Blinatumomab in induction therapy improves molecular response in untreated adults with Ph- B-cell precursor acute lymphoblastic leukemia

Blinatumomab, a bispecific anti-CD3/CD19 T-cell engager, is effective in treating relapsed or refractory B-cell precursor acute lymphoblastic leukemia (B-ALL), though most patients relapse despite achieving measurable residual disease (MRD) negativity.[1] In the MRD setting, blinatumomab induced MRD negativity (MRDneg) in 78% of patients, with 85% achieving MRD $<10^{-4}$. Patients treated in their first complete remission (CR) showed better outcomes than those treated in later remissions.[2] These findings support integrating blinatumomab into first-line polychemotherapy, as early MRD clearance significantly improves survival and reduces risk of relapse.[3]

The open-label phase II Blina-CELL trial evaluated the effects of one cycle of blinatumomab following 7-day pretreatment with dexamethasone and chemotherapy in adult patients with Philadelphia (Ph)-negative B-ALL. Conducted at four centers in the Czech Republic, the trial assessed MRDneg rates after a short pre-induction, one cycle of blinatumomab, and one cycle of high-dose chemotherapy. The study was approved by central and institutional review boards, and registered on clinicaltrials.gov (Identifier: NCT04554485). All participants provided informed consent in accordance with the Declaration of Helsinki.

Patients underwent a pre-induction phase comprising dexamethasone 10 mg/m² (days 1-7), cyclophosphamide 200 mg/m² (days 3-5), vincristine 2 mg (day 6), and daunorubicin 45 mg/m² (days 6-7). Induction phase I began on day 12 with a 28-day continuous infusion of blinatumomab. The dosage was adjusted on the basis of bone marrow lymphoblast levels on day 11: patients with ≤50% blasts received the target dose of 28 μg/day (days 12-40), while those with >50% blasts started at 9 μg/day, escalating to 28 μg/day on day 19. This was followed by induction phase II starting on day 50. Consolidation and maintenance chemotherapy adhered to the pediatric-inspired GMALL 07/2003 protocol.[4] Central nervous system (CNS) prophylaxis consisting of 9 administrations of intrathecal chemotherapy was given during the induction and consolidation phases. The treatment schedule and details regarding the consolidation treatment are illustrated in *Online Supplementary Figure S1*. Hematopoietic stem cell transplantation (HSCT) was indicated solely on the basis of MRD response and was not part of the study. Patients in CR with MRD $\geq 10^{-4}$ at week 18 or later during consolidation or maintenance were eligible. After reconfirmation of CD19 expression, they were pretreated with 1-2 cycles of MRD-triggered blinatumomab to achieve MRDneg status.

The primary objective was the percentage of MRDneg at week 11. The null hypothesis was based on data from patients with Ph-negative ALL treated with the GMALL 07/2003 protocol[5] in Prague and Brno in 2007-2017 where the rate of MRDneg after two induction cycles was 60%. The aim was to improve this to 85%. Secondary objectives included MRD levels after blinatumomab infusion, event-free survival (EFS), overall survival (OS), HSCT rates for suboptimal MRD response, and adverse event incidence.

Measurable residual disease analyses were centralized and assessed by quantitative PCR using patient-specific assays to detect leukemia-specific clonal immunoglobulin or T-cell receptor (IG/TR) gene rearrangements according to Euro-MRD standards.[6] The minimum sensitivity and quantitative range was 10^{-4}. Samples with positive non-quantifiable MRD detected at week 11 were re-evaluated by next generation amplicon sequencing (NGS) using the EuroClonality-NGS Working Group protocols to discriminate low level MRD from non-specific amplification.[7] MRDneg was defined as undetectable MRD in an assay with sensitivity of at least 10^{-4}.

The study aimed to enroll 45 subjects; however, recruitment was terminated prematurely following a decision made by the investigational drug supplier. Between May 2019 and March 2022, a total of 29 patients were enrolled. One patient withdrew before completing induction phase I due to a recurrent grade 3 elevated activity of transaminases (ALT/AST). Clinical and biological characteristics of the cohort are reported in Table 1.

Twenty-six (93%) patients achieved CR by the end of blinatumomab infusion on day 40, while 2 patients (7%) were refractory. No patient died. Of the 25 patients with an IG/TR target, 14 (56%) achieved MRDneg, 10 (40%) had positive non-quantifiable MRD, and one patient (4%) had quantifiable MRD $>10^{-4}$.

The primary endpoint was assessed at week 11. Among the 25 patients who achieved CR and were evaluable for molecular response, 21 (84%) achieved MRD negativity. Two patients (8%) each had either positive non-quantifiable MRD or quantifiable MRD $>10^{-4}$ (Figure 1). The target was not met, likely due to the strict definition of molecular response. Recognizing the prognostic importance of low MRD levels,[8,9] MRD negativity in this study was defined as an undetectable MRD, rather than the more commonly used threshold of MRD $<10^{-4}$.[10]

Measurable residual disease-triggered blinatumomab was administered to 5 patients. Two of these patients showed evidence of molecular failure at week 18 and received one

cycle of blinatumomab. One of them achieved MRDneg and underwent HSCT, the other progressed to hematologic relapse.

Molecular relapse was diagnosed in 3 patients 14, 25 and 37 months after the initiation of treatment. All 3 received 2 cycles of blinatumomab, achieved MRDneg already after the first cycle, and proceeded to HSCT. Apart from the 4 patients who were transplanted following MRD-triggered blinatumomab administration, 2 other patients were transplanted during their first CR based on the treating physician's discretion; one of these was due to high-risk features (B-I phenotype, *KMT2A* rearrangement), and the other was due to the absence of IG/TR target.

With a median follow-up of 37 months and a minimum follow-up of 25 months for patients alive at data cutoff, 9 events were reported. Two patients were refractory, 3 experienced molecular relapse, one had a hematologic relapse, one had a CNS relapse (22 months after HSCT), and 2 developed secondary myelodysplastic neoplasm (MDS). Both patients who were refractory to blinatumomab induction had an *IKZF1*plus genotype.[11] They were salvaged with inotuzumab ozogamicin, to which they also proved refractory, and subsequently received chimeric antigen receptor (CAR)-T cell therapy. Loss of CD19 expression at the time of relapse was not confirmed in any patient. Detailed characteristics of relapsed and refractory patients are shown in *Online Supplementary Table S1*. Six patients died: 3 due to relapsed or refractory ALL, one from severe SARS-CoV-2 infection, one due to infectious complications following HSCT, and one as a result of secondary MDS. At the 2-year follow-up, the EFS rate was 75% (95% CI: 59-91%) and OS was 86% (95% CI: 73-99%). Median EFS was 47 months, while the median OS was not reached. The cumulative incidence of relapse in CR1 at one and two years was 4% and 12%, respectively (*Online Supplementary Figure S2A-C*).

The most common adverse event during blinatumomab infusion was elevated ALT/AST, followed by cytokine release syndrome (CRS), infections, neurologic events, and laboratory abnormalities (Table 2). Of these, only 48%, 3%, 14%, 0%, and 10%, respectively, were classified as grade 3 or 4. All but one CRS cases were grade 1 or 2, with symptoms occurring in a median of one day (range, 0-22 days) after the start of blinatumomab infusion, and in 4 cases, after the dose step from 9 μg/day to 28 μg/day. No neurologic event exceeded grade 2, contrasting with the 13% grade 3 incidence in registration studies.[1,12] Blinatumomab infusion was interrupted seven times, including twice in the same patient. Most interruptions occurred 1-4 days after infusion initiation due to elevated ALT/AST (lasting 2-12 days) or CRS (lasting 1-3 days). In response to grade 3 ALT/AST elevation observed in 4 of the first 7 patients, a protocol amendment was implemented. This adjustment involved administering a reduced dose of blinatumomab during the first seven days, followed by the target dose for the remaining 21 days. Following this modification, no treatment interruptions were necessary. We hypothesize that the increase in transaminase levels shortly after the initiation of blinatumomab infusion may reflect its impact on leukemic cells infiltrating the liver, rather than direct hepatotoxicity. Treatment with blinatumomab enabled rapid hematologic recovery, with median times to neutrophils >0.5x10^9/L and platelets >50x10^9/L of eight days from the start of blinatumomab infusion (range, 1-16 days).

Two other studies have investigated blinatumomab for induction treatment in adult B-ALL, both utilizing multiple cycles also during consolidation. The SWOG 1318 study,[13] conducted in an elderly population, included four cycles of blinatumomab followed by prednisone, vincristine, 6-mercaptopurine, and methotrexate (POMP) maintenance. The remission rate was 66%, indicating that blinatumomab may

Table 1. Patient characteristics.

Characteristic	Values
Total N evaluable	28
Median age in years (range)	41 (19-65)
Male / Female, N (%)	19 (68) / 9 (32)
Median blood leukocyte count, x10^9/L (range)	5.9 (0.6-67.7)
Median BM blasts, % (range)	81 (24-98)
Immunophenotype, N (%)	
B-I (ProB)	5 (18)
B-II (CommonB)	15 (54)
B-III (PreB)	8 (28)
Karyotype, N (%)	
Normal	12 (43)
t(9;22)	0
t(X;11)	2 (7)
t(2;8)	1 (3)
Low hypodiploidy/near triploidy	3 (11)
Hyperdiploidy	3 (11)
Complex	4 (14)
Unsuccessful cultivation	3 (11)
High risk genomic subgroups, N (%)	
Ph-like	4 (14)
*IKZF1*plus	8 (29)
CNS involvement, N (%)	
CNS1	24 (86)
CNS2	0
CNS3	0
TLP$^+$	0
TLP$^-$	4 (14)
Median BM blasts on day 11, % (range)	5 (0-97)
Proportion of blasts in BM on day 11, N (%)	
≤50%	20 (71)
>50%	8 (29)

BM: bone marrow; CNS: central nervous system; N: number; Ph-like: Philadelphia-like; TLP: traumatic lumbar puncture.

be less effective in elderly populations. The HOVON-146 study[14] recruited patients up to 70 years old and included also Ph-positive ALL cases. Blinatumomab was administered during a pre-phase lasting 14 days from day 5, followed by two 4-week blocks of blinatumomab alternating with consolidation chemotherapy. While CR and molecular response rates were comparable to our study, the HOVON study reported a higher incidence of grade 3 CRS during the initial administration of blinatumomab.

In conclusion, administering one cycle of blinatumomab following a 7-day pre-induction chemotherapy regimen is feasible as an induction treatment for adult Ph-negative ALL. This approach resulted in high CR rates and significantly improved early molecular responses. While blinatumomab has already established its role in the consolidation phase of treatment,[15] it remains debatable which patients might

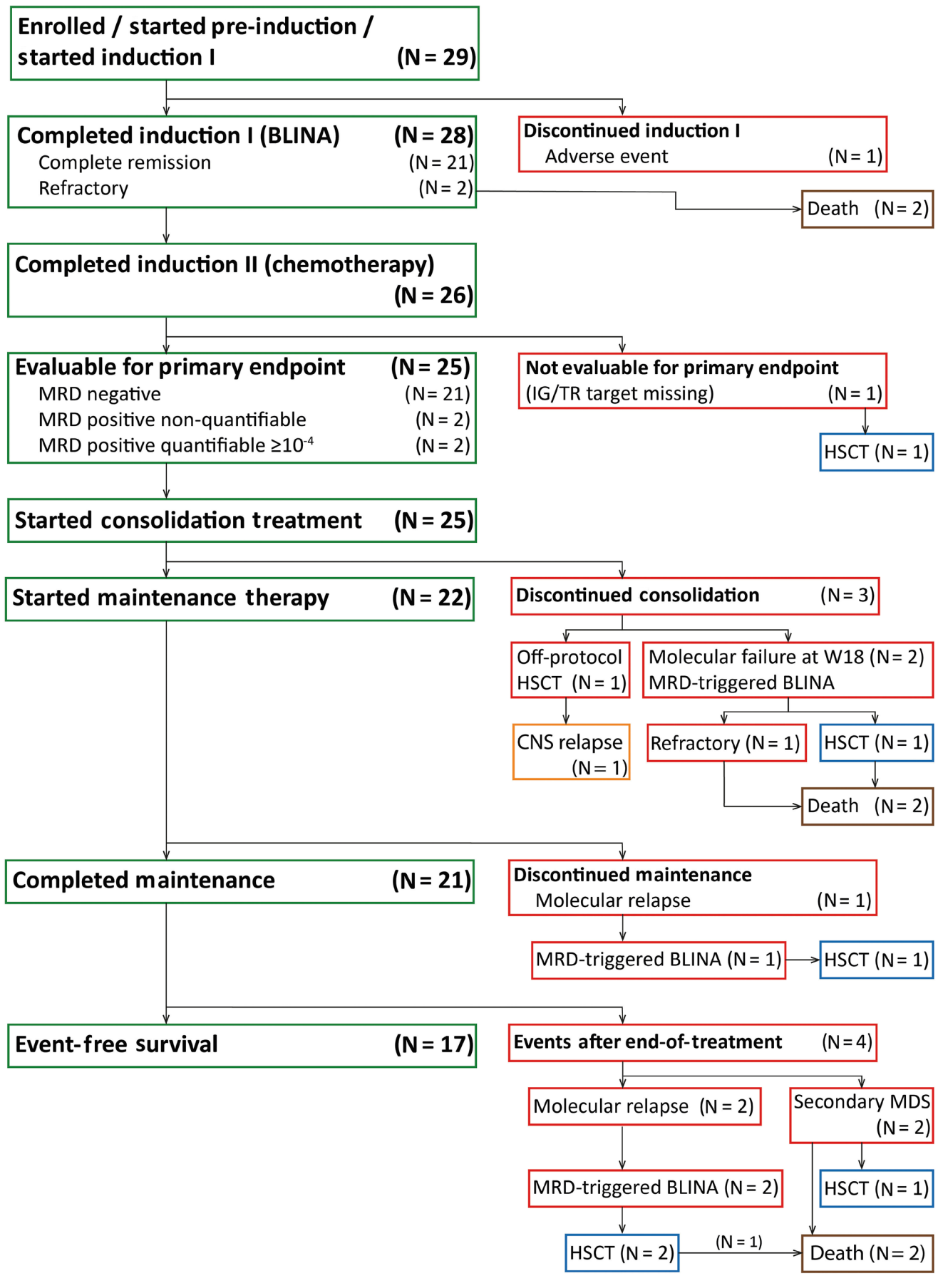

Figure 1. Flowchart illustrating the course of patients through the study. BLINA: blinatumomab; CNS: central nervous system; CR: complete remission; HSCT: hematopoietic stem cell transplantation; IG/TR: immunoglobulin and/or T-cell receptor gene rearrangement; MDS: myelodysplastic neoplasm; MRD: measurable residual disease; N: number; W: week.

Table 2. Non-hematologic adverse events (N=29).

Adverse events	All grades N (%)	Grade 3 and 4 N (%)
Hepatic impairment	26 (90)	14 (48)
Bilirubin increased	7 (24)	1 (3)
ALT increased	18 (62)	9 (31)
AST increased	12 (41)	3 (10)
GGT increased	22 (76)	8 (28)
Cytokine release syndrome	19 (66)	1 (3)
Infection	8 (28)	4 (14)
Febrile neutropenia	3 (10)	2 (7)
Soft tissue infection	3 (10)	1 (3)
Catheter-related infection	1 (3)	1 (3)
SARS-CoV-2 infection	1 (3)	-
Neurologic adverse events	5 (17)	-
Paresthesia	2 (7)	-
Ataxia	1 (3)	-
Attention disturbance	1 (3)	-
Muscle cramps	1 (3)	-
Laboratory abnormalities	5 (17)	3 (10)
Hypophosphatemia	3 (10)	1 (3)
Hypofibrinogenemia	1 (3)	1 (3)
Hypoalbuminemia	1 (3)	1 (3)

The table summarizes all grade 3-4 adverse events, and lower grade adverse events if they occurred in ≥2 patients during induction treatment with blinatumomab, or if they were the reason for treatment interruption. Includes the patient who withdrew before completion of induction phase I due to recurrent grade 3 ALT/AST elevation. ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

benefit from its use in earlier stages. This is particularly relevant given its lower toxicity compared to chemotherapy, especially concerning the duration of cytopenia and the incidence of serious infections.

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Contributions

CS designed and coordinated the study, treated patients, collected and analyzed data, and wrote the manuscript. SH, FF and MD designed the study, treated patients, collected and analyzed data, and contributed to writing the manuscript. ZK and JMH coordinated the study, treated patients and collected data. PS and BD treated patients. PP conducted statistical analysis and designed the figures. EF, LRR and JT analyzed and interpreted MRD. VP, JK, KMP, ZV and HH performed genomic studies. PC represented the sponsoring institution and supervised the study. All authors reviewed and approved the manuscript.

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Data-sharing statement

The datasets generated during the study are available from the corresponding author on reasonable request.

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