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

Authors:
Cyril Salek[1,2], Stepan Hrabovsky[3], Frantisek Folber[3], Zdenek Koristek[4], Jan M. Horacek[5,6], Eva Fronkova[7], Leona Rezkova Reznickova[7], Pavla Pecherkova[1], Petr Soukup[1], Barbora Dluhosova[4], Vaclava Polivkova[1], Jitka Krizkova[1], Katerina Machova Polakova[1], Zuzana Vrzalova[3,8], Hana Halamova[3,8], Jan Trka[7], Petr Cetkovsky[1,2], Michael Doubek[3,8]

Affiliations:
1 Institute of Hematology and Blood Transfusion, Prague, Czech Republic
2 Institute of Clinical and Experimental Hematology, First Faculty of Medicine, Charles University, Prague, Czech Republic
3 Internal Hematology and Oncology Clinic, Faculty Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic
4 Department of Hematooncology, University Hospital Ostrava and Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic
5 Department of Internal Medicine IV - Hematology, University Hospital Hradec Kralove and Faculty of Medicine, Charles University, Hradec Kralove, Czech Republic
6 Department of Military Internal Medicine and Hygiene, Military Faculty of Medicine, University of Defence, Hradec Kralove, Czech Republic
7 CLIP - Childhood Leukemia Investigation Prague, Department of Pediatric Hematology and Oncology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic
8 Central European Institute of Technology (CEITEC), Masaryk University, Brno, Czech Republic

Corresponding author:
Cyril Salek MD PhD, Institute of Hematology and Blood Transfusion, U Nemocnice 2094/1, 12800 Prague, Czech Republic; e-mail: cyril.salek@uhkt.cz.

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Authors' 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 manuscript writing. 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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The datasets generated during the study are available from the corresponding author on reasonable request.

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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 relapse risks.[3]
The open-label phase 2 Blina-CELL trial evaluated the effects of one cycle of blinatumomab following 7-day pretreatment with dexamethasone and chemotherapy in adult patients with 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 (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 based on 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 Supplementary Figure 1.
Hematopoietic stem cell transplantation (HSCT) was indicated solely based on 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.

MRD 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 EuroMRD standards.[6] The minimum sensitivity and quantitative range was 10^{-4}. Samples with positive non-quantifiable MRD detected at week 11 were reevaluated 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 the sensitivity of at least 10^{-4}.

The study aimed to enroll 45 subjects, however, recruitment was terminated prematurely due to 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 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 two 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 1 (4%) patient 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]
MRD-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 hematological relapse.
Molecular relapse was diagnosed in three patients 14, 25 and 37 months after the initiation of treatment. All three 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 them due to high-risk features (B-I phenotype, *KMT2A* rearrangement), the other 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, nine events were reported. Two patients were refractory, 3 experienced molecular relapse, 1 had a hematological relapse, 1 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 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 Supplementary Table 1.
Six patients died: three due to relapsed or refractory ALL, one from severe SARS-CoV-2 infection, 1 due to infectious complications following HSCT, and 1 as a result of secondary MDS.
At the 2-year follow-up, the EFS rate was 75% (95%CI 59–91%), and OS rate was 86% (95%CI 73–99%). The median EFS was 47 months, while the median OS was not reached. The cumulative incidence of relapse in CR1 at 1 and 2 years was 4% and 12%, respectively (Supplementary Figures 2A, 2B, 2C).

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 1 day (range 0–22) after the start of blinatumomab infusion, and in four 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 four of the first seven 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 >0.5 × 10^9/L and platelets >50 × 10^9/L of 8 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% indicates that blinatumomab may 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 four-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 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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Table 1. Patient characteristics.

Measure	N (%), median (range)
Total evaluable	28
Age (years)	41 years (19–65)
Male / Female	19 (68) / 9 (32)
Leukocyte count in blood ($\times 10^9$/L)	5.9 (0.6–67.7)
Bone marrow blasts (%)	81 (24–98)
Immunophenotype	
B-I (ProB)	5 (18)
B-II (CommonB)	15 (54)
B-III (PreB)	8 (28)
Karyotype	
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	
Ph–like	4 (14)
*IKZF1*plus	8 (29)
CNS involvement	
CNS1	24 (86)
CNS2	0
CNS3	0
TLP+	0
TLP–	4 (14)
Bone marrow blasts on day 11 (%)	5 (0–97)
Proportion of blasts in bone marrow on day 11	
≤50%	20 (71)
>50%	8 (29)

Abbreviations: CNS, central nervous system; TLP, traumatic lumbar puncture.

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

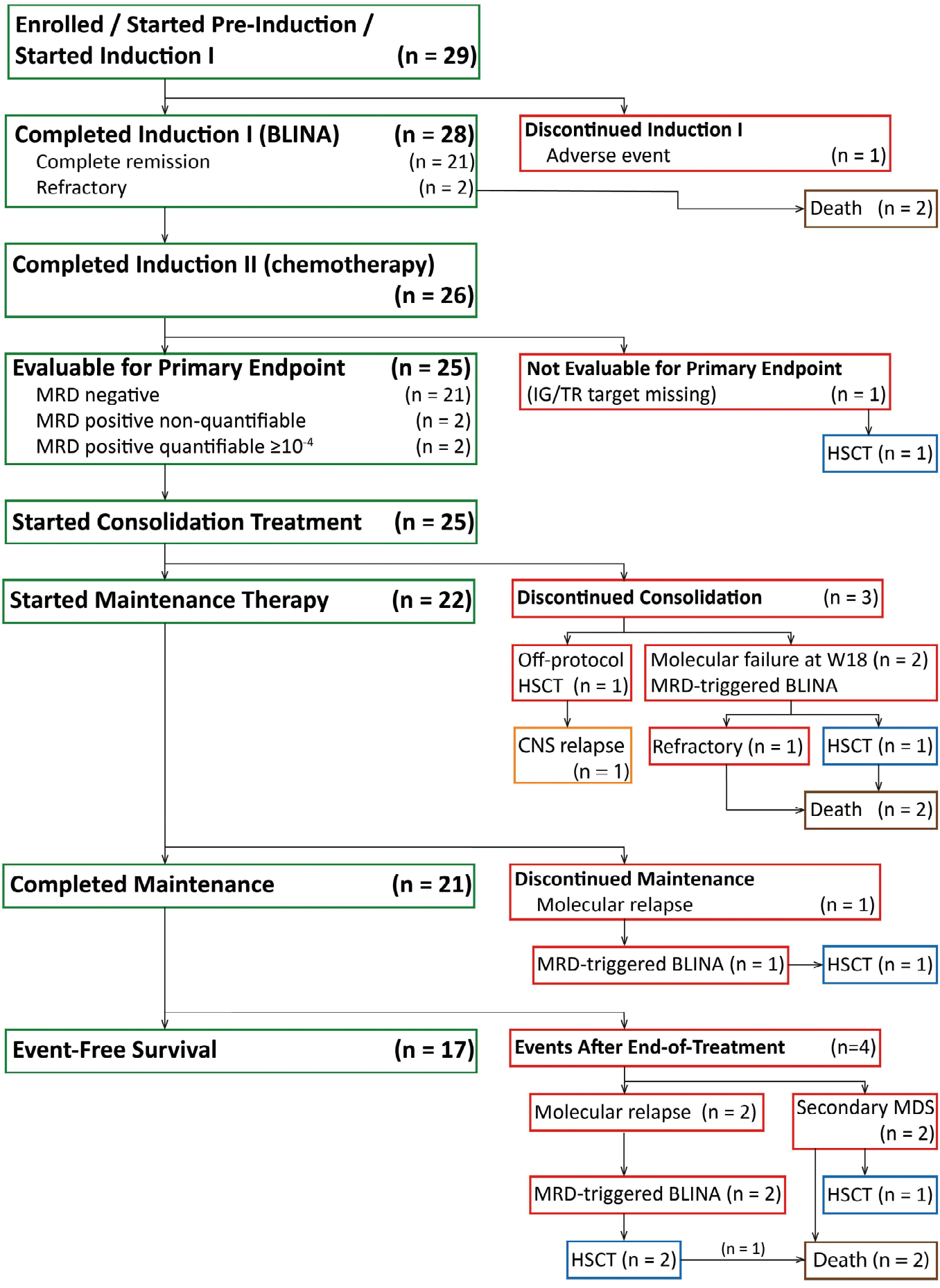
	All grades, N (%)	Grade 3 and 4, N (%)
Hepatic impairment	**26 (90)**	**14 (48)**
Bilirubin increased	7 (24)	1 (3)
ALT increased	18 (62)	9 (31)
AST increased	12 (41)	3 (10)
GGT increased	22 (76)	8 (28)
Cytokine release syndrome	**19 (66)**	**1 (3)**
Infection	**8 (28)**	**4 (14)**
Febrile neutropenia	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. Patient who withdrew before completion of Induction I due to recurrent grade 3 ALT/AST elevation is included.

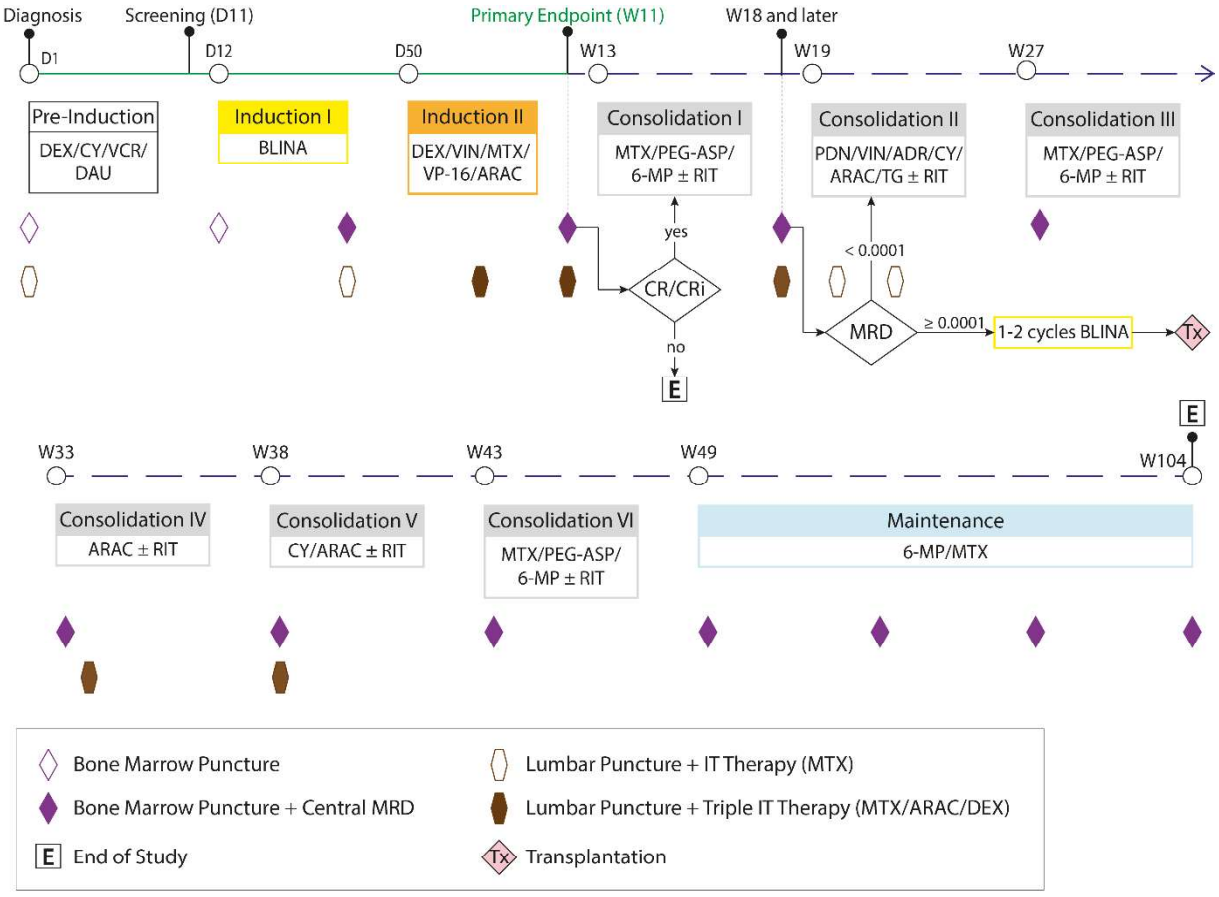
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

Figure 1. Flowchart illustrating the course of patients through the study.

Abbreviations: 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; W, week.


Enrolled / Started Pre-Induction / Started Induction I (n = 29)
Completed Induction I (BLINA) (n = 28)
Complete remission (n = 21)
Refractory (n = 2)
Discontinued Induction I
Adverse event (n = 1)
Death (n = 2)
Completed Induction II (chemotherapy) (n = 26)
Evaluable for Primary Endpoint (n = 25)
MRD negative (n = 21)
MRD positive non-quantifiable (n = 2)
MRD positive quantifiable ≥10-4 (n = 2)
Not Evaluable for Primary Endpoint
(IG/TR target missing) (n = 1)
HSCT (n = 1)
Started Consolidation Treatment (n = 25)
Started Maintenance Therapy (n = 22)
Discontinued Consolidation (n = 3)
Off-protocol HSCT (n = 1)
Molecular failure at W18 (n = 2)
MRD-triggered BLINA
CNS relapse (n = 1)
Refractory (n = 1)
HSCT (n = 1)
Death (n = 2)
Completed Maintenance (n = 21)
Discontinued Maintenance
Molecular relapse (n = 1)
MRD-triggered BLINA (n = 1)
HSCT (n = 1)
Event-Free Survival (n = 17)
Events After End-of-Treatment (n=4)
Molecular relapse (n = 2)
Secondary MDS (n = 2)
MRD-triggered BLINA (n = 2)
HSCT (n = 1)
HSCT (n = 2)
(n = 1)
Death (n = 2)

Supplementary Figure 1. Treatment schedule of the Blina-CELL trial.

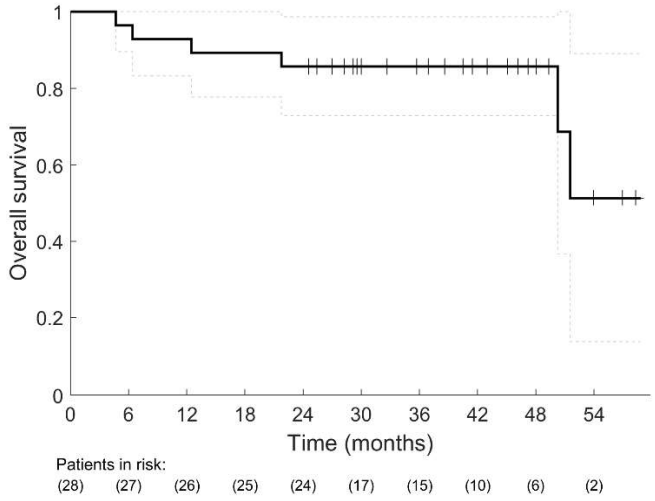


Composition of treatment blocks: Pre-Induction: DEX 10 mg/m² PO D1–7, CY 200 mg/m² IV D3–5, VCR 2 mg IV D6, DAU 45 mg/m² IV D6–7. **Induction I:** BLINA 9 µg/day CIV D12–19, BLINA 28 µg/day CIV D19–40, DEX 20 mg IV D12+19. **Induction II:** DEX 10 mg/m² PO D50–54, VIN 3 mg/m² IV D50, MTX 1.5 g/m² IV D50, VP-16 250 mg/m² IV day 53-54, ARAC 2x 2 g/m² IV D54. **Consolidation I, III and VI:** MTX 1.5 g/m² IV D1+15, PEG-ASP 2000 U/m² IV D2+16, 6-MP 60 mg/m² PO D 1–7 and D15–21, TG 60 mg/m² PO D15–28. **Consolidation II:** PDN 3x 20 mg/m² PO D1–14, VIN 3 mg/m² IV D1+7, ADR 50 mg/m² IV D1+7, CY 1000 mg/m² IV D15, ARAC 75 mg/m² IV D17–20 and D24–27. **Consolidation IV:** ARAC 1000 mg/m² IV D1+3+5. **Consolidation V:** CY 1000 mg/m² IV D1, ARAC 500 mg/m² IV D1. **Rituximab** 375 mg/m² IV D0 of all consolidation cycles if CD20+ at diagnosis (any positivity). **Maintenance:** 6-MP 60 mg/m² PO daily, MTX 20 mg/m² PO weekly. **IT therapy (arrows):** ARAC 40 mg IT, DEX 4 mg IT, MTX 15 mg IT.

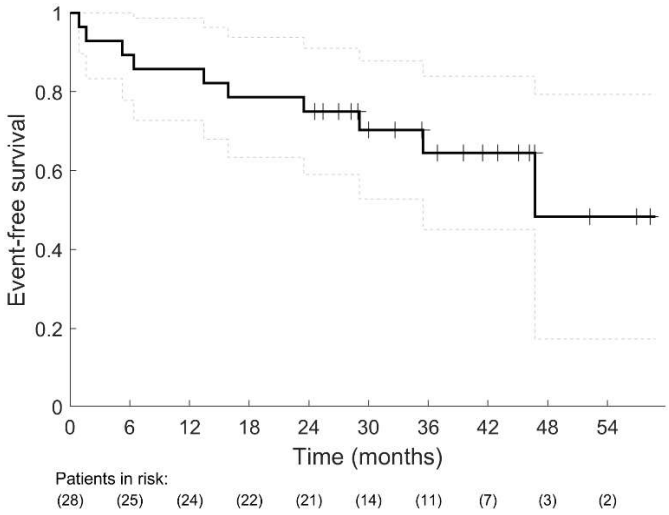
Abbreviations: 6-MP, mercaptopurine; ADR, adriamycine; ARAC, cytarabine; BLINA, blinatumomab; CIV, continuous intravenous infusion; CR, complete remission; CRi, complete remission with incomplete blood count recovery; CY, cyclophosphamide; D, day; DAU, daunorubicin; DEX, dexamethasone; IT, intrathecally; IV, intravenously; MRD; measurable residual disease; MTX, methotrexate; PDN, prednisone; PEG-ASP, pegylated asparaginase; RIT, rituximab; TG, thioguanine; Tx, transplantation; VCR, vincristine; VIN, vindesine; VP-16, etoposide, W, week.

Supplementary Figure 2. Overall survival (A), event-free survival (B), and cumulative incidence of relapse in CR1 (C).

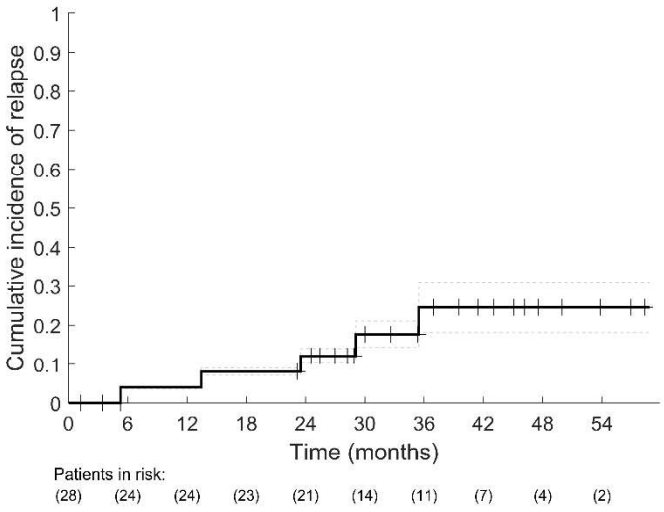
A.



B.



C.



Supplementary Table 1. Clinical and laboratory characteristics of relapsed and refractory patients.

Patient Number	Age [yrs]	WBC at Dg [× 10^9/L]	Pheno-type	Karyotype	Mutations	Fusion Gene	Subtype	MRD D40	MRD W11	MRD W18	Time To Relapse [months]	Previous Malignancy
Refractory												
1-02	65	11.5	B-II	complex	FLT3 D835Y	–	B-other; IKZF1plus	–	–	–	–	no
5-01	52	23.3	B-III	low hyperdiploid	wt	–	B-other; IKZF1plus	–	–	–	–	no
Molecular Response												
2-05	38	16.1	B-II	low hyperdiploid	JAK2 R683G; NF1 I2412Pfs	CRLF2::IGH	Ph-like	nq	neg	neg	24	no
2-06	45	4.6	B-I	normal	SETD2 Q1219X; KMT2D I5497del; KMT2D T4271Afs; KMT2D K3573X; PAX5 S55C, KRAS G13D	DUX4::IGH	DUX4r; IKZF1plus	nq	nq	nq	36	no
2-12	39	6.2	B-II	normal	NRAS G12V; IDH1 R132C	–	B-other; IKZF1plus	neg	neg	neg	14	no
Hematological Relapse												
5-04	22	25.2	B-I	47,XY,t(7,11;12),+19	wt	KMT2A::TNRC18	KMT2Ar	10e-2	10e-3	10e-3	5	no
CNS Relapse												
2-16	23	2.4	B-III	normal	wt	–	B-other	nq	nq	nq	29	no
Secondary MDS												
1-02	65	11.5	B-II	N/A	TP53 H193R, EZH2 G743D	–	Low hypodiploid	neg	neg	neg	47	no
5-01	52	23.3	B-III	near triploid	TP53 P278S; DNMT3A K766Rfs; DNMT3A I670delinsHfs	–	Low hypodiploid; IKZF1plus	nq	neg	neg	16	breast carcinoma