Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2024 San Diego

Zelluläre Therapie und Stammzelltransplantation

Prof. Dr. med. Wolfgang Bethge

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Themen

Stammzelltransplantation:
#505: Nagler: MRD, MUD oder Haplo für AML Allo
#507: Vanegas: Conditioning for T-cell lymphoma
#507: Risitano: Role of Age in Allo for SAA

Zelluläre Therapie:
#94: Wald: Ultrafast CAR-T cell production Phase I UF-Kure19
#920: Gonzalez: Memory CAR-T cell therapy for Hodgkin Lymphoma
#512: Locatelli: Exa-cel Gentherapy for Thalassemia and Sickle Cell Anemia
#679: Combined CD19/CD22 allogeneic CAR-T cells and allogeneic HCT
#684: Müller: CD19 CAR-T cells for autoimmune disease

Oral #505: Nagler: MRD, MUD oder Haplo für AML Allo

EBMT European Society for Blood and Marrow Transplantation

SHEBA Tel HaShomer | Cancer Center

IACH

Non-T-depleted Haploidentical transplantation compared to Allogeneic Transplantation from matched siblings or unrelated donors in patients with secondary AML in first complete remission: A Study from the ALWP/EBMT

Arnon Nagler, Allain Thibeault Ferhat, Nicolaus Kröger, Matthias Eder, Gérard Socié, Didier Blaise, Thomas Schroeder, Hélène Labussière-Wallet, Johan Maertens , Alessandro Busca, Edouard Forcade, Tobias Gedde-Dahl, Alessandro Rambaldi, Claude Eric Bulabois, Ali Bazarbachi, Bipin Savani, Fabio Ciceri, Mohamad Mohty

Oral #505: Nagler: MRD, MUD oder Haplo für AML Allo

HaploSCT compared to HSCT from MSD or 9-10/10 MUD for sAML

Aim

To compare outcomes of HaploSCT to those of HSCT from MSD or MUD (9-10/10) in patients with sAML in the first complete remission (CR1)

Materials and Methods

A retrospective cohort study of patients reported to the EBMT database

Selection criteria

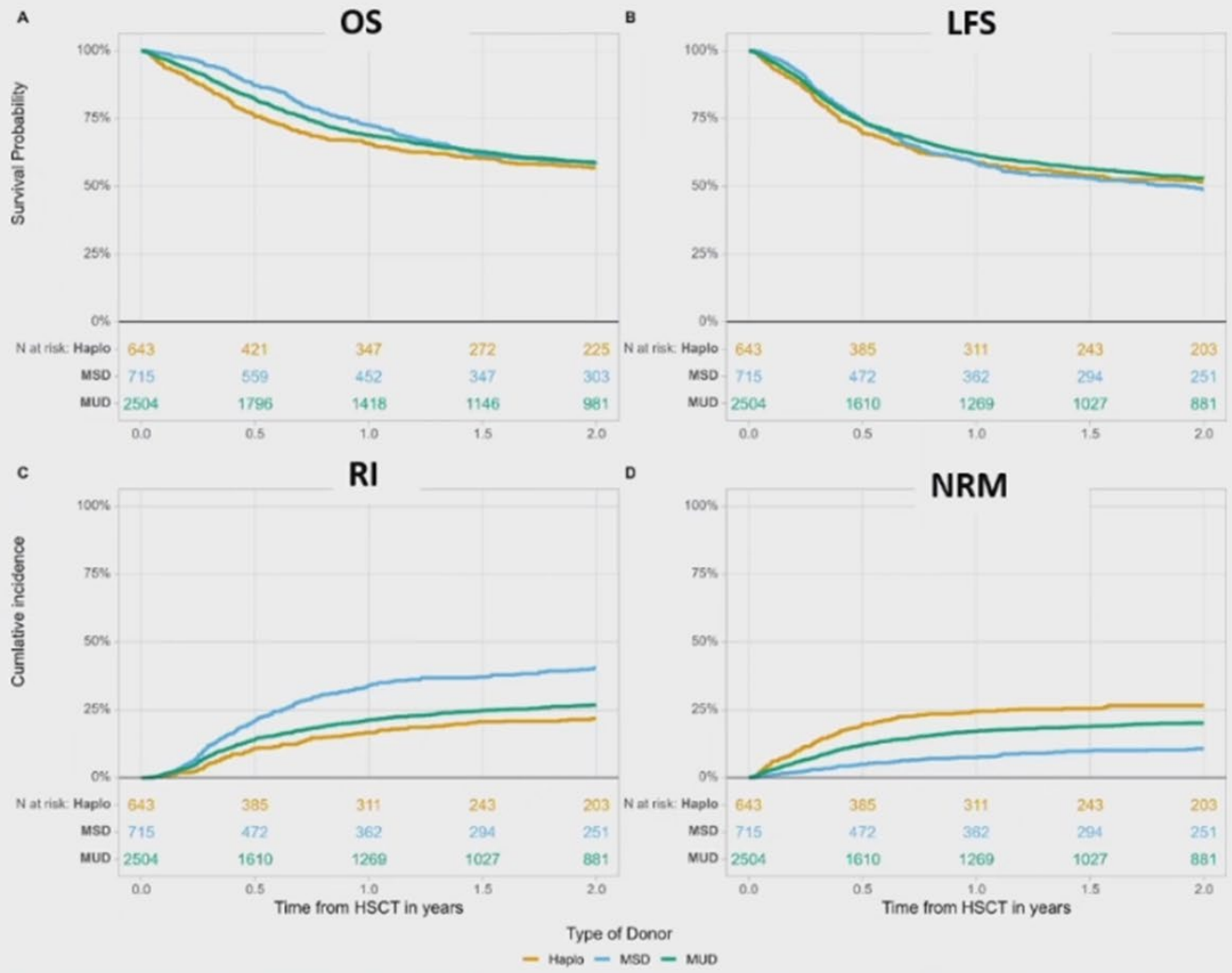
- Adult patients (≥18 years)
- sAML
- Disease status: CR1
- First non-T-cell depleted HaploSCT; HSCT from MSD or 9-10/10 MUD
- Conditioning: MAC or RIC
- Graft: BM or PB
- Transplant year: 2010 - 2022

Patient and transplant characteristics - I

Variable	Overall	Haplo	MSD	MUD	p-value
	N = 3862	N = 643	N = 715	N = 2504	
Year of transplantation, Median	2017 (2014-2020)	2019 (2016-2021)	2017 (2014-2019)	2017 (2014-2020)	<0.001
Median FU (y)	3.3 (3.1 - 3.5)	2.6 (2.3 - 3)	4 (3.4 - 4.7)	3.3 (3.1 - 3.7)	
Age of the Patient at HSCT (years), Median	60.5 (53.0-65.8)	61 (52.8-66.8)	58.9 (51.8-64.0)	60.9 (53.4-66.1)	<0.001
Age of the Donor at HCT (years)Median	33.5(25.9, 46.1)	36(28.2, 45.0)	56.8(48.9, 61.6)	29.2(24.1, 36.5)	<0.001
Cytogenetic AML classification					0.066
Favorable	35 (1.2%)	5 (1.0%)	12 (2.3%)	18 (1.0%)	
Intermediate	1821 (64%)	318 (62%)	323 (62%)	1180 (65%)	
Adverse	995 (35%)	192 (37%)	190 (36%)	613 (34%)	
Missing	1011	128	190	693	
Previous diagnosis					
MDS/MPN	1872 (48%)	354 (55%)	342 (48%)	1176 (47%)	
MPN	266 (6.9%)	43 (6.7%)	57 (8.0%)	166 (6.6%)	
Hematological Malignancies	126(3.3%)	18(2.9%)	25(3.4%)	83(3.3%)	
Solid tumour	292(7.7%)	39(6.1)	64(9%)	189(7.6%)	
Non malignant disease	16 (0.4%)	1 (0.2%)	3 (0.4%)	12 (0.5%)	
Type of donors					<0.001
Haplo	643 (17%)	643 (100%)	0 (0%)	0 (0%)	
MSD	715 (19%)	0 (0%)	715 (100%)	0 (0%)	
UD 10/10	2012 (52%)	0 (0%)	0 (0%)	2012 (80%)	
UD 9/10	492 (13%)	0 (0%)	0 (0%)	492 (20%)	
Karnofsky score					0.92
>= 90	2630 (72%)	442 (71%)	484 (71%)	1704 (72%)	
< 90	1045 (28%)	181 (29%)	193 (29%)	671 (28%)	
Missing	187	20	38	129	

Oral #505: Nagler: MRD, MUD oder Haplo für AML Allo

Transplantation Outcomes: OS; LFS; RI; NRM



	Haplo (reference MSD)		Haplo (reference MUD)	
	HR (95% CI)	p value	HR (95% CI)	p value
RI	1.64 (1.24-2.17)	0	1.14 (0.88-1.49)	0.328
NRM	0.32 (0.22-0.46)	0	0.63 (0.47-0.85)	0.002
LFS	0.88 (0.71-1.09)	0.238	0.86 (0.71-1.04)	0.126
OS	0.76 (0.6-0.95)	0.018	0.82 (0.66-1.01)	0.061
GRFS	0.84 (0.69-1.02)	0.084	0.87 (0.73-1.04)	0.124

Oral #505: Nagler: MRD, MUD oder Haplo für AML Allo

HaploSCT compared to HSCT from MSD or 9-10/10 MUD for sAML: Conclusions

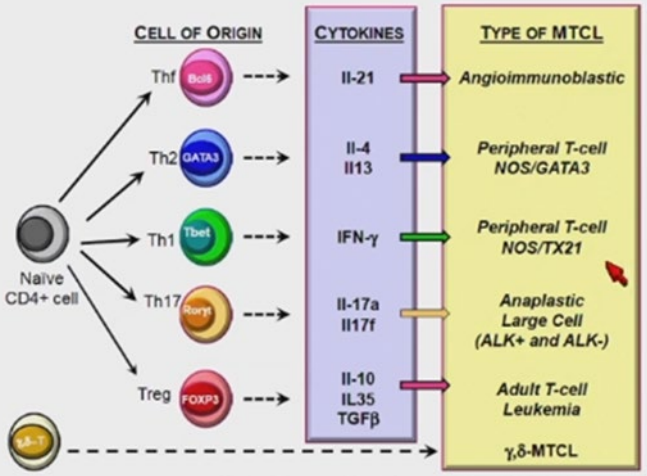
- In this registry-based retrospective analysis of HSCT for sAML in CR1 comparing various donor types, best transplantation outcomes were observed with HSCT from MSDs
- In the absence of MSD both Haplo and MUD are potential alternatives
- Incidence of NRM was higher in HaploSCT compared to HSCT from MSDs and MUDs
- Notably, HaploSCT was able to rescue ~60% of the pts with this devastating leukemia
- Study limitations include the risk of selection bias and the possibility of unavailable data that could not have been considered, such as frontline therapies as well as molecular and measurable residual disease
- Future studies in HSCT for sAML should be aimed at reducing both transplant-related toxicity and relapse rate
- Vyxeos as well as other novel targeted compounds will hopefully improve the outcome of transplant in sAML

Oral #507: Vanegas: Conditioning for T-cell lymphoma

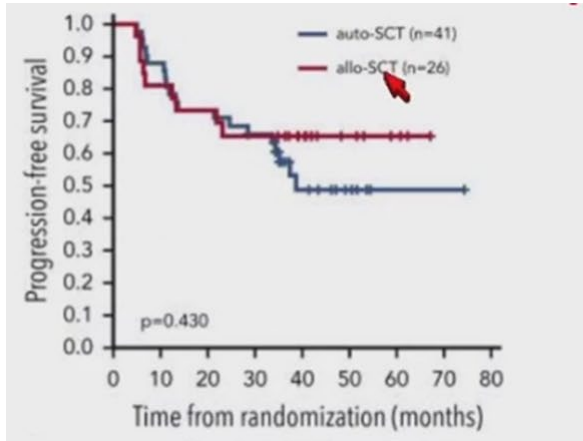
Oral #507: Vanegas: Conditioning for T-cell lymphoma

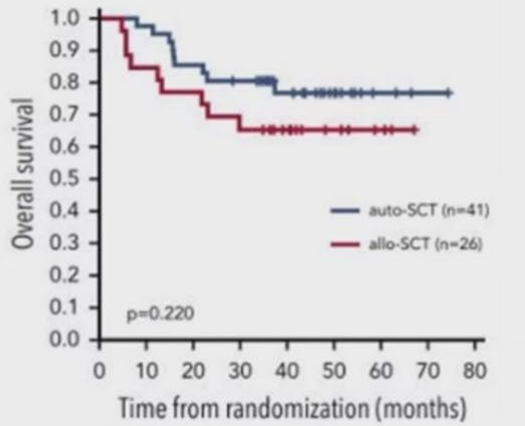
Background

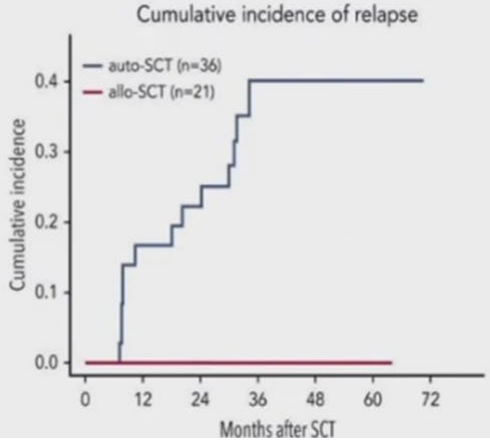
- Mature T-cell lymphomas (MTLs) are a group of rare aggressive lymphoid malignancies accounting for 10-15% of all cases of NHLs
- They arise from mature post-thymic lymphocytes. Due to the heterogeneity and diagnostic complexity research focusing on treatment is limited.
- First line of therapy →CHOP based regimens with consideration for consolidation with autologous stem cell transplant in chemo sensitive cases.

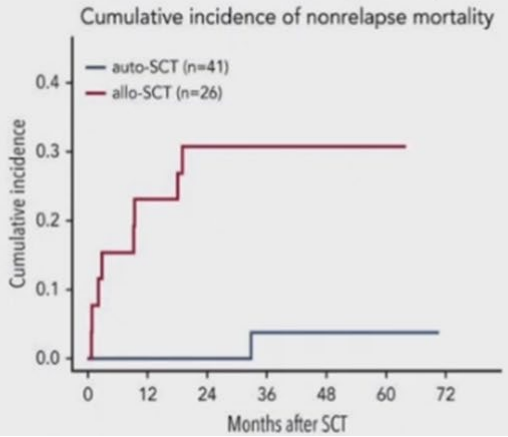


Marchi E et al. (2020) Cancer J Clin 2020;70:47–70









- None of the responding patients that received allo-HCT relapsed, but 31% died of transplant related toxicities.
- 36% of patients that received auto-HCT relapsed, and none died of transplant related toxicities.

Schmitz el al 2021. Blood. 2021 May 13;137(19):2646–2656.

Oral #507: Vanegas: Conditioning for T-cell lymphoma

sease characteristics

Characteristics	Overall (N=75)
Primary Diagnosis:	
• PTCL NOS (%)	42 (56%)
• AITL (%)	13 (17.3%)
• ALCL (%)	2 (2.7%)
• ALCL ALK- (%)	3 (4%)
• ALCL ALK+ (%)	4 (5.3%)
• Extranodal NK/T (%)	4 (5.3%)
• Gamma delta T cell lymphoma (%)	2 (2.7%)
• Hepatosplenic (%)	3 (4.0%)
• Panniculitis-like	2 (2.7%)
Stage:	
• I and II	17 (23.9%)
• III and IV	53 (74.6%)
Prior Auto-HCT	26 (35%)
Median number of lines prior to transplant (Range)	3 (1-8)

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PTCL- NOS- Peripheral T cell lymphoma not otherwise specified; AITL – Angioimmunobla
lymphoma; ALCL – anaplastic large cell lymphoma; auto-HCT – autologous stem cell trans

Transplant characteristics

Characteristics	Overall (N=75)
Disease status prior to transplant	
• CR	45 (63.4%)
• PR	26 (36.6%)
Donor	
• MUD	34 (45%)
• MRD	24 (32%)
• Haplo	8 (10.7%)
• Other	9 (11.9%)
Cell source	
• PB	72 (96%)
• BM	1 (1.3%)
• CBT	1 (1.3%)
Conditioning Regimen	
• MAC	22 (29.3%)
• RIC/NMA	53 (70.7%)
TBI containing conditioning regimen	20 (26.7%)
• MAC TBI	12 (60%)
• RIC TBI	8 (40%)
• Median TBI dose (cGy)	1200
PTCy based GVHD prophylaxis	10 (13%)

Oral #507: Vanegas: Conditioning for T-cell lymphoma

Outcomes- PFS

	Univariate Analysis 3-year PFS (CI95%)	P value	Multivariate Analysis HR (95%CI)	P value
All	64.2% (53.5%, 77.0%)	-		
PTCy based GVHD prophylaxis • Yes • No	88.9% (70.6%, 100.0%) 60.0% (48.3%, 74.5%)	0.11		
Disease status prior to transplant: • CR • PR	67.17% (53.8%, 83.8%) 57.29% (40.2%, 81.6%)	0.18		
Regimen intensity: • MAC • RIC/NMA	38.1% (22.1%, 65.7%) 75.3% (63.4%, 89.4%)	<0.001	3.36 (1.37, 8.22)	0.00803
TBI: • Yes • No	44.9% (26.9%, 74.93%) 70.4% (58.3%, 85.05%)	0.017	1.51 (0.61, 3.71)	0.37302
MAC TBI: • Yes • No	18% (5%, 64%) 86% (63%, 100%)	0.007		

Conclusions

- Allo-HCT remains a curative option in patients with MTLs and can overcome the poor prognosis associated with R/R disease
- In our cohort, MAC conditioning regimens were associated with worse PFS, OS and NRM
- Moreover, TBI containing conditioning regimens were associated with worse PFS and NRM
- MAC TBI was associated with worse OS, PFS and NRM in the univariate analysis only
- Larger cohorts focusing on the use of TBI are needed to determine its effect on allo-HCT outcomes in patients with MTL.

Not included in the MVA due to small n

PFS- progression free survival; MVA- multivariate analysis; HR- hazard ratio

Oral #507: Risitano: Role of Age in Allo for SAA

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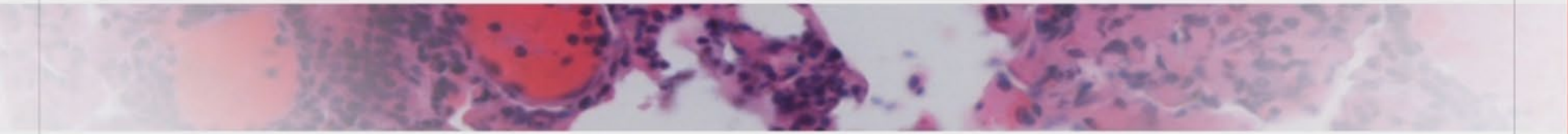

Role of age and donor type in 3646 severe aplastic anemia patients undergoing hematopoietic stem cell transplantation in 2011-2020: a retrospective EBMT-SAAWP Study

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EBMT

On behalf of **the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation**

Oral #507: Risitano: Role of Age in Allo for SAA

EBMT

Introduction

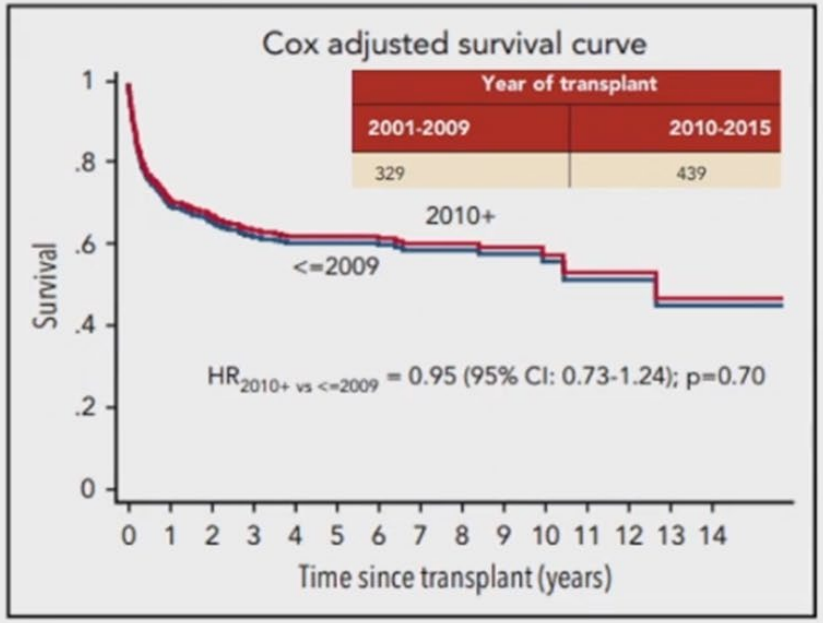
- Allogeneic HSCT is a key treatment SAA, either as 1st or 2nd line therapy
- In current treatment algorithm, 40 yo is the age limit to offer HSCT as first line therapy (if a sibling donor is available)
- Outcome of HSCT in AA patients >40 yo is dismal
- In patients >40yo, no improvement in the outcome of HSCT was observed even in most recent years

TO THE EDITOR:

Transplant outcome for patients with acquired aplastic anemia over the age of 40: has the outcome improved?

Sabrina Giammarco,[1] Régis Peffault de Latour,[2] Simona Sica,[1] Carlo Dufour,[3] Gerard Socie,[2] Jakob Passweg,[4] Nicolaus Kröger,[5] Eefke Petersen,[6] Maria Teresa Van Lint,[7] Rosi Oneto,[1] Alessio Signori,[8] and Andrea Bacigalupo,[1] for the European Group for Blood and Marrow Transplantation Severe Aplastic Anemia Working Party

blood® 26 APRIL 2018 | VOLUME 131, NUMBER 17 1989



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Oral #507: Risitano: Role of Age in Allo for SAA

EBMT

Results

Transplant period - univariable

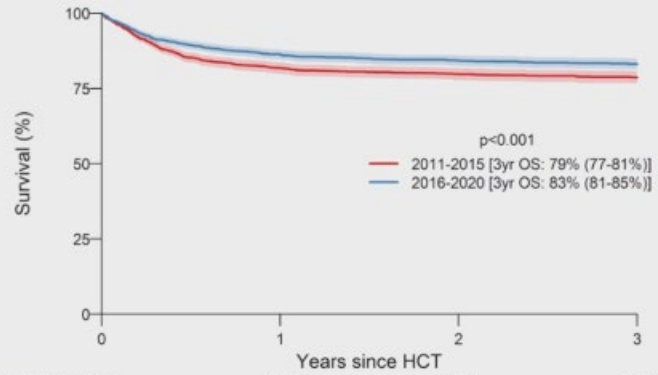
Overall survival by year of HSCT

	Group	Total
		Missing N (%)
total		3646 (100%)
Year of this treatment	2011-2015	1789 (49.1%)
	2016-2020	1857 (50.9%)

		OS (95% CI)		
Group	N	1y	3y	p
2011-2015	1789	82% (80-84%)	79% (77-81%)	<0.001
2016-2020	1857	86% (85-88%)	83% (81-85%)	

Continuous effect of age (univariable)

	n	d	HR (95% CI)	p
Age at this treatment (decades)	3646	628	1.29 (1.24-1.35)	<0.001



2011-2015: 1789	1197	1009	907
2016-2020: 1857	1292	961	666

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EBMT

Results

Age and overall survival - univariable

Overall survival by age

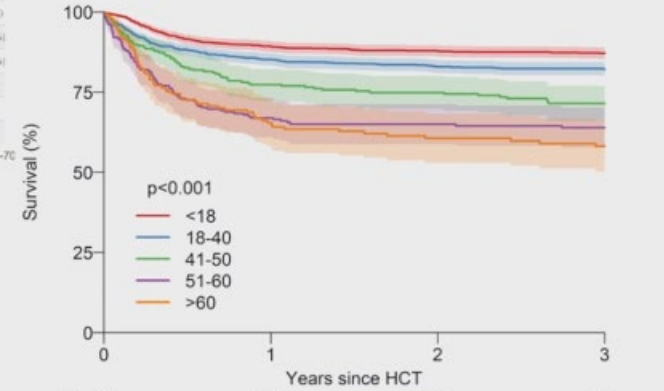
	Group	Total
		Missing N (%)
total		3646 (100%)
Age at this treatment	<18	1492 (40.9%)
	18-40	1456 (39.9%)
	41-50	287 (7.9%)
	51-60	242 (6.6%)
	>60	169 (4.6%)

- As there are only 23 cases in the category 71-80, these have been merged with the category 61-70

		OS (95% CI)		
Group	N	1y	3y	p
<18	1492	89% (88-91%)	87% (85-89%)	<0.001
18-40	1456	85% (83-87%)	82% (80-84%)	
41-50	287	77% (72-82%)	72% (66-77%)	
51-60	242	67% (61-73%)	64% (58-70%)	
>60	169	65% (58-73%)	58% (50-66%)	

Continuous effect of age (univariable)

	n	d	HR (95% CI)	p
Age at this treatment (decades)	3646	628	1.29 (1.24-1.35)	<0.001



<18: 1492	1056	831	667
18-40: 1456	992	772	611
41-50: 287	200	165	137
51-60: 242	141	123	95
>60: 169	100	79	63

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Oral #507: Risitano: Role of Age in Allo for SAA

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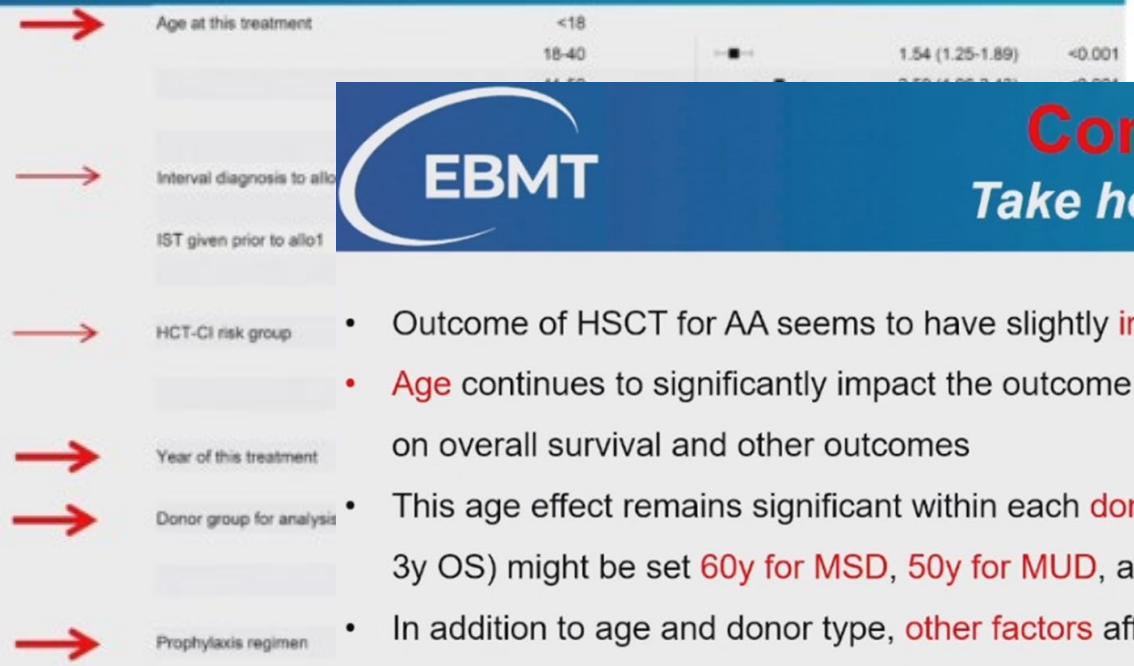
Results

Age and overall survival - multivariable

Multivariable analysis for overall survival



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Conclusions

Take home messages

- Outcome of HSCT for AA seems to have slightly improved over the past decade
- Age continues to significantly impact the outcome of HSCT for AA, with meaningful differences on overall survival and other outcomes
- This age effect remains significant within each donor type; age cut-offs for a “safe” HSCT (>70% 3y OS) might be set 60y for MSD, 50y for MUD, and no more than 40y for MMUD and Haplo
- In addition to age and donor type, other factors affecting HSCT outcome for AA patients include: year of treatment, interval from diagnosis, HCT-CI, previous IST and GVHD prophylaxis (but not stem cell source or conditioning regimen)
- Knowing that 2y OS with IST (triple therapy) is >90%, these data should inform treatment decisions (especially for 1st line HSCT)

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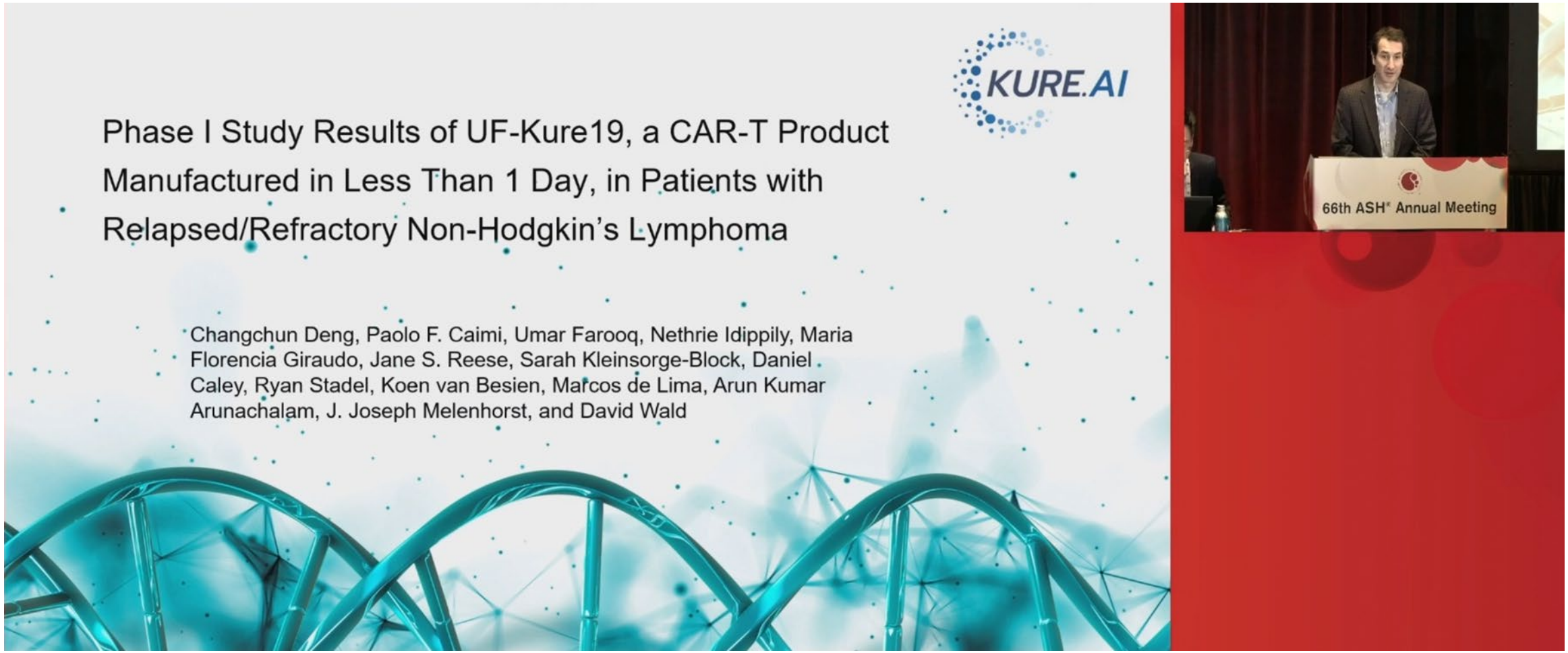
Oral #94: Wald: Ultrafast CAR-T cell production Phase I UF-Kure19



Oral #94: Wald: Ultrafast CAR-T cell production Phase I UF-Kure19

Advantages of CAR-T products enriched for naïve/stem T cells

- Kure.ai Ultra-fast **preserves**

T stemness

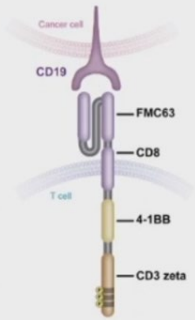
Traditic

Ultra-fast CAR manufacturing workflow

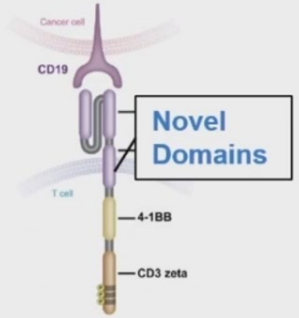
UF-Kure19 cells exhibit marked enhancement of in vivo CAR-T proliferation

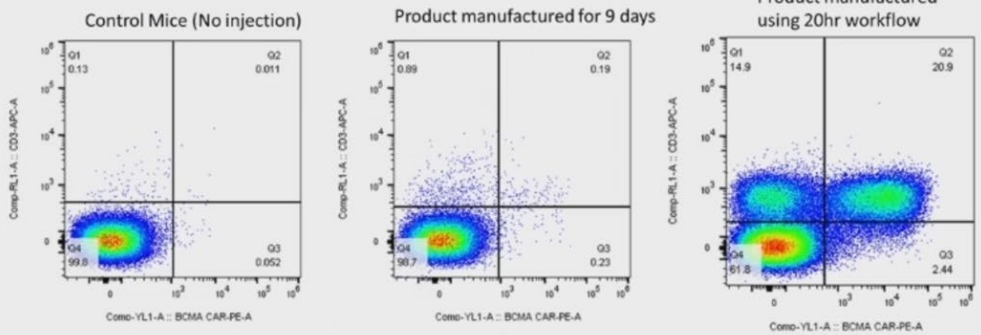
Novel CAR Design

Traditional CAR

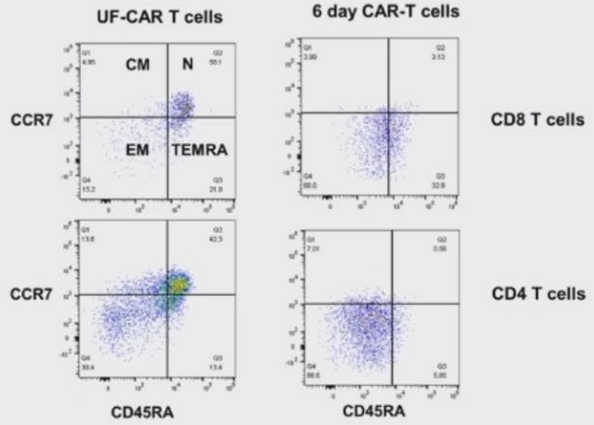


UF-KURE19 CAR





UF CAR-T cells exhibit >100 fold increased proliferation in mouse tumor models



UF-CAR T cells are primarily naïve T cells

Oral #94: Wald: Ultrafast CAR-T cell production Phase I UF-Kure19

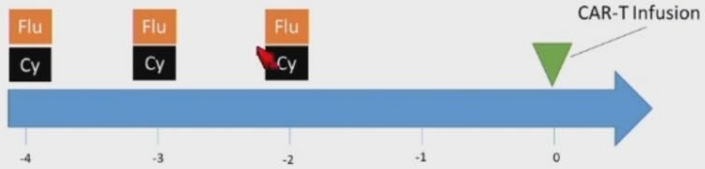
UF-Kure19 Phase 1 Clinical Trial

UF-KURE19 Clinical Study

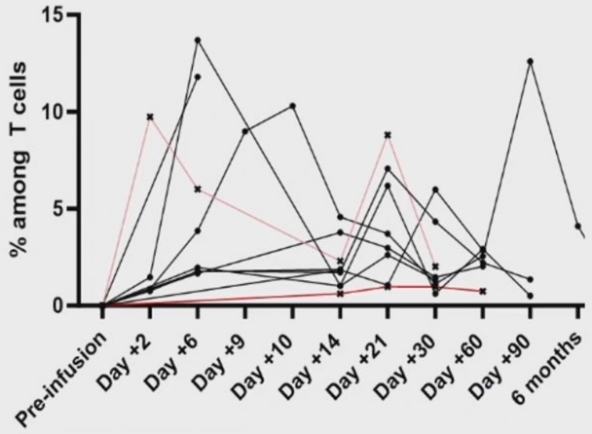
- High CR rate and low and rapidly reversible side effects
- All CRS and Neurotoxicities resolved to grade 1 or less within 1 day

Diagnosis	Age	Sex	Best Response	Cytokine Release Syndrome	Time to resolution to Gr1 or less (days)	Neurotox	Time to resolution of Neurotox (days)
Mantle Cell Lymphoma	74	M	CR	None		Gr3	1
Follicular lymphoma	72	M	CR	None		None	
Plasmablastic Lymphoma	65	M	SD	Gr1		None	
Follicular Lymphoma	50	M	CR	None		None	
Diffuse Large B-cell Lymphoma	83	M	CR	Gr2	1		
Follicular Lymphoma	75	F	CR	None			
Diffuse Large B-cell Lymphoma	45	F	SD	None			
Mantle Cell Lymphoma	64	M	CR	None			
Diffuse Large B-cell Lymphoma	62	M	CR	None			
Follicular Lymphoma	55	M	CR	None			

Study schema



CAR T-cell percentages



smablastic Lymphoma (n=1)

	Cytokine Release Syndrome	Neurotoxicity
UF-Kure19	20%	10%
Yescarta (NHL)	90%	78%
Kymriah (DLBCL)	74%	60%
Breyanzi (NHL)	54%	31%

Oral #94: Wald: Ultrafast CAR-T cell production Phase I UF-Kure19

Conclusions

- CAR-T therapy is clinically efficacious, but has many limitations for patients with NHL
- Naïve/early memory CAR-T cell enriched products may lead to improved in vivo proliferation, more durable efficacy and improved safety profiles
- A PBMC-based rapid CAR-T manufacturing process has the potential to address many of the key limitations of CAR-T therapy for NHL patients
- Additional clinical testing is necessary to extend and confirm upon the initial results with UF-Kure19

Oral #920: Gonzalez: Memory CAR-T cell therapy for Hodgkin Lymphoma

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Barcelona

HSP-CAR30, an Academic Memory-Enriched CART30, for the Treatment of Relapsed or Refractory Hodgkin Lymphoma and CD30+ T Cell Lymphoma: Clinical Results of a Phase I/II Trial

Ana Carolina Caballero González, Laura Escribà-Garcia, Cristina Ujaldón-Miró, Paula Pujol Fernández, Rosanna Montserrat-Torres, Eva Escudero-López, Irene García-Cadenas, Albert Esquirol, Maria Guardiola-Perello, Paola Jara-Bustamante, Rodrigo Martino, Jorge Sierra, Carmen Alvarez-Fernández and Javier Briones

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Oral #920: Gonzalez: Memory CAR-T cell therapy for Hodgkin Lymphoma

Clinical trials with CART30 therapy

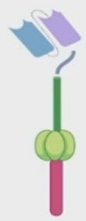
HRS3

- Phase 1/2 clinical trials
- **CD30⁺ lymphoma** patients after **≥2 lines** of therapy:
  - **41 HL**
- Conditioning:
  - Bendamustine
  - Bendamustine – Flu
  - Flu – Cy days
- **Dose:** 0.2x10⁸, 1x10⁸, 2x10⁸ CAR⁺T-cells/m²
- **ORR: 72% CR 59%**

AJ8786061

- Phase 1 clinical trial
- **18 patients:**
  - 17 HL
  - 1 ALCL
- Conditioning:
  - Flu – Cy
  - Gemcitabine – Mustargen – Cy
  - Paclitaxel – Cy
- **Dose:** 1 – 3x10⁷ CAR⁺ T-cells/kg
- **ORR: 39% CR 0%**

5F11



- Phase 1 clinical trial
- **CD30⁺ lymphoma** patients after **≥2 lines** of therapy:
  - 20 HL
  - 1 ALCL
- Conditioning:
  - Flu – Cy
- **Dose:** 0.3×10⁶, 1×10⁶, 3×10⁶ or 9×10⁶ CAR⁺ T-cells/kg
- **ORR: 43% CR 4.7% (1pt).**

Wang CM, Clinical Cancer Research, 2017.
Ramos CA, Journal of Clinical Oncology, 2020.
Brudno J, Blood Advances, 2024

American Society of Hematology

HSP-CAR30: Timeline

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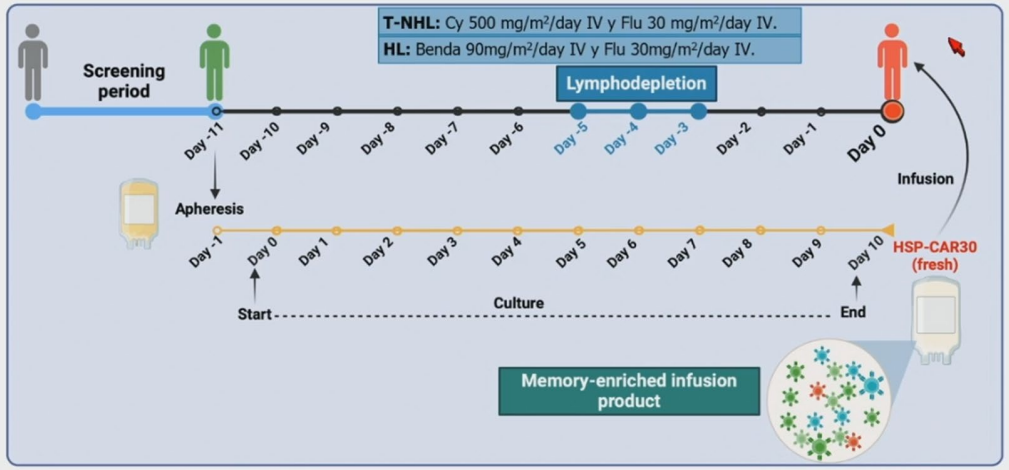

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Oral #920: Gonzalez: Memory CAR-T cell therapy for Hodgkin Lymphoma

HSP-CAR30: Efficacy assessment

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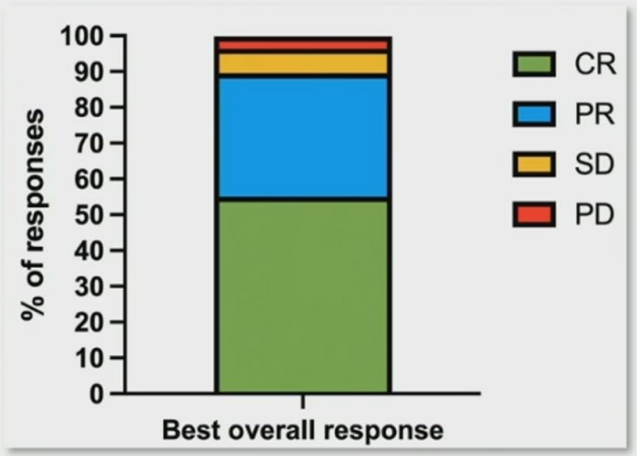
Follow-up (N=29)	
Median follow-up time	15 months (range: 2-44 months)
Overall response rate: 26 (90%)	
Best overall response	
CR	**16 (55%)**
PR	10 (35%)
SD	2 (7%)
PD	1 (3%)



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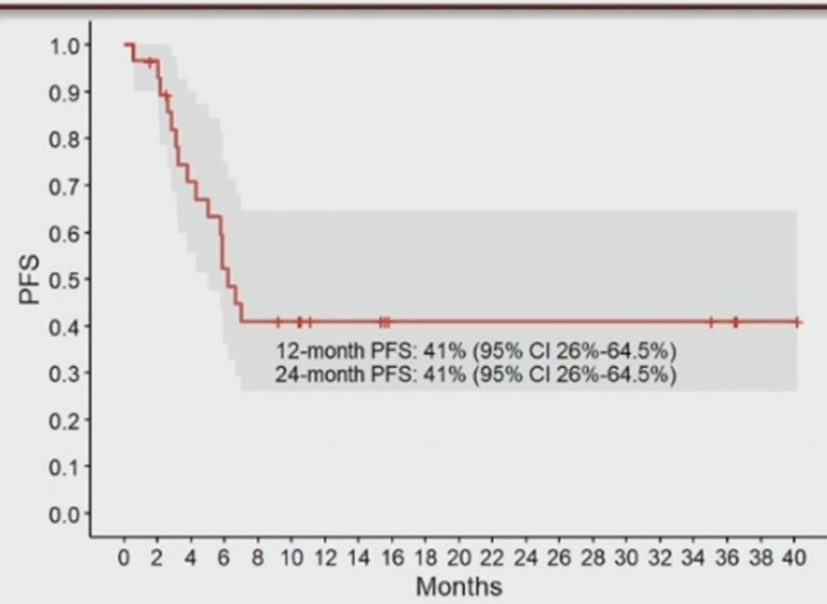
PFS (all evaluable patients)



Only mild CRS and a single case of neurotoxicity were observed.

Oral #512: Locatelli: Exa-cel Gentherapy for Thalassemia and Sickle Cell Anemia

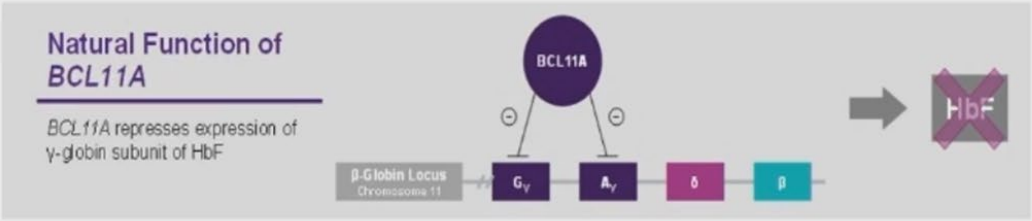
Durable Clinical Benefits with Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia

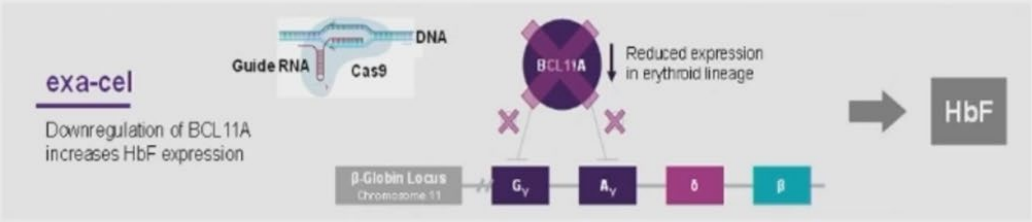
Franco Locatelli,[1] Peter Lang,[2] Roland Meisel,[3] Donna Wall,[4] Selim Corbacioglu,[5] Amanda M. Li,[6] Josu de la Fuente,[7] Ami J. Shah,[8] Ben Carpenter,[9] Janet L. Kwiatkowski,[10] Markus Mapara,[11] Robert I. Liem,[12] Maria Domenica Cappellini,[13] Mattia Algeri,[14] Antonis Kattamis,[15] Sujit Sheth,[16] Stephan Grupp,[10] Hayley Merkeley,[17] Kevin H.M. Kuo,[18] Joachim Rupprecht,[2] Puja Kohli,[19] Gang Xu,[19] Leorah Ross,[19] Yael Bobruff,[19] Bo Tong,[19] William Hobbs,[19] Haydar Frangoul[20]

[1]IRCCS, Ospedale Pediatrico Bambino Gesù Rome, Catholic University of the Sacred Heart, Rome, Italy; [2]University of Tübingen, Tübingen, Germany; [3]Division of Pediatric Stem Cell Therapy, Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany; [4]The Hospital for Sick Children/University of Toronto, Toronto, Canada; [5]University of Regensburg, Regensburg, Germany; [6]BC Children's Hospital, University of British Columbia, Vancouver, Canada; [7]Imperial College Healthcare NHS Trust, St Mary's Hospital, London, UK; [8]Stanford University, Palo Alto, CA, USA; [9]University College London Hospitals NHS Foundation Trust, London, UK; [10]Children's Hospital of Philadelphia and Perlman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [11]Division of Hematology and Oncology, Columbia University, New York, NY, USA; [12]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [13]University of Milan, Milan, Italy; [14]IRCCS, Ospedale Pediatrico Bambino Gesù Rome; Magna Graecia University of Catanzaro, Catanzaro, Italy; [15]National and Kapodistrian University of Athens, Athens, Greece; [16]Joan and Sanford I Weill Medical College of Cornell University, New York, NY, USA; [17]Department of Medicine, The University of British Columbia, [18]Division of Hematology, University of Toronto, Toronto, Canada; [19]Vertex Pharmaceuticals Incorporated, Boston, MA, USA; [20]Sarah Cannon Research Institute at The Children's Hospital at TriStar Centennial, Nashville, TN, USA

Oral #512: Locatelli: Exa-cel Gentherapy for Thalassemia and Sickle Cell Anemia

Exa-cel: The First Approved CRISPR/Cas9 Gene Editing Therapy





- Exa-cel (Casgevy) is approved for treatment of patients aged 12 and older with[1]:
  - Transfusion-dependent β-Thalassemia (TDT), and
  - Sickle Cell Disease (SCD) with recurrent vaso-occlusive crises
- Exa-cel is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of BCL11A in CD34+ HSPCs to reduce erythroid-specific expression of *BCL11A*
- Exa-cel results in reactivation of HbF synthesis to levels known to result in reduced morbidity and mortality in patients with hemoglobinopathy and hereditary persistence of HbF[2,3]
- Exa-cel Phase 1/2/3 clinical trial data have demonstrated reactivation of the synthesis of HbF to levels that eliminate the need for transfusion in TDT[4] and eliminate VOCs in SCD[5]
- Updated data will be presented demonstrating durable clinical benefit over a median follow-up of over 3 years and a longest follow-up to over 5 years

BCL11A, B-cell lymphoma/leukemia 11A; **CRISPR,** clustered regularly interspaced short palindromic repeats; **Cas9,** CRISPR-associated 9 nuclease; **exa-cel,** exagamglogene autotemcel; **Hb,** hemoglobin; **HbF,** fetal hemoglobin; **HSPC,** hematopoietic stem and progenitor cell; **RBC,** red blood cells; **SCD**: sickle cell disease; **TDT,** transfusion-dependent β-thalassemia.

1. Refer to regional label for specific indication. **2**. Musallam, KM, et al. *Blood*. 2013;121:2199-2212. **3**. Bauer DE, et al. *Curr Opin Gene Dev*. 2015;33:62-70. **4**. Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676. **5** Frangoul H, et al. *N Engl J Med*. 2024;390(18):1649-1662.

Oral #512: Locatelli: Exa-cel Gentherapy for Thalassemia and Sickle Cell Anemia

Exa-cel Pivotal Phase 3 Program in Patients with TDT and SCD

	TDT: CLIMB THAL-111 (NCT03655678)	SCD: CLIMB SCD-121 (NCT03745287)
Study Design	Global, multicenter, open-label, single-arm, 2-year Phase 1/2/3 trial of a single infusion of exa-cel	
Participants	12 to 35 years of age with TDT defined as a history of ≥100 mL/kg/year or ≥10 units/year of RBC transfusions in the previous 2 years	12 to 35 years of age with severe SCD and a history of ≥2 severe VOCs per year in the previous 2 years
Primary and Key Secondary Efficacy Endpoint	**Primary**: Proportion of participants **transfusion independent for ≥12 consecutive months** while maintaining a weighted average hemoglobin ≥9 g/dL **(TI12)**	**Primary:** Proportion of participants **free of severe VOCs for ≥12 consecutive months (VF12)** **Key Secondary:** Proportion of participants **free from in-patient hospitalization for severe VOCs for ≥12 consecutive months (HF12)**
Secondary And Additional Efficacy Endpoints	• **Duration transfusion independence for participants who achieved T112** • **Total Hb and HbF levels** • **Allelic editing at the intended locus in bone marrow CD34+ HSCs and peripheral blood cells** • **Patient-reported outcomes (PRO) measures**	• **Duration of VOC freedom for participants who achieved VF12**

CLIMB 131 (NCT04208529)

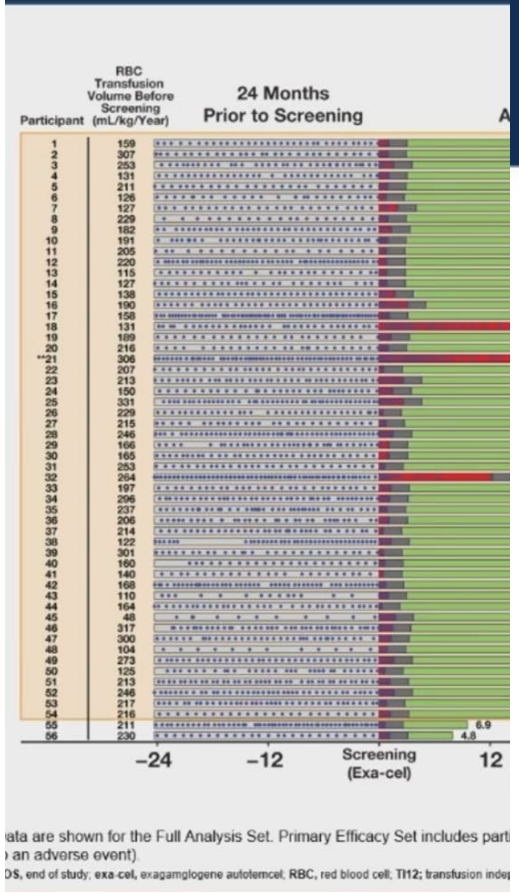
Global, multicenter, open-label, rollover Phase 3 study to provide up to 15 years of long-term efficacy and safety follow-up

Updated data from CLIMB THAL-111 and 131 demonstrates durable clinical benefit in TDT with the longest follow-up of ~5 years

Data from CLIMB SCD-121 and are being presented in POSTER #4954; also demonstrate durable clinical benefit in SCD

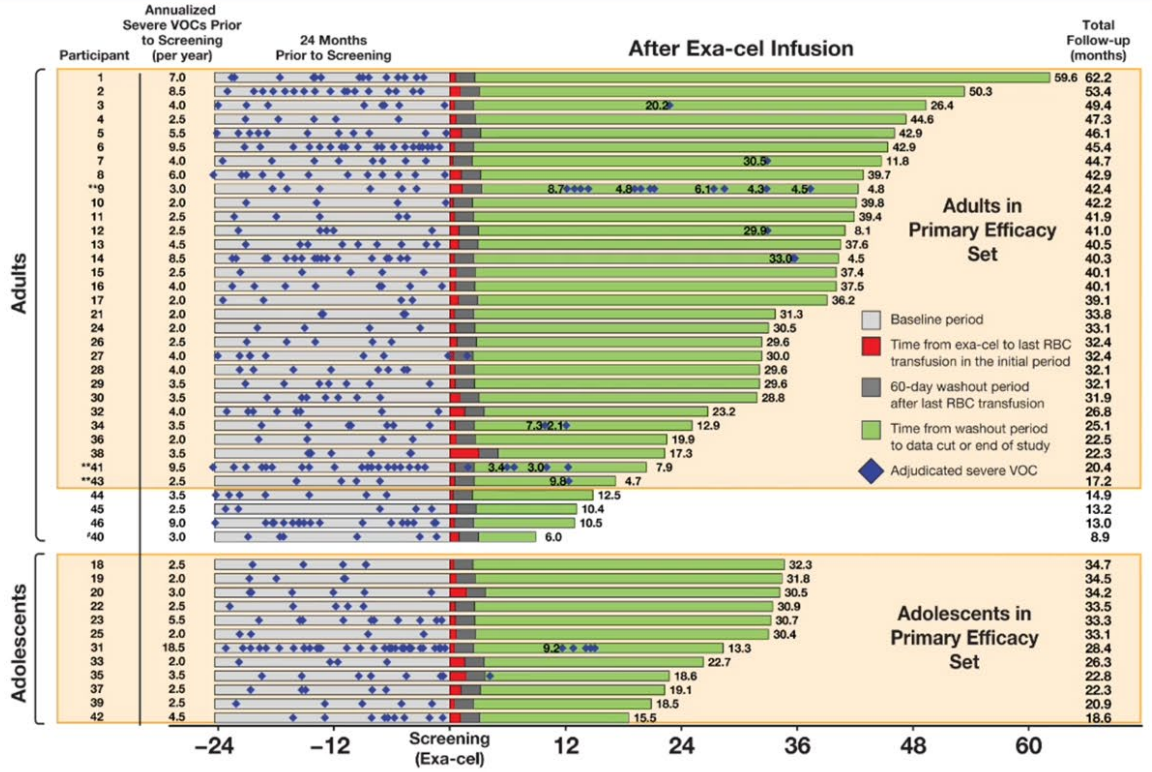
Oral #512: Locatelli: Exa-cel Gentherapy for Thalassemia and Sickle Cell Anemia

TDT: Durable Transfusion Independence After Exa-cel (CLIMB THAL-111 and 131):
Transfusion Independence Achieved in 98% and Maintained for up to ~5 years



ata are shown for the Full Analysis Set. Primary Efficacy Set includes part
an adverse event).
DS, end of study; exa-cel, exagamglogene autotemcel; RBC, red blood cell; TI12; transfusion indep

Figure 4: Consistent Durable VOC-Free Benefit Across Age Subgroups After Exa-cel (CLIMB SCD-121 and 131)



**participants who have not yet achieved VF12; #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.

Some participants had VOCs after the washout period; numerical values before the VOC indicate the number of months a participant was VOC-free since the washout period/previous VOC. Data shown are based on the Full Analysis Set as of Aug 2024. 34 participants have completed CLIMB SCD-121, and all 34 have enrolled in CLIMB-131

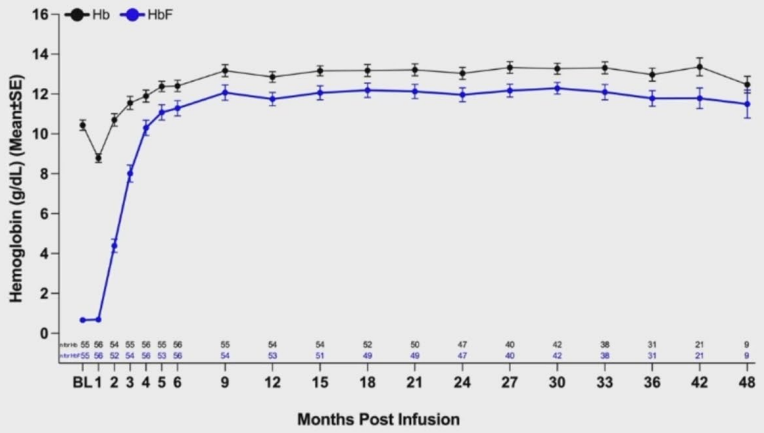
Similar proportion of participants achieved VF12 across age and genotype subgroups

- **Age:** 90% (27/30) of adults and 100% (12/12) of adolescents (Figure 4)
- **Genotype:** 92% (36/39) of β^S/β^S and 100% (3/3) of non-β^S/β^S (includes β^s/β^0 and β^s/β^+ genotypes)

Oral #512: Locatelli: Exa-cel Gentherapy for Thalassemia and Sickle Cell Anemia

Durable Increases in Total and Fetal Hemoglobin in TDT

Normal or Near Normal Levels of Total Hb



- Durable high (>95%) proportion of red blood cells containing HbF (F-cells) observed after exa-cel in TDT
- Similar results observed in CLIMB SCD-121 with all participants demonstrating a durable increase in total Hb to normal or near norma levels and fetal hemoglobin to ~40% with pancellular distribution after exa-cel (**Poster #4954**)

Data shown are based on the Full Analysis Set as of Aug 2024. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.

BL, baseline; **Hb,** hemoglobin; **HbF,** fetal hemoglobin; **SE,** standard error; **TDT,** transfusion-dependent β-thalassemia; **SCD,** sickle cell disease.

TDT: Exa-cel Safety Profile Is Consistent With Myeloablative Busulfan Conditioning and Autologous HSCT

AE Overview in CLIMB THAL-111	Exa-cel N = 56
Participants with	
Any AEs, n (%)	56 (100.0)
AEs related to exa-cel, n (%)[a]	16 (28.6)
AEs related to busulfan, n (%)[a]	55 (98.2)
AEs Grade 3/4, n (%)	50 (89.3)
SAEs, n (%)	19 (33.9)
SAEs related to exa-cel, n (%)[a,b]	2 (3.6)
AEs leading to death, n (%)	0
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets. Data are presented from exa-cel infusion to Month 24.
[a]Includes related and possibly related AEs (or SAEs). [b]SAEs previously reported in 2 participants and fully resolved. One participant had SAEs starting peri-engraftment and in context of HLH (HLH, acute respiratory distress syndrome, and headache were related to exa-cel; idiopathic pneumonia syndrome was related to exa-cel and busulfan). One participant had SAEs of delayed neutrophil engraftment and thrombocytopenia both related to exa-cel and busulfan (neutrophil engraftment achieved on Day 56 without use of backups cells).

In CLIMB THAL-131, of 47 participants enrolled, there were no new AEs related to exa-cel; 5 (10.6%) had new SAEs (none were related to exa-cel); no malignancies or deaths.

Common AE: Preferred Term in CLIMB THAL-111, n (%)	Exa-cel N = 56
Febrile neutropenia	34 (60.7)
Headache	31 (55.4)
Stomatitis	30 (53.6)
Thrombocytopenia	25 (44.6)
Anemia	25 (44.6)
Nausea	24 (42.9)
Mucosal inflammation	23 (41.1)
Vomiting	23 (41.1)
Abdominal pain	23 (41.1)

Table includes common AEs occurring in ≥40% of participants from exa-cel infusion through Month 24.

7 (12.5%) participants had VOD events
- all events were related to busulfan conditioning
- all events resolved after defibrotide treatment without any participant receiving ventilatory support or dialysis

Most AEs occurred in the first 6 months with rates decreasing over time; safety is consistent in adolescents and adults.
Overall safety results consistent in SCD (Poster #4954)

Oral #512: Locatelli: Exa-cel Gentherapy for Thalassemia and Sickle Cell Anemia

Conclusions

- Exa-cel is the first and only approved CRISPR-Cas9 gene editing therapy
- Long-term follow-up to over 5 years demonstrates that all TDT and SCD participants achieved durable clinical benefits
  - TDT: 98% achieved transfusion independence
  - SCD: 93% achieved freedom from VOC
  - Consistent efficacy in adults and adolescents and across genotypes
  - Durable increases in HbF resulting in total hemoglobin at normal or near normal levels
  - Stable allelic editing in bone marrow and peripheral blood, demonstrates durable editing of long-term HSCs
- Clinically meaningful improvements in measures of iron overload and quality-of-life in TDT
- Safety profile in TDT consistent with myeloablative busulfan conditioning and autologous HSCT; no malignancies or deaths

Exa-cel benefit was durable and has the potential to provide a one-time functional cure

Oral #679: Combined CD19/CD22 allogeneic CAR-T cells and allogeneic HCT

Safe and Effective Combination of Donor-Derived, Allogeneic CD19/CD22-CAR T Cells with Myeloablative Graft-Engineered Allo-HCT for High-Risk B-ALL

66th ASH Annual Meeting and Exposition

December 8, 2024

Lori Muffly, MD, Snegha Ananth, MBBS, Lindsay Danley, Caroline Wagner, Diana Kordek, Kimi DeNoble, Ayesha Fraser, Emily Egeler, Alfonso Molina, MD, MPH, Zachary Ehlinger, MS, Moksha Desai, MS, Hossein Daghagh, Ramya Tunuguntla, PhD, Annie K. Brown, MS*, Raquel Ibañez, Anne Marijn Kramer, MD, PhD, Zinaida Good, PhD, Sally Arai, MD, Laura Johnston, MD, Robert Lowsky, MD, Andrew R. Rezvani, Judith Shizuru*, Lekha Mikkilineni, MD, MA, Parveen Shiraz, Surbhi Sidana, MD, Wen-Kai Weng, MD, PhD, Vanessa E. Kennedy, MD, Sushma Bharadwaj, MD, Saurabh Dahiya, MD, Matthew J. Frank, MD, PhD, Everett H. Meyer, MD, PhD, Robert S. Negrin, MD, Steven A. Feldman, PhD, Crystal L. Mackall, MD, Bita Sahaf, David B. Miklos, MD, PhD and **Melody Smith, MD, MS**

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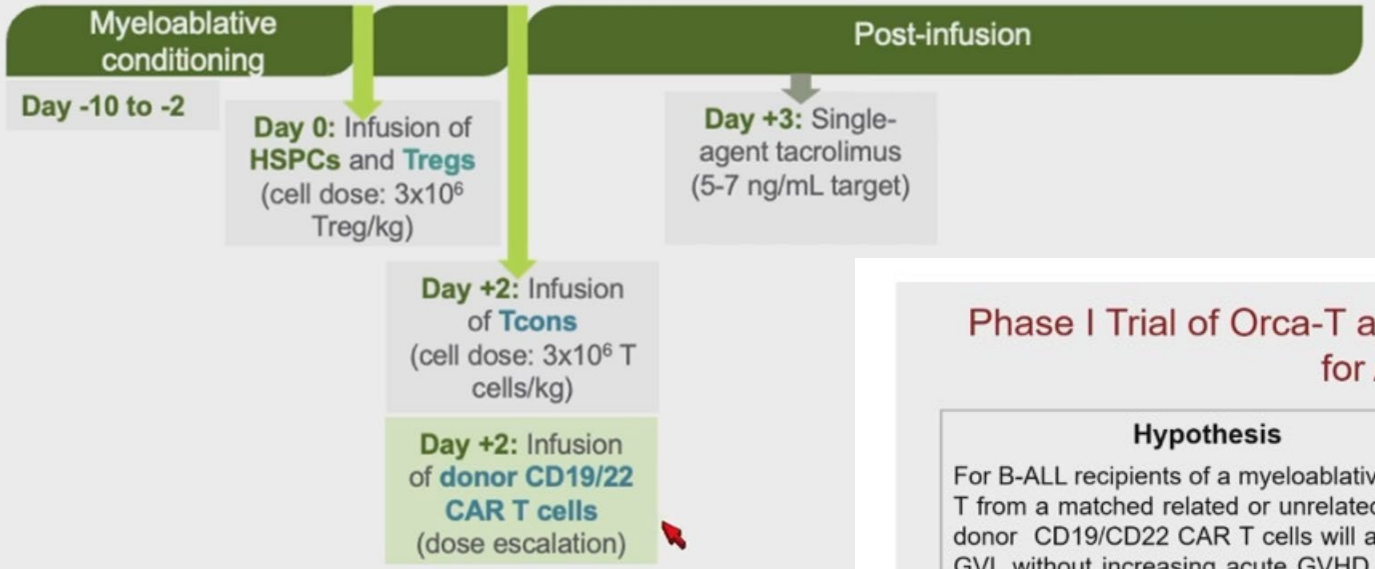
Oral #679: Muffly: CD19/CD22 allogeneic CAR-T cells

Phase I Trial of Orca-T and Allogeneic CD19/CD22-CAR T cells for Adults with B-ALL



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Phase I Trial of Orca-T and Allogeneic CD19/CD22-CAR T cells for Adults with B-ALL

Hypothesis

For B-ALL recipients of a myeloablative Orca-T from a matched related or unrelated donor, donor CD19/CD22 CAR T cells will augment GVL without increasing acute GVHD or graft failure.

Key Eligibility

- Age 18 to 65
- ECOG 0 to 2
- CD19+ B-ALL
- High-Risk Features
- Available MRD or MUD

Primary Endpoint

Incidence of engraftment without Grade III to IV acute GVHD at Day 42

Key Secondary Endpoints

- Relapse, disease progression, and NRM at 1 year
- Incidence of Grade 3 infectious complications

CAR-T Cell Dose Escalation

Dose Level	CAR-T cell Dose
1	1x10⁶ CAR+ cells/kg
2	2x10⁶ CAR+ cells/kg
3	3x10⁶ CAR+ cells/kg

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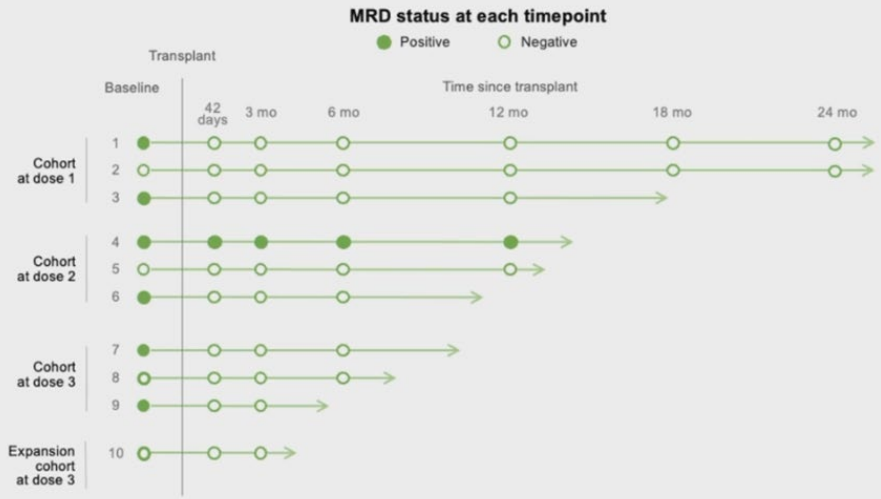
Oral #679: Muffly: CD19/CD22 allogeneic CAR-T cells

Clinical Outcomes of Patients



Median follow-up time 381 days (range, 61-762, including 6 patients with >12 months of follow-up)

Arrowhead = most recent follow-up, patient alive

Conclusion

- We have successfully enrolled 14 and treated 13 patients on our single-center, Phase I study incorporating an engineered allograft (Orca-T) and donor CD19/22 CAR-T cells for adult patients with high-risk B-ALL.
- Among the ten evaluable patients, none developed acute or chronic GVHD or severe CAR-related toxicity.
- All patients achieved a flow ± BCR-ABL MRD-negative complete response (except one subject with single-digit clonoSEQ® MRD positivity).
- Correlative data demonstrate that donor CD19/22 CAR-T cells persist beyond 1 year.

Oral #684: Müller: CD19 CAR-T cells for autoimmune disease

66th ASH® Annual Meeting and Exposition
December 7-10, 2024 • San Diego, CA

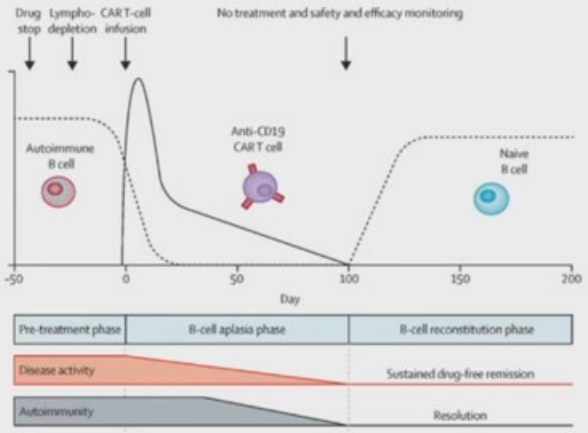
Abstract #684:
Update on Single-Center CD19-CAR T-Cell Therapy in 35 Patients with Autoimmune Disease

PD Dr. med. habil. Fabian Müller
Head of the CAR T cell programm
Department of Hematology & Oncology; University Hosptital of Erlangen
Friedrich-Alexander-Universität Erlangen Nürnberg

Uniklinikum Erlangen · BZKF Bayerisches Zentrum für Krebsforschung · CCC WERA · DZI Deutsches Zentrum Immuntherapie · FAU Friedrich-Alexander-Universität Medizinische Fakultät

Oral #684: Müller: CD19 CAR-T cells for autoimmune disease

Hypotheses on CD19 CAR T in AID



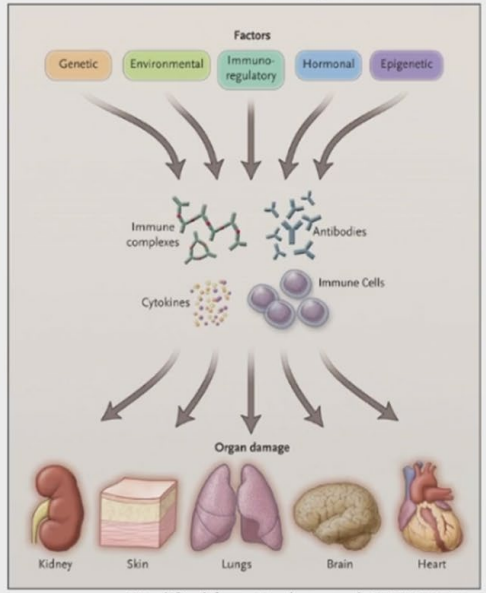
- Broader depletion of autoantibody producing B cells
- Deeper depletion within tissue
- Deeper reset of B cells
- Abrogation of autoantibodies

Schett, Lancet, Volume 402, Issue 10416, 2034 - 2044

Abstract #684 – ASH 2024 – F Müller, CARs in AID

Systemic Autoimmune Diseases (SLE)

SLE as an example



Modified from Tsokos et al. NEJM 2011

Rheumatologic Diseases with auto-antibodies:

➔Systemic Lupus erythematoses	→ anti-dsDNA
➔Systemic Sclerosis	→ e.g. SCL-70
➔Idiopathic Inflammatory Myositis	→ Anti-Synthetase (e.g. Jo-1)
➔ANCA-associated vasculitis	→ ANCAs
➔Sjogren's syndrome	→ SS-A & SS-B antibodies

Neurologic Diseases with auto-antibodies:

➔Multiple Sclerosis
➔Mystenia Gravis
➔Neuromyelitis optica disorder

Hematologic Diseases with auto-antibodies:

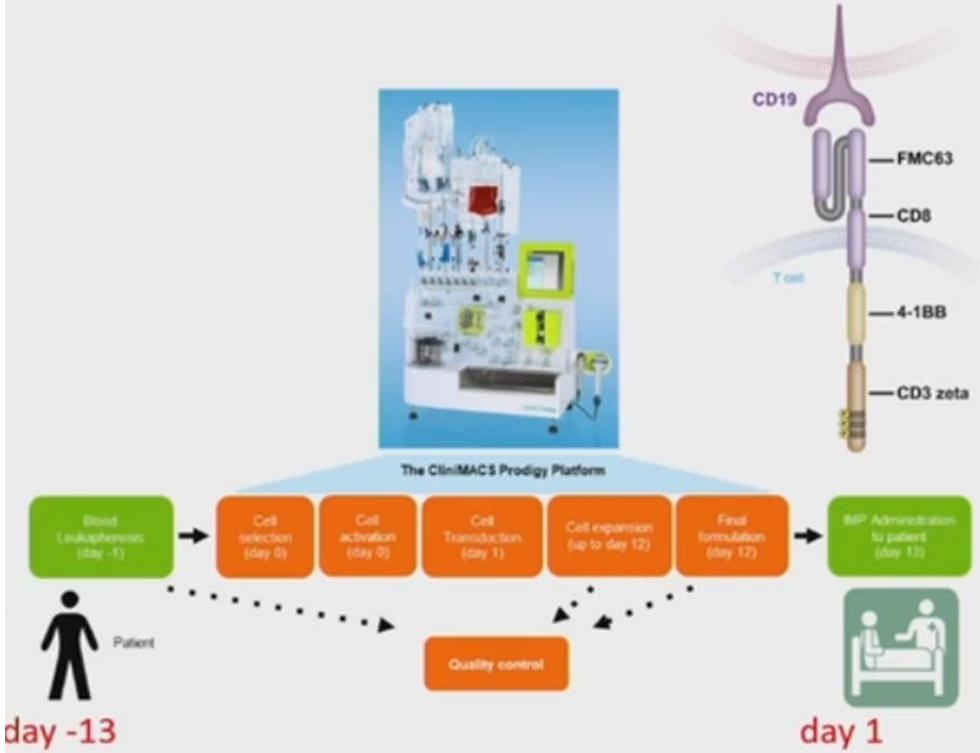
➔Immune Thrombocytopenia
➔Auto-Immune Hemolytic Anemia
➔Aquired ADAMTS13 Deficiency

Abstract #684 – ASH 2024 – F Müller, CARs in AID

Oral #684: Müller: CD19 CAR-T cells for autoimmune disease

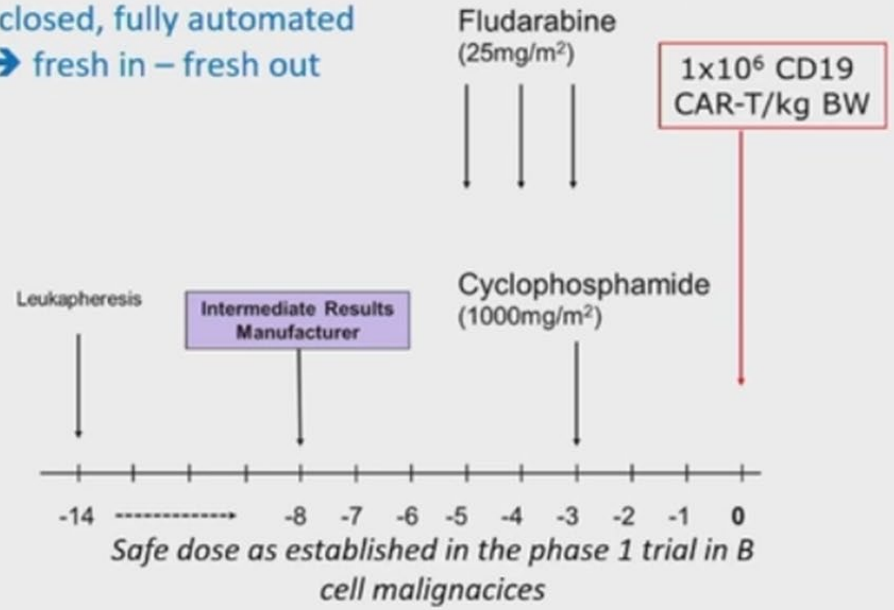
CD19-Targeted CAR-T Cells in Refractory SLE

Production Pipeline & Time Line



Licensed cell manufacturing unit within the clinic

- closed, fully automated
- fresh in – fresh out



Safe dose as established in the phase 1 trial in B cell malignacices

Mackensen et al. ASH 2021, #704

Abstract #684 – ASH 2024 – F Müller, CARs in AID

Oral #684: Müller: CD19 CAR-T cells for autoimmune disease

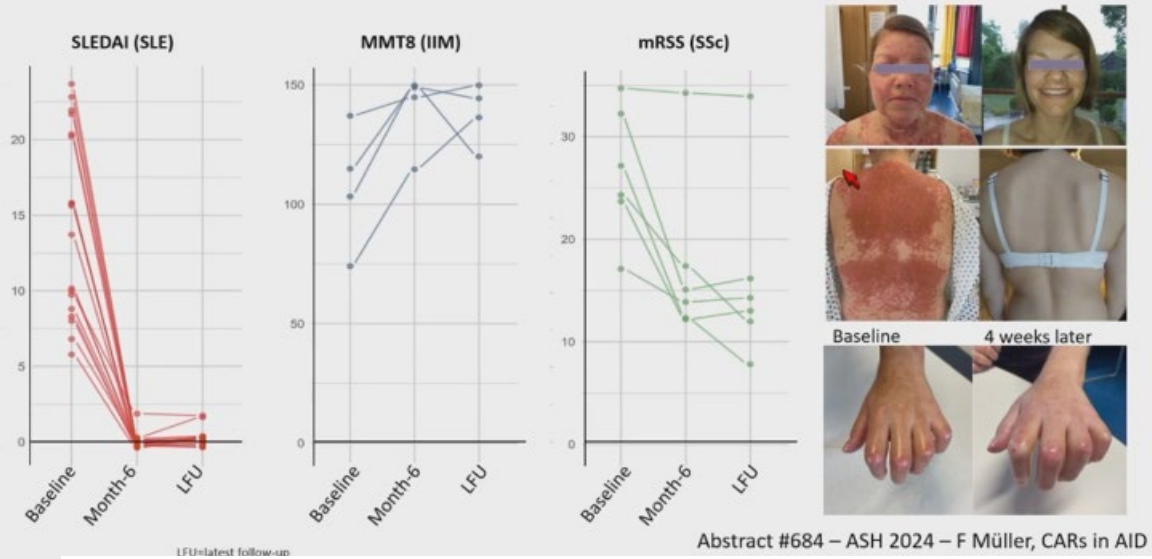
All patients treated at Erlangen as of September 2024

Patient Characteristics	SLE	IIM	SSc	Total
Patients, N	19	5	11	**35**
Age, years (mean)	28	50	42	**35**
Female, %	74%	80%	36%	**63%**
mean duration, years	7	2	4	**5**
Mean prior treatment, N	7	5	4	**5**
Mean follow-up, months	18	17	11	**15**
≥ 6 months Follow-up, N	18	4	6	**28**

Data-cut-off was September, 30th 2024

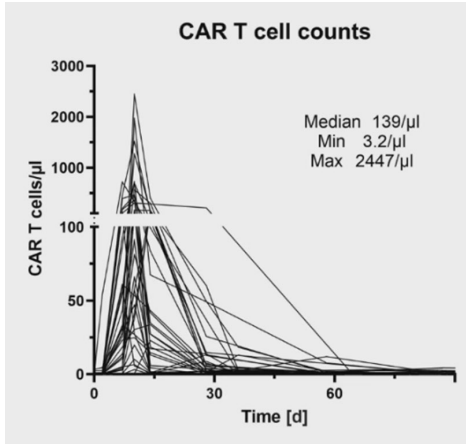
Abstract #684 – ASH 2024 – F Müller, CARs in AID

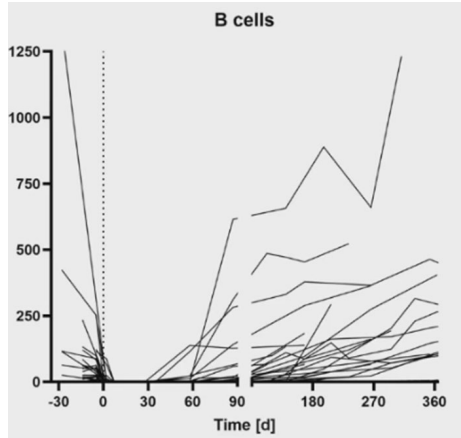
100% responses at month 6, 100% treatment-free



Abstract #684 – ASH 2024 – F Müller, CARs in AID

	SLE 19	IIM 5	SSc 11	Total 35
CRS grade 1, N (%)	13 (68)	2 (40)	6 (55)	21 (60)
CRS grade 2, N (%)	1 (5)	1 (20)	1 (9)	3 (9)
CRS >grade 2, N (%)	0	0	0	0
ICANS any grade, N (%)	0	1*	0	0





Innere Medizin II: Zugelassene CAR-T Zellen seit 2019

- **Gilead: Axucabtagene Cliloleucel (Yescarta®), second generation, CD28, CD19**
  EMA: Zulassung bei Erwachsenen NHL August 2018
  Relapsed/refractory NHL (diffuse large B-cell lymphoma (**DLBCL**), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma, **Follikuläres Lymphom** mit Rezidiv >3 Vortherapien (2022)
  zertifiziert

- **Novartis: Tisagenlecleucel (CTL019, Kymriah®), second generation, 4-1BB, CD19**
  EMA: Zulassung **ALL** bei Kindern und jungen Erwachsenen ≤25, Erwachsenen mit diffusem großzelligem B-Zell-Lymphom ((**DLBCL**) August 2018), **Follikuläres Lymphom** mit Rezidiv >2 Vortherapien (2022)
  zertifiziert

- **Gilead: Tecartus®, second generation, CD28 CD19**
  EMA: Zulassung zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem Mantelzell-Lymphom (**MCL**) nach zwei oder mehr systemischen Therapien, die einen Bruton-Tyrosinkinase-(BTK-)Inhibitor einschließen (Dezember 2020), **R/R ALL**>= 26 Jahre
  zertifiziert

- **BMS/Celgene: Abecma®** (idecabtagene vicleucel, zugelassen 2021), Anti-BCMA CAR-T (bb121) für Behandlung von Erwachsenen Patienten mit Multiplen Myelom >3 Vortherapien (inkl. Immunmodulator, anti-CD38 und Proteasominh.), **Breyanzi®** (lisocabtagene maraleucel) Anti CD19 für **LBCL**, zugelassen 2022 LBCL >3 Vortherapien, **zertifiziert**

- **Janssen:** Ciltacabtagene Autoleucel (**Cilta-cel, Carvykti®**) Anti-BCMA, **Myelom, zertifiziert**

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CAR-T Zellen Studien

Entität	Beschreibung	Rahmenbedingungen
Lymphome/ Car-T-Zellen	**Phase-II-Studie zur Bewertung der Wirksamkeit und Sicherheit von MB-CART2019.1 im Vergleich zur Standardtherapie bei Teilnehmern mit rezidiviertem/refraktärem diffus-großzelligem B-Zell-Lymphom (R-R DLBCL) |** DALY 2-EU	**geschlossen** Infos: Prof. Dr. Bethge
Myelom/ Car-T-Zellen	**Linientherapie für nicht-transplant-fähige Patienten mit VRD gefolgt von Ciltacabtagene Autoleucel vs VRD gefolgt von Lenalidomid Erhaltung |** Cartitude-5	**geöffnet** Infos: Dr. Besemer
Lymphome/ALL CAR-T Zellen	**Behandlungsmöglichkeit mit eigenhergestellten anti-CD19 gerichteten CAR-T Zellen bei rezidivierten oder therapie-refraktären akuten lymphatischen Leukämien und B-Zell-Lymphomen** **A phase I/II safety, dose finding and feasibility trial of MB-CART19.1 in patients with relapsed or refractory CD19 positive B cell malignancies**	**geöffnet** Infos: Prof. Dr. Bethge
Autoimmun	**CAR-T Zellen gegen CD19 für SLE, Sklerodermie, MS und weitere**	**Geöffnet SLE, Basket Vorbereitung** Infos: Dr. Pecher/Prof. Henes
Lymphome/ALL CAR-T Zellen	**A phase I/II dose finding and efficacy study of MB-CART-CD19/CD22 in patients with relapsed/refractory B-cell malignancies**	**eingereicht** Infos: Prof. Dr. Bethge

Universitätsklinikum Tübingen – Innere Medizin II

Hämatologie, Onkologie, klinische Immunologie und Rheumatologie

Stammzelltransplantation Studien

Entität	Beschreibung	Rahmenbedingungen
Spender	Matched Unrelated vs. Haploidentical Donor for Allogeneic Stem Cell Transplantation in Patients with Acute Leukemia with Identical GVHD Prophylaxis – A Randomized Prospective European Trial (HaploMUD Studie)	geöffnet Infos: Prof. Dr. Bethge
Immunsuppression	Graft vs Host Disease Prophylaxis in unrelated donor transplantation: a randomized clinical trial comparing PTCY vs ATG (GRAPPA)	geschlossen Infos: Prof. Dr. Bethge
GVHD	A Randomised, Open-label, Multicentre, Phase 3 Trial of First-line Treatment with Mesenchymal Stromal Cells MC0518 Versus Best Available Therapy in Adult and Adolescent Subjects with Steroid-refractory Acute Graft-versus-host Disease After Allogeneic Haematopoietic Stem Cell Transplantation (IDUNN Trial)	geöffnet Infos: Prof. Dr. Bethge
GVHD	A randomized, double-blind, multicenter, Phase 3 study to evaluate efficacy and safety of belumosudil in combination with corticosteroids versus placebo in combination with corticosteroids in participants at least 12 years of age with newly diagnosed chronic graft versus host disease (cGVHD)	geöffnet Infos: Prof. Dr. Bethge

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und am Ende….

Vielen Dank für Ihre Aufmerksamkeit

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