QUADRUPLETS VERSUS TRIPLETS FOR ELDERLY NEWLY DIAGNOSED MYELOMA

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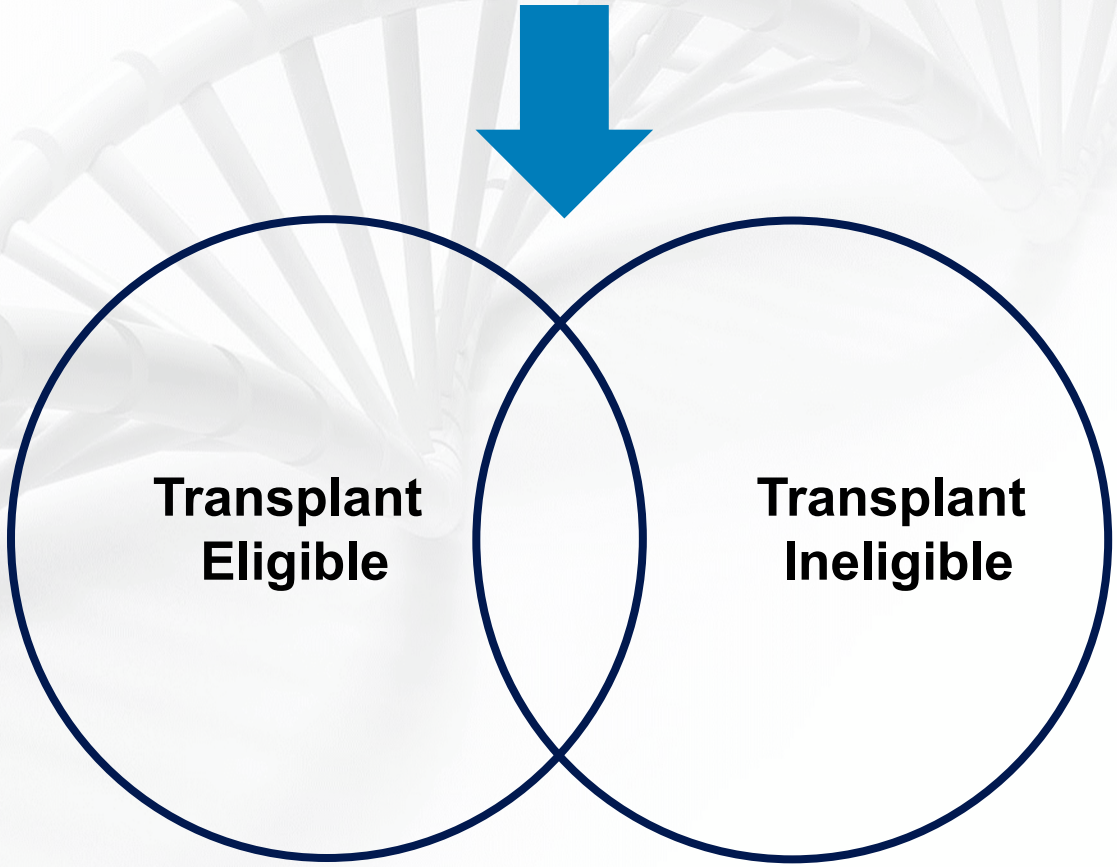
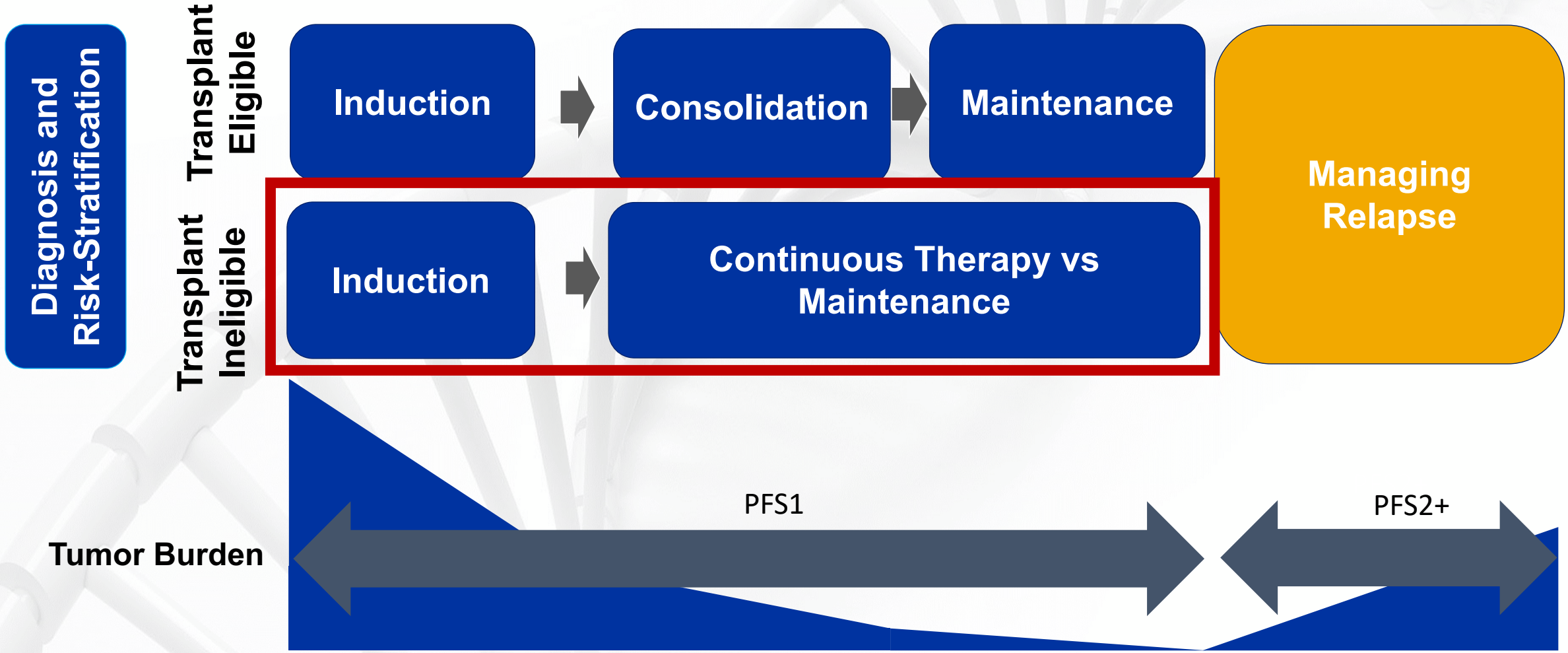
DISCLOSURES

Consultant/Advisor/Speaker: BMS, GSK

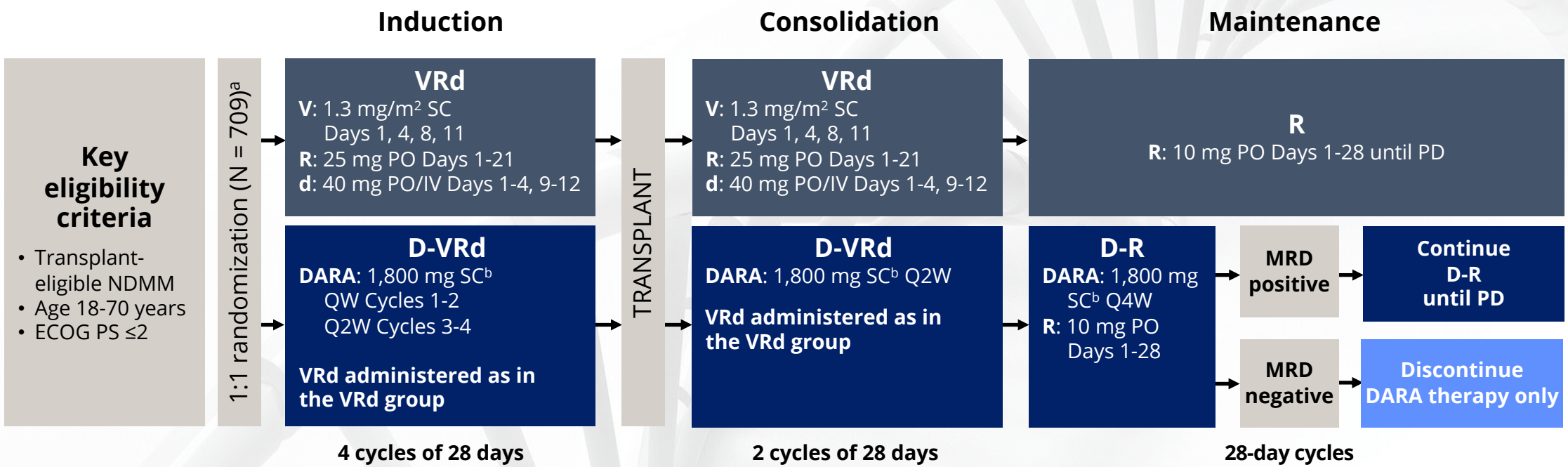
HOW DO WE DEFINE FRAILTY?



MM TREATMENT PARADIGM



PERSEUS: STUDY DESIGN



Primary endpoint: PFS[c]

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

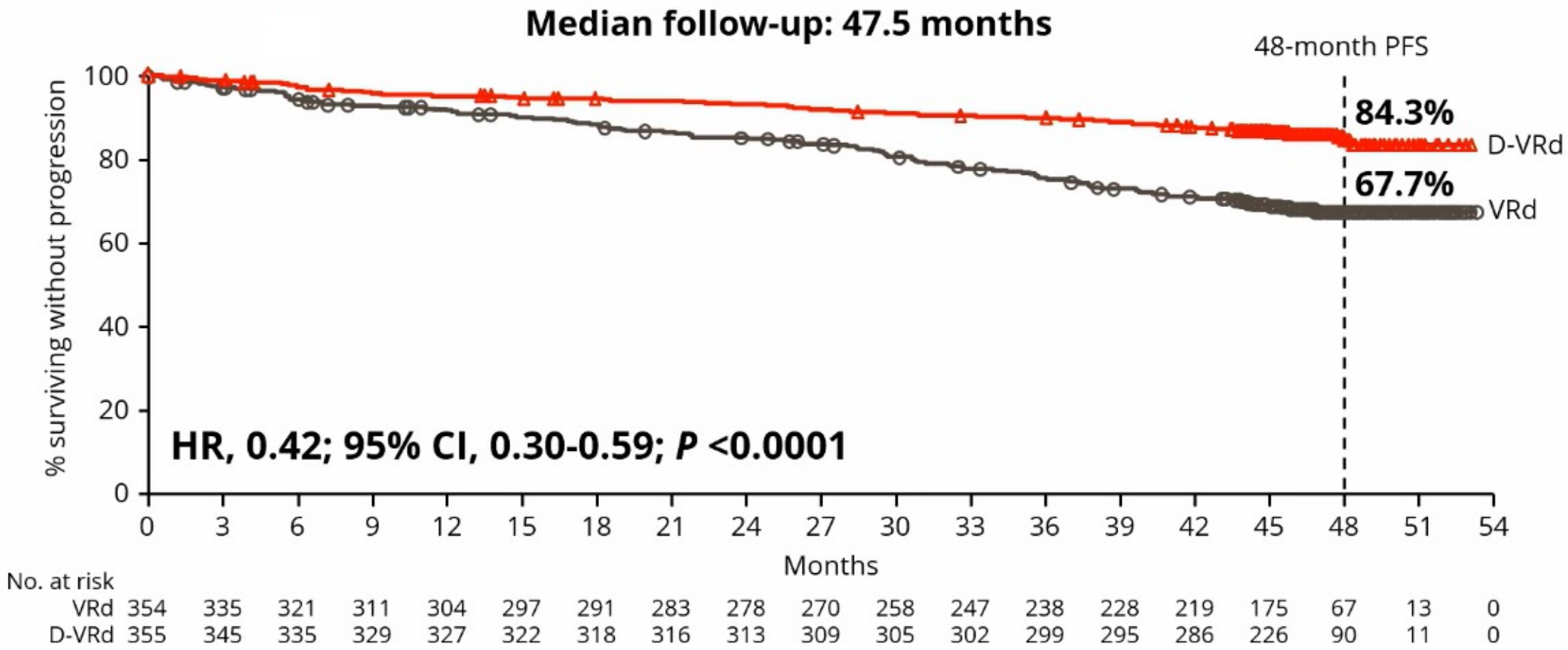
Discontinue DARA therapy only after ≥24 months of D-R maintenance for patients with ≥CR and 12 months of sustained MRD negativity

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

ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA).

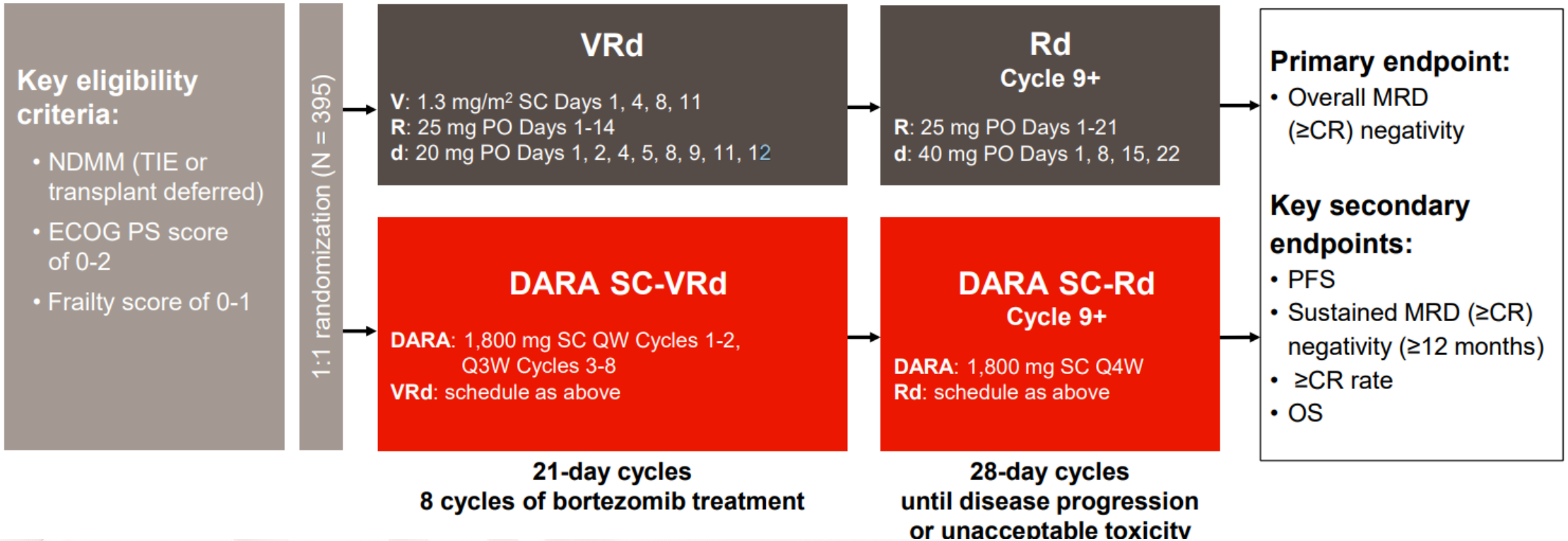
[c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time.

PERSEUS: PROGRESSION-FREE SURVIVAL



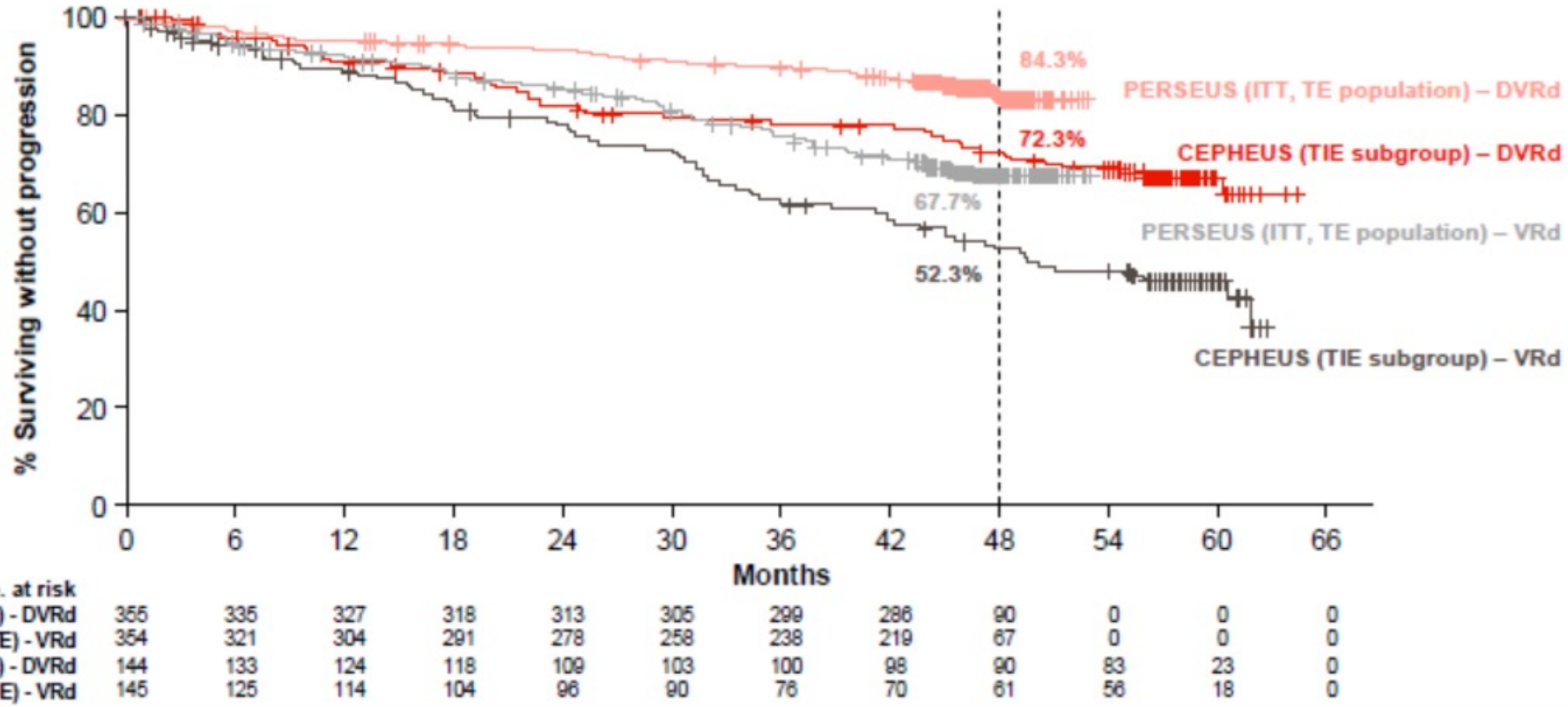
- **58% reduction in the risk of progression or death in patients receiving D-VRd**

CEPHEUS: PHASE 3 TRIAL OF D-RVD VS RVD IN TIE OR TRANSPLANT-DEFERRED



Usmani et al, IMS 2024

Median PFS With DVRd Not Reached in Both PERSEUS and CEPHEUS Trials



No. at risk												
PERSEUS (TE) - DVRd	355	335	327	318	313	305	299	286	90	0	0	0
PERSEUS (TE) - VRd	354	321	304	291	278	258	238	219	67	0	0	0
CEPHEUS (TIE) - DVRd	144	133	124	118	109	103	100	98	90	83	23	0
CEPHEUS (TIE) - VRd	145	125	114	104	96	90	76	70	61	56	18	0

Median PFS with DVRd not reached in TE patients in PERSEUS and TIE patients in CEPHEUS trials

DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ITT, intent-to-treat; PFS, progression-free survival; TE, transplant-eligible; TIE, transplant-ineligible; VRd, bortezomib, lenalidomide, and dexamethasone.

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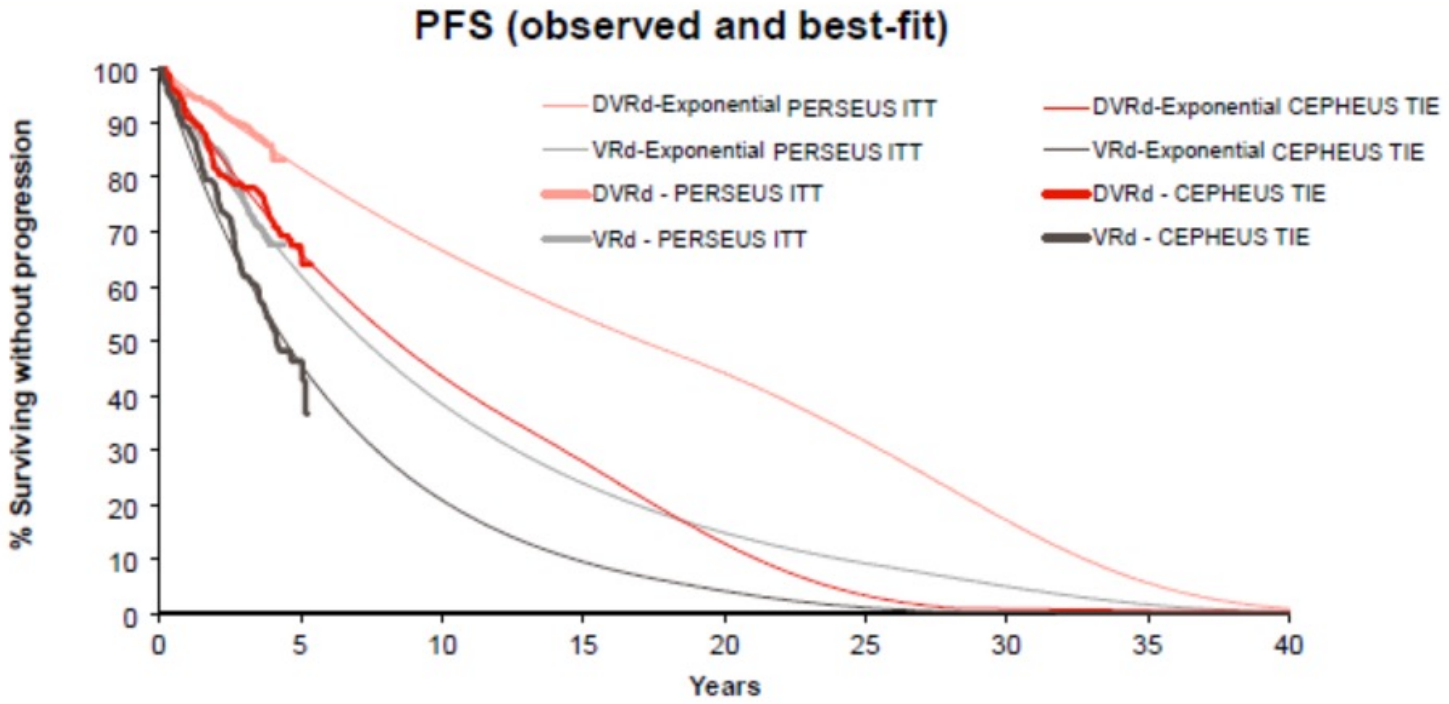
Sonneveld et al, EMN 2025

Significantly Longer Projected PFS With DVRd vs VRd for the Best-Fit Distribution



Estimated PFS, DVRd vs VRd

PERSEUS: **205 months (17.1 years)** vs 87 months (7.3 years)

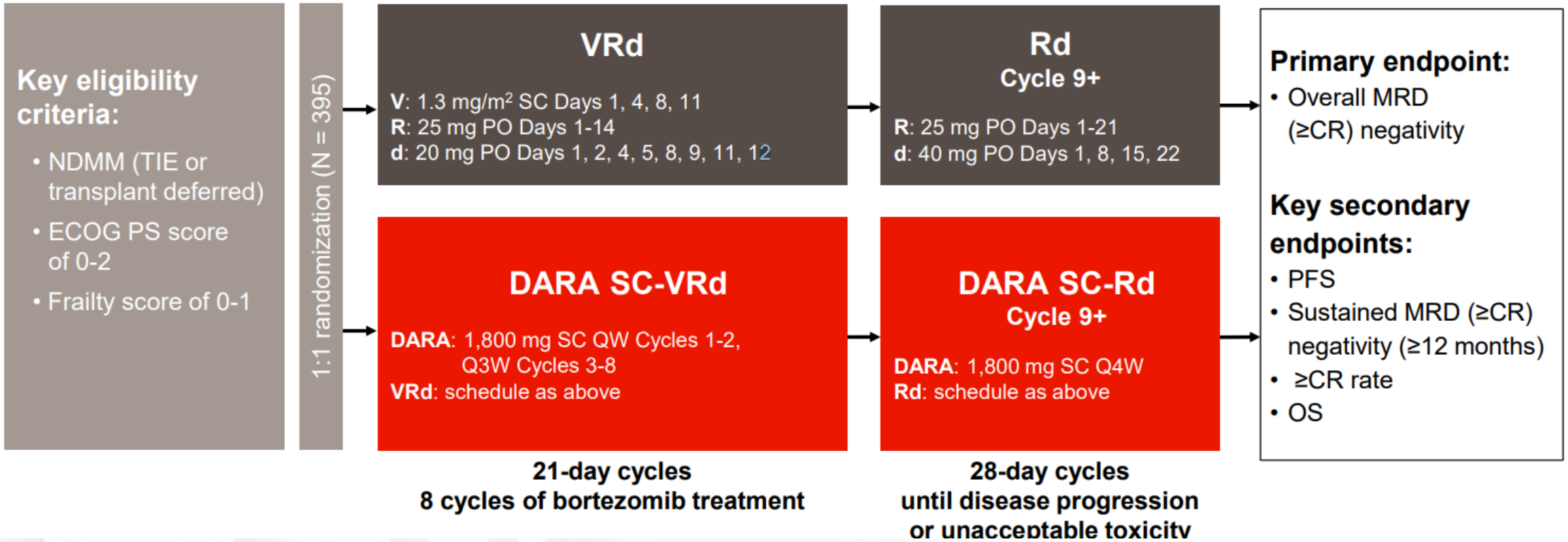
CEPHEUS: **100 months (8.3 years)** vs 53 months (4.4 years)

DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; f/u, follow-up; ITT, intent-to-treat; PFS, progression-free survival; TE, transplant-eligible; TIE, transplant-ineligible; VRd, bortezomib, lenalidomide, and dexamethasone[14]

Presented by S Zweegman at the 6th European Myeloma Network (EMN) meeting; April 10, 2025; Athens, Greece

Sonneveld et al, EMN 2025

CEPHEUS: PHASE 3 TRIAL OF D-RVD VS RVD IN TIE OR TRANSPLANT-DEFERRED



Usmani et al, IMS 2024

CEPHEUS: BASELINE DEMOGRAPHIC & CLINICAL CHARACTERISTICS

	D-VRd (n = 197)	VRd (n = 198)
Age		
Median (range), years	70.0 (42-79)	70.0 (31-80)
Category, n (%)		
<65 years	36 (18.3)	35 (17.7)
65 to <70 years	52 (26.4)	53 (26.8)
≥70 years	109 (55.3)	110 (55.6)
Male, n (%)	87 (44.2)	111 (56.1)
ECOG PS score, n (%)[a]		
0	71 (36.0)	84 (42.4)
1	103 (52.3)	100 (50.5)
2	23 (11.7)	14 (7.1)
Frailty score, n (%)[b]		
0 (fit)	124 (62.9)	132 (66.7)
1 (intermediate fitness)	73 (37.1)	66 (33.3)
Transplant deferred, n (%)	53 (26.9)	53 (26.8)
Transplant ineligible, n (%)	144 (73.1)	145 (73.2)

	D-VRd (n = 197)	VRd (n = 198)
Type of myeloma by immunofixation or serum FLC assay, n (%)		
IgG	130 (66.0)	114 (57.6)
IgA	38 (19.3)	52 (26.3)
IgD	2 (1.0)	3 (1.5)
Light chain	22 (11.2)	25 (12.6)
Biclonal	5 (2.5)	3 (1.5)
Unknown	0	1 (0.5)
Extramedullary plasmacytomas, n (%)	11 (5.6)	13 (6.6)
ISS disease stage, n (%)[c]		
I	68 (34.5)	68 (34.3)
II	73 (37.1)	75 (37.9)
III	56 (28.4)	55 (27.8)
Cytogenetic risk profile, n (%)[d]		
Standard risk	149 (75.6)	149 (75.3)
High risk	25 (12.7)	27 (13.6)
Indeterminate[e]	23 (11.7)	22 (11.1)

Treatment arms were well balanced

Usmani et al, IMS 2024

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Transplant ineligible, n (%)	144 (73.1)	145 (73.2)

No patients over 80 years

45% are under 70 years

90% have an ECOG PS 0-1

No frail pts by IMWG

25% of pts were deferred ASCT

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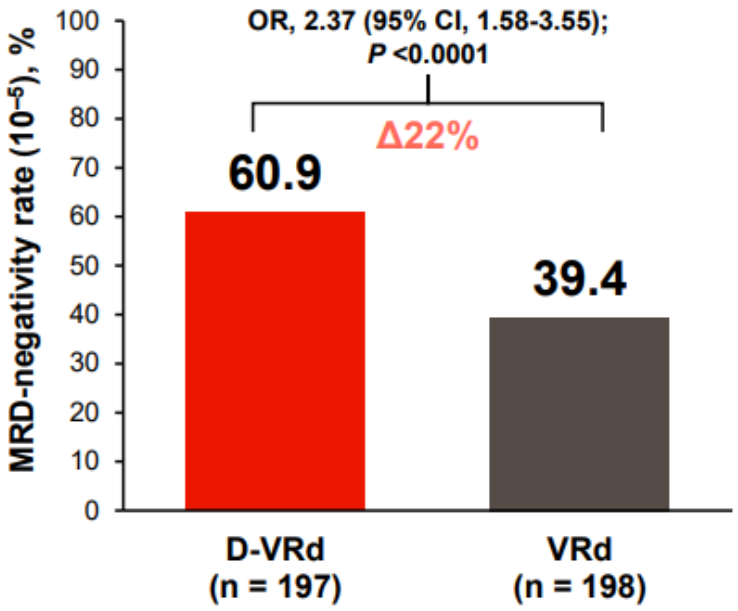
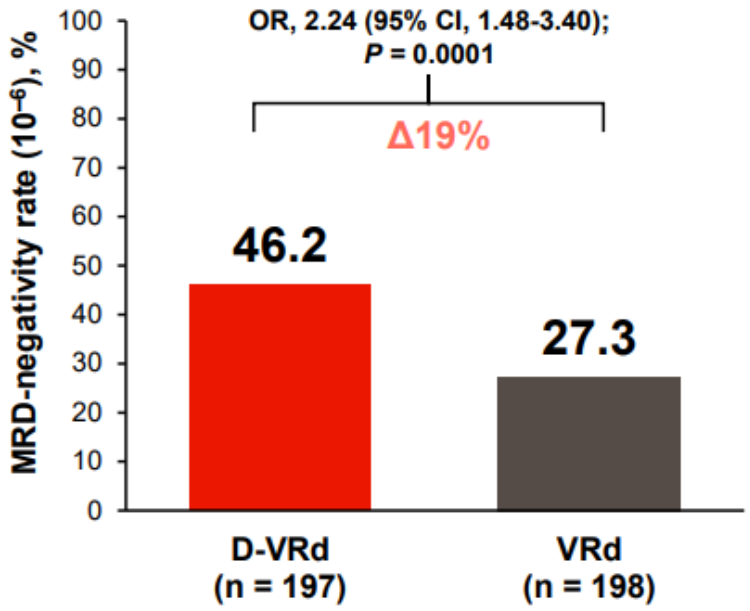
CEPHEUS: OVERALL AND SUSTAINED MRD NEGATIVITY RATES

Primary endpoint

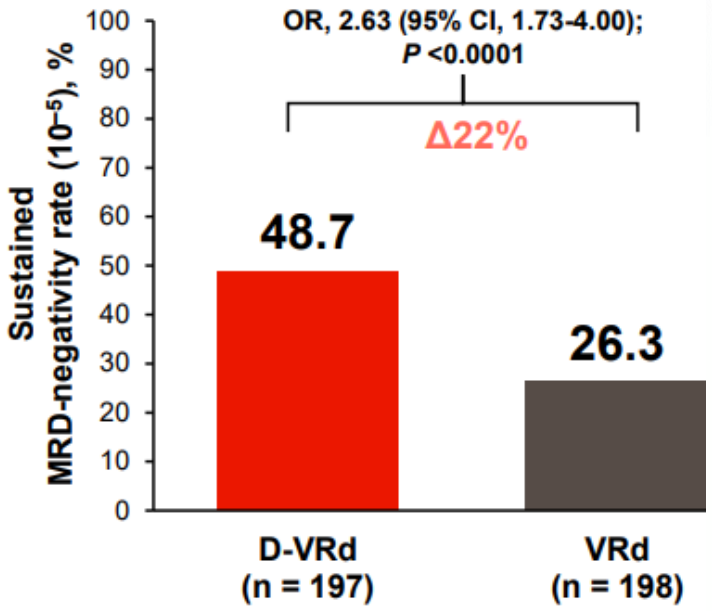
Overall MRD-negativity rate (10^{-5})



Overall MRD-negativity rate (10^{-6})



Sustained MRD-negativity rate (10
≥12 months



Daratumumab led to deeper MRD responses at 10^{-6} and a higher sustained MRD-negativity rate

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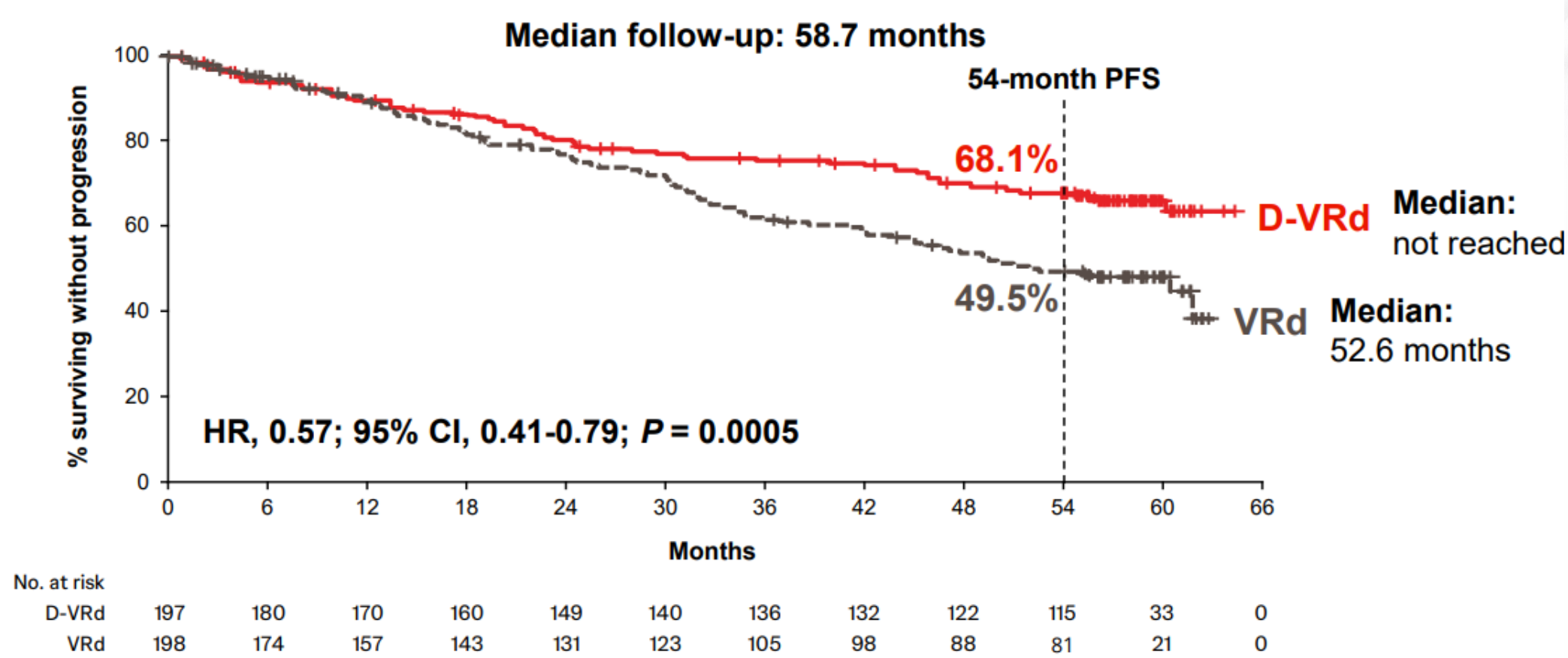
CEPHEUS: PFS IN ITT POPULATION



Daratumumab significantly improved PFS, with a 43% reduction in the risk of disease progression or death

CEPHEUS: SAFETY

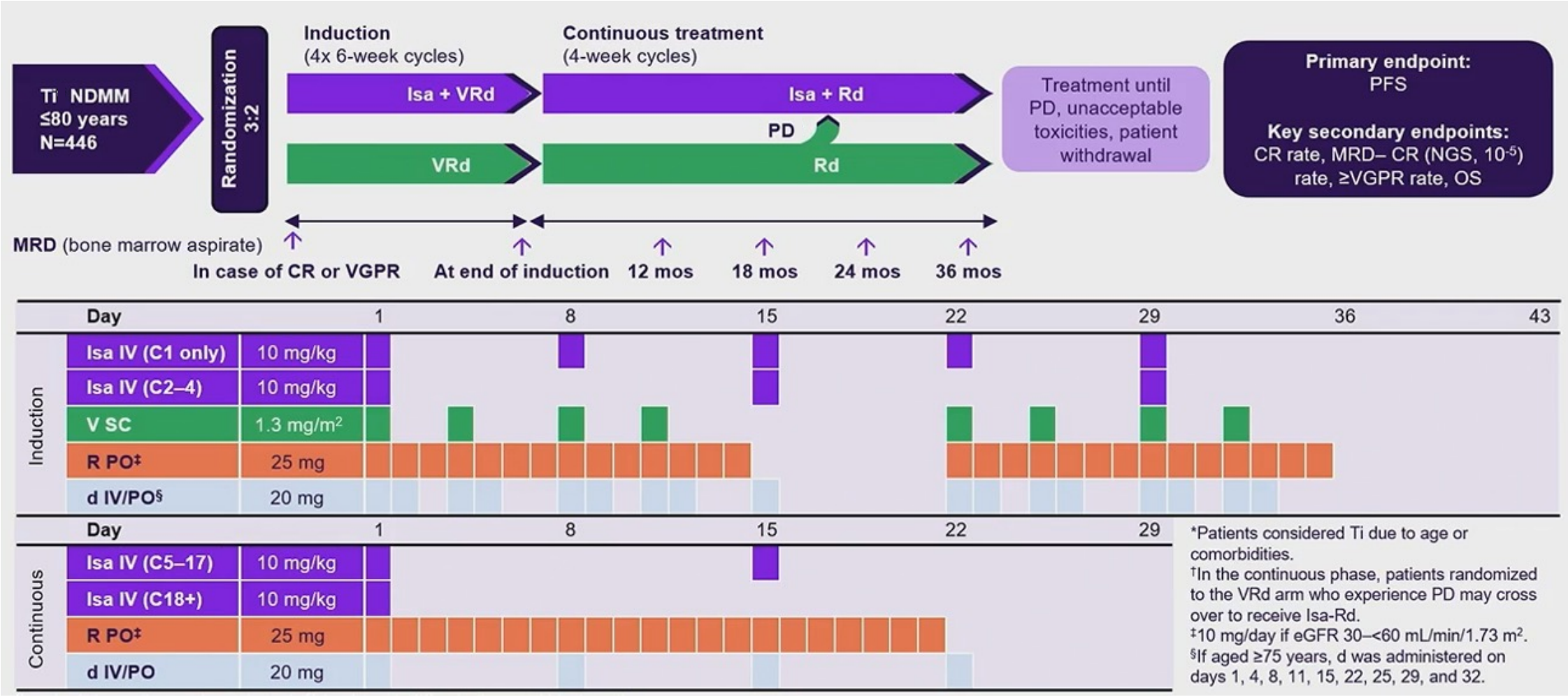
TEAE, n (%)	D-VRd (n = 197)		VRd (n = 195)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
HEMATOLOGIC				
Blood and lymphatic system disorders	163 (82.7)	126 (64.0)	126 (64.6)	98 (50.3)
Neutropenia	110 (55.8)	87 (44.2)	76 (39.0)	58 (29.7)
Thrombocytopenia	92 (46.7)	56 (28.4)	66 (33.8)	39 (20.0)
Anemia	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)

Safety data was consistent with the established safety profile of each individual drug

IMROZ: PHASE 3 STUDY OF ISATUXIMAB, BORTEZOMIB, LENALIDOMIDE, AND DEX (ISA-VRD) VS VRD FOR TRANSPLANT-INELIGIBLE PATIENTS WITH NDMM

VRd +/- Isatuximab in Transplant-Ineligible NDMM

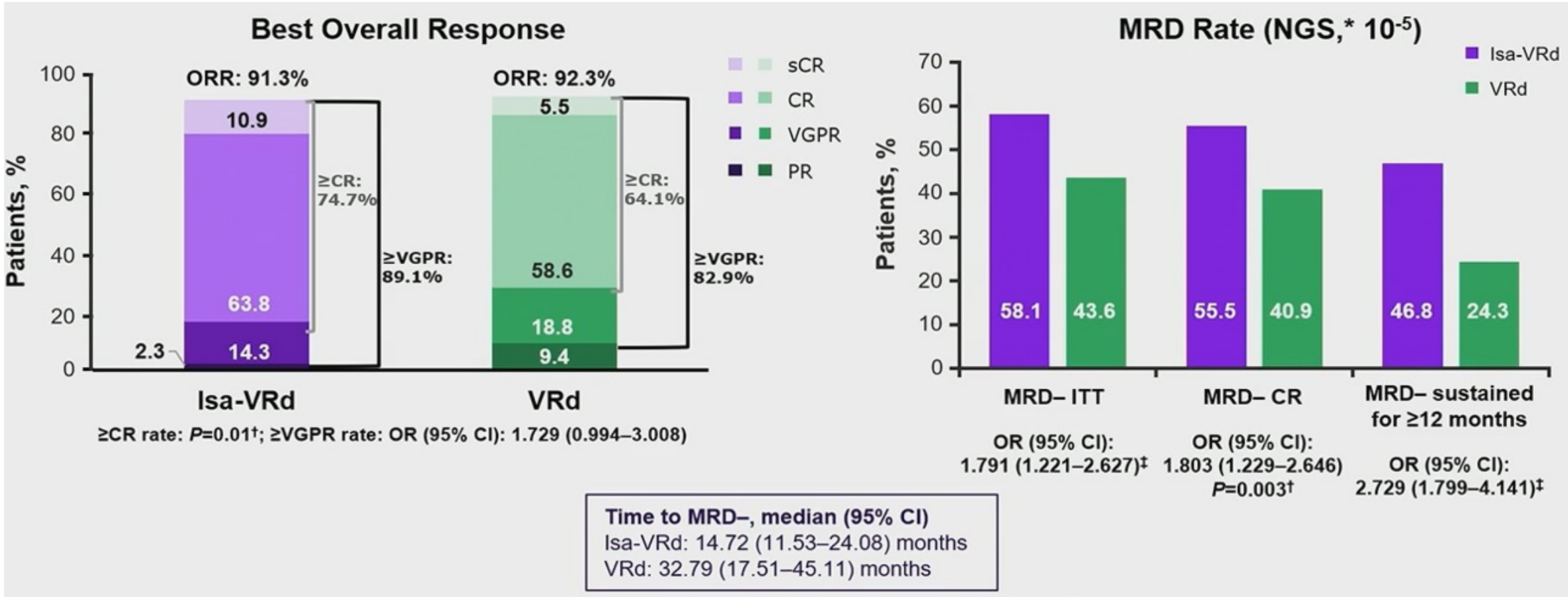


C, cycle; CR, complete response; d, dexamethasone; eGFR, estimated glomerular filtration rate; Isa, isatuximab; IV, intravenous; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; R, lenalidomide; Rd, lenalidomide and dexamethasone; SC, subcutaneous; Ti, transplant-ineligible; V, bortezomib; VRd, bortezomib, lenalidomide, and dexamethasone; VGPR, very good partial response.

Facon T, et al. J Clin Oncol. 2024;42(suppl 16):7500.

IMROZ DEPTH OF RESPONSE

Depth of Response in ITT Population



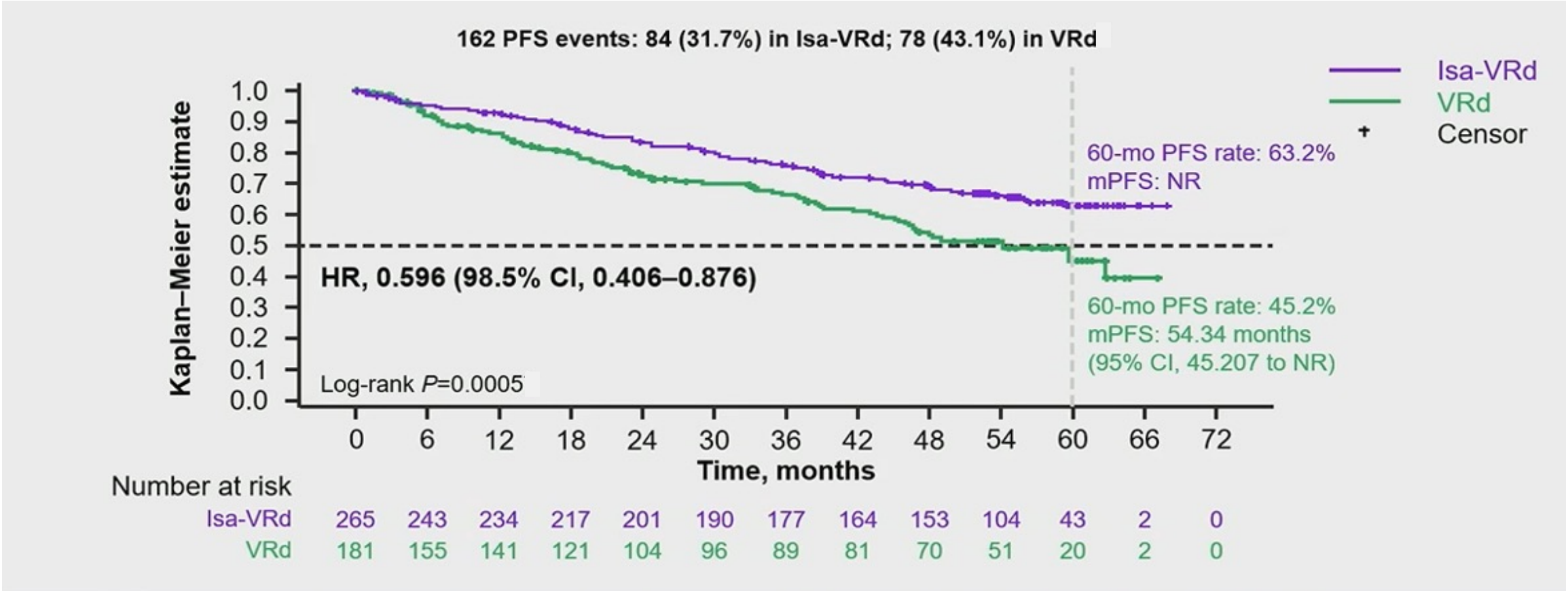
Isa-VRd followed by Isa-Rd resulted in deep response rates, with a significant improvement in the MRD− CR rate, as well as higher rates of MRD− and sustained MRD− for 12 months

HR, hazard ratio; IRC, independent review committee; ITT, intent to treat; NR, not reached.

Facon T, et al. J Clin Oncol. 2024;42(suppl 16):7500.

IMROZ PFS

Primary Endpoint Met: Interim PFS Analysis by IRC Assessment in ITT Population



At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

HR, hazard ratio; IRC, independent review committee; ITT, intent to treat; NR, not reached.

Facon T, et al. J Clin Oncol. 2024;42(suppl 16):7500.

IMROZ SAFETY

Safety Summary (Safety Population)

Preferred term, n (%)	Isa-VRd (n=263)		VRd (n=181)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic laboratory abnormalities				
Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Nonhematologic adverse events				
Infections	240 (91.3)	118 (44.9)	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)	2 (1.1)	2 (1.1)
Event rate per patient-year[a]				
Infections	1.181	-	1.166	-
Secondary primary malignancies[b]	0.041	-	0.026	-

Isa-VRd was well tolerated, and the safety profile remains consistent with the known safety profiles of each agent

a. Calculated as number of patients with an event divided by total patient-years. Patients were followed yearly; b. Included non-melanoma skin cancer.

Facon T, et al. J Clin Oncol. 2024;42(suppl 16):7500.

MAIA: D-RD VS RD IN TRANSPLANT INELIGIBLE NDMM

Key eligibility criteria
- TIE NDMM
- ECOG PS score 0-2
- CrCl ≥30 mL/min

Stratification Factors
- ISS (I vs II vs III)
- Region (NA vs other)
- Age (<75 vs ≥75 years)

1:1 Randomization

D-Rd (n=369)

Daratumumab: 16 mg/kg IV
QW Cycles 1-2, Q2W Cycles 3-6, then Q4W thereafter until PD

Lenalidomide: 25 mg PO, Days 1-21 until PD

Dexamethasone: 40 mg PO or IV, Days 1, 8, 15, 22 until PD

Rd (n=368)

Lenalidomide: 25 mg PO, Days 1-21 until PD

Dexamethasone: 40 mg PO, Days 1, 8, 15, 22 until PD

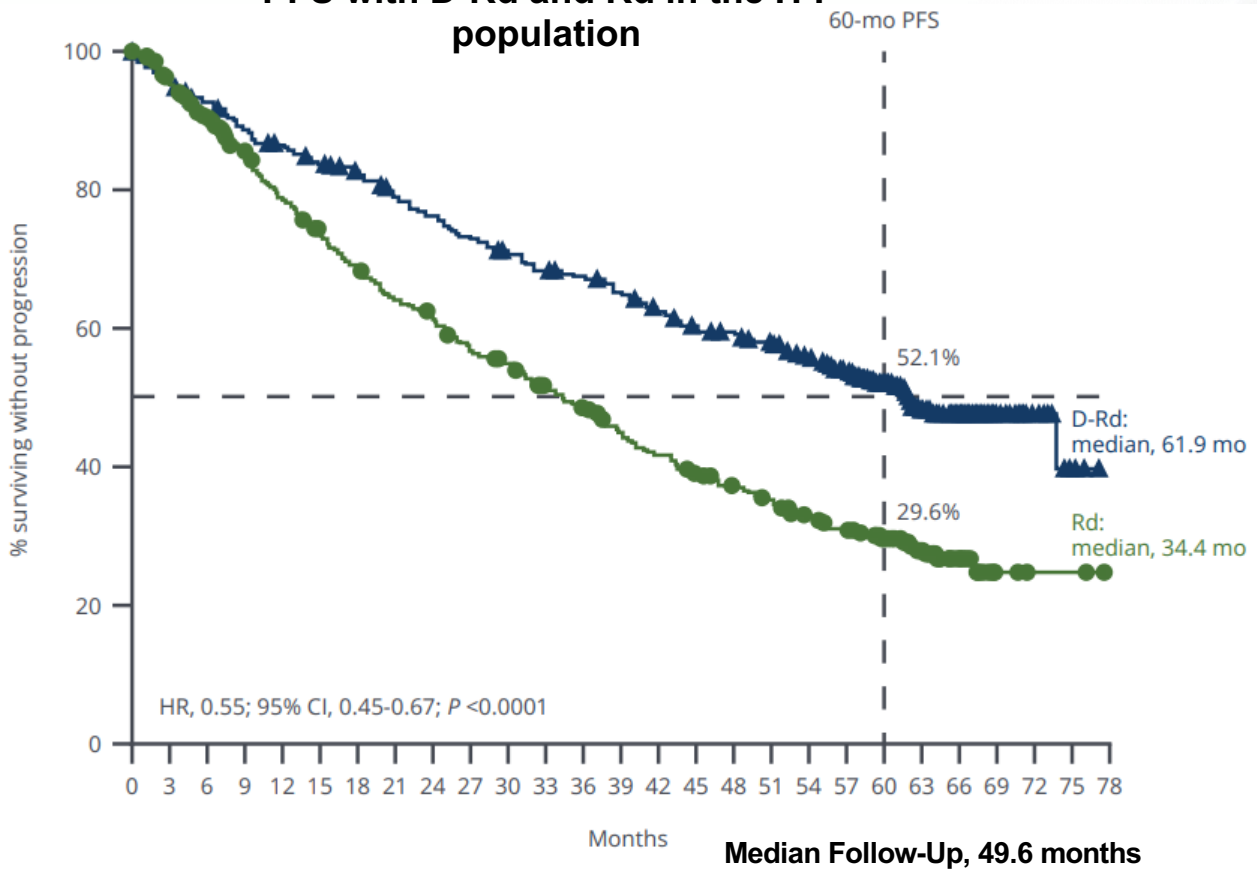
Primary Endpoint:
- PFS

Key Secondary Endpoints:
- ORR
- ≥CR rate
- MRD (NGS; 10^{-5})
- OS

Cycle: 28 Days

MAIA: PFS AND OS

PFS with D-Rd and Rd in the ITT population

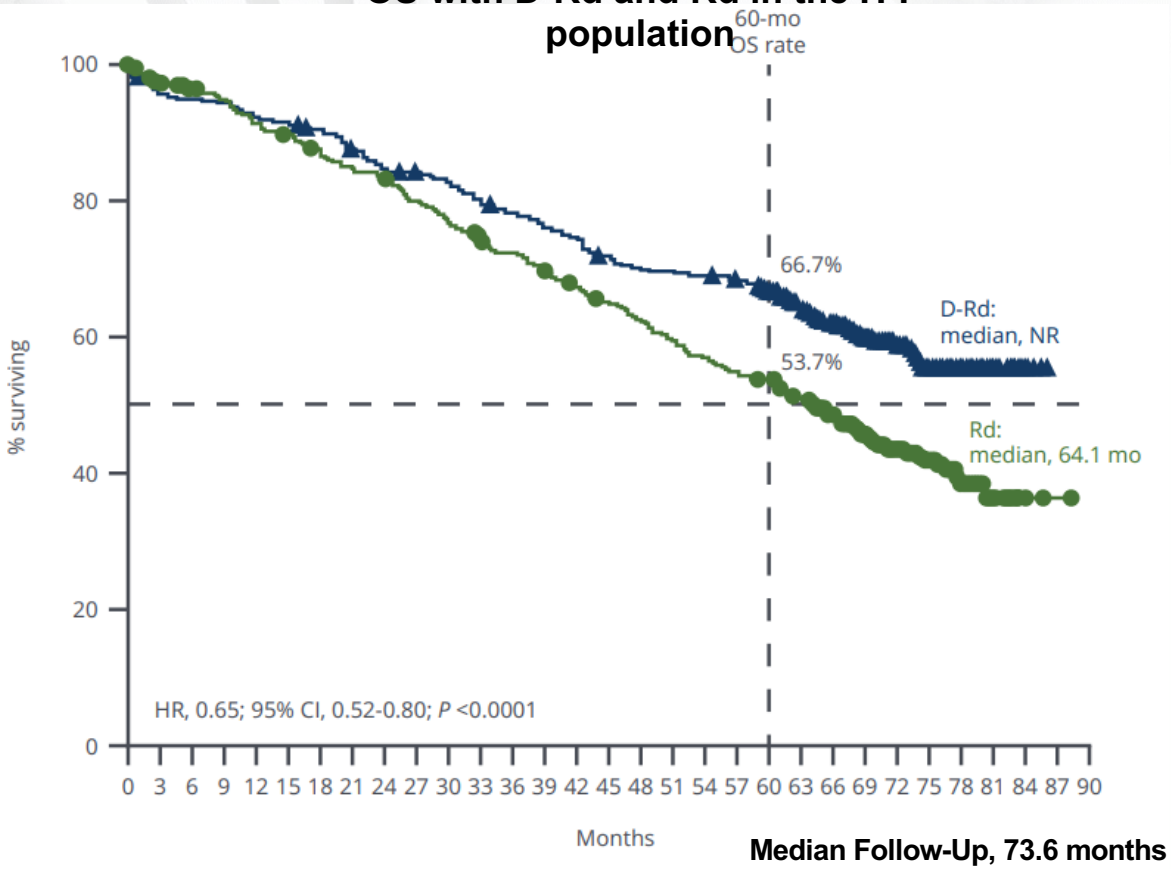


Median Follow-Up, 49.6 months

No. at risk

Rd	369	333	307	280	255	237	220	205	196	179	172	156	147	134	124	114	106	99	88	81	64	47	20	4	2	2	0
D-Rd	368	347	335	320	309	300	290	276	266	256	246	237	232	223	211	200	197	188	177	165	132	88	65	28	11	3	0

OS with D-Rd and Rd in the ITT population



Median Follow-Up, 73.6 months

No. at risk

Rd	369	351	343	336	324	317	308	300	294	281	270	258	251	241	232	223	214	204	195	188	183	170	154	134	97	68	35	11	3	1	0
D-Rd	368	350	346	344	338	334	328	316	305	302	297	286	280	273	266	255	249	248	246	241	228	206	190	163	128	82	56	26	10	0	0

MAIA: TEAES

Grade 3/4 infection rates were 42.6% with D-Rd and 29.6% with Rd

The most common serious TEAE in both arms was pneumonia (D-Rd, 18.7%; Rd, 10.7%)

The rate of treatment discontinuation due to TEAEs was lower in the D-Rd arm (14.6%) versus the Rd arm (23.8%)

	D-Rd (n = 364)		Rd (n = 365)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic, n (%)				
Neutropenia	224 (61.5)	197 (54.1)	166 (45.5)	135 (37.0)
Anemia	154 (42.3)	62 (17.0)	150 (41.1)	79 (21.6)
Nonhematologic, n (%)				
Diarrhea	240 (65.9)	33 (9.1)	188 (51.5)	22 (6.0)
Fatigue	164 (45.1)	33 (9.1)	114 (31.2)	17 (4.7)
Constipation	157 (43.1)	6 (1.6)	137 (37.5)	2 (0.5)
Peripheral edema	155 (42.6)	10 (2.7)	117 (32.1)	3 (0.8)
Back pain	155 (42.6)	14 (3.8)	109 (29.9)	14 (3.8)
Asthenia	136 (37.4)	19 (5.2)	101 (27.7)	18 (4.9)
Nausea	133 (36.5)	7 (1.9)	88 (24.1)	2 (0.5)
Insomnia	125 (34.3)	11 (3.0)	116 (31.8)	14 (3.8)
Bronchitis	124 (34.1)	12 (3.3)	87 (23.8)	7 (1.9)
Pneumonia	113 (31.0)	71 (19.5)	66 (18.1)	39 (10.7)
Cough	123 (33.8)	2 (0.5)	65 (17.8)	0
Dyspnea	119 (32.7)	12 (3.3)	63 (17.3)	4 (1.1)
Weight decreased	112 (30.8)	10 (2.7)	69 (18.9)	11 (3.0)
Muscle spasms	111 (30.5)	2 (0.5)	86 (23.6)	5 (1.4)
Peripheral sensory neuropathy	111 (30.5)	9 (2.5)	66 (18.1)	2 (0.5)

TAKE HOME MESSAGES

- Quads > Triplets IF the patient can tolerate the regimen
- ASCT > No ASCT

TRANSPLANT ELIGIBLE/FIT

Monoclonal anti-CD38+ RVD → ASCT

TRANSPLANT-INEGLIGIBLE and NON-FRAIL or TRANSPLANT DEFERRED (<80)

Monoclonal anti-CD38+ RVD → MoAb +Len maint

TRANSPLANT INELIGIBLE/ FRAIL

Dara/len/dex Doublet?