



# How I Treat Newly Diagnosed MM

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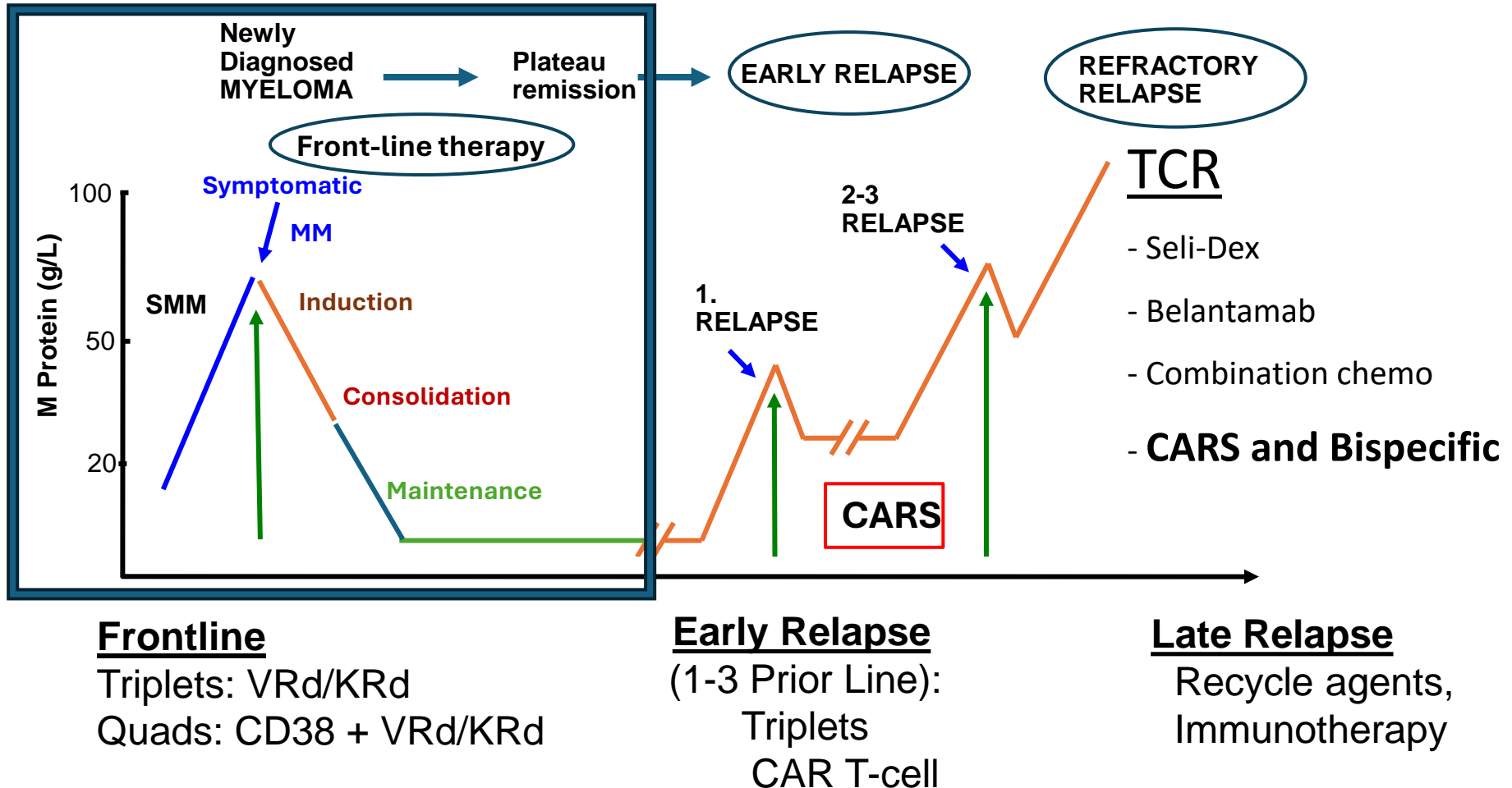
UCSF Medical Center

San Francisco, California



# Therapy for NDMM and RRMM:

*A plethora of options – which are BEST?*



# AGENTS APPROVED for MULTIPLE MYELOMA

Proteasome Inhibitors	IMiDs	Alkylating Agents	Monoclonal Antibodies	Targeted Agents	Bispecific Antibodies	CAR T-cells BCMA-directed
Bortezomib	Lenalidomide	Cyclophosphamide (PO>IV)	Daratumumab	(CTs)	(CTs)	(CTs)
Carfilzomib		Melphalan (IV)	Isatuximab			
Ixazomib	Pomalidomide	Doxorubicin (liposomal)	Elotuzumab	Selinexor	Elranatamab Teclistamab	Ciltacabtagene autoleucel
		PACE/CVAD Cyclophosphamide (IV>PO)		<i>Belantamab</i> <i>Venetoclax</i>	Talquetamab	Idecabtagene vicleucel

**NDMM:** multiple options for 3 and 4 drug combinations: with corticosteroids used in most (except Frail)

**RRMM:** Almost an infinite # of combinations of these agents: with corticosteroids in most (Dex)

*Where and When to use these agents* → **Sequencing**

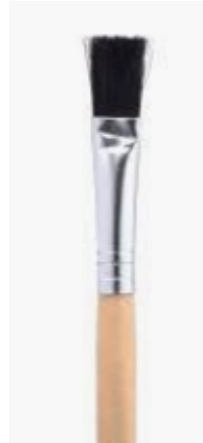
# NDMM: Many Scenarios and Questions => ART of MM

- Best induction/strategies

- Standard/High-risk MM
- Renal insufficiency
- MM with amyloidosis
- Add-in for Frail

- Maintenance

- Forever or time limited
- 1, 2 or 3 drugs
- CD38 before/after/both



- Questions with many answers

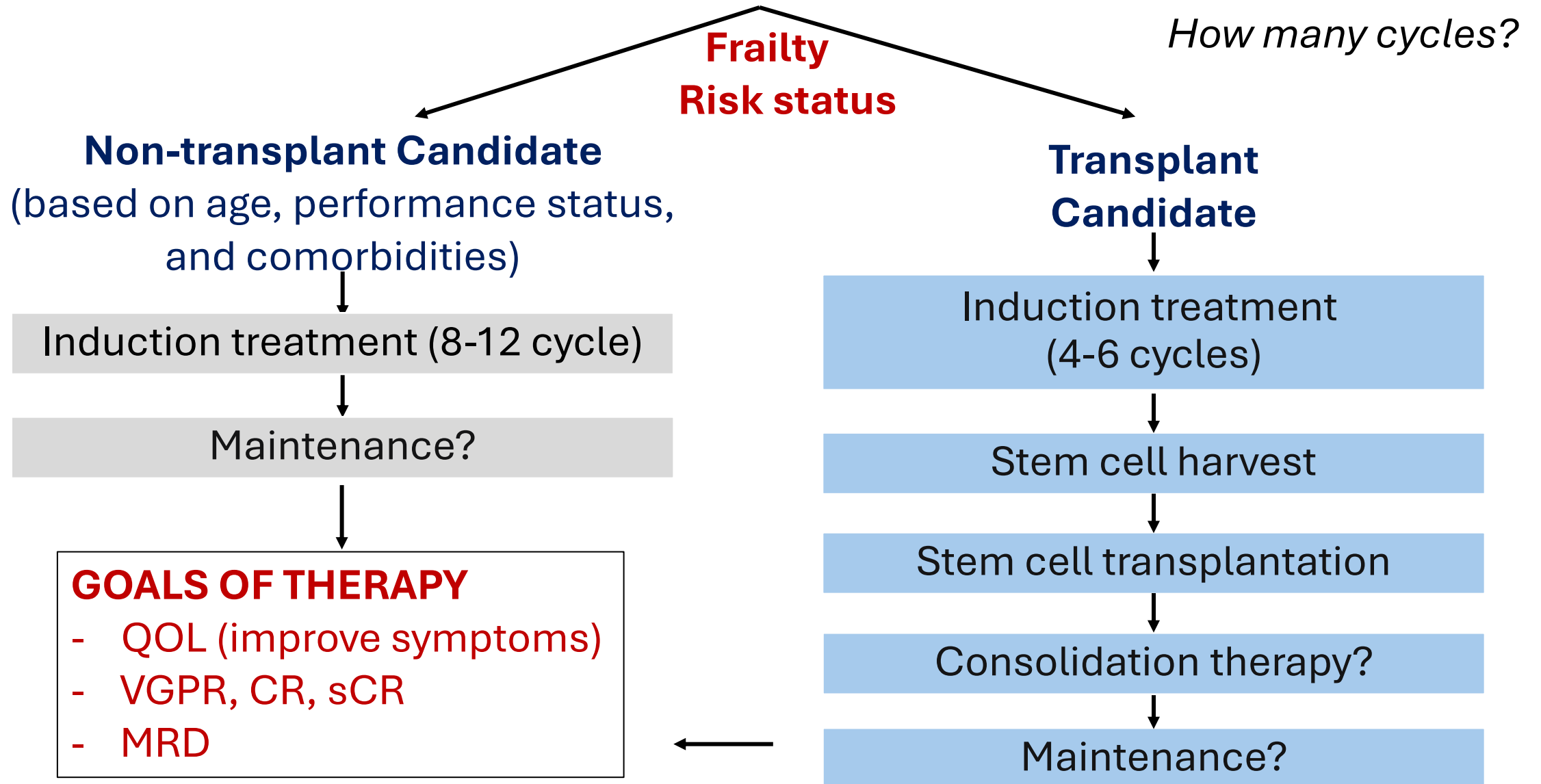
- How many cycles to give
- When to collect stem cells (VGPR?)
- When to stop Dexamethasone

- Should MRD be measured in all?

- Used to stop therapy?
- Used to escalate therapy?

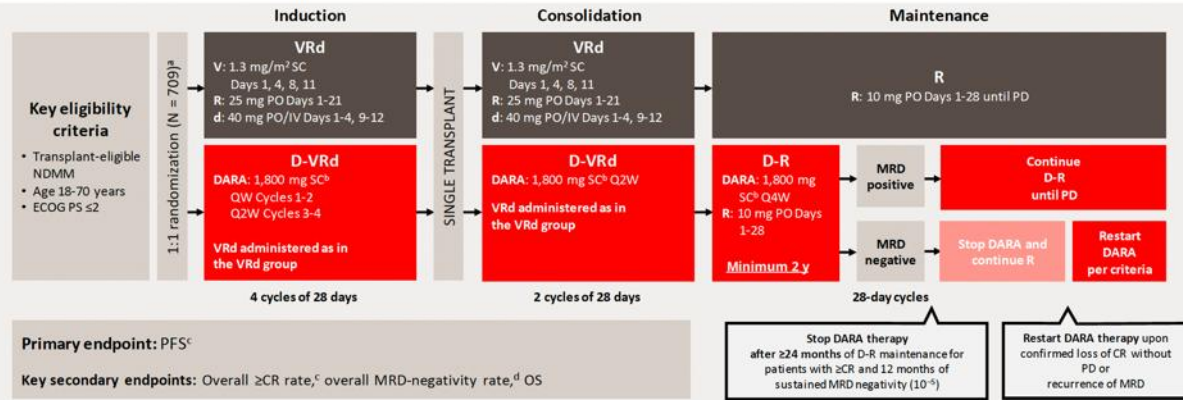


# Initial Approach to Treatment of Myeloma

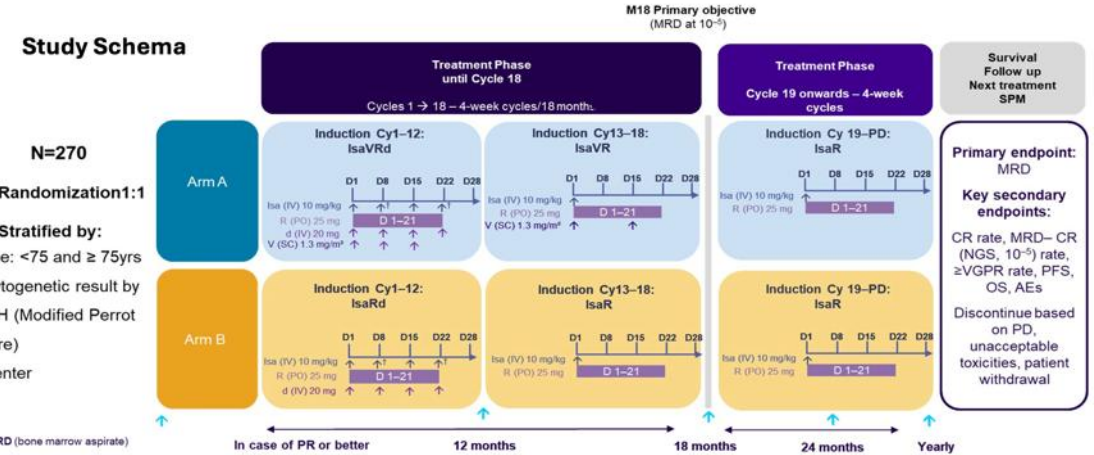


# Frontline for TE/TI: Quads (CD38 - VRd for ALL?)

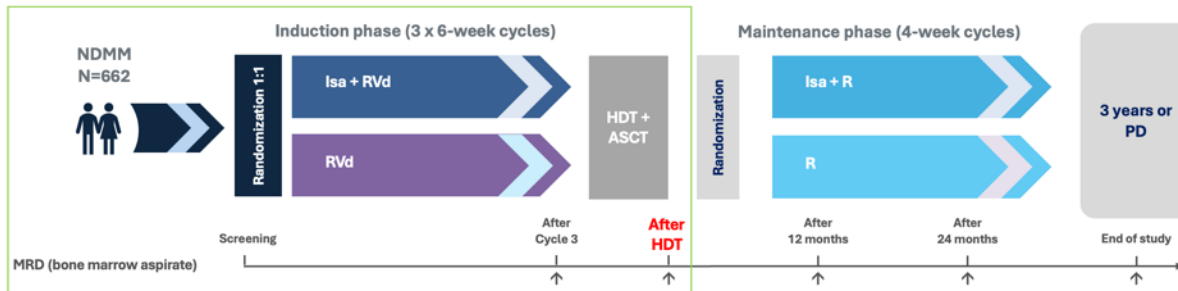
## PERSEUS: Study Design



## BENEFIT Trial: Isa-VRd vs. Isa-RD in TI NDMM



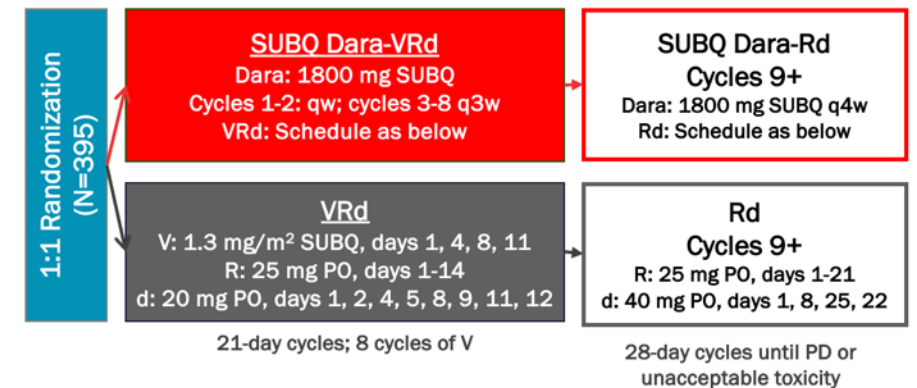
## GMMG-HD7 interim analysis: MRD negativity after HDT + ASCT (intensification)



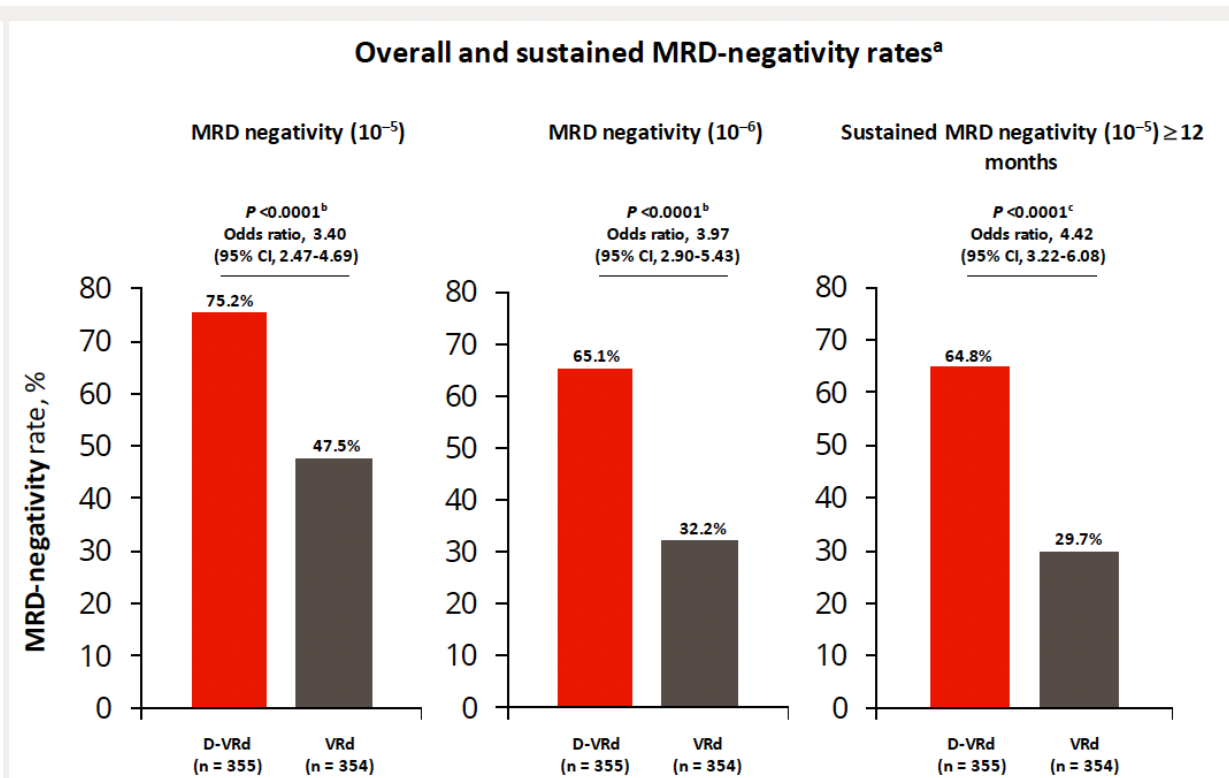
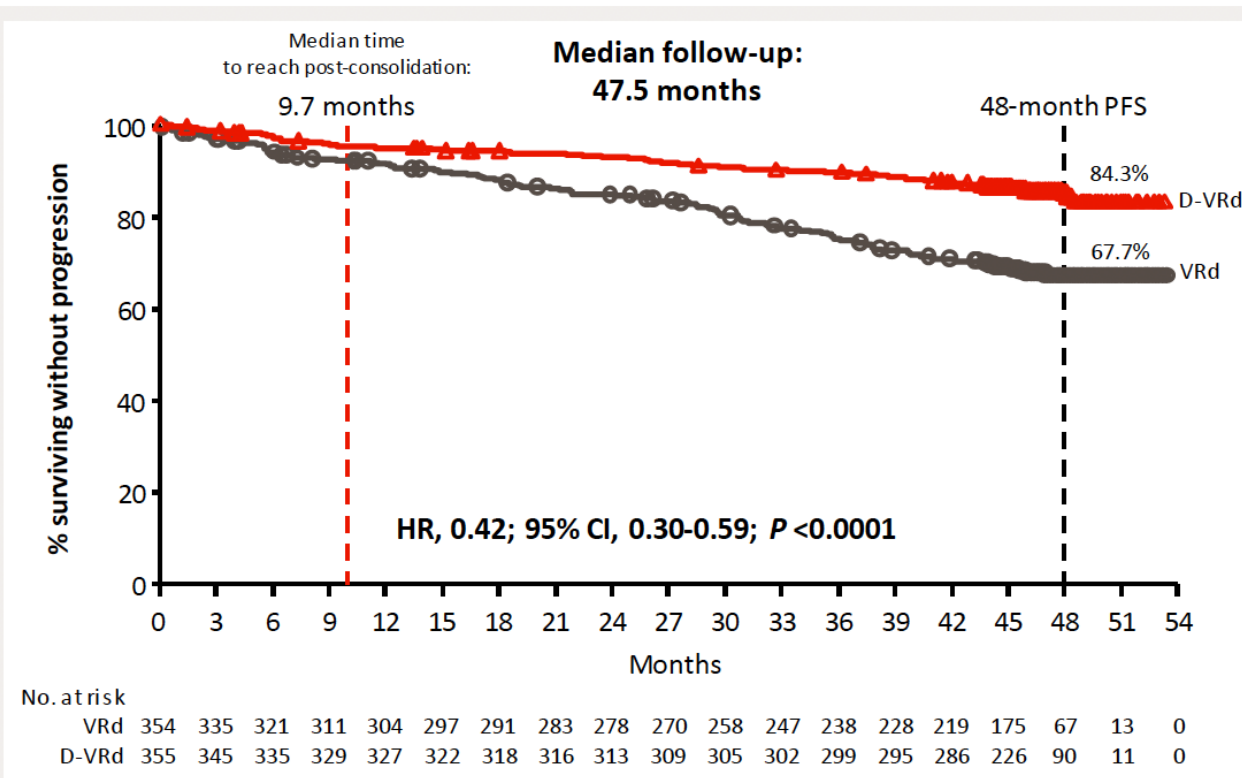
## Key Eligibility Criteria

- NDMM (transplant ineligible or deferred)
- ECOG PS 0-2; frailty score of 0-1

## CEPHEUS



# PERSEUS Primary Analysis: D-VRd Followed by D-R Maintenance Significantly Improved PFS and Depth of Response Versus VRd Followed by R Maintenance<sup>1</sup>



**58% reduction in the risk of progression or death in patients receiving D-VRd**

**Deep and durable MRD negativity achieved with D-VRd**

HR, hazard ratio; CI, confidence interval. <sup>a</sup>MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and  $\geq$ CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). <sup>b</sup>P values were calculated with the use of the stratified Cochran–Mantel–Haenszel chi-square test.

<sup>c</sup>P value was calculated with the use of Fisher’s exact test.

1. Sonneveld P, et al. *N Engl J Med.* 2024;390(4):301-313.

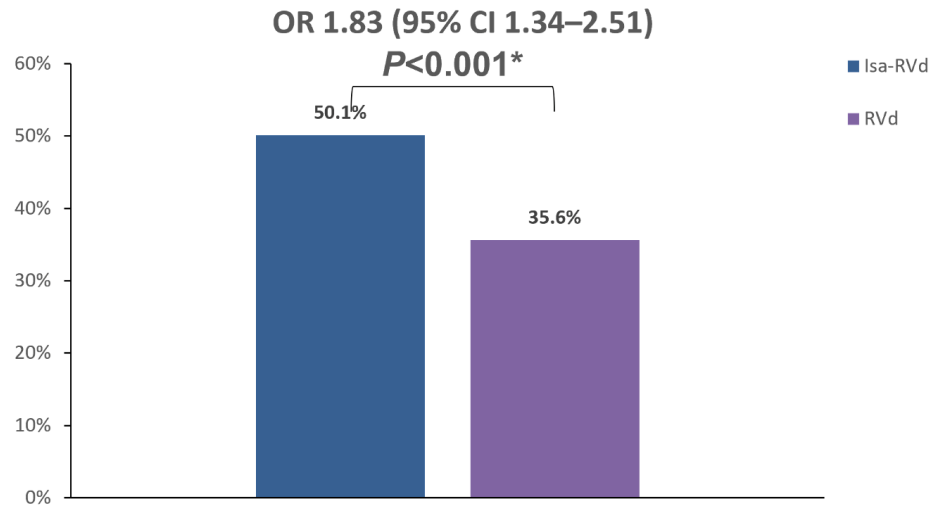


# Isa in TE: RESULTS

## GMMG-HD7: Isa-RVd

### - Interim analyses:

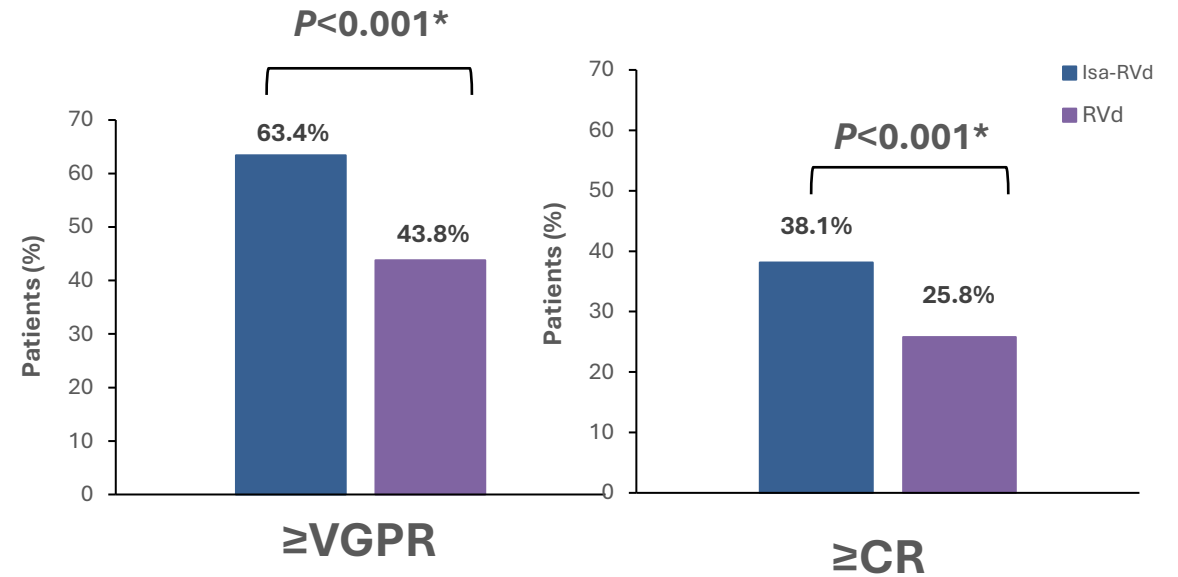
Patients with MRD negativity at the end of induction therapy



Low number of not assessable/missing† MRD status: Isa-RVd (10.6%) and RVd (15.2%)

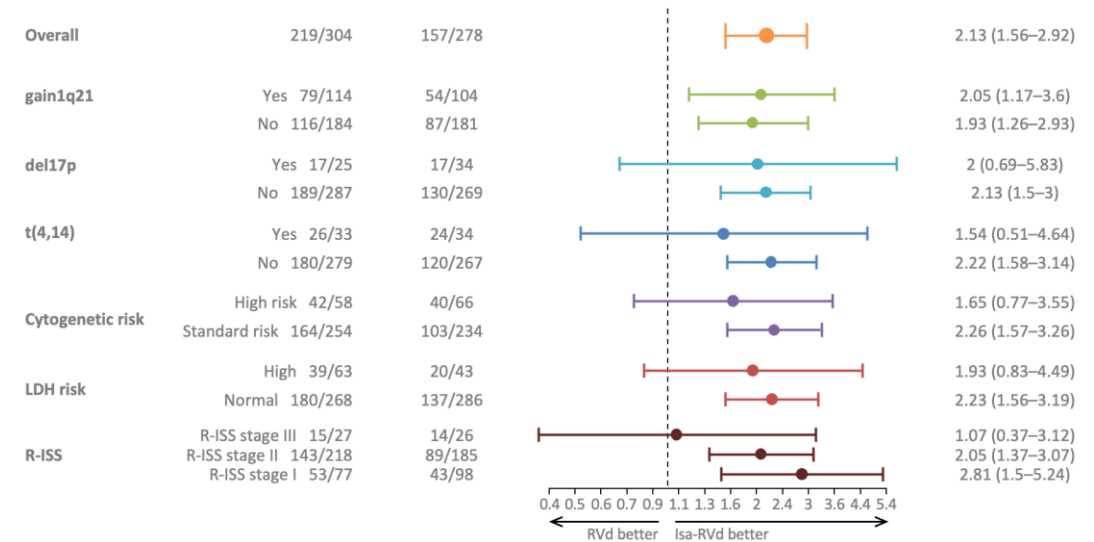
- MRD negativity reported at ASH 2021
- Updated at IMS 2024

\*P value derived from stratified conditional logistic regression analysis.  
CR, complete response; d, dexamethasone; Isa, isatuximab; ITT, intent to treat; MRD, minimal residual disease; NGF, next-generation flow; R, lenalidomide; V, bortezomib; VGPR, very good partial response.



Patients with MRD negativity, in indicated response status, after Intensification

### MRD negativity benefit of Isa-RVd across risk groups\*



# Results: MRD in TI - NDMM

## BENEFIT

### Primary endpoint

OR (95% CI):  
3.16 (1.89–5.28)  
P<0.0001

53

26

10<sup>-5</sup>

OR (95% CI):  
2.74 (1.54–4.87)  
P=0.0006

36

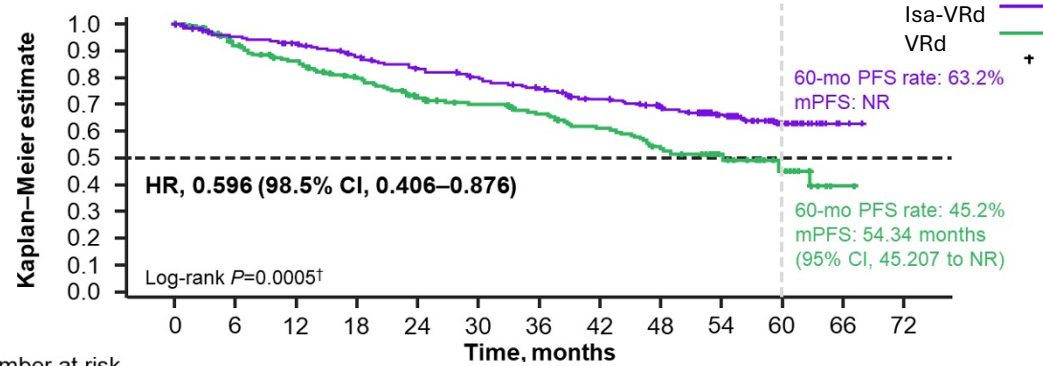
17

10<sup>-6</sup>

F/u=24m; too early for PFS

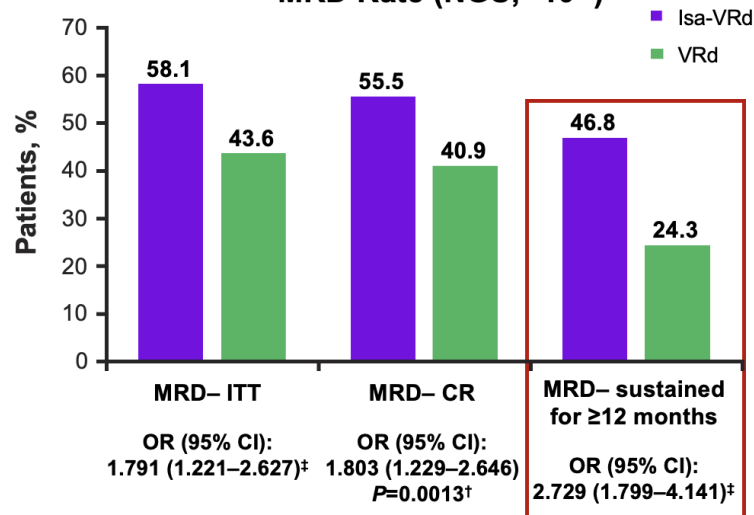
## IMROZ (F/u ~60m)

162 PFS events: 84 (31.7%) in Isa-VRd; 78 (43.1%) in VRd\*



Number at risk

## MRD Rate (NGS,\* 10<sup>-5</sup>)

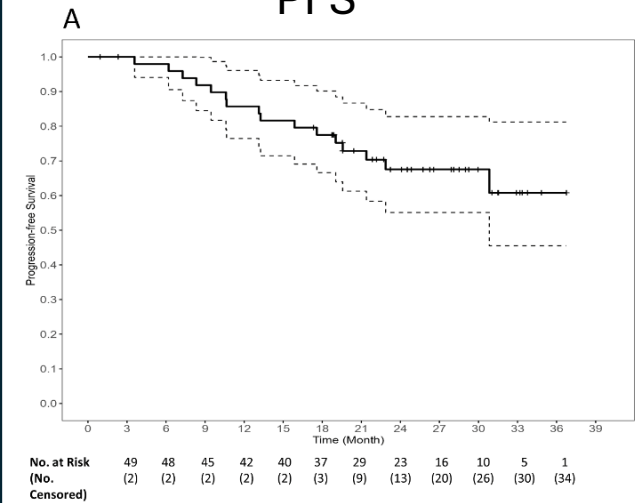


## REST (TI, and >79)

### Primary Endpoint

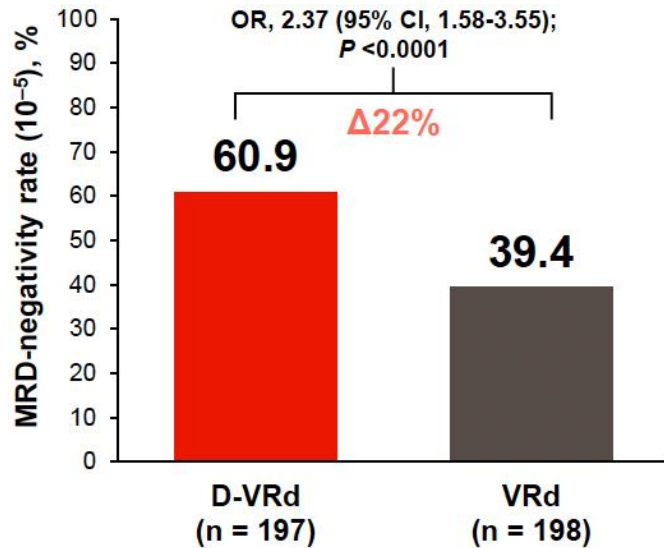
- MRD (-) CR
- N=50
- 37%

## PFS

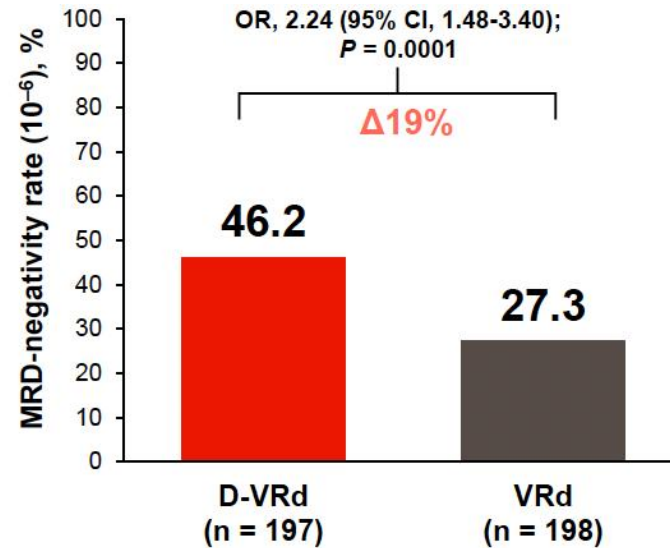


# CEPHEUS Phase 3 Study of SUBQ Dara-VRd vs VRd in TI or –Deferred Patients With NDMM: MRD-Negative and Response Rates

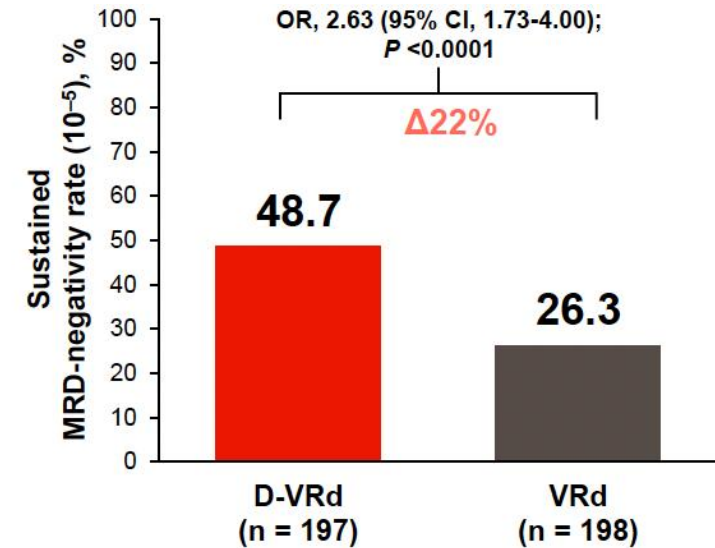
Overall MRD-Negative Rate ( $10^{-5}$ )



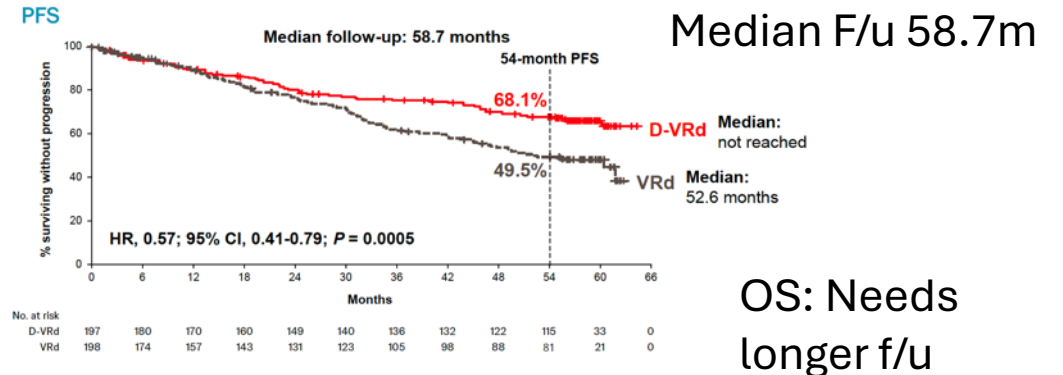
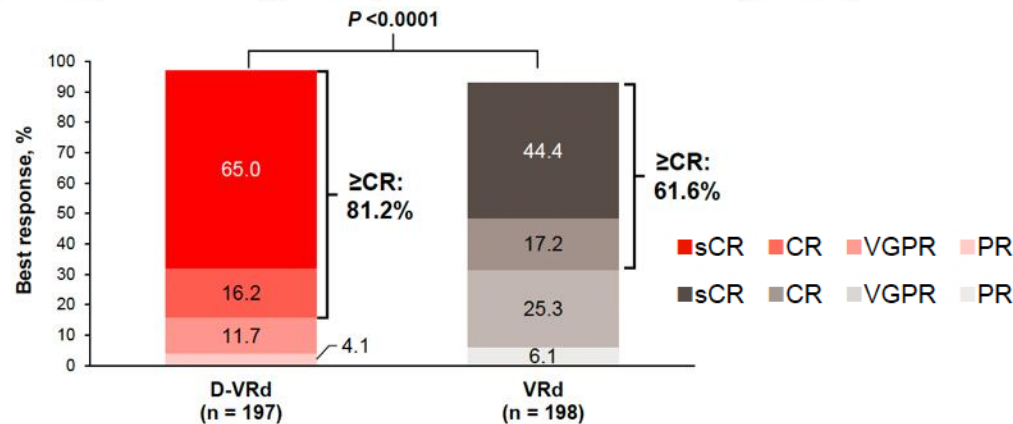
Overall MRD-Negative Rate ( $10^{-6}$ )



Sustained MRD-Negative Rate ( $10^{-5}$ )  $\geq 12$  Months

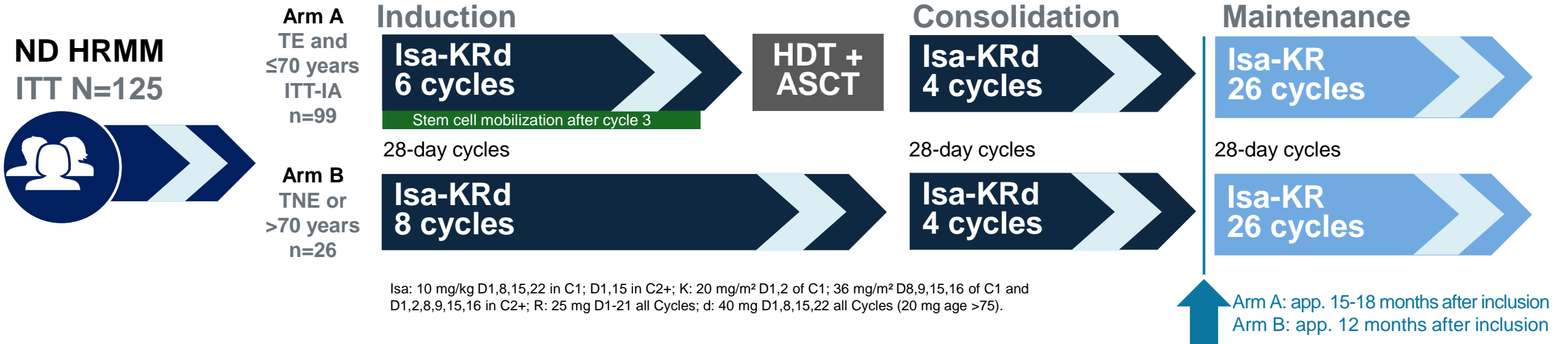


$\geq$ CR Rate



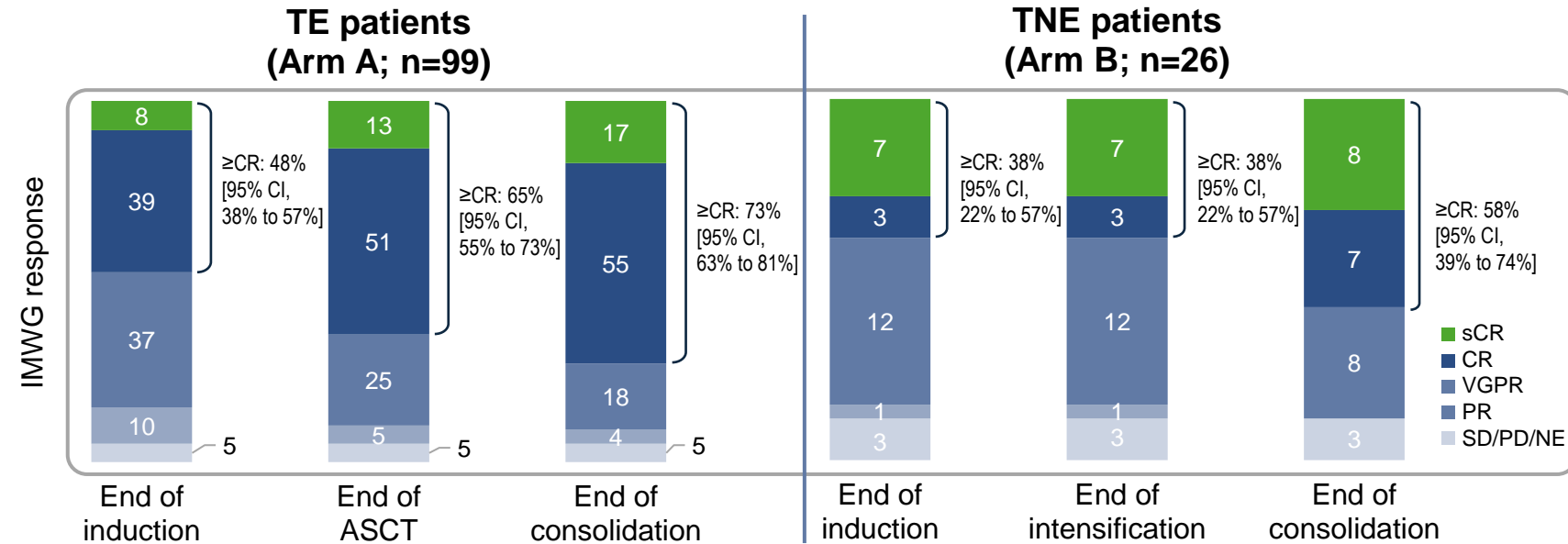
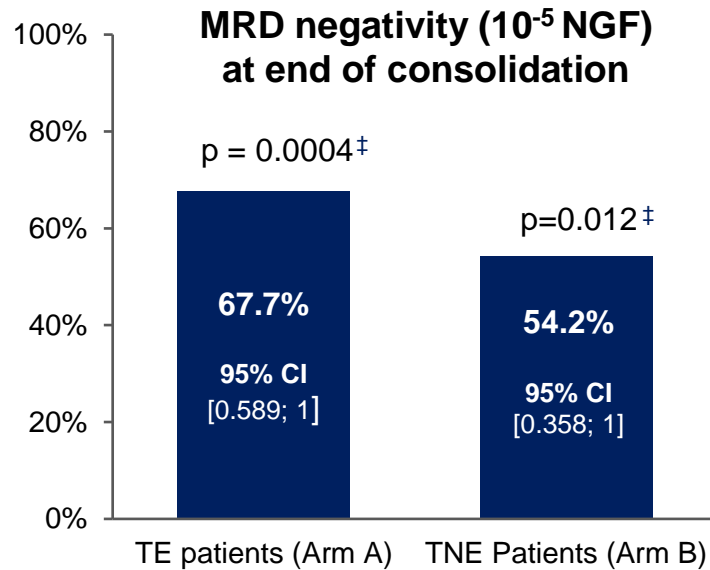
OS: Needs longer f/u

# GMMG CONCEPT TRIAL: Study Design



**HRMM criteria:** ISS stage II or III **PLUS** ≥1 of: del(17p), t(4;14), t(14;16) and/or >3 copies 1q21 (amp1q21)  
**Primary objective:** MRD negativity after consolidation (NGF, 10<sup>-5</sup>)  
**Secondary objective:** PFS; Key tertiary objectives: ORR, OS, safety

# CONCEPT Trial: MRD Negativity and IMWG Response



MRD status, n (%)	TE patients (Arm A) (n=93*)	TNE patients (Arm B) (n=24†)
Negative	63 (67.7)	13 (54.2)
Positive	3 (3.2)	0 (0)
Not done/missing	2 (2.2)	0 (0)
Time point not reached	25 (27.0)	11 (45.8)

6 TE and 2 TNE patients were not assessable

Footnotes

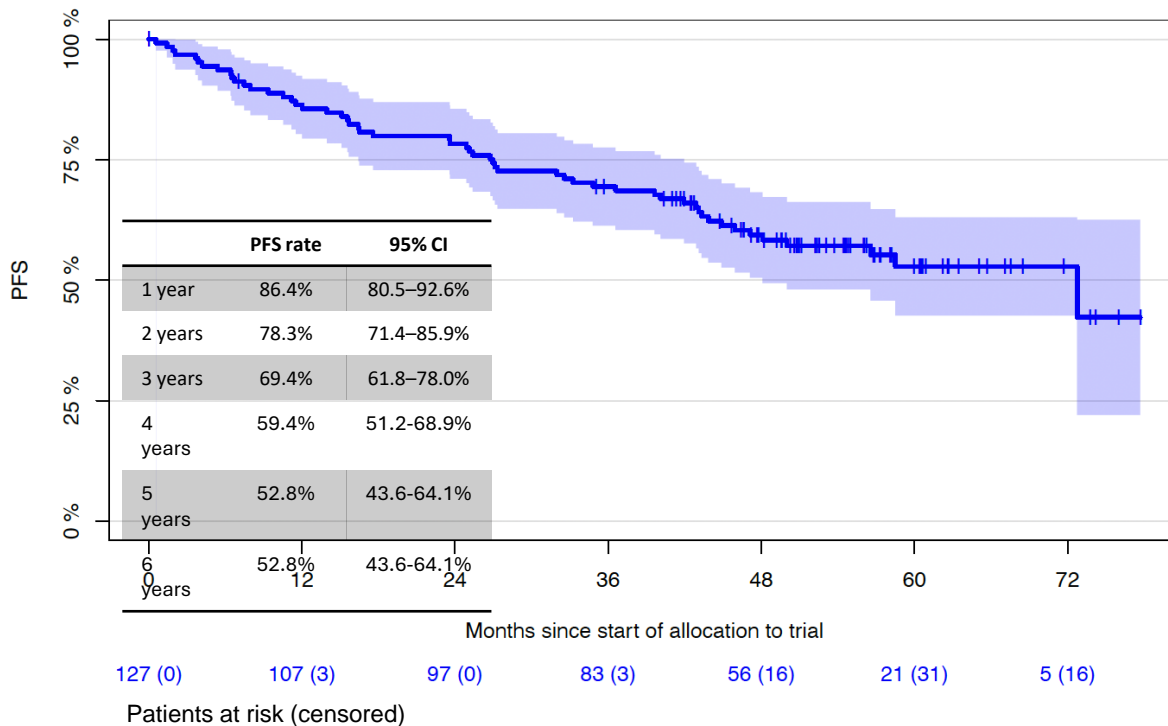
- The trial met its primary endpoint with MRD negativity rates of 67.7% (TE) and 54.2% (TNE) at the end of consolidation
- Responses deepened over time with  $\geq$ CR-rates of 72.7% (TE) and 57.7% (TNE) as best response

# CONCEPT: Progression-free Survival

## ≥4-Year-Follow-Up

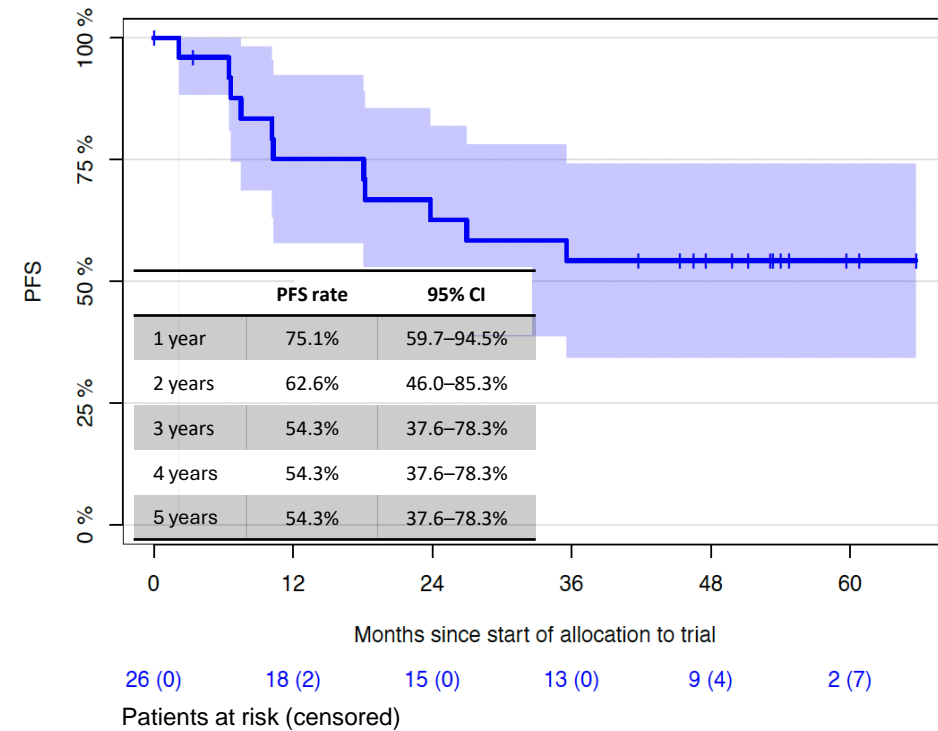
### Transplant-eligible patients

Median follow-up of 54 months (range, 0-77.7)



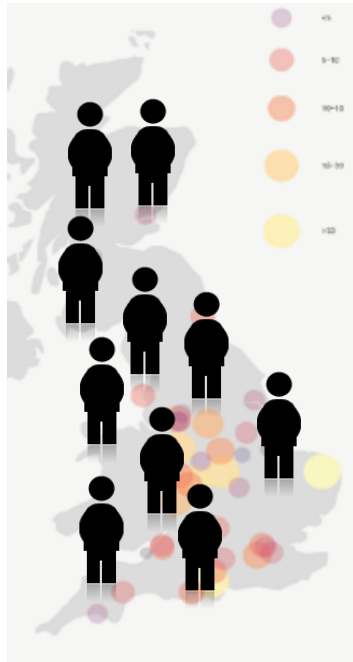
### Transplant-noneligible patients

Median follow-up of 51 months (range, 0-67.7)

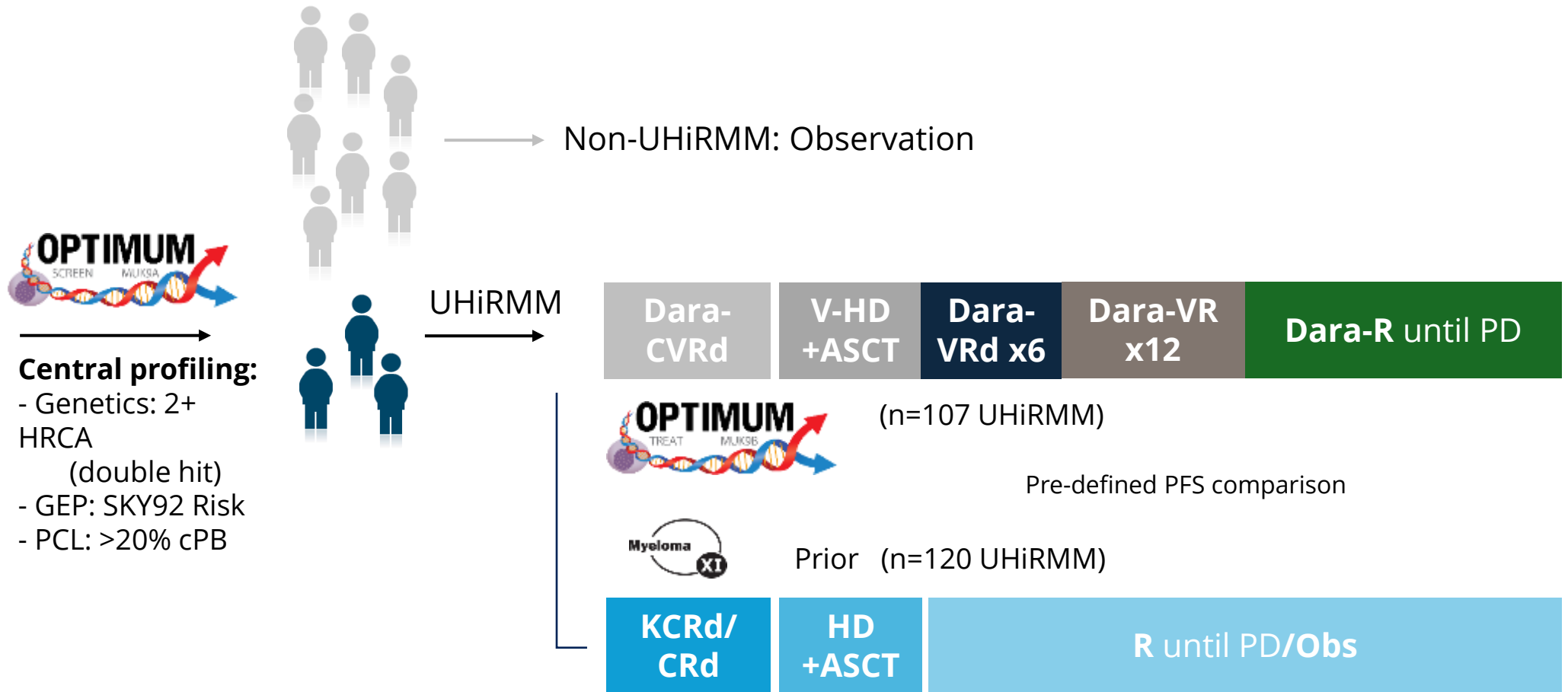


**Six years after treatment initiation, more than 50% of patients are alive and progression-free**

# OPTIMUM/MUKnine – Screening and Treatment Trial



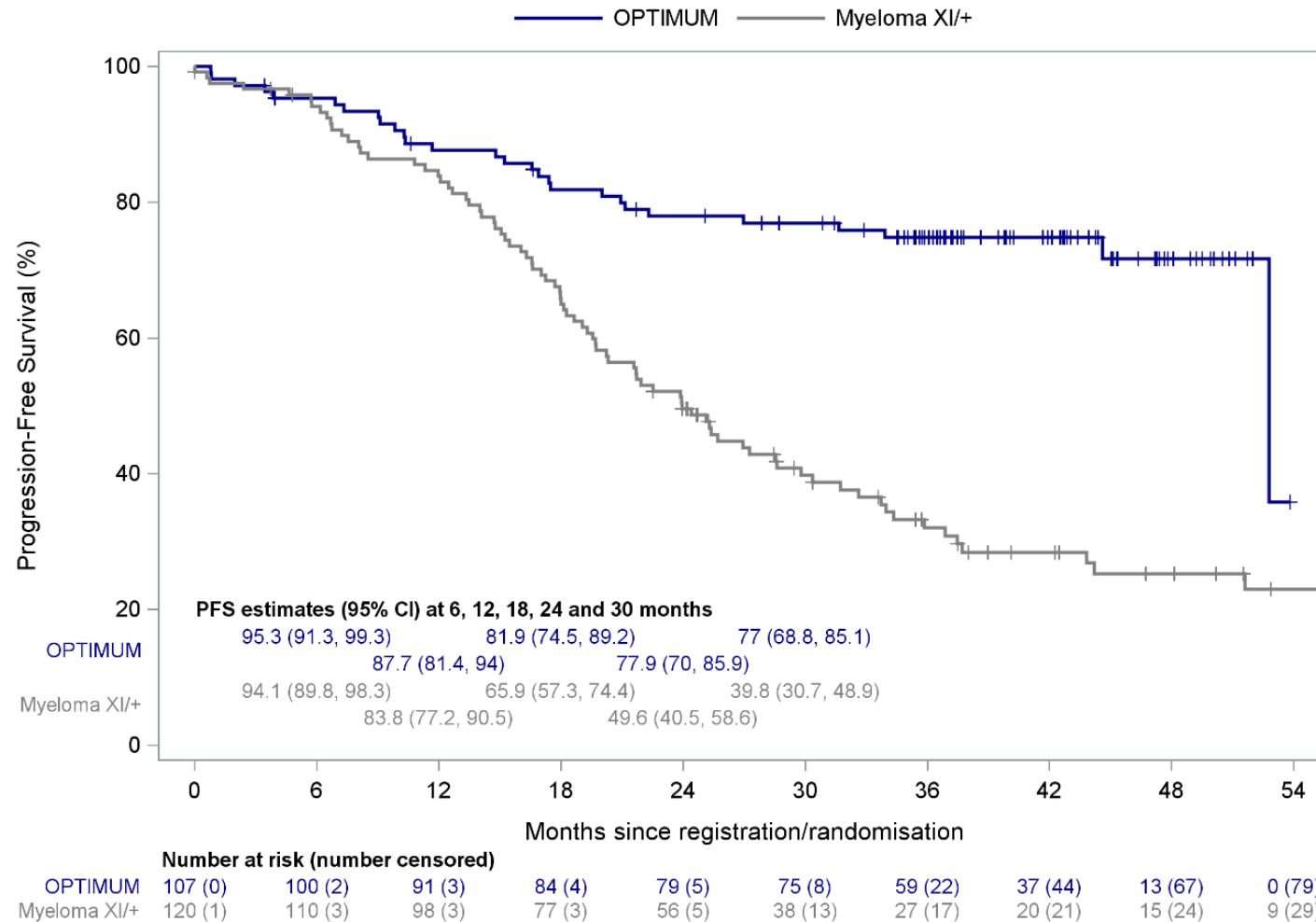
**All-comer TE NDMM**  
 No age limit  
 No screening delay  
 39 NHS hospitals  
**472 patients**



Identified via **same central profiling** methods and UHiRMM criteria  
 From 590 all-comer TE NDMM

**In total, 1,062 All-comer NDMM patients screened**

# OPTIMUM (MUKnine) vs. Myeloma XI: PFS



**Median follow-up  
41.2 months**

**How I Treat: TE and TI → GOAL is to get to sCR (MRD(-)) at end of consolidation  
Continue 3 drug maintenance for 2-3+ yrs, ongoing**

# Initial Approach to Treatment of Myeloma

*How do I Treat?*

*How many cycles?*

**Non-transplant Candidate**

**Transplant Candidate**

Induction treatment (8-12 cycle)

Induction treatment (4-6 cycles)

SR  
DRd/D-VRd

HR  
D-VRd

QUADS

SR  
D-VRd

HR  
D-VRd/Dara (Isa)-KRd

DR

D-VR

Maintenance?

DR

SCTx

D-VRd/D-KRd (2-6 cycles)

D-VR /D-KR (24 cycles)

at Least 3 years

Based on tolerance  
til PD

How long

Til MRD (-)

## GOALS OF THERAPY

- QOL (improve symptoms)
- VGPR, CR, sCR → MRD

\*2<sup>nd</sup> auto SCT – almost never

# Defining HR- MM

## New HR Definition (Barcelona 2024)

### Genomic abnormalities

del17p (at least 20%) or TP53 mutation

Biallelic deletion of 1p32, or del1p32 and 1q21 gain

### Double hit abnormalities

T(4;14) or t (14;16) or t(14;20) plus  
1q21 gain or Del 1p32

High B2M (normal CrCl)

- What are we missing?
  - Frailty
  - EMD or CNS disease
  - Circulating PCs //Plasma cell Leukemia
  - Clinically aggressive disease
  - APOBEC/Chromothripsis
- ? R-ISS-2/3 with 1 HR cytogenetic abnl

How do we actually get these data/results=> **Sequencing panels**

## Defining HR will be with Sequencing panels

### Sequencing Panels

- One example
  - PlasmaSeq
    - NCGM
    - Apex, NC
- Many more companies

Test Code	Test Name	Biomarkers Used	Clinical Significance	Incidence	FISH	NGS
MH020	PLASMASEQ	<i>TP53 mutation</i>	High-Risk	1-7%	✘	✔
		<i>ATM</i>	Poor Prognosis	~4%	✘	✔
		<i>DIS3</i>	Poor Prognosis	10%	✘	✔
		<i>t(6;14)IGH::CCND3</i>	Standard-Risk	~4%	✔ / ✘	✔
		<i>t(14;20) IGH :: MAFB</i>	High-Risk	<2%	✔ / ✘	✔
		<i>Trisomies &amp; Hyperdiploidy across the genome</i>	Standard-Risk	>40%	✔ / ✘	✔
		<i>Del (1p32)</i>	Poor Prognosis	~8%	✔	✔
		<i>Del (17p)</i>	High-Risk	5-20%	✔	✔
		<i>1q21 amplification/ gain</i>	Standard-Risk	40%	✔	✔
		<i>t(4;14) IGH::FGFR3</i>	High-Risk	15%	✔	✔
<i>t(14;16) IGH::MAF</i>	High-Risk	3.5%	✔	✔		
<i>t(11;14) IGH::CCND1</i>	Standard-Risk	15%-20%	✔	✔		

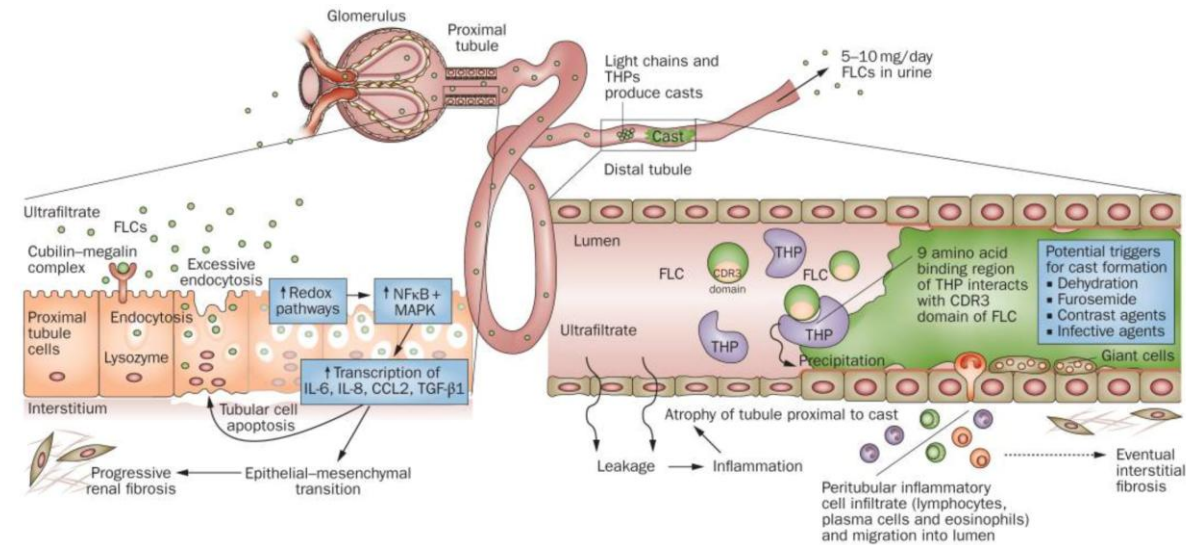


✔ Covered
✘ Not Covered
✔/✘ Not Routinely Covered

# NDMM with Renal Insufficiency

- NDMM and AKI: CrCl <30 (Cr >2)
  - Identify the cause of kidney injury
    - Dehydration, hypercalcemia
    - Cast nephropathy
    - Amyloid deposition
- Work-up
  - Standard NDMM work-up PLUS...
  - Consider kidney biopsy (albuminuria)
  - Fat pad biopsy/congo red on BMBx

**How I treat: Urgency is of utmost importance**



## Start supportive care urgently

Hydration and restore Calcium to normal

**Denosumab** (avoid BP if Crcl<30 ml/min)

**Pulse dex** (20-40mg => 4 on, 4 off – for 1-2 cycles)

Avoid Nephrotoxins

Contrast agents, NSAIDs, ACE Inhibitors

Dialysis and plasma exchange as needed

**PE:** 3-5 sessions in first 5-10 days

SFLC labs at least weekly

# NDMM with AKI

## • Start systemic Treatment

- Vd, VCd, CD38-Vd, **CD38-VCd**
- Pulse dex for 1-2 cycles (antibiotics)
- Caveats – dose adjustments for medications
  - C1+C2: Bortezomib Day 1, 4, 8, 11 preferred
  - Transplant is preferred



SCTx

**How I treat: Dara-VCd; switch to Dara-VRd when possible**

Dimopoulos MA et al. Lancet Oncol 2023. 24:7 e293-311

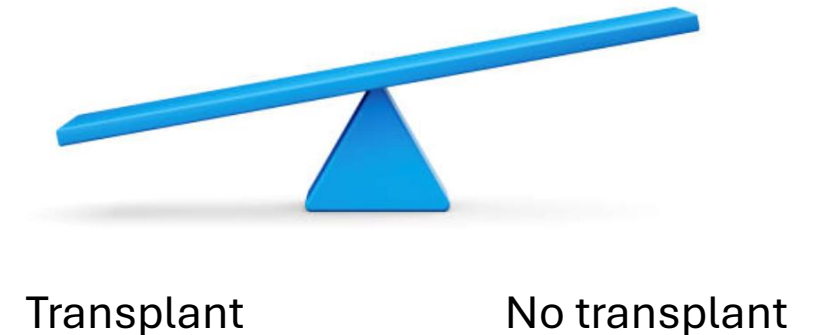
## Medication Dosing Changes in AKI

	Creatinine clearance				On dialysis
	≥60 mL/min	30–59 mL/min	15–29 mL/min	<15 mL/min	
Dexamethasone (orally or intravenously)	20–40 mg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Melphalan	0.15–0.25 mg/kg per day orally; high dose: 200 mg/m <sup>2</sup> intravenously	Reduction by 25% orally; high dose: 140 mg/m <sup>2</sup> intravenously	Reduction by 25% orally; high dose: 140 mg/m <sup>2</sup> intravenously	Reduction by 50% orally; high dose: 140 mg/m <sup>2</sup> intravenously	Reduction by 50% orally; high dose: 140 mg/m <sup>2</sup> intravenously
Doxorubicin (intravenously)	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Cyclophosphamide (orally or intravenously)	According to regimen	No dose modification needed	No dose modification needed	No dose modification needed*	No dose modification needed
Bortezomib (subcutaneously)	1.3 mg/m <sup>2</sup>	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Carfilzomib (intravenously)	Loading dose/full dose: 20/27 mg/m <sup>2</sup> or 20/56 mg/m <sup>2</sup> or 20/70 mg/m <sup>2</sup>	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed, after dialysis
Ixazomib (orally)	4 mg	4 mg	3 mg	3 mg	3 mg
Thalidomide (orally)	50–200 mg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Lenalidomide (orally)	25 mg per day	10 mg per day, can be increased to 25 mg per day if no toxicity occurs	15 mg every other day or 10 mg per day, can be increased to 15 mg per day if no toxicity occurs	5 mg per day, can be increased to 15 mg per day if no toxicity occurs	5 mg per day after dialysis, can be increased to 15 mg per day if no toxicity occurs
Pomalidomide (orally)	4 mg per day	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed, after dialysis
Daratumumab	16 mg/kg intravenously or 1800 mg subcutaneously	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Isatuximab (intravenously)	10 mg/kg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Elotuzumab (intravenously)	10 mg/kg	No dose modification needed	No dose modification needed	No dose modification needed	No dose modification needed
Belantamab mafodotin (intravenously)	2.5 mg/kg	No dose modification needed	Not determined yet	Not determined yet	Not determined yet
Selinexor (orally)	80 mg	No dose modification needed	No dose modification needed	Not determined yet	Not determined yet
Idecabtagene vicleucel (intravenously)	260–500 × 10 <sup>6</sup> CAR-positive, viable T cells	Not determined yet	Not determined yet	Not determined yet	Not determined yet
Ciltacabtagene autoleucel (intravenously)	0.5–1.0 × 10 <sup>6</sup> CAR-positive, viable T cells	Not determined yet	Not determined yet	Not determined yet	Not determined yet
Teclistamab (subcutaneously)	1.5 mg/kg	No dose modification needed with creatinine clearance >40 mL/min	Not determined yet	Not determined yet	Not determined yet
Venetoclax: off-label for patients with t(11;14)(q13;q32)	800 mg per day orally	No dose modification needed	No dose modification needed	Not determined yet	Not determined yet

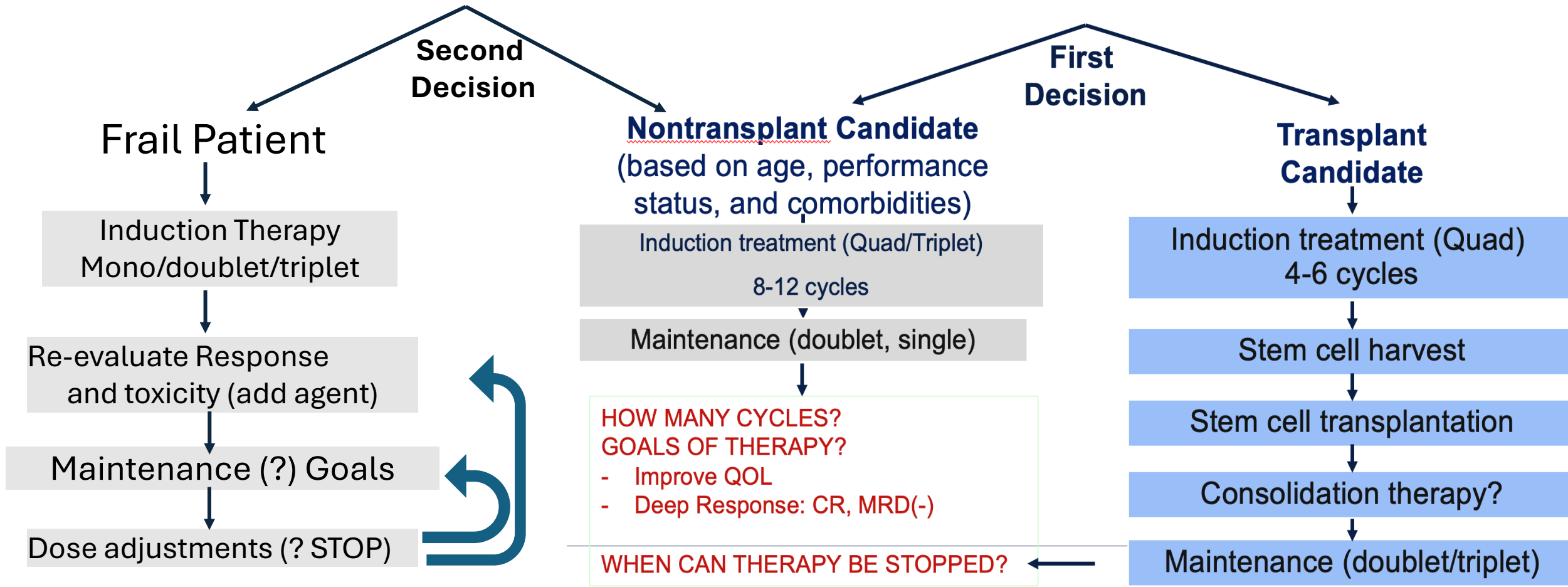
# NDMM with Amyloidosis

## How I treat:

- Assess for organ involvement
  - Identify the extent of disease
  - Work-up
    - SFLCs, 24 hour urine – TP, UPEP/IFE
    - Echocardiogram
    - Fat pad biopsy/ marrow congo red stain
    - Organ biopsy as indicated
- Start treatment cautiously
  - **CD38-Vd, CD38-VCd, CD38-VRd, CD38d**
  - Caveats
    - Dex may need dose adjustment
    - Cyclophosphamide and bortezomib can be cardiotoxic
  - Favor transplant in first remission



# Initial Approach to Treatment of NDMM - Frail



# Toxicity of Therapy to Consider for Frail - Mono, Doublet, Triplet

## How I treat:

Start Small with add on Approach

### CD38

Side effects:

- IRR
- Infection
- Fatigue
- Cytopenias

### PI (Bort)

Side effects:

- PN
- GI Tox
- Local skin reaction

## What Combo

Limiting Toxicity is Paramount

- Start with monotherapy or a doublet
- ADD-IN drugs as tolerated

### IMiD

Side effects:

- Rash
- GI Tox
- Fatigue
- Cytopenias/DVTs

### Steroid

Side effects:

- Insomnia
- Infection
- irritability
- HTN/Sugars

# Dose Adjustment for Frail - Each patient is unique (Mono, doublet, triplet)

## CD38

Adjustments:

- None
- ? Maybe
- **No pre-meds after C#1**

## PI (Bort)

Adjustments:

- **Weekly dosing**
- 1.3 => 1 => 0.7 mg/m<sup>2</sup>

Dose adjustments are needed for most

What  
Combo

Limiting Toxicity is Paramount

## IMiD

Adjustments:

- **Renal Insuff**
- Cytopenias
- DVT (OK on anticoag)

## Steroid

Adjustments:

- >75 Dex 20 mg
- >85(?) Dex 10 mg
- Alternatives to Dex
- **Less is MORE**

**How I treat: be cautious in frail, frequent adjustments to therapy needed**

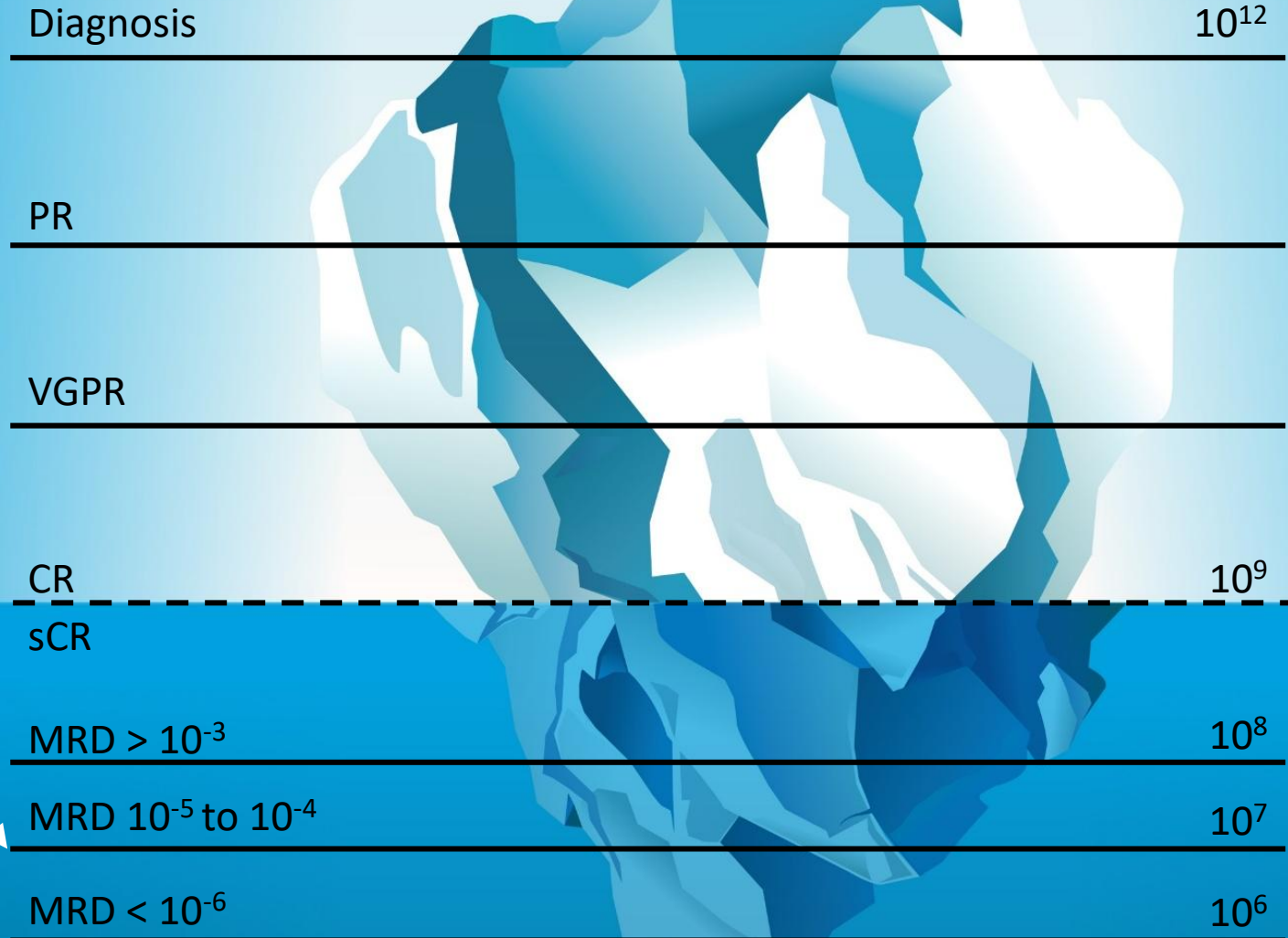
**D – Add R => DR – add V => assess response => GOALS??**

# What is MRD?

The Lonial-berg

## MRD

- Current definition of Molecular CR is  $10^{-5}$
- NGS not possible to obtain in all patients
- Flow MRD is sensitive only down to  $10^{-5}$
- As a result  $<10^{-5}$  is considered mol CR



# Maintenance in NDMM: AURIGA: Post-HDT/ASCT Dara-R vs R

## Study Design

### Key eligibility criteria

- 18-79 years of age
- NDMM with  $\geq 4$  cycles of induction therapy and underwent ASCT within 12 months of the start of induction
- $\geq$ VGPR at screening<sup>a</sup>
- MRD<sup>b</sup>-positive ( $10^{-5}$ ) post-ASCT
- No prior anti-CD38
- Randomization within 6 months of ASCT date

### Stratification factor

- Cytogenetic risk<sup>c</sup> (standard risk/unknown vs high risk)

1:1 RANDOMIZATION (N = 200)

Maintenance: up to 36 cycles<sup>d</sup> (28-day cycles)

**D-R**

**D:** 1,800 mg SC<sup>e</sup> QW Cycles 1-2,  
Q2W Cycles 3-6, Q4W Cycles 7+

**R:** 10 mg PO daily Days 1-28  
(after Cycle 3, 15 mg PO daily if tolerated)

**R**

**R:** 10 mg PO daily Days 1-28  
(after Cycle 3, 15 mg PO daily if tolerated)

MRD-negativity status was assessed regardless of response and obtained after 12, 18, 24, and 36 cycles<sup>b</sup>

### Primary endpoint

- MRD-negative ( $10^{-5}$ ) conversion rate (NGS) from baseline to 12 months after maintenance treatment
- N = 214 planned to achieve  $\geq 85\%$  power to detect 20% improvement

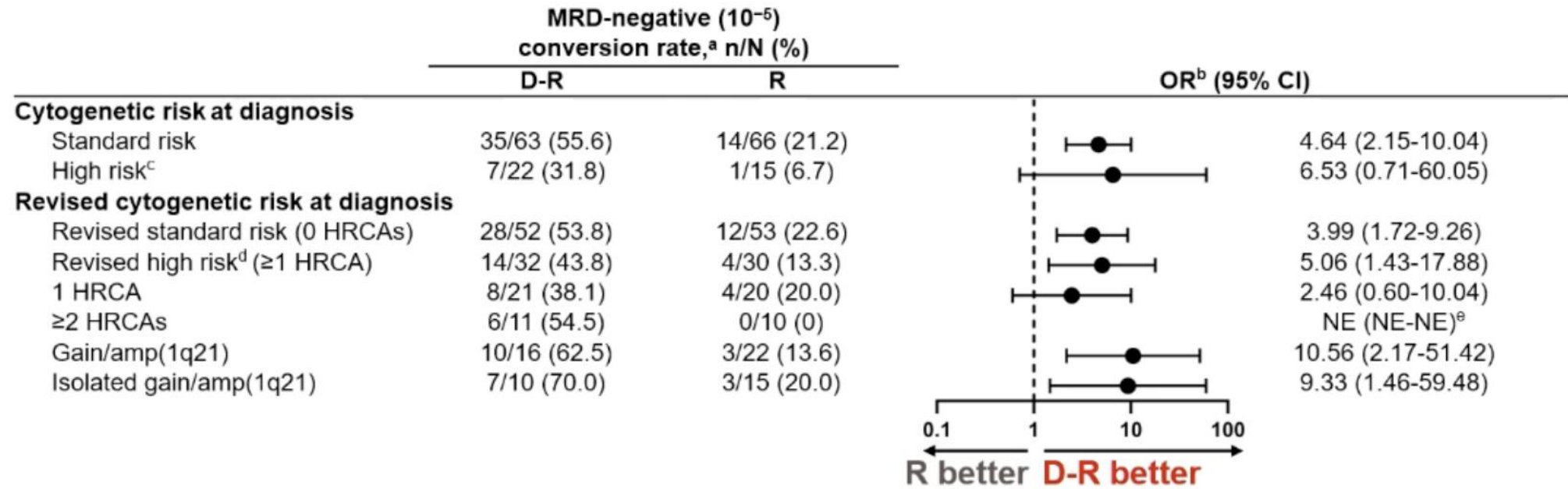
### Secondary endpoints

- PFS, overall MRD-negative conversion rate, sustained MRD-negative rate, response rates, duration of  $\geq$ CR, OS, safety

VGPR, very good partial response; D, daratumumab; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PO, orally; PFS, progression-free survival; CR, complete response; OS, overall survival; IMWG, International Myeloma Working Group; NGS, next-generation sequencing. <sup>a</sup>As assessed by IMWG 2016 criteria. <sup>b</sup>MRD based upon NGS (clonoSEQ<sup>®</sup>; Adaptive Biotechnologies). <sup>c</sup>For stratification, cytogenetic risk was evaluated per investigator assessment, in which high risk was defined as the presence of  $\geq 1$  of the following cytogenetic abnormalities: del(17p), t(4;14), or t(14;16). <sup>d</sup>Study treatment continued for a planned maximum duration of 36 cycles or until progressive disease, unacceptable toxicity, or withdrawal of consent. After the end of the study treatment period of 36 months and after the end of the study, patients benefiting from treatment with DARA and/or R could continue receiving treatment per the investigator's discretion. <sup>e</sup>DARA SC (DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE<sup>®</sup> drug delivery technology; Halozyme, Inc., San Diego, CA, USA]).

# AURIGA: 12-Month MRD- ( $10^{-5}$ ) Conversion Rate

## Risk-Stratified Subgroup Analysis



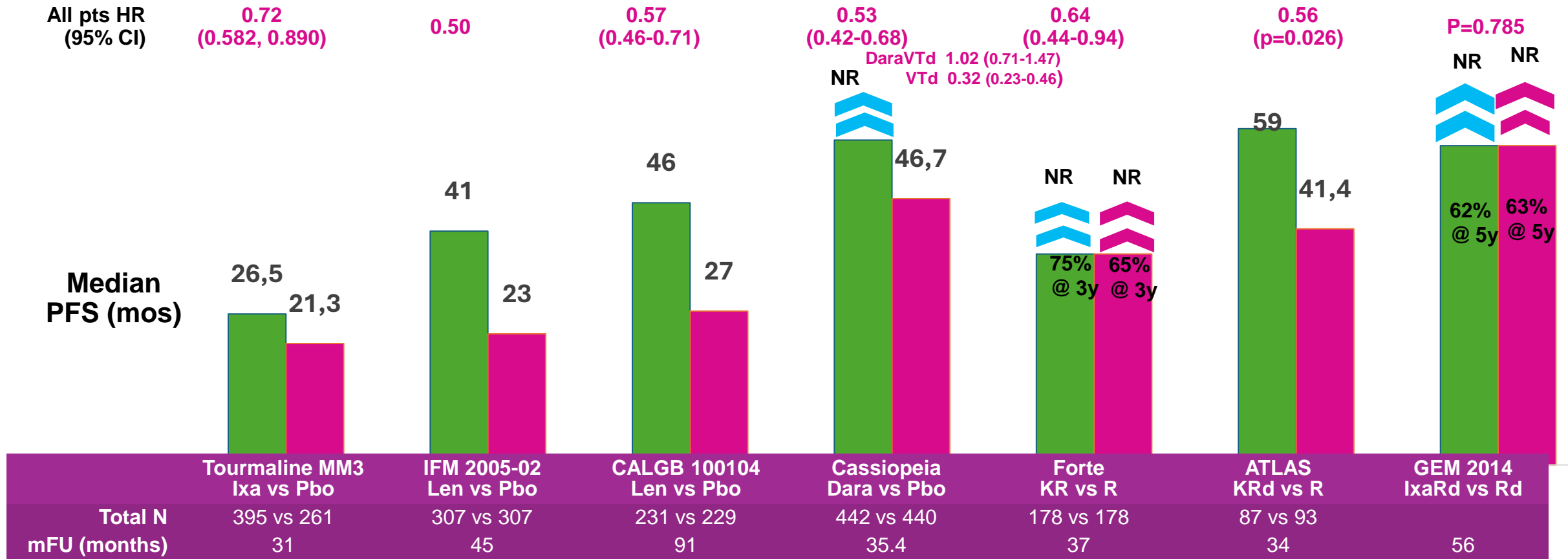
**D-R improved MRD-negative conversion rate by 12 months versus R even among patients with ultra-high-risk disease, as well as standard-risk disease**

NE, not estimable. <sup>a</sup>Defined as the proportion of patients who achieved MRD-negative status (at  $10^{-5}$ ) by NGS by 12 months after maintenance treatment and prior to progressive disease or subsequent antimyeloma therapy.

<sup>b</sup>Mantel-Haenszel estimate of the common OR for unstratified tables is used. An OR  $>1$  indicates an advantage for D-R. <sup>c</sup>High-risk cytogenetics per the standard definition are defined as  $\geq 1$  abnormality including del(17p), t(4;14), or t(14;16). <sup>d</sup>Revised high-risk cytogenetics per the revised definition are defined as  $\geq 1$  abnormality including del(17p), t(4;14), t(14;16), t(14;20), or gain/amp(1q21). <sup>e</sup>Not evaluable because no patient in the R arm had MRD-negative conversion.



# Maintenance Post ASCT



1. Dimopoulos MA et al. Lancet 2018
2. Attal M, et al. N Engl J Med. 2012;366
3. Holstein et al Lancet Heme 2017.
4. Moreau et al ASCO 2021

5. Gay et al ASCO 2021
6. Dytfeld et al. ASCO
7. Rosinol et al ASH 2021

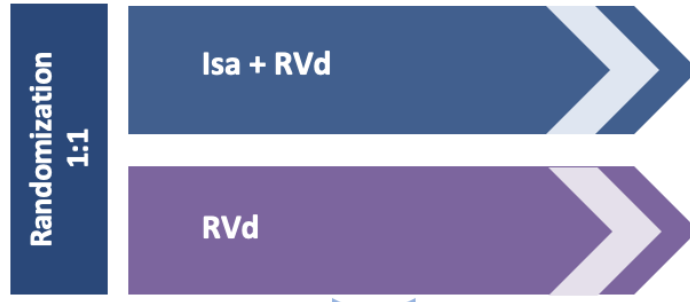
# GMMG-HD7: The first phase 3 study evaluating Isa + RVd for induction and maintenance in patients with Te NDMM

NDMM  
N=662



- Key eligibility criteria<sup>1</sup>**
- ✓ Age 18–70 years
  - ✓ NDMM and eligible for HDT + ASCT

## Induction phase (3 x 6-week cycles)



*Second randomization will inform maintenance*

## Maintenance phase (4-week cycles)



3 years or PD



Awaiting Results

“4 Curves”

\*\*Primary Endpoint: MRD (-); Secondary PFS

# Conclusion

- Quadruplet therapy should be attempted in most
  - HR Myeloma needs SCT and long-term Quad/Triplet therapy
    - Currently consider all double/triple hit HR
    - Also consider R-ISS3, elevated B2M with normal CrCl HR
- Pulse Dex still have a roll in AKI, cord compression, aggressive MM
- Individualization based on genetics, clinical presentation and frailty
- Goal is MRD(-), especially if HR, if MRD(+) →?? Next steps
- Novel targeted therapies will hopefully allow us to reach this goal and improve outcomes in MM