pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The 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-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process 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 Funding Request:** For the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia (ALL)	
Submitted By: Amgen Canada Inc.	**Manufactured By:** Amgen Canada Inc.
NOC Date: December 22, 2015	**Submission Date:** August 24, 2015
Initial Recommendation: February 4, 2016	**Final Recommendation:** April 1, 2016

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) does not recommend funding blinatumomab (Blincyto) for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) and who have had only one prior systemic chemotherapy. The Committee was not confident of the net clinical benefit of blinatumomab in this patient population compared to combination chemotherapy due to limitations in the evidence from available clinical trials. pERC was unable to assess the magnitude of benefit of blinatumomab compared to combination chemotherapy in regard to outcomes such as rates of allogeneic stem cell transplant, overall survival, relapse free survival, toxicities, and quality of life. The uncertainty in the clinical benefit of blinatumomab compared to combination chemotherapy and whether there is an unmet need given available options with combination chemotherapy (eg. hyper-CVAD, FLAG-IDA, or other combination chemotherapy) led pERC to conclude that blinatumomab only partially aligned with patient values.

In adult patients with Ph- relapsed or refractory B precursor ALL and who have had at least two prior lines of systemic therapy, pERC recommends funding blinatumomab (Blincyto) conditional on cost-effectiveness being improved to an acceptable level. Treatment should be in patients with a good performance status and continued until unacceptable toxicity, disease progression or a maximum of 5 cycles. pERC made this recommendation because it considered there may be a net clinical benefit of blinatumomab based on a substantial need for treatment options in this small population of patients who have had at least two prior lines of systemic therapy. There is demonstrated efficacy with the use of blinatumomab based on the rates of remission, allogeneic stem cell transplant, overall survival and relapse free survival in a heavily pre-treated population. However, pERC acknowledged there was considerable uncertainty around the magnitude of this clinical benefit due to limitations in the evidence from available clinical trials. In addition, pERC made this recommendation acknowledging that this treatment brings significant toxicities; also, there is a lack of quality of

	life data for this treatment. pERC noted that the use of blinatumomab aligned with patient values as there is a need for more effective treatment options for patients who have had at least two prior lines of systemic therapy. The Committee concluded that at the submitted price and given the high level of uncertainty in the clinical data, blinatumomab was not cost-effective in this population.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied that there may be a net clinical benefit of blinatumomab in patients with Ph- relapsed or refractory B precursor ALL who have had at least two prior lines of systemic therapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of blinatumomab to an acceptable level. pERC noted that the cost of blinatumomab was extremely high and that 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 likely be required in order to improve cost-effectiveness. **Access to Expertise in Managing Side Effects** pERC noted that some of the potential neurological side effects of blinatumomab are severe and 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 centers that have the expertise to monitor and manage these potential side effects. **Collecting Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and the Cost-Effectiveness of Blinatumomab** Given the uncertainty in the magnitude of clinical benefit of blinatumomab in patients with Ph- relapsed or refractory B precursor ALL who have had at least two prior lines of systemic therapy, pERC concluded that additional prospective evidence should be collected to decrease the uncertainty in the incremental effect and provide a greater understanding of the true cost-effectiveness of blinatumomab. **Awaiting Evidence to Reduce Uncertainty in Net Clinical Benefit of Blinatumomab Compared to Currently Available Options** There is uncertainty in the net clinical benefit of blinatumomab compared to currently available treatment options in patients with Ph- relapsed or refractory B precursor ALL and who have had only one prior systemic chemotherapy. pERC acknowledged that a phase III study (TOWER) comparing blinatumomab and physicians' choice combination chemotherapy is expected to provide data to address this uncertainty. **Resource Use and Adoption Feasibility** pERC noted that the 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 of specialized infusion pumps, training of pharmacy and nursing staff, coordination of outpatient and hospital resources, and monitoring and treatment of adverse events, all of which may require significant output of cost and human resources. **Wastage and Budget Impact Likely Impact Adoption Feasibility** pERC noted that the EGP estimates were unable to include the potential for wastage and therefore the potential impact on the cost-effectiveness

	estimates is unknown. pERC expects that there may be considerable wastage with blinatumomab given the restriction on jurisdictions to use only the 48 hour infusion pumps. Depending on the cycle of treatment and dose of blinatumomab used, pERC anticipates wastage could range from 16%-45% of the vial. pERC therefore agreed that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a funding recommendation; these may include advocating for the availability of a smaller vial size.

SUMMARY OF pERC DELIBERATIONS

Acute lymphoblastic leukemia (ALL) is a highly aggressive hematologic malignancy characterized by bone marrow infiltration and marrow failure and represents approximately 20% of all leukemia's in adults. ALL is associated with a particularly poor prognosis for patients who are 30 years of age or older, or who have a lack of initial response to induction combination chemotherapy, or cytogenetic abnormalities. In contrast to upfront treatment, there is no standard treatment for patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B precursor ALL. pERC noted that the available treatment options include salvage treatment (ie. second line treatment) with combination chemotherapy (i.e. hyper-CVAD or any regimen not used in upfront treatment) to achieve remission and if possible, potentially curative allogeneic hematopoietic stem cell transplant (allo-HSCT) in consolidation of remission. There is currently a high degree of uncertainty as to the response rates achieved with regimens used for salvage therapy, with slightly higher rates reported for patients treated after first relapse than later in the disease course after multiple relapses. However, there is a small subgroup of patients who relapse on currently available salvage combination chemotherapy or who are not candidates for allo-HSCT (i.e. have had at least 2 prior lines of systemic therapy including induction and one salvage therapy). These patients are currently treated with palliative options including supportive care, blood transfusion, and low-dose chemotherapy. As there are limited treatment options available for these patients who relapse after 2 lines of systemic therapy, pERC acknowledged the need for more effective treatments in this setting.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of two non-randomized, non-comparative studies evaluating blinatumomab (MT 103-211 and MT 103-206) included in the pCODR systematic review. While pERC considered that the two trials were appropriately conducted non-randomized studies, the Committee noted that only limited conclusions could be drawn from these studies because there were no direct comparisons to currently available options. pERC also considered the results of an unpublished historical cohort of patients with ALL provided by the submitter. pERC had several concerns with the comparability of the historical cohort to the MT 103-211 study, including:

- different treatment patterns as data from the historical cohort were gathered from 1990 to 2014;
- differences in patient characteristics (more patients had no prior allo-HSCT, a lower proportion of patients had ≥50% bone marrow blast, and a higher proportion of patients were in first or second relapse) and
- differences in the definition of the complete remission (the primary outcome)

pERC also noted that the impact of blinatumomab on quality of life (QoL) is unknown, as it was not measured in either study. Therefore, although pERC agreed that there is activity with blinatumomab, there was considerable uncertainty in the magnitude of effect given the lack of comparative data and long term outcome data on patient important outcomes such as rates of allo-HSCT, overall survival, and relapse free survival. Overall, given other currently available treatment options (eg. combination chemotherapy), pERC was unable to accept the considerable uncertainty in clinical benefit for the use of blinatumomab in the broad Ph- relapsed or refractory B precursor ALL population (ie. patients who have not had prior salvage therapy). pERC further noted that it is feasible to conduct a randomized controlled trial (RCT) of blinatumomab versus currently available treatment options in this setting as there is an ongoing phase III RCT (TOWER) which will provide data on overall survival and patient reported outcomes and which pERC expects will provide clarity on the comparative effectiveness of blinatumomab versus currently available treatment options.

pERC however acknowledged that there is a substantial need for treatment options in patients who have received at least two prior lines of systemic therapy and therefore concluded that there may be a net clinical benefit for these patients. pERC considered the results of the MT 103-211 and MT 103-206 studies, which showed encouraging complete remission/complete hematologic remission (CR/CRh) rates, allo-HSCT rates, overall survival, and relapse free survival. pERC acknowledged that a proportion of patients

in the MT 103-206 study survived beyond 30 months after the start of blinatumomab treatment. pERC noted the long term survival seen in some patients who received blinatumomab is uncommon in this disease where the prognosis is particularly poor in later lines of therapy. pERC noted the impact of blinatumomab on QoL is unknown, as it was not measured in either study. pERC discussed the toxicity profile of blinatumomab and noted it to be similar to combination chemotherapy, including infections or cytopenias which may result in patients needing hospitalization or their death. In addition, pERC noted that significant neurological toxicity and severe cytokine release syndrome are unique to treatment with blinatumomab and occurred in both studies. However, given the lack of a comparator arm in either study, pERC considered the safety data to be preliminary. Overall, pERC acknowledged that toxicities with blinatumomab were similar to combination chemotherapy and are well-known to hematologists with experience in treating ALL. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding conclusions made on the toxicity profile of blinatumomab. Given the absence of comparative safety data and uncertainty in those reported from within the literature, pERC relied on the expertise of the Clinical Guidance Panel to make a conclusion. Based on this, pERC re-iterated that the toxicity profile of blinatumomab is substantial, without adequate comparative evidence to suggest that the agent is safer than combination chemotherapies currently used in this patient population. pERC further noted that results from the phase III RCT (TOWER) will help clarify the toxicity profile of blinatumomab as compared with combination chemotherapies. Upon reconsideration of the Initial Recommendation, pERC also considered feedback from Provincial Advisory Group regarding the performance status of patients to be included in the funding population. While pERC acknowledged that the trial inclusion criteria allowed for the entry of patients with an ECOG PS of 0-2, in this instance the Committee re-iterated that treatment should be restricted to patients who have a good performance status and can tolerate treatment with blinatumomab.

Furthermore, pERC discussed that treatment with blinatumomab should be limited to specialized centers with experience and resources for the drug preparation and the monitoring of patients undergoing this treatment. Considering all of these factors, pERC considered that there may be a net clinical benefit with blinatumomab for patients who have Ph- relapsed or refractory B precursor ALL, have had at least two prior lines of systemic therapy (such as hyper-CVAD). However, pERC noted the limited number of patients in both non-comparative studies and the considerable uncertainty in the magnitude of clinical benefit with blinatumomab. pERC acknowledged the ongoing TOWER study will provide clarity on the magnitude of comparative effectiveness of blinatumomab versus currently available treatment options. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding its conclusion on the net clinical benefit of blinatumomab in the broader patient population (ie. patients who have had only one previous systemic therapy). pERC noted that current available therapies used as a first salvage regimen may lead to stem cell transplant and potential cure in patients. pERC also noted the CGP's conclusion that the benefit of blinatumomab does not diminish when used as second salvage therapy compared to first and agreed that it is reasonable to reserve the use of blinatumomab for patients in second salvage where pERC acknowledged a need for therapeutic options as there are currently no options beyond palliation of symptoms in these patients. Given this rationale, the inclusion of mostly third line or beyond patients in the Topp 2015 study and the lack of comparative efficacy data with blinatumomab, pERC re-iterated that the use of blinatumomab should be reserved for patients that have had at least two systemic therapies. pERC acknowledged feedback from the Submitter that the phase III RCT (TOWER) was recently stopped early for superiority in overall survival. This information was made publically available as a news brief after the posting of the pERC Initial Recommendation. pERC noted that new information provided in the feedback by any stakeholder will not be considered by the Committee in their reconsideration of an Initial Recommendation, as outlined in the pCODR Procedures. pERC re-iterated that the TOWER study may help to reduce the uncertainty in the magnitude of benefit with blinatumomab and help to clarify the potential patient population. Furthermore, pERC agreed that when the full data are available, the TOWER study may form the basis of a resubmission to pCODR.

pERC deliberated on patient advocacy group input, which indicated that patients with ALL value disease control and the management of side effects related to current therapies and ALL. The Committee expressed concerns with blinatumomab's significant toxicity profile and the lack of QoL data in the MT 103-211 and MT 103-206 studies. However, for patients who have had at least two prior lines of systemic therapy, pERC concluded that there is a clear unmet need and blinatumomab aligned with patient values if patients and their caregivers were willing to commit to the intensive treatment schedule and toxicities associated with blinatumomab. pERC also acknowledged the financial burden such as loss of productivity to patients and their caregivers. However, for patients with Ph- relapsed or refractory B precursor ALL who have had only one prior systemic chemotherapy, pERC concluded that blinatumomab only partially aligned with patient values since there is uncertainty in the magnitude of effect of blinatumomab in

comparison to other relevant treatments options, no QoL data on the use of blinatumomab and substantial toxicity. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group on the need for patients to access blinatumomab after one systemic therapy. pERC acknowledged this feedback and re-iterated that the evidence available to move blinatumomab into this earlier stage of therapy is uncertain and comparative efficacy and safety data would be required to expand the funding population. pERC anticipates the TOWER study will help answer this question.

pERC deliberated upon the cost-effectiveness of blinatumomab and concluded that blinatumomab is not cost-effective when compared to hyper-CVAD. pERC accepted the Economic Guidance Panel's (EGP) re-analysis estimates and noted several limitations in the submitted analysis, particularly, the clinical data for blinatumomab from non-comparative studies. pERC also noted that assumptions around wastage and the proportion of patients with prior transplant would impact the cost-effectiveness estimates, however, these inputs were not modifiable in the submitter's model and their impact could not be explored. pERC also considered that blinatumomab has an extremely high cost and would need a substantial price reduction in order for it to be considered cost-effective. Overall, pERC considered that even at the most optimistic estimates provided by the EGP, blinatumomab is not cost-effective relative to hyper-CVAD.

pERC considered the feasibility of implementing a funding recommendation for blinatumomab. pERC agreed with the Provincial Advisory Group's concerns about the uncertainty in the long-term efficacy and safety data for blinatumomab. Although there is a very small population of patient with Ph- relapsed or refractory B precursor ALL, the potential budget impact could be large given the high cost of blinatumomab and the potential for wastage as the one vial size of blinatumomab is larger than the recommended daily dose of blinatumomab (38.5 µg vial vs 28 µg daily dose). pERC noted that specialized pumps are also needed for blinatumomab infusion and these may not be currently available in all outpatient chemotherapy centers. This would also increase the budget impact of funding blinatumomab. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer and PAG related to anticipated drug wastage with blinatumomab. pERC noted that wastage varies with the cycle of treatment and the type of infusion pump. Based on feedback from PAG, jurisdictions will likely use the 48 hour infusion pumps exclusively as the battery life span of the 96 hour infusion pump may not last long enough. pERC agreed that there are instances where most of a vial is used and wastage is minimal (ie. 48 hour IV bag for 28ug/day with 16% of vial being wasted). However, pERC noted that a restriction to using only the 48 hour pump may result in substantially more wastage. pERC agreed that the estimate for wastage could be 16-45% depending on the cycle of treatment and dose of blinatumomab. Additionally, pERC also acknowledged that the preparation, administration and monitoring of blinatumomab infusion is very resource intensive and would increase workload in clinics, particularly for pharmacy and nursing resources. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the PAG on the significant resource use required to administer blinatumomab. pERC agreed with the PAG and noted that the preparation, administration and monitoring of blinatumomab infusion will present considerable implementation challenges.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from two patient advocacy group (Canadian Cancer Survivor Network)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Canadian Cancer Survivor Network)
- the Submitter (Amgen Inc.)

In adult patients with Ph- relapsed or refractory B precursor ALL who have had only one prior systemic chemotherapy, the pERC Initial Recommendation was to not recommend funding blinatumomab (Blincyto). In adult patients with Ph- relapsed or refractory B precursor ALL who have had at least two prior lines of systemic therapy, the pERC Initial Recommendation was to recommend funding blinatumomab, conditional on cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the patient advocacy group and pCODR's Provincial Advisory Group agreed in part with the initial recommendation. The manufacturer disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of blinatumomab as a monotherapy compared to an appropriate comparator, on patient outcomes in the treatment of adults with Philadelphia chromosome-negative (Ph-) relapsed or refractory B precursor acute lymphoblastic leukemia (ALL).

Studies included: Two non-comparative studies

The pCODR systematic review included two phase II non-randomized interventional trials, MT 103-211 and MT 103-206 which enrolled adult patients with Ph- relapsed or refractory B precursor ALL.

- For study MT 103-211 key inclusion criteria required that patients have primary refractory or relapsed leukemia(refractory or relapsed defined as: first relapse within 12 months of first remission; relapse within 12 months of allogeneic hematopoietic stem-cell transplantation (allo-HSCT); or no response to or relapse after first salvage (ie. second line therapy). Patients were also required to have at least 10% bone marrow blasts and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Patients with minimal residual disease (MRD), Ph+ ALL, ALL in the central nervous system (CNS) or testes, and pediatric patients were excluded from enrollment in this study. Blinatumomab was administered in a stepwise manner at 9 µg/day for 1 week, then 28 µg/day for 3 weeks in order to reduce the risk of cytokine release syndrome. Dexamethasone premedication was provided to patients along with blinatumomab.
- For study MT 103-206 key inclusion criteria required the presence of >5% leukemic blasts in the bone marrow in patients with primary refractory disease or relapse after induction and consolidation chemotherapy or after allo-HSCT, an ECOG PS of 0-2, and a life expectancy of at least 12 weeks. Patients with MRD, Ph+ ALL eligible for dasatinib or imatinib treatment, history or presence of clinically relevant CNS pathology, active CNS leukemia, and pediatric patients were excluded from enrollment in this study. There were three sequential dose cohorts in the dose finding period of the study, however, 5 µg/m^2/day for week 1, then 15 µg/m^2/day for 3 weeks was used in the extension phase of the study.

pERC noted that the non-randomized design of the two studies made interpreting the efficacy and safety results difficult, especially when assessing outcomes such as remission rate and relapse free survival, endpoints that are more open to subjective bias. In addition to the MT 103-211 and MT 103-206 trials, the pCODR review also included contextual information on the critical appraisal of results from study 20120310 which provided historical efficacy data on treatments used for patients with relapsed or refractory B precursor ALL.

Patient populations: Majority of patients with ≥1 prior salvage therapy

Study MT 103-211 enrolled 189 patients with primary refractory, relapsed or refractory, Ph- B precursor ALL. MT 103-206 enrolled 36 patients with relapsed or refractory B precursor ALL. Baseline characteristics were similar in the two trials. In both trials, treatment with blinatumomab continued until disease progression, unacceptable toxicity or a maximum of 5 cycles.

Notable characteristics in the patient population for MT 103-211 and MT 103-206, respectively, included the following: median age of patients was 39 and 32, majority of patients had an ECOG PS of 0 (33.9% and 41.7%) or 1 (49.2% and 52.8%), and the majority of patients had not had prior allo-HSCT (66% and 58%). pERC noted that most patients in the larger study (MT 103-211) were in their second or later salvage therapy with combination chemotherapy, with 41%, 22% and 17% having 1, 2 or >2 prior salvage therapies.

Key efficacy results: Clinically meaningful improvement in CR/CRh rates, OS, and RFS

The key efficacy outcomes deliberated on by pERC included complete remission or complete remission with partial count recovery (CR/CRh)within the first two treatment cycles, overall survival (OS), relapse free survival (RFS), and percentage of patients who received an allo-HSCT after treatment with blinatumomab.

The CR/CRh rate within the first two cycles of treatment with blinatumomab in the MT 103-211 study was 43% (95%CI: 36-50) and in the MT 103-206 study was 69% (95%CI: 52-84). pERC agreed with the Clinical Guidance Panel's (CGP) opinion that the rates of complete remission/complete remission with partial count recovery (CR/CRh) observed with blinatumomab in the two studies were similar to response rates observed with current treatment options. Among patients achieving CR/CRh, 40% and 52% of patients in the MT 103-211 and MT 103-206 studies, went on to receive allo-HSCT. pERC also discussed improvements in median OS and RFS. In the MT 103-211 and MT 103-206 studies, median OS was 6.1 and 9.8 months and median RFS was 5.9 and 7.6 months, respectively. pERC noted that although there is efficacy with blinatumomab, the magnitude of the effect was uncertain given the lack of comparative and long term outcome data. However, pERC also noted that in the MT 103-206 study, a proportion of patients survived beyond 30 months after initiation of blinatumomab treatment. pERC noted that the long term survival seen in some patients who received blinatumomab is uncommon in this disease where the prognosis is poor, especially in a heavily pre-treated cohort. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding pERC's conclusion on the CR/CRh rate observed with blinatumomab. In the absence of comparative efficacy data, pERC considered results from an historical comparator, clinical opinion from the CGP and response rates reported in the literature. pERC discussed that there is considerable uncertainty in the reported response rates for currently available treatment options, based on evidence from the literature as well as the submitted historical cohort. Given this uncertainty, pERC was comfortable to re-iterate that the currently available data suggests response rates for combination chemotherapies and blinatumomab are relatively similar. pERC acknowledged that the TOWER study, an RCT comparing blinatumomab to physician's choice combination chemotherapy, will be able to provide information on the comparative efficacy and safety between these therapeutic options.

Quality of life: Not measured

pERC noted that improvement in QoL was an important outcome for patients as symptoms and problems with ALL affected patients' QoL and ability to enjoy life. For patients with Ph- relapsed or refractory ALL, currently available treatments are associated with severe side effects that have a substantial impact on QoL.

Quality of life was however not measured in the MT 103-211 or MT 103-206 studies. pERC expressed disappointment that Quality of Life was not measured, and was unable to comment on the impact of blinatumomab on quality of life.

Safety: Significant toxicities requiring intensive and specialized management

pERC discussed the adverse events observed in the MT 103-211 and MT 103-206 studies. In study MT 103-211, grade 5 adverse events (AEs) was experienced by 28 (15%) of patients with the majority due to infections. Grade 3 and 4 AEs were experienced by 38% and 30% of patients, respectively. pERC noted that although there was no comparative data on safety outcomes in either study, the Committee agreed with the CGP's opinion that the toxicity associated with blinatumomab was consistent with currently available combination chemotherapy (grade 3/4 cytopenias, high rates of infection, and potential to cause neurological toxicity), with the exception of the apparent increase in neurological toxicities in patients receiving blinatumomab. Neurological toxicities of grade 3 and 4 were experienced by 11% and 2% of patients, respectively, these included encephalopathy, confusional state, and ataxia. Three (2%) patients experienced grade 3 cytokine release syndrome (CRS). In study MT 103-206, 22 of 36 patients died including six patients who died as a result of infections during the study period. Two of the 36 patients had grade 3 CRS. pERC considered that the neurological toxicities and CRS associated with treatment with blinatumomab were unique and felt strongly that treatment with blinatumomab should be limited to specialized centers with experience and resources for the drug preparation and the monitoring of patients undergoing this treatment. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding conclusions made on the toxicity profile of blinatumomab. In the absence of comparative safety data and uncertainty in those reported from within the literature, pERC relied on the expertise of the Clinical Guidance Panel and pERC re-iterated that the toxicity profile of blinatumomab is substantial and there is a lack of evidence to demonstrate that this agent is safer than combination chemotherapies currently used in patients. pERC further noted that results from the phase III RCT (TOWER) will help clarify the toxicity profile of blinatumomab as compared to combination chemotherapies.

Limitations: No comparative data with currently available therapies

pERC discussed several limitations in the two studies using blinatumomab in Ph- relapsed or refractory B precursor ALL. Both studies were non-comparative, thus there is substantial uncertainty regarding the magnitude of benefit with blinatumomab compared to other therapies. pERC further discussed the limitations of non-randomized, non-comparative studies and considered that, although the MT 103-211 and MT 103-206 studies were appropriately conducted, the conclusions that can be drawn from non-randomized, non-comparative data are not as robust as those that can be drawn from randomized controlled trials. pERC also discussed the contextual information on results from Study 20120310 which provided historical efficacy data on treatments used for patients with Ph- relapsed or refractory B precursor ALL. pERC considered the results of this analysis and noted several limitations. While statistical methods were used to adjust for differences in age and prior lines of therapy between Study 20120310 and MT 103-211, pERC agreed important differences remained in baseline characteristics that may have an impact on the estimates of efficacy between the two cohorts. These included differences in proportion of patients with elevated blast counts at baseline, unaccounted differences in prior lines of therapy (20% of patients in MT 103-211 had no prior salvage treatment) and lack of information on the performance status of patients in the historical cohort. Additionally, pERC discussed the potential impact changes in treatment practices may have had on the results of the historical data, as the data was collected over 25 years (1990-2014). Overall, pERC agreed with the CGP that the historical data must be interpreted with caution. pERC also noted that there is an ongoing randomized study (TOWER) of blinatumomab versus physicians choice combination chemotherapy that may address some of the limitations noted and provide more certainty on the effectiveness of blinatumomab.

Need: More effective treatment options for Ph- relapsed or refractory B precursor ALL

For patients with Ph- relapsed or refractory B precursor ALL, the currently available upfront treatment option is combination chemotherapy (such as hyper-CVAD) to induce remission and if possible, proceed to potentially curative allo-HSCT. Upon first relapse, regimens used for salvage (eg. second line treatment with combination chemotherapy not used in upfront therapy) are reported to be successful 20% to 83% of the time, with slightly higher rates reported for patients treated after first relapse than later in the disease course. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer regarding response rates observed within the literature. Generally, pERC agreed that there is no clear indication on the precise estimates for response rates for patients receiving combination chemotherapy as there is a wide range of estimates observed within the literature, considerable heterogeneity in the studied populations, and uncertainty in the appropriateness of evidence provided by the manufacturer through an historical cohort. Given this uncertainty, pERC agreed that the best available evidence suggests response rates for blinatumomab and combination chemotherapy appear to be relatively similar. pERC awaits further clarity on this once the full data for the TOWER study are available. For patients who relapse following first salvage with combination chemotherapy or patients

who are not eligible for allo-HSCT, there are no curative options and patients are treated with palliative intent. Therefore pERC agreed that for patients who have had at least two prior lines of systemic therapy, there remains an unmet need for more effective and tolerable therapies.

PATIENT-BASED VALUES

Values of patients with ALL: Quality of life, disease control, fewer side effects

pERC deliberated on patient advocacy group input and noted that disease control and management of side effects related to current therapies were important to patients. Important disease related symptoms to control included tiredness, neutropenia, infections, bleeding, bruising, discomfort in bones or joints and depression. Patient advocacy group input indicated that the symptoms and problems identified by respondents affected patients' QoL and ability to enjoy life. pERC noted that for patients with Ph- relapsed or refractory ALL, currently available treatments are associated with severe side effects that have a substantial impact on QoL. Upon reconsideration of the pERC Initial Recommendation, pERC expressed regret that patients experience with blinatumomab could not be considered in the deliberation for the initial recommendation since the Patient Advocacy Group input did not include information from patients who had experience with blinatumomab. pERC agreed that this would have aided in pERC's understanding of the impact blinatumomab has on patients.

Patient values on treatment: More treatment options, delay progression

Patients indicated that current therapies were effective at controlling common aspects of Ph- relapsed or refractory B precursor ALL, these treatments were however associated with side effects. Among these side effects of current treatments upset stomach, fatigue, infection and anemia were the most difficult to manage. Patients expressed a desire to stop disease progression, gain better control of symptoms related to ALL and side effects from current medications, and better ease of use. While recognizing the difficulty patient advocacy groups have in accessing patients with first-hand experience with a new treatment, pERC considered that it would be helpful to get input from patients who had experience with blinatumomab. Overall, for patients who have had only one prior systemic chemotherapy, the uncertainty in the clinical benefit of blinatumomab compared to combination chemotherapy and whether there is an unmet need given currently available treatment options(eg. hyper-CVAD), and the lack of quality of life data, led pERC to conclude that blinatumomab only partially aligned with patient values. For adult patients with Ph- relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) and who have had at least two prior lines of systemic therapy, pERC concluded that the use of blinatumomab aligned with patient values as there is a need for more effective treatment options. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Patient Advocacy Group on the need for patients to access blinatumomab after one systemic therapy. pERC further re-iterated that the evidence available in this patient population is uncertain and comparative efficacy and safety data would be required to move blinatumomab into this earlier stage of therapy. pERC anticipates the TOWER study will help answer this question.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis comparing blinatumomab to currently available treatments for patients with Ph- relapsed or refractory B precursor ALL. The comparator was comprised of salvage therapy with Hyper-CVAD (combination chemotherapy). The economic evaluation was based on non-comparative data with statistical adjustments to make baseline patient characteristics similar between MT 103-211 and a historical cohort study (study 20120310). The submitted model was a partitioned-survival model.

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

Given the lack of long term, head-to-head data, there was considerable uncertainty in the clinical inputs for the economic evaluation.A historical cohort study was provided and statistical adjustments were used to derive comparative efficacy data for all efficacy inputs used in the economic model.

Costs considered in the model provided by the submitter included drug costs, drug administration costs, palliative care costs, allo-HSCT costs, inpatient costs, and follow up costs. Cost for AEs were not considered as they were assumed to be equivalent between blinatumomab and the comparator. The key clinical outcomes were OS and CR/CRh estimates (based on study MT 103-211 and a historical cohort) and utility values from the literature.

Drug costs: Very high drug costs, especially compared to salvage therapy
Blinatumomab costs $2,978.27 per vial (38.5 mcg/vial). At the recommended dose of 9 mcg/day for week 1 and subsequent cycles increased to 28 mcg/day starting week 2 through week 4 of the first cycle and all further cycles for the entire 4 week cycle, the daily cost of blinatumomab is $1187.66-1443.75 per day. The cost per 28 day cycle of blinatumomab is $33,257.25-40,424.93.

Hyper-CVAD which consists of cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate, and cytarabine, costs $126.29 per day and the cost per 28 day cycle of hyper-CVAD is $3536.19.

Cost-effectiveness estimates: Substantial uncertainty due to no direct comparative data
pERC deliberated upon the economic analysis submitted providing estimates on the cost-effectiveness of blinatumomab compared to hyper-CVAD. pERC noted that the submitter derived comparative efficacy data using the MT 103-211and a historical cohort study. pERC noted there was substantial uncertainty in the magnitude of the clinical benefit associated with blinatumomab in comparison to the historical data. This made it challenging to estimate the incremental effect of treatment with blinatumomab and, therefore, the resulting incremental cost-effectiveness of blinatumomab. Furthermore, drug cost was a major driver of the incremental cost-effectiveness ratios when compared to all other costs in the economic evaluation. pERC also noted that assumptions around the proportion of patients with prior transplant, adverse events, and wastage would impact the cost-effectiveness estimates, however, these inputs were not modifiable in the submitted model and their impact is unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: No long-term data on efficacy and safety, small patient population, and high drug cost, and significant wastage
pERC discussed factors affecting the feasibility of implementing a positive funding recommendation for blinatumomab. Input from the Provincial Advisory Group (PAG) indicated concerns about the long-term safety and efficacy data for blinatumomab. pERC discussed PAG's input highlighting the absence of a comparator arm in the studies and that there is an ongoing randomized comparative trial in this setting. Although there is a very small population of patients with Ph- relapsed or refractory B precursor ALL, the potential budget impact could be large given the high cost of blinatumomab and the potential for wastage given the one vial size. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the manufacturer and PAG related to anticipated drug wastage with blinatumomab. Based on feedback from PAG, jurisdictions are more likely to use the 48 hour infusion pumps available as the battery life span of the 96 hour infusion pump may not last long enough. While agreeing that there are instances where most of a vial is used (9ug day for week 1 of cycle 1 or 28ug day for all subsequent cycles), pERC noted that restriction to the 48 hour infusion pump could lead to substantially more wastage. pERC agreed that the estimate for wastage could be 16% to 45% of the vial. Additionally, preparation, administration and monitoring of blinatumomab infusion is very resource intensive and would increase workload in clinics, particularly for pharmacy and nursing resources. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the PAG on the significant resources required to administer blinatumomab. pERC agreed with PAG and re-iterated that the preparation, administration and monitoring of blinatumomab infusion will present considerable implementation challenges. pERC also noted that the current scope of review focused on the adult form of the disease and could not comment on the efficacy and safety of blinatumomab in pediatric and adolescent patients. Data on the efficacy and safety of blinatumomab in pediatric and adolescent patients is forthcoming and would require a separate submission to pCODR given the very different character of this disease in pediatric patients. Additionally, there was no information to determine the effectiveness of blinatumomab when used as induction therapy prior to stem-cell transplant or post-transplant as maintenance.

DRUG AND CONDITION INFORMATION

Drug Information	• First-in-class bispecific T-Cell engaging (BiTE) antibody construct • 38.5mcg/vial • Recommended dose of 9 mcg/day for week 1 escalated to 28 mcg/day for 3 weeks, followed by 2 week treatment-free interval, and then up to 4 subsequent cycles of 28 mcg/day for 4 weeks (each followed by a 2 week treatment-free interval)
Cancer Treated	• Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia
Burden of Illness	• Acute lymphoblastic leukemia represents about 20% of all leukemias in adults • Leading cause of cancer-related death for age group of 15 to 30 years • Prognosis of patients who relapse after primary therapy is poor and prolonged survival is rare for patients who fail to achieve remission with salvage chemotherapy
Current Standard Treatment	• Salvage combination chemotherapy (e.g. hyper-CVAD or any chemotherapy not used in upfront therapy) followed by allogeneic-HSCT where possible • For those who fail salvage (second line treatment) with combination chemotherapy, palliative care option consists of supportive care, blood transfusion and low-dose chemotherapy
Limitations of Current Therapy	• There is no standard of care for patients with Ph- relapsed or refractory B precursor ALL, particularly those who fail to achieve remission with salvage chemotherapy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Carole McMahon, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Karen MacCurdy-Thompson, Pharmacist
Danica Wasney, Pharmacist

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

- Scott Berry, Kelvin Chan, and Catherine Moltzan who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate
- Valerie MacDonald who did not vote due to her role as a patient member-in-training

All members participated in deliberations and voting on the final recommendation except:

- Scott Berry, Kelvin Chan, and Maureen Trudeau who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate
- Valerie MacDonald who did not vote due to her role as a patient member-in-training

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 pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of blinatumomab for Acute Lymphoblastic Leukemia (ALL), through their declarations, three members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee 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 their 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 pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*

Use of this recommendation

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