DRAFT Reimbursement Review

Review Report

BLINATUMOMAB (BLINCYTO)

(Non-Sponsored Review)

Therapeutic area: Acute lymphoblastic leukemia, pediatrics

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Key Messages

What is pediatric Philadelphia-negative B-cell Acute Lymphoblastic Leukemia (Ph-negative B-ALL) at first relapse?

- ALL is the most common childhood cancer, with the Canadian Cancer Society reporting that 205 children under the age of 15 were diagnosed in 2019, and 10 deaths occurred in 2022.
- Ph-negative B-ALL, the most common subtype of childhood ALL, originates from immature B-lymphocytes and disrupts normal blood production in the bone marrow, leading to symptoms like fatigue, recurrent infections, bruising and bleeding. While most children respond well to initial treatment, around 10 to 15% experience relapse, which is associated with poor prognosis, with 5-year overall survival rates ranging from 35% to 50%.

What are the Treatment Goals and Current Treatment Options for pediatric Ph-negative B-ALL at first relapse?

- The main treatment goals are prolonging time to next relapse, improving overall survival, achieving a deep molecular response, and enabling high-risk patients to proceed to hematopoietic stem cell transplantation (HSCT), while managing or limiting SAEs.
- Currently in Canada, treatment involves reinduction therapy to achieve a second complete remission followed by consolidation therapy. Consolidation therapy options include multi-agent chemotherapy, immunotherapy where available, and/or possibly HSCT for high-risk patients.

What is Blinatumomab and Why Did We Conduct This Review?

- The drug under review is blinatumomab, which is available as an intravenous infusion. Health Canada has approved blinatumomab for the treatment of adult patients with Ph-negative CD19 positive B-ALL in first or second hematologic complete remission with minimal residual disease (MRD) greater than or equal to 0.1% and in pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-ALL.
- At the request of the participating public drug programs, we reviewed blinatumomab to inform a recommendation on whether it should be reimbursed for patients aged 1 to 18 years old with Ph-negative B-ALL who are in first relapse~~, with or without extramedullary disease~~.

How did We Evaluate Blinatumomab?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of blinatumomab versus other treatments used in Canada for the treatment of patients with Ph-negative B-ALL at first relapse. Multi-drug chemotherapy was considered a relevant treatment to compare with blinatumomab.
- The clinical evidence was identified through a systematic search for available studies. We consulted 2 clinical specialists with expertise in the diagnosis and management of B-ALL as part of the review process. The review was also informed by 1 patient group submission, 1 clinician group submission, and 1 industry submission in response to our call for input and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation.

What Did We Find?

Clinical Evidence

- We reviewed the following clinical evidence:
    - 1 trial (Locatelli et al.) comparing blinatumomab with multi-drug chemotherapy in pediatric patients with Ph-negative B-ALL at high-risk (HR) first relapse
    - 1 trial (COG AALL1331) comparing blinatumomab with multi-drug chemotherapy in patients aged 1 to 30 years old with Ph-negative B-ALL at intermediate- and high-risk (IR/HR) and low-risk (LR) first relapse

- For IR/HR first relapse patients:
    - The evidence from Locatelli et al. and COG AALL1331 suggested that blinatumomab may offer clinically meaningful benefits in event-free survival (EFS), disease-free survival (DFS), overall survival (OS), minimal residual disease (MRD) remission, and progression to HSCT compared to standard chemotherapy.
- For LR first relapse patients:
    - The COG AALL1331 trial provided insufficient evidence of benefit for DFS and OS in LR patients, and MRD remission was not reported.
- There is uncertainty in the findings based on potential risk of bias, incomplete reporting, lack of formal statistical testing, and absence of adjustments for multiple testing.
- HRQoL outcomes were not reported.
- The safety profile of blinatumomab was as expected with no new safety signals observed.

Economic Evidence

- Reimbursing blinatumomab for the treatment of pediatric patients with Ph-negative relapsed or refractory B-ALL is expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
B-ALL	B-cell precursor acute lymphoblastic leukemia
BFM	Berlin-Frankfurt-Münster
BM	bone marrow
CI	confidence interval
CNS	central nervous system
COG	Children's Oncology Group
CR	complete remission
CRS	cytokine release syndrome
DFS	disease-free survival
EFS	event-free survival
EM	extramedullary
HR	hazard ratio
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
ICANS	immune effector cell-associated neurotoxicity syndrome
IR/HR	intermediate- and high-risk
IEM	isolated extramedullary relapse
IntReALL	International study for treatment of childhood relapsed acute lymphoblastic leukemia
ITT	intention to treat
IV	intravenous
LR	low risk
MRD	minimal residual disease
OR	odds ratio
OS	overall survival
NR	not reported
Ph	Philadelphia
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
T-ALL	T-cell precursor acute lymphoblastic leukemia
WDAE	withdrawal due to adverse event

Background and Review Methods

Introduction

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Blinatumomab (Blincyto), 38.5 mcg/vial, lyophilized powder for solution, intravenous infusion
Relevant Health Canada indication	• Patients with Philadelphia chromosome-negative CD19 positive B-cell precursor acute lymphoblastic leukemia (B-ALL) in first or second hematologic complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. • Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL.
Mechanism of action	Blinatumomab is a bispecific T-cell engager molecule that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells, including B-ALL cells.[1]
Data protection status	End date: June 24, 2024
Status of biosimilars	None
Information on the CDA-AMC review	
Requestor	Provincial Advisory Group
Indication under consideration for reimbursement	Patients aged 1 to 18 years old with Philadelphia chromosome negative B-cell precursor ALL (B-ALL) who are in first relapse~~, with or without extramedullary disease~~.
Clinical review focus	Population: As defined in the indication under consideration for reimbursement Subgroups: risk of resistance or relapse post-induction (low vs. intermediate vs. high) Intervention: Blinatumomab 15mcg/m^2 once daily as continuous IV infusion over 28 days Comparators: Multi-drug Chemotherapy Outcomes: • Efficacy: OS, EFS, DFS, CR, MRD, time to next relapse, ability to proceed to HSCT, HRQoL • Harms: AEs, SAEs, Grade ≥3 AEs, WDAEs, mortality, AESIs (CRS, neurologic events [encephalopathy, seizures, febrile neutropenia, ICANS], infections)

AE = adverse event; AESI = adverse event of special interest; CR = complete remission; CRS = cytokine release syndrome; DFS = disease-free survival; EFS = event-free survival; HRQoL = health-related quality of life; HSCT = hematopoietic stem cell transplantation; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous, MRD = minimal residual disease; OS = overall survival; SAE = serious adverse event; WDAE = withdrawal due to adverse event

Objective

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of blinatumomab (Blincyto), 38.5 mcg/vial, lyophilized powder for solution, intravenous infusion in the treatment pediatric patients with Philadelphia chromosome negative relapsed/refractory B-ALL who are in first relapse, with or without EM disease. The focus will be placed on comparing blinatumomab to relevant comparators and identifying gaps in the current evidence. The Economic Review

consists of a cost comparison for blinatumomab compared with relevant comparators. The comparator considered relevant to the review was chemotherapy.

Review Methods

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from patient groups, clinician groups, the public drug programs that participate in the Non-Sponsored Reimbursement Review process, and industry.

Calls for patient group, clinician group, and industry input are issued for each Non-sponsored Reimbursement Review. The full submissions received are available in the consolidated input document <insert hyperlink or citation>. Input from patient and clinician groups is considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient and clinician group input and industry input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized separately <insert hyperlink to DPI document here>.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two pediatric oncologists with expertise in the diagnosis and management of Philadelphia chromosome negative relapsed/refractory B-ALL who are in first relapse, with or without EM disease in pediatric patients participated as part of the review team, with representation from Ontario and BC.

Submitted Input From Patient Groups, Clinician Groups, and Industry

Four patient advocacy groups, the Leukemia & Lymphoma Society of Canada (LLSC) Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Ontario Patients Advocating for Children with Cancer (OPACC), and Childhood Cancer Canada, jointly provided input for this review. Information was collected from caregivers of pediatric patients with ALL via an online survey, which focused on their experiences with blinatumomab. A total of nine participants responded to the survey.

Input was also provided by the Pediatric Oncology Group of Ontario (POGO), a clinician group. Their input was prepared through a consultative process, with one clinician responsible for leading the discussion and submitting the group's input.

Additionally, Amgen Canada Inc submitted input for this review.

Disease Background

ALL is the most common cancer diagnosed in children under 15 years old.[2] According to the Canadian Cancer Society, 205 children between the ages of 0 and 14 were diagnosed with ALL in 2019, and 10 deaths were attributed to the disease in 2022.[3] Pediatric B-ALL, a subtype of ALL that originates from immature B-lymphocytes responsible for producing antibodies accounts for approximately 80-85% of childhood ALL cases. This type of leukemia is characterized by the rapid proliferation of abnormal B-cell precursors, which disrupt normal blood cell production in the bone marrow, leading to symptoms such as fatigue, recurrent infections, bruising and bleeding, due to life-threatening bone marrow failure.[4,5]

Marrow involvement in acute leukemia, as observed by light microscopy, is classified as M1 with fewer than 5% blast cells, M2 with 5% to 25% blast cells, and M3 with more than 25% blast cells. Blast cells are immature precursor cells that can mature into B-lymphocytes in the bone marrow, and their excessive presence can crowd out healthy blood cells.[4]

A significant prognostic factor in B-ALL is the presence or absence of the Philadelphia chromosome (Ph-positive or Ph-negative). Ph-positive B-ALL, which involves a translocation between chromosomes 9 and 22, occurs in approximately 3% of pediatric B-ALL cases and is associated with poorer outcomes and higher relapse rates. However, Ph-negative B-ALL, the more common subtype, generally has a better prognosis.[4] Various risk classification systems have been used by clinical trial groups to assign pediatric B-ALL patients to treatment regimens based on their estimated risk of treatment failure. Contemporary risk classification systems consider clinical factors such as age and white blood cell (WBC) count at diagnosis, as well as cytogenetics/genomic alterations and minimal residual disease (MRD) levels at the end of induction therapy.[4] Common risk classification systems used are from the Children's Oncology Group (COG), Berlin-Frankfurt-Münster (BFM), and the IntReALL (International study for treatment of childhood relapsed ALL).

While most children with B-ALL respond well to initial treatment using risk-stratified multi-agent chemotherapy,[6] around 10 to 15% experience relapse. Relapse is associated with a poor prognosis, with 5-year overall survival (OS) rates ranging from 35% to 50%.[7] The risk of relapse is highest in the first year after treatment, decreasing by 7% to 10% annually over the next three years. Relapses occurring after four years are rare.[8] Relapsed B-ALL occurs when the disease returns after achieving complete remission (CR), with MRD levels at the end of induction and/or at the end of consolidation having largely replaced morphological assessment as the best indicator of long-term prognosis.[6]

Input from the patient group highlighted that pediatric cancer relapse has a profound impact on both the child and their family, affecting not only physical health but also daily routines, emotional well-being, and financial stability. The heightened risks of immunosuppression and ongoing treatment contribute to stress, anxiety, and emotional exhaustion, making support systems critical for managing these challenges.

Current Management

Treatment Goals

According to the clinical experts consulted by CDA-AMC, the goals of treatment for pediatric Ph-negative B-ALL at first relapse focus on prolonging time to next relapse, improving overall survival, achieving a deep molecular response, and enabling high-risk patients to proceed to hematopoietic stem cell transplantation (HSCT), while managing or limiting SAEs. The clinical experts consulted noted that pediatric patients with Ph-negative B-ALL at first relapse face poor survival outcomes when treated with intensive chemotherapy, with or without HSCT.

Input from patient groups emphasized the desire for treatments that are both innovative, effective and convenient, while minimizing severe side effects and undue harm.

Current Treatment Options

Treatment for pediatric Ph-negative B-ALL at first relapse involves reinduction therapy to achieve a second CR, along with central nervous system (CNS) management. CNS management can be administered either prophylactically or as treatment for CNS leukemic involvement. Following reinduction, consolidation therapy is used to eliminate residual disease and may include chemotherapy, immunotherapy where available, and/or possibly HSCT for high-risk patients.[4,8]

Reinduction therapy typically consists of risk-stratified, multi-drug combination chemotherapy, with drugs selection, dosages and schedules that vary across institutions and guided by cancer cooperative group protocols. Currently, no RCTs have directly compared specific regimens for relapsed disease, and there is no one universally preferred regimen, though various contemporary protocols suggest comparable outcomes, according to clinical opinion.[4,6]

At the end of reinduction, the bone marrow is examined to confirm remission based on morphology and to assess MRD levels. Generally, patients with isolated extramedullary (IEM) relapse fare better than those with bone marrow involvement, and patients with early relapse typically have poorer outcomes compared to those with late relapse.[4] Monitoring for MRD levels determines the response to treatment and risk of leukemia relapse and is also used to modify the intensity and duration of chemotherapy. MRD

levels are also a determinant of post-therapeutic progress and are used by clinicians for risk assignment strategies and therapy decisions.[9]

Post-remission management after reinduction involves consolidation therapy, which aims to eradicate any remaining leukemic cells after achieving a second CR.[8] The intensity and approach of consolidation therapy are guided by the patient's risk category, which is determined by clinical characteristics, the biology of the leukemic blasts, and the response to reinduction therapy.[4,8]

Consolidation therapy with multi-drug chemotherapy, based on institutional protocols, is the current standard treatment option. For patients with high-risk features, HSCT is often considered following reinduction and consolidation. HSCT is typically recommended for those who experience early relapse or exhibit poor prognostic factors.[4,8]

Input from the clinician group regarding current treatment options was aligned with the above, indicating that, as with upfront therapy, treatment approaches for relapsed B-ALL is stratified according to risk with particular attention placed towards the timing of the relapse and the site of relapse. Their input indicated that the current risk stratification approach in most Canadian pediatric oncology centres aligns with that from COG. Input from the clinician group aligned with the above, indicating that, as with initial therapy, treatment for Ph-negative B-ALL at first relapse is stratified according to risk. Special attention is given to the timing and site of relapse. The clinician group indicated that most Canadian pediatric oncology centers follow risk stratification protocols similar to those of the COG.

According to clinical experts consulted by the CDA-AMC, there is currently no pan-Canadian consensus document for the treatment and management of pediatric Ph-negative B-ALL at first relapse. The experts estimate that approximately 80% of Canadian institutions follow COG protocols and anticipate that other institutions' protocols adhere to similar principles.

Unmet Needs and Existing Challenges

The patient group highlighted that relapse and immunosuppression severely limit children's ability to engage in normal activities, placing a significant emotional and physical burden on both the child and their family. Families experience intense stress, financial strain, and disrupted daily routines, with caregivers often facing severe impacts on their mental health. There is a significant unmet need for more effective, less toxic therapies that improve quality of life by reducing treatment burden and minimizing the need for frequent hospital visits. Outpatient treatment options that decrease hospital stays was also cited as being crucial for maintaining normalcy and reducing stress for both patients and their families.

For low-risk patients, the clinician group indicated that clinicians historically used three intensive blocks of chemotherapy before moving on to consolidation and maintenance, which helped avoid the toxicity and late effects of HSCT. The clinician group highlighted that one of the chemotherapy blocks, block 3, is "highly toxic" and typically requires extensive hospitalization and poses significant risks of infection, sepsis, and mucositis. Clinicians have historically treated intermediate- and high-risk B-ALL patients with first relapse using three cycles of intensive cytotoxic chemotherapy, requiring extensive hospitalization before proceeding to HSCT.

The clinical experts highlighted that a substantial number of patients fail to respond adequately to currently available treatments. Intensive chemotherapy is associated with life-threatening or fatal toxicities, especially in high- and intermediate-risk populations, which can prevent these patients from progressing to curative HSCT. Treatment options that enhance the clearance of leukemia in patients with incomplete responses to chemotherapy and that result in deeper molecular response are needed. Such therapies may enable more patients with relapsed disease to proceed successfully to consolidative HSCT.

Clinical Review

Methods

Eligibility Criteria

We included studies that adhered to the a priori eligibility criteria, detailed in Working Papers, Table 1. Eligible studies included published and unpublished phase III and IV RCTs relevant to patients aged 1 to 18 years with Philadelphia chromosome negative B-ALL in first relapse, ~~with or without extramedullary disease,~~ being treated with blinatumomab. We considered risk of resistance or relapse post-induction (low vs. intermediate vs. high) to be important subgroups for informing the reimbursement recommendation. ~~As the reimbursement request is for patients with or without extramedullary disease, we also presented results for patients with and without extramedullary disease, when available.~~ Relevant comparators included drugs used in clinical practice in Canada to treat patients described in the indication under review and those included in the Economic Review. Relevant comparators included multi-drug chemotherapy.

We selected outcomes for review considering clinical expert input, and patient and clinician group inputs. Selected outcomes are those considered relevant to expert committee deliberations. These included overall survival (OS), event-free survival (EFS), disease-free survival (DFS), complete remission (CR), minimal residual disease (MRD), time to next relapse, ability to proceed to HSCT, health-related quality of life (HRQoL), adverse events (AEs), serious adverse events (SAEs), grade ≥3 AEs, withdrawals due to adverse events (WDAEs), mortality, and AEs of special interest (AESIs) (CRS, neurologic events [encephalopathy, seizures, febrile neutropenia, ICANS], infections).

Search Strategy

An information specialist conducted a peer reviewed literature search of key bibliographic databases, trial registries, and grey literature sources. The initial search was completed on July 10, 2024, with alerts maintained until the Formulary Management Expert Committee meeting on November 21, 2024. Refer to the Working Papers document for detailed search strategies.

Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report.

Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical experts, and patient and clinician groups, with input from a methodologist. Critical appraisal of the included studies was guided by version 2 of the Cochrane risk of bias tool for randomized trials.[10] One reviewer assessed the credibility of reported subgroups effects using the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN)[11] tool, with input from a methodologist.

Clinical Evidence

From the search for primary studies, we identified 337 unique records via the searches of databases and registers, of which we excluded 327 by title and abstract. We screened 10 records by full text and included 3 reports of 2 studies in the systematic review.

A list of excluded studies, including reasons for exclusion, is in the Working Papers, Table 3.

Systematic Review

Description of Studies

The Locatelli et al. study[12] was a phase III, randomized, open-label, multicenter trial sponsored by Amgen, conducted at 47 centers across 13 countries, which did not include Canada. The trial, which began in November 2014, aimed to evaluate event-free survival (EFS) in children (28 days to 18 years) with Philadelphia chromosome negative, high-risk first-relapse B-ALL after a third consolidation course with either blinatumomab or standard of care chemotherapy before undergoing HSCT. Patients received reinduction therapy (which could be from any of the following protocols at the investigators' discretion: IntReALL HR 2010, ALL-REZ BFM 2002, ALL R3, COOPRALL, and AIEOP ALL REC 2003) and 2 blocks of consolidation therapy and were then assessed for eligibility before proceeding to randomization.

Eligible patients were required to have M1 marrow or M2 marrow at randomization. Risk groups were defined per IntReALL and Berlin-Frankfurt-Münster criteria (see Working Papers, Table 4). Key exclusion criteria included clinically relevant CNS pathology requiring treatment such as unstable epilepsy, evidence of current CNS involvement by ALL, abnormal hepatic or renal function prior to start of treatment day 1, and uncontrolled chronic infection. Patients who were refractory to induction or who relapsed during the first 2 blocks of consolidation chemotherapy were excluded.

Patients received either one cycle of blinatumomab at a dose of 15 mcg/m²/day administered as a continuous intravenous infusion for 4 weeks with pre-treatment using dexamethasone 5mg/m² before the start of blinatumomab infusion on day 1, or consolidation chemotherapy as their third consolidation therapy. Consolidation chemotherapy regimens used in the trial are detailed in the Working Papers, Table 5. The primary endpoint was EFS, defined as the time from randomization to the date of relapse or M2 marrow after achieving complete remission, failure to achieve complete remission at the end of treatment, development of a second malignancy, or death from any cause, whichever occurred first. Secondary endpoints included overall survival (OS), defined as the time from randomization to death, minimal residual disease (MRD) remission at the end of treatment, underwent HSCT at the end of treatment and safety outcomes.

The COG AALL1331 trial[7,13] was a phase III, randomized, open-label, multicenter study sponsored by National Cancer Institute, conducted across 155 sites in 15 countries with 13 sites in Canada. The trial, which began in December 2014, aimed to evaluate the efficacy and safety of blinatumomab compared with standard chemotherapy in patients aged 1 to 30 years with first-relapse Philadelphia chromosome negative B-ALL. Key exclusion criteria included Down syndrome, Philadelphia chromosome–positive ALL, previous transplant, and previous blinatumomab treatment. This trial was designed to assess outcomes across different risk groups (low, intermediate, or high), with findings reported in two publications: Brown et al. (2021) and Hogan et al. (2023). The design of the trial is shown in the Working Papers, Figure 1.

Patients received Block 1 reinduction chemotherapy according to the UKALL R3 protocol and were then assessed to either be low-risk (LR), intermediate-risk (IR) or high-risk (HR) and assigned to either the LR cohort or the combined IR and HR cohort. The HR and IR patients were grouped together, citing previous studies[14,15] that demonstrated similar survival outcomes in both groups. Each group was then randomized to receive either blinatumomab or standard chemotherapy as part of their treatment regimen.

IR/HR patients randomized into the blinatumomab group received two cycles of blinatumomab at a dose of 15 mcg/m²/day administered as a continuous intravenous infusion for 4 weeks, separated by a 7-day break, with pre-treatment using dexamethasone 5mg/m² before the start of blinatumomab infusion on day 1 of cycle 1, and age-based intrathecal (IT) therapy on days 15 and 29 of each cycle with methotrexate for CNS1/2 involvement or with triple IT (methotrexate, hydrocortisone, and cytarabine) for CNS3 involvement and isolated CNS relapse.

LR patients randomized into the blinatumomab arm received Block 2 chemotherapy, followed by 1 cycle of blinatumomab at a dose of 15 mcg/m²/day administered as a continuous intravenous infusion for 4 weeks, with pre-treatment using dexamethasone 5mg/m² before the start of blinatumomab infusion on day 1 of cycle 1, and age-based intrathecal (IT) therapy on day 8 and 29 with methotrexate for CNS1/2 involvement or with triple IT (methotrexate, hydrocortisone, and cytarabine) for CNS3 involvement. This

was followed by continuation chemotherapy intercalated with two 4-week blinatumomab blocks at a dose of 15 mcg/m²/day administered as a continuous intravenous infusion for 4 weeks, followed by maintenance therapy.

Reinduction and consolidation therapy regimens used in the trial are detailed in the Working Papers, Tables 6, 7, and 8.

The primary endpoint of the trial was disease-free survival (DFS), defined as the time from randomization to the first occurrence of relapse, development of a second malignancy, or death, whichever came first. Secondary endpoints included overall survival (OS), defined as the time from randomization to death of any cause, and safety outcomes. Exploratory end points for the high- and intermediate-risk group were the rate of MRD negativity and whether patients proceeded to HSCT.

Results

Patient Disposition

Patient disposition for each included study is summarized in the following publications: Locatelli et al. (2021) Figure 1[12]; Brown et al. (2021) Figure 1[13]; and Hogan et al. (2023) Figure 1[7].

Of the 108 patients randomized into the Locatelli et al. study, 54 were each assigned to the blinatumomab and chemotherapy groups. Three patients randomized to the chemotherapy group were not treated. Numerically more patients in the chemotherapy group discontinued treatment (41%) compared to the blinatumomab group (20%). In the chemotherapy group, numerically more patients discontinued treatment due to death (30% vs 15%).

The COG AALL1331 trial enrolled 669 patients with first-relapse B-ALL. Discrepancies were noted in the reporting of patient disposition prior to randomization across the 2 contributing publications. The discrepancies (±1 or 2 patients) were deemed to be minor and values reported in the publication by Hogan et al. (2023) are reported herein. Of these, 661 (99%) patients began block 1 chemotherapy, and 629 (94%) patients completed the evaluation for risk of relapse/recurrence after block 1. Among the 629 evaluated patients, 43 (7%) were identified as having early treatment failure. The remaining patients were classified into risk groups, with 187 patients assessed as HR, 105 patients as IR, and 294 patients as LR.

- Of 291 eligible IR/HR patients, 216 (74%) were randomized (107 to blinatumomab and 109 to chemotherapy). Of the patients not randomized, most (89%) were due to patient or physician preference. 102 (95%) patients assigned to blinatumomab received cycle 1 of blinatumomab, 88 (82%) proceeded to cycle 2 of blinatumomab, and 74 (69%) proceeded to HSCT. 97 (89%) patients assigned to chemotherapy received cycle 1 chemotherapy, 62 (57%) proceeded to cycle 2 chemotherapy, and 44 (40%) proceeded to HSCT.

- Of 294 eligible LR patients, 255 (87%) were randomized (127 to blinatumomab and 128 to chemotherapy). Of the patients not randomized, most (85%) were due to patient or physician preference. 126 (99%) patients assigned to the blinatumomab group received block 2 chemotherapy, 121 (95%) proceeded to cycle 1 of blinatumomab, 119 (94%) proceeded to continuation 1 chemotherapy, 114 (90%) proceeded to cycle 2 of blinatumomab, 112 (88%) proceeded to continuation 2 chemotherapy, 105 (83%) proceeded to cycle 3 of blinatumomab and 104 (82%) proceeded to receive maintenance therapy for a total of 2 years of treatment. Of the 104 patients, 1 patient had proceeded directly to maintenance after blinatumomab cycle 1 and 1 patient proceeded directly after blinatumomab cycle 2.

  128 patients assigned to chemotherapy received block 2 chemotherapy, 118 (92%) proceeded to block 3 chemotherapy, 111 (87%) proceeded to continuation 1 chemotherapy, 104 (81%) proceeded to continuation 2 chemotherapy and 102 (80%) proceeded to receive maintenance therapy for a total of 2 years of treatment.

Baseline Characteristics

Patients' baseline characteristics from each included study are detailed in the following publications: Locatelli et al. (2021) Table 1[12], Brown et al. (2021) Table 1[13] and Hogan et al. (2023) Table 1[7].

In the Locatelli et al. study, the median age of patients was between 5 and 6 years (range, 1 to 17 years) across groups. Seventy to 72% of patients across groups were aged 9 or younger. The chemotherapy group had more female patients (59.3% vs. 44.4% in the

blinatumomab group). Most patients were White, with a greater proportion in the blinatumomab compared with the chemotherapy group (92.6% vs. 79.6%).

Among the IR/HR cohort of the COG AALL1331 trial, baseline characteristics were well-balanced between the blinatumomab (n=105) and chemotherapy (n=103) groups. The median age was 9 years in both groups (range 6-16 in the blinatumomab group and 5-16 in the chemotherapy group), with most (52% to 53% across groups) being between 1 and 9 years. Fourteen to 17% of patients across groups were over 18 years of age. Most (74% to 83% across groups) patients were White and there were slightly more males (52% to 54% across groups) than females (46% to 48% across groups). There were more Black or African American patients in the chemotherapy group (20.2% vs. 8.4% in the blinatumomab group), and more White patients in the blinatumomab group (83.1% vs. 74.2% in the chemotherapy group). Across groups, approximately two-thirds of patients were HR and one-third were IR.

Among the LR cohort of the COG AALL1331 trial, baseline characteristics were well-balanced between the blinatumomab (n=127) and chemotherapy (n=128) groups. Most (52.4% to 53.4% across groups) patients were between 1 and 9 years old, with 12.5% to 14.2% of patients across groups being over 18 years of age. There were more males (59.4% to 59.8% across groups) than females (40.2% to 40.6% across groups). Most patients were White (78.5% to 82.5% across groups), Black or African American (7.9% to 8.6% across groups), or Asian (7.0% to 8.6% across groups). Across groups, the site of relapse was the marrow for approximately two-thirds of patients and isolated extramedullary for the remaining one-third.

Treatment Exposure and Concomitant Medications

Adherence, concomitant medications, subsequent treatments were not reported in either trial.

Efficacy

Results for outcomes important to this review are in Tables 2 and 3. Kaplan-Meier curves for EFS and OS as reported for HR patients by Locatelli et al. are in Figure 1. Kaplan-Meier curves for DFS and OS as reported for the COG AALL1331 trial are in Figures 2 (IR/HR group) and 3 (LR group). Key results include the following:

Among IR and HR patients (Locatelli et al. and COG AALL1331):

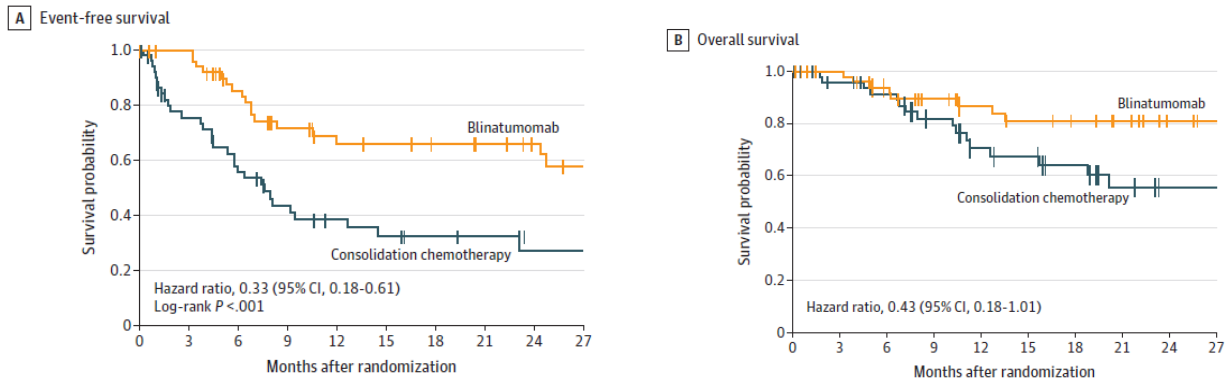
- Point estimates for the hazard ratios favoured blinatumomab over chemotherapy for EFS (Locatelli et al.) and DFS (COG AALL1331); however, results for DFS did not reach statistical significance. At 24 months follow-up, point estimates suggested an increased probability of EFS and DFS with blinatumomab; however, 95% CIs were not reported.
- Point estimates for the hazard ratios for OS favoured blinatumomab over chemotherapy in both trials; however, in Locatelli et al. statistical significance was not tested and the 95% CI included the potential for no difference between groups. At 24 months follow-up, point estimates in both trials suggested increased probability of survival with blinatumomab; however, 95% CIs were not reported.
- In both trials, more patients in the blinatumomab than the chemotherapy groups achieved MRD. The between-group difference was not tested statistically in Locatelli et al.
- In both trials, numerically more patients in the blinatumomab than the chemotherapy groups proceeded to HSCT. Absolute differences with 95% CIs were not reported in either trial and in Locatelli et al. the between-group difference was not tested statistically.

Among LR patients (COG AALL1331):

- For both DFS and OS, the trial was insufficient to show a difference between blinatumomab and chemotherapy. Ninety-five percent CIs for the hazard ratios were wide suggesting that either treatment may be favoured. Between-group differences with 95% CIs for the probabilities of EFS and OS at clinically relevant time points were not reported.

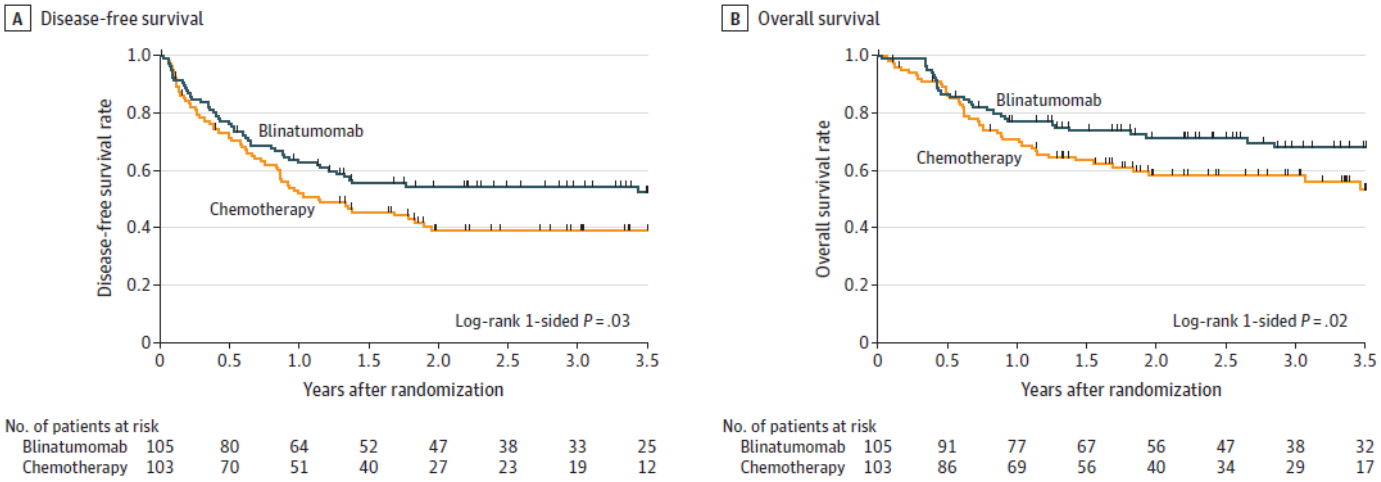
Other efficacy outcomes important to interested parties (CR, HRQoL, time to next relapse) were not reported in either trial.

Figure 1: Kaplan-Meier Estimates of Efficacy End Points in Locatelli et al. (2021)



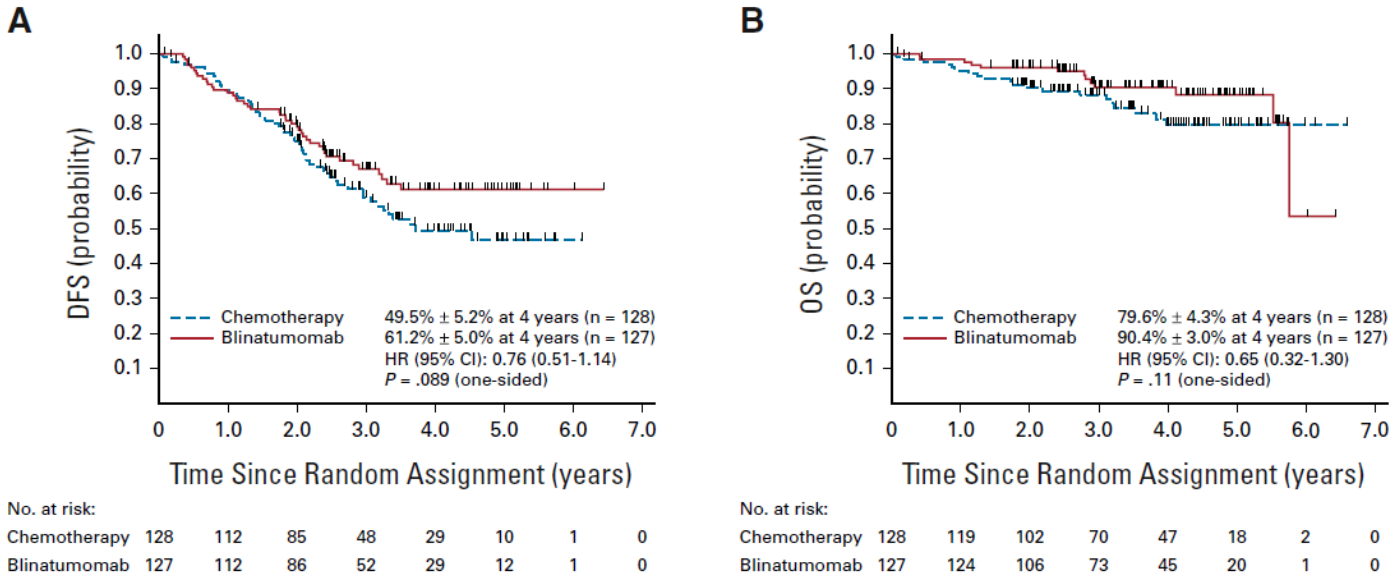
CI = confidence interval. Vertical bars indicate censoring.
A Event-free survival defined as time from randomization to relapse, all-cause death, second malignancy, or failure to achieve complete remission.
B Overall survival defined as time from randomization to death from any cause.
Source: Locatelli et al. (2021).[12] Reproduced with permission from [JAMA. 2021;325(9):843-854]. Copyright © (2021) American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies

Figure 2: Kaplan-Meier Estimates of Efficacy End Points in COGAALL1331 Intermediate- and High-Risk Group



CI = confidence interval. Vertical bars indicate censoring.
A Disease-free survival defined as time from randomization to late treatment failure (≥5% marrow blasts after first course of randomized therapy), relapse, second malignancy, or death. (Hazard Ratio 0.70 [95%CI, 0.47 to 1.03])
B Overall survival defined as time from randomization to death from any cause. (Hazard Ratio 0.62 [95%CI, 0.39 to 0.98])
Source: Brown et al. (2021)[13] Reproduced with permission from [JAMA. 2021;325(9):833-842]. Copyright © (2021) American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Figure 3: Kaplan-Meier Estimates of Efficacy End Points for COGAALL1331 Low-Risk Group



CI = confidence interval; HR = hazard ratio. Vertical bars indicate censoring.
A Disease-free survival defined as time from randomization to relapse, second malignancy, or death.
B Overall survival defined as time from randomization to death from any cause.
Source: Hogan LE, Brown PA, Ji L, et al. Children's Oncology Group AALL1331: Phase III Trial of Blinatumomab in Children, Adolescents, and Young Adults With Low-Risk B-Cell ALL in First Relapse. *J Clin Oncol.* 2023;41(25):4118-4129.[7] "The Creative Commons license does not apply to this content. Use of the material in any format is prohibited without written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com for further information."

Table 2:Summary of Key Efficacy Results for Intermediate- and High-Risk Groups

Variable	Locatelli et al. (2021)		COG AALL1331	
	Blinatumomab N = 54	Chemotherapy N = 54	Blinatumomab N = 105	Chemotherapy N = 103
Primary end point[a]:	**Event-Free Survival**		**Disease-free Survival**	
Follow-up time, median (range)	22.4 months (IQR, 8.1 to 34.2)		2.9 years (0 to 5.6 years)	
Events, n (%)	17 (31)	31 (57)	48 (46)	59 (57)
Total relapses	13 (24)	29 (54)	35 (33)	32 (31)
Death	4 (7)	2 (4)	12 (11)	18 (17)
Late treatment failure (M2 marrow after cycle 1)	-	-	1 (1)	9 (9)
EFS or DFS (months), median (95% CI)	NR	NR	NR	NR
Hazard Ratio (95% CI)[b,c], p-value	0.33 (0.18 to 0.61), p<0.001		0.70 (0.47 to 1.03), p=0.03[f]	
Probability (%) of EFS or DFS at 24 months (95% CI)	66.2 (50.1 to 78.2)	27.1 (13.2 to 43.0)	54.4 (NR)	39.0 (NR)
Difference (%) (95% CI)	39.1 (NR)		15.4 (NR)	
Overall Survival				
Follow-up time, median (range)	19.5 months (0.1 to 44.1)		2.9 years (0 to 5.6 years)	
Events, n (%)	8 (14.8)	16 (29.6)	-	-

Variable	Locatelli et al. (2021)		COG AALL1331	
	Blinatumomab N = 54	Chemotherapy N = 54	Blinatumomab N = 105	Chemotherapy N = 103
OS (months), median (95% CI)	NR	NR	NR	NR
Hazard Ratio (95% CI)[b,c], p-value[d]	0.43 (0.18 to 1.01); NR		0.62 (0.39 to 0.98), p=0.02[f]	
Survival probability (%) at 6 months, (95% CI)	93.9 (82.3 to 98.0)	91.4 (78.6 to 96.7)	-	-
Difference in survival probability (%) (95% CI)	2.5 (NR)		-	
Survival probability (%) at 12 months, (95% CI)	86.7 (72.6 to 93.9)	70.6 (53.7 to 82.3)	-	-
Difference in survival probability (%) (95% CI)	15.8 (NR)		-	
Survival probability (%) at 24 months, (95% CI)	81.1 (65.5 to 90.2)	55.8 (36.9 to 71.0)	71.3 (NR)	58.4 (NR)
Difference in survival probability (%) (95% CI)	25.3 (NR)		12.9 (NR)	
Survival probability (%) at 36 months, (95% CI)	81.1 (65.5 to 90.2)	55.8 (36.9 to 71.0)	-	-
Difference in survival probability (%) (95% CI)	25.3 (NR)		-	
Minimal Residual Disease				
Negative MRD[e] at baseline and remained negative, n/total evaluable (%)	17/20 (85)	20/23 (87)	-	-
Absolute difference, % (95% CI)	-2.0 (-31.2 to 28.0)		-	
MRD ≥0.01% at baseline and achieved negative MRD[e], n/total evaluable (%)	27/29 (93)	6/25 (24)	-	-
Absolute difference, % (95% CI)	69.1 (45.4 to 85.5)		-	
Total, n/total evaluable (%)	44/49 (90)	26/28 (54)	-	-
Absolute difference, % (95% CI)	35.6 (15.6 to 52.5)		-	
Negative MRD[e] at the end of reinduction, n (%)	-	-	26 (25)	31 (30)
OR, (95% CI), p-value[d]	-		0.76 (0.4 to 1.5), p=0.39	
Negative MRD[e] at the end of cycle 1, n (%)	-	-	79 (75)	33 (32)
OR, (95% CI), p-value[d]	-		6.4 (3.4 to 12.4), p<0.001	
Negative MRD[e] at the end of cycle 2, n (%)	-	-	69 (66)	33 (32)
OR, (95% CI), p-value[d]	-		4.1 (2.2 to 7.6), p<0.001	
Proceeded to HSCT				
Underwent HSCT, n %	48 (89)	38 (70)	74 (70)	44 (43)
OR, (95% CI), p-value[d]	-		3.2 (1.7 to 5.9), p<0.001	

CI = confidence interval; DFS = disease-free survival; EFS = event-free survival; HSCT = hematopoietic stem cell transplant; MRD = minimal residual disease; NR = not reported; OR = odds ratio; OS = overall survival

a The primary end point was event-free survival defined as time from randomization to relapse, all-cause death, second malignancy, or failure to achieve complete remission in Locatelli et al (2021) and disease-free survival defined as time from randomization to late treatment failure (≥5% marrow blasts after first course of randomized therapy), relapse, second malignancy, or death in the intermediate- and high-risk groups in COGAALL1331.

b For Locatelli et al, this was based on a stratified Cox proportional hazards regression model that adjusted for age, bone marrow involvement, MRD categories, sex, time to relapse, and extramedullary disease at relapse.

c For COGAALL1331, this was based on a Cox proportional hazards regression model that was tested using graphical diagnostics and verified based on scaled Schoenfeld residuals.

d P value has not been adjusted for multiple testing so there is increased risk of type I error.

e Negative MRD is defined as <0.01% blast cells on a bone marrow aspirate, as assessed by PCR and flow cytometry.

f One-sided stratified log-rank test was used to compare DFS and OS between randomized groups, with a significance threshold of 1-sided P = .025, as the analysis was designed to test for a positive treatment effect.

Source: Locatelli et al. (2021)[12]; Brown et al. (2021)[13]

Table 3: Summary of Key Efficacy Results for Low-Risk Group

Variable	COG AALL1331	
	Blinatumomab N = 127	Chemotherapy N = 128
Follow-up time, median (range)	3.5 years (25 days to 6.6 years)	
Primary end point[a]: Disease-free survival		
Events, n (%)	42 (33)	55 (43)
4-year DFS rate, %	61.2 ± 5.0	49.5 ± 5.2
Hazard Ratio (95% CI)[b]; p-value[c,d]	0.76 (0.51 to 1.14); p=0.89	
Overall survival		
4-year OS rate, %	90.4 ± 3.0	79.6 ± 4.3
Hazard Ratio (95% CI)[b]; p-value[c,d]	0.65 (0.32 to 1.30); p=0.11	

CI = confidence interval; DFS = disease-free survival; OS = overall survival

a The primary end point was disease-free survival defined as time from randomization to relapse, second malignancy, or death.

b Based on a stratified Cox proportional hazards regression model that was tested using graphical diagnostics and verified based on scaled Schoenfeld residuals.

c P value has not been adjusted for multiple testing.

d One-sided stratified log-rank test was used to compare DFS and OS between randomized groups, with a significance threshold of 1-sided P = .025, as the analysis was designed to test for a positive treatment effect.

Source: Hogan et al. (2023)[7]

Subgroups and Sensitivity Analyses

In Locatelli et al., results of a sensitivity analysis estimating the treatment effect of OS conditioned on the time 13 patients in the chemotherapy group received blinatumomab were consistent with the main analysis. Results of post-hoc analysis of EFS accounting for the effect of study center were also aligned with those for the main analysis.

In the COG AALL1331 IR/HR group, pre-specified subgroup analyses based on risk category (HR vs IR) for DFS, OS, MRD and rates of transplant were consistent with the main analyses, except for OS in the IR subgroup, where no statistical difference between groups was observed (2-year OS was 85.5% for blinatumomab vs 85.2% for chemotherapy, (HR 0.79 (95% CI, 0.25 to 2.6; one-sided p=0.35)). The KM curves for OS in the IR subgroup did not appear to meaningfully separate at any time during follow up.

In the LR group, post-hoc subgroup analyses of DFS and OS were performed based on the site of first relapse (BM ± EM vs IEM). Results for patients with BM ± EM relapse favoured blinatumomab over chemotherapy for DFS and OS, whereas although point estimates favoured blinatumomab over chemotherapy in the IEM group, the results were not statistically significant. Results for this subgroup analysis can be found in the Working Papers, Table 9.

Harms

Detailed results for harms for each included study are in the following publications: Locatelli et al. (2021) Table 3[12], Brown et al. (2021) Table 3[13], and Hogan et al. (2023) Table 3[7].

Although ICANS was considered important to this review, it was not reported in the included studies.

Table 4: Summary of Key Harms

Adverse events	Locatelli et al.		COG AALL1331 (IR/HR)		COG ALL1331 (LR)	
	Blinatumomab (N = 54)	Chemotherapy (N = 51)	Blinatumomab (N = 102)	Chemotherapy (N = 97)	Blinatumomab (N = 121)	Chemotherapy (N = 118)
AEs, n (%)	54 (100)	49 (96.1)	99 (97.1)	91 (93.8)	117 (97)	105 (89)
SAEs, n (%)	13 (24.1)	22 (43.1)	45 (42.1)[a]	26 (23.9)[a]	69 (54.3)[a]	16 (12.4)[a]
Grade ≥3 AEs, n (%)	31 (57.4)	42 (82.4)	83 (81.4)	90 (92.8)	104 (86)	105 (89)
WDAEs, n (%)	2 (3.7)	0	0	2 (2.1)	2 (1.7)	2 (1.7)
Deaths due to AEs, n (%)	0	0	0	5 (5.2)	1 (0.8)	3 (2.5)
AESI, n (%)						
CRS	NR	NR	22 (22)	NR	18 (15)	NR
Neurologic events	26 (48.1)	15 (29.4)	NR	NR	NR	NR
Encephalopathy	NR	NR	15 (15)	NR	35 (29)	NR
Febrile neutropenia	2 (3.7)	13 (25.5)	6 (5.9)	56 (57.7)	12 (10)	57 (48)
ICANS	NR	NR	NR	NR	NR	NR
Seizures	NR	NR	5 (5)	NR	7 (6)	NR
Infections	3 (5.6)	4 (7.8)	28 (27)	68 (70)	37 (31)	70 (59)

AEs = adverse events; AESI = adverse event of special interest; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; NR = not reported; SAEs = serious adverse events; WDAEs = withdrawal due to AEs

a Data from the total number of randomized patients as reported on ClinicalTrials.gov (NCT02101853).

Source: Locatelli et al. (2021)[12]; Brown et al. (2021)[13], Hogan et al. (2023)[7], NCT02101853[16]

Key results across both trials include the following:

- Across the trials, nearly all patients in both the blinatumomab and chemotherapy groups experienced at least one AE, with rates ranging from 89% to 100% across all groups.
- SAEs occurred more frequently in the blinatumomab groups in the COG AALL1331 trials compared to the chemotherapy groups, while the opposite was observed in Locatelli et al., where the chemotherapy group had a higher rate of SAEs compared to blinatumomab.
- Grade ≥3 AEs were common in both treatment groups, with higher frequencies in the chemotherapy groups in both trials. The difference appeared smaller in the COG ALL1331 trials compared with the Locatelli et al. trial.
- Treatment discontinuations due to AEs were infrequent in both groups across the trials, with rates generally below 4% in all cohorts.
- Deaths due to AEs were infrequent across all trials, with no deaths in the Locatelli et al. study and a small number in the COG AALL1331 trials.
- For AESIs, febrile neutropenia occurred more frequently in the chemotherapy groups across both trials. Infections occurred more frequently in the chemotherapy group in the COG AALL1331 trials. In Locatelli et al., infections appeared less frequent and occurred in similar proportions of patients across groups. Encephalopathy was reported among 15% and 29% of IR/HR and LR patients, respectively in the blinatumomab groups. Encephalopathy was not reported by Locatelli et al.

Critical Appraisal

Internal Validity

In both trials, randomization procedures were appropriate for limiting risk of bias in the randomization process. However, due to the small sample size (n = 108) in the Locatelli et al. trial, there is an increased risk that prognostic balance was not achieved, as evidenced by imbalances in patients' baseline disease and demographic characteristics (sex, race, history of extramedullary relapse

at diagnosis of first high-risk relapse, performance score). As such, it is possible that the observed effects were either over- or under-estimated and may have been driven by prognostic differences between the 2 groups (i.e., may not be reflective of the true treatment effect). In the COG AALL1331 trial, imbalances by race and cytogenetic factors were noted in the IR/HR cohort; however, these were deemed likely compatible with chance and therefore would not introduce risk of bias.

Both trials were open-label, meaning patients, caregivers, and trial personnel were aware of treatment assignments, introducing the potential for bias due to deviations from intended interventions. In the Locatelli et al. trial, 13 patients in the chemotherapy group received blinatumomab; however, sensitivity analyses of OS conditioned on the time these patients received blinatumomab were consistent with the main analyses, so it was judged that important risk of bias was not introduced. In both trials, details about protocol deviations were inadequate to inform a complete judgment of the risk of bias due to deviations from the intended interventions. The open-label nature of the trials increases the risk of bias in the measurement of subjective outcomes, namely subjective harms (e.g., nausea or fatigue). Major toxicities such as severe infections, febrile neutropenia, and cytokine release syndrome (CRS) were more objective and less prone to bias. Similarly, the efficacy outcomes (OS, EFS, DFS, MRD, proceeding to HSCT) were objective so risk of bias in their measurement is less likely.

In the Locatelli et al. trial there were 2 planned interim analyses (after 50% and 75% of planned EFS events had occurred). At the time of the 50% analysis, enrollment was terminated early due to the observed benefit of blinatumomab, meeting the prespecified efficacy stopping rule ($P < 0.004$ for the analysis of EFS). As the results are from an interim analysis, there is an increased risk that the treatment effect of blinatumomab relative to chemotherapy in this trial is overestimated[17] (i.e., may be more favourable than at the time of the final analysis). The final analysis of Locatelli et al. was planned for January 2023, but the results are not yet published. In the IR/HR cohort of the COG ALL1331 trial, 2 interim analyses were planned and randomization ended early after an interim analysis due to favourable DFS, OS, and MRD, and lesser toxicity in the blinatumomab group, though the efficacy stopping boundary for DFS ($P = 0.004$) was not met. Results were presented for the final analysis. The trial may have been underpowered for EFS in the IR/HR cohort due to cessation of randomization prior to reaching the planned sample size.

Both trials followed pre-specified analysis plans with limited evidence of selective reporting. In the IR/HR cohort of the COG AALL1331 trial, proceeding to transplant was a post-hoc efficacy end point; as such, it is possible that the results presented were among multiple analyses of the data. Additionally, there was no formal statistical approach for subgroup differences in the pre-specified subgroup analyses, which included analyses based on risk category (HR vs IR). The IR subgroup was small and potentially underpowered to detect a significant treatment effect. In both trials, patients were analyzed in their randomized treatment group, regardless of the treatment received post-randomization (intention-to-treat analysis), which is appropriate for informing the effect of assignment to the interventions. In both trials, there was no control for multiple testing. As such, for statistically significant results there is an increased risk that the null hypothesis was erroneously rejected. In the LR cohort of the COG AALL1331 trial, the authors reported “striking differences” in OS and DFS by site of first relapse (BM ± EM vs. IEM) based on post-hoc subgroup analyses with P values adjusted for multiple testing via the Bonferroni method. Results favoured blinatumomab over chemotherapy for OS and DFS in the BM ± EM group, whereas although point estimates favoured blinatumomab over chemotherapy in the IEM group, the results were not statistically significant. These subgroup analyses were considered by the CDA-AMC review team to be of low credibility as the analyses were not pre-planned and there were no tests for treatment-by subgroup interactions. Further, comparing statistical significance in one group versus another is not a valid method for inferring effect modification.[18] In these analyses, the IEM subgroup included 81 patients (compared with 174 in the BM ± EM subgroup); as such, there may not have been adequate power to show a statistically significant difference in the IEM subgroup (i.e., may be reflective of a lack of information rather than a smaller or absent effect). Additionally, clinical experts consulted by the CDA-AMC raised concerns regarding the use of blinatumomab in patients with IEM relapse, noting that there is a lack of evidence to support blinatumomab’s ability to cross the blood-brain barrier, which could limit its effectiveness in treating IEM disease.

In the Locatelli et al. trial, there was no testing for the plausibility of the proportional hazards assumption underlying the survival analyses for EFS and OS. Visual inspection of the Kaplan-Meier (KM) curves for EFS did not suggest any major violations of the assumption; however, for OS the KM curves for blinatumomab and chemotherapy crossed multiple times during the first 6 to 9 months of follow-up, suggesting that hazard ratios are not constant over time. As such, the hazard ratio presented for this end point could be misleading. In the COG AALL1331 trial, the plausibility of the proportional hazards assumption was tested via graphical diagnostics and Schoenfeld residuals; however, the results were not reported. Among the LR cohort, for DFS the KM curves for blinatumomab and chemotherapy crossed multiple times during the first 2 years of follow up before separating. For OS, the curves begin to separate around 1 year and then converge again around 3 years before separating again. Among the IR/HR cohort, the curves for DFS separate early and remain separated throughout follow-up. For OS, the curves separate early but converge and cross a number of times around 0.5 years, before remaining separated for the remainder of follow-up. As such, based on visual

inspection of the KM curves, hazard ratios for DFS and OS in the LR cohort and for OS in the IR/HR cohort do not appear constant and the reported hazard ratios could be misleading.

Incomplete reporting in the publications of both trials hindered a full appraisal of the precision of the effect estimates. For example, in both trials, 95% CIs were not reported for between-group differences in the probabilities of EFS, DFS, and OS at clinically relevant follow-up times. As such, although the point estimates favoured blinatumomab, it cannot be confirmed whether the effect estimates are precise; that is, whether they exclude the potential for little to no difference between blinatumomab and chemotherapy, or effects favouring chemotherapy. For proceeding to HSCT, only a relative between-group difference (OR) was provided in the COG AALL1331 trial, and no measure of between-group differences was provided in the trial by Locatelli et al. As such, the precision of the absolute between-group differences could similarly not be assessed. Formal statistical testing appeared to be lacking for some end points (e.g., OS, MRD, proceeding to HSCT) in the trial by Locatelli et al. precluding strong conclusions about efficacy.

External Validity

The Locatelli et al. study used patient selection criteria based on combined IntReALL and BFM, while the COGAALL1331 trial applied the COG risk criteria. According to the clinical experts, COG guidelines represent a reasonable standard of care, particularly in North American institutions where COG criteria and treatment regimens are predominantly followed. However, the IntReALL/BFM definitions are considered similar enough to the COG risk criteria. While most Canadian institutions adopt the COG definitions, a few centers in Quebec follow the IntReALL/BFM criteria.

In the Locatelli et al. trial, blinatumomab replaced only one course of consolidation chemotherapy, which raises uncertainty about the potential benefits of additional cycles or broader replacement of chemotherapy blocks. Experts noted that for HR patients, the goal is to achieve sustained deep remission to qualify for HSCT, if eligible. The experts posited that the option to use more than one cycle of blinatumomab could potentially increase the chances of achieving this target remission, thereby enhancing the likelihood of successful transplantation.

Most outcomes considered important to the review were reported in the included studies; however, evidence for HRQoL and time to next relapse were not identified. As such, the effect of blinatumomab compared with chemotherapy on these outcomes remains unknown. Evidence of the validity of EFS and DFS as surrogates for OS among pediatric patients with relapsed B-ALL was not identified by the CDA-AMC review team. Experts indicated that emerging immunotherapies in B-ALL have just been introduced, and as such, there may not yet be data to confirm the surrogacy of EFS or DFS for OS. As per the experts, in pediatric relapsed B-ALL, EFS and DFS reflects disease control—if a patient experiences an event, it signals the need to switch to another line of therapy.

The COG AALL1331 trial enrolled patients over 18, who generally have more aggressive disease biology and more comorbidities compared to younger patients.[4] According to the clinical experts, treatment-related toxicity is a greater concern in this population, often leading to dose reductions and treatment delays, which can compromise efficacy. The inclusion of adult patients may limit the generalizability of the results to pediatric populations, as differences in disease biology and treatment tolerance between children and adults could skew the findings. The trial also excluded key patient populations, including individuals with Down syndrome, prior HSCT, and prior blinatumomab exposure. These exclusions introduce further uncertainties, as according to the clinical experts, these groups represent clinically relevant populations often seen in practice.

Discussion

A summary of clinician input on the place in therapy of blinatumomab for pediatric patients with Philadelphia chromosome negative relapsed/refractory B-ALL who are in first relapse, with or without EM disease is available in the Working Papers, in the Place in Therapy section.

Efficacy

The patient group emphasized that pediatric B-ALL imposes significant physical, emotional, and financial burdens on both the child and their family. Managing relapse often involves prolonged immunosuppression, which disrupts daily routines and heightens stress and anxiety. Both patient and clinician groups expressed the need for treatments that prolong time to relapse, improve OS, achieve deep molecular responses, and increase chances of proceeding to HSCT (if eligible), while minimizing SAEs.

In the Locatelli et al. trial, clinical experts agreed that the EFS results suggested a clinically meaningful benefit of blinatumomab over chemotherapy; however, it should be noted that 95% CIs were not reported for between-group differences in the probability of EFS at clinically relevant time points, precluding judgments of the precision of these effect estimates. While the secondary endpoint, OS, showed a trend toward improvement there appeared to be a lack of statistical testing for this end point (P value not reported) and the effect estimate for the hazard ratio included the potential for no difference between blinatumomab and chemotherapy. Nonetheless, the >10% difference in the rate of deaths at data cut-off and the survival probability differences at 12, 24, and 36 months were considered clinically meaningful by experts; however, as per EFS the precision of these estimates could not be judged. It is possible that these could include the potential for little to no difference or for chemotherapy to be favoured. Other endpoints such as MRD remission and the ability to proceed to HSCT appeared to support a benefit for blinatumomab over chemotherapy; however, formal statistical testing appeared lacking for these end points and for proceeding to HSCT, no between-group difference (relative or absolute) was reported, precluding definitive judgments. As the results from Locatelli et al. are from an interim analysis, there is increased risk that potential benefits in all end points are overestimated.

In the COG AALL1331 trial, blinatumomab showed a trend toward improvement in DFS in the IR/HR group; however, the effect did not reach statistical significance. Despite this, experts found the point estimate for the between-group difference in the 24-month DFS probabilities to be clinically meaningful; however, the precision of these estimates could not be judged because 95% CIs were not reported. At a median 2.9 (range: 0 to 5.6) years of follow up, there was a statistically significant improvement in OS; however, the 95% CI for the hazard ratio approached the null, suggesting the potential for little to no difference in OS between groups. The analysis of this end point was not adjusted for multiple testing, so there is an increased risk that the null hypothesis was erroneously rejected. The clinical experts considered the point estimate for the difference in survival probability at 24 months to be clinically relevant; however, the 95% CI for the estimate was not reported, precluding conclusions regarding its precision. MRD remission and the proportion of patients proceeding to HSCT were increased among patients treated with blinatumomab compared with chemotherapy. Absolute between-group differences with 95% CIs were not reported, precluding judgments about the precision of these differences. The analysis of these end points was not adjusted for multiple testing so there is an increased risk that the null hypothesis was erroneously rejected.

Additionally, for the IR/HR group, a pre-specified subgroup analyses based on risk category (HR vs IR) for DFS, OS, MRD and rates of transplant were consistent with the main analyses, except for OS in the IR subgroup, where no difference between groups was observed. This subgroup analysis is limited due to small sample size and lack of a formal statistical approach to test for subgroup differences. Nevertheless, these results suggest uncertainty as to the survival benefit of blinatumomab in IR patients. The clinical experts suggested that blinatumomab might appear less effective in the IR group due to the aggressive nature of high-risk B-ALL, where blinatumomab may have greater relative benefit. In IR patients, who are more sensitive to chemotherapy, blinatumomab's relative advantage may be less pronounced. The experts pointed to the unmet need, in that blinatumomab may improve the clearance of leukemia in patients who have incomplete response to chemotherapy, improve the depth of molecular remission, and may also offer an alternative option to getting patients to the same remission that chemotherapy would with less of the toxicities associated with chemotherapy.

In the low-risk (LR) group of the COG AALL1331 trial, results for DFS and OS were not statistically significant; the estimated hazard ratio was affected by imprecision (wide 95% CI spanning the null). MRD negativity was not reported in the LR cohort of the COG AALL1331 trial. Results of post-hoc subgroup analyses by site of first relapse (BM ± EM vs. IEM) favoured blinatumomab over chemotherapy for OS and DFS in the BM ± EM group, whereas although point estimates favoured blinatumomab over chemotherapy in the IEM group, the results were not statistically significant. However, the CDA-AMC review team deemed the subgroup analyses to be of low credibility as they were not pre-specified, lacked treatment-by-subgroup interaction testing, used an inappropriate method for inferring effect modification, and may have been underpowered to detect meaningful differences, particularly within the IEM subgroup. The clinical experts consulted by the CDA-AMC also raised concerns about blinatumomab's ability to cross the blood-brain barrier, potentially limiting its efficacy in cases of IEM relapse. From a clinical relevance perspective, the lack of significant DFS and OS improvement in the low-risk group introduces uncertainty about the universal applicability of blinatumomab across all risk categories.

The clinician group and clinical expert input highlighted the importance of achieving MRD negativity in facilitating progression to HSCT for IR/HR patients, aligning with the patient group's goals of reducing relapse and improving long-term survival. Although both trials reported that more patients in the blinatumomab groups proceeded to HSCT, these findings were limited by post-hoc analyses

without absolute between-group differences or 95% CIs and lacked adjustment for multiple testing (COG AALL1331), as well as interim results without statistical testing or between-group estimates (Locatelli et al.).

Harms

Across both trials, nearly all patients in both the blinatumomab and chemotherapy groups experienced at least one AE, with rates ranging from 89% to 100%. In COG AALL1331, SAEs were more frequent with blinatumomab, whereas in Locatelli et al., chemotherapy resulted in more SAEs. Grade ≥3 AEs were common but occurred more frequently in the chemotherapy groups in both trials. Withdrawals due to AEs were rare (≤4%), suggesting most patients completed treatment despite these events. Febrile neutropenia and infections, which increase the risk of life-threatening complications, were more frequent in chemotherapy groups. Patient and caregiver input emphasized the need for safe, tolerable treatments that minimize infections and immunosuppression, which disrupt school, activities, and family life. The clinical experts also acknowledged that intensive chemotherapy poses ongoing challenges due to infection risks. Seizures occurred in small numbers with blinatumomab (5-6%) in COG AALL1331 while seizures were not reported in Locatelli et al., and experts emphasized the need for monitoring and managing seizures in patients receiving blinatumomab. In COG AALL1331, 5 deaths due to AEs were reported in the chemotherapy arm of the IR/HR group and 3 deaths in the chemotherapy arm of the LR group while 1 death was reported in the blinatumomab arm of the LR group. The experts acknowledged that the AEs observed were unsurprising and manageable given what is known in patients in this population and that there were no new safety signals.

Other Considerations

Blinatumomab in the First-Line Setting

The clinical experts and the clinician group highlighted that the Children's Oncology Group is conducting a phase III randomized controlled trial to evaluate the efficacy of blinatumomab in combination with chemotherapy for patients aged 1 to 10 years with newly diagnosed, standard-risk B-lymphoblastic leukemia or B-lymphoblastic lymphoma, with or without Down syndrome (NCT03914625), also referred to as COG AALL1731.[19] The clinicians expressed strong support for the use of blinatumomab in the first-line setting based on interim efficacy results from the COGAALL1731 trial. They emphasized that emerging data from this trial strongly supports the inclusion of blinatumomab as part of first-line therapy across most subsets of the pediatric B-ALL population, except for those classified as Standard-Risk Favorable. As this trial did not meet the eligibility criteria for the systematic review, its results were not summarized or appraised herein. As such, the CDA-AMC review team cannot comment on the certainty of evidence or clinical relevance of the results for any end point assessed.

Additionally, Amgen has provided advance notification of its intent to submit blinatumomab (Blincyto) for CDA-AMC review for use in Philadelphia chromosome-negative, CD19-positive B-cell precursor acute lymphoblastic leukemia during the consolidation phase of multiphase chemotherapy, with an anticipated submission date of October 18, 2024.

Conclusion

Patient group advocates and clinicians have expressed the need for treatments in pediatric patients with Ph-negative B-ALL at first relapse that prolongs time to next relapse, improves OS, achieves deep molecular responses, and increases chances of proceeding to HSCT (if eligible), while minimizing SAEs. Evidence from Locatelli et al. and COG AALL1331, two randomized, phase III, open-label, multicenter trials, suggested that blinatumomab may offer clinically meaningful benefits in EFS, DFS, OS, MRD remission, and progression to HSCT compared to standard chemotherapy, particularly in IR/HR patients. The COG AALL1331 trial provided insufficient evidence of benefit for DFS and OS in LR patients, and MRD remission was not reported. There is uncertainty in the findings based on potential risk of bias, incomplete reporting, lack of formal statistical testing, and absence of adjustments for multiple testing. HRQoL outcomes were not reported, and the safety profile of blinatumomab was as expected with no new safety signals observed.

Economic Review

The economic review consisted of a cost comparison for blinatumomab compared with chemotherapy for the treatment of pediatric patients with Ph-negative relapsed or refractory B-ALL.

Based on public list prices, the per-patient cost of blinatumomab is expected to cost $250,376 to $494,053 in LR patients and $166,784 to $333,568 in IR/HR patients over the course of treatment (Table 1). The per patient cost associated with block 3 chemotherapy is $25,094 in LR patients. The per patient cost of block 2 and block 3 is $31,485 in IR/HR patients. Therefore, blinatumomab is expected to cost $225,282 to $468,959 more per patient in LR patients, and $135,299 to $302,083 more per patient in IR/HR patients compared to chemotherapy over the course of treatment. As such, the reimbursement of blinatumomab for the treatment of pediatric patients with Ph-negative relapsed or refractory B-ALL is expected to increase overall drug acquisition costs. Additional items for consideration are provided in the following bullets:

- Based on the clinical review, blinatumomab may offer clinically meaningful benefits in EFS, DFS, OS, MRD remission, and progression to HSCT compared to standard chemotherapy, particularly in IR/HR patients; however, there is insufficient evidence of benefit for DFS and OS in LR patients. The safety profile of blinatumomab was as expected with no new safety signals observed.
- The treatment protocol and dosing were obtained from two key studies, Hogan et al. (2023) and Brown et al. (2021),[7,13] identified by the CDA-AMC clinical review and validated with clinical expert feedback. However, according to the clinical expert input, there may be variations in treatment dosing across different institutions. Clinical experts expected these differences to be minor (i.e. variations in scheduling of dose administration). They are unlikely to have a meaningful impact on overall costs.
- According to the product monograph,[1] hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle of blinatumomab. For all subsequent cycle starts and reinitiations (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. However, clinical expert input noted that patients are typically hospitalized for 48 to 72 hours in clinical practice, generally at the beginning of treatment cycle, if treatment is discontinued or if IV bag is disconnected. The clinical expert feedback also noted that the duration for hospitalization may be 4-6 weeks for HR patients. Because costs and uncertainty with hospital use to administer blinatumomab are not included, this cost-comparison may be underestimating the overall costs associated with blinatumomab treatment as incurred by the healthcare system.
- According to the clinical expert feedback and the product monograph,[1] patients will be treated with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg, prior to the first dose of blinatumomab in the first cycle, prior to a step dose and when restarting an infusion after an interruption of 4 or more hours in the first cycle.
- The clinical expert feedback highlighted that blinatumomab replaces block 3 chemotherapy in the treatment protocol, which is associated with high toxicity. The expert feedback anticipated that the replacement of block 3 chemotherapy with blinatumomab may reduce the cost of hospital and healthcare use due to decreased treatment-related morbidity and mortality as well as future relapse(s) of ALL, which may be partially offset by the cost of hospitalization needed to administer blinatumomab. A cost-effectiveness analysis would be necessary to comprehensively quantify the economic impact of blinatumomab on toxicity-related adverse events and improved patient outcomes.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on October 15, 2024. Two studies conducted in France and Mexico were identified that evaluated the cost-effectiveness of blinatumomab for the treatment of pediatric HR patients with first-relapsed Ph-negative B-ALL. The study by Caillon et al., 2023 concluded that blinatumomab was more effective and more costly than high-risk consolidation chemotherapy from a French healthcare payer and societal perspective.[20] The study by Diaz et al., 2024 similarly found that blinatumomab treatment was associated with a life-year gain and increased costs compared to standard consolidation chemotherapy but did not estimate quality-adjusted life-years.[21] Notably, both studies adopted a cure assumption for patients who remained alive beyond 5 years.
- CDA-AMC has previously reviewed blinatumomab for the treatment of adult patients with Ph-negative relapsed or refractory B-ALL who have had one prior systemic chemotherapy and issued a “do not reimburse” recommendation.[22] However, in adult patients with Ph-negative relapsed or refractory B-ALL who have had two prior lines of systemic chemotherapy, blinatumomab received a positive recommendation with clinical criteria and/or condition.

- CDA-AMC further notes that the pan-Canadian Pharmaceutical Alliance concluded negotiations with a letter of intent for blinatumomab for adult and pediatric patients with ALL.[23,24] As such, blinatumomab has a confidential negotiated price, and is currently funded for adult patients by jurisdictional cancer formularies.[25] The CDA-AMC cost comparison is based on the publicly available price of blinatumomab, which may be different than the confidential price and may influence the results of this cost-comparison.

Conclusion

The reimbursement of blinatumomab for the treatment of pediatric patients with Ph-negative relapsed or refractory B-ALL is expected to increase overall drug acquisition costs. Based on the clinical review conclusions, blinatumomab may provide a clinically meaningful benefit on health outcomes for IR/HR patients; however, the benefit in LR patients remains uncertain. The safety profile of blinatumomab was as expected with no new safety signals observed.

Blinatumomab is associated with increased drug acquisition costs and increased benefit in terms of event-free survival and similar benefits in terms of overall survival compared with chemotherapy. According to clinical expert feedback, the replacement of block 2 and block 3 chemotherapy with blinatumomab is expected to reduce the incidence and severity of treatment-related toxicities, as well as the need for additional future therapies, which may decrease overall costs. Other costs such as costs associated with treatment administration, patient monitoring, management of treatment-related adverse events and treatment of subsequent ALL relapse(s) were not considered in this cost comparison. The administration of blinatumomab requires the use of hospital resources, which are expected to increase treatment administration costs compared with chemotherapy. Given that blinatumomab is associated with increase drug acquisition costs and increased benefit in terms of event-free survival, a cost-effectiveness analysis would be required to assess the impact of blinatumomab on overall costs and quality-adjusted life-years relative to chemotherapy in the indicated population. As this was not available, the cost-effectiveness of blinatumomab relative to chemotherapy for the treatment of pediatric patients with Ph-negative relapsed or refractory B-ALL could not be determined.

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