pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review

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

## Blinatumomab (Blincyto) for Acute Lymphoblastic Leukemia

April 1, 2016

**Feedback on pERC Initial Recommendation**

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| Name of the Drug and Indication(s): | Blinatumomab (Blincyto) for the treatment of patients with Philadelphia chromosome negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) |
| Role in Review (Submitter and/or Manufacturer): | Manufacturer |
| Organization Providing Feedback: | Amgen Canada Inc. |

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 ____ agrees in part _X_ 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.

1. Amgen disagrees with the recommendation that blinatumomab should be reserved for patients with Ph- relapsed or refractory B precursor ALL and who have had at least two prior lines of systemic therapy. Amgen believes that blinatumomab fills an unmet medical need for adult patients with Ph-B-precursor relapse or refractory (R/R) ALL.
2. Amgen does not consider the toxicity profile of blinatumomab to be similar to that associated with combination chemotherapy
3. Amgen disagrees with the pCODR assessment that the CR/CRh observed with blinatumomab is similar to current salvage treatments.
4. Amgen disagrees that the 38.5mcg vial size results in significant wastage.
5. Amgen disagrees with the pERCs estimate of 20-83% remission with combination chemotherapy, and believes that the results from the historical comparator study provide the best available reflection of the clinical outcomes among R/R ALL patients that are similar to patients in study MT103-211.
6. On Feb 4, 2016 Amgen announced that a prespecified interim analysis showed that the primary endpoint of improved overall survival was met in the Phase 3 TOWER study, with the independent data monitoring committee recommending that the study be ended early due to blinatumomab efficacy.

   **Amgen requests that the recommendation be revised to state "adult patients with Ph- relapsed or refractory B-precursor ALL and who have had at least one prior line of systemic therapy (i.e., patients who are refractory or patients who are in first or later relapse)"**

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 within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation. Recommendation does not require reconsideration by pERC.

__X__ Do not support conversion to final recommendation. 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?

pERC recommends funding blinatumomab for adult patients with Ph- relapsed or refractory B-precursor ALL and who have had at least two prior lines of systemic therapy. Reference to "prior lines of therapy" is not usual terminology used by ALL treaters and further clarification is required. Amgen suggests the recommendation be revised to "adult patients with Ph- relapsed or refractory B-precursor ALL and who have had at least one prior line of systemic therapy (i.e., patients who are refractory or patients who are in first or later relapse)"

For reasons outlined in section 3.2, Amgen does not feel the recommendation accurately reflects the clinical and economic evidence.

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 |
|---|---|---|---|
| 1 | pERC Recommendation | Paragraph 2, Line 1 | **Amgen believes that blinatumomab meets an unmet medical need for adult patients with Ph- B-precursor relapse/refractory (R/R) ALL.** -the heterogeneous nature of the published data on the |

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| 4 | Summary of pERC Deliberations | (1st reference: "..at least two prior lines…"<br><br>Paragraph 2, line 6 | management of R/R disease, in particular with respect to definitions of types of relapse and types of response, makes direct comparison of these data to the MT103-211 results inappropriate<br>-pERC's estimate of 20-83% success with regimens used for salvage is inaccurate because they do not have a similar prognostic profile as patients enrolled in MT 103-211<br>-blinatumomab demonstrated benefits across all salvage therapy groups, with a suggestion of higher CR rates among patients with fewer salvage therapies[i]<br>-the ability to cure patients with acute ALL diminishes with each round of therapy, due to increasing resistance caused by increased genetic heterogeneity of the leukemia. Median OS is ~6 months for patients in first relapse[ii,iii] and only 3 months for patients in second or greater relapse[iv]. Thus, the best available therapeutic option should be used as early as possible, when the window for potential cure through transplant remains<br>-by limiting blinatumomab to patients with at least 2 prior lines of therapy, patients' chance of a successful HSCT and cure may be lessened due to continued clonal evolution and treatment resistance<br>- In Canada, ALL patients are almost universally treated with pediatric-like protocols (e.g. DFCI) which are more intensive with respect to types of agents and doses administered. There is little desire to repeat chemotherapy in these patients<br>-Among the SAP requests received by Amgen to date, 50% are for patients with only 1 prior line of therapy. The rationale supporting these requests has invariably included description of a) a desire to use blinatumomab in order to spare patients the toxicities associated with chemotherapy; and/or b) the perception that recycling chemotherapy agents on which patients have already progressed through successive salvage regimens is futile; and/or c) the perception that patients would be in a more fit state to receive HSCT in the event of achieving remission than if treated with chemotherapy |
| 5 | Summary of pERC Deliberations | Paragraph 3, line 9<br><br>(1st Reference: "…toxicity profile of blinatumomab and noted it to be similar to combination chemotherapy") | **Amgen does not consider the toxicity profile of blinatumomab to be similar to combination chemotherapy**<br>-combination chemotherapy regimens are often poorly tolerated and may be associated with a range of severe toxicities.<br>-in contrast, blinatumomab is a non-chemotherapeutic, monotherapy treatment whose toxicities can be managed with close monitoring, prophylactic medications, immediate treatment, and dose adjustment or discontinuation<br>-in the adult R/R ALL receiving blinatumomab, 12.0% experienced CRS; <1% experienced ≥ grade 4 events, and 1.8% reported serious CRS events; 4 subjects experienced CRS that led to study treatment |

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| | | | interruption, and only 1 subject experienced CRS that led to permanent treatment discontinuation.<br>-the AEs observed in the TOWER study were consistent with the known safety profile of blinatumomab (see TOWER response below) |
| 7 | Key Efficacy Results | Paragraph 2, line 2<br><br>(1st reference: "…CR/CRh observed with blinatumomab were similar to response rates observed with current treatment options") | **Amgen disagrees with the pCODR assessment that the CR/CRh observed with blinatumomab is similar to current salvage treatments.**<br>-when comparing CR/CRh rates across published studies, it is critical that the study populations are similar, or data from these studies are appropriately subsetted or adjusted for key prognostic factors to make more appropriate and valid comparisons<br>-limitations to using the current literature to compare the results seen with blinatumomab include 1) subgroups may be defined differently across published studies; 2) subgroups are not mutually exclusive (e.g., a patient may be in second relapse and relapsed after HSCT); 3) the risk strata can vary (e.g. patients who relapse after HSCT may be in first, second, or third or later salvage and later salvages may infer more severe disease); and 4) definitions of complete remission may include CR, CRi, and even bone marrow response. In the historical comparator study (study 20120310), prognostic factors were accounted for in the calculation of CR, allowing a more accurate calculation of CR in R/R ALL<br>-several studies present response to salvage therapy in the R/R B-precursor ALL population (i.e., early first relapse, refractory, relapse after HSCT, and second or greater relapse; the same population as in MT103-211)[iv,v,vi,vii,]. The CR rates from these studies ranged from 19.0% to 38.6%<br>-the CRsg results from the historical comparator study provides the best available reflection of the clinical outcomes among R/R ALL patients that are similar to patients in study MT103-211. The sample size was the largest ever assembled in the US or EU, the patient level data reflect results across a number of major academic centers in several different countries, and the statistical methods, weighted and stratified analyses provide optimal data summaries, and sensitivity analyses generated consistent results.<br>- Further, results of a prespecified interim analysis showed that the primary endpoint of improved OS was met in the Phase 3 TOWER study and the study was ended early (see TOWER response below) |
| 2 | Potential Next Steps for Stakeholders | Paragraph 5, line 3<br><br>(1st reference: "pERC expects | **Amgen believes the 38.5mcg vial size is the most appropriate vial size and does not result in significant wastage**<br>-the 38.5 mcg vial size was selected: i) to align with the 28 mcg therapeutic dose, which is the dosage used in all but the first 7 days; ii) 32.5 mcg is required for a 24-hour IV bag of the 28 mcg/day dose that is admixed per the BLINCYTO Product Monograph to account for |

| Page Number | Section Title | Paragraph, Line Number | Comments related to Submitter or Manufacturer-Provided Information |
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| | | there would be considerable wastage…" | the priming volume of the IV line during administration; and iii) to account for residual volume in the vial encountered during admixing.<br>-For the first 7 days, admixing a 96-hour bag, followed by a 48-hour bag for the 9 mcg/day dose as described in BLINCYTO Product Monograph would result in the use of 3 vials, significantly reducing wastage. |
| 7 | Limitations | Paragraph 1, line 15 | **Amgen believes that the results from the historical comparator study provide the best available reflection of the clinical outcomes among R/R ALL patients that are similar to patients in study MT103-211.**<br>-the time period for 20120310 was based on clinical input and it was their opinion that no new treatments or improvements for R/R ALL had emerged since the 1990's.<br>-~ 70% of the patients were treated from the year 2000 and beyond (2000+). For the CRsg analyses, the weighted estimate for all data from 1990-2013 was 0.24 (95% CI, 0.20, 0.27) and when limited to data from 2000+, the weighted CRsg was not significantly different at 0.26 (95% CI, 0.21, 0.31). Thus, there has been no evolution in treatment options for R/R ALL and data from the entire period is relevant to evaluating outcomes with treatments available in 2016.<br>-ad-hoc analyses showed that there was little difference in CR between the two time periods and OS was 3.3 months vs 3.8 months pre- and post-2000 respectively |
| 2 | Potential Next Steps for Stakeholders | Paragraph 4, line 4<br><br>(1st reference: "pERC acknowledged that a phase III study (TOWER)…" | **On Feb 4, 2016 Amgen announced that the results of a prespecified interim analysis showed that the primary endpoint of improved overall survival was met in the Phase 3 TOWER study.**[viii]<br>-the independent data monitoring committee recommended, and Amgen has accepted, that the study end early for efficacy. This is the first study to demonstrate an OS benefit for these patients with an immunotherapy and this result should remove any ambiguity around blinatumomab's clinical benefit over SOC chemotherapy.<br>-Amgen requests that the recommendation be revised to state that the "results of a prespecified interim analysis showed that the primary endpoint of improved overall survival was met in the Phase 3 TOWER study and the study was ended early." |

## 3.3 Additional Comments About the Initial Recommendation Document

None

## 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.*

References

[i] Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *The Lancet Oncology.* 2015;16(1):57-66.
[ii] Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood.* 2007;109(3):944-950.
[iii] Tavernier E, Boiron JM, Huguet F, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia.* 2007;21(9):1907-1914.
[iv] O'Brien S, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. *Cancer.* 2008;113(11):3186-3191.
[v] Gokbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood.* 2012;120(10):2032-2041.
[vi] Kantarjian HM, Thomas D, Ravandi F, et al. Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. *Cancer.* 2010;116(24):5568-5574
[vii] Oriol A, Vives S, Hernandez-Rivas JM, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica. 2010;95(4):589-596.

[viii] News Release. Phase 3 Study of BLINCYTO® (Blinatumomab) Met Primary Endpoint Of Overall Survival In Patients With B-Cell Precursor Acute Lymphoblastic Leukemia. http://wwwext.amgen.com/media/news-releases/2016/02/phase-3-study-of-blincyto-blinatumomab-met-primary-endpoint-of-overall-survival-in-patients-with-bcell-precursor-acute-lymphoblastic-leukemia/