POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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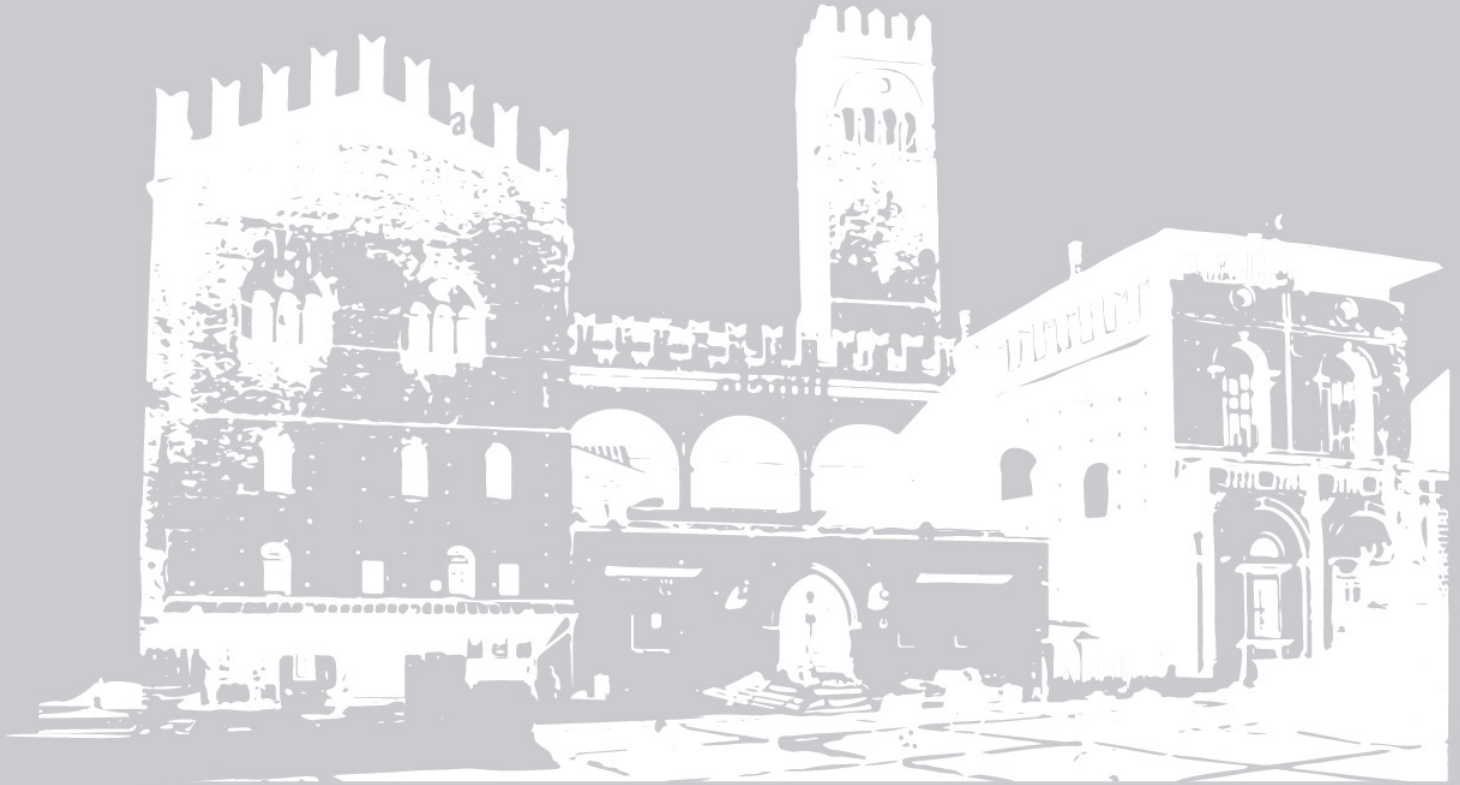

CAR-T nel mieloma multiplo

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Disclosures of Elena Zamagni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Johnson & Johnson						X	X
BMS						X	X
Pfizer						X	X
Amgen						X	X
Sanofi						X	X
Oncopeptide						X	X
Menarini-Stemline						X	X

Current EMA approved/recommended use of CART cells in MM: IMS/ASH 2024 updates

- Cilta-cel (anti BCMA) II line
- Ide-cel (anti BCMA) and Cilta-cel III line
- Ide-cel and Cilta-cel IV line and beyond

Newer CART cells in MM: ASH 2024 updates

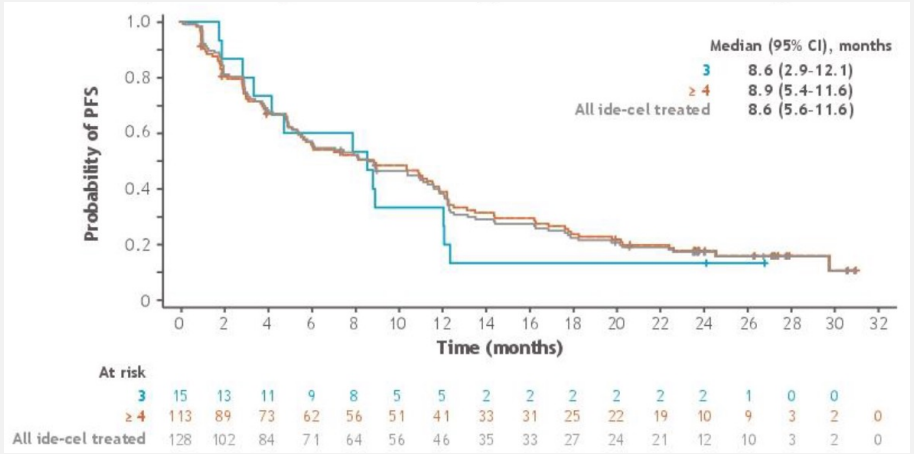
- Anito-cel
- Arlo-cel
- Allo CART

Idecabtagene Vicleucel (Ide-cel):
FDA/EMA Approved in 2021-AIFA approved June 2024 in triple-exposed patients

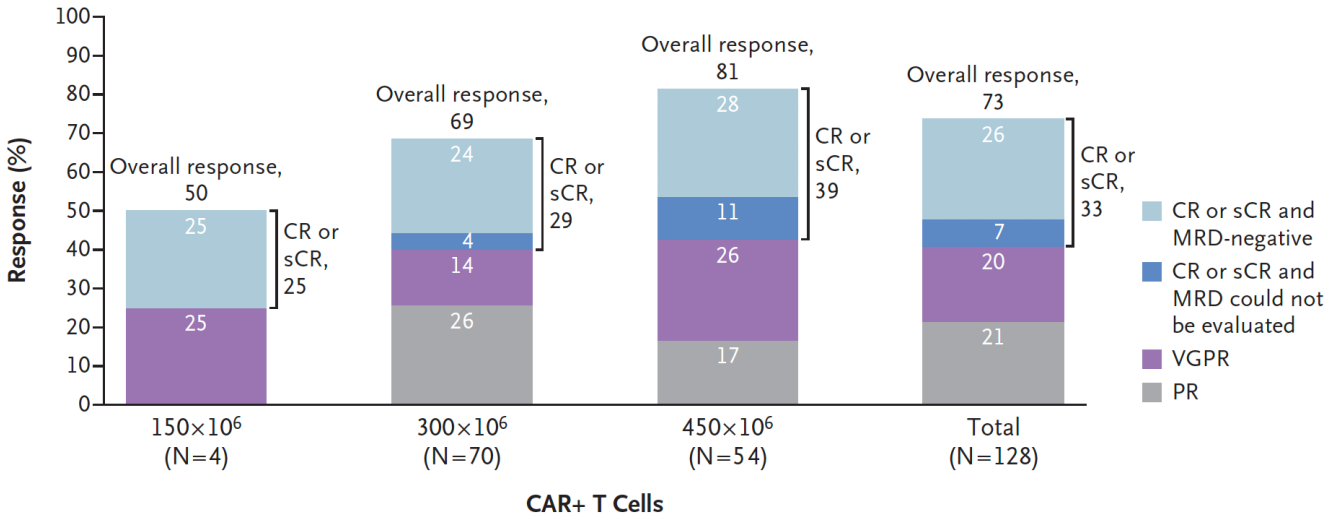
Baseline Characteristics	N=128
Median age	61 years
Target dose	300-450 million
Median Prior Lines	**6**
Triple Class Refractory	**84%**
Penta Refractory	26%
Bridging Therapy	88%

- Overall response rate: 73%, CR rate: 33%
- MRD negativity: 26%
- Very tight usefulness in EMD patients

PFS by number of prior lines of therapy and in all ide-cel treated patients[2]



Tumor Response, Overall and According to Target Dose



Survival Outcomes	
Median PFS	**8.8 months**
Median PFS in CR	**20.2 months**
Median OS	**24.8 months**

Munshi et al. NEJM 2021;384(8):705-716

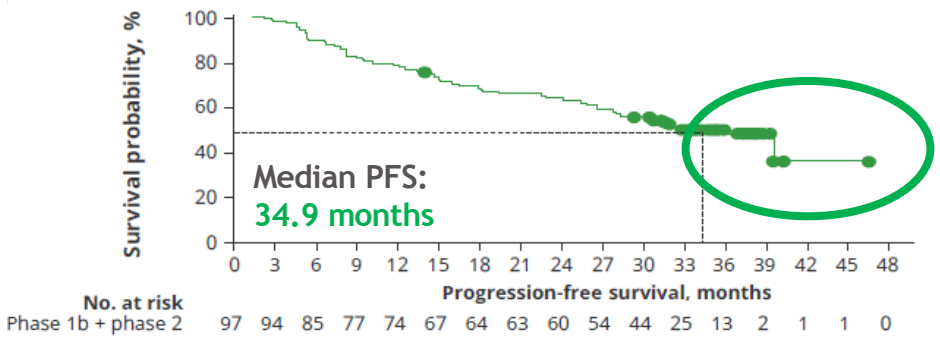
Ciltacabtagene autoleucel (CILTA-CEL): FDA/EMA Approved in 2022 in triple-exposed patients , AIFA pending

CARTITUDE-1 Phase 1b/2 study of cilta-cel in heavily pre-treated patients with RRMM: final results

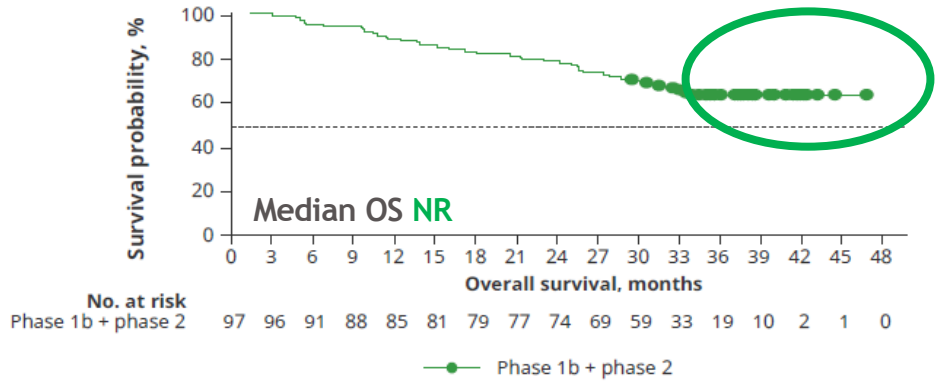
Potential 20% plateau in PFS and OS curves

At a **median follow-up of 33.4 months, 97 patients with RRMM** after a median of **6 prior lines of therapy** (88% triple refractory) were included in the final analysis

PFS[1]



OS[2]



Other key efficacy data

PFS subgroups	Median PFS, months (95% CI)	30-month PFS, %	36-month PFS, %
All patients (n=97)	34.9 (25.2–NE)	54.2	47.5
≥CR[a] (n=76)	38.2 (34.9–NE)	66.8	59.8
12-month sustained MRD negativity (n=26)[b]	NR (NE–NE)	74.9	NE
12-month sustained MRD-negative ≥ CR (n = 20)[b]	NR (NE–NE)	78.5	NE

- **ORR: 98% (**CR/sCR: 82.5%)
- **MRD-negativity:** Of 49 MRD-evaluable patients, **26 (53%) and 18 (37%)** had **sustained MRD negativity at 12 and 18 months,** respectively

San Miguel J et al, NEJM 2023

Mateos MV et al, IMS 2024

Cilta-cel in MM: Real world (US MM CART consortium) vs. Trial Data

	RWE Cilta-cel (N=236)	CARTITUDE-1 (N=97)[1]
Age, median (range)	64 y (30-84)	61 y (56-68)
Age ≥ 70 years	62 (26%)	-
Race: Black	26 (11%)	17 (18%)
Ethnicity: Hispanic	19 (8%)	6 (6%)
ECOG PS, 0-1	183 (89%)	93 (96%)
High-risk cytogenetics*	81 (39%)	23 (24%)
R-ISS stage III	30 (19%)	ISS-3:14 (14%)
Extramedullary Disease**	60 (26%)	13 (13%)
BM Plasma cells ≥ 50%	35 (18%)	≥ 60%= 21 (22%)
H/o plasma Cell Leukemia	13 (6%)	0
H/o AL amyloidosis	8 (3%)	0

*High-risk cytogenetics: Del 17p, t(14;16), t(4;14)
**EMD included patients with plasmacytomas non-contiguous from bone lesions

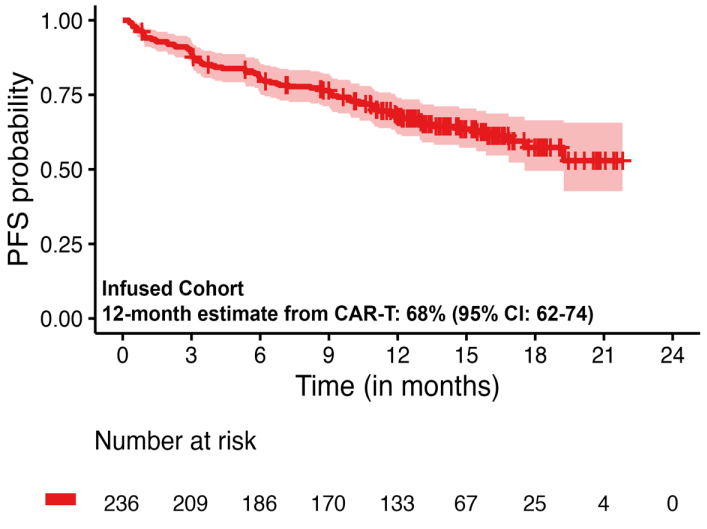
	RWE Cilta-cel (N=236)	CARTITUDE-1 (N=97)[1]
Prior Lines of Therapy	6 (2-18)	6 (4-8)
Prior Auto SCT	200 (85%)	87 (90%)
Triple Class Refractory	163 (69%)	85 (88%)
Penta Drug refractory	70 (30%)	41 (42%)
Prior BCMA Therapy	33 (14%)	0%

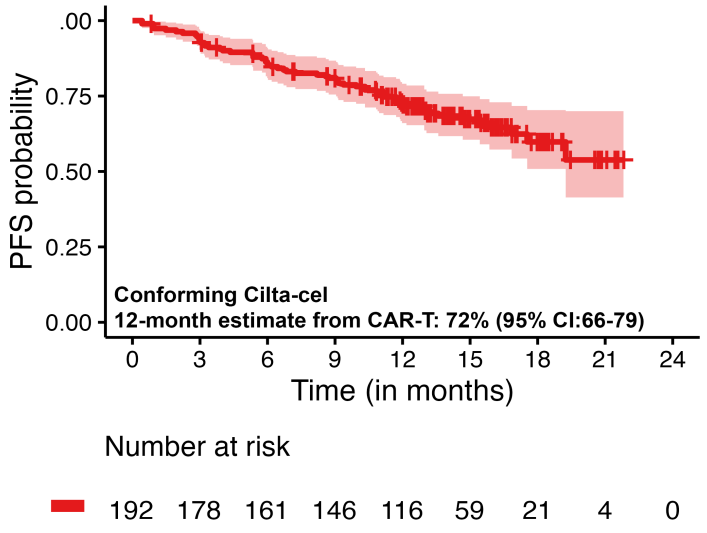
56% of real-world patients would have been ineligible for CARTITUDE-1

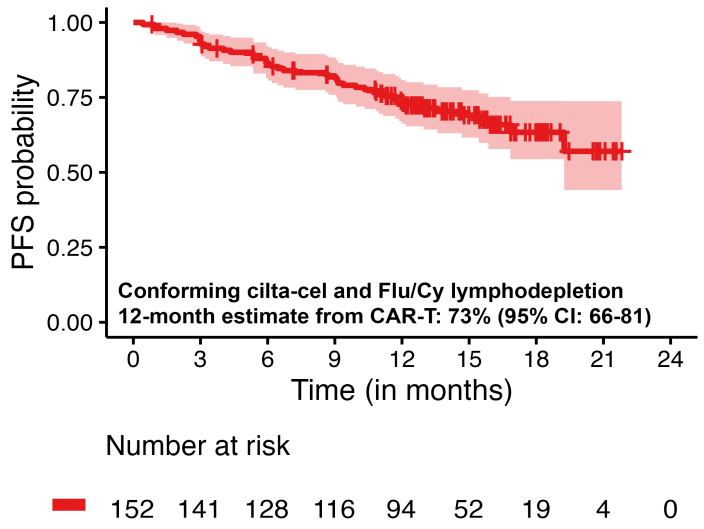
- Cytopenias (17%)
- Organ function (12%)
- Performance Status (12%)
- Prior BCMA therapy (12%)
- PCL/Amyloid/POEMS (12%)
- CNS pathology (6%)

Sidana S et al, IMS 2024, Blood 2025

Progression Free Survival







Median follow-up: 13 months from CAR-T infusion

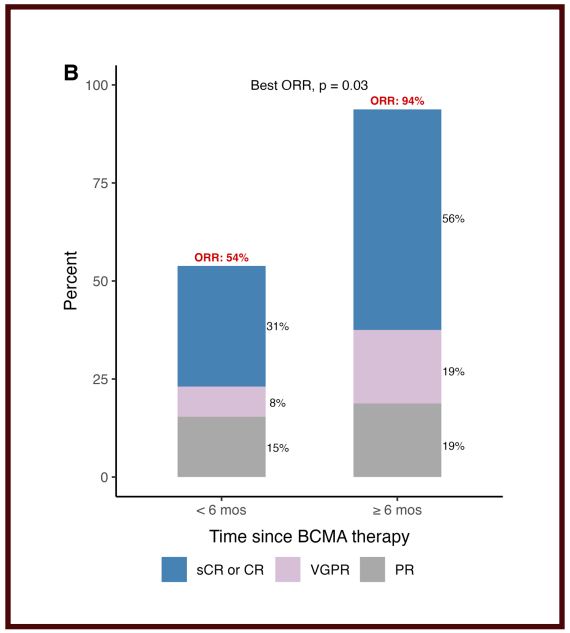
	Infused cohort N=236	Conforming cilta-cel N=192	Conforming + Flu/Cy LD N=152	CARTITUDE-1 [1-3] N=97
PFS: 12-month estimate (95% CI)	68% (62-74)	72% (66-99)	73% (66-81)	12m : 77%[1] Median: 34.9 m

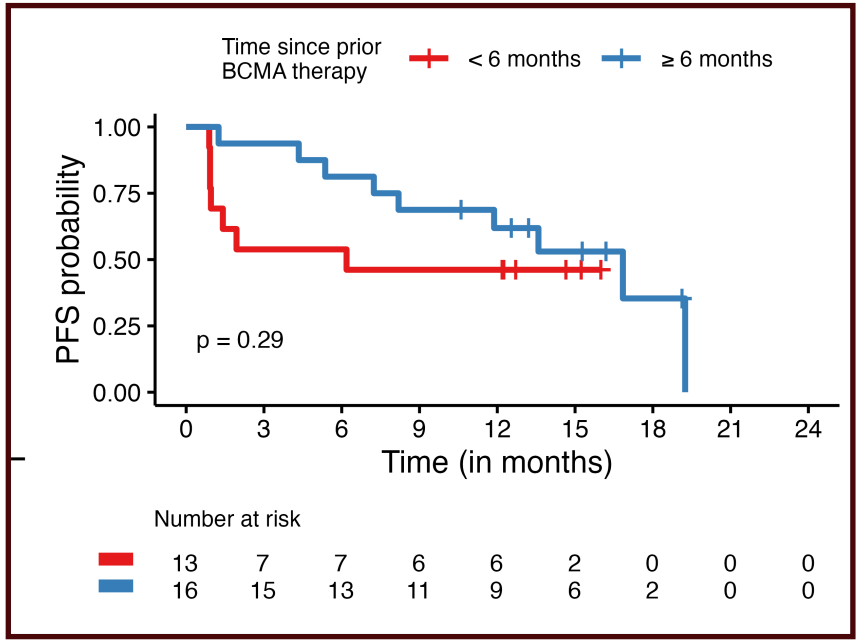
Sidana S et al, IMS 2024, Blood 2025

1.. Berdeja et al. Lancet 398:314-324, 2021; 2. Martin et al. J Clin Oncol 41:1265-1274, 2023. 3. Lin et al ASCO 2023

Cilta-cel after Prior BCMA Therapy: Timing Matters!

Time from last BCMA Therapy Exposure	N=29/33
Median time	7.1 months
≥6 months	16 (55%)
< 6 months	13 (45%)
Unknown	4





Patients with last BCMA targeted therapy < 6 months prior to cilta-cel had lower response rates and numerically lower PFS

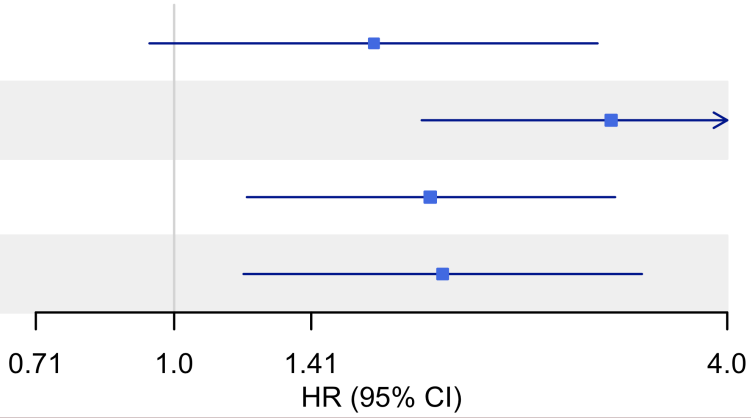
Efficacy Measure	Last BCMA exposure < 6 months vs. ≥6 months
Overall response Rate	54% vs 94%, p=0.03
Complete Response Rate	31% vs. 56% p=0.2
Median PFS	6.2 vs 16.8 months, p=0.29

Sidana S et al, IMS 2024, Blood 2025

Multivariable Analysis: PFS and OS

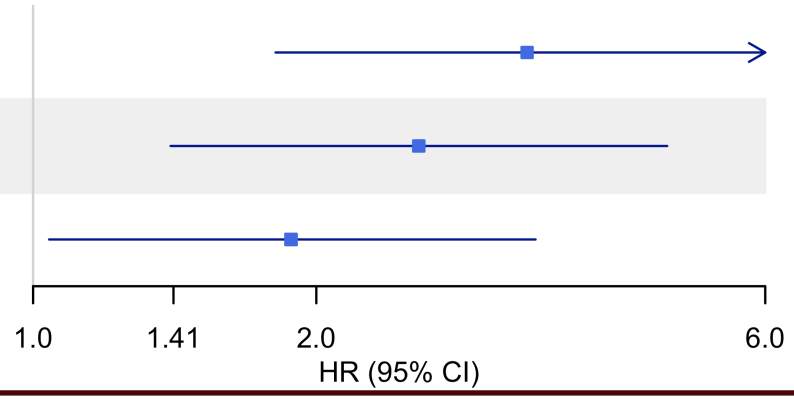
PFS

Variable	HR (95% CI)	P-value
Prior BCMA-TT (Yes vs. No)	1.65 (0.94, 2.89)	0.08
Ferritin (≥ 400 vs. < 400 ng/mL)	2.99 (1.86, 4.80)	<0.001
High-risk cytogenetics (Yes vs. No)	1.90 (1.20, 3.02)	0.006
Extramedullary disease (Yes vs. No)	1.96 (1.19, 3.23)	0.009



OS

Variable	HR (95% CI)	P-value
Ferritin (≥ 400 vs. < 400 ng/mL)	3.35 (1.81, 6.19)	<0.001
High-risk cytogenetics (Yes vs. No)	2.57 (1.40, 4.72)	0.005
Extramedullary disease (Yes vs. No)	1.88 (1.04, 3.42)	0.04



Cox Proportional Hazards model using a stepwise variable selection approach.

Sidana S et al, IMS 2024, Blood 2025

Safety of SOC Cilta-cel: CRS/ICANs and other neurotoxicities/SPMs

	Real-world N=236	CARTITUDE-1 [1-2] N=97
CRS - Any grade Grade ≥ 3	177 (75%) 12 (5%)	95% 4%
Median time to onset of CRS	7 days (0-14)	
ICANS – Any grade Grade ≥ 3	32 (14%) 9 (4%)	17% 2%
Delayed neurotoxicity **Parkinsonism** **Cranial nerve palsy** Others	24 (10%) 5 (2%) 11 (5%) 8	 12% 6% -
IEC-HS/HLH	5 (2%)	~1%
Severe infections	49 (21%)	20%
SPMs		
All cancers -Skin 505% -MDS/AML 1.3% -T cell lymphoma 1	20 (8.5%) (1yr median fup)	16.5% (2 year median fup)

Multivariable Analysis for neurotoxicities:

- **Grade ≥ 2 CRS**: poor performance status and high baseline ferritin increased risk
- **ICANS**: poor performance status and penta-refractory status increased risk

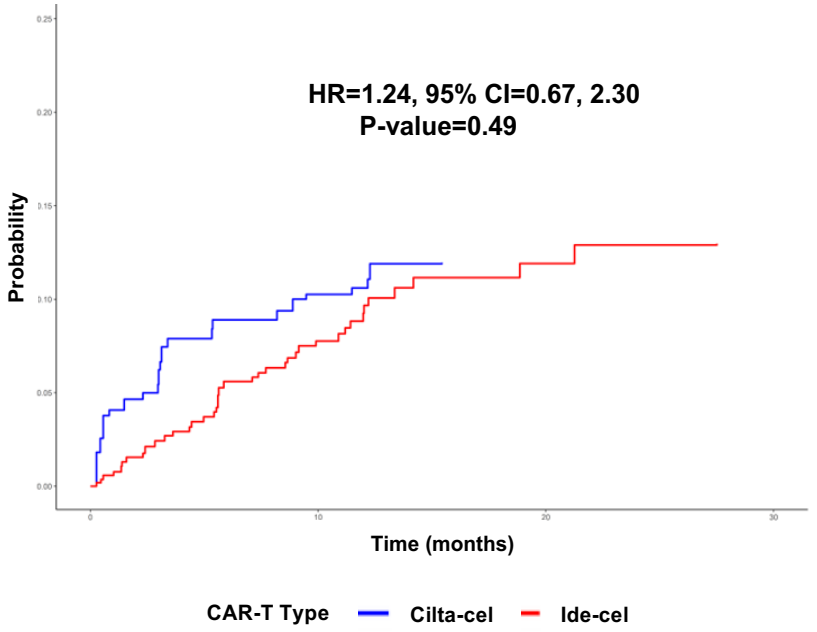
Sidana S et al, IMS 2024, Blood 2025

1. Berdeja et al. Lancet 398:314-324, 2021; 2. Martin et al. J Clin Oncol 41:1265-1274, 2023.

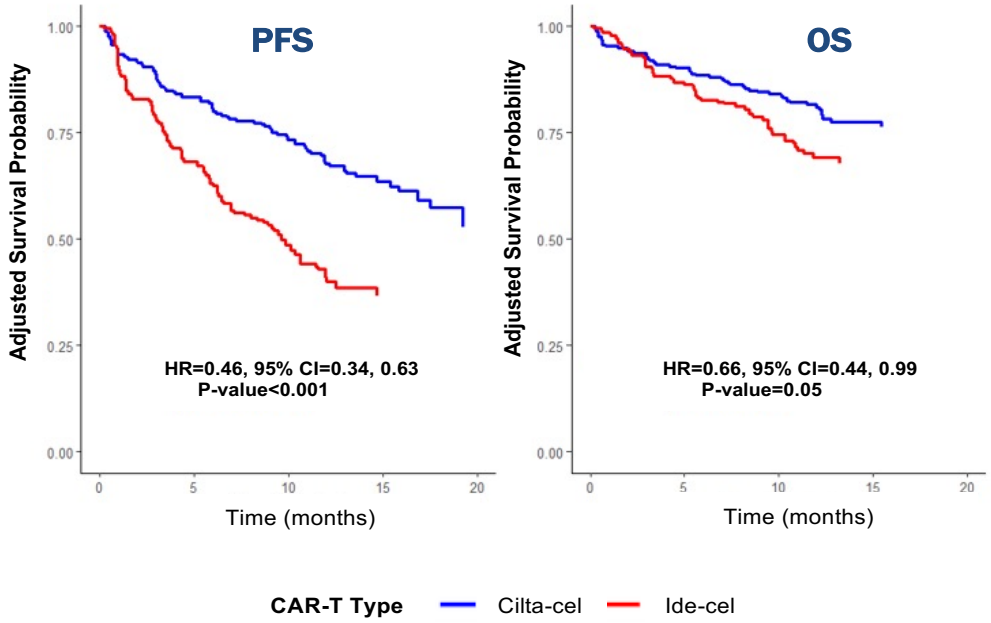
Choice of CART in later lines
cilta-cel vs ide-cel in real life

Key efficacy and toxicity outcomes reported in the comparison between ide-cel and cilta-cel

Non-Relapse Mortality



PFS and OS Restricted to ≥ March 2022

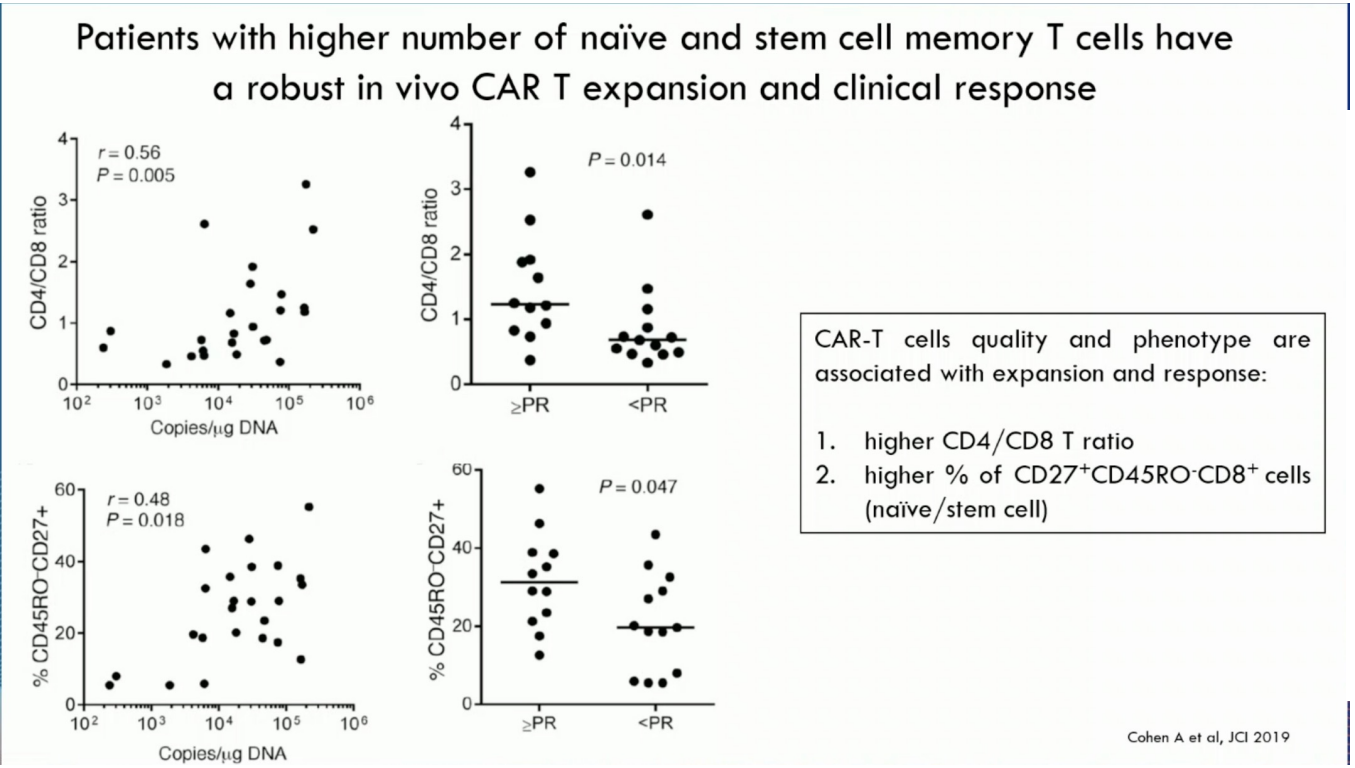


Patients treated with **cilta-cel** were **more likely** to experience:
Infections, severe CRS, delayed neurotoxicity, best response of ≥CR, **superior PFS**

CI, confidence interval; CR, complete response; CRS, cytokine release syndrome; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

1. Hansen D, et al. ASH 2024 (Abstract No. 936)

Advantages of earlier use of CAR-T cells



The benefit of CAR-T cell therapies may be improved when administered earlier vs later in the RRMM treatment pathway due to:[1,2]

More functional T cells

During MM progression, T cell exhaustion can occur, reducing effector function

Treatment with bispecific antibodies is also associated with T cell exhaustion[1,2]

No loss of BCMA expression

Prior exposure to anti-BCMA therapies may reduce BCMA expression, thereby reducing clinical response to BCMA-directed CAR-T[1]

Increased patient fitness

Patients tend to be healthier earlier vs later in MM disease and may be able to better tolerate CAR-T and any associated AEs[1,2]

Less aggressive disease

MM tends to be less aggressive and have less tumour bulk earlier in disease, allowing time for leukapheresis washout and CAR-T manufacturing[1,2]

Earlier phases of MM are associated with:

1. increased choices of more effective bridging therapies
2. less frequent presence of unfavourable disease characteristics
3. More fit T cells

AE, adverse event; IMWG, International Myeloma Working Group; MM, multiple myeloma; RRMM, relapsed or refractory multiple myeloma.

1. Lin Y, et al. Lancet Oncol 2024;25:e374-e3871; 2. Anderson Jr LD, et al. Transplant Cell Ther 2024;30:17-37.

CARTITUDE-4,Phase III trial, showed the efficacy of cilta-cel vs SoC at 2L+, leading to FDA and EMA approval 2024 in PI/len-exposed patients[1–4]

Study design[1]

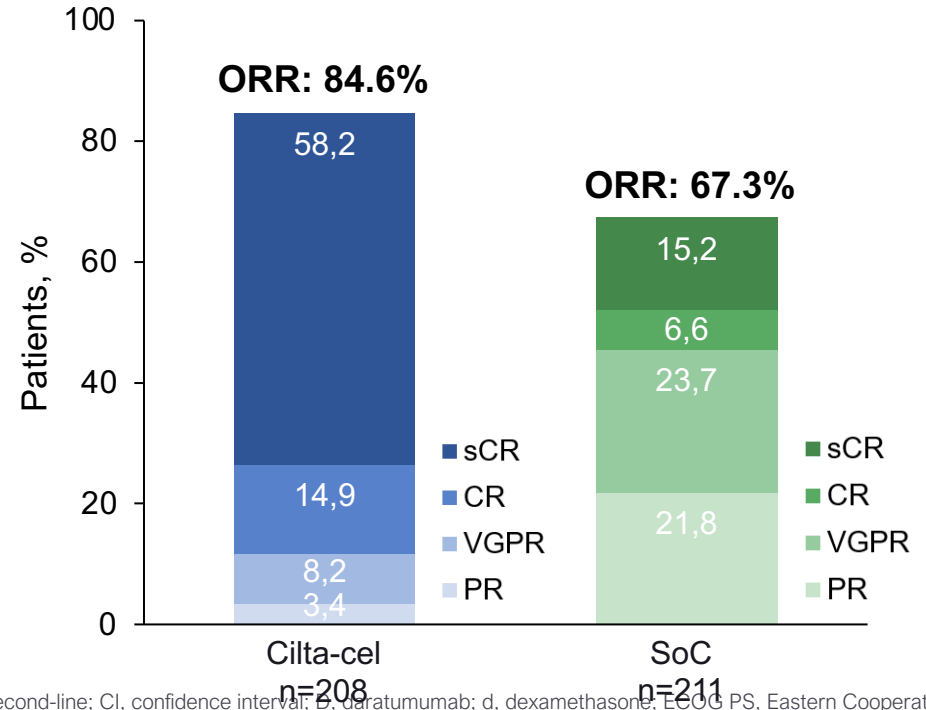
- RRMM
- ECOG PS 0–1
- Len-refractory
- **1–3 prior LOT**, including PI and IMiD

Rn 1:1
N=419

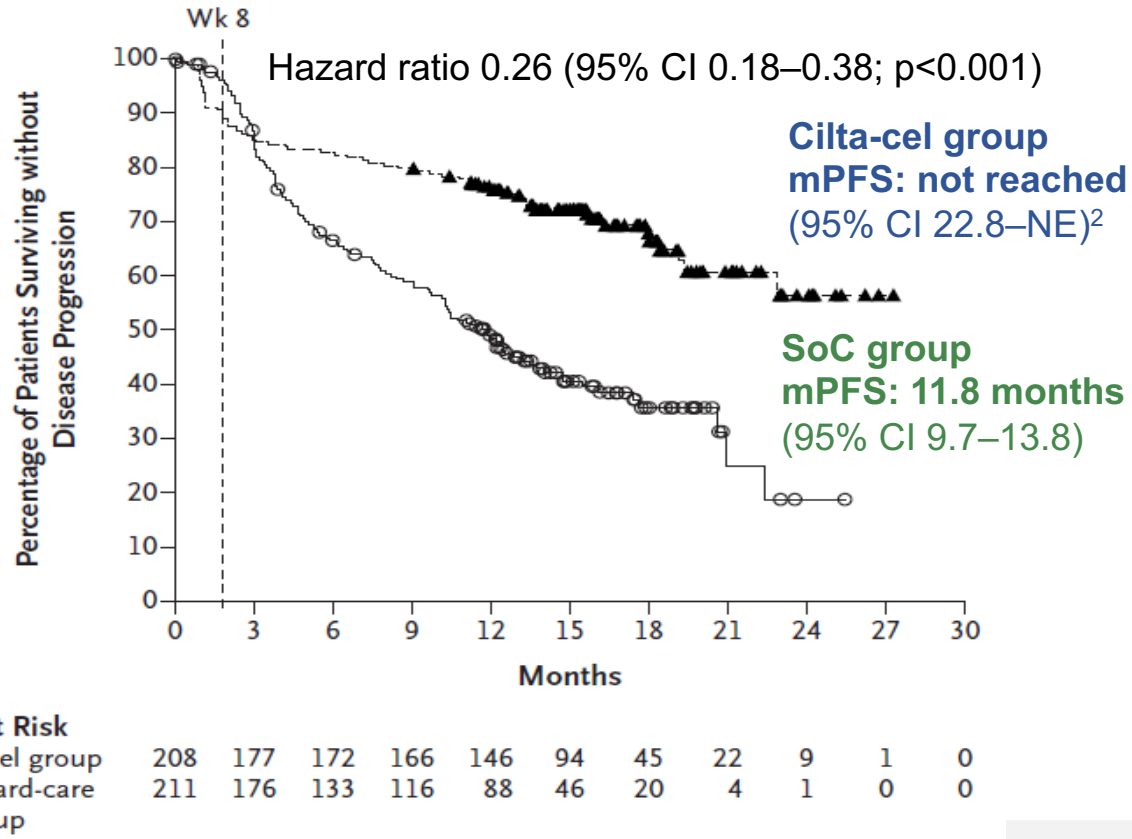
Cilta-cel (n=208)

SoC (**PVd or DPd**; n=211)

Response rates[1]



PFS (primary endpoint)[1]



No. at Risk											
Cilta-cel group	208	177	172	166	146	94	45	22	9	1	0
Standard-care group	211	176	133	116	88	46	20	4	1	0	0

Median follow-up: **~15.9 months**[1]

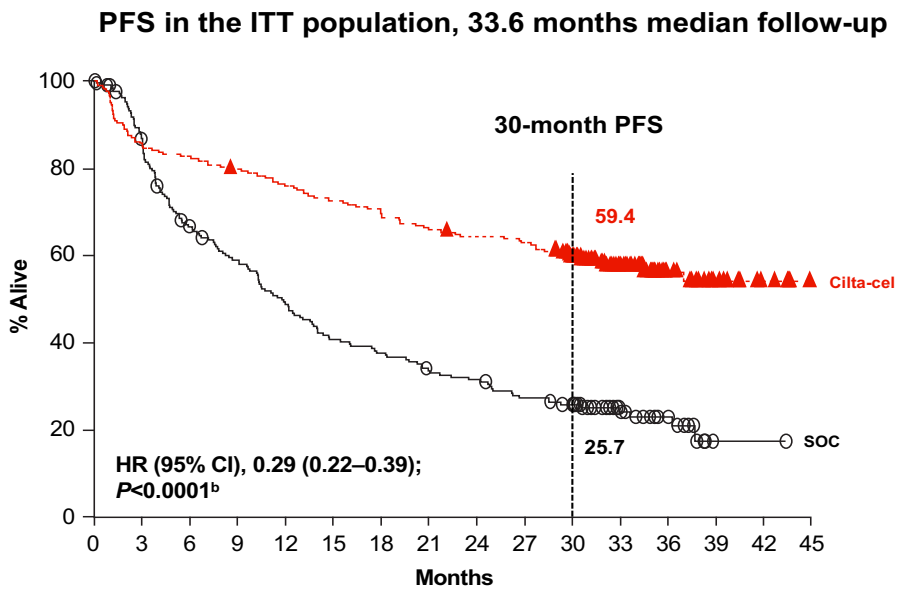
At data cut-off:[1]

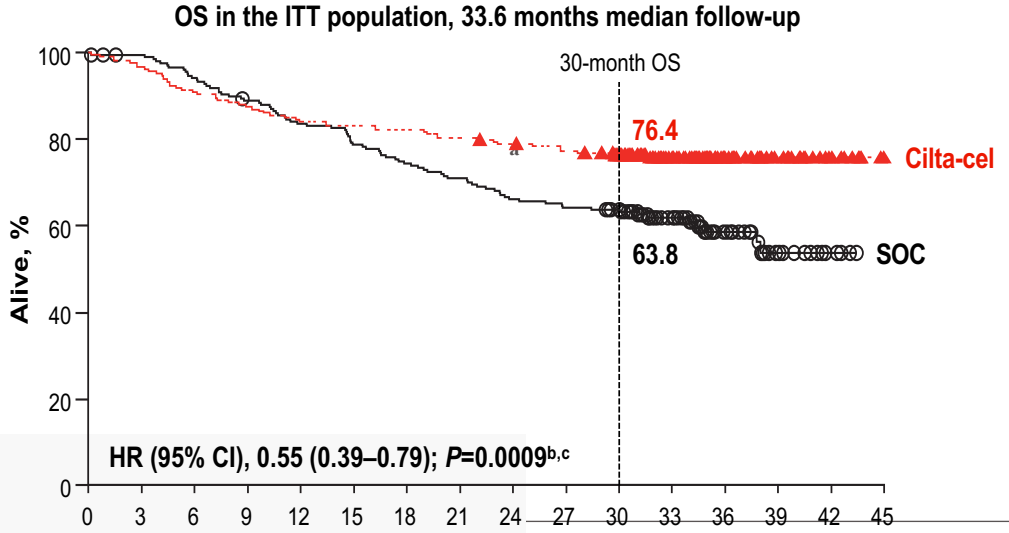
- **mPFS not reached** in the **cilta-cel** group
- **mOS not reached** in either treatment group

2L, second-line; CI, confidence interval; D, daratumumab; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; len, lenalidomide; LOT, line(s) of therapy; mOS, median overall survival; (m)PFS, (median) progression-free survival; RRMM, relapsed/refractory multiple myeloma; SoC, standard of care; V, bortezomib.

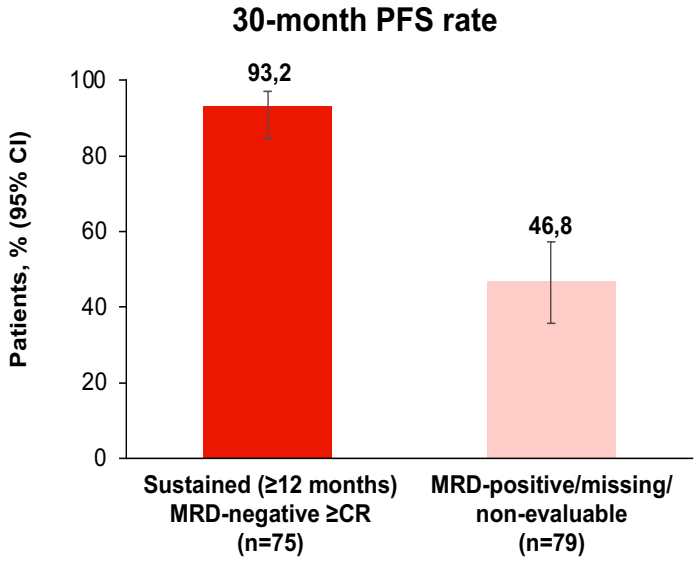
1. San Miguel J, et al. N Engl J Med 2023;389:335–347; 2. Dhakal B, et al. ASCO 2023 (Abstract No. LBA106 – oral presentation); 3. Press release. Available at: https://www.jnj.com/media-center/press-releases/

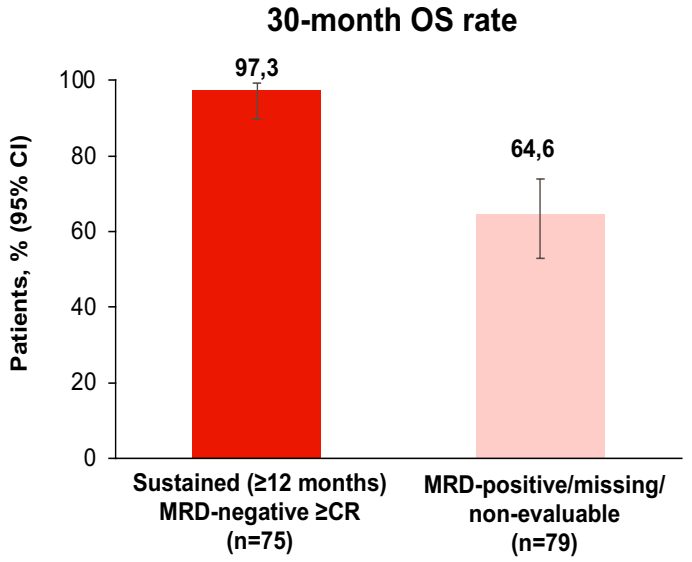
Phase 3 CARTITUDE-4 trial: Long-term follow-up results (34 months)[1]: OS results and survival in sutained MRD negative patients





- **High rates of overall MRD-negativity are rapidly achieved with cilta-cel**, and almost all cilta-cel patients negative at 10^{-5} **were also negative at** 10^{-6}
- Across subgroups, cilta-cel **increased overall MRD-negativity rates** at the 10^{-5} threshold vs SoC



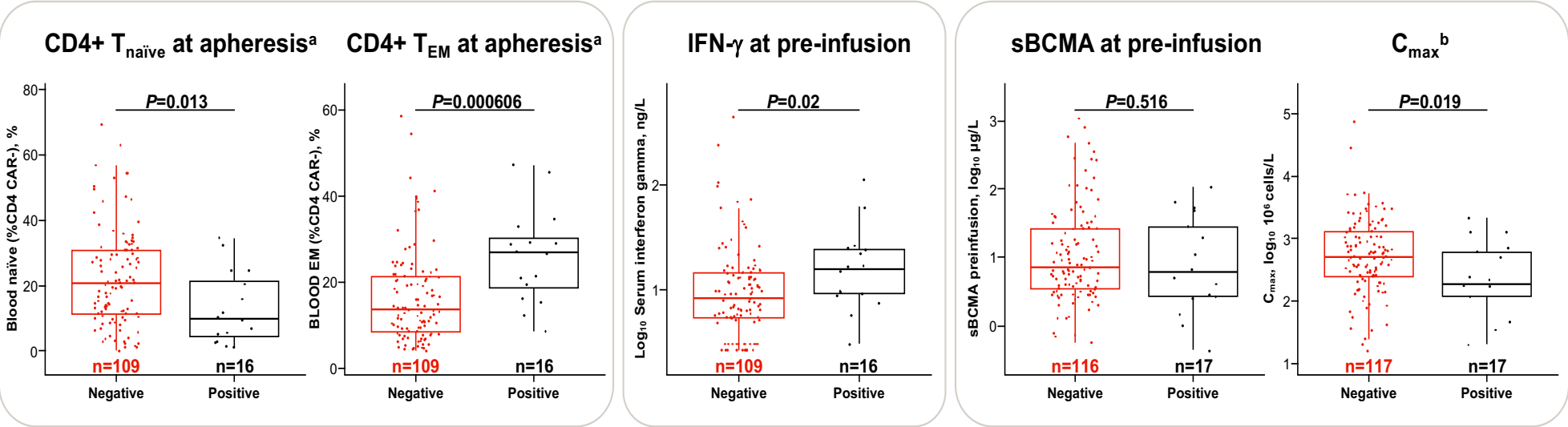


30-month PFS and OS rates were >93% in patients with sustained (≥12 month) MRD-negative ≥CR[a]

1. Popat R, et al. ASH 2024 (Abstract No. 1032)

Phase 3 CARTITUDE-4 trial: MRD-negativity analysis[1]

- Comparison of patients with MRD-positive ≥CR and patients with MRD-negative ≥CR



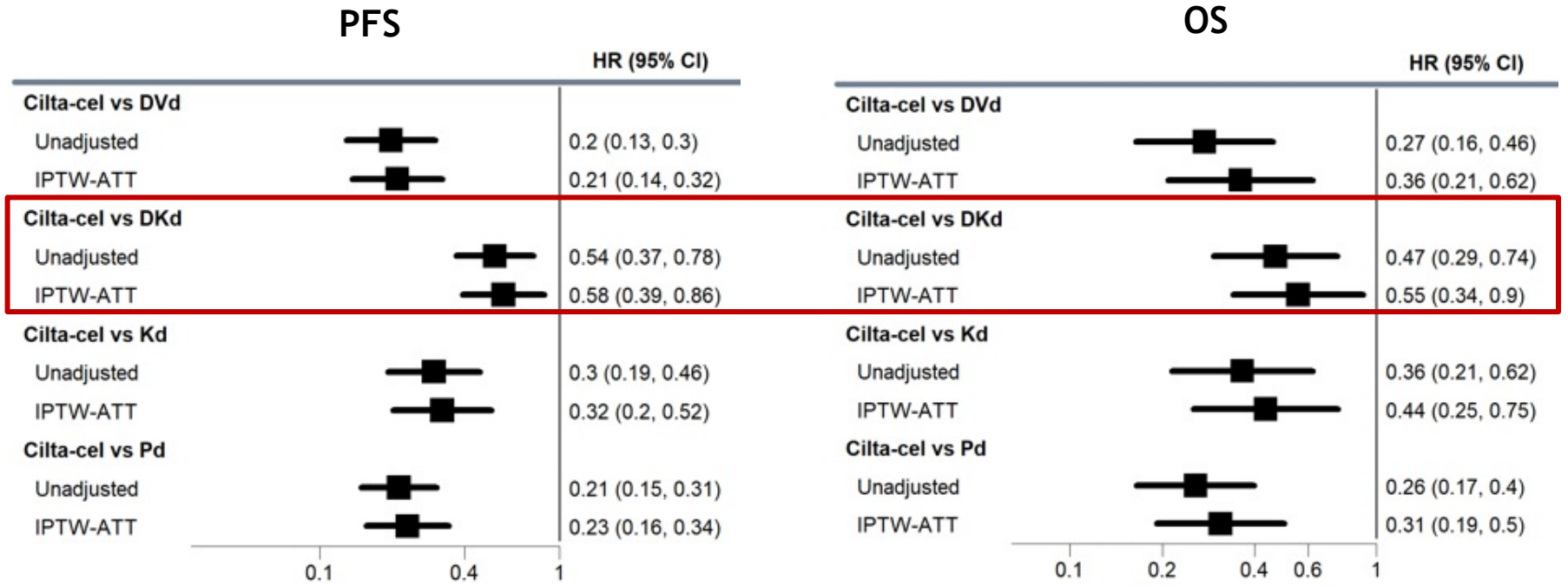
MRD-negative ≥CR status was associated with **enhanced immune fitness at apheresis, lower inflammatory cytokines pre-infusion**, and **higher CAR+ T-cell expansion** vs those with MRD-positive ≥CR; these covariates were **previously associated with longer PFS in CARTITUDE-1**[2]

CR, complete response; EM, effector memory; IFN, interferon; MRD, minimal residual disease; PFS, progression-free survival; sBCMA, serum B-cell maturation antigen.

1. Popat R, et al. ASH 2024 (Abstract No. 1032 – oral presentation); 2. Montes dO, et al. ASH 2023 (Abstract No. 2009 – poster).

Phase 3 CARTITUDE-4 trial: IPTW analysis[1]: cilta-cel vs current SOC, including K-based regimens

Comparative efficacy of cilta-cel vs standard regimens (DVd, DKd, Kd, Pd) using inverse probability of treatment weighting (IPTW) in patients with Len-refractory RRMM and 1-3 prior LOT, based on updated data from CARTITUDE-4 compared with data from CASTOR, CANDOR and APOLLO trials[a]



Response

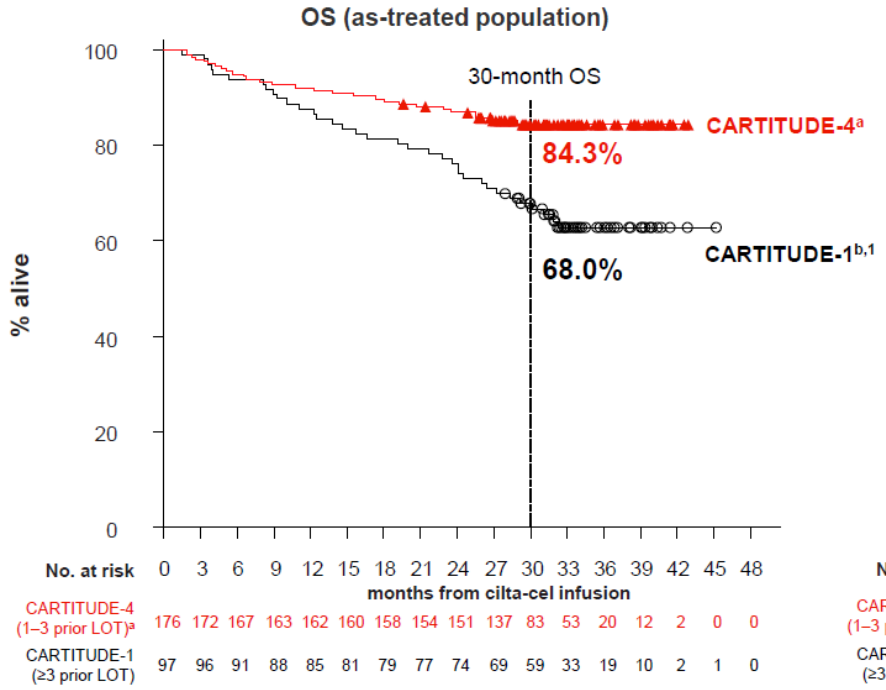
- Increased chance of achieving response with cilta-cel, by 1.1-fold vs DKd, 1.1-fold vs DVd, 1.2-fold vs Kd, and a significant 2.0-fold vs Pd
- Significant increased chance of achieving ≥VGPR and ≥CR with cilta-cel vs standard regimens

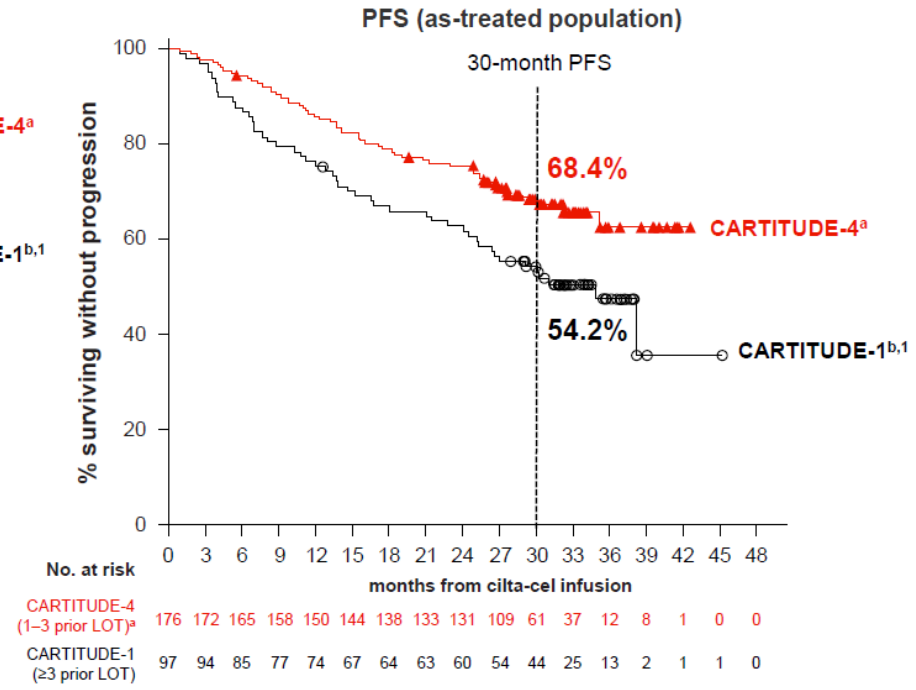
[a] Median follow-up: CARITITUDE-4, 34 months; CASTOR, 73 months; CANDOR, 50 months; APOLLO, 40 months.

ATT, average treatment effect in the treated; CI, confidence interval; CR, complete response; d, dexamethasone; D, daratumumab; HR, hazard ratio; IPTW, inverse probability of treatment weighting; K, carfilzomib; LOT, lines of therapy; OS, overall survival; P, prednisone; PFS, progression-free survival; RRMM, relapsed or refractory multiple myeloma; V, bortezomib; VGPR, very good partial response.

1. Fonseca R, et al. ASH 2024 (Abstract No. 2005)

Cilta-cel 1-3 prior LOT vs cilta-cel 4 LOT +





Response, %	15.9 months FU	33.6 months FU
Cilta-cel		
ORR	84.6	84.6
≥CR	73.1	76.9
SoC		
ORR	-	67.3
≥CR	-	24.2

[a]Re-baselined to begin at time of cilta-cel infusion for patients who received cilta-cel as study treatment, with median follow-up of 30.5 months; [b]33.4-month median follow-up.
CR, complete response; FU, follow-up; LOT, lines of therapy; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SoC, standard of care.

1. Mateos MV et al. IMS 2024 (Abstract No. OA-65 – oral presentation).

KARMMA-3,Phase III trial, showed the efficacy of ide-cel vs SoC at 3L+, leading to FDA and EMA approval 2024 in triple-exposed patients[1–3]

Study design[1]

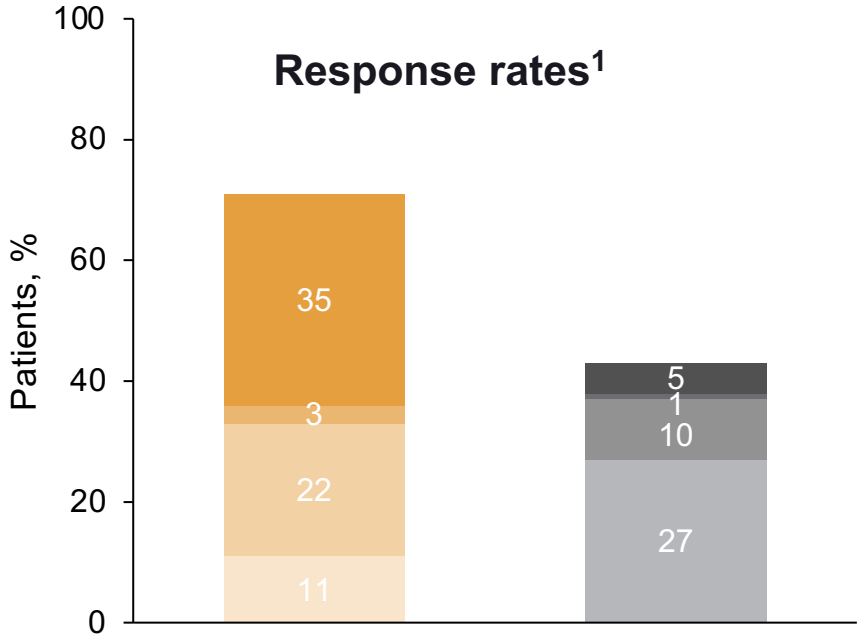
- RRMM
- ECOG PS 0–1
- **2–4 prior LOT**, including PI, IMiD, dara

Rn 2:1
N=386

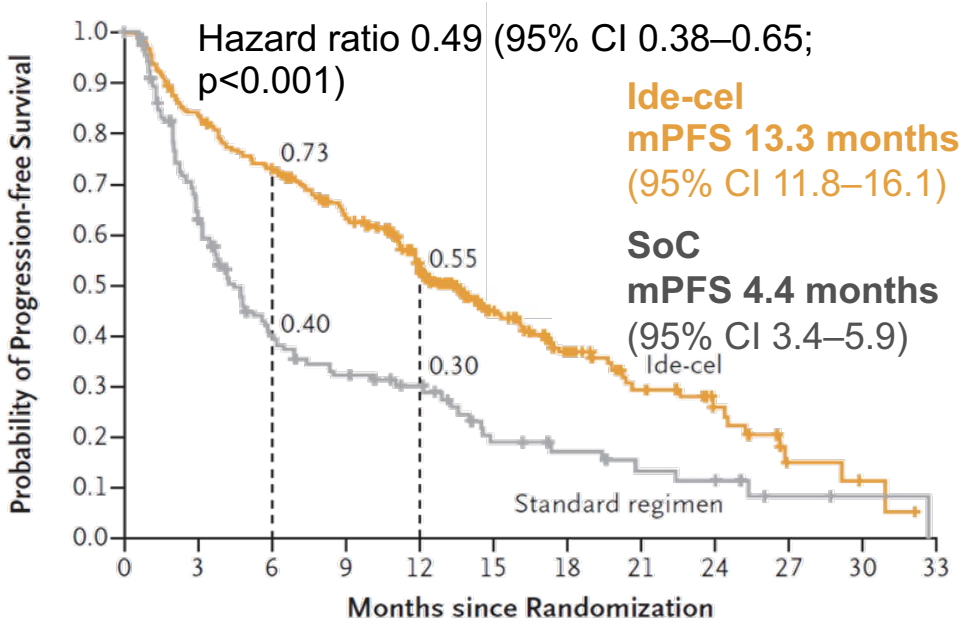
Ide-cel (n=254)

SoC (DPd, DVd, IRd, Kd or EPd; n=132)

Response rates[1]



PFS (primary endpoint)[1]



No. at Risk

Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimen	132	75	42	32	25	13	10	7	6	2	1	0

Median follow-up: **~18.6 months**[1]

At data cut-off:

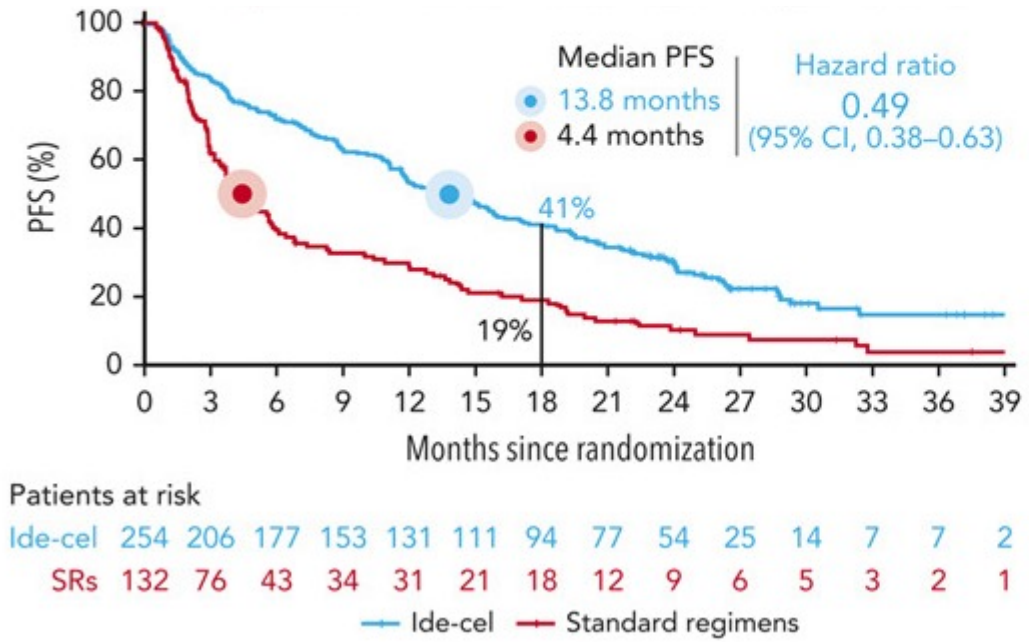
- **mOS not reached** in either treatment group[1]

CI, confidence interval; d, dexamethasone; D/dara, daratumumab; E, elotuzumab; ECOG PS, Eastern Cooperative Oncology Group performance status; EMA, European Medicines Agency; FDA, US Food and Drug Administration; I, ixazomib; IMiD, immunomodulatory drug; K, carfilzomib; LOT, line(s) of therapy; mOS, median overall survival; (m)PFS, (median) progression-free survival; P, pomalidomide, PI, proteasome inhibitor; R, lenalidomide; Rn, randomisation; RRMM, relapsed/refractory multiple myeloma; SoC, standard of care; V, bortezomib.

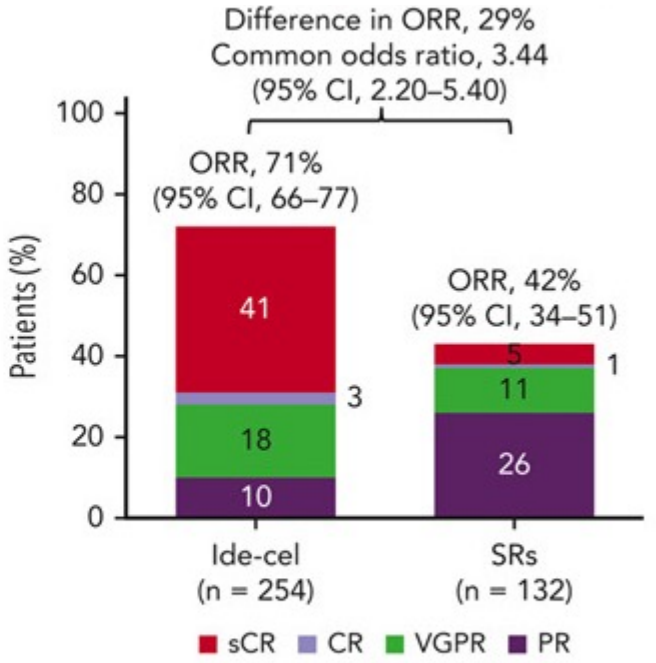
1. Rodriguez-Otero P, et al. N Engl J Med 2023;388:1002–1014; 2. Press release. Available at: https://news.bms.com/news/details/2024/

Phase 3 KarMMa-3 trial: Updated analyses (30.9 months)[1,2]

PFS



ORR



OS

- Median (95% CI) OS was 41.4 (30.9–NR) with ide-cel vs 37.9 (23.4–NR) months with SR (HR: 1.01; 95% CI, 0.73–1.40)
  - OS was confounded by crossover from SRs to ide-cel
  - Crossover adjustment showed a trend of improved OS with ide-cel vs SRs

Safety

- Safety profile of ide-cel was consistent with previous reports with no parkinsonism, Guillain-Barré syndrome, or second primary malignancies of T-cell origin reported

CI, confidence interval; CRS, cytokine release syndrome; HR, hazard ratio; ITT, intention to treat; mo, month; NR, not reached; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; (s)CR, (stringent) complete response; SPM, second primary malignancy; SR, standard regimen; VGPR, very good partial response.

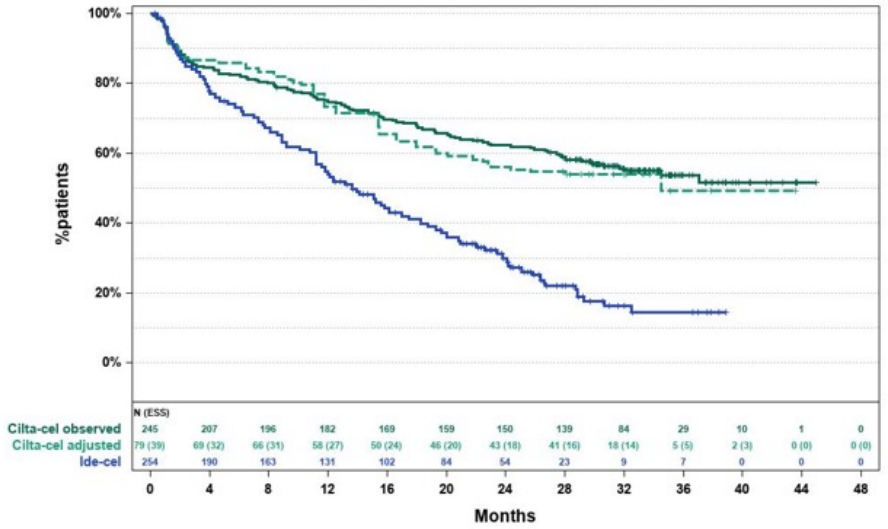
1. Ailawadhi S, et al. Blood 2024;144:2389-2401 (abstract); 2. Ailawadhi S, et al. Blood 2024;144:2389-2401 (visual abstract).

Choice of CART in later lines

MAIC: cilta-cel (CARTIDUDE-4) vs ide-cel (KARMMA-3)

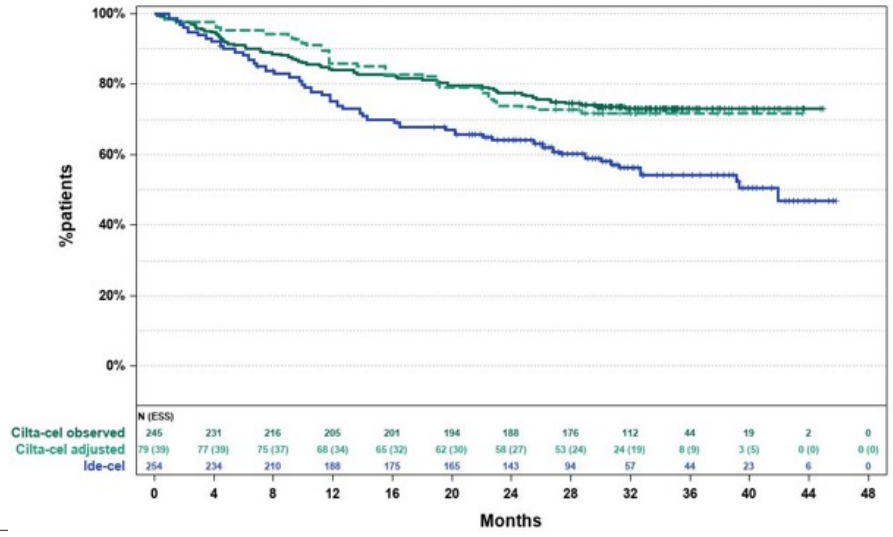
- Improved response with cilta-cel vs ide-cel
  - 1.2 times more likely to achieve ORR
  - 1.4 times more likely to achieve ≥VGPR
  - 1.8 times more likely to achieve ≥CR
- Significant 58% reduction in risk of disease progression or death with cilta-cel vs ide-cel
- Significant 42% reduction in risk of death with cilta-cel vs ide-cel

Comparative efficacy of PFS for cilta-cel vs ide-cel



Cilta-cel vs Ide-cel		
Observed HR (95% CI)	Adjusted HR (95% CI)	p value
0.39 (0.30, 0.49)	0.42 (0.26, 0.68)	0.0004

Comparative efficacy of OS for cilta-cel vs ide-cel



Cilta-cel vs Ide-cel		
Observed HR (95% CI)	Adjusted HR (95% CI)	p value
0.54 (0.40, 0.74)	0.58 (0.34, 0.99)	0.0452

CI, confidence interval; CR, complete response; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison ORR, overall response rate; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response.

1. Lopez-Muñoz N, et al. ASH 2024 (Abstract No. 3390)

Ongoing Phase I CAR-T studies[1]

Study drug	Treatment line	N	Key data (efficacy and/or safety)
CART-ddBCMA[1,2] (Anito-cel)	Median 4 prior lines	38	ORR: 100%; ≥CR: 79%; PFS: 30.2 months; OS: NR No delayed or non-ICANS neurotoxicities at mFU 38.1 months, no SPMs of T-cell origin
Arlo-cel (GPRC5D-CAR-T)[3]	Median 5 prior lines	84[a]	ORR: 87%; ≥CR: 53%; PFS: 18.3 months; OS: NR Hematologic TEAEs were the most frequent; low occurrence of grade 3/4 infections (19%) CRS in 82% and ICANS in 10%, mostly G1-2; other neurotoxicity in 12% (7% G3-4)
P-BCMA-ALLO1[4]	Median 6 prior lines	21[b]	ORR: 91%; mTTR: 16 days No grade ≥3 CRS or ICANS, grade ≥3 infection rate: 17%
Dual BCMA-CD19 Fast CAR-T[5]	1L NDMM	8	ORR: 100%; MRD- and MRD- sCR: 100% All CRS were G1 and resolved within 8 days No ICANs or neurotoxicity

[a]Efficacy evaluable for PFS, n=79;[b]Interim safety analysis on patients (n=23) given an infusion of P-BCMA-ALLO1 and with a minimum of 4 weeks follow-up, but N=21 patients enrolled in Arm C analysis excludes patients retreated with p-BCM-ALLO1. Total study enrollment as of the data cutoff (July 31, 2024) included 72 unique patients.

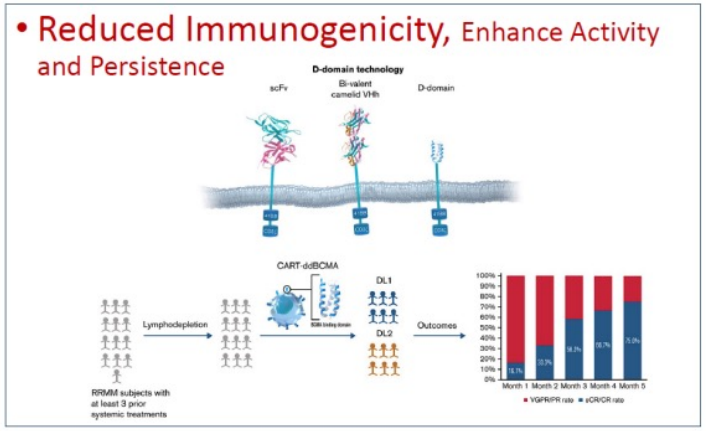
1L, first line; CR, complete response; G, grade; ICANS, Immune effector cell-associated neurotoxicity syndrome; mFU, median follow-up; MRD-, minimal residual disease negativity; mTTR, median time to response; NDMM, newly diagnosed multiple myeloma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SPM, second primary malignancy; TEAE, treatment emergent adverse event.

1. Bishop, et al. ASH 2024 (Abstract No. 4825 – poster); 2. Frigault M, et al. ASH 2023 (Abstract No. 1023 – oral presentation); 3. Bal S, et al. ASH 2024 (Abstract No. 922 – oral presentation); 4. Dholaria, et al. ASH 2024 (Abstract No. 4828 – poster); 5. Du J, et al. ASH 2024 (Abstract No. 2072 – poster).

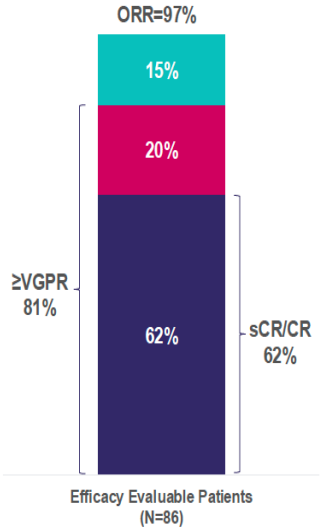
ANITO-CEL: Phase 1/2 Study of CART-ddBCMA for the Treatment of Patients with triple-exposed RRMM: iMMagine-1 registration study

- 129 patients were leukoapheresed → 117 dosed → **98 safety-evaluable** (followed for ≥1 month by data cut-off of October 31, 2024) and **86 efficacy-evaluable** (followed for ≥2 months by data cut off of October 31, 2024)

	Safety evaluable population (n=98)	Efficacy evaluable population (n=86)
Median age, years (min-max)	**65** (38-78)	**65** (38-78)
Number of PL (range)	**4 (3-8)**	**4 (3-8)**
EMD, n (%)	16 **(16%)**	13 **(15%)**
HRCA, n (%)	39 **(40%)**	33 **(38%)**
TCR, n (%)	85 **(87%)**	74 **(86%)**
PCR, n (%)	41 **(42%)**	37 **(43%)**
Bridging therapy	65 **(66%)**	61 **(71%)**
Outpatient administration	8 **(8%)**	5 **(6%)**



Efficacy Evaluable Patients (N=86)



- At a median follow-up of 9.5 months, ORR was 97% and sCR/CR rate was 62%
- 93.1% (n=54/58) of evaluable patients were MRD negative at minimum of 10^{-5} sensitivity

	Evaluable Patients	Months (min - max)
Median time to first response	83	1.0 (0.9 - 7.3)
Median time to MRD negativity of $\leq 10^{-5}$	54	1.0 (0.9 - 6.4)

Anito-cel utilizes a novel, synthetic, compact and stable **D-Domain binder**
D-Domain facilitates high CAR surface expression, low risk of tonic signaling
Recommended Phase 2 Dose selected as 115±10 million CAR+ T cells

	PFS Rate (%) (95% CI)	OS Rate (%) (95% CI)
6-Month	93.3% (84.4%, 97.2%)	96.5% (89.6%, 98.9%)
12-Month	78.5% (63.5%, 87.9%)	96.5% (89.6%, 98.9%)

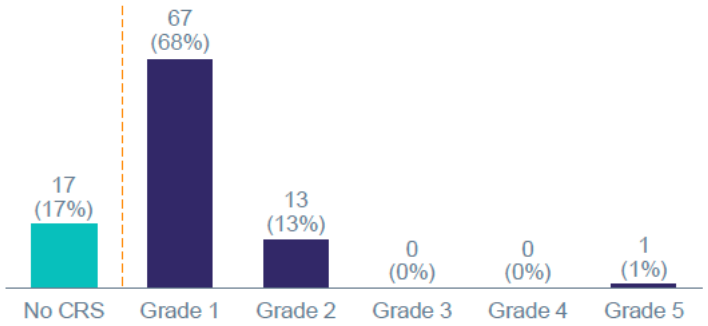
Median follow-up,9.5 months

CI, confidence interval; EMD, extramedullary disease; HRCA, high-risk cytogenetic abnormalities; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PCR, penta-class refractory; PFS, progression-free survival; PL, prior lines; PR, partial response; RRMM, relapsed or refractory multiple myeloma; (s)CR, (stringent) complete response; TCR, triple-class refractory; VGPR, very good partial response.

1. Freeman C, et al. ASH 2024 (Abstract No. 1031 – oral presentation)

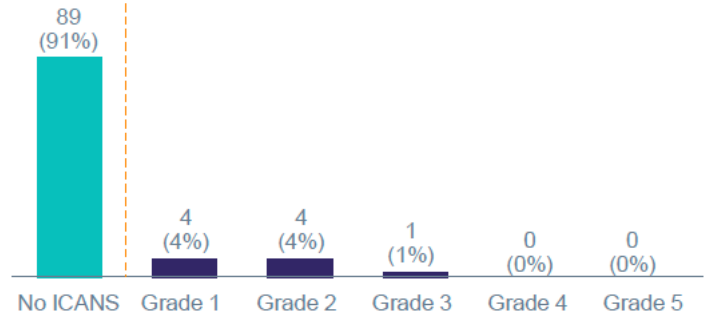
ANITO-CEL: Phase 1/2 Study of CART-ddBCMA for the Treatment of Patients with triple-exposed RRMM: Safety

Maximum CRS Grade (N=98)



- 83% (81/98) of patients had CRS of any Grade; the median onset was 4 days
- 86% (84/98) of patients had CRS Grade 1 or less, including 17% (17/98) with no CRS
- % of patients with either no CRS or CRS that resolved by:
  - ≤7 days of anito-cel infusion: 63% (62/98)
  - ≤10 days of anito-cel infusion: 92% (90/98)
  - ≤14 days of anito-cel infusion: 98% (96/98)

Maximum ICANS Grade (N=98)



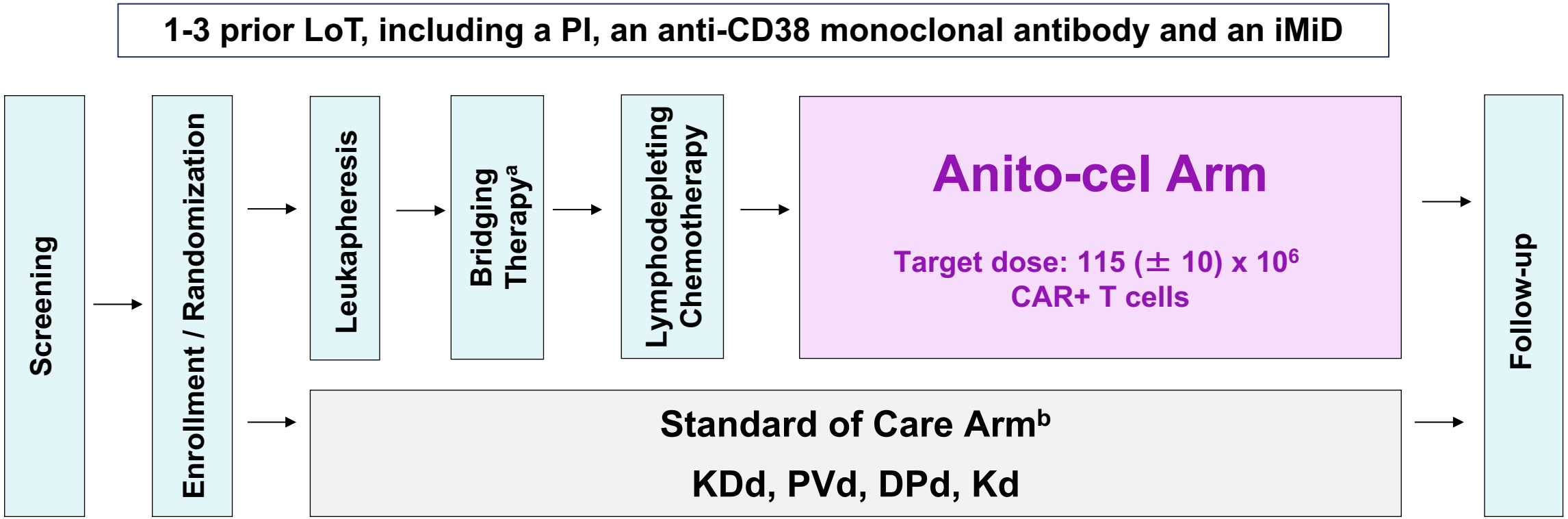
- 9% (9/98) of patients had ICANS of any grade; all cases resolved
- No delayed or non-ICANS neurotoxicities were observed, including no incidence of Parkinsonism, no cranial nerve palsies, and no Guillain-Barré syndrome (n=98)
- Similarly, no delayed or non-ICANS neurotoxicities have been observed in the Phase 1 study[1] (n=38, median follow-up of 38.1 months with minimum follow-up of 25 months)

- The most common G3 or higher treatment-emergent AEs were **cytopenias**
- **Infections occurred in 45%** (any grade); G3-4 infections occurred in 10% of patients
- **No replication competent lentiviruses** detected and **no SPM of T-cell origin**
- **No other than ICANS neurotoxicities**
- **Three deaths due to TEAEs**: retroperitoneal hemorrage,[a] CRS and fungal infection

[a]At baseline prior to infusion, the patient developed plasma cell leukemia, which was an exclusion criteria. Evidence of Grade 4 hemophagocytic lymphohistiocytosis at time of death (only case to date).
AE, adverse event; CRS, cytokine release syndrome; G, grade; ICANS, Immune effector cell-associated neurotoxicity syndrome; RRMM, relapsed or refractory multiple myeloma; SPM, second primary malignancy; TEAE, treatment-emergent adverse event.

1. Freeman C, et al. ASH 2024 (Abstract No. 1031 – oral presentation)

Phase 3 randomized iMMagine-3 trial: ANITO-CEL vs SOC in triple-class exposed patients



STUDY DESIGN

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

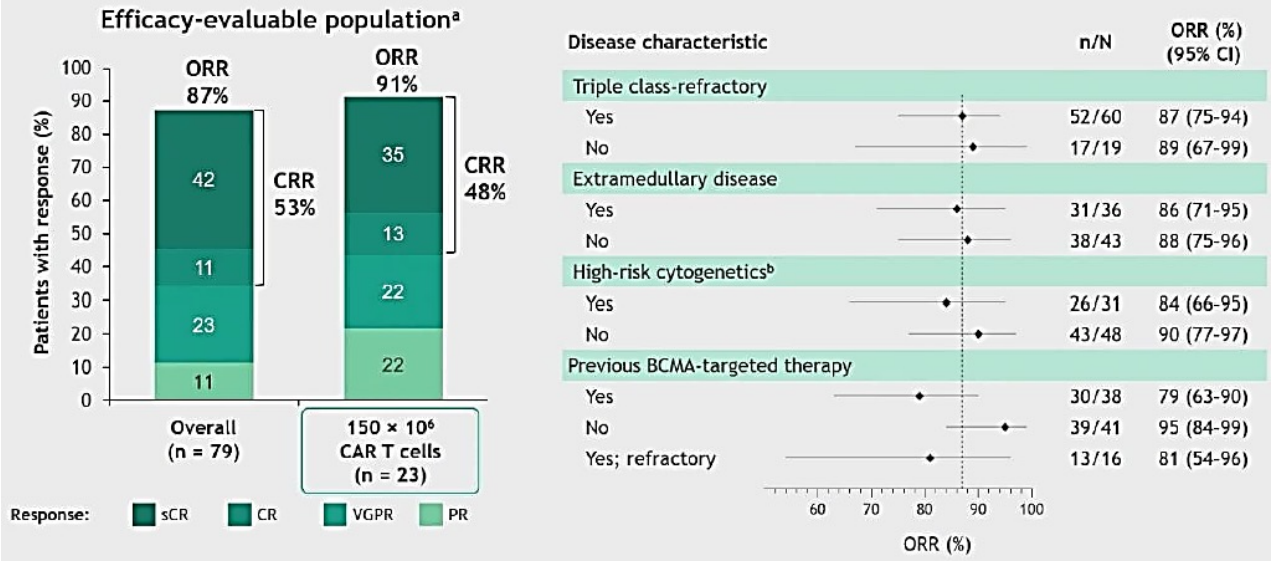
STUDY ENDPOINTS

- Primary Endpoint: PFS
- Key Secondary Endpoints: CR rate, MRD, OS, safety

[a] Optional Bridging therapy will be the SOC regimen selected prior to randomization
[b] Cycles will continue until unacceptable toxicity, progression as per IMWG criteria, or patient withdrawal of consent

ARLO-CEL (anti GPRC5D-CAR-T) in heavily pre-treated RRMM: phase 1 study extended follow-up[1]

- 84 patients with median age of 63 years
- Median number of prior lines: **5**
- **TCR: 80%; PCR: 40%; prior BCMA TT 45%, prior BCMA-TT refractory: 16%**
- **Median follow-up: 15 months**



Median PFS	mo (95% CI)
All evaluable patients (n = 79)	18.3 (11.8 -21.9)
Prior anti-BCMA therapy (n = 38)	19.0 (8.9-NA)
No prior anti-BCMA therapy (n = 41)	18.3 (11.8-23.9)

OS	All Patients (n = 84)
Median OS, mo	NR
12-mo OS rate, % (95% CI)	90 (81-95)
18-mo OS rate, % (95% CI)	87 (76-93)
21-mo OS rate, % (95% CI)	84 (72-91)

Among efficacy-evaluable responders, soluble BCMA profiles indicate deep and sustained tumor clearance independent of previous anti-BCMA therapy

- Patients treated with arlo-cel had a high rate of MRD-negative CR/sCR
- MRD-evaluable patients: 48/84 (57%)
  - Achieved MRD-negative CR/sCR: 22/48 (46%)
- Among MRD-evaluable patients with a ≥CR, 22/26 (85%) achieve MRD-negative status

- Hematologic TEAEs were the most frequent; low occurrence of grade 3/4 infections (19%)
- **CRS in 82% and ICANS in 10%, mostly G1-2; other neurotoxicity in 12% (7% G3-4)**
- **Skin abnormalities in 30%, nails events in 19% and oral toxicities in 32%.** Most resolved

Bal S, et al. ASH 2024 (Abstract No. 922 – oral presentation).

ARLO-CEL (anti GPRC5D-CAR-T) in 1-3 prior LOT RRMM: phase 1 study, safety and efficacy results[1]

- **31 patients** with median age of 62 years and after a median of **2 PL (1-3).**
- 100% of patients exposed to PI and iMiD's and 71% triple exposed, 55% of patients are TCR
- Median follow-up: 8.8 months

Table 2. Adverse events

	All treated patients (N = 31)	
n (%)	Any grade	Grade 3/4
Patients with ≥ 1 TEAE	31 (100)	26 (84)
Select AEs		
CRS	26 (84)	0
On-target/off-tumor event[a]		
Oral	12 (39)	0
Nail	11 (35)	0
Skin	8 (26)	0
Infections and infestations[b]	15 (48)	0
ICANS	3 (10)	0
Other select neurotoxicity[c]	1 (3)	0
Most common hematologic TEAEs[d]		
Neutropenia	25 (81)	24 (77)
Thrombocytopenia	21 (68)	9 (29)
Anemia	14 (45)	8 (26)
Most common non-hematologic TEAEs[d,e]		
Hypocalcemia	13 (42)	0
Hyperglycemia	11 (35)	1 (3)
Constipation	10 (32)	0
Dysgeusia	10 (32)	N/A
Hypophosphatemia	9 (29)	1 (3)
Nail disorder	9 (29)	0
Fatigue	8 (26)	0
Nausea	8 (26)	0
Dry mouth	7 (23)	0
Diarrhea	7 (23)	0

- **Infections** occurred in **48%** of patients but all of them G1-2
- One patient **(3%)** experienced **other select neurotoxicity** (**ataxia G2**) that developed 142 days after GPRC5D-CAR-T, was treated with IV IGs and MP, and was ongoing at the data cutoff
- **Skin, nail, and/or oral on-target off tumour** events were reported in 17 patients **(55%):** all of them were **G1-2**:
  - —Oral events: 39% and most of them resolved in 2 months
  - —Nail events: 35% and most resolved in 3 months
  - —Skin events: 26% and resolved in 1 month

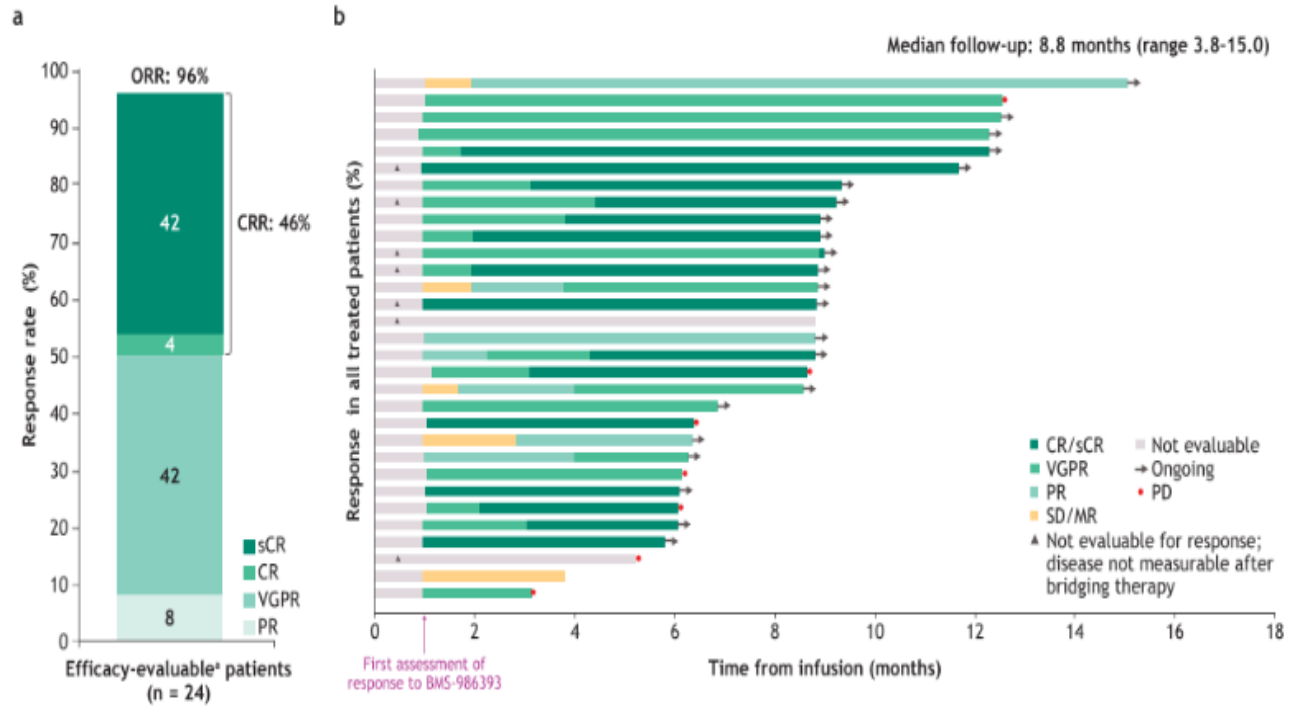
  Weight loss in just 1 patient

AE, adverse event; G, grade; ICANS, immune effector cell-associated neurotoxicity syndrome; IG, immunoglobulin; iMiD, immunomodulatory drug; IV, intravenous; mAB, monoclonal antibody; MP, methylprednisolone; PI, proteasome inhibitor; PL, prior lines; RRMM, relapsed or refractory multiple myeloma; TEAE, treatment-emergent adverse event.

Bal S, et al. ASH 2024 (Abstract No. 2069)

ARLO-CEL (anti GPRC5D-CAR-T) in 1-3 prior LOT RRMM: phase 1 study, safety and efficacy results[1]

Figure 3. a) Response rates, b) responses over time



Data cutoff: August 23, 2024. Responses were assessed per IMWG criteria. Responses to BMS-986393 were recorded following the first post-infusion assessment on approximately day 29. [a]The efficacy-evaluable set includes all patients who received conforming BMS-986393 cell product, had measurable disease at the most recent disease assessment prior to BMS-986393 infusion, had ≥ 1 post-infusion disease response assessment, and was irrespective to any possible response to bridging therapy. Seven patients (indicated with the triangle symbol in Fig 3b) were not included in the efficacy-evaluable set because their disease was no longer measurable after bridging therapy; at data cutoff, 5 of these 7 had ongoing responses, no additional data was available for 1 patient, and 1 patient had progressive disease. CR, complete response; CRR, complete response rate; IMWG, International Myeloma Working Group; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

- ORRs were 93%-100% in patients with **EMD**(6/6), **TCR disease** (13/14), or disease with **HR cytogenetics**(7/7)
- At the data cutoff date, 74% of responses were ongoing (17/23 in the efficacy-evaluable population) and no patients had died

- Several additional trials investigating BMS-986393 in RRMM are planned or active:
  - A phase 1 study examining BMS-986393 in combination with other treatments (NCT06121843)[6]
  - QUINTESSENTIAL: a phase 2 study of BMS-986393 monotherapy for patients with quadruple drug class-exposed disease (NCT06297226)[7]
  - QUINTESSENTIAL-2: a randomized phase 3 study comparing BMS-986393 with standard regimens in patients with lenalidomide-refractory RRMM and 1-3 prior lines of therapy (NCT06615479)[8]

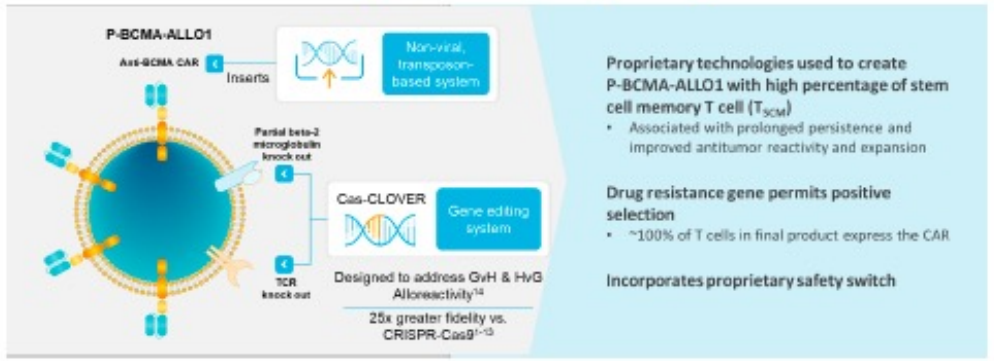
QUINTESSENTIAL QUINTESSENTIAL-2

MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; (s)CR, (stringent) complete response; SD, stable disease; VGPR, very good partial disease.

Bal S, et al. ASH 2024 (Abstract No. 2069)

A phase 1 study of P-BCMA-ALLO1, a non-viral allogeneic BCMA-directed CAR-T for RRMM: results from the optimised lymphodepletion cohort: safety[1]

P-BCMA-ALLO1 is an investigational non-viral, stem cell memory T cell-rich, allogeneic CAR-T



- **21 patients** have received 2 x10^6 P-BCMA Allo 1 with Cy750 and Flu30 as LD
- Median age: 61; median prior LOT: **6** (2-14)
- 62% previously exposed to BCMA/GPRC5D-targeted therapy
- 62% had HRCA and 38% EMD

CAR-T associated adverse events

No grade 3 or higher CRS or ICANS, no GvHD, no HLH/MAS, no parkinsonism, no cranial neuropathies observed

CAR-T Associated Adverse Events	Arm C (N=23)	
	Grade 1/2	Grade ≥3
CRS, n (%)	9 (39)	0
Median time to onset, days (range)	7 (4-8)	-
Median time to resolution, days (range)	9 (5-12)	-
Neurotoxicity (ICANS), n (%)	3 (13)	0
Median time to onset, days (range)	4 (3-6)	-
Median time to resolution, days (range)	5 (3-10)	-
Infections, n (%)	7 (30)	4 (17)
Median time to onset, days (range)	11 (4-36)	27 (6-74)

P-BCMA-ALLO1 has a well-tolerated safety profile (N=23)

TEAEs in ≥20% of all patients treated in Arm C

Adverse Event	Any Grade	Grade ≥3	Related* Grade ≥3
	n (%)	n (%)	n (%)
Patients with TEAEs	23 (100)	22 (96)	17 (74)
Leukopenia	**19 (83)**	**19 (83)**	**12 (52)**
Neutropenia	**18 (78)**	**18 (78)**	**13 (57)**
Anemia	**14 (61)**	**12 (52)**	**9 (39)**
Thrombocytopenia	**14 (61)**	**11 (48)**	**8 (35)**
CRS	**9 (31)**	-	-
Hypocalcemia	8 (35)	1 (4)	-
Febrile neutropenia	6 (26)	6 (26)	3 (13)
Hypotension	6 (26)	-	-
Fatigue	5 (22)	1 (4)	1 (4)
Hypokalemia	5 (22)	-	-
Stomatitis	5 (22)	-	-

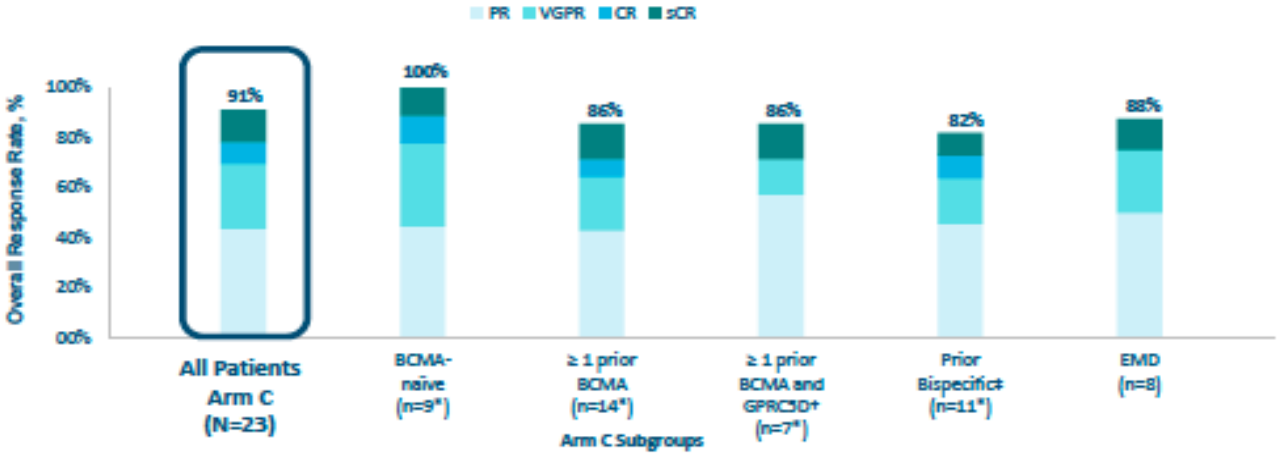
* Related is defined as treatment-emergent (from the start of P-BCMA-ALLO1) adverse events for which the investigator assessed there was a reasonable possibility that P-BCMA-ALLO1 caused the adverse event.
Patient totals includes 2 subjects that have been retreated.

CRS, cytokine release syndrome; EMD, extramedually disease; GvHD, graft-versus-host disease; HLH, hemophagocytic lymphohistiocytosis; HRCA, high-risk cytogenetic abnormalities; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, lymphodepletion; MAS, macrophage activation syndrome; PL, prior lines; RRMM, relapsed or refractory multiple myeloma; TEAE, treatment-emergent adverse event.

1. Dholaria, et al. ASH 2024 (Abstract No. 4828)

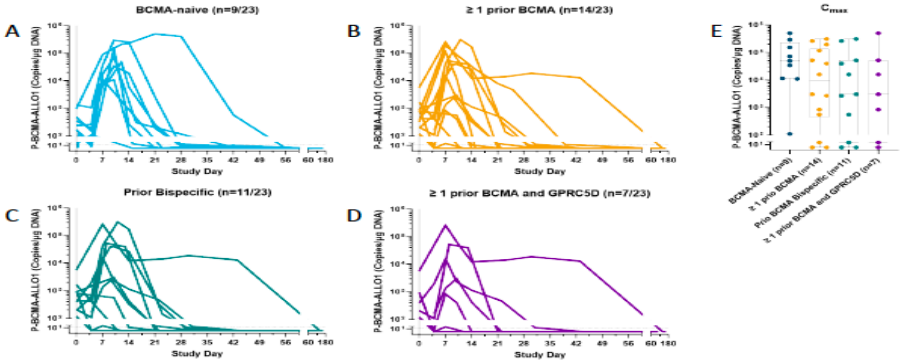
A phase 1 study of P-BCMA-ALLO1, a non-viral allogeneic BCMA-directed CAR-T for RRMM: results from the optimised lymphodepletion cohort: efficacy[1]

P-BCMA-ALLO1 was highly clinically active in BCMA-naïve, BCMA-exposed, and patients with EMD



ORR = sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Evaluable patients: Obtained first response assessment by IMWG M-protein criteria or PD/death and completed Week 4 visit. Arm C LD = Cy 750 mg/m², Flu 30mg/m². All dosed Cohort 2 = range 2.0 to <6.0 × 10^6 cells/kg.
Note: 2 retreated patients included in Arm C.
* Includes 1 retreated patient.
† Talquetamab, a GPRC5D bispecific T-cell engager.
‡ Patients may have received another BCMA-targeted agent in addition to bispecific.

Expansion and persistence of P-BCMA-ALLO1 by exposure to prior BCMA therapy



Cellular kinetics of Arm C patients (n=23) by prior BCMA therapy. A. 9/23 patients were BCMA-naïve. B. 14/23 patients with prior BCMA exposure. C. 11 of the 14 prior BCMA-exposed patients received a BCMA bispecific. D. 7 of the 14 prior BCMA-exposed patients in Arm C were exposed to a GPRC5D bispecific T cell engager. E. P-BCMA-ALLO1 C_{max} by prior BCMA therapy. 1 of 2 retreated patients was BCMA-naive and is included in graph (A). The other retreated patient was BCMA- and GPCR5D-exposed, and is included in graphs B-D.

CAR-T signal persisted up to Week 8 post-CAR infusion in both BCMA-naïve and BCMA-exposed patients

Study (NCT04960579) is ongoing, currently enrolling patients in Phase 1b utilising optimised LD

1. Dholaria, et al. ASH 2024 (Abstract No. 4828)

Conclusion

- **Ide-cel and cilta-cel are SoC in RRMM** in triple-exposed patients, after at least 2/3 prior LOT; **Ide-cel after 3 prior LOT** only currently **AIFA reimbursed**

- **Cilta-cel is also approved in RRMM after at least 1 PL** in patients **refractory to len,** with established PFS and OS benefit and is currently the only “one shot” therapy offering such deep and prolonged responses (MRD, PFS), superior to current SOC, including newer ones

- According to availability and patient’ status, consensus suggests to use **CART before bispecifics**, in particular if targeting the same antigen

- **On-going trials** with **up-front use of cilta-cel**, both in TE and NTE patients, and with **other novel BCMA- and GPRC5D-targeting CAR-T cells in RRMM after 1 prior LOT** are showign **very promising results**