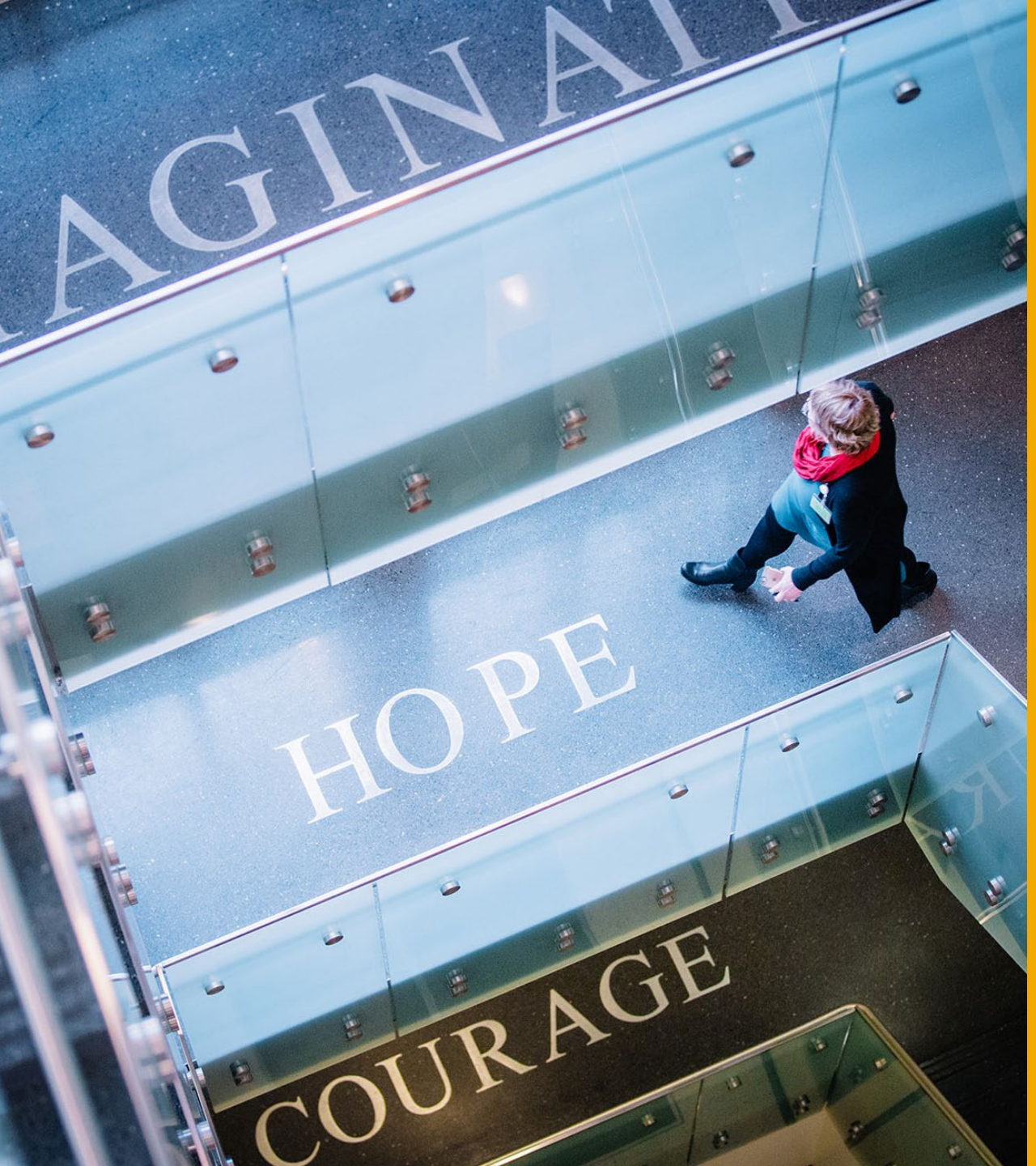


MY EVOLVING MANAGEMENT OF TRANSPLANT –ELIGIBLE AND –INELIGIBLE PATIENTS WITH NDMM

Ajay K. Nooka, MD MPH
Professor, Department of Hematology and Medical Oncology
Director, Myeloma Program
Associate Director of Clinical Research
Winship Cancer Institute, Emory University School of Medicine

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

CONFLICT OF INTEREST DISCLOSURE

I hereby declare the following potential conflicts of interest concerning my presentation:

Consultancy and Honoraria: AstraZeneca, Blue Earth Diagnostics, Cellectar biosciences, GlaxoSmithKline, Janssen, KITE therapeutics, ONK therapeutics, OPNA, Pfizer, Perceptive informatics LLC, Premier Research Sanofi and Sebia

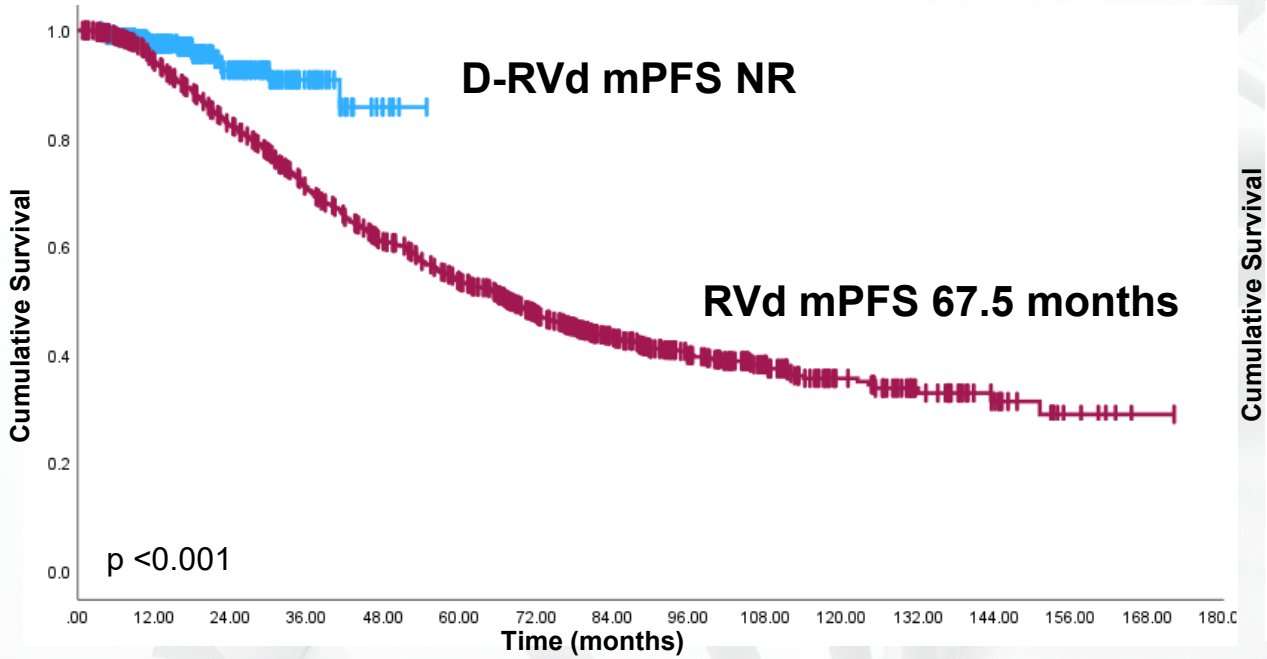
Research Funding (to institution): Aduro Biotech, Amgen, Arch Oncology, Bristol Myers Squibb, Cellectis, Cellectar, Genentech, GlaxoSmithKline, Janssen, OPNA, Karyopharm, Kite Pharma, Merck, Pfizer, Skyline diagnostics and Takeda

Discussion of off-label drug use: None

	Transplant-eligible	Transplant-ineligible
Bortezomib	• PERSEUS • GMMG-HD7	• CEPHEUS • IMROZ • BENEFIT
Carfilzomib	• IsKia EMN24	• ADVANCE • GMMG-CONCEPT

SURVIVAL OUTCOMES: EMORY COHORT

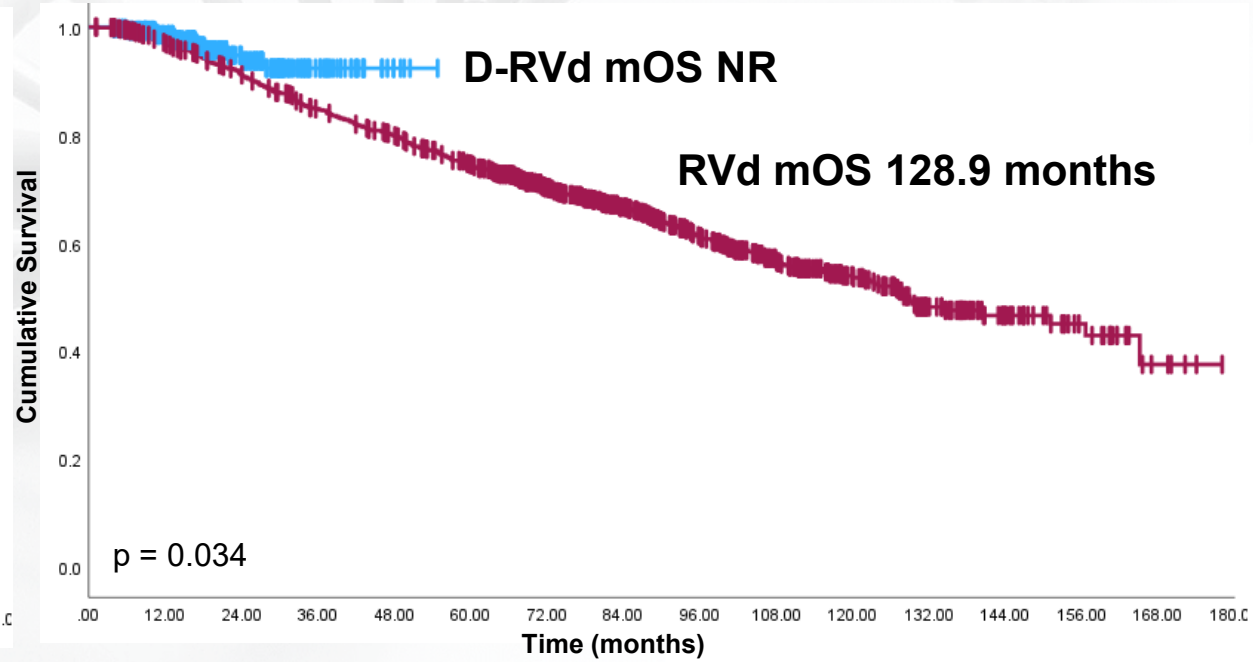
Progression Free Survival



1-year PFS, D-RVd vs RVd: 98% vs 93%
2-year PFS, D-RVd vs RVd: 93% vs 82%

Median follow up DRVd: 19.1 months, RVd: 87 months

Overall Survival

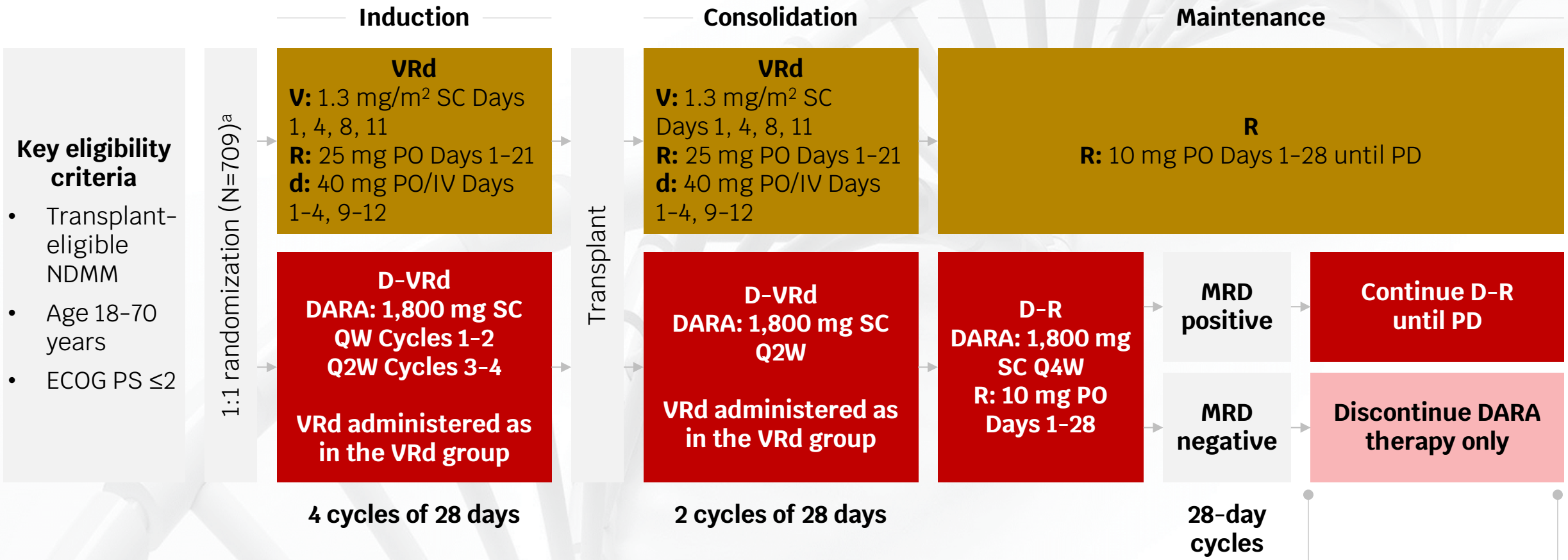


1-year OS, D-RVd vs RVd: 99% vs 97%
2-year OS, D-RVd vs RVd: 94% vs 91%

Median follow up DRVd: 19.1 months, RVD: 96 months

Joseph NS, et al. Quadruplet therapy for newly diagnosed myeloma: comparative analysis of sequential cohorts with triplet therapy lenalidomide, bortezomib and dexamethasone (RVd) versus daratumamab with RVD (DRVd) in transplant-eligible patients. Blood Cancer J. 2024 Sep 13;14(1):159.

NDMM- TRANSPLANT ELIGIBLE: PHASE III PERSEUS STUDY DESIGN



Primary endpoint: PFS[c]

Key secondary endpoints: Overall ≥CR rate,[c] overall MRD-negativity rate,[d] OS

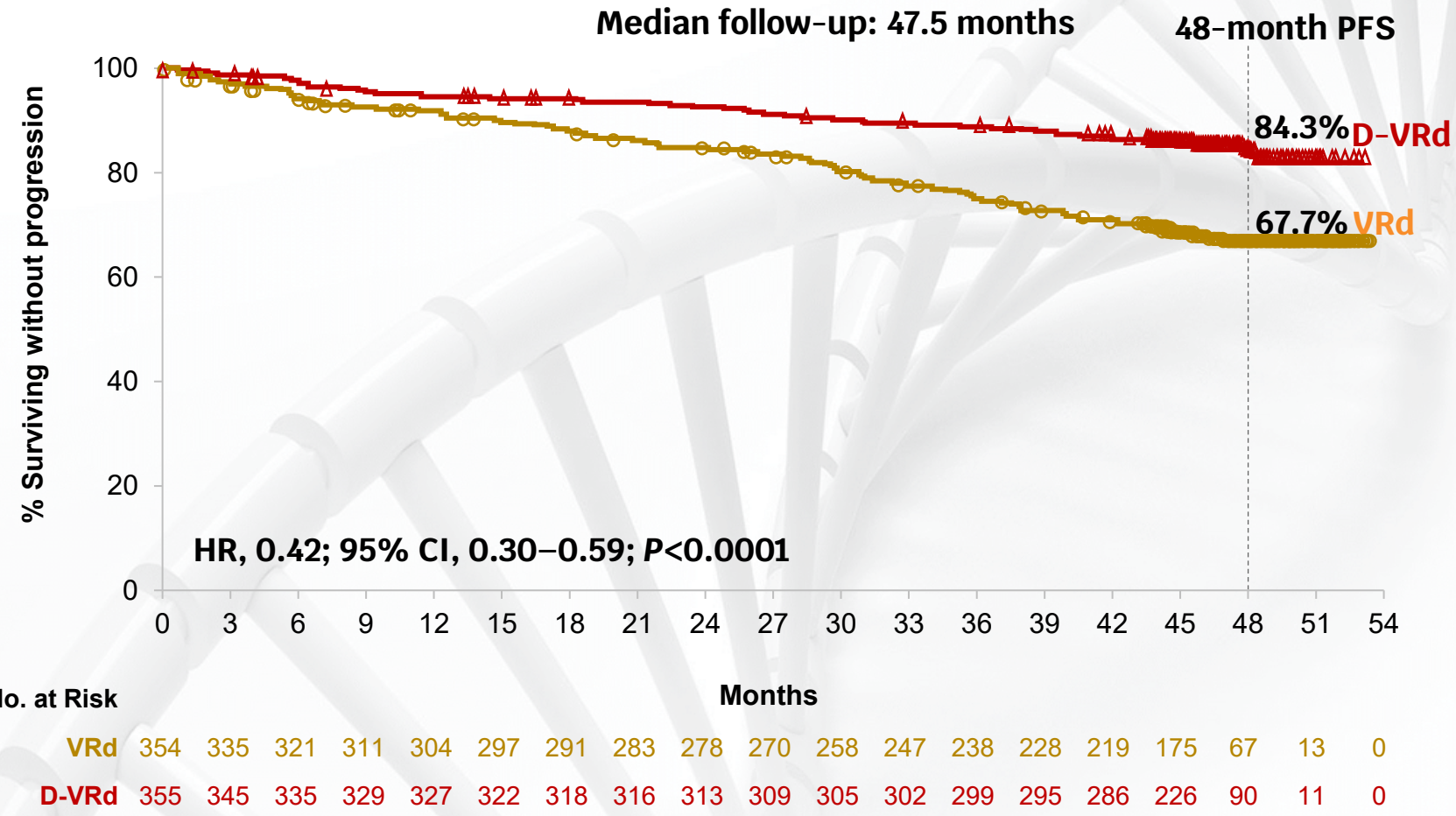
Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

Restart DARA therapy upon confirmed loss of CR without PD or recurrence of MRD

Sonneveld et. al. Late-breaking Abstracts Session, ASH 2023. Accessed from: https://ash.confex.com/ash/2023/webprogram/Paper191911.html

PERSEUS PHASE III RESULTS

PFS

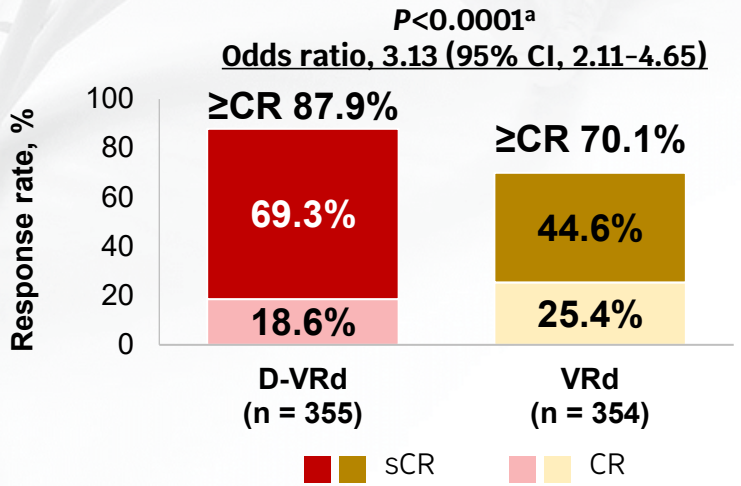


No. at Risk

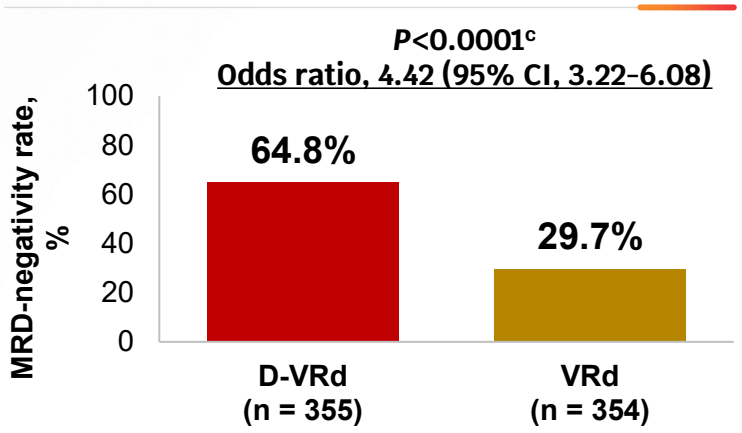
VRd	354	335	321	311	304	297	291	283	278	270	258	247	238	228	219	175	67	13	0
D-VRd	355	345	335	329	327	322	318	316	313	309	305	302	299	295	286	226	90	11	0

58% reduction in the risk of progression or death with D-VRd

Overall ≥ CR Rates



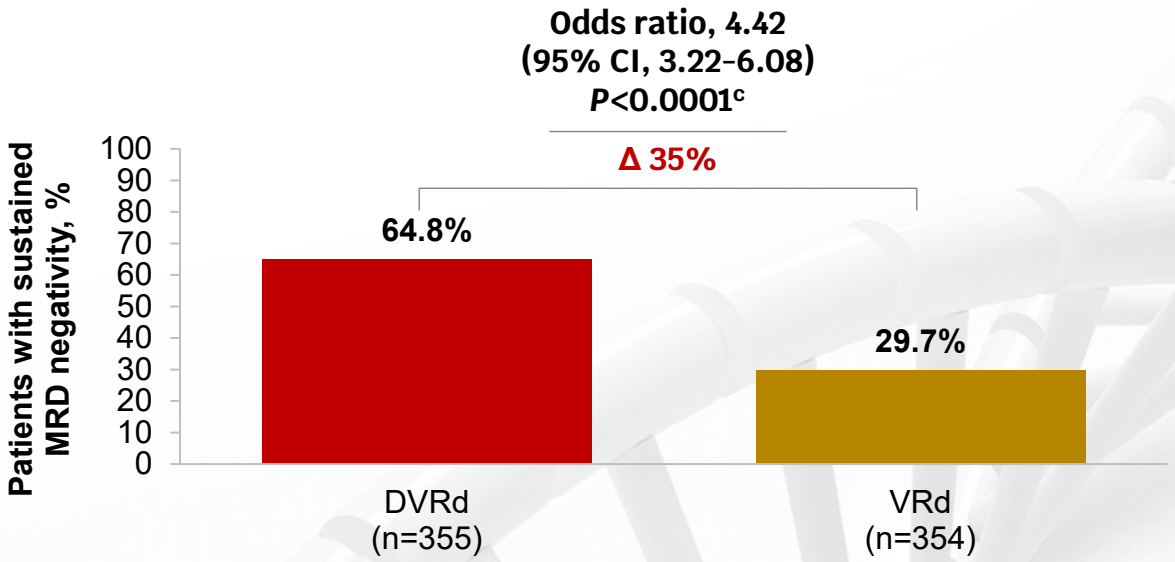
Sustained MRD negativity (10^{-5}) ≥ 12 mos



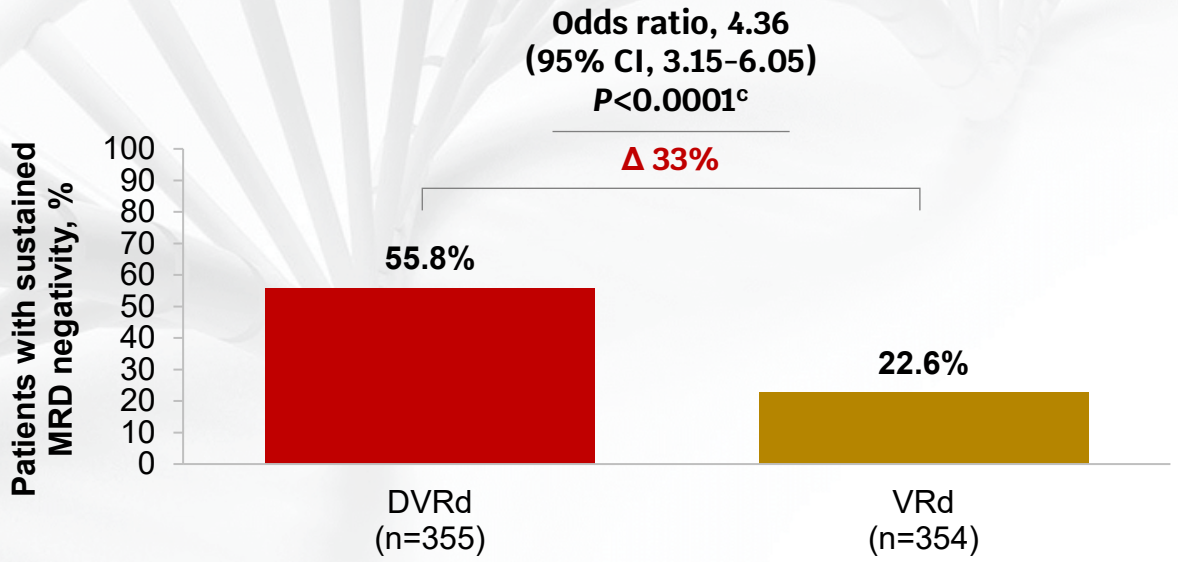
Swerdlow et al. Blood. 2017;129:3064-3074. Updated from: https://ash.confex.com/ash/2023/webprogram/Paper191911.html

PERSEUS: SUSTAINED MRD-NEGATIVITY (10^{-5}) ≥CR RATES

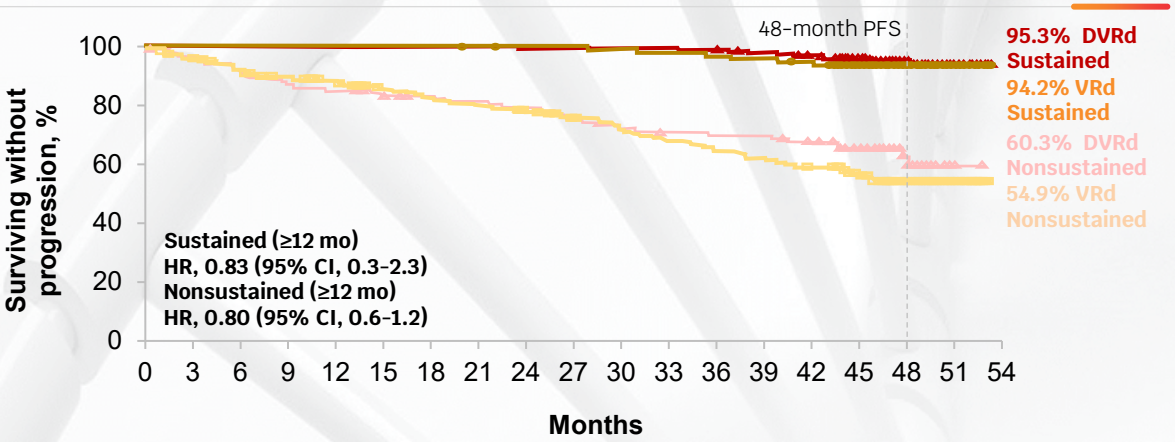
Sustained MRD-negativity[a] (10^{-5}) ≥CR rate ≥12 months[b]



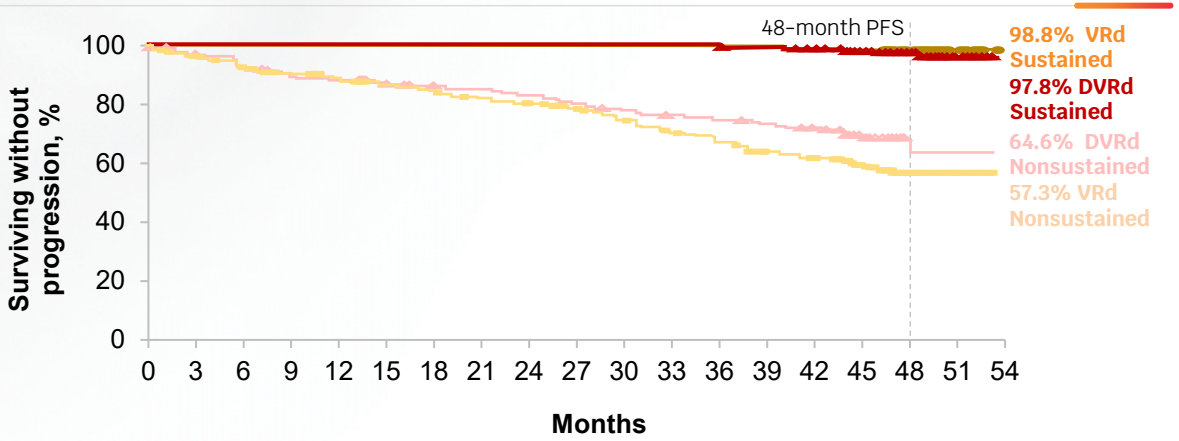
Sustained MRD-negativity[a] (10^{-5}) ≥CR rate ≥24 months[d]



PFS by sustained MRD-negativity (10^{-5}) ≥CR status ≥12 months



PFS by sustained MRD-negativity (10^{-5}) ≥CR status ≥24 months



NDMM- TRANSPLANT ELIGIBLE: GMMG-HD7: TRIAL SUMMARY

- Open-label, randomized, multicenter phase III trial

Adults with NDMM who are eligible for HDT and ASCT (N = 662)

Induction (3 x 6-Wk Cycles)

Isatuximab 10 mg/kg* + **Bortezomib** 1.3 mg/m²† + **Lenalidomide** 25 mg† + **Dexamethasone** 20 mg† (n = 331)

Bortezomib 1.3 mg/m² + **Lenalidomide** 25 mg + **Dexamethasone** 20 mg† (n = 329)

HDT ASCT

Maintenance (4-Wk) Cycles)

Isatuximab 10 mg/kg‡ + **Lenalidomide** 10 → 15 mg§ + **Dexamethasone** 20 mg‖

Lenalidomide 10 → 15 mg§ + **Dexamethasone** 20 mg‖

3 yr or PD

*Cycle 1: D1, 8, 15, 22, 29; cycles 2-3: D1, 15, 29.
†Bortezomib D1, 4, 8, 11, 22, 25, 29, 32; lenalidomide Days 1-14 and 22-35; dexamethasone D1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, 33.
Data cutoff: April 2021.

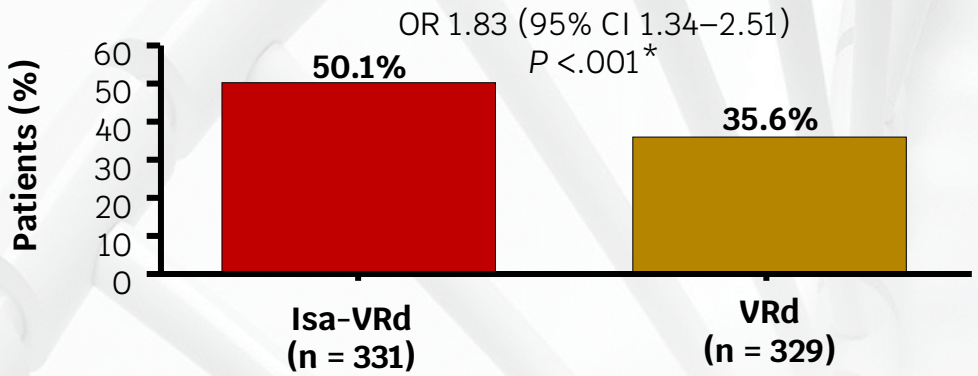
‡Cycle 1: D1, 8, 15, 22;
Cycles 2-3: D1, 15; Cycle 4+: D1.
§Days 1-28. Increase dose to 15 mg after 3 mos
‖Dexamethasone D1, 8, 15, 22 in C1.

Primary endpoint: MRD negativity at end of induction (NGF, sensitivity 10^{-5})

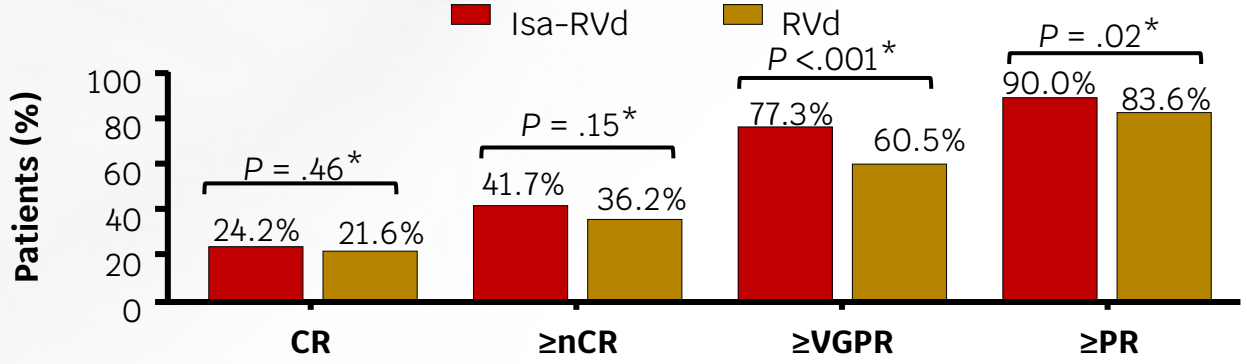
Secondary endpoints: CR after induction, safety

MRD negativity assessed after cycle 3, HDT, 12 mos, and 24 mos as well as at end of study

Patients with MRD Negativity at End of Induction



Response Rates at End of Induction



Goldschmidt. ASH 2021. Abstr 463.

NDMM-TRANSPLANT ELIGIBLE: PHASE III ISKIA EMN24 STUDY DESIGN

42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021

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

Induction
Four 28-day cycles

4x KRd
K: 20 mg/m² IV dd 1 cc 1 only; followed by 56 mg/m² IV dd 8,15 cc 1 and dd 1, 8, 15 cc 2-4
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1, 8, 15, 22

4x Isa-KRd
Isa: 10 mg/kg IV dd 1, 8, 15, 22 cc 1, followed by 10 mg/kg IV dd 1 and 15 cc 2 to 4.
K: 20 mg/m² IV dd 1 cc 1 only; followed by 56 mg/m² IV dd 8, 15 cc 1 and dd 1, 8, 15 cc 2-4
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1, 8, 15, 22

MOBILIZATION
Cy: 2-3 g/m²
followed by
G-CSF for stem-cell collection

and

MEL200-ASCT
MEL: 200 mg/m²
followed by
ASCT

Post-ASCT consolidation
Four 28-day cycles

4x KRd
K: 56 mg/m² IV dd 1, 8, 15 cc 5-8
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1, 8, 15, 22

4x Isa-KRd
Isa: 10 mg/kg IV dd 1, 15 cc 5-8
K: 56 mg/m² IV dd 1, 8, 15 cc 5-8
R: 25 mg PO daily dd 1-21
d: 40 mg PO dd 1, 8, 15, 22

Light consolidation
Twelve 28-day cycles

12x KRd
K: 56 mg/m² IV dd 1,15
R: 10 mg PO dd 1-21
d: 20 mg PO dd 1,15

12x Isa-KRd
Isa: 10 mg/kg IV d 1
K: 56 mg/m² IV dd 1,15
R: 10 mg PO dd 1-21
d: 20 mg PO dd 1,15

MRD by NGS

MRD by NGS

MRD by NGS

MRD by NGS

Primary endpoint:
MRD negativity by NGS after post-ASCT consolidation

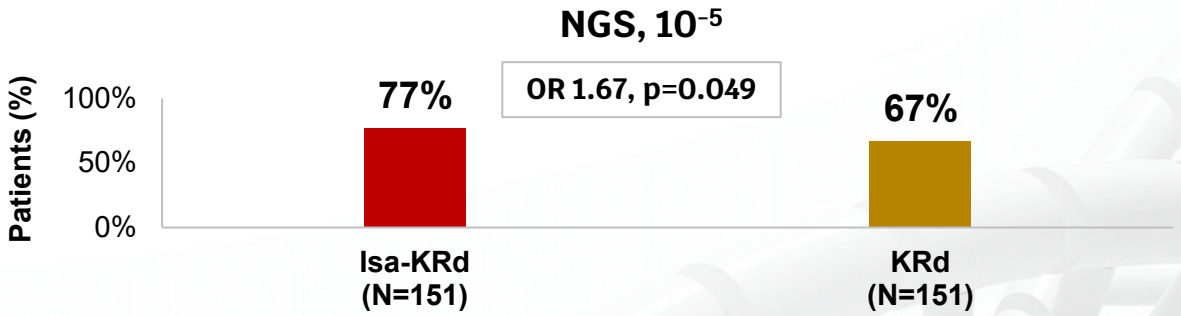
Key secondary endpoint:
MRD negativity after induction; PFS

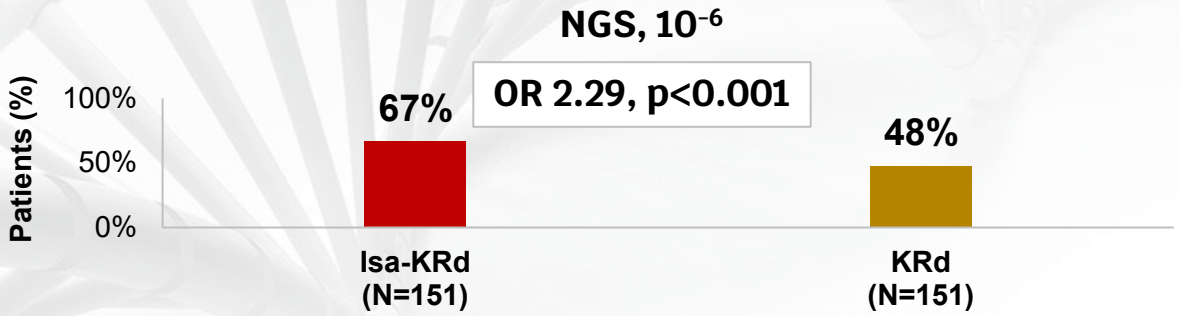
Other secondary endpoint:
Sustained MRD negativity

Reformatted from Franchesca Gay, MD. ASH 2023 Oral Presentation.

ISKIA: PRIMARY ENDPOINT

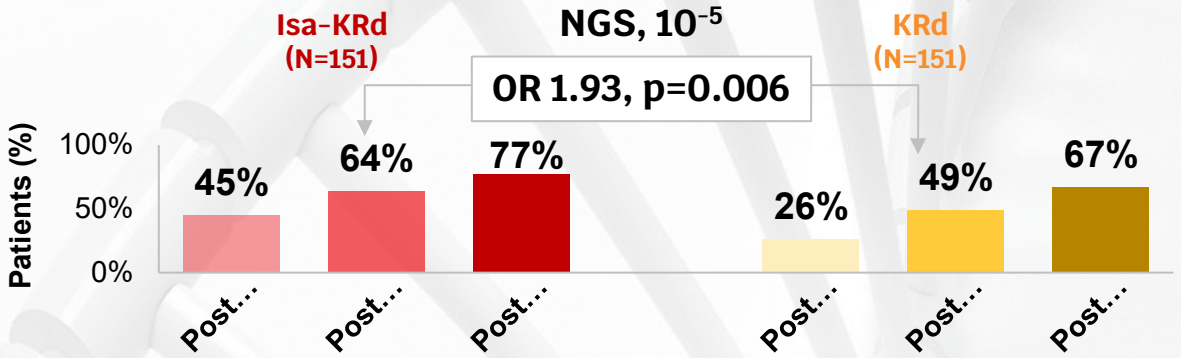
Post Consolidation MRD negativity (ITT)

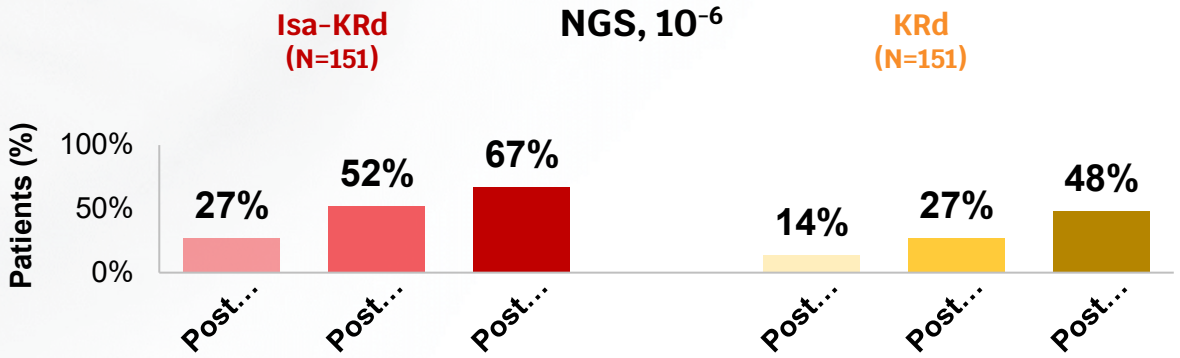




≥VGPR after consolidation was 94% in both arms; ≥CR 74%vs 72% and sCR 64% vs 67% in the IsaKRd vs KRd arms.
High MRD compliance and sample quality (97-100% of sample evaluable at 10^{-5} and 10^{-6} cut-offs).
Consistent MRD results were detected by next-generation flow
In the logistic regression analysis, ORs, 95% CIs, and p-values were adjusted for stratification factor.

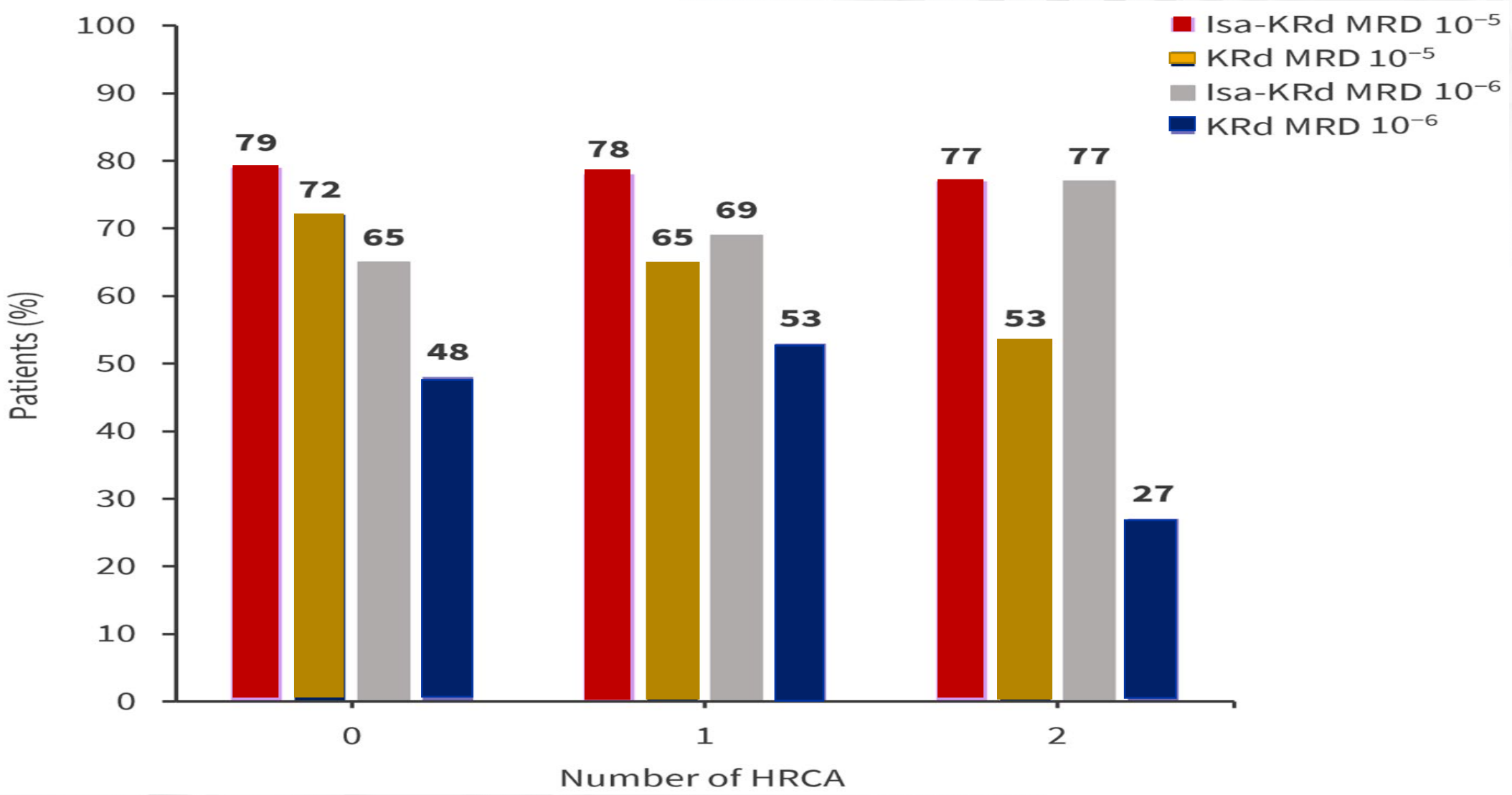
MRD negativity rates improved over time



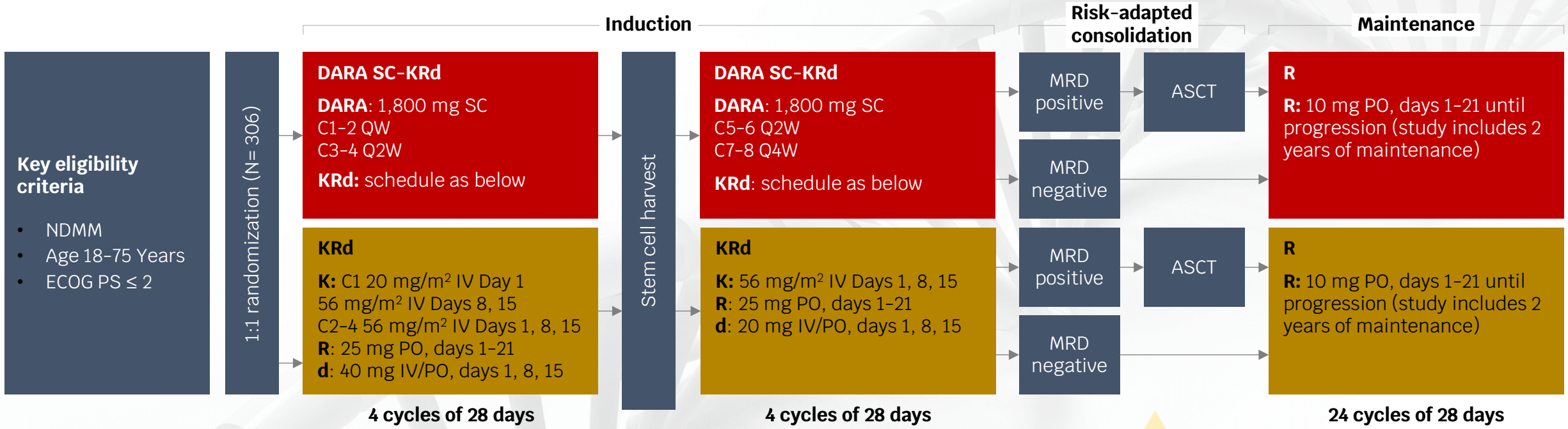


Key secondary endpoint: Currently, no difference in PFS (95% at 1 year); (mFU, 20 months, IQR 18-23).

ISKIA: MRD IN PATIENTS WITH HIGH-RISK CYTOGENETIC ABNORMALITIES



NDMM- TRANSPLANT ELIGIBLE AND INELIGIBLE: ADVANCE STUDY DESIGN



Primary endpoint: Overall MRD negativity rate ≥VGPR

Key secondary endpoints: PFS, EFS, ≥CR, OS, Safety, MRD negativity rate in peripheral blood

Transplant-eligible patients with MRD ≥10^{-5} by NGS after combination therapy were recommended to proceed with high-dose melphalan chemotherapy followed by autologous stem cell transplant (ASCT)

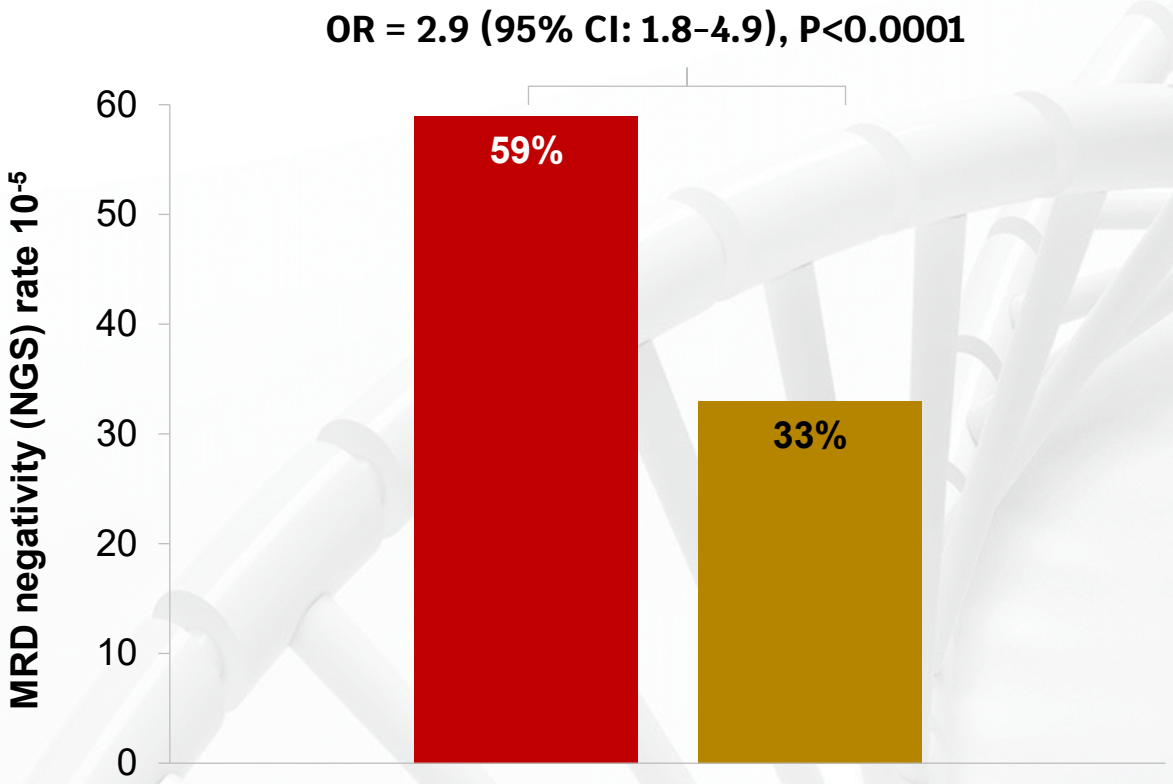
MRD negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥VGPR in the ITT population. Patients who were not evaluable for MRD testing were considered MRD positive.

ECOG PS, Eastern Cooperative Oncology Group performance status; C, carfilzomib; IV, intravenous; R, lenalidomide; PO, oral; d, dexamethasone; DARA SC (DARA 1,800 mg co-formuleted with recombinant human hyaluronidase PH20 [rHuPH20, 2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc, San Diego, CA, USAI); QW, weekly, Q2W, every 2 weeks; Q4W, every 4 weeks; ASCT, Autologous stem cell transplantation; y, year; PR, partial response; ITT, intention to treat; CR, complete response; ISS, International Staging System; IMWG, International Myeloma Working Group: [a]Stratified by ISS stage and age. [b]MRD was assessed using the clonoSEQ assay (Adaptive Biotechnologies, Seattle, WA, USA) using bone marrow aspirate samples obtained at baseline, at the time of suspected ≥CR, end of induction, and at end of C12 and C24 maintenance. [c]Response and disease progression were assessed based on IMWG response criteria. Overall, the MRD negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time. ClinicalTrials.gov Identifier: NCT04268498. Accessed April 9, 2025.

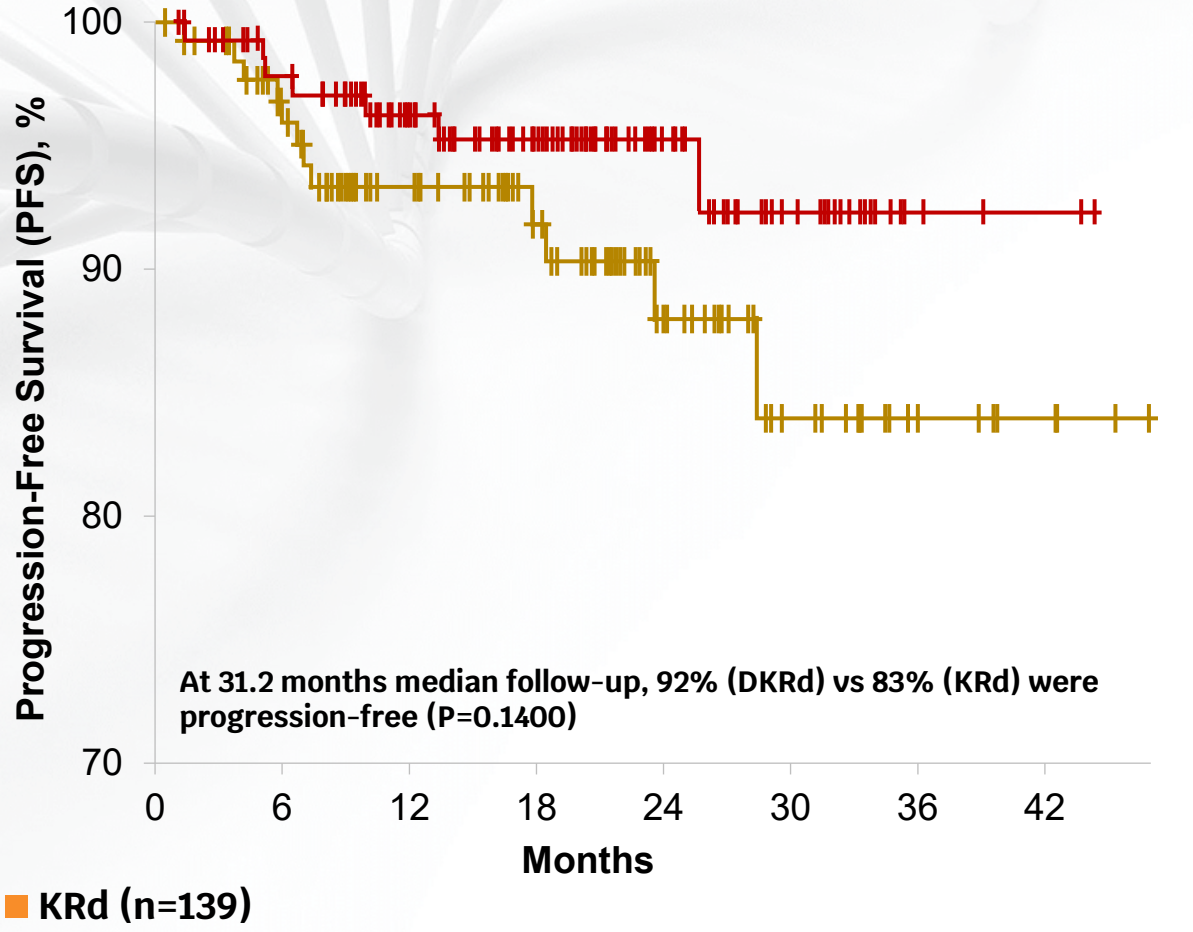
Landgren et. al. ASCO 2025. Oral Presentation. Abstract 7503.

ADVANCE: KEY EFFICACY FINDINGS

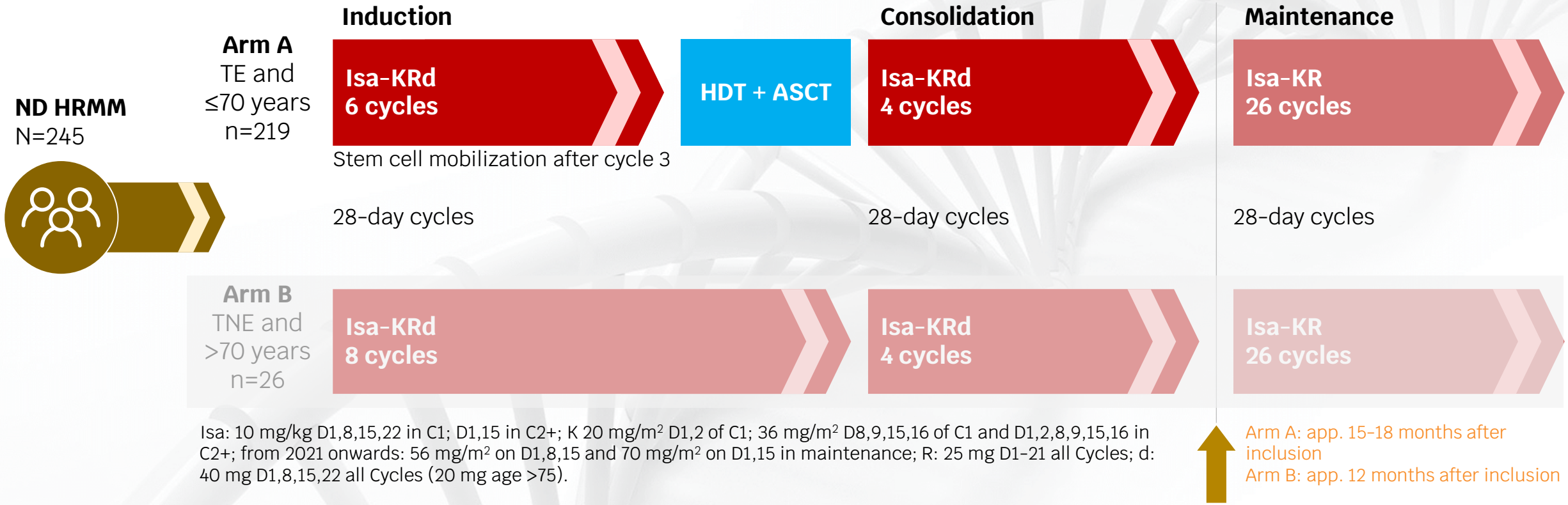
MRD Neg 10^{-5} in ITT Population



Progression-Free Survival



NDMM- TRANSPLANT ELIGIBLE AND INELIGIBLE: GMMG-CONCEPT TRIAL DESIGN



Isa: 10 mg/kg D1,8,15,22 in C1; D1,15 in C2+; K 20 mg/m^2 D1,2 of C1; 36 mg/m^2 D8,9,15,16 of C1 and D1,2,8,9,15,16 in C2+; from 2021 onwards: 56 mg/m^2 on D1,8,15 and 70 mg/m^2 on D1,15 in maintenance; R: 25 mg D1-21 all Cycles; d: 40 mg D1,8,15,22 all Cycles (20 mg age >75).

Arm A: app. 15-18 months after inclusion
Arm B: app. 12 months after inclusion

HRMM criteria: ISS stage II or III **PLUS** ≥1 of: del(17p), t(4;14), t(14;16) and/or ≥3 copies 1q21 (amp1q21)

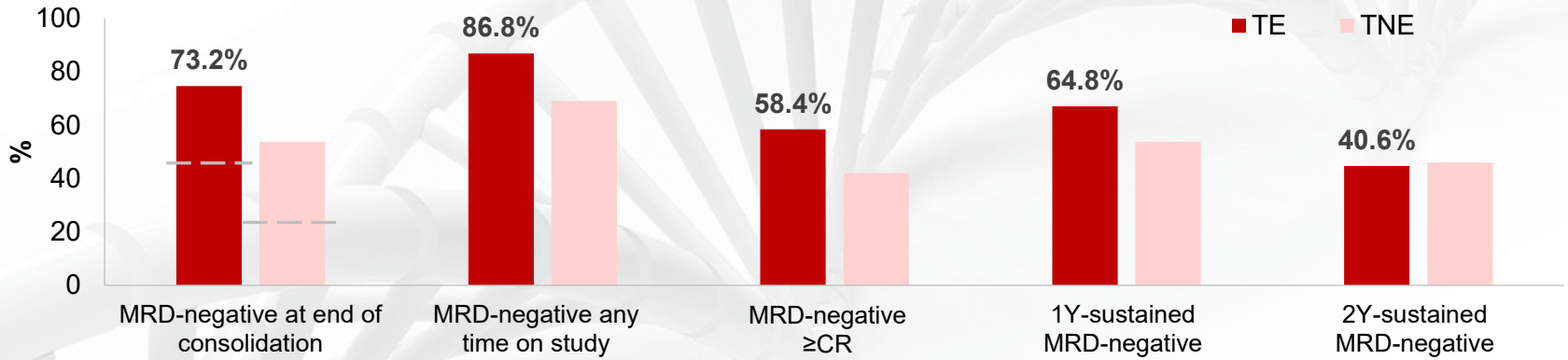
Primary objective: MRD negativity after consolidation (NGF, 10^{-5})
Secondary objective: PFS; Selected tertiary objectives: ORR, OS

ASCT, autologous stem-cell transplant; d, dexamethasone; HDT, high-dose therapy; HRMM, high-risk multiple myeloma; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MRD, minimal residual disease; ND, newly-diagnosed; NGF, next-generation flow; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, lenalidomide; TE, transplant-eligible; TNE, transplant-ineligible. Following a protocol amendment in 2021, carfilzomib application was switched to once weekly 56 mg/m^2.

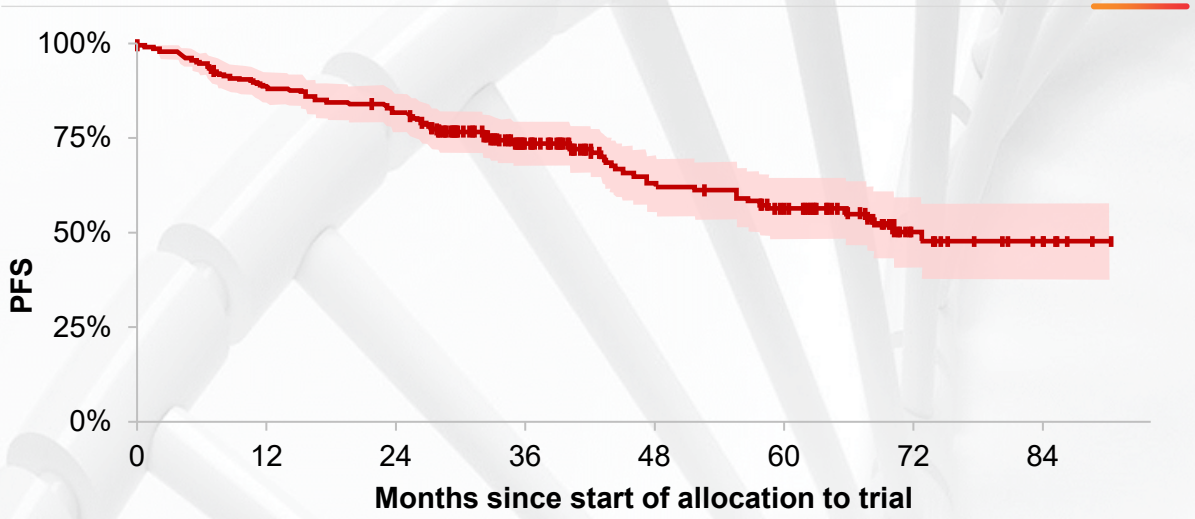
Leypoldt et.al ASCO 2025 Oral Presentation. Abstract 7509.

GMMG-CONCEPT: KEY EFFICACY OUTCOMES @ 43 MONTHS FU

- Primary endpoint met with an MRD-negativity rate after consolidation of 73.2% (153/209), p= 1.91 x 10^{-13}
- Overall, 86.8% reached MRD-negativity at any time
- 58.4% reached MRD-negative ≥CR
- 64.8% and 40.6% retained ≥1-year and ≥2-year sustained MRD-negativity

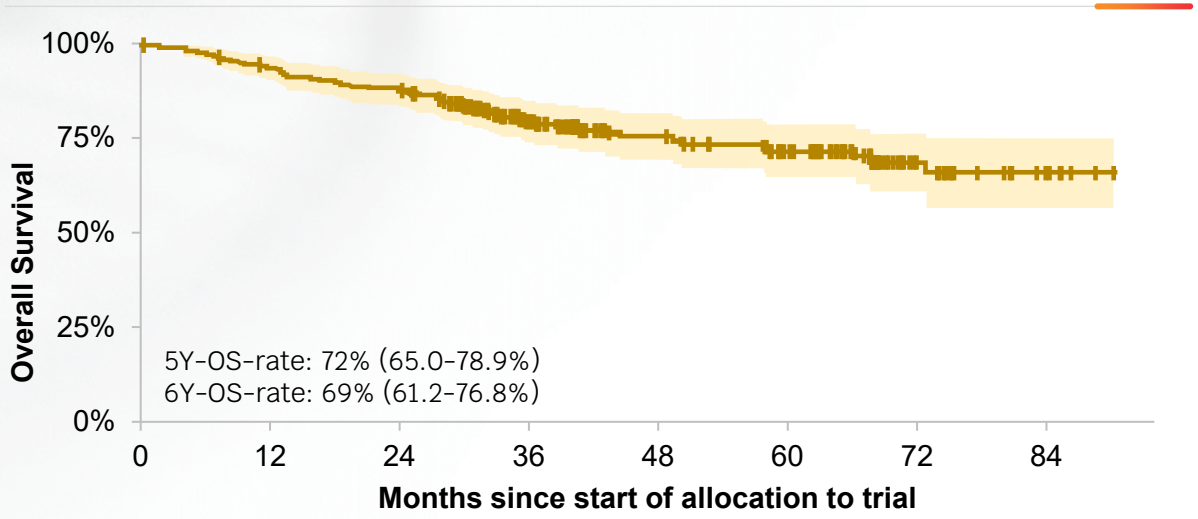


mPFS 72.8 months



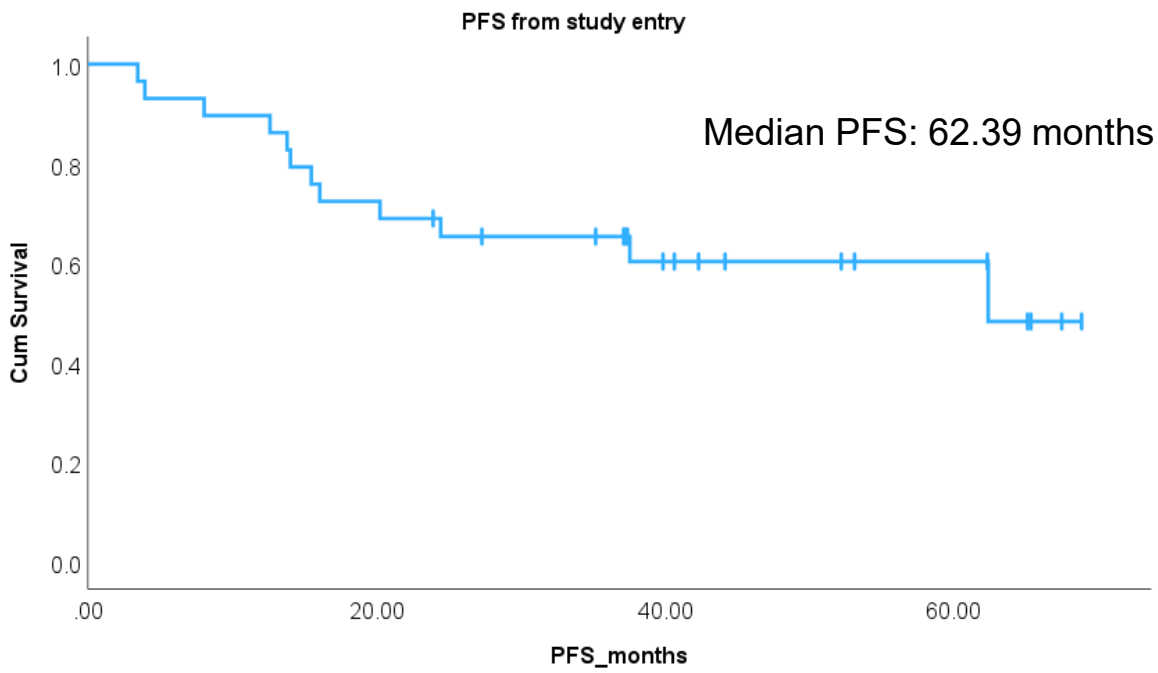
219 (0) 193 (2) 177 (1) 109 (52) 68 (29) 53 (8) 20 (29) 5 (14)

mOS not reached

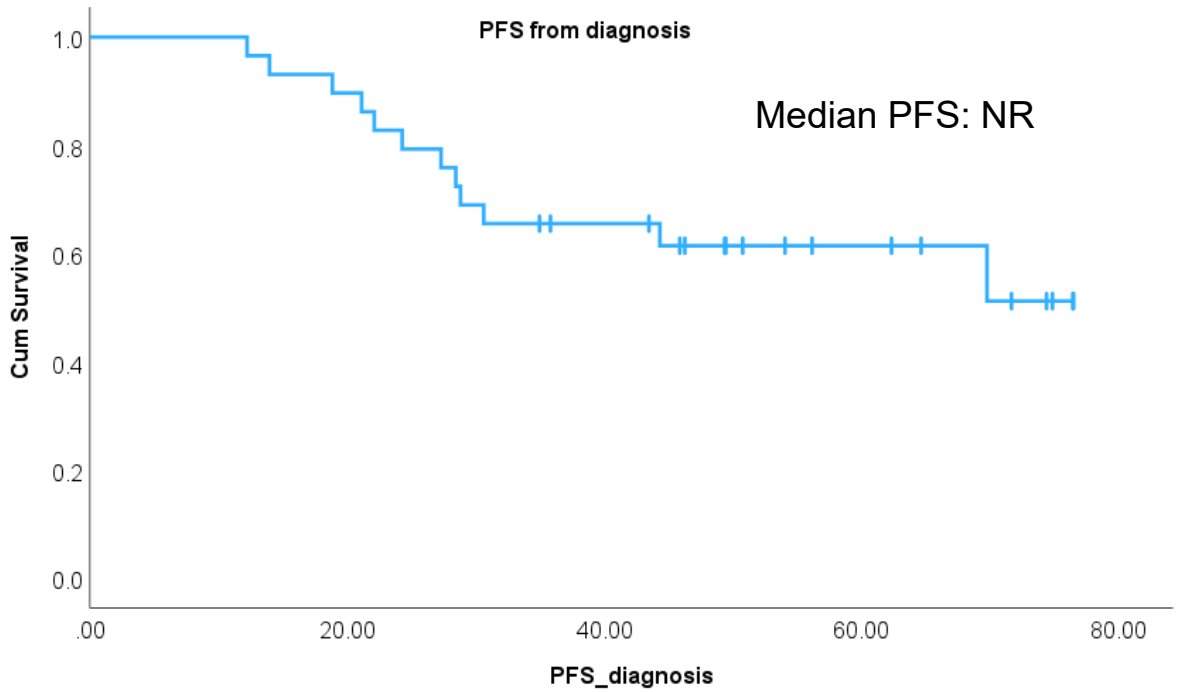


219 (0) 203 (3) 190 (0) 122 (52) 82 (35) 66 (12) 24 (40) 6 (17)

PFS WITH KPD MAINTENANCE



Median follow up: 44 months



Median follow up: 56 months

Nooka et al, ASCO 2023
Data cut off May 2025

EMN30/MAJESTEC-4: STUDY DESIGN

Key eligibility criteria:

- NDMM
- ECOG PS score of 0-2
- Received 4-6 cycles of 3- or 4-drug induction therapy (PI and/or IMiD ± anti-CD38 antibody) and ASCT[a] ± consolidation with ≥PR

SRI

- **SRI Cohort 1: Tec-Len** — Tec QW → Q4W
- **SRI Cohort 2: Tec-Len** — Tec Q4W
- **SRI Cohort 3: Tec** — Tec Q4W

Phase 3, randomized study

N≈1500
1:1:1 randomization

- → **Tec-Len** — Tec Q4W
- → **Tec** — Tec Q4W
- → **Len**

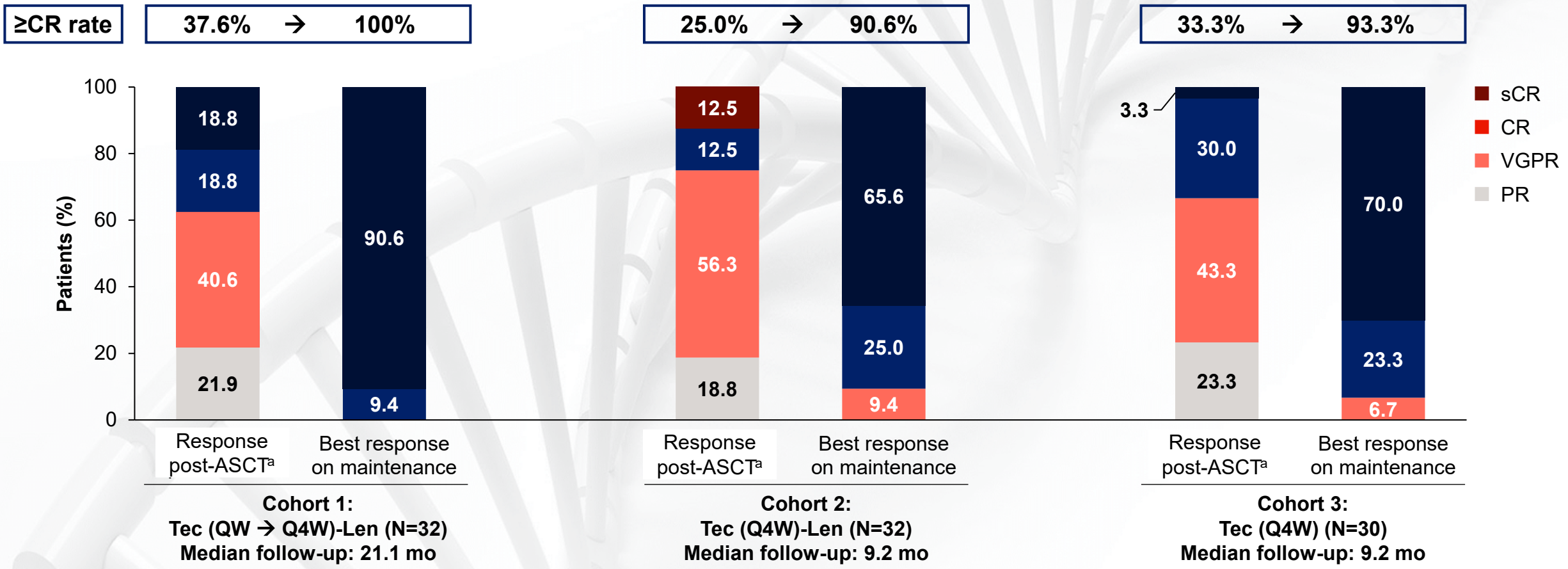
Dual primary endpoints:

- PFS
- 12-month MRD-negative CR (by NGF; 10^{-5})

Select secondary endpoints:

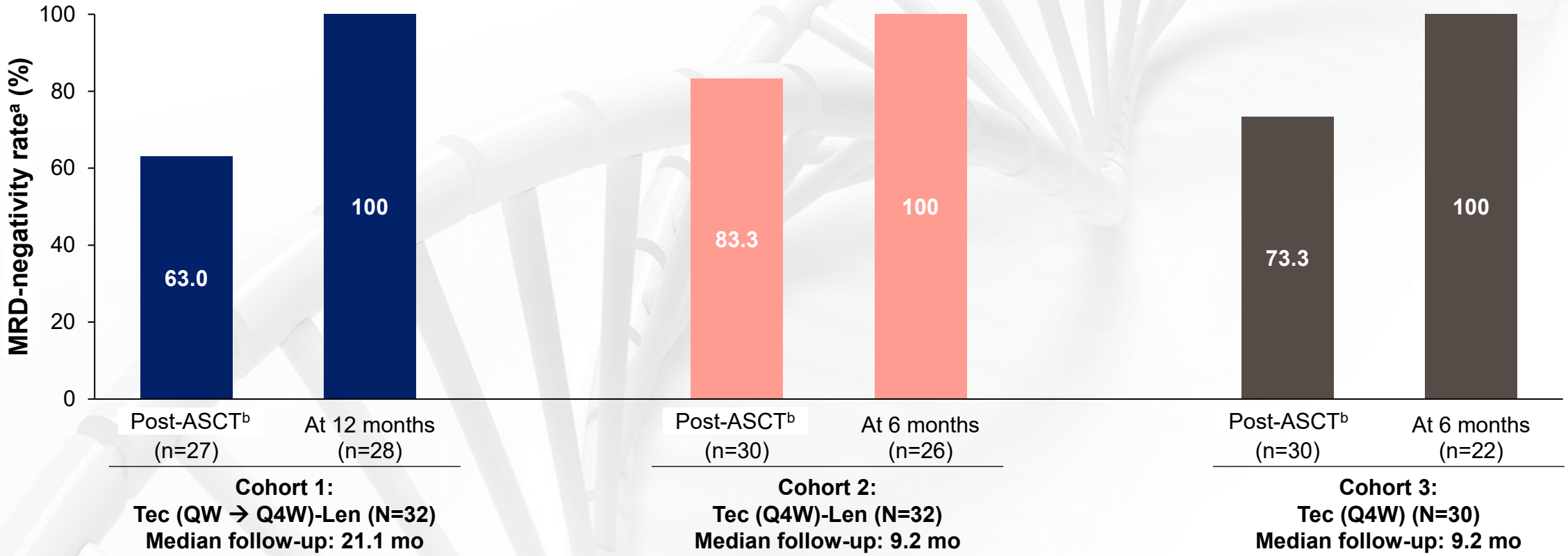
- OS
- ≥CR
- CR conversion
- MRD-negative conversion
- MRD negativity/sustained MRD negativity
- PFS2
- TTNT
- Safety

EMN30/MAJESTEC-4 SRI: RESPONSE RATES POST-ASCT AND DURING MAINTENANCE



Responses deepened during maintenance in all treatment cohorts

EMN30/MAJESTEC-4 SRI: MRD NEGATIVITY (10^{-5}) IN EVALUABLE PATIENTS POST-ASCT AND DURING MAINTENANCE



100% of evaluable patients were MRD negative during maintenance

NDMM- TRANSPLANT INELIGIBLE: : CEPHEUS TRIAL SUMMARY

Key eligibility criteria:

- NDMM (TIE or transplant deferred)
- ECOG PS score of 0–2
- Frailty score of 0–1

1:1 randomization (N = 395)

VRd
V: 1.3 mg/m² SC Days 1, 4, 8, 11
R: 25 mg PO Days 1–14
d: 20 mg PO Days 1, 2, 4, 5, 8, 9, 11, 12

Rd Cycle 9+
R: 25 mg PO Days 1–21
d: 40 mg PO Days 1, 8, 15, 22

DARA SC-VRd
DARA: 1,800 mg SC QW Cycles 1–2, Q3W Cycles 3–8
VRd: schedule as above

DARA SC-Rd Cycle 9+
DARA: 1,800 mg SC Q4W
Rd: schedule as above

21-day cycles
8 cycles of bortezomib treatment

28-day cycles until disease progression or unacceptable toxicity

Primary endpoint:

- Overall MRD (≥CR) negativity

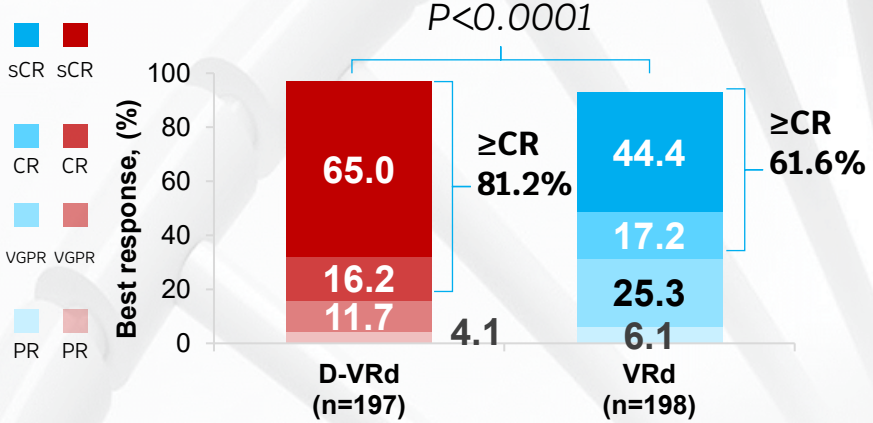
Key secondary endpoints:

- PFS
- Sustained MRD (≥CR) negativity (≥12 months)
- ≥CR rate
- OS

Primary endpoint

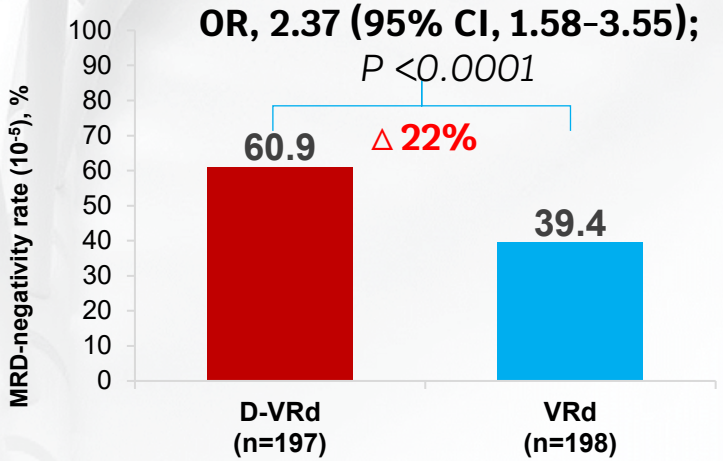
≥CR rate

OR, 2.73 (95% CI, 1.71–4.34);
P<0.0001



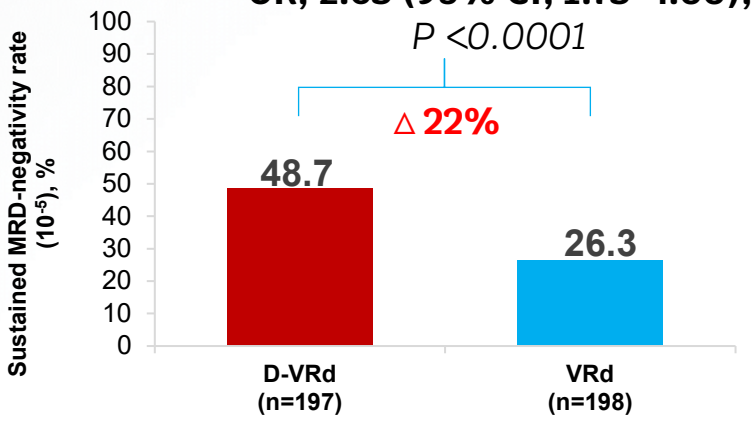
Overall MRD-negativity rate (10^{-5})

OR, 2.37 (95% CI, 1.58–3.55);
P <0.0001



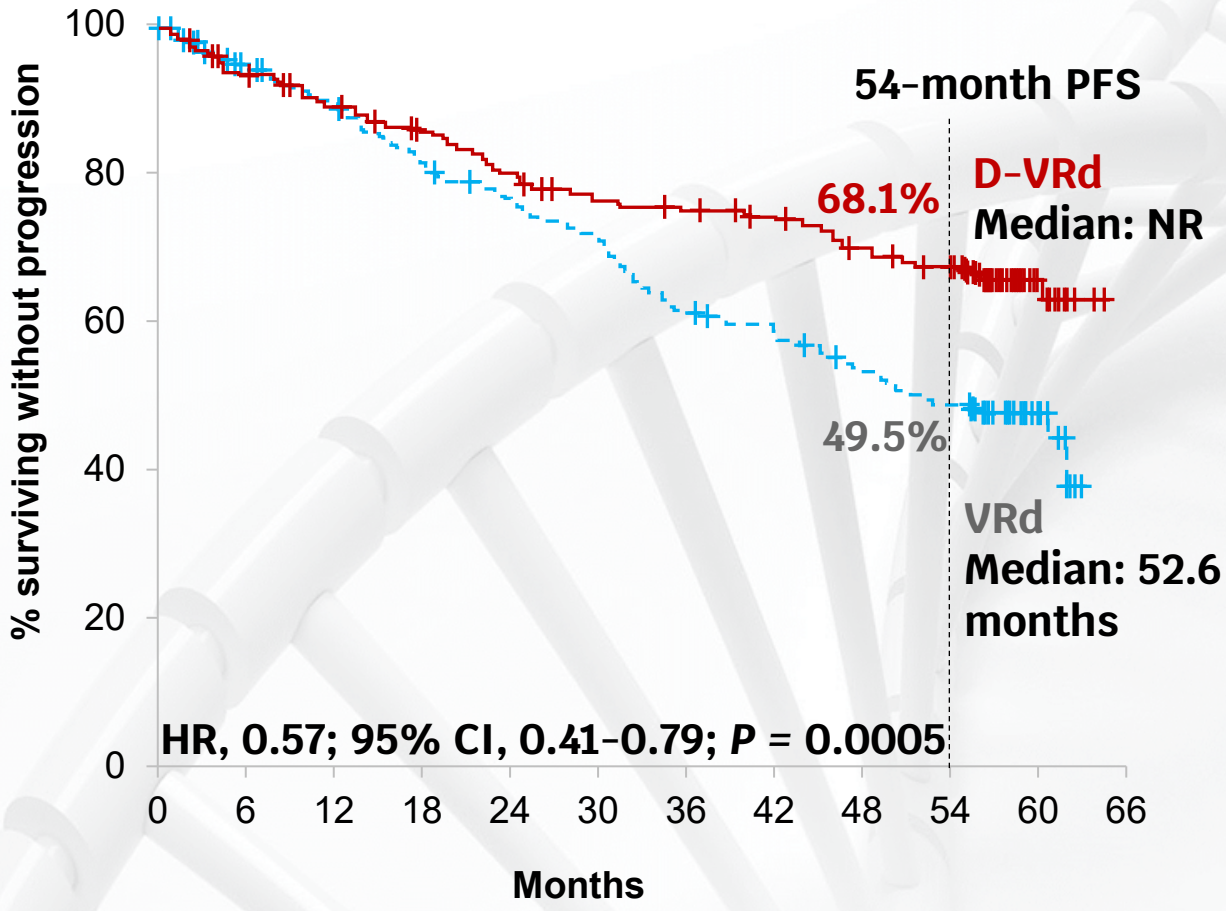
Sustained MRD-neg rate (10^{-5}) ≥12 months

OR, 2.63 (95% CI, 1.73–4.00);
P <0.0001

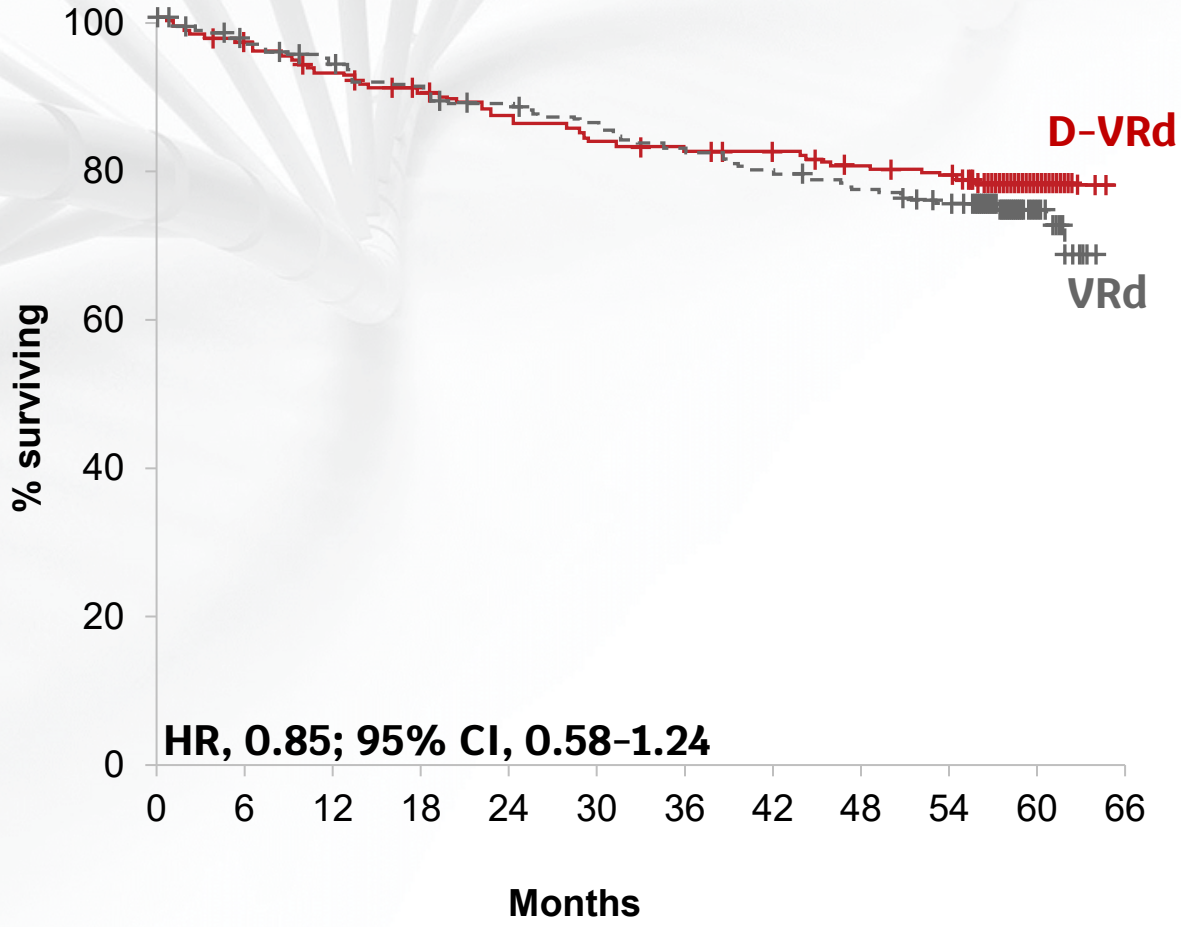


CEPHEUS: KEY SECONDARY ENDPOINTS @ 58.7 MONTHS

PFS (ITT)



OS (ITT population)



Reformatted from: SZ Usmani at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

CEPHEUS: SAFETY

TEAE, n (%)	D-VRd (n = 197)		VRd (n = 195)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
HEMATOLOGIC				
Blood and lymphatic system disorders	163 (82.7)	126 (64.0)	126 (64.6)	98 (50.3)
Neutropenia	110 (55.8)	87 (44.2)	76 (39.0)	58 (29.7)
Thrombocytopenia	92 (46.7)	56 (28.4)	66 (33.8)	39 (20.0)
Anemia	73 (37.1)	26 (13.2)	62 (31.8)	23 (11.8)
NONHEMATOLOGIC				
Gastrointestinal disorder	157 (79.7)	41 (20.8)	159 (81.5)	40 (20.5)
Diarrhea	112 (56.9)	24 (12.2)	115 (59.0)	18 (9.2)
Constipation	75 (38.1)	4 (2.0)	82 (42.1)	5 (2.6)
General disorders and administration-site conditions	159 (80.7)	40 (20.3)	147 (75.4)	28 (14.4)
Peripheral edema	83 (42.1)	4 (2.0)	76 (39.0)	1 (0.5)
Fatigue	63 (32.0)	18 (9.1)	60 (30.8)	16 (8.2)
Psychiatric disorders	91 (46.2)	10 (5.1)	96 (49.2)	10 (5.1)
Insomnia	63 (32.0)	4 (2.0)	63 (32.3)	2 (1.0)
Infections	181 (91.9)	79 (40.1)	167 (85.6)	62 (31.8)
Upper respiratory tract infection	78 (39.6)	1 (0.5)	64 (32.8)	1 (0.5)
COVID-19	75 (38.1)	22 (11.2)	48 (24.6)	9 (4.6)
Second primary malignancies	15 (7.6)	-	18 (9.2)	-

	Any grade	Grade 2	Grade 3 or 4	Any grade	Grade 2	Grade 3 or 4
Peripheral sensory neuropathy	110 (55.8)	60 (30.5)	16 (8.1)	119 (61.0)	70 (35.9)	16 (8.2)

NDMM- TRANSPLANT INELIGIBLE: : IMROZ: TRIAL SUMMARY

Patients with NDMM
N = 446

RANDOMIZATION 3:2

= 265 patients

= 181 patients

Induction phase:
Cycles 1-4
(6-week cycles)

Isatuximab + VRd | **VRd**

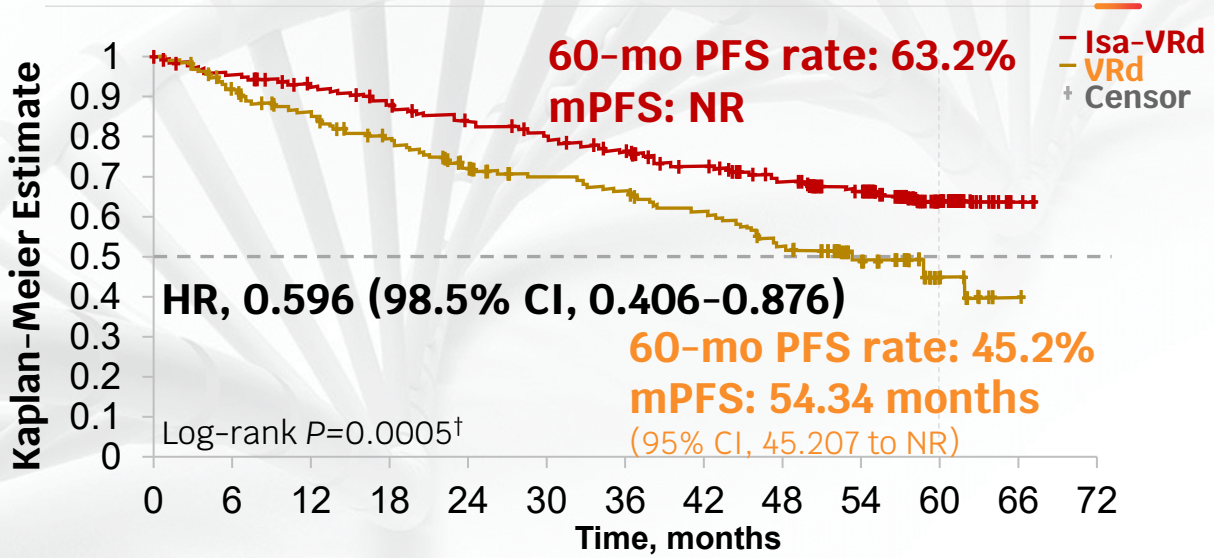
Continuous phase:
Cycles 4 onwards
(4-week cycles)

Isatuximab + Rd | PD | **Rd**

Disease progression, unacceptable AEs, patient withdrawal

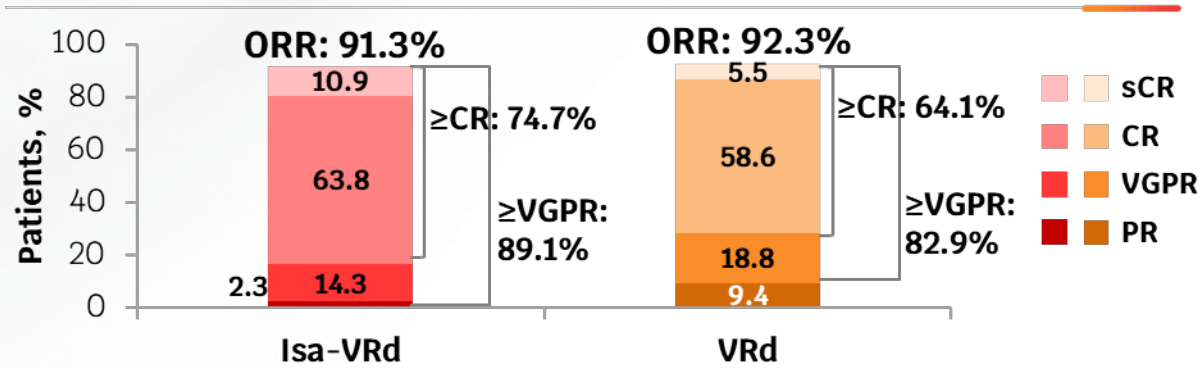
Primary Outcome: PFS
Secondary Outcomes: CR rate, MRD negativity in patients with CR, ≥ VGPR rate, OS, ORR, TTP, DoR, TT1R, TTBR, PFS2, PFS in MRD- pts, Sustained MRD- ≥ 12 months, Aes, Assessment of PK parameter (Ctrough), Immunogenicity, PROs

Primary Endpoint: PFS by IRC in ITT



Overall Survival Rates	Isa-VRd	VRD	HR
	72.3%	66.3%	0.776 (95% CI, 0.407-1.48

Best Overall Response



Facon et. al., PHASE III (IMROZ) STUDY DESIGN: ISATUXIMAB PLUS BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE (VRD) VERSUS VRD IN TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA.Abstract release date: 05/17/18) EHA Library. Facon T. 06/14/18; 216012; PB2185

IMROZ: SAFETY SUMMARY

AE Preferred Term, n (%)	Isatuximab + VRd (n = 263)		VRd (n = 181)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hematologic lab abnormalities				
▪ Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Nonhematologic AEs				
▪ Infections	240 (91.3)	118 (44.0)	157 (86.7)	69 (38.1)
▪ Pneumonia	79 (30.0)	53 (20.2)	35 (19.3)	23 (12.7)
▪ Upper respiratory tract infection	90 (34.2)	2 (0.8)	61 (33.7)	2 (1.1)
▪ Diarrhea	144 (54.8)	20 (7.6)	88 (48.6)	15 (8.3)
▪ Peripheral sensory neuropathy	143 (54.4)	19 (7.2)	110 (60.8)	11 (6.1)
▪ Cataract	100 (38.0)	41 (15.6)	46 (25.4)	20 (11.0)
Invasive second primary malignancies				
▪ Solid tumors	22 (8.4)	14 (5.3)	8 (4.4)	6 (3.3)
▪ Hematologic	3 (1.1)	1 (0.4)	1 (1.1)	1 (1.1)
Event rate per patient-year				
▪ Infections	1.181	--	1.166	--
▪ Secondary primary malignancies	0.041	--	0.026	--

IFM2020-05/BENEFIT: PHASE 3 STUDY OF ISATUXIMAB PLUS LENALIDOMIDE AND DEXAMETHASONE WITH/WITHOUT BORTEZOMIB: TRIAL SUMMARY

- 270 NTE NDMM patients, aged 65-79 years old and non-frail, randomized 1:1 ratio to Isa-Rd or Isa-VRd lite
- Patients receive isatuximab IV 10 mg/kg on days 1,8,15, and 22 of cycle 1, days 1 and 15 from cycle 2 to 12 and day 1 from cycle 13 onward, 28-day cycles
- Bortezomib was administered weekly and subcutaneously on days 1, 8, 15 at 1.3 mg/m2 from cycle 1 to 12 and on days 1, 15 from cycle 13 to 18, and then stopped
- Patients will then continue receiving Isa-Rd until progression in both arms

Primary Endpoint:
MRD- rate @18 months

Key secondary:
OS, PFS, EFS, TTNT, Response rates, DoR and safety

Patient Characteristics

- Median age: 73.2 years
- 90 patients (33%) were >75 years
- 23 (9%) had high-risk cytogenetic (IFM score >1)
- 181 (76%) had R-ISS2+3
- 47 (17%) had impaired renal function (eGFR <60 mL/min)

N (%) (ITT Population) [95%CI] at 18 Months	IsaRd (n=135)	Isa-VRd (n=135)	p-value
≥CR	24 (18) [12 – 25]	54 (40) [32 – 49]	0.0001
≥CR- MRD- 10-5	16 (12) [7 – 19]	29 (21) [15 – 29]	0.04
MRD- 10^{-6}	20 (15) [9 – 22]	46 (34) [26 – 43]	0.0004
PFS at 18 months	86% [80 – 92]	87.2% [82 – 93]	0.47
OS at 18 months	93.6% [90 – 98]	92.4% [88 – 97]	0.77

Leleu et. al., Phase 3 randomized study of isatuximab (Isa) plus lenalidomide and dexamethasone (Rd) with bortezomib versus isard in patients with newly diagnosed transplant ineligible multiple myeloma (NDMM TI) ASCO 2024, Abstract 7501

IFM 2021-01 TECLILLE - STUDY DESIGN

Phase 2 study of Tec-Dara and Tec-Len in TNE NDMM (n = 74)

NDMM
Age > 65yo
TNE
ECOG 0-2

Cohort A (n=37)

Teclistamab
2 step-up dose then 1.5mg/kg D8 and D15 then 3mg/kg Q4W thereafter

Daratumumab
1800 mg SC, QW for 8 weeks, Q2W for 16 weeks, Q4W thereafter

Cohort B (n=37)

Teclistamab
2 step-up dose then 1.5mg/kg D8 and D15 then 3mg/kg Q4W thereafter

Lenalidomide
25mg per day 21/28

Pre-specified safety and efficacy analysis after 18 patients have received ≥ 2 cycles

Pre-specified safety and efficacy analysis after 10 and 18 patients have received ≥ 2 cycles

Primary endpoint

- Rate of VGPR or better after 4 cycles

Secondary endpoints

- Rate of responses (PR, VGPR, CR, sCR)
- PFS
- OS
- TTNT
- MRD 10^{-6} at 6 months
- Sustained MRD 10^{-6}

- Treatment-emergent adverse events

MRD evaluation — **M6** — **M18** — **M30** — **M42**

Current amendment:
Teclistamab 3mg/kg Q8W after C13 if CR or better and treatment interruption if 2-years sustained MRD -

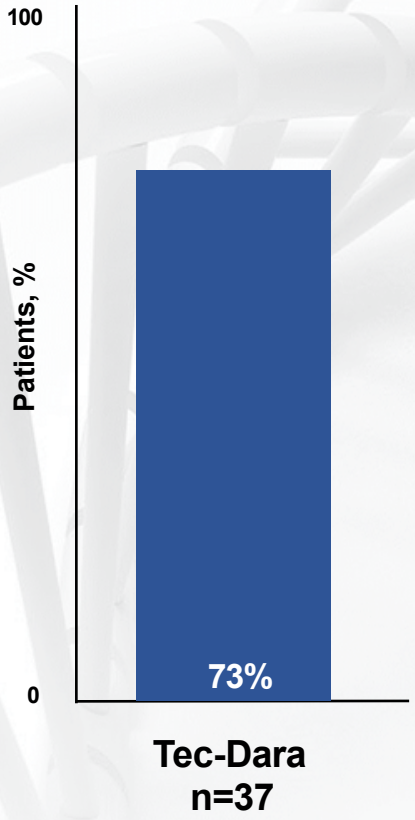
IFM 2021-01 TECLILLE – COHORT A: TEC-DARA MRD NGS 10^{-6} EVALUATION

All 37 patients had MRD evaluation by NGS (Clonoseq) at 6 months. For technical reason, 27 patients were evaluable at 10^{-6}:

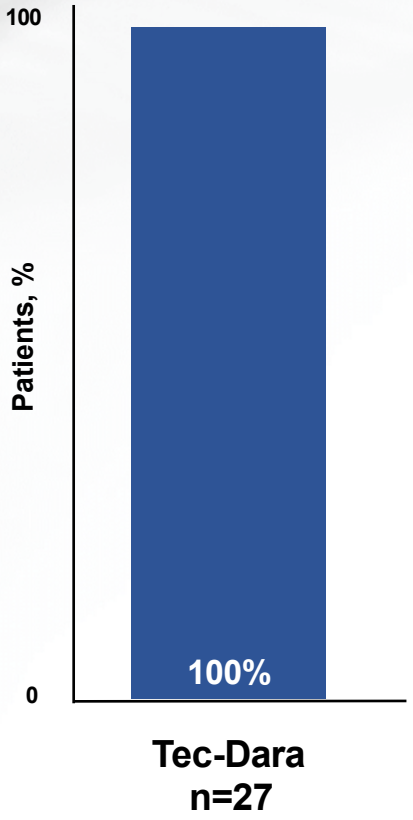
Missing causes	n
Calibration failure	4
Missing samples	3
Only evaluable at 10^{-5}	3

No patients had a positive MRD status.

MRD by NGS 10^{-6} at 6 months
ITT



MRD by NGS 10^{-6} at 6 months
Evaluable samples



All evaluable samples were MRD negative at 10^{-6} by NGS at 6 months

AURIGA: STUDY DESIGN

- **Objective: To better understand the evolution of MRD status during maintenance and its impact on long-term outcomes**

Key eligibility criteria

- 18-79 years of age
- NDMM with ≥4 cycles of induction therapy and underwent ASCT within 12 months of the start of induction
- ≥VGPR at screening[a]
- MRD[b] positive (10^{-5}) after ASCT
- No prior anti-CD38
- Randomization within 6 months of the ASCT date

Stratification factor

- Cytogenetic risk[c] at diagnosis (standard/unknown vs high risk)

1:1 RANDOMIZATION (N = 200)

Maintenance: up to 36 cycles[d] (28-day cycles)

D-R

DARA: 1,800 mg SC[e] 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)

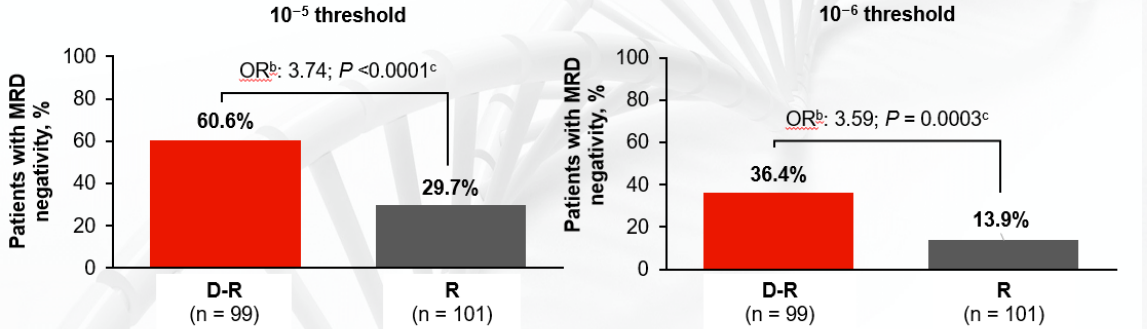
MRD[b] obtained after 12, 18, 24, and 36 cycles, enabling analysis of MRD dynamics

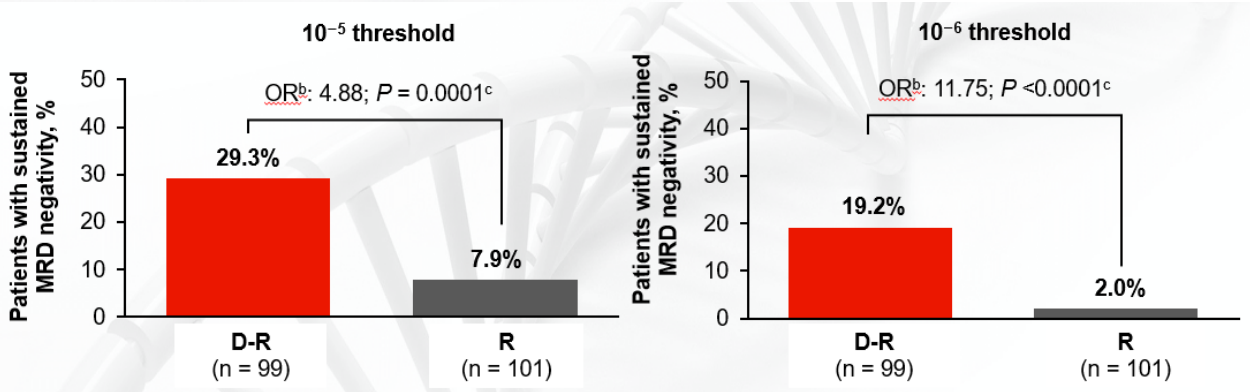
Primary endpoint

- MRD-negative (10^{-5}) conversion rate from baseline to 12 months after maintenance treatment

Secondary endpoints

- Overall MRD-negative conversion rate, sustained MRD-negative rate, PFS, response rate, duration of ≥CR, OS, safety





CC-220-MM-001: IBERDOMIDE + DARA-DEX
CELMOD TRIPLETS FOR TRANSPLANT-INELIGIBLE NDMM

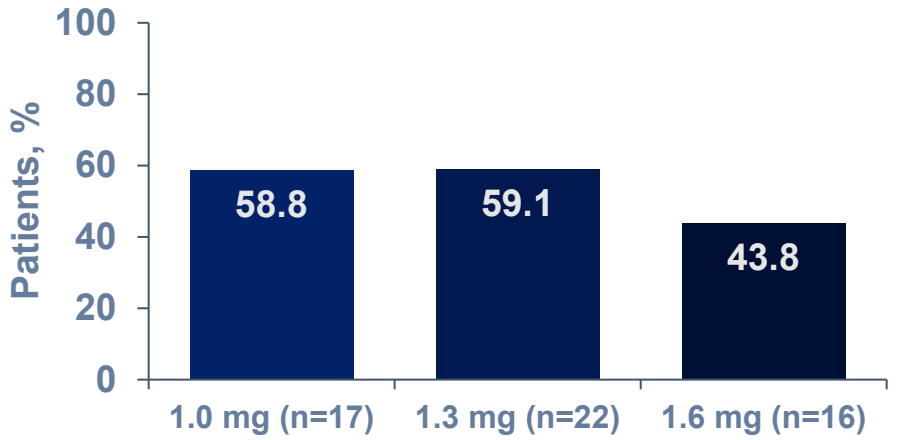
75 transplant-ineligible NDMM patients

- Iberdomide 1.0, 1.3, 1.6 mg
- 25 patients at each dose level
- NDMM with no planned or recommended ASCT due to age or comorbidities
- Biomarker defined populations: IHC, WGS, RNAseq analyses

Markers

- High-risk markers: 3 *TP53* mutations, 2 del(17p), 2 1qAmp, 1 t(4;14)
- All patients responded to IberDd in each subgroup
- High-risk gene expression signatures (n=15) showed similar PFS in patients with high and low EMC92 and UAMS70 scores
- Immune compartment: similar baseline levels and changes in T, B, and NK cells and T-cell subsets – activated (HLA-DR+, ICOS+), naive, memory, and exhausted (PD1+, LAG3+, TIM3+) CD4 and CD8 T cells – across patient subgroups

MRD-neg in ≥VGPR patients



Activity

- > 90% sFLC reductions across all dose levels
- ORR 100%
- 6 patients proceeded to ASCT
- At 3 months post-ASCT, ORR 100% (3 CRs, 2 VGPRs, 1 PR)
- 1 patient with documented sCR and MRD-neg at data cutoff
- Median PFS not reached

ACST, autologous stem cell transplant; CR, complete response; IberDd, iberdomide-daratumumab-dexamethasone; IHC, immunohistochemistry; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PFS, progression free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; WGS, whole-genome sequencing

Amatangelo. *Blood*. 2024;144(Supplement 1):1973.

CC-220-MM-001: IBERDOMIDE + BORTEZOMIB-DEX
CELMOD TRIPLETS FOR TRANSPLANT-INELIGIBLE NDMM

18 transplant-ineligible NDMM patients

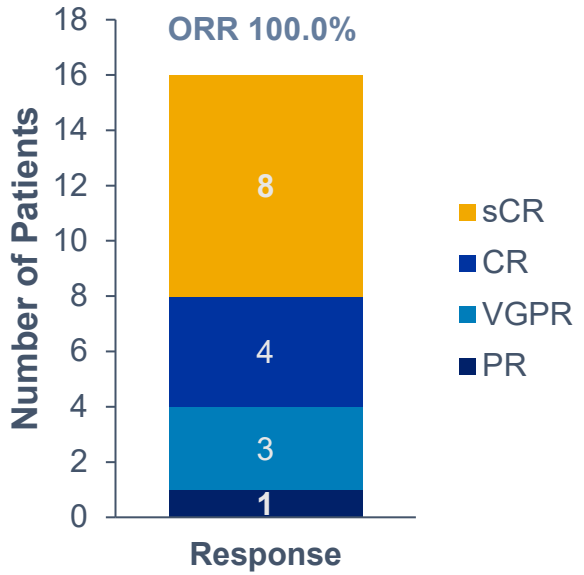
- Iberdomide: Days 1–14 (21-d cycle, Cycles 1–8); Days 1–21 (28-d cycle, ≥ Cycle 9)
- Bortezomib: Days 1, 4, 8, 11 (Cycles 1–8)
- Dexamethasone: intensive early (Cycles 1–8), weekly (≥ Cycle 9)
- Endpoints: Efficacy, safety, pharmacokinetics, MRD by flow cytometry
- Median follow-up: 25 months

Safety

- In the safety population (n = 17), 14 (82.4%) pts had grade 3/4 treatment-emergent AEs (TEAEs), primarily infections (47.1%)
- The most common hematologic grade 3/4 TEAE was neutropenia (29.4%)
- 2 (11.8%) pts had grade 3–4 peripheral neuropathy
- IBER dose interruptions and reductions due to TEAEs occurred in 14 (82.2%) and 10 (58.8%) pts, respectively
  - Dose reductions were mainly due to peripheral neuropathy (23.5%), neutropenia (11.8%), and thrombocytopenia (11.8%)
- TEAEs were manageable with dose modifications/interruptions and G-CSF use.

Efficacy

Iberdomide + Bortezomib-dex (n = 16)



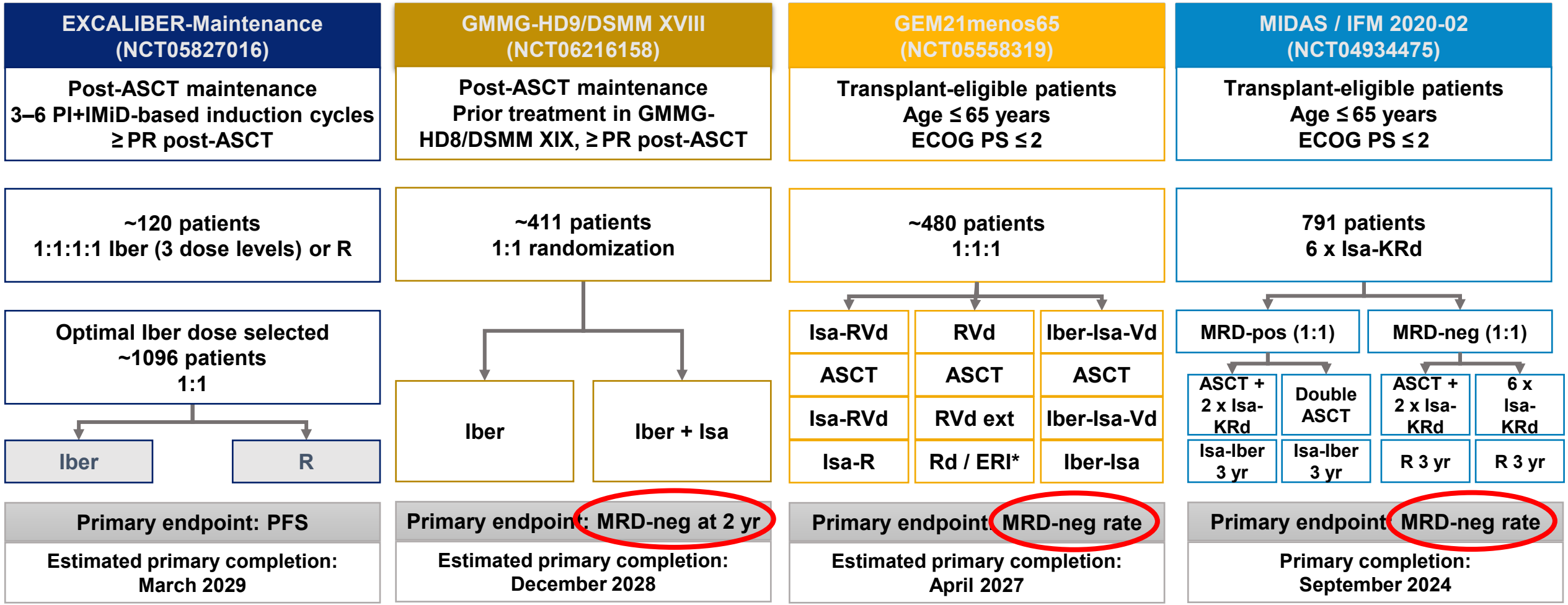
- Median time to response: 0.7 mo
- Median duration of response: not reached
- MRD negativity (10^{-5}): 8 pts (50%), all had ≥CR

CR, complete response; G-CSF, granulocyte colony-stimulating factor; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; TEAEs, treatment-emergent adverse events;; VGPR, very good partial response

White, et al. ASCO 2025. Abstract 7532. White et al. *HemaSphere*, 2025;9(S1):PF737

Phase 3 Studies of IBERDOMIDE IN NDMM: A REPLACEMENT FOR LENALIDOMIDE?

CELMoD Quadruplets and Maintenance Regimens in Transplant-Eligible NDMM



*Early rescue intervention: Isa-Iber-d

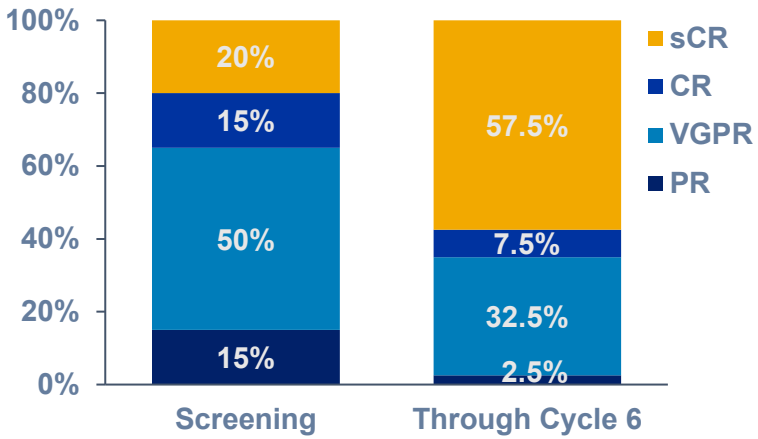
ASCT, autologous stem Acell transplant; PI, proteosome inhibitor; IMiD, immunomodulatory drug; Iber, iberdomide; R, lenalidomide; PFS, progression free survival; MRD, minimal residual disease; Isa, isatuximab; V, bortezomib; d, dexamethasone; K, carfilzomib

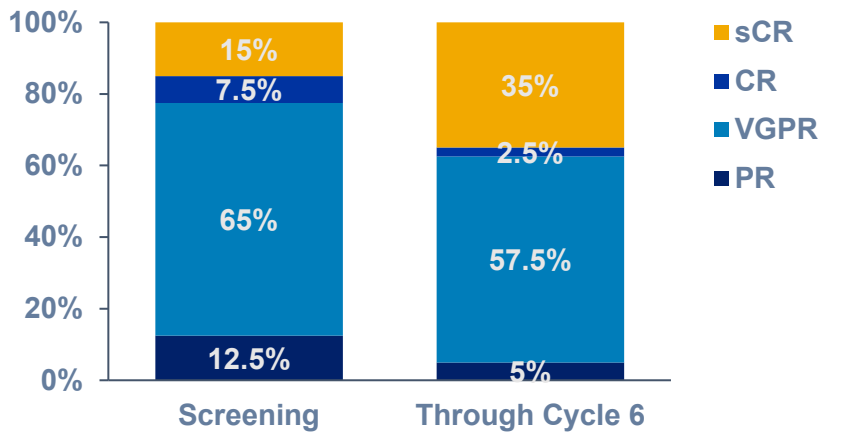
ClinicalTrials.gov, December 9, 2024. Liu. *Expert Rev Hematol.* 2024;17(8):445–65. Perrot. *Blood*. 2025;2024026230. Perrot. ASCO 2025. Abstract 7500.

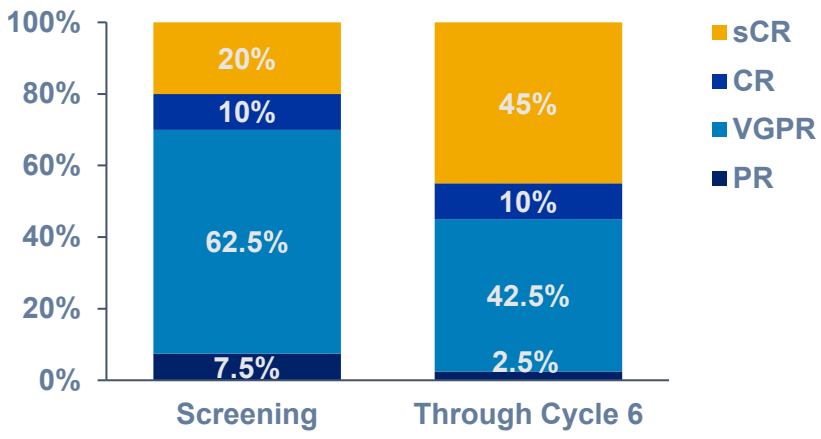
EMN26: IBERDOMIDE AS POST-ASCT MAINTENANCE

120 NDMM patients

- ≥PR after PI-IMiD-containing induction, 1/2 ASCT, ± consolidation
- Median age 59 years, 54% male
- 31% / 57% / 12% R-ISS stage I / II / III
- 21% high-risk cytogenetics
- 40 patients per dose cohort (0.75, 1.0, 1.3 mg)







0.75 mg cohort, n = 40

- 66% improved response depth through cycle 6
- NR through cycle 12
- 30% MRD-pos to MRD-neg
- 12-month PFS 95%
- Grade ≥3 neutropenia 30%, infections 2%

1.0 mg cohort, n = 40

- 32% improved response depth through cycle 6
- 47% through cycle 12
- 32% MRD-pos to MRD-neg
- 12-month PFS 87%
- Grade ≥3 neutropenia 42%, infections 15%

1.3 mg cohort, n = 40

- 41% improved response depth through cycle 6
- 59% through cycle 12
- 53% MRD-pos to MRD-neg
- 12-month PFS 90%
- Grade ≥3 neutropenia 52%, infections 10%

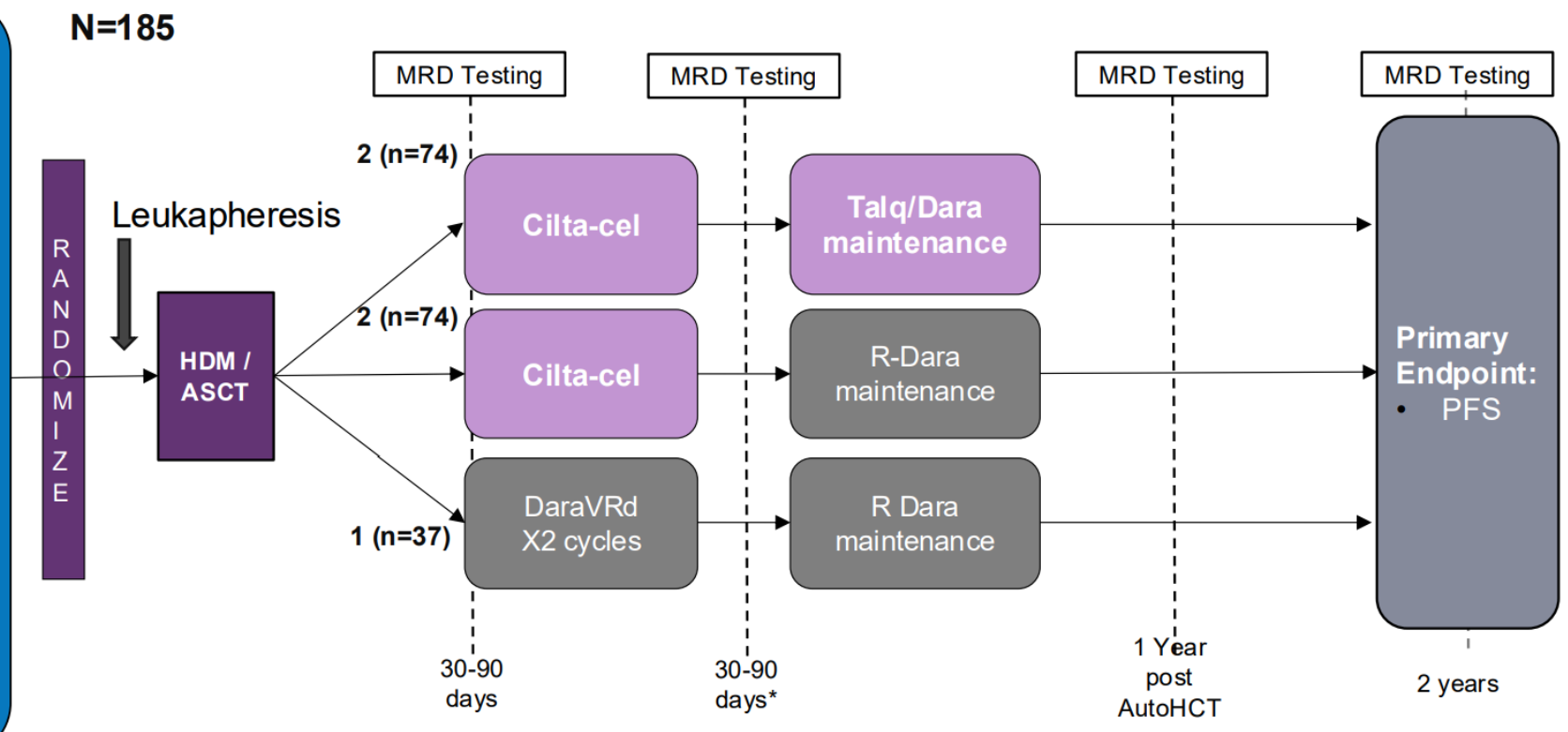
ASCT, autologous stem cell transplant; CR, complete response; IMiD, immunomodulatory drug; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression free survival; PI, proteosome inhibitor; PR, partial response; sCR, stringent complete response, VGPR, very good partial response;

Gay. *Hemasphere.* 2024;8(S1):1703-4.

TRIUMpH Trial: Phase 3 US BMT Collaborative Study in Newly Diagnosed High-Risk Multiple Myeloma

Patient Selection

- Revised ISS-3
- Revised ISS-2 with:
  - FISH for t(4;14), t(14;16), t(14;20), Del17p, ≥3 copies of chr 1q21
  - Genomic: GEP70hl, SKY92hl, biallelic TP53 deletion, c-Myc rear / mut
  - Imaging: >3 FDG avid bone lesions on PET-CT
- Extra-medullary disease at diagnosis
- Circulating plasma cells >5% at diagnosis
- Minimum DaraRVD X4 cycles
- Available mobilized peripheral hematopoietic cell graft.



BMT CTN
Blood & Marrow Transplant Clinical Trials Network

Slide courtesy: Binod Dhakal, co-PI along with Saad Usmani

CARTITUDE-5

- The randomized phase 3 CARTITUDE-5 study (NCT04923893) will compare the efficacy of VRd induction followed by cilta-cel versus VRd induction followed by Rd maintenance in pts with NDMM for whom ASCT is not planned as initial therapy

Key Eligibility Criteria

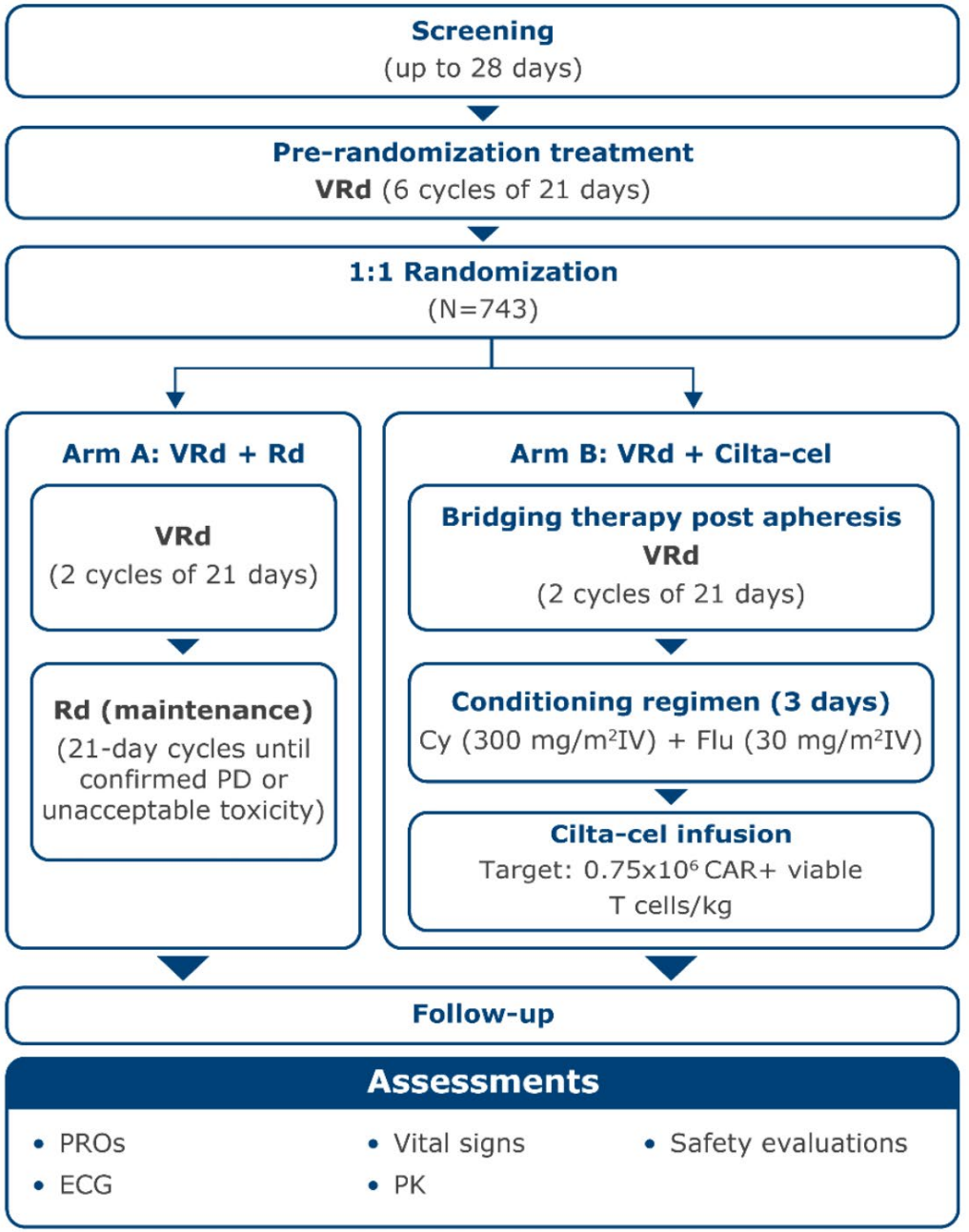
- MM per IMWG criteria
- ECOG PS 0 or 1
- Measurable disease
- Not considered for HDCT with ASCT
- No prior BCMA therapy
- Clinical laboratory values of:
  - Hb ≥8.0 g/dL[a]
  - Platelets ≥75x10^9/L
  - ALC ≥0.3x10^9/L
  - ANC ≥1.0x10^9/L[b]
  - ALT/AST ≤3xULN
  - eGFR ≥40 mL/min/1.73 m^2
  - Total bilirubin ≤2xULN[c]

Primary Outcome

- PFS

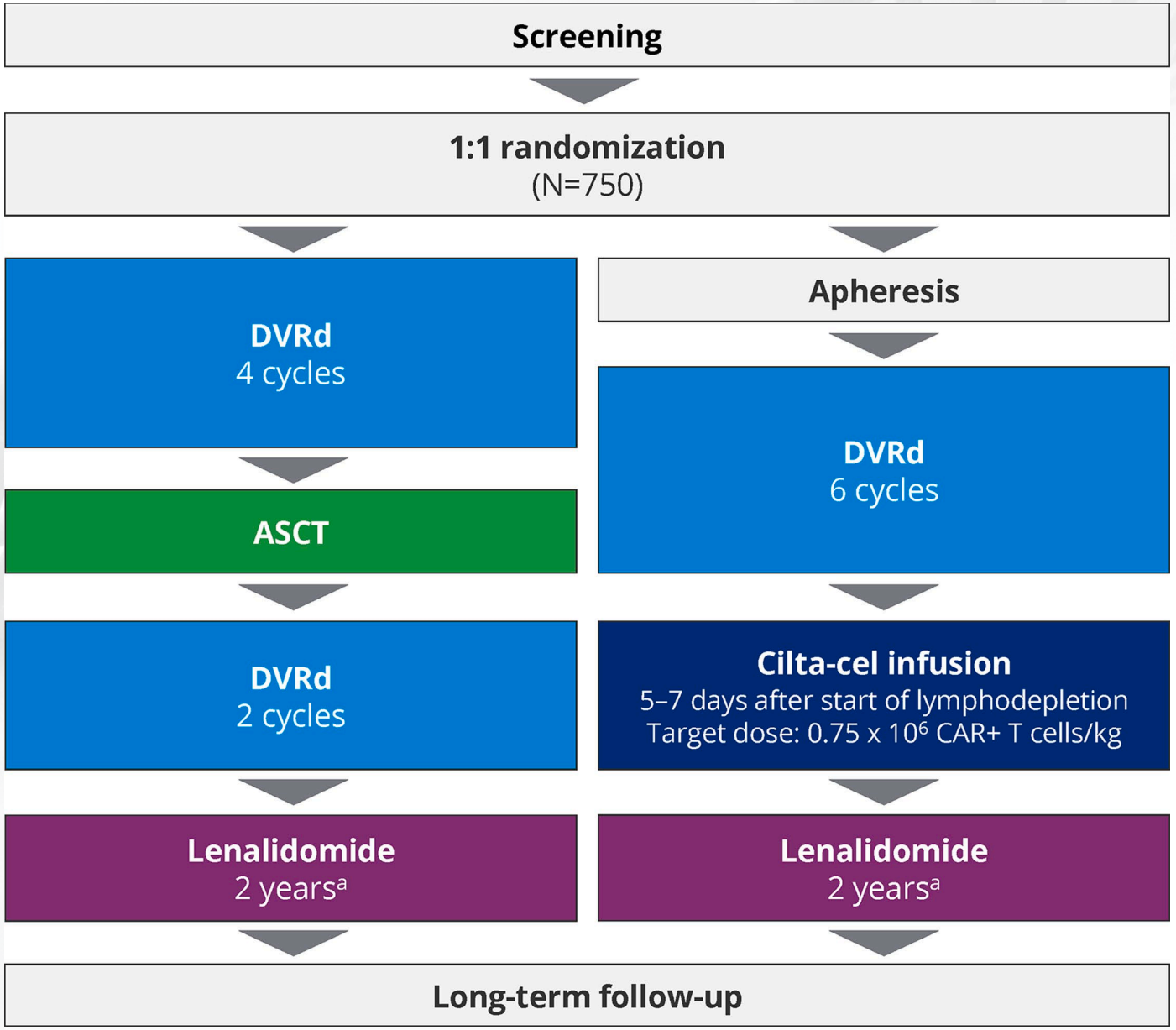
Key Secondary Outcomes

- Sustained MRD-negative CR[d]
- MRD-negative CR at 9 months
- Overall MRD-negative CR
- OS
- CR or better
- PFS2
- Time to next antimyeloma therapy
- Safety



CARTITUDE-6

- Randomized, open-label, global, multicenter, phase 3 *EM*agine/ CARTITUDE-6 study (EMN28/ 68284528MMY3005; NCT05257083)
- To compare the efficacy of DVRd followed by cilta-cel and lenalidomide versus DVRd followed by ASCT, DVRd, and lenalidomide



[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.

Myeloma Team

Sagar Lonial
Jonathan L. Kaufman
Lawrence H. Boise
Madhav Dhodapkar
Nisha Joseph
Craig Hofmeister
Vikas Gupta
Nishi Shah
Richa Parikh
Donald Harvey
Mala Shanmugam
Shannon Matulis
Benjamin Barwick
Manoj Bhasin
Joel Andrews
Rosie Pruitt
Rachael Morffi
Charise Gleason

Clinical Research team

Pauline Newlands
Bryan Burton
Adam Burgess
Shawn Reece
Patrick Mazzeo

Research labs

Boise lab
Lonial lab
Shanmugam lab
Bhasin lab
Gupta lab

Myeloma Patients

MM RF MULTIPLE MYELOMA Research Foundation

International Myeloma Society

International Myeloma Foundation

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