



# Novel advances in myeloma as frontline therapy

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**CANCER  
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# mSMART 3.0: Risk Stratification in Active MM

## High-Risk

- **High Risk genetic Abnormalities** <sup>a,b</sup>

- t(4;14)
- t(14;16)
- t(14;20)
- Del 17p
- p53 mutation
- Gain 1q

- **RISS Stage 3**

**GEP: High risk signature**

- **Double Hit Myeloma: Any 2 high risk genetic abnormalities**
- **Triple Hit Myeloma: 3 or more high risk genetic abnormalities**

## Standard-Risk<sup>a</sup>

**All others including:**

- **Trisomies**
- t(11;14)
- t(6;14)

Revised-International Staging System:

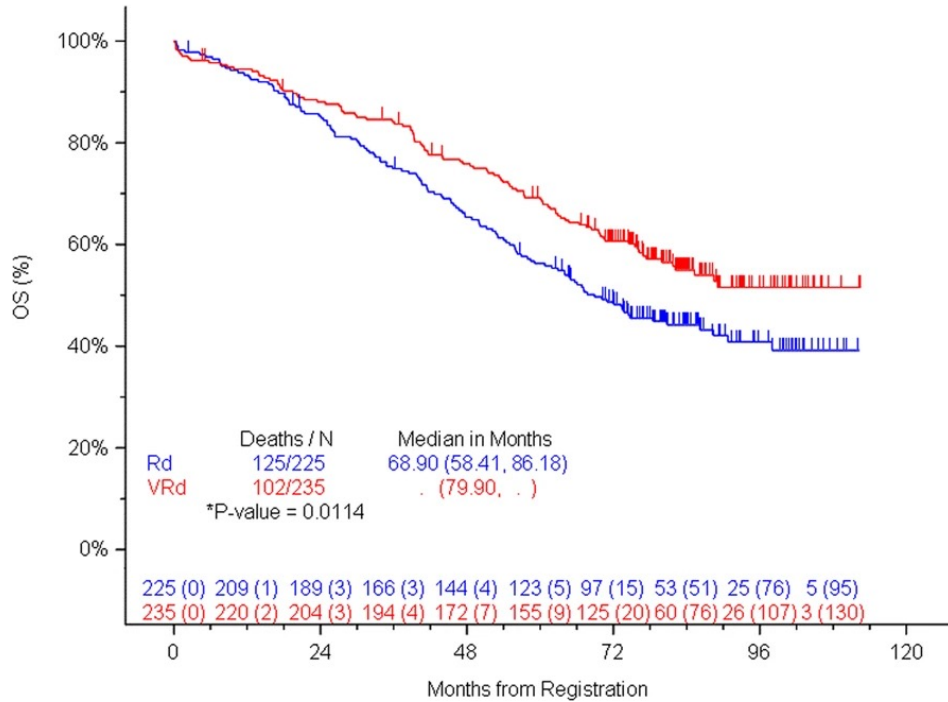
- I -  $\beta 2M < 3.5$ ; alb  $> 3.5$ ; nl LDH, standard CA
- II - neither I nor III
- III -  $\beta 2M > 3.5$ ; high-risk CA **or** high LDH

# Initial Approach to NDMM

- Initial work-up MUST include the following:
  - myeloma labs **including UPEP**
  - BM with FISH and ClonoSeq ID
  - LDH
  - PET/CT: **full body (not to thigh)**
- Overarching goal of therapy:
  - Achieve the deepest and most durable response
  - MRD negativity
  - Prolonged time to next therapy

# Quadruplets Improve Outcomes in NDMM

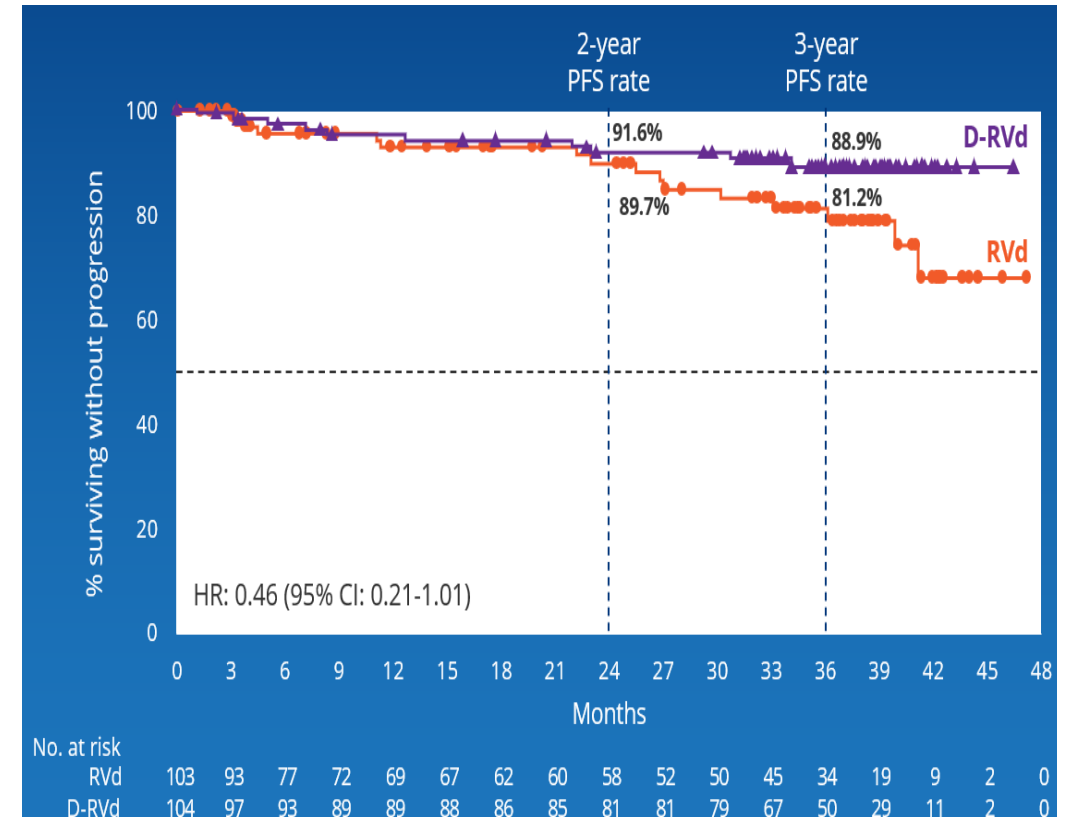
## VRd vs Rd



Median >84 months  
5 year OS: 69%

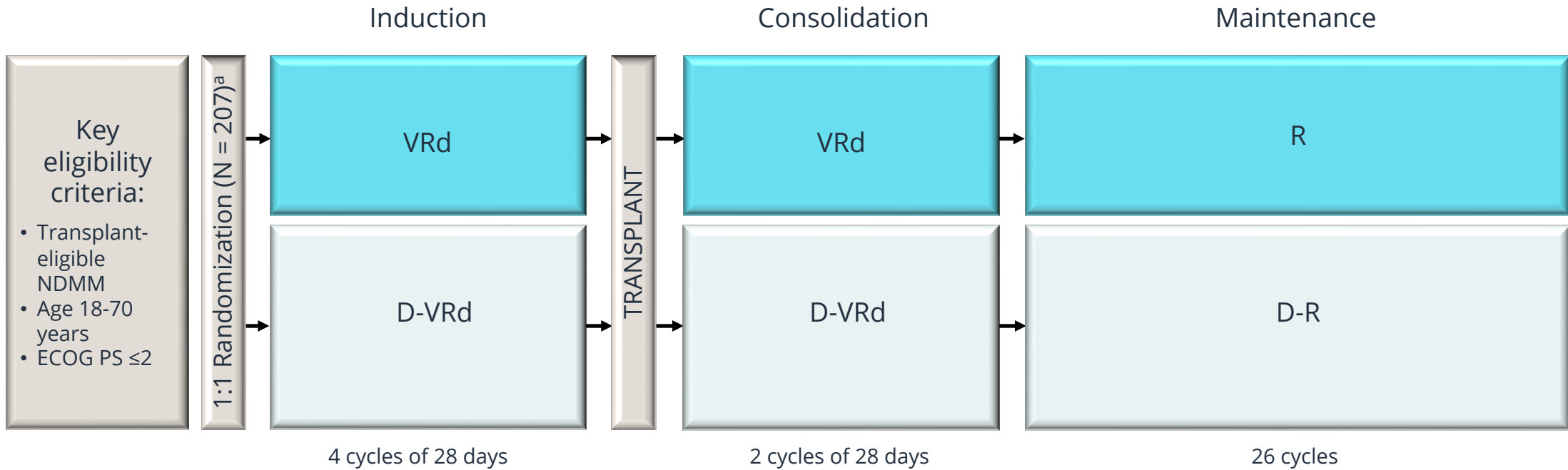
Durie B. Blood Cancer Journal. 2020;10:53.

## • Dara-RVd vs RVd

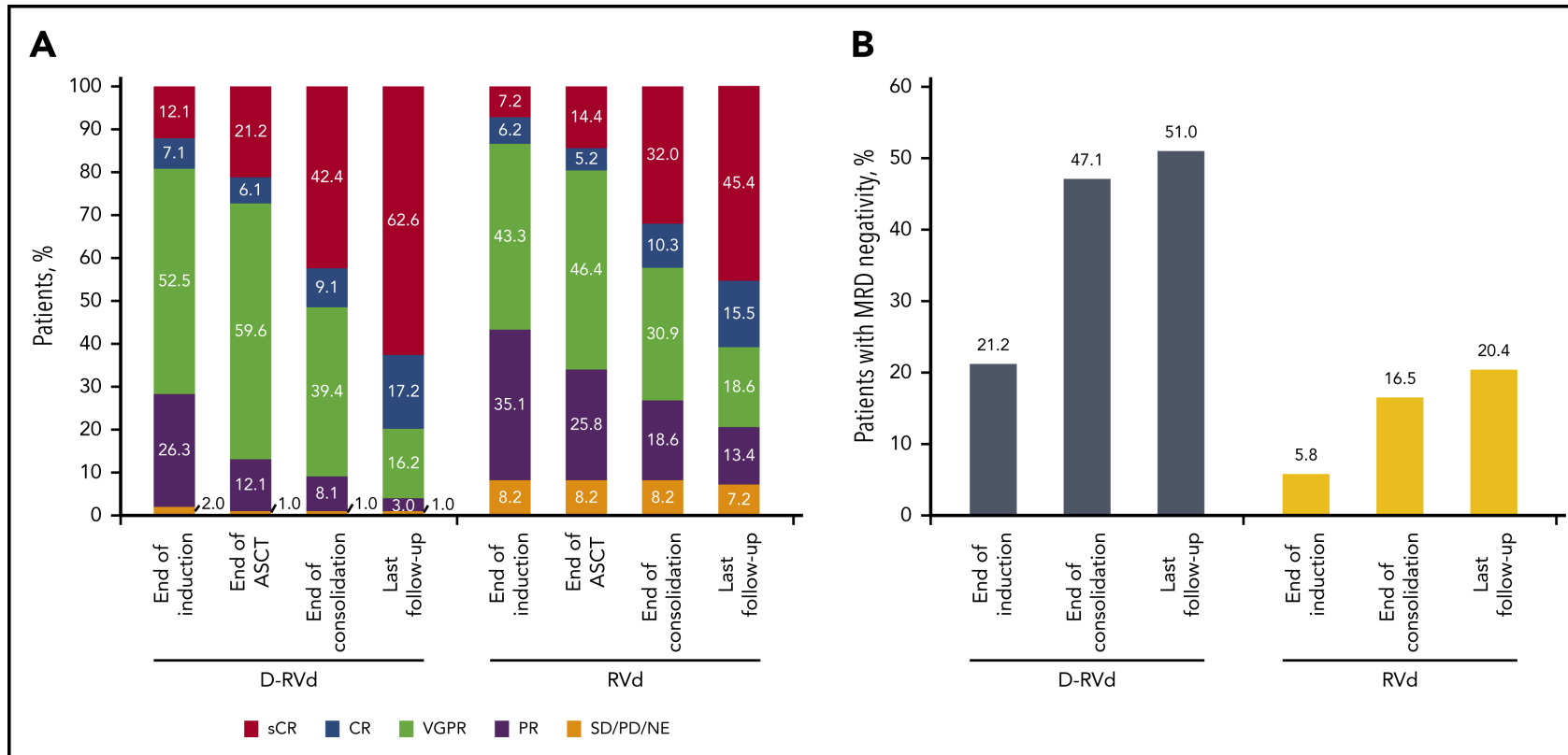


Laubach J, et al. ASH 2021. Abstr 79.

# Griffin Trial Design



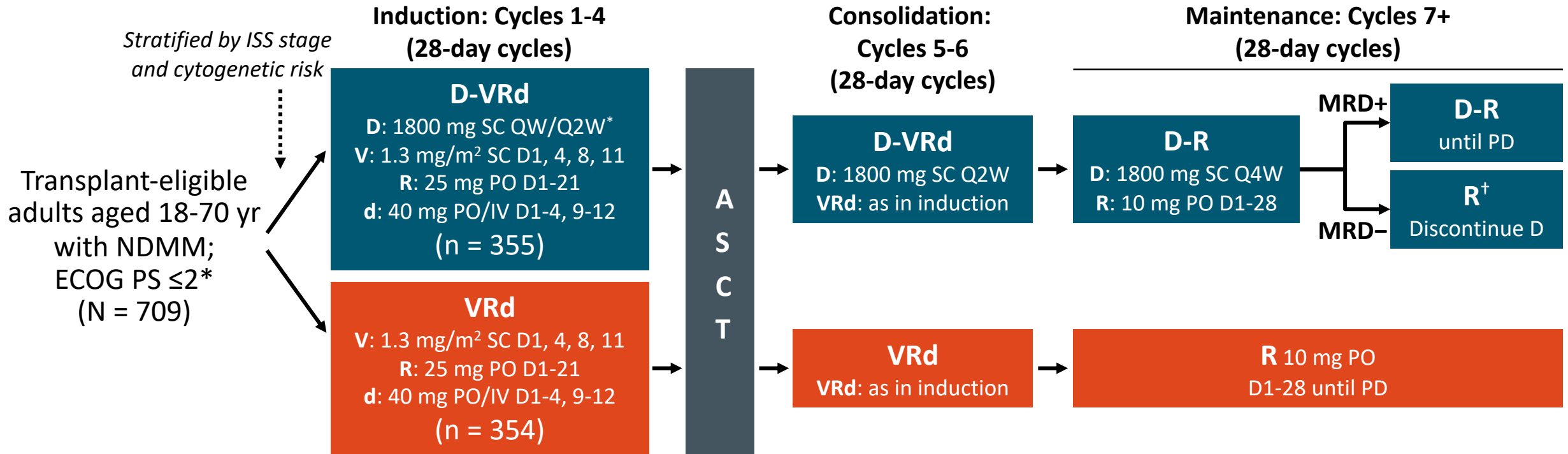
# Griffin Trial: Deeper response with ongoing therapy



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

# PERSEUS: Study Design

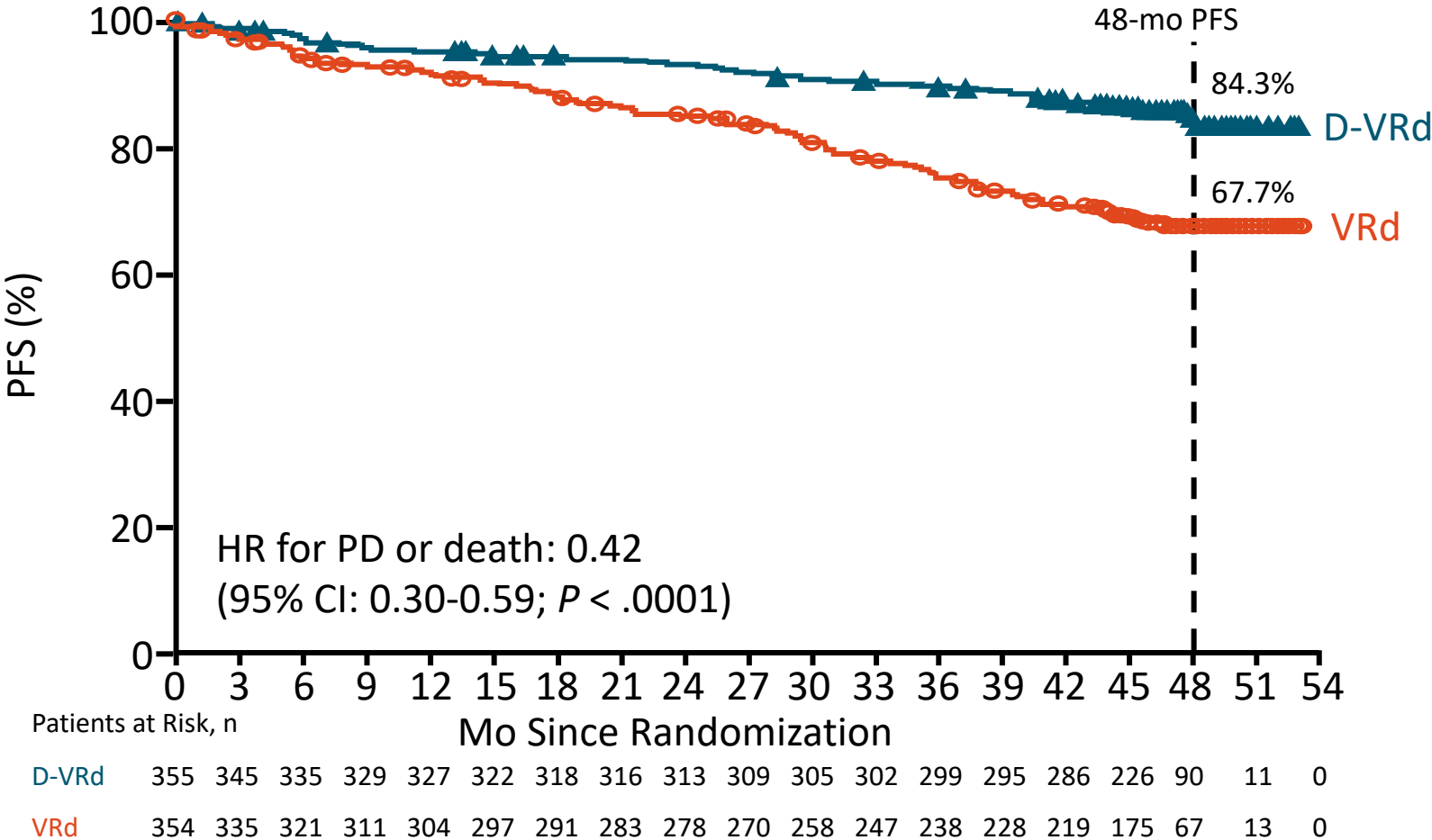
- Multicenter, open-label, randomized phase III trial; current analysis median f/u: 47.5 mo



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

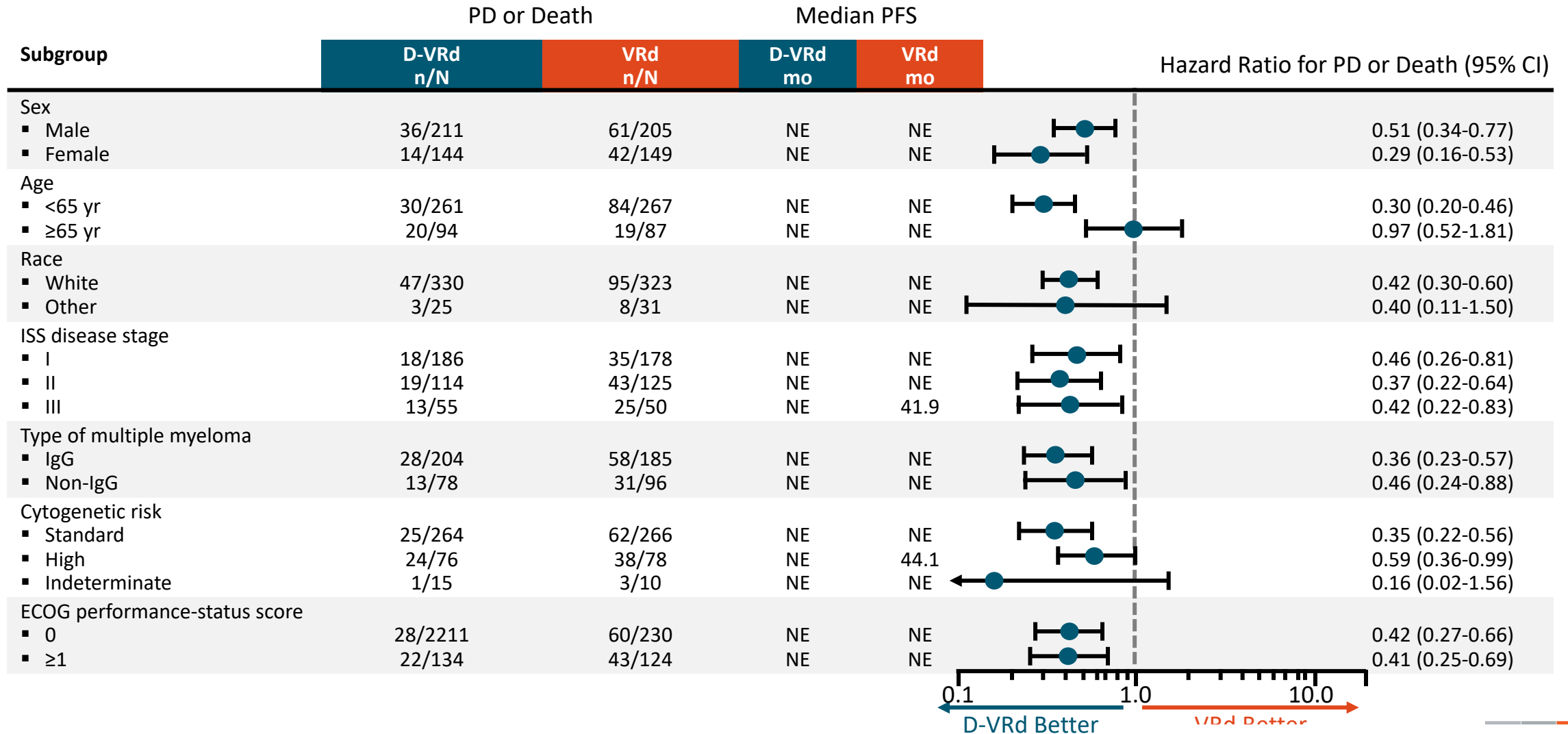
- Primary endpoint: PFS**
- Key secondary endpoints:  $\geq$ CR rate, MRD negativity rate, OS**

# PERSEUS Primary Analysis: PFS (Primary Endpoint)





# PERSEUS Primary Analysis: PFS Subgroup Analysis



# 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 <sup>-5</sup>	75.2	47.5	3.40 (2.47-4.69)	<.0001
▪ 10 <sup>-6</sup>	65.1	32.2	3.97 (2.90-5.43)	<.0001
Sustained MRD negativity (10 <sup>-5</sup> ) ≥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 <sup>-5</sup> ) over time, %			
▪ Post consolidation	57.5	32.5	25.0
▪ Overall	75.2	47.5	27.7
MRD negativity (10 <sup>-6</sup> ) 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)

# IsKia EMN24 Study Design

Induction  
*Four 28-day cycles*

Post-ASCT consolidation  
*Four 28-day cycles*

Light consolidation  
*Twelve 28-day cycles*

Key eligibility criteria:  
TE NDMM patients aged <70 years

Stratification:  
- Centralized FISH (standard risk/missing vs. high risk defined as del(17p) and/or t(4;14) and/or t(14;16);  
- ISS (I vs. II and III)

R

4× KRd

MOBILIZATION

Cy: 2-3 g/m<sup>2</sup>  
*followed by*  
G-CSF

for stem-cell collection

*and*

MEL200-ASCT

MEL: 200 mg/m<sup>2</sup>  
*followed by*  
ASCT

4× KRd

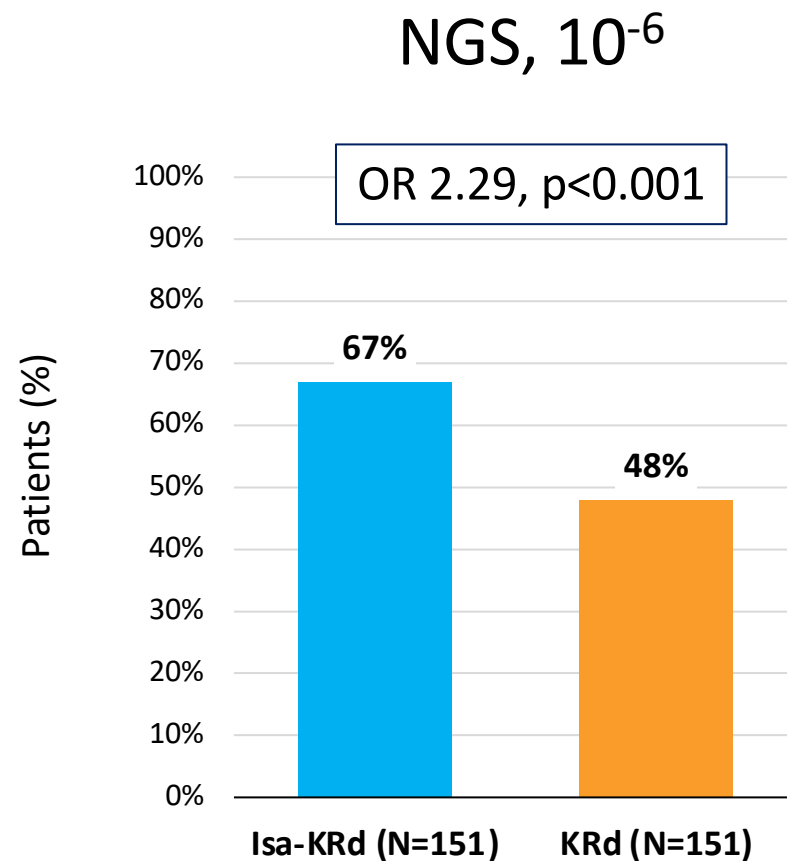
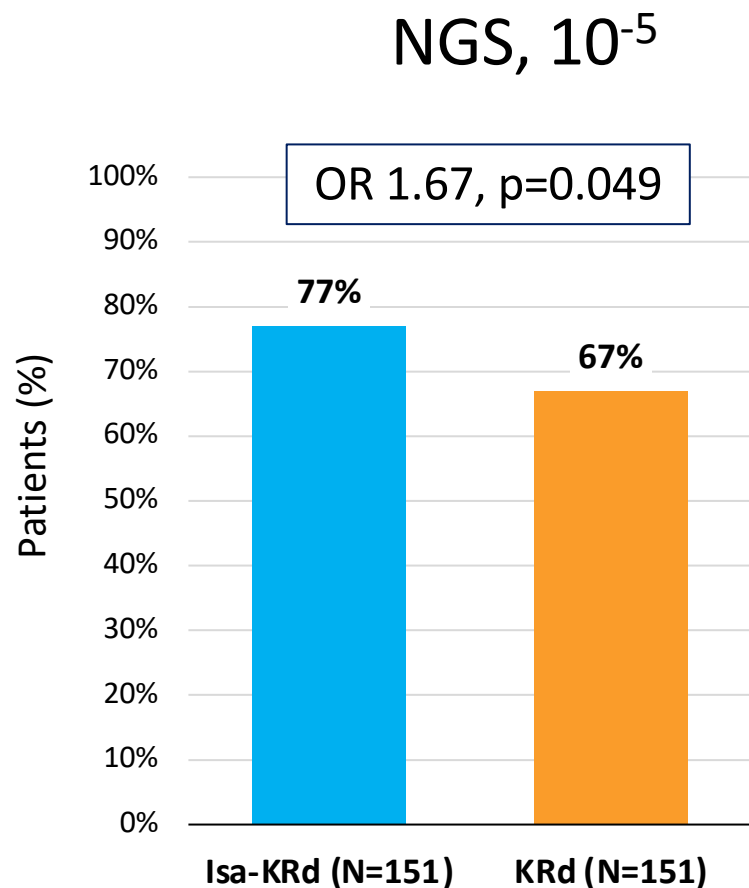
12× KRd

4× Isa-KRd

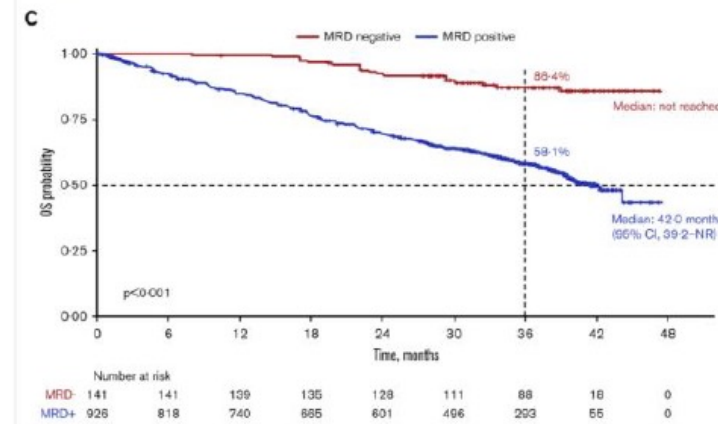
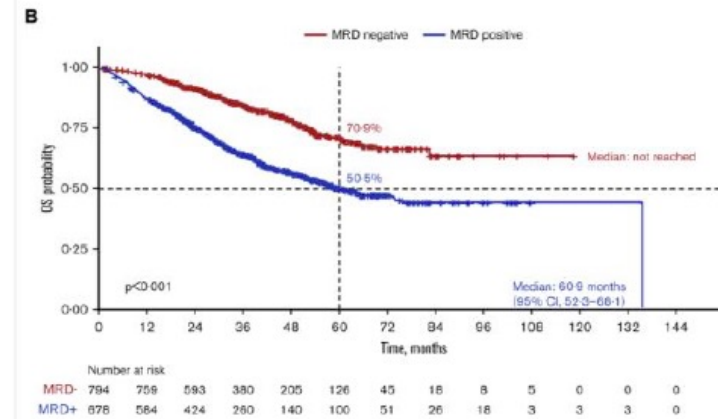
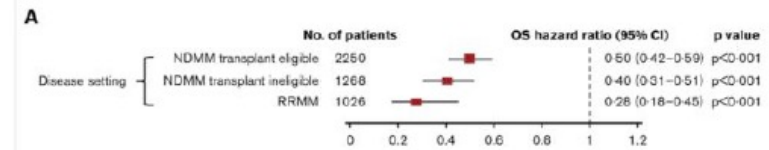
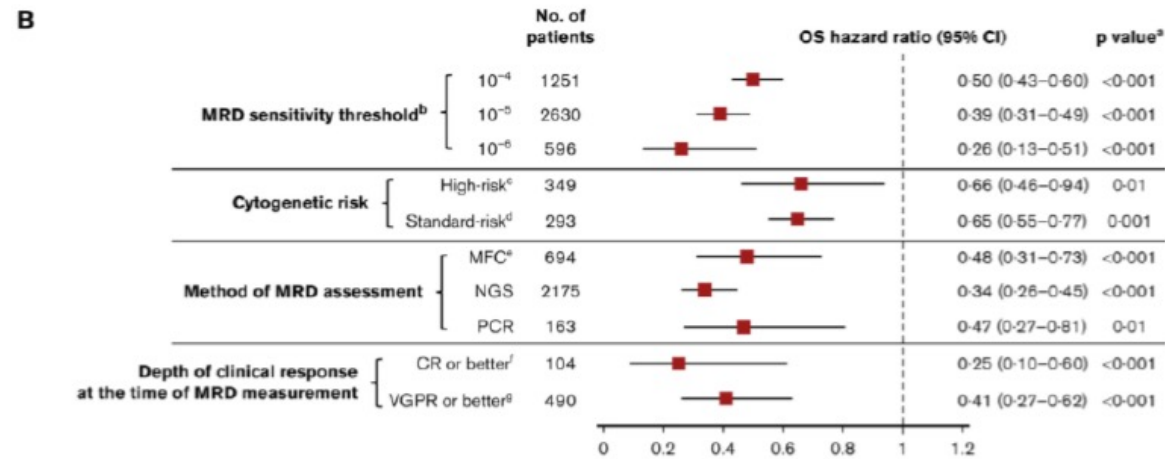
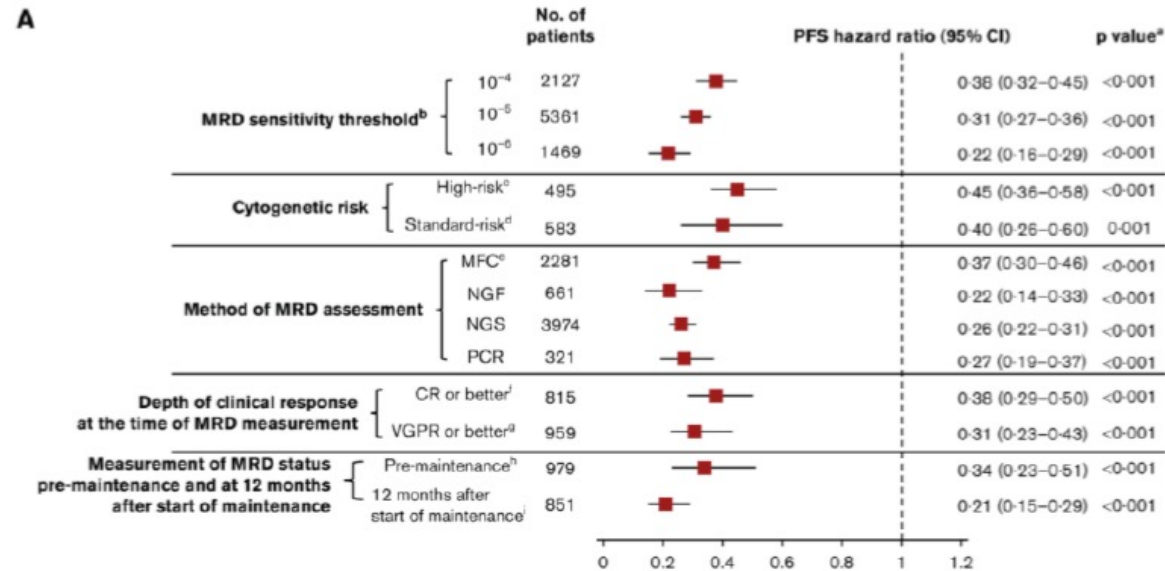
4× Isa-KRd

12× Isa-KRd

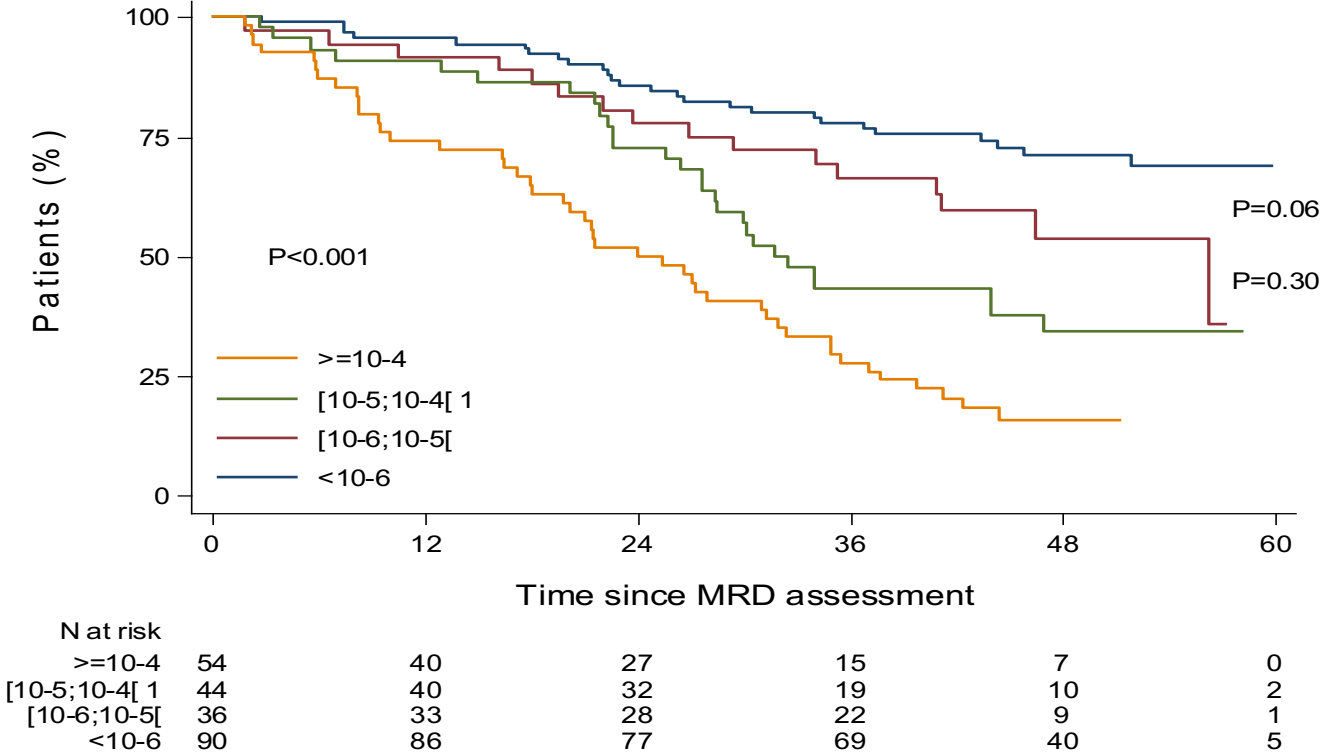
# Primary Endpoint: Post-consolidation MRD negativity (ITT analysis)



# Three Meta-Analyses Validated MRD for Prognosis

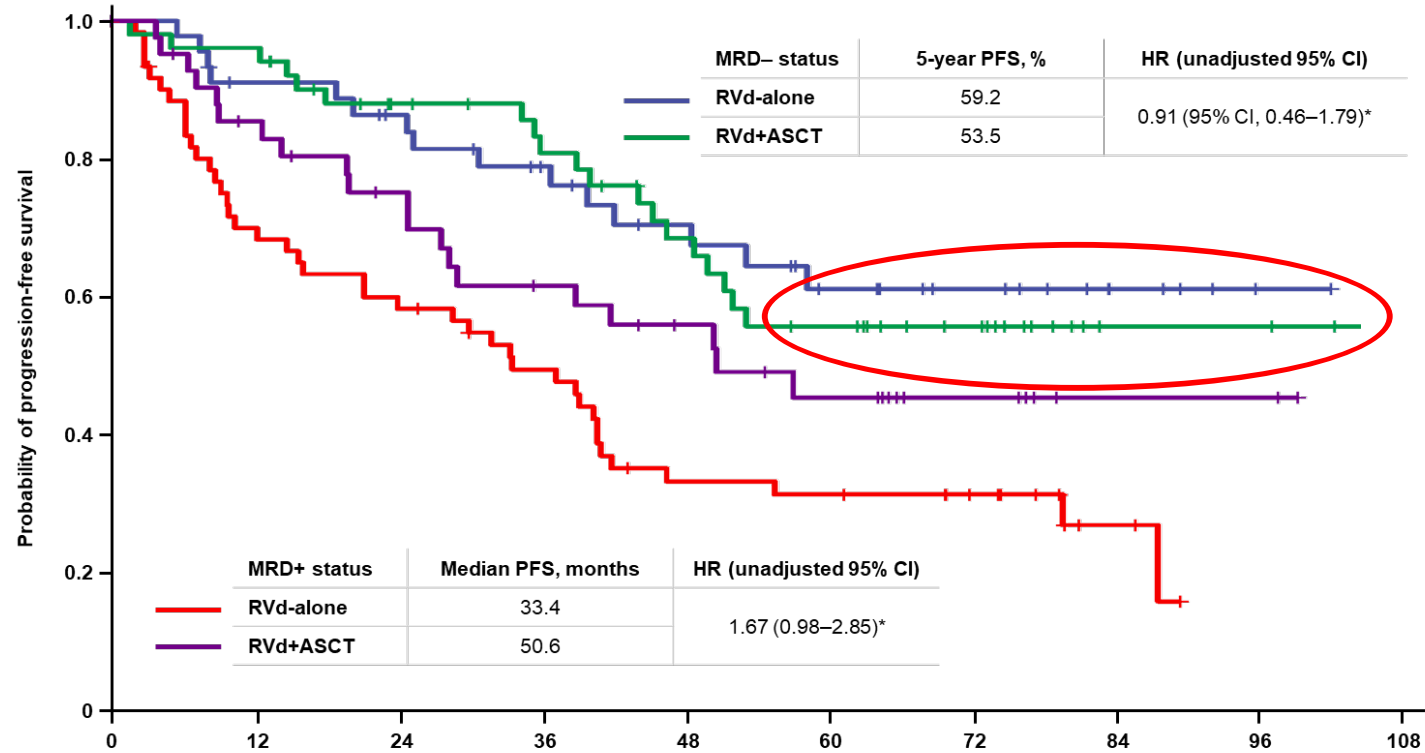


# Depth of Response Improves Outcomes : IFM 2009



# DETERMINATION: PFS by MRD Status

MRD was measured at the end of induction therapy

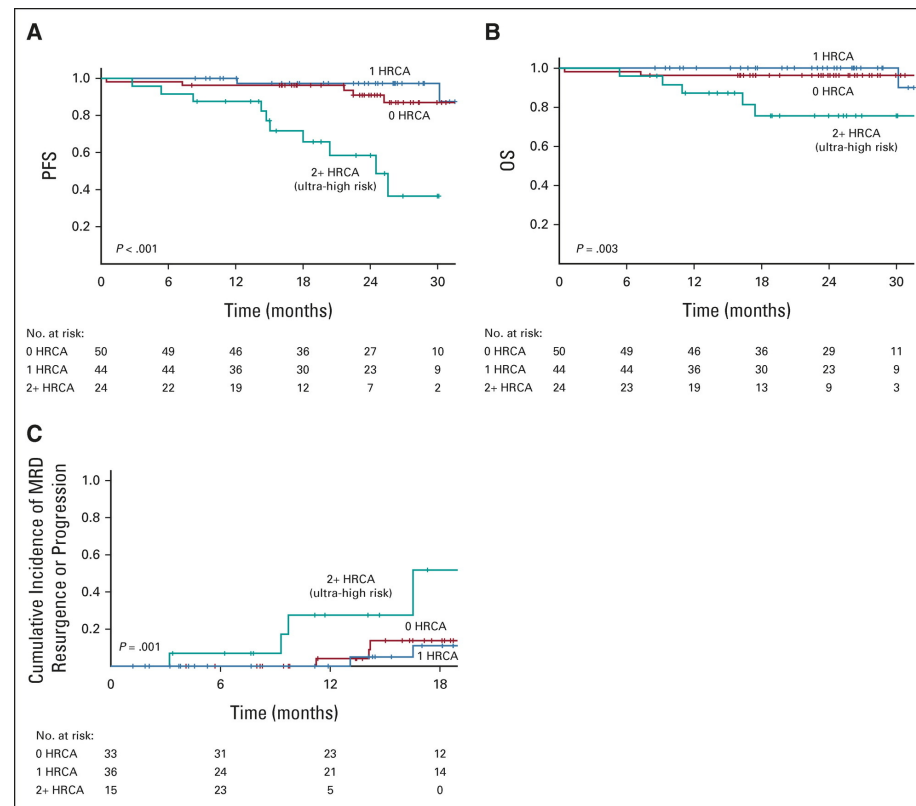
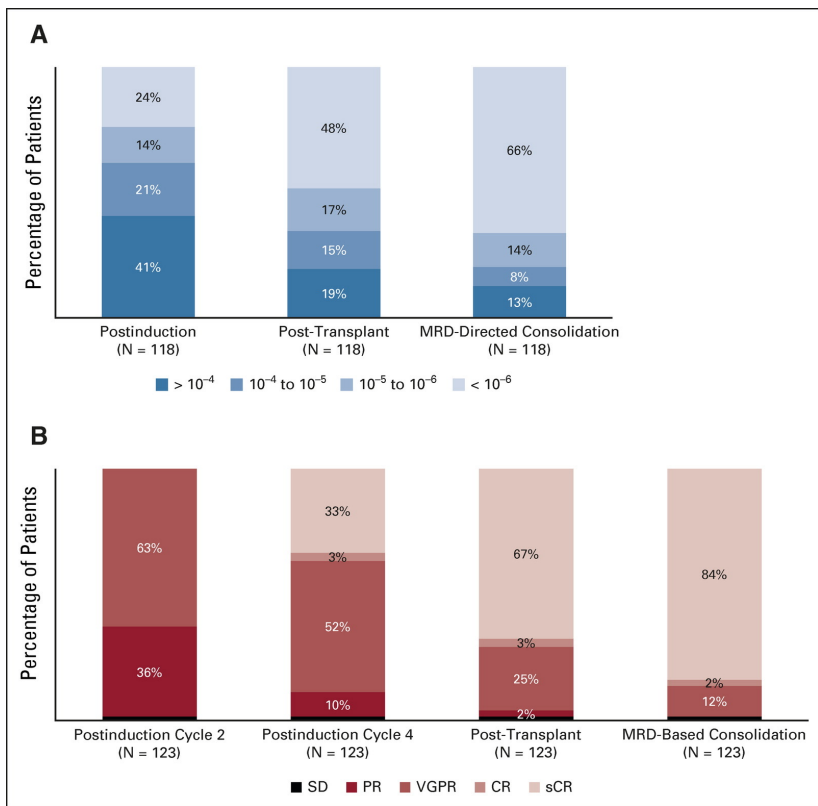


Patients at risk		Time since MRD evaluation at start of maintenance (months)									
		0	12	24	36	48	60	72	84	96	108
RVd-alone, MRD-	43	37	33	28	22	16	11	5	1	0	
RVd+ASCT, MRD-	49	47	37	32	25	19	13	3	3	0	
RVd-alone, MRD+	65	39	32	25	15	14	10	3	0	0	
RVd+ASCT, MRD+	41	32	26	20	15	11	6	2	2	0	

• Richardson P, et al. *NEJM* 2022; DOI: 10.1056/NEJMoa2204925.

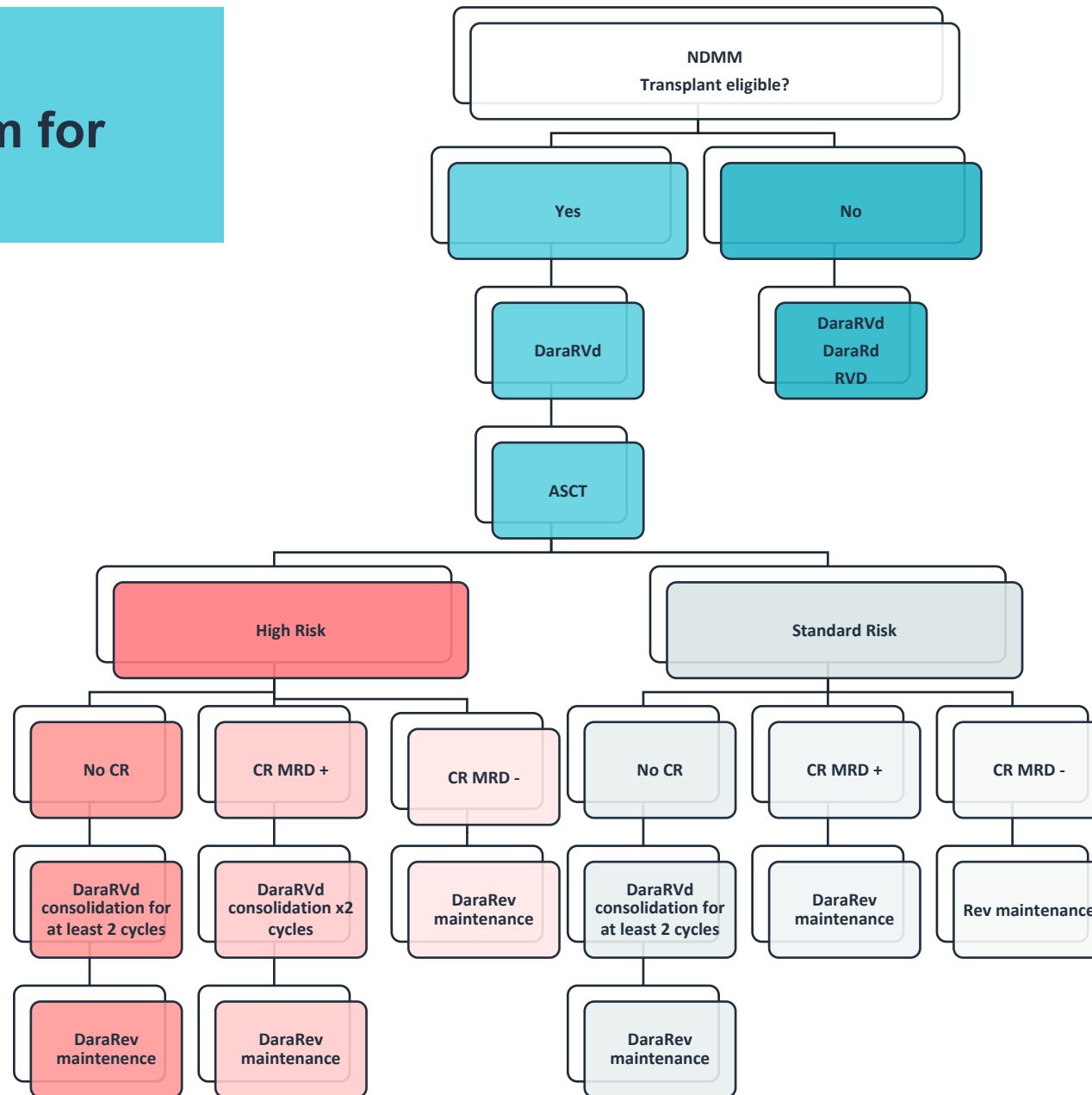
• \*There were multiple MRD timepoints in this study, but only the data for this timepoint has been presented to date.

# Master Trial: MRD Response Over Time and Impact of Cytogenetics





# TGH Response-Adjusted Algorithm for NDMM





Requirements:

initial seeding/sodding

fertilization

ongoing lawn maintenance – watering and mowing

# Conclusions

- While incurable, PFS and OS is improving significantly
- 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