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Convegno Educazionale GITMO

LE TERAPIE CELLULARI IN EMATOLOGIA
TRA PASSATO, PRESENTE E FUTURO

Brescia, 28-29 novembre 2025

Centro Paolo VI

Nel mieloma: qual è la linea ottimale di utilizzo delle CAR-T?

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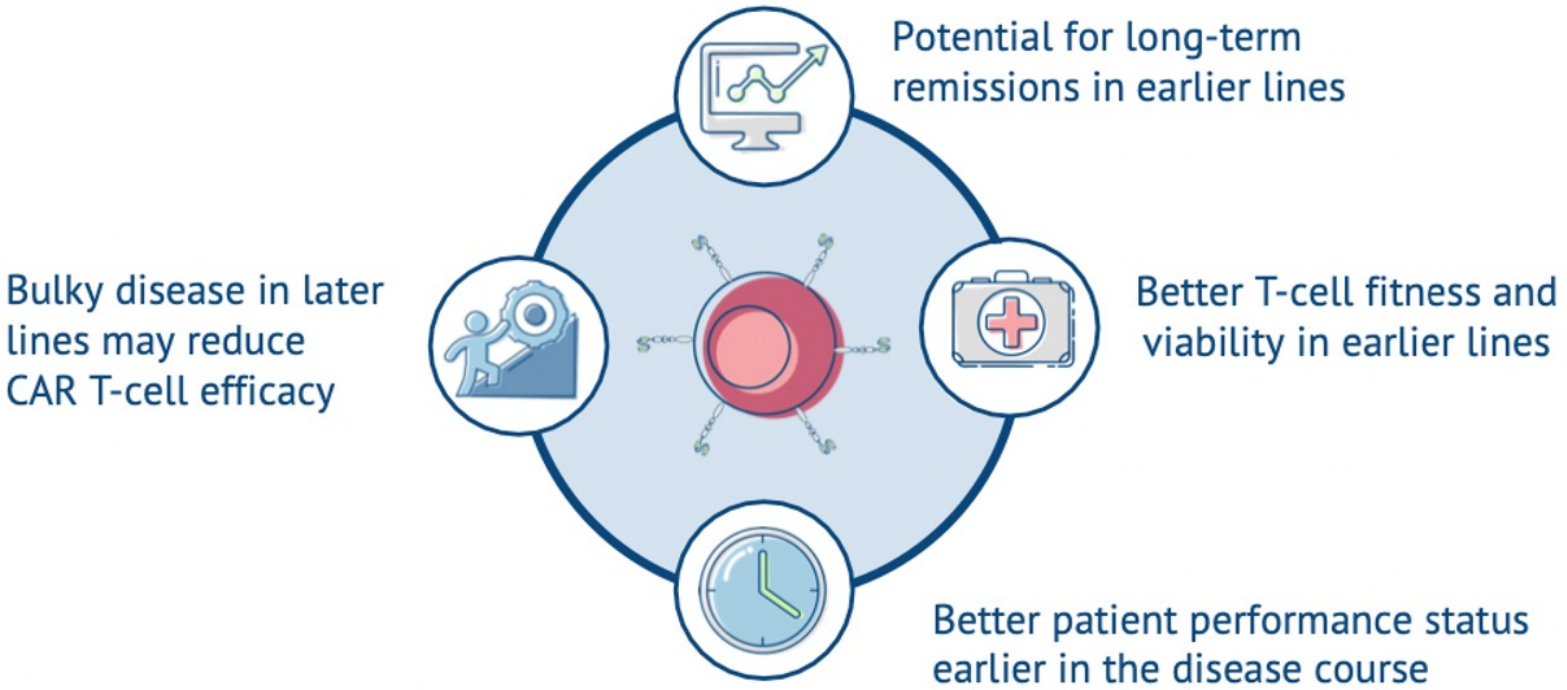
Disclosures – Angelo Belotti

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						x	
J&J						x	
GSK						x	
Pfizer						x	
Sanofi						x	
Menarini Stemline						x	

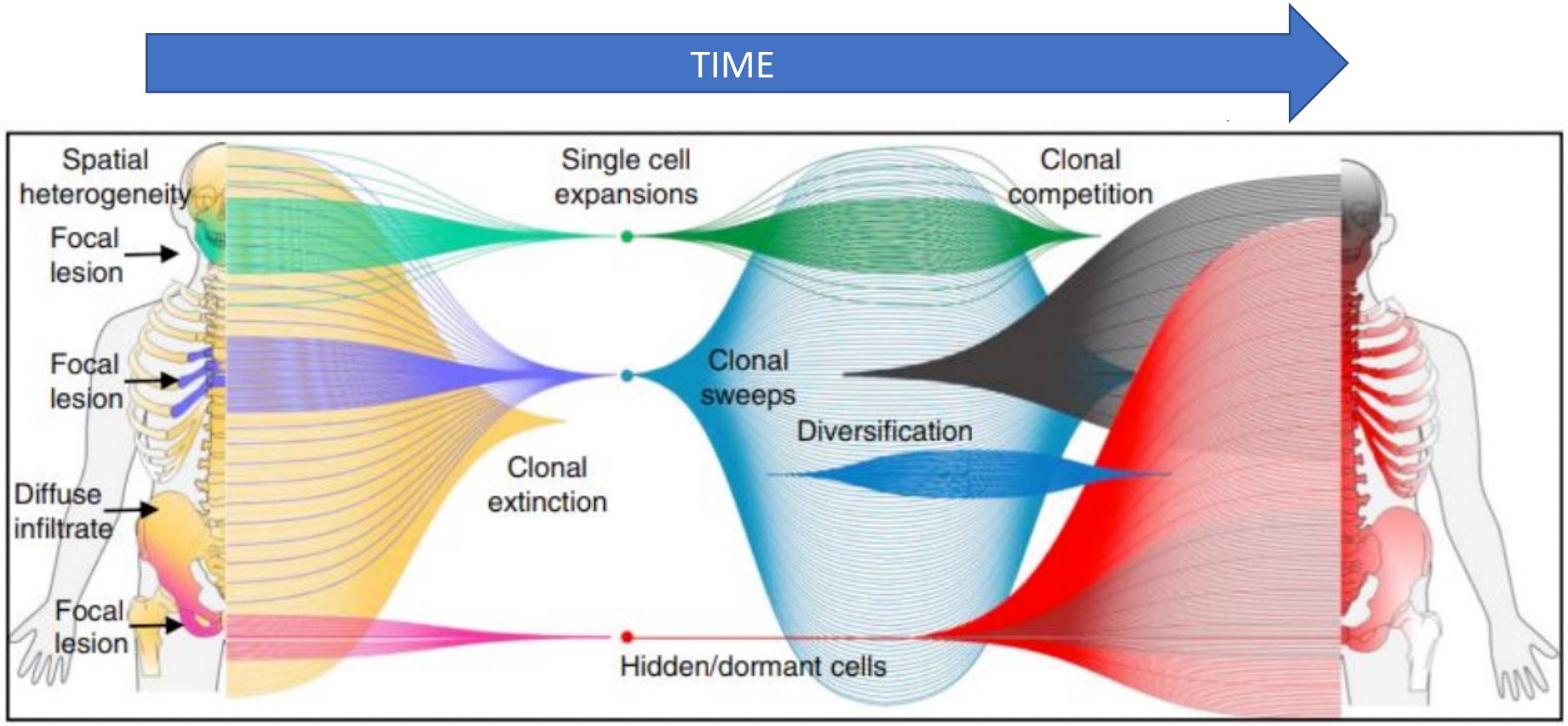
Rationale for incorporating Car-T cell therapy into earlier lines of therapy



- Improved T-cell health
- Better patient condition
- Improved safety
- Treatment free interval allowing for a potential better salvage treatment

Anderson LD Jr et al. Transplant Cell Ther. 2024

Limitations of CAR T cell therapy in late lines RRMM



- Multi-resistant disease and high prevalence of high-risk clinical features such as EMD

•Poor patient condition due to cumulative relapses and prior therapies (cytopenias, ongoing toxicities, immunosupression...)

•Limited therapeutical options for bridging

Adapted from Rasche L et al, Nat Comm 2022

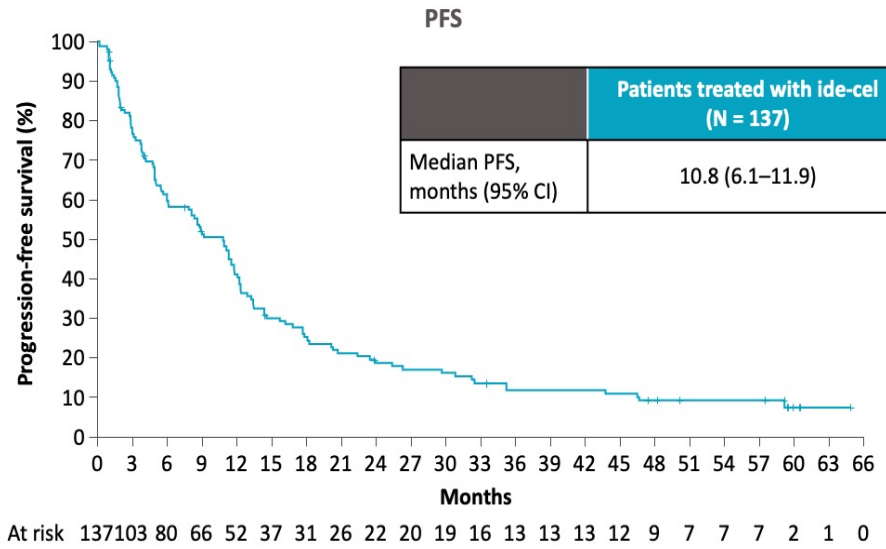
CAR-T CELL THERAPY: Ide-cel & Cilta-cel (anti – BCMA)

	Ide-cel (KarMMa)[1]		Cilta-cel (CARTITUDE-1)[2-3]
	All (N = 128)	450 x10^6 (N = 54)	N= 97
Median follow up	13.3 mos	13.3	33.4 mos
Prior lines, N	6	5	6
Triple refractory	100%	81%	88%
Extramedullary disease	39%	49%	13%
High Risk cytogenetics	25%	44%	24%
Received bridging therapy	100%	88% (4% responders)	75% (45% responders, 52% SD/NR)
ORR	73%	81%	97%
≥CR	33%	39%	67% sCR
MRD NEG (10^{-5})	33/42 CR (79%)	15/21 CR (71%)	53/57 (93%) in eval pts (≥CR)
Median PFS	8.8 mos	12.1 mos	34.9 mos (sCR: NR)
Median OS	24.8 months		NR (estimated 62.9%@36 months)

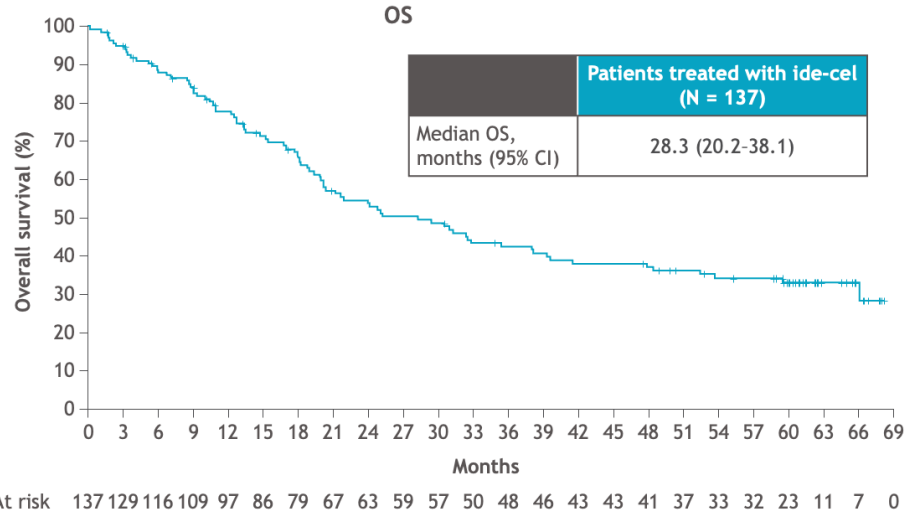
1: Munshi N et al, NEJM 2021; 2: Berdeja J et al, Lancet 2021; 3: Munshi N et al, Hemasphere 2023

Long term follow up

KARMMA (IDE-CEL), Median follow up 63 months

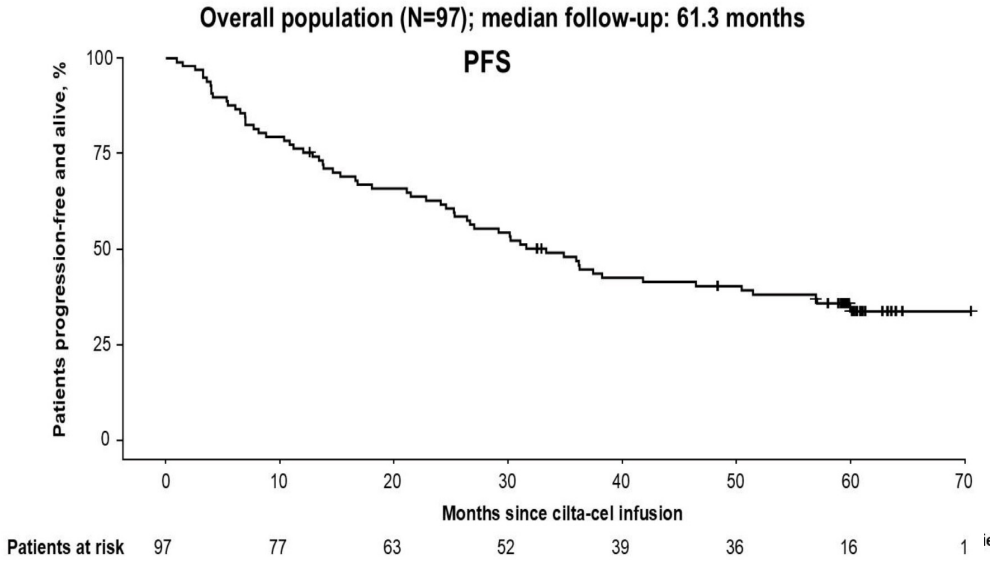


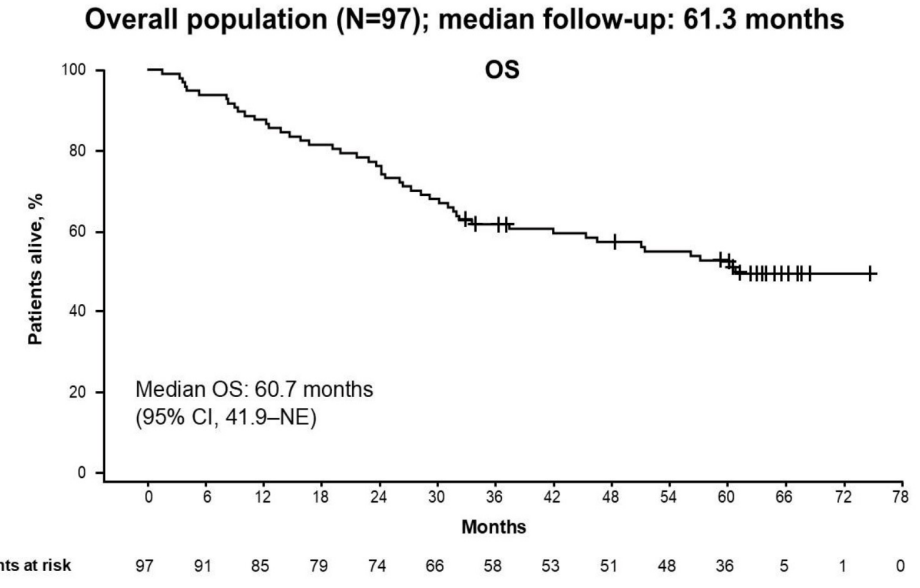
	Patients treated with ide-cel (N = 137)
Median PFS, months (95% CI)	10.8 (6.1–11.9)



	Patients treated with ide-cel (N = 137)
Median OS, months (95% CI)	28.3 (20.2-38.1)

CARTITUDE-1 (CILTA-CEL), Median follow up 61 months





Anderson LD et al, IMS 2024; Jagannath S et. al JCO 2025

CAR-T cell therapy – Real world data: IDE-CEL

US consortium

- Retrospective analysis: IDE-CEL in 196 patients (2021-2022), **median f-up 6.1 months**
- 77% ineligible for KarMMa trial, most commonly due to comorbidities (31%), prior anti-BCMA therapy (22%), thrombocytopenia (21%)

Parameter, %	KarMMa (N = 128)	Real World (N = 196)
Median age, yr (range)	61 (33-78)	64 (36-83)
Extramedullary disease	39	47
Penta-refractory	26	44
ECOG PS ≥2	2	20
Ide-cel manufacturing failure	<1	6*
Bridging therapy	88	77
Any-grade/grade ≥3 CRS	84/5	82/3
Any-grade/grade ≥3 ICANS	18/3	18/6
Best ORR/≥sCR	73/33	86/42
OS rate	12-mo: 78%	6-mo: 84%

Real world patients less fit, more often penta-refractory

- Similar safety profile
- Similar efficacy
- **Median PFS: 8.5 months**
- Median OS:12.5 months

Inferior PFS associated with:

- **Prior anti-BCMA therapies (HR: 2,81, P = 0,003)**
- **HR cytogenetics (HR: 2,31, P = 0,003)**
- **ECOG PS ≥ 2 (HR: 2,19, P = 0,016)**
- **Younger age (HR: 0,97 per year, P = 0,043).**

Hansen DK et al, ASCO 2022
Hansen DK et al, JCO 2023

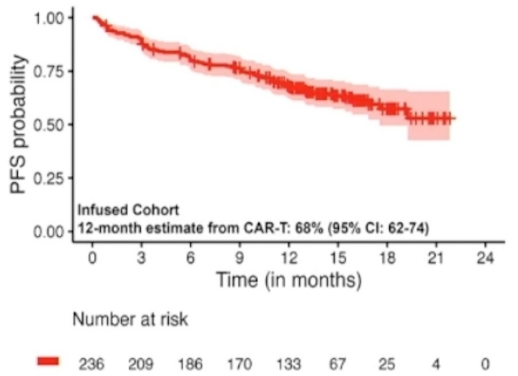
CAR-T cell therapy – Real world data: CILTA-CEL

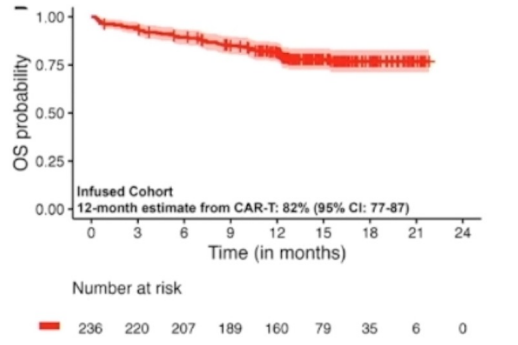
US consortium

N= 255 (236 infused), ~ 55% would have been ineligible for CARTITUDE-1 trial
Median follow-up: 13 months

- **69% TCR**
- **median prior lines: 6**
- **26% EMD**
- **39% HR cytogenetics**

CARTITUDE-1 trial Exclusion Criteria at leukapheresis	Apheresed patients N=144 (56%)	Infused patients N=128 (54%)
Organ dysfunction (renal, cardiac, hepatic)	31 (13%)	27 (12%)
Creatinine clearance < 40 ml/min	22 (9%)	18 (8%)
Prior anti-BCMA therapy	38 (15%)	33 (14%)
Cytopenias	45 (18%)	37 (16%)
ECOG PS ≥ 2	28 (11%)	25 (11%)
Active or prior plasma cell leukemia, amyloidosis or POEMS	28 (11%)	24 (10%)
H/o CNS myeloma/other CNS pathology	12 (5%)	12 (5%)



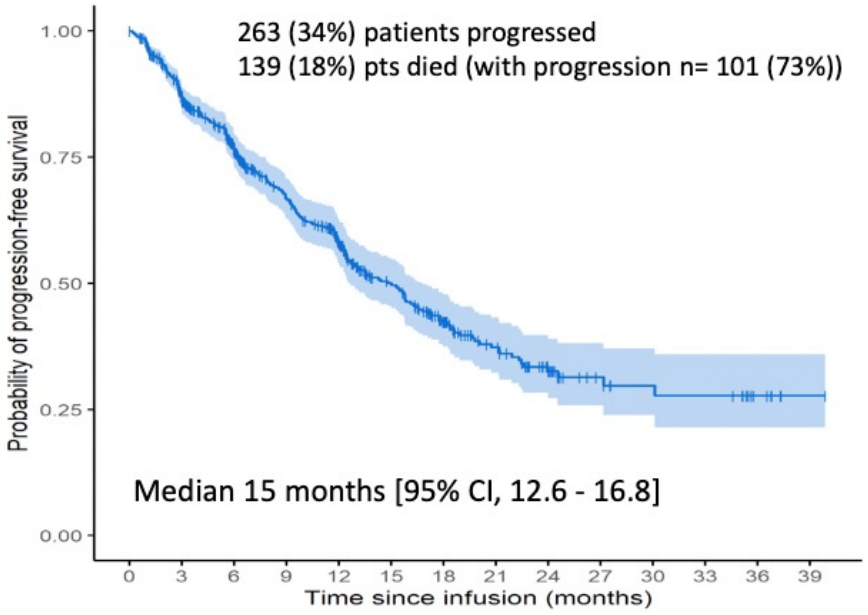


PFS @ 12months: 68% (77% in Cartitude-1, median 34.9 months);
OS @12 months: 82% (89% in Cartitude-1)
ORR: 89%, CR: 70% (93/98 evaluable patients MRD neg)

Sidana S et al, Blood 2024 & IMS 2024

Super-FENIX: An IFM study from the descar-T registry (2021-2025)

Median follow-up: 11.8 months



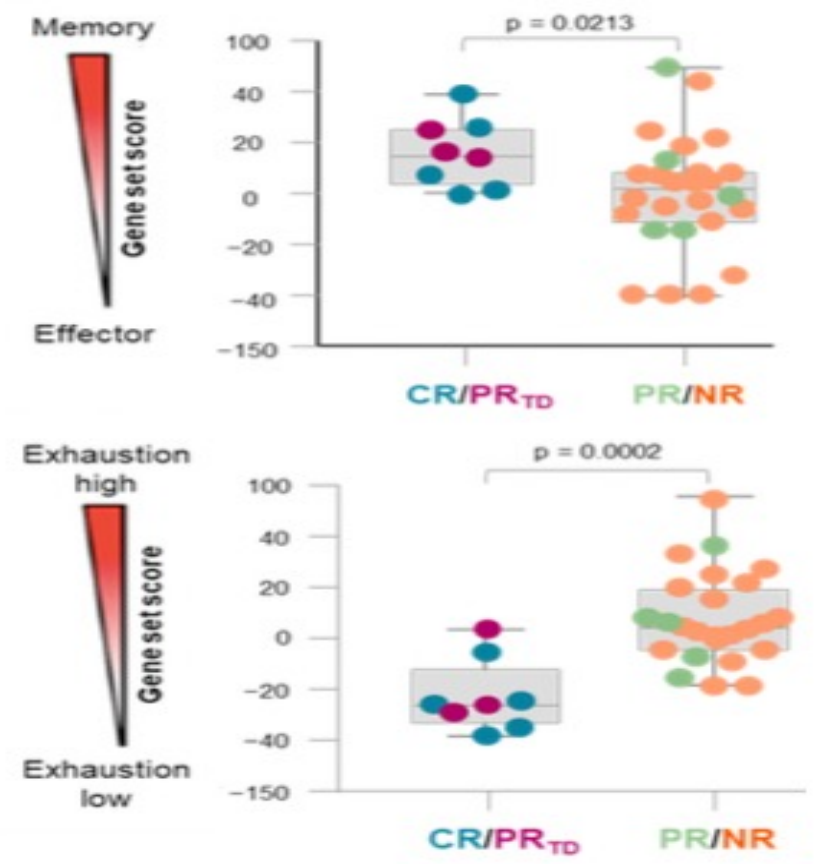
Adequate patient selection leads to improved survival

Parameters	Super Fenix N= 771	US Consort. (4) N=159	CIBMTR(3) N=821
Age, median yrs (range)	66 (29-85)	64 (36-83)	66 (29-80)
ECOG 0-1 (%)	92	81	94
ISS/R-ISS III, (%)	31	27	16
EMD (%)	10	48	17
High risk cytogenetics (del(17p or t(4;14) (%)* *missing data 330/771	37	35	27
Prior lines of treatment (LOT), median (range)	3 (2-13)	7 (4-18)	7 (4-21)
Triple-refractory (%) Penta-refractory (%)	73 22	84 44	- -
Prior anti-BCMA bispecific (%)	3	21	15
Bridging therapy (%) Response to Bridging > PR (%)	82 34	77 11	54 -
KarMMa exclusion criteria at LK (%)	21	75	77

Arnulf B et al, IMS 2025; Sidana et al, Blood 2025; Hansen et al, JCO 2023

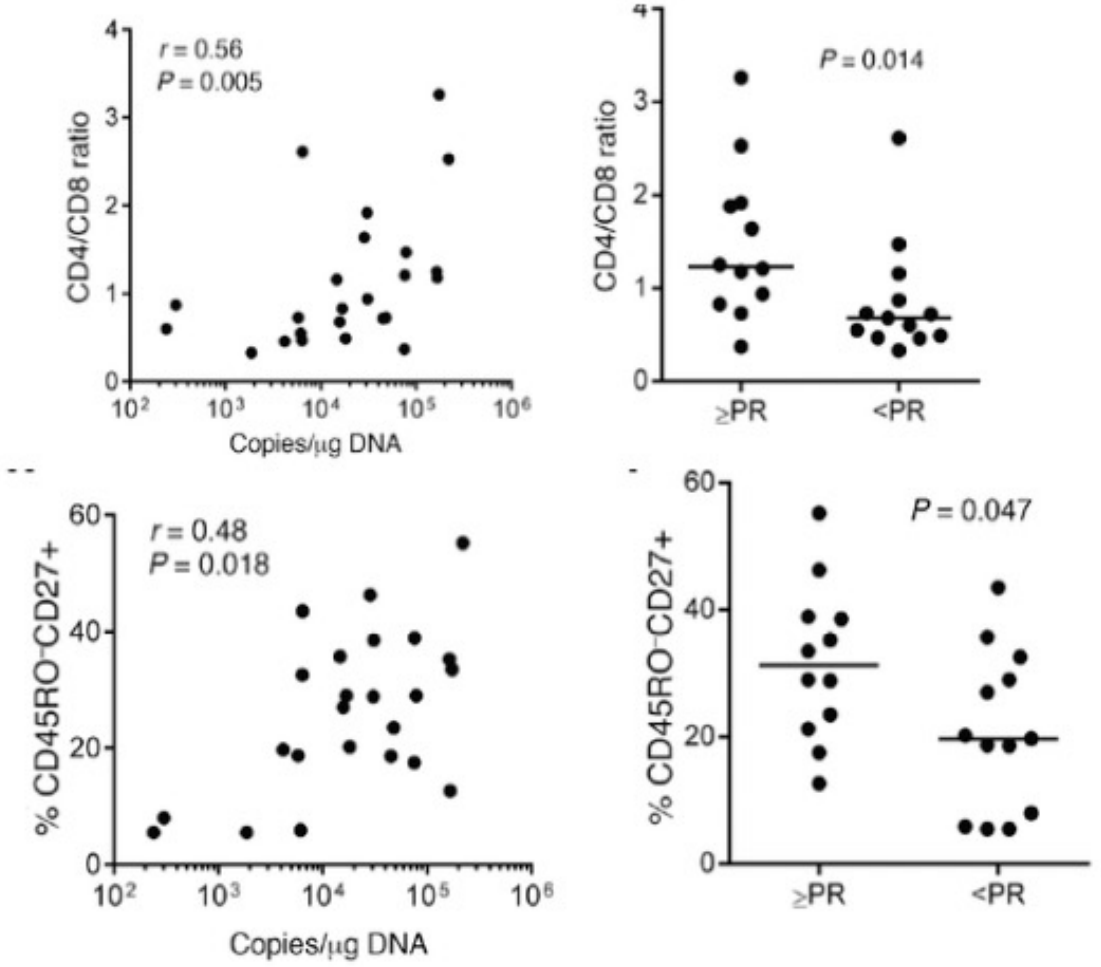
Phenotype of pre-manufactured CAR-T cells is associated with expansion and response

Less proportion of memory phenotypes (TSCM, TCM, and TEM) and higher proportion of terminally differentiated and TEFF populations among non-responders



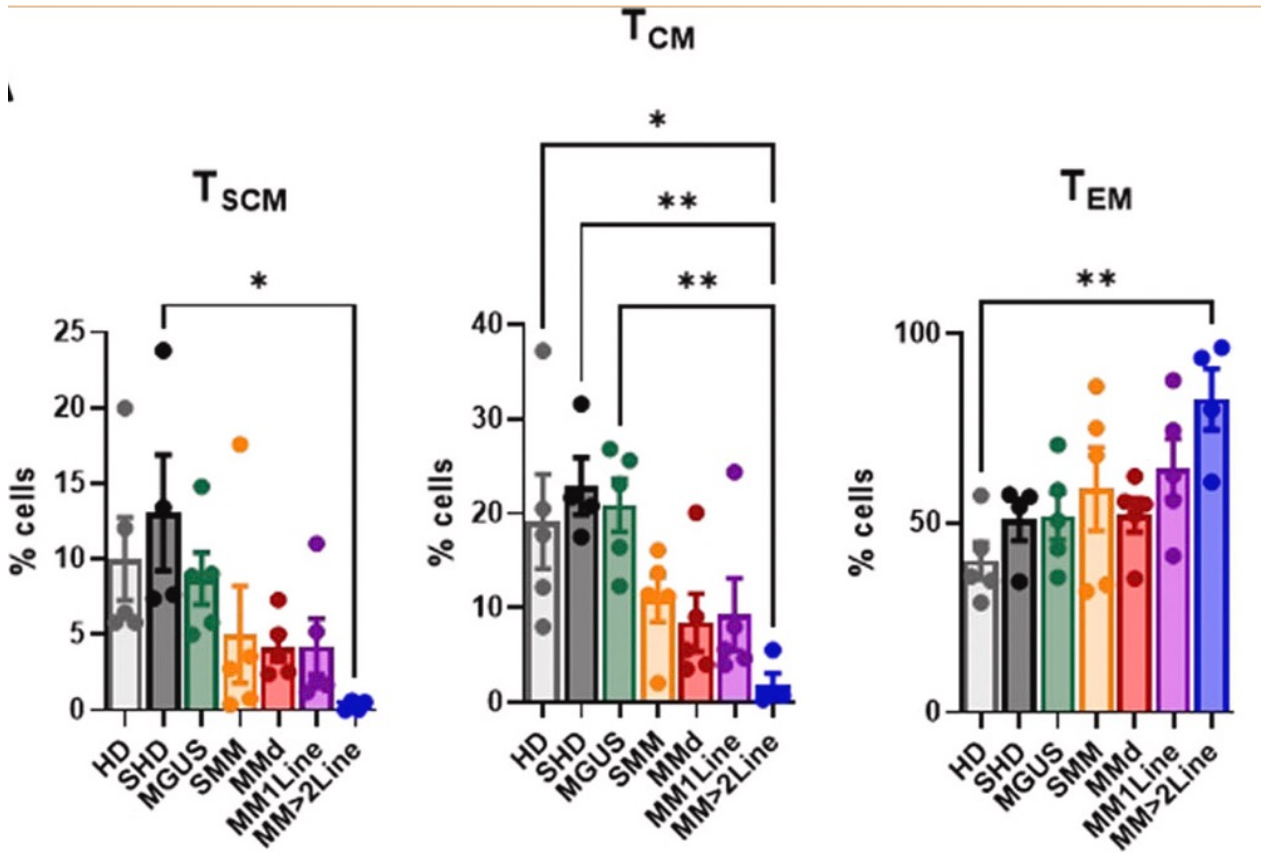
Fraietta JA, et al. Nat Med. 2018

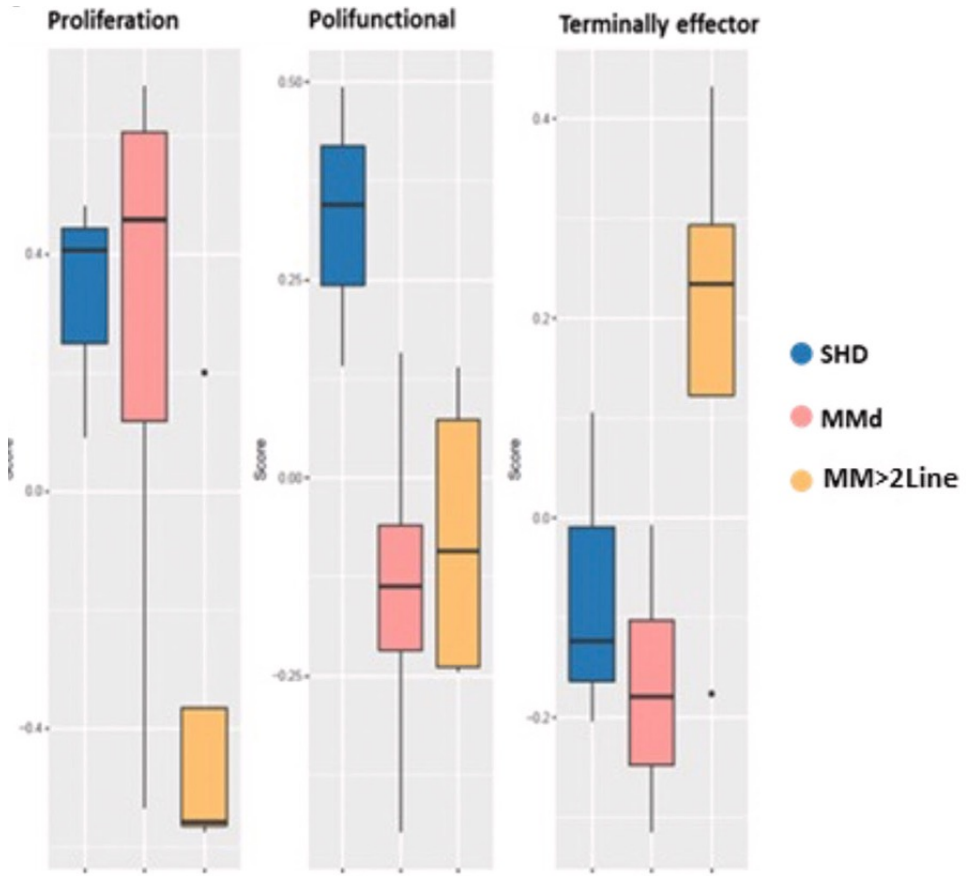
The percentage of Naïve and early memory CD8+ cells in the leukapheresis product correlates with in vivo peak expansion and response



Cohen AD, et al. J Clin Invest. 2019

Early stages of the disease are associated with better T-cell fitness and polyfunctionality





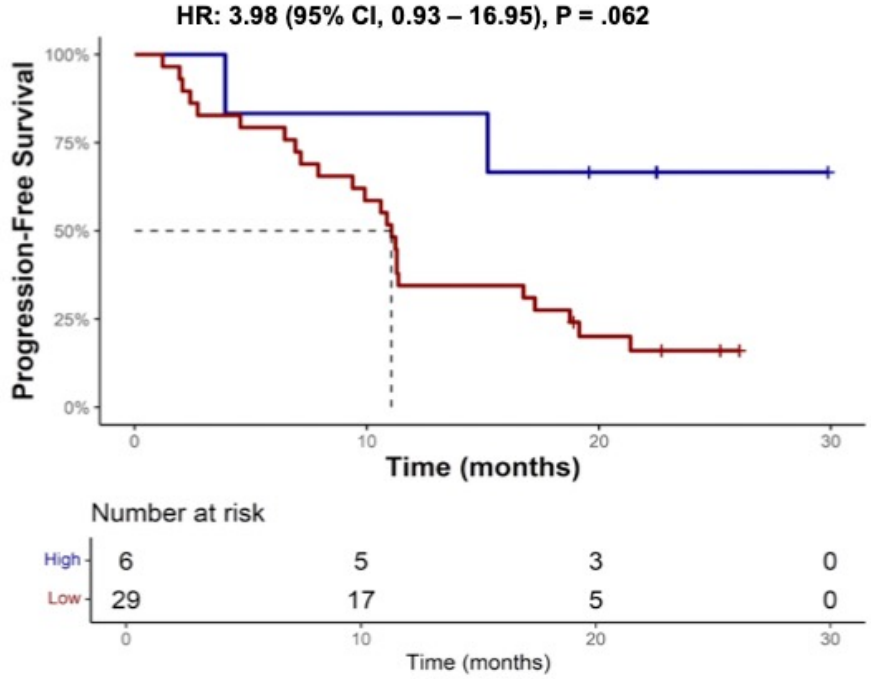
- CAR T cells from later MM stages present reduced levels of memory phenotype (Tscm and Tcm)
- Genomic data supports the phenotypic and functional differences observed within SHD (senior healthy donor), MMd (newly diagnosed) and RRMM CAR T cells produced

Martin Mallo A et al, ASH 2022

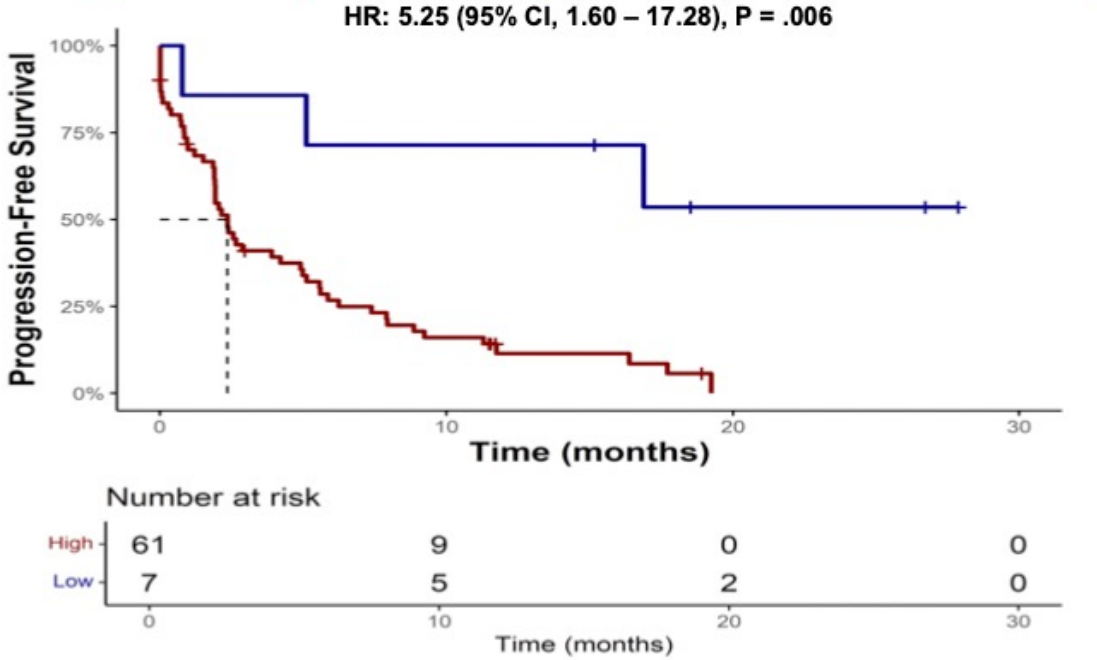
T-cell phenotypes prior to lymphocyte apheresis are associated with PFS

Immune profiling in the KarMMa clinical trial (ide-cel)

CD3+CD4+CD8-CD27+CD45RA-CD95-CD197lo (CD4 central memory)*



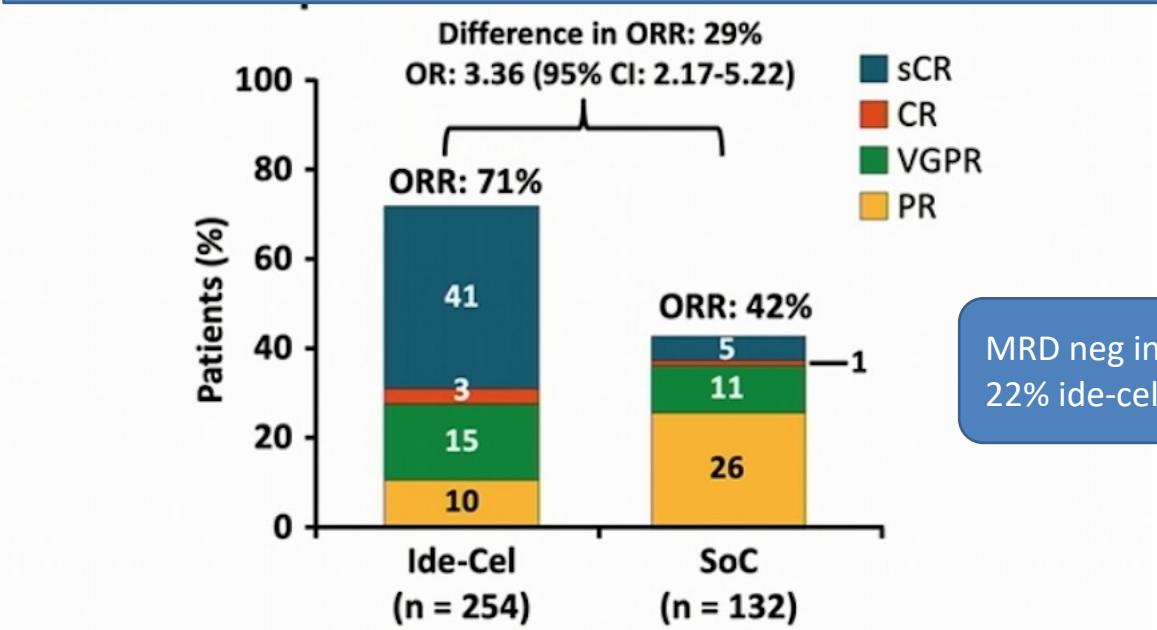
CD3+CD4+CD8-CD25+CD127lo+ICOS+TIGIT- (potentially chronically activated and exhausted)



Paiva B et al, IMS 2025

KarMMa-3: IDE-CEL vs Standard of Care

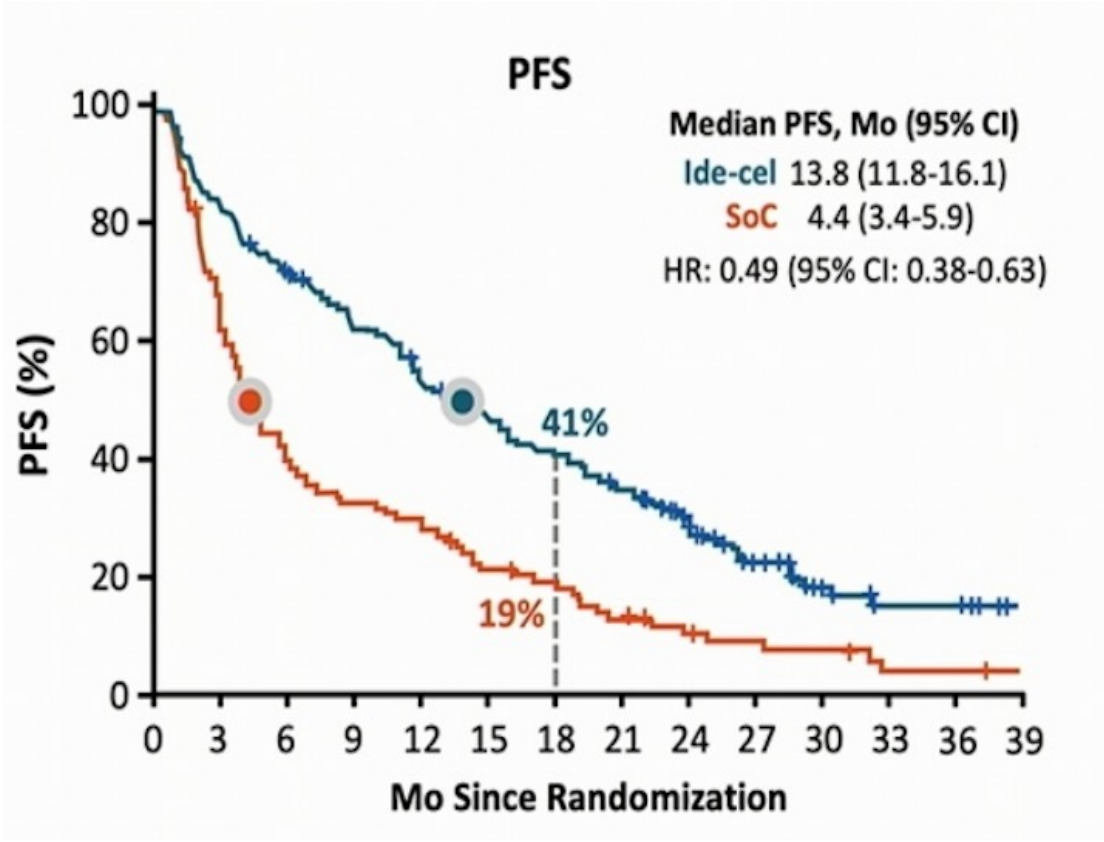
Median follow-up: 30.9 months, 2-4 PL (triple class exposed)



Secondary Outcomes	Ide-Cel (n = 254)	SoC (n = 132)
Median DoR, mo (95% CI)	16.6 (12.1-19.6)	9.7 (5.5-16.1)
Median EFS, mo (95% CI)	13.3 (11.3-15.7)	3.9 (3.0-5.3)
Median TTNT, mo (range)	20.9 (16.6-24.2)	7.0 (5.3-8.5)

MRD neg in ≥ CR:
22% ide-cel vs 1% SoC

	IDE-CEL (N= 254)	SoC (N = 132)
Median prior lines	3 (2-4)	3 (2-4)
TRIPLE CLASS REFRACTORY	65%	67%
High Risk Cytogenetics	42%	46%
EMD	24%	24%

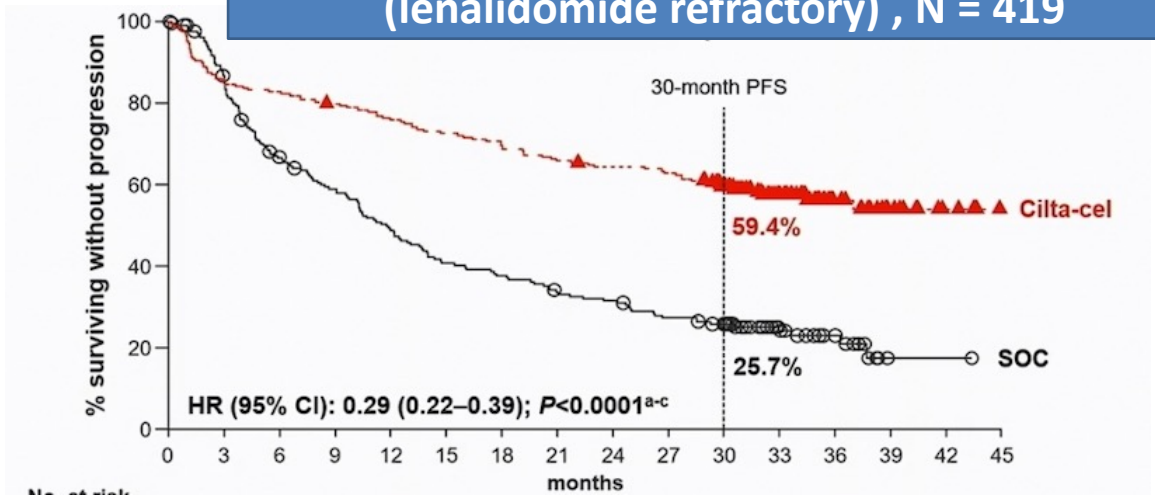


Rodriguez-Otero P et al, NEJM 2023; Rodriguez-Otero P et al, ASH 2023

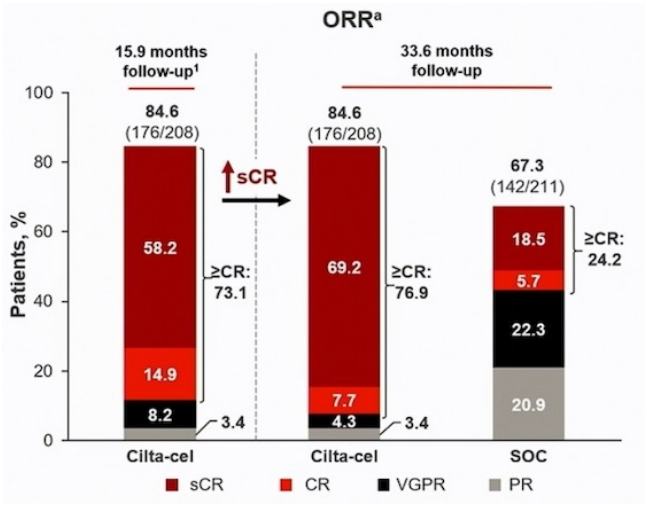
CARTITUDE-4: CILTA-CEL vs Standard of Care (Dara-PD or PVD)

	CILTA-CEL (N=208)	SoC (N=211)
Median prior lines	2 (1-3)	2 (1-3)
TRIPLE CLASS REFRACTORY	14%	16%
High Risk Cytogenetics	59%	63%
EMD	21%	17%

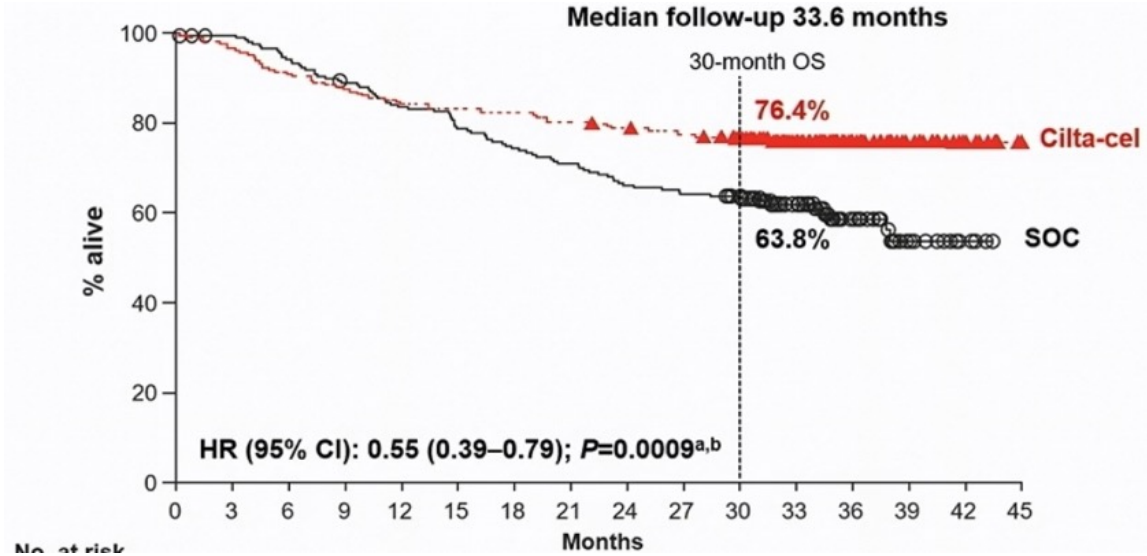
Median follow-up: 34 months, 1-3 PL (lenalidomide refractory) , N = 419



* **Median PFS: NR vs 11,8 months (30 months PFS: 59,4% vs 25,7%)**
* **30 months OS: 76,4% vs 63,8%**
* **Duration of response, median: NR vs 18,7 months**

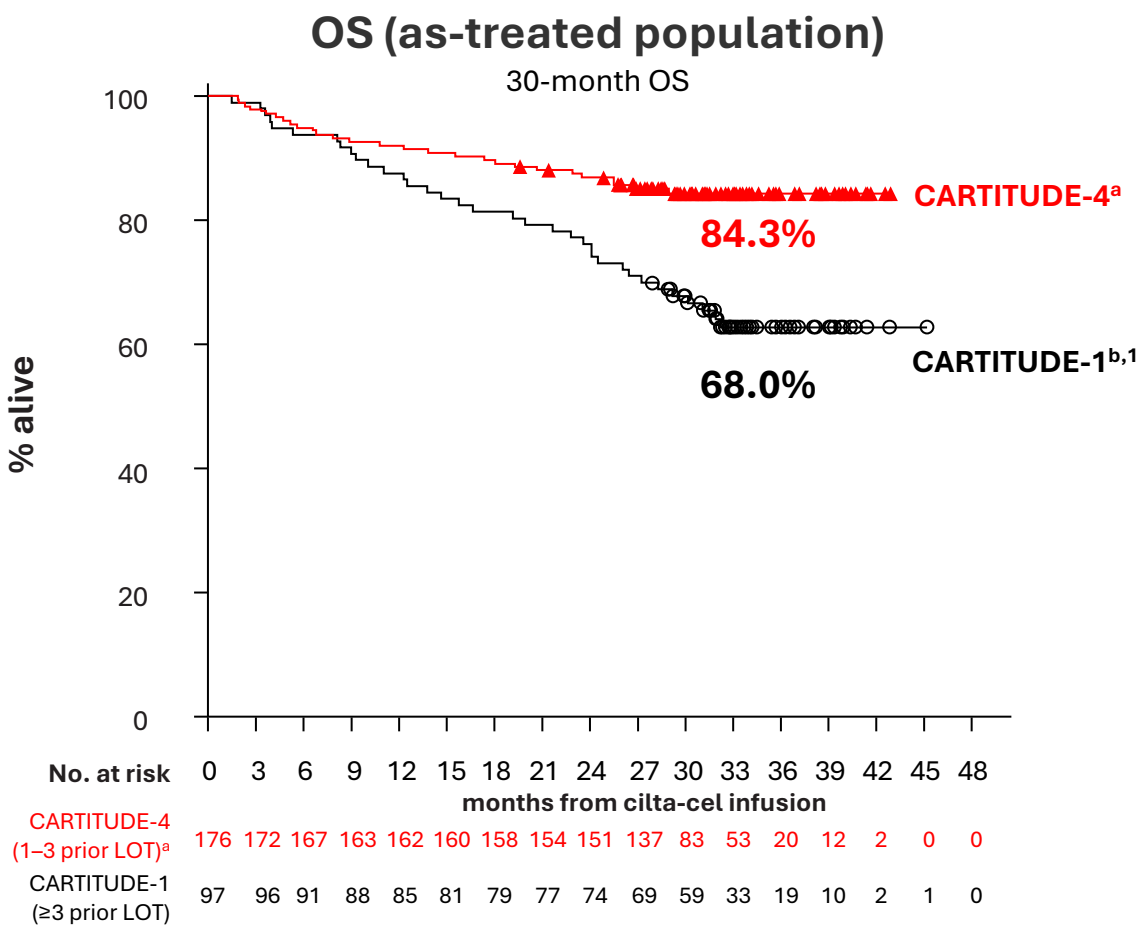


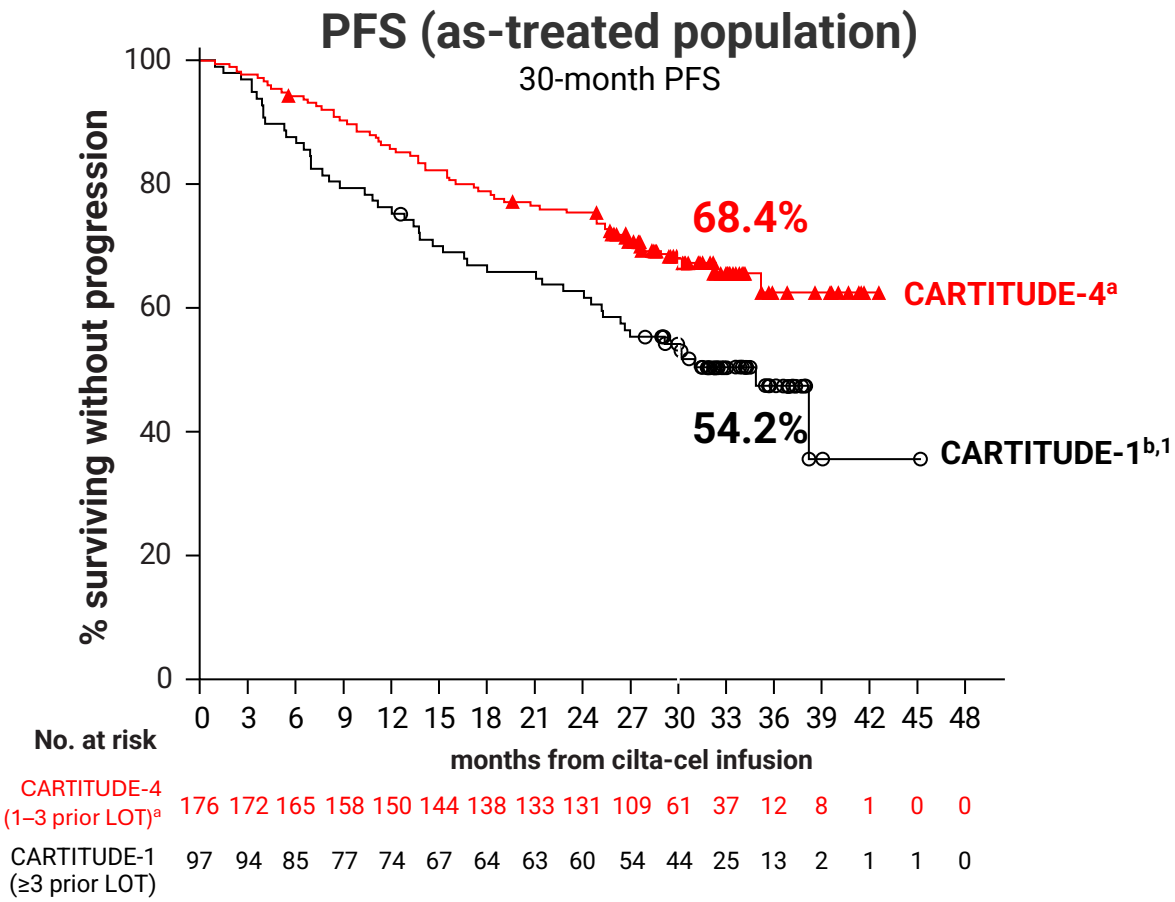
MRD neg (10-5):
89% cilta-cel vs 38% SoC



Mateos MV et al, IMS 2024

Cilta-cel may be more efficacious in early relapses than late

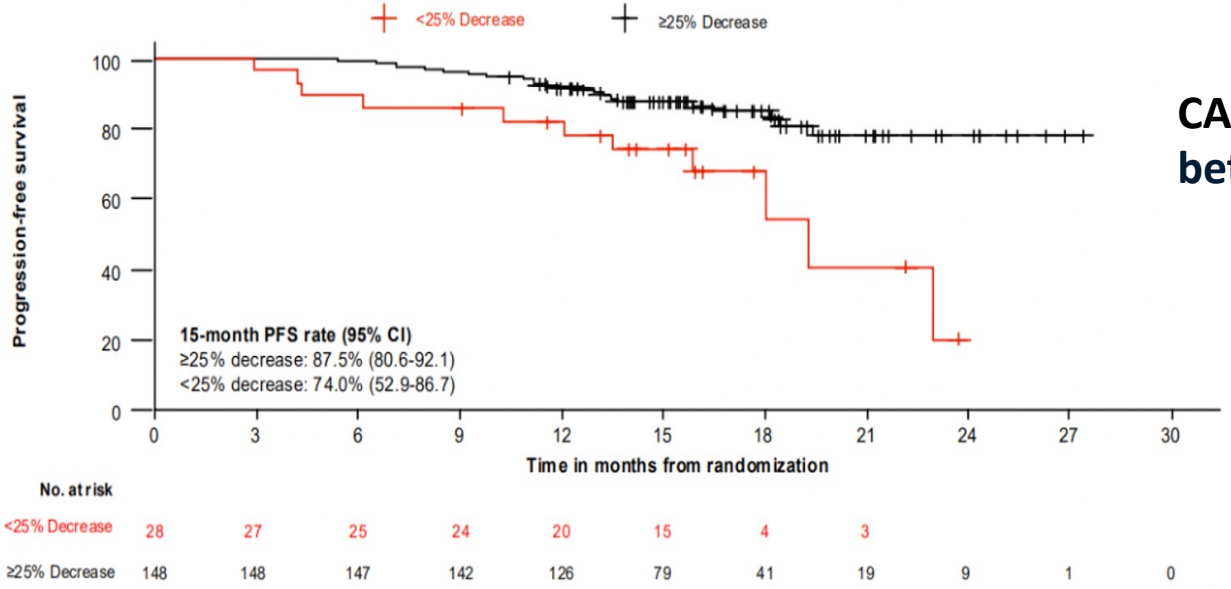




Cilta-cel use in earlier lines demonstrated numerically higher rates of overall and progression-free survival

Dhakal B et. al ASCO 2023

Response to bridging therapy correlates with survival after CAR-T cell therapy

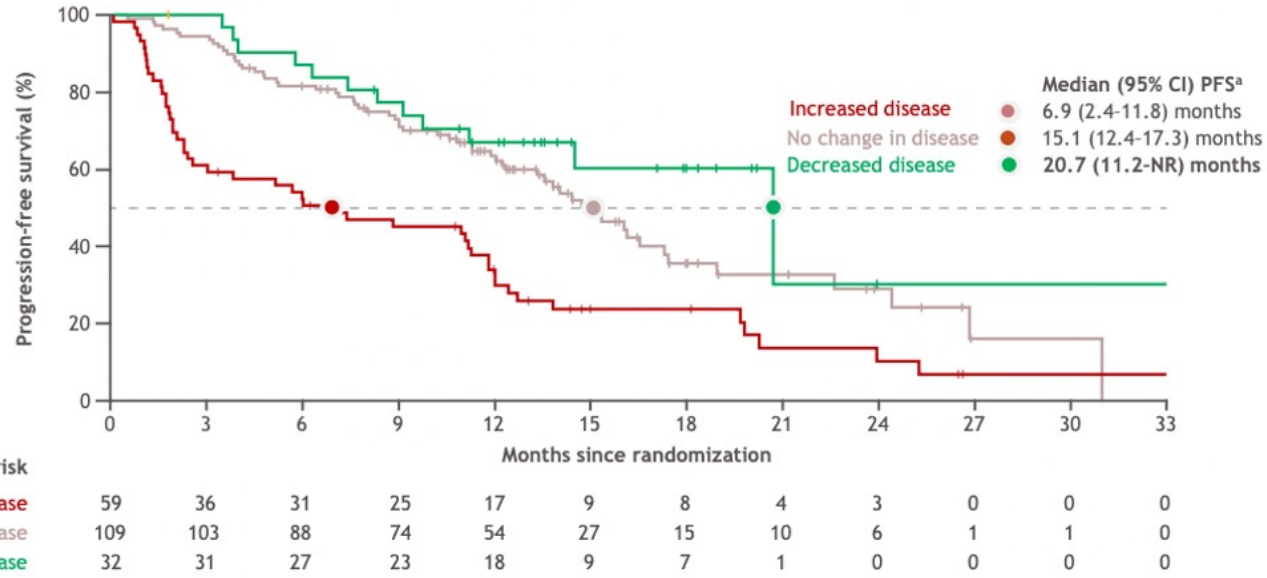


CARTITUDE-4: PFS by tumor burden change ≥ 25% between baseline and start of lymphodepletion

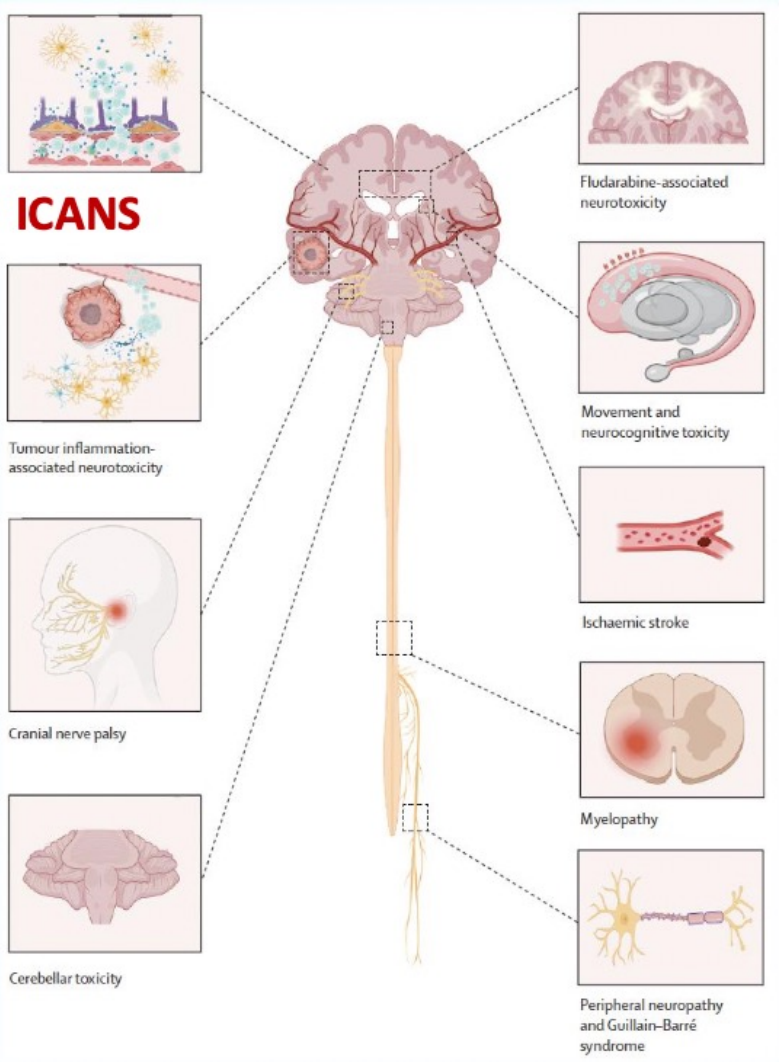
Popat R et al, ASH 2024

KARMMA-3: ide-cel combined with effective Bridging therapy can be associated with prolonged PFS

Einsele H et al, IMS 2023



Potential better safety profile when CAR-T are used earlier



CARTITUDE-1 vs CARTITUDE-4 – delayed neurological toxicity

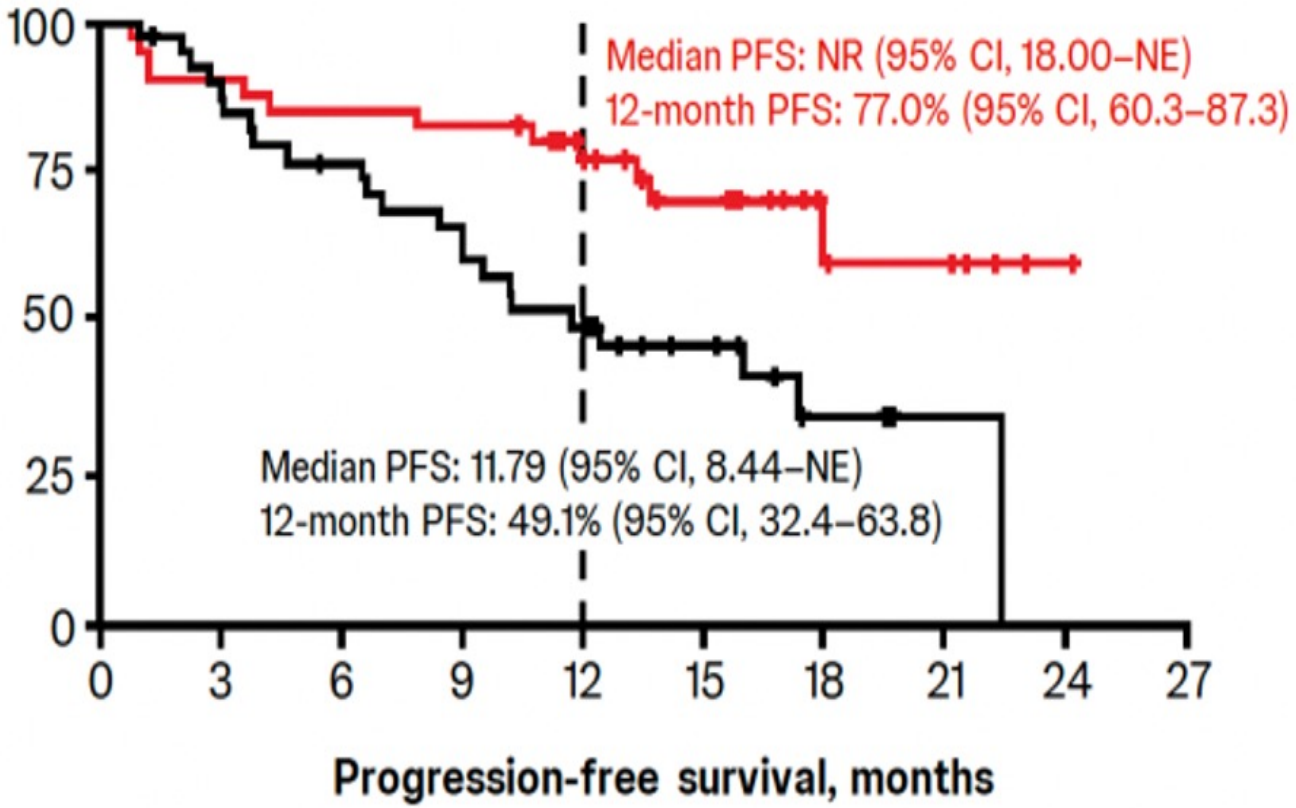
	CARTITUDE-1	CARTITUDE-4	Trend with earlier line
CRS (any grade)	95 %	76 %	↓ frequency
CRS ≥ Grade 3	4 %	1 %	↓ frequency
ICANS (any grade)	21 % *	4.5 %	↓↓ frequency
ICANS ≥ Grade 3	10 % *	0 %	↓↓ frequency
Onset of CRS (median, days)	7	8	≈ similar timing
MNT (movement & neurocognitive events)	12 % *	< 1 %	↓↓ frequency

Berdeja JG et al, Lancet 2021, Einsele H et al, EHA 2023, San Miguel J et al, NEJM 2023

TREATMENT OPTIONS FOR FUNCTIONAL HIGH RISK AT FIRST RELAPSE: CAR-T

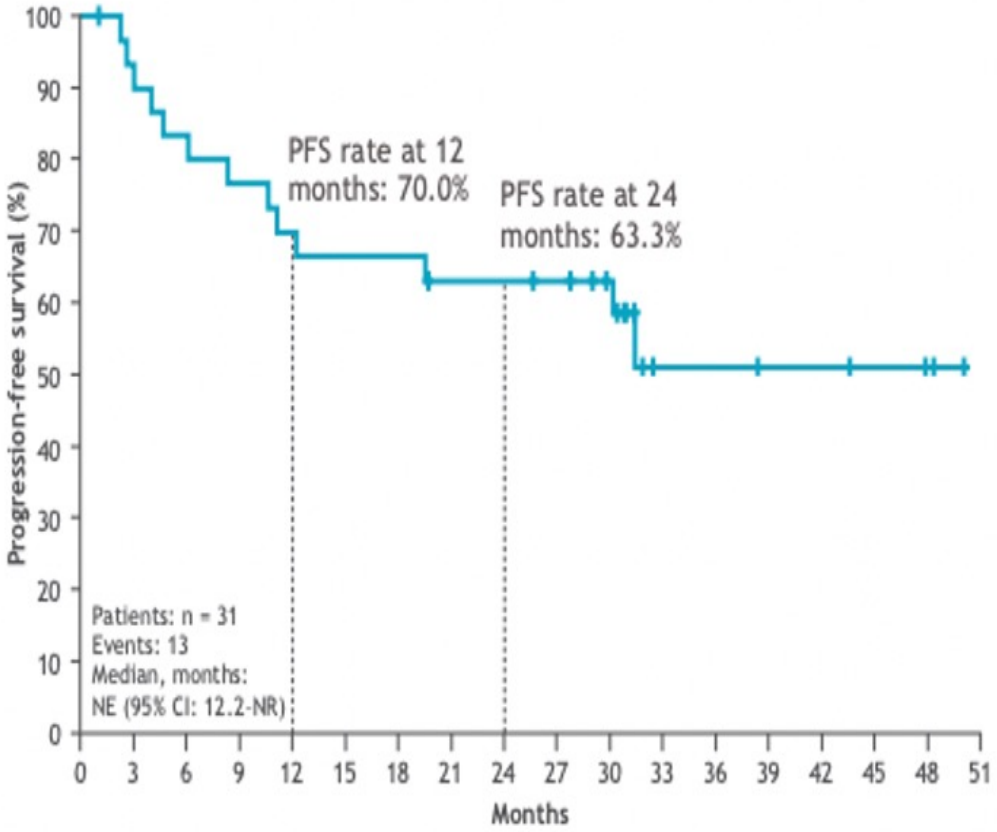
CILTA-CEL
CARTITUDE-4 subgroup analysis
Early relapse < 18months from ASCT or treatment start

Weisel K et al, EHA 2024



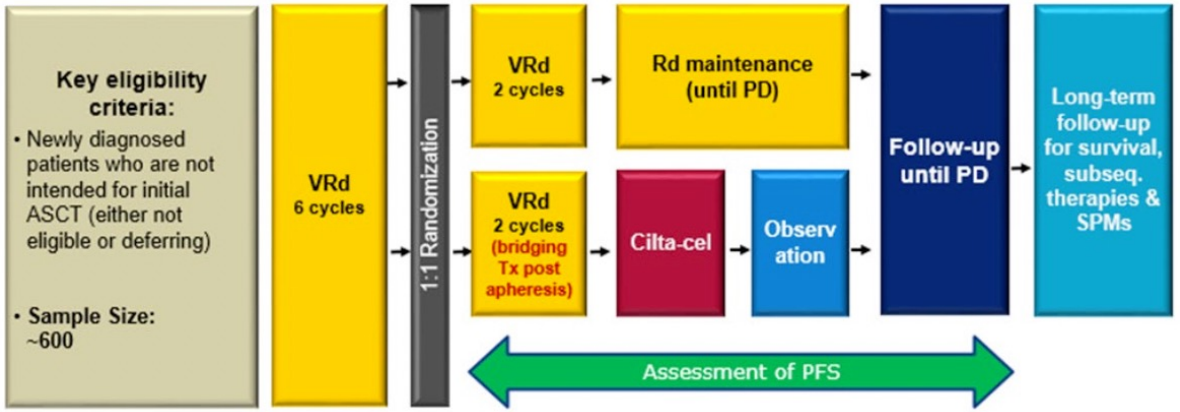
IDE-CEL
KARMMA-2 cohort 2B
Early relapse < 18months from treatment start non ASCT

Leleu X et al, EHA 2024



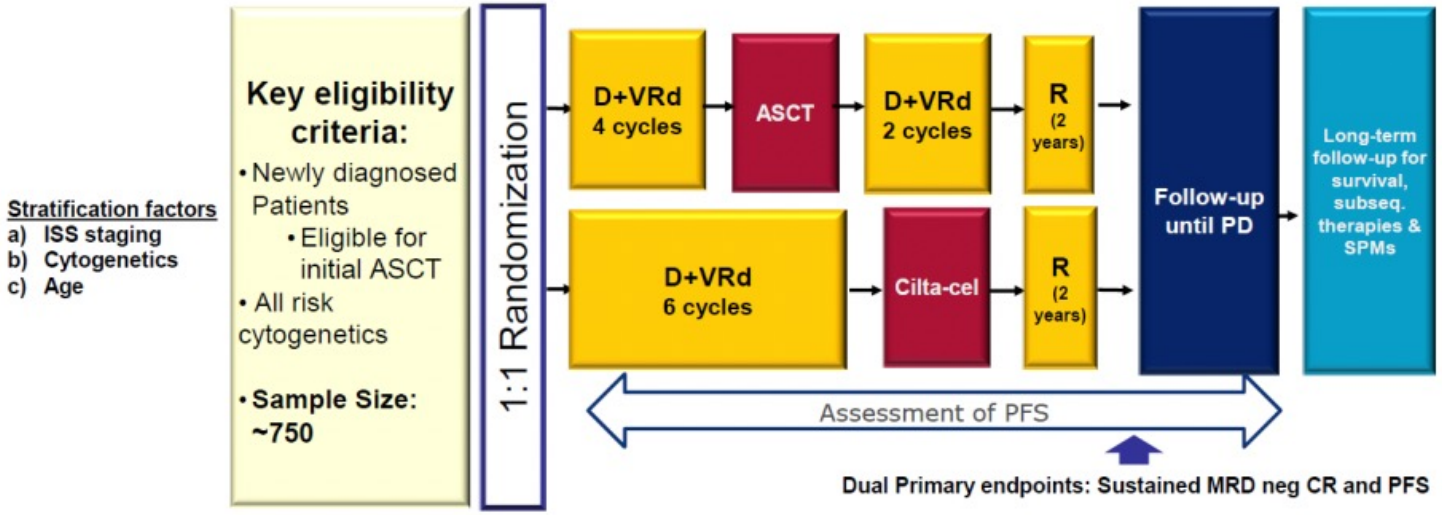
Car-T can be an option for functional high risk patients at first relapse, if available (Cilta-cel with 2nd line approval)

CARTITUDE-5: VRd Followed By Cilta-cel vs VRd Followed By Lenalidomide/Dexamethasone (Rd) Maintenance in NDMM for whom ASCT is not planned as initial therapy



CAR-T FIRST LINE

CARTITUDE-6 (EMN28) D-Vrd followed by cilta-cel vs D-Vrd followed by ASCT in transplant eligible MM



Sequence of BCMA-Targeted Therapies Impacts Efficacy Outcomes

BCMA-targeted TCEs administered to patients after prior BCMA-targeted CAR T-cell therapies[1].

	Study	*N*	ORR	CRR	PFS	DOR	Particularities/ unique toxicities
Teclistamab	Touzeau	15	53%	27%	mPFS 4.4 mo.	n.a	Dedicated MajesTEC-1 cohort
Elranatamab	Nooka	36	53%	20%	mPFS 10 mo.	n.a	Pool from clinical trials
Teclistamab	Riedhammer	21	33%	16%	mPFS 1.8 mo.	n.a	RWE, all prior CAR T-cells were ide-cel
Teclistamab	Dima	43	63%	28%	n/a	n.a	RWE, 38/42 prior CAR T-cells were ide-cel

BCMA-targeted CAR T-cell therapy administered to patients after prior BCMA-targeted TCEs or ADCs[1,2].

		Study	*N*	ORR	CRR	PFS	DOR	Particularities/ unique toxicities
TCE	**Cilta-cel**	Cohen	7	57%	14%	mPFS 5.3mo.	mDOR 8.2 mo.	Dedicated CARTITUDE-2 cohort
	Ide-cel	Ferreri	7	86%	43%	mPFS 2.8 mo.	mDOR 2.8 mo.	RWE
ADC	**Cilta-cel**	Cohen	13	62%	38%	mPFS 9.5mo	mDOR 11.5mo	Dedicated CARTITUDE-2 cohort
	Ide-cel	Ferreri	37	68%	22%	mPFS 3.2 mo.	mDOR 7.4 mo.	RWE
Prior BCMA-Targeted Therapy*	**Cilta-cel**	Sidana	33	70%	42%	mPFS 13.6 mo.	n.a	RWE (Note: shorter interval from last BCMA-targeted therapy was associated with inferior outcomes)

1. Costa LJ et al, Leukemia 2025. 2. Sidana S et al, Blood 2025

*Type of prior BCMA targeted therapy: ADC (N=16), ADC and CAR-T (N=2). ADC and BCMA TCE (N=1), BCMA TCE (N=8), BCMA CAR-T (N=6)

SUMMARY

- **Earlier disease stages are associated with better T-cell fitness, a higher proportion of memory phenotypes, and greater T-cell polyfunctionality, ultimately resulting in more potent CAR T cells and improved clinical outcomes.**

- **More effective bridging options in earlier disease settings → lower disease burden at the time of CAR-T infusion → better outcomes.**

- **Less refractory and less aggressive disease biology → better outcomes.**

- **CAR T-cell therapy as a "one-and-done" treatment offers a prolonged, treatment-free interval, preventing the disease to become refractory to conventional agents used until progression and preserving better therapeutic options at the time of CAR-T relapse.**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