ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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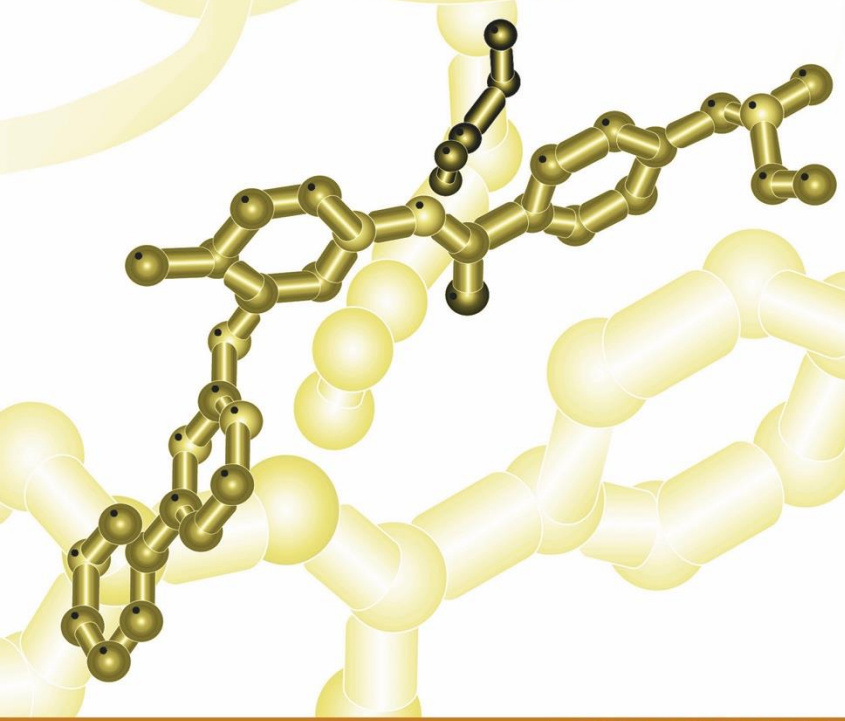

# New Drugs in Hematology

**President:** Pier Luigi Zinzani
**Co-President:** Michele Cavo

**Bologna,**
**Royal Hotel Carlton**
**January 15-17, 2024**

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

# II generation anti-BCMA and anti-GPRC5D autologous CAR-T

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EMN Trialist Group

# Disclosures 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)

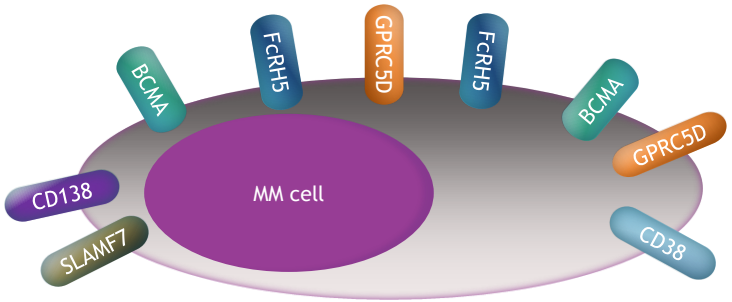



Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.
APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FcRH5, Fc receptor-like 5; GPRC5D, G-protein 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.

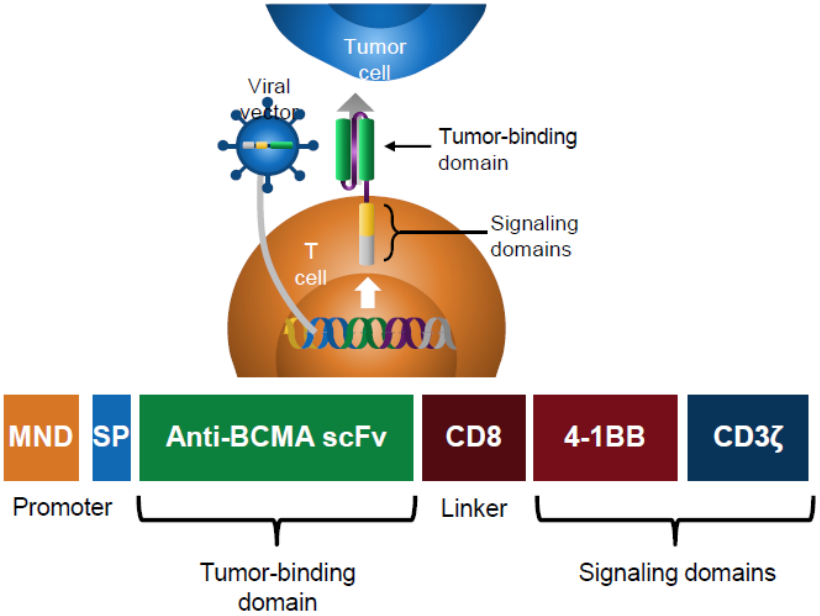
# BCMA-targeting CAR-T cells

| | 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 |

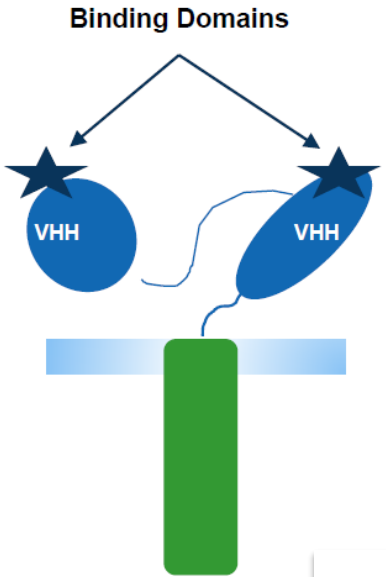

1. Munshi N, et al. ASCO 2020; 2. Usmani S, et al. ASCO 2022; 3. Rodrigues Otero, EBMT 2023; 4. Einsele H, et al. ASCO 2023; 5. Fernández de Larrea C, et al. EHA 2022; 6. Frigault MJ, et al. ASCO 2022; 7. Li C, et al. EHA 2022; 7. Du J, et al. ASCO 2022; 8. Sperling et al. ASCO 2023; 9. Huang H, et al.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

# Structure of BCMA CAR-T Constructs Approved in RRMM

**Ide-Cel structure:**
Anti-BCMA single-chain variable fragment (svFv) fused to CD8 linker region and the CD137 (4-1BB) costimulatory; CD3ζ signaling domains[1]



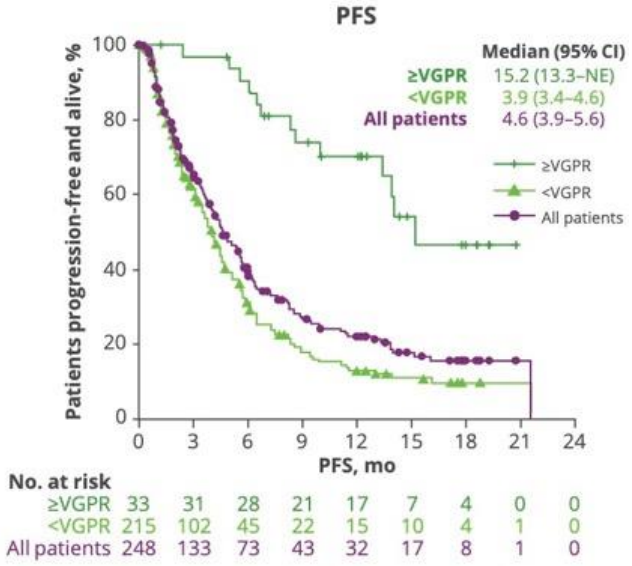

**Cilta-cel structure:**
Two BCMA-targeting domains designed to confer avidity plus a 4-1BB costimulatory domain[2]

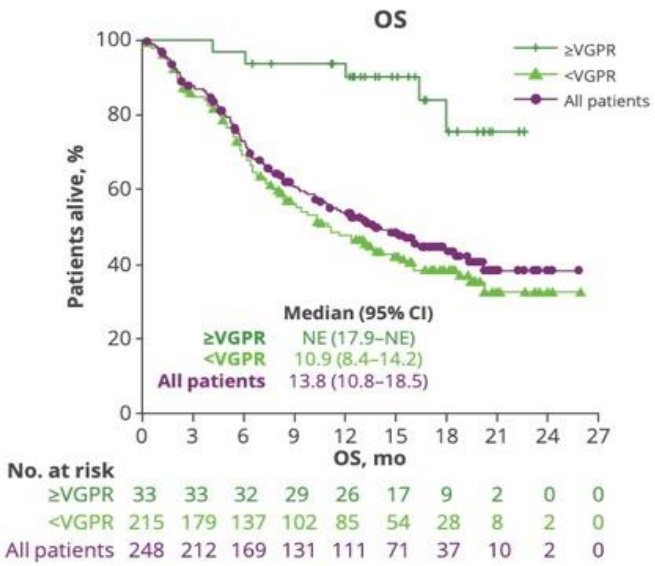



1. Raje NS et al. ASCO 2018. Abstract 8007. 2. Madduri D et al. ASH 2020. Abstract 177.

# 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

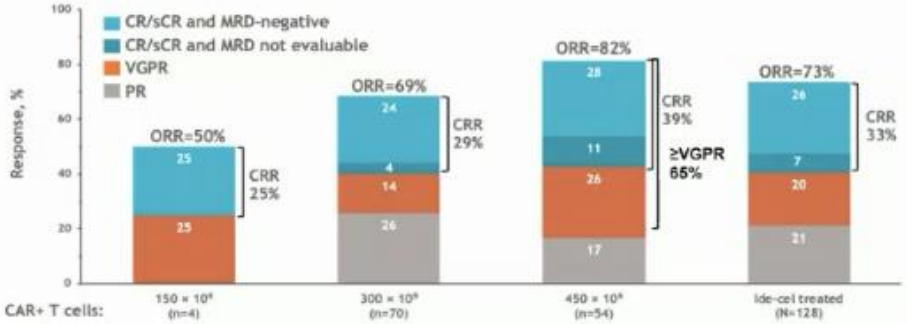
Mateos MV et al, Leukemia 2022

# Ide-cel approval: the KarMMa trial

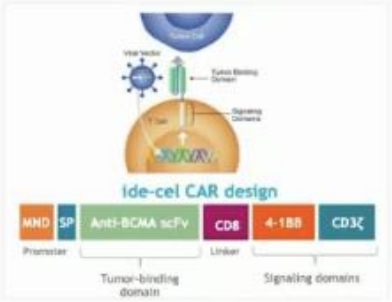
FDA approved in 2021
EMA approved in 2021

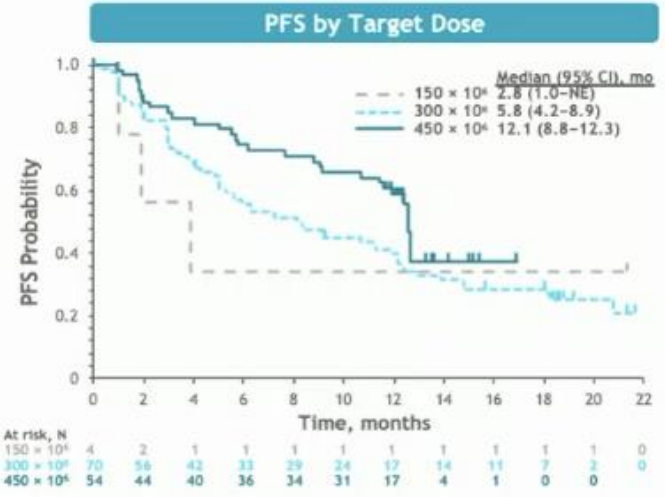
**Second generation CAR-T cell, anti-BCMA murine scFv, 4-1BB costimulatory domain**

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




| 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) |



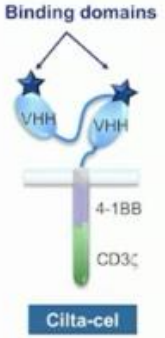

**mOS = 24.8 mo**

Munshi N, et al. *NEJM* 2021

# Cilta-cel approval: the CARTITUDE-1 trial

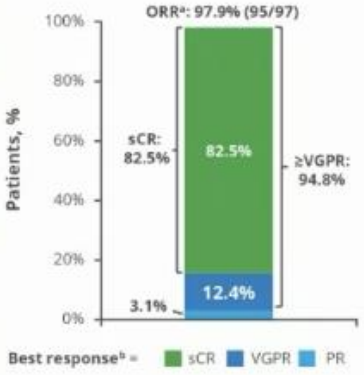
FDA approved in 2022
EMA approved in 2022

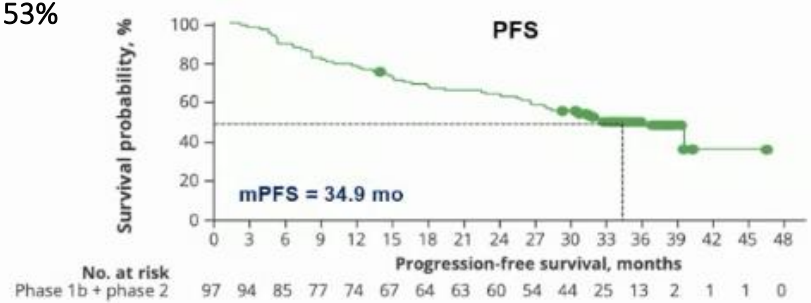
**Second generation CAR-T cell, 2 anti-BCMA camelid VHH single domains, 4-1BB costimulatory domain**

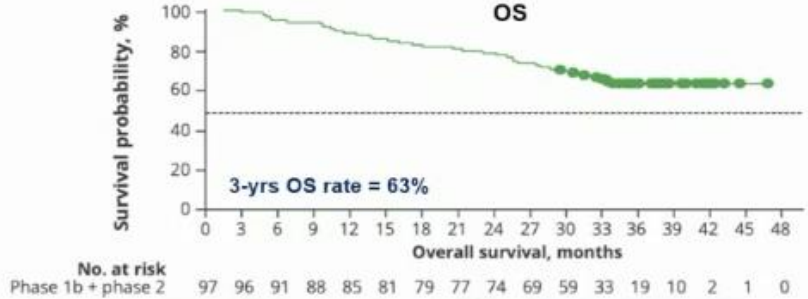



| CARTITUDE-1, phase 2 study (N = 97) | | |
|---|---|---|
| Median prior lines: 6 (3–18) | 88% of patients were triple-class refractory | Bridging possible Flu-Cy lymphodepletion |

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



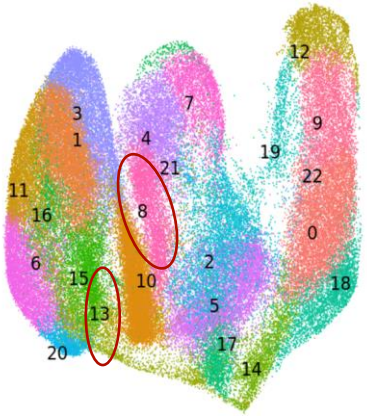

| AE, n (%) | Cilta-cel-Treated (N=97) | |
|---|---|---|
| | Any Grade | Grade ≥3 |
| **Hematologic** | | |
| Neutropenia | 93 (96) | 92 (95) |
| Anemia | 79 (81) | 66 (68) |
| Thrombocytopenia | 77 (80) | 58 (60) |
| **CRS** | 92 (95) | 6 (5) |
| **Neurotoxicity** | 20 (21) | 10 (10) |

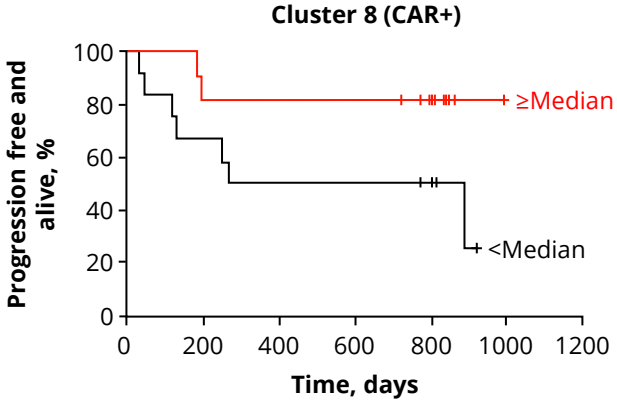
Berdeja J, et al. *Lancet* 2022;
Lin Y. et al. ASCO 2023

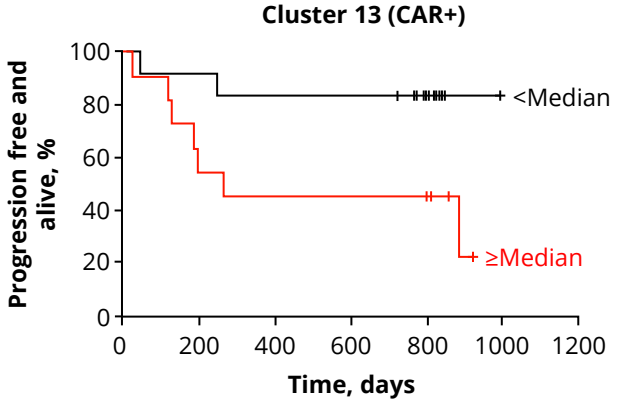
# Longer PFS Was Associated With a CAR+CD8+ Stem Cell–Like Phenotype in the Drug Product

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

| 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 |



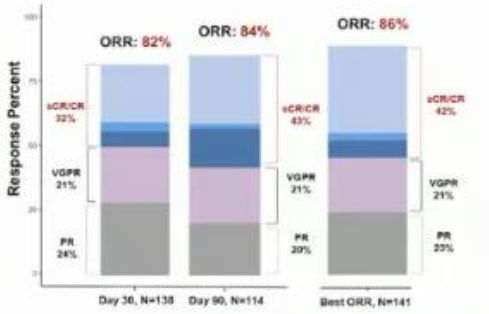

**Longer PFS was directly associated with a CAR+CD8+ T-stem cell–like phenotype and inversely correlated with a CAR+CD4+ Treg cell–like phenotype in the drug product**

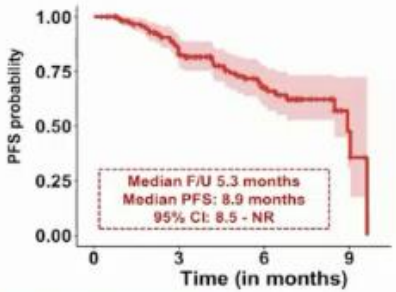
Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq) analysis of drug product. CAR, chimeric antigen receptor; PFS, progression-free survival; $T_{cm}$, central memory T cell; $T_{em}$, effector memory T cell.

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

# Real-world data (US consortium)

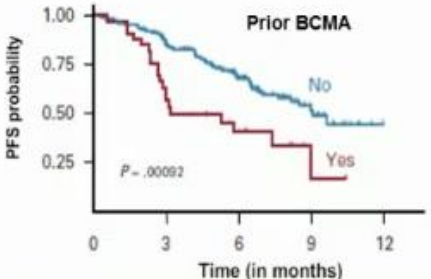
## Ide-cel, n= 159



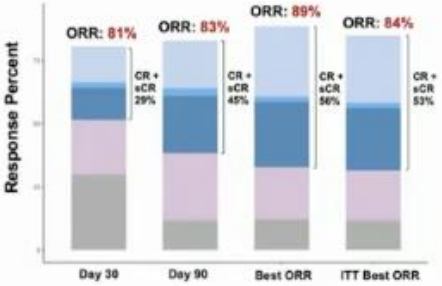

77% of patients (N=150) would have been ineligible for participation in the KarMMa trial

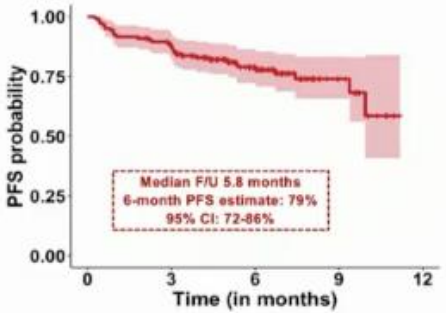
| KarMMa-1 exclusion criteria at leukapheresis | No. (%) |
|---|---|
| Organ failure (renal, cardiac, hepatic) | 60 (31) |
| Prior anti-BCMA therapy | 43 (22) |
| Platelets < 50,000/μL | 42 (21) |
| Hemoglobin < 8g/dL | 33 (17) |
| ECOG PS ≥ 2 | 33 (17) |
| ANC < 1000/uL | 29 (15) |
| PCL, POEMS, amyloidosis, non-secretory myeloma | 26 (13) |




Hansen et al. ASCO 2022 & *JCO* 2023

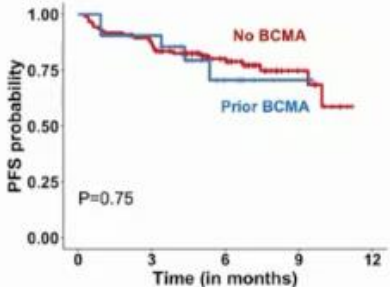
## Cilta-cel, n= 143




57% of patients (N=81) would have been ineligible for participation in the CARTITUDE-1 trial

| CARTITUDE-1 exclusion criteria at leukapheresis | No. (%) |
|---|---|
| Cytopenias | 24 (17) |
| Oligosecretory/Non-secretory | 23 (16) |
| Organ dysfunction | 17 (12) |
| Prior anti-BCMA | 17 (12) |
| ECOG PS ≥ 2 | 14 (10) |
| Plasma Cell Leukemia | 10 (7) |
| History of CNS Pathology | 9 (6) |
| Amyloid | 4 (3) |




Hansen et al. ASCO 2023

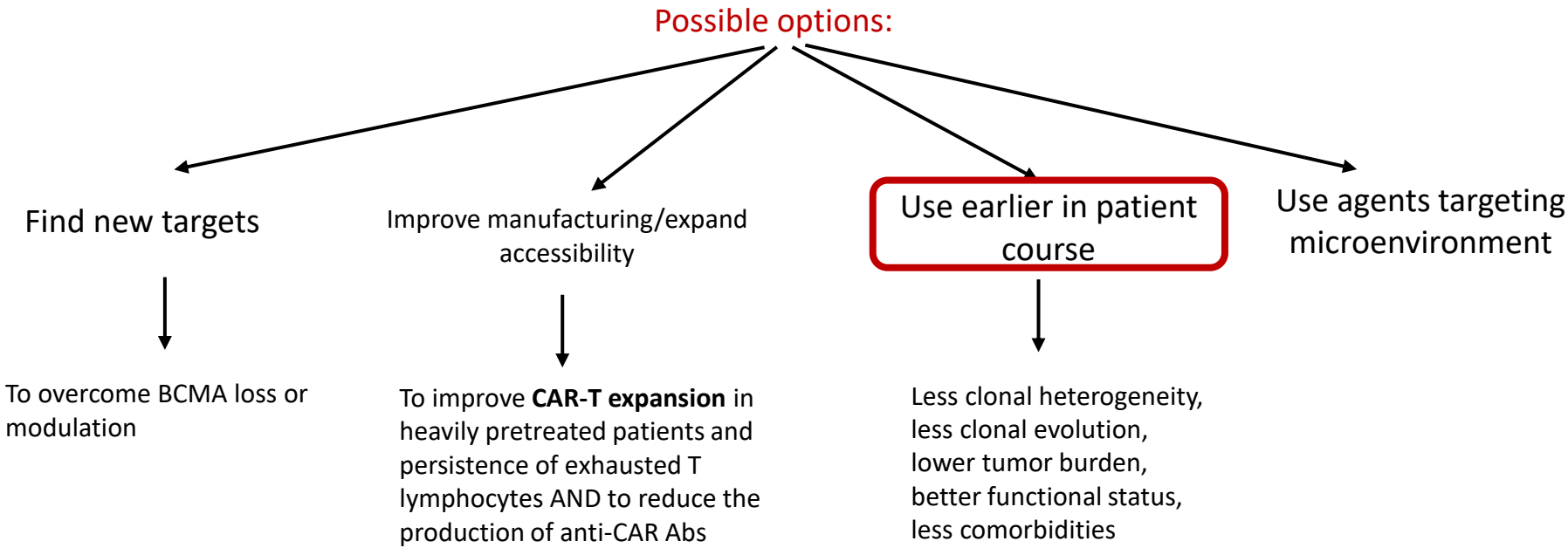
# Outcomes of BCMA-Directed CART Therapy in Patients with RRMM with EMD

## still an unmet need…

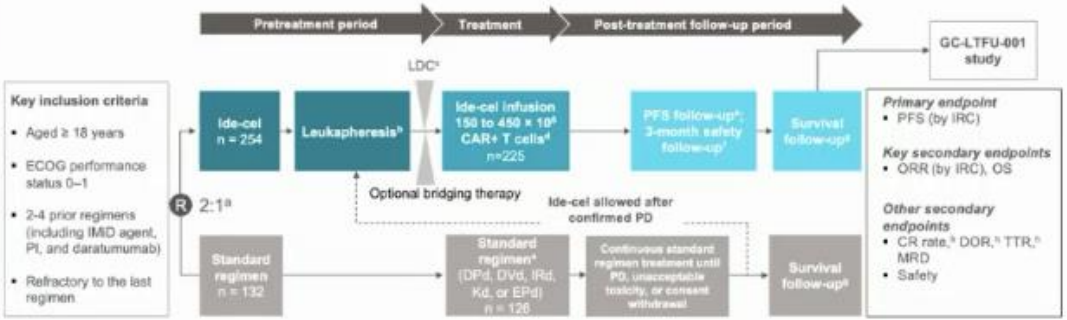
- Real life analysis on 132 pts treated with ide-cel and cilta-cel as per SOC
- 48% previous/current history of EMD prior to CART; pair matched with rest of population
- No different in toxicities (CRS, ICANS, infections)
- No difference in response rate/CR rate
- **Significantly shorter PFS and OS**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

Dima D, et al ASH 2023

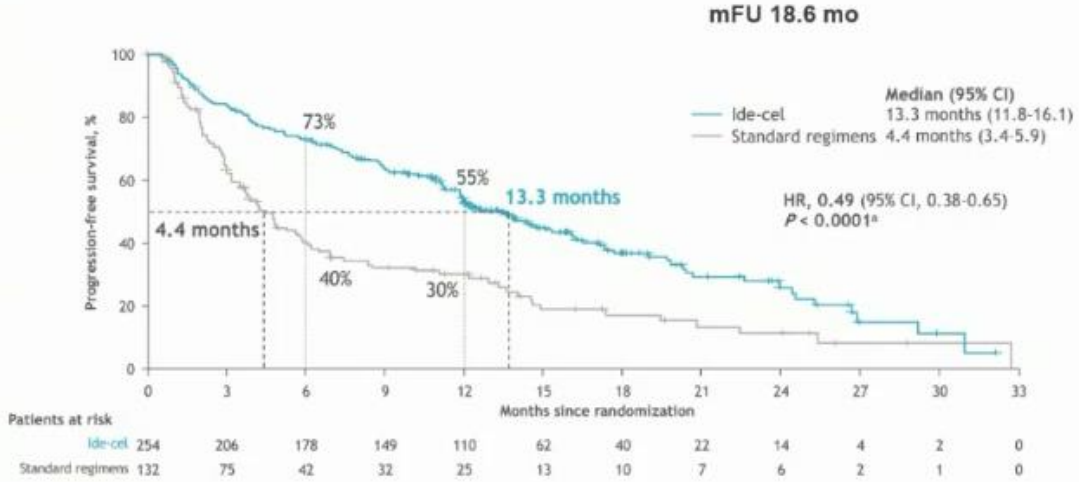
# Further developments in CAR-Ts use in MM



# 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) |

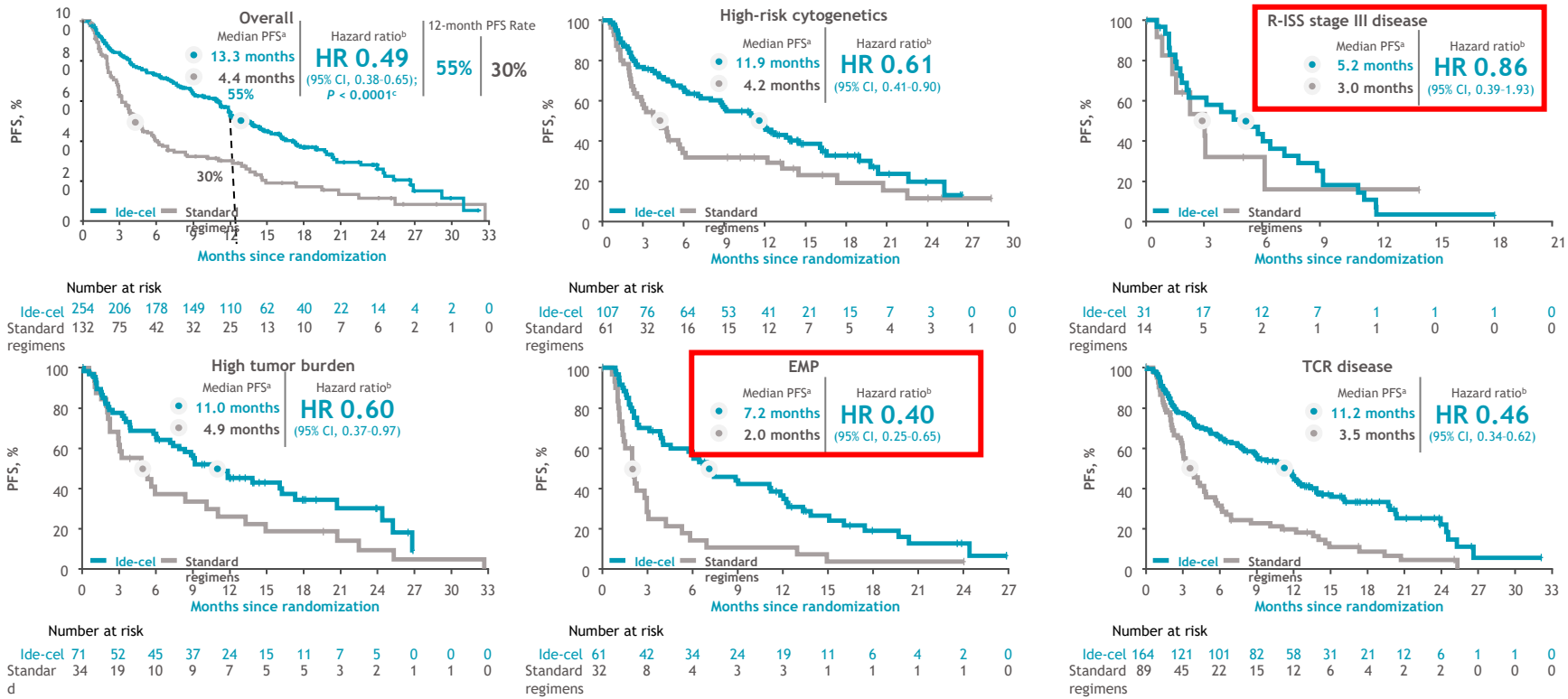



| All-cause AEs occurring in ≥ 20% patients, n (%) | Ide-cel (n = 250) | | | Standard regimens (n = 126) | | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3/4 | Grade 5 | Any grade | Grade 3/4 | Grade 5 |
| Any | 248 (99) | 233 (93) | 36 (14) | 123 (98) | 94 (75) | 8 (6) |
| Other | | | | | | |
| 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)



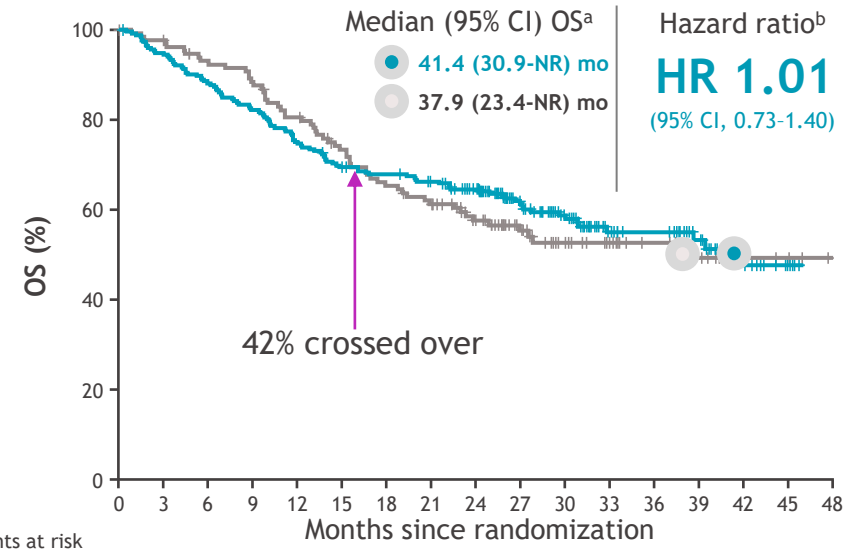

**Median PFS was longer in patients treated with ide-cel vs standard regimens in the overall population and high-risk subgroups; interpretation in patients with R-ISS stage III disease was limited due to small subgroup size**

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

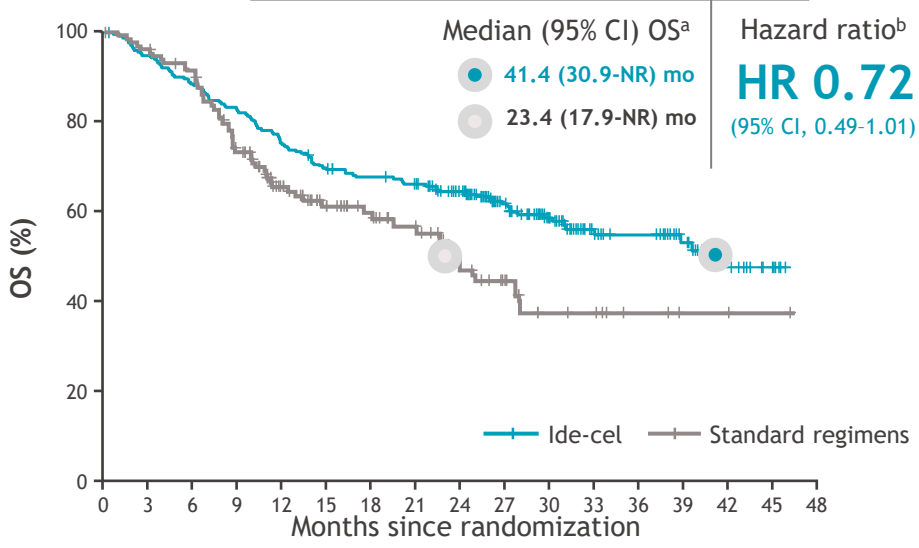
## ITT population




Patients at risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ide-cel | 254 | 240 | 223 | 208 | 190 | 175 | 169 | 161 | 143 | 103 | 75 | 48 | 44 | 30 | 13 | 4 | 0 |
| Standard regimens | 132 | 128 | 120 | 114 | 103 | 91 | 81 | 75 | 59 | 45 | 32 | 24 | 18 | 11 | 4 | 3 | 0 |

## Sensitivity analysis adjusted for crossover[c]




| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 254 | 240 | 223 | 208 | 190 | 175 | 169 | 161 | 143 | 103 | 75 | 48 | 44 | 30 | 13 | 4 | 0 |
| 132 | 126 | 118 | 93 | 67 | 50 | 42 | 34 | 21 | 14 | 9 | 8 | 4 | 2 | 1 | 1 | 0 |

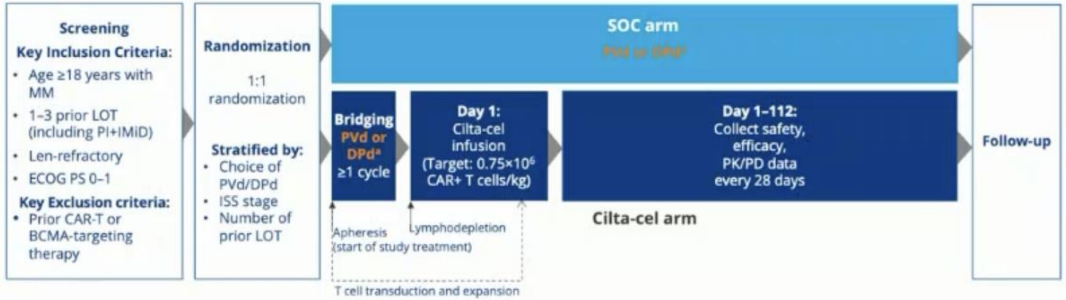
**More than half of patients in SOC arm received ide-cel as subsequent therapy upon PD, most of them within 3-16 mos from randomization**

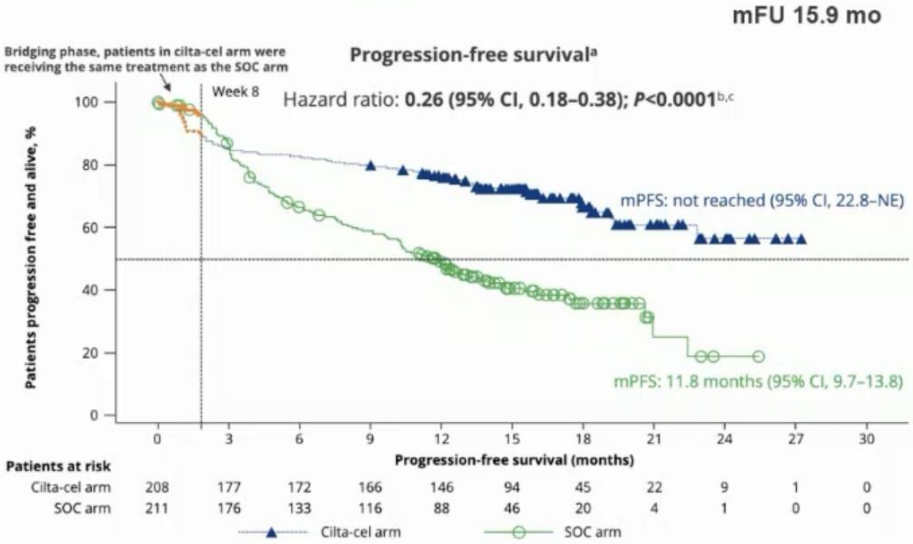
**Prespecified crossover-adjusted analysis shows OS benefit of ide-cel**

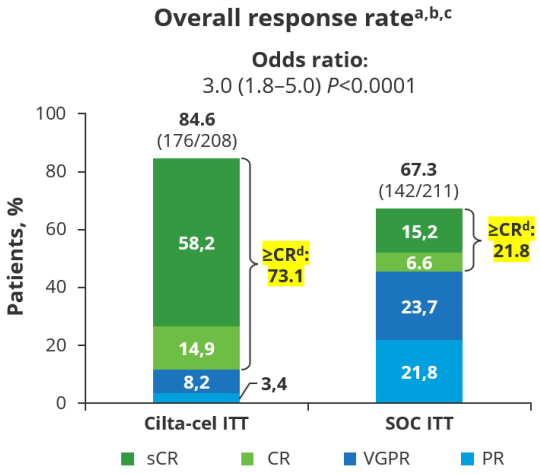
**Early deaths in ide-cel arm occurred in pts with multiple high-risk features, due to PD, and mostly in patients who never received ide-cel (value of bridging therapy)**

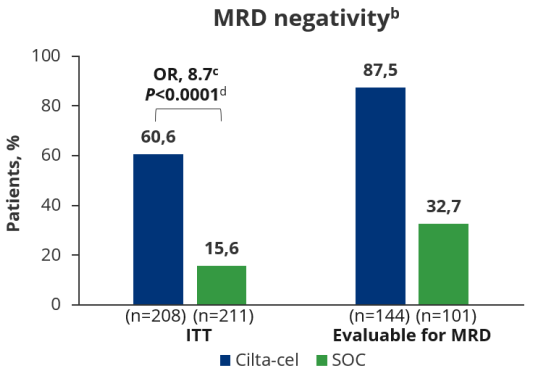
Information fraction for OS was 74% (n = 164/222 required events). [a]Based on Kaplan-Meier approach; [b]Stratified HR is based on the univariate Cox proportional hazards model. CI is 2-sided and calculated by bootstrap method; [c]Two-stage Weibull model without recensoring (prespecified analysis).

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



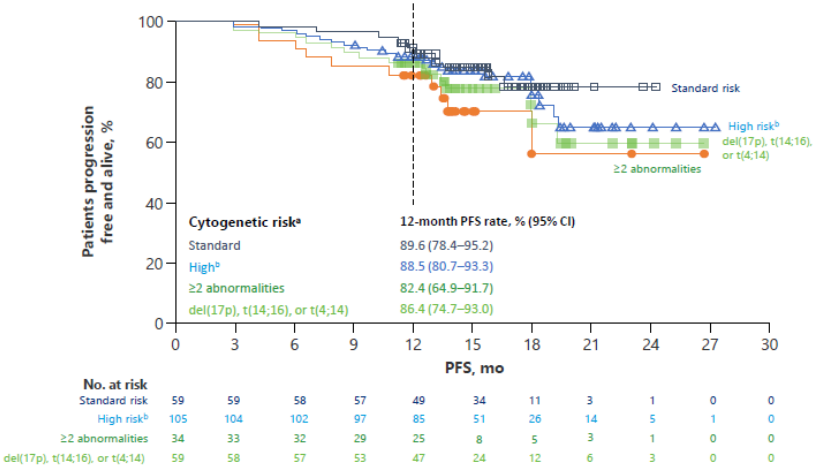



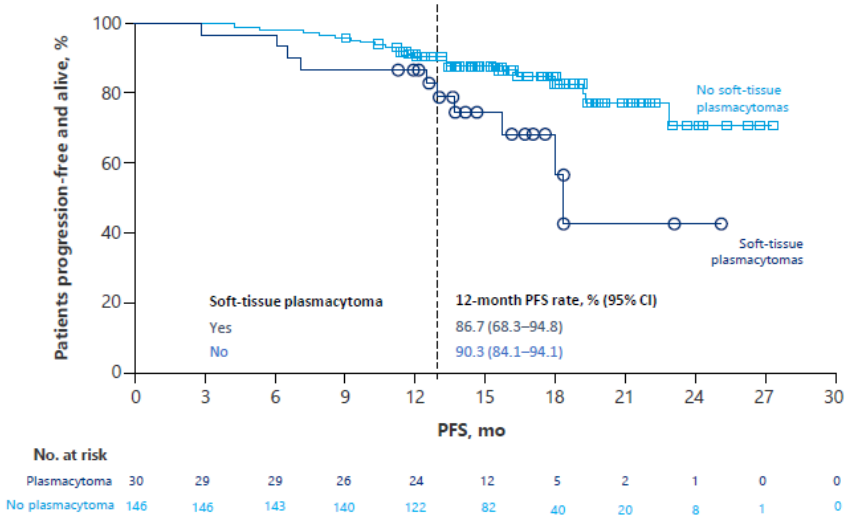




*San Miguel J et al, NEJM 2023*

Dhakal et al. ASCO 2023

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



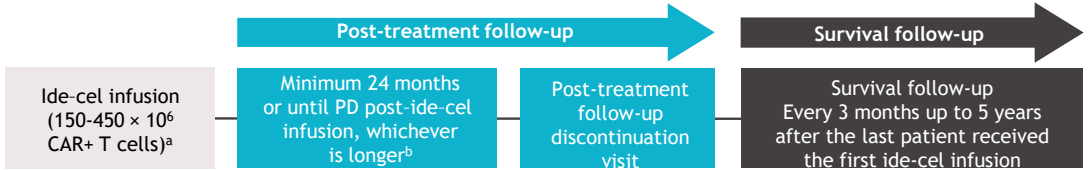

Manier S et al, IMS Athens, 2023

# 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

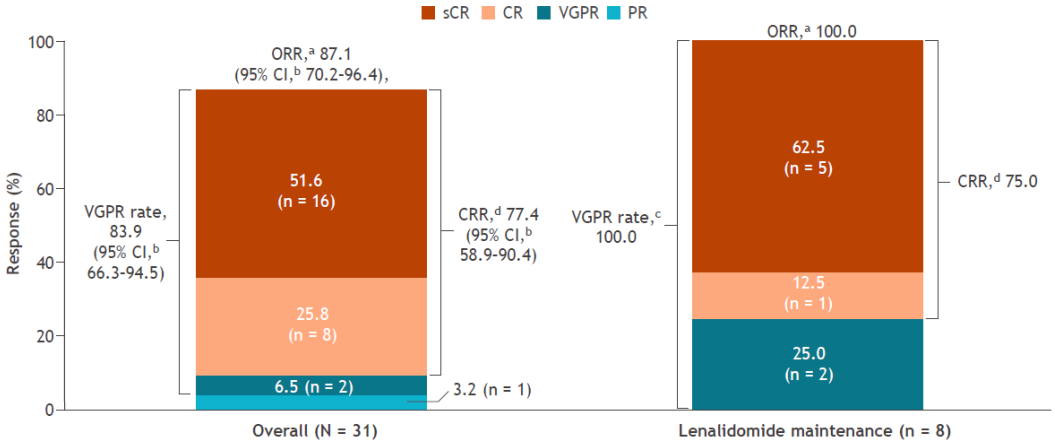
- Efficacy and safety were analyzed in all patients who received ide-cel

[a]After lymphodepletion (cyclophosphamide 300 mg/m$^2$ + fludarabine 30 mg/m$^2$ × 3), patients received a single infusion of ide-cel at a range of 150-450 × 10$^6$ 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.

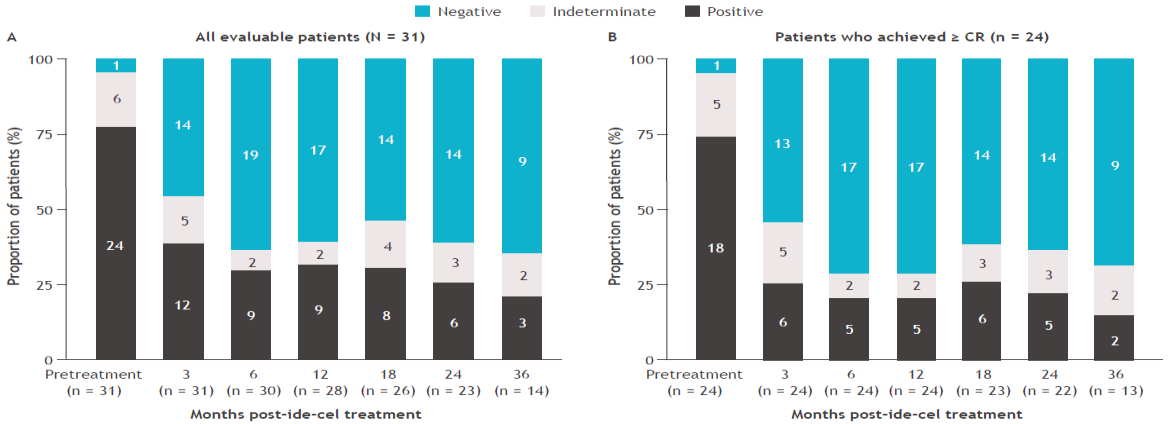
***Dhodapkar M et al, ASH 2023***

# 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**



# 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]

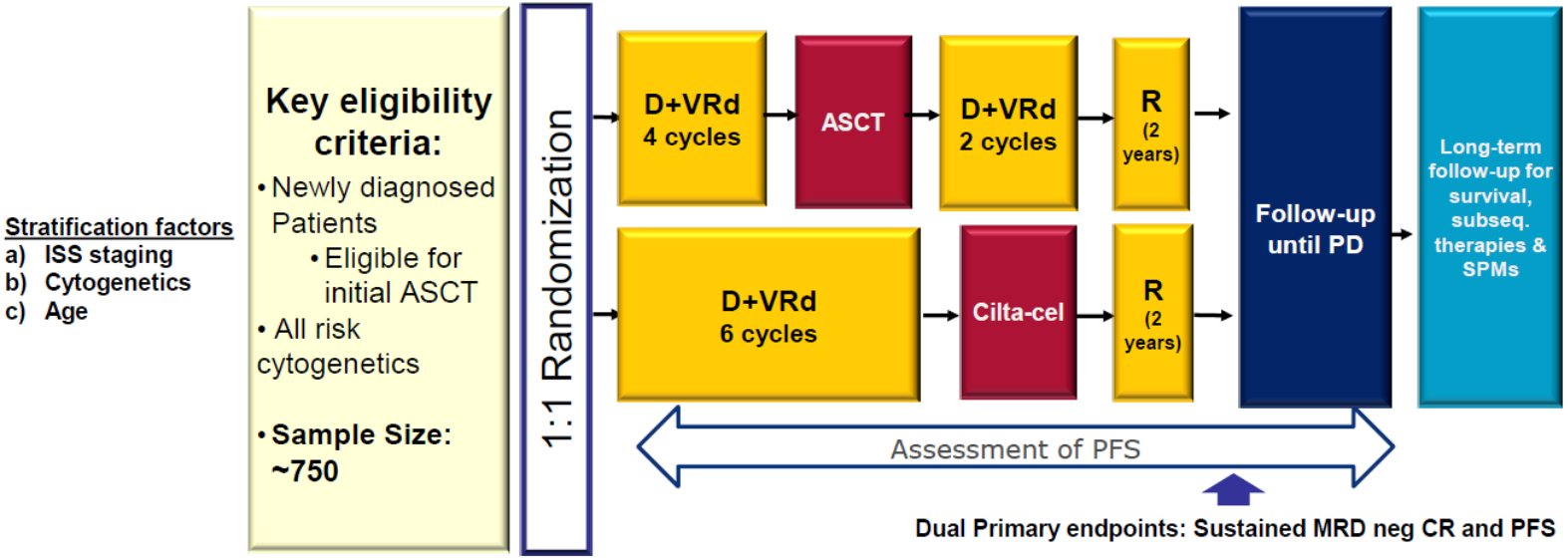
- Patients treated with cilta-cel in earlier LOT in cohort A and B experienced deep and durable responses
- No new CAR-T–related safety signals, except for 1 additional CAR-T cell neurotoxicity in cohort B, were reported

| | 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.

# CAR-T as first-line therapy in NDTEMM: EMN 28- CARTITUDE 6 trial

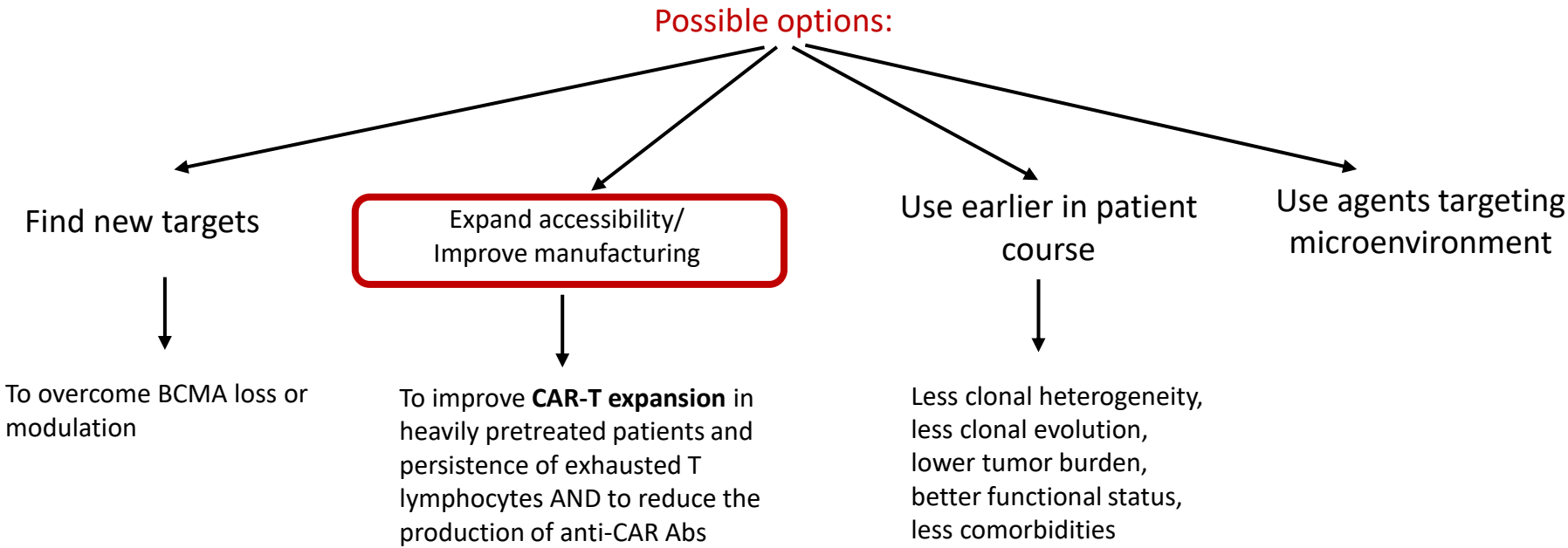
**Dual primary endpoints:**
Sustained MRD-neg CR and PFS




ASCT, autologous stem cell transplant; CR, complete response; D, daratumumab; EMN, European Myeloma Network; ISS, international staging system; MRD, minimal residual disease; PD, progressive disease; PFS, progression-free survival; R, lenalidomide; SPM, second primary malignancies; VRd, bortezomib-lenalidomide-dexamethasone

1. NCT05257083. Available at: https://clinicaltrials.gov/ct2/show/NCT05257083. Accessed June 2022
2. Gay F et al. EMN 2022: (oral presentation)

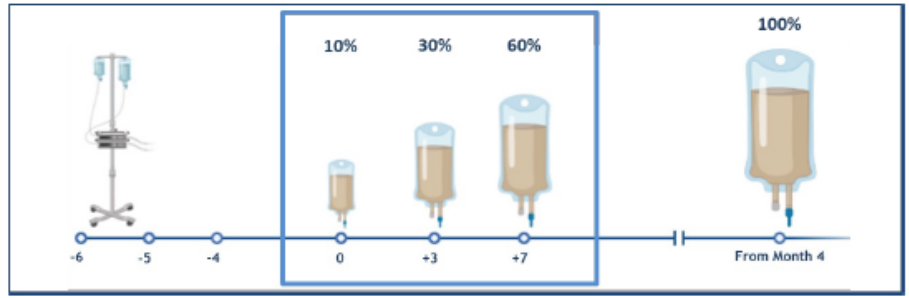
# Further developments in CAR-Ts use in MM



# Fractionated initial infusion and booster dose of ARI0002h, a humanised, BCMA-directed CAR T-cell therapy, for patients with relapsed or refractory multiple myeloma (CARTBCMA-HCB-01): a single-arm, multicentre, academic pilot study

*Aina Oliver-Caldés, Verónica González-Calle, Valentín Cabañas, Marta Español-Rego, Paula Rodríguez-Otero, Juan Luis Reguera, Lucía López-Corral, Beatriz Martín-Antonio, Aintzane Zabaleta, Susana Inogés, Sara Varea, Laura Rosiñol, Ascensión López-Díaz de Cerio, Natalia Tovar, Raquel Jiménez, Miriam López-Parra, Luis Gerardo Rodríguez-Lobato, Andrés Sánchez-Salinas, Eulàlia Olesti, Maria Calvo-Orteu, Julio Delgado, José Antonio Pérez-Simón, Bruno Paiva, Felipe Prósper, Joaquín Sáez-Peñataro, Manel Juan, José M Moraleda, María-Victoria Mateos, Mariona Pascal, Alvaro Urbano-Ispizua, Carlos Fernández de Larrea*

***Lancet Oncol* 2023; 24: 913–24**



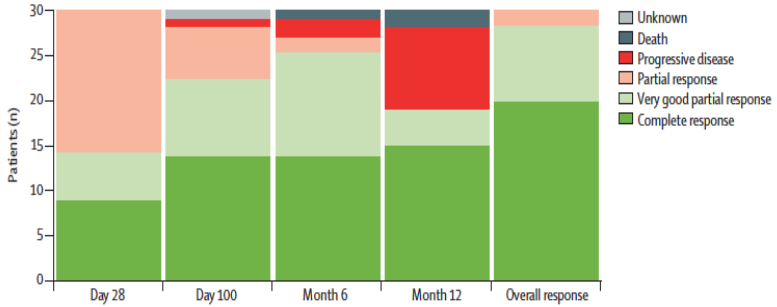

**Fludarabine 30** mg/m2/day
**Cyclophosphamide 300** mg/m2/day

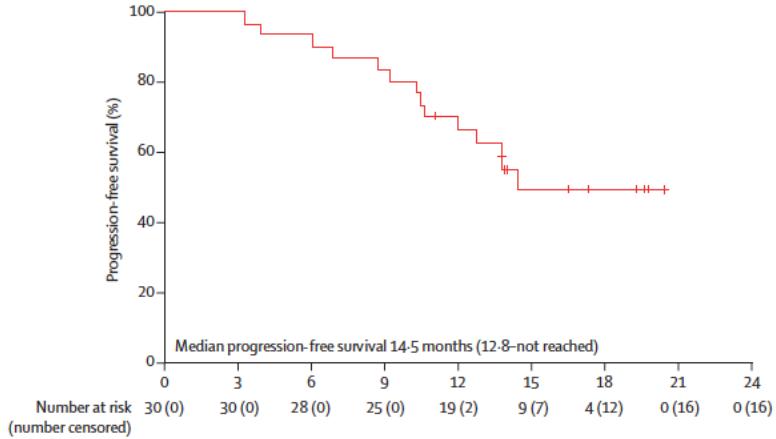
**3x10⁶ CART/kg**
Fractionated

**Up to 3x10⁶ CART/kg**
single dose

| | 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.

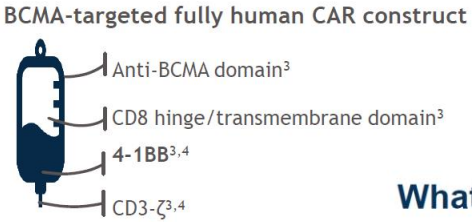


# «Next generation» anti-BCMA CART

**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

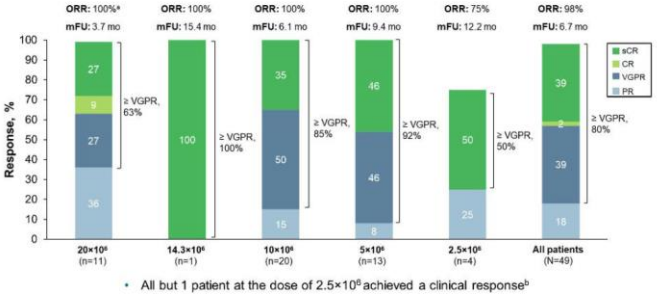




Costa L et al, ASH 2022

## 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

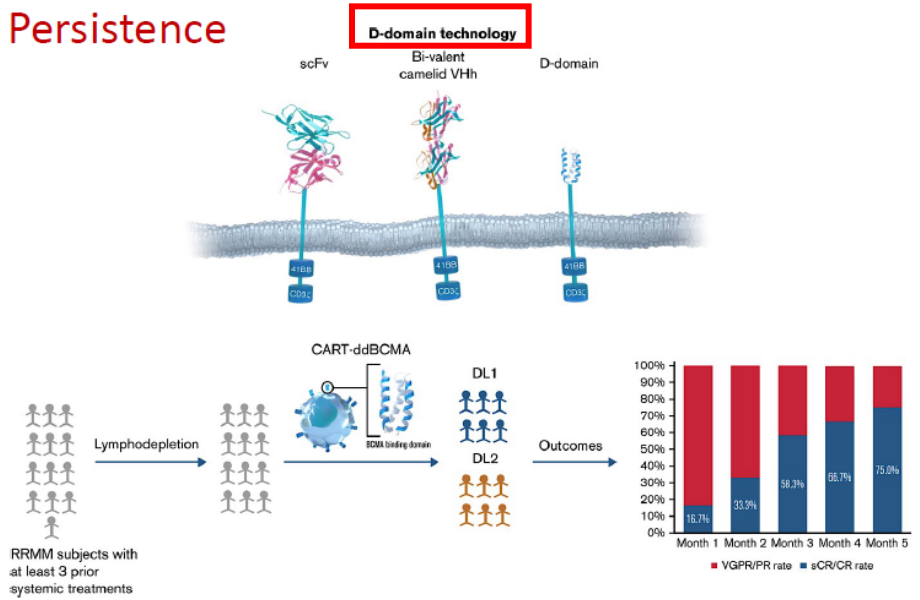



- All but 1 patient at the dose of $2.5\times10^8$ achieved a clinical response[b]

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

# ddBCMA CART in R/R MM

- **Reduced Immunogenicity,** Enhance Activity and Persistence



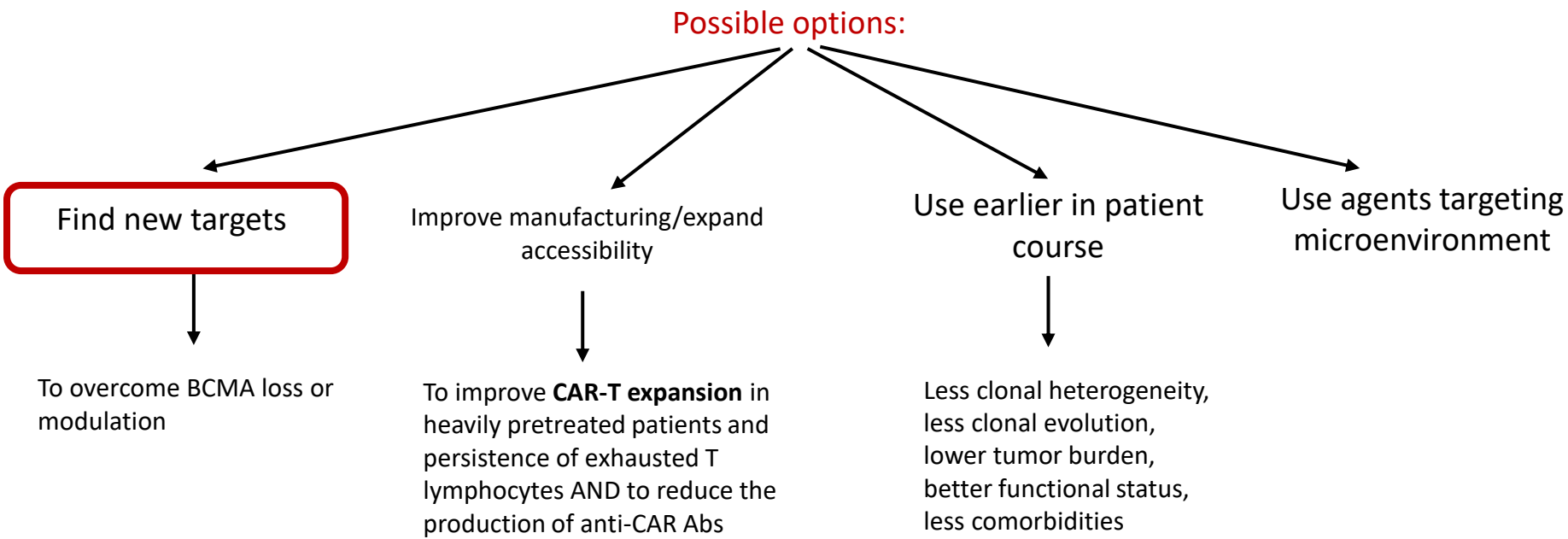

## ddBCMA phase 1 trial

- N=25 RR MM patients
- LoT median ~5 (3-16)
- EMD 40%
- ORR 100%
- CR/sCR 67%
- ≥VGPR 88%
- Responses beyond 18 months including in patients with EMD
- CRS 100%, most Gr ≤2; 4 patients had ICANS (2 had Gr3)

Phase 2 ddBCMA-CAR T currently open and actively enrolling patients at MGH site

M. Frigault et al, Phase 1 Study of CART-Ddbcma for the Treatment of Patients with Relapsed and/or Refractory Multiple Myeloma: Results from at Least 1-Year Follow-up in All Patients, Abstract 1023, ASH 2023

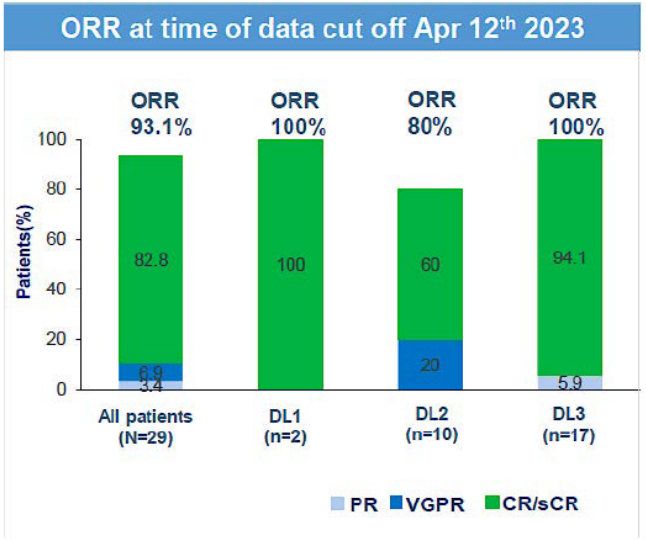
# Further developments in CAR-Ts use in MM



# 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)

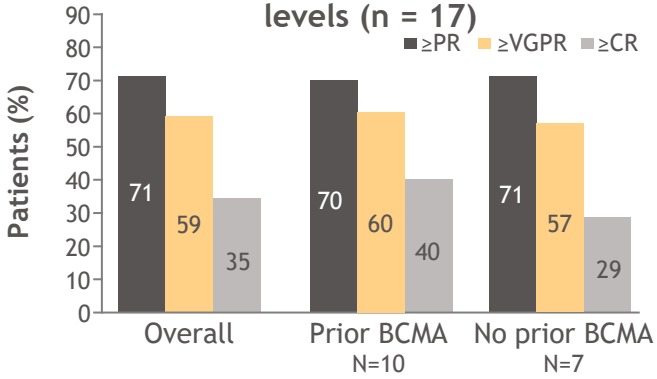
Juan Du et al. UPDATED RESULTS OF A PHASE I, OPEN-LABEL STUDY OF BCMA/CD19 DUAL-TARGETING FASTCAR-T GC012F FOR PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM). Hemasphere. 2023 Aug; 7(Suppl ): e84060of.

# 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)

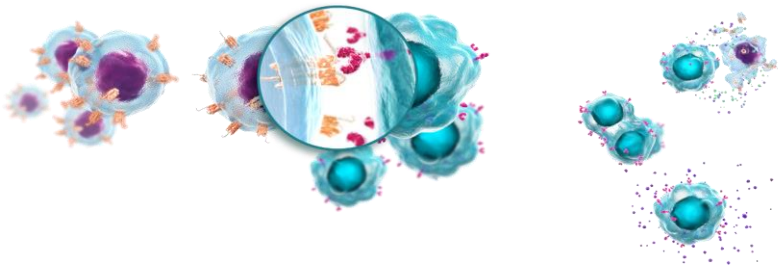



50% of patients were MRD negative

**Schedule: dose escalation:**
$25\times10^6$ (n = 3); $50\times10^6$ (n = 3); $150\times10^6$ (n = 6); $450\times10^6$ (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%**

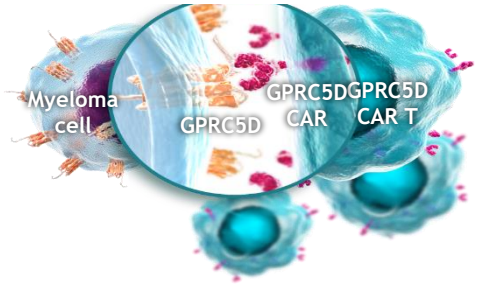
- More frequent loss or reduced expression of GPRC5D at relapse

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





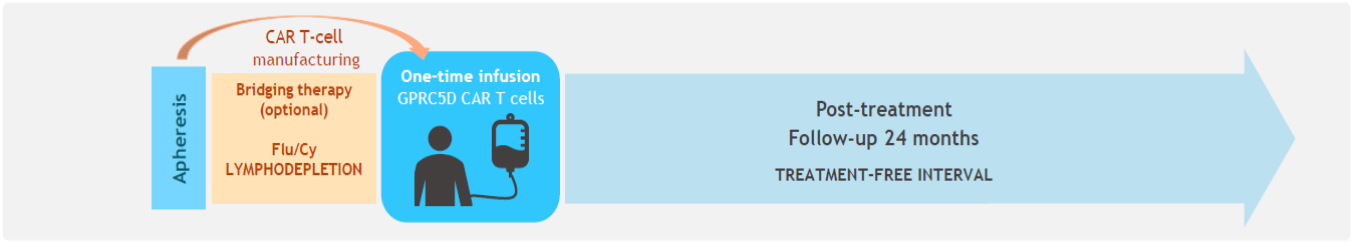
Anti-GPRC5D domain[5]

Hinge and transmembrane domain[5]

4-1BB[5,7]

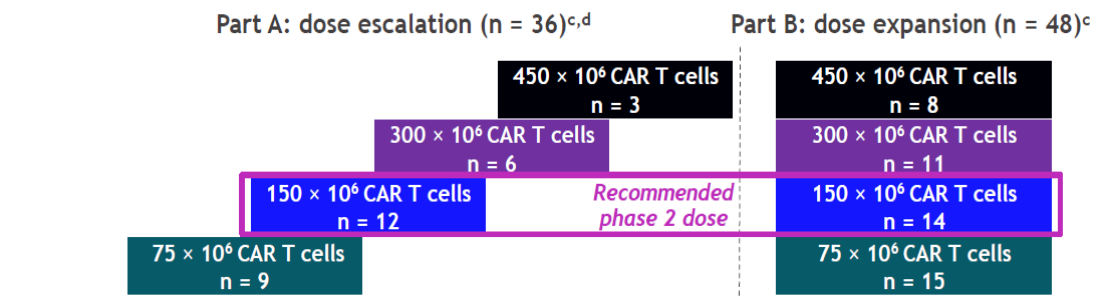
CD3-zeta[5,7]

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



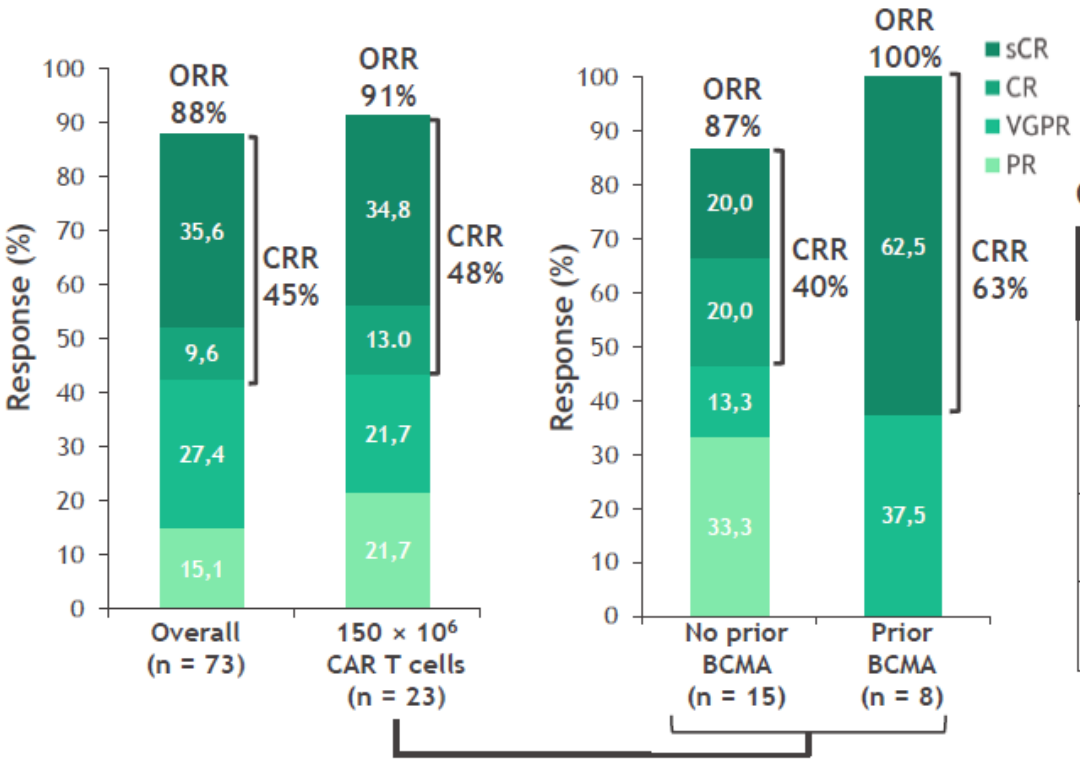

- **Primary objective:** safety and tolerability, MTD/RP2D
- **Secondary objectives:** PK, antitumor activity

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

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

Bal S et al. – Abs 364 ASH 2023

# 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

Bal S et al. – Abs 364 ASH 2023

# 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) |

Bal S et al. – Abs 364 ASH 2023

# 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;** CAR-T cell therapy will be compared head-to-head to ASCT in up-front treatment

- **«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

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