POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

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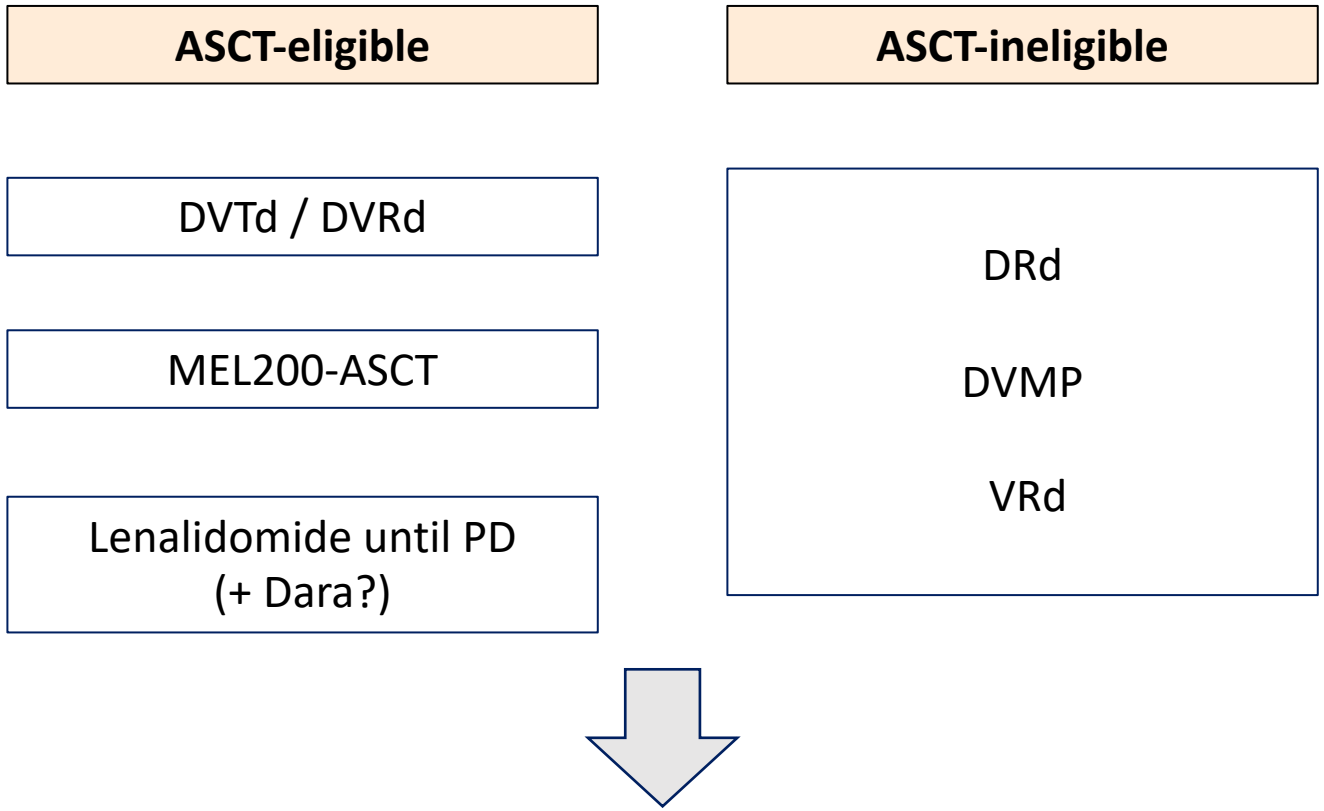
GSK						x	x
Takeda						x	
Amgen						x	
Pfizer						x	
Menarini Stem-line							x

FRONTLINE TREATMENT for NDMM PATIENTS



What treatment at relapse for triple-class exposed/refractory patients?

Roberto Mina, personal communication

D, daratumumab; V, bortezomib; T, thalidomide; R, lenalidomide; M, melphalan; P, prednisone; ASCT, autologous stem cell transplantation

Agenda

- Is there a role for salvage autologous stem cell transplant?
- Will CAR T-cell therapy become the standard salvage option at 1° relapse?
- How can we effectively bridge patients from 1° relapse to T-cell redirecting therapy in late lines?
- Patients with t(11;14): is it time for target therapy?

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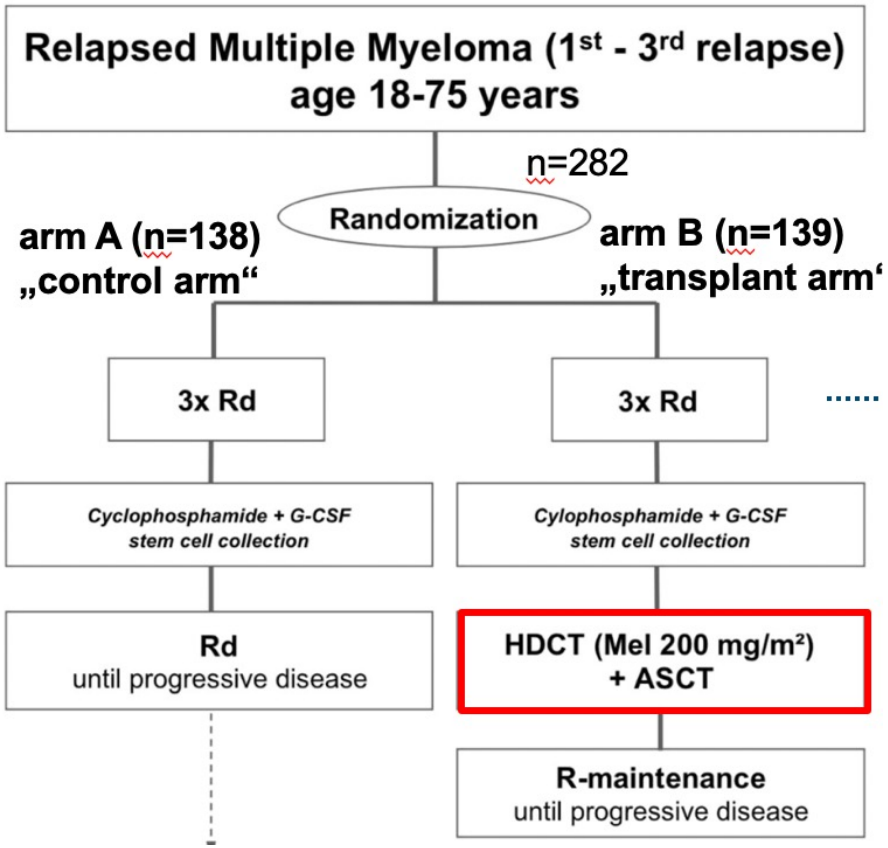
Is salvage ASCT still fashionable?

Study design
Rd-ASCT-R vs Rd



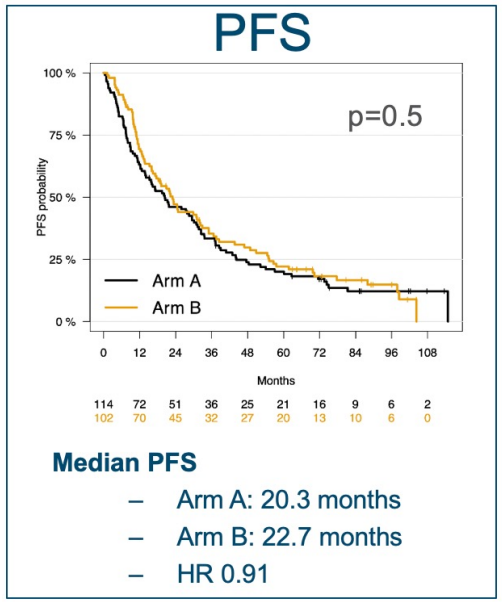
Baseline characteristics

	arm A (n=138) n (%)	arm B (n=139) n (%)
Interval diagnosis to randomization [years]	4.1 (0.7-16.5)	3.9 (0.2-19.4)
Prior lines of therapy		
1	129 (94)	131 (94)
2	8 (6)	5 (4)
3	1 (1)	3 (2)
Frontline HDCT/ASCT	130 (94)	129 (93)
Single	71 (55)	83 (64)
Tandem	59 (45)	46 (36)
Prior therapy		
Bortezomib	106 (77)	107 (77)
Thalidomide	25 (18)	31 (22)
Lenalidomide	18 (13)	12 (9)
Interferone	9 (7)	9 (6)
Chemoth. only	10 (7)	14 (10)

Marc-Marc-Andrea Baertsch et al. ASH2023

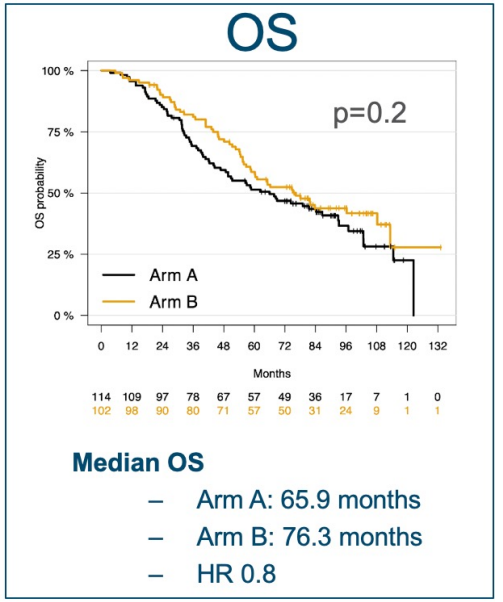
No PFS and OS advantage for patients receiving ASCT intensification

Intention-to-treat



Median PFS

- Arm A: 20.3 months
- Arm B: 22.7 months
- HR 0.91



Median OS

- Arm A: 65.9 months
- Arm B: 76.3 months
- HR 0.8

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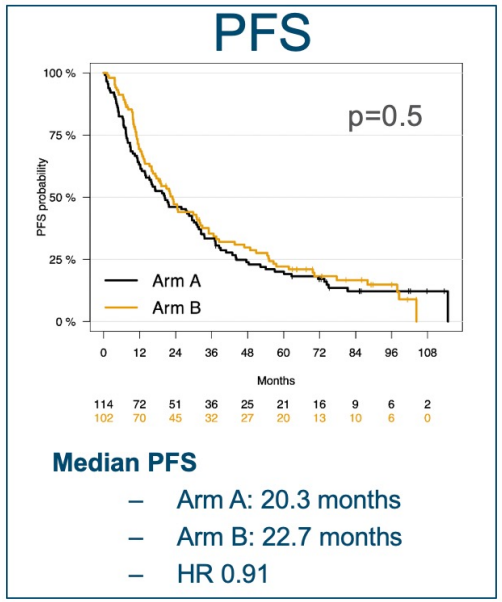

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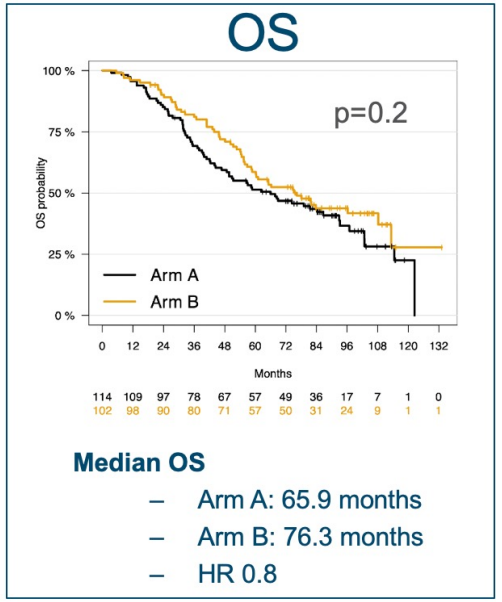
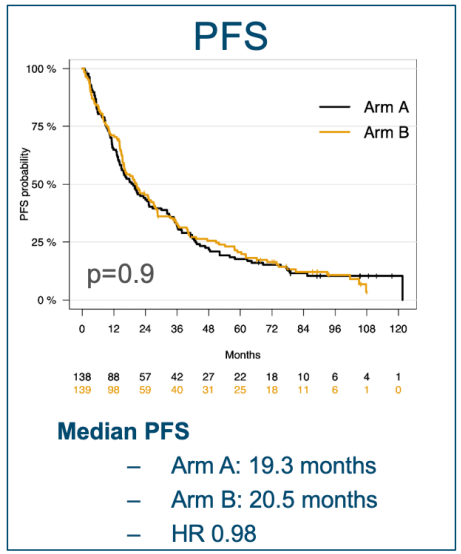


Median OS

- Arm A: 65.9 months
- Arm B: 76.3 months
- HR 0.8

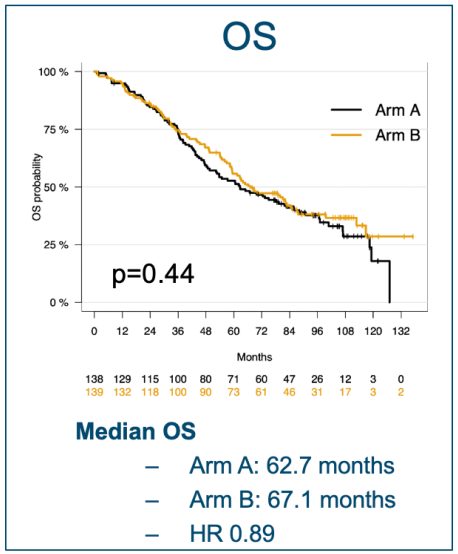
In multivariate analysis, noPFS/OS difference in any of the subgroups analyzed (ISS, FISH, duration of 1° remission

Per protocol



Median PFS

- Arm A: 19.3 months
- Arm B: 20.5 months
- HR 0.98



Median OS

- Arm A: 62.7 months
- Arm B: 67.1 months
- HR 0.89

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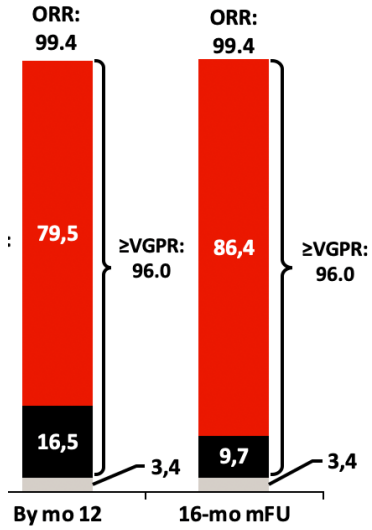
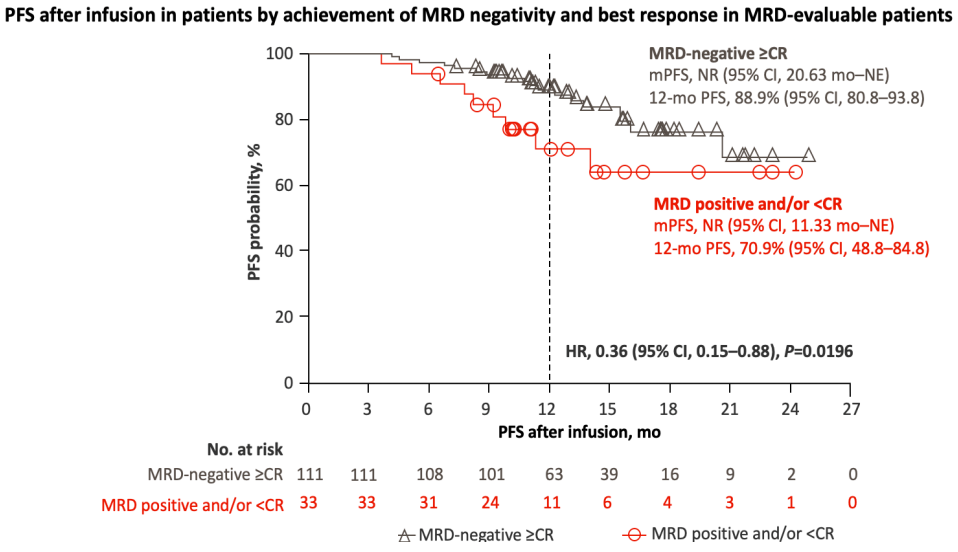
Advancing anti-BCMA CAR T-cell to early lines

CARTITUDE-4: 1-3 prior lines, lenalidomide-refractory
Per protocol analysis





MRD neg 10^{-5}:
88%*

* Among evaluable patients

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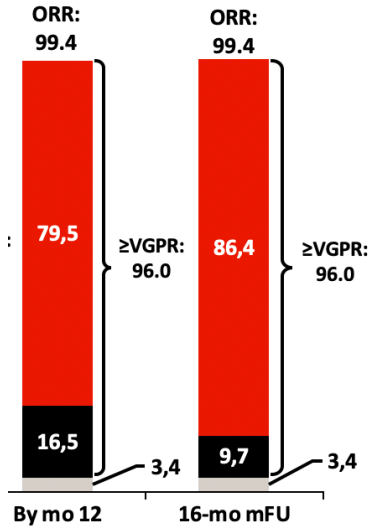
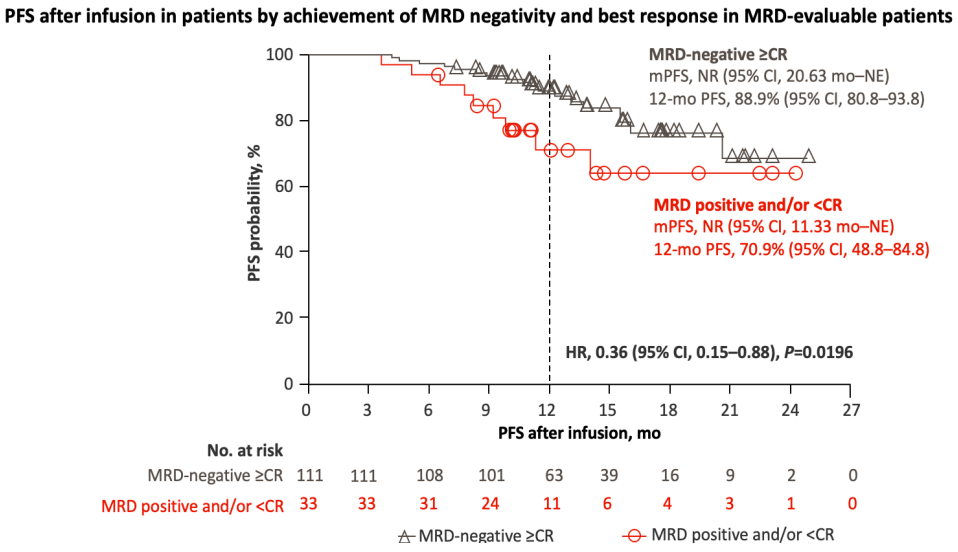
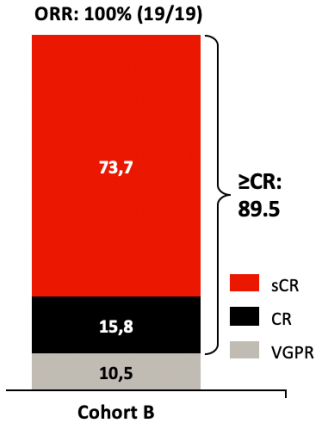


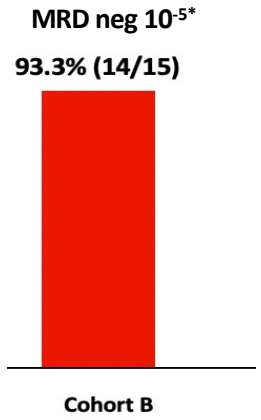


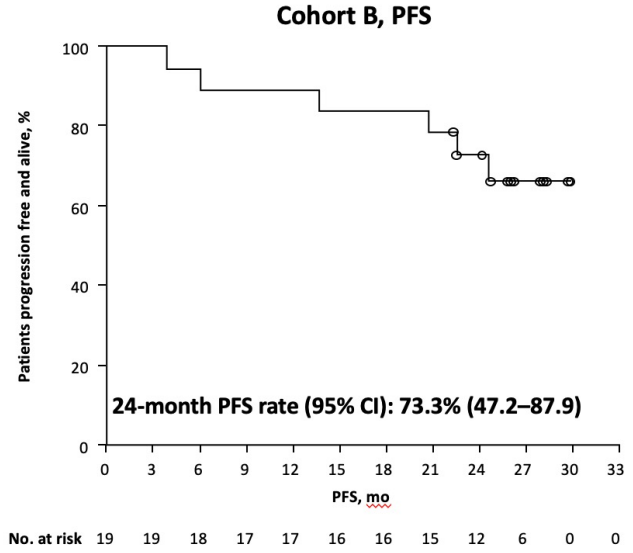
MRD neg 10^{-5}: 88%*

* Among evaluable patients

CARTITUDE-2: Early relapse
PD ≤12 months after ASCT or start of therapy





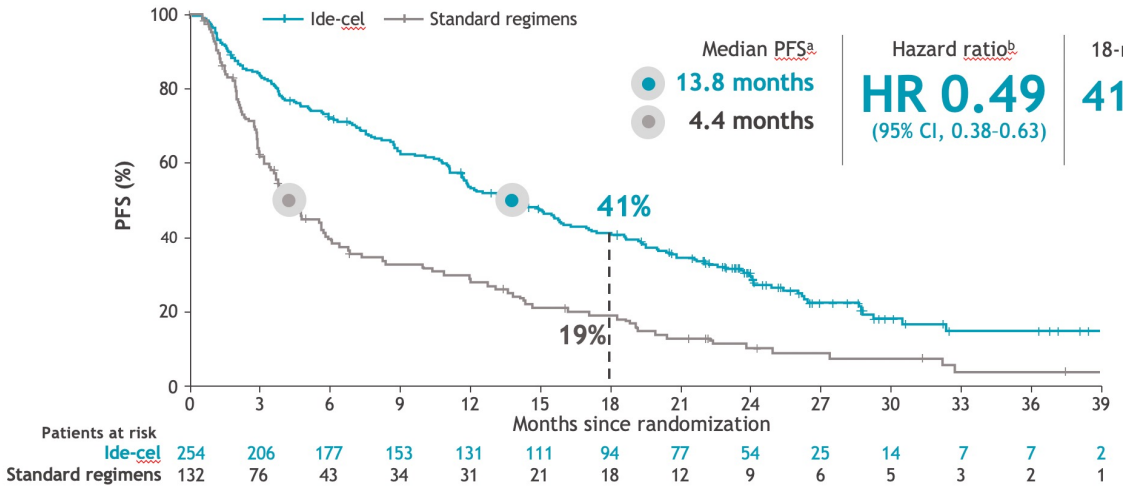


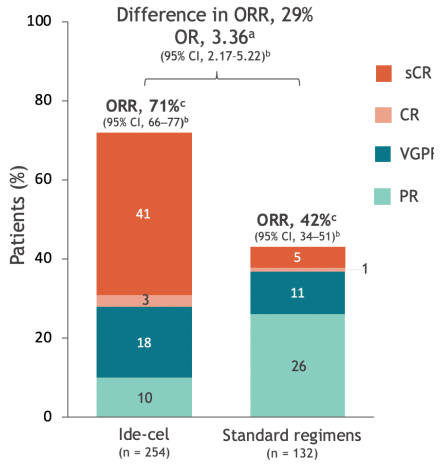
24-month PFS and OS rates: 73% and 84%

M Hasib Sidiqi, ASH2023, Hillengass J. Et al. ASH 2023;

Advancing anti-BCMA CAR T-cell to early lines

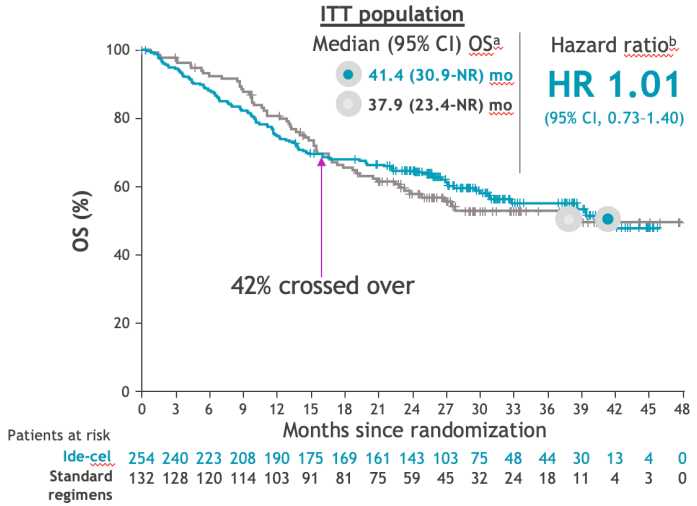
Progression-free survival

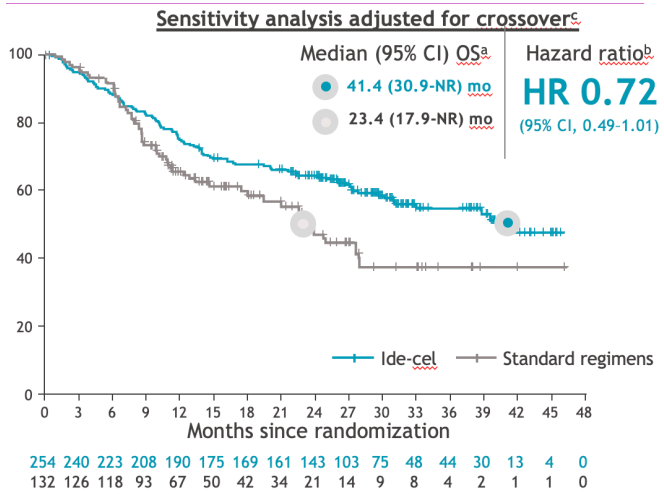




Secondary endpoint	Ide-cel (n = 254)	Standard regimens (n = 132)
CR rate (95 % CI), %[d]	44 (38-50)	5 (2-9)
MRD-negative CR rate, n/N (%) (95% CI)[e]	57/163 (35) (28-42)	1/54 (2) (0-5)
Median (95% CI) DOR, months	16.6 (12.1-19.6)	9.7 (5.5-16.1)
Median PFS2, months	23.5	16.7
HR (95% CI)	0.79 (0.60-1.04)	

Overall survival: ITT and by cross-over

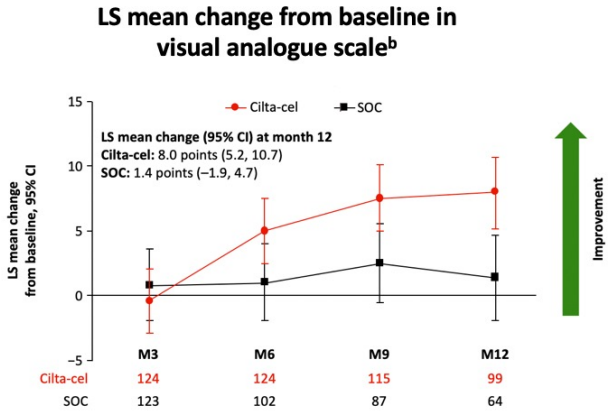


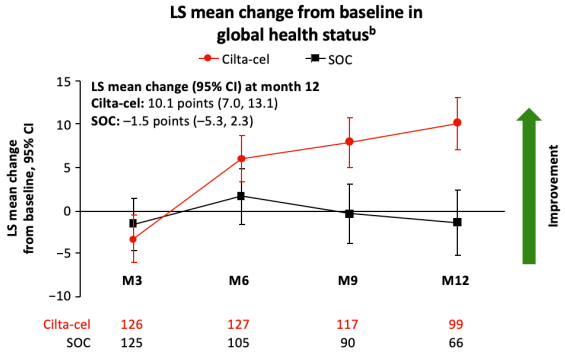


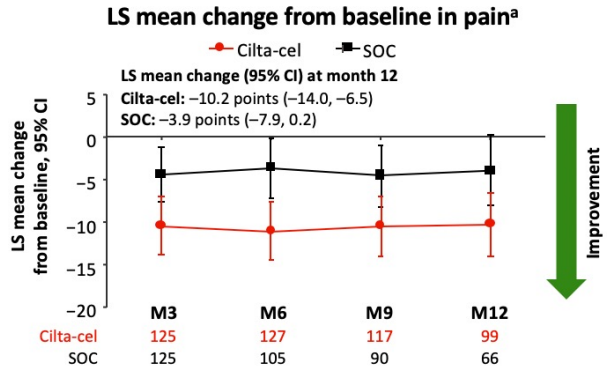
Rodriguez-Otero P. et al ASH 2023

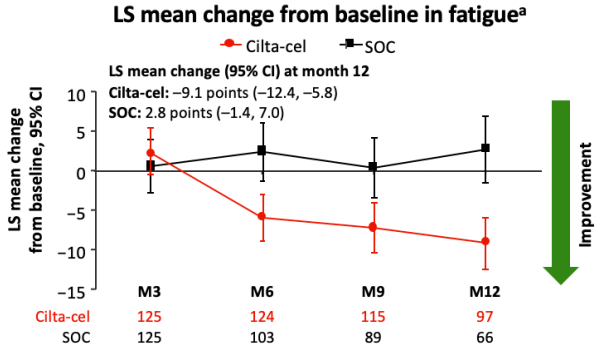
Anti-BCMA CAR T-cell therapy improves QoL in RRMM

CARTITUDE-4: ciltacel vs SoC
1-3 prior lines







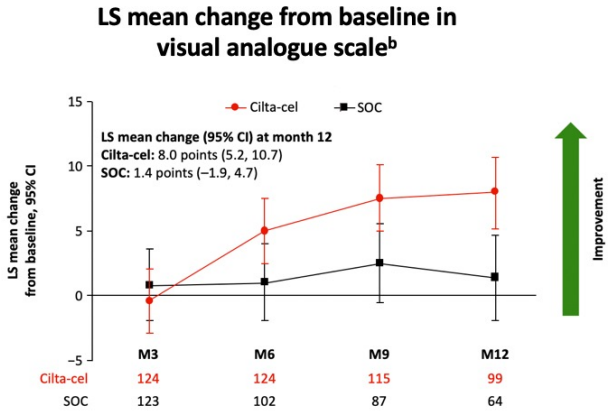


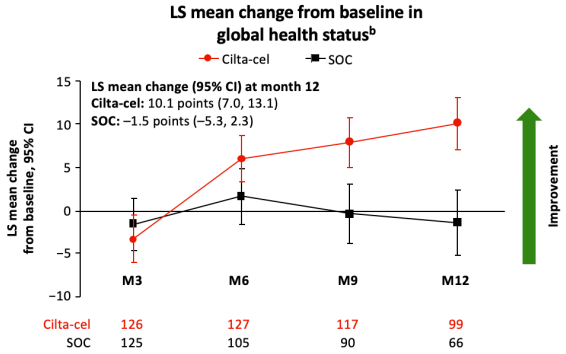
Mina R. et al ASH 2023

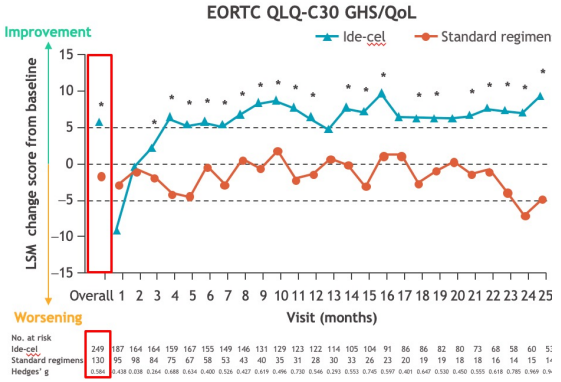
Anti-BCMA CAR T-cell therapy improves QoL in RRMM

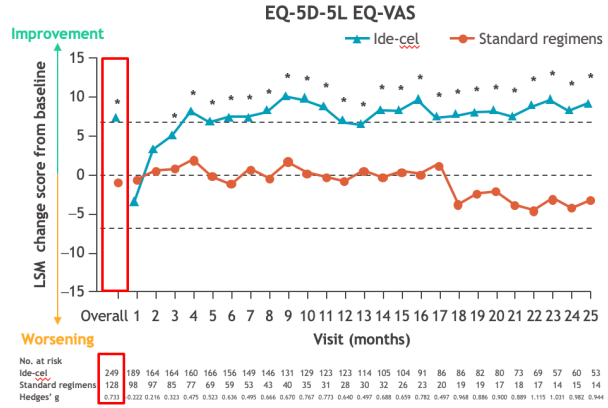
CARTITUDE-4: ciltacel vs SoC
1-3 prior lines

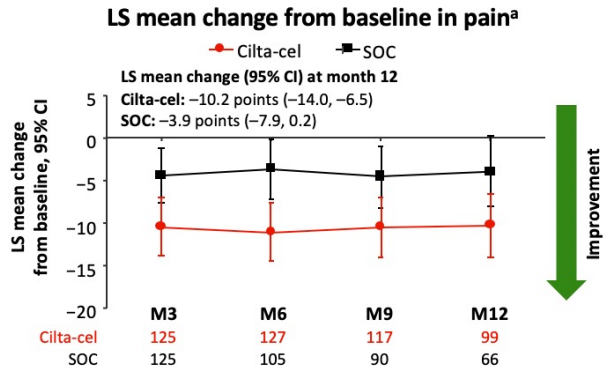
KarMMa-3: Ide-cel vs SoC
2-4 prior lines of therapy

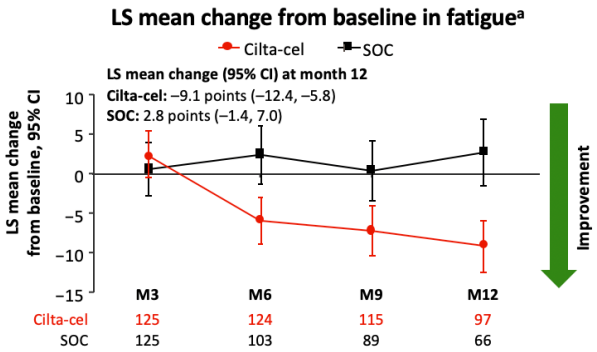


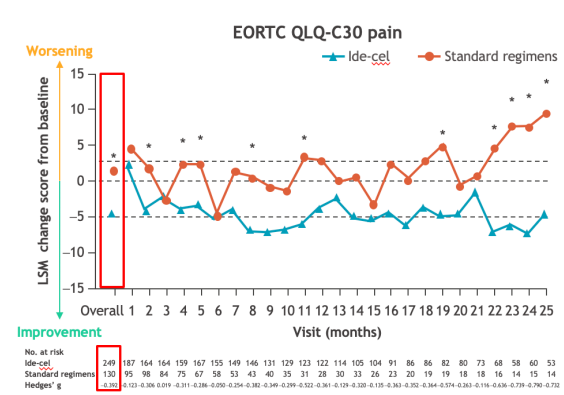


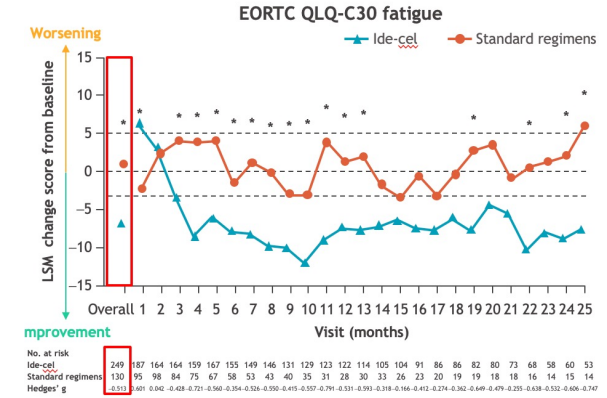












Mina R. et al ASH 2023

Delforge M. et al ASH 2023

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Pomalidomide and dexamethasone with or without cyclophosphamide in RRMM patients

Multicenter, phase 3, randomized study

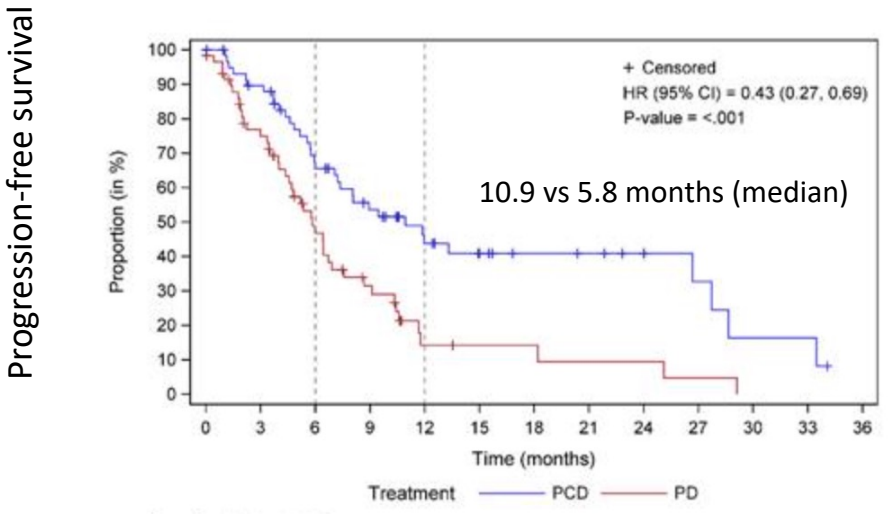
Len and Pi exposed RRMM patients

- **Pom-dex (n=60)**
- **Pom-dex + cyclo (400 Q1W x 3 w) (n=62)**

Table 1. Baseline Patient Characteristics

Characteristic N (%) / median [range]		PCD (N=62)	PD (N=60)
Age		68.5 [47-88]	67.2 [48-85]
Male gender		35 (56.5)	29 (48.3)
ISS stage I or II		45 (72.6)	45 (75.0)
ECOG performance score 0 or 1		55 (88.7)	50 (83.3)
Number of lines of prior treatment		3.0 [1-6]	3.0 [1-6]
Previously received therapies			
(i)	Bortezomib	47 (75.8)	46 (76.7)
(ii)	Carfilzomib	24 (38.7)	18 (30)
(iii)	Ixazomib	7 (11.3)	8 (13.3)
(iv)	Lenalidomide	61 (98.4)	60 (100)
(v)	Thalidomide	34 (54.8)	28 (46.7)
(vi)	Cyclophosphamide	29 (46.8)	19 (31.7)
Prior autologous transplant		27 (43.5)	24 (40)

Overall response rate, 55% vs 32%
Median DOR, 12 vs 5.7 months



Treatment-emergent AEs: 82% vs 82% (neutropenia, anemia and infections)
Death rate, 2% vs 3%

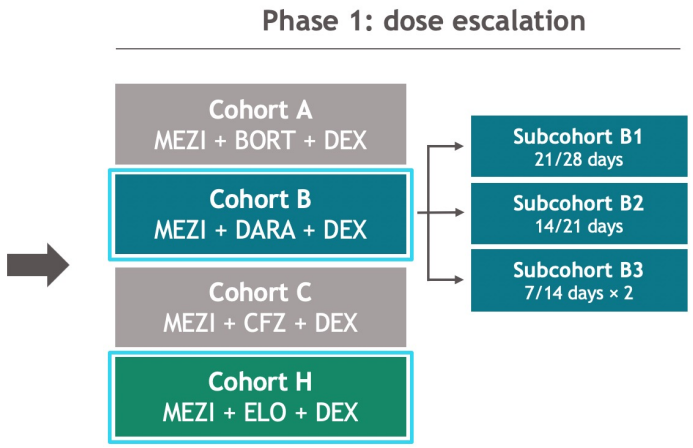
Song Y. Et al, ASH abstract 2023

Mezigdomide + dex and dara or elo RRMM: CC-92480-MM-002 trial

Mezigdomide is an oral CRBN E3 ligase modulator (CELMoD™) showing in preclinical studies rapid degradation of target proteins and apoptosis in MM cell lines and synergy with DEX, PIs, and anti-CD38 mAb

Key eligibility criteria

- Documented diagnosis of MM and measurable disease
- 2-4 prior regimens
- Documented disease progression during or after the last anti-myeloma therapy
- MR or better to ≥ 1 prior regimen

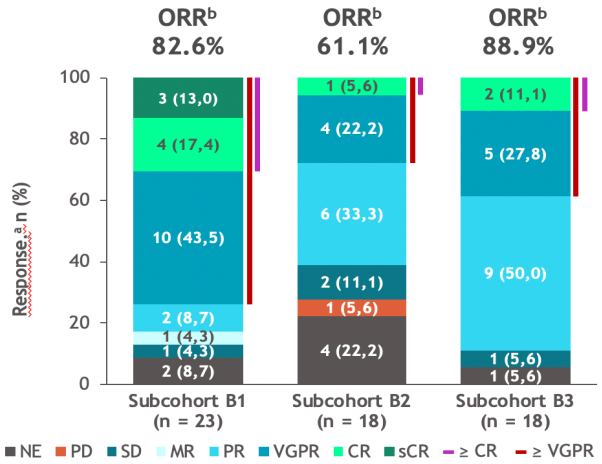


Characteristic[a]	Cohort B MeziDd (N = 59)	Cohort H MeziEd (N = 20)
Prior therapies, median (range), n	3 (2–5)	3 (2–5)
Stem cell transplantation, n (%)	8 (13.6)	4 (20.0)
PI, n (%)	58 (98.3)	19 (95.0)
IMiD agent, n (%)	59 (100)	20 (100)
IMiD/CELMoD agent refractory, n (%)	50 (84.7)	16 (80.0)
LEN refractory, n (%)	42 (71.2)	14 (70.0)
POM refractory, n (%)	18 (30.5)	6 (30.0)
IBER refractory, n (%)	1 (1.7)	0
PI refractory, n (%)	37 (62.7)	9 (45.0)
BORT refractory, n (%)	18 (30.5)	5 (25.0)
IXA refractory, n (%)	15 (25.4)	1 (5.0)
CFZ refractory, n (%)	6 (10.2)	6 (30.0)
Prior anti-CD38 mAb, n (%)	5 (8.5)	17 (85.0)
Anti-CD38 mAb refractory, n (%)	0	16 (80.0)
DARA refractory, n (%)	0	16 (80.0)
ISA refractory, n (%)	0	1 (5.0)
Triple-class refractory,[b] n (%)	0	6 (30.0)

Richardson PG. et al. ASH23 abstract

Mezigdomide-based combinations in RRMM: efficacy and safety results

MeziDaradex

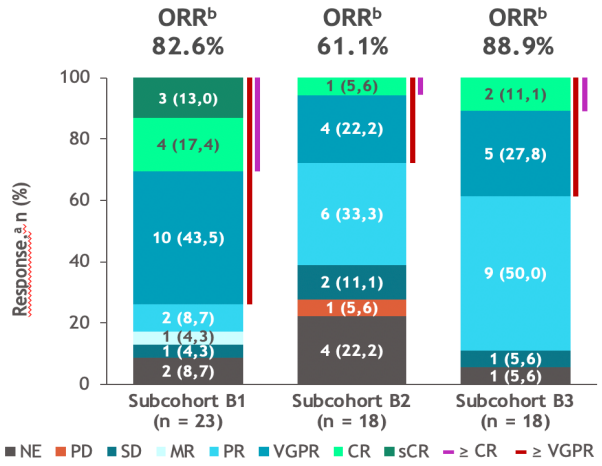


Most common (≥ 25% all grade) TEAEs and events of interest,[a] n (%)	Cohort B MeziDd Subcohort B1 21/28 days (n = 23)		Subcohort B2 14/21 days (n = 18)		Subcohort B3 7/14 days × 2 (n = 18)	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Neutropenia	19 (82.6)	16 (69.6)	11 (61.1)	11 (61.1)	12 (66.7)	11 (61.1)
Febrile neutropenia	1 (4.3)	1 (4.3)	0	0	0	0
Anemia	12 (52.2)	6 (26.1)	3 (16.7)	0	2 (11.1)	0
Thrombocytopenia	9 (39.1)	3 (13.0)	3 (16.7)	0	5 (27.8)	2 (11.1)
Non-hematologic TEAEs						
Fatigue	**11 (47.8)**	1 (4.3)	**5 (27.8)**	0	3 (16.7)	0
Infections	18 (78.3)	9 (39.1)[c]	7 (38.9)	1 (5.6)[d]	12 (66.7)	3 (16.7)[e]

Richardson PG. et al. ASH23 abstract

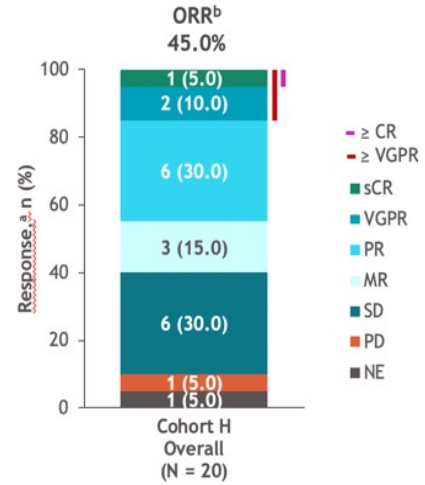
Mezigdomide-based combinations in RRMM: efficacy and safety results

MeziDaradex



Most common (≥ 25% all grade) TEAEs and events of interest,[a] n (%)	Cohort B MeziDd Subcohort B1 21/28 days (n = 23) All grade	Subcohort B1 21/28 days (n = 23) Grade 3/4	Subcohort B2 14/21 days (n = 18) All grade	Subcohort B2 14/21 days (n = 18) Grade 3/4	Subcohort B3 7/14 days × 2 (n = 18) All grade	Subcohort B3 7/14 days × 2 (n = 18) Grade 3/4
Neutropenia	19 (82.6)	16 (69.6)	11 (61.1)	11 (61.1)	12 (66.7)	11 (61.1)
Febrile neutropenia	1 (4.3)	1 (4.3)	0	0	0	0
Anemia	12 (52.2)	6 (26.1)	3 (16.7)	0	2 (11.1)	0
Thrombocytopenia	9 (39.1)	3 (13.0)	3 (16.7)	0	5 (27.8)	2 (11.1)
Non-hematologic TEAEs						
Fatigue	**11 (47.8)**	1 (4.3)	**5 (27.8)**	0	3 (16.7)	0
Infections	18 (78.3)	9 (39.1)[c]	7 (38.9)	1 (5.6)[d]	12 (66.7)	3 (16.7)[e]

MeziElodex



Most common (≥ 25% all grade) TEAEs and events of interest,[a] n (%)	Cohort H MeziEd (N = 20) All grade	Cohort H MeziEd (N = 20) Grade 3/4
Hematologic TEAEs		
Neutropenia	10 (50.0)	8 (40.0)
Febrile neutropenia	1 (5.0)	**1 (5.0)**
Thrombocytopenia	7 (35.0)	2 (10.0)
Non-hematologic TEAEs		
Diarrhea	8 (40.0)	0
Fatigue	7 (35.0)	1 (5.0)
Infections	13 (65.0)	7 (35.0)[c]

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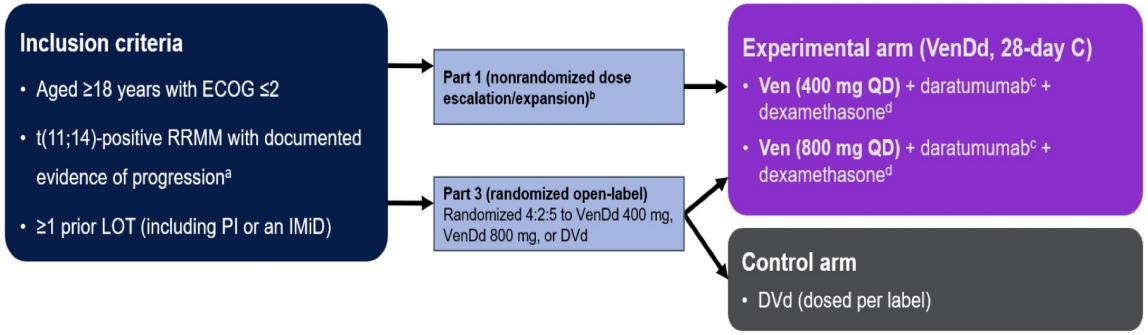
Agenda

- Is there a role for salvage autologous stem cell transplant?
- Will CAR T-cell therapy become the standard salvage option at 1° relapse?
- How can we effectively bridge patients from 1° relapse to T-cell redirecting therapy in late lines?
- Patients with t(11;14): is it time for target therapy?

Daratumumab, venetoclax and dexamethasone vs. daratumumab, bortezomib and dexamethasone in t(11;14) RRMM patients



	VenDd (n=55)	DVd (n=26)
Age, median (range), years	62.0 (31–88)	69.5 (51–80)
Prior LOT		
1	29 (52.7)	10 (38.5)
2	9 (16.4)	13 (50.0)
3	8 (14.5)	2 (7.7)
≥3	9 (16.4)	1 (3.8)
Prior CD38 MAb	1 (1.8)	1 (3.8)
Len-refractory	41 (74.5)	20 (76.9)
Bort-refractory	16 (29.1)	3 (11.5)
ISS stage		
Stage 1	19 (34.5)	6 (23.1)
Stage 2	17 (30.9)	7 (26.9)
Stage 3	9 (16.4)	5 (19.2)
NE	7 (12.7)	8 (30.8)
Unknown	3 (5.5)	0
ECOG status		
Grade 1	24 (43.6)	16 (61.5)
Grade 2	1 (1.8)	2 (7.7)
High-risk cytogenetics		
Del(17p)	6 (10.9)	6 (23.1)
Gain(1q) (≥3 copies)	14 (25.5)	5 (19.2)

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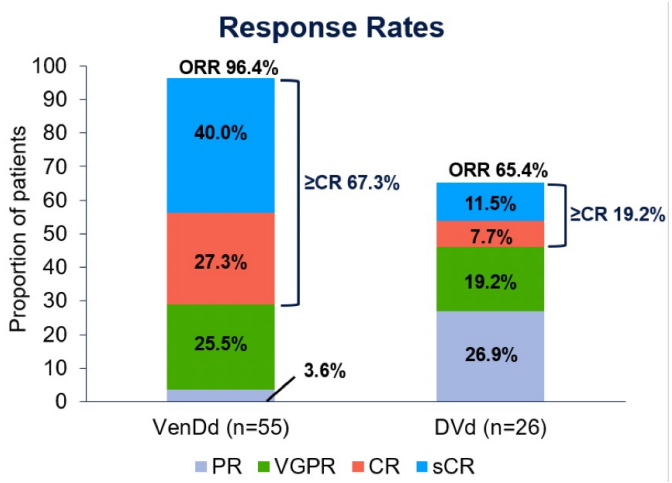
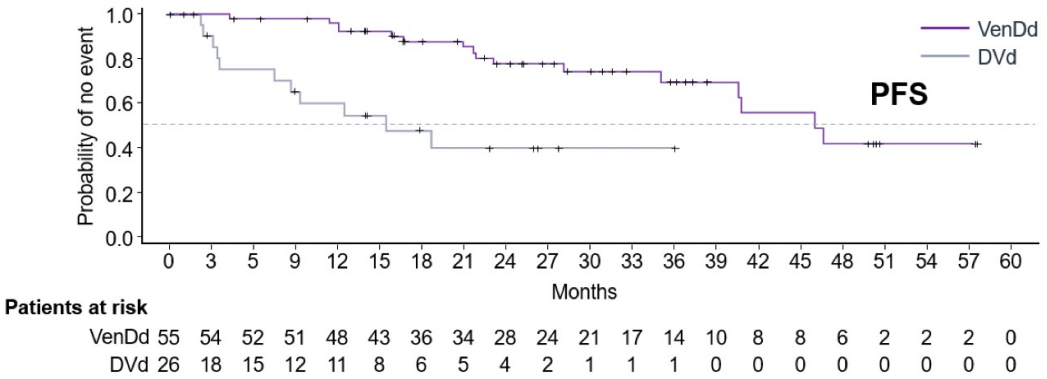
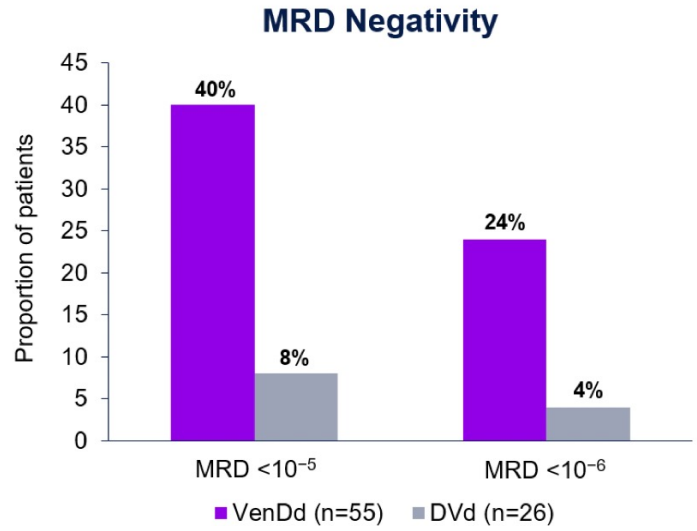
Venetoclax, daratumumab and dexamethasone vs. daratumumab, bortezomib and dexamethasone in t(11;14) RRMM patients



Median progression-free survival:
VenDd 46 vs DVd 15 months





	VenDd (n=55)	DVd (n=24)[a]
Treatment exposure (months)		
Duration, mean (SD)	26.3 (14.4)	11.9 (10.3)
Duration, median (range)	24.8 (1.2–57.8)	9.6 (0.5–35.8)
All grade AE	54 (98.2)	23 (95.8)
Grade ≥3 AE	43 (78.2)	18 (75.0)
All grade neutropenia	9 (16.4)	1 (4.2)
Grade 3/4 neutropenia	7 (12.7)	0
All grade thrombocytopenia	4 (7.3)	8 (33.3)
Grade 3/4 thrombocytopenia	2 (3.6)	6 (25.0)
Any SAE	28 (50.9)	7 (29.2)
All deaths	8 (14.5)	5 (20.8)
SAE resulting in death[b]	1 (1.8)	0

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Conclusions

Is there a role for **salvage** autologous stem cell **transplant**?	Salvage ASCT is becoming marginal in the era of triplets and immunotherapy
Will **CAR T-cell therapy** become the standard salvage option at 1° relapse?	BCMA CAR T-cells: new SoC at 1° relapse; high efficacy and improved QoL as compared to SoC triplets
How can we effectively **bridge** patients from 1° relapse to **T-cell redirecting** therapy in late lines?	Pomalidomide is the backbone for standard salvage triplets MEZI: safe and potentially more effective (ORR: MeziDaradex 78% vs DPd 68%; MeziElodex 45% vs EloPd 32%)
Patients with **t(11;14)**: is it time for **target therapy**?	Venetoclax confirmed to be effective in RRMM with t(11;14): high MRD 10^5 neg rates (40%) and median PFS (46 months): third time's a charm?

ACKNOWLEDGEMENTS

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