EFFICACY IN MRD+ B-ALL

BLINCYTO® WAS STUDIED IN AN INTERNATIONAL, OPEN-LABEL, MULTICENTRE, SINGLE-ARM PHASE II STUDY IN PATIENTS WITH MRD+ B-ALL (BLAST)[1]

Gökbuget N *et al. Blood* 2018;131:1522–31.

- This single-arm phase II study was the first international, multicentre trial with MRD-based patient inclusion with the endpoint of complete MRD response after the first cycle of treatment[1]

BLAST STUDY DESIGN[1]

Adults ≥18 years of age with B-ALL[1]:

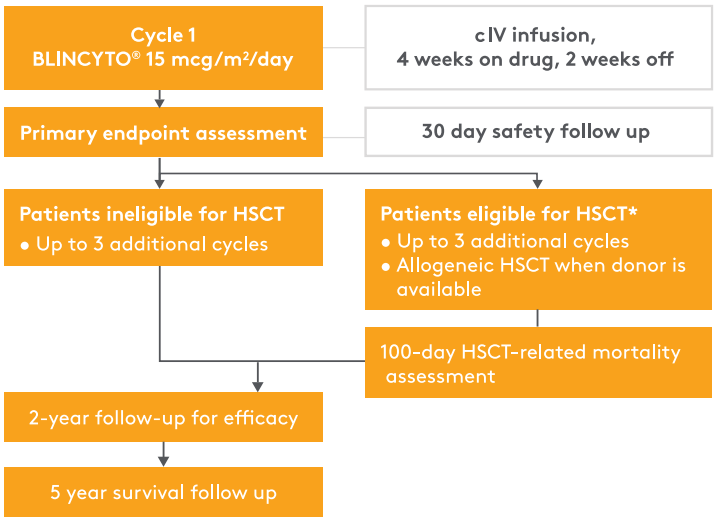
- In haematologic CR
  - <5% blasts in bone marrow
  - ANC ≥1,000/mcL
  - Platelets ≥50,000/mcL
  - Haemoglobin ≥9 g/dL
- With an MRD level of ≥10*$^{-3}$ after ≥3 intensive chemotherapy treatments

AND WITHOUT

- Prior allogeneic HSCT
- Current extramedullary disease or CNS pathology, including active ALL in the CNS
- Prior chemotherapy (within 2 weeks) or radiotherapy (within 4 weeks)

*In an assay with a minimum sensitivity of 10^{-4}.

BLAST TREATMENT OVERVIEW[1]



*HSCT was offered to eligible patients at any time after cycle 1.
Adapted from Gökbuget *et al.* 2018[1]

MRD EVALUATION[1]

- Patients were enrolled based on PCR- or flow cytometry-determined MRD level of ≥10^{-3}
- The reference lab confirmed MRD level and status at inclusion by quantitative PCR of individual clonal immunoglobulin and/or T-cell receptor gene rearrangements according to standardised methodology

STUDY ENDPOINTS[1]

Primary	• Complete MRD response rate after 1 cycle (minimum sensitivity 10^{-4})
Secondary	• OS • Haematologic RFS at 18 months • Duration of complete MRD response • Time to haematologic relapse • Incidence and severity of adverse events

A stringent definition of complete MRD response (no detectable leukaemic blasts by PCR with at least 10^{-4} sensitivity) was used.[1]

ANC: absolute neutrophil count; **CNS:** central nervous system.

Reference: 1. Gökbuget N *et al. Blood* 2018;131:1522–31.

EFFICACY IN MRD+ B-ALL

PATIENT POPULATION[1]

BLINCYTO® WAS STUDIED IN PATIENTS WITH PERSISTENT OR RECURRENT MRD AFTER A MINIMUM OF 3 BLOCKS OF INTENSIVE CHEMOTHERAPY[1]

BASELINE CHARACTERISTICS OF PATIENTS (N=116)	
Sex, n (%)	
Male	68 (59)
Median age (range), years	45 (18-76)
Age, n (%)	
≥18 to <35 years	36 (31)
≥35 to <55 years	41 (35)
≥55 to <65 years	24 (21)
≥65 years	15 (13)
Median (range) time from prior treatment, months	2 (0-55)
Relapse history, n (%)	
In first complete remission (CR1)	75 (65)
In second complete remission (CR2)	39 (34)
In third complete remission (CR3)	2 (2)
Baseline MRD levels, n (%)*	
$\geq 10^{-1}$ to <1	9 (8)
$\geq 10^{-2}$ to $<10^{-1}$	45 (39)
$\geq 10^{-3}$ to $<10^{-2}$	52 (45)

65% were in CR1

36% were in CR2 or CR3

47% had high MRD burden ($\geq 10^{-2}$)

*10 (9%) patients had MRD $<10^{-3}$, below the lower limit of quantification, or unknown MRD.

NOTE: Percentages may not add up 100% due to rounding.

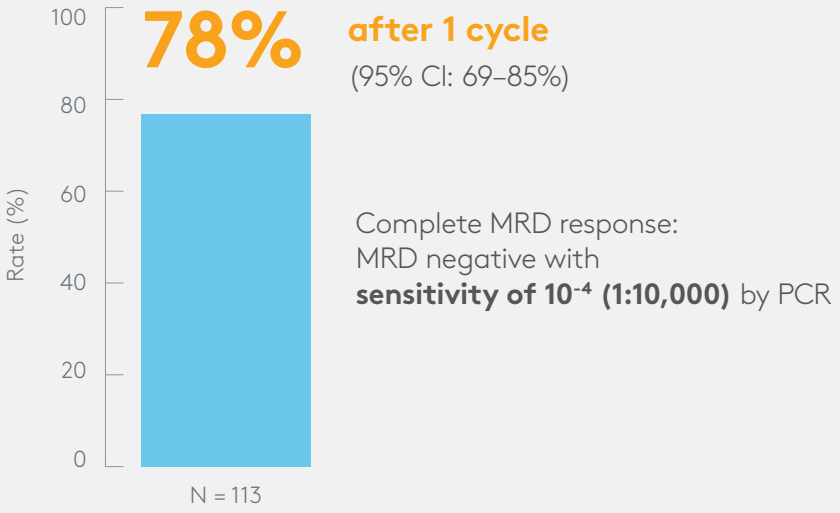
The majority of patients studied were in first complete remission (MRD positive after frontline chemotherapy).[1]

Reference: 1. Gökbuget N *et al. Blood* 2018;131:1522–31.

78% OF ADULT PATIENTS WITH MRD+ B-ALL ACHIEVED A COMPLETE MRD RESPONSE AFTER ONE CYCLE OF BLINCYTO®[1]

BLAST study: An open-label, single-arm phase II trial of 116 poor-prognosis patients in haematologic complete response (first or later) who remained MRD+ after intensive chemotherapy[1]

COMPLETE MRD RESPONSE (PRIMARY ENDPOINT FULL ANALYSIS SET)[1]



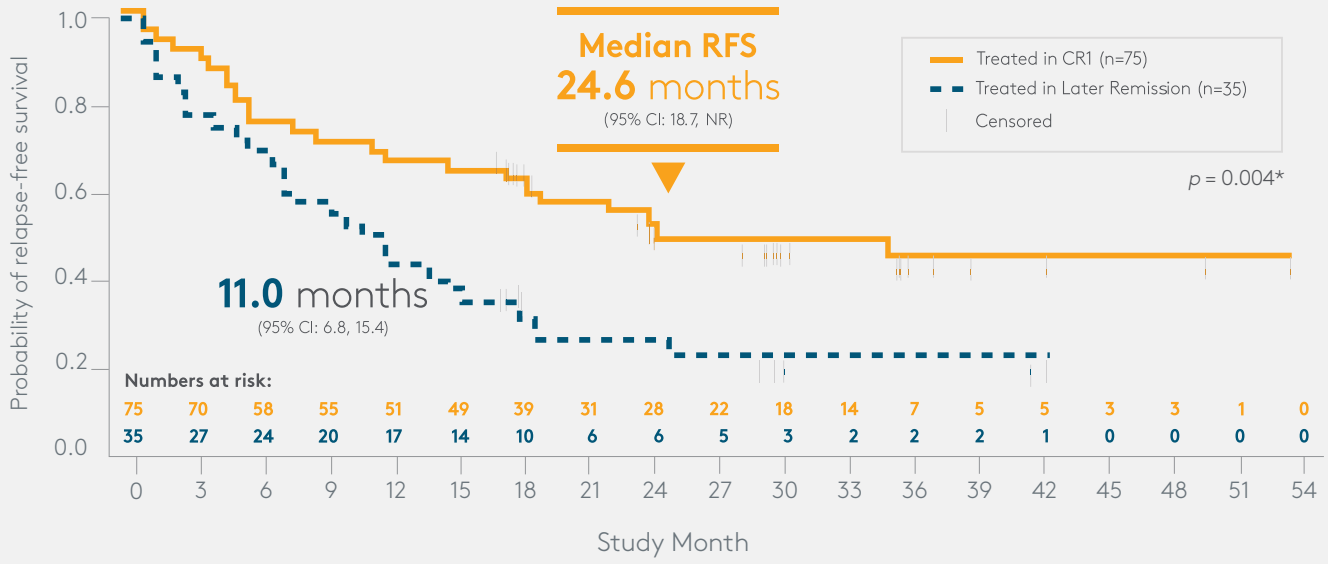
Adapted from Gökbuget *et al.* 2018.[1]

Complete MRD response was numerically higher in B-ALL patients treated with BLINCYTO® in first complete remission vs later complete remission, suggested that intervening earlier with BLINCYTO® may be beneficial[1]

BLINCTYO®-TREATED PATIENTS ACHIEVED OVER 2X LONGER RELAPSE-FREE SURVIVAL (RFS) WHEN TREATED IN CR1 VS LATER CR

(24.6 vs 11 months; unadjusted HR, 2.09; 95% CI, 1.26–3.48; p=0.004)[1,2]

RFS IN PATIENTS TREATED WITH BLINCYTO® IN CR1 VS LATER REMISSION[1]

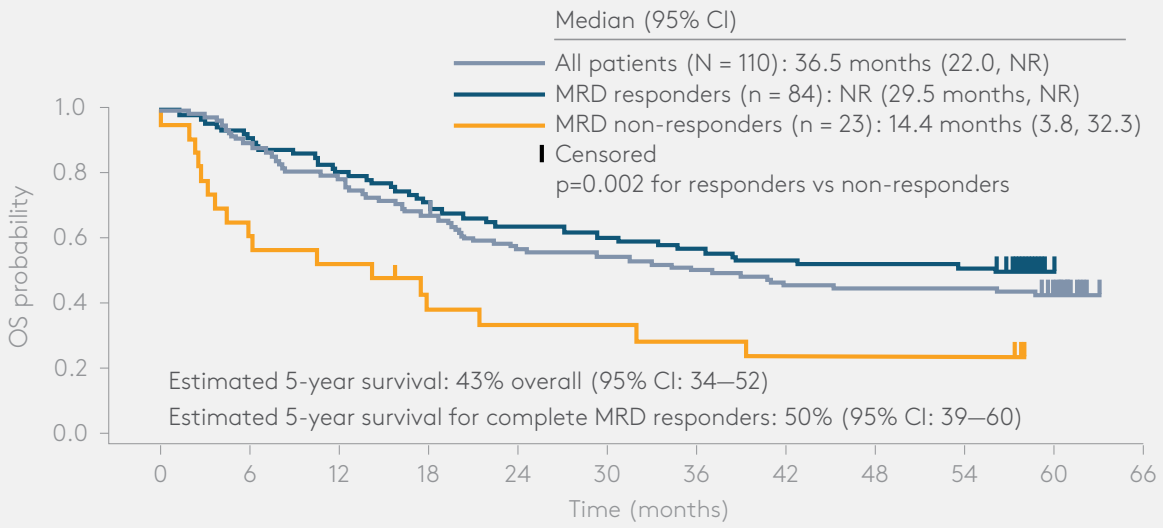


*Log Rank P value
Adapted from Gökbuget N *et al.* 2018.[1]

Reference: 1. Gökbuget N *et al. Blood* 2018;131:1522–31. **2.** BLINCYTO® (blinatumomab) Product Information. www.amgen.com.au/Blincyto.PI.

MEDIAN OVERALL SURVIVAL WAS NOT REACHED WITH 5 YEARS OF FOLLOW-UP IN BLAST STUDY PATIENTS WHO ACHIEVED COMPLETE MRD RESPONSE WITH BLINCYTO®[1,2]

OVERALL SURVIVAL BY COMPLETE MRD RESPONSE STATUS AT A MEDIAN FOLLOW-UP OF 59.8 MONTHS[1†]



Adapted from Gökbuget *et al.* 2019.[1] Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}.
[†]After cycle 1 of BLINCYTO® treatment.

Median overall survival was also not reached among:[1]

- Patients who achieved a complete MRD response with BLINCYTO® in CR1
- Patients who received HSCT in CCR after BLINCYTO®

NCCN guidelines recommend BLINCYTO® for MRD+ patients with B-cell precursor ALL in complete haematological remission[2]

Reference: 1. Gökbuget N, *et al.* Presented at: 24th Congress of the European Hematology Association; June 13-16, 2019; Amsterdam, the Netherlands. Oral Presentation S1619. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Lymphoblastic Leukemia. Version 1.2020 — January 15, 2020

SAFETY IN MRD+ B-ALL

BLINCYTO®: CHEMOTHERAPY-FREE IMMUNOTHERAPY WITH A MANAGEABLE TOLERABILITY PROFILE[1]

ALL ADVERSE EVENTS REGARDLESS OF CAUSALITY THAT OCCURRED DURING THE TREATMENT PERIOD PLUS 30 DAYS (FULL ANALYSIS SET)[1]

	ALL PATIENTS (N = 116)	
	Any Grade	Grade 3/4
Any adverse event, n (%)	**116 (100)**	**69 (60)**
Non-neurologic adverse events, worst grade ≥3 occurring in ≥3% of patients		
Pyrexia	103 (89)	9 (8)
Headache	44 (38)	4 (3)
Neutropenia	18 (16)	18 (16)
Leukopenia	8 (7)	7 (6)
Anaemia	7 (6)	5 (4)
ALT increased	7 (6)	6 (5)
Thrombocytopenia	6 (5)	5 (5)
AST increased	5 (4)	4 (4)
Any neurologic adverse event, n (%)*	**61 (53)**	**15 (13)**
Neurologic events, worst grade ≥3		
Tremor	35 (30)	6 (5)
Aphasia	15 (13)	1 (1)
Dizziness	9 (8)	1 (1)
Confused state	6 (5)	1 (1)
Encephalopathy	6 (5)	5 (5)
Seizure	3 (3)	2 (2)
Disorientation	3 (3)	1 (1)
Depressed level of consciousness	1 (1)	1 (1)
Generalised tonic-clonic seizure	1 (1)	1 (1)

Thirty-six patients (31%) had treatment interruptions because of treatment-emergent adverse events, mainly as a result of neurologic events and flu-like symptoms. Those occurring in ≥2% of patients included pyrexia (8%) and aphasia, encephalopathy, overdose, tremor, ALT increased, AST increased, and chills (3% each).

*Among all patients. Multiple events may have occurred in some patients.
Adapted from Gökbuget N *et al.* 2018.
Please see Adverse Event Management section for further details.

- Serious adverse events were managed with treatment interruption or discontinuation[1]
- Most patients who interrupted treatment due to grade3/4 neurologic events resumed BLINCYTO® treatments after the event resolved[1]

BLINCYTO® is the first and only PBS-listed therapy for the treatment of MRD+ B-ALL.[2]

AST: aspartate aminotransferase; **ALT:** alanine aminotransferase.
References: 1. Gökbuget N *et al. Blood* 2018;131:1522–31. **2.** Pharmaceutical Benefits Scheme. Available from www.pbs.gov.au. Accessed January 2020.

BLINCYTO®
(blinatumomab)

For more information on BLINCYTO® or to report any adverse events or product complaints involving BLINCYTO® please contact Australia Medical Information on 1800 803 638

PBS Information: Section 100 listed. Authority required.
Refer to PBS Schedule for full Authority listing.

***WARNING*:** *The following have occurred in patients receiving BLINCYTO®:*
• Cytokine Release Syndrome, which may be life-threatening or fatal • Neurological toxicities, which may be severe, life-threatening, or fatal • Reactivation of JC viral infection
Interrupt or discontinue BLINCYTO® as recommended if any of these adverse events occur
(See Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration).

REFER TO FULL PRODUCT INFORMATION BEFORE PRESCRIBING; AVAILABLE FROM AMGEN AUSTRALIA PTY LTD, PH: 1800 803 638 OR AT WWW.AMGEN.COM.AU/BLINCYTO.PI

For more information about BLINCYTO® or to report an adverse event or product complaints about BLINCYTO®, please contact Amgen Medical Information on 1800 803 638.

BLINCYTO® Minimum Product Information: Indication: treatment of relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukaemia (ALL); treatment of minimal residual disease (MRD) positive ALL in patients in complete haematological remission. **Contraindications:** hypersensitivity to blinatumomab, CHO-derived proteins or any excipient. **Precautions:** neurologic events; increased risk for serious infections; cytokine release syndrome; infusion reactions; tumour lysis syndrome, pancreatitis. Management of these adverse reactions may require interruption or discontinuation of treatment. Neutropenia and febrile neutropenia; elevated liver enzymes; leukoencephalopathy; medication errors – strictly follow preparation and administration instructions. Pregnancy Category: C. Use contraception during and for 48 hours after treatment. Discontinue breast-feeding during and for at least 48 hours after treatment. Do not use recommended adult fixed dose in paediatric patients. No data in patients aged less than 28 days. **Interactions:** low potential of clinically meaningful drug interaction with BLINCYTO® mediated cytokine elevation. Vaccination with live viral vaccines not recommended 2 weeks prior to or during treatment, and until recovery of B lymphocytes to normal range following last treatment cycle. **Adverse Reactions:** Common: infections, pyrexia, infusion-related reactions, headache, anaemia, febrile neutropenia, neutropenia, thrombocytopenia, oedema, increased liver enzymes, fatigue, nausea, tremor, hypokalaemia, diarrhoea, chills. See also Precautions for serious adverse reactions. **Dosage & Administration:** R/R ALL: Single cycle is 4 weeks continuous intravenous (cIV) infusion then 2 week treatment free interval. *For patients greater than or equal to 45 kg (fixed dose)*: Cycle 1 – starting dose 9 micrograms/day for days 1-7, then 28 micrograms/day for days 8-28. All other cycles 28 micrograms/day for 4 weeks. For patients less than 45 kg (body surface area based dose): Cycle 1 – starting dose 5 micrograms/m^2/day for days 1-7 (do not exceed 9 micrograms/day), then 15 micrograms/m^2/day (do not exceed 28 micrograms/day); all other cycles, 15 micrograms/m^2/day (do not exceed 28 micrograms/day). For maintenance, 28 day cIV infusion, then 56 days treatment free. Hospitalise at least first 9 days of Cycle 1 and first 2 days of Cycle 2. Supervision or hospitalisation for other cycle starts and reinitiation. Adults: premedicate with 20 mg IV dexamethasone prior to initiation of each cycle. Intrathecal chemotherapy prophylaxis recommended before and during therapy. Treat with dexamethasone (≤ 24 mg/day) if high tumour burden. Paediatrics: premedicate with dexamethasone 10 mg/m2 (not to exceed 20 mg) oral or IV 6 to 12 hours prior to start of BLINCYTO® (Cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 oral or IV within 30 minutes of start of BLINCYTO® (Cycle 1 day 1). **MRD+ ALL:** 28 day cIV infusion then 14 days treatment free, for up to 4 cycles; premedicate with prednisone 100 mg IV or equivalent 1 hour prior to start of BLINCYTO® each cycle; hospitalise first 3 days Cycle 1 and first 2 days Cycle 2, supervise/hospital for subsequent cycle starts and reinitiation – see full PI. R/R & MRD+ ALL – Interrupt BLINCYTO® if grade 3 neurological events, Cytokine Release Syndrome or other clinically relevant adverse reactions occur see full PI.

BLINCYTO® (blinatumomab)

AMGEN®