MRD in the context of cellular therapy for adult, Ph negative lymphoblastic leukemia

Guido Kobbe
Department of Hematology, Oncology and clinical Immunology
University Hospital
Heinrich Heine University Düsseldorf

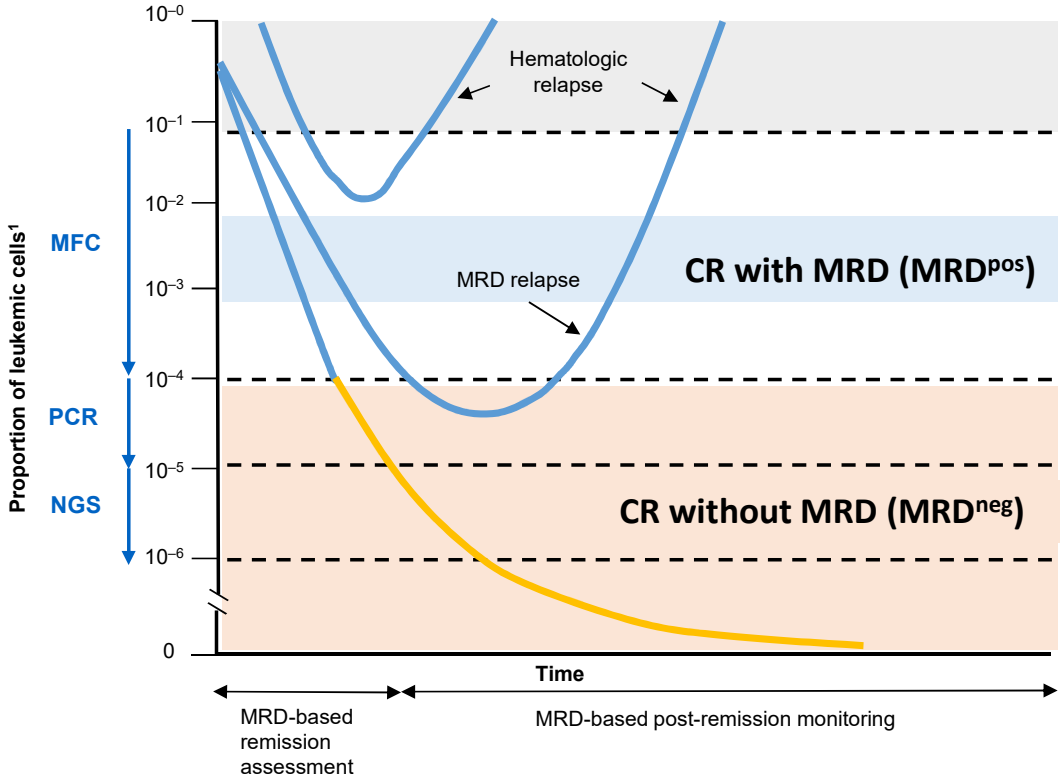
UKD Universitätsklinikum Düsseldorf

hhu Heinrich Heine Universität Düsseldorf

Conflict of interest, Guido Kobbe

1. **Employment or Leadership Position**
   -
2. **Advisory Role or Speaker Honoraria**
   Novartis, MSD, Pfizer, Amgen, Gilead, BMS-Celgene, Abbvie, Biotest, Takeda, Eurocept
3. **Stock Ownership**
   -
4. **Patent, Copyright, Licensing**
   -
5. **Financing of Scientific Research**
   BMS-Celgene, Amgen, Abbvie, Medac, Eurocept

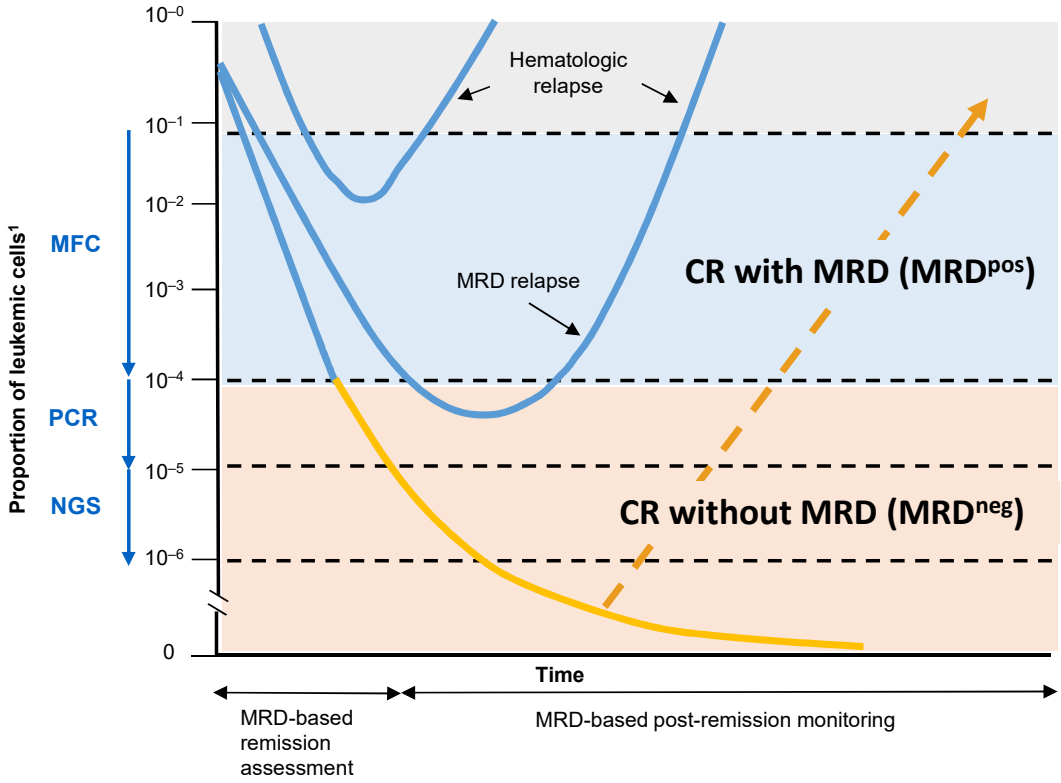
MRD in B-lymphoblastic leukemia



- **Sophisticated methods for the detection of „measurable / minimal residual disease“ have been developed in recent years. These include Multicolor Flow Cytometry (MFC) clone specific quantitative PCR and NGS.**

- **MRD at different time points has different implications. In first-line therapy, MRD implies major prognostic information, whereas in later stages of the disease MRD post therapy gives less information regarding long term remission and cure.**

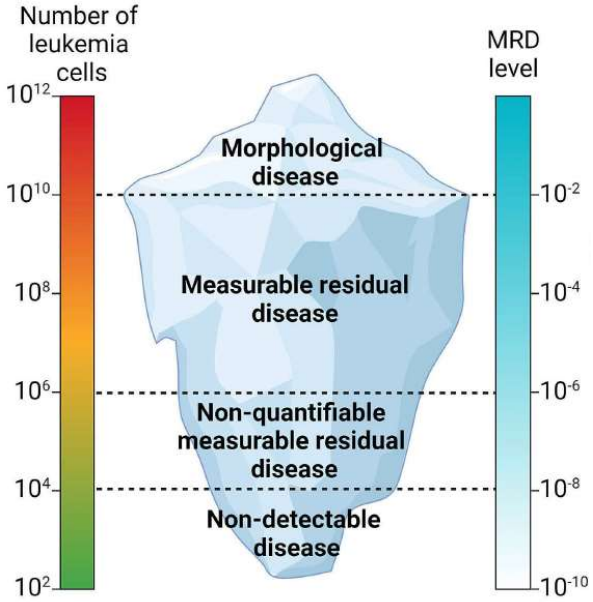
MRD in B-lymphoblastic leukemia



- **Sophisticated methods for the detection of „measurable / minimal residual disease“ have been developed in recent years. These include Multicolor Flow Cytometry (MFC) clone specific quantitative PCR and NGS.**
- **MRD at different time points has different implications. In first-line therapy, MRD implies major prognostic information, whereas in later stages of the disease MRD post therapy gives less information regarding long term remission and cure.**
- **However, MRD negativity does not imply unconditional freedom from relapse.**

Role of MRD at different time points

1. **Before alloHSCT**
    a. ***Relevance***
    b. ***Strategies for improvement***
2. **After alloHSCT**
    1. ***Relevance***
    2. ***Strategies for improvement***
3. **After Second line therapy**
    a. ***Relevance***
    b. ***Strategies for improvement***



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Long-Term Results of Allogeneic Stem Cell Transplantation in Adult Ph- Negative High-Risk Acute Lymphoblastic Leukemia

Dietrich W. Beelen[1], Renate Arnold[2], Matthias Stelljes[3], Nael Alakel[4], Arne Brecht[5], Gesine Bug[6], Donald Bunjes[7], Christoph Faul[8], Jürgen Finke[9], Georg-Nikolaus Franke[10], Ernst Holler[11], Guido Kobbe[12], Nicolaus Kröger[13], Wolf Rösler[14], Christof Scheid[15], Stefan Schönland[16], Michael Stadler[17], Johanna Tischer[18], Eva Wagner-Drouet[19], Knut Wendelin[20], Monika Brüggemann[21], Lena Reiser[6], Dieter Hoelzer[6], Nicola Gökbuget[6,*]

Covariates	HR	P†
Overall survival (N = 84)		
Age (≤35 versus >35)	3.471 (1.486 – 8.105)	**.0040**
MRD week 16 (mol CR versus mol failure)	3.653 (1.556 – 8.575)	**.0029**
aGvHD (grade 0/I versus II-IV)	–	.1525
Disease-free survival (N = 114)		
Age (≤35 versus >35)	–	.1750
Gender (male versus female)	–	.8661
MRD week 16 (mol CR versus mol failure)	3.294 (1.767 – 6.139)	**.0002**
Non-related mortality (N = 420)		
Age (≤35 versus >35)	1.906 (1.226 – 2.963)	**.0041**
Trial (06/99 versus 07/03)	0.444 (0.281 – 0.701)	**.0005**
aGvHD (grade 0/I versus II-IV)	2.626 (1.667 – 4.137)	**<.0001**
Relapse risk (N = 84)		
Gender (male versus female)	–	.2163
MRD week 16 (mol CR versus mol failure)	7.568 (2.337 – 24.508)	**.0007**
aGvHD (grade 0/I versus II-IV)	–	.6175

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n=542 (1999-2013)

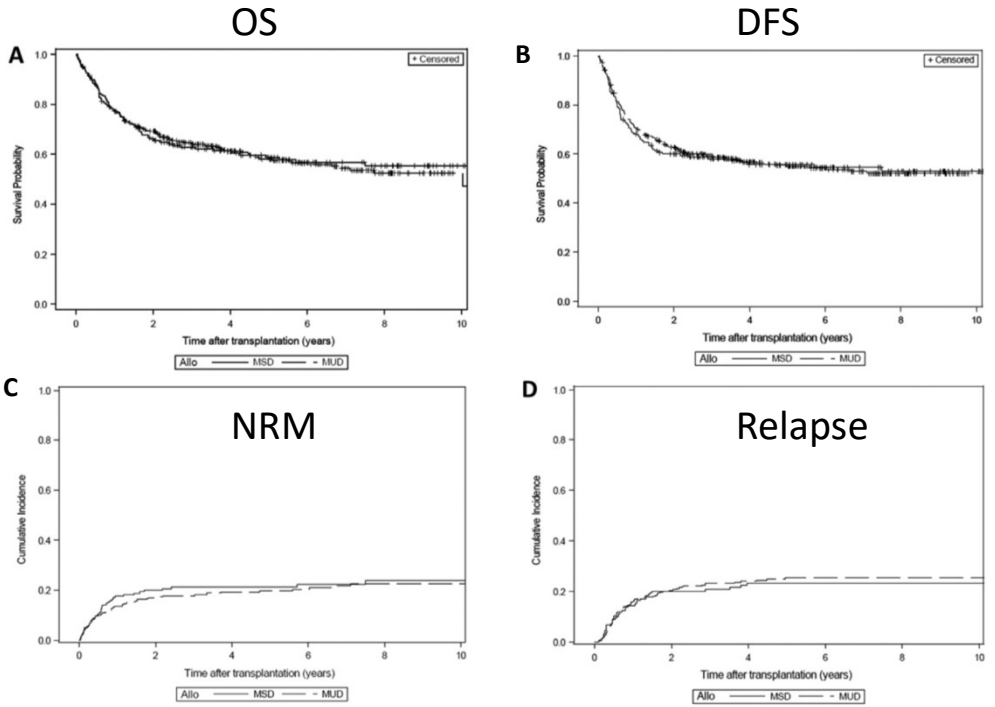

Figure 2. (A) OS according to donor type. (B) DFS according to donor type. (C) NRM according to donor type. (D) RR according to donor type. (A) OS according to donor type: MSD (N = 176), 5-year probability 0.59 (95% CI, 0.51-0.66); MUD (N = 366), 5-year probability 0.58 (95% CI, 0.52-0.63); p = 0.877. (B) DFS according to donor type: MSD (N = 176), 5-year probability 0.56 (95% CI, 0.48-0.63); MUD (N = 366), 5-year probability 0.55 (95% CI, 0.49-0.60); *P* = .861. (C) NRM according to donor type: MSD (N = 176), 5-year probability 0.21 (95% CI, 0.15-0.28); MUD (N = 366), 5-year cumulative risk 0.20 (95% CI, 0.16-0.24); *P* = .592. (D) RR according to donor type: MSD (N = 176), 5-year probability 0.23 (95% CI, 0.17-0.30); MUD (N = 366), 5-year cumulative risk 0.25 (95% CI, 0.21-0.30); *P* = .667.

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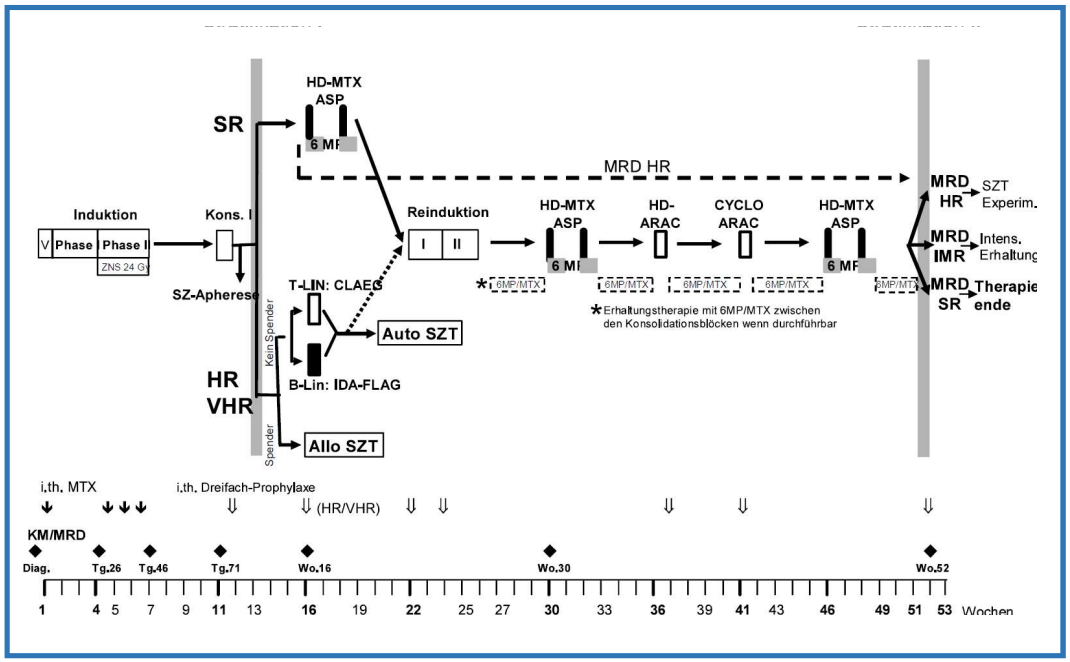

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According to MRD at week 16

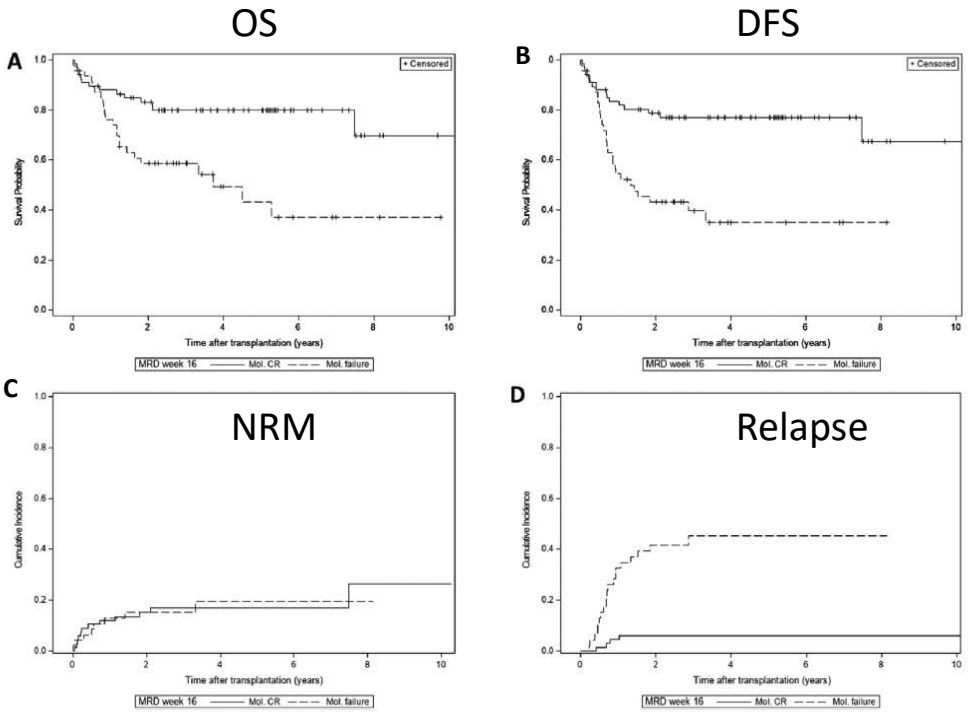

Figure 3. (A) OS according to MRD status at week 16. (B) DFS according to MRD status at week 16. (C) NRM according to MRD status at week 16. (D) RR by MRD status at week 16. (A) OS according to MRD: Mol CR (N = 67) 5-year probability 0.80 (95% CI, 0.68-0.88); Mol failure (N = 47), 5-year probability 0.43 (95% CI, 0.25-0.60); $P = .001$. (B) DFS according to MRD: Mol CR (N = 67) 5-year probability 0.77 (95% CI, 0.65-0.85); Mol failure (N = 47), 5-year probability 0.35 (95% CI, 0.20-0.50); $P < .0001$. (C) NRM according to MRD: Mol CR (N = 67) 5-year cumulative risk 0.17 (95% CI, 0.09-0.27); Mol failure (N = 47), 5-year probability 0.20 (95% CI, 0.08-0.34); $P = .984$. (D) RR according to MRD: Mol CR (N = 67) 5-year cumulative risk 0.06 (95% CI, 0.02-0.14); Mol failure (N = 47), 5-year probability 0.45 (95% CI, 0.30-0.60); $P < .0001$.

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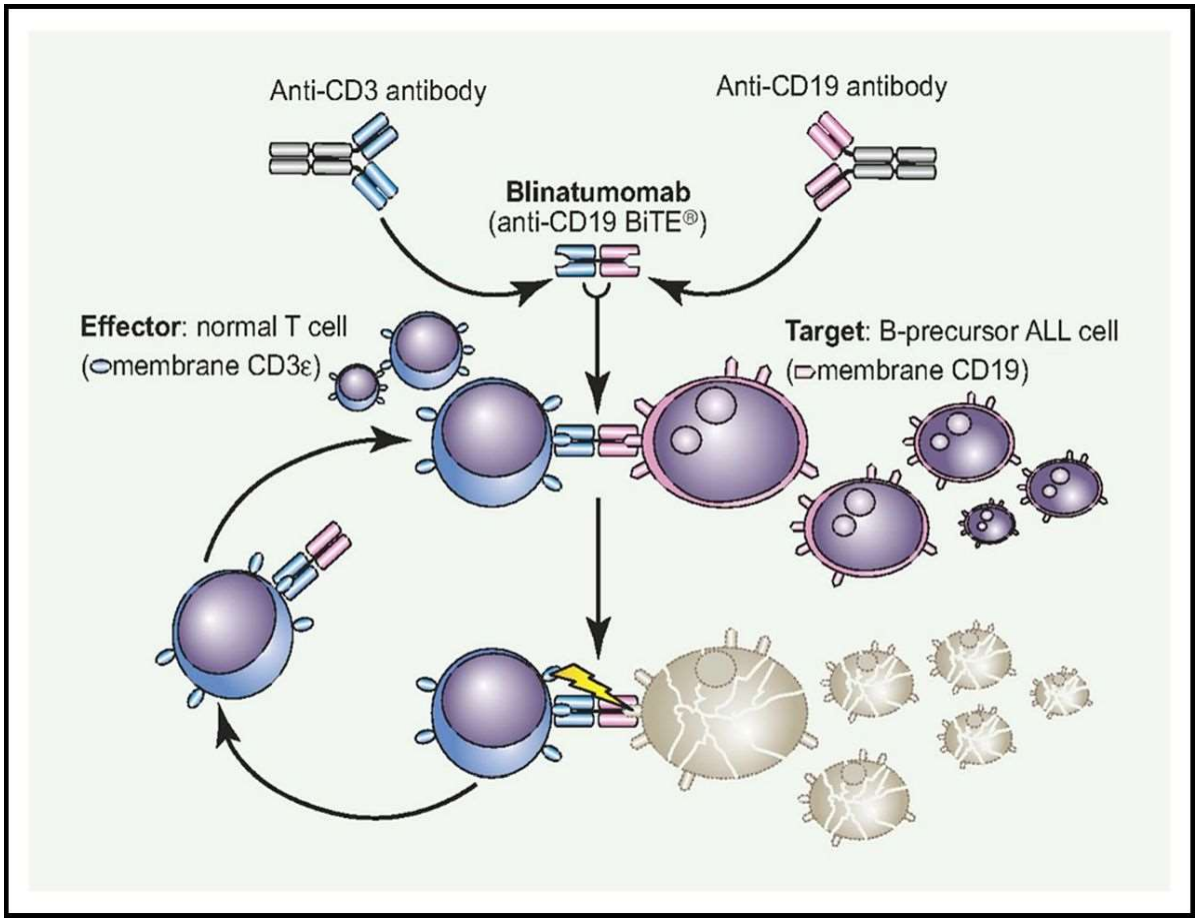
Strategies to achieve MRD negativity before transplantation in B-lymphoblastic leukemia

- chemotherapy +/-unarmed (naked antibodies), e.g. Rituximab
- armed (=conjungated antibodies), e.g. Inotuzumab
- bispecific T-cell engagers (BiTE®), e.g. Blinatomomab
- chimeric antigen receptor (CAR) T-cells, e.g. Tisagenlecleucel or KTE-X19

Blinatumomab



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Blood 2018

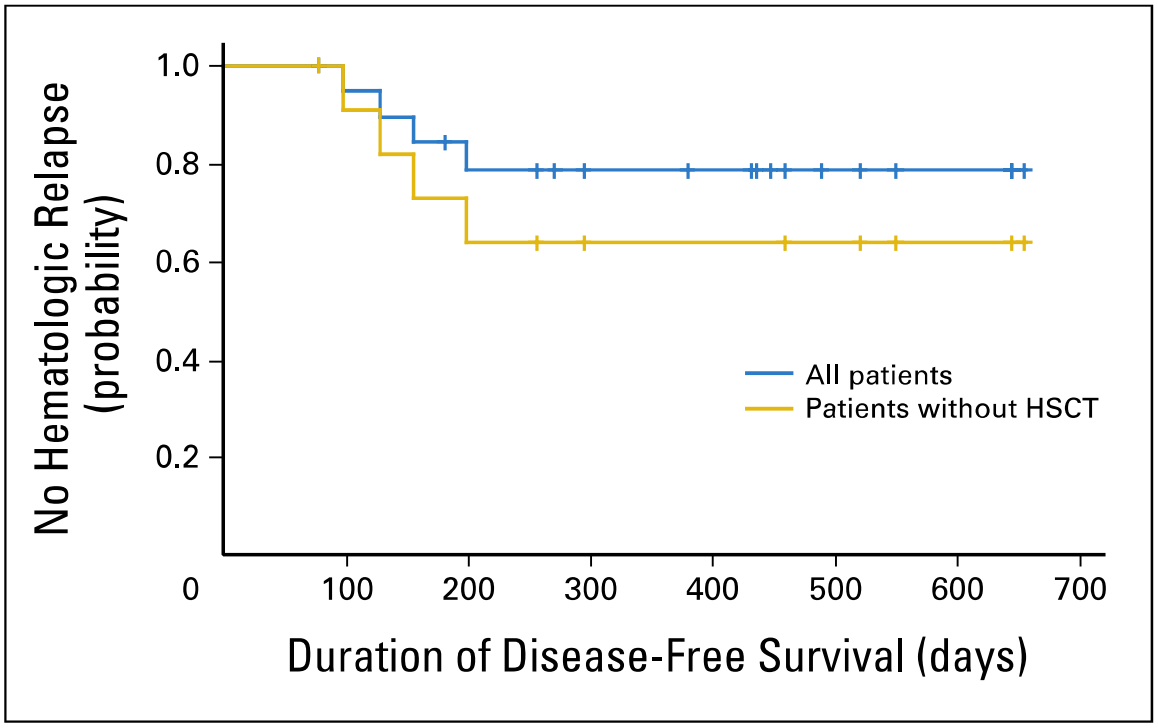
Targeted Therapy With the T-Cell–Engaging Antibody Blinatumomab of Chemotherapy-Refractory Minimal Residual Disease in B-Lineage Acute Lymphoblastic Leukemia Patients Results in High Response Rate and Prolonged Leukemia-Free Survival

Max S. Topp, Peter Kufer, Nicola Gökbuget, Mariele Goebeler, Matthias Klinger, Svenja Neumann, Heinz-A. Horst, Thorsten Raff, Andreas Viardot, Mathias Schmid, Matthias Stelljes, Markus Schaich, Evelyn Degenhard, Rudolf Köhne-Volland, Monika Brüggemann, Oliver Ottmann, Heike Pfeifer, Thomas Burmeister, Dirk Nagorsen, Margit Schmidt, Ralf Lutterbuese, Carsten Reinhardt, Patrick A. Baeuerle, Michael Kneba, Hermann Einsele, Gert Riethmüller, Dieter Hoelzer, Gerhard Zugmaier, and Ralf C. Bargou

Table 2. Overview of Response Data to Blinatumomab

Response Category	No. of Patients at Enrollment	No. of Responders
Evaluable for response*	20	16
Response according to prior course		
Molecularly refractory disease	15	12
Molecular relapse	5	4
Response according to MRD level before blinatumomab treatment†		
$\geq 10^{-2}$	11	10
$< 10^{-2}$ to $\geq 10^{-3}$	5	4
$< 10^{-3}$ to $\geq 10^{-4}$	4	2

NOTE. MRD response onset was achieved in all responding patients after 4 weeks of treatment.
Abbreviation: MRD, minimal residual disease.
*Five patients were *BCR-ABL* positive (three of these patients responded).
†Levels determined by quantitative polymerase chain reaction.



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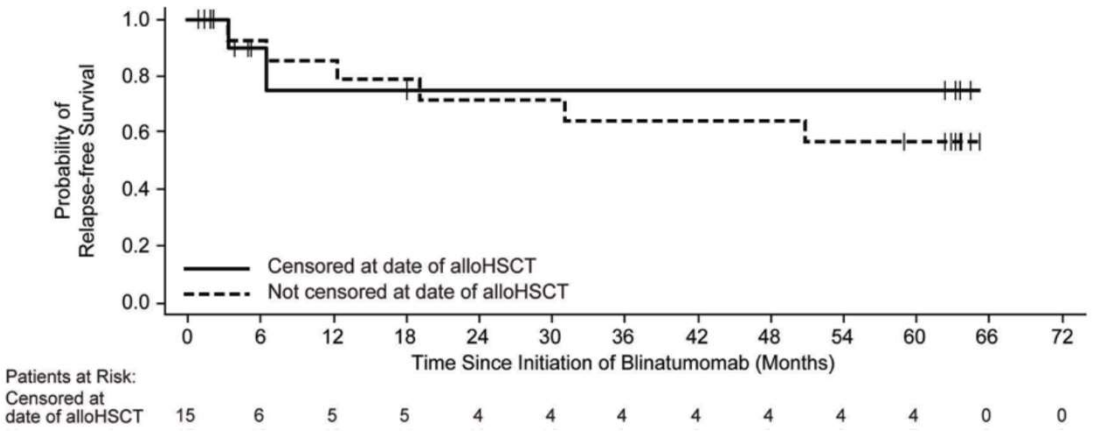
Long-term relapse-free survival in a phase 2 study of blinatumomab for the treatment of patients with minimal residual disease in B-lineage acute lymphoblastic leukemia

Nicola Gökbuget,[1] Gerhard Zugmaier,[2*] Matthias Klinger,[2] Peter Kufer,[2] Matthias Stelljes,[3] Andreas Viardot,[4] Heinz A. Horst,[5] Svenja Neumann,[5] Monika Brüggemann,[5] Oliver G. Ottmann,[6] Thomas Burmeister,[7] Dorothea Wessiepe,[8] Max S. Topp[9**] and Ralf Bargou[10**]*

Patient N.	Sex	Baseline characteristics: Age (y)	Ph status	MolF/ MolR	CR1/ CR2+	MRD	Dose Incr.	MRD response: Response	Duration (mo.)	Time to HSCT (mo.)	RFS: Duration (mo.)	≥5 y	Type of event	CD19-positive relapse
1	F	42	Ph–	MolF	CR1	≥10^{-3}	No	Yes	0.5*	–	1.4**	No	–	–
2	F	62	Ph–	MolR	CR1	≥10^{-3}	No	No	–	–	3.2	No	Hematologic	No
3	F	67	Ph+	MolF	CR1	≥10^{-3}	No	Yes	3.3	–	4.2	No	Extramedullary	Yes
4	F	72	Ph+	MolR	CR1	<10^{-3}	No	Yes	2.8	–	5.1	No	Hematologic	No
5	M	62	Ph–	MolF	CR1	≥10^{-3}	No	Yes	5.6	–	6.5	No	Extramedullary	Yes
6	M	20	Ph–	MolR	CR1	≥10^{-3}	No	Yes	1.4*	2.5	12.4	No	Hematologic	Unknown
7	M	47	Ph–	MolR	CR2+	≥10^{-3}	No	Yes	1.6*	2.8	19.1	No	Death in remission	–
8	F	37	Ph–	MolF	CR1	≥10^{-3}	No	Yes	1.4*	2.7	31.0	No	Hematologic	Unknown
9	M	69	Ph+	MolR	CR1	≥10^{-3}	No	Yes	7.3	–	44.3	No	Hematologic	Yes
10	M	28	Ph–	MolF	CR1	≥10^{-3}	No	Yes	14.4	18.7	50.8	No	Hematologic	Yes
11	F	31	Ph–	MolF	CR1	<10^{-3}	No	Yes	0.5*	1.9	59.5*	Yes	–	–
12	M	40	Ph+	MolF	CR1	≥10^{-3}	No	No	–	3.1	61.9*	Yes	–	–
13	F	63	Ph–	MolF	CR1	≥10^{-3}	No	Yes	62.1*	–	62.9*	Yes	–	–
14	F	34	Ph–	MolF	CR1	<10^{-3}	Yes	No	–	5.6	63.4*	Yes	–	–
15	F	68	Ph–	MolF	CR1	≥10^{-3}	No	Yes	46.7*	–	63.8*	Yes	–	–
16	F	77	Ph–	MolF	CR1	≥10^{-3}	No	Yes	29.9*	–	64.3*	Yes	–	–
17	F	23	Ph–	MolF	CR1	≥10^{-3}	No	Yes	4.2*	5.8	64.4*	Yes	–	–
18	F	57	Ph–	MolF	CR1	≥10^{-3}	No	Yes	64.2*	–	65.0*	Yes	–	–
19	M	31	Ph–	MolF	CR1	≥10^{-3}	Yes	Yes	2.9*	4.4	65.8*	Yes	–	–
20	M	65	Ph+	MolF	CR1	<10^{-3}	Yes	No	–	–	70.1*	Yes	–	–

*Censored at the end of follow-up. **Patient was censored after 43 days (1.4 months) because of withdrawal of consent. –: not applicable; HSCT: hematopoietic stem cell transplantation; CR1: first hematologic complete remission; CR2+: second or greater hematologic CR; extramedullary: extramedullary relapse; F: female; hematologic: hematologic relapse; incr.: increased M: male; mo.: months; MolF: molecularly refractory; MolR: molecular relapse; MRD: minimal residual disease; N.: number; Ph–: Philadelphia chromosome–negative disease; Ph+: Philadelphia chromosome–positive disease; RFS: relapse-free survival; y: year.

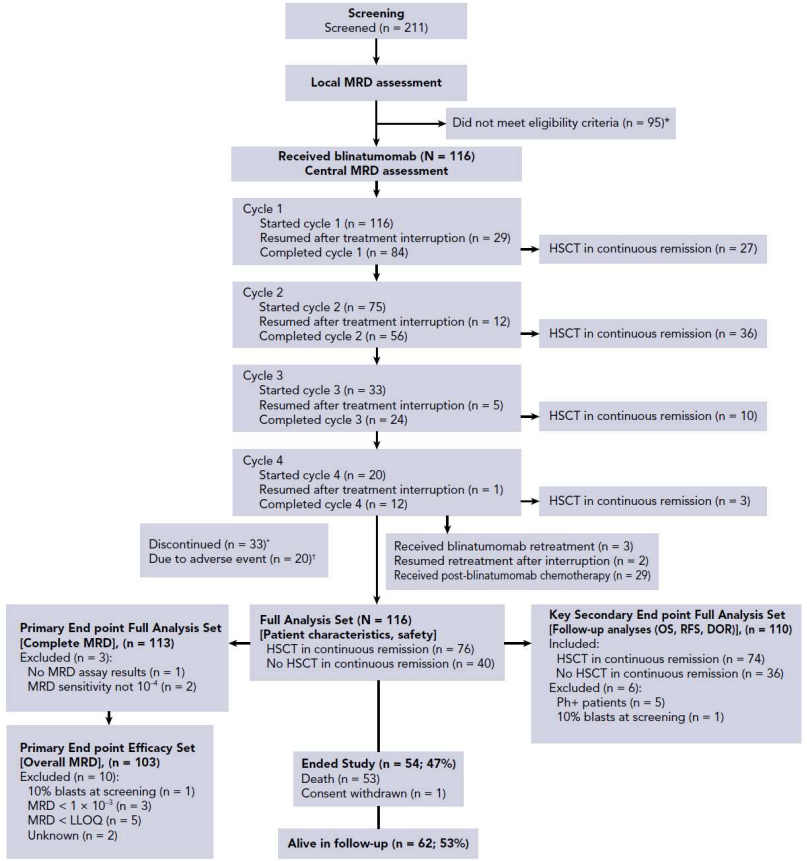
15 - MRD+ disease during chemotherapy (molecular failure)
5 - MRD+ relapse (molecular relapse)

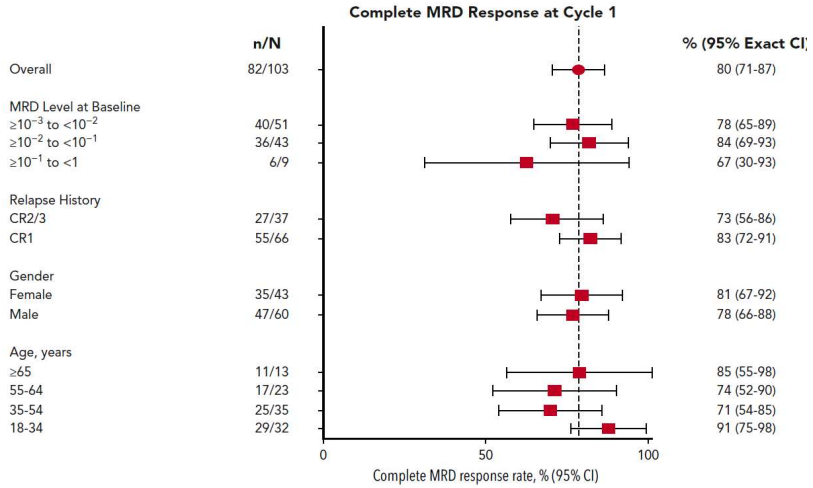


Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

Nicola Gökbuget,[1] Hervé Dombret,[2] Massimiliano Bonifacio,[3] Albrecht Reichle,[4] Carlos Graux,[5] Christoph Faul,[6] Helmut Diedrich,[7] Max S. Topp,[8] Monika Brüggemann,[9] Heinz-August Horst,[9] Violaine Havelange,[10] Julia Stieglmaier,[11] Hendrik Wessels,[11] Vincent Haddad,[12] Jonathan E. Benjamin,[13] Gerhard Zugmaier,[11] Dirk Nagorsen,[13] and Ralf C. Bargou[14]

Characteristic	Patients (N = 116)
Sex, n (%)	
Male	68 (59)
Female	48 (41)
Median (range) age, years	45.0 (18-76)
Age group, years, n (%)	
18 to <35	36 (31)
35 to <55	41 (35)
55 to <65	24 (21)
≥65	15 (13)
Cytogenetics/molecular genetics, n (%)	
t(9;22)/BCR-ABL⁺	5 (4)
t(4;11)/MLL-AF4⁺	5 (4)
Relapse history, n (%)*	
Patients in first CR	75 (65)
Patients in second CR	39 (34)
Patients in third CR	2 (2)
Median (range) time from last prior treatment, months	2.0 (0-55)
Baseline MRD levels, n (%)†	
$\geq 10^{-1}$ to <1 (≥10% to <1)	9 (8)
$\geq 10^{-2}$ to $<10^{-1}$ (≥1% to <10%)	45 (39)
$\geq 10^{-3}$ to $<10^{-2}$ (≥0.1% to <1%)	52 (45)
$<10^{-3}$ (<0.1%)	3 (3)
Below LLOQ	5 (4)
Unknown‡	2 (2)





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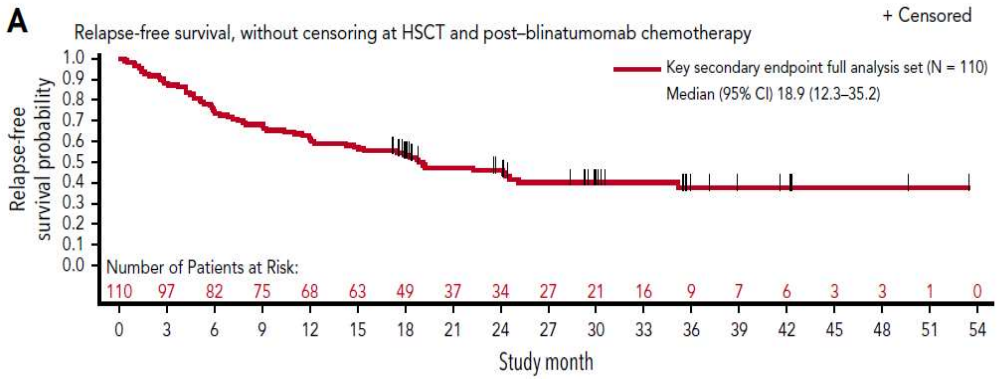

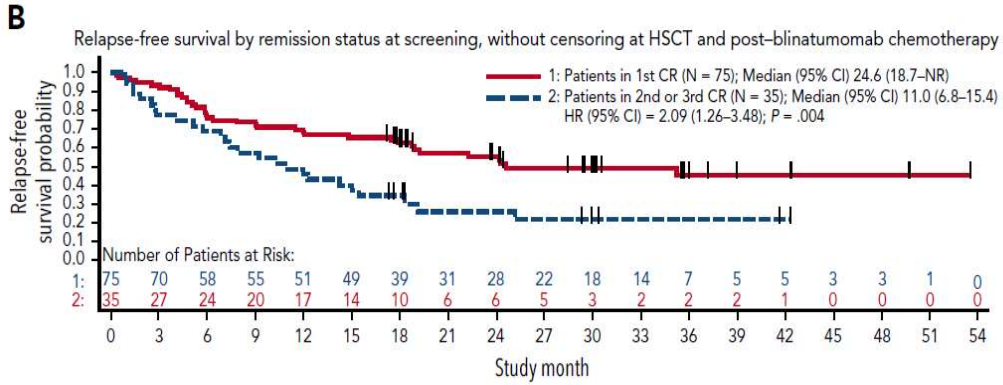

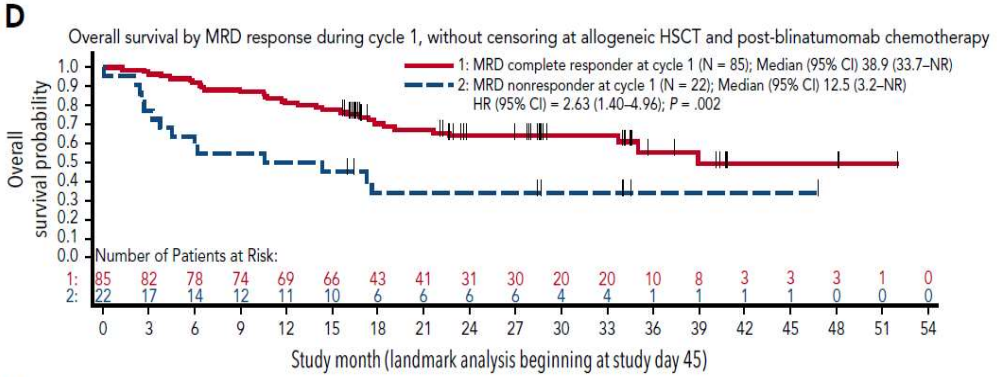

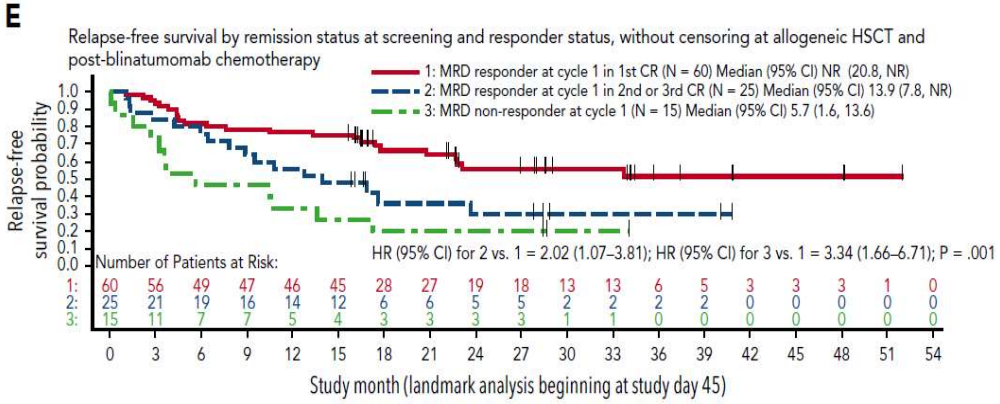

Conclusion I

- **Achieving MRD negativity before alloHSCT in high-risk ALL is of high relvance for cure**
- **Currently Blinatumomab is the drug of choice to eradicate MRD before alloHSCT in B-lineage ALL**
- **There currently is no standard option to improve MRD status in T-ALL (Nelarabine? Venetoclax + X? Improved conditioning?)**

Role of MRD at different time points

1. **Before alloHSCT**
    a. ***Relevance***
    b. ***Strategies for improvement***
2. **After alloHSCT**
    1. ***Relevance***
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3. **After Second line therapy**
    a. ***Relevance***
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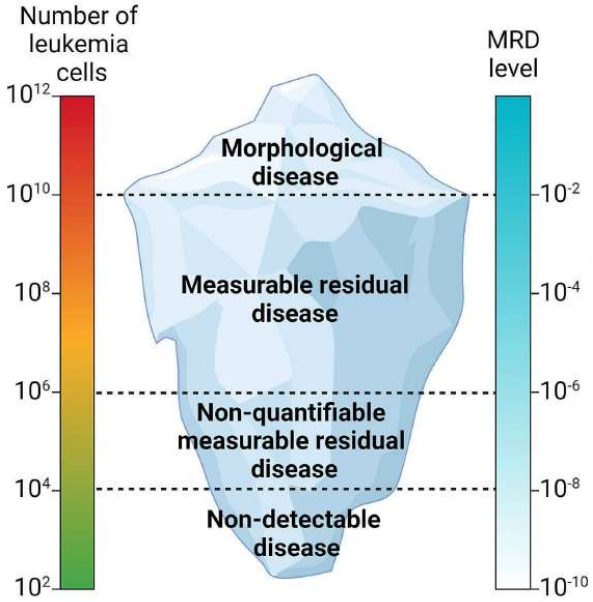

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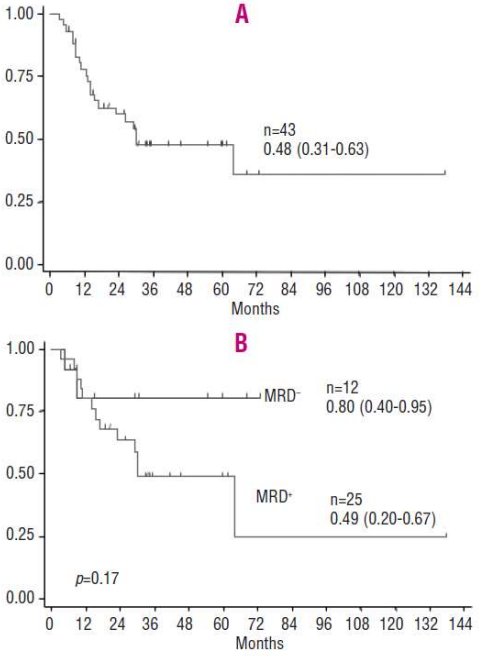
Clearance of minimal residual disease after allogeneic stem cell transplantation and the prediction of the clinical outcome of adult patients with high-risk acute lymphoblastic leukemia

Orietta Spinelli, Barbara Peruta, Manuela Tosi, Vittoria Guerini, Anna Salvi, Maria Cristina Zanotti, Elena Oldani, Anna Grassi, Tamara Intermesoli, Caterina Micò, Giuseppe Rossi, Pietro Fabris, Giorgio Lambertenghi-Deliliers, Emanuele Angelucci, Tiziano Barbui, Renato Bassan, Alessandro Rambaldi

Number of patients	43
Male/female	27/16
Median age at transplantation (range)	30 (18-63)
Diagnosis	
T-ALL	6
B-precursor ALL	37
Status at transplant	
First complete remission	29
Second complete remission	8
Active disease	6
Cytogenetics	
Normal	12
t(9;22)	20
t(4;11)	2
Abnormal	6
Unknown	3
Donor	
Related	24
Unrelated	19
Conditioning	
*Myeloablative	41
Reduced intensity	2

**Myeloablative: cyclophosphamide 60 mg/kg/die × 2 + total body irradiation 12 Gy (n=38) or busulfan 1 mg/kg/die × 4 (n=3).*



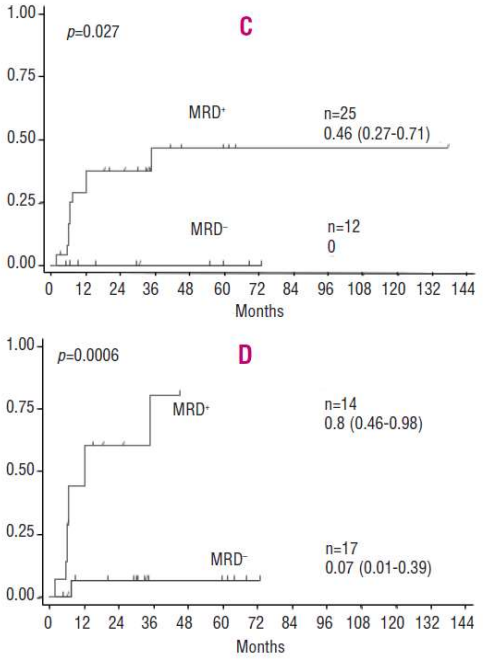
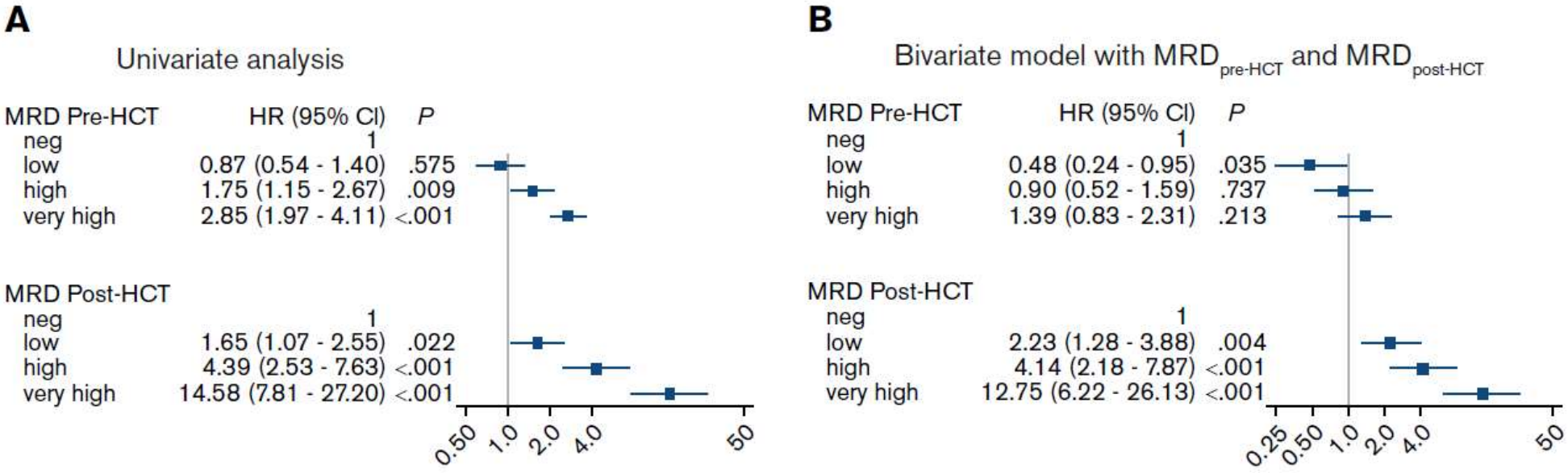


Figure 3. Overall survival and cumulative incidence of relapse. Overall survival of the 43 transplanted patients (Panel A). Overall survival according to MRD status before transplantation (Panel B), cumulative incidence of relapse by MRD status at transplanta tion (Panel C) and by MRD status at day +100 (Panel D) of patients undergoing transplantation in complete hematologic remission.

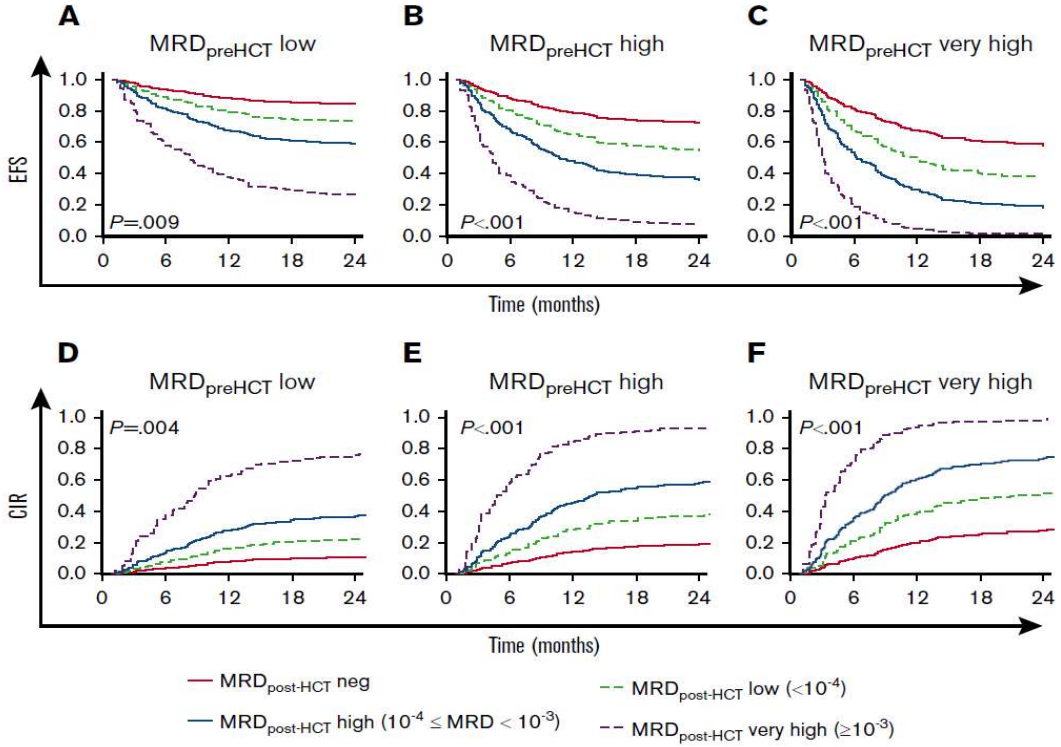
More precisely defining risk peri-HCT in pediatric ALL: pre- vs post-MRD measures, serial positivity, and risk modeling

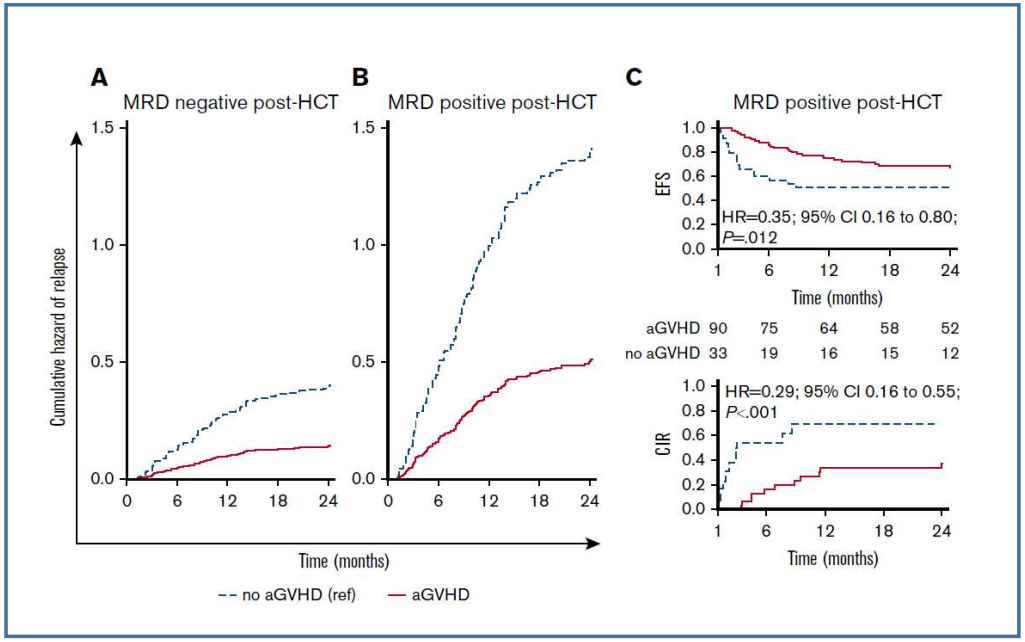
Peter Bader,[1] Emilia Salzmann-Manrique,[1] Adriana Balduzzi,[2] Jean-Hugues Dalle,[3] Ann E. Woolfrey,[4] Merav Bar,[4] Michael R. Verneris,[5] Michael J. Borowitz,[6] Nirali N. Shah,[7] Nathan Gossai,[8] Peter J. Shaw,[9] Allen R. Chen,[10] Kirk R. Schultz,[11] Hermann Kreyenberg,[1] Lucia Di Maio,[2] Gianni Cazzaniga,[2] Cornelia Eckert,[12] Vincent H. J. van der Velden,[13] Rosemary Sutton,[14] Arjan Lankester,[15] Christina Peters,[16] Thomas E. Klingebiel,[1] Andre M. Willasch,[1] Stephan A. Grupp,[17] and Michael A. Pulsipher,[18] on behalf of the Children's Oncology Group, the Pediatric Blood & Marrow Transplant Consortium, the Australian Transplantation Group, the International Berlin-Frankfurt-Münster Study Group, the Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation, and the Westhafen Intercontinental Group



More precisely defining risk peri-HCT in pediatric ALL: pre- vs post-MRD measures, serial positivity, and risk modeling

Peter Bader,[1] Emilia Salzmann-Manrique,[1] Adriana Balduzzi,[2] Jean-Hugues Dalle,[3] Ann E. Woolfrey,[4] Merav Bar,[4] Michael R. Verneris,[5] Michael J. Borowitz,[6] Nirali N. Shah,[7] Nathan Gossai,[8] Peter J. Shaw,[9] Allen R. Chen,[10] Kirk R. Schultz,[11] Hermann Kreyenberg,[1] Lucia Di Maio,[2] Gianni Cazzaniga,[2] Cornelia Eckert,[12] Vincent H. J. van der Velden,[13] Rosemary Sutton,[14] Arjan Lankester,[15] Christina Peters,[16] Thomas E. Klingebiel,[1] Andre M. Willasch,[1] Stephan A. Grupp,[17] and Michael A. Pulsipher,[18] on behalf of the Children's Oncology Group, the Pediatric Blood & Marrow Transplant Consortium, the Australian Transplantation Group, the International Berlin-Frankfurt-Münster Study Group, the Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation, and the Westhafen Intercontinental Group





Strategies to achieve MRD negativity after transplantation in lymphoblastic leukemia

- Additional chemotherapy (maintenance)+/unarmed (naked antibodies), e.g. Rituximab
- armed (=conjungated antibodies), e.g. Inotuzumab
- bispecific T-cell engagers (BiTE®), e.g. Blinatomomab
- chimeric antigen receptor (CAR) T-cells, e.g. Tisagenlecleucel or KTE-X19
- Donor lymphocyte infusion
- 2nd allogeneic blood stem cell transplantation

clinical case, Miss T., born 1993

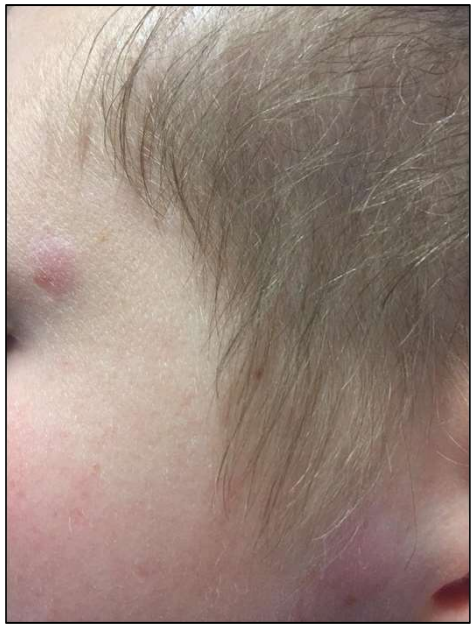
10/2013	Diagnosis common B-ALL, GMALL high-risk (leukocytosis) multiple valid MRD markers (UKSH Hematology Laboratory Kiel)
Until 01/2014	therapy analogous to GMALL 07/03 protocol initially insufficient MRD decline (d46), thereafter MRD increase (d71) -> MRD level after cons I before alloPBSCT positive, < 3E-04
02/2014	allo-PBSCT: etoposide/12Gy TBI, PBSC of HLA-identical sister, complicated transplant course, severe VOD, C-diff. Infection -> molecular CR
01/2015	1st relapse, hematological: treatment within standard arm of the TOWER trial (Blinatumomab vs SOC) -> Clofarabine, etoposide, cyc, i.th. triple -> molecular CR
04/2015	2nd allo-SCT: thiotepa/treosulfan, PBSC of HLA-identical sister, VOD prophylaxis with defibrotide, mild VOD, HMPV pneumonia. -> d+28 molecular CR

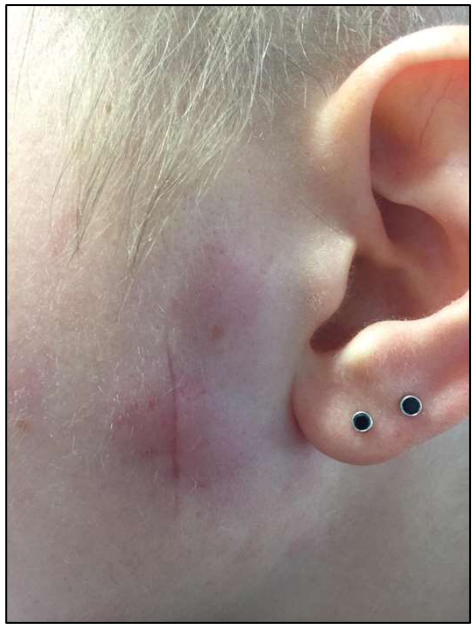
clinical case, Miss T., born 1993

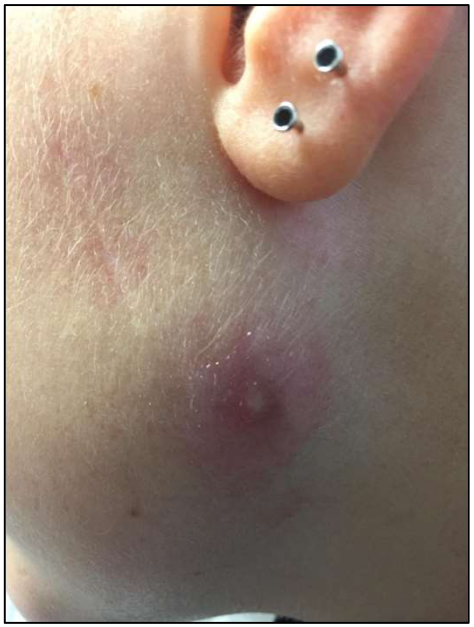
06/2015	2nd relapse (+63), molecular, increase in MRD at day +100. Treatment with 1 cycle of blinatumomab, no continuation due to Hepatotoxicity, -> molecular CR
09/2016	severe, cutaneous, sclerodermiform as well as hepatic cGvHD, immunosuppression initially with prednisolone 2mg/kg, steroid refractory, in addition CSA and ruxolitinib with clinical response.
03/2017	3rd recurrence, extramedullary as multiple small chloromas (left upper eyelid, left periumbilical), persistent MRD negativity in BM; stop of immunosuppression -> regression of chloromas
05-10/2017	5 cycles of blinatumomab -> complete regression of chloromas, -> in BM persistent MRD negativity.

clinical case, Miss T., born 1993

05/2018 4th recurrence, extramedullary as chloromas (left temple, left preauricular, left mandibular angle), -> MRD positivity in BM





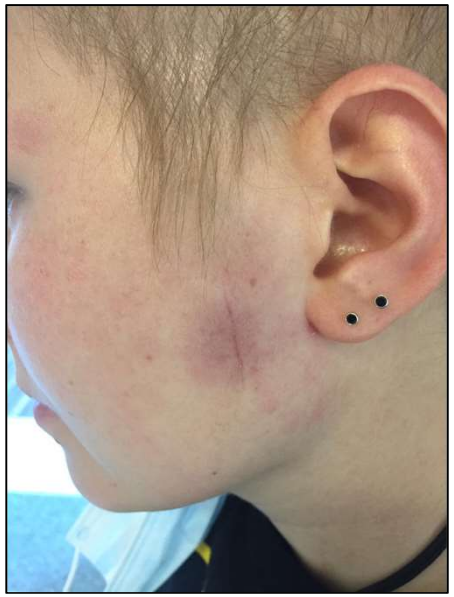


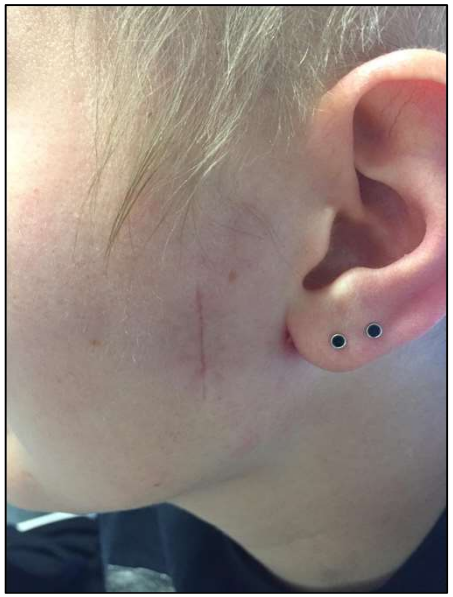
clinical case, Miss T., born 1993

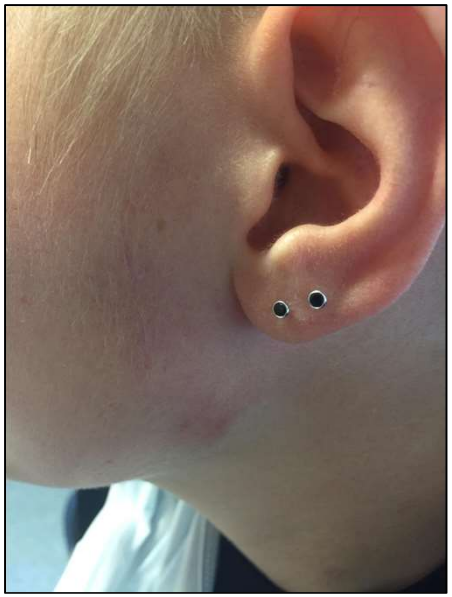
05/2018	4th recurrence, extramedullary as chloromas (left temple, left preauricular, left mandibular angle), -> MRD+ in BM
07-08/2018	2 cycles of blinatumomab with minimal regression of chloromas, -> persistent MRD+ in BM
08/2018	1st DLI with 1 Mio CD3+/kg, no response of chloromas -> persistent MRD+ in BM
11/2018	T-cell apheresis University Hospital Frankfurt, Prof. Bader
12/2018	Administration of CAR-T cells (Kymriah®, tisagenlecleucel).

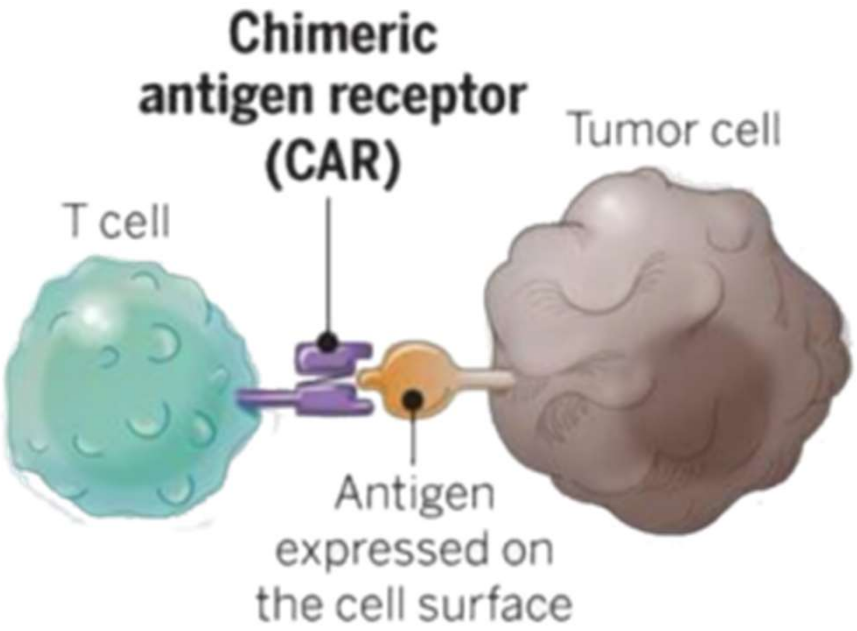
clinical case, Miss T., born 1993

Since then,	- complete regression of chloromas.
Last FU	- persistent MRD negativity in BM
01/23	- no detection of CD19+ B cells in peripheral blood
Day + 2843	- regular substitution of iv IgG
	- overall no therapy-associated side effects









Emily Whitehead in 2012 and in 2022

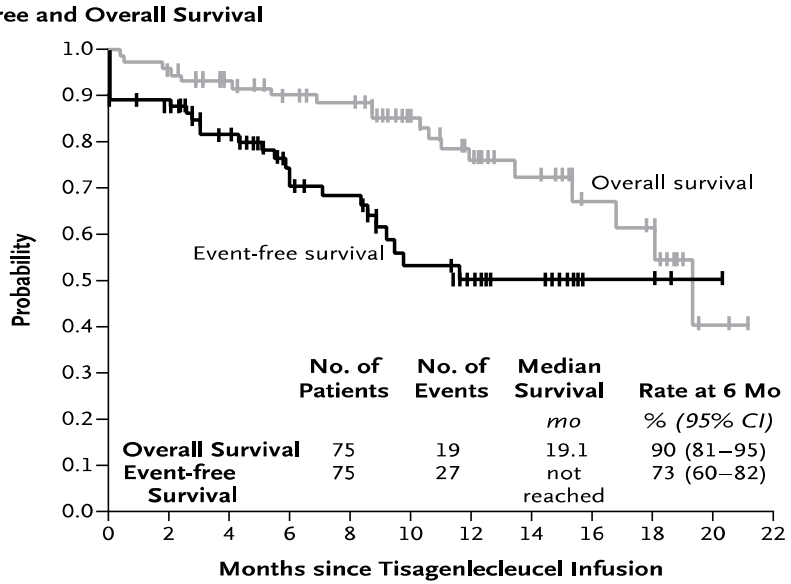
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

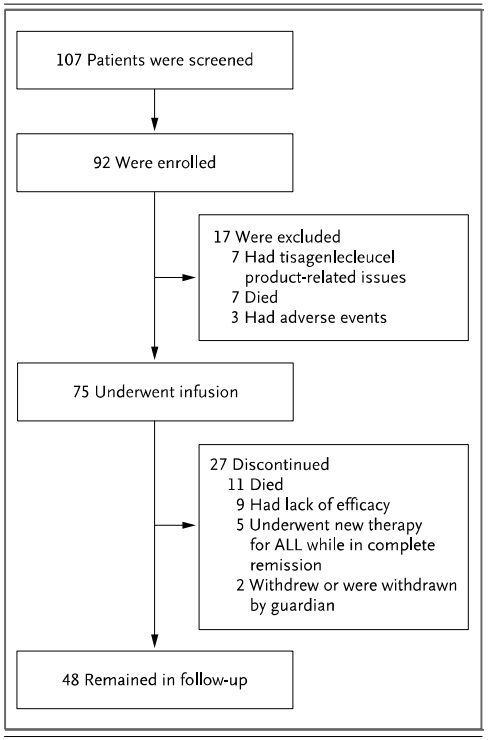
S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

CR 60%
CRi 21%
81%, all MRD^{neg}

Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

Type of Event	Any Grade (N=75)	Grade 3 (N=75)	Grade 4 (N=75)
	number of patients (percent)		
Any adverse event of special interest	67 (89)	26 (35)	30 (40)
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Neurologic event	30 (40)	10 (13)	0
Infection	32 (43)	16 (21)	2 (3)
Febrile neutropenia	26 (35)	24 (32)	2 (3)
Cytopenia not resolved by day 28	28 (37)	12 (16)	12 (16)
Tumor lysis syndrome	3 (4)	3 (4)	0





64% had previous alloHSCT

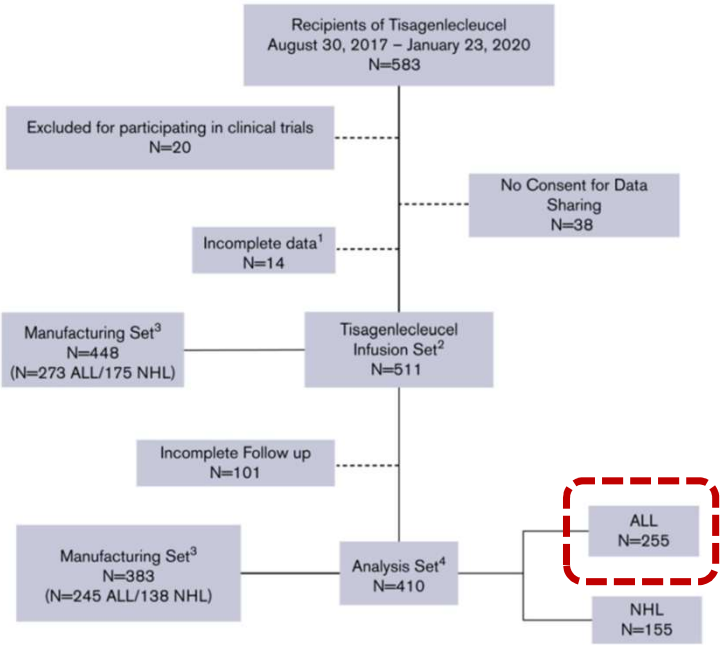
Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma

Marcelo C. Pasquini,[1] Zhen-Huan Hu,[1] Kevin Curran,[2] Theodore Laetsch,[3] Frederick Locke,[4] Rayne Rouce,[5] Michael A. Pulsipher,[6] Christine L. Phillips,[7] Amy Keating,[8] Matthew J. Frigault,[9] Dana Salzberg,[10] Samantha Jaglowski,[11] Joshua P. Sasine,[12] Joseph Rosenthal,[13] Monalisa Ghosh,[14] Daniel Landsburg,[15] Steven Margossian,[16] Paul L. Martin,[17] Manali K. Kamdar,[18] Peiman Hematti,[19] Sarah Nikiforow,[20] Cameron Turtle,[21] Miguel-Angel Perales,[22] Patricia Steinert,[1] Mary M. Horowitz,[1] Amy Moskop,[1] Lida Pacaud,[23] Lan Yi,[23] Raghav Chawla,[24] Eric Bleickardt,[25] and Stephan Grupp[3,26]

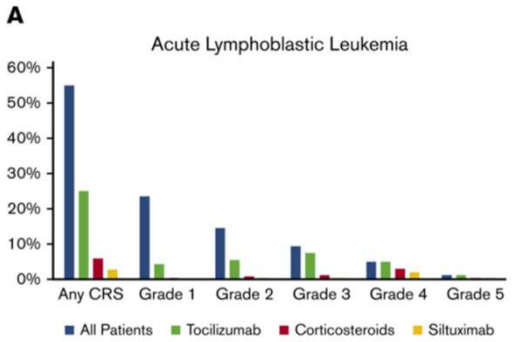
Heinrich Heine Universität Düsseldorf

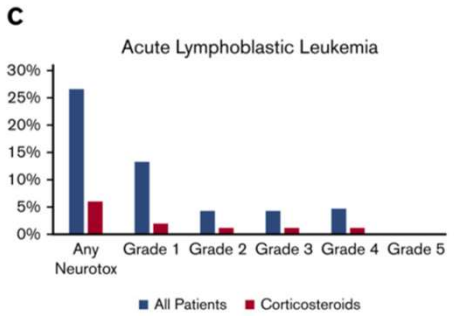
At infusion 37% in CR
17% MRD^{neg}

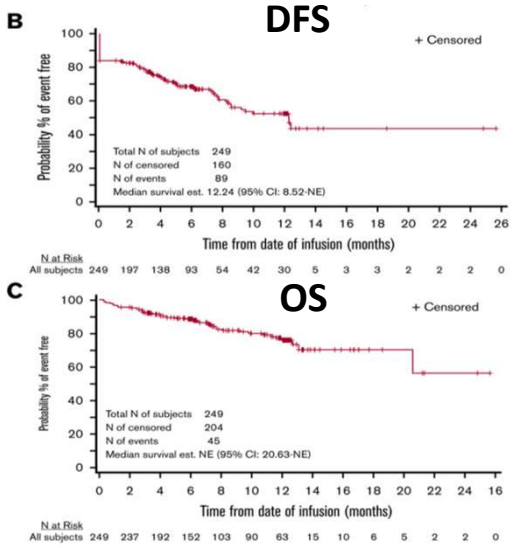
After infusion. CR 85.5%
of these 99% MRD^{neg}



28% of ALL patients had previous alloHSCT

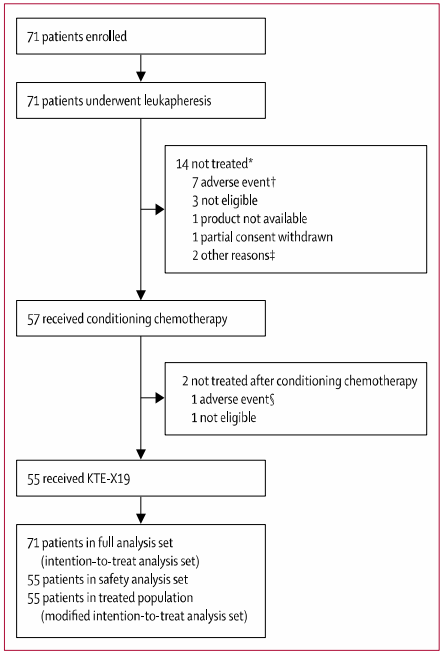






KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study

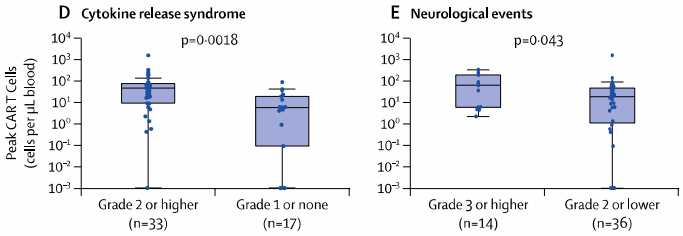
Bijal D Shah, Armin Ghobadi, Olalekan O Oluwole, Aaron C Logan, Nicolas Boissel, Ryan D Cassaday, Thibaut Leguay, Michael R Bishop, Max S Topp, Dimitrios Tzachanis, Kristen M O'Dwyer, Martha L Arellano, Yi Lin, Maria R Baer, Gary J Schiller, Jae H Park, Marion Subklewe, Mehrdad Abedi, Monique C Minnema, William G Wierda, Daniel J DeAngelo, Patrick Stiff, Deepa Jeyakumar, Chaoling Feng, Jinghui Dong, Tong Shen, Francesca Milletti, John M Rossi, Remus Vezan, Behzad Kharabi Masouleh, Roch Houot

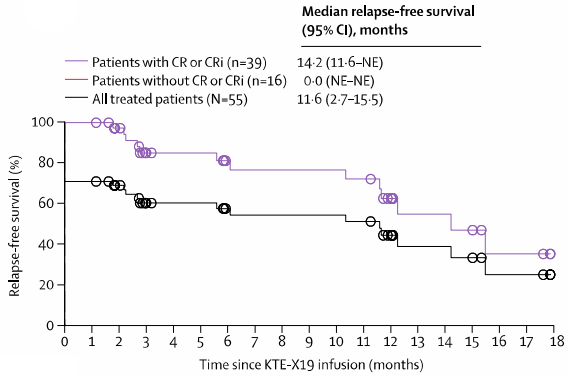


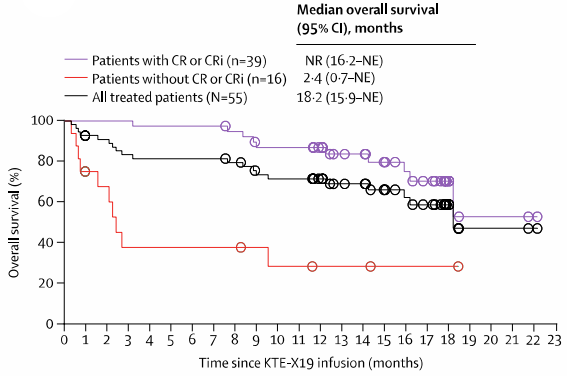
	Treated patients (n=55)	Enrolled patients (n=71)
(Continued from previous column)		
Bone marrow blasts at screening		
n	55	70
Median (IQR)	65% (24–87)	70% (25–89)
≤5%‖	0	1 (1%)
>5% to 25%‖	16 (29%)	17 (24%)
M3 bone marrow involvement (>25% blasts)‖	39 (71%)	52 (73%)
Bone marrow blasts at baseline‡		
n	55	70
Median (IQR)	60% (17–90)	67% (34–90)
≤5%‖	5 (9%)	6 (8%)
>5% to 25%‖	10 (18%)	10 (14%)
M3 bone marrow involvement (>25% blasts)‖	40 (73%)	54 (76%)
Bone marrow blasts at preconditioning after bridging chemotherapy		
n	46	48
Median (IQR)	59% (25–87)	63% (27–89)
≤5%‖	5 (9%)	5 (7%)
>5% to 25%‖	7 (13%)	7 (10%)
M3 bone marrow involvement (>25% blasts)‖	34 (62%)	36 (51%)

	Treated patients (n=55)
Overall complete remission or complete remission with incomplete haematological recovery	39 (71%)*
Complete remission	31 (56%)
Complete remission with incomplete haematological recovery	8 (15%)
Blast-free hypoplastic or aplastic bone marrow	4 (7%)
No response	9 (16%)
Unknown or not evaluable†	3 (5%)

Data are n (%). *95% CI 57–82, p<0·0001. †The three patients who were unknown or not evaluable died (at days 8, 15, and 18) before the first disease assessment.







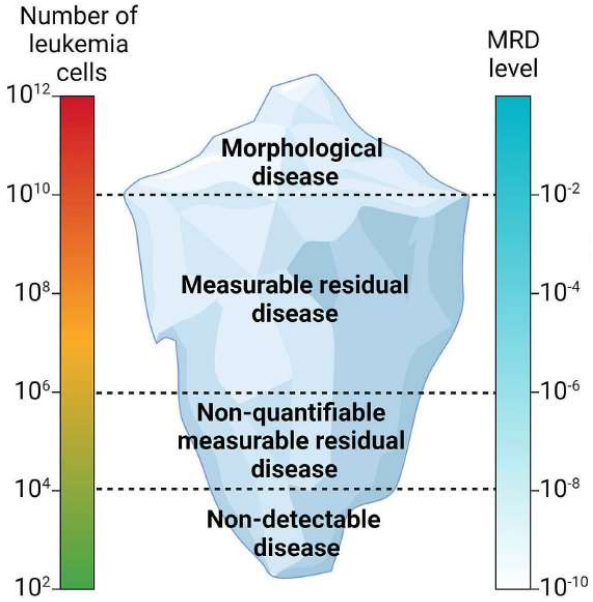
www.thelancet.com **Published online June 4, 2021 https://doi.org/10.1016/S0140-6736(21)01222-8**

Conclusion II

- **MRD status after alloHSCT is of even higher relvance for cure**
- **Currently only Blinatumomab and DLI are approved for the treatment of persistent or emerging MRD after alloHSCT**
- **Inotuzumab and especially CAR-T cells are additional options that have to be studied in prospective studies**

Role of MRD at different time points

1. **Before alloHSCT**
    a. ***Relevance***
    b. ***Strategies for improvement***
2. **After alloHSCT**
    1. ***Relevance***
    2. ***Strategies for improvement***
3. **After Second line therapy**
    a. ***Relevance***
    b. ***Strategies for improvement***



https://doi.org/10.3324/haematol.2022.280638

UKD Universitätsklinikum Düsseldorf

hhu Heinrich Heine Universität Düsseldorf

Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation

Nicola Gökbuget,[1] Daniel Stanze,[1] Joachim Beck,[2] Helmut Diedrich,[3] Heinz-August Horst,[4] Andreas Hüttmann,[5] Guido Kobbe,[6] Karl-Anton Kreuzer,[7] Lothar Leimer,[8] Albrecht Reichle,[9] Markus Schaich,[10] Stefan Schwartz,[11] Hubert Serve,[1] Michael Starck,[12] Matthias Stelljes,[13] Reingard Stuhlmann,[14] Andreas Viardot,[15] Knut Wendelin,[16] Mathias Freund,[17] and Dieter Hoelzer,[1] on behalf of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

Table 3. Response to second salvage therapy in patients with relapse during/after chemotherapy

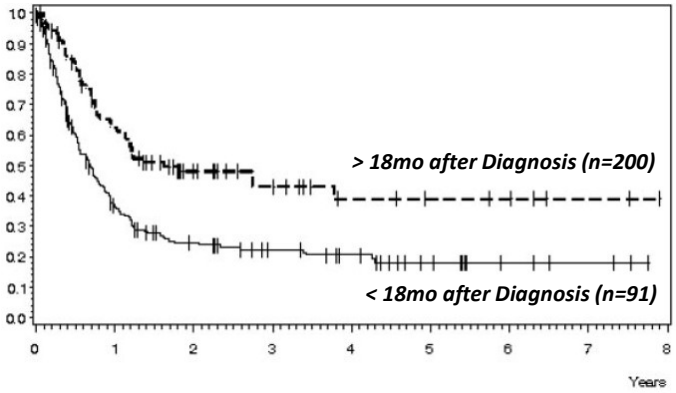
	Total			B-lineage			T-lineage		
	n	CR		n	CR		n	CR	
	82	27 (33%)*	*P*	48	12 (25%)*	*P*	34	15 (44%)*	*P*
FLAG-IDA	10	2 (20%)	> .05	9	1	> .05	1	1	> .05
CLAEG	4	1		0	0		4	1	
Nelarabine	16	8 (50%)		0	0		16	8 (50%)	
HDAC ± Mitox	4	0		3	0		1	0	
SCT in relapse†	26	8 (31%)		22	7 (32%)		4	1	
Other	22	8 (36%)		14	4 (29%)		8	4	

Patients with evaluable information about the type of salvage therapy, without CNS involvement and with Ph/*BCR-ABL*–negative ALL.
HDAC indicates high-dose cytarabine; and Mitox, mitoxantrone.
*No percentage was calculated in subgroups with total number of cases less than 10.
†Patients received SCT as their first salvage treatment; and CR rate indicates the remission rate after SCT.

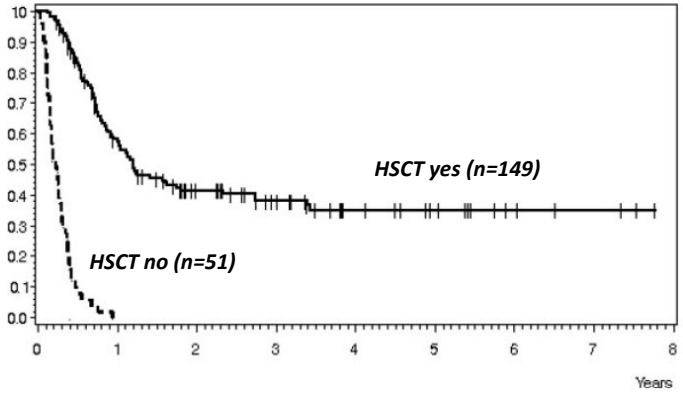
Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation

Nicola Gökbuget,[1] Daniel Stanze,[1] Joachim Beck,[2] Helmut Diedrich,[3] Heinz-August Horst,[4] Andreas Hüttmann,[5] Guido Kobbe,[6] Karl-Anton Kreuzer,[7] Lothar Leimer,[8] Albrecht Reichle,[9] Markus Schaich,[10] Stefan Schwartz,[11] Hubert Serve,[1] Michael Starck,[12] Matthias Stelljes,[13] Reingard Stuhlmann,[14] Andreas Viardot,[15] Knut Wendelin,[16] Mathias Freund,[17] and Dieter Hoelzer,[1] on behalf of the German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

Survival according to time to relapse



Survival according to performance of HSCT



proceeding to transplant in CR is the ultimate goal in relapsed ALL!

Strategies to treat relapse after conventional therapy in B-lymphoblastic leukemia

- chemotherapy +/-unarmed (naked antibodies), e.g. Rituximab
- armed (=conjungated antibodies), e.g. Inotuzumab
- bispecific T-cell engagers (BiTE®), e.g. Blinatomomab
- chimeric antigen receptor (CAR) T-cells, e.g. Tisagenlecleucel or KTE-X19

The NEW ENGLAND JOURNAL of MEDICINE

UKD Universitätsklinikum Düsseldorf

ORIGINAL ARTICLE

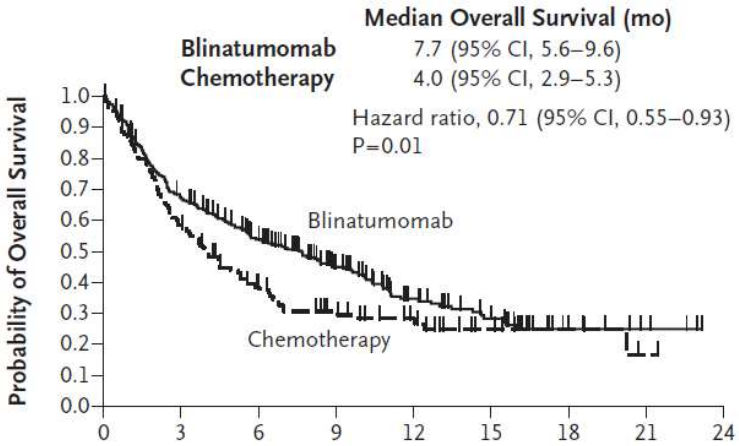
hhu Heinrich Heine Universität Düsseldorf

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

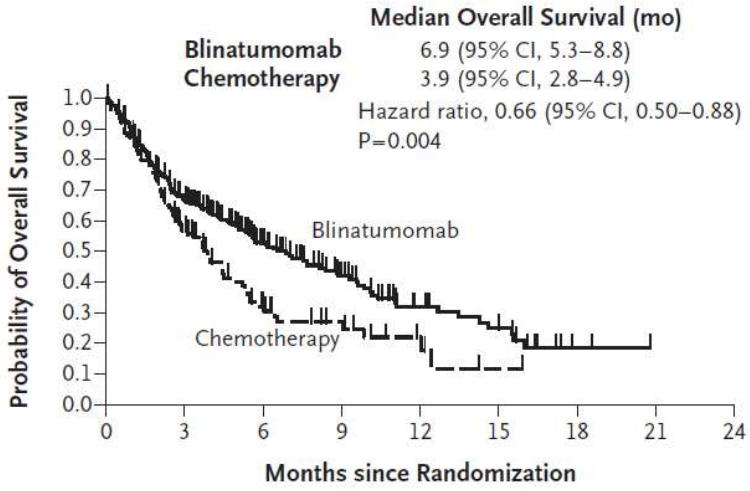
Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., Julie Bergeron, M.D., Fatih Demirkan, M.D., Ewa Lech-Maranda, M.D., Ph.D., Alessandro Rambaldi, M.D., Xavier Thomas, M.D., Ph.D., Heinz-August Horst, M.D., Ph.D., Monika Brüggemann, M.D., Wolfram Klapper, M.D., Ph.D., Brent L. Wood, M.D., Ph.D., Alex Fleishman, M.S., Dirk Nagorsen, M.D., Ph.D., Christopher Holland, M.S., Zachary Zimmerman, M.D., Ph.D., and Max S. Topp, M.D.

Percentage of patients	*Blina*	*SOC*
… achieving CR	*43.9%*	*24.6%*
… of CR pts MRD^{neg}	*76.0%*	*48.0%*
… receiving alloHSCT	*24,0%*	*24.0%*

Overall Survival

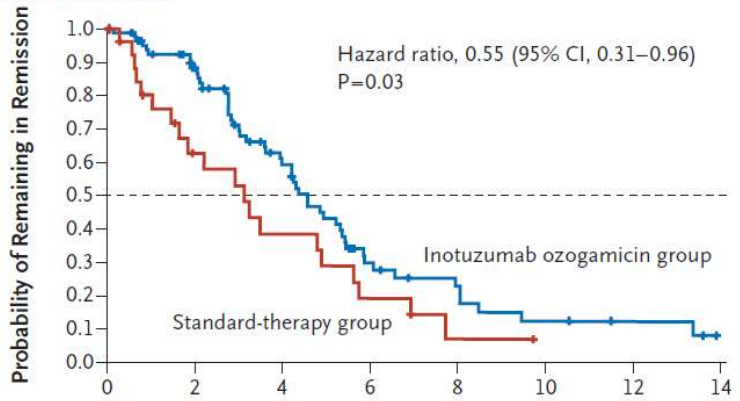


Overall Survival Censored at Time of Stem-Cell Transplantation

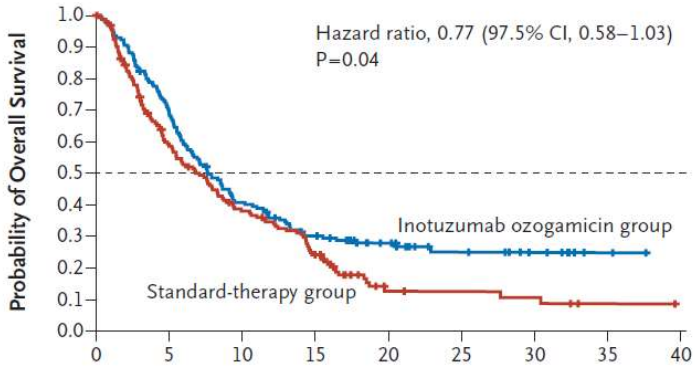


Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

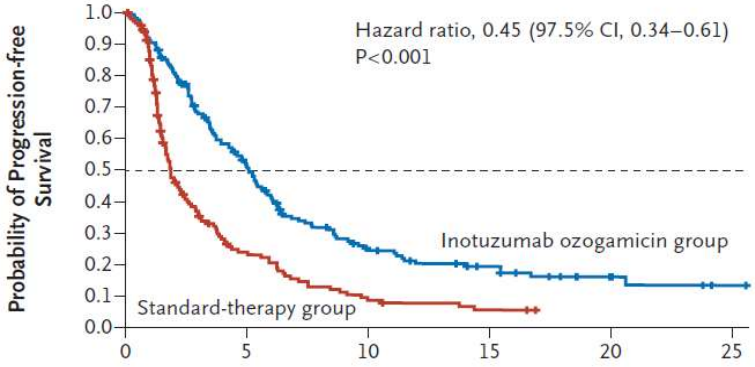
Duration of Remission



Overall Survival



Progression-free Survival

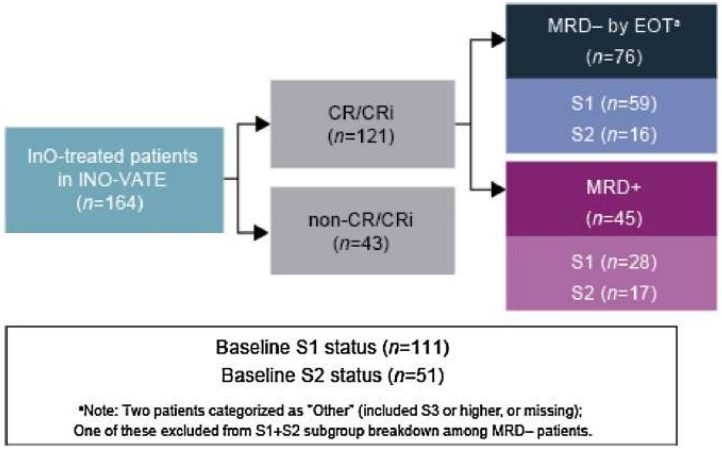


Percentage of patients	*Ino*	*SOC*
… achieving CR	*80.7%*	*29.4%*
… achieving MRD^{neg} CR	*78.4%*	*28.1%*
… receiving alloHSCT	*44,0%*	*18.3%*

Kantarjian et al, NEJM 2016

Impact of minimal residual disease status in patients with relapsed/ refractory acute lymphoblastic leukemia treated with inotuzumab ozogamicin in the phase III INO-VATE trial

Elias Jabbour[a,1,*], Nicola Gökbuget[b,1], Anjali Advani[c], Matthias Stelljes[d], Wendy Stock[e], Michaela Liedtke[f], Giovanni Martinelli[g], Susan O'Brien[h], Tao Wang[i], A. Douglas Laird[j], Erik Vandendries[i], Alexander Neuhof[k], Kevin Nguyen[l], Naveen Dakappagari[l], Daniel J. DeAngelo[m], Hagop Kantarjian[a]



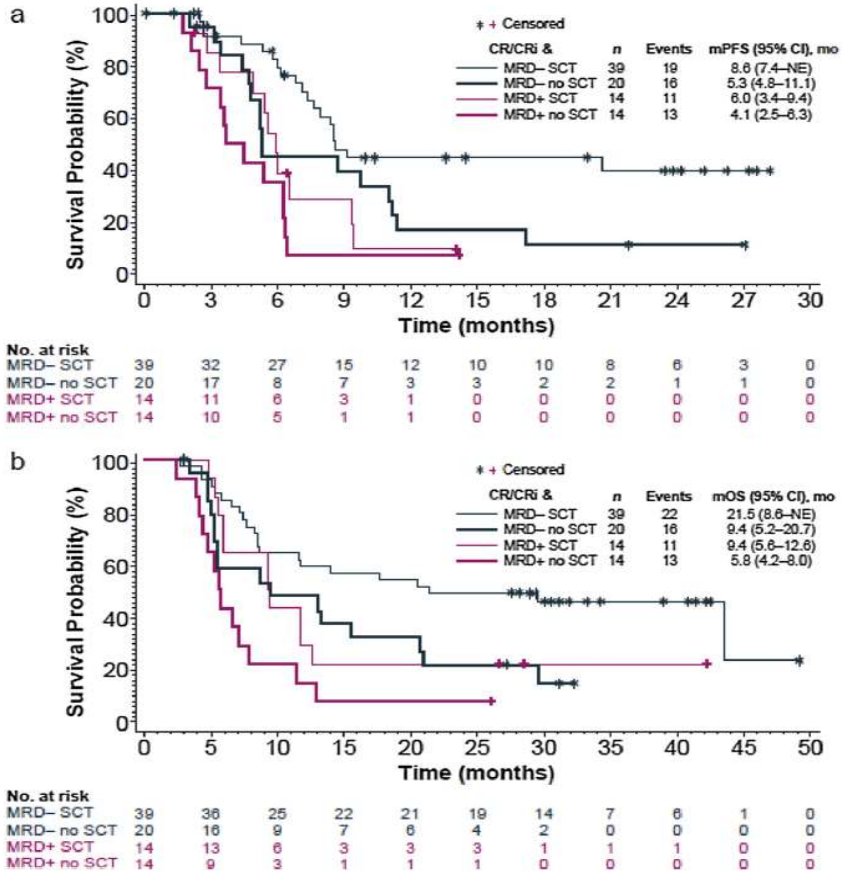
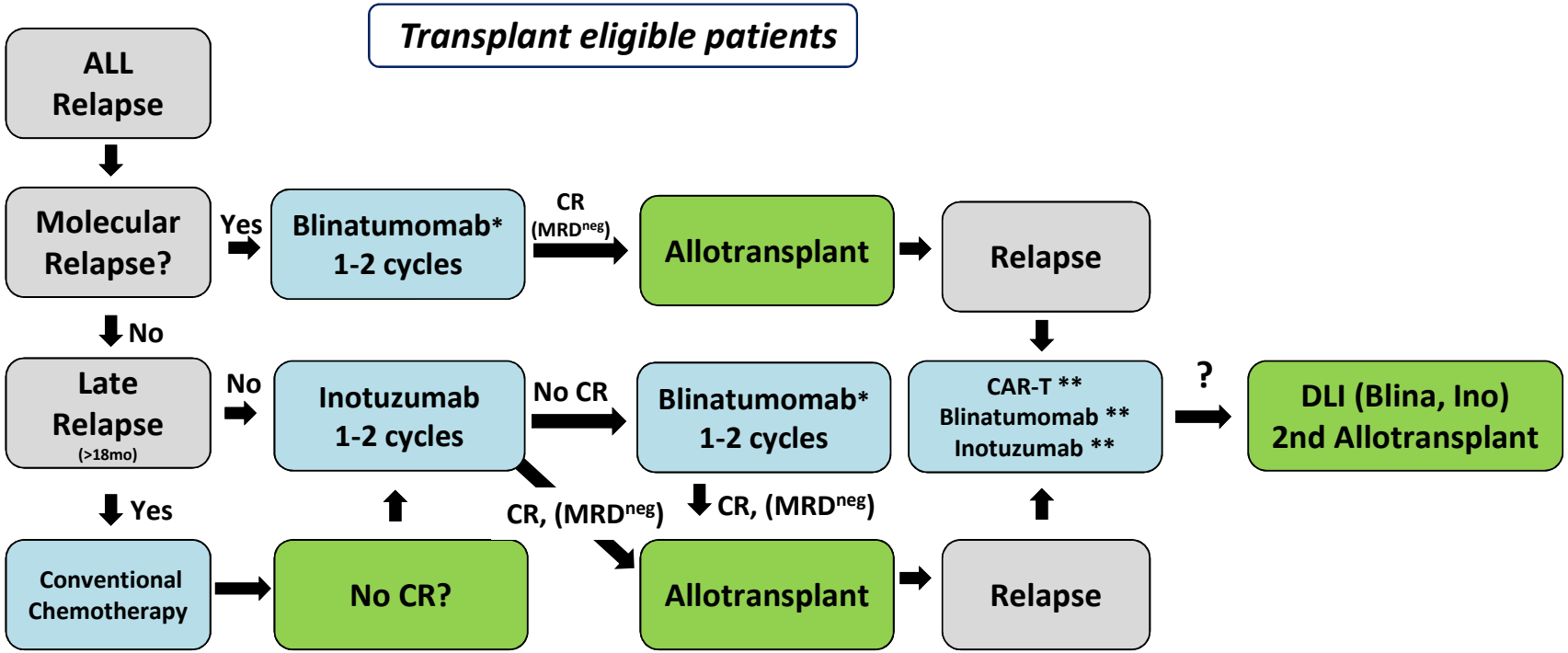


Fig. 5. Outcomes of patients taking InO who achieved minimal residual disease negativity after first salvage treatment, stratified by allogeneic stem cell transplantation (SCT). (A) Median progression-free survival (mPFS) and (B) median overall survival (mOS). *CI* confidence interval, *MRD* minimal residual disease.

Local treatment algorithm for r/r ALL Ph$^{neg.}$ in adults at the UKD



*For patients after failure of Inotuzumab and Blinatumomab ➡ Tisagenlecleucel (<26 years) or KTE-X19 (>26 years)

** Depending on response to previous therapies

Un grand merci à
à la solide équipe médicale et
l'équipe soignante et tous ceux qui nous soutiennent !

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

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