RUOLO E TIMING DEI CAR-T NEL MIELOMA

F. Patriarca-Università di Udine

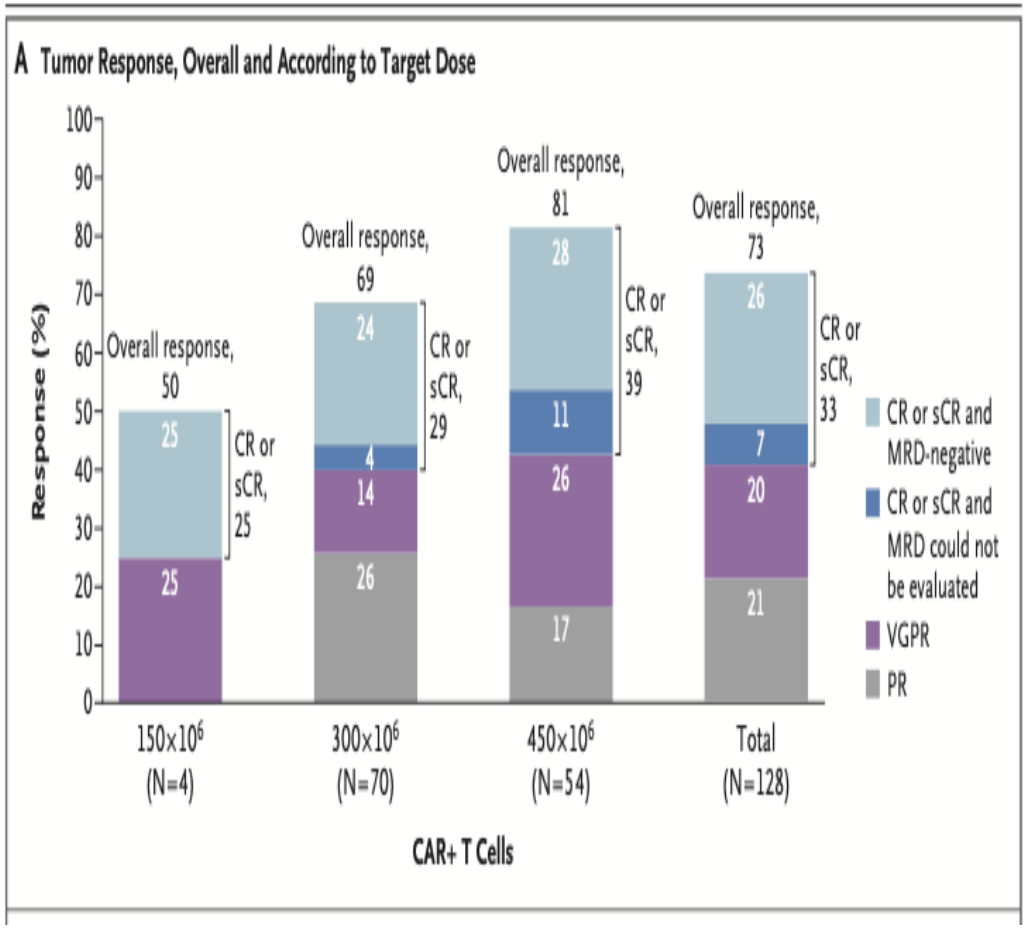
	Ide-cabtagene vicleucel (ide-cel)	Ciltacabtagene autocel (cilta-cel)
Construct	**Anti-BCMA-41BB-CD3z**	**Anti-BCMA2-41BB-CD3z**
EMA approval	• **Adults with RR MM after at least 3 prior therapies, including an IMID, a PI and a antiCD38-monoclonal antibody (20/8/21)**	• **Adults with RR MM after at least 3 prior therapies, including an IMID, a PI and a antiCD38-monoclonal antibody (26/5/22)** • **Adult patients with RR MM who have received at least 1 prior line of therapy, including a PI and an IMiD, and who are refractory to lenalidomide (5/4/2024)**
AIFA approval Status	• **Reimbursed since May 2024**	• **Pending reimbursement in RR MM after 1 line**

Outline

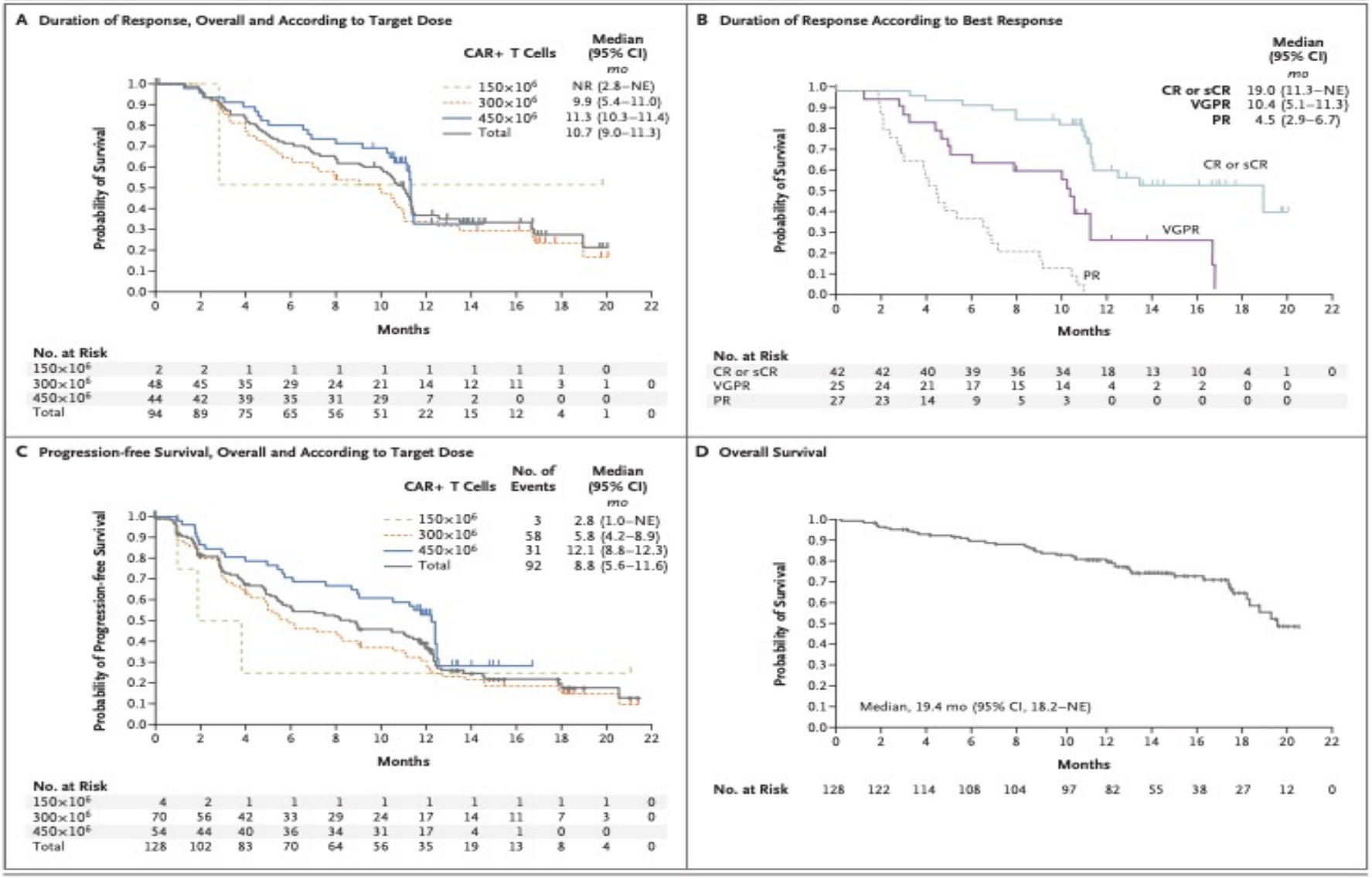
- Ide-cel : phase I-II study in triple-exposed patients
- Ide-cel: real-word and real-life in Udine
- Cilta-cel: phase II study in triple- exposed patients
- Cilta-cel: phase III study in second line

KarMMa phase 1-2 study

	Ide-cel bb2121
Author	Munshi et al, NEJM 2021
Study phase	II
N° pts	128
High risk cytogenetics	35%
N° previous lines	6 (3-16)
Triple class refractory	84%
Penta drug refractory	26%
Median follow-up (months)	13



Munshi et al, NEJM 2021



Munshi et al, NEJM 2021

ADVERSE EFFECTS in KarMMa phase 1-2 study

	Ide-cel
Study name	KarMMa
N° pts	128
CRS All grades ≥ Grade 3 Grade 5 **Median onset (range)**	 107 (84%) 7 (6%) 1 (> 1%) **1 (1-12)**
Neurotoxicities all grades **Grade 3-4** Grade 5	ICANS 23 (18%) **4(3%)** 4 (3%)
Hematological tx Neutropenia all grades Neutropenia grade 3-4 Thrombocytopenia all grades Thrombocytopenia grade 3-4	 117 (91%) 114 (89%) 81 (63%) 67 (52%)
Infections all grades % Infections grade 3-4 %	69% 22%

The 5-year follow-up analysis from KarMMa

Figure 2. Progression-free survival

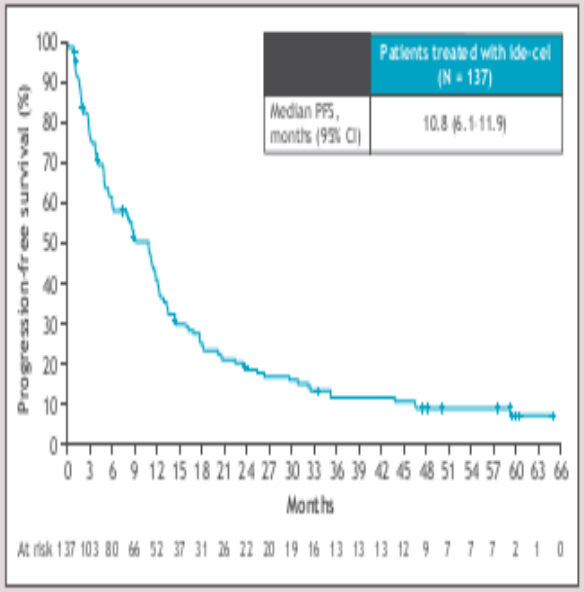
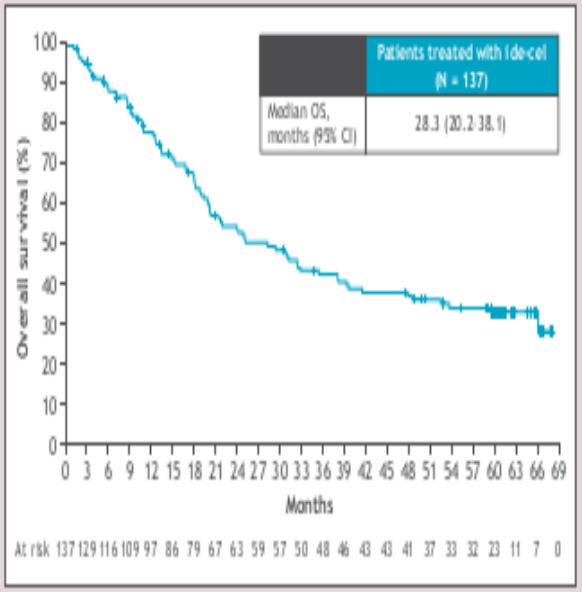


Figure 3. Overall survival



- At data cutoff (December 20, 2023), median PFS was 10.8 months (95% CI, 6.1-11.9), consistent with previous reports (Figure 2)
- Nine (6.6%) patients were still in remission at this data cutoff (DOR, 48.8-64.9 months) despite being heavily pretreated and having high-risk features
- Median OS improved from 24.8 months (95% CI, 19.9-31.2) since the last data cutoff (median follow-up, 24.8 months) to 28.3 months (95% CI, 20.2-38.1) in this close-out (Figure 3)

Rate of grade III-IV hematological toxicity and infections similar at median follow-up of 13 and 60 months

Incidence of SPM 3,7 x 100 patients/year with 3 hematological tumors, none T-cell related

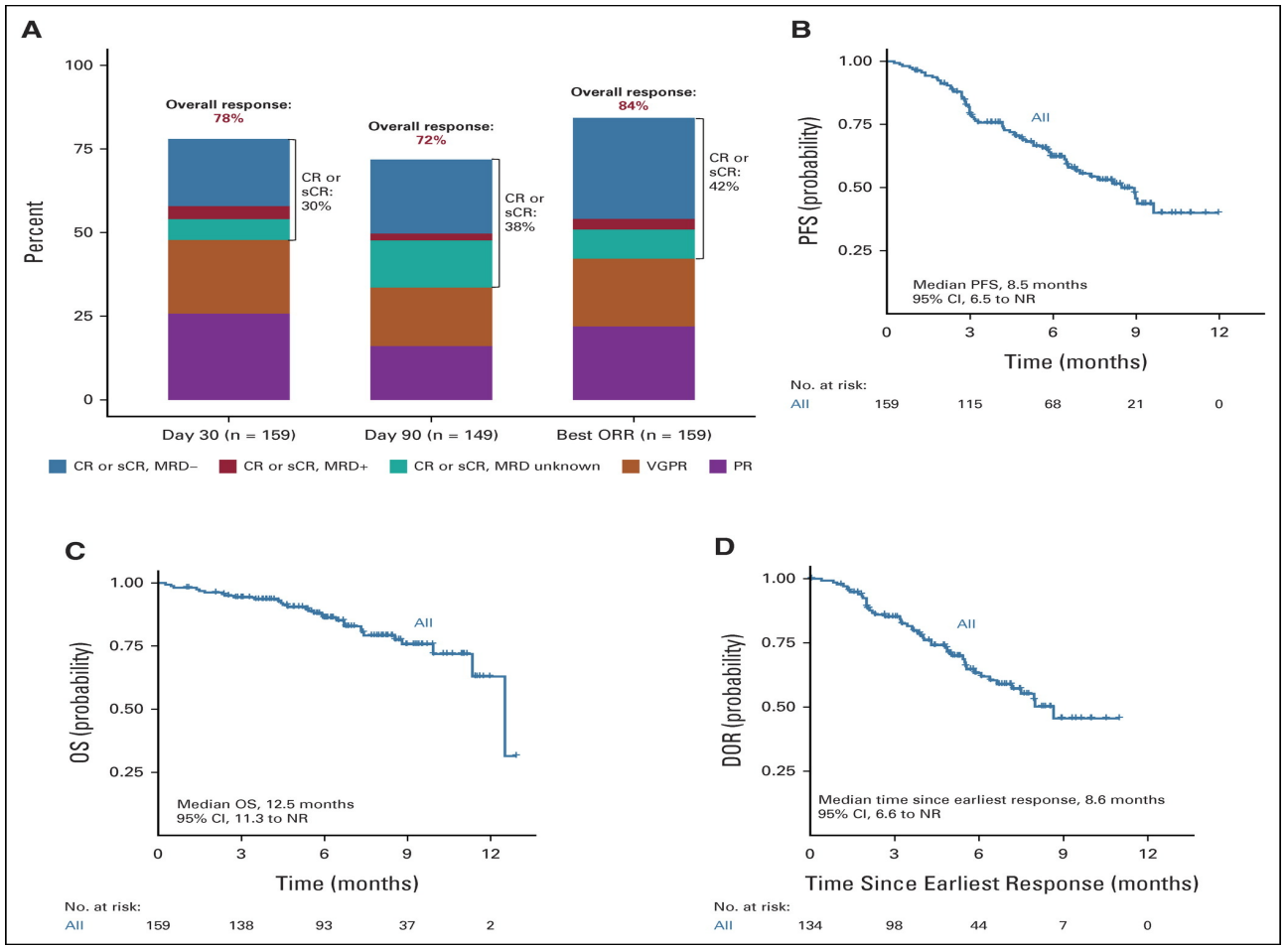
Munshi et al, 2023

USA real-word experience with ide-cel

196 pts leukaphered

159 pts (81%) infused

120 pts (75%) ineligible in karMMA study due to comorbidities, organ failures, prior antiBCMA, MM complications

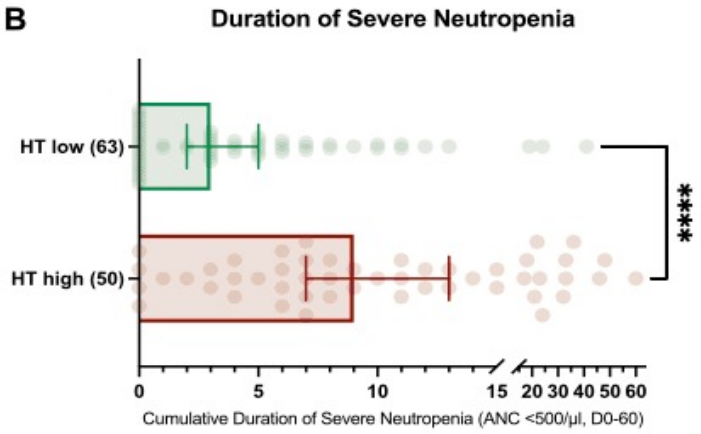


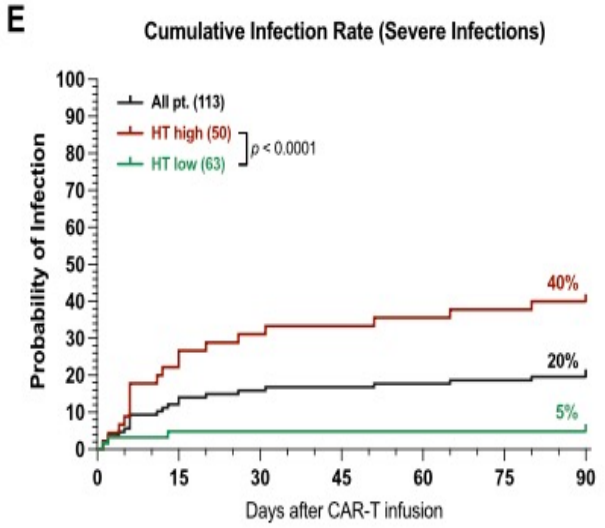
Hansen D et al, JCO 2022

SCORE HEMATOX AND OUTCOME

Retrospective study on 113 r/r multiple myeloma patients treated mainly with ide-cel across six international CAR-T centers.

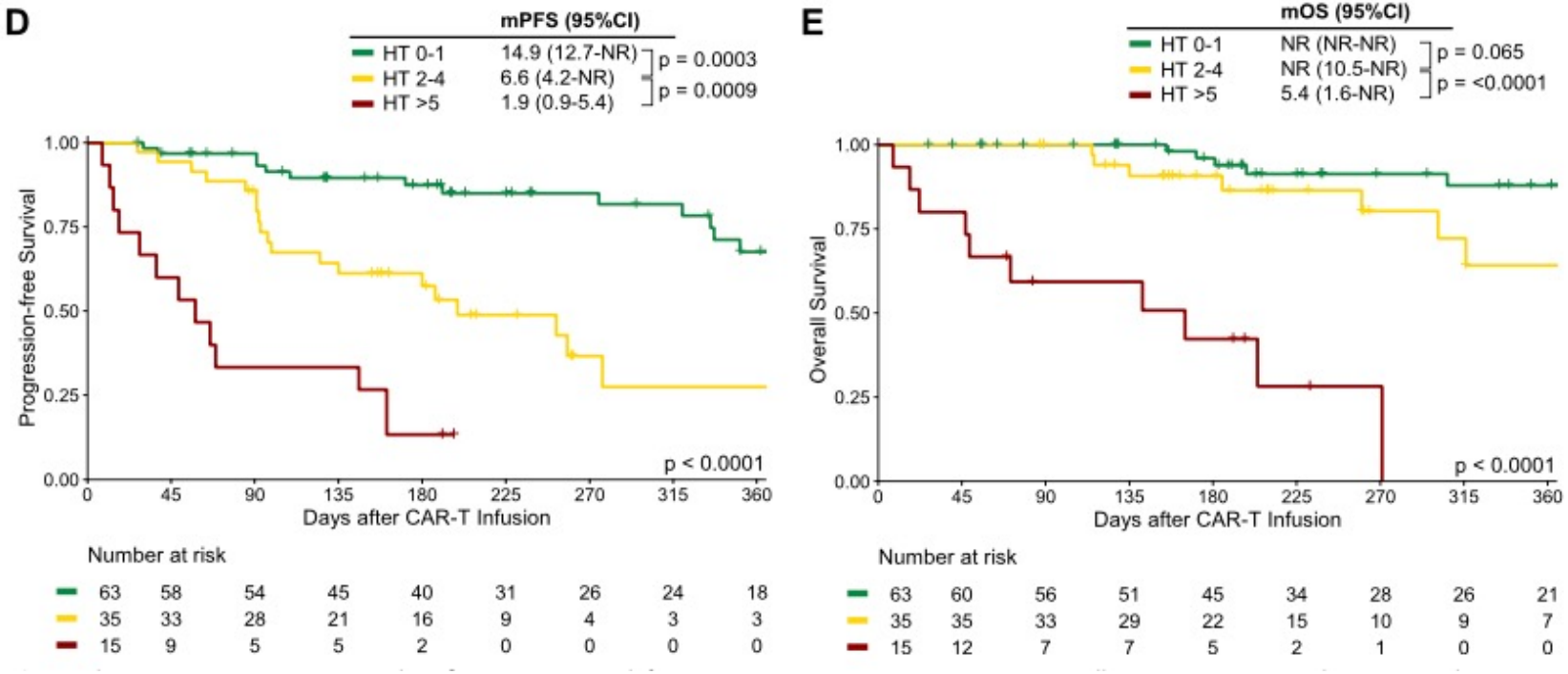
One point was allotted for the following criteria: ANC≤1200/µl, hemoglobin≤9.0 g/dl, platelet count 76–175 G/l, CRP≥3.0 mg/dl, and ferritin 650–2000 ng/ ml. Two points were provided for a platelet count≤75 G/l and ferritin ≥ 2000 ng/ml.
A sum score of 2 or greater was classified as high risk (HThigh), a score of 0–1 as low risk (HTlow).UHThigh >5





Rejeski K et al, J Hematology &Oncology 2023

SCORE HEMATOX AND OUTCOME



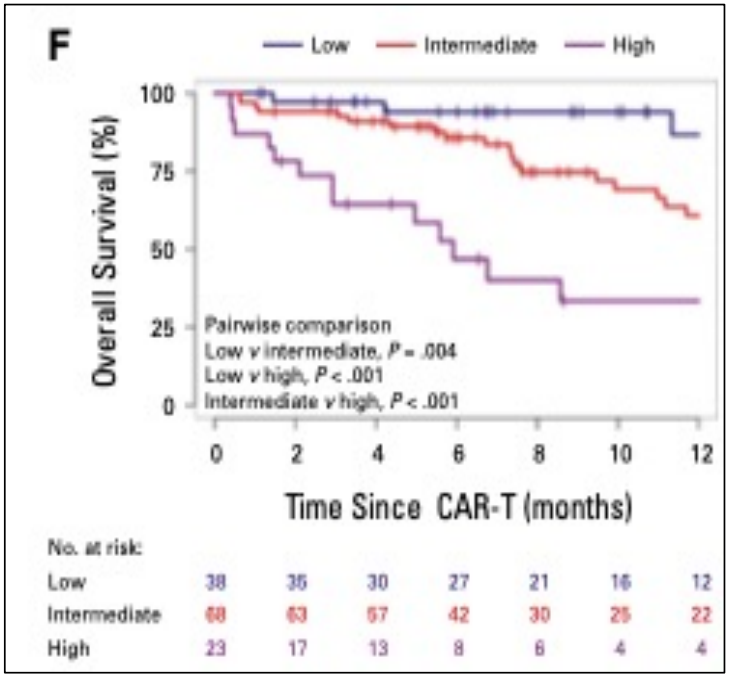
Rejeski K et al, J Hematology &Oncology 2023

Myeloma CAR-T Relapse [MyCARe] model

International retrospective observational study including patients with RRMM infused with currently available commercial or academically produced anti–B-cell maturation antigen (BCMA) CAR-T in Europe (136) and the United States (133).

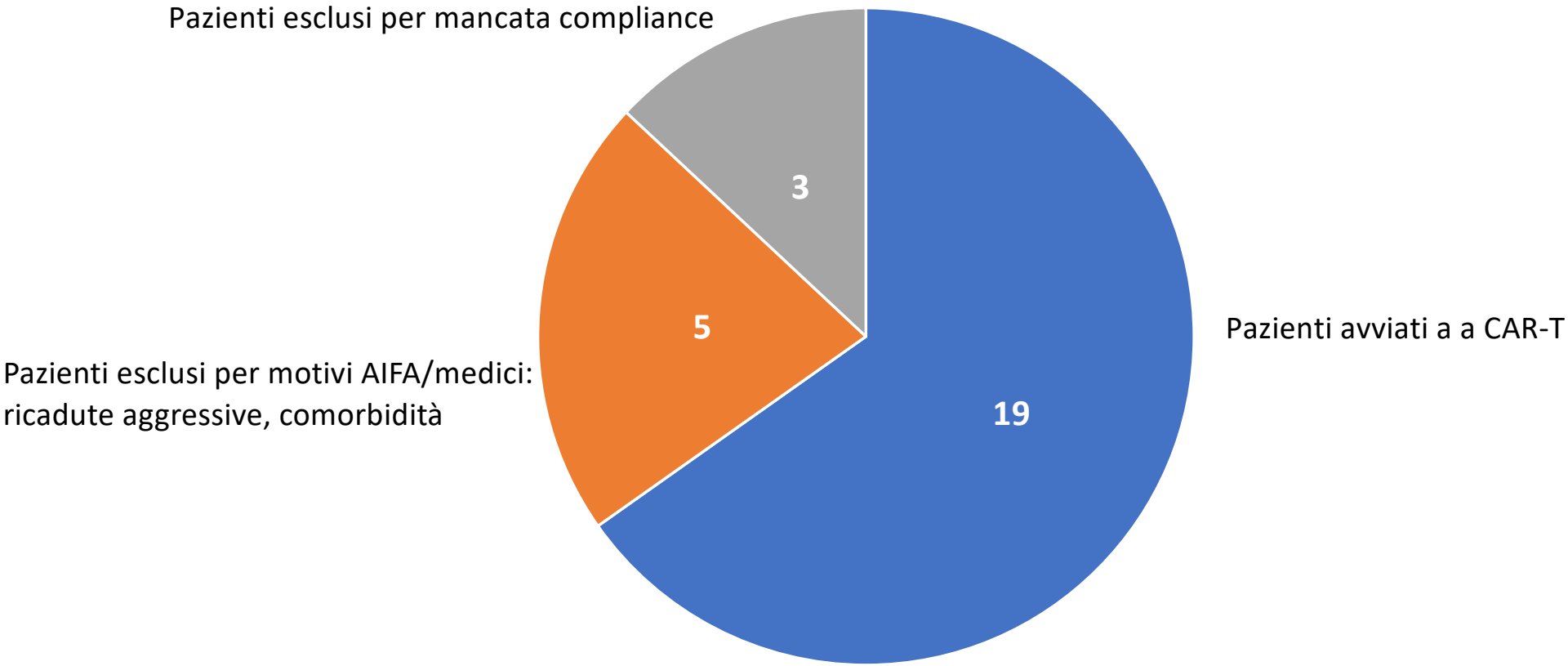
TABLE 2. Multivariable Modeling of Early Relapse/Progression

Factor	HR	95% CI	*P*	Score
EMD or PCL present	1.92	1.30 to 2.82	<.001	1
High-risk cytogenetics	1.95	1.31 to 2.92	.001	1
Ferritin > NL (sex-/age-adjusted)	1.59	1.07 to 2.37	.02	1
Lenalidomide refractoriness	1.69	1.02 to 2.82	.04	1
MyCARe risk				
Low (score 0-1)	Ref			
Intermediate (score 2-3)	3.27	1.87 to 5.72	<.001	
High (score 4)	7.89	4.21 to 14.79	<.001	



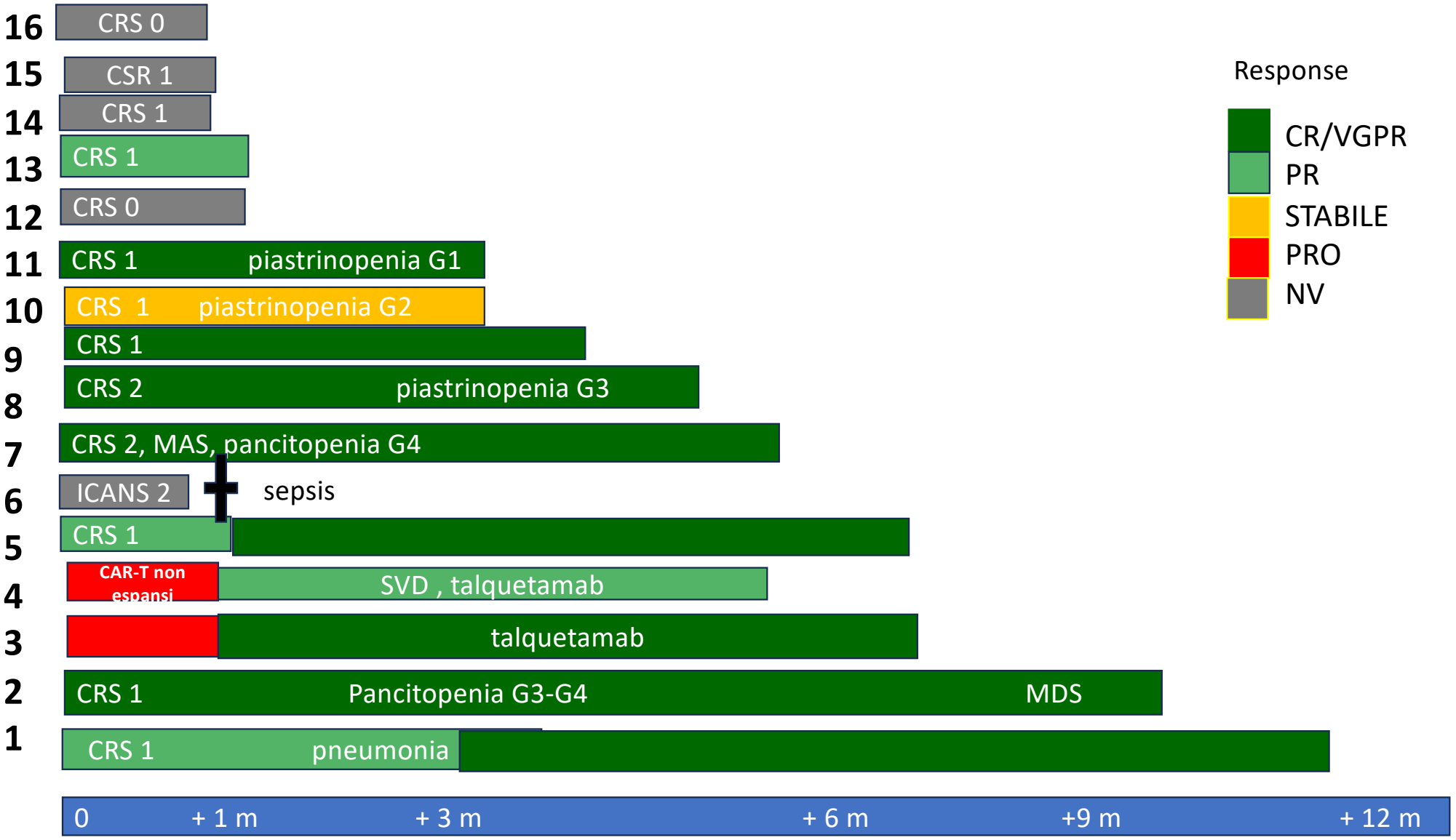
Gagelmann et al, JCO 2024

Esperienza Udine-Triveneto nel trattamento con Ide-cel
settembre 2024-ottobre 2025

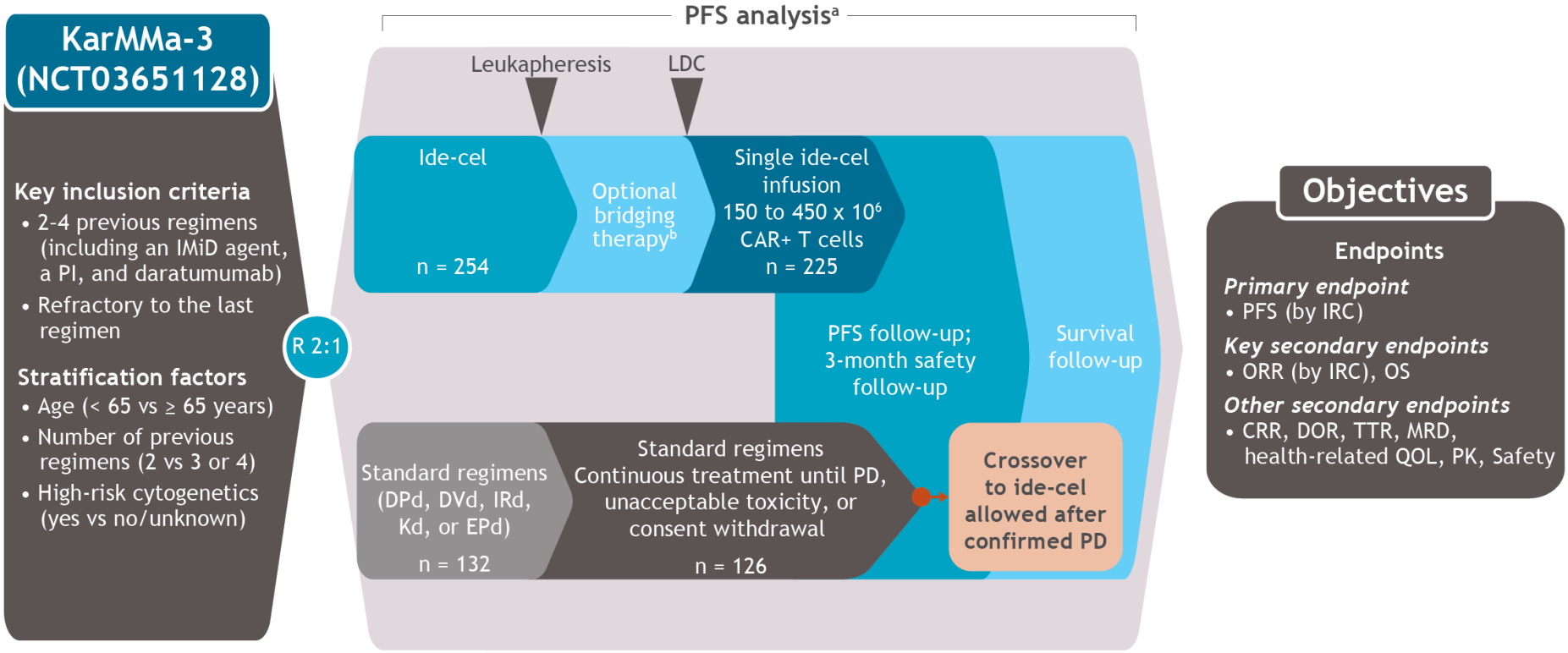


UDINE CAR-T MM

	Sex/birth year	dx	Treating center	N° previous line	Progression type	bridging	response	HEMATO-TOX score MyCARE MM
1	F , 68	2009	Udine	5	Clinical (Pathological fracture)	KD	PRO	0 low
2	M, 68	2013	CRO	4	Clinical (PET)	D-PACE	PR	2 high
3	F 58	2018	Padova	3	Clinical with hypercalcemia	D-PACE	PR	2 high , 3 int
4	M , 57	2019	Treviso	3	biochemical	Se-VD	STABLE	1 low , 3 int
5	5, 67	2021	Udine	3	biochemical	SE-Dexa	STABLE	1 low, 1 low
6	F, 52	2019	Udine	3	clinical	Dexa-CTX	PRO	2 high, 4 high
7	M 64	2019	Padova	3	clinical	Se-VD	STABLE	High, high
8	M 63	2018	Padova	4 (anche talquetamab)	Clinical	DT-PACE	PR	Low, low
9	F 50	2013	Padova	4	Clinical (PET)	Se-Vd	STABLE	Low, low
10	M 65	2015	Padova	5	biochemical	Elo-PD	STABLE	High, low
11	M 66	2017	CRO	4	Clinical (PET)	Se-VD	PRO	High , low
12	M 59	2021	Padova	3	biochemical	Elo-PD	RP	Low, low
13	F 56	2016	Padova	3	biochemical	Se-VD	RP	Low, int
14	M 62	2021	Treviso	3	Clinical (PET)	KD	RP	Low, int
15	F 66	2015	Mestre	3	biochemical	/	Stable	Low,low
16	M 58	2020	Trieste	3	biochemical	VD	stable	Low, low
17	M 65	2020	Padova	5 (anche talquetamab)	Clinical with hypercalcemia	Se-VD	Stable	High, high


16
CRS 0
15
CSR 1
14
CRS 1
13
CRS 1
12
CRS 0
11
CRS 1
piastrinopenia G1
10
CRS 1
piastrinopenia G2
9
CRS 1
8
CRS 2
piastrinopenia G3
7
CRS 2, MAS, pancitopenia G4
6
ICANS 2
sepsis
5
CRS 1
4
CAR-T non espansi
SVD , talquetamab
3
talquetamab
2
CRS 1
Pancitopenia G3-G4
MDS
1
CRS 1
pneumonia
0
+ 1 m
+ 3 m
+ 6 m
+9 m
+ 12 m
Response
CR/VGPR
PR
STABILE
PRO
NV

KarMMa-3 study design



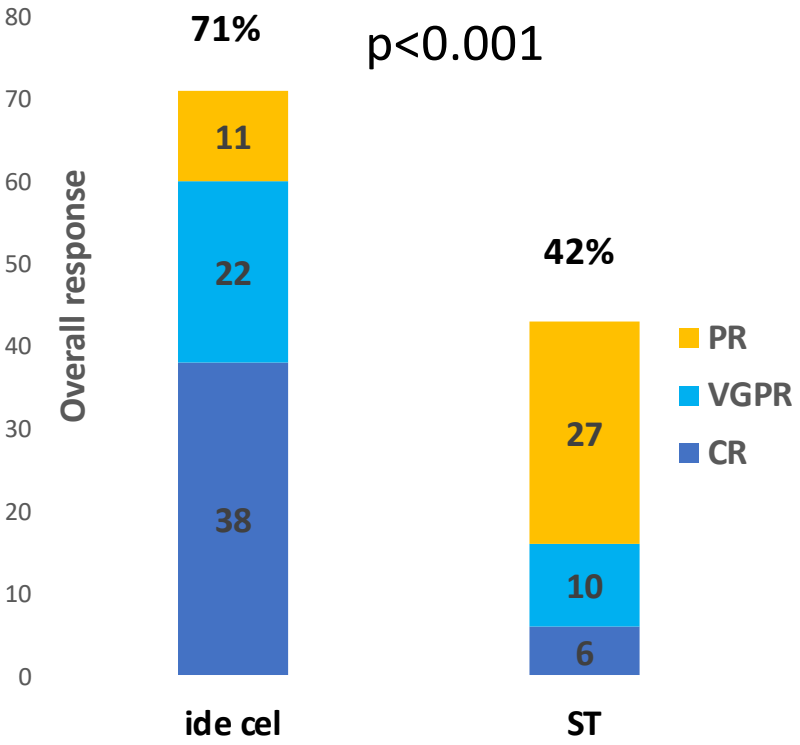
[a]Time from randomization to the first occurrence of disease progression or death from any cause according to IMWG criteria.
[b]Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as bridging therapy with a minimum of 14 days of washout.
CAR, chimeric antigen receptor; CRR, complete response rate; DOR, duration of response; DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EPd, elotuzumab/pomalidomide/dexamethasone; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory agent; IMWG, International Myeloma Working Group; IRC, independent review committee; IRd, ixazomib/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasoneLDC, lymphodepleting chemotherapy; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteosome inhibitor; PK, pharmacokinetics; QOL, quality of life; R, randomization; TTR, time to resolution.

Rodriguez-Oter et al, NEJM 2023

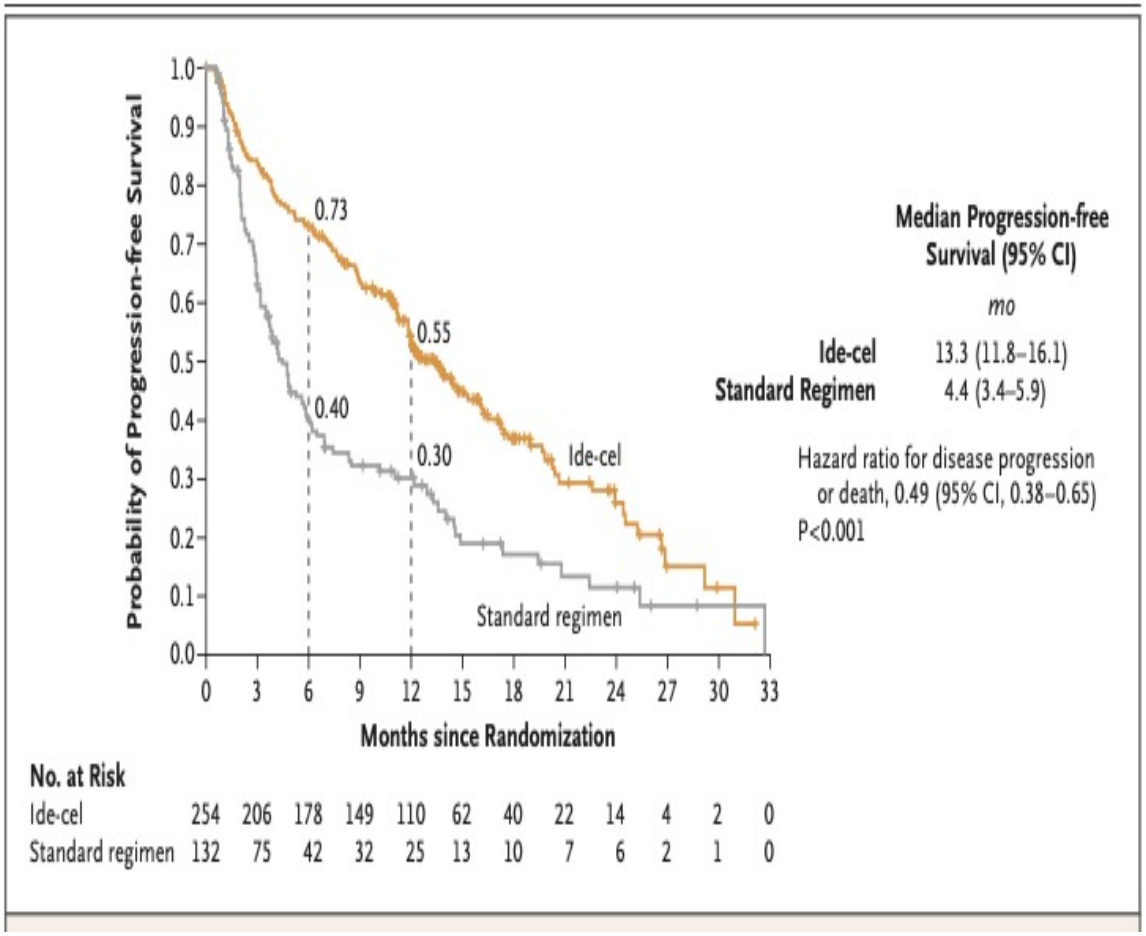
Ide-cel or standard treatments in RR MM after 2-4 prior regimens

	Ide-cel	Standard therapy
N° pts	254	132
High risk cytogenetics	42%	46%
Extramedullary MM	24%	24%
N° previous lines	3(2-4)	3 (2-4)
Triple class refractory	65%	67%
Penta drug refractory	6%	4%

Rodriguez-Oter et al, NEJM 2023

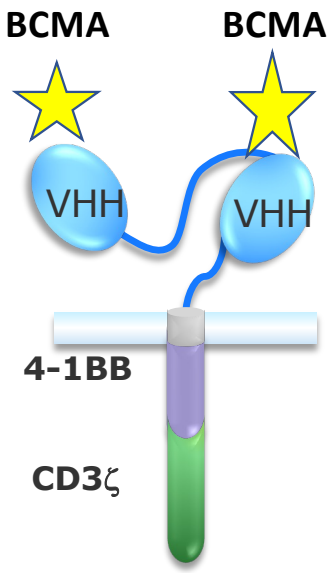


p<0.001



Rodriguez-Oter et al, NEJM 2023

CARTITUDE-1 STUDY



	Cilta-cel
Author	Berdeja Lancet 2021, Martin ASH 2021 Jannagath JCO2025
Study phase	Ib/II
N° pts	97
High risk cytogenetics	24%
N° previous lines	6 (3-18)
Triple class refractory	88%
Penta drug refractory	42%
Median follow-up (months)	33 (1-45), 60

Efficacy in CARTITUDE 1

	Cilta-cel
Author	Berdeja et al, Lancet 2021 Martin et al, JCO 2023 Jannagath et al, JCO 2025
N° pts	97
OR%	98
CR%	82
Median PFS (months)	34.9
Median OS (months)	60.7

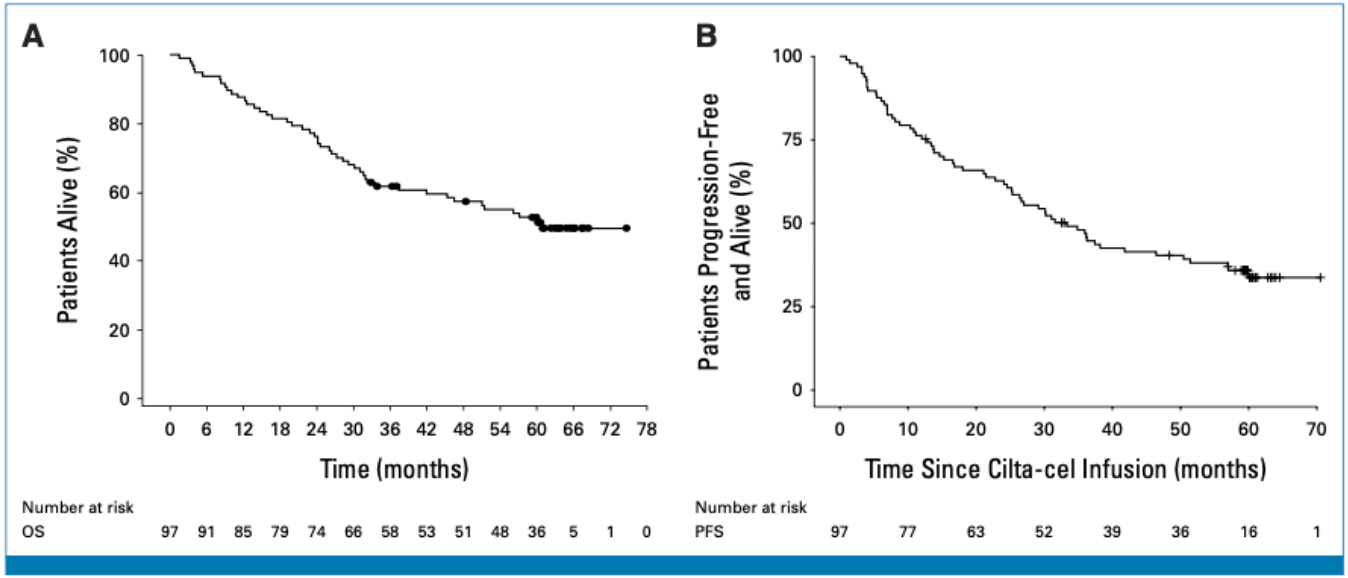


FIG 2. (A) OS. (B) Progression-free survival. Cilta-cel, ciltacabtagene autoleucel; OS, overall survival.

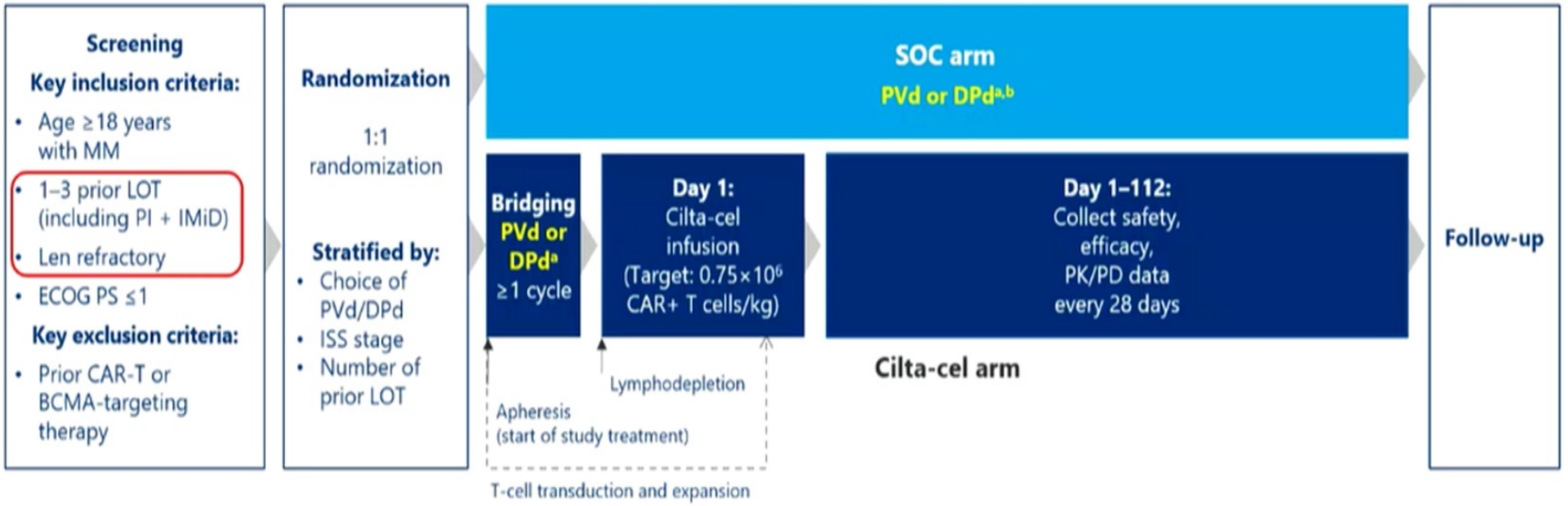
32/97 (33%) were progression-free for ≥5 years.

A trend of lower baseline tumor burden, higher hemoglobin and platelets at baseline , higher fraction of naïve T-cells in the cilta-cel drug product, higher CAR- T-cell peak expansion were associated with ≥5-year progression-free status.

ANTI-BCMA CAR-T ADVERSE EFFECTS

	Cilta-cel
Study name	Cartitude-1
N° pts	97
CRS All grades ≥ Grade 3 Grade 5 **Median onset (range)**	 92 (95%) 5 (4%) 1 (<1%) **7 (5-8)**
Neurotoxicities all grades **Grade 3-4** Grade 5	ICANS%parkinsonism%cranial nerve palsy 21 (21%) **11(12%)** 1 (1%)
Hematological tx Neutropenia all grades Neutropenia grade 3-4 Thrombocytopenia all grades Thrombocytopenia grade 3-4	 93 (96%) 92 (95%) 77 (79%) 58 (60%)
Infections all grades % Infections grade 3-4 %	58% 20%

CARTITUDE-4: Study Design and Endpoints



Primary endpoint

- PFS[c]

Secondary endpoints

- Efficacy: ≥CR, ORR, MRD negativity, OS
- Safety
- PROs

[a]Physicians' choice. [b]Administered until disease progression. [c]Time from randomization to disease progression/death.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; ISS, International Staging System; len, lenalidomide; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone; SOC, standard of care.

Einsele H et al, EHA2023
San Miguel et al, NEJM 2023
Mateos MV, et al. IMS 2024 OA-65
Popat et al, ASH 2024

CARTITUDE-4: Baseline Demographics and Disease Characteristics

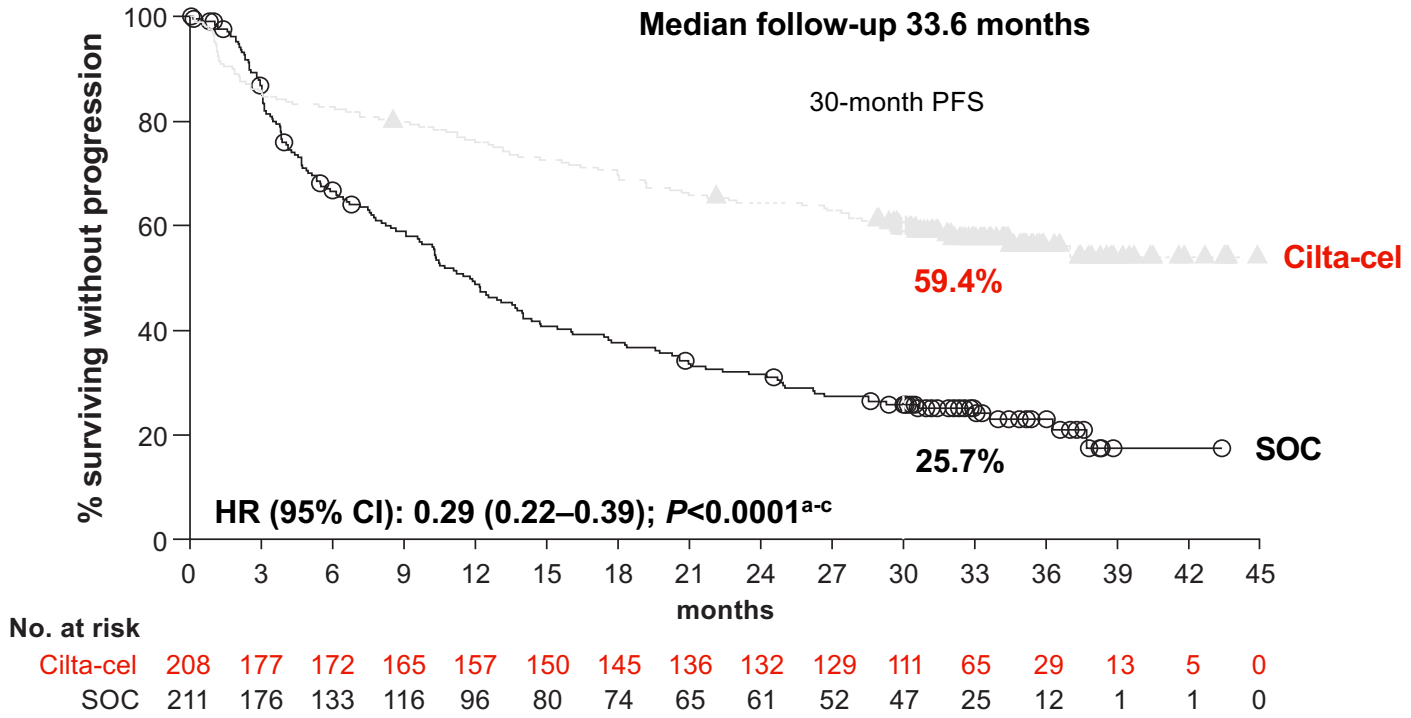
Baseline characteristic	ITT population	
	Cilta-cel (n=208)	SOC (n=211)
Age, median (range), years	61.5 (27–78)	61.0 (35–80)
Male, n (%)	116 (55.8)	124 (58.8)
White, n (%)	157 (75.5)	157 (74.4)
ECOG PS ≤1, n (%)[a,b]	207 (99.5)	210 (99.5)
ISS stage, n (%)		
I	136 (65.4)	132 (62.6)
II	60 (28.8)	65 (30.8)
III	12 (5.8)	14 (6.6)
Bone marrow plasma cells ≥60%,[c] n (%)	42 (20.4)	43 (20.7)
Presence of soft tissue plasmacytomas,[d] n (%)	44 (21.2)	35 (16.6)
Years since diagnosis, median (range)	3 (0.3–18.1)	3.4 (0.4–22.1)
Prior LOT, median (range)	2 (1–3)	2 (1–3)
1 prior LOT, n (%)	68 (32.7)	68 (32.2)
2 or 3 prior LOT, n (%)	140 (67.3)	143 (67.8)

Baseline characteristic	ITT population	
	Cilta-cel (n=208)	SOC (n=211)
Cytogenetic high risk, n (%)[e]	123 (59.4)	132 (62.9)
del(17p)	49 (23.7)	43 (20.5)
t(14;16)	3 (1.4)	7 (3.3)
t(4;14)	30 (14.5)	30 (14.3)
gain/amp(1q)	89 (43.0)	107 (51.0)
2 or more high-risk cytogenetic features	43 (20.8)	49 (23.3)
del(17p), t(14;16), or t(4;14)	73 (35.3)	69 (32.9)
Triple-class[f] exposed, n (%)	53 (25.5)	55 (26.1)
Penta-drug[g] exposed, n (%)	14 (6.7)	10 (4.7)
Refractory status, n (%)		
Triple-class refractory[f,h]	30 (14.4)	33 (15.6)
Bortezomib	55 (26.4)	48 (22.7)
Pomalidomide	8 (3.8)	9 (4.3)
Daratumumab	48 (23.1)	45 (21.3)
Any PI	103 (49.5)	96 (45.5)

[a]1 patient in each arm had ECOG PS of 2. [b]Latest nonmissing ECOG PS score on or prior to apheresis/cycle 1 day 1 is used. [c]In 206 (cilta-cel arm) and 208 (SOC arm) patients, maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available. [d]Including extramedullary and bone-based plasmacytomas with measurable soft tissue component. [e]In 207 (cilta-cel arm) and 210 (SOC arm) patients. [f]Including 1 PI, 1 IMiD, and 1 anti-CD38 monoclonal antibody. [g]Including ≥2 PI, ≥2 IMiDs, and 1 anti-CD38 monoclonal antibody. [h]2 patients (cilta-cel arm) and 1 patient (SOC arm) were penta-drug refractory, including ≥2 PI, ≥2 IMiDs, and 1 anti-CD38 monoclonal antibody. cilta-cel, ciltacabtagene autoleucel; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intent-to-treat; LOT, line of therapy; PI, proteasome inhibitor; SOC, standard of care.

Einsele H et al, EHA2023, San Miguel et al N EJM 2023, Mateos MV et al, IMS2024

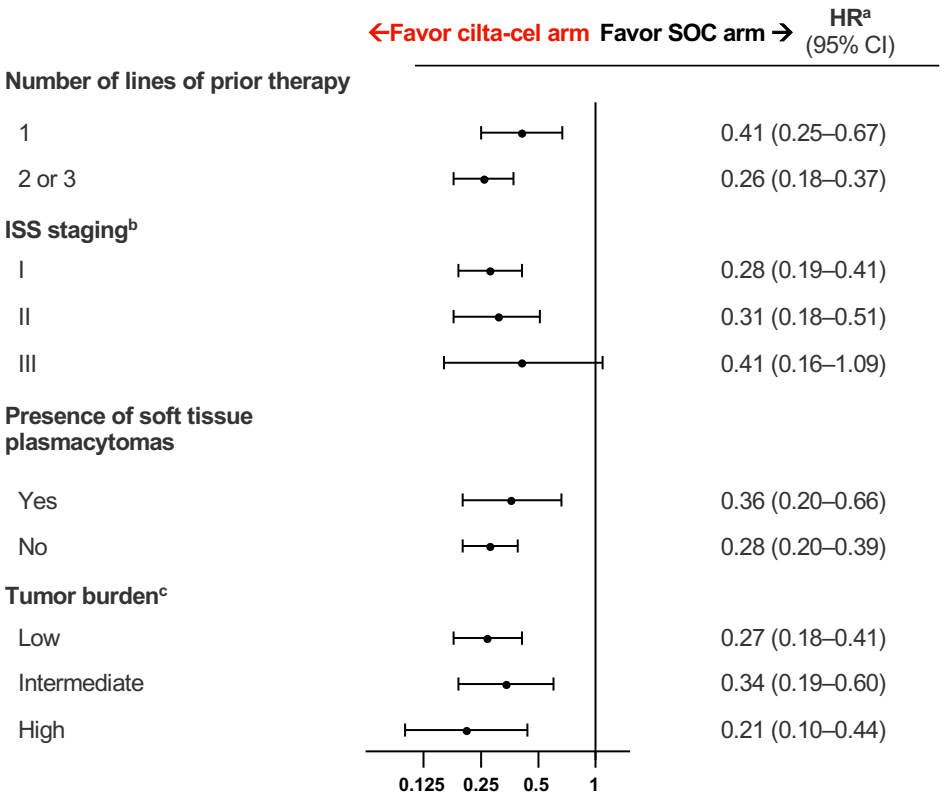
Long-Term CARTITUDE-4 Update (34 Months): Cilta-cel Maintained Significant Improvement in Progression-Free Survival

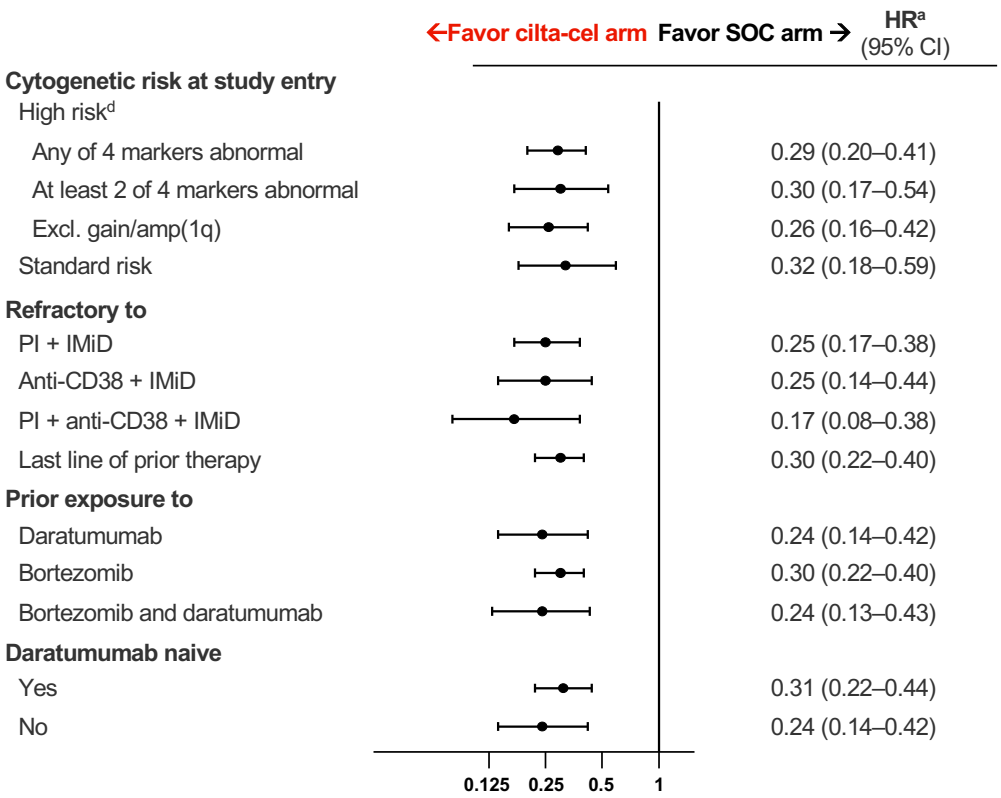


~70% reduction in the risk of progression or death in patients who received cilta-cel and mPFS has not been reached

Mateos MV, et al. IMS 2024 OA-65

Long-Term CARTITUDE-4 Update (34 Months): Consistent Progression-Free Survival Benefit for Cilta-cel Across All Prespecified Subgroups

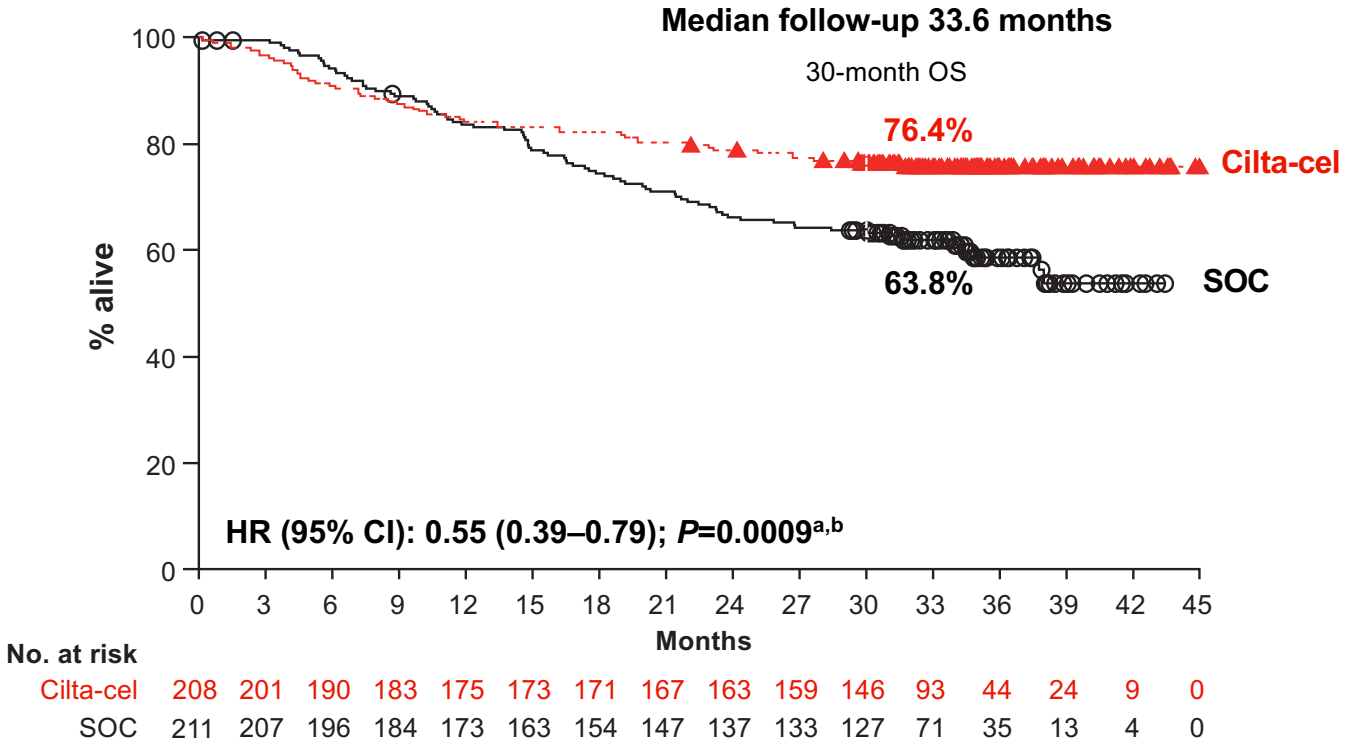




Consistent reduction in the risk of progression or death across all prespecified subgroups

Mateos MV, et al. IMS 2024 OA-65

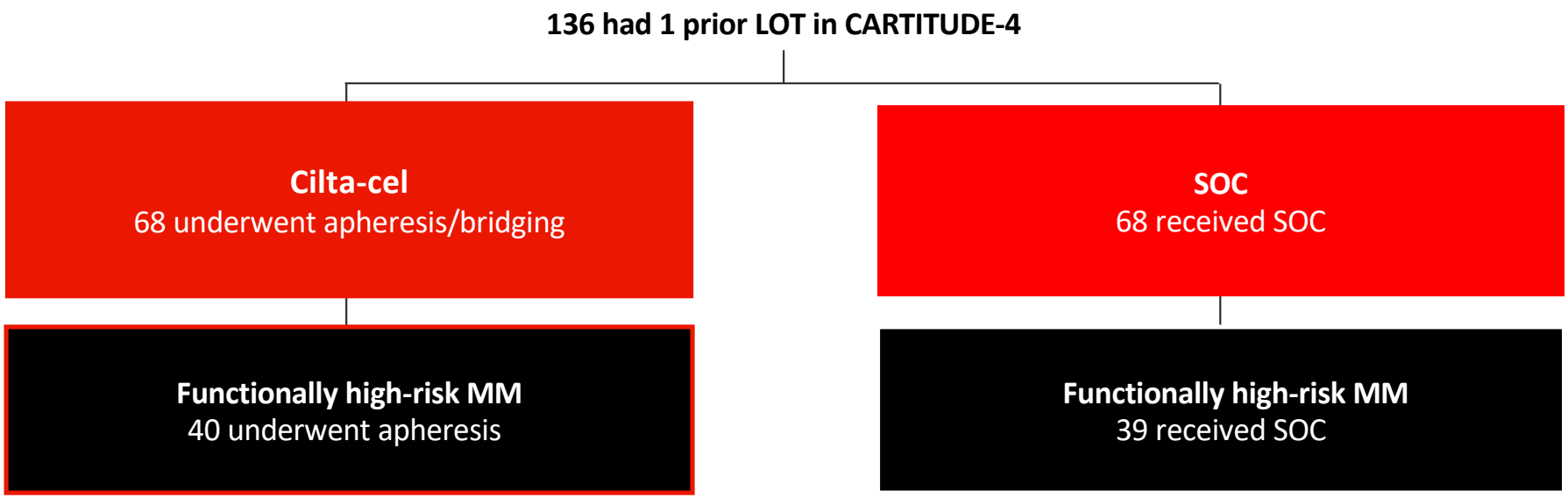
Long-Term CARTITUDE-4 Update (34 Months): Cilta-cel Significantly Improved Overall Survival



First CAR-T to demonstrate overall survival benefit in multiple myeloma

Mateos MV, et al. IMS 2024 OA-65

CARTITUDE-4 Subgroup Analysis: Patient Population



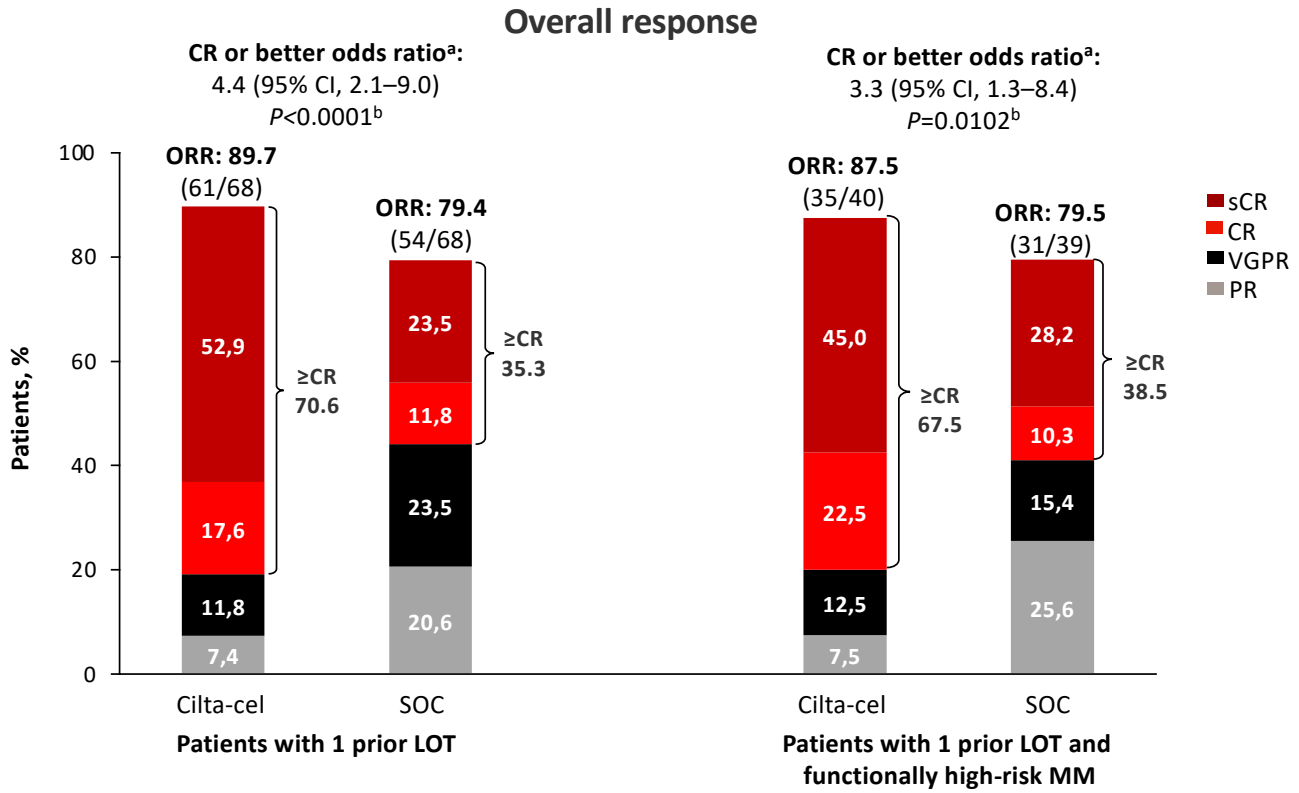
Functionally high-risk MM defined as PD ≤18 months after receiving ASCT or the start of initial frontline therapy in patients with no ASCT

At the November 2022, data cut-off date, median follow-up was 15.9 months (range, 0.1–27.3). Among 68 patients who received 1 prior LOT in the cilta-cel arm, 60 received cilta-cel as study treatment, 5 received cilta-cel as subsequent therapy, and 3 never received cilta-cel. Among 40 patients who received 1 prior LOT and functionally high-risk MM in the cilta-cel arm, 35 received cilta-cel as study treatment. Study treatment includes any portion of the following sequence: apheresis, bridging, lymphodepletion, and cilta-cel.

ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; MM, multiple myeloma; PD, progressive disease; SOC, standard of care.

Weisel, et al. ORAL P959 EHA 2024

CARTITUDE-4 Subgroup Analysis: Consistently Deeper Responses Achieved With Cilta-cel vs SOC in Patients With 1 Prior LOT and Those With 1 Prior LOT and Functionally High-Risk MM



Treatment response was assessed by a validated computerized algorithm, based on International Myeloma Working Group consensus criteria. ORR was defined as the proportion of patients who achieve a PR or better.
[a]Mantel-Haenszel estimate of the common odds ratio for unstratified tables is used. [b]*P* value from the Cochran-Mantel-Haenszel chi-squared test. cilta-cel, ciltacabtagene autoleucel; CR, complete response; LOT, line of therapy; MM, multiple myeloma; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SOC, standard of care; VGPR, very good partial response.

Weisel, et al. ORAL P959 EHA 2024

2025 EHA–EMN Evidence-Based

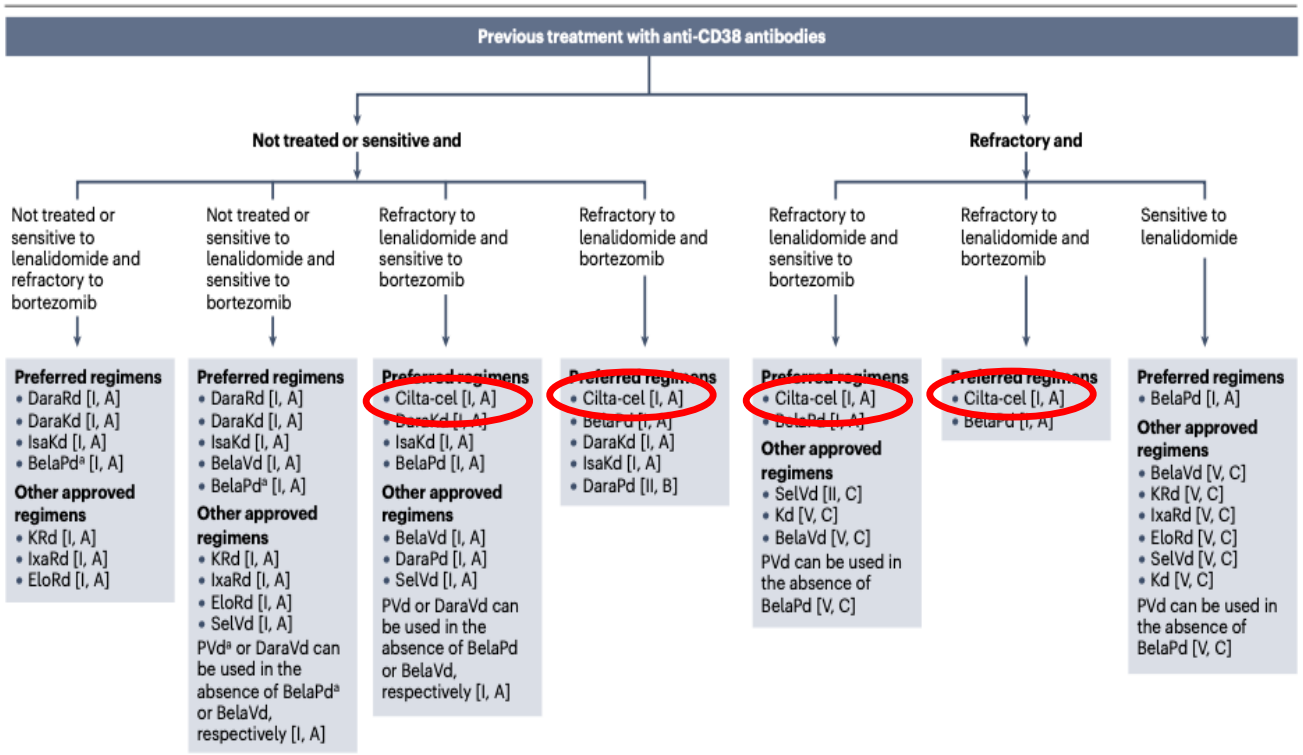


Fig. 2 | Recommendations for the treatment of patients with relapsed and/or refractory multiple myeloma at second line. Recommendations include supporting levels of evidence and have been graded[170] (Supplementary Table 1). [a]Only in patients exposed to lenalidomide. Bela, belantamab mafodotin; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; P, pomalidomide; R, lenalidomide; Sel, selinexor.

Nature Reviews Clinical Oncology 2025

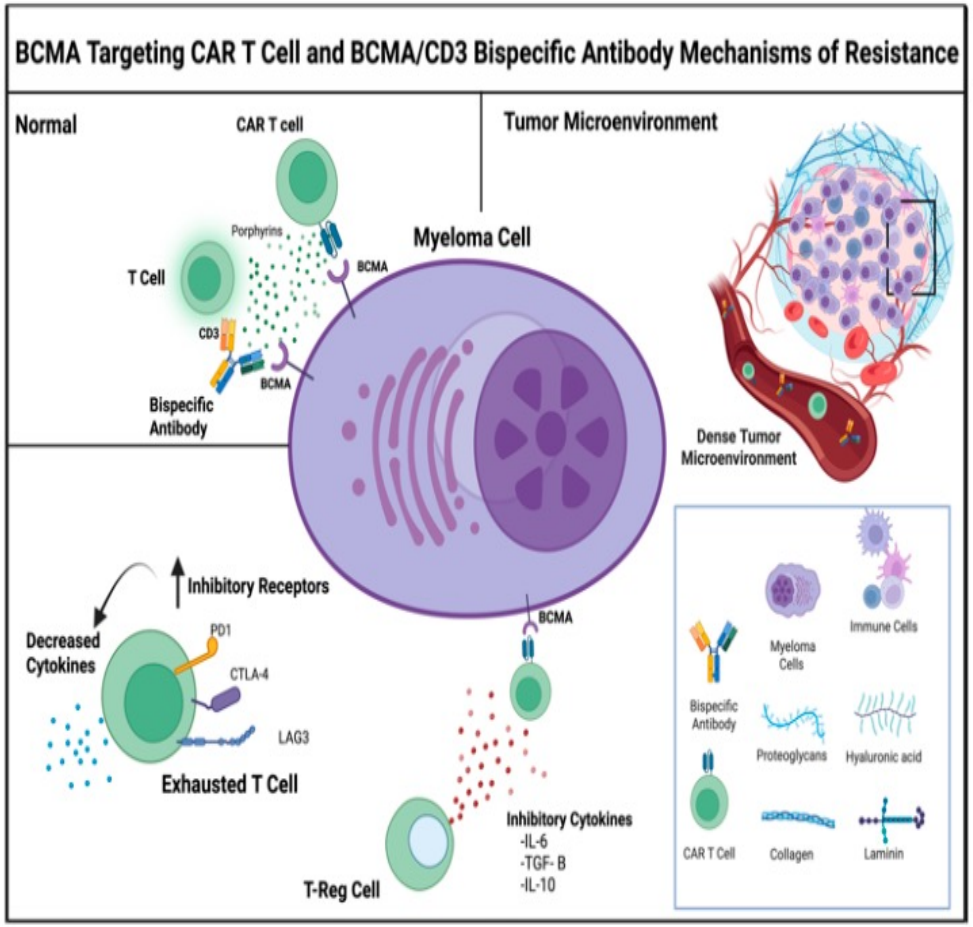


Table 1. Summary of BCMA Targeting Therapy Mechanisms of Resistance.

BCMA Targeting Mechanisms of Resistance Table Summary		
Tumor Intrinsic	**Tumor Extrinsic/Host-Related**	**Tumor Microenvironment**
Loss of BCMA expression through mutations in TNFRSF17 Gene	T Cell Fitness (CAR-T Therapy)	Presence of MDSCs
Downregulation of BCMA	T Cell Exhaustion (BsAb and CAR-T Therapy)	Activation of T-regulator cells
BCMA shedding through Secretase via Secretase Enzyme	Age	Increased Inhibitory Cytokine release such as IL-10, TGF-B
Trogocytosis	Genetic Factors that compromise immune fitness	Physical barriers causing poor therapeutic infiltration
Upregulation of Anti-Apoptotic Proteins and MHC Class I Loss		

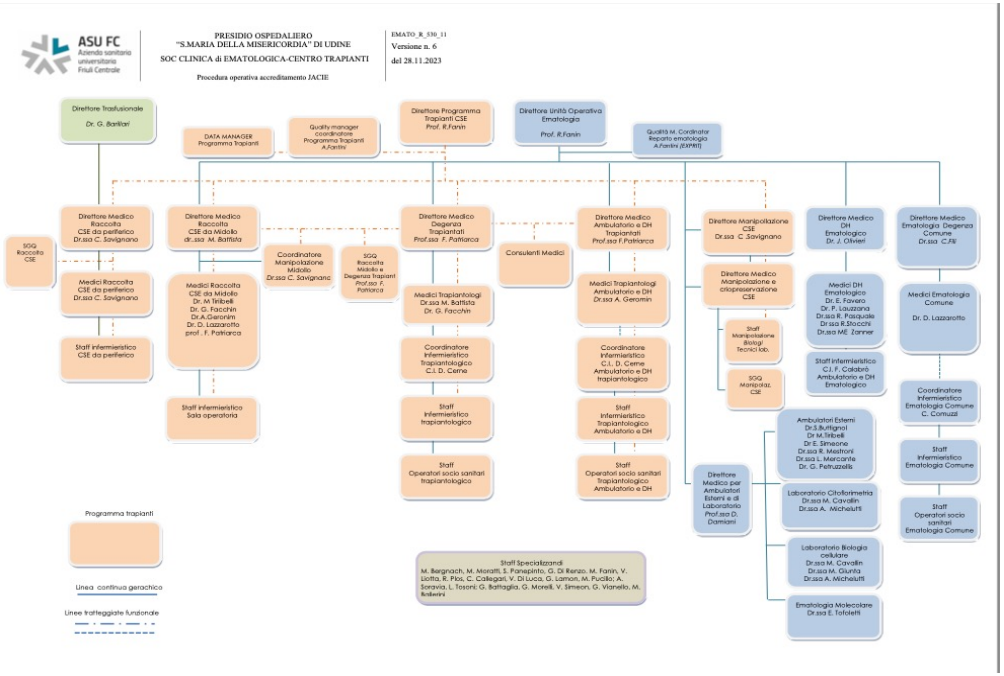
Tedder B et al, Cells 2025

Beyond commercial anti-BCMA CAR-T cells

- Anito-cel: anti BCMA CAR-T with D-domain with ongoing phase 3 studies
- Anti GPRC5D CAR-T with ongoing phase 3 studies
- Dual targeting CAR-T: BCMA/CD19, BCMA/CD38, BCMA/CD24
- Allogeneic CAR-T
- BCMA CAR-T-NK

	2022	2023	2024	2025*
N° pazienti	9	9	28	33
Età mediana (range)	69 (42-77)	57 (48-77)	66 (37-78)	65 (22-72)
Indicazione • DLBCL • PMBCL • MCL • FL • LAL • MM	 5 (56%) 1 (11%) 1 (11%) 0 1 (11%)	 5 (56%) 1 (11%) 3 (33%) 1 (11%) 0	 14 (50%) 0 3 (11%) 6 (21%) 3 (11%) 2 (7%)	 11 (33%) 1 (3%) 4 (12%) 4 (12%) 0 13 (40%)
2° linea/ >2° linea	0/9	0/9	9/28	8/33
Prodotto: • Tisa-cel • Axi-cel • Brexu-cel • Ide-cel	 5 (56%) 2 (22%) 2 (22%)	 2 (22%) 5 (56%) 2 (22%)	 7 (25%) 13 (46%) 5 (21%) 2 (7%)	 1 (3%) 12 (36%) 4 (12%) 13 (40%)
Δt aferesi-infusione (giorni)	42 (33-62)	42,5 (31-94)	46 (35-74)	49 (31-105)

*primi 3 trimestri



Grazie!

LATE ADVERSE EVENTS

	Ide-cel	Cilta-cel
Study name	KarMMa	Cartitude-1
N° pts	128	97
Severe adverse events	9 (7%)	6 (6%)
< 2 months	3 (CRS, lung aspergillosis, gastrointestinal hemorraghe)	2 (CRS, sepsis)
2-6 months	1 (CMV pneumonia)	3 (sepsis, lung ascess, respiratory failure)
6-24 months	5 7% SPM 1% myeloid neoplams	1 (neurotoxicity) 21% SPM 9% myeloid neoplasm 1% T-lymphoma