# pCODR EXPERT REVIEW COMMITTEE
## FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

**pERC Final Recommendation**
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

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| **Drug:** Blinatumomab (Blincyto) | |
| **Submitted Reimbursement Request:** Patients with Philadelphia chromosome-negative CD19 positive B-precursor acute lymphoblastic leukemia in first or second hematologic complete remission with minimal residual disease greater than or equal to 0.1% | |
| **Submitted by:** Amgen Canada Inc. | **Manufactured by:** Amgen Canada Inc. |
| **NOC date:** December 19, 2019 | **Submission date:** January 20, 2020 |
| **Initial Recommendation:** September 3, 2020 | **Final Recommendation:** October 29, 2020 |

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| **Approximate per patient drug costs, per month (28 days)** | $2,978 per 38.5 mcg vial<br>At the recommended dose of 28 mcg per day, blinatumomab costs $83,391 per 28 day cycle |

**pERC RECOMMENDATION**

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions**[a]

☐ **Do not reimburse**

[a] If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of blinatumomab for the treatment of Philadelphia chromosome-negative (Ph-), CD19 positive (CD19+), B-cell precursor acute lymphoblastic leukemia (BCP-ALL) adult and pediatric patients who are in first or second hematologic complete remission (CR) and are minimal residual disease positive (MRD+), if the following condition is met:

- Cost-effectiveness being improved to an acceptable level.

Eligible patients include those with good performance status and those in first or second CR with MRD+ disease, defined as MRD detected at a level greater than or equal to 0.1% (i.e., $\geq 10^{-3}$). Patients should have received, over the course of their treatment for BCP-ALL, a minimum of three intensive chemotherapy blocks of a treatment regimen that is age-appropriate and given with curative intent before proceeding to blinatumomab therapy. Treatment should be continued until unacceptable toxicity, hematologic relapse, MRD relapse, treatment with hematopoietic stem cell transplant (HSCT), or up to the completion of four cycles.

pERC made this recommendation because it was satisfied that there may be a net clinical benefit for adult patients based on two single-arm phase II studies of blinatumomab that showed high rates of complete MRD response, and that the quality of life was maintained for patients in the BLAST trial. pERC noted that a significant number of patients were able to proceed to HSCT after achieving MRD negativity, which may improve clinical outcomes for high-risk patients who achieve MRD negativity before HSCT compared to those who are MRD+ prior to HSCT. For pediatric patients, pERC was satisfied that there may be a net clinical benefit based on the requested funding indication and the submitted evidence, which

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| | comprised one unpublished, retrospective, observational study which showed fairly similar rates of MRD response as the adult population. pERC noted that blinatumomab has been studied extensively in the relapsed or refractory (R/R) setting in pediatric patients, and safety data from the R/R setting would be applicable to the indication under review and is generally consistent with the safety data in the adult population.<br><br>pERC agreed that blinatumomab aligns with patients' values of better disease management and maintaining quality of life. pERC noted that the toxicity of blinatumomab in this population was manageable, but not insignificant, in the included trials.<br><br>The committee concluded that, based on the sponsor's economic analysis at the submitted price, blinatumomab is not considered cost-effective for adult patients in first CR compared to the historical comparator. pERC also noted that the cost-effectiveness in pediatric patients and patients in their second CR was highly uncertain as the evidence presented in the economic model was only applicable to adult patients in first CR. Therefore, blinatumomab would require a price reduction to improve the cost-effectiveness to an acceptable level. |
| **POTENTIAL NEXT STEPS FOR STAKEHOLDERS** | **Pricing Arrangements to Improve Cost-Effectiveness**<br>Given pERC was satisfied that blinatumomab may have a net clinical benefit in adult and pediatric patients with Ph−, CD19+, BCP-ALL who are in their first or second hematologic CR and are MRD+, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of blinatumomab to an acceptable level. pERC noted the cost of blinatumomab was a key driver of the incremental cost-effectiveness estimates. Therefore, to offset substantial uncertainty in the clinical effect estimates, pERC concluded that a considerable reduction in drug price would be required in order to improve cost-effectiveness to an acceptable level.<br><br>**Collecting Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and the Cost-Effectiveness of Blinatumomab in Pediatric Patients**<br>pERC noted that the economic model submitted did not adequately address the pediatric population. CADTH requested a revised economic model for the pediatric population during the review, however the sponsor did not submit one. Given the uncertainty in the magnitude of clinical benefit of blinatumomab in pediatric patients with Ph-, CD19+, BCP-ALL who have achieved first or second hematologic CR and are MRD+ based on the submitted evidence, pERC concluded that additional prospective evidence should be collected to decrease the uncertainty in the clinical efficacy and safety, and to provide a greater understanding of the cost-effectiveness in pediatric patients. pERC noted that, when such prospectively collected data become available, jurisdictions will need to review these new data.<br><br>**Consideration of Additional Populations — Pediatric Patients with High-Risk First Relapse of BCP-ALL who are Minimal Residual Disease Negative (MRD-)**<br>pERC acknowledged that there is a significant unmet need for high-risk BCP-ALL pediatric patients in first relapse who are MRD−. pERC discussed emerging evidence from the COG AALL1331 trial and input from clinicians and patient groups; however, this patient population was not included in the funding request submitted by the sponsor. pERC could not deliberate on data for the COG AALL1331 trial, given that the trial population was beyond the funding request and indication under review, and because only |

early results have been published and it was not submitted by the sponsor or systematically reviewed.

**Access to Expertise in Managing Side Effects**
pERC noted that some of the potential neurological side effects of blinatumomab are severe, have life-threatening consequences, and require the expertise of hematologists experienced in dealing with these side effects. Therefore, pERC strongly supports restricting administration of blinatumomab to treatment centres that have the expertise to monitor and manage these potential side effects.

**Resource Use and Adoption Feasibility**
pERC noted that the preparation, administration, and management of blinatumomab is resource intensive. Therefore, pERC noted that jurisdictions will need to consider the incremental costs associated with, but not limited to, purchasing specialized infusion pumps, training pharmacy and nursing staff, coordinating outpatient and hospital resources, and monitoring and treating adverse events, all of which may require significant expenditures in human resources.

**Wastage and Budget Impact Likely to Affect Adoption Feasibility**
pERC noted that drug wastage may be a significant issue, given there is only one vial size for blinatumomab, and smaller doses are required for pediatric patients who weigh less than 45 kg. Additionally, there may be significant wastage due to insufficient stabilizer available to maximize the use of blinatumomab vials, and vial sharing is unlikely. pERC noted that 5.5 mL of stabilizer is required to prepare each infusion bag and there is only 10 mL of stabilizer included with each package of blinatumomab. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package. pERC agreed jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation; this may include advocating for the availability of a smaller vial size, or that stabilizer should be made available separately from the package of blinatumomab vial. Alternatively, a larger volume of stabilizer could be made available by the manufacturer to facilitate the preparation of more than one infusion bag per vial of drug.

**Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

# SUMMARY OF pERC DELIBERATIONS

ALL is a highly aggressive hematological malignancy and is the most common cancer diagnosis in children and adolescents. Mortality rates from ALL are lowest in children younger than 15, and increases with age, particularly for adults over 40. Five-year overall survival (OS) rates range between 67% and 78% in adolescents and young adults; however, among older adults, five-year OS is less favourable at around 54%. Prognosis is influenced by several factors including the patient's age, the level of white blood cell count at diagnosis, immunophenotype, and specific chromosomal abnormalities. pERC acknowledged one of the most important and independent prognostic factors predictive of relapse is MRD positivity after achieving morphological CR, which occurs in approximately one-third of patients who achieve CR. pERC noted the 10-year event-free survival of patients who are MRD- is 64% compared to 21% in patients who are MRD+ (hazard ratio [HR] = 0.28), and patients who have MRD negativity have improved OS compared to those who do not (HR = 0.28).

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

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| **CLINICAL BENEFIT** | **PATIENT-BASED VALUES** |
| **ECONOMIC EVALUATION** | **ADOPTION FEASIBILITY** |

Current treatment options for patients with Ph-, CD19+, BCP-ALL include induction therapy for one to two months, consolidation/intensification therapy for six to eight months, followed by maintenance treatment for 24 to 30 months. pERC discussed that treatment options for patients with MRD+ disease following intensive chemotherapy may include allogeneic hematopoietic stem cell transplants (HSCTs), if eligible, or observation. pERC noted that outcomes for patients with MRD+ disease before transplant are inferior to those patients who are MRD-, and therefore, there is a need for novel therapies to achieve MRD negativity. pERC further noted that blinatumomab has been previously reviewed and recommended by pERC for the treatment of adult and pediatric patients with Ph-, BCP-ALL with R/R disease. The use of blinatumomab for patients with Ph-, CD19+, BCP-ALL in first or second CR with MRD+ disease is a new indication.

pERC deliberated on two, single-arm, open-label, phase II trials (BLAST and MT-103-202) that assessed the efficacy and safety of blinatumomab in adult patients with BCP-ALL who were in any CR and were MRD+ (defined as MRD detected at a level greater than or equal to 0.1%). pERC additionally deliberated on the Neuf study, which was an unpublished, observational, retrospective cohort study that explored the effectiveness of blinatumomab in BCP-ALL adult and pediatric patients, with a focus on the MRD+ patient population that was included as a subgroup in the study. pERC discussed the primary end points of the BLAST and MT103-202 trials, complete MRD response rate after one cycle of blinatumomab and complete MRD response rate after four cycles of blinatumomab, respectively. pERC discussed the secondary end point of the Neuf study, which was MRD response rate after two cycles. pERC agreed that all three studies showed high MRD response rates for the adult population, and blinatumomab represented an effective bridge to HSCT as almost half of patients in the BLAST trial and one-third of patients in the MT103-202 trial were able to proceed to HSCT after achievement of MRD negativity. pERC discussed the registered clinician input, specifically the strong support expressed by clinicians for the use of blinatumomab as a bridge to transplant as HSCT is still considered an important part of the treatment strategy to cure this particular disease. pERC acknowledged that although MRD response rate is not a validated surrogate outcome for established efficacy end points (i.e., relapse-free survival [RFS] or OS), pERC believed it was reasonable to use MRD response as a measure for improved outcomes, given the strong prognostic significance of achieving MRD negativity and high transplant rates in the patient population under review. pERC also discussed the difficulties in interpreting secondary end points such as RFS and OS in the absence of a direct comparator, as well as the high degree of censoring for HSCT, which introduced uncertainty in the magnitude of the clinical benefit.

pERC further discussed the pediatric population, where evidence on the effectiveness of blinatumomab was limited to the Neuf study results submitted by the sponsor. pERC noted the MRD response rate reported for children was slightly lower than what was reported for the adult population. pERC acknowledged there were significant limitations to the Neuf study due to the observational nature, and

that the lower response rate may have been reflective of the heterogeneity of the patient population and small sample size. pERC agreed that there is a significant unmet need in the pediatric population, and discussed the supplemental pediatric data summarized in section 8 of the Clinical Guidance Report. pERC briefly discussed the randomized phase III, COG-AALL1331 trial, which showed early results of high rates of MRD clearance in R/R pediatric patients treated with blinatumomab compared to intensive chemotherapy following one standard block of reinduction chemotherapy. It was also noted from the MT103-205 trial, more than half of R/R patients who achieved CR with blinatumomab treatment, achieved MRD negativity. pERC agreed with the registered clinicians who believed this evidence from the R/R setting would support the use of blinatumomab in patients in CR with MRD+ disease, and that the results from the adult population would be applicable to the pediatric population. pERC noted that a significant proportion of pediatric patients in the Neuf study proceeded to allogeneic HSCT and agreed that blinatumomab would be particularly useful in pediatric patients as part of a curative strategy to bridge pediatric patients to transplant. pERC concluded that while uncertainties exist in the magnitude and extent of clinical benefit in terms of efficacy outcomes such as RFS and OS, blinatumomab demonstrated high MRD response rates and high transplantation rates, which are important factors to improve prognosis in both adult and pediatric patient populations.

Additionally, pERC deliberated on the safety of blinatumomab and noted that all patients experienced side effects. The pooled safety analysis from the BLAST and MT103-202 trials showed that common adverse events (AEs) of any grade among adult patients were fever, headache, tremor, chills, fatigue, nausea, and vomiting; and common grade greater than or equal to three AEs included neutropenia and leukopenia. pERC discussed neurotoxicities and cytokine release syndrome (CRS), which were considered manageable when blinatumomab is administered in an appropriate clinical care setting. pERC noted that most neurologic side effects resolved in patients. Safety data for the pediatric population was limited to supplemental data and experience from the R/R setting. Data from MT103-205, a single-arm, international, phase I/II trial investigating blinatumomab treatment in pediatric and young adult patients with R/R BCP-ALL, indicated that side effects in children were comparable to the adult population, although higher rates of anemia were noted. Overall, pERC considered the side effects of blinatumomab to be manageable and recognized that most centres have experience with blinatumomab for both adult and pediatric patients from the R/R setting and, thus, toxicities are known and can be managed.

In the absence of direct comparative evidence, the sponsor submitted an indirect treatment comparison (ITC) using a propensity score analysis comparing blinatumomab using data from the BLAST trial to a historical comparator study (i.e., patients who did not receive blinatumomab), which was deliberated by pERC. Only adult patients in their first CR with MRD detected at a level of 0.1% or higher were included in the comparison. pERC noted there was a significant reduction in the risk of relapse or death with blinatumomab compared to the historical comparator, and OS also favoured blinatumomab. pERC discussed the limitations of the submitted ITC, including the timeline of the historical comparator and noted that many patients were treated in the early 2000s and, thus, data may not be clinically relevant or completely applicable to current clinical practice. pERC also discussed that the historical comparator study was a retrospective, observational study, which is subject to biases and there may be unmeasured confounders that cannot be accounted for in the analysis. pERC agreed that these limitations introduced uncertainty to the magnitude of the clinical benefit reported in the ITC, but the ITC results suggested there may be improved RFS and OS associated with blinatumomab compared to not treating patients with blinatumomab.

pERC concluded that there may be a net clinical benefit of blinatumomab in Ph-, CD19+, BCP-ALL adult and pediatric patients in first or second hematological CR who are MRD+, defined as MRD detected at a level of 0.1% or higher. pERC came to this conclusion based on high MRD conversion rates in adult and pediatric patients, high transplant rates in the adult population, and manageable side effects.

pERC deliberated on one patient submission made on behalf of four patient advocacy groups: Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Leukemia and Lymphoma Society of Canada (LLSC), Ontario Parents Advocating for Children with Cancer (OPACC), and Helena's Hope. This submission focused on pediatric patients and no patient input representing the adult patient population was received. pERC discussed the significant toxicities associated with intensive chemotherapy, which were reported to greatly reduce quality of life (QoL) for pediatric patients. Further, the submission noted there were limited treatment options for pediatric patients, with blinatumomab being the only alternative to the more toxic chemotherapy option with extensive short- and long-term side effects. Patients with experience with blinatumomab indicated positive experiences in terms of better disease management and improved QoL. pERC also discussed health-related quality of life (HRQoL) data that was collected in the

BLAST trial, which indicated no detriment to QoL in the adult patient population. pERC noted that the toxicity profile of blinatumomab is manageable, but not insignificant. Thus, pERC agreed that blinatumomab aligns with patient values of providing better disease management and maintaining QoL.

pERC deliberated on the cost-effectiveness of blinatumomab versus standard of care (SOC). pERC noted there was significant uncertainty with the data that was used in the economic analysis given that efficacy of SOC was based on a historical comparison that included data that was up to 20 years old. pERC concluded that blinatumomab was not cost-effective at the submitted price versus SOC and that a reduction in drug price would be required to improve cost-effectiveness to an acceptable level. pERC noted the evidence presented was only applicable to adults in first hematologic CR and therefore the cost-effectiveness in pediatric patients, as well as those in second hematologic CR was highly uncertain. Uncertainty regarding cost-effectiveness in pediatric patients could be reduced by an economic evaluation that utilized available pediatric data.

pERC also discussed the budget impact analysis (BIA) and noted that factors that most influenced the estimated budget impact were the drug acquisition costs, the eligible patient population, post-relapse drug costs, and the market share. pERC noted there was considerable uncertainty regarding post-relapse drug costs due to the survival data used to inform the proportion of patients who relapsed after one year. Likewise, pERC noted there was potential for blinatumomab to take a larger market share which would further increase the budget impact, as estimated in an Economic Guidance Panel (EGP) reanalysis. MRD testing costs were not included in the BIA and were included in an EGP reanalysis. The impact of including fees for MRD diagnostics contributed to 0.4% of the budget impact. Based on this, pERC felt the sponsor's BIA estimate was likely an underestimate and that the true estimate would fall closer to the EGP base case. Jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability.

Finally, pERC deliberated on the input from PAG regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

Upon reconsideration of the Initial Recommendation, pERC reviewed the feedback received from all stakeholder groups and focused its deliberation on the feedback received from the registered clinicians, the patient group (joint submission that included feedback from Advocacy for Canadian Childhood Oncology Research Network [Ac2orn], Ontario Parents Advocating for Children with Cancer [OPACC], and Helena's Hope), and PAG. All three stakeholder groups agreed only in part with the recommendation and did not support early conversion of the Initial Recommendation to Final Recommendation. The clinician group and patient group had similar concerns regarding the recommendation requirement of a minimum of three intensive chemotherapy blocks to achieve CR in the setting of first relapse for pediatric patients. Both groups mentioned the COG AALL1331 trial, from which early results showed compelling evidence that earlier use of blinatumomab in the setting of first relapse showed superior efficacy and reduced toxicity in the pediatric patient population. Both groups agreed that it was unacceptable to subject patients to unnecessary toxicity by administering three blocks of intensive cytotoxic therapy before administration of blinatumomab for patients in first relapse when there is strong evidence to support earlier use of blinatumomab. Both the clinician and patient feedback noted that all pediatric patients will have received three cycles of cytotoxic therapy to achieve first complete remission, and the first reinduction block in first relapse to achieve second CR would be a fourth block of therapy. Further, the Clinical Guidance Panel (CGP) clarified that for both adult and pediatric patients in first relapse, response is assessed after one block of reinduction therapy. Patients who achieve CR at that time would then be tested for MRD and administered blinatumomab if eligible. pERC agreed that patients should have received a minimum of three blocks of intensive therapy over the course of their disease and treatment, which would include the number of chemotherapy blocks that were administered to achieve first CR when considering patients in second CR.

Furthermore, both the patient and clinician group feedback highlighted that the COG AALL1331 trial provided strong evidence for the use of blinatumomab after one standard reinduction chemotherapy block for patients irrespective of MRD status (i.e., patients who are MRD+ and MRD-). Both groups noted that pediatric patients in first relapse who have high-risk BCP-ALL that achieve MRD clearance post-reinduction would also derive significant clinical benefit and would experience less toxicity from blinatumomab treatment based on the interim results of the COG AALL1331 trial. By not providing funding access, the clinician and patient groups believed it was inequitable and this small patient group of BCP-ALL patients

in second CR who are MRD- following one block of reinduction therapy represent a significant unmet need with the current recommendation. pERC agreed with the patient and clinician groups that this group of patients represented a significant unmet need, and that pediatric patients are often excluded from oncology clinical trials and regulatory/health technology assessment submissions. pERC acknowledged that this patient population was beyond the funding request and indication under review, and while the COG AALL1331 trial was included in supplementary information, it was an abstract that only included early results and it was not critically appraised, or reviewed according to pCODR procedures. Thus, pERC struggled to balance ethical considerations, patient values, unmet need, and the possibility the sponsor may not submit a funding request for this small patient population with the early results available from the COG AALL1331 trial. pERC concluded that in the absence of a funding request and formal review of the evidence, pERC could not make a recommendation for the broader pediatric population despite the significant unmet need.

Additionally, PAG recognized the large amount of clinician input received for this submission and the uncertainty in the clinical evidence for pediatric patients, and requested a summary of additional information on how pediatric patients would be treated from the clinician perspective in the Evidence in Brief section, which has been included. PAG sought clarification if there would be a preference for polymerase chain reaction (PCR) or flow cytometry for MRD testing. The CGP clarified that PCR is a more sensitive test; however, both tests can detect the minimum threshold requirement or MRD for blinatumomab eligibility. Both tests are considered acceptable to test for MRD.

# EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- a joint input on blinatumomab focused on the pediatric population from four patient advocacy groups (Ac2orn, LLSC, OPACC, and Helena's Hope)
- input from registered clinicians: (one group input on behalf of the Pediatric Oncology Group of Ontario [POGO], and eight individual clinician input by oncologists from Ontario [four clinicians], Alberta [two clinicians], British Columbia [one clinician], and Nova Scotia [one clinician])
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one joint input from three patient advocacy groups: Ac2orn, OPACC, and Helena's Hope
- one clinician group, POGO; and one individual clinician
- PAG
- the sponsor, Amgen Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of blinatumomab for the treatment of Ph-, CD19+, BCP-ALL adult and pediatric patients who are in first or second hematologic CR and are MRD+ conditional on cost-effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the sponsor and one individual registered clinician's input agreed with the Initial Recommendation and supported its early conversion to a Final Recommendation, while one registered clinician group (POGO), PAG, and input from a joint patient advocacy group (on behalf of Ac2orn, OPACC, and Helena's Hope) agreed in part with the Initial Recommendation and did not support early conversion. The joint patient advocacy group and the registered clinician group, POGO, cited concerns related to the requirement for three intensive chemotherapy blocks to achieve CR in the first relapse setting for pediatric patients, given that emerging evidence suggests earlier use of blinatumomab can avoid unnecessary toxicity and improve clinical outcomes. The joint patient advocacy group and registered clinician group also identified the need to expand the patient population regardless of MRD status. PAG had concerns about the lower level of evidence used in the recommendation for pediatric patients, and was seeking clarification on additional clinical perspectives on how to treat pediatric patients, as well as preferred testing methods for MRD.

## OVERALL CLINICAL BENEFIT

### pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of blinatumomab for the treatment of patients with Ph-, CD19+, BCP-ALL, who are in first or second hematologic complete remission (CR) with MRD greater than or equal to 0.1%.

### Studies included: Two non-randomized single-arm, phase II trials; one retrospective observational cohort study

The pCODR systematic review included two non-randomized, single-arm, phase II trials (the MT103-203 [BLAST] and MT103-202 trials), and one unpublished, observational, retrospective cohort study (the Neuf study) provided by the sponsor.

The BLAST trial was an international, open-label, single-arm, multi-centre, phase II study of blinatumomab for adult patients with MRD+ BCP-ALL. Patients were treated with blinatumomab administered through IV infusion at a dose of 15 mcg/$m^2$/day at a constant flow rate over four weeks, followed by an infusion-free interval of two weeks. Each cycle was six weeks, and patients could be

treated for up to four cycles. Corticosteroid pre-treatment for prophylaxis of neurologic events and cytokine release syndrome was required. Patients could undergo allogeneic HSCT any time after cycle 1.

MT103-202 was an exploratory, proof-of-concept, open-label, multi-centre, single-arm, phase II study to investigate the efficacy of blinatumomab in adult patients with MRD+, BCP-ALL. Patients were treated with 15 mcg/$m^2$/day continuous IV infusion at a constant flow rate over weeks, followed by an infusion-free interval of two weeks. Each cycle was six weeks, and patients could be treated for up to 10 cycles.

The Neuf study was a retrospective, observational cohort study of adult and pediatric patients with BCP-ALL who received blinatumomab through expanded access programs in Europe and Russia between January 1, 2014 and June 30, 2017. The study included patients with MRD+ and R/R disease, as well as Ph+ and Ph- disease. Only a description of the study and results as relevant to the indication under review (MRD+, Ph-, BCP-ALL) are discussed.

### Patient populations: Adults and pediatric patients with CD19+, BCP-ALL in any CR who are MRD+ (defined as MRD greater than or equal to 0.1%)

Key eligibility criteria in the BLAST trial included age greater than or equal to 18 years, in CR defined as less than 5% blasts in the bone marrow after a minimum of three intensive chemotherapy blocks, an Eastern Oncology Group Performance Status (ECOG PS) of 0 or 1, and an MRD at a level of great than or equal to $10^{-3}$ (i.e., molecular failure or molecular relapse) using an assay with a minimum sensitivity of $10^{-4}$. Patients with Ph- or Ph-positive (Ph+) disease were included. Patients with prior HSCT were excluded. A total of 116 patients were enrolled, and 59% were male, 88% were white, and the median age was 45.0 years. Overall, 65% of patients were in first CR (CR1), and 35% were in second CR (CR2) or third CR (CR3). Most patients were either standard risk (53%) based on local/national standards or high risk (31%). Only five patients were Ph+. The median time from last anti-leukemic treatment to initiation of blinatumomab was 2.0 months, ranging from 0 to 55 months. A total of 44 (37.9%) patients had the German multicenter ALL (GMALL) treatment protocol as a prior therapy.

A total of 21 patients were enrolled in the MT103-202 trial. Eligibility criteria included age greater than or equal to 18 years with an MRD level greater than or equal to $10^{-4}$ or breakpoint cluster region/c-Abelson (BCR/ABL) and/or t (4;11) translocation at any detection level, and in hematologic CR with molecular failure or relapse. A total of 57% were female, all patients were white, and the median age was 47 years. Almost all patients in MT103-202 were in CR1 (95%). Only five patients were Ph+.

A total of 83 adults and 39 pediatric patients were included in the Neuf study. Patients were eligible if their medical charts were available for data extraction and if they had not received blinatumomab through another expanded access program for patients with R/R BCP-ALL called RIALTO. A total of 47% of patients were female, and the median age of adults at time of blinatumomab initiation was 35. Most adult patients (78.3%) were in CR with full hematologic recovery at the time of blinatumomab initiation and a total of 10.8% had HSCT before starting blinatumomab therapy. Among pediatric patients, 41% were female, and the median age was 8.0 years old, with just over half of patients falling into the children category (age 2 to 11). Of the pediatric patients, 82.1% had molecular failure and 17.9% had molecular relapse. Most pediatric patients were in CR with full hematological recovery (87.2%) at the time of blinatumomab initiation and a total of 20.5% of patients had HSCT before blinatumomab initiation.

### Key efficacy results: High MRD response and transplantation rates; ITC results suggesting clinical benefit

The key efficacy outcome deliberated by pERC was MRD response rate from each of the three trials. Additional outcomes explored in each of the trials are also summarized below.

The primary end point of the BLAST study was complete MRD response rate, defined as the proportion of patients who achieved MRD response (a complete MRD response or detectable MRD < $10^{-4}$) after one cycle of treatment with blinatumomab. A complete MRD response rate was achieved in 87 out of 113 patients in the primary efficacy data set (MRD response rate = 77%; 95% CI, 68 to 84) within one cycle of treatment. This was considered to be clinically meaningful and statistically significant, as the lower limit of the 95% CI exceeded the pre-specified null hypothesis threshold of 44%. Secondary outcomes include RFS, OS, duration of MRD response, and time to hematologic relapse (TTHR). At the time of final analysis the median RFS was 19.4 months (95% CI, 12.3 to 27.3) in patients who were not censored at time of HSCT or post-blinatumomab therapy; whereas median RFS was 27.3 months (95% CI, 6.3, to not estimable [NE]) in

patients who were censored at HSCT or post-blinatumomab therapy. pERC noted the proportion of patients censored for HSCT or post-blinatumomab therapy before an event was high, which limited interpretation of the analyses where this censoring rule was applied. At the time of the final analysis without censoring patients for HSCT or post-blinatumomab therapy, the median OS was 33.7 months (95% CI, 19.7 to NE), the median duration of MRD response was 17.9 months (95% CI, 13.3 to 23.2), and the median TTHR in was 27.3 months (95% CI, 7.1 to NE).

In the MT103-202 trial, the primary end point was MRD response rate, which was defined as the incidence of MRD negativity within four cycles of treatment with blinatumomab. The MRD response rate was 80% (16 out of 20 evaluable patients; 95% CI, 56.3 to 94.3), which met the pre-specified primary end point for statistical significance. All 16 patients achieved MRD response after the first cycle of blinatumomab. Secondary outcomes included RFS, time to MRD progression, and median duration of MRD response. The median RFS had not been reached (95% CI, 12.4 to NE) after a median follow-up of 50.8 months (> 4 years). A total of seven (35%) patients had MRD progression, and the median time to MRD progression was 7.2 months (95% CI, 3.3 to NE). Among patients who had an MRD response, the median duration of MRD response was 13.0 month (95% CI, 2.8 to NE).

In the Neuf study, the primary end point was to descriptively characterize clinical and treatment characteristics. The secondary outcomes included complete MRD response after two cycles, with an additional analysis of MRD response after one cycle. Other secondary outcomes included disease-free survival (DFS), which was considered equivalent to the definition of RFS in the BLAST and MT103-202 trials, and OS. In the adult population, a total of 51 patients had evaluable response for cycle 1; of those, 47 patients achieved a complete MRD response (MRD response rate = 92%; 95% CI, 71 to 88). A total of 64 patients had evaluable MRD assessment data for two cycles of treatment, and the MRD response was 89% (95% CI, 79 to 96). DFS in the adult population was highly consistent with RFS in the BLAST trial. In the pediatric population, a total of 27 patients had evaluable MRD data for cycle 1; of those, 18 patients achieved a complete MRD response (MRD response rate = 67%; 95% CI, 46 to 84). A total of 32 patients had evaluable MRD assessment data for two cycles, and of those, 71.9% (95% CI, 5.3 to 86.3) had a MRD response. In the pediatric population, based on a median follow-up of 12.4 months, the median DFS was 13.6 months (95% CI, 7.3 to NE) without censoring for HSCT. In both the adult and the pediatric population, the median OS had not been reached by the end of observational study period.

pERC also discussed the proportion of patients who proceeded to HSCT following blinatumomab treatment, as HSCT is considered an important part of the treatment strategy for patients at high risk to achieve improved long-term outcomes. In the BLAST trial, 77.6% of patients had HSCT, with 49.1% that achieved MRD negativity before HSCT, 16.3% that had persistent MRD positivity after blinatumomab treatment and before HSCT, and 12.1% who experience hematologic relapse before HSCT. In MT103-202, 42.9% of patients received HSCT after blinatumomab, and 33.3% achieved MRD negativity before transplant. In the Neuf study, 72% of pediatric patients proceeded to HSCT, although confirmation of achievement of MRD negativity before transplant cannot be ascertained due the observational nature of the study.

pERC noted that the interpretation of outcomes such as RFS and OS were limited in the absence of direct comparative evidence, and deliberated on the sponsor-submitted ITC that used a propensity score analysis to compare the efficacy of blinatumomab, from the BLAST trial, with no blinatumomab from a historical comparator study. Based on the results of the average treatment effect of the treated (ATT) approach, patients treated with blinatumomab had a 56% reduction in the risk of relapse or death compared to patients in the historical comparator who were not treated with blinatumomab (HR = 0.44; 95% CI, 0.31 to 0.62), with a median RFS of 28.1 months in the blinatumomab arm compared to 6.9 months in the historical comparator. Similarly, the OS results also favoured blinatumomab, with a 37% reduction in the risk of death (HR = 0.63; 95% CI, 0.43 to 0.93) compared to the historical comparator with a median OS of 42.9 months compared to 19.6 months in the historical comparator. pERC noted a number of limitations including the time period of the historical comparator study, as many patients were treated in the early 2000s and, thus, data may not be clinically relevant to patients who are treated in current clinical practice. pERC also discussed that the historical comparator study was a retrospective, observational study, which is subject to biases and there may be unmeasured confounders that cannot be accounted for in the analysis. pERC agreed that the limitations introduced uncertainty to the magnitude of the clinical benefit reported in the ITC, but the ITC results suggested that there may be improved RFS and OS associated with blinatumomab compared to not treating patients with blinatumomab.

### Patient-reported outcomes: QoL was maintained

There was variation in available data at various timepoints from baseline for HRQoL in the BLAST study, as patients were treated with one to four cycles of treatment before entering efficacy follow-up. The mean change from baseline to the end of the core study was minimal for global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning scales, as well as single-item symptom scales (fatigue, nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). There was an improvement of 14.9 points in social functioning. Since only 14 patients or fewer (≤ 12%) completed the EQ-5D at the first follow-up visit and beyond, the interpretation of any clinically relevant changes in HRQoL on the EQ-5D domains is inconclusive. HRQoL data were not collected in the MT103-202 trial and in the Neuf study.

### Limitations: Lack of comparative data; biases related to the study design; limited pediatric patient data; MRD response rate as an efficacy end point; statistical analyses; and contribution to the uncertainty in the reported results

All three studies lacked comparative data as both the BLAST and MT103-202 trials were single-arm studies, and the Neuf study was an observational study. The sponsor submitted an ITC that was subject to a number of limitations and, therefore, firm conclusions on the magnitude of the clinical benefit could not be made. The open-label study design of the BLAST and MT103-202 trials may have introduced patient selection bias, performance bias, reporting bias and detection bias, which all contributed to the uncertainty in the results.

Submitted pediatric data were limited to the Neuf study, which only included effectiveness data for a small sample of patients. There was uncertainty about the completeness, reliability, validity and quality of the data. In addition, due to the observational and retrospective nature of the study, the patient population could be considered quite heterogenous and, thus, introducing uncertainty to the reported results. There was no safety data specific to the indication under review for pediatric patients, and thus, supplemental data were considered. pERC also discussed the applicability of the results of the adult population from the BLAST and MT103-202 trials to the pediatric populations.

pERC discussed the limited evidence to suggest MRD response rate is a surrogate end point for the established end points such as OS and RFS in patients with ALL. While MRD positivity at the end of induction therapy is a prognostic indicator for the risk of relapse, whether the introduction of therapies to induce MRD negativity translates directly into clinical benefit (i.e., correlation with established end points) is yet to be established; thus, this contributes to uncertainty around the efficacy of blinatumomab.

pERC further noted limitations related to the statistical analyses of the BLAST trial, which included the use of different analysis sets instead of using the full analysis set, which would be closest to an intention-to-treat population in a single-arm trial. RFS was calculated from the time of blinatumomab initiation, instead of from the time for achievement of CR, until the date of relapse event, and time from last anti-leukemic treatment varied from one month to 4.5 years. Patients with a longer time in CR may have inflated RFS benefit as they would have a favourable prognosis. Results with censoring for HSCT or post-blinatumomab therapy were limited by the high proportion of censoring, and thus there was uncertainty in the reported results using this censoring rule.

### Safety: Manageable, but not insignificant, toxicities

A safety analysis was performed on pooled data (N = 137) from all patients who received any infusion of blinatumomab in the BLAST (n = 116) or MT103-202 trials (n = 21). All patients experienced an any-grade AE, of which 97.1% were considered treatment-related. A total of 64.2% of patients experienced grade ≥ 3 AEs. The most common any-grade AEs were pyrexia (90.5%), headache (39.4%), and tremor (29.2%). The most common grade ≥ 3 AEs were neutropenia (13.1%), leukopenia (7.3%), lymphopenia (6.6%), pyrexia (6.6%), alanine aminotransferase (ALT) increased (5.1%), and thrombocytopenia (4.4%). Serious adverse events (SAEs) occurred in 83 (60.6%) patients. SAEs included pyrexia (12.4%) and tremor (5.8%). AEs of clinical interest included neurologic AEs that were experienced by 71.5% of patients, 22.6% were considered serious, and 16.1% were grade greater than or equal to three. Most neurologic events resolved. A total of 2.9% of patients experienced CRS), with two patients that experienced grade 3 CRS, and no

grade 4 or 5 CRS events. A total of 16.6% of patients discontinued treatment permanently with blinatumomab due to AEs. The most frequently reported AEs leading to treatment discontinuation were nervous system disorders (9.5%). A total of two (1.5%) fatal AEs occurred.

### Need and burden of illness: Need for treatment options for MRD+ patients

ALL is an uncommon disease in Canada which significantly hampers the ability to perform well-powered randomized controlled trial of new therapeutic approaches. Practitioners are reliant on phase II studies such as the BLAST trial to provide information on novel treatment strategies, especially in the setting of resistant ALL, where randomized comparisons are difficult or impractical to perform. Approximately one-third of patients with BCP-ALL in CR will have evidence of MRD despite the use of aggressive induction and therapy intensification strategies. The presence of MRD is widely considered as one of the most important and independent prognostic predictors of subsequent relapse. These patients are at a very high risk of relapse or progression despite the use of additional systemic chemotherapy. Current treatment options may include HSCT or observation; however, patients who are MRD+ before HSCT have inferior outcomes to patients who are MRD- before HSCT.

pERC noted blinatumomab has been previously reviewed and recommended for the treatment of R/R patients with Ph-, BCP-ALL, and thus clinical care centres are familiar with this drug. In the setting of MRD+ disease following the achievement of CR with standard chemotherapy, blinatumomab may be effective in producing molecular CR for a high-risk group of patients.

### Registered clinician input: Clinicians endorse the reimbursement of blinatumomab for adult and pediatric patients

A total of nine registered clinicians provided input: one group, the POGO and eight individual oncologists from Ontario (four clinicians including one pediatric oncologist), Alberta (two clinicians), British Columbia (one clinician), and Nova Scotia (one clinician). Overall, the clinicians agreed that blinatumomab should be reimbursed for both adult and pediatric patients, noting that data can be extrapolated from adults to children and that evidence from the R/R setting is supportive to the indication under review.

Clinicians agreed blinatumomab may be used for patients with central nervous system (CNS) involvement or who relapse with CNS involvement, but not for patients with active CNS disease. Clinicians also agreed blinatumomab could be used in patients with Ph+ ALL but did not recommend the use of blinatumomab for patients with MRD- status or patients with unknown MRD status. For patients with prevalent MRD+ status in hematological CR or those under observation, a time frame of within two weeks after determining MRD positivity was suggested by most clinicians as reasonable to initiate treatment of blinatumomab; other clinicians suggested time frames of within three or four months to initiate treatment with blinatumomab. However, all clinicians agreed that patients face a high relapse rate and that starting treatment sooner rather than later is preferred. Contraindications to blinatumomab identified were: CD19 negativity, severe biochemical abnormalities, uncontrolled serious infections, pregnancy, severe neurological complications, or other contraindications as outlined by the manufacturer.

From the pediatric perspective, clinicians agreed that treatment options are limited and patients who remain MRD+ following three blocks of therapy have a poor prognosis. Current standard of care for this patient population carries a significant toxicity risk and generally includes more intensive cytotoxic therapy to achieve MRD negativity, and those that achieve MRD- status would proceed to HSCT. However, it was noted that patients who are MRD+ at the end of induction therapy are at high risk for treatment failure with continued chemotherapy, and one clinician also indicated that HSCT may not be associated with significant clinical benefit in MRD+ pediatric patients based on one study. Pediatric clinicians acknowledged that the data for blinatumomab for use in pediatric patients for the indication under review is poor; however, they believed that the results of the BLAST trial in the adult population are generalizable to pediatric patients. Clinicians also acknowledged that the COG AALL1331 trial does not directly match the indication under review. However, for R/R pediatric patients clinicians recommended blinatumomab treatment should be used earlier as per the COG AALL1331 trial after one block of induction therapy in order to maximize efficacy and minimize toxicity, instead of after three blocks of therapy as per the BLAST trial. Further, some clinicians agreed that blinatumomab should be used in the relapsed setting regardless of MRD status.

## PATIENT-BASED VALUES

### Experience of patients with ALL: Current therapies associated with difficult physical and emotional side effects; significant impact to QoL

One patient input on blinatumomab focused on pediatric patients with ALL was provided as a joint submission from the following groups: Ac2orn, LLSC, OPACC, and Helena's Hope. No patient input focusing on the adult population was provided. The most common symptoms of the disease reported by patients as having a large or extremely large impact on their QoL were fatigue, pain and loss of appetite, and/or weight loss. Patients reported having received chemotherapies that were described as "extremely difficult" resulting in side effects that were challenging to tolerate and could significantly impact QoL. Common side effects of current frontline treatments include neutropenia, hair loss, nausea, vomiting, and reduced mobility. In addition to physical side effects, traditional frontline treatments for pediatric ALL were also reported to result in anxiety, mood swings, stunted emotional growth, and n loss of education and social development.

### Patient values, experience on or expectations for treatment: Positive experience with blinatumomab; patients value better disease management with fewer side effects and improved QoL

Five respondents reported having experience with blinatumomab. Overall, respondents described their experiences with blinatumomab positively. Side effects of treatment with blinatumomab were described as minor or manageable, and infrequent compared to chemotherapy. The most commonly reported side effects were fever, low platelet count, low red blood cell count, and low white blood cell count. Respondents reported an improved QoL with blinatumomab compared to traditional treatments. Overall, patients value treatments that result in better disease management with fewer side effects and improved QoL. Patients also prefer having the option of treatments that are more targeted to the disease, without the risk of long-term impairment, which are recommended to them by their physician.

## ECONOMIC EVALUATION

Blinatumomab is available as a 38.5 mcg vial of lyophilized powder for solution for infusion. The recommended dose of blinatumomab is 28 mcg per day. Blinatumomab should be administered, using an infusion pump, as a continuous intravenous infusion at a constant flow rate over 28 days, followed by a two-week period of no treatment. Patients may receive one cycle of induction treatment followed by three additional cycles of blinatumomab as consolidation treatment. At the sponsor's submitted price of $2,978.26 per vial, the drug acquisition cost of four treatment cycles is $333,565 per patient ($83,391 per cycle per patient).

The sponsor submitted a cost-utility analysis comparing blinatumomab versus SOC in adults (≥18 years) with MRD+ Ph- BCP-ALL. The model population comprised adults in first hematologic CR, and as such, was narrower than the Health Canada indication for blinatumomab given exclusions of the pediatric population and adults in second hematologic complete remission. The model structure included a decision tree that illustrated MRD status (MRD+; MRD-) after treatment with blinatumomab or SOC. Within the decision tree, 82% of patients receiving blinatumomab and 8% receiving SOC achieved an MRD- response at week six, as determined by the BLAST trial and expert opinion respectively. If patients were MRD-, then they entered the MRD- semi-Markov model. If patients were MRD+, they entered the MRD+ semi-Markov model. Both models were structurally identical but the likelihood of transitioning between the states was influenced by the patients MRD status. Patients could not transition between the MRD- model and the MRD+ model. Both semi-Markov models captured movement between five health states: first CR before HSCT; remaining relapse free after receiving HSCT; receiving inotuzumab following relapse; receiving conventional chemotherapy following relapse; and death. Parameters in this model were mainly derived from the BLAST trial, the TOWER trial, and a 20-year-old historic cohort study.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The modelled population was restricted to adults in first CR and did not address the Health Canada indication for children with MRD+ Ph- BCP-ALL or for adults in second CR. A scenario analysis was conducted to estimate the cost-effectiveness of blinatumomab in the pediatric

population with MRD+ Ph- BCP-ALL but this was based entirely on adult data and was therefore not appropriate. Compared with SOC, the cost-effectiveness of blinatumomab for the pediatric population and for adults in second CR remains unknown.

- The impact of certain structural uncertainties in the semi-Markov model could not be explored. The model only explicitly linked HSCT to cure in those patients who received HSCT before relapse and did not incorporate the effects on relapsed patients.
- The number of inpatient hospital days for treatment with blinatumomab and within the pre-relapse health state did not reflect clinical practice in Canada. The clinical experts consulted by CADTH for this review expected the frequencies to be higher for all treatment cycles and lower for the pre-relapse health state.
- The use of 20-year-old data for HSCT related parameters (e.g., patient eligibility for HSCT, access to HSCT, or clinical decisions to perform HSCT within existing clinical practice) is unlikely to reflect current practice and, therefore, introduced considerable uncertainty in the time to HSCT modelled for SOC.
- The distribution of patients with relapsed disease who received conventional multi-drug chemotherapies versus a newer approved therapy, inotuzumab ozogamicin, had limited clinical plausibility.

CADTH undertook a reanalysis to address limitations relating to the application of inpatient hospital days, the time to treatment with HSCT for the SOC comparator, and the distribution of treatments among all patients who relapsed. Based on CADTH's reanalysis for a subgroup of the Health Canada indication (adults in first CR), the incremental cost-effectiveness ratio (ICER) for blinatumomab versus SOC was estimated to be $118,234 per additional quality-adjusted life-year gained. These results were based on 20-year-old matched data on the risk of relapse for the SOC comparator. The use of this data likely underestimates the effectiveness of current SOC chemotherapies and was shown to be a notable source of uncertainty in CADTH's exploratory analyses. Therefore, the presented ICER likely represents an underestimation of the true ICER for blinatumomab compared with SOC. Additional scenario and exploratory analyses were undertaken, which highlighted the uncertainty associated with the use of 20-year-old data on the risk of relapse for the SOC comparator.

The results of CADTH's reanalysis were restricted to adults in first CR. CADTH was unable to assess the cost-effectiveness of blinatumomab compared to SOC for the full Health Canada indication. As such, the cost-effectiveness of blinatumomab for children with MRD+ Ph- BCP-ALL in first or second CR and for adults in second complete remission is unknown.

## ADOPTION FEASIBILITY

### Considerations for Implementation and Budget Impact: Submitted BIA is underestimated

Factors that most influenced the estimated budget impact were the drug acquisition costs, the eligible patient population, post-relapse drug costs, and the market share. pERC noted there was considerable uncertainty regarding post-relapse drug costs due to the survival data used to inform the proportion of patients who relapsed after one year. Likewise, pERC noted there was potential for blinatumomab to take a larger market share, which would further increase the budget impact, as estimated in an EGP reanalysis. MRD testing costs were not included in the BIA and were included in an EGP reanalysis. The impact of including fees for MRD diagnostics contributed to 0.4% of the budget impact. Based on this, pERC noted the sponsor's BIA estimate was likely an underestimate and that the true estimate would fall closer to the EGP base case. Jurisdictions may want to consider pricing arrangements and/or cost structures that would improve affordability.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

# ABOUT THIS RECOMMENDATION

### The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:
Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair

- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair
- Dr. W. Dominika Wranik, who was not present for the meeting.

### Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of blinatumomab for ALL, through their declarations, one member had a real, potential, or perceived conflict; therefore, based on application of the CADTH *pCODR Conflict of Interest Guidelines* no member was excluded from voting. For the Final Recommendation, through their declarations, one member had a real, potential, or perceived conflict; therefore, based on application of the CADTH *pCODR Conflict of Interest Guidelines* no member was excluded from voting.

### Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and PAG input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR Guidance Reports for more detail on their content.

### Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

### Use of this Recommendation

This recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

# APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

| PAG implementation questions | pERC Recommendation |
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| **Eligible patient population** | |
| PAG is seeking guidance on whether the eligibility for blinatumomab can be extended to:<br>• patients with a history of CNS involvement or who relapse with CNS involvement<br>• patients in hematological CR who have MRD- or unknown MRD status. If so, which patients (all, or those with high-risk features)?<br>• Ph+ patients<br><br>PAG noted that patients who had a minimum of three blocks of intensive chemotherapy before initiation of blinatumomab were eligible. PAG is seeking clarity on the minimum number of blocks of intensive chemotherapy before initiation of blinatumomab after which MRD status is determined.<br><br>PAG is seeking guidance on whether there is a subgroup of patients (e.g., based on baseline MRD level) that are expected to derive the greatest benefit from blinatumomab, and whether treatment should be limited to these patients.<br><br>PAG noted that prevalent MRD+ patients in hematological CR or patients on observation, would need to be addressed on a time-limited basis. PAG is also seeking guidance on the time frame after achieving CR in which blinatumomab treatment should be initiated by.<br><br>PAG noted there is a potential for indication creep to use blinatumomab as maintenance or consolidation therapy for patients with MRD- BCP-ALL. | • pERC noted that the BLAST trial excluded patients with a history of, or current relevant CNS pathology. pERC agrees with the CGP that it may be possible to see benefit in this patient population, but additional monitoring would be required as existing CNS pathology may add to blinatumomab-associated neurotoxicities.<br>• pERC agrees with the CGP that there is no evidence to extrapolate results of the included studies to MRD- or MRD unknown populations based on the submitted evidence. For pediatric patients, patient and clinician groups strongly supported treatment with blinatumomab for high-risk BCP-ALL patients who are MRD-, noting clinical benefit and reduced toxicities in both MRD+ and MRD- pediatric patients in first relapse. pERC noted that this was an unmet need in this small patient population, jurisdictions may want to consider exploring mechanisms for providing access to pediatric patients with high-risk BCP-ALL in first relapse with MRD- disease after reinduction therapy when more evidence is available.<br>• pERC noted only five Ph+ patients were included in the BLAST trial, which were included in the primary end point analysis (complete MRD response rate), but were excluded from the key secondary end point analysis (i.e., RFS). Given the small number of patients and other treatment options available to Ph+ patients, pERC concluded that Ph+ patients would not be eligible for blinatumomab.<br><br>pERC agrees with CGP that the minimum number of intensive chemotherapy blocks to achieve CR should be a minimum of three blocks, and pERC further clarified a minimum of three blocks given with curative intent over the course of the patient's treatment for BCP-ALL.<br><br>pERC agrees with CGP that there were no specific subgroups from the trial data that may derive the greatest benefit.<br><br>pERC noted that in the BLAST trial, MRD detection should have occurred after a minimum of two weeks following the last dose of systemic treatment. pERC also noted the median time from last anti-leukemic treatment to first dose of blinatumomab was 2.1 months and ranged from 1 month to 55 months. pERC agrees with the CGP that blinatumomab should be initiated as soon as the patient is deemed MRD+ following at least three blocks of intensive chemotherapy as assessed by the treating physician.<br><br>pERC agrees with the CGP that there is no data to support the use of blinatumomab as a maintenance therapy, and that continued treatment with blinatumomab should not be considered. |

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| **Implementation factors** | |
| • PAG is seeking guidance on the use of the weight-based dosing up to a flat-fixed dose (e.g., fixed dose for those ≥ 45 kg).<br>• PAG is seeking guidance on whether further blinatumomab treatment would be considered for patients who have not progressed after receiving four cycles of blinatumomab, but do not go on to receive alloSCT. | • pERC agrees with the CGP that dosing should be as per the Health Canada Product Monograph, which noted a fixed dose for patients who weigh 45 kg or more, and weight-based dosing for patients who are less than 45 kg.<br>• pERC agrees with the CGP that there is no data to support using blinatumomab after four cycles of treatment. |
| **Sequencing and priority of treatments** | |
| • PAG is seeking guidance on whether patients who receive blinatumomab for MRD+ disease followed by alloSCT would be eligible for repeat blinatumomab treatment for relapsed disease occurring post-alloSCT. If re-treatment is appropriate, what would be the appropriate time frame from completion of blinatumomab in this setting and initiation in the relapsed/refractory setting? | • pERC agrees with the CGP that re-treatment for adult patients should not be permitted as there is a lack of evidence to support this, and similarly, re-treatment of pediatric patients should not be permitted. |
| **Companion diagnostic testing** | |
| • PAG is seeking clarity on the proportion of ALL patients who would be MRD+ and thus eligible for blinatumomab. | • pERC noted that there is variability across jurisdictions in MRD testing of patients with Ph- and BCP-ALL. pERC noted that, where MRD testing is not currently available, implementation of MRD testing would be required.<br>• pERC agrees with CGP that the proportion of patients who achieve a first CR is high ranging up to 91%, and all of these patients would require testing for MRD. Of these, one-third would have MRD positivity and thus be eligible for blinatumomab. There would be additional patients who achieve a second CR and existing patients in their first or second CR who would be eligible for MRD testing and, of these, additional patients eligible for blinatumomab would be identified. |

– = negative; + = positive; alloSCT = allogeneic stem cell transplant; BCP-ALL = B-cell precursor acute lymphoblastic leukemia; CGP = Clinical Guidance Panel; CNS = central nervous system; CR = complete remission; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; Ph = Philadelphia chromosome; MRD = minimal residual disease; RFS = relapse-free survival.