L’evoluzione della strategia trapiantologica nelle LAL-B e il ruolo di blinatumomab

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What are the current results of allogeneic HSCT in the treatment of ALL in children?

Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study

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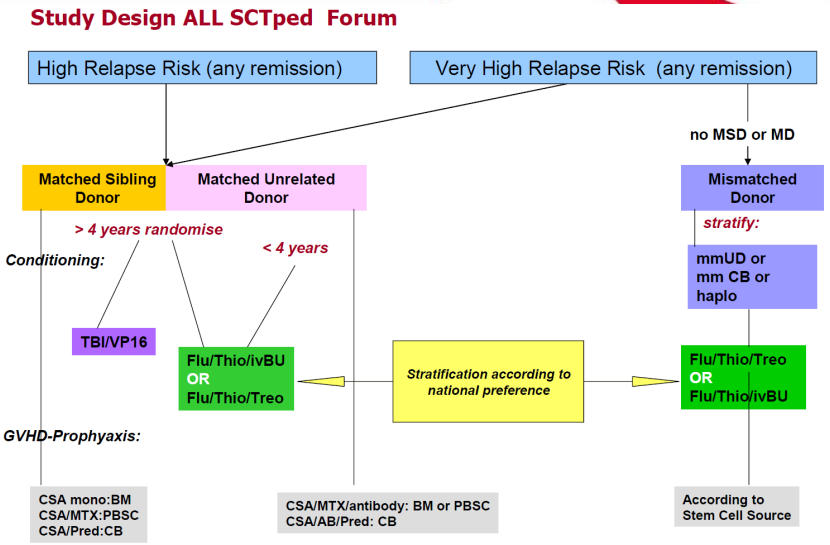
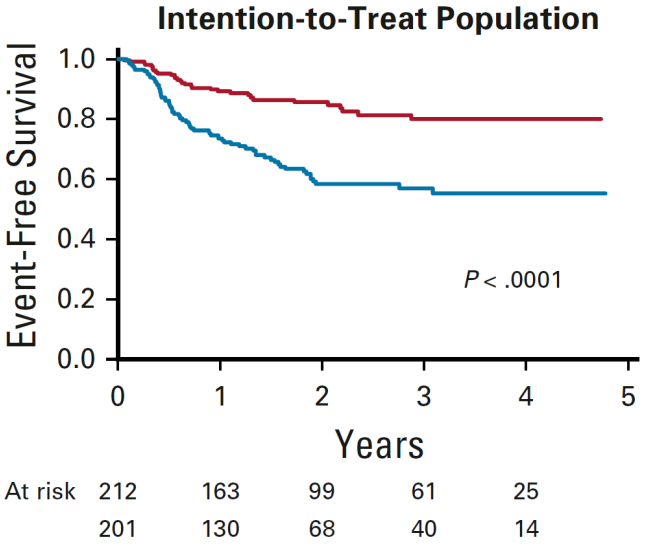
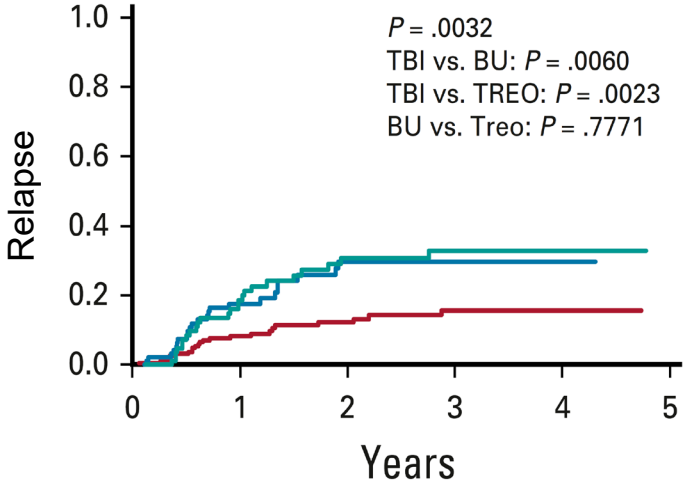


- Patients < 18 years at diagnosis, 4-21 years at HSCT, in complete remission, and with an HLA-compatible related or unrelated donor
- 543 patients were screened between April 18, 2013, and March 31, 2019.
- 413 patients were randomly assigned to receive a myeloablative conditioning with fractionated 12 Gy TBI and etoposide versus fludarabine, thiotepa, and either busulfan or treosulfan.

ALL SCTped FORUM - Results: EFS



	Patients	Eval.	Events	2-year EFS
TBI	212	209	31	0.86 (0.79-0.90)
CHC	201	200	72	0.58 (0.50-0.66)



	Patients	Eval.	Relapses	2-year CIR
TBI	194	194	23	0.12 (0.08-0.17)
BU	96	96	23	0.30 (0.19-0.41)
TREO	90	90	24	0.31 (0.20-0.42)

Who is currently eligible for allogeneic HSCT?

AIEOP-BFM ALL 2000 study

Table 2. Indications for allogeneic HSCT by subgroup

Subgroup	Indications for allogeneic HSCT	Type of donor: MFD	Type of donor: MUD
1	PPR and: WBC count ≥100 000/mm^3 or T-cell ALL or pro–B-cell ALL or MRD ≥10^{-2} at TP1*	Yes	No
2	MRD-HR 10^{-3} at TP2* or t(4;11) and PGR	Yes	No
3	MRD-HR ≥10^{-2} at TP2* or no remission at +33 or t(4;11) and PPR	Yes	Yes

PGR, prednisone good response.

*MRD level 10^{-3} indicates the interval of values between ≥5×10^{-4} and <5×10^{-3}; MRD level ≥10^{-2} includes all values ≥5×10^{-3}.

Eligible patients = 11%

AIEOP-BFM ALL 2009 study

Indicazioni ad alloHSCT		Risultati PCR-MRD [a]: MRD-SR	MRD-MR[b]	MRD-HR: MRD TP2 ≥10^{-3}- <10^{-2}	MRD-HR: MRD TP2 ≥10^{-2}	no risultati MRD
criteri (ordine gerarchico)	No CR g+33	no[f]	MMD	MMD	MMD	MMD
	t(4;11)[c]	no	MD	MD	MMD	MD
	ipodiploidia < 44 cromosomi[d]	no	MD	MD	MMD	MD
	PPR + T-LLA	no	no	MD	MMD	MD
	nessuna delle caratteristiche di cui sopra[e]	no	no	MD	MMD	no

Eligible patients = 6%

Indications to AlloHSCT in first CR according to study AIEOP-BFM ALL 2017 for all patients **except for infants <1 year** of age **with pB-ALL and evidence of *KMT2A* rearrangement**. The table includes HR as well as non-HR patients.

		PCR-MRD results				
				MRD-HR		
		TP1 neg	TP1 or TP2 pos and TP2 < $5x10^{-4}$	MRD TP2 ≥ $5x10^{-3}$ and < $5x10^{-4}$	MRD TP2 ≥ $5x10^{-3}$	no MRD result
	TCF3-HLF t(17;19)	MMD	MMD	MMD	MMD	
Hierachical criteria	no CR d33	n.a.	MD	MMD	MMD	MMD
	KMT2A-AFF1 t(4;11)	no	MD	MD	MMD	MD
	hypodiploidy < 44 chrom. or DNA index < 0.8	no	MD	MD	MMD	MD
	IKZF1^{plus} and FCM-MRD d+15 ≥ 10%	no	MD	MD	MMD	MD
	IKZF1^{plus} and FCM-MRD d+15 < 10%	no	no	MD	MMD	MD
	PPR + T-ALL	no	no	MD	MMD	MD
	none of the above features	no	no	MD	MMD	no

Expected number of eligible patients = 6%

TABLE 1. Demographics and Clinical Characteristics of Patients According to Randomized Arm and Chemoconditioning Regimen

Patient and Disease Characteristic, n (%)	All (N = 413)	TBI (n = 212)	Chemoconditioning		
			Total (n = 201)	Busulfan (n = 102)	Treosulfan (n = 99)
Donor					
MSD	108 (27%)	54 (26%)	54 (27%)	34 (34%)	20 (21%)
MD	299 (73%)	156 (74%)	143 (73%)	66 (66%)	77 (79%)
Remission status					
CR1	225 (54%)	118 (56%)	107 (53%)	47 (46%)	60 (61%)
CR2	164 (40%)	85 (40%)	79 (39%)	46 (45%)	33 (33%)
CR3	18 (4%)	7 (3%)	11 (5%)	7 (7%)	4 (4%)

HSCT in relapsed ALL (CR2): IntReALL2010

RISK STRATIFICATION: LINEAGE, TIME AND SITE OF RELAPSE

9.1.2 Definition of the SR and HR group

Two risk groups are defined: standard risk (SR) and high risk (HR).

Standard Risk (SR): Late or early isolated extramedullary relapse of BCP or T-ALL; late or early combined bone marrow / extramedullary relapse, late isolated bone marrow relapse of BCP ALL.

High Risk (HR): Very early isolated extramedullary relapse of BCP or T-ALL, early isolated or any very early bone marrow relapse of BCP-ALL, any bone marrow relapse of T-ALL.

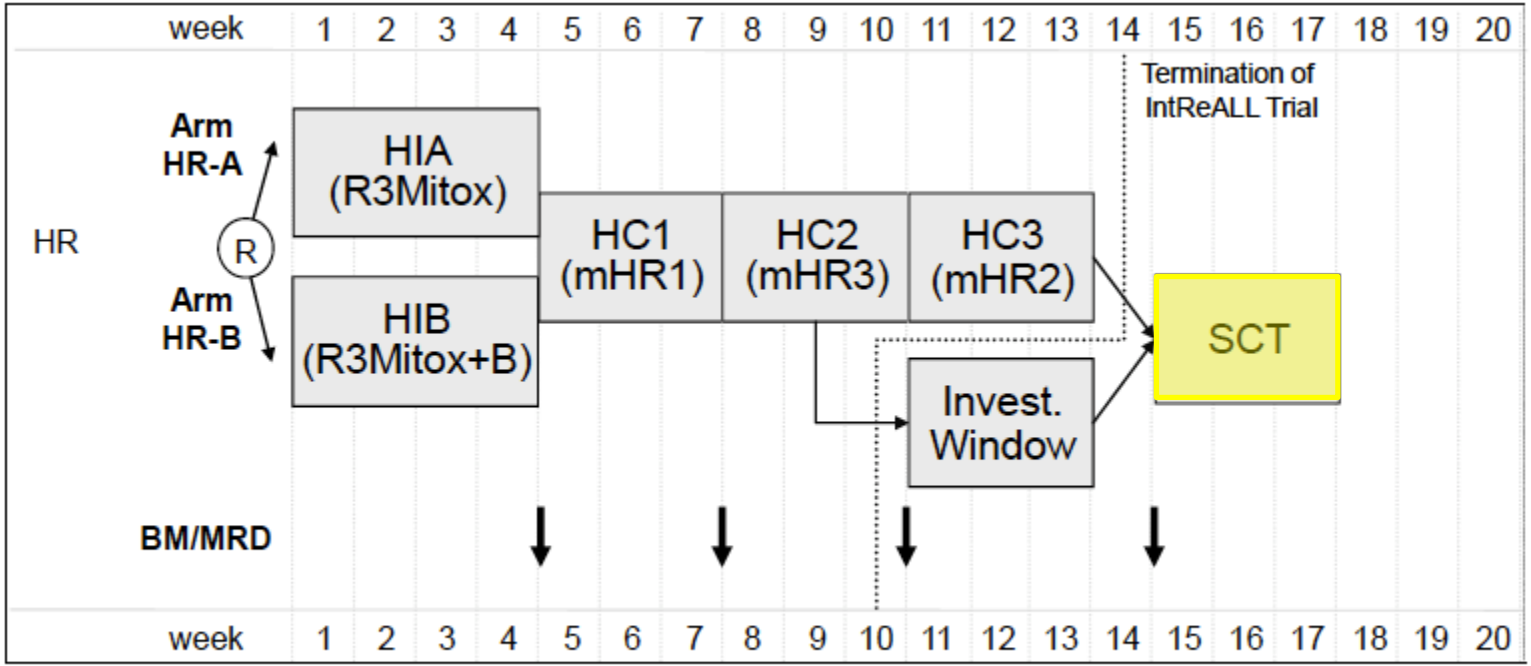
Table 3 Definition of IntReALL SR/HR 2010 risk groups

	Immunophenotype: B-cell precursor			Immunophenotype: (pre) T		
\ Site Time-point \	Extramed. Isolated	Bone marrow combined	Bone marrow isolated	Extramed. isolated	Bone marrow combined	Bone marrow isolated
Very early	HR	HR	HR	HR	HR	HR
Early	SR	SR	HR	SR	HR	HR
Late	SR	SR	SR	SR	HR	HR

Table 1 Definition of time point of relapse

Time-point	After primary diagnosis		After completion of primary therapy
Very early	< 18 months	and	< 6 months
Early	≥ 18 months	and	< 6 months
Late			≥ 6 months

HSCT in relapsed ALL: IntReALL 2010 High Risk



Arrow down (↓), bone marrow puncture with CR/MRD assessment; B, Bortezomib; HIA/B: HR induction arm A/B; HC1-3: HR consolidation 1-3; HR: high risk group; Invest., investigational; mHR1-3, modified BFM HR1-3 courses; MRD: minimal residual disease; R: randomization; R3Mitox, ALL-R3 backbone with mitoxantrone; SCT: stem-cell transplantation

Table 4 **Indication for allogeneic stem cell transplantation, IntReALL SR 2010 protocol**

SCT	SR							
	Late isolated or combined BM relapse			Early combined BM relapse			Isolated EM relapse	
	MRD GR	MRD PR	MRD ND	MRD GR	MRD PR	MRD ND	Late	Early
MD*	No	Yes	Yes	Yes	Yes	Yes	No	Yes
MMD**	No	Yes	No	No	Yes	Yes	No	No

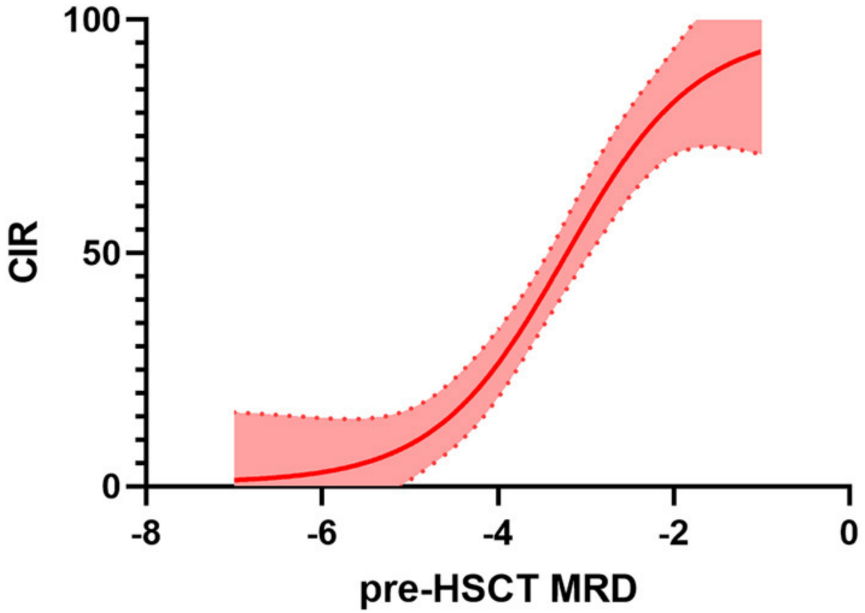
- **Minimal residual disease (MRD) good response**

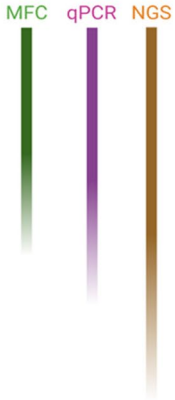
Arm A: MRD at day 1 of week 5 of < 10^{-3}; arm B: MRD at day 1 of week 6 of <10^{-4}.

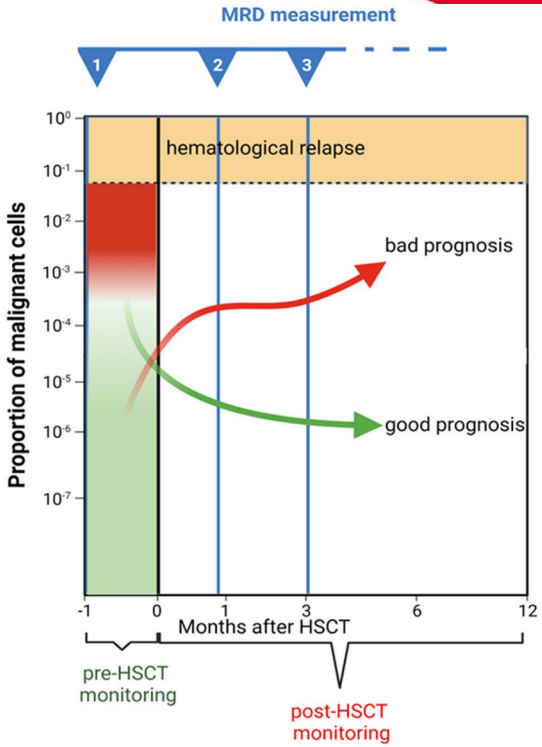
- **MRD poor response**

Arm A: MRD at day 1 of week 5 of ≥ 10^{-3}; arm B: MRD at day 1 of week 6 of ≥10^{-4}.

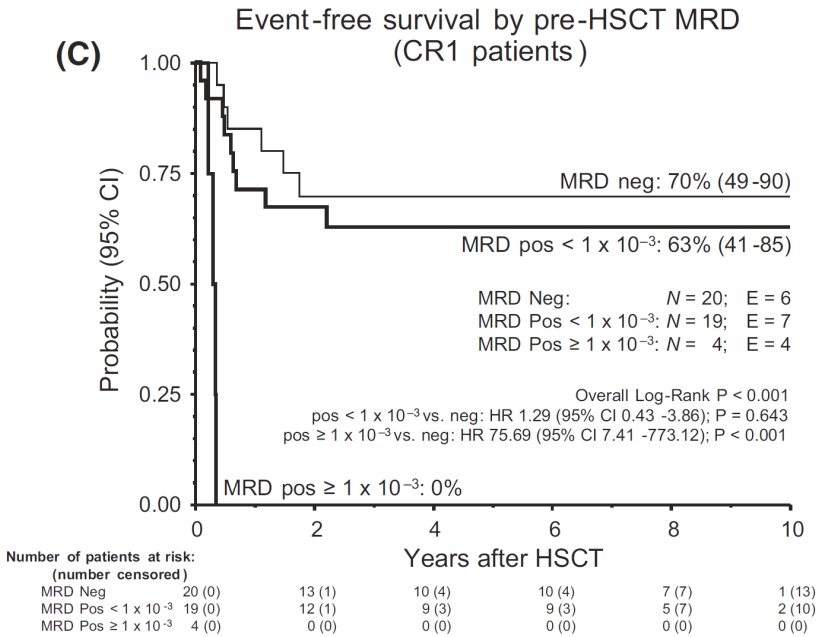
The role of minimal residual disease

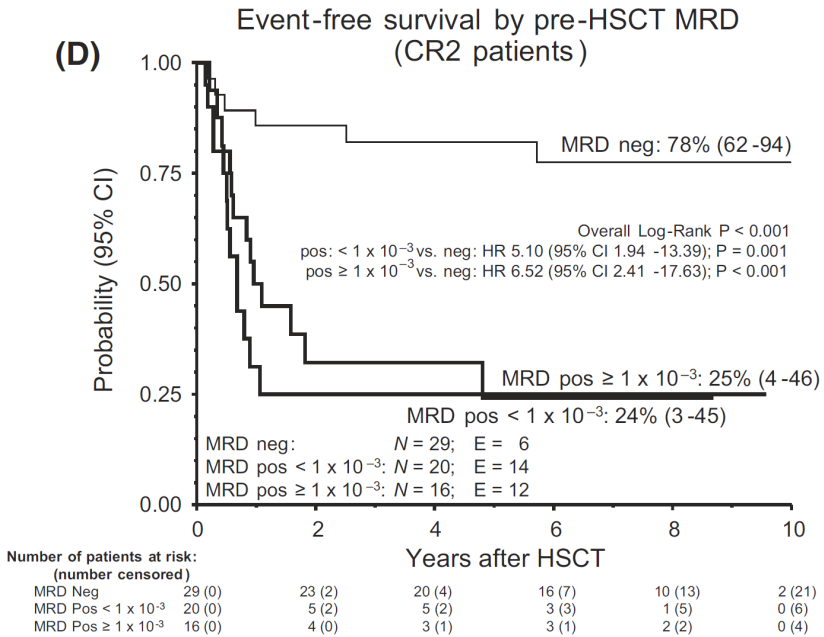

100
50
0
CIR
-8
-6
-4
-2
0
pre-HSCT MRD


MFC
qPCR
NGS


MRD measurement
1
2
3
hematological relapse
bad prognosis
good prognosis
Proportion of malignant cells
Months after HSCT
pre-HSCT monitoring
post-HSCT monitoring

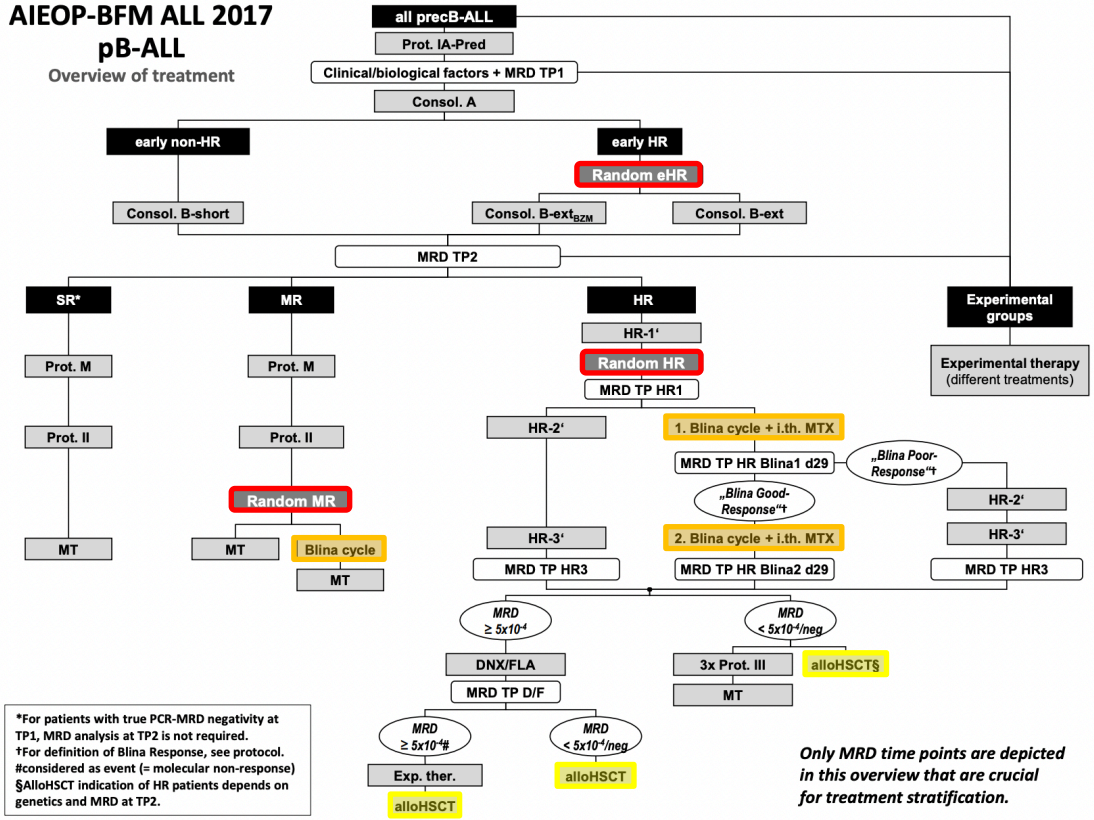
Prognostic significance of MRD levels **before** HSCT





Pre-HSCT immunotherapy for high-risk patients in first remission

Enrollment closed on August 31st, 2023



Pre-HSCT immunotherapy for high-risk patients in first remission:

- special populations

Infant ALL: historical data

Table 1. Summary of published outcomes for infants treated on collaborative group protocols over the past 25 years according to *KMT2A* status

Study	Year	*KMT2A*-rearranged			*KMT2A*-germline			Reference
		Number of infants	5-year EFS, %	5-year OS, %	Number of infants	5-year EFS, %	5-year OS, %	
CCG-1953	1996–2000	79	33.6	—	36	60.3	—	39
COG P9407	2001–2006	100	35.5	—	35	69.7	—	40
COG AALL0631	2008–2014	146	34	41	64	87.3	93.6	4,6
Interfant-99	1999–2005	311[a]	35.9[a,b]	43.2[a,b]	79	74.5[b]	83.4[b]	5,41
Interfant-06	2006–2016	476	36.4[b]	48.0[b]	167	73.9[b]	87.2[b]	
JILSG MLL96	1995–1998	80	38.6	50.8	22	95.5	95.5	42
JILSG MLL98	1998–2001							
JPLSG MLL03	2004–2009	62	43.2[c]	67.2[c]	—	—	—	43
JPLSG MLL-10	2011–2015	75	66.2	82.0	15	93.3	100	44

CCG, Children's Cancer Group; JILSG, Japan Infant Leukemia Study Group; JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; OS, overall survival; —, not reported.

[a]Data obtained following personal communication with the Interfant Trial Data Center.

[b]Six-year EFS and OS.

[c]Four-year EFS and OS.

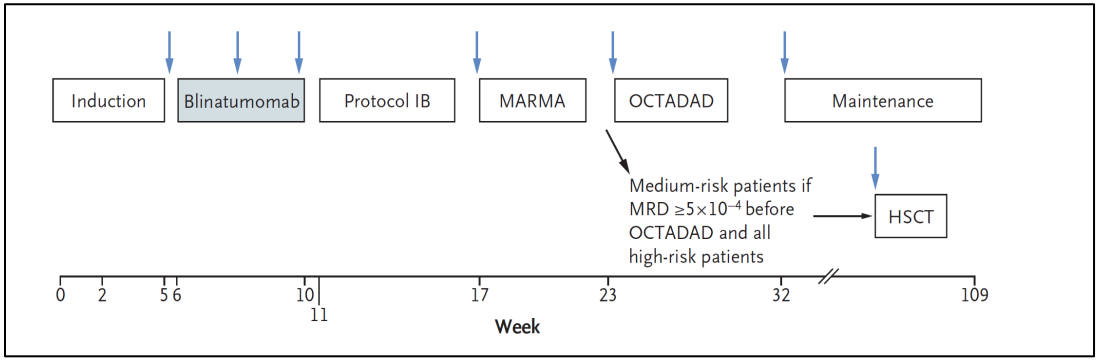
The NEW ENGLAND JOURNAL of MEDICINE

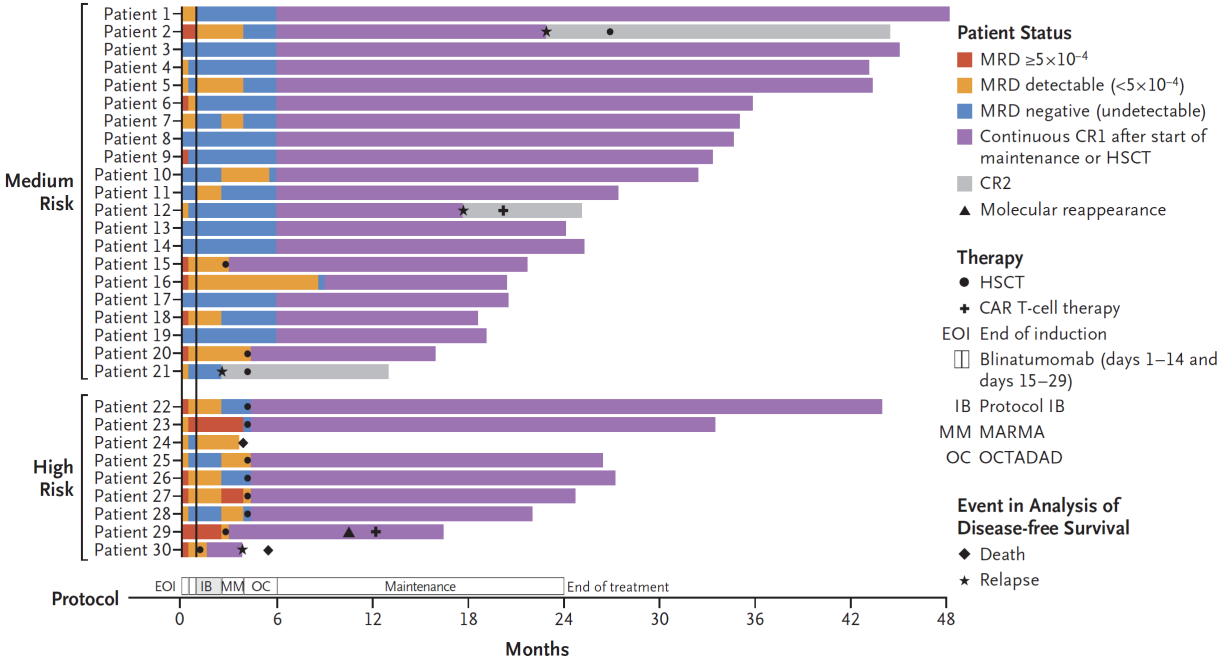
Original Article

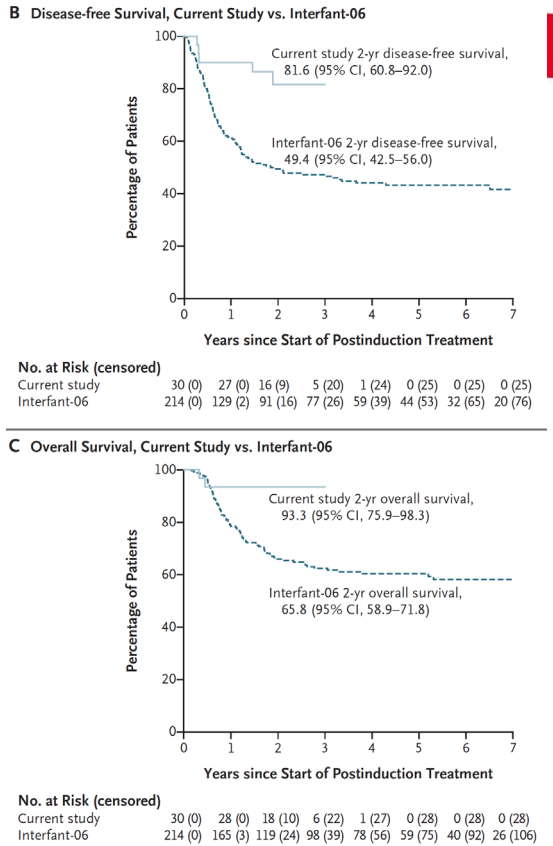
Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia

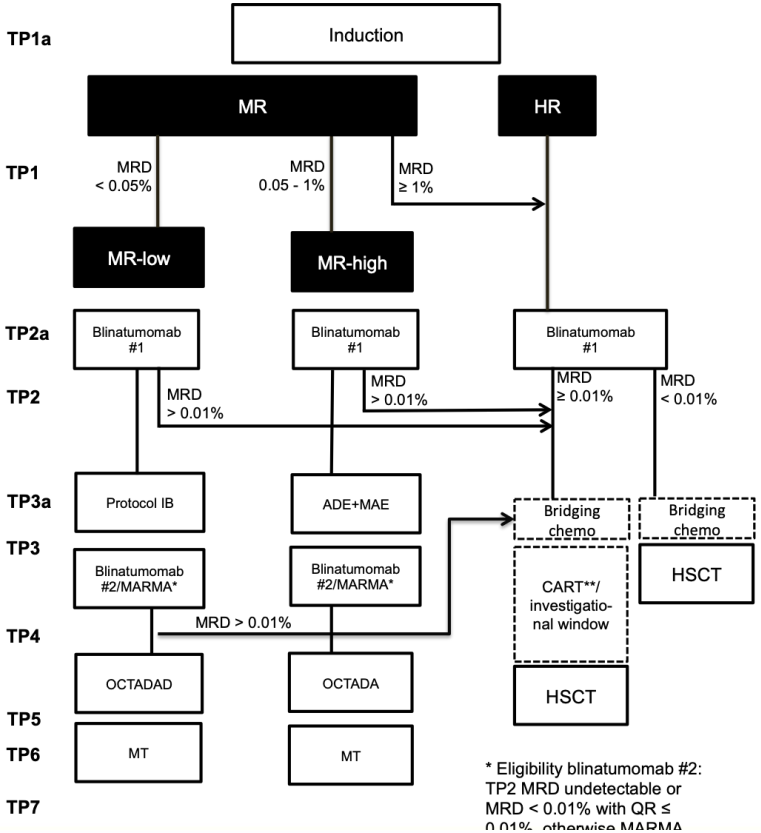
Prospective, single-group, international, multicenter, phase 2 study involving patients with **newly diagnosed KMT2A-rearranged ALL in the first year of life.** Outcome data were compared with historical control data from the Interfant-06 trial.

- **Inclusion criteria:** pts younger than 1 year of age with ND KMT2A-rearranged ALL that had been treated according to the Interfant-06 protocol with <25% blasts in the BM at the EOI
- The risk classification in accordance with Interfant-06:
  - **HR**: Age < 6 months at diagnosis with WBC ≥ 300×10^9 per liter at diagnosis or a poor response to prednisone;
  - **MR:** all other patients with KMT2A-rearranged ALL
- **Primary endpoint**: clinically relevant toxic effects, defined as any toxic effect that was possibly or definitely attributable to blinatumomab
- **Secondary endpoint**: SEAs, MRD response, % of medium-risk pts with MRD of at least 5×10^{-4} before OCTADAD, DFS and OS




Medium Risk
High Risk
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Patient 21
Patient 22
Patient 23
Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Protocol
EOI
IB
MM
OC
Maintenance
End of treatment
0
6
12
18
24
30
36
42
48
Months
Patient Status
MRD ≥5×10⁻⁴
MRD detectable (<5×10⁻⁴)
MRD negative (undetectable)
Continuous CR1 after start of maintenance or HSCT
CR2
Molecular reappearance
Therapy
HSCT
CAR T-cell therapy
EOI End of induction
Blinatumomab (days 1–14 and days 15–29)
IB Protocol IB
MM MARMA
OC OCTADAD
Event in Analysis of Disease-free Survival
Death
Relapse


B Disease-free Survival, Current Study vs. Interfant-06
Current study 2-yr disease-free survival, 81.6 (95% CI, 60.8–92.0)
Interfant-06 2-yr disease-free survival, 49.4 (95% CI, 42.5–56.0)
Percentage of Patients
Years since Start of Postinduction Treatment
No. at Risk (censored)
Current study 30 (0) 27 (0) 16 (9) 5 (20) 1 (24) 0 (25) 0 (25) 0 (25)
Interfant-06 214 (0) 129 (2) 91 (16) 77 (26) 59 (39) 44 (53) 32 (65) 20 (76)
C Overall Survival, Current Study vs. Interfant-06
Current study 2-yr overall survival, 93.3 (95% CI, 75.9–98.3)
Interfant-06 2-yr overall survival, 65.8 (95% CI, 58.9–71.8)
Percentage of Patients
Years since Start of Postinduction Treatment
No. at Risk (censored)
Current study 30 (0) 28 (0) 18 (10) 6 (22) 1 (27) 0 (28) 0 (28) 0 (28)
Interfant-06 214 (0) 165 (3) 119 (24) 98 (39) 78 (56) 59 (75) 40 (92) 26 (106)



Interfant-21

Medium risk (MR)	1. Age ≥-6 months **OR** 2. Age <-6 months **AND** WBC ≥-300 x 10^9/L **AND** prednisone good response
High risk (HR)	1. Age at diagnosis <6 months **AND** 2. WBC ≥300 x 10^9/L and/or prednisone poor response **OR** 3. MR patients not in CR at day 33 or MRD >0.01% post cycle 1 blinatumomab

Major changes to Interfant 06

1. One cycle of blinatumomab following induction in all patients
2. A second cycle of blinatumomab will replace MARMA in medium risk patients
3. All HR patients and MR patients with insufficient MRD response are eligible for SCT
4. HR and MR patients with insufficient MRD response are eligible for experimental therapy

Received: 14 April 2019 | Revised: 2 June 2019 | Accepted: 9 June 2019
DOI: 10.1002/pbc.27898
Pediatric Blood & Cancer
WILEY

BRIEF REPORT

Blinatumomab as a bridge to further therapy in cases of overwhelming toxicity in pediatric B-cell precursor acute lymphoblastic leukemia: Report from the Israeli Study Group of Childhood Leukemia

- 11 patients with ALL treated with blinatumomab following chemotherapy-associated toxicity, 4 has underlying genetic syndromes including DS.
- Five events were caused by gram-negative bacteria and four fungal infections and 7 of 11 required prolunged ICU admission.
- The median interval without chemotherapy was 122 days.
- The goal of bridging to further therapy was achieved in all 11 patients without further toxicity.

Received: 30 June 2017 | Revised: 24 August 2017 | Accepted: 25 August 2017
DOI: 10.1002/pbc.26824
WILEY Pediatric Blood & Cancer

BRIEF REPORT

Blinatumomab activity in a patient with Down syndrome B-precursor acute lymphoblastic leukemia

Abstract

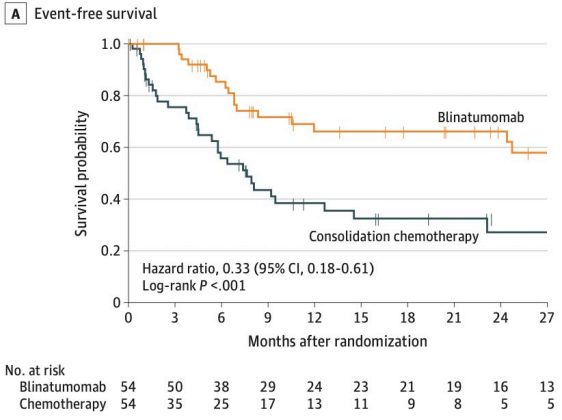
Persistent minimal residual disease (MRD) after consolidation may indicate chemotherapy insensitivity in B-precursor acute lymphoblastic leukemia (BP-ALL). Given the strong association of MRD and outcome in non-Down syndrome (non-DS) BP-ALL, it is likely that MRD levels are also of prognostic significance in DS BP-ALL. We report here the successful use of blinatumomab, a bispecific T-cell engager antibody construct, in a patient with DS BP-ALL and persistent MRD at the end of consolidation. Blinatumomab has been shown to have excellent results in patients with relapsed/refractory BP-ALL. This patient had no significant toxicity and achieved MRD negativity after only one cycle of blinatumomab.

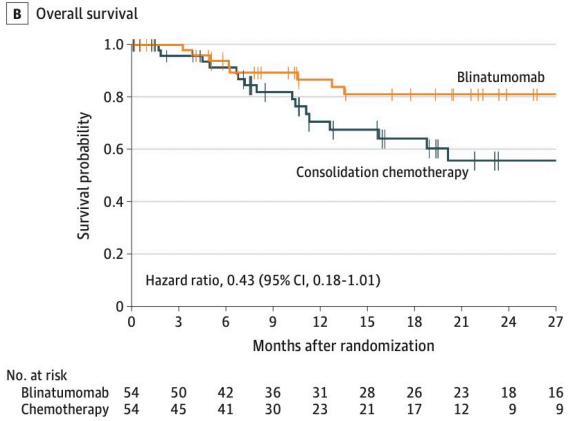
Pre-HSCT immunotherapy for patients in second remission

JAMA | Original Investigation

Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia
A Randomized Clinical Trial

Franco Locatelli, MD, PhD; Gerhard Zugmaier, MD; Carmelo Rizzari, MD; Joan D. Morris, MD; Bernd Gruhn, MD; Thomas Klingebiel, MD; Rosanna Parasole, MD; Christin Linderkamp, MD; Christian Flotho, MD; Arnaud Petit, MD, PhD; Concetta Micalizzi, MD; Noemi Mergen, MD; Abeera Mohammad, MSc; William N. Kormany, MD; Cornelia Eckert, PhD; Anja Möricke, MD; Mary Sartor, PhD; Ondrej Hrusak, MD, PhD; Christina Peters, MD; Vaskar Saha, MD, PhD; Luciana Vinti, MD, PhD; Arend von Stackelberg, MD





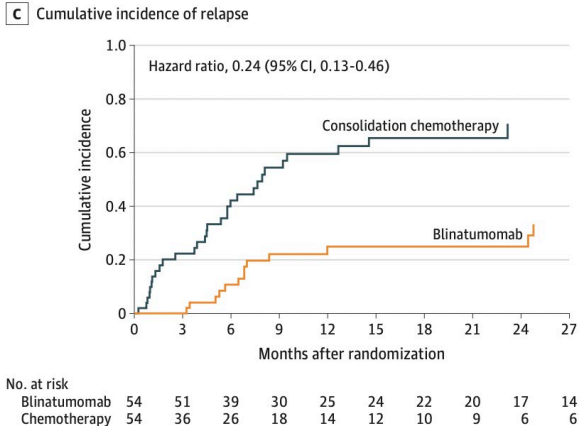


Table 2. Event-Free Survival, Overall Survival, Minimal Residual Disease Remission, and Allogeneic Hematopoietic Stem Cell Transplant Outcomes

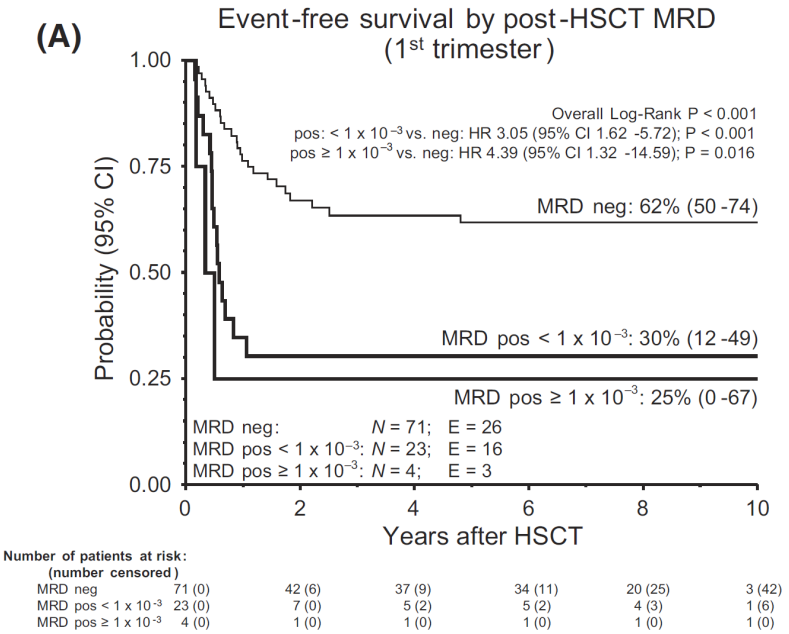
	No. (%)		
	Blinatumomab (n = 54)	Consolidation chemotherapy (n = 54)	Absolute difference, % (95% CI)
Minimal residual disease remission by minimal residual disease status at baseline (minimal residual disease evaluable set)[d,e,f]	Blinatumomab remission, No./total evaluable (%)	Consolidation chemotherapy remission, No./total evaluable (%)	
Minimal residual disease remission	17/20 (85)	20/23 (87)	−2.0 (−31.2 to 28.0)
No minimal residual disease remission	27/29 (93)	6/25 (24)	69.1 (45.4 to 85.5)
Total	44/49 (90)	26/48 (54)	35.6 (15.6 to 52.5)
	Blinatumomab (n = 48)	Consolidation chemotherapy (n = 38)	
Subset of patients who underwent allogeneic hematopoietic stem cell transplant in second complete remission			
Died after receiving a hematopoietic stem cell transplant			
Transplant-related death[h]	4 (8)	4 (11)	
Due to relapse/disease progression	3 (6)	8 (21)	

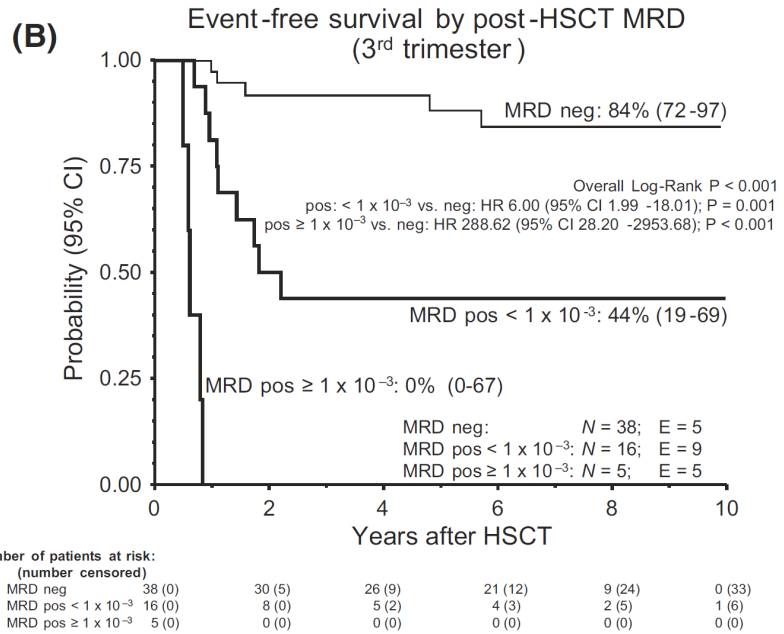
Modified from: Locatelli F et al. JAMA. 2021;325:843-854

Post-HSCT immunotherapy

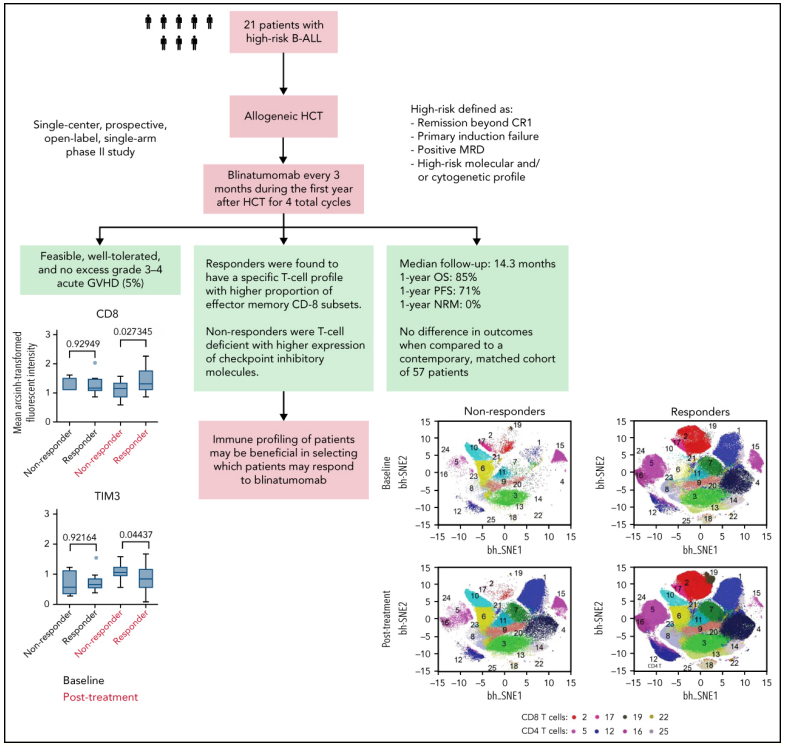
- Immunomodulation
- Prophylaxis
- Preemptive therapy

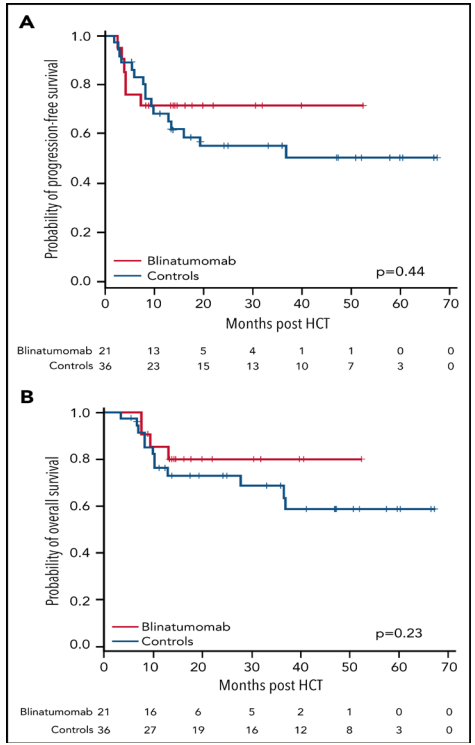
Prognostic significance of MRD levels **after** HSCT





Blinatumomab maintenance after allogeneic HSCT for adult B-lineage ALL





KEY POINTS

- **Blinatumomab is safe and feasible for use in B-ALL after allogeneic HCT.**
- **The composition of a patient's T-cell subsets at the time of treatment is indicative of whether they will respond to blinatumomab.**

Post-HSCT prophylaxis with blinatumomab

Blinatumomab After TCR Alpha Beta/CD19 Depleted HSCT

ClinicalTrials.gov Identifier: NCT04746209
Rachel Phelan, Medical College of Wisconsin
First posted February 9, 2021

Blina AFTER HSCT

Study objectives

- **Primary objective:** Safety and feasibility
- **Primary endpoint:** Percentage of patients who are able to receive the blinatumomab infusion at day +100 post-HCT and complete a minimum of 14/28 planned days.
- **Secondary objectives**:
  - Cumulative incidence of treatment-related events;
  - Overall survival;
  - Disease-free survival.

Post-HSCT preemptive treatment with blinatumomab

ALL SCTped 2012 FORUM Add-on Study Blina
Post HSCT
ClinicalTrials.gov Identifier: NCT04785547
Prof. Christina Peters, St. Anna Kinderkrebsforschung
First posted March 8, 2021

Blina AFTER HSCT

Recruitment status: recruiting

Study objectives

- **Primary objective:** can blinatumomab induce MRD-negativity in children who were MRD-positive after allogeneic HSCT without causing grade ≥ 2 aGVHD?
- **Primary endpoint:** rate of MRD negativity after blinatumomab treatment post-trasplant.
- **Secondary objectives**:
  - Feasibility of administering blinatumomab post HSCT;
  - Toxicities of blinatumomab when given in the post-HSCT setting in children and young adults;
  - Evaluate the 1-year OS rate.

Take home messages

- Blinatumomab is a standardized and off-the-shelf drug.
- The current indications for Blinatumomab are limited to patients over the age of 1 year with BCP ALL who are:
  - refractory or in relapse after HSCT or after two prior therapies;
  - in first HR relapse as part of consolidation therapy.
- Blinatumomab is under investigation in first-line protocols.
- High risk ALL subgroups as infants with KMT2A-rearranged ALL, as well as other poor prognosis subgroups could benefit from Blinatumomab treatment.
- Fragile populations (Down syndrome or patients with toxiciy) could also benefit from the addition of Blinatumomab to first-line therapy.
- Post-transplant immunotherapy is under evaluation; prophylactic or preemptive administration of Blinatumomab could reduce the risk of relapse and further improve transplant outcome.