

## Update on long-term outcomes of a cohort of patients with TCF3::HLF positive acute lymphoblastic leukemia treated with blinatumomab and stem cell transplantation

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## Update on long-term outcomes of a cohort of patients with *TCF3::HLF* positive acute lymphoblastic leukemia treated with blinatumomab and stem cell transplantation

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Running head: *TCF3::HLF* ALL treated with blinatumomab and HSCT

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*TCF3::HLF* rearranged B-cell acute lymphoblastic leukemia (B-ALL) is a rare and very aggressive subtype of B-ALL<sup>1-3</sup>. It is characterized by high rates of chemotherapy resistance, treatment failure, and early relapse. These patients, are typically unsalvageable with standard chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT), resulting in a dismal prognosis<sup>2, 4, 5</sup>.

Due, however, to an almost universally CD19-positive immunophenotype the emerging CD19-directed immunotherapies, such as the bispecific T-cell engager antibody blinatumomab or chimeric antibody receptor T-cells (CAR-T) have become viable therapeutic options, which may improve the long-term outcomes of these patients<sup>6-8</sup>. Nonetheless, because of the rarity of *TCF3-HLF* B-ALL, these approaches have not yet been widely evaluated.

Here we report the outcomes of a cohort of seventeen pediatric and two adult patients with *TCF3-HLF* B-ALL, who received an early intervention with blinatumomab as a bridge to HSCT. The patients were treated between 2015 and early 2024 by members of the international AEIOP- Berlin-Frankfurt-Münster (BFM), ALLtogether, and GRAALL study groups. The initial outcomes and acute toxicity data for patients 1-9 have been previously reported in 2019<sup>6</sup>. We now update these outcomes with a longer follow-up and report on ten additional, similarly treated patients (patients 10- 19). This retrospective study has been approved by the Cantonal Ethics Committee of Zurich.

MRD assessment were performed according to the EuroMRD Guidelines<sup>9</sup>, used in the AEIOP-BFM Study group and MRD negativity was defined as non-detectable disease using molecular MRD.

A summary of demographic data and treatment is shown in Table 1. The median age of the patients was 10 (range 3- 52) and only three had extramedullary disease.

Seventeen patients achieved a minimal residual disease (MRD) negativity either before or with blinatumomab treatment. In most cases, one blinatumomab cycle was sufficient for this. Patient 16 additionally received venetoclax and dexamethasone between the two cycles of blinatumomab, after already achieving MRD negativity.

Patients 13 and 19 failed to attain MRD negativity with blinatumomab. In both cases it was subsequently achieved with CD19-directed CAR-T cell therapy, followed by a planned HSCT in patient 19 and HSCT due to loss of CAR-T cell persistence in patients 13.

All but two patients underwent a HSCT. Patient 5 had an early CD19-negative relapse before reaching HSCT. This patient subsequently died from a severe infectious complication during relapse therapy. Patient 18 likewise suffered a relapse after receiving three cycles of blinatumomab and received HSCT in the second remission after CAR-T cell therapy.

Patient outcomes are depicted in Table 2, Figure 1 and Supplemental figure 1. The median follow-up from the start of blinatumomab treatment for the complete cohort was 25 months (range 2- 104). Ten out of nineteen patients (2, 3, 7, 10, 11, 13, 14, 16, 17, 19) are alive after a median follow-up of 42 months (range 8- 104). Eight patients (patients 2, 3, 7, 10, 13, 16, 17 and 19) remain MRD negative after a median follow-up of 53 months (range 25- 104). This corresponds to 2-year overall survival (OS) and 2-year event-free survival (EFS) of 63.1 % and 52.6% respectively (Supplemental figure 1). Two patients received additional prophylactic blinatumomab cycles after HSCT as an attempt to further consolidate the MRD-negative remission (patients 2 and 3). Patient 4 received additional courses of blinatumomab after a relapse post-HSCT and achieved MRD negativity but succumbed to an infectious complication after the second HSCT.

Five patients died from infectious complications, three while in remission (patients 4, 8, and 15), and two following relapse (patients 5 and 6). Four patients died due to disease progression or non-infectious treatment-related mortality during relapse (patients 1, 9, 18, and 12 respectively).

Seven patients relapsed post-blinatumomab-HSCT (patients 1, 4, 6, 9, 11, 12 and 14). The majority of relapses were CD-19 positive. Five out of seven relapses occurred within a year post-transplantation (patients 4, 6, 9, 11 and 14). Most post-relapse salvage therapies were unsuccessful. Two patients underwent a second HSCT, with one later dying from an infectious complication, and the second due to a subsequent relapse (patients 4 and 1 respectively). Two patients are still undergoing treatment following a second relapse (patients 11 and 14).

In summary, this case series confirms the profound resistance of this ALL subtype to chemotherapy, as the most common indication for blinatumomab therapy was MRD persistence after conventional consolidation therapy. Only two patients achieved MRD negativity before receiving blinatumomab therapy, one of whom also received venetoclax as a part of a clinical trial (patient 15). The data also show an excellent response to CD19-directed immunotherapy with most other patients achieving MRD negativity after blinatumomab therapy. Furthermore, eight patients achieved sustained molecular remissions after consolidation with HSCT post-blinatumomab. One of those patients (19) required CAR-T cell therapy as bridge to transplant due to poor response to blinatumomab. Patient 4 also demonstrates that blinatumomab is a therapeutic option for relapse post-HSCT.

We could not identify any clinical markers or characteristics to predict relapse in this cohort, as nearly all patients responded to blinatumomab quickly and the time to relapse varied greatly among the patients. However, in contrast to pre-immunotherapy era, we documented several late relapses. Further research into molecular characteristics is warranted to answer this question.

Five patients also received CAR-T cell therapy, either as therapy of relapse after blinatumomab-HSCT (patients 1 and 11) or before HSCT due to non-response to or early relapse after blinatumomab (patients 13, 19 and 18 respectively). This suggests that CD19-directed CAR-T cell therapy is a viable strategy even post-blinatumomab.

Since our initial report on the blinatumomab-based approach to *TCF3::HLF* B-ALL, other investigators have also reported a limited number of cases where sustained remissions had been achieved using CD19- and CD22-directed CAR-T cell therapy<sup>2,7,8</sup>. Several European patients also underwent therapy with CD19-directed CAR-T cell therapy in the meantime, but their outcomes have not yet been reported [personal communication]. It is therefore yet to be determined how CAR-T cell therapy will compare to blinatumomab and HSCT. For patients with *TCF3::HLF*-B-ALL experts may recommend consolidation with HSCT even after CAR-T cell therapy<sup>10</sup>. The role of additional blinatumomab cycles post-transplantation remains unclear.

An alternative bridging therapy, based on drug resistance profiles from preclinical models, was reported using the combination of the CD22 antibody-drug conjugate inotuzumab ozogamicin with BCL2-inhibitors, demonstrating the still largely untapped potential of combination therapies<sup>4,11</sup>.

Other rationales for biologically driven treatments include MEK inhibition, SRC family kinase inhibition, and Aurora kinase inhibition, but no clinical data on the effectiveness of such therapeutic agents have been reported to date<sup>4,12</sup>.

Our case series suggests that a long-term cure for *TCF3::HLF* B-ALL, which is considered incurable by conventional therapy, may be achieved with CD19-directed immunotherapy. Since our initial publication<sup>6</sup> there has been a shift towards using more immunotherapy and our current data further confirms that this approach should be considered as an early intervention in the front-line therapy of *TCF3::HLF* B-ALL. In general, we recommend the addition of venetoclax in combination with induction chemotherapy and a rapid bridge to CD19- directed immunotherapy. As first choice we bridge these patients as early as possible with blinatumomab to stem cell transplantation at first diagnosis already. This approach is recommended in treatment protocol by the AIOEP-BFM-ALL study group. We plan a retrospective international study of the experience with CAR-T cell therapy before providing a guideline. Prospective studies should evaluate the optimal bridge to CAR-T cell therapy

without stem cell transplantation and more efforts are needed to understand the underlying functional dependencies of this rare but fatal leukemia subtype in order to further improve the outcome of patients with TCF3::HLF positive ALL.

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Table 1: Demographic data and treatment details of the patients treated with blinatumomab and hematopoietic stem cell transplantation

ID	Age at starting Blina (years)	Sex	EMD	First-line treatment protocol	Indication for Blina-HSCT	Number of Blina cycles to MRD negativity	HSCT post-Blina (Donor type)	Conditioning regimen	Treatment with Blina post-HSCT	Total number of Blina cycles received
1	13	F	No	AALL1131	Refractory disease after induction therapy	1	Yes (MUD)	Bu, Thio, Cy	No	2
2	14	F	No	AIEOP-BFM	First relapse (after HSCT)	1	Yes (MUD; 2 <sup>nd</sup> HSCT)	Bu, Cy, VP16	2 cycles	3
3	8	M	CNS2b	AIEOP-BFM	Persistent MRD after consolidation	1	Yes (MUD)	TBI, VP16	2 cycles	4
4	7	F	CNS3	AIEOP-BFM	Persistent MRD after consolidation	1	Yes (haploidentical)	Mel, Flu, Thio	No	3
5	10	M	No	FRALLE	Persistent MRD after consolidation	1	No suitable donor identified	NA	NA	3
6	3	F	CNS2b	AIEOP-BFM	First relapse	1	Yes (MRD*)	TBI, VP16	No	1
7	8	F	No	AIEOP-BFM	Persistent MRD after consolidation	2	Yes (haploidentical)	TBI, Thio, Flu	No	2
8	5	F	No	UKALL	Persistent MRD after consolidation	1	Yes (MUD)	TBI, Cy	No	2
9	7	M	No	AIEOP-BFM	Persistent MRD after consolidation	1	Yes (MUD)	Bu, Thio, Flu	No	2
10	8	M	No	NOPHO ALL 2008 induction, ALLTogether	Bridge to HSCT (planned a priori due to disease biology)	1	Yes (MSD)	TBI, VP16	No	1
11	13	F	No	ALLTogether	Bridge to HSCT (planned a priori due to disease biology)	0 (negative beforehand at EOC)	Yes (MSD)	TBI, VP16	No	1
12	12	M	No	UKALL	Persistent MRD after consolidation	1	Yes (MUD)	TBI, Cy	No	2
13	11	M	CNS3	UKALL	Persistent MRD after consolidation	Never achieved with Blina	Yes but after bridging with CAR-T cell therapy (MUD)	TBI, VP16	No	2
14	9	F	No	ALLTogether	Bridge to HSCT (planned a priori due to disease biology)	1	Yes (MSD)	TBI	No	2
15	8	M	No	AIEOP-BFM, Venetoclax	Based on the 2019 Haematologica paper <sup>6</sup>	0 (negative beforehand at EOC)	Yes (MMD)	Cy, Thio, TBI	No	1

<b>16</b>	12	M	No	CoALL 2020 Registry	Refractory disease after induction therapy	1	Yes (MSD)	TBI, VP16, cranial boost	No	2; Venetoclax and Dex therapy between cycles
<b>17</b>	48	F	No	GRAALL-2014	Persistent MRD after induction, toxicity	2	Yes (MSD)	Flu, TB	No	2
<b>18</b>	52	F	No	GRAALL-2014	Disease biology	1	No	NA	No	3
<b>19</b>	12	M	CNS3	UKALL 2019 interim guidelines	Persistent MRD after consolidation	Never achieved with Blina	Yes but after bridging with CAR-T cell therapy (MUD)	VP16, TBI	No	2

Blina: Blinatumomab; EMD: extramedullary disease; HSCT: hematopoietic stem cell transplantation; CNS: central nervous system; MRD: minimal residual disease; EOC: end of consolidation; MUD: matched unrelated donor; MRD\*: matched related donor; MSD: matched sibling donor, MMD: mismatched donor; CAR-T cell: chimeric antibody T-cell; Bu: busulfan; Cy: cyclophosphamide; Thio: Thiotepa; VP16: etoposide; TBI: total body irradiation, Mel: melphalan; Flu: fludarabine; Dex: dexamethasone.



Table 2: Long-term outcomes of the patients treated with blinatumomab and hematopoietic stem cell transplantation

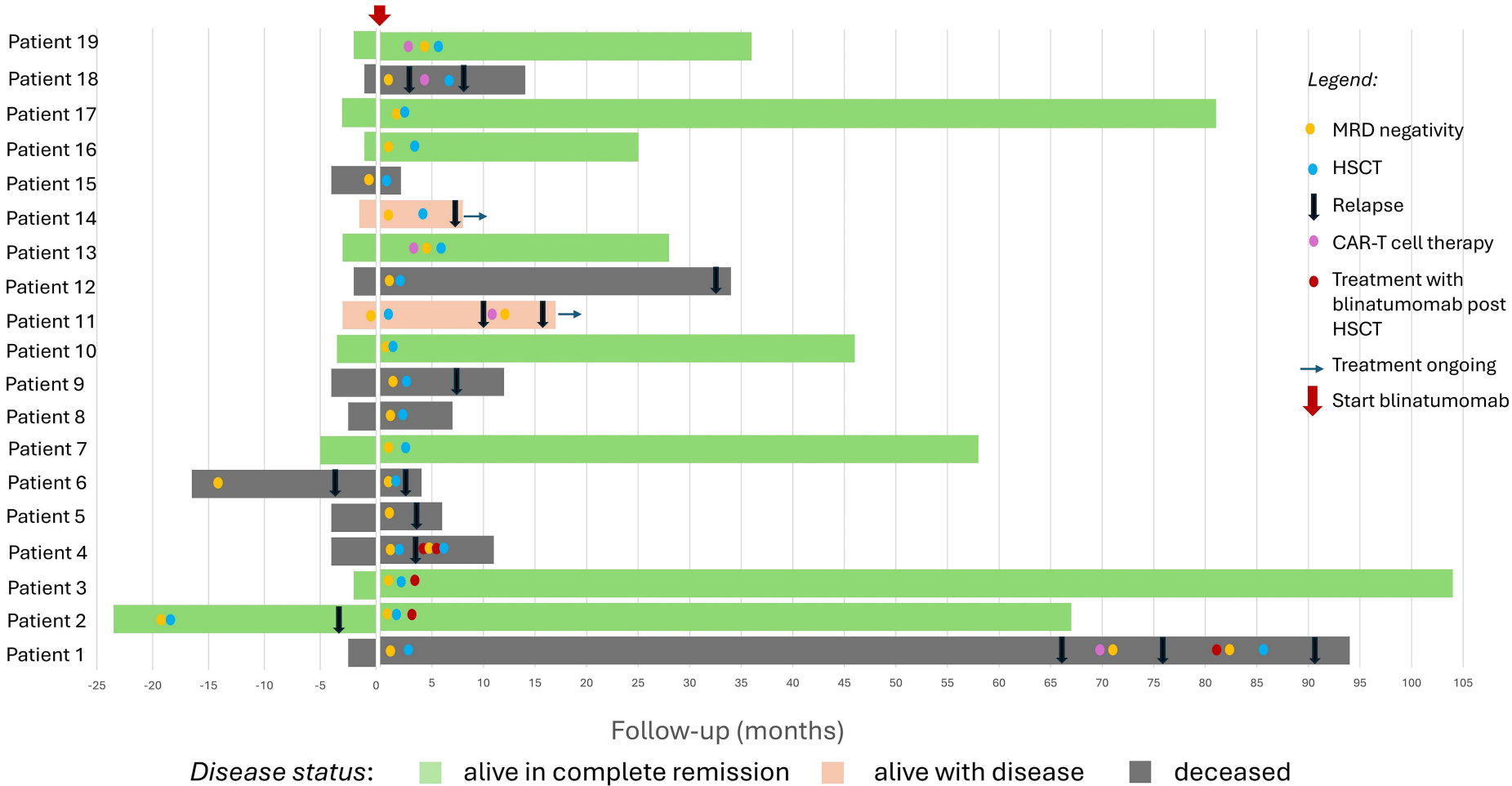
ID	Relapse post Blina- HSCT	Relapse treatment	Disease status post-HSCT	Follow-up after Blina Start (months)	Cause of death
1	5 years after HSCT	CD19-directed CAR-T cell therapy with a subsequent extramedullary 2nd relapse after 6 months. Treatment with lenalidomide, InO, Blina, and 2 <sup>nd</sup> HSCT. 3 <sup>rd</sup> relapse 4 months after the HSCT with ensuing therapy with venetoclax and InO and palliative end-of-life care.	Deceased	94	Relapse
2	No	NA	ACR	67	NA
3	No	NA	ACR	104	NA
4	2.5 months after HSCT	Achieved MRD negativity after one cycle of Blina. Subsequently received treatment with venetoclax, Dex, VCR, L-ASP as well as a second course of Blina before the 2 <sup>nd</sup> HSCT.	Deceased	11	Adenoviral infection 10 months after 2 <sup>nd</sup> HSCT
5	No HSCT performed	CD19-negative relapse was treated with dasatinib, venetoclax, and InO.	Deceased	6	Infection during CD19-negative relapse
6	1 month after HSCT	Treatment attempt with venetoclax, bortezomib, thioguanine, etoposide, and cytarbine.	Deceased	4	Infection during relapse
7	No	NA	ACR	58	NA
8	No	NA	Deceased	7	Adenoviral infection 4.5 months after HSCT
9	4 months after HSCT	Palliative end-of-life care	Deceased	12	Relapse
10	No	NA	ACR	46	NA
11	8 months after HSCT	Two doses of InO and subsequent switch to therapy analogous to IntReALL SR Induction week 3 (Dex, Ara-C, VCR, triple intrathecal therapy) due to loss of CD22. Lymphodepletion with Flu and Cy followed by CD19-directed CAR-T cell therapy. Second combined extramedullary and bone marrow relapse 6 months after CAR-T cell therapy (mixed CD19-positive and negative phenotype).	AWD	17	NA
12	28 months after HSCT	InO	Deceased	34	Treatment-related toxicity while de-bulking with InO before planned CD19-

					directed CAR-T cell therapy
<b>13</b>	No* required CART to achieve remission pre HSCT	NA	ACR	28	NA
<b>14</b>	3 months after HSCT	Planned treatment with a modified HyperCVAD protocol including Blina and InO as bridging to CD19-directed CAR-T cell therapy.	AWD	8	NA
<b>15</b>	No	NA	Deceased	2	RSV infection on day +18 post-HSCT
<b>16</b>	No	NA	ACR	25	NA
<b>17</b>	No	NA	ACR	81	NA
<b>18</b>	Early relapse after 3 cycles of blinatumomab, before HSCT	Allogenic-HSCT was performed in CR2 after a salvage treatment with CD19-directed CAR-T cells. The second relapse 3 weeks after HSCT, was treated with supportive care with VCR and 6-MP.	Deceased	14	Refractory disease
<b>19</b>	No* required CART to achieve remission pre HSCT	NA	ACR	36	NA

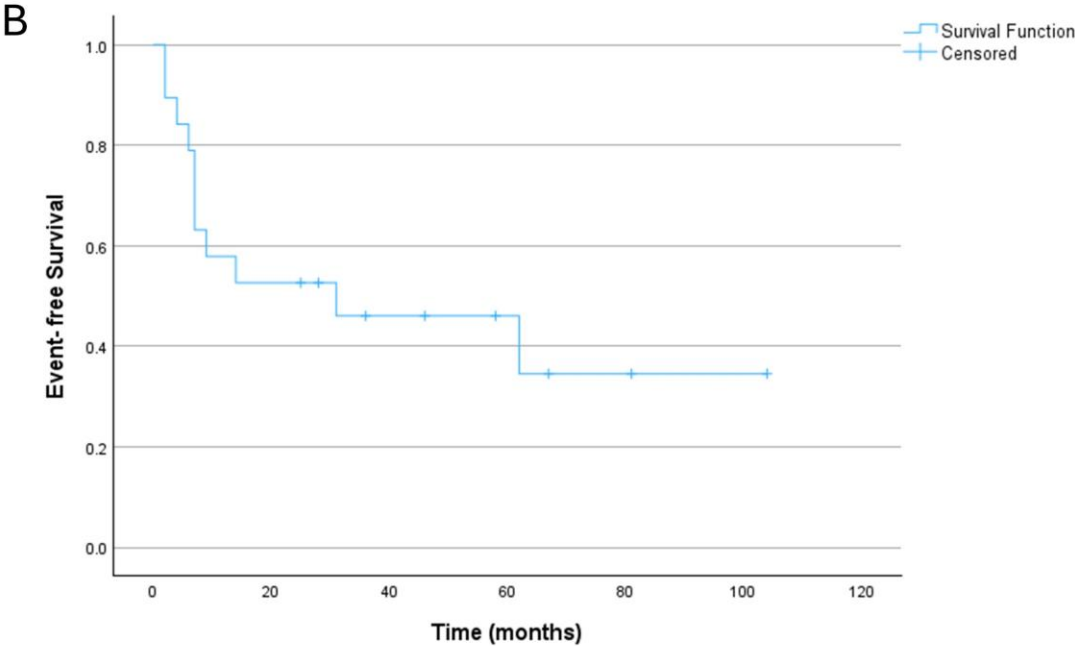
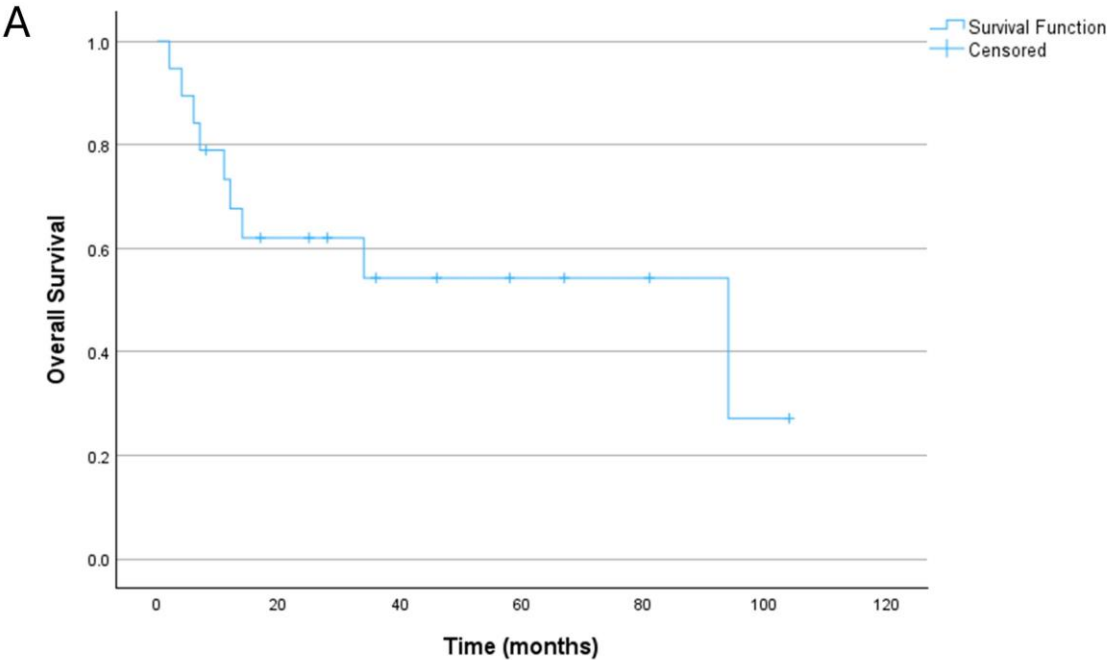
Blina: Blinatumomab; HSCT: hematopoietic stem cell transplantation; CAR-T cell: chimeric antibody T-cell; InO: inotuzumab ozogamicin; MRD: minimal residual disease; ACR: alive in complete remission; AWD: alive with disease; Dex: dexamethasone; Ara-C: cytarabine; L-ASP: pegylated L-asparaginase; VCR: vincristine; CVAD: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone; RSV: respiratory syncytial virus; CR2: second complete remission; 6-MP: 6-mercaptopurine.

Figure 1: **Swimmer's plot depicting the disease course of patients with *TCF3::HLF*-positive B-acute lymphoblastic leukemia.**

MRD: minimal residual disease; HSCT: hematopoietic stem cell transplantation; CAR-T cell: chimeric antibody T-cell.



Supplemental figure 1: Survival curves



A: Overall survival; B: Event-free survival.