CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Clinical Guidance Report

Blinatumomab (Blincyto) for Philadelphia chromosome positive Acute Lymphoblastic Leukemia

January 31, 2019

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding blinatumomab and relapsed or refractory Philadelphia chromosome positive (Ph+) B-cell precursor (BCP) acute lymphoblastic leukemia (ALL). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding blinatumomab Ph+ BCP ALL conducted by the leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy group; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted patient advocacy group input on blinatumomab Ph+ BCP ALL, a summary of submitted Provincial Advisory Group Input on blinatumomab Ph+ BCP ALL, and a summary of submitted Registered Clinician Input on blinatumomab Ph+ BCP ALL, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the effect of blinatumomab for the treatment of adult patients with refractory or relapsed (R/R) Philadelphia-chromosome positive (Ph+) B-cell precursor acute lymphoblastic leukemia (ALL).

As it states in its Health Canada Product Monograph, *"Blinatumomab activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells, including B-precursor ALL cells. The proximity induced by blinatumomab leads to the formation of a cytolytic synapse and triggers target cell-specific cytotoxicity which closely resembles a natural cytotoxic T-cell reaction. Blinatumomab is associated with transient up regulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines and proliferation of T-cells, and results in elimination of CD19+ cells."*[1]

On March 5, 2018, a Notice of Compliance was issued by Health Canada for the following indication: blinatumomab for the treatment adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).[1] Blinatumomab is also indicated for pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (NB: a Notice of Compliance with Conditions).[1]

The request reimbursement criteria are for adult patients (i.e., >= 18 years) with Ph+ BCP-ALL, who have relapsed after or are refractory to at least one second-generation or later tyrosine kinase inhibitor (TKI), or are intolerant to second-generation or later TKIs and intolerant or refractory to imatinib (NB: the requested reimbursement criteria align with the patient population in the ALCANTARA trial).

According to the Product Monograph, "*blinatumomab is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2 week) treatment-free interval. Patients may receive 2 cycles of induction treatment followed by 3 additional cycles of blinatumomab consolidation treatment. Blinatumomab infusion bags should be admixed to infuse over 24 hours, 48 hours, 72 hours, 96 hours, or 7 days.*"[1]

The available strength is lyophilized powder for solution for infusion, 38.5 (mcg). The recommended dose is as follows: (≥ 45 kg): 9 mcg/day in cycle 1 on days 1-7, 28mcg/day on days 8-28, and 28 mcg/day for subsequent cycles on days 1-28.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one single-arm phase 2 trial.

ALCANTARA

ALCANATRA was an open-label, single-arm, multicentre, phase 2 trial to assess the efficacy and tolerability of single-agent blinatumomab in patients with elapsed or refractory Ph+ B-precursor ALL who progressed after or were intolerant to a second-generation or later TKI.[2] The trial consisted of a 21-day screening and enrollment phase, an induction treatment period (two 6-week cycles of blinatumomab), a consolidation treatment period (up to 3 additional cycles of blinatumomab for subjects who achieved a hematologic complete remission within 2 induction cycles of treatment), a 30-day safety follow up visit, and long-term follow up visits for response duration and survival (every 3 months for 18 months).[3] A total of 45 eligible patients were included in the study and received blinatumomab as a continuous intravenous infusion at fixed stepwise doses (9 µg/day /day in week 1 of cycle 1 and 28 µg/day thereafter) over four weeks followed by a 2-week treatment-free interval (6-week cycles).

The primary end point of the study was CR or CRh* (CR/CRh*) response, defined as the proportion of patients who achieved CR/CRh* within the first two cycles of blinatumomab treatment. Secondary end points included minimal residual disease (MRD) response rate during the first two cycles of treatment, relapse-free survival (RFS), duration of response, overall survival (OS), allogeneic hematopoietic stem cell transplant (HSCT) after blinatumomab-induced remission, other best overall response rates (CR, CRh*, or CR/CRh*/Cri) and safety. The response variables were defined as follows:

- CR (complete response): ≤5% bone marrow blasts, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/µL and ANC > 1000/µL
- CRh* (complete response with partial hematologic recovery): ≤ 5% bone marrow blasts, no evidence of disease, and partial recovery of peripheral blood counts: platelets > 50,000/µL and ANC > 500/µL
- Cri (complete response with incomplete hematologic recovery): ≤ 5% bone marrow blasts, no evidence of disease, and incomplete recovery of peripheral blood counts: platelets > 100,000/µL or ANC > 1000/µL

The median age was 55 years (range 23 to 78); 47% of the patients were female; and 58% had other cytogenetic abnormalities in addition to Philadelphia chromosome.[2] All but three patients (93.3%) had between 1 and 3 prior relapses of ALL, and 68.9% had received ≥1 previous salvage regimens.[3] fifty-six percent of patients were refractory to prior TKI therapy; 33% had relapsed on previous TKIs, and 11% had disease progression after their prior TKI therapy. Eighty-four percent of patients had received ≥2 prior TKIs, and 44% had a history of prior allogeneic hematopoietic stem cell transplant (HSCT).[2] Eighty percent of patients had an ECOG performance status score of 0 or 1.[4]

No comparator was used in the ALCANTARA trial. The Clinical Guidance Panel (CGP), registered clinicians providing input, and the Provincial Advisory Group (PAG) all identified inotuzumab ozogamicin (InO) as a relevant comparator. Therefore, pCODR requested the Submitter to provide an indirect comparison of blinatumomab versus inotuzumab ozogamicin, as inotuzumab had

received a Notice of Compliance (NOC) from Health Canada and funding recommendation. However, the Submitter stated that an indirect treatment comparison (ITC) of blinatumomab and inotuzumab ozogamicin was not feasible for the following reasons:

- Inability of the submitter to use traditional network meta-analysis (NMA) methods due to the single-arm trial design of the ALCANATRA trial and, hence, the lack of a common comparator upon which the analysis could be anchored.
- Inability of the submitter to use matching-adjusted indirect treatment comparison (MAIC) and other population-adjusted indirect treatment comparison methods (e.g., Simulated Treatment Comparison): the ALCANTARA trial specifically included patients with Ph+ ALL, whereas INO-VATE (pivotal study for inotuzumab) included patients with Ph+ or Ph− ALL. The INO-VATE trial publications reported insufficient data on patient demographics for the Ph+ subgroup.
- Small sample sizes of both the ALCANTARA and INO-VATE trials due to the low incidence of Ph+ BCP-ALL in adults. Further sample size reduction was anticipated if attempting to conduct a MAIC.
- Difference in key outcomes evaluated in the ALCANTARA trial and INO-VATE trial with respect to the definition and timing of evaluation.[4]

The review team noted that in the pCODR inotuzumab ozogamicin review, a technical report of an indirect treatment comparison using the INO-VATE study in InO and the TOWER study (Ph negative relapsed/refractory ALL) in blinatumomab was submitted and critically appraised; in this review, the comparison was considered hypothesis generating and insufficient in clarifying whether there exists a basis to choose one agent over the other.

It is worth noting that the Submitter did provide a comparison to standard of care which is described in further detail and critically appraised in Section 7.

Efficacy

The key efficacy outcomes of the ALCANTARA trial are presented in Table 1.1.

Best hematologic response (CR/CRh*) rate

As of the 20-May-2015 data cut-off date, after a median follow-up of 9.0 months, 16/45 patients (36%) achieved CR/CRh* during the first two cycles, with 14 patients (31%) showing a CR and two patients (4%) achieving a CRh*. Two additional patients achieved CRi at the end of cycle 2.[2] The CR/CRh* rate achieved with blinatumomab was considered to be clinically meaningful, as the lower limit of the 95% CI exceeded the pre-specified null hypothesis threshold (ineffective rate) of 10% (Table 1.1).[3]

In subgroup analyses of the primary endpoint, more favorable response rates were observed in patients who received more than three previous TKI therapies as well as patients who did not receive previous allogeneic HSCT. However, given the overlapping CIs, none of the observed differences were statistically significant.[2]

Minimal Residual Disease (MRD) Response

Among 16 CR/CRh* responders, a complete MRD response was achieved in 14 patients (88%, the remaining two responders (who achieved Cri) had persistent measurable MRD and relapsed during subsequent cycles of therapy.[2]

Twelve of the 14 patients with CR (86%) and both patients with CRh* (100%) achieved a complete MRD response.[2]

Relapse-free Survival (RFS)

RFS was assessed in in 16 subjects who achieved a CR/CRh*. As of the 20-May-2015 data cut-off date, with a median follow-up of 9.0 months, seven of the 16 responders (44%) were alive without relapse, eight (50%) had relapsed, and one patient had died in CR after allogeneic HSCT. The median RFS was 6.7 months (95% CI: 4.4, not estimable).[2]

Among the 14 patients who achieved a complete MRD response, the median RFS was similar to that of the entire CR/CRh* responders (6.8 months;95% CI, 4.4, not estimable).[2] Censoring for allogeneic HSCT did not have a statistically significant impact on the RFS results.[2]

At the time of the final analysis(06-Jan-2017), after a median follow-up of 16.1 months (maximum follow-up 22.6 months), 5/16 (31%) patients who achieved a CR/CRh* within two cycles of blinatumomab treatment remained alive and in remission. Median RFS for CR/CRh responders was 6.8 months (95% CI 4.4, not estimable). After censoring for HSCT, the median RFS was 6.7 months (95% CI 3.8, not estimable) based on a median follow-up of 10.6 months (Figure 6.4).[3]

Duration of hematologic remission

The median duration of response was 6.8 months without censoring at the time of allogeneic HSCT and 6.7 months with censoring at the time of allogeneic HSCT).[3]

Overall Survival (OS)

As of the 20-May-2015 data cut-off date, 22 out of 45 patients (48.9%) had died.[2] With a median follow-up of 8.8 months, the median OS was 7.1 months (95%CI: 5.6, not estimable), regardless of censoring for HSCT.[2] In the landmark OS analysis (starting at the end of cycle 2 of blinatumomab treatment), based on a median follow-up of 5.3 months, the median OS was not reached for patients who achieved a complete MRD response, and was 3.9 months (95% CI 3.0 to not estimable) among MRD non-responders.[2]

At the time of the final analysis, 8/45 (18%) patients in the Full Analysis Set (FAS) remained alive. Median OS was 9.0 months (95% CI 5.7, 13.5) based on a median follow-up of 25.1 months (95% CI 5.7, 13.5); Figure 6.5). After censoring for allogeneic HSCT, the median OS was also 9.0 months (95% CI 5.7, 13.5), with a median follow-up of 24.8 months.[3]

Post-baseline Allogeneic HSCT

Seven (44%) of the 16 CR/CRh* responders received an allogeneic HSCT, four of whom remained in continuous blinatumomab-induced remission without any additional anti-leukemia therapy. The 100-day mortality rate for these four patients was 25.0% (95% CI 4%, 87%;).[2]

Quality of Life

Health-related quality of life was not assessed in the ALCANTARA study; no other data were identified for this patient population

Harms

As of the 20-May-2015 data cut-off date, all 45 patients (100%) experienced ≥1 treatment-emergent AE. The most frequent AEs included pyrexia (58%), febrile neutropenia (40%), and headache (31%). Thirty seven patients (82%) were reported to have grade 3 and higher treatment-emergent AEs (TEAEs). The most common grade 3 and higher TEAEs (occuring in ≥ 15% of patients) were febrile neutropenia (27%), thrombocytopenia (22%), and anemia (16%). The proportion of grade 3 or higher TEAEs that could possibly be related to blinatumomab (as per the investigator's

assessment) was 44%, most commonly, febrile neutropenia and increased levels of alanine aminotransferase (11% each).[2]

Cytokine release syndrome (CRS) was reported in three patients; however, all of the CRS events were grade 1 or 2) and did not result in discontinuation or interruption. Neurologic events were reported in 47% of patients, with the most common neurologic AEs being paresthesia (13%), confusional state (11%), dizziness (9%), and tremor (9%).[2]

Table 1.1: Highlights of Key Outcomes in the ALCANTARA trial

		ALCANTARA	
Primary Outcome			
	Patients with evaluable data	**n**	**% (95% CI)**
Best hematologic response			
Patients with CR/CRh*	45 FAS	16	36 (22, 51)
Patients with CR/CRh/CRi	45 FAS	18	40 (26, 56)
– CR		14	31 (18, 47)
– CRh		2	4 (1, 15)
– CRi		2	4 (1, 15)
Secondary efficacy Outcomes			
	Patients with evaluable data	**n**	**% (95% CI)**
Complete MRD response	16 Responders	14	88 (62, 98)
AlloHSCT after blinatumomab-induced remission	16 Responders	4	25 (7, 52)
100-day post-transplant mortality rate	4 AlloHSCT	1	25 (4, 87)
	Patients with evaluable data	**Median time to event**	**(95% CI)**
RFS, months			
– Primary analysis†	16 Responders	6.7	(4.4, NE)
– Final analysis††	16 Responders	6.8	(4.4, NE)
OS, months			
– Primary analysis†	45 FAS	7.1	(5.6, NE)
– Final analysis††	45 FAS	9.0	(5.7, 13.5)
HRQoL			
		Not Available	
Safety Outcomes†, n (%)	**Patients with evaluable data**	**N (%)**	
TEAEs any grade	45 FAS	45 (100)	
Grade ≥3 TEAEs		37 (82)	
Cytokine release syndrome, any grade		3 (7)	
Neurologic events, any grade		21 (47)	
Grade ≥3 blinatumomab-related AEs		20 (44)	
WDAE		3(7)	
TEADs leading to death		5 (11)	

AE = adverse event; **alloHSCT** = allogeneic hematopoietic stem cell transplant; **CI** = confidence interval; **CR** = complete remission; **CRh*** = complete remission with partial hematologic recovery; **CRi** = CR with incomplete hematologic recovery; **HRQoL** = health-related quality of life, **MRD** = minimal residual disease; **NE** = not estimable; **NR** = not reported; **OS** = overall survival; **RFS** = relapse-free survival; **TEAE** = treatment-emergent adverse event, **WDAE** = withdrawal due to adverse event

† Primary analysis data cut-off date: 20-May-2015

†† Final OS analysis data cut-off date: 06-Jan-2017

1.2.2 Additional Evidence

Patient Advocacy Group Input

One patient advocacy group, the Leukemia & Lymphoma Society of Canada (LLSC), provided input on blinatumomab (Blincyto) for Philadelphia chromosome positive (Ph+) B-cell precursor (BCP) acute lymphoblastic leukemia (ALL). For refer details, refer to Section 3.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified clinical and economic factors that could impact the implementation of blinatumomab for Ph+ ALL. For refer details, refer to Section 4.

Registered Clinician Input

Two registered clinician submissions provided input on blinatumomab (Blincyto) for the treatment of relapsed or refractory Ph+ BCP ALL. For refer details, refer to Section 5.

Summary of Supplemental Questions

In the absence of a trial directly comparing blinatumomab with a relevant comparator, the Submitter conducted an indirect treatment comparison using a propensity score analysis to compare the efficacy of blinatumomab in the single arm ALCANTARA study (N = 45) to that of standard of care (SOC; cytotoxic chemotherapy and/or TKI) in a historical comparator study (Study 20160462; N=55).[3] The results of this analysis were used to inform the Submitter's pharmacoeconomic evaluation. Therefore, a critical appraisal of propensity score analysis was performed by the Methods Team. For refer details, refer to Section 7.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.

Table 1.2: Assessment of generalizability of evidence for blinatumomab

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG performance score	In the ALCANTARA trial, 80% of patients had an ECOG performance status score of 0 or 1.	Are the trial results (efficacy and toxicity) applicable to patients with an ECOG PS of 2 or greater? Why (why not)?	Patients with ECOG 3 or greater are not good clinical candidates for blinatumomab. The trial included patients with ECOG ≤ 2
	Age	The median age of the ALCANTARA population was 55 years (range 23 to 78)	Do the trial results apply to all adult patients? Why (why not)?	Tolerability in frail elderly has not been assessed
	Prior type of TKI	PAG noted that funding of second generation TKIs varies by jurisdiction. PAG is seeking information on the generalizability	Do the trial results apply to patients with exposure to different second generation TKI therapy?	Patients who have relapsed after or have refractory disease following treatment with <u>any</u> second generation or later TKI (dasatinib, nilotinib, bosotinib or ponatinib) and are refractory to imatinib would meet criteria to receive blinatumomab

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		of the trial based on prior TKI and number of prior TKI treatments. In the ALCANTARA trial, patients had relapsed after or were refractory to at least one second-generation or later TKI (dasatinib, nilotinib, bosutinib, ponatinib), or were intolerant to second generation or later TKIs and intolerant or refractory to imatinib		
Intervention	Dosing schedule	In the ALCANTARA trial, blinatumomab was administered as continuous IV infusion in 6-weeks cycles: 4 weeks of treatment with 9 µg/day in week 1 of cycle 1, and 28 µg/day thereafter followed by a 2-week treatment-free interval	Are there other dosing schedules used in Canada for the treatment of adults with Ph+ ALL? If so, are the trial results applicable to the Canadian practice?	No, there are no other dosing schedules in Canada for the treatment of adults with Ph+ ALL. See table below for weight based dosing for those under 45kg Blinatumomab Recommended Dosage for Relapsed or Refractory B-ALL Patient Weight / Treatment Cycle 1: Days 1-7, Days 8-28, Days 29-42 / Subsequent Cycles: Days 1-28, Days 29-42 ≥ 45 kg: 9 mcg/day; 28 mcg/day; No; 28 mcg/day; No <45 kg: 5 mcg/m²/day; 15 mcg/m²/day; Treatment; 15 mcg/m²/day; Treatment *Taken from blinatumomab product monograph Amgen Canada[1]
	Line of therapy	Eighty-four percent of patients had received ≥2 prior TKIs	Do the trial results apply to patients who have previously been treated with one previous TKI? Why (why not)?	It would be reasonable to consider exposure to 2 prior TKIs before considering treatment with blinatumomab in adult patients who have B-ALL and harbour a PH positive clone
Comparator	Standard of care	ALCANTARA was a single-arm trial (no comparator).	Is the comparator used in the historical cohort (local chemotherapy	Yes

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		The submitter provided an indirect treatment comparison (propensity score analysis) of blinatumomab with standard of care chemotherapy (and/or TKI) in a historical comparator study that was conducted in Italy and Spain.	protocols used in Italy and Spain) applicable in the Canadian setting?	
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary outcome: best hematologic response (CR/CRh*) within 2 cycles of blinatumomab therapy Secondary outcomes: MRD response rate, OS, RFS, duration of response, alloHSCT after blinatumomab-induced remission, 100-day mortality after alloHSCT	Were the primary and secondary outcomes appropriate for the trial design?	Yes Shortcoming: HRQOL was not included as part of the trial design.
Setting	Countries participating in the Trial	The ALCANTARA trial was conducted at 19 centers in Europe and the United States. Canada was not among the participating countries.	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	No

alloHSCT = allogeneic hematopoietic stem cell transplant; **CR** = complete remission; **CRh*** = complete remission with partial hematologic recovery; **ECOG** = Eastern Cooperative Oncology Group; **MRD** = minimal residual disease; **OS** = overall survival; **RFS** = relapse-free survival

1.2.4 Interpretation

Adult Acute B cell lymphoblastic leukemia (B-ALL) represents approximately 10% of adult acute leukemias. About 20% of adult ALL harbour a Philadelphia chromosome (Ph+). 50-60% of younger patients with Ph+ B-ALL who undergo intensive pediatric like protocols and or who undergo hematopoietic stem cell transplantation (HSCT) will have the expectation of cure. For patients who are refractory or who relapse cure may be achieved following HSCT, however only a small proportion of refractory or relapsed patients are able to successfully obtain a remission to allow effective HSCT. There is no standard therapy that is curative for Ph+ B-ALL patients who relapse following HSCT. There is a need for more effective therapies to allow patients with relapsed/refractory disease to obtain remissions to allow delivery of definitive therapy such as HSCT in the setting of Ph+ B-ALL.

The role of blinatumomab in adult patients (≥ 18) with relapsed or refractory Ph+ B-ALL was assessed in an open-label, single-arm, multicentre, phase 2 trial conducted in 19 European and US centers. (ALCANTARA study) Eligible patients were adults with Ph+ B-ALL who were relapsed or refractory to at least one second generation or later tyrosine kinase inhibitor (dasatinib, nilotinib, bosutinib, ponatinib) (TKI) or were intolerant to second generation or later TKIs and intolerant or refractory to imatinib. Patients in the ALCANTARA trial received 2 initial cycles of blinatumomab (induction). Patients who achieved a hematological complete remission following induction could receive 3 further cycles of blinatumomab.

45 patients were accrued to the trial with a median age of 55 years (23-78). 84% of patients received ≥ 2 TKIs before trial entry and 44% had a prior HSCT. The primary end point was the proportion of patients who achieved a CR/CRh during the first two cycles of blinatumomab treatment. In the final analysis the CR/CRh rate was 36% (16/45) with a median relapse free and overall survival for the cohort of 6.8 (4.4 -NE) months and 9.0 (5.7-13.5) months; seven of the 16 patients achieving a CR/CRh (44%) went on to receive a HSCT.

As the ALCANTARA study was a single arm phase II study, the submitter conducted a post hoc propensity analysis to compare the efficacy of blinatumomab to a historical cohort receiving standard of care (SOC). The historical cohort consisted of adult patients with Ph+ B-ALL from Spain and Italy who participated in trials by the submitter who met the inclusion criteria of the ALCANTARA trial. The propensity analysis results are summarized in Table 7.2. The propensity analysis revealed (i) the percentage of patients achieving a CR/CRh was numerically [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). (ii) median OS was [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). Hazard ratio for median OS comparing blinatumomab to historical controls is [redacted] ([redacted]-[redacted]). The propensity analysis did not control for performance status of patients. On balance the CGP feels that the propensity analysis suggests a [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

All 45 patients enrolled in the ALCANTARA study experienced ≥ 1 treatment emergent adverse event (TEAE). The most frequent AEs included pyrexia (58%), febrile neutropenia (40%), and headache (31%). The most common grade 3 and higher TEAEs (occurring in ≥ 15% of patients) were febrile neutropenia (27%), thrombocytopenia (22%), and anemia (16%). 11% of the ALCANTARA cohort 5/45 patients experienced a TEAE leading to death.

The ALCANTARA trial did not report on HRQOL. The TOWER study[5]examined the role of blinatumomab in a phase 3 study in patients with PH- B-ALL. Patients were randomized to receive blinatumomab versus SOC. The TOWER study reported on HRQOL.[6] In the TOWER study those treated with blinatumomab had improved HRQOL compared to those receiving SOC. In the absence of available data it would be reasonable to infer that patients treated with blinatumomab in the ALCANTARA trial (Ph+ B-ALL would have a similar HRQOL benefit being treated with blinatumomab versus SOC as those who are PH- (TOWER study).

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a **net clinical benefit** from treatment with blinatumomab in patients with Ph+ B-ALL who have been treated with at least two prior TKIs and have relapsed or refractory disease with an ECOG of ≤ 2. Net clinical benefit is supported by several observations:

- The ALCANTARA trial demonstrated the clinical effectiveness of blinatumomab in patients with Ph+ B-ALL. Blinatumomab was associated with a CR/CRh rate of 36% after 2 cycles of blinatumomab and a median overall survival of 9 months.
- The propensity analysis submitted comparing blinatumomab therapy versus historical SOC also [redacted] in the relapsed refractory Ph+ B-ALL population. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).
- While the ALCANTARA trial is a single arm study the TOWER study (previously reviewed by PCODR) in PH- B-ALL is a larger phase III study which supports the use of blinatumomab in a relapsed refractory B-ALL patients indicating a consistency of results across both the ALCANTARA and TOWER trials.
- Given the small numbers of patients with relapsed or refractory Ph+ B-ALL, it is highly unlikely that a phase 3 study exploring the role of blinatumomab will be undertaken.
- The outcomes reported in the ALCANTARA trial are clinically meaningful in this patient population.
- The adverse event profile as reported is felt to be acceptable.

In response to the Provincial Advisory Group:

- The Clinical Guidance Panel does not have specific information on the comparative effectiveness of Inotuzumab ozogamacin (InO) and blinatumomab. The Submitter did not provide an indirect comparison of InO compared to blinatumomab. Inotuzumab ozogomacin may be administered in an ambulatory setting and does not require a continuous infusion strategy whereas blinatumomab requires inpatient care as well as a continuous infusion. It is not possible for the Clinical Guidance Panel to identify an optimal sequencing strategy. However, the Clinical Guidance Panel feel that patients with Ph+ B-ALL who have been treated with InO in the past and require further therapy would be eligible for blinatumomab therapy as long as the patients have met the criteria for blinatumomab therapy outlined above.
- The ALCANTARA trial provided a maximum of 5 cycles of blinatumomab; patients did not receive blinatumomab maintenance in this study. The submitter did not provide data

regarding the role of maintenance therapy in PH+ B-ALL. The TOWER study did allow for maintenance therapy in patients treated with blinatumomab in the relapsed and refractory setting in those with Ph- B-ALL. The Clinical Guidance Panel feels that it would be reasonable to consider maintenance therapy for Ph+ B-ALL patients who are treated with blinatumomab in the refractory or relapsed setting.

- Extrapolating from the TOWER study to the refractory or relapsed Ph+ B-ALL population, there is an HRQOL benefit to patients treated with blinatumomab compared to SOC treatments used in this setting.
- The Clinical Guidance Panel acknowledges that Ph+ B-ALL patients who were intolerant to second generation or later TKIs and intolerant to imatinib could have participated in the ALCANTARA protocol. Patients who have intolerance to TKI therapy have many alternative therapies available to them and therefore the CGP does not feel a recommendation for these patients is required.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Acute Lymphoblastic Leukemia (ALL) is an 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. 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. The most common form of ALL is of the precursor B cell sub type (B-ALL). About a quarter of adult patients presenting with B-ALL will harbor a Philadelphia Chromosome (t(9;22)(q34.1;q11.2) – Ph+ B-ALL.[7] Ph+ B-ALL increases in frequency with increasing patient age at presentation.

2.2 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 adult ALL Canadian incidence estimates are available for 2013. 480 Canadians were diagnosed with ALL and 138 individuals with ALL died as a result of the disease.[8] 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. While on treatment patient treatment HRQOL is adversely affected. PH+ B-ALL cells are sensitive to the effects of tyrosine kinase inhibitors (TKIs) and this therapy has changed the prognosis of patients with PH+ B-ALL.

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. Historically patients with PH+ B-ALL were noted to have poor outcomes with therapy, however with the introduction of tyrosine kinase inhibitor therapy, the majority of patients are able to achieve a complete hematological response regardless of age at presentation. 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 or who have evidence of minimal residual disease at end of induction[9] 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.

With modern treatment protocols pediatric ALL is curable in as many as 90% of cases. The majority of adolescents and young adults with ALL (15-39) whether or not they harbor the PH chromosome can expect 5 year event free survival in excess of 70% when treated on a pediatric like protocol.[10-13] In younger fit patients with PH+ B-ALL who have suboptimal response to initial induction therapy allogeneic transplantation and maintenance TKI therapy post transplantation is

pursued. TKI therapy provides a framework to treat patients with PH+ B-ALL who are older. A recent study treated patients up to 83 years of age with dasatinib in combination with chemotherapy yielding a 5 year overall survival for the entire cohort of 36%.[14]
There is no standard treatment for patients with relapsed or refractory (R/R) ALL. The prognosis of patients at this stage is poor and prolonged survival is rare for patients who fail to achieve remission with salvage treatment. PH+ B-ALL patients with R/R disease will usually undergo salvage therapy with a different TKI than used during initial treatment which may be combined with either salvage chemotherapy or immunotherapy with the goal of inducing a remission and, if possible, proceeding to an allogeneic hematopoietic cell transplant or if available chimeric antigen receptor therapy. Chemotherapy 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.[15] In the PH- B-ALL setting blinatumomab induces complete remission rates of between 43-69% with median overall survivals of between 6.1-9.8 months in the R/R setting.[3] Patients with B-ALL who fail to achieve remission with a salvage strategy are treated with palliative intent.

2.3 Evidence-Based Considerations for a Funding Population

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. Patients with B-ALL would be expected to respond to this therapy regardless of PH status. Adverse effects reflect this mechanism of action and include cytokine release syndrome, tumour lysis syndrome, infections and febrile neutropenia, and encephalopathy.

2.4 Other Patient Populations in Whom the Drug May Be Used

While there is no evidence available to extend the use of blinatumomab into other patient populations, patients with CD19+ diseases such as low-grade lymphoma or CLL could potentially benefit from treatment with blinatumomab. Pediatric patients with B-ALL may also benefit from this therapy. The Clinical Guidance 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 post allotransplant with evidence of persisting minimal residual disease. These patient populations were not within the scope of the current review and have not been included in the economic analysis.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, the Leukemia & Lymphoma Society of Canada (LLSC), provided input on blinatumomab (Blincyto) for Philadelphia chromosome positive (Ph+) B-cell precursor (BCP) acute lymphoblastic leukemia (ALL).

Information was collected about blinatumomab through two online surveys conducted via Survey Monkey. The two surveys addressed topics such as patient and caregiver awareness of the drug, any expectations they may have for the drug, and the most important symptoms they expect the drug will manage.

A total of 12 participants responded to the two surveys, all of whom were Canadian. The first survey ("Survey #1") was given to known ALL patients through an e-mailed link, which yielded nine responses. Six (one female, four males, one non-specified) were from patients currently receiving treatment and three (two females, one male) were from patients no longer receiving treatment. Healthcare professionals and LLSC staff distributed the second survey ("Survey #2") to current and previous caregivers of patients with ALL. All three of the caregivers who responded were female, two of whom were caregivers for a patient currently receiving treatment and the third was a caregiver for a patient who was in remission. The distribution of respondents by age group is summarized in Table 1.

Table 1. Survey respondents by age group

Age Group	Survey #1 Patients (N = 9)	Survey #2 Caregivers (N = 3)
≤ 19 years	1	0
20 to 29	1	1
30 to 39	0	0
40 to 49	2	1
50 to 59	2	0
60 to 69	1	0
70 to 79	2	1
80 and older	0	0

The patient group acknowledged the small sample size for the surveys, but also noted that Ph+ BCP-ALL is a rare disease and due to the similarity among responses, they believed the information still holds value for the pCODR process.

From a patient perspective, living with Ph+ BCP-ALL is disruptive to the daily lives of patients, with extreme fatigue and a loss of appetite/weight loss being the most challenging symptoms associated with the disease. There are three main approaches to treatment of ALL, which include chemotherapy, targeted therapy, and allogeneic stem cell transplants. Undergoing treatment is an intense process that may involve a combination of treatment approaches and is broken down into three stages: induction, consolidation, and maintenance stage. Side effects due to treatment are very common (experienced by all of the survey respondents) and include pain, nausea and vomiting, fatigue, infections/non-cancer illness, and fertility and sexual side effects. Patients value reaching remission, improvement in quality of life and managing key symptoms such as fatigue, pain, bruising and/or bleeding. Caring for a patient undergoing treatment and living with ALL is also difficult for caregivers, who reported feelings of loneliness and anxiety, a need for support, and a significant time and money commitment associated with providing care. Lastly,

patients who had experience with blinatumomab reported a positive experience, noting an improvement of quality of life compared to that associated with previous therapies.

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 are reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients with Ph+ BCP-ALL

According to the patient input response, being diagnosed with Ph+ BCP-ALL has disrupted the daily lives of patients in many ways. Patients were asked to rank the symptoms they were experiencing on a scale of 1 (not at all difficult) to 7 (extremely difficult). A summary of the symptoms that were rated as 4 or more has been provided in Table 2, with extreme fatigue rated as at least four by the greatest proportion of patients (55%) followed by loss of appetite/weight loss (44%).

Table 2. Summary of ALL symptoms rated by level of difficulty for the daily lives of patients

Symptom	% of respondents who rated ≥ 4	Total number of respondents
Extreme fatigue	55	9
Loss of appetite/weight loss	44	9
Numbness and tingling	22	9
Fever/night sweats	33	9
Pain	33	9
Lumps	22	9
Other (n=2 for nausea; and n=1 for: joint pain, acid reflux, diarrhea, headaches, low libido)	50	8

The common symptoms of ALL, such as fatigue, fever and night sweats, and weight loss, were experienced by all nine of the respondents. Patients also reported that the fatigue affected their daily routines including activities, sleeping patterns, and physical and emotional intimacy. More specifically, it was difficult for one patient to make plans as the fatigue made them unreliable. Despite the fatigue, six of the patients reported having trouble falling asleep at night or staying asleep throughout the night. One patient reported that “sleeping involves medication” and another patient had “no more than 2 hours consecutive sleep” and “were up multiple times a night”.

About half of patients reported that a loss of appetite and fluctuations of weight had a large impact on their daily lives, as one lost the ability to eat spicy foods, and others reported a significant loss or gain of weight. For example, one patient reported that they had gained “20 lbs weight for the first part of treatment and had 65 lbs of weight gain since then”. Further, patients reported having symptoms related to intimacy, due to impotency (reported by 2 patients), vaginal dryness (1), lack of sex drive (1), and fatigue (1). Intimacy was described by one as “difficult” and that the “weight gain and fatigue make it even harder”; while another patient had lost interest in any form of intimacy.

3.1.2 Patients’ Experiences with Current Therapy for Ph+ BCP-ALL

According to the LLSC, treatment for ALL is an intense process that lasts approximately two years. There are three main approaches to treatment, namely, chemotherapy, targeted therapy, and allogeneic stem cell transplants.

Chemotherapy is handled in three phases: induction, consolidation or "intensification", and maintenance. The induction phase is the initial phase of chemotherapy that is altered specifically for the patient depending on factors such as age, white blood cell (WBC) count, specific features of leukemia and the overall health of the patient. The goal is to achieve remission, and this phase may be repeated if blast cells are still present. Once the patient goes into remission, the consolidation phase begins to reduce the number of remaining leukemic cells, and is typically provided in cycles for four to six months with several drugs used in combination. These drugs may be administered using a lumbar puncture, which one patient described as the *"worst part of treatment"*. An allogeneic stem cell transplant may be used at this time for patients who are at a high risk for relapse. The final phase is the maintenance phase, which is continued for about two years to prevent disease relapse. More specific to patients with the Ph+ subtype of BCP-ALL, tyrosine kinase inhibitors (TKIs) are used for treatment of the disease along with the multidrug chemotherapy.

The patients who responded to the online survey have all received chemotherapy treatment for Ph+ BCP-ALL. Six of these patients were receiving treatment when they completed the survey and the remaining three were previously receiving treatment with chemotherapy. Two of the six patients currently on treatment had also received radiation and were awaiting an allogeneic stem cell transplant. Two patients had been treated following the Dana-Farber chemotherapy protocol. Of the three who were not receiving treatment, they had previously experienced radiation and chemotherapy, and one also had a stem cell transplant.

The patient respondents indicated that access to treatment was easy. More than three quarters of patient respondents believed the current treatment was able to sufficiently manage their cancer symptoms, however all reported having some variation of side effects associated with their treatments and therapies. Despite this, side effects of the treatment and therapies were experienced by all, which were temporary and associated with the therapies and included: pain, nausea and vomiting, fatigue, infections/non-cancer illness, and fertility and sexual side effects.

3.1.3 Impact of Ph+ BCP-ALL and Current Therapy on Caregivers

The second survey conducted by the LLSC was distributed to caregivers, three of whom responded. Two of the caregivers were caring for a spouse or partner with ALL and one was caring for a child with ALL. The caregiver response reported that caring for a person who has been diagnosed with ALL elicits an emotional response, including feelings of anxiety and loneliness. Caregivers reported the difficulty of hearing the ones they are caring for say that they would rather die than live having to take daily pill and dealing with the side effects, while another commented on witnessing the loss of interest in life and drive to live. The caregivers noted the need for support while caring for a patient with ALL as "the strain in the beginning especially was pretty severe, but we had great friends who helped by bringing lots of food", which was said to help refresh caregivers for "the long haul".

Caring for a patient with ALL is also very time-consuming and physically demanding, as caregivers take on additional responsibilities that the patient can no longer perform or help with, such as household chores, while also managing appointments and medical obligations for the patient. One caregiver stated that "they have spent the majority of their time in a hospital room since diagnosis" and this type of caring not only leads to a loss of work, but also "missing out" on experiencing their own lives as well. A respondent truly described the commitment by mentioning that "had to quit [their] job and rent a second residence to be close to the hospital and [they] stayed there during most of the week".

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with blinatumomab (Blincyto)

The surveys asked about the knowledge of and experience respondents had with blinatumomab. Three of nine patient respondents had previously used blinatumomab, and of the rest who had not, only one reported having access to the drug. One of the caregiver's patients was treated with blinatumomab. Based on two responses for additional information about experiences with blinatumomab, the experience was positive overall with one patient noting that it "has been the only positive of all the treatments so far" and another agreed with a statement regarding improved quality of life compare to previous therapies used. No additional side effects were reported and one patient reported they had stopped taking an anti-nausea medicine since receiving blinatumomab.

Patients who did not have experience with blinatumomab were asked what the most important symptoms of cancer for blinatumomab to control were. A total of six patients had no experience with blinatumomab, four patients responded to the question and two patients did not respond:

Fifty-percent of them chose fatigue, pain, bruising and/or bleeding, rashes/skin changes, and loss of appetite; and 25% selected fever and/or night sweats, and lumps. In terms of which side effects patients were more willing to tolerate, patients said they would be willing to deal with "short-term" side effects such as nausea, diarrhea, edema, and loss of appetite but would be less willing to tolerate "more severe" side effects such as pain, bruising, and bleeding.

3.3 Additional Information

The patient group provided an overview of ALL in their submission, which is one of four major types of leukemia. The submission stated that approximately 400 diagnoses of ALL are made each year in Canada, with more than half among children. Moreover, it is the most common type of cancer in children (under the age of 14), although it affects persons of all ages. This type of cancer rapidly progresses, affecting the bone marrow and blood, and is caused by either an acquired or genetic injury to the DNA of a developing cell of the bone marrow. The cell will multiply uncontrollably once it becomes a leukemia cell, and is then referred to as a "leukemic blast". As they multiply, they hinder the production of normal cells and therefore reduces the number of healthy cells to lower than normal. Further, the patient submission also noted that the term "acute" refers to the rapid progression of disease, which can be fatal within a few months if not treated quickly.

B-cell precursor leukemia specifically, was described as an aggressive type of leukemia according to the patient submission, where too many B-cell lymphoblasts (immature white blood cells) are found in the bone marrow and blood. Further, it was noted that although the most common type of ALL is BCP, Ph+ BCP ALL is a rare disease with poor prognosis.

The LLSC included additional information about treatment for ALL, referring to the "refractory leukemia" stage, which is when patients who had initially achieved remission have residual leukemic cells after the intensive treatment phase. Patients may relapse at this point, marked by the return of leukemia cells in the marrow. Blinatumomab is an immunotherapy drug used as a second-line treatment for patients with Ph- or refractory B-cell precursor ALL, but may also be used for patients who have not been able to reach remission or have relapsed since the use of other treatments. Currently, blinatumomab has been approved by the FDA for the treatment of adults and children with relapsed or refractory B-cell precursor ALL and Ph+ ALL patients.

Lastly, the response emphasized the significant impact of infection as a result of depleted WBCs, with the most severe illness reported being an "anal abscess that required surgery and caused many issues for 15+ years". Two other patients noted an increased susceptibility to colds and

being hospitalized for thrush and shingles. Vaccinations are recommended for ALL patients to decrease the chance of infection.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Sequencing with current therapies

Economic factors:

- Significant wastage due to insufficient stabilizer available
- Clarity on maximum number of cycles

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that current treatments for Ph+ B-cell precursor ALL include tyrosine kinase inhibitors (TKIs; e.g., second-generation dasatinib) in combination with multi-agent chemotherapy. At relapse, patients would receive different TKIs and multi-agent chemotherapy.

4.2 Factors Related to Patient Population

PAG noted the ALCANTARA trial for Ph+ ALL only included patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. PAG is seeking confirmation that blinatumomab would be limited to patients with ECOG ≤ 2, as patients can be very ill at relapse with ECOG ≥ 3 and there may be consideration of blinatumomab eligibility in these cases where ECOG is felt to be disease-related.

PAG noted that the reimbursement request is for relapsed or refractory Ph+ B-cell ALL. In the trial, patients were eligible if they had relapsed after or were refractory to at least one second-generation or later TKI (dasatinib, nilotinib, bosutinib, ponatinib), or were intolerant to second generation or later TKIs and intolerant or refractory to imatinib. PAG is seeking confirmation that the trial criteria would be applied to the funding criteria.

PAG also noted that funding of second-generation or later TKIs varies by jurisdiction. PAG is seeking information on the generalizability of the trial based on prior TKI and number of prior TKI treatments.

PAG identified that there may be some patients who have received inotuzumab ozogamicin through a clinical trial or special access programme. PAG is seeking clarity on whether patients who received inotuzumab ozogamicin would be eligible for blinatumomab.

4.3 Factors Related to Dosing

Since the stability of the reconstituted vials is 24 hours refrigerated and the stability of the prepared infusion bags is 10 days refrigerated, PAG noted that the one vial can be used to prepare more than one infusion bag. However, 5.5mL of stabilizer is required to prepare each infusion bag and there is only 10mL of stabilizer included with each vial of drug. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package. PAG noted there would be significant wastage due to insufficient stabilizer available to maximize the use of blinatumomab vials.

The funding request indicated that patients may receive five cycles of treatment (two cycles of induction followed by three additional cycles of consolidation treatment). However, PAG noted in the TOWER trial for Ph- ALL, patients were able to receive 12 months of maintenance therapy post five cycles. PAG is seeking clarity on the maximum dosing of blinatumomab for Ph+ ALL.

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

4.4 Factors Related to Implementation Costs

PAG noted that inotuzumab ozogamicin was recently reviewed for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). PAG is seeking guidance on sequencing of blinatumomab and inotuzumab ozogamicin in this setting.

4.5 Factors Related to Health System

None identified.

4.6 Factors Related to Manufacturer

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two registered clinician submissions from a total of three clinicians provided input on blinatumomab (Blincyto) for the treatment of relapsed or refractory Ph+ BCP ALL and their input is summarized below.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for this Ph+BCP-ALL

Clinician input noted that currently, there are very limited options for patients with Ph+ relapsed/refractory ALL. Salvage multi-agent chemotherapeutic regimens with tyrosine kinase inhibitors (TKIs) are used as the current standard treatment for this type of cancer. One clinician provided additional detail about the combination chemotherapy, noting the use of FLAG-Ida (i.e., fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin) followed by allo-hematopoietic stem cell transplantation (HSCT) in CR. Further, they stated that a TKI is typically used if it is known to be effective against the patient's specific mutation, which is determined by mutation analysis, and also if they have not already been challenged TKIs. The other clinician stated that TKIs are increasingly toxic.

They also noted that other monoclonal antibodies, such as inotuzumab and chimeric antigen receptor (CAR) T-cell cell therapies could potentially be treatment options in the future.

5.2 Eligible Patient Population

One clinician stated that as an adult hematologist specializing in leukemia, the patient population that was described in the funding request, as well as the inclusion and exclusion criteria of the clinical trial are what would be seen in their clinical practice. The second clinician also agreed that the patient population was appropriate and reflects reasonable inclusion/exclusion criteria that could be applied in clinical practice. The other clinician elaborated, by highlighting that if blinatumomab were to become available, they would prescribe it for all patients who meet the criteria of the clinical trial and not prescribe currently available treatments for any of them, and both clinicians mentioned that this may change with the funding of other new therapies currently undergoing review, with one stating that blinatumomab may be a reasonable option for patients that relapse post-transplant if CAR T-cell therapies are an option.

5.3 Relevance to Clinical Practice

According to both of the clinicians providing input, blinatumomab is very important and a "must have novel agent" as there is a significant unmet medical need for treatment of Ph+ BCP-ALL. It was noted that options for treating patients with refractory or relapsed ALL are very limited, and that repeating treatments that have previously failed does not provide significant long-term outcomes. The clinician also noted that blinatumomab is a novel therapy with a different mechanism of action allowing patients to achieve better remission and long-term survival. In addition, the clinician believes that this treatment would be used to achieve complete remission in patients who are refractory to initial treatment, which would in turn, allow more patients to proceed to stem cell transplantation. It may also provide relapsed patients with the option for a second transplant and this could possibly lead to longer-term survival than the current life expectancy after a relapse post-transplant, which is a few months.

Both of the clinicians providing input for this review have had experience with blinatumomab, with one reporting that they had used it through a special access program. Both the new drug and

current therapies require hospitalization; however, the new drug was reported as being better tolerated than chemotherapy with less long-term side effects compared to TKIs. The other clinician did not elaborate about their experience with prescribing blinatumomab, but stated that it appears to have superior efficacy, equivalent safety and better tolerability, which is similar to the experience described by the other clinician.

5.4 Sequencing and Priority of Treatments with blinatumomab (Blincyto)

One clinician explained that in refractory patients, blinatumomab would be used after traditional multi-agent chemotherapy to induce a remission prior to transplant, therefore replacing the current standard of using more and more varied combinations of toxic drugs or even palliation. In relapsed patients, blinatumomab could be used as initial therapy, by allowing a patient to proceed to transplantation in a healthier state without the toxicities associated with standard chemotherapy.

Another clinician highlighted the following sequence: Diagnosis: First line, consisting of HCVAD (or hyper-CVAD, where CVAD stands for a combination of drugs including: cyclophosphamide, vincristine, doxorubicin [Adriamycin], and dexamethasone) induction/TKI followed by Allo-HSCT if persistent disease post induction, second line, consisting of a different TKI based on mutation analysis or FLAG-IDA salvage if refractory, third line consisting of blinatumomab (or CAR-T) followed by allogeneic stem cell transplantation (allo-SCT) in patients in first CR (CR1). If patients relapse post-allo transplantation, this clinician would use blinatumomab/TKI based on mutation. As well, this clinician noted that blinatumomab would replace palliation which is the current standard. It would also likely be chosen ahead of donor leukocyte infusion in the relapse post-allo setting. They felt that in some circumstances, blinatumomab may replace allo-SCT, if a sustained response is achieved post-blinatumomab and donor options/comorbidity index are sub-optimal, therefore making treatment related mortality for an allo-SCT higher than usual.

5.5 Companion Diagnostic Testing

Not applicable, as testing is already available and funded.

5.6 Additional Information

None

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of this review is to evaluate the effect of blinatumomab for the treatment of adult patients with refractory or relapsed (R/R) Philadelphia-chromosome positive (Ph^+) B-cell precursor acute lymphoblastic leukemia (ALL).

Note: The following Supplemental Issue, most relevant to the pCODR review and to the Provincial Advisory Group, was identified while developing the review protocol and is outlined in section 7.

- Issue 1: Summary of the propensity score analysis provided by the submitter to compare efficacy outcomes in the ALCANTARA study with a historical comparator study (Study 20160462)

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 will be chosen for inclusion in the review based on the criteria in Table 6.1. The literature search strategy and detailed methodology used by the pCODR Methods Team is provided in Appendix A in the Clinical Guidance Report.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of Blinatumomab for Ph^+ B-precursor ALL will be included.	Adult patients with Ph+ BCP-ALL, who have relapsed after or are refractory to at least one second-generation or later TKI, or are intolerant to second-generation or later TKIs and intolerant or refractory to imatinib Subgroups: – Age groups (18 to <35 vs. 35 to <55 vs. 55 to <65 vs. ≥65 years) – ECOG status (0 vs 1 vs 2) – Previous lines of therapy for disease relapse (# of treatments/iterations of therapy)	Blinatumomab (continuous intravenous infusion) at: • fixed stepwise doses of 9 µg /day in week 1 of cycle 1 followed by 28 µg /day thereafter(trial dosing schedule) • Other dosing schedules	• Standard of care (including TKIs, TKIs + chemotherap, or chemotherapy) • Inotuzumab ozogamicin • CAR T-cell therapy	Efficacy • CR/CRh* within the first two cycles of treatment • MRD response (MRD < 10^{-4}) rate within two cycles • Best overall response • OS • PFS • RFS • AlloHSCT after blinatumomab-induced remission • 100-day mortality after HSCT HRQoL Safety • AEs • SAEs • WDAE

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	– Previous TKI therapies (1 vs 2 vs ≥ 3) – History of alloHSCT (Yes vs No) – Bone marrow blasts (<50% vs ≥50%)			

ALL = acute lymphoblastic leukemia; **alloHSCT** = allogeneic hematopoietic stem cell transplant; CAR T-cell = chimeric antigen receptor T-cell; **CR** = complete remission; **CRh*** = complete remission with partial hematologic recovery; **CRi** = CR with incomplete hematologic recovery; **µg** = microgram; **HSCT** = Hematopoietic Stem Cell Transplant; **HRQoL** = health-related quality of life; **MRD** = minimal residual disease; **OS**= overall survival; **PFS** = progression-free survival; **Ph⁺** = Philadelphia-chromosome positive; **RCT**=randomized controlled trial; **RFS** = relapse-free Survival **SAE**=serious adverse events; **vs.** = versus; **WDAE**=withdrawal due to adverse events

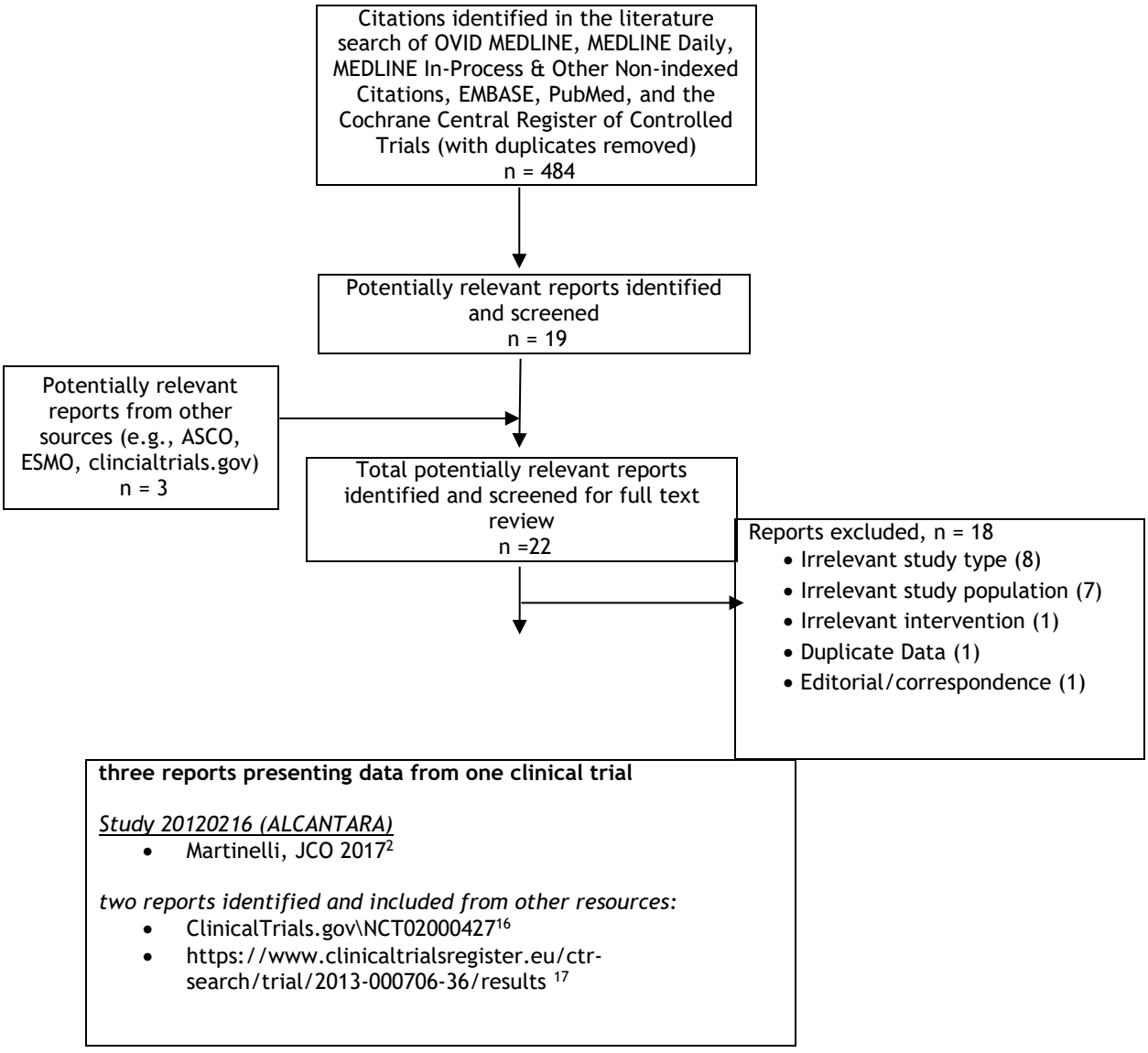
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 22 potentially relevant citations identified, three citations, reporting data from one clinical trial, were included in the pCODR systematic review,[2,16 17] and 18 studies were excluded. Studies were excluded because they were irrelevant study types,[18-25] did not use the intervention of interest,[26] included irrelevant patient population,[27-33]. Comments or editorials,[34] and conference abstracts reporting duplicate data from the included full articles[35] were also excluded. Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 6.1. PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the ALCANATRA trial were also obtained through requests to the Submitter by pCODR[3,4]

6.3.2 Summary of Included Studies

One single arm, ALCANTARA, was identified that met the eligibility criteria of the pCODR systematic review.[2,16] Characteristics of the trial are summarized in Table 6.2 and specific aspects of trial quality are summarized in Table 6.3.

No comparator was used in the ALCANTARA trial. The clinical guidance panel (CGP), registered clinicians providing input, and the provincial advisory group (PAG) all identified inotuzumab ozogamicin as a relevant comparator. At the protocol development phase, the review team also identified CAR T-cell therapy as a potential comparator. Therefore, pCODR requested the Submitter to provide an indirect comparison of blinatumomab versus inotuzumab ozogamicin, as inotuzumab had received a Notice of Compliance (NOC) from Health Canada and funding recommendation. However, the Submitter stated that an indirect treatment comparison (ITC) of blinatumomab and inotuzumab ozogamicin was not feasible for the following reasons:

- Inability of the submitter to use traditional network meta-analysis (NMA) methods due to the single-arm trial design of the ALCANATRA trial and, hence, the lack of a common comparator upon which the analysis could be anchored.
- Inability of the submitter to use matching-adjusted indirect treatment comparison (MAIC) and other population-adjusted indirect treatment comparison methods (e.g., Simulated Treatment Comparison): the ALCANTARA trial specifically included patients with Ph+ ALL, whereas INO-VATE (pivotal study for inotuzumab) included patients with Ph+ or Ph— ALL. The INO-VATE trial publications reported insufficient data on patient demographics for the Ph+ subgroup.
- Small sample sizes of both the ALCANTARA and INO-VATE trials due to the low incidence of Ph+ BCP-ALL in adults. Further sample size reduction was anticipated if attempting to conduct a MAIC.
- Difference in key outcomes evaluated in the ALCANTARA trial and INO-VATE trial with respect to the definition and timing of evaluation.[4]

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study 20120216 (ALCANTARA)[2] NCT02000427[16] Characteristics: Single arm-phase 2, multicentre N= 45 Number of centres and number of countries; 19 centres in Europe and US Patient Enrolment Dates: 03-Jan-2014 to 20-May-2015 Data cut-off dates:	<u>Key Inclusion Criteria:</u> patients with Ph+ BCP-ALL: • ≥ 18 years of age • > 5% bone marrow blasts • Relapsed after or were refractory to ≥ 1 second-generation TKI (dasatinib, ponatinib, bosutinib, or nilotinib), or intolerant to second-generation TKIs and intolerant or refractory to imatinib • ECOG PS ≤ 2 <u>Key Exclusion Criteria:</u>	<u>Intervention:</u> Blinatumomab administered as continuous IV infusion in 6-weeks cycles: 4 weeks of treatment with *9 µg/day in week 1 of cycle 1, and 28 µg/day thereafter* followed by a 2-week treatment-free interval	<u>Primary:</u> • CR/CRh response within 2 cycles of blinatumomab therapy <u>Secondary:</u> • MRD response rate (MRD < 10-4) within 2 cycles • Other best overall response rates (CR, CRh*, and CR/CRh*/CRi • OS • RFS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Interim analyses 02-Sept-2014 (for early stopping) Primary analysis 20-May-2015 Final analysis 06-Jan-2017 Funding: Amgen	• Isolated extramedullary involvement • A history of clinically relevant or current CNS pathology • Active GVHD; and prior allogeneic HSCT (within 12 weeks) • Chemotherapy (within 2 weeks), or immunotherapy (within 4 weeks)	Comparator: None	• duration of response • allogeneic HSCT after blinatumomab-induced remission • 100-day mortality after HSCT
CNS = central nervous system; CR = complete remission; CRh* = complete remission with partial hematologic recovery; Cri = CR with incomplete hematologic recovery; ECOG PS = Eastern Cooperative Oncology Group performance status; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; IV = intravenous; MRD= minimal residual disease; OS = overall survival; RFS = relapse-free survival; TKI = tyrosine kinase inhibitor; *µg* = microgram			

Table 6.3: Select quality characteristics of included studies of [drug] in patients with [disease]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
Study 20120216 (ALCANTARA)	Blinatumomab vs No comparator	CR/CRh* response within 2 cycles	41	45	No	No	No	No (modified ITT)	Yes	No	Yes

a) Trials

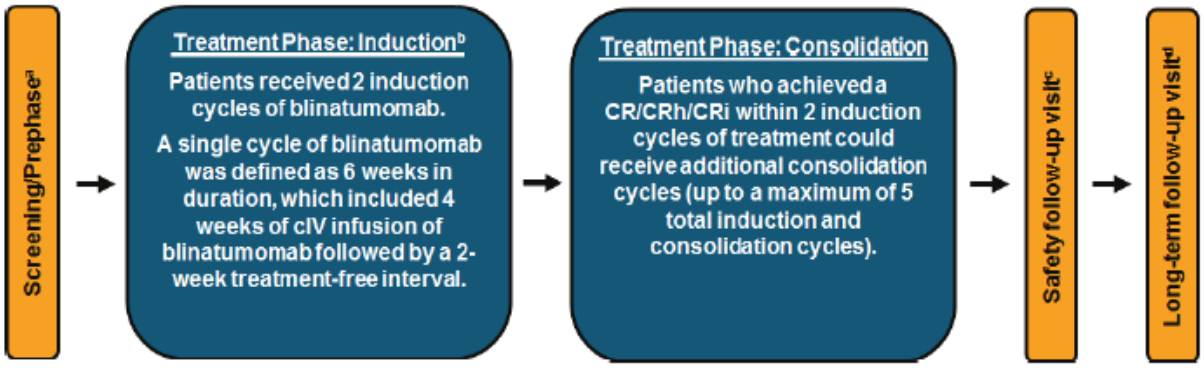
ALCANTARA

Trial design

ALCANATRA was an open-label, single-arm, multicentre, phase 2 trial to assess the efficacy and tolerability of single-agent blinatumomab in patients with elapsed or refractory Ph+ B-precursor ALL who progressed after or were intolerant to a second-generation or later TKI. The trial was conducted at 19 centers in Europe and the United States.[2]

A schematic illustration of the ALCANTARA study design is presented in Figure 6.2. As shown, the study consisted of a 21-day screening and enrollment phase, an induction treatment period (two 6-week cycles of blinatumomab), a consolidation treatment period (up to 3 additional cycles of blinatumomab for subjects who achieved a hematologic complete remission within 2 induction cycles of treatment), a 30-day safety follow up visit, and long-term follow up visits for response duration and survival (every 3 months for 18 months).[3]

Figure 6.2: Design of the ALCANTARA Trial



[a] Prephase period for administration of dexamethasone. [b] The primary analysis for the primary endpoint occurred after the last patient completed 2 induction cycles. [c] A safety follow-up visit was required 30 days after the last dose of blinatumomab. [d] Long-term follow-up visits were carried out every 3 months for 18 months to assess time-to-event endpoints (eg, overall survival).
cIV, continuous intravenous; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery
Source: Amgen Data on File, 2017 [60]

Source: pCODR manufacturer submission[3]

Study endpoints and disease assessment

The primary end point of the study was CR or CRh* (CR/CRh*) response, defined as the proportion of patients who achieved CR/CRh* within the first two cycles of blinatumomab treatment.

Key secondary end points included minimal residual disease (MRD) response rate during the first two cycles of treatment, relapse-free survival (RFS), duration of response, overall survival (OS), allogeneic hematopoietic stem cell transplant (HSCT) after blinatumomab-induced remission, and other best overall response rates. The definitions of the efficacy endpoints are provided in Table 6.4.

Hematologic and molecular responses were assessed using bone marrow aspiration or biopsy samples on day 29 of each cycle at a central reference laboratory. For patients who achieved CR/CRh* during the induction cycles, MRD response was measured through BCR-ABL1 quantification. RFS was measured from the time of first CR/CRh* to hematologic or extramedullary relapse or death resulting from any cause. OS was measured from the time of the first blinatumomab dose to death resulting from any cause. Probabilities of RFS and OS over time were estimated using the Kaplan-Meier (KM) method. A landmark analysis was performed to evaluate OS among MRD responders in order to minimize immortal bias (only patients who survived to their first MRD assessment were included in the analysis). Data on adverse events (AEs) and serious AES were collected from treatment start until at least 30 days after termination of the treatment, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.[2]

Sample size and statistical analysis

Sample size was estimated for a Simon's mini-max two-stage design,[36] based on the proportion of subjects who achieved a CR or CRh* within two cycles of blinatumomab treatment (i.e., primary efficacy endpoint). The sample size was estimated at 23 patients in stage 1, and 41 evaluable patients in total, based on a one-sided type 1 error (α) of 0.025 and a power of 90% to detect the effective response rate assumption of ≥30% over an ineffective treatment rate of ≤10%.[2] The study

was to be stopped at stage 1 if fewer than 3 of 23 patients were observed with CR or CRh* in stage 1. The null hypothesis (ineffective treatment assumption) would be rejected if ≥ 9 out of 41 subjects showed a CR or CRh* within two cycles of treatment with blinatumomab at the end of stage 2.[3]

An interim analysis was performed, at the 02-Sept-2014 data cut-off date, after the first 23 patients enrolled in stage 1 had either discontinued treatment or completed their first two treatment cycles. The purpose of this interim analysis was to determine if the second stage should be conducted. The primary analysis of the ALCANTARA study was performed at the 20-May-2015 data cut-off date, after the last patient had received two cycles of blinatumomab treatment. The final analysis was performed at the 06-Jan-2017 study completion date, after all patients completed the long-term follow-up period.[3]

The primary analysis was based on the Full Analysis Set (FAS), which included all patients who received at least one infusion of blinatumomab. Sensitivity analyses were performed on subjects who met the definition of a prospectively defined per protocol set (PPS).[3] Missing data was not imputed. For the primary endpoint, patients with missing response were considered as non-responders. The Kaplan-Meier (KM) method was used for time to event endpoints (i.e., RFS; OS; 100-day mortality rate after allogeneic HSCT). Safety analyses were performed on patients in the FAS. Descriptive subgroup analyses were pre-planned based on the following potential covariates: BCR-ABL mutations, number of previous TKI therapy, previous HSCT, relapse after HSCT (1st vs. 2nd vs. 3rd relapses after HSCT), relapse without prior HSCT, and refractory disease after first relapse.[3]

No adjustments for multiplicity were planned for the analyses of the efficacy endpoints.[3]

Protocol amendments

The original study protocol was issued on 02-Apr-2013. There were two protocol amendments during the study. The key changes to the protocol are summarized below: [17]

- Amendment 1.0 (27-Jun-2013) added an external independent data monitoring committee (DMC) to oversee the interim analysis and assess safety approximately every 6 months provided an adequate enrollment rate.
- Amendment 2.0 (15-Sept-2014) clarified timing and scope of study procedures; specified that tyrosine kinase inhibitor therapy within 2 weeks before start of blinatumomab was not exclusionary, but was to be completed before start of treatment; provided instructions on blinatumomab overdose reporting (> 10%) as a serious AE under the criterion of "other medically important serious event"; clarified requirements for medical coverage and safety monitoring in the outpatient setting; provided specific guidance for blinatumomab dose modifications from grade 3 infection events; clarified criteria for discontinuation of blinatumomab, definitions for evaluation of treatment response, and details of statistical analyses.

Table 6.4: Efficacy endpoints in the ALCANTARA trial

Endpoint		Definition
Primary endpoint	CR/CRh response	The proportion of patients who achieved a best response of CR or CRh within 2 cycles of treatment with blinatumomab • CR was defined as ≤ 5% bone marrow blasts, no evidence of disease, and full recovery of peripheral blood counts: platelets > 100,000/μL and ANC > 1000/μL • CRh was defined as ≤ 5% bone marrow blasts, no evidence of disease, and partial recovery of peripheral blood counts: platelets > 50,000/μL and ANC > 500/μL
Secondary endpoint	Other best overall response rates	• The proportions of patients who achieved a best response within 2 cycles of treatment with blinatumomab of: ▪ CR ▪ CRh ▪ CR/CRh/CRi • CRi was defined as ≤ 5% bone marrow blasts, no evidence of disease, and incomplete recovery of peripheral blood counts: platelets > 100,000/μL or ANC > 1000/μL
Secondary endpoint	MRD response	The proportion of patients who achieved an MRD response within 2 cycles of treatment with blinatumomab • MRD response was defined as MRD < 10^{-4}, measured by PCR or flow cytometry • MRD complete response, defined as no detectable leukemia cells by PCR (ie, MRD–), was also assessed
Secondary endpoint	Overall survival	Time from first infusion of blinatumomab until death due to any cause
Secondary endpoint	Relapse-free survival	Time from detection of response until earliest of documented hematologic relapse, extramedullary disease, or death due to any cause
Secondary endpoint	Allogeneic HSCT and 100-day mortality after HSCT	• The proportion of patients who underwent allogeneic HSCT in remission due to blinatumomab (ie, among patients who achieved a CR/CRh within 2 cycles) • 100-day mortality was assessed from the time of allogeneic HSCT until death from any cause in patients who achieved a CR/CRh within 2 cycles and did not receive further antileukemia treatment prior to HSCT

ANC, absolute neutrophil count; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; PCR, polymerase chain reaction
Source: Martinelli et al, 2017 [56] and Amgen Data on File, 2014 [100]

Source: pCODR manufacturer submission[3]

b) Populations

Eligibility criteria

The ALCANTARA study included adult patients (18 years of age or older) who:

- had a diagnosis of Ph+ B-precursor ALL (Philadelphia chromosome was detected by cytogenetics, fluorescence in situ hybridization, and/or BCR-ABL1 PCR); and
- had relapsed after or were refractory to at least one second-generation or later TKI (dasatinib, nilotinib, bosutinib, ponatinib), or were intolerant to second generation or later TKIs and intolerant or refractory to imatinib.

The study eligibility criteria also required patients to have a more than 5% bone marrow blasts (as determined by a central laboratory), and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.

Patients were excluded if they received allogeneic HSCT within 12 weeks prior to the initiation of blinatumomab treatment, had an active acute or chronic (grade 2 to 4) graft-versus-host disease, underwent systemic treatment of graft-versus-host disease within two weeks before the start of treatment; or if they had a previous or existing clinically relevant central nervous system (CNS) pathology, active CNS ALL, or isolated extramedullary disease.[2]

Baseline characteristics of the study population

The baseline and disease characteristics of the ALCANTARA population are summarized in Table 6.5. The median age was 55 years (range 23 to 78); 47% of the patients were female; and 58% had other cytogenetic abnormalities in addition to Philadelphia chromosome.[2] All but three patients (93.3%) had between 1 and 3 prior relapses of ALL , and 68.9% had received ≥1 previous salvage regimens.[3] As shown in Table 6.5, 56% of patients were refractory to prior TKI therapy; 33% had relapsed on previous TKIs, and 11% had disease progression after their prior TKI therapy. Eighty-four percent of patients had received ≥2 prior TKIs, with the most common prior TKIs being dasatinib (87%) and imatinib (56%). Fifty one percent of patients had received a prior third-generation TKI (i.e., ponatinib), and 44% had a history of prior allogeneic HSCT.[2] Eighty percent of patients had an ECOG performance status score of 0 or 1.[4]

Table 6.5: Baseline demographic and disease characteristics of participants in the ALCANTARA trial

Table 1. Patient Demographic and Clinical Characteristics at Baseline

Characteristic	Patients (N = 45) No.	%
Sex		
Male	24	53
Female	21	47
Median age, years (range)	55 (23-78)	
Age group, years		
18 to < 55	22	49
≥ 55	23	51
Cytogenetics and molecular analyses*		
Philadelphia chromosome and other cytogenetic abnormalities	22/38	58
ABL1 kinase domain mutations	17/37	46
T315I mutation	10/37	27
No. of prior TKI treatments†		
1	7	16
2	21	47
3	13	29
4	4	9
Prior TKI‡	45	100
Imatinib	25	56
Dasatinib	39	87
Nilotinib	16	36
Ponatinib	23	51
Prior alloHSCT		
Yes	20	44
No	25	56
Bone marrow blasts (central review)		
< 10%	2	4
10% to < 50%	9	20
50% to < 75%	6	13
≥ 75%	28	62

Abbreviations: ABL1, Abelson murine leukemia viral oncogene homolog 1; alloHSCT, allogeneic hematopoietic stem-cell transplantation; TKI, tyrosine kinase inhibitor.

*Philadelphia chromosome was detected by cytogenetics/metaphase spread, fluorescence in situ hybridization, or *BCR-ABL1* polymerase chain reaction. Numerators indicate the number of patients in each subgroup, and denominators indicate the number of evaluable patients tested by a specific methodology.

†One patient had acute lymphoblastic leukemia that was resistant to imatinib and was never exposed to a second-generation or later TKI (protocol deviation).

‡Prior TKI use was not mutually exclusive.

Source: Martinelli et al. J Clin Oncol. Vol.35(16): 1795-1802.

c) Interventions

Treatment Dosing Schedule

In the ALCANTARA study patients were treated with blinatumomab as a continuous intravenous infusion at fixed stepwise doses (9 µg/day /day in week 1 of cycle 1 and 28 µg/day thereafter) over four weeks followed by a 2-week treatment-free interval (6-week cycles).Patients who achieved hematologic complete remission (CR, CRh*, or CR with incomplete hematologic recovery [Cri]) within two initial cycles could receive up to three additional cycles of consolidation, if they

remained in remission (unless allogeneic HSCT was scheduled earlier).[2] Patients did not receive blinatumomab as maintenance after the maximum of five cycles.[4] the median number of blinatumomab cycles received was 2 (range 1 to 5).[2] All eligible patients with a suitable donor could proceed to HSCT at any time at the investigators' discretion.[2]

Concomitant interventions

Pre-phase treatment (protocol-mandated premedication) with dexamethasone was permitted within the 21-day screening period to reduce tumor burden and the incidence of tumour lysis syndrome.[3] Patients with a high baseline blast count (>50% bone marrow blasts or ≥ 15000/mL peripheral blast count, as determined by a local laboratory) received pre-phase dexamethasone 10 mg/m^2/day (for up to five days) up to an absolute maximum of 24 mg/day.[2,3] All patients received mandatory premedication with 20 mg intravenous dexamethasone within one hour prior to start of treatment in each treatment cycle, and within one hour prior to dose step to prevent cytokine release syndrome. Patients received a mandatory CNS prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines (e.g., methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4 mg or equivalent steroid dose) within one week (+ 3 days) prior to start of blinatumomab and at the end of each treatment cycle (after bone marrow aspiration on day 29).[2,3]
Any TKI therapy, antitumor therapy other than blinatumomab (e.g., cytotoxic chemotherapy, radiation therapy, immunotherapy), chronic systemic (> 7 days) high-dose corticosteroid therapy, other immunosuppressive therapies, or any other investigational agents were not permitted during the induction and consolidation phases of treatment.[3]

Dose modifications, interruptions, and discontinuation

Dose modifications – For AEs, blinatumomab could temporarily or permanently be reduced to 9 mg/day, if necessary at the investigators' discretion. Patients with dose reductions had the option to receive the higher dose level of 28 mg/day once the AE resolved to grade 1 or better for ≥ 7 days. For all patients who restarted blinatumomab treatment, dexamethasone pre-treatment was required within one hour before restarting treatment. For patients with signs of cytokine release syndrome, oral or intravenous dexamethasone 8 mg was given three times per day for up to three days and reduced stepwise over four days.[2]

Dose interruptions – For grade ≥3 cytokine release syndrome, tumor lysis syndrome, and disseminated intravascular coagulation/ coagulopathy, treatment was interrupted until the event resolved to grade 1 or better. For grade ≥ 3 infections, blinatumomab was interrupted until the infection was adequately controlled or resolved based on investigator's opinion. The treatment was allowed to restart at 9 mg/day. Patients who had dose interruptions due to a neurologic event received dexamethasone at least 24 mg/day, with stepwise reductions over 4 days.[2]

Treatment discontinuation – Blinatumomab was permanently discontinued for grade 4 AEs that were possibly related to blinatumomab or for AEs that lasted ≥ 2weeks. For grade ≥3 neurologic events, blinatumomab was stopped immediately, and the patient was assessed by physical examination, vital signs, and safety laboratories. For grade 3 neurologic events or serious AEs leading to treatment interruption, treatment was restarted no earlier than 72 hours after stopping infusion but within two weeks. Blinatumomab was also discontinued in any of the following circumstances: hematological or extramedullary relapse subsequent to CR/CRh*/CRi on protocol treatment; failure to achieve CR/CRh*/CRi within two treatment cycles; and Investigator's decision to change the treatment (including immediate HSCT).[3]

d) Patient Disposition

Of the 61 patients who were assessed for eligibility between 03-Jan-2014, and 20-May-2015, 45 patients were enrolled in the study and treated with blinatumomab; three patients met the eligibility criteria but did not participate in the study, and the remaining 13 patients did not meet the eligibility criteria (Figure 6.3).

As of the 20-May-2015 data cut-off date, 23 out of 45 patients (51.1%) remained in the study (two were receiving blinatumomab, and 21 discontinued treatment but continued to be followed), and 22 patients (48.9%) had died.[2] As of the 06-Jan-2017 study completion date, a total of 37 patients (82.2%) had died and eight patients (17.8%) completed the study.[3]

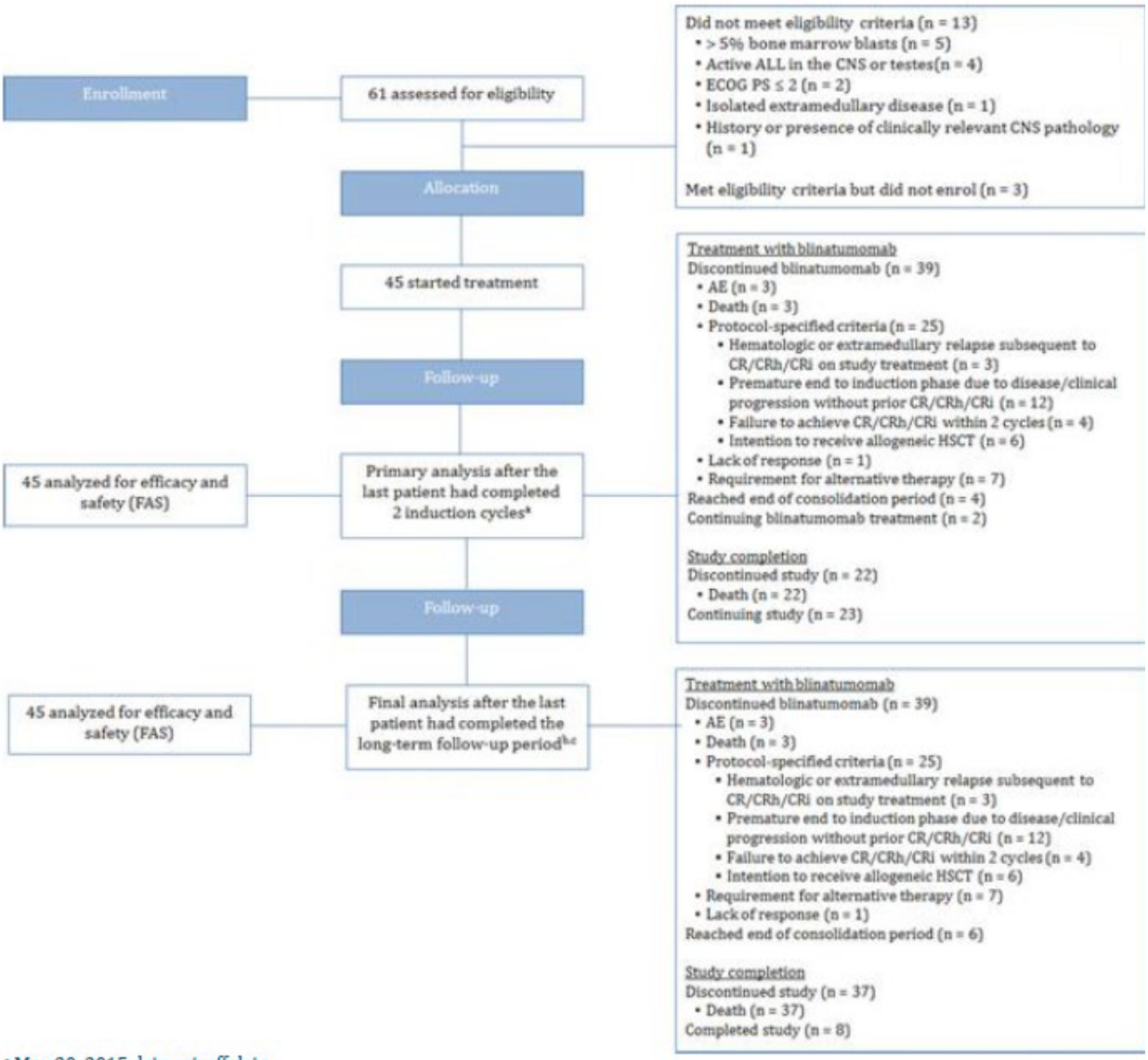
Protocol deviations

A total of 13 patients (28.9%) had at least one protocol deviation; of those, seven patients (15.6%) received the wrong treatment or incorrect dose during the study.[4]

e) Limitations/Sources of Bias

- ALCANTARA was a single arm study with no active treatment or placebo control groups. As a result, a direct comparison of the efficacy and safety of blinatumomab relative to relevant comparators is not possible. However, the submitter provided an indirect treatment comparison (propensity score analysis) of blinatumomab with standard of care chemotherapy in a historical comparator study that was conducted in Italy and Spain. The details of this analysis are discussed in section 7 of this report.
- The open label nature of the study might introduce the risk of reporting and performance biases, as the study participants and the investigators were aware of the study intervention (i.e. blinatumomab). This could particularly be important in recruitment of patients, their subsequent care, attitudes of patients to the treatments, reporting of subjective outcomes (e.g., AEs) by the patients and care providers, handling of withdrawals and protocol violations, or exclusion of data from analysis.
- The efficacy and safety analyses in the ALCANTARA study was performed in a modified intention-to-treat (ITT) fashion; as a result, the efficacy analysis was limited to data from patients who received at least one infusion of blinatumomab. The analysis did not account for three patients who met the eligibility criteria but did not enroll in the study. Exclusion of patients who are less compliant with the study criteria (e.g., refuse to participate in the study) may lead to more optimistic (favorable) results.
- Although the subgroup analyses were pre-specified in the ALCANTARA study, the results should be interpreted with caution with attention to the fact that the sample sizes in the majority of the subgroups are smaller than 10, and that the study was not powered to detect differences in the specific subgroups.
- Patient-reported quality of life outcomes have not been measured in the ALCANTARA study.
- No adjustments were made for multiplicity introduced by analysing secondary endpoints or subgroup analyses. Therefore, these analyses are considered exploratory. Multiple testing can increase the probability of type 1 error and, therefore, lead to false positive conclusions.

Figure 6.3: Patient disposition in the ALCANTARA trial



[a] May 20, 2015 data cut-off date
[b] Long-term follow-up visits were required every 3 months for 18 months
[c] January 6, 2017 study completion date
AE, adverse event; ALL, acute lymphoblastic leukemia; CNS, central nervous system; CONSORT, Consolidated Standards of Reporting Trials; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; HSCT, hematopoietic stem cell transplant
Source: Amgen Data on File, 2015 [102], Amgen Data on File, 2017 [60], and Amgen Data on File, 2018 [118]

Source: pCODR manufacturer submission[3]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Best hematologic response (CR/CRh*) rate

The analysis of the primary efficacy endpoint of CR/CRh* rate within the first 2 cycles of blinatumomab treatment was performed using data from the FAS (Table 6.6). As of the 20-May-2015 data cut-off date, 16/45 patients (36%, 95% CI 22%, 51%) achieved CR/CRh* during the first two cycles, with 14 patients (31%, 95% CI 18%, 47%) showing a CR and two patient (4%, 95% CI 1%, 15%) achieving a CRh*. Two additional patients achieved CRi at the end of cycle 2.[2] The CR/CRh* rate achieved with blinatumomab was considered to be clinically meaningful, as the lower limit of the 95% CI exceeded the pre-specified null hypothesis threshold (ineffective rate) of 10%.[3]

Subgroup analyses of the primary endpoint showed differences in the point estimates effect, based on pre-specified baseline characteristics of the study population (Table 6.6): the observed response rates were lower in patients who were older, had a higher ECOG status score, and had ≥50% bone marrow blasts at baseline. More favorable response rates were observed in patients who received more than three previous TKI therapies as well as patients who did not receive previous allogeneic HSCT. However, given the overlapping CIs, none of the observed differences were statistically significant. In addition, the subgroup analysis should be considered exploratory due to the small sample sizes (range 0 to 11) in each subgroup category.[2]

Efficacy data for the primary endpoint in the ALCANTARA full analysis set, therefore remained unchanged in the final analysis (06-Jan-2017 study completion date): a total of 36% patients (16/45) achieved a CR/CRh within 2 cycles of treatment with blinatumomab.[4]

Minimal Residual Disease (MRD) Response

MRD response within the first two cycles of treatment was a secondary endpoint and was assessed in patients who achieved CR/CRh* during the first two treatment cycles. Among 16 CR/CRh* responders, a complete MRD response was achieved in 14 patients (88%, 95% CI 62%, 98%); the remaining two responders (who achieved Cri) had persistent measurable MRD and relapsed during subsequent cycles of therapy.[2]

Relapse-free Survival (RFS)

RFS was a secondary endpoint and assessed for patients who achieved a hematologic response during the first two cycles of blinatumomab therapy. As of the 20-May-2015 data cut-off date, after a median follow-up of 9.0 months, the median RFS (relapse or death due to any reason) was 6.7 months (95% CI: 4.4, not estimable) in 16 subjects who achieved a CR/CRh*.[2] Among the 14 patients who achieved a complete MRD response, the median RFS was similar to that of the entire CR/CRh* responders (6.8 months;95% CI, 4.4, not estimable).[2] The analysis of RFS was performed with and without censoring at the time of allogeneic HSCT. Censoring for allogeneic HSCT did not have a statistically significant impact on the RFS results.[2]

As of the data cut-off date, 7/16 (44%) responders were alive without relapse, 8/16 (50%) had relapsed with a median time to relapse of 6.7 months (95% CI 4.4, not estimable), and one patient died in CR after allogeneic HSCT (133 days after achieving CR).[2] Of the eight patients who had relapsed, three had relapsed during treatment, two relapsed without receiving allogeneic HSCT, and three relapsed after receiving HSCT.[2]

At the time of the final analysis, after a median follow-up of 16.1 months (maximum follow-up 22.6 months), 5/16 (31%) patients who achieved a CR/CRh* within two cycles of blinatumomab treatment remained alive and in remission. Median RFS for CR/CRh responders was 6.8 months

(95% CI 4.4, not estimable). After censoring for HSCT, the median RFS was 6.7 months (95% CI 3.8, not estimable) based on a median follow-up of 10.6 months (Figure 6.4).[3]

Table 6.6:Efficacy endpoints in the ALCANTARA study (Full Analysis Set and pre-specified patient subgroups)

Outcome	Patients (n/N1)*	Proportion (%)	95% CI
Primary end point			
CR/CRh during the first two cycles	16/45	36	22 to 51
Philadelphia chromosome and other cytogenetic abnormalities	10/22	45	24 to 68
ABL1 kinase domain mutations	6/17	35	14 to 62
T315I mutation	4/10	40	12 to 74
p190 BCR/ABL1 isoform†	10/26	39	20 to 59
p210 BCR/ABL1 isoform†	5/16	31	11 to 59
No. of prior TKI therapies			
1	1/7	14	< 1 to 58
2	7/21	33	15 to 57
≥ 3	8/17	47	23 to 72
Prior ponatinib	8/23	35	16 to 57
Prior alloHSCT	5/20	25	9 to 49
Age 18 to < 55 years	8/22	36	17 to 59
Age ≥ 55 years	8/23	35	16 to 57
Bone marrow blasts < 50%	7/11	64	31 to 89
Bone marrow blasts ≥ 50%	9/34	27	13 to 44
Secondary end points			
Best response during the first two cycles			
CR	14/45	31	18 to 47
CRh	2/45	4	1 to 15
Complete MRD response‡	14/16	88	62 to 98
alloHSCT after blinatumomab-induced remission§	4/16	25	7 to 52
Age 18 to < 55 years	2/8	25	3 to 65
Age ≥ 55 years	2/8	25	3 to 65
100-day post-transplant mortality rate§	1/4	25	4 to 87

Abbreviations: alloHSCT, allogeneic hematopoietic stem-cell transplantation; *ABL1*, Abelson murine leukemia viral oncogene homolog 1; *BCR*, breakpoint cluster region; CR, complete remission; CRh, CR with partial hematologic recovery; MRD, minimal residual disease; TKI, tyrosine kinase inhibitor.

*n/N1, number of responders/total number of patients with evaluable data under each category.

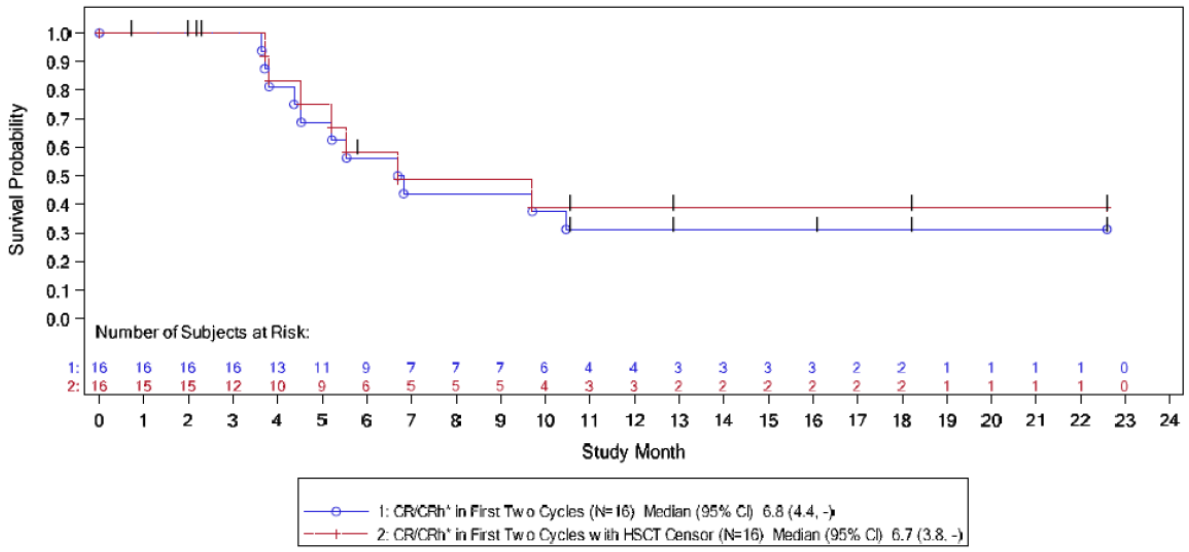
†Isoform designation was determined by MRD status at baseline by using reverse transcription quantitative polymerase chain reaction (PCR) on pretreatment bone marrow aspirates. A subset of patients (n = 10) had both *p190* and *p210* transcripts, although in all of these patients, *p210* was 2.1- to 3.5-log higher; the transcripts were thus assigned a designation of *p210*. Further details are provided in Patients and Methods.

‡Among CR/CRh responders only; includes all four CR/CRh patients with the T315I mutation.

§For patients who received alloHSCT during blinatumomab-induced remission without other antileukemia therapy. Complete MRD response was defined as no detectable PCR amplification of *BCR-ABL1* genes (sensitivity ≥ 10^{-5}) as assessed by a central laboratory.

Source: Martinelli et al. J Clin Oncol. Vol.35(16): 1795-1802.

Figure 6.4: Relapse-free survival with and without censoring for HSCT in ALCANTARA trial (final analysis)



CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; HSCT, hematopoietic stem cell transplant; RFS, relapse-free survival
Source: Amgen Inc, 2017 [60]

Source: pCODR manufacturer submission[3]

Duration of hematologic remission

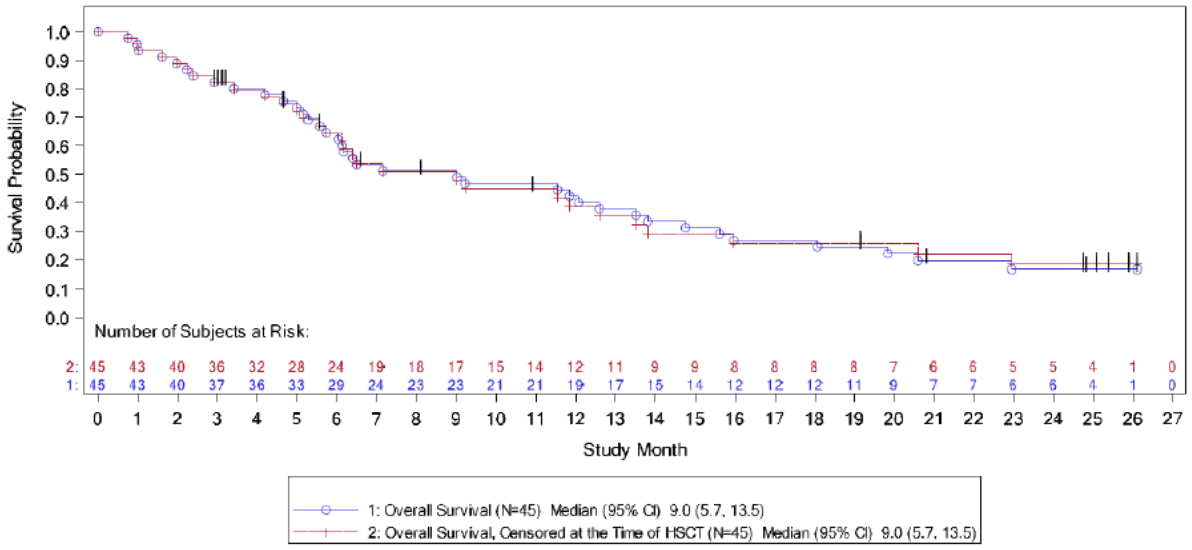
Duration of hematologic remission was a secondary outcome in the ALCANTARA study. The definitions of duration of CR/CRh* response and RFS were similar, except that the analysis of duration of response only included deaths due to disease progression. Therefore, the point estimates for median RFS and median duration of response were reported to be identical: 6.8 months without censoring at the time of allogeneic HSCT and 6.7 months with censoring at the time of allogeneic HSCT).[3]

Overall Survival (OS)

OS was a secondary outcome in the ALCANTARA study and was assessed for all patients from the time of initiation of blinatumomab treatment until death from any cause or the date of the last follow-up. As of the 20-May-2015 data cut-off date, 22 out of 45 patients (48.9%) had died, and 23 patients (51.1%) were alive (censored).[2,3] With a median follow-up of 8.8 months, the median OS was 7.1 months (95%CI: 5.6, not estimable), regardless of censoring for HSCT.[2] In the landmark OS analysis (starting at the end of cycle 2 of blinatumomab treatment), based on a median follow-up of 5.3 months, the median OS was not reached for patients who achieved a complete MRD response, and was 3.9 months (95% CI 3.0, not estimable) among MRD non-responders.[2]

At the time of the final analysis, 8/45 (18%) patients in the FAS remained alive. Median OS was 9.0 months (95% CI 5.7, 13.5) based on a median follow-up of 25.1 months (95% CI 5.7, 13.5); Figure 6.5). After censoring for allogeneic HSCT, the median OS was also 9.0 months (95% CI 5.7, 13.5), with a median follow-up of 24.8 months.[3]

Figure 6.5: Overall survival with and without censoring for HSCT in ALCANTARA trial (final analysis)



CI, confidence interval; CR, complete remission; CRh, CR with partial hematologic recovery; HSCT, hematopoietic stem cell transplant; OS, overall survival
Source: Amgen Data on File, 2017 [60]

Source: pCODR manufacturer submission[3]

Post-baseline Allogeneic HSCT

Seven (44%) of the 16 CR/CRh* responders received an allogeneic HSCT, four of whom remained in continuous blinatumomab-induced remission without any additional anti-leukemia therapy. The remaining three patients received blinatumomab with other anti-leukemia therapy (one received other anti-leikemia therapy prior to HSCT and remained in remission, and two had relapsed before proceeding to HSCT).[2]

100-days post-baseline allogeneic HSCT mortality

The four who received an allogeneic HSCT while in remission (CR/CRh*) after 2 cycles of blinatumomab treatment were evaluated for 100-day post-baseline HSCT mortality. The 100-day mortality rate for these patients was 25.0% (95% CI 4%, 87%; Table 6.6).[2]

Quality of Life

Health-related quality of life was not assessed in the ALCANTARA study.

Harms Outcomes

In the ALCANTARA study, 45 patients received at least one infusion of blinatumomab. A summary of AEs reported in the ALCANTARA study is provided in Table 6.7. The median duration of infusion for the whole treatment period was 53.8 days (range 11 to 141).[16]

As of the 20-May-2015 data cut-off date, all 45 patients (100%) experienced ≥1 treatment-emergent AE. The most frequent AEs included pyrexia (58%), febrile neutropenia (40%), and headache (31%). Thirty-seven patients (82%) were reported to have grade 3 and higher treatment-emergent AEs (TEAEs). The most common grade 3 and higher TEAEs (occuring in ≥ 15% of patients) were febrile neutropenia (27%), thrombocytopenia (22%), and anemia (16%). The proportion of

grade 3 or higher TEAEs that could possibly be related to blinatumomab (as per the investigator's assessment) was 44% (20 patients), most commonly, febrile neutropenia and increased levels of alanine aminotransferase (11% each).[2]

Five patients (none of whom achieved CR/CRh) had fatal AEs, including one case of multi-organ failure (age 55 years), two cases of infection (sepsis, age 40 years; septic shock, age 33 years), one case of cerebral hemorrhage (age 25 years), and one case of respiratory failure (age 42 years). One fatal AE (septic shock) was considered treatment-related by the investigator. This patient had disease persistence and died 13 days after protocol-directed discontinuation of blinatumomab.[2]

Cytokine release syndrome (CRS) was reported in three patients; however, all of the CRS events were grade 1 or 2) and did not result in discontinuation or interruption. Neurologic events were reported in 47% of patients, with the most common neurologic AEs being paresthesia (13%), confusional state (11%), dizziness (9%), and tremor (9%). Three patients had grade 3 neurologic events (aphasia, hemiplegia, and nervous system disorder or depressed level of consciousness); one of which required treatment interruption (aphasia). All but one of the grade 3 neurologic events were resolved, with a maximum duration of 15 days. No patients had grade 4 or 5 neurologic events.[2]

Table 6.7: Summary of adverse events reported in the ALCANTARA study (Full Analysis Set; primary analysis)

	Grade							
	Any		1 to 2		3		4	
Event	No.	%	No.	%	No.	%	No.	%
Patients with AEs	45	100	45	100	33	73	16	36
AEs of grade ≥ 3 occurring in ≥ 5% of patients*								
Pyrexia	26	58	24	53	5	11	0	0
Febrile neutropenia	18	40	9	20	12	27	0	0
Headache	14	31	13	29	3	7	0	0
Anemia	13	29	9	20	7	16	1	2
Thrombocytopenia	10	22	4	9	5	11	7	16
Pain	7	16	4	9	4	9	0	0
Increased aspartate aminotransferase	6	13	3	7	3	7	2	4
Increased alanine aminotransferase	5	11	1	2	5	11	0	0
Device-related infection	5	11	3	7	3	7	0	0
Neutropenia	3	7	0	0	0	0	3	7
Patients with neurologic events	21	47	20	44	3	7	0	0
Neurologic events occurring in two or more patients								
Paresthesia	6	13	6	13	0	0	0	0
Confusional state	5	11	5	11	0	0	0	0
Dizziness	4	9	4	9	0	0	0	0
Tremor	4	9	4	9	0	0	0	0
Aphasia	2	4	1	2	1	2	0	0
Cerebellar syndrome	2	4	2	4	0	0	0	0
Memory impairment	2	4	2	4	0	0	0	0
Nervous system disorder	2	4	1	2	1	2	0	0

Abbreviation: AE, adverse event.
*Cutoff based on grade ≥ 3 AEs.

Source: Martinelli et al. J Clin Oncol. Vol.35(16): 1795-1802.

A summary of the safety data analysis (06-Jan-2017 data cut-of date) including treatment-emergent AEs and blinatumomab-related AEs is provided in Table 6.8. As shown in the table, all patients experienced at least 1 treatment-emergent AE; in 91% of the patients the AE was considered to be related to blinatumomab. Serious AEs were reported in 62% of patients. The rate

of grade ≥ 3 treatment-emergent AEs was 84%. Five (11%) fatal AEs occurred within 30 days of the last dose of blinatumomab during the study.

Treatment interruptions due to treatment-emergent AEs and treatment-related AEs were reported in 38% and 27% of patients, respectively. In three patients (7%), treatment-emergent AEs resulted in permanent discontinuation of blinatumomab. Permanent discontinuation due to blinatumomab-related AEs was reported in 27% of patients.

The incidence of treatment-emergent events of interest (EOIs) in the ALCANTARA trial, along with the incidence of EOIs that are considered as blinatumomab safety signals (i.e., neurologic events, CRS, elevated liver enzymes, and medication errors) are provided in Table 6.9.

Table 6.8: Summary of adverse events reported in the ALCANTARA study (Full Analysis Set; final analysis)

Event	Treatment-emergent AEs (N = 45) n (%)	Treatment-related AEs (N = 45) n (%)
All AEs	45 (100)	41 (91)
Serious	28 (62)	12 (27)
Grade ≥ 3	38 (84)	20 (44)
Grade ≥ 4	18 (40)	7 (16)
Fatal[a]	5 (11)	1 (2)
Leading to permanent discontinuation of blinatumomab	3 (7)	2 (4)
Serious	2 (4)	1 (2)
Grade ≥ 3	3 (7)	2 (4)
Grade ≥ 4	1 (2)	1 (2)
Fatal[a]	0 (0)	0 (0)
Leading to interruption of blinatumomab	17 (38)	12 (27)
Serious	13 (29)	7 (16)
Grade ≥ 3	13 (29)	8 (18)
Grade ≥ 4	1 (2)	1 (2)
Fatal[a]	0 (0)	0 (0)

Note: Severity was graded using CTCAE v4.03
[a] Fatal events that occurred within 30 days of last blinatumomab treatment
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events
Source: Amgen Data on File, 2017 [60, 106] and Amgen Data on File, 2018 [107]

Source: pCODR manufacturer submission[3]

Table 6.9: Treatment-emergent Events of Interest in the ALCANTARA trial

Event	Treatment-emergent EOIs (N = 45) n (%)
All treatment-emergent EOIs	44 (98)
Serious	18 (40)
Grade ≥3	28 (62)
Fatal	2 (4)
Neurologic events[a]	28 (62)
Serious	6 (13)
Grade ≥3	6 (13)
Cytokine release syndrome[a]	4 (9)
Serious	1 (2)
Grade ≥3	0 (0)
Medication errors[a]	2 (4)
Serious	2 (4)
Grade ≥3	0 (0)
Elevated liver enzymes[a]	8 (18)
Serious	1 (2)
Grade ≥3	6 (13)
Infections	22 (49)
Serious	9 (20)
Grade ≥3	11 (24)
Leukoencephalopathy[a]	1 (2)
Serious	0 (0)
Grade ≥ 3	0 (0)
Neutropenia (including febrile neutropenia)[a]	21 (47)
Serious	4 (9)
Grade ≥ 3	15 (33)
Acute pancreatitis[a]	0 (0)
Serious	0 (0)
Grade ≥ 3	0 (0)
Tumor lysis syndrome[a]	1 (2)

Event	Treatment-emergent EOIs (N = 45) n (%)
Serious	1 (2)
Grade ≥ 3	1 (2)

Note: AEs coded using MedDRA v19.1. Severity was graded using CTCAE v4.03
[a] No fatal events were identified in this category
AE, adverse event, CTCAE, Common Terminology Criteria for Adverse Events; EOI, event of interest; MedDRA, Medical Dictionary for Regulatory Activities
Source: Amgen Data on File, 2017 [60]

Source: pCODR manufacturer submission[3]

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of Blinatumomab for relapsed/refractory Ph+ BCP ALL:

- Summary of the manufacturer-submitted propensity score analysis to compare efficacy outcomes in the ALCANTARA study with a historical comparator study (Study 20160462)

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary of the manufacturer-submitted propensity score analysis

7.1.1 Objective

In the absence of a trial directly comparing blinatumomab with a relevant comparator, the Submitter conducted an indirect treatment comparison using a propensity score analysis to compare the efficacy of blinatumomab in the single arm ALCANTARA study (N = 45) to that of standard of care (SOC; cytotoxic chemotherapy and/or TKI) in a historical comparator study (Study 20160462; N=55).[3]

The results of this analysis were used to inform the Submitter's pharmacoeconomic evaluation.

7.1.2 Methods

The Submitter sponsored a retrospective, non-interventional, cohort study using data owned by investigators as part of previous or ongoing clinical studies in centres in Italy and Spain. Data were collected using a study-specific electronic case report form from August 2017 to December 2017. The earliest date of qualifying salvage treatment was in March 2006 and the last date for follow-up was in January 2018, with the maximum duration of follow-up from initiation of qualifying salvage treatment being 57 months.

The objective of the historical comparator study was to estimate clinical efficacy in relapsed/refractory Ph+ BCP ALL patients who received salvage therapy. The primary outcome of the study was the proportion of patients who achieved a hematologic complete remission (CR, CRh, CRi, and combinations thereof) following salvage therapy and secondary outcomes were OS, RFS, and the proportion of patients who underwent allogeneic HSCT. Patients in the historical comparator study were followed until death or loss to follow-up while patients in the ALCANTARA study were followed for up to about 26 months. Local practice SOC included a mixture of TKIs (imatinib, dasatinib, nilotinib, or ponatinib) and/or cytotoxic chemotherapy.

In order to balance baseline covariates and increase the homogeneity within the two study populations, a propensity score analysis was conducted using patient level data from a post-hoc primary analysis set which consisted of all 45 patients from the ALCANTARA study and 55 participants from the historical comparator study.

The following inclusion and exclusion criteria were used for the historical comparator study.

Inclusion Criteria:

- Adult patients with Ph+ BCP ALL
- One of the following:

    - Refractory to or relapsed after at least one second-generation TKI (dasatinib, ponatinib, bosutinib, or nilotinib)
    - Intolerant to a second-generation TKI and intolerant or refractory to imatinib mesylate
- Greater than 5% blasts in bone marrow at the time of qualifying salvage therapy
- At least 18 years of age at the time of qualifying salvage therapy
- Received initial treatment after January 1, 2000

Exclusion Criteria:

- History of malignancy other than ALL within five years before the start of qualifying salvage therapy
- Central nervous system or isolated extramedullary disease
- Prior treatment with blinatumomab

The inclusion criteria for the historical comparator study were identical to those for the ALCANTARA study, aside from the lack of the ECOG criterion (ECOG status ≤ 2) that was in the ALCANTARA study and the addition of the criterion regarding date of initial treatment.

In addition to the exclusion criteria specified for the historical comparator study, the ALCANTARA study also had the following exclusion criteria:[2]

- Allogeneic HSCT within 12 weeks before the start of blinatumomab treatment
- Active acute or chronic graft-versus-host disease
- Systematic treatment of graft-versus-host disease within two weeks before the start of blinatumomab treatment
- Active ALL in the central nervous system or testes
- Eligibility for allogeneic HSCT (defined by disease status, performance status, and donor availability)
- Cancer chemotherapy or any investigational drug within two weeks
- Immunotherapy within four weeks
- Prior anti-CD19 therapy

Data from the two studies were merged and an estimated propensity score (i.e., the predicted probability of being assigned to blinatumomab if a comparative trial was being conducted during the period of historical study) was assigned to each patient based on the following set of selected covariates:

- Sex
- Age (≤ 53 years or > 53 years)
- Prior allogeneic HSCT
- Number of prior therapies (≤ 2 or > 2)
- Time since diagnosis (≤ 20.9 months or > 20.9 months)
- Time since last therapy (≤ 4 months or > 4 months)

Continuous variables (age, number of prior therapies, time since diagnosis, and time since last therapy) were coded dichotomously with thresholds determined by the median of distribution of the variable in the combined studies. Propensity scores were derived for each patient using a logistic regression model with treatment status as the dependent variable (value of one for ALCANTARA patients and value of zero for historical comparator patients) and the covariates as the independent variables.

For the estimation of treatment effects, the propensity score analysis weighted patients based on the inverse probability of treatment (IPTW). The average treatment effect of the treated (ATT) method was used in the primary analysis. The ATT approach assigns all patients who received the study treatment (i.e. blinatumomab) an equal weight of 1.0, while control patients with large propensity scores receive larger weights and control patients with small propensity scores receive smaller weights. A sensitivity analysis was conducted using the average treatment effect (ATE) method. With this approach, control patients with high propensity scores and blinatumomab-treated patients with low propensity scores receive larger weights while control subjects with low propensity scores and blinatumomab-treated patients with high propensity scores receive smaller weights. To balance the sample sizes in the two studies, the ATE weights in each cohort were multiplied by the number of patients in that cohort as a proportion of the total combined number of patients.

According to the Manufacturer, the ATT approach was considered as the primary adjustment approach in the pCODR submission because this approach had the ability to make the control patients more like the blinatumomab-treated patients with respect to their baseline covariates.

The outcomes assessed were: the percentage of patients achieving CR or CRh, OS, and the percentage of patients receiving allogeneic HSCT. The definitions of CR and CRh were identical between the two studies. The proportion of patients who achieved CR or CRh within two cycles of blinatumomab treatment in the ALCANTARA study was compared to the proportion of patient who achieved CR or CRh after qualifying salvage therapy in the historical comparator study. In the historical comparator study, the timing of response assessment relative to the start of salvage therapy varied due to the different treatment cycle lengths within the SOC.

7.1.3 Findings

Table 7.1 shows the balance in covariates between the patients in the ALCANTARA and historical comparator cohorts, before and after IPTW adjustment using the ATT method. [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

Table 7.1: Covariate balance before and after IPTW Propensity Score adjustments using ATT weights
(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).
Source: pCODR manufacturer submission[3]

The results of the ATT propensity score analyses are presented in Table 7.2. RFS results were not reported as the proportion of patients in the historical comparator cohort who achieved a CR/CRh and had evaluable RFS data ([redacted] out of [redacted]) was small. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

Based on the ATT analysis (Table 7.2):

- The percentage of patients achieving a CR/CRh was [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).
- Median OS was [redacted]. The Kaplan-Meier curves for OS are presented in Figure 7.1. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).
- The percentage of patients who were eligible for and underwent allogenic HSCT was [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

While there was variation in the timing of hematological response assessment in the historical comparator study, the median time to response in this cohort suggested that the timing of response assessment in terms of the number of treatment cycles was [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

Table 7.2: Propensity score analysis results for efficacy outcomes

	Comparison of ALCANTARA patients and historical SOC cohort	
	Blinatumomab (N=)	**SOC (N=)**
% of patients achieving CR/CRh (95% CI)	[redacted]	
OR (95% CI)		
Median overall survival, months (95% CI)		
HR (95% CI)		
% of patients who underwent allogeneic HSCT		

Note: Average treatment effect of the treated weights were used for inverse probability of treatment weighting.

Source: pCODR manufacturer submission[3]

CI = confidence interval; CR = complete remission, CRh = complete remission with partial hematological recovery; HR = hazard ratio; HSCT = hematopoietic stem cell therapy; OR = odds ratio; SOC = standard of care.

(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

Figure 7.1: OS results from the propensity score analysis (IPTW, ATT Weighting)
(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).
ATT = average treatment effect of the treated; IPTW = inverse probability of treatment weighting; OS = overall survival. **Source:** pCODR manufacturer submission[3]

7.1.4 Summary

The submitted propensity score analysis was conducted to compare the efficacy of blinatumomab with SOC chemotherapy and/or TKI in adult patients with relapsed/refractory Ph+ BCP ALL. The propensity score analysis used patient level data from the ALCANTARA single arm trial (N = 45) and a historical comparator study (Study 20160462; N=55) and estimated treatment effects through IPTW weighting.

The analysis attempted to balance the following baseline characteristics between the two study cohorts: sex, age, prior allogeneic HSCT, number of prior therapies, time since diagnosis, and time since last therapy. Following adjustment, there were no notable differences in these baseline characteristics between the two cohorts. However, continuous variables were dichotomized due to the limited sample sizes in the studies, reducing the ability of the propensity scores to remove residual confounding.

The results of the submitted propensity score analysis suggested that blinatumomab was associated with [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). Blinatumomab may also be associated with a [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). The proportion of patients who underwent allogeneic HSCT was numerically greater in the SOC group though similar between the two groups. RFS was not compared between the cohorts due to the limited number of relapse events that occurred. Safety results were not provided for the historical comparator study.

According to the Methods Team, the Submitter's justification for using the ATT approach for the main analysis appears to be reasonable. However, it is important to note that the results were sensitive to the choice of IPTW approach. While the ATT approach showed [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information*

Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier).

Prior therapies and qualifying salvage therapy in the historical comparator study may not have reflected the SOC for Ph+ BCP ALL at the time of the ALCANTARA study as later generations of TKIs and the use of pediatric-like chemotherapy regimens in adults were introduced during the period of the historical comparator study. The ALCANTARA study enrolled patients from 2014 to 2015 while the date of initiation of the first qualifying salvage therapy was in 2006 and the last date of follow-up was in 2018 for the historical comparator study. If these developments in SOC improved CR/CRh and OS, then it is possible that SOC efficacy in the historical cohort was worse than it would have been in an ALCANTARA study SOC arm or in current clinical practice. Therefore, differences in SOC not accounted for in the propensity score analysis could have biased the results in favour of blinatumomab.

As well, it is worth noting that a limitation of the propensity score analysis is that patients' ECOG status and the percentage of patients who had never achieved remission were covariates that were not included in the propensity score analysis. The CGP identified these variables as important covariates. The Submitter confirmed however that these data were not available for the historical comparator study and therefore, these variables could not be incorporated into the propensity score analysis. The absence of patients' ECOG status and the percentage of patients who had never achieved remission from the propensity score analysis does contribute of the uncertainty to the results. Nonetheless, although [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until June 30, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

8 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.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on blinatumomab Ph+ BCP 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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

The Leukemia Clinical Guidance Panel is comprised of blinatumomab Ph+ BCP ALL. 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 AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2018, Embase 1974 to 2018 September 17, Ovid MEDLINE(R) ALL 1946 to September 17, 2018

#	Searches	Results
1	(Blincyto* or blinatumomab or MT-103 or MT103 or AMG-103 or AMG103 or MEDI-538 or MEDI538 or 4FR53SIF3A).ti,ab,ot,kf,kw,hw,rn,nm.	1523
2	exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/	74151
3	(acute adj3 (lymphocytic or lymphoblastic or lymphoid or lymphatic or lymphocyte or B-Cell or T-Cell or Pre B-ALL or T-ALL) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	88181
4	((precursor cell lymphoblast* or precursor B-Cell or precursor B-cells or pre-B-cell or pre-B-cells or precursor T-cell or precursor T-cells or CALLA-positive or mixed-cell or null-cell) adj3 (leukemia* or leukaemia*)).ti,ab,kf,kw.	2209
5	(acute adj (leukemia* or leukaemia*)).ti,ab,kf,kw.	50884
6	(lymphoblastic lymphoma* or lymphoblastic leukemia* or lymphoblastic leukaemia*).ti,ab,kf,kw.	79652
7	or/2-6	152552
8	1 and 7	969
9	8 use medall	211
10	8 use cctr	44
11	*blinatumomab/ or (Blincyto* or blinatumomab or MT-103 or MT103 or MEDI-538 or MEDI538 or AMG-103 or AMG103).ti,ab,kw,dq.	1008
12	exp Acute lymphoblastic leukemia/	74151
13	(acute adj3 (lymphocytic or lymphoblastic or lymphoid or lymphatic or lymphocyte or B-Cell or T-Cell or Pre B-ALL or T-ALL) adj3 (leukemia* or leukaemia*)).ti,ab,kw,dq.	88126
14	((precursor cell lymphoblast* or precursor B-Cell or precursor B-cells or pre-B-cell or pre-B-cells or precursor T-cell or precursor T-cells or CALLA-positive or mixed-cell or null-cell) adj3 (leukemia* or leukaemia*)).ti,ab,kw,dq.	2595
15	(acute adj (leukemia* or leukaemia*)).ti,ab,kw,dq.	50740
16	(lymphoblastic lymphoma* or lymphoblastic leukemia* or lymphoblastic leukaemia*).ti,ab,kw,dq.	79742
17	or/12-16	152498
18	11 and 17	684
19	18 use oemezd	449
20	19 and conference abstract.pt.	194
21	limit 20 to yr="2013-current"	169
22	19 not 20	255
23	9 or 10 or 22	510
24	remove duplicates from 23	317
25	21 or 24	486
26	limit 25 to english	471

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#12	Search (#11 AND publisher[sb]) Filters: English	6
#11	Search (#3 AND #9) Filters: English	203
#10	Search (#3 AND #9)	209
#9	Search (#4 OR #5 OR #6 OR #7 OR #8)	108364
#8	Search (Lymphoblastic lymphoma*[tiab] OR lymphoblastic leukemia*[tiab] or lymphoblastic leukaemia*[tiab])	31964
#7	Search (Acute[tiab] AND (leukemia*[tiab] OR leukaemia*[tiab]))	100228
#6	Search ((Precursor cell lymphoblast*[tiab] OR precursor B-Cell[tiab] OR precursor B-cells[tiab] OR pre-B-cell[tiab] OR pre-B-cells[tiab] OR precursor T-cell[tiab] OR precursor T-cells[tiab] OR CALLA-positive[tiab] OR mixed-cell[tiab] OR null-cell[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab]))	2161
#5	Search (acute[tiab] AND (lymphocytic[tiab] OR lymphoblastic[tiab] OR lymphoid[tiab] OR lymphatic[tiab] OR lymphocyte[tiab] OR B-Cell[tiab] OR T-Cell[tiab] OR Pre B-ALL[tiab] or T-ALL[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab]))	42641
#4	Search Precursor Cell Lymphoblastic Leukemia-Lymphoma[mh]	26248
#3	Search (#1 OR #2)	304
#2	Search (Blincyto*[tiab] OR blinatumomab[tiab] OR MT-103[tiab] OR MT103[tiab] OR AMG103[tiab] OR AMG-103[tiab] OR MEDI-538[tiab] OR MEDI538[tiab] OR 4FR53SIF3A[rn])	304
#1	Search "blinatumomab" [Supplementary Concept]	128

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

4. Grey Literature search via:

Clinical Trial Registries:

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

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

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

Select international agencies including:

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

European Medicines Agency (EMA):

http://www.ema.europa.eu/

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

Conference abstracts:

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

American Society of Hematology (ASH)
http://www.hematology.org/

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

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-17Sept2018) with in-process records & daily updates via Ovid; Embase (1974-17Sept2018) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were blinatumomab, Blincyto and acute lymphoblastic leukemia.

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

The search is considered up to date as of January 3, 2019.

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

Study Selection

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

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

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

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

Writing of the Review Report

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

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

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