pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Blinatumomab (Blincyto) Acute Lymphoblastic Leukemia – Resubmission

August 31, 2017

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Blincyto® (blinatumomab) for ALL (Resubmission)
Role in Review (Submitter and/or Manufacturer):	Submitter
Organization Providing Feedback	Amgen Canada Inc.

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees _X_ agrees in part ____ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*
Amgen Canada Inc., as the Submitter and Manufacturer of Blincyto:
1) Agrees with the recommendation to reimburse Blincyto in the patient population described.
2) Agrees with pERC recognizing the net clinical benefit of blinatumomab based on statistically significant and clinically meaningful improvement in overall survival (OS) and less deterioration in quality of life (QoL) compared with chemotherapy.
3) Disagrees with the statement about "the high level of uncertainty in the magnitude of long term benefit" and the EGP re-analysis approach of setting OS of blinatumomab and standard of care (SOC) to be equal after 18 months. Amgen further argues that the EGP, in conducting a re-analysis that combines extreme scenarios, has not accounted for all possible outcomes in a fair and balanced manner.
4) Disagrees with the statement about "the incomplete accounting for complex resource intensity of administration". Blinatumomab was compassionately available to appropriate patients since the initial Health Canada approval in 2015 and following the previous pCODR recommendation has been reimbursed by several jurisdictions for several months now. In general, issues pertaining to resource use and adoption feasibility have all been mitigated. Centres have established protocols and processes for blinatumomab administration and have implemented blinatumomab successfully.

Comments:

- By setting the OS of blinatumomab and SOC to be equal after 18 months, the EGP implies that there is no long-term benefit of blinatumomab and that the long-term survival projections are the same for patients treated with SOC and blinatumomab.
- This is in direct contrast to the CGP statement that "The CGP therefore agree that the benefit of blinatumomab is in its ability to allow a greater number of patients to achieve CR and live longer both of which may help get patients to transplant where they may have the potential for a cure."[i]
- In addition, registered clinician input "indicated that [blinatumomab] has shown superiority over a variety of SOC protocols and it is expected more patients will proceed to stem cell transplant due to treatment with blinatumomab."[ii]

- This is also in direct contrast to the EGP assumption for time horizon, where a 10-year time horizon was used. By not allowing any long term benefit beyond 18 months, the 10-year time horizon became a moot point as the model only captured an 18-month time horizon in the analysis.
- Blinatumomab provides a long term survival benefit compared to current SOC options. In the TOWER trial (which was stopped early after meeting its primary efficacy endpoint of OS) blinatumomab was associated with a statistically significant improvement in OS compared to SOC chemotherapy with a hazard ratio (HR) of 0.71 (CI: 0.55 to 0.93)[iii]. This HR for the treatment effect was estimated using the whole OS curves and thus represents the average treatment effect during the full trial observation period.
- Although the Kaplan–Meier (KM) plots diverge in the 3 months after randomisation and separation becomes more pronounced over time, the curves appear to converge at approximately 15 months and start to diverge again at 20 months. However the tail of the KM curves should be interpreted with caution and in the context of the small patient numbers at risk beyond 15 months, the treatment effects seen at the tail of the curve are highly imprecise and unstable and should not be over interpreted. The uncertainty in the tail of the KM curves is also reflected in the wide confidence intervals indicating that limited conclusions can be drawn from month 15 onwards. That no death was observed in the SOC arm between months 12-20 and that the KM curve of the SOC flattens out (while the blinatumomab KM curve continues to decrease) is most likely an artefact due to the extremely small patient numbers and the heavy censoring in the tail of the SOC KM curve.
- It should also be noted that potential confounding effects of allogeneic-stem cell transplantation (allo-SCT) and switching to subsequent therapies during long-term follow-up treatment might have caused the convergence of the KM curves of the groups at around 15 months. The transplantation-censored OS curves for the blinatumomab and SOC arms are shown in Figure 1B of Kantarjian 2017[iii]. Separation was observed at 3 months and the curves didn't converge over the full follow-up time period.
- For patients in long-term follow-up, blinatumomab was used in 5.2% of patients in the SOC arm after protocol-specified treatment was completed (only 1.5% of patients in the blinatumomab arm received blinatumomab after protocol-specified treatment). The mean time to blinatumomab treatment in the SOC arm was 4.3 months. These patients were most likely to remain alive at the tail of the curve and could have contributed to the flat shaped OS curve in the SOC arm.
- The survival analysis conducted for the submission followed the rigorous approach outlined in the CADTH[iv] and NICE[v] guidelines fitting parametric survival curves to the SOC and blinatumomab treatment arms. Parametric curve fitting takes into account that survival data is censored and that the tail of the survival curves is uncertain due to the low number of patients at risk.
- Amgen's choice of a Gompertz model for overall long-term survival projection was based on clinically meaningful parameters (i.e., long-term plausibility) as well as statistical parameters. Information used to inform modeling should be clinically meaningful as well as statistically meaningful. This approach with the Gompertz model was recently accepted by NICE in their assessment of blinatumomab[vi,vii].
- Although Amgen believes that the submitted base case is the most likely scenario, an alternative conservative scenario is presented below, modeling a possible waning of the treatment effect. This analysis, which the EGP can perform by setting cell F24 in "Settings" to a value of 18 (to reflect a maximum duration of benefit of 18 months),

assumes that there is no further treatment effect after 18 months; the weekly hazards in the blinatumomab arm and the SOC arm are assumed to be the same. Although conservative, this is a more realistic and clinically plausible scenario than the one proposed by the EGP which immediately and prematurely truncates survival benefits. The ICER in this scenario would be CAD $96,981/QALY.

- It should further be noted that this resubmission was provided to pCODR in order to expand the reimbursement criteria in adult patients who are refractory or who are in first or later relapse, a population of patients who gain the best outcomes following treatment with blinatumomab (as demonstrated by the TOWER study – see Figure 2A in Kantarjian 2017[iii]). Although the original submission to pCODR for blinatumomab did not have RCT comparative data, there was less uncertainty and a lower ICER with the EGP re-analysis at that time[viii]. However, this resubmission that was based on the TOWER RCT, according to pERC, produced more clinical-effect uncertainty and the EGP re-analysis produced a higher ICER. The logic of this is counter intuitive, especially given the information noted above regarding the small patient numbers and opportunity for patients in the SOC arm to receive blinatumomab at the latter end of the survival curve. Further, in the subgroup which was not eligible for reimbursement following the initial pCODR recommendation, the TOWER first salvage chemotherapy treatment group, clear separation was observed between the blinatumomab and SOC chemotherapy KM curves[ix].
- Finally, the tone of the recommendation suggests that centres in Canada have no experience with blinatumomab, when in fact, the opposite is true. Even prior to reimbursement being in place, many clinical sites gained experience with blinatumomab from Amgen compassionate supply, therefore mitigating these logistical concerns. In the "Resource Use and Adoption Feasibility" section, many of the "incremental costs associated with, but not limited to, purchasing specialized infusion pumps… and treating adverse events" have been addressed with the implementation of reimbursement for blinatumomab in adult patients with Ph- R/R B-precursor ALL and who have had at least two prior lines of systemic therapy[x].

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

____	Support conversion to final recommendation.	_X_	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
p.3	Summary of pERC deliberations	Paragraph 2, lines 7-8: "there is uncertainty as to whether or not blinatumomab provides a long-term OS benefit"	Due to the acute nature of lymphoblastic leukemia, the Manufacturer provided the following information to pCODR: "Clinicians have stated that patients who survive at least two years have higher chances of being long-term survivors and most will be back into the workforce and contributors to society."[xi] Given this information combined with the recommendation by CADTH that "the time horizon should be long enough to capture all potential differences in costs and outcomes associated with the interventions being compared"[iv] and "When modelling chronic conditions, or when the interventions have differential effects on mortality, a lifetime horizon is most appropriate"[xii], the Manufacturer's estimation of long term survival through extrapolation is appropriate and clinically valid.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
p.3	Summary of pERC deliberations	Paragraph 2, Lines 10-11: "pERC acknowledged that QoL data were available only for the first 28 days of treatment"	This is incorrect as the QOL data was reported for the entire follow up period for the TTD analyses. It happened that there were only a few patients left for the chemotherapy arm at the end of month 3 due to relapse/transplant/death. The Submitter believes that the comparative QOL results for BLIN vs. SOC are the most relevant in the first cycle, as many other factors could impact the QOL of patients beyond that including HSCT, relapse, and subsequent treatment.
p.9	Cost-effectiveness estimates: Extrapolation of OS benefit	Paragraph 1, Lines 7-8: "The pCODR Clinical Guidance Panel suggested a 10-year time horizon would be more clinically plausible in this patient population."	Due to the acute nature of lymphoblastic leukemia, the Manufacturer provided the following information to pCODR: "Clinicians have stated that patients who survive at least two years have higher chances of being long-term survivors and most will be back into the workforce and contributors to society."[xiii] Given this information combined with the recommendation by CADTH that "the time horizon should be long enough to capture all potential differences in costs and outcomes associated with the interventions being compared"[iv] and "When modelling chronic conditions, or when the interventions have differential effects on mortality, a lifetime horizon is most appropriate"[xiv], the Manufacturer's estimation of long term survival through extrapolation is appropriate and clinically valid. Finally, the EGP have acknowledged that the model submitted to NICE appears to be nearly identical to the model submitted to pCODR. Amgen can confirm that this is true and that NICE arrived at a different conclusion in their review: "NICE concluded that the company's survival extrapolation was acceptable for decision making".[vii,xv]
p. 9	Cost-effectiveness estimates: Extrapolation of OS benefit	Paragraph 1, Lines 8-11: "The manufacturer also chose a parametric model for	The choice of a parametric distribution should be based on clinically meaningful parameters (i.e., long-term plausibility) in addition to statistical parameters. CADTH states in its guidelines for economic evaluation of health technologies that "In the reference case analysis this would entail

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
		estimating long-term survival based on predictions from a historical cohort. The EGP altered this by using a parametric model that had the best statistical fit to the TOWER study data."	the need for clinically meaningful outcomes to inform the duration and quality of life." And "of critical importance is the degree to which any such simplification may be at odds with the real world, and the implications this may have in terms of producing potentially misleading results"[iv]. Choosing a parametric model based on the best statistical fit to trial data alone is not appropriate given the short duration of the trial and that long-term outcomes for this patient group are available from a historical comparator group of patients with R/R ALL. Information used to inform modeling of survival curves should therefore be both clinically meaningful and have a good statistical fit in line with CADTH guidelines for Economic Evaluations[iv]. As earlier stated by the Submitter "Based on visual inspection of goodness of fit, statistical fit and long-term plausibility informed by the historical comparator data the restricted Gompertz model was selected for modelling OS for all TOWER patients (FAS)." In addition, the EGP have acknowledged that the model submitted to NICE appears to be nearly identical to the model submitted to pCODR, and NICE stated that the overall structure of the model was appropriate. The model submitted to NICE also used the Gompertz distribution for modeling OS for all TOWER patients (FAS).

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.

[i] Blinatumomab (Blincyto) ALL Resubmission – Initial Clinical Guidance Report. p. 7. June 29, 2017
[ii] Blinatumomab (Blincyto) ALL Resubmission – pERC Initial Recommendation, p. 7. June 29, 2017
[iii] Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376:836-47.
[iv] Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar. https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition
[v] NICE Guide to the methods of technology appraisal 2013 (PMG9). https://www.nice.org.uk/process/pmg9/chapter/the-reference-case
[vi] https://www.nice.org.uk/guidance/ta450/documents/final-appraisal-determination-document
[vii] Full technical document of the Blinatumomab (Blincyto) ALL Resubmision – Initial Economic Guidance Report. June 29, 2017.
[viii] Blinatumomab (Blincyto) Acute Lymphoblastic Leukemia – Final Economic Guidance Report. Published April 1, 2016. https://www.cadth.ca/sites/default/files/pcodr/blinatumomab_blincyto_all_fn_egr.pdf
[ix] Amgen data on file. Provided to pCODR on February 24, 2017.
[x] Blinatumomab (Blincyto) ALL. pCODR Expert Review Committee (pERC) Final Recommendation, April 1, 2016.
[xi] Amgen data on file. Provided to pCODR on April 26, 2017
[xii] Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar. https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Section 6. Time Horizon
[xiii] Amgen data on file. Provided to pCODR on April 26, 2017
[xiv] Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa: CADTH; 2017 Mar. https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Section 6. Time Horizon

[xv] NICE Final appraisal determination: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. April 2017. https://www.nice.org.uk/guidance/ta450/documents/final-appraisal-determination-document).