PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Blinatumomab (Blincyto) for Acute Lymphoblastic Leukemia

April 1, 2016

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TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

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

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two Phase II non-randomized interventional trials, MT 103-211[1] and MT 103-206[2] which enrolled adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL). Baseline characteristics were similar in the two trials. In both trials, treatment continued until disease progression or unacceptable toxicity.

- Study MT 103-211 enrolled 189 patients with primary refractory or relapsed Philadelphia chromosome-negative B-precursor ALL. The median age of patients was 39, the majority of patients had and ECOG PS of 0 (33.9%) or 1 (49.2%) and a small minority of patients had and ECOG PS of 2 (16.4%). The majority of patients had prior salvage therapy (80%) and no prior allogenic stem cell transplant (66%). Among patients with prior salvage therapy, the majority had one (41%), 2 (22%) or greater than 2 (17%) previous salvage therapies. Twenty percent of patients were primary refractory or in first salvage and had no prior salvage therapy. Blinatumomab was administered with dexamethasone premedication at 9 µg/day for 1 week, then 28 µg/day for 3 weeks in order to reduce the risk of cytokine release syndrome. Patients with minimal residual disease (MRD), Ph+ ALL and paediatric patients were excluded from enrollment in this study. See Section 6.3.2.1a for details on key inclusion criteria.[1]

- Study MT 103-206 enrolled 36 patients with relapsed or refractory B-precursor ALL. The median age of patients was 32, the majority of patients had and ECOG PS of 0 (41.7%) or 1 (52.8%) and a small minority of patients had and ECOG PS of 2 (5.6%). The majority of patients had not had prior allogenic stem cell transplant (58%). Among patients with no prior allogenic HSCT, the majority had at least one (31%) or 2 (19%) previous salvage therapies. There were 3 cohorts of blinatumomab in the dose-finding stage of the study, however 5 µg/m^2/day for week 1, then 15 µg/m^2/day for 3 weeks was used in extension phase of the study. Patients with MRD, Ph+ ALL eligible for dasatinib or imatinib treatment and pediatric patients were excluded from enrollment in this study. See Section 6.3.2.1a for details on key inclusion criteria.

The dose of blinatumomab was fixed in the larger MT 103-211 trial (9 µg/day for 1 week, then 28 µg/day for 3 weeks followed by 28ug/day for 4 weeks in subsequent cycles) while weight based dosing was used in the smaller MT 103-206 study (5 µg/m^2/day for week 1, then 15 µg/m^2/day for 3 weeks). When using 1.7m^2 to represent the weight of the average patient (standard of 1.7m^2 is used in pCODR reviews for the average weight of patients), the daily dose of blinatumomab between the two studies is nearly equivalent.

Efficacy

The primary outcome in both studies was complete remission or complete hematological remission with partial hematological recovery of peripheral blood counts (CR/CRh) within 2 treatment cycles (within first two cycles of treatment, 12 weeks), hereafter referred to as CR/CRh, with overall survival (OS) and relapse free survival (RFS) as secondary outcomes.

The CR/CRh rate within the first 2 cycles of treatment with blinatumomab was 43% (95% CI: 36%-50%) and 69% (95% CI: 52%-84%) in studies MT 103-211 and MT 103-206, respectively. Among patients achieving CR/CRh, 40% and 52%, respectively in each study went on to receive HSCT. CR/CRh rates were similar or higher to the overall results within most subgroups of patients based on prior salvage therapy.

In the MT 103-211 and MT 103-206 studies, OS was 6.1 and 9.8 months and RFS was 5.9 and 7.6 months, respectively. Censoring the results for subsequent HSCT did not have an impact on RFS in either study however censoring resulted in OS reduction to 5.1 months in MT 103-211 and an increase to 14.9 months in the MT 103-206 study.

Quality of life was not measured in either study.

Harms

In study MT 103-211, grade 5 AE were experienced by 28 (15%) of patients. The majority of fatal/grade 5 AE's, 23 (12%), were due to infections. Grade 3 and 4 AE's were experienced by 38% and 30% of patients, respectively. Grade 3 and 4 neurological toxicities were experienced by 11% and 2% of patients, respectively. While most of these toxicities resolved, 3 patients died of unrelated causes after the onset of neurological toxicity. All grades neurological toxicity, mostly grade 1 and 2 in severity, were experienced by 52% of patients. Three (2%) patients experienced grade 3 cytokine release syndrome. Two of these patients achieved CR or CRh, including one patient in whom treatment had to be interrupted temporarily; the third patient died of disease progression. There was no information on all grades CRS in this study.

In study MT 103-206, 22 of 36 patients died. Six patients died as a result of infections during the core study period. Of these, five deaths were reported during or after blinatumomab therapy but before HSCT. One death was reported as possibly being related to blinatumomab and occurred in a patient who had undergone HSCT before treatment. The patient died as a result of disseminated fungal infection of the brain.[2] Two of 36 patients had grade 4 CRS.

1.2.2 Additional Evidence

pCODR received input on blinatumomab (Blincyto) for acute lymphoblastic leukemia from one patient advocacy group, Canadian Cancer Survivor Network (CCSN). Provincial Advisory Group input was obtained from seven of the nine provinces participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of blinatumomab and is discussed as supporting information:

- Critical Appraisal of Results from Study 20120310 Providing Historical Efficacy Data on Treatments Used for Patients with Relapsed/Refractory (R/R) B-cell Precursor Acute-Lymphoblastic Leukemia (ALL).

1.2.3 Interpretation and Guidance

Acute Lymphoblastic Leukemia (ALL) is a highly aggressive hematological malignancy characterized by bone marrow infiltration and marrow failure. While incrementally better outcomes have been reported for initial treatment, the burden on individual patients and their families after relapse occurs is significant. Notably, patients who relapse after conventional treatment require prolonged hospitalizations that interrupt employment and education and that have high associated healthcare costs. The prognosis of these patients is poor and prolonged survival is vanishingly rare for patients who fail to achieve remission with salvage chemotherapy. Reinduction is generally attempted with chemotherapy combinations not used in up-front therapy. These regimens are reported to be successful 20% to 83% of the time (eg. Remission rates of 39% to 83% with FLAG-IDA and 44% to 47% with Hyper-CVAD, with slightly higher rates reported for patients treated after first relapse than later in the disease course.[4] Patients with relapsed/refractory ALL are encouraged to proceed to allogeneic hematopoietic cell transplantation at the earliest opportunity as cure is not expected with salvage therapy alone.

Based on study MT 103-211, the majority of patients that received blinatumomab were in second or later line of salvage in 151 (80%), 38 (20%) of patients being in first relapse. Responses were seen in 81 of 189 (43%) patients (CR in 63 (33%), CRh in 18 (10%)). Response rates among patients in first and second relapse were similar (50% and 47%, respectively) while response rates for patients in third or later relapse were slightly lower (36% and 34%, respectively). Median relapse-free and overall survivals were 5.9 months and 6.1 months, respectively. It is expected that responses were likely less among patients with a greater degree of bone marrow infiltration. In the smaller Topp 2014 study (n=36), the highest proportion of responses (CR/CRh) was observed in patients treated at first relapse (11/11) although treatment later in the course was also successful (6/10 at second salvage and 8/15 relapsed after HCT). The overall response rate in this study was 69% and median relapse-free survival was 7.6 months.[2]

Based on clinical opinion, toxicity with blinatumomab was consistent with conventional salvage regimens (eg. grade III/IV cytopenias, high rates of infections and have the potential to cause neurological toxicity (peripheral neuropathy or cerebellar toxicity)). In the MT-103-206 study, the most common > grade 3 adverse events with blinatumomab were leukopenia and thrombocytopenia and infections were seen in 33% of patients in the MT 103-206 study. Neurological toxicity was observed in 17% of patients in the MT 103-206 study and severe cytokine release syndrome occurred in 6%. In the MT 103-211 study, grade III and IV neurological events were observed in 11% and 2% of patients, respectively. Grade 5 AE's occurred in 15% (28/189) of patients in the MT 103-211 study with the majority (12%) of deaths occurring mostly due to infection.

In response to feedback received from stakeholders regarding conclusions made on the toxicity profile of blinatumomab, the CGP noted that the data presented in the studies under review must be considered in the context toxicity data available within the literature and clinical experience. Based on this, the CGP re-iterated that the toxicity profile of blinatumomab is similar to those described in available literature and clinical experience of the Panel. [23, 24]

Based on this evidence and clinical opinion, the response rates and toxicity of blinatumomab are similar to those of standard combination chemotherapy regimens. Data on a historical control group provided by the submitter offered a potentially useful comparator against which to evaluate the efficacy and incremental cost effectiveness of blinatumomab in relapsed and refractory Philadelphia-negative ALL. The CGP however identified several strengths and weaknesses inherent to this data and suggest that caution should be exercised in interpreting the results. It is expected that a randomized controlled

trial (NCT02101853) of blinatumomab versus standard reinduction, currently underway (estimated primary completion date of August 2016), will settle to role of blinatumomab in relapsed/refractory ALL more definitively than the current body of evidence.

In response to feedback received from stakeholders regarding response rates observed with blinatumomab, the CGP further described further re-iterated that CR rate reported in the two studies is similar or slightly lower that median CR rates described in the literature (Ref- Frey and Luger (2015) While the CGP appreciates the utility of the historical comparator arm provided by the submitter, given the limitations described with this data, the Panel agreed that this information should not be considered in isolation from those reported in the literature. Overall, the CGP re-iterated that response rates observed with blinatumomab appear similar to those of standard combination chemotherapy regimens.

Additionally, the CGP noted that subgroup data from Topp et al. (2015) suggests blinatumomab does not lose efficacy as a second salvage therapy compared to use in first salvage therapy. The CGP also noted that current first salvage therapies may be curable in a small number of patients (by allowing patients to proceed to HSCT). Given this information and uncertainty in the comparative efficacy of blinatumomab against currently available first line salvage therapies, the CGP re-iterated their conclusion that blinatumomab should be reserved for use in second salvage or later until further evidence is available to support the move of blinatumomab up to first salvage therapy. The CGP anticipates the results of the TOWER study will help answer this question once the data is made available for review.

1.3 Conclusions

The pCODR Leukemia Clinical Guidance Panel concluded that there may be net clinical benefit with blinatumomab for selected patients with relapsed/refractory ALL. This conclusion is based on one phase II non randomized study which reported CR/CRh rate of 43% in patients. Whether this translates to an improvement in OS is uncertain due to limitations of trial design and limitations of the historical controls. A smaller supportive phase II non randomized study also reported similar results. The CGP agreed that the majority of patients in the larger study had received a line of reinduction prior to blinatumomab. Therefore the use of blinatumomab should be reserved for patients who fail at least one line of reinduction.

In making this conclusion, the CGP also considered that:

- While results from randomized trials are not yet available, response rates and toxicity of blinatumomab appear similar to those of standard combination chemotherapy regimens.
- A historical comparator group was developed by the submitter. While conservative estimates of comparative efficacy can be determined through this data, several strengths and weaknesses were identified inherent to the use of this data and the CGP therefore urged that caution be used in interpreting these results.
- A randomized, controlled trial (NCT02101853) of blinatumomab versus standard reinduction is currently underway (estimated primary completion date of August 2016) and is expected to settle to role of blinatumomab in relapsed/refractory ALL more definitively than the current body of evidence.
- There is no data on the impact of blinatumomab on quality of life.
- While blinatumomab may be given on an outpatient basis the supportive care and pharmacy requirements for patients with relapsed ALL who are receiving this medication would likely require that patients remain in close proximity of hospital for the duration of therapy. For

instance, patients will need access to transfusion support for cytopenias, nursing care for pump maintenance and expedited admissions for complications such as febrile neutropenia, neurological impairment and cytokine release. It is likely that patients would spend at least part of their course in hospital.

- While there may be a response to blinatumomab in children and adolescents, the scope of this review considered only adult patients and data on the pediatric/adolescent population would need to be reviewed separately to determine efficacy in that population.

2 CLINICAL GUIDANCE

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 (Blincyto) for 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 [drug name and indication] conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; 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. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on blinatumomab (Blincyto) for ALL and a summary of submitted Provincial Advisory Group Input on blinatumomab (Blincyto) for ALL are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Acute Lymphoblastic Leukemia (ALL), representing about 15% of adult cases of acute leukemia, is a highly-aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure, organ infiltration and systemic complaints. Traditionally, age and cytogenetics have been viewed as the most important prognostic factors in ALL. The most recent ALL incidence available is for 2010. It is expected that 435 Canadians were diagnosed with ALL and 236 will dies from it.[22]

The majority of young adult patients with ALL can expect to be cured with modern chemotherapy protocols and complete remission rates of 89% have been reported with pediatric inspired protocols, and five-year relapse free survival of 71%.[8,9] 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. 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. Regimens used for reinduction are reported to be successful in 20% to 83% of the time (eg. Remission rates of 39% to 83% with FLAG-IDA and 44% to 47% with Hyper-CVAD, with slightly higher rates reported for patients treated after first relapse than later in the disease course.

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.

2.1.2 Objectives and Scope of pCODR Review

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).

2.1.3 Highlights of Evidence in the Systematic Review

Two non-randomized interventional trials met the inclusion criteria for this systematic review, MT 103-211 and MT 103-206.[1,2]

Both studies MT 103-211 and MT 103-206 were phase II, open-label single-arm studies that enrolled adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL). Study MT 103-211 was conducted in Europe at twenty-three centres and the USA at fourteen centres.[1] Study MT 103-206 was conducted at nine centres in Germany. Baseline characteristics were similar in the two trials.

Study MT 103-211[1]

The study included 189 patients with primary refractory or relapsed Philadelphia chromosome-negative B-precursor ALL. Patients enrolled were primary refractory, relapsed within 12 months of first remission, within 12 months of allogeneic HSCT, or did not respond to or relapsed after first salvage therapy.[3] Patients were required to have at least 10% bone marrow blasts and an ECOG performance status of 0-2.

Blinatumomab was administered as a continuous infusion in 4 week cycles. Premedication with dexamethasone (20mg) was required within 1 hour before a treatment cycle began and before the dose step in cycle 1. For cycle 1 a step wise dosing was conducted for blinatumomab (9 µg/day for 1 week then 28 µg/day for 3 weeks) to reduce the risk of cytokine release syndrome.[1] Subsequent cycles were at 28ug for 4 weeks. All 189 patients received cycle one of treatment with blinatumomab. Please see Section 6.3.2.1d in the systematic review for further details on patient disposition.

Study MT 103-206[2]

The study included 36 patients with relapsed or refractory B-precursor ALL who were treated with blinatumomab in cycles of 4-week continuous infusion followed by a 2-week treatment-free interval. There were two patients (6%) with Ph (+) disease who were included. This study included a dose-finding stage and an extension stage.

All patients enrolled had at least 5% blasts in the bone marrow, an ECOG performance status of 0-2, and a life expectancy of at least 12 weeks. Due to the tolerability profile, the dose cohort of 5 µg/m²/day for 1 week, followed by 15 µg/m²/day for the remainder of the treatment period with a 2 week break between cycles became the preferred dosing schedule for the study (See Section 6 for details on dose cohorts). In order to reduce the incidence of cytokine release syndrome (CRS) and for tumour debulking, prephase treatment with dexamethasone daily for 5 days or cyclophosphamide 200 mg/m²was permitted.

In both trials, treatment continued until disease progression or unacceptable toxicity. Patients achieving CR/CRh had the option to transfer to transplant, if eligible, or receive 3 additional cycles of blinatumomab as consolidation. Treatment was discontinued if patients did not achieve CR/CRh within 2 cycles, in patients with grade IV neurologic toxicities, those with more than one seizure, and those whose therapy was delayed by more than 2 weeks due to toxicity.

Key efficacy outcomes and response to treatment in both trials are summarized in the table below.

Table 1. Baseline Patient Characteristics in the included studies of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).[1,2,12]		
	MT 103-211, n=189[1]	MT 103-206, n=36[2]
Age, median	39 (18-79)	32 (18-77)
Sex		
Men	119 (63%)	22(61%)
Women	70(37%)	14(39%)
ECOG performance status		
0	64(33.9)	15(41.7)
1	93(49.2)	19(52.8)
2	31(16.4)	2(5.6)
›2	0(0.0)	0(0.0)
Missing	1(0.5)	0(0.0)
Previous lines of salvage therapy		
0	38(20%)	NR
1	77(41%)	NR
2	42(22%)	NR
>2	32(17%)	NR
Disease States		
Previous allogenic HSCT	64(34%)	15 (42%)
No previous allogenic HSCT	**125(66%)**	**21(58%)**
• No previous salvage/primary refractory[α]	29(15%)	14/36 (39%)*
• 1 previous salvage/first salvage after first CR	55(29%)	7(19%)[#]
• ≥2 previous salvage	41(22%)	

Notes: * Proportion represents a combination of patients that were primary refractory (3/36, 8%) and patients in 1st relapse or at 1st salvage (11/36, 31%). These data was provided by Amgen through the Verification of Non-disclosable Information step in the pCODR process.
[α]Includes patients that are primary refractory (patient had never achieved a CR/CRh) and patients in 1st relapse or 1st salvage (ie. patient has never relapsed and therefore never received a salvage treatment prior to study enrolment)
[#]Proportion included patients that have had 1 or more salvage ie. ≥2nd salvage (patient has relapsed at least once and received at least one salvage treatment)
NR: not reported

Effectiveness:

Study MT 103-211[1]

In the Topp 2015 study, the primary outcome was CR/CRh within 2 cycles of treatment with blinatumomab, using the best response.

The CR/CRh rate within the first 2 cycles of treatment with blinatumomab was 43% (95% CI: 36%-50%). Complete remission was achieved by 33% of patients (63/189), and CRh was achieved by 10% of patients (18/189). Seventy nine percent (64/81) of responders achieved CR/CRh in cycle 1 of their treatment.[7] Of the 43% (81/189) patients who achieved CR/CRh within 2 cycles of treatment, 32 (40%) went on to undergo allogeneic HSCT.

The median overall survival was 6.1 months at a median follow-up of 9.8 months, with no difference after censoring for allogeneic HSCT.[1] For patients achieving CR/CRh after two treatment cycles compared to those without CR/CRh, OS was better (median of 9.9 months

vs. 2.7 months).[7] At a median follow-up of 8.9 months, the median relapse-free survival was 5.9 months.

Study MT 103-206[2]

The CR/CRh rate within the first 2 cycles of treatment with blinatumomab was 69% (25/36), Of these, 13 proceeded to receive HSCT while still in remission.

In the Topp 2014 study, the highest proportion of patients with a CR or CRh were observed among those in first salvage who were treated in early or late relapse, five of five and six of six patients responded, respectively. This was followed by patients in second salvage with relapsed disease (six of 10 patients responded). The proportion of patients was lowest among those who had relapsed after HSCT, with eight of 15 responding.

Median Relapse-free survival (RFS) was 7.6 months (median follow-up time of 9.7 months). If censored for subsequent HSCT, median RFS was 7.9 months. There was no difference observed in RFS for patients who achieved a CR versus CRh.

Median Overall survival (OS) was 9.8 months with a follow-up of 12.1 months as of the primary data collection date of March 2012. Please see section 6.3.2.1 of the systematic review for further details on a long-term follow-up analysis presented for study MT 103-206 and historical comparator results.

Safety:

MT 103-211[1]

In the Topp et al 2015 study, grade 3, 4 and 5 AE's were experienced by 38%, 30% and 15% of patients, respectively. Grade 5 AE were experienced by 28 (15%) of patients. The majority of fatal/grade 5 AE's, 23 (12%), were due to infections. Additionally, there were five cases of disease progression or relapse which were reported as being fatal adverse events. Dose reductions were needed in 19 (10%) of patients and 34 (18%) patients discontinued permanently because of adverse events, 18 (10%) of whom discontinued because of adverse events thought to be treatment-related by the investigators.

In the Topp 2015 study, approximately half (52% of 189 patients) of patients had neurologic events, mainly of grade 1 or 2 in severity. There were 20 patients (11%) and 4 patients (2%) that had grade III and IV neurologic toxicities, respectively. All of these toxicities resolved, however 3 patients died of apparently unrelated causes after the onset of toxicity.

MT 103-206[2]

The most common grade ≥3 AEs were transient leukopenia and thrombocytopenia. Sixty-seven percent of patients had SAEs, primarily infections (33%) and nervous system and psychiatric disorders (22%). Six of the 36 patients (17%) treated had nervous system or psychiatric disorders requiring treatment interruption or permanent discontinuation. In five of the six patients, nervous system or psychiatric disorders were recorded within the first week of a cycle. There were 3 patients with epilepsy or convulsions who had treatment interruption but successfully resumed treatment with antiseizure prophylaxis.

Overall, 22 of 36 patients died. Six patients died as a result of infections during the core study period. Of these, five deaths were reported during or after blinatumomab therapy

but before HSCT. Four of the five deaths were reported as not related and one as possibly related to blinatumomab. The death which was possibly related to blinatumomab occurred in a patient who had undergone HSCT before treatment and died as a result of disseminated fungal infection of the brain.[2]
Two of 36 patients had grade 4 cytokine release syndrome (CRS). Both patients had a high burden of disease (~90% blasts in marrow), and one of these patients who presented with tumor lysis syndrome permanently discontinued treatment, and the other patient was re-exposed to blinatumomab after interruption of treatment.[2]

2.1.4 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.

2.1.5 Summary of Supplemental Questions

Critical Appraisal of Results from Study 20120310 Providing Historical Efficacy Data on Treatments Used for Patients with Relapsed/Refractory (R/R) B-cell Precursor Acute-Lymphoblastic Leukemia (ALL) can be found in the Supplemental Questions section 7.1

2.1.6 Other Considerations

Patient Advocacy Group Input

From a patient perspective, symptoms of Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia include tiredness, frequent minor infections, discomfort in bones or joints, neutropenia, bruising or bleeding, depression, anemia, enlarged spleen, liver or lymph nodes, mild fever, thrombocytopenia. CCSN remarked that half (4 of 8) of the respondents rated neutropenia, tiredness, frequent minor infections, discomfort in bones or joints, and depression as the top five symptoms that were the most important to control. While some treatments, such as radiation and cyclophosphamide, have been successful at controlling common aspects of Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia for certain patients; however, there are a number of side effects. Common side effects of treatment included: fatigue, nausea and vomiting, upset stomach, hair loss, diarrhea or loose bowels, and infection. Patients reported that upset stomach, fatigue, infection, and anemia were the most difficult side effects to manage. CCSN indicated that there is a need for additional treatments with fewer side effects, as well as, treatment that stops disease progression.

Please see Section 4 for more detailed Patient input on individual parameters.

PAG Input

Input was obtained from seven of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. At the time the input was provided, PAG identified the following as factors that could impact the implementation of blinatumomab:

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:

- Very small patient population
- Complex and highly resource intensive to prepare and administer since infusion bag changed every 24 or 48 hours 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 Section 5 for more detailed PAG input on individual parameters.

Other

There is an ongoing phase III randomised controlled trial (TOWER study) of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).[13] The study compares blinatumomab as a continuous infusion to four commonly used standard of care chemotherapy regimens. The primary outcome of the study is OS and secondary outcomes include patient reported outcomes. The study was started in December 2013 and enrolled 405 patients. The estimated completion date is August 2016.

Please see Section 6.4 for more on this ongoing trial.

2.2 Interpretation and Guidance

Burden of Illness and Need:

Acute Lymphoblastic Leukemia (ALL) is a highly aggressive hematological malignancy characterized by bone marrow infiltration and marrow failure. With some modern treatment protocols 71% of young adults and 57% of older adults remain alive and in remission five years after starting treatment.[8,9] Population-based studies, however, continue to show that a substantial proportion of adults with ALL die of their disease.[10,11] The prognosis of patients who relapse after primary therapy is poor and prolonged survival is vanishingly rare for patients who fail to achieve remission with salvage chemotherapy. Reinduction is generally attempted with chemotherapy combinations not used in up-front therapy. These regimens are reported to be successful 20% to 83% of the time (eg. Remission rates of 39% to 83% with FLAG-IDA and 44% to 47% with Hyper-CVAD, with slightly higher rates reported for patients treated after first relapse than later in the disease course.[4] 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.

Applying lessons learned from the treatment on children with ALL to adults has been an effective strategy overall and has resulted in incrementally better outcomes over time. Despite these improvements, however, the burden on individual patients and their families after relapse occurs is significant. Notably, patients who relapse after conventional treatment require prolonged hospitalizations that interrupt employment and education and that have high associated healthcare costs. Patients who fail to achieve remission have very poor outlooks with little prospect of cure. In general palliative care for acute leukemia patients consists of supportive care, blood transfusions and low-dose chemotherapy for symptom control. Patients who live far from the tertiary centers with expertise in managing these patients may have no option but to leave home and family to access care. An effective outpatient treatment for relapsed/refractory ALL would be of benefit to patients and their families.

Efficacy Interpretation

The effectiveness of blinatumomab in relapsed/refractory ALL was evaluated in two phase II studies by Topp et al.[1,2] The larger of these studies, a multi-center phase II study describes the outcome of blinatumomab treatment in 189 patients with relapsed Philadelphia-negative ALL with at least 10% bone marrow blasts and ECOG performance status 0-2.[1] Patients with active CNS or testicular leukemia, Burkitt leukemia or other diseases that might interfere with interpretation of this study were excluded. Response was assessed by bone marrow biopsy at the end of each cycle and the primary endpoint was CR or CRh after two cycles. Blinatumomab was the first line of salvage for 38 (20%) patients and second or later line of salvage in 151 (80%). Responses were seen in 81 of 189 (44%) patients (CR in 63 (34%), CRh in 18 (10%)). Median relapse-free and overall survivals were 5.9 months and 6.1 months, respectively. Responses were less likely among patients with a greater degree of bone marrow infiltration.

The second smaller study reports the outcome of salvage in 36 patients with ALL who had failed initial induction (n=3), relapsed after chemotherapy (first relapse (n=11) or beyond first relapse (n=7)) or relapsed after HCT (n=15).[2] The highest proportion of responses (complete remission (CR) plus complete remission with incomplete hematological recovery (CRh)) was observed in patients treated at first relapse (11/11) although treatment later in the course was also successful (6/10 at second salvage and 8/15 relapsed after HCT). The overall response rate in this study was 69% and median relapse-free survival was 7.6 months .[2]

In reviewing the evidence available for current treatment options for relapsed or refractory Ph-ALL, the CGP reviewed data on a historical control group provided by the submitter. Overall, the impression of the CGP was that this cohort offered a potentially useful comparator against which to evaluate the efficacy and incremental cost effectiveness of blinatumomab in relapsed and refractory Philadelphia-negative ALL. The CGP identified several strengths and weaknesses inherent in the use of this data, and suggest that caution should be exercised in interpreting these results. Factors that the CGP felt worthy of note and which may impact the comparability of results to the MT 103-211 study regarding the historical cohort include the following:

- The cohort is one of the largest cohorts of ALL patients described so far.
- The source of the data, the purpose of its collection and the process by which it was collected is unclear from the information provided.
- The timeframes within which patients received treatment in the historical and blinatumomab cohorts differ.
- The overall CR rate for the historical cohort was based on a weighted analysis of six strata based on age and number of prior lines of therapy. Although the weighting of each stratum was proportional to Topp et al. 2015, differences in prognostic factors within these strata were not considered. It is unclear how differences in these prognostic factors may have affected the outcome of the comparisons.
- The data has been extensively manipulated statistically.

Despite these limitations, conservative estimates of comparative efficacy can be drawn using these data however caution should be exercised in interpreting these results.

In response to feedback received from stakeholders regarding response rates with blinatumomab, the CGP further described considerations taken to come to a conclusion on the efficacy of blinatumomab. The CGP noted that the Topp et al. (2015) reported an overall response rate of 43% after two cycles of treatment. This is comprised of 33% achieving complete responses (CR) and 10% complete responses with incomplete haematological recovery (CRh). The smaller Topp et al. (2014) data suggests a higher overall response rate of 69% comprised of 42% CR and 27% CRh.

While the reason for the discrepant response rates between the two trials is unclear, the CGP acknowledged that the results of dose finding studies, such as Topp et al. (2014), may not be fully representative of later experience with new or novel agents due to the nature of the populations studied. A recent review describing the management of relapsed/refractory Philadelphia-negative ALL (Ref- Frey and Luger (2015)) reports CR rates of between 20-83%, with a median CR rate of 41%. The CR rate reported in Topp et al. (2014) is similar to this median while that reported in the larger study is slightly lower than this (33%). Based on this, the CGP concluded that response rates observed with blinatumomab appear similar to those of standard combination chemotherapy regimens. Additionally, while the CGP appreciates the utility of the historical comparator arm provided by the submitter, given the limitations described with this data, the Panel agreed that this information should not be considered in isolation from those reported in the literature.

Additionally, in reaching the conclusion that blinatumomab should be reserved for patients who have received at least two prior lines of therapy the panel reviewed subgroup data from Topp et al. (2015), demonstrating that responses to blinatumomab are not substantially different for patients who have received no prior lines or one prior line of salvage therapy (50% vs. 47% response rate, with overlapping 95% confidence intervals). This data suggests that blinatumomab does not lose efficacy as a second salvage therapy compared to use in first salvage therapy. Given this information, uncertainty in the presented evidence as compared to salvage regimens used in first relapse and that currently available first line salvage therapies may be curable in a small number of patients (by allowing patients to proceed to HSCT), the CGP re-iterated their conclusion that blinatumomab should be reserved for use in second salvage or beyond until further evidence is available to support its move up to first salvage therapy. The CGP anticipates the results of the TOWER study will help answer this question once the data is made available for review.

Harms Interpretation

Conventional chemotherapy protocols for patients with relapsed/refractory ALL are associated with high rates of toxicity. All such protocols are expected to cause significant (grade III/IV) cytopenias, a high rate of infections and have the potential to cause neurological toxicity (peripheral neuropathy or cerebellar toxicity). Based on clinical opinion, toxicity with blinatumomab is consistent with that seen with conventional salvage regimens. In study MT 103-206 the most common $\geq$ grade 3 adverse events were leukopenia and thrombocytopenia and infections were seen in 33% of patients in the single-center study. Neurological toxicity was observed in 17% of patients and severe cytokine release syndrome occurred in 6%. In study MT 103-211 febrile neutropenia was observed in 28% of patients. Grade I-II neurological toxicity occurred in 52% of patients and was a common event that did not require withholding of medication to resolve. Grade III and IV neurological events were observed in 11% and 2% of patients, respectively. Toxic deaths occurred in 12% of patients, mostly due to infection.

In response to feedback received from stakeholders regarding conclusions made on the toxicity profile of blinatumomab, the CGP further described considerations taken to come to a conclusion on toxicity. Consideration was given to the published estimates of toxicity from blinatumomab as described in the Topp et al. 2015 study which reported rates of grade 3 and grade 4 adverse events at 38% and 30%, respectively. Additionally, 12% of patients who received blinatumomab died during re-induction. Rates of infection reported in this study were 28% for febrile neutropenia, 10% for pneumonia and 7% for sepsis. Given comparative toxicity data was not available during the current review, these rates were considered in the context the available literature and clinical experience. Based on this, the CGP re-iterated that the toxicity profile of blinatumomab are similar to those described in series of patients treated with re-induction chemotherapy as is described in available literature and clinical experience of the Panel. [23, 24]

2.3 Conclusions

The pCODR Lymphoma Clinical Guidance Panel concluded that there may be net clinical benefit with blinatumomab for selected patients with relapsed/refractory ALL. This conclusion is based on one phase II non randomized study which reported CR/CRh rate of 43% in patients. Whether this translates to an improvement in OS is uncertain due to limitations of trial design and limitations of the historical controls. A smaller supportive phase II non randomized study also reported similar results. The CGP agreed that the majority of patients in the larger study had received a line of reinduction prior to blinatumomab. Therefore the use of blinatumomab should be reserved for patients who fail at least one line of reinduction.

In making this conclusion, the CGP also considered that:

- While results from randomized trials are not yet available, response rates and toxicity of blinatumomab appear similar to those of standard combination chemotherapy regimens.
- A historical comparator group was developed by the submitter. While conservative estimates of comparative efficacy can be determined through this data, several strengths and weaknesses were identified inherent to the use of this data and the CGP therefore urged that caution be used in interpreting these results.
- A randomized, controlled trial (NCT02101853) of blinatumomab versus standard reinduction is currently underway (estimated primary completion date of August 2016) and is expected to settle to role of blinatumomab in relapsed/refractory ALL more definitively than the current body of evidence.
- There is no data on the impact of blinatumomab on quality of life.
- While blinatumomab may be given on an outpatient basis the supportive care and pharmacy requirements for patients with relapsed ALL who are receiving this medication would likely require that patients remain in close proximity of hospital for the duration of therapy. For instance, patients will need access to transfusion support for cytopenias, nursing care for pump maintenance and expedited admissions for complications such as febrile neutropenia, neurological impairment and cytokine release. It is likely that patients would spend at least part of their course in hospital.
- While there may be a response to blinatumomab in children and adolescents, the scope of this review considered only adults and data on the pediatric population would need to be reviewed separately to determine efficacy in that population.

3 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.

3.1 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 blast at presentation and the diagnosis is confirmed by bone marrow histology and ancillary tests like flow cytometry and immunohistochemistry.

3.2 Accepted Clinical Practice

ALL represents the most common childhood malignancy and with modern treatment protocols pediatric ALL is curable in as many as 90% of cases. The most recent ALL Canadian incidence estimates are available for 2010. It is expected that 435 Canadians were diagnosed with ALL and 236 will die as a result of the disease.[22] 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. 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.[8,9] 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. Regimens used for reinduction are reported to be successful 20% to 83% of the time (eg. Remission rates of 39% to 83% with FLAG-IDA and 44% to 47% with Hyper-CVAD), with slightly higher rates reported for patients treated after first relapse than later in the disease course.[4] Generally, toxicity with currently used therapies indicates that treatment related deaths occur in just over 10% of patients. Infections are also common roughly occurring in 47-92% of patients.[23, 24] 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.

3.3 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.

3.4 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 clinical panel 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.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Canadian Cancer Survivor Network (CCSN), provided input on blinatumomab (Blincyto) for the treatment of patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia.

CCSN conducted a survey in September 2015 on SurveyMonkey, which was publicized on CCSN's website (survivornet.ca) and in a CCSN e-letter. CCSN also received help in fielding this survey from the Leukemia and Lymphoma Society of Canada.

A total of eight (8) respondents completed the survey: five (5) patients and three (3) caregivers. None of the respondents have had experience with blinatumomab (Blincyto). All quotations in the following text were taken from completed surveys.

From a patient perspective, symptoms of Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia include tiredness, frequent minor infections, discomfort in bones or joints, neutropenia, bruising or bleeding, depression, anemia, enlarged spleen, liver or lymph nodes, mild fever, thrombocytopenia. CCSN remarked that half (4 of 8) of the respondents rated neutropenia, tiredness, frequent minor infections, discomfort in bones or joints, and depression as the top five symptoms that were the most important to control. While some treatments, such as radiation and cyclophosphamide, have been successful at controlling common aspects of Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia for certain patients; however, there are a number of side effects. Common side effects of treatment included: fatigue, nausea and vomiting, upset stomach, hair loss, diarrhea or loose bowels, and infection. Patients reported that upset stomach, fatigue, infection, and anemia were the most difficult side effects to manage. CCSN indicated that there is a need for additional treatments with fewer side effects, as well as, treatment that stops disease progression.

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Acute Lymphoblastic leukemia

According to CCSN, patients with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia are both physically and psychologically impacted by this disease.

When CCSN asked respondents, what symptoms or problems were experienced with Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia, they replied as follows:

Symptoms or Problems Experienced	No. of patients†
Tiredness	5 of 6 patients
Frequent minor infections	4 of 8 patients
Discomfort in bones or joints	4 of 8 patients
Neutropenia	4 of 8 patients
Bruising or bleeding	4 of 8 patients
Depression	4 of 8 patients
Anemia	1 of 3 patients
Enlarged spleen, liver or lymph nodes	1 of 3 patients
Mild fever	1 of 3 patients
Thrombocytopenia	1 of 5 patients

† not all 8 respondents responded to the question

In particular, CCSN remarked that half (4 of 8) of the respondents rated neutropenia, tiredness, frequent minor infections, discomfort in bones or joints, and depression as the top five symptoms that were the most important to control. CCSN also noted that 5 of 6 patients suffer from tiredness, and half (4 of 8) of patients deal with neutropenia, frequent minor infections, bone/joint discomfort, and depression.

CCSN submitted that all of the symptoms and problems identified by the respondents affect their quality-of-life and the ability to enjoy life, especially those of young patients and their caregivers.

4.1.2 Patients' Experiences with Current Therapy for ALL

According to CCSN, when asked what treatments patients had used or were using, respondents answered the following:

Type of Treatment	No. of patients†
Ara C	1 of 5 patients
Cyclophosphamide	2 of 5 patients
Doxorubicin	2 of 5 patients
Vincristine	2 of 5 patients
Dexamethasone	2 of 5 patients
Methotrexate	2 of 5 patients
Radiation	3 of 5 patients
CNS prophylaxis	0 of 5 patients
Hyper-CVAD	0 of 5 patients
Flag Ida	0 of 5 patients
Cy VP16	0 of 5 patients
Individualized treatment	0 of 5 patients

†not all 8 respondents responded to the question

CCSN noted that a total of 6 respondents answered the survey question on which therapies were most effective at controlling common aspects of Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia. CCSN indicated that among the 6 respondents, radiation, cyclophosphamide, individualized treatment and treatment received during clinical trials were rated the most successful at controlling common aspects of Philadelphia chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukemia.

When CCSN asked respondents, what treatment side effects were experienced, they replied as follows:

Treatment Side Effects Experienced	No. of patients†
Fatigue	6 of 7 patients
Nausea and vomiting	5 of 7 patients
Upset stomach	5 of 7 patients
Hair loss	4 of 7 patients
Diarrhea or loose bowels	4 of 7 patients
Infection	4 of 7 patients
Neutropenia	3 of 7 patients
Fever and chills	3 of 7 patients
Anemia	2 of 7 patients
Bacterial, viral, or fungal infection	2 of 7 patients
Thrombocytopenia	1 of 7 patients
Bleeding	0 of 7 patients

†not all 8 respondents responded to the question

According to CCSN, respondents reported that upset stomach, fatigue, infection, and anemia were the most difficult side effects to manage. One respondent noted: "mouth ulcers, extreme pain in veins in arm when a port/Hickman's line was not used, headache from lumbar punctures."

When CCSN asked about access to treatment, 3 of 7 respondents answered having difficulty in accessing treatment. Two respondents cited travel costs related to treatment, while 1 reported limited availability in the community and 1 reported financial hardship due to cost. (Note: some respondents indicated more than one issue when attempting to access treatment).

4.1.3 Impact of ALL and Current Therapy on Caregivers

A total of 3 parents/caregivers responded to questions for caregivers related to challenges they faced and how their day-to-day lives have been affected by acute lymphoblastic leukemia. To help illustrate the caregivers' experiences, CCSN included the following quotations from these respondents:

- *"Learning disabilities, sleep problems, low immune systems."*
- *"Bone pain tummy pain, nausea."*
- *"Emotional, fatigue, financial, splitting family up due to treatment (we have a younger child who we were separated from), managing side effects, being away from the world to protect her because of immune system."*
- *"It's so hard to meet her needs especially when she's too little to express all of them. We have learned her 'language' for how she describes feeling awful, but it 'takes us to the mat'. Her hair loss was especially hard for me because it was her newborn hair, but she was OK with it. It is so gut-wrenching to know what could be her, could be her life, and cancer/cancer treatment takes so much of it away."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Blinatumomab

CCSN did not receive input from patients who received blinatumomab (Blincyto) as a treatment for acute lymphoblastic leukemia.

Respondents however reported their expectations on the outcomes that they would like to see with blinatumomab. According to CCSN, respondents reported the following: to better control symptoms (3 of 6 patients); to better control side effects from current medications/treatments (5 of 6 patients); for better ease of use (1 of 6 patients); and to stop disease progression (3 of 6 patients).

In view of these responses, CCSN indicated that there is a need for additional treatments with fewer side effects, as well as, treatment that stops disease progression.

4.3 Additional Information

N/A

5 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 CADTH website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from seven of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. At the time the input was provided, PAG identified the following as factors that could impact the implementation of blinatumomab:

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:

- Very small patient population
- Complex and highly resource intensive to prepare and administer since infusion bag changed every 24 or 48 hours 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 detailed PAG input on individual parameters.

5.1 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 (e.g. Hyper-CVAD).

PAG noted that the pivotal trial for this submission is a phase 2 open-label, single arm study with short follow-up and that there is an ongoing phase 3 randomized trial but data from the phase 3 trial is not yet available.

5.2 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.

PAG is seeking data on the use of blinatumomab in pediatric and adolescent patients.

PAG noted that blinatumomab may be requested to achieve remission prior to going to stem-cell transplant. PAG is seeking information on the use of blinatumomab as induction therapy for stem-cell transplant and whether there is information on use post stem-cell transplant.

5.3 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 but each infusion bag is infused over 24 or 48 hours. PAG indicated that the preparation of the infusion bags every 24 to 48 hours is resource and labour intensive and that patients are required to be near a tertiary care centre with the appropriate resources to prepare, administer and monitor for 28 days. This would be a barrier to implementation and access to treatment would be limited to certain centres.

5.4 Factors Related to Implementation Costs

PAG identified that the preparation, administration and monitoring of blinatumomab infusion is very resource intensive due to

- Hospitalization for administration for the first nine days of the first cycle and the first two days of the second cycle
- Hospitalization for administration over the weekends
- Pre-medication with intravenous dexamethasone prior to first dose of each cycle and whenever infusion is interrupted for more than four hours
- Preparation of infusion bag every 24 or 48 hours for 28 days
- 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 52% incidence and 13% at grade 3 or higher
- The need for outpatient cancer clinics to purchase the specified type of infusion pump and tubing compatible for continuous infusion or for patients to be admitted to hospital with the appropriate equipment
- Drug wastage in unused portion of vial, which has very short stability and only one vial size is available, and from remaining drug in infusion bags and tubing

5.5 Factors Related to Health System

Blinatumomab, being an intravenous drug, would be administered in an outpatient chemotherapy center or inpatient hospital for appropriate administration and monitoring of toxicities. If recommended for funding, intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients. This would be an enabler as there would be no co-pays or deductibles for patients.

However, 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.

PAG also noted that replacing the infusion bag every 24 to 48 hours would be a challenge to outpatient cancer clinics that are generally not open on weekends and a challenge to weekend staff at tertiary hospitals.

5.6 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.

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).

A supplemental question relevant to the pCODR review and to the Provincial Advisory Group was identified while developing the review protocol and is outlined in section 7.

- Critical Appraisal of Results from Study 20120310 Providing Historical Efficacy Data on Treatments Used for Patients with Relapsed/Refractory (R/R) B-cell Precursor Acute-Lymphoblastic Leukemia (ALL)

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel 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.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*†	Outcomes
Published and unpublished RCTs or non RCTs In the absence of RCT data, fully published clinical trials investigating the efficacy of blinatumomab should be included. Reports of trials with only a dose-escalation design should be excluded. Reports of trials with a mixed design are to be included only if separate data were reported for the cohort of patients who were included in the efficacy-determining phase of the study.	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 including but not limited to • Hyper-CVAD • Flag Ida • Cy VP16	OS **PFS** Hematologic Response Cytogenic Response Molecular Response DOR TTR CR **QoL** SAEs AEs WDAEs

[Abbreviations] **Ph-** = Philadelphia negative; **ALL**= Acute lymphoblastic leukemia; **hyper-CVAD**= hyper fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone; **Flag Ida**= Fludarabine, cytarabine, granulocute colony-stimulating factor, idarubicin; **OS**= Overall survival; **PFS**= progression-free survival; **DOR**= duration of response; **TTR**= time to response; **CR**= complete remission; **QOL**=quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **AE**=adverse events; **WDAE**=withdrawals due to adverse events

** All treatments in combination with supportive care.*

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

6.2.2 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-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (July 2015) 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 concept was blinatumomab (Blincyto).

No filters were applied to limit the retrieval by study type. The search was limited to English language documents, but not limited by publication year. The search is considered up to date as of January 07, 2016.

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. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were limited to the last five years. 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.

6.2.3 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. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

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

6.2.4 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.

A data audit was conducted by another member of the pCODR Review Team.

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

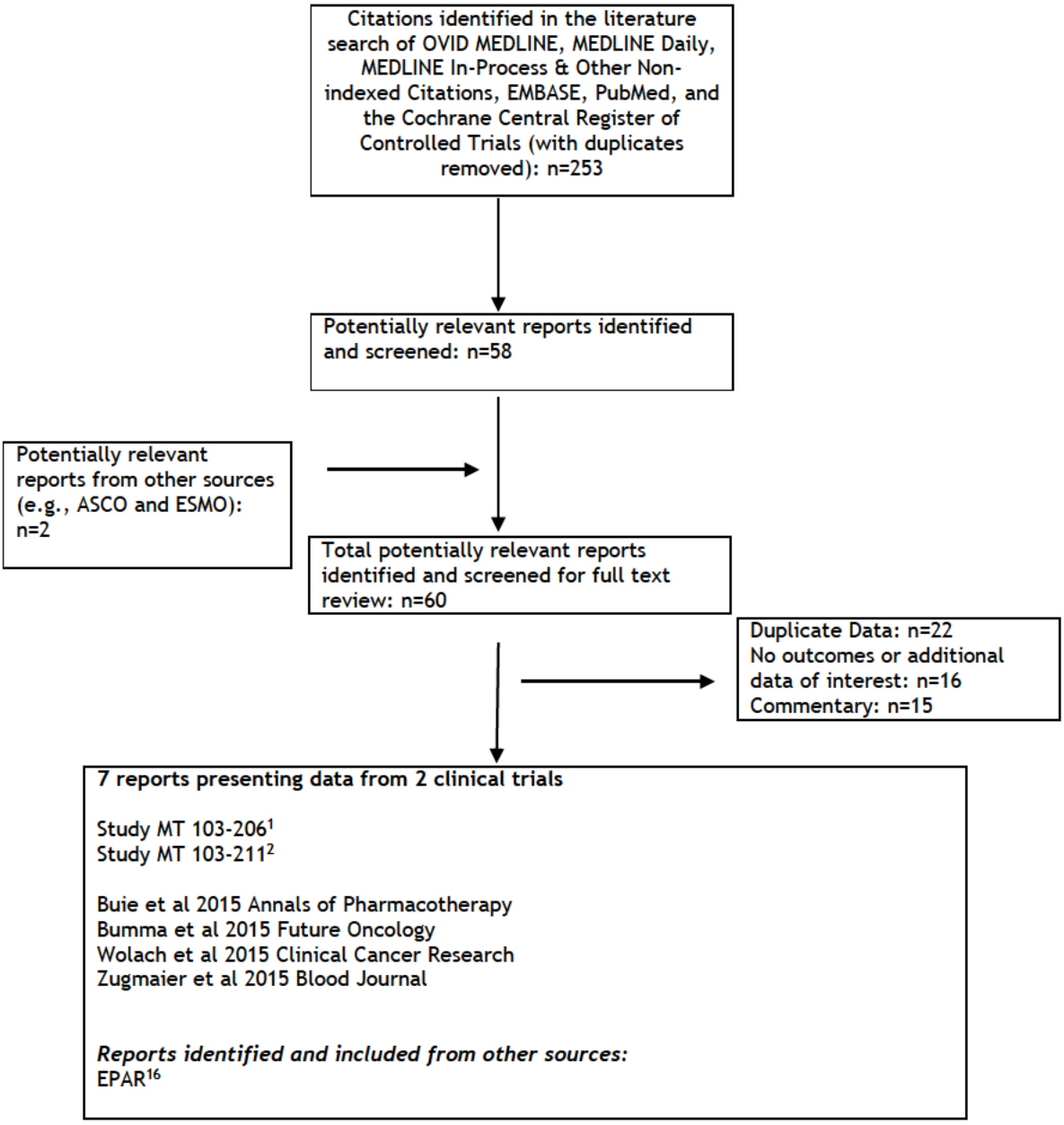
This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

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

6.3 Results

6.3.1 Literature Search Results

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



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

6.3.2 Summary of Included Studies

Two non-randomized interventional trials were identified that met the eligibility criteria of this systematic review (see Table 6).

6.3.2.1 Detailed Trial Characteristics

Table 6. 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).

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
MT 103-211[1,13]			
NCT01466179 Phase II, open-label, multicenter, single-arm study Non-randomized Enrollment: 189 Study Start date: December 2011 Estimated Study Completion Date: June 2017 Primary Completion Date: October 2013 (Final data collection for primary outcome measure) Funded by Amgen Research (Munich) GmbH	Adults (aged ≥18) Patients with Philadelphia chromosome (Ph)-negative B-precursor ALL, with any of the following: • relapsed or refractory with first remission duration less than or equal to 12 months in first salvage or • relapsed or refractory after first salvage therapy or • relapsed or refractory within 12 months of allogeneic hematopoietic stem cell transplantation (HSCT) 10% or more blasts in bone marrow In case of clinical signs of additional extramedullary disease: measurable disease ECOG PS of ≤ 2.	<u>Intervention:</u> Blinatumomab continuous intravenous infusion at target dose of 28 µg/day in 4 week cycles + 2 treatment-free weeks Step wise dosing used in study to reduce risk of cytokine release syndrome 9 µg/day for 1 week & 28 µg/day for 3 weeks	<u>Primary:</u> CR or CRh within first two treatment cycles (12 weeks) <u>Secondary:</u> Time to Hematological Relapse Percentage of Participants Who Received an Allogeneic Hematopoietic Stem Cell Transplant (HSCT) During Blinatumomab Induced Remission Percentage of Participants With a Best Response of CR within 2 Cycles of treatment Percentage of Participants With a Best Response of CRh within 2 Cycles of Treatment Percentage of Participants With a Best Response of Partial Remission Within 2 Cycles of Treatment Relapse-free Survival Event-free Survival OS 100 day mortality after allogenic HSCT Treatment-emergent AEs
MT 103-206 [2,13]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
NCT01209286 Phase II, open-label, multicenter,	Adults (aged ≥18) Patients with B-precursor ALL relapsed after at least induction	<u>Intervention:</u> 4 weeks of continuous treatment + 2 treatment free weeks	<u>Primary:</u> CR or CRh within 2 treatment cycles (time frame: within first two cycles of treatment, 12 weeks)

exploratory, single-arm study Non-randomized Enrollment: 36 Study Start Date: October 2010 Estimated Study Completion Date: December 2016 Primary Completion Date: March 2012 (Final data collection for primary outcome measure) Funded by Amgen Research (Munich) GmbH	and consolidation or having refractory disease More than 5% leukemic blasts in bone marrow life expectancy ≥12 weeks ECOG PS ≤ 2	Three sequential dose cohorts were evaluated in the dose finding period. Arm 1:Blinatumomab 15 µg Participants received blinatumomab 15 µg/m^2/day as a continuous intravenous infusion at a constant flow rate over 4 weeks followed by a 2-week treatment-free interval for up to 5 consecutive cycles Arm 2a. Blinatumomab 5/15 µg. Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m^2/day for the first 7 days of treatment, followed by 15 µg/m^2/day starting from Week 2 of treatment. Arm 2b. Blinatumomab 5/15/30 µg. Participants received blinatumomab by continuous intravenous infusion over 4 weeks followed by a treatment-free interval of 2 weeks for up to 5 consecutive cycles. The initial dose was 5 µg/m^2/day for the first seven days of treatment, a dose of 15 µg/m^2/day in the subsequent 7 days, followed by 30 µg/m^2/day starting from Week 3 of treatment.	<u>Secondary:</u> Percentage of participants with a best response of partial remission within 2 Cycles of Treatment Percentage of participants with a MRD Response during the core study Percentage of participants who received an allogeneic HSCT after treatment with blinatumomab Time to hematological relapse (analyzed by Kaplan-Meier methods) Relapse-free survival OS Treatment-emergent AEs Steady state blinatumomab concentration Clearance of blinatumomab Serum cytokine peak levels
Notes: Ph- = Philadelphia-negative; **ECOG** = Eastern Cooperative Oncology Group; **PS** = performance status; **CR**= complete remission; **CRh** = complete remission with partial hematological recovery; **MRD**= minimal residual disease; **HSCT**= hematopoietic stem cell transplant; **DOR**= duration of response; **OS**= overall survival; **AEs**= adverse events			

a) Trials

Two non-randomized interventional trials met the inclusion criteria for this systematic review.[1,2]

<u>MT 103-211[1]:</u>

The Topp 2015 study is a phase II, open-label single-arm study that enrolled adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL). The study included 189 patients with first relapse within 12 months of first remission, relapse within 12 months of allogeneic haemopoietic stem-cell transplantation (HSCT), or no response to or relapse after first salvage therapy. Patients were

also required to have atleast 10% bone marrow blasts and an ECOG PS of 0-2. Patients with MRD, Ph +ALL, ALL metastasis to the CNS or testes and paediatric patients were excluded from enrollment in this study. The study was conducted at twenty-three centres in Europe (Germany, France, UK, Italy and Spain), and at fourteen centres in the USA.[1] The primary endpoint of the study was complete remission (CR) or complete remission with partial hematological recovery (CRh) within first two treatment cycles (12 weeks). Secondary outcomes included, relapsed free survival and overall survival. All secondary outcomes are listed in Table 6. An exploratory secondary endpoint of this study included MRD response (i.e. MRD negativity) within the core of the study or 2 treatment cycles. MRD response was defined as $<1 \times 10^{-4}$ detectable blasts with use of an allele specific RT-PCR for clonal rearrangements of immunoglobulin or T-cell receptor genes. Patients who achieved the primary outcome underwent consolidation with up to a maximum of three additional cycles of blinatumomab. Therefore, patients were treated for a maximum of 5 cycles.[6] Patients were offered allogeneic hematopoietic stem cell transplant (HSCT) at any time at the discretion of the investigator.[1]

Sample size calculation[1,14]

Topp 2015 was designed as a Simon two-stage study with a third stage and an additional evaluation cohort. This design is often used for phase II clinical trials to establish whether or not a treatment demonstrates sufficient anti-tumour effect and warrants further investigation in a phase III trial. As the name implies, a Simon two-stage design is conducted in two stages with the option to stop the trial after the first or second stage, based on the efficacy observed at each stage. Over 20% of all phase II studies in oncology with a reported statistical design were Simon designs and 45% were two-stage designs.[15]

In the Topp 2015 study, for Simon stages 1 and 2, there was a planned estimate sample size of 61 patients to have 80% power to test a null hypothesis with a one-sided α 2.5% that the true Cr or CRh frequency after two treatment cycles is 20% or less compared to 36% or more in the alternative hypothesis.

For Stage 3, a sample size of 140-190 patients across all three study stages was required for a final hypothesis test. Assuming CR/CRh in 45% of patients for the alternative hypothesis and controlling the one-sided α at 2.5%, a minimum of 140 patients were needed to have 96% power to reject the null hypothesis of CR or CRh occurring in 30% or fewer patients. Upon completion of stage 3, a fourth stage was initiated.

Stage 4 was to test for statistically significant changes from baseline in abnormal neurological examination. A sample size of 30 subjects provided approximately 80% power to detect a mean change from baseline that was greater than 0, indicating an increase in abnormal neurologic examination results after blinatumomab use.[16]

The pCODR methods team could not confirm if the criteria for each stage of the analysis was met as pre-specified in the power calculation.

MT 103-206[2]:

The Topp 2014 study is a phase II, open-label, single-arm study that enrolled adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL). Key inclusion criteria included the presence of >5% leukemic blasts in the bone marrow in patients with primary refractory disease or relapse after induction and consolidation chemotherapy or after HSCT, an ECOG performance status of 0-2, and a life expectancy of at least 12 weeks. Patients with MRD, Ph+ ALL eligible for dasatinib or imatinib treatment, history or presence of clinically relevant CNS pathology, active CNS leukemia and paediatric patients were excluded from enrollment in this study. The study was conducted at nine centres in Germany. This study included a dose-finding stage and an extension stage.

The primary endpoint of the study was complete remission (CR) or complete remission with partial hematological recovery (CRh) within first two treatment cycles (12 weeks). Secondary outcomes included, relapsed free survival and overall survival. All secondary outcomes are listed in Table 6.

The sample size for the study was calculated based on a modified Simon two-stage design where differing doses were evaluated in stage 1 and the cohort with the best tolerability chosen for stage two of the study.

b) Populations

Table 7. Baseline Patient Characteristics in the included studies of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).[1,2,12]

	MT 103-211, n=189[1]	MT 103-206, n=36[2]
Age, median	39 (18-79)	32 (18-77)
Sex		
Men	119 (63%)	22(61%)
Women	70(37%)	14(39%)
ECOG performance status		
0	64(33.9)	15(41.7)
1	93(49.2)	19(52.8)
2	31(16.4)	2(5.6)
›2	0(0.0)	0(0.0)
Missing	1(0.5)	0(0.0)
Previous lines of salvage therapy		
0	38(20%)	NR
1	77(41%)	NR
2	42(22%)	NR
>2	32(17%)	NR
Disease States		
Previous allogenic HSCT	64(34%)	15 (42%)
No previous allogenic HSCT	**125(66%)**	**21(58%)**
• No previous salvage/primary refractory[&]	29(15%)	14/36 (39%)*
• 1 previous salvage/first salvage after first CR	55(29%)	7(19%)[#]
• ≥2 previous salvage	41(22%)	

Notes: * Proportion represents a combination of patients that were primary refractory (3/36, 8%) and patients in 1st relapse or at 1st salvage (11/36, 31%). These data was provided by Amgen through the Verification of Non-disclosable Information step in the pCODR process.
[&]Includes patients that are primary refractory (patient had never achieved a CR/CRh) and patients in 1st relapse or 1st salvage (ie. patient has never relapsed and therefore never received a salvage treatment prior to study enrolment)
[#]Proportion included patients that have had 1 or more salvage ie. ≥2nd salvage (patient has relapsed at least once and received at least one salvage treatment)
NR: not reported

In the Topp 2015 study, 189 patients were enrolled and started treatment with blinatumomab in 4-week of continuous intravenous infusion (cIV) followed by a 2-week treatment-free interval. Patients enrolled were relapsed within 12 months of first remission, within 12 months of allogeneic HSCT, or did not respond to or relapsed after first salvage therapy.[3] Patients

were required to have at least 10% bone marrow blasts and an ECOG performance status of 0-2. Most patients enrolled had not undergone previous allogenic HSCT (66%, n=125). In addition, a high percentage of patients had greater than 50% bone marrow blasts (69%, n=130).

In the Topp 2014 study, 36 patients were enrolled and started treatment with blinatumomab. All patients enrolled had at least 5% blasts in the bone marrow, an ECOG performance status of 0-2, and a life expectancy of at least 12 weeks. In order to reduce the incidence of cytokine release syndrome (CRS) and for tumour debulking, prephase daily treatment with dexamethasone for 5 days or cyclophosphamide 200 mg/m² was permitted. Patients also received CNS relapse prophylaxis with intrathecal chemotherapy.[3]

Baseline characteristics were similar in the two trials with patients in the larger (n=189, Topp 2015) study having at least 10% bone marrow blasts while patients in the smaller (n=36, Topp 2014) study had <5% leukemic blasts in bone marrow. In the Topp 2014 study, there were two patients (6%) with Ph (+) disease who were included.

c) Interventions

Details of the dosing and administration of the study drug used in the treatment of each trial can be found in Table 6. In Topp 2015, patients enrolled received 1 to 5 cycles of blinatumomab as a continuous intravenous (cIV) infusion at an initial dose of 9 µg/day for the first 7 days of cycle 1. During cycle one, dosing was stepwise, as established in the Topp 2014, phase II dose-finding study. Starting at week 2, the dose was escalated to 28 µg/day and continued at that dose for the rest of cycle 1 and for all subsequent cycles. Each treatment cycle was six weeks long with 4 weeks of treatment followed by a 2 week treatment free interval. All 189 of these patients received cycle one of treatment.

In Topp 2014; there was a dose-finding stage which included three sequential dose cohorts, 15 µg/m²/day, 5 to 15 µg/m²/day, and 5 to 15 to 30 µg/m²/day (as described in table 6). Due to the tolerability profile, the dose cohort of 5 µg/m²/day for 1 week, followed by 15 µg/m²/day for the remainder of the treatment period with a 2 week break between cycles became the preferred dosing schedule. There were 7 patients treated at a dose of 15 µg/m2/day, 23 patients treated at 5-15 µg/m2 /day, and 6 patients treated at 5-15- 30 µg/m2 /day.

In both trials, treatment continued until disease progression or unacceptable toxicity. Blinatumomab treatment was discontinued in patients with grade IV neurologic toxicities, those with more than one seizure, and those whose therapy was delayed by more than 2 weeks due to toxicity.[17] In both the Topp 2015 and Topp 2014 studies, dexamethasone premedication was given within 1 hour before treatment initiation, and before the step wise dosing in cycle one. Dexamethasone dosing was 20mg and 16 mg in the 2015 and 2015 studies. This was done to minimise infusion reactions to blinatumomab and reduce the risk of cytokine release syndrome (CRS).

d) Patient Disposition[1,2,17]

In the Topp 2015 study all 189 patients enrolled received cycle one of treatment and 98 patients received cycle two. Of these patients, 43 continued treatment beyond cycle two. All 43 patients received cycle three, 22 patients received cycle four, and 12 who received cycle 5. The remaining 146 patients received no further treatment with blinatumomab. This was due to 88 patients who had no response to therapy (no CR or CRh), 40 who had CR or CRh but did not continue blinatumomab, 9 who died before first response assessment and 9 who discontinued before a first response assessment.

At the time of data cut-off as of October 10, 2013, 72 patients were still in the study. Of these patients, 70 were in follow-up and 2 were still receiving treatment. A total of 117 patients had ended study participation. This was due to 115 patients who died, 1 who withdrew consent and 1 who was lost to follow-up.[1] All 189 patients in the Topp 2015 study were included in the safety analysis.

In the Topp 2014 study, all 36 enrolled and treated patients were included in the full analysis set. The median number of treatment days across the entire study was 55 days with a range of 1-150 days. A total of 25 out of 36 patients achieved a CR or CRh. Of these, 13 proceeded to receive HSCT while still in remission. Six patients out of the 13, died as a result of treatment-related mortality and two relapsed. Three out of thirteen patients had undergone prior transplantation before receiving blinatumomab. Twelve out of the twenty-five responders did not undergo HSCT while in remission. Eight out of twelve patients relapsed, four relapsed during and four after treatment with blinatumomab. In total, there were no patients who underwent HSCT and five patients who did not undergo HSCT after blinatumomab that completed five cycles of treatment. Overall, of the 10 relapses, three were CD19 negative, four were CD19 positive, and one was of unknown CD19 status. There were no observed CNS relapses. There were seven responders in total who died without a documented relapse.[2]

e) Limitations/Sources of Bias

Overall, results from both the Topp et al 2015 and Topp et al 2014 studies are limited by their level of evidence and ability to inform comparative efficacy against relative comparators in the Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL) setting. Therefore, the following biases and limitations should be noted:

- Both the Topp 2015 and Topp 2014 are single-arm non-randomized open-label trials that lack blinding of all participants and investigators in the trial, and thus are at risk for a number of different biases that can affect the internal validity. Examples of such biases are patient selection as part of inclusion criteria for eligibility and performance bias due to knowledge of the study treatment. It is important to also note that investigators, study personnel, clinicians and patients involved in both the trials were aware of the study drug treatment assigned, which can introduce the potential to bias results and outcomes in favour of whether the assessor (investigator or patient) believes the study drug is likely to provide a benefit greatly limiting the robustness of the efficacy results. The single-arm non-randomized design also makes interpreting the efficacy and safety/adverse events attributable to blinatumomab challenging, since all patients received the same treatment in both studies.

- Patient reported outcomes (PROs) were not collected in either study. The submitter stated that due to a lack of validated instruments, the small number of patients available for trials, and the need for large numbers of patients for HRQoL studies, the use of HRQoL as an endpoint for ALL trials is problematic.

6.3.2.1 Detailed Outcome Data and Summary of Outcomes

a) Efficacy Outcomes

Table 8. Efficacy outcomes & Response to treatment in the included studies of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).[1,2]

	MT 103-211[1], n=189	MT 103-206[2], N=36
CR or CRh CR CRh	**81 (43%)** 63 (33%) 18 (10%)	**25 (69%)** 15 (42%) 10 (28%)
No response to therapy	**90 (48%)**	**NR**
Not evaluable	18 (10%)	2 (6%)
Went onto receive HSCT HSCT among CR/CRh	**32/189 (17%)** 32/81 (40%)	**13/36 (36%)** 13/25 (52%)
RFS*, median	5.9 months (95% CI 4.8-8.3) not censored for HSCT 5.9 months (95% CI 4.2-6.9) censored for HSCT	7.6 months (95% CI 4.5-9.5) not censored for HSCT 7.9 months (95% CI 2.8-NE) censored for HSCT
OS, median	6.1 months (95% CI 4.2-7.5) not censored for HSCT 5.1 months (95% CI 4.1-7.1) censored for HSCT	9.8 months (95% CI 8.5-14.9) not censored for HSCT 14.9 (95% CI 8.2-21.9) censored for HSCT

Notes: *RFS, total number of patients, n=25
CR= complete remission; CRh= complete remission with partial hematological recovery; RFS= Relapse free survival ; OS= Overall Survival; NR = not reported

Table 9. CR/CRh achieved in patients based on previous salvage therapy[1,2]

	MT 103-211[1], n=189	MT 103-206[2], N=36
Overall CR/CRh	**43% (81/189)**	**69% (25/36)**
Prior HSCT	45% (29/64)	53% (8/15)
No Prior HSCT	42% (52/125)	81% (17/21)
No previous salvage	41% (12/29)	100% (11/11)
First Salvage After first CR (≤12 months) After first CR (≥12 months)	49% (27/55) NA NA	N/R 5/5 6/6
Second Salvage or primary refractory	NA	60% (6/10)
>2 Salvage	32% (13/41)	NA

Notes: CR= complete remission; CRh = complete remission with partial hematological recovery; HSCT= hematopoietic stem cell transplant; NA= not available.

MT 103-211[1]

Primary endpoint: CR/CRh

In the Topp 2015 study, the primary outcome was CR/CRh within 2 cycles of treatment with blinatumomab, using the best response. Complete remission (CR) was defined as ≤5% blasts in the bone marrow, no evidence of disease, and full hematological recovery (platelets ›100,000/µL ANC ›1,000/µL). CRh was defined as less than or equal to 5% blasts in the bone marrow, no evidence of disease, and partial hematological recovery (platelets ›50,000/µL and ANC ›500µL).

Of the 189 patients treated, 43% (81/189) (95% CI: 36%-50%) achieved CR/CRh within the first 2 cycles of treatment with blinatumomab. Among these Complete remission was achieved by 33% of patients (63/189), and complete remission with partial hematological recovery was achieved by 10% of patients (18/189). In a subgroup of elderly patients (≥ 65 years of age), the CR/CRh rates were also similar (44%, 11/25).[7]

Secondary endpoint: Proportion of patients who receive an allogenic HSCT during blinatumomab induced remission[16]

All patients who achieved CR/CRh were considered eligible for allogeneic HSCT for analysis purposes. Among these patients, 39.5% (32/81, 95% CI: 28.8, 51) received an allogeneic HSCT without any other subsequent anti-leukemic medication (excluding conditioning regimens). Of these patients, 28/32 had been in CR during the first 2 cycles of treatment, and 4/32 had been in CRh. This corresponds to an HSCT rate of 44.4% (95%CI: 31.9% to 57.5%) and 22.2% (95%CI: 6.4% to 47.6%) for patients who achieved CR and CRh during the first 2 treatment cycles, respectively. See table 9 below for details on responders who did not undergo transplantation. The most common reason for patients who achieved CR/CRh not going onto HSCT was relapse and disease progression and patient decision.

The 100-day post-HSCT mortality rate (relative to transplant date) for the 32 patients who underwent HSCT in blinatumomab remission was 11.3% (95% CI: 0.0, 23.4). The survival rate was 88.7% at day 100 after transplant.

Secondary endpoint: Overall Survival

The median OS for all patients was 6.1 months (95% CI: 4.2, 7.5) at median follow-up of 9.8 months, with no difference after censoring for follow-up at allogenic HSCT. When censored for patients with HSCT, the median OS was 5.1 months (95% CI: 4.1, 7.1), with a median observation time of 6.0 months. The median observation time was 9.8 months. The survival probabilities were 50% (95% CI: 43, 57) at 6 months and 28% (95% CI: 20, 36) at 12 months.

At the time of last follow-up, 38.6% (73/189) of patients were alive (censored, and 61.4% (116/189) had died.

The OS was observed as being significantly better for patients achieving CR/CRh after two treatment cycles compared to those achieving CR/CRh after more than two treatment cycles (median of 9.9 months vs. 2.7 months, respectively).[7]

Exploratory secondary endpoint: MRD Response Rate during the first 2 treatment cycles[16]

MRD response (or MRD negativity) rate within the core of the study period was an exploratory endpoint in the Topp 2015 study .Of the 81 patients that achieved CR or CRh within the first 2 cycles, 73 were available for MRD evaluation. For these 73 patients, the MRD response (MRD negativity) rate was 82.2% (60/73), and the complete MRD response rate (defined as no residual disease detected within 2 treatment cycles of blinatumomab) was 69.9% (51/73). For patients who achieved CR within the first 2 treatment cycles, the

MRD response rate was 86.2% (50/58) and the complete MRD response rate was 74.1% (43/58).

Table 10. Reasons why responders did not undergo transplantation in Study MT 103-211[16]	
	Number of Subjects
Responders who did not undergo transplantation for medical-related reasons	
Relapse and disease progression	15/43
Previous allogeneic HSCT	4/43
Moved to new therapy	2/43
Death	2/43
Age of patient	2/43
Lack of donor	2/43
General poor health	1/43
Did not achieve CR	1/43
History of GVHD	1/43
Total	30/43
Responders who did not undergo transplantation for non-medical reasons or for reasons unknown to be medical-related	
Patient decision	7/43
Investigator decision	3/43
Other-unknown	3/43
Total	13/43
Abbreviations: GVHD: acute graft-versus-host disease; CR: complete remission; HSCT: allogenic hematopoietic stem cell transplant	

MT 103-206[2]

Primary endpoint: CR/CRh

In the Topp 2014 study the primary outcome was the same as for Topp 2015, CR/CRh within 2 cycles of treatment with blinatumomab. CR/CRh rate was 69% (25/36), with 15 (41.7%, 95% CI: 25.5% - 59.2%) patients who achieved a CR and 10 (27.8%, 95% CI: 14.2% - 45.2%) patients who achieved a CRh. In the subgroup of elderly patients (≥ 65 years of age) 4 of 5 (80%) also achieved CR/CRh within 2 treatment cycles with blinatumomab.

The highest proportion of patients with a CR or CRh were observed among those in first salvage who were treated in early or late relapse, with 5/5 and 6/6 patients responding, respectively. This was followed by patients in second salvage with relapsed disease (6/10 patients responded). The lowest proportion of patients was among those who had relapsed after HSCT, with 8/15 responding.

Secondary endpoint: Proportion of patients who receive an allogenic HSCT during blinatumomab induced remission[16]

In the overall cohort 36% (13/36) of patients went onto receive HSCT following treatment with blinatumomab. This figure is 52% (13/25) of patients who achieved CR or CRh. Three of the 13 patients had undergone prior transplantation before receiving blinatumomab, with 2 of those patients being in ongoing OS follow-up. Twelve of the 25 responders did not undergo HSCT while in remission.[2] This is due to 8/12 patients that relapsed, 4 during and 4 after blinatumomab treatment. The remaining 4 patients are still in remission.

Secondary endpoint: Overall Survival

Median Overall survival (OS) was 9.8 months with a follow-up of 12.1 months as of the primary data collection date of March 2012. When measured from the start of remission, patients with a CR (n=15) and patients with a CRh (n=10) had a median OS of 13.2 and 8.3 months, respectively.

Long-term follow-up analysis of Study MT 103-206[2,18]

The Topp 2014 study analyzed OS with a median follow-up of 12.1 months. The long-term analysis presented by Zugmaier et al 2015 describes a follow-up analysis of relapse free survival (28.9 months) and overall survival (32.6 months). Long-term survivors were defined as patients with an OS ≥30 months. The definition of long-term overall survival by duration of at least 30 months is based on published data, which show most events occurring within the first 24 months.[18]

Patients in this analysis were divided into three groups. The first group included 10 patients who were long-term survivors defined as OS ≥30 months after start of blinatumomab treatment, all of whom achieved an MRD response. The second group included the 15 patients with MRD who were not long-term survivors, and the third group included 11 MRD non-responders. None of the MRD non-responders were long-term survivors.

In this updated analysis, median OS for the overall cohort was 13.0 months (95% CI: 8.5, 21.9 months) at a follow up time of 32.6 months (range, 0.8-41.9). A plateau was reached for OS after approximately 33 months. The Mantel-Byar odds ratio was 0.33 (p=.009). There was a 67% risk reduction associated with an MRD response. There was no difference detected in OS between patients with and without prior allogeneic HSCT.

The Mantel-Byar method was used for purposes of survival analysis in order to effectively evaluate responders vs. non-responders and to eliminate any bias. One such bias that is inherent in survival analysis is due to the fact that patients must survive long enough to be eligible for transplantation, and those who die during the induction period are always counted in the non-transplant arm. These donor versus non-donor comparisons tend to be inaccurate.[19]

The Mantel-Byar method eliminates this bias as time starts at the moment of treatment initiation, and all patients begin in the 'non-response' arm. Patients who eventually respond to therapy enter the 'response' state at the time of response and remain there until death or censoring. Those who do not respond always remain in the non-response arm. Therefore, using this method, patients are compared according to their response status at various periods during follow-up.[19]

Secondary endpoint: Relapse-free Survival (RFS)

Median Relapse-free survival (RFS) was 7.6 months (median follow-up time of 9.7 months). If censored for subsequent HSCT, median RFS was 7.9 months. There was no difference observed in RFS for patients who achieved a CR versus CRh.

Long-term follow-up analysis of Study MT 103-206[2,18]

At a median follow-up time of 28.9 months (range, 0.5-34.5), median RFS was 8.8 months (95% CI: 5.7, 13.2) among all 25 patients with CR/CRh. At approximately 18 months, a plateau was reached for RFS with six patients not having a documented relapse after this time. Of the six patients with long-term RFS, four patients underwent allogeneic SCT as consolidation for blinatumomab and two patients received three additional cycles of

blinatumomab instead of allogeneic SCT. The three patients with CR/CRh and no MRD response had relapses after 0.5, 2.0 and 9.0 months respectively.

Secondary endpoint: MRD Response Rate during the first 2 treatment cycles

Of the 25 patients that achieved CR or CRh within the first 2 cycles, 88% (22/25) achieved an MRD response.

Quality of life was not collected in either study. Based on additional information received through the Checkpoint Meeting, the submitter stated that health-related quality of life (HRQoL) is under-reported for patients with R/R Ph (-) ALL and few instruments are available for measuring HRQoL in ALL. The submitter also stated that the lack of validated instruments, the small number of patients available for trials, and the need for large numbers of patients for HRQoL studies; make using HRQoL tools as an endpoint for ALL trials problematic. The submitter confirmed that, currently there are no published data on HRQoL from this patient population in Canada.

b) Harms Outcomes

Study MT 103-211[1]

In the Topp et al 2015 study, 99% percent of patients experienced an adverse event of any grade with the most frequent being pyrexia: 113 (60%), headache: 65 (34%), febrile neutropenia: 53 (28%), peripheral oedema: 49 (26%), nausea: 46 (24%), hypokalaemia: 45 (24%), constipation: 39 (21%), and anaemia: 38 (20%). Grades 1 or II neurological disorders also occurred in 52% of patients with 11% experiencing grade 3 neurological disorders.

Grade 3, 4 and 5 AE's were experienced by 38%, 30% and 15% of patients, respectively. Grade 5 AE were experienced by 28 (15%) of patients. The majority of fatal/grade 5 AE's, 23 (12%), were due to infections. Additionally, there were five cases of disease progression or relapse which were reported as being fatal adverse events. Dose reductions were needed in 19 (10%) of patients and 34 (18%) patients discontinued permanently because of adverse events, 18 (10%) of whom discontinued because of adverse events thought to be treatment-related by the investigators.

Study MT 103-206[2]

Adverse events in the Topp 2014 study were somewhat similar to those reported in the larger Topp et al 2015 study. The most frequently occurring AE's regardless of grade or causality, were pyrexia (81%), fatigue (50%), headache (47%), tremor (36%), and leukopenia (19%). The most common grade ≥3 AEs were transient leukopenia and thrombocytopenia. Sixty-seven percent of patients had SAEs, primarily infections (33%) and nervous system and psychiatric disorders (22%). Six (17%) of the 36 patients treated had nervous system or psychiatric disorders requiring treatment interruption or permanent discontinuation. In five of the six patients, nervous system or psychiatric disorders were recorded within the first week of a cycle.

Overall, 22 of 36 patients died. Six patients died as a result of infections during the core study period. Of these, five deaths were reported during or after blinatumomab therapy but before HSCT. Four of the five deaths were reported as not related and one as possibly related to blinatumomab. The death which was possibly related to blinatumomab occurred in a patient who had undergone HSCT before treatment and died as a result of disseminated fungal infection of the brain.

Table 11. Select Adverse Events occurring in the Topp 2015 study[1]	
	MT 103-211[1], n= 189
Patients with adverse events (all grades)	**188(99%)**
Worst grade 1-2	33(17%)
Worst grade 3	71(38%)
Worst grade 4	56(30%)
Worst grade 5	28(15%)
Patients with neurologic events	**98(52%)**
Worst grade 1-2	74(39%)
Worst grade 3	20(11%)
Worst grade 4	4(2%)
Worst grade 5	0(0%)
Grades 3, 4 and 5 events occurring in ≥5% of patients	
Grade 3	**71(38%)**
Febrile neutropenia	46(24%)
Neutropenia	9(5%)
Anaemia	25(13%)
Pneumonia	13(7%)
Hyperglycaemia	15(8%)
Alanine aminotransferase increased	12(6%)
Hypokalaemia	10(5%)
Pyrexia	13(7%)
Grade 4	**56(30%)**
Neutropenia	21(11%)
Thrombocytopenia	14(7%)
Grade 5	**28(15%)**

Table 12. Number and proportion of patients with treatment related AEs leading to drug discontinuation according to treatment cycle		
Study MT103-211[1,12]		
Treatment Cycle	Number and proportion of patients n (%)	TRAE's leading to drug discontinuation at this cycle - n (%)
1	189 (100)	14 (7.4)
2	98 (51.9)	3 (3.1)
3	43 (22.8)	1 (2.3)
4	22 (11.6)	0
5	12 (6.3)	0
Study MT 103-206 [2,12]		
Treatment Cycle	Number and proportion of patients n (%)	TRAE's leading to drug discontinuation at this cycle - n (%)
1	36 (100)	3 (8.3)
2	21 (58.3)	0
3	11 (30.6)	1 (9.1)
4	8 (22.2)	0
5	5 (13.9)	0

Cytokine Release Syndrome (CRS)[2]

In the Topp 2015 study, a total of 33 TRAE's of cytokine release syndrome (CRS) were reported for 24/189 patients (12.7%). No patient experienced an event of CRS that led to permanent study drug discontinuation.

In the Topp 2014 study, 2 of 36 patients had grade 4 CRS. Both patients had a high burden of disease (~90% blasts in marrow), and one of these patients who presented with tumor lysis syndrome permanently discontinued treatment, and the other patient was re-exposed to blinatumomab after interruption of treatment.[2] A step-wise dosing approach in the first treatment cycle and steroid pre-treatment for patients with greater than 50% blasts in bone marrow, peripheral blasts ›15,000 x 10^9/L , or elevated LDH per investigator discretion resulted in only 2% of patients experiencing grade 3 CRS. In both trials, patients with higher grade CRS responded well to therapy, with 4 of 5 patients achieving CR.[17]

Neurological Toxicities[1,2,16]

Neurologic toxicities are reported across diagnoses, disease burden and dosing levels, and was mostly reported early in therapy (within the first week).

In the Topp 2015 study, approximately half (52% of 189 patients) of patients had neurologic events, mainly of grade 1 or 2 in severity. There were 20 patients (11%) and 4 patients (2%) that had grade III and IV neurologic toxicities, respectively. All of these toxicities resolved, however 3 patients died of apparently unrelated causes after the onset of toxicity.

According to dose modification criteria set in the protocol for study MT 103-211[1], blinatumomab was discontinued in patients with grade IV neurologic toxicity, those with more than one seizure, and those whose therapy was delayed by more than 2 weeks due to toxicity. All other patients with high grade neurologic toxicities were eligible for retreatment with blinatumomab at the same or lower dose with steroid premedication once toxicity resolved to grade 1 or baseline.

The dose modification criteria resulted in treatment interruption in 29 patients in the Topp 2015 study. 10 of these patients had already achieved remission before treatment was interrupted. Approximately 8 of the remaining 19 patients achieved remission after treatment was restarted.

In the Topp 2014 study, nervous system and psychiatric disorder AEs led to temporary or permanent discontinuation in six patients; all were resolved clinically within 72 hours of stopping treatment. There were 3 patients with epilepsy or convulsions who had treatment interruption but successfully resumed treatment with antiseizure prophylaxis.

6.4 Ongoing Trials

Table 13: Ongoing trials of blinatumomab in adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory (R/R) B-precursor acute lymphoblastic leukemia (ALL).[13]

Trial Design	Key Inclusion Criteria	Interventions and Comparators	Outcomes
Trial NCT02013167 Phase III, randomized, open-label study TOWER study Start date: December 2013 Estimated Primary Completion Date: August 2016 Estimated Completion Date: August 2016 Enrollment: 405 Study Sponsor: Amgen	Subjects with Philadelphia negative B-precursor ALL, with any of the following: • refractory to primary induction therapy or refractory to salvage therapy, • in untreated first relapse with first remission duration <12 months • in untreated second or greater relapse • or relapse at any time after allogeneic HSCT • Subject has received intensive combination chemotherapy for the treatment of ALL for initial treatment or subsequent salvage therapy. • Greater than 5% blasts in the bone marrow • ECOG performance status ≤ 2 • Age ≥ 18 years at the time of informed consent • Subject has provided informed consent or subject's legally acceptable representative has provided informed consent when the subject has any kind of condition that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent.	<u>Intervention:</u> Blinatumomab as a continuous intravenous infusion (CIVI). In the first induction cycle, the initial dose of blinatumomab will be 9 µg/day for the first 7 days of treatment which then will be escalated (dose step) to 28 µg/day starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles (beginning with the second induction cycle and continuing through consolidation and maintenance, for applicable subjects) 28 µg/day will be the dose for all 4 weeks of continuous treatment. <u>Active Comparator:</u> Standard of Care Chemotherapy Subjects randomized to receive SOC chemotherapy will be assigned to one of four chemotherapy regimens per investigator´s choice	Primary: Overall Survival Secondary: • Number of Participants with CR within 12 weeks of treatment initiation • Duration of CR • Duration of CR/CRh*/Cri • Number of participants with MRD remission • Time to a 10 point decrease from baseline in global health status and QoL scale using EORTC QLQ-C30, or EFS event • Number of participants with AlloHSCT with or without blinatumomab treatment • Number of participants with adverse events • Number of participants reaching 100-day mortality after alloHSCT • Number of participants with anti-blinatumomab antibody formation • Number of participants with a change in select vital sign and laboratory parameters • Number of Participants with CR/CRh*/CRi within 12 weeks of treatment initiation • Number of Participants with event Free Survival (EFS)

Trial NCT02412306 Phase Ib/II, open-label combined two-part multi-centre study Horai Study Recruitment Status: Recruiting Estimated primary completion date: November 2018 Estimated completion date: April 2021 Estimated enrolment: 39 Sponsor: Amgen	Adult subjects with Philadelphia-negative B-precursor ALL, with any of the following: • Relapsed or refractory after first line therapy with first remission duration ≤ 12 months; or • Relapsed or refractory after first salvage therapy; or • Relapsed or refractory within 12 months of alloHSCT • 5% or more blasts in bone marrow • In case of clinical signs of extramedullary disease in addition to medullary disease, disease must be measurable (at least one lesion ≥ 1.5 cm)	Intervention: Blinatumomab as a continuous intravenous infusion (CIVI). Each cohort in the study will receive a combination of 2 dose levels. In the first induction cycle, the initial dose will be the lower assigned dose level (Days 1-7), then escalated (dose step) to the higher assigned dose (Days 8-29). For all subsequent cycles (beginning with the second induction cycle and continuing through consolidation and maintenance, for applicable subjects) the higher assigned dose level will be the dose for all 4 weeks of continuous treatment. Active Comparator: N/A	Primary: Phase 1= Incidence of DLT (dose limiting toxicities) Phase 2 = CR/CRh* within 12 weeks of treatment with blinatumomab Secondary: Phase 1: • Incidence and severity of AEs • number of subjects with complete remission (CR/CR*h/Cri) • TTHR • OS • RFS • PK parameters • serum cytokine concentrations • incidence of anti-blinatumomab antibody formation Phase 2: • TTHR • AlloHSCT after treatment with blinatumomab • Best overall response • OS • RFS • Incidence and severity of AEs • 100 day mortality rate after alloHSCT • PK parameters • Serum cytokine concentrations • incidence of anti-blinatumomab antibody formation

Trial NCT02143414 Phase II, non-randomized, open-label study Start date: January 2015 Expected Primary completion date: July 2019 Status: Recruiting Estimated enrollment: 44 Sponsor: National Cancer Institute (NCI)	Patients 65 years and older must have a new morphologic diagnosis of precursor B cell acute lymphoblastic leukemia (ALL) (non T cell) based on WHO criteria Patients must have a diagnosis of Ph - ALL or Ph + ALL by cytogenetics, FISH or PCR Patients must have evidence of ALL in their marrow or peripheral blood with at least 20% lymphoblasts present in blood or bone marrow collected within 14 days prior to registration Patients must have a Zubrod performance status of 0-2 Patients must have serum creatinine =< 1.5 mg/dl	<u>Intervention:</u> COHORT I: Philadelphia negative chromosome patients receiving blinatumomab, POMP. INDUCTION: Patients receive blinatumomab (IV) continuously over 24 hours on days 1-28. Treatment repeats every 42 days for 2 courses in the absence of disease progression or unacceptable toxicity RE-INDUCTION: Patients not achieving CR or CRi after Induction, receive blinatumomab IV continuously over 24 hours on days 1-28 in the absence of disease progression or unacceptable toxicity. POST-REMISSION: Patients receive blinatumomab IV continuously over 24 hours on days 1-28. Treatment repeats every 42 days for 3 courses in the absence of disease progression or unacceptable toxicity MAINTENANCE: Patients receive prednisone orally (PO) on days 1-5, vincristine sulfate IV on day 1, mercaptopurine PO on days 1-28, and methotrexate PO on days 1, 8, 15, and 22.	<u>Primary</u>: • Incidence of dose-limiting toxicity, defined as any grade 3-4 non-hematologic toxicity in the first cycle of post-remission therapy (blinatumomab/dasatinib) (Cohort II) • OS (Cohort I) <u>Secondary</u>: • Complete response (CR + CRi) rate (Cohort I) • Disease-free survival • Incidence of toxicity • MRD negativity • OS (Cohort II) • Response rates (Cohort II) • Time to achieve MRD negativity

		Treatment repeats every 28 days for 18 courses in the absence of disease progression or unacceptable toxicity. Cohort II: Philadelphia chromosome positive patients receiving dasatinib, prednisone, blinatumomab.	
ECOG= Eastern Cooperative Oncology Group;**RCT**= randomized controlled trial; **PS**= performance status; **AEs**= adverse events; **TTHR**= time to hematological relapse, **RFS**= relapse free survival; **AlloHSCT**= allogeneic hematopoietic stem cell transplant;			

7 SUPPLEMENTAL QUESTIONS

The following supplemental issue was identified as relevant to the pCODR review of blinatumomab (Blincyto) for Philadelphia chromosome negative relapsed/refractory (R/R) B-cell precursor acute-lymphoblastic leukemia (ALL). Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of Results from Study 20120310 Providing Historical Efficacy Data on Treatments Used for Patients with Relapsed/Refractory (R/R) B-cell Precursor Acute-Lymphoblastic Leukemia (ALL)

Objective:

The two pivotal studies included in the pCODR systematic review to assess the efficacy and safety of blinatumomab in the specified patient population were non-randomised studies. To provide information on potential comparators used in this patient population, the manufacturer provided information on a study (Study 20120310) that reported efficacy outcomes from 1990-2014 for a historical cohort of patients with Philadelphia chromosome negative relapsed/refractory (R/R) B-cell precursor acute-lymphoblastic leukemia (ALL). Outcomes reported included haematological remission rates and survival.

Methodology:[12,16]

Study 20120310 was conducted between October 2013 and April 2014 with a primary completion date (final data collection date for the primary outcome) of January 2014. The inclusion criteria for study 20120310 was adult patients with R/R B-precursor ALL, ≥15 years old at time of de novo (initial) diagnosis of ALL, having an initial diagnosis of ALL in the year 1990 or later, having no CNS involvement at relapse, no isolated extramedullary relapse and no previous treatment with blinatumomab. As of May 22, 2014, 2373 patients were included in the study.

To select for patients that reflected those in the trial population within Study MT 103-211, further inclusion criteria were applied. These included patients that were 18 years or older, in first relapse or salvage treatment after a first remission duration of ≤12 months, or refractory to initial treatment, or relapsed/refractory after first or later salvage (e.g. second, third, or later relapse), or relapsed/refractory within 12 months of alloHSCT. Data was therefore available on 1139 patients treated in Europe or the United States between 1990 and 2014. The analysis was of patient-level data performed to estimate the proportion of patients who would achieve CR in a population with the same distribution of prognostic factors as Study MT 103-211[1]. No data has so far been peer-reviewed and/or published on the results of this study. All information provided within this document on the historical data has been provided through the pCODR submission, through requests for additional information from pCODR, the EPAR report and/or clinicaltrials.gov.

The primary endpoint in Study 20120310 was the rate of CR per study group (CRsg) defined as the percentage of patients who achieved ≤5% blasts in the bone marrow with full (CR), partial (CRp) or incomplete (Cri) hematological recovery. It is important to note that the definition of CRsg differed from the CR/CRh definition used in Study MT 103-211, and included patients experiencing CR, CR with incomplete hematologic recovery, or bone marrow responses only. Secondary endpoints included overall survival, duration of complete remission and proportion of patients receiving allogenic hematological stem cell transplantation.

Table 1. Side by side comparison of baseline demographics of patients in study 20120310 (historical comparator) and study MT 103-211.[1,12]			
	Study 20120310[12]		MT 103-211
	Patients providing CRsg or OS (N = 1139) n (%)	Patients providing CRsg (N = 807) n (%)	n=189[1]
Sex			
Male	**657 (58)**	**474 (59)**	**119 (63%)**
Female	**482 (42)**	**333 (41)**	**70 (37%)**
Age (years)			
Mean	37.5	38.5	-
SD	14.2	14.8	-
Median	35	36	39 (18-79)
Q1, Q3	25, 49	26, 49	-
Min, Max	18, 83	18, 83	-
Age Grouping			
18-34 years	542 (47.6)	372 (46.1)	90 (48%)
35-54 years	**436 (38.3)**	**299 (37.1)**	**46 (24%)**
55-64 years	117 (10.3)	92 (11.4)	28 (15%)
>=65 years	**44 (3.9)**	**44 (5.5)**	**25 (13%)**
Lines of prior treatment			
No previous salvage	-	-	**38 (20%)**
In first salvage	**763 (67)**	**431 (53)**	**77 (41%)**
In second or higher salvage	**370 (32)**	**370 (46)**	**74 (39%)**
Refractory to primary treatment			
Yes	142 (12)	142 (18)	-
No	995 (87)	663 (82)	-
Prior alloHSCT			
Yes	**189 (17)**	**113 (14)**	**64 (34%)**
No	**932 (82)**	**676 (84)**	**125 (66%)**
Year of diagnosis - n (%)			
1990 to 1999	366 (32)	257 (32)	-
2000 or later	773 (68)	550 (68)	-
Bone marrow blasts at diagnosis - n (%)**			
<50%	**29 (3)**	**18 (2)**	**59 (31%)**
50% or higher	**618 (54)**	**336 (42)**	**130 (69%)**
Not available for patient	142 (12)	103 (13)	-
Not available for study group	350 (31)	350 (43)	-
Notable differences in baseline characteristics are highlighted. alloHSCT: allogenic hematopoetic stem cell transplant; CRsg: Complete remission defined by study group; OS: overall survival; SD: standard deviation.			

Although data on 1139 select patients from the full cohort in Study 20120310 were available for the study, data were not available for the entire cohort for all outcomes of interest. Therefore, data in the study cohort was available for CRsg in 694 patients, OS in 1112 patients, RFS in 108 patients, and HSCT in 808 patients. It is important to note that 773/1139 or two thirds of the patients in the database were diagnosed in the year 2000 or later. The manufacturer was also asked to provide information on the ECOG performance status of patients and information on what type of treatments were used in patients. pCODR was informed though the Checkpoint meeting that Amgen was not able to collect data on ECOG performance status for the historical comparator study (Study 20120310) as the databases from the study groups already existed. Amgen also

informed pCODR that they did not have complete information on most of the participating study groups or centers on which prior therapies were used.

Data Analysis:

The data were analysed through a weighted analysis where patients in the 20120310 study were weighted across 6 strata (based on 2 variables: age and prior treatment lines) using the proportion of patients in each strata in study MT 301-211 to calculate a combined/weighted CRsg for the historical study. Essentially, the CRsg result was changed to reflect the value one would expect if that study had included similar proportions of patients in each strata as the blinatumomab study (MT 301-211).This weighted analysis was done for CRsg, OS, RFS, AlloHSCT after salvage treatment in all patients, and AlloHSCT after salvage treatment in in association with CRsg. Please see Tables 4 and 5.

Table 2. Strata-specific and combined weighted estimate of Complete Remission (CRsg) (Ph- primary analysis set*, all regions)[16]

Stratum	Age of treatment	Prior lines of treatment	n/N	Stratum (%)	Patients with missing endpoint data	CRsg Proportion (95% CI)**	Stratum % Observed in MT103-211
1	<35	alloHSCT	14/48	6.9%	16	0.29 (0.17, 0.44)	21.2%
2	<35	In 1st salvage	52/119	17.1%	21	0.44 (0.35, 0.53)	5.3%
3	<35	In 2nd + salvage	27/150	21.6%	5	0.18 (0.12, 0.25)	21.2%
4	≥35	alloHSCT	11/41	5.9%	6	0.27 (0.14, 0.43)	12.7%
5	≥35	In 1st salvage	57/187	26.9%	37	0.30 (0.24, 0.38)	10.1%
6	≥35	In 2nd + salvage	25/149	21.5%	4	0.17 (0.11, 0.24)	29.6%
Combined/Weighted Summary						0.24 (0.20, 0.27)	

Notes:
*Ph- Primary Analysis Set: Patients with R/R ALL with first remission duration of ≤12 months, are refractory to previous treatments, relapsed/refractory within 12 months of alloHSCT, or in 2nd or greater salvage treatment
**For CRsg corresponding to Stratum 1-6, these proportions are calculated directly from historical data and do not reflect any type of weighting.
Combined/Weighted summary is the weighted average of Stratum 1-6 weighted by the proportions in the MT 103-211 study

Table 3. Strata and Combined Estimate of 12-Month Overall Survival (OS) (Ph- Primary Analysis Set*, All Regions)[16]						
Stratum	**Age**	**Prior lines of treatment**	**N**	**Patients with missing endpoint data**	**12-Month OS Kaplan-Meier Rate (95% CI)**	**Stratum % Observed in MT 103-211**
1	<35	alloHSCT	108	0	0.14 (0.08, 0.21)	21.2%
2	<35	In 1st salvage	258	0	0.25 (0.20, 0.30)	5.3%
3	<35	In 2nd + salvage	161	2	0.16 (0.11, 0.22)	21.2%
4	≥35	alloHSCT	79	0	0.20 (0.12, 0.29)	12.7%
5	≥35	In 1st salvage	341	1	0.15 (0.11, 0.19)	10.1%
6	≥35	In 2nd + salvage	165	0	0.13 (0.08, 0.19)	29.6%
Combined					0.15 (0.13, 0.18)	

Notes:
*Ph- Primary Analysis Set: Patients with R/R ALL with first remission duration of ≤12 months, are refractory to previous treatments, relapsed/refractory within 12 months of alloHSCT, or in 2nd or greater salvage treatment.

Results:

The primary study endpoint was CR following relapse or salvage treatment, and secondary endpoints included estimates of OS rates, RFS rates, and the proportion of patients receiving alloHSCT. Please see Tables 6 and 7 below. Overall unweighted results were not provided for CRsg, OS or any of the other outcomes of interest. All reported results are based on a weighted analysis using the identified 6 strata unless otherwise labeled.

Overall weighted estimates for CRsg, OS and the other outcome of interest are provided in table 6. The weighted median OS rate was 3.3 months (95% CI: 2.8 to 3.6 months) and was calculated from the start of the last salvage treatment or the first relapse (if start of the last salvage date was unavailable) until the time of death. The weighted OS rate at 6 and 12 months was 30% (95% CI: 27% to 34%) and 15% (95% CI: 13% to 18%), respectively. Among the patients who achieved CR (108 patients), the weighted median RFS rate was 5.0 months (95% CI: 1.2 to 6.6 months).

Among the 808 patients who received alloHSCT after salvage therapy, 18% (95% CI: 15% to 21%) received alloHSCT following the last line of salvage therapy, and among patients who achieved CR, 7% (95% CI: 5% to 9%) received alloHSCT.

Table 4. Weighted endpoints, overall and by age[12]			
	Overall	**By age: <60 years**	**By age: ≥60 years**
Endpoint	(95% CI)*	(95% CI)**	(95% CI)**
CRsg, %	24 (20, 27)	24 (19, 28)	25 (13, 38)
Median OS, in months	3.3 (2.8, 3.6)	3.3 (2.9, 3.7)	4.9 (2.7, 7.5)

Relapse-free survival (RFS), in months	5.0 (1.2, 6.6)	3.7 (0.7, 4.6)	9.9 (5.6, 15.3)
AlloHSCT after salvage treatment in all patients, %	18 (15, 21)	18 (15, 21)	6 (0, 10)
AlloHSCT in association with CRsg after salvage treatment in all patients, %	7 (5, 9)	7 (5, 9)	5 (0, 10)

Notes:
*Overall weighted estimate adjusts for 6 strata including age(<35 years versus ≥35 years) and prior treatment history (with prior alloHSCT, in 1st salvage, or in 2nd or later salvage)
**Weighted estimate by age adjusts for 3 strata based on prior treatment history only (with prior alloHSCT, in 1st salvage, or in 2nd salvage)

Table 5. Endpoints, weighted and by line of salvage[12]

		By line of salvage			
	Overall	**1st**	**2nd**	**3rd**	**4th or higher**
Endpoint	Weighted estimate*	Unweighted estimate (95% CI)			
CRsg, %	23 (19, 26)	34 (29, 39)	25 (20, 32)	13 (8, 21)	15 (6, 30)
Median OS, in months	3.1 (2.6, 3.5)	4.3 (3.9, 4.7)	3.0 (2.3, 3.9)	2.6 (1.8, 3.1)	2.8 (2.0, 4.9)
Relapse-free survival (RFS), in months	4.8 (1.0, 6.5)	4.2 (3.3, 6.1)	4.2 (2.6, 5.8)	3.1 (2.4, 7.4)	9.4 (1.2, 29.2)

Notes:
* Overall weighted estimate adjusts for 4 stratum by line of salvage (1st salvage, 2nd salvage, 3rd salvage, and 4th or higher salvage)

Limitations of the historical comparator study:

- Baseline characteristics between study 20120130 and study MT 301-211 had important differences as is observed in Table 1. Of note, there were more men in study 211 compared to study 20120310 (63% vs. 59%), more patients with no prior alloHSCT in study 20120310 (66% vs. 84%) therefore most patients in the historical arm did not have prior alloHSCT, more patients in study 211 had ≥50% bone marrow blasts (69% vs. 42%) and less patients in study 211 were in 1st or 2nd relapse (99% vs 80%). Additionally, 20% of patients in study MT 103-211 did not have prior salvage therapy. These differences may have an impact on the prognosis of patients and expected outcome following treatment limiting the comparability of results between the two data sets. Furthermore, some may be effect modifiers for blinatumomab or other historical treatments.
- While the weighted analysis provided results for the historical data that are proportional to study MT 301-211 (based on the selected stratum), this does not balance for the confounding effect of patient characteristics that may result in a better or worse prognosis. Therefore patients in a specific stratum may have had better or worse outcomes that expected due to their baseline characteristics, limiting the comparability of results.
- The definitions of CR/CRh and CRsg were also different between the two study cohorts. CRsg defined as the percentage of patients who achieved ≤5% blasts in the bone marrow with full (CR), partial (CRp) or incomplete (Cri) hematological recovery. CR was defined as ≤5% blasts in the bone marrow, no evidence of disease, and full hematological recovery (platelets ›100,000/µL ANC ›1,000/µL). CRh was defined as less than or equal to 5% blasts in the bone marrow, no evidence of disease, and partial hematological recovery (platelets ›50,000/µL and ANC ›500µL). It is not clear how comparable CRsg is to CR/CRh and whether this difference

may have an impact on the interpretation of the data. Differences in the assessment of an outcome between studies means that there is uncertainty in what the different values mean.

- Considering that the data within the historical comparator arm was gathered from 1990 to 2014, it is not clear what impact changes in treatment patterns, treatment practices or supportive treatments may have had on the outcomes observed within the study and whether the outcomes are comparable to expected outcomes with current treatment patterns.
- Data on ECOG PS was not available, therefore is not clear what differences there may have been in the performance status of patients between the two data sets and what impact this may have had on the comparability of results. Similar uncertainty exists on the treatment regimens used in the historical comparator arm as this data was not available and whether they reflected outcomes expected with current treatment regimens.

Propensity Score Analysis[16,20]

Within the EPAR report, the manufacturer provided an additional analysis to account for the non-randomised comparison within the two sets of data (historical comparison vs. Study MT 301-211). This methodology uses the probability, conditional on observed baseline characteristics, of treatment assignment or the propensity score[21] to adjust for differences in baseline patient characteristics that may impact the results.

Methodology used:

Propensity scores are a statistical method of adjusting for bias from confounding by indication. Through the use of a prediction model the likelihood or propensity of treatment based on a specified set of patient characteristics is predicted. By applying the propensity score to two non-equivalent groups, one is able to balance differences in observed characteristics and potentially obtain less biased estimates of treatment effects. Essentially, propensity scoring attempts to simulate randomization of subjects as would occur in a randomized controlled trial.[20]

Propensity scores are calculated by selecting all covariates that are expected to have an impact on the expected results (eg. patient characteristics, disease severity, and characteristics of the treatment). The eventual utility of the propensity score therefore greatly depends on the ability to identify all potential confounding factors and including them into the propensity score calculation. Additionally, the exclusion of potential confounders or the presence of unknown confounders, which would be accounted for during randomization, remains a source of potential bias when using propensity score. Once calculated, the score is applied to the data under question through 1 of 4 methodologies.

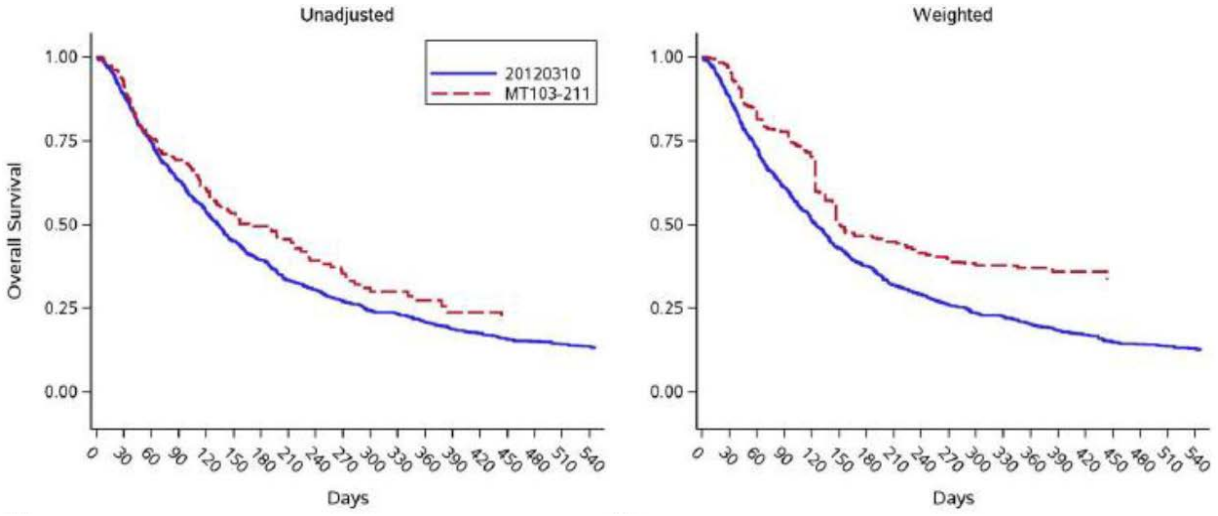
For the two studies being compared, (historical comparison vs. Study MT 301-211) a propensity score analysis was conducted. Of the 1139 patients, the primary analysis was based on a subgroup of 773 patients that were diagnosed in the year 2000 or later in Study 20120310. Two sensitivity analysis were conducted using the entire cohort (n=1139) or using patients diagnosed after 2002.

Results:

The primary method of analysis used to apply the propensity score to the two data sets (historical comparison vs. Study MT 301-211) was stabilized Inverse Probability of Treatment Weights (sIPTW). This method of treatment weighting was chosen in order to reduce selection bias. The hazard ratio and 95% CI from the primary comparison using the sIPTW was HR: 0.64 (95%CI 0.39-1.06). This indicated a 36% reduction in the risk of death associated with blinatumomab treatment compared to standard of care therapy. In the primary analysis

population, the odds ratio (OR) for CRsg was 1.84 (95% CI 0.897-3.775). Based on the forest plot in the EMA report, it was not clear if the OR favoured the blinatumomab or historical arm.

Figure 1. Overall Survival Cox Model Estimates by Treatment Group, Unadjusted and Adjusted Using Stabilized Weights (Primary Analysis with Diagnosis Year >=2000)[16]



Limitations of the historical comparator study:

- There was no description of the covariates used to determine the propensity score and therefore it is unclear whether all confounding factors were accounted for during the generation of the propensity score. Additionally, any unknown confounders or any covariates that are either not measured or measured incorrectly would not be accounted for within the propensity score. As an example, it is not clear if ECOG PS data was included in the calculation of the score. Performance status is a powerful predictor of prognosis, treatment choice and is also a predictive factor for response to therapy. Omitting the ECOG PS as one of the factors (covariates) in the analysis can reduce the effectiveness of the propensity scoring method.
- The propensity scores were also not identified within the report.
- There was no information provided on how appropriate the sIPTW methodology was for applying the propensity score to the data (as opposed to using other methodologies such as matching or stratification). Information on the distribution of the generated propensity scores would have been informative to understand whether the propensity score was balanced between the treatment and control groups. As an example, in Figure 1. the application of the propensity score appears to be driving the MT 301-211 OS curve and not having a large impact on the historical comparator OS curve possibly suggesting that the methodology selected to apply the score may not have been the most appropriate. Similarly, baseline covariates used to calculate the propensity scores between the two cohorts, in those patients that had similar scores, would have been useful to determine if the method chosen to apply the score was appropriate.

Conclusion:

The pCODR methods team provided a critical appraisal of the data from Study 20120310 which was used to provide historical efficacy results as a comparator to the outcomes observed with blinatumomab. Based on the results of this appraisal several limitations were identified around the comparability of the two patient populations as related to baseline characteristics, unknown impact of treatment practices between the time points in which

the two data sets were collected and differences in the definition of primary outcomes (CR/CRh vs. CRsg). The Methods team also notes that key information (e.g. ECOG PS) which may have an impact on prognosis of patients and outcomes of treatment was not available for the historical cohort. These factors may have an impact on the conclusions that can be drawn from a comparison between the two data sets. Two methodologies were used to adjust for these differences (weighted analysis and use of a propensity score), however a number of limitations still remain as described in the limitations sections above. Therefore, the results of this comparison must be interpreted with caution.

8 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 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.

The Leukemia Clinical Guidance Panel is comprised of 3 medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s):

EBM Reviews - Cochrane Central Register of Controlled Trials July 2015,
Embase 1974 to 2015 August 31,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations,
Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	(Blinatumomab* or Blincyto* or AMG103 or AMG-103 or MT-103 or MT103 or MEDI-538 or MEDI538).ti,ot,kw,ab,sh,rn,hw,nm.
2	(853426-35-4 or 4FR53SIF3A).rn,nm.
3	or/1-2
4	3 use cctr,pmez
5	*blinatumomab/
6	(Blinatumomab* or Blincyto* or AMG103 or AMG-103 or MT-103 or MT103 or MEDI-538 or MEDI538).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	4 or 8
10	remove duplicates from 9
11	limit 10 to english language

2. Literature search via PubMed

Search	Add to builder	Query
#2	Add	Search (#1 AND publisher[sb]) Filters: English
#1	Add	Search Blinatumomab* OR Blincyto* OR "AMG103" OR "AMG-103" OR "MT-103" OR "MT103" OR "MEDI-538" OR "MEDI538"

3. **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 terms: blinatumomab/Blincyto

Select international agencies including:

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

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

Search terms: blinatumomab/Blincyto

Conference abstracts:

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

ASH Annual Meeting - American Society of Hematology
http://www.hematology.org/Annual-Meeting/

Search terms: blinatumomab/Blincyto, last 5 years

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