CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Clinical Guidance Report

# Blinatumomab (Blincyto) Resubmission for Acute Lymphoblastic Leukemia

**August 31, 2017**

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# 1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding Blinatumomab for Acute Lymphoblastic Leukemia (ALL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding Blinatumomab for Acute Lymphoblastic Leukemia conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on Blinatumomab for Acute Lymphoblastic Leukemia, a summary of submitted Provincial Advisory Group Input on Blinatumomab for Acute Lymphoblastic Leukemia, and a summary of submitted Registered Clinician Input on Blinatumomab for Acute Lymphoblastic Leukemia, and are provided in Sections 2, 3, 4, and 5 respectively.

## 1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of blinatumomab (Blincyto) as a monotherapy on patient outcomes, in the treatment of adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL), including those who have had one prior line of therapy (i.e., refractory, 1st relapse).

The appropriate comparators for blinatumomab involve multi-agent chemotherapy regimens appropriate in the Canadian setting (e.g, Hyper-CVAD, Flag Ida or Cy VP16). The patient population under review is similar to the Health Canada approved indication for blinatumomab.

Blinatumomab, a novel bispecific T-cell engager (BiTE) antibody construct, is a new treatment option currently under review for adult R/R Ph- B-precursor ALL. Blinatumomab is administered as a continuous infusion as follows: induction and consolidation treatments administered in 6 week cycles and maintenance administered in 12 week cycles. For induction and maintenance, patients were given 4 weeks of treatment and 2 treatment free weeks. During cycle 1 of week 1, patients received 9 µg/day as induction therapy followed by 28 µg/day for all remaining days for the remaining 4 week of treatment. Maintenance treatment given as a 4-week continuous infusion every 12 weeks. Induction was given up to 2 cycles, consolidation up to 3 cycles and maintenance up to 12 months. Patients moved onto subsequent phases of treatment with blinatumomab based on having ≤5% blasts count.

## 1.2 Key Results and Interpretation

### 1.2.1 Systematic Review Evidence

One randomized controlled trial was identified as part of the systematic review. The TOWER study is a Phase III, prospective, open-label, multicenter, comparative study in

adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) comparing blinatumomab to chemotherapy. The study randomized 405 patients in a 2:1 ratio to either blinatumomab or chemotherapy. Included participants were adults greater or equal to 18 years of age who were either refractory to primary induction therapy or to salvage with intensive combination chemotherapy, who were in first relapse with the first remission lasting less than 12 months, in second or greater relapse or relapse at any time after allogenic stem-cell transplantation. In addition, for patients to be included in the trial they had to have 5% or more blasts in bone marrow and an ECOG performance status of ≤2. The primary endpoint for the study was overall survival (OS). Key secondary endpoints included complete remission with full hematological recovery within 12 weeks after initiation of treatment; complete remission with full, partial or incomplete hematological recovery within 12 weeks of initiation of treatment; event free survival (time from randomization until relapse after achieving a complete remission with full, partial or incomplete hematological recovery or death); and Health Related Quality of Life (HRQoL).

Two hundred and seventy one patients were randomized to blinatumomab and 134 patients to chemotherapy. Close to half of the patients (48.1%; 195/405) had an ECOG performance status of 1. Of the patients enrolled in the trial, 150 (37.0%) patients had a previous allogeneic stem-cell transplantation. For 179 (44.2%) patients this was their first salvage treatment phase.

- An interim analysis conducted following 251 recorded deaths demonstrated statistically significantly longer OS in the blinatumomab treated patients compared to the chemotherapy group with the median overall survival of 7.7 months (95% CI: 5.6 to 9.6) in the blinatumomab group as compared to the chemotherapy group who achieved a median OS of 4.0 months (95% CI: 2.9 to 5.3) with a hazard ratio for death, HR = 0.71; 95% CI: 0.55 to 0.93, P=0.01. The median duration of follow-up for the blinatumomab and chemotherapy treated patients were 11.7 and 11.8 months, respectively.
- Estimated event-free survival, defined as the time from randomization until relapse or death after achieving a complete remission with full, partial, or incomplete hematological recovery, at 6 months from the TOWER study was 31% in the blinatumomab group as compared to 12% in the chemotherapy group HR 0.55 (95% CI: 0.43 to 0.71, P<0.001).
- Remission rates were higher in the blinatumomab group as compared to the chemotherapy group following 12 weeks after treatment initiation, with complete remission (CR) with full hematologic recovery being 33.6% (95% CI 28.0 – 39.5) versus 15.7% (95% CI 10.0 - 23.0) (P<0.001), respectively. For complete remission with full, partial or incomplete recovery, similar differences were observed between the blinatumomab (43.9%) and chemotherapy (24.6%) groups, P<0.001.
- Blinatumomab treated patients had better HRQoL as compared to chemotherapy. Functional scores favoured blinatumomab as clinically meaningfully decline was reported in the chemotherapy group for physical functioning, role functioning, social functioning. A clinically meaningfully decline was also reported in the chemotherapy group for fatigue, pain, nausea and vomiting, appetite loss and diarrhea on the symptom scale. As EORTC-QLQ-C30 was measure on days 8, 15 and 29 of each cycle, the reported clinically meaningful decline occurred on at least one of these measurement days. Time to treatment discontinuation (TTD) also favoured blinatumomab for global health status/quality of life (HR: 0.67, 95% CI: 0.52 to 0.87, P=0051), physical functioning (HR: 0.66, 95% CI: 0.51 to 0.85, P=0.0189), role functioning (HR: 0.66, 95% CI: 0.51 to 0.85, P=0.0083) cognitive functioning (HR: 0.70, 95% CI: 0.55 to 0.90, P=0.0194), emotional functioning (HR: 0.64, 95% CI: 0.50 to 0.83, P=0.0022) and social functioning (HR: 0.67, 95%CI: 0.52 to 0.86), P=0.0124) and all symptom-scores for except insomnia and fatigue.

- Grade 3 or higher adverse events were reported in 86.5% of the blinatumomab group and in 91.7% of individuals receiving chemotherapy. Serious adverse events occurred in 61.8% of blinatumomab treated patients and in 45% of chemotherapy treated individuals. The event rate for serious adverse events was determined to be 349.4 events per 100 patient-years in the blinatumomab group as compared to 641.9 per 100 patient-year in the chemotherapy group.

**Table 1: Key Outcomes from TOWER Study[1]**

| | Tower Study | |
|---|---|---|
| | Blinatumomab (N=271) | Chemotherapy (N=134) |
| Overall Survival, median | 7.7 months (95% CI: 5.6 to 9.6) | 4.0 months (95% CI: 2.9 to 5.3) |
| HR (95%CI) | 0.71 (95%CI: 0.55 to 0.93) | |
| p-value | 0.01 | |
| Remission Rate within 12 weeks, % | 43.9% | 24.6% |
| OR (95%CI) | 2.40 (95%CI: 1.51 to 3.80) | |
| p-value | 0.001 | |
| Harms Outcome, n (%) | Blinatumomab (N= 267) | Chemotherapy (N=109) |
| Grade ≥3 | 231 (86.5) | 100 (91.7) |
| AE (any grade) | 263 (98.5) | 108 (99.1) |
| Serious AE | 165 (61.8) | 49 (45.0) |
| Fatal Serious AE | 51 (19.1) | 19 (17.4) |
| WDAE | 33 (12.4) | 9 (8.3) |

AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, SD = standard deviation, WDAE = withdrawal due to adverse event
*HR < 1 favours [arm]

### 1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

#### *Patient Advocacy Group Input*

From a patient's perspective, fatigue, fever and night sweats and weight loss are common symptoms of ALL. Another commonly reported symptom was related to physical and emotional intimacy. Extreme fatigue had the most impact on daily life. Loss of or change in appetite and unexplained weight fluctuations were other ALL symptoms reported to have a large impact on daily lives. The main types of treatment used for ALL are chemotherapy, targeted therapy and allogeneic stem cell transplant. More than two thirds of patient respondents indicated the current treatment did do a sufficient job in managing their cancer symptoms, although all patient respondents reported having some variation of side effects associated with their treatments and therapies. LLSC noted that most ALL treatment side effects are temporary and subside once the body adjusts to therapy or when therapy is completed. Common side effects of the current ALL treatment include: pain, nausea and vomiting, fatigue, infections/non-cancer illness, and fertility and sexual side effects.

#### *Provincial Advisory Group (PAG) Input*

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- New class of drug that fills gap in therapy for relapsed/refractory ALL
- Unusual dosing schedule of 28-day continuous infusion with 2 weeks off
- High rate of toxicities, particularly neurotoxicities, to monitor and treat

Economic factors:

- Complex and highly resource intensive to prepare and administer and rigorous monitoring for toxicities
- Access to treatment an issue since hospitalization required for administration in the first two cycles and proximity to tertiary care centres required
- High cost of drug

### *Registered Clinician Input*

Adult ALL is a rare entity. Current treatment is combination chemotherapy according to the Hyper-CVAD or Flag-Ida protocols followed by a stem cell transplant, if not transplanted in first complete remission.

Blinatumomab would replace combination chemotherapy as the remission inducing treatment at first relapse. Given that blinatumomab is less toxic than chemotherapy, transplants after blinatumomab should be easier and less toxic to the patient, which means less costly to manage.

### *Summary of Supplemental Questions*

There were no supplemental questions identified for this review.

### *Comparison with Other Literature*

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

### 1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

**Table 2: Assessment of generalizability of evidence for blinatumomab**

| Domain | Factor | Evidence | Generalizability Question | CGP Assessment of Generalizability |
|---|---|---|---|---|
| **Comparator** | Chemotherapy treatments used in the TOWER trial are not aligned with current Canadian Practice and choice of therapies. | Chemotherapy in TOWER trial:<br>• FLAG±anthracycline was given to 49/109 patients in the trial.<br>• HiDAC±anthracycline was given to 19/109 patients in the trial.<br>• High-dose methotrexate was given to 22/109 patients on the trial.<br>• Clofarabine single given to 19/109 patients on the trial.<br><br>Chemotherapy in Canadian clinical practice:<br>• Hyper-CVAD<br>• Flag Ida<br>• Cy VP16 | Are the results for the chemotherapy group from the TOWER trial generalizable to treatment outcomes expected with chemotherapies used in the Canadian setting? | Hyper-CVAD and Flag/ida are the two main treatments options used. Some centers might try the others mentioned in the study. These are well known treatment options and the CGP is not concern about the generalizability of the TOWER trial results into the Canadian context. |
| **Outcomes** | None | | | |
| **Setting** | Patients mainly recruited from Europe and other parts of the globe. Two Canadian sites. | The study was conducted at 101 centres and in 21 countries Clinicaltrials.gov NCT02013167 {XX}. The majority of the 405 participants were enrolled in Europe 265 (65.4%). A total of 64 participants (15.8%) were enrolled from Canada and the United States. | Is there any known difference in the practice pattern between the other countries and Canada? Differences that may impact the clinical outcomes or the resources used to achieve the outcomes? | No |

### 1.2.4 Interpretation

Burden of Illness and Need:

Adult Acute lymphoblastic leukemia represents 15% of all leukemia's. About 20% are Ph positive and 80% are Ph negative. With conventional therapy using modified pediatric acute leukemia treatment protocols or undergoing a hematopoietic stem cell transplant (HSCT) for high risk patients in 1st remission. Approximately 60-70% of adult patients with Ph negative ALL can be expected to be cured. For those that are refractory to treatment or relapse, the only chance of a cure is HSCT if a second remission can be achieved. The chances of achieving a second remission with conventional chemotherapy are about 30 - 40% for those who have not undergone HSCT. For those undergoing HSCT, cure rates can be expected to be about 50%, with the remaining 50% dying from relapse of ALL or toxicity from HSCT.

For every 100 adult ALL patients who have not undergone HSCT and relapse, approximately 30-40% will go into remission. About 80% of these (24-32) will likely proceed to HSCT of whom about 50% (12-16) will be cured of their leukemia. The remaining 50% die either due to relapse of their leukemia or mortality due to HSCT. As such newer more effective treatments are required to get patients into remission and the potential for cure via HSCT for their relapsed/refractory ALL. There is no standard therapy that is curative for patients who relapse post HSCT.

Effectiveness:

The TOWER study was a prospective, open label multi center trial in 101 centers in 21 countries comparing blinatumomab to conventional chemotherapy using a 2:1 randomization. The primary study endpoint was overall survival. The randomization was stratified by age (<35 vs >35 years), previous salvage therapy and previous HSCT. Inclusion criteria included age >18 years, refractory to induction therapy or salvage with intensive combination chemotherapy, first remission less than 12 months and second or greater relapse or relapse at any time after HSCT and ECOG performance status of 2 or less. Key exclusion criteria included other cancers, isolated extramedullary leukemia and autoimmune disease.

Blinatumomab was compared to one of 4 chemotherapy regimens – FLAG ± anthracylcine, HiDAC ± anthracylcine or high dose methotrexate based regimens, or clofarabine. The CGP noted the difference in the choice of treatments currently used in Canadian centers and agreed that the overall trial results are generalizable to the Canadian clinical setting.

Both the arms were balanced for disease refractory to primary therapy or salvage therapy, first relapse with duration of remission <12 months, untreated second or greater relapse and relapse after HSCT, number of prior salvage regimens, previous HSCT and degree of marrow involvement.(table 6). There are some biases as for instance, 25 (18.7%) of patients in the chemotherapy arm did not receive the treatment as assigned. Given that the analysis was done on an Intent to treat (ITT) as opposed to actual treatment received, the impact of this bias should be minimised.

The study was stopped early after a planned interim analysis of 75% of the total number of required deaths at the recommendation of the independent data and safety monitoring committee, due to the benefit observed according to the O'Brien\-Fleming stopping boundary.

### *Efficacy Outcomes*

#### *a) Remission Rates*

Remission rates in the TOWER study were higher in the blinatumomab group as compared to the chemotherapy group 12 weeks after treatment initiation with complete remission (CR) with full hematologic recovery being 33.6% versus 15.7% (P<0.001), respectively. For complete remission with full, partial or incomplete recovery demonstrated similar differences between the blinatumomab (43.9%) and chemotherapy (24.6%), P<0.001. The CGP agree that the achievement of complete remission in a greater proportion of patients in the blinatumomab arm is a clinically meaningful outcome as it allows a greater number of patients the opportunity to qualify for stem cell transplant, however the CGP noted that the number of patients who went on to HSCT were the same in both arms (24%). While some of the reasons could be due to co-morbidities that precluded patients from receiving HSCT, lack of availability of donor or relapsing while waiting to proceed to HSCT, the TOWER study did not specify the reasons.

#### *b) Event-Free Survival*

Estimated event-free survival (EFS), was defined as being the time from randomization until relapse or death after achieving a complete remission with full, partial, or incomplete hematological recovery. At 6 months EFS was statistically significant - 31% in the blinatumomab group as compared to 12% in the chemotherapy group HR 0.55 (95% CI: 0.43 to 0.71, P<0.001). The CGP therefore agreed that the benefit of blinatumomab appears to be within the first 6 months of treatment.

#### *c) Overall Survival*

In the TOWER study for the interim analysis following 251 recorded deaths, overall survival in the blinatumomab treated patients was statistically significantly longer than the chemotherapy group with a median overall survival in the blinatumomab group of 7.7 months (95% CI: 5.6 to 9.6) as compared to the chemotherapy group median survival of 4.0 months (95% CI: 2.9 to 5.3; hazard ratio for death, 0.71; (0.55 to 0.93, P=0.01) (Figure 2a). Among those individuals that received study treatment, blinatumomab (98.5%) or chemotherapy (81.3%) the overall survival benefit was similar as in the ITT analysis [7.7 versus 4.1 months respectively with a hazard ratio for survival of 0.69 (95% CI: 0.52 to 0.91, P= 0.009)]

Furthermore, when the overall survival was censored to account for those individuals that underwent stem-cell transplantation, the median overall survival for those treated with blinatumomab was 6.9 months (95% CI: 5.3 to 8.8) and for the chemotherapy group median overall survival was 3.9 months (95% CI: 2.8 to 4.9) with a hazard ratio for death of 0.66 (95% CI: 0.50 to 0.88).

Overall survival was analysed by predetermined subgroups including age less than 35 years, salvage treatment phase, previous allogeneic stem-cell transplantation and bone marrow blasts less than 50%. The overall survival benefit was found to be statistically significantly different for individuals undergoing their first salvage treatment (HR: 0.60, 95% CI: 0.39 to 0.91), second salvage treatment (HR: 0.59, 95% CI: 0.38 to 0.91), and in patients without previous stem-cell transplantation (HR: 0.70, 95% CI: 0.51 to 0.96)

Remission rates, EFS and overall survival were statistically significant for blinatumomab compared with conventional chemotherapy. The CGP therefore agree that the benefit of blinatumomab is in its ability to allow a greater number of patients to achieve CR and live longer both of which may help get patients to transplant where they may have the potential for a cure.

### *d) Allogeneic Stem-Cell Transplantation*

A similar percentage of individuals (24%) underwent allogeneic stem-cell transplantation in the blinatumomab (N=65) and chemotherapy groups (N=32), including 14% (N =38) and 9% (N=12) of patients in each group respectively who achieved remission without the use of another treatment. Of those patients that achieved remission, and who had an allogeneic stem-cell transplantation, there was no difference in outcome between the two groups - 26% compared to 25% in the blinatumomab and chemotherapy group died with a median follow-up period of 206 and 279 days, respectively. As a higher number of patients in the blinatumomab arm achieved a CR, one would have expected a higher proportion of patients in the Blinatumomab arm to have undergone HSCT. The reasons why this did not occur is not clear.

A total of 140 patients who had relapsed post HSCT were enrolled in the TOWER trial (94 and 46 in the Blinatumomab and chemotherapy groups, respectively). Median survival was 7.7 months versus 5.3 months in the blinatumomab versus chemotherapy group respectively with a HR of 0.81 (0.51-1.26). CGP concluded that blinatumomab in this setting can be considered palliative, not curative.

Following the posting on the pERC initial recommendation, the submitter provided feedback on the impact of blinatumomab in allowing a greater number of patients to proceed to stem cell transplant. The CGP considered this and references made by the submitter to the registered clinician input indicating that blinatumomab should allow a greater number of patients to proceed to stem cell transplant. While the CGP agreed that a greater number of patients in the blinatumomab did achieve CR and have statistically significant OS, this did not translate into a greater proportion of patients proceeding to HSCT as the available evidence demonstrates similar numbers within the two treatment groups received transplant. It is notable that the trial was not designed to assess the impact of blinatumomab on eligibility of patients for transplant. As well, a number of other factors could have contributed to why a similar number of patients received transplant. As previously noted by the CGP, this was not explained by the submitter and remains unknown. The submitter also speaks to information previously available in the submission indicating that clinicians who treat ALL consider "patients who survive at least two years have a higher chance of being long-term survivors…" The CGP noted that this statement usually applies to patients who have undergone bone marrow transplant and not patients who have been treated with chemotherapy. The submitter has yet to show that patients who received blinatumomab are long term survivors as the follow up beyond 2 years is short and by their own assertions caution is needed when interpreting outcomes beyond 15 months.

The CGP further noted feedback from the submitter cautioning the interpretation of the tail of the Kaplan-Meir curves for OS (beyond 18 months). The submitter indicates that few patients were available near the tail of the curves and therefore uncertainty is to be expected on the shape of the KM curves. The CGP agree that the benefit of blinatumomab is evident between months 3 to 15/18 for OS. There is however considerable uncertainty following the end of the trial period. In the absence of any other data to help understand the long term impact of blinatumomab on OS, the CGP agree caution is appropriate and justifies the need for a more conservative approach in interpreting the data both in the clinical and economic evaluation (eg. choice of time horizon, assumption of no OS benefit as a scenario in the economic evaluation). The submitter points out that the survival curves do separate beyond 18 months when the results are censored for patients who

received stem cell transplant. The CGP however re-iterates that caution must be used in interpreting the tail of the KM curves, as previously highlighted by the submitter.

The submitter lastly indicated that the 5% of patients who crossed from the chemotherapy to blinatumomab arm could have impacted the tail of the KM curves. The CGP however agree that this is a very low cross over rate and extremely unlikely to have an effect on overall survival of patients in the control group. It is also notable that there was no evidence presented to support the submitter's assertion that the 5% of patients who crossed from the chemotherapy to blinatumomab arm could have impacted the tail of the KM curves.

Furthermore, the CGP noted feedback from the submitter regarding the resource intensive nature of administering blinatumomab, as is discussed in the initial recommendation. The CGP note that blinatumomab is certainly a complicated treatment to administer. The extra resources required to train staff and administer the treatment are justified. The CGP also agree that centers that routinely treat ALL would have had experience with blinatumomab already therefore the concerns outlined will be limited. However there would be significant training and resources required to use this drug in a medium or small centre. Given the rarity of ALL, the use of Blinatumomab in smaller communities is unlikely as use should likely be restricted to centres that routinely treat ALL.

Quality of Life

Health related quality of life was measured in the TOWER study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and was measured at baseline, day 8, day 15, day 29 in each cycle of therapy and at day 1, day 15, and day 29 during each consolidation cycle, and at the safety follow-up visit. HRQoL data was available at baseline and at least one follow-up time point for 247/267 (92.5%) of blinatumomab patients and for 95/109 (87.2%) of chemotherapy treated patients. Functional scores and time to deterioration favoured blinatumomab for global health status/quality of life (HR: 0.67, 95% CI: 0.52 to 0.87, P=0.0051), physical functioning (HR: 0.66, 95% CI: 0.51 to 0.85, P=0.0189), role functioning (HR: 0.66, 95% CI: 0.51 to 0.85, P=0.0083) cognitive functioning (HR: 0.70, 95% CI: 0.55 to 0.90, P=0.0194), emotional functioning (HR: 0.64, 95% CI: 0.50 to 0.83, P=0.0022) and social functioning (HR: 0.67, 95%CI: 0.52 to 0.86), P=0.0124) and all symptom-scores for except Insomnia.[9] Much of the detriment in the Quality of life data was attributable to the time on treatment, which for the majority of the chemotherapy group was only 1 cycle. Therefore the measurement of quality of life is truly for the first 28 days of the study for the majority of the chemotherapy group, with only 2 individuals having data at 3 months.

Safety:

Adverse events were similar between the two treatment groups. Grade 3 or greater AE's were reported in 86.5% of patients in the blinatumomab arm vs 91.7% in the chemotherapy arm and any grade AE in 98.5% of patients in the blinatumomab arm vs 99.1% in the chemotherapy arm. Fatal serious AE were also similar between the blinatumomab and chemotherapy groups (19.1% and 17.4%, respectively). However, serious AE were higher in the blinatumomab arm compared with the chemotherapy arm (61.8% vs 45.0%, respectively).

**1.3 With respect to SAE by organ and systems, there were more SAE in the blinatumomab group compared with chemotherapy – especially general disorders and administrative site issues (10.1% vs 1.8%), immune system (4.1% vs 0%), injury, poisoning (error in calculation so a higher dose blinatumomab was given) and procedural complications (5.6% vs 0.9%), cytokine release syndrome – 7 ( 2.6% vs 0 for chemotherapy), metabolism and nutritional disorders (3.7% vs 1.8, nervous system (7.1% vs 3.7%) and respiratory, thoracic and mediastinal disorders (5.6% vs 3.7%). Conclusions**

The Clinical Guidance Panel concluded that there is a net overall clinical benefit with the use of blinatumomab for the treatment of adults with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL). The CGP based this conclusion on the evidence of the TOWER study which demonstrated a statistically significant and clinically meaningful improvement in median overall survival for patients receiving blinatumomab (7.7months) compared to chemotherapy (4.0 months), statistically significant and clinically meaningful improvement in EFS in favour of blinatumomab compared to chemotherapy (31% versus 12%, respectively) at 6 months with a HR of 0.55.

In making this conclusion, the Clinical Guidance Panel also considered that:

- A statistically significant and clinically meaningful improvement in overall survival benefit in patients receiving blinatumomab as first or second salvage treatment and those who had not previously undergone HSCT
- Among patients randomised to chemotherapy, 18.7% of patients did not receive treatment and the chemotherapy offered in the TOWER study may not reflect current Canadian treatment practice. Despite these limitations, the CGP agreed that the overall trial results are generalizable to the Canadian clinical setting.
- The adverse event and severe adverse event were similar between the two treatment groups.
- Quality of life data was limited as only the first 28 days was reported for chemotherapy. The data available suggests that quality of life is probably better for patients treated with blinatumomab compared to chemotherapy as measured by EORTC QLQ-C30 in the areas of global health status, physical, emotional, cognitive, and social functioning.
- The use of blinatumomab compared with chemotherapy for patients who had previously undergone HSCT offered no clear advantage.
- Therefore blinatumomab cannot be considered a curative treatment but more as a bridge to other salvage treatments such as allogeneic HSCT. CGP came to this conclusion as the outcomes for refractory patients and those relapsing post-HSCT are similar whether patients received conventional chemotherapy or blinatumomab.

# 2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Leukemia Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

## 2.1 Description of the Condition

Acute Lymphoblastic Leukemia (ALL) is a highly-aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure (fatigue, dyspnea, bleeding, bruising or infection), organ infiltration (lymph nodes or central nervous system (CNS)) and systemic complaints (chiefly fevers, fatigue and night sweats). Patients typically present to hospital acutely ill, often with infection in neutropenia, electrolyte disturbances related to tumour lysis syndrome or with neurological abnormalities. The majority of patients have circulating blasts at presentation and the diagnosis is confirmed by bone marrow histology and ancillary tests like flow cytometry and immunohistochemistry.

## 2.2 Accepted Clinical Practice

ALL represents approximately 15% of adult cases of acute leukemia and adult treatment protocols are based largely on the principles that led to successful outcomes in children. These principles include the use of sequential multi-drug combinations for remission induction. Agents with activity in ALL induction include corticosteroids, cyclophosphamide, methotrexate, anthracyclines and L-asparaginase. Early application of CNS-directed therapy by direct intrathecal administration and whole-brain radiotherapy is intended to address occult CNS disease. Intensification and maintenance phases may last up to 30 months with some protocols and impose significant personal and financial burdens on affected patients and their families.

A number of factors determine prognosis in ALL. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors in ALL. Newer treatment protocols, however, have proven effective across the spectrum of cytogenetic abnormalities and seem to have abrogated some of the risk associated with high-risk cytogenetics in this disease. The presence of the Philadelphia chromosome (which results from a balanced translocation between chromosomes 9 and 22) confers sensitivity to tyrosine kinase inhibitors and while Philadelphia-positive ALL is not curable with conventional treatment, the use of TKI's can be associated with durable remissions and good quality of life. Patients who present with an increased white blood cell count (WBC > 30 x 109/L for B-Cell and > 100 x 109/L for T-Cell) and those over age 34 are at higher risk of adverse outcomes, and patients with both of these risk factors or who fail to achieve complete remission within four weeks of starting treatment are considered for allogeneic HCT in first remission.

The majority of young patients with ALL can expect to be cured with modern chemotherapy protocols. For instance, Storring et al.[3] reported the results of their experience using a modified version of the Dana-Farber Cancer Institute protocol at the Princess Margaret Hospital. This pediatric-inspired protocol resulted in 89% of patients achieving a complete remission, and five-year relapse free survival of 71% was reported.[3,4] In contrast to initial treatment, where the standard approach is pediatric-inspired protocols, there is no standard treatment for patients with relapsed or refractory ALL. The prognosis of patients at this stage is poor and prolonged survival is vanishingly rare for patients who fail to achieve remission with salvage chemotherapy. In general patients receive an intensive chemotherapy regimen with chemotherapy combinations not used in up-front therapy to induce a remission and, if possible, proceed to an allogeneic

hematopoietic cell transplant. Multi-agent chemotherapy regimens appropriate in the Canadian setting may include Hyper-CVAD, Flag Ida or Cy VP16 among others. Regimens used for reinduction are reported to be successful 40-60% of the time, with slightly higher rates reported for patients treated after first relapse than later in the disease course.[5] Treatment-related deaths are observed in 5-15% of patients receiving salvage therapy. Relapsed/refractory ALL patients are encouraged to proceed to allogeneic hematopoietic cell transplantation at the earliest opportunity as cure is not expected with salvage therapy alone. Patients who fail reinduction or for whom HCT is not feasible due to comorbidities or lack of donor have no curative options and are treated with palliative intent. Survival of this cohort of relapsed/refractory patients is limited.

## 2.3 Evidence-Based Considerations for a Funding Population

The management of B-Cell non-Hodgkin lymphoma was revolutionized by the introduction of monoclonal anti-CD20 antibodies into clinical practice. These agents however show only limited activity in ALL. Blinatumomab represents the first novel therapeutic agent in Philadelphia-negative ALL in over thirty years. Blinatumomab is a first-in-class bispecific T-Cell engaging (BiTE) antibody with sites to engage CD19 expressed on B-ALL tumour cells and CD3 on T-Lymphocytes. By bringing these two cell types into close approximation a T-Cell mediated immune response is simulated, which results in clearance of malignant cells by the redirected immune system. Adverse effects reflect this mechanism of action and include cytokine release syndrome, tumour lysis syndrome, infections and febrile neutropenia, and encephalitis.

In a 2015 review with pCODR-CADTH, evidence from two phase II non-randomized interventional trials (MT 103-211 and MT 103-206) was evaluated. At the time, the pCODR Expert Review Committee (pERC) recommendation was to fund blinatumomab only for adult patients with Ph- relapsed or refractory B precursor ALL and who have had at least two prior lines of systemic therapy. In 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, pERC did not recommend funding because it 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 current review is a resubmission for blinatumomab based on the results of the TOWER study, evaluating blinatumomab (Blincyto) as a monotherapy on patient outcomes, in the treatment of all adult patients with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL), including those who have had one prior line of therapy.[6]

## 2.4 Other Patient Populations in Whom the Drug May Be Used

While there is no evidence available to extend the use of blinatumomab into other patient populations, patients with CD19+ diseases such as low-grade lymphoma or CLL could potentially benefit from treatment with blinatumomab. The CGP acknowledges that there is no data on the magnitude of benefit in this group and use of blinatumomab should not be put into practice until studies confirming its effectiveness and cost-effectiveness compared to other available alternatives is established. Blinatumomab may also be used/offered to patients with Ph+ disease and to pediatric patients but these patient populations were not within the scope of the current review and have not been included in the economic analysis.

# 3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on blinatumomab (Blincyto) for adult acute lymphoblastic leukemia (ALL) and their input is summarized below: the Leukemia & Lymphoma Society of Canada (LLSC).

An online survey (Survey #1) was posted on Survey Monkey and distributed by LLSC staff asking for input from patients who were currently in treatment or in remission from ALL. The link to the survey was distributed to known ALL patients through email. A total of nine responses were received: six responses from patients currently receiving treatment (one female, four males, one non-specified), and three responses from patients who are no longer receiving treatment (two female and one male). Of these nine patient respondents, three patients had experience with blinatumomab. All patient respondents were diagnosed with ALL as adults.

A second online survey (Survey #2) was posted on Survey Monkey and distributed by healthcare professionals and LLSC staff asking for input from current and previous caregivers of patients with ALL. A total of three responses were received: two from caregivers (both female) whose patients are currently receiving treatment, and one caregiver (female) whose patient is currently in remission.

Both surveys addressed questions regarding blinatumomab such as whether or not patients or caregivers had heard about the drug; what, if any, expectations they had about the drug; and what symptoms were most important for the drug to manage.

Overall, the results in this submission included responses from twelve respondents, all of whom are Canadian.

| | Survey #1 -Patients (Total of 9 Respondents) | Survey #2 -Caregivers (Total of 3 respondents) |
|---|---|---|
| Age Range | Number of Patients | Number of Caregivers |
| 19 and younger | 1 | 0 |
| 20-29 | 1 | 1 |
| 30-39 | 0 | 0 |
| 40-49 | 2 | 1 |
| 50-59 | 2 | 0 |
| 60-69 | 1 | 0 |
| 70-79 | 2 | 1 |
| 80 and older | 0 | 0 |

From a patient's perspective, fatigue, fever and night sweats and weight loss are common symptoms of ALL. Another commonly reported symptom was related to physical and emotional intimacy. Extreme fatigue had the most impact on daily life. Loss of or change in appetite and unexplained weight fluctuations were other ALL symptoms reported to have a large impact on daily lives. The main types of treatment used for ALL are chemotherapy, targeted therapy and allogeneic stem cell transplant. More than two thirds of patient respondents indicated the current treatment did do a sufficient job in managing their cancer symptoms, although all patient respondents reported having some variation of side effects associated with their treatments and therapies. LLSC noted that most ALL treatment side effects are temporary and subside once the body adjusts to therapy or when therapy is completed. Common side effects of the current ALL treatment include: pain, nausea and vomiting, fatigue, infections/non-cancer illness, and fertility and sexual side effects.

For patients who had never taken blinatumomab, fatigue, pain, bruising and or bleeding, numbness and tingling, among others were the most important cancer symptoms for blinatumomab to control. 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 and bruising and bleeding. Two patients who have had experience with blinatumomab reported to having suffered no additional side effects from the treatment and one stated that they no longer had to take anti-nausea medicine during blinatumomab treatment.

Please see below for a summary of specific input received from LLSC. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

Please see below for a summary of specific input received from the patient advocacy groups.

## 3.1 Condition and Current Therapy Information

### 3.1.1 Experiences Patients have with Adult Acute Lymphoblastic Leukemia

LLSC noted that ALL is one of the four major types of leukemia. It is a rapidly progressing cancer of the bone marrow and blood. ALL results from either an acquired or a genetic injury to the DNA of a developing cell in the bone marrow. Once the marrow cell becomes a leukemia cell, that cell multiplies uncontrollably into billions of cells. These cells are known as "leukemic blasts". The presence of these cells blocks the production of normal cells and as a result, the number of healthy cells is lower than normal. The term "acute" means that the leukemia can progress very quickly, and if not treated quickly, could be fatal within a few months. Whilst the disease affects persons of all ages, it is the most common type of cancer in children (under the age of 14).

All patient respondents (Survey #1) were diagnosed as adults. Although these patients were diagnosed between 1997 and 2016, seven of the nine respondents were diagnosed within the last five years. LLSC noted that most patients who are diagnosed with ALL show symptoms that are also associated with a number of other less serious diseases such as: a pale complexion, signs of bleeding and bruising, fever, fatigue, frequent minor infections, gum bleeding, discomfort in bones or joints, enlarged spleen, liver or lymph nodes and shortness of breath. LLSC stated that it is therefore crucial that patients displaying these symptoms do a "complete blood count" (CBC) test at their local clinic or doctor's office.

All patients indicated that, as a result of their diagnosis, they experienced many disruptions to their daily lives which are listed in the table below, ranked on a scale of 1 (not at all difficult) to 7 (extremely difficult):

| Symptom | % of respondents who rated a 4 or more | Total # of Respondents | Rating Average |
|---|---|---|---|
| Extreme Fatigue | 55% | 9 | 4.2 |
| Loss of Appetite/Weight Loss | 44% | 9 | 3.2 |
| Numbness and Tingling | 22% | 9 | 1.8 |
| Fever/Night Sweats | 33% | 9 | 2.7 |
| Pain | 33% | 9 | 2.6 |
| Lumps | 22% | 9 | 2 |

| Symptom | % of respondents who rated a 4 or more | Total # of Respondents | Rating Average |
|---|---|---|---|
| Other* | 50% | 8 | 3.1 |
| **Notes:**<br>*joint pain (1 respondent), acid reflux (1 respondent), nausea (2 respondents), diarrhea (1 respondent), headaches (1 respondent), and low libido (1 respondent). | | | |

LLSC reported common symptoms of ALL such as fatigue, fever and night sweats and weight loss, were experienced by all nine respondents. Each respondent ranked all the symptoms they were experiencing on a scale of 1 to 7. According to LLSC, the symptom that had the most impact on daily life was extreme fatigue. A total of five respondents (55% of surveyed patients) rated extreme fatigue as having a "*large impact*" on their daily life. LLSC noted that this fatigue impacted their daily routines and led to a disruption in activities, sleeping patterns and physical and emotional intimacy. One patient respondent stated that during treatment she "*had no ability to plan as she was very unreliable with fatigue and various sources of pain*". Another patient respondent stated that they were "*weaker and less energetic.*" Interestingly, whilst all patient respondents reported having some level of fatigue, six respondents indicated that they had problems falling asleep at night. One patient said that "*sleeping involves medication*," whilst another stated that they had "*no more than 2 hours consecutive sleep*" and "*were up multiple times a night*".

Other symptoms reported by about half of patient respondents surveyed as having a large impact on daily lives, was a loss of or change in appetite (one patient said they could no longer eat spicy foods) and unexplained weight fluctuations. LLSC noted that one patient respondent who began treatment in August 2015, said they put on "*20 lbs weight for the first part of treatment and had 65 lbs weight gain since then*". Another patient respondent lost about 10 lbs during treatment.

Another commonly reported symptom was related to physical and emotional intimacy. This was due to a variety of similar factors including "*impotency*" (2), "*vaginal dryness*" (1), "*lack of sex drive*" (1) and "*fatigue*" (1). One patient respondent said intimacy was very "*difficult*" and that "*weight gain and fatigue make it ever harder*," whilst another patient respondent claimed to have simply lost interest in any form of intimacy.

### 3.1.2 Patients' Experiences with Current Therapy for Adult Acute Lymphoblastic Leukemia

LLSC noted that the main types of treatment used for ALL are chemotherapy, targeted therapy and allogeneic stem cell transplants. Treatment for the disease typically lasts for about 2 years and it is often intense, especially in the first few months. There are three parts or phases in the treatment of ALL. These are induction, consolidation (also called "intensification") and maintenance. Consolidation and maintenance are therapies given after remission.

The initial phase of chemotherapy is called "induction". The specific drugs, dosages and timing, depend on several factors including the patient's age, white blood cell count (WBC), the specific features of the leukemia and the overall health of the patient. The goal of this phase of treatment is to achieve remission, which means all signs and symptoms of leukemia have disappeared from the blood and marrow. After the first course of induction chemotherapy, a second course may be given if blast cells are still evident. The second phase, consolidation therapy, takes place when the leukemia goes into remission and is usually given in cycles for four to six months. Generally, several chemotherapy drugs are used in combination. Sometimes, these drugs are administered directly into the spinal canal. For two patients surveyed, they had drugs administered this way.

One patient respondent said that these lumbar punctures were the worst part of treatment. The goal of this phase of treatment is to reduce the number of remaining leukemic cells. Some patients in this phase who are at high risk for relapse will undergo an allogeneic stem cell transplant. After consolidation, the patient is generally put on a maintenance therapy phase which usually lasts for about two years. The goal of this phase is to prevent disease relapse.

The most common abnormality in the leukemia cells of people with ALL is the Philadelphia chromosome. The Philadelphia chromosome is a translocation, or rearrangement, of chromosomes 9 and 22. This translocation creates the BCR-ABL fusion gene, which leads to the development of ALL. About one in five adults with ALL will have Philadelphia chromosome-positive ALL. To treat this subtype, doctors will usually combine multidrug chemotherapy with targeted therapy drugs called tyrosine kinase inhibitors (TKIs). Another type of Philadelphia chromosome abnormality is relapsed Philadelphia chromosome-negative ALL. In this subtype, allogeneic stem cell transplant in second remission is the only curative approach. According to LLSC, currently, there is no standard chemotherapy regimen for the relapsed disease.

All of the patient respondents have received treatment: six respondents are currently receiving treatment and are either in the induction or consolidation phase, and three respondents are no longer receiving treatment.

Of the six patient respondents who are currently receiving treatment (one patient did not specify the treatments being received or symptoms associated with treatment), all have received chemotherapy and in addition, two have received radiation and are waiting on an allogeneic stem cell transplants. Two of these patients are being treated via the Dana-Farber Chemotherapy protocol. Three of the patients surveyed are not currently receiving treatment, but all of them have been treated with chemotherapy. Two of them have undergone radiation treatment in addition to chemotherapy and another patient received chemotherapy, radiation and a stem cell transplant.

All of the patients surveyed were asked if they had difficulty accessing their treatments and all reported that they had easy access to treatment options. More than two thirds of patient respondents indicated that in their opinion, the current treatment did do a sufficient job in managing their cancer symptoms, although all patient respondents reported having some variation of side effects associated with their treatments and therapies.

According to LLSC, most ALL treatment side effects are temporary and subside once the body adjusts to therapy or when therapy is completed.

All respondents stated that they experienced the following common side effects of the current ALL treatment:

- Pain
- Nausea and vomiting
- Fatigue
- Infections/non-cancer illness
- Fertility and sexual side effects

All respondents had some form of infection/non-cancer illness. During treatment, the deficiency of white blood cells can lead to infections from bacteria normally present in the environment, on the skin, in the nose and mouth, on the gums, or in the colon. When the white blood cell count is low, the patient has an increased risk of developing an infection. The most severe illness reported was an "*anal abscess that required surgery and caused many issues for 15+ years*". One

respondent stated that they were more "*susceptible to colds*" whilst another was "*hospitalized for thrush and shingles*".

LLSC stated that since patients have such an increased risk of developing an infection, medical staff, family and friends are advised to practice frequent and vigorous hand washing and to take other precautions to avoid exposing patients to bacteria and viruses. ALL patients are also advised to receive certain vaccinations such as the flu, pneumonia and influenza vaccines.

### 3.1.3 Impact of Adult Acute Lymphoblastic Leukemia and Current Therapy on Caregivers

According to LLSC, caregivers are essential components of a patient's treatment and recovery. A diagnosis of blood cancer dramatically affects the lives of families and all others who have a relationship with the patient. All of the caregivers who responded to the survey are caring for a family member. LLSC acknowledged that these caregivers are a vital extension of the healthcare team as blood cancers are often treated on an outpatient basis. Of the three caregivers who responded to Survey #2, two are currently caring for their spouse/partner with ALL and one is currently caring for a child with ALL.

LLSC reported that all of the caregivers surveyed expressed a negative emotional response to their loved one's diagnosis and all of them felt some form of anxiety regarding diagnosis and treatment. One caregiver respondent stated "*the most difficult thing for me is hearing 'wanting to die' rather than living with having to take a pill every day and dealing with nausea and diarrhea*". Another caregiver respondent said, about their patient, "*he has lost his interest in hobbies, his will to enjoy life, his will to travel, his interest to do anything besides laying on the sofa*".

LLSC stated that the new time commitment for the caregiver as they assume more of the household chores as well as ensuring the patient maintains their medical obligations does have a significant impact on their lifestyles. One respondent, stated that "*they have spent the majority of their time in a hospital room since diagnosis*" and as such "*have missed out on everything that people our age are able to do."* According to LLSC, caregivers all experience a degree of loss of work due to their loved one' diagnosis. Since patients are in hospitals for an extended period of time, they most often wish to be with them. This was best exemplified by a caregiver who stated that "*I had to quit my job and rent a second residence to be close to the hospital and I stayed there during most of the week*".

LLSC expressed that being a caregiver can often feel quite lonely and it is important to reach out to others for support. Caregivers who refresh themselves can be there for the long haul. One caregiver surveyed said that as a result of good support mechanisms, they were able to provide better support to their patient, "*the strain in the beginning especially was pretty severe but we had great friends who helped by bringing lots of food*".

LLSC noted that when the two surveys (Survey #1 and #2) are compared, it appears that the survey distributed to caregivers demonstrates a greater emotional impact of the cancer diagnosis. According to LLSC, whilst the patients may be experiencing intense physical side effects of the treatments, the caregivers appear to experience very pessimistic emotional states that are impacting their health and personal lives.

## 3.2 Information about the Drug Being Reviewed

### 3.2.1 Patient Expectations for and Experiences To Date with Blinatumomab

According to LLSC, most patients achieve an initial remission. However, some patients have residual leukemic cells in their marrow even after intensive treatment. This is referred to as "refractory leukemia." Other patients achieve remission but then have a decreased number of normal blood cells and a return of leukemia cells in the marrow. This situation is called a "relapse." Blinatumomab is an immunotherapy treatment for the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B precursor ALL. It can be used when patients have tried other treatments and didn't reach remission or have relapsed. Once the disease is in remission, an allogenic stem cell transplantation, is often considered.

LLSC' surveys asked both patients and caregiver respondents about their knowledge and experience with blinatumomab. All nine patient respondents were asked if "*they were currently on or have ever used Blincyto.*" Three out of nine patients responded that they had previously used blinatumomab. The other six patients responded that had never been on blinatumomab and one patient reported having access to the drug. According to LLSC, the caregivers surveyed had more knowledge of blinatumomab then the patients. One of the caregivers' patients was treated with blinatumomab.

The patient respondents who had never taken blinatumomab responded to a series of follow-up questions regarding their expectations for the new drug. When respondents were asked '*what are the most important cancer symptoms for Blincyto to control*', they responded:

- Fatigue (50%)
- Pain (50%)
- Bruising and or bleeding (50%)
- Numbness and tingling (50%)
- Loss of appetite (40%)
- Fever and/or night sweats (25%)
- Lumps (25%)
- Rashes/skin changes (50%)

Patient respondents were also asked to rate what side effects they were willing to tolerate with a new medication. They indicated that they 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 and bruising and bleeding.

Of the 3 patients who have had experience with blinatumomab, two patients responded to follow up questions regarding their experiences with the drug. One patient respondent stated that "*Blincyto has been the only positive of all the treatments so far*". Another patient respondent strongly agreed with the statement "*Blincyto has improved my quality of life compared to previous therapies that I used*". Additionally, both respondents reported to having suffered no additional side effects from the treatment and one stated that they no longer had to take anti-nausea medicine during blinatumomab treatment.

## 3.3 Additional Information

LLSC stated that immunotherapy is a type of treatment that engages with parts of the body's own immune system and is not a form of chemotherapy. LLSC also noted that blinatumomab has been approved by the Food and Drug Administration (FDA) and at the time this input was provided, was under "conditional" approval by Health Canada under Health Canada's Notice of Compliance with conditions (NOC/c) policy.

# 4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

**Overall Summary**

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- New class of drug that fills gap in therapy for relapsed/refractory ALL
- Unusual dosing schedule of 28-day continuous infusion with 2 weeks off
- High rate of toxicities, particularly neurotoxicities, to monitor and treat

Economic factors:

- Complex and highly resource intensive to prepare and administer and rigorous monitoring for toxicities
- Access to treatment an issue since hospitalization required for administration in the first two cycles and proximity to tertiary care centres required
- High cost of drug

Please see below for more details.

## 4.1 Factors Related to Comparators

Patients with Philadelphia chromosome negative ALL who are not eligible for stem-cell transplant would be currently treated with multi-agent chemotherapy. The comparator arm in the TOWER trial was investigator's choice of four chemotherapy regimens. PAG noted that clofarabine is not commonly used in relapsed setting. FLA-IDA (fludarabine, cytarabine, idarubicine), high dose cytarabine and high dose methotrexate are appropriate comparators. Other treatments include Hyper-CVAD and or dose modified Dana-Farber protocol.

## 4.2 Factors Related to Patient Population

PAG indicated that the number of patients with relapsed/refractory Philadelphia-chromosome negative ALL is very small. There are limited options available and blinatumomab is a new class of drug that may fill the gap in therapy.

## 4.3 Factors Related to Dosing

PAG has concerns that the dosage and administration schedule is very unusual. Blinatumomab is administered by continuous infusion for 28 days. PAG noted that there is information in the product monograph indicating stability of the infusion is 96 hours and in some centres, infusions pumps for 96 hour continuous infusion is available.

## 4.4 Factors Related to Implementation Costs

PAG identified that the preparation, administration and monitoring of blinatumomab

infusion is very resource intensive due to

- 28 day continuous infusion, requiring coordination of resources to change infusion bags
- Hospitalization for administration for the first nine days of the first cycle and the first two days of the second cycle
- Pre-medication with intravenous dexamethasone prior to first dose of each cycle and whenever infusion is interrupted for more than four hours
- Significant pharmacy and nursing staff training to prevent medication error
- Strict adherence and intensive staff training for the very complex preparation process that includes pre-coating infusion bags with the provided solution stabilizer
- Monitoring and treatment of toxicities, particularly neurotoxicities with 50% incidence and 15% at grade 3 or higher

PAG noted that drug wastage is minimized with the 96 hour stability of infusion solution.

## 4.5 Factors Related to Health System

Blinatumomab would be administered in an outpatient chemotherapy center or in hospital or both. Access would be limited to treatment centres with the appropriate resources and the administration of blinatumomab requires considerable coordination of inpatient care in tertiary hospital and outpatient cancer clinics

## 4.6 Factors Related to Manufacturer

PAG identified the high cost of the drug, the one vial size and the lack of long term data would be barriers to implementation.

# 5 SUMMARY OF REGISTERED CLINICIAN INPUT

One registered clinician provided individual input on blinatumomab for adult acute lymphoblastic leukemia (ALL).

Please see below for a summary of specific input received from the registered clinician(s).

## 5.1 Current Treatment(s) for this Acute Lymphoblastic Leukemia

The clinician providing input noted that current treatment is combination chemotherapy according to the HyperCVAD or Flag-Ida protocols followed by a stem cell transplant, if not transplanted in first complete remission.

## 5.2 Eligible Patient Population

Adult ALL is a rare entity. The clinician providing input noted that there may be five adult patients per year in their particular jurisdiction and some patients are cured with first line treatment.

## 5.3 Identify Key Benefits and Harms with Blinatumomab

Blinatumomab is an entirely novel agent in the treatment of ALL. The clinician providing input indicated that blinatumomab

- has been shown to be superior to a variety of standard of care protocols in a randomized fashion. More patients achieve a second complete remission which should allow more patients to proceed to a stem cell transplant. This has translated in an increase in overall survival
- has different side effects than chemotherapy but these have been found to be manageable if one follows the manufacturer's recommendations
- although a high cost drug, it can be administered as an outpatient, cutting back on the significant cost of hospitalization
- has less infectious side effects, which should also save on costs of managing side effects.

## 5.4 Advantages of Blinatumomab Over Current Treatments

The clinician providing input noted that blinatumomab is more efficacious with better quality of life while on treatment compared to standard combination chemotherapy. The key benefits were identified in the above section.

## 5.5 Sequencing and Priority of Treatments with Blinatumomab

The clinician providing input noted that blinatumomab would replace combination chemotherapy as the remission inducing treatment at first relapse. Patients would then proceed to transplant which would be the same no matter how they achieve the second remission. However given that blinatumomab is less toxic than combination chemotherapy, the clinician providing input indicated that the transplants after blinatumomab should be easier and less toxic to the patient, which means less costly to manage.

## 5.6 Companion Diagnostic Testing

Not applicable. Flow cytometry for CD19 is done routinely.

## 5.7 Additional Information

The clinician providing input noted that the best therapies should be used as early as possible in the treatment of malignancies

# 6 SYSTEMATIC REVIEW

## 6.1 Objectives

To evaluate the safety and efficacy of blinatumomab as a monotherapy on patient outcomes, in the treatment of adults with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

## 6.2 Methods

### 6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

**Table 6.1. Selection Criteria**

| Clinical Trial Design | Patient Population | Intervention | Appropriate Comparators*† | Outcomes |
|---|---|---|---|---|
| Published and unpublished RCTs. | Adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) | Blinatumomab administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump | All appropriate multi-agent chemotherapy regimens aligned with Canadian practice. | • OS<br>• PFS<br>• CR<br>• Hematologic<br>• Response,<br>• Cytogenic Response,<br>• Molecular Response<br>• DOR<br>• TTR<br>• HRQoL<br>• SAEs<br>• AEs<br>• WDAEs |

**[Abbreviations]** AE=adverse events; ALL= Acute lymphoblastic leukemia; CR= complete remission; DOR= duration of response; HRQoL=quality of life; OS= Overall survival; PFS= progression-free survival; Ph- = Philadelphia negative; TTR= time to response; RCT=randomized controlled trial; R/R = relapsed or refractory; SAE=serious adverse events; WDAE=withdrawals due to adverse events

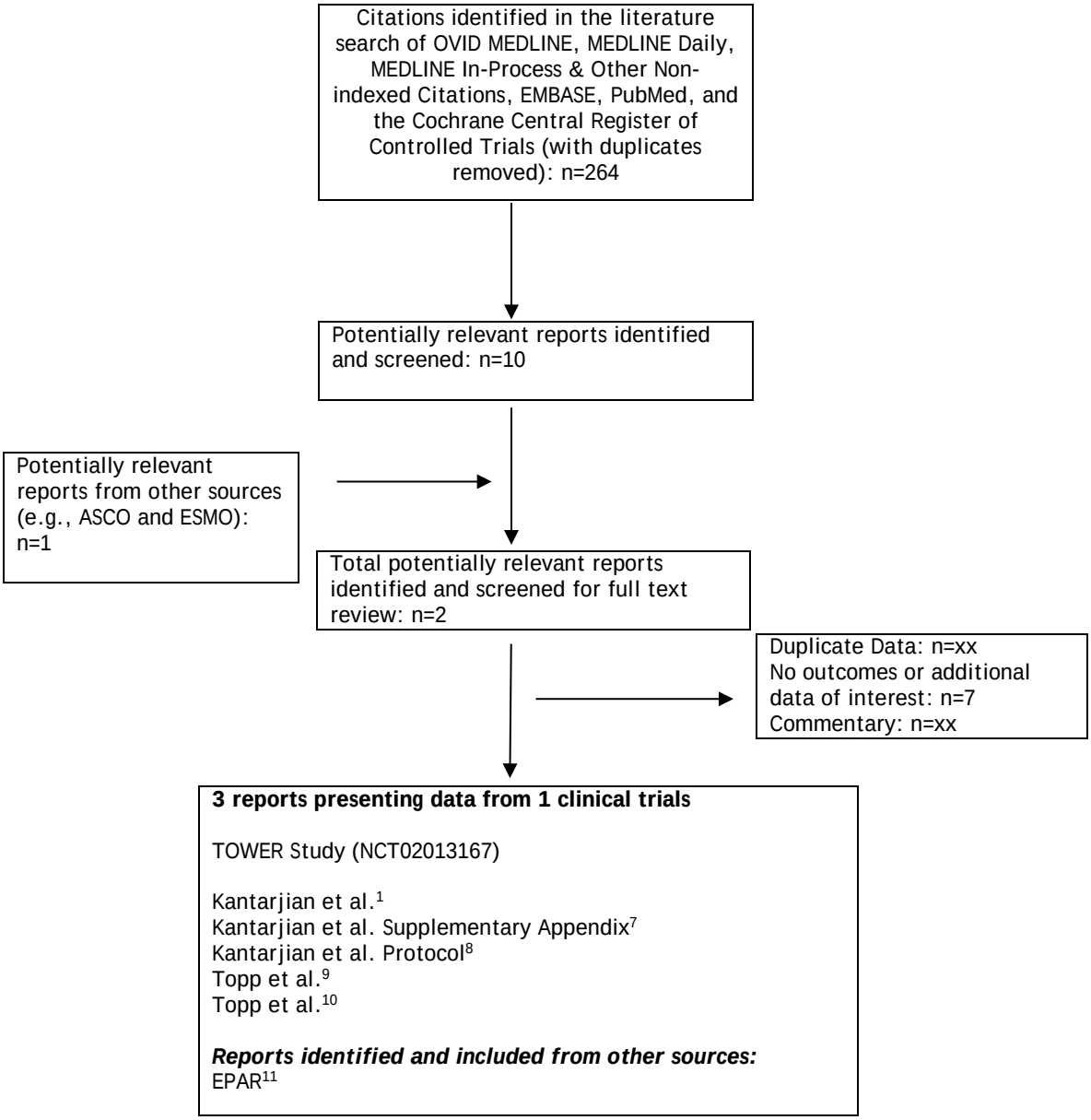
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

## 6.3 Results

### 6.3.1 Literature Search Results

Of the 264 potentially relevant reports identified, 1 study was included in the pCODR systematic review with information from 1 published paper and 2 abstracts. 7 citations provided data on non-randomized studies and were excluded.

**Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies**




Note: Additional data related to studies[1] were also obtained through requests to the Submitter by pCODR[12]

### 6.3.2 Summary of Included Studies

One randomized controlled trial was identified that met the eligibility requirements of this systematic review (see Table 6.2)

#### 6.3.2.1 Detailed Trial Characteristics

**Table 6.2 Summary of Trial characteristics of the included studies investigating blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).**

**TOWER Study[1,8]**

| Trial Design | Inclusion Criteria | Intervention and Comparator | Outcomes |
|---|---|---|---|
| NCT02013167[2]<br><br>Phase III, prospective, open-label, multicenter, comparative study with 2:1 randomization<br><br>Stratified Randomization by:<br>• Age (<35 vs. >= 35)<br>• Previous Salvage therapy<br>• Previous allogeneic stem-cell transplantation<br><br>Randomized N=405<br><br>Treated n=376<br><br>101 Centres in 21 countries<br><br>Participant Enrollment:<br><br>January 2014 to September 2015<br><br>Trial Stopped Early due to benefit observed with blinatumomab therapy.<br><br>Data Cut-off Date: January 4, 2016<br><br>Funded by Amgen | <u>Key Inclusion Criteria</u><br><br>Adults (aged ≥18)<br><br>Patients with Philadelphia chromosome (Ph)-negative B-precursor ALL, with any of the following stages:<br>• Refractory to primary induction therapy or to salvage with intensive combination chemotherapy.<br>• First relapse with the first remission lasting less than 12 months<br>• Second or greater relapse or relapse at any time after allogenic stem-cell transplantation.<br>5% or more blasts in bone marrow and an ECOG performance status of 2 or less<br><br><u>Key Exclusion Criteria</u><br><br>Other active cancers<br><br>Clinically relevant pathologic condition of the CNS<br><br>Isolated extramedullary disease<br><br>Autoimmune disease<br><br>Acute graft-versus-host-disease (GVHD) of grade 2 or higher or active chronic GVHD | <u>Intervention:</u><br>Blinatumomab continuous infusions<br><br>Induction and consolidation treatments administered in 6 week cycles<br>4 weeks continuous intravenous infusions with 9 µg/day during week 1 of induction cycle 1 and 28 µg/day afterwards in 4 week cycles + 2 treatment-free weeks<br><br>Maintenance treatment given as a 4-week continuous infusion every 12 weeks.<br><br><u>Comparison</u>:<br><br>Chemotherapy of the investigators choice to 1 or 4 regimens:<br>• Fludarabine, high-dose cytosine arabinoside and granulocyte colony-stimulating factor with or without anthracycline.<br>• High dose cytosine arabinoside-based regimen<br>• High dose methotrexate-based regimen<br>• Clofarabine-based regimen | <u>Primary:</u><br>Overall survival - time from randomization to death from any cause<br><br><u>Secondary:</u><br>Complete remission with full hematological recovery within 12 weeks after initiation of treatment. Complete remission was defined as 5% or less bone marrow blasts and no evidence of disease as well as a platelet count of greater than 100,000 per microliter and absolute neutrophil count of greater than 1000 per microliter).<br><br>Complete remission with full, partial or incomplete hematological recovery within 12 weeks of initiation of treatment<br><br>Event free survival (time from randomization until relapse after achieving a complete remission with full, partial or incomplete hematological recovery or death<br><br>Duration of complete remission<br><br>Minimal residual disease remission<br><br>Rate of allogenic stem cell transplantation<br><br>Adverse events Graded according to NCI-CTCAE<br><br>HRQoL (EORTC QLQ-C30) Change from baseline<br><br>Time-to-deterioration (TTD) |

| Trial Design | Inclusion Criteria | Intervention and Comparator | Outcomes |
|---|---|---|---|
| | Before randomization:<br>• Allogeneic stem-cell transplantation within 12 weeks<br>• Autologous stem-cell transplantation within 6 weeks<br>• Chemotherapy or radiotherapy within 2 weeks<br>• Immunotherapy within 4 weeks<br>Ongoing use or within less than 30 days since receiving an investigational treatment | | |

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer - quality of life questionnaire—30 item; GVHD = graft-versus-host-disease; HRQoL = health-related quality of life; NCI-CTCAE = National Cancer Institute - common terminology criteria for adverse events; Ph- = Philadelphia chromosome-negative; R/R = relapsed or refractory; TTD = time to deterioration.

### *a) Trials*

One randomized controlled trial was identified and is summarized in Table 6.3 and Table 6.4.

TOWER Study

The TOWER study is a Phase III, prospective, open-label, multicenter, comparative study in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) comparing blinatumomab to chemotherapy. The study was sponsored by Amgen.

Between January 2014 and September 2015, 468 patients were screened for participation in the study with 405 patients randomized. Included participants were adults greater or equal to 18 years of age who were either refractory to primary induction therapy or to salvage with intensive combination chemotherapy. Patients in first relapse with the first remission lasting less than 12 months, second or greater relapse or relapse at any time after allogenic stem-cell transplantation. In addition, for patients to be included in the trial they had 5% or more blasts in bone marrow and an ECOG performance status of 2 or less.

Patients were randomized in a 2:1 ratio to either blinatumomab or chemotherapy. The study was conducted at 101 centres and in 21 countries. Centres were based out of Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Ireland, Israel, Italy, Korea, Mexico, Poland, Russia, Spain, Taiwan, Turkey, United Kingdom or the United States.[2] The majority of the 405 participants were enrolled in Europe 265 (65.4%). A total of 64 participants (15.8%) were enrolled from Canada and the United States.

The primary endpoint for the study was overall survival. The study was designed for an enrollment of 400 patients with approximately 330 deaths required to provide 85% power to detect a hazard ratio for death of 0.70 in the blinatumomab group as compared to chemotherapy

with a two-sided alpha of 0.05. Secondary outcomes (Table 6.2) included complete remission with full hematological recovery within 12 weeks after initiation of treatment, complete remission with full, partial or incomplete hematological recovery within 12 weeks of initiation of treatment, event free survival (time from randomization until relapse after achieving a complete remission with full, partial or incomplete hematological recovery or death, duration of complete remission, minimal residual disease remission, Health Related Quality of Life (HRQoL) as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and safety among others.

Patients were randomized to receive either blinatumomab administered as a continuous infusion or chemotherapy. Treatment with blinatumomab was administered as follows: Induction and consolidation treatments administered in 6 week cycles and maintenance administered in 12 week cycles. For induction and maintenance, each cycle consisted of 4 weeks of treatment followed by 2 treatment-free weeks. During cycle 1 of week 1, patients received 9 µg/day as induction therapy followed by 28 µg/day for all remaining days for the remaining 4 week of treatment. Maintenance treatment given as a 4-week continuous infusion every 12 weeks. Induction was given up to 2 cycles, consolidation up to 3 cycles and maintenance up to 12 months. Patients moved onto subsequent phases of treatment with blinatumomab based on having ≤5% blasts count. Chemotherapy was provided using 1 of 4 regimens that were selected by the treating clinician investigators. The 4 treatment regimens used in the study included: 1) fludarabine, high-dose cytosine arabinoside and granulocyte colony-stimulating factor with or without anthracycline; 2) a high dose cytosine arabinoside-based regimen; 3) high dose methotrexate-based regimen or 4) a clofarabine-based regimen.

The TOWER study was stopped early after 75% of the total number of planned deaths at the recommendation of an independent data and safety monitoring committee due to the benefit observed with blinatumomab therapy according to the O'Brien-Fleming stopping boundary at the time of the planned interim analysis calculated with the use of a Lan-DeMets alpha-spending function.[13,14]

**Table 6.3 Select quality characteristics of included studies of blinatumomab in patients with acute lymphoblastic leukemia**

| Study | Tower Study (NCT 02013167)[1] |
|---|---|
| Treatment vs. Comparator | Yes |
| Primary outcome | Overall survival |
| Required sample size[A] | 400 patients with approximately 330 deaths |
| Sample size | 405 patients randomized with 251 deaths recorded |
| Randomization method[B] | Interactive voice-response system, stratified |
| Allocation concealment | Yes |
| Blinding | No |
| ITT Analysis | Yes |
| Final Analysis | Yes |
| Early termination[C] | Yes |
| Ethics Approval | Yes |
| Abbreviations: ITT = intention to treat | |
| [A] An enrollment target of 400 patients and a total of approximately 330 deaths would give the trial approximately 85% power to detect a hazard ratio for death of 0.70 in the blinatumomab group as compared with chemotherapy at a two-sided alpha level of 0.05; this calculation was based on an assumed median overall survival of 4.2 months in the chemotherapy group and a 10% dropout rate.<br>[B] Stratified according to age (<35 vs. ≥35 years), previous salvage therapy (yes vs. no), and previous allogeneic stem-cell transplantation (yes vs. no)<br>[C] Trial stopped early after 75% of the total number of planned deaths at the recommendation of an independent data and safety monitoring committee due to the benefit observed with blinatumomab therapy according to the O'Brien-Fleming stopping boundary at the time of the planned interim analysis calculated with the use of a Lan-DeMets alpha-spending function. | |

### *b) Populations*

| Table 6.4 Baseline Patient Characteristics in the TOWER study of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).[1,7] | | |
|---|---|---|
| | **Blinatumomab (n=271)** | **Chemotherapy (n=134)** |
| Age,<br>mean ± SD<br>Range<br>> 35 years of age n (%) | <br>40.8 ± 17.1<br>18-80<br>123 (45.4) | <br>41.1 ± 17.3<br>18-78<br>60 (44.8) |
| Sex<br>Men n (%) | <br>162 (59.8) | <br>77 (57.5) |
| ECOG performance status n (%)<br>0<br>1<br>2<br>Missing | <br>96 (35.4)<br>134 (49.4)<br>41 (15.1)<br>0 | <br>52 (38.8)<br>61 (45.5)<br>20 (14.9)<br>1 (0.7) |
| Key Inclusion Criteria n (%) | | |
| Disease refractory to primary therapy or salvage therapy | 115 (42.4) | 54 (40.3) |
| First relapse, with duration of first remission < 12 months | 76 (28.0) | 37 (27.6) |
| Untreated second or greater relapse | 32 (11.8) | 16 (11.9) |
| Relapse after allogenic stem-cell transplantation | 46 (17.0) | 27 (20.1) |
| Not specified | 2 (0.7) | 0 |
| Number of Prior Salvage Regimens n (%)[7] | | |
| 0 | 114 (42.1) | 65 (48.5) |
| 1 | 91 (33.6) | 43 (32.1) |
| 2 | 45 (16.6) | 16 (11.9) |
| 3 | 14 (5.2) | 5 (3.7) |
| >3 | 7 (2.6) | 5 (3.7) |
| Previous allogenic stem cell transplantation n (%) | | |
| Yes | 94 (34.7) | 46 (34.3) |
| No | 176 (64.9) | 87 (64.9) |
| Unknown | 1 (0.4) | 1 (0.7) |
| Maximum central or local bone marrow blasts - no. (%) | | |
| Less than 5% | 0 | 0 |
| > 5 to < 10% | 9 (3.3) | 7 (5.2) |
| 10 to < 50% | 60 (22.1) | 23 (17.2) |
| >=50% | 201 (74.2) | 104 (77.6) |
| Unknown | 1 (0.4) | 0 |

In the TOWER study 271 patients were randomized to blinatumomab and 134 patients to chemotherapy. Close to half of the patients (48.1%; n=195/405) were ECOG performance status 1. The most common key trial inclusion criteria for inclusion into the study was related to disease refractory to primary therapy or salvage therapy. Of the patients enrolled in the trial, 150 (37.0%) patients had a previous allogeneic stem-cell transplantation. For 179 (44.2%) patients enrolled in the trial, they had not received any prior salvage treatment.[1]

### c) Interventions

Patients randomized to blinatumomab received induction and consolidation treatment in six-week cycles while maintenance was given in 12-week cycles. Induction was given up to 2 cycles, consolidation up to 3 cycles, followed by maintenance up to 12 months. Patients moved onto subsequent phases of treatment with blinatumomab or chemotherapy based on having ≤5% blasts count. For induction and consolidation patients received four weeks of treatment by continuous infusion of 9 µg/day (only for week 1 of cycle 1), then 28 µg/day for weeks 2-4 of cycle 1 and all subsequent cycles followed by two treatment-free weeks; dexamethasone was given prior to administration of blinatumomab to prevent cytokine release syndrome. For maintenance, blinatumomab was given in 12-week cycles. This consisted of four weeks on treatment and eight weeks off treatment.[7] Interruption or discontinuation of therapy with blinatumomab was required if neurologic or other selected adverse events occurred where if grade 4 events occurred which are deemed to be possibly related to blinatumomab, patients would be required to permanently discontinue treatment. Of the 271 patients randomized to blinatumomab, 267 (98.5%) received at least 1 dose. The median number of cycles of blinatumomab was 2 (range, 1 to 9). Consolidation therapy was given in 32% of patients receiving blinatumomab.[1]

Chemotherapy was provided according to the investigators choice using one of four regimens. These regimens included:[7]

1. FLAG ± anthracycline based regimen (such as Idarubicin 10 mg/m$^2$ days 1, 3; fludarabine 30 mg/m$^2$ days 1-5; cytarabine 2g/m$^2$ days 1-5). For patients > 60 years of age: Idarubicin 5 mg/m$^2$ day 1,3; fludarabine 20 mg/m$^2$ days 1-5; cytarabine 1 g/m$^2$ days 1-5). This regimen base was used in 49 (45%) of patients.
2. HiDAC based regimen that utilize doses of cytarabine arabinoside at least 1 g/m$^2$ or greater per day ± anthracycline and/or in combination with other drugs such as native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents. This regimen was used in 19 (17%) of patients.
3. High-dose methotrexate based regimen (such as 500 mg/m$^2$ - 3 g/m$^2$ HDMTX (infusion time up to 24 hours) in combination with other drugs such as native E.coli asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide or alkylating agents. This regimen was used in 22 (20%) of patients.
4. Clofarabine or clofarabine based regimens. Clofarabine use as a single agent should follow the recommended prescribing information. Clofarabine combination based regimens used ≥ 20 mg/m$^2$/day for up to 5 days. This regimen was used in 19 (17%) of patients.

Discontinuation of the protocol-specified chemotherapy regimen could be at any time after the first treatment cycle. Of the 134 patients randomized to chemotherapy, 109 (81.3%) received study treatment. The median number of cycles in the chemotherapy group was 1 (range, 1 to 4). Consolidation was provided to 3% of the treated patients with chemotherapy.[1]

### d) Patient Disposition

All patients who were randomized were included in the efficacy analysis as an intention-to-treat population. For safety and efficacy sensitivity analyses, all patients who received at least 1 dose of trial treatment were included. The disposition of the patients for the TOWER study are outlined in the table below (Table 6.5).

**Table 6.5 Patient Disposition - TOWER Study[7]**

| | | |
|---|---|---|
| Screened | 468 | |
| Randomized | 405 | |
| **Allocation** | **Blinatumomab** | **Chemotherapy** |
| Randomized | 271 | 134 |
| Did not receive allocated treated | 4 (1.5) | 25 (18.7) |

| Table 6.5 Patient Disposition - TOWER Study[7] | | |
|---|---|---|
| (reasons below) | | |
| • Adverse event | 0 | 2 (1.5) |
| • Patient request | 1 (0.4) | 22 (16.4) |
| • Death | 2 (0.7) | 1 (0.7) |
| • Protocol specified criteria | 1 (0.4) | 0 |
| • Clinical deterioration prior to treatment | 1 (0.4) | 0 |
| **Disposition** | | |
| Received treatment | 267 (98.5) | 109 (81.3) |
| Continuing on treatment | 22 (8.1) | 0 |
| Discontinued study treatment | 245 (90.4) | 109 (81.3) |
| • Ended Induction Early | 60 (22.1) | 24 (17.9) |
| • Intention to receive AlloHSCT | 59 (21.8) | 31 (23.1) |
| • Adverse event | 33 (12.2) | 5 (3.7) |
| • Relapsed after CR/CRh/CRi on treatment | 33 (12.2) | 3 (2.2) |
| • Death | 20 (7.4) | 17 (12.7) |
| • Intention to receive other therapy | 18 (6.6) | 23 (17.2) |
| • Completed induction without CR/CRh/CRi | 13 (4.8) | 2 (1.5) |
| • Patient request | 6 (2.2) | 4 (3.0) |
| • Reached end of maintenance period | 3 (1.1) | 0 |
| **Study Completion Accounting** | | |
| Ongoing study participation | 93 (34.3) | 33 (24.6) |
| Discontinued Study | 178 (65.7) | 101 (75.4) |
| Patient withdrew consent | 14 (5.2) | 15 (11.2) |
| Sponsor decision | 3 (1.1) | 1 (0.7) |
| Lost to follow-up | 1 (0.4) | 0 |
| Death | 160 (59.0) | 85 (63.4) |
| Abbreviations: AlloHSCT = allogeneic hematopoietic stem cell transplant; CR = complete remission, CRh = complete remission with partial hematologic recovery; Cri = complete remission with incomplete hematologic recovery. | | |

### *e) Limitations/Sources of Bias*

The TOWER study is a generally well designed study however there are a few limitations that need to be considered when interpreting the results of the trial. These limitations include the study withdrawal of a disproportionate number of participants randomized to chemotherapy, relative to the blinatumomab, prior to receiving assigned treatment, short-term measurement of HRQoL, where possible blinded adjudication of subjective outcomes, limited representation of Canadian sites and participants and finally the lack of use of hyper CVAD, the more commonly used treatment regimen in Canada, as a comparative treatment in the chemotherapy arm. 25/134 (18.7) did not receive the study treatment.

Of the participants that were randomized to chemotherapy (n=134), 25 (18.7%) did not receive treatment with 22/134 (16.4 %) not receiving study treatment at the patient's request. The withdrawal of patients from the chemotherapy arm may confound the results of the study. It should be noted that the demographics of the intention to treat population and the treated per-protocol patients however are not appreciably different between those randomized chemotherapy group, as compared to the treated chemotherapy patients. Comparison of the intention to treat analysis and the per-protocol analysis for overall survival does not show difference between the two groups.[7] Interpretation of the study results should be made considering both the IIT and per-protocol analyses.

The measurement of health related quality of life in the TOWER study was limited to the time when participants were on receiving treatment with measurement was measured at baseline, day 8, day 15, day 29 in each cycle of therapy and at day 1, day 15, and day 29 during each consolidation cycle, and at the safety follow-up visit. As a result, HRQoL is short-term in duration, especially for the chemotherapy treated participants with data up to only 3 months following randomization being available.[9] Extrapolation of the HRQoL benefit related to blinatumomab beyond a short-time horizon should consider the timing of the actual measurement of outcomes.

The TOWER study was an open-label trial without blinding of either treatment or outcome measurements which may bias treatment duration, adverse event reporting and subjective outcome measures. There is no mention in the paper of blinded adjudication of events related to event-free survival or other outcomes.

The generalizability of the TOWER study to the Canadian healthcare system should be considered when interpreting the study results. The study was conducted in a limited number of Canadian sites (N=2) with enrollment of 64 participants (15.8%) being enrolled from Canada and the United States. Accompanying the limited Canadian enrollment, Hyper CVAD, which is more commonly used in Canada as the primary chemotherapy regimen, is not used as a treatment an alternative in the chemotherapy arm. Depending on the relative efficacy of the Hyper-CVAD, compared to the 4 regimens used in the study, the results of the TOWER study may be less generalizable to the Canadian practice setting.

### 6.3.2.2 Detailed Outcome Data and Summary of Outcomes

#### *a) Efficacy Outcomes*

#### *Overall Survival – primary outcome*

In the TOWER study for the interim analysis following 251 recorded deaths, overall survival, by intention-to-treat analysis, was statistically significantly longer in the blinatumomab treated patients than in the chemotherapy group, with the median overall survival 7.7 months (95% CI: 5.6 to 9.6) as compared to 4.0 months (95% CI: 2.9 to 5.3), respectively, with a hazard ratio for death of 0.71; 95% CI: 0.55 to 0.93, P=0.01 (Figure 2a). The median duration of follow-up for the blinatumomab and chemotherapy treated patients were 11.7 and 11.8 months, respectively. In a per-protocol analysis (i.e., among those individuals that received study treatment, blinatumomab [98.5%] or chemotherapy [81.3%]) the overall survival was 7.7 months (95% CI: 5.7 to 9.9) and 4.1 months (95% CI: 3.0 to 5.9), respectively with a hazard ratio for survival of 0.69 (95% CI: 0.52 to 0.91, P= 0.009).[7] Furthermore, when the overall survival was censored to account for those individuals that underwent stem-cell transplantation, the medial overall survival for those treated with blinatumomab was 6.9 months (95% CI: 5.3 to 8.8) and for the chemotherapy group median overall survival was 3.9 months (95% CI: 2.8 to 4.9) with a hazard ratio for death of 0.66 (95% CI: 0.50 to 0.88, p=0.004) (Figure 2b).

**Figure 2. Overall Survival TOWER Study[1]**

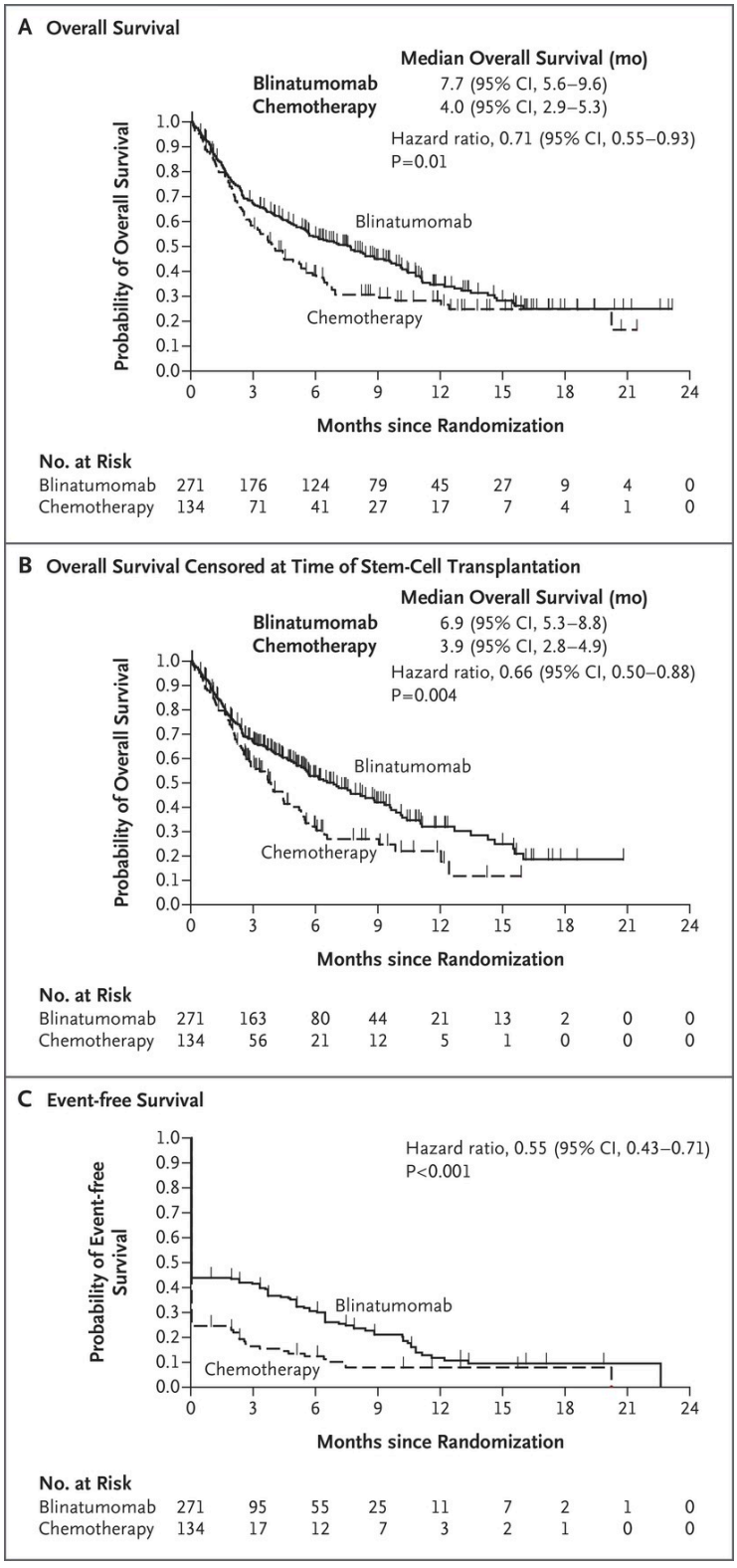



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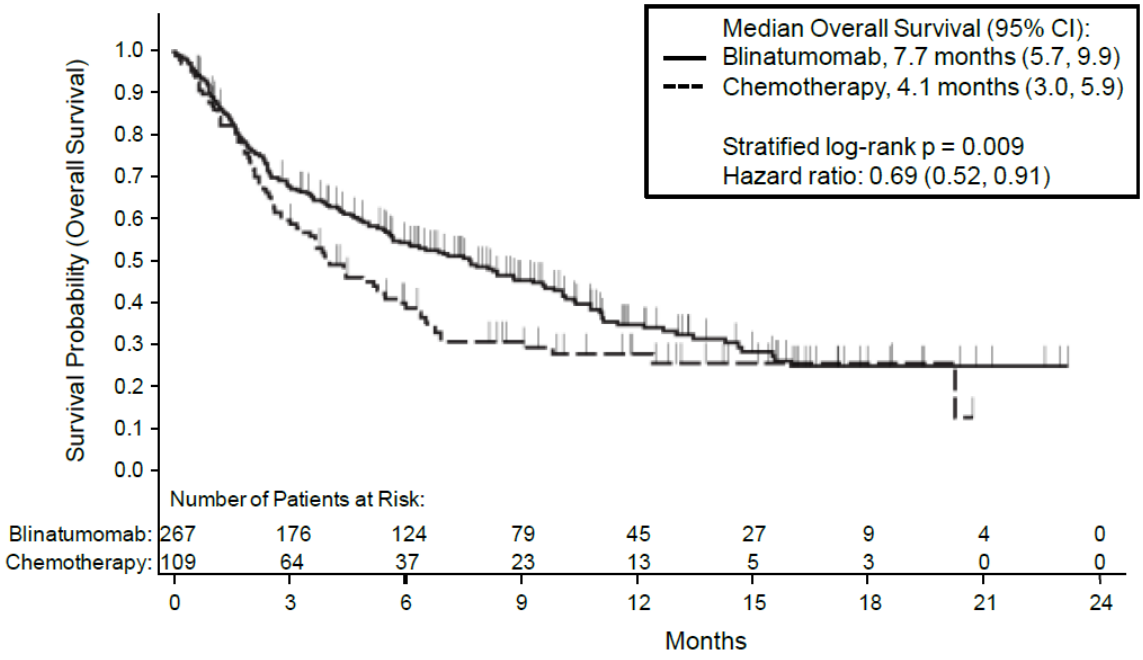
**Figure 3. Overall survival from TOWER study among patients who received study treatment[7]**




Estimated survival of randomized participants at 6 months was 54% in the blinatumomab treated patients and 39% in the chemotherapy treated individuals. Overall survival was analysed by predetermined subgroups including age less than 35 years, salvage treatment phase, previous allogeneic stem-cell transplantation and bone marrow blasts less than 50%. The overall survival benefit was found to be statistically significantly in favour of the blinatumomab group for individuals undergoing their first salvage treatment (HR: 0.60, 95% CI: 0.39 to 0.91), second salvage treatment (HR: 0.59, 95% CI: 0.38 to 0.91), and in patients without previous stem-cell transplantation (HR: 0.70, 95% CI: 0.51 to 0.96). However, significance was not demonstrated for patients in third or later salvage treatment.[1] Notably, none of these subgroup analyses were powered to detect a significant difference.

### *Secondary Outcomes*

### *Event-Free Survival*

Estimated event-free survival, defined as the time from randomization until relapse or death after achieving a complete remission with full, partial, or incomplete hematological recovery, at 6 months was 31% in the blinatumomab group as compared to 12% in the chemotherapy group (HR 0.55 [95% CI: 0.43 to 0.71, P<0.001]) (Figure 2c).[1]

### *Remission Rates (Including complete remission (CR) with full hematological recovery within 12 weeks after initiation of treatment; CR with full, partial or incomplete hematological recovery within 12 weeks of initiation of treatment)*

Remission rates were higher in the blinatumomab group as compared to the chemotherapy group. Complete remission (CR) with full hematologic recovery was 33.6% (95% CI 28.0 - 39.5) versus 15.7% (95% CI 10.0 – 23.0) (P<0.001), respectively. For complete remission with full, partial or incomplete recovery, similar differences were observed between the blinatumomab (43.9% [95% CI 37.9 – 50.0]) and chemotherapy (24.6% [95% CI 17.6 – 32.8]) groups, P<0.001. Remission rates for full, partial or incomplete hematological recovery were consistently improved in the

blinatumomab treated patients compared to the chemotherapy treated patients across all pre-specified sub-group analyses.[1]

### *Duration of Complete Remission*

For those individuals with complete remission with full, partial or incomplete hematological recovery, the median duration of remission for blinatumomab was 7.3 months (95% CI: 5.8 to 9.9) as compared to 4.6 months (95% CI: 1.8 to 19.0) in the chemotherapy treated group.[1]

### *Allogeneic Stem-Cell Transplantation*

Twenty-four percent of individuals underwent allogeneic stem-cell transplantation in the blinatumomab and chemotherapy groups, including 14% and 9% of patients in each group respectively who achieved remission without the use of another treatment. Of those patients that had complete remission with full, partial, or incomplete hematologic recovery, and who had an allogeneic stem-cell transplantation, 26% (10/38) of patients in the blinatumomab group died with a median follow-up period of 206 days. Similarly, 25% (3/12) in the chemotherapy group died, with a median follow-up period of 279 days.[1] Among the patients who received post-baseline alloHSCT, the median time from post-baseline alloHSCT to death were not estimable (95% CI blinatumomab: 8.3 months, NE; SOC: 4.8 months, NE). At month 18, the number of subjects at risk was 3 for the blinatumomab arm and 1 for the SOC arm.[12]

### *Quality of Life*

From a published abstract[9] and the published protocol[8] health related quality of life was measured in the TOWER study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and was measured at baseline, day 8, day 15, day 29 in each cycle of therapy and at day 1, day 15, and day 29 during each consolidation cycle, and at the safety follow-up visit. EORTC QLQ C30 and ALLSS was not collected during the maintenance period (cycle 6-9) or in the long-term follow-up period.[8] Time to deterioration in HRQoL, was defined as the time from baseline to a 10-point deterioration in the EORTC QLQ-C30, or EFS event. A 10-point change in deterioration or improvement in the EORTC QLQ-C30 is considered is a minimal important difference (MID) for the questionnaire.

In the patients that received at least 1 dose (n=376) HRQoL data was available at baseline and at least one follow-up time point for 247/267 (92.5%) of blinatumomab patients and for 95/109 (87.2%) of chemotherapy treated patients. Blinatumomab treated patients had better HRQoL as compared to chemotherapy. Functional scores and symptom scales on the EORTC-QLQ-C30 did not demonstrate a meaningful change from baseline with blinatumomab. In the chemotherapy group, a clinically meaningful decline was reported for physical functioning, role functioning, social functioning. A clinically meaningfully decline was also reported in the chemotherapy group for fatigue, pain, nausea and vomiting, appetite loss and diarrhea on the symptom scale. As EORTC-QLQ-C30 was measure on days 8, 15 and 29 of each cycle, the reported clinically meaningful decline occurred on at least one of these measurement days. TTD also favoured blinatumomab for global health status/quality of life (HR: 0.67, 95% CI: 0.52 to 0.87, P=0051), physical functioning (HR: 0.66, 95% CI: 0.51 to 0.85, P=0.0189), role functioning (HR: 0.66, 95% CI: 0.51 to 0.85, P=0.0083) cognitive functioning (HR: 0.70, 95% CI: 0.55 to 0.90, P=0.0194), emotional functioning (HR: 0.64, 95% CI: 0.50 to 0.83, P=0.0022), social functioning (HR: 0.67, 95%CI: 0.52 to 0.86, P=0.0124) and all symptom-scores except for insomnia and fatigue.[9] Quality of life data from the TOWER study was only acquired up to a maximum 3 months in the chemotherapy arm following randomization.[8,15] Notably, the reported results on QoL are based on measurements of the first 28 days of treatment. Therefore much of the detriment in quality of life in the chemotherapy group can be attributed to the time on treatment, which for the majority of patients was only one cycle as only 2 patients contributed to the data at 3 months.

### *Harms Outcomes*

### *Adverse Events*

For the purposes of adverse event reporting only those individuals that actually received at least 1 dose of the assigned treatment were evaluated, with 267 patients in the blinatumomab group and 109 in the chemotherapy treatment group. Across both treatment groups any adverse event (AE) was reported in 99% of all patients. Serious adverse events (SAE) occurred in 62% (n=165) of the blinatumomab group and in 45% (n=49) of the chemotherapy treated group. Among grade 3 or 4 adverse events, infections occurred less in the blinatumomab compared to chemotherapy group (34% and 52%, respectively). Serious infections and infestation were however similar between group (28% and 30%, respectively). Classification of SAEs by system organ class are summarized in Table 6.6.

**Table 6.6 Adverse Events in the TOWER study of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) and SAEs' by System Organ Class for treated patients and most common SAE within selected System Organ Classes.[7]**

| | Blinatumomab (n=267) n (%) | Chemotherapy (n=109) n (%) |
|---|---|---|
| Grade ≥3 | 231 (86.5) | 100 (91.7) |
| AE (any grade) | 263 (98.5) | 108 (99.1) |
| Serious AE | 165 (61.8) | 49 (45.0) |
| Fatal Serious AE | 51 (19.1) | 19 (17.4) |
| WDAE | 33 (12.4) | 9 (8.3) |
| **SAE's by System Organ Class** | | |
| Blood and lymphatic system disorders | 36 (13.5) | 17 (15.6) |
| Febrile neutropenia | 23 (8.6) | 12 (11.0) |
| Cardiac disorders | 6 (2.2) | 3 (2.8) |
| Congenital, familial and genetic disorders | 1 (0.4) | 0 |
| Gastrointestinal disorders | 8 (3.0) | 2 (1.8) |
| General disorders and administration site conditions | 27 (10.1) | 2 (1.8) |
| Pyrexia | 16 (6.0) | 1 (0.9) |
| Hepatobiliary disorders | 2 (0.7) | 2 (1.8) |
| Immune system disorders | 11 (4.1) | 0 |
| Cytokine release syndrome | 7 (2.6) | 0 |
| Infections and infestations | 75 (28.1) | 33 (30.3) |
| Sepsis | 13 (4.9) | 7 (6.4) |
| Pneumonia | 10 (3.7) | 2 (1.8) |
| Injury, poisoning and procedural complications | 15 (5.6) | 1 (0.9) |
| Overdose | 8 (3.0) | 0 |
| Accidental overdose | 3 (1.1) | 0 |
| Investigations | 8 (3.0) | 0 |
| Metabolism and nutrition disorders | 10 (3.7) | 2 (1.8) |
| Tumor lysis syndrome | 3 (1.1) | 0 |
| Musculoskeletal and connective tissue disorders | 5 (1.9) | 1 (0.9) |
| Nervous system disorders | 19 (7.1) | 4 (3.7) |
| Psychiatric disorders | 2 (0.7) | 0 |

| Table 6.6 Adverse Events in the TOWER study of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) and SAEs' by System Organ Class for treated patients and most common SAE within selected System Organ Classes.[7] | | |
|---|---|---|
| | Blinatumomab (n=267) n (%) | Chemotherapy (n=109) n (%) |
| Renal and urinary disorders | 4 (1.5) | 3 (2.8) |
| Respiratory, thoracic and mediastinal disorders | 15 (5.6) | 4 (3.7) |
| Skin and subcutaneous tissue disorders | 2 (0.7) | 0 |
| Surgical and medical procedures | 1 (0.4) | 0 |
| Vascular disorders | 1 (0.4) | 4 (3.7) |
| AE = adverse event, SAE = Serious adverse event, WDAE = withdrawal due to adverse event | | |

Fatal adverse events occurred in 19% and 17% of the blinatumomab and chemotherapy treated patients, respectively. Grade 3 or higher adverse events were reported in 86.5% of the blinatumomab group and in 91.7% of individuals receiving chemotherapy. In addition, the event rate for serious adverse events was determined to be 349.4 events per 100 patient-years in the blinatumomab group as compared to 641.9 per patient-year in the chemotherapy group.[1]

### *Cytokine release syndrome*

Cytokine release syndrome of any grade occurred in 38 (14.2%) patients in the blinatumomab group and none in chemotherapy. Grade 3 or higher cytokine release syndrome occurred in 13 or 4.9% of individuals receiving blinatumomab with no treatment interruptions required. None were reported in the chemotherapy group. Of the reporting of cytokine release syndrome 2.6% (n=7) were considered serious adverse events and in all patients reporting were considered grade 3 or higher.[1]

### *Neurologic events*

Neurologic events were grade 3 or higher were reported in 25 patients (9.4%) of individuals receiving blinatumomab and in 9 patients (8.3%) receiving chemotherapy. Discontinuation of therapy due to neurologic events occurred in 4% of blinatumomab and 1% of chemotherapy treated patients.[1]

## 6.4 Ongoing Trials

No ongoing trials meeting the review's inclusion criteria were found.

# 7 SUPPLEMENTAL QUESTIONS

No relevant supplemental questions were identified.

# 8 COMPARISON WITH OTHER LITERATURE

No relevant information important relevant to the review was identified.

# 9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on blinatumomab (Blincyto) for acute lymphoblastic leukemia ALL). Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

# APPENDIX A: LITERATURE SEARCH STRATEGY

*See Appendix B for more details on literature search methods.*

### 1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2017**, Embase** 1974 to 2017 March 07**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

| Line # | Searches | Results |
|---|---|---|
| 1 | (Blinatumomab* or Blincyto* or AMG103 or AMG-103 or MT-103 or MT103 or MEDI-538 or MEDI538 or 853426-35-4 or 4FR53SIF3A).ti,ab,ot,kf,kw,hw,rn,nm. | 1032 |
| 2 | Precursor Cell Lymphoblastic Leukemia-Lymphoma/ | 37636 |
| 3 | exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ | 45251 |
| 4 | (acute adj3 (lymphocytic or lymphoid or lymphatic or lymphocyte) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw. | 15403 |
| 5 | ((B-cell or B-cells or B precursor or Pro-B or Pre-B or Burkitt*) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw. | 17834 |
| 6 | lymphoblast*.ti,ab,kf,kw. | 112647 |
| 7 | or/2-6 | 155194 |
| 8 | and/1,7 | 638 |
| 9 | 8 use pmez | 137 |
| 10 | 8 use cctr | 9 |
| 11 | *blinatumomab/ | 228 |
| 12 | (Blinatumomab* or Blincyto* or AMG103 or AMG-103 or MT-103 or MT103 or MEDI-538 or MEDI538).ti,ab,kw. | 599 |
| 13 | or/11-12 | 607 |
| 14 | exp Acute lymphoblastic leukemia/ | 69249 |
| 15 | (acute adj3 (lymphocytic or lymphoid or lymphatic or lymphocyte) adj3 (leukemia* or leukaemia*)).ti,ab,kw. | 15381 |
| 16 | ((B-cell or B-cells or B precursor or Pro-B or Pre-B or Burkitt*) adj3 (leukemia* or leukaemia*)).ti,ab,kw. | 17800 |
| 17 | lymphoblast*.ti,ab,kw. | 112530 |
| 18 | or/14-17 | 155226 |
| 19 | and/13,18 | 405 |
| 20 | 19 use oemezd | 270 |
| 21 | conference abstract.pt. | 2478574 |
| 22 | and/20-21 | 118 |
| 23 | limit 22 to yr="2012 -Current" | 99 |
| 24 | 20 not 21 | 152 |
| 25 | or/9-10,24 | 298 |

| | | |
|---|---|---|
| 26 | 23 or 25 | 397 |
| 27 | limit 26 to english language | 388 |
| 28 | remove duplicates from 27 | 274 |

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

| Search | Query | Items found |
|---|---|---|
| #9 | Search **#7 AND #8** | 9 |
| #8 | Search **publisher[sb]** | 510764 |
| #7 | Search **#1 AND #6** | 137 |
| #6 | Search **#2 OR #3 OR #4 OR #5** | 78156 |
| #5 | Search **lymphoblast*[tiab]** | 47620 |
| #4 | Search **(B-Cell[tiab] OR B-cells[tiab] OR B precursor[tiab] OR Pro-B[tiab] OR Pre-B[tiab] OR Burkitt*) AND (leukemia*[tiab] OR leukaemia*[tiab])** | 19484 |
| #3 | Search **acute[tiab] AND (lymphocytic[tiab] OR lymphoid[tiab] OR lymphatic[tiab] OR lymphocyte[iab]) AND (leukemia*[tiab] OR leukaemia*[tiab])** | 18909 |
| #2 | Search **Precursor Cell Lymphoblastic Leukemia-Lymphoma[mh]** | 24257 |
| #1 | Search **Blinatumomab* OR Blincyto* OR "AMG103" OR "AMG-103" OR "MT-103" OR "MT103" OR "MEDI-538" OR "MEDI538"** | 198 |

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

**Clinical trial registries:**

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

**Select international agencies including:**

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

**Conference abstracts:**

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology
http://www.hematology.org/

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia - last 5 years

# APPENDIX B: DETAILED METHODOLOGY OF LITERATURE REVIEW

Provide full details of search strategies used to identify the relevant literature, including databases searched and search terms. Include ongoing trials search strategy as well.

## Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017 March 07) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017 March 07) via Ovid; The Cochrane Central Register of Controlled Trials (February 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were blinatumomab, Blincyto and acute lymphoblastic leukemia.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of May 30, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

## Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

## Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team.

SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

## Data Analysis

Additional data analyses are not expected for pCODR reviews. If they are required, as determined in consultation with pCODR, provide details on any additional statistical analyses and details on software programs used. If additional data analyses are not conducted, insert the following:

No additional data analyses were conducted as part of the pCODR review.

## Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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