VANDERBILT UNIVERSITY MEDICAL CENTER

2024 MLS Nashville

Multiple Myeloma Updates In 2024

Saturday Jun 22

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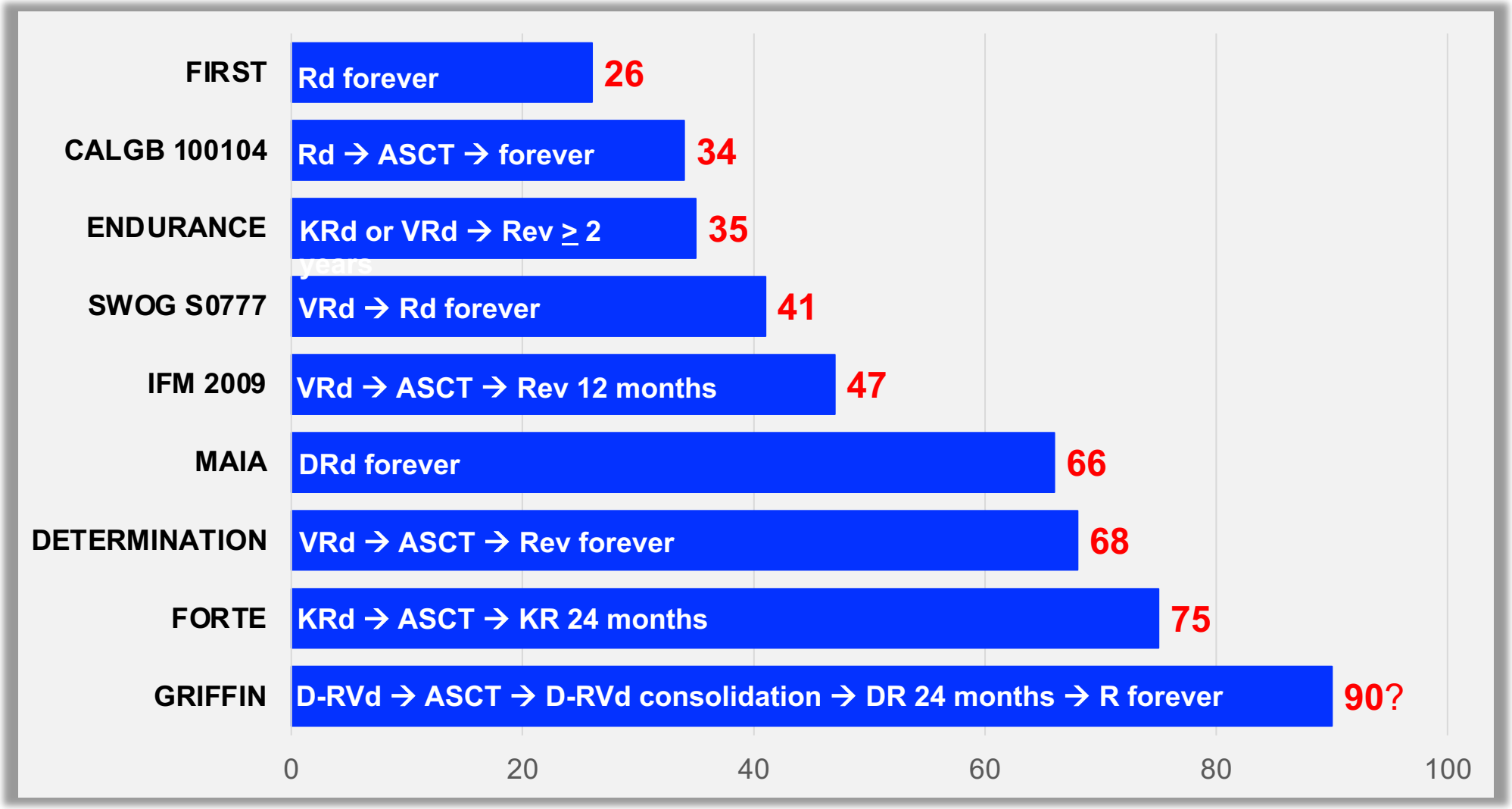
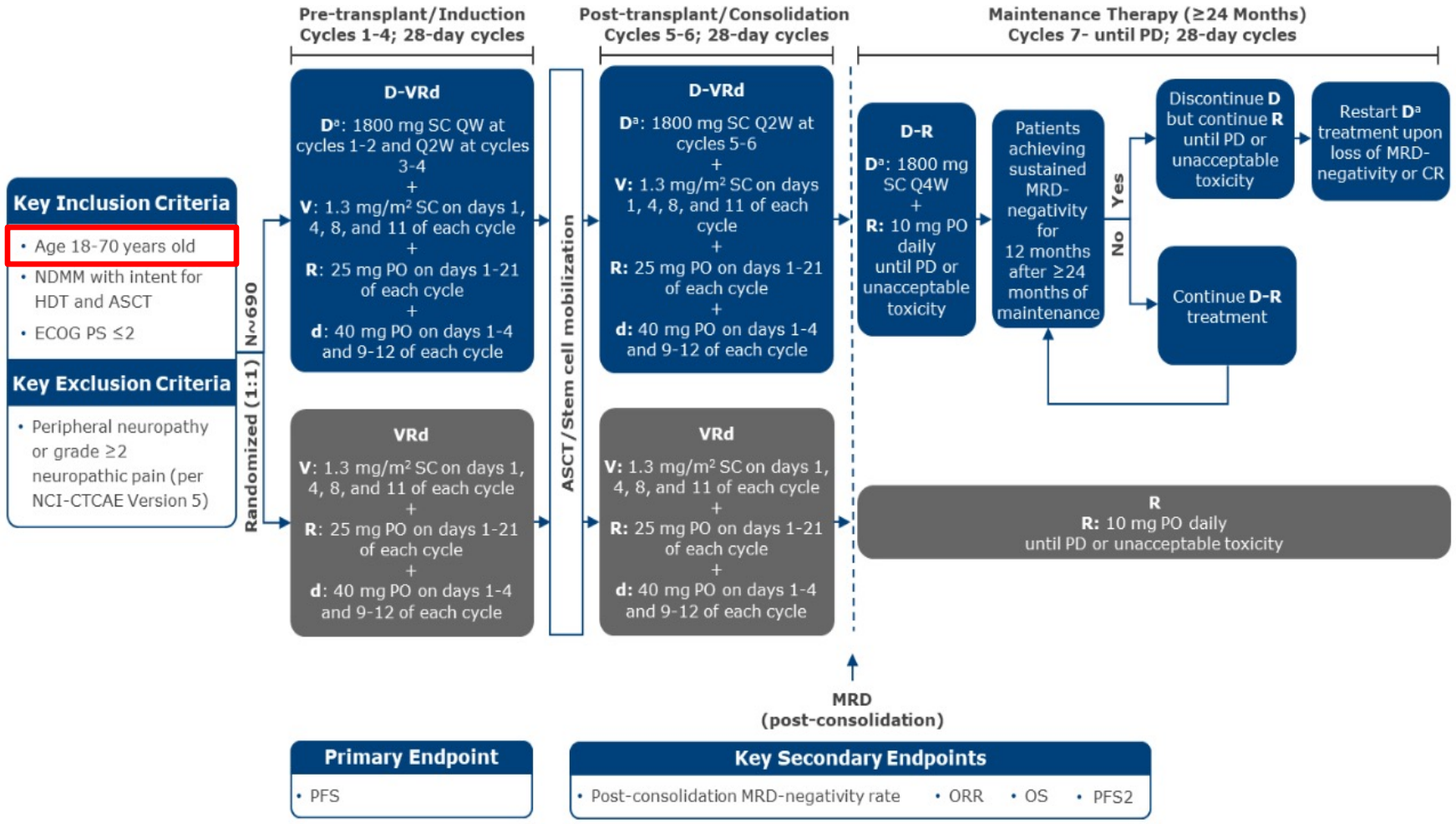
Last Decade of NDMM Space: Median PFS-1 (months)

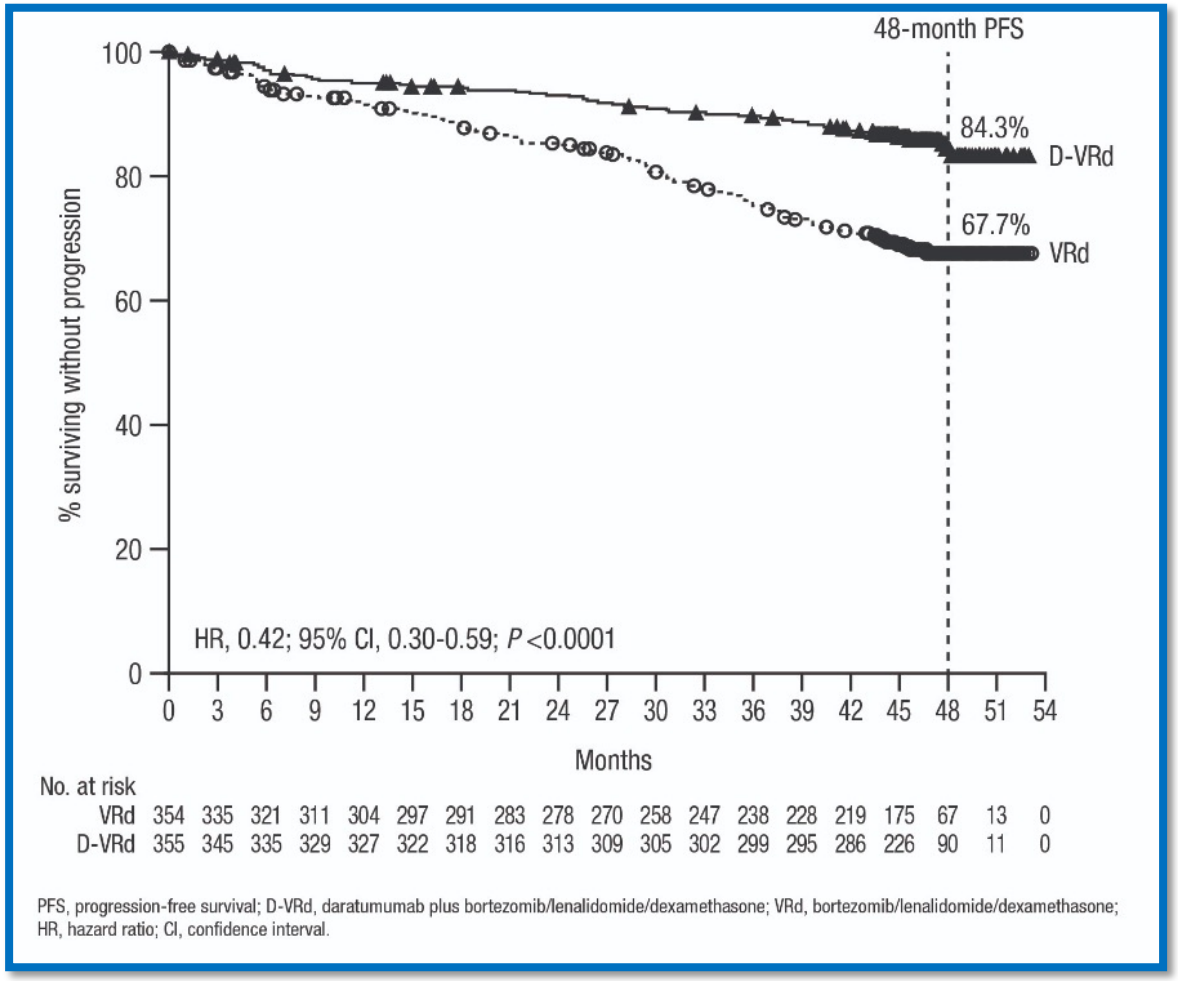


Phase 3 PERSEUS Trial: DVRd vs VRd in TE NDMM



Supplement to Sonneveld P, et al. N Eng J Med. 2023.

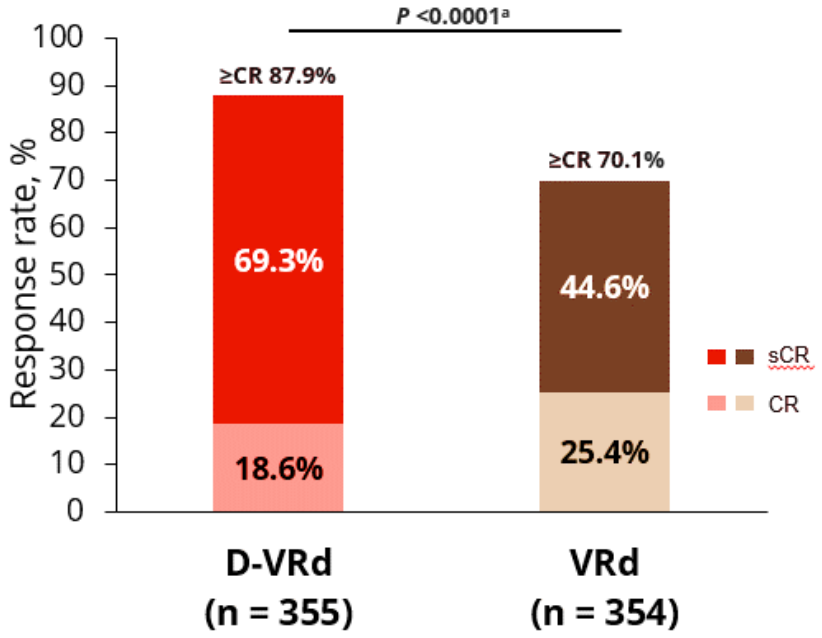
PERSEUS: PFS in Transplant-Eligible NDMM

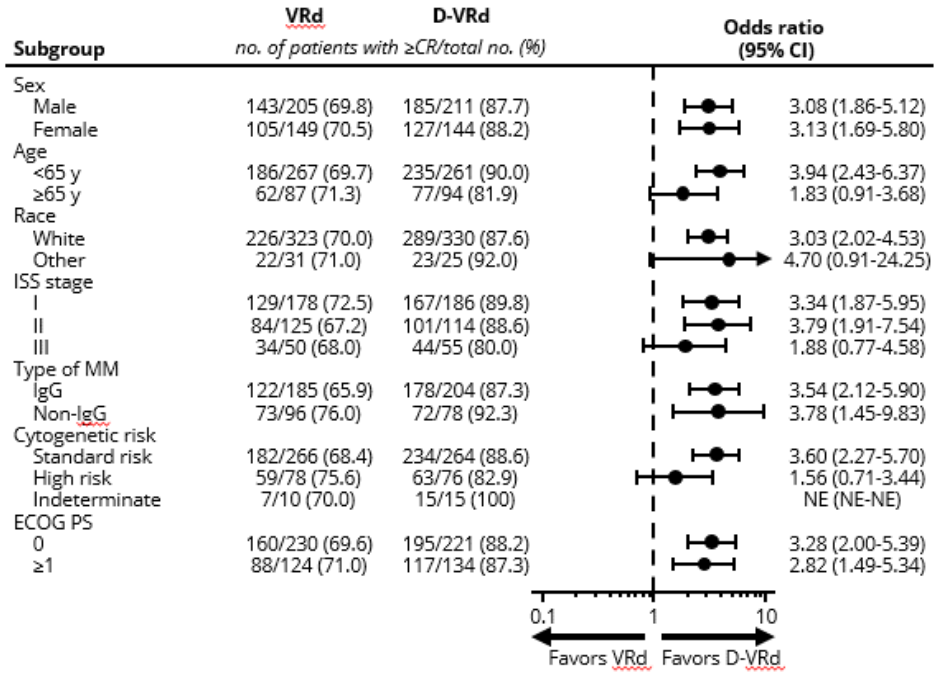


PFS, progression-free survival; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

Supplement to Sonneveld P, et al. N Eng J Med. 2023.

PERSEUS: Outcomes and Subgroup Analysis

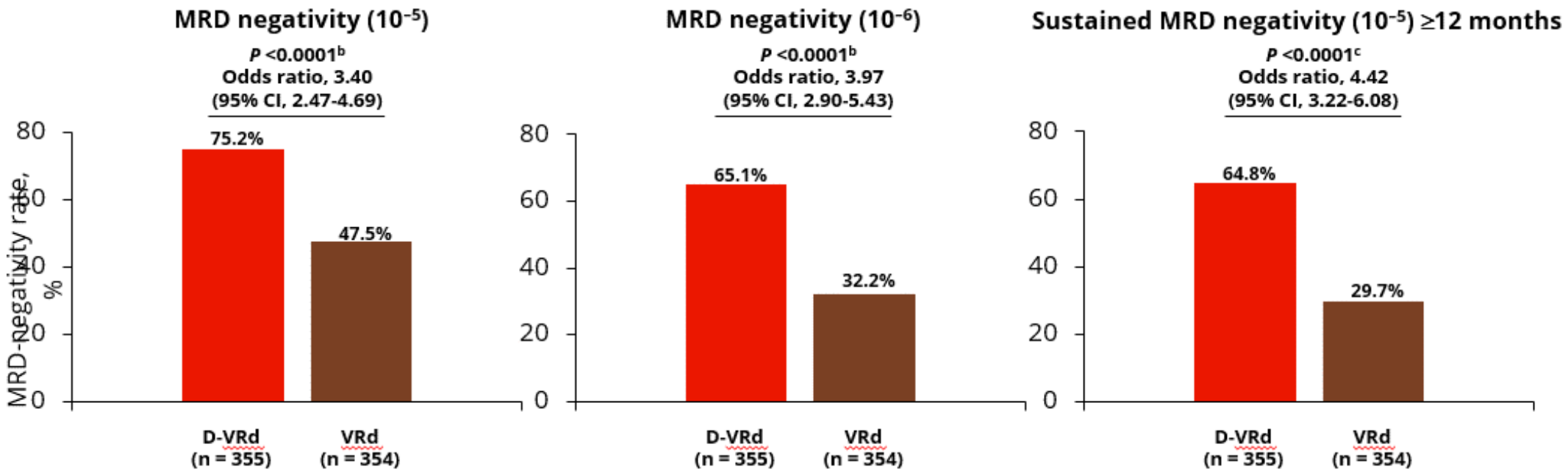




- Overall ≥CR rate was significantly higher with D-VRd versus VRd.
- ≥CR rate was improved with D-VRd versus VRd across subgroups.

Supplement to Sonneveld P, et al. N Eng J Med. 2023.

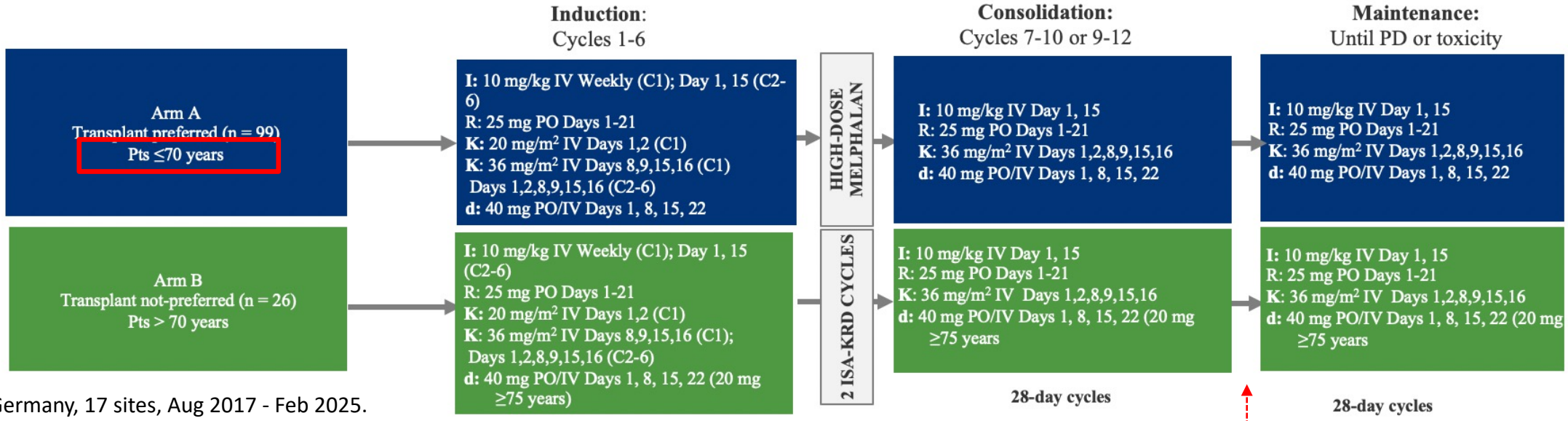
PERSEUS: Overall and Sustained MRD-Negativity Rates



- 64% of patients receiving maintenance in the D-VRd group discontinued Dara after achieving sustained MRD negativity.

Supplement to Sonneveld P, et al. N Eng J Med. 2023.

Phase 2 GMMG-CONCEPT: IsaKRd in HR-TE/TNE-NDMM



Germany, 17 sites, Aug 2017 - Feb 2025.

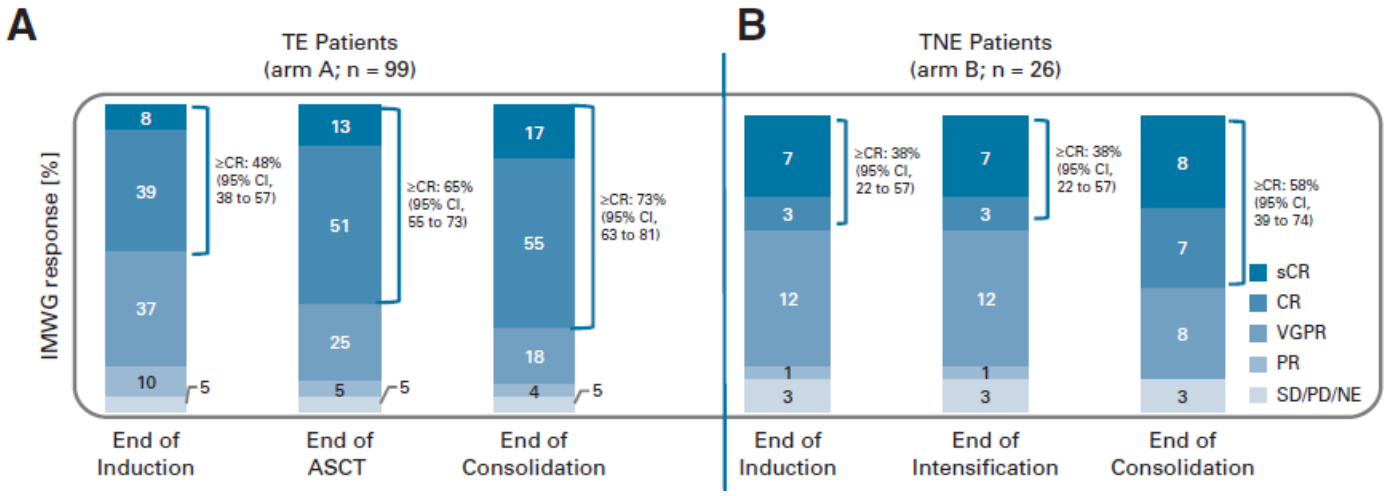
Key eligibility criteria

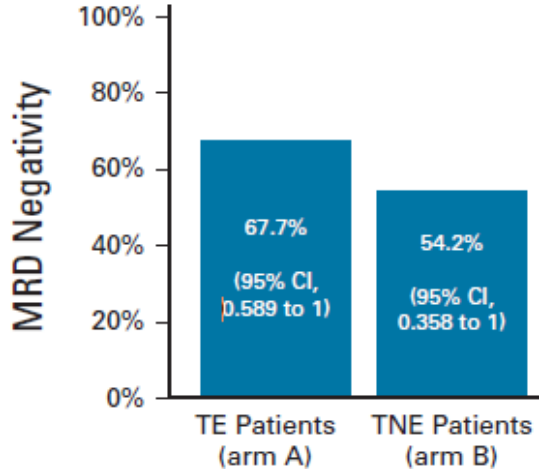
- High-risk NDMM
  - -Del(17p) in ≥ 10% of purified cells: t(4;14); ≥ 3 copies +1q21; t(14;16) by FISH
  - -ISS Stage II or III
- ≥18 years of age
- WHO PS score 0-3 (3 only if caused by MM)

ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PO, oral; SC, subcutaneous; MRD negativity at a minimum threshold of 10^{-5}.

Leypoldt LB et al. J Clin Oncol. 2024 Jan 1;42(1):26-37.

GMMG-CONCEPT: Best Response and MRD Negativity

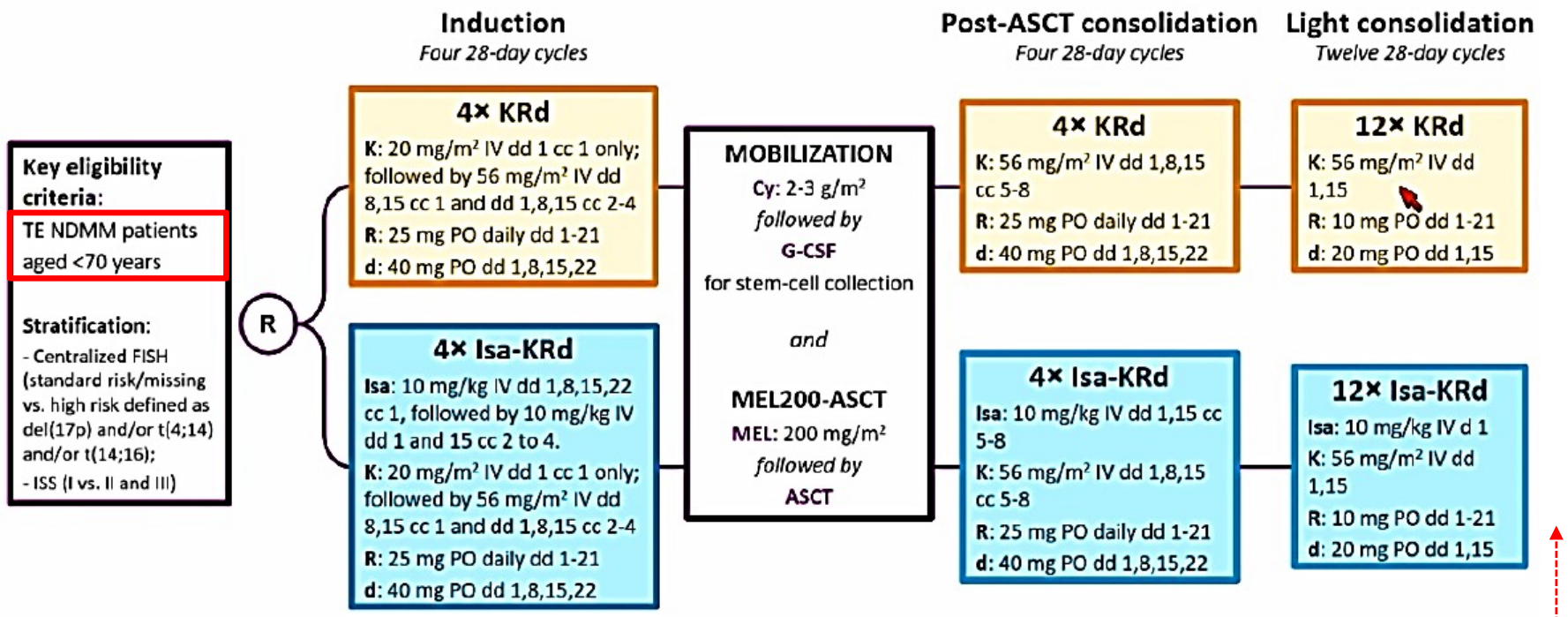




No. (%)	TE Patients (n = 99)	TNE Patients (n = 26)
MRD negative (any time point)	81 (81.8)	18 (69.2)
Sustained MRD negativity for ≥6 months	72 (72.7)	14 (53.8)
Sustained MRD negativity for ≥12 months	62 (62.6)	12 (46.2)

Leypoldt LB et al. J Clin Oncol. 2024 Jan 1;42(1):26-37.

Phase 3 IsKia Trial: IsaKRd vs KRd in TE NDMM

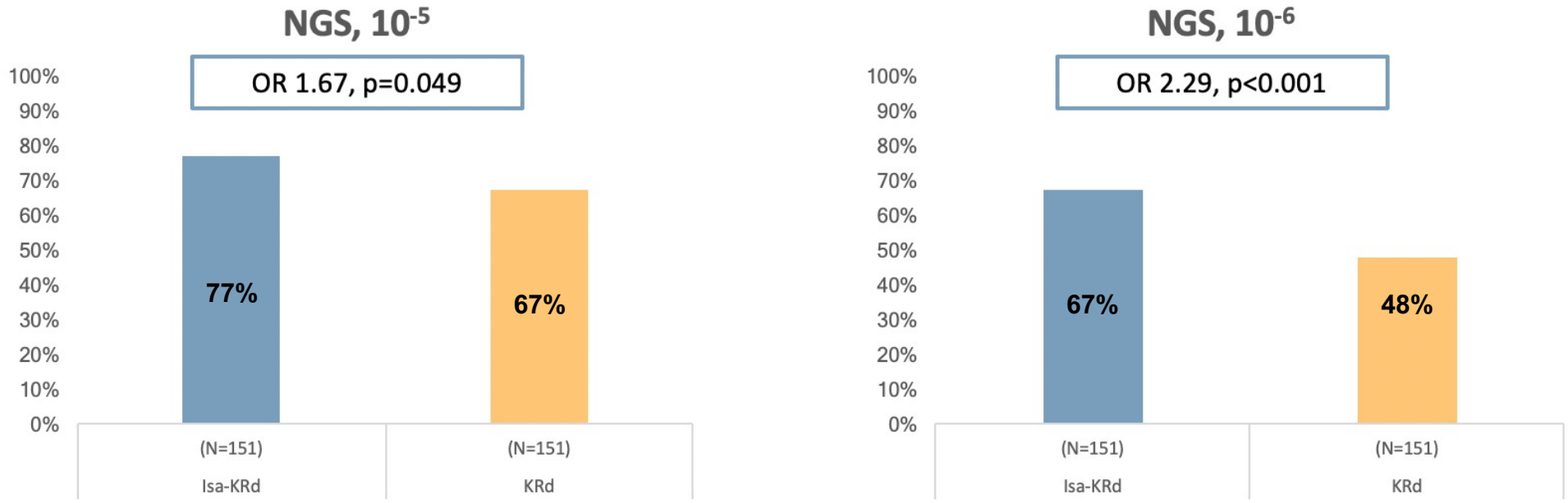


Primary Endpoint: MRD neg rate (NGS x 10^{-5}) after post-ASCT consolidation

Secondary Endpoints: MRD neg rate (NGS x 10^{-5}) after induction, PFS, sustained MRD negativity

Gay F, et al. Blood. 2023; 142(Supple 1):LBA4.

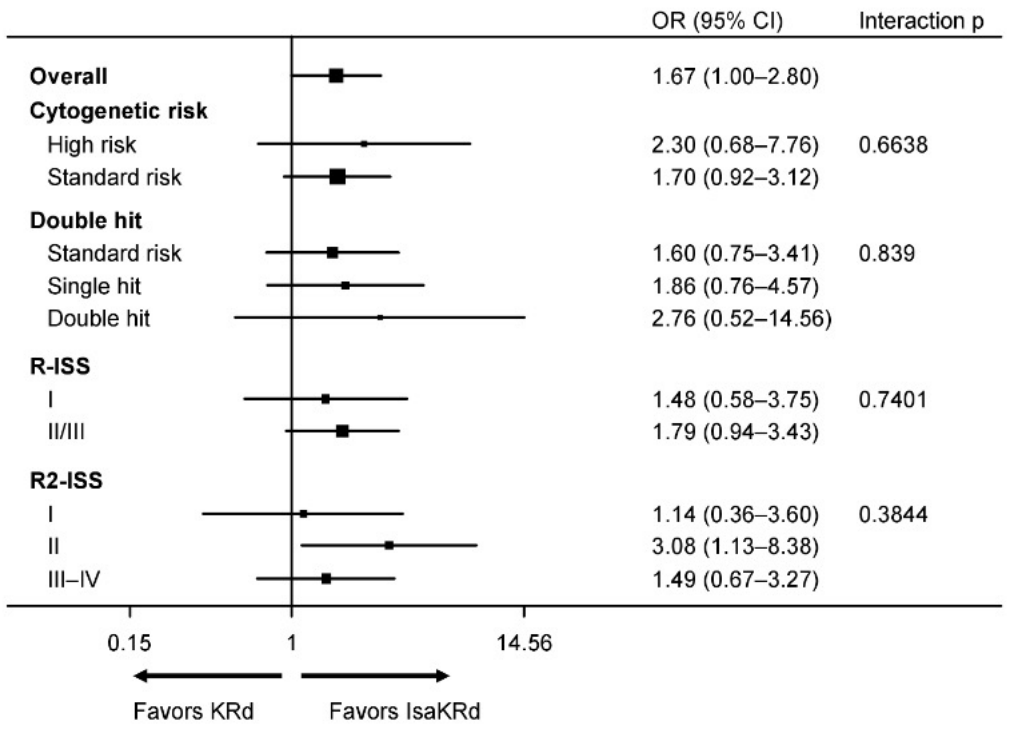
IsKia Trial: Post-Consolidation MRD Negativity

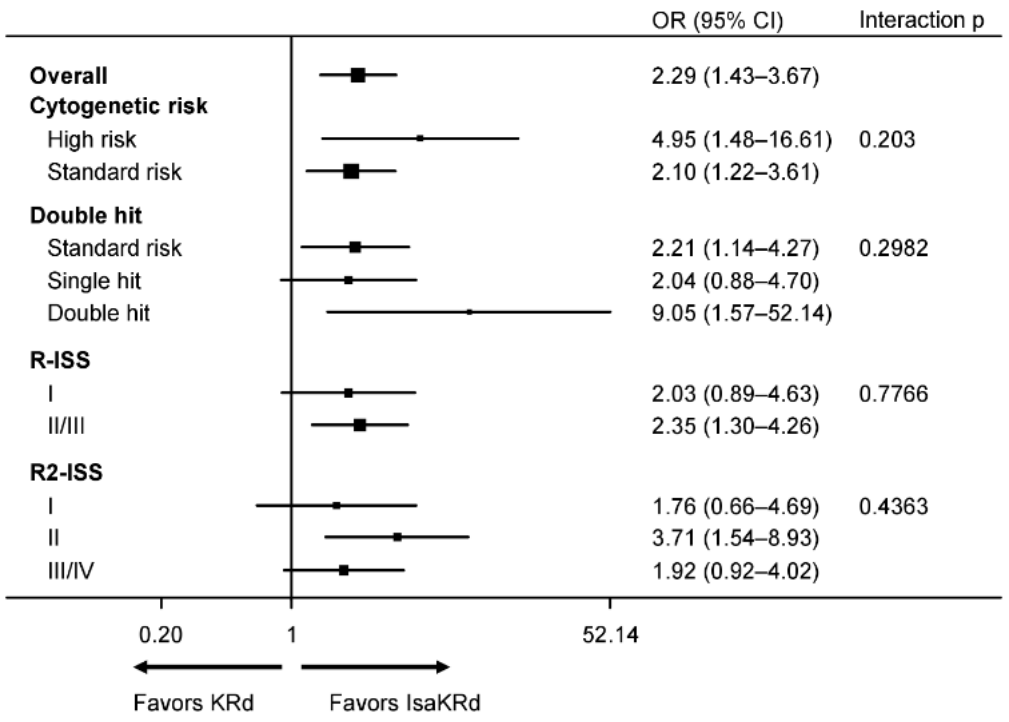


- VGPR response after consolidation: 94% both arms.
- ≥CR 74% vs 72% and sCR 64% vs 67% in IsaKRd vs KRd arms.
- MRD compliance and sample quality: 97-100% of evaluable samples at 10-5 and 10-6 cut-offs.

Gay F, et al. Blood. 2023; 142(Supple 1):LBA4.

IsKia Trial: Subgroup Analysis MRD Negativity Post-Consolidation



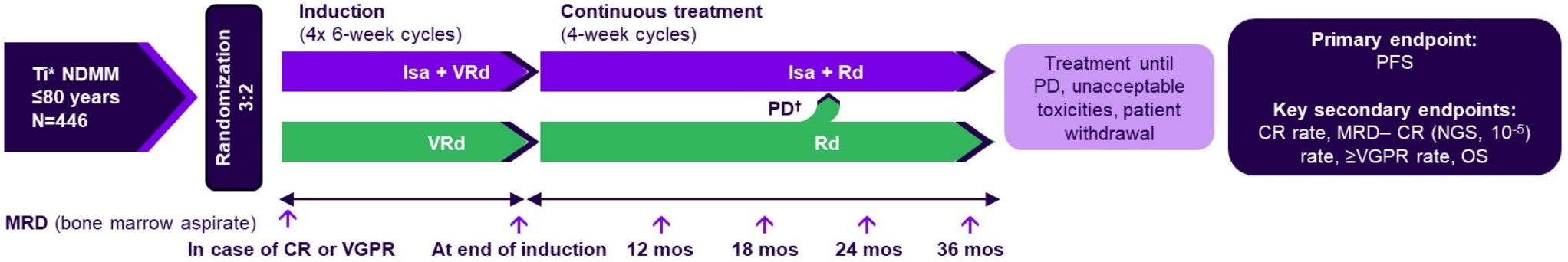


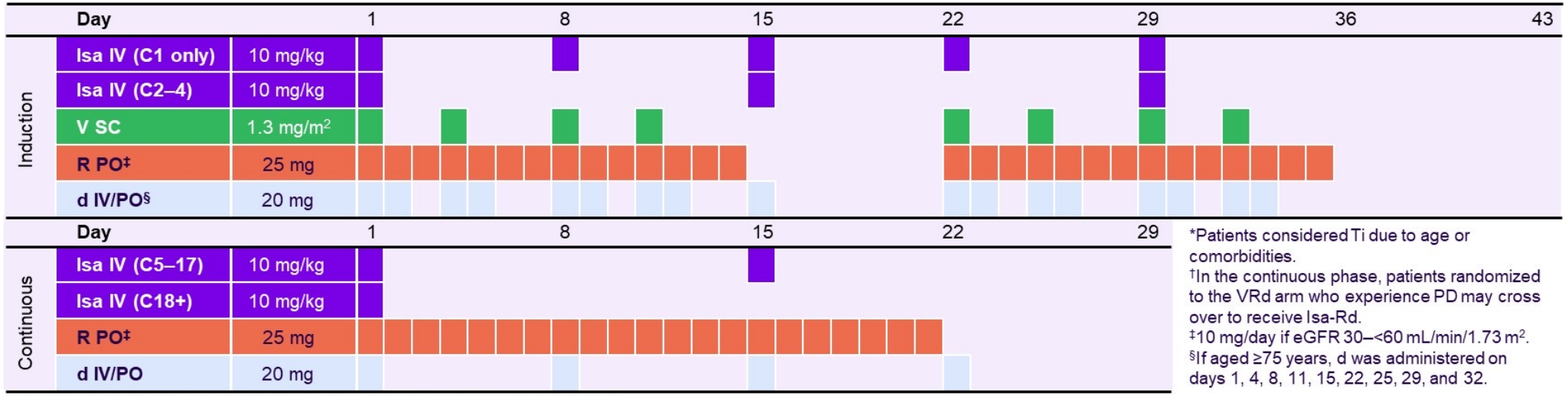
MRD, minimal residual disease; OR, odds ration; CI, confidence interval; p, p-value; R-ISS, Revised International Staging System stage; R@-ISS, Second Revision of the International Staging System stage; K, carfilzomib; R, lenalidomide; d, dexamethasone; Isa, isatuximab.

Gay F, et al. Blood. 2023; 142(Supple 1):LBA4.

Study design: Isa-VRd vs VRd in transplant-ineligible NDMM

IMROZ

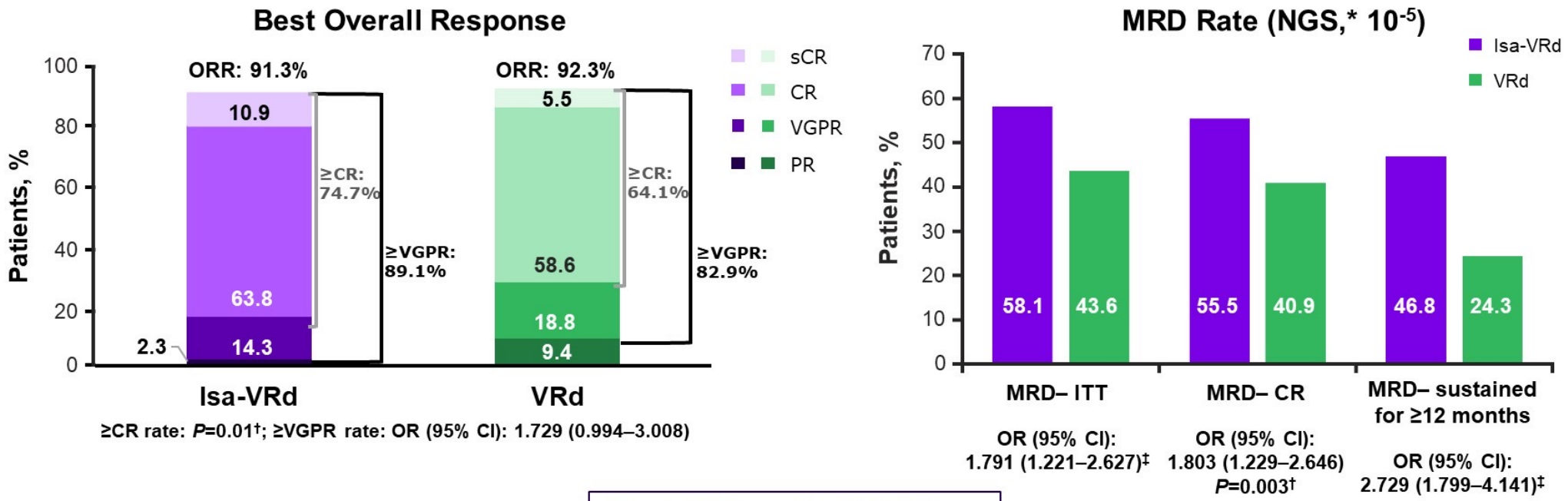




*Patients considered Ti due to age or comorbidities.
†In the continuous phase, patients randomized to the VRd arm who experience PD may cross over to receive Isa-Rd.
‡10 mg/day if eGFR 30–<60 mL/min/1.73 m2.
§If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

C, cycle; d, dexamethasone; Isa, isatuximab; R, lenalidomide; SC, subcutaneous; V, bortezomib.
Orlowski RZ, et al. ASCO 2018.

Depth of response in ITT population



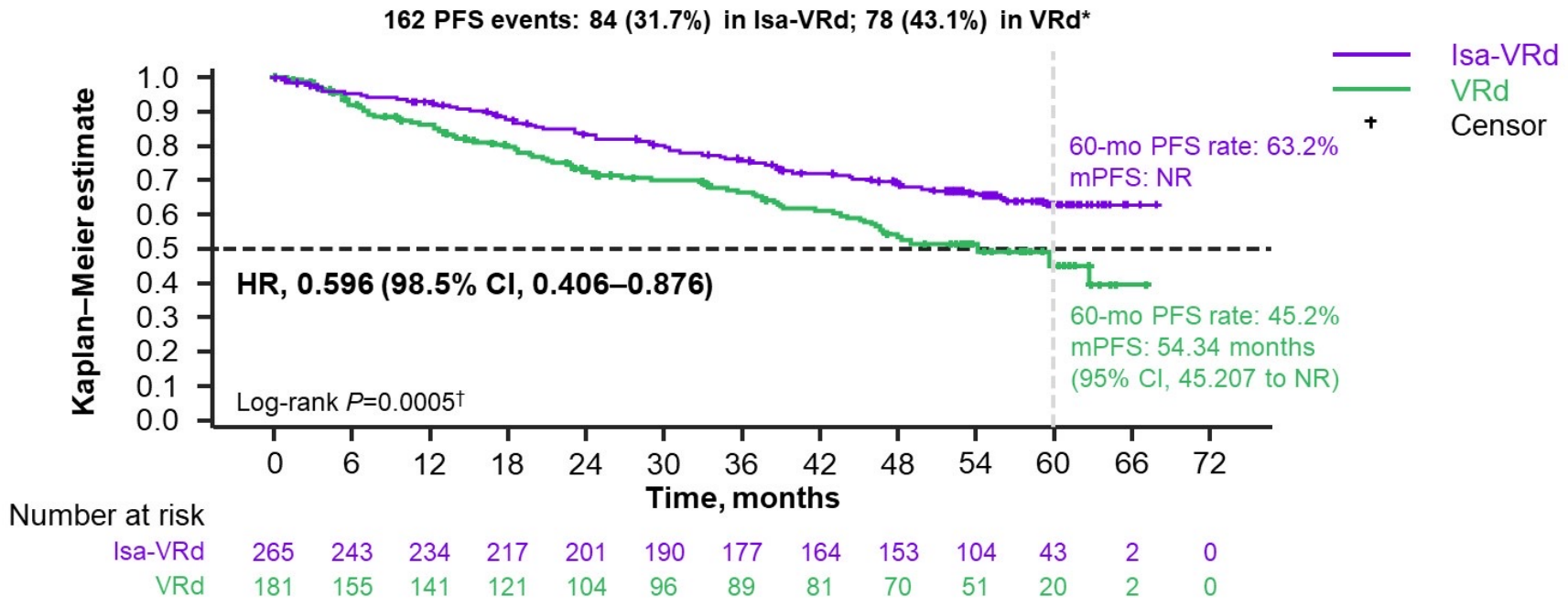
Time to MRD–, median (95% CI)
Isa-VRd: 14.72 (11.53–24.08) months
VRd: 32.79 (17.51–45.11) months

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

*Adaptive Biotechnologies clonoSEQ®. †Stratified Cochran-Mantel-Haenszel test. Two-sided significance level is 0.025. ‡*P* value not reported; not a key secondary endpoint.
MRD–, minimal residual disease negativity.

Primary endpoint met: Interim PFS analysis–IRC assessment in ITT population

IMROZ

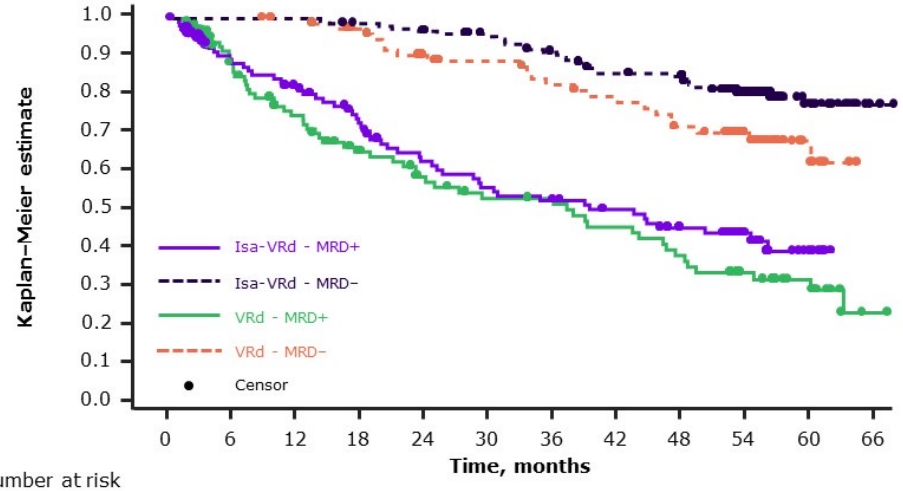


At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

*Cutoff date for PFS analysis: September 26, 2023 (median follow-up, ~5 years). †Nominal one-sided *P* value.
NR, not reached.

PFS by MRD* status

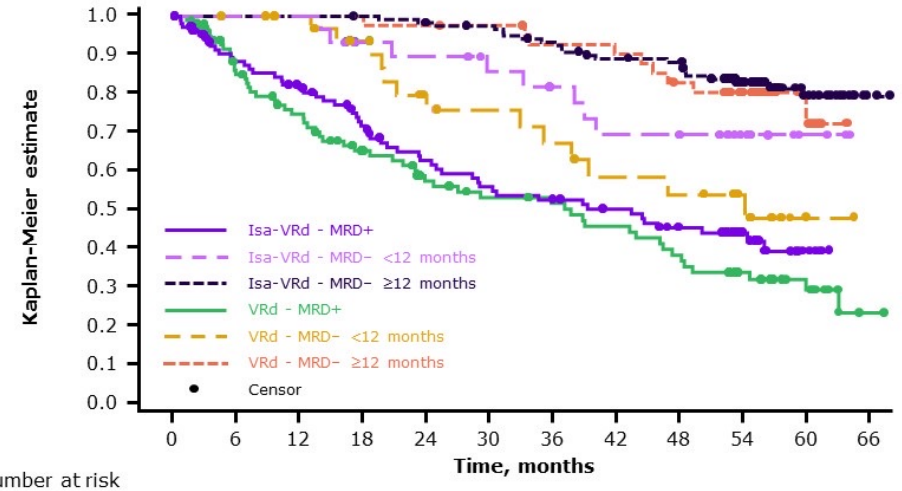
MRD– vs MRD+



Number at risk

Isa-VRd - MRD+	111	89	80	67	56	50	46	42	35	21	6	0
Isa-VRd - MRD–	154	154	154	150	145	140	131	122	118	83	37	2
VRd - MRD+	102	77	65	51	42	37	35	31	25	19	11	2
VRd - MRD–	79	78	76	70	62	59	54	50	45	32	9	0

MRD– Sustained ≥12 Months vs <12 Months



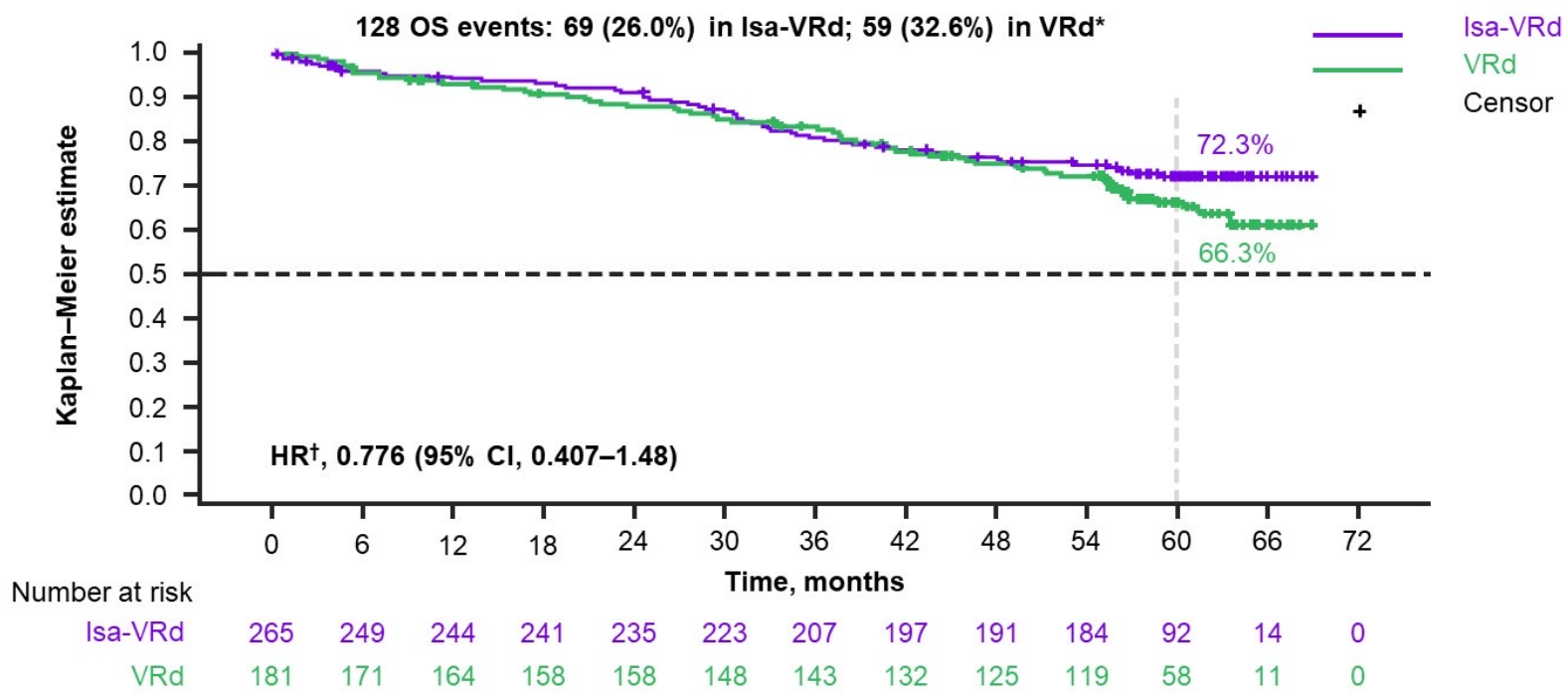
Number at risk

Isa-VRd - MRD+	111	89	80	67	56	50	46	42	35	21	6	0
Isa-VRd - MRD– <12 months	30	30	30	26	25	22	20	17	16	11	4	0
Isa-VRd - MRD– ≥12 months	124	124	124	124	120	118	111	105	102	72	33	2
VRd - MRD+	102	77	65	51	42	37	35	31	25	19	11	2
VRd - MRD– <12 months	35	34	32	28	20	18	16	13	12	8	1	0
VRd - MRD– ≥12 months	44	44	44	42	42	41	38	37	33	24	8	0

There was a PFS benefit among patients with MRD– vs MRD+ and among patients with MRD– sustained ≥12 months vs <12 months. Among patients with MRD–, PFS trended in favor of Isa-VRd, and the proportion with MRD– sustained ≥12 months was higher for Isa-VRd (80.5%) than VRd (55.7%)

*Adaptive Biotechnologies NGS; 10^{-5} threshold.
MRD, minimal residual disease.

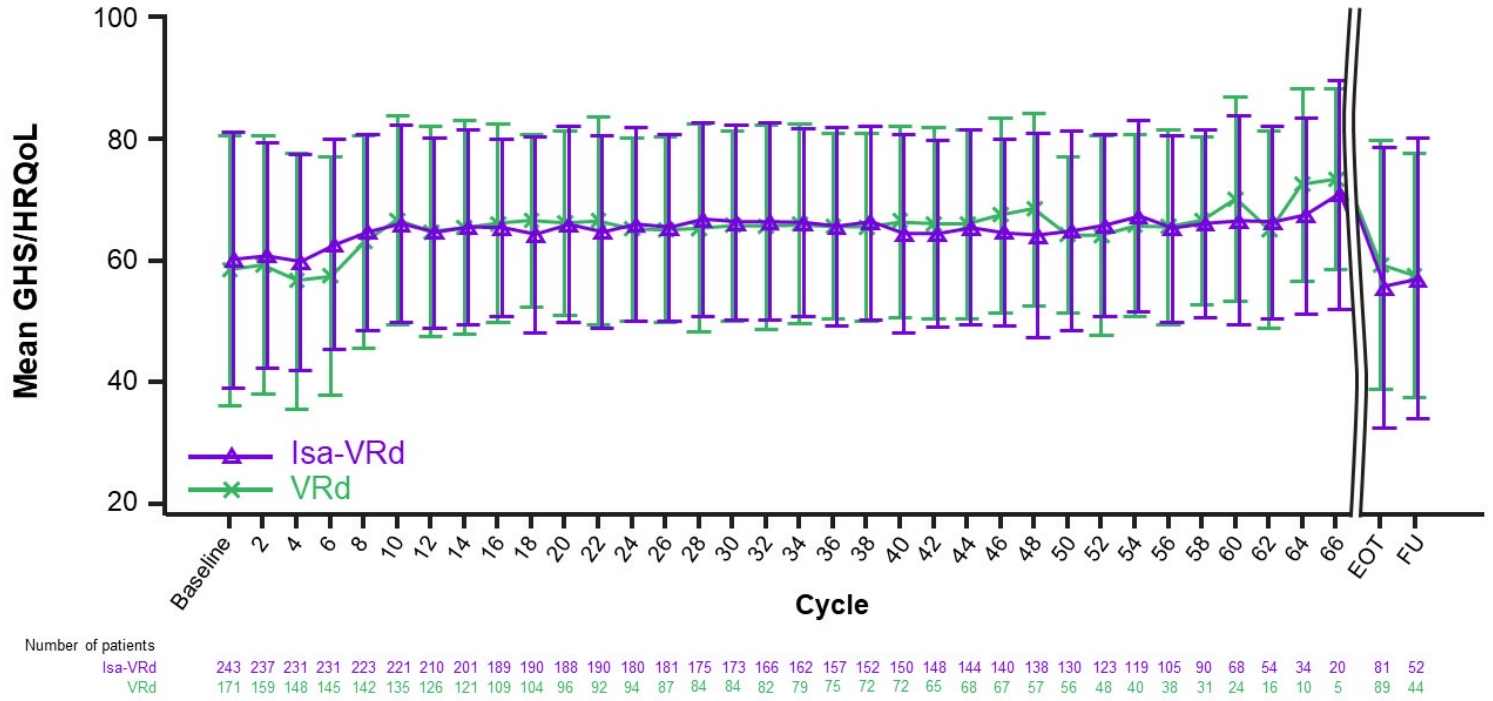
Interim OS analysis in ITT population



At a median follow-up of 5 years, OS is still immature; however, a favorable trend was observed for the Isa-VRd arm, with a 22.4% risk reduction compared with the VRd arm

*Cutoff date for analysis: September 26, 2023. †HR passed the prespecified futility threshold (>1.1); follow-up is ongoing.

Mean EORTC QLQ-C30 GHS/HRQoL score over time



Number of patients

Isa-VRd	243	237	231	231	223	221	210	201	189	190	188	190	180	181	175	173	166	162	157	152	150	148	144	140	138	130	123	119	105	90	68	54	34	20	81	52
VRd	171	159	148	145	142	135	126	121	109	104	96	92	94	87	84	84	82	79	75	72	72	65	68	67	57	56	48	40	38	31	24	16	10	5	89	44

Overall QoL, measured by the EORTC QLQ-C30 GHS, remained stable over time in both groups, with no negative impact from adding isatuximab

QoL analysis is ongoing. A higher score represents a better level of QoL. Error bars represent standard deviation. Cycles with fewer than 20 patients overall are not presented. EOT and FU were 30 and 90 days after last study treatment administration, respectively.
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer-specific module with 30 items; EOT, end of treatment; FU, follow-up; GHS, global health status; HRQoL, health-related quality of life.

Safety summary (Safety population)

TEAE overview, n (%)	Isa-VRd (n=263)	VRd (n=181)
Median treatment duration	**53.2 months**	**31.3 months**
Patients still on treatment	**125 (47.2)**	**44 (24.3)**
Any TEAE	262 (99.6)	178 (98.3)
Grade ≥3 TEAEs	241 (91.6)	152 (84.0)
Grade 5 TEAEs*	29 (11.0)	10 (5.5)
Serious TEAEs	186 (70.7)	122 (67.4)
Any TEAE leading to definitive treatment discontinuation	60 (22.8)	47 (26.0)
Event rate per patient-year†		
Any TEAE	13.39	12.69
Grade ≥3 TEAEs	1.17	0.99
Grade 5 TEAEs	0.03	0.02
Serious TEAEs	0.37	0.43
Any TEAE leading to definitive treatment discontinuation	0.07	0.09

The exposure-adjusted incidence rates suggest the difference in incidence of grade 5 TEAEs between arms was largely driven by the difference in treatment exposure

*Causes of death occurring during the treatment period for the Isa-VRd group included COVID-19 pneumonia (n=7), COVID-19 pneumonia/multiorgan failure (n=1), renal tubular acidosis/TLS (n=1), septic shock (n=1), pneumonia (n=4), sudden death (n=4), undetermined (n=1), pneumonia pseudomonal (n=1), candida sepsis (n=1), hepatic cirrhosis (n=1), neuroendocrine carcinoma of the skin (n=1), pulmonary embolism (n=1), febrile neutropenia (n=1), pneumonia klebsiella and sepsis (n=1), respiratory failure (n=1), dyspnea (n=1), and sepsis (n=1). Causes of death occurring during the treatment period for the VRd group included pneumonia (n=2), COVID-19 (n=2), pneumonia aspiration (n=1), undetermined (n=1), pulmonary embolism (n=1), pleural effusion (n=1), sepsis (n=1), and bronchitis (n=1). †Calculated as number of patients with an event divided by total patient-years.

Safety summary (Safety population) (cont'd)

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*				
Infections	1.181	-	1.166	-
Secondary primary malignancies†	0.041	-	0.026	-

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

*Calculated as number of patients with an event divided by total patient-years. Patients were followed yearly. †Including non-melanoma skin cancer.

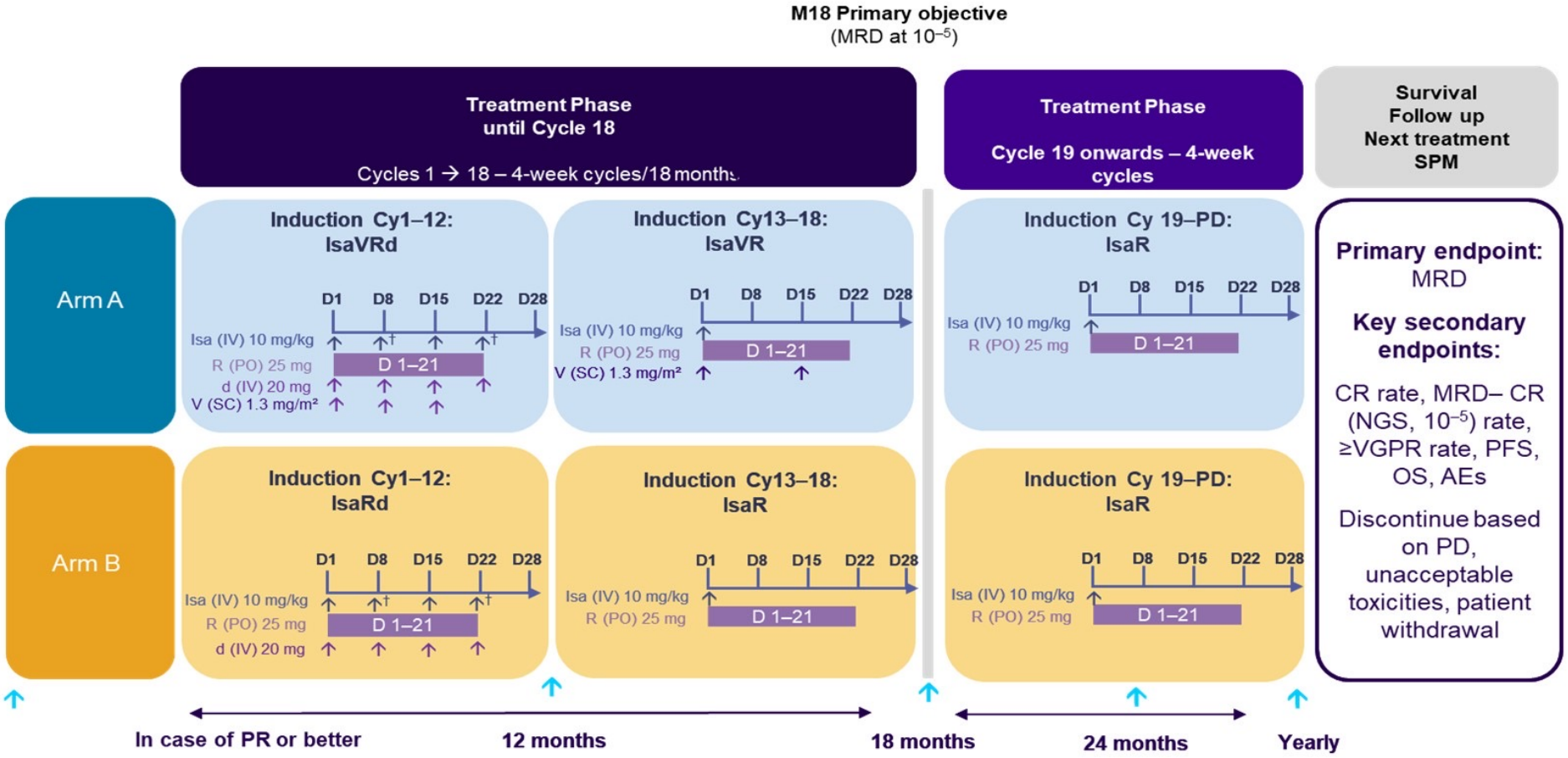
Study design: Isa-VRd vs Isa-Rd in Ti NDMM

BENEFIT trial

N=270

- **Randomization1:1**
- **Stratified by:**

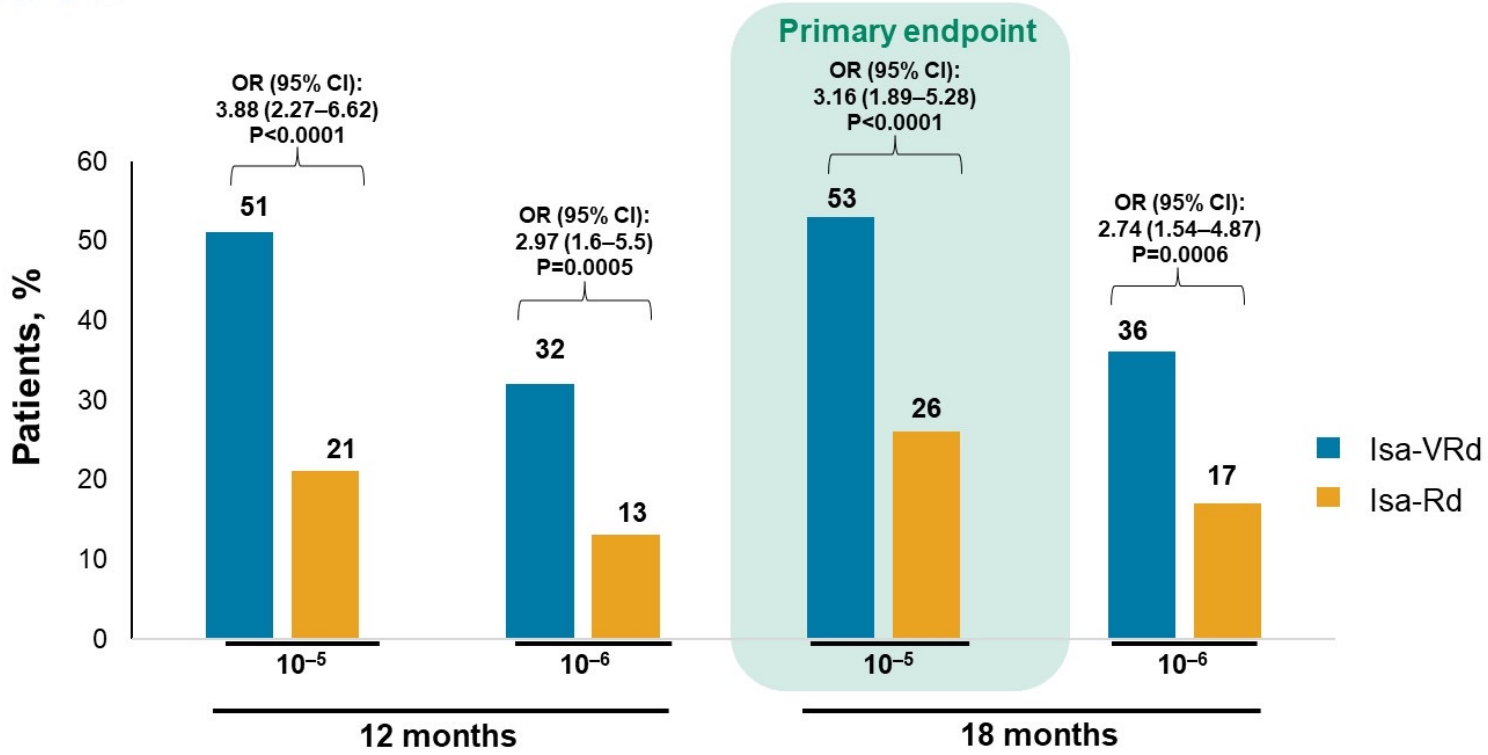
- Age: <75 and ≥ 75yrs
- Cytogenetic result by FISH (Modified Perrot score)
- Center



†Cycle 1 only. CR, complete response; Cy, cycle; d, dexamethasone; D, day; Isa, isatuximab; M, month; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, lenalidomide; SPM, second primary malignancy; Ti, transplant-ineligible; V, bortezomib; VGPR, very good partial response.

Primary endpoint: MRD–* rate at 18 months – ITT population

BENEFIT trial

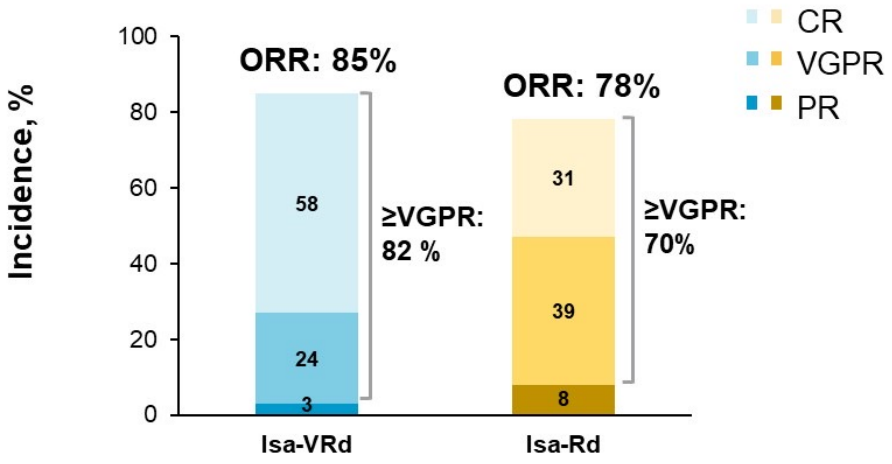


Isa-VRd resulted in deep response rates, with a significant improvement in the MRD at 12 and 18 months, and at 10^{-5} and 10^{-6} in the ITT population

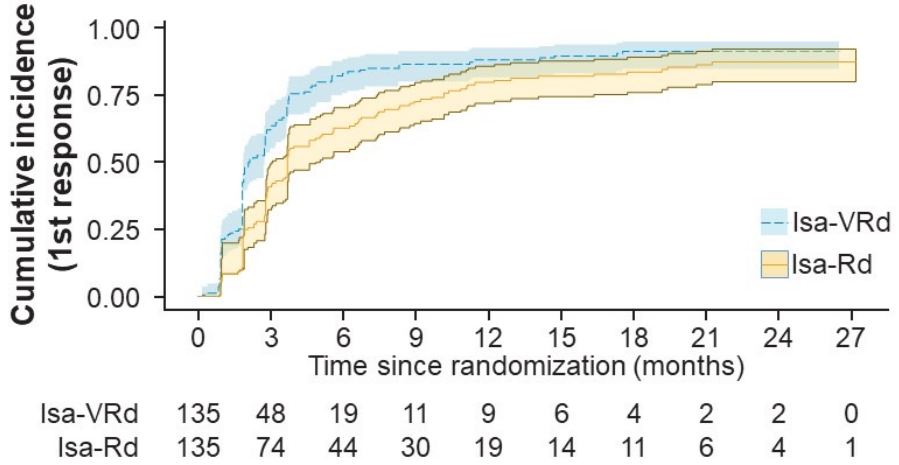
*MRD was assessed on the basis of IMWG recommendations.[1]
CI, confidence interval; Isa, isatuximab; ITT, intent-to-treat; MRD–, minimal residual disease negativity; NGS, next generation sequencing; OR, odd ratio; R, lenalidomide; V, bortezomib.
1. Kumar S, et al. *Lancet Oncol* 2016;17:e328–e346.

Depth of response* at 18 months and the first occurrence of a CR - ITT Population

BENEFIT trial



≥CR rate 58% vs. 31%, OR (95% CI): 2.97 (2–5), p<0.0001



≥VGPR†

HR: 1.65 (95% CI, 1.27 to 2.14, p=0.0002)

VGPR, median (95% CI)
Isa-VRd: 2.1 (95%CI, 1.9–2.9) months
Isa-Rd: 3.7 (95%CI, 3–4.9) months

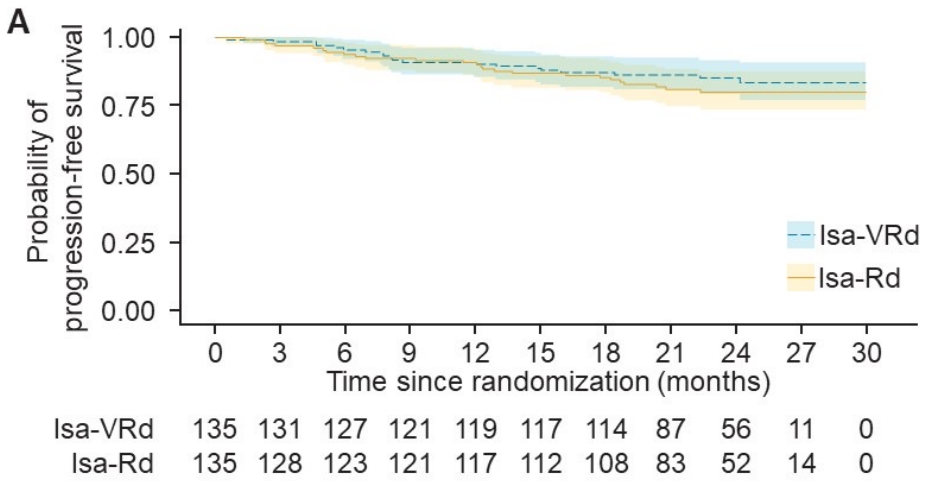
Isa-VRd resulted in deep response rates, particularly ≥CR rate at 18 months, and a shorter time to the first occurrence of a confirmed response ≥VGPR in the ITT population

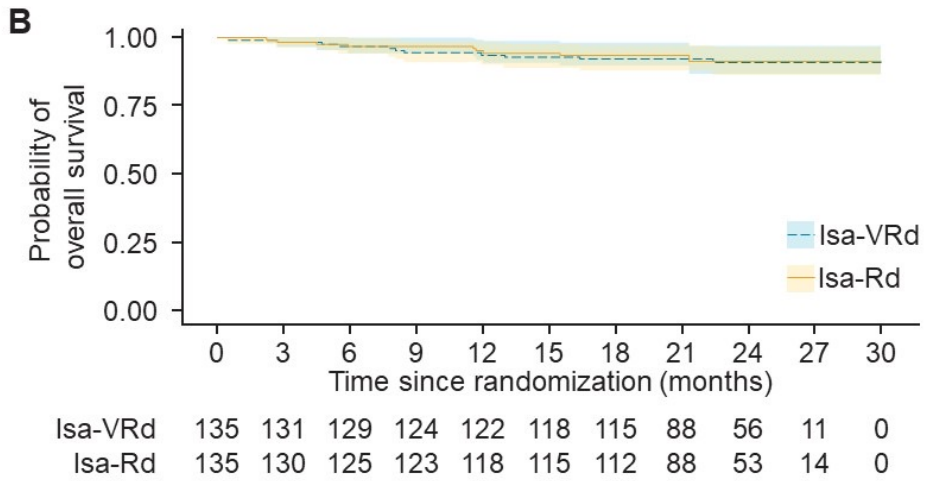
*Response was assessed on the basis of IMWG recommendations[1]; †Distribution of time to ≥VGPR were compared between arm using a Cox cause specific proportional Hazard model to account for competing risk of death or progressive disease with treatment as explanatory variable and adjusting for randomization stratification factors. CI, confidence interval; CR, complete response; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intent-to-treat; ORR, overall response rate; PR, partial response; R, lenalidomide; V, bortezomib; VGPR, very good partial response

PRESENTED BY: Xavier Leleu, MD, PhD

Survival analysis-IRC assessment in ITT population

BENEFIT trial





Estimated 24 months PFS
85.2% (95%CI 79.2–91.7) for Isa-VRd
80.0% (95% CI 73.3–87.4) for Isa-Rd

Estimated 24 months OS
91.1% (95%CI 86.1–96.4) for Isa-VRd
91.5% (95%CI 86.5–96.8) for Isa-Rd

At a median follow-up of 23.5 months, survival is still immature

d, dexamethasone; Isa, isatuximab; IRC, independent review committee; ITT, intent-to-treat; CI, confidence interval; OS, overall survival; PFS, progression-free survival; R, lenalidomide; V, bortezomib.

PRESENTED BY: Xavier Leleu, MD, PhD

Safety summary (safety population*)

BENEFIT trial

TEAE overview, n (%)	Isa-VRd (n=135)	Isa-Rd (n=135)
Any TEAE	134 (99)	128 (95)
Grade ≥3 TEAEs	93 (69)	91 (67)
Serious TEAEs	46 (34)	47 (35)
Any TEAE leading to definitive treatment discontinuation		
Isatuximab	3 (2)	4 (3)
Lenalidomide	14 (10)	13 (10)
Dexamethasone	14 (10)	7 (5)
Bortezomib	14 (10)	0
Event rate per patient-year†		
Any TEAE	12.53	5.57
Grade ≥3 TEAEs	0.96	0.88
Serious TEAEs	0.26	0.28
Any TEAE leading to definitive treatment discontinuation (all treatments)	0.01	0.01

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

*The safety population included all patients who received at least one dose of study treatment; †Calculated as number of patients with an event divided by total patient-years. d, dexamethasone; Isa, isatuximab; R, lenalidomide TEAE, treatment-emergent adverse event; V, bortezomib

PRESENTED BY: Xavier Leleu, MD, PhD

Safety summary (Safety population*)

BENEFIT trial

Event, no. of patients (%)	Isa-VRd (n=135)		Isa-Rd (n=135)	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Hematologic adverse events				
Neutropenia	77 (57)	53 (40)	82 (61)	61 (45)
Lymphopenia	53 (39)	44 (33)	38 (28)	33 (24)
Anemia	30 (22)	13 (10)	27 (20)	7 (5)
Thrombocytopenia	37 (27)	16 (12)	19 (14)	8 (5)
Event, no. of patients (%)	**Any Grade**	**≥Grade 2**	**Any Grade**	**≥Grade 2**
Nonhematologic adverse events				
Diarrhea	66 (49)	39 (29)	65 (48)	30 (22)
Constipation	52 (39)	30 (22)	41 (30)	19 (14)
Rash	21 (16)	12 (9)	16 (12)	9 (7)
Asthenia	41 (30)	24 (18)	48 (36)	18 (14)
Peripheral Oedema	48 (36)	18 (14)	27 (20)	10 (7)
Muscle spasms	27 (20)	7 (5)	28 (21)	9 (7)
Psychiatric disorders	33 (24)	22 (16)	32 (24)	17 (13)
Vascular disorders	36 (27)	21 (15)	34 (25)	23 (17)

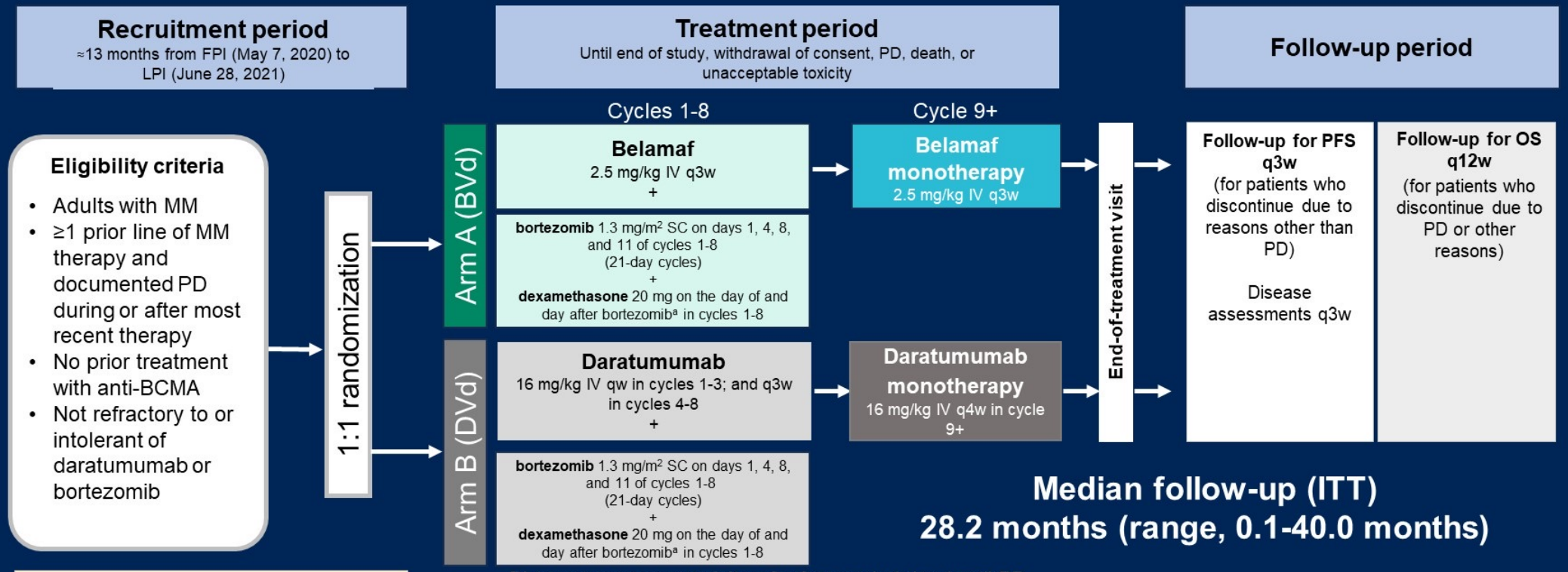
Event, no. of patients (%)	Isa-VRd (n=135)		Isa-Rd (n=135)	
	Any Grade	≥Grade 2	Any Grade	≥Grade 2
Nonhematologic adverse events (cont'd)				
Eye disorders	20 (15)	10 (7)	19 (14)	12 (8)
SPMs	6 (4)	6 (4)	6 (4)	6 (4)
Infections and infestations				
Infection of other types	61 (45)	48 (36)	48 (36)	35 (28)
Infection of the respiratory system	65 (48)	47 (35)	64 (47)	54 (40)
Covid-19	55 (41)	34 (24)	59 (44)	31 (23)
Nervous system disorders				
Peripheral neuropathy	70 (52)	37 (27)†	38 (28)	13 (10)‡
Other	38 (28)	19 (14)	41 (30)	17 (13)

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

*The safety population included all patients who received at least one dose of study treatment; †Four patients had a Grade 3 event in Isa-VRd arm; ‡One patient had a Grade 3 event in the Isa-Rd. d, dexamethasone; Isa, isatuximab; R, lenalidomide; SPM, second primary malignancies; V, bortezomib.

PRESENTED BY: Xavier Leleu, MD, PhD

DREAMM-7: study design

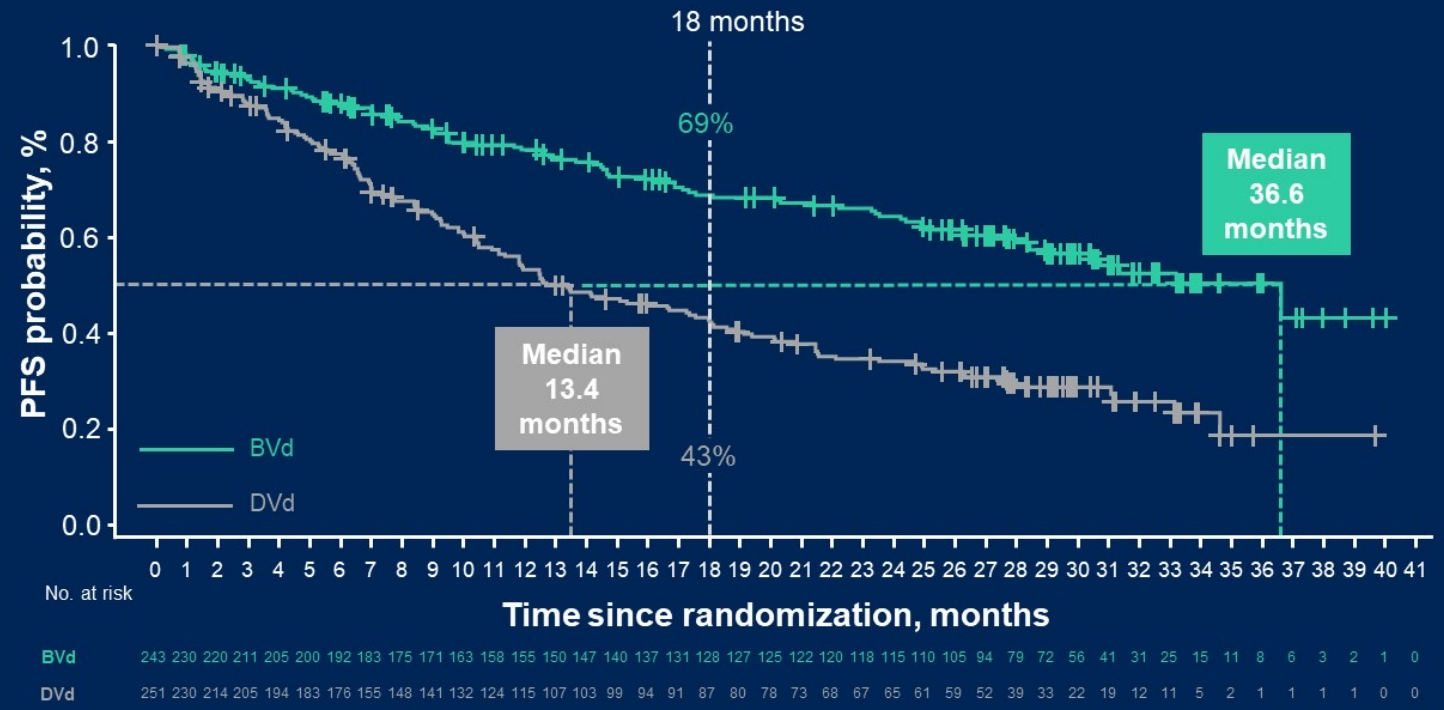


AE, adverse event; BCMA, B-cell maturation antigen; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; FPI, first patient in; IRC, independent review committee; ITT, intent-to-treat; IV, intravenous; LPI, last patient in; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; q4w, every 4 weeks; q12w, every 12 weeks; QOL, quality of life; qw, once weekly; R-ISS, Revised International Staging System; SC, subcutaneous; TTP, time to progression; TTR, time to response.

[a] Starting dose of dexamethasone may be reduced to 10 mg for patients aged >75 years, who have a body-mass index of less than 18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting dose.

DREAMM-7: ITT population

BVd led to a significant increase in PFS vs DVd



PFS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	91 (37)	158 (63)
PFS, median (95% CI), mo[b]	36.6 (28.4-NR)	13.4 (11.1-17.5)
HR (95% CI)[c]	0.41 (0.31-0.53)	
P value[d]	<.00001	

BVd demonstrated a statistically significant and clinically meaningful PFS benefit, with a median PFS that was 23 months longer than that with DVd (36.6 vs 13.4 months)

Median follow-up: 28.2 months (range, 0.1-40.0 months)

HR, hazard ratio; ITT, intent to treat; NR, not reached; PFS, progression-free survival; R-ISS, Revised International Staging System.

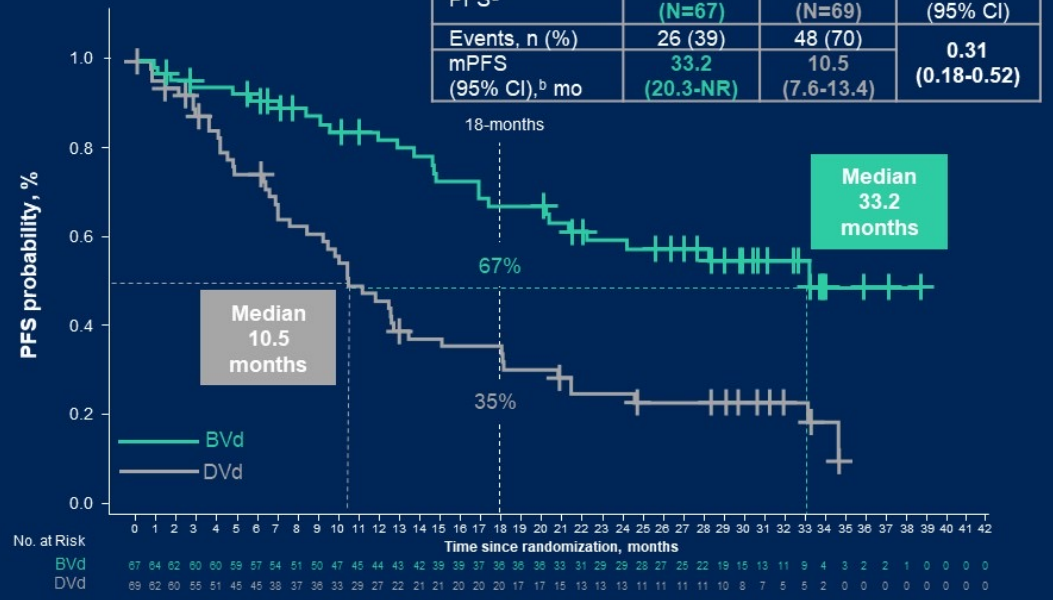
[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III), with a covariate of treatment. [d] *P* value from 1-sided stratified log-rank test.

DREAMM-7: subgroup by cytogenetic risk

Progression-free survival (high risk and standard risk)

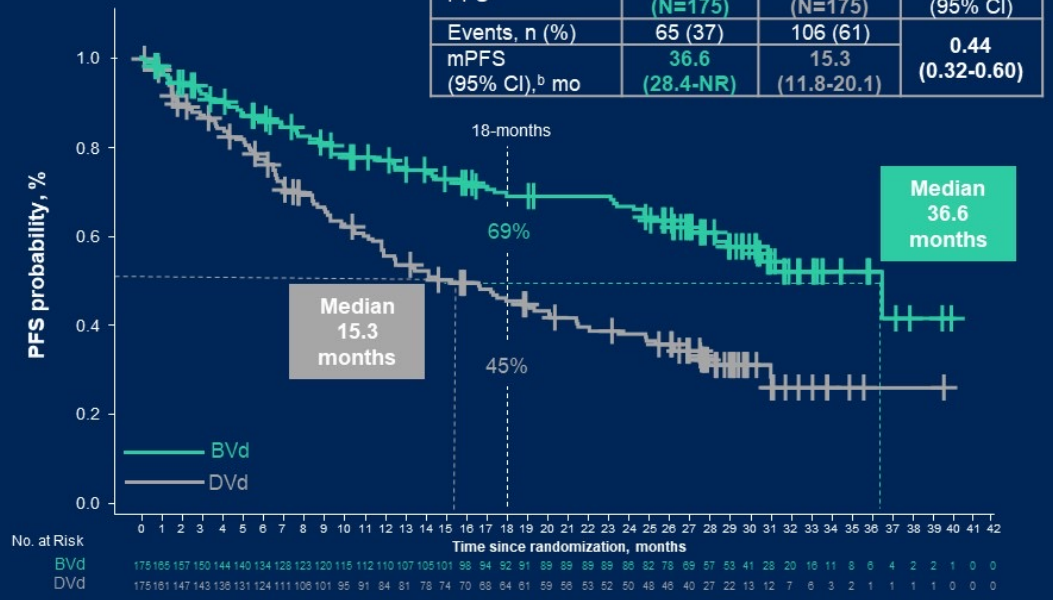
High Risk

PFS[a]	BVd (N=67)	DVd (N=69)	HR[c] (95% CI)
Events, n (%)	26 (39)	48 (70)	0.31 (0.18-0.52)
mPFS (95% CI),[b] mo	33.2 (20.3-NR)	10.5 (7.6-13.4)	



Standard Risk

PFS[a]	BVd (N=175)	DVd (N=175)	HR[c] (95% CI)
Events, n (%)	65 (37)	106 (61)	0.44 (0.32-0.60)
mPFS (95% CI),[b] mo	36.6 (28.4-NR)	15.3 (11.8-20.1)	



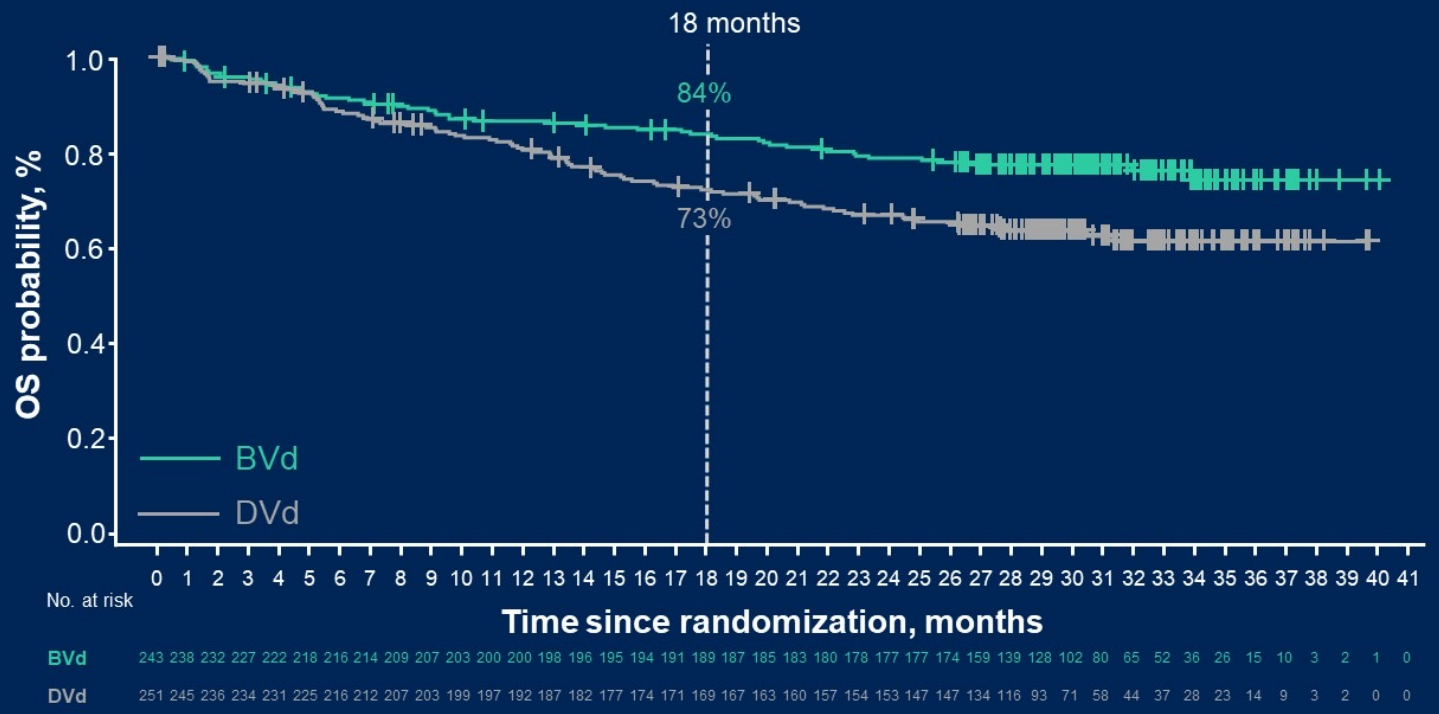
BVd led to strong PFS benefit (more than double to triple the median PFS) regardless of cytogenetic risk status compared with DVd

[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method. 95% CIs were not adjusted for multiplicity and cannot be used for hypothesis testing. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III), with a covariate of treatment.

PRESENTED BY: María Victoria Mateos, MD, PhD

DREAMM-7: ITT population

Early OS trend favoring BVd vs DVd



OS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	54 (22)	87 (35)
OS, median (95% CI), mo[b]	NR	NR
HR (95% CI)[c]	0.57 (0.4-0.8)	
P value[d]	.00049[e]	

OS showed an early, strong, and clinically meaningful trend favoring the BVd arm; additional OS follow-up is ongoing

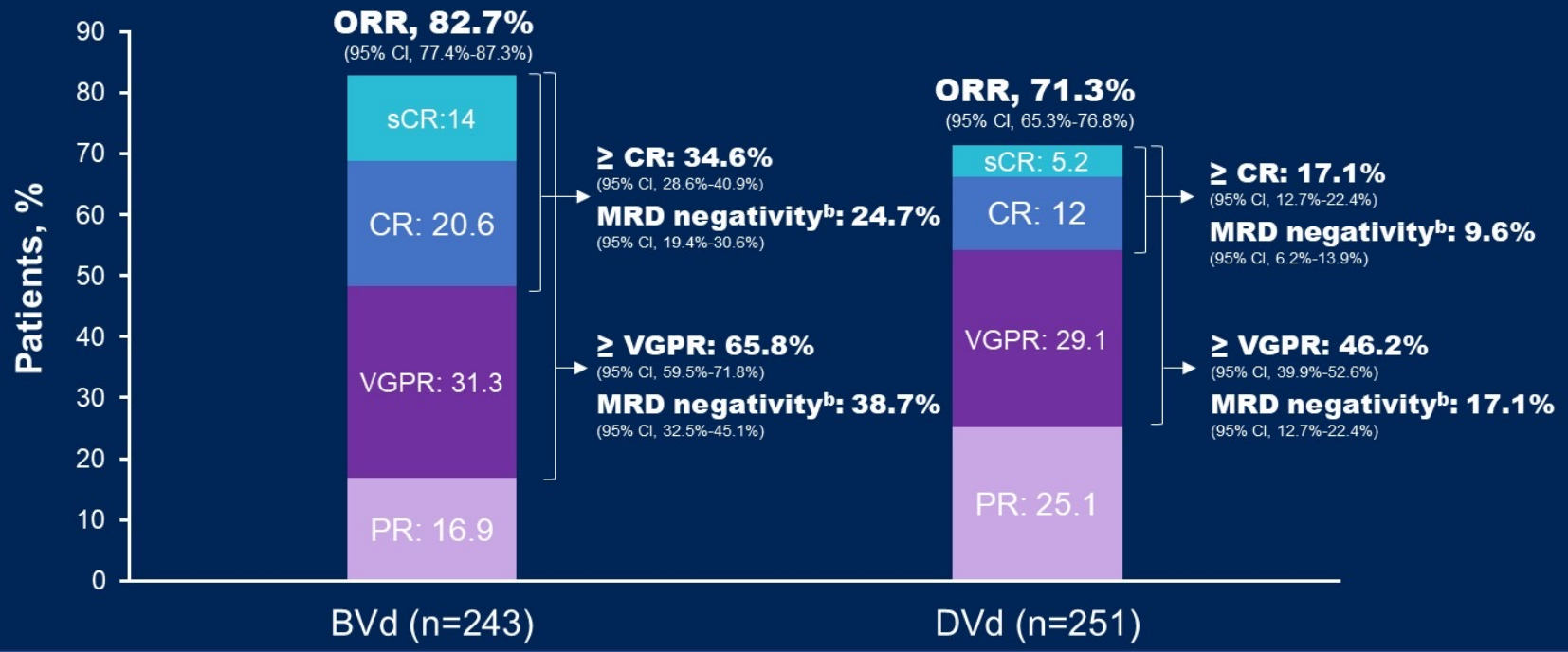
Median follow-up: 28.2 months (range, 0.1-40.0 months)

HR, hazard ratio; ITT, intent to treat; NR, not reached; OS, overall survival; R-ISS, Revised International Staging System.

[a] Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] CIs were estimated using the Brookmeyer-Crowley method. [c] HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III), with a covariate of treatment. [d] *P* value is from 1-sided stratified log-rank test. [e] The *P* value has not yet reached criteria for statistical significance (*P*≤.00037) at this interim analysis. Follow-up for OS is ongoing.

DREAMM-7: ITT population

Deeper responses and increased MRD negativity rate with BVd vs DVd[a]



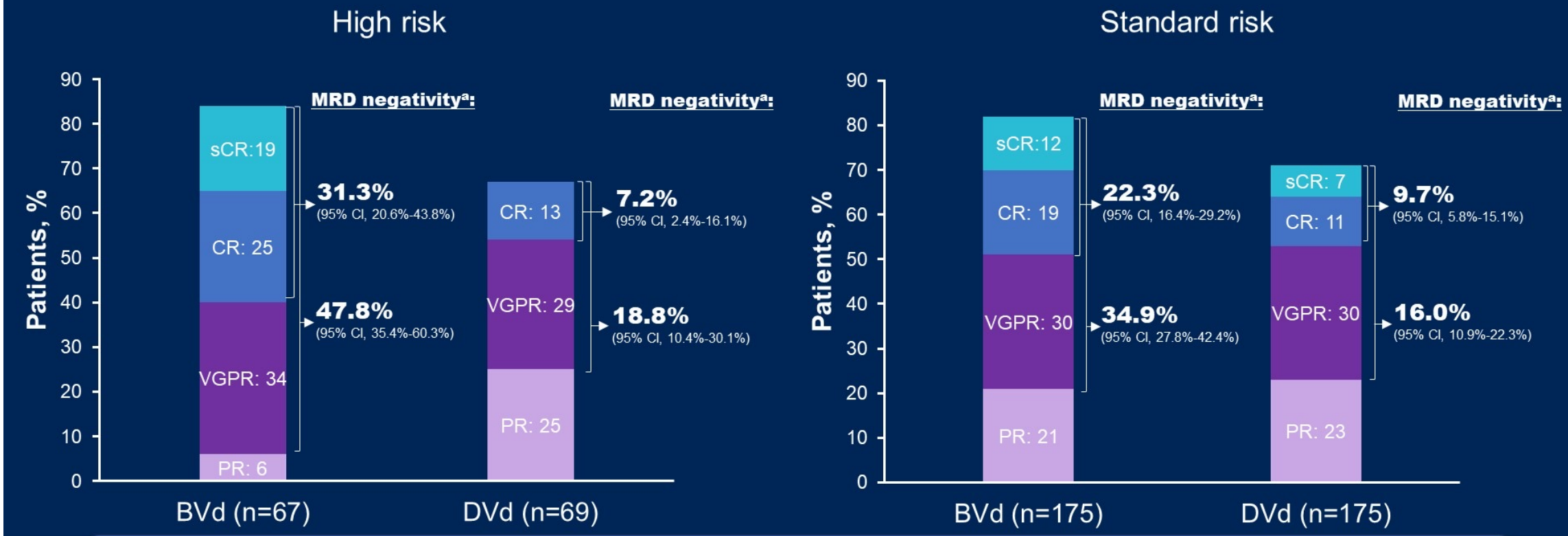
- BVd was associated with greater depth of response, with a ≥ CR rate that was double that with DVd
- MRD negativity rate (sensitivity of 10^{-5}) in patients treated with BVd was more than double that in patients treated with DVd (*P*<.00001)[c]

CR, complete response; ITT, intent to treat; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; PR, partial response; R-ISS, Revised International Staging System; sCR, stringent complete response; VGPR, very good partial response.

[a] CIs were based on the exact method. Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique patients in this output. [b] MRD negativity rate was defined as the percentage of patients who were MRD negative by NGS based on a sensitivity of 10^{-5}. [c] Nominal *P* value. Cochran–Mantel–Haenszel test was used and adjusted for stratification factors, including number of prior lines of therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS stage at screening (I vs II/III).

DREAMM-7: subgroup by cytogenetic risk

MRD negativity rates



Treatment with BVd was associated with higher MRD negativity rates vs DVd regardless of cytogenetic risk status

Post hoc analyses.
CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
[a] MRD negativity rate was defined as percentage of patients who were MRD negative by NGS based on a sensitivity of 10^{-5}.

DREAMM-7: grade ≥3 AEs of special interest by cytogenetic risk status

Occurring in ≥5% of patients in any subgroup

Preferred term, n (%)	BVd (N=242)			DVd (N=246)		
	Cytogenetic risk[a]		Total	Cytogenetic risk[a]		Total
	High (n=66)	Standard (n=175)	N=242	High (n=68)	Standard (n=171)	N=246
Any	53 (80)	144 (82)	198 (82)	35 (51)	82 (48)	120 (49)
Thrombocytopenia	34 (52)	99 (57)	134 (55)	26 (38)	58 (34)	87 (35)
Platelet count decreased	14 (21)	30 (17)	44 (18)	9 (13)	17 (10)	26 (11)
Vision blurred	16 (24)	37 (21)	53 (22)	1 (1)	1 (<1)	2 (1)
Visual impairment	2 (3)	11 (6)	13 (5)	0	1 (<1)	1 (<1)
Dry eye	3 (5)	14 (8)	17 (7)	0	0	0
Eye irritation	1 (2)	11 (6)	12 (5)	0	0	0

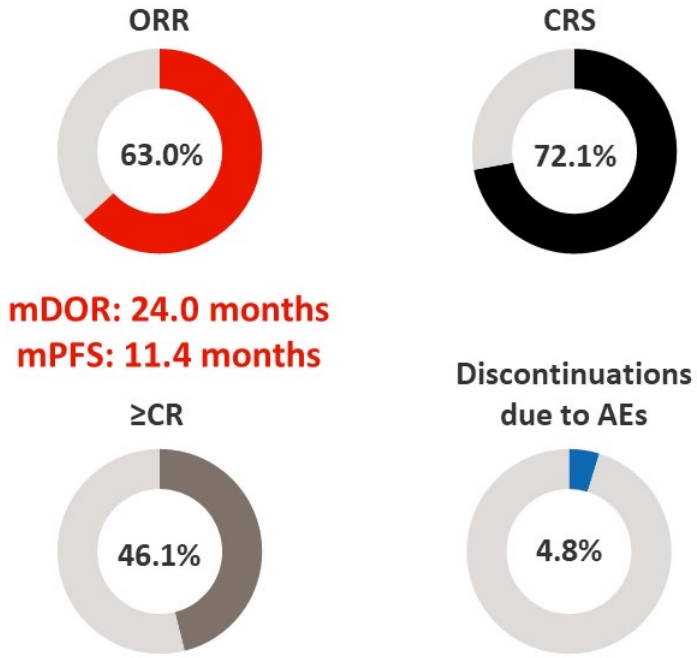
The rates of grade ≥3 AEs of special interest in the BVd arm were consistent with those reported in the overall population regardless of cytogenetic risk status

Post hoc analyses.
[a] One patient in the BVd arm and 7 patients in the DVd arm had missing or nonevaluable cytogenetic risk.
AEs were graded according to NCI-CTCAE version 5.0.
AE, adverse event; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

MajesTEC-1 Prophylactic Tocilizumab Cohort: Introduction

- Teclistamab is the first approved BCMA×CD3 BsAb for TCE RRMM, with weight-based dosing and longest study follow-up of any BsAb in MM[1-3]
- In the pivotal MajesTEC-1 study, 72.1% of patients had CRS (all grade 1/2 except 1 grade 3 event in 1 patient)[3,4]
- Teclistamab has been given successfully in the outpatient setting, using prophylactic tocilizumab to manage CRS[5–9]
- In a separate cohort, prophylactic tocilizumab prior to step-up dose 1 reduced the incidence of CRS to 26% (all grade 1 and 2) at 2.6 months median follow-up[10]
  - Here, we present data with a longer median follow-up of 8.1 months in the prophylactic tocilizumab cohort (n=24) in MajesTEC-1

MajesTEC-1 pivotal cohort (30.4 months median follow-up)[11]



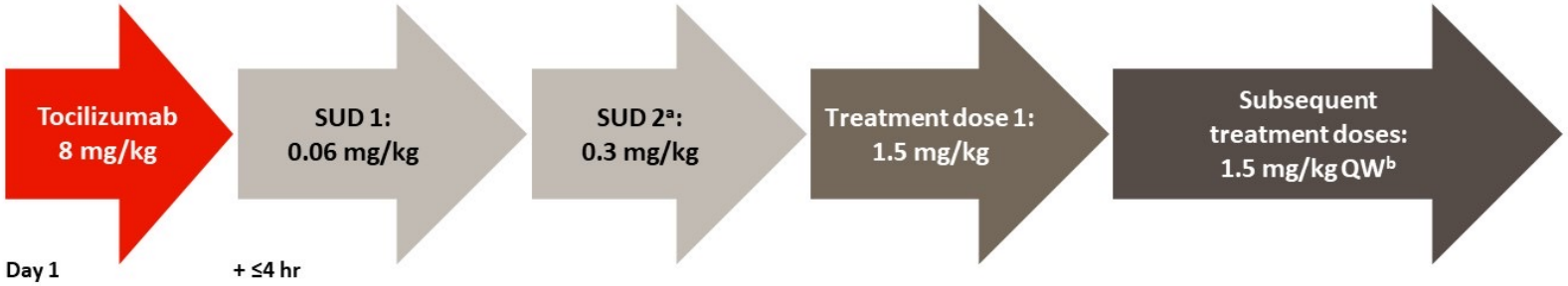
BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CD3, cluster of differentiation 3; CRS, cytokine release syndrome; mDOR, median duration of response; MM, multiple myeloma; mPFS, median progression-free survival; RRMM, relapsed/refractory multiple myeloma; TCE, triple-class exposed.

1. TECVAYLI (teclistamab). Summary of Product Characteristics. Leiden, The Netherlands. Janssen Biologics BV; 2022. 2. TECVAYLI (teclistamab-cqyv). Prescribing Information. Horsham, PA: Janssen Biotech, Inc; 2022. 3. Moreau P, et al. *NEJM* 2022;387:495-505. 4. Martin TG, et al. *Cancer* 2023;129(13):2035-2046. 5. Trudel S, et al. *Blood* 2022;140(Suppl 1):1363-5. 6. Kauer J, et al. *J Immunother Cancer* 2020;8:e000621. 7. Scott, S et al. *Blood Cancer J* 2023;13(1):191. 8. Kowalski A, et al. Blood (2023) 142 (Supplement 1): 4709. 9. Varshavsky-Yanovsky AN, et al. *Hemasphere* 2023;7(Suppl):e605007f. 10. van de Donk NWCJ, et al. Presented at ASCO; June 2-6, 2023; Chicago, IL, USA. Poster #8033. 11. Garfall AL, et al. Presented at ASCO; May 31-June 4, 2024; Chicago, IL, USA. Poster #7540.

Presented by NWCJ van de Donk at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA & Virtual

MajesTEC-1 Prophylactic Tocilizumab Cohort: Study Design

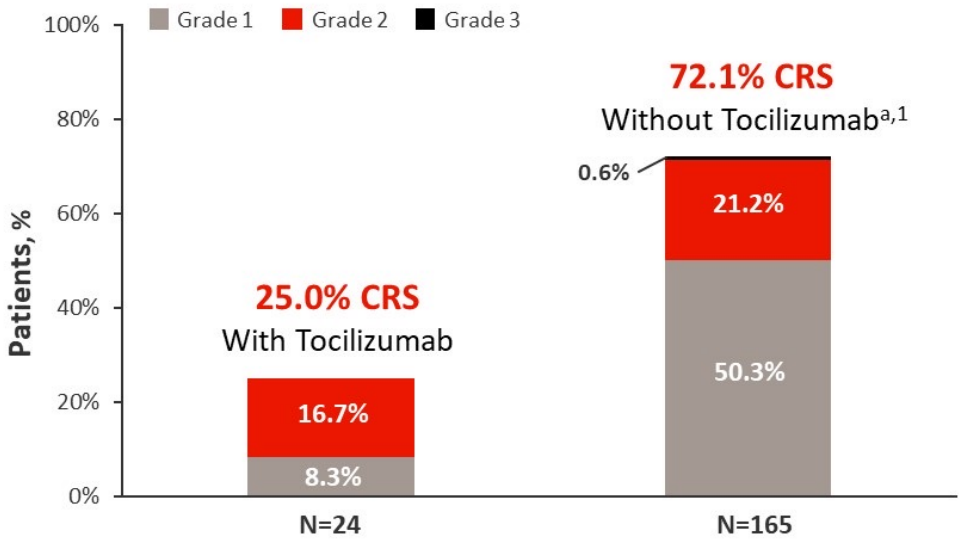
- Patients received teclistamab 1.5 mg/kg weekly (phase 1 exploratory cohort) or a comparable fixed dose after a single dose of tocilizumab and SUD
  - Tocilizumab 8 mg/kg was administered intravenously ≤4 hours before the first teclistamab SUD
  - Premedications during the teclistamab SUD schedule were dexamethasone, acetaminophen, and diphenhydramine
  - Hospitalization was required for 48 hours after each SUD and after the first treatment dose
- CRS management with tocilizumab treatment was permitted for grade 1 and recommended for grade ≥2
- CRS as an AE was graded per Lee et al[1]



[a]2–4 days were allowed between SUD 1, SUD 2, and treatment dose one. [b]Less frequent dosing (e.g., Q2W) starting cycle 3.
CRS, cytokine release syndrome; IV, intravenous; PR, partial response; QW, weekly; Q2W, every other week; RP2D, recommended phase 2 dose; SC, subcutaneous; SUD, step-up dose.
1. Lee DW, et al. *Blood* 2014;124:188-95.

Presented by NWCJ van de Donk at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA & Virtual

MajesTEC-1 Prophylactic Tocilizumab Cohort : CRS Incidence and Severity



Prophylactic tocilizumab cohort (N=24)			
Characteristic	**No CRS (n=18)**	**CRS Grade 1 (n=2)**	**CRS Grade 2 (n=4)**
BMPCs, % median (range)	8.0 (0–80)	19 (8–30)	62.5 (30–80)
ISS stage[b], %			
I	72.2	50	50
II	22.2	50	50
III	5.6	0	0
No. of EMPs, median (range)	0 (0–4)	0 (0)	0 (0–2)

- **25% CRS with prophylactic tocilizumab**
  - Grade 1 (n=2), grade 2 (n=4); no grade 3 events
  - All initial events occurred during SUD; 3 recurrent events
  - Median time to onset: 2 days (range, 1–3)
  - Median duration: 2 days (range, 2–4)
  - All events resolved

- **No disease characteristic associated with CRS, consistent with pivotal cohort**
  - Small sample size precludes clinically meaningful conclusions

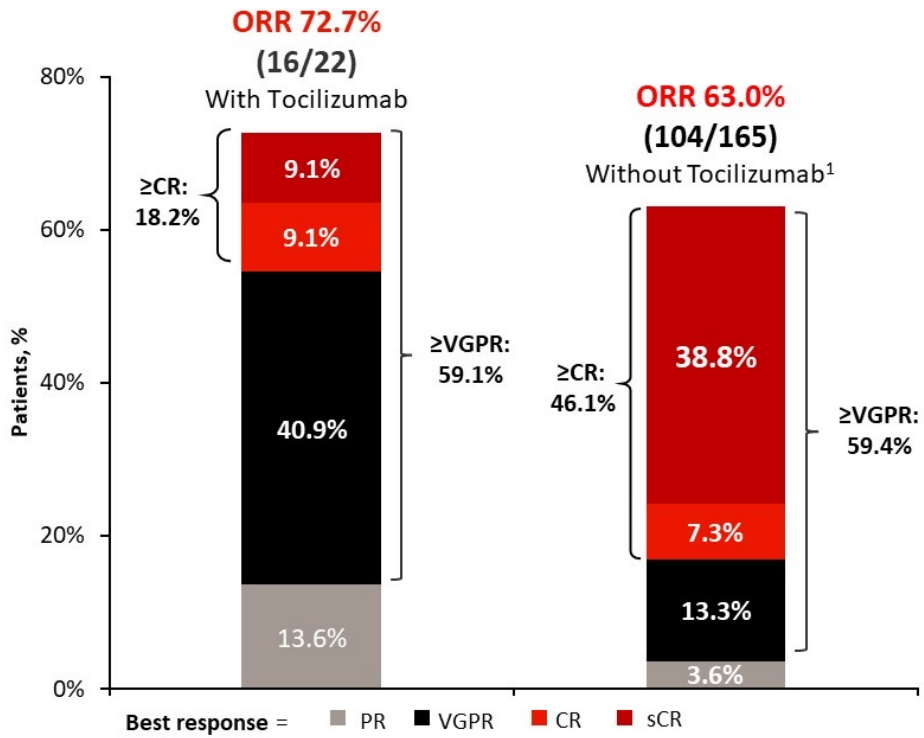
[a]Pivotal MajesTEC-1 population. [b]Derived based on the combination of serum β2-microglobulin and albumin.
BMPC, bone marrow plasma cell; CRS, cytokine release syndrome; EMP, extramedullary plasmacytoma; ISS, International Staging System; SUD, step-up dosing.
1. Martin TG, et al. *Cancer* 2023;129(13):2035-2046.

Presented by NWCJ van de Donk at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA & Virtual

MajesTEC-1 Prophylactic Tocilizumab Cohort: Efficacy Outcomes

Response to teclistamab (22 of 24 patients evaluable)[a]

- Responses were similar to the MajesTEC-1 pivotal population[1]
  - The lower ≥CR rate in the prophylactic tocilizumab cohort is likely due to limited availability of bone marrow samples to confirm CR and duration of follow-up
  - At 8.1 months median follow-up, no impact on teclistamab efficacy was observed



[a]Response evaluable patients received ≥ 1 study treatment and have ≥ 1 post-baseline response evaluation by the investigator.
CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
1. Garfall AL, et al. Presented at ASCO; May 31-June 4, 2024; Chicago, IL, USA. Poster #7540.

Presented by NWCJ van de Donk at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA & Virtual

MajesTEC-1 Prophylactic Tocilizumab Cohort: Safety Generally Consistent with MajesTEC-1 Pivotal Cohort[1]

- Grade 3/4 (25%) infections included:
  - Pneumonia (n=4)
  - Bacterial infection (n=1)
  - Diverticulitis (n=1)
  - CMV infection (n=1)
  - Sepsis (n=1)
  - Septic shock (n=1)
- 5 patients had 10 neurotoxicity[a] events including:
  - Headache, ICANS, myoclonus, dizziness, and insomnia
  - All events were grade 1–2
  - All events resolved except for grade 2 headache
- Grade 5 pulmonary embolism occurred 20 days after the last teclistamab dose

Prophylactic tocilizumab cohort (N=24)		
TEAE, n[b] (%)	Any grade	Grade 3/4
Infections[c]	19 (79.2)	6 (25.0)
Neutropenia	15 (62.5)	15 (62.5)
Anemia	14 (58.3)	6 (25.0)
Thrombocytopenia	12 (50.0)	6 (25.0)
Lymphopenia	9 (37.5)	9 (37.5)
Leukopenia	6 (25.0)	5 (20.8)
Increased lipase	6 (25.0)	5 (20.8)

[a]Neurotoxicity is defined as a neurological adverse event considered related by investigator. [b]TEAEs are listed if occurring at grade 3/4 in ≥20% of patients. [c]Rate of any grade infections and grade 3/4 in the MajesTEC-1 pivotal was 63.0% and 30.9%, respectively, at 7.2 months median follow-up.
CMV, cytomegalovirus; ICANS, immune effector cell-associated neurotoxicity syndrome; TEAE, treatment-emergent adverse event.
1. Garfall AL, et al. Presented at ASCO; May 31-June 4, 2024; Chicago, IL, USA. Poster #7540.

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Concept #EAA232: **DT** vs **DPd** or **DKd** in HR RRMM in First Relapse

Key Eligibility:

- Diagnosed with high-risk multiple myeloma (HR-MM)
- Relapsed/Refractory after only one prior line of therapy. May have lost MRD-negative status or experienced biochemical relapse, without official progressive disease per IMWG criteria.
- Daratumumab naïve or daratumumab sensitive and at least 365 days from last dose of daratumumab.
- An identifiable dominant sequence established based on Adaptive Biotechnologies clonoSEQ® assay.

Stratification Factors:

- Prior Daratumumab Induction: Yes vs. No
- Investigator's Choice of Therapy if assigned to Arm B: DPd vs DKd

RANDOMIZATION

Arm A
Daratumumab -Teclistamab (DT)[1]

Arm B[2]
Daratumumab-Pomalidomide-Dexamethasone (DPd)[1]
OR
Daratumumab-Pomalidomide-Dexamethasone (DKd)[1]

Treatment will continue until disease progression or unacceptable toxicity[2]

Follow-Up[3]

Primary Endpoint: **6-mo MRD(-) rate** [clonoSEQ MRD x 10^{-5}]

Secondary Endpoints: MRD at 12 mo, toxicity, PFS, OS, ORR

1. Refer to Section 5.1 for detailed dosing instructions. 1 Cycle = 28 Days.
2. MRD test required after 6 cycles of therapy in patients achieving very good partial response or better with no measurable protein detected by SPEP/UPEP but may have serum and/or urine immunofixation positive only. Only clonoSEQ® platform accepted for this study.
3. Upon discontinuation of protocol therapy, patients will be followed for response until progression, even if non protocol therapy is initiated, and for survival according to the schedule outlined in Section 5.7.

Myeloma 2024 Conclusions

- **TE NDMM**
  - Anti-CD38 Ab quad combinations are SOC induction approach + *dual maintenance*

- **TIE NDMM**
  - IMROZ: **Isa-VRd** vs VRd x 4 (6W) → IsaRd vs Rd (4W) until PD
  - BENEFIT: **Isa-VRd** vs IsaRd x 18 (4W) → IsaR (4W) until PD
  - *CEPHEUS: D-RVd vs RVd x 8 (3W) → DRd vs Rd (4W)* until PD

- **RRMM**
  - HRMM remains unmet need at any stage
  - *Belantamab mafodotin expected to return to the market (DREAMM-7 and DREAMM-8)*
  - MRD guided era increasingly maturing and soon prime time
  - Optimal sequencing of auto/allo (single/multi-target) CAR T and BsAb/TsAbs
  - Importance and value of T cell fitness/exhaustion in bridging considerations

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THANK YOU!

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