POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

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CAR-T nel mieloma multiplo

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EMN
Trialist Group

Disclosures of of ELENA ZAMAGNI

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
JANSSEN						X	X
BMS						X	X
PFIZER						X	X
SANOFI						X	X
ONCOPEPTIDE						X	X
GSK						X	X
MENARINI						X	X

Current targets for CAR-T- in MM

BCMA

- BCMA is a member of the TNF receptor superfamily
- APRIL and BAFF are known ligands, leading to activation of the NF-κB pathway
- **BCMA promotes plasma cell survival**, growth, resistance to apoptosis, adhesion, and angiogenesis
- γ-secretase cleaving causes shedding of soluble BCMA
- BCMA is expressed on **malignant PCs, at low levels on normal PCs and mature B lymphocytes** and is absent in non-hematological tissues

GPRC5D

- GPRC5D is a member of the G protein-coupled receptor family with an **unknown function**
- It is highly expressed on **malignant PCs,** as well as hard **keratinized structures** (hair shaft, nail, and central region of the tongue)

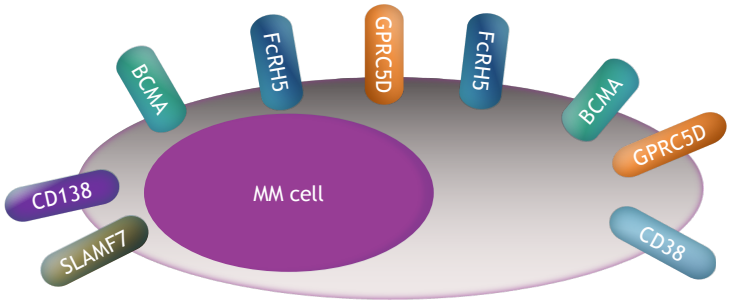
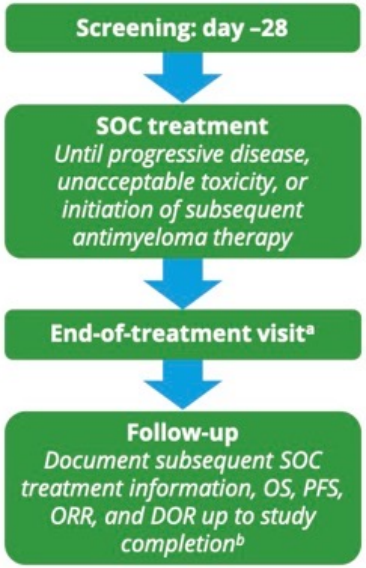
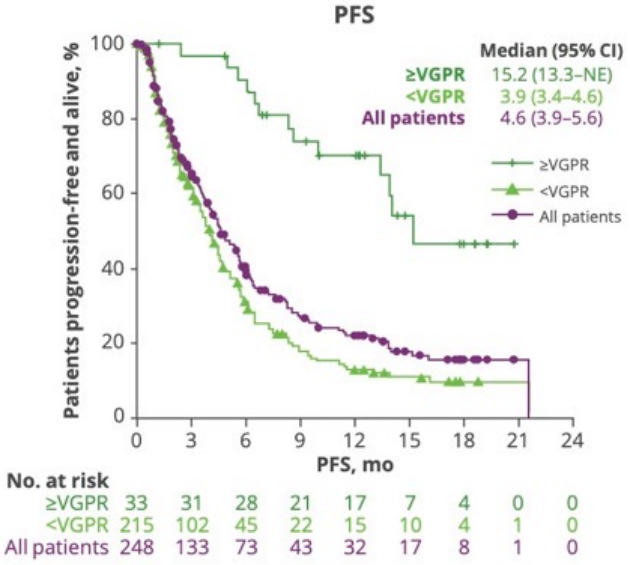


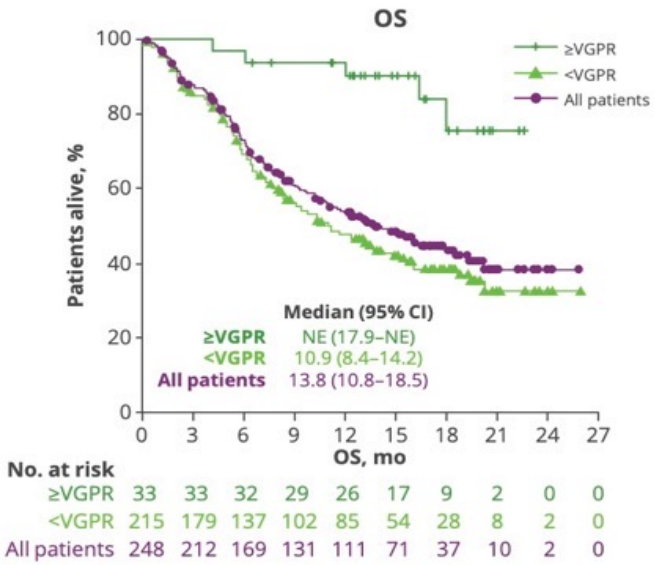
Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.
APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FcRH5, Fc receptor-like 5; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; MM, multiple myeloma; NF-κB, nuclear factor Bs; PC, plasma cell; SLAMF7, signaling lymphocytic activation molecule family member 7; TNF, tumor necrosis factor.
1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538–49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij CPM, et al. Blood Adv. 2020;5;2196-215. 5. Smith EL, et al. Sci Transl Med. 2019;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-95. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155. 8. Lancman G, et al. Blood Cancer Discov. 2021;2:423-33.

LocoMMotion: Real-life current standards of care in patients with RRMM who received ≥3 prior lines of therapy



[a]End-of-treatment visit is defined as ~30 days after completion of the last dose of the first SOC therapy used within the study. [b]End of the study is defined as 24 months after the first dose of SOC treatment for the last patient included in the study, except in cases of patient death that would end the study early.
DOR, duration of response.





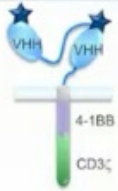
- Median age: 68 years
- Median prior lines: 4 (2–13)
- Triple-class refractory: 73.4%
- ORR: 31.5%
- mDOR: 7.7 months

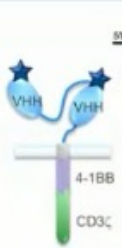
mDOR, median duration of response; NE, not evaluable; SOC, standard of care

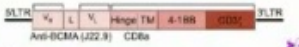
Mateos MV et al, Leukemia 2022

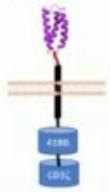
BCMA-targeting CAR-T cells

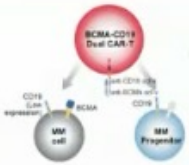
	Approved CARs		Phase 3		Academic	Alternative construct	Short manufacturing		Allo-CAR
	Ide-cel KarMMa[1] (n = 196)	Cilta-cel CARTITUDE-1[2] (n = 97)	Ide-cel KarMMa-3[3] (n = 254)	Cilta-cel CARTITUDE-4[4] (n =208)	ARI0002h[5] (n = 30)	CART-ddBCMA[6] (n = 31)	FasT CAR-T GC012F[7] (n=29)	PHE885[8] (n= 50)	ALLO-715 UNIVERSAL[9] (n = 43)
Phase	II	Ib/II	III	III	I/II	I/II	I	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA/CD19	GPRC5D	BCMA
scFv	Chimeric mouse	Chimeric llama	Chimeric mouse	Chimeric llama	Humanized	Synthetic protein	Not specified	Human	Human
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	NA	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Allogenic

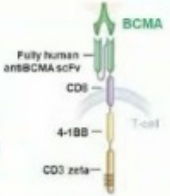


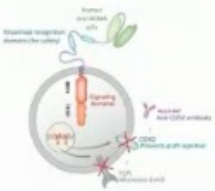












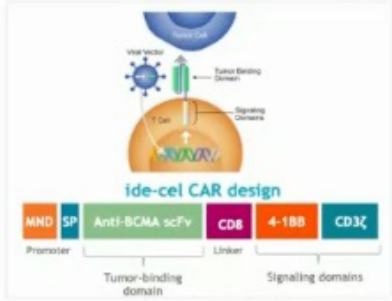
1. Munshi N, et al. ASCO 2020; 2. Usmani S, et al. ASCO 2022; 3. Rodrigues Otero, EBMT 2023; 4. Einsele H, et al. ASCO 2023; 5. Fernández de Larrea C, et al. EHA 2022; 6. Frigault MJ, et al. ASCO 2022; 7. Li C, et al. EHA 2022; 7. Du J, et al. ASCO 2022; 8. Sperling et al. ASCO 2023; 9. Huang H, et al. ASCO 2022;

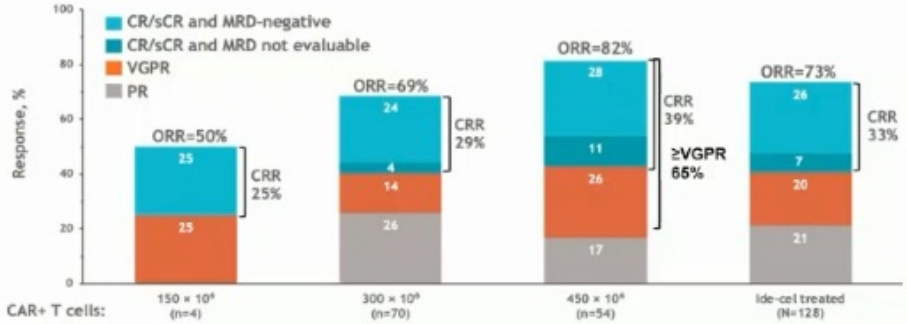
Ide-cel approval: the KarMMa trial

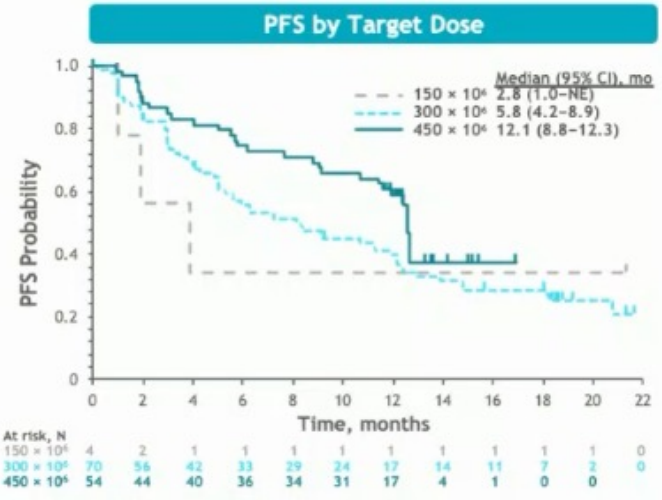
FDA approved in 2021
EMA approved in 2021

Second generation CAR-T cell, anti-BCMA murine scFv, 4-1BB costimulatory domain

KarMMa, phase 2 study (N = 128)		
Median prior lines: 6 (3–16)	84% of patients were triple-class refractory	Bridging possible Flu-Cy lymphodepletion







mOS = 24.8 mo

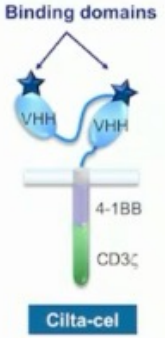
AE,* n (%)	Ide-Cel-Treated (N=128)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
CRS	107 (84)	7 (5)
Neurotoxicity	23 (18)	4 (3)

Munshi N, et al. *NEJM* 2021

Cilta-cel approval: the CARTITUDE-1 trial

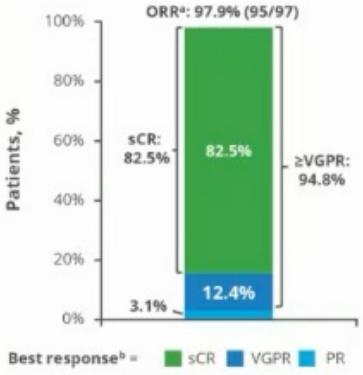
FDA approved in 2022
EMA approved in 2022

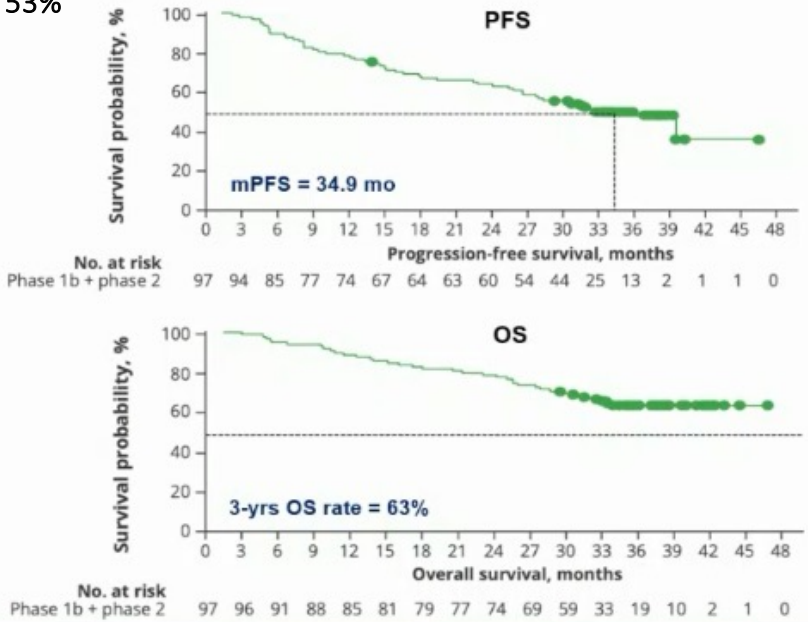
Second generation CAR-T cell, 2 anti-BCMA camelid VHH single domains, 4-1BB costimulatory domain



CARTITUDE-1, phase 2 study (N = 97)		
Median prior lines: 6 (3–18)	88% of patients were triple-class refractory	Bridging possible Flu-Cy lymphodepletion

12 mos sustained MRD rate: 53%
PFS @ 30 mos: 75%





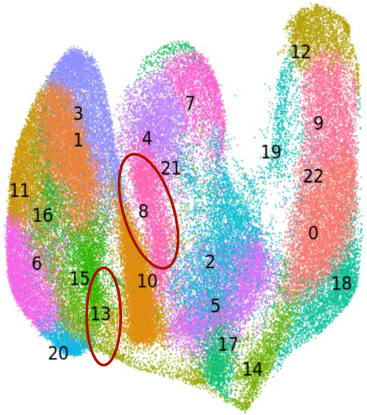
AE, n (%)	Cilta-cel-Treated (N=97)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	93 (96)	92 (95)
Anemia	79 (81)	66 (68)
Thrombocytopenia	77 (80)	58 (60)
CRS	92 (95)	6 (5)
Neurotoxicity	20 (21)	10 (10)

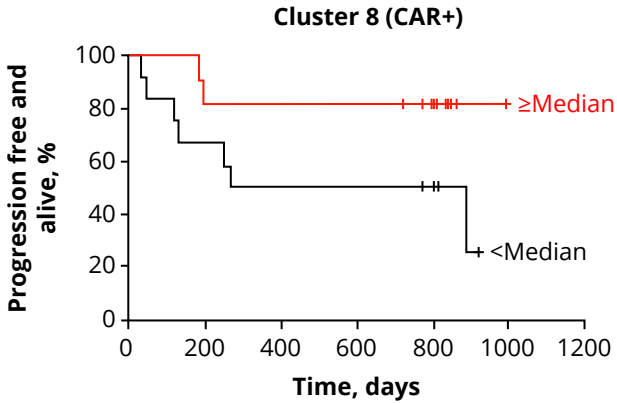
Berdeja J, et al. *Lancet* 2022;
Lin Y. et al. ASCO 2023

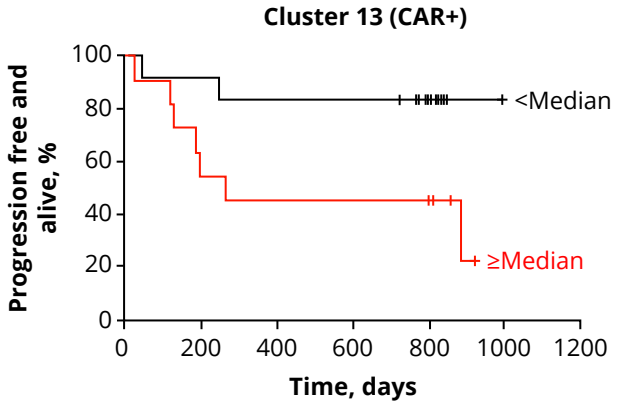
QUALITY OF CART COMPOSITION: DATA FROM CLINICAL TRIAL (CARTITUDE-1)

Longer PFS Was Associated With a CAR+CD8+ Stem Cell–Like Phenotype in the Drug Product

Cluster	Hazard ratio	*P* value	Marker	Phenotype
8	**0.62**	**0.032**	CD8+TCF7+LEF1+CCR7+	CAR+CD8+ stem cell–like T cells with ability to proliferate into T_{cm} and T_{em}
13	**1.62**	**0.006**	CD4+FOXP3+	CAR+CD4+ Treg cell–like phenotype







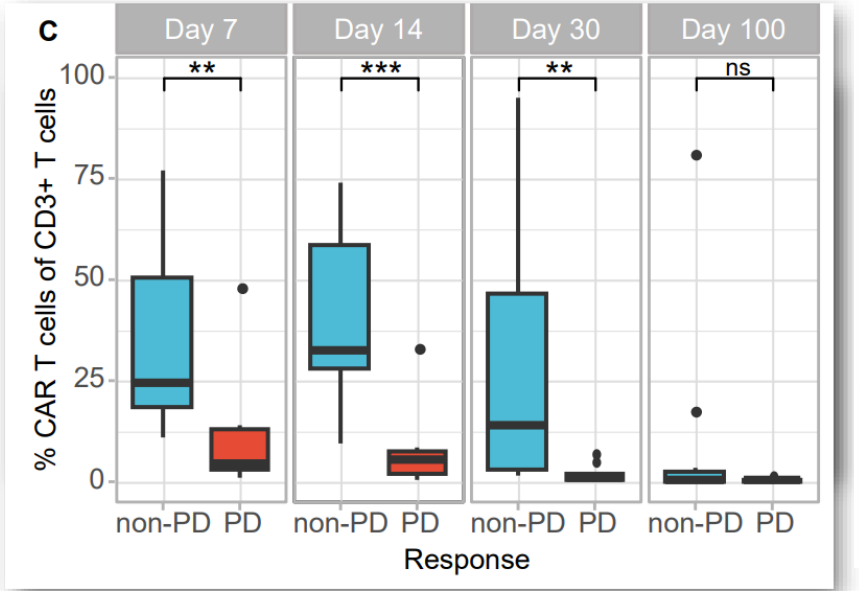
Longer PFS was directly associated with a CAR+CD8+ T-stem cell–like phenotype and inversely correlated with a CAR+CD4+ Treg cell–like phenotype in the drug product

Presented by R Montes de Oca at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA

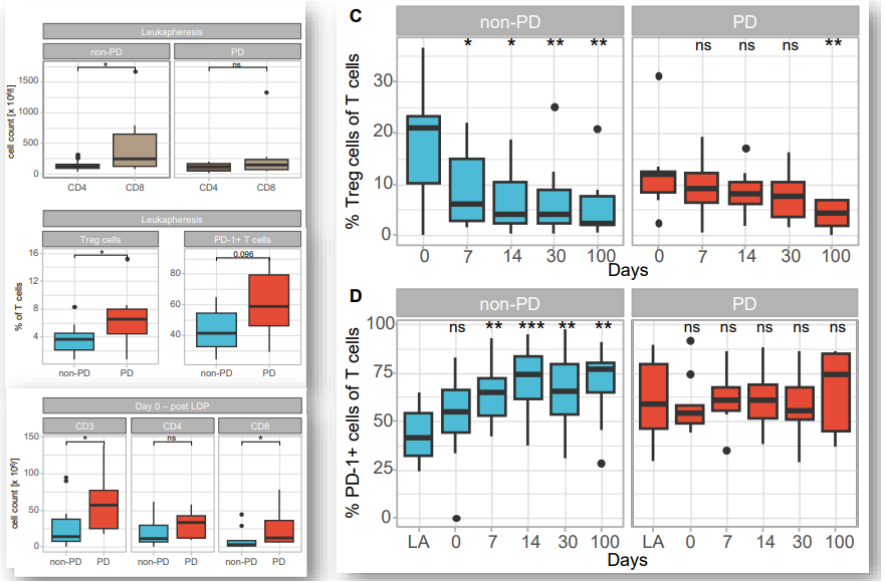
Montes de Oca R, et al. ASH 2023. Poster 2099

QUALITY OF CART COMPOSITION: data from real life (ide-cel)

Results II – Infusion and expansion



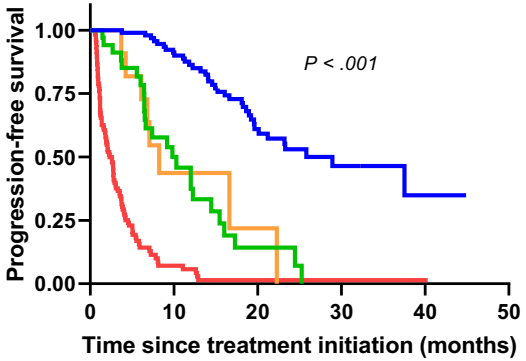
Results III – Apheresis, LDP, Tregs and PD1



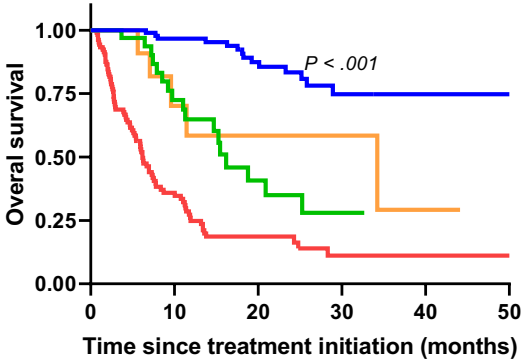
- **Real-life analysis on 25 pts treated with ide-cel: early relapse vs long-term disease control**
- **CAR-T cell expansion** is associated with response
- Differences between responders and non-responders can be identified at time of leukapheresis
- **Depletion of Tregs and increase of PD1** expression is associated with response

Merz M et al, ASH 2023

Role of MRD in RRMM pts treated with CAR T cells and TCE



Number at risk						
CR/MRD-	102	78	33	11	1	0
CR/MRD+	11	4	1	0	0	0
No CR/MRD-	34	13	2	0	0	0
No CR/MRD+	105	5	1	1	1	0



Number at risk						
CR/MRD-	102	82	47	20	5	1
CR/MRD+	11	6	3	2	1	0
No CR/MRD-	34	20	7	2	0	0
No CR/MRD+	105	30	11	4	2	1

Group	Median PFS
CR/MRD-	29
CR/MRD+	8
No CR/MRD-	10
No CR/MRD+	2

Group	Median OS
CR/MRD-	NR
CR/MRD+	34
No CR/MRD-	16
No CR/MRD+	6

Prolonged survival in patients achieving CR and undetectable MRD

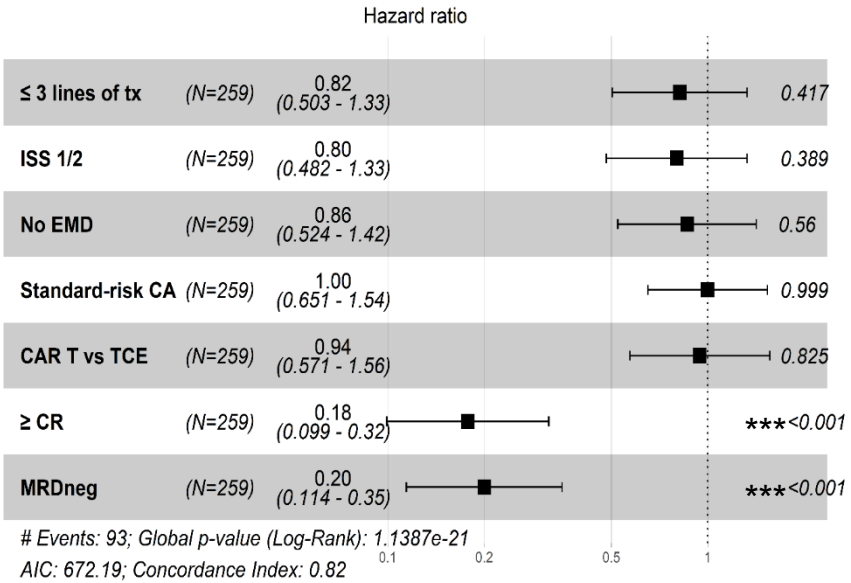
- Retrospective real-life analysis of 259 patients with RRMM treated with TCR therapies in Spain between 2017-203
- Median follow-up, 11 months

Zabaleta A et al, ASH 2023

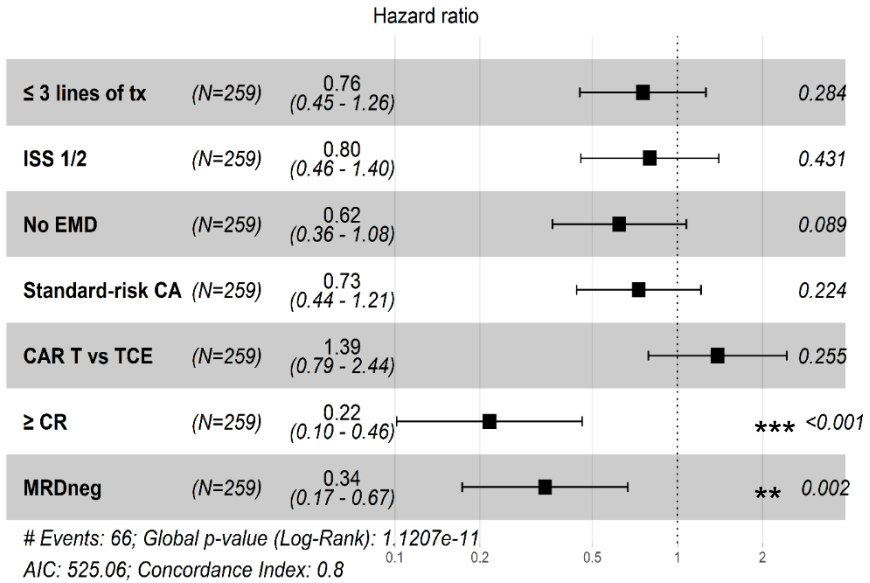
CR and MRD status are the most relevant prognostic factors

Multivariate analysis

Progression-free survival



Overall survival

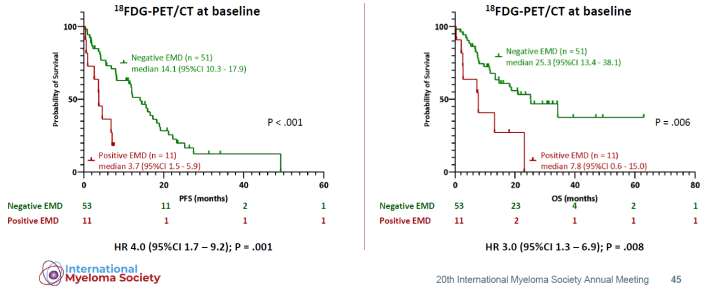


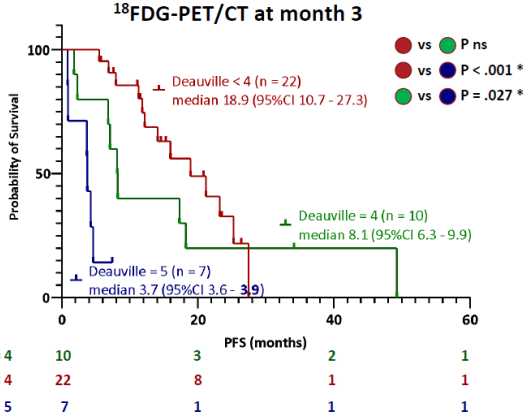
- In contrast to newly-diagnosed MM, achieving CR does matter in MRD negative RRMM patients with respect to response durability after CAR T cells and TCE

Definition of PET imaging response in patients receiving CARTs

Association of basal ^{18}FDG-PET/CT variables with progression-free (PFS) and overall (OS) survival

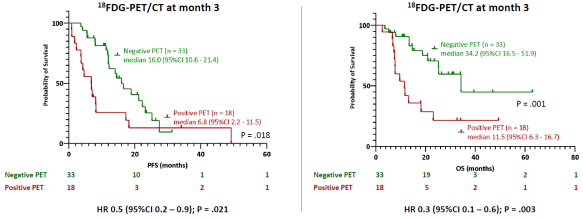
At baseline **EMD** was the only variable associated with inferior PFS and OS





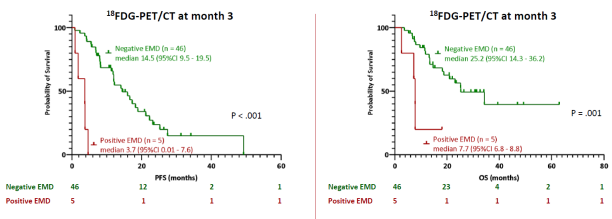
Association of ^{18}FDG-PET/CT scan status (positive or negative) before and after therapy with PFS and OS survival

A negative scan at 3 months was associated with both improved PFS and OS



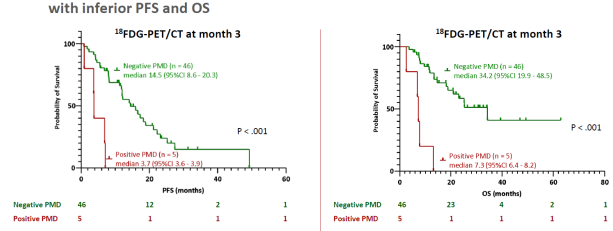
Association of ^{18}FDG-PET/CT variables after therapy with PFS and OS

The presence of **EMD** at 3 months was still associated with worse PFS and OS



Association of ^{18}FDG-PET/CT variables after therapy with PFS and OS

Conversely to basal scans, persistent hypermetabolic **PMD** at month 3 was associated with inferior PFS and OS



- Retrospective analysis on **62 pts** treated in Spain with anti-BCMA CARTs (2018-2023), studied by FDG PET/CT at **baseline, @ 1 mos (92%) and @ 3 mos (82%)**
- 79% PET pos baseline, 58% @ 1 mos, 35% @ 3 mos
- **No role on PFS of early 1 mos PET**

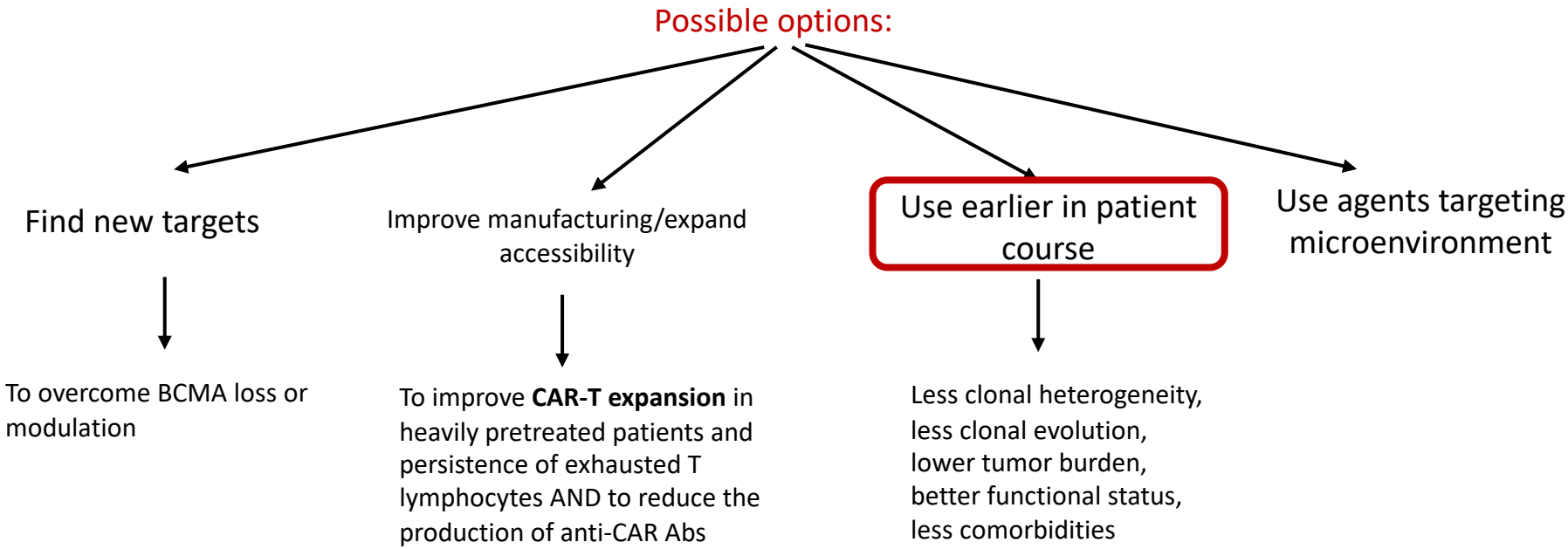
Tamariz-Amador LE et al, IMS Athens 2023

Outcomes of BCMA-Directed CART Therapy in Patients with RRMM with EMD

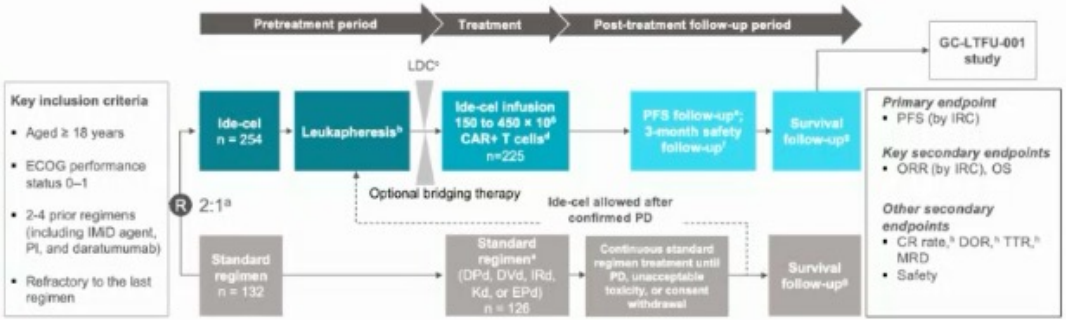
- Real life analysis on 132 pts treated with ide-cel and cilta-cel as per SOC
- 48% (64 pts) previous/current EMD prior to CART; pair matched with rest of population
- No difference in toxicities (CRS, ICANS, infections)
- No difference in response rate/CR rate
- **Significantly shorter PFS and OS** ($p = 0.02$ and 0.03, respectively)
- Studies on mechanisms of resistance and influence of extra-medullary microenvironment on relapse/resistance currently on-going

Dima D, et al ASH 2023

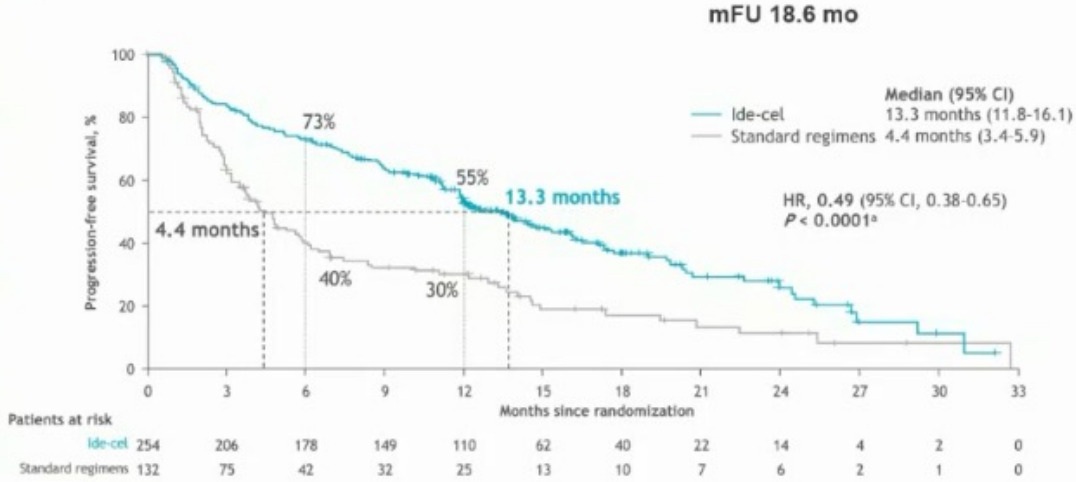
Further developments in CAR-Ts use in MM



KarMMa-3, phase 3 trial (2-4 prior lines)



Characteristic	Ide-cel (n = 254)	Standard regimens (n = 132)
Median (range) age, years	63 (30-81)	63 (42-83)
Sex, male, n (%)	156 (61)	79 (60)
Median (range) time from diagnosis to screening, years	4.1 (0.2-21.8)	4.0 (0.7-17.7)
High tumor burden, n (%)[a]	71 (28)	34 (26)
Extramedullary disease, n (%)[b]	61 (24)	32 (24)
High-risk cytogenetics, n (%)[c]	107 (42)	61 (46)
del(17p)	66 (26)	42 (32)
t(4;14)	43 (17)	18 (14)
t(4;16)	8 (3)	4 (3)
Refractory status, n (%)		
IMiD agent refractory	224 (88)	124 (94)
PI refractory	189 (74)	95 (72)
Daratumumab refractory[a]	242 (95)	123 (93)
Double-class refractory[b]	169 (67)	91 (69)
Triple-class refractory[c]	164 (65)	89 (67)

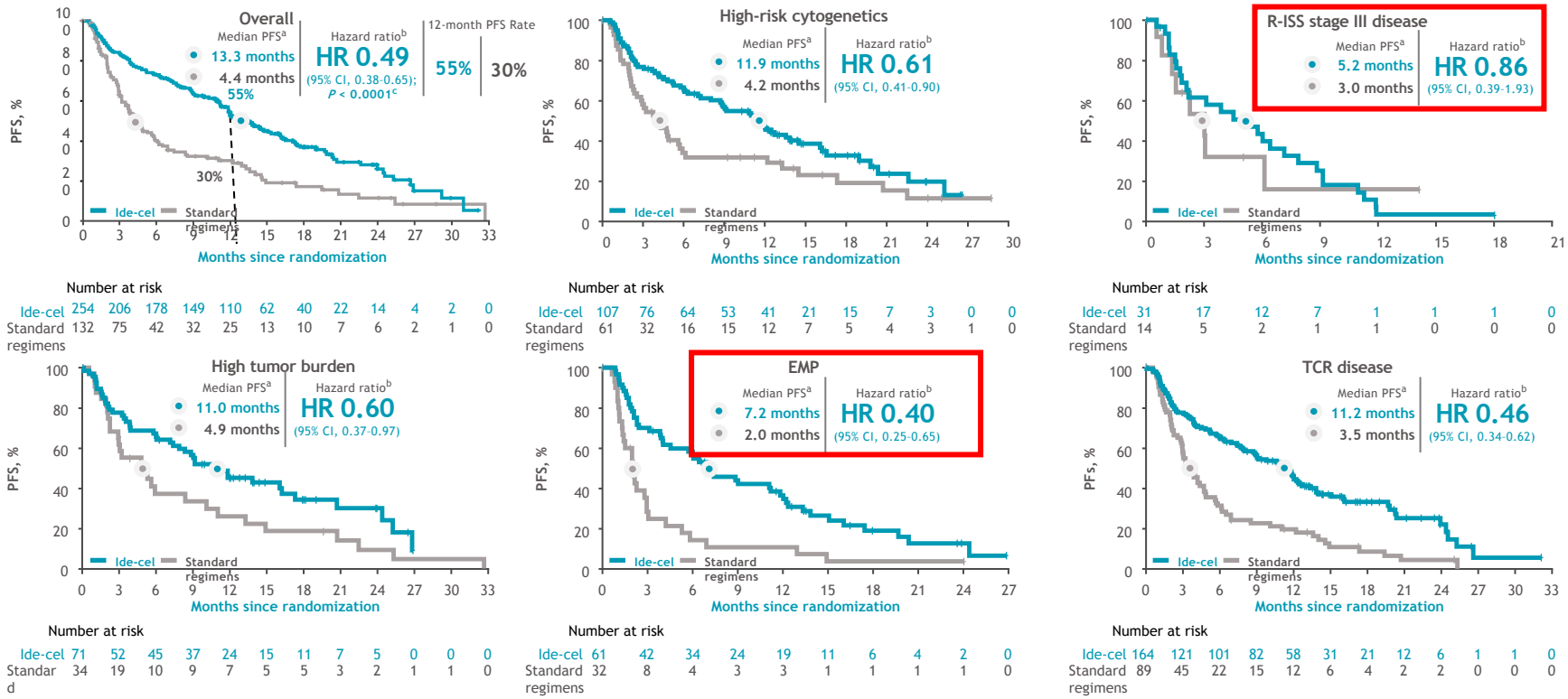


All-cause AEs occurring in ≥ 20% patients, n (%)	Ide-cel (n = 250)			Standard regimens (n = 126)		
	Any grade	Grade 3/4	Grade 5	Any grade	Grade 3/4	Grade 5
Any	248 (99)	233 (93)	36 (14)	123 (98)	94 (75)	8 (6)
Other						
Infections	146 (58)	61 (24)	11 (4)	68 (54)	23 (18)	3 (2)
Upper respiratory tract infections	29 (12)	4 (2)	0	9 (7)	0	0
Pneumonia	26 (10)	18 (7)	2 (1)	9 (7)	5 (4)	0

	Ide-cel (n = 225)
CRS,[a] n (%)	
Any grade	197 (88)
Grade 3/4	9 (4)
Grade 5	2 (1)
iINT,[c] n (%)	
Any grade	34 (15)
Grade 3/4	7 (3)
Grade 5	0

Giralt et al. ASTCT 2023, Rodrigues Otero et al. *NEJM* 2023

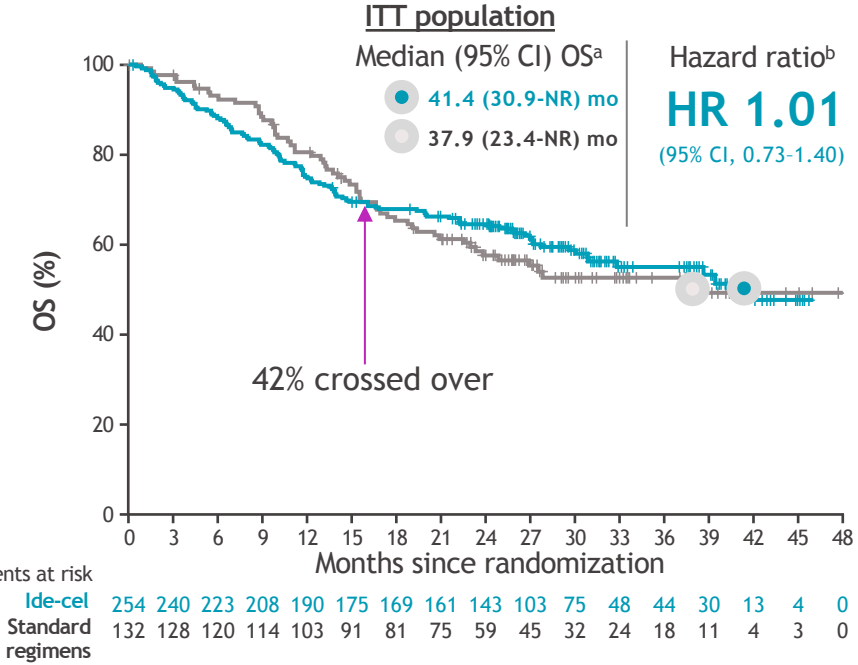
Progression-free survival (ITT and high-risk subgroups)

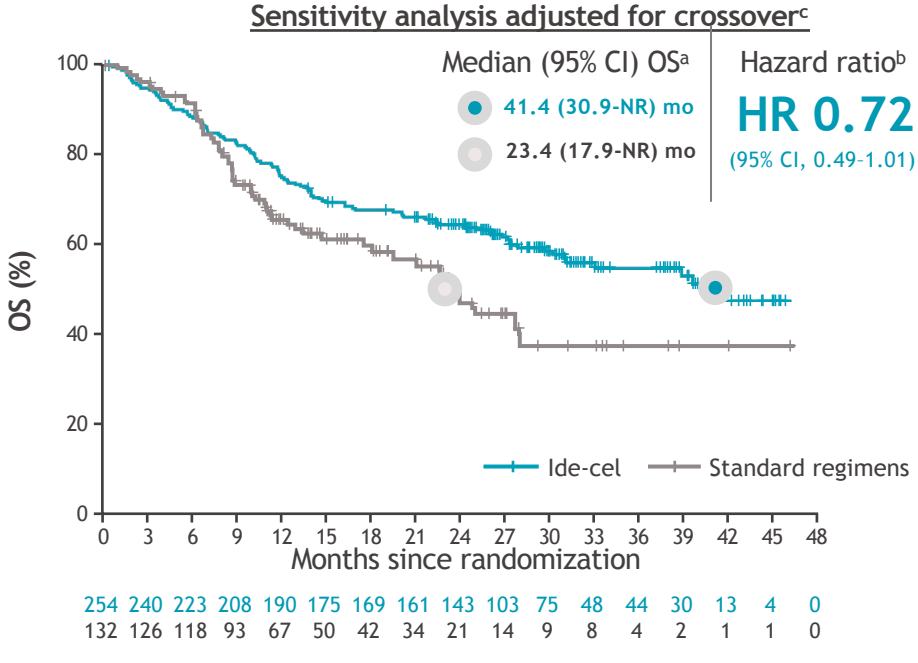


Median PFS was longer in patients treated with ide-cel vs standard regimens in the overall population and high-risk subgroups; interpretation in patients with R-ISS stage III disease was limited due to small subgroup size

PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion.
PFS based on IMWG criteria per IRC. [a]Based on Kaplan-Meier approach; [b]Unstratified HR based on univariate Cox proportional hazard model. CI is two-sided; [c]Based on stratified log-rank test. IMWG, International Myeloma Working Group. 1. Rodríguez-Otero P, et al. *N Engl J Med* 2023;388:1002-1014.

OS analysis confounded by substantial crossover



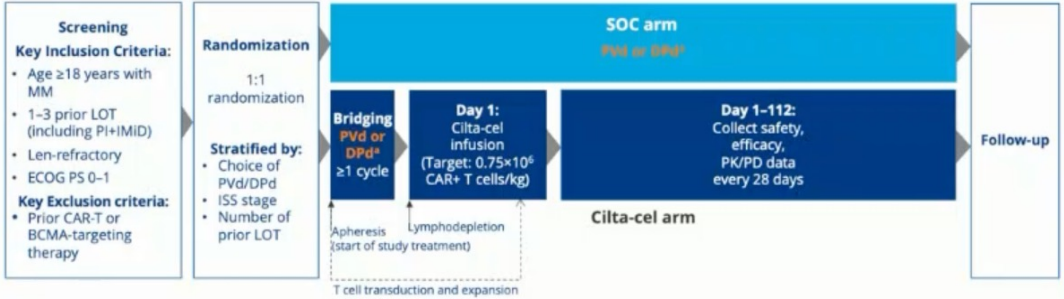


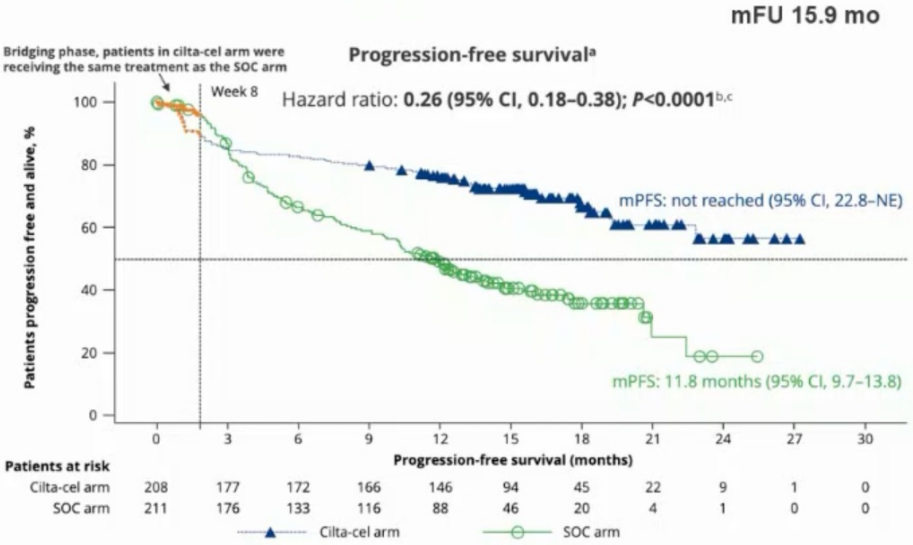
More than half of patients in SOC arm received ide-cel as subsequent therapy upon PD, most of them within 3-16 mos from randomization

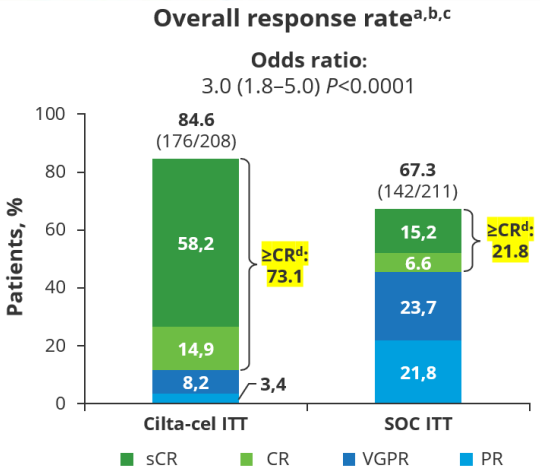
Prespecified crossover-adjusted analysis shows OS benefit of ide-cel

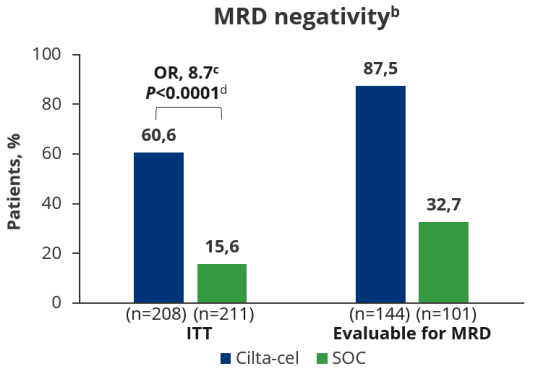
Early deaths in ide-cel arm occurred in pts with multiple high-risk features, due to PD, and mostly in patients who never received ide-cel (value of bridging therapy)

CARTITUDE-4, phase 3 trial (1 to 3 prior lines)





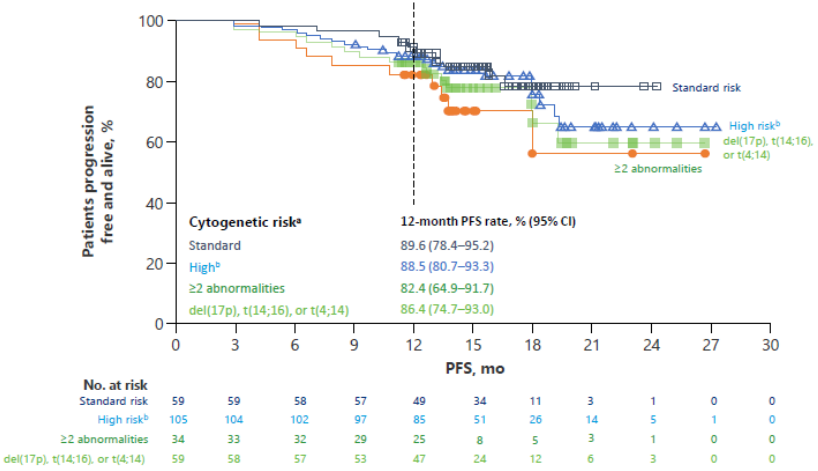


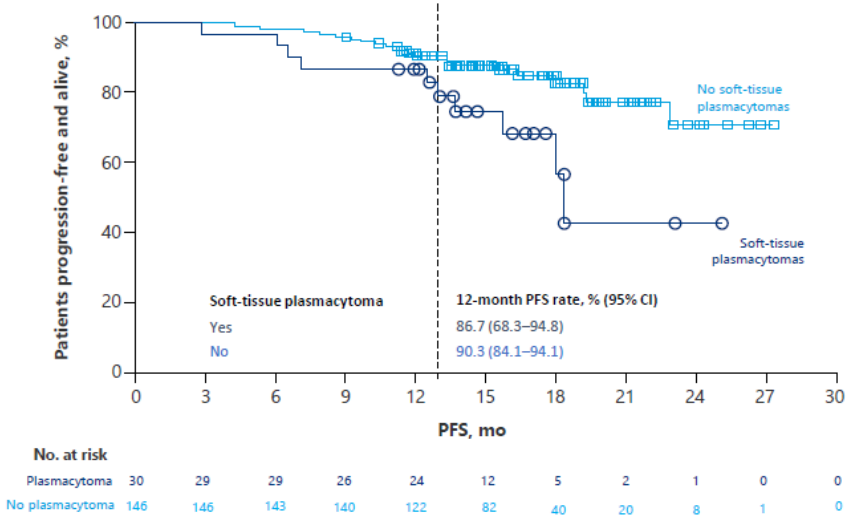


San Miguel J et al, NEJM 2023

Dhakal et al. ASCO 2023

CARTITUDE-4 As-Treated Population:
The 12-Month PFS Rate in Patients With High-Risk Cytogenetics and EMD





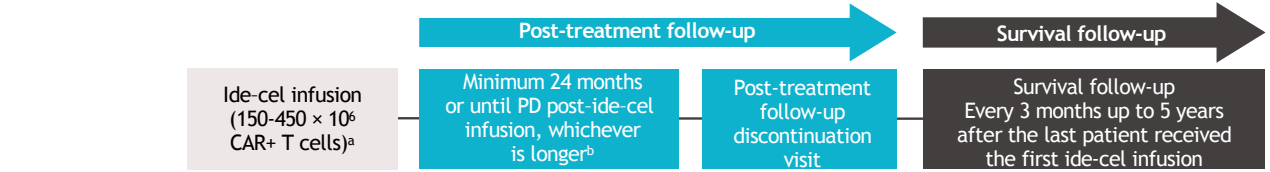
Manier S et al, IMS Athens, 2023

NOT Two of the Same Kind

	CARTITUDE-4[1]	KARMMA-3[2]
LOT eligibility	1-3	2-4
Exposure eligibility	IMiD and PI	IMiD, PI, anti-CD38
Refractoriness eligibility	Lenalidomide	Last line
Age	61.5	63
Median prior LOT	2	3
Refractory to anti-CD38	24%	95%
Refractory to IMiD	100%	88%
Triple-class refractory	14%	65%
t(4;14), t(14;16), or del(17p)	35%	42%
Extramedullary plasmacytoma	21%	24%
Carfilzomib allowed control arm	No	Yes
CAR T on control arm after PD	No	Yes
ORR of control arm	67%	42%
mPFS of control arm (mo)	11.8	4.4
HR for PFS (95% CI)	0.26 (0.18-0.38)	0.49 (0.38-0.65)

1. San-Miguel J, et al. N Engl J Med. 2023;389:335-347; 2. Rodriguez-Otero P, et al. N Engl J Med. 2023;388:1002-1014.

KarMMa-2 cohort 2: ide-cel for "functional" HR MM



Cohort 2 (N = 99)
Clinical high-risk MM (1 regimen)

Cohort 2a (n = 37)
Early relapse (PD < 18 months from front-line therapy including ASCT)

Cohort 2b (n = 31)
Early relapse (PD < 18 months from front-line therapy without ASCT)

Cohort 2c (n = 31)

Key inclusion criteria
- **Inadequate response (< VGPR; excluding PD) 70-110 days post-ASCT (single/tandem)**
- ≥ 18 years of age
- Measurable disease[c]
- Received ≥ 3 cycles of induction therapy[d]
- ECOG performance status score ≤ 1

Primary endpoint
Cohort 2c: **CRR (CR and sCR;** by investigator per IMWG criteria)

Secondary endpoints
Cohort 2c: ORR, VGPR rate, TTR, DOR, PFS, TTP, OS, safety, PK, immunogenicity (anti-CAR antibody response), HRQoL

Exploratory endpoints
Cohort 2c: MRD, biomarkers

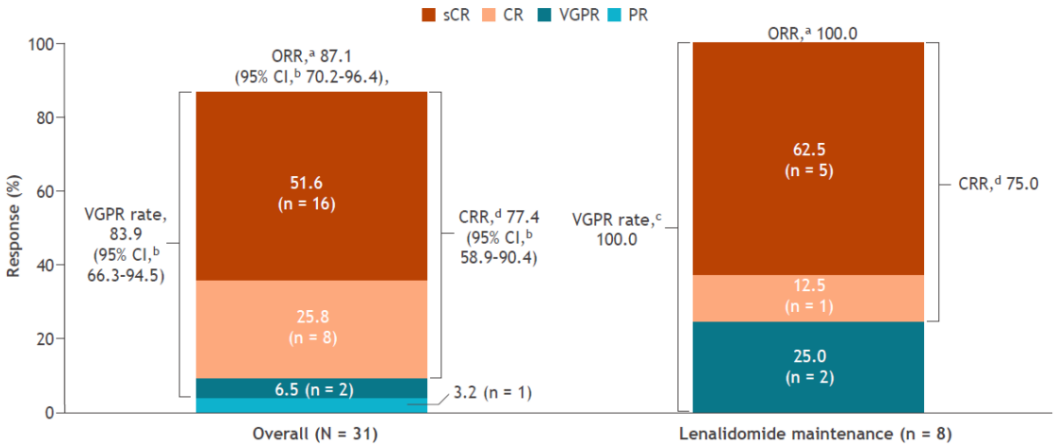
- Efficacy and safety were analyzed in all patients who received ide-cel

[a]After lymphodepletion (cyclophosphamide 300 mg/m² + fludarabine 30 mg/m² × 3), patients received a single infusion of ide-cel at a range of 150-450 × 10⁶ CAR+ T cells (up to an additional 20%; 20% over the protocol-specified dose constituted overdose); [b]**At investigator discretion, patients could receive maintenance treatment post-infusion;** [c]Measurable disease determined by M protein (serum protein electrophoresis ≥ 0.5 g/dL or urine protein electrophoresis ≥ 200 mg/24 hours) and/or light chain MM without measurable disease in serum or urine (serum immunoglobulin free light chain ≥ 10 mg/dL and abnormal serum immunoglobulin κ:λ free light chain ratio); [d]Must contain a PI, an IMiD® agent, and dexamethasone.

ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; CR, complete response; CRR, complete response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; sCR, stringent complete response; TTP, time to progression; TTR, time to response; VGPR, very good partial response.

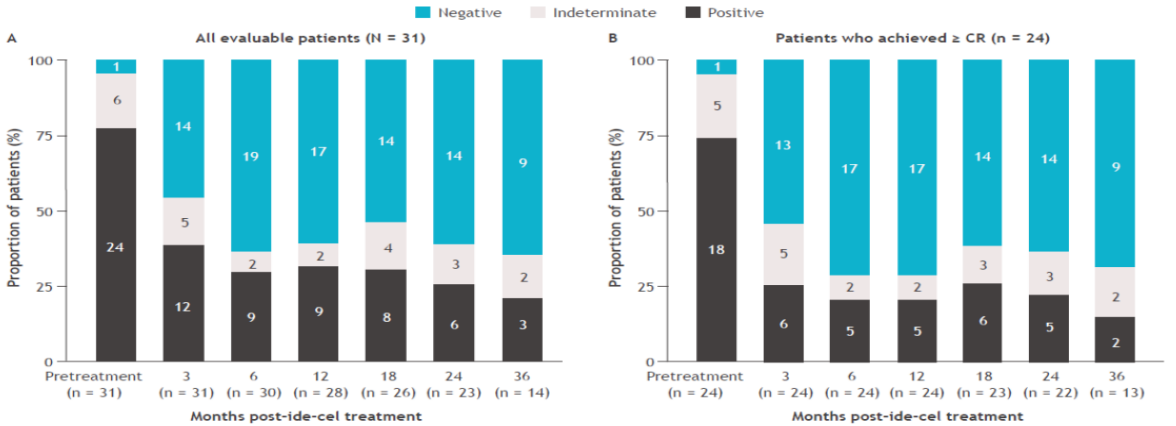
Dhodapkar M et al, ASH 2023

Best ORR and MRD in cohort 2c



- With a **median follow-up of 39.4 months**, median DOR and PFS NR
  - **36 months DOR 81%, PFS 77%**
  - **12 and 24 months sustained MRD 71% and 64%**

KARMMA-9 phase III R trial ide-cel vs len currently on-going



Dhodapkar M et al, ASH 2023

Longer-Term Findings From CARTITUDE-2 in Different Early Treatment Settings

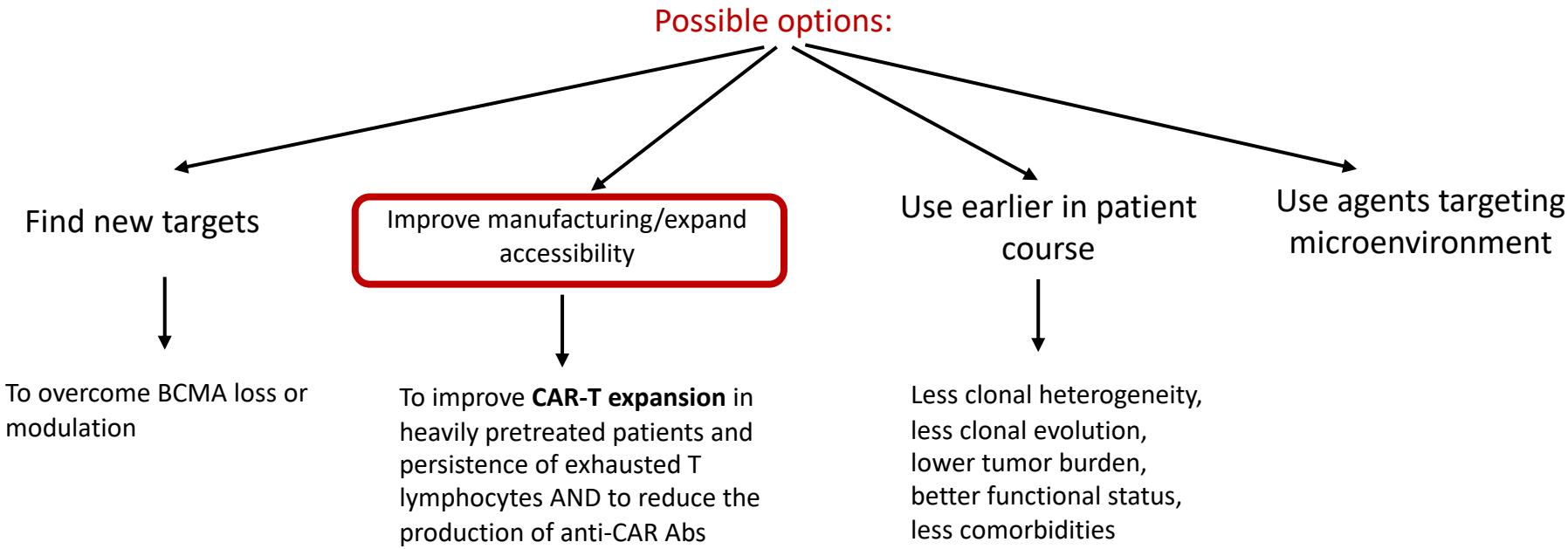
Updated Efficacy: Patients Receiving 1-3 Prior Lines of Therapy (Cohort A) and Those With Early Relapse After 1L Treatment (Cohort B)[1]

- Patients treated with cilta-cel in earlier LOT in cohort A and B experienced deep and durable responses
- No new CAR-T–related safety signals, except for 1 additional CAR-T cell neurotoxicity in cohort B, were reported

	Cohort A (N = 20)	Cohort B (N = 19)
Follow-up (mo), median (range)	29.9 (3.3-35.6)	27.9 (5.2-32.1)
Overall MRD negativity (10^{-5}), n (%)	17 (100)	14 (93.3)
Sustained MRD negativity ≥6 mo (10^{-5}), n (%)	8 (40.0)	10 (52.6)
Sustained MRD negativity ≥12 mo (10^{-5}), n (%)	7 (35.0)	7 (36.8)
ORR, % (95% CI)	95.0 (75.1-99.9)	100.0 (82.4-100)
sCR, % (95% CI)	85.0 (62.7-96.8)	73.7 (48.8-90.9)
CR, % (95% CI)	5.0 (0.1-24.9)	15.8 (3.4-39.6)
VGPR, % (95% CI)	5.0 (0.1-24.9)	10.5 (1.3-33.1)
PR, % (95% CI)	0	0
DOR (mo), median (95% CI)	NE (23.4-NE)	NE (23.7-NE)
24-mo DOR rate, % (95% CI)	73.3 (47.2-87.9)	70.5 (42.5-86.7)
PFS (mo), median (95% CI)	NE (12.9-NE)	NE (22.6-NE)
24-mo PFS rate, % (95% CI)	75.0 (50.0-88.7)	73.3 (47.2-87.9)
OS (mo), median (95% CI)	NE (21.9-NE)	NE (NE-NE)
24-mo OS rate, % (95% CI)	75.0 (50.0-88.7)	84.2 (58.7-94.6)

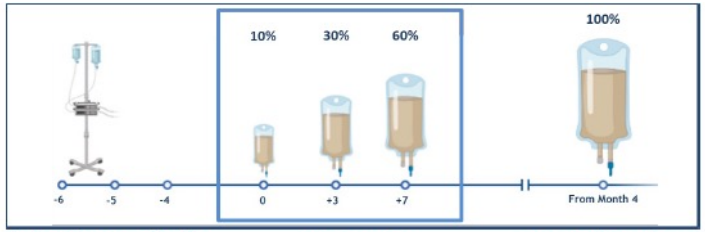
1. Hillengass J et al. ASH 2023. Abstract 1012.

Further developments in CAR-Ts use in MM

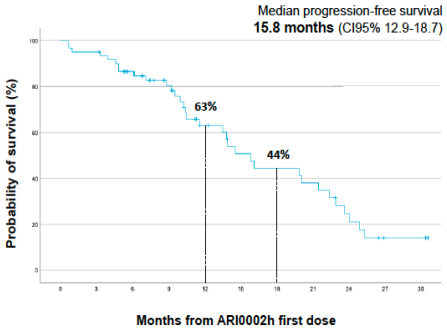


Ari0002h: BCMA-CART in RRMM patients: academic experience

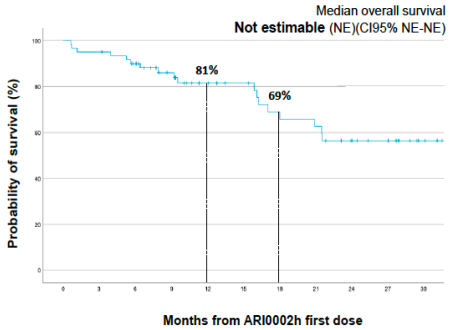
- **60 RRMM pts** after a median of 3PL, 18% EMD, TCR 59%
- **Manufacturing process: 10 days**. Median turnaround time, defined as days from apheresis reception to product liberation, was 41 days.
- Infusion was **fractionated 10-30-60% to mitigate toxicity**
- Second dose 4 months after the first infusion



Progression-free survival



Overall survival



Median follow-up **23.1 months** (95%CI 9.2-37.1)

- Median PFS in:
  - TCR: 14.5 months
  - HRCA: 10.4 months
  - EMD: 6.1 months
- None of the pts lost BCMA at relapse
- 32% of patients relapsed and CAR-T was detectable

	Grade 1	Grade 2	Grade 3–4
Cytokine release syndrome	15/24 (63%)	9/24 (38%)	0
Immune effector cell-associated neurotoxicity syndrome	0	0	0
Infusion reaction	1/30 (3%)	0	0
Tumour lysis syndrome	0	1/30 (3%)	0
Persistent cytopenias	0	0	20/30 (67%)

Data are n (%). Adverse events of special interest are depicted per MedDRA preferred term.

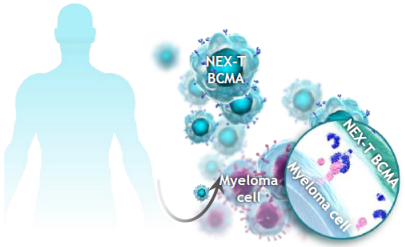
The academic humanised BCMA CAR-T overcomes basically all challenges we have with CAR-T cells: costs, affordability and manufacturing timing

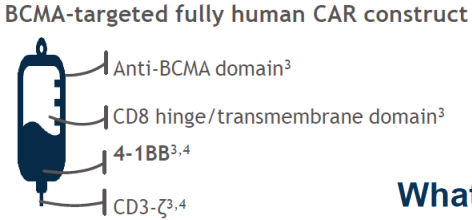
Oliver-Caldés A, et al Lancet Oncology 2023

«Next generation» anti-BCMA CART

CC-98633/BMS-986354 is a **BCMA CAR T-cell** drug product that contains a fully **human CAR construct** and is **manufactured** using the **NEX-T™ process** (shorten manufacturing and improved potency)

- enriched in **less-differentiated** memory subtypes, composed primarily of **naive-like** and **central memory CAR T** cells, and fewer effector and terminally differentiated CAR T cells
- has ~10-fold **increased proliferative capacity**
- has **superior tumor control** at equivalent CAR T cell dose





NEX-T and T-Charge Platforms:

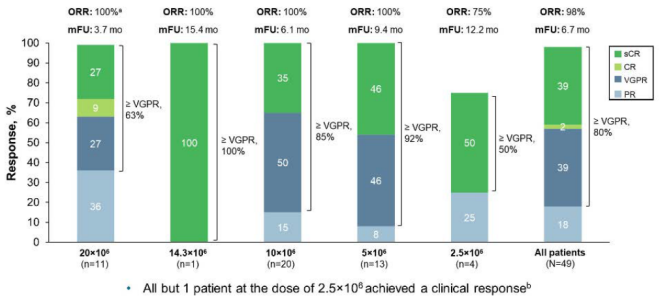
BMS986354 and Durca-cel

Costa L et al, ASH 2022

What if CAR-T Could Be Manufactured Faster?

Phase 1 Study Results of Durcabtagene Autoleucel , a T-Charge Manufactured BCMA-Directed CAR-T Cell Therapy, for Patients With RRMM[1]

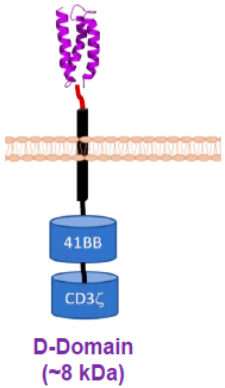
- Durcabtagene autoleucel is manufactured using the T-Charge platform
- Reduces ex vivo culture time to about 24 hours and takes <2 days to manufacture
- Relies entirely on in vivo expansion after CAR-T cell infusion



• All but 1 patient at the dose of 2.5×10^8 achieved a clinical response[b]

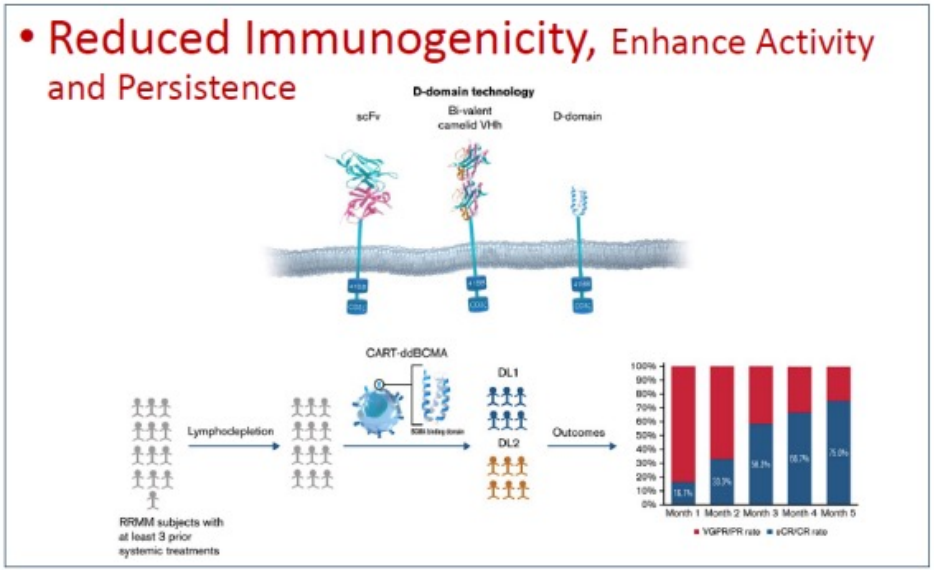
1.Sperling AS et al. ASCO 2023. Abstract 8004.

ANITO-CEL: Phase 1/2 Study of CART-ddBCMA for the Treatment of Patients with RRMM



D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

Size	Small D-Domain construct facilitates high transduction efficiency, CAR positivity, and CAR density on the T-cell surface[2-4]
Stability	Rapid D-Domain folding, lack of disulfide bonds, and a hydrophobic core enables stability at and beyond physiologic conditions[5,6]
Structure	Due to small size and compact structure, D-Domain CARs have a low risk of tonic signaling[6] and potentially more efficient Multiple Myeloma cell killing



Anito-cel utilizes a novel, synthetic, compact and stable **D-Domain binder**

D-Domain facilitates high CAR surface expression, low risk of "basal, tonic" signaling

Recommended Phase 2 Dose selected as 115±10 million CAR+ T cells

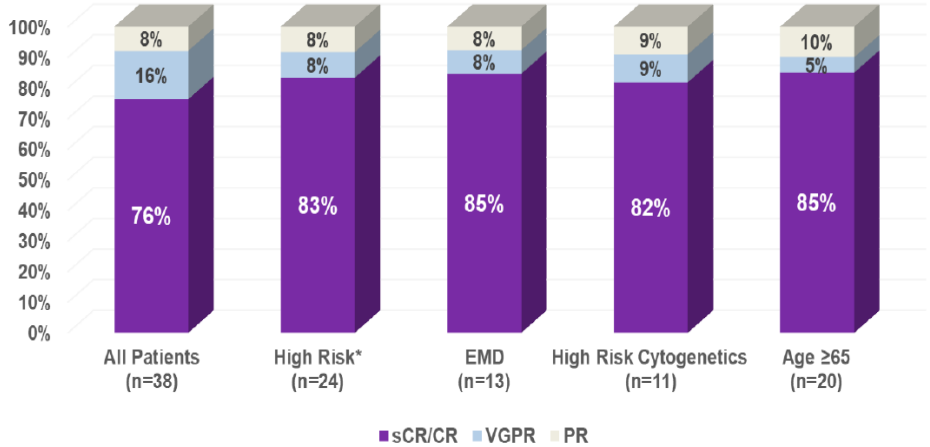
- **38 RRMM patients** all of them TCR received two dose levels of Anito-cel
- **Median number of prior lines: 5**
- EMD: 34%; ISS III: 18%; High tumor burden: 24%
- 68% of patients received bridging therapy

Frigault M, et al. ASH 2023 (Abstract No. 1023 – oral presentation)

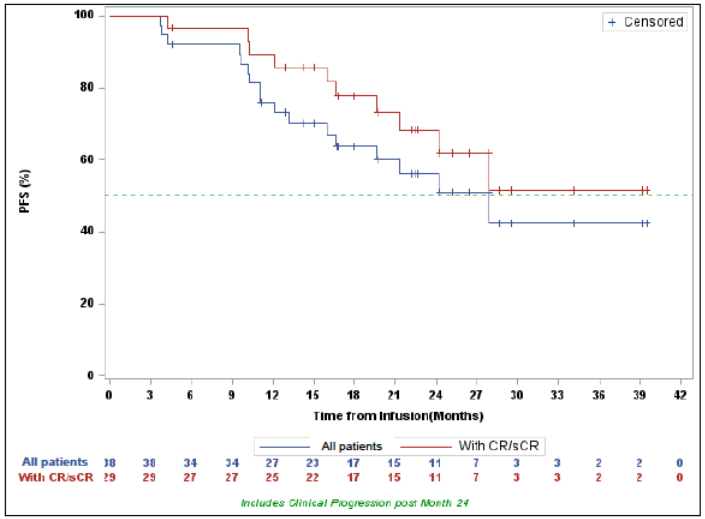
ANITO-CEL: Phase 1/2 Study of CART-ddBCMA for the Treatment of Patients with RRMM

Anito-cel Phase 1 Results: Best Overall Response

All Patients & High-Risk Sub-Groups



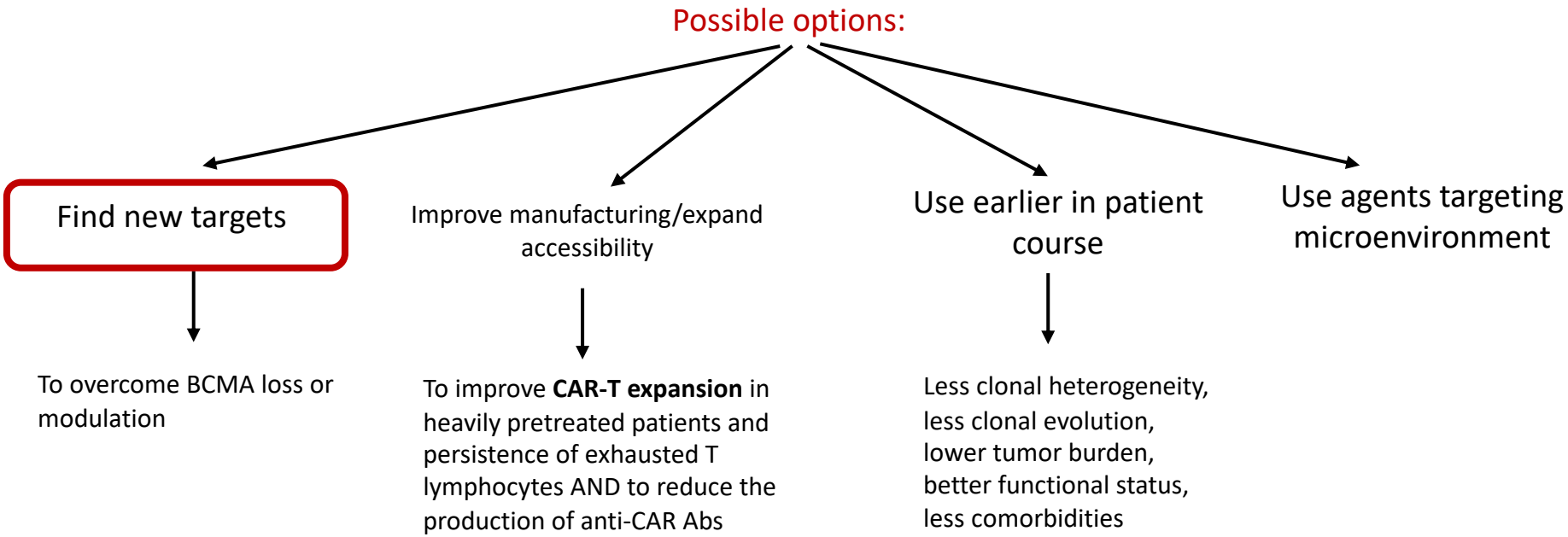
PFS (median f/u: 26 m)



- Median PFS for all pts has not been reached
- 89% (25/28) evaluable patients reached MRD-ve

Frigault M, et al. ASH 2023 (Abstract No. 1023 – oral presentation)

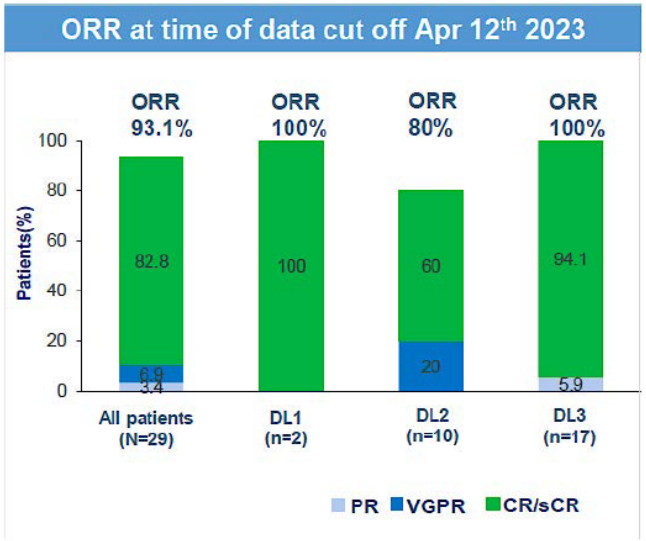
Further developments in CAR-Ts use in MM



BCMA/CD19 Fast CART GC012F

- **Dual targeting**
  - GC012F targets both BCMA and CD19
  - Dual specificity approach to maximize efficacy
  - GC012F showed stable CAR expansion and effective functionality

- BCMA/CD19 FAST phase 1 trial



- N=29 R/R MM, 97% heavily pre-treated, with 93% refractory to their last therapy.
- ORR 93%, with 38% of patients achieving MRD negativity
- Median DOR 38 mos
- CRS 86.2%, mostly Gr ≤2; no ICANS

Phase 2 trial currently on-going in ND HR (comprehensive definition) MM, primary end-point MRD 10^{-5}
(Du J et al, ASH 2023)

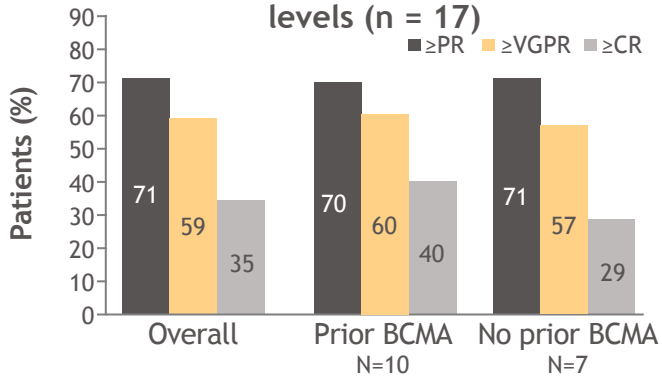
Juan Du et al. UPDATED RESULTS OF A PHASE I, OPEN-LABEL STUDY OF BCMA/CD19 DUAL-TARGETING FASTCAR-T GC012F FOR PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM), Hemasphere. 2023 Aug; 7(Suppl): e84060of.

MCARH109 (GPRC5D-targeted CAR T cell therapy)

Phase 1 first-in-class trial in RRMM

Key inclusion criteria: RRMM ≥3 prior lines, prior IMiD™ agent, prior PI and anti-CD38 mAb.
Key baseline characteristics: median age: 60y (38-76); high-risk cytogenetics: 76%; EMD, 41%, median prior lines: 6 (4-14); prior BCMA: 59%; prior BCMA-targeting CAR T cells: 47%; triple-class refractory 94%

Response rates across all dose levels (n = 17)

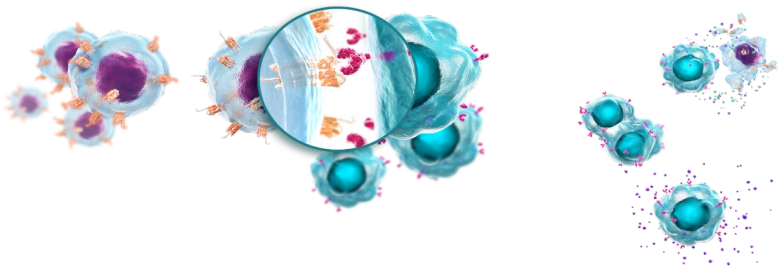


50% of patients were MRD negative

Schedule: dose escalation:
25×10^6 (n = 3); 50×10^6 (n = 3); 150×10^6 (n = 6); 450×10^6 (n = 5)

mDoR	7.8 months (95% CI, 5.7 to not reached)
mF/U	10.1

Response over time



AEs any grade (grade ≥ 3) (n = 17):

- CRS 88% (6%)
- Neurological complications 6% (6%)
- **Cerebellar toxicity (GPRC5D in inferior olivary nodule)**
- MAS 6% (6%)
- Infections 18% (12%)
- Maculopapular rash (grade 1) 18%
- Neutropenia (grade ≥ 3) 100%
- Thrombocytopenia (grade ≥ 3) 65%
- **Dysgeusia (grade 1) 12%**
- **Nail changes (grade 1) 65%**

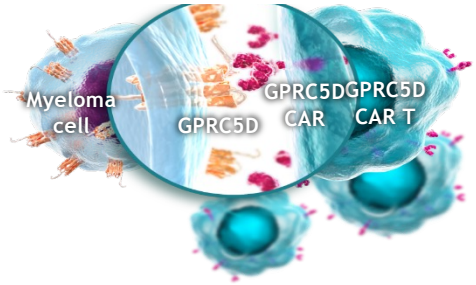
- More frequent loss or reduced expression of GPRC5D at relapse

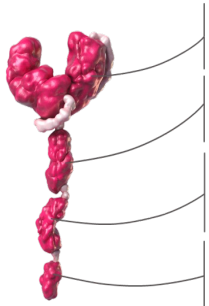
Mailankody S, et al. N Engl J Med, 2022;387:1196-206

«Next generation» anti-GPRC5D CART

BMS-986393 (CC-95266), a **GPRC5D-targeted** autologous CAR T-cell therapy, in patients with R/R MM, phase I/II study

BMS-986393 mechanism of action





Anti-GPRC5D domain[5]

Hinge and transmembrane domain[5]

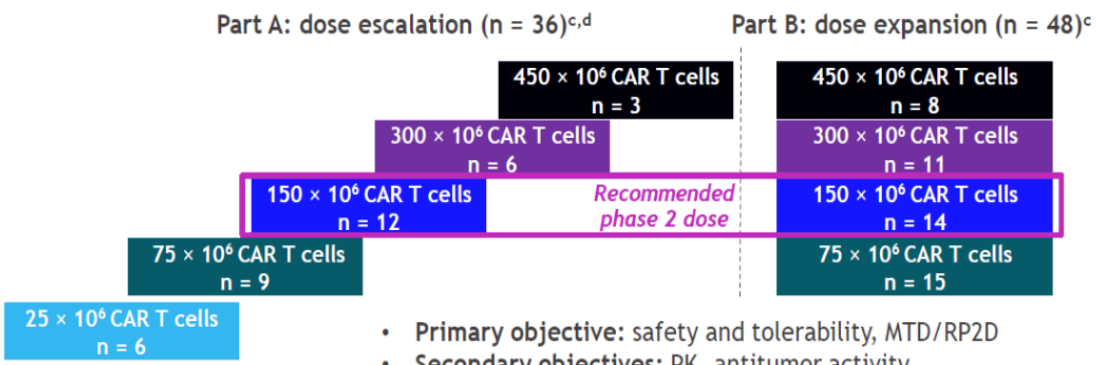
4-1BB[5,7]

CD3-zeta[5,7]

GPRC5D-targeted CAR construct

Key eligibility criteria

- RRMM
- ECOG PS 0-1
- ≥ 3 prior regimens, including ASCT,[a] a PI, an IMiD, and an anti-CD38 antibody
- Progressed < 12 months of last regimen[b]
- Prior BCMA-directed therapies allowed, including CAR T cells



- **Primary objective:** safety and tolerability, MTD/RP2D
- **Secondary objectives:** PK, antitumor activity

84 pts (26 at 150 dose), 5 median prior LOT, median follow-up:9 months

- **46% any prior anti-BCMA** therapy (36% CAR-T)

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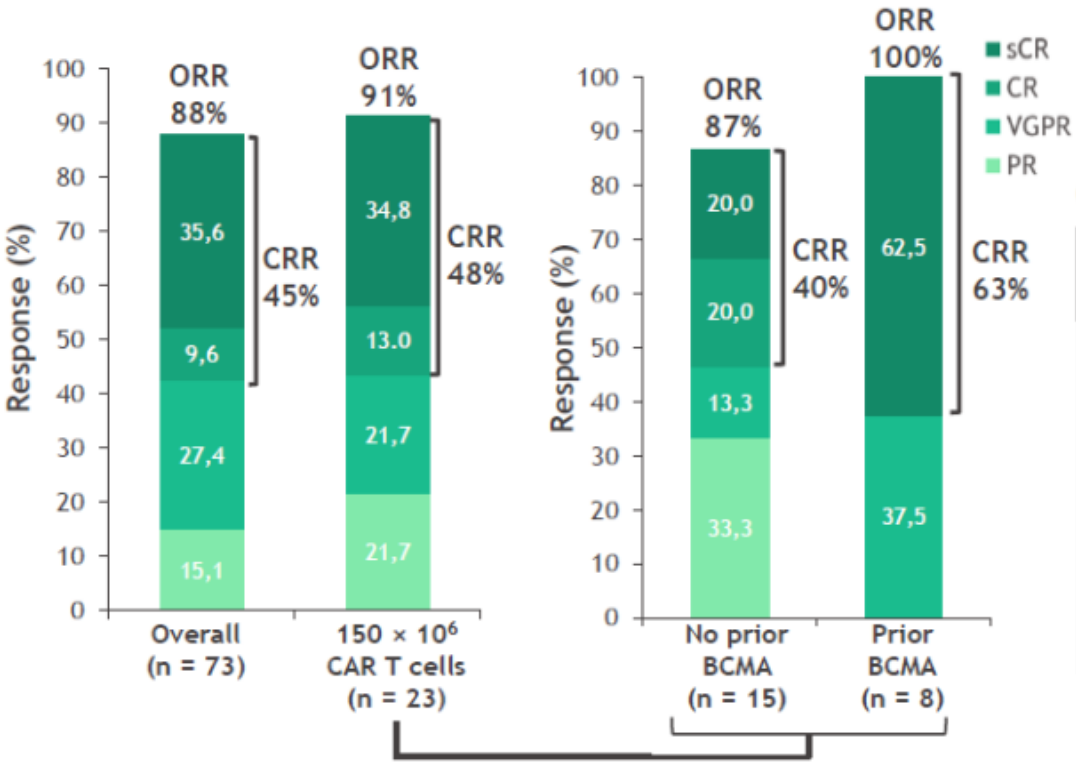
Efficacy



ORR in subgroups of interest (all dose levels)

Disease characteristic, % (n/N)	Present	Absent
Prior BCMA treatment	78% 25/32	95% 39/41
Extramedullary disease	84% 26/31	91% 38/42
High-risk cytogenetics[b]	83% 24/29	91% 40/44
Triple-class refractory	88% 50/57	88% 14/16

- Median DOR 13 mos

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Toxicity

	All treated patients (n = 84)		150 × 10^6 CAR T cells (n = 26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TEAE, n (%)	77 (91.7)	69 (82.1)	26 (100)	24 (92.3)
Hematologic TEAEs (≥ 30% of all treated patients), n (%)				
Neutropenia	54 (64.3)	52 (61.9)	20 (76.9)	18 (69.2)
Anemia	40 (47.6)	25 (29.8)	13 (50.0)	11 (42.3)
Thrombocytopenia	36 (42.9)	22 (26.2)	10 (38.5)	5 (19.2)
Non-hematologic TEAEs (≥ 30% of all treated patients), n (%)				
CRS	64 (76.2)	3 (3.6)	23 (88.5)	0 (0)
Infections and infestations	34 (40.5)	11 (13.1)	9 (34.6)	3 (11.5)
Hypokalemia	31 (36.9)	4 (4.8)	12 (46.2)	2 (7.7)
Hypocalcemia	28 (33.3)	2 (2.4)	7 (26.9)	0 (0)
Headache	27 (32.1)	1 (1.2)	8 (30.8)	0 (0)
Hypophosphatemia	26 (31.0)	2 (2.4)	11 (42.3)	1 (3.8)

TEAEs related to BMS-986393	All treated patients (n = 84)		150 × 10^6 CAR T cells (n = 26)	
On-target/off-tumor, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4
Dysgeusia/taste disorder	21 (25.0)	0	8 (30.8)	0
Skin[a]	17 (20.2)	0	4 (15.4)	0
Nails[b]	11 (13.1)	0	3 (11.5)	0
Dysphagia	3 (3.6)	0	1 (3.8)	0
Neurotoxicity, n (%)	Any grade	Grade 3 only	Any grade	Grade 3 only
ICANS-type neurotoxicity[c]	8 (9.5)	2 (2.4)	1 (3.8)	0
Non-ICANS-type neurotoxicity[d]	9 (10.7)	3 (3.6)	4 (15.4)	1 (3.8)

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CONCLUSION

- **CARTs, within new immune therapies,** represent a new standard of care, after 3/4 line of treatment, where they significantly improved survival outcomes
- **2 anti-BCMA CARTs**, ide-cel and cilta-cel, are FDA and EMA approved for RRMM who received at least 3/4 prior LOT; **anti-GPRC5D CARTs** are under investigation

- Multiple on-going programs include **combinations and earlier lines of treatments, since diagnosis;** this strategy **may improve/overcome "functional" HR MM**
- **«Next generation» CARTs,** with improved and faster manufactoring, showed impressive efficacy and lower toxicity

- **Tailoring and sequencing** immunotherapies for RR/MM is an on-going challenge

- **Limited access to CAR-T** cells remains a challenge in real-life clinical practice

THANKS!

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