Novel advances in myeloma as frontline therapy

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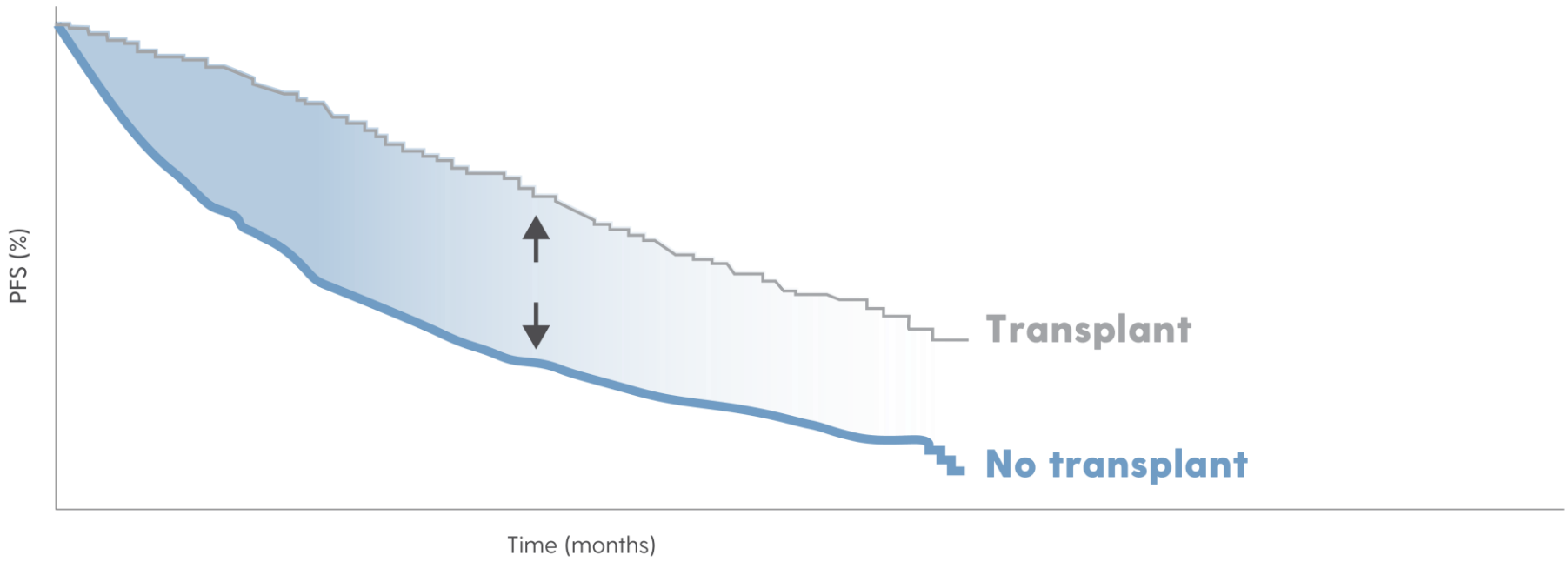
Key Points to Treatment of NDMM

- Goal of treatment: achieve MRD negativity
- 4 drugs better than 3 drugs
  - should include anti-CD38 antibody, proteosome inhibitor, IMID and steroid
- Duration of treatment likely more important than intensity for most patients
- High risk MM still represents significant challenges

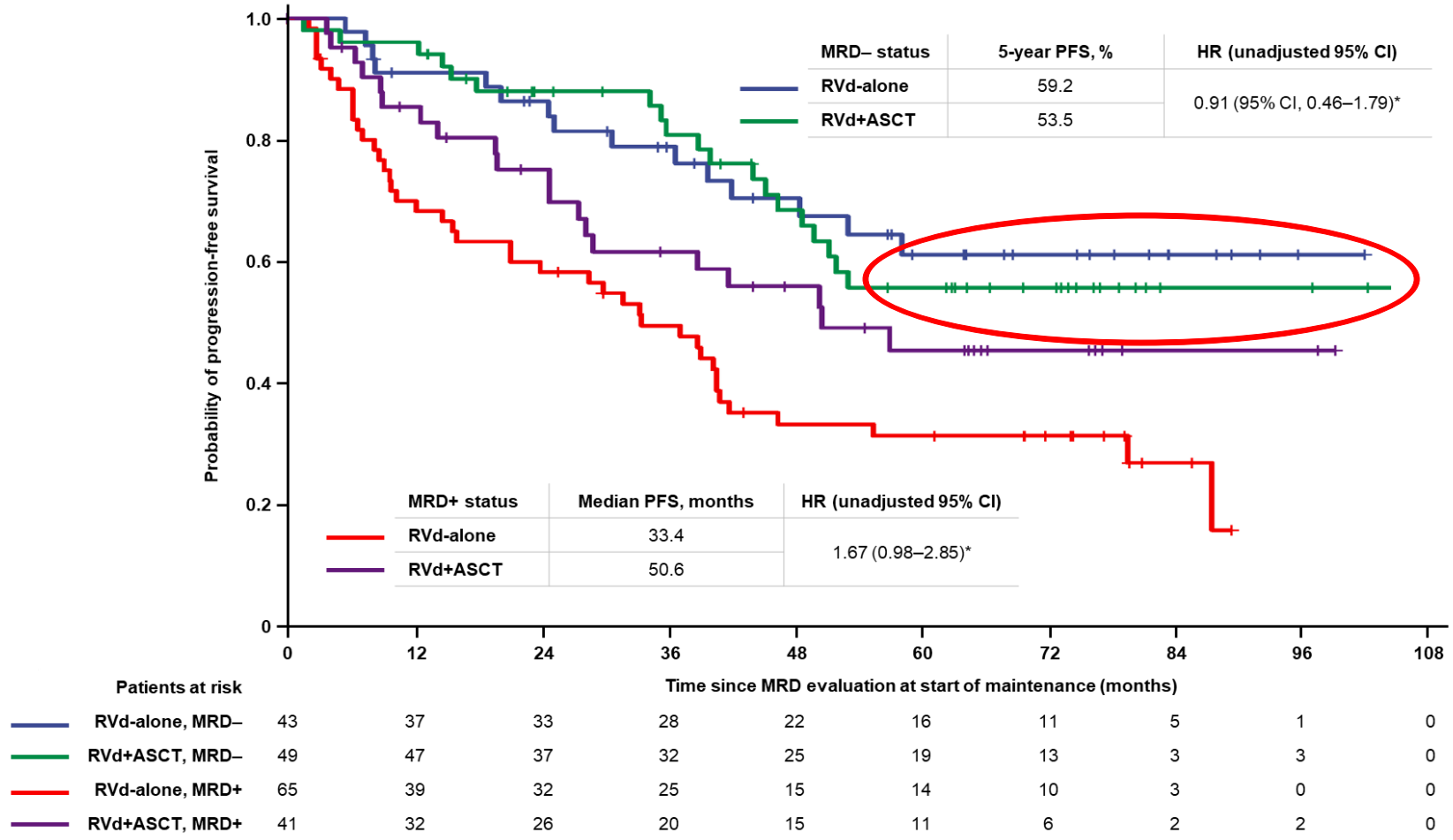
Transplant Improves PFS



Richter J et al. *Eur J Haematol*. 2023;4(4):984-994.

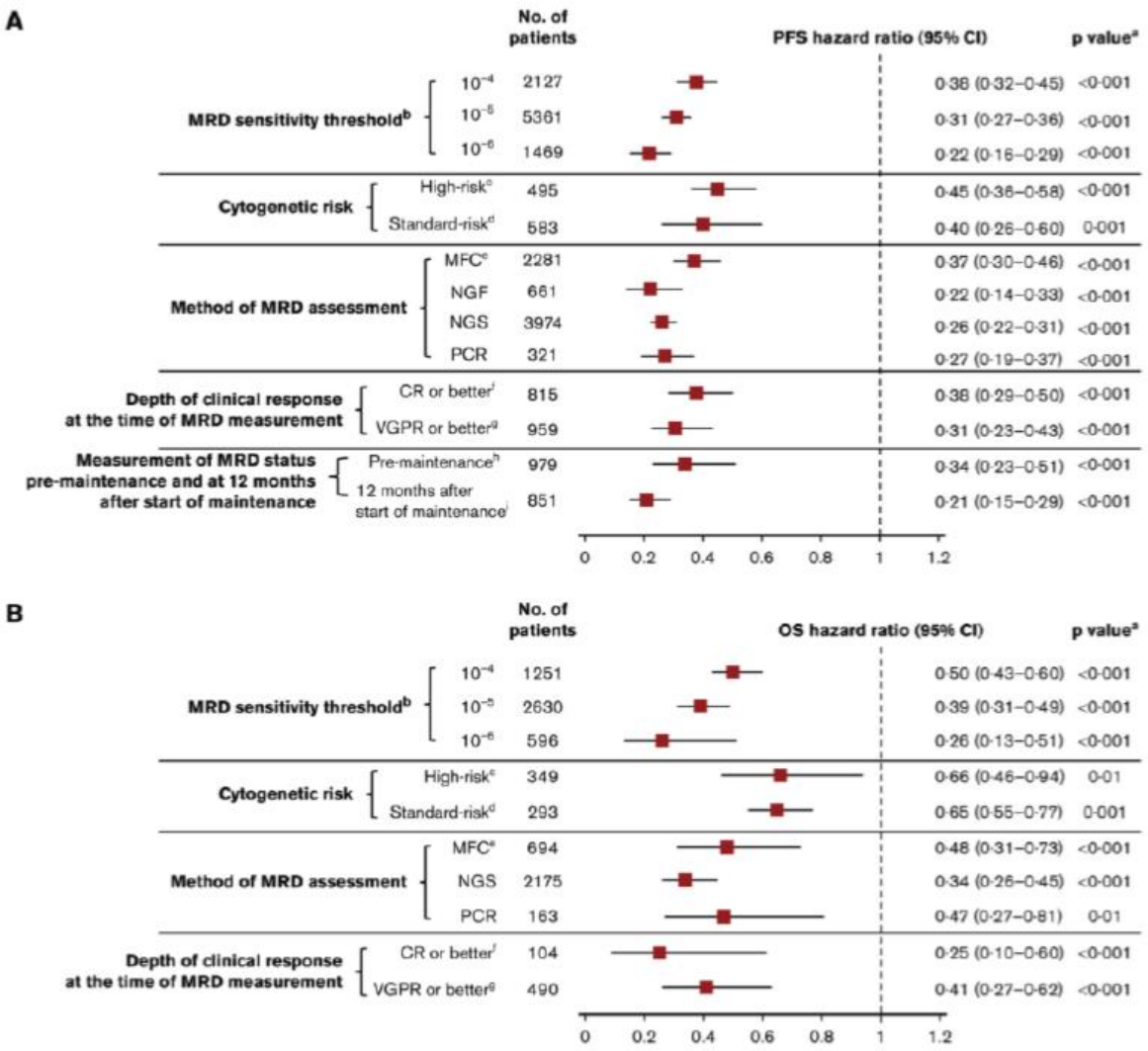
DETERMINATION: PFS by MRD Status

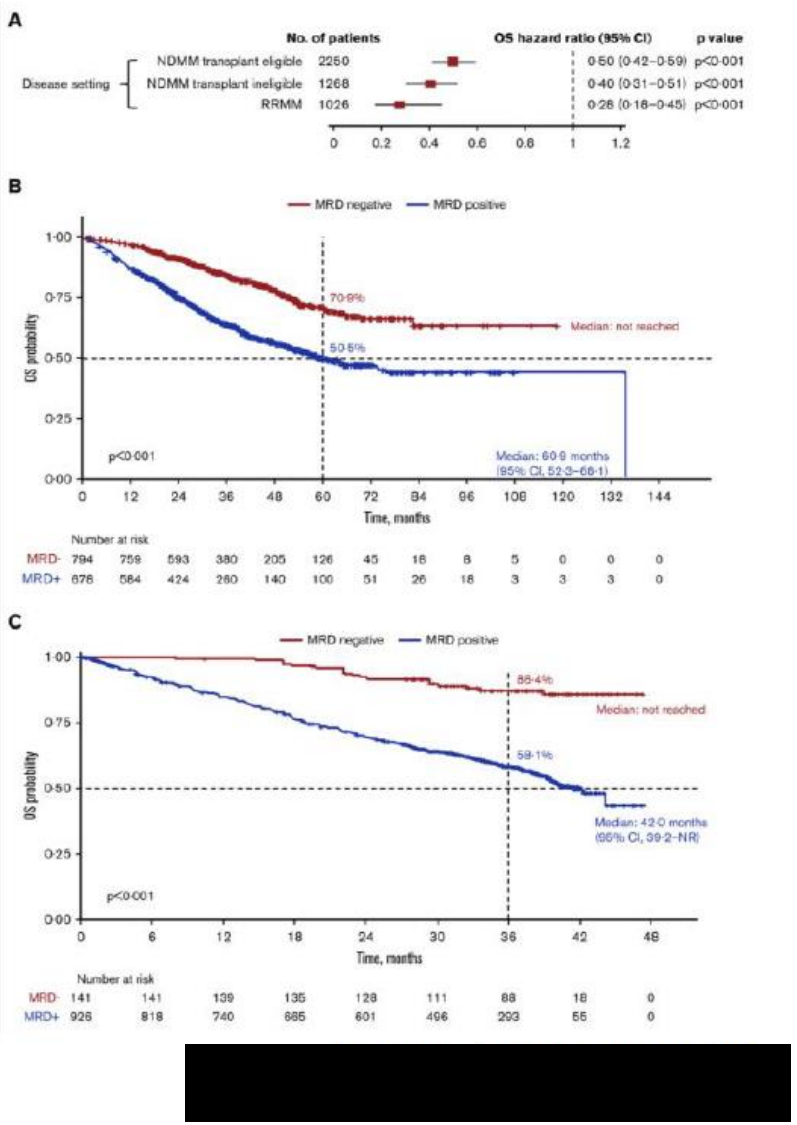
MRD was measured at the end of induction therapy



- Richardson P, et al. *NEJM* 2022; DOI: 10.1056/NEJMoa2204925.
- *There were multiple MRD timepoints in this study, but only the data for this timepoint has been presented to date.

Three Meta-Analyses Validated MRD for Prognosis



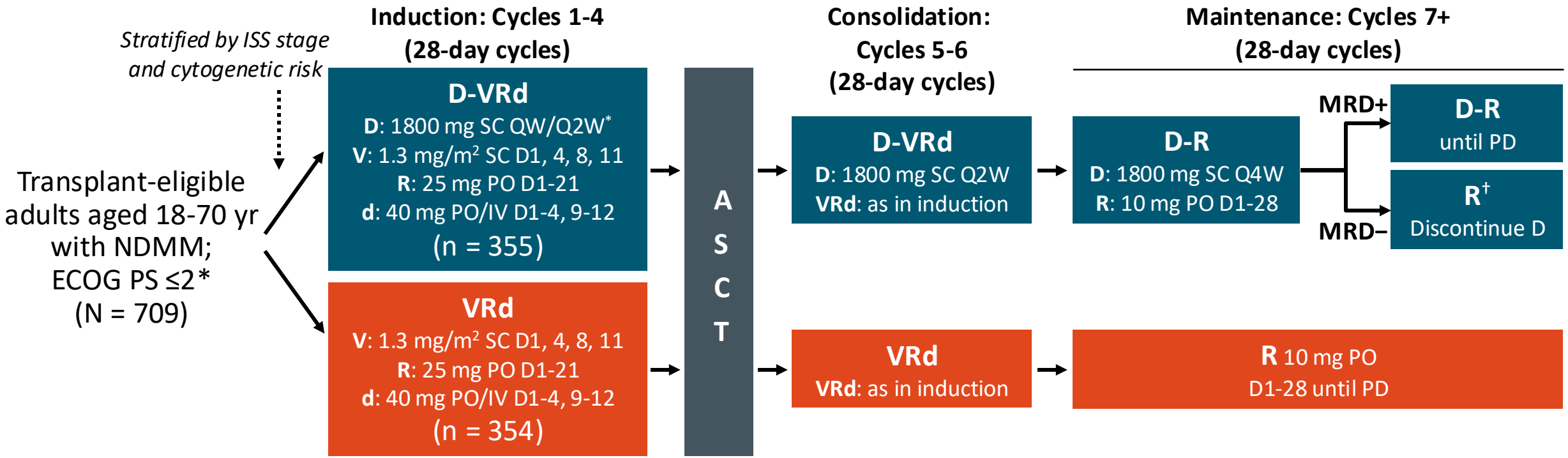


[redacted]

Munshi et al Blood Adv. 2020 Dec 8;4(23):5988-5999
Landgren, O et al Bone Marrow Transplantation 2016 51:1568
Munshi et al JAMA Oncol. 2017;3(1):28-35

PERSEUS: Study Design

- Multicenter, open-label, randomized phase III trial; current analysis median f/u: 47.5 mo

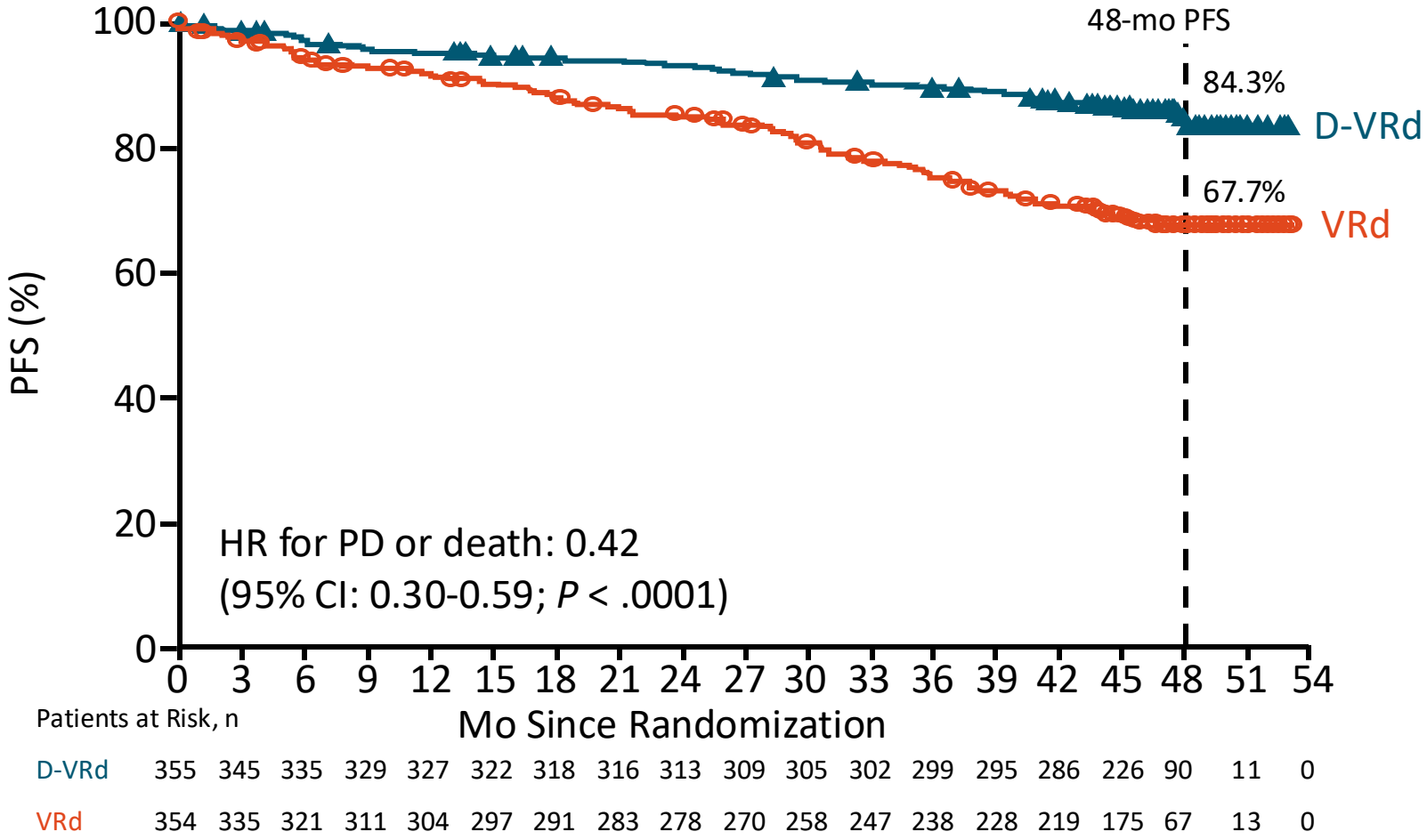


*QW during cycles 1-2, Q2W during cycles 3-4. †D discontinued after ≥24 mo in patients with ≥CR and 12 mo sustained MRD negativity; D restarted upon confirmed loss of CR without PD or MRD recurrence.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** ≥CR rate, MRD negativity rate, OS

Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2023;[Epub].

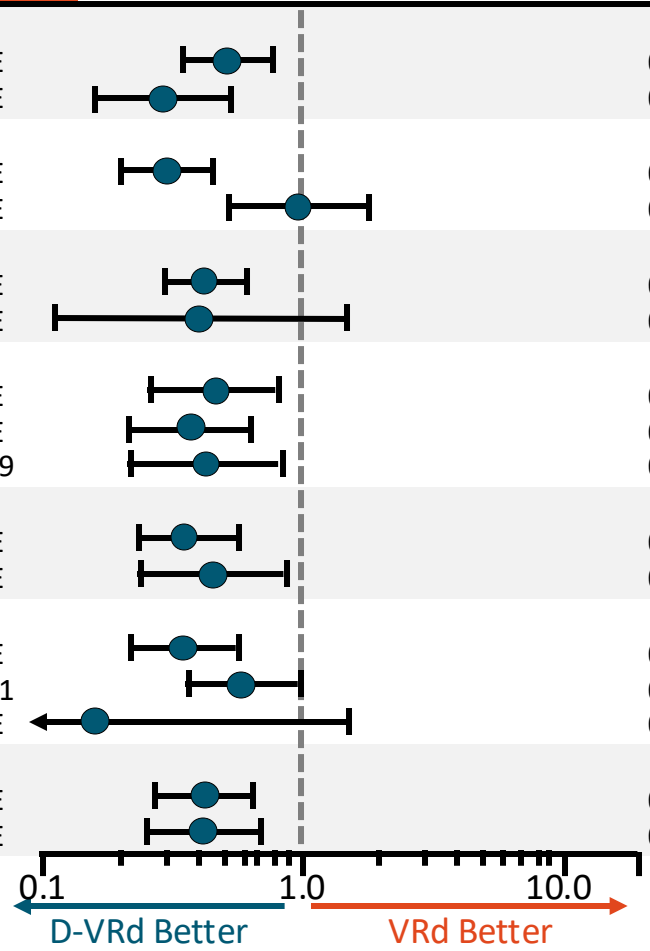
PERSEUS Primary Analysis: PFS (Primary Endpoint)



Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2023;[Epub].

PERSEUS Primary Analysis: PFS Subgroup Analysis

Subgroup	PD or Death		Median PFS		Hazard Ratio for PD or Death (95% CI)
	D-VRd n/N	VRd n/N	D-VRd mo	VRd mo	
Sex					
▪ Male	36/211	61/205	NE	NE	0.51 (0.34-0.77)
▪ Female	14/144	42/149	NE	NE	0.29 (0.16-0.53)
Age					
▪ <65 yr	30/261	84/267	NE	NE	0.30 (0.20-0.46)
▪ ≥65 yr	20/94	19/87	NE	NE	0.97 (0.52-1.81)
Race					
▪ White	47/330	95/323	NE	NE	0.42 (0.30-0.60)
▪ Other	3/25	8/31	NE	NE	0.40 (0.11-1.50)
ISS disease stage					
▪ I	18/186	35/178	NE	NE	0.46 (0.26-0.81)
▪ II	19/114	43/125	NE	NE	0.37 (0.22-0.64)
▪ III	13/55	25/50	NE	41.9	0.42 (0.22-0.83)
Type of multiple myeloma					
▪ IgG	28/204	58/185	NE	NE	0.36 (0.23-0.57)
▪ Non-IgG	13/78	31/96	NE	NE	0.46 (0.24-0.88)
Cytogenetic risk					
▪ Standard	25/264	62/266	NE	NE	0.35 (0.22-0.56)
▪ High	24/76	38/78	NE	44.1	0.59 (0.36-0.99)
▪ Indeterminate	1/15	3/10	NE	NE	0.16 (0.02-1.56)
ECOG performance-status score					
▪ 0	28/2211	60/230	NE	NE	0.42 (0.27-0.66)
▪ ≥1	22/134	43/124	NE	NE	0.41 (0.25-0.69)



Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2023;[Epub].

PERSEUS Primary Analysis: Key Secondary Endpoints

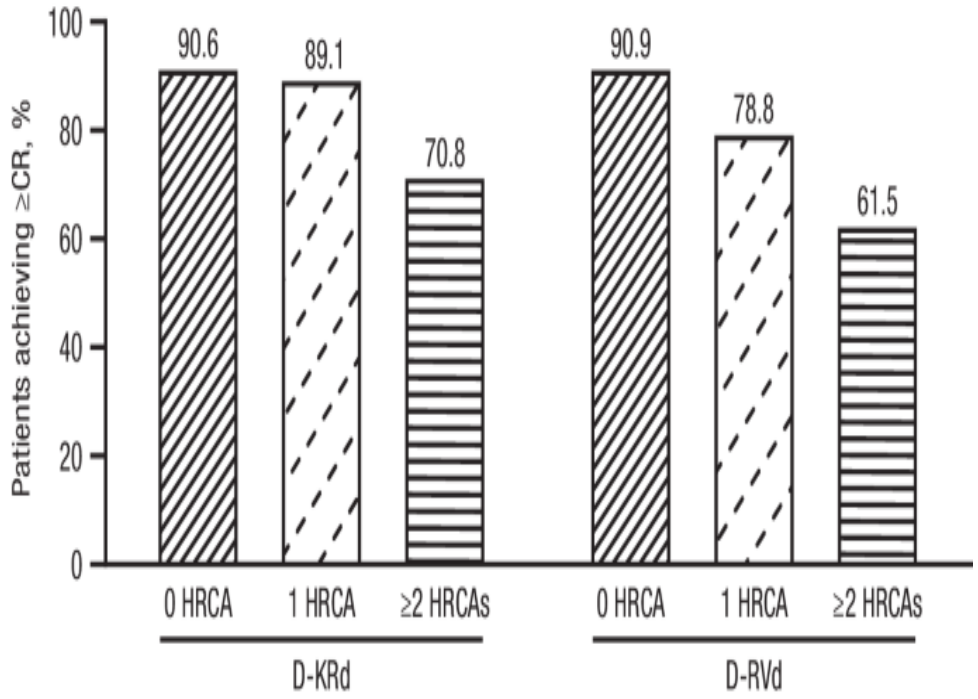
Efficacy Outcome	D-VRd (n = 355)	VRd (n = 354)	OR (95% CI)	*P* Value
≥CR, %	87.9	70.1	3.13 (2.11-4.65)	<.001
▪ sCR	69.3	44.6		
▪ CR	18.6	25.4		
MRD negativity, %				
▪ 10^{-5}	75.2	47.5	3.40 (2.47-4.69)	<.0001
▪ 10^{-6}	65.1	32.2	3.97 (2.90-5.43)	<.0001
Sustained MRD negativity (10^{-5}) ≥12 mo, %	64.8	29.7	4.42 (3.22-6.08)	<.0001

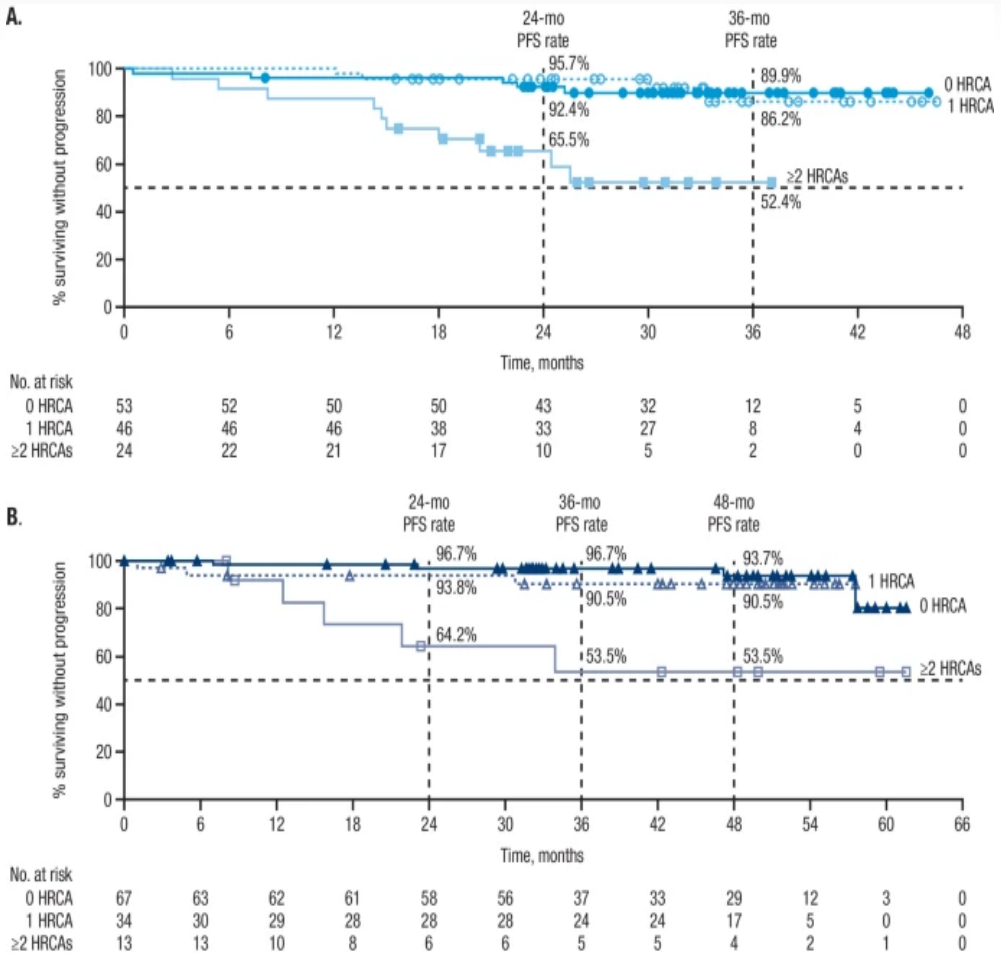
Efficacy Outcome	D-VRd (n = 355)	VRD (n = 354)	Difference Between Arms
MRD negativity (10^{-5}) over time, %			
▪ Post consolidation	57.5	32.5	25.0
▪ Overall	75.2	47.5	27.7
MRD negativity (10^{-6}) over time, %			
▪ Post consolidation	34.4	16.1	18.3
▪ Overall	65.1	32.2	32.9

- Improvements in ≥CR rates with D-VRd vs VRd observed across all subgroups
- 64% of patients in D-VRd arm + D-R maintenance discontinued D after reaching sustained MRD negativity per protocol
- OS data immature
  - Current mortality rate with D-VRd vs VRd: 9.6% vs 12.4% (HR: 0.73)

Sonneveld. ASH 2023. Abstr LBA-1. Sonneveld. NEJM. 2023;[Epub].

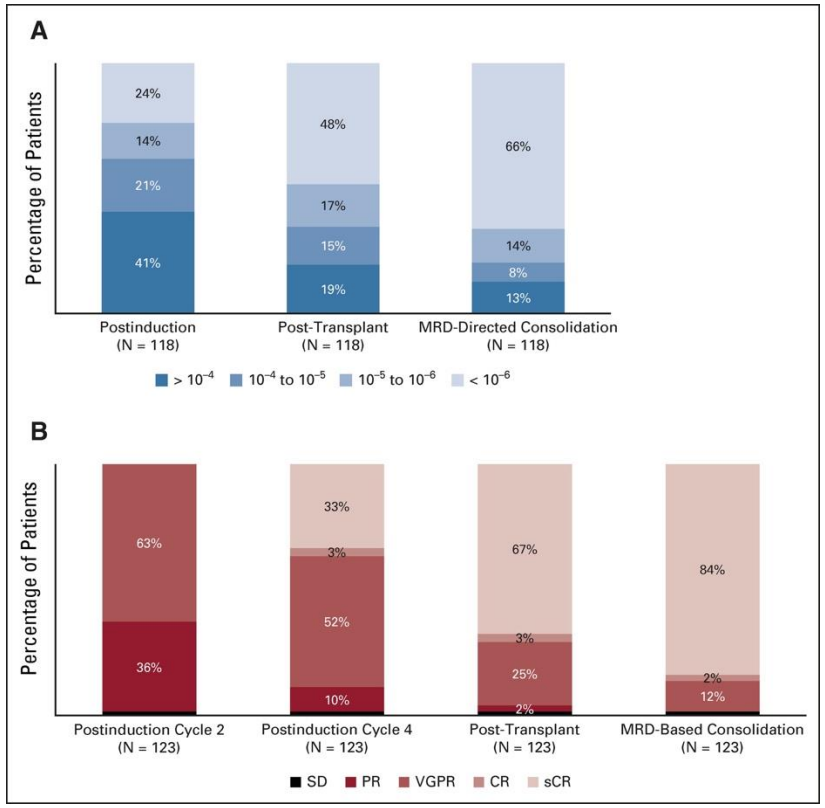
Dara-based Regimens in transplant eligible HRMM -number of HRCA impacts OS-

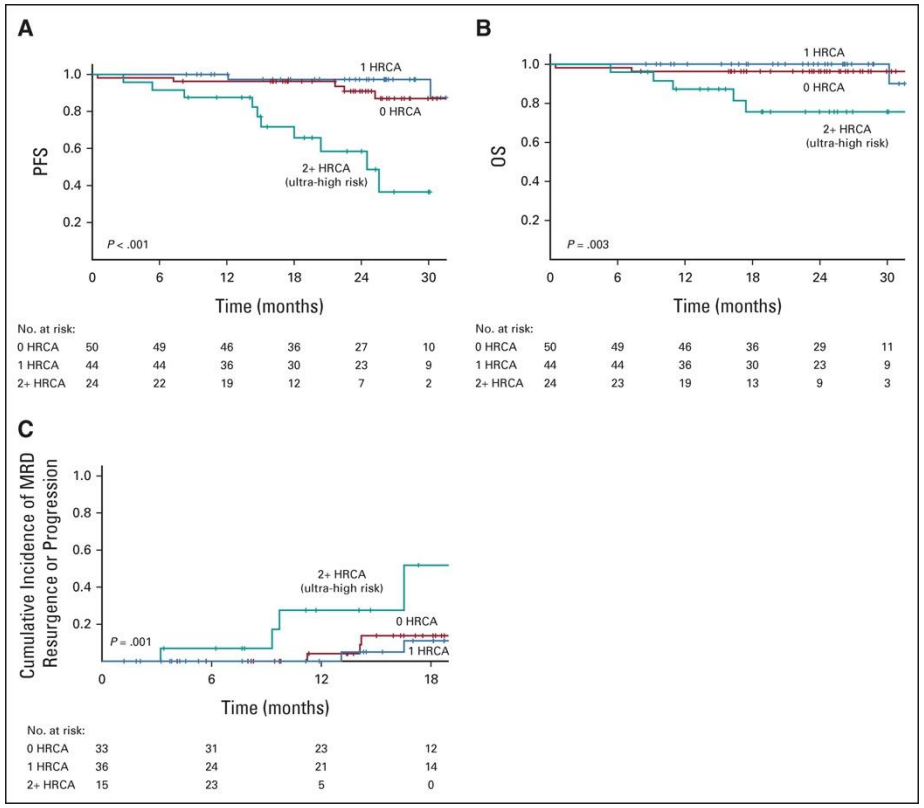




Collander et al Blood Ca J 2024

Master Trial: MRD Response Over Time and Impact of Cytogenetics



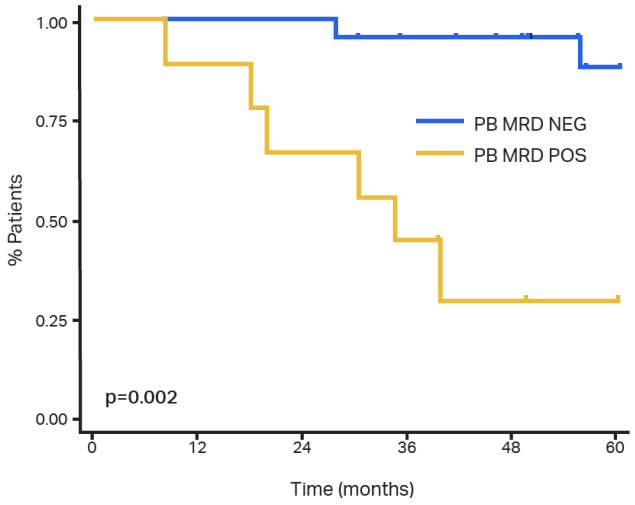


Costa L JCO 2021

Peripheral MRD is prognostic of PFS after 4 cycles

- Early peripheral blood minimal residual disease status by NGS in patients with newly diagnosed multiple myeloma on a phase 2 trial receiving elotuzumab, carfilzomib, lenalidomide, and dexamethasone (Elo-KRd)

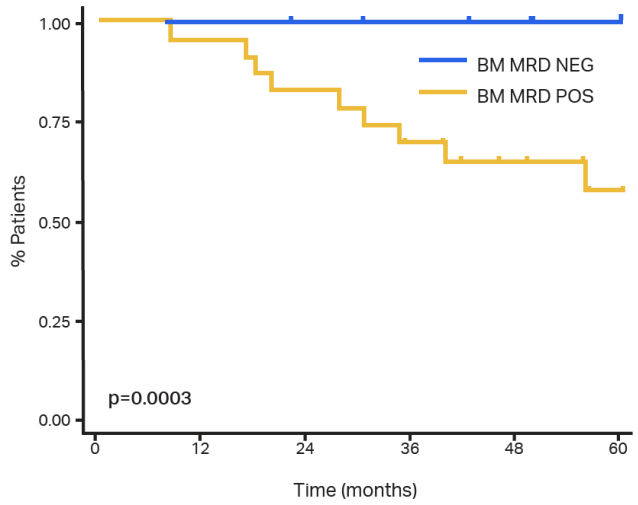
Peripheral blood



Number at risk

PB MRD NEG	22	(0)	22	(0)	22	(1)	19	(0)	17	(1)	10
PB MRD POS	9	(1)	8	(2)	6	(2)	4	(1)	2	(0)	1

Bone marrow



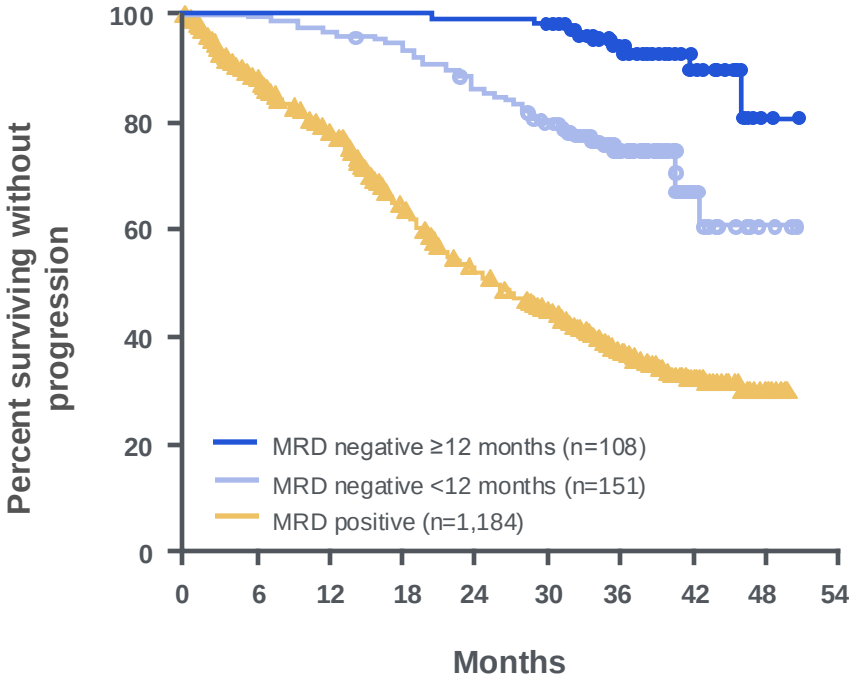
Number at risk

BM MRD NEG	11	(0)	11	(0)	10	(0)	9	(0)	8	(0)	5
BM MRD POS	23	(1)	22	(3)	19	(3)	15	(1)	11	(1)	6

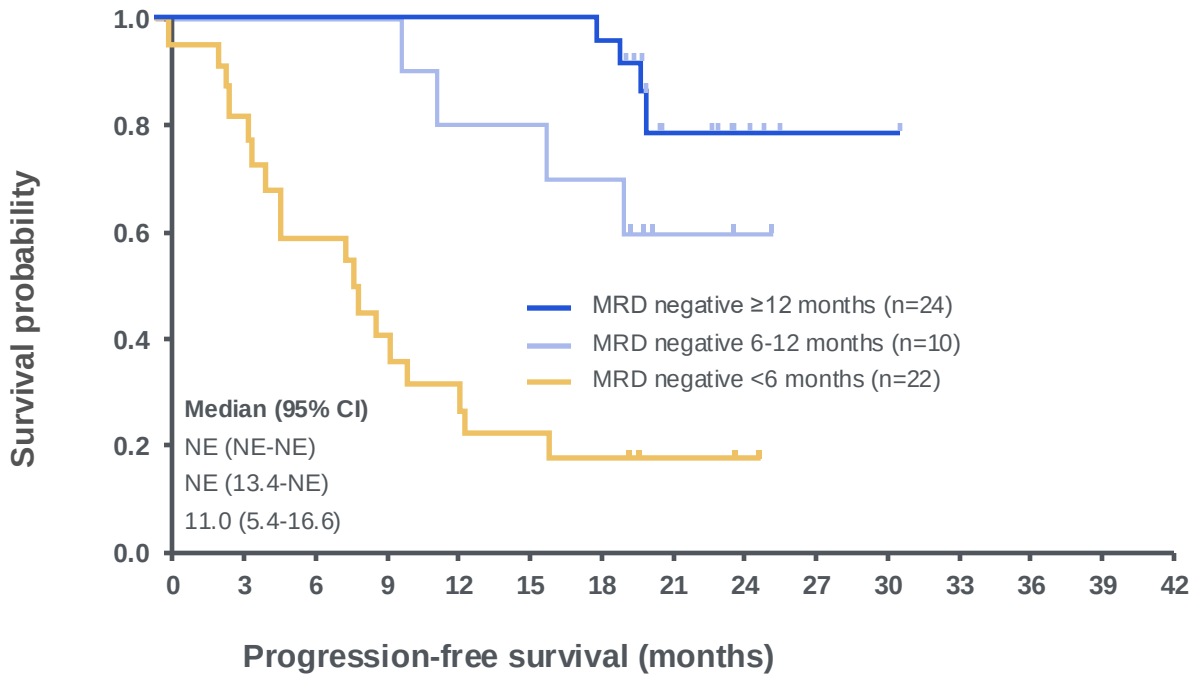
Peripheral MRD should NOT be considered a substitute for BM MRD

Sustained MRD negativity was associated with longer progression-free survival in patients with new diagnosed and relapsed/refractory multiple myeloma

Progression-free survival stratified by MRD response in newly diagnosed MM patients pooled from MAIA and ALCYONE[1]



Progression-free survival stratified by MRD response in relapsed/refractory MM patients in CARTITUDE-1[2]

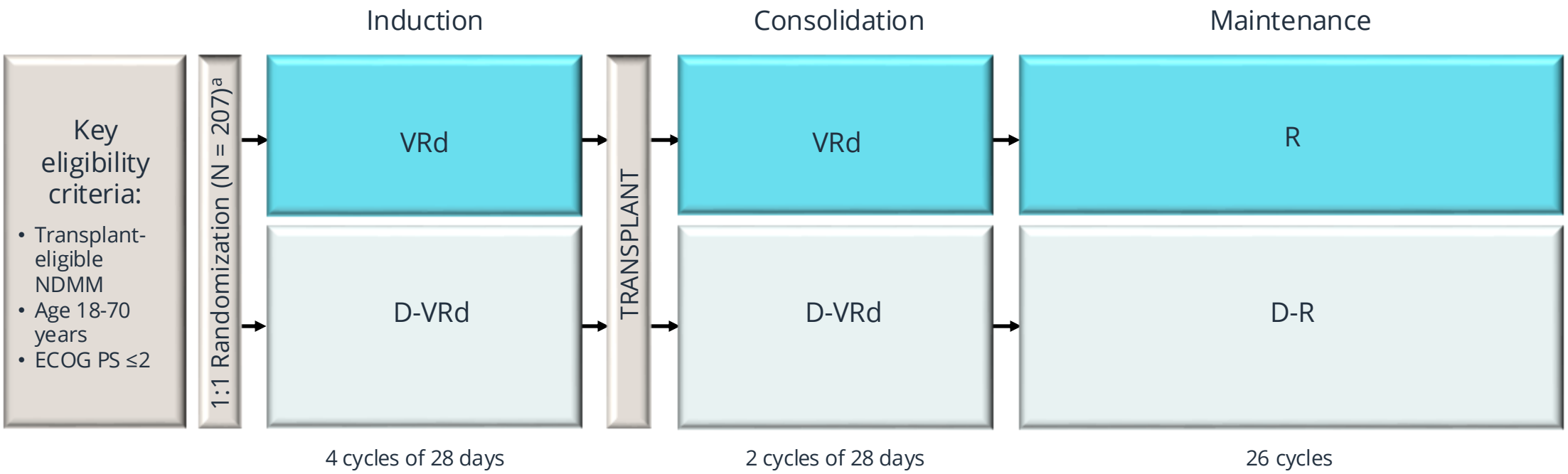


NGS MRD at 10^{-5} in bone marrow. Landmark analyses were conducted at 6 and 12 months. Median follow-up of 28 months. Patients received a single cilta-cel infusion at a target dose of 0.75 x 106 CAR T cells/kg. Cilta-cel, ciltacabtagene autoleucel; MRD: minimal residual disease.

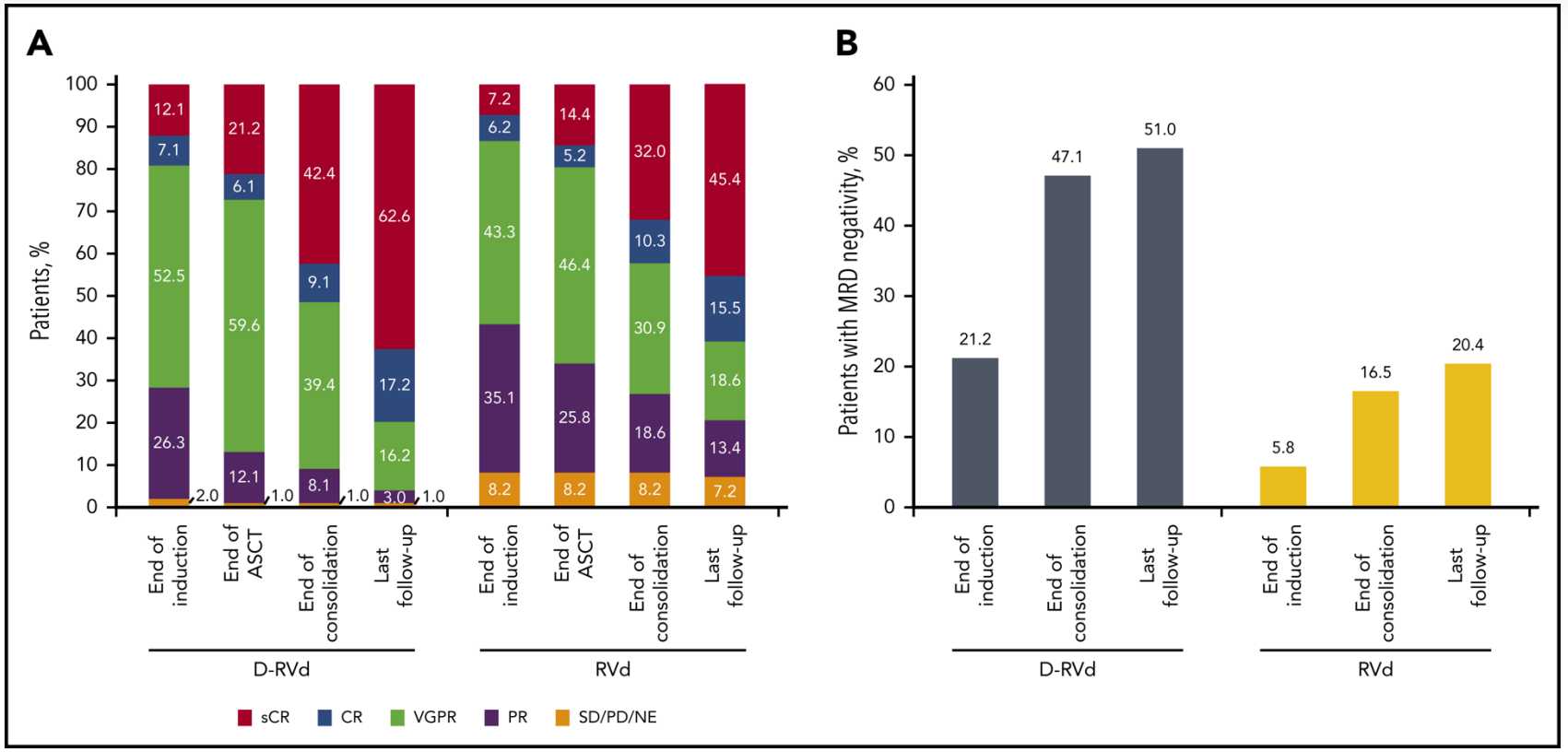
1) San Miguel J et al. Blood. Published July 16, 2021. https://doi.org/10.1182/blood.2020010439. 2) Munshi et al. ASH 2022. Abstract 2030. https://ash.confex.com/ash/2022/webprogram/Paper159141.html.

TGH Tampa General Hospital

Griffin Trial Design

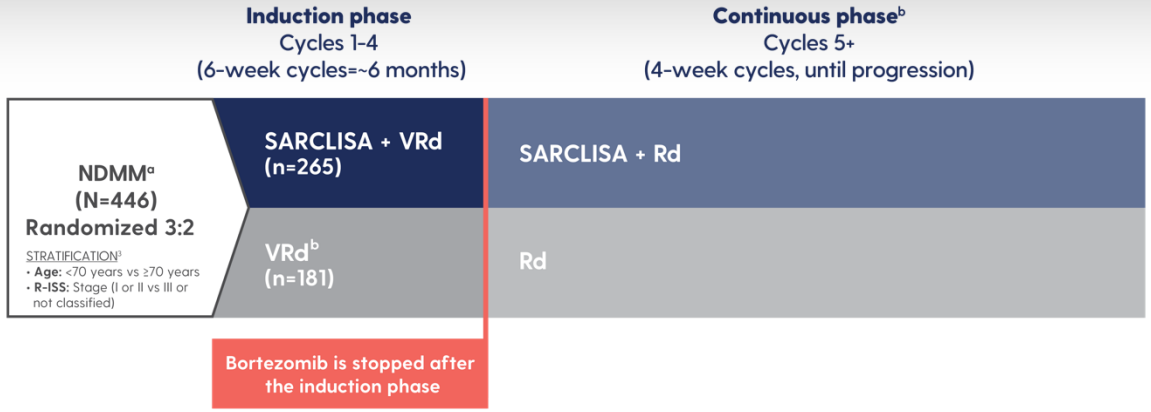


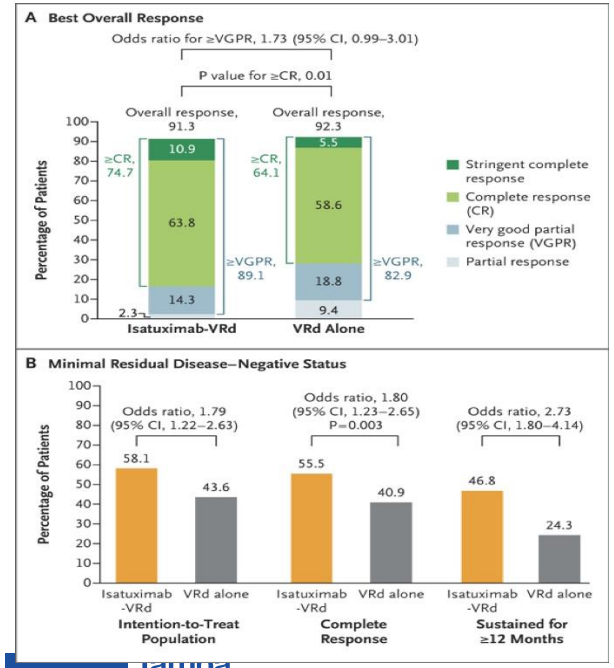
Griffin Trial: VRD +/- Dara in NDMM + ASCT
Deeper responses with ongoing therapy

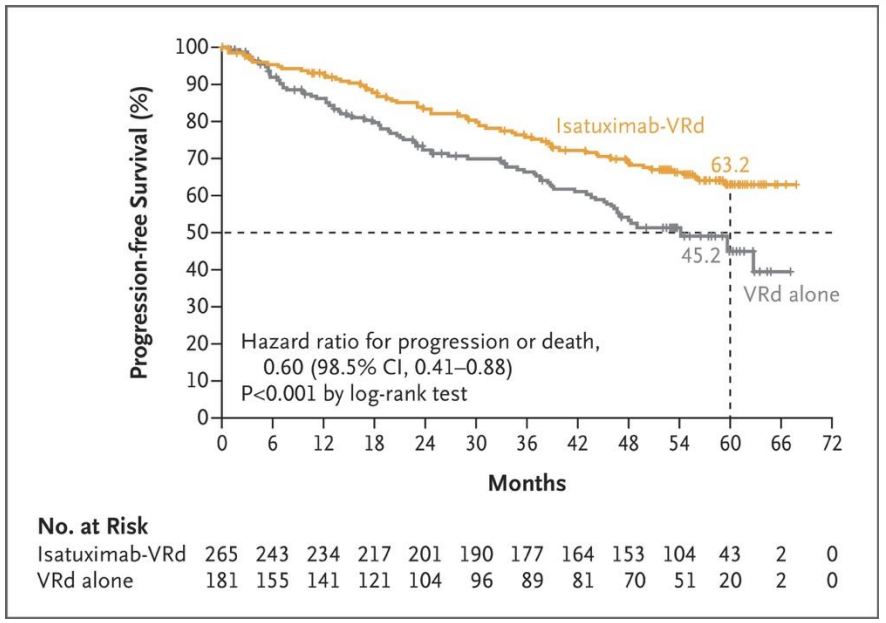


Myeloma is not a curable disease!
Improved outcomes require ongoing treatment

IMROZ: Isa-VRD v VRD for non-BMT eligible patients



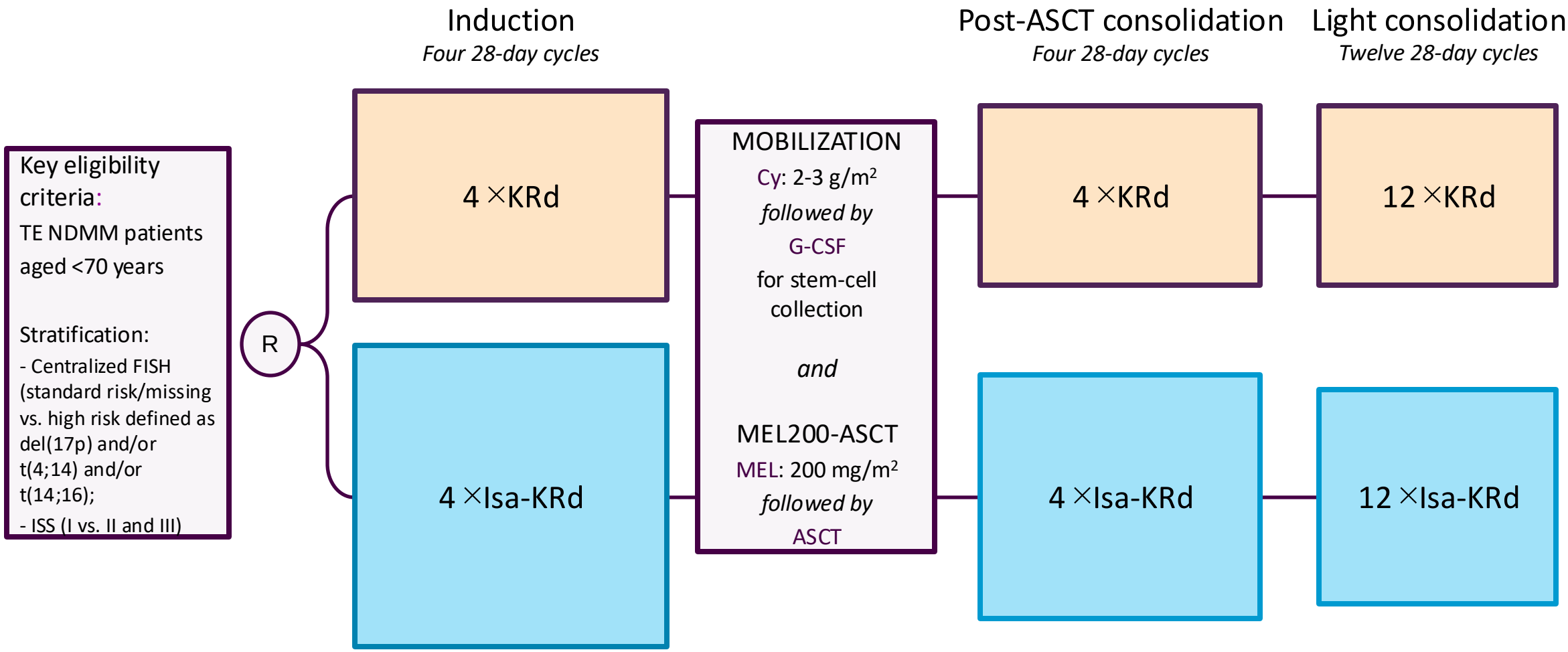




- Isa-VRD does not necessarily increase the overall response
- Isa-VRD deepens the response and increases MRD negativity
- Isa-VRD improves PFS

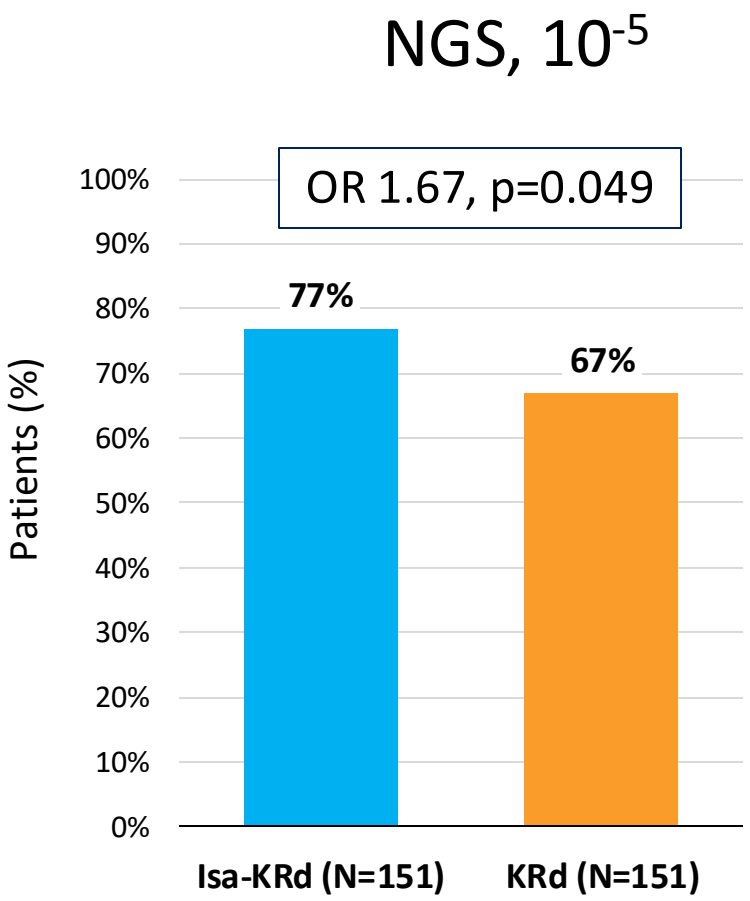
Facon et al N Engl J Med. 2024 Oct 31;391(17):

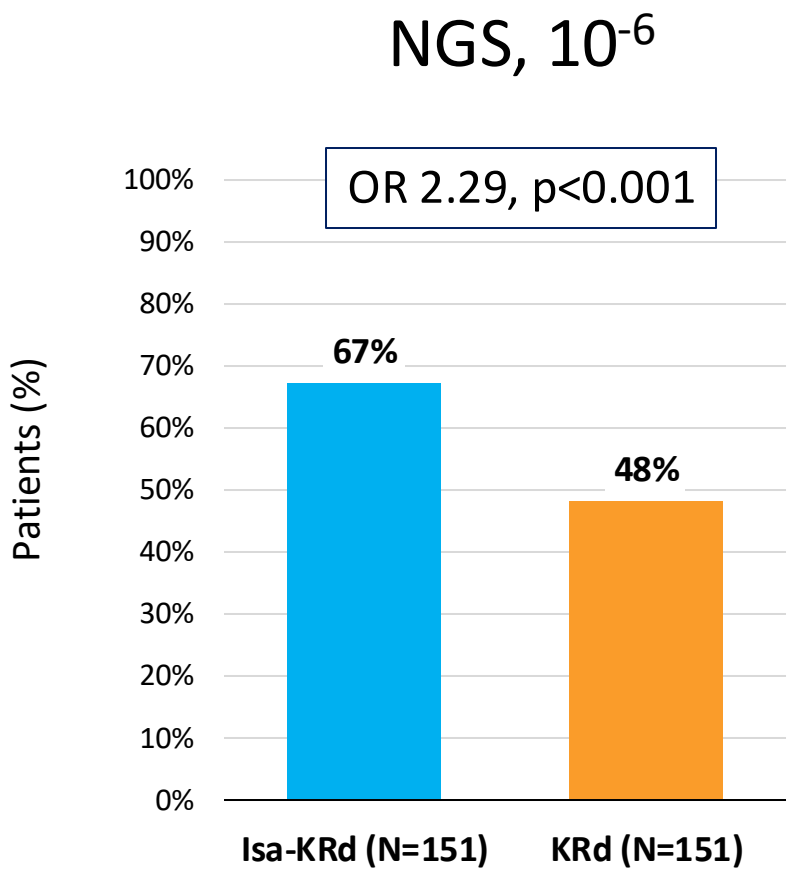
IsKia EMN24 Study Design



Gay, ASH 2023. Abstract 4.

IsKia Primary Endpoint: Post-consolidation MRD negativity (ITT analysis)





Conclusions

- While incurable, PFS and OS is improving significantly with better therapies
- Goal of therapy is to deepen response to achieve MRD negativity
  - Quadruplets > Triplets
  - For MRD +, transplant > no transplant
  - Consolidation post-transplant is standard of care
  - Longer maintenance can deepen response
- Risk adapted response criteria can maximize efficacy and reduce toxicity
- The field is beginning to question to the role of transplant in low-risk patients that achieve MRD negativity