BLINCYTO®
(blinatumomab)

RE-THINK WHAT'S POSSIBLE.

With BLINCYTO® survival data in MRD+ and R/R B-ALL.[1-8]

PHASE III

The TOWER STUDY: Ph- R/R B-ALL[2-4]

A phase III trial comparing BLINCYTO® versus SOC chemotherapy in 405 difficult-to-treat adult patients with Ph- R/R B-ALL, including those with early first relapse, post-transplant relapse, second or later relapse, and primary refractory disease.

PHASE I/II

The BLAST Study: MRD+ B-ALL[5,6]

A phase II trial of 116 adult patients in haematologic CR (first or later) who remained MRD+ after intensive chemotherapy.

Paediatric R/R B-ALL[7]

A phase I/II trial in heavily pre-treated paediatric R/R B-ALL patients (n=70 received the recommended dose), including those with relapse after HSCT, with refractory disease, and in second or later relapse.

The ALCANTARA Study: Ph+ R/R B-ALL[8]

A phase II trial of 45 adult patients with Ph+ R/R B-ALL who progressed after or were refractory or intolerant to second- or later-generation TKI therapy.

B-ALL: B-cell precursor acute lymphoblastic leukaemia; CR: complete remission; HSCT: haematopoietic stem cell transplantation; MRD: minimal residual disease; Ph: Philadelphia chromosome; R/R: relapsed or refractory; SOC: standard of care; TKI: tyrosine kinase inhibitor.

PHASE III

Ph- R/R B-ALL

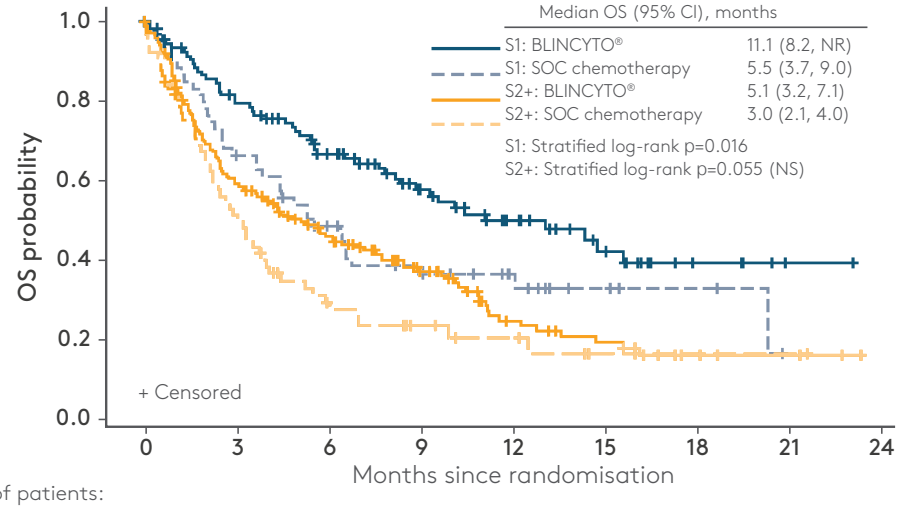
In the landmark TOWER trial, **BLINCYTO® demonstrated superior OS versus SOC chemotherapy in patients with Ph- R/R B-ALL[2]**

About this study: The TOWER Study in Ph- R/R B-ALL[2]

The TOWER Study was a phase III, randomised, open-label trial comparing BLINCYTO® versus SOC chemotherapy in 405 difficult-to-treat adult patients with Ph- R/R B-ALL, including those with early first relapse, post-transplant relapse, second or later relapse, and primary refractory disease. Patients were randomised 2:1 to receive BLINCYTO® (n = 271) or treatment with investigator choice of one of four protocol-defined SOC chemotherapy regimens (n=134). The primary endpoint was OS.

- **Median OS was 7.7 months (95% CI: 5.6–9.6) with BLINCYTO®, versus 4.0 months (95% CI: 2.9–5.3) with SOC chemotherapy (p=0.01)[2]**

OS AMONG PATIENTS TREATED AT FIRST (S1) OR SECOND OR LATER (S2+) SALVAGE [2,3]



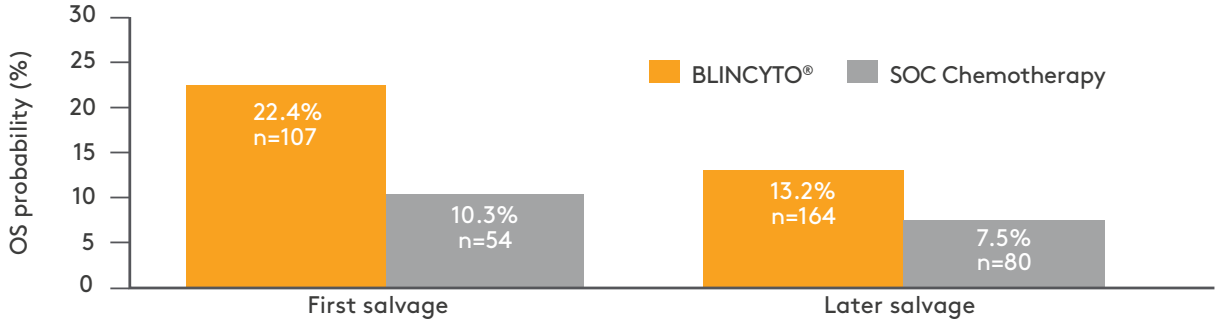
No of patients:									
S1: BLINCYTO®	104	80	59	39	26	14	5	1	0
S1: SOC chemotherapy	63	39	26	18	11	5	3	0	
S2+: BLINCYTO®	167	96	65	40	19	13	4	3	0
S2+: SOC chemotherapy	71	32	15	9	6	2	1	1	0

- Early use of BLINCYTO® (as first salvage) more than doubled OS compared with SOC chemotherapy (11.1 vs 5.5 months, p=0.016)[3]

Adapted from: Dombret *et al.* 2019.[3]
Analysis of salvage status adjudicated separately from prior randomisation status.
NR: not reached; NS: not significant.

Improved median OS among patients who received BLINCYTO® versus SOC chemotherapy and who had no prior salvage treatment supports early use of BLINCYTO® in adults with Ph- R/R B-ALL.[2,3]

PREDICTED 5-YEAR OS VERSUS SOC CHEMOTHERAPY[4]



†A partitioned survival model with a lifetime (50-year) time horizon was used to estimate expected life-years and quality-adjusted life-years gained for BLINCYTO® versus SOC chemotherapy in subgroups of patients who had not previously received salvage therapy versus those who had received at least one prior line of salvage therapy (i.e. early versus late treatment).

Adapted from Severin *et al.* 2018.[4]

In an analysis† estimating long-term survival outcomes in the TOWER trial, patients treated with BLINCYTO® had a higher probability of 5-year OS versus SOC chemotherapy, regardless of use in first or later salvage (p values not reported).[4]

OS: overall survival.

PHASE II

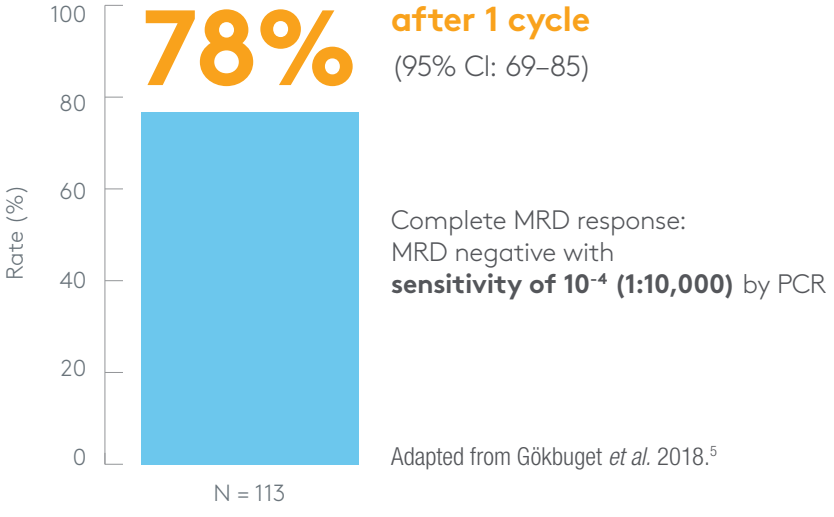
MRD+ B-ALL

In the BLAST study, **78% of adult patients with MRD+ B-ALL achieved a complete MRD response after one cycle of BLINCYTO®[5]**

About this study: The BLAST Study in MRD+ B-ALL[5]

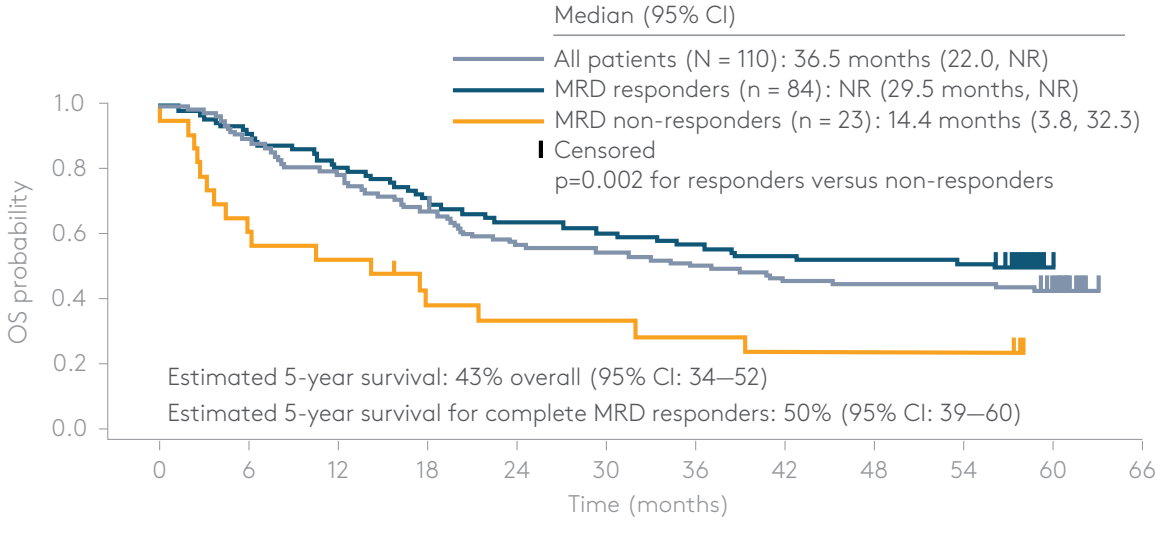
The BLAST study was an international, open-label, multicentre, single-arm phase II study in 116 patients with MRD+ B-ALL. Patients were in haematologic complete response (first or later) and had remained MRD+ after intensive chemotherapy. The primary endpoint was complete MRD response rate after 1 cycle (minimum sensitivity 10^{-4}).

COMPLETE MRD RESPONSE (PRIMARY ENDPOINT FULL ANALYSIS SET)[5]



Complete MRD response was numerically higher in B-ALL patients treated with BLINCYTO® in first versus later CR, suggesting that intervening earlier with BLINCYTO® may be beneficial.[5]

OS BY COMPLETE MOLECULAR RESPONSE STATUS AT A MEDIAN FOLLOW-UP OF 59.8 MONTHS AFTER CYCLE 1 OF BLINCYTO® TREATMENT[6]



Adapted from Gökbuget *et al.* 2019.[6]
Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}.

Long-term BLAST follow-up results demonstrate the durable OS benefit associated with BLINCYTO® in adults with MRD+ B-ALL, particularly in those who achieve complete molecular response.[6]

NR: not reached.

PHASE II

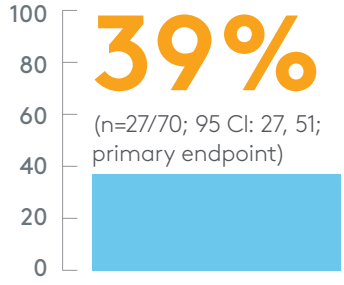
PAEDIATRIC R/R B-ALL

In an open-label, multicentre, single-arm phase I/II study of BLINCYTO® in heavily pre-treated paediatric patients, **39% of patients achieved CR within the first 2 treatment cycles[7]**

About this study: Paediatric R/R B-ALL[7]

BLINCYTO® use was investigated in an open-label, multicentre, single-arm phase I/II trial in heavily pre-treated paediatric R/R B-ALL patients (n = 70 received the recommended dose), including those with relapse after HSCT, with refractory disease, and in second or later relapse. The primary endpoint was maximum tolerated dose (Phase I) and rate of CR within the first 2 cycles of BLINCYTO® treatment (Phase II).

39% OF PAEDIATRIC PATIENTS TREATED WITH BLINCYTO® ACHIEVED CR WITHIN THE FIRST TWO TREATMENT CYCLES[7]



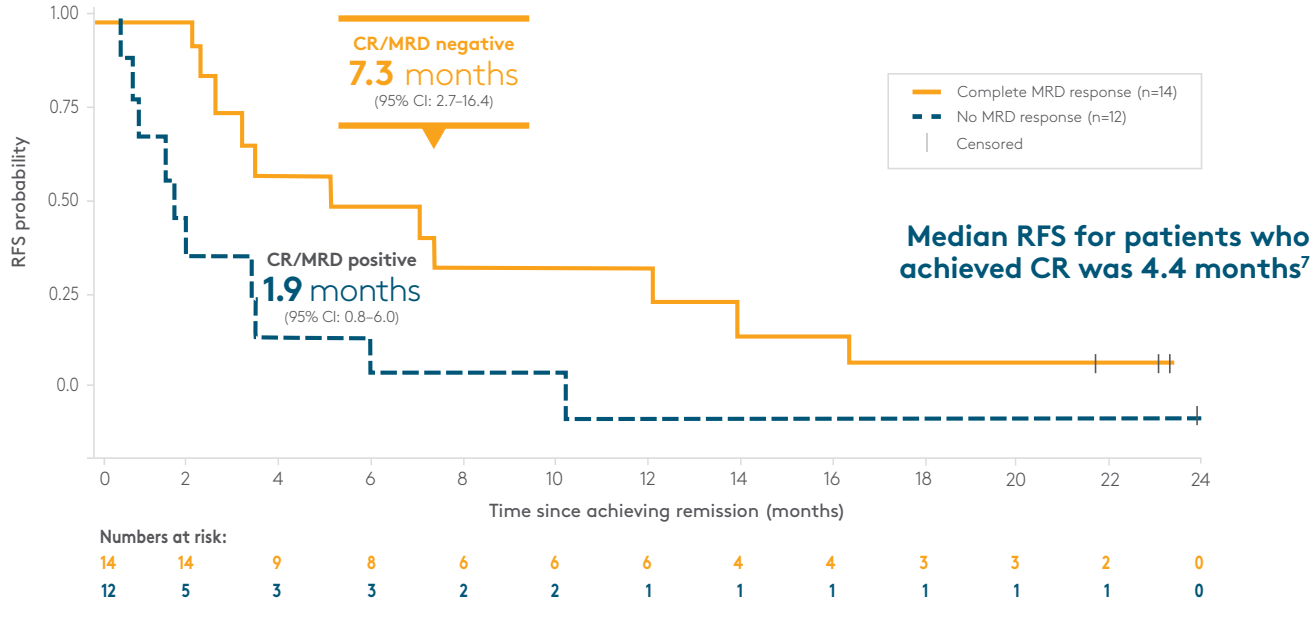
74% achieved CR in Cycle 1 (n=20/27); 26% in Cycle 2 (n=7/27).

CR defined as no evidence of circulating blasts or extramedullary disease and <5% of bleeds in bone marrow (M1). Patients in the study were considered very high risk on the basis of baseline tumour load, multiple prior relapses, short interval between latest treatment and start of BLINCYTO®, previous allogeneic HSCT, and/or cytogenetic profile.

Adapted from von Stackelberg *et al*, 2016.[7]

- **52%** of patients who achieved a CR were **MRD negative** (95% CI: 32 –71)[7]
- **48%** of patients who achieved a CR went on to receive **allogeneic HSCT[7]**

MEDIAN RFS BASED ON MRD STATUS OF PATIENTS IN CR[7]



Median RFS for patients who achieved CR was 4.4 months[7]

Adapted from von Stackelberg *et al.* 2016.[7]

Median RFS with BLINCYTO® was 7.3 months in MRD- patients versus 1.9 months for MRD+ patients.[7]

RFS: relapse-free survival.

PHASE II

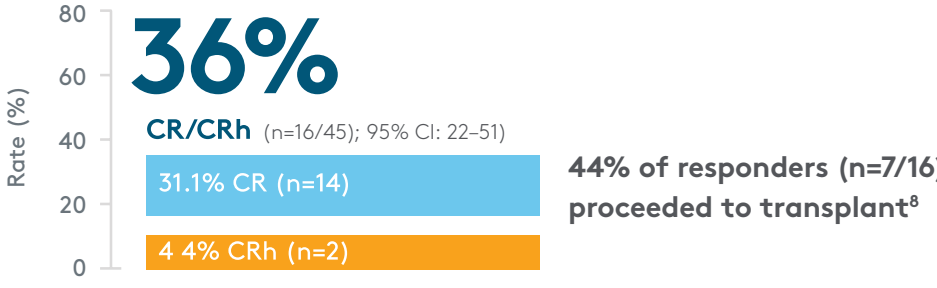
Ph+ R/R B-ALL

BLINCYTO® induced CR/CRh in more than one third of Ph+ R/R B-ALL patients in the ALCANTARA study[8]

About this study: The ALCANTARA Study in Ph+ R/R B-ALL[8]

The ALCANTARA Study was an open-label, multicentre, single-arm phase II trial of 45 patients with Ph+ R/R B-ALL who progressed after or were refractory or intolerant to second- or later-generation TKI therapy. The primary endpoint was CR or CRh during the first two cycles.

CR/CRh RATE WITHIN THE FIRST TWO BLINCYTO® TREATMENT CYCLES[8]



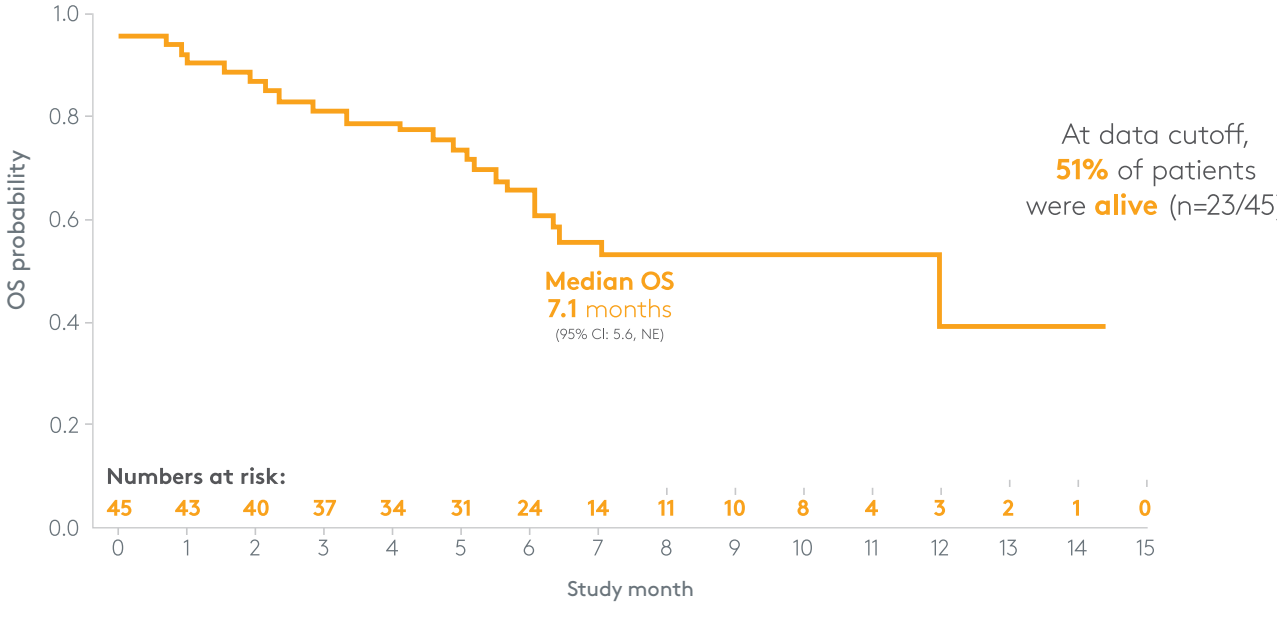
44% of responders (n=7/16) proceeded to transplant[8]

Two additional patients achieved CRh. Complete MRD response (MRD negativity) was defined as no RT-PCR amplification of *BCR-ABL1* at a sensitivity of 10^{-5}.
Adapted from Martinelli *et al.* 2017.[8]

The majority of patients who achieved CR/CRh with BLINCYTO® had a complete MRD response: 88% (n = 14/16) were MRD negative within 2 treatment cycles.[8]

Haematologic and molecular responses were independent of mutational status, including presence of the T315I mutation.[8]

MEDIAN OS FOR ALL PATIENTS TREATED WITH BLINCYTO® WAS 7.1 MONTHS[8]



Adapted from Martinelli *et al.* 2017.[8]

Median RFS among patients who achieved CR/CRh was 6.7 months (95% CI: 4.4 – NE).[8]

CRh: CR with partial haematologic recovery; NE: not evaulable.

BLINCYTO® SAFETY PROFILE

BLINCYTO®: Chemotherapy-free immunotherapy with a generally manageable tolerability profile[1]

- In the randomised phase III clinical study in Ph- R/R B-ALL patients:[1]
  - **The most common adverse reactions with BLINCYTO® were:** infections (64.0%), pyrexia (60.3%), infusion-related reactions (34.1%), headache (28.8%), anaemia (27.3%), febrile neutropenia (24.0%), thrombocytopenia (24.0%), neutropenia (23.2%), oedema (17.2%), and increased liver enzymes (16.9%).
  - **The most serious adverse reactions with BLINCYTO® were:** infections (28.1%), neutropenia/febrile neutropenia (10.5%), neurologic events (6.7%), cytokine release syndrome (3.7%), and tumour lysis syndrome (1.1%).
- The adverse reaction profile in **BLINCYTO®-treated Ph+ R/R B-ALL patients and MRD+ B-ALL** adult patients was similar in type to those seen in the randomised phase III clinical study in Ph- R/R B-ALL patients.[1]
- The adverse reactions in **BLINCYTO®-treated paediatric patients** were similar in type to those seen in adult patients. Adverse reactions that were observed more frequently (≥10% difference) in the paediatric population compared to the adult population were: anaemia, thrombocytopenia, leukopenia, pyrexia, infusion-related reaction, hypertension and weight increase[1].

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

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/m^2 (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.

References: 1. BLINCYTO® (blinatumomab) Approved Product Information. Available at: www.amgen.com.au/Blincyto.PI. **2.** Kantarjian H *et al. N Engl J Med.* 2017;376:836–47. **3.** Dombret H *et al. Leuk Lymphoma* 2019;60:2214–22. **4.** Severin F *et al.* Poster presented at: 23rd Annual Meeting of the European Hematology Association; June 14-17, 2018; Stockholm, Sweden. Abstract #PS1427. **5.** Gökbuget N *et al. Blood.* 2018;131:1522–31. **6.** Gökbuget N *et al.* Presented at: 24th Congress of the European Hematology Association; June 13–16, 2019; Amsterdam, the Netherlands. Oral Presentation S1619. **7.** von Stackelberg A *et al. J Clin Oncol* 2016;34:4381–9. **8.** Martinelli G *et al. J Clin Oncol* 2017;35:1795–802.

BLINCYTO® (blinatumomab)

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