CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Patient Advocacy Group)

Blinatumomab (Blincyto) for Minimal Residual Disease (MRD)-Positive B-Cell Precursor Acute Lymphoblastic Leukemia (BCP ALL)

Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)

October 29, 2020

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Blinatumomab MRD, Pediatric
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical	Patient Group
Organization Providing Feedback	Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees x agrees in part ☐ disagree

We are writing to you today concerning the CADTH/pERC decision on blinatumomab for childhood patients with relapsed and refractory B Lineage Acute Lymphoblastic Leukemia (BCP-ALL) and are minimal residual disease (MRD) positive.

Below is the Patient Input feedback response to points that are presented in the CADTH/pERC decision on blinatumomab. It provides further clinical information about the efficacy of blinatumomab in the pediatric cancer population, how the consideration of blinatumomab for adults and children together creates blanket recommendations that are not effective for children, and how the recommendations of this decision increase current barriers to access for pediatric cancer patients as well as create new ones.

The Children's Oncology Group (COG) AALL1331 clinical trial examined the provision of chemotherapy with or without blinatumomab to patients with relapsed and refractory BCP-ALL prior to possible allogenic hematopoietic stem cell transplant (HSCT). For many children with relapsed BCP-ALL, HSCT is the recommended treatment; however, many patients are unable to proceed to HSCT due to adverse events from chemotherapy or they are unable to achieve MRD negative status, which is known to be associated with optimal HSCT results.

AALL1331 was stopped early due to the effectiveness of the addition of blinatumomab which showed improved disease-free survival, superior overall survival, reduced toxicity and effective MRD clearance. These results established a new standard of care for first relapse/refractory childhood BCP-ALL. Blinatumomab was superior to standard chemotherapy as treatment prior to HSCT, resulting in more patients being able to move on to HSCT – 45% of patients who received standard chemotherapy went on to HSCT while 73% of patients who received blinatumomab were able to proceed to HSCT.[1]

Blinatumomab has established itself as an effective and directive treatment for relapsed and refractory childhood BCP-ALL. Because of this, blinatumomab has been carefully and efficiently moved into frontline clinical trials for newly diagnosed patients with pediatric BCP-ALL through COG. The success of AALL1331 has directly led to the design and opening of a new COG clinical trial, AALL1731, that incorporates blinatumomab into frontline treatment as a risk stratification approach for newly diagnosed B-ALL or B-lympoblastic lymphoma (B-LLy). In AALL1731, children with newly diagnosed standard risk B-ALL or B-LLy are randomized into different arms, with the

[1] https://ashpublications.org/blood/article/134/Supplement_2/LBA-1/428839/A-Randomized-Phase-3-Trial-of-Blinatumomab-Vs

experimental arm of the study introducing two blocks of blinatumomab. Interestingly, this study also examines a therapy reduction for male patients from three years to two years, something which may not have been possible without the incorporation of blinatumomab.

In early 2020, Amgen Canada Inc. submitted blinatumomab to CADTH for consideration through the pCODR process for adult and childhood cancer patients with MRD positive BCP-ALL. In September 2020, pERC provided their initial recommendation on this submission. Unfortunately, the pERC recommendation requires patients to receive "a minimum of three intensive chemotherapy blocks of a treatment regimen that is age-appropriate and given to achieve CR with the best long-term outcome". However, this is not how pediatric patients with relapsed and refractory BCP-ALL are treated. This may be the case for adult patients; however, pERC did not take into account that three intensive chemotherapy blocks of treatment may be inappropriate for the pediatric population. These children have already been heavily pre-treated and this recommendation could result in significant over-treatment for this smaller population. Notwithstanding, this statement of "three intensive chemotherapy blocks" for adults <u>and children</u> illustrates a lack of consideration for the current treatment reality for children with relapsed and refractory BCP-ALL. We would like to recommend that pERC reconsider this for the pediatric population and not require a certain number of chemotherapy blocks prior to treatment with blinatumomab.

In addition, the pERC recommendation states that patients should have MRD positive disease and does not allow for those patients who are able to achieve MRD negative status. Unfortunately, this will create a system of inequality of access to blinatumomab between those patients with MRD negative and positive disease. Due to the findings of AALL1331, blinatumomab plays a critical role in helping patients to become MRD negative and remaining MRD negative. The combination of blinatumomab and chemotherapy as standard of care is critical for navigating more relapsed and refractory childhood BCP-ALL patients to HSCT. As previously stated, MRD negative disease is critical and proven as a condition for optimal HSCT response.

As it stands today, patients with relapsed and refractory BCP-ALL are unable to access blinatumomab unless the drug is purchased at full cost by the hospital. Amgen is unwilling to provide the drug through a compassionate access program due to a conservative and risk-averse interpretation of Canadian regulations. This approach is understandable; however, it is also highly problematic for those children with relapsed and refractory BCP-ALL. This standard of care is almost unobtainable, which is a far different situation to patients in the USA. (It is important to note that Amgen Canada does provide support through their Victory Program; however, this is for patients with limited financial resources and not all patients may qualify for this program.)

As stated in the initial Patient Input Response for blinatumomab that was provided by four different Canadian childhood cancer organizations, families found blinatumomab significantly less challenging than traditional treatments experienced such as chemotherapy. Patients experienced side-effects from blinatumomab; however, these were manageable, transient, and less damaging. All respondents to our survey stated that they had a positive experience while on blinatumomab and that it provided a good impact on their quality of life.

Ali was diagnosed with high-risk ALL in 2012 at 7 years old. Originally from Kuwait, Ali was treated on the European protocol; however, he relapsed right after treatment finished. Ali's family made the courageous decision to come to Canada to pursue treatment for their son. Unfortunately, cytogenetics was not performed on Ali's cancer at diagnosis and when this was done by the Hospital for Sick Children, it was found that Ali's cancer was Philadelphia chromosome positive which meant that he did not receive the proper frontline therapy. SickKids had to re-treat his cancer and Ali experienced many different and serious complications from chemotherapy. Unfortunately, Ali relapsed during maintenance which meant that he could not go onto transplant. To try and get Ali into remission, he was given blinatumomab and everything went smoothly. He was able to achieve remission and go onto transplant in good condition. Ali's Dad, Agha, expressed that blinatumomab was less harmful to his son and he was able to have a more normal life during that treatment. Ali did not have the same side-effects as chemotherapy – there was no pain, nausea, vomiting, hair loss, mood swings and fatigue. He simply took tablets and did not have side-effects. Chemotherapy really impacted Ali's quality of life and the side-effects he experiences today are from the traditional therapies. For example, today Ali can't run or walk long distances because of side-effects from vincristine. Agha said that the trauma of treatment over Ali's six years has left him and his family shattered and they are still coming back together, even after being off treatment now for 2 years. A childhood cancer diagnosis involves the entire family. Agha feels that if Ali had been given this targeted therapy from the very beginning, the family may not have suffered so much. Agha strongly recommends that targeted therapies such as blinatumomab are offered to pediatric cancer patients earlier so that they do not suffer the severe side-effects of traditional treatments such as chemotherapy.

Ethan was diagnosed with BCP-ALL in December 2019 at 16 years old. During his treatment so far, he has experienced different reactions to the various chemotherapy drugs. Methotrexate made him very sick and he ended up in the ICU with a serious case of pancreatitis. With of all of the fluid in his pancreas, he could not continue with standard chemotherapy. Because Ethan needed to carry on with treatment, his care team applied to Amgen Canada's Victory Fund where he was provided with two courses of blinatumomab. Ethan's Mom, Vanesta, said that he was able to eat, which he wasn't able to do in the past. He did not have any nausea and vomiting. Ethan himself said, "it is like a break. Your body is normal, you just carry your bag around. With the other chemos you feel nauseous and you are not your normal self. I could eat whatever I wanted. I just had to be careful with the line and the bag. It was cool. I could eat and sleep."

At first, Abigale could not see colour but this escalated to blurry vision and not being able to see. She then became hysterical and could not be calmed – that was when Staci and her husband took their daughter to the hospital. After a lot of bloodwork and tests, Abi was diagnosed with BCP-ALL in May 2020. Abi's Mom and Dad made the decision to enroll Abi on the COG clinical trial AALL1731 which introduces to rounds of blinatumomab to standard chemotherapy. Before receiving blinatumomab, Abi received a block of chemotherapy called "consolidation". During this time, Staci said that Abi was not herself – she was nauseous, vomiting, and could not eat. She was also not herself, weaker, and often lose her footing causing her to trip. After consolidation, Abi had a tiny amount of minimal residual disease which meant she would receive blinatumomab next (July/August). Abi was the second child at her home hospital to receive blinatumomab and was the first to be able to go home with the pump and not have to be admitted. Even though Abi carried the backpack everywhere, she was full of energy. It didn't stop her from jumping and running everywhere. She also didn't have any nausea or vomiting, which meant that she didn't have any trouble eating. Staci described being on blinatumomab as "smooth sailing".

Blinatumomab has been transformational for childhood cancer patients with BCP-ALL. Relapsed and refractory BCP-ALL patients who were heavily pre-treated have been able to achieve MRD negative status and navigate to HSCT when it wasn't possible with traditional therapies, all because of blinatumomab. For children with relapsed and refractory BCP-ALL, this is now considered standard of care; however, Canadian relapsed and refractory patients are unable to access blinatumomab due to a strict interpretation of the regulations by the pharmaceutical company. Additionally, the guidelines laid out in the September 3rd, 2020 recommendations by pERC place further restrictions on what patients can, and can't, access blinatumomab.

We would like to encourage CADTH/pERC to reconsider the details of their recommendations of blinatumomab for children with relapsed and refractory BCP-ALL. We hope that you would consider the evidence and findings of AALL1331 and remove some of the restrictions that will make it even harder for pediatric patients to access this treatment. We understand that this

request requires CADTH to act in a way that is outside of current processes. We also understand that this is more than what was provided in the initial submission from Amgen Canada. We believe that CADTH has an opportunity to lead in the development of new systems and approval mechanisms to ensure that there is not an unacceptable delay in how Canadian children with relapsed BCP-ALL can access blinatumomab. With this submission, there is a chance to try something different, to consider the implementation of a conditional approval, much like that is done for clinical trials, and to examine the benefits of blinatumomab in a wider context, especially for the pediatric population who are either MRD positive or negative. Blinatumomab is a drug that is changing the stories for children and adolescents with relapsed and refractory BCP-ALL in a positive way. We hope that we can work together to look at this submission with a progressive lens for children who are relapsing with BCP-ALL today, tomorrow and in the very near future. This letter was also reviewed by members of Helena's Hope and Ontario Parents Advocating for Children with Cancer (OPACC).

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ agrees x ☐ agrees in part ☐ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes New Information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

c) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence or provisional algorithm) 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 Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder 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.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder 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 program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, including the provisional algorithm, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	**Section Title**	**Paragraph, Line Number**	**Comments related to Stakeholder Information**