National algorithm of (cellular) therapy in ALL - children

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Cellular Therapies for pedALL in Germany

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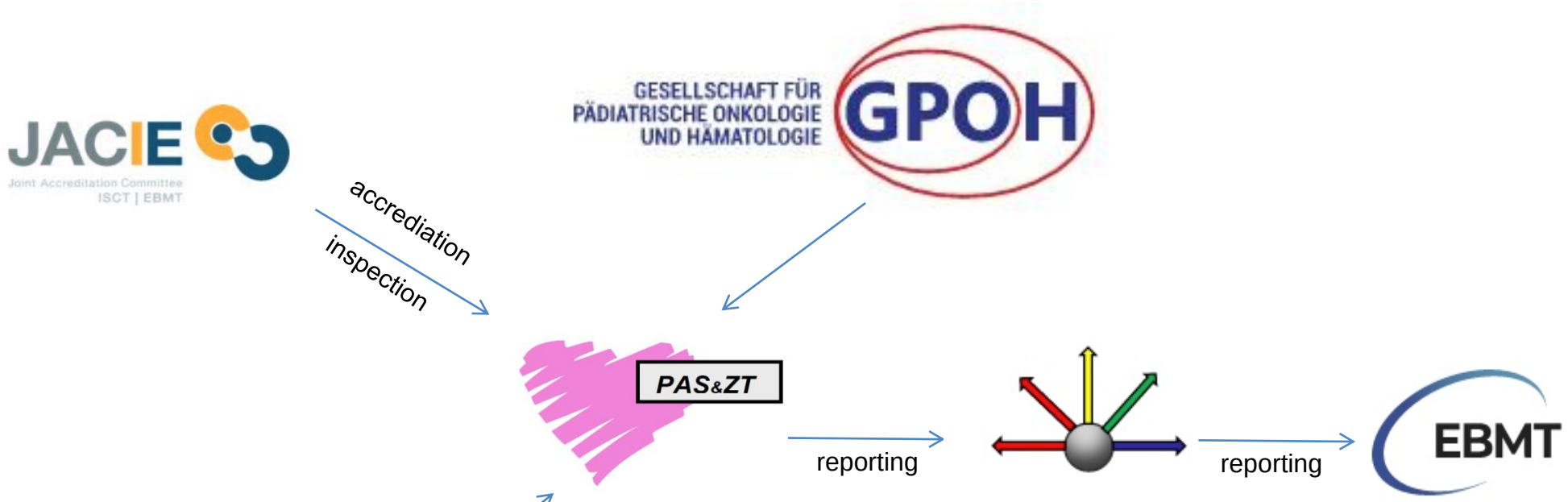
alloHCT

33 allo/auto HCT centers
(approx. 26 actively reporting)

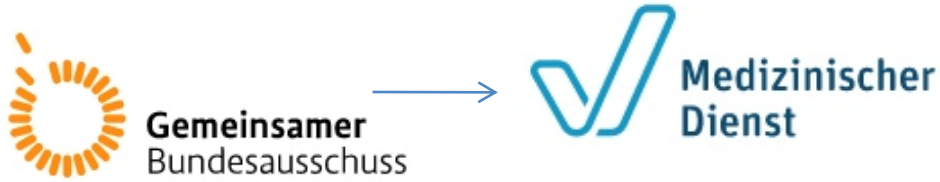
>20 procedures: 12 centers
10-20 procedures: 4 centers
1-8 procedures: 17 centers



PRST
pediatric register for
stem cell transplantation

CAR-T

12 pediatric CAR-T
centers reporting



national institution

federal institution
accreditation/inspection
case-by-case review

ALL primary treatment according AIEOP-BFM ALL 2017

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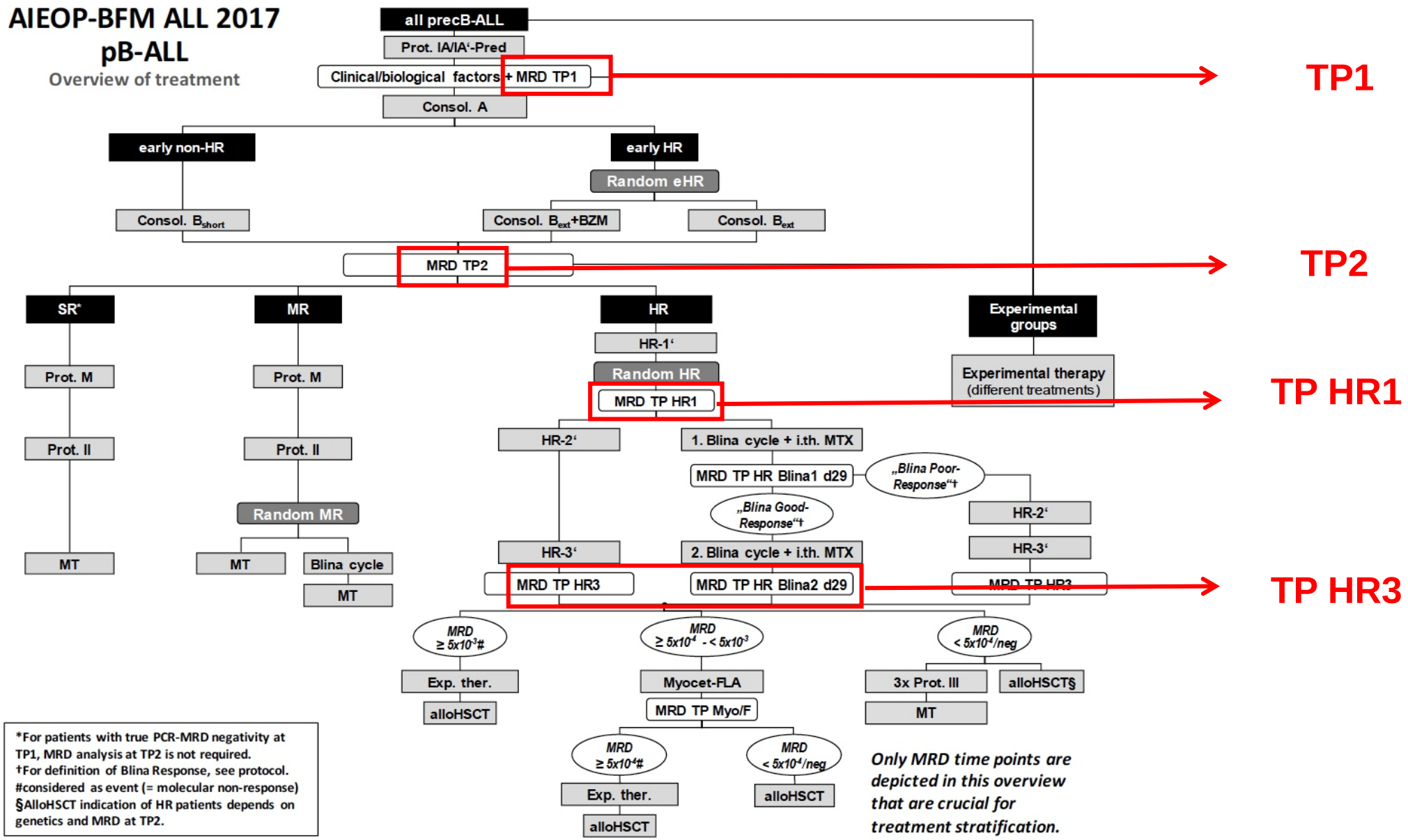

*For patients with true PCR-MRD negativity at TP1, MRD analysis at TP2 is not required.
†For definition of Blina Response, see protocol.
#considered as event (= molecular non-response)
§AlloHSCT indication of HR patients depends on genetics and MRD at TP2.

Only MRD time points are depicted in this overview that are crucial for treatment stratification.

Indications for alloHCT in pediatric ALL - front line

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AIEOP-BFM ALL 2017		PCR-MRD results				
		TP1 neg	TP1 or TP2 pos and TP2 < $5x10^{-4}$	MRD-HR: MRD TP2 ≥ $5x10^{-4}$- < $5x10^{-3}$	MRD-HR: MRD TP2 ≥ $5x10^{-3}$	no MRD result
criteria hierarchical	*TCF3-HLF*	MMD	MMD	MMD	MMD	MMD
	no CR d33	no[b]	MD[b]	MMD	MMD	MMD
	KMT2A-AFF1	no	MD	MD	MMD	MD
	hypodiploidy < 44 chr. or DNA index < 0.8[a]	no	MD	MD	MMD	MD
	IKZF1[plus] and FCM-MRD d15 ≥ 10%	no	MD	MD	MMD	MD
	IKZF1[plus] and FCM-MRD d15 < 10%	no	no[c]	MD	MMD	MD
	T-ALL + PPR a/o FCM-MRD d15 ≥ 10%	no	no[c]	MD	MMD	MD
	none of the above features	no	no[c]	MD	MMD	no

Indications for HCT:

Induction Failure

Persistent MRD
+/- Genetics

High-Risk Genetics

Indications for alloHCT in pediatric ALL - second line

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SCT Indications
ALL-REZ BFM SR/HR 2010

SCT	SR								HR
	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	-	+	+	+	+	+	-	+	+
MMD	-	+	-	-	+	+	-	-	+

trigger factors for HCT: early vs. late relapse, MRD response

Indications for alloHCT in pediatric ALL

Indications defined by AIEOP-ALL BFM 2017

induction failure
persistent MRD
± genetic risk factors

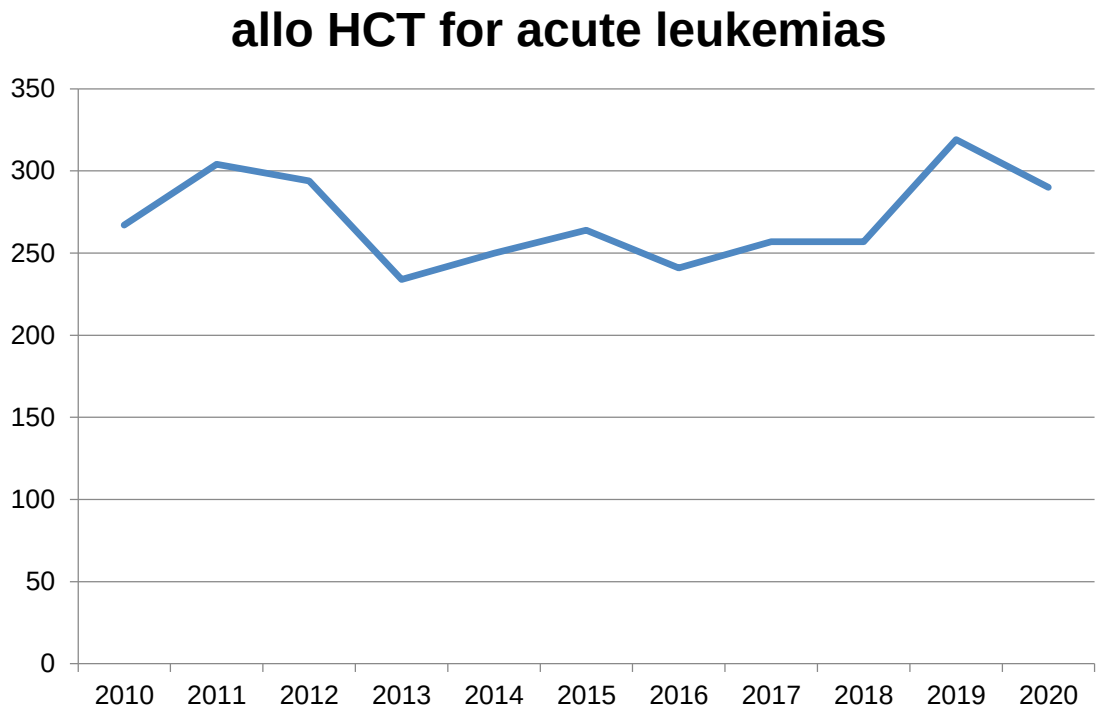
or ALL-REZ BFM 2010

early relapse
persistent MRD

Patients should be transplanted according to the

ALL-SCTped FORUM protocol

2-year OS 91% after TBI/Eto conditioning
Peters C. et al. JClinOncol 2021



source: PRST report 2020

CAR-T Cells

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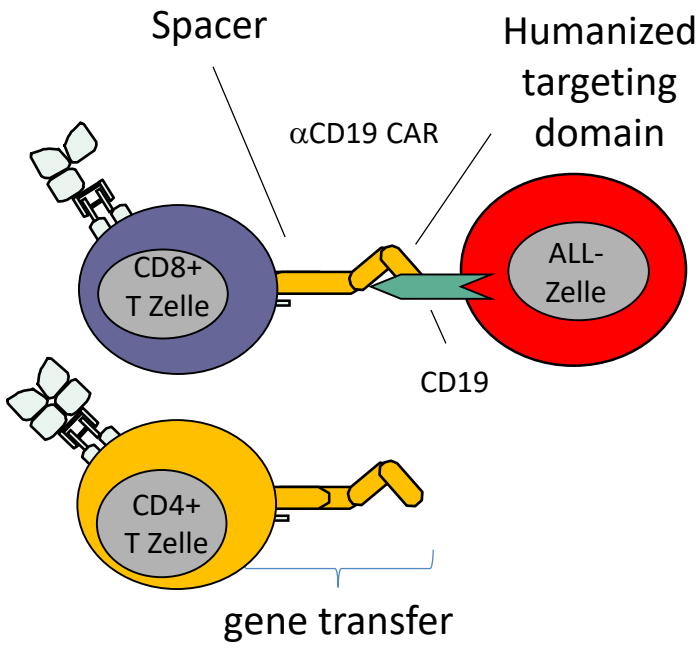
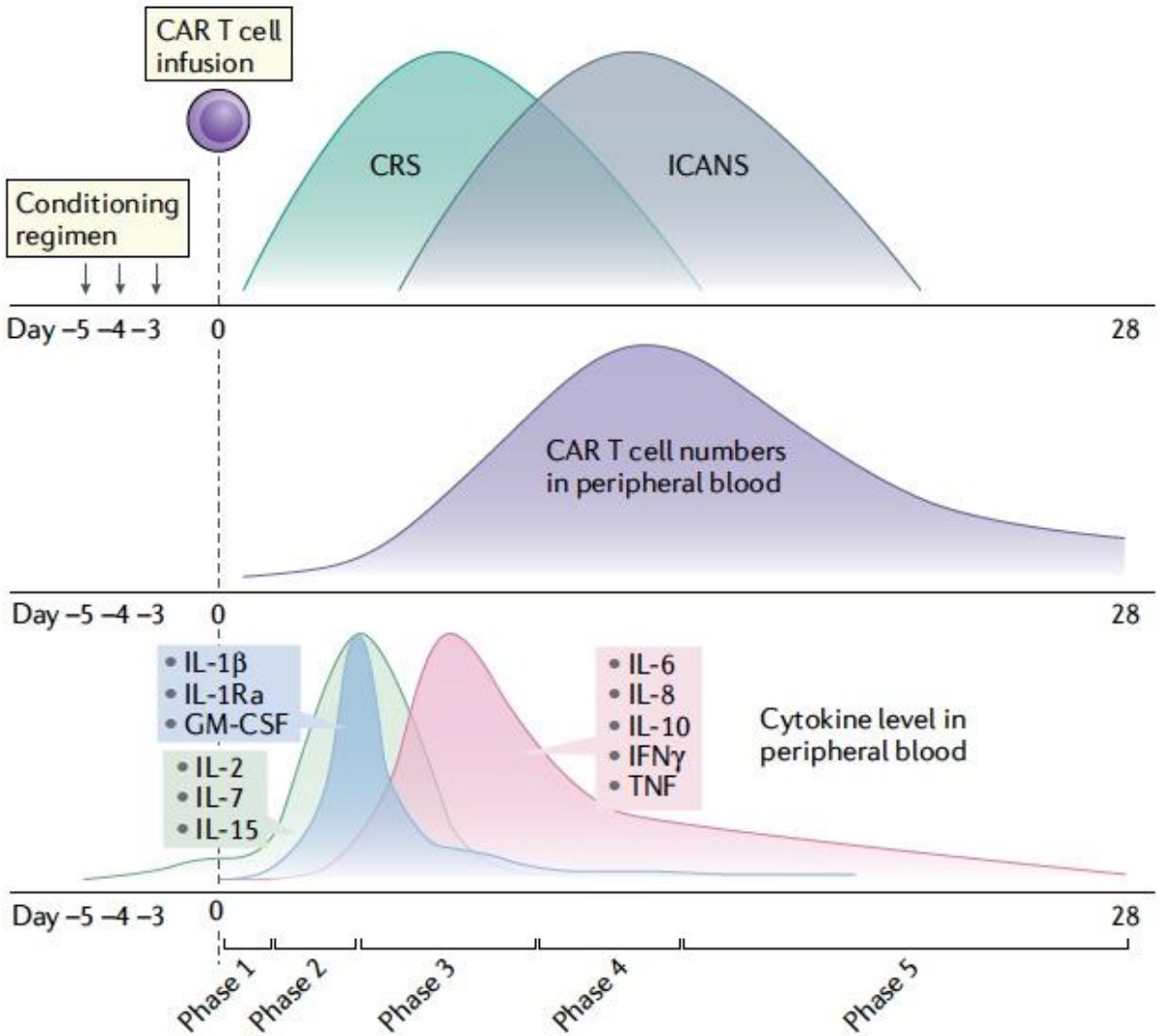
CAR T Cells



Side Effects



Indication:
relapsed/refractory B-cell ALL since 2018

Morris EC et al. Nature Rev Immunol 2021

G-BA Decision 07.03.2019

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Beschluss

Gemeinsamer Bundesausschuss

des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Tisagenlecleucel (akute lymphatische B-Zell-Leukämie)

Vom 7. März 2019

updated 04. Nov 2021 as *ATMP-QM-Guideline*
annices for Kymriah, Zolgensma

- based on ELIANA- and ENSIGN-trials
- ALL-relapse after alloHCT or second or further relapse
- children and adolescents up to 25 years

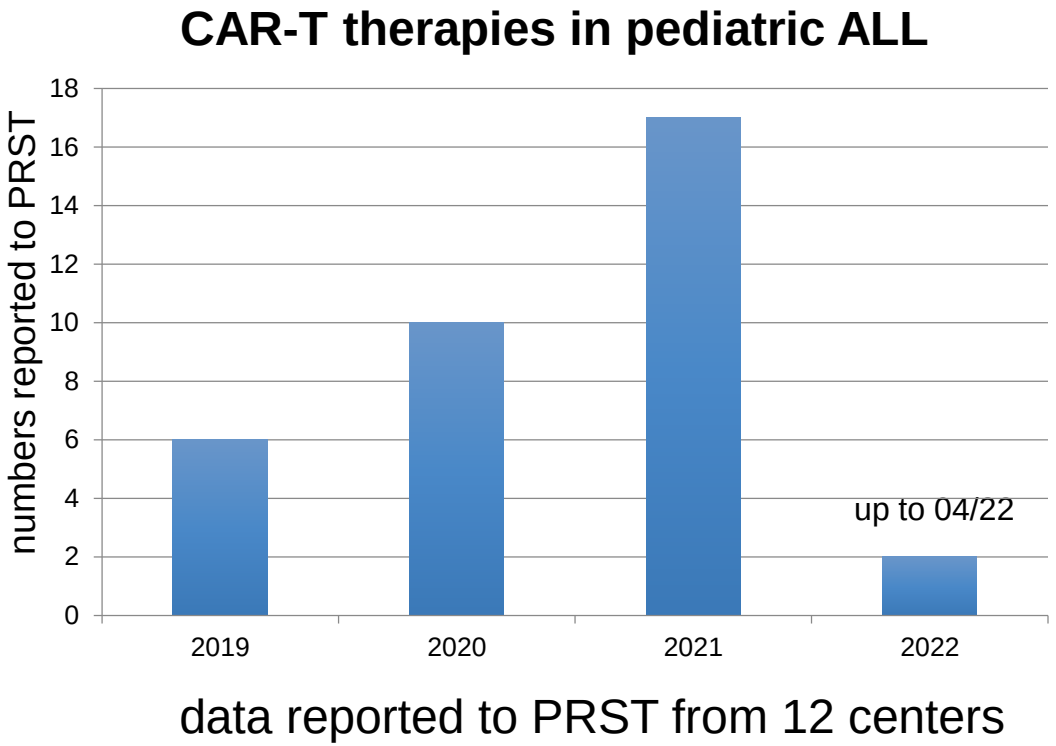
- requirements personnel
  nurses, physicians, consultation etc.
- requirements institution & organisation
  conformity with GBA, QM, SOPs
- requirements documentation
  -> PRST -> EBMT
- requirements follow-up
  appropriate outpatient setting

CAR-T in pedALL: Indications and Numbers

Case-by-case application to MDK and review

Indications:
- Relapsed or refractory B-cell ALL < 25 years
- Relapse after alloHCT or second or greater BM relapse
- 5% blasts in BM, CD19-expression (confirmed by reference)
- CSF without blasts
- No HBC, HCV, HIV infection
- Karnofsky >50%

Exclusion critieria:
- Isolated extramedullary disease
- Active testicular/CNS only relapse
- Active GvHD or on immunosuppression



data reported to PRST from 12 centers

CAR-T in pedALL: Fuzzy Edges

- CAR-T before alloHCT?
  - MRD between $5x10^{-3}$ and10^{-4}
  - any MRD in combination with HR genetics (e.g. TP53)
  - positive MRD after end of consolidation (EoC)

Pediatric CAR-T trials:

- Miltenyi CAR19.1 (Münster, Tübingen, Erlangen, Würzburg, München, Berlin)
  - decentralised academic CAR-T production (Erlangen, Tübingen)

- TRANSCEND PEDALL (BMS, Frankfurt)
  - including patients with first relapse and MRD $\geq$ 0.01% after reinduction

- CASSIOPEIA (Novartis, Frankfurt, München)
  - CAR-T in primary treatment with MRD $\geq$ 0.01% after EoC

Merci beaucoup!

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EIN HERZ FÜR KINDER

TOUR DER HOFFNUNG

TRANSCAN

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Deutsche Kinderkrebsstiftung

Bristol Myers Squibb

CellSOURCE

ALL (cellular) immuntherapies – mode of action

allogeneic
stem cell transplantation

allogeneic donor-T-cells

target: minor/major histocompatibility antigens

indications: ALL, AML, NHL

in

remission

Chimeric Antigen Receptor
(CAR-) T cells

autologous/allogeneic T cells

target: defined, singular surface antigens (e.g. CD19)

indications: ALL, DLBCL, MM

elapsed/refractory

local / systemic
immunosuppression ⊣

anti-leukemic
CTL response

⊣ antigen loss

immune checkpoint inhibitors
RNA vaccines

CAR-T in pädiatrischer ALL

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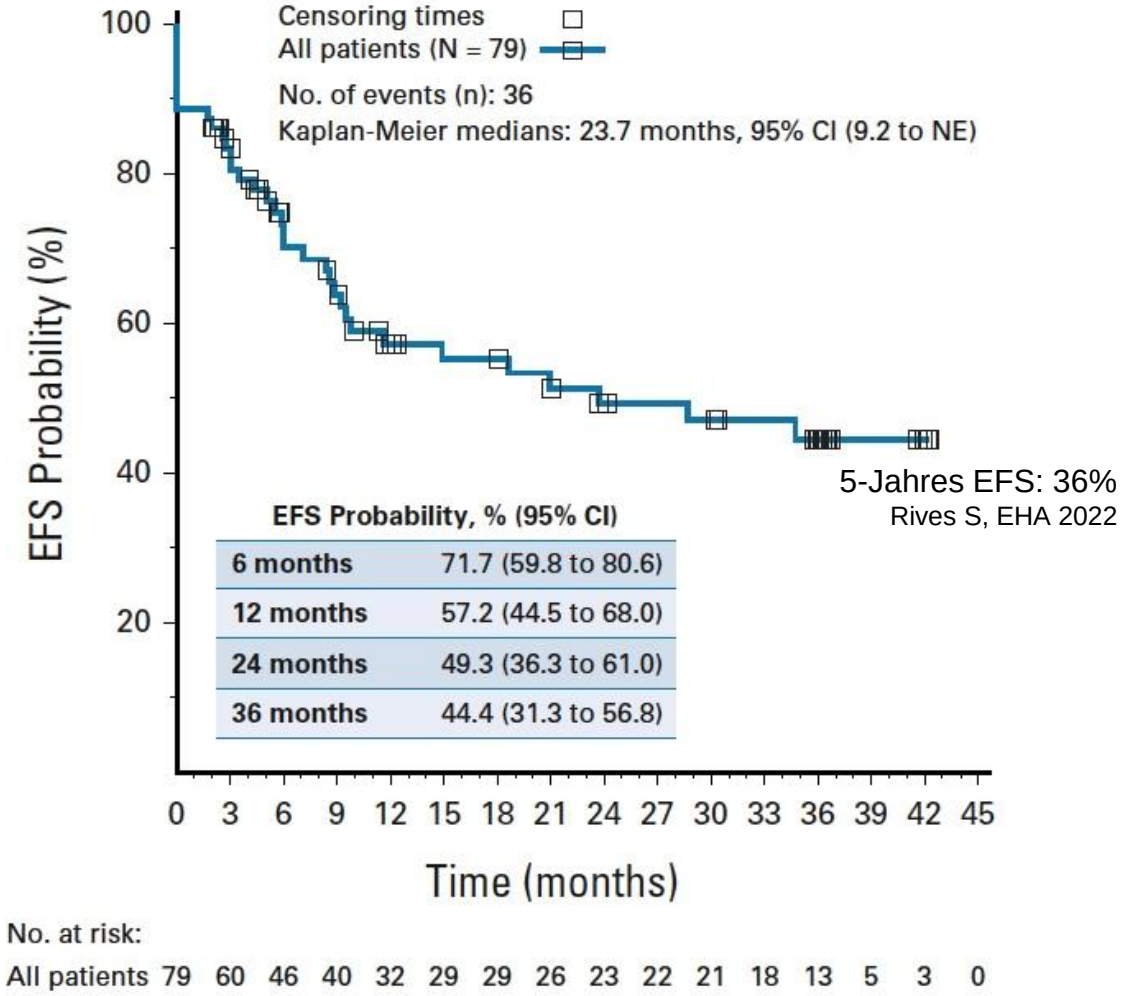
Remissionsraten nach drei Monaten: 82%



5-Jahres EFS: 36%
Rives S, EHA 2022

Three-Year Update of Tisagenlecleucel in the ELIANA Trial
Laetsch T et al. JCO 2022

positive Faktoren:

- niedrige Krankheitslast
  Talleur AC et al. Blood Adv 2022
- höhere T-Zelldosis
  Stefanski H et al. Blood Adv 2023
- mehr Fludarabine in der Zwischentherapie
  Fabrizio V et al. Blood Adv 2022

negative Faktoren:

- früher MRD-Anstieg nach 1-3 Monaten
- früher B-Zellanstieg nach 3-6 Monaten