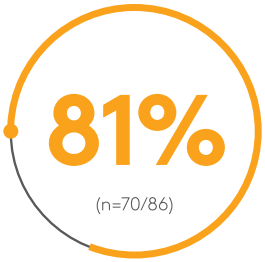
BLINCYTO® (blinatumomab) for injection
35 mcg single-dose vial

# In the BLAST study, BLINCYTO® converted most patients to MRD(–)[1,2]

**The BLAST study was a single-arm phase 2 study of BLINCYTO® treatment for adult patients with MRD(+) B-cell precursor ALL[1,2]**

Primary endpoint: complete MRD response[1,2,*]




of patients **had no detectable MRD[†,‡]**

- 74% (n=45/61) of patients in CR1 and 56% (n=14/25) in CR2 proceeded to HSCT[1]

Blinatumomab (BLINCYTO®) is the only therapeutic agent recommended by the **NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)** for patients with Ph(–) B-cell precursor ALL who test MRD(+) after induction treatment[3]

*Defined as the absence of detectable MRD, or complete MRD response, confirmed in an assay with a minimum sensitivity of 0.01% for 6 patients and ≤ 0.005% for 80 patients. Undetectable MRD was achieved by 65/80 patients with an assay sensitivity of at least 0.005%.[1]

†Assessed after 1 treatment cycle.[1]

‡Following the primary endpoint assessment, patients could receive up to 3 additional cycles of BLINCYTO®. Patients could receive HSCT at any time after cycle 1 at the investigator's discretion.[2]

ALL, acute lymphoblastic leukemia; CR1, first complete remission; CR2, second complete remission; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual disease; Ph(–), Philadelphia chromosome–negative.

## INDICATION

BLINCYTO® is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children.

This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

## IMPORTANT SAFETY INFORMATION

**WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES**

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® and treat with corticosteroids as recommended.**
- **Neurological toxicities, which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**

### Contraindications

BLINCYTO® is contraindicated in patients with a known hypersensitivity to blinatumomab or to any component of the product formulation.

Please see additional Important Safety Information, including **Boxed WARNINGS**, throughout.

# BLINCYTO® was studied in a wide range of patients[1]

| Demographics and baseline characteristics | |
|---|---|
| **Characteristics** | **BLINCYTO® (N=86)** |
| **Age** | |
| Median, years (min, max) | 43 (18, 76) |
| ≥ 65 years, n (%) | 10 (12) |
| **Males,** n (%) | 50 (58) |
| **Race,** n (%) | |
| Asian | 1 (1) |
| Other (mixed) | 0 (0) |
| White | 76 (88) |
| Unknown | 9 (11) |
| **Philadelphia chromosome disease status, n (%)** | |
| Positive | 1 (1) |
| Negative | 85 (99) |
| **Relapse history, n (%)** | |
| Patients in 1st CR | 61 (71) |
| Patients in 2nd CR | 25 (29) |
| **MRD level at baseline,† n (%)** | |
| ≥ 10% | 7 (8) |
| ≥ 1% and < 10% | 34 (40) |
| ≥ 0.1% and < 1% | 45 (52) |

- The treated population included 86 patients in first or second hematologic complete remission (CR1 or CR2). Following treatment with BLINCYTO®, 45 out of 61 (73.8%) patients in CR1 and 14 out of 25 (56.0%) patients in CR2 underwent allogeneic hematopoietic stem cell transplantation in continuous hematologic complete remission[1]

†Assessed centrally using an assay with minimum sensitivity of 0.01%.[1]
CR, complete remission; MRD, minimal residual disease.

## IMPORTANT SAFETY INFORMATION

### Warnings and Precautions

- Cytokine Release Syndrome (CRS): CRS, which may be life-threatening or fatal, occurred in 15% of patients with R/R ALL and in 7% of patients with MRD-positive ALL. The median time to onset of CRS is 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Closely monitor and advise patients to contact their healthcare professional for signs and symptoms of serious adverse events such as fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBILI), and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO® overlap with those of infusion reactions, capillary leak syndrome, and hemophagocytic histiocytosis/macrophage activation syndrome. If severe CRS occurs, interrupt BLINCYTO® until CRS resolves. Discontinue BLINCYTO® permanently if life-threatening CRS occurs. Administer corticosteroids for severe or life-threatening CRS.

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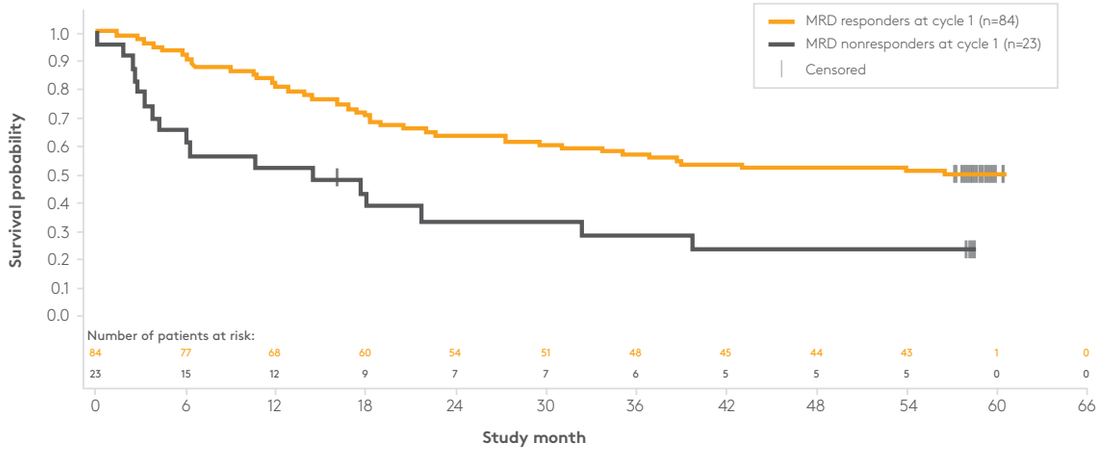
At 5 years, median OS was not reached for patients who achieved MRD(–)[4,‡]

# Median OS in patients with vs without a complete MRD response[4,§]




| Patient response | n | Median OS | 95% CI |
|---|---|---|---|
| MRD responders at cycle 1 | 84 | NR | 29.5–NE |
| MRD nonresponders at cycle 1 | 23 | 14.4 months | 3.8–32.3 |

- Median follow-up for OS was 59.8 months[4]
- An OS benefit has not been demonstrated in a randomized controlled trial
- This indication is approved under accelerated approval as a responder analysis based on MRD response rate and hematological relapse-free survival. OS in patients with MRD on BLINCYTO® vs chemotherapy is currently under evaluation as a phase 3 study[1]
- Due to the differential effect of HSCT on OS, interpretation of the results of OS cannot exclude potential confounding of HSCT[2]
- It is unknown whether achieving MRD negativity alone provides an OS benefit comparable to that of HSCT. Therefore the survival benefit cannot be isolated to BLINCYTO® treatment alone
- In the BLAST study, OS was not a primary objective and the study was not powered to assess OS efficacy[2]
- Median OS was 36.5 months (95% CI: 22.0–NE) overall‡ following treatment with BLINCYTO® and reached a plateau[4]
- Median OS was not estimable (ie, not reached) among the subsets of patients who had achieved a complete MRD response with BLINCYTO® in CR1 or who proceeded to HSCT in CCR[4]

‡OS was evaluated in patients with Ph(–) B-cell precursor ALL with less than 5% blasts at enrollment, and includes 74 patients who received HSCT while in CCR after BLINCYTO®. Analyses of OS by complete MRD response after cycle 1 included 107 patients, of which patients with no central MRD assay (n=1) or inadequate MRD test sensitivity (n=2) were excluded.[4]

§Patients in this population differ from PI population. Analysis includes additional patients: patients who achieved CRh* and CRi and/or are in CR3.[1,2,5,6]

ALL, acute lymphoblastic leukemia; CCR, continuous complete remission; CI, confidence interval; CR1, first complete remission; CR3, third complete remission; CRh*, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; HSCT, allogeneic hematopoietic stem cell transplantation; NE, not estimable; NR, not reached; OS, overall survival; Ph(–), Philadelphia chromosome–negative.

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# Majority of the most common adverse reactions (≥ 20% incidence) were mild to moderate[1,7]

| Most common adverse reactions (≥ 20%) (N=137)[1,*] | | |
|---|---|---|
| Adverse reaction | Any Grade[†] n (%) | ≥ Grade 3[†] n (%) |
| **General disorders and administration site conditions** | | |
| Pyrexia[‡] | 125 (91) | 9 (7) |
| Chills | 39 (28) | 0 (0) |
| **Infections and infestations** | | |
| Infections—pathogen unspecified | 53 (39) | 11 (8) |
| **Injury, poisoning, and procedural complications** | | |
| Infusion-related reaction[§] | 105 (77) | 7 (5) |
| **Nervous system disorders** | | |
| Headache | 54 (39) | 5 (4) |
| Tremor** | 43 (31) | 6 (4) |

- Adverse reactions of Grade 3 or higher were reported in 64% of patients[1]

*The safety of BLINCYTO® in patients with MRD(+) B-cell precursor ALL was evaluated in two single-arm clinical studies with a total of 137 patients.[1]

[†]Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, in which Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe or medically significant but not immediately life-threatening, and Grade 4 is life-threatening.[1,7]

[‡]Pyrexia includes body temperature increased and pyrexia.[1]

[§]Infusion-related reaction is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and the event lasted ≤ 2 days: cytokine release syndrome, eye swelling, hypertension, hypotension, myalgia, periorbital edema, pruritus generalized, pyrexia, and rash.[1]

**Tremor includes essential tremor, intention tremor, and tremor.[1]

ALL, acute lymphoblastic leukemia; MRD, minimal residual disease.

## IMPORTANT SAFETY INFORMATION

- Neurological Toxicities: Approximately 65% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. The median time to the first event was within the first 2 weeks of BLINCYTO® treatment and the majority of events resolved. The most common (≥ 10%) manifestations of neurological toxicity were headache and tremor. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 13% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. Monitor patients for signs or symptoms and interrupt or discontinue BLINCYTO® as outlined in the PI.

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- Infections: Approximately 25% of patients receiving BLINCYTO® in clinical trials experienced serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections, some of which were life-threatening or fatal. Administer prophylactic antibiotics and employ surveillance testing as appropriate during treatment. Monitor patients for signs or symptoms of infection and treat appropriately, including interruption or discontinuation of BLINCYTO® as needed.
- Tumor Lysis Syndrome (TLS), which may be life-threatening or fatal, has been observed. Preventive measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used during BLINCYTO® treatment. Monitor patients for signs and symptoms of TLS and interrupt or discontinue BLINCYTO® as needed to manage these events.
- Neutropenia and Febrile Neutropenia, including life-threatening cases, have been observed. Monitor appropriate laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO® infusion and interrupt BLINCYTO® if prolonged neutropenia occurs.
- Effects on Ability to Drive and Use Machines: Due to the possibility of neurological events, including seizures, patients receiving BLINCYTO® are at risk for loss of consciousness, and should be advised against driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO® is being administered.
- Elevated Liver Enzymes: Transient elevations in liver enzymes have been associated with BLINCYTO® treatment with a median time to onset of 3 days. In patients receiving BLINCYTO®, although the majority of these events were observed in the setting of CRS, some cases of elevated liver enzymes were observed outside the setting of CRS, with a median time to onset of 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients. Monitor ALT, AST, gamma-glutamyl transferase, and TBILI prior to the start of and during BLINCYTO® treatment. BLINCYTO® treatment should be interrupted if transaminases rise to > 5 times the upper limit of normal (ULN) or if TBILI rises to > 3 times ULN.
- Pancreatitis: Fatal pancreatitis has been reported in patients receiving BLINCYTO® in combination with dexamethasone in clinical trials and the post-marketing setting. Evaluate patients who develop signs and symptoms of pancreatitis and interrupt or discontinue BLINCYTO® and dexamethasone as needed.
- Leukoencephalopathy: Although the clinical significance is unknown, cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO®, especially in patients previously treated with cranial irradiation and antileukemic chemotherapy.

## IMPORTANT SAFETY INFORMATION (continued)

- Preparation and administration errors have occurred with BLINCYTO® treatment. Follow instructions for preparation (including admixing) and administration in the PI strictly to minimize medication errors (including underdose and overdose).
- Immunization: Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO® treatment, during treatment, and until immune recovery following last cycle of BLINCYTO®.
- Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative: Serious and fatal adverse reactions including "gasping syndrome," which is characterized by central nervous system depression, metabolic acidosis, and gasping respirations, can occur in neonates and infants treated with benzyl alcohol-preserved drugs including BLINCYTO® (with preservative). When prescribing BLINCYTO® (with preservative) for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO® (with preservative) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known. Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO® solution for infusion with preservative contain benzyl alcohol and are not recommended for use in any patients weighing < 22 kg.

### Adverse Reactions

- The most common adverse reactions (≥ 20%) in clinical trial experience of patients with MRD-positive B-cell precursor ALL (BLAST Study) treated with BLINCYTO® were pyrexia (91%), infusion-related reactions (77%), headache (39%), infections (pathogen unspecified [39%]), tremor (31%), and chills (28%). Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection.
- Adverse reactions that were observed more frequently (≥ 10%) in the pediatric population compared to the adults with relapsed or refractory B-cell precursor ALL were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).
- In pediatric patients less than 2 years old (infants), the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different; the only event terms reported were agitation, headache, insomnia, somnolence, and irritability. Infants also had an increased incidence of hypokalemia (50%) compared to other pediatric age cohorts (15-20%) or adults (17%).

### Dosage and Administration Guidelines

- BLINCYTO® is administered as a continuous intravenous infusion at a constant flow rate using an infusion pump which should be programmable, lockable, non-elastomeric, and have an alarm.
- It is very important that the instructions for preparation (including admixing) and administration provided in the full Prescribing Information are strictly followed to minimize medication errors (including underdose and overdose).

## INDICATION

BLINCYTO® is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children.

This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**References: 1.** BLINCYTO® (blinatumomab) prescribing information, Amgen. **2.** Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood.* 2018;131:1522-1531. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia v.1.2020. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed March 17, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **4.** Goekbuget N, Dombret H, Zugmaier G, et al. Blinatumomab for minimal residual disease (MRD) in adults with Bcell precursor acute lymphoblastic leukemia (BCP ALL): median overall survival (OS) not reached at 5 years for complete MRD responders. Presented at: 24th European Hematology Association Congress: June 16, 2019; Amsterdam, The Netherlands. Abstract S1619. **5.** Data on file, Amgen; 2018. **6.** Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia. *Blood.* 2018;131:1522-1531. Supplementary Appendix. **7.** National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed March 17, 2020.

**Please see full Prescribing Information, including Boxed WARNINGS and Medication Guide, for BLINCYTO®.**

AMGEN®



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