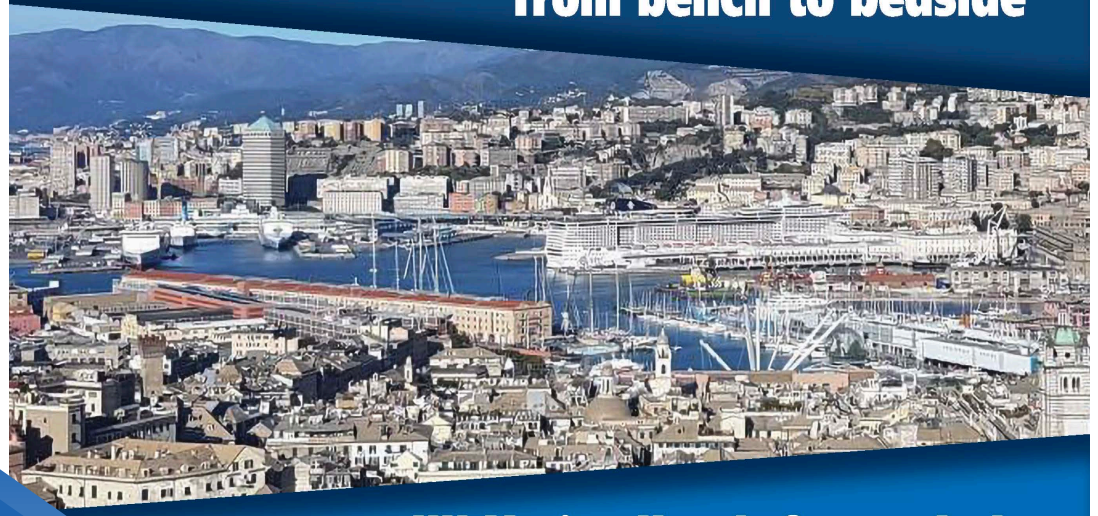
2023 Multiple Myeloma updates:
from bench to bedside



NH Marina Hotel, Genoa, Italy
20-21 November 2023

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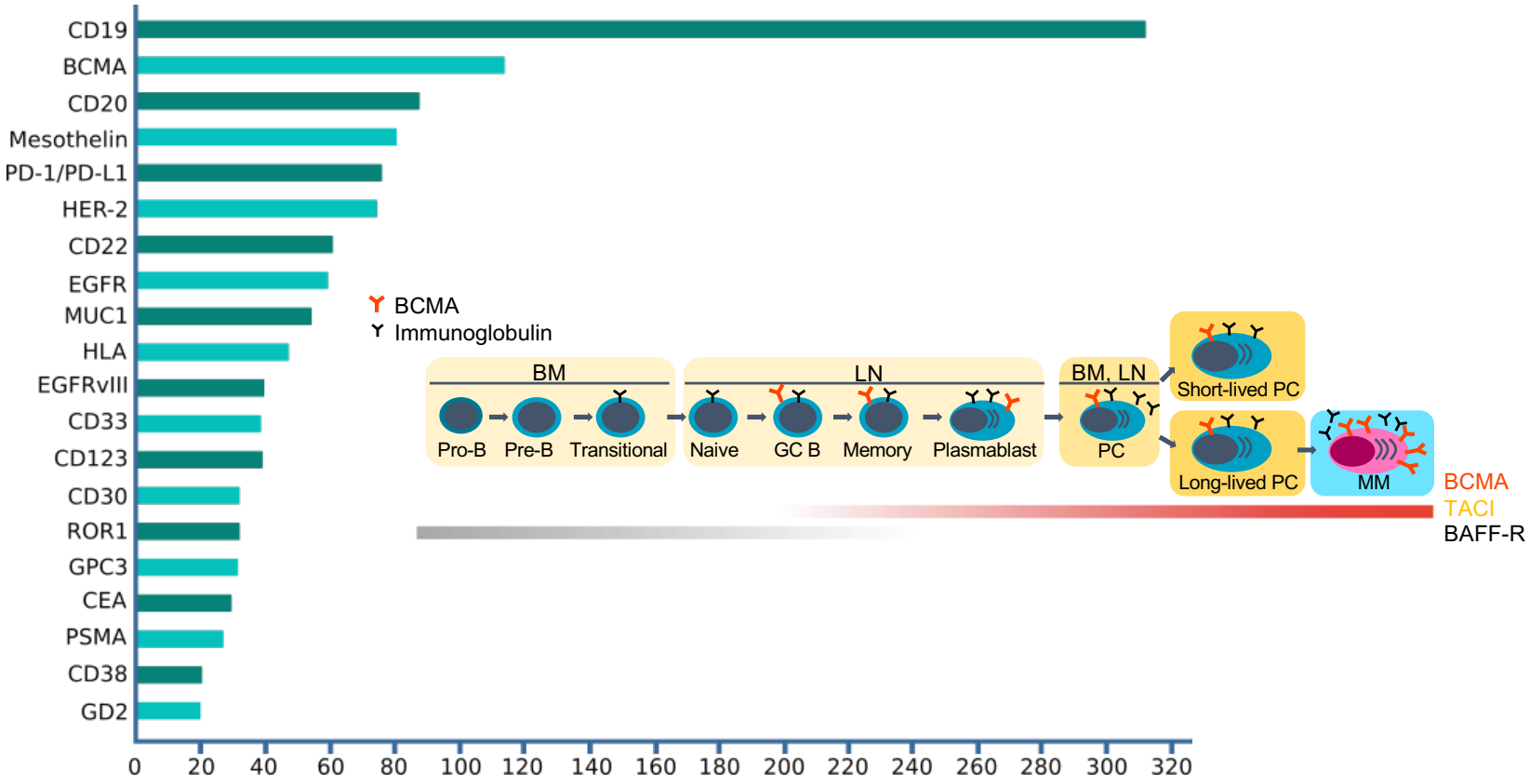
CAR T cells and bispecific antibodies in MM: how to tailor immunotherapy?

In conformità alla normativa prevista dalla Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

Disclosures of Benedetto BRUNO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GENENTA							X
JAZZPHARMA					X	X	
JANSSEN	X						X
NOVARTIS							X
BD SCIENCES					X		
AMGEN						X	
GSK					X		
INCYTE					X		
ABBVIE					X		
BEIGENE					X		

CAR-T Immunotherapy: The most popular CAR-T Targets



data from the U.S. Patent and Trademark Office (USPTO)

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

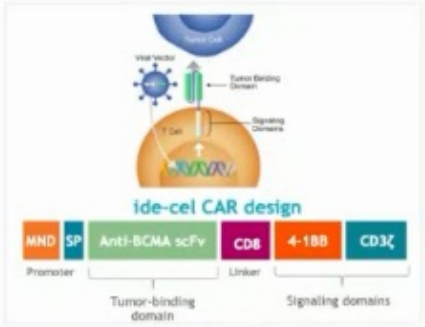
1. Munshi N, et al. ASCO 2020; 2. Usmani S, et al. ASCO 2022; 3. Rodrigues Otero, EBMT 2023; 4. Einsele H, et al. ASCO 2023; 5. Fernández de Larrea C, et al. EHA 2022; 6. Frigault MJ, et al. ASCO 2022; 7. Li C, et al. EHA 2022; 7. Du J, et al. ASCO 2022; 8. Sperling et al. ASCO 2023; 9. Huang H, et al.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

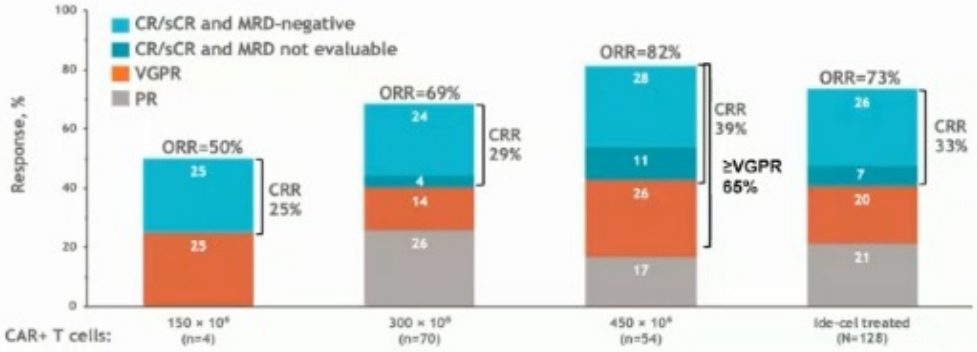
Ide-cel approval: the KarMMa trial

FDA approved in 2021
EMA approved in 2021

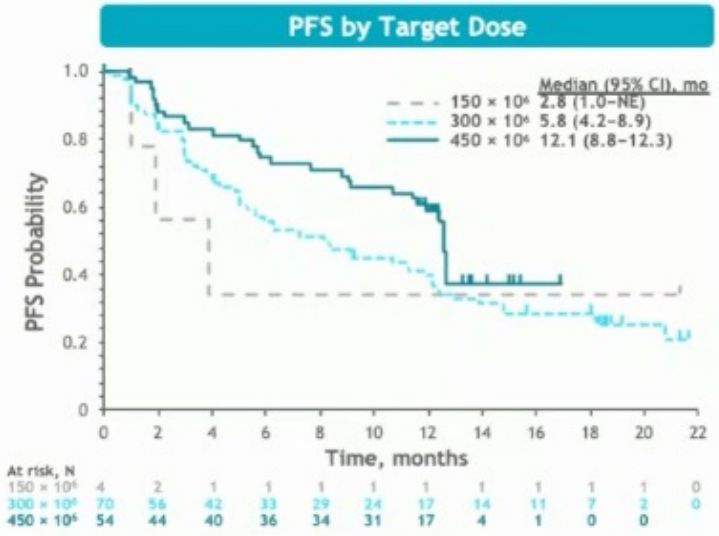
Second generation CAR-T cell, anti-BCMA murine scFv, 4-1BB costimulatory domain

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





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)



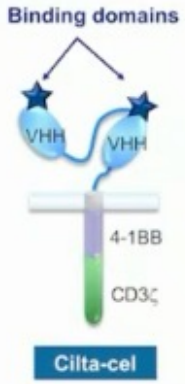
mOS = 24.8 mo

Munshi N, et al. *NEJM* 2021

Cilta-cel approval: the CARTITUDE-1 trial

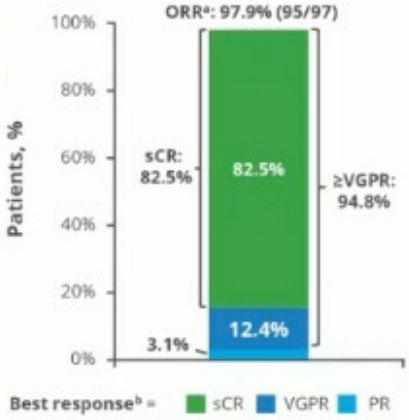
FDA approved in 2022
EMA approved in 2022

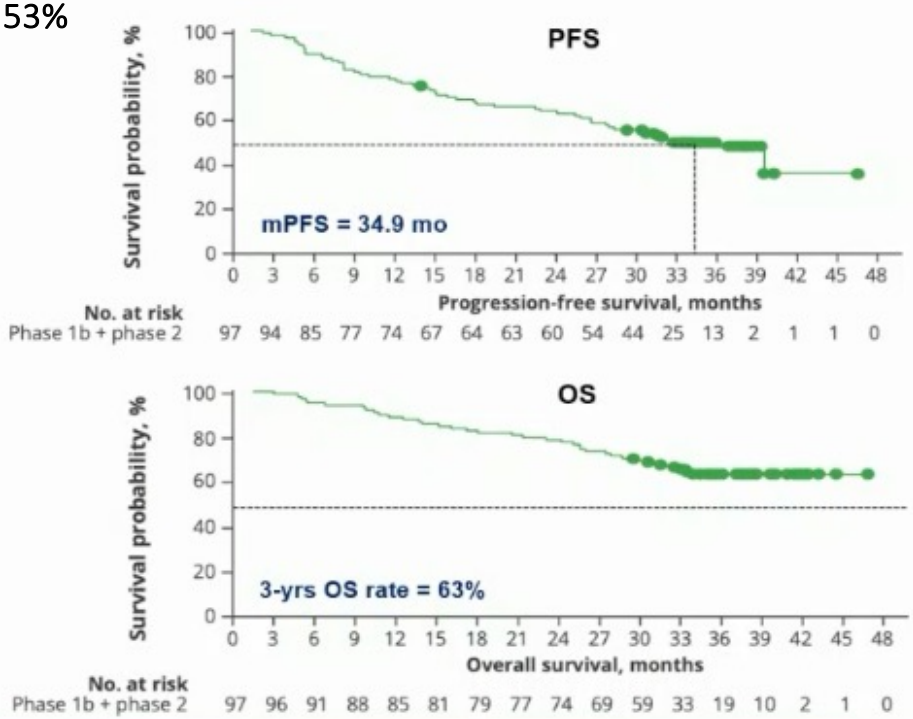
Second generation CAR-T cell, 2 anti-BCMA camelid VHH single domains, 4-1BB costimulatory domain



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%

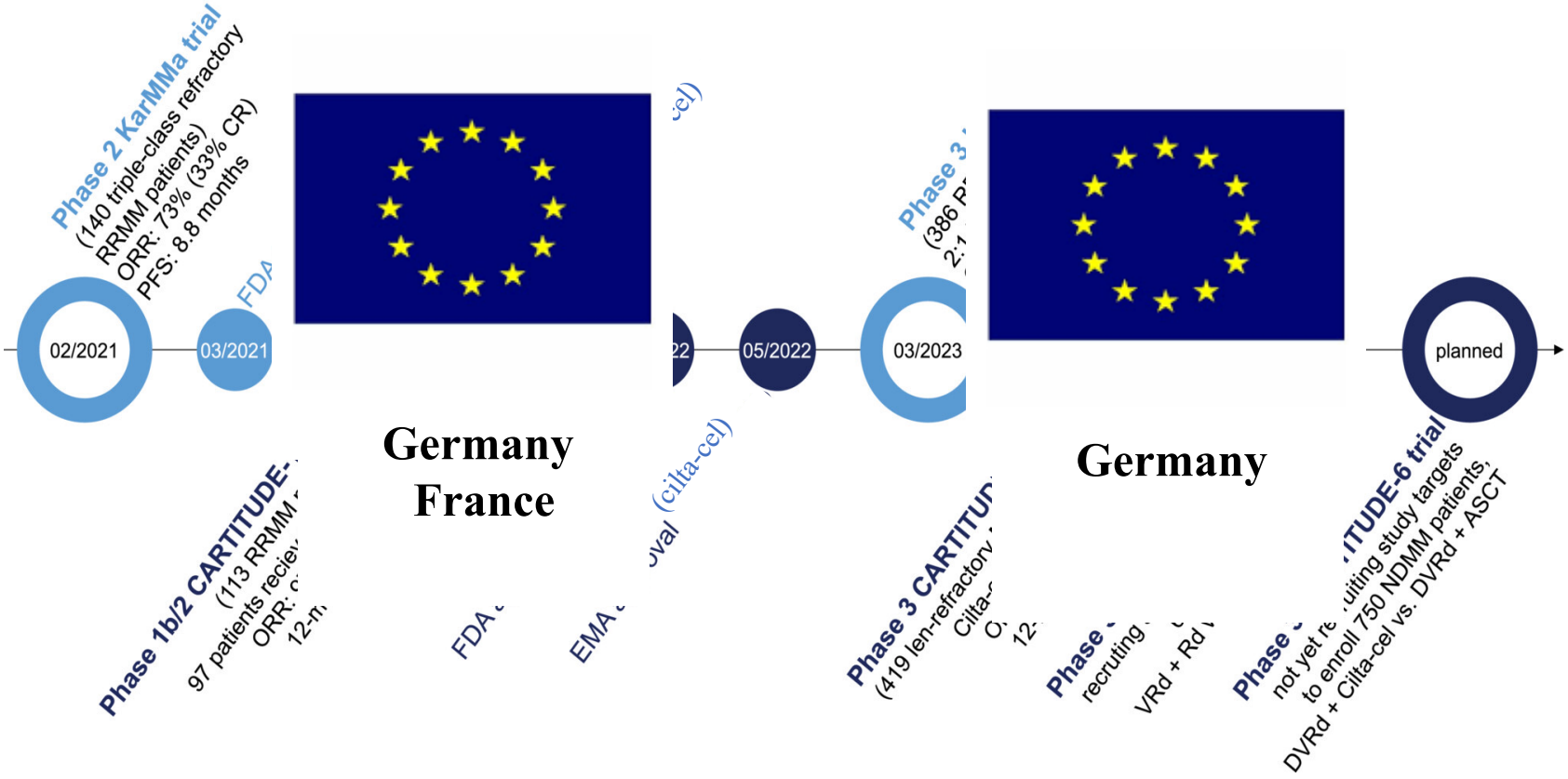




AE, n (%)	Cilta-cel-Treated (N=97)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	93 (96)	92 (95)
Anemia	79 (81)	66 (68)
Thrombocytopenia	77 (80)	58 (60)
CRS	92 (95)	6 (5)
Neurotoxicity	20 (21)	10 (10)

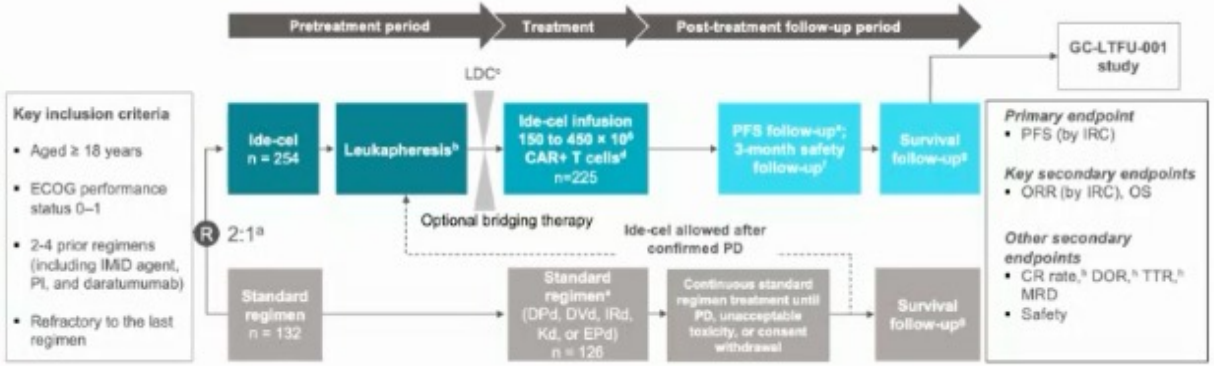
Berdeja J, et al. *Lancet* 2022;
Lin Y. et al. ASCO 2023

Timeline of approval of CAR T cell therapies in multiple myeloma

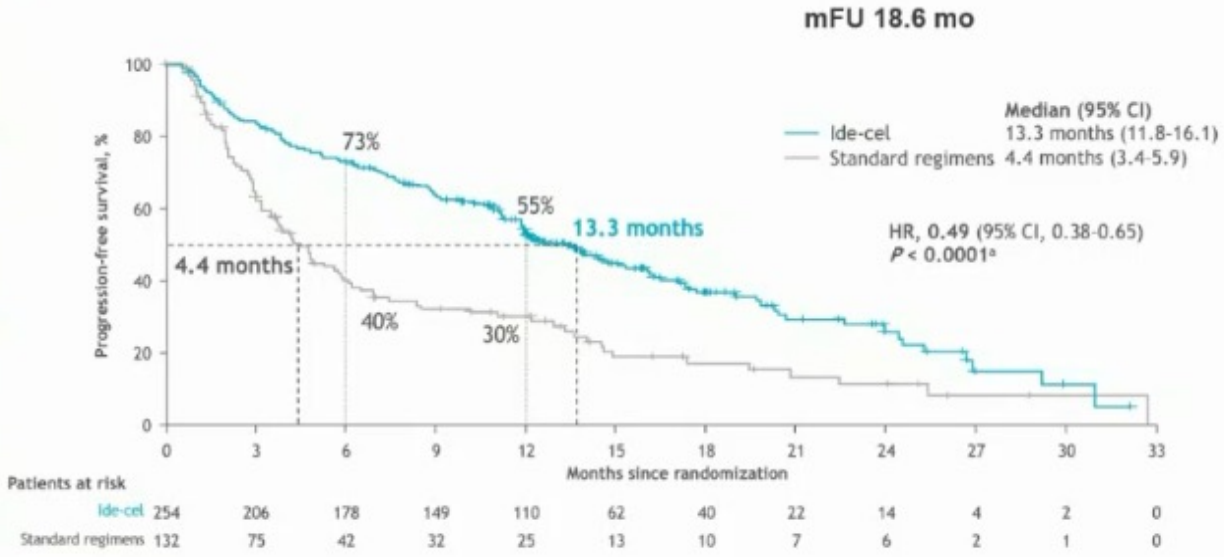


Adapted from Fisher et al. European J of Haematology, 2023

KarMMa-3, phase 3 trial (2 to 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)



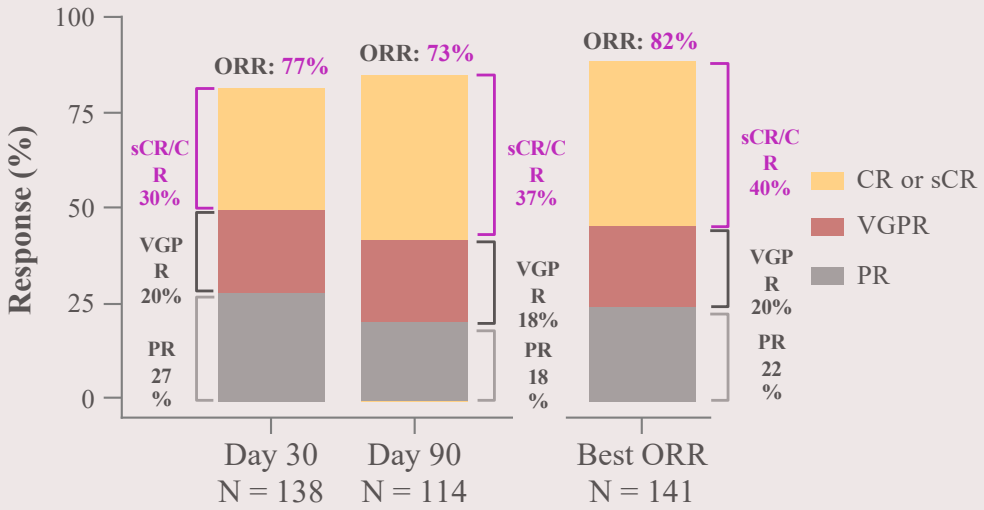
All-cause AEs occurring in ≥ 20% patients, n (%)	Ide-cel (n = 250) Any grade	Ide-cel (n = 250) Grade 3/4	Ide-cel (n = 250) Grade 5	Standard regimens (n = 126) Any grade	Standard regimens (n = 126) Grade 3/4	Standard regimens (n = 126) Grade 5
Any	248 (99)	233 (93)	36 (14)	123 (98)	94 (75)	8 (6)
Other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

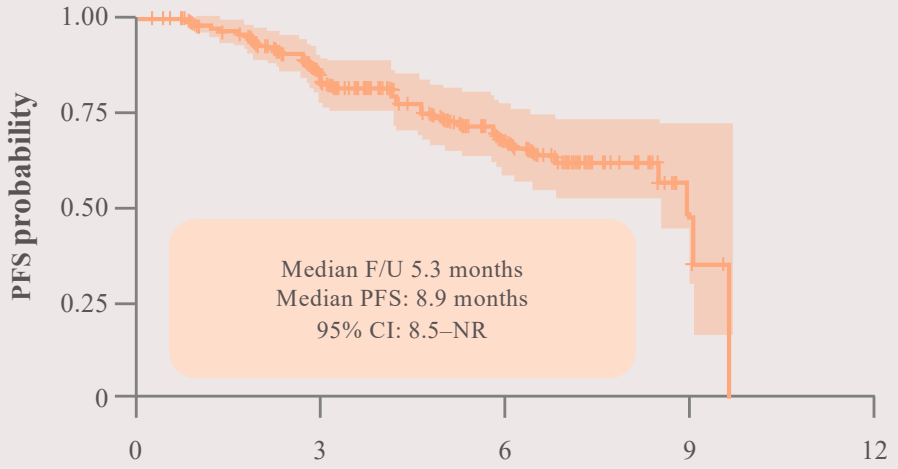
Giralt et al. ASTCT 2023, Rodrigues Otero et al. *NEJM* 2023

Real-world outcomes of patients treated with ide-cel

Day 30, 90, and best overall tumor responses



Real world PFS



Real world data with Ide-cel mirrors data from clinical trial[1]

1Hansen DK, et al. Poster presented at IMS 2022:abstract OAB-004. J Clin Oncol 2023

RESEARCH SUMMARY

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Rodriguez-Otero P et al. DOI: 10.1056/NEJMoa2213614

CLINICAL PROBLEM

Idecabtagene vicleucel (ide-cel) — a chimeric antigen receptor (CAR) T-cell therapy that targets B-cell maturation antigen expressed on myeloma cells — is approved in the United States for the treatment of relapsed or refractory multiple myeloma after the receipt of at least four previous lines of therapy. Its efficacy in less heavily pretreated disease is unclear.

CLINICAL TRIAL

Design: An international, phase 3, open-label, randomized trial assessed the efficacy and safety of ide-cel, as compared with standard regimens, in adults with triple-class–exposed relapsed and refractory multiple myeloma who had received two to four lines of therapy previously and who had disease refractory to the most recent regimen.

Intervention: 386 patients whose previous lines of therapy included daratumumab, immunomodulatory agents, and proteasome inhibitors and who had progressive disease within 60 days after completing the last therapy were assigned in a 2:1 ratio to receive a single infusion of ide-cel or to one of five standard regimens. The primary end point was progression-free survival. Key secondary end points were overall response (partial response or better) and overall survival.

RESULTS

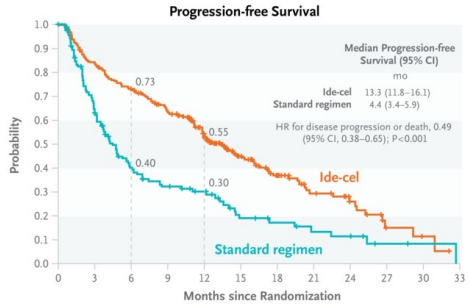
Efficacy: At a median follow-up of 18.6 months, progression-free survival was significantly longer in the ide-cel group than in the standard-regimen group.

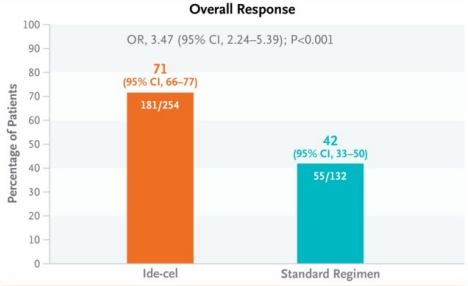
Safety: Grade 3 or 4 adverse events occurred more often with ide-cel than with standard regimens. Most ide-cel recipients had cytokine release syndrome, which usually was low-grade. Neurotoxic effects also occurred in the ide-cel group.

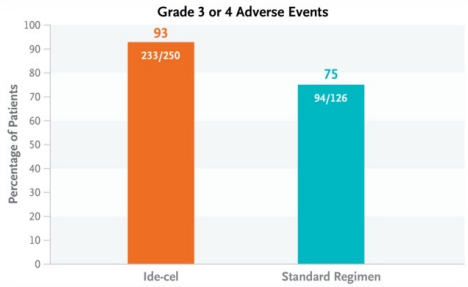
LIMITATIONS AND REMAINING QUESTIONS

- The proportion of Black patients was not balanced between the groups.
- The investigators' choice of standard regimens may have introduced treatment heterogeneity in that group.
- Mechanisms underlying ide-cel resistance remain unknown.

Links: Full Article | NEJM Quick Take





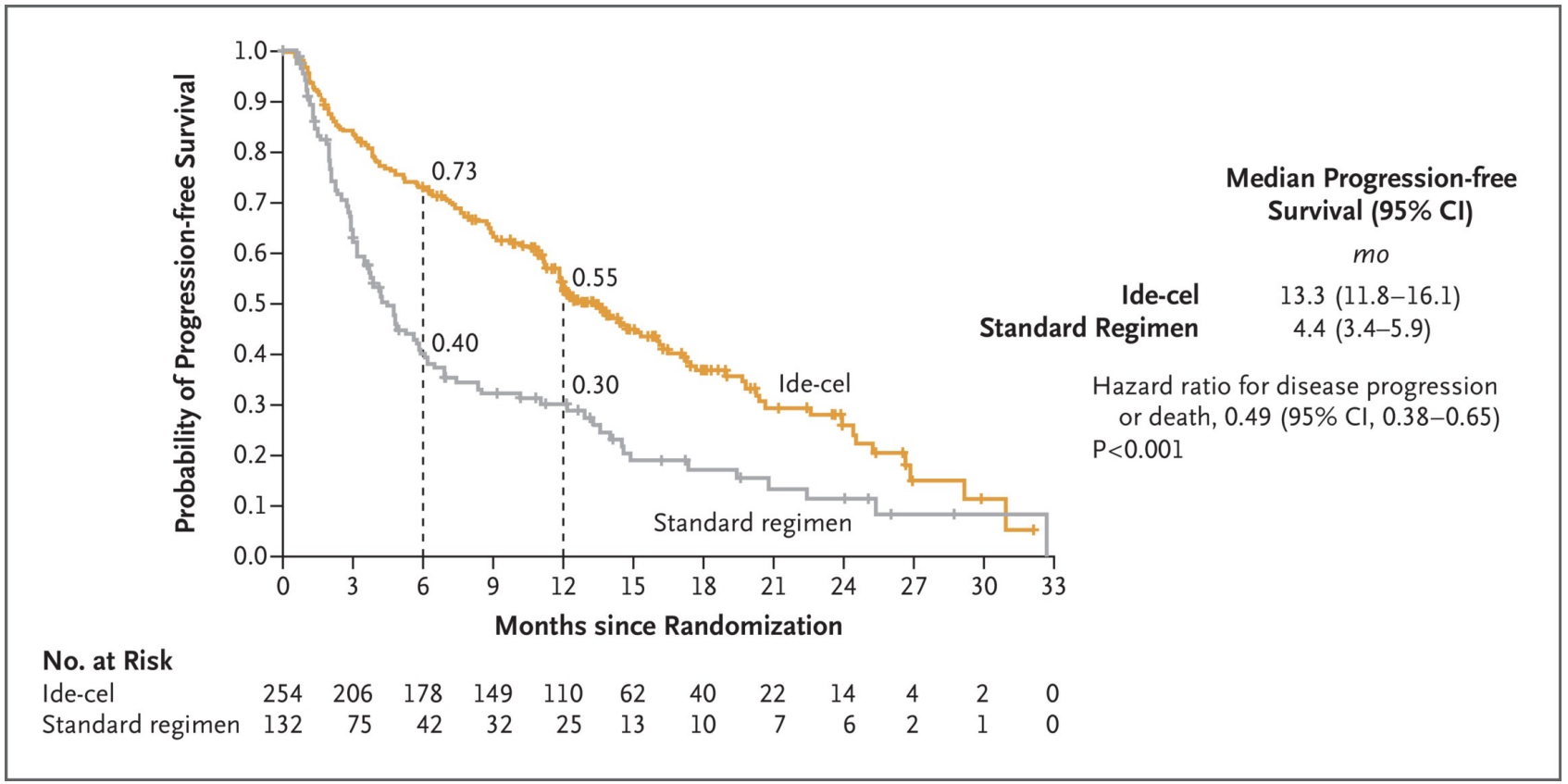


CONCLUSIONS

Among adults with heavily pretreated relapsed and refractory multiple myeloma who had received two to four lines of therapy previously, the CAR T-cell therapy ide-cel led to significantly longer progression-free survival than standard regimens.

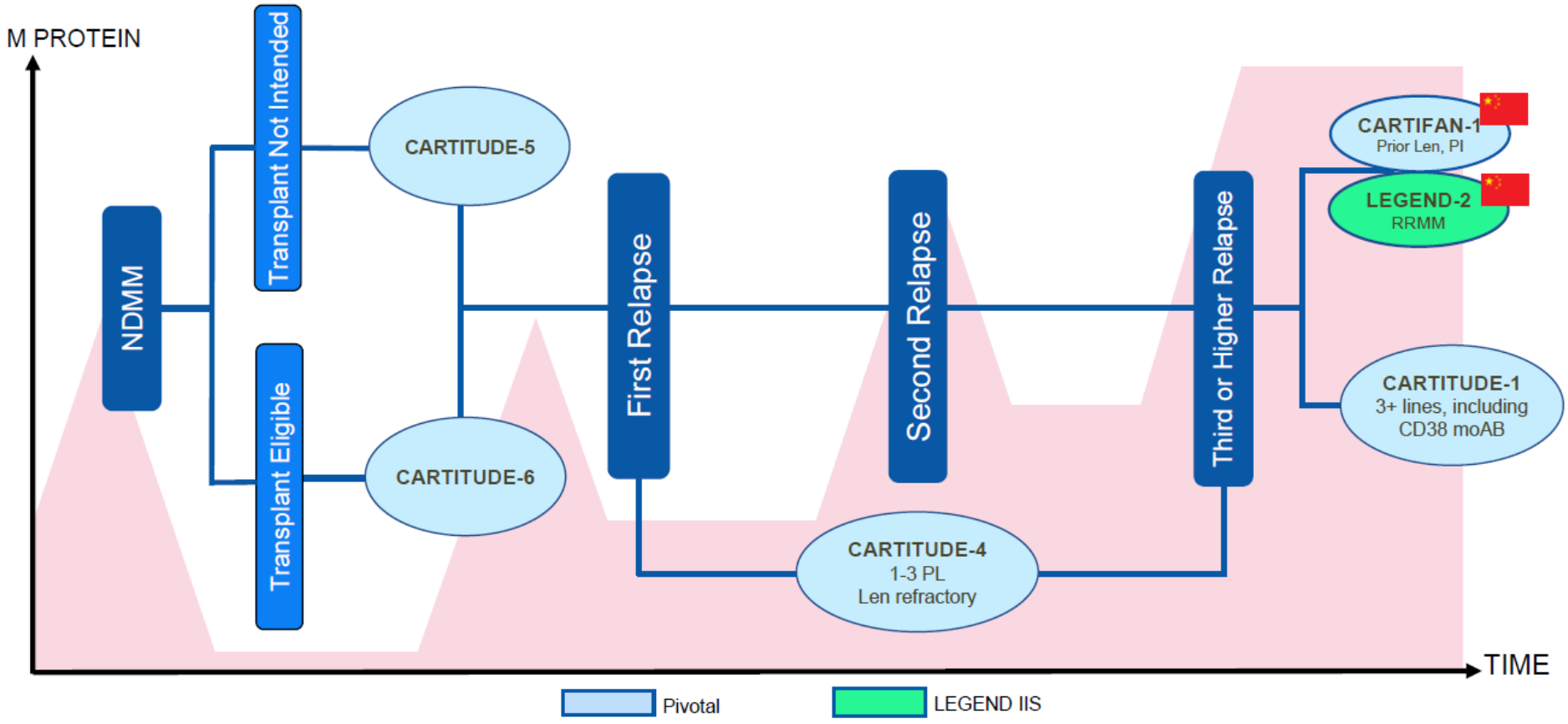
P Rodriguez-Otero et al. N Engl J Med 2023

Progression-free Survival (Intention-to-Treat Population)

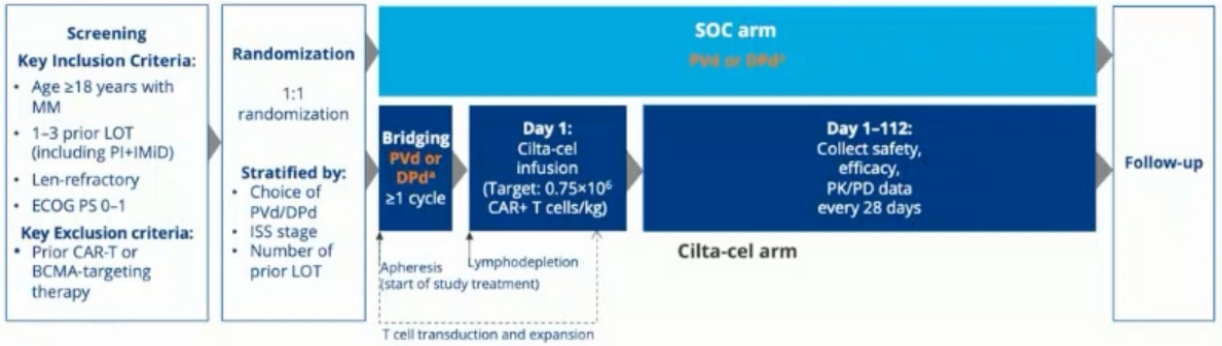


P Rodriguez-Otero et al. N Engl J Med 2023

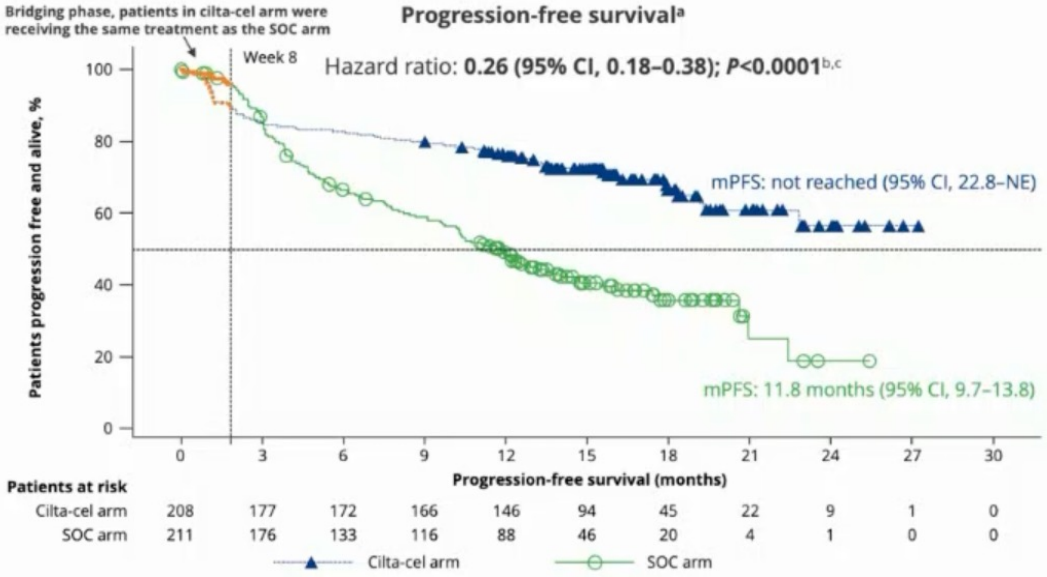
Overview of Cilta-cel clinical trials

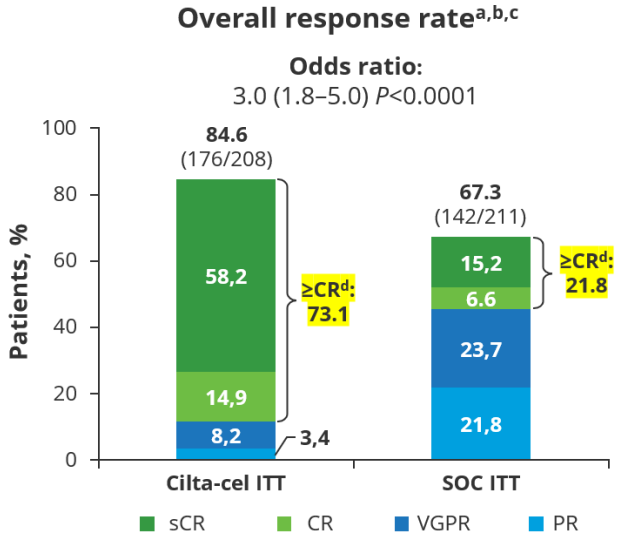


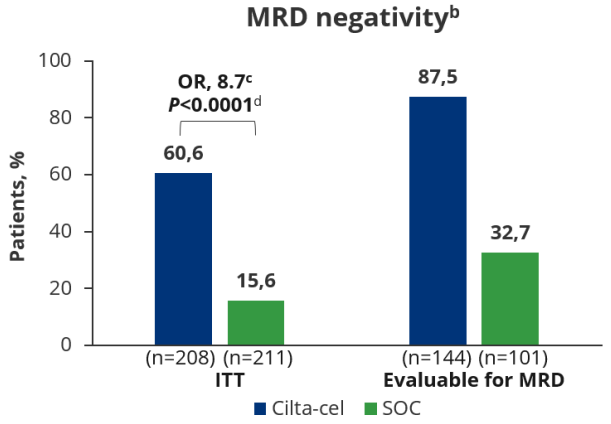
CARTITUDE-4, phase 3 trial (1 to 3 prior lines)



mFU 15.9 mo



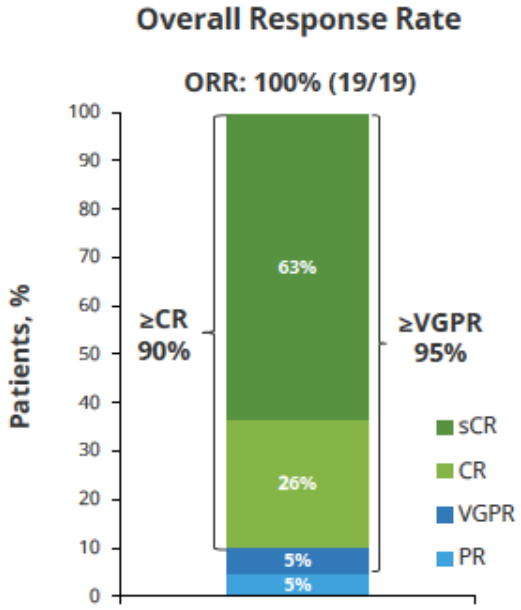


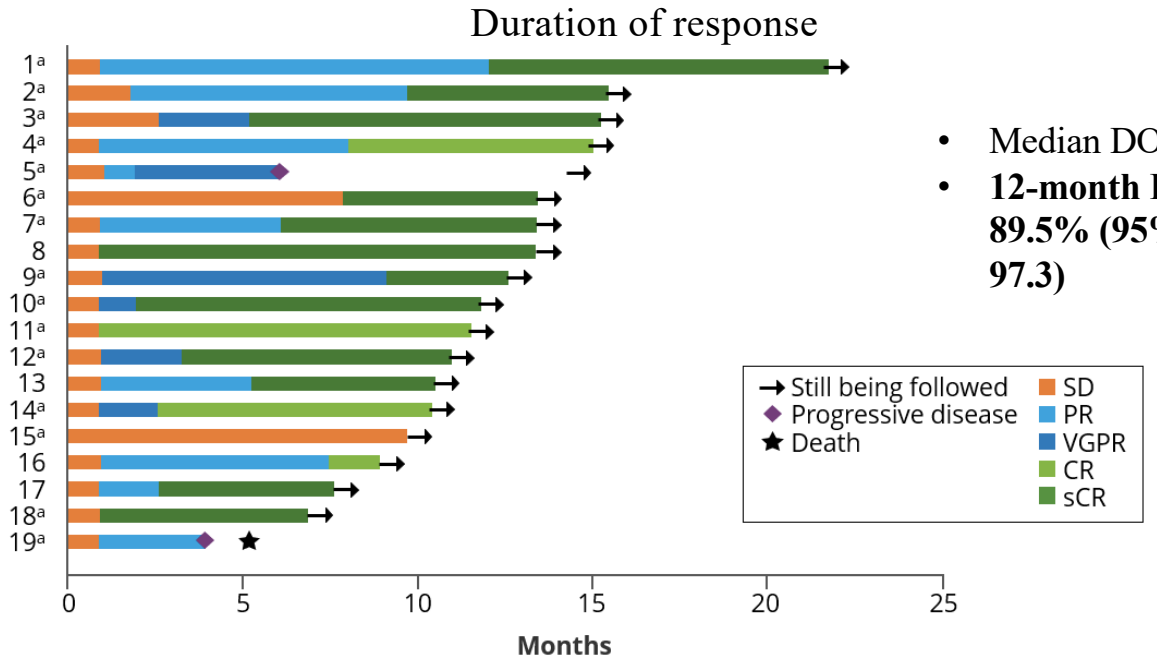


Dhakal et al. ASCO 2023

CARTITUDE-2 Cohort B:
Cilta-cel in patients with MM an early relapse after initial therapy (n=19)

Patient population: early relapse after initial therapy with a PI and IMID withing 12 m after ASCT or after initiation of therapy.
Triple-class exposed 21.1%, refractory to last line of therapy 78.9%





- Median DOR was NR
- **12-month PFS rate was 89.5% (95% CI, 64.1–97.3)**

- Of the 15 patients with MRD-evaluable samples at 10-5threshold, 14 (93.3%, [95% CI, 68.1–99.8]) were MRD negative
- Median time to first response 1 m (0.9-9.7 m)

- Safety was manageable and comparable to safety reported in CARTITUDE-1
- Grade 3/4 neutropenia and thrombocytopenia not recovered at day 60 was 11% and 16%, respectively
- CRS occured in 16/19 patients (G3/4 1 patient). Tocilizumab used 63%. Median time to onset 8 days.
- ICANs: 1 patient (G1). MNT 1 patients at day +38 still ongoing (grade 3).

van de Donk N et al. ASH 2022; abstract 3354 (poster presentation)

CARTITUDE-6 (MMY3005, NCT05257083)

Primary objective

- To compare efficacy of DVRd followed by cilta-cel and lenalidomide vs. DVRd followed by ASCT, DVRd consolidation, and lenalidomide, in terms of sustained MRD negative CR rate and PFS

Secondary objectives

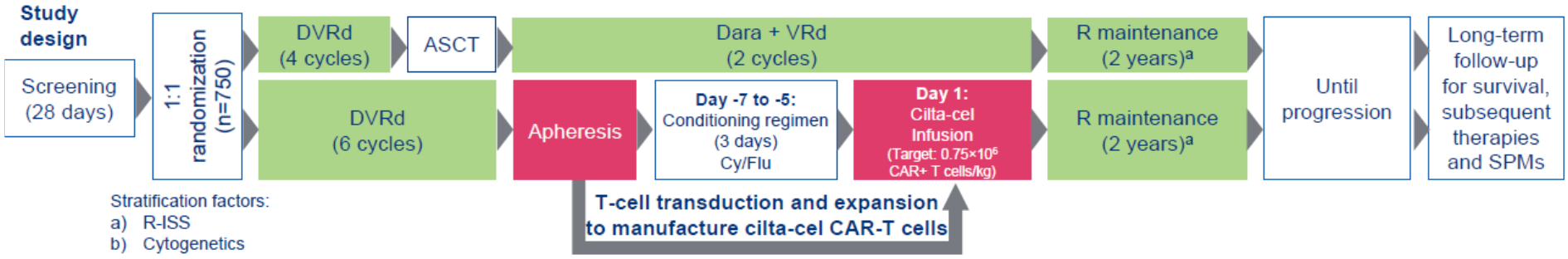
- To further compare efficacy: ORR, ≥CR, overall MRD- CR, time to subsequent anti-myeloma therapy, PFS2, OS
- To characterize safety, PK, and PD

Key inclusion criteria

- Age ≥18 years
- NDMM, per IMWG criteria, with measurable disease at screening
- Intended for ASCT
- ECOG 0 or 1

Key exclusion criteria

- Prior CAR-T therapy (any target)
- Prior therapy directed at BCMA
- Prior therapy for MM or SMM
- Active malignancies other than MM

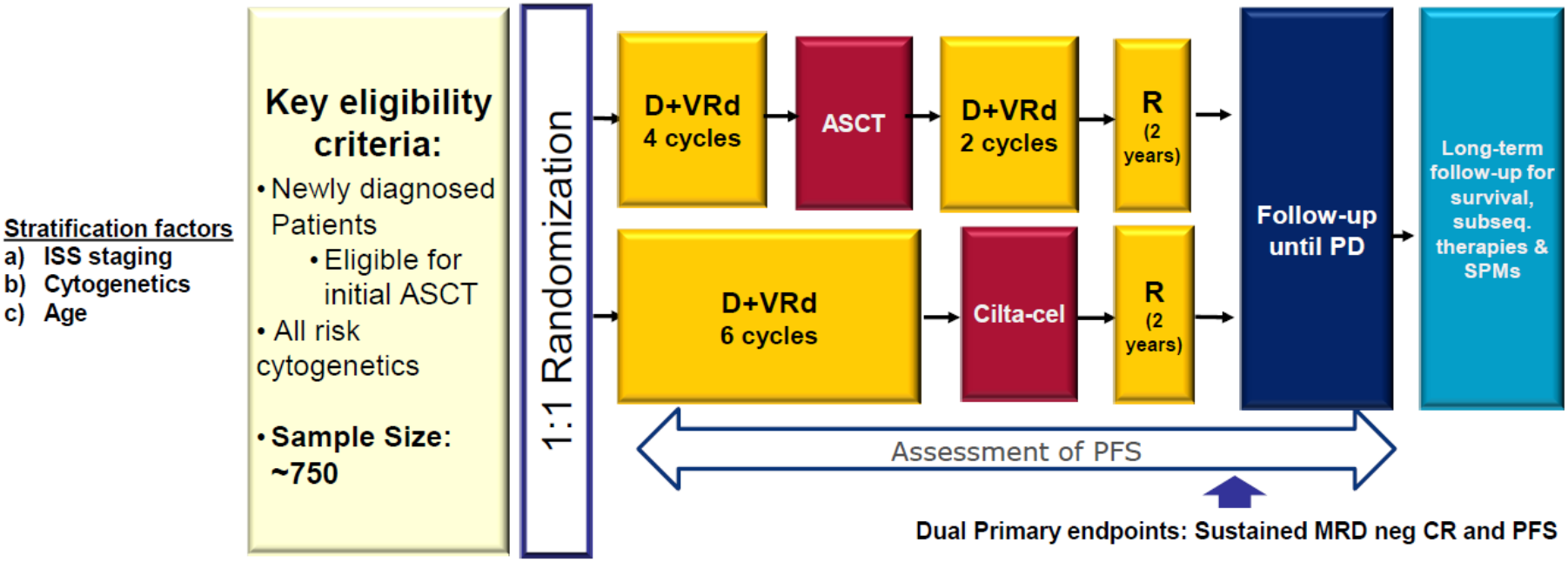


While R maintenance is limited to 2 years, a small subset of patients may receive R until progression at investigator's discretion. There is the potential to further amend the protocol to balance the arms egarding use of R for 2 years vs. use of R until disease progression. Our goal would be to keep the proportion receiving Revlimid >2 years to be quite low (ie, <20%).
Clinicaltrials.gov NCT05257083.

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)

CAR-T as first-line therapy in ND NTEMM: CARTITUDE-5: A Randomized, Phase 3 Study

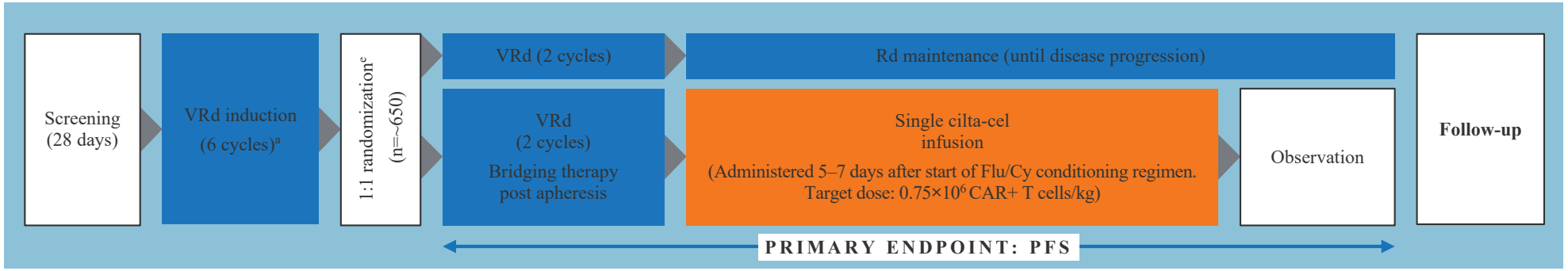
All patients will complete 6[a] cycles (21 days each) of VRd induction therapy[b] prior to randomization (1:1)

VRd + cilta-cel arm

- Apheresis and 2 more cycles of VRd as bridging therapy
- Lymphodepletion daily for 3 days[c]
- Cilta-cel as a single infusion

VRd + Rd arm (SOC)

- Two more cycles of VRd
- Rd maintenance therapy[d] continues until progressive disease or unacceptable toxicity



[a]Participants who received 1 cycle of VRd prior to screening will only receive 5 cycles of VRd between screening and randomization
[b]Bortezomib 1.3 mg/m^2 subcutaneously on days 1, 4, 8, and 11, lenalidomide 25 mg orally on days 1–14, dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12
[c]Cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2
[d]28-day cycle: lenalidomide 25 mg orally on days 1–21 and dexamethasone 40 mg orally on days 1, 8, 15, and 22
[e]At randomization, patients will be stratified by the following factors: R-ISS (I,II,III); age/transplant eligibility (≥70 years or <70 years and ASCT ineligible due to comorbidities or <70 years and ASCT deferred); response to VRd induction (≥VGPR, ≤PR)
ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; Cy, cyclophosphamide, Flu, fludarabine; PR, partial response; Rd, lenalidomide-dexamethasone; R-ISS, revised international staging system; SOC, standard of care; VGPR, very good partial response; VRd, bortezomib-lenalidomide-dexamethasone

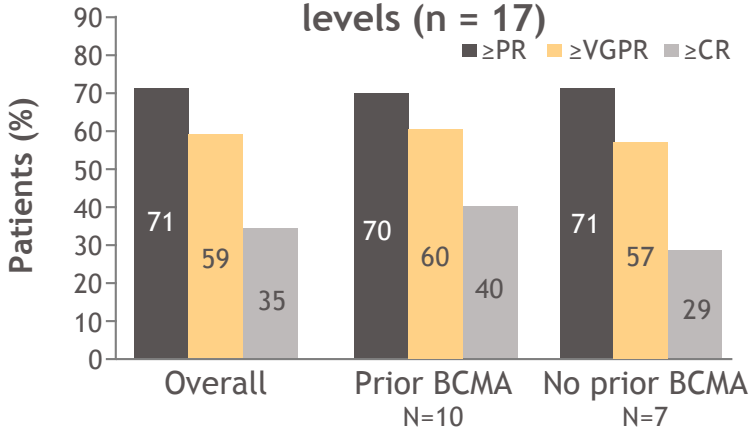
Dytfeld D et al. ASH 2021: Abstract 1835 (poster)

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)

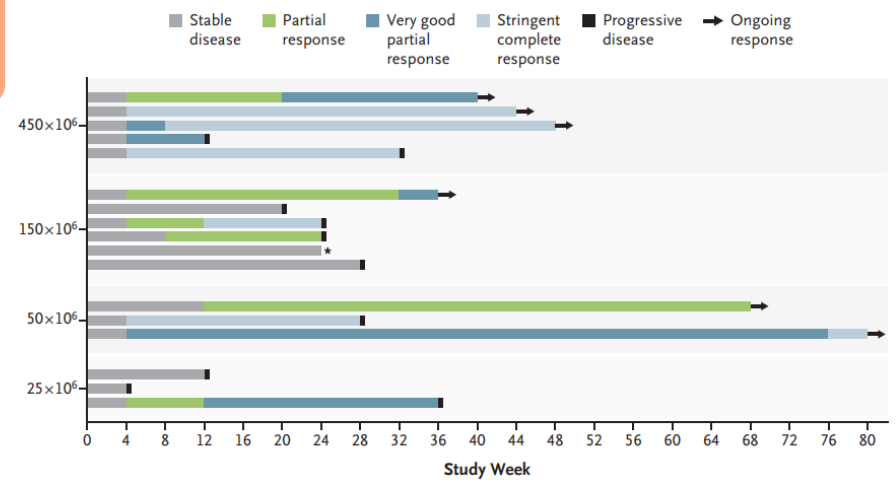


50% of patients were MRD negative

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%)
- 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%**

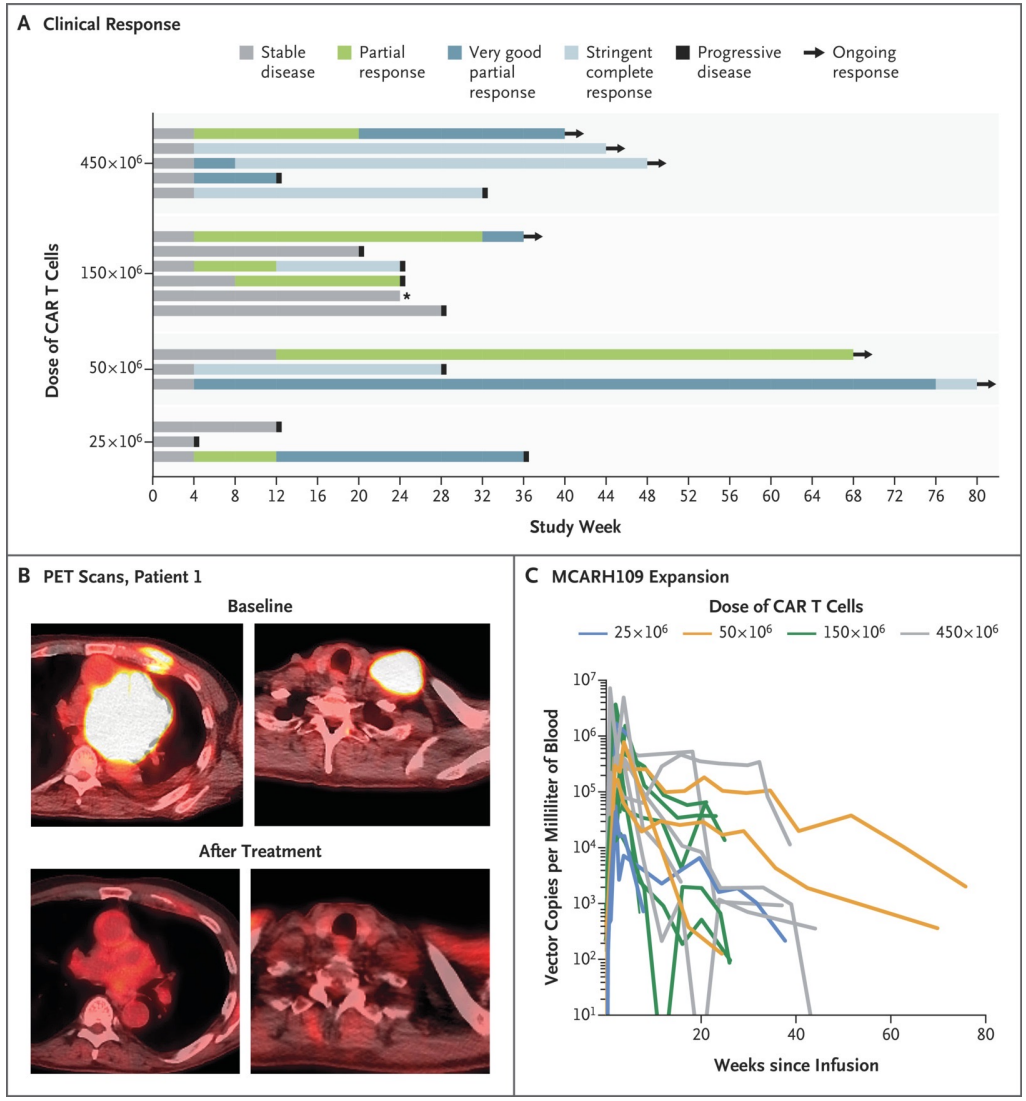
MCARH109 is an investigational product and has not been approved by any regulatory agency

EMD, extramedullary disease; MAS, macrophage activation syndrome.

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

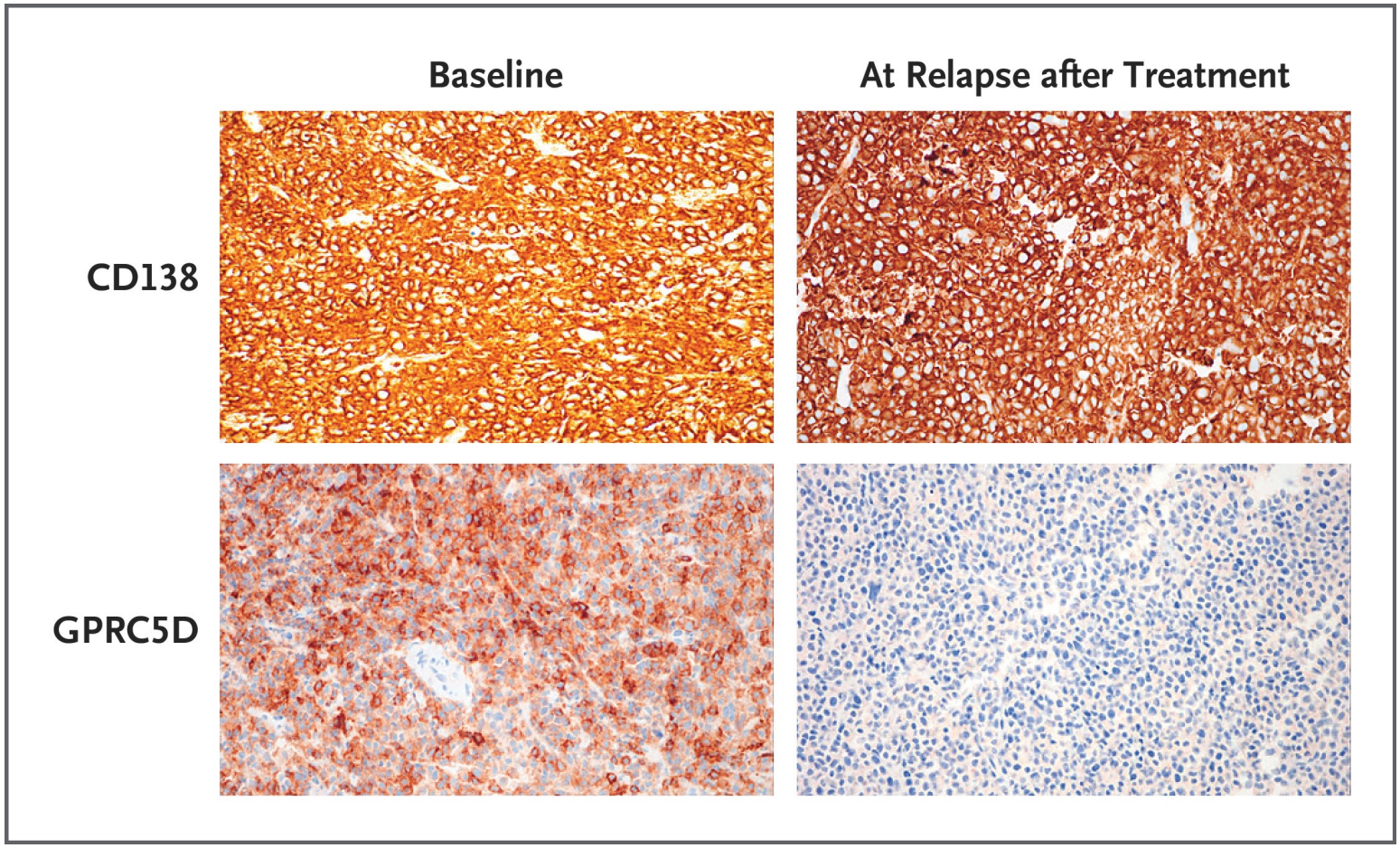
Mailankody S et al. N Engl J Med 2022

Clinical Responses to GPRC5D-Targeted Chimeric Antigen Receptor (CAR) T-Cell Therapy.



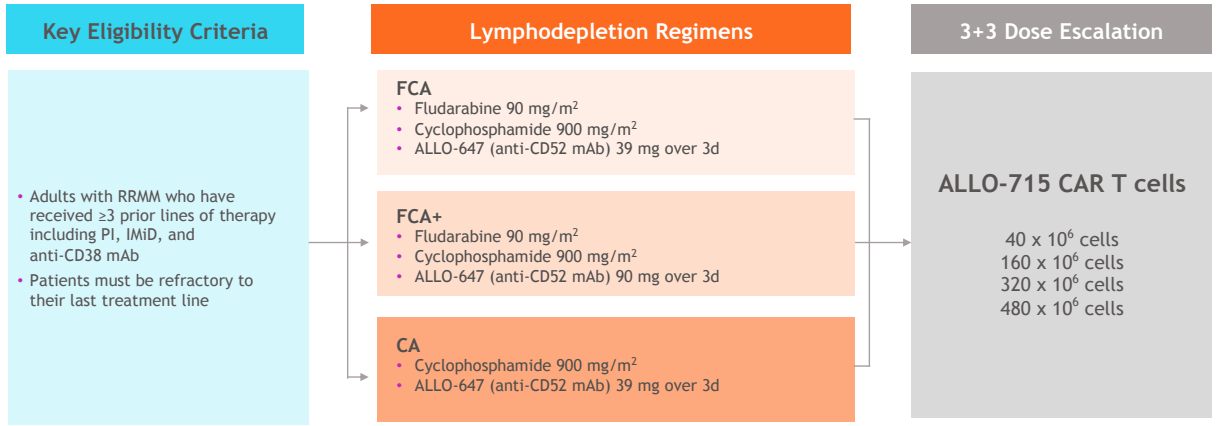
Mailankody S et al. N Engl J Med 2022

Loss of GPRC5D on Immunohistochemical Analysis at Relapse after MCARH109 Infusion.



Mailankody S et al. N Engl J Med 2022

ALLO-715: Anti-BCMA Allogeneic CAR T in RRMM
Study Design: Phase 1, 3 + 3 Dose Escalation



Analysis on **43 pts**, 5 median prior LOT, 42% penta-refractory

AE of Interest* (N=43)	Grade 1-2 n (%)	Grade ≥3 n (%)
Cytokine Release Syndrome†	24 (55.8)	1 (2.3)
ICANS†	6 (14)	0
Infection‡	20 (47)	7 (17)
Infusion Reaction to ALLO-647	12 (28)	0

Cell dose and LD regimen[a]	40×10⁶ CAR⁺ T cells	160×10⁶ CAR⁺ T Cells	320×10⁶ CAR⁺ T cells				480×10⁶ CAR⁺ T Cells	
	FCA39*n*=3	FCA39*n*=4	FCA39*n*=11	FCA60*n*=10	FCA90*n*=3	All FCA*n*=24	FCA39*n*=3	FCA60*n*=3
ORR[b], *n* (%) (95% CI)	0	2 (50) (6.8, 93.2)	7 (64) (31, 89)	8 (80) (44, 98)	2 (67) (9, 99)	17 (71) (49, 87)	1 (33) (0.8, 91)	2 (67) (9, 99)
VGPR⁺ rate, *n* (%)	0	1 (25)	5 (46)	5 (50)	1 (33)	11 (46)	0	2 (67)
CR/sCR rate, *n* (%)	0	0	3 (27)	3 (30)	0	6 (25)	0	0
mDOR, months (95% CI)	N/A	5.6 (1.4, 5.6)	8.3 (3.4, 11.3)	NE (5.6, NE)	3.1 (2.4, 3.1)	8.3 (3.4, 11.3)	1.4 (NE, NE)	NE (1.5, NE)
Median follow-up, months (range)[c]	11 (3, 17)	5 (1, 8)	4 (1, 14)	5 (1, 12)	4 (3, 13)	4 (1,14)	3 (1, 13)	10 (2,12)

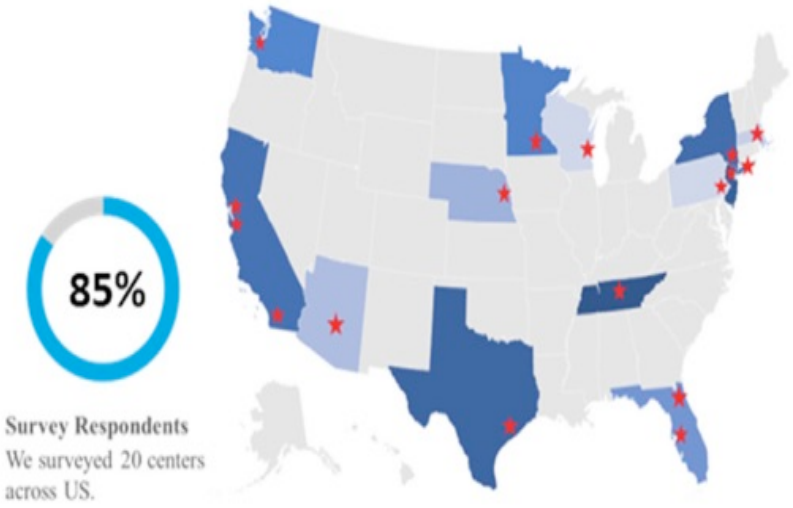
[a]FCA conditioning with fludarabine, cyclophosphamide and varying doses of ALLO-647 including total doses of 39 mg (13 mg per day; FCA39), 60 mg (20 mg per day; FCA60) and 90 mg (30 mg per day, FCA90). [b]Clinical response evaluation was based on International Myeloma Working Group response criteria[36] and an objective response is defined as a partial response or better. [c]Follow-up time (months) is calculated as the time between ALLO-715 administration and either the end of study date or date of data cutoff. N/A, not applicable; NE, not estimatable.

Mailankody S et al, Nat Med, 2023

Shadows in the use of CAR-T therapy

Financial toxicity

Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience



1 or 2 ide-cel slot was allocated per month per center,

However, the median number of patients per center on the waitlist since ide-cel approval was 20 per month (range, 5 to 100).

patients remained on the waitlist for a median of 6 months prior to leukapheresis (range, 2 to 8).

results reported across 14 centers showed that **approximately 25% of patients received a leukapheresis slot for commercial CAR-T therapy, 25% enrolled on another non-CAR-T clinical trial, 25% enrolled on a CAR-T clinical trials, and approximately 25% died or enrolled in hospice**

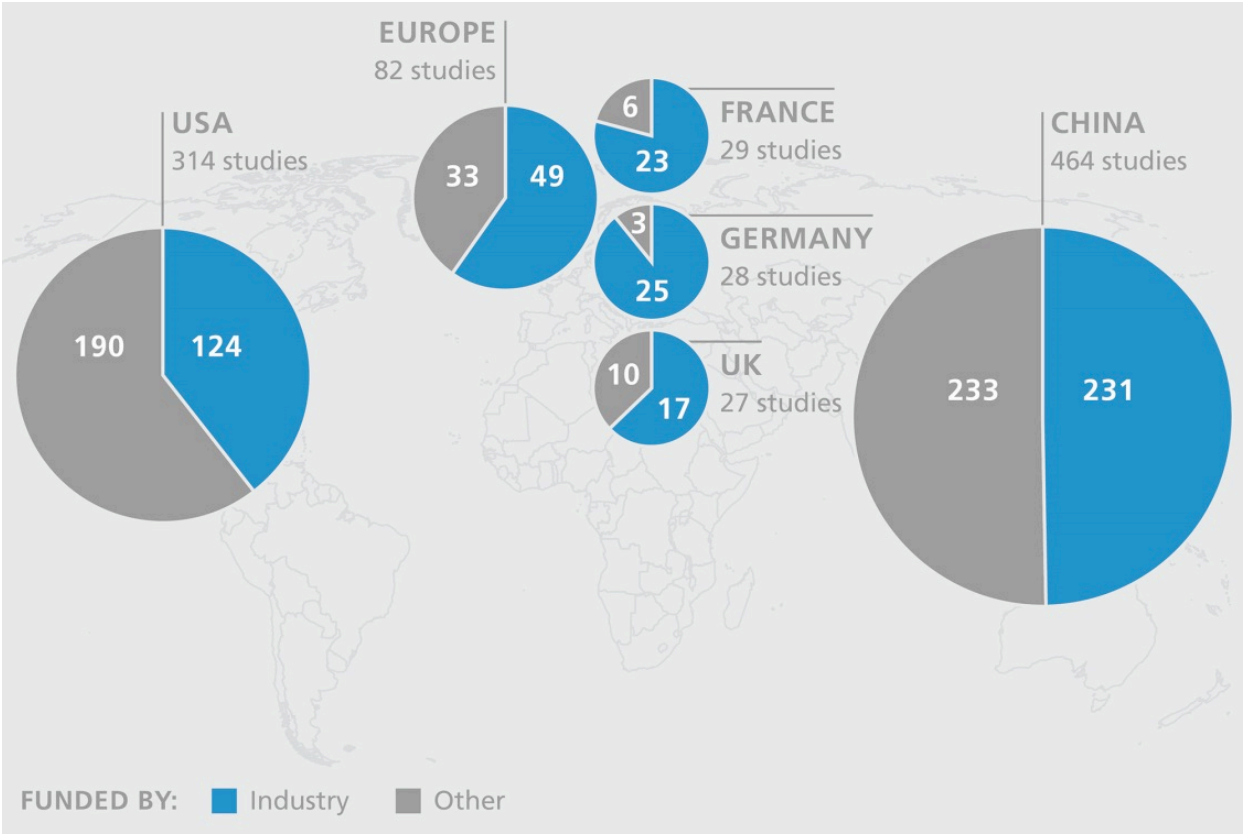
Kourelis et al. Transplant Cell Ther. 2023 Apr;29(4):255-258

Role of Academia

The current Biotech Report of the Boston Consulting Group shows that only around 10%-15% of studies are coordinated in Europe

in Europe an average of 60% of the studies are sponsored by industry (the level is even significantly higher in some member countries)

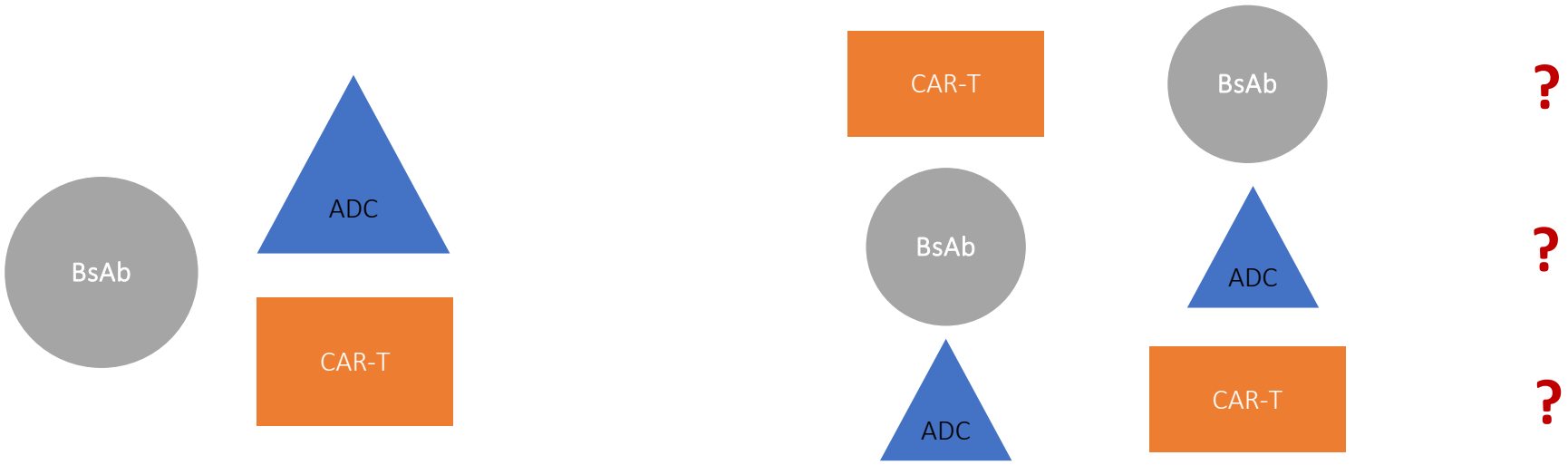
Top 5 countries of clinical CAR T cell studies with funding type (source: ClinicalTrials.gov).



Adapted from Vucinic V. et al. Frontiers in Medicine

Sequencing of anti-BCMA immune-therapies: is there a role?

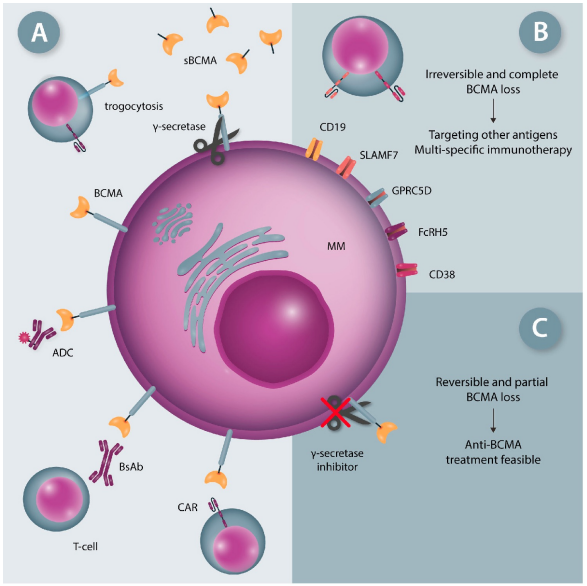
- Is BCMA still present?
- Do we know what was the mechanism of resistance leading to relapse under BCMA?
- What do we currently know about sequencing of anti-BCMA directed therapies?



ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell

What happens during anti-BCMA directed therapy?

BCMA Loss following target Immunotherapies



Authors	Year of publication	Type of immunotherapy	Product	Clinical trial identifier	Time point of BCMA loss	Methods	Frequency of BCMA loss in the study#	Biological mechanism of BCMA loss	Major findings	Reference
Ali *et al.*	2016	CAR T-cell	CAR-BCMA	NCT02215967	2 months after treatment	Flow cytometry	1/12	NR	Partial loss of BCMA expression in MM cells at progression in one patient	52
Brudno *et al.*	2018	CAR T-cell	CAR-BCMA	NCT02215967	56 weeks after treatment	Flow cytometry	1/16	NR	Mixed BCMA expression in one patient, with some MM cells negative for BCMA	53
Green *et al.*	2018	CAR T-cell	NR	NR	60 days after treatment	Flow cytometry	1/7	NR	Presence of BCMA-negative MM cells in one patient. On MM cells retaining BCMA expression: 70% reduction of BCMA expression and 5-fold reduction in BCMA antigen binding capacity in this patient	54
Cohen *et al.*	2019	CAR T-cell	CART-BCMA	NCT02546167	1 month after treatment	Flow cytometry	12/18	NR	Reduction of BCMA expression intensity in 67% (n=12) of the patients, including 8 of 9 responders and 4 of 9 non-responders	55
Truger *et al.*	2021	BsAb	AMG420	NCT02514239	6 months after treatment	IHC, WGS and RNA-seq	Case report	Homozygous *BCMA* gene deletion	Complete BCMA loss caused by homozygous *BCMA* gene deletion in one patient	56
Da Vià *et al.*	2021	CAR T-cell	Idecabtagene-vicleucel	NCT03361748	5 months after treatment	IHC, WGS and RNA-seq	Case report	Homozygous *BCMA* gene deletion	Complete BCMA loss caused by homozygous *BCMA* gene deletion in one patient	15
Samur *et al.*	2021	CAR T-cell	Idecabtagene-vicleucel	NCT02658929	8 months after treatment	IHC, WGS and RNA-seq	Case report	*BCMA* gene deletion + mutation	Biallelic BCMA loss (mutation + deletion) in one patient	14
Leblay *et al.*	2020	CAR T-cell	NR	NR	NR	Cellular indexing of transcriptomes and epitopes by sequencing	Case report	Homozygous *BCMA* gene deletion	Complete BCMA loss caused by homozygous *BCMA* gene deletion in one patient	16
Munshi *et al.*	2021	CAR T-cell	Idecabtagene-vicleucel	NCT03361748	NR	NR	3/71	NR	Loss of tumor BCMA expression was suspected in 3 of 71 patients (4%) at progression	51
Wang *et al.*	2022	CAR T-cell	China	ChiCTR-OIC-17011272	NR	Flow cytometry	1/21	NR	One (5%) patient relapsed with BCMA-negative MM cells	76

ICMA: B-cell maturation antigen; BsAb: bispecific antibody; CAR T-cell: chimeric antigen receptor modified T-cell; IHC: immunohistochemistry; MM: multiple myeloma; NR: not eported; RNA-seq: single-cell RNA sequencing; WGS: whole-genome sequencing; #Among the patients with evaluable BCMA expression at baseline and relapse.

ADC: antibody drug conjugate; BCMA: B-cell maturation antigen; BsAb; bispecific antibody; CAR T-cell; chimeric antigen receptor modified T cell; FcRH5: Fc receptor-homolog 5; GPRC5D; G protein coupled receptor class C group 5 member D; MM: multiple myeloma; RR: relapsed/refractory; sBCMA; soluble BCMA; SLAMF7: signaling lymphocytic activation molecule F7

Zhou X et al, Haematologica .2023; 108(4):958-968

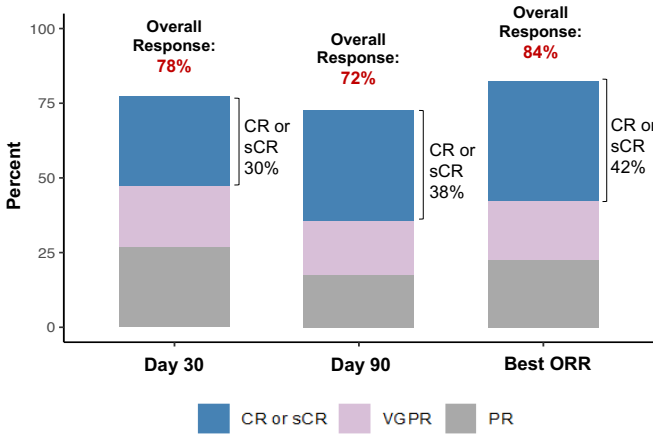
Idecel Real word data

Characteristics Differentiating Real-World Patients from KarMMa

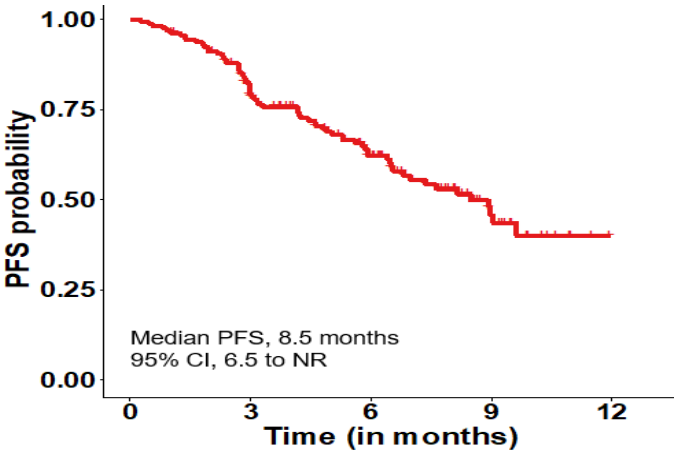
75% (N=120) of patients would have been ineligible for participation in the KarMMa clinical trial

KarMMa Exclusion Criteria	N (%)
Organ dysfunction (renal, cardiac, hepatic)	45 (28)
Prior anti-BCMA therapy	33 (21)
Platelets < 50,000/μL	33 (21)
Hemoglobin < 8 g/dL	25 (16)
ECOG Performance status ≥ 2	28 (18)
ANC < 1000/μL	22 (14)
PCL, POEMS, amyloidosis, non-secretory	11 (7)
CNS myeloma and other CNS pathology	13 (8)
Prior allogeneic SCT	9 (6)
Other malignancies	10 (6)

Day 30, Day 90, and Best Overall Tumor Responses for SOC Ide-Cel



Real World PFS



Median F/U 6.1 months
Median PFS: 8.5 months
95% CI: 6.5 – Not reached

Hansen DK et al JCO2023, presented at IMS workshop Boston 2023

Anti-BCMA CAR-T in anti-BCMA exposed/refractory: ide-cel real life data

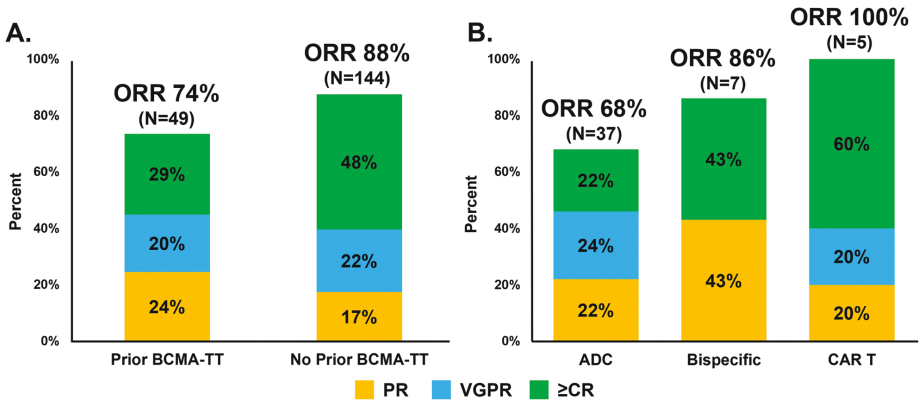


Fig. 1 Response rates to ide-cel. Overall response rate and depth of response outcomes for the prior BCMA-TT cohort compared to the no prior BCMA-TT cohort (**A**), and stratified by the specific type of prior BCMA-TT (**B**). ORR overall response rate, CR complete response, VGPR very good partial response, PR partial response.

Table 3. Selected variables for ide-cel responders compared to non-responders in the prior BCMA-TT cohort.

Variable	Responders ($N = 36$)	Non-responders ($N = 13$)	P
Duration of therapy with prior BCMA-TT in days, median (range)[a]	23 (1–208)	63 (1–370)	0.025
Time from last BCMA-TT to apheresis in days, median (range)	169.5 (30–1066)	84 (1–286)	0.017
Time from last BCMA-TT to ide-cel infusion in days, median (range)	209 (16–1118)	128 (32–362)	0.052
Ide-cel cell dose ($\times 10^6$), mean (SD)	392.3 (58.9)	397.7 (43.7)	0.95
Received systemic therapy between last BCMA-TT and apheresis, *n* (%)	28 (78%)	9 (69%)	0.539

[a]Note that prior anti-BCMA CAR T was recorded as 1 day for duration of prior BCMA-TT.

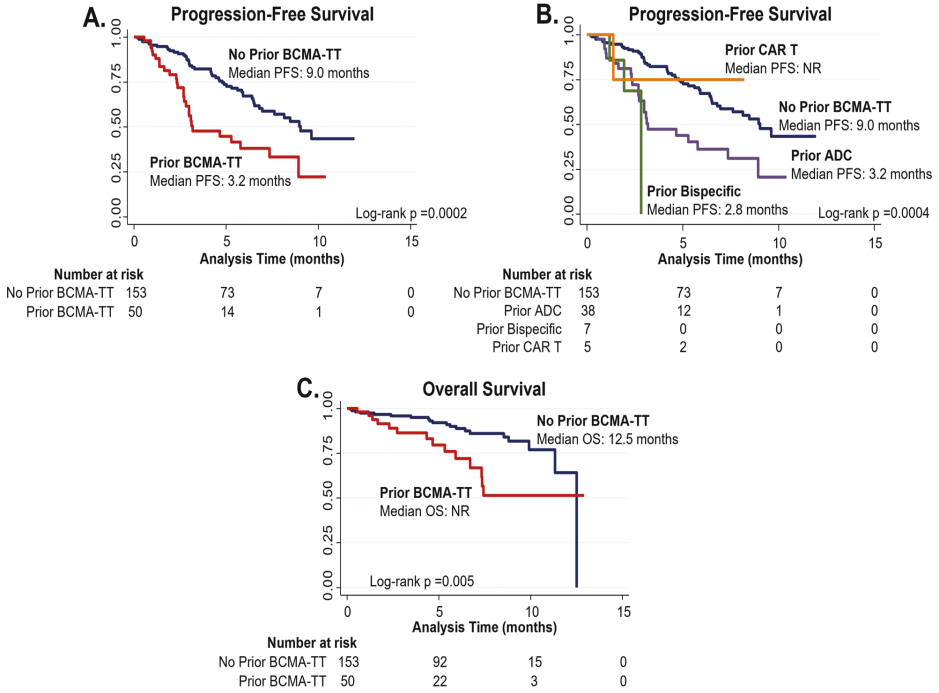


Fig. 2 Progression-free survival and overall survival. Kaplan–Meier curves demonstrating PFS in the prior BCMA-TT cohort compared to the no prior BCMA-TT cohort (**A**), PFS stratified by the specific type of prior BCMA-TT (**B**), and overall survival in the prior BCMA-TT cohort compared to the no prior BCMA-TT cohort (**C**).

Ferreri C et al. Blood Cancer Journal 2023

Cilta-cel real word data

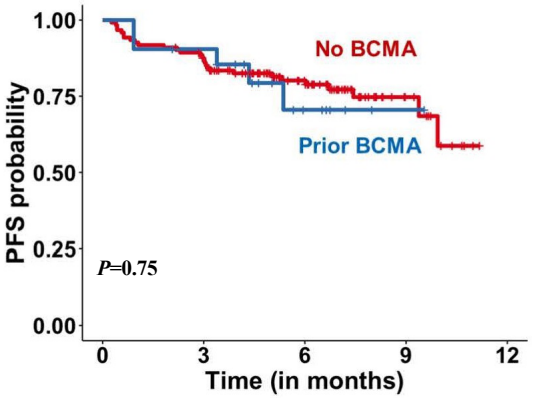
BCMA-targeted therapy | BCMA-targeted CAR-T

Retrospective study: multicenter observational study of patients with RRMM who received standard of care cilta-cel treatment after relapse on prior BCMA-targeted therapy or non–BCMA-targeted therapy

Patient characteristics

Patient characteristics	All patients (N=143)[a]
Median prior LOT, n (range)	6 (3-18)
High-risk cytogenetics, n (%)	51 (41)
Triple-refractory,[b] n (%)	102 (71)
Penta-refractory,[c] n (%)	48 (34)
Prior treatment with a BCMA-targeted agent, n (%)	17 (12)

PFS by prior BCMA-targeted treatment



Multivariable analysis for efficacy

	Best ORR		PFS		OS	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Prior anti-BCMA vs no prior anti-BCMA	0.58 (0.10-3.89)	0.5	1.65 (0.59-4.58)	0.3	1.49 (0.38-5.83)	0.6

Prior use of BCMA-targeted therapy did not significantly impact survival outcomes

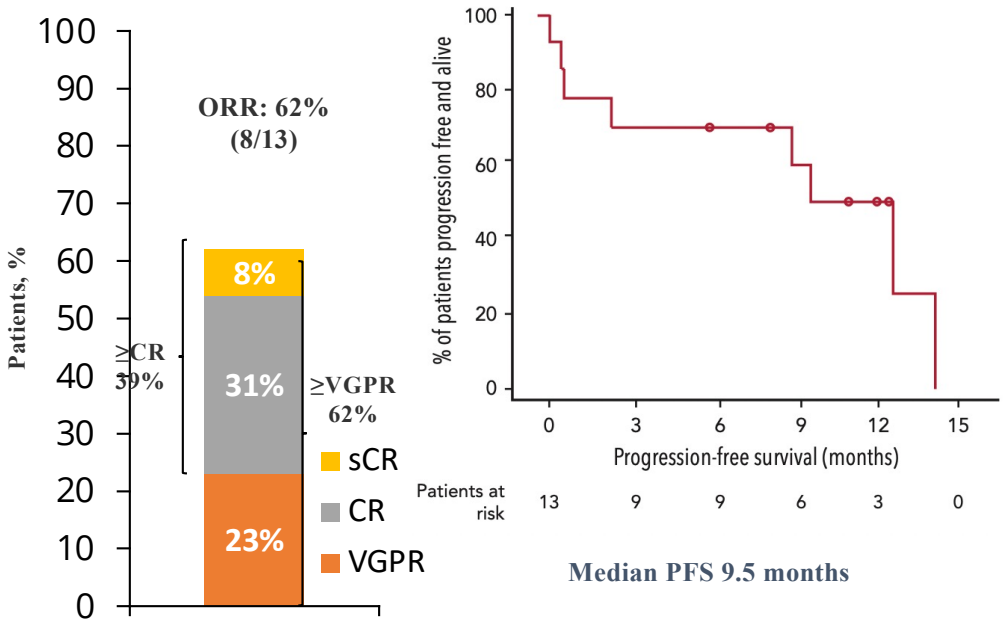
[a] 153 patients underwent leukapheresis for planned SOC cilta-cel. [b] Refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb. [c] Refractory to 2 immunomodulatory agents, 2 proteasome inhibitors, and an anti-CD38 antibody.
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CI, confidence interval; LOT, lines of therapy; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

Hansen D, et al. Presented at the American Society of Clinical Oncology Annual Meeting. June 2-6, 2023. Chicago, IL. Abstract 8012.

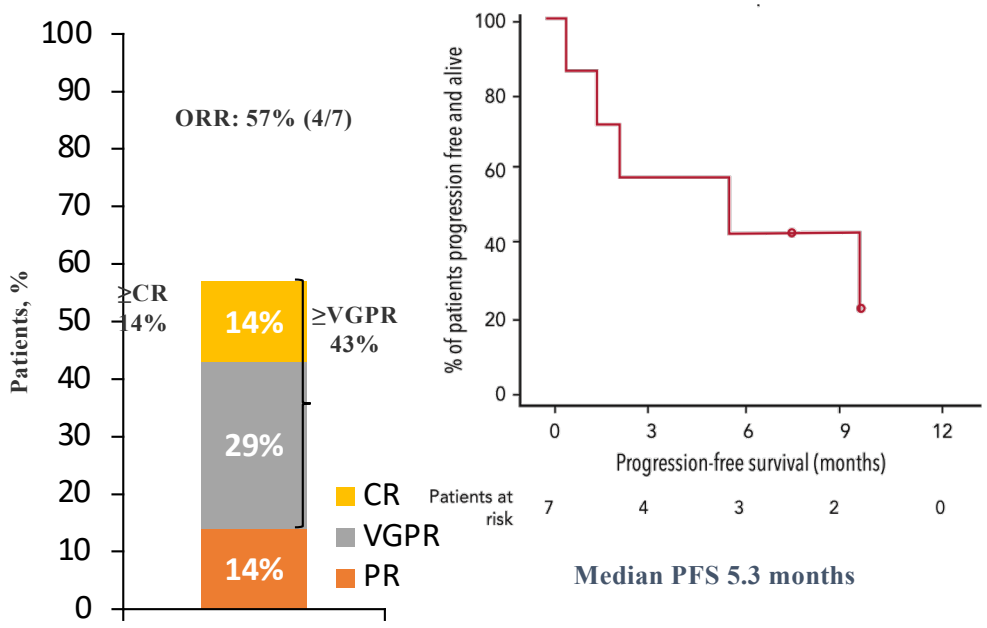
Anti-BCMA CAR-T in anti-BCMA exposed/refractory MM CARTITUDE-2 Cohort C

Population: Relapsed/refractory multiple myeloma after PI, IMiD, anti-CD38, **and anti- BCMA therapy**
20 patients were treated:
- 13 ADC exposed
- 7 BsAb exposed
- 1 in the ADC group also had prior BsAb exposure

ADC exposed



Bispecific exposed



ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CR, complete response; cilta-cel, ciltacabtagene autoleucel; ORR, overall response rate; PR, partial response; PFS, progression free survival; PD, progressive disease; sCR, stringent complete response; VGPR, very good partial response

Cohen AD et al. Blood. 2023;141:219-230.

Anti-BCMA CAR-T in anti-BCMA exposed/refractory MM CARTITUDE-2 Cohort C

Timing of BCMA-targeting after ADC treatment

Treatments	Responders (n=8)	Nonresponders (n=5)
Duration of last anti-BCMA ADC treatment, days		
Median	22.5	63.0
Range	1–277	22–527
Time from last anti-BCMA ADC treatment to apheresis, days		
Median	150.0	56.0
Range	26–695	40–895
Time from last anti-BCMA ADC treatment to cilta-cel infusion, days		
Median	226.5	116.0
Range	62–749	95–944

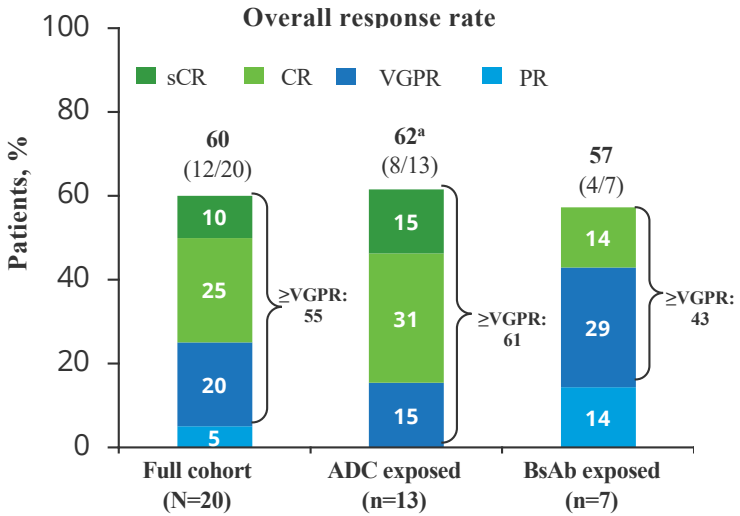
Timing of BCMA-targeting after BsAb treatment

Treatments	Responders (n=4)	Nonresponders (n=3)
Duration of last anti-BCMA BsAb treatment, days		
Median	53.5	130.0
Range	23–127	15–260
Time from last anti-BCMA BsAb treatment to apheresis, days		
Median	220.5	84.0
Range	28–281	77–251
Time from last anti-BCMA BsAb treatment to cilta-cel infusion, days		
Median	276.0	124.0
Range	84–329	119–307

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel

Cohen AD et al. Blood. 2023;141:219-230.

CARTITUDE-2 Cohort C: Efficacy and Safety at a Median Follow-Up of 18 months



Median DOR, PFS, and OS

Estimate, months (95% CI)	Full cohort (N=20)	ADC exposed (n=13)	BsAb exposed (n=7)
DOR	12.3 (7.2–NE)	13.3 (7.2–NE)	8.2 (4.4–NE)
PFS	9.1 (1.5–13.2)	9.5 (1.0–15.2)	5.3 (0.6–NE)
OS	16.0 (8.3–NE)	21.0 (9.4–NE)	13.2 (0.6–NE)

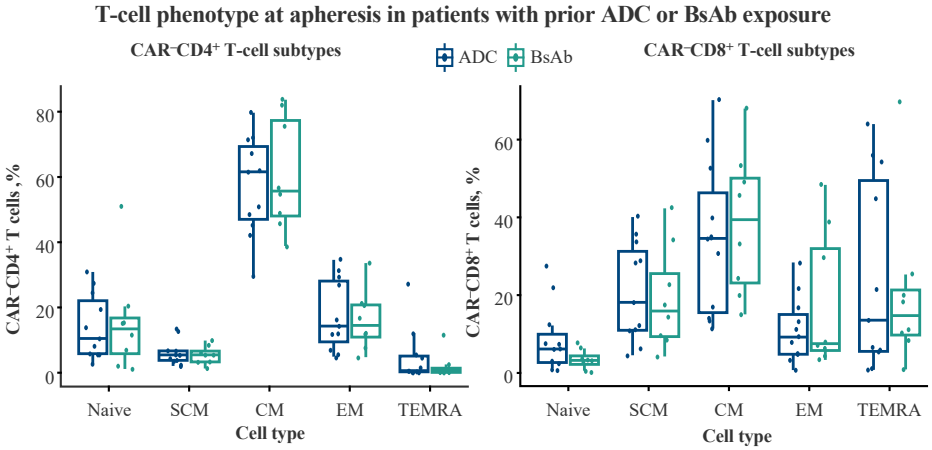
- **Safety profile of cilta-cel in patients who received prior anti-BCMA therapies was consistent with that in CARTITUDE-1[1]**

[a]Percentages may not sum appropriately due to rounding.
1. Cohen AD, et al. *Blood* 2023;141:219-30. 2. Cohen A, et al. Presented at ASH; December 10–13, 2022; New Orleans, LA. ADC, antibody-drug conjugates; BCMA, B-cell maturation antigen; BsAb, bispecific antibodies; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel, CR, complete response; DOR, duration of response; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MRD, minimal residual disease; NE, not evaluable, OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor, PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

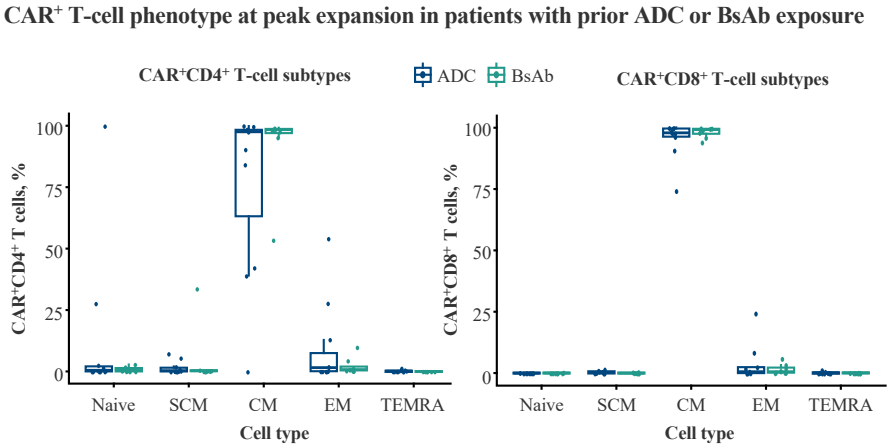
Cohen et al, presented at IMS meeting 2023Athens

CARTITUDE-2 Cohort C: T Cell Phenotypes at Apheresis and at Peak Expansion

- At apheresis, the majority of $CD4^+$ T cells were central memory cells, and $CD8^+$ T cells consisted of significant proportions of central memory cells, along with stem cell–like memory cells and TEMRA cells



- At peak CAR^+ T-cell expansion, central memory CAR^+ T cells were dominant in both $CD4^+$ and $CD8^+$ T-cell compartments in ADC and BsAb groups



In patients with prior exposure to a noncellular anti-BCMA therapy, central memory cells were the dominant T cell phenotype in both CD4 and CD8 compartments at apheresis and after transduction and in *vivo* expansion; distribution of T cell subsets in ADC vs BsAb groups were not significantly different

ADC, antibody-drug conjugates; BCMA, B-cell maturation antigen; BsAb, bispecific antibodies; CAR, chimeric antigen receptor; CM, central memory cell; EM, effector memory cell; ORR, Overall response rate; SCM, stem cell–like T cell; TEMRA, TEMRA T cell.

Cohen et al, presented at IMS meeting 2023Athens

Patients responded to teclistamab after receiving a BCMA-directed ADC or CAR-T therapy[1]

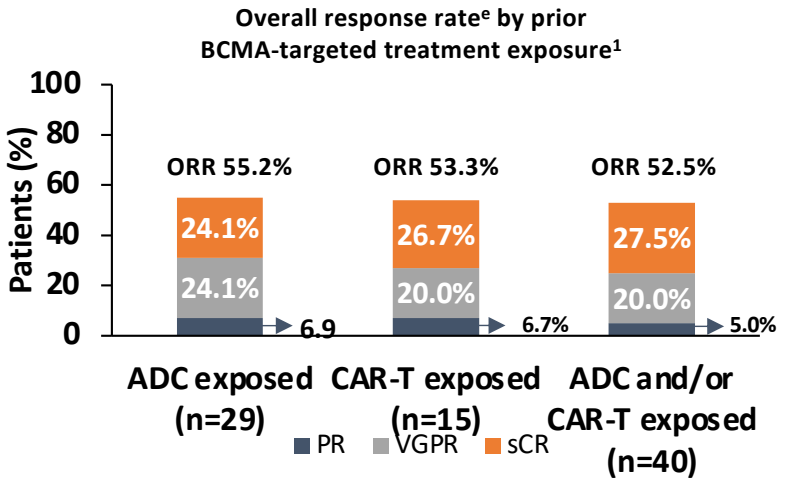
BCMA-targeted therapy → BCMA-targeted bispecific

MajesTEC-1 cohort C: a phase 1/2, open-label, multicohort, multicenter study to evaluate teclistamab in patients with TCE RRMM[1,2]

Patient characteristics[1]

Patient characteristics	Cohort C (N=40)
High-risk cytogenetics,[a] n (%)	12 (33.3)
TCR,[b] n (%)	34 (85)
Penta-drug refractory,[c] n (%)	14 (35.0)
Prior BCMA-targeted therapy,[d] n (%)	**40 (100)**
BCMA-targeted ADC	29 (72.5)
BCMA-targeted CAR-T	15 (37.5)

3 of the 4 patients with prior ADC and CAR-T treatment had a response with teclistamab[1]



[a] Del(17p), t(4;14), and/or t(14;16); percentage calculated from n=36.[1] [b] ≥1 PI, ≥1 immunomodulatory agent, and ≥1 anti-CD38 mAb.[1] [c] ≥2 PIs, ≥2 immunomodulatory agents, and ≥1 anti-CD38 mAb.[1] [d] Four patients had previously received both ADC and CAR-T.[1] [e] PR or better, IRC assessed, per IMWG 2016 criteria.[1]

1. *Touzeau C et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, IL. Poster 8013.*
2. *2. ClinicalTrials.gov identifier: NCT04557098. Updated June 21, 2022. Accessed July 1, 2022. www.clinicaltrials.gov/ct2/show/NCT04557098*

Patients responded to teclistamab after receiving a BCMA-directed ADC or CAR-T therapy

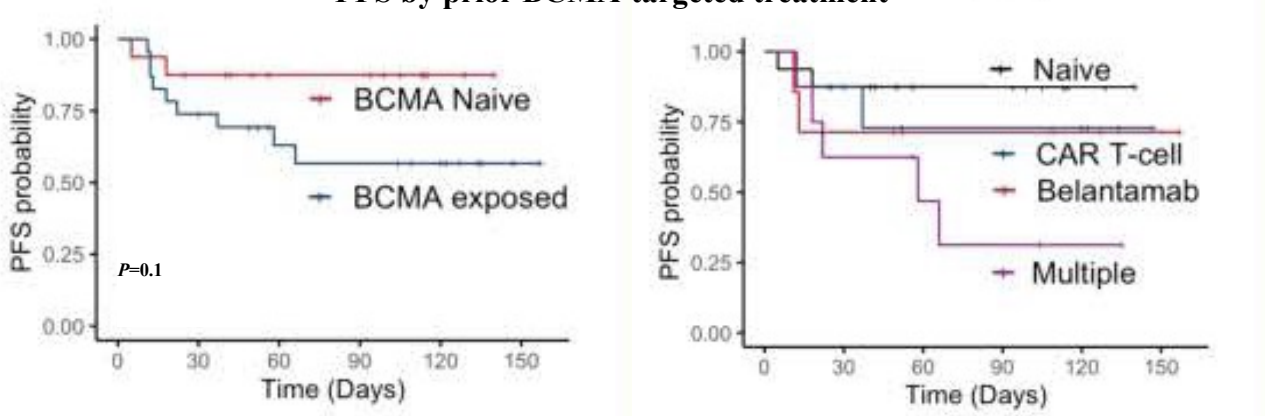
BCMA-targeted therapy → BCMA-targeted bispecific

Retrospective real-world analysis: patients with RRMM who received commercial teclistamab at Memorial Sloan Kettering Cancer Center

Patient characteristics

Patient characteristics	Commercial cohort (N=40)
Median prior LOT, n (range)	7 (4-13)
High-risk cytogenetics, n (%)	11 (28)
Penta-drug refractory, n (%)	31 (78)
Prior BCMA-targeted therapy, n (%)	23 (58)
BCMA-targeted ADC	15 (38)
BCMA-targeted CAR-T	16 (40)
BCMA-targeted bispecific antibody	1 (3)
Multiple prior anti-BCMA agents	8 (20)

PFS by prior BCMA-targeted treatment



Among 29 evaluable patients, ORR was 66% (19/29). In patients with prior BCMA-targeted treatment, ORR was 56% (10/18)

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; LOT, line of therapy; ORR, overall response rate; PFS, progression-free survival.
Firestone R, et al. Presented at the American Society of Clinical Oncology Annual Meeting. June 2-6, 2023. Chicago, IL. Abstract 8049.

Patients previously treated with BCMA-targeted therapy responded to subsequent treatment with belantamab mafodotin

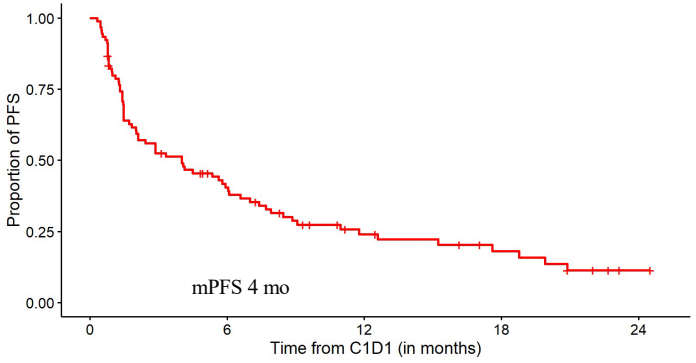
BCMA-targeted therapy → BCMA-targeted ADC

Retrospective study: single-center analysis of patients with RRMM[a] who had received any BCMA-targeted CAR-T therapy prior to treatment with belantamab mafodotin

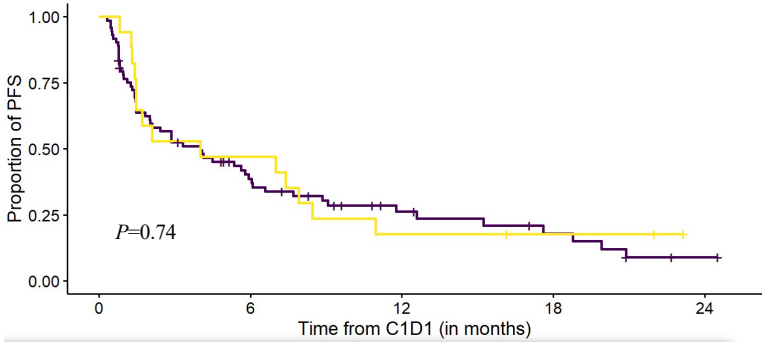
Patient characteristics

Patient characteristics	All patients (N=90)
Median prior LOT, n (range)	6 (2-14)
High-risk cytogenetics,[b] n (%)	50 (61)
Prior treatment with a BCMA-targeted agent, n (%)	17 (19)
CAR-T, n	12
Bispecific antibody, n	6
Belantamab mafodotin, n	2

PFS in total cohort



PFS in BCMA exposed vs unexposed



The response to belantamab mafodotin was similar in those with prior BCMA exposure vs BCMA-naive patients

[a] Patients who completed ≥1 cycle of commercial belantamab mafodotin treatment outside clinical trials between October 1, 2020, and October 31, 2022, and had prior exposure to an immunomodulatory agent, a PI, and an anti-CD38 antibody.
[b] Including 1q+, 1p-, t(4;14), t(14;16), and complex karyotype.
ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; C, cycle; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; D, day; LOT, lines of therapy; mPFS, median progression-free survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.
Hultcrantz M et al. Presented at the 64th American Society of Hematology Annual Meeting & Exposition. December 10-13, 2022. New Orleans, LA. Abstract 3225.

Conclusions

CARTs have become a standard of care after third line treatment

Several trials are in progress to evaluate combinations and earlier application during the disease course

Sequencing different anti BCMA agents is a challenge, few data available, mechanisms of resistance still to be unraveled, bispecifics after CAR-T may work

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

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Thank you for your attention!!

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