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Novità dal Meeting della Società Americana di Ematologia

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CAR-T nel mieloma multiplo

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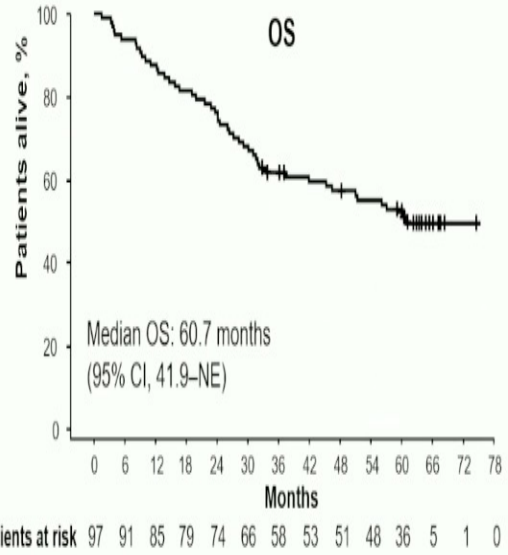
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GSK					x		
AMGEN					x		
J&J						x	
BMS						x	
Menarini						x	
Pfizer					x		
Alexion						x	
Sanofi					x		

Outline

- Management of cilta-cel in real-life (abs 92, 93, 1034)
- Updated results of phase II study of anito-cel (abs 256)
- In vivo gene therapy anti BCMA (LBA-1)

CARTITUDE-1: Median Overall Survival Was 5 Years

Overall population (N=97); median follow-up: 61.3 months



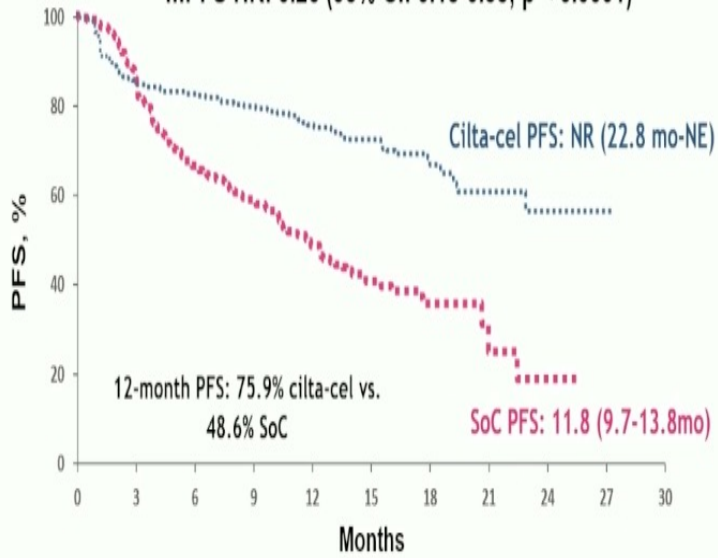
NE, not estimable; OS, overall survival

32 of 97 (33%) patients were treatment- and progression-free at ≥ 5 years

Jagannath S, et al. *J Clin Oncol*. 2025; 43(25):2766-2771.

CARTITUDE-4: Cilta-cel in Patients with LEN-Refractory RRMM After 1–3 Prior Regimens – Efficacy (Median F/U 15.9-Months)

mPFS HR: 0.26 (95% CI: 0.18-0.38; p < 0.0001)



ORR 84.6% cilta-cel vs. **67.3%** SoC
- sCR: 58.2% vs 15.2%
- CR: 14.9% vs 6.6%

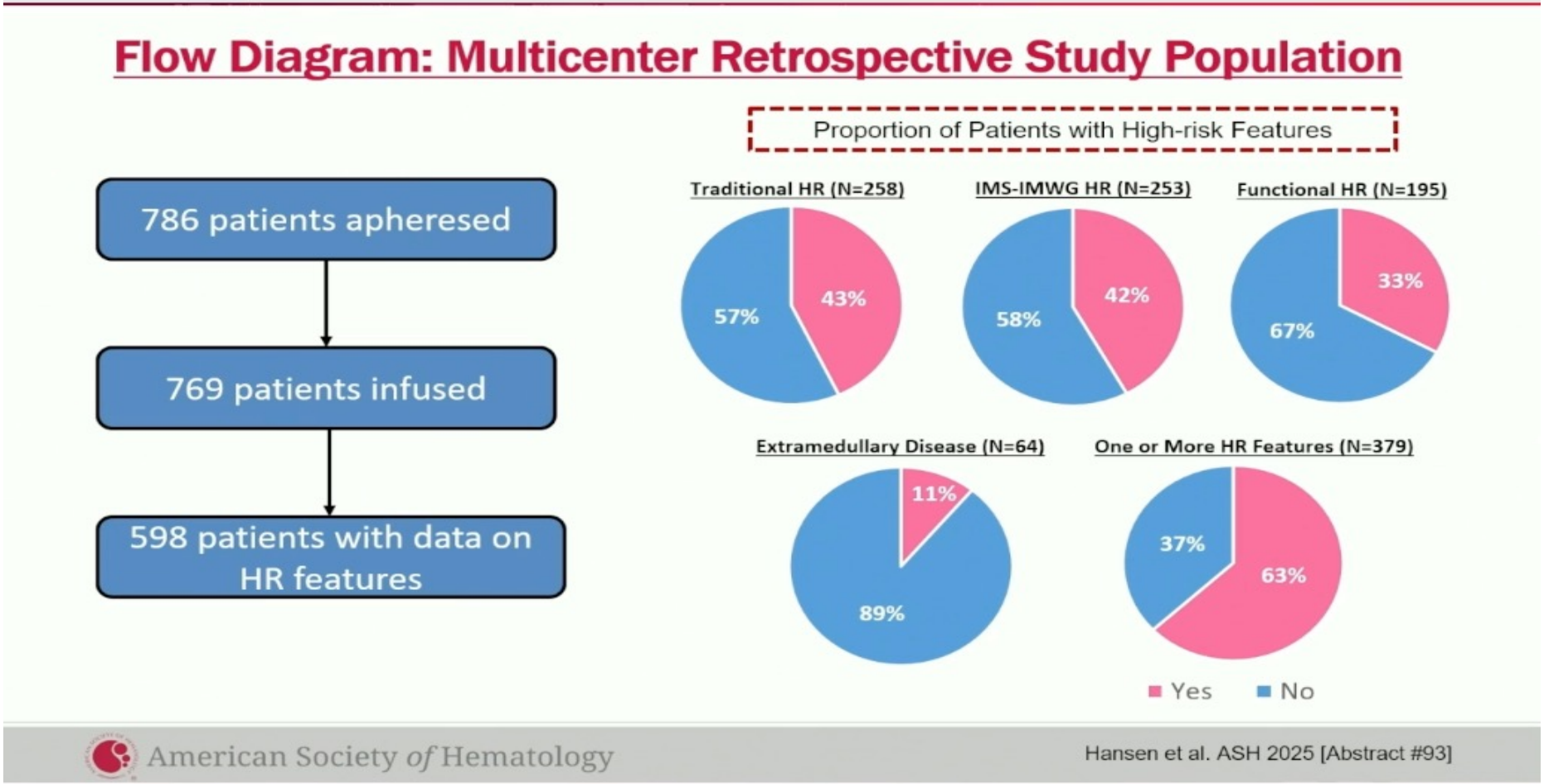
In MRD-evaluable pts.
- **MRD [-]** occurred in **87.5%** vs. **32.7%** SoC

Overall, 208 assigned to receive cilta-cel (ITT population)→ 32 patients did not receive cilta-cel (n=20 received cilta-cel after disease progression, during bridging therapy)

HR: hazard risk, f/u: follow-up, NR: not reached, ITT: intention to treat

San-Miguel J, et al. *N Engl J Med*. 2023;389:335-347; Dhakal B, et al. *J Clin Oncol*. 2023;41(17 Suppl). Abstract LBA106. Figure adapted/recreated

Clinical and Biological Features Associated with Early Relapse and Inferior Survival Following Cilta-cel

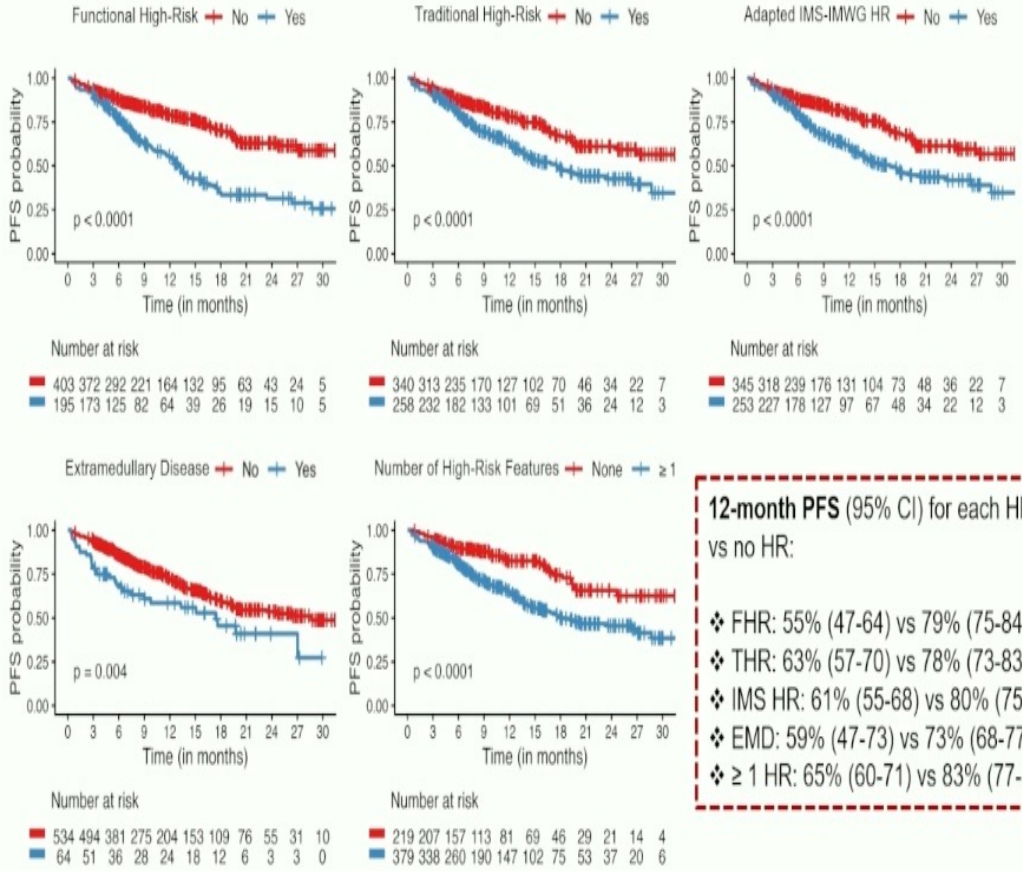


Baseline Characteristics

Characteristic	Overall (N=598)	No High-Risk Features (N=219)	≥1 High-Risk Feature (N=379)	*p*-value
Patient age, median (range)	65 (33, 83)	66 (37, 82)	65 (33, 83)	0.01
Male sex, n (%)	344 (58)	129 (59)	215 (57)	0.6
Race and Ethnicity, n (%)				0.9
Non-Hispanic White	397 (67)	148 (69)	249 (66)	
Non-Hispanic Black	86 (15)	31 (14)	55 (15)	
Non-Hispanic Asian/Pacific Islander	60 (10)	18 (8)	42 (11)	
Hispanic	41 (7)	14 (7)	27 (7)	
Non-Hispanic Other	8 (1%)	3 (1)	5 (1)	
ECOG PS, n (%)				0.06
0-1	510 (87)	194 (90)	316 (85)	
≥ 2	78 (13)	21 (10)	57 (15)	
Number of prior lines of therapy, median (range)	5 (1, 18)	5 (1, 15)	5 (2, 18)	0.4
High plasma cell burden (≥50%) , n (%)	90 (17)	14 (7)	76 (22)	<0.001
Ferritin ≥ ULN, n (%)	158 (29)	39 (19)	120 (35)	<0.001
Prior BCMA therapy, n (%)	47 (8)	10 (5)	37 (10)	0.02
Penta-Refractory status, n (%)	160 (27)	51 (23)	109 (29)	0.15
Time from Diagnosis to Infusion (years)	5.4 (0.3, 23.9)	6.8 (0.3, 23.9)	4.5 (0.3, 21.0)	<0.001

BCMA: B-cell maturation antigen, ECOG: Eastern Cooperative Oncology Group, ULN: Upper limit of normal

High-Risk Features Are Associated with Inferior PFS in RRMM



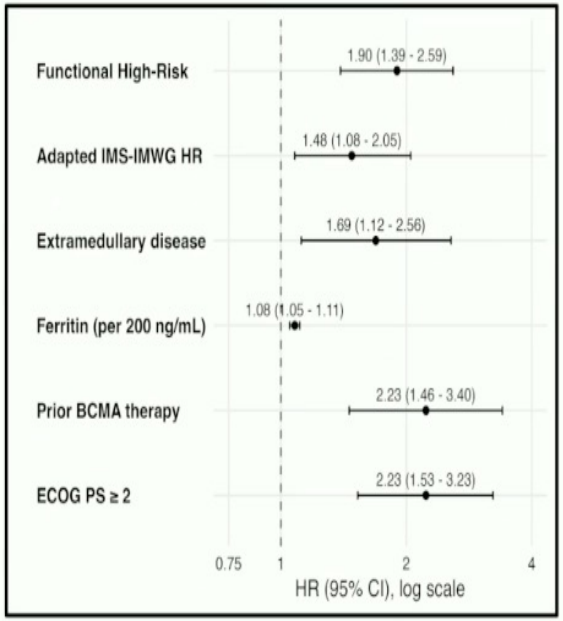
12-month PFS (95% CI) for each HR vs no HR:

- FHR: 55% (47-64) vs 79% (75-84)
- THR: 63% (57-70) vs 78% (73-83)
- IMS HR: 61% (55-68) vs 80% (75-85)
- EMD: 59% (47-73) vs 73% (68-77)
- ≥ 1 HR: 65% (60-71) vs 83% (77-89)

Hansen et al. ASH 2025 [Abstract #93]

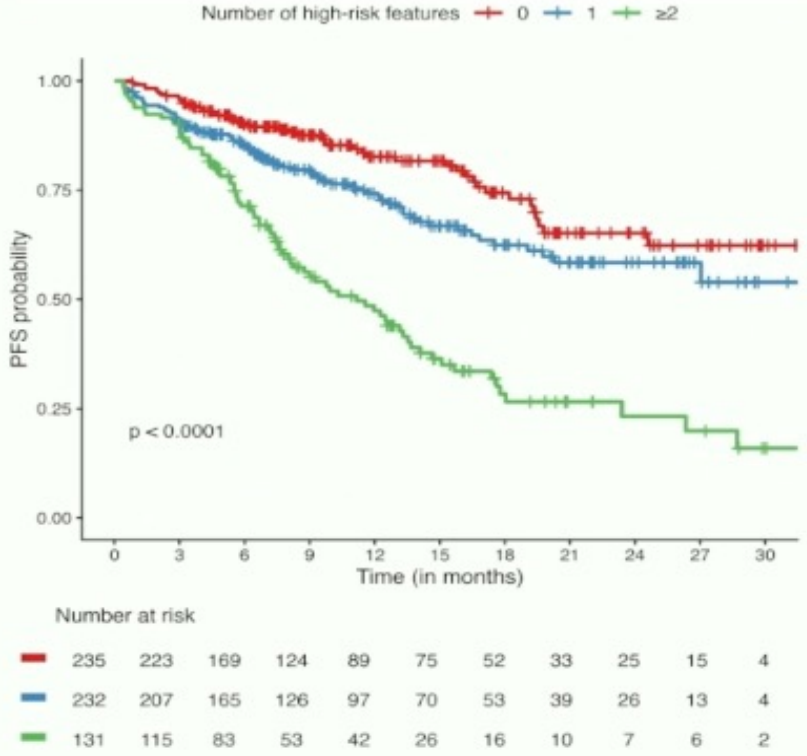
High-risk Features Are Associated with Inferior PFS

Multivariable Analysis for Progression-Free Survival

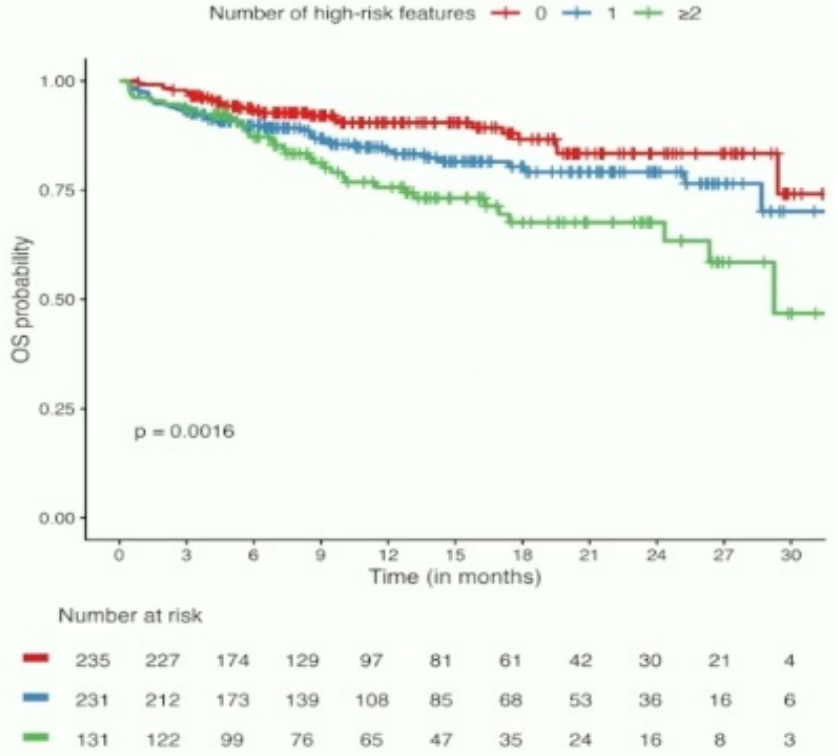


Increasing High-Risk Features Are Associated with Inferior PFS and OS

Progression-Free Survival



Overall Survival



Hansen et al. ASH 2025 [Abstract #93]

Cilta-cel: Delayed Neurotoxicity and NRM

	US RWE[1] N=236	CARTITUDE-1 [2-3] N=97	CARTITUDE-4[4] N=208
Delayed Neurotoxicity	10%	12%	12%
Parkinsonism	**2%**	**6%**	**0.5%**
Cranial Nerve Palsy	5%	-	9%
Others	3%[#]	-	3%[##]
Non-Relapse Mortality	**10%**	**6%***	**6%**

*NRM in CARTITUDE-1:17 deaths due to reasons other than progression. Only 6 deaths attributed to cilta-cel per investigator assessment (6%). #Other delayed NT: Diplopia in 4, posterior reversible encephalopathy syndrome (PRES) in 2, dysautonomia in 1 patient, and polyneuropathy in 1 patient . ## CAR-T related peripheral neuropathy

1. Sidana et al. Blood. 2025;145(1):85-97; 2. Berdeja et al. Lancet 398:314-324, 2021. 3. Martin et al. J Clin Oncol 41:1265-1274, 2023. 4. Mateos et al IMS 2024

Study Design

Population

- Patients with relapsed MM receiving standard of care cilta-cel
- Sites: 15 U.S centers
- **N=761** (May 2022 to December 2024)

Definitions

- **Delayed neurotoxicity (DNT) or Non-ICANS neurotoxicity (NINT):** Neurotoxicity events except ICANS including Parkinsonism, cranial nerve palsy, neuropathy, etc
- **NRM** was defined as death due any cause except myeloma progression

Analysis

- Risk factors for Parkinsonism and NRM were evaluated by univariable and multivariable analysis.
- Any NRM events occurring after disease progression were censored for analysis, except second primary malignancies

Sidana et al. ASH 2025, Abstract #1034

Safety and Efficacy of SOC Cilta-cel

- Median follow up was 10.1 months
- Overall response rates: 92%
- CR rate of 70%.
- 1-year PFS estimate: 72%

	All grades (≥3)
CRS	76% (3%)
ICANS	20% (5%)
IEC-HS	5%
Infections	33% (14%)

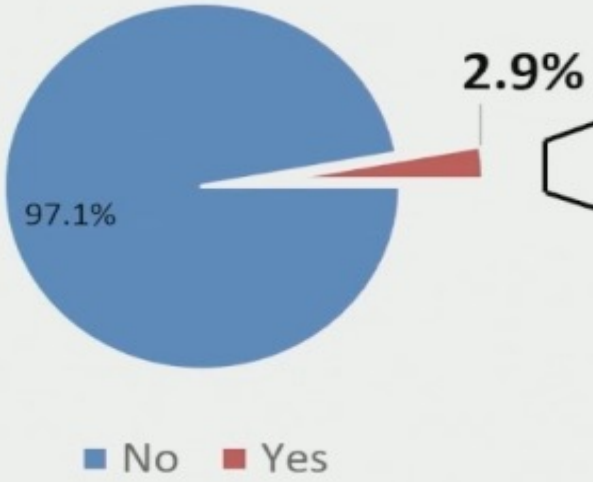
Delayed neurotoxicity*	% (n)
Any DNT/NINT	10% (75)
Parkinsonism	2.9% (22)
Cranial nerve palsy	4.6% (35)
Other delayed NT/NINT	2.4% (18)

*Some patients experienced more than one type of DNT.
Median time to Parkinsonism onset: 30 days (range: 17-214)

Sidana et al. ASH 2025, Abstract #1034

Non-response to Bridging: 10x Risk of Parkinsonism with Cilta-cel

Parkinsonism with SOC Cilta-cel
22 cases of 761 (2.9%)

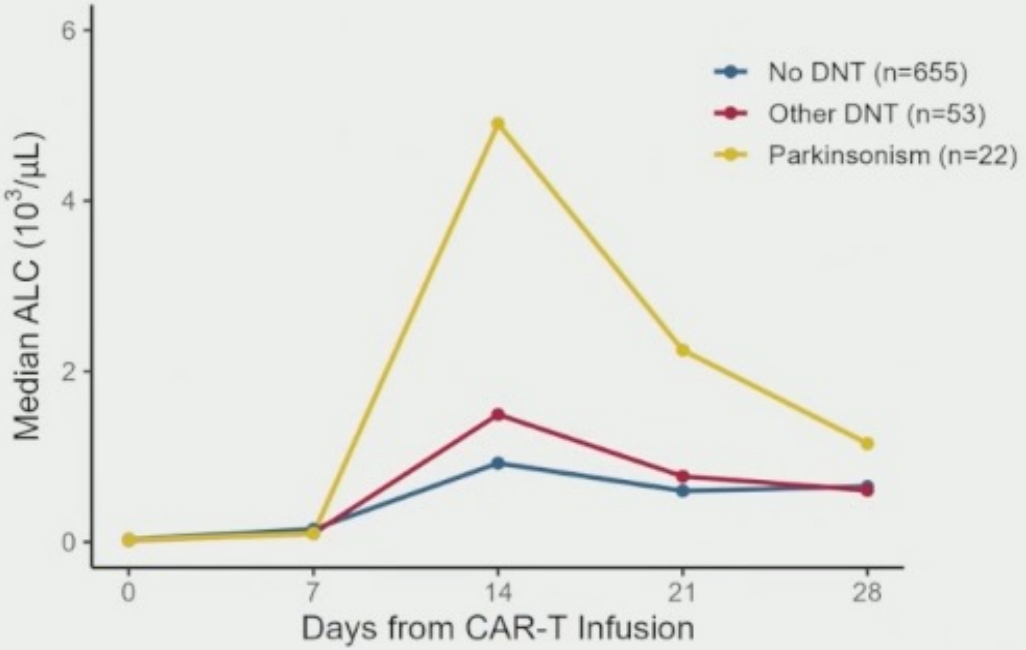


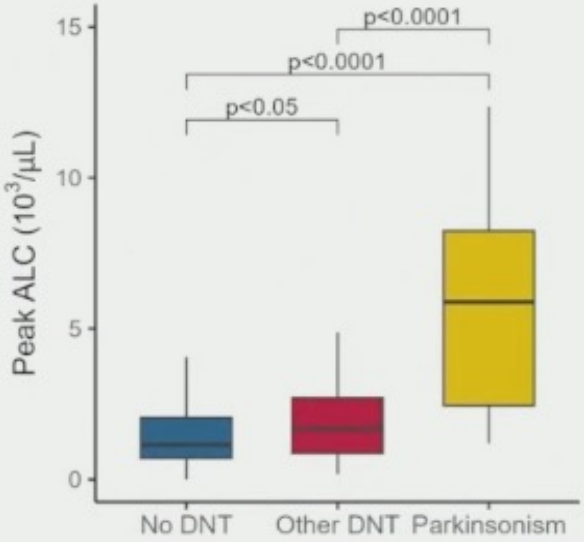
Risk of Parkinsonism in non-responders vs responders to bridging (PR or better):
5% vs 0.5% ($p<0.05$)

- Of 22 cases of Parkinsonism, 21 (95%) patients did not respond to bridging
- Post CAR-T response rate in these patients was 91% and CR rate of 68%

Sidana et al. ASH 2025, Abstract #1034

ALC Expansion and Risk of Delayed NT





- Patients with Parkinsonism had significantly higher ALC in first month post cilta-cel
- Median peak ALC in patients with and without Parkinsonism: 5.88 vs 1.17 x 10^3 /uL (p<0.001).

Sidana et al. ASH 2025, Abstract #1034

ALC Thresholds and Risk of Parkinsonism

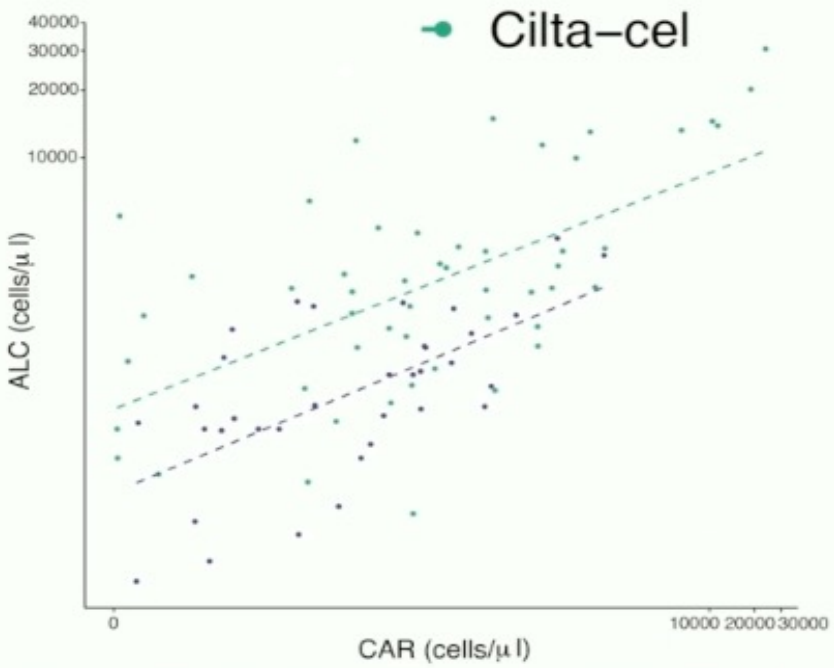
ALC threshold	Parkinsonism	P-value
ALC≥ 3000/uL vs < 3000/uL	12% vs 1%	<0.001
ALC≥ 2500/uL vs < 2500/uL	9% vs 1%	<0.001

Parkinsonism	ALC ≥ 1000/uL	ALC ≥ 2500/uL	ALC ≥ 3000/uL
Yes	100%	73%	68%
No	57%	19%	19%

- A cut-off of 2500 or 3000/uL can identify majority of patients who subsequently developed Parkinsonism
- If an intervention is effective in reducing risk to baseline (1%), Number needed to treat: 9

Sidana et al. ASH 2025, Abstract #1034

Concordance of Peak CAR T-cells and ALC

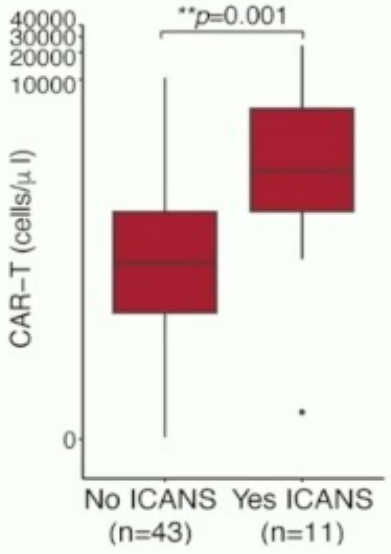


Peak CAR T cell levels and ALC demonstrated moderate to strong concordance

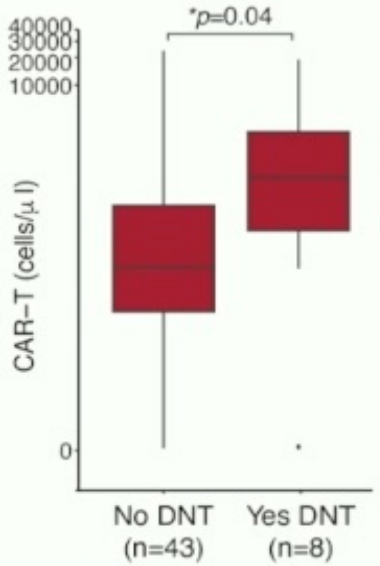
Hosaya et al, abstract 96

Higher Cilta-cel Peak Expansion is Associated with Increased Risk of ICANS and DNT

CAR-T expansion by FC in patients with ICANS vs not



CAR-T expansion by FC in patients with DNT vs not



Peak CAR T expansion measured by flow cytometry was significantly higher in patients developing ICANS or delayed neurotoxicity

Hosaya et al, abstract 96

Non-Relapse Mortality

1-year NRM estimate: 9%
2-year NRM estimate: 10%

Non-relapse mortality (NRM) events, N=63 (8%)	N (%)
Infections	35 (56%)
Acute immune mediated toxicity	14 (22%)
CRS	4
IEC-HS	6
ICANS	4
Delayed immune mediated toxicity	6 (9.5%)
Parkinsonism/NINT	4
IEC-Colitis	2
Second primary malignancies	5 (7.9%)
Other	3 (8%)

- Infection related mortality remained relatively stable in the first year
- Immune mediated toxicity deaths were uncommon after 6 months
- SPMs were uncommon within the first 6 months.

Sidana et al. ASH 2025, Abstract #1034

Risk Factors for NRM: Multivariable Analysis

	Odds Ratio	95% CI	P-value
Response to bridging: SD/PD vs PR	2.41	1.07, 6.19	**0.046**
No bridging therapy vs PR	2.06	0.67, 6.40	0.2
ECOG PS ≥ 2 vs 0-1	3.97	1.98, 7.77	**<0.001**
High Risk cytogenetics, yes vs no	2.39	1.27, 4.55	**0.007**
Age ≥ 70 years vs not	2.65	1.40, 5.01	**0.003**

A multivariate model was built using bidirectional stepwise regression using AIC criteria. Variables entered into the model included the following. For the final model, all variables selected with AIC had p <=0.05. Age ≥ 70 years, performance status, bone marrow plasma cells > 50%, EMD, Prior lines of treatment (1-3 vs. 4+), High risk cytogenetics (yes/no), Bridging response (no bridging, SD/PD, PR or better), Baseline Ferritin (<400 vs >400 ng/mL), Peak ALC (> 3k),

Sidana et al. ASH 2025, Abstract #1034

- Effective tumor debulking with bridging is critical to decrease the risk of Parkinsonism and NRM with cilta-cel
- Peak ALC ≥ 2500/uL can serve as a biomarker to identify patients for preemptive interventions and risk mitigation measures
- A prospective observational study is ongoing to evaluate risk reduction of DNT with dexamethasone prophylaxis in patients with elevated ALC

Sidana et al, ASH 2025, abstract 1034

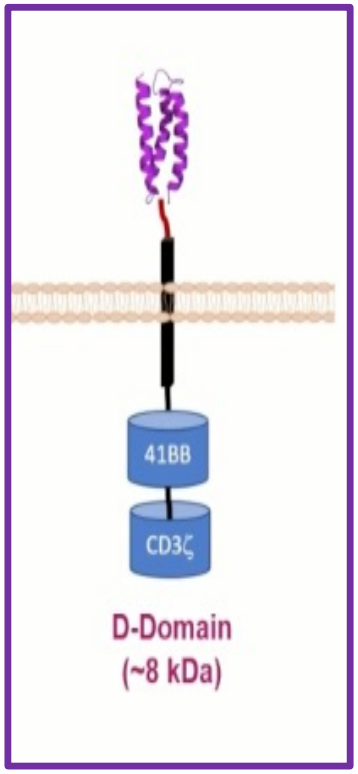
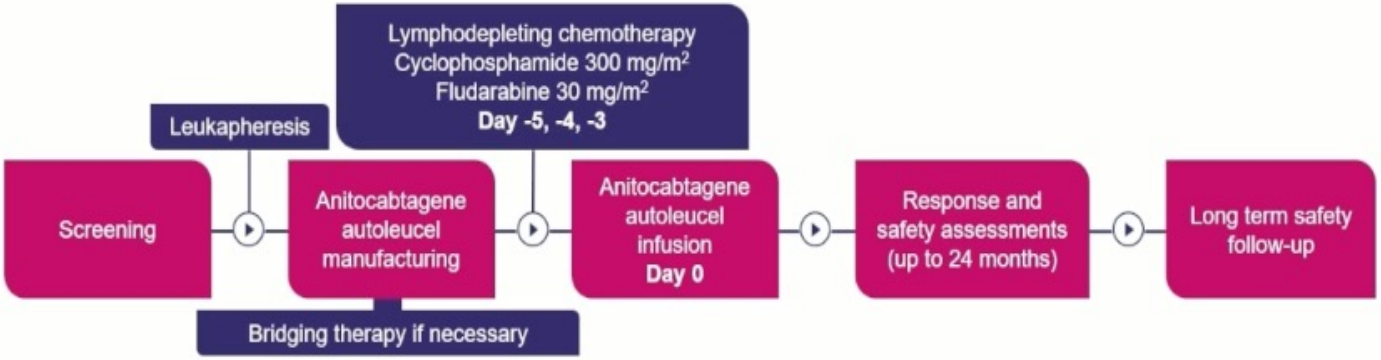


iMMagine-1: Phase 2 Study Design



Key Eligibility Criteria

- Prior IMiD, PI, and CD38-targeted therapy
- Received ≥3 prior lines of therapy
- Refractory to the last line of therapy
- ECOG PS of 0 or 1
- Evidence of measurable disease

Primary Endpoint:

- ORR, per 2016 IMWG criteria

Key Secondary Endpoints:

- sCR/CR rate, per 2016 IMWG criteria
- ORR in patients limited to 3 prior LoT, per 2016 IMWG criteria

Target Dose of 115 x 10^6 CAR+ T cells

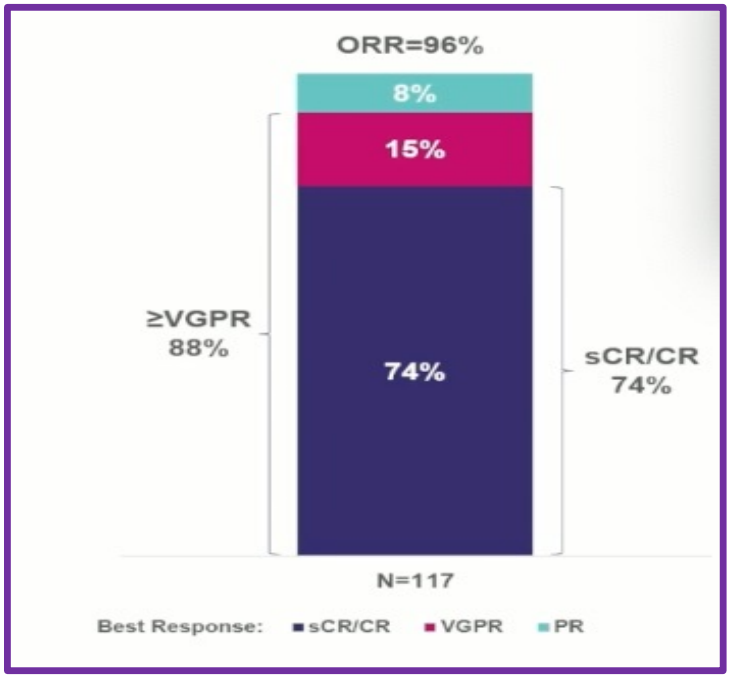
Primary and key secondary endpoints to be assessed per Independent Review Committee (IRC); Investigator assessment of response per IMWG also permitted per protocol.
CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; LoT, line of therapy; ORR, overall response rate; PI, proteosome inhibitor; sCR, stringent complete response.

iMMagine-1: Patient and Disease Characteristics

Characteristics	N=117
Age (years), median (min - max)	64 (38 – 78)
Age ≥ 65	58 (50%)
Age ≥ 70	33 (28%)
Age ≥ 75	10 (9%)
Gender (male / female)	66 (56%) / 51 (44%)
Race	
White	90 (77%)
Black / African American	17 (15%)
Asian / Other	10 (9%)
ECOG PS 0 / 1	54 (46%) / 63 (54%)
Extramedullary disease[a]	21 (18%)
Bone marrow plasma cells[b]	
≤ 30%	74 (65%)
> 30% to < 60%	19 (17%)
≥ 60%	20 (18%)
High risk cytogenetics[c]	47 (40%)

Characteristics	N=117
Refractory to last line of therapy	117 (100%)
Triple refractory	102 (87%)
Penta refractory	48 (41%)
Prior lines of therapy, median (min - max)	3 (3 – 8)
3 Prior LoT	65 (56%)
Time since diagnosis (years), median (min - max)	7.5 (1.0 – 23.1)
Prior ASCT	92 (79%)
Bridging therapy	89 (76%)
Outpatient administration	9 (8%)

a) Presence of a non-bone based plasmacytoma; b) 113 patients had bone marrow disease assessments done at screening or baseline; c) Defined as the presence of Del 17p, t(14;16), or t(4;14).
Note: Updates to data resulting from ongoing data review; ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LoT, line of therapy



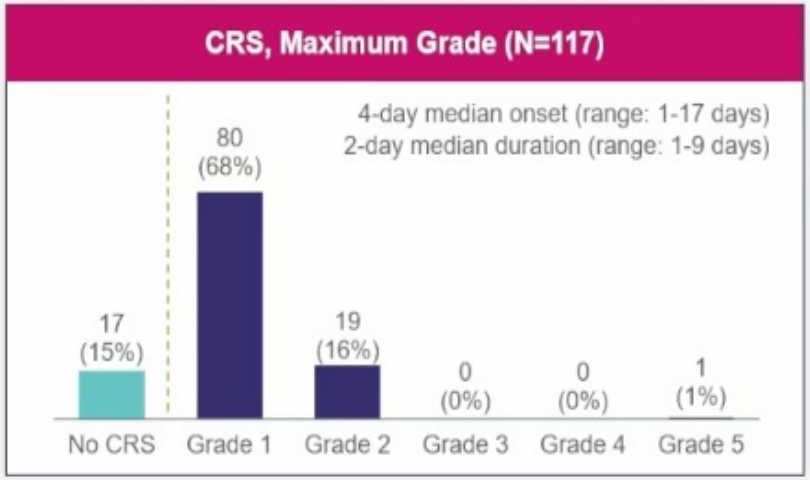
MRD Negativity at 10^{-5} Sensitivity Level	
Overall MRD negativity, % (n/N)	95% (91/96)
Median time to MRD negativity, months (min – max)	1.0 (0.9 – 6.4)
MRD negativity sustained for ≥ 6 months, % (n/N)	83% (54/65)

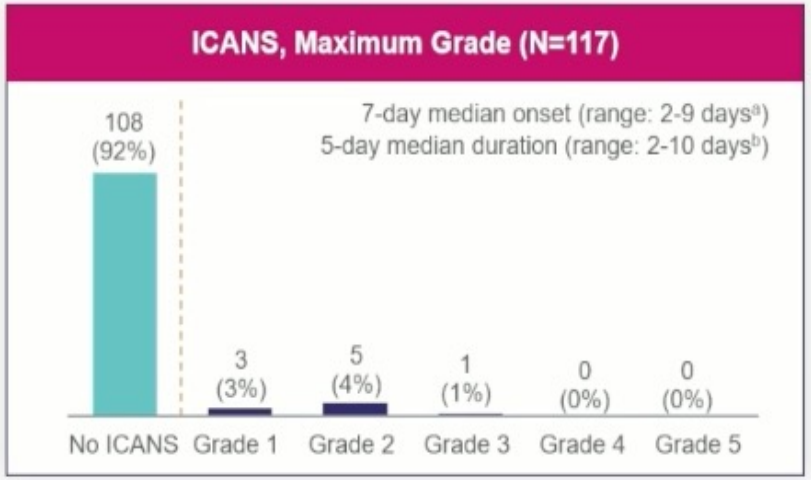
Median PFS and OS were not reached

N=117	PFS Rate (%) (95% CI)	OS Rate (%) (95% CI)
6-Month	93.1 (86.7, 96.5)	95.7 (90.0, 98.2)
12-Month	82.1 (73.6, 88.1)	94.0 (87.8, 97.1)
18-Month	67.4 (55.4, 76.8)	88.0 (78.8, 93.4)
24-Month	61.7 (48.0, 72.8)	83.0 (70.7, 90.5)

Median follow-up 15.9 months

iMMagine-1: Safety Update



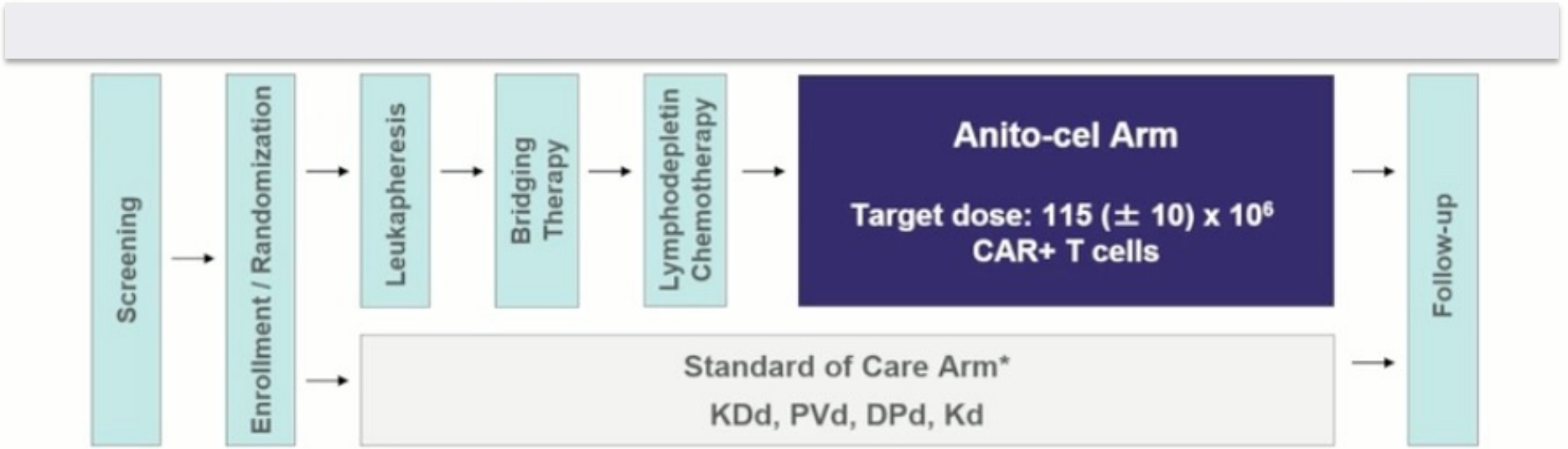


- 95% (111/117) of patients had either no CRS or CRS that resolved by ≤10 days of anito-cel infusion
- No new treatment-related or treatment-emergent deaths have occurred since the previous May 1, 2025 datacut
- No secondary primary malignancies of T-cell origin have occurred
- No replication competent lentivirus detected

No delayed or non-ICANS neurotoxicities, including no Parkinsonism, no cranial nerve palsies, and no Guillain-Barré syndrome, and no immune effector cell-associated enterocolitis have been observed to date at ≥10 months since anito-cel infusion

iMMagine-3 Design, Global Phase 3 Study – Now Enrolling

iMMagine-3 (NCT06413498) is a global, Phase 3 trial comparing anito-cel to standard of care therapy in patients with RRMM after 1-3 prior LoT, including an anti-CD38 monoclonal antibody and an iMiD



Study Design

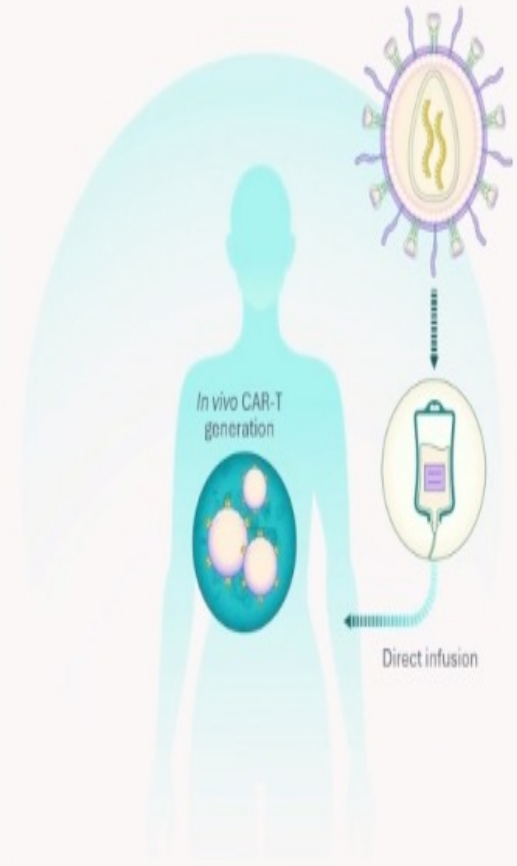
- 1:1 Randomization
- n = Approximately 450, ~130 sites globally

Study Endpoints

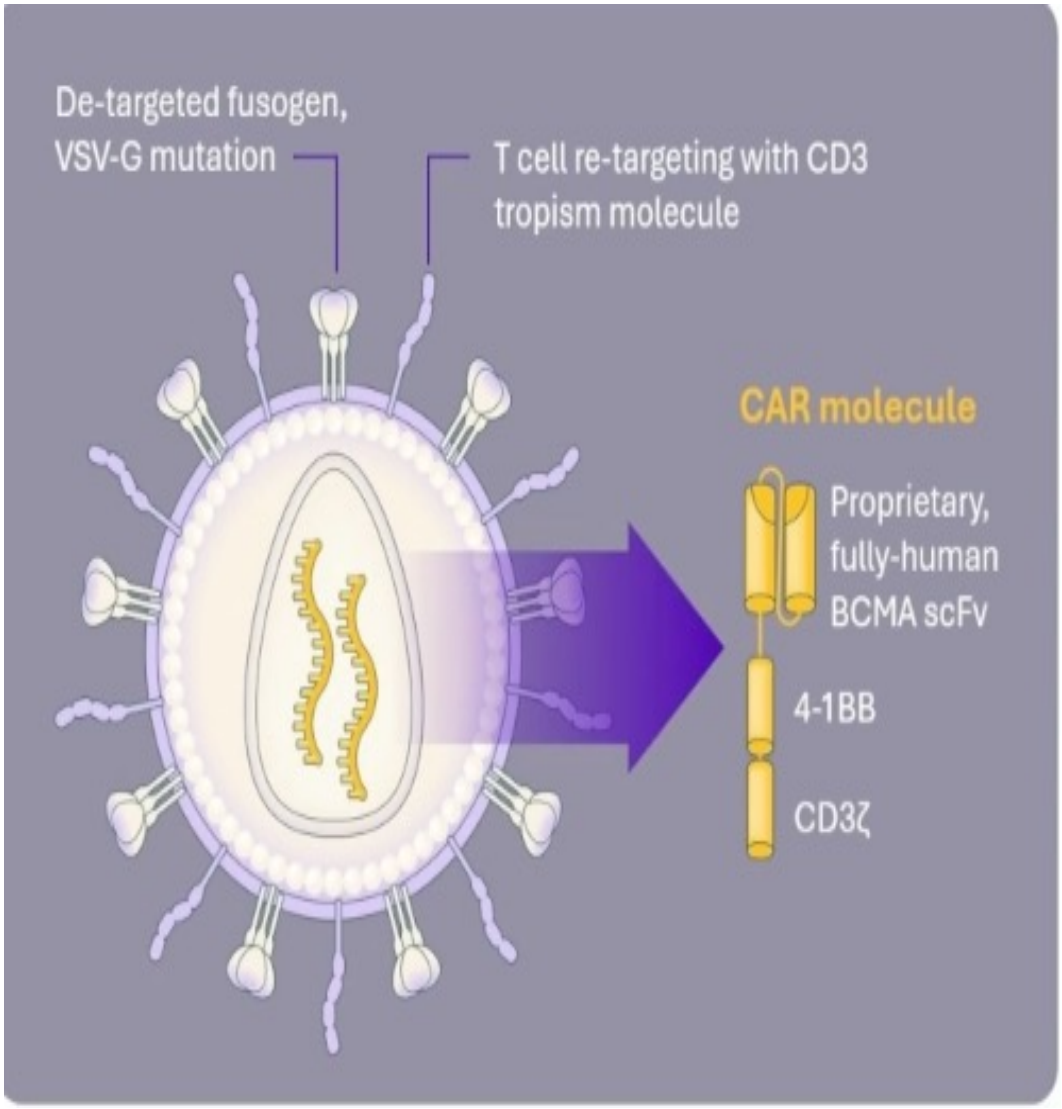
- Primary Endpoints:
  - PFS
  - MRD-negative CR rate at 9 months
- Key Secondary Endpoints: CR rate, MRD, OS, safety

Cycles will continue until unacceptable toxicity, progression as per IMWG criteria, or patient withdrawal of consent

In vivo CAR T with KLN-1010 lentiviral particles



- Eliminates preconditioning lymphodepletion ☑
- Greatly simplified logistics to expand access ☑
- No *ex vivo* culture may increase T-cell fitness ☑
- Reduced cost of goods and manufacturing ☑



inMMyCAR, a first-in-human Phase 1 study of KLN-1010

Dose escalation: 3+3 and backfill (N~20) → **Expansion (N~20), RP2D**

Patient population
- RRMM after ≥3 lines of therapy; prior PI, IMiD, CD38 mAb
- ECOG Performance Status of 0, 1
- Adequate bone marrow and end organ function

Endpoints
- **Primary:** Safety & tolerability, RP2D
- **Secondary:**
  - CAR T-cell expansion and persistence
  - ORR (IMWG criteria), MRD, DOR, PFS

Study sites
Peter MacCallum Cancer Center
The Alfred Hospital
Royal Prince Alfred Hospital

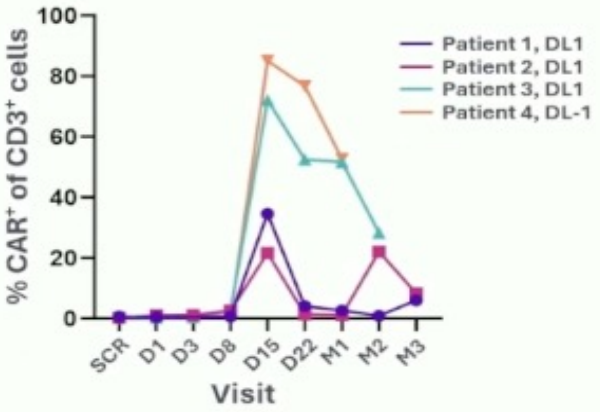
ClinicalTrials.gov ID: NCT07075185

CAR, chimeric antigen receptor; CD38, cluster of differentiation 38; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IU, infectious unit; mAb, monoclonal antibody; MRD, minimal residual disease; ORR, objective response rate; PFS, progression-free survival; PI, proteosome inhibitor; RP2D, recommended Phase 2 dose; RRMM, relapsed and refractory multiple myeloma.

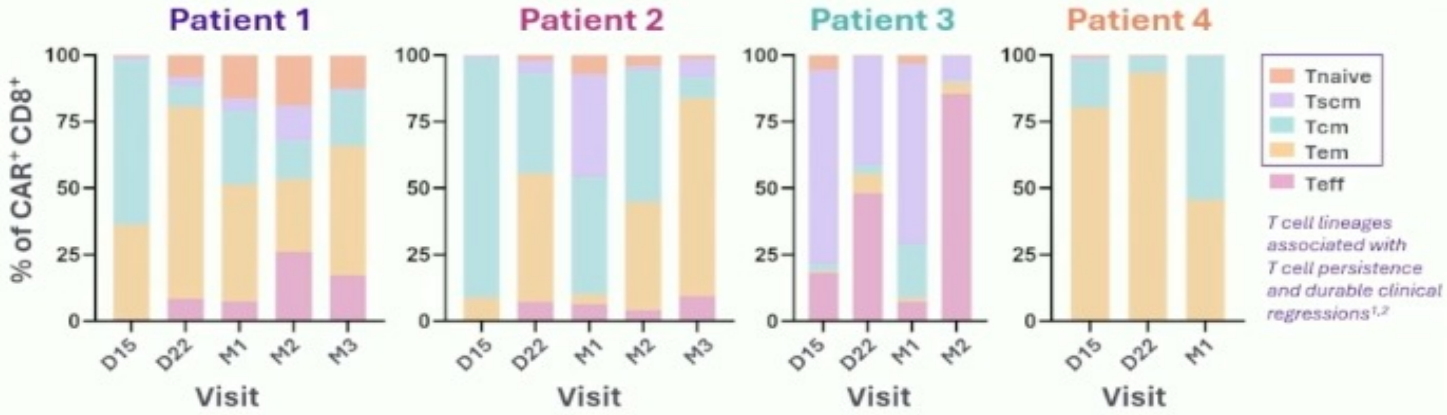
kelonia inMMyCAR

Persistent memory T cells in all patients

% CAR⁺ of CD3⁺ cells in blood



Circulating BCMA CAR-T cells



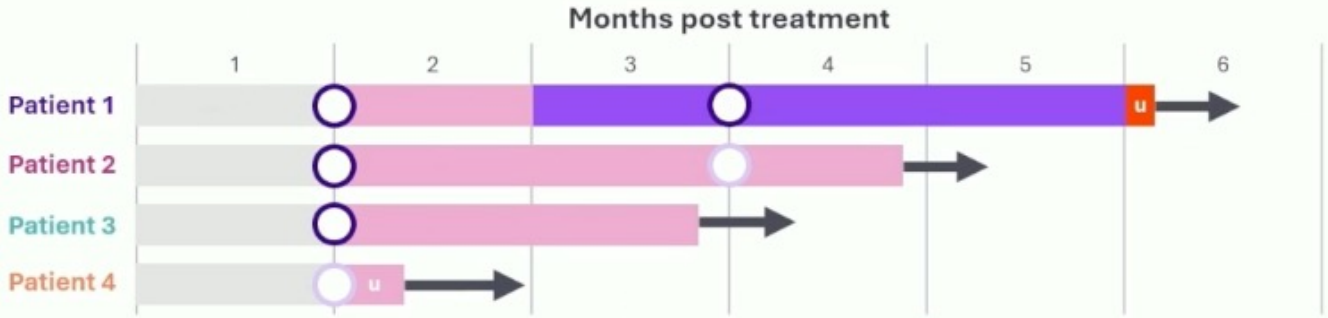
- Memory T cells are **associated with persistent CAR-T cells and durable multiple myeloma regressions** after approved CAR-T therapies[1,2]
- **Phenotypic evidence of memory CAR-T cell formation in blood** after KLN-1010 treatment

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD3, cluster of differentiation 3; CD8, cluster of differentiation 8; D, study day; DL, dose level; IU, infectious unit; M, study month; SCR, screening; Tcm, central memory T cells; Teff, T-effector; Tem, effector memory T cells; Tnaive, naive T cells; Tscm, stem cell memory T cells.

1. Caffrey M. Persistence of CAR T cells seen in "next-generation" anti-BCMA therapy, bluebird bio's ide-cel. Published December 23, 2019. Accessed November 25, 2025. https://www.ajmc.com/view/persistence-of-car-t-cells-seen-in-nextgeneration-antibcma-therapy-bluebird-bios-idecel **2.** Atanackovic D et al. *Nat Commun*. 2025;16(1):6154. doi:10.1038/s41467-025-60980-2

kelonia inMMyCAR

Deep, ongoing MRD-negative responses were observed across first 4 patients



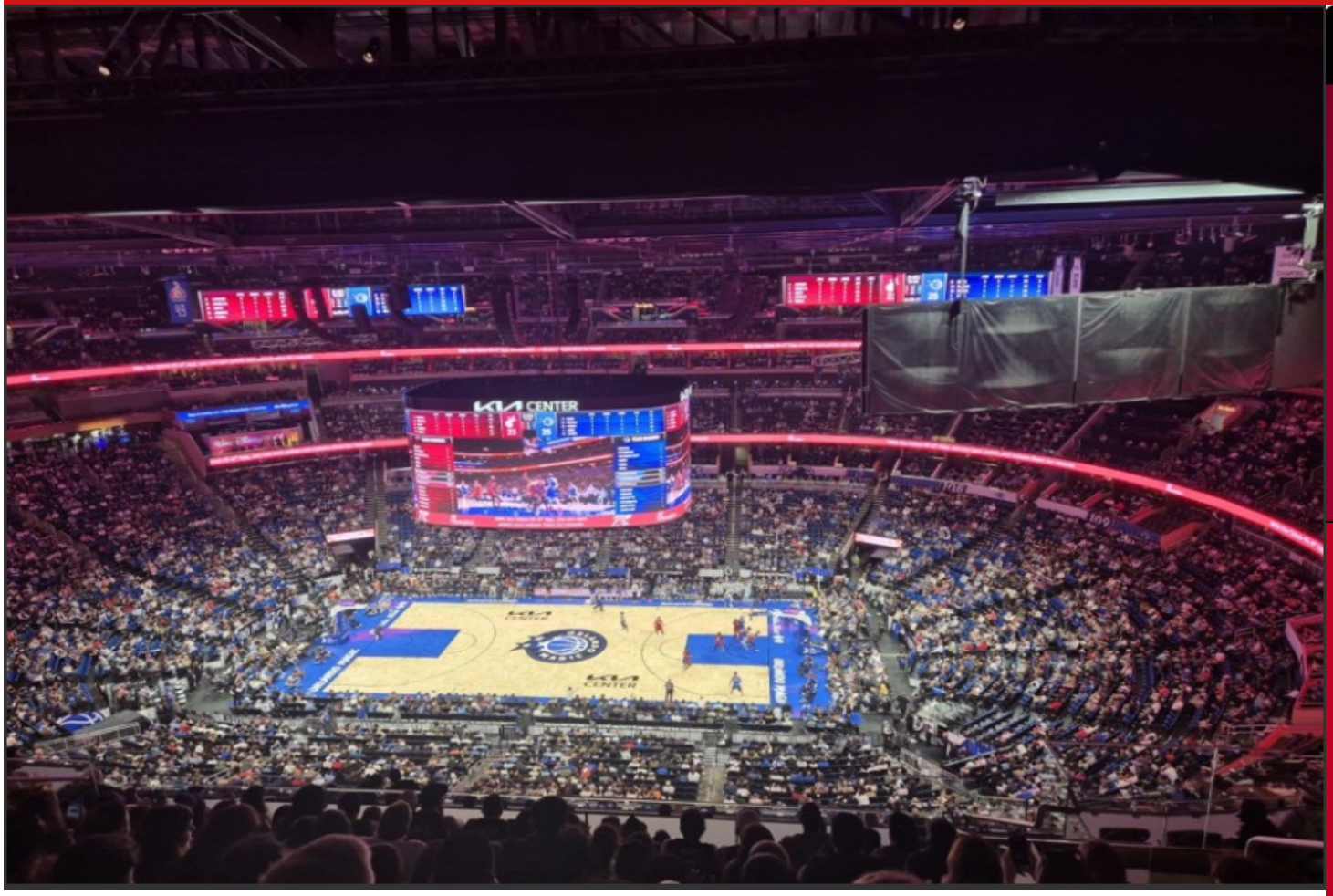
No ICANS or delayed neurotoxicity; all instances of CRS were Grade 1-2

Take Home Messages

- Functional high-risk, IMS high-risk and EMD are predictors of early relapse after cilta-cel.
- 10% late neurotoxicity (including 2,9% parkinsonism) can be predicted by no response to bridging and lymphocyte count >2500/µl.
- Anito-cel effective (74% CR, 62% 2y-PFS) without any severe CRS and neurotoxicity.
- «Proof of principle» of efficacy and no early toxicity in 4 pts after «in vivo» anti-BCMA CAR-T with lentiviral particles.

Novità dal Meeting della Società Americana di Ematologia

Torino, 19-21 Febbraio 2026



GRAZIE!