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Relapsed and refractory precursor B-ALL in children and adolescents – which cellular therapy first?

Peter Bader, Frankfurt 27-01-2023

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Disclosures

- Research Grants: Neovii, Riemser, Medac
- Consulting fees: Novartis, Medac, Amgen
- Advisory boards: Novartis, Medac, Amgen
- Travel grants/honoraria: Amgen. Novartis, Jazz, Riemser, Neovii
- Patent and Royalties: Medac

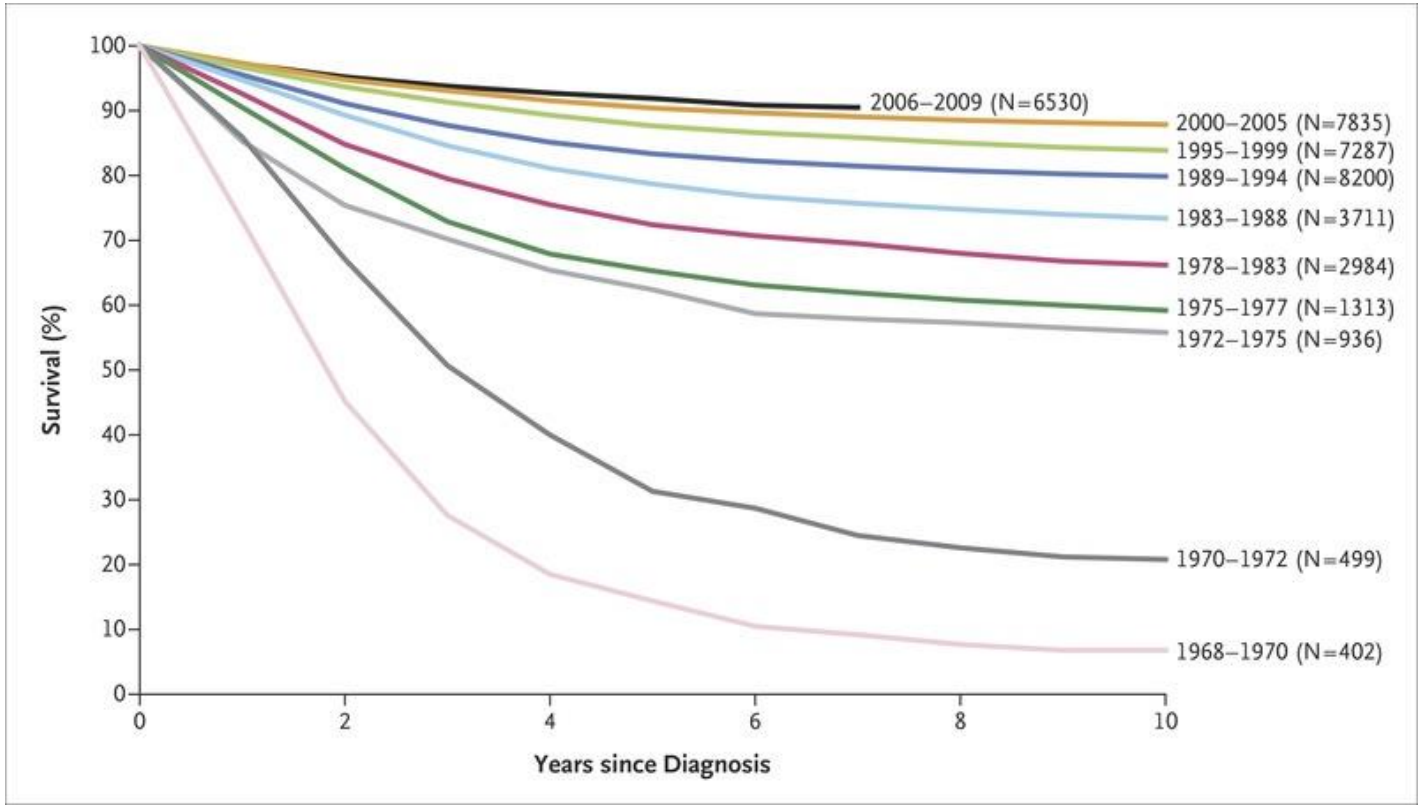
Development in Children And Adolescent ALL

- 5 Year survival rates in ped ALL reaching 90%
- Further intensification of chemotherapy leads to toxicity and lack of efficacy
- Allogeneic SCT has an important contribution to this sucess
- Targeted therapies are coming:
  - Improve efficacy
  - Reduce toxicity

- ALL diagnoses in pediatrics:

  85-93% B-lineage

  7-15% T-ALL



Hunger-S et al.: N Engl J Med 2015; 373:1541-1552

ALL-SCT BFM 2003:
Characteristics of study and patients

- Study period: September 2003 – September 2011
- Final analysis: February 2014
- Participating centres: n=27 (Germany, Austria, Switzerland)
- Transplanted patients: n=471
- Median observation time: 4.4 years

Peters C et al. JCO 2015

ALL Goldstandard MSD and MUD
TBI 12 Gy and VP-16

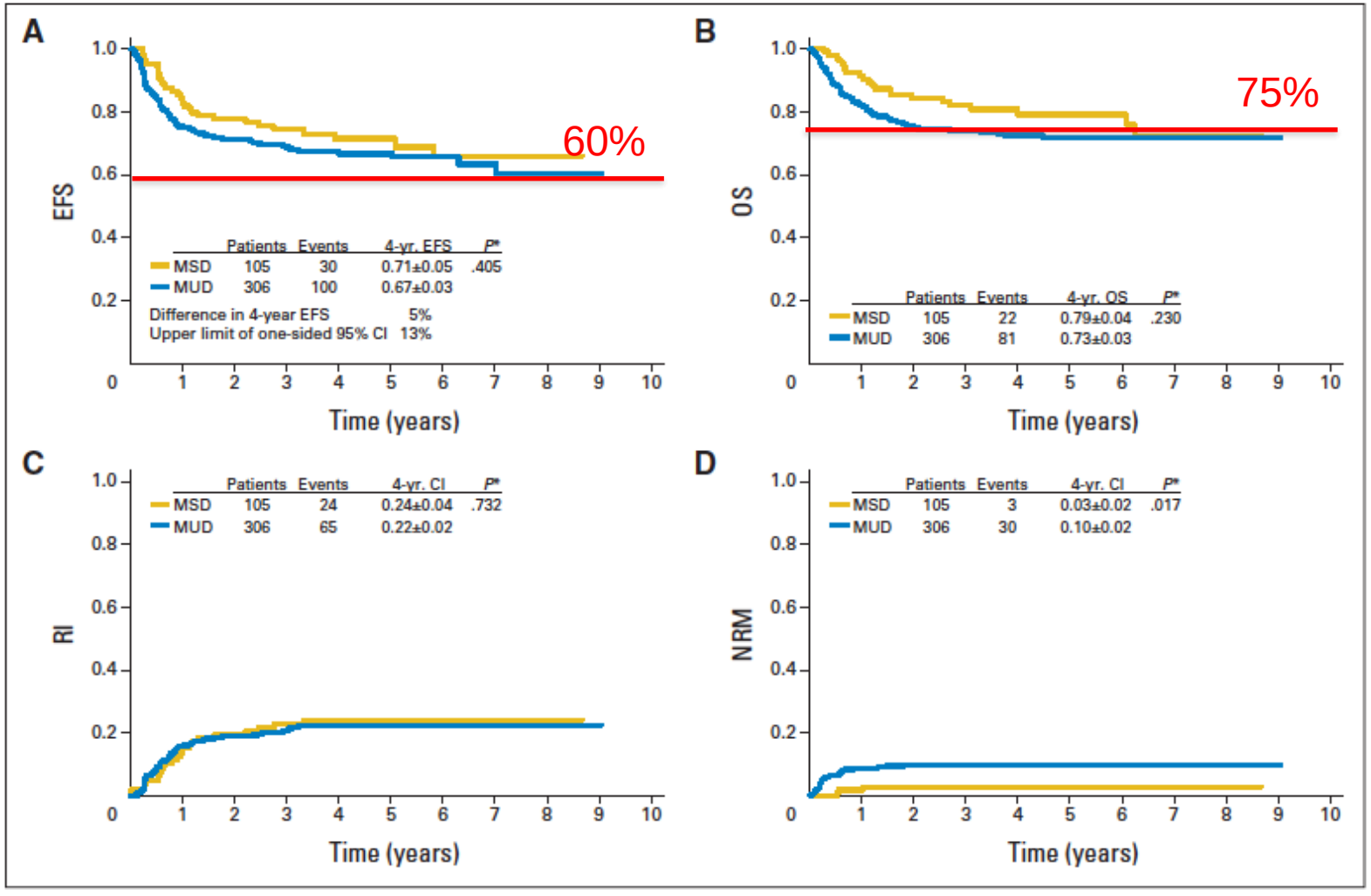


Fig 3. Four-year (A) event-free survival (EFS), (B) overall survival (OS), (C) relapse incidence (RI), and (D) nonrelapse mortality (NRM). MSD, HLA-matched sibling donor; MUD, HLA-matched unrelated donor. (*) Based on pseudovalues at 4 years.

Peters C et al. JCO 2015

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High Remission Rates In Pediatric Patients With Resistant Acute Lymphoblastic Leukemia Treated With Blinatumomab: Updated Analysis Of An Expanded Access Study (RIALTO)

Franco Locatelli[1], Gerhard Zugmaier[2], Peter Bader[3], Sima Jeha[4], Paul-Gerhardt Schlegel[5], Jean-Pierre Bourquin[6], Rupert Handgretinger[7], Benoit Brethon[8], Claudia Rossig[9], Christiane Chen-Santel[10]

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Locatelli F, et al. ASH 2019; Abstract 1294 and poster presentation.

High Remission Rates In Pediatric Patients With Resistant Acute Lymphoblastic Leukemia Treated With Blinatumomab: Updated Analysis Of An Expanded Access Study (RIALTO)

Is blinatumomab safe and efficacious for children with CD19+ R/R B-ALL?

RIALTO multicenter, open-label, expanded access study

Population

110 patients

62 males

48 females

Children > 28 days and < 18 years with CD19+ R/R B-ALL in ≥ 2 bone marrow relapse, any relapse after alloHSCT, or refractory to prior treatments

Intervention

Blinatumomab

- Cycle: 4 weeks cIV, 2 weeks off
- 2 cycles for induction
- If CR achieved, up to 3 cycles for consolidation

Adverse events of interest (treatment-related)

Cytokine release syndrome, grade 3–4

2 patients (1.8%)

Neurologic event, grade 3 (no grade 4)

4 patients (3.6%)

Efficacy (after 2 cycles of blinatumomab)

Response was independent of genetic abnormalities

Patient achieving MRD-negative complete remission (CR)

All patients: 52% MRD-negative CR

t(12;21)/*TEL-AML1*: 5/6 (83%)

Hyperdiploidy: 2/5 (40%)

Constitutional trisomy 21: 4/4 (100%)

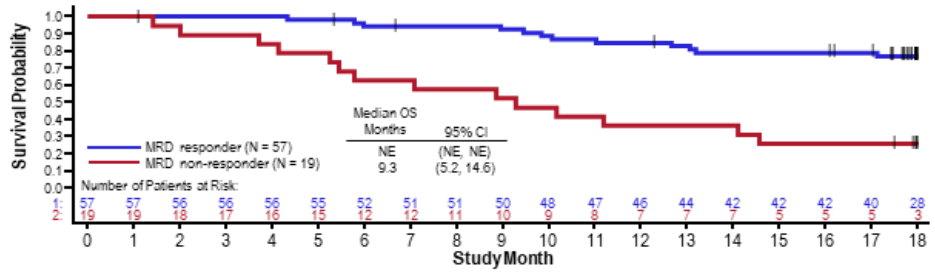
t(17;19): 2/2 (100%)

t(9;22)/*BCR-ABL*: 2/4 (50%)

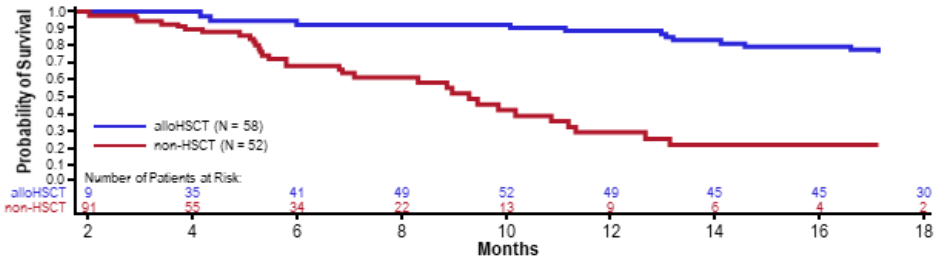
***MLL* re-arrangement:** 4/9 (44%)

MRD response and alloHSCT post-blinatumomab showed the best outcome

Overall Survival by MRD response



Overall Survival by alloHSCT status post-blinatumomab



Locatelli et al.: Blood Cancer J. 2020 Jul 24;10(7):77.

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Research

JAMA | Original Investigation

Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia

A Randomized Clinical Trial

Patrick A. Brown, MD; Lingyun Ji, PhD; Xinxin Xu, MS; Meenakshi Devidas, PhD; Laura E. Hogan, MD; Michael J. Borowitz, MD, PhD; Elizabeth A. Raetz, MD; Gerhard Zugmaier, MD; Elad Sharon, MD, MPH; Melanie B. Bernhardt, PharmD; Stephanie A. Terezakis, MD; Lia Gore, MD; James A. Whitlock, MD; Michael A. Pulsipher, MD; Stephen P. Hunger, MD; Mignon L. Loh, MD

Brown, P et al: JAMA 2021; 325 (9): 833-842

Stratifications

- Risk group (HR vs IR)
- For HR:
  - Site (BM vs iEM)
  - For BM: CR1 duration (<18 vs 18-36mo)

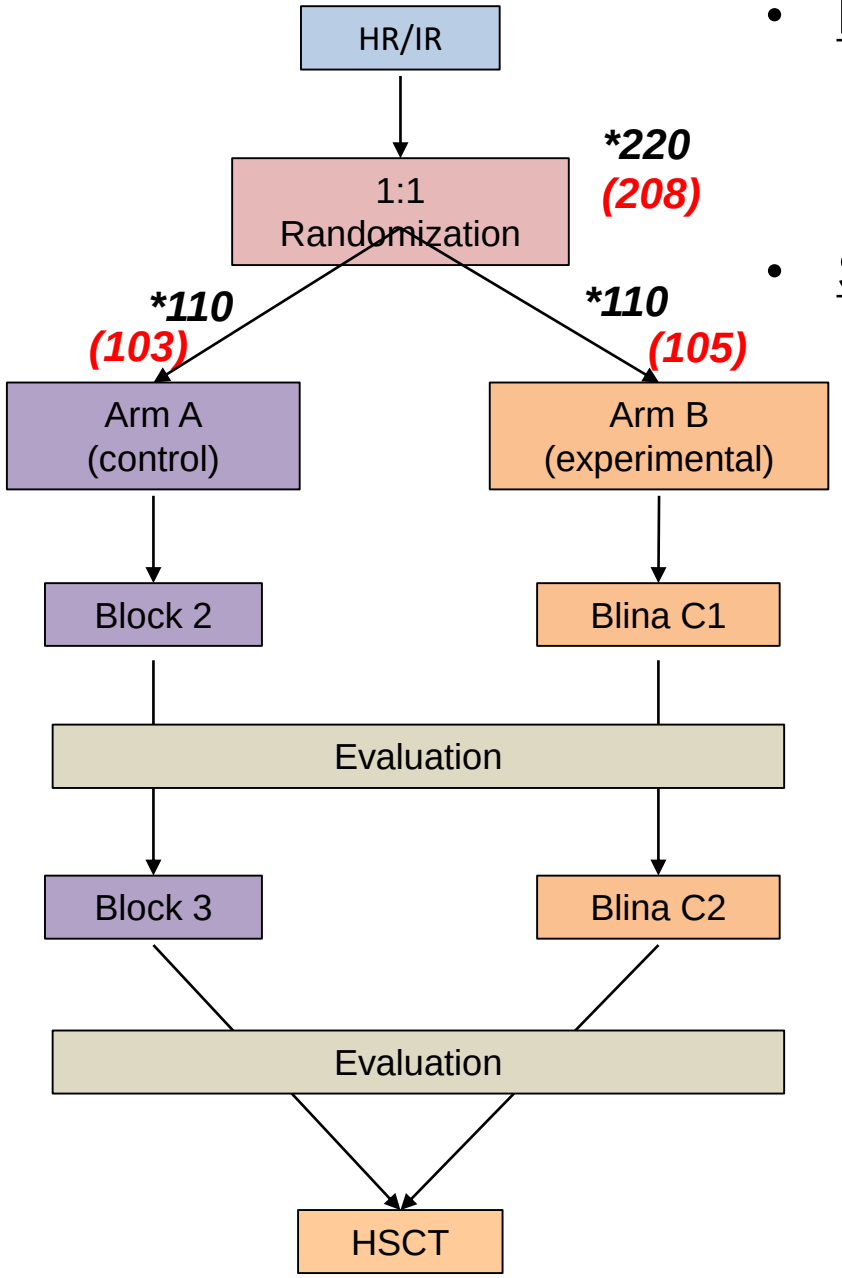
UKALLR3, Block 2*

- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

UKALLR3, Block 3*

- VCR, DEX week 1
- HD ARAC, Erwinia Weeks 1-2
- ID MTX, Erwinia Week 4
- IT MTX or ITT

*UKALLR3 reference: *Parker, et al. Lancet. 2010; 376: 2009-17*



- Endpoints
  - Primary: DFS
  - Other: OS, MRD response, ability to proceed to HSCT
- Sample size n=220 (110 per arm)
  - Power 85% to detect HR 0.58 with 1-sided α=0.025
  - Increase 2 yr DFS from 45% to 63%

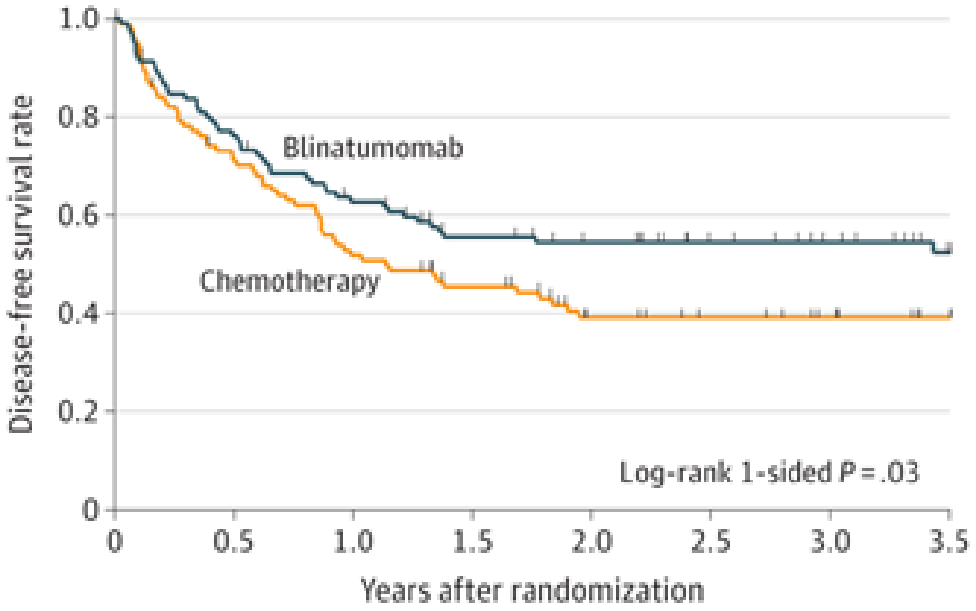
Blina C1 and Blina C2

- Blinatumomab 15 ug/m2/day x 28 days, then 7 days off
- Dex 5 mg/m2/dose x 1 premed (C1 only)

- ***First patient randomized Jan 2015***
- ***Randomization halted Sep 2019 (95% projected accrual)***

Brown PA, et al. ASH 2019; Abstract LBA-1 and oral presentation.

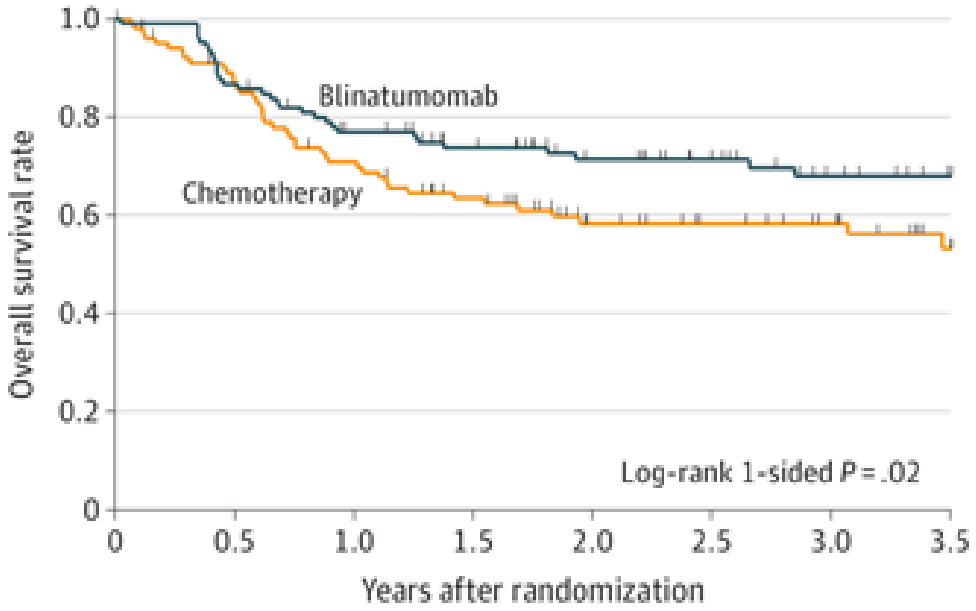
A Disease-free survival



No. of patients at risk

Blinatumomab	105	80	64	52	47	38	33	25
Chemotherapy	103	70	51	40	27	23	19	12

B Overall survival



No. of patients at risk

Blinatumomab	105	91	77	67	56	47	38	32
Chemotherapy	103	86	69	56	40	34	29	17

Brown, P et al: JAMA 2021; 325 (9): 833-842

JAMA | Original Investigation

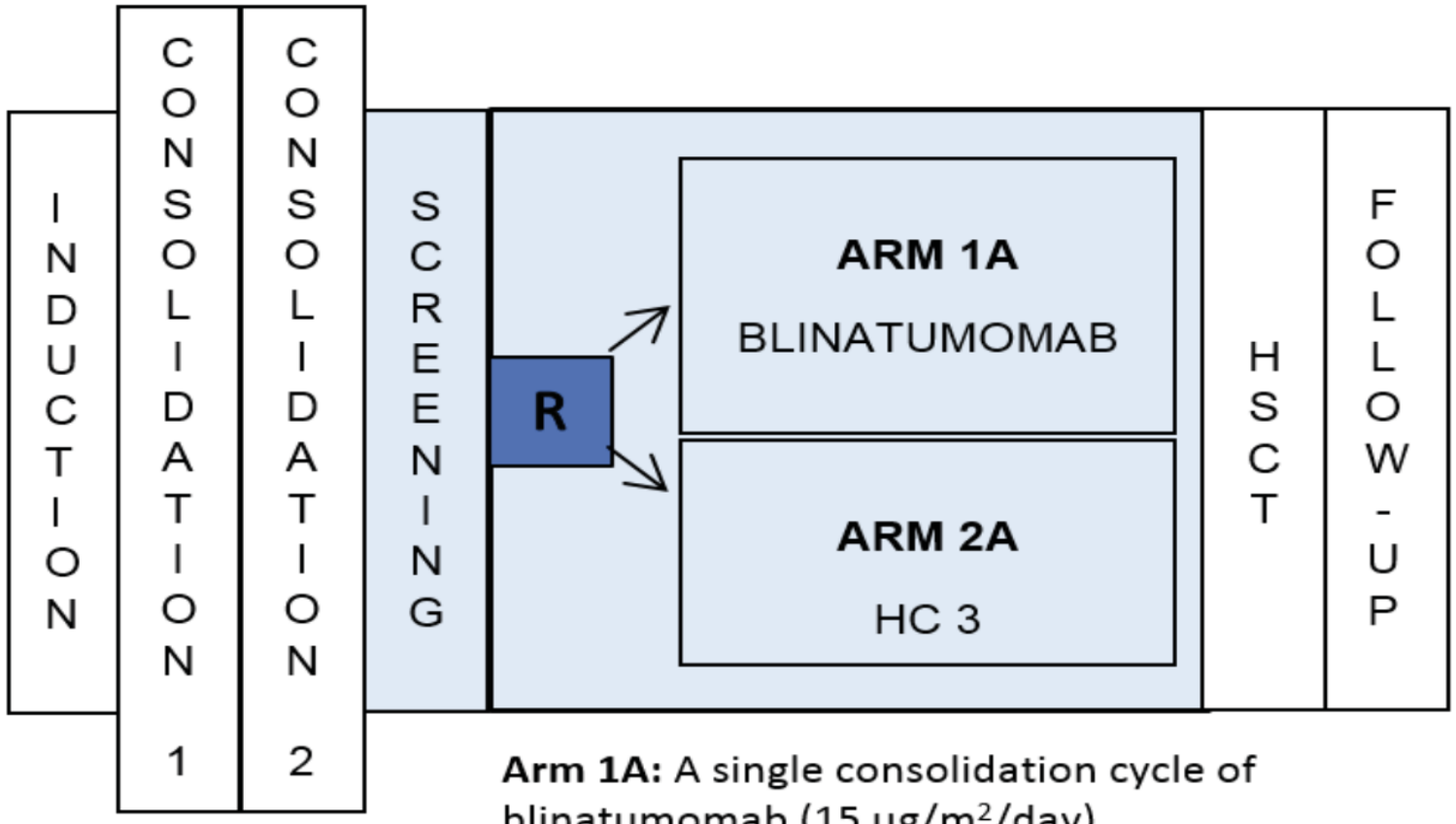
Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia
A Randomized Clinical Trial

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

IMPORTANCE Blinatumomab is a CD3/CD19-directed bispecific T-cell engager molecule with efficacy in children with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL).

OBJECTIVE To evaluate event-free survival in children with high-risk first-relapse B-ALL after a third consolidation course with blinatumomab vs consolidation chemotherapy before allogeneic hematopoietic stem cell transplant.

Study Design and Treatment Schema



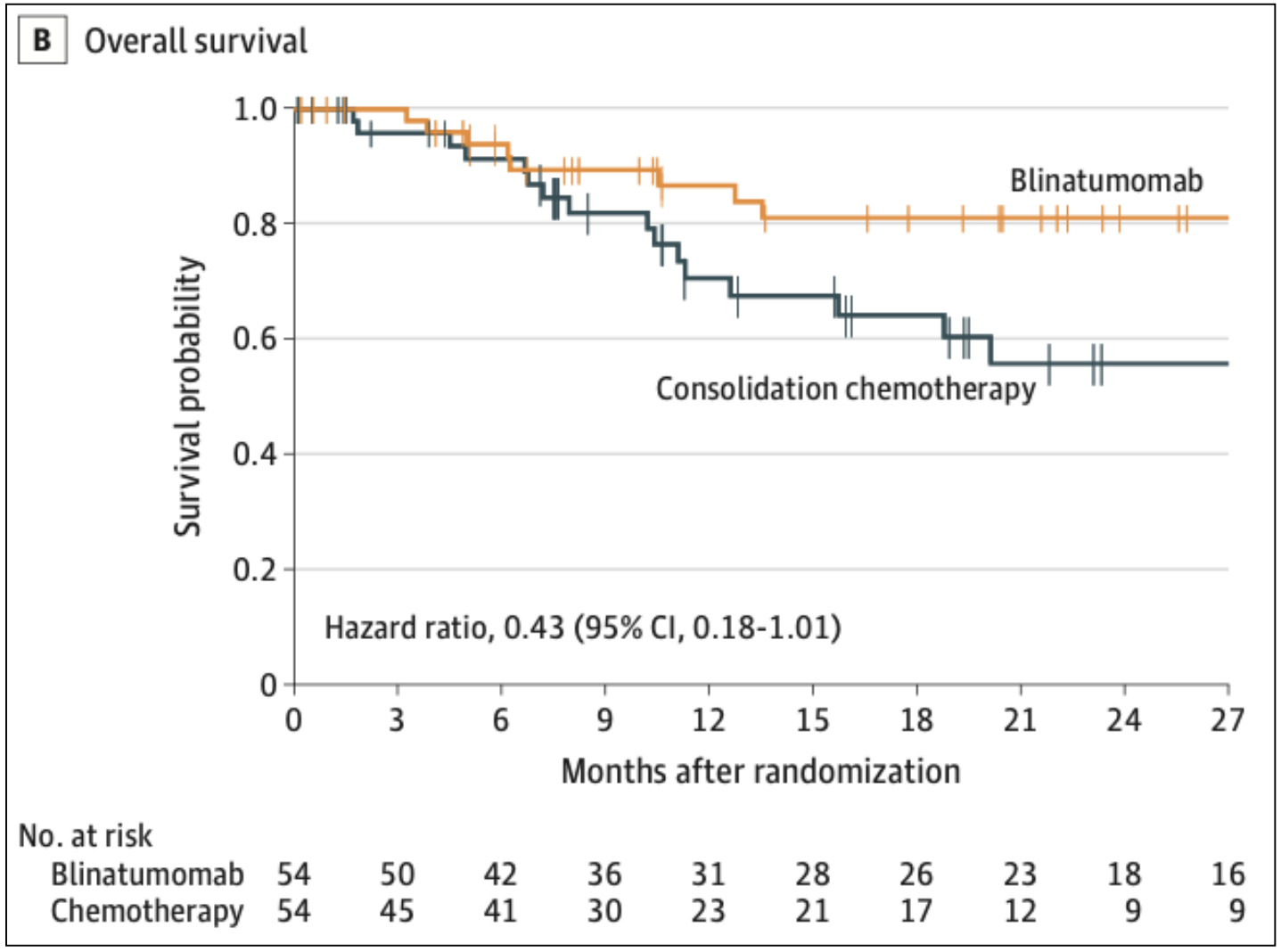
Arm 1A: A single consolidation cycle of blinatumomab (15 µg/m²/day)

Arm 2A: A single consolidation cycle HC3

HC = high risk consolidation; HSCT = hematopoietic stem cell transplantation; R = randomization

Locatelli et al. *JAMA*. 2021

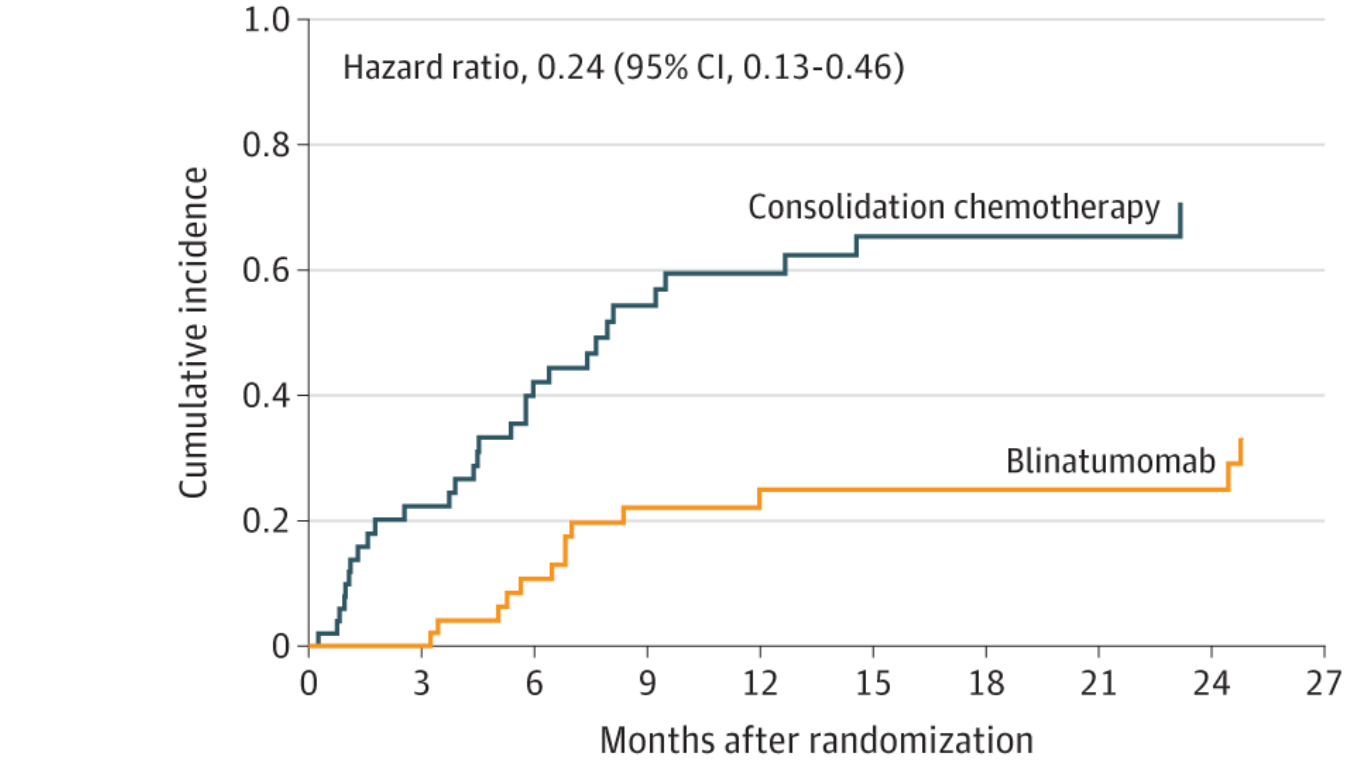
Outcome: OS



Locatelli et al. *JAMA*. 2021

Cumulative Incidence of relapse

C Cumulative incidence of relapse



No. at risk

Blinatumomab	54	51	39	30	25	24	22	20	17	14
Chemotherapy	54	36	26	18	14	12	10	9	6	6

Locatelli et al. *JAMA*. 2021

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Check f update

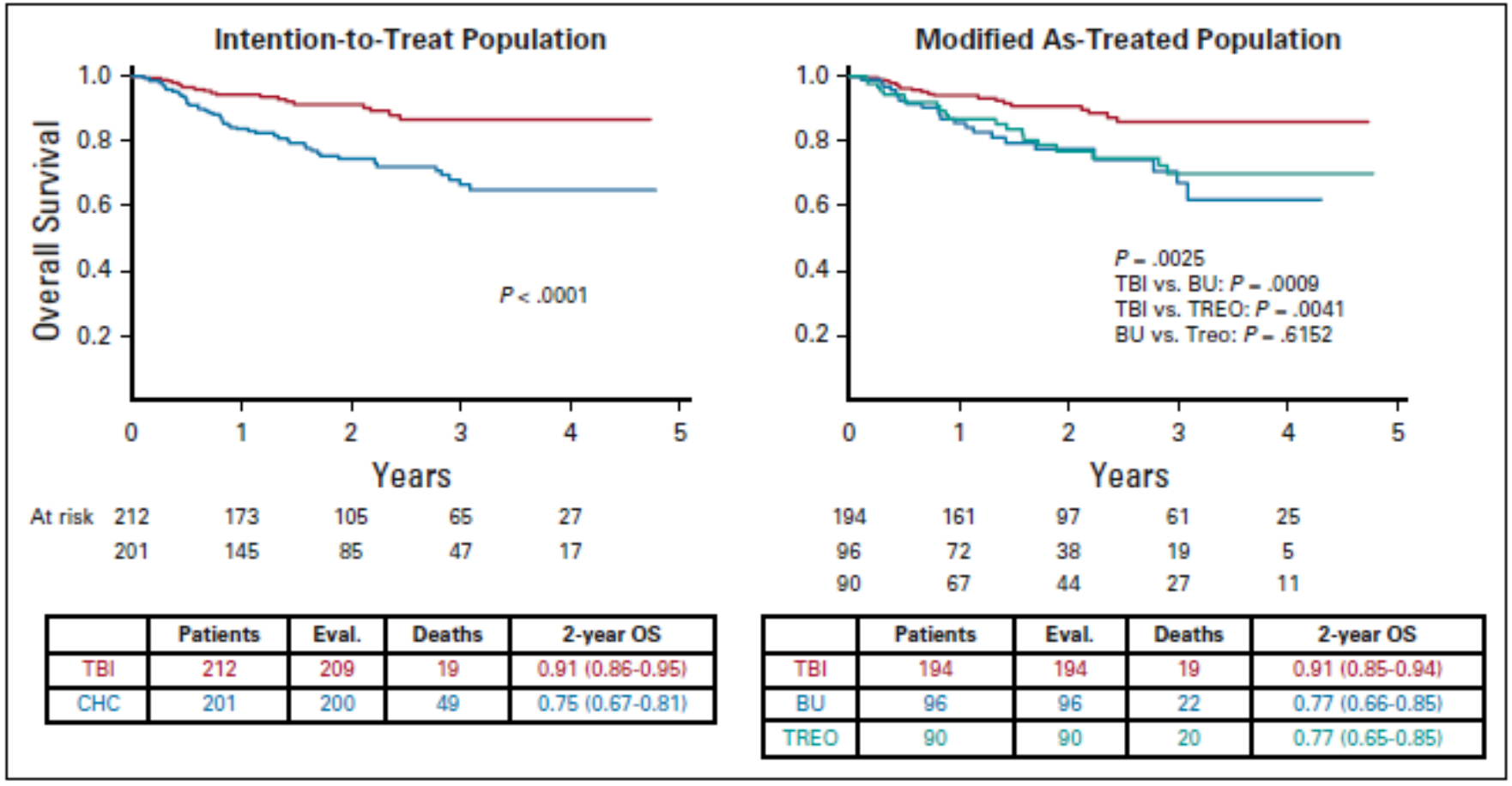
original reports

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

Christina Peters, MD[1]; Jean-Hugues Dalle, MD, PhD[2]; Franco Locatelli, MD, PhD[3]; Ulrike Poetschger, PhD[4]; Petr Sedlacek, MD[5]; Jochen Buechner, MD, PhD[6]; Peter J. Shaw, MD[7]; Raquel Staciuk, MD[8]; Marianne Ifversen, MD, PhD[9]; Herbert Pichler, MD[1]; Kim Vettenranta, MD, PhD[10]; Peter Svec, MD, PhD[11]; Olga Aleinikova, MD, PhD[12]; Jerry Stein, MD[13]; Tayfun Güngör, MD[14]; Jacek Toporski, MD[15]; Tony H. Truong, MD, MPH[16]; Cristina Diaz-de-Heredia, MD[17]; Marc Bierings, MD, PhD[18]; Hany Ariffin, MD, PhD[19]; Mohammed Essa, MD[20]; Birgit Burkhardt, MD, PhD[21]; Kirk Schultz, MD[22]; Roland Meisel, MD[23]; Arjan Lankester, MD, PhD[24]; Marc Ansari, MD[25]; and Martin Schrappe, MD, PhD,[26] on behalf of the IBFM Study Group; Arend von Stackelberg, MD,[27] on behalf of the IntReALL Study Group; Adriana Balduzzi, MD,[28] on behalf of the I-BFM SCT Study Group; Selim Corbacioglu, MD,[29] on behalf of the EBMT Paediatric Diseases Working Party; and Peter Bader, MD[30]

Peters-C: J Clin Oncol. 2021 Feb 1;39(4):295-307.

Allogeneic SCT: Superiority for TBI-VP-16



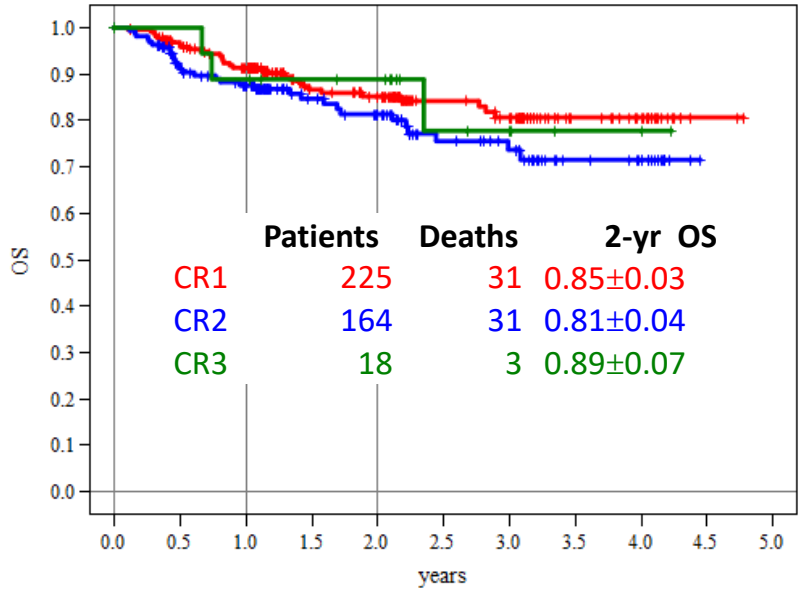
	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

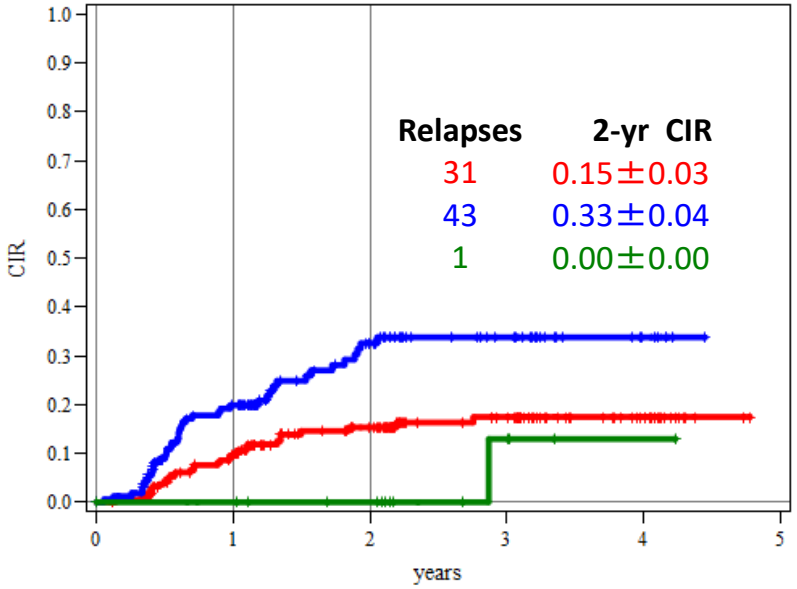
	Patients	Eval.	Deaths	2-year OS
TBI	194	194	19	0.91 (0.85-0.94)
BU	96	96	22	0.77 (0.66-0.85)
TREO	90	90	20	0.77 (0.65-0.85)

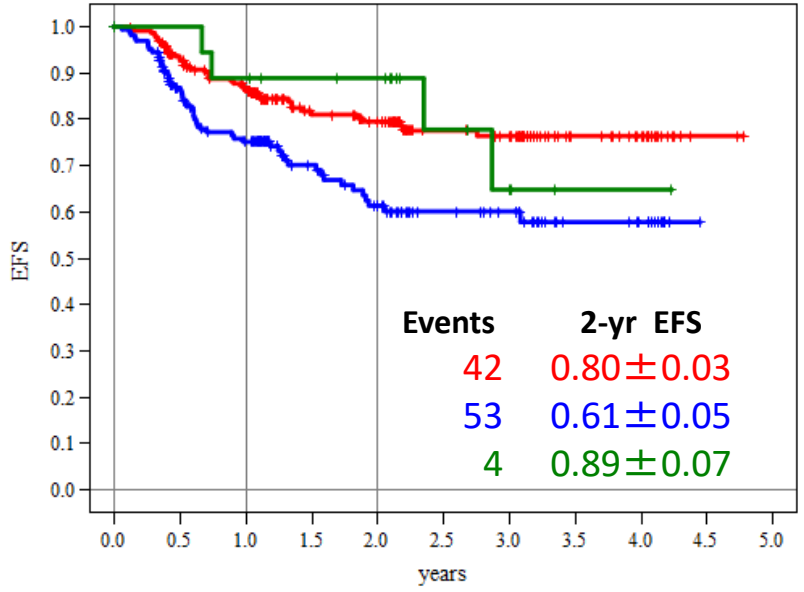
FIG 2. Primary end point: Overall survival. BU, busulfan; CHC, chemo-conditioning; CIR, cumulative incidence of relapse; EFS, event-free survival; OS, overall survival; TBI, total body irradiation; TREO, treosulfan; TRM, treatment-related mortality.

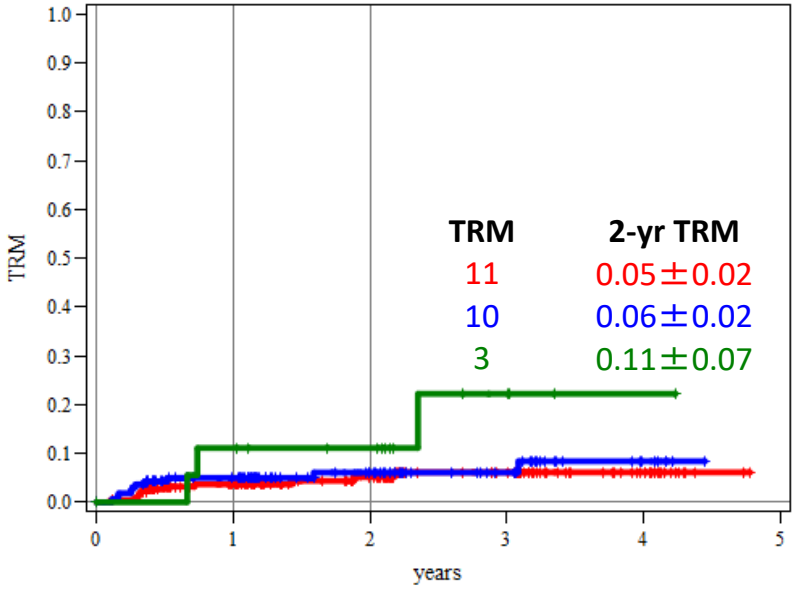
Peters-C: J Clin Oncol. 2021 Feb 1;39(4):295-307.

Results: Remission Status









HSCT in Children and Adolescents

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- TBI and VP-16 Gold standard conditioning regimen
- ≥ 9/10 high resolution matched donors
  - Very low complication rate and very good anti-leukemia efficacy

- Excellent results for
  - CR1: very high risk patients
  - CR 2: high risk and very high risk patients
  - **EFS: 80%**
- Pre-treatment with Blinatumomab is promising even improvement of these results

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CAR-T Cell Treatment for Relapse after Allo-HSCT

REGULAR ARTICLE

blood advances

CD19 CAR T cells are an effective therapy for posttransplant relapse in patients with B-lineage ALL: real-world data from Germany

Peter Bader,[1] Claudia Rossig,[2] Martin Hutter,[1] Francis Ayuketang Ayuk,[3] Claudia D. Baldus,[4] Veit L. Buecklein,[5] Halvard Bonig,[6] Gunnar Cario,[7] Hermann Einsele,[8] Udo Holtick,[9] Christian Koenecke,[10] Shahrzad Bakhtiar,[1] Annette Künkele,[11] Roland Meisel,[12] Fabian Mueller,[13] Ingo Müller,[14] Olaf Penack,[15] Eva Rettinger,[1] Martin G. Sauer,[16] Paul-Gerhardt Schlegel,[17] Jan Soerensen,[1] Arend von Stackelberg,[11] Brigitte Strahm,[18] Julia Hauer,[19,20] Tobias Feuchtinger,[21,*] and Andrea Jarisch[1,*]

Bader-P et al.: Blood Advances 2023 in press

Patient characteristics

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All patients	81	(100%)	All patients	81	(100%)
Diagnosis			**Age**	12	
CD19 pos prec. B ALL	81	(100)	**(median [range])**	[1-25]	
Indication			**Bodyweight**	42 Kg	
Relapse after SCT	65	(80)	**(median [range])**	[8 – 135]	
1st refrac. relapse	1	(1)			
2nd refrac. relapse	15	(19)			
Leukemia site involvement			**Time from HSCT to relapse**		
Isol. BM	41	(51)	< 6 months	22	(34)
Isol. CNS	7	(9)	≥ 6 months	43	(66)
BM + CNS	13	(16)			
Other	20	(25)			

Bader-P et al.: Blood Advances 2023 in press

All Patients - N = 81

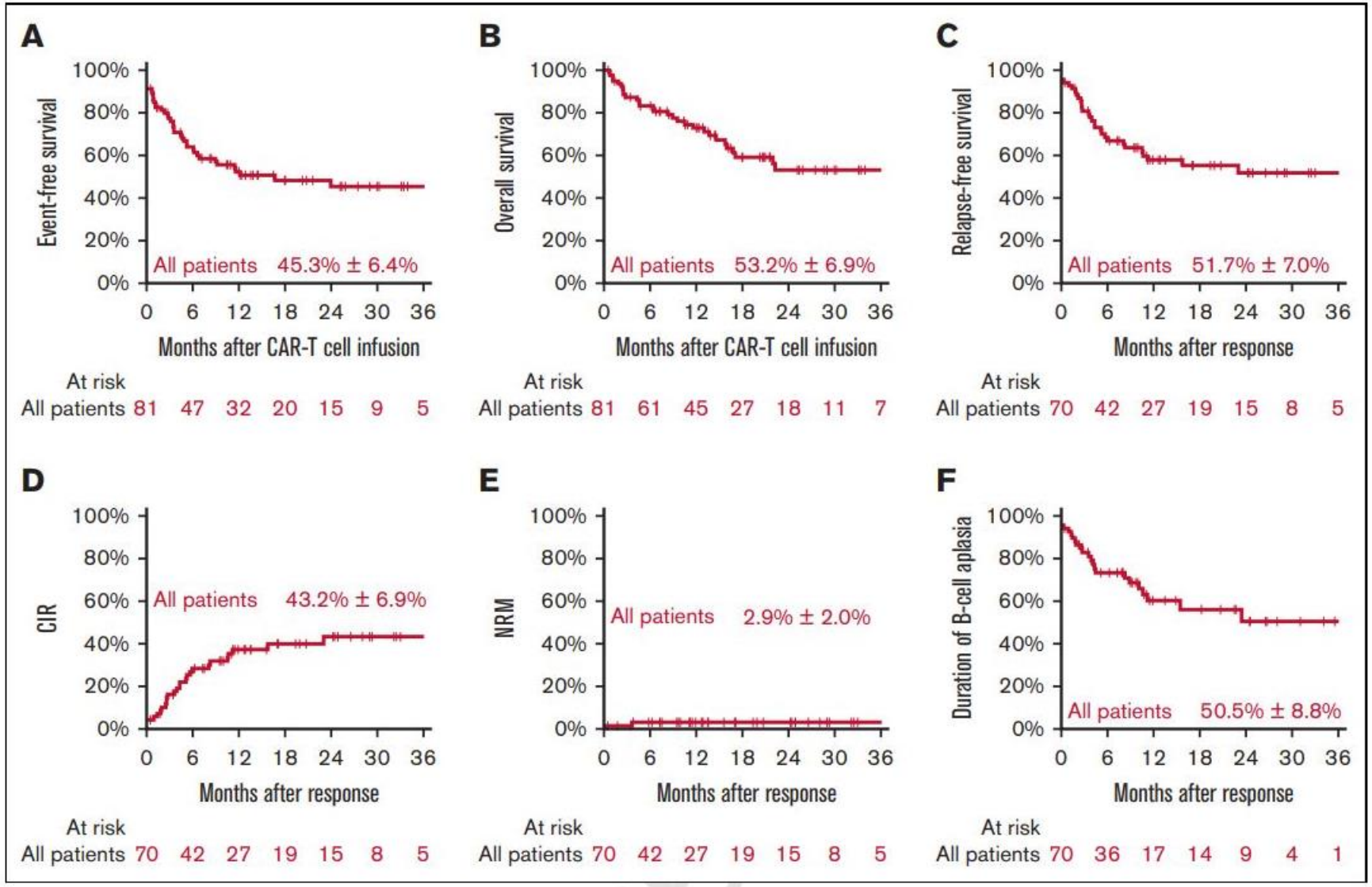

Figure 1. All patients. Event-free survival (A), overall survival (B) with estimates for 24 months after CAR T-cell infusion, relapse-free survival (C), CIR (D), NRM (E), and duration of B-cell aplasia with estimates for 24 months after response.

Bader-P et al.: Blood Advances 2023 in press

Patients with/without Prior SCT

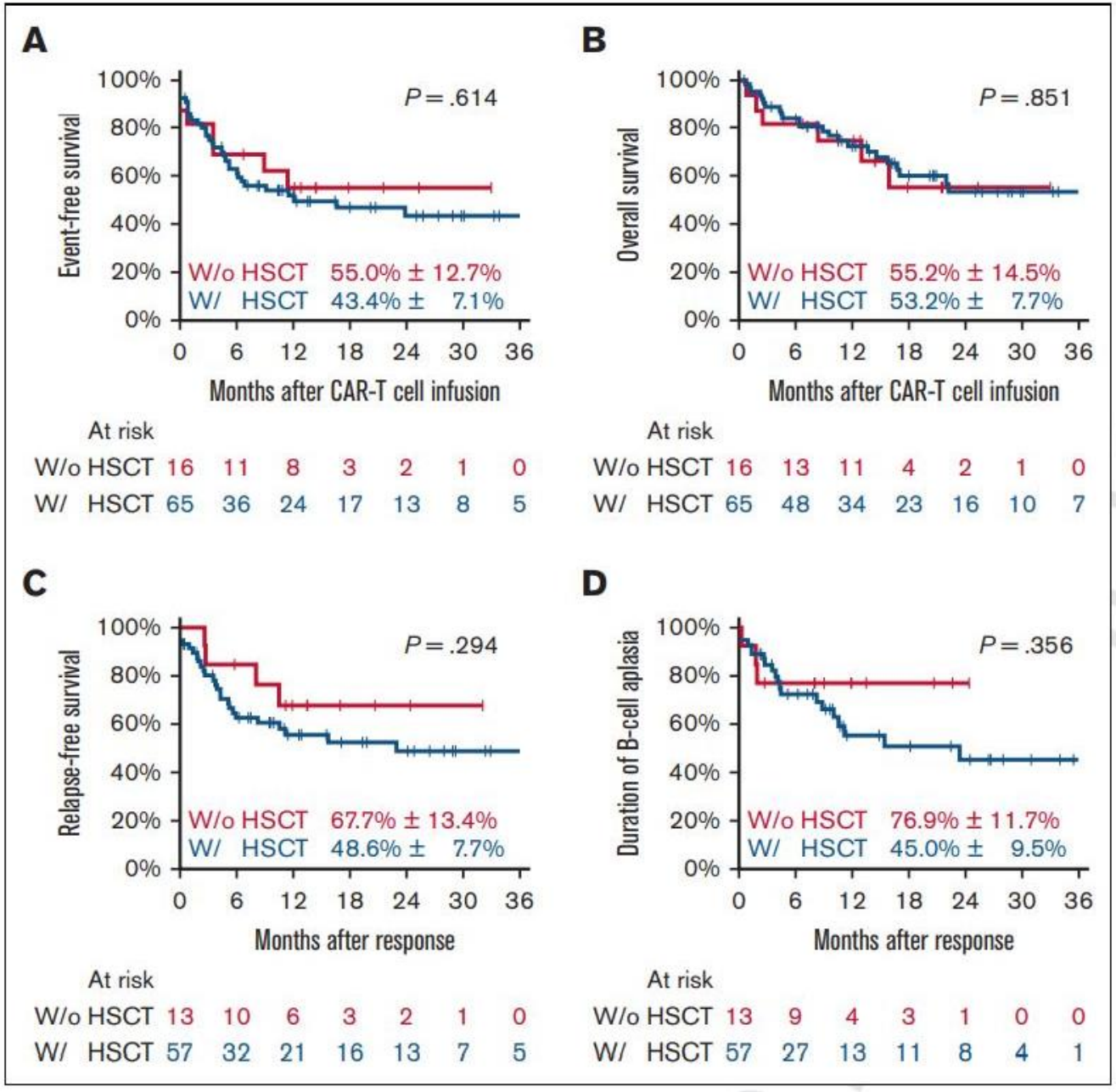

Figure 2. All patients according to previous allo-HSCT. Event-free survival (A), overall survival (B) with estimates for 24 months after CAR T-cell infusion, relapse-free survival (C), and duration of B-cell aplasia (D) with estimates for 24 months after response. w/, with' w/o, without.

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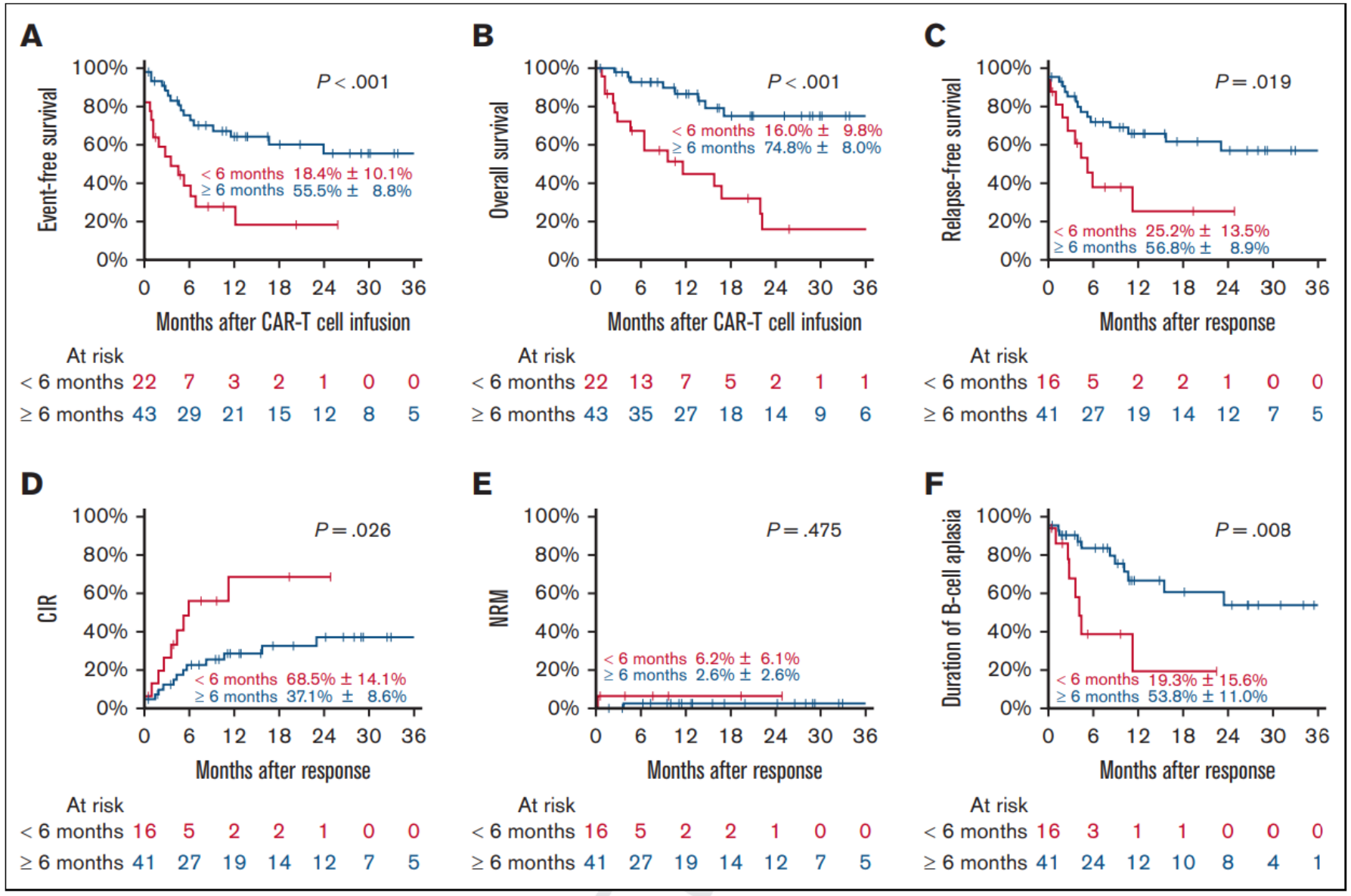
Time from HSCT to Relapse N= 65



Bader-P et al.: Blood Advances 2023 in press

Summary

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- Relapsed and refractory precursor B-ALL in children and adolescents – which cellular therapy first?

- Allogeneic HSCT leads to EFS 80%
- Real World Data on CAR-T leads to EFS of 40-50%

  - Therefore: Allogeneic HSCT - First!

Pediatric Stem Cell Transplantation & Immunology: Peter Bader / Evelyn Ullrich / Jan-Henning Klusmann

Physicians
Eva Rettinger
Shahrzad Bakhtiar
Andre Willasch
Julia Fekadu
Laura Moser
Jan Robert Heusel
Andrea Jarisch

Nurses
Kathy Lubrich
Cornelia Duda
Lisa Manser
and all nurses
of the SCT Division

CIK / T Cell Therapy
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Leonie Gossel
Laura Moser
Cathrin Heim
Michael Merker

Mesenchymal Stromal Cells
Zyrafete Kuçi
Selim Kuçi
Natasch Piede

Clinical Trial Office
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Ernesta Jarukaite
Gudrun Sach

Graft Manipulation, Cell Therapeutics
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Claudia Cappel
Melanie Bremm
Claudia Wunram
Olga Zimmermann
Laura Puth
Stefanie Erben
Julia Banisharif
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Martin Hutter

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