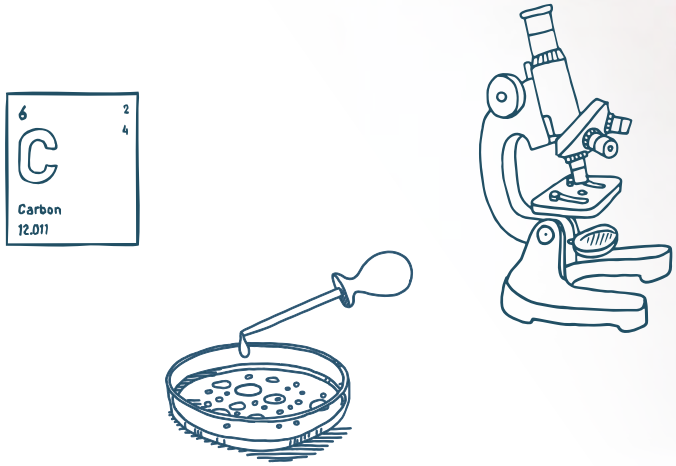
In first relapse of pediatric and AYA Ph(–) B-cell precursor ALL[1,2]

Two randomized, phase 3 studies strengthen the body of evidence for BLINCYTO®[1-3,*]



Pediatric NCCN Clinical Practice Guidelines in Oncology (**NCCN Guidelines®**) recommend blinatumomab (BLINCYTO®) as a treatment option for pediatric patients with B-cell precursor ALL in first relapse[4]

*In high-risk and/or intermediate-risk patients aged 1–27 years.[1,2]
ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; NCCN, National Comprehensive Cancer Network; Ph(–), Philadelphia chromosome–negative.

INDICATION

BLINCYTO® is indicated for the treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

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.**

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

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

Two prior studies established the response and survival benefit of BLINCYTO® in the R/R setting[5-7]

MT103-205 Study | Phase 1/2

The pivotal study of BLINCYTO® in pediatric patients with R/R B-cell precursor ALL[5]

BLINCYTO® was evaluated in an international, open-label, single-arm, phase 1/2 clinical study of patients < 18 years of age with > 25% bone marrow blasts who were primary refractory, in first relapse after full salvage induction, in second or later relapse, or in any relapse after HSCT.[5,6]

- 32.9% (n=23/70) of patients on BLINCYTO® achieved CR/CRh* within the first 2 cycles (95% CI: 22–45)[5,†]
- The most common AEs were pyrexia, anemia, nausea, and headache[6]
- BLINCYTO® was studied as a single-agent therapy via continuous intravenous infusion (4 weeks on, 2 weeks off). Phase 1 was dose-finding, and phase 2 dosing was 5/15 mcg/m²/day (5 mcg/m²/day for the first week of the first cycle followed by 15 mcg/m²/day thereafter)[6]

TOWER Study | Phase 3

The landmark study of BLINCYTO® vs chemotherapy in adult patients with Ph(–) R/R B-cell precursor ALL[5,7]

BLINCYTO® single-agent immunotherapy was compared with chemotherapy in a large, international, randomized, controlled, phase 3 study of 405 patients ≥ 18 years of age who were refractory to primary induction therapy or to last therapy, in first relapse (first remission duration < 12 months), in second or later relapse, or in any relapse after HSCT.[5,7]

- A significantly longer median OS was achieved in the BLINCYTO® arm vs chemotherapy, 7.7 months (n=271) vs 4.0 months (n=134); *P* = 0.012; HR: 0.71 (95% CI: 0.55–0.93)[5,7]
- The most common AEs included infections, pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia[5]
- BLINCYTO® was studied as single-agent therapy via continuous intravenous infusion (4 weeks on, 2 weeks off). Dosing was 9 mcg/day on days 1–7 of cycle 1 and 28 mcg/day thereafter[7]

†CR was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extramedullary disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and ANC > 1,000/microliter). CRh* was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extramedullary disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).[5]

AE, adverse event; ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; CI, confidence interval; CR, complete remission; CRh*, complete remission with partial hematologic recovery; HR, hazard ratio; HSCT, allogeneic hematopoietic stem cell transplantation; OS, overall survival; Ph(–), Philadelphia chromosome–negative; R/R, relapsed or refractory.

IMPORTANT SAFETY INFORMATION

Contraindications

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

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.

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

Two randomized, phase 3 studies‡ evaluated BLINCYTO® in high-risk and intermediate-risk pediatric and AYA patients in first relapse[1-3]

Amgen 20120215 Study | Phase 3

Study design: A randomized, controlled, open-label, phase 3 study of BLINCYTO® vs chemotherapy as post-reinduction consolidation therapy prior to HSCT in 108 pediatric patients with high-risk§ first relapse of B-cell precursor ALL.[1,8]

Primary endpoint: Event-free survival[1]

Select secondary endpoints:[1]

- Overall survival
- Incidence of relapse
- MRD response
- Incidence of AEs

COG AALL1331 Study | Phase 3

Study design: A randomized, controlled, open-label, phase 3 study of BLINCYTO® vs chemotherapy as post-reinduction consolidation therapy in 208 high-risk** and intermediate-risk†† pediatric and AYA patients in first relapse of B-cell precursor ALL.[2,3,9]

Primary endpoint: Disease-free survival[2]

Secondary endpoint: Overall survival[2]

Exploratory endpoint: MRD response[2]

Post hoc endpoint: Ability to proceed to HSCT[2]

‡Amgen 20120215 and COG AALL1331 studies are not in the USPI but were deemed to be consistent with the label for BLINCYTO® use in relapsed or refractory CD19-positive B-cell precursor ALL for pediatric and AYA populations.

§High risk was defined as very early or early iBM relapse, very early combined BM + EM relapse, or very early iEM relapse. Very early relapse was defined as < 18 months after primary diagnosis, and early relapse was defined as ≥ 18 months after primary diagnosis and < 6 months after completion of primary therapy.[10]

**Patients who had an iBM or combined BM + EM relapse < 36 months or who had an iEM relapse < 18 months were assigned to the high-risk group.[2]

††Patients who had an iBM or combined BM + EM relapse ≥ 36 months or who had an iEM relapse ≥ 18 months and MRD ≥ 0.1% at end of induction were assigned to the intermediate-risk group.[2]

AYA, adolescent and young adult; BM, bone marrow; CD, cluster of differentiation; COG, Children's Oncology Group; EM, extramedullary; iBM, isolated bone marrow; iEM, isolated extramedullary; MRD, measurable or minimal residual disease.

IMPORTANT SAFETY INFORMATION

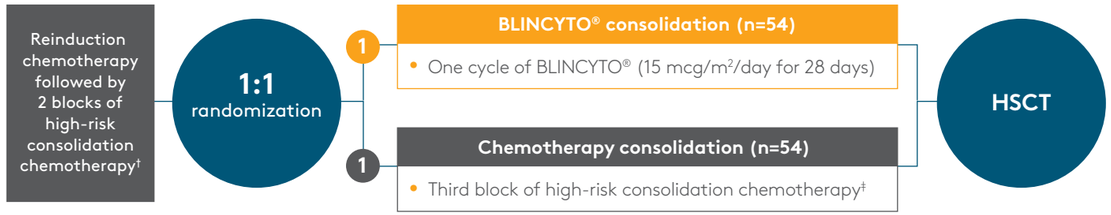
Warnings and Precautions

- 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.

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

A randomized, controlled, phase 3 study evaluated BLINCYTO® vs chemotherapy as post-reinduction consolidation therapy for pediatric patients in high-risk first relapse[1,8]

Patients > 28 days and < 18 years of age with Ph(–) B-cell precursor ALL in high-risk first relapse[1,8,*]



BLINCYTO® was studied in high-risk pediatric patients in first relapse[1]

Key inclusion criteria:[1]

- High-risk B-cell precursor ALL in first relapse
- < 5% blasts or between 5%–25% blasts in bone marrow

Key exclusion criteria:[8]

- Clinically relevant CNS pathology requiring treatment
- Evidence of current CNS (CNS2, CNS3) involvement by ALL§
- Abnormal renal or hepatic function prior to start of treatment

Primary endpoint:[1]

- Event-free survival

Select secondary endpoints:[1]

- Overall survival
- Incidence of relapse
- MRD response
- Incidence of AEs

Enrollment was closed early based on the statistically significant difference in efficacy of BLINCYTO® vs chemotherapy at a predefined efficacy threshold of 50% EFS events interim analysis[1]

*High risk was defined as very early or early iBM relapse, very early combined BM + EM relapse, or very early iEM relapse. Very early relapse was defined as < 18 months after primary diagnosis, and early relapse was defined as ≥ 18 months after primary diagnosis and < 6 months after completion of primary therapy.[10]

†Induction therapy and cycles of HC1 and HC2 chemotherapy, administered according to the IntReALL HR 2010, ALL-REZ BFM 2002, ALL R3, COOPRALL, and AIEOP ALL REC 2003 protocols.[1]

‡Third block of consolidation chemotherapy, HC3, included: dexamethasone IV/vincristine IV/daunorubicin IV/methotrexate IV/ifosfamide IV/PEG-asparaginase IV/IM.[11]

§CNS2, patients with WBC count in CSF < 5 microliter and having blasts in the CSF; CNS3, patients with WBC count in CSF ≥ 5 microliter and having blasts in the CSF.[12]

AE, adverse event; ALL, acute lymphoblastic leukemia; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; EFS, event-free survival; EM, extramedullary; HC1, high-risk consolidation block 1; HC2, high-risk consolidation block 2; HC3, high-risk consolidation block 3; HSCT, allogeneic hematopoietic stem cell transplantation; iBM, isolated bone marrow; iEM, isolated extramedullary; IM, intramuscular; IV, intravenous; MRD, measurable or minimal residual disease; Ph(–), Philadelphia chromosome-negative; WBC, white blood cell.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- 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.

Amgen 20120215 Study
Phase 3

Demographic and clinical characteristics of children at randomization in the trial of BLINCYTO® vs chemotherapy in high-risk first relapse[1]

	BLINCYTO® (n=54) n (%)	Chemotherapy (n=54) n (%)
Age at enrollment (years)		
Median (interquartile range)	6 (1–17)	5 (1–17)
Distribution		
1–9	39 (72.2)	38 (70.4)
10–18	15 (27.8)	16 (29.6)
Sex		
Boys	30 (55.6)	22 (40.7)
Girls	24 (44.4)	32 (59.3)
Genetic abnormalities at diagnosis of first high-risk relapse		
Favorable prognosis	8 (14.8)	10 (18.5)
Hyperdiploidy	6 (11.1)	6 (11.1)
t(12;21)(p13;q22)/*TEL-AML1*	2 (3.7)	4 (7.4)
Unfavorable prognosis[a]	7 (13.0)	9 (16.7)
t(v;11q23)/*KMT2A* rearranged	2 (3.7)	6 (11.1)
t(1;19)(q23;p13.3)/*E2A-PBX1*	2 (3.7)	2 (3.7)
Hypodiploidy	2 (3.7)	0 (0.0)
Prognosis undefined	5 (9.3)	6 (11.1)

[a]One patient in the blinatumomab group with *IAMP21* and one in the consolidation chemotherapy group with t(17;19)(q22;p13)/*TCF3-HLF* also carried a genetic abnormality predicting an unfavorable prognosis.[1]

IMPORTANT SAFETY INFORMATION

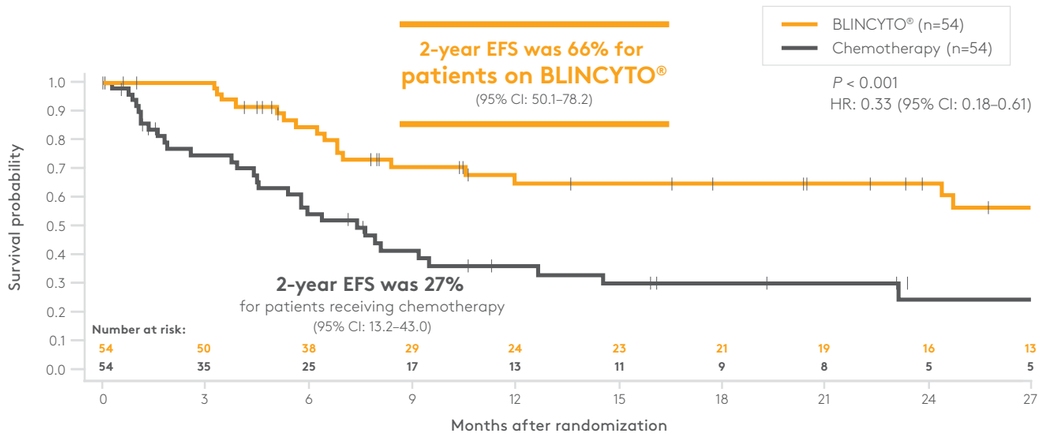
Warnings and Precautions

- 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.

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

BLINCYTO® demonstrated superior event-free survival and improved overall survival vs chemotherapy in children with B-cell precursor ALL in high-risk first relapse[1,11]

Event-free survival for BLINCYTO® vs chemotherapy[1]



Patients who did not achieve remission or died before assessment were assigned one day of event-free survival. Patients alive and event free were censored on their last assessment date.

- At the median follow-up of 22.4 months, EFS was 69% for BLINCYTO® and 43% for chemotherapy

2-year OS for BLINCYTO® vs chemotherapy[11]

81% (95% CI: 65.5–90.2)
BLINCYTO®
(n=54)

56% (95% CI: 36.9–71.0)
chemotherapy
(n=54)

- At the median follow-up of 19.5 months, the HR for OS was 0.43 (95% CI: 0.18–1.01)[1]

ALL, acute lymphoblastic leukemia; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- 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.

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

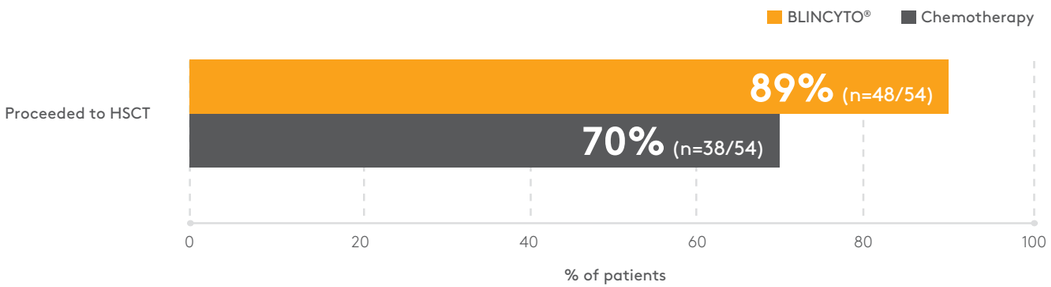
Amgen 20120215 Study
Phase 3

BLINCYTO® converted most patients to MRD(–)* and more patients proceeded to HSCT vs chemotherapy[1]

MRD response rate
90%
(n=44/49)

of patients who received BLINCYTO® achieved MRD(–)* vs **54%** (n=26/48) of patients who received chemotherapy[1]

More patients who received BLINCYTO® proceeded to HSCT while in remission[1]



- Number of patients who proceeded to HSCT while in remission was part of a post hoc analysis. Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn

*MRD < 10^{-4}, evaluated in a central laboratory by PCR.[1,8]
HSCT, allogeneic hematopoietic stem cell transplantation; MRD, measurable or minimal residual disease; PCR, polymerase chain reaction.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- 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.

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

AEs reported with > 5% incidence for patients receiving BLINCYTO® or chemotherapy[11]

	BLINCYTO® (n=54) n (%)	Chemotherapy (n=51) n (%)
Pyrexia	44 (81.5)	10 (19.6)
Nausea	22 (40.7)	9 (17.6)
Headache	19 (35.2)	9 (17.6)
Stomatitis[a]	19 (35.2)	31 (57.4)
Vomiting	16 (29.6)	11 (21.6)
Anemia	12 (22.2)	23 (45.1)
Erythema/rash[b]	12 (22.2)	5 (9.8)
Thrombocytopenia[c]	11 (20.4)	20 (39.2)
Diarrhea	11 (20.4)	9 (17.6)
Neutropenia[d]	10 (18.5)	18 (35.3)
Abdominal pain	7 (13.0)	11 (21.6)
Hypertension	7 (13.0)	4 (7.8)
Hypokalemia	7 (13.0)	5 (9.8)
Hypotension	7 (13.0)	4 (7.8)
Hypogammaglobulinemia	6 (11.1)	2 (3.9)
Pruritus	6 (11.1)	5 (9.8)
Constipation	5 (9.3)	7 (13.7)
Epistaxis	5 (9.3)	7 (13.7)
Tremor	5 (9.3)	0 (0.0)
Elevated liver enzymes[e]	5 (9.3)	12 (23.5)
Abdominal pain upper	4 (7.4)	3 (5.9)
Agitation	4 (7.4)	1 (2.0)
Cough	4 (7.4)	1 (2.0)
Fluid overload	4 (7.4)	0 (0.0)
Immunodeficiency[f]	4 (7.4)	0 (0.0)
Febrile neutropenia	3 (5.6)	13 (25.5)

[a]Adverse events for combined preferred terms stomatitis and mucosal inflammation.[11]
[b]Adverse events for combined preferred terms erythema, rash, and rash maculopapular.[11]
[c]Adverse events for combined preferred terms thrombocytopenia and platelet count decreased.[11]
[d]Adverse events for combined preferred terms neutropenia and neutrophil count decreased.[11]
[e]Alanine aminotransferase increased, alanine aminotransferase, aspartate aminotransferase increased, aspartate aminotransferase, gamma-glutamyltransferase increased, and/or hypertransaminasemia.[11]
[f]Low immunoglobulin.[11]

AE, adverse event.

Amgen 20120215 Study
Phase 3

Incidence of grade ≥ 3 AEs for BLINCYTO® vs chemotherapy[1]

	BLINCYTO® (n=54) n (%)	Chemotherapy (n=51) n (%)
Thrombocytopenia[a]	10 (18.5)	18 (35.3)
Stomatitis[b]	10 (18.5)	16 (31.4)
Neutropenia[c]	9 (16.7)	16 (31.4)
Anemia	8 (14.8)	21 (41.2)
Leukopenia[d]	4 (7.4)	4 (7.8)
Pyrexia	3 (5.6)	0 (0.0)
Elevated liver enzyme levels[e]	3 (5.6)	9 (17.6)
Aplasia	2 (3.7)	4 (7.8)
Febrile neutropenia	2 (3.7)	13 (25.5)
Hypotension	2 (3.7)	1 (2.0)
Hypokalemia	1 (1.9)	2 (3.9)
Epistaxis	0 (0.0)	3 (5.9)
Cytopenia[f]	0 (0.0)	2 (3.9)
Hepatotoxicity not otherwise specified	0 (0.0)	2 (3.9)

- Incidence of AEs higher than Grade 3 were 57% in the BLINCYTO® arm vs 82% in the chemotherapy arm[1]
- All patients receiving BLINCYTO® experienced an AE vs 96% of patients receiving chemotherapy[1]
- 24% of patients receiving BLINCYTO® and 43% of patients receiving chemotherapy experienced serious AEs. No fatal AEs were reported in either treatment arm[1]
- Grade ≥ 3 neurologic event incidence was 6% for patients receiving BLINCYTO® and 2% for patients receiving chemotherapy[11]
- No Grade ≥ 3 CRS or serious CRS events were reported in either treatment arm[1,11]
- One patient receiving BLINCYTO® and one patient receiving chemotherapy experienced CD19-negative relapse[1]

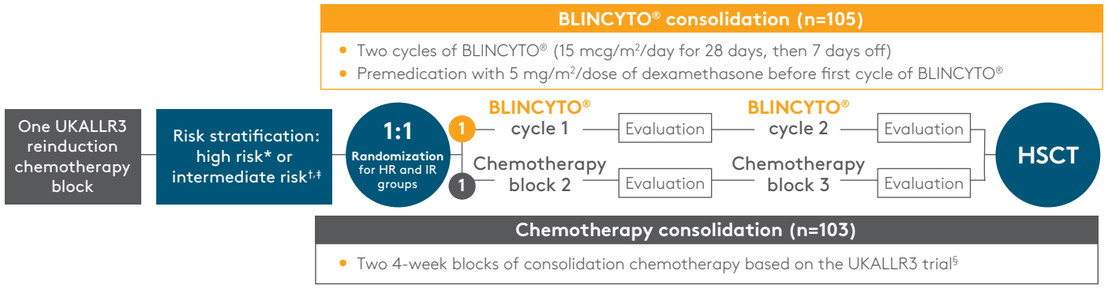
[a]Adverse events for MedDRA-preferred terms "thrombocytopenia" and "platelet count decreased."[1]
[b]Adverse events for MedDRA-preferred terms "stomatitis" and "mucosal inflammation"; occurred after completion of blinatumomab treatment and considered to be unrelated to blinatumomab treatment.[1]
[c]Adverse events for MedDRA-preferred terms "neutropenia" and "neutrophil count decreased."[1]
[d]Adverse events for MedDRA-preferred terms "leukopenia" and "white blood cell count decreased."[1]
[e]Alanine aminotransferase increased, alanine aminotransferase, aspartate aminotransferase increased, aspartate aminotransferase, gamma-glutamyltransferase increased, or hypertransaminasemia.[1]
[f]One patient had pancytopenia, and 1 had cytopenia in 2 cell lines.[1]

CD, cluster of differentiation; CRS, cytokine release syndrome.

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

Children's Oncology Group conducted a randomized, controlled, phase 3 study evaluating BLINCYTO® as post-reinduction consolidation therapy vs chemotherapy[2,3]

Patients 1–27 years of age with Ph(–) B-cell precursor ALL in high-risk or intermediate-risk first relapse[2,3,12]



Key inclusion criteria:[2]

- B-cell precursor ALL in first relapse

Key exclusion criteria:[2]

- Down syndrome
- Ph(+) B-cell precursor ALL
- Previous HSCT or BLINCYTO® treatment

Primary endpoint:[2]

- Disease-free survival

Secondary endpoint: Overall survival[2]

Exploratory endpoint: MRD response[2]

Post hoc endpoint: Ability to proceed to HSCT[2]

Enrollment was terminated early in the HR and IR groups due to encouraging efficacy and lower rates of serious toxicity in the BLINCYTO® arm vs chemotherapy, based on a recommendation from the independent Data Safety Monitoring Committee (DSMC)[2]

*Patients who had an iBM or combined BM + EM relapse < 36 months or who had an iEM relapse < 18 months were assigned to the high-risk group.[2]

†Patients who had an iBM or combined BM + EM relapse ≥ 36 months or who had an iEM relapse ≥ 18 months and MRD ≥ 0.1% at end of induction were assigned to the intermediate-risk group.[2]

‡A low-risk randomization arm was also part of the study.[2]

§UKALLR3: induction, IT methotrexate/dexamethasone oral/mitoxantrone IV or idarubicin IV/vincristine IV/pegaspargase IM; consolidation, dexamethasone oral/vincristine IV/IT methotrexate/methotrexate IV/pegaspargase IM/cyclophosphamide IV/etoposide IV; maintenance, IT methotrexate/dexamethasone oral/vincristine IV/cytarabine IV/Erwinase IM/methotrexate IV; before HSCT, fludarabine IV/cytarabine IV/liposomal daunorubicin citrate IV.[2,12,13]

ALL, acute lymphoblastic leukemia; BM, bone marrow; COG, Children's Oncology Group; EM, extramedullary; HR, high risk; HSCT, allogeneic hematopoietic stem cell transplantation; iBM, isolated bone marrow; iEM, isolated extramedullary; IM, intramuscular; IR, intermediate risk; IT, intrathecal; IV, intravenous; MRD, measurable or minimal residual disease; Ph(–), Philadelphia chromosome–negative; Ph(+), Philadelphia chromosome–positive.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- 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.

COG AALL1331 Study
Phase 3

BLINCYTO® was evaluated in high-risk and intermediate-risk pediatric and AYA patients in first relapse[2]

Baseline characteristics[2]

	BLINCYTO® (n=105) n (%)	Chemotherapy (n=103) n (%)
Age at enrollment (years) *Median (interquartile range)*	9 (6–16)	9 (5–16)
1–9	55 (52.4)	55 (53.4)
10–12	10 (9.5)	11 (10.7)
13–17	25 (23.8)	19 (18.4)
18–20	8 (7.6)	10 (9.7)
21–27	7 (6.7)	8 (7.8)
Sex		
Female	48 (45.7)	49 (47.6)
Male	57 (54.3)	54 (52.4)
Risk group assignment after reinduction		
High risk	69 (65.7)	69 (67.0)
Intermediate risk	36 (34.3)	34 (33.0)
Cytogenetic group at diagnosis		
Favorable	21 (23.3)	16 (17.6)
ETV6-RUNX1, No.	12	8
Hyperdiploid with +4, +10, No.	9	8
Unfavorable	7 (7.8)	10 (11.0)
KMT2A-rearranged, No.	7	9
Hypodiploid, No.	0	1
Other	62 (68.9)	65 (71.4)
Unknown, No.	15	12

~66% of patients were high risk

AYA, adolescent and young adult.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- 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.

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

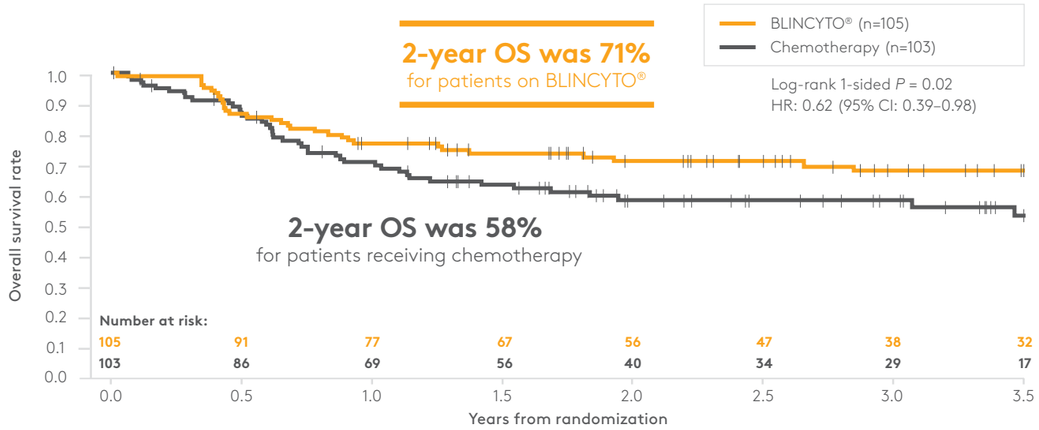
BLINCYTO® demonstrated improved disease-free survival and overall survival vs chemotherapy for high-risk and intermediate-risk pediatric and AYA patients[2,*]

2-year DFS for BLINCYTO® vs chemotherapy[2]

54%
BLINCYTO®
(n=105)

39% (HR: 0.70 [95% CI: 0.47–1.03]; *P* = 0.03)[†]
chemotherapy
(n=103)

Overall survival for BLINCYTO® vs chemotherapy[2]



- Median follow-up was 2.9 years[2]

*Intermediate risk was defined as iBM or combined BM + EM relapse ≥ 36 months or iEM relapse ≥ 18 months and MRD ≥ 0.1% at end of induction. High risk was defined as iBM or combined BM + EM relapse < 36 months or iEM relapse < 18 months.[2]
[†]The difference was not statistically significant.[2]

AYA, adolescent and young adult; BM, bone marrow; CI, confidence interval; COG, Children's Oncology Group; DFS, disease-free survival; EM, extramedullary; HR, hazard ratio; iBM, isolated bone marrow; iEM, isolated extramedullary; MRD, measurable or minimal residual disease; OS, overall survival.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- 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.

COG AALL1331 Study
Phase 3

More patients achieved an MRD response and proceeded to HSCT with BLINCYTO® vs chemotherapy[2]

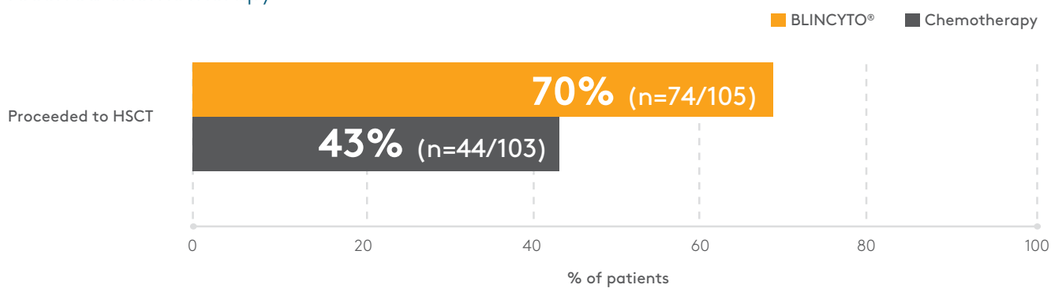
MRD response after cycle 1 of BLINCYTO® vs block 2 of chemotherapy[2,‡]

MRD[§] response rate
75%
(n=79/105)

of patients who received BLINCYTO® achieved MRD(–) vs **32%** (n=33/103) of patients who received chemotherapy**

- MRD response was an exploratory endpoint. Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn[2]

More patients who received BLINCYTO® proceeded to HSCT vs those who received chemotherapy[2]



- Number of patients who proceeded to HSCT while in remission was part of a post hoc analysis. Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn[2]

[‡]All patients received one block of chemotherapy prior to randomization. Data reflect MRD response for patients who received the first cycle of BLINCYTO® in the BLINCYTO® treatment arm vs patients who received the second block of chemotherapy in the chemotherapy treatment arm.[2,3]
[§]MRD < 0.01%, evaluated in a central laboratory by flow cytometry.[2,3]
**In this analysis, positive MRD or no MRD data are considered as not having negative MRD. The rationale for including patients with no MRD data is that the lack of MRD data was due to death, relapse, or removal from protocol therapy because of an AE or other poor response to therapy, so it is appropriate to include them as the converse of the optimal outcome of being able to submit a sample and have negative MRD.[2]

AE, adverse event; HSCT, allogeneic hematopoietic stem cell transplantation.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- 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).

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

Incidence of AEs for patients receiving BLINCYTO® vs chemotherapy[2]

	BLINCYTO® Cycle 1 (n=102)		Chemotherapy Block 2 (n=97)		BLINCYTO® Cycle 2 (n=88)		Chemotherapy Block 3 (n=62)	
Adverse event	Any Grade n (%)	Grades ≥ 3[a] n (%)	Any Grade n (%)	Grades ≥ 3[a] n (%)	Any Grade n (%)	Grades ≥ 3[a] n (%)	Any Grade n (%)	Grades ≥ 3[a] n (%)
Patients with any adverse event	99 (97)	77 (76)	89 (92)	88 (91)	81 (92)	49 (56)	55 (89)	52 (84)
Anemia	77 (76)	15 (15)	63 (65)	51 (53)	39 (44)	4 (5)	36 (58)	35 (57)
White blood cell decreased	67 (66)	25 (25)	59 (61)	55 (57)	50 (57)	13 (15)	30 (48)	30 (48)
Alanine aminotransferase increased	65 (64)	12 (12)	62 (64)	38 (39)	37 (42)	6 (7)	27 (44)	8 (13)
Fever	54 (53)	6 (6)	24 (25)	5 (5)	20 (23)	2 (2)	20 (32)	6 (10)
Neutrophil count decreased	51 (50)	34 (33)	58 (60)	57 (59)	43 (49)	25 (28)	32 (52)	31 (50)
Aspartate aminotransferase increased	49 (48)	9 (9)	51 (53)	14 (14)	26 (30)	1 (1)	24 (39)	3 (5)
Hypoalbuminemia	47 (46)	0	43 (44)	6 (6)	18 (21)	0	23 (37)	1 (2)
Lymphocyte count decreased	43 (42)	37 (36)	32 (33)	30 (31)	33 (38)	18 (21)	16 (26)	15 (24)
Platelet count decreased	43 (42)	8 (8)	63 (65)	56 (58)	18 (21)	3 (3)	37 (60)	34 (55)
Hyperglycemia	32 (31)	2 (2)	24 (25)	6 (6)	31 (35)	2 (2)	19 (31)	8 (13)
Hypocalcemia	31 (30)	2 (2)	36 (37)	6 (6)	12 (14)	0	18 (29)	0
Hypokalemia	28 (28)	7 (7)	36 (37)	19 (20)	21 (24)	2 (2)	28 (45)	14 (23)
Hypophosphatemia	18 (18)	0	18 (19)	5 (5)	8 (9)	0	7 (11)	2 (3)
Hypotension	16 (16)	1 (1)	11 (11)	7 (7)	12 (14)	3 (3)	7 (11)	4 (7)
Blood bilirubin increased	15 (15)	2 (2)	31 (32)	7 (7)	4 (5)	0	16 (26)	2 (3)
Infection[b]	15 (15)	10 (10)	48 (49)	39 (40)	20 (23)	9 (10)	42 (68)	38 (61)
Vomiting	14 (14)	0	20 (21)	2 (2)	15 (17)	1 (1)	13 (21)	4 (7)
GGT increased	12 (12)	4 (4)	9 (9)	5 (5)	5 (6)	1 (1)	3 (5)	1 (2)
Anorexia	11 (11)	4 (5)	15 (16)	12 (12)	6 (7)	2 (2)	8 (13)	4 (7)
Febrile neutropenia	6 (6)	5 (5)	43 (44)	43 (44)	0	0	28 (45)	28 (45)
Mucositis oral	4 (4)	0	44 (45)	25 (26)	2 (2)	1 (1)	16 (26)	5 (8)
Sepsis	1 (1)	1 (1)	13 (13)	13 (13)	2 (2)	2 (2)	14 (23)	14 (23)
Typhlitis	0	0	1 (1)	1 (1)	0	0	4 (7)	4 (7)

[a]Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grading ranges from 1 to 5, with 3 indicating severe or medically significant but not immediately life-threatening; 4, life-threatening and indicating urgent intervention; and 5, death. Grades were assigned by the treating physician and select serious adverse events, as defined in the protocol, are reported per federal guidelines.[2,14]

[b]Includes catheter-related, lung, skin, upper respiratory tract, and urinary tract infections.[2]

AE, adverse event; COG, Children's Oncology Group; GGT, gamma-glutamyl transferase.

COG AALL1331 Study
Phase 3

Incidence of AEs considered specific to BLINCYTO®

Select AEs for patients receiving BLINCYTO®[2]

	BLINCYTO® Cycle 1 (n=102)		BLINCYTO® Cycle 2 (n=88)	
	Any Grade n (%)	Grades ≥ 3 n (%)	Any Grade n (%)	Grades ≥ 3 n (%)
CRS	22 (22)	1 (1)	1 (1)	0
Encephalopathy	11 (11)	2 (2)	7 (8)	2 (2)
Seizure	4 (4)	1 (1)	1 (1)	0

- Incidence of most AEs decreased from cycle 1 to cycle 2 of BLINCYTO®[2]
- The majority of AEs were mild to moderate in severity[2,*]
- All AEs related to BLINCYTO® were fully reversible, and there were no deaths related to AEs[2]
- There were 5 toxic deaths during blocks 2 and 3 of the chemotherapy arm (all infections) and none in the BLINCYTO® arm. Four of the five toxic deaths were AYA patients[2]

*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.[2,14]

AYA, adolescent and young adult; CRS, cytokine release syndrome.

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

Meet Miles

Patient information

Name: Miles Taylor

Age: 14 years old

Diagnosis: High-risk Ph(–) B-cell precursor ALL in first relapse

Cytogenetics: *KMT2A* rearranged

MRD status: MRD(+) with M1 bone marrow

Treatment history:

- Experienced a bone marrow relapse after completing primary therapy 5 months ago
- Completed reinduction chemotherapy
- Remains MRD(+) following one cycle of consolidation chemotherapy

More about Miles

- Has one sibling, a younger brother
- Honor student
- Enjoys playing drums in a music school program

What are your next steps for Miles, who remains MRD(+) following one cycle of consolidation chemotherapy?

ALL, acute lymphoblastic leukemia; M1, bone marrow blasts < 5%; MRD, measurable or minimal residual disease; Ph(–), Philadelphia chromosome–negative.

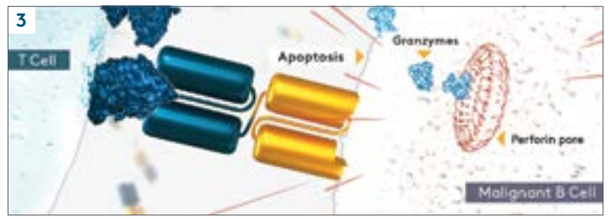
BLINCYTO® is a BiTE® immunotherapy[5,15] that binds CD3 and CD19

Target

BLINCYTO® targets malignant and benign B cells via the CD19 cell surface antigen while simultaneously engaging the patient's own T cells through the CD3 antigen.[15]

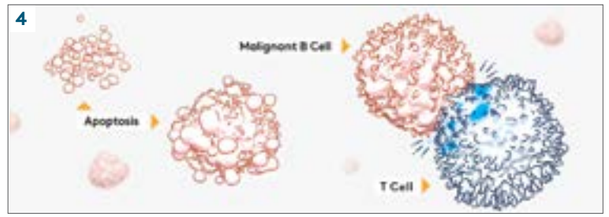
Activate

BLINCYTO® activates the T cell resulting in the formation of a synapse between the T cell and malignant B cell.[5,16]



Fight

The activated T cell then fights the malignant B cell by releasing perforin and granzymes through the perforin pore to induce apoptosis.[5,16,17]



Persist

The activated T cells persist in the blood stream, allowing for serial lysis of multiple target cells. Sustained activation of T cells results in local proliferation and enhanced polyclonal expansion of memory T cells, helping to fight cancer cells.[16,17]

BiTE, Bispecific T-cell Engager; CD, cluster of differentiation.

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.**

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

BLINCYTO® provides flexible dosing options to fit each patient's needs[5]

- Patients with R/R CD19-positive B-cell precursor ALL may receive up to 2 cycles of induction treatment, followed by 3 additional cycles of BLINCYTO® consolidation treatment (up to a total of 5 cycles)[5]
- Continued therapy of up to 4 additional cycles may be given following consolidation treatment[5]

BSA-based dosing for patients weighing < 45 kg[5]

CYCLE 1

Starting dose	Full dose	Treatment-free
Days 1–7	Days 8–28	Days 29–42
5 mcg/m²/day (not to exceed 9 mcg/day)	**15** mcg/m²/day (not to exceed 28 mcg/day)	**14-day** interval

CYCLES 2–5

Subsequent doses	Treatment-free
Days 1–28	Days 29–42
START AT 15 mcg/m²/day (not to exceed 28 mcg/day)	**14-day** interval

CYCLES 6–9

Subsequent doses	Treatment-free
Days 1–28	Days 29–84
15 mcg/m²/day (not to exceed 28 mcg/day)	**56-day** interval

Fixed dosing for patients weighing ≥ 45 kg[5]

CYCLE 1

Starting dose	Full dose	Treatment-free
Days 1–7	Days 8–28	Days 29–42
9 mcg/day	**28** mcg/day	**14-day** interval

CYCLES 2–5

Subsequent doses	Treatment-free
Days 1–28	Days 29–42
28 mcg/day	**14-day** interval

CYCLES 6–9

Subsequent doses	Treatment-free
Days 1–28	Days 29–84
28 mcg/day	**56-day** interval

Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.[5]

ALL, acute lymphoblastic leukemia; BSA, body surface area; CD, cluster of differentiation; R/R, relapsed or refractory.

BLINCYTO® offers 3 infusion duration options, allowing you to customize a treatment plan that best fits your patients' needs[5]

10 mL/hour for a duration of 24 hours

5 mL/hour for a duration of 48 hours

0.6 mL/hour for a duration of 7 days
A convenient 1-week bag is available.*

***A 7-day bag is available for patients weighing 22 kg or more. 7-day infusion bags are not recommended for use in patients weighing < 22 kg due to the addition of the benzyl alcohol preservative.[5]**

IMPORTANT SAFETY INFORMATION

- 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).
- 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.

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

Dose adjustments due to adverse events[5]

Interruption after an adverse reaction[5]

≤ 7 days Continue the same cycle of BLINCYTO®
28 days total, including days before and after interruption

> 7 days Start a new cycle of BLINCYTO®

Adverse Reaction	Grade*	Patients weighing ≥ 45 kg	Patients weighing < 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	**Interrupt** BLINCYTO®. **Administer** dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days, and taper thereafter over 4 days. When CRS is resolved, restart BLINCYTO® at 9 mcg/day, and escalate to 28 mcg/day after 7 days if the adverse reaction does not recur.	**Interrupt** BLINCYTO®. **Administer** dexamethasone 5 mg/m^2 (maximum 8 mg) every 8 hours intravenously or orally for up to 3 days, and taper thereafter over 4 days. When CRS is resolved, restart BLINCYTO® at 5 mcg/m^2/day, and escalate to 15 mcg/m^2/day after 7 days if the adverse reaction does not recur.
	Grade 4	**Discontinue** BLINCYTO® permanently. Administer dexamethasone as instructed for Grade 3 CRS.	
Neurological Toxicity†	Seizure	**Discontinue** BLINCYTO® permanently if more than one seizure occurs.	
	Grade 3	**Withhold** BLINCYTO® until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO® at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the adverse reaction does not recur. If the adverse reaction occurred at 9 mcg/day, or if the adverse reaction takes more than 7 days to resolve, discontinue BLINCYTO® permanently.	**Withhold** BLINCYTO® until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO® at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the adverse reaction does not recur. If the adverse reaction occurred at 5 mcg/m^2/day, or if the adverse reaction takes more than 7 days to resolve, discontinue BLINCYTO® permanently.
	Grade 4	**Discontinue** BLINCYTO® permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	**Withhold** BLINCYTO® until no more than Grade 1 (mild), then restart BLINCYTO® at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the adverse reaction does not recur. If the adverse reaction takes more than 14 days to resolve, discontinue BLINCYTO® permanently.	**Withhold** BLINCYTO® until no more than Grade 1 (mild), then restart BLINCYTO® at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the adverse reaction does not recur. If the adverse reaction takes more than 14 days to resolve, discontinue BLINCYTO® permanently.
	Grade 4	**Consider discontinuing** BLINCYTO® permanently.	

*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.[5,14]

†Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO® treatment. The majority of neurologic events resolved following interruption of BLINCYTO®, but some resulted in treatment discontinuation.[5]

AMGEN ASSIST 360™: SUPPORT FROM EVERY ANGLE

FROM BLINCYTO® TREATMENT INITIATION THROUGH THE CONTINUUM OF CARE, WE'RE HERE TO HELP!

RESOURCES FOR YOUR PATIENTS

SUPPORT FROM AMGEN NURSE NAVIGATOR‡

Patients are connected with the Amgen Nurse Navigator team to help them find resources that are most important to them.§ Resources include putting them in touch with programs that may help them afford their medication, such as Amgen FIRST STEP™.

REFERRALS TO DAY-TO-DAY LIVING RESOURCES§

Patients can learn about independent nonprofit organizations that may provide community resources, one-on-one counseling services, local support groups, transportation, and lodging.

RESOURCES FOR HEALTHCARE PROFESSIONALS

REIMBURSEMENT COUNSELORS

Call an Amgen Reimbursement Counselor directly or schedule a visit with a specialist at your office.

BENEFITS VERIFICATION

Submit, store, and retrieve benefit verifications for all patients currently on Amgen medications electronically and with ease from our secure system.

‡Amgen Nurse Navigators are there to support, not replace, your treatment plan and do not provide medical advice or case management services. Patients should always consult their healthcare provider regarding medical decisions or treatment concerns.

§Resources include referrals to independent nonprofit patient assistance programs. Eligibility for resources provided by independent nonprofit patient assistance programs is based on the nonprofits' criteria. Amgen has no control over these programs and provides referrals as a courtesy only.

HELP YOUR ELIGIBLE PATIENT ENROLL TODAY.

VISIT AMGENASSIST360.COM/ENROLL
OR CALL 888-4ASSIST (888-427-7478)

MONDAY TO FRIDAY, 9 AM TO 8 PM ET

AMGEN ASSIST 360™
Support, Simplified

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.

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.
- 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.
- 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.
- 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 Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (TOWER Study) treated with BLINCYTO® were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse reactions were reported in 62% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, CRS, bacterial sepsis, device related infection, and bacteremia.
- 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 relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

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

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

Phase 3 data add to the existing evidence for BLINCYTO®, a BiTE® molecule, in high-risk and intermediate-risk pediatric and AYA patients*,† with first relapse of B-cell precursor ALL[1-3,5]

Amgen 20120215 Study: BLINCYTO® vs chemotherapy[1,11]

Event-free survival at 2 years **66%** vs **27%** ($P < 0.001$)

MRD response **90%** vs **54%** achieved MRD(–)‡

Overall survival at 2 years **81%** vs **56%**

Proceeded to HSCT **89%** vs **70%** while in remission

Number of patients who proceeded to HSCT while in remission was part of a post hoc analysis. Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

COG AALL1331 Study: BLINCYTO® vs chemotherapy[2]

Disease-free survival at 2 years **54%** vs **39%** ($P = 0.03$)

MRD response **75%** vs **32%** achieved MRD(–)§,**

MRD response was an exploratory endpoint. Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

Overall survival at 2 years **71%** vs **58%**

Proceeded to HSCT **70%** vs **43%**

Number of patients who proceeded to HSCT while in remission was part of a post hoc analysis. Analysis is exploratory and has not been adjusted for multiple comparisons. No conclusions of statistical or clinical significance can be drawn.

Please see pivotal trial data on page 2.

*In the Amgen 20120215 Study, high-risk was defined as very early or early iBM relapse, very early combined BM + EM relapse, or very early iEM relapse. Very early relapse was defined as < 18 months after primary diagnosis, and early relapse was defined as ≥ 18 months after primary diagnosis and < 6 months after completion of primary therapy.[10]

†In the COG AALL1331 Study, intermediate-risk patients had iBM or combined BM + EM relapse ≥ 36 months or iEM relapse ≥ 18 months and MRD ≥ 0.1% at end of induction. High-risk patients had iBM or combined BM + EM relapse < 36 months or iEM relapse < 18 months.[2]

‡MRD < 10^{-4}, evaluated in a central laboratory by PCR.[1,8]

§All patients received one block of chemotherapy prior to randomization. Data reflect MRD response for patients who received the first cycle of BLINCYTO® in the BLINCYTO® treatment arm vs patients who received the second block of chemotherapy in the chemotherapy treatment arm.[2,3]

**In this analysis, positive MRD or no MRD data are considered as not having negative MRD. The rationale for including patients with no MRD data is that the lack of MRD data was due to death, relapse, or removal from protocol therapy because of an AE or other poor response to therapy, so it is appropriate to include them as the converse of the optimal outcome of being able to submit a sample and have negative MRD.[2]

AE, adverse event; ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; BiTE, Bispecific T-cell Engager; BM, bone marrow; COG, Children's Oncology Group; EM, extramedullary; HSCT, allogeneic hematopoietic stem cell transplantation; iBM, isolated bone marrow; iEM, isolated extramedullary; MRD, measurable or minimal residual disease; PCR, polymerase chain reaction.

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.**

References: **1.** Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325:843-854. **2.** Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325:833-842. **3.** Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325(suppl):833-842. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia v.2.2021. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed March 24, 2021. 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. **5.** BLINCYTO® (blinatumomab) prescribing information, Amgen. **6.** von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol*. 2016;34:4381-4389. **7.** Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376:836-847. **8.** Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325(suppl):843-854. **9.** ClinicalTrials.gov. Blinatumomab in treating younger patients with relapsed B-cell acute lymphoblastic leukemia. https://clinicaltrials.gov/ct2/show/NCT02101853. Accessed March 4, 2021. **10.** Data on file, Amgen; 2020. **11.** Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325(suppl 3):843-854. **12.** Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325(suppl 2):833-842. **13.** Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet*. 2010;376:2009-2017. **14.** National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_ 4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed March 18, 2021. **15.** Yuraszeck T, Kasichayanula S, Benjamin JE. Translation and clinical development of bispecifc T-cell engaging antibodies for cancer treatment. *Clin Pharmacol Ther*. 2017;101:634-645. **16.** Baeuerle PA, Kufer P, Bargou R. BiTE: Teaching antibodies to engage T-cells for cancer therapy. *Curr Opin Mol Ther*. 2009;11:22-30. **17.** Nagorsen D, Baeuerle PA. Immunomodulatory therapy of cancer with T cell-engaging BiTE antibody blinatumomab. *Exp Cell Res*. 2011;317:1255-1260.

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

AMGEN®

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