9:35–10:20 AM

Frontline Myeloma

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THE 2nd ANNUAL HemOnc Pulse LIVE | AUSTIN 2025

Presenter

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UC San Diego Health

Updates in Newly Diagnosed Multiple Myeloma

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Disclosures

- Consultancy/Honoraria: AstraZeneca, BMS, Janssen, Pfizer, Karyopharm, Genentech, Kite
- Research Funding: AstraZeneca, BMS, Janssen, Pfizer, Kite, Poseida

Goals of Induction Therapy

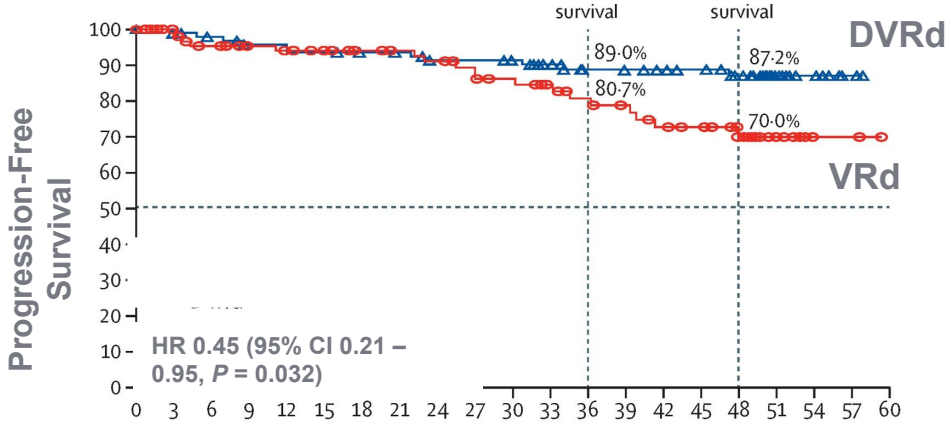
- High rate of response (at least VGPR, MRD neg)
- Achieve rapid disease control
- Minimal Toxicity
- Adequate stem cell harvest

Fit Patients and Upfront Transplant

CD38 mAb / IMiD / PI Quadruplets + Upfront Autologous Stem Cell Transplantation in Newly Diagnosed Myeloma

Randomized phase II (GRIFFIN) and phase III (PERSEUS) studies of VRd ± daratumumab (4 cycles induction, 2 cycles post-transplant consolidation) □ ASCT □ lenalidomide ± daratumumab maintenance (GRIFFIN: 2 years of daratumumab maintenance; PERSEUS: 2 years of daratumumab maintenance if CR and MRD- for ≥1 year)

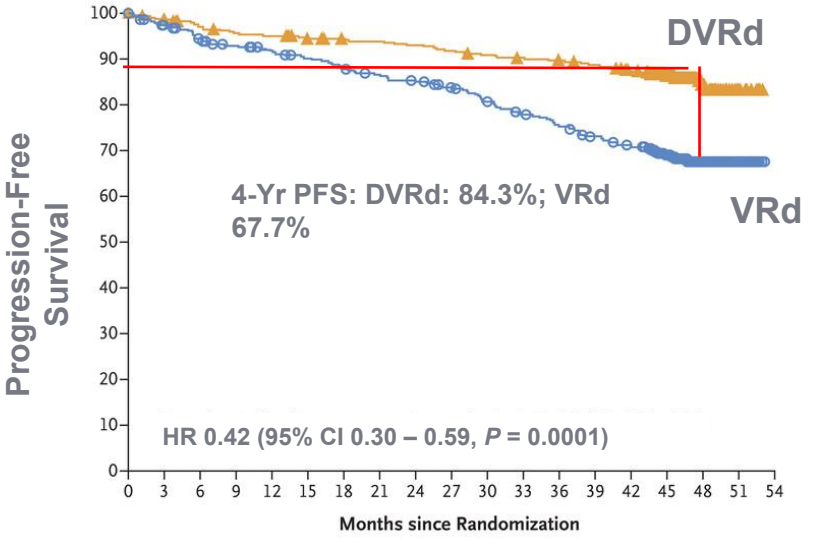
GRIFFIN



Number at risk (number censored)

RVd	103	93	77	72	70	68	63	61	59	53	51	46	42	39	35	33	25	12	3	3	0
	(0)	(9)	(22)	(27)	(28)	(30)	(35)	(37)	(37)	(40)	(42)	(46)	(48)	(50)	(51)	(53)	(60)	(73)	(82)	(82)	(85)
D-RVd	104	98	94	90	90	89	86	85	81	81	79	68	59	58	56	54	45	23	12	3	0
	(0)	(5)	(8)	(10)	(10)	(10)	(12)	(13)	(15)	(15)	(17)	(27)	(35)	(36)	(38)	(40)	(48)	(70)	(81)	(90)	(93)

PERSEUS



No. at Risk

D-VRd	355	345	335	329	327	322	318	316	313	309	305	302	299	295	286	226	90	11	0		
VRd	354	335	321	311	304	297	291	283	278	270	258	247	238	228	219	175	67	13	0		

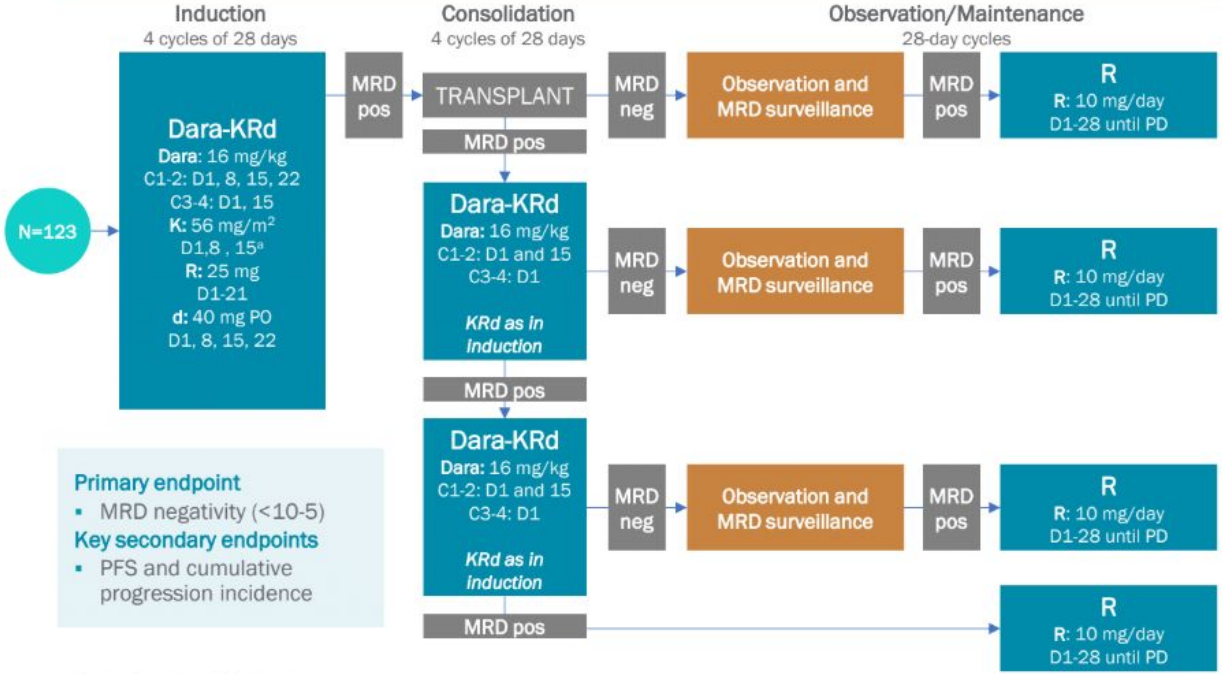
Sborov D et al. Lancet Haematol 2023;10:e825-e837. Sonneveld P et al. New Engl J Med 2024;390:132-147

MASTER: Dara-KRd to R as MRD-Guided Therapy in Transplant-Eligible NDMM

Study Design and Patients

Key Eligibility Criteria

- Transplant-eligible NDMM; aged ≥18 years; ECOG PS 0-2



Primary endpoint

- MRD negativity (<10-5)

Key secondary endpoints

- PFS and cumulative progression incidence

Patient Characteristics		Dara-KRd (N=123)
Median age (IQR), years		61 (55-68)
ECOG PS, n (%)	0-1	99 (80)
	2	24 (20)
ISS stage, n (%)	I	48 (39)
	II	46 (37)
	III	29 (24)
Cytogenetic abnormality, n (%)	Hyperdiploidy	51 (41)
	del(13q)	57 (46)
	Gain or amplification of 1q	44 (36)
	del(1p)	12 (10)
	t(11;14)	21 (17)
	t(4;14)	21 (17)
	t(14;16)	6 (5)
	del(17p)	26 (21)
MRD trackable by clonoSEQ, n (%)		118 (96)

[a] Omitted D1; 20 mg/m² D8 on C1.

Costa LJ, et al. Lancet Haematol. 2023;10(11):e890-e901

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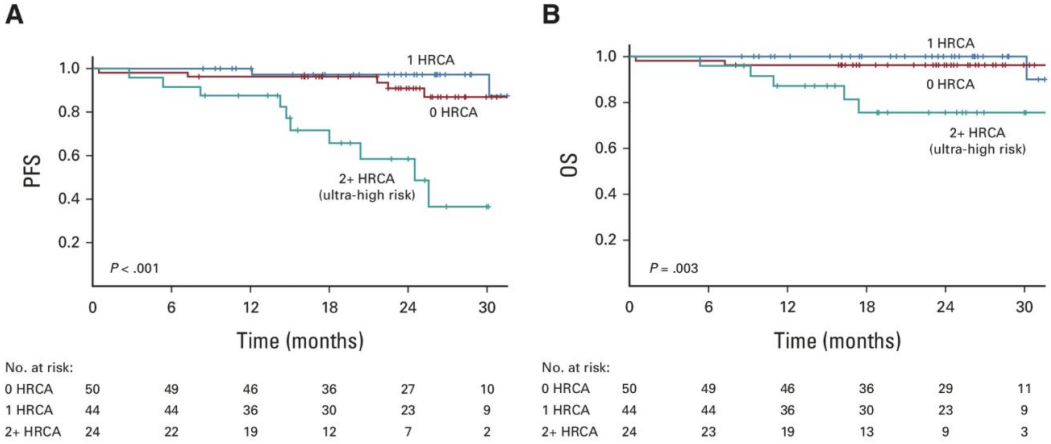
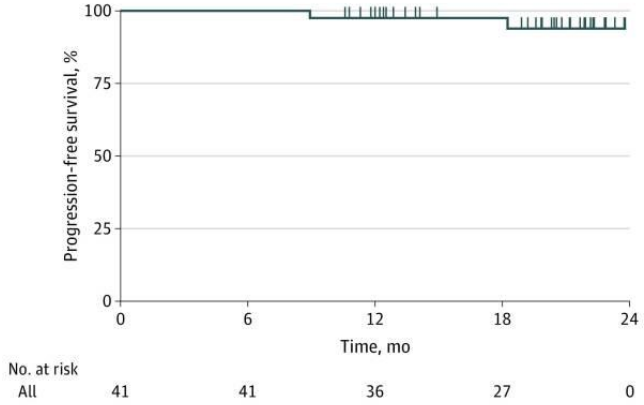
Dara-KRd Induction

MASTER



MANHATTAN



- Single Arm Trials of DKRd induction
- MRD negativity as primary endpoints
- Can carfilzomib-based quads overcome HRCA?

Summary of Data in Transplant-Eligible NDMM

	PERSEUS[1]	GMMG-HD7[2]	GRIFFIN[3,4]	MASTER[5]	GMMG-CONCEPT[6]	IsKia[7]
Induction Maintenance	Dara-RVd vs RVd Dara-R vs R	Isa-RVd vs RVd Isa-R vs R	Dara-RVd vs RVd Dara-R vs R	Dara-KRd R/MRD surveillance	Isa-KRd Isa-KR	Isa-KRd vs KRd R
Total N	355 vs 354	331 vs 329	104 vs 103	123	99 (transplant eligible, high-risk disease)	151 vs 151
Median follow-up	47.5 mo	NA	49.6 mo	42.2 mo	44 mo	21 mo
≥VGPR[a] ≥CR[a]	NA 88% vs 70%	83% vs 69% 44% vs 34%	90% vs 73% 52% vs 42%	NA 72%	91% 73%	94% vs 94% 74% vs 72%
MRD-neg 10^{-5} [a]	75% vs 48%	66% vs 48%	50% vs 20%	81%	68%	77% vs 67%
PFS[a]	4 year: 84% vs 68%	NA	4 year: 87% vs 70%	NA	3 year: 69%	1 year: 95% vs 95%

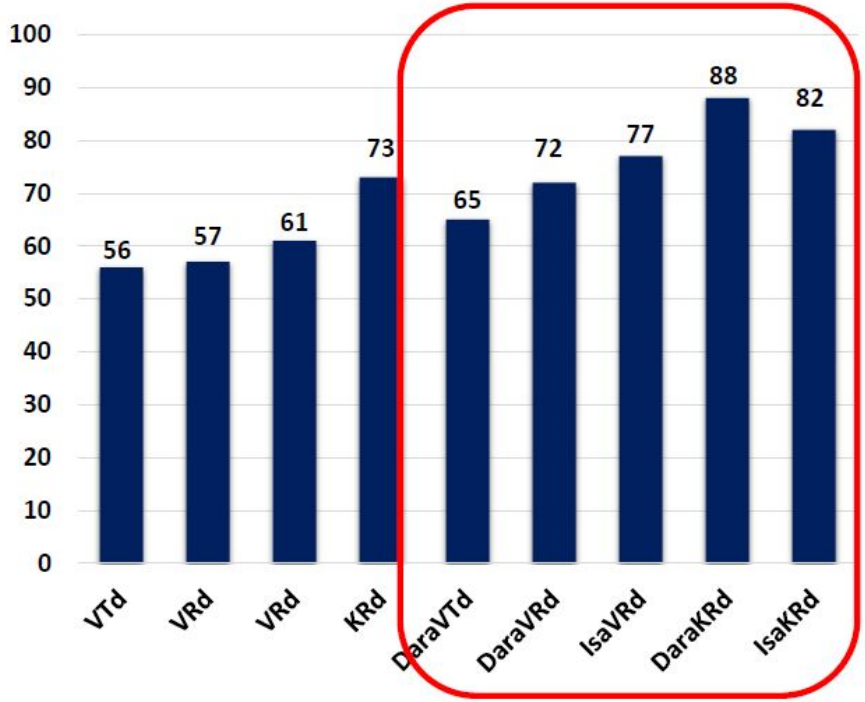
No direct comparisons can be made without head-to-head studies.

[a] Post-consolidation in transplant-eligible patients.

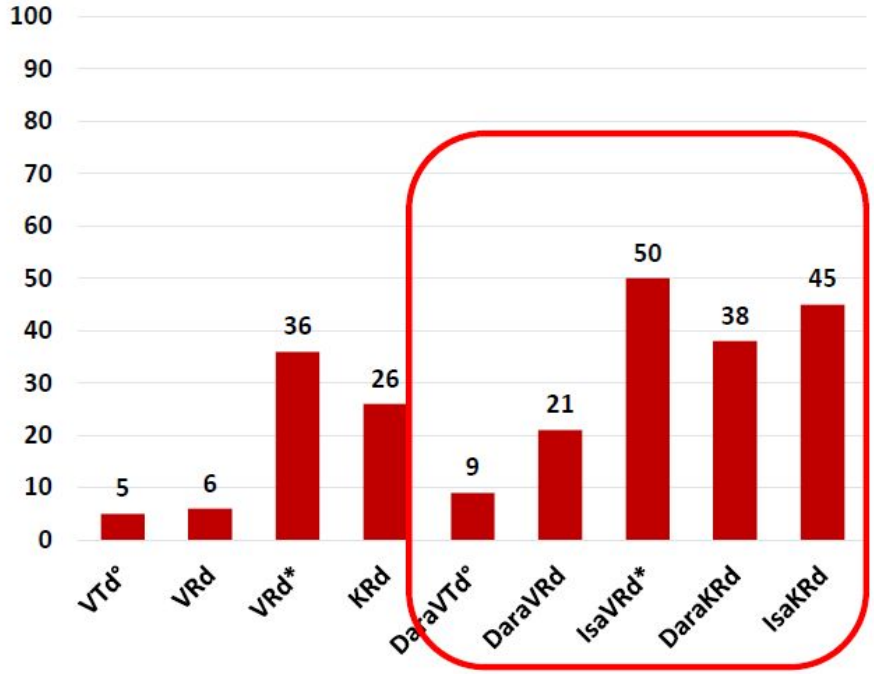
1. Sonneveld P, et al. ASH 2023. Abstract LBA-1. **2.** Raab MS, et al. EHA 2024. Abstract S202. **3.** Voorhees PM, et al. *Lancet Haematol*. 2023;10(10):e825-e837. **4.** Sborov DW, et al. IMS 2022. Abstract OAB-057. **5.** Costa LJ, et al. *Lancet Haematol*. 2023;10(11):e890-e901. **6.** Leypoldt LB, et al. *J Clin Oncol*. 2024;42(1):26-37. **7.** Gay F, et al. ASH 2023. Abstract 4.

Response and MRD negativity post induction

Post-induction ≥ VGPR rates



Post-induction MRD negativity rates

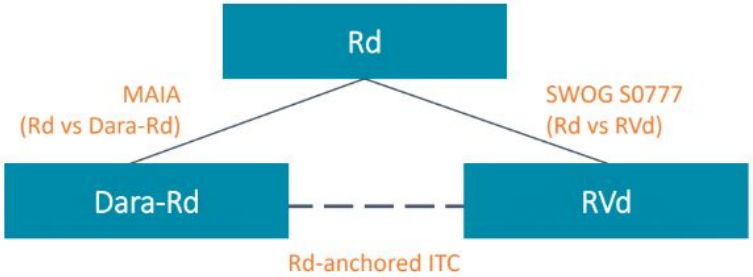


Avet Loiseau H, et al. Blood 2021;138 (Suppl 1):82 (oral presentation); Voorhees et al Blood 2020, Goldschmidt H et al Lancet haem 2022; Gay F et al ASH 2023 and manuscript under review; Costa L et al JCO 2022; Abbreviations: MRD measurable residual disease; VGPR: very good partial response; V: Bortezomib; R: Lenalidomide; d: dexamethasone; K: Carfilzomib; Dara: Daratumumab; Isa: Isatuximab, T: talidomide. All MRD evaluation by next generation sequencing, except * that was evaluated byy next generation flow.°MRD plus CR.

Transplant Ineligible or Deferred

SWOG S0777 vs MAIA[1,2]

Adjusted Indirect Treatment Comparison of PFS



Study Design

- Harmonized inclusion criteria (NDMM, aged ≥65 years, ECOG PS ≤2) were applied to both trial populations[a]
- Propensity score reweighting was used to balance the 2 study populations on key baseline patient characteristics[b,c]
- After alignment of inclusion criteria and PS reweighting, PFS HRs within MAIA and SWOG S0777 trials were used to conduct an indirect inference of PFS for Dara-Rd vs RVd

	SWOG 0777 VRd vs Rd	MAIA Dara-Rd vs Rd
Total N	198	727
Median age	72.67 years	72.70 years
PFS	41 vs 29 mo HR=0.88 (95% CI, 0.63-1.23) *P*=0.46	62 vs 34 mo HR=0.53 (95% CI, 0.41-0.68) *P*<0.0001
ITC: Dara-RD vs RVd	HR=0.60 (95% CI, 0.39-0.90) *P*=0.02	

[a] Aged ≥65 years served as a proxy for transplant-ineligible status, as SWOG S0777 enrolled a mixed population of patients without intent for immediate ASCT. [b] Absolute standardized differences were <0.1 for all covariates, indicating good covariate balance. [c] High cytogenetic risk was defined in MAIA and SWOG S0777 as the presence of ≥1 high-risk cytogenetic abnormality (del[17p], t[14;16] or t[4;14]).

1. Durie BGM, et al. ASCO 2023. Abstract 8037. **2**. Durie BGM, et al. *Adv Ther*. 2024;41(5):1923-1937.

CD38 mAb / IMiD / PI Quadruplets in Newly-Diagnosed Myeloma: Transplant Deferred and Ineligible

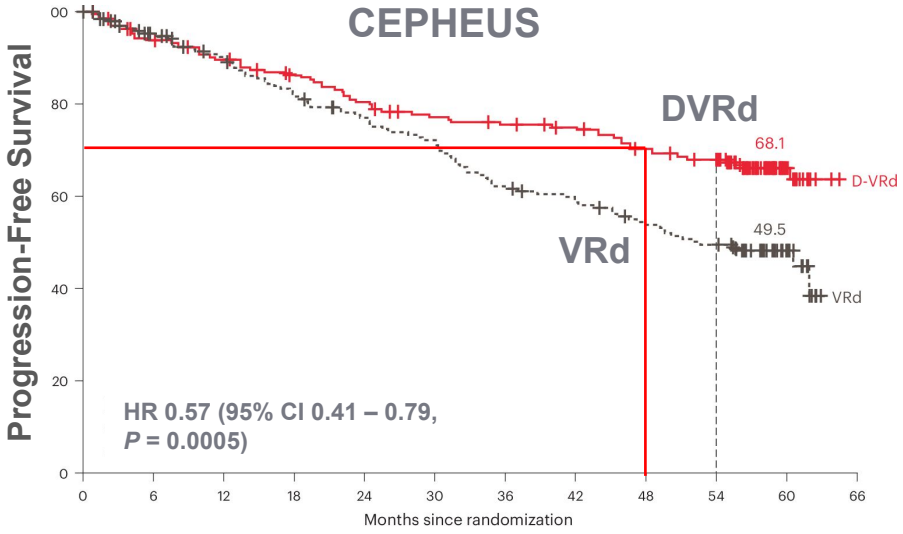
Randomized phase III studies of VRd ± CD38 mAbs (CEPHEUS: Daratumumab; IMROZ: Isatuximab)

Key Eligibility Criteria
- ECOG PS 0 – 2; Frailty index <2
- Transplant ineligible: Age 70 – 80, <70 with comorbidities
- Transplant deferred allowed

DVRd vs VRD
- Median age: 70 (42 – 79) vs 70 (31 – 80)
- ≥70 y/o: 55.3% vs 55.6%
- Transplant deferred: 26.9% vs 26.8%

Key Eligibility Criteria
- ECOG PS 0 – 2, age ≤80
- Transplant ineligible: Age ≥65 or comorbidities precluding ASCT

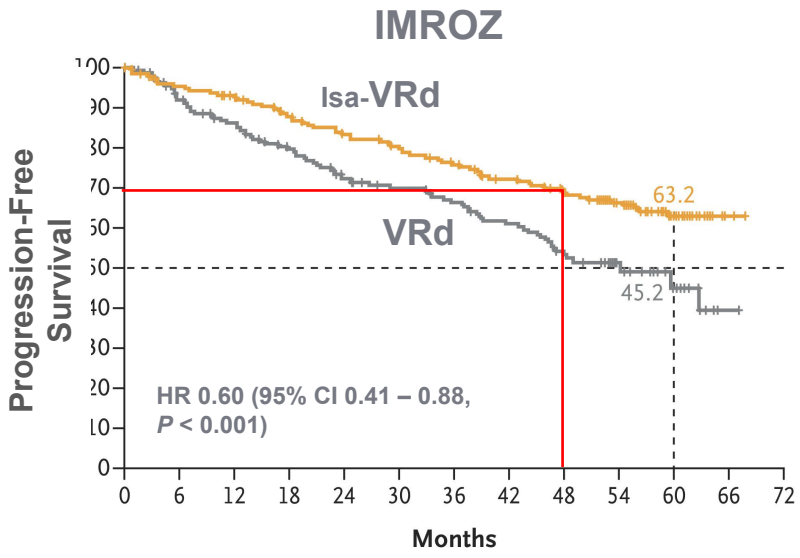
Isa-VRD vs VRD
- Median age: 72 (60 – 80) vs 72 (55 – 80)
- ≥70 y/o: 69.4% vs 69.1%



No. at risk

D-VRd	197	180	170	160	149	140	136	132	122	115	33	0
VRd	198	174	157	143	131	123	105	98	88	81	21	0

Usmani S et al. Nature Med 2025;ePub ahead of print.



No. at Risk

Isatuximab-VRd	265	243	234	217	201	190	177	164	153	104	43	2	0
VRd alone	181	155	141	121	104	96	89	81	70	51	20	2	0

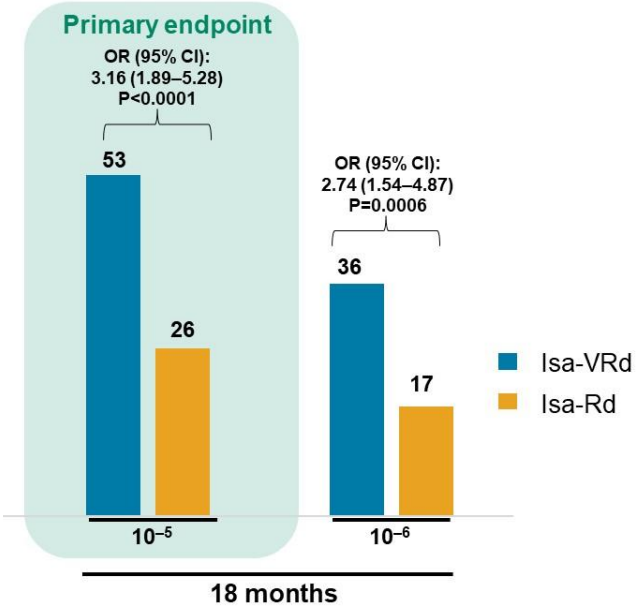
Facon T et al. New Engl J Med 2024;391:1597-1609

CD38 mAb / IMiD / PI Quadruplets in Transplant-Ineligible Patients with Newly-Diagnosed Myeloma: The BENEFIT of Bortezomib

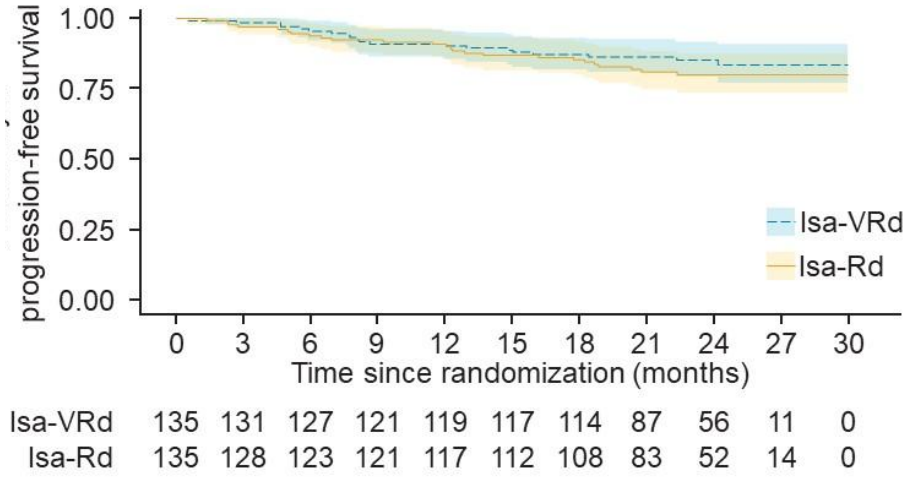
Phase III study of Isa-Rd ± Bortezomib

Study Design: Isa-Rd x 12 cycles □ Isa-R cycles 13+. For the Isa-VRd arm, bortezomib on days 1, 8 and 15 of cycles 1 – 12 and days 1 and 15 of cycles 13 – 18 added.
Key Eligibility Criteria: Deemed not transplant eligible, ages ≥65 – 79 years, frailty score <2, ECOG PS 0 – 2

Measurable Residual Disease



Progression-Free Survival



Estimated 24 months PFS
85.2% (95%CI 79.2–91.7) for Isa-VRd
80.0% (95% CI 73.3–87.4) for Isa-Rd

Leleu X et al. Nat Med 2024;30:2235-2241

Transplant-Ineligible/-Deferred NDMM

		SWOG S0777[1]		MAIA[2-4]		IMROZ[5,6]		CEPHEUS[7]		BENEFIT[8-10]	
		VRd (n=235)	Rd (n=225)	DRd (n=368)	Rd (n=369)	Isa-VRd (n=285)	VRd (n=190)	D-VRd (n=197)	VRd (n=198)	Isa-VRd (n=135)	Isa-Rd (n=135)
	Population	Patients ≥18 y[a] (includes transplant-deferred patients)		Inclusive of frail & older (>80 y) patients		Patients 18-80 y (excludes patients >80 y)		Patients ≥18 y (includes transplant-deferred patients)		Nonfrail patients 65-79 y (excludes frail & ≥80 y)	
	Median follow-up	84 mo		89.3 mo		59.7 mo		58.7 mo		23.5 mo	
EFFICACY	≥CR rate	24.2%	12.1%	51.1%[b]	30.1%[b]	74.7%	64.1%	81.2%	61.6%	58%	31%
EFFICACY	≥CR, MRD-neg (10^{-5}) rate	N/A	N/A	32.1%[b]	11.1%[b]	58.1%	43.6%	60.9%	39.4%	53%	26%
EFFICACY	PFS	41 mo	29 mo	60-mo: 52.1% Median: 61.9 mo[b]	60-mo: 29.6% Median: 34.4 mo[b]	60-mo: 63.2% Median: NR	60-mo: 45.2% Median: 54.3 mo	54-mo: 68.1%	54-mo: 49.5%	24-mo: 85.2% Median: NR	24-mo: 80% Median: NR
EFFICACY	OS	NR	69 mo	60-mo: ~67% Median: 90.3 mo	60-mo: ~54% Median: 64.1 mo	60-mo: 72.3%	60-mo: 66.3%	NR	NR	24-mo: 91.1%	24-mo: 91.5%
SAFETY	Grade 5 AEs	<3%	<2%	6.9%	6.3%	11.0%	5.5%	10.7%[c]	7.7%[c]	Not reported	Not reported
SAFETY	Serious TEAEs	N/A	N/A	62.9%	62.7%	70.7%	67.4%	Not reported	Not reported	34%	35%
SAFETY	Discontinuation due to TRAEs	N/A	N/A	7.1%	25.8%	22.8%	26.0%	Not reported	Not reported	Not reported	Not reported
SAFETY	Infections	19% gr 3/4	14% gr 3/4	42.6% gr 3/4	29.6% gr 3/4	44.9% gr ≥3	38.1% gr ≥3	40.1% gr 3/4	31.8% gr 3/4	35% grade ≥2[d]	40% grade ≥2[d]
SAFETY	Peripheral neuropathy	Gr ≥3 neurologic AEs: 34.6%	Gr ≥3 neurologic AEs: 11.3%	2.5% gr 3/4	0.5% gr 3/4	7.2% gr ≥3	6.1% gr ≥3	8.1% gr 3/4	8.2% gr 3/4	27% grade ≥2	10% grade ≥2

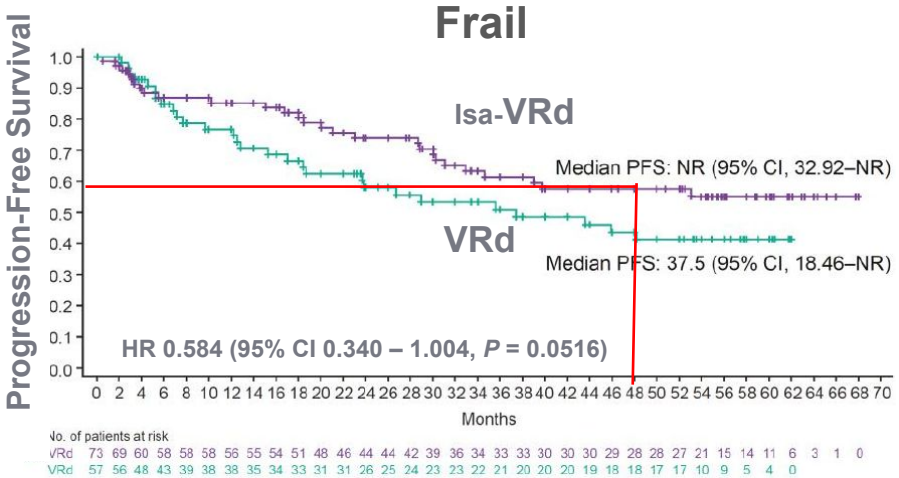
No direct comparisons can be made without head-to-head studies.
[a] Aged ≥65 years served as a proxy for transplant-ineligible status, as SWOG S0777 enrolled a mixed population of patients without intent for immediate ASCT. [b] Median follow-up of 64.5 months. [c] Non-COVID grade 5 events. [d] Infections of the respiratory system. [e] Absolute standardized differences were <0.1 for all covariates, indicating good covariate balance. [f] High cytogenetic risk was defined in MAIA and SWOG S0777 as the presence of ≥1 high-risk cytogenetic abnormality (del[17p], t[14;16] or t[4;14]).

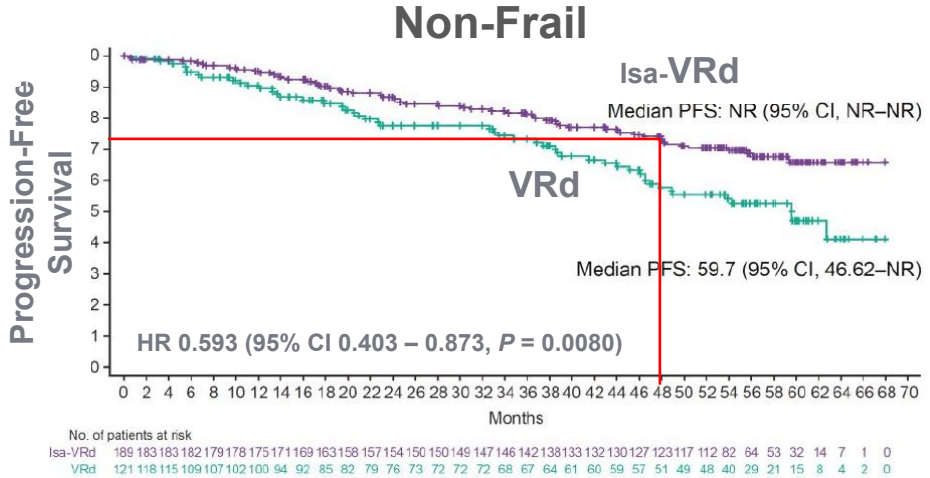
1. Durie BGM, et al. *Blood Cancer J.* 2020;10(5):53. **2.** Facon T, et al. EHA 2024. Abstract P968. **3.** Kumar S, et al. ASH 2022. Poster 4559. **4.** Facon T, et al. *N Engl J Med.* 2019;380(22):2104-2115. **5.** Facon T, et al. N Engl J Med. June 3, 2024. **6.** Facon T, et al. ASCO 2024. Abstract 7500. **7.** Usmani SZ et al. IMS, 2024. Abstract OA63.**8.** Leleu X, et al. *Nat Med.* 2024. **9.** Leleu XP, et al. ASCO 2024. Abstract 7501. **10.** Leleu XP, et al. EHA 2024. Abstract S203.

Frail Patients

CD38 mAb / IMiD / PI Quadruplets in Frail Patients with NDMM: An IMROZ Subset Analysis

- **Key Eligibility Criteria: ECOG PS 0 – 2, transplant ineligible (age 65 – 79 or any age with comorbidities precluding safe transplant)**
- **Modified IMWG Frailty Score: Based on age, modified Charlson Comorbidity Index, ECOG PS.**
- **Frailty score 0 or 1: Non-frail; ≥2: Frail.**
- **29% of patients were deemed frail (Isa-VRd 28%; VRd 32%)**
- **Frail group enriched for patients with higher ECOG PS and ISS stage**





- **OS worse in frail vs non-frail patients**
- **No difference in OS between Isa-VRD vs VRd arms for frail (HR 0.826, 95% CI 0.490 – 1.392, *P* = 0.4720) and non-frail (HR 0.734, 95% CI 0.453 – 1.188, *P* = 0.2076) patients**

Manier S et al. IMS 2024.

CD38 mAb / IMiD / PI Quadruplets in Frail Patients with NDMM: An IMROZ Subset Analysis

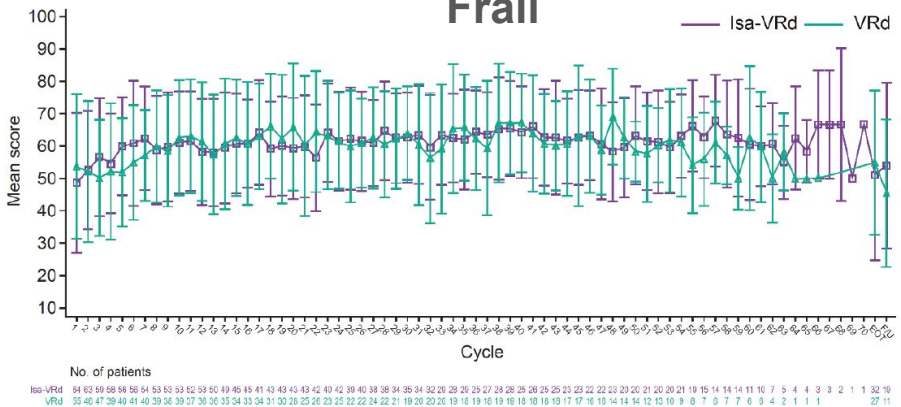
Median duration of treatment (Isa-VRD vs RVd)
- Frail: 31.5 vs 23.7 mos
- Non-Frail: 55.2 vs 36.6 mos

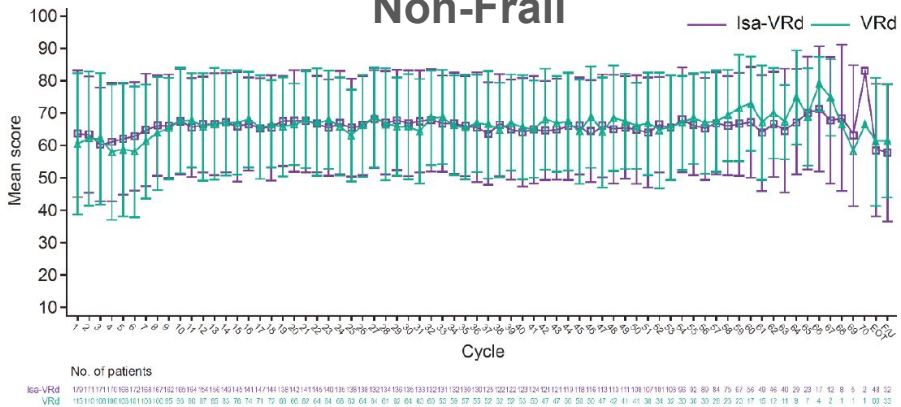
Median Relative Dose Intensity for Isa
- Frail vs Non-Frail: 92.1% vs 94.0%

Median Relative Dose Intensity for Bortezomib
- Frail: 90.3% vs 83.4%
- Non-Frail: 90.0% vs 87.5%

Safety Metric	Frail		Non-Frail	
	Isa-VRd	VRd	Isa-VRd	VRd
D/C for any reason	71.23%	82.46%	46.03%	72.73%
D/C 2/2 Adverse Events	30.14%	35.09%	20.11%	24.79%
Any ≥Grade 3 TEAE (event rate per year)	2.221	3.248	1.832	2.141
Any Grade 5 TEAE (event rate per year)	0.975	1.979	0.509	0.416
Any TE SAE (event rate per year)	1.051	1.340	0.989	1.296

QoL as measured by the EORTC-QLQ-C30



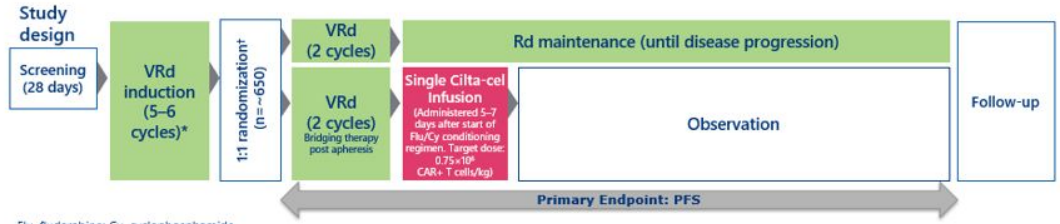


Manier S et al. IMS 2024.

The Future?

CARTITUDE 5 & 6 – the role of CART as consolidation

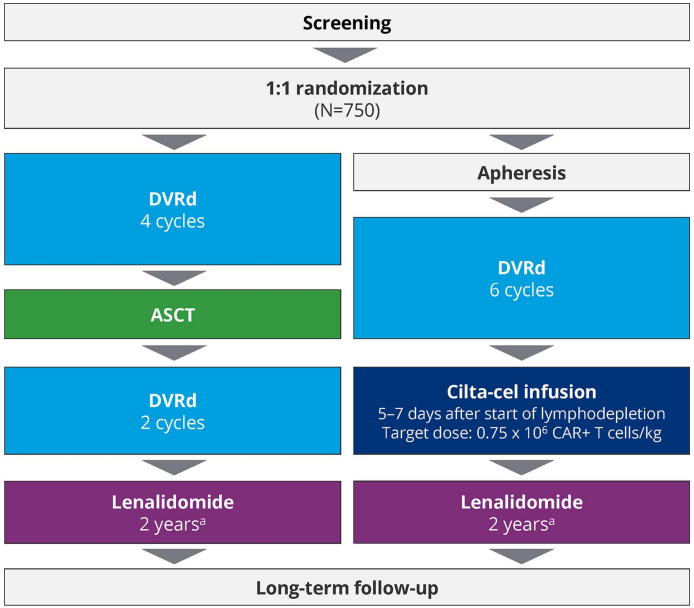
Figure: CARTITUDE-5 study design



Flu, fludarabine; Cy, cyclophosphamide
*1 cycle VRd allowed prior to screening
†Stratification factors: R-ISS (I,II,III); Age/transplant eligibility (≥70 years or <70 years and ASCT ineligible due to comorbidities or <70 years and ASCT deferred); Response to VRd induction (≥VGPR, ≤PR)

NDMM Transplant ineligible/ not intended
Primary endpoint: PFS

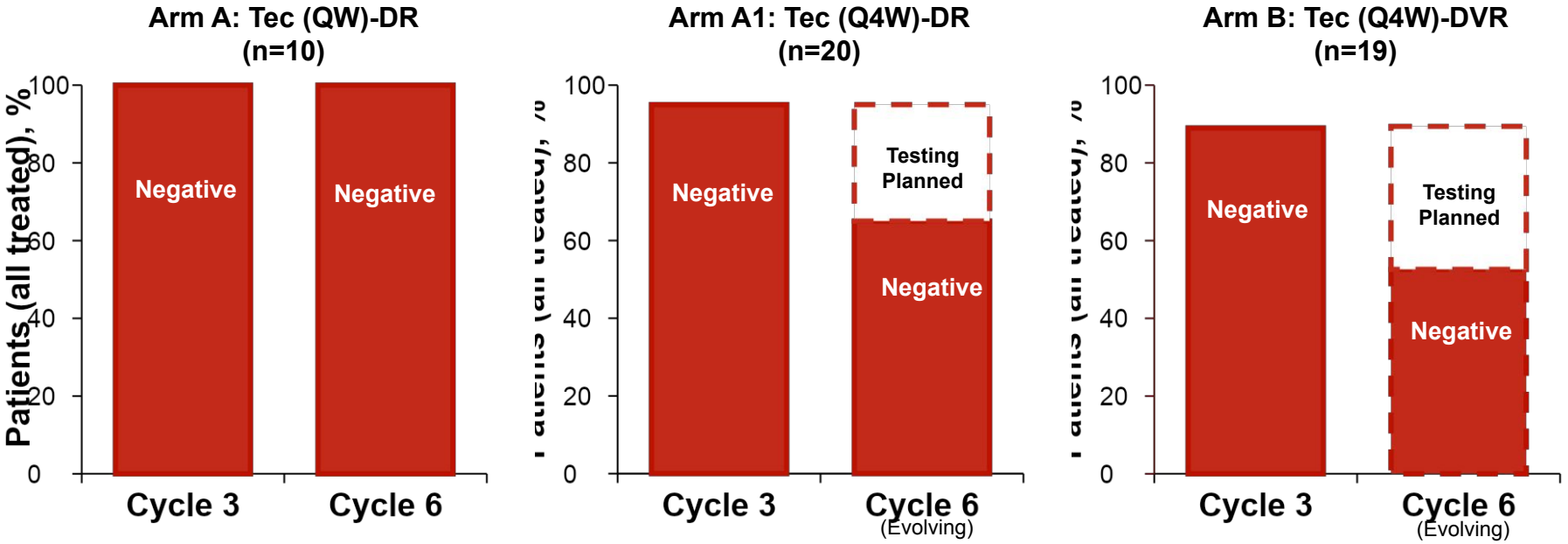
CARTITUDE-6



[a]Patients benefiting from therapy have the option to continue lenalidomide therapy until progressive disease per investigator's discretion after benefit-risk assessment and review by the medical monitor.

NDMM Transplant eligible/Fit patients
Primary endpoint: PFS and MRD12m

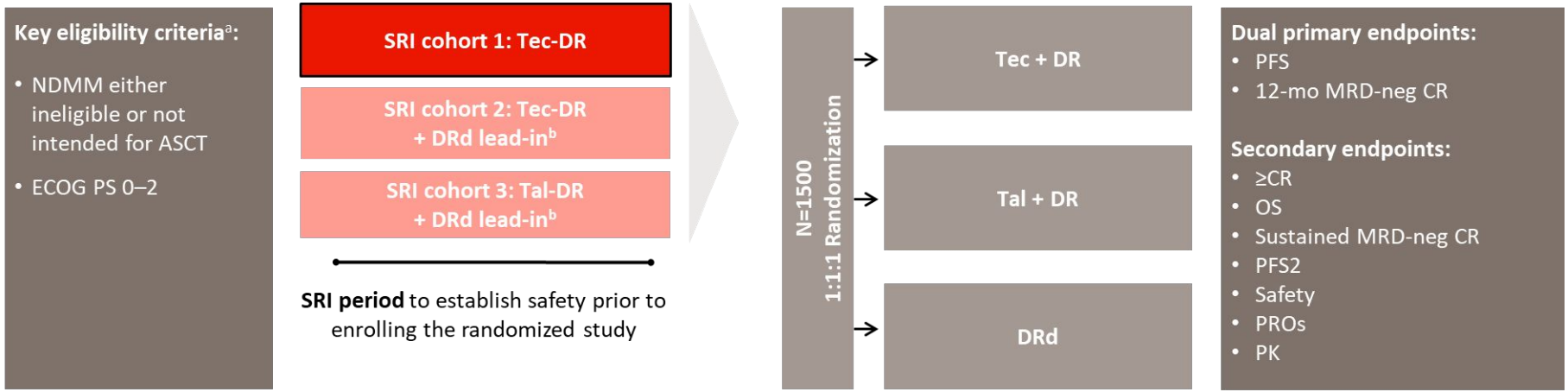
Teclistamab-Based Triplets and Quadruplets in Transplant Eligible Patients with Newly Diagnosed Myeloma: MajesTEC-5



100% of evaluable patients achieved MRD negativity by C3; no patients were MRD positive

Raab M et al. ASH 2024

Teclistamab-Based Quadruplets in Transplant Ineligible Patients with NDMM: MajesTEC-7 Safety Run-In



SRI cohort 1: Tec-DR	mFU	Cycle 1	Cycle 2	Cycle 3–6	Cycle 7+ until PD
	13.8 mo (range, 2.0–15.4)	Tec step-up[c] + D	Tec 1.5 mg/kg QW + DR	Tec 3 mg/kg Q2W + DR	Tec 3 mg/kg Q4W + DR

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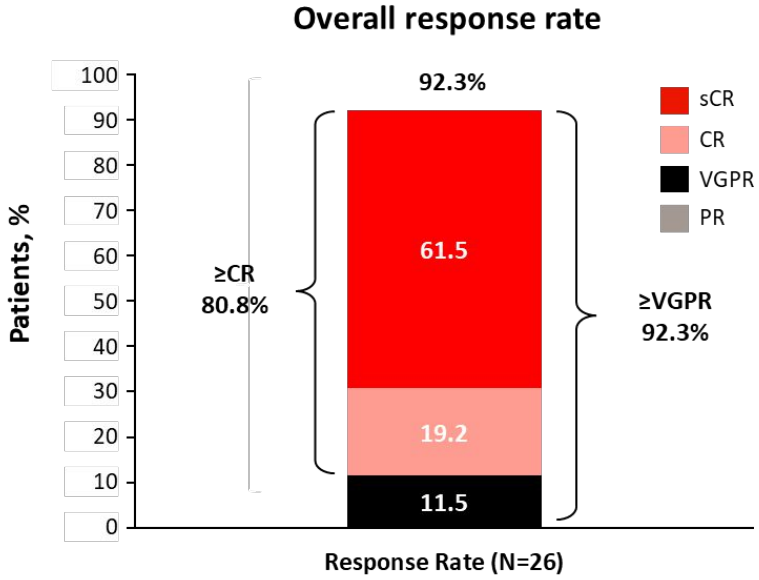
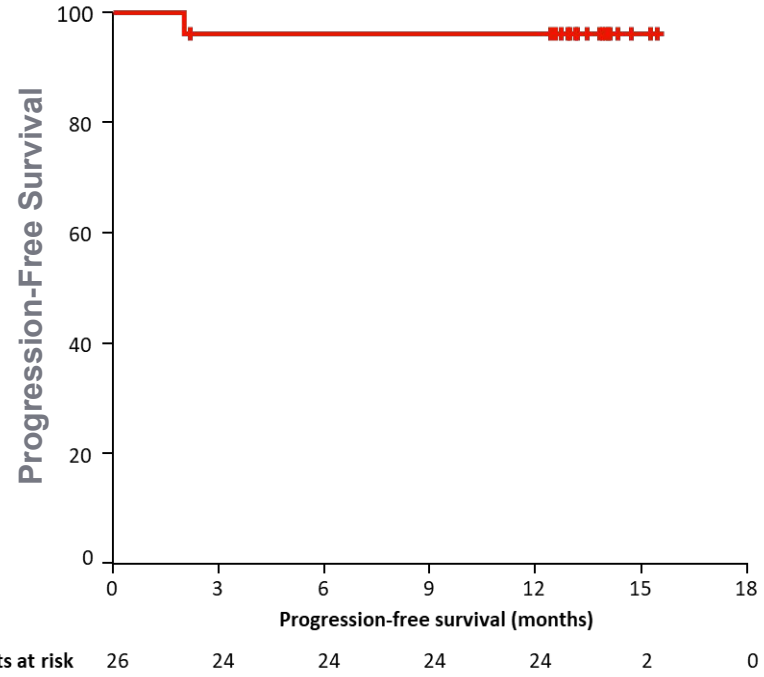
Teclistamab-Based Quadruplets in Transplant Ineligible Patients with NDMM: MajesTEC-7 Safety Run-In

Median Follow-Up: 13.8 months





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Conclusions

- Quadruplets are a new standard of care for patients with newly diagnosed myeloma
  - Triplets remain an important standard of care: Age ≥80, frail patients defined more rigorously
- The best PFS outcomes are those with quadruplets and upfront transplant
- MRD as the right clinical endpoint?
- Promising early data with T cell redirecting therapies in the management of newly diagnosed patients

THANK YOU