatment at home. It was assumed patients would need a nurse home visit for infusion bag change twice per week (every 3.5 days). The CGP panel noted that more frequent visits (i.e., every 48 hours) may be required (depending on battery life of the pumps, follow-up/monitoring protocols) in different jurisdictions. PAG members also noted that combinations of 24, 48, 72 or 96-hour bags may be used in different provinces with multi-day preparations mostly used in outpatient settings. Furthermore, some provinces will continue administering all cycles of blinatumomab in an inpatient setting until logistics are in place for outpatient administration. The frequency of infusion bag change was tested in EGP reanalysis.

1.4 Detailed Highlights of the EGP Reanalysis

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

- **Time horizon:** The lifetime horizon was considered clinically not plausible by CGP, and a 10-year time horizon was considered more appropriate. The EGP tested the effect of decreasing the time horizon to 5 years and 10 years. The 10-year will be time horizon used by EGP to obtain the best case estimate.
- **Initial utility:** The EGP tested the assumption of initial utility by assigning 0.740 to the initial state in both arms (an estimate used by the submitter for the initial state in blinatumomab arm).
- **Frequency of change of infusion pumps:** The EGP tested if the infusion pumps and bags are changed every 2 days (48 hours) instead of every 3.5 days. The change had very little effect on the ICER.
- **Number of inpatient days for blinatumomab administration**: Since resource utilization data were not reported in ALCANTARA trial no direct data were available on average inpatient hospitalization days for blinatumomab administration. The recommended number of inpatient days for blinatumomab to observe for adverse events/toxicities is 9 days during 1st cycle and 2 days during 2nd cycle (11 days in total). A prior pCODR submission for the use of blinatumomab in similar but Ph- patients (based on TOWER study) conservatively assumed the drug would be administered in an inpatient setting for the first 12 days of cycles 1 and 2. The EGP used this approach to test the effect of this parameter on ICER. A further consultation with PAG members revealed that in most centres patients will stay hospitalized until stable on dose escalation (~9th day) and will be hospitalized for the first few days of cycle 2. Therefore, in the final reanalysis the EGP kept the estimate originally used by the submitter (11 days in total).
- **Number of inpatient days for SOC chemotherapy (ie, hyper-CVAD) administration:** The submitter assumed patients receiving this chemotherapy will be hospitalized for the full duration of treatment which was 1.2, 42 day cycles (50 days in total). This was based on a survey of clinician experts in five European countries. Our targeted search of peer-reviewed literature on in-patient hospitalization duration for chemotherapy in this patient population resulted in few studies:

Source	In-patents stay
Blinatumomab pCODR submission	Patient population: for R/R Ph- BCP-ALL patients (based on TOWER study, reference for estimate: PMCC protocol, OCCI) Duration of in-patient stay: 18.9 days for hyper-CVAD
Delea et al[4] (US)	Patient population: PE model, R/R Ph- BCP-ALL patients, based on TOWER study, reference for estimate: Barlev et al 10.8 days for standard of care chemotherapy (note, no patient

Source	In-patents stay
	received hyper-CVAD in this trial)
Barlev et al[5] (US)	Patient population: Ph- relapsed BCP-ALL patients on chemotherapy Duration of in-patient stay: 13.1 (SD=15.7) days; 45% of reasons for hospitalization was chemotherapy
Kreuzer et al[6] (Germany)	Patient population: Ph- BCP R/R ALL patients on chemotherapy Duration of in-patient stay: 25 (SD=20) days
Dombret et al[7] (France)	Patient population: Ph- BCP R/R ALL patients on chemotherapy Duration of in-patient stay: 16.8 (SD =14.8) days
Abro et al[8] (single centre experience)	Patient population: newly diagnosed acute lymphoblastic leukaemia/ lymphoma (ALL) Duration of in-patient stay: 23% of A cycles and 43% of B cycles delivered in an inpatient setting

The EGP, therefore, tested two scenarios: when the total duration for inpatient days was 18.9 days (16 days per 1 cycle or 19 days in total per 1.2 cycle) for an upper and 25 days (21 days per cycle) for a lower ICER estimate. The choice of the range of this parameter was also supported by the Clinical Panel Lead.

Table 3. Detailed Description of EGP Reanalysis

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER*
1. Time horizon = 5 years	66,510	0.37	0.45	181,667	116,281
2. Time horizon = 10 years	66,473	0.68	0.55	119,931	54,545
3. 'Initial' utility = 0.740 for both comparators	66,340	0.99	1.25	66,768	1,382
4. Frequency of infusion pump change - every 48 hours	66,712	1.01	1.25	66,204	818
5. Inpatient days for blinatumomab administration: first 12 days of cycles 1 and 2	84,825	1.01	1.25	84,180	18,794
6. Inpatient days for hyper-CVAD administration: 19 days	111,923	1.01	1.25	111,071	45,685
7. Inpatient days for hyper-CVAD administration: 25 days	103,157	1.01	1.25	102,372	36,986
EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE QALY	ΔE LYs	ICUR	Δ from baseline submitted ICER**
Baseline (Submitter's best case)	67,981	1.00	1.24	68,185	--
LOWER BOUND					
Combination of 2 and 7	104,685	0.55	0.67	190,084	121,899
UPPER BOUND					
Combination of 2 and 6	113,389	0.55	0.67	205,889	137,704

**Compared to ICER received from deterministic analysis (65,386/QALY).*
***Compared to ICER received from probabilistic analysis (68,185/QALY).*

1.5 Evaluation of Submitted Budget Impact Analysis

Factors that most influence the budget impact analysis include epidemiologic estimates for proportion of patients with (i) B-lineage ALL, (ii) B-cell lineage that is precursor to B-cell, (iii) B-cell and Ph+, and (iv) B-cell and Ph+ and R/R and the duration of use/cost of ponatinib.

The key limitation of the BIA model includes the lack of consideration of drug administration cost for both comparators. More specifically, the cost of hospitalization for blinatumomab or hyper-CVAD chemotherapy was not considered. It is likely that these costs will be higher for the chemotherapy patients. The EGP was unable to modify the model to explore this further.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for blinatumomab when compared to standard of care therapy is:

- Between $190,084/QALY and $205,889/QALY.
- The extra cost of blinatumomab is between $104,685 and $113,389. The major cost drivers include medication and hospitalization costs.
- The extra clinical effect of blinatumomab is 0.55 QALY and was mostly driven by the survival benefit. The information on extra clinical benefit however was based on an indirect comparison and should be interpreted with caution.

Overall conclusions of the submitted model:

- *The indirect comparison and use of a historical cohort to establish treatment benefits introduces a great uncertainty to results. In addition, utilities were not measured in any of the arms and came from a different study.*
- *Resource utilization was not reported in the studies that provided information on clinical effectiveness (except blinatumomab use) and introduced additional uncertainty. For example, it is unclear how different is the actual average length of hospital stay for blinatumomab compared to recommended (9 days in total) duration. This parameter was uncertain for the standard of care chemotherapy administration arm as well. The EGP tested scenarios with these parameters and provided upper and lower ICER estimates.*

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 for Ph+ ALL. A full assessment of the clinical evidence of blinatumomab for Ph+ 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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