Allogene Stammzelltransplantation bei akuten Leukämien: Akute Lymphatische Leukämie

Eva Wagner-Drouet

ONKOPEDIA – Online Seminar 06. Oktober 2023

Interessenskonflikte

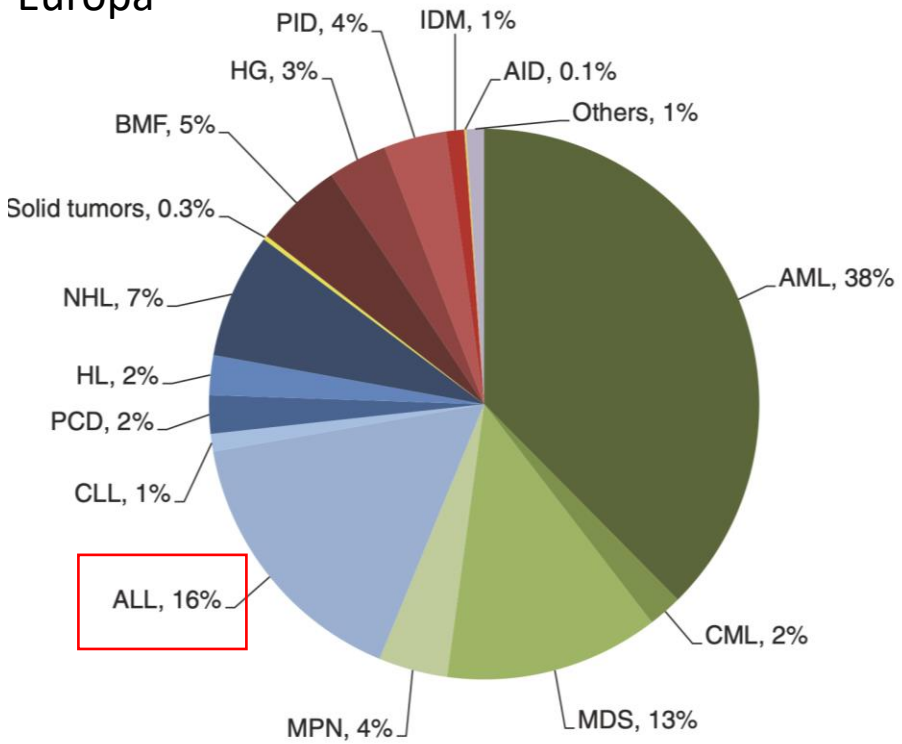
- **1. Anstellungsverhältnis oder Führungsposition: -**
- **2. Beratungs- bzw. Gutachtertätigkeit: -**
- **3. Besitz von Geschäftsanteilen, Aktien oder Fonds: -**
- **4. Patent, Urheberrecht, Verkaufslizenz: -**
- **5. Honorare:** Takeda, Kite Gilead, Novartis, Medac, BMS, Pfizer, MSD
- **6. Finanzierung wissenschaftlicher Untersuchungen:** Mikrogen
- **7. Andere finanzielle Beziehungen: -**
- **8. Immaterielle Interessenkonflikte: -**

Agenda

- ALL – HSZT in Deutschland
  - GMALL-Risiko-Stratifizierung
- Einflussfaktoren
  - Spender / Konditionierung / MRD / Follow up
- Relapse
- Ph pos ALL

Allogene HSCT

Europa



ALL CR1 1780 patients, >CR1 1185 patients

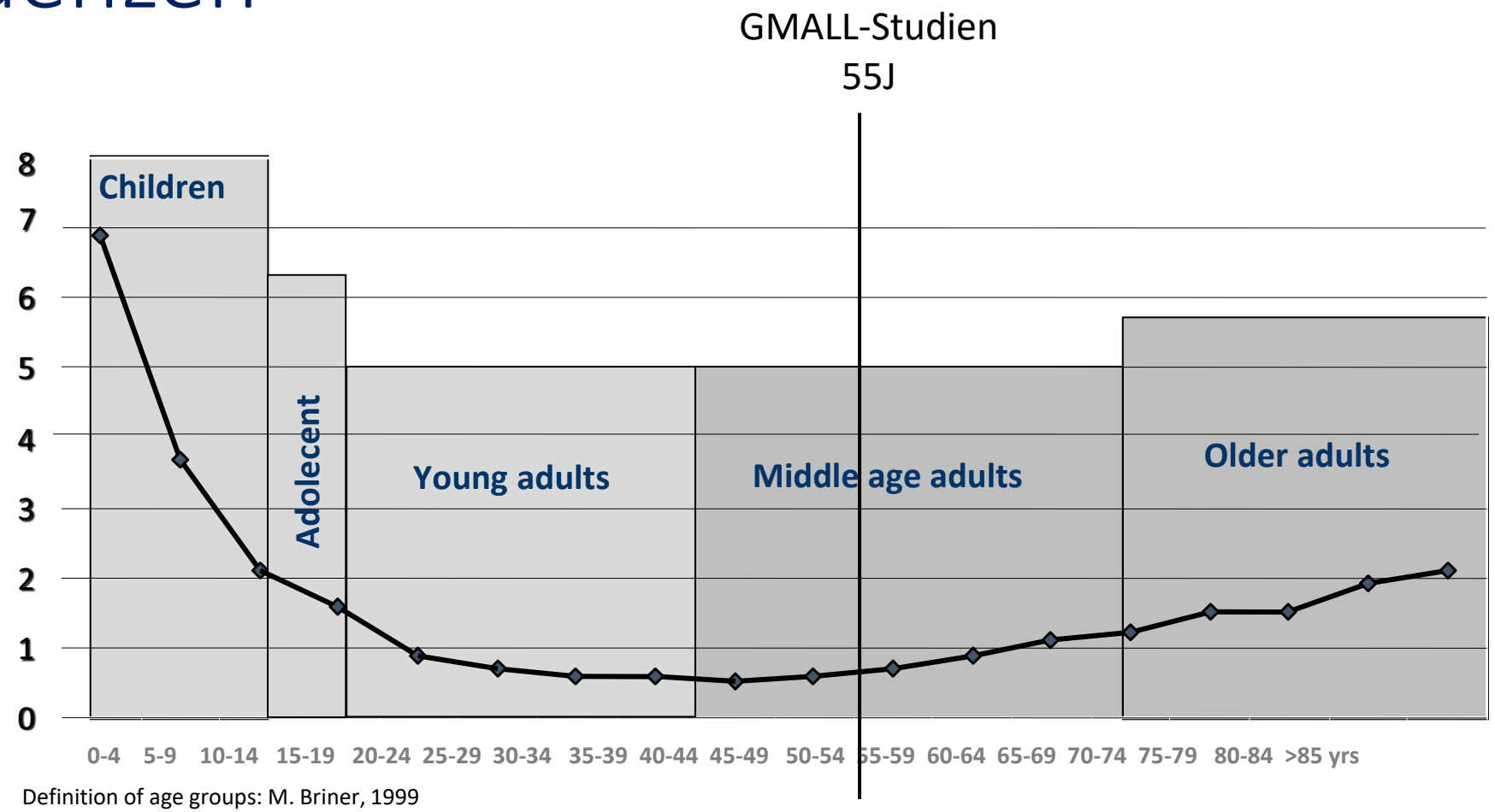
Passweg JR, et al. Bone Marrow Transplant 2020;55:1604–1613

Deutschland

Allo HSCT	2014	2015	2016	2017	2018	2019	2020	2021	2022
in CR1	165	154	147	177	178	200	190	195	195
>CR1	**64**	**91**	**86**	**76**	**93**	**73**	**60**	**49**	**73**
% of all allo HSCT	approx. 7-8% of allo HSCTs in Germany								
CAR-T (adult)					**5**	**15**	**19**	**8**	**26**

DRST, German Registry for Stem Cell Transpl.

Inzidenzen

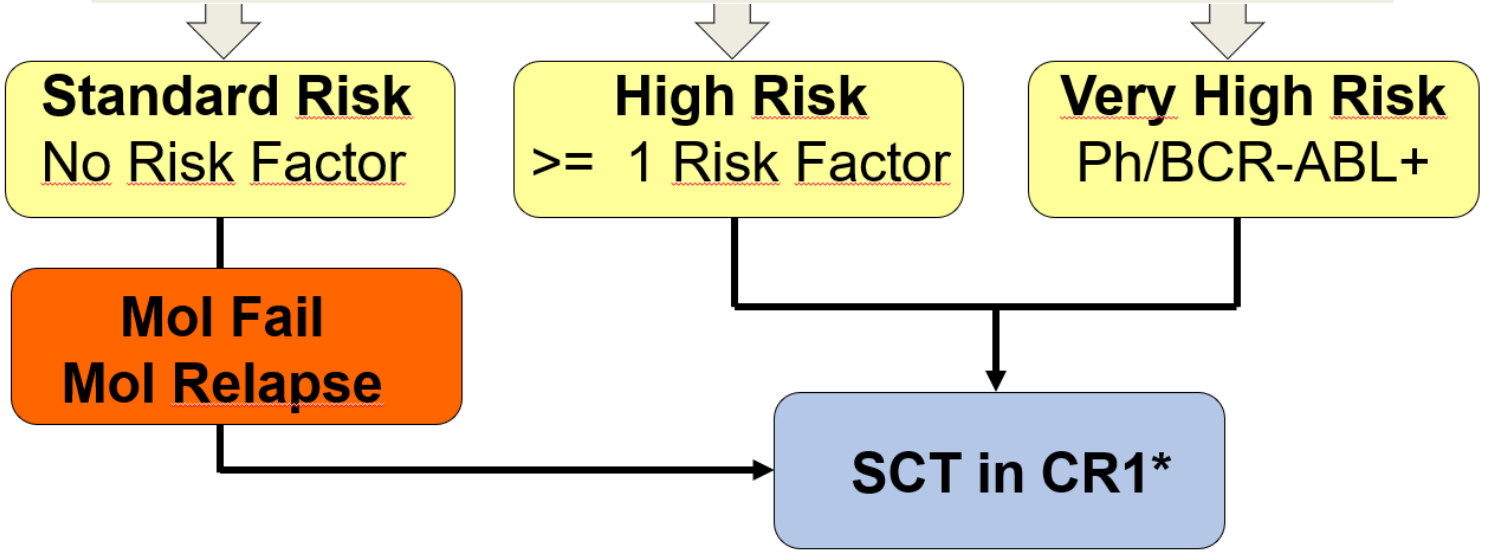


Definition of age groups: M. Briner, 1999

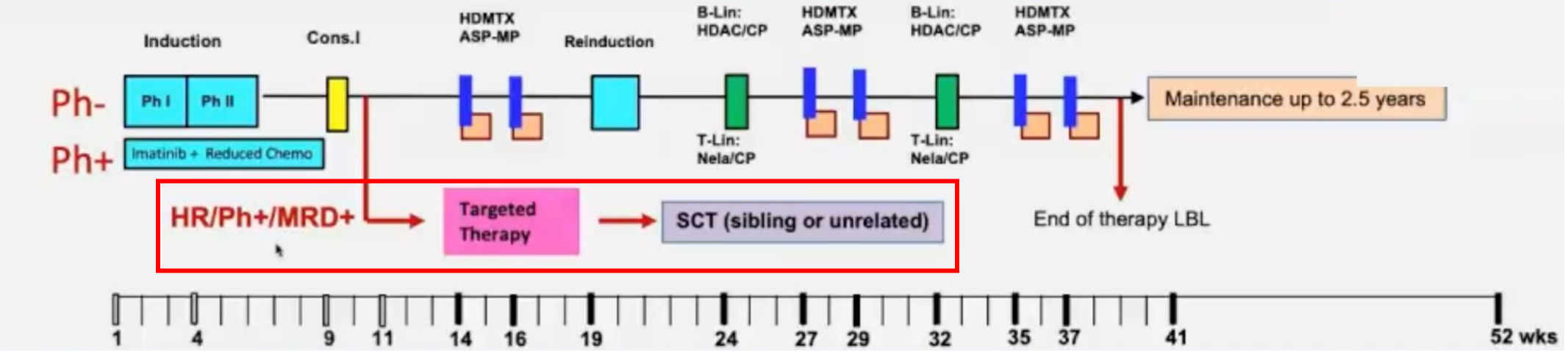
SEER Program (www.seer.cancer.gov)
Public-Use, Nov 2003 (incidences 1992-2001)

Risiko-Stratifizierung GMALL

	B-Precursor	T-ALL
High WBC	>30.000/µl	
Subtype	pro B	early T mature T
Genetic	t(9;22)/BCR-ABL t(4;11)/KMT2A-AFF1	



GMALL 08/2013 Protokoll (<55J)



- BFM-based ‚pediatric' regimen
- Dexa during induction/consolidation I
- 9 x PEG-asparaginase (2000 - 1000 – 500 U/m²)
- 7x HDMTX (1.5 g/m²)
- Reinduction
- Risk-adapted SCT indication

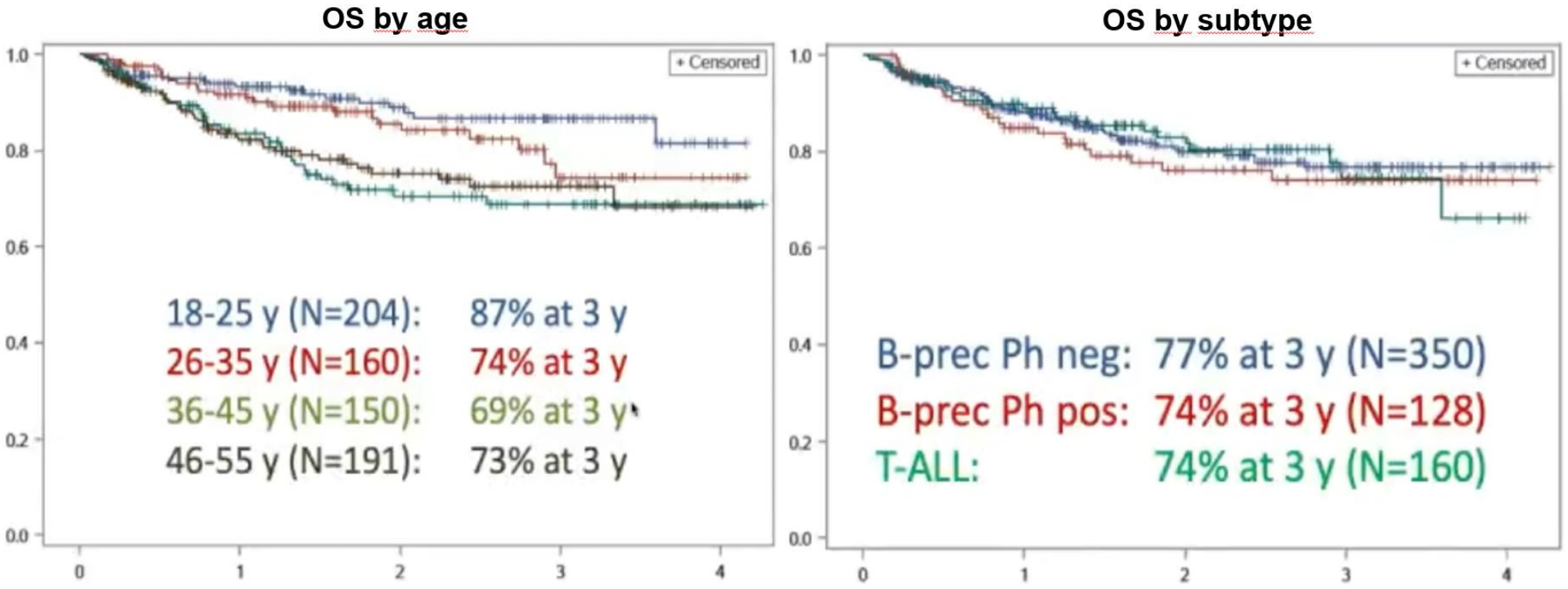
Risk stratifikation: HR: >= 1 risk factor
- pro-B-ALL and / or KMT2A
- early / mature T
- B-precursor: WBC > 30.000
- No CR after induction I

+ Molecular Failure after Consolidation I

<u>Randomization I:</u>
CNS irradiation versus i.th. prophylaxis in B-ALL/LBL

<u>Randomization II:</u>
SCT versus standard therapy in HR pts with MolCR after induction.

Overall Survival



Gökbuget et., ASH 2021

N=705 (GMALL 08/2013 <55)

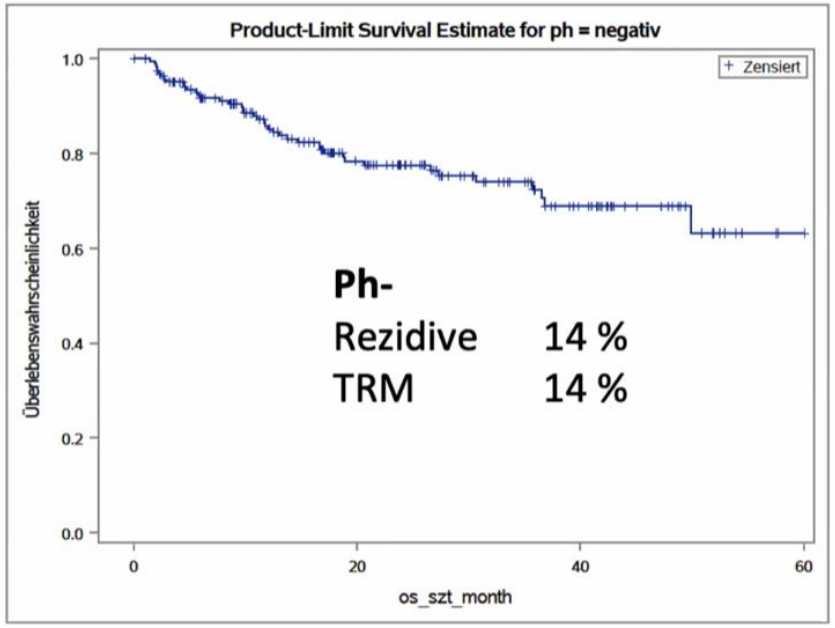
Response nach Kons 1

	Total	B-ALL Ph-	B-ALL PH+	T-ALL	B/T SR	B/T HR
N Evaluable	599	326	122	151	261	217
Hematologic CR	**93%**	**94%**	**95%**	**89%**	**96%**	**88%**
Early death	4%	5%	3%	5%	3%	7%
Failure/PR	3%	1%	2%	7%	1%	4%
N Evaluable	542	306	116	120	248	178
Molecular CR	61%	65%	41%	67%	74%	54%
Molecular Failure	19%	18%	28%	11%	10%	25%
MRD Low Pos	14%	11%	17%	20%	12%	16%
Molecular NE	6%	6%	13%	3%	4%	5%
Molecular Response	**75%**	**76%**	**58%**	**87%**	**86%**	**70%**

Gökbuget et., ASH 2021

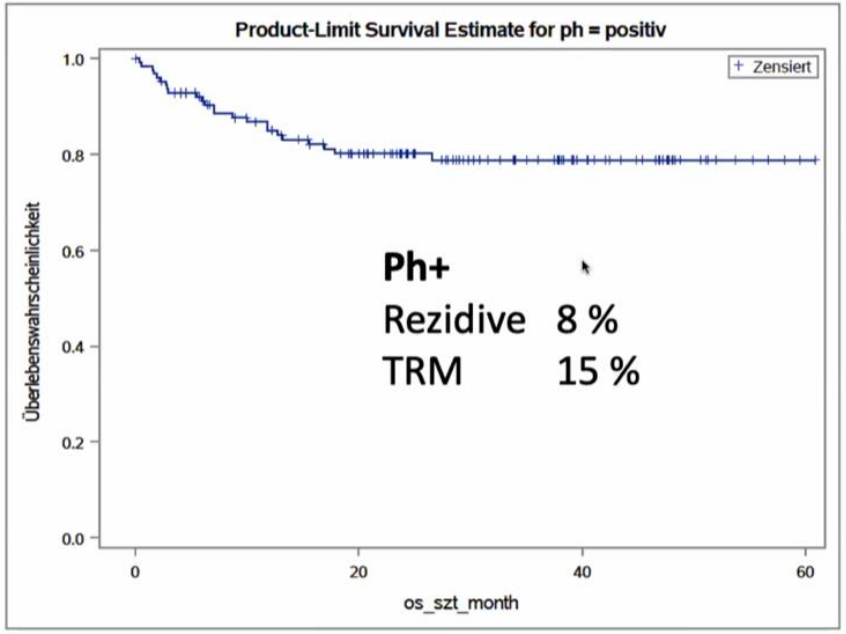
Overall Survival alloTx in CR1 GMALL

Ph-NEG



N = 192
Survival at 1 year: 85 %
Survival at 3 years: 72 %

Ph-POS



N = 130
Survival at 1 year: 85 %
Survival at 3 years: 79 %

GMALL 08/2013

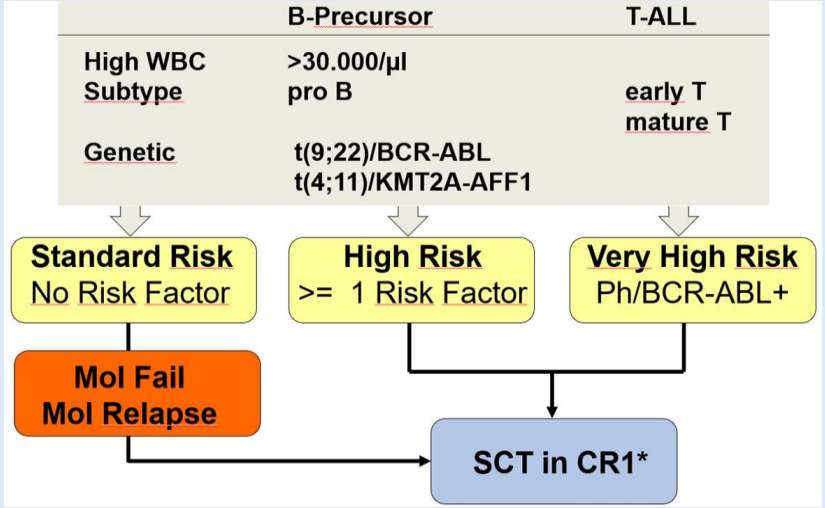
Fallbeispiel

43 jährige Patientin

Diagnose: c-B-ALL, bcr-abl neg

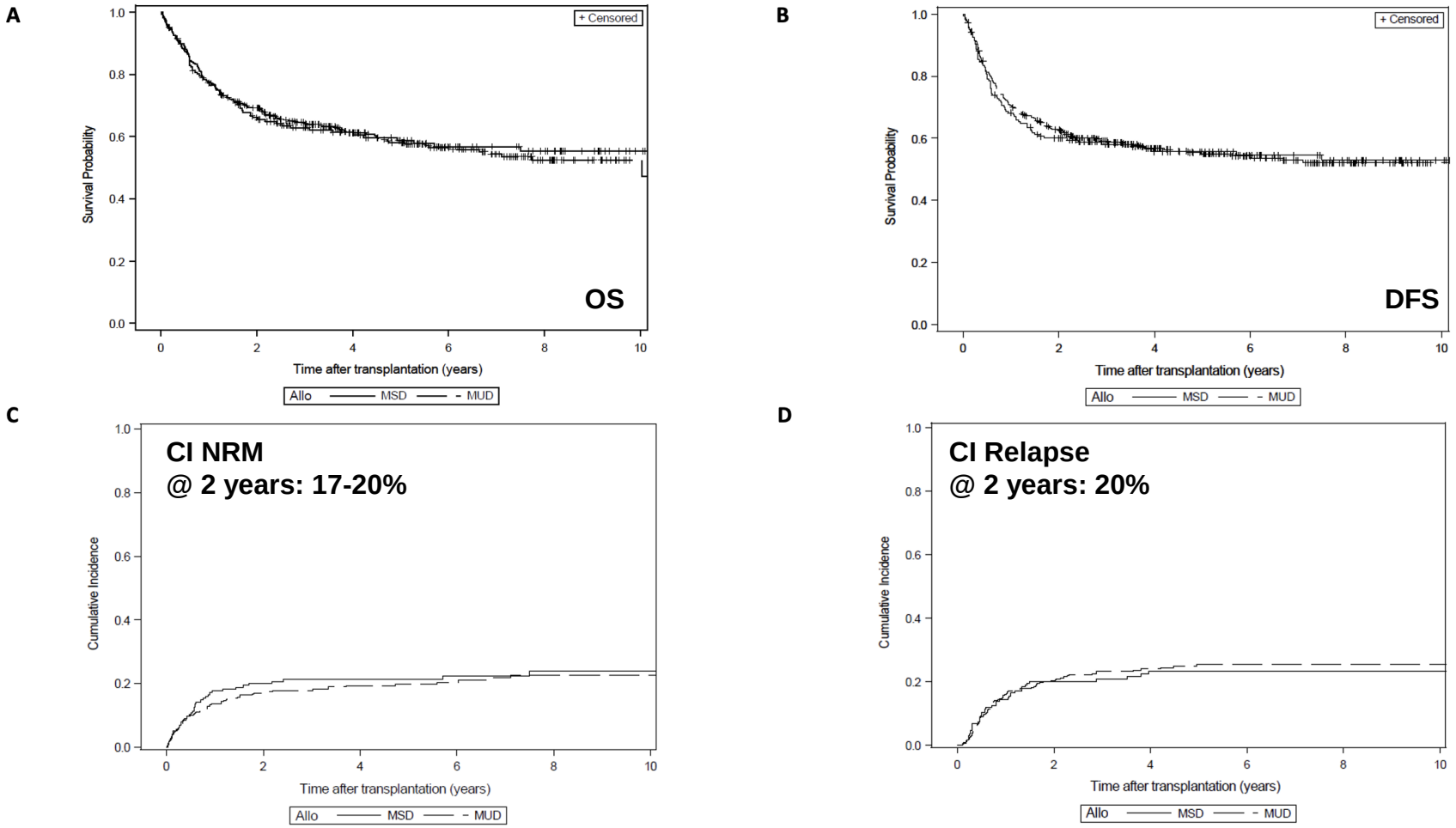
GMALL-younger Protokoll

- Vorphase + **Induktion 1**
  - keine CR
- **Induktion 2**, zytolog. CR,
  - molek. pos (MRD level 10^{-3})
- **Konsolidierung 1**, zytolog. CR
  - molek. pos (MRD level 10^{-3})



2 HLA-idente Fremdspender
1 haploidenter Bruder

Spenderauswahl - GMALL (Tx 1999-2013)

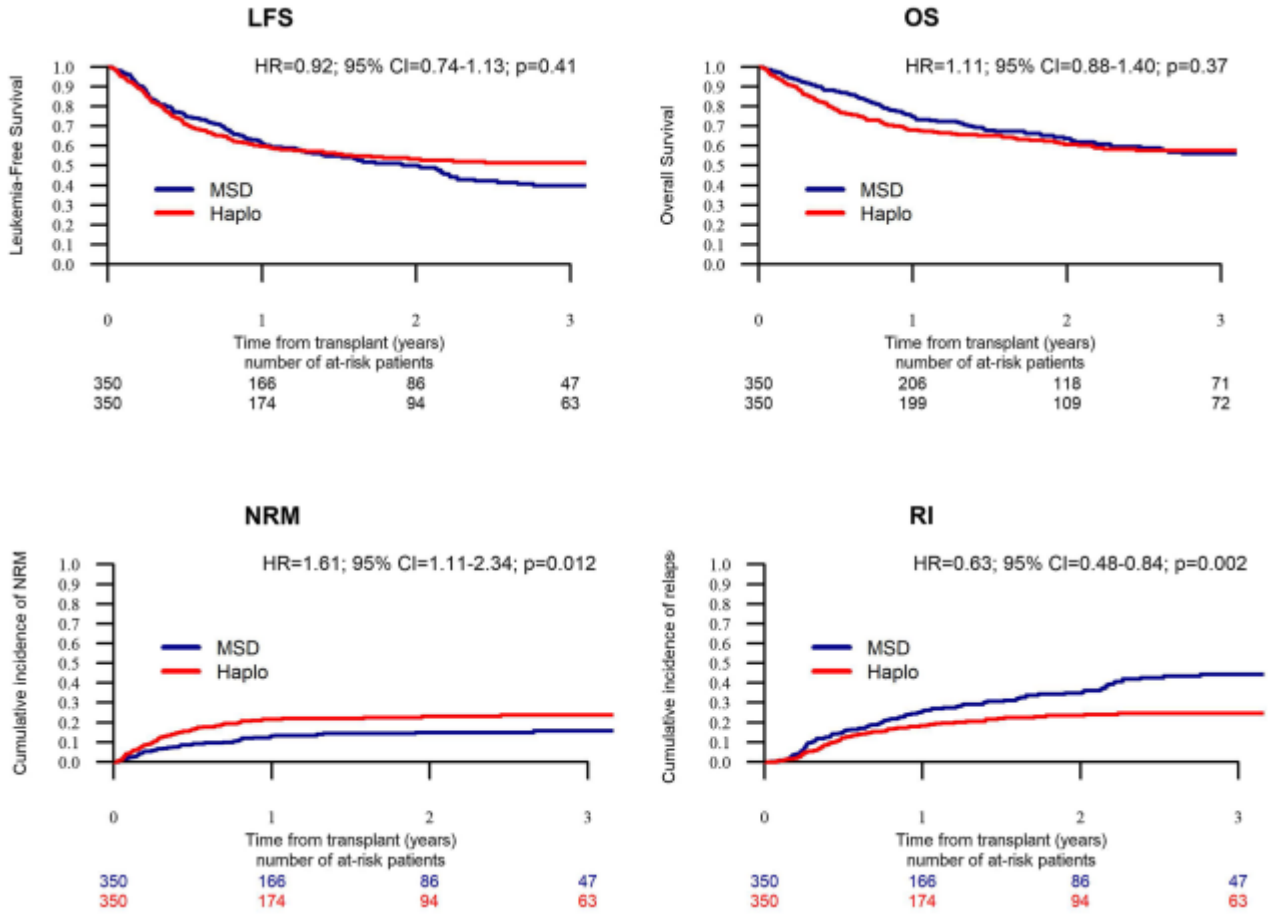


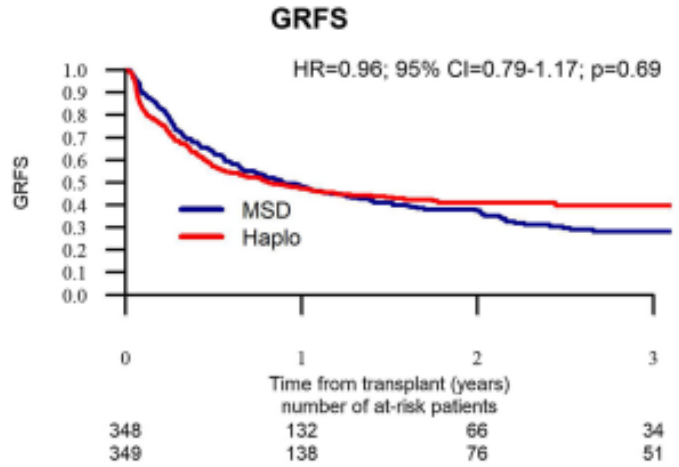
MUD: 366
Med age: 32 y

MRD: 176
Med age: 33 y

Beelen, Arnold, Stelljes et al., TCT 2022

Haplo vs matched sibling?

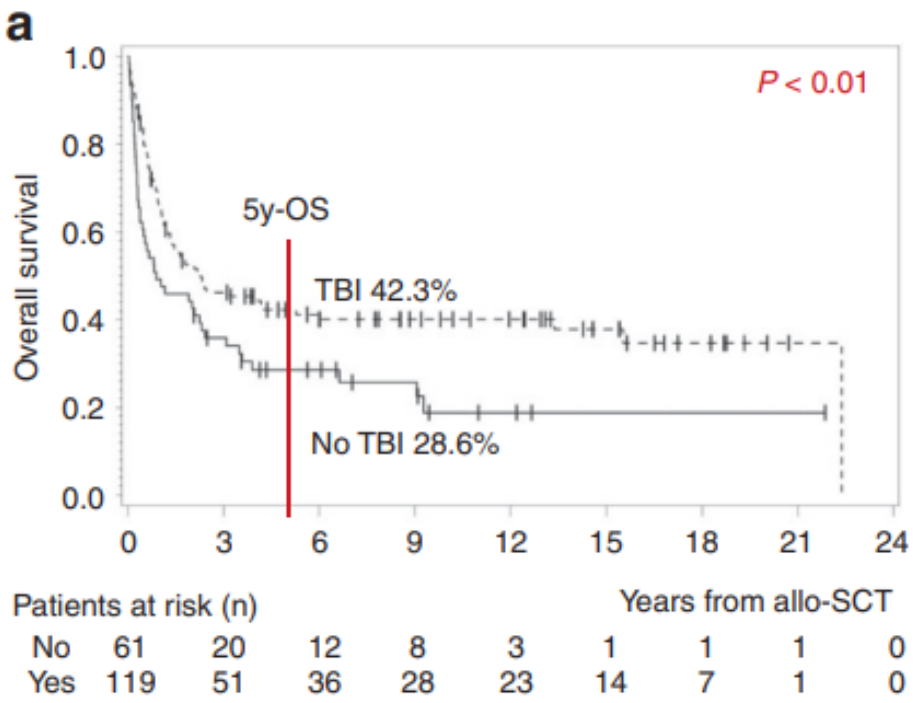


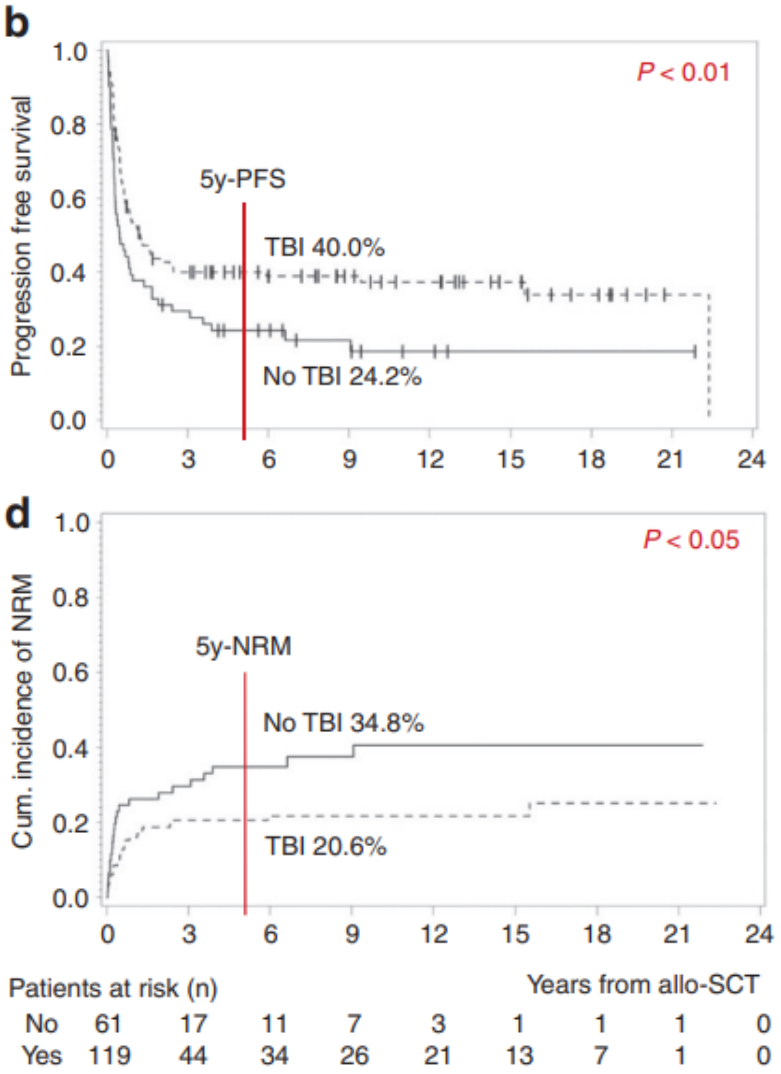


N=2304, retrospective

Nagler et al J Hematol Oncol 2021

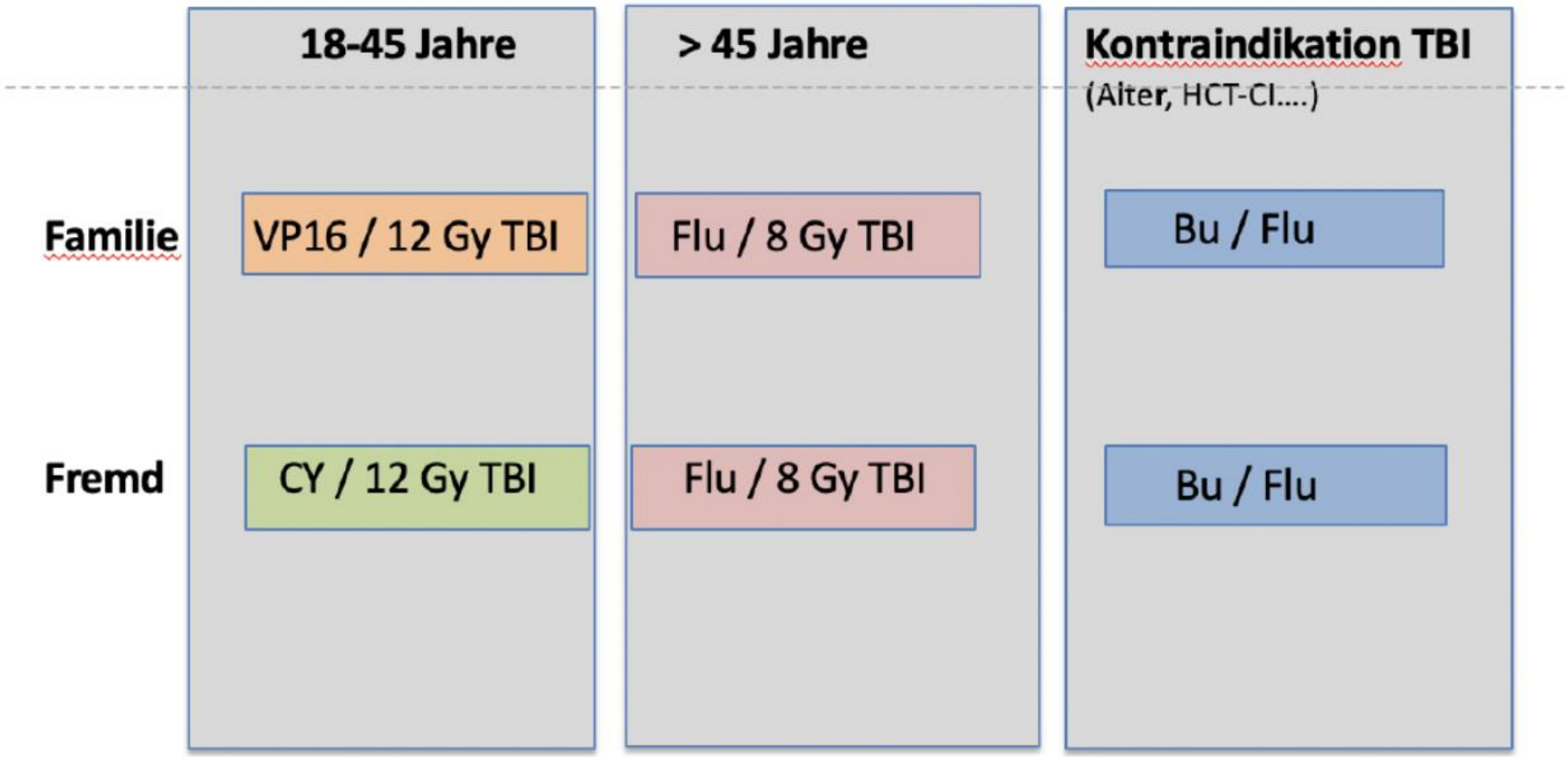
Konditionierung?





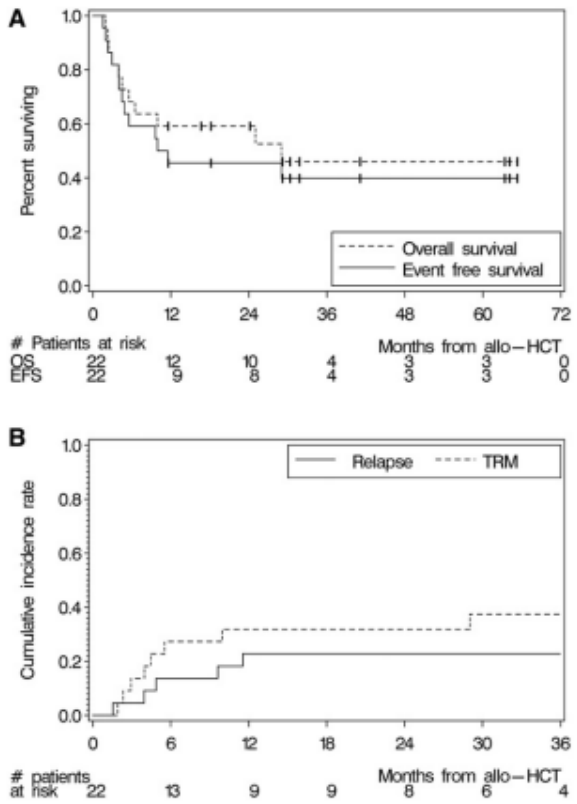
Greil et al, BMT 2021

Konditionierug - GMALL



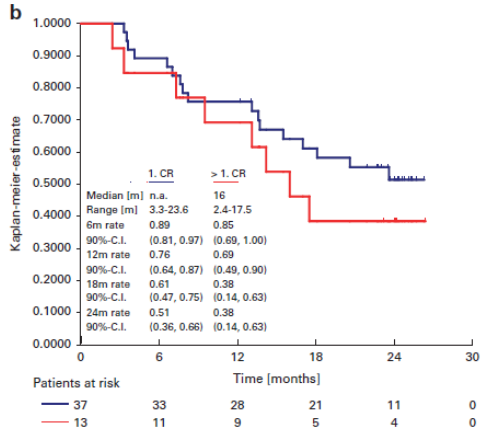
TBI-frei (keine GMALL-Empfehlung)

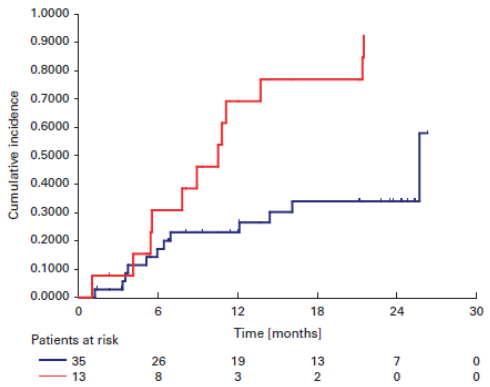
- Flu 25mg/m2 d-6 bis d-4
- Carmustin 400mg/m2 d-6
- Thiotepa 5mg/kg 2x d-5 & d-4

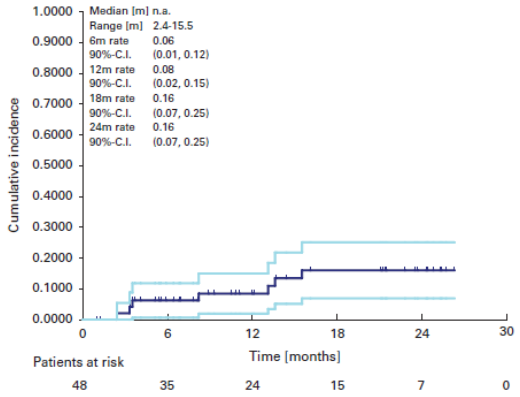


Christopoulos et al BBMT 2012

- Treo 12g/m2 d-7 bis d-5
- Etoposid 30mg/kg d-4
- Cyclo 60mg/kg d-3 & d-2







Kröger et al BMT 2015

Einflussfaktoren GMALL

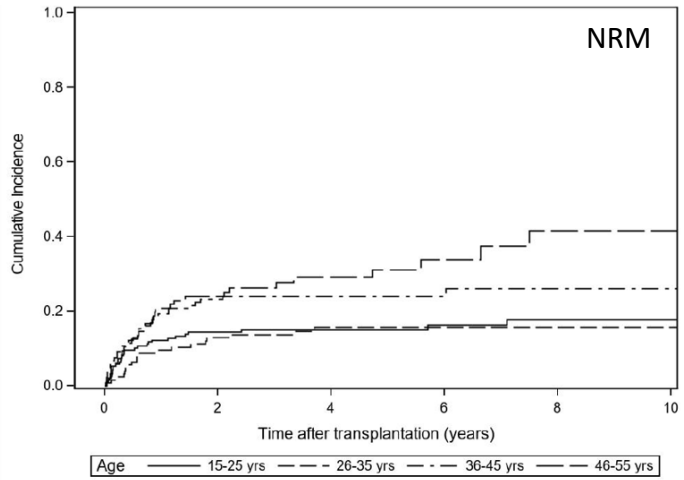
Multivariate Analysis of Significant Covariates: Overall Survival (N = 84)*

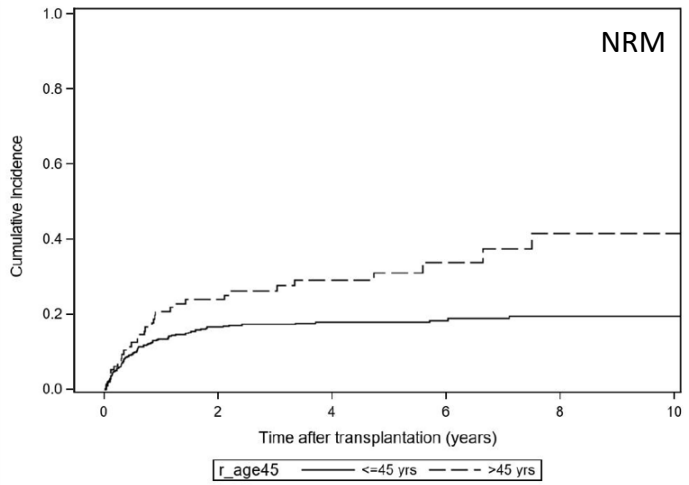
Covariates	HR	P†
Overall survival (N = 84)		
Age (≤35 versus >35)	3.471 (1.486 – 8.105)	**.0040**
MRD week 16 (mol CR versus mol failure)	3.653 (1.556 – 8.575)	**.0029**
aGvHD (grade 0/I versus II-IV)	–	.1525
Disease-free survival (N = 114)		
Age (≤35 versus >35)	–	.1750
Gender (male versus female)	–	.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

HR indicates hazard ratio; mol, molecular; aGvHD, acute graft-versus-host-disease.
* Only patients with all parameters available will be considered.
† Chi-squared.

- **Alter** – stärkster Prädiktor für NRM (Infektionen)
- **MRD** – stärkster Prädiktor für Relapse (45% mol. failure vs 6% mol CR)

Einflussfaktoren Alter & MRD (GMALL)

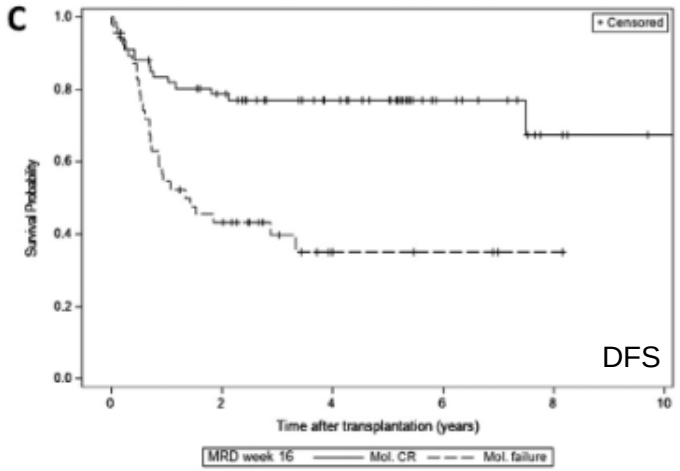


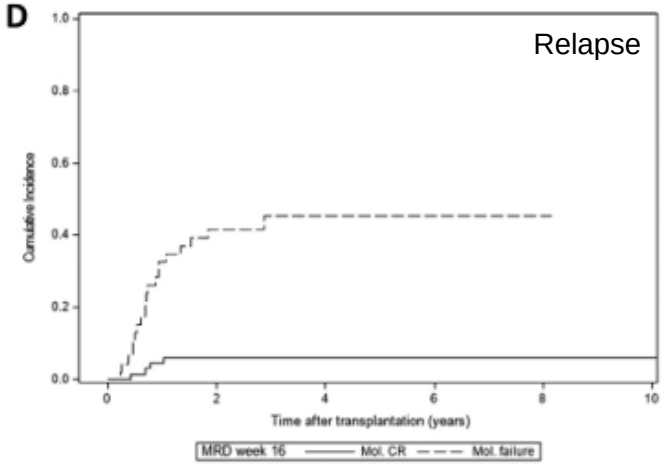


Alter

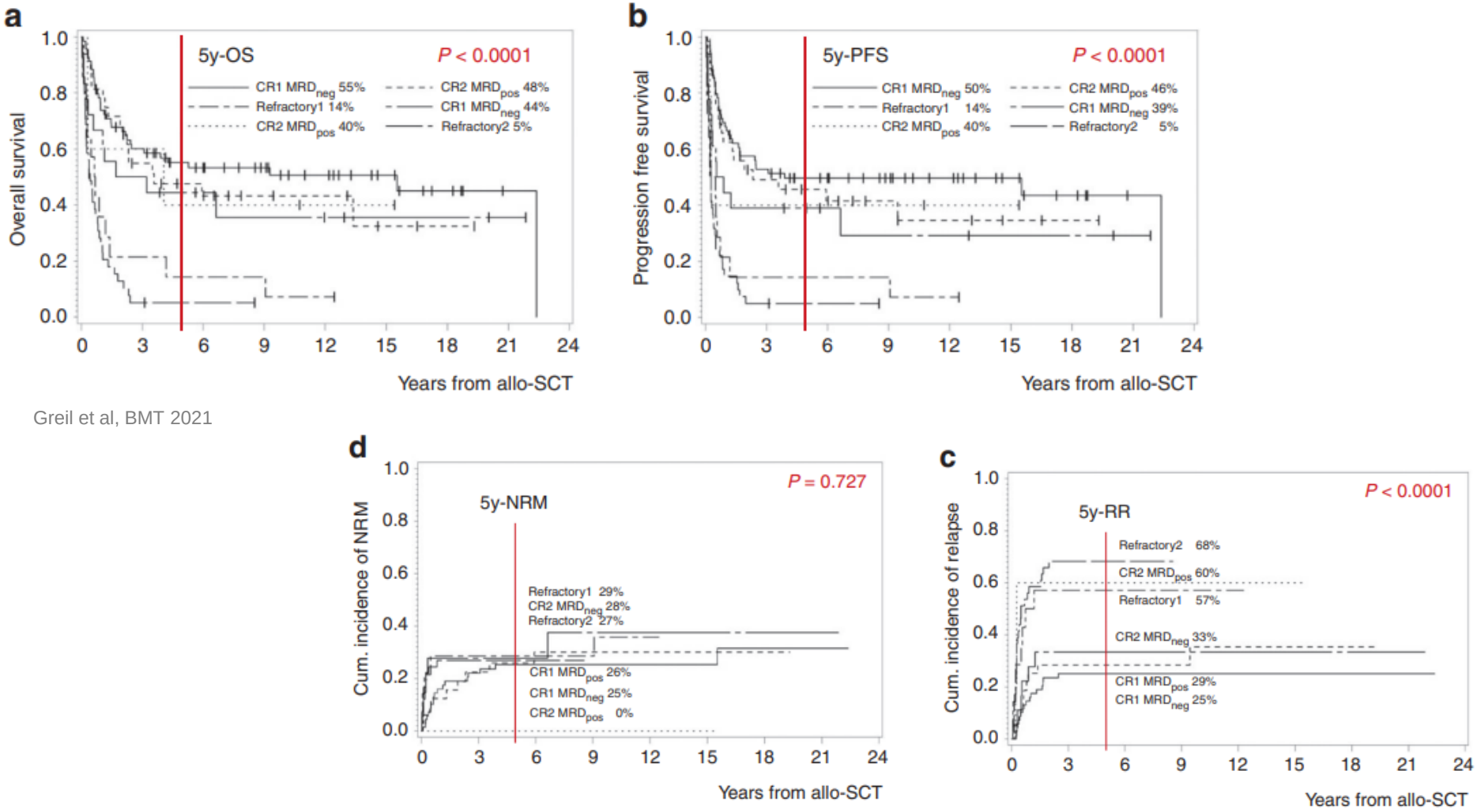
➡ >45 reduzierte TBI-Dosis

MRD Wo 16





Prognostic factor MRD



Greil et al, BMT 2021

Nagler et al J Hematol Oncol 2021

Fallbeispiel

43 jährige Patientin

c-B-ALL, bcr-abl neg, SR

GMALL-younger Protokoll

- keine zytolog. CR nach Induktion 1
- persistierend molek. pos nach Kons 1(MRD level 10^{-3})

2 Zyklen Blinatumomab

- MRD neg CR

allogene Stammzelltransplantation vom HLA-identen Fremdspender

- Konditionierung TBI 12Gy / Cy + ATG
- GvHD-Prophylaxe: MTX + CSA
- Pneumonie
- Mucositis III°

GMALL-Empfehlung

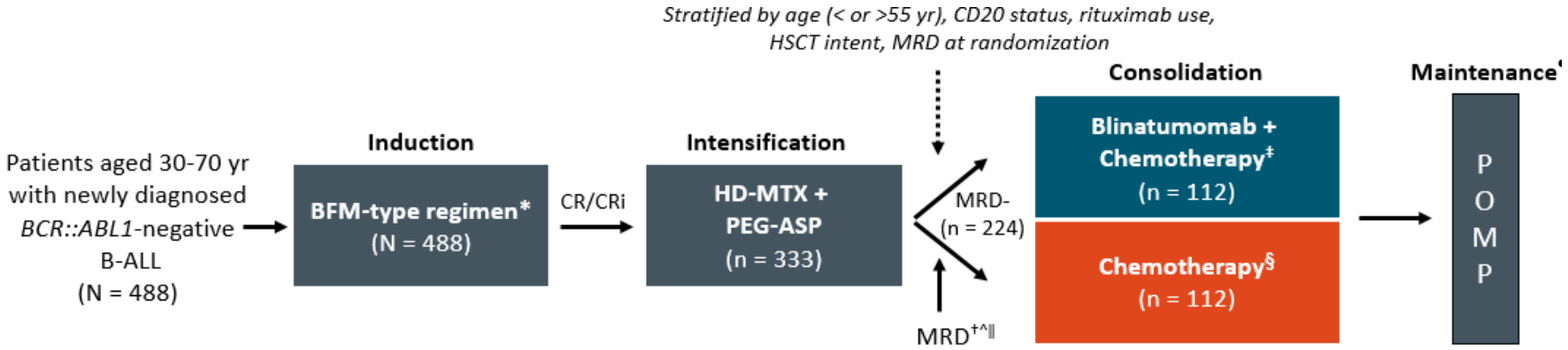
bei MRD-Positivität:

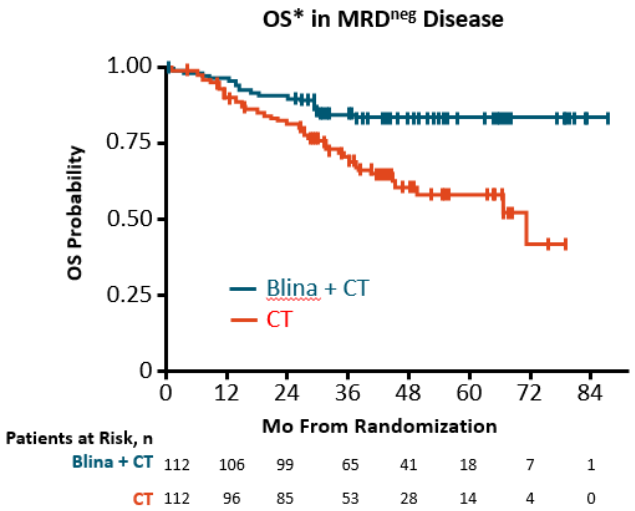
- ➢ zielgerichtete Therapie
- ➢ möglichst niedriges MRD-Niveau vor HSZT

– Blinatumomab (B-ALL)
– TKI-Wechsel (PH+ B-ALL)
– Nelarabine (T-ALL)

ECOG-ACRIN E1910-Study

Blina bei MRD neg





	Blina + CT (n = 112)	CT (n = 112)	HR (95% CI)	P
mOS,* mo	NR	71.4	0.42 (0.24-0.75)	.003
▪ 3.6-yr OS, %	83	65		
▪ Deaths, n	17†	39‡		
mRFS, mo	NR	22.4	0.46 (0.27-0.78)	.004

*Primary endpoint. †n = 8 secondary to ALL, n = 9 NRM.
‡n = 20 secondary to ALL, n = 17 NRM, n = 2 unknown.

Litzow ASH 2022, Abstr LBA1

Fallbeispiel

43 jährige Patientin

c-B-ALL, bcr-abl neg, SR

GMALL-younger Protokoll

- Z.n. Vorphase & Induktion 1, keine CR
- Induktion II & Kons 1, persistierend molek. pos (MRD level 10^{-3})
- 2 x Blinatumomab, MRD neg

allogene Stammzelltransplantation vom HLA-identen Fremdspender

Konditionierung TBI 12Gy / Cy + ATG

- d270: MRD pos (MRD level 10^{-4})
- d300: MRD pos (MRD level 10^{-3})
- 2x Blinatumomab + DLI
- seitdem MRD neg
- chronische GvHD der Mundschleimhaut + Augen

Follow up nach HSCT

– engmaschiges **MRD-Monitoring**

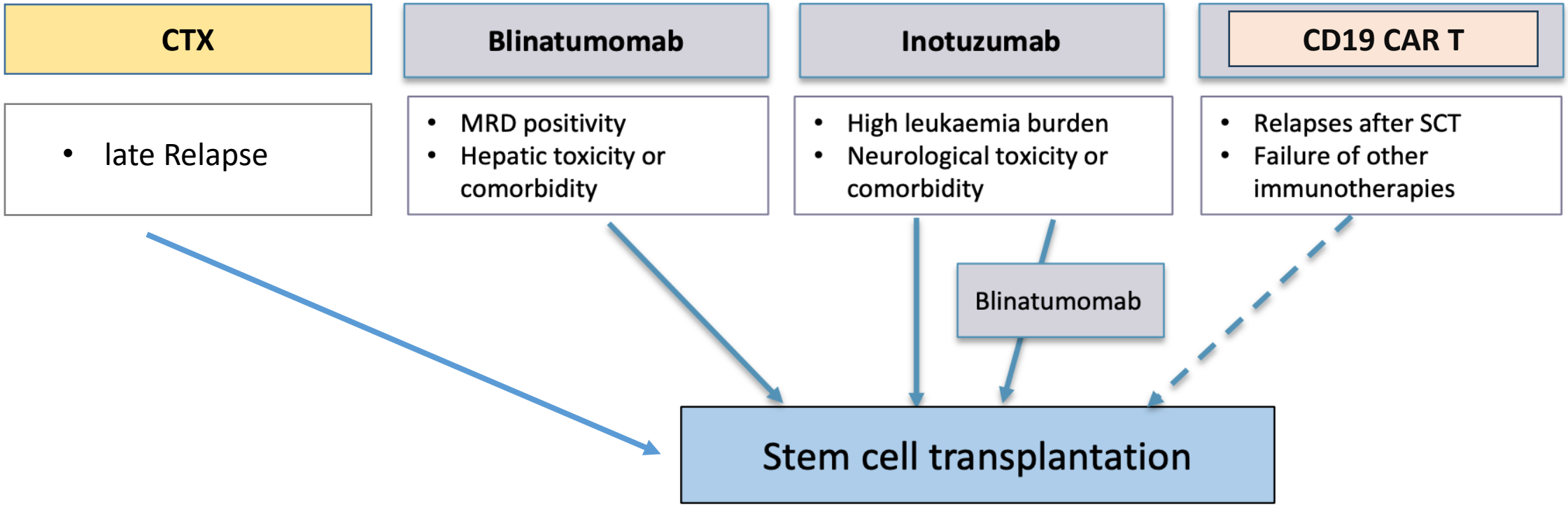
d30-60; d100, d180, d270, d360, d450, d540, d630, d720

MRD pos nach Tx:

- Reduktion Immunsuppression
- Donor Lymphozyten-Infusion
- Zielgerichtete Therapie: z.B. Blinatumomab, TKI…
- CAR T-Zell-Therapie?

…

Rezidiv – Tx in CR2



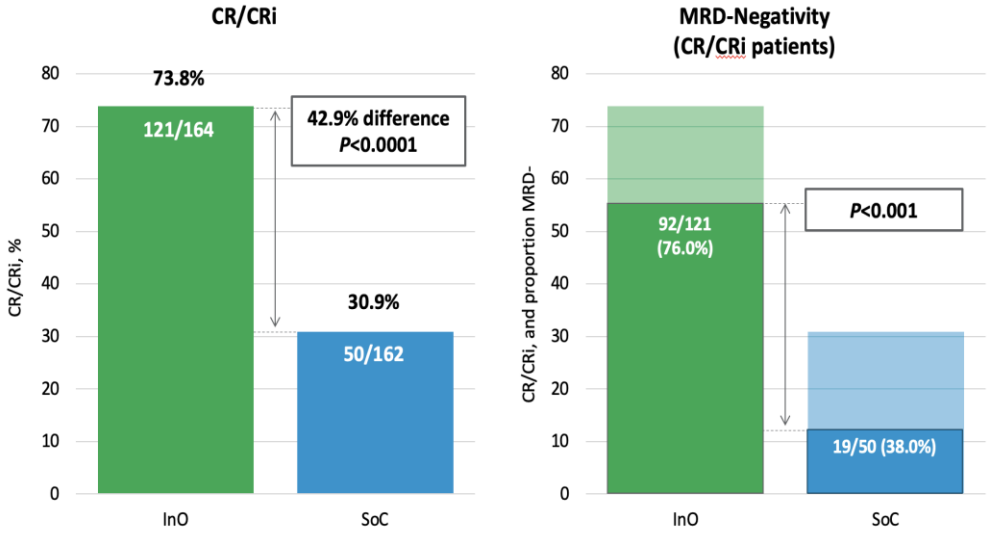
➡ GMALL-Rezidiv-Empfehlungen

adapted from Dhakal P, et al. Leuk Lymphoma 2020;61:7–17.

Remissions-Induktion

INOVATE trial: chemo vs. inotuzumab

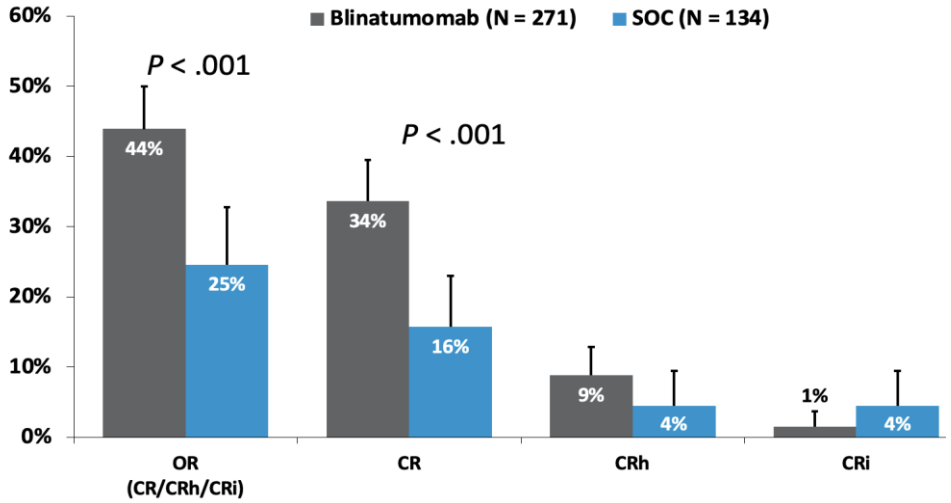
Kantarjian HM, et al. Cancer 2019;125(14):2474–2487.



SCT after	InO	vs	SOC
Total	47%.	vs.	20%
direct SCT	43%.	vs.	11%

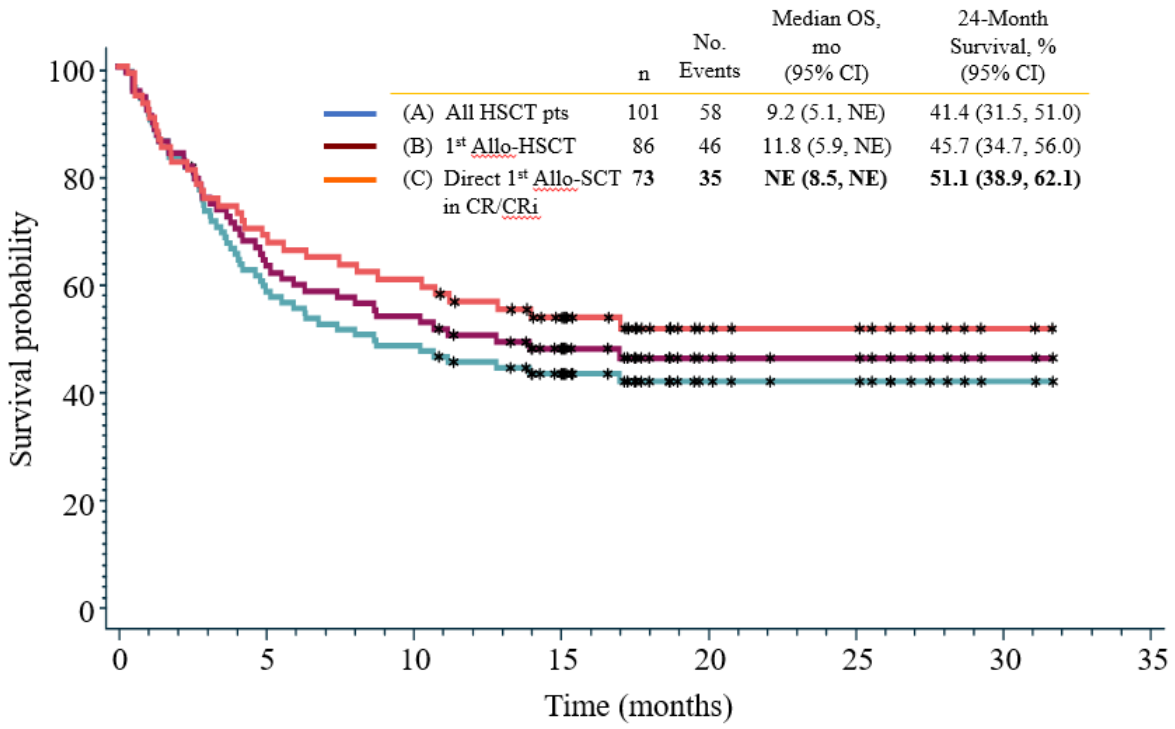
Tower trial: chemo vs. blinatumomab

Kantarjian HM, et al. N Engl J Med 2017;376:836–47.

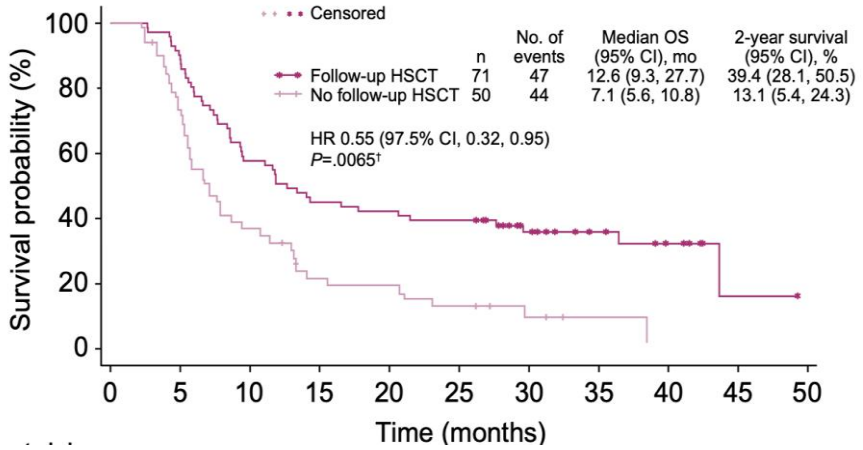


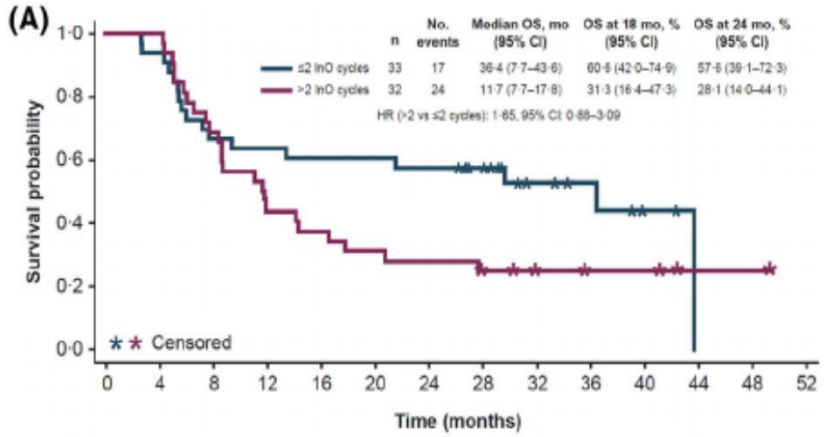
SCT after Blina	vs	SOC
Total	24%. vs.	14%
In CCR	14%. vs.	9%

HSCT nach Inotuzumab



Marks et al. Biol Blood Marrow Transplant. 2019 Sep;25(9):1720-1729.

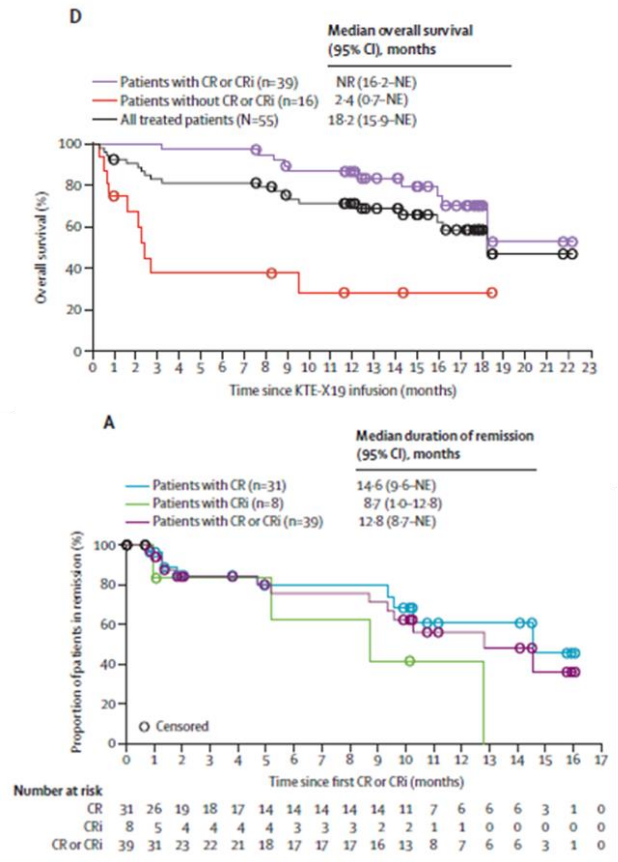




Cassaday RD et al.. Br J Haematol. 2020

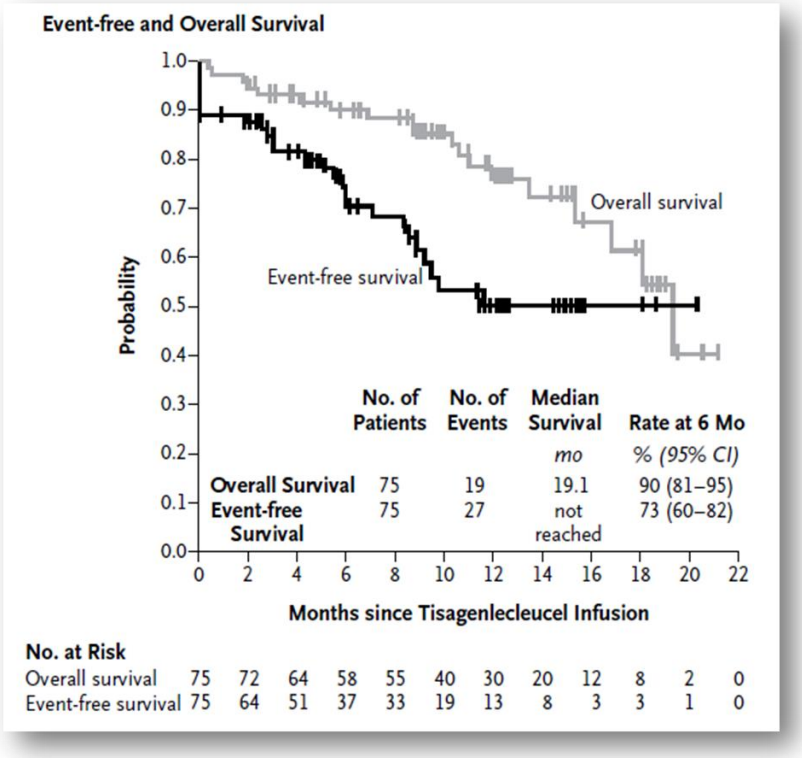
CD19 CAR T

Tecartus (>25J)



Shah B et al, Lancet 2021

Kymriah (<25J)



Maude SL et al. N Engl J Med. 2018;439-48.

hohe CR Rate (>80%)

Relapse ca 50% ohne alloTx

- CD19-Verlust
- CAR-Persistenz

alloTx nach CAR T?

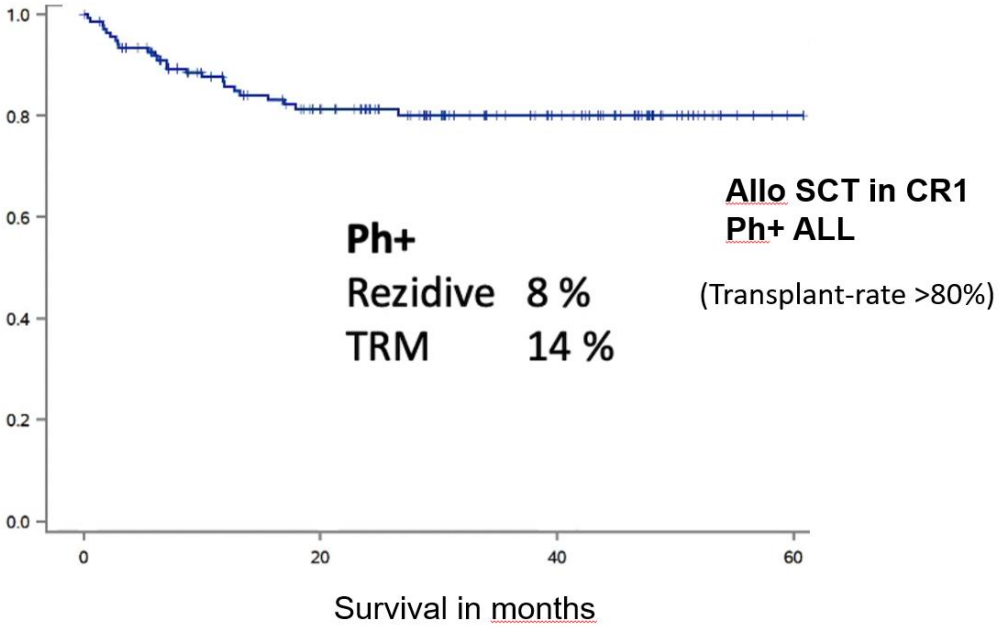
		Allo-HCT post CAR-T infusion	
	Structure of CAR-T	**Yes**	No
Park et al. (2018) *n* = 43	CD19-28z	*n*=17 Relapse, 6/17 (**35%**); TRM, 6/17 (35%)	*n* = 26 Relapse, 17/26 (**65%**)
Lee et al. (2015) *n* = 51	CD19-28z	*n*=21 Relapse, 2/21 (**9%**); LFS not reached (*P* = 0.0006)	*n*=7 Relapse, 6/7 (**86%**); LFS 4.9 mo
Pan et al. (2017) *n* = 45	CD19-4-1BBz	*n* = 27 relapse, 2/27 (**7%**) (*P* = 0.023); TRM, 2/27 (7%); 6-mo LFS, 81.3%	*n* = 18 Relapse, 9/18 (**50%**)
Pan et al. (2019) *n*=23	CD22-4-1BBz	*n*=11 relapse, 1/11 (**9%**); TRM, 2/11 (18%); LFS at 1 year, 71.6%	*n*=7 Relapse, 4/7 (**51%**)
Jacoby et al. (2018) *n*=20	CD19-28z	*n*=14 relapse 2/14 (**14%**); 1-year EFS, 73%; OS, 90%	*n*=4 Relapse, 2/4 (**50%**)
Shalabi et al. (2018) *n*=85	CD19-28z (*n* = 52); CD22-4- 1BBz (n=33)	25 went to allo-HCT; 2-year relapse, **13.5%**	n/a

Greenbaum et al, Front Oncol, 2020

PH pos ALL

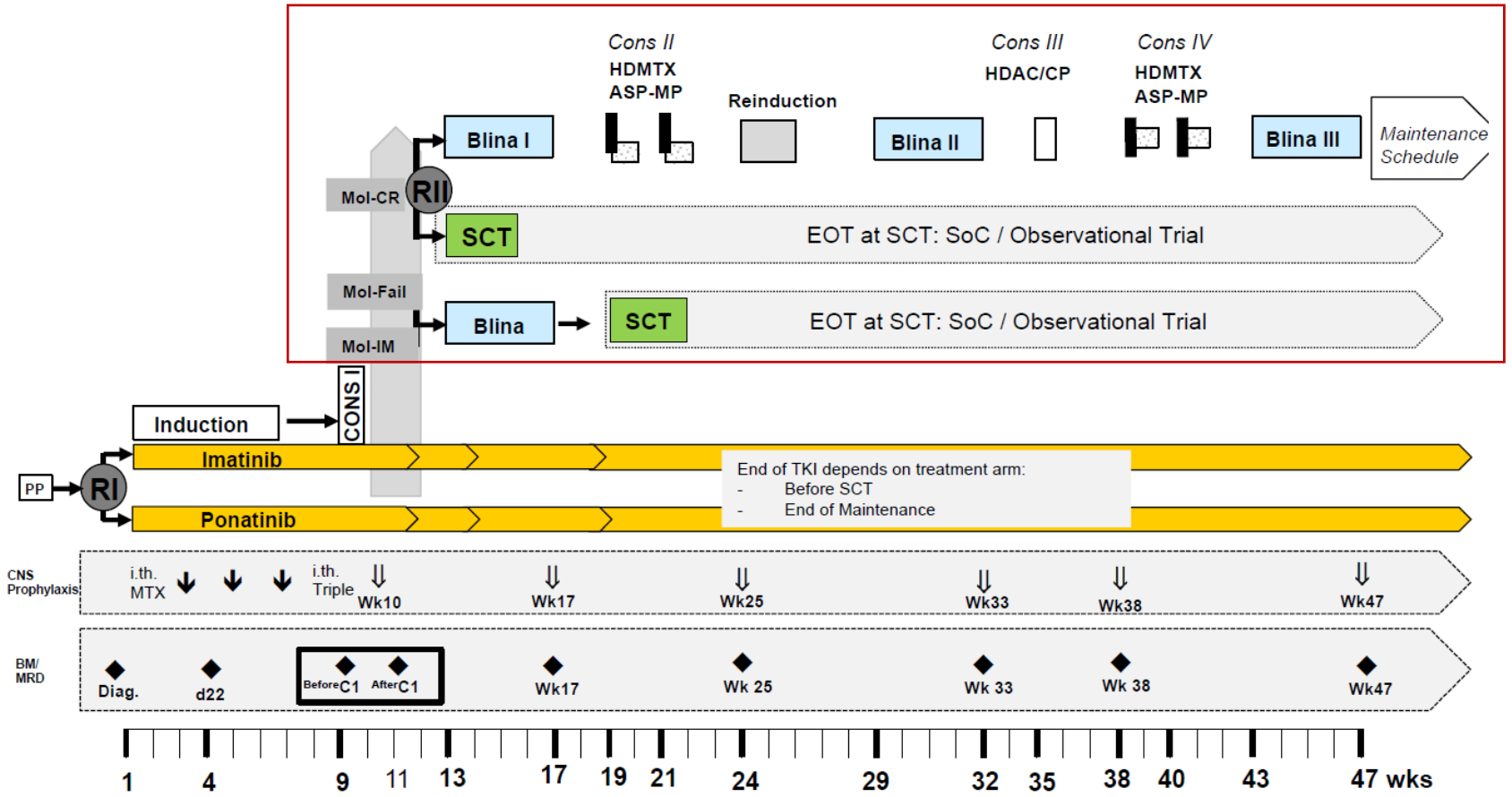
OS nach alloTx in CR1 (GMALL 08/2013)

Gökbuget et., ASH 2021



- TKI-Erhaltungstherapie (prophylaktisch)
- MRD-getriggert TKI (präemptiv)

GMALL: EVOLVE-Studie (ongoing)



Zusammenfassung

Erstlinie:

- **Risikostratifizierung**
  - initiale Parameter (Subtyp / Genetik…)
  - Verlauf / Ansprechen
- allogene HSCT in **CR1**, **MRD möglichst niedrig**
- **TBI**-Konditionierung, verwandte & unverwandte Spender
- **MRD-Monitoring** / Therapie-Steuerung **nach HSCT**
- Optimierung innerhalb GMALL-Studienprotokoll

Rezidiv:

- Standard-Konsolidierung nach Remissionsinduktion möglichst in CR2

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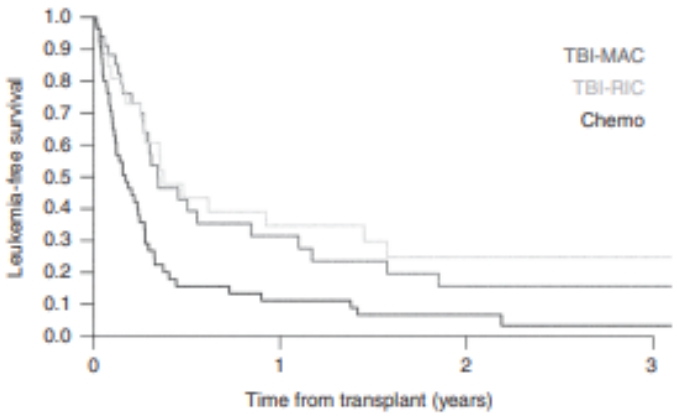
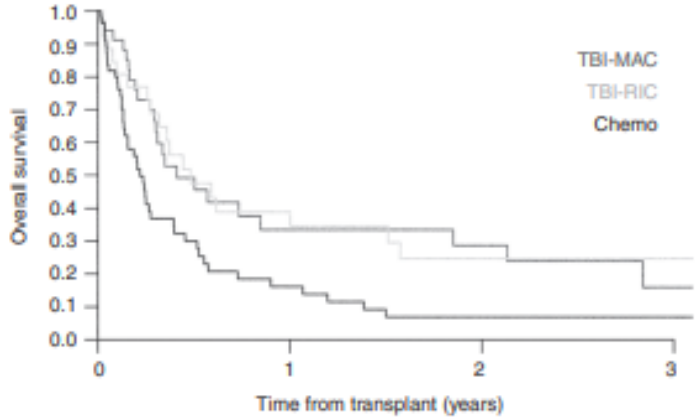
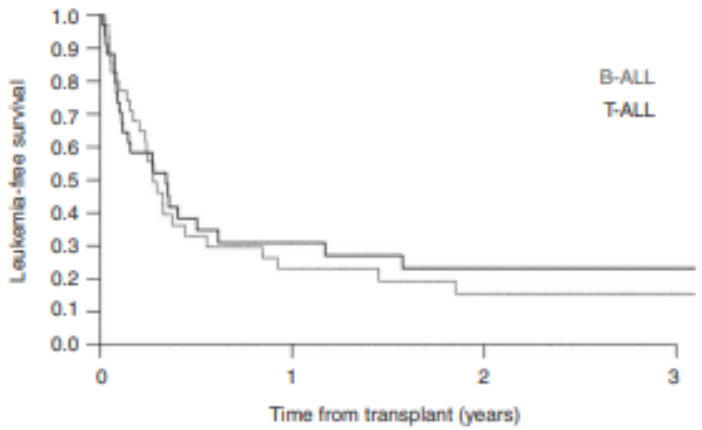
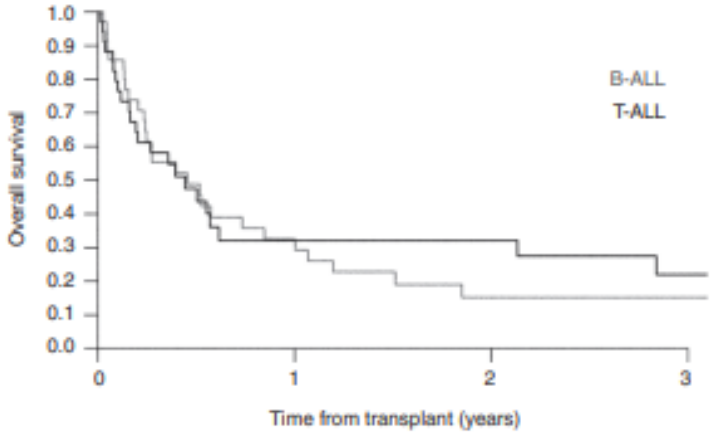
Sequentielle Konditionierung





115 Patienten, 19-66J, retrospektiv
74% relapse, 26% primary refractory
50% T-ALL, 23% Ph-pos ALL





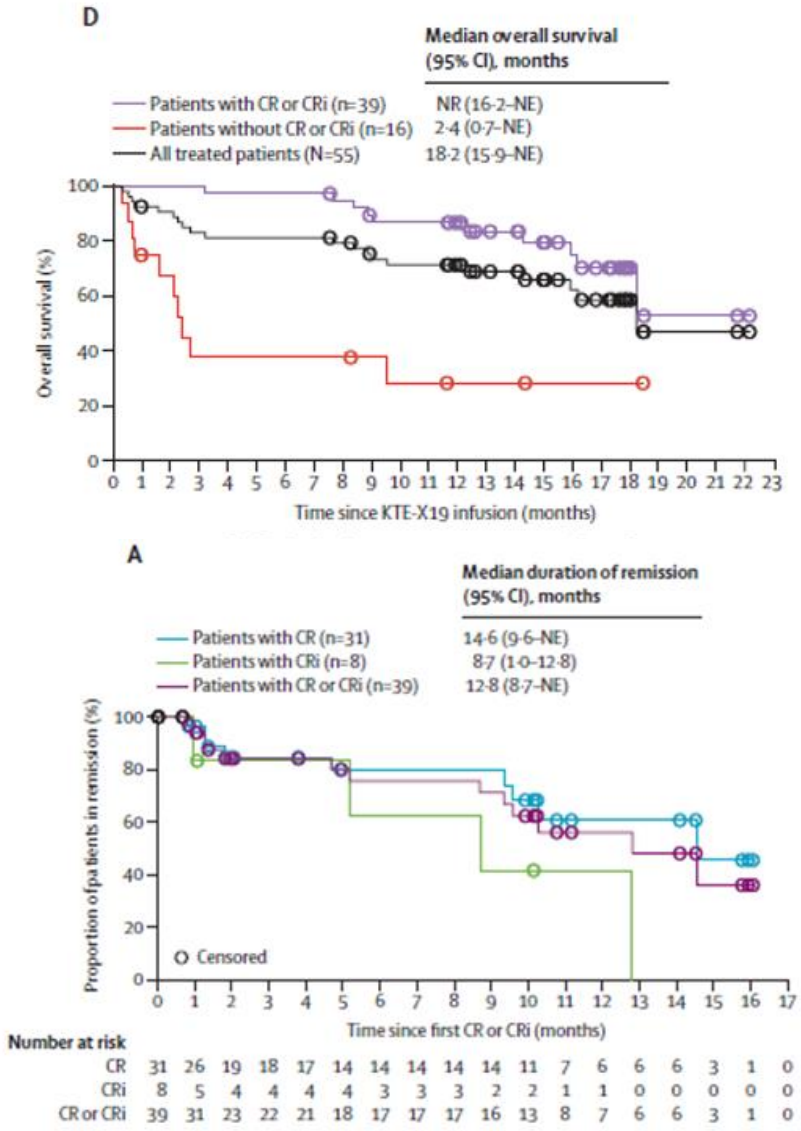
Bazarbachi et al, BMT 2020

CD19 CAR T (Tecartus)

	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.

Table 2: **Rate of overall complete remission or complete remission with incomplete haematological recovery based on central assessment**



Shah B et al, Lancet 2021