Blinatumomab

Application for Inclusion of Blinatumomab in the WHO Essential Medicines List for Children

Proposal: children with B-lineage acute lymphoblastic leukemia.

***NOTE**: some data is included in this submission that frames use and impact in adult populations. While the benefit of blinatumomab can stand on its own in the pediatric setting, given the low incidence of ALL and the development program of blinatumomab, at times the extra context of adult use in this submission is warranted.*

Submitted by Resonance

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1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION

This application proposes the inclusion of blinatumomab on the WHO Essential Medicines List for Children (EMLc) **for the treatment of pediatric patients with CD19-positive frontline, relapsed, or refractory B-lineage acute lymphoblastic leukemia (B-ALL).**

B-ALL is the most common curable cancer in children and is one of the six index cancers of the WHO Global Initiative for Children with Cancer (GICC). It affects about 100,000 children each year, of whom only 15% live in high-income countries (HICs). Cure rates after frontline therapy in HICs exceed 90% with standard therapy plus blinatumomab. However, they are much lower in low- and middle-income countries (LMICs), where lack of access to essential medications, barriers to diagnosis and risk stratification, suboptimal supportive care, and inadequate logistical support can lead to excess relapse, toxic death, and abandonment of therapy.

In this application, the efficacy, safety, comparative efficacy, and cost-effectiveness of blinatumomab in first-line, second-line, and third-line therapy are documented. The goal is to include blinatumomab in the EMLc as the next step to achieving universal access for children with B-ALL, which is estimated to cure an additional 20% of the disease burden in LMICs.

In HICs, 87% of children with ALL are cured with frontline therapy and another 7% with salvage therapy, while the remaining 6% die from leukemia or toxicities of treatment (**Table 1**).

However, 85% of children with ALL live in LMICs, where without blinatumomab, less than half of children are cured with frontline therapy and a very small percentage of those who fail frontline therapy are cured with salvage therapy. Access to blinatumomab would improves the cure rate for frontline patients by an estimated 20%, and the rate of successful salvage therapy of those who relapse by about 30%, which would save 20,500 children each year (**Table 1**).

Table 1. Estimated numbers of children with acute lymphoblastic leukemia (ALL) cured after frontline or second-line therapy in high-income versus low- and middle-income countries with and without access to blinatumomab

Patient outcomes	High-income countries	Low- and middle-income countries assuming no blinatumomab	Low- and middle-income countries assuming universal access to blinatumomab
Children with ALL	15,000	85,000	85,000
Cured after frontline therapy	87% (13,050)	47% (40,000)	67% (67,000)
Cured after second-line therapy	7% (1,050)	5% (4,500)	9% (8,000)
Death from leukemia or toxicity	**6% (900)**	**48% (40,500)**	**24% (20,000)**

Finally, blinatumomab is highly cost-effective for children with ALL in the settings in which it is reimbursed. Even in the relapse setting in a middle-income country, the incremental cost-effectiveness ratio is less than US $3900 per year with public prices. Addition to the EML will allow the opportunity for public or donor procurement for LMICs and the possibility of special access programs that could support safe and effective implementation of this life-saving medicine.

INTRODUCTION

B-ALL is the most common of the six index cancers of the WHO GICC (**Figure 1**). Cure rates for children with B-ALL after frontline therapy in high-income countries (HIC) exceed 80% with standard therapy and 90% with standard therapy plus blinatumomab. However, they are much lower in low- and middle-income countries (LMICs), where lack of access to essential medications, barriers to diagnosis and risk stratification, suboptimal supportive care, and inadequate logistical support can lead to excess relapse, toxic death, and abandonment of therapy.

Access to new, less toxic, treatments for B-ALL are needed to reduce relapse without increasing toxic death. Access requires a strong evidence base documenting efficacy and safety, which is described in this application. Access also requires feasible, cost-effective, sustainable, and uninterrupted provision of new (and established) therapies in LMICs, which will be facilitated by the Global Platform for Access to Childhood Cancer Medicines, a partnership with St. Jude Children's Research Hospital, WHO, UNICEF and the PAHO Strategic Fund (https://www.who.int/news/item/13-12-2021-who-and-st.-jude-to-dramatically-increase-global-access-to-childhood-cancer-medicines).

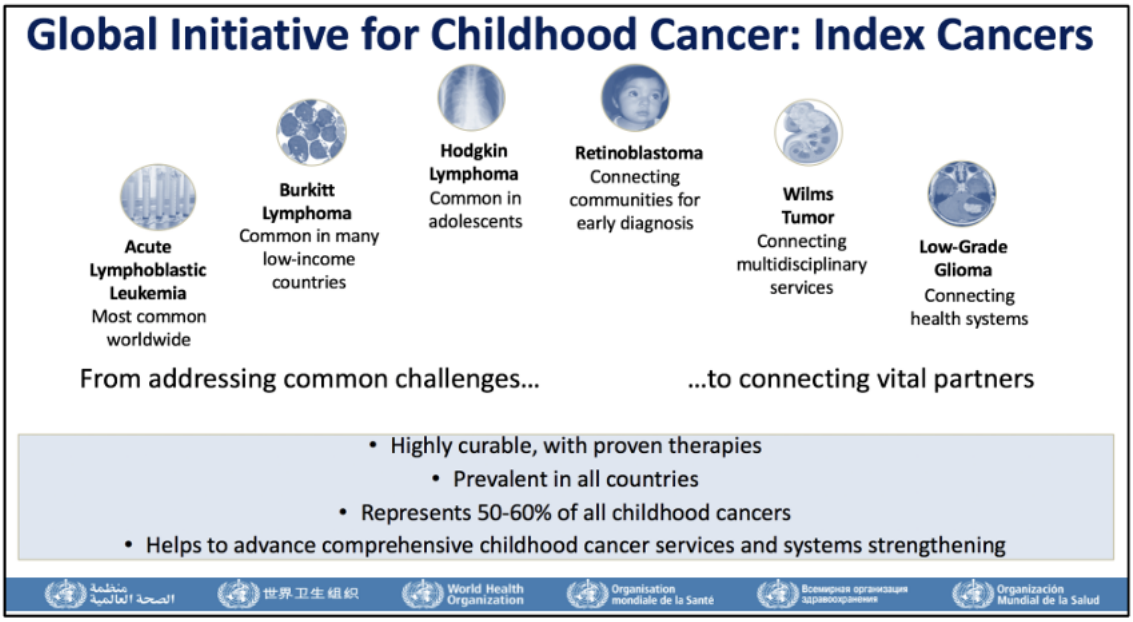


Figure 1: Six index childhood cancers (WHO, Global Initiative for Childhood Cancer)

Blinatumomab is a bispecific T-cell engager (BiTE) immunotherapy that bridges CD19-positive B-lymphoblasts and CD3-positive T cells to direct cytotoxic T-cell activity against B-ALL cells.[1,2] The therapeutic efficacy of blinatumomab has been demonstrated in pediatric populations in the frontline setting and where traditional chemotherapy regimens have failed, providing a potent alternative with the potential to significantly improve survival rates. The high-quality evidence supporting its efficacy and safety, combined with the unmet clinical need for effective frontline and salvage therapy for pediatric B-ALL, especially in LMICs, justifies the addition of blinatumomab to the EMLc.

Cure rates in frontline therapy have been improved substantially by blinatumomab.[3-10] It is now used as part of standard care combined with chemotherapy protocols for both lower-risk and higher-risk newly-diagnosed children with B-ALL, recommended by international guidelines (e.g., NCCN Guidelines Version 1.2025 Pediatric Acute Lymphoblastic Leukemia), and covered by payers (in high-income countries). Even the ARIA guidelines (www.ARIAguide.org), which are specifically designed for use in LMICs, will include blinatumomab in its recommendations, in anticipation of increasing access to this life-saving therapy in resource-limited settings.

For patients who relapse or have refractory disease, blinatumomab has proven effective to achieve a second remission, to deepen that remission until there is no detectable measurable residual disease, and provide a bridge to consolidation therapies for relapsed/refractory disease, including allogeneic hematopoietic stem cell transplantation (HSCT).[3,6,11-24] Blinatumomab has also been used in regimens with reduced doses of chemotherapy (or chemotherapy-free regimens) for older patients who may be unable to tolerate standard regimens for B-ALL.[25-27]

In pediatric patients with relapsed/refractory B-ALL, a condition associated with extremely poor outcomes, blinatumomab has demonstrated efficacy in inducing remission, with significant rates of complete remission (CR) and measurable residual disease (MRD)-negative status, a strong predictor of long-term survival.[28] It also shows a manageable safety profile, especially when considering the toxicities associated with alternative treatments, such as intensified salvage chemotherapy or HSCT.[29-34]

Given that B-ALL is the most common pediatric malignancy worldwide, and relapsed/refractory cases are fatal without appropriate treatment, blinatumomab offers an important therapeutic option in the frontline setting to prevent relapse, and for children who fail standard therapies and require treatment for relapsed or refractory disease.

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

The submitter has engaged with the WHO NCD (Cancer) Section in consideration of preparation of the current submission, and also sought the advice of the WHO EML Section with respect to content that may be useful in support of the application. No other WHO technical departments were consulted. Letters of support are anticipated to be sent directly to the WHO EML Section.

3. OTHER ORGANIZATIONS CONSULTED AND SUPPORTING THE SUBMISSION

Members of global oncology organizations, professional societies, non-governmental charitable organizations, and pediatric cancer centers were consulted with respect to the content and their

support for the submission. Letters of support are anticipated to be sent directly to the WHO EML Section.

Global oncology organizations

- Access to Oncology Medicines Coalition (ATOM) of the Union for International Cancer Control (UICC)
- City Cancer Challenge Foundation (C/Can)

Professional societies

- International Pediatric Oncology Society (SIOP), Global
- Sociedad Latinoamericano de Oncologia Pediátrica (SLAOP), Latin America
- Asociación de Hemato-Oncologia Pediátrica de Centroamérica (AHOPCA), Central America
- Group Franco-Africain d'Oncologie Pédiatrique (GFAOP), Francophone Africa
- Indian Pediatric Hematology-Oncology Group (INPHOG), India
- Programa Infantil Nacional de Drogas Antineoplásicas (PINDA), Chile

Charitable foundations

- City of Smile, Armenia
- Ayúdame a Vivir, El Salvador
- CanKids KidsCan, India

Pediatric cancer centers

- St. Jude Children's Research Hospital, USA
- Hospital for Sick Children, USA
- Yeolyan Cancer Center, Armenia
- TMC Kolkata, India
- TMH Mumbai, India
- Aga Khan, Pakistan
- BP Koirala Memorial Cancer Hospital, Nepal
- Kanti Children's Hospital, Nepal
- Hospital Benjamin Bloom, El Salvador

4. KEY INFORMATION FOR THE PROPOSED MEDICINES

International non-proprietary name (INN) of the proposed medicine

- Blinatumomab

Anatomical therapeutic chemical (ATC) code of the proposed medicines

- **L01FX07** (Other monoclonal antibodies and antibody drug conjugates), as updated in March, 2021 (See new classification list here) and found at this Link.
- Blinatumomab is classified within the ATC system under the category of monoclonal antibodies and antibody drug conjugates.
- While a range of monoclonal antibodies are included L01FX code, these are not interchangeable with blinatumomab.

Indications

Blinatumomab is indicated for precursor B-lymphoblastic neoplasms. The relevant ICD-11 code is **2A70** – Precursor B-lymphoblastic neoplasms. Link to relevant ICD-11 listing here.

5. LISTING AT AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS/THERAPEUTIC GROUP

The proposal relates to an individual medicine – **blinatumomab**.

Blinatumomab is not interchangeable with any other medicine and has no therapeutic alternatives. The ATC code L01FX includes a range of monoclonal antibodies, but these medicines are for specific and separate indications, are targeted toward different antigens, and do not have similar pharmacological class effects. Currently, blinatumomab does not have biosimilars.

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE (NEW MEDICINES)

B-lineage acute lymphoblastic leukemia is the most common childhood cancer and is highly curable when patients have access to modern therapies and supportive care. It affects about 100,000 children per year, of whom 85,000 live in low- and middle-income countries. Background about leukemia in general and ALL in particular is provided below.

Leukemia is a progressive malignant disease in which the bone marrow produces increased numbers of immature or abnormal white blood cells (lymphoblasts). Lymphoblasts can infiltrate the bone marrow, spleen, liver, blood, and other organs, impair function and lead to infection, pancytopenia, fatigue, bruising, bleeding, enlarged lymph nodes, and fever.[35-37] Other symptoms may result from central nervous system (CNS) involvement, including headache, weakness, seizures, and vomiting; though for some pediatric patients with ALL, pain in the joints or extremities may be the only presenting symptom.[38] Leukemia is classified into acute or chronic types and acute leukemias include ALL (malignant lymphoblasts) and acute myeloid leukemia (AML, malignant myeloblasts).[39,40] Acute leukemias are characterized by a sudden onset and rapid progression. Without treatment, patients with acute leukemias die within months. Diagnosis of ALL requires examination of lymphoblasts in bone marrow or peripheral blood (if hyperleukocytosis is present), and almost all patients are admitted to the hospital for the diagnostic evaluation and to begin therapy.[38]

ALL is the most common pediatric malignancy representing three-quarters of all childhood leukemias and a fourth of all childhood cancer.[41-44] While ALL can affect adults and children, approximately half of all diagnosed cases are pediatric.[42-45] Pediatric ALL is classified by the type (B-cell or T-cell) and maturity of lymphocytes from which the leukemic cells are derived. Most pediatric ALL cases are B-cell precursor ALL (BCP-ALL, **Table 1**).[46-53]

Table 2. Acute Lymphoblastic Leukemia Subtypes

Precursor cell type[46,54-57]	**Approximate proportion**
B-lineage	85%
T-lineage	13%
Mixed lineage and others	2%
Cytogenetics in children relevant for use of tyrosine kinase inhibitors[42,46,58,59]	
Philadelphia chromosome positive	4%
Philadelphia chromosome negative	96%

Pediatric BCP-ALL can be further classified by cytogenetic subtype, including by presence of the Philadelphia chromosome translocation between chromosomes 9 and 22, which results in a BCR-ABL fusion gene.[60] Whilst the presence of the Philadelphia chromosome (referred to as Ph+) represents the most common genetic abnormality in ALL overall, it is relatively uncommon in pediatric patients. Only 3% to 5% of pediatric patients with BCP-ALL have Ph+ disease.[42,46,60-62]

Pediatric BCP-ALL can also be classified according to whether patients have relapsed disease or whether their disease is refractory to treatment. Relapsed disease refers to disease that returns after a period of hematologic remission (occurring in approximately 15% of children who achieve remission with frontline treatment), and refractory disease refers to disease in which a hematologic remission is not achieved (occurring in approximately 1% to 2% of patients who receive frontline treatment).[63-65]

The distribution of ALL incidence is bimodal, with a peak in early childhood (around 5 years of age) and a gradual increase at approximately 50 years of age.[66,67] The median age at diagnosis for ALL is 15 years, with 55.4% of patients diagnosed at younger than 20 years of age.[42] The incidence of ALL among children aged 1 to 4 years is approximately twice as high as the incidence among children aged 5 to 9 years, which is in turn approximately twice as high as the incidence among children and young adults aged 15 to 19 years.[44,65]

In high-income countries, 98% of children with ALL achieve a CR and 85% are cured following frontline treatment.[63,64,68] However, of those patients who relapse, approximately 50% ultimately die as a result of the disease.[63,64,69]

Therefore, relapsed/refractory (R/R) ALL remains one of the most frequent causes of cancer-related mortality in children.[70] For each pediatric ALL death, the number of years of life lost due to the disease is substantial; in most countries, patients with pediatric ALL who do not survive the disease die on average 70 to 75 years prematurely.[44]

Survival for pediatric patients with ALL depends on a range of prognostic factors that confer a poor prognosis: age at diagnosis (age < 1 year or ≥ 10 years), immunophenotype (T-cell ALL),

cytogenetics (e.g., presence of mixed-lineage leukemia [MLL] gene rearrangements), higher initial white blood cell count (≥ 50,000 mm3), and response to treatment (e.g., refractory disease or presence of measurable residual disease [MRD] following treatment).[71,72] The prognosis for pediatric patients with relapsed ALL largely depends on time to relapse (shorter time to relapse associated with worse prognosis), site/extent of relapse (bone marrow relapse associated with worse prognosis), immunophenotype, cytogenetics, and presence of MRD following salvage treatment.[71,73,74] Prognosis also depends on access to new therapies, including blinatumomab.[62,67,70,75,76] The prognosis for pediatric patients with ALL in LMICs is exceptionally poor.[77-86]

7. TREATMENT DETAILS

Indication

Blinatumomab has regulatory approval in many high-income countries and some middle-income countries (see Section 11). **For the purposes of this submission, utilisation of the current FDA-approved indications is proposed**. The regulatory approvals for both FDA and EMA are included below.

UNITED STATES

- Blinatumomab is indicated in the United States for the **treatment of patients one month or older with**:
  - CD19-positive B-cell precursor acute lymphoblastic leukemia in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
  - Relapsed or refractory CD19-positive B-cell precursor ALL
  - CD19-positive Philadelphia chromosome-negative B-cell precursor ALL in the consolidation phase of multiphase chemotherapy
- USA Package Insert available here: www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf).

Late-breaking data has abruptly changed the standard of care for children with newly-diagnosed ALL

Recent data from the Children's Oncology Group (COG) study AALL1731 showed a significant benefit when blinatumomab is used in frontline therapy, so much so that the study closed early after interim analysis and all patients in the control arm were offered blinatumomab. A parallel randomized trial was also closed early and all patients offered blinatumomab. These data will be published in December 2024, but have already been distributed to governments, payers, and clinicians to alert them that the standard of care for frontline therapy for children with ALL is chemotherapy plus blinatumomab.

EUROPE

- Blinatumomab is approved by the EMA as monotherapy for the following therapeutic indications:
  - Treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome-positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options
  - Treatment of adults with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
  - Treatment of **paediatric patients** aged 1 year or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation
  - Treatment of **paediatric patients** aged 1 year or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy
- EMA Summary of Product Characteristics available here: https://www.ema.europa.eu/en/documents/product-information/blincyto-epar-product-information_en.pdf

Please note that the request for EML consideration does not include the full regulatory approval label – that is, including adults - but is proposed for addition for pediatric use only at this time.

Dosage form and strengths, route of administration, dosage, and duration of therapy

- **Dosage forms and strengths**: Blinatumomab is supplied as a powder for concentrate for solution for infusion. Each vial contains 35 mcg of available blinatumomab. The final solution is administered through continuous intravenous infusion. There are two dosage forms for blinatumomab, depending on the regulatory environment for the registered country. Each vial contains the same amount of medicine that can be withdrawn (35 mcg), with 3.5 mcg remaining as a residual volume in the vial. Regardless of the vial format, 35 mcg is available for use.
  - 38.5 mcg/vial is the most common regulatory approval
  - 35 mcg/vial is the alternative regulatory approval in a minority of countries.
- **Route of administration**: Blinatumomab is administered as a continuous intravenous infusion (CIVI) over a period of 28 days per cycle. It must be delivered via central venous access due to the potential for local irritation and because peripheral intravenous catheters are not suitable for the 28-day prolonged infusion schedule.
- **Recommended dosage**:

- **For adults and children weighing ≥45 kg**: The recommended dose is 9 mcg/day from day 1 to day 7 in cycle 1, and 28 mcg/day from day 8 to day 28. In cycle 2 and subsequent cycles, the dose is 28 mcg/day continuously for 28 days.
- **For children weighing <45 kg**: The dose is 5 mcg/m²/day from day 1 to day 7, followed by 15 mcg/m²/day (maximum dose 28 mcg/day) from day 8 to day 28 in cycle 1. In subsequent cycles, the dose is 15 mcg/m²/day continuously for 28 days.
- If infusion interruptions occur once the higher-dose infusion schedule is achieved, treatment should be resumed at full dose, without another 7-day period at the lower dose.

- **Duration of therapy**: Blinatumomab is typically administered in up to five treatment cycles, with each cycle consisting of a 28-day continuous infusion followed by a 14-day treatment-free interval. The duration of therapy can vary based on the patient's response and tolerability, with the potential for extended treatment if remission is achieved but MRD remains detectable. The duration of therapy also depends on other components of the treatment regimen, including multi-agent chemotherapy in the case of frontline patients and the potential for consolidation with allogeneic stem cell transplantation in relapsed or refractory patients.

Public Health Relevance

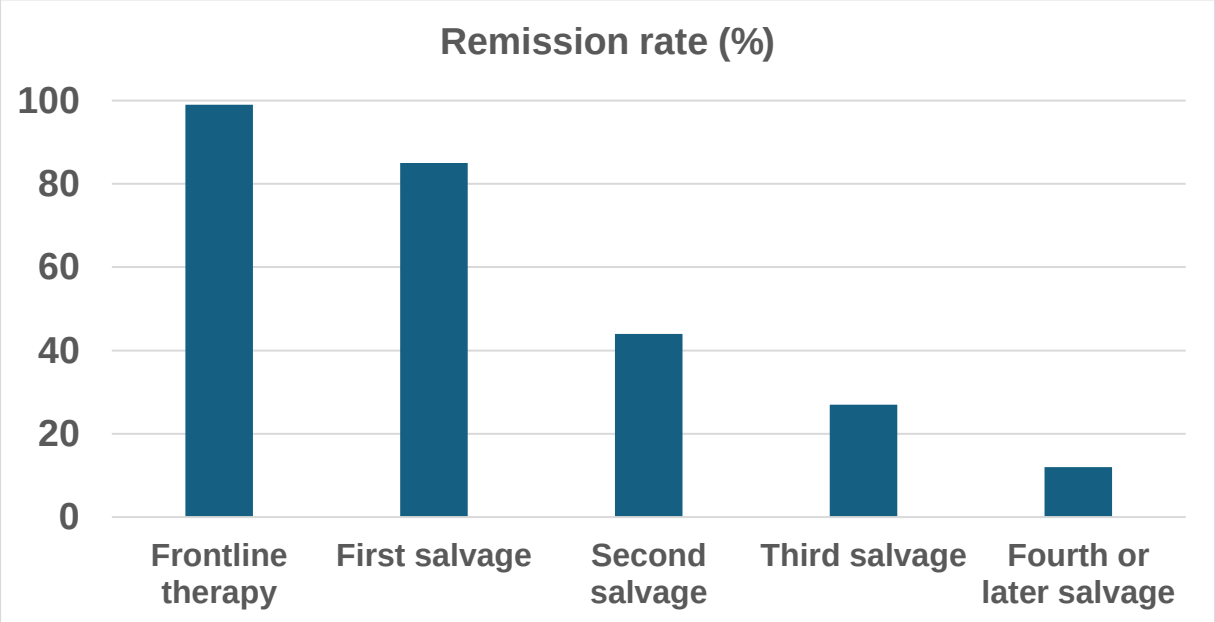


Figure 2. Remission rates in pediatric acute lymphoblastic leukemia by line of therapy[69]

Before the approval of blinatumomab there had been no meaningful progress in the treatment of pediatric R/R BCP-ALL for decades, and no targeted treatments were licensed specifically for the disease. A series of clinical trials documented the efficacy of blinatumomab in R/R patients, then high-risk frontline patients with measurable residual disease, then other groups of frontline

patients, including infants, children, adolescents, young adults, and older adults. Not surprisingly, the benefits were greatest when blinatumomab was used as part of frontline therapy or first salvage after a single relapse (**Figure 2**).[69] These benefits occurred despite the fact that ALL regimens typically include 10-12 chemotherapy agents administered in combinations over 2.5 years, such that addition of a single additional agent (blinatumomab) may not have been expected to have a large impact on overall results. Conventional frontline treatment for pediatric patients diagnosed with ALL involves systemic, multidrug chemotherapy regimens (used more intensively for high-risk first relapse) comprising different cytotoxic agents given in distinct phases.[46] These phases include:

- Induction (commonly used agents include vincristine, corticosteroids, and asparaginase, with most regimens adding an anthracycline, usually doxorubicin or daunorubicin)
- Consolidation/intensification (commonly used agents include mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide, and cytarabine)
- Maintenance (typically low intensity therapy with methotrexate and mercaptopurine)

Patients with involvement of the CNS typically also receive intrathecal administration of chemotherapy or CNS-directed systemic chemotherapy, with or without cranial radiation.[46]

Global epidemiology:

B-ALL affects about 100,000 children annually, including about 15,000 in HICs and 85,000 in LMICs. Reported incidence is somewhat lower in LMICs, where lack of diagnosis is an important cause of treatment failure.[87] Minor differences in incidence are dwarfed by massive differences in outcomes, which are often significantly worse in LMICs due to lack of access to effective treatment regimens, misdiagnosis, inadequate risk stratification, excess toxic death, and abandonment of therapy (**Figure 3**).[78,79,88-93] Relapsed/refractory cases represent a major challenge, especially in settings where access to HSCT is limited or unavailable.

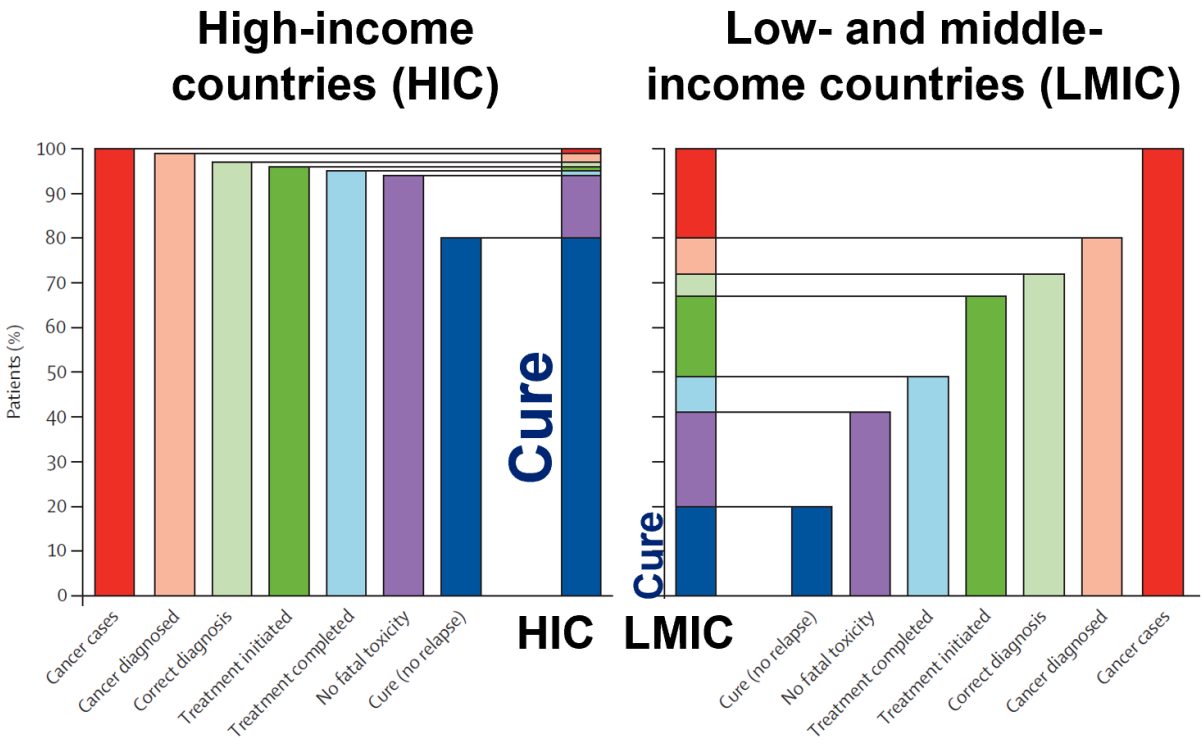


Figure 3. Causes of treatment failure for children with B-ALL in low- and middle-income countries (LMIC) compared with those in high-income countries (HIC)[87]

Disease burden:

- **Frontline ALL therapy (in first remission)**

  Pediatric ALL is the most common childhood cancer, accounting for approximately 25% of all pediatric cancers, or about 100,000 new cases per year worldwide. In high-income countries, 80-90% of children with B-ALL are cured with frontline therapy that includes multiple blocks of treatment delivered over 2.5 years: remission induction, consolidation, delayed intensification, and maintenance. Recent data has confirmed that blinatumomab improves outcomes for almost all children with newly diagnosed B-ALL, including infants, standard-risk patients, and patients whose MRD is positive at the end of induction. These results make it all the more important to accelerate access to blinatumomab for children in LMICs.

  In LMICs, delivery of this intense and prolonged therapy can be associated with gaps in access to quality-assured, uninterrupted chemotherapy, which is associated with excess relapse. The WHO Global Platform for Access to Childhood Cancer Medicines is addressing this critical need and inclusion of blinatumomab will improve event-free survival with frontline therapy by an estimated 15%, and will be especially important for higher risk subgroups like infants and patients with high-risk genetic features, for whom further escalation of the intensity of standard chemotherapy is not possible because it leads to unacceptable toxicity (in both HIC and LMICs).

- **Relapsed/refractory B-ALL therapy**

  Among children with B-ALL, relapse occurs in 10-20% of cases in HIC despite initial treatment with intensive chemotherapy and in 20-50% of cases in LMICs. Because most children live in LMICs, the global burden of relapsed or refractory B-ALL is approximately 30,000 children per year (of the 100,000 who develop ALL each year).

  For relapsed or refractory patients, particularly those who do not achieve second remission with conventional salvage chemotherapy, the prognosis is poor, with long-term survival rates typically below 20%. This challenge is even greater in resource-limited settings where access to advanced treatments like hematopoietic stem cell transplantation (HSCT) or novel immunotherapies is often restricted. With the addition of blinatumomab, cure rates after relapse of B-ALL have increased to 50% or higher because of several benefits. First, blinatumomab monotherapy for relapsed disease is associated with high rates of complete response and undetectable MRD, which positions patients to have the best prognosis after HSCT. Furthermore, in patients who do not qualify for HSCT because of comorbidities or lack of a suitable donor, blinatumomab therapy followed by chemotherapy consolidation and maintenance can lead to lasting remissions. When one considers LMICs, it is estimated that 30% of patients (30,000 per year) and only 20% of them (6,000 per year) are cured after salvage therapy, which means that 24,000 children die of B-ALL each year (Figure 3). With the addition of blinatumomab in the frontline setting, relapse is expected to decrease to 15% (15,000 children per year) and the salvage rate of those who do relapse to increase to 50% (7,500 children per year). Thus, universal access to blinatumomab in the frontline and relapse settings should reduce death from B-ALL by two thirds (from 24,000 children per year to 7,500, **Figure 3**). WHO As the Global Platform for Access to Childhood Cancer Medicines increases access to an uninterrupted, quality-assured supply of other key medicines for B-ALL, including mercaptopurine, asparaginase, and methotrexate, death from B-ALL should decrease even more.

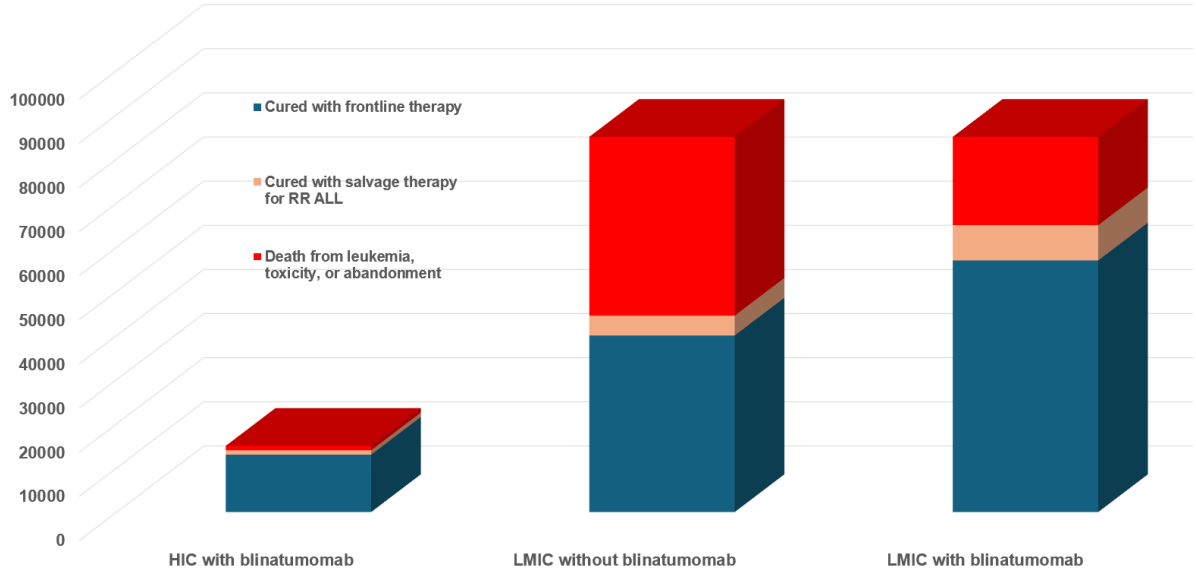


Figure 4. Rates of cure with frontline therapy, cure with salvage therapy, and death from leukemia for children with B-lineage acute lymphoblastic leukemia in high-income countries versus low- and middle-income countries without and with blinatumomab

HIC, high-income countries; LMIC, low- and middle-income countries; RR, relapsed or refractory; ALL, acute lymphoblastic leukemia

Figure 4 illustrates the fact that 87% of children with ALL in HIC are cured with frontline therapy and another 7% with salvage therapy (a little over half of the 13% who are not cured with frontline therapy, shown in orange). By contrast, in LMIC without blinatumomab, less than half of children are cured with frontline therapy and a very small percentage of those who fail frontline therapy can be cured with salvage therapy. Addition of blinatumomab improves the cure rate for frontline patients by an estimated 20% (blue in **Figure 4**), but also improves the rate of successful salvage therapy of those who relapse (orange in **Figure 4**). The figure also highlights the fact that more than 85% of children with ALL live in LMIC, so the need for improved care and outcomes in LMIC is that much more poignant.

Unmet needs in pediatric oncology: a matter of equity

- **Frontline B-lineage ALL therapy**

  In LMICs, 20-50% of children with ALL relapse. This wide range in the incidence of relapse results from large differences in access to correct diagnosis, risk stratification, quality-assured uninterrupted chemotherapy, gaps in adherence, logistical barriers to receive timely treatment, and other obstacles that differ by country, cancer center, and socioeconomic situation of the patient. Access to blinatumomab will not solve all these problems. However, it serves as a key component of the multi-pronged support that children with B-ALL need to achieve cure and can be administered safely in LMICs.[94,95]

- **Relapsed/refractory B-ALL therapy**

  Relapsed/refractory B-ALL in children is a catastrophic condition. Children who fail first-line therapy face limited treatment options, and many succumb to their disease if not provided with an effective salvage regimen. Conventional therapies are associated with high relapse rates, toxicities, and minimal long-term survival benefits. Blinatumomab provides an alternative that targets specific cancer antigens, reducing the burden of nonspecific toxicities and offering a higher likelihood of achieving remission. Currently, more than half of children with relapsed B-ALL in HICs can be cured with a combination of blinatumomab plus consolidation therapies.[16,18,96]

8. REVIEW OF EVIDENCE FOR BENEFITS AND HARMS

Evidence of Efficacy and Safety

The clinical development of blinatumomab for B-ALL has been supported by a series of rigorous clinical trials for each indication, demonstrating its efficacy and safety in children with frontline B-ALL and relapsed/refractory disease (Appendix 1). As the studies have been completed, blinatumomab use, its approved indications, and standards of care in high-income countries have moved progressively from multiply relapsed/refractory adults and children to first relapse in adults and children, to frontline therapy in adults and children with MRD at the end of induction, and recently to frontline therapy for all adults and children.

Blinatumomab's role in frontline, second-line, and refractory ALL has now been established. Remaining questions will focus on the number of cycles, safely removing more toxic components of therapy while preserving high rates of event-free survival, sequencing and combinations with other therapies. Ongoing chemotherapy-free protocols have shown extremely promising results in adults and will be suitable for clinical trials for children in upcoming years. However, with frontline use of 1 to 5 cycles of blinatumomab, cure rates range from 90% to 98% for most subgroups of pediatric ALL, so major changes in therapy must be undertaken with extreme caution. Most importantly, providing universal access to these high cure rates to all children, regardless of where they are treated, warrants extreme focus.

Meta-Analysis: Comparative Efficacy and Safety

Meta-analyses of clinical trials involving blinatumomab compared to conventional salvage chemotherapy demonstrated the superiority of blinatumomab in achieving CR, prolonging overall survival (OS), and inducing MRD negativity.[33,34,97,98] Blinatumomab's targeted mechanism of action results in fewer long-term toxicities and a more favorable safety profile relative to chemotherapy, which is associated with significant risks of myelosuppression, infection, and secondary malignancies.[33,97]

Summary of Comparative Effectiveness

Frontline B-ALL patients

The best outcome for people with ALL is to be cured with frontline therapy. Blinatumomab improved EFS and OS by 15% to 30% in patients with MRD-positive bone marrow at the end of induction and in those who achieve an MRD-negative remission and by similar amounts in those with relapsed disease.[6,11,12,23,27,29,99] For example, adults aged 30 to 70 years who had achieved MRD-negative ALL were randomized to receive chemotherapy with or without blinatumomab. The study closed early due to the superior outcomes in the patients who received blinatumomab. Their overall survival rate at 3 years was 85%, compared with 68% in the chemotherapy arm (p=0.002), and additional events occurred after 36 months in the chemotherapy group but not among patients who received blinatumomab, widening the survival difference even more (**Figure 5**).[23] Results like these in adults have been replicated in children. The pediatric study COG AALL1731 randomized children with standard-risk B-ALL to receive 2 cycles of blinatumomab in addition to standard

chemotherapy. The study closed early when interim analysis showed superior results with blinatumomab (data under embargo but will be publicly available December 2024).

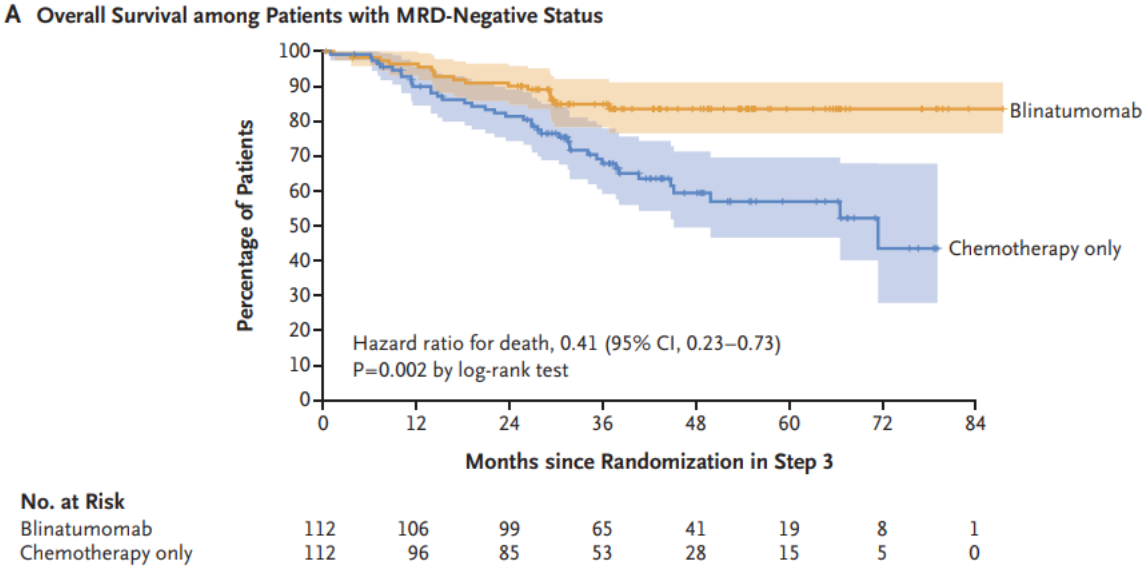


Figure 5. Overall survival of adults with MRD-negative ALL treated with blinatumomab plus chemotherapy versus chemotherapy.[23]

Toxicities were similar in both treatment arms (**Figure 6**), with one death from toxicity in each arm (1%) and expected rates of cytopenias, febrile neutropenia, and sepsis.

Event	Blinatumomab + Chemotherapy (N = 112)			Chemotherapy Only (N = 112)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
	percentage of patients					
Anemia	20	1	0	35	2	0
Leukopenia	4	27	0	2	52	0
Neutropenia	3	55	0	1	86	0
Lymphopenia	3	8	0	6	17	0
Thrombocytopenia	9	40	0	10	59	0
Febrile neutropenia	16	1	0	21	2	0
Sepsis	0	4	1	0	6	1
Hyperglycemia	3	1	0	6	2	0
Fatigue	3	0	0	4	0	0
ALT increased	3	0	0	5	1	0
AST increased	1	0	0	1	2	0
Hypertriglyceridemia	0	3	0	1	3	0
Nausea	3	0	0	1	0	0
Vomiting	2	0	0	3	0	0
Headache	3	0	0	5	0	0
Syncope	3	0	0	3	0	0
Other infection	2	1	0	2	1	0
Catheter-related infection	1	0	0	3	1	0
Upper respiratory tract infection	1	0	0	3	0	0

* Grade 3 to 5 adverse events that were reported in at least 3% of the patients in either group are listed. The worst grade of event was summarized by consolidating the reports of a given type of adverse event for a patient over all cycles during consolidation therapy. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

Figure 6. Toxicities in the two randomized arms[23]

At the other end of the age spectrum, children younger than 1 year of age were treated with blinatumomab and chemotherapy identical to the previously-used infant ALL protocol (the Interfant-06 multi-country trial), which provided historical controls.[100] Infants treated with blinatumomab had a 2-year DFS of 82%, compared with 49% of controls and 2-year OS of 93% versus 66% ($p<0.01$, Figure 7).

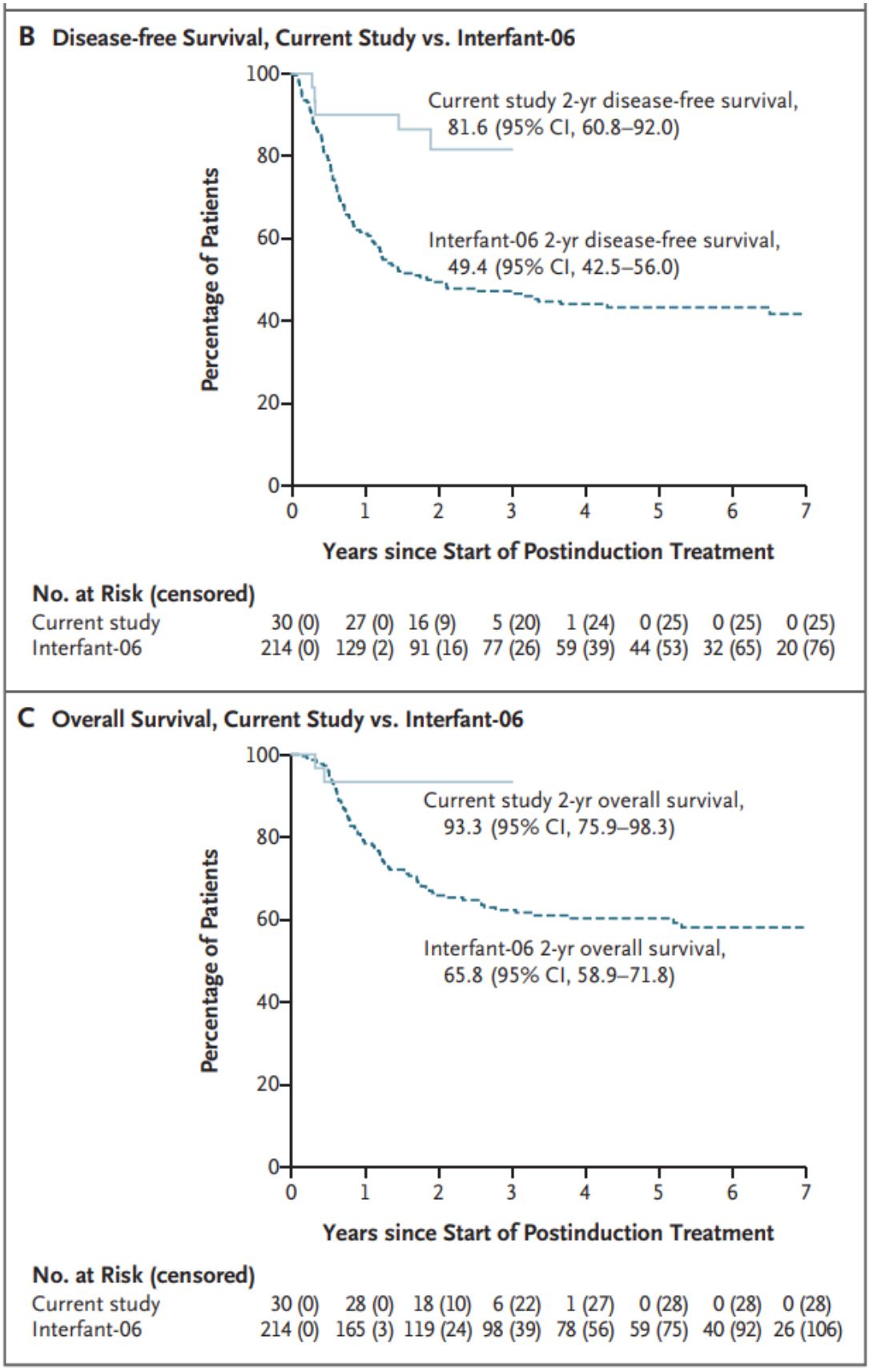


Figure 7. Survival of infants treated with chemotherapy plus blinatumomab compared with matched historical control patients treated with chemotherapy alone.[100]

Relapsed/Refractory B-ALL patients

Blinatumomab offers significant advantages over conventional chemotherapy for relapsed/refractory B-ALL in pediatric patients.[97,101-106] For example, in the Children's Oncology Group randomized trial of children with ALL in first bone marrow relapse (without extramedullary relapse), DFS at 4 years improved from 54% to 73% (p=0.02) and OS at 4 years from 85% to 97% (p=0.02, Figure 7).[107] Note that DFS and EFS may be better measures of blinatumomab efficacy since patients who fail chemotherapy would be expected to cross over and receive a blinatumomab-containing regimen, which may lead to successful salvage therapy in the subsequent line of therapy.

- **Complete remission (CR) rates**: Blinatumomab consistently achieves CR rates of 40-45%, significantly higher than those seen with conventional salvage chemotherapy, where CR rates typically range between 20-30%.
- **MRD negativity**: Achieving MRD negativity is a critical prognostic factor for long-term survival in pediatric leukemia. Blinatumomab has demonstrated MRD negativity in 52-76% of pediatric patients, compared to less than 30% with conventional chemotherapy.
- **Long-term outcomes**: Long-term survival outcomes are promising with blinatumomab, especially in patients achieving MRD-negative remissions. This contrasts sharply with the poor long-term prognosis associated with conventional therapies in children with relapsed/refractory disease.

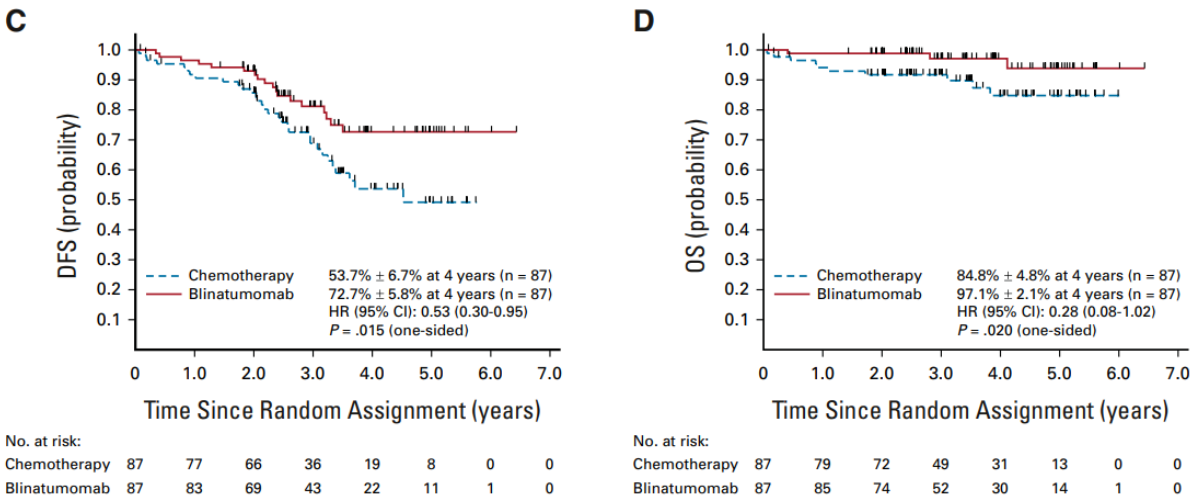


Figure 7. Disease-free survival and overall survival for children with first relapse of acute lymphoblastic leukemia randomized to receive blinatumomab versus chemotherapy.[107]

A recent systematic review and meta-analysis of blinatumomab use in relapsed/refractory B-ALL in children documented its benefits for response, disease-free survival, and overall survival across multiple studies (Figures 12, 13, and 14).[108]

Summary of Comparative Safety

The safety profile of blinatumomab is more favorable compared to conventional chemotherapy.[97,102-104] Key points include:

- **Cytokine release syndrome (CRS)**: While CRS is a known risk, it is typically mild to moderate and can be managed effectively with corticosteroids or tocilizumab (which is now widely available after its utility was documented during the Covid19 pandemic) and temporary discontinuation of therapy.
- **Neurotoxicity**: Neurologic adverse events, including seizures and encephalopathy, are the most serious risks associated with blinatumomab. However, these events are largely reversible, and the incidence of severe, permanent neurologic sequelae is low.
- **Reduced hematologic toxicity**: Unlike chemotherapy, blinatumomab does not cause significant myelosuppression, reducing the risk of life-threatening infections, bleeding, and transfusion dependence.

In comparison, conventional chemotherapy carries substantial risks of severe myelosuppression, infection, mucositis, organ damage, and secondary malignancies, particularly with prolonged or intensified regimens. Ultimately, the benefits of blinatumomab in randomized clinical trials of frontline and relapsed/refractory patients document its safety profile relative to alternative therapies.

Feasibility of Use in Low- and Middle-Income Countries (LMICs)

Blinatumomab has been provided in LMICs through access programs in collaboration with St. Jude Children's Research Hospital and major academic centers in India, Pakistan, and Vietnam.[94] Its use has proven feasible in a wide variety of settings, provided that personnel receive adequate training in detection and management of toxicities and have access to colleagues with experience using it.[29,94,109-113]

- **Availability**: Blinatumomab is approved for use in multiple high-income countries, and ongoing efforts by global health organizations aim to improve its availability in LMICs. Programs that support expanded access to novel cancer treatments, including partnerships between pharmaceutical companies and global health organizations, could facilitate its wider distribution. Indeed, a central motivation for including blinatumomab on the EML is so that it could qualify for expanded access programs for which EML inclusion is pre-requisite.
- **Cost considerations**: In high-income countries, blinatumomab is generally funded via national health coverage or health insurance schemes. It has proven cost-effective because of its curative potential and the avoidance of the substantial costs associated with alternative (less effective) intense chemotherapy salvage therapies followed by HSCT and the associated prolonged hospital stays due to chemotherapy-induced complications.[114-116] Tiered pricing and donation programs can help address cost barriers in LMICs.
- **Infrastructure requirements**: Administering blinatumomab requires basic infrastructure commonly available in tertiary oncology centers, including infusion pumps, trained medical

personnel, and central venous access. Special tubing and filters (non-DEHP) are needed for the infusions. These resources are available in most tertiary care centers in LMICs, and are similar to the infrastructure required for the administration of complex chemotherapy regimens, such as those used to treat acute myeloid leukemia, non-Hodgkin lymphoma and many solid tumors.[94] With programs of a similar design to that currently employed by St Jude Children's Research Hospital, there is every reason to suspect beneficial clinical outcomes can be achieved in many LMICs.[94]

9. SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES

The most recently updated, globally recognized guidelines for management of ALL come from the European Society of Medical Oncology (ESMO) and were updated in 2024.[117] They recommend immunotherapy, generally with blinatumomab, for people with B-lineage ALL in the frontline setting and in relapsed or refractory disease (Figures 8 and 9). The National Comprehensive Cancer Network (NCCN) also updated their ALL guidelines in 2024 and recommend blinatumomab for frontline and relapsed therapy (Figures 10 and 11, https://www.nccn.org/professionals/physician_gls/pdf/all.pdf).

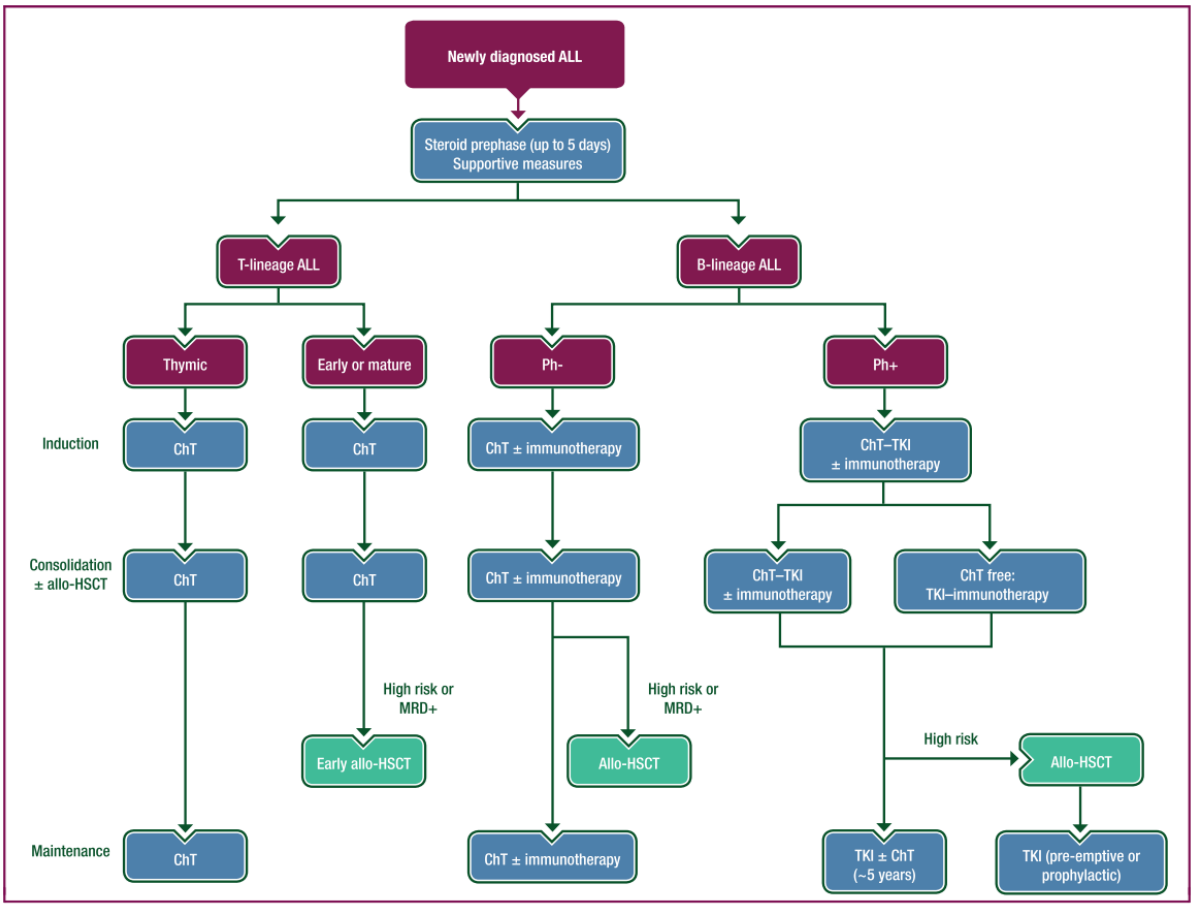


Figure 1. Treatment algorithm for newly diagnosed ALL.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
Systemic ChT should be accompanied by intrathecal ChT for prevention of CNS relapse in all patient categories.
ALL, acute lymphoblastic leukaemia; allo-HSCT, allogeneic haematopoietic stem cell transplantation; ChT, chemotherapy; CNS, central nervous system; MRD+, minimal residual disease positive; Ph+, Philadelphia chromosome positive; Ph−, Philadelphia chromosome negative; TKI, tyrosine kinase inhibitor.

Figure 8. ESMO guidelines for frontline acute lymphoblastic leukemia.[117]

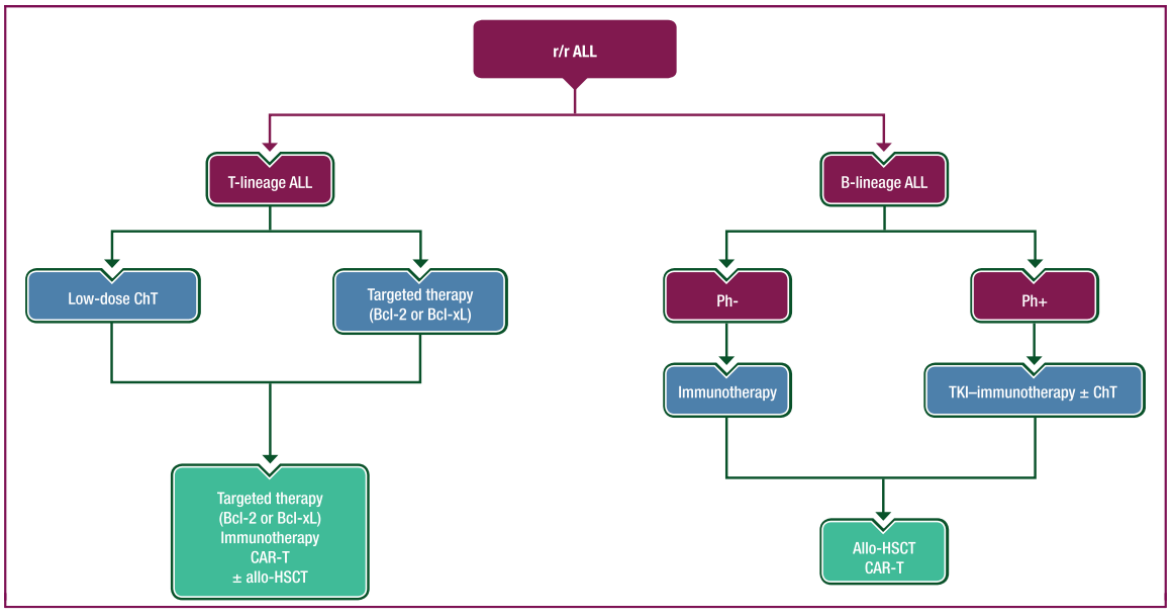


Figure 2. Treatment algorithm for r/r ALL.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments.
ALL, acute lymphoblastic leukaemia; allo-HSCT, allogeneic haematopoietic stem cell transplantation; Bcl, B-cell lymphoma; CAR-T, chimeric antigen receptor T cell; ChT, chemotherapy; Ph+, Philadelphia chromosome positive; Ph−, Philadelphia chromosome negative; r/r, relapsed or refractory; TKI, tyrosine kinase inhibitor.

Figure 9. ESMO guidelines for relapsed or refractory acute lymphoblastic leukemia.[117]

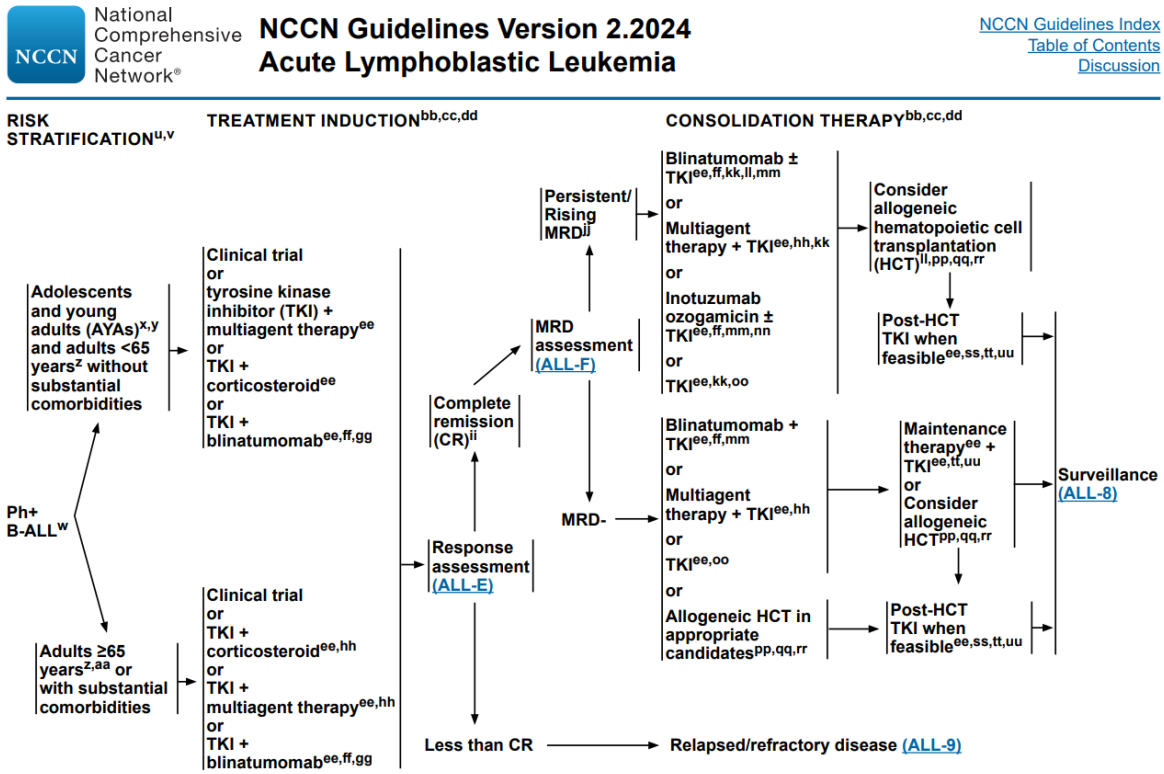


Figure 10. NCCN Guidelines for frontline acute lymphoblastic leukemia (https://www.nccn.org/professionals/physician_gls/pdf/all.pdf).

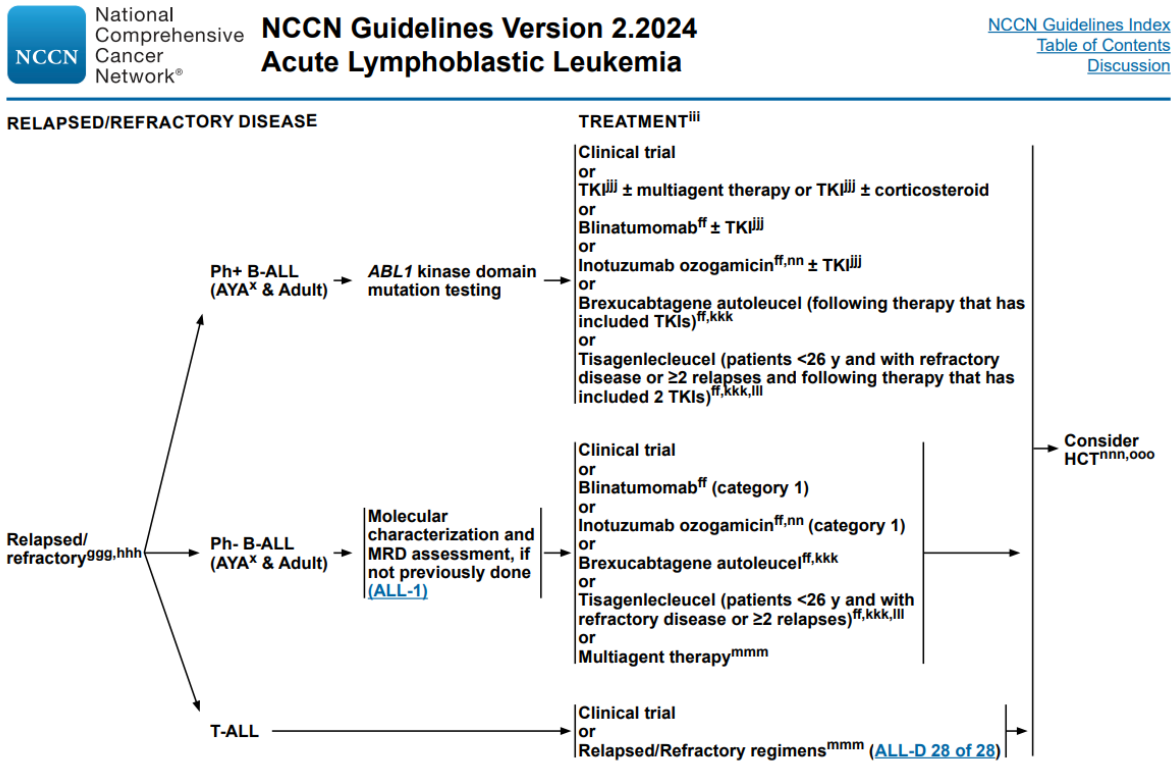


Figure 11. NCCN Guidelines for relapsed or refractory acute lymphoblastic leukemia (https://www.nccn.org/professionals/physician_gls/pdf/all.pdf).

The Children's Oncology Group provides guidelines for supportive care and management of late toxicities of therapy but does not provide guidelines for cancer therapy in children. However, blinatumomab is included in the standard arm of both frontline and relapse protocols for B-lineage ALL, is considered the standard of care for children with ALL, and was the subject of an urgent (confidential) memo urging that all patients on study arms not receiving blinatumomab should receive it, based on its compelling efficacy at the time of interim analysis (COG confidential memo that will become public December 2024).

Analysis of goodness-of-fit of blinatumomab for LMICs using the ESMO Magnitude of Clinical Benefit Scale

The European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS) was developed from 2013 to provide a methodology to consistently categorize the magnitude of clinical benefit from new therapeutic approaches.[118-120] The rationale was developed to distinguish therapies delivering a high level of benefit to patients from those in which benefits were small or marginal. This was considered increasingly important as the pace of new oncology medicine approvals were increasing rapidly in the 2010s. Since its introduction the ESMO MCBS has been accepted as a robust tool to evaluate the magnitude of clinical benefit reported in trials for oncological therapies. The methodology of the ESMO MCBS with respect to solid tumor assessment has been thoroughly evaluated and validated.[118-123] ESMO also maintains a comprehensive website with scorecards (https://www.esmo.org/guidelines/esmo-mcbs), which

has provided a useful framework for previous WHO EML reviews. Indeed, since 2019 the WHO Expert Committee on Selection and Use of Medicines acknowledge the role of the ESMO-MCBS as a screening tool to identify cancer treatments that have potential therapeutic value that warrants full evaluation for the Essential Medicines List (EML) listing. Potential new EML cancer medicines, in general, should have a score on the ESMO-MCBS of A or B in the curative setting and of 4 or 5 in the non-curative setting (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-in-action). Blinatumomab fits in the curative category in the frontline and second-line setting and potentially in the third-line setting when combined with additional consolidation therapies.

After developing and validating the ESMO-MCBS for solid tumors, the ESMO-MCBS Working Group continued to develop the scale and methodology, has collaborated with the European Hematology Association (EHA) to develop a version for haematological malignancies (ESMO-MCBS:H) to apply the system in evaluating the magnitude of clinical benefit derived from clinical studies in haematological malignancies.[124] Blinatumomab has been evaluated in relapsed/refractory ALL and received a score of 5 on the MCBS:H (the highest score for life-extending therapies).[124]

The submitter and a group of clinical experts will commit to assessing the paediatric trials of blinatumomab using the ESMO-MCBS:H tools and reporting these outcomes as a supplement to this EML submission.

Table 3: Field-testing assessment for one indication of blinatumomab in adults using the newly developed ESMO-Magnitude of Clinical Benefit Scale for Haematological Malignancies on data from the TOWER study.[124-127]

Medication	Trial Name	Setting	Primary Outcome	PFS/ EFS Control	PFS/ EFS Gain	PFS/EFS HR	OS Control	OS Gain	OS HR	RR (DoR)	QoL	Toxicity	ESMO-MCBS:H
Blinatumomab vs SOC	TOWER	Relapsed/ refractory	OS	12% 6 months EFS	19%	0.55 (0.43-0.71)	**4 months**	**3.7 months**	**0.71 (0.55-0.93)**	44% vs. 25% CRR, gain 19%	Improved		**5 (Form 2a)**

Chen and colleagues[124] conducted a meta-analysis to provide more comprehensive evidence on the efficacy and safety of blinatumomab in children with relapsed refractory B-cell ALL, which is the most contemporaneous analysis to date in the pediatric population. The review was carried out according to the reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, and 12 studies were included in the meta-analysis.

The primary endpoints were CR (defined as <5% blasts in the bone marrow), OS (defined as the time from the first blinatumomab administration and the last follow-up or death for any reason), event-free survival (EFS; defined as time from the first blinatumomab infusion to relapse, progression, second malignant neoplasm, death or last contact), MRD response (defined as<1 × 10−4 leukemic cells in the bone marrow (BM) by flow cytometry (FC) or polymerase chain reaction (PCR) analysis), and allogeneic HSCT. Secondary end points included adverse events (AEs) and relapse rates.

Figures 12, **13** and **14** summarise the evidence for blinatumomab's effectiveness in children with relapsed/refractory (R/R) B-ALL, including these highlights:

- The pooled CR rate after blinatumomab treatment was 56%, indicating that blinatumomab is effective in the treatment of R/R B-ALL in children.
- OS and EFS were significantly prolonged after blinatumomab as compared to chemotherapy, suggesting that blinatumomab treatment prolongs survival of children with R/R B-ALL.
- Blinatumomab was more effective in eliminating MRD than chemotherapy (OR 4.71, 95% CI 2.84–7.81). The pooled MRD response rate was 51% with blinatumomab.
- The main AEs after blinatumomab treatment were cytokine release syndrome and neurological events, which were manageable.

RCT									
Study	Country	Sample size (female)		Age (years IQR)		Intervene		Follow up (months IQR)	Out come
		EG	CG	EG	CG	EG (does)	CG		
Locatelli et al. (2021)	Italy	54 (24)	54 (32)	6 (1–17)	5 (1–17)	15 ug/ m^2/day	Chemotherapy	22.4 (8.1–34.2)	M1; M2; M3; M4; M5;
Brown et al. (2021)	United States	105 (48)	103 (49)	6 (3–13)	6 (3–13)	15 ug/ m^2/day	Chemotherapy	34.8 (21.6–46.8)	M1; M2; M3; M4; M5
Single-arm study									
Study	Country	Sample size (female)		Age (years IQR)		Dose		Follow up	Out come
Beneduce et al. (2022)	Italy	39 (17)		5.3 (.2–20.4)		5 to 28 μg/m^2/day		16 (0–67)	M1; M2; M3; M4; M5; M6;
Wasikowska (2022)	Poland	13 (5)		5.0 (.67–10)		5 to 15 mcg/m^2/day		25.4 (1–47)	M2; M3; M5; M6
Locatelli et al. (2022)	Italy	110 (48)		8.5 (.4–17.0)		5 to 15 ug/m^2/day		NR	M1; M2; M3; M6
Horibe et al. (2020)	Japan	9 (5)		11 (7–17)		5 to 15 ug/m^2/day		24	M2; M3; M5; M6
Ampatzidou et al. (2020)	Greece	9 (4)		4.1 (.2–12.1)		5 to 45 ug/m^2/day		NR	M1; M2; M3; M5; M6
Sutton et al. (2020)	Australia	24		NR		15 ug/m^2/day		26 (14–42)	M1; M2; M3; M5; M6
Queudeville et al. (2020)	Germany	38 (14)		9.8 (1.1–20.7)		5 to 30 ug/m^2/day		54 (8.9–113)	M1; M2; M3; M4; M5; M6
Schlegel et al. (2014)	Germany	9 (4)		10.4 (4.3–18.5)		5 to 30 ug/m^2/day		49.7 (22.5–61.7)	M1; M3; M5; M6
Stackelberg (2016)	Germany	70 (23)		8 (<1–17)		5 to 15 ug/m^2/day		23.8	M1; M2; M3; M5; M6
Fuster et al. (2020)	Spain	15				NR		NR	M1; M2; M3; M5; M6

Abbreviations: RCT, Randomized controlled trial; EG, Blinatumomab group; CG, control group; IQR, Interquartile Range; NR, not report; M1: EFS, event-free survival; M2: OS, overall survival; M3: MRD, minimal residual disease response; M4: Relapse; M5: AE, adverse events; M6: CR, complete remission. MRD, response rate was defined by the incidence of negative MRD.

Figure 12. Studies of blinatumomab for relapsed or refractory ALL in children.[108]

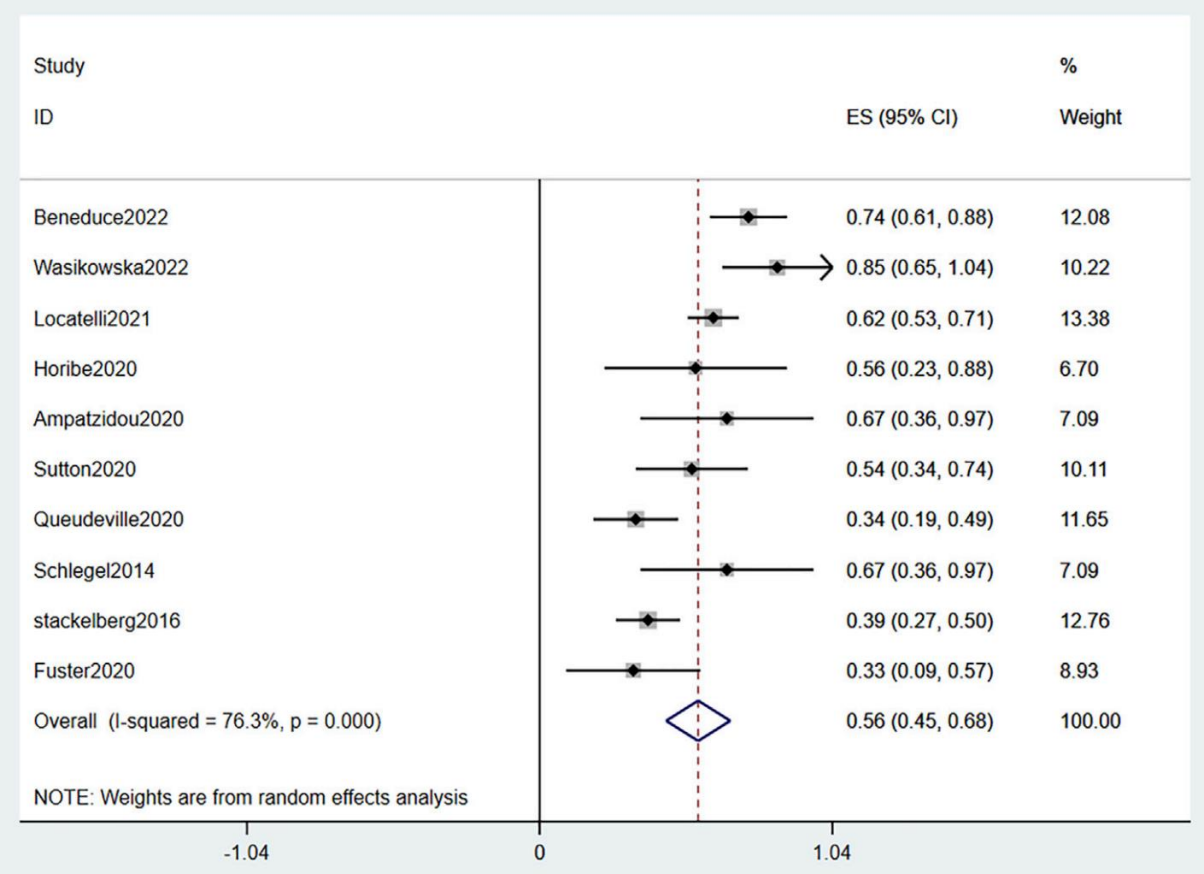


Figure 13. Complete response rates to blinatumomab versus standard therapy for relapsed or refractory ALL in children.[108]

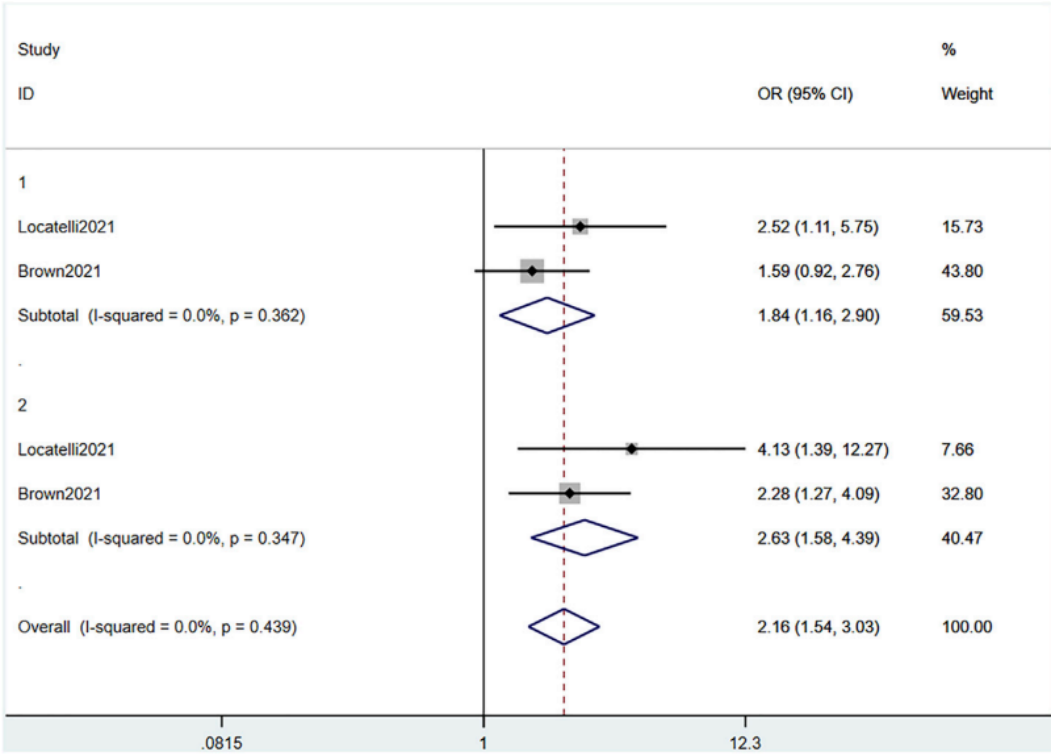


Figure 14. Event-free survival after treatment with blinatumomab versus standard therapy for relapsed or refractory ALL in children.[108]

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS (NEW MEDICINES)

Affordability and Cost-Effectiveness

Although blinatumomab is relatively expensive, it has proven cost-effective in both frontline and relapsed settings because it induces durable remissions and reduces the need for more expensive interventions, such as repeated hospitalizations, intensive chemotherapy, HSCT, and CAR-T cell therapy.[112,114-116,128,129]

Economic burden of pediatric ALL

Costs of care for relapsed or refractory ALL are high with or without blinatumomab

It is difficult to provide data on the economic burden of ALL in low- and middle-income countries, which are the ones that will most benefit from an EML listing of blinatumomab. Regardless of setting, pediatric ALL can potentially be cured, and its treatment has been shown to be cost-effective in LMICs.[130] Relapsed ALL, however, is associated with high mortality and morbidity for patients and high economic costs to healthcare systems. To be monitored and treated for toxicities associated with conventional salvage chemotherapy, pediatric patients with ALL typically must spend repeated and prolonged periods in the hospital, and inpatient stays are a key driver of direct costs.[131,132]

Multiple retrospective cohort studies in the US indicate that that pediatric R/R ALL is associated with substantial hospitalization (estimated mean of 65 days) and related costs.[131-133] Although no specific costs were reported for patients with R/R disease, 1 study showed that when compared with patients who remained in remission, patients with relapsed disease incurred more than 3 times greater costs per 6-month period ($P < 0.001$), had more than 4 times longer hospital stays ($P < 0.001$), and had 4 times more admissions ($P < 0.001$).[131] Among patients who go on to receive an alloHSCT, the burden of hospitalization is likely to be particularly high.[133,134] In a retrospective evaluation of the direct costs for 209 patients who underwent alloHSCT in the US between 2002 and 2013, an average of 3.1 inpatient admissions were required (total duration: 68 days) in the first year after alloHSCT, as well as 49 days of outpatient visits and 29 days of laboratory services.[133] The mean total costs in the first year after alloHSCT were US $683,099 (median: $511,021), with the initial alloHSCT hospitalization accounting for almost two-thirds (62%) of these costs.

Available literature suggests that the economic burden associated with hospitalization for pediatric ALL more broadly is substantial.[135-137] In a retrospective cost-effectiveness analysis of the ALL10 Dutch Childhood Oncology Group pediatric ALL treatment protocol, mean total direct costs were estimated to be US $163,350 per patient, and hospital admissions were the most significant driver of direct costs, accounting for 57% of total costs.[135] Another retrospective evaluation of direct costs incurred for pediatric patients with ALL treated with the Berlin-Frankfurt-Münster (BFM) and Dana-Farber Cancer Institute (DFCI) protocols showed that mean total costs per patient over the duration of therapy were US $88,480 and US $93,026, respectively.[136] Furthermore, another retrospective evaluation of direct costs associated with Nordic pediatric ALL protocols showed

that basic hospital costs accounted for 53% of the total costs, with treatment and hospitalization for infections also notably accounting for almost one-fifth (18%) of total costs.[137]

Cost-effectiveness of adding blinatumomab to relapsed/refractory pediatric ALL therapy

Published studies of resource utilization and the economic burden associated with pediatric ALL that are specific to the R/R setting outside the US are few. A cost-effectiveness analysis comparing blinatumomab to salvage chemotherapy in Mexico is the only such study published from an LMIC, and demonstrated favorable incremental cost-effectiveness ratios (ICERs), including quality-adjusted life years (QALYs) and overall survival (**Figure 15**).[112] Furthermore, blinatumomab was found to remain cost-effective with an acceptable incremental cost-effectiveness ratio (ICER) under a wide range of assumptions (**Figure 16**). These analyses were conducted using drug acquisition costs for blinatumomab in 2023 in Mexico (17.8 pesos to 1 USD), and in the sensitivity analysis, the authors included the impact of lower drug costs on ICER as measured by life years (LY) gained (**Figure 17**). The base case documented an ICER of 121,536 pesos/LY, or US $6829/LY. A 15% discount in blinatumomab price led to an ICER of 105,228 pesos/LY, or US $5911/LY, and further price discounts that could result from having blinatumomab on the WHO EML and in various negotiated access programs would be expected to improve cost-effectiveness even more (**Figure 18**). A similar study was conducted in Brazil, and found that blinatumomab was cost-effective for children with a first, high-risk relapse.[129] The methods and results were similar to those in Mexico, but the authors highlighted one aspect of the sensitivity analysis, which is the optimal use and sharing of vials, which reduced costs by 50% when use of each vial was optimized (**Figure 19**).

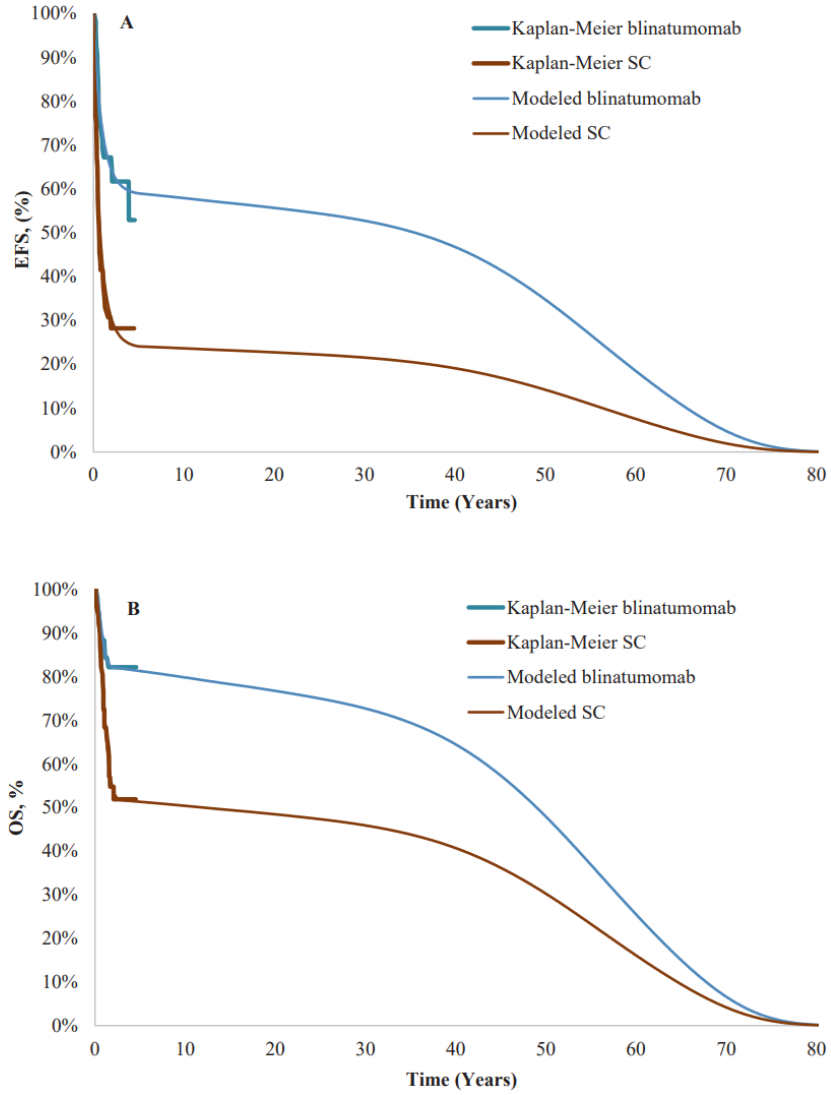


Fig. 1. Modelled event-free survival curves for blinatumomab and SC. (A) EFS fit; (B) OS. EFS event-free survival, SC consolidation chemotherapy, OS overall survival.

Figure 15. Cost-effectiveness of blinatumomab versus chemotherapy for children with acute lymphoblastic leukemia in first relapse.[112]

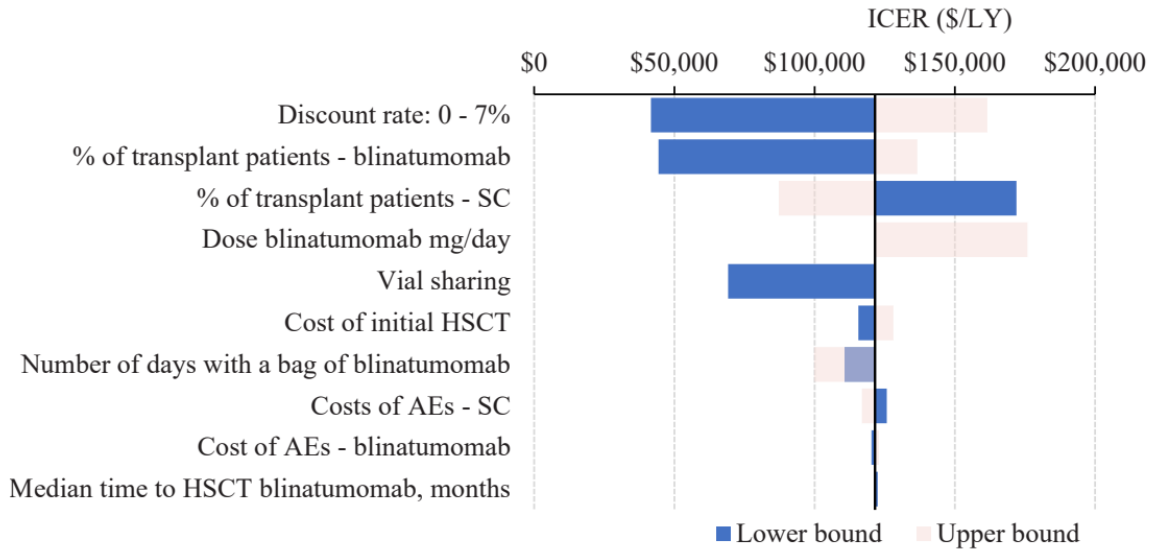


Figure 16. Deterministic sensitivity analysis results on incremental cost-effectiveness (in Mexican pesos, 17.8 per USD) of blinatumomab versus chemotherapy for children with acute lymphoblastic leukemia in first relapse under a wide range of assumptions.[112]

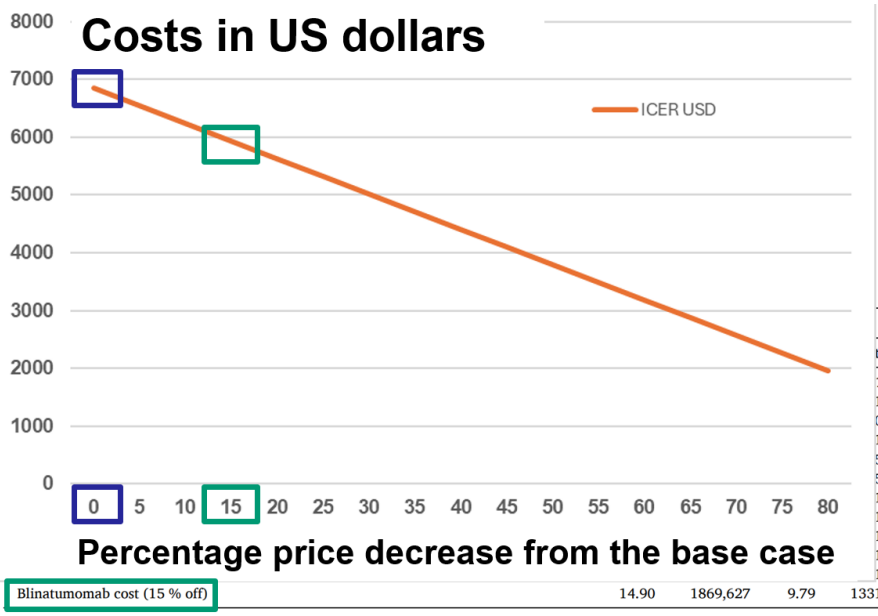
The base case in this analysis assumes no vial sharing. In fact, vial sharing is universally practiced in LMICs, and decreases the ICER by 43%, from 121,535 Mexican pesos (US $6827)/life year gained to 69,275 Mexican pesos (US $3892)/life year gained.[112] Even more important, all analyses were done using the public list price of blinatumomab in Mexico. If payers have alternative confidential arrangements in place with the medicines sponsor, the actual ICER in practice may be considerably lower than US $3900/life year gained.

Table 3
Scenario analysis results.

	Blinatumomab		SC		Incremental		ICER
	LY	Cost ($)	LY	Cost ($)	LY	Cost ($)	$/LY
Base case	**14.90**	**1952,966**	**9.79**	**1331,855**	**5.11**	**621,111**	**121,536**
Exponential mixture-cure model for EFS and OS	14.86	1955,458	9.01	1331,553	5.85	623,905	106,709
Gompertz standard model for EFS and OS	14.88	1955,063	8.79	1330,537	6.08	624,526	102,642
Gompertz standard model for OS; Weibull mixture-cure EFS	14.90	1955,470	9.79	1331,623	5.11	623,848	122,045
KM curves up to 27 months, then application of the cure assumption for both EFS and OS	14.92	1964,310	9.80	1335,436	5.11	628,873	122,980
KM curves up to 54 months, then application of the cure assumption for both EFS and OS	3.47	1964,504	2.58	1335,478	0.90	629,026	702,745
SMR decreasing by level (Dixon et al. [28])	14.55	1952,964	9.57	1331,854	4.98	621,109	124,788
Time horizon of 63 years	14.86	1952,966	9.76	1331,855	5.10	621,111	121,899
Time horizon of 49 years	14.52	1952,966	9.55	1331,855	4.97	621,111	124,931
Time horizon of 10 years	6.60	1952,966	4.55	1331,855	2.05	621,111	302,947
Blinatumomab cost (5 % off)	14.90	1980,745	9.79	1331,855	5.11	648,891	126,971
Blinatumomab cost (15 % off)	14.90	1869,627	9.79	1331,855	5.11	537,772	105,228

EFS event-free survival, OS overall survival, LY life year KM Kaplan–Meier, SMR standardized mortality ratio, ICER incremental cost-effectiveness ratio, SC consolidation chemotherapy.

Figure 17. Cost-effectiveness of blinatumomab for children with acute lymphoblastic leukemia in first high-risk bone marrow relapse in Mexico under a range of scenarios (currency shown is Mexican pesos, 17.8 per USD).[112]



				Incremental		ICER
			t ($)	LY	Cost ($)	$/LY
			1,855	5.11	621,111	121,536
			1,553	5.85	623,905	106,709
			0,537	6.08	624,526	102,642
			1,623	5.11	623,848	122,045
			5,436	5.11	628,873	122,980
			5,478	0.90	629,026	702,745
			1,854	4.98	621,109	124,788
			1,855	5.10	621,111	121,899
			1,855	4.97	621,111	124,931
			1,855	2.05	621,111	302,947
			1,855	5.11	648,891	126,971
Blinatumomab cost (15 % off)			14.90	1869,627	9.79	1331,855	5.11	537,772	105,228

EFS event-free survival, OS overall survival, LY life year KM Kaplan–Meier, SMR standardized mortality ratio, ICER incremental cost-effectiveness ratio, SC consolidation chemotherapy.

Figure 18. Cost-effectiveness of blinatumomab for children with acute lymphoblastic leukemia in first high-risk bone marrow relapse in Mexico showing the impact of price reductions on the incremental cost-effectiveness ratio (currency shown is Mexican pesos, 17.8 per 1 USD)

Tabela 3. Custo do blinatumomabe por ciclo dependendo do tempo de infusão em que a bolsa foi preparada

Tempo de infusão	Nº de bolsas por ciclo	Nº de frascos por bolsa*	Nº de frascos por ciclo†	Custo por ciclo (R$)
24 horas (caso base)	28	1	28	249.318
48 horas	14	1	14	124.659
72 horas	9‡	2	19	169.180
96 horas	7	2	14	124.659

* Número de bolsas arredondado para baixo; para cobrir o dia restante do ciclo, adiciona-se 1 frasco-ampola ao total de 18 frascos por ciclo. †O número de frascos por bolsa considerando uma dose de 15 mcg foi obtido do Resumo das Características do Medicamento do blinatumomabe.

Figure 19. Impact of vial sharing and optimal use on the cost of blinatumomab per cycle of therapy.[129]

Indirect costs

In addition to the direct costs associated with pediatric R/R ALL incurred by healthcare systems, the disease is likely to result in substantial indirect costs to patients and their families due to out-of-pocket expenses (e.g., travel to specialist treatment centers) and lost income.[138-140] A cross-sectional survey of the perceived financial burden to primary caregivers of pediatric patients with cancer treated in the US during 2010 to 2012 (n=310) showed that approximately one-third of primary caregivers either changed or left their jobs as a result of their child's cancer diagnosis.[138] A retrospective questionnaire study in children and adolescents diagnosed with cancer during 1990 to 1996 in Canada (n=111) similarly showed the substantial impact of cancer on the employment status of parents; 92% of mothers and 25% of fathers of children with leukemia left their jobs,

which were higher than rates seen for other cancer types.[139] A population-based analysis of the economic burden of caregiving (in terms of lost income) on families of children and adolescents with cancer in Italy diagnosed during 2000 to 2005 (n=899) further showed that leukemia was associated with a median cost of US $13,493 at 3 years of follow-up.[140] The estimated economic burden incurred by caregivers was higher for leukemia than for any of the other cancer types evaluated in this study.

Public list price information

Table 3 provides details of the list price information of blinatumomab in jurisdictions where pricing information is available. It includes the price in local currency and converted to US dollars (at mid-market rate on 22 October 2024). For the purposes of review, Argentina (outlier) and the United States have been removed. When doing so, the median price per vial in these countries is US $2244 (rounded).

The table also provides classification according to the World Bank Atlas method. For operational and analytical purposes, the World Bank divides economies among income groups according to 2023 gross national income (GNI) per capita in US dollars. For the 2025 fiscal year, the thresholds are defined as follows:

- low income ($1,145 or less)
- lower middle income ($1,146 to $4,515)
- upper middle income ($4,516 to $14,005)
- high income (more than $14,005)

Further details on the World Bank Atlas method can be found at their website https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
And technical details are provided in the accompanying Excel sheet https://datacatalogapi.worldbank.org/ddhxext/ResourceDownload?resource_unique_id=DR0090755

Most countries in which blinatumomab has public list price information are high-income countries. This is expected, given the nature of high-income countries and their health systems, which include the generalized adoption of contemporary clinical practice, as well as usually having reimbursement agencies (or health insurance systems) that use health technology appraisal methodology to assess the value of medicines to their health systems (that is, economic analysis that assess the relative safety and efficacy and the cost effectiveness of new medicines). Furthermore, high-income countries have sufficient resources to invest in their healthcare systems, and accept a willingness-to-pay value for each life year or QALY that is significantly higher than those feasible in LMICs.

Table 3: List price information by country of registration

Country	WB Atlas*	Mcg per vial	List price per vial	Currency	USD*
High-income countries					
Australia	HIC	38.5	2760	AUD	1844
Austria	HIC	38.5	2826	EUR	3059
Belgium	HIC	38.5	2073	EUR	2244
Bulgaria	HIC	38.5	3972	BGN	2198
Canada	HIC	38.5	2978	CAD	2153
Croatia	HIC	38.5	2393	EUR	2591
Cyprus	HIC	38.5	2583	EUR	2795
Czech Rep.	HIC	38.5	50118	CZK	2146
France	HIC	38.5	2073	EUR	2244
Germany	HIC	38.5	2125	EUR	2299
Greece	HIC	38.5	2043	EUR	2211
Iceland	HIC	38.5	17842	DKK	2588
Ireland	HIC	38.5	2378	EUR	2574
Israel	HIC	38.5	9611	ILS	2542
Italy	HIC	38.5	2826	EUR	3058
Japan	HIC	35	285961	JPY	1896
Luxembourg	HIC	38.5	2073	EUR	2244
Poland	HIC	38.5	9245	PLN	2316
Romania	HIC	38.5	10076	RON	2191
Russia	HIC	35	156072	RUB	1615
Slovakia	HIC	38.5	2031	EUR	2198
Slovenia	HIC	38.5	2087	EUR	2258
South Korea	HIC	35	1934540	KRW	1403
Switzerland	HIC	38.5	2302	CHF	2659
Taiwan	HIC	35	56984	TWD	1778
UK	HIC	38.5	2017	GBP	2617
USA	HIC	35	5145	USD	5145
Upper middle-income countries					
Argentina	UMIC	38.5	10475631	ARS	10654
Colombia	UMIC	38.5	6798734	COP	1591
Mexico	UMIC	35	27696	MXN	1389
South Africa	UMIC	38.5	27791	ZAR	1577
Türkiye	UMIC	38.5	2073	EUR	2244

Importance of the WHO EML in driving cost reductions in low- and middle-income countries

In LMICs, cost barriers can be addressed through initiatives such as differential pricing, voluntary licensing agreements, or access programs supported by non-governmental organizations (NGOs) and international health bodies. The cost of blinatumomab in relation to its current countries of reimbursement is justified by the survival benefits and reduced need for costly supportive care and long-term hospitalization and is relevant to those country contexts (that is, is cost-effective in those contexts). The medicine sponsor, Amgen, has a stated policy on their website with respect to medicines pricing and note that one of those principles is to employ flexible approaches to ensure access, particularly noting a balanced approach that considers the need for patient access to innovation and the limited ability to pay in low- and middle-income countries.

Negotiated prices significantly lower than the current list prices in HICs would be associated with extreme cost-effectiveness and access in LMICs may be facilitated by inclusion of blinatumomab in the WHO EML (**Figure 15**). Finally, now that blinatumomab will be used as part of frontline therapy for B-ALL, much larger volumes will be needed, and can be the subject of price negotiations to limit total expenditures. The cost savings of curing patients with frontline therapy are substantial, since they then do not require expensive and morbid salvage therapy and HSCT, and this can be part of the business case for universal frontline access that member states can evaluate during pricing negotiations.

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

Availability of Pharmacopeial Standards

Blinatumomab is produced and regulated under stringent pharmacopeial standards set by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These standards ensure the quality, safety, and efficacy of the drug and provide robust guidance for its global manufacture and distribution. International standards for biologic therapies, including monoclonal antibodies like blinatumomab, are well established and ensure consistency across different batches and geographies.

Worldwide Marketing Approval Status

Blinatumomab was first approved on 03 December 2014 for the treatment of adult patients with Philadelphia chromosome negative (Ph-) relapsed or refractory (R/R) B-cell precursor ALL at the approved dose of 9 µg/day on days 1 to 7 and 28 µg/day on days 8 to 28 for the first cycle and 28 µg/day for subsequent cycles in the United States (US). As of **28 October 2024**, blinatumomab has been approved in **69 markets,** listed in **Table 4**.

Table 4. Blinatumomab (trade name BLINCYTO) Worldwide Marketing Approval Status

Country	Date of Initial Approval	Launch Date	Indication
United States	03 Dec 2014	03 Dec 2014	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e] Adults and Pediatrics Consolidation
Mexico	23 Jun 2015	28 Aug 2015	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e] Adults and Pediatrics Consolidation
Australia	30 Oct 2015	May 2016	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL
South Korea	03 Nov 2015	May 2016	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
European Union[c]	23 Nov 2015	07 Dec 2015	Adults and Pediatric[f,g] Ph- R/R B-precursor ALL[b] Adults Ph+ R/R B-precursor ALL[b] Adults Ph- MRD ALL[e]
United Kingdom	23 Nov 2015	12 Jan 2016	Adults and Pediatric[f,g] Ph- R/R B-precursor ALL Adults Ph+ R/R B-precursor ALL[b] Adults Ph- MRD ALL[e]
Norway	23 Nov 2015	11 Mar 2016	Adults and Pediatric[f,g] Ph- R/R B-precursor ALL Adults Ph+ R/R B-precursor ALL[b] Adults Ph- MRD ALL[e]
Iceland	16 Dec 2015	17 Feb 2020	Adults and Pediatric[f,g] Ph- R/R B-precursor ALL Adults Ph+ R/R B-precursor ALL[b] Adults Ph- MRD ALL[e]
Canada	22 Dec 2015	03 Oct 2016	Adults and Pediatric Ph- R/R B-precursor ALL Adults Ph+ R/R B-precursor ALL Adults and Pediatric Ph- MRD ALL[e]

Switzerland	25 Feb 2016	19 May 2016	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL[b] Adults and Pediatric MRD ALL Adults and Pediatrics Consolidation
Liechtenstein	01 Apr 2016	Not launched	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL
Lebanon	21 Apr 2016	06 Aug 2018	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Israel	31 Jul 2016	19 Jan 2017	Adults and Pediatric[f,g] Ph- R/R B-precursor ALL Adult Ph+ R/R B-precursor ALL[b] Adults Ph- MRD ALL[e]
Kuwait	06 Sep 2016	09 Nov 2018	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Singapore	18 Oct 2016	28 Feb 2017	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B- precursor ALL Adults and Pediatric MRD ALL[e]
Malaysia	31 Oct 2016	July 2018	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults MRD ALL[e]
Bahrain	28 Nov 2016	21 May 2019	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B precursor ALL Adults and Pediatric MRD ALL[e]
Qatar	20 Dec 2016	02 Jul 2021	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Russian Federation[h,i]	22 Dec 2016	30 Oct 2017	Adults and Pediatric[f] Ph- R/R B-precursor ALL Adults Ph+ R/R B-precursor ALL[b] Adults Ph- MRD ALL[e]

Taiwan, Republic Of China	23 Feb 2017	13 Jun 2017	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Hong Kong, Republic of China	29 Mar 2017	Jun 2017	Adults and Pediatric[f,g] Ph- R/R B-precursor ALL[b] Adults Ph- MRD ALL[e] Adults Ph+ R/R B-precursor ALL[b]
Brazil	17 Apr 2017	18 Jul 2017	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults MRD ALL
Jordan	25 Apr 2017	22 Feb 2019	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Oman	21 May 2017	13 May 2019	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Saudi Arabia	15 Jul 2017	13 Apr 2018	Adults and Pediatric Ph- R/R B-precursor ALL Adults MRD ALL[e]
Colombia	29 Aug 2017	18 Oct 2017	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults MRD ALL
Turkey	14 Sep 2017	03 Sep 2018	Adults and Pediatric Ph- Relapse B-precursor ALL[d] Adults and Pediatric Ph+ Relapse[d] B-precursor ALL Adults and Pediatric MRD ALL[d]
United Arab Emirates	25 Apr 2017	26 Jul 2017	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e] Adults and Pediatrics Consolidation
Macau	29 Nov 2017	Feb 2018	Adults and Pediatric Ph- R/R B-precursor ALL
Thailand	17 Apr 2018	Jun 2019	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]

Japan	21 Sep 2018	Nov 2018	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL
Morocco	10 Apr 2019	27 Jan 2021	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Algeria	16 Jul 2019	16 Jun 2023	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B precursor ALL Adults and Pediatric MRD ALL[e]
Argentina	09 Oct 2019	09 Marach 2020	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e] Adults and Pediatrics Consolidation
Peru	22 Sep 2020	05 Mar 2021	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Belarus	13 Oct 2020	07 Jun 2021	Adults and Pediatric[f] Ph- R/R B-precursor ALL Adults Ph- MRD ALL[e]
Ecuador	17 Nov 2020	29 Jun 2021	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
China Mainland	02 Dec 2020 27 Apr 2022	16 Aug 2021	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL
Chile	04 Aug 2021	13 Dec 2021	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
South Africa	30 Nov 2021	01 Apr 2022	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Uruguay	28 Apr 2022	Not Launched	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]

Libya	15 Jun 2022	Not Launched	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL[e]
Guatemala	17 Nov 2022	31 March 2023	Adults and Pediatric Ph- R/R B-precursor ALL Adults and Pediatric Ph+ R/R B-precursor ALL Adults and Pediatric MRD ALL

ALL, acute lymphoblastic leukemia; Ph-, Philadelphia chromosome negative; Ph+, Philadelphia chromosome positive; R/R, relapsed/refractory

[a] For at least 45 kg: 9 µg/day on days 1 to 7 and 28 µg/day on days 8 to 28 for the first cycle and 28 µg/day for subsequent cycles. For less than 45 kg: 5 µg/m²/day on days 1 to 7 and 15 µg/m²/day on days 8 to 28 for the first cycle and 15 µg/m²/day for subsequent cycles

[b] Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

[c] Centralized process covering all 27 member states: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden

[d] In patients undergoing allogeneic hematopoietic stem cell transplantation despite receiving at least 2 prior therapies (standard of care + salvage therapy) or Allo HSCT

[e] Treatment of B-cell precursor ALL in first or second CR with MRD greater than or equal 0.1%

[f] Treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.

[g] Treatment of paediatric patients aged 1 year or older with high-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy

[h] indications approved as part of Eurasian Economic Union (EAEU) recognition procedure, consists of Russian, Kazakhstan, Belarus, Armenia, and Kyrgyzstan.

[I] Blincyto is only marketed in Russia

Conclusion

Acute lymphoblastic leukemia is the most common and one of the most curable cancers of children and therefore was included in WHO's Global Initiative for Children with Cancer. Many of the medicines needed to cure childhood ALL are already included in the GPACCM, and the addition of blinatumomab will complete the bundle of therapies needed to manage ALL, such that children in LMICs will have access to exactly the same therapies as those in HIC.

The inclusion of blinatumomab on the WHO EMLc is justified given its demonstrated efficacy in achieving complete remission and MRD negativity in pediatric patients with frontline or relapsed/refractory B-ALL. The significant survival benefits with its use, combined with a manageable safety profile and the potential for broader access in LMICs, make blinatumomab a critical addition to the EMLc.

In HIC, frontline B-ALL is highly curable even without blinatumomab, but adding blinatumomab to standard chemotherapy improves EFS by 10-20%, and obviates the need to escalate conventional chemotherapy doses, which can lead to death from toxicity in LMICs.[77-86,90] Therefore, the benefits in the frontline setting may be even greater in LMICs than in HIC, where the risk of toxic death from conventional chemotherapy is low. With appropriate staff training and technical assistance, blinatumomab administration is feasible, acceptable, and appropriate in LMICs and access to this therapy provides unique relative advantages for children with B-ALL in LMIC due to it curative potential and safety profile compared to traditional chemotherapy.

The risk of toxic death from conventional chemotherapy is now relatively low in HICs, with much of this risk being reduced over time due to the emergence of more effective and safer cancer agents ('targeted therapies'), and the presence of supportive care regimens that can better manage adverse events related to chemotherapeutic use. It is worth remembering, however, that chemotherapy-related toxicity was quite prevalent into the turn of the century, and still now requires careful management of individual cases where chemotherapeutic regimens are used. In general, chemotherapy-related toxicity (and toxic death) remains prevalent in many LMICs, which is further exacerbated by the low use of supportive care regimens (often out of pocket costs) and a reliance on older chemotherapeutic agents.

In HICs, frontline B-ALL is highly curable even without blinatumomab, but adding blinatumomab to standard chemotherapy improves EFS by 10-20%, and obviates the need to escalate conventional chemotherapy doses.[78-87,93]

The benefits of blinatumomab in the frontline setting may be even greater in LMICs than in HICs, given the risk of toxic death from conventional chemotherapy is higher and gaps in access to other components of the chemotherapy regimen are more common than in HICs, as are logistical, financial, nutritional, and other obstacles (**Figure 20**).[78,80,81,87,141]

Relapsed/refractory B-ALL has a poor prognosis and disproportionately affects patients in LMIC, where relapse is more common and salvage therapies less available. By providing an effective, less toxic, targeted treatment option, blinatumomab can also improve survival in this vulnerable pediatric population by 20-30%.

Universal access to blinatumomab is expected to improve childhood ALL survival in LMICs by 20%. Noting that ALL comprises a fourth of all childhood cancer, extrapolation of these two data points would suggest that this single intervention, implemented at scale, could improve overall childhood cancer survival by 5% (averaging the 20% gain in ALL over all children with cancer) and bring the world considerably closer to the 2030 GICC target. With successful addition to the EML and effective implementation, this pathway to accelerated and universal access will provide proof of principle for the next new therapy to rapidly benefit children in LMICs.

Finally, blinatumomab access is only the beginning for patients with ALL in LMICs. Companion interventions to increase diagnosis, assure correct diagnosis, reduce abandonment, prevent toxic death, and reduce relapse through access to blinatumomab and all other components of therapy for children with ALL will be critical to achieve cure rates comparable to those in high-income countries (**Figure 20**).[141]

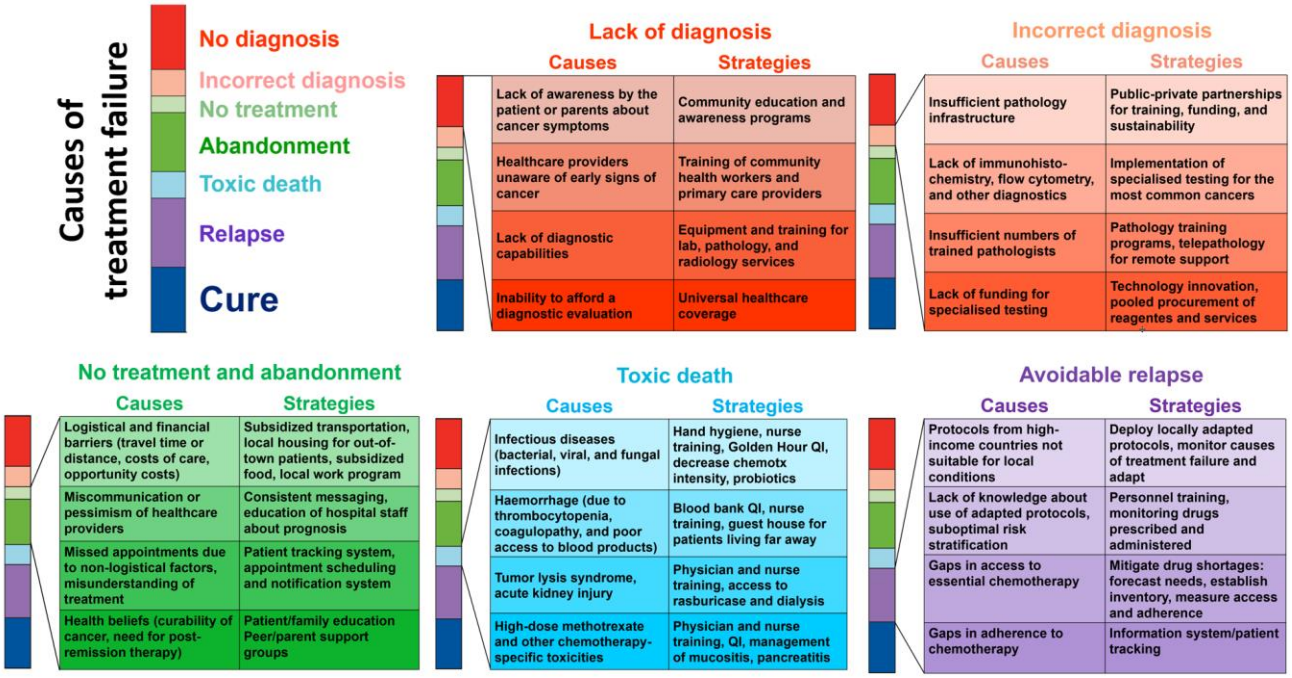


Figure 19. Causes and sub-causes of treatment failure for children with cancer in low- and middle-income countries and proven strategies to address them.[142]

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Appendix 1. Summary of clinical trials of blinatumomab in newly diagnosed, relapsed, and refractory acute lymphoblastic leukemia

Table 1. Clinical trials of blinatumomab in newly diagnosed B-ALL

Study	Blinatumomab design	Number of patients	Median age	CR rate	MRD Negativity	OS	EFS, RFS, DFS	HSCT
GIMEMA LAL 2116 D-ALBA Phase II	ND Ph+ B-ALL Dasatinib induction for 85 days and then 2-5 cycles of therapy with Blina plus Dasatinib	63 newly diagnosed Ph+ B-ALL	54 (24-82)	98%	After induction 29% After consolidation 60%	4-year 80.7% (lower for IKZF1plus)	4-year DFS : 75.8% EFS : 74.6%	39%
Phase II NCT 02143414	Dasatinib/Prednisone induction therapy then Blina and Dasatinib for 3 cycles, then Dasatinib/Prednisone maintenance	24 newly diagnosed Ph+ B-ALL	73 (65-87)	88% (after induction therapy) 95% (after Blinatumomab)	63% by RT-PCR	3-year OS 87% mOS 6.5 years	3-year EFS 77% mDFS not reached	
Phase II NCT 03263572	5 cycles of Ponatinib/Blina, followed by Ponatinib monotherapy.	40 Newly diagnosed Ph+ (ND); 14 R/R Ph+ B-ALL; 6 CML lymphoid blast phase	51 (36-68)	95% (ND) 85% (R/R)	87% (ND) 79% (R/R) 33% (CML)	2-year 89%	2-year EFS 77%	3%
GIMEMA LAL 2317 Phase II	Adult Ph- B-ALL patients treated with induction chemotherapy and then with six consolidation-therapy cycles; at cycles 3 and 6 Blina was added	149 12 KMT2A r 5 TCF3/PBX1 31 Ph-like	41 (18-65)	88% (after induction) 18-40 yr 90% 40-50 yr 92% >55 yr 64% 95% (after Blina)	70% (after induction) 93% (after Blina)	71% 18-40yr 76% 40-50yr 74% >55yr 49%	DFS 66% 18-40yr 71% 40-50yr 62% >55yr 42% CIR 27.5% MRD- 17.5% Ph-like 42.5%	NR
GRAAL-2014-QUEST Phase II	B-ALL patients in remission after induction and consolidation 1, received treatment with Blina	95 High-risk Ph- B-ALL	35 (18-60)	82%	Pre-Blina MRD<0.01% 56% Post-Blina MRD<0.01% 74%	Follow-up 18 months 92%	Follow-up 18 months DFS 78%	42%

GRAAL-2014-QUESTB Phase II	Blina was administered during consolidation to adult Ph- B-ALL patients and compared to a group of patients receiving only chemotherapy during consolidation	198 104 Chemotherapy 94 Blinatumomab	34 (18-59)	100% (before treatments)	After consolidation 2 72% (Blina) 76% (Chemo)	2.5 years 79% (Blina) 76% (chemo)	2.5 years DFS 72% (Blina) 54% (Chemo) 2.5 years CIR 20% (Blina) 41% (Chemo)	47% (Blina) 37% (Chemo)

NR, not reported; chemo, chemotherapy; blina, blinatumomab; CIR, cumulative incidence rate; DFS, disease-free survival; MRD, measurable residual disease; mOS, median overall survival;, mDFS, median disease-free survival; mPFS, median progression-free survival; mo, months; NE, not evaluable.

Table 2. Clinical trials of blinatumomab in patients with MRD-positive B-ALL in first or later complete remission

Study	Blinatumomab design	Number of patients	Median age (years) (range)	MRD Negativity	Overall Survival	EFS RFS DFS	CRS % NE %	HSCT
BLAST, phase II	Single-arm, open-label to evaluate safety and efficacy of Blinatumomab in adult B-ALL patients in CR with MRD≥10-3	116 (total) 64% CR1 34% CR2 2% CR3 96% Ph-	45 (18-76)	78% (after first cycle) 80% (after second cycle)	After a follow-up of 59.8 months mOS 36.5 mo MRD- NR MRD+ 16.5 mo Patients in CR1 41.2 mo Patients in CR 2 23.1 mo	After a follow-up of 29.9 months mPFS 18.9 mo MRD- 23.6 mo MRD+ 5.7 mo Patients in CR1 14.6 mo Patients in CR2 5.7 mo	NE 9% (first cycle) 3% (second cycle)	CRS: 0 (chemo) 4.9 (Blina) NE: 8.3 (chemo) 9.4 (Blina)
Phase II	Prospective single-arm phase II study with adult B-ALL, MRD >10-4 after first or later CR	37 73% CR1 27% CR2,3 53% Ph- 47% Ph+	43 (22-84)	65% (after the first cycle) 80% (after the second cycle)	3-year OS MRD- 72% MRD+ 52% CR1 72% CR2 51% HSCT 71% No-AHSCT 66%	3-year RFS MRD- 66% MRD+ 52% CR1 68% CR2 37% HSCT 71% No-HSCT 58%	CRS 3% NE 8%	41% HSCT 10/15 HSCT surviving 12/18 without HSCT and responding to Blina
Real-world study GRAALL group	Retrospective analysis on B-ALL patients with CR, MRD-positive	35 MRD level >1% 28% 0.1-1% 30% 0.01-0.1% 28% <0.01% 14%	32 (17-74)	89%	Median OS not reached 3-yr OS >1% 33% 0.1-1% 58% <0.1% 86%	mRF not reached 3-yr PFS >1% 33% 0.1-1% 58% <0.1% 78%	Not reported	66% HCT

HSCT, allogeneic hematopoietic stem cell transplantation; OS, overall survival; NR, not reported; chemo, chemotherapy; blina, blinatumomab; CIR, cumulative incidence rate; DFS, disease-free survival; MRD, measurable residual disease; mOS, median overall survival;, mDFS, median disease-free survival; mPFS, median progression-free survival; mo, months; NE, not evaluable; CRS, cytokine release syndrome

Table 3. Clinical trials of blinatumomab in relapsed/refractory B-ALL

Study	Blinatumomab design	Number of patients	Median age (years) (range)	CR rate %	MRD negativity	Overall Survival	EFS RFS DFS	CRS % NE %
TOWER, phase III, randomized	R/R B-ALL patients randomized to chemotherapy or Blinatumomab	405 (total) 134 (chemo) 271 (Blina)	41 (18-80)	16 (chemo) 34 (Blina)	In patients in CR: 48% (chemo) 76% (Blina)	4.0 months (chemo) 7.7 months (Blina)	EFS: 4.6 months (chemo) 7.7 (Blina)	CRS: 0 (chemo) 4.9 (Blina) NE: 8.3 (chemo) 9.4 (Blina)
Pooled analysis of 5 trials	R/R B-ALL	683 166(pediatric) 517(adult)	33 Pediatric 8.3 (0-17) Adult 41 (18-80)	Pediatric <50% bBMB 65% >50% bBMB 38% Adult <50% bBMB 69% >50% bBMB 34%	Pediatric <50% bBMB 51% >50% bBMB 25% Adult <50% bBMB 54% >50% bBMB 27%	Pediatric <50% bBMB 48% >50% bBMB 32% Adult <50% bBMB 33% >50% bBMB 21%	EFS Adult <50% bBMB 20% >50% bBMB 10%	CRS <50% bBMB 1% >50% bBMB 4% NE <50% bBMB 7.6% >50% bBMB 8.2%
Phase III randomized clinical trial 20120215	Open-label phase III trial in Ph- patients, high-risk, first relapse post-induction and two consolidation cycles, MRD-positive	104 Randomized to receive chemotherapy or Blinatumomab 57 Chemo 54 Blina	5.5 (1-17)	NR	54% Chemo 90% Blina	4-yr OS 27% Chemo 59% Blina	4-yr EFS 43% Chemo 69% Blina	CRS 2% (Chemo) 5.6% (Blina) NE 2% (Chemo) 3.7% (Blina)
RIALTO Phase II	R/R B-ALL patients received up to 5 cycles of Blinatumomab	110	8.5 (0.4-17)	52%	52%	14.6 months MDR- NE MDR+ 9.3 m	RFS 8 months MDR- 8 m MDR+ 2.8 m	CRS 1.8% NE 3.6%
ALL1331 Phase III	Low-risk B-ALL treated with chemo alone or chemo plus Blina	255 174 BM±EM 81 IEM	(1-30) 10 Chemo 11 Blina	NR	NR	4-yr OS Blin 90.4% Chemo 79.6% Blin 97% Chemo 72% Blina 76% Chemo 68%	4-yr DFS Blin 61% Chemo 49.5% Blin 84% Chemo 53% Blina 36% Chemo 38%	CRS 3% (Blina) NE 5% (Blina)

HSCT, allogeneic hematopoietic stem cell transplantation; OS, overall survival; NR, not reported; chemo, chemotherapy; blina, blinatumomab; CIR, cumulative incidence rate; DFS, disease-free survival; MRD, measurable residual disease; mOS, median overall survival; mDFS, median disease-free survival; mPFS, median progression-free survival; mo, months; NE, not evaluable; CRS, cytokine release syndrome; EM, extramedullary