pCODR EXPERT REVIEW COMMITTEE (pERC)
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.

Drug: Blinatumomab (Blincyto) **Submitted Reimbursement Request: Adult patients (i.e., 18 years and older) with Philadelphia Chromosome positive B-cell precursor Acute Lymphoblastic Leukemia, who have relapsed after or are refractory to at least one second generation or later tyrosine kinase inhibitor (TKI), or are intolerant to second generation or later TKIs and intolerant or refractory to imatinib.**	
Submitted By: Amgen Canada Inc.	**Manufactured By:** Amgen Canada Inc.
NOC Date: March 5, 2018	**Submission Date:** August 31, 2018
Initial Recommendation: January 31, 2019	**Final Recommendation:** April 4, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Submitted list price of $2,978 per 38.5 mcg vial When cost calculations are based on six-week cycles (42 days, i.e., four weeks of treatment, followed by a two-week treatment-free period), blinatumomab costs: • $71,472 per 42-day cycle (cycle 1)* • $83,384 per 42-day cycle (cycle 2-5) * Assumes that three vials can be shared and will be used for days 1 to 7 of cycle 1 and that one 38.5 mcg vial will be used for all other treatment days (28 vials for 28 days of infusion)

pERC RECOMMENDATION

pERC conditionally recommends the reimbursement of blinatumomab (Blincyto) for the treatment of adult patients with Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukemia (Ph+ BCP-ALL) who have been treated with at least two prior tyrosine kinase inhibitors (TKIs) and have relapsed or refractory (R/R) disease only if the following condition is met:

- Cost-effectiveness being improved to an acceptable level.

If the aforementioned condition cannot be met, pERC does not recommend reimbursement of blinatumomab. Eligible patients include those with Ph+ BCP-ALL who have been treated with at least two prior TKIs and have R/R disease with good performance status, and does not include patients who were intolerant to second generation or later TKIs and intolerant to imatinib. Treatment should be continued until unacceptable toxicity or disease progression to a maximum of two cycles for induction and three cycles for consolidation.

pERC made this recommendation because there may be a net clinical benefit of blinatumomab based on demonstrated activity with use of

blinatumomab including the rates of complete remission, minimal residual disease (MRD), and subsequent allogeneic hematopoietic stem cell transplantation (alloHSCT) in a heavily treated population, and on the need for effective treatments to reach remission. pERC made this recommendation while acknowledging there was an absence of data on quality of life and noting that this treatment has considerable, but manageable toxicities.

The Committee also concluded that blinatumomab aligns with patient values of reaching remission and managing disease-related symptoms. However, pERC noted that the impact of blinatumomab on patients' quality of life (QoL) compared with other treatments is uncertain.

pERC concluded that, at the submitted price, blinatumomab could not be considered cost-effective compared with the submitter's choice of comparator (standard of care [SOC] comprised of a TKI [i.e., ponatinib], chemotherapy [i.e., hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone (hyper-CVAD)] or TKI plus chemotherapy combination) because of the considerable uncertainty in the cost-effectiveness due to a lack of direct comparative data in the submitted economic evaluation. In fact, pERC felt that given the uncertainty, the incremental cost-effectiveness estimates could be considerably higher than the pCODR Economic Guidance Panel's (EGP's) upper estimate. Therefore, pERC concluded that blinatumomab would require a substantial price reduction to improve the cost-effectiveness to an acceptable level.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given pERC was satisfied that blinatumomab may have a net clinical benefit in adult patients with Ph+ BCP-ALL who have been treated with at least two prior TKIs and have R/R disease, 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 extremely high and that the drug price was a key driver of the incremental cost-effectiveness estimates. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a substantial reduction in drug price would be required in order to improve cost-effectiveness.

Resource Use and Adoption Feasibility
pERC noted that the preparation, administration, and management of blinatumomab is complex and unusually 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 (AEs), all of which may require significant expenditures of human resources. pERC noted that experience in the use of blinatumomab does not lessen concerns about the complexity and unusually resource-intensive requirements to prepare and administer the drug and to manage the associated AEs related to this therapy.

Wastage and Budget Impact Likely to Affect Adoption Feasibility
pERC also noted that the submitted model assumes vial-sharing in the first seven days of treatment and that all subsequent doses will use full vials. However, pERC expects that there may be considerable wastage with blinatumomab, given the challenges associated with implementing blinatumomab protocols (e.g., different infusion durations per preparation bag [between 24 and 96 hours], different pump infusion rates with different durations of infusion, etc.). pERC concluded that 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.

Collecting Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and the Cost-Effectiveness of Blinatumomab
Given the considerable uncertainty in the magnitude of clinical benefit of blinatumomab in adult patients with Ph+ BCP-ALL who have been treated with at least two prior TKIs and have R/R disease, pERC concluded that additional prospective evidence of long-term overall survival, QoL, and alloHSCT eligibility should be collected to decrease the uncertainty in the incremental effect and cost-effectiveness of blinatumomab. pERC noted that, when such prospectively collected data become available, jurisdictions will need to review these new data.

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

The Committee noted that ALL represents approximately 15 % of adult acute leukemia patients and of those, 20% have ALL Ph+ BCP. In 2013, a total of 480 Canadians were diagnosed with ALL and 138 individuals with ALL died as a result of the disease. pERC also noted a number of traditional prognostic factors in ALL, which included age, cytogenetics, white blood cell count, and acknowledgement that newer treatment protocols that include TKIs have abrogated some of these risk factors. As well, pERC discussed that between 50% and 60% of younger patients with Ph+ BCP disease undergo intensive multi-agent chemotherapy and intrathecal prophylaxis followed by hematopoietic stem cell transplant (HSCT) with an expectation of cure, and that older patients are treated with TKI therapy plus chemotherapy. pERC acknowledged that health-related QoL is affected by the intensity and length of treatment, and that only a small proportion of patients with relapsed or refractory disease are able to successfully obtain remission to be eligible for HSCT. pERC also noted that there was no standard therapy for either younger or older relapsed or refractory patients and recognized that blinatumomab is a new line of therapy for both younger and older patients. Therefore, pERC concluded that there is a continued need for more effective treatment options that allow patients with Ph+ BCP-ALL who have been treated with at least two prior TKIs and have relapsed or refractory disease to obtain remission, improve QoL, and ultimately prolong patients' survival. However, pERC felt that patients who were intolerant to second generation or later TKIs and intolerant to imatinib have alternative therapies available to them. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter regarding the recommended reimbursement patient population. Similar to the Clinical Guidance Panel (CGP), pERC acknowledged that patients with Ph+ B-ALL who were intolerant to second generation or later TKIs and intolerant to imatinib could have participated in the ALCANTARA trial. However, pERC reiterated their agreement with the CGP in that patients who have intolerance to TKI therapy have alternative therapies available to them and therefore did not recommend blinatumomab in this patient population.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Upon reconsideration of the Initial Recommendation, pERC noted that patient group feedback was not provided, and that both registered clinicians and the Provincial Advisory Group (PAG) feedback agreed with the Initial Recommendation and supported conversion to a Final Recommendation, while the submitter agreed only in part with the Initial Recommendation and did not support conversion to Final Recommendation. pERC recognizes that pERC's decisions must be equitable, transparent, timely, and accountable to patients, health care funders, and the public to ensure that effective treatment options are considered for public funding. pERC noted that the issues raised by the submitter had been addressed in the Initial Recommendation. In light of this, pERC expressed dismay at receiving feedback that the submitter did not support early conversion to Final Recommendation, delaying timely access to public funding of effective treatment options such as blinatumomab.

pERC discussed the feasibility of conducting a randomized controlled trial (RCT) of blinatumomab in patients with Ph+ BCP-ALL. pERC noted that only 20% of adults with ALL are Ph+ BCP and felt that it would be difficult to accrue a sufficient number of patients for an RCT. However, pERC recalled that it was possible to conduct an RCT that combined both Ph+ and Philadelphia negative (Ph–) BCP-ALL patients: the INO-VATE ALL trial was a phase III RCT that compared inotuzumab ozogamicin with investigator's choice of chemotherapy and included patients with both Ph+ and Ph– BCP-R/R ALL. However, pERC noted that the INO-VATE ALL trial was largely comprised of Ph– BCP-ALL patients. This led pERC to question and discuss the submitter's choice for conducting two separate trials: ALCANTARA for Ph+ BCP- ALL and TOWER for Ph– BCP-ALL (TOWER was an RCT that evaluated the efficacy and safety of blinatumomab compared with chemotherapy in adult patients with Ph– BCP- R/R ALL). In the end, the Committee concluded that the eligibility criteria differed between the ALCANTARA and TOWER trials and that the TOWER trial investigated the use of blinatumomab as an earlier line of therapy than in the ALCANTARA trial and, therefore, the TOWER trial could not have included a Ph+ BCP population that was similar to the population in the ALCANTARA trial. Therefore, pERC concluded that conducting an RCT in a population of patients with Ph+ BCP-ALL is likely not feasible.

The Committee deliberated on the results of a single-arm phase II, multicenter, open-label trial, ALCANTARA, which evaluated the efficacy and tolerability of blinatumomab in patients with R/R Ph+ BCP-ALL. pERC concluded that there was demonstrated activity with the use of blinatumomab and acknowledged that the rates of complete remission (36%) were comparable with the TOWER trial. Furthermore, pERC felt that the complete MRD response (14 out of 16 respondents) results were impressive and considered MRD to be a good surrogate for long-term remission. As well, pERC noted that four patients had alloHSCT after blinatumomab-induced remission and that three of these patients remained alive after the trial ended. pERC considered this (three out of 45 patients) to be a meaningful outcome.

pERC discussed the toxicity profile of blinatumomab and highlighted that neurologic toxicity and cytokine release syndrome events were of concern. Overall, the Committee recognized that AEs experienced by patients treated with blinatumomab were considerable, but were similar to other treatment options for R/R Ph+ BCP-ALL. QoL data were not collected in the ALCANTARA trial. pERC acknowledged the CGP's statement regarding the extrapolation of QoL data from the TOWER trial (Ph– patients) to the population in the ALCANTARA trial in the absence of available data; however, the Committee agreed that the impact of blinatumomab on patients' QoL compared with other treatments is uncertain.

The Committee also deliberated on the results of the manufacturer-submitted propensity score analysis, which compared efficacy outcomes in the ALCANTARA study with a historical comparator study. pERC acknowledged that the results of the propensity score analysis demonstrated a trend in improvement in overall survival compared with chemotherapy and/or a TKI; however, the Committee discussed the limitations of the historical comparison and agreed that ALCANTARA included a more contemporary cohort than the historical comparator, and as a result, the treatment patients received in the historical comparator were not entirely comparable nor reflective of the treatment landscape at the time of the ALCANTARA trial. Therefore, pERC felt that this contributed to the uncertainty in the clinical benefit of blinatumomab compared with chemotherapy and/or a TKI.

Overall, pERC agreed that the results were promising; however, the Committee felt that, given the lack of a direct comparison and limitations of the ALCANTARA trial, uncertainty remained in the clinical benefit of blinatumomab. Therefore, the Committee concluded that there may be a net clinical benefit of blinatumomab.

The Committee deliberated on patient input from one patient advocacy group and recognized that patients value reaching remission, improving QoL, and managing disease-related symptoms such as fatigue, pain, bruising and/or bleeding. pERC discussed these patient values and agreed that blinatumomab had promising results in reaching remission and, although considerable, toxicities were manageable and similar to other treatment options. Overall, pERC agreed that blinatumomab aligned with patient values in reaching remission and managing disease-related symptoms; however, the impact of blinatumomab on patients' QoL compared with other treatments is uncertain.

pERC deliberated on the cost-effectiveness of blinatumomab compared with the submitter's choice of comparator (standard of care comprised of a TKI [i.e., ponatinib], chemotherapy ([i.e., hyper CVAD], or TKI plus chemotherapy combination). Among the key data sources used in the model, pERC noted that the clinical information for the SOC comparator came from the historical comparison described above and reiterated their concerns regarding the comparability of the historical patient population to the ALCANTARA patient population. pERC noted the extrapolation of the utility data from the TOWER trial (Ph– patients) to the population in the ALCANTARA trial; however, the Committee reiterated that the impact of blinatumomab on patients' QoL compared with other treatments is uncertain. pERC recognized that a large limitation of the submitted model was an inability to fully test some of the assumptions in the model, such as the hazard ratios inputs. As well, the Committee noted the following factors had an impact on the incremental cost-effectiveness estimates: cost of blinatumomab, cost of in-patient stay on SOC, time horizon, and time-cure input. pERC discussed the EGP's reanalyses, which focused on the time horizon, in-patient cost for blinatumomab and SOC, frequency of pump changes, and the utility in the initial disease state. Overall, the Committee accepted the range of cost-effectiveness estimates provided by the EGP and, therefore concluded that blinatumomab did not appear to be cost-effective at the submitted price. In fact, pERC felt that given the uncertainty, the incremental cost-effectiveness estimates could be considerably above the EGP's upper estimate; this was largely owing to the model function, sensitivity to important parameters such as cure rate, and the historical comparator. pERC

concluded that blinatumomab would require a substantial price reduction to improve the cost-effectiveness to an acceptable level.

pERC considered the feasibility of implementing a reimbursement recommendation for blinatumomab. The Committee noted that the factors that most influenced the budget impact analysis (BIA) included epidemiologic estimates for proportion of patients with (1) B-lineage ALL, (2) B-cell lineage that is precursor to B-cell, (3) B-cell and Ph+, and (4) B-cell and Ph+ and R/R, and the duration of use/cost of ponatinib. pERC discussed the key limitations of the BIA model noted by the EGP, which included the lack of consideration of drug administration cost for both comparators, and more specifically, the cost of hospitalization for blinatumomab or hyper-CVAD chemotherapy. pERC also agreed with the EGP in that it is likely that these costs will be higher for the patients receiving chemotherapy, and noted that the EGP was unable to modify the model to explore this further. pERC appreciated that the BIA assumed a substantial market share for the treatment-funded scenario compared with the submitter's choice of SOC: chemotherapy, TKI, or TKI plus chemotherapy combination. However, the Committee agreed that the use of the historical data to reflect the historical comparator study may not have been reflective of Canada. Furthermore, pERC felt that the number of eligible patients was underestimated and therefore agreed that the budget impact was underestimated.

Lastly, the Committee deliberated on input from PAG, in particular on factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. First, pERC noted that there was no standard therapy for either younger or older R/R patients and recognized that blinatumomab is a new line of therapy for both younger and older patients. pERC also discussed PAG's request for clarity on the eligible patient population. The Committee acknowledged that the ALCANTARA trial included patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less and agreed that patients with good performance status would be appropriate clinical candidates for blinatumomab. As well, pERC agreed that patients who have relapsed after or have refractory disease following treatment with any second generation or later TKI (dasatinib, nilotinib, bosutinib, or ponatinib) and are refractory to imatinib would meet criteria to receive blinatumomab. As previously noted, the Committee acknowledged that patients with Ph+ BCP-ALL who were intolerant to second generation or later TKIs and intolerant to imatinib could have participated in the ALCANTARA trial, but felt that these patients have alternative therapies available to them and therefore would not meet their criteria to receive blinatumomab. As a result, the pERC recommended that the eligible population was adult patients with Ph+ BCP-ALL who have been treated with at least two prior TKIs and have R/R disease with a good performance status.

As well, the Committee discussed implementations factors noted by PAG. pERC recognized the challenges in preparing each infusion bag and the amount of stabilizer required versus the amount packaged with each vial. While the submitter provided a response to the concern regarding the insufficient amount of stabilizer packaged with blinatumomab, pERC concluded that the lack of sufficient stabilizer could lead to significant wastage.

pERC also noted that the submitted model assumed vial-sharing in the first seven days of treatment and that all subsequent doses would use full vials. However, pERC expected that there may be considerable wastage with blinatumomab, given the challenges associated with implementing blinatumomab protocols (e.g., different infusion durations per preparation bag [between 24 and 96 hours], different pump infusion rates with different durations of infusion, etc.). pERC noted that wastage was not included in the incremental cost-effectiveness estimates and that a sensitivity analysis to consider wastage was not performed; pERC felt that the inclusion of wastage would have led to a greater incremental cost-effectiveness ratio. pERC concluded that 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. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the submitter related to wastage. Notwithstanding the submitter's statement regarding the vial size of blinatumomab, pERC reiterated that they expected that there will be considerable wastage with blinatumomab, given the challenges associated with implementing blinatumomab protocols.

pERC noted that maintenance therapy was not part of the ALCANTARA trial, but acknowledged the CGP's statement regarding maintenance therapy. In addition, pERC noted that EGP was unable to perform reanalysis to consider maintenance therapy in the Submitter's economic model. As a result, pERC concluded that the clinical and economic evidence on the use of blinatumomab after the fifth cycle was unknown for this setting.

pERC noted that health care professionals are already familiar with blinatumomab and considered this to be an enabler to implementation. However, the Committee felt that experience in the use of blinatumomab does not lessen their concerns about the complexity and unusually resource-intensive requirements to prepare and administer the drug and to manage the associated AEs related to this therapy.

Finally, pERC discussed PAG's request for guidance on the optimal sequencing and priority treatment with respect to inotuzumab ozogamicin and blinatumomab for R/R Ph+ BCP-ALL. pERC noted that there is currently no clinical trial evidence to inform this and concluded that the optimal sequencing of blinatumomab and inotuzumab in this setting is unknown.

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
- input from one patient advocacy group — The Leukemia & Lymphoma Society of Canada (LLSC)
- input from registered clinician – Two submissions from a total of three clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group input from two clinicians.
- The PAG.
- The submitter [Amgen Canada Inc.].

The pERC Initial Recommendation was to recommend reimbursement of blinatumomab (Blincyto) for the treatment of adult patients with Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukemia (Ph+ BCP-ALL) who have been treated with at least two prior tyrosine kinase inhibitors (TKIs) and have relapsed or refractory (R/R) disease only if cost-effectiveness is improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that PAG and the registered clinician group agreed with the Initial Recommendation, and the submitter agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of blinatumomab for the treatment of adult patients with refractory or relapsed (R/R) Philadelphia chromosome positive (Ph+) B-cell precursor acute lymphoblastic leukemia (BCP-ALL) (i.e., adult patients [18 years and older] with Ph+ BCP-ALL, who have relapsed after or are refractory to at least one second generation or later tyrosine kinase inhibitor [TKI], or are intolerant to second generation or later TKIs and intolerant or refractory to imatinib.)

Studies included: Single-arm phase II trial

The pCODR systematic review included the ALCANTARA trial (one single-arm phase II, multicenter, open-label trial involving 19 countries), which assessed the efficacy and tolerability of single-agent blinatumomab in patients with R/R Ph+ BCP-ALL who progressed after or were intolerant to a second generation or later TKI. pERC noted that there were 61 patients who were assessed for eligibility between January 3, 2014, and May 20, 2015, 45 patients were enrolled in the study and treated with blinatumomab; three patients met the eligibility criteria but did not participate in the study, and the remaining 13 patients did not meet the eligibility criteria. None of the patients were Canadian. Patients received blinatumomab as a continuous intravenous infusion at fixed stepwise doses (9 mcg per day in week 1 of cycle 1 and 28 mcg per day thereafter) over four weeks followed by a two-week treatment-free interval (six-week cycles). The Committee noted that the primary end point of the study was complete response or complete response with partial hematologic recovery(CR/CRh), defined as the proportion of patients who achieved CR/CRh within the first two cycles of blinatumomab treatment. Secondary end points included minimal residual disease (MRD) response rate during the first two cycles of treatment, relapse-free survival, duration of response, overall survival (OS), allogeneic hematopoietic stem cell transplant (HSCT) after blinatumomab-induced remission, other best overall response rates (CR, CRh, or CR/CRh/ complete response with incomplete hematologic recovery [Cri]), and safety. The sample size was estimated for a Simon's mini-max two-stage design, based on the proportion of subjects who achieved a CR or CRh within two cycles of blinatumomab treatment (i.e., primary efficacy end point). The sample size was estimated at 23 patients in stage I, and 41 evaluable patients in total, based on a one-sided type I error (α) of 0.025 and a power of 90% to detect the effective response rate assumption of 30% or higher over an ineffective treatment rate of 10% or lower.

The pCODR review also provided contextual information on the critical appraisal of an indirect treatment comparison using a propensity score analysis that compared the efficacy of blinatumomab in the single-arm ALCANTARA study (N = 45) with that of standard of care (SOC; cytotoxic chemotherapy and/or TKI) in a historical comparator study (Study 20160462; N = 55).

Patient populations: Heavily treated patient population

pERC noted the median age of 55 years (23 to 78), that 84% of patients received 2 or more TKIs before trial entry, and that 44% had a prior HSCT.

Key efficacy results: demonstrated activity, impressive MRD rates, but uncertainty in net clinical benefit remains

The key outcomes deliberated on by pERC were CR/CRh, MRD, and OS.

In the final analysis the CR/CRh rate was 36% (16/45) with a median relapse free and OS for the cohort of 6.8 (4.4 to not estimable) months and 9.0 (5.7 to 13.5) months; seven of the 16 patients achieving a CR/CRh (44% of the responders) went on to receive an HSCT. Among 16 CR/CRh responders, a complete MRD response was achieved in 14 patients (88%; 95% confidence interval [CI] 62% to 98%); the remaining two responders (who achieved Cri) had persistent measurable MRD and relapsed during subsequent cycles of therapy. Four out of 45 patients had alloHSCT after blinatumomab-induced remission and three of these patients remained alive after the trial ended. The median OS was 9.0 months (95% CI, 5.7 to 13.5) based on a median follow-up of 25.1 months (95% CI, 5.7 to 13.5).

Patient-reported outcomes: not measured

Quality of life (QoL) was not measured in the ALCANTARA trial; as such, the impact of blinatumomab on patients' QoL compared with other treatments is uncertain.

Safety: Considerable toxicity profile, but similarly found to other treatment options

All patients experienced at least one treatment-emergent adverse event (AE); in 91% of the patients the AE was considered to be related to blinatumomab. Serious AEs were reported in 62% of patients. The rate of grade 3 or higher treatment-emergent AEs was 84%. Five (11%) fatal AEs occurred within 30 days of the last dose of blinatumomab during the study. Neurologic events were reported in 47% of patients, with the most common neurologic AEs being paresthesia (13%), confused state (11%), dizziness (9%), and tremor (9%). Cytokine release syndrome events were reported in 7% of patients, all were grade 1 or 2.

Limitations: No direct comparative data with currently available therapies, historical comparison study not entirely comparable to the ALCANTARA patient population

With respect to the historical comparison study and propensity score analysis, the ALCANTARA study included a more contemporary cohort (enrolment from 2014 to 2015) than the historical cohort (enrolment from 2006 to 2018), and the study populations differed in important prognostic factors in unadjusted baseline comparisons.

Need and burden of illness: Need for effective treatment options for patients with Ph+ BCP-ALL who have been treated with at least two prior TKIs and have R/R disease.

ALL represents approximately 15 % of adult acute leukemia cases and of those, 20% of adults have ALL Ph+ BCP. In 2013, a total of 480 Canadians were diagnosed with ALL and 138 individuals with ALL died as a result of the disease. Traditional prognostic factors in ALL included age, cytogenetics, white blood cell count, and pERC acknowledged that newer treatment protocols, which include TKI, have abrogated some of these risk factors. Between 50% and 60% of younger patients with Ph+ BCP-ALL who undergo intensive multi-agent chemotherapy and intrathecal prophylaxis followed by HSCT have the expectation of cure, and older patients are treated with TKI therapy plus chemotherapy. Health-related QoL is affected by the intensity and length of treatment; only a small proportion of R/R patients are able to successfully obtain remission to be eligible for HSCT. pERC also noted that there was no standard therapy for either younger or older R/R patients and recognized that blinatumomab is a new line of therapy for both younger and older patients. The Clinical Guidance Panel acknowledged that patients with Ph+ B-ALL who were intolerant to second generation or later TKIs and intolerant to imatinib could have participated in the ALCANTARA trial, and felt that patients who have intolerance to TKI therapy have many alternative therapies available to them. pERC felt that patients who were intolerant to second generation or later TKIs and intolerant to imatinib have alternative therapies available to them.

Registered clinician input: Need for more treatment options

According to the registered clinician input, there are very limited options for patients with Ph+ BCP R/R ALL and there is a significant unmet medical need for treatment of Ph+ BCP-ALL. The patient population in the ALCANTARA trial was appropriate and reflects reasonable inclusion and exclusion criteria that could be applied in clinical practice. According to the clinician input, blinatumomab is a very important "must have novel agent" that has a different mechanism of action, allowing patients to achieve better remission and long-term survival. According to the input, blinatumomab appeared to have superior efficacy, equivalent safety, and better tolerability than other available treatment options. Both registered clinician submissions provided input on the sequencing of blinatumomab for R/R patients.

PATIENT-BASED VALUES

Values of patients with ALL: Reaching remission, improving quality of life, and managing disease-related symptoms

A total of 12 participants responded to the two surveys, all of whom were Canadian. All patient respondents were diagnosed as adults within the last five years. Patients experienced various disease-related symptoms that have a large impact on their daily lives. ALL symptoms include pale complexion; bleeding and bruises; fever; fatigue; frequent minor infections; gum bleeding; discomfort with bones and joints; enlarged spleen, liver or lymph nodes; and shortness of breath. The goal of treatment is to achieve remission.

Patients were also asked to rate what side effects they were willing to tolerate with a new medication; patients would be more willing to deal with short-term side effects like nausea, diarrhea, edema, and loss of appetite as opposed to tolerating more severe side effects like pain, bruising, and bleeding.

Patient values on treatment: Positive experience for patients on blinatumomab

There were three patients with experience with blinatumomab. Based on two responses for additional information about experiences with blinatumomab, the experience was positive overall with one patient noting that it "has been the only positive of all the treatments so far" and another agreed with a statement regarding improved QoL compare with previous therapies used. No additional side effects were reported and one patient reported they had stopped taking an anti-nausea medicine since receiving blinatumomab.

A total of six patients had no experience with blinatumomab, four patients responded when asked about the most important symptoms of cancer for blinatumomab to control: 50% of them chose fatigue, pain, bruising and/or bleeding, rashes or skin changes, and loss of appetite; and 25% selected fever and/or night sweats, and lumps. In terms of which side effects patients were more willing to tolerate, patients said they would be willing to deal with "short-term" side effects such as nausea, diarrhea, edema, and loss of appetite but would be less willing to tolerate "more severe" side effects such as pain, bruising, and bleeding.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The cost-effectiveness and utility analysis submitted to pCODR by the manufacturer compared blinatumomab with SOC for adults with Ph+ R/R BCP-ALL and aligns with the ALCANTARA study. SOC was comprised of a TKI (i.e., ponatinib), chemotherapy (i.e., hyper-central venous access devices [CVAD]), or TKI plus chemotherapy combination.

Basis of the economic model: Historical control used as a comparator in cost-utility analysis

The submitted model was a partitioned-survival model comprised of five health states: 1) initial (pre-response), 2) response, 3) R/R, 4) cured, and 5) dead. All patients started from the initial (pre-response) state where they stayed for 12 weeks (unless they died) at which point patients were defined as having a response or R/R. Those who responded were at risk of relapse for the first three years of therapy. If no relapse occurred at three years, patients were considered cured. Patients in R/R state had a risk of ALL mortality during the first three years, after which they entered cured state with a subsequent risk of non-ALL mortality.

A historical comparator study was provided and statistical adjustments were used to derive indirect comparative efficacy data used in the economic model. Key cost drivers included medication and hospitalization costs. Utilities were not measured and came from a different study (TOWER for Ph- patients).

Drug costs: Very high drug costs, especially compared with hyper-CVAD and ponatinib

Blinatumomab costs $2,978 per 38.5 mcg vial. The recommended dose in cycle 1 is 9 mcg per day for the first week of cycle 1, and the subsequent cycles increased to 28 mcg per day starting week 2 through week 4 of the first cycle (all subsequent cycles [cycles 2 to 5] dosed at 28 mcg per day through the entire four-week cycle.

When cost calculations are based on six-week cycles (42 days, i.e., four weeks of treatment, followed by a two-week treatment-free period), blinatumomab costs:
• $71,472 per 42-day cycle (cycle 1).*
• $83,384 per 42-day cycle (cycle 2 to 5).
* Assumes that three vials can be shared and will be used for days 1 to 7 of cycle 1 and that one 38.5 mcg vial will be used for all other treatment days (28 vials for 28 days of infusion).

Hyper-CVAD (multi-drug chemotherapy) costs:
• 3,375.66 per 42-day cycle
• $2250.44 per 28-day course.

Ponatinib costs:
• 45 mg per day (1 tablet)
• $331.48 per day
• $ 9281.44 per 28-day course.

Cost-effectiveness estimates: Uncertainty in estimate owing to model function, sensitivity to cure rate, and the historical comparator

A large limitation of the incremental cost-effectives estimates was the functionality of the model (i.e., the pCODR Economic Guidance Panel [EGP] was unable to fully test relevant assumptions in the model such as the hazard ratios inputs). As well, the following factors had an impact on the incremental cost-effectiveness estimates: cost of blinatumomab, in-patient stay on SOC, time horizon, and time-cure input. The EGP's reanalyses focused on time horizon, in-patient cost for blinatumomab and SOC, frequency of pump changes, and initial utility.

The EGP's best estimate of incremental cost and incremental effect for blinatumomab when compared with SOC therapy is:

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

The EGP's overall conclusions of the submitted model:

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

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: budget impact underestimated
Factors that most influenced the budget impact analysis (BIA) included: epidemiologic estimates for the proportion of patients with B-cell lineage ALL, B-cell lineage that is precursor to B-cell, B-cell and Ph+, and B-cell and Ph+ and R/R with values, and the duration of use and cost of ponatinib. The key limitation of the BIA model was the lack of consideration of drug administration cost for both comparators, more specifically, the cost of hospitalization for blinatumomab or hyper-CVAD chemotherapy. The EGP noted that it is likely that these costs will be higher for the chemotherapy patients. EGP was unable to modify the model to explore this further. The BIA assumed a substantial market share for the treatment-funded scenario compared with the submitter's choice of SOC: chemotherapy, TKI, or the TKI plus chemotherapy combination. However, the use of the historical data to reflect the historical comparator study may not have been reflective of Canada. pERC felt that the number of eligible patients was underestimated and therefore concluded that the budget impact was underestimated.

No patients in the ALCANTARA trial received inotuzumab ozogamicin. The CGP felt that patients with Ph+ BCP--ALL who have been treated with inotuzumab ozogamicin in the past and require further therapy would be eligible for blinatumomab therapy as long as the patients have met the previously outlined criteria for blinatumomab therapy.

PAG considered the potential drug wastage due to insufficient amount of stabilizer as an important barrier that needs to be considered in economic analysis if implementing a funding recommendation for Blinatumomab. As per submitter response, each vial of blinatumomab is packaged with a 10 mL IV solution stabilizer (IVSS) and only 5.5mL of stabilizer is needed for each infusion bag. The blinatumomab dose can be prepared in a 24, 48, 72 and 96-hour bag. The bags can be prepared in advance and refrigerated for up to 10 days. When preparing multi-day (e.g., 48, 96 hours) infusion bags the requirement of IVSS is still 5.5mL/bag and therefore, over time there will be IVSS left over amounts in centres preventing blinatumomab wastage. There were noted challenges in preparing each infusion bag (e.g., the amount of stabilizer required versus available per vial) and therefore there is a potential for wastage due to insufficient stabilizer available to maximize the use of blinatumomab vials.

The submitted model assumed vial-sharing in the first seven days of treatment and that all subsequent doses will use full vials. However, there may be considerable wastage with blinatumomab, given the challenges associated with implementing blinatumomab protocols (e.g., different infusion durations per preparation bag [between 24 and 96 hours] and different pump infusion rates with different durations of infusion).

No maintenance therapy was given in the ALCANTARA trial; however, the CGP felt that it would be reasonable to consider maintenance therapy for patients with Ph+ BCP-ALL who are treated with blinatumomab in the R/R setting. However, pERC noted that the EGP was unable to perform a reanalysis to consider maintenance therapy. As a result, the clinical and economic evidence on the use of blinatumomab after the fifth cycle remained unknown for this setting.

Health care professionals are already familiar with blinatumomab and this is an enabler to implementation.

There is currently no clinical trial evidence to inform this sequencing and therefore, the optimal sequencing of blinatumomab and inotuzumab in this setting is unknown.

DRUG AND CONDITION INFORMATION

Drug Information

- First-in-class bispecific T-cell engaging (BiTE) antibody construct
- 38.5 mcg per vial
- Blinatumomab is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 28 days (four weeks) of continuous infusion followed by a 14-day (two-week) treatment-free interval. Patients may receive two cycles of induction treatment followed by three additional cycles of blinatumomab as consolidation treatment.

For adults, the recommended dose is as follows:

Patient Weight	Cycle 1		Subsequent Cycles
	Days 1-7	Days 8-28	Days 1-28
Greater than or equal to 45 kg	9 mcg/day	28 mcg/day	28 mcg/day

Cancer Treated

- Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
- Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (Notice of Compliance with conditions).

Burden of Illness

- ALL represents approximately 15 % of adult acute leukemia and of those, 20% have ALL Ph+ BCP. In 2013, at total of 480 Canadians were diagnosed with ALL and 138 individuals with ALL died as a result of the disease.

Current Standard Treatment

- No standard therapy for either younger or older relapsed or refractory patients. Between 50% and 60% of younger patients with Philadelphia chromosome positive BCP-ALL who undergo intensive multi-agent chemotherapy and intrathecal prophylaxis followed by hematopoietic stem cell transplantation (HSCT) have the expectation of cure, and that older patients are treated with tyrosine kinase inhibitors therapy plus chemotherapy.

Limitations of Current Therapy

- Health-related quality of life is affected by the intensity and length of treatment, and that only a small proportion of relapsed or refractory patients are able to successfully obtain remission to be eligible for HSCT.

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 Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
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. Kelvin Chan and Dr. Winson Cheung, who were not present for the meeting
- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation

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

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

- Dr. Kelvin Chan and Dr. Marianne Taylor, who were not present for the meeting.
- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest.
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of blinatumomab for Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukemia, through their declarations, eight members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one of these members 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 Provincial Advisory Group 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 pCODR 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 pERC 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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responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

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

PAG Implementation Questions	pERC Recommendation
Currently Funded Treatments • PAG identified that current treatments for Ph+ B-cell precursor ALL include tyrosine kinase inhibitors (TKIs; e.g., second generation dasatinib) in combination with multi-agent chemotherapy. At relapse, patients would receive different TKIs and multi-agent chemotherapy.	pERC noted that there was no standard therapy for both younger and older relapsed or refractory patients and recognized that blinatumomab is a new line of therapy for both younger and older patients.
Eligible Patient Population • PAG noted the ALCANTARA trial for Ph+ BCP- ALL only included patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. PAG is seeking confirmation that blinatumomab would be limited to patients with ECOG ≤ 2, as patients can be very ill at relapse with ECOG ≥ 3 and there may be consideration of blinatumomab eligibility in these cases where ECOG is felt to be disease-related. • PAG noted that the reimbursement request is for relapsed or refractory Ph+ BCP-ALL. In the trial, patients were eligible if they had relapsed after or were refractory to at least one second generation or later TKI (dasatinib, nilotinib, bosutinib, ponatinib), or were intolerant to second generation or later TKIs and intolerant or refractory to imatinib. PAG is seeking confirmation that the trial criteria would be applied to the funding criteria. • PAG also noted that funding of second generation or later TKIs varies by jurisdiction. PAG is seeking information on the generalizability of the trial based on prior TKI and number of prior TKI treatments. • PAG identified that there may be some patients who have received inotuzumab ozogamicin through a clinical trial or special access program. PAG is seeking clarity on whether patients who received inotuzumab ozogamicin would be eligible for blinatumomab.	The Committee acknowledged that the ALCANTARA trial included patients with ECOG ≤ 2 and concluded that patients with good performance status would be good clinical candidates for blinatumomab. As well, pERC agreed with CGP that patients who have relapsed after or have refractory disease following treatment with any second generation or later TKI (dasatinib, nilotinib, bosutinib or ponatinib) and are refractory to imatinib would meet criteria to receive blinatumomab. The Committee acknowledged that patients with Ph+ B-ALL who were intolerant to second generation or later TKIs and intolerant to imatinib could have participated in the ALCANTARA trial, but felt that these patients have alternative therapies available to them and therefore would not meet criteria to receive blinatumomab. As a result, the pERC recommended eligible population was adult patients with Ph+ BCP-ALL who have been treated with at least two prior TKIs and have relapsed or refractory disease with a good performance status. Furthermore, the Committee acknowledged that no patients in the ALCANTARA trial received inotuzumab ozogamicin; though the CGP felt that if patients received inotuzumab ozogamicin, there would be no reason to believe that patients would not expect a response with blinatumomab. pERC reiterated that the optimal sequencing with inotuzumab ozogamicin is unknown.

Implementation Factors • PAG noted that the one vial can be used to prepare more than one infusion bag. However, 5.5 mL of stabilizer is required to prepare each infusion bag and there is only 10 mL of stabilizer included with each vial of drug. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package. PAG noted there would be significant wastage due to insufficient stabilizer available to maximize the use of blinatumomab vials. • The funding request indicated that patients may receive five cycles of treatment (two cycles of induction followed by three additional cycles of consolidation treatment). However, PAG noted in the TOWER trial for Ph– ALL, patients were able to receive 12 months of maintenance therapy after the five initial cycles. PAG is seeking clarity on the maximum dosing of blinatumomab for Ph+ ALL. • Health care professionals are already familiar with blinatumomab. This is an enabler to implementation.	As well, the Committee discussed implementations factors noted by PAG. pERC recognized the challenges in preparing each infusion bag and the amount of stabilizer required versus available per vial. While the submitter provided a response to the concern regarding the insufficient amount of stabilizer packaged with blinatumomab, pERC concluded that the lack of sufficient stabilizer could lead to significant wastage. pERC also noted that the submitted model assumed vial-sharing in the first seven days of treatment and that all subsequent doses will use full vials. However, pERC expected that there may be considerable wastage with blinatumomab, given the challenges associated with implementing blinatumomab protocols (e.g., different infusion durations per preparation bag [between 24 and 96 hours], different pump infusion rates with different durations of infusion, etc.). pERC concluded that 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. pERC noted that no maintenance therapy was given in the ALCANTARA trial, but acknowledged the CGP's statement regarding maintenance therapy. However, pERC noted that the EGP was unable to perform a reanalysis to consider maintenance therapy. As a result, pERC concluded that the clinical and economic evidence on the use of blinatumomab after the fifth cycle was unknown for this setting. pERC noted that health care professionals are already familiar with blinatumomab and considered this to be an enabler to implementation. However, the Committee felt that experience in the use of blinatumomab does not lessen their concerns about the complexity and unusually resource-intensive requirements to prepare and administer the drug and to manage the associated adverse events related to this therapy.
Sequencing and Priority of Treatments • PAG noted that inotuzumab ozogamicin was recently reviewed for the treatment of relapsed or refractory B-cell precursor ALL. PAG is seeking guidance on sequencing of blinatumomab and inotuzumab ozogamicin in this setting.	Finally, pERC discussed PAG's request for guidance on the optimal sequencing and priority treatment with respect to inotuzumab ozogamicin and blinatumomab for relapsed or refractory Ph+ BCP-ALL. pERC noted that there is currently no clinical trial evidence to inform this and pERC concluded that the optimal sequencing of blinatumomab and inotuzumab in this setting is unknown.

ALL = acute lymphoblastic leukemia; CGP = Clinical Guidance Panel; ECOG = Eastern Cooperative Oncology Group; EGP = Economic Guidance Panel; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; Ph+ = Philadelphia positive; Ph– = Philadelphia negative; TKI = tyrosine kinase inhibitor.