April 17, 2025

Dear WHO Expert Committee Members,

After submission of the application in support of inclusion of blinatumomab in the WHO Essential Medicines List for Children, it came to my attention that the EMLc is only focused on recommendations for medicines for children up to the age of 13 years. As the Cancer Expert Committee highlighted in their report ("Expert Consultation meeting on cancer medicine candidates for the 2025 Model Lists of Essential Medicines; 23-24 January 2025"), blinatumomab is relevant for people with ALL of all ages:

> *"Recognizing that blinatumomab is recommended for B-ALL in most frontline regimens, and in all relapsed/refractory settings by authoritative guidelines in both children and adults, the Cancer Experts suggested that an application should be sought for the inclusion of blinatumomab for adults on the EML in the future."*

Even within pediatrics (my personal focus), management of adolescents up to age 21 years of age and on certain protocols up to age 39 years is routine for the pediatric oncology community.

The submission was developed with acknowledgement that the Expert Committee makes recommendations that have far-reaching implications for medicines adoption, particularly in low-resource settings. In that regard the request for consideration of blinatumomab was prepared with a 'childhood cancer' community in mind (not a full adult population), and with due reference to the current international childhood cancer initiatives underway. The commitment from WHO and collaborators to address the needs of children with cancer in low-resource settings has been demonstrated in multiple ways, but especially via actions in support of the Global Initiative for Childhood Cancer, and subsequently (in collaboration with St Jude Children's Research Hospital), the development and launch of the Global Platform for Access to Childhood Cancer Medicines. Both initiatives expressly or implicitly frame childhood cancer across the childhood-adolescent life span (0-19) and acknowledge ALL as the most common childhood cancer (accounting for 19% of total childhood cancer incidence worldwide).

While it is acknowledged that the adult data (which was included in the submission) is extremely compelling, it is considered most important at this time to consider the data presented as it pertains to a broadly-defined childhood cancer population, such that a recommendation (if made) is considered to be broad enough to reflect the aims of the GICC and GPACCM.

For convenience, I have extracted all the relevant data from studies in adults into the attached document (Appendix). Please consider whether this is sufficient to justify inclusion in a recommendation that supports access for adolescents, as well as younger children, to blinatumomab.

Sincerely,

Scott Howard, MD, MSc
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Deputy Director, Yeolyan Hematology Oncology Center, Yerevan, Armenia
International Development Officer, Hospital Sant Joan de Déu Barcelona, Spain

Appendix – Adolescent and Adult data included in the original submission

Blinatumomab for WHO EML inclusion for adolescents, young adults, and adults – extracted from the original submission for the WHO EMLc

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] Cure rates for B-lineage ALL 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 newly-diagnosed adolescents and adults with B-ALL, is approved for use in adolescents and adults by many stringent regulatory authorities, and is recommended by NCCN and ESMO international guidelines for frontline therapy, first relapse, and refractory disease. 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] 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] Blinatumomab is essential for children with ALL, but also for adolescents, young adults and adults.

B-lineage acute lymphoblastic leukemia affects about 100,000 adults each year. 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, such that 50% of cases occur in children, 10% in adolescents (14 to 19 years old), and 40% in adults.[35,36] The median age at diagnosis for ALL is 15 years, with 55.4% of patients diagnosed at younger than 20 years of age.[37] Prognosis also depends on access to new therapies, including blinatumomab.[36,38-41]

1. TREATMENT DETAILS

Indication

Blinatumomab has regulatory approval in many high-income countries and some middle-income countries. **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).

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%
- EMA Summary of Product Characteristics available here: https://www.ema.europa.eu/en/documents/product-information/blincyto-epar-product-information_en.pdf

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**:
  - 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.
  - 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

Before the approval of blinatumomab there had been no meaningful progress in the treatment of 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.[42]

2. 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 frontline B-ALL and relapsed/refractory disease in adults (Appendix 1). Blinatumomab is now approved and used in frontline therapy for adults, and its role in second-line, and refractory ALL is established.

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.[33,34,43,44] 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.[33,43]

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.[6,11,12,23,27,29,45] Adults aged 30 to 70 years who achieved MRD-negative ALL were randomized to receive chemotherapy with or without blinatumomab. The survival rate of the blinatumomab group 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]

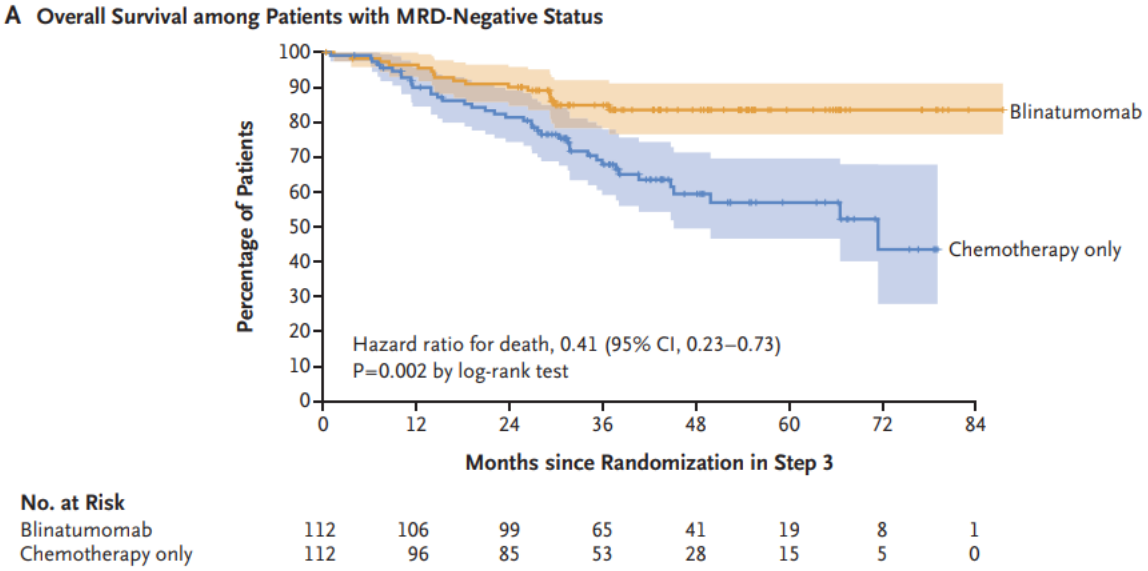

Figure 5. Overall survival of adults with MRD-negative ALL treated with blinatumomab plus chemotherapy versus chemotherapy.[23]

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]

3. SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES (IN ADULTS)

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.[46] 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, Appendix 1 Tables, and https://www.nccn.org/professionals/physician_gls/pdf/all.pdf).

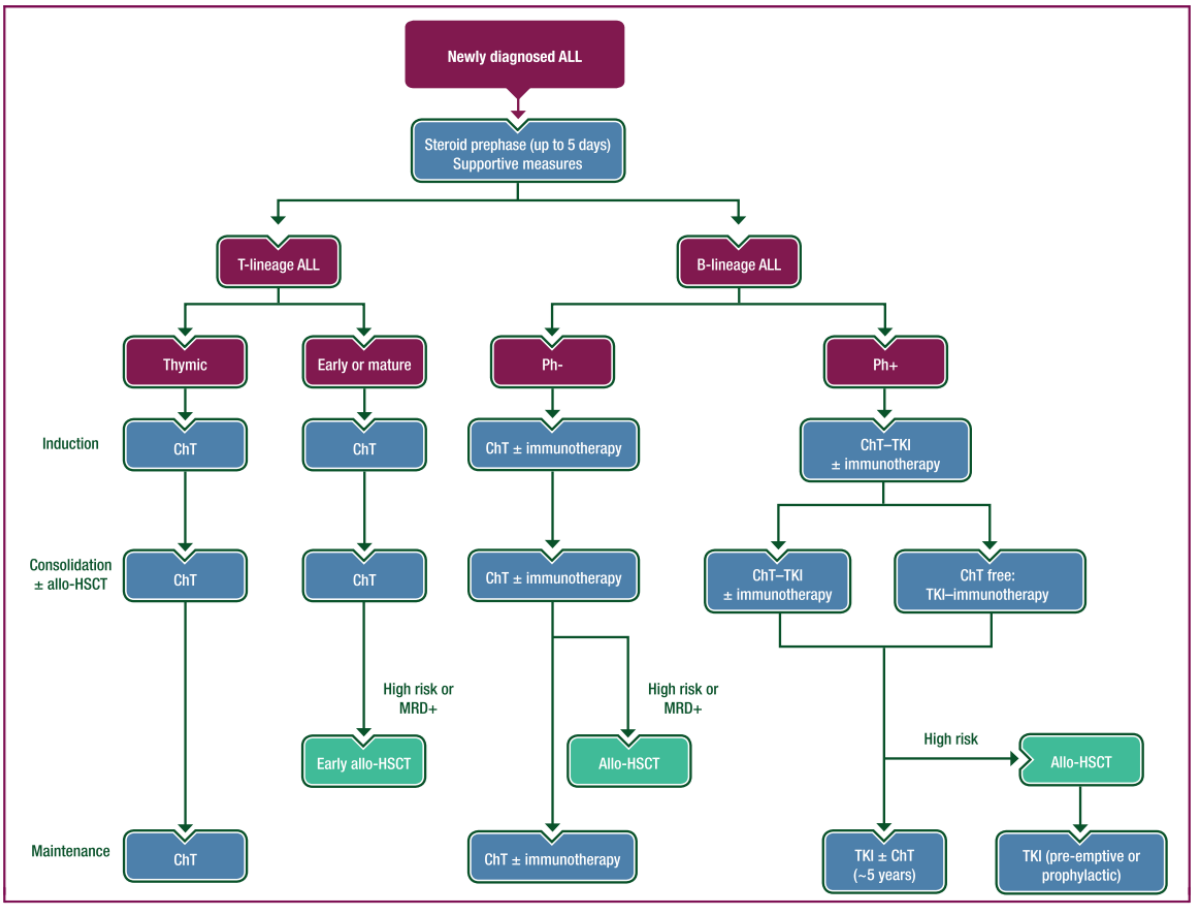

Figure 1. Treatment algorithm for newly diagnosed ALL.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
Systemic ChT should be accompanied by intrathecal ChT for prevention 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.[46]

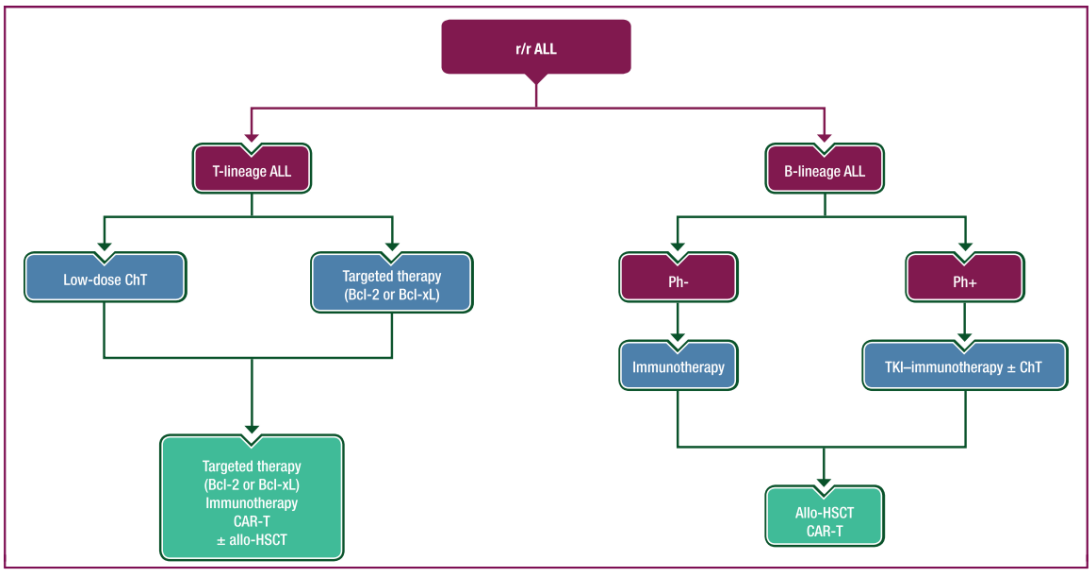

Figure 2. Treatment algorithm for r/r ALL.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments.
ALL, acute lymphoblastic leukaemia; allo-HSCT, allogeneic haematopoietic stem cell transplantation; Bcl, B-cell 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.[46]

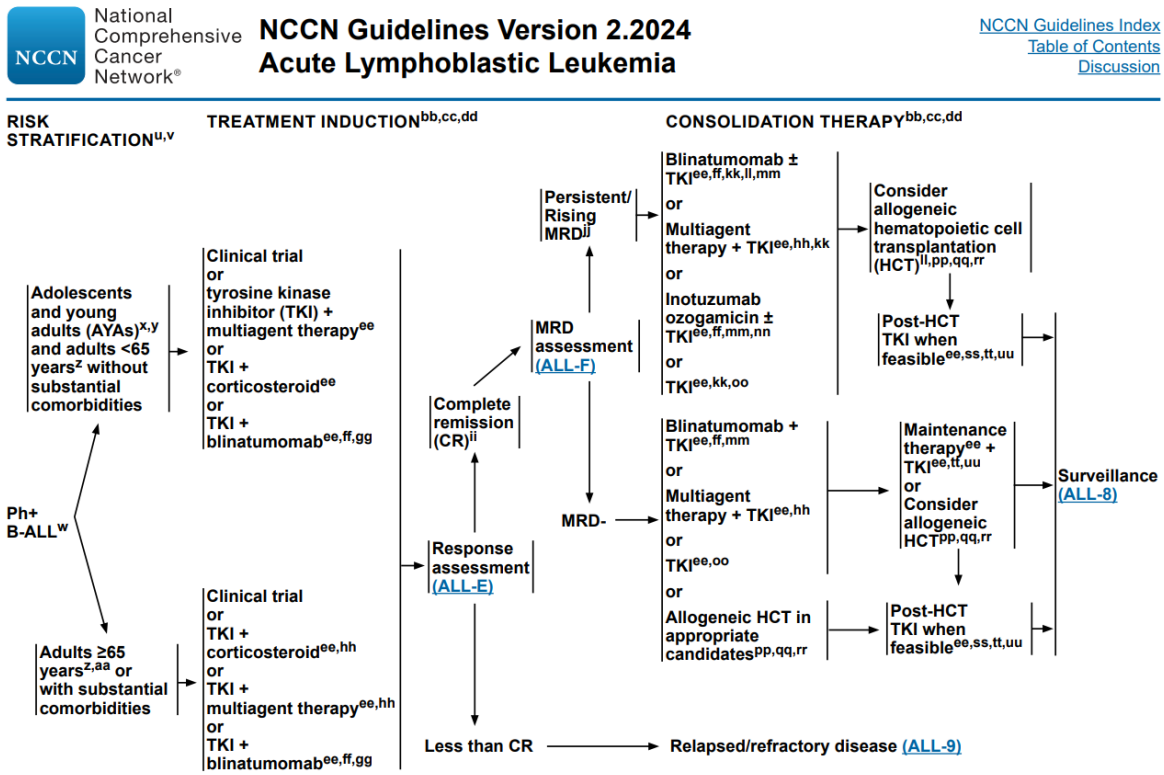

Figure 10. NCCN Guidelines for frontline acute lymphoblastic leukemia (https://www.nccn.org/professionals/physician_gls/pdf/all.pdf).

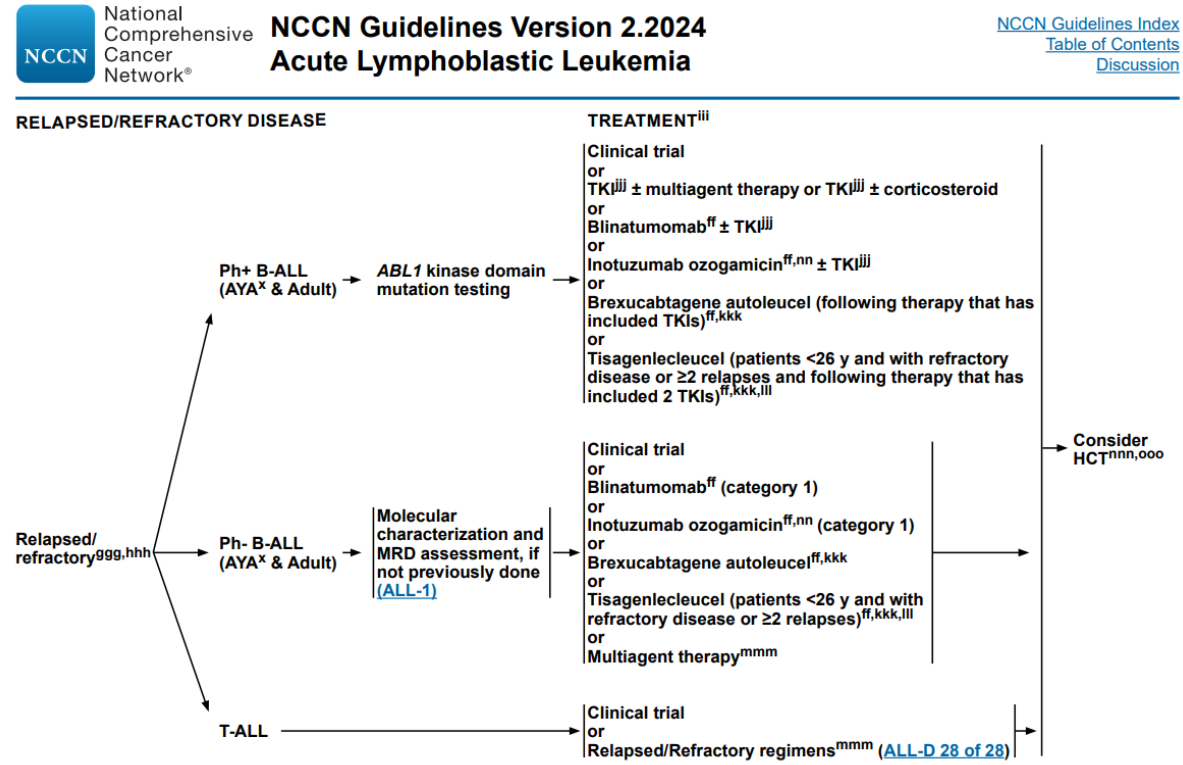

Figure 11. NCCN Guidelines for relapsed or refractory acute lymphoblastic leukemia (https://www.nccn.org/professionals/physician_gls/pdf/all.pdf).

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.[47-49] 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.[47-52] 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.[53] 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).[53]

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.[53-56]

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[53] 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.

4. 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.[57-62]

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 LMICs, which are the ones that will most benefit from an EML listing of blinatumomab. Regardless of setting, ALL can potentially be cured, and its treatment has been shown to be cost-effective in LMICs.[63]

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.[64-66] 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 ($P < 0.001$).[64] Among patients who go on to receive an alloHSCT, the burden of hospitalization is likely to be particularly high.[66,67] 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.[66] 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.

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. *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

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.

5. 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

The inclusion of blinatumomab on the WHO EML and 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 EML and EMLc.

In HICs, frontline B-ALL treated with blinatumomab plus 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.[68-78] Therefore, the benefits in the frontline setting may be even greater in LMICs than in HICs, 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 adults with B-ALL in LMIC due to it curative potential and safety profile compared to traditional chemotherapy alone. In HICs, adding blinatumomab to standard chemotherapy for frontline B-ALL improves EFS by 10-20%, and obviates the need to escalate conventional chemotherapy doses.[78-87,93]

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 population by 10-30%. Universal access to blinatumomab is expected to improve ALL survival in LMICs by approximately 20%. With successful addition to the EML and effective implementation, this pathway to accelerated and universal access will provide proof of principle for other new therapies.

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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 chemotx 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