Blinatumomab (Blincyto®) for the treatment of patients with Philadelphia chromosome positive B-precursor acute lymphoblastic leukaemia (ALL)

General information

Drug description [1]	Indication [2]
Blinatumomab is a bispecific T-cell–engaging antibody construct that binds simultaneously to CD3-positive cytotoxic T cells and CD19-positive B cells and allows endogenous T cells to recognize and eliminate CD19-positive ALL blasts.	Blinatumomab is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-precursor ALL. Patients with Philadelphia chromosome positive (Ph+) B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.

Current treatment [3]

- ❖ TKIs are used to treat Ph+ ALL by inhibiting the BCR-ABL protein from sending signals that cause leukaemia cells to form.
- ❖ TKIs are added to a combination chemotherapy regimen; the following TKIs are available to treat Ph+ ALL:
  - Imatinib is approved for adult patients with relapsed or refractory Ph+ ALL and paediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy
  - Dasatinib is approved for:
    - Adults with Ph+ ALL with resistance or intolerance to prior therapy
    - Paediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.
  - Ponatinib is approved for the treatment of adult patients with T315I-positive Ph+ ALL.

Regulatory status

EMA [2]	FDA
Approval status for this indication: On 15 October 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Blincyto®. The CHMP adopted an extension to an existing indication as follows: ❖ Blinatumomab is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-precursor ALL. Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 TKIs and have no alternative treatment options. **Other indications**: ❖ Blinatumomab is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. ❖ Blinatumomab is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation. ✓ **Orphan status** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: not approved **Other indications**: Blinatumomab is indicated for the treatment of adults and children with: ❖ B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1% (accelerated approval) ❖ Relapsed or refractory B-cell precursor ALL [4].

Costs [5]

Blincyto® powder for concentrate for solution for infusion 38.5 µg = € 2,826.08 (ex-factory price)

Posology [6]

- ❖ For the treatment of relapsed or refractory B-precursor ALL, **hospitalisation** is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle.
- ❖ In patients with a history or presence of **clinically relevant central nervous system (CNS) pathology,** hospitalisation is recommended at a minimum for the first 14 days of the first cycle. In the second cycle, hospitalisation is recommended at a minimum for 2 days, and clinical judgment should be based on tolerance to blinatumomab in the first cycle. Caution should be exercised as cases of late occurrence of first neurological events have been observed.
- ❖ For all **subsequent cycle starts and reinitiation** (e.g. if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.
- ❖ **Premedication and additional medication recommendations:**
  - In adult patients, dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of blinatumomab therapy.

- In paediatric patients, dexamethasone 10 mg/m² (not to exceed 20 mg) should be administered orally or intravenously 6 to 12 hours prior to the start of blinatumomab (cycle 1, day 1). This should be followed by dexamethasone 5 mg/m² orally or intravenously within 30 minutes prior to the start of blinatumomab (cycle 1, day 1).
- Anti-pyretic use (e.g. paracetamol) is recommended to reduce pyrexia during the first 48 hours of each treatment cycle.
- Intrathecal chemotherapy prophylaxis is recommended before and during blinatumomab therapy to prevent CNS ALL relapse.

❖ **Pre-phase treatment for patients with high tumour burden:**

- For patients with ≥ 50% leukaemic blasts in bone marrow or > 15,000/microlitre peripheral blood leukaemic blast counts treat with dexamethasone (not to exceed 24 mg/day).

Warning [7]

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

Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving blinatumomab. Interrupt or discontinue blinatumomab as recommended.

Study characteristics

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
NCT02000427, ALCANTARA	45 (Blinatumomab Study) 55 (external SOC[1])	Blinatumomab IV at a dose of 9 µg/d in week 1 of cycle 1 and at a dose of 28 µg/d thereafter	SOC chemotherapy	OS, CR/CRh	open-label, single-arm, multicentre, phase 2 clinical trial	-	Amgen, Inc.	Link

Efficacy (I vs. C)

CR/CRh rate (primary analysis data): 36% after 2 cycles, with 14 patients (31%) achieving CR and 2 patients (4%) achieving CRh.

Median OS was 7.1 months (95% CI, 5.6 to not estimable.[3]

The Bayesian-augmented (80% power) odds ratio estimate for **CR/CRh:** was 1.70 (95% CrI, 0.94-2.94) and favoured blinatumomab over the external SOC.

Corresponding CR/CRh rate estimates for the blinatumomab and external SOC cohorts: 36% (95% CrI, 28%-46%) and 25% (95% CrI, 17%-34%), respectively.

Non-Bayesian (65% power) odds ratio: 1.54 (95% CI, 0.61-3.89)

The Bayesian-augmented (80% power) HR comparing the OS of blinatumomab with the OS of the external SOC: 0.77 (95% CrI, 0.61-0.96) suggesting a statistically significant 23% reduction in the risk of death associated with blinatumomab in comparison with the external SOC.

Partial remission: 4.4% (95% CI, 0.5-15.1)

Complete MRD response[4]: 40.0% (95% CI, 25.7-55.7)

Median relapse[5]-free survival for CR/CRh: 6.7 months (95% CI, 4.4.-NE)

Safety (I vs. C)[2]

Grade 3 AEs: n=33 (73%)

Grade 4 AEs: n=16 (36%)

Treatment-emergent grade ≥3 AEs: n=37 (82%)

Treatment-emergent grade ≥3 AEs that were considered possibly related to blinatumomab (per investigator's assessment: n=20 (44%)

Fatal AEs: n=5; one fatal AE (septic shock) was considered treatment-related by the investigator.

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
no	No	no, open-label	unclear[6]	yes[7]	high risk

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Abbreviations: AE=adverse event, AJ=adjustment, ALL=acute lymphoblastic leukaemia, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete remission, CRh=complete remission with partial hematologic recovery, CrI=credible interval, CRS=cytokine release syndrome, EMA=European Medicines Agency, FDA=Food and Drug Administration, HR=hazard ratio, I=intervention, Int.=intention,

[1] external cohort of similar patients receiving SOC chemotherapy
[2] Primary analysis data (Martinelli et al.)
[3] Primary analysis data (Martinelli et al.)
[4] Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 10^{-4}.
[5] Relapse was defined as haematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.
[6] Partly primary analysis data
[7] Medical writing and editorial assistance was supported by the sponsor.

IV=intravenous, MG=median gain, MRD=minimal residual disease, n=number of patients, NE=not estimable, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, Ph+=Philadelphia chromosome positive, QoL=quality of life, SAE=serious adverse event, SOC=standard of care, TKIs=tyrosine kinase inhibitors

References:

1. Rambaldi A, Ribera J, Kantarjian H, Dombret H, et al. Blinatumomab compared with standard of care for the treatment of adult patients with relapsed/refractory Philadelphia chromosome–positive B-precursor acute lymphoblastic leukemia. Cancer 2020;126:304-310.
2. European Medicines Agency (EMA). Medicines. Blincyto. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/blincyto-1.
3. The Leukemia & Lymphoma Society (LLS). Ph-positive ALL therapy [Available from: https://www.lls.org/leukemia/acute-lymphoblastic-leukemia/treatment/ph-positive-all-therapy.
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8. Martinelli G, Boissel N, Chevallier P, Ottmann O, Gokbuget N, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. J Clin Oncol 35:1795-1802.