HOSPITAL UNIVERSITARIO DE SALAMANCA

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CIC CENTRO DE INVESTIGACIÓN DEL CÁNCER

University of Salamanca

CAR-T cell immunotherapy in Multiple Myeloma: Clinical results in early lines

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IBSAL

Disclosures

- Honoraria derived from lectures and participation in advisory boards from Janssen, Celgene, Takeda, Amgen, GSK, AbbVie, Pfizer, Regeneron, Roche, Sanofi, Oncopeptides, Kite

Treatment landscape in Multiple Myeloma

1st line

ASCT elegible

AntiCD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

AntiCD38 + PI + IMiD + Dex

2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

3rd line

Anti-CD38 + Pomalidomide-dex

Elotuzumab-Pomalidomide-dex

Previous combos if pt elegible

Ide-cel

Other drugs

Melflufen

Sel-dex

4th line

BCMA-targeted therapy

CAR-T

Ide-cel

Cilta-cel

BsAbs

Teclistamab

Elranatamab

GPRC5D-targeted therapy

BsAbs

Talquetamab

The label is for RRMM after at least 3 PL of therapy including PI, IMiD and antiCD38 and refractory to the last line of therapy

Mateos MV, personal communication. Dimopoulos MA et al. EHA/ESMO guidelines. Annals of Oncology 2021

Treatment landscape in Multiple Myeloma today: realistic situation

1st line

ASCT elegible

AntiCD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

AntiCD38 + PI + IMiD + Dex

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Selinexor-bortezomib-dex

Carfilzomib-dex

3rd line

Anti-CD38 + Pomalidomide-dex

Elotuzumab-Pomalidomide-dex

Previous combos if pt elegible

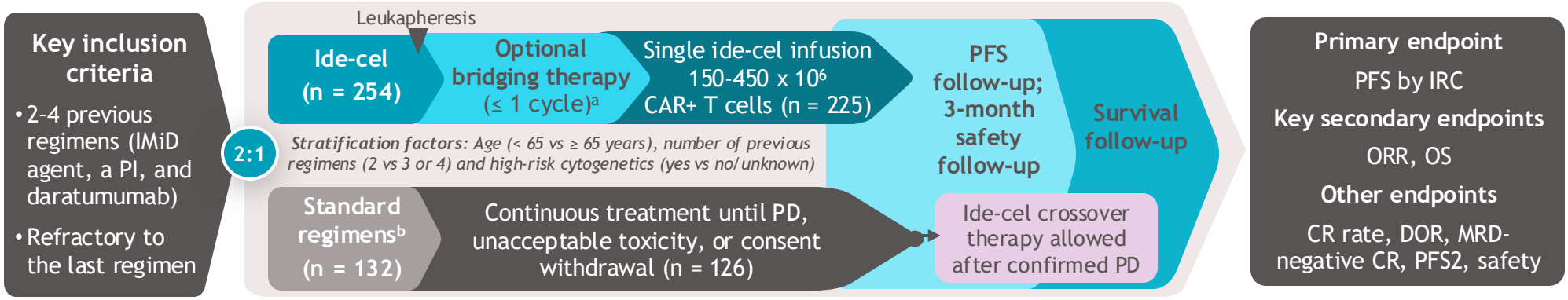
We are now entering into the TCR population

Ide-cel based on the KarMMa-3

The label is for RRMM after at least 2 PL of therapy including PI, IMiD and antiCD38

Mateos MV, personal communication. Dimopoulos MA et al. EHA/ESMO guidelines. Annals of Oncology 2021

KarMMa-3 study: Ide-cel versus standard regimens in patients with triple-class-exposed RRMM



Characteristic	Ide-cel (n = 254)	SOC (n = 132)
Median age, years (range)	63 (30–81)	63 (42–83)
Median time from diagnosis to screening, years (range)	4.1 (0.6–21.8)	4.0 (0.7–17.7)
Previous autologous HSCT, n (%)	214 (84)	114 (86)
R-ISS I/II/III, n (%)	50 (20)/150 (59)/31 (12)	26 (20)/82 (62)/14 (11)
EMP, n (%)	61 (24)	32 (24)
High tumor burden, n (%)[c]	71 (28)	34 (26)
High-risk cytogenetics, n (%)[d]		
del(17p)/t(4;14)/t(14;16)/1q gain/amplification	166 (65)/66 (26)/43 (17)/8 (3)/124 (49)	82 (62) /42 (32)/18 (14)/4 (3)/51 (39)
Ultra-high-risk[e]	67 (26)	29 (22)
Median time to progression on last antimyeloma therapy, months (range)	7.1 (0.7–67.7)	6.9 (0.4–66.0)
Daratumumab refractory, n (%)	242 (95)	123 (93)
Triple-class-refractory, n (%)[f]	164 (65)	89 (67)

[a] Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as bridging therapy with a minimum 14 days washout; [b] **DPd, DVd, IRd, Kd, or EPd**; [c] ≥ 50% CD138+ plasma cells in bone marrow; [d] Included del(17p), t(4;14), t(14;16), or 1q gain/amplification; [e] ≥ 2 of del (17p), t(4;14), t(14;16), t(14;20), or 1q gain/amplification; [f] Refractory to ≥ 1 each of an IMiD agent, a PI, and an anti-CD38 antibody. CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; DOR, duration of response; DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EMP, extramedullary plasmacytoma; EPd, elotuzumab/pomalidomide/dexamethasone; HSCT, hematopoietic stem cell transplant; ide-cel, idecabtagene vicleucel; IRC, independent review committee; ITT, intent-to-treat; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PI, proteasome inhibitor; PFS, progression-free survival; PFS2, PFS on next line of therapy; R-ISS, revised International Staging System; RRMM, relapsed or refractory multiple myeloma; SOC, standard of care.

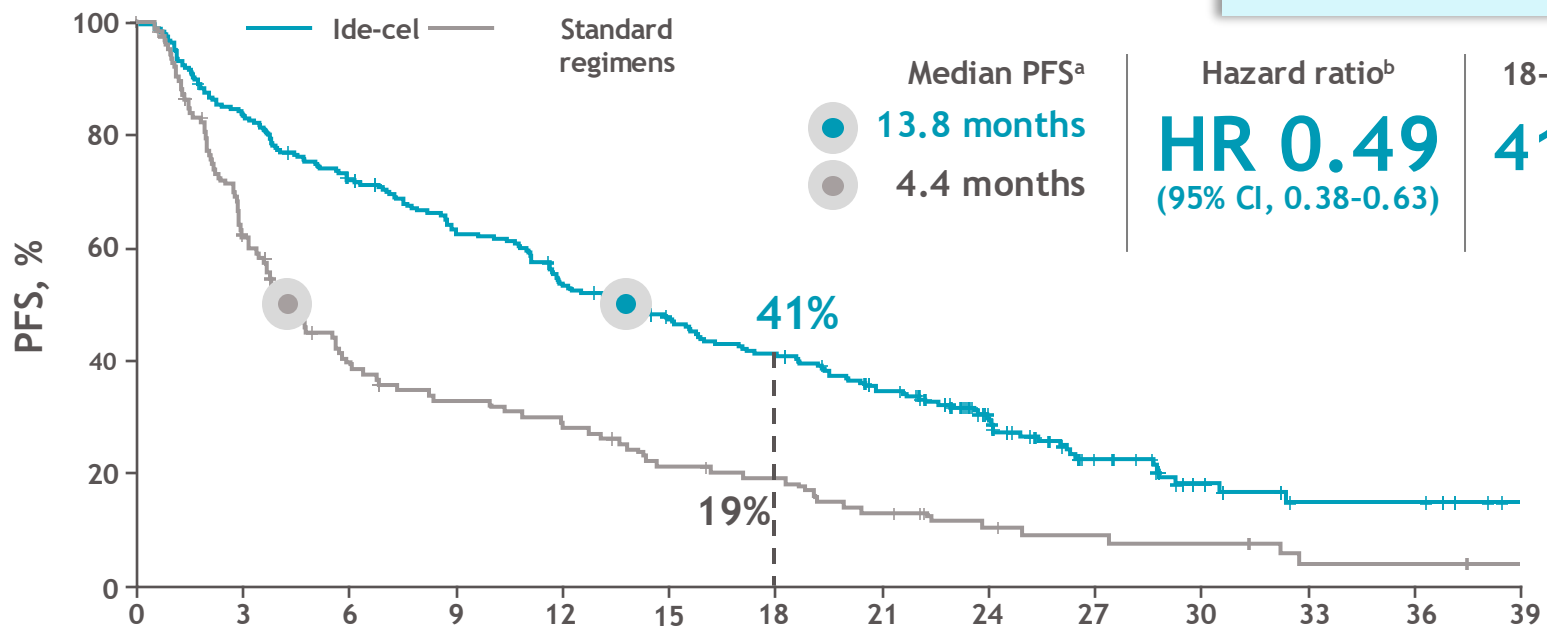
Rodriguez Otero P, et al. ASH 2023. Abstract 1028.

KarMMa-3 study: Efficacy outcomes

ORR was **71%** with ide-cel vs 42% with SOC

- sCR/CR: 44% vs 6%
- MRD-negative CR: 35% vs 2%

Significant benefit with ide-cel at final PFS analysis (ITT population)



	Median PFS[a]	Hazard ratio[b]	18-month PFS rate	
Ide-cel	13.8 months	HR 0.49 (95% CI, 0.38-0.63)	41%	
Standard regimens	4.4 months			19%

Patients at risk

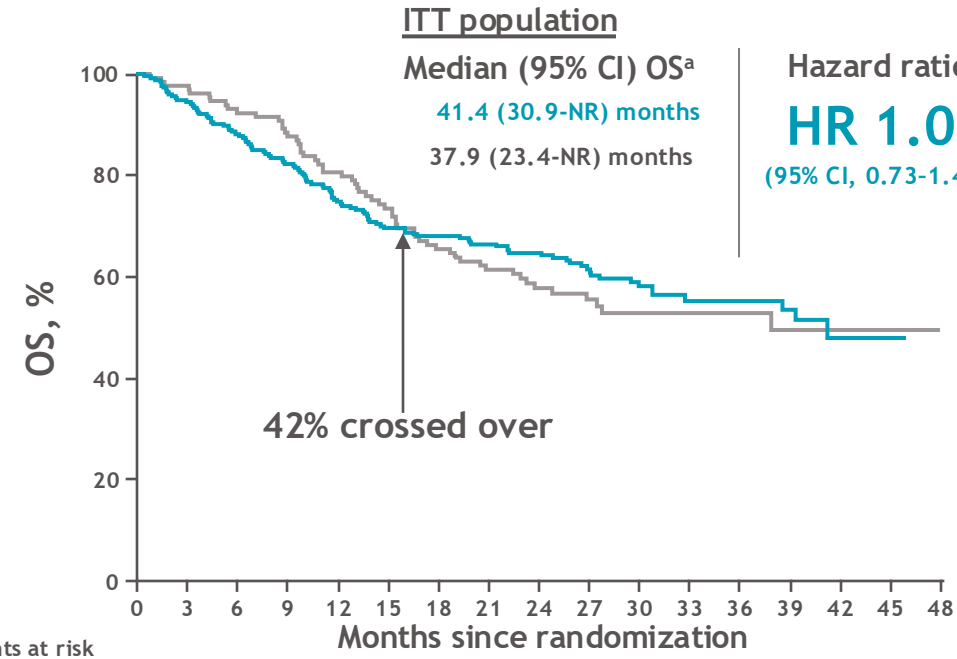
Ide-cel	254	206	177	153	131	111	94	77	54	25	14	7	7	2
Standard regimens	132	76	43	34	31	21	18	12	9	6	5	3	2	1

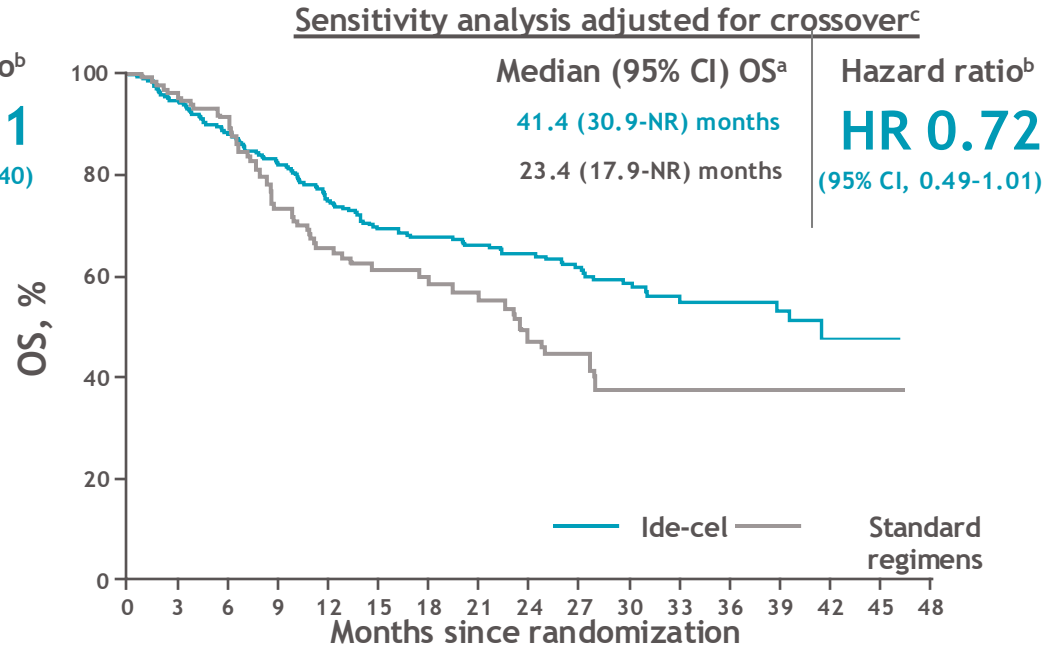
PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion. PFS based on IMWG criteria per IRC.

[a] Based on Kaplan-Meier approach; [b] Stratified HR based on univariate Cox proportional hazard model. CI is 2-sided. CI, confidence interval; CR, complete response; HR, hazard ratio; ide-cel, idecabtagene vicleucel; ITT, intent-to-treat; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; sCR, stringent complete response; SOC, standard of care.

Rodriguez Otero P, et al. ASH 2023. Abstract 1028.

KarMMa-3 study: OS analysis confounded by substantial crossover





More than half of patients in standard regimens arm received ide-cel as subsequent therapy upon confirmed PD and the majority received ide-cel within 3-16 months of randomization

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

Information fraction for OS was 74% (n = 164/222 required events). [a] Based on Kaplan-Meier approach; [b] Stratified HR is based on the univariate Cox proportional hazards model. CI is 2-sided and calculated by bootstrap method; [c] Two-stage Weibull model without recensoring (prespecified analysis). CI, confidence interval; HR, hazard ratio; ide-cel, idecabtagene vicleucel; ITT, intent-to-treat; NR, not reached; OS, overall survival.

Rodriguez Otero P, et al. ASH 2023. Abstract 1028.

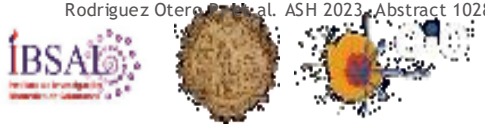
KarMMa-3 study: Safety outcomes

Safety Treated population, n (%)	Ide-cel (n = 225)	SOC (n = 126)
Any-grade AE	225 (100)	124 (98)
Serious AE	105 (47)	52 (41)
ITT population, n (%)	**Ide-cel (n = 254)**	**SOC (n = 132)**
Overall deaths	106 (42)	58 (44)
Cause of death		
Disease progression	64 (25)	37 (28)
AEs	17 (7)	8 (6)
Other causes	23 (9)	12 (9)
SPMs[a]	2 (1)	1 (1)

Treated population, n (%)	Ide-cel (n = 225)
CRS	
Any grade	197 (88)
Grade 3/4	9 (4)
iiNT	
Any grade	34 (15)
Grade 3/4	7 (3)
Infections	
Any grade	125 (56)
Grade 3/4	50 (22)

The safety profile of ide-cel was manageable and consistent with previous studies

[a] Deaths due to SPMs in the ide-cel arm were leukemia (n = 1) and pancreatic adenocarcinoma (n = 1); death due to SPMs in the SOC arm was malignant neoplasm of unknown primary site (n = 1).
AE, adverse event; CRS, cytokine release syndrome; ide-cel, idecabtagene vicleucel; iiNT, investigator-identified neurotoxicity; SOC, standard of care; SPM, second primary malignancy.
Rodriguez Otero P, et al. ASH 2023. Abstract 1028.



KarMMa-3 study: Bridging therapy

Bridging therapy was allowed in the KarMMa-3 study, which included up to one cycle of DPd, DVd, IRd, Kd or EPd Overall, 212 (83%) patients received bridging therapy

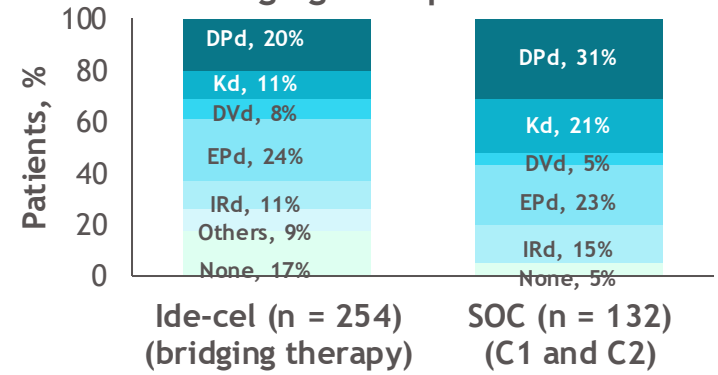
Early deaths

Patients who died ≤ 6 months from randomization, n (%)	Ide-cel (n = 254)	SoC (n = 132)
Patients who died	30 (12)	9 (7)
Did not receive study treatment	17 (7)	0
Received study treatment	13 (5)	9 (7)
Primary cause of death		
AEs	8 (3)	3 (2)
Myeloma progression	18 (7)	6 (5)
Other causes[a]	4 (2)	0

- Importantly, 17/30 deaths reported in the ide-cel arm did not receive ide-cel but were included in the analysis
- The most common cause of death in both arms was myeloma progression

This study highlights the importance of effective bridging therapy to reduce tumor burden

Bridging therapies and SoC



Effective bridging regimens were used less in the ide-cel arm

- DPd and Kd — regimens with the most disease burden reduction during bridging therapy

Lower dose intensity bridging therapy was used in the ide-cel arm

- 17% of patients had no bridging therapy; median 24-day washout period before ide-cel infusion

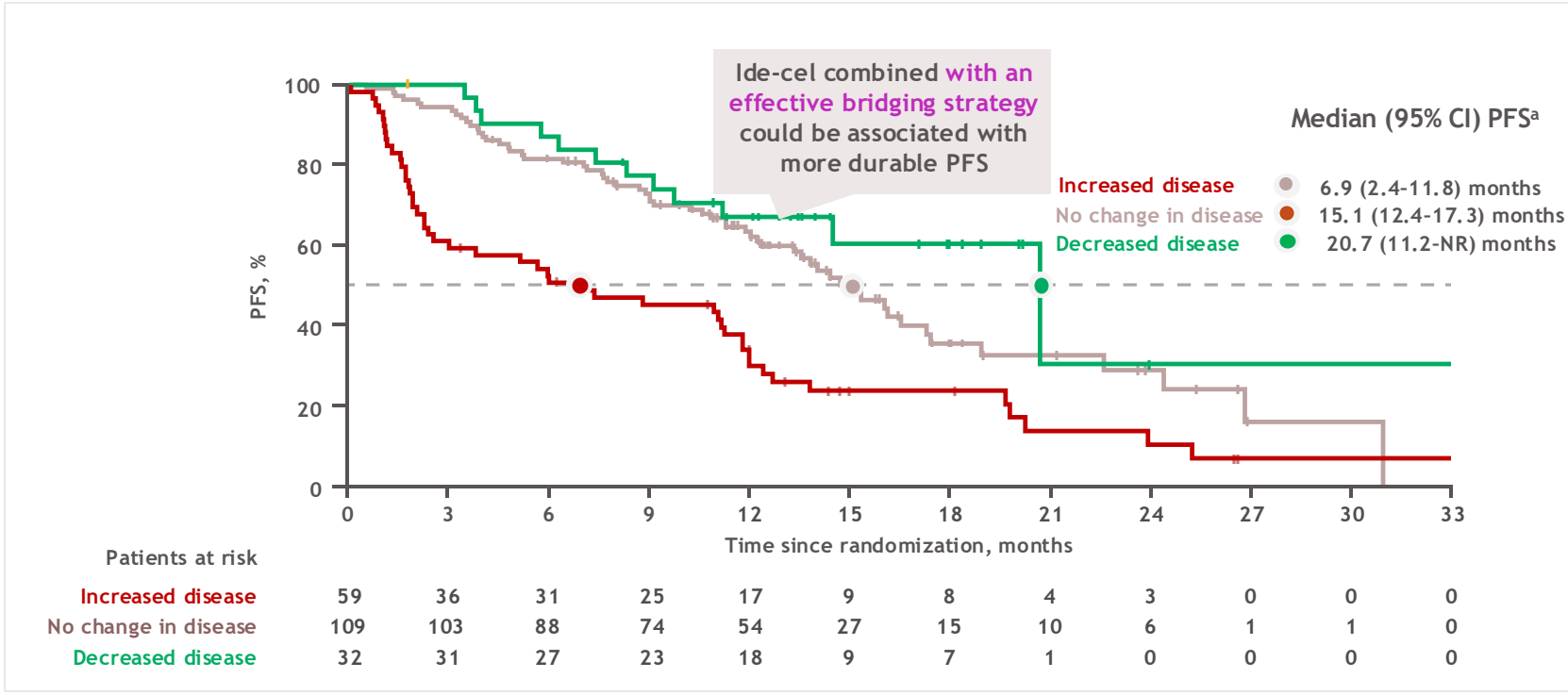
Median (range) time without therapy within the first 60 days

- Ide-cel: 26 (1-60) days vs SoC: 6 (0-60) days

[a] Deaths due to SPMs in the ide-cel arm were leukemia (n = 1) and pancreatic adenocarcinoma (n = 1); death due to SPM in the SoC arm was malignant neoplasm of unknown primary site (n = 1).
AE, adverse event; C, Cycle; DPd, daratumumab, pomalidomide and dexamethasone; DVd, daratumumab, bortezomib and dexamethasone; EPd, elotuzumab, pomalidomide and dexamethasone; ide-cel, idecabtagene vicleucel; IRd, ixazomib, lenalidomide and dexamethasone; Kd, carfilzomib and dexamethasone; SoC, standard of care; SPM, second primary malignancy.
Rodriguez Otero P, et al. ASH 2023. Abstract 1028.

KarMMa-3 study: Ide-cel bridging subanalysis suggests that there is an opportunity to optimize ide-cel patient outcomes

KarMMa-3: Impact of Bridging therapy on PFS - ITT



[a] PFS per IRC based on IMWG criteria according to FDA censoring rules. Median and 95% CI are based on Kaplan-Meier approach.
CI, confidence interval; FDA, U.S. Food and Drug Administration; ide-cel, idecabtagene vicleucel; IMWG, International Myeloma Working Group; IRC, independent review committee; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.
Einsele H, et al. IMS 2023. Poster P-008.

Treatment landscape in Multiple Myeloma

1st line

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AntiCD38 + PI + IMiD + Dex

ASCT

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Dara-Len-dex

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2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

Cilta-cel

New combinations:

Teclistamab-Dara /Tec mono /Elra monotherapy

Talquetamab-Dara/ Talquetamab-Pom

Tec-Tal

Belantamab-Vd (DREAMM-7)

Belantamab-Pd (DREAMM-8)

3rd line

Anti-CD38 + Pomalidomide-dex

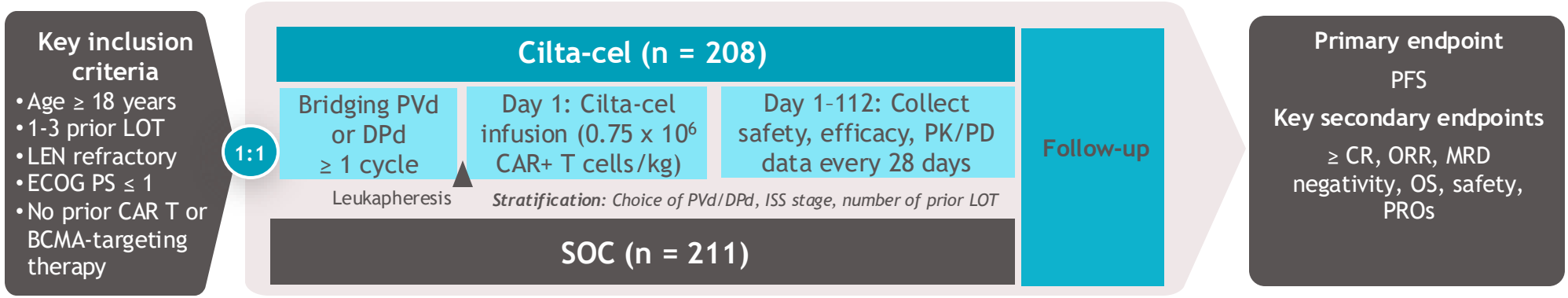
Elotuzumab-Pomalidomide-dex

Previous combos if pt elegible

Ide-cel

Mateos MV, personal communication. Dimopoulos MA et al. EHA/ESMO guidelines. Annals of Oncology 2021

Cartitude-4 study: Cilta-cel versus PVd/DPd in LEN-refractory MM patients after 1-3 prior LOT[1,2]

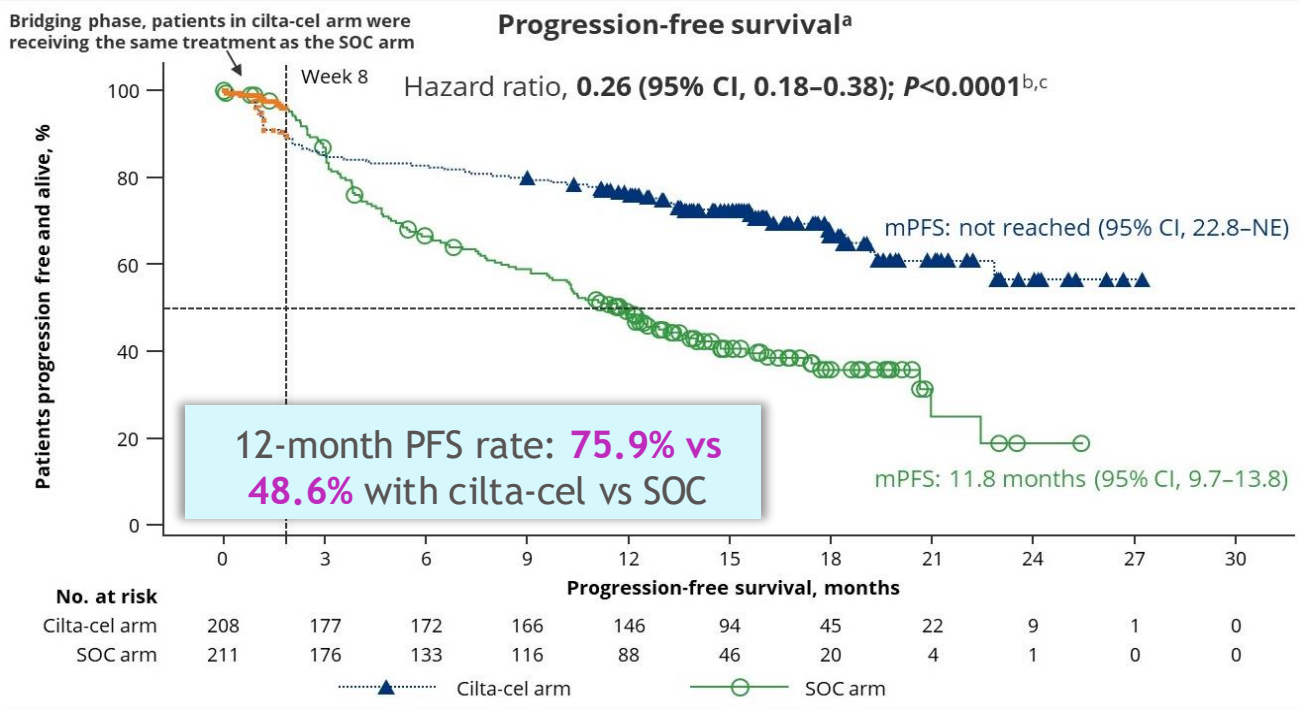


Characteristic	Cilta-cel (n = 208)	SOC (n = 211)
Median age, years (range)	61.5 (27-78)	61.0 (35-80)
Median time since diagnoses, years (range)	3.0 (0.3-18.1)	3.4 (0.4-22.1)
ECOG PS 0/1/2, n (%)	114 (54.8)/93 (44.7)/1 (0.5)	121 (57.3)/89 (42.2)/1 (0.5)
ISS I/II/III, n (%)	136 (65.4)/60 (28.8)/12 (5.8)	132 (62.6)/65 (30.8)/14 (6.6)
High-risk cytogenetics, n (%)[a]	123 (59.4)	132 (62.9)
1q gain/amplification/del(17p)/t(4;14)/t(14;16)	89 (43.0)/49 (23.7)/30 (14.5)/3 (1.4)	107 (51.0)/43 (20.5)/30 (14.3)/7 (3.3)
With ≥ 2 high-risk abnormalities	43 (20.8)	49 (23.3)
With del(17p), t(4;14) or t(14;16)	73 (35.5)	69 (32.9)
Triple-class exposure, n (%)	53 (25.5)	55 (26.1)
Daratumumab refractory, n (%)	48 (23.1)	45 (21.3)
Triple-class-refractory, n (%)[b]	30 (14.4)	33 (15.6)
Penta-drug refractory, n (%)[c]	2 (1.0)	1 (0.5)

[a] Data for 207 patients with cilta-cel and 210 patients with SOC; [b] Includes one PI, one IMiD and one anti-CD38 mAb; [c] Includes ≥ 2 PIs, ≥ 2 IMiDs and one anti-CD38 mAb. BCMA, B-cell maturation antigen receptor; CAR, chimeric antigen receptor; CD, cluster of differentiation; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DPd, daratumomab, pomalidomide and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance score; IMiD, immunomodulatory drug; ISS, International Staging System; LEN, lenalidomide; LOT, lines of therapy; mAb, monoclonal antibody; MM, multiple mieloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall safety; PD, pharmacodynamics; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib and dexamethasone. 1. Dhakal ASCO 2023 LBA-106; 2. San Miguel JF, et al. N Engl J Med. 2023;389:335-47.

PFS outcomes in the CARTITUDE-4 study

Overall, 208 patients were assigned to receive cilta-cel (ITT population); 32 patients did not receive cilta-cel (of these, 20 patients received cilta-cel after disease progression during bridging therapy)[1,2]



- **ORR** was **84.6%** with cilta-cel vs **67.6%** with SOC
  - sCR: **58.2%** vs **15.2%**
  - CR: **14.9%** vs **6.6%**
- In MRD-evaluable patients, MRD negativity occured in **87.5%** vs **32.7%** of patients, respectively

A sustained benefit was observed across different subgroups of patients

CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; mPFS, median progression-free survival; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival sCR, stringent complete response; SOC, standard of care.

1. Dhakal ASCO 2023 LBA-106; 2. San Miguel JF, et al. N Engl J Med. 2023;389:335-47.

CARTITUDE-4 study: Safety

Safety, n (%)	Cilta-cel (n = 208)	SOC (n = 208)
Any-grade AE	208 (100)	208 (100)
Serious AE	92 (44.2)	81 (38.9)
Grade 3/4 events	201 (96.6)	196 (94.2)
SPMs	9 (4.3)	14 (6.7)
Infections		
Any grade, n (%)	129 (62.0)	148 (71.2)
Grade 3/4, %	26.9	24.5
Grade 3/4 hematologic events		
Neutropenia	187 (89.9)	171 (82.2)
Thrombocytopenia	86 (41.3)	39 (18.8)
Anemia	74 (35.6)	30(14.4)
Lymphopenia	43 (20.7)	25 (12.0)
CRS	(n = 176)	
Any grade	134 (76.1)	
Grade 3/4	2 (1.1)	
Neurotoxicity	(n = 176)	-
Any grade	36 (20.5)	
Grade 3/4	9 (2.8)	
ICANS	(n = 176)	
Any grade	8 (4.5)	
Grade 3/4	1 (0.1)	

AE, adverse event; CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; HR, hazard ratio; ICANS, immue effector cell-associated neurotoxicity syndrome; ITT, intent-to-treat; mPFS, median progression-free survival; PFS, progression-free survival SOC, standard of care; SPM, second primary malignancy.

San Miguel JF, et al. N Engl J Med. 2023;389:335-47.

Patient-Reported Outcomes in the Phase 3 CARTITUDE-4 Study of Ciltacabtagene Autoleucel vs Standard of Care in Patients with Lenalidomide-Refractory Multiple Myeloma After 1-3 Lines of Therapy

- PRO assessments were administered at baseline[a] and at months 3, 6, 9, 12, 18, and 24 in both arms
  - Change from baseline[a] was calculated for patients with assessments at baseline[a] and at the given time point
- EORTC QLQ-C30, EQ-5D-5L, and MySIm-Q questionnaires were administered to all patients until disease progression[b]

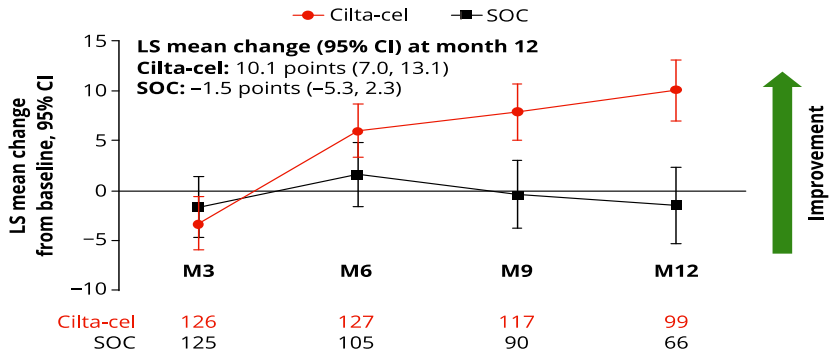
EORTC QLQ-C30[1,c]
- Cancer-specific questionnaire
  - Scores range from 0–100
- Global health status scale
- 3 symptom scales
  - Fatigue
  - Nausea and vomiting
  - Pain
- 5 functional scales
  - Physical
  - Role
  - Emotional
  - Cognitive
  - Social

EQ-5D-5L[2]
- Generic measurement of health
- Visual analogue scale
  - Patients' self-rated health between 100 (best imaginable health) and 0 (worst imaginable health)

MySIm-Q[3,d]
- MM-specific questionnaire
  - Assesses 17 single items across 8 domains on a 5-point verbal scale
- Symptom subscale
  - Assesses pain, neuropathy, fatigue, digestive, and cognitive symptom domains
- Impact subscale
  - Assesses activity, social, and emotional impact domains

Global health status scores at baseline for both treatment arms were lower than benchmark scores for the general population, suggesting worse overall health

LS mean change from baseline in global health status[b]



EORTC QLQ-C30 functional scale change from baseline at month 12[a]

Scale	LS mean change (95% CI)	
	Cilta-cel (n=99)	SOC (n=66)
EORTC QLQ-C30 functional scales		
Cognitive functioning	0.5 (–2.4, 3.5)	–7.5 (–11.2, –3.9)
Emotional functioning	9.5 (6.6, 12.5)	2.2 (–1.3, 5.7)
Physical functioning	6.5 (3.8, 9.1)	–2.1 (–5.0, 0.7)
Role functioning	7.7 (3.7, 11.7)	–1.7 (–6.3, 2.9)
Social functioning	6.1 (2.1, 10.0)	–0.1 (–4.2, 4.0)

Green indicates improvement; dark gray indicates worsening.

Mean improvements in pain symptoms in the cilta-cel arm vs the SOC arm were greater at months 3–12, and fatigue symptoms improved over time in the cilta cel arm but not the SOC arm

Visual analogue scale score improved over time in the cilta-cel arm but not the SOC arm

Median time to sustained symptom worsening was 23.7 months in the cilta-cel arm vs 18.9 months in the SOC arm

Mina R, et al. ASH 2023 (Abstract No. 1063 – oral presentation).

Treatment landscape in Multiple Myeloma

1st line

ASCT elegible

AntiCD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

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Dara-VMP/RVd

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2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

Cilta-cel

New combinations:

Teclistamab-Dara /Tec mono /Elra monotherapy

Talquetamab-Dara/ Talquetamab-Pom

Tec-Tal

Belantamab-Vd (DREAMM-7)

Belantamab-Pd (DREAMM-8)

3rd line

Anti-CD38 + Pomalidomide-dex

Elotuzumab-Pomalidomide-dex

Previous combos if pt elegible

Ide-cel

Although both Ide-cel and Cilta-cel have been approved in earlier lines of therapy, the situation is different:

- Idel-cel continues being an option for less pretreated patients but triple class exposed
- What about Cilta-cel.. is it going to be the new SoC after 1PL in all patients?

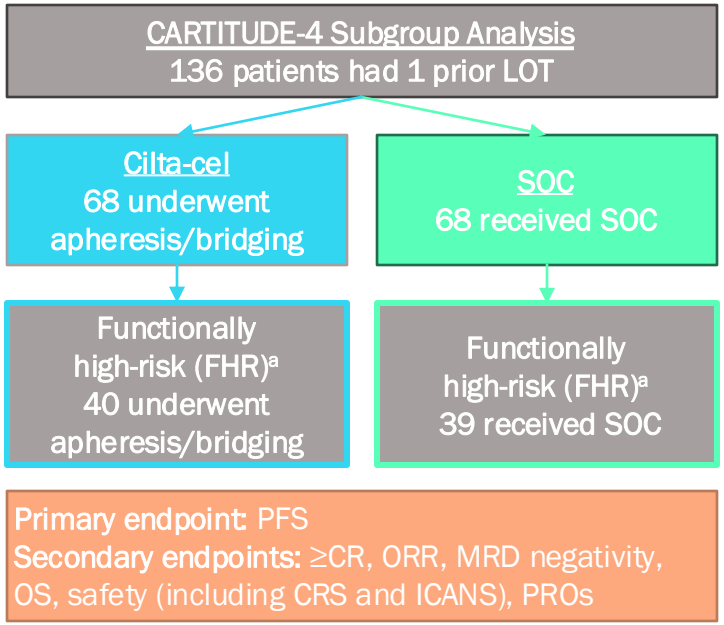
Mateos MV, personal communication. Dimopoulos MA et al. EHA/ESMO guidelines. Annals of Oncology 2021

Subgroup Analysis of the CARTITUDE-4 Phase 3 Trial of Cilta-cel vs SOC in Functional High-Risk RRMM: Study Design and Patients

Functionally high risk (FHR): PD ≤18 months after ASCT or the start of initial 1L therapy in patients with no ASCT.

Key Eligibility Criteria

- RRMM with 1-3 prior LOT (including PI + IMiD)
- Len refractory
- ECOG PS ≤1
- No prior CAR T-cell or BCMA-targeting therapy



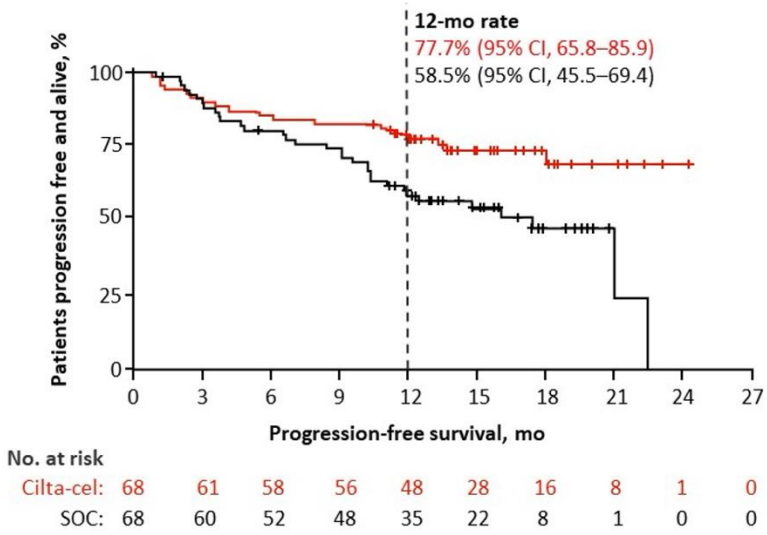
Primary endpoint: PFS
Secondary endpoints: ≥CR, ORR, MRD negativity, OS, safety (including CRS and ICANS), PROs

Patient Characteristics	1 Prior LOT		1 Prior LOT + FHR[a]	
	Cilta-cel (n=68)	SOC (n=68)	Cilta-cel (n=40)	SOC (n=39)
Median age (range), years	60.5 (27-78)	60.0 (35-78)	60.0 (27-71)	60.0 (40-78)
ISS stage II/III, n (%)	20 (29.4)	22 (32.4)	12 (30.0)	14 (35.9)
Prior ASCT, n (%)	56 (82.4)	60 (88.2)	33 (82.5)	33 (84.6)
Prior anti-CD38 mAb, n (%)	2 (2.9)	3 (4.4)	2 (5.0)	1 (2.6)
High-risk cytogenetics, n (%)	39 (57.4)	45 (66.2)	22 (55.0)	27 (69.2)
del17p	14 (20.6)	15 (22.1)	9 (22.5)	9 (23.1)
t(4;14)	13 (19.1)	10 (14.7)	8 (20.0)	6 (15.4)
t(14;16)	1 (1.5)	3 (4.4)	0	2 (5.1)
Gain/amp(1q)	34 (50.0)	38 (55.9)	20 (50.0)	23 (59.0)
≥2 abnormalities	20 (29.4)	20 (29.4)	13 (32.5)	12 (30.8)
High tumor burden, n (%)	9 (13.2)	8 (11.8)	5 (12.5)	4 (10.3)
Soft tissue plasmacytoma, n (%)	12 (17.6)	7 (10.3)	6 (15.0)	4 (10.3)

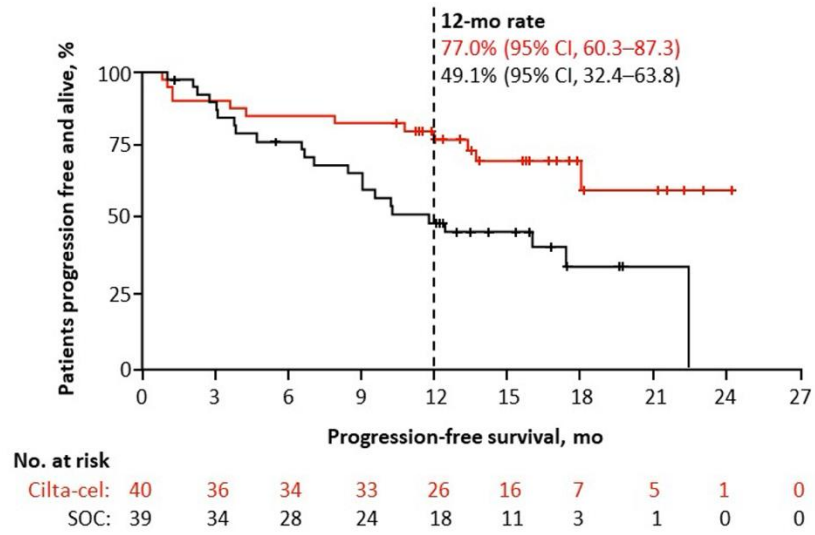
[a] Costa L, et al. ASCO 2024. Abstract 7504. Weisel K, et al. EHA 2024. Abstract P959.

Subgroup Analysis of the CARTITUDE-4 Phase 3 Trial of Cilta-cel vs SOC in Functional High-Risk RRMM: PFS

PFS in Patients With 1 Prior LOT



PFS in Patients With 1 Prior LOT + FHR

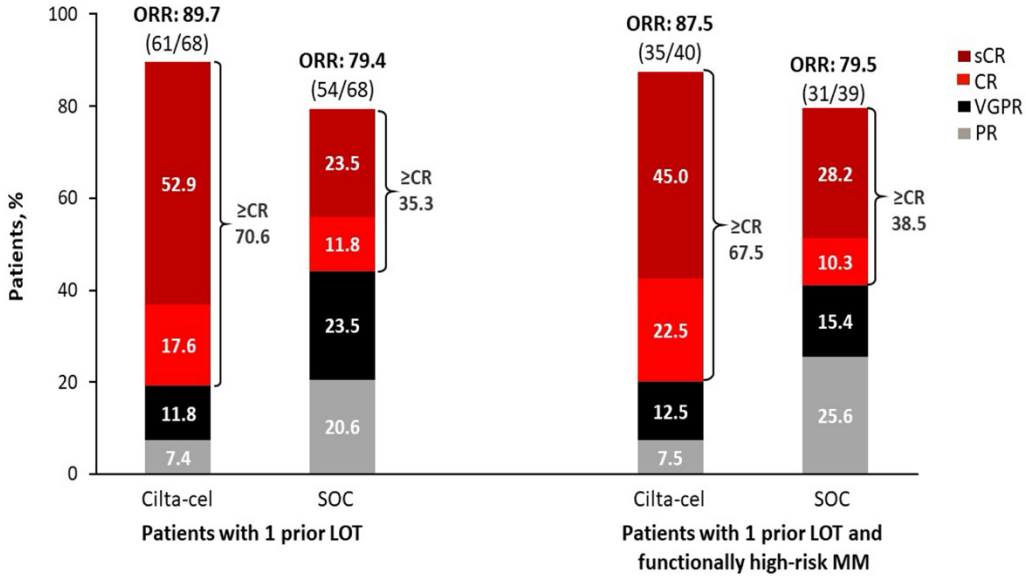


PFS	1 Prior LOT		1 Prior LOT + FHR	
	Cilta-cel (n=68)	SOC (n=68)	Cilta-cel (n=40)	SOC (n=39)
Median (95% CI), months	NR (NE-NE)	17.41 (11.10-NE)	NR (18.00-NE)	11.79 (8.44-NE)
HR (95% CI); *P* value	0.35 (0.19-0.66); 0.0007		0.27 (0.12-0.60): 0.0006	

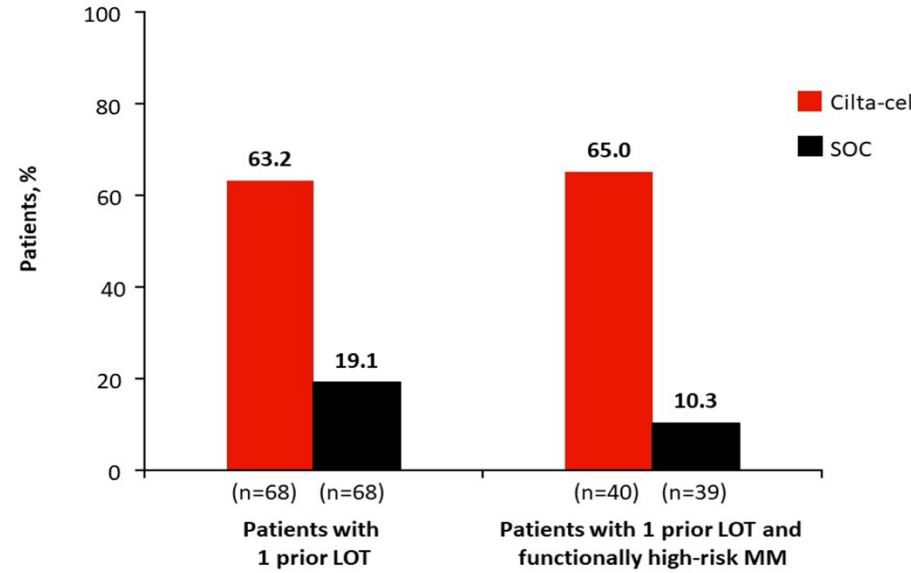
Costa L, et al. ASCO 2024. Abstract 7504. Weisel K, et al. EHA 2024. Abstract P959.

Subgroup Analysis of the CARTITUDE-4 Phase 3 Trial of Cilta-cel vs SOC in Functional High-Risk RRMM: ORR and MRD

ORR



MRD Negativity (10^{-5})



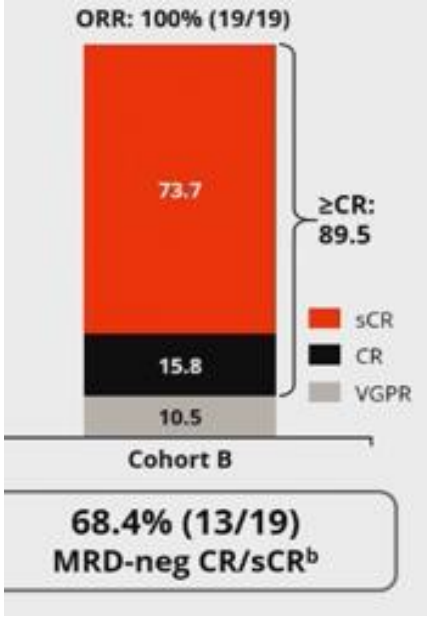
Overall Response	1 Prior LOT	1 Prior LOT + FHR
≥CR Odds Ratio	4.4	3.3
95% CI	(2.1-9.0)	(1.3-8.4)
P value	<0.0001	0.0102

MRD Negativity	1 Prior LOT	1 Prior LOT + FHR
Odds Ratio	7.3	16.3
95% CI	(3.3-15.9)	(4.8-55.1)
P value	<0.0001	<0.0001

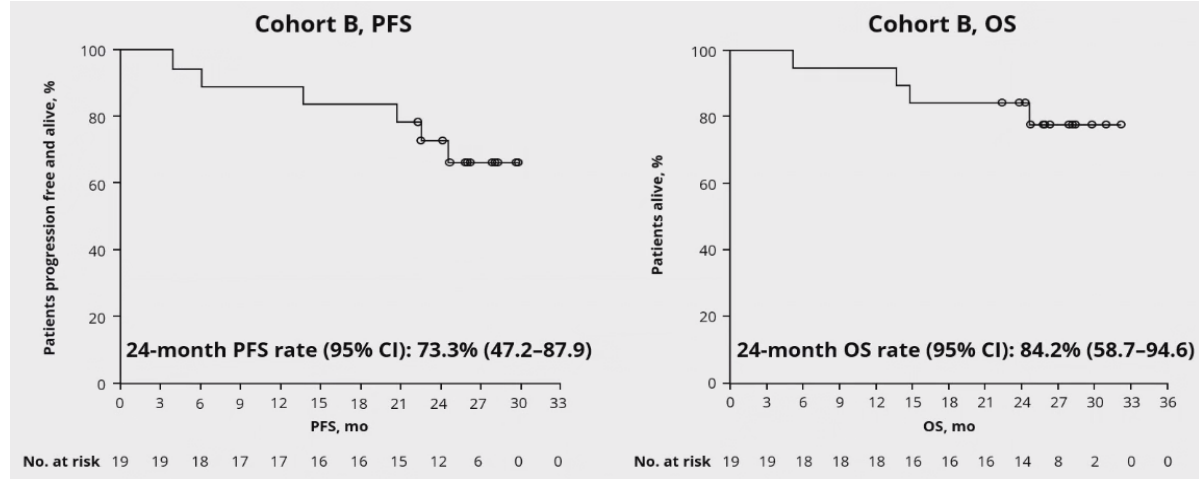
Costa L, et al. ASCO 2024. Abstract 7504. Weisel K, et al. EHA 2024. Abstract P959.

CARTITUDE-2B: Cilta-cel in patients with progressive MM following early relapse after initial therapy that included a PI and IMiD

Early relapse defined as PD less than 12m after ASCT or from initiation of frontline therapy for MM patients not eligible for ASCT
19 pts after 1.15 years from initial diagnosis were included: HRCA in 20% and 78.9% had received ASCT
Median follow up is 28 months



- 10/13 patients sustained MRD-ve at 6 months
- 8/13 patients sustained MRD-ve at 12 months



AEs, n (%)	Cohort B (N=19)				
	Any Grade	Grade 3/4	Median time to onset, days	Median duration, days	Resolved, n
CRS	16 (84.2)	1 (5.3)	8	4	16
CAR-T cell neurotoxicity	6 (31.6)	1 (5.3)	–	–	–
ICANS	1 (5.3)	0	11	4	1
Other[b]	5[c] (26.3)	1 (5.3)	22	128	3
MNT	1[d] (5.3)	1 (5.3)	38	–[e]	–[e]

Longer-term results from CARTITUDE-2 showed deep and durable responses, even in a functionally high-risk population who progressed on frontline therapy within 12 months, without new safety signals

Hillengass J, et al. ASH 2023 (Abstract No. 1021 – oral presentation).

What are the key messages?

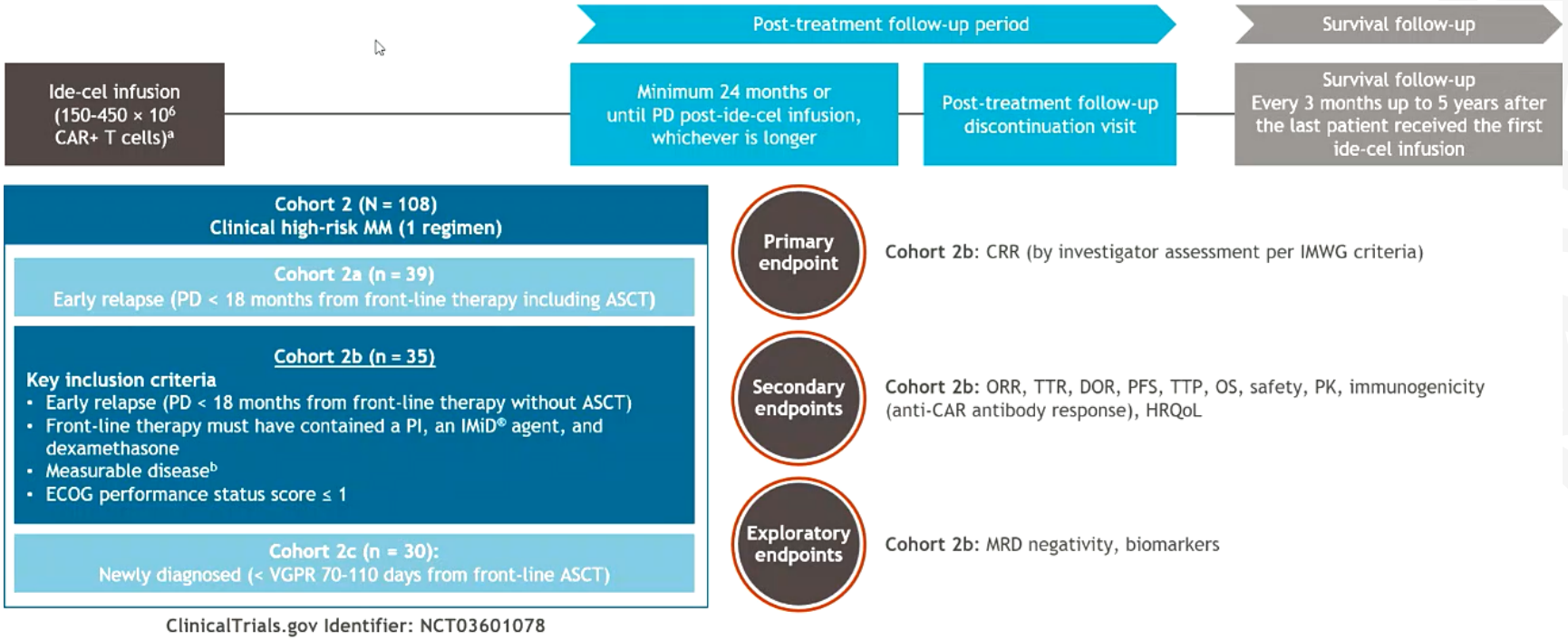
1. In functional HR patients, it seems reasonable to use Cilta-cel if it would be available

2. In the rest of patients... it is also approved although not reimbursed in most EU countries and I would like to wait to see long term efficacy and safety although cilta-cel is approved in RRMM after 1 PL and refractory to lenalidomide

1. ide-cel for functional high-risk TIE patients in first relaspe is encouraging but we need confirmation of these data

KarMMa-2 trial Cohort 2b: Idecabtagene vicleucel (ide-cel) in clinical high-risk early relapse MM without frontline ASCT

KarMMa-2 is a multicohort phase II multicentre trial evaluating efficacy and safety of ide-cel in patients with relapsed/refractory multiple myeloma and functional high-risk disease
Cohort 2b: high-risk disease, early relapse after frontline therapy excluding autologous stem cell transplant



ClinicalTrials.gov Identifier: NCT03601078

KarMMa-2 trial Cohort 2b: Idecabtagene vicleucel (ide-cel) in clinical high-risk early relapse MM without frontline ASCT

Baseline characteristics and frontline and/or bridging therapy status

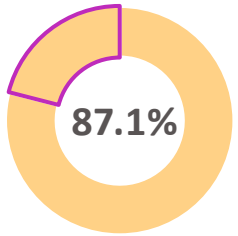
- Early relapse (PD <18 months from frontline therapy without ASCT)
- Frontline therapy included PI, IMiD and dexamethasone
- Measurable disease
- ECOG PS ≤1

30.1 months median follow-up (1.0-51.4)

	Treated (n=31)
Age, years (range)	60 (32-77)
Median time to progression on frontline tx, months (range)	7.1 (1.7-16.5)
High tumour burden, %	45.2
High-risk cytogenetics, %	38.7
Extramedullary disease, %	12.9
Double-class refractory, %	67.7
Triple-class refractory, %	16.1

Frontline therapy (%)	Treated (n=31)
VRd/VTd	38.7
KRd	9.7
Ixad	3.2
Rd	3.2
DRd	3.2
Other	41.9

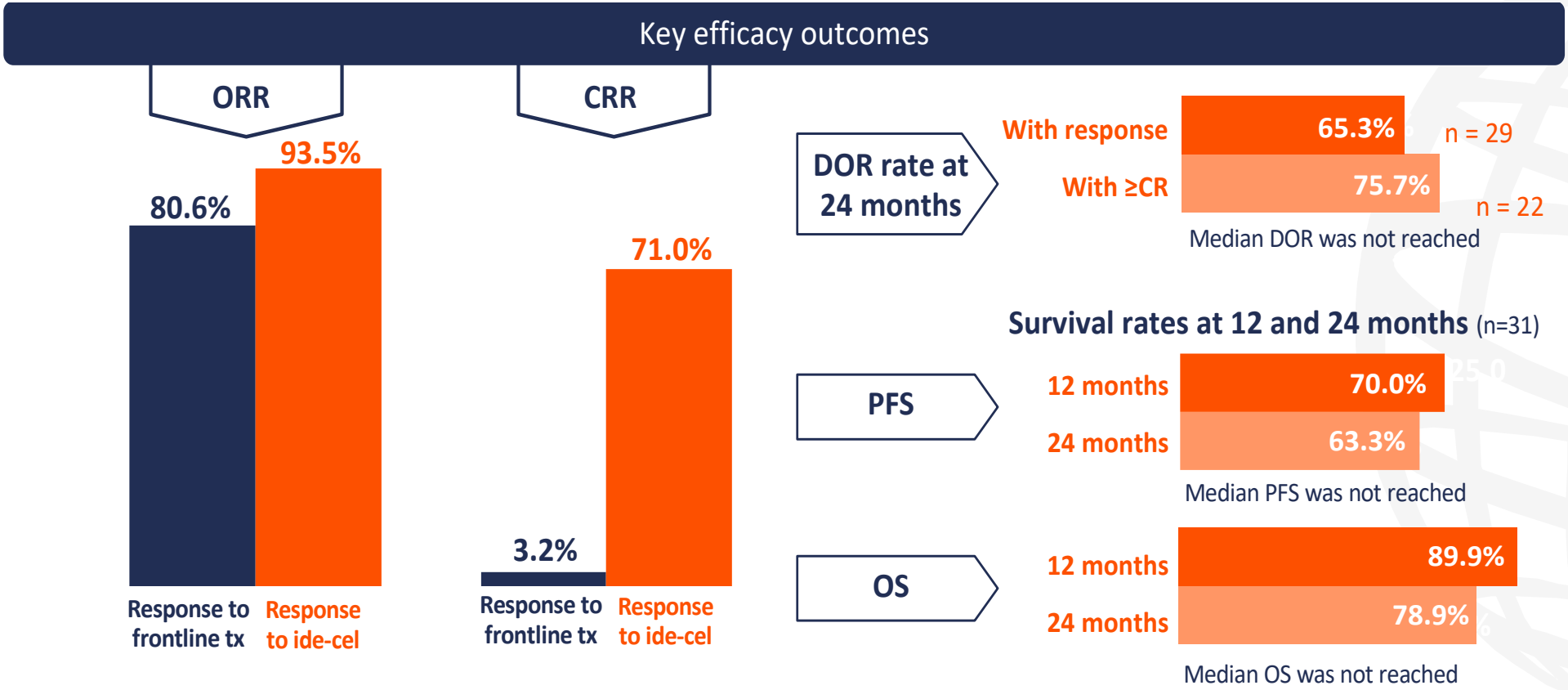
Bridging therapy



Regimen type
- Bortezomib: 25.9%
- Carfilzomib: 44.4%
- Daratumumab: 11.1%
- Other: 18.5%

ASCT, autologous stem cell transplant; D, daratumumab; d, dexamethosone; ECOG PS, European Cooperative Oncology Group Performance Status; IMiD, immunomodulatory drug; Ixa, ixazomib; K, carfilzomib; MM, multiple myeloma; PD, progressive disease; PI, proteasome inhibitor; R, lenalidomide; T, thalidomide; tx, treatment; V, bortezomib; Wu X, et al. Presented at EHA2024, Madrid, Spain (June 13–16). Abstract: S208.

KarMMa-2 trial Cohort 2b: Idecabtagene vicleucel (ide-cel) in clinical high-risk early relapse MM without frontline ASCT



ASCT, autologous stem cell transplant; CR, complete response; CRR, CR rate; DOR, duration of response; MM, multiple myeloma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; tx, treatment.

Lelu X, et al. Presented at EHA2024, Madrid, Spain (June 13–16). Abstract: S208.

KarMMa-2 trial Cohort 2b: Idecabtagene vicleucel (ide-cel) in clinical high-risk early relapse MM without frontline ASCT

Safety profile

Grade ≥3 AEs, %	n=31
Any AE	93.5
Haematologic AEs	
Neutropenia	93.5
Anaemia	54.8
Lymphopenia	45.2
Leukopenia	38.7
Thrombocytopenia	35.5

- Grade 3/4 infection and infestations occurred in 19.4% of patients

CRS	n=31
Grade 1/2	83.9%
Median time to onset, days (range)	1.0 (1–9)
Median duration, days (range)	3.0 (1–16)

94.4% of CRS events were managed with tocilizumab

iiNT	n=31
Grade 1/2	9.7%
Median time to onset, days (range)	2.0 (1–16)
Median duration, days (range)	6.0 (1–11)

Events were managed with:
- Tocilizumab (33.3%)
- Steroids (33.3%)
- Anakinra (33.3%)

⚠ No grade 3/4 CRS or iiNT events were observed

Ide-cel showed a favourable risk–benefit profile in clinical high-risk patients with MM who experienced relapse on frontline therapy (excluding ASCT), highlighting potential use in earlier lines of therapy

AE, adverse event; ASCT, autologous stem cell transplant; CRS, cytokine release syndrome; iiNT, investigator-identified neurotoxicity; MM, multiple myeloma.

Lelu X, et al. Presented at EHA2024, Madrid, Spain (June 13–16). Abstract: S208.

What are the key messages?

1. In functional HR patients, it seems reasonable to use Cilta-cel if it would be available

2. In the rest of patients... it is also approved although not reimbursed in most EU countries and I would like to wait to see long term efficacy and safety although cilta-cel is approved in RRMM after 1 PL and refractory to lenalidomide

3. ide-cel for functional high-risk TIE patients in first relaspe is encouraging but we need confirmation of these data

Treatment landscape in Multiple Myeloma

1st line

ASCT elegible

AntiCD38 + PI + IMiD + Dex

ASCT

Len/Dara-Len

ASCT ineligible

Dara-Len-dex

Dara-VMP/RVd

AntiCD38 + PI + IMiD + Dex

2nd line

Based on sensitivity/refractoriness to Daratumumab and Lenalidomide

Anti-CD38 + Carfilzomib-dex

Anti-CD38 + Pomalidomide-dex

Pomalidomide-bortezomib-dex

Selinexor-bortezomib-dex

Carfilzomib-dex

Cilta-cel

New combinations:

Teclistamab-Dara /Tec mono /Elra monotherapy

Talquetamab-Dara/ Talquetamab-Pom

Tec-Tal

Belantamab-Vd (DREAMM-7)

Belantamab-Pd (DREAMM-8)

- Challenges of the use of Cilta-cel in first relapse: i) the majority of TE patients will be triple exposed but sensitive to daratumumab and elegible, therefore, for antiCD38 plus Kd and antiCD38 plus Kd was not SoC in CARTITUDE-4; ii) safety profile in the long term f/u
- On the other side, the major benefit is the Treatment-free interval for the patient
- We will have in the near future other options like BsAbs-based combos and Belantamab-based combinations

Mateos MV, personal communication. Dimopoulos MA et al. EHA/ESMO guidelines. Annals of Oncology 2021

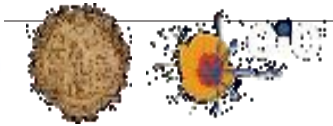
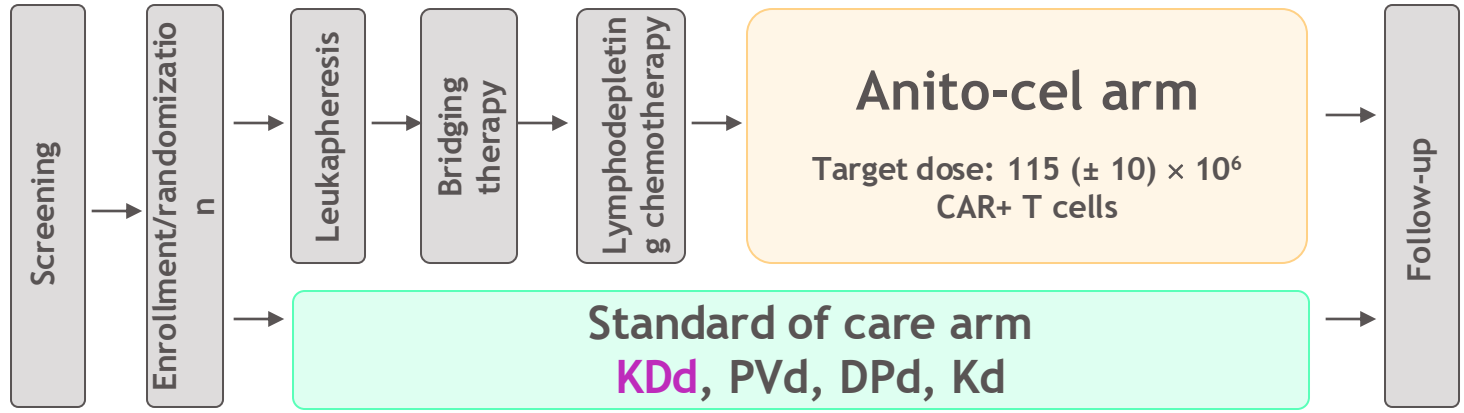


iMMagine-3 phase 3 trial

Anito-cel, a BCMA-CAR T cell therapy in RRMM

Inclusion Criteria

- RRMM treated with at least 3 prior regimens of systemic therapy including proteasome inhibitor, IMiD agents and anti-CD38 antibody and are refractory to the last line of therapy.



Study design

- 1:1 randomization
- N = approximately 450, ~130 sites globally

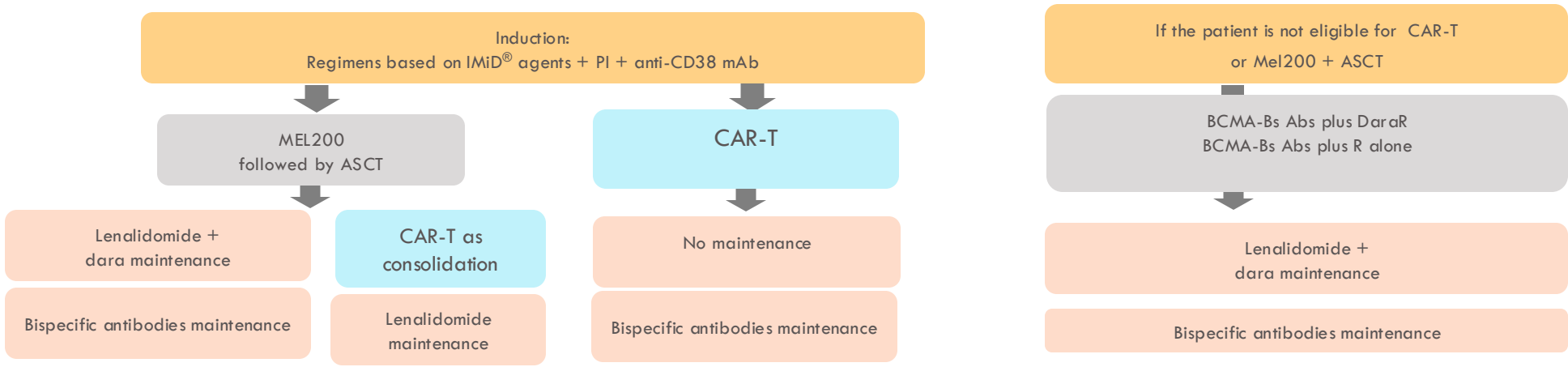
Study endpoints

- Primary endpoint: PFS
- Key secondary endpoints: CR rate, MRD, OS, safety

Anito-cel is an investigational product, currently not approved by any regulatory agency.

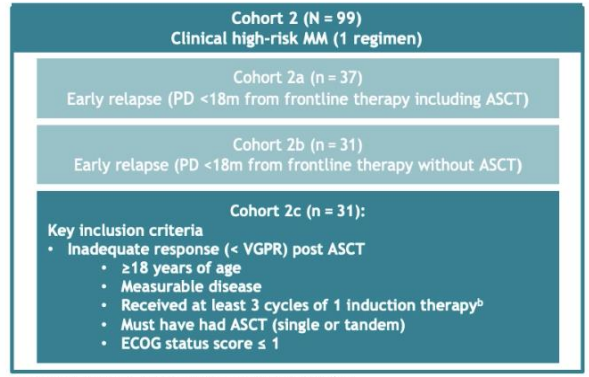
Anito-cel, anitocabtagene autoleucel; CAR, chimeric antigen receptor. NCT06413498, ClinicalTrial.gov, accessed May 2024.

Summary : envisioning the future

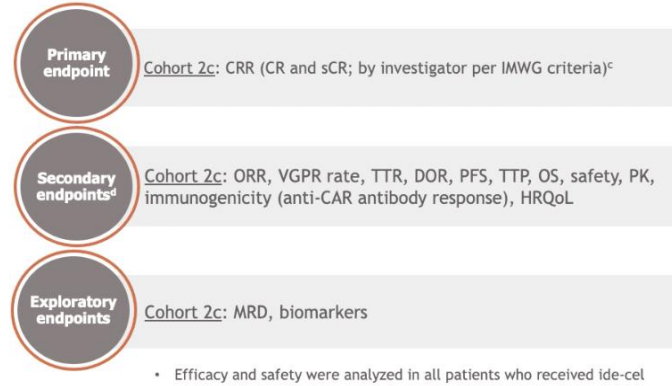


KarMMa-2 Cohort 2c: Efficacy and Safety of Idecabtagene Vicleucel in Patients with Inadequate Response to Frontline Autologous Stem Cell Transplantation: extended follow-up

- 31 patients after a median of 1 year from diagnosis
- 2 pts with EMD
- All pts exposed to lenalidomide and dex; 80% to bortezomib and 38% to carfilzomib
- The median dose of infused CAR+T cells was 440.0 x106
- 87% of pts were in PR to ASCT
- 8 pts received Len maintenance after ide-cel



ClinicalTrials.gov Identifier: NCT03651128



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

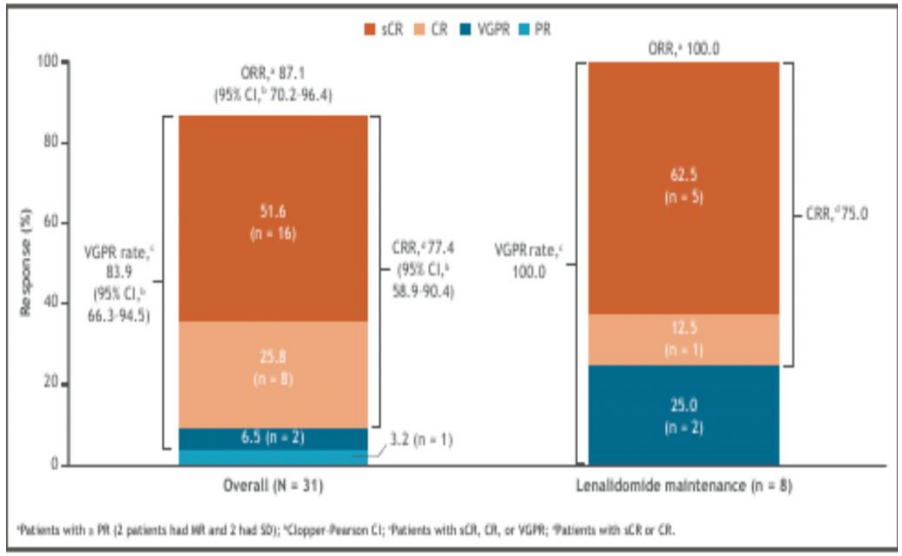
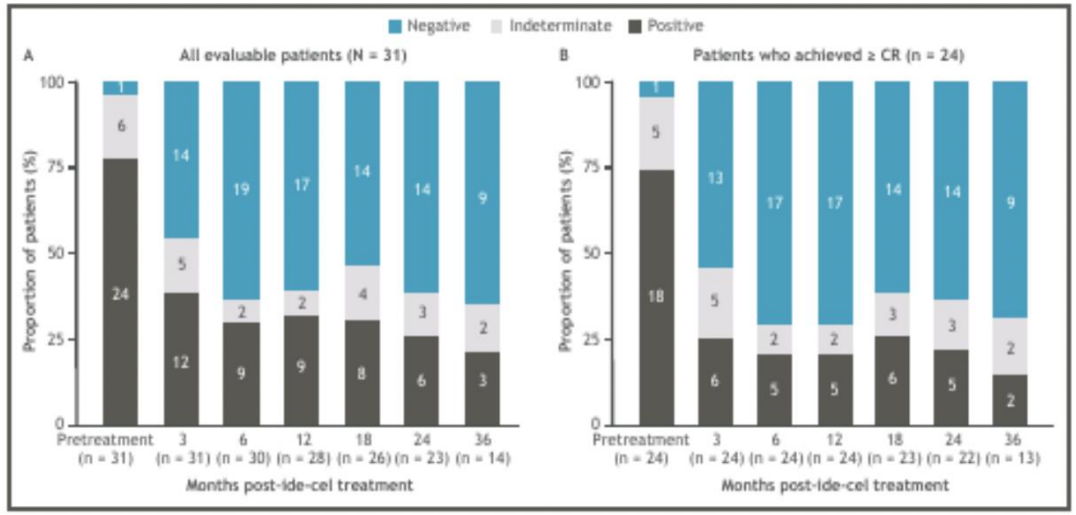


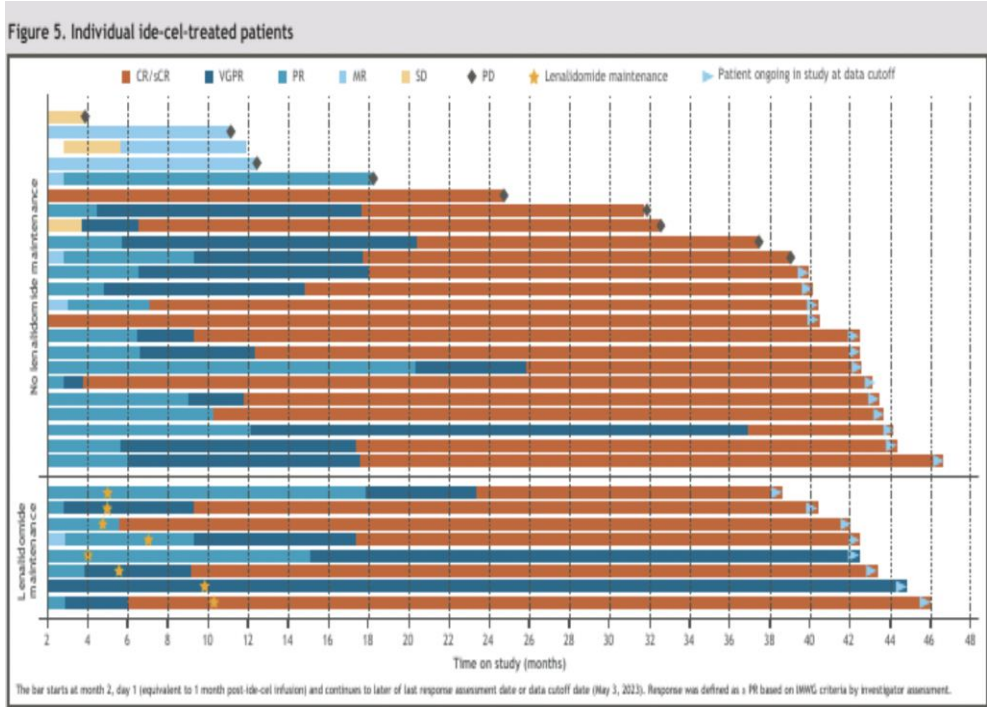
Figure 4. MRD negativity



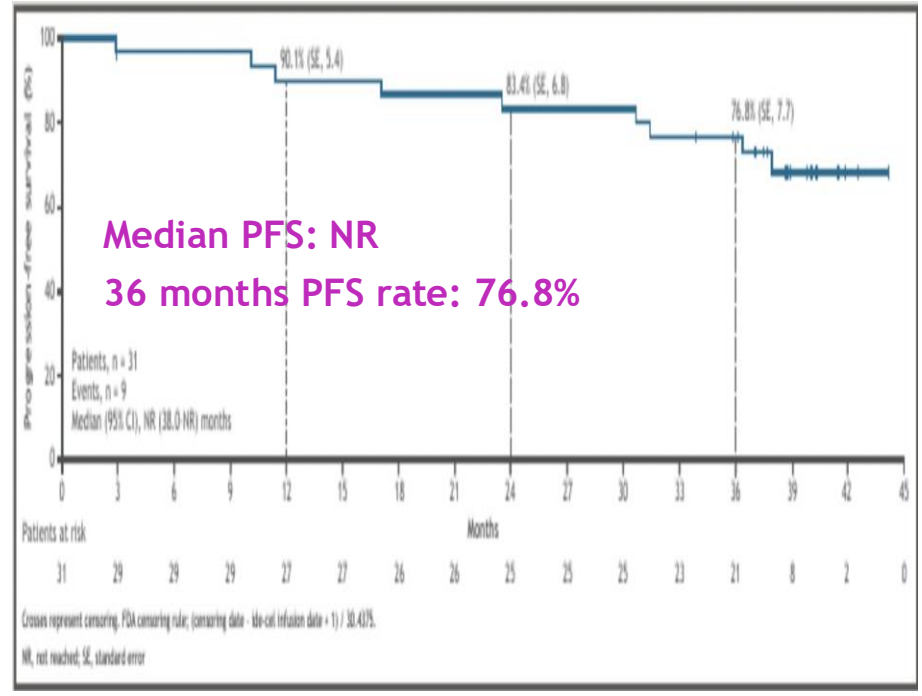
Dhodapkar M et al. ASH 2023 (Abstract No. 2101 – poster).

KarMMa-2 Cohort 2c: Efficacy and Safety of Idecabtagene Vicleucel in Patients with Inadequate Response to Frontline Autologous Stem Cell Transplantation: extended follow-up

Median follow up: 39.4 months



PFS



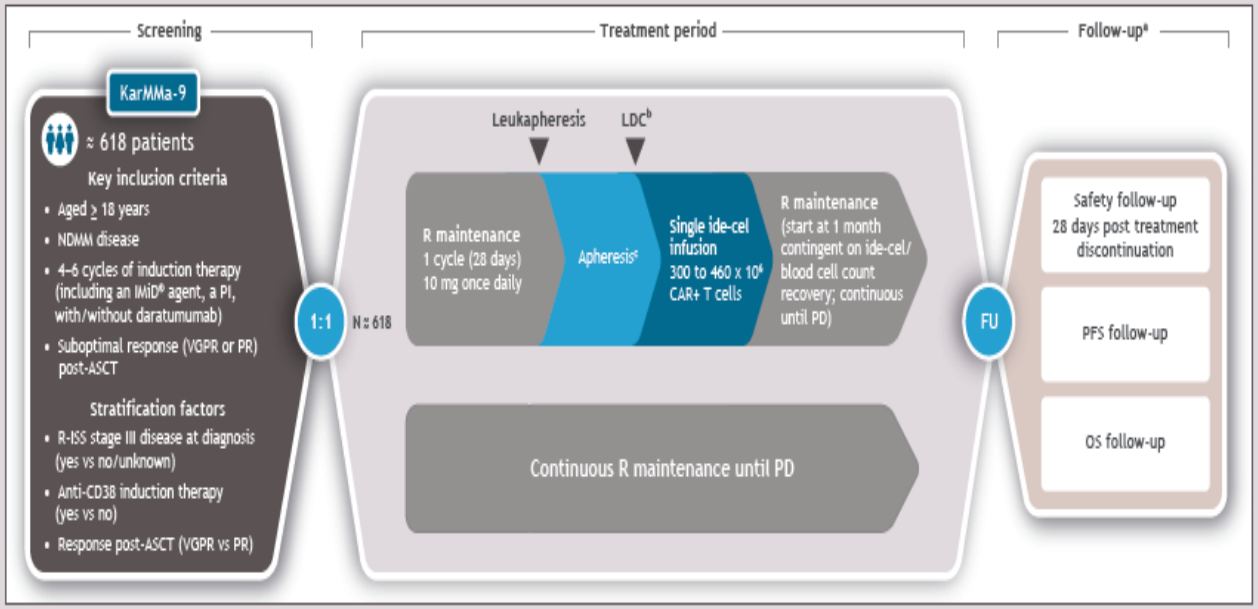
Safety profile is acceptable: CRS in 58% (No G3-4); ICANS in 6.5% (G3 in 1 pt); neutropenia G3-4 in 80.6% and infections in 58% (G3-4 in 3.2%)

These results support to evaluate ide-cel in this population as consolidation after HDM-ASCT and KarMMa-9 is a phase 3 trial comparing ide-cel post ASCT versus lenalidomide

Dhodapkar M et al. ASH 2023 (Abstract No. 2101 – poster).

KarMMa-9 phase 3 clinical trial

Figure 3. KarMMa-9 trial design



Patients must not have had PD since commencing induction and must not have received consolidation or maintenance treatment.
[a]End of trial is defined as the last patient's last visit. This will be either the date of receipt of the last data point for the study endpoints or approximately 60 months after the last patient randomized, whichever occurs later; [b]Fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² on days -5, -4, and -3 prior to ide-cel infusion; [c]Apheresis to be performed within 14–42 days after last dose of R.
ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; FU, follow-up; LDC, lymphodepleting chemotherapy; IMiD®, immunomodulatory agent; ide-cel, idecabtagene vicleucel; NDMM, newly diagnosed multiple myeloma; OS overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; R-ISS, Revised International Staging System; VGPR, very good partial response.

- KarMMa-9 (NCT06045806) is a multicenter, randomized, controlled, phase 3 trial evaluating the efficacy and safety of ide-cel with lenalidomide (R) maintenance versus R maintenance alone in patients with NDMM who had a suboptimal response (PR or VGPR) to ASCT
- Combining ide-cel with standard of care maintenance therapy is expected to deepen responses post-ASCT and extend PFS in patients with clinically high-risk NDMM

Cartitude-2 Cohort 2c: Efficacy and Safety of Ciltacabtagene autoleucel in Patients with Inadequate Response to Frontline Autologous Stem Cell Transplantation

- 17 patients after a median of 0.9 months from diagnosis
- All pts exposed to lenalidomide and PI; 17% antiCD38-exposed

Key eligibility criteria

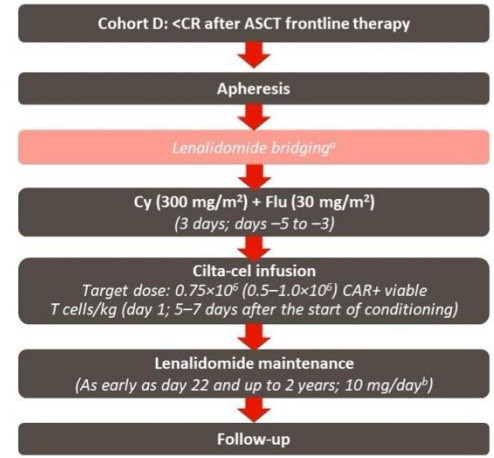
- History of 4–8 cycles of initial therapy, including induction, high-dose chemotherapy, and ASCT with or without consolidation
- Overall best response <CR

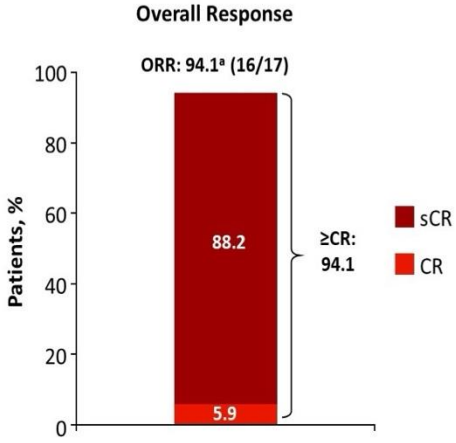
Primary endpoint

- MRD negativity (10^{-5} threshold) assessed by NGS or NGF

Key secondary endpoints

- ORR per IMWG response criteria[1]
- DOR
- Time to response
- PFS and OS
- Incidence and severity of AEs,[c] including CRS,[2,d] ICANS,[2,d] and neurotoxicity
- Pharmacokinetics





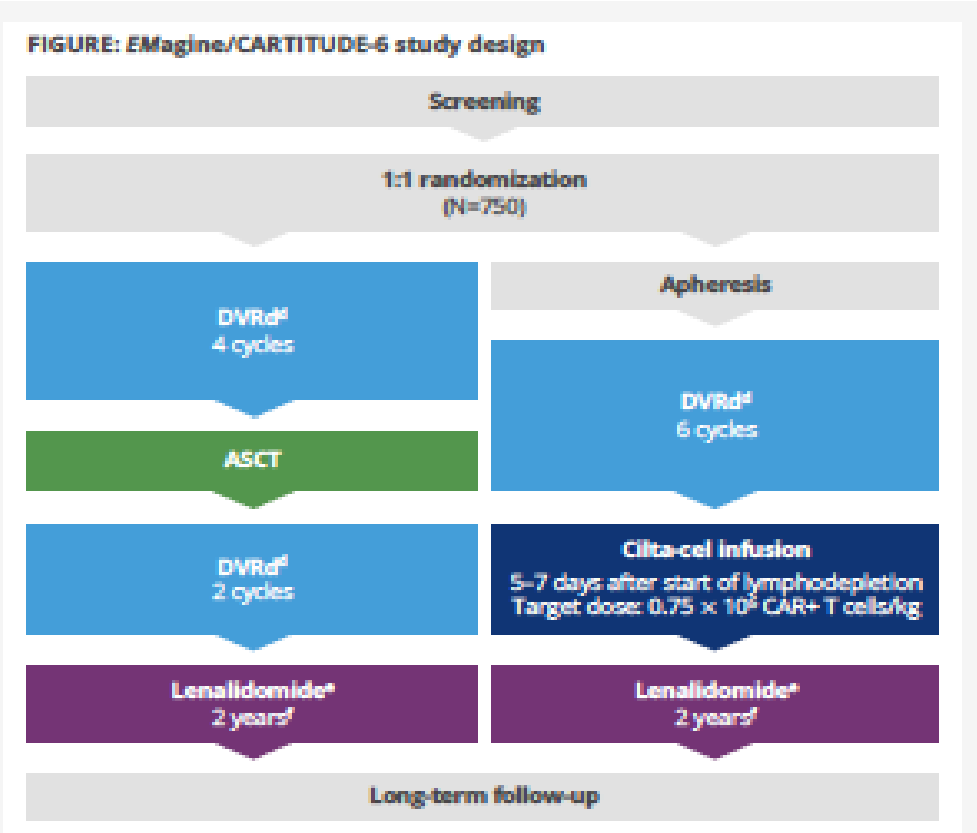
	Cohort D (N=17)
Time to response among responders, median (range), months	
First response	1.3 (0.9–12.5)
Best response	1.9 (0.9–12.5)
≥CR	1.7 (0.9–12.5)
MRD negativity (10^{-5}), n/N (%)	
Overall	12/17 (70.6)
MRD-evaluable patients[b]	12/15 (80.0)

- 1 patient was lost to follow-up, and 1 patient was not evaluable for disease response

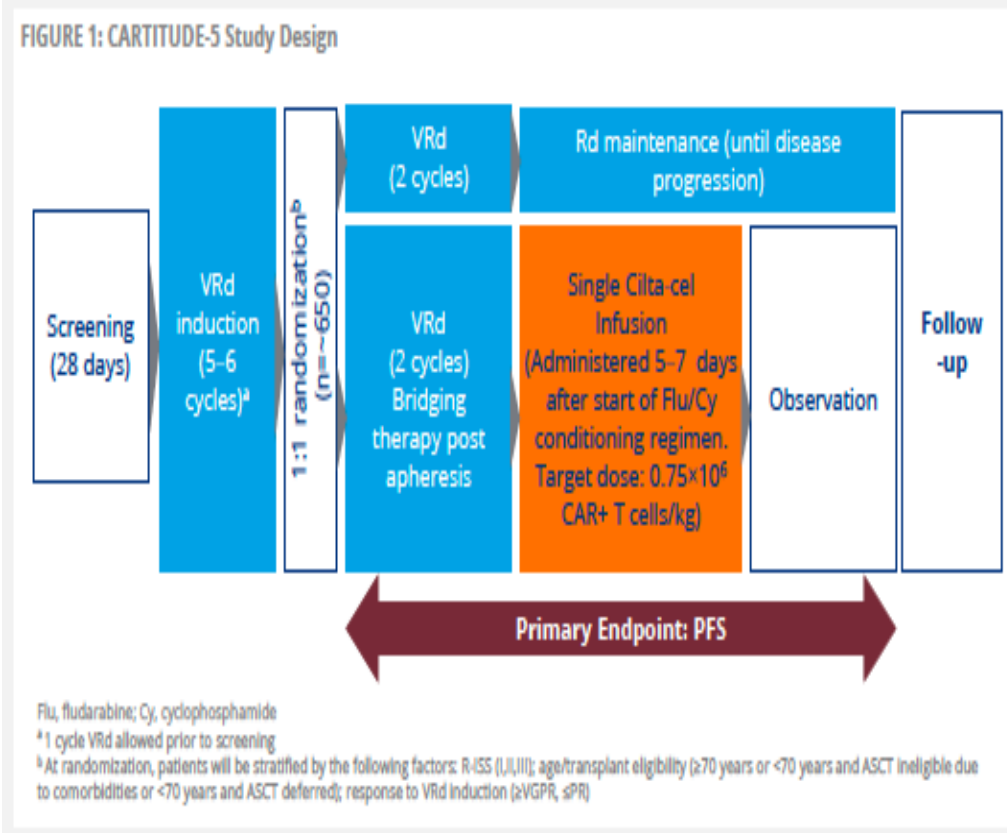
- Safety profile as expected
- No MNTs
- 1 case of MDS as SPM

BCMA-CAR-Ts in NDMM patients TE

CARTITUDE-6 TRIAL



Cartitude-5



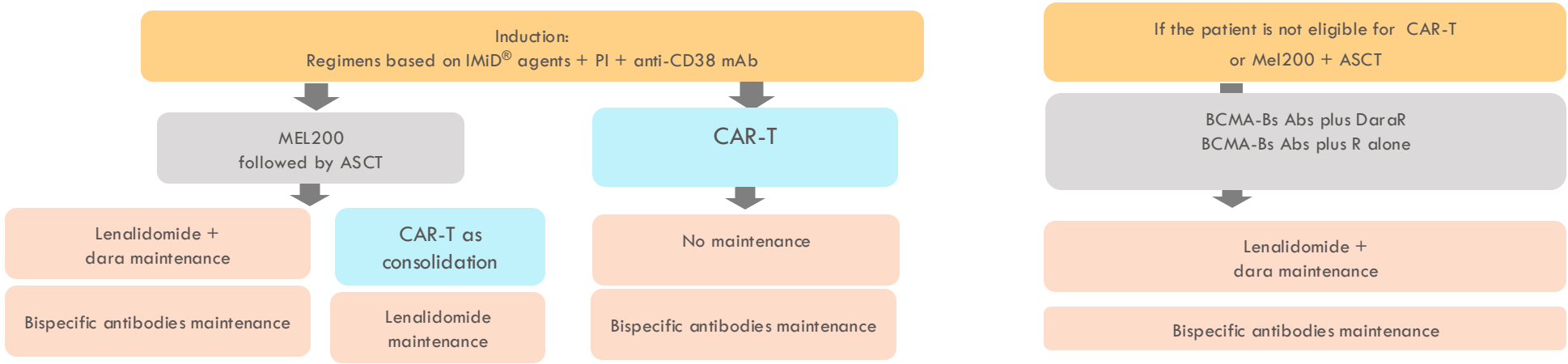
Information in clinicaltrials.gov

What are the challenges of the use of BCMA-CAR T in first line of therapy

- CARTITUDE-6 is a very attractive clinical study with a very rapid recruitment
- Cilta-cel can replace ASCT but this is challenging because ASCT is effective, cheap and world wide available

- CARTITUDE-5 has already completed the recruitment
- It is very attractive to use CAR-T in FIT patients when ASCT is not planned but the problem is the control arm is VRd and the comparator today would be AntiCD38-RVd in this population

Summary: envisioning the future

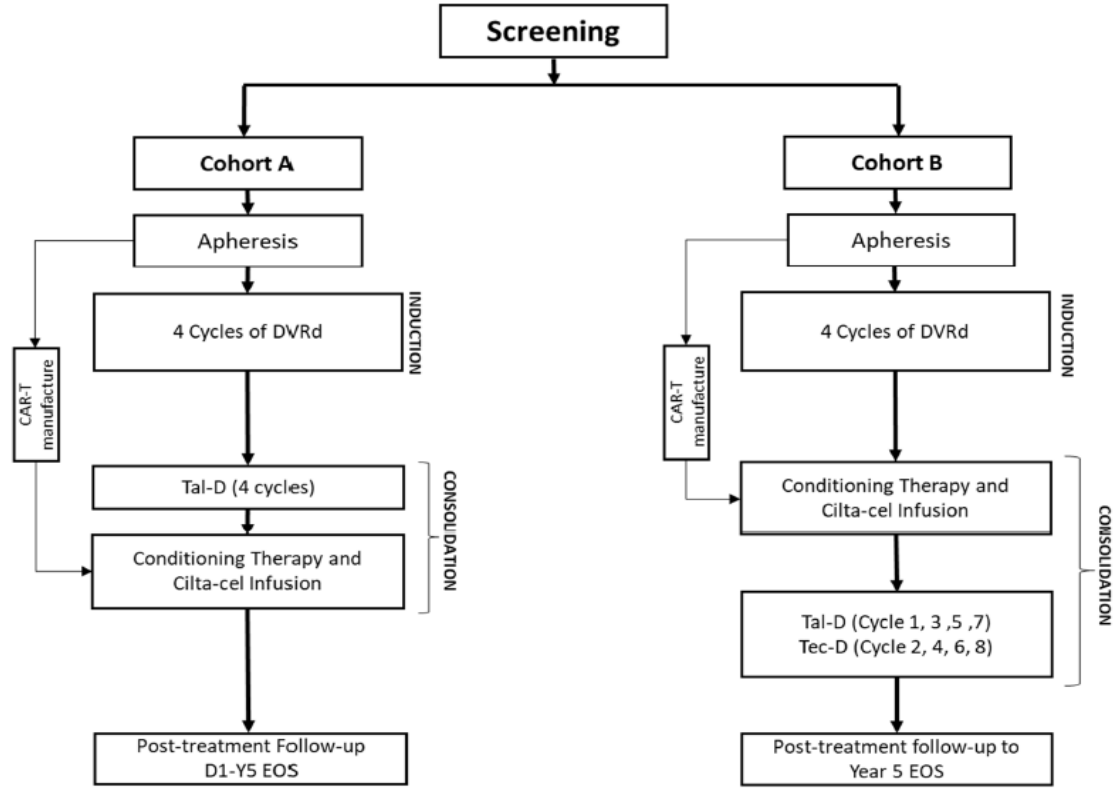


- CAR-T cell therapy will move to the first line of therapy for the patients elegible
- There are also proposals investigating Cilta-cel in High-risk Smoldering Myeloma
- We have also other T-cell redirecting therapies that can complement the CAR-T cell therapy with a curative approach

Ammbition clinical trial for NDMM patients

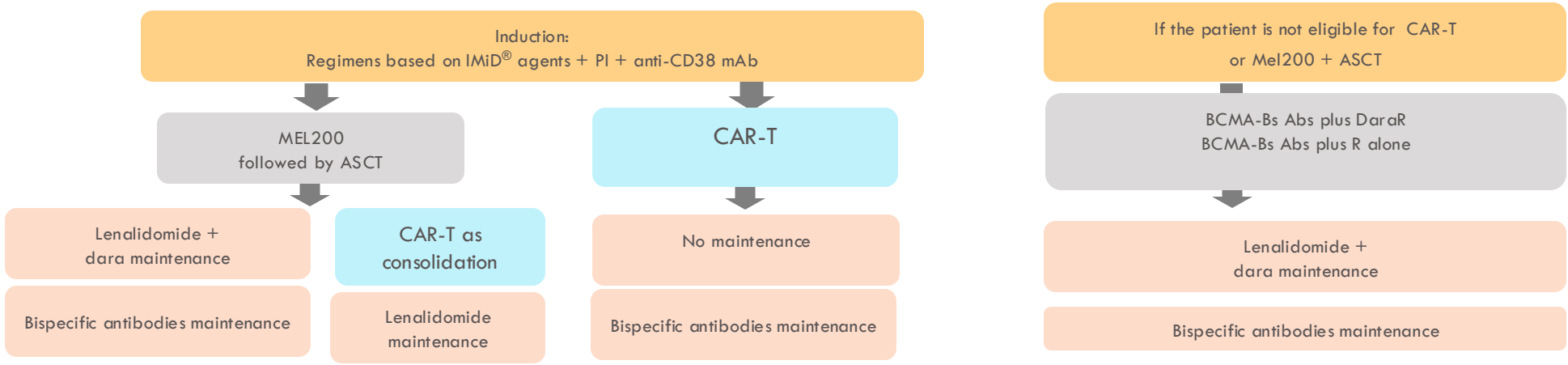
1.2. Schema

Figure 1: Schematic Overview of the Study



Cycles during induction and during Tal-D given as part of consolidation =28 days
Each Cycle during consolidation in Cohort B with alternating Tal-D and Tec-D after cilta-cel has an 84-day duration

Summary: envisioning the future



- CAR-T cell therapy will move to the first line of therapy for the patients elegible
- There are also proposals investigating Cilta-cel in High-risk Smoldering Myeloma
- We have also other T-cell redirecting therapies that can complement the CAR-T cell therapy with a curative approach
- These approaches will contribute to reach the dream of curing patients with MM
- In addition, the approval of the MRD as endpoint for the accelerated approval by FDA will help to achieve the milestones earlier on and accelerate the way to have access