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CADTH PCODR INITIAL CLINICAL GUIDANCE REPORT

Clinical Report

BLINATUMOMAB (BLINCYTO)

AMGEN

Indication: For the treatment of patients with Philadelphia chromosome-negative, CD19-positive, B-cell precursor acute lymphoblastic leukemia in first or second hematologic complete remission with minimal residual disease greater than or equal to 0.1%.

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Initial
Publication Date:	September 3, 2020
Report Length:	132 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	Adverse event
ALL	Acute lymphoblastic leukemia
alloSCT	Allogeneic stem cell transplant
ALT	Alanine aminotransferase
ATE	Average treatment effect
ATT	Average treatment effect of the treated
B-ALL	B-cell acute lymphoblastic leukemia
BCP-ALL	B-cell precursor acute lymphoblastic leukemia
BCR/ABL	Breakpoint cluster region/c-Abelson
BSA	Body surface area
CAR-T	Chimeric antigen receptor T-cell
CGP	Clinical Guidance Panel
CI	Confidence interval
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRh	Complete remission with partial hematologic recovery
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DRC	Data review committee
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EFS	Event-free survival
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, core 30

EPAR	European Public Assessment Report
EP FAS	Endpoint full analysis set
EQ-5D-3L	European Quality of Life Scale, 5-Dimensions, 3-Level
FAS	Full analysis set
GHS	Global health status
GMALL	German Multicentre Study Group on Adult Acute Lymphoblastic Leukemia
HR	Hazard ratio
HR/IR	High risk and intermediate risk
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
IPTW	Inverse probability of treatment weighting
Ig	Immunoglobulin
qPCR	Quantitative polymerase chain reaction
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan-Meier
Key Sec EP FAS	Key secondary endpoint full analysis set
MCID	Minimal clinically important difference
MRD	Minimal residual disease
NCI	National Cancer Institute
NE	Not estimable
NSAID	Non-steroidal anti-inflammatory drug
OS	Overall survival
PAG	Provincial advisory group
PCR	Polymerase chain reaction
PD	Progressive disease
pERC	pCODR Expert Review Committee
PFS	Progression-free survival
Ph	Philadelphia chromosome

PK	Pharmacokinetic
Prim EP FAS	Primary endpoint full analysis set
PS	Propensity score
QoL	Quality of life
RCT	Randomized controlled trial
RFS	Relapse-free survival
R/R	Relapsed and refractory
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SD	Standard deviation
TCR	T-cell receptor
TKI	Tyrosine kinase inhibitor
TRAE	Treatment-related adverse event
TTHR	Time to hematologic relapse
VAS	Visual analogue scale
WBC	White blood cell
WDAE	Withdrawals due to adverse events

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding blinatumomab for Philadelphia chromosome (Ph)-negative (Ph-), CD19 positive (CD19+), B cell-precursor (BCP) acute lymphoblastic leukemia (ALL) patients who are minimal residual disease (MRD) positive (MRD+). 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 conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review, supplemental issues, and comparison with other literature are fully reported in Sections 6, 7, and 8. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted PAG Input, and a summary of submitted Registered Clinician Input, are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of blinatumomab for the treatment of adult and pediatric patients with Ph-, CD19+, BCP-ALL, who are in first or second hematologic complete remission (CR) with MRD greater than or equal to 0.1%.

The reimbursement request for blinatumomab is for the treatment of patients with Ph-, CD19+, BCP-ALL in first or second hematologic CR with MRD greater than or equal to 0.1%. Health Canada issued a Notice of Compliance with conditions (NOC/c) for blinatumomab for this indication on December 19, 2019. As per the Health Canada indication, patients are to be selected for treatment based on detection of MRD as determined by an accredited laboratory using validated assay methods.[1] The reimbursement request is aligned with the Health Canada NOC/c.

Blinatumomab is administered as a continuous intravenous (IV) infusion through an infusion pump which delivers at a constant flow rate. A single cycle of treatment with blinatumomab is 28 days (4 weeks) of continuous infusion which is followed by a 14-day (2 week) treatment free interval. Patients may receive one cycle of induction treatment followed by three additional cycles of blinatumomab as consolidation treatment. As per the product monograph, patients weighing greater than or equal to 45 kg received a fixed dose. For patients weighing less than 45 kg, the dose is calculated and based on the patient's body surface area (BSA).[1] The Health Canada dosing schedules are noted below.

Patient's weight greater than or equal to 45 kg:[1]

- Induction cycle 1

  Days 1-28: 28 mcg/day
  Days 29-42: 14-day treatment free interval

- Consolidation Cycles 2-4

  Days 1-28: 28 mcg/day
  Days 29-42: 14-day treatment-free interval

Patients weight less than 45 kg (BSA-based dose):[1]

- Induction Cycle 1

  Days 1-28: 15 mcg/m^2/day (not to exceed 28 mcg/day)
  Days 29-42: 14-day treatment-free interval

- Consolidation Cycles 2-4

Days 1-28: 15 mcg/m^2/day (not to exceed 28 mcg/day)
Days 29-42: 14-day treatment-free interval

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The systematic review included two studies with adult patients, which were non-randomized, single-arm, phase II trials (the MT103-203 [BLAST] and MT103-202 trials). One additional unpublished observational study (the Neuf study), which included both adult and pediatric patients, was provided by the sponsor and was included in the systematic review of the evidence. Results for all three studies are summarized in Table 1, and study details are outlined below:

BLAST trial

BLAST was an international, open-label, single-arm, multicentre, phase II study of blinatumomab for adult patients with MRD+ BCP-ALL. Eligible patients were ≥ 18 years of age, in CR defined as less than 5% blasts in the bone marrow after a minimum of three intensive chemotherapy blocks, who had an Eastern Oncology Group Performance Status (ECOG PS) of 0 or 1, and MRD at a level of ≥ 10^{-3} (i.e., molecular failure or molecular relapse) using an assay with a minimum sensitivity of 10^{-4}. Patients with Ph- or Ph-positive (Ph+) disease were included. Patients with prior hematopoietic stem cell transplant (HSCT) were excluded. Patients who met the eligibility criteria were treated with blinatumomab administered through IV infusion at a dose of 15 mcg/m^2/day for up to four cycles as described under section *6.3.2.1 Detailed Trial Characteristics* in the *c) Intervention* section. Patients could undergo allogeneic HSCT any time after cycle 1.[2]

The primary endpoint of the study was complete MRD response rate, defined as the proportion of patients who achieved a MRD response (a complete MRD response or detectable MRD < 10^{-4}) after one cycle of treatment with blinatumomab. The key secondary endpoint was defined as the hematological relapse-free survival (RFS) rate at 18 months following initiation of blinatumomab. Other secondary endpoints included overall survival (OS), duration of complete MRD response from the time of onset of MRD negativity until relapse or confirmation of MRD positive status, and time to hematologic relapse (TTHR) from the time of blinatumomab initiation to hematologic or extramedullary relapse.[2,3] Analysis populations varied for each endpoint, for example, MRD response rate (primary endpoint) was assessed among all patients with a MRD assay result and MRD sensitivity of at least 10^{-4} leaving a total of 113 patients evaluable. The key secondary endpoint (RFS) and TTHR were analyzed in patients with hematological CR and Ph- disease, which resulted in a total sample size of 110 patients; OS was assessed in the Full Analysis Set (FAS) including 116 patients (FAS was used at the time of final analysis; and was analyzed with the secondary analysis population at the time of the secondary analysis with 110 patients); and duration of MRD response was assessed among MRD responders in CR with Ph- disease resulting in a total sample size of 84 patients.[2,4,5] Health-related quality of life (HRQoL) was measured using the EORTC-QLQ-C30 questionnaire, which scores HRQoL on 15 scales: global health status (GHS)/quality of life (QoL), five functional scales, three symptom scales, and six single items assessing additional symptoms commonly reported by cancer patients; and with the European Quality of Life 5-Dimensions, 3-Level (EQ-5D-3L) questionnaire, which captures the health state index on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the overall health rating using a visual analogue scale (VAS).[6] Safety and adverse events (AEs) were monitored regularly throughout the study until 30 days after the last infusion of blinatumomab and included all patients who received at least one dose of the assigned treatment.[2]

Study Population

A total of 116 patients were included in the BLAST trial and received at least one dose of blinatumomab. The majority of patients were male (68 out of 116; 59%) and white (102 out of 116; 88%). The median age was 45.0 years (range = 18.0 to 76.0), with 13% (15 out of 116) of patients being in the 65 years of age or older group. Overall, 65% of patients were in first CR (CR1), and 35% were in second CR (CR2) or third CR (CR3).[3] A total of 106 (92%) patients were enrolled with MRD ≥ 10^{-3}; five (4%) patients were Ph+, and five (4%) patients had a t(4;11) translocation/MLL-AF4 fusion gene. Most patients were either standard risk (53%) based on local/national standards or high risk (31%). The median time from last anti-leukemic treatment to initiation of blinatumomab was 2.0

months, ranging from 0 to 55 months. A total of 44 (37.9%) patients had the German Multicentre Study Group on Adult ALL (GMALL) treatment protocol as a prior therapy.[3]

Efficacy

Complete MRD response rate was assessed for statistical significance as of the primary analysis data cut-off date (February 21st, 2014); the key secondary endpoint of RFS was assessed at the secondary analysis data cut-off date (August 5th, 2015); and the final analysis for evaluation of OS was conducted as of the final analysis (5-year follow-up) data cut-off date (January 7th, 2019).

- **Complete MRD response rate:** This outcome was achieved in 87 out of 113 patients in the primary efficacy data set (MRD response rate = 77%; 95% confidence interval [CI], 68 to 84) within one cycle of treatment. The complete MRD response rate achieved with blinatumomab was considered to be clinically meaningful and statistically significant, as the lower limit of the 95% CI exceeded the pre-specified null hypothesis threshold of 44%.[5]
- **RFS:** The median duration of follow-up at the time of the secondary analysis was 29.9 months. The median Kaplan-Meier (K-M) estimate for RFS at 18 months with censoring for HSCT or post-blinatumomab therapy was 54% (95% CI, 33 to 70), which exceeded the prespecified boundary of 28%, thereby meeting the key secondary endpoint.[2] At the time of the final analysis, median RFS was [redacted] without censoring patients at the time of HSCT or post-blinatumomab therapy, whereas median RFS was [redacted] with censoring patients at the time of HSCT or post-blinatumomab therapy.[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*
- **OS:** At the time of the final analysis, the median OS was [redacted] without censoring patients for HSCT or post-blinatumomab therapy, whereas it was [redacted] with censoring patients for subsequent HSCT or post-blinatumomab therapy.[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*
- **Duration of MRD response:** At the time of the final analysis, the median duration of MRD response was 17.9 months (95% CI, 13.3 to 23.2) without censoring patients for HSCT or post-blinatumomab therapy, and 22.9 months (95% CI, 8.1 to NE) with censoring patients for HSCT or post-blinatumomab therapy.[4]
- **TTHR:** At the time of the final analysis, the median TTHR without censoring patients for HSCT or post-blinatumomab therapy was 27.3 months (95% CI, 7.1 to NE); and with censoring for HSCT or post-blinatumomab therapy, the median TTHR was NE (95% CI, 24.6 to NE).[4]

HRQoL

As patients were treated with one to four cycles of treatment before entering efficacy follow-up, there was variation in available data at various timepoints from baseline for HRQoL. The mean change from baseline to end of the core study (i.e. 30 days after the end of the last infusion) was minimal for GHS, physical functioning, role functioning, emotional functioning, and cognitive functioning scales, as well as single-item symptom scales (fatigue, nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). There was an improvement of 14.9 points in social functioning, which was larger than the pre-specified minimal clinically important difference (MCID) of 10 points.[5,6] The EQ-5D results were presented descriptively (unweighted and were not transformed into summary scores) and 14 patients or less (≤ 12%) completed the EQ-5D at the first follow-up visit and beyond, and thus interpretation of clinically relevant changes in patient HRQoL on any of the EQ-5D domains is limited.[4]

MT103-202

MT103-202 was an exploratory, proof-of-concept, open-label, multicentre, single-arm, phase II study to investigate the efficacy of blinatumomab in adult patients with MRD+, BCP-ALL.[7] Eligibility criteria included age greater than of equal to 18 years with a MRD

level ≥ 10^{-4} or breakpoint cluster region/c-Abelson (BCR/ABL) and/or t(4;11) translocation at any detection level, and in hematologic CR with molecular failure or relapse.[3] Patients received blinatumomab as continuous IV infusion at a dose of 15 mcg/m^2/24 hours over four weeks, followed by a treatment-free period of two weeks. One treatment cycle was six weeks. Patients who had an allogeneic donor were able to have HSCT at any time after the first cycle of blinatumomab.[8] Responders (i.e. those who achieved MRD negativity) could receive three additional cycles of blinatumomab as consolidation therapy, up to a maximum of 10 cycles. Patients who showed neither MRD progression nor response received up to seven cycles of treatment.[3] A dose increase could be considered to 30 mcg/m^2 by the Data Review Committee (DRC) if there was evidence of insufficient activity.[9]

The primary endpoint was MRD response rate, which was defined as the incidence of MRD negativity within four cycles of treatment with blinatumomab. Secondary endpoints included RFS, time to MRD progression, and duration of MRD response. HRQoL was not collected or evaluated in this study. Safety data was monitored regularly throughout the study.[7]

Study Population

In the MT103-202 trial, a total of 21 patients were enrolled and treated with blinatumomab. A higher proportion of patients were female (n = 12; 57%) compared to the BLAST trial (n = 48; 41%). The median age was 47 years, comparable to the BLAST trial, ranging from 20 to 77 years.[2,8] A higher proportion of patients in MT103-202 were 65 years of age or older (n = 6; 29%) compared to the BLAST trial (n = 15; 13%).[2,3] All patients in MT103-202 were of white race.[3] Almost all patients in MT103-202 were in CR1 (n = 19; 95%), which was higher compared to the BLAST trial (65%).[2,3] There was a smaller proportion of patients that had a baseline MRD level ≥ 10^{-3} (n = 16; 76%) in the MT103-202 trial compared to the BLAST trial. A total of five (24%) patients were Ph+, which was a higher proportion than in the BLAST trial (4%).[2,8] There were two (10%) patients that had MLL-AF4 in MT103-202, which was higher than in the BLAST trial (4%).[3,8]

Efficacy

The data cut-off date for the primary analysis for the primary endpoint was January 14th, 2010. The data cut-off date for the long-term follow-up analysis for secondary endpoints was November 3rd, 2014.

- **MRD response rate within the first four cycles**: MRD response rate within the first four cycles was 80% (16 out of 20 evaluable patients; 95% CI, 56.3 to 94.3), which met the pre-specified primary endpoint for statistical significance. All patients had responded after cycle 1.[3]
- **RFS:** After a median follow-up of 50.8 months (>4 years), the median RFS had not been reached (95% CI, 12.4 to NE).[3,10]
- **MRD progression:** A total of 7 (35%) patients had MRD progression, and the median time to MRD progression was 7.2 months (95% CI, 3.3 to NE).[3]
- **Duration of MRD response:** The median duration of MRD response was 13.0 month (95% CI, 2.8 to NE) among patients who had an MRD response (n = 16).[3]

Pooled Safety Data for BLAST and MT103-202

The safety data presented is based on pooled data (N = 137) from all patients who received any infusion of blinatumomab in the BLAST (n = 116) or MT103-202 trials (n = 21). Safety data are presented as of the key secondary analysis (August 5th, 2020) in the BLAST trial, as safety data were not collected during the follow-up period. Safety data in MT103-202 are presented as of the primary analysis data (January 14th, 2010).[11]

All patients experienced an any-grade AE, of which 97.1% (n = 133) were considered treatment-related and a total of 88 (64.2%) of patients experienced grade ≥ 3 AEs. The most common any-grade AEs were pyrexia (90.5%; n = 124), headache (39.4%; n = 54), and tremor (29.2%; n = 40).[5] The most common grade ≥ 3 AEs included neutropenia (13.1%; n = 18), leukopenia (7.3%; n = 10), lymphopenia (6.6%; n = 9), pyrexia (6.6%; n = 9), increased alanine aminotransferase (ALT) (5.1%; n = 7), and thrombocytopenia (4.4%; n = 6).[7]

Serious adverse events (SAEs) occurred in 83 (60.6%) patients. SAEs included pyrexia (12.4%; n = 17) and tremor (5.8%; n = 8).[11] A total of 23 (16.6%) patients discontinued treatment permanently with blinatumomab due to AEs.[5] The most frequently reported AEs

leading to treatment discontinuation included nervous system disorders (9.5%; n = 13): tremors (3.6%; n = 5), seizures (2.9%; n = 4), encephalopathy (2.2%; n = 3), and aphasia (2.2%; n = 3).[3,7] A total of two (1.5%) fatal AEs occurred.[5]

Neuf Study

The Neuf study was a retrospective, observational, cohort study of adult and pediatric patients with BCP-ALL who received blinatumomab through expanded access programs in Europe and Russia between January 1st, 2014 and June 30th, 2017. Patients were eligible if their medical charts were available for data extraction; and adult and pediatric patients had not received blinatumomab through another expanded access program for patients with relapsed/refractory (R/R) BCP-ALL called RIALTO. The Neuf study included patients with MRD+ and R/R disease, as well as Ph+ and Ph- disease. For the purposes of this CADTH report, only description of the study and results as relevant to the indication under review (MRD+, Ph-, BCP-ALL) are reported in this CGR.[5]

The primary endpoint was to evaluate clinical and treatment characteristics. Relevant secondary endpoints included MRD response rate defined as MRD ≤ 10^{-4} in the first two cycles of blinatumomab (additionally reported for the first cycle in this report for consistency/comparability with the MRD response rate evaluations of the phase II trials), disease-free survival (DFS) (DFS; considered equivalent in definition to RFS of the phase II trials), and OS.[5] Safety and HRQoL data were not collected or evaluated in this study.

Study Population

Adults: A total of 83 adults were included. [redacted][12] [redacted][2,8,12] [redacted][2,3,12] [redacted][12]

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Pediatric: A total of 39 pediatric patients were included. [redacted][12]

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Effectiveness

The end of the study period for the Neuf study was December 31st, 2017.[13]

- **MRD response within the first cycle:** [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

- **DFS** [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*
- **OS:** [redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Table 1: Highlights of Key Outcomes

	BLAST trial	MT103-202	Neuf Study	
	Blinatumomab (N=116)	Blinatumomab (N=21)	Blintatumomab Adult (N=83)	Blinatumomab Pediatric (N=39)
Primary Outcome				
Complete MRD response rate (number of evaluable patients)	113	20	[redacted]	[redacted]
Complete MRD response rate; % (95% CI)	77 (68, 84)[a]	80 (56.3, 94.3)[d]	[redacted]	[redacted]
Secondary Outcomes				
RFS (number of evaluable patients)†	110	20	[redacted][g]	[redacted]
RFS at 18 months; % (95% CI)	54 (33, 70)[b]	N/A	N/A	N/A
RFS; median months (95% CI)	[redacted][c]	NR (12.4, NE)[e]	[redacted]	[redacted]
OS (number of evaluable patients)	116	N/A	[redacted][g]	[redacted][g]
OS; median months (95% CI)	[redacted][c]	N/A	[redacted]	[redacted]
Duration of MRD response (number of evaluable patients)	84	16	N/A	N/A
Duration of MRD response; months (95% CI)	17.9 (13.3, 23.2)[c]	13.0 (2.8, NE)	N/A	N/A
TTHR (number of evaluable patients)	110	N/A	N/A	N/A
TTHR, median months (95% CI)	NE (24.6, NE)[c]	N/A	N/A	N/A
HrQoL	**Blinatumomab (N=74)**			
Change in GHS from baseline to end of core study; mean (SE)	3.9 (2.4)	N/A	N/A	N/A
Harms Outcome, n (%)	**Pooled (BLAST & MT103-202) Group (N=137)[f]**			
AE (any grade)	137 (100.0)		N/A	N/A
TRAE (any grade)	133 (97.1)		N/A	N/A
Grade ≥3 AE	88 (64.2)		N/A	N/A
TRAE (Grade ≥3)	73 (53.3)		N/A	N/A
WDAE	23 (16.6)		N/A	N/A
Deaths	2 (1.5)		N/A	N/A

[a]Data cut-off date for primary outcome assessment: February 21st, 2014 (met pre-specified statistical significance threshold)

[b]Data cut-off date for key secondary outcome assessment: August 5th, 2015 (met pre-specified statistical significance threshold)

[c]Data cut-off date for the final analysis: January 7th, 2019

[d]Data cut-off date for primary analysis: January 14th, 2010 (met pre-specified statistical significance threshold)

[e]Data cut-off date for long-term follow-up: November 3rd, 2014

[f]Data cut-off date for BLAST as of the secondary analysis (August 5th, 2014) and primary analysis of MT103-202 (January 14th, 2010)

[g]Patients that were excluded from the full analysis populations was due to missing data on dates.

† In MT103-202, TTHR was considered equivalent in definition to RFS in the BLAST trial; in the Neuf study DFS was considered equivalent in definition to RFS in the BLAST trial.

Abbreviations: AE = adverse event; CI = confidence interval; GHS = global health score; HRQoL = health-related quality of life; MRD = minimal residual disease; N/A = not applicable; NE = not estimable; OS = overall survival; RFS = relapse-free survival; SE = standard error; TRAE = treatment-related adverse event; TTHR = time to hematological relapse; WDAE = withdrawal due to adverse event

Sources: Amgen Clinical Summary, 2020;[5] Amgen BLAST Clinical Study Report, 2019;[4] Clinicaltrials.gov, 2010;[6] European Public Assessment Report (EPAR), 2018;[3] Gokbuget et al., 2017;[10] Health Canada Module 2.7.4., 2019[11]

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Limitations:

- Study design
    - Lack of comparative data: Both the BLAST trial and MT103-202 were single-arm studies, and Neuf was an observational study. Direct comparison of efficacy, safety, and HRQoL of blinatumomab with standard treatment was not conducted, and therefore firm conclusions on the magnitude of the clinical benefit cannot be drawn. An indirect treatment comparison (ITC) using PS analysis was submitted by the sponsor to compare blinatumomab with a historical comparator group, which provided some evidence of clinical benefit of blinatumomab compared to a historical comparator cohort; however, due to limitations of the historical comparator, uncertainty in the magnitude of the benefit remains.
    - Open-label study design (BLAST and MT103-202): the results of the trials are subject to a number of biases including patient selection bias (investigators may have selected healthier patients and those that were likely to comply with treatment), performance bias (patients were aware of treatment and may have reported more favorable responses to HRQoL questionnaires), reporting bias (investigators may have assessed AEs at lower grade or as unrelated to study drug and/or patients may have overreported specific AEs believe to be related to study drug), and detection bias (confirmation of relapse by hematologic assessment may have been delayed if clinical symptoms were present). These biases may have contributed to uncertainty in the magnitude and direction of the treatment effect by overestimation of efficacy and potentially may have overestimated or underestimated the reported safety of blinatumomab.
    - Observational, retrospective study design using data from medical records (Neuf study): Data was collected from medical records kept as per routine clinical practice for the documentation and decision-making for a patient's care, and thus the completeness (and/or clarity), reliability (i.e. consistency of assessments), validity (i.e. accuracy of data capture), and quality (no quality control or data audits) are uncertain. Given the design was retrospective, any unmeasured data on important covariates or prognostic factors cannot be ascertained. There also may be information bias present, as there may be detailed records of more complicated or severe outcomes. Any patients who died during the time period of retrospective data collection could not consent for their data to be accessed for the purposes of the Neuf study, and as such those included in the study may have had a longer survival time indicative of selection bias. Since the Neuf study included patients who accessed blinatumomab via expanded access, which started in 2015, blinatumomab was likely received in earlier stages of development and patients may have had more severe disease and less treatment options. These limitations of the study design contribute to uncertainty in the clinical benefit reported from the study as the direction of confounding cannot be ascertained.
- Patient population
    - There is a lack of efficacy and safety data to specifically address the use of blinatumomab in pediatric patients with MRD+, Ph-, BCP-ALL who are in CR, which is included in the patient population under review. Data on effectiveness in pediatric populations primarily relies on one observational study (the Neuf study), which is supported by MRD response rates in R/R ALL patients. The safety data is primarily available from clinical trials in pediatric patients with R/R BCP-ALL, and there is a lack of safety data for blinatumomab specific to MRD+, Ph-, BCP-ALL pediatric patients. Refer to section 8 for more details.
- Statistical analyses and assessment of outcomes
    - Selection of MRD response rate as a primary endpoint: There is limited evidence to suggest MRD response rate is a surrogate endpoint for established endpoints such as OS, and event-free survival (EFS) in patients with ALL. While MRD positivity at the end of induction therapy is a prognostic indicator for the risk of relapse, whether the

introduction of therapies to induce MRD negativity translates directly into clinical benefit (i.e. correlation with established endpoints) is yet to be established.

- Analysis sets: The FAS, which would be considered the intention-to-treat (ITT) population, was not used uniformly as the primary dataset for evaluation of all outcomes, and instead, subsets of the population were selected for specific outcomes. This may have biased the results by overestimating the magnitude of efficacy outcomes. For example, for the primary analysis, patients with Ph+ disease were included, and patients with no MRD assessment or patients tested with a different MRD assay sensitivity were excluded. While the number of patients excluded based on the MRD criterion were small (n=3), a more conservative approach would have been to include these patients and consider them non-responders to provide an estimate that would represent the general population, especially given the numerous limitations of the study design (open-label, single-arm). In addition, Ph+ patients were not included in the patient population used to analyze key secondary outcomes such as RFS (and, thus by exclusion RFS may have been inflated). While patients with Ph+ disease may be considered to respond similarly to Ph- patients in terms of MRD response, these patients generally have a poorer prognosis (i.e., worse RFS and OS).[14] These subtle differences in patient populations create inconsistencies in interpretation of the evidence. However, since generally small numbers of patients were excluded, the impact on outcomes is considered minimal.
- Definition of RFS:
  - RFS was calculated from the time of blinatumomab initiation until the date of documented hematological relapse, progressive disease (PD), extramedullary relapse, or death due to any cause. Typically, RFS is calculated from time of CR or CR with partial hematological recovery is detected.[3,15] The time from last anti-leukemic treatment (i.e. achievement of CR) varied, ranging from 1 month to 4.5 years with a median of 2.0 months.[3] Patients with longer intervals between time to CR to first dose of blinatumomab may have biased RFS and OS in favour of blinatumomab as duration of CR1 in this patient population is a favourable prognostic marker.[16]
  - Additionally, the primary analysis of RFS included a censoring rule to censor at the time of HSCT or initiation of post-blinatumomab therapy prior to relapse, and supportive analyses that did not include this in the censoring rules were provided and were generally consistent. Patients who were censored at the time of HSCT or initiation of post-blinatumomab therapy prior to relapse were assumed to have similar risk of relapse as those who were not censored; this may bias the results due to the high proportion of patients undergoing HSCT. Specifically, this approach may inflate the magnitude of the benefit, as HSCT is associated with a mortality risk. Since blinatumomab is a therapy that may be used as a bridge to transplant, this mortality risk should be accounted for in the RFS estimate. Patients who could not tolerate or discontinued blinatumomab prior to relapse for any reason and started another therapy should also have been accounted for in the primary analysis of RFS as a more conservative approach.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

One patient input on blinatumomab for children with ALL was provided as a joint submission from the following groups: Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Leukemia and Lymphoma Society of Canada (LLSC), Ontario Parents Advocating for Children with Cancer (OPACC), and Helena's Hope. No input was received from a patient group that was focused on the use of blinatumomab for the adult population.

Respondents reported choosing treatment with blinatumomab as it was the *"only option"*, or that the only alternative was *"more of the same chemo that didn't work the first time."* Respondents commented on the negative experiences they had with chemotherapy and their desire for alterative treatments. Respondents described their experiences with blinatumomab positively; side effects of treatment with blinatumomab were described as minor or manageable, and infrequent compared to chemotherapy. The most commonly reported side effects were fever, low platelet count, low red blood cell count, low white blood cell (WBC) count (n = 3 for all). Respondents also commented on the superior QoL blinatumomab was able to allow for patients compared to traditional frontline treatment. Respondents indicated blinatumomab treatment as being much less challenging overall compared to other treatments for ALL and reported an overall positive experience with blinatumomab.

Overall, patients value treatments with fewer side effects, better disease management and improved QoL. In addition, patients prefer having the option of treatments more targeted to the disease, without the risk of long-term impairment, and which are recommended to them by their physician.

PAG Input

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

Clinical factors:

- Eligibility for patients with central nervous system (CNS) involvement
- Re-treatment following relapse post-allogeneic stem cell transplant (alloSCT)

Economic factors:

- Significant wastage due to insufficient stabilizer available
- Different dosing schedule than relapsed or refractory B-cell precursor ALL

Registered Clinician Input

A total of nine registered clinician inputs were provided: one group input on behalf of the Pediatric Oncology Group of Ontario (POGO), and eight individual clinician input by oncologists from Ontario (four clinicians including one pediatric oncologist), Alberta (two clinicians), British Columbia (one clinician), and Nova Scotia (one clinician).

No specific treatments aimed at patients with MRD+, B-cell ALL were identified by the clinicians providing input. However, clinicians from POGO did state that patients who remain MRD+ after three blocks of chemotherapy face a poor prognosis; these patients require intensification therapy to achieve a positive outcome. Further, therapy for B-cell ALL was stated to be based on the risk status of the patient, which is determined by MRD testing. The BLAST trial inclusion and exclusion criteria were considered by the clinicians to be reasonable and applicable to clinical practice; the trial population were stated to represent a large and clinically significant patient population with unmet need. MRD status (i.e. MRD conversion rate) was stated to be a suitable endpoint by clinicians; however, it was also acknowledged that modern MRD testing is able to detect MRD at lower levels of MRD at 0.01%, which may be similar to higher levels of 0.1%. Clinicians also strongly urged for the reimbursement of blinatumomab for pediatric patients. Clinicians acknowledged that a trial for pediatric patients is recommended, but that currently available evidence in adults may be extrapolated to suggest efficacy among pediatric patients, and evidence in the R/R setting is supportive of the indication under review.

Clinicians agreed that blinatumomab may be used for patients with CNS involvement or who relapse with CNS involvement; however, blinatumomab should not be used to treat patients with active CNS disease. Clinicians also agreed that blinatumomab may be used for patients with Ph+ ALL. Clinicians did not agree that blinatumomab should be used for patients with MRD-negative (MRD-) status; further evidence would be needed to fully support the use of blinatumomab among this population of patients. Clinicians were supportive of using blinatumomab along with tyrosine kinase inhibitor (TKI) therapy for patients who are Ph+, either in sequence or in combination; these two treatments were stated to be complementary in this setting. TKI therapies and blinatumomab were stated to have different mechanisms of action and non-overlapping toxicity profiles. Pediatric oncologists also urged for the use of this treatment combination among pediatric patients. Regarding patients with prevalent MRD+ status in hematological CR or those

under observation, a time frame of within two weeks after determining MRD positivity was suggested by most clinicians to be a reasonable time to initiate treatment of blinatumomab; other clinicians suggested timeframes of within three or four months to initiate treatment with blinatumomab. However, all clinicians agreed that patients face a high relapse rate and that starting treatment sooner rather than later is preferred. Contraindications to blinatumomab were stated to include CD19 negativity, severe biochemical abnormalities, uncontrolled serious infections, pregnancy, severe neurological complications or other contraindications as outlined by the manufacturer.

In terms of sequencing, clinicians suggested that blinatumomab would be provided to patients after initial induction and consolidation therapy, which would replace the cytotoxic chemotherapy that patients currently receive. Upon progression of blinatumomab, chimeric antigen receptor T-cell (CAR-T) cell therapy, inotuzumab, chemotherapy and allogenic HSCT were suggested as potential treatment options. Specific treatment suggestions were provided by clinicians based on patient's CD19, CD22, or Ph statuses. Regarding re-treatment with blinatumomab for MRD+ ALL patients post allogenic HSCT, clinicians agreed that each patient may be considered based on their clinical conditions, immunophenotype status and previous therapies. Uncertainty was expressed regarding an appropriate timeframe for re-treatment with blinatumomab. Some clinicians agreed that a predetermined interval may not be necessary for re-treatment with blinatumomab based on its mechanism of action; however, other clinicians stated that re-treatment may be considered only if it was six months post original treatment, and if no other treatment options were available for the patient.

Companion diagnostic testing was stated to be required prior to administration of blinatumomab to determine the MRD status. Clinicians acknowledged that there is an inconsistency in availability of testing across Canada, and that there is a need for standardized and centralized testing. The clinicians providing indicated that experience with testing should be intermediate or advanced in most institutions in their respective jurisdictions, and that many healthcare staff were already trained as blinatumomab has been used for relapsed disease. However, they acknowledged that smaller institutions may face issues with lack of access to resources and lack of staff training.

Summary of Supplemental Questions

In the absence of a trial directly comparing blinatumomab with a relevant comparator, the sponsor conducted an ITC using a propensity score (PS) analysis to compare the efficacy of blinatumomab demonstrated in the BLAST trial (N = 116) to no blinatumomab in a historical comparator study (Study 148; N = 287). The historical comparator study was a retrospective, non-interventional cohort study, which included outcome data from patients from selected study centres across Europe that also contributed to the BLAST study data.[5] The results of this analysis were used to inform the sponsor's pharmacoeconomic evaluation. The sponsor-submitted ITC was critically appraised and is detailed in section 7. A summary of the ITC results is provided below.

To align the study populations, inclusion and exclusion criteria were applied; and key criteria included age (≥ 18 years), MRD level of ≥ 10^{-3}, and being in first hematologic CR1. A total of 73 patients from the BLAST trial and 182 patients from the comparator study (historical cohort) were included in the PS analysis. To address remaining differences in prognostic factors, candidate covariates were included in a logistic regression model to identify covariates to be retained in the PS model, if the threshold was met (P < 0.3). The final PS model included age, time from primary diagnosis to MRD baseline data, baseline MRD level, prior GMALL chemotherapy, and an interaction term between prior GMALL chemotherapy and time from diagnosis to baseline MRD data. Inverse probability of treatment weighting (IPTW) was used for making PS adjustments and for estimation of treatment effects, and two methods were explored: the average treatment effect (ATE) and average treatment effect of the treated (ATT).[5] The ATT approach was considered the most appropriate approach by the sponsor and presented as the primary analysis, however of note, in the primary publication of this ITC and in the European Public Assessment Report (EPAR) and FDA reports, the ATE approach was presented.[3,5,7,17]

Based on the ATT approach, patients treated with blinatumomab had a [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the*

Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.) A number of limitations were identified including the time period when patients were initially diagnosed in the historical comparator (32.4% were diagnosed before 2004), and thus patients in the historical comparator may have had worse outcomes as they did not benefit from advances in treatment and improvements in diagnosing ALL over time as patients in the BLAST trial did.[7] The retrospective nature of the historical comparator study raises concerns about the reliability, validity, quality, and completeness of databases from which data on covariates, outcomes, and exposures were collected in the study compared to data from the BLAST trial; and there may have been unmeasured confounders such as ECOG PS, that may have influenced outcomes. The clinical review team concluded the there was a clinical benefit of treating patients with blinatumomab compared to no blinatumomab, however the limitations introduced uncertainty in the magnitude of the treatment effect.

Comparison with Other Literature

Evidence of blinatumomab effectiveness in pediatric patients with MRD+, Ph-, BCP-ALL is limited to one observational study (the Neuf study), and there is no data on safety in this patient population. A number of studies were identified by the Methods team, the CGP, and the sponsor which have been conducted in the R/R setting that provide supportive evidence of the effectiveness and safety of blinatumomab in pediatric patients. A summary and brief critical appraisal of these relevant studies are provided in section 8.

1.2.3 Factors Related to Generalizability of the Evidence

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

Table 2: Assessment of Generalizability of Evidence for Blinatumomab in MRD+, Ph-, BCP-ALL

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	CNS involvement	Patients with a history of relevant CNS pathology or current relevant CNS pathology (e.g., seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder) were excluded from the BLAST trial.	Can the evidence on blinatumomab be applied to patients with a history of CNS involvement or who relapse with CNS involvement?	Please see Table 3 CADTH CGP Response to PAG Implementation Questions.
	MRD status unknown or negative (i.e. MRD-)	Patients with an unknown MRD status or negative MRD status were not included in any of the trials or in the observational study.	Can the evidence on blinatumomab in patients with MRD+ BCP-ALL be applied to patients who are MRD- or MRD status is unknown (in particular, patients that may have specific high-risk features that would be treated with transplant)?	Please see Table 3 CADTH CGP Response to PAG Implementation Questions. .

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Baseline MRD level</td><td>The subgroup analyses were generally consistent with the primary analysis results for MRD response rate and RFS, however, due to small sample sizes and the exploratory nature of these analyses, results should be interpreted with caution.

Subgroup analyses of MRD response rate:<table><tr><td>Baseline MRD level</td><td>Prim EP FAS (N=113) n/N</td><td>Complete MRD response rate, % (95% CI)</td></tr><tr><td>$\geq 10^{-1} < 1$</td><td>6/9</td><td>67 (30, 93)</td></tr><tr><td>$\geq 10^{-2} < 10^{-1}$</td><td>35/44</td><td>80 (65, 90)</td></tr><tr><td>$\geq 10^{-3} < 10^{-2}$</td><td>40/51</td><td>78 (65, 89)</td></tr><tr><td>$< 10^{-3}$</td><td>3/3</td><td>100 (29, 100)</td></tr></table>Source: Amgen Clinical Summary, 2020[5]
Subgroup analyses of RFS:<table><tr><td>Baseline MRD level</td><td>Prim EP FAS (N=110) n/N</td><td>Median months</td><td>HR (95% CI)</td></tr><tr><td>$\geq 10^{-2} < 1$</td><td>37/51</td><td>18.9</td><td>1.33 (0.84, 2.13)</td></tr><tr><td>$< 10^{-2}$</td><td>34/57</td><td>23.5</td><td>Ref</td></tr></table>Source: Amgen BLAST Clinical Study Report, 2019[4]</td><td>Are there any subgroups of patients based on baseline MRD level that are expected to derive the greatest benefit from blinatumomab? Should treatment be limited to these patients?</td><td>Please see Table 3 CADTH CGP Response to PAG Implementation Questions.</td></tr>
<tr><td></td><td>Ph+</td><td>While Ph+ patients were not excluded from the BLAST trial, only 5 (4.3%) enrolled.[2] The key secondary analysis for secondary endpoints (RFS, OS, etc.) excluded Ph+ patients, however the primary endpoint, MRD response rate, included Ph+ patients.</td><td>Can the results be applied to MRD+, Ph+, BCP-ALL patients?</td><td>Please see Table 3 CADTH CGP Response to PAG Implementation Questions.</td></tr>
<tr><td></td><td>Patients with incomplete blood count recovery</td><td>In the BLAST trial, patients were eligible if they were in CR with an ANC count of >1,000/mcL, which was consistent with NCCN guidelines, or a platelet count (>50,000/mcL), which was lower than that of NCCN guidelines (>100,000/mcL) to be considered CR. Per NCCN guidelines, 26.7% (n=31) of patients would be considered to have CR with incomplete blood count recovery.[3,14]</td><td>Can the results be applied to all patients with CR and incomplete hematologic recovery (i.e., if ANC is <1,000/mcL, platelets are <100,000/mcL per NCCN guidelines, or platelets <50,000/mcL per the BLAST trial)?</td><td>Yes; however, the CGP noted that the safety in this population is unknown. It is also important to note the cytopenias are a side effect of the drug which would require careful monitoring.</td></tr>
<tr><td>Intervention</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>Re-treatment with blinatumomab</td><td>Patients who experienced disease relapse were not retreated with blinatumomab in any of the clinical trials. In the BLAST trial, patients who had a complete MRD response and experienced MRD relapse 4 weeks post-discontinuation of last blinatumomab</td><td>Would patients who receive blinatumomab for MRD+ disease followed by alloSCT be eligible for repeat blinatumomab for relapsed disease? Or</td><td>For the pediatric patients, the CGP noted that re-treatment would be a possibility.

For the adult patients, the CGP noted that re-</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		infusion and 18 months after the start of first blinatumomab infusion, and who never underwent allogeneic HSCT could be retreated with blinatumomab.[2] Only 3 patients in the BLAST trial were retreated with blinatumomab following MRD relapse with an overall exposure of 0.29 patient-years.[18]	for MRD relapse (i.e. MRD positivity returns)?	treatment should not be allowed for these patients as this is a different population than what was studied in the trial.
Comparator	No comparator	In the absence of a direct comparator of blinatumomab versus standard care, an ITC with a historical comparator study was provided. The results of the ITC suggested blinatumomab compared to no blinatumomab in the historical comparator study resulted in improved RFS and OS.	Is the comparator used in the historical cohort (local chemotherapy protocols used in Europe) applicable in the Canadian setting?	The CGP noted that the historical comparator is most likely an appropriate comparator. The agents included in the historical comparator are used in Canada with different dosing schedules.
Outcomes	Appropriateness of primary outcome	The primary outcome was MRD response rate. There is no available literature to suggest that MRD response rate is correlated with validated clinical endpoints such as RFS and OS. However, the key secondary endpoint was RFS, which was controlled for multiplicity and was statistically significant. OS was an additional secondary endpoint.	Was the primary outcome appropriate to address clinical benefit or efficacy? Are the secondary outcomes supportive?	The CGP noted that the primary and secondary outcomes are appropriate to address clinical benefit for this population.
Setting	Countries participating in the trial	No Canadian sites or patients were included in any of the clinical trials or studies on blinatumomab included in this report.	Are there any known differences in the practice patterns between other participating countries and Canada (that might impact the clinical outcomes, or the resources used to achieve the outcomes)? Are the number of blinatumomab cycles used in the trial relevant in the Canadian setting?	The CGP noted that there are no substantial differences between participating countries and Canada. The CGP also noted that the use of HSCT for patients who are MRD+ or responding to therapy is similar to Canadian practice.

Abbreviations: - = negative; + = positive; ALL = acute lymphoblastic leukemia; ANC = absolute neutrophil count; BCP = B-cell precursor; CGP = clinical guidance panel; CI = confidence interval; CNS = central nervous system; CR = complete remission; HSCT = hematopoietic stem cell transplant; HR = hazard ratio; ITC = indirect treatment comparison; MRD = minimal residual disease; NCCN = National Comprehensive Cancer Network; Ph = Philadelphia chromosome; Prim EP FAS = Primary Endpoint Full Analysis Set; OS = overall survival; RFS = relapse-free survival; TKI = tyrosine kinase inhibitor

1.2.4 Interpretation

Burden of Illness and Need

Despite the use of aggressive induction and therapy intensification strategies, approximately one-third of patients with BCP-ALL in CR will have evidence of MRD.[19,20] The presence of MRD is widely considered as an independent predictor of poor outcomes. These patients are at a very high risk of relapse or progression despite the use of additional systemic chemotherapy.[19] The CGP noted that there is no current recognized standard of care for the treatment of patients with MRD+, BCP-ALL in Canada, and there is variability in the testing for MRD across provincial jurisdictions. Treatment options may include HSCT for generally fit patients, or observation. Results of meta-analyses in both adult and pediatric patients show that patients with MRD+ ALL have a more than doubled risk of hematologic relapse and death compared to those who are MRD-.[21] Blinatumomab has produced a higher MRD response rate than chemotherapy in adult and pediatric patients with R/R ALL and improved OS, suggesting that it may be non-cross-resistant to chemotherapy by engaging an effective target T cell immune response.[22,23] Health Canada has conditionally approved blinatumomab for the treatment of adults and pediatric patients with R/R, Ph-, BCP-ALL (NOC/c).[1] In the setting of MRD+ blood or bone marrow following standard chemotherapy, blinatumomab may be effective in producing molecular CR in those who remain MRD+ and are thus, at risk for subsequent relapse.

ALL is an uncommon disease in Canada, significantly hampering the ability to perform well-powered randomized controlled trials (RCTs) of new therapeutic approaches. Practitioners are reliant on phase II studies such as the BLAST trial to provide information on novel treatment strategies, especially in the setting of resistant ALL, where randomized comparisons are difficult or impractical to perform.

Effectiveness

Adults

The pilot study (MT103-202) of blinatumomab in MRD+ patients and the confirmatory phase II BLAST trial in a larger cohort study of patients with MRD+ ALL at a higher threshold (MRD level of 10^{-3} versus 10^{-4} in MT103-202) demonstrated a high molecular complete MRD response rate (i.e. MRD-) of 80% (16 out of 20 patients) in the MT103-202 trial, and 77% (87 out of 113 patients) in the BLAST trial.[5,8] In the BLAST trial, the median RFS with 5 years of follow-up was [redacted], and median RFS was longer by 19.3 months in patients who achieved a complete MRD response in any cycle compared to those who did not have a MRD response. Overall survival at the time of the final analysis after 5 years of follow-up was [redacted], which is considered clinically important for this life-threatening disease.[5] [5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* Censoring for allogeneic HSCT, the RFS and OS observed seem durable, although there is uncertainty in the estimates due to the small proportion of patients that did not receive HSCT (high censoring). A total of 90 (77.6%) patients in the BLAST trial received subsequent allogeneic HSCT, and of those, 49.1% achieved MRD negativity and were in hematologic CR prior to transplant, representing an effective bridge to transplant.[3] Durable MRD responses were seen in patients in first hematologic CR as well as those in CR2 or CR3, although subgroup analyses (not powered to detect statistical significance) suggested patients in CR2 or CR3 may have had shorter RFS compared to those in CR1. The results of the observational study, the Neuf study, [redacted][5] [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* No clinically significant detriment to QoL was observed, although this is limited in the absence of comparative data.

The sponsor also submitted an ITC comparing the efficacy of blinatumomab based on the BLAST trial with a historical comparator study, which found a [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* Although there is some uncertainty in the magnitude of benefit due to the limitations associated with

the historical comparator study, the ITC demonstrated there is a clinical benefit of treating patients with blinatumomab for MRD+, Ph-, BCP-ALL.

Pediatric

The Neuf study supports effectiveness of blinatumomab in pediatric patients with MRD+, Ph-, BCP-ALL [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* A small retrospective analysis of 16 pediatric patients by Keating et al., 2019, investigated the use of blinatumomab as a bridge to transplant for MRD+, BCP-ALL, and 93% achieved MRD- status and underwent HSCT, further supporting the effectiveness of blinatumomab in pediatric patients.[24]

Additional evidence from the R/R ALL, include the Children's Oncology Group (COG) trial AALL1121 (MT103-205), a phase I/II study conducted by COG and the I-BFM European childhood leukemia cooperative group, which enrolled 70 patients with R/R B-cell acute lymphoblastic leukemia (B-ALL). Among patients receiving the recommended dose of blinatumomab, 39% achieved CR and of those 52% achieved MRD negativity. When restricted to those with relapsed disease the CR rate was 48%.[23]

COG-AALL1331 randomized patients with high risk and intermediate risk (HR/IR) first relapse BCP-ALL between standard chemotherapy versus standard re-induction therapy but with two blocks of intensive chemotherapy replaced with two cycles of blinatumomab for post-induction therapy. In September 2019, the HR/IR randomization was closed early due to efficacy. Patients receiving the experimental arm including blinatumomab were found to have superior DFS and OS, higher rates of MRD negativity, and lower rates of toxicity compared to patients receiving standard therapy.[25]

Current MRD assessment (flow cytometry, quantitative polymerase chain reaction [qPCR]) is the most powerful predictor of outcome in pediatric ALL, and is routinely tested in clinical practice for pediatric patients.

Safety

Adults

Blinatumomab is given by continuous IV infusion over 4 weeks, in a 6-week cycle, due to its short half life. Overall, toxicities were manageable, with 76.7% of patients experiencing grade ≥ 3 AEs across the BLAST trial and MT103-202 trial. The most common AEs of any grade were fever, headache, tremor, chills, fatigue, nausea, and vomiting, and common grade ≥ 3 AEs included neutropenia and leukopenia. Neurologic toxicities were experienced by 71.5% of patients, and included headache, tremor, insomnia, aphasia, dizziness, confusion, encephalopathy and seizures. Serious neurological events were experienced by 22.6% of patients. The median time to first onset was two days, and the median duration of neurologic AEs was 10.0 days (95% CI, 6.0 to 15.0).[5,18] Most neurologic AEs were mild to moderate in severity and data from the BLAST study showed that neurologic events resolved in 97% of patients, and most patients who experienced a ≥ grade 3 neurological event resumed blinatumomab treatment after the event resolved.[5] A total of four patients experienced cytokine release syndrome (CRS), with two patients that experienced grade ≥ 3 CRS.[2] Appropriate expertise is required to manage neurotoxicity and monitor for the potential for CRS, and blinatumomab should be administered in an appropriate clinical setting to monitor for these side effects. Overall, blinatumomab is shown to have a manageable toxicity profile.

Pediatric

Though there is a lack of safety data with blinatumomab specific to MRD+, Ph-, BCP-ALL pediatric patients, the safety profile of blinatumomab in pediatric populations is well documented from a number of studies in the R/R BCP-ALL setting, which include hundreds of patients (see section 8 for more details). Specifically, data from a phase I/II trial in R/R BCP-ALL (MT103-205) which included 70 patients that received blinatumomab at the current recommended dose for pediatric patients, experienced AEs that were similar to the adult population and included fever, nausea, and headache. Anemia was also experienced by 41% of patients (any grade; 36% grade ≥3). Neurologic toxicities occurred in 24% of patients, and included tremor, dizziness, and drowsiness. CRS occurred in 11% of patients, of which 6% were grade ≥ 3, which reinforces the need for appropriate expertise and monitoring when administering blinatumomab. Six fatal AEs occurred, 3 of which were after HSCT, and 3 that included multiorgan failure, fungal infection, and thrombocytopenia.[23] Preliminary data available from the COG-ALL1331 trial (N = 208), indicated that grade ≥ 3 febrile neutropenia (44% vs. 4%), infections (41% vs. 10%), sepsis (14% vs. 1%), and mucositis (25% vs. 0%) occurred in a higher proportion of patients immediately after the second block of standard of care chemotherapy compared to the first cycle of blinatumomab. Any-grade CRS occurred in 22% of patients, seizures occurred in 4% of patients, and other neurotoxicities (e.g., tremor, cognitive disturbance, etc.) occurred in 14% of patients treated with blinatumomab.[25] The safety profile of blinatumomab in pediatric populations is generally consistent with the adult population and represents a manageable toxicity profile when administered in the appropriate clinical setting.

1.3 Conclusions

The CGP concluded that there is a net clinical benefit to the treatment of pediatric patients with blinatumomab who have achieved hematologic remission of ALL and are MRD+ following intensive induction and consolidation chemotherapy. This is based on the Neuf study, and on blinatumomab being a highly effective drug in the treatment on R/R BCP-ALL in the pediatric aged cohort. The COG trial AALL1121 (MT103-205), a phase I/II study conducted by COG and the I-BFM European childhood leukemia cooperative group enrolled 70 patients with relapsed/refractory B-ALL. Among patients receiving the recommended dose of blinatumomab, 39% achieved CR and of those 52% achieved MRD negativity.[23]

In making this conclusion, the CGP also considered the following:

- The cytokine effect and neurological toxicities need to be monitored while patients are receiving blinatumomab
- Though there is no data on the impact of blinatumomab on QoL in the pediatric setting, the side effect and safety profile of blinatumomab demonstrate that there may be no detriment to QoL
- The CGP noted that a randomized phase III trial would be needed to definitively answer the role of blinatumomab in the pediatric MRD+, BCP-ALL setting
- MRD testing is routinely performed for the pediatric patient population
- The CGP noted that there is a lack of efficacy and safety data to specifically address the use of blinatumomab in pediatric patients with MRD+, Ph-, BCP-ALL who are in CR, which is the patient population under review. Data on effectiveness in pediatric populations primarily relies on one observational study (the Neuf study), which is supported by MRD response rates in R/R ALL patients, and safety data is primarily from clinical trials in pediatric patients with R/R BCP-ALL. The CGP noted that the group conducting the study, COG group, is highly regulated in Canada and in the US and this adds considerable credibility the results.

The CGP concluded that there may be a net clinical benefit to the treatment of adult patients with blinatumomab who have achieved hematologic CR of BCP-ALL and are MRD+ following intensive induction and consolidation chemotherapy. This is based on two single arm phase II studies that showed a high complete MRD response rate and high RFS in eligible patients treated with blinatumomab. A significant number of patients were able to proceed to HSCT after achieving MRD negativity, which is associated with a better outcome than those who are MRD+. The toxicity of blinatumomab in this population was relatively mild in the included trials, and while approximately half of patients experienced neurologic toxicity, the incidence of AEs decreased in subsequent blinatumomab cycles and AEs were mostly reversible.

In making this conclusion, the CGP also considered the following:

- The conclusion is based on the pilot study (MT103-202) of blinatumomab in MRD+ patients and the confirmatory phase II BLAST trial in a larger cohort study of patients with MRD+ ALL at a higher threshold (MRD level of 10^{-3} versus 10^{-4} in MT103-202) which demonstrated a high complete MRD response rate (i.e. MRD negativity) of 80% (16 out of 20 patients) in the MT103-202 trial, and 77% (87 out of 113 patients) in the BLAST trial.[5,8] The median RFS with 5 years of follow-up was [redacted], in the BLAST trial. Overall survival at the time of the final analysis after 5 years of follow-up was [redacted], which is considered clinically important for this life-threatening disease.[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*
- A direct comparison of efficacy, safety, and HRQoL outcomes of blinatumomab with standard treatment was not conducted; and therefore, firm conclusions on the magnitude of the clinical benefit cannot be drawn. An ITC using PS analysis was submitted by the sponsor to compare blinatumomab with a historical comparator group, which provided some evidence of clinical benefit of blinatumomab compared to a historical comparator cohort. However, due to limitations of the historical comparator, uncertainty in the magnitude of the benefit remains. Hence, caution should be exercised in interpreting these

results. The CGP noted that historical comparators are not ideal and a randomized phase III trial would be needed to confirm the comparative effects of blinatumomab in the adult MRD+ Ph-, BCP-ALL setting.

- While no detriment to QoL was observed as reported by patients, the manageable safety profile of blinatumomab may suggest improved clinical outcomes and subsequently QoL

Table 3: CADTH CGP Response to PAG Implementation Questions

PAG Implementation Questions	CGP Response
Eligible Patient Population	
Can eligibility for blinatumomab be extended to patients with a history of CNS involvement or who relapse with CNS involvement?	Although patients with a history of, or current, relevant CNS pathology were excluded from the BLAST trial, it is possible that benefit may also be seen in this population. However, the CGP noted that existing CNS pathology has the potential to add to blinatumomab associated neurotoxicity.
Can eligibility for blinatumomab be extended to patients in CR whose MRD status is negative (ie., MRD-) or unknown? If so, which patients (all or those with specific features as high-risk features would be treated with transplant)?	There is no evidence to extrapolate the results from this trial to the MRD- or MRD unknown populations and these patients were not included in any of the trials or in the observational study.
What are the minimum number of blocks of intensive chemotherapy required prior to MRD determination and initiation of blinatumomab?	The minimum chemotherapy blocks should be as per the trial data. As per the BLAST trial, patients were required to be in CR after a minimum of 3 intense chemotherapy blocks, as such, the trial results are not generalizable to patients who received fewer than three intense chemotherapy blocks and there is no evidence to support this.
Are there any subgroups of patients based on baseline MRD level that are expected to derive the greatest benefit from blinatumomab? Should treatment be limited to these patients?	The CGP did not note any specific subgroups from the trial data that may derive the greatest benefit; however, the CGP noted that there may be subgroups for which data is not available.
How long after achieving CR should blinatumomab be initiated by?	The CGP noted that the drug should be implemented as soon as the patient is deemed MRD+ following at least 3 blocks of intensive chemotherapy as assessed by the treating physician.
Can eligibility for blinatumomab be extended to patients with Ph+ disease?	The CGP noted that patients with MRD+, Ph+ BCP-ALL disease should be able to receive blinatumomab; however, switching to a TKI such as ponatinib or dasatinib may also be considered for these patients.
Implementation Factors	
PAG is seeking guidance on the use of the weight-based dosing up to a flat-fixed dose (e.g. fixed dose for those ≥ 45 kg).	The CGP noted dosing as per the Health Canada Product Monograph should be followed. The guidance from Health Canada notes a fixed dose for patients weighing 45 kg or more and a weight-based dosing for patients weighing less than 45 kg.
PAG is seeking guidance on whether further blinatumomab treatment would be considered for patients who have not progressed after receiving four cycles of blinatumomab, but do not go on to receive alloSCT.	The CGP noted that there is no data to support using blinatumomab after four cycles of treatment.
Sequencing and Priority of Treatments	
PAG is seeking guidance on whether patients who receive blinatumomab for MRD+ disease followed by alloSCT would be eligible for repeat blinatumomab treatment for relapsed disease occurring post-alloSCT.	For pediatric patients, the CGP noted that re-treatment would be a possibility.

PAG Implementation Questions	CGP Response
If re-treatment is appropriate, what would be the appropriate timeframe from completion of blinatumomab in this setting and initiation in the relapsed/refractory setting?	For adult patients, the CGP noted that re-treatment should not be allowed for these patients as this is a different population than what was studied in the trial. In addition, the CGP noted that there is no data to support using blinatumomab as a maintenance therapy and further treatment should not be considered.
Companion Diagnostic Testing	
PAG is seeking clarity on the proportion of ALL patients who would be MRD+ and thus eligible for blinatumomab.	The CGP noted that the proportion of patients with ALL who achieve a first CR can range up to 91% as reported in the literature. Of these patients, approximately one-third would have MRD positivity, and would thus be eligible for blinatumomab. Additional patients in second remission who achieve CR with MRD+ disease would also be eligible.

Abbreviations: - = negative; + = positive; ALL = acute lymphoblastic leukemia; alloSCT = allogeneic stem cell transplant; CGP = Clinical Guidance Panel; CNS = central nervous system; CR = complete remission; MRD = minimal residual disease; PAG = Provincial Advisory Group; Ph = Philadelphia chromosome

2 Background Clinical Information

This section was prepared by the pCODR Hematology CGP for blinatumomab. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Acute lymphoblastic leukemia is a highly-aggressive hematological malignancy that presents with signs or symptoms of bone marrow failure (fatigue, dyspnea, bleeding, bruising or infection), organ infiltration (enlarged lymph nodes, mediastinum, liver and spleen) and systemic complaints (fevers, fatigue joint/bony pain and night sweats). Extramedullary disease can also be present in the CNS and as testicular disease. Patients typically present to hospital acutely ill with infection and neutropenia, bleeding and thrombocytopenia, and electrolyte disturbances related to tumour lysis syndrome. The majority of patients have peripheral blasts at presentation.[26,27] Diagnosis is confirmed by bone marrow histology, immunophenotyping, cytogenetics and occasionally molecular biology specialized techniques. Prognosis is influenced by a number of factors including patient age, the level of WBC count at diagnosis, immunophenotype (B-cell versus T-cell), specific chromosomal abnormalities detected by bone marrow cytogenetics or PCR evaluation.[28]

ALL is the most common cancer diagnosis in children and adolescents. The mortality rate from ALL is lowest in individuals diagnosed at an age younger than 15 years, and 90% of children below 15 years of age are cured when treated appropriately.[29] Mortality increases with age especially in patients age greater than 40 years. Intensity of treatment should be administered according to prognostic characteristics at diagnosis.[27]

Approximately one-third of patient with ALL will exhibit MRD despite hematologic CR.[19] Additionally, outcomes of allogeneic HSCT are inferior for patients with persistent MRD positivity, compared to those who are MRD-. MRD negativity has been shown in a meta-analysis to be associated with 10-year EFS of 64% vs 21% for those who are MRD+ (HR = 0.28) and improved OS (HR = 0.28).[21] In children there is an ongoing trial within the COG testing blinatumomab for MRD+ patients in in hematological CR.

2.2 Accepted Clinical Practice

Treatment of ALL consists of induction chemotherapy lasting 1 to 2 months, consolidation/intensification therapy for 6 to 8 months, followed by maintenance treatment for 24 to 30 months. Patients with BCP-ALL bearing the Ph (i.e. Ph+) also benefit from addition of a BCR-ABL TKI such as imatinib or dasatinib. Adolescent and young adults (< 40 years of age) are treated with an intense chemotherapy protocol that includes steroids, vincristine, asparaginase with or without daunomycin and CNS-directed treatment. The 5-year OS ranges between 67% and 78% in adolescents and young adults. For older adults, results are less favourable, with a 5-year DFS of 25% and OS of 54%.[28]

A number of risk factors have been identified that portend treatment failure in patients with ALL. One of the most important factors identified in the last decade is the detection of MRD in those achieving morphological CR by conventional bone marrow assessment (< 5% bone marrow blasts and normal peripheral blood counts).[30] Use of real time quantitative PCR (RT-qPCR) to detect leukemia-specific rearrangements of immunoglobulin (Ig) or T-cell antigen rearrangements or fusion transcripts can be applied to more than 95% of patients with ALL, and has a sensitivity of one in 10,000 or 100,000 cells (10^{-4} to 10^{-5}).[30,31]

Flow cytometry evaluation may also be used to detect MRD. This may be applied to 90% of patients with ALL and has a more rapid turnaround time. This technique is about one log less sensitive than PCR tested MRD. Adult patients with B lineage ALL who continue to exhibit MRD in bone marrow despite ongoing treatment have a median time to relapse of 5 to 8 months.[20] Patients with MRD require novel treatments.

While the utilization of allogeneic HSCT in first remission in Ph- ALL remains controversial, results of cohort studies of this therapy for patients who are MRD+ (> 10^{-3}) following induction therapy have shown improved outcomes compared to consolidation and maintenance treatment.[32] In some studies, the use of allogeneic HSCT for patients who were MRD+ resulted in superior outcomes, regardless of risk factors present at the time of diagnosis or study enrollment. Transplant from a related or unrelated stem cell donor is recommended for all patients with a poor early MRD response.[30,33]

2.3 Evidence-Based Considerations for a Funding Population

Blinatumomab is a bispecific T-cell engager antibody, which binds to CD19 on B-lineage ALL blast cells, and to CD3 on T-cells. In a randomized phase III trial in adults with relapsed or refractory Ph- B-lineage ALL, the complete response to blinatumomab was 44%, compared to 25% for standard chemotherapy. Blinatumomab resulted in superior 6-month EFS and longer OS.[22] In a pilot study of patients who were MRD+ after induction and first consolidation treatment, 16 of 20 evaluable patients (80%) achieved MRD negativity after 4 cycles of treatment with a median follow-up of 33 months. Twelve patients remained in CR.[8,34] Of the 11 patients who did not undergo allogeneic HSCT, six remained in hematologic remission with no further therapy.[34]

In a larger phase II open-label trial, 113 patients with BCP-ALL in first or subsequent hematologic CR, who were MRD+ ($> 10^{-3}$) after at least three cycles of intensive chemotherapy, received blinatumomab for up to four cycles (continuous infusion for 4 weeks, followed by a 2 week break each cycle). MRD was assessed by PCR or by flow cytometry.[2] Eighty-seven of 113 patients achieved MRD negativity ($< 10^{-4}$), and the estimated RFS at 18 months was 54%.[5] Seventy-six patients underwent allogeneic HSCT while in CR after 1 (n = 27), 2 (n = 36), or 3 to 4 cycles (n = 13) of blinatumomab.[2] Of these 76 patients, 57 were MRD- prior to HSCT and 19 had persistent MRD positivity prior to HSCT (an additional 14 patients had HSCT following relapse).[3] Median RFS was 23.6 months versus 5.7 months ($P = 0.002$) and median OS was 38.9 vs 12.5 months ($P = 0.002$) in patients with and without a complete MRD response in cycle 1, respectively.[2] Blinatumomab represents a novel treatment option that appears to be non-cross-resistant with chemotherapy, and may allow patients to undergo potentially curative allogeneic HSCT in complete molecular remission, and potentially experience a more favourable outcome. Standardized assessments of MRD by PCR or multi-colour flow cytometry exist in most large leukemia centres. To utilize blinatumomab for MRD+ patients, it is necessary to accurately identify patients who are MRD+ after at least 3 cycles of intensive chemotherapy who are at highest risk of relapse.

2.4 Other Patient Populations in Whom the Drug May Be Used

Blinatumomab is currently approved for relapsed or refractory BCP- ALL, based on the phase III trial conducted by Kantarjian, et al.[22] It is currently being studied as part of induction treatment in BCP-ALL through the Canadian Cancer Trials Group (CCTG) in collaboration with the ECOG-American College of Radiology Imaging Network (ECOG-ACRIN) cooperative group. It is also under trial for lymphoblastic lymphoma.

3 Summary of Patient Advocacy Group Input

One patient input on blinatumomab (Blincyto) for children with ALL was provided as a joint submission from the following groups: Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Leukemia and Lymphoma Society of Canada (LLSC), Ontario Parents Advocating for Children with Cancer (OPACC), and Helena's Hope. No input was received from a patient group that was focused on the use of blinatumomab for adult population.

Ac2orn, LLSC and OPACC jointly created an online survey which was administered to respondents in English between January 22 and January 31, 2020, through Survey Monkey. The survey was administered by Ac2orn, LLSC, OPACC and Helena's Hope through social media channels and directly by email. The survey was directed at patients and families who were treated for childhood leukemia, and who both did and did not have experience with blinatumomab. A total of 26 responses were collected. However, after removal of four respondents (two due to being adults, one due to incomplete data, and one for not having a confirmed diagnosis of ALL), data from a total of 22 respondents reporting on pediatric ALL were used for the survey analysis and this included two adult patients who were under the age of 18 years at the time of diagnosis. All respondents were Canadian, and most were caregivers. Table 4 provides a breakdown of respondents' characteristics. It should be noted that the age ranges provided are of the children diagnosed with ALL, most being reported on behalf of a caregiver.

Table 4: Characteristics of the Survey Respondents

Characteristic	n (%)
Patients	2
Caregivers	20
Geographical location	
Alberta	6
Saskatchewan	3
Nova Scotia	1
Age range	
0-5 years	9
6-12 years	6
13-17 years	5
18-24 years	1 [a]
25-34 years	1 [b]

[a] Patient was diagnosed in 2018
[b] Patient was diagnosed in 2015

Many respondents indicated having previously received various chemotherapies. The experiences with chemotherapy were described as being *"extremely difficult,"* resulting in side effects that were difficult to tolerate and greatly impacting QoL. Common side effects from traditional frontline treatments include neutropenia, hair loss, nausea, vomiting and reduced mobility. In addition to physical side effects, traditional frontline treatments for pediatric ALL were also reported to result in anxiety, mood swings, stunt emotional growth and result in loss of education. Respondents' comments revealed mostly negative experiences with traditional frontline treatments.

Of the 22 survey respondents, five reported having experience with blinatumomab. It should be noted that blinatumomab has been approved in the R/R setting for pediatric patients with ALL; the indications of the five respondents reporting experience with blinatumomab may not completely align with the indication under review. There was also one phone interview conducted with the mother of a child with ALL, who received treatment with blinatumomab; direct quotes were transcribed from this interview which took place over 50 minutes.

Respondents reported choosing treatment with blinatumomab as it was the *"only option"*, or that the only alternative was *"more of the same chemo that didn't work the first time."* Respondents commented on the negative experiences they had with chemotherapy and their desire for alternative treatments. Respondents described their experiences with blinatumomab positively; side effects of treatment with blinatumomab were described as minor or manageable, and infrequent compared to chemotherapy. The most commonly reported side effects were fever, low platelet count, low red blood cell count, low WBC count (n = 3 for all). Respondents

also commented on the superior QoL blinatumomab was able to allow for patients compared to traditional frontline treatment. Respondents indicated blinatumomab treatment as being much less challenging overall compared to other treatments for ALL and reported an overall positive experience with blinatumomab.

Overall, patients value treatments with fewer side effects, better disease management and improved QoL. In addition, patients prefer having the option of treatments more targeted to the disease, without the risk of long-term impairment, and which are recommended to them by their physician.

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

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

The survey asked respondents to rate on a scale from 1 (indicating no impact) to 5 (indicating extremely large impact) how much a list of diseases symptoms affected their QoL. Table 5 provides a breakdown of the number of respondents who reported symptoms that were identified as a 4 (indicating large impact) or 5. The most common symptoms patients reported as having a large or extremely large impact on their QoL were fatigue, pain and loss of appetite and/or weight loss.

Table 5: Disease Symptoms Affecting QoL

Symptom	n
Fatigue	13
Pain	13
Loss of appetite and/or weight loss	10
Fever and/or night sweats	9
Feeling dizzy/light headedness	9
Constipation	9
Rashes/skin changes	8
Headaches	8
Nausea	8
Vision changes	7
Bruising	6
Broken bones	3

3.1.2 Patients' Experiences with Current Therapy

Ac2orn, LLSC, OPACC and Helena's Hope indicated that while the time to diagnosis for pediatric ALL patients varies greatly, the time from diagnosis to start of intensive treatment is extremely short. The survey asked respondents to indicate which frontline treatments they received after their diagnosis (prior to being classified as relapsed or refractory); treatments reported included chemotherapy (n=15), high-dose chemotherapy (n=10), maintenance therapy (n=9), surgery (n=3), radiation (n=3), immunotherapy (n=2), and stem cell or bone marrow transplant (n=2). Some quotes were provided describing the difficulty of frontline ALL treatment. The following quotes indicate the respondents difficult experience with the toxicities and side effects of frontline treatments, However, they also reflect the respondents' positive experiences with the healthcare-providers:

- *"**Extremely difficult**. High dose chemotherapy caused life threatening conditions resulting in intensive care stays due to allergic reactions, infection and toxic overload"*
- *"Honestly, there was **nothing positive about it**. Frontline was very hard. Filled with mental, physical and emotional exhaustion. Some phases were easier than others but they all came with their own side effects. She experienced the following: - portacath stopped working and needed replacement during frontline - neurotoxicity due to IT methotrexate that caused two seizures rendering her catatonic and admitted to PCCU - chemo induced diabetes twice during frontline - she broke her foot - she had mucositis so severe that she was on a morphine pump and TPN for 10 days - she had a blood*

clot in her hip - she was constantly retching/gagging/vomiting even with anti-nausea medications. - she spent over 200 days inpatient during frontline. There were not too many positive experiences. - she was MRD negative after induction which was a huge relief - the nursing staff at our hospital were amazing !!! - she enjoyed art and music therapy - her oncologist was wonderful - she always listened to me and took my thoughts into account. I felt heard.

- *"Extremely **hard on the body physically**. Infection risk was high and ended up in ICU due to complications. Experienced many side effects. Healthcare staff were very good to us!"*

The survey asked patients to rate on a scale from 1 (indicating no impact) to 5 (indicating extremely large impact) how side effects experienced during frontline ALL treatment impacted QoL. Table 6 lists the side effects which were identified by the respondents as being a 4 (indicating large impact) or 5. The most common side effects with a large or extremely large impact on QoL were reported to be neutropenia, hair loss, nausea, vomiting, and reduced movement or ability to take part in physical activities. Additional side effects acknowledged by respondents were cognitive impairment, emotional trauma, drop foot, bone fractures and loss of fertility.

Table 6: Side Effects Impacting QoL due to Frontline ALL Treatment

Side Effect	n
Neutropenia	14
Hair loss	12
Nausea	11
Vomiting	11
Reduced movement, ability to take part in physical activities	11
Fevers	8
Constipation	8
Pain	7
Organ damage	5
Eyesight changes	5
Neuropathic pain	3

The survey also asked respondents to rate on a scale from 1 (indicating no impact) to 5 (indicating extremely large impact) how frontline treatment for ALL impacted aspects of their lives and development. Table 7 reports those aspects which were given a score of 4 (large impact) or 5 by the respondents. Frontline ALL treatment was reported to have a large or extremely large impact on all aspects of living and development that had been listed in the questionnaire. Some quotes also highlight the challenges that pediatric patients with ALL experience during frontline treatment:

- *"a lot more anxiety at school, around friends. A lot of anger, mood swings and inpatient".*
- *"loss of education during critical years of development has lasting effect on educational achievement which will result in reduced employment opportunities. Years of protective isolation to reduce deadly infections stunts emotional and social growth with peers".*
- *"Having to bring her everywhere in a stroller, can't get dressed alone, potty training took the back burner, doesn't like to eat anymore and when does she pukes and gags super easy now."*

Table 7: Aspects of Life and Development Affected by Frontline ALL Treatment

Aspect of living	n
Changes to physical activity	12
Social development	12
Anxiety	11
Mental health and overall happiness	10
Educational development	9
Eating challenges	8

The following quotes further highlight the extreme difficulties of frontline treatment on patients which result in social isolation, anxiety, cognitive impairment and physical and mental challenges.

- *"My son was 6 now 14 he is so afraid of his own shadow. Has no friends feels alone and his anxiety is through the roof."*
- *"Treatment has created anxiety, medically induced PTSD. My daughter has become very attached to me, doesn't like to be away from me (220 days inpatient). She also now has poor bone density due to treatment. Also has speech/neuro-cognitive delays due to neurotoxicity from chemo. The processing delays are causing frustration due to communication issues. She cannot find the words she needs to speak or completely forgets what she is trying to say. She has constant fear about it coming back."*
- *"My child missed 2 years of school which impacted her socially and also cognitive impairments (memory issues)"*
- *"Had a huge impact on mood and social life as he missed basically three years of school with classmates. Had been treated for social anxiety and suicidal ideation now age 16 to 17."*

However, two quotes were provided which indicated positive frontline treatment experiences for ALL.

- *"My daughters treatment has gone very well. She went into remission after her first round of induction. She has only had one infection resulting in having to be admitted in hospital for 10 days, 3 of those days spent in observation due to a very high heart rate and laboured breathing. She's has had no complications other than having to hold/delay treatment due to low blood counts and receiving occasional blood/platelet transfusion."*
- *"Positive. I had nothing to compare it to."*

Overall, Ac2orn, LLSC, OPACC and Helena's Hope highlight the challenges from frontline treatment, including the intensity, side-effects, duration of treatment, and both short- and long-term impacts on patients.

When asked about difficulties in accessing treatments, eight respondents reported that they had no issues:

- *"Healthcare was very easy to access although sometimes frustrating with differing opinions from different drs."*
- *"No. Live in Thornhill. Mainly at SickKids for treatment. Once able to then also at POGO clinic at Southlake. Distance is essentially the same to each but much easier to get to Southlake. Saved on paying for parking once he could walk or go in while I found street parking".*

One respondent reported having challenges in accessing treatment due to the distance from their home to hospitals in big cities; this respondent described that local hospitals were not properly equipped to address the needs of their daughter, which required them having to travel to Saskatoon:

- *"We have to travel 2.5 hours to Saskatoon for treatment. In the beginning my daughter refused to have her arm poked so we would travel to Saskatoon for blood work. The nurses at our local hospital are not experienced enough in accessing her port to draw blood. On one occasion 2 different nurses tried multiple times before finally drawing blood from her arm. This is also an issue in big city hospitals, it seems a lot of nurses working in emergency departments and even on paediatric wards are not trained/experienced enough to successfully access ports. Multiple failed attempts is painful and traumatizing for the child and heartbreaking for parents watching them go through this. In the last two months my daughter has allowed the nurses at our local hospital draw blood from her arm, saving us an extra trip to the city just for blood work."*

3.1.3 Impact on Caregivers

Quotes were provided on behalf of caregivers describing how their QoL was affected during the treatment of pediatric ALL. The quotes reveal the guilt that parents feel for their child who must go through treatment, and for the lack of attention they are able to give their other children and spouses. The quotes also describe changes in family dynamics, altered daily routines, abandoned careers and social lives, and loss of assets:

- *"Sleeping over 200 nights in a row on a thin mat on parent bed at hospital, isolation periods, loneliness, pets having to stay with relatives, less money, no time to do anything besides drive to and from hospital."*
- *"Stress, anxiety and fear. Sadness that my child has to go through this and for myself/husband and other child. Guilt for having to miss my other child activities and having to send him to stay with other family while I have to be away with my daughter for treatment. My son struggles with separation anxiety since his sisters ALL diagnosis. My husband works away and has had much stress and fear of being away if something happens or there is an emergency. When he is away at work it can be challenging and stressful to juggle taking care of both my children on my own, one with ALL, having to travel for treatment and the other with school, activities and trying to give him as much normalcy as possible."*
- *"Complete abandonment of social life, psychological and emotional impact to siblings, inability to work, some relationships improve but most others get neglected."*
- *"Impacts on everything around us. Life style routines and even meal times nothing is normal or fair about all of this."*
- *"Effects every facet of life social, school, family and friend relationships."*
- *"We are busy living life when his neutrophils are good and homebound when they are not. We are more vigilant on healthy people coming into our home, and cancel plans when others aren't well. Living with the day to day plan making."*
- *"Years of isolation causing delayed education, lost friendships/socialization, lost income of parents, loss of assets (to help pay for loss of income), loss of health due to stress."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Ac2orn, LLSC, OPACC and Helena's Hope reported that current treatments for pediatric ALL include an array of harsh chemotherapies, radiation, surgery, transplant, and other therapies that last for years without any respite. The patient groups providing input also noted that a number of short- and long-term side effects are experienced by patients as a result of the traditional "poison, slash and burn" therapies, otherwise known as chemotherapy, surgery and radiation. These side effects are likely to affect patients in the long-term and for the rest of the patient's lives, often with significant morbidities and early mortality. In terms of expectations, parents and caregivers reported a need for treatments with fewer side effects, that are more targeted to the disease and without risk of long-term impairment. The following quotes reveal patients' expectations for newer treatments, including blinatumomab:

- *"We need better treatments for kids that won't have long term side effects. We need more immunotherapy and less chemo and radiation."*
- *"It's harsh. And the long term effects are not ok for kids."*
- *"Extremely long treatment program (2.5 - 3.5 years). Life is put on hold to some extent during this time."*
- *"The drugs our kids are taking are adult drugs, not designed for children. We need better, safer treatment for our kids."*
- *"Blincyto was a vastly superior treatment for quality of life than standard chemotherapy. It should be a front line treatment for the induction of remission for all pediatric ALL patients."*

Possible impact on disease, QoL and recommendation from a physician (n=11 for each) were the most commonly reported factors that respondents indicated they consider when making a decision about a new cancer treatment. Other factors considered included whether it was an outpatient treatment (n=3) and religious considerations (n=1).

3.2.2 Patient Experiences to Date

A total of five respondents reported having experience with blinatumomab. Respondents indicated accessing blinatumomab through compassionate use (n = 2), a clinical trial (n =2), and a special access program (n = 1). Respondents were asked to rate the difficulty experienced accessing blinatumomab on a five-point scale from "Not difficult at all" to "Extremely difficult." Respondents accessing blinatumomab through compassionate use reported no difficulties in accessing treatment, and those accessing blinatumomab through a clinical trial reported a normal to low level of difficulty in accessing treatment. The respondent who access blinatumomab through a special access program reported difficulty in accessing treatment. Respondents also included comments illustrating some of the difficulties experienced during the process of trying to receive blinatumomab:

- *"Drs and pharmacists handled for us- got financial support, had to stay admitted for 30 days straight connected to iv to get treatment- this was hard as son was not feeling ill."*
- *"Our daughter was on trial and so we had to roll a dice essentially to know if she would have access to the drug or not. That was complete torture."*
- *"Waiting on government approval because he didn't meet the requirements for clinical trials due to age."*
- *"Medical system was not prepared to administer medication as part of trial. Nurses unfamiliar with procedures and timing. Medical gear (bag for cad pump, tubing, etc.) not designed for small children, had to improvise."*

None of the patients reported needing to travel to access blinatumomab as it was provided at their home hospital. Also, aside from normal costs associated with cancer treatment, none of the respondents reported having to incur any additional financial costs due to treatment with blinatumomab. Respondents were asked to describe how they decided to go forward with treatment with blinatumomab; these quotes show that, for these respondents, blinatumomab was *"best"* or the *"only option"* to choose from:

- *"Best option presented by drs to get kid into remission/mrd negative status before bmt to ensure success of bmt"*
- "*The **alternative was more of the same chemo** that didn't work the first time and that had horrible side effects."*
- *"Was the **only option**."*
- *"CNS relapse of ALL during maintenance therapy. Presented with trial opportunity by oncologist and decided to do it. Research medication myself. Was a **less harmful option than chemo** with less harmful side effects."*

Respondents were also asked to describe their overall experience with blinatumomab for treatment of ALL. Overall, respondents reported positive experiences with blinatumomab:

- "***Good,** no side effects."*
- *"It worked while our daughter was on it. It **got her from MRD negative with a small amount of disease present to remission**. It was nice to be able to be home with our daughter while receiving this drug and the side effects were quite minimal. That being said, as soon as she stopped receiving the drug, her leukemia returned."*
- *"**Experience was excellent**. No treatment based symptoms. Administration was manageable once gear and process worked out."*
- *"Everything **went very smooth** with the exception of one neurological issue we had were the medication needed to be stopped because my son lost control over his body and could not site up and his 1 leg wouldn't stop twitching."*

Further comments from respondents indicated that blinatumomab helped their loved ones manage their condition for some time before relapsing; one of the respondents that treatment with blinatumomab was able to eliminate their child's cancer without relapse, while two others noted that treatment with blinatumomab was able to eliminate their child's cancer for some time before relapsing. One of the respondents noted that blinatumomab treatment "Got us into remission but relapsed as soon as blinatumomab was stopped."

Table 8 reports the number of respondents reporting each side effect, and the severity of those side effects; respondents were provided with the options of "minor", "manageable", "serious" or "very serious" when reporting on the severity of the side effects. Most respondents indicated all side effects as being "minor" or "manageable". The most frequently reported side effects were fever, low platelet count, low red blood cell count, low WBC count (n = 3 for all). The patient groups reported that none of the respondents indicated the severity of any of the side effects as being "major". Further, the patient groups commented that compared to frontline treatment for pediatric ALL, side effects experienced as a result of blinatumomab were remarkable less in terms of both severity and frequency.

Table 8: Side Effects Reported due to Treatment with Blinatumomab

Side effect	n, severity	n of patients who did not experience side effect
Tremors	1, Manageable	4 Did not experience
Dizziness	2, Minor / Manageable	3 Did not experience
Confusion	1, Manageable	4 Did not experience
Seizures	1, Minor	4 Did not experience
Fever	3, Minor/Manageable	2 Did not experience
Nausea	2, Manageable	3 Did not experience
Headache	1, Manageable	4 Did not experience
Low platelet count	3, Minor/Manageable	2 Did not experience
Low red blood cell count	3, Minor/Manageable	2 Did not experience
Low WBC count	3, Minor/Manageable	2 Did not experience
Low potassium	1, Minor	4 Did not experience
Sleepiness	2, Minor	3 Did not experience
Low blood pressure	1, Minor	4 Did not experience
Pain	1, Minor	4 Did not experience

In an interview with a caregiver, it was stated that their loved one did not experience any side effects at all, and that the patient's *"**quality of life was vastly superior**."* The caregiver further described how their loved one was able to engage in day-to-day activities with minimal interference by the treatment: *"She had an appetite, she had energy, she had a great mood, she was active, she was able to go to school and visit with friends. We didn't have the same concerns around infection as it only affected a portion of her immune system. There were no mouth sores, no sleeping issues, no mood issues. She appeared to have the quality of life of a perfectly healthy child while on blinatumomab."* For comparison, the caregiver also provided commentary about the experience of blinatumomab compared to frontline treatment for their child: *"On frontline treatment, we were in ICU three times with infections. We had life-threatening allergic reactions to the chemotherapy. She didn't eat, she was in a lot of pain. There was the hair loss. It is hard to find the words to describe how bad the side-effects are in frontline. No physical strength, neuropathy, nausea, vomiting. There is the psycho-social aspect – on chemo she was largely in isolation at home and couldn't have extended time with family and no educational advancement."*

Comments from the four other respondents also indicated agreement that blinatumomab helped to improve their child's QoL compared to other treatments:

- *"Blina **saved my kid's life** and did more than any chemo he received."*
- *"Being home was extremely important to all of mental health. The **minimal side-effects** were a big positive as well."*
- *"Helped get **my son to transplant and now is 2 year cancer free**."*
- *"Blincyto allowed for symptom free quality of life and good health during treatment. My child was happy, had energy and appetite and enjoyed physical activity. **She was a 'normal' child**."*

The respondents were also asked to rate on a scale from 1 (significantly less challenging) to 5 (significantly more challenging) how blinatumomab treatment compared to other treatments for ALL. Compared to other treatments for pediatric ALL, two respondents reported that blinatumomab was "significantly less challenging" and two others reported it was "less challenging." Previous therapies

received by patients included various chemotherapies, including doxorubicin, daunorubicin, cyclophosphamide, etoposide, vincristine, and cytarabine; these treatments were stated to result in numerous side effects, including diarrhea (n = 5), nausea (n = 5), vomiting (n = 5), low white cell count (n = 5), low red blood cells (n = 5), low platelets (n = 5), hair loss (n = 5), infections (n = 5), fatigue (n = 5), constipation (n = 4), allergic reactions (n = 4), respiratory and breathing issues (n = 4), mobility changes (n = 4), pain (n = 4), organ damage (n = 3), high blood pressure (n = 3), low blood pressure (n = 1), physical disability (i.e., amputation) (n = 1), and pancreatitis (n = 1). The patient groups noted this stark contrast of patient experiences with other frontline treatments compared to blinatumomab, as all five respondents indicated that blinatumomab had a positive impact on their QoL. The following quotes were provided:

- *"Positively impacted. My son received this more than once, side effects minimal and it took him to remission."*
- *"Other than managing the 24 hour/30 day infusion cad pump and visits every 48 hours, the experience was inherently positive. We had a healthy child with a functioning immune system who was happy."*

3.3 Companion Diagnostic Testing

No information was provided on the companion diagnostic testing.

3.4 Additional Information

No additional information was provided.

4 Summary of PAG Input

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

Overall Summary

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

Clinical factors:

- Eligibility for patients with CNS involvement
- Re-treatment following relapse post-alloSCT

Economic factors:

- Significant wastage due to insufficient stabilizer available
- Different dosing schedule than relapsed or refractory B-cell precursor ALL

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that current treatments for Ph-, MRD+, BCP-ALL include multi-agent chemotherapy regimens (and alloSCT if eligible) or observation.

4.2 Eligible Patient Population

PAG noted that the MT103-202 and MT-103-203 trials both excluded certain patient subpopulations and is seeking guidance on whether eligibility for blinatumomab should be extended to:

- patients with a history of CNS involvement or who relapse with CNS involvement,
- patients in hematological CR whose MRD status is negative or unknown, if so, which patients (all or those with specific features as high-risk features would be treated with transplant)?

In the trial patients were eligible after a minimum of three blocks of intensive chemotherapy. PAG is seeking confirmation on the minimum number of blocks of chemotherapy administered prior to initiation of blinatumomab after which MRD status is determined.

PAG is seeking guidance on whether there is a subgroup of patients that are expected to derive the greatest benefit from blinatumomab, and whether treatment should be limited to these patients (e.g., certain baseline MRD level, patients in their first CR or subsequent CR).

If recommended for reimbursement, PAG noted that prevalent MRD+ patients in hematological CR or patients on observation, would need to be addressed on a time-limited basis. PAG is also seeking guidance on the time frame after achieving CR in which blinatumomab treatment should be initiated by.

There is a potential for indication creep to Ph+ patients as well as use as maintenance or consolidation therapy for patients with MRD- BCP- ALL.

4.3 Implementation Factors

The recommended dosing/schedule for MRD+ BCP-ALL differs from relapsed or refractory BCP-ALL, PAG noted this may lead to potential dosing errors. In the MT103-202 trial, the dose of blinatumomab was permitted to be increased to 30 mcg/m^2 per day if there was insufficient response to treatment. For patients with a high BSA, more than one vial per day may be required. PAG is seeking guidance on the use of the weight-based dosing up to a flat-fixed dose (e.g. fixed dose for those ≥ 45 kg), PAG noted this would minimize drug wastage.

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, 5.5 mL of stabilizer is required to prepare each infusion bag and there is only 10 mL of stabilizer included with each vial of drug. Thus, to prepare additional bags from one vial of drug, additional stabilizer is required from a different package. PAG noted there would be significant wastage due to insufficient stabilizer available to maximize the use of blinatumomab vials and vial sharing is unlikely. Furthermore, to account for volume remaining in lines, there is a need to compound a preparation that contains more than the prescribe dose (e.g. prepare 32.5 mcg for a 28 mcg dose). In response to PAG's concerns about drug wastage, the sponsor commented that based on clinician feedback the preferred preparation of blinatumomab for most cycles is a 7-day bag. The sponsor further clarified that as per the Health Canada product monograph, blinatumomab can be prepared as a 24, 48, 72, or 96 hour bag, or a 7-day bag using preservative sodium chloride and when a multiday bag is prepared, multiple vials of blinatumomab are typically required. However, the required volume of stabilizer that is to be added to the bag remains the same (i.e., 5.5 mL per 24, 48, 72, 96-hour bag). The sponsor added that the only role of the stabilizer is to prevent adhesion to the bag and line, and that over time, centers will have vials of intravenous solution stabilizer left over that can be used to further minimize wastage. The sponsor concluded that drug wastage associated with insufficient stabilizer should not be considered a significant concern.

In the trial, patients received blinatumomab for up to four cycles (where a single cycle of treatment is 4 weeks of continuous infusion followed by a 2-week treatment-free interval). PAG is seeking guidance on whether further blinatumomab treatment would be considered for patients who have not progressed after receiving four cycles of blinatumomab, but do not go on to receive alloSCT.

Blinatumomab, being an IV drug, would be administered in an outpatient chemotherapy center or inpatient hospital for appropriate administration and monitoring of toxicities. Access would be limited to treatment centres with the appropriate resources to administer and monitor. The administration of blinatumomab requires considerable coordination of inpatient care in tertiary hospital and outpatient cancer clinics.

In addition, infusion pumps used to administer blinatumomab must be programmable, lockable, non-elastomeric, and have an alarm. PAG noted that this type of pumps are not readily available in all treatment centres and may increase need for hospitalization. Furthermore, daily pump changes can have a large impact to nursing resources in an inpatient/outpatient setting. In some jurisdictions, blinatumomab would require patients to be admitted in hospital for the entire duration of the 28-day continuous infusion. This would increase overall healthcare costs (e.g., nursing, pharmacy, and inpatient bed capacity).

Although the overall number of patients with ALL is relatively small, PAG noted there may be significant incremental budget impact given the increased number of patients who would be eligible for treatment for blinatumomab with MRD status testing, in addition to the burden of additional resources required for administration and monitoring of toxicities.

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

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on available treatments following blinatumomab in this setting. PAG is seeking guidance on whether patients who receive blinatumomab for MRD+ disease followed by alloSCT would be eligible for repeat blinatumomab treatment for relapsed disease occurring post-alloSCT. If re-treatment is appropriate, what would be the appropriate timeframe from completion of blinatumomab in this setting and initiation in the relapsed/refractory setting?

4.5 Companion Diagnostic Testing

Blinatumomab is indicated for all patients with Ph-, MRD+ ALL, and this may increase the number of tests evaluation for MRD status. PAG is seeking clarity on the proportion of Ph- ALL patients who would be MRD+, and thus eligible for blinatumomab. MRD testing is routinely completed for Ph+ ALL patients (not Ph- ALL), this is a barrier to implementation. PAG indicated that there may be delays in obtaining MRD testing. For jurisdictions that need to send out samples for MRD testing, the turnaround time is a concern. Therefore, the number of patients requiring MRD testing and access to MRD testing (methods for MRD assessment and sensitivity) may be a barrier to implementation.

4.6 Additional Information

PAG noted the availability of a pre-mixed product for fixed dose administration would relieve some pressures on pharmacy resources.

5 Summary of Registered Clinician Input

A total of nine registered clinician inputs were provided: one group input on behalf of the Pediatric Oncology Group of Ontario (POGO), and eight individual clinician input by oncologists from Ontario (four clinicians including one pediatric oncologist), Alberta (two clinicians), British Columbia (one clinician), and Nova Scotia (one clinician).

No specific treatments aimed at patients with MRD+ BCP-ALL were identified by the clinicians providing input. However, clinicians from POGO did state that patients who remain MRD+ after three blocks of chemotherapy face a poor prognosis; these patients require intensification therapy to achieve a positive outcome. Further, therapy for B-cell ALL was stated to be based on the risk status of the patient which is determined by MRD testing. The BLAST trial inclusion and exclusion criteria were considered by the clinicians to be reasonable and applicable to clinical practice; the trial population were stated to represent a large and clinically significant patient population with unmet need. MRD status (i.e. MRD conversion rate) was stated to be a suitable endpoint by clinicians; however, it was also acknowledged that modern MRD testing is able to detect MRD at lower levels of MRD at 0.01%, which may be similar to higher levels of 0.1%. Clinicians also strongly urged for the reimbursement of blinatumomab for pediatric patients. Clinicians acknowledged that a trial for pediatric patients is recommended, but that currently available evidence in adults may be extrapolated to suggest efficacy among pediatric patients, and evidence in the R/R setting is supportive of the indication under review.

Clinicians agreed that blinatumomab may be used for patients with CNS involvement or who relapse with CNS involvement; however, blinatumomab should not be used to treat patients with active CNS disease. Clinicians also agreed that blinatumomab may be used for patients with Ph+ ALL. Clinicians did not agree that blinatumomab should be used for patients with MRD- status; further evidence would be needed to fully support the use of blinatumomab among this population of patients. Clinicians were supportive of using blinatumomab along with TKI therapy for patients who are Ph+, either in sequence or in combination; these two treatments were stated to be complementary in this setting. TKI therapies and blinatumomab were stated to have different mechanisms of action and non-overlapping toxicity profiles. Pediatric oncologists also urged for the use of this treatment combination among pediatric patients. Regarding patients with prevalent MRD+ status in hematological CR or those under observation, a time frame of within two weeks after determining MRD positivity was suggested by most clinicians to be a reasonable time to initiate treatment of blinatumomab; other clinicians suggested timeframes of within three or four months to initiate treatment with blinatumomab. However, all clinicians agreed that patients face a high relapse rate and that starting treatment sooner rather than later is preferred. Contraindications to blinatumomab were stated to include CD19 negativity, severe biochemical abnormalities, uncontrolled serious infections, pregnancy, severe neurological complications or other contraindications as outlined by the manufacturer.

In terms of sequencing, clinicians suggested that blinatumomab would be provided to patients after initial induction and consolidation therapy, which would replace the cytotoxic chemotherapy that patients currently receive. Upon progression of blinatumomab, CAR-T cell therapy, inotuzumab, chemotherapy and allogenic HSCT were suggested as potential treatment options. Specific treatment suggestions were provided by clinicians based on patient's CD19, CD22 or Ph statuses. Regarding re-treatment with blinatumomab for MRD+ ALL patients post allogenic HSCT, clinicians agreed that each patient may be considered based on their clinical conditions, immunophenotype status and previous therapies. Uncertainty was expressed regarding an appropriate timeframe for re-treatment with blinatumomab. Some clinicians agreed that a predetermined interval may not be necessary for re-treatment with blinatumomab based on its mechanism of action; however, other clinicians stated that re-treatment may be considered only if it was six months post original treatment, and if no other treatment options were available for the patient.

Companion diagnostic testing was stated to be required prior to administration of blinatumomab to determine the MRD status. Clinicians acknowledged that there is an inconsistency in availability of testing across Canada, and that there is a need for standardized and centralized testing. The clinicians providing indicated that experience with testing should be intermediate or advanced in most institutions in their respective jurisdictions, and that many healthcare staff were already trained as blinatumomab has been used for relapsed disease. However, they acknowledged that smaller institutions may face issues with lack of access to resources and lack of staff training.

Please see below for details from the clinician inputs.

5.1 Current Treatments

CADTH identified the following treatments currently available for the treatment of MRD+ BCP-ALL patients: multi-agent chemotherapy regimens (and alloSCT if eligible) or observation. Clinicians providing input agreed with the listed treatments CADTH had identified for ALL patients. For patients who are Ph+, TKIs with a multi-agent chemotherapy regimen are available in Canada. One clinician included hyper-CVAD as one of the chemotherapy regimens, while another clinician included imatinib, dasatinib, and ponatinib as TKIs that may be available to patients. For eligible patients, stem cell transplantation would be prioritized. However, a clinician stated that current treatment approaches are clinically suboptimal and may be associated with extreme toxicity and mortality; another clinician supported this by stating that chemotherapy is less effective, more toxic and increases the risk for subsequent transplant complications for MRD+ patients.

No treatments aimed specifically at patients who are MRD+ with B-cell ALL were stated to currently be used in practice, highlighting an unmet need for treatment. With the approval of blinatumomab, the treatments mentioned were stated to become unnecessary or inappropriate. One of the clinicians stated they would plan on using blinatumomab as part of a multi-agent chemotherapy regimen per the COG study AALL1331 which was closed by the Data and Safety Monitoring Board (DSMB) for efficacy in the intermediate and high-risk arms of the trial for relapsed ALL. This clinician stated they would continue to use only chemotherapy for low risk patients until the trial results are released.

Clinicians from POGO stated that pediatric patients are enrolled in the COG trials, where available. For patients who remain MRD+ following three blocks of therapy, including one induction block and two 4-week blocks referred to collectively as consolidation therapy, a poor prognosis is expected; this requires intensification of therapy in attempts to achieve a positive outcome. For example, the current standard of care would proceed to include a more intensive cytotoxic chemotherapy regimen including high dose cytarabine or cloraforbine in hopes of achieving MRD-negativity; MRD- patients would then proceed to alloSCT. Therapy for relapsed B-cell ALL patients was stated to be dictated by risk stratification. MRD status is used to escalate therapy in the intermediate risk population (late bone marrow or combined relapsed). These patients are escalated from a chemotherapy only approach to planned allogenic transplant.

5.2 Eligible Patient Population

The BLAST trial population was considered reasonable by clinicians; inclusion and exclusion criteria of the trial were considered applicable to clinical practice. In addition, the overall trial population and the patient population in the reimbursement request were stated to define a large and clinically significantly unmet need. MRD status was stated to be a suitable endpoint. However, one clinician indicated the use of blinatumomab to patients with MRD levels ≥ 0.1%, and that this cut-off is a historical artifact of clinical trials; modern MRD testing was stated to be able to detect MRD at lower levels (e.g. 0.01%), and that the clinical significant of lower levels of MRD is the same as that of higher levels (e.g. ≥ 0.1%). This clinician strongly argued that blinatumomab should be approved for patients with MRD levels ≥ 0.01%. This clinician also suggested that use of blinatumomab not be restricted to use among a subset of BCP-ALL patients with MRD, rather it should be available to all BCP-ALL patients.

Another individual clinician input indicated that, currently, children with ALL who are MRD+ and remain MRD+ until the end of induction therapy are at high risk of treatment failure with continued chemotherapy. For children who remain MRD+ at end the of induction therapy, alloSCTis considered the standard of care. However, the clinician providing input stated that this approach was not shown to be associated with clinical benefit, as indicated by the publication by Pulsipher et al. 2015.[35] This clinician also indicated that there is a significant risk of toxicity in this population from both the stem cell transplant and preceding intensive chemotherapy intended to reduce MRD levels prior to HSCT with the belief that this improves outcomes for patients. While no well-characterized data evaluating the role of blinatumomab in a pediatric population currently exists, this clinician suggested that the available data from adult populations is compelling and reasonable enough to suggest similar benefit among children. The COG AALL1331 randomized trial of post-reinduction blinatumomab among pediatric patients with first relapse of ALL was referenced by the clinicians providing input; the results of which were stated to show markedly superior DFS and OS in both patients with high-risk BCP-ALL and intermediate risk BCP-ALL patients who were MRD+ after one block of reinduction chemotherapy when the second and third

traditional cytotoxic courses were replaced with blinatumomab and intrathecal therapy. The results of this trial were also stated to show that children with HR/IR first relapse of ALL who are MRD-positive and received blinatumomab post-reinduction therapy (in experimental arm B) were found to have higher levels of conversion to MRD-negativity and substantially lower levels of significant toxicity than those receiving intensive chemotherapy (in standard arm A). It was stated in the individual clinician input that the results of the COG AALL1331 led the COG DSMC to close this aspect of the trial and recommend that all HR/IR patients be switched to the blinatumomab arm (experimental arm B). Clinicians from POGO noted that, in the COG AALL1331 trial, the classification of patients to high risk group was done purely based on clinical factors including isolated bone marrow, combined relapse within 36 months of initial complete response, or isolated extramedullary relapse less than 18 months; MRD was not considered part of the stratification for this group. Clinicians from POGO believed that both pediatric BCP-ALL patients, including both at high risk for relapse and intermediate risk for relapse with MRD-positivity, should be eligible to receive blinatumomab.

A clinician providing individual input acknowledged that the results from the COG AALL1331 trial are not directly translatable to frontline pediatric ALL patients who are MRD+ at end-consolidation. This clinician suggested that COG AALL1331 trial results in conjunction with the adult trial data showed that blinatumomab is likely to be more effective and less toxic for frontline pediatric ALL patients who are MRD+ at end-consolidation than existing intensive chemotherapy-based approaches. The clinician also stated that a well-designed trial for pediatric patients in this setting should be performed to generate the necessary evidence; however, the completion of such a trial should not delay the availability of blinatumomab for children who are MRD+ at end-consolidation.

5.2.1 In clinical practice, is there evidence to extend the use of blinatumomab to (provided all other eligibility criteria are met:

Patients with a history of central nervous system (CNS) involvement or who relapse with CNS involvement

In general, despite the lack of direct evidence for the use of blinatumomab among patients with a history of CNS involvement or those who relapse with CNS involvement, clinicians agreed that the use of blinatumomab among these patients is acceptable. However, isolated events of CNS relapse or active CNS disease should not be treated with blinatumomab. One clinician acknowledged that patients with overt, untreated CNS involvement are excluded from clinical trials due to the theoretical risk of increased neurotoxicity. However, ongoing real-world use of blinatumomab has shown that it is safe in patients with prior or current CNS disease after the CNS disease has been treated with intrathecal chemotherapy. This clinician stated that blinatumomab could be provided to patients with treated CNS disease. Two individual clinicians stated that, should patients experience systemic relapse that includes CNS relapse, blinatumomab would be an acceptable treatment for patients in combination with CNS directed therapy such as intrathecal chemotherapy with or without subsequent radiotherapy. One clinician stated that there would be no reasonable argument to exclude these patients.

Two individual clinician inputs as well as the joint input from clinicians from POGO referred to the COG ALL1331 trial, which included pediatric patients with CNS relapse. Both an individual clinician and clinicians from POGO highlighted the greater risk of subsequent systemic bone marrow relapse among children who suffer from an early isolated CNS or combined bone marrow/CNS relapse. The COG AALL1331 trial was stated to show that patients with early isolated CNS relapse are likely to be among HR/IR patients who benefit from post-reinduction blinatumomab versus standard intensive chemotherapy. Clinicians from POGO recommended that these patients should not be excluded from therapy if they are otherwise classified as HR/IR with MRD positivity after the first block of reinduction chemotherapy. However, the individual clinician acknowledged that longer follow-up data and subset analyses are required to confirm this impression.

Patients with Ph+ ALL

Clinicians agreed that the use of blinatumomab should be extended for patients with Ph+ ALL. However, there were slight differences in how blinatumomab would be used among Ph+ patients. Ph+ ALL patients who are also MRD+ were stated by one clinician to first be treated with a second or third line TKI plus chemotherapy; these patients who remain MRD+ after treatment should be considered for treatment with blinatumomab. In agreement, two clinicians also stated that patients who are not responsive to or are intolerant of TKIs should be eligible for blinatumomab. Another clinician pointed out that Ph+ patients were excluded from the efficacy analyses [of OS and RFS] in the MT103-203 (BLAST) trial to maintain patient homogeneity within the study. However, blinatumomab was

stated by this clinician to be highly efficacious among Ph+ BCP-ALL patients. The combination of a TKI with blinatumomab was stated to be particularly potent and complimentary for this indication under review. Another individual clinician stated that blinatumomab should be extended not only for Ph+ patients, but also for Ph– patients.

Input from the POGO clinicians was consistent with the input of other clinicians, noting that Ph+ BCP-ALL patients have a high risk of recurrence. These clinicians stated that they favoured treatment with blinatumomab for Ph+ patients with persistent or recurrent disease. An individual clinician wrote that, based on their anecdotal experience, blinatumomab plays an important role in the management of patients with relapsed Ph+ ALL; this clinician was strongly in favour of funding blinatumomab for patients in this setting, acknowledging that there is unlikely to be sufficient pediatric data to confirm this impression.

Patients in hematological CR whose MRD status is negative or unknown

In general, clinicians agreed that currently available evidence does not support the use of blinatumomab for patients with negative MRD status, specifically in the first line. One of the clinicians indicated that they would not use blinatumomab until results of the COG AALL1331 trial were released for low-risk patients. If the trial revealed that blinatumomab was effective for these patients, this clinician stated they would use blinatumomab.

One clinician discussed the appropriateness of the current threshold used for determining MRD+ status and eligibility for blinatumomab (≥ 0.1%). One of the clinicians referred to the MRD threshold of ≥ 0.1% as a historical artifact of clinical trials, and that modern MRD testing can detect MRD at lower levels than 0.01%. This clinician stated that the clinical significance of lower levels (e.g. 0.01%) is the same as higher levels (e.g. ≥ 0.1%) of MRD; in Canada, MRD- status would imply a level of < 0.01% with intermediate ranges of MRD being between 0.01% and 0.1%. Therefore, this clinician suggested that blinatumomab be funded for patients with MRD levels < 0.1%, but ≥ 0.01%. The clinician providing input noted that some patients with MRD levels below 0.01% may still have residual leukemia. The clinician stated that although this is lower than the detection threshold of any assay, it could be argued that these patients could potentially benefit from blinatumomab by reducing their MRD levels even lower. The clinician also discussed patients with unknown MRD status. While there is no evidence as of yet for using blinatumomab among patients with unknown MRD status, it could be argued that such patients may still benefit from treatment with blinatumomab. However, this clinician acknowledged that the use of blinatumomab among patients with unknow MRD status or those with MRD levels below 0.01% is not justified outside clinical trials.

The clinician providing input described that currently only a subset of their patients is sent to transplant in first remission, which includes:

- Ph- patients with translocations or other genetic abnormalities involving 11q23;
- Ph+ patients not achieving a deep molecular response (as assessed by molecular MRD at 3 to 4 months);
- patients defined by further testing as being ‘Ph-like’;
- patients with high-level MRD after induction therapy; and
- patients who have relapsed and have achieved a second, or higher, CR with re-treatment

5.3 Relevance to Clinical Practice

All clinicians providing input for this review indicated having experience with blinatumomab. One clinician stated that patient characteristics in the BLAST trial were considered to be suitable for treatment; specifically, patients who received at least three blocks of intensive chemotherapy prior to receiving blinatumomab. Unmet need was highlighted as patients aligning with this indication generally have poor outcomes and there is a lack of available treatments to compare with blinatumomab. MRD status (i.e., MRD conversion rate) was considered to be an appropriate surrogate endpoint for some harder endpoints. However, the lack of randomization and the absence of a comparator arm were noted the major limitations of the trial.

Blinatumomab would be used for MRD+ patients prior to curative allogenic transplant who are intermediate or high risk for relapse. One clinician specified that blinatumomab is associated with significantly lower rates of systemic toxicity and infectious complications compared to intensive multi-agent cytotoxic regimens. The clinician stated that, as per the COG AALL1331 trial, blinatumomab can be used for:

- post-reinduction therapy for first relapse of ALL to bridge to allogenic HSCT; and
- reinduction therapy for multiple relapsed patients prior to allogenic HSCT.

Another clinician specified that they would use blinatumomab for patients with CD19+ B-cell ALL who are in CR after intensive induction with or without intensification chemotherapy, and who are still MRD+ at ≥ 0.1%. This clinician further explained that the achievement of MRD negativity of approximately 80% in the BLAST trial is greater than their local experience with intensive second-line chemotherapy (e.g. hyper-CVAD), which showed approximately 35% achievement. The clinician stated that evidence suggests that patients who are MRD+ and at high risk of relapse but who achieve MRD negativity show superior outcomes, especially after subsequent alloSCT. Therefore, this clinician would want to use blinatumomab in the following indications:

- as a bridge to transplant, to render patients MRD- prior to transplant; and
- for patients who are unable to tolerate further intensification chemotherapy (e.g., due to organ dysfunction or deconditioning) even if they are not subsequently transplanted.

Another clinician agreed with the above bullet points as they would use blinatumomab as a bridge to transplant in transplant-eligible patients, and to increase the long-term DFS in those who are not transplant eligible. This clinician as well as another clinician described that blinatumomab as an efficacious and more tolerable drug than most regimens in this setting for MRD+ BCP-ALL patients. For example, blinatumomab was stated to be more tolerable than allogenic HSCT; it can also increase the efficacy of allogenic HSCT as patients who proceed to allogenic HSCT with lower MRD levels experience longer OS compared to patients with higher MRD. Blinatumomab was also stated to be able to be administered in an outpatient setting compared to most regimens available in this setting.

One of the clinicians stated that patients who are eligible for blinatumomab must be in CR; therefore, patients with untreated CNS leukemia or extramedullary disease should not be considered. In addition, benefit from blinatumomab therapy, in the form of improved RFS or OS, may still be experienced by patients who are intolerant to TKIs and those considered to be ineligible for allogenic HSCT (due to age, comorbidities, or donor unavailability). Further, this clinician stated that patients with CD22-negative disease may not be eligible for treatment with inotuzumab but would be candidates for blinatumomab. For patients who will eventually receive an allogenic HSCT, blinatumomab would be preferred over inotuzumab.

One of the individual clinician inputs also highlighted the desire to use blinatumomab in pediatric patients with persistent MRD positivity following two or more courses of intensive chemotherapy. Clinicians from POGO stated that clinicians in the pediatric oncology community are experienced in prescribing blinatumomab, and that centres from across Ontario have accessed treatment through the COG AALL1331 trial through compassionate access and the currently funded indication. Highest priority for the use of blinatumomab was stated to be in the relapsed setting, regardless of MRD status. Front-line pediatric patients who fail to achieve MRD negativity following induction and consolidation therapy were also stated to benefit substantially from blinatumomab. Patients on blinatumomab were stated to require close monitoring and management for evidence of CRS, particularly in their first cycle. Mirroring the other clinician inputs, clinicians from POGO stated that, following the first week of treatment with blinatumomab, the toxicity profile is superior to traditional cytotoxic chemotherapy. Patients who received blinatumomab in the COG AALL1331 trial were stated to experience strikingly lower rates of grade 3 or 4 febrile neutropenia, infection, sepsis, mucositis and toxic death. Clinicians from POGO stated that, due to common toxicities of cytotoxic therapies, such as infection and mucositis, blinatumomab is favourable for patients at highest risk of these complications; patients who may be at highest risk were stated to include those with active fungal disease or conditions, such as Down Syndrome, that leave patients more susceptible to cytotoxic therapy. Another individual oncologist was also supportive of using this treatment combination for pediatric patients, as the biology of Ph+ ALL disease is similar between adult and pediatric populations; this clinician also stated that a clinician trial of this treatment combination is unlikely for pediatric populations, and that it may be appropriate to extrapolate data from adult studies to pediatric Ph+ ALL patients.

This clinician also identified the ALCANTARA trial, where blinatumomab was used as a single agent in the relapsed Ph+ ALL population.

Contraindications to blinatumomab were stated to include: CD19 negativity, severe biochemical abnormalities, uncontrolled serious infections, pregnancy, or other contraindications as outlined by the manufacturer. One clinician stated that they would not want to use blinatumomab prior to using CD19-directed CAR-T cell therapy, as initial treatment with blinatumomab may promote selection of CD19 subpopulation of blasts which could escape treatment. Clinicians from POGO agreed with this contraindication as some preliminary data suggests less efficacy of CAR-T cell therapy in patients previously exposed to blinatumomab. Another clinician stated that they would be cautious of using blinatumomab for patients who previously received it and experienced severe neurological or other complications requiring discontinuation. However, the clinician pointed out that many of these complications would be considerations for other treatments that have already been used for patients in this line of therapy.

5.4 Sequencing and Priority of Treatments with Blinatumomab

Clinicians from POGO provided the following treatment sequencing approach for patients:

- one cycle of induction chemotherapy plus two cycles of consolidation chemotherapy followed by first cycle of traditional cytotoxic chemotherapy (i.e., mitoxantrone, pegaspargase, vincristine, dexamethasone, intrathecal therapy); or
- one cycle of induction chemotherapy plus two cycles of consolidation chemotherapy followed by blinatumomab and then allogenic HSCT.

Clinicians from POGO further clarified that patients considered high risk or intermediate risk with subsequent MRD-positivity would receive two cycles of blinatumomab prior to allogenic HSCT which would replace the traditional two cycles of intensive cytotoxic chemotherapy. The clinicians agreed that blinatumomab would be given to MRD+ patients following consolidation chemotherapy. One clinician also stated that blinatumomab may be provided to patients if MRD+ status was detected prior to planned allogenic transplant. Another clinician stated that the choice to use blinatumomab would precede other options including inotuzumab, allogenic HSCT, and CAR-T cell therapy; prior treatment with blinatumomab would not serve as a contraindication to these treatments as long as patients remain CD19+. This clinician further explained that treatment with TKIs would likely be optimized for patients with Ph+ BCP-ALL; and that the use of TKIs may in some cases precede the use of blinatumomab. For both Ph+ and Ph- BCP-ALL patients, treatment with blinatumomab would likely lead to a reduction in intensive and toxic, multi-agent reinduction attempts at using salvage chemotherapy protocols. The use of CAR-T cell therapy, third line TKIs (i.e. ponatinib), and allogenic HSCT in the long run were stated to be expected to decrease with the introduction of blinatumomab.

5.4.1 Please consider if there is evidence to support the optimal treatment sequencing with blinatumomab with available treatments for ALL:

What treatment options would be available to patients upon progression with blinatumomab?

A number of different treatment options were suggested for patients upon progression on blinatumomab including inotuzumab, CAR-T cell therapy, chemotherapy and stem cell transplant.

One clinician stated that CAR-T cell therapy is the only option currently available for patients in certain subgroups of B-cell ALL, and, agreeing with clinicians from POGO, that inotuzumab would be a good option for patients with ALL who are CD22-positive; however, inotuzumab was stated not to be currently funded in Ontario. Another clinician indicated that a number of clinical scenarios are possible after progression on blinatumomab. This clinician clarified that if patients progress on blinatumomab, it is expected that their MRD status has worsened and suggested the following pathways:

- Ph- patients should likely proceed to receive allogenic HSCT. Another clinician agreed with this statement, indicating that, based on their local experience, Ph- patients who are MRD+ at a level of > 0.1% after intensive induction therapy (i.e. with DFCI protocol) have a relapse risk of 50% with further chemotherapy alone. Therefore, this clinician agreed with leading patients toward transplant following blinatumomab after one cycle. This clinician further explained that additional intensive chemotherapy is unlikely to result in MRD negativity as this disease is inherently more chemoresistant. In addition, intensive

salvage chemotherapy may cause further organ toxicities and deconditioning which may potentially comprise outcomes following an allogenic HSCT.

- Ph+ patients should receive TKIs. If treatment with TKIs does not change these patients' MRD status, then they should proceed to allogenic HSCT.

This clinician also acknowledged that some patients may qualify for clinical trials, and agreed with other clinicians that inotuzumab is indicated for MRD+ disease, although this is not yet an established treatment.

> Is re-treatment with blinatumomab appropriate for patients who received blinatumomab for MRD+ ALL prior to allogeneic stem cell transplant at the time of relapse post-allogeneic stem cell transplant? If re-treatment is appropriate, what would be the appropriate timeframe from completion of blinatumomab in this setting and initiation in the relapsed/refractory setting?

In general, clinicians providing input acknowledged the lack of available data to support re-treatment with blinatumomab, but that it may be appropriate on a case-by-case consideration for patients who relapse post-allogenic HSCT.

One clinician further described that considerations that would need to be made to determine if re-treatment with blinatumomab was appropriate would include prior therapies received, immunophenotype of the relapse and clinical condition of the patient. The clinicians also agreed that blinatumomab would be considered appropriate for patients who continue to be CD19+. One individual input stated that clinicians would prefer treatments alternative to chemotherapy or blinatumomab re-treatment for these patients. However, another clinician, while acknowledging that re-treatment with blinatumomab would be an option for patients who continue to be CD19+, stated that treatment would likely move to an alternate agent after progression is experienced after blinatumomab. The clinicians from POGO indicated a variety of treatment possibilities for patients who have a disease progression after blinatumomab: for patients who are CD19+, CAR-T cell therapy may be appropriate, while inotuzumab may be appropriate for patients who are CD19-negative. Cytotoxic chemotherapy followed by allogeneic transplant was also identified by the POGO clinicians as another treatment possibility for these patients, particularly for those who have not previously undergone stem cell transplantation.

Regarding appropriate timeframe for re-treatment with blinatumomab, one clinician felt uncertain about an appropriate interval but stated that, based on the mechanism of action, they did not foresee any necessary pre-determined interval. Another individual clinician also agreed that blinatumomab could be used at the time of post-allogenic HSCT relapse regardless of the timeframe from completion of pre-allogenic HSCT blinatumomab. However, another clinician stated that re-treatment may be considered only after a time period of six months or greater from the original treatment, and likely if no other treatments are available for the patient.

5.5 Companion Diagnostic Testing

Clinicians providing input indicated that the MRD testing to determine patient's eligibility for blinatumomab therapy can be performed using flow cytometry to identify leukemia -associated phenotype and molecular testing (e.g. PCR).

The clinicians noted that for the appropriate use of blinatumomab in the MRD setting an appropriate MRD test should be available. MRD assessment was stated by three individual clinicians to ideally be performed using molecular testing in a centralized manner in labs that use standardized accredited methods. One clinician stated that non-centralized, flow cytometry based MRD approaches are inadequate for the purpose of determining patients' eligibility for blinatumomab and cannot be considered as equivalent to molecular testing.

The joint input from POGO clinicians as well as the input from individual pediatric oncologist indicated that MRD testing through flow cytometry is available in Ontario for pediatric patients with ALL. The POGO clinicians noted that flow cytometry is required in all pediatric oncology centres in Ontario to confirm CD19 expression, and that MRD testing by flow cytometry is available in two Ontario centres (SickKids, LHSC) that serve as COG provincial reference labs. However, the clinician inputs indicated variability in availability of MRD testing throughout Canada for adults. One clinician from Ontario indicated that molecular testing (qPCR) is not routinely done in Canada; this clinician stated that more information regarding the implementation of this testing technology would be provided in Cancer Care Ontario's Program in Evidence-Based Care (PEBC) guidelines that are expected to be published in Spring 2020.

Another clinician from Ontario stated that MRD testing needs to be standardized in Ontario from a funding perspective and with respect to centralizing testing in an accredited/validated lab. A clinician from Alberta indicated that depending on the availability of MRD testing flow cytometry may to identify leukemia-associated phenotype, or molecular testing to identify specific molecular gene rearrangements can be used. This clinician stated that not all centres are equipped in their jurisdiction to perform MRD testing; however, none are far from a centre that does offer the testing and is COG accredited. Another clinician from Alberta agreed that testing for CD19 expression is part of routine testing prior to the administration of the blinatumomab. The clinician from British Columbia also stated that, in their jurisdiction, the MRD testing is available and funded for all patients with ALL. The clinician from Nova Scotia stated that companion testing is not required for CD19 expression, but that flow cytometry is routinely available to test for CD19 expression if required. This clinician further stated that MRD testing is required to risk stratify patients, and that this testing is routinely available as a standard of care.

The clinicians providing input agreed that turnaround time for MRD testing should be within 72 hours of sampling, or, ideally, within 24 hours to promptly guide further therapy. Longer turnaround times may be acceptable for monitoring MRD-recurrence but should still be within a five-day window.

5.6 Implementation Questions

5.6.1 Is there evidence to support blinatumomab treatment for patients with Ph+ ALL who require TKI therapy? If yes, would blinatumomab be used in combination with a TKI or sequenced with the TKI therapy?

Clinicians providing input that mature evidence to fully support blinatumomab either in sequence or in combination with a TKI is unavailable, acknowledging that clinical trials are ongoing. While all clinicians agreed that Blinatumomab and TKI combination would be used in Ph+ ALL patients, they varied in their statements regarding sequencing, as some stated they would use blinatumomab in sequence with a TKI, while others supported the combination.

Regarding the use of blinatumomab in sequence with TKI therapy, a clinician stated that for a Ph+ ALL patient who is TKI-sensitive with no tolerance issues related to recommended TKI dosing and is no longer responsive to TKIs, or for those who have developed TKI intolerance, blinatumomab may be sequenced after initial TKI therapy. Another individual clinician also expected that this combination would be both safe and effected.

Regarding the combination of blinatumomab and TKI therapy, an individual clinician explained that the combination would be appropriate given that the two treatments have different mechanisms of action. Clinicians from POGO stated that studies in adult patients have suggested that the combination of blinatumomab and TKIs is efficacious in adult ALL patients. The POGO clinicians indicated that some evidence from case reports is available for the use in the pediatric population. Given the lack of overlapping toxicities of blinatumomab and TKIs, clinicians from POGO would support the careful combination of both agents.

A number of clinicians providing input were also supportive of using blinatumomab and TKI therapy either as a combination or in sequence. One individual clinician stated that treatment of Ph+ ALL required optimization of the TKI therapy, regardless of whether blinatumomab is available; this was also highlighted especially for patients whose decision to undergo allogenic HSCT is based on the depth of molecular response achieved. The clinician stated that blinatumomab and TKI therapy can be used concurrently, but that this treatment would have already been preceded by some TKI tweaking. TKI therapy and blinatumomab were stated to be complementary in this scenario.

One of the clinicians stated that there is no evidence for the use of blinatumomab and TKI therapy upfront outside of a clinical trial. However, this clinician agreed that it may be permitted for patients who are persistently MRD+ at ≥ 0.1% despite adequate trials of at least two different TKIs in combination with chemotherapy, as a bridge to transplant. These patients were stated to be at high risk of relapse.

5.6.2 If recommended for reimbursement, PAG noted that prevalent MRD+ patients in hematological CR or patients on observation, would need to be addressed on a time-limited basis. PAG is also seeking guidance on the time frame after achieving CR in which blinatumomab treatment should be initiated by.

Most clinicians agreed that a time frame of within a week or ≤ 2 weeks after determining MRD positivity would be reasonable for initiation of blinatumomab for patients who are in hematological CR. These clinicians favoured timely initiation of treatment due to the risk of rapid progression of disease in the absence of effective therapy. One clinician stated that they would use blinatumomab even after a full initial induction therapy (i.e. DFCI), and that once cycle of blinatumomab is usually sufficient. Input from an individual pediatric oncologist stated that they would use the protocol of the COG AALL1331 trial to direct timing of use of blinatumomab as that study provides best evidence for sequencing.

Two different clinicians from Ontario provided alternative timeframes for initiation of blinatumomab for patients with CR. One clinician stated that three months would be a reasonable timeframe for initiating blinatumomab treatment. Another clinician stated that prevalent MRD+ patients would have proceeded to allogenic HSCT in most centres, so of the size of this patient population who would need to be addressed on a time-limited basis would be small. Patients who are in CR but who did not go through HSCT and remain on observation were stated to represent a slightly larger group of patients. These patients may undergo MRD testing but would have no prior MRD data for comparison to determine if there is a trend in MRD levels. This clinician further provided evidence showing that 55% of patient relapses occur within the first year, with an additional 20% to 25% occurring in the second year indicating a need for treatment to prevent relapse of these patients.[36,37] Additional information was referenced from the BLAST trial showing that eligible patients were in first or later hematologic CR and with persistent or recurrent MRD ≥ 10^{-3} after a minimum of three blocks of intensive chemotherapy; the median treatment from last prior treatment was stated to be two months (range = 0 to 55 months).[2] Therefore, this clinician suggested that it may be reasonable to include prevalent patients for up to two years after the completion of a minimum of three blocks of intensive chemotherapy. In the Canadian setting, this was estimated to be 12 to 16 weeks after diagnosis. This clinician stated that an earlier post-induction MRD time point should not be used to define blinatumomab eligibility, while acknowledging the clinical usefulness form a prognostic point of view in chemotherapy-treated patients. The clinician also stated that a significant proportion of such patients will become MRD- within 12 to 16 weeks.

5.6.3 With respect to MRD testing, is there available access to MRD testing for patients with ALL? Is there resources and expertise to delivery blinatumomab on an outpatient basis (i.e., access to programmable infusion pumps and on-call staff to manage problems if they arise)? Please identify other considerations for implementation of MRD testing (i.e., turnaround time, methods for MRD assessment and sensitivity).

The individual pediatric oncologist from Ontario believed that, based on the widespread participation of pediatric COG centres across Canada in the COG AALL1331 trial, sufficient expertise is available for flow cytometry for B-cell lineage. Another clinician as well as clinicians from POGO agreed, stating that most centres have been using blinatumomab for relapsed disease and will already have access to programmable pumps to deliver treatment, as well as protocols to manage complications. The clinician from Nova Scotia also stated that their institution has access to outpatient management including pumps and staff who have all been trained. Further support regarding expertise was provided by another clinician who indicated having treated more than 50 patients over the past 5 to 6 years. However, the pediatric oncologist providing individual input acknowledged that, while their institution has access to adequate access to programmable infusion pumps and on-call staff, other smaller institutions may face significant issues.

5.7 Additional Information

No additional information.

6 Systematic Review

6.1 Objectives

The objective of this systematic review is to evaluate the effectiveness and safety of blinatumomab for the treatment of adult and pediatric patients with Ph-, CD19+, BCP-ALL, who are in first or second hematologic CR with MRD ≥ 0.1%.

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

Supplemental Issue: The review team identified no trials directly comparing blinatumomab with a relevant comparator. A summary and critical appraisal of the sponsor-submitted ITC is provided in section 7.

Comparison with Other Literature: Available evidence for the effectiveness of blinatumomab in pediatric patients with MRD+, Ph-, BCP-ALL was limited to one observational study, and no data was identified on the safety of blinatumomab in this patient population. A number of studies identified by the CADTH Methods team, CGP, and the sponsor have been conducted in the R/R setting that provide supportive evidence of the effectiveness and safety of blinatumomab in pediatric patients. A summary and brief critical appraisal of these relevant studies is provided in section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 9. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 9: 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-, MRD+, BCP-ALL will be included.	Adult and pediatric patients with Ph- BCP-ALL in first or second hematological CR with MRD ≥0.1% <u>Subgroups:</u> • Age • CNS involvement at baseline • Ph chromosome status • History of HSCT • Time from last treatment • Relapse history • Baseline MRD level • Number of previous therapies	Blinatumomab	• Multi-agent chemotherapy regimens (and allogenic HSCT if eligible) • Observation	Primary: • Proportion of patients who achieve complete MRD response rate • Hematologic RFS rate Secondary: • OS • **Duration of complete MRD response (MRD negativity)** • Time to hematological relapse • Survival status following allogeneic HSCT • Effect on MRD level • **HRQoL**

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				Safety: • **AEs (type, incidence, severity)** • WDAE

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

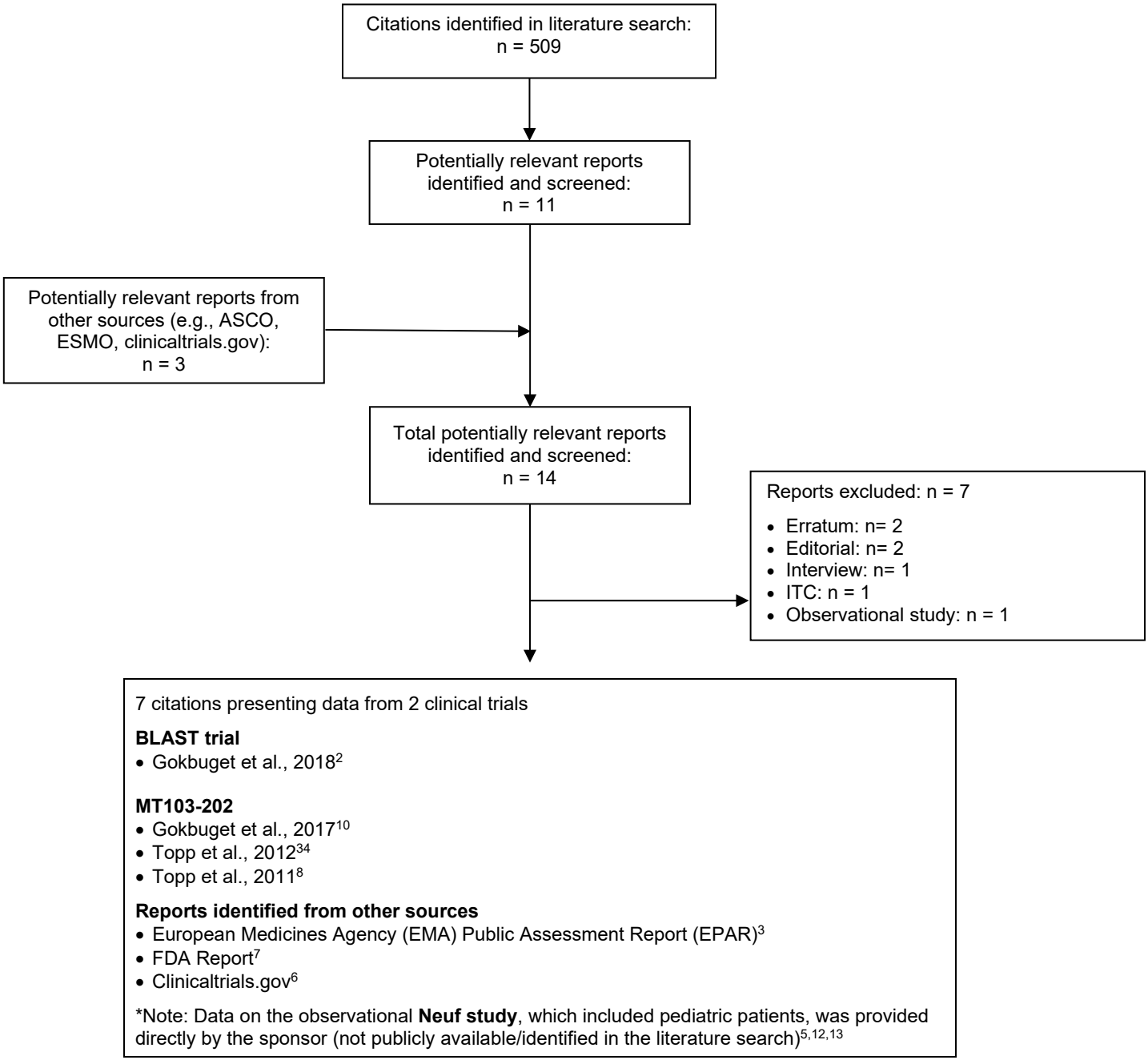
Abbreviations: - = negative; **+** = positive; **AE =** adverse event; **ALL** = acute lymphoblastic leukemia; **BCP** = B-cell precursor; **CNS** = central nervous system; **CR** = complete remission; **HRQoL** = health-related quality of life; **HSCT =** hematopoietic stem-cell transplantation; **MRD** = minimal residual disease; **OS** = overall survival; **Ph** = Philadelphia chromosome; **RCT** = randomized controlled trial; **RFS** = relapse-free survival; **WDAE** = withdrawals due to adverse events

6.3 Results

6.3.1 Literature Search Results

Of the 14 potentially relevant reports identified, seven citations reporting data from the BLAST trial and MT103-102 were included in the pCODR systematic review[2,3,6-8,10,34] and seven citations were excluded. Citations were excluded because they were editorials,[38,39] interviews,[40] or errata.[41,42] An ITC comparing the BLAST trial with a retrospective, observational historical comparator study (Study 148),[17] as well as details and results of Study 148 were also identified,[43] but were excluded from the systematic review results in section 6 because the studies did not meet the inclusion criteria (i.e. irrelevant study type) of the systematic review protocol. The results of the ITC are presented in section 7. An exception was made to include sponsor-provided data on the observational study, the Neuf study, in the systematic review of the evidence in section 6), due to it being the only source of data for the pediatric population for the indication under review.[5,12,13] Data on the pediatric population from the Neuf study is not currently published or publicly available.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to studies (BLAST, MT103-202, Neuf study, and the ITC of BLAST versus Study 148) were also obtained through requests to the sponsor by CADTH.[4,5,9,11-13,18,44-46]

6.3.2 Summary of Included Studies

There were two clinical trials included that met the systematic review protocol criteria, MT103-203 (the BLAST trial) and MT103-202 with adult patients. One additional observational study was identified and provided by the sponsor that addresses the pediatric population, the Neuf study. Key study characteristics including study design, eligibility criteria, intervention details, and trials outcomes are summarized in Table 10.

6.3.2.1 Detailed Trial Characteristics

Table 10: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[2,3,5,6] MT103-203 (BLAST) Clinicaltrials.gov: NCT01207388 EudraCT: #2010-018314-75 **Characteristics:** Confirmatory, single-arm, open-label, nonrandomized, phase II trial **N =** 116 **Number of centres and number of countries:** 46 centres in 11 countries (Austria, Belgium, Czech Republic, France, Germany, Italy, Netherlands, Romania, Spain, UK and Russia) **Patient Enrolment Dates:** November 2010 – February 2014 ***Data cut-off dates*** **Primary analysis:** 21-Feb-2014 **Secondary analysis:** 05- Aug-2015	**Key Inclusion Criteria:** • Aged ≥ 18 years • BCP-ALL in hematologic CR (< 5% bone marrow blasts) after ≥ 3 intense chemotherapy blocks • Intense chemotherapy defined as age-appropriate treatment given to achieve a CR and the best long-term outcome (e.g., GMALL induction I-II/consolidation I, induction/intensification/ consolidation or 3 blocks of Hyper-CVAD) • Hematologic criteria for remission include < 5% blasts, ANC ≥ 1000/ mcL; platelets ≥ 50,000/mcL; hemoglobin ≥ 9 g/dL (transfusion permitted) • MRD at a level of ≥ 10^{-3} (molecular failure or molecular relapse) in an assay with a sensitivity and a lower level of quantification of 10^{-4} documented after an interval of at least 2 weeks from last systemic chemotherapy • MRD evaluation must have at least 1 molecular marker based on individual rearrangements of Ig or TCR genes of a flow cytometric marker profile evaluated by a national or local reference lab approved by the sponsor • Bone marrow or peripheral blood specimen from primary ALL diagnosis/relapse with sufficient DNA for clone-specific central lab MRD assessment • ECOG PS ≤ 1 • Adequate renal and hepatic function • Negative HIV, HBV, and HCV tests **Key Exclusion Criteria:** • Presence of circulating blasts or current extramedullary involvement by ALL • Current or history of relevant CNS pathology • Current infiltration of cerebrospinal fluid by ALL • History of relevant active autoimmune disease	**Intervention:** Blinatumomab 15 mcg/m^2/day continuous IV infusion at a constant flow rate over 4 weeks, followed by an infusion-free interval of 2 weeks Each cycle was 6 weeks, and patients could be treated for up to 4 cycles. Corticosteroid pre-treatment for prophylaxis of neurologic events and CRS was required **Comparator:** No comparator	**Primary:** • Rate of MRD response after cycle 1 • Overall MRD response **Secondary:** • Hematologic RFS rate at 18 months following initiation of blinatumomab (Ph- patients only) • OS • Mortality within 100 days after allogeneic HSCT • TTHR • Duration of complete MRD response • Change in MRD level from baseline to end of cycle 1 • Safety and tolerability (overall incidence and severity of AEs) • Effect of blinatumomab on the kinetics of MRD • Patient's QoL during and after therapy (change from baseline in

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Final Analysis Date: 07-Jan-2019 **Funding:** Amgen Research (Munich) GmbH	• Prior allogeneic HSCT at any time or autologous HSCT within 6 weeks • Eligibility for treatment with TKIs (i.e., Ph+ patients with no documented treatment failure of or intolerance/contraindication to at least 2 TKIs) • Radiotherapy, mAb, or investigational product within 4 weeks of starting study treatment • Systemic cancer chemotherapy within 2 weeks of starting study treatment • Active malignancy other than ALL with the exception of basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix (Germany also excluded patients with another malignancy within 5 years) • Active infection		EORTC QLQ-C30 and EQ-5D) **Exploratory:** • Assess biological predictors of response
Study:[3,8,47] MT103-202 NCT00560794 **Characteristics:** Exploratory, single-arm, open-label, nonrandomized, phase II trial **N=** 21 **Number of centres and number of countries:** 6 centres in Germany **Patient Enrolment Dates:** May 2008 - November 2009 ***Data cut-off dates*** **Primary analysis:** 14-Jan-2010 **Final Analysis Date:** 03-Nov-2014 **Funding:** Amgen Research (Munich) GmbH	**Key Inclusion Criteria:** • Aged ≥ 18 years • BCP-ALL in hematologic CR at any time after consolidation 1 of frontline therapy within GMALL standards or at any time outside GMALL standards • MRD+ (≥ 10^{-4}), as defined by the protocol† • ECOG PS ≤ 1 **Key Exclusion Criteria:** • Current extramedullary involvement • Current or history of relevant CNS pathology • Current infiltration of cerebrospinal fluid by ALL (previous infiltration allowed) • History of or current autoimmune disease • History of allogeneic HSCT at any time or autologous HSCT within 6 weeks prior to study entry • Cancer chemotherapy, radiotherapy, or investigational agent within 4 weeks prior to study treatment • Treatment with mAbs within 6 weeks of study start • Presence of human anti-murine antibodies • Abnormal bone marrow, renal, or hepatic function • Indication for a hypercoagulative state • History of malignancy other than ALL within 5 years prior to study entry, with the exception of basal cell carcinoma of the skin or cervix carcinoma in situ • Active severe infection	**Intervention:** Blinatumomab 15 mcg/m²/day continuous IV infusion at a constant flow rate over weeks, followed by an infusion-free interval of 2 weeks Each cycle was 6 weeks, and patients could be treated for up to 10 cycles. **Comparator:** No comparator(s)	**Primary:** • Rate of MRD response within 4 cycles of treatment **Secondary:** • Rate of MRD response after each treatment cycle • TTHR • Time to MRD progression • Time to MRD relapse • Safety and tolerability: overall incidence and severity of AEs • Change in B-cell and T-cell count from baseline to cycle 1 • PKs • Pharmacodynamics

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• HIV, HBV, or HCV infection		
Study:[5,18] Neuf Study 20160441 **Characteristics:** Retrospective observational cohort study **N (Adult) =** 373 **MRD+ Ph- Adults:** n = 83 **N (Pediatric) =** 41 **MRD+ Ph- Pediatric:** n=39 **MRD+ Ph- Pediatric (evaluable):** [redacted] **Number of centres and number of countries:** France, Italy, Spain, UK, and Russia **(Retrospective) Patient Enrolment Dates:** January 2014 – June 2017 (through expanded access program) **Data cut-off date:** 31-Dec-2017 **Funding:** Amgen Inc.	**Key Inclusion Criteria:** • Adult and pediatric patients • Medical charts available for data extraction • BCP-ALL **Key Exclusion Criteria:** • Pediatric and adolescent patients who received blinatumomab through RIALTO expanded access program not eligible	**Intervention:** Blinatumomab No protocol-specified dose or dosing schedule defined **Comparator:** No comparator(s)	**Primary:** • Clinical and treatment characteristics **Secondary:** • MRD response rate after first 2 cycles of blinatumomab (additional analysis of MRD response rate after 1st cycle included) • DFS‡ • OS • Rate of allogeneic HSCT

† MRD was defined as BCR-ABL gene fusion and/or t(4;11) translocation at any detection level measured by real-time PCR or individual arrangements of Ig or T-cell receptor (TCR) genes measured by an assay with a sensitivity ≥ 1 x 10^{-4}.

‡ Considered equivalent to RFS in the BLAST trial and TTHR/RFS in MT103-202

Abbreviations: - = negative; **+** = positive; **AE** = adverse event; **ALL** = acute lymphoblastic leukemia; **ANC** = absolute neutrophil count; **BCP** = B-cell precursor; **CNS** = central nervous system; **CR** = complete remission; **CRS** = cytokine release syndrome; **CVAD** = cyclophosphamide, vincristine, doxorubicin (also known by its trade name, Adriamycin), and dexamethasone; **DFS** = disease-free survival; **dl** = decilitre; **DNA** = deoxyribonucleic acid; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **EORTC QLQ-C30** = European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire; **EQ-5D**= EuroQol 5-dimension health survey; **g** = gram; **GMALL**= German Multicentre Study Group on Adult Acute Lymphoblastic Leukemia; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HSCT** = hematopoietic stem cell transplant; Hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone; Ig = immunoglobulin; **IV** = intravenous; **m** = metre; **mAb** = monoclonal antibody; **MRD** = minimal residual disease; **OS** = overall survival; **Ph** = Philadelphia chromosome; **PK** = pharmacokinetic; **RFS** = relapse-free survival; **TCR** = T-cell receptor; **TKI** = tyrosine kinase inhibitor; **TTHR** = time to hematologic relapse; **UK** = United Kingdom

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Table 11: Select Quality Characteristics of Included Studies of Blinatumomab in Patients with BCP-ALL

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 MT103-203 (BLAST)	Blinatumomab vs. no comparator	Complete MRD response rate	100	116	None	No	No	No	Yes	No	Yes
Study MT103-202	Blinatumomab vs. no comparator	MRD response rate	7+7	21	None	No	No	No	Yes	No	Yes
Neuf Study	Blinatumomab vs. no comparator	Clinical and treatment characteristics	N/A	110*	N/A	N/A	N/A	N/A	Yes	N/A	Yes

*Includes 83 adult patients and 39 pediatric MRD+ Ph- BCP-ALL patients. A total of 373 adults and 41 pediatric BCP-ALL patients comprised the Neuf study population.

Abbreviations: - = negative; **+** = positive; **ALL** = acute lymphoblastic leukemia; **BCP** = B-cell precursor; **ITT** = intention-to-treat; **MRD** = minimal residual disease; **N/A** = not applicable; **Ph** = Philadelphia chromosome

a) Trials

The pivotal trial was MT103-203 (hereafter referred to as the BLAST trial), which was a confirmatory, multicentre, nonrandomized, single-arm, open-label, phase II trial of blinatumomab for adult patients with MRD+, BCP-ALL. The BLAST trial was conducted at 46 sites across 11 countries listed in Table 10.[2] This trial was supported by MT103-202, which was an exploratory, nonrandomized, single-arm, open-label phase II trial of blinatumomab for adult patients with MRD+, BCP-ALL, which was conducted at six sites in Germany.[47] The BLAST trial and MT103-202 trial have been completed. The Neuf study was an observational, retrospective, cohort study that included both adult and pediatric patients with BCP-ALL who received blinatumomab treatment through an expanded access program in Europe and Russia. The Neuf study included patients with MRD+ or R/R disease, as well as Ph- and Ph+ patients.[5] All three studies did not include any Canadian sites or patients.[2,3,5]

MT103-203 (BLAST)

Trial Design

Screening

A schematic illustration of the BLAST trial is presented in Figure 2. Adult (≥ 18 years of age) patients were assessed for eligibility based on the criteria outlined in Table 10 during a 21-day screening period and must have had bone marrow or a peripheral blood specimen from primary ALL diagnosis or at relapse for the clone-specific MRD assessment. To be eligible for participation in the study patients were required to be in first or later CR and have persistent or recurrent MRD ≥ 10^{-3} (i.e., molecular failure or molecular relapse) using an assay with a minimum sensitivity of 10^{-4} after a minimum interval of two weeks from their last systemic chemotherapy, which would have included a minimum of three intensive chemotherapy blocks (treatment regimen selected at the discretion of the treating physician with the intent to achieve a CR/durable long-term outcome). Baseline MRD evaluation was performed mostly at the central reference laboratory (University of Kiel, Kiel, Germany) or in national reference laboratories (approved by the sponsor) using RT-qPCR of clonally rearranged Ig and/or T-cell receptor (TCR) gene rearrangements or using flow cytometry. Bone marrow or peripheral blood specimen from primary ALL diagnosis/relapse with sufficient DNA for clone-specific MRD assessment was required. Key exclusion criteria included the presence of circulating blasts or current active extramedullary disease, history of clinically relevant CNS pathology, or any prior allogeneic HSCT.[2]

Treatment

Eligible study participants were treated with blinatumomab at a dose of 15 mcg/m^2/day for up to four cycles with a protocol that is described under section *c) Intervention*. Patients could undergo allogeneic HSCT any time after cycle 1[2]. The study assessments included ECOG PS, physical examination, vital signs, neurological examination, electrocardiogram (ECG), laboratory assessments, HRQoL questionnaires, concomitant medications and AEs assessment, bone marrow aspiration or biopsy, and examination of cerebrospinal (CSF) fluid by spinal tap (at the end of cycles 2 and 4).[45]

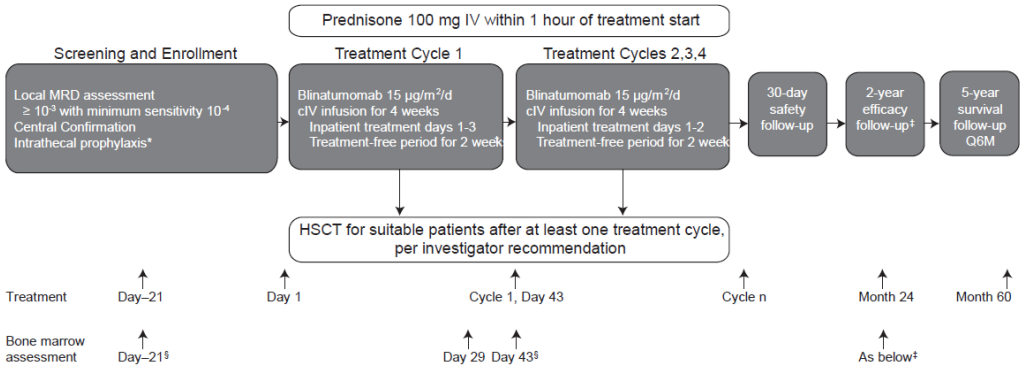
Treatment Discontinuation

Treatment with blinatumomab was discontinued in the event of any of the following: hematologic relapse; investigator's decision that it was in the patient's best interest; patient or investigator not compliant with the study protocol; progression of a medical condition that, in the opinion of the investigator, should lead to treatment discontinuation; administration of relevant nonpermitted concomitant medication(s); occurrence of an AE that made discontinuation from treatment desirable or necessary in the investigator's and/or the patient's opinion; and central laboratory determination that the patient's screening bone marrow demonstrated that the patient was ineligible for study treatment owing to MRD negativity at the time of enrollment.[2]

Follow-Up

Thirty days after treatment discontinuation, a safety follow up visit occurred which included the following assessments: ECOG PS, physical examination, vital signs, neurological examination, ECG, laboratory assessments, HRQoL questionnaires, concomitant medications and AEs assessment. Efficacy follow-up began after treatment initiation and patients with only 1 cycle of blinatumomab had visits at 3, 6, 9, 12, 18 and 24 months (patients who had 2 to 3 cycles of blinatumomab had an efficacy follow-up visit starting at six months, patients with 4 cycles of blinatumomab ended their cycle at six months), which included the following assessments: ECOG PS, physical examination and vital signs, bone marrow aspiration/biopsy, CSF examination and prophylaxis (every three months at the investigator's discretion), laboratory assessments, HRQoL questionnaires, concomitant medications and AEs assessment (AEs potentially related to blinatumomab treatment). Survival follow-up occurred every six months via telephone after study treatment initiation.[45]

Figure 2: BLAST trial Study Design



cIV, continuous IV; HSCT, hematopoietic stem cell transplantation; IV, intravenous; LLOQ, lower limit of quantitation; MRD, minimal residual disease; Q6M, once every 6 months.
*During screening or within 4 weeks of treatment initiation; at day 29 of cycles 2 and 4; and every 3 months following treatment for up to 18 months. Treatment comprised dexamethasone 4 mg (or equivalent), methotrexate 15 mg, and cytosine arabinoside 40 mg.
†May be extended by up to 7 days.
‡At 3, 6, 9, 12, 18 and 24 months after treatment start.
§Baseline bone marrow aspirations were obtained during screening or within 4 weeks prior to treatment start. Confirmatory bone marrow aspirations were performed on day 43 of cycle 1 if the central MRD result was not yet available or if there was an unclear MRD result (between LLOQ and sensitivity).

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Disease Assessments

Identification of MRD required sufficient DNA from patient's primary diagnostic sample of leukemia cells prior to initiation of induction therapy in order to identify the clone specific individual Ig or TCR gene rearrangements, and thus this was required at screening. MRD evaluation was performed by bone marrow aspiration or biopsy and occurred at the end of the first treatment cycle (Day 29) using RT-qPCR, performed exclusively by the central MRD laboratory (University of Kiel, Germany). A second bone marrow sample may have been collected in case the first specimen did not clearly reveal MRD response (second sample would be considered confirmatory of complete MRD response).[3] MRD evaluations were also conducted every three months for the first year after initiation of blinatumomab (i.e., 3, 6, 9, and 12 months), and every six months thereafter (i.e., 18 and 24 months) up to two years.[45] Treatment responses were defined as:

Complete MRD was defined as no PCR amplification of individual rearrangements of Ig- or TCR-genes detected. All patients with established PCR based MRD assay who had been treated with blinatumomab within the first cycle and had post-treatment bone marrow sample at the end of cycle 1 were evaluable for MRD assessment.[3]

MRD response was defined as patients with a complete MRD or patients with detectable MRD < 10^{-4}.[2]

MRD relapse was defined as the reappearance of Ig- or TCR-genes over or equal to the lower limit of quantification (LLOQ; usually 10^{-4}) for at least one individual marker measured by an assay with a sensitivity of a minimum of 10^{-4} in patients who had achieved MRD response.[3]

MRD progression was defined as the increase in the MRD level by one log compared to baseline (equivalent of a 10-fold increase in the number of MRD cells).[3]

At the end of every treatment cycle (day 29) and during efficacy follow-up for up to 24 months after treatment initiation (details for efficacy follow-up outlined in Follow-Up section), bone marrow aspiration or biopsy was also performed by the local laboratory to evaluate the degree of bone marrow infiltration by the percentage of leukemic blasts in the bone marrow as per cytological assessment.[3] **Hematologic relapse** was defined as unequivocal detection of >5% leukemia cells in bone marrow as measured by cytological, microscopic assessment, presence of circulating leukemia blasts or extramedullary leukemia.[3]

Sample Size

The primary efficacy endpoint (the proportion of patients who achieve a complete MRD response after one cycle with blinatumomab discussed in the next section under *Study Endpoints and Statistical Analyses*) was based on Fleming's standard single-stage procedures, but using the exact binomial distribution. The statistical hypothesis was H_0: n ≤ 44% vs H_1: ≥ 61%, where at a one-sided type 1 error of 2.5% and a power of 90%. The estimated MRD response rate under the null hypothesis (≤ 44%) was determined based on the MRD conversion rate after allogeneic HSCT (a generally accepted treatment to be an appropriate intervention for patients with MRD+ ALL) that was estimated in a study by Spinelli et al., 2007.[11,48] Blinatumomab would not be worth studying further in the patient population of interest, if the null hypothesis was true, whereas if the alternative hypothesis was true, then the MRD response probability was 61% or higher and the further study of blinatumomab would be of interest.[3]

The study was planned to include a sample size of 100 evaluable patients, which would provide 90% power of demonstrating that the 97.5% one-sided CI for the MRD response rate excluded 44%, if the true unknown response rate was 61%. If 55% (55 out of 100) patients showed a complete MRD response after one cycle of treatment, the null hypothesis could be rejected. Based on the EMA scientific advice report, higher recruitment of patients was desirable and up to 130 patients were planned. In the event more than 100 evaluable patients were recruited, the parameters for the primary efficacy endpoint were to be adjusted as follows:

- N = 110: H_0 could be rejected with 55% (60 out of 100) MRD- patients
- N = 120: H_0 could be rejected with 53% (64 out of 120) MRD- patients
- N = 130: H_0 could be rejected with 53% (69 out of 130) of MRD- patients[3]

For the key secondary outcome (i.e. hematologic RFS rate at 18 months), sample size determination was based on assumptions of historical data of 80 patients, which show 17.5% (14 out of 80) are hematological relapse-free after one year. In a conservative manner, this data was used for the estimate at the 18-month time point, with an upper limit of 28% for the 95% CI. Thus, the hematological relapse-free rate at 18 months was considered clinically meaningful if the lower limit of the 95% CI excluded 28% (i.e. blinatumomab patients have at least a 28% probability to be hematologic relapse-free at 18 months).[45] The statistical hypothesis was H_0: $n \leq p_0$ vs H_1: $\geq p_1$.

The power calculation of the secondary endpoint with a p_0 of 28% and a one-sided type I error rate of 2.5% was done by simulation based on sampling from an exponential distribution. There were 10,000 trials generated for hematologic relapse-free rates after 18 months ranging between 48 to 55% (p_1) with a random drop-out probability of 10% and for varying rates of HSCT (60%, 67%, and 75%). If available, the onset of HSCT was simulated after 1.5 months on-study from an exponential distribution with a median time to transplant of 1.5 months to ensure no transplant earlier than 1.5 months and most transplants occurring within first 6 months. The rate of significant trials (trials in which the lower boundary of the two-sided 95% Greenwood CI was greater than 28%) among 10,000 repetitions was calculated as the power under respective rates. The study had 90% power of demonstrating the lower boundary of the 95% CI (based on Greenwood's formula) for the K-M point estimate of RFS rate at 18 months excludes 28% if the true unknown rate of patients without hematologic relapse rate at 18 months is 55%, and if the HSCT availability rate is not greater than 67%. Under these assumptions, if the observed K-M rate at 18 months was approximately 43%, then the H_0 could be rejected.[3]

Study Endpoints and Statistical Analyses

The FAS included all patients who received any infusion of blinatumomab, which is a definition considered consistent with the ITT principle in single-arm open-label studies.[3] Analysis sets are summarized in Table 12.

Table 12: Analysis Sets for the Evaluation of the BLAST study Outcomes

Data set	Patient number	Definition	Analysis
Full analysis set (FAS)	116	All patients who received at least 1 dose of blinatumomab	Patient characteristics Safety Overall outcome
Primary endpoint FAS (EP-FAS)	113	Patients from FAS with MRD test and sensitivity of MRD test of at least 10^{-4}	Complete MRD response after cycle 1 (primary endpoint)*
Primary endpoint efficacy set (EP-ES)	103	All patients from EP-FAS with hematologic CR and MRD > 10^{-3}	MRD response
Key secondary endpoint FAS	110	All patients from FAS with Ph-negative ALL and hematologic CR	Relapse-free survival (key secondary endpoint) All other outcome analyses

ALL, acute lymphoblastic leukemia; CR, complete remission; MRD, minimal residual disease; Ph, Philadelphia chromosome.

*Data on complete MRD response after cycle 1 were available for 112 patients; 1 patient died in cycle 1 due to pneumonia without postbaseline MRD evaluation.

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Primary Endpoint – Complete MRD Response Rate

The primary outcome of the BLAST study was the proportion of patients who achieved a MRD response (a complete MRD response or detectable MRD < 10^{-4}; response definitions outlined above under *Disease Assessments*) after one cycle of treatment with

blinatumomab, divided by the all patients in the respective data set. Complete MRD response rate was calculated using two-sided exact 95% CI for all patients and in subgroups defined by baseline covariates.[2] The analysis of MRD response rate was repeated after cycle 2, 3, 4, and at any time during the study on the primary endpoint full analysis set (Prim EP FAS).[44]

The primary endpoint analysis population was a subset of the FAS, the **Prim EP FAS,** which included all patients with an Ig or TCR PCR MRD assay with a minimum required sensitivity of 10^{-4} at central lab established at baseline.

Supportive analyses using the primary endpoint efficacy set (Prim EP Efficacy Set) and the primary endpoint per protocol set (Prim EP PPS) were also conducted, defined below:

- Prim EP Efficacy Set: Patients in the Prim EP FAS, and in hematologic CR at treatment start, with MRD > 10^{-3} as per central lab at screening, and one follow-up sample in cycle 1 at central lab (unless samples are unavailable due to discontinuation of a blinatumomab-related AE or PD/relapse).
- Prim EP PPS Set: Patients in the Prim EP FAS, and who did not have major relevant protocol violations that could impact the primary efficacy endpoint (initial and early stage violations).[3]

Complete MRD response rate on the Prim EP FAS was reported for the following baseline covariates outlined the statistical analysis plan (SAP): age (15 to 24, 35 to 54, 55 to 64, and ≥65); gender; patients by Ph+ disease, patients by t(4:11) translocation and/or MLL-AF4+ ALL; patients by remission number (CR1, CR2, etc.); MRD level at baseline (< 10^{-2}, ≥ 10^{-2}); WBC at first diagnosis (≤ 30,000/mm^3, > 30,000mm^3); prior treatment regimen for ALL (therapy type and, if applicable, drug-name); chemoresistance after the first week of chemotherapy; need of a second induction course for hematological CR; previous anti-tumor radiotherapies; and haploid or near-triploid ALL.[44]

Secondary Endpoints

Relapse-free Survival at 18 months

The key secondary endpoint was defined as the hematological RFS rate at 18 months (+ 2 weeks to account for flexibility of study assessment schedule) following initiation of blinatumomab.[2,44] An event for RFS included hematologic relapse (defined above under *Disease Assessments*), extramedullary relapse, or death due to any cause (whichever occurred first), and the diagnosis of a secondary leukemia was evaluated as an event for the key secondary endpoint as well.[44]

The key secondary analysis population was the **key secondary endpoint full analysis set (Key Sec EP FAS)**, which excluded patients from the FAS who had Ph+ disease or ≥ 5% bone marrow blasts at study entry (i.e. only included patients in hematologic CR). Supportive analyses that were conducted included the key secondary endpoint per protocol set (Key Sec EP PPS), which included patients from the Key Sec EP FAS who did not have any major relevant protocol violations that could impact the key secondary efficacy endpoint (late stage protocol violation).[3]

For the primary analysis of RFS at 18 months, K-M estimates with 2-sided 95% CI was used and patients were censored if they had HSCT before an RFS event (censored at the date of HSCT), if they had post-blinatumomab chemotherapy prior to relapse (censored at first dose of post-blinatumomab therapy), if no event occurred at time of data cut-off (censored at time of last hematological assessment), and if no event occurred and no hematological assessment after 1st dose of blinatumomab (censored at date of 1st dose). RFS was also summarized for the baseline covariates outlined under *Primary Endpoint – Complete MRD Response Rate*. The HR and 95% CI between the covariate levels were also be assessed with a Cox's proportional hazards (PH) model.

Sensitivity analyses: included RFS not censored for HSCT or post-blinatumomab; and not considering death unrelated to leukemia or blinatumomab as events (these patients would be censored at the time of their last hematological assessment).

RFS from HSCT and landmark analyses: Two landmark analyses for patients who received HSCT were also performed, one from 3 months and another from 6 months after the first dose of blinatumomab. For each analysis, cohorts of transplanted and non-transplanted patients (subset from the Key Sec EP FAS) were defined as of the landmark time (i.e. patients who received HSCT after landmark time were included in non-transplanted cohort), and the K-M estimates of median RFS and 95% CI were reported at 3, 6, 12, 18 ,and 24 months subsequent to the landmark analysis.

MRD response and HSCT: K-M estimates of median RFS and 95% CI were reported at 3, 6, 12, 18, and 24 months by MRD response on patients who had an end of cycle 1 assessment from the Key Sec EP FAS. RFS was recalculated from the date of the bone marrow aspiration.[44]

OS

Overall survival was defined as the time from treatment initiation with blinatumomab until death, and patients without an event were censored at the date of last contact. K-M curves as well as KM estimates of median OS and associated 95% CI were reported at 3, 6, 12, 18, and 24 months were presented for the FAS and the Sec EP PPS.

Sensitivity analyses: OS was analyzed as per the primary OS analysis, by MRD response on the FAS, censoring at time of HSCT or post-blinatumomab therapy.

Landmark analyses: Similar the RFS landmark analyses, two were performed at the 3- and 6-month timepoints after first dose of blinatumomab in transplanted and non-transplanted patients (defined at the time as of the landmark time). The analysis was conducted as per the primary OS analysis using the Key Sec EP FAS.

OS by MRD response: Analyses were conducted as per the primary OS analysis by MRD response on the Prim EP FAS who had an end of cycle 1 assessment. OS was recalculated from the date of bone marrow aspiration scheduled at cycle 1.

Overall survival by baseline covariates as outlined under the *Primary Endpoint – Complete MRD Response Rate* was also analyzed, and the HR and 95% CI between covariate levels was also assessed using Cox's PH model.[44]

TTHR

Time to hematologic relapse was analyzed from blinatumomab initiation until the time of hematologic or extramedullary relapse. Patients who died, had secondary leukemia, or received HSCT or post-blinatumomab therapy were censored at their last hematologic assessment prior to the first occurrence of the aforementioned events. K-M estimates of median TTHR and associated 95% CI were presented at 3, 6, 12, 18, and 24 months using the Key Sec EP FAS and the HSCT Sec EP FAS.

Duration of Complete MRD Response

Duration of complete MRD response was analyzed as the time from onset of MRD negativity until MRD or hematologic relapse, or date of last confirmation of negative MRD status using K-M estimates. Duration of complete MRD response was reported on the Prim EP FAS as follows:

- Patients with CR after cycle 1, with and without censoring at the time of HSCT or post-blinatumomab therapy
- Patients with CR at any time during the study, with and without censoring at the time of HSCT or post-blinatumomab therapy

The analysis was also conducted on the patients who were transplanted in MRD CR and had a post-transplant MRD assessment; duration of MRD response was recalculated from the day of transplant.[44]

Analyses and Multiplicity

The primary analysis was performed on February 21st, 2014 with the purpose of assessing the primary efficacy outcome (i.e. complete MRD response) and safety. A secondary pre-planned analysis was performed on August 5th, 2015 to evaluate the secondary study outcomes and to update the safety analysis after all patients had either completed at least 18 months of follow-up or discontinued study. A final analysis of OS was conducted after 5 years of follow-up, with a data cut-off date of January 7th, 2019.[5]

The analysis of primary and secondary endpoints was hierarchal. Only if the null hypothesis of the primary endpoint (i.e. rate of patient with a MRD response) was rejected, then the statistical test for the key secondary endpoint (i.e. RFS at 19 months) would be performed in a confirmatory manner.[44]

Safety

AEs were monitored from the date of informed consent until 30 days after the last blinatumomab infusion and were graded per Common Terminology Criteria for Adverse Events (CTCAE) version (v.) 4.0. AEs occurring 30 days after treatment discontinuation were only recorded if considered possibly related to blinatumomab treatment. Safety was analyzed using the FAS and summarized descriptively.[2]

Health-related Quality of Life

The EORTC-QLQ-C30 questionnaire was used to assess the HRQoL of cancer patients in the BLAST trial. Respondents obtained scores on 15 scales: GHS/QoL, five functional scales, three symptom scales, and six single items assessing additional symptoms commonly reported by cancer patients. Scores may range from 0 to 100. Higher scores for the GHS/QoL and five functional scales indicate better functioning. Higher scores on the nine symptom scales indicate more intense symptomology (i.e. a negative change from baseline indicates improvement in symptoms).[6] A ≥ 10-point improvement was used as the threshold to define a MCID for each of the EORTC QLQ-C30 GHS/QoL and functional scales. Similarly, a ≥ 10-point worsening was used as the threshold to define a clinically meaningful deterioration for each of the scales. For symptom scales, a deterioration was defined as a ≥ 10-point increase from baseline.[49] Descriptive analyses were summarized at Day 29 of each cycle, and 30 days after the last infusion (or up to the end of the core study). Analyses were conducted on the FAS and included patients with available data at each time point.[6]

HRQoL was also measured using the EQ-5D-3L questionnaire. The EQ-5D-3L is a self-administered questionnaire, which captures the health state index and the overall health rating using a VAS. The health state index measures five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), on a scale that ranges from no problems (score = 1), some problems (score = 2), to extreme problems (score = 3). Descriptive analyses were summarized at the end of each treatment cycle, and 30 days after the last infusion (or up to the end of the core study), for each dimension. Analyses were conducted on the FAS and included patients with available data at each time point.[6]

Protocol Amendments

The first version of the study protocol was issued on April 22nd, 2010 and the protocol was amended six times. There were 3 major protocol amendments, which are summarized below:

Amendment #3 (February 17th, 2012) clarified and modified procedures needed to be followed in the event of grade ≥ 3 neurologic events, which included:

- In the case of neurologic AEs, dexamethasone was administered at a dose of at least 24 mg/day for up to three days. The dexamethasone dose was then stepwise reduced over up to four days.
- If the neurologic event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of, for example, phenytoin or levetiracetam was administered during restart and during start of the following new treatment cycle.
- Diagnostic measures were conducted to exclude potential infectious causes after neurologic events of CTCAE grade ≥ 3.
- In case of CTCAE grade 3 neurologic events, the infusion of the investigational drug was stopped immediately, and the following investigations were performed: physical examination, vital signs, safety laboratory evaluation, cranial magnetic resonance imaging, and assessment of cerebrospinal fluid (if appropriate). If the event decreased to CTCAE grade ≤ 1 within one week, treatment could be restarted within two weeks, but not earlier than 72 hours (3 days) after the infusion was stopped. For these patients, the infusion was restarted at the lower dose level of 5 mcg/m^2/day. The infusion was restarted in the hospital, under supervision of the investigator, and the patient remained hospitalized for at least two days. After dose reduction to 5 mcg/m^2/d, re-escalation to 15 mcg/m^2/d was not permitted.
- In the case of a CTCAE grade 4 neurologic event, or in case of occurrence of more than one seizure, the infusion of the blinatumomab was stopped immediately and treatment was permanently discontinued and not restarted.

Amendment #4 (July 11th, 2012) clarified criteria for treatment discontinuation. According to this amendment the study treatment would be discontinued in case of extramedullary relapse; infusion interruption of more than two weeks due to a non-hematological AE; or occurrence of a neurologic event meeting one or more of the following criteria:

- Neurologic event of grade 4 severity, per National Cancer Institute (NCI) CTCAE v. 4.0 (May 28, 2009), or occurrence of more than one seizure (see above)
- Neurologic event leading to treatment interruption that needed more than one week to resolve to CTCAE grade ≤ 1

Amendment #5 (March 6th, 2014) modified the key secondary endpoint of RFS by censoring at the time of allogeneic HSCT, rather than analyzing only the subset of patients who did not receive HSCT within 18 months of initiating treatment with blinatumomab.[2]

MT103-202

MT103-202 was an exploratory, proof-of-concept, open-label, multicentre, single-arm, phase II study to investigate the efficacy of blinatumomab in adult patients with MRD+ BCP-ALL.[7]

Trial Design

Screening

Adult (≥ 18 years of age) patients were assessed for eligibility based on the criteria outlined in Table 10, and must have had a molecular marker for evaluation of MRD, which was either BCR/ABL and/or t(4;11) translocation at any detection level measured by reverse transcriptase polymerase chain reaction (RT-PCR); or individual rearrangement of Ig or TCR genes measured by an assay with a sensitivity of minimum 10^{-4} with one marker at a quantitative level ≥ 10^{-4}. To be eligible for participation in the study patients were required to be in hematological CR with molecular failure or relapse starting any time after consolidation I of front-line therapy within GMALL standard or at any time outside GMALL standards.[3] Screening assessments were conducted during a 14 day screening period and included ECOG PS, vital signs, physical and neurological examination, bone marrow aspiration/biopsy, CSF examination, ECG, cranial MRI, laboratory assessments, concomitant medications, and bloods samples for PK, PD, and immunogenicity assessments.[9]

Treatment

Patients received blinatumomab as continuous IV infusion at a dose of 15 mcg/m^2/24 hours over four weeks, followed by a treatment-free period of two weeks. One treatment cycle was six weeks. Patients who had an allogeneic donor were able to have HSCT at any time after the first cycle of blinatumomab.[8] Responders (i.e. those who achieved MRD negativity) could receive three additional cycles of blinatumomab as consolidation, up to a maximum of 10 cycles. Patients who showed neither MRD progression nor response received up to seven cycles of treatment.[3] Patients who achieved MRD remission and relapsed could be re-challenged with blinatumomab. A dose increase could be considered to 30 mcg/m^2 by the DRC if there was evidence of insufficient activity based on the following criteria:

- At least one patient did not respond within four treatment cycles
- At least one patient relapsed after MRD response within two years after completion of treatment

Patients were treated until any of the following occurred: hematologic relapse, MRD relapse, MRD progression, investigator decision, withdrawal of patient consent, patient or investigator was no compliant with study protocol, administration of non-permitted concomitant medication, occurrence of an unacceptable AE or medical condition precluding further participation.[9]

Follow-Up

Efficacy follow-up visits occurred until hematological relapse every six weeks post discontinuation of blinatumomab. Assessments during follow-up included ECOG PS, vital signs, physical examination, bone marrow biopsy/aspiration, laboratory assessments, concomitant medications, AE/SAE assessment, and blood samples for PK, PD, and immunogenicity assessments.[9]

Disease Assessments

Bone marrow aspiration or biopsy was used to evaluate MRD by BCR/ABL and/or t(4;11) translocation, and/or individual rearrangements of Ig or TCR at the end of each infusion period.[3] At the time of detection of first MRD negativity, a second bone marrow biopsy/aspiration was obtained within two weeks to confirm MRD negativity.[8]

MRD response was achieved if BCR/ABL and/or t(4;11) was below the detection limit, and/or if Ig or TCR-genes were below 10^{-4}. All patients who had received at least one cycle of treatment were evaluable for response.

MRD relapse was defined by the reappearance of BCR/ABL and/or t(4;11) translocation at any detection level, and/or by individual rearrangements of Ig or TCR genes ≥10^{-4} measured by an assay with a minimum sensitivity of 10^{-4}, and relapse was to be confirmed within six weeks.

MRD progression was defined by the increase of MRD by one log (i.e. 10-fold increase) compared to the baseline level, and progression was to be confirmed within six weeks.[3]

Sample Size

The sample size was determined using Simon's two-stage MinMax design with 80% power (beta = 0.2) at the significance level of alpha = 0.05 and response rates of p_0 = 0.05 and p_1 = 0.3, which resulted in two stages with seven patients each. The sample size was expanded to 21 patients to enroll more patients with BCR-ABL translocation.[8] The first four patients were enrolled in stage 1 and after one cycle of treatment, the DRC reviewed the data from these patients as prespecified in the protocol.[3]

Study Endpoints and Statistical Analyses

The primary and secondary endpoints and analyses are summarized in Table 13.

Analyses and Multiplicity

The data cut-off date for the primary analysis was January 14th, 2010. The data cut-off for the long-term follow-up analysis was November 3rd, 2014.[3]

The testing of multiple endpoints was not controlled for multiplicity.

Table 13: MT103-202 Study Endpoints and Statistical Analyses

Study Endpoints and Statistical Analyses			
	Definition	**Statistical Analyses**	**Censoring**
Primary Endpoint			
MRD Response Rate[7]	MRD response rate was the incidence of MRD negativity/response within 4 cycles of treatment with blinatumomab. MRD negativity/response was defined as bcr/abl and/or t(4;11) translocations that were below the detection limit and/or individual rearrangements of Ig or TCR genes below 10^{-4}. Analysed using the FAS (all patients who completed at least 1 treatment cycle and had at least 1 MRD response assessment).	The following hypotheses were tested in this study: H_0: π ≤ p0 = 5% vs. H1: π ≥ p1 = 30% Blinatumomab was not worth studying further if the MRD response probability (p_0) was estimated to be ≤5%. The future use of blinatumomab would be of considerable interest if the true MRD response probability was ≥30% (p_1).	N/A

Study Endpoints and Statistical Analyses			
	Definition	**Statistical Analyses**	**Censoring**
Secondary Endpoints			
TTHR/RFS[7]	Calculated from the start of the first infusion until hematologic relapse (≥5% leukemia cells in bone marrow) or death. Analyzed using the FAS.	K-M estimate of the median RFS and associated 2-sided 95% CI.	Censored at last available date of bone marrow aspiration/ biopsy.
Time to MRD progression[7]	Calculated from start of first infusion until MRD progression or hematologic relapse in patients who did not achieve MRD negativity. MRD progression was defined as an increase in MRD level by 1 log compared with baseline Analyzed using the FAS.	K-M estimate of the median RFS and associated 2-sided 95% CI.	Same as above
Time to MRD relapse/ duration of MRD response[7]	Calculated for patients from the time of first detection of MRD response until the first detection of MRD relapse was measured. Analyzed using the FAS.	K-M estimate of the median and associated 2-sided 95% CI.	Same as above
Safety[47]	Overall incidence and severity of AEs. All treated patients were included in the safety analysis set.	Summarized with descriptive statistics	N/A
HRQoL	Was not evaluated in this trial	N/A	N/A

Abbreviations: **AE** = adverse event; **BCR/ABL** = breakpoint cluster region/gene on human chromosome #9 (named after a researcher whose last name was Abelson); **CI** = confidence interval; **FAS** = full analysis set; **HRQoL** = health-related quality of life; **Ig** = immunoglobulin; **K-M** = Kaplan-Meier; **MRD** = minimal residual disease; **N/A** = not applicable; **PCR** = polymerase chain reaction; **RFS** = relapse-free survival; **TCR** = T-cell receptor; **TTHR** = time to hematologic relapse

Protocol Amendments

The first version of the study protocol was issued on 04-Jan-2007 and the protocol was amended three times on 21-Apr-2008, 27-Oct-2008 and 24-Mar-2009.[3,9] The two later amendments were issued to permit dose escalation of blinatumomab to 30 mcg/m^2/day after cycle 1 for patients without a positive response to the study treatment.[3]

The Neuf Study

Trial Design

The Neuf study was a retrospective observational cohort study of BCP-ALL adult and pediatric patients that received blinatumomab through expanded access programs in Europe and Russia between January 1st, 2014 and June 30th, 2017. As outlined in Table 10, patients were eligible if their medical charts were available for data extraction, and adult and pediatric patients had not received blinatumomab through another expanded access program for patients with R/R BCP-ALL called RIALTO. The Neuf study included patients with MRD+ or R/R disease, as well as Ph+ and Ph- disease. For the purposes of this report, only description of the study and results as relevant to the indication under review (MRD+, Ph-, BCP-ALL) will be reported.[5]

The baseline period was defined as the time from a patient's initial ALL diagnosis date until the day of blinatumomab initiation in the expanded access setting (clinical and treatment characteristics were collected prior to blinatumomab initiation). As this was a retrospective study data was only collected at one timepoint and was not collected on an ongoing basis; however, the study follow-up period was defined as the period from the start of blinatumomab until death, entry into a clinical trial, end of follow-up data, or end of the study period, whichever was earliest. The end of the study period was defined as December 31st, 2017.[13]

Primary Endpoint

According to the study protocol, the primary endpoint was to evaluate clinical and treatment characteristics.[5]

Secondary Endpoints

Secondary endpoints included:

- MRD Response Rate: defined as MRD ≤ 10^{-4} in the first 2 cycles of blinatumomab, subcategorized as:
    - Molecular CR: no detectable MRD using an assay with minimum sensitivity of ≥ 10^{-4} (aligned with BLAST definition)
    - Molecular remission (low-level non-quantifiable MRD <10^{-4})[5]
- DFS: time from initiating treatment to earliest hematological relapse or death (equivalent to RFS in BLAST and TTHR in MT103-202)
- OS
- Rate of allogeneic HSCT[5]
- Proportion of patients receiving subsequent chemotherapy or immunotherapy[13]

Statistical Analyses

No formal hypothesis testing or sample size calculations were conducted.

All analyses were descriptive, and were summarized by mean, median, standard deviation (SD), lower and upper quartiles, and range. Categorical variables were summarized by number and percentage of patients in each category, with 95% CIs when appropriate. Time-to-event endpoints were presented with K-M curves and K-M proportions at select time points. Patients were not excluded because of missing data. Primary and secondary analyses were also presented for subgroups of patients (if the subgroup included more than10 patients). Subgroup analyses for the indication under review included patients in CR1, in CR2 or higher, MRD relapse, MRD failure, in CR1 with MRD failure with or without HSCT, greater than 2 lines of TKIs, and T315I mutation.[13]

b) Populations

Demographic characteristics and descriptions for the BLAST trial, MT103-202, and the Neuf study are outlined in Table 14, 15, and 16, respectively.

BLAST

Demographic Characteristics

A total of 116 patients were included In the BLAST study and received at least one blinatumomab infusion (Table 14a). The majority of patients were male (68 out of 116; 59%) and white (102 out of 116; 88%). The median age was 45 years (range = 18.0 to 76.0), with 13% (15 out of 116) of patients being in the 65 years of age or older group.[3]

Disease Characteristics

Overall, 65% of patients were in first CR, and 35% were in second or third CR (Table 14b).[3] Of note, 27% (n = 31) had CR with incomplete blood count recovery, as per the National Comprehensive Cancer Network Guidelines (NCCN). While the BLAST trial

had the same criteria for ANC count as NCCN, a lower cut-off for platelets (> 50,000/mcl) was used in the BLAST trial for the definition of CR compared to NCCN guidelines (> 100,000/mcL).[3,14] A total of 106 (91%) patients were enrolled with MRD ≥ 10^{-3}; five (4%) patients were Ph+, and five (4%) patients had a t(4;11) translocation/MLL-AF4 fusion gene. Most patients were either standard risk (53%) based on local/national standards, followed by high risk (31%).

At diagnosis, 67% patients had a WBC less than or equal to 30,000 mm^3, 33% required a second induction course of salvage chemotherapy to achieve CR, and 44% had prior radiotherapy. The median time from last anti-leukemic treatment to initiation of blinatumomab was 2.0 months, ranging from 0 to 55 months.[3]

A total of 80 (69%) had pre-phase front line therapy, 44 (38%) had GMALL, 11 (10%) had a combination regimen, 11 (10%) had GMALL elderly, eight (7%) had Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) regimen, seven (6%) had the United Kingdom Acute Lymphoblastic Leukemia (UKALL) protocol, and six (5%) had Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) regimen. Less than 5% of patients received a number of other regimens in front line treatment, which included, but were not limited to, the Programa para el Tratamiento de Hemopatias Malignas (PETHEMA) regimen, the Northern Italy Leukemia Group (NILG) protocol, FLAG-IDA (fludarabine, cytarabine, granulocyte colony stimulating factor, and idarubicin), and TKI.[3]

Table 14: Demographic and Disease Characteristics in the BLAST trial

A. Demographic Characteristics

	Full Analysis Set (N = 116)
Sex - n (%)	
Male	68 (58.6)
Female	48 (41.4)
Race - n (%)	
White	102 (87.9)
Asian	1 (0.9)
Other (mixed)	1 (0.9)
Unknown	12 (10.3)
Age (years)	
n	116
Mean	44.6
SD	16.4
Median	45.0
Q1, Q3	29.5, 60.5
Min, Max	18, 76
Age Group - n (%)	
≥ 18 and < 35 years	36 (31.0)
≥ 35 and < 55 years	41 (35.3)
≥ 55 and < 65 years	24 (20.7)
≥ 65 years	15 (12.9)

Source: EPAR, 2018[3]

B. Disease Characteristics

	Full Analysis Set (N = 116)
Philadelphia chromosome disease status - n (%)	
Positive	5 (4.3)
Negative	111 (95.7)
Confirmed t(4;11) translocation / MLL-AF4+ ALL - n (%)	
Yes	5 (4.3)
No	88 (75.9)
Unknown	23 (19.8)
Risk Stratification based on local/national standards - n (%)	
Standard	61 (52.6)
Low	2 (1.7)
Intermediate	5 (4.3)
High	36 (31.0)
Very high	5 (4.3)
Unknown	7 (6.0)
Relapse history - n (%)	
Patients in 1st CR	75 (64.7)
Patients in 2nd CR	39 (33.6)
Patients in 3rd CR	2 (1.7)
Subject in CR per Cheson criteria - n (%)	
Patients in CR (BM blast ≤5% & ANC >1,000/mm^3 & Platelets >100,000/mm^3)	85 (73.3)
Patients not in CR per Cheson criteria	31 (26.7)
MRD level at baseline by central lab - n (%)	
≥10xE-1 and <10xE0	9 (7.8)
≥10xE-2 and <10xE-1	45 (38.8)
≥10xE-3 and <10xE-2	52 (44.8)
<10xE-3	3 (2.6)
Below LLOQ	5 (4.3)
Unknown	2 (1.7)

WBC at first diagnosis - n (%)	
≤30,000/mm^3	78 (67.2)
>30,000/mm^3	18 (15.5)
Unknown	20 (17.2)
WBC at screening - n (%)	
≤30,000/mm^3	116 (100.0)
>30,000/mm^3	0 (0.0)
Chemoresistance after the first week of chemotherapy - n (%)	
Yes	8 (6.9)
No	5 (4.3)
Unknown	103 (88.8)
Need of a second induction course (salvage) for complete haematological remission - n (%)	
Yes	38 (32.8)
No	77 (66.4)
Unknown	1 (0.9)
Previous anti-tumor radiotherapies - n (%)	51 (44.0)
Time from last anti-leukaemia treatment to first dose of blinatumomab (months)	
n	116
Mean	5.0
SD	8.9
Median	2.0
Q1, Q3	1.4, 3.7
Min, Max	0, 55
Time from last anti-leukaemia treatment to first dose of blinatumomab - n (%)	
<1 month	7 (6.0)
≥1 – <4 months	81 (69.8)
≥4 – <7 months	12 (10.3)
≥7 months	16 (13.8)
Time from diagnosis to first dose of blinatumomab (months)	
n	116
Mean	20.4
SD	31.0
Median	8.1
Q1, Q3	5.1, 22.9
Min, Max	3, 206

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N=Number of subjects in the analysis set. CR=Complete remission. MRD=Minimal residual disease. LLOQ=Lower limit of quantification. WBC=White blood cell.

Source: EPAR, 2018[3]

MT103-202

Demographic and Disease Characteristics

In the MT103-202 trial, a total of 21 patients were enrolled and treated with blinatumomab according to GMALL protocols (Table 15). A higher proportion of patients were female (57%) compared to the BLAST trial (41%). The median age was 47 years, comparable to the BLAST trial, ranging from 20 to 77 years.[2,8] A higher proportion of patients in MT103-202 were 65 years of age or older (29%) compared to the BLAST trial 1(3%).[2,3] All patients in MT103-202 were of white race.[3]

Almost all patients in MT103-202 were in CR1 (95%), which was higher compared to the BLAST trial (65%).[2,3] There was a smaller proportion of patients that had a baseline MRD level ≥ 10^{-3} (76%) in the MT103-202 trial compared to the BLAST trial. A total of 5 (24%) patients were Ph+ (and all were refractory to TKIs - imatinib and/or dasatinib), which was a higher proportion than in the

BLAST trial (4%).[2,8] There were two (10%) patients that had MLL-AF4 in MT103-202, which was higher than in the BLAST trial (4%).[3,8]

Of the 20 patients who were evaluable for MRD response, 15 (75%) patients had never become MRD- before enrollment in the MT103-202 study and were classified as molecularly refractory to conventional treatment.[8]

Table 15: Demographic and Disease Characteristics in MT103-202

Demographic and disease characteristics

Characteristic	No. of Patients	%
No. of patients enrolled		
Enrolled	21	
Evaluable for response	20	
Age, years		
Median	47	
Range	20-77	
Sex		
Female	12	
Male	9	
MRD		
TCR/Ig rearrangements	14	
BCR/ABL	5	
MLL-AF4	2	
No. of MRD assessments per patient before study enrollment		
Median	4	
Range	2-19	
Prior chemotherapy		
Pre-phase	13	62
Induction	21	100
Consolidation I	21	100
Consolidation II	11	52
Consolidation III	5	24
Consolidation IV	4	19
Consolidation V	3	14
Consolidation VI	1	5
Relapse therapy	2	10

Abbreviations: Ig, immunoglobulin; MRD, minimal residual disease; TCR, T-cell receptor.

Source: Topp et al: J Clin Oncol. 29(18), 2011:2493-2498. Reprinted with permission. © 2011 American Society of Clinical Oncology. All rights reserved.[8]

Neuf Study

Adult Demographic and Disease Characteristics

[redacted][12]

[redacted].[2,8,12]

[redacted][2,3,12] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

[redacted][12,46]

[redacted][12]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Pediatric Demographic and Disease Characteristics

[redacted]

[redacted][12,46]

[redacted][1]

[2] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Table 16: Demographic and Disease Characteristics of MRD+, Ph- BCP-ALL Adult and Pediatric Patients in the Neuf study

Demographic and disease characteristics by adult and pediatric populations

Characteristic	Adults (N = 83)	Children (N=39)
Sex – n (%)	[redacted]	
Male		
Female		
Age*, (years)		
Median (range)		
Age group – n (%)		
Infants (<2 years)		
Children (≥2 to <12 years)		
Adolescents (≥12 to <18 years)		
Adults (≥18 to <65 years)		

Adults (≥65 years)	[redacted]
Disease status* - n (%)	
Molecular failure	
Molecular relapse	
CD19 expression* – n (%)	
Yes	
No	
Unknown	
Bone marrow blasts* - n (%)	
≤5%	
6 to 9%	
10 to 49%	
≥50%	
Unknown	
Prior TKI	
Yes**	
No	
Unknown	
Response to frontline therapy	
CR/CRh/CRi	
Refractory	
Unknown	
HSCT prior to blinatumomab initiation	
Yes	
No	

*At time of blinatumomab initiation

** Prior TKIs used included imatinib (n=2) and dasatinib (n=1)

Abbreviations: CR = complete remission; **CRh** = complete remission with partial hematologic recovery; **CRi** = complete remission with incomplete hematologic recovery; HSCT = hematopoietic stem cell transplant; **N/A** = not applicable; **TKI** = tyrosine kinase inhibitor

Sources: Amgen Clinical Summary, 2020[5]; Amgen Neuf CSR, 2019[12]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

c) Interventions

BLAST and MT103-202

Intervention details of the BLAST trial and MT103-202 are outlined in Table 17 below.

Table 17: Intervention Details in the BLAST trial and MT103-202

	BLAST trial	MT103-202
Number of patients treated	116	21
Treatment dosing schedule	Blinatumomab 15 mcg/m2/day IV infusion over four weeks followed by a treatment-free period of two weeks.	Blinatumomab 15 mcg/m2/day IV infusion over four weeks followed by a treatment-free period of two weeks. A dose increase could be considered to 30 mcg/m^2 by the DRC if a patient did not respond after 2 cycles. A total of 3 patients had dose increased to 30 mcg/m^2.
Treatment cycle duration	Each cycle was 6-weeks (4 weeks of treatment/2 weeks treatment-free) and patients could be treated for up to 4 cycles.	Each cycle was 6-weeks (4 weeks of treatment/2 weeks treatment-free). Responders (i.e. those who achieved MRD negativity) could receive 3 additional cycles of blinatumomab as consolidation, up to a maximum of 10 cycles. Patients who showed neither MRD progression nor response received up to 7 cycles of treatment.
Treatment exposure	All 116 patients started at least 1 cycle of treatment with blinatumomab. A total of 84 (72%) completed 1 cycle of treatment, 56 (48%) completed 2 cycles, 24 (21%) completed 3 cycles, and 12 (10%) completed 4 cycles. The median duration of treatment exposure was 55 days (range= 1 to 113). The median cumulative dose was 820.7 mcg (range= 10.5 to 1689.0).	All 21 patients initiated treatment with blinatumomab, however 1 patient did not complete one full cycle of treatment. Thus, 95.2% (n = 20) of patients completed 1 cycle of treatment. The median number of completed treatment cycles was 3.
HSCT	Allowed any time after cycle 1 at the investigator's discretion. A total of 90 (77.6%) had HSCT after blinatumomab treatment, of which 76 (65.5%) patients underwent HSCT while in CR. There were 19 (16.3%) patients that were MRD+, 57 (49.1%) patients that were MRD-, and 14 (12.1%) that had hematologic relapse prior to HSCT. Of the patients who were in CR (n = 76), a total of 27 (23.2%) underwent HSCT after cycle 1, 36 (31.0%) after cycle 2, and 13 (11.2%) after cycles 3 to 4.	Eligible patients with a donor were offered allogeneic HSCT after the first cycle of blinatumomab. A total of 9 (42.9%) patients received allogenic HSCT after blinatumomab treatment. A total of 7 (33.3%) patients were MRD- prior to transplant.
Dosing modification	For non-hematologic grade 3 to 4 AEs that could not be controlled with medical management, blinatumomab was stopped. Study treatment	For grade 3 to 4 AEs and CNS-related AEs, blinatumomab was stopped. Study treatment could be restarted if treatment was interrupted within 14 days if the clinical

	BLAST trial	MT103-202
guidelines	could be restarted after recovery from the AE to grade ≤ 2. Treatment delays of > 2 weeks and reappearance of the same clinically relevant non-hematologic grade 3 to 4 AEs resulted in permanent discontinuation of treatment.	situation allowed according to the assessment of investigator.
Re-treatment with blinatumomab	Patients who completed the initial 4 cycle treatment could receive blinatumomab re-treatment if they had a complete MRD response of ≥ 4 weeks duration, did not receive HSCT/chemotherapy, and had MRD relapse within 18 months of the initiation of treatment. Blinatumomab re-treatment was not offered to patients who experienced hematologic relapse. A total of 3 (2.6%) patients were retreated with blinatumomab.	Re-treatment with blinatumomab was not permitted.
Concomitant medications	CNS prophylaxis (intrathecal dexamethasone 4 mg or equivalent, methotrexate 15 mg, and cytosine arabinoside 40 mg) was recommended before cycle 1 and after cycles 2 and 4. All patients received prednisone 100 mg or equivalent ≤ 1 hour before each cycle as prophylaxis for neurologic events and CRS. If neurologic or CRS events occurred, blinatumomab infusion was interrupted and patients could receive dexamethasone (24 mg/d for up to 3 days, then tapered over 4 days)	TKIs were permitted for patients with BCR/ABL positive MRD if patients developed MRD release on TKIs or MRD persisted on TKIs for > 8 weeks. Intrathecal prophylaxis was recommended to be conducted on a regular basis as per GMALL protocols in order to prevent CNS relapse. Five (23.8%) patients had BCR/ABL translocation, and all were refractory to imatinib and/or dasatinib. One patient continued to receive imatinib and underwent transplantation after 1 cycle of blinatumomab, and one patient continued to receive dasatinib while on treatment with blinatumomab up to cycle 3, where concomitant dasatinib was discontinued.
Restricted medications	Other antitumor therapies other than blinatumomab (including chemotherapy, radiation therapy, and immunotherapy), other investigational agents, chronic systemic high-dose corticosteroid therapy (i.e. > 20 mg prednisone daily), immunosuppressive therapies (other than protocol mandated corticosteroids), NSAIDs (except paracetamol/acetaminophen), and TKIs.	Other antitumor therapies other than blinatumomab (including chemotherapy, radiation therapy, and immunotherapy; except TKIs for BCR/ABL positive MRD ALL), other investigational agents, chronic systemic high-dose corticosteroid therapy, immunosuppressive therapies, NSAIDs (except paracetamol/acetaminophen), and stem-cell transplantation.
Subsequent therapies	A total of 48 (41.4%) received post protocol treatment medications, of which 29 (25%) received subsequent chemotherapy. The most frequently administered subsequent therapies included: antimetabolites (n = 33; 28..4%); alkylating agents (n = 21; 18.1%); plant alkaloids and other natural products (n = 21; 18.1%); corticosteroids for systemic use (n = 20; 17.2%), other antineoplastic agents (n = 20; 17.2%); and cytotoxic antibodies and related substances (n =	Information unavailable.

	BLAST trial	MT103-202
	18; 15.5%).	

Abbreviations: AE = adverse event; **ALL** = acute lymphoblastic leukemia; **CNS** = central nervous system; **CRS** = cytokine release syndrome; **BCR/ABL** = breakpoint cluster region/gene on human chromosome #9 (named after a researcher whose last name was Abelson); **DRC** = data review committee; **GMALL** = German Multicentre Study Group on Adult Acute Lymphoblastic Leukemia; **HSCT** = hematopoietic stem cell transplant; **IV** = intravenous; **m** = metre; **mcg =** microgram; **MRD** = minimal residual disease; **NSAID** = non-steroidal anti-inflammatory drug; **TKI** = tyrosine kinase inhibitor

Sources: Amgen, Protocol (BLAST);[45] Amgen, Protocol (MT103-202);[9] Amgen, Checkpoint Responses;[18] EPAR, 2018;[3] Gokubuget et al., 2018;[2] Topp et al., 2012;[34] Topp et al., 2011[8]

The Neuf Study

Due to the retrospective nature of the study, there was no protocol-specified dose or dosing schedule defined for blinatumomab as treatment was administered through an expanded access program. Among the MRD+, Ph- BCP-ALL adult population, the median number of cycles was 2 (range = 1 to 6), and the median cumulative dose was 772 mcg (range= 9 to 1352.5). Most patients received 1 to 2 cycles of blinatumomab, 31.3% started a third cycle, and 9.6% started more than 4 cycles. This was broadly consistent with the BLAST trial.[18]

[redacted][46] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Among pediatric MRD+, Ph- BCP-ALL patients (n=39), the median number of started cycles was 1 (range = 1 to 6) and the median cumulative dose was 424.7 mcg (range = 18.6 to 787.7). Most patients received 1 to 2 cycles similar to the adult population, 10.3% started a third cycle, and 2.6% started more than four cycles.[18]

[redacted][46]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Other subsequent therapies for both populations included chemotherapy and TKIs.[46]

d) Patient Disposition

BLAST trial

The patient disposition diagram as of the key secondary analysis (August 5th, 2015) for the BLAST trial is outlined in Figure 3. Overall, 116 adults with MRD+ BCP-ALL were enrolled in the BLAST study and received treatment between November 2010 and February 2014. As the figure shows, 211 patients were screened for eligibility; of whom, 95 patients (45%) patients failed screening. Reasons for not meeting eligibility criteria included: MRD level lower than the required ≥ 10^{-3} (n = 48); not in hematologic CR (n = 31); technical reasons (n = 5); CNS relapse (n = 2); active infection (n = 2); alternative therapy (n = 2); neurologic disorder (n = 2); negative CD19 (n = 1); hepatic disorder (n = 1); and withdrawal of consent (n = 1). All 116 patients received blinatumomab treatment.

A total of 33 (28%) patients discontinued treatment, with 20 (17%) patients that discontinued due to AEs, 10 (9%) patients that discontinued due to disease relapse; 2 (2%) patients that discontinued due to physician decision, and 1 (1%) that discontinued for other reasons. A total of 54 (47%) of patients had permanently discontinued the trial, primarily due to death (n = 53; 46%). One patient withdrew consent. A total of 62 (53%) of patients were alive and in follow-up.[2]

At the time of long-term follow-up (January 7th, 2019), 41% (n = 48) had completed follow-up, 58% (n = 67) had died, and 1% (n = 1) had withdrawn.[5]

As outlined in *a) Trials* under the BLAST trial, there were 4 analysis sets, which included:

1) FAS; n = 116: included all patients that initiated treatment with blinatumomab and was used to describe patient characteristics and safety at the time of the secondary analysis, and for OS at the time of the final analysis.
2) Prim EP FAS; n = 113: subset of the FAS that excluded those that did not have MRD results or did not have MRD testing with an assay sensitivity of at least 10^{-4}; thus, the Prim EP FAS included patients with Ph+ disease. This analysis set was used for the complete MRD rate analysis after cycle 1.
3) Primary Endpoint Efficacy Set (Prim Efficacy Set); n = 103: subset of the Prim EP FAS that further excludes those without hematological CR or with MRD ≤ 10^{-3}; thus the Prim Efficacy Set includes those with Ph+ disease. This analysis set was used for overall MRD rate, which represented the intended study population.
4) Key Sec EP FAS; n = 110: subset of the FAS that excluded those with Ph+ disease and those that did not have hematological CR. This analysis set was used for the analysis of RFS, and secondary endpoints at the time of the key secondary analysis.[2]

Protocol Deviations

Relevant major protocol deviations are summarized in Table 18. Overall, 54 (46.6%) patients had at least one protocol deviation. A total of 11 (9.5%) patients did not fulfill eligibility criteria, 11 (9.5%) did not have treatment administer per protocol, 7 (6.0%), patients did not have assessments done, 7 (6.0%) patients did not have assessment done per protocol, 5 (4.3%) patients had prohibited medication, and 1 (0.9%) had a visit out of schedule.[3] The most common eligibility criteria not fulfilled was related to bone marrow screening not being done > 2 weeks after the last dose of systemic therapy (n = 5), and the most common treatment not administered as per protocol violation was related to pre-phase dexamethasone administration (n = 5). A total of 32 (27.6%) of patients had “other” protocol violations (error in Table 18 that indicated 31 instead of 32), most commonly related to informed consent (e.g. obtaining signatures for updated to consent forms), and timeliness of AE reporting.[18]

Figure 3: Patient Disposition Flow Diagram for the BLAST trial

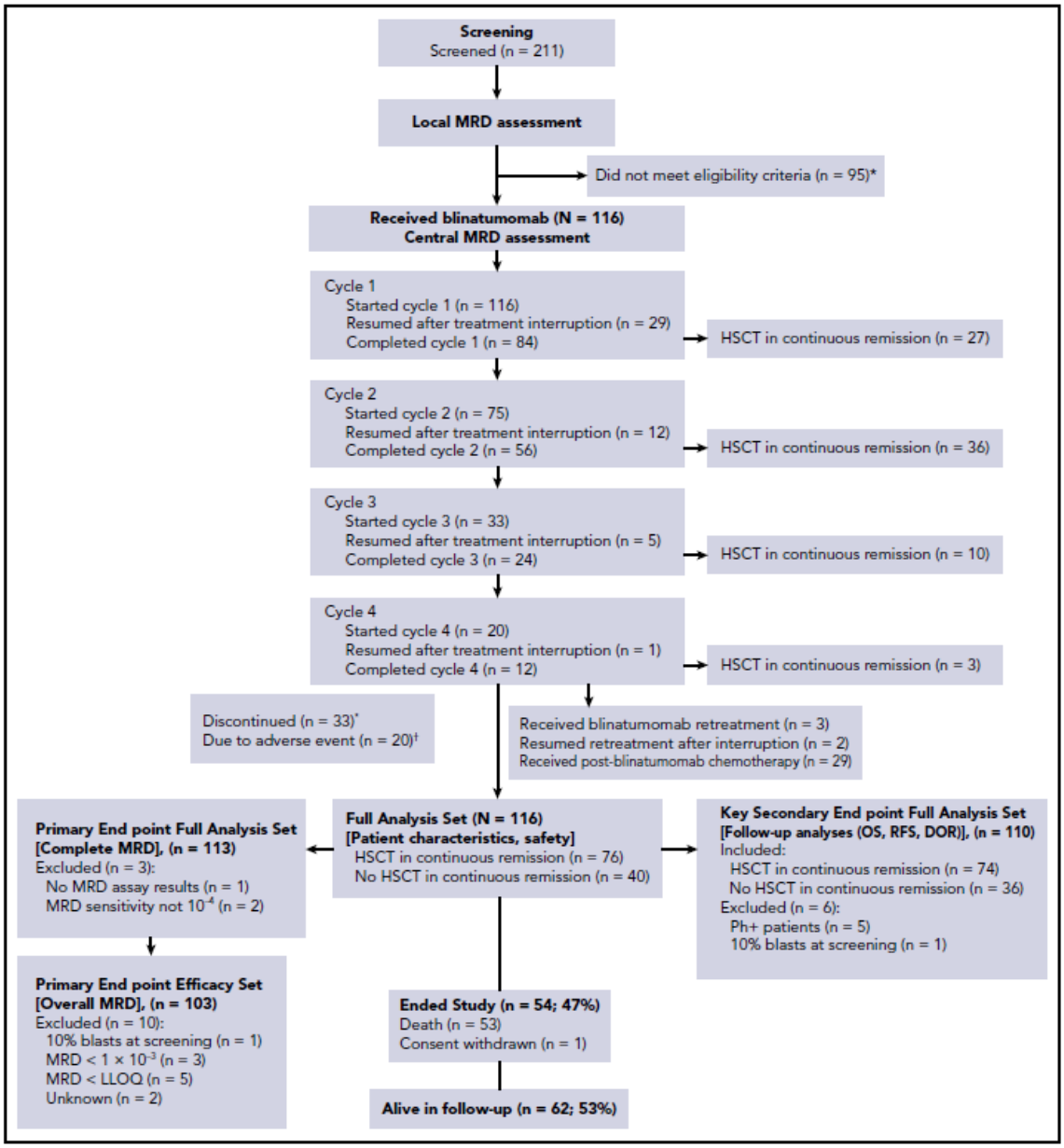

Figure 1. Disposition of patients in the study. *Reasons for not meeting eligibility criteria included: MRD level lower than the required ≥10^{-3} (therefore, inclusion criterion not fulfilled because disease burden too low; n = 48); not in hematologic CR (ie, overt relapse; n = 31); technical (n = 5); central nervous system relapse (n = 2); active infection (n = 2); alternative therapy (n = 2); neurologic disorder (n = 2); CD19^{-} (n = 1); hepatic disorder (n = 1); and consent withdrawn (n = 1). †Reasons for discontinuation (n = 33) included: adverse event (n = 20 [17.2%]), disease relapse (n = 10 [8.6%]), physician decision (n = 2 [1.7%]), and other (n = 1 [0.9%]). DOR, duration of hematologic remission; LLOQ, lower limit of quantitation; RFS, relapse-free survival.

Data cut-off: August 5th, 2015

Source: Republished with permission of American Society of Hematology, from Gokbuget et al., Blood. 2018;131(14):1522-1531. Copyright 2018; permission conveyed through Copyright Clearance Center, Inc.[2]

Table 18: Summary of Relevant Protocol Deviations

	Full Analysis Set (N = 116) n (%)
Number of subjects with at least one relevant protocol violation	54 (46.6)
Other	31 (26.7)
Not fullfilling Inclusion / Exclusion criteria	11 (9.5)
Treatment not administered per protocol	11 (9.5)
Assessment not done	7 (6.0)
Assessment not done per protocol	7 (6.0)
Forbidden medication	5 (4.3)
Visit out of schedule	1 (0.9)

CRF = case report form; N = Number of subjects in the analysis set.
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.

Source: EPAR, 2018[3]

MT103-202

The patient disposition flow diagram for MT103-202 is presented in Table 19. Between May 2008 and November 2009, a total of 32 patients were assessed for eligibility; of those, 21 patients were enrolled in the MT103-202 study.[3,8] All treated patients were included in the safety analysis. One patient had completed less than one cycle of blinatumomab and did not have at least one MRD assessment, and thus was not included in the FAS (n = 20), which was used for the primary efficacy analyses. At the time of data cut-off (January 14th, 2010), 10 (50.0%) patients completed the study (8 patients reached the end of study and two patients received a bone marrow transplant after four cycles of treatment), and 10 (50.0%) patients terminated the study prematurely. Reasons for premature study termination included: patient received a bone marrow transplant between one to three cycles of blinatumomab treatment (n = 6; 30.0%), AE (n = 1; 5%), patient was not compliant (n = 1; 5%), hematological relapse (n = 1; 5%), and MRD relapse (n = 1; 5%).[3]

Table 19: Patient Disposition in the MT103-202 trial, FAS (n=20)

	Blinatumomab Cohorts					
	Constant Dose [15 µg/m²/d] (N=17)		Dose Increase [15/30 µg/m²/d] (N=3)		Total (N=20)	
	n	%	n	%	n	%
Patient Completed the Study	8	(47.1%)	2	(66.7%)	10	(50.0%)
Reason for Study Termination						
End of Study	7	(41.2%)	1	(33.3%)	8	(40.0%)
Other: Patient received a bone marrow transplant after 4 cycles of treatment	1	(5.9%)	1	(33.3%)	2	(10.0%)
Patient Terminated the Study Prematurely	9	(52.9%)	1	(33.3%)	10	(50.0%)
Reason for Study Termination						
Adverse Event	1	(5.9%)	0	(0.0%)	1	(5.0%)
Patient was not Compliant	1	(5.9%)	0	(0.0%)	1	(5.0%)
Hematological Relapse	1	(5.9%)	0	(0.0%)	1	(5.0%)
MRD Relapse	1	(5.9%)	0	(0.0%)	1	(5.0%)
Other: Patient received a bone marrow transplant after at least 1 or maximal 3 cycles of treatment	5	(29.4%)	1	(33.3%)	6	(30.0%)

Page 2 of 2

Note: Subject 111-005 documented as reason for study termination "End of study" and was transplanted afterwards. Therefore, this subject was evaluated as "Other: Patient received a bone marrow transplant after 4 cycles of treatment".
MRD: minimal residual disease
Source: Table 14-1.2

Source: EPAR, 2018[3]

The Neuf Study

The Neuf study included a total of 414 patients, of which 373 (90.1%) were adult patients and 41 (9.9%) were pediatric patients with R/R or MRD+ (Ph+ or Ph-), BCP-ALL.

The Neuf Study included a total of 122 (29.5%) patients that were MRD+, Ph-, BCP-ALL patients. Hereafter, the report will describe the results reflective of this patient population, and 122 MRD+, Ph-, BCP ALL patients will be referred to as the total population. Of the 122 total patients, 83 (68.0%) were adults and 39 (32.0%) were pediatric patients with MRD+, Ph-, BCP-ALL.[5]

e) Limitations/Sources of Bias

The efficacy and safety of blinatumomab in adults with MRD+, Ph-, BCP-ALL is largely based on one single-arm, phase II confirmatory trial (BLAST), which included validated secondary outcomes such as RFS and OS, and the study has 90% power to detect statistical differences in both the primary and secondary outcomes that were controlled for multiplicity. The efficacy and safety data is supported by a pilot phase II study, MT103-202, and a retrospective, observational study, the Neuf study.

The effectiveness of blinatumomab in pediatric patients with MRD+, Ph-, BCP-ALL is limited to one retrospective, observational study. There is no direct safety evidence for the pediatric population, however safety data from the R./R setting in patients with BCP-ALL is characterized from numerous studies and summarized in Section 8.

To address the lack to comparative evidence in adult patients, an ITC was submitted that compared blinatumomab to no blinatumomab based on a historical comparator study and is summarized in Section 7.

Limitations included:

Factor	Description of limitation
Study design	Lack of comparative data: Both the BLAST trial and MT103-202 were single-arm studies, and Neuf was an observational study. Direct comparison of efficacy, safety, and HRQoL of blinatumomab with standard treatment was not conducted, and therefore firm conclusions on the magnitude of the clinical benefit cannot be drawn. An ITC using PS analysis was submitted by the sponsor to compare blinatumomab with a historical comparator group. Details of this analysis and associated limitations is presented in Section 7.
	Open-label study design (BLAST and MT103-202): The open-label nature of the studies may have introduced several biases. Investigators may have referred patients for participation in the clinical trial that were generally in good health or fitness given their diagnosis, and patients who more motivated and likely to comply with treatment, resulting in patient selection bias in the studies. Since patients were aware of treatment, they may have had indicated more favourable responses to HRQoL questionnaires resulting in performance bias. Reporting biases by both the investigator and patient were possible, as the investigator may have assessed AEs as lower grade or unrelated to study drug, and patients may have overreported specific AEs if they believed they were related to the drug. There may have been detection bias by investigators, as confirmation of hematologic relapse in the presence of clinical symptoms may have been delayed until the protocol defined timepoints (e.g., clinical symptoms may have suggested relapse and patients were treated appropriately but hematologic confirmation may have been delayed; timepoint for RFS depends on hematologic confirmation of relapse).
	Observational, retrospective study design using data from medical records (Neuf study): Data was collected from medical records kept as per routine clinical practise for the documentation and decision-making for a patient's care, and thus the completeness (and/or clarity), reliability (i.e. consistency of assessments), validity (i.e. accuracy of data capture), and quality (no quality control or data audits) are uncertain. Given the design was retrospective, any unmeasured data on important covariates or prognostic factors cannot be ascertained. Data may not be missing at random, in cases where care was sought elsewhere or off-site. There also may be information bias present, as there may be detailed records of more complicated or severe outcomes. Any patients who died during the time period of retrospective data collection could not consent for their data to be accessed for the purposes of the Neuf study and, as such, those included in the study may have had a longer survival time indicative of selection bias. Since the Neuf study included patients who accessed blinatumomab via expanded access, which started in 2015, blinatumomab was likely received in earlier stages of its development and patients might have had more severe disease and less treatment options.
Patient population	Lack of efficacy and safety data on pediatric patients: There was limited data available on pediatric patients. The Neuf study had a number of limitations, described earlier in this table under Study Design. Only 27 patients were included in the analysis. There was no safety data available on patients with MRD+, BCP-ALL and supplemental safety information on blinatumomab in pediatric patients for other ALL populations are described in section 8.
Statistical analyses and assessment of outcomes	Selection of MRD response rate as a primary endpoint: There is limited evidence to suggest MRD response rate is a surrogate endpoint for established endpoints such as OS, and EFS in patients with ALL. While MRD positivity at the end of induction therapy is a prognostic indicator for relapse risk, whether the introduction of therapies to induce MRD negativity translates directly into clinical benefit (i.e. correlation with established endpoints) is yet to be established. This combined with the limitations of the study design, introduce uncertainty in the conclusions on the efficacy of blinatumomab.

Factor	Description of limitation
	Subpopulation analysis sets: The BLAST trial used different analysis sets for evaluation of each outcome. At the time of secondary analysis, the FAS, which would be considered the ITT population, was not used uniformly as the primary dataset for evaluation of all outcomes, and instead, subsets of the population were selected for specific outcomes. This may have introduced reporting bias to the study results by overestimating the magnitude of efficacy outcomes. For example, for the primary analysis, patients with Ph+ disease were included, and patients with no MRD assessment or patients tested with a different MRD assay sensitivity were excluded. While the number of patients from MRD response rate excluded were small, (n = 3), a more conservative approach would have been to include these patients and consider them non-responders to provide an estimate that would represent the general population, especially given the numerous limitations of the study design (open-label, single-arm). In addition, Ph+ patients were not included in the patient population used to analyze key secondary outcomes such as RFS (and, thus by exclusion RFS may have been inflated). While patients with Ph+ disease may be considered to respond similarly to Ph- patients in terms of MRD response , these patients generally have a poorer prognosis (i.e., worse RFS and OS).[14] These subtle differences in patient populations create inconsistencies in interpretation of the evidence. However, since generally small numbers of patients were excluded, the impact on outcomes is considered minimal.
	Definition of RFS: RFS was calculated from the time of blinatumomab initiation until the date of documented hematological relapse, PD, extramedullary relapse, or death due to any cause. Typically, RFS is calculated from time of CR or CR with partial hematological recovery is detected.[15] The time from last anti-leukemic treatment (i.e. achievement of CR) varied, ranging from 1 month to 4.5 years with a median of 2.1 months.[3] Patients with longer intervals between time to CR to first dose of blinatumomab may have biased RFS and OS in favour of blinatumomab as duration of CR1 in this patient population is a favourable prognostic marker.[16] Additionally, the primary analysis of RFS included a censoring rule to censor at the time of HSCT or initiation of post-blinatumomab therapy prior to relapse, and supportive analyses that did not include this in the censoring rules were provided and were generally consistent. Censoring patients at the time of HSCT or initiation of post-blinatumomab therapy prior to relapse are assumed to have similar risk of relapse as those who are not censored, which may bias the results especially due to the high proportion of patients undergoing HSCT. Specifically, this approach may inflate the magnitude of the benefit, as HSCT is associated with a mortality risk. Since blinatumomab is a therapy that acts as a bridge to transplant, this mortality risk should be accounted for in the RFS estimate. Patients who could not tolerate or discontinued blinatumomab prior to relapse for any reason and started another therapy should also have been accounted for in the primary analysis of RFS as a more conservative approach.
	Additional note on the impact of HSCT and MRD status: A total of 90 (77.6%) had HSCT after blinatumomab treatment, of which 76 (65.5%) patients underwent HSCT while in CR and 14 (12.1%) that underwent HSCT after hematologic relapse. Of those that were in CR, 19 (16.3%) patients were MRD+ and 57 (49.1%) patients that were MRD-. Two landmark analyses conducted at 3- and 6-month timepoints for RFS and OS with and without censoring for HSCT or post-blinatumomab therapy suggested that patients who had subsequent HSCT had lower RFS and OS than those patients who did not. It is not clear if there was an increased mortality risk due to HSCT alone or due to some synergistic effect of blinatumomab and HSCT that led to lower RFS and OS. It is possible that patients who did not receive subsequent HSCT perhaps had low-risk disease characteristics, which resulted in better outcomes, however < 25% of the BLAST trial did not have subsequent HSCT. Further subgroup analyses were requested that suggested patients who achieved MRD-negativity prior to transplant, compared to those with persistent MRD-positivity, had RFS and OS that was higher than reported in the primary analyses of these

Factor	Description of limitation
	endpoints; Patients with persistent MRD-positivity who received subsequent HSCT had much worse outcomes that were significantly lower than that of the primary analyses. It is possible that the lower RFS and OS observed without censoring for HSCT or post-blinatumomab therapy may have been driven by worse outcomes of patients who had persistent MRD-positivity or hematologic relapse prior to transplant. Nonetheless, there is uncertainty surrounding the impact of HSCT following blinatumomab on efficacy outcomes.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

BLAST trial

Primary Endpoint: Complete MRD Response Rate

The data cut-off date for the primary analysis was February 21st, 2014. As outlined in Table 20, a complete MRD response was achieved in 77% (95% CI, 68 to 84) of patients in in the Prim EP FAS (n = 113) within one cycle of treatment.[5] The complete MRD response 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 of 44%. Complete MRD response rate using the Prim EP Efficacy Set (n = 103), and the Prim EP PPS (n = 98) were consistent with the primary outcome results in the Prim EP FAS.[3]

An additional three patients achieved complete MRD response after cycle 2, resulting in an overall complete MRD response rate (i.e. response within and beyond cycle 1) of 80% (95% CI, 71 to 87) in the Prim EP FAS (n= 113). The median time to complete MRD response was 29 days (range = 5 to 428).[5] Two of the three patients achieved a response in cycle 2, and one patient achieved a response on day 428. The patient who achieved a response on day 428 experienced hematologic relapse following treatment with blinatumomab and received subsequent anticancer therapy before a complete MRD response was observed.[46]

Subgroup analyses in the Prim EP FAS were generally consistent with the primary results. MRD responses were seen in all subgroups of interest, including age, baseline MRD level, relapse history, and time from last treatment. Of note, patients with baseline MRD levels ≥ 10^{-1} to < 1 seemed to have lower MRD response (complete MRD response rate = 66.7%; 95% CI, 29.9 to 92.9) with a lower limit of the 95% CI that was below 44%, similar to those with an MRD < 10^{-3} where although the response rate was 100%, the lower limit of the 95% CI was below 44% (complete MRD response rate = 100.0%; 95% CI, 29.2 to 100.0). The subgroup analyses also suggested that patients beyond first CR (i.e., CR2 or CR3), may have had lower MRD response rates than patients who are in CR1. In addition, patients who received blinatumomab less than or equal to 6 months from their last treatment had a lower MRD response rate than those who were treated with blinatumomab for greater than 6 months after their previous threatment.[5] However, these subgroup analyses were not powered for statistical significance and some had small sample sizes and thus, results must be interpreted with caution.

Table 20: Subgroup Analyses of Complete MRD Response (Within 1 cycle of Treatment) in the BLAST trial, Prim EP FAS (n=113)

Demographic		Primary Endpoint FAS[a] (N = 113) n/N	Complete MRD Response Rate, % (95% CI)
Overall		87/113	77.0 (68.1, 84.4)
Age group	18 to < 35 years	29/36	80.6 (64.0, 91.8)
	35 to < 55 years	28/38	73.7 (56.9, 86.6)
	55 to < 65 years	18/24	75.0 (53.3, 90.2)
	≥ 65 years	12/15	80.0 (51.9, 95.7)
Sex	Male	50/67	74.6 (62.5, 84.5)
	Female	37/46	80.4 (66.1, 90.6)
Baseline MRD levels, n (%)	$\geq 10^{-1} < 1$	6/9	66.7 (29.9, 92.85)
	$\geq 10^{-2} < 10^{-1}$	35/44	79.5 (64.7, 90.2)
	$\geq 10^{-3} < 10^{-2}$	40/51	78.4 (64.7, 88.7)
	$< 10^{-3}$	3/3	100.0 (29.2, 100.0)
Relapse history	CR1	60/73	82.2 (71.5, 90.2)
	CR2	26/38	68.4 (51.3, 82.5)
	CR3	1/2	50.0 (1.3, 98.7)
Time from last treatment	≤ 6 months	69/95	72.6 (62.5, 81.3)
	> 6 months	18/18	100.0 (81.5, 100.0)
Experienced neurologic event during cycle 1	Yes	40/52	76.9 (63.2, 87.5)
	No	47/61	77.0 (64.5, 86.8)

Source: Amgen Clinical Summary, 2020[5]

Secondary Endpoints

Analyses were conducted at the time of the secondary analysis (data cut-off: August 5th, 2015) and at the time of the final analysis (January 7th, 2019). The BLAST final analysis was conducted after a median follow-up of 59.8 months.[5]

Hematologic RFS rate at 18 months

Hematologic RFS rate was conducted with the Key Sec EP FAS (n = 110). At the time of the secondary analysis, the median duration of follow-up was 29.9 months for RFS. The median K-M estimate for RFS at 18 months with censoring for HSCT or post-blinatumomab therapy was 54% (95% CI, 33 to 70), which exceeded the prespecified boundary of 28%, thereby meeting the key secondary endpoint.[2] This was consistent with the K-M RFS estimate at 18 months without censoring for HSCT or post-blinatumomab therapy (53%; 95% CI, 44 to 62). Median RFS was 18.9 months (95% CI, 12.3 to 35.2) without censoring patients at the time of HSCT or post-blinatumomab therapy, whereas median RFS was NE (95% CI, 6.3 to NE) with censoring patients at the time of HSCT or post-blinatumomab therapy.[3]

[redacted][5] [5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* The K-M curves are available in Figure 4.

Figure 4: K-M Curves of Hematologic Relapse-free at Survival by Patients who were Censored and Not Censored at HSCT or Post-blinatumomab Therapy in the BLAST trial, Key Sec EP FAS (n=110)

Note: Data from the

BLAST final analysis (January 7th 2019)

Source: Amgen Clinical Summary, 2020[5]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Hematologic RFS Rate: HSCT and Landmark Analyses

As pre-specified in the statistical analysis plan (SAP), two landmark analyses were conducted at 3- and 6-month post blinatumomab initiation by transplantation status at the landmark time (i.e. patients who did not have HSCT by the landmark time were considered "non-transplanted" even if transplantation occurred after the landmark time). A total of 97 patients (34 in the transplanted and 63 in the non-transplanted arm) and 82 patients (63 in the transplanted and 19 in the non-transplanted) were included in the 3-month and 6-month landmark analyses, respectively.[3] At the time of the final analysis, median RFS from the 3-month landmark time was 22.1 months (95% CI, 12.0 to 42.0) in non-transplanted patients and 18.0 months (95% CI, 11.3 to NE) in those who were transplanted. Median RFS from the 6-month landmark time was 39.0 months (95% CI, 4.4 to NE) in those without a transplant and 29.2 months (95% CI, 16.1 to NE) in those without a transplant.[4] These analyses should be interpreted with caution, as patients who had fatal AEs, discontinued due to toxicities, were intolerant of blinatumomab, or withdrew potentially due to reasons related to blinatumomab prior to the landmark time were not included. These estimates reflect RFS of those who had prognostic characteristics and experienced benefit with blinatumomab and/or HSCT and provided a more optimistic estimate of clinical benefit from specific time points.

Hematologic RFS Rate: MRD response and Day 45 landmark analysis

A prespecified landmark analysis was conducted starting from day 45 to assess the impact of MRD response on RFS. Patients who had relapsed or died, and those who had been censored before day 45 (the day by which all cycle 1 MRD responses had been assessed) were excluded. A total of 107 patients were included (84 with MRD response at any cycle and 16 non-MRD responders). In the landmark analysis conducted at the time of final analysis, the median RFS was longer by 19.3 months in patients who achieved a complete MRD response at any cycle (26.6 months; 95% CI, 17.8 to NE) versus those who did not have a complete MRD response (7.3 months; 95% CI, 2.7 to 13.6).[5] Similar to the 3- and 6-month landmark analyses, these results should be interpreted with caution due to the small proportion of patients that were MRD non-responders, and the exclusion of patients who may have had blinatumomab-related events (i.e., adverse or fatal reaction leading to discontinuation, or voluntary withdrawal), which presents a more optimistic estimate of RFS.

Hematologic RFS Rate: Subgroup Analyses

At the time of the final analysis, subgroup analyses showed median RFS was generally consistent with the primary RFS analysis. Of note, numerically median RFS was shorter in the 35 to 54 years (median RFS = 17.9 months) and 55 to 64 years (median RFS = 12.3 months) age groups, in females (median RFS = 18.2 month), and in patients with MRD levels ≥ 10^{-2} and < 1.0 (median RFS = 18.9 months); however, none were statistically significant. Relapse history was significantly associated with longer hematologic RFS (P = 0.022), as patients in CR1 (median RFS = 24.6 months) had RFS that was twice that of patients in CR2 or CR3 (median RFS = 11.0 months).[4] Subgroup analyses are exploratory and included small sample sizes, and thus should be interpreted with caution.

OS

Overall survival was assessed in the Key Sec EP FAS (n = 110) at the time of the secondary analysis (August 5th, 2015). At the time of the secondary analysis, the median duration of follow-up was 30.0 months for OS. A total of 48 deaths out of 100 patients (43.6%) had occurred. The median OS was 36.5 months (95% CI, 19.8 to NE) without censoring patients for HSCT or post blinatumomab therapy, whereas it was NE with censoring for HSCT or post-blinatumomab therapy.[2]

Overall survival was assessed in the FAS (n = 116), which was considered consistent with the ITT principle, at the time of the final analysis. A total of 67 deaths (58%) had occurred in the FAS.

[redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Figure 5: OS with and without Censoring at HSCT and Post-blinatumomab Therapy in the BLAST trial, FAS (n=116)

[redacted]

Note: Data from the BLAST final analysis (January 7th 2019)

Source: Amgen Clinical Summary, 2020[5]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

OS: HSCT and landmark analyses

Landmark analyses at 3 and 6 months post-blinatumomab initiation by HSCT status was conducted, which included patients who were alive at each of the landmark timepoints using a subset of the FAS. In the 3-month landmark analyses 113 (37 transplanted, 76 non-transplanted) patients were included; and in the 6-month landmark analysis 103 (73 transplanted, 30 non-transplanted) patients were included. OS from the 3-month landmark timepoint in patients who received HSCT was 21.2 months (95% CI, 13.0 to NE) and for patients who were not transplanted was 34.4 months (95% CI, 19.0 to NE). OS from the 6-month landmark timepoint in patients who received HSCT was 38.6 months (95% CI, 17.5 to NE) and for patients who were not transplanted was 43.1 months (95% CI, 16.0 to NE).[4] As mentioned in the RFS landmark section, these results should be interpreted with caution as they likely represent patients with better prognostic factors and those who experienced clinical benefit, rather than all patients who may be exposed to blinatumomab.

OS: MRD response and day 45 landmark analyses

The impact of MRD response on OS was assessed based on day 45 landmark time. This analysis included a subset of patients 112 patients from the FAS who were alive and without relapse at day 45. A total of 87 patients who had an MRD response at cycle 1 and 25 patients without MRD response were included. The median OS was 45.8 months longer in patients with a complete MRD response at any cycle (median OS = 56.4 months; 95% CI, 27.3 to NE) compared to patients who were MRD non-responders (median OS = 10.6 months; 95% CI, 4.5 to 21.6).[4]

OS: Subgroup analyses

At the time of the final analysis, subgroup analyses showed median OS was generally consistent with the primary OS analysis. Of note, the median OS was numerically shorter in the 55 to 64 years age group (median OS = 19.2 months), in females (median OS = 21.3 months), in patients in CR2 or CR3 (median OS = 19.8 months), and in patients with MRD levels at baseline that were ≥ 10^{-2} and < 1.0 (median OS = 28.8 months); however, none of these were statistically significantly associated with shorter OS. Patients with Ph+ disease had significantly worse OS, with a median OS of 7.2 months compared to 36.5 months in patients with Ph- disease (P = 0.044).[4] Subgroup analyses are exploratory and included small sample sizes, and thus should be interpreted with caution.

Duration of MRD response

Duration of MRD response included 84 patients from the Key Sec EP FAS and Prim EP FAS who had an MRD response (i.e. achieved MRD negativity) at cycle 1. As noted earlier, the number of patients with MRD response from the Prim EP FAS was 87; three patients who achieved MRD response were additionally excluded from the analysis of duration of MRD response based in the Key Sec EP FAS due to having Ph+ disease or having > 10% blasts at screening. At the time of the final analysis, the median duration of MRD response was 22.9 months (95% CI, 8.1 to NE) with censoring patients at the time of HSCT or post-blinatumomab therapy, and 17.9 months (95% CI, 13.3 to 23.2) without censoring patients for HSCT or post-blinatumomab therapy.[4] An exploratory sensitivity analysis was requested by the Methods team to include all 87 patients who achieved MRD response that showed the median duration of MRD response was 17.9 months (95% CI, 12.6 to 23.2). This was slightly lower than the MRD response duration estimated in the primary analysis suggesting that Ph+ patients or those with > 10% blasts at screening may have a shorter duration of MRD response.[46]

TTHR

TTHR was conducted in the Key Sec EP FAS, which included a total of 110 patients. At the time of the final analysis, median TTHR without censoring patients at the time of HSCT or post-blinatumomab therapy was 27.3 months (95% CI, 7.1 to NE) and with censoring for HSCT or post-blinatumomab therapy median TTHR was NE (95% CI, 24.6 to NE).[4]

Ad-hoc, exploratory, subgroup analyses: Impact of HSCT on RFS and OS

Additional exploratory analyses were requested by the Methods team to further explore the impact of HSCT on outcomes. A total of 57 (49.1%) patients were MRD- following blinatumomab treatment who went on to receive subsequent HSCT, and a total of 19 (16.4%) patients had persistent MRD positivity following blinatumomab treatment and went on to receive subsequent HSCT. Using a 3-month landmark analysis, median RFS was 32.2 months (95% CI, 16.7 to NE) in patients who achieved MRD negativity prior to HSCT, and median RFS was 9.1 months (95% CI, 3.8 to 25.8) in patients who had persistent MRD positivity prior to transplant,

indicating that achievement of MRD negativity prior to transplant supported better outcomes. The 3-month landmark analysis of OS among patients who received post-baseline HSCT in the subgroups of patients who were MRD- (median OS = 32.2 months; 95% CI, 16.7 to NE) compared to those who were MRD+ (median 0S = 9.1 months; 95% CI, 3.8 to 25.8) showed similar results to RFS.[46]

Another 3-month landmark analysis was performed in the subgroup of patients who were in CR prior to HSCT (including 57 patients who were MRD+ and 19 patients who were MRD- for a total of 76 patients) compared to the subgroup of patients who were in hematologic relapse prior to HSCT (n = 4). The median RFS was 21.2 months (95% CI, 15.3 to NE) in patients in CR prior to HSCT compared to 2.4 months (95% CI, 1.2, 2.9) in those in hematologic relapse prior to HSCT. In a 3-month landmark analysis of OS in the subgroup of patients in CR prior to HSCT (n=76) compared to the subgroup of patients who were in hematologic relapse (n=14), the median OS was 37.2 months (95% CI, 16.8 to NE) in patients in CR prior to HSCT and 12.2 months (95% CI, 3.5 to NE) in patients not in CR prior to HSCT (note: the 3-month landmark analysis of OS excluded patients who did not die prior to the landmark analysis time and included patients with relapse prior to the landmark time).[46] Given that these subgroup analyses included small sample sizes and were exploratory in nature, the results must be interpreted with caution.

MT103-202

Primary endpoint – MRD response rate within the first 4 cycles

The data cut-off date for the primary analysis was January 14th, 2010. MRD response within the first 4 cycles was achieved by 16 out of 20 evaluable patients (MRD response rate = 80%; 95% CI, 56.3 to 94.3), which met the pre-specified criterion for statistical significance of the primary endpoint. All patients had responded after cycle 1. Of the 16 MRD responders, 15 had received the 15 mcg/m^2 dose and one patient achieved MRD complete response with escalated dose to 30 mcg/m^2.

By MRD level at screening, MRD response was achieved in 90% of patients with MRD level ≥ 10^{-2}, 83% of patients with MRD level <10^{-2} to ≥ 10^{-3}, and 50% of patients with MRD level <10^{-3} to ≥ 10^{-4}.[3]

Secondary endpoints

RFS

The data cut-off date for the long-term follow-up analysis was November 3rd, 2014. This endpoint was described as TTHR in the study protocol, but was considered equivalent in definition to RFS and was described in publications as RFS.[3,8] After a median follow-up of 50.8 months (> 4 years), the median RFS had not been reached (95% CI, 12.4 to NE).[3,10]

MRD progression

A total of 7 (35%) patients had MRD progression, and the median time to MRD progression was 7.2 months (95% CI, 3.3 to NE).[3]

Duration of MRD response

The median duration of MRD response was 13.0 month (95% CI, 2.8 to NE) among patients who had an MRD response (n = 16). The median duration of follow-up for patients who did not experience MRD relapse (n = 11) ranged from 15 to 1955 days.[3]

The Neuf Study

Adults

[redacted]5 5

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information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.) Results for other relevant endpoints in the adult subgroup included:

- [redacted][5]
- [redacted][4]
- [redacted].[5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Pediatric

[redacted][55] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* Results for other relevant endpoints included:

- [redacted]
- [redacted]
- [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

HRQoL

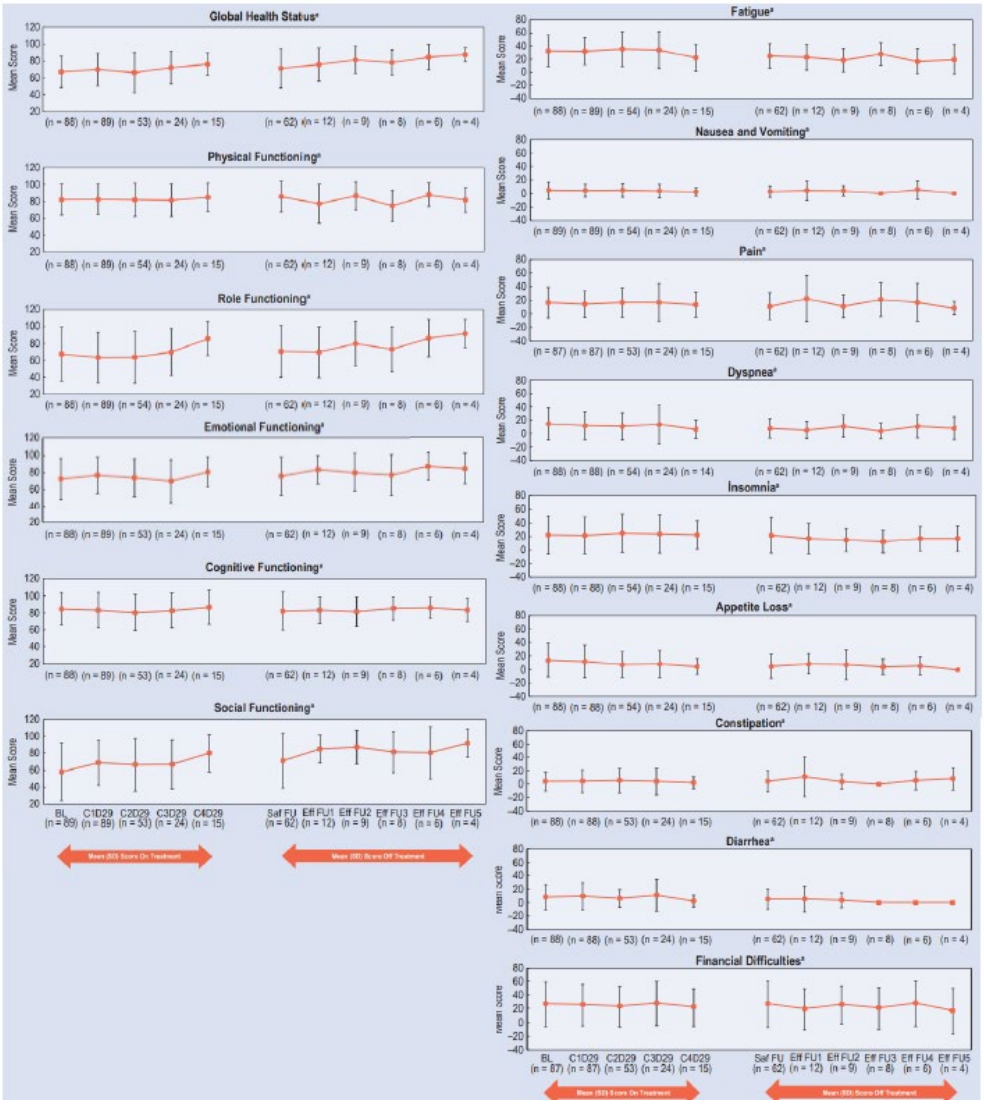
Health-related QoL was summarized for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, core 30 (EORTC-QLQ-C30) and EQ-5D-3L questionnaires from baseline, with data available up to the 8th efficacy follow-up visit for the FAS. As patients were treated with anywhere from 1 to 4 cycles of treatment before entering efficacy follow-up, there was variation in available data at various timepoints.

For the EORTC-QLQ-C30, GHS assessment, a total of 88 (75.9%) patients had data available at baseline, 89 patients had data available at cycle 1 day 29, 53 patients had data available at cycle 2 day 29, 24 patients had data available at cycle 3 day 29, and 15 patients had data available at cycle 4 day 29. At the safety follow-up time point, a total of 62 (53.4%) patients had EORTC-QLQ-C30 data available, which dropped to 12 patients at the efficacy follow-up 1, and further down to 4 patients at efficacy follow up 5, as shown in Figure 6. The mean change from baseline to end of cycle 1 or to the end of the core study (i.e. 30 days after the last infusion of blinatumomab) was minimal for GHS, physical functioning, role functioning, emotional functioning, and cognitive functioning scales, as well as single-item symptom scales (fatigue, nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). There was an improvement of 10.4 points in social functioning, which was larger than the pre-specified MCID of 10-points from baseline to the end of cycle 1 and an improvement of 14.9 points from baseline to the end of core study.[5,6]

EQ-5D results are shown in Table 21, and [redacted].[5 4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* The EQ-5D results were presented descriptively (unweighted and were not transformed into summary scores) and 14 patients or less (≤ 12%) completed the EQ-5D at the first follow-up visit and beyond, and thus interpretation of clinically relevant changes in patient HRQoL on any of the EQ-5D domains is limited.

No data on QoL was collected in MT103-202 or in the Neuf study.

Figure 6: Mean EORTC QLQ-C30 GHS, Functional Scale, and Symptom Scale/Single-item Scores at Each Scheduled Assessment in BLAST



Data cut-off: 2015-August-05

Source: Amgen Clinical Summary, 2020[5]

Table 21: Summary of Change in Mean EQ-5D-5L Scores by Dimension during Treatment with Blinatumomab in the BLAST trial

Source: Amgen Clinical Summary, 2020[5]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

Harms Outcomes

The safety data presented is based on pooled data (N = 137) from all adult patients who received any infusion of blinatumomab in BLAST (n=116) or MT103-202. Safety data are presented as of the key secondary analysis (August 5th, 2020) in the BLAST trial, as safety data were not collected during the follow-up period. Safety data in MT103-202 are presented as of the primary analysis data (January 14th, 2010).[11]

A summary of treatment exposure is presented under 6.3.2.1 *c) Interventions*, for the BLAST and MT103-202 trials, respectively. For the pooled MRD+, BCP-ALL population, the median duration of treatment was 55.5 days (range = 0.7 to 195.7). A total of four patients were retreated, for a median duration of treatment of 28.4 days (range = 28.0 to 48.5). The median number of completed cycles was 1.0 (range = 0.0, 7.0), and the median number of started cycles was 2.0 (range = 1.0 to 7.0).[11]

Safety data was not collected in the Neuf study, and thus safety data in pediatric patients with MRD+ BCP-ALL is unavailable. Safety data of blinatumomab for the treatment of other indications in pediatric patients is summarized in Section 8.

AEs

As shown in Table 22, all adult patients included in the pooled analysis experienced an any-grade AE, of which 97.1% (n = 133) were considered treatment-related AEs (TRAEs). A total of 88 (64.2%) of patients experienced grade ≥ 3 AE, of which 73 (53.3%) were considered TRAEs.

The most common any-grade AEs were pyrexia (90.5%; n = 124), headache (39.4%; n = 54), tremor (29.2%; n = 40), chills (28.5%; n = 39), fatigue (26.3%; n = 36), nausea (23.4%; n = 32), vomiting (21.2%; n = 29), hypokalemia (20.4%; n = 28), and diarrhea (20.4%).[5]

The most common grade ≥ 3 AEs included neutropenia (13.1%; n = 18), leukopenia (7.3%; n = 10), lymphopenia (6.6%; n = 9), pyrexia (6.6%; n = 9), increased ALT (5.1%; n = 7), and thrombocytopenia (4.4%; n = 6).[7]

SAEs

Serious adverse events occurred in 83 (60.6%) of patients, of which 69 (50.4%) were considered treatment-related. SAEs included pyrexia (12.4%; n = 17), tremor (5.8%; n = 8), encephalopathy (4.4%; n = 6), aphasia (4.4%; n = 6), lymphopenia (4.4%; n = 6), neutropenia (3.6%; n = 5), overdose (3.6%; n = 5) device-related infection (2.9%; n = 4), and seizure (2.9%; n = 4).[11]

Adverse events of special interest (AESIs)

Neurologic AEs

Neurologic AEs were experienced by 71.5% (n = 98) of patients in the pooled adult MRD+ BCP-ALL population. Neurologic events included headache (39.4%; n = 54), tremor (29.2%; n = 40), insomnia (16.1%; n = 22), aphasia (11.7%; n = 16), and dizziness (10.2%; n = 14).[3,5] Serious neurological events was experienced by 22.6% of patients. The median time to first onset was 2 days, and the median duration of neurologic AEs was 10.0 days (95% CI, 6.0 to 15.0).[5,18] Most neurologic AEs were mild to moderate in severity, as only 16.1% of patients experienced a grade 3 or higher AE, and none of these events were fatal. Data from the BLAST study showed that neurologic events resolved in 97% of patients with neurologic events of any severity grade, and most patients who experienced a grade 3 or higher neurological event in BLAST resumed blinatumomab treatment after the event resolved.[5]

In the BLAST trial, 11 out of 116 patients (9.5%) had neurologic events that resulted in permanent discontinuation of treatment, and 12 (10.3%) patients had neurologic events resulting in blinatumomab interruption; and as such, most patients who experienced neurologic events were able to continue receiving study treatment with blinatumomab.[3]

CRS

A total of four (2.9%) patients experienced CRS, with two patients that experienced grade 3 CRS, and no grade 4 or 5 CRS events. Treatment was interrupted for one patient because of CRS.[5]

Withdrawals due to Adverse Events (WDAEs) and Treatment Interruptions

A total of 23 (16.8%) of patients discontinued treatment permanently with blinatumomab due to AEs, of which 16 (11.7%) were considered treatment-related.[5]The most frequently reported AEs leading to treatment discontinuation included nervous system disorders (9.5%; n = 13), such as tremors (3.6%; n = 5), seizures (2.9%; n = 4), encephalopathy (2.2%; n = 3), and aphasia (2.2%; n = 3).[3,7]

A total of 39 (28.5%) patients had AEs that led to interruption of blinatumomab; of which, 35 (25.5%) were considered TRAEs. The most common AEs leading to blinatumomab interruption included pyrexia (6.6%; n = 9), overdose (2.9%; n = 4), encephalopathy (2.9%; n = 4), tremor (2.9%; n = 4), aphasia (2.9%; n = 4), chills (2.2%; n = 3), increased ALT (2.2%; n = 3), aspartate aminotransferase increase (2.2%; n =3), and hypotension (2.2%; n = 3).[11]

Deaths

A total of two (1.5%) fatal AEs occurred, of which 1 (0.7%) was considered treatment-related. Fatal events were deaths that occurred during treatment and up to 30 days after the last treatment with blinatumomab. Both occurred in the BLAST trial, and included one event of atypical pneumonia and one event of subdural hemorrhage.[5]

In the BLAST trial, a total of 65 deaths occurred after the 30 days post blinatumomab discontinuation, with 51 that occurred in patients with on-study HSCT: 28 patients died in CR primarily due to infection and 23 died after relapse primarily from disease progression and infection. The other 14 deaths occurred in patients without HSCT: 12 patients died after relapse primarily due to disease progression and 2 patients died in CR with the cause of death unknown.[4]

Table 22: Incidence of AEs in the Pooled Adult MRD+ BCP-ALL Population, n=137

Event	Treatment-emergent AEs (N = 137) n (%)	Treatment-related AEs (N = 137) n (%)
All AEs	137 (100.0)	133 (97.1)
Serious	83 (60.6)	69 (50.4)
Grade ≥ 3	88 (64.2)	73 (53.3)
Grade ≥ 4	39 (28.5)	32 (23.4)
Fatal[a]	2 (1.5)	1 (0.7)
Leading to permanent discontinuation of blinatumomab	23 (16.8)	16 (11.7)
Serious	17 (12.4)	13 (9.5)
Grade ≥ 3	18 (13.1)	13 (9.5)
Grade ≥ 4	6 (4.4)	4 (2.9)
Fatal[a]	2 (1.5)	1 (0.7)
Leading to interruption of blinatumomab	39 (28.5)	35 (25.5)
Serious	29 (21.2)	26 (19.0)
Grade ≥ 3	22 (16.1)	20 (14.6)
Grade ≥ 4	8 (5.8)	7 (5.1)
Fatal[a]	0 (0.0)	0 (0.0)

Note: Data from the BLAST study based on the prespecified key secondary analysis (5 August 2015 data cutoff date).
[a]Fatal events that occurred within 30 days of last blinatumomab treatment.
AE, adverse event; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; MRD, minimal residual disease
Source: Amgen Data on File, 2017 [152]

Source: Amgen Clinical Summary, 2020[5]

6.4 Ongoing Trials

Seven ongoing and relevant clinical trials were identified that included patients with BCP-ALL. One ongoing clinical (NCT03109093) trial, referred to as the BLAST success trial, met disease indication of the systematic review protocol (MRD+, Ph-, BCP ALL in CR) that is designed to expand on previous clinical trials (including the BLAST trial) to address additional specific questions that included efficacy and tolerability of blinatumomab in patients with MRD >10^{-3} including patients that had MRD after HSCT; and efficacy and tolerability of blinatumomab in patients with MRD between 10^{-4} and 10^{-3}, MRD <10^{-4}, or nonquantifiable MRD.[46,50] Of the other six trials, two were specific to MRD+ patients[51,52] and four were not specific to MRD+ patients.[53-56] Of these six trials, four trials were not specific to Ph- patients (included both Ph+ and Ph- patients).[51,52,55,56] The six trials covered evidence gaps and implementation questions identified by PAG, which included adding blinatumomab to consolidation and/or maintenance therapy for patients with BCP-ALL achieving CR (NCT03709719; NCT02877303; NCT02458014);[52,53,56] adding cycles of blinatumomab to first-line therapy after achievement of CR with chemotherapy untreated Ph-, CD19+, BCP-ALL (NCT03367299);[54] and blinatumomab used post-transplant (NCT03114865; NCT04044560).[51,55] Two of the six trials were phase II trials that included pediatric patients (NCT02877303 and NCT04044560).[51,53]

Table 23: Ongoing Trials of Blinatumomab in Ph-, MRD+, BCP-ALL

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[56] GRAALL-QUEST (NCT03709719) **Characteristics:** Open-label, single-arm, phase II trial **Estimated enrolment:** N= 95 **Number of centres and number of countries:** 1 site in 1 country (France) **Patient enrolment dates:** October 20, 2018 – (ongoing) **Estimated primary study completion:** October 30, 2026 **Funding:** Assistance Publique - Hôpitaux de Paris	**Key Inclusion Criteria:†** • Adults aged 18-59 years old with high-risk BCP-ALL • First hematologic CR after 1 induction course of standard chemotherapy • With or without CNS or testis involvement • High-risk defined as: KMT2A/MLL gene arrangement and/or IKZF1 intra-genic deletion and/or high post-induction Ig-TCR MRD level (≥10^{-4}) • Blood and bone marrow explorations have been completed before the steroids pre-phase • Untreated B-lineage ALL according to WHO definition with >20% blasts • Karotype does not include t(9;22) and/or absence of BCR-ABL marker • ECOG PS ≤3 • No other evolving cancer (except basal cell carcinoma of the skin or “in situ” carcinoma of the cervix), or its treatment was completed ≥6 months ago • With health insurance coverage • With or without allogeneic donor **Key Exclusion Criteria:**	**Intervention:** Blinatumomab added to second consolidation phase (after first consolidation chemotherapy cycle) in combination with 3 intra-thecal chemotherapy injections For patients receiving allogeneic HSCT: successive cycles with blinatumomab will be received until HSCT For patients not receiving allogeneic HSCT: the second consolidation phase with blinatumomab (cycle 1) and chemotherapy will be followed by late intensification, then third consolidation chemotherapy including another blinatumomab cycle (cycle 2) and maintenance chemotherapy with 3 additional blinatumomab cycles for 5 cycles maximum with blinatumomab	**Primary:** • DFS at 3 years **Secondary:** • OS at 3 years • Cumulative incidence of relapse at 3 years • Non-relapse related mortality • MRD on day 1 of first and second consolidation • MRD at intensification or pre-allogeneic HSCT evaluation • MRD at maintenance phase or 100 days after allogeneic HSCT

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Abnormal protocol-defined laboratory values after consolidation • Active uncontrolled infection or concurrent disease or medical condition • NYHA Functional Classification 3-4 cardiac disease • Positive for HIV, HBV, or HCV	**Comparator:** None	
Study:[54] LAL2317 (NCT03367299) **Characteristics:** Open-label, single-arm clinical trial **Estimated enrolment:** N= 149 **Number of centres and number of countries:** 63 sites in 1 country (Italy) **Patient enrolment dates:** August 22, 2018 – (ongoing) **Estimated primary study completion:** August 22, 2023 **Estimated study completion:** August 22, 2023 **Funding:** Gruppo Italiano Malattie EMatologiche dell'Adulto	**Key Inclusion Criteria:** • Adults aged 18-65 • Untreated Ph-, CD19+, BCP-ALL de novo or secondary to chemo-radiotherapy for another cancer • Full cytological, cytochemical, immunophenotypic, cytogenetic, and molecular disease characterization according to EGIL and WHO classifications • Bone marrow and peripheral blood sampling for MRD evaluation • ECOG ≤2; ECOG PS 3 allowed if unequivocally caused by disease and not existing comorbidities and considered reversible following application of anti-leukemic therapy **Key Exclusion Criteria:** • Diagnosis of Burkitt's leukemia/lymphoma; CD19- BCP-ALL; Ph+ ALL; T-ALL; lymphoblastic lymphoma (bone marrow involvement by blast cells <25%) • Active CNS leukemia within 5 days prior to first blinatumomab administration; or clinical sign/symptom ascribable to symptomatic/document CNS disease at time of each planned blinatumomab course • Down's syndrome • Pre-existing, uncontrolled pathology such as heart failure, severe liver disease, kidney function impairment, and severe neuropsychiatric disorder • Presence of serious, active, uncontrolled infections • HIV positive	**Intervention:** Eight courses of chemotherapy and two courses of blinatumomab; patients not in CR after 2nd course of chemotherapy will go off-study **Comparator:** None	**Primary:** • Numbers of patients to obtain MRD negativity **Secondary:** • Number of patients in CR • Number of patients that reach DFS • Number of patients that relapse • Number of patients that die due to treatment • Number of SAEs

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• History of cancer that is not in a remission phase and life expectancy <1 year		
Study:[53] NCT02877303 **Characteristics:** Open-label, single-arm, phase II trial **Estimated enrolment:** N= 60 **Number of centres and number of countries:** 1 site in 1 country (US) **Patient enrolment dates:** November 1, 2016 – (ongoing) **Estimated primary study completion:** November 1, 2020 **Estimated study completion:** November 1, 2020 **Funding:** M.D. Anderson Cancer Center	**Key Inclusion Criteria:** • Adolescents and adults aged ≥ 14 years • Newly diagnosed, previously untreated B-lineage ALL or lymphoblastic lymphoma; or achieved CR after one course of induction chemotherapy • Failure to one induction course of chemotherapy allowed (analysed separately) • ECOG PS ≤ 3 • Adequate laboratory values and cardiac function • No active or co-existing malignancy with life expectancy of < 12 months **Key Exclusion Criteria:** • Ph+ ALL • HIV positive • Active uncontrolled disease or infection • Active hepatic or biliary disease • Clinically relevant CNS pathology • Current autoimmune disease with potential CNS involvement or CNS consequences • Patients who weight <45 kg	**Intervention:** Intensive phase: Up to 4 cycles of hyper-CVAD Blinatumomab phase: Up to 4 cycles of blinatumomab Maintenance phase: mercaptopurine, methotrexate, vincristine sulfate every 6 weeks for 12 months; blinatumomab after every 3 cycles of maintenance therapy for a total of 15 cycles **Comparator:** None	**Primary:** • RFS **Secondary:** • OS • ORR • MRD negativity rate • Safety (AEs)
Study:[52] NCT02458014 **Characteristics:** Open-label, single-arm, phase II trial **Estimated enrolment:** N=40 **Number of centres and number of countries:** 1 site in 1 country (US) **Patient enrolment dates:**	**Key Inclusion Criteria:†** • Adults aged 18 years or older • B-lineage ALL in hematologic CR with molecular failure or molecular relapse at any time point after 3 months of frontline therapy; MRD value of at least 0.01% detected by flow cytometry or NGS • ECOG PS ≤ 2 • Adequate laboratory values • No active or co-existing malignancy with life expectancy <12 months	**Intervention:** Blinatumomab for up to 5 cycles Patients who do not proceed to HSCT may receive IV maintenance for up to 4 cycles Patients in MRD remission for at least 3 months and become MRD positive can be retreated **Comparator:**	**Primary:** • RFS **Secondary:** • EFS • OS • MRD negativity rate • Safety (AEs)

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
September 14, 2015 **Estimated primary study completion:** September 30, 2020 **Estimated study completion:** September 30, 2020 **Funding:** M.D. Anderson Cancer Center	• Ph+ patients can be enrolled in CR1 or ≥CR2; MRD level of ≥0.1% by PCR; TKI added at treating physician discretion **Key Exclusion Criteria:** • HIV positive • Active and uncontrolled disease/infection • Active CNS or extramedullary disease • Monoclonal antibodies therapy within 2 weeks before study entry • Radiotherapy, cancer chemotherapy, or investigational drugs within 2 weeks before study entry	None	
Study:[51] OZM-097 NCT04044560 **Characteristics:** Open-label, single-arm, phase II trial **Estimated enrolment:** N= 50 **Number of centres and number of countries:** 1 site in 1 country (Canada) **Patient enrolment dates:** September 2020 (initiation) **Estimated primary study completion:** February 2022 **Estimated study completion:** September 2026 **Funding:** University of British Colombia	**Key Inclusion Criteria:†** • Child or adults over 1 years old • Pre-B-ALL in CR (<5% blasts) with an intention to proceed to allogeneic HSCT; morphologic CR on bone marrow from same data as MRD detection prior to treatment • First CR or later • Detectable MRD prior to transplant permitted/detectable MRD (≥10^{-4}) prior to treatment with blinatumomab • Ph positive or negative permitted • CD19 expression if patient received prior CD19-directed therapy • Eligible for HSCT • ECOG PS ≤2 (adult) or Lansky ≥50% (pediatric) • Chronic HBV infection allowed if receiving treatment to prevent reactivation and have undetectable HBV DNA • Adequate organ, liver, and renal functional the time of treatment **Key Exclusion Criteria:** • Active CNS involvement or other extramedullary disease • Uncontrolled infection until resolved	**Intervention:** Blinatumomab for up to 4 cycles **Comparator:** None	**Primary:** • MRD response **Secondary:** • Safety and tolerability (TEAEs and incidence and severity of acute and chronic GVHD) • OS • EFS • MRD post-HSCT • Patient recruitment • Turnaround time of centralized MRD testing • Time to delivery of blinatumomab following MRD detection

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Burkitt lymphoma/leukemia or mixed phenotype leukemia • Chronic HCV infection unless previously treated with undetectable HCV RNA for 6 months or longer • HIV 1/2 infection • Active acute GVHD (grade II-IV) or active moderate-severe chronic GVHD (NIH grade) at the time of MRD detection are ineligible for treatment until GVHD resolves or quiescent		
Study:[55] NCT03114865 **Characteristics:** Open-label, single-arm, phase I trial **Estimated enrolment:** N= 12 **Number of centres and number of countries:** 1 site in 1 country (US) **Patient enrolment dates:** September 5, 2017 **Estimated primary study completion:** May 2020 **Estimated study completion:** May 2020 **Funding:** Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	**Key Inclusion Criteria:†** • Adults aged 18 years or older • Pre-B ALL patients (who underwent allogeneic HSCT using post-transplant CY GVHD prophylaxis) in CR1 with high-risk features such as adverse cytogenetics including t(9;22), t(4;11) or other MLL rearrangements, t(8;14), complex karyotype (≥5 chromosomal abnormalities), hypodiploidy (<44 chromosomes), low hypodiploidy (30-39 chromosomes)/near triploidy (60-68 chromosomes), high WBC count at presentation (≥30,000), lack of achievement of CR after standard induction chemotherapy (but achieved CR1 following salvage or consolidation), or persistence of detectable disease after induction and consolidation (intensification) or pre-transplant as documented on any of routine clinical tests (morphology, flow cytometry, cytogenetics or molecular studies) OR all Pre-B ALL patients in second and higher CR • Low and high grade NHL patients (who underwent allogeneic HSCT using post-transplant CY GVHD prophylaxis) following nonmyeloablative (reduced-intensity conditioning) transplant irrespective of pre-transplant disease status • Between 60-180 days from transplant with documented count recovery and no evidence of PD • ECOG PS 0-2	**Intervention:** Blinatumomab **Comparator:** None	**Primary:** • OS (of patients with transplant and subsequent blinatumomab) **Secondary:** • Non-relapse mortality • PFS • DFS • OS at 2 years • MRD negativity rate

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Any number of prior regimens to achieve remission including prior therapy with blinatumomab (unless unacceptable toxicities were experienced) **Key Exclusion Criteria:** • Lack of engraftment • Active or untreated disease in CNS or testis • Chemotherapy or radiotherapy with the exception of intrathecal prophylactic chemotherapy within 2 weeks of starting blinatumomab • Active uncontrolled infection or illness • Active acute GVHD (grade II-IV) and active moderate or severe chronic GVHD with GVHD therapy initiation or escalation within 28 days of starting treatment; patients requiring steroids must be off for at least 2 weeks prior to enrolment • Patients requiring calcineurin inhibitors or other systemic immunosupressants for GVHD prophylaxis • Inadequate organ function • Ph+ ALL eligible for post-transplant TKI maintenance • Evidence of PD post-transplant • Clinically relevant CNS pathology • History of CNS leukemia or lymphoma allowed if recent imaging and CSF confirm absence at time of study entry • HIV, HBV, or HCV infection • Weight <45 kg • Concurrent active malignancy		
Study:[50] NCT03109093 **Characteristics:** Open-label, single-arm, phase II **Estimated enrolment:**	**Key Inclusion Criteria:** • Adults aged 18 years or older • CD19+, BCP-ALL in hematological CR (<5% blasts) after at least 3 intense chemotherapy blocks	**Intervention:** Blinatumomab (patients considered discontinued as per protocol if transfer to allogeneic HSCT after cycle 1 or later; permanent	**Primary:** • MRD response after one cycle

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
N= 60 **Number of centres and number of countries:** 22 sites in 1 country (Germany) **Patient enrolment dates:** March 15, 2017 **Estimated primary study completion:** June 16, 2020 **Estimated study completion:** January 2021 **Funding:** Goethe University	• Presence of MRD (at a level of ≥10^{-4} to <10^{-3}; OR MRD positive non-quantifiable at level below 10^{-4} [MolNE1]; OR MRD positive below 10^{-4} [MolNE2]; OR presence of MRD. non-quantifiable [MolNE3]) • Adequate bone marrow, renal, and hepatic function • Negative for HIV, HBV, HCV • ECOG PS ≤1 • Participation in GMALL registry **Key Exclusion Criteria:** • Ph/BCR-ABL positive ALL • Presence of circulating blasts or current extramedullary involvement by ALL • Presence of clinically relevant CNS pathology • Detection of ALL blast cells in CSF • History of active relevant autoimmune disease • Systemic chemotherapy or live vaccination ≤2 weeks prior to study treatment; or radiotherapy ≤4 weeks • Autologous HSCT ≤6 weeks prior to study treatment, allogeneic HSCT ≤12 weeks prior to study treatment • GVHD grade II-IV according to Glucksberg criteria or active chronic GVHD ≤2 weeks of study treatment • Monoclonal antibodies or investigational products ≤4 weeks prior to study • History of malignancy other than ALL ≤5 years prior to study start, except adequately treated non melanoma skin cancer or lentigo maligna, cervical carcinoma in situ, breast ductal carcinoma in situ • Active infection • Prior treatment with any other anti-CD19 therapy	discontinuation if hematological extramedullary relapse) **Comparator:** None	**Secondary:** • Continuous CR • RFS • OS • Relapse localisations • Biological evaluation of hematological and extramedullary relapse • Safety (SAEs; evaluation of GVHD) • MRD response after 2 cycles • Complete MRD response after 2 cycles • Duration of MRD response • Time to MRD response • Treatment-related mortality after subsequent HSCT • Treatment-related mortality • Quality of life

† Not specific to Ph negative patients

Abbreviations:- = negative; + = positive; AE = adverse event; ALL = acute lymphoblastic leukemia; BCP = B-cell precursor; CD19 = cluster of differentiation 19; CNS = central nervous system; CR = complete remission; CSF = cerebrospinal fluid; DFS = disease-free survival; DNA = deoxyribonucleic acid; ECOG PS = Eastern Cooperative

Oncology Group Performance Status; EFS = event-free survival; EGIL = European Group for the Immunological Classification of Leukemias; GMALL = German Multicentre Study Group on Adult Acute Lymphoblastic Leukemia; GVHD = graft versus host disease; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSCT = hematopoietic stem cell transplant; hyper-CVAD = hyper fractionated therapy with cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and dexamethasone (methotrexate and cytarabine also used); Ig = immunoglobulin; kg = kilogram; IV = intravenous; MRD = minimal residual disease; NGS = next generation sequencing; NHL = non-Hodgkin's lymphoma; NYHA = New York Heart Association; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; Ph = Philadelphia chromosome; RFS = relapse-free survival; RNA = ribonucleic acid; SAE = serious adverse event; T-ALL = therapy-related acute lymphoblastic leukemia; TEAE = treatment-emergent adverse event; TCR = T-cell receptor; TKI = tyrosine kinase inhibitor; WBC = white blood cell

7 Supplemental Questions

The following supplemental issue was identified during development of the review protocol as relevant to the pCODR review of blinatumomab for the treatment of patients with Ph-, MRD+, BCP- ALL:

- **Issue:** There is no trial directly comparing blinatumomab with a relevant comparator. A summary and critical appraisal was conducted of the sponsor-submitted ITC using a PS analysis to compare the efficacy of blinatumomab to no blinatumomab in a historical comparator study.

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

7.1 Summary of Sponsor-submitted PS Analysis

7.1.1 Objective

An ITC was conducted using a PS analysis to compare efficacy of blinatumomab in the single-arm BLAST trial (N=116) to no blinatumomab in a historical comparator study (Study 148; N=287).

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

7.1.2 Methods

Historical comparator study: Study 20120148 (Study 148)

For the PS analysis, the sponsor submitted a retrospective, observational, cohort study (study 20120148 and hereafter, referred to as Study 148), as the historical comparator study. The main objectives of Study 148 were to estimate hematologic RFS and OS of patients with MRD+, BCP-ALL not treated with blinatumomab in Europe.[5] In this study, patient-level data were obtained from ALL study group databases across European study centres (including Czech Republic, France, Germany, United Kingdom, Italy, Poland, Spain, and Russia) with protocols that included prospective MRD testing in national reference laboratories.[43] The selected study centres also contributed to data in the BLAST study.[5] Data were entered into study-specific electronic case report forms by central staff at each study group to ensure a standardized and quality-controlled data collection process.[43] The study was sponsored by Amgen; however data are owned by the investigators as part of previous or ongoing clinical studies. Patients were eligible if the inclusion and exclusion criteria outlined below were met.

Inclusion criteria:

- Ph-, BCP-ALL in hematologic CR defined as <5% blasts in bone marrow after ≥3 intensive chemotherapy blocks[5]
- MRD at a level of ≥ 10^{-4} by RT-qPCR) of clonally rearranged Ig or MRD at a level of ≥ 10^{-3} by flow cytometry at a reference lab[43]
- Age ≥ 15 years old at initial ALL diagnosis
- Initial ALL diagnosis in the years 2000 to 2014
- Availability of data on the history of ALL treatment (including response to first therapy and number of prior relapses)
- Availability of data on the relapse status and disease follow-up after time point of MRD detection[5]

Exclusion criteria:

- Extramedullary involvement at time of MRD detection
- Treatment with blinatumomab within 18 months of MRD detection
- Prior allogeneic HSCT (at the time of MRD detection)[5]

Data were captured for a total of 287 patients.[43]

Alignment of BLAST trial and Study 148 Population for the Propensity Score Analysis

In order to align the patient populations for the PS analysis, a post-hoc primary analysis set (PAS) was defined for both the BLAST trial and Study 148, since an important underlying assumption in ITCs is that patient populations are broadly homogenous. As illustrated in Figure 7, to enable a clinically valid comparison additional eligibility criteria were employed to enable a clinically valid comparison:

From the BLAST trial, patients were included if they:

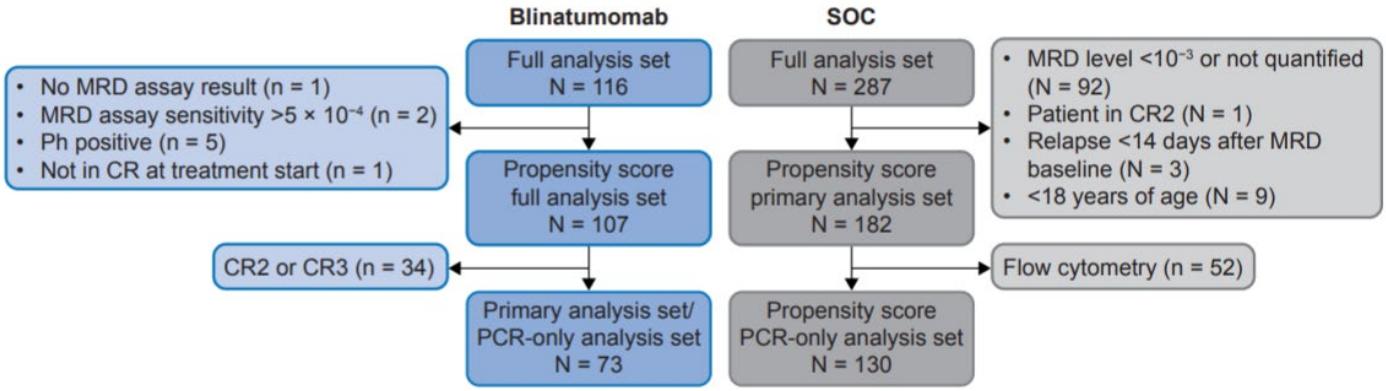
- Had Ph-, BCP-ALL in hematologic CR (defined as <5% blasts in the bone marrow) after at least three intensive chemotherapy blocks
- Had MRD ≥ 10^{-3} as detected by PCR
- Were in CR1
- Had received any infusion of blinatumomab

From Study 148, patients were included if:

- Were aged ≥ 18 years at the time of MRD baseline date
- Had Ph-, BCP-ALL in hematologic CR (defined as < 5% blasts in the bone marrow) after at least 3 intensive chemotherapy blocks
- Had MRD ≥ 10^{-3} irrespective of detection method
- Were in CR1[5]
- Had time to relapse from the date of MRD detection ≥ 14 days (the median time between MRD positivity assessment and initiation of blinatumomab in the BLAST trial; this restriction mirrors BLAST where potential participants became screening failures if they experienced hematologic relapse during the screening period)[7]

A total of 73 patients from the BLAST trial and 182 patients from the historical comparator study were included in the aligned PAS.[5]

Figure 7: PS CONSORT Diagram



Note: The sponsor-submitted ITC utilized the **PS primary analysis set** (n = 182) as outlined in this figure for the standard of care (i.e. no blinatumomab) treatment arm.

Source: Gökbuget et al., Eur J Haematol. 2019;104(4):299-309. Copyright 2019. The Authors. European Journal of Haematology. Reprinted in accordance with CC BY-NC 4.0.[17]

PS Analysis – Methodology and Rationale

To address remaining differences in prognostic factors and to account for potential regional differences in treatment practices, data from the two studies was merged and a PS analysis (i.e. the predicted probability of and individual patient being assigned to a specific treatment) was performed. The first version of the analysis was published and conducted based on the BLAST key secondary analysis (data cut-off August 5th, 2015). This analysis was updated to incorporate data from the final BLAST analysis (data cut-off January 7th, 2019), which will be presented in this section.[5] Since Study 148 was a retrospective observational study, data was entered at a single point in time, which occurred between October 2nd, 2013 and March 14th, 2014.[46]

Candidate covariates were included in a logistic regression model, and a stepwise variable selection algorithm was used to identify covariates to be kept in the PS model if the threshold was met (P < 0.30). The following candidate covariates were identified through discussions between the sponsor's study team and clinicians consulted by the sponsor:

- age at primary diagnosis
- sex
- country
- baseline MRD level
- time from primary diagnosis to MRD baseline data
- presence and type of molecular aberrations (specifically T411mll4)
- WBC count at diagnosis
- type of prior chemotherapy (specifically, GMALL)

Age at primary diagnosis (years), baseline MRD level (recode into an ordinal variable), and time from diagnosis to baseline MRD level (months) were continuous variables in the model; sex (male versus female), country (Germany versus not Germany), WBC at diagnosis (≤ 30,000/mm^3 versus > 30,000/mm^3), T411mll4 mutation (yes versus no), and prior GMALL chemotherapy (yes versus no) were binary variables in the model.

The final PS model included:

- age at primary diagnosis
- time from primary diagnosis to MRD baseline data
- baseline MRD level
- prior GMALL chemotherapy (yes versus no)
- interaction term between prior GMALL chemotherapy and time from diagnosis to baseline MRD data

IPTW was considered the most appropriate approach for PS adjustment for the estimation of treatment effects. Two IPTW methods were explored: ATE and average treatment effect on the treated (ATT). The ATE approach adjusts weights in both the treated and untreated populations by assuming they were drawn from a single homogenous population (i.e. average treatment effect if all patients in the merged dataset received blinatumomab compared to if all patients in the dataset did not receive blinatumomab; representing the treatment effect in the population). Whereas the ATT approach adjusts the weights only in the untreated population to resemble to treated population (i.e. average treatment effect if all patients in blinatumomab treatment arm did not receive blinatumomab representing the average gain from treatment of those who were actually treated). ATT was considered the most appropriate approach for the submission under review by the sponsor, as patients in Study 148 would resemble patients in the BLAST trial. Therefore, the ATT analysis is presented as the primary analysis and the ATE analysis as the sensitivity analysis.[5] In the

primary publication, the EPAR report, and the FDA report, the primary approach presented was the ATE PS adjustment (and results are only presented for the key secondary analysis data cut-off date).[3,7,17]

RFS and OS were analyzed using Cox proportional hazard model weighted by the methods described above with the patient's treatment status (blinatumomab versus no blinatumomab) as an independent factor. Robust variance estimation was used for calculation of 95% CIs and the HR for the respective analyses.[7]

7.1.3 Findings

Table 24 shows the balance in covariates between the patients in the historical comparator and BLAST population, before and after ATT-IPTW adjustment. Before adjustment, age at primary diagnosis (older in BLAST), country (percentage from Germany higher in Study 148), time from diagnosis to baseline (greater in BLAST), and prior chemotherapy (GMALL protocol chemotherapy used in a higher percentage of patients in BLAST) had statistically significant differences across groups.[5]

The balance between the two groups was considered satisfactory when the univariate P value were non-significant, and the standardized differences were < 0.20.[17] As shown in the table, [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Table 24: Covariate Balance before and after IPTW PS Adjustments using ATT Weights

[redacted]

Source: Amgen Clinical Summary, 2020[5]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

The results of the PS analysis of outcomes in the BLAST trial and Study 148 at the time of the final analysis are presented in Table 25.

[redacted][5]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is

earlier.) There were 43 RFS events in the blinatumomab (60%) arm compared to 131 (72%) in the historical comparator (ATT-weighted RFS events: 49.2; 78%).[18]

[redacted].[5,46] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* A total of 39 (54%) deaths occurred in the blinatumomab arm compared to 107 (59%) in the historical comparator (ATT-weighted deaths: 62%).[18]

The sensitivity analyses with the ATE weights, which is an approach that mirrors the objective of a randomized study, were generally consistent with the analysis using the ATT weights.

[redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

There were a [redacted] of patients that underwent HSCT in the BLAST trial (n = 90; 78%)

[redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Table 25: Summary of the Primary Outcomes of the PS analysis at the Time of Final Analysis

	ATT-IPTW		ATE-IPTW	
	Blinatumomab	**Standard of care**	**Blinatumomab**	**Standard of care**
RFS				
Median RFS (95% CI)	[redacted]			
HR (95% CI)	[redacted]			
OS				
Median OS (95% CI)	[redacted]			
HR (95% CI)	[redacted]			

Abbreviations: ATE = average treatment effect; ATT = average treatment effect of the treated; CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment; NE = not estimable; OS = overall survival; RFS = relapse-free survival

Sources: Amgen Clinical Summary, 2020;[5] Amgen Additional Checkpoint Response, 2020[46]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)

7.1.4 Summary

The submitted PS analysis was conducted to compare RFS and OS in patients treated with blinatumomab in the BLAST trial with no blinatumomab in Study 148 in adult patients with MRD+ BCP-ALL. The PS analysis used patient level data from the BLAST single arm trial (73 of 116 patients) and Study 148 (182 of 287 patients), and estimated treatment effects through two IPTW weighting methods — ATT and ATE — as described above.[5,17]

The analysis attempted to balance a selected set of covariates between the two study populations, including age at primary diagnosis, sex, country, baseline MRD level, time from primary diagnosis at baseline, WBCs at diagnosis, T411mll4 mutation, and the type of prior chemotherapy.

The results of the submitted PS analysis suggested that blinatumomab is associated with a survival benefit in patients with MRD+ BCP-ALL; both RFS and OS were estimated to be longer in blinatumomab treated patients, when compared to patients who did not receive blinatumomab. However, these results should be interpreted with caution due to the limitations that arise from the following issues:

- Given that Study 148 was a historical comparator study that involved patients diagnosed between 2000 to 2014, the time period did not generally overlap with the BLAST trial. Over 90% of patients were diagnosed before 2010, with approximately one-third (32.4%) that were diagnosed between 2000 to 2004.[7] This may have introduced bias in the following ways:
    - Detection and measurement bias: patients were eligible for Study 148 based on MRD assessment using any detection method, whereas in BLAST it was based on PCR only. If testing methods did not have comparable sensitivity and specificity as PCR and/or present day methods, it is possible that some patients who were MRD+ during the Study 148 time period may have never been detected and thus, not included in Study 148; and/or patients may have been included in Study 148 who were not actually MRD+ (false positives). The use of any MRD detection method may have also affected the reliability/validity of baseline MRD level measurements as well. The impact of this bias is unknown.
    - Treatments may have changed over time, such as induction, maintenance, and consolidation therapies. There may have been improvements in diagnosing ALL over time, which may have introduced bias as well. For these reasons, patients included in the BLAST trial may have had RFS and OS benefit simply due to advances in medicine compared to the time period of Study 148, which may have biased the PS results in favour of blinatumomab. As an example, RFS was estimated at 6.9 months in Study 148, whereas in literature from 2012, RFS for MRD+ BCP-ALL patients in CR who did not have allogeneic HSCT median RFS was 7.6 months.[5,57]
    - As discussed with the CGP, there is presently variability across Canada in MRD testing, and thus, MRD testing may have been even more variable and selective during the time period of Study 148. Patients who had MRD testing in Study 148 occurred at study group centres, which was likely in the context of clinical trials. This would have introduced selection bias. Patients included in Study 148 may have been healthier or more fit than patients not referred to clinical trials or academic trials for MRD testing in Study 148, however this bias would also apply to patients who were enrolled into BLAST.
    - As patients included in Study 148 were enrolled from study databases, these patients may not have received standard of care therapies and results may be influenced in favour of blinatumomab. Namely, there is no recognized standard treatment for patients with MRD in CR.
- Due to the retrospective nature of Study 148, there are concerns about the validity, reliability, quality, and completeness, of the databases from where information on covariates, exposures, and outcomes was collected. in the study. Accordingly, it was unlikely comparable to the data collection and recording methods of that in the BLAST trial. Only covariates common to

both studies could be included in the analysis. There may be other unmeasured confounders not accounted for such as performance status, which may not have been balanced between treatment arms.

- There was a [redacted][5] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* This may reflect the fact that treatments have changed over time, as there may be more options in induction, maintenance, and consolidation therapy that may delay time to testing for MRD. This imbalance may favour the blinatumomab arm.

- There were a higher proportion of patients who underwent transplantation in patients who received blinatumomab compared to those who received standard of care in Study 148, which may have contributed to better survival in blinatumomab-treated patients. This could in part be due to higher MRD response rates seen in the BLAST trial. Given the context of Study 148, it is difficult to confirm this. The availability of unrelated donors between 2001 to 2012 increased from 7 to 21 million, and at present day is estimated at 36 million.[58,59] Advances in medicine may have contributed to better induction regimens to achieve CR (and, thus improve transplantation rates), as well as safer techniques to reduce complications following transplant for patients in the BLAST trial compared to patients in Study 148. However, the IPTW-ATE results, which would mirror a RCT, [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* These results could be due to overall poor survival with MRD+ BCP-ALL or mortality rates associated with HSCT. The results of RFS and OS adjusted for HSCT as a time-dependent covariate were consistent with the primary analysis results. The impact of higher transplantation rates with the blinatumomab study are uncertain.

- While the [redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until March 03, 2021 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)* This discrepancy underlies the differences in the ATT and ATE approach. The ATT approach aims to assess outcomes if patients treated with blinatumomab did not receive blinatumomab and represents the treatment gain for patients treated with blinatumomab compared to no blinatumomab by weighing the historical comparator arm to resemble the blinatumomab arm. The ATE approach aims to assess what RFS and OS would be if all patients were treated or not treated (similar to a RCT) by considering both populations from Study 148 and BLAST as homogenous (through weighing both treatment arms). The ATE approach may be less biased as it addresses the selection bias described for both the BLAST trial and Study 148, thus, the results suggest if all patients are considered from a homogenous population, there may be a RFS benefit of treating patients with blinatumomab, but OS benefit is uncertain.

- The submitted PS analysis did not compare safety results between the two study populations, and thus, uncertainty in the safety of blinatumomab compared to standard of care remains.

- There were few patients 65 years of age or older in the PS analysis, which included 1 (0.5%) patient from Study 148 and 6 (8.2%) patients from the BLAST trial.[46] Thus, limited conclusions can be drawn for elderly patients.

- Due to the limited sample size, the PS analysis may not have been powered to detect clinically meaningful difference between treatment groups.

The Methods team and CGP concluded that while the magnitude of the treatment effect is uncertain due to the above limitations, a clinically relevant treatment effect was observed when comparing patients treated with blinatumomab compared to those who were not treated with blinatumomab.

8 Comparison with Other Literature

Evidence of blinatumomab effectiveness in MRD+, Ph-, BCP-ALL in pediatric patients is limited to the one observational study, and there is no safety data in this patient population. A number of studies identified by the CADTH Methods team, CGP, and the sponsor have been conducted in the R/R setting that provide supportive evidence of the effectiveness and safety of blinatumomab in pediatric patients; thus, a summary and brief critical appraisal of these relevant studies is provided in this section. Brief summaries of the following studies are presented: the phase III RCT COG-AALL1331 trial[25], a phase I/II trial, MT103-205 (COG-AALL1121),[23] and two retrospective, observational studies by Keating et al.[24] and Elitzur et al.,[60] respectively. The indications for the pediatric patients of the studies listed below are not identical to the indication for this review, which is for the treatment of patients with MRD+, Ph-, BCP-ALL, however the clinical review team, registered clinicians, and CGP deemed these studies appropriate for consideration as additional evidence to support the efficacy and safety of blinatumomab for the treatment of pediatric patients with MRD+, Ph-, BCP-ALL.

Table 26: Overview and Key Characteristics of Included Pediatric Studies

Study	COG-AALL1331 (NCT10210853)[25] (Ongoing)	COG-AALL1121 (NCT01471782)[23]	Keating et al., 2019[24]	Elitzur et al. 2019[60]
Study Characteristics				
Study Design	Phase III RCT	Phase I/II single arm trial	Retrospective observational	Retrospective observational
Indication	R/R, Ph-, B-cell ALL	R/R BCP-ALL	CR, MRD+ BCP-ALL	Patients with B-cell ALL who experienced overwhelming chemotherapy-associated toxicity
Sample size	N=208 n=105 receiving blinatumomab n=103 receiving standard of care chemotherapy	**Total (Phase I and II)** N=93 **Phase I** N=49 **Phase II** N=44 **Total patients from Phase I and II that received the RP2D:** n= 70	N=15	N=11
Patient population (age and sex)	**Median Age:** 9 years (range: 1 to 25) **Sex:** Male: n=57 (54%) Female: n=48 (46%)	**Phase II (N=44)** **Age:** <2 years: n=2 (5%) 2-6 years: n=11 (25%) 7-17 years: n=31 (70%) **Sex:** Male: n=32 (73%) Female: n=12 (27%) **Total (N=93)** **Age:** <2 years: n=10 (11%) 2-6 years: n=34 (37%) 7-17 years: n=49 (53%) **Sex:**	**Median Age:** 9 years (range: 0.5 to 19) **Sex:** Male: n=9 (60%) Female: n=6 (40%)	**Median Age:** 6 years (range: 2.5 to 17) **Sex:** Male: n=5 (45%) Female: n=6 (55%)

Study	COG-AALL1331 (NCT10210853)[25] (Ongoing)	COG-AALL1121 (NCT01471782)[23]	Keating et al., 2019[24]	Elitzur et al. 2019[60]
		Male: n=60 (65%) Female: n=33 (36%)		
Intervention and Comparator	**Intervention** Blinatumomab **Comparator** Chemotherapy	**Intervention** Blinatumomab **Comparator** None	**Intervention** Blinatumomab **Comparator** None	**Intervention** Blinatumomab **Comparator** None
Blinatumomab dose and usage	2 cycles, continuous infusion over 28 days at 15 mcg/m^2, after a uniform first block of re-induction chemotherapy (both treatment arms)	**Phase I** Blinatumomab provided at the following doses: 5mcg/m^2/day, 15 mcg/m^2/day, 30 mcg/m^2/day and a step-wise dosage of 15/30 mcg/m^2/day whereby patients were given 15 mcg/m^2/day for the first seven days, and 30 mcg/m^2/day thereafter **Phase II** Blinatumomab provided at the following dose: stepwise dosage of 15/30 mcg/m^2/day Blinatumomab was provided as a bridge to HSCT or chemotherapy	Dosage NR Blinatumomab provided as bridge to transplant (given to eliminate MRD prior to receiving HSCT)	Dosage NR Provided as a bridge to further therapy
Primary and secondary endpoints	**Primary** DFS **Secondary** OS MRD response by flow cytometry Ability of patients to proceed to HSCT	**Primary**[c] CR rate **Secondary** AEs % of patients undergoing HSCT RFS OS	OS[a] LFS[a] Time to relapse[a] Death from transplantation[a]	NR
Transplantation rate	n=75/103 (73%)	NR	n=14/15 (93.3%)	n=3/11 (27%)
Efficacy outcomes**				
MRD response rate or clearance rate*	79% (57 of 72 patients) vs. 21% (12 of 57 patients); P <0.0001[d]	**Phase II** N=8/14 (57%) **Phase I/II**[e] N=14/27 (52%)	n=14 (93.3%)	NR
RFS (or DFS or EFS)	2-year DFS: 59.3 (±5.4%) blinatumomab vs. 41.0% (±6.2%) in the chemotherapy arm; P = 0.05, 1-sided)	Median RFS: 4.4 months (95% CI: 2.3 to 7.6)[e]	NR	1-year EFS: 71%

Study	COG-AALL1331 (NCT10210853)[25] (Ongoing)	COG-AALL1121 (NCT01471782)[23]	Keating et al., 2019[24]	Elitzur et al. 2019[60]
OS	2-year OS: 79.4% (±4.5%) blinatumomab vs. 59.2% (±6.0%) in the chemotherapy arm (P = 0.0005, 1-sided)	Median OS: 7.5 months (95% CI: 4.0 to 11.8)[e]	1-year OS: 93.3%	1-year OS: 80%
Key safety outcomes				
Any grade AEs	**Cycle 1** Seizure: 4%	Pyrexia: 80%[e] Anemia: 41%[e] Nausea: 33%[e] Headache: 30%[e]	NR	Seizure: 3 Encephalopathy: 1 *Staphylococcus aureus:* 1
Grade ≥ 3 AEs	**Cycle 1** Febrile neutropenia: 4% Infections: 10% Sepsis 1% Seizure: 1% **Cycle 2** Infections: 11%a Sepsis 2% Mucositis 1%	Anemia: 36%[e] Thrombocytopenia: 21% [e]	Seizure: 1[b]	NR
Neurologic AEs	**Cycle 1** Any grade: 14% Grade ≥3: 2% **Cycle 2** Any grade: 11% Grade ≥3: 2%	Grade II: 13% [d] Grade III: 4% [d]	NR	NR
CRS	**Cycle 1** Any grade: 22% Grade ≥3: 2% **Cycle 2** Any grade: 1% Grade ≥3: 0%	11% [d]	NR	NR
Deaths	NR	6[f]	2[g]	2[h]

Notes:
*Not all studies may have measured or defined MRD negativity and response similarly
**Efficacy outcomes may have been defined and measured differently across studies
[a] Outcomes were not specified as being primary or secondary
[b] This AE was graded retrospectively. This patient was diagnosed with CNS3 leukemia and received CNS directed medication associated with lowering the seizure threshold at the time of the event.
[c] The COG-AALL1121 Trial consisted of two phases, the primary and secondary outcomes indicated are specified for phase II of the trial
[d] MRD clearance rate after the first cycle of blinatumomab and second cycle of chemotherapy among patients who had MRD following the uniform first cycle of chemotherapy for both treatment arms
[e] Results as per the RP2D population (n=70), which included patients from phase I and II who received a dose of 5/15 mcg/m^2/day of blinatumomab
[f] Three deaths occurred after HSCT following blinatumomab-induced CR
[g] One death occurred due to complications related to HSCT (chronic graft versus host disease) and one death occurred due to PD
[h] Death was experienced by two patients due to toxicities following subsequent treatment phases; one patient experienced septic shock during maintenance and one patient experienced transplant-related toxicity

Abbreviations: AE = adverse event; BCP-ALL = B-cell precursor acute lymphoblastic leukemia; CNS = central nervous system; CR = complete remission; CRS = cytokine release syndrome; DFS = disease free survival; EFS =event-free survival; HSCT = hematopoietic stem cell transplant; LFS = leukemia-free survival; MRD = minimal

residual disease; NR= Not reported; OS = overall survival; R/R = relapsed and refractory; RCT = randomized controlled trial; RFS = relapse-free survival; RP2D = recommended phase 2 dose

COG-AALL1331 Trial (NCT0210853)[5,25,61,62]

Methods

This trial was a phase III RCT assessing the efficacy and safety of blinatumomab compared with standard combination chemotherapy in patients aged 1 to 30 years with relapsed, Ph-, BCP-ALL. Patients were randomized to receive either two intensive chemotherapy blocks or two cycles of blinatumomab (continuous infusion over 28 days at 15 mcg/m^2/day) after a uniform first block of re-induction chemotherapy. This trial used treatment with blinatumomab as a bridge to transplant as many relapsed patients are not able to proceed to HSCT due to AEs resulting from chemotherapy, or from being unable to reach MRD- status. MRD testing was performed using flow cytometry with a threshold for MRD+ defined as ≥ 0.1%.

The primary endpoint of the COG-AALL1331 trial was DFS. Secondary endpoints of the trial included OS, MRD response assessed by flow cytometry in a central lab, and ability of patients to proceed to HSCT were other secondary outcomes also assessed between patient groups.

Results

A total of 208 intermediate or high-risk patients were randomized within the COG-AALL1331 trial, with 103 patients randomized to the standard of care chemotherapy group and 105 patients randomized to the blinatumomab group; these patients encapsulated the ITT population and were used for analyses of DFS and OS. Baseline characteristics, including age at enrollment, gender, NCI risk group at diagnosis, site of relapse and duration of CR1, risk group assignment after block 1 of therapy, and cytogenetic group, were similar between both treatment groups. Results of DFS and OS for both treatment groups are reported in Table 27. Median follow-up of patients at this interim analysis was 1.4 years. The two-year DFS was higher among patients in the blinatumomab group compared to the standard of care chemotherapy group; analysis for DFS was based on a pre-specified one-sided test with a resulting P value of 0.05 just reaching statistical significance. It should be noted that the improvement in DFS for patients in the blinatumomab group did not cross the predefined superiority threshold at the time of this interim analysis. The two-year OS was also higher among patients in the blinatumomab group compared to the standard of care chemotherapy group; although these results reached statistical significance, they were based on a 1-sided test.

Table 27: Efficacy Results of the COG-AALL1331 trial

	Standard of Care Chemotherapy Group	Blinatumomab Group
Median follow-up (years)	1.4	
DFS, % (± SE)	41.0 (6.2)	59.3 (5.4)
P value	0.05[a]	
OS	59.2 (6.0)	79.4 (4.5)
P value	0.005[b]	

[a] 1-sided per pre-specified statistical plan

[b] 1-sided

Abbreviations: DFS = disease free survival; OS = overall survival; SE = standard error

Table 28 reports the rates of MRD clearance among patients in both treatment groups. Fifty-seven (55.3%) patients had detectable MRD levels ≥ 0.01% after competing their first block of chemotherapy in the standard of care chemotherapy group, compared to 72

patients (68.6%) in the blinatumomab group. A greater proportion of patients achieved undetectable MRD levels (< 0.01%) after receiving their first cycle of blinatumomab (79%) compared to 21% of patients who achieved undetectable MRD levels after receiving a second block of chemotherapy (P < 0.0001). After receiving their second cycle of blinatumomab, proportions of patients achieving undetectable MRD levels continued to be higher compared to patients who received third block of intensive chemotherapy, although chi-square testing did not indicate a statistically significant difference in MRD-negative status among patients between the two treatment groups. The proportions of patients who remained at undetectable MRD levels (i.e. MRD < 0.01%) after Block 2 of chemotherapy to after Block 3 of chemotherapy was similar to those who achieved undetectable MRD level after cycle 1 of blinatumomab to after cycle 2 of blinatumomab, which suggests a durable MRD response in both treatment groups. However, this should be interpreted with caution as due to small cell counts.

Table 28: Rates of MRD Clearance*

	Arm A	Arm B	p-value^
Of MRD ≥0.01% after Block 1, # clearing MRD <0.01% after Block 2/Blina C1	12 of 57 (21%)	57 of 72 (79%)	<0.0001
Of MRD ≥0.01% after Block 2/Blina C1, # clearing MRD <0.01% after Block 3/Blina C2	17 of 27 (63%)	5 of 7 (71%)	0.68
Of MRD <0.01% after Block 2/Blina C1, # remaining MRD <0.01% after Block 3/Blina C2	14 of 16 (88%)	59 of 69 (86%)	0.84

*This table excludes patients with no MRD data (due to death, severe toxicity, treatment failure, 2nd relapse, poor quality sample, data pending); ^chi square

Source: Republished with permission of American Society of Hematology, from Brown et al., Blood. 2019;134(Suppl 2):LBA-1. Copyright 2019; permission conveyed through Copyright Clearance Center, Inc.[25]

Safety

A total of four post-induction toxic deaths occurred in the COG-AALL1331 trial, with all of them occurring in the standard of care chemotherapy arm; all these deaths were reported to be due to infection (P = 0.05). Table 29 reports the proportions of grade 3 or higher AEs occurring after blocks two and three in the standard of care chemotherapy group, and after cycles one and two of blinatumomab. Febrile neutropenia, infections, sepsis, and mucositis were all reported more frequently among patients in the standard of care chemotherapy group compared to the blinatumomab group after each block/cycle of treatment. Specific blinatumomab-related AEs are reported in Table 30; most AEs were reported after cycle 1 of blinatumomab, and all AEs related to blinatumomab were reported to be fully resolved.

Table 29: AEs for Both Treatment Groups

AEs Grade ≥3 [a]	Standard of Care Chemotherapy Group		Blinatumomab Group	
	Block 2	Block 3	Cycle 1	Cycle 2
Febrile neutropenia	44%	46%	4%	0%
Infections	41%	61%	10%	11%
Sepsis	14%	21%	1%	2%
Mucositis	25%	7%	0	1%

[a] AEs reported based on the CTCAE version 4

Table 30: Blinatumomab-related AEs after Cycles 1 and 2

AEs[a]	Cycle 1		Cycle 2	
	Any-grade	Grade ≥ 3	Any-grade	Grade ≥ 3
Cytokine release syndrome	22%	1%	1%	0
Seizure	4%	1%	0	0
Other neurotoxicity (e.g., cognitive disturbance, tremor, ataxia, dysarthria)	14%	2%	11%	2%

[a] AEs reported based on the CTCAE version 4

Regarding patients who successfully proceeded from randomization to HSCT at the September 30, 2019 data cut, 44 of the 98 patients (45%) who received standard of care chemotherapy proceeded to HSCT; this was statistically significantly lower compared to the 75 of 103 patients (73%) who received blinatumomab and proceeded to HSCT (P < 0.0001). Improved DFS, superior OS, lower toxicity, superior MRD clearance and greater likelihood of proceeding to HSCT among patients randomized to the blinatumomab compared to the standard of care chemotherapy group, suggests that treatment with blinatumomab in children, adolescents, and young adults with intermediate or high risk BCP-ALL in first relapse is efficacious.

Summary of critical appraisal:

- Analyses for DFS and OS were conducted using one-sided tests. Utility of one-sided tests in this study may be considered appropriate for detection of whether blinatumomab is more efficacious compared to chemotherapy. In addition, the one-sided tests increase the power of the study to detect an effect from treatment with blinatumomab compared to standard of care chemotherapy considering this is a rare indication among pediatric patients
- Analyses of efficacy and harms outcomes were preliminary (based on interim data) and results were presented in an abstract (i.e. not peer-reviewed). The study was stopped following a recommendation from the COG data monitoring committee at the time of the interim analysis due to favourable outcomes (i.e., efficacy and tolerability) of blinatumomab among pediatric patients. However, as the final analysis has not yet been conducted, the long-term effect of blinatumomab among these patients remains unknown at this time. The final data collection date is estimated to be in December 2022.
- It was not made clear whether analyses for secondary outcomes were adjusted for multiplicity.
- Subgroup analyses of patients with MRD positivity following the first block of induction by treatment group were not provided; thus, interpretation of the clinical benefit in terms of validated outcomes (e.g., DFS or OS) to the indication under review (MRD+, BCP-ALL) are limited based on the available evidence. Detailed safety data from this trial is not yet available.

Study MT103-205 [23]

Methods

Study MT103-205 was an open-label, single-arm, international phase I/II trial investigating blinatumomab treatment in pediatric and young adult patients with BCP-ALL who were refractory, in their first relapse after full salvage induction, in second or later relapse, and/or in any relapse after receiving an allogenic HSCT. Patients were recruited from 26 centres across Europe and the US and were less than 18 years of age (2 to 17 years of age in phase I dose escalation) with a diagnosis of BCP-ALL with > 25% bone marrow blasts. Patients who were Ph+ were eligible to enroll. This trial consisted of two phases: during phase I, blinatumomab was administered to patients at four different doses: 5 mcg/m^2/day, 15 mcg/m^2/day, 30 mcg/m^2/day and a step-wise dosage of 15/30 mcg/m^2/day whereby patients were given 15 mcg/m^2/day for the first seven days, and 30 mcg/m^2/day thereafter. After the

recommended dosage was determined (stepwise 5/15 mcg/m^2/day) by an independent DSMB, and additional patients were recruited to assess PKs and safety across three age groups (7 to 17 years; 2 to 6 years; and < 2 years) before initiation of phase II.

During phase II, patients received blinatumomab as a 4-week continuous IV infusion followed by a 2-week treatment-free interval. As treatment was provided in a stepwise manner (5/15 or 15/30 mcg/m^2/day), the lower dose was provided for the first week of the first cycle, followed by the higher dose (30 mcg/m^2/day) for the remaining three weeks and subsequent cycles. Patients who achieved CR within the first two cycles could receive up to three additional cycles of blinatumomab or were withdrawn from treatment to receive either consolidation chemotherapy or HSCT determined by the investigator's choice.

Patients who experienced AEs which met criteria for dose-limiting toxicities (DLTs) were permanently discontinued from treatment. Patients experiencing AEs related to blinatumomab which did not meet DLT criteria but required infusion interruption were allowed to restart blinatumomab treatment at one dosage level lower after resolution to grade ≤ 1.

The primary endpoint for phase I of the study was maximum-tolerated dosage (MTD), the maximal dosage at which one or fewer of six patients experienced a DLT. Secondary endpoints were PKs and incidence of AEs. The primary endpoint for phase II of the study was CR rate within the first two cycles of blinatumomab; secondary endpoints were AEs incidence, proportion of patients undergoing allogenic HSCT after receiving blinatumomab, RFS, and OS. Exploratory endpoints during both trial phases included MRD response and complete MRD response.

Results

During phase I of the study 49 patients were treated, with 23 patients enrolled in the four treatment arms of the trial and 26 patients enrolled in the PK expansion arm. A total of 44 patients were treated during phase II. At the end of the study, all patients had completed the two-year follow-up, withdrawn from the study or died.

Phase I

Seven of the 23 patients (30%) during the dose-escalation part of phase I achieved CR within the first two cycles of blinatumomab; two of these patients were in the stepwise dosage arm while three were in the 15 mcg/m^2/day arm of the trial. All patients who achieved CR also achieved a complete MRD response. Five patients who achieved CR proceeded to allogenic HSCT; one of these patients was in the stepwise arm while two were in the 15 mcg/m^2/day arm. Six of 23 patients did not achieve a response, one of whom was in the stepwise arm and three were in the 15 mcg/m^2/day arm.

Phase II

During phase II, 14 of the 44 patients (32%) who received the recommended stepwise 5/15 mcg/m^2/day dose achieved CR within the first two-cycles. Complete MRD response was achieved in eight of the 14 patients who experienced CR. Of these 14 patients achieving CR, 10 experienced relapse or death during the efficacy follow-up; these patients did not receive chemotherapy or allogenic HSCT between the end of treatment with blinatumomab and relapse. When considering all patients who received the recommended dose (all patients in phase I and II who received 5/15 mcg/m^2/day of blinatumomab; n = 70), 27 patients (39%) achieved CR within the first two-cycles. Complete MRD response was achieved in fourteen of the 27 (52%) patients who achieved CR. Relapse or death was reported by seven of the 27 patients. Median RFS among the 27 responders was 4.4 months (95% CI, 2.3 to 7.6 months). Median RFS was higher for patients with complete MRD response at 7.3 months (95% CI, 2.7 to 16.4) compared to patients without MRD response at 1.9 months (95% CI, 0.8 to 6.0). Median OS after two years among all 70 patients was 7.5 months (95% CI, 4.0 to 11.8 months).

Safety

Phase I

During phase I, four patients experienced DLTs, one of whom was receiving the recommended step-wise dosage of blinatumomab continued during phase II; this patient experienced respiratory failure with cardiac arrest occurring seven days after receiving an infusion of blinatumomab at 15 mcg/m^2/day (the dosage of 30 mcg/m^2/day was not administered to this patient). Shortly before receiving their infusion of blinatumomab, this patient had experienced febrile neutropenia and pneumonia. Another patient in the 15 mcg/m^2/day arm of the trial experienced a DLT due to grade 4 CRS deemed to be related to grade 4 GI hemorrhage. The remaining

two patients experiencing DLTs were in the 30 mcg/m^2/day arm due to grade 4 CRS. Based on the four DLTs, the MTD was determined to be 15 mcg/m^2/day. None of the patients receiving blinatumomab at 5 mcg/m^2/day experienced DLTs. DLTs were not collected formally during the PK expansion arm in phase I of the study; however, the study investigators concluded that none of the AEs that occurred would have met the definition of a DLT. Therefore, based on the MTD and overall toxicity profile, the stepwise dosage of 5/15 mcg/m^2/day was recommended by the independent DSMB for further evaluation in phase II.

Phase II

Safety data was reported for all 70 patients receiving blinatumomab at the recommended dose during phase II. All 70 patients experienced at least one AE. Most AEs were stated to have occurred during the first few days of cycle 1. The most common AEs were pyrexia (80%), anemia (41%), nausea (33%) and headache (30%). CRS occurred in 11% of patients. Neurologic/psychiatric events occurred in 17 patients (24%); tremor (n = 4, 6%), dizziness (n = 3, 4%) and somnolence (n = 3, 4%) were the most common neurologic events. Nine of the 17 (13%) neurologic events were considered to be treatment-related; these events primarily consisted of grade 2 tremor and dizziness that eventually resolved.

AEs of grade 3 or higher occurring in at least 5% of patients were reported in 61 of 70 patients (87%); of these anemia (36%) and thrombocytopenia (21%) were the most common (Table 31). Grade 3 neurologic events occurred in three patients (4%); two of these events were somnolence and one was neuralgia. Somnolence was noted to be a symptom of CRS in one patient and associated with stroke in another.

Treatment interruption occurred for 10 patients (14%); two of these patients experienced grade 3 CRS and two patients experienced neurologic events related to seizure. Four patients (6%) experienced treatment discontinuation permanently due to AEs. Treatment discontinuation was considered to be due to treatment with blinatumomab for two of the four patients who experienced grade 3 and 4 CRS. Investigators reported that no patients developed anti-blinatumomab antibodies during the study. Fatal AEs occurred in six patients (9%); three patients died after allogenic HSCT after blinatumomab-induced remission.

Table 31: AEs Occurring in Patients Receiving the Recommended Dose of Blinatumomab at 5/15 mcg/m^2/day

Adverse Event	All Patients (N = 70)*
Patients with adverse events	70 (100)
Adverse events of worst grade ≥ 3 occurring in ≥ 5% of patients	61 (87)
Anemia	25 (36)
Thrombocytopenia	15 (21)
Febrile neutropenia	12 (17)
Hypokalemia	12 (17)
Neutropenia	12 (17)
Alanine aminotransferase increased	11 (16)
Platelet count decreased	10 (14)
Pyrexia	10 (14)
Neutrophil count decreased	9 (13)
Aspartate aminotransferase increased	8 (11)
Leukopenia	7 (10)
White blood cell count decreased	7 (10)
Cytokine-release syndrome	4 (6)
Hypertension	4 (6)
Fatal adverse events on study†	6 (7)
Multiorgan failure‡	2 (3)
Sepsis‡	1 (1)
Fungal infection	1 (1)
Respiratory failure‡	1 (1)
Thrombocytopenia	1 (1)

NOTE. Table shows adverse events regardless of relationship to treatment that occurred during the treatment period and until 30 days after the last treatment or before allogeneic hematopoietic stem-cell transplantation or start of chemotherapy.

*All patients who received the recommended dose of 5/15 μg/m^2/d in phase I or II.

†Does not include two deaths caused by disease progression, including one patient who died as a result of recurrent leukemia. These deaths were reported by the investigators as adverse events.

‡Patient died after allogeneic hematopoietic stem-cell transplantation after blinatumomab-induced remission (only one of the patients with multiorgan failure).

Source: von Stackelberg et al: J Clin Oncol. 34(36), 2016 : 4381-4389. Reprinted with permission. © 2016 American Society of Clinical Oncology. All rights reserved.[23]

Summary of critical appraisal:

- Ph+ patients were eligible to enrol in this study. However, the potential for confounding from the inclusion of Ph+ patients is expected to be minimal, as only three patients were recorded as Ph+.
- As this was a phase I/II trial, patients and investigators were not blinded to treatment allocation of blinatumomab. However, investigators employed an independent DSMB to determine the recommended dose for further exploration in phase II of the study.
- It should be noted that this trial explored the safety of administration of blinatumomab at four different doses; the step-wise dosing with the lower dose (5/15 or 15/30 mcg/m^2/day) being provided for the first cycle and the higher dose for the remaining three weeks and subsequent cycles. This dosing schedule does not completely align with the funding request of

the sponsor (Table 32). In addition, the sponsor's funding request specified that patients must be MRD+; however, the MT103-205 study did not specify that all patients enrolled must be MRD+.

- The lack of a comparison group limits the ability of determining the efficacy and safety of blinatumomab to other relevant treatments in this disease space.
- During phase II of the study, results were powered to determine whether achievement of CR within the first two cycles of blinatumomab was ≤ 10% versus the alternative hypothesis of 27.5% (the primary outcome); however, statistical analyses of RFS and OS were not adjusted for multiplicity and should be considered exploratory and interpreted with caution. Pooled analyses including all patients receiving the recommended dose should also be considered exploratory.

Table 32: Blinatumomab Recommended Dosage for Pediatric Patients with MRD-positive B-cell Precursor ALL

Patient Weight	Induction Cycle 1		Consolidation Cycles 2-4	
	Days 1-28	Days 29-42	Days 1-28	Days 29-42
Greater than or equal to 45 kg *(fixed dose)*	28 mcg/day	14-day treatment-free interval	28 mcg/day	14-day treatment-free interval
Less than 45 kg *(BSA-based dose)*	15 mcg/m^2/day (not to exceed 28 mcg/day)		15 mcg/m^2/day (not to exceed 28 mcg/day)	

Source: Amgen Product Monograph, 2019[1]

Keating et al.[24]

Methods

The study by Keating et al.[24] was a retrospective analysis of patients 0 to 21 years of age with B-ALL who were transplanted at five different Foundation for the Accreditation of Cellular Therapy-accredited pediatric HSCT centres. Patients in the study had complete morphological remission (CR; < 5% blasts in the bone marrow) but had persistent MRD. MRD testing was performed via flow cytometry per standards of the COG reference laboratory. Patients received blinatumomab between 2016 and 2017 with the goal of reducing or eliminating MRD prior to HSCT.

Outcomes assessed included OS and leukemia-free survival which were reported using the K-M function using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.Rproject.org/). The cumulative incidence function was used to report time to relapse with death from transplantation treated as a competing risk.

Results

A total of 15 patients with B-ALL were included in the analysis. At the time of blinatumomab treatment, the median age of patients was 9 years (range = 0.5 to 19). Patients also showed a large variety of cytogenetic abnormalities. At the time of blinatumomab treatment/HSCT, most of the patients were in their first remission (n = 10; CR1); the remaining patients were in their second remission (n =5; CR2). The median MRD level prior to treatment with blinatumomab was 0.57% (range = 0.01% to 2.2%). The median follow-up time for patients was 371 days (range = 134 to 749) post-HSCT. After treatment with blinatumomab, MRD levels were reduced to undetectable levels in 93.3% of patients (n = 14). The 14 patients who achieved MRD negative status after treatment with blinatumomab then proceeded to HSCT. Patients proceeded to HSCT without delay, as the median time to preparative regimen after the end of blinatumomab treatment was 14 days (range = 1 to 35). The one-year OS for these patients was 93.3%.

Safety

It was reported that a single patient experienced a grade 3 seizure during blinatumomab therapy that was graded retrospectively. It should be noted that this patient was diagnosed with CNS3 leukemia (> 5% blasts in the CSF at diagnosis/relapse) and received

CNS directed medication associated with lowering the seizure threshold at the time of the event. No other grade 3 or 4 toxicities or CRS events were reported.

Among the 14 patients who proceeded to HSCT, only one patient experienced a significant HSCT-related complication within the first 30 days after HSCT. This patient experienced respiratory distress from mucositis. Two of 14 (14.3%) patients experienced grade 2 or 3 acute GVHD, and 3 out of 14 (21.4%) patients experienced extensive chronic GVHD; these five patients all received alternative donor HSCTs. The authors reported that alternative donors were the prominent stem cell source for transplant among this cohort of patients; only six of the 14 patients received a stem cell source from a matching family member. Four patients were reported to have experienced a relapse of CD19-positive ALL at a median time of 355 days post HSCT, for a cumulative incidence at one-year post HSCT of 27.8%.These four patients achieved successful remission with CD19-positive directed therapy and were reported to have remained in CR at the time of publication of the article by Keating et al.[24]

No transplant related deaths were reported within the first 100 days post HSCT. However, one death was reported for a patient related to chronic GVHD, and another death was reported for a patient who did not proceed to HSCT due to disease progression. The authors of this study reported that CRS may be of some concern with blinatumomab therapy, as blinatumomab activates the immune system and any lymphocyte activation prior to HSCT could negatively influence donor engraftment or increase rates of GVHD.

Summary of critical appraisal:

- Due to the retrospective nature of this study by Keating et al.,[24] a number of biases are introduced into the analyses, including selection bias and misclassification bias. In addition, the analyses may be subject to confounding.
- The overall sample of patients included in this cohort was small (n = 15), limiting the generalizability of the results to pediatric and young adult patients.
- The dose of blinatumomab provided to patients was not made clear. As this was a retrospective analysis, it is possible that patients received varying doses, and there is potential for misalignment with the sponsor's funding request.
- Most patients (8 out of 14) in the analysis received HSCTs from unrelated donors. Blinatumomab was stated to provide a low toxicity therapeutic bridge to transplant for patients while they wait for an alternative donor. In addition, the rates of grade 2 to 4 acute GVHD and chronic GVHD were low despite the use of alternative donors for HSCT. However, due to the small sample size results should be interpreted with caution.
- The lack of a comparator limits the ability for readers to determine the comparative effectiveness of blinatumomab as a bridge to transplant relative to usual care.

Elitzur et al.[60]

Methods

This study was a retrospective multicentre analysis of pediatric patients who received blinatumomab due to overwhelming chemotherapy-associated toxicity.

Medical records of children and young adults diagnosed with frontline or relapsed BCP-ALL in six hematology centres in Israel were collected between May 1, 2015 and December 1, 2018; these records were retrospectively reviewed. A total of 36 patients were reported to have been treated with blinatumomab; among whom 11 (30%) were treated with blinatumomab due to overwhelming chemotherapy-associated toxicity which caused prolonged delay of leukemia therapy. For these 11 patients, blinatumomab was used as a bridge to further therapy. The following results summarize the experiences of these 11 patients.

Results

The median age of patients was 6 years (range = 2.5 to 17). Underlying genetic conditions of patients included Down's syndrome (n = 2), neurofibromatosis (n=1) and psychomotor retardation with dysmorphic features (n = 1). Toxicity occurred during front-line

therapy for eight patients, during treatment of late bone marrow relapse for two patients and during treatment of early bone marrow relapse for one patient. Six patients (55%) experienced toxicity during the induction period of their treatment (during the first month of treatment), while the remaining experienced toxicity during delayed intensification therapy (n = 2), high-risk Berlin Frankfurt Munster (BFM) consolidation (n = 1), high-dose methotrexate (n = 1), and after receiving salvage therapy with fludarabine, cytarabine, granulocyte colony stimulating factor, and idarubicin (FLAG-IDA) (n = 1).

The median amount of time from toxicity presentation to receipt of blinatumomab was 50 days (range = 15 to 90). The median interval of time without chemotherapy ranged from 75 days to 210 days, with a median of 122 days. Most of these 11 patients received one (n = 6) or two (n =4) cycles of blinatumomab, and one patient received four cycles. Patients were followed-up for a median duration of 12 months. The EFS was reported to be 71% and the OS was reported to be 80%.

Blinatumomab was successfully used as a bridge to further therapy in all 11 patients; all toxicities experienced by patients were reported to be resolved. Four patients went on to resume standard chemotherapy protocols, another four patients were bridged to maintenance therapy as they were unable to tolerate standard chemotherapy due to residual comorbidities, and three patients who were high-risk received allogeneic HSCT. Nine patients who were MRD- before receiving blinatumomab retained their MRD- status after receiving blinatumomab. Of two patients with measurable MRD, one had an MRD- response and the other had no MRD response and developed extramedullary disease at the end of their first cycle of blinatumomab; the latter patient was further treated with chemotherapy and CD19 chimeric antigen receptor T cells, and was the only patient to experience relapse.

Safety

The researchers reviewed complete blood count of patients due to previous concerns of neutropenia in previous R/R settings in ALL. Researchers observed an initial drop in lymphocytes on the first day of treatment with blinatumomab which was related to immune engagement and T-cell activation; however, there were no cases of significant neutropenia (i.e. absolute neutrophil count < 500/mcL). AEs were classified using CTCAE v.4, and included grade 2 seizures (n = 3), grade 2 encephalopathy (n = 1) and one case of *Staphylococcus aureus* bacteremia which was treated with IV antibiotics. Two patients died due to toxicities following subsequent treatment phases; one patient experienced septic shock during maintenance and one patient experienced transplant-related toxicity.

Summary of critical appraisal:

- The authors conducted a retrospective analysis of patient data, which may confound the results.
- The doses of blinatumomab provided to patients were not reported. It is not possible to know if the dose provided to these patients matches the funding indication reviewed by the CADTH Team.
- Authors reported that the lack of significant neutropenia observed in these 11 patients may have been related to higher neutrophil count at baseline, a prolonged gap since last cytotoxic chemotherapy, and lower overall disease burden as most patients were MRD- leading to reduced immune activation and CRS-associated cytopenia. In addition, patients with MRD- status were incorporated into these analyses, which does not match the indication reviewed by the CADTH.
- Blinatumomab enabled recovery from chemotherapy-induced toxicity and was successful as a bridge to further therapy in all patients. However, calculation of EFS and OS outcomes were not clear, which may limit comparability of results across trials. The lack clarity regarding outcome measures and the small sample size of the study warrant caution when interpreting results.

Conclusions

Four additional studies were summarized describing the use of blinatumomab among pediatric and young adult patients with R/R BCP-ALL. Three studies assessed the use of blinatumomab as a bridge to transplant (COG-AALL1331 trial; Keating et al., 2019; and Elitzur et al., 2019). The MT103-205 study aimed to determine a safe and effective dose in pediatric patients. None of these studies were limited to MRD+ patients or investigated the use of blinatumomab while patients were in remission. The studies presented with limitations that must be considered when assessing the efficacy of blinatumomab as a treatment, and as a bridge to transplant for pediatric and young adult patients with BCP-ALL. The COG-AALL1331 trial[25] and the study by Keating et al.[24] suggest that

blinatumomab may be safe and effective at reducing or eliminating MRD prior to HSCT for patients that have R/R disease. The study by Elitzur and colleagues suggested that blinatumomab may be efficacious among both MRD+ and MRD- patients, as many of the patients were MRD- prior to receiving blinatumomab. Longer term data is necessary to determine if blinatumomab is more efficacious compared to standard therapies over time. Study MT103-205[23] highlighted important safety considerations for patients receiving blinatumomab; CRS was indicated as an AE that may warrant extra caution, which aligns with the results of the study by Keating et al.[24] Study MT103-205[23] also indicated that neurological/psychiatric AEs may be more likely with blinatumomab. The patient populations in these studies did not directly match the indication under CADTH review, thus, evidence gaps remain. Namely, whether the results in the R/R setting can be used to appropriately address the funding request of the use of blinatumomab in first or second remission with MRD positivity. The evidence from the studies summarized above suggest that blinatumomab may be efficacious for use among younger patients, but that monitoring for CRS and neurological/psychiatric AEs may be necessary. Limitations of each of the studies should be considered and evidence should be interpreted with caution.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Hematology CGP and supported by the CADTH Methods Team. This document is intended to advise the pERC regarding the clinical evidence available on blinatumomab (Blincyto) for Ph-, CD19+, MRD+, BCP-ALL. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH 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 Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, Amgen Canada Inc., 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.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Databases: EBM Reviews - Cochrane Central Register of Controlled Trials December 2019, Embase 1974 to 2020 January 27, Ovid MEDLINE(R) ALL 1946 to January 27, 2020

Search Strategy:

#	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,nm,rn.	2174
2	exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/	55138
3	((B-Cell or B-Cells or BCP or B acute or B precursor or precursor B or pre B or B lymphoblastic or B lymphocyt*) and (leuk?emia* or lymphoma* or ALL)).ti,ab,kf,kw.	216783
4	(B lymphocyt* and (leuk?emia* or lymphoma* or ALL)).ti,ab,kf,kw.	24893
5	B-ALL.ti,ab,kf,kw.	133374
6	or/2-5	384734
7	1 and 6	1463
8	7 use medall	221
9	7 use cctr	63
10	*blinatumomab/ or (Blincyto* or blinatumomab* or MT-103 or MT103 or MEDI-538 or MEDI538 or AMG-103 or AMG103).ti,ab,kw,dq.	1481
11	exp Acute Lymphoblastic Leukemia/	81976
12	(B-Cell or B-Cells or BCP or B acute or B precursor or precursor B or pre B or B lymphoblastic or B lymphocyt*).ti,ab,kw,dq.	430504
13	11 and 12	13786
14	((B-Cell or B-Cells or BCP or B acute or B precursor or precursor B or pre B or B lymphoblastic) and (leuk?emia* or lymphoma* or ALL)).ti,ab,kw,dq.	205617
15	(B lymphocyt* and (leuk?emia* or lymphoma* or ALL)).ti,ab,kw,dq.	25114
16	B-ALL.ti,ab,kw,dq.	133361
17	or/13-16	341900
18	10 and 17	833
19	18 use oemezd	565
20	19 not conference abstract.pt.	232
21	8 or 20	453
22	limit 21 to english language	435
23	9 or 22	498
24	remove duplicates from 23	301
25	19 and conference abstract.pt.	333
26	limit 25 to english language	333
27	limit 26 to yr="2015 -Current"	254
28	24 or 27	555

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Results
#15	Search: **#13 publisher [sb]**	13
#13	Search: **#3 AND #12**	219
#12	Search: **#7 OR #8 OR #9 OR #10**	66,195
#10	Search: **B-ALL[tiab]**	4,470
#9	Search: **B lymphocyte*[tiab] AND (leukemia*[tiab] OR leukaemia*[tiab] OR lymphoma*[tiab])**	4,968
#8	Search: **(B-Cell[tiab] OR B-Cells[tiab] OR BCP[tiab] OR B acute[tiab] OR B precursor[tiab] OR precursor B[tiab] OR pre B[tiab] OR B lymphoblastic[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab] OR lymphoma*[tiab] OR ALL[tiab])**	61,156

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

WHO International Clinical Trials Registry
http://apps.who.int/trialsearch/

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

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

Select international agencies including:

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

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

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

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

Search: Blincyto/blinatumomab, acute lymphoblastic leukemia — last five years

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[63]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) 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 Blincyto, blinatumomab 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 July 23, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[64]

Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, the WHO International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's 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), the European Society for Medical Oncology (ESMO), 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 CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

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

Quality Assessment

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

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

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