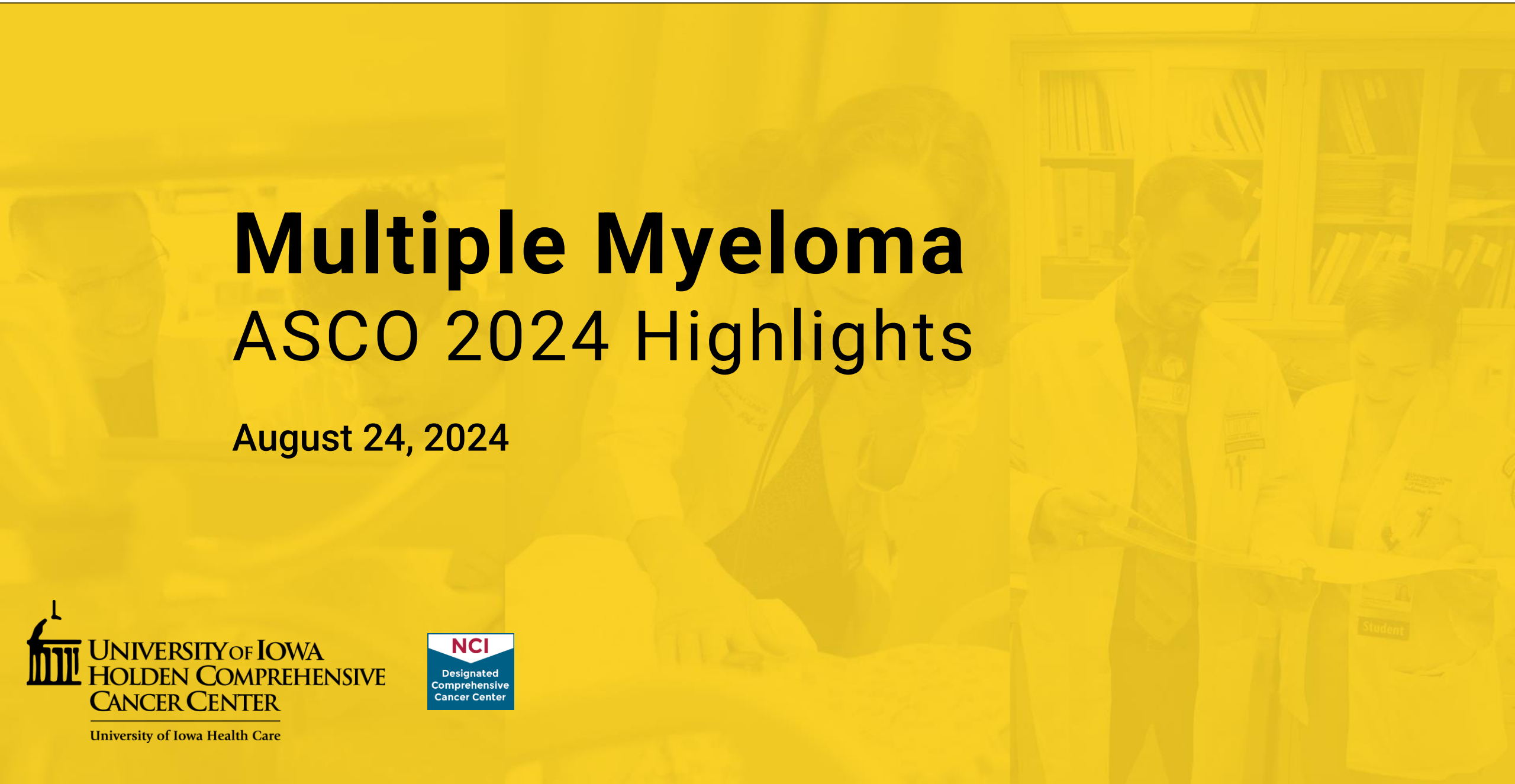
Multiple Myeloma
ASCO 2024 Highlights

August 24, 2024



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Disclosures

- No financial disclosures.

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  - Dr. Trudel (Abstract # LBA105)
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  - Dr. Leleu (Abstract # 7501)
  - Dr. Mateos (Abstract # 439572)

Multiple Myeloma in Numbers

2nd most common hematologic malignancy after lymphoma, globally[2]

In the United States,

Incidence

nearly, **32,270** individuals were diagnosed with multiple myeloma, in 2020[3]

1.8% of all new cancer cases[3]

Incidence has steadily increased over the past 15 years[3]

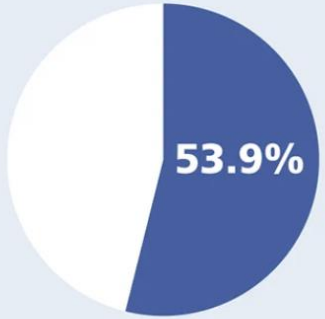
Prevalence

140,779 people are estimated to be living with multiple myeloma*[3]

*2017 estimates

Mortality

nearly, **12,830** individuals lost their lives to the multiple myeloma, in 2020[3]



Overall 5-year relative survival rate (2010-2016)[3]

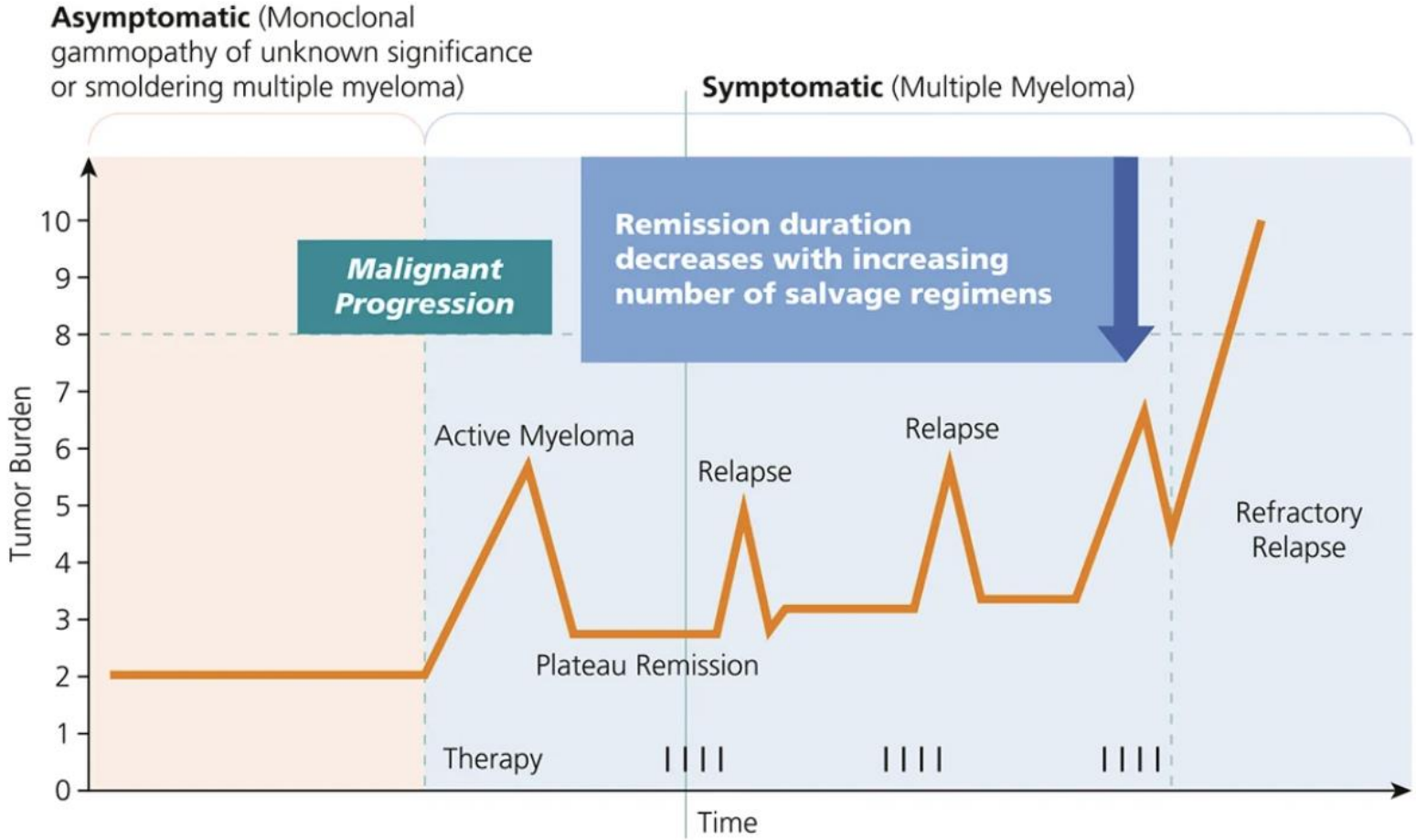
Median age at diagnosis 69 years[3]

Incidence is higher in males than females[3]

Incidence is higher in individuals of African-American descent[3]

Disease Course

Multiple Myeloma is characterized by a pattern of remission and relapse following conventional chemotherapy[5]



Shorter remission times are suggestive of:

- The development of drug resistance which eventually results in refractory disease[5]
- Presence of residual disease following treatment even after attaining complete response[5]

Pillars of Myeloma Treatment

PIs:
- Bortezomib
- Carfilzomib
- Ixazomib

Alkylating
- Cyclophosphamide
- Melphalan
- Bendamustine

IMiDs©:
- Thalidomide
- Lenalidomide
- Pomalidomide

Anti-SLAM-F7:
- Elotuzumab

Anti-CD38:
- Daratumumab
- Isatuximab

Selinexor

High Dose Melphalan (Transplant)

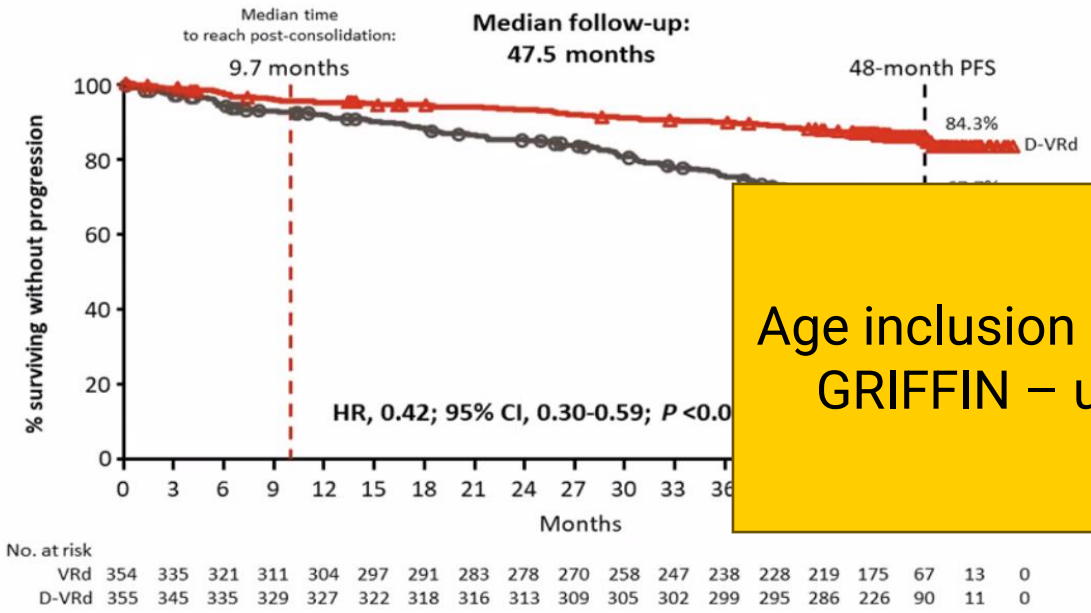
Belantamab

CAR T:
- Idecabtagene
- Ciltacabtagene

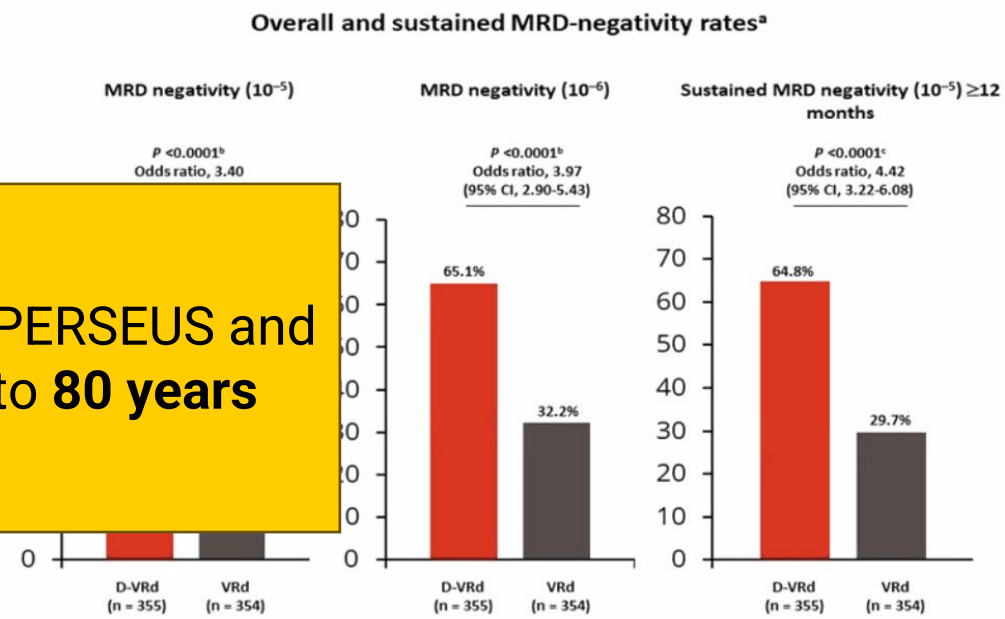
Venetoclax

Bispecific
- Teclistamab
- Elrantamab
- Talquetamab

Quads in Transplant-eligible
PERSEUS (DRVd vs RVd)



Age inclusion in PERSEUS and GRIFFIN – up to **80 years**



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

Deep and durable MRD negativity achieved with D-RVd

[a]MRD-negativity was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA).
[b]*P* values were calculated with the use of the stratified Cochran-Mantel-Haenszel chi-square test. [c]*P* value was calculated with the use of Fisher's exact test.

CI, confidence interval; CR, complete response; d, dexamethasone; D, daratumumab; HR, hazard ratio; MRD, minimal residual disease; PFS, progression-free survival; R, lenalidomide; V, bortezomib.

Quads in transplant-ineligible

2024 ASCO® ANNUAL MEETING

IMROZ

Phase 3 Study Results of Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone (Isa-VRd) Versus VRd for Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma (IMROZ)

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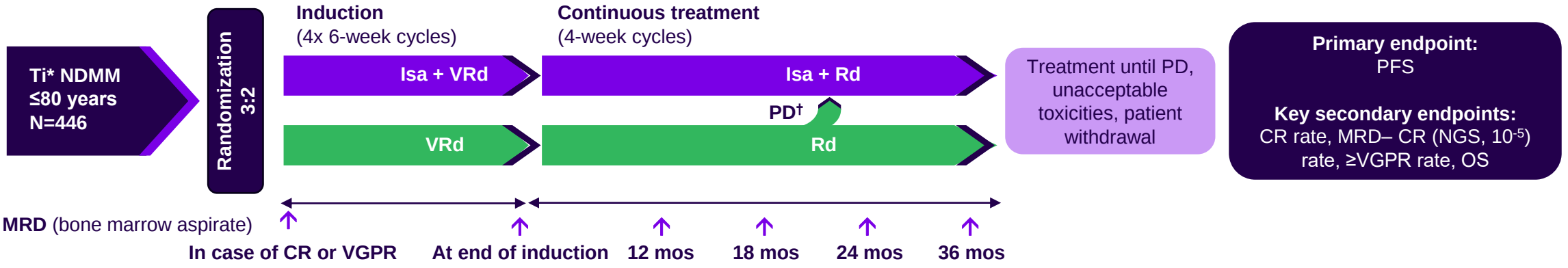
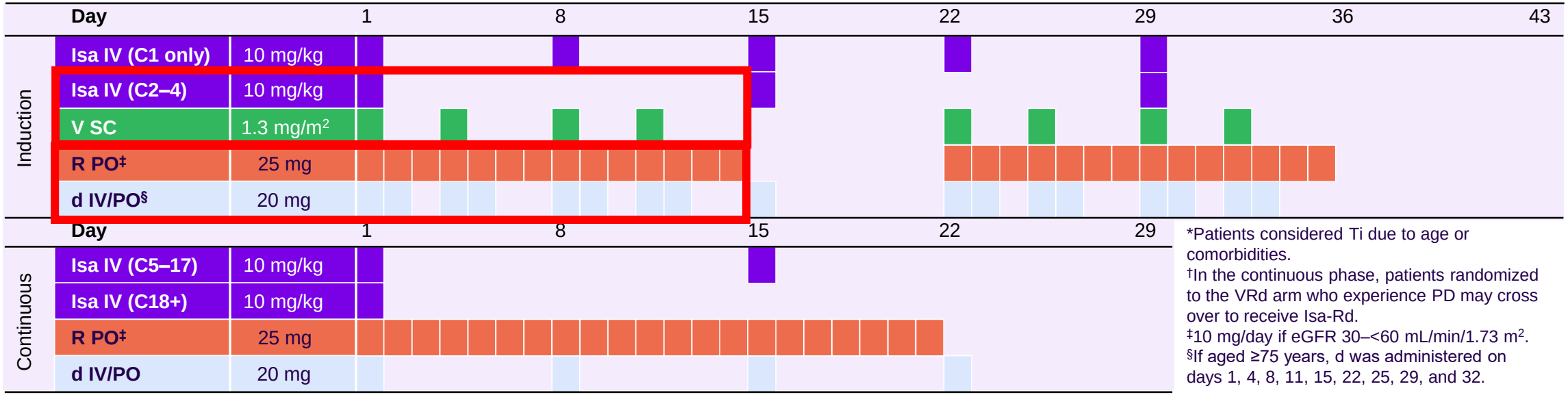
Study design: Isa-VRd vs VRd in transplant-ineligible NDMM

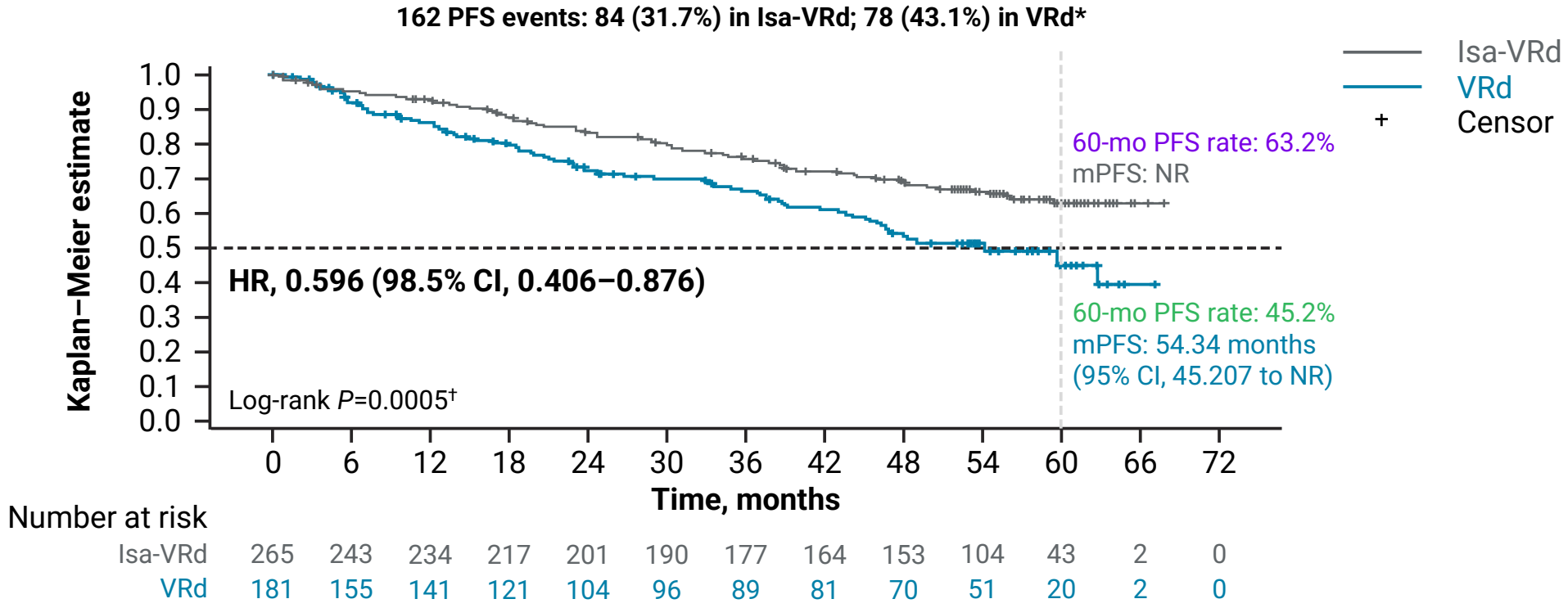




*Patients considered Ti due to age or comorbidities.
†In the continuous phase, patients randomized to the VRd arm who experience PD may cross over to receive Isa-Rd.
‡10 mg/day if eGFR 30–<60 mL/min/1.73 m^2.
§If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

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

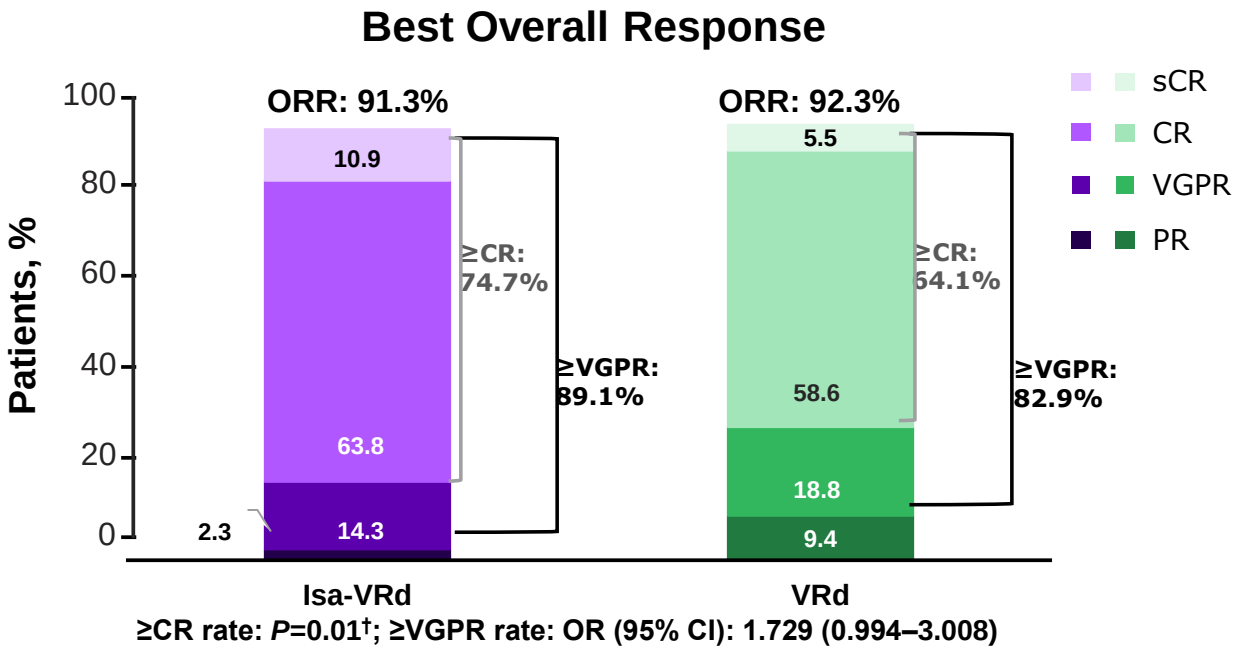
Primary endpoint met: Interim PFS analysis–IRC assessment in ITT population

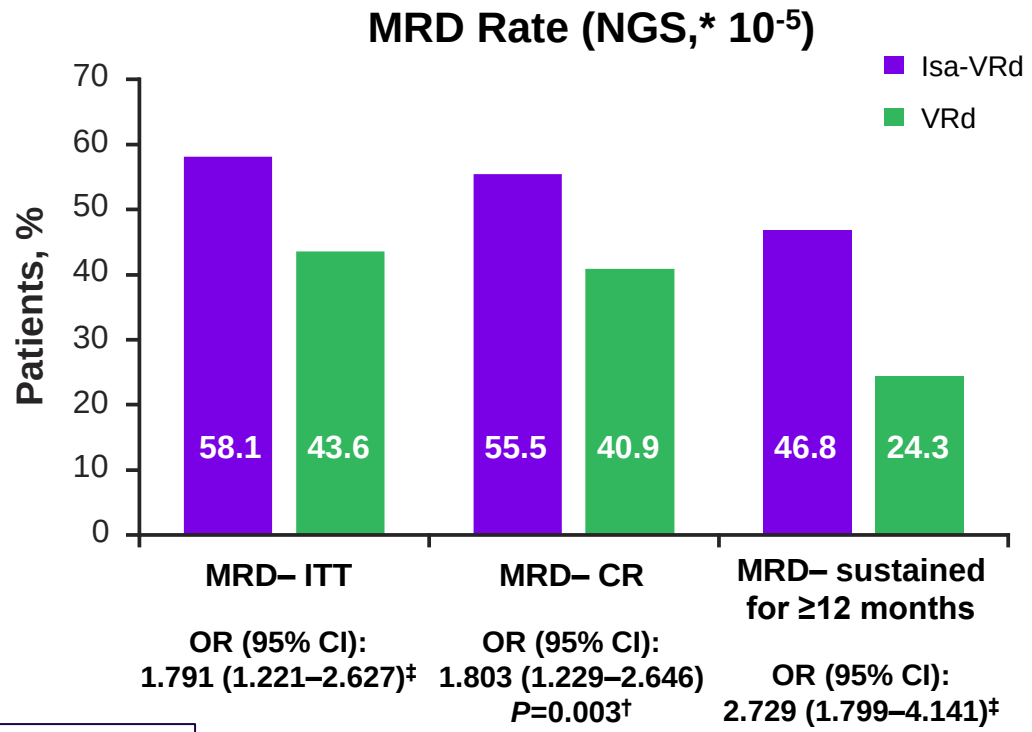


At a median follow-up of 5 years (59.7 months), Isa-VRd followed by Isa-Rd led to a statistically significant reduction in the risk of progression or death by 40.4%

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

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.

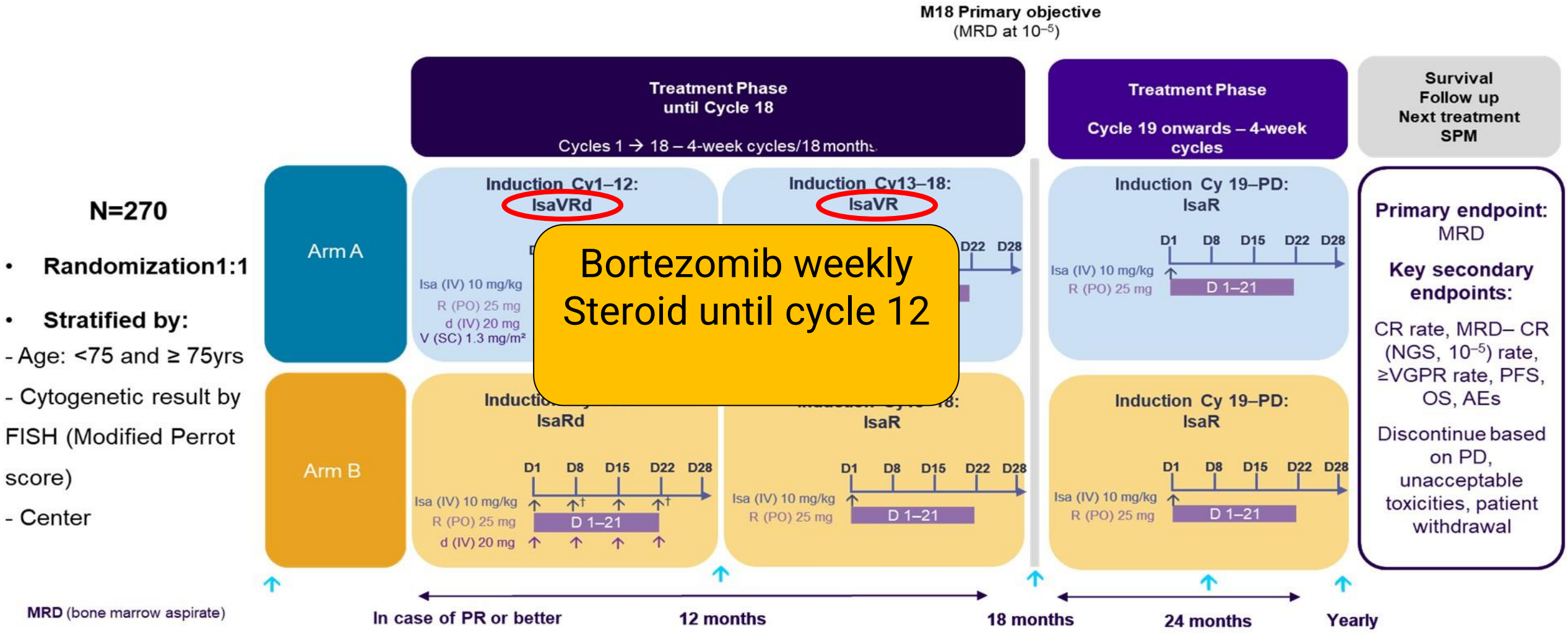
What role does addition of bortezomib play in transplant ineligible upfront treatment?

2024 ASCO® ANNUAL MEETING

Isatuximab plus lenalidomide and dexamethasone with weekly bortezomib versus isatuximab plus lenalidomide and dexamethasone in newly diagnosed transplant ineligible Multiple Myeloma. The BENEFIT (IFM 2020-05) study

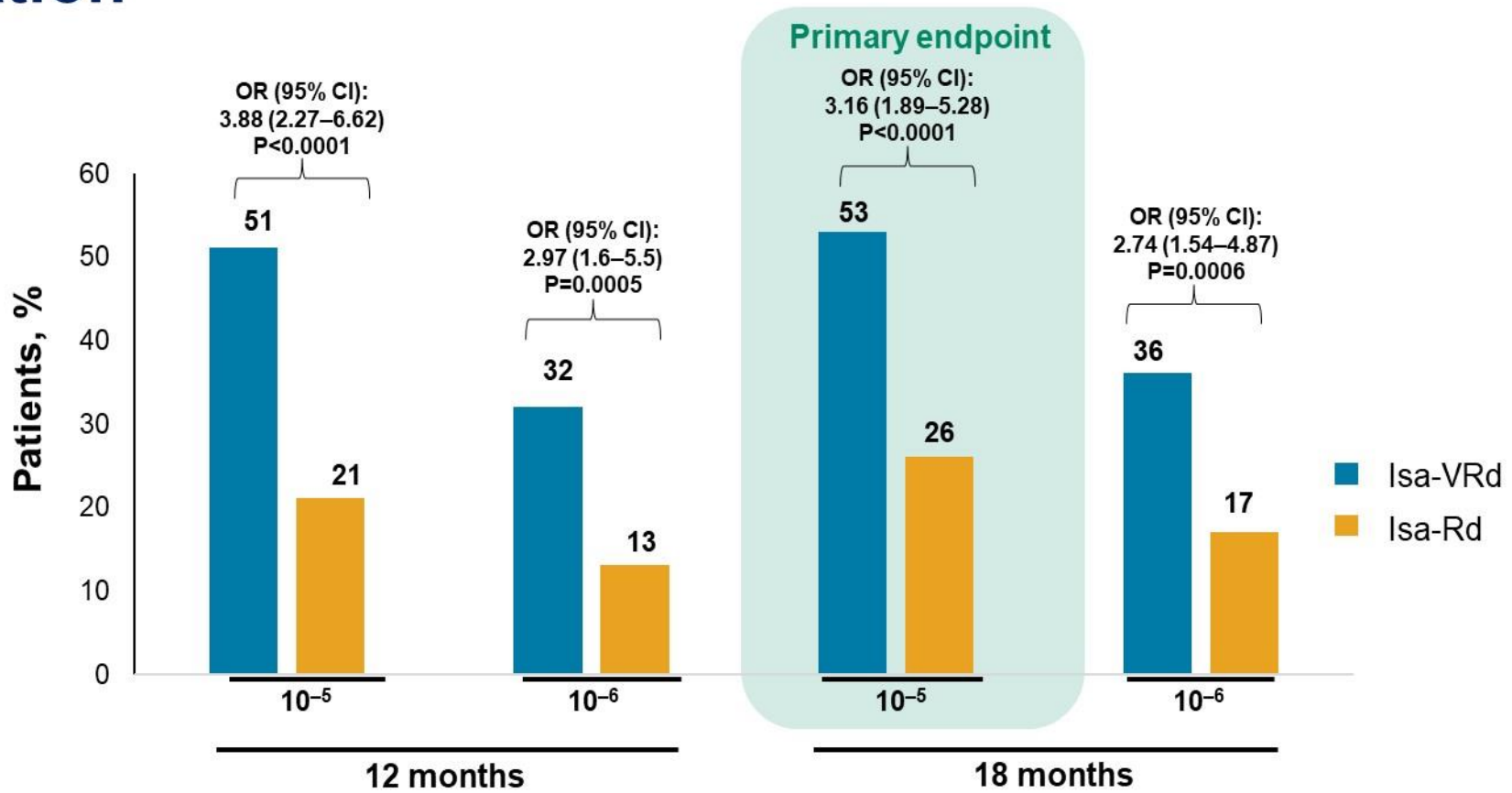
Xavier Leleu[1] and Cyrille Hulin[2], Lambert Jerome[3], Arthur Bobin[1], Aurore Perrot[4], Lionel Karlin[5], Roussel Murielle[6], Lydia Montes[7], Brieuc Cherel[8], Thomas Chalopin[9], Borhane Slama[10], Marie-Lorraine Chretien[11], Kamel Laribi[12], Claire Dingremont[13], Christophe Roul[14], Clara Mariette[15], Sophie Rigaudeau[16], Claire Calmettes[17], Mamoun Dib[18], Mourad Tiab[19], Laure Vincent[20], Jacques Delaunay[21], Alberto Santagostino[22], Margaret Macro[23], Emmanuelle Bourgeois[24], Frederique Orsini-Piocelle[25], Julie Gay[26], Benoit Bareau[27], Noemie Bigot[3], François Vergez[28], Pierre Lebreton[29], Reza Tabrizi[30], Agathe Waultier-Rascalou[31], Laurent Frenzel[32], Ronan Le Calloch[33], Emilie Chalayer[34], Thorsten Braun[35], Florence Lachenal[36], Selim Corm[37], Celine Kennel[38], Rakiba Belkhir[39], Jean-Sebastien Bladé[40], Bertrand Joly[41], Valentine Richez-Olivier[42], Helene Demarquette[43], Daniela Robu-Cretu[44], Laurent Garderet [45], Muriel Newinger-Porte[46], Amine Kasmi[47], Bruno Royer[48], Olivier Decaux[49], Bertrand Arnulf[48], Karim Belhadj[50], Cyrille Touzeau[51], Mohamad Mohty[52], Salomon Manier[53], Philippe Moreau[51], Hervé Avet-Loiseau[28], Jill Corre[28], Thierry Facon[53]

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



†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.

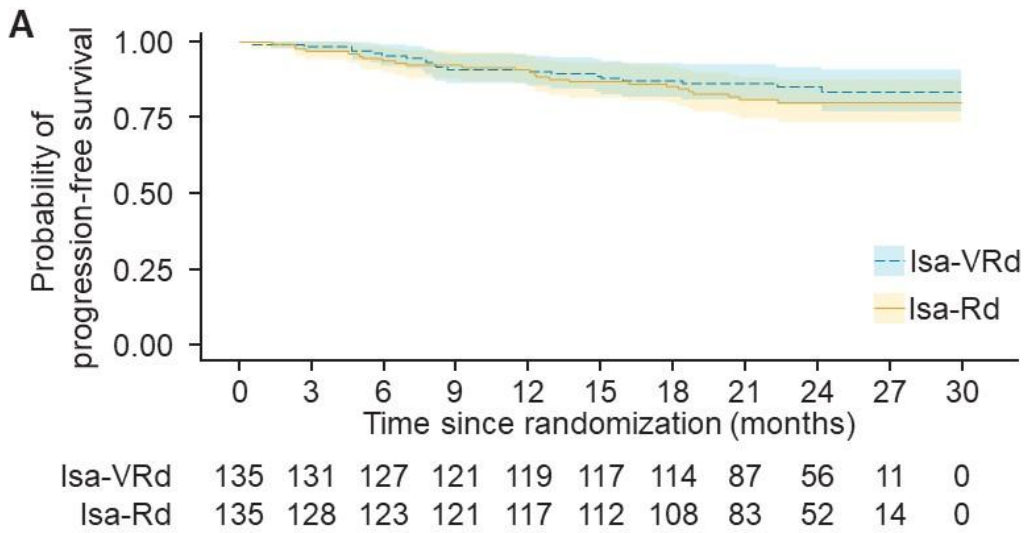
Primary endpoint: MRD–* rate at 18 months – ITT population

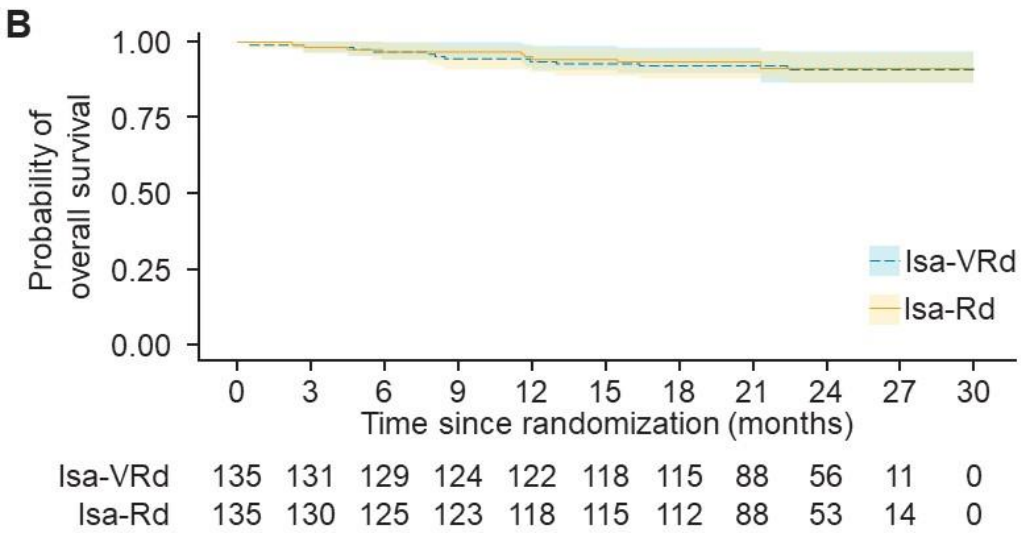


Isa-VRd resulted in deep response rates, with a significant improvement in the MRD at 12 and 18 months, and at 10^{-5} and 10^{-6} in the ITT population

*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.

Survival analysis-IRC assessment in ITT population





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

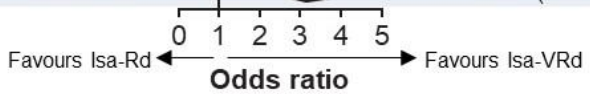
Estimated 24 months OS
91.1% (95%CI 86.1–96.4) for Isa-VRd
91.5% (95%CI 86.5–96.8) for Isa-Rd

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.

MRD subgroup analyses

Subset		Isa-VRd Events/Pts	Isa-Rd Events/Pts	OR (95% CI)	P-value for interaction
Sex	Male	37/74	16/71	3.44 (1.67–7.06)	**0.79**
	Female	34/61	19/64	2.98 (1.43–6.23)	
Age	≤ 75 yr	48/93	22/87	3.15 (1.68–5.93)	**0.95**
	> 75 yr	23/42	13/48	3.26 (1.35–7.86)	
Cytogenetic profile (LP FISH)	LP HR-	62/119	31/124	3.26 (1.9–5.62)	**0.66**
	LP HR+	9/16	4/11	2.25 (0.47–10.88)	
Cytogenetic profile (NGS)	Standard risk	58/107	29/112	3.39 (1.92–5.98)	**0.62**
	High risk	10/22	4/15	2.29 (0.55–9.47)	
ISS	I	27/50	15/51	2.82 (1.24–6.4)	**0.91**
	II	33/64	13/57	3.6 (1.64–7.93)	
	III	11/21	7/27	3.14 (0.93–10.58)	
eGFR (MRDR Formula)	<60	8/19	8/28	1.82 (0.53–6.19)	**0.34**
	≥60	63/116	27/107	3.52 (1.99–6.22)	
	All patients	71/135	35/135	3.17 (1.9–5.29)	



A consistent MRD benefit was observed with Isa-VRd vs Isa-Rd across most subgroups, including difficult-to-treat populations with negative prognostic factors

CI, confidence interval; d, dexamethasone; eGFR, estimated glomerular filtration rate; FISH, fluorescent in situ hybridation; Isa, isatuximab; ISS, international staging system; MRD, minimal residual disease; MDRD, modification of diet in renal disease; NGS, next generation sequencing; OR, odd ratio; R, lenalidomide; V, bortezomib.

PRESENTED BY: Xavier Leleu, MD, PhD

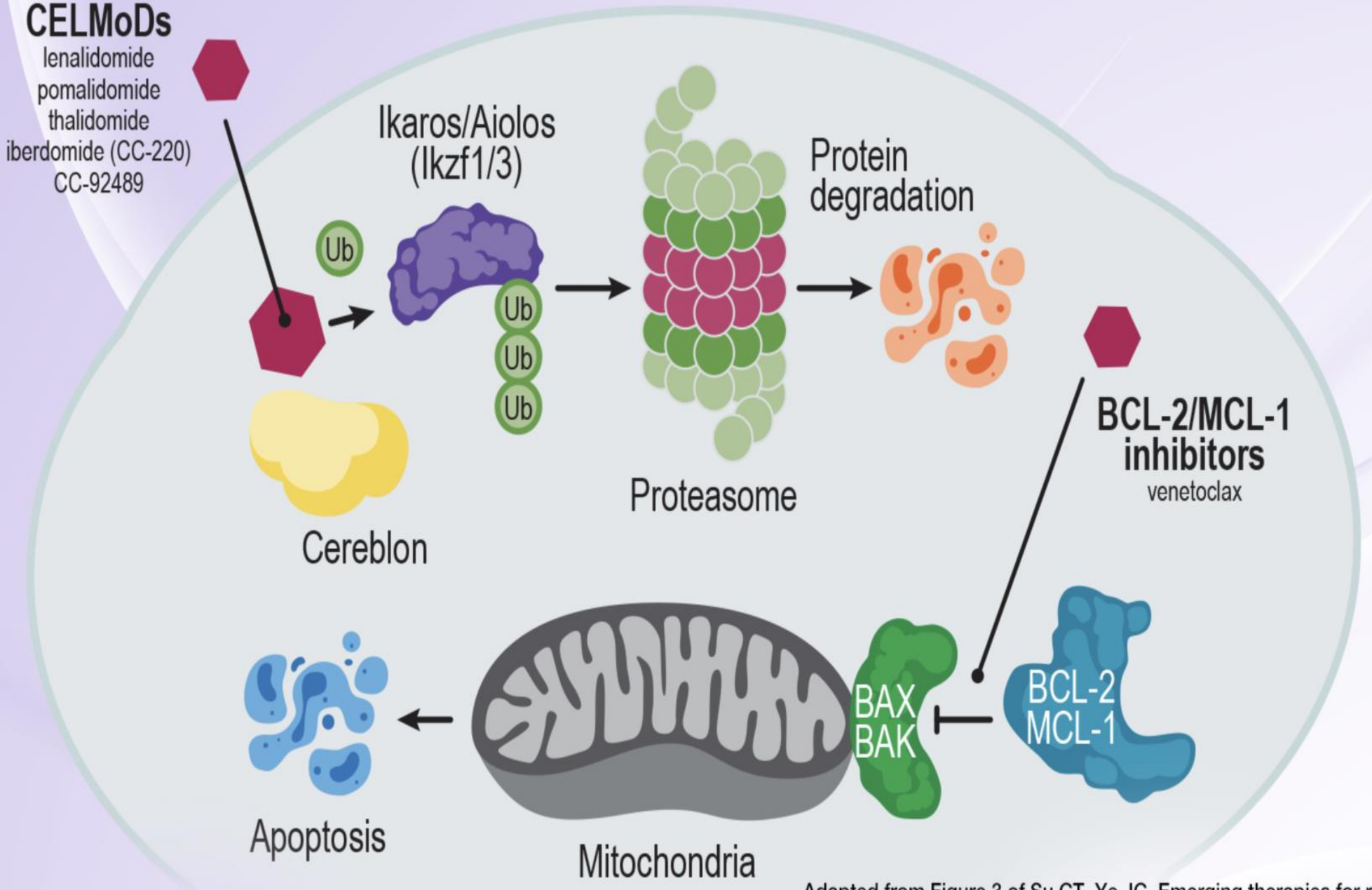
Patterns Across the Trials: Safety

Safety is dependent on the 4th drug being added

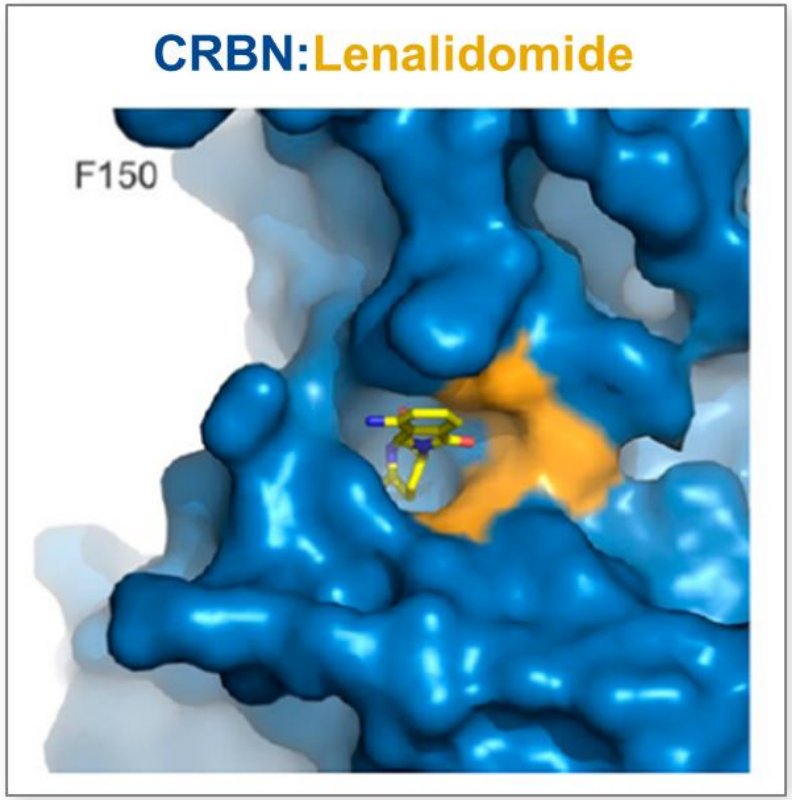
	IMROZ trial		BENEFIT trial		PERSEUS trial	
Combination regimen	Isa-VRd	VRd	Isa-VRd	Isa-Rd	Dara-VRd, transplant	VRd, transplant
Maintenance	Isa-Rd	Rd	Isa-R	Isa-R	Dara-R	R
What is the 4th drug?	Isatuximab	N/A	Bortezomib	N/A	Daratumumab	N/A
Any infection	91% any grade, 45% grade ≥3	87% any grade, 38% grade ≥3	93% any grade, 71% grade ≥2	83% any grade, 68% grade ≥2	86% any grade, 32% grade ≥3	73% any grade, 23% grade ≥3
Pneumonia	30% any grade, 20% grade ≥3	19% any grade, 13% grade ≥3	48% any grade, 35% grade ≥2	47% any grade, 40% grade ≥2	23% any grade, 14% grade ≥3	13% any grade, 8% grade ≥3
Peripheral neuropathy	54% any grade; 7% ≥grade 3	61% any grade; 6% ≥grade 3	52% any grade; 27% ≥grade 2	28% any grade; 10% ≥grade 2	NR	NR

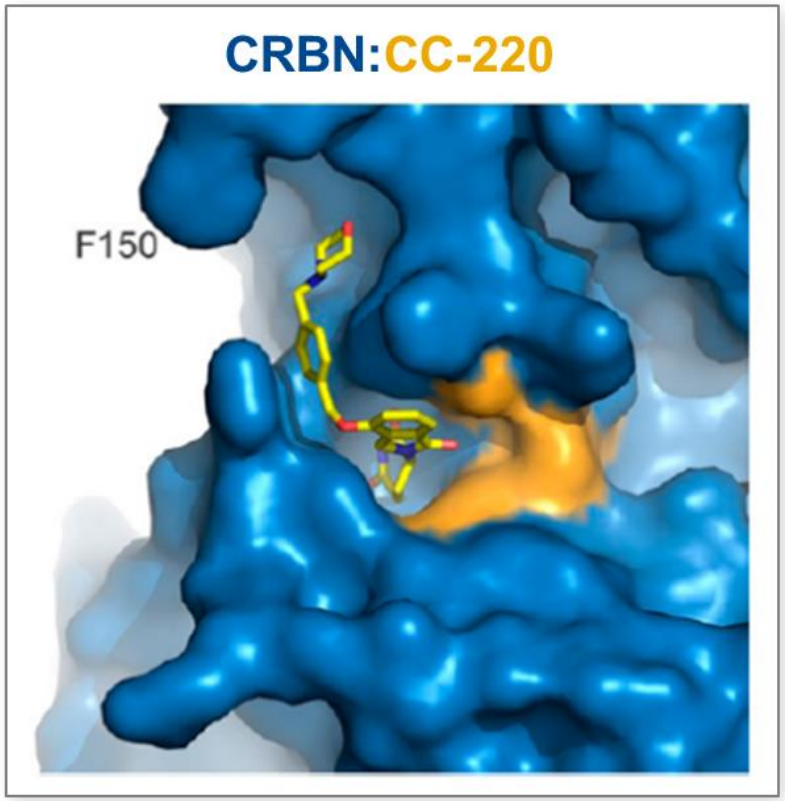
- Infections were manageable and did not result in an excess risk of death
- Grade 2 peripheral neuropathy is characterized by moderate symptoms that limit instrumental activities of daily living (ADLs)

Relapsed Refractory



Adapted from Figure 3 of Su CT, Ye JC. Emerging therapies for relapsed/refractory multiple myeloma: CAR-T and beyond. *J Hematol Oncol.* 2021;14(1):115.





Compound	CRBN Binding Affinity (IC_{50})[3]	Active CRBN Confirmation[4]
Lenalidomide	~1.5uM	20-25%
Pomalidomide	~1.2uM	20-25%
Iberdomide	~0.06uM	50%

1. Dimopoulos et al. Ann Oncol 2021 ; 2 Lonial et al. Lancet Haematol 2022. 3. Matyskiela ME, et al. J Med Chem 2018;61:535-542. 4. Watson ER, et al. Science 2022;378:549-553.

2024 ASCO® ANNUAL MEETING

All-oral triplet iberdomide ixazomib and dexamethasone in elderly patients with multiple myeloma at first relapse : results of the IFM phase 2 study I2D

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I2D study design

Key inclusion criteria:

- **Age ≥ 70**
- **Relapsed myeloma ; 1 prior line of therapy**
- ECOG 0-2
- Creatinine Cl ≥ 30 mL/min
- ANC >1000 G/L ; Plt > 75 G/L

Objectives:

- Primary Objective :
Very good partial response (VGPR) rate

- Secondary Objectives:
Safety, ORR, DOR, PFS, OS

Cycle 1 and 2	Cycle 3 to 6	Cycle 7 +
Iberdomide 1.6 mg D1-D21 **Ixazomib** 3 mg D1,8,15 **Dexamethasone** 20mg D1,8,15,22	**Iberdomide** 1.6 mg D1-D21 **Ixazomib** 3 mg D1,8,15 **Dexamethasone** 10mg D1,8,15,22	**Iberdomide** 1.6 mg D1-D21 **Ixazomib** 3 mg D1,8,15

28-day cycle; treatment given until disease progression or unacceptable toxicity

Patient characteristics

	N=70
Median age (range), years	76 (70-87)
Age >80 (%)	20 (29)
ECOG PS (n,%)	
0-1	65 (94%)
2	4 (6%)
IMWG frailty score (n,%)	
0-1(fit/intermediate fit)	35 (50%)
≥2 (frail)	35 (50%)
High-risk cytogenetics (n=54)	
t(4;14)	8 (15%)
del(17p)*	10 (18.5%)

	N=70
Median time from MM diagnosis to study enrolment (range), months	28 (5-130)
Prior proteasome inhibitor	31 (44%)
Prior lenalidomide	61 (87%)
Len refractory	52 (74%)
Prior anti CD38	28 (40%)
Anti CD38 refractory	26 (37%)
Anti CD38 + Len refractory	26 (37%)

** positivity cut-off : 30%*

I2D Safety

Hematologic treatment related AE:

	Any grade n(%)	Grade 3/4 n(%)
Neutropenia	34 (54%)	29 (46%)
Anemia	7 (11%)	1 (2%)
Thrombocytopenia	7 (11%)	6 (9%)

AE leading to treatment discontinuation (n=4):
Skin rash (n=1), cytopenia (n=2), peripheral neuropathy (n=1)

Grade 3-4 infection (n=5)
COVID-19 (n=2) ; pneumonia (n=2) , septicemia (n=1)

Death due to AE (n=2)
Septic shock (n=2)

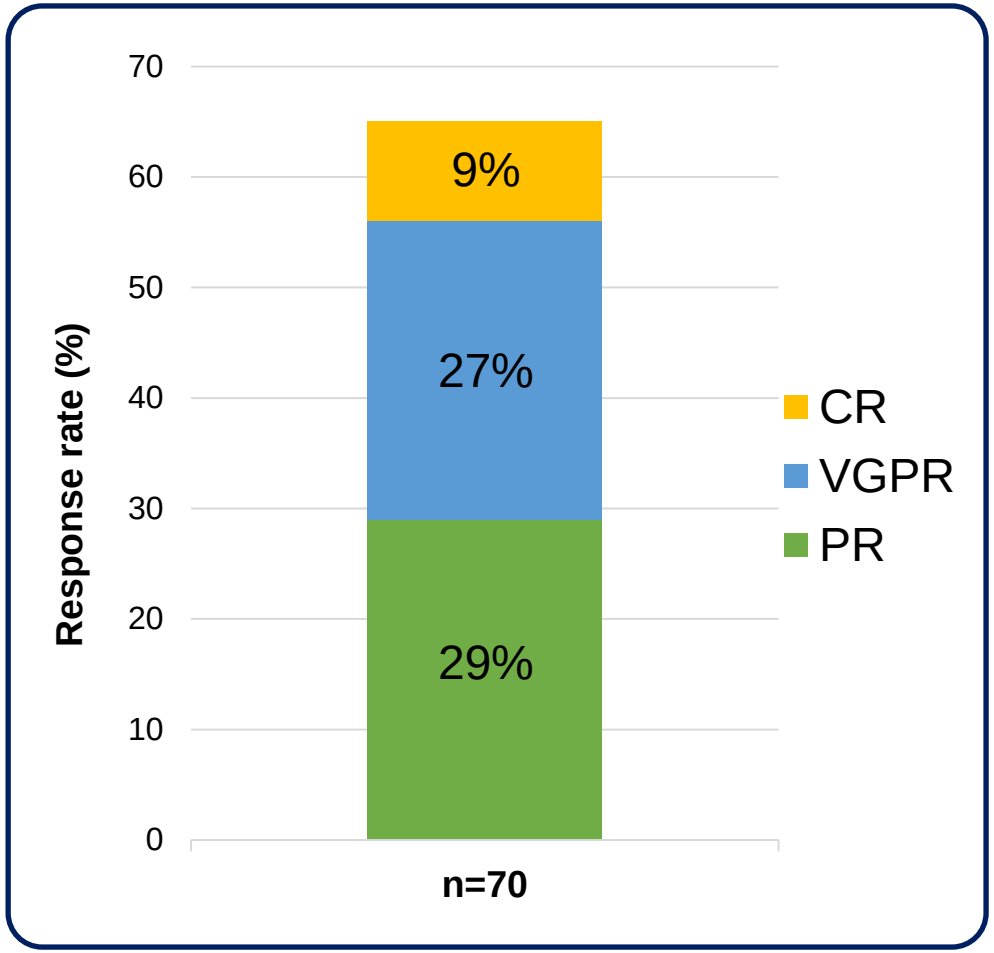
Most common (>5%) non hematologic treatment related AE:

	Any grade n(%)	Grade 3/4 n(%)
GI disorders	23 (36%)	3 (5%)
Infection	19 (30%)	5 (8%)
Fatigue	14 (22%)	2 (4%)
Insomnia/sleep disorders	14 (22%)	0
Peripheral neuropathy	14 (22%)	0
Muscle spasms	7 (11%)	1 (2%)
Skin rash	6 (9%)	3 (5%)

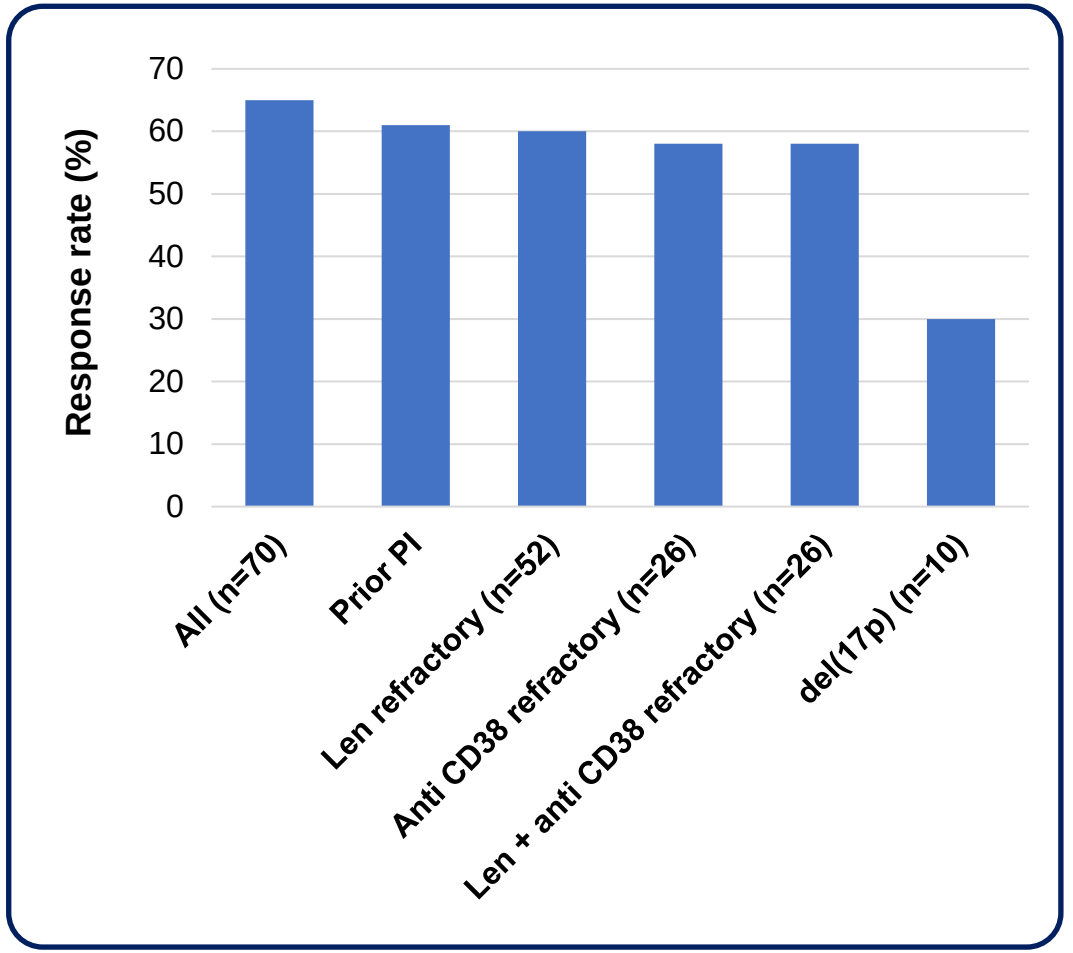
AE, adverse event ; GI, gastro intestinal

I2D Response rates

Overall response rate : 65%

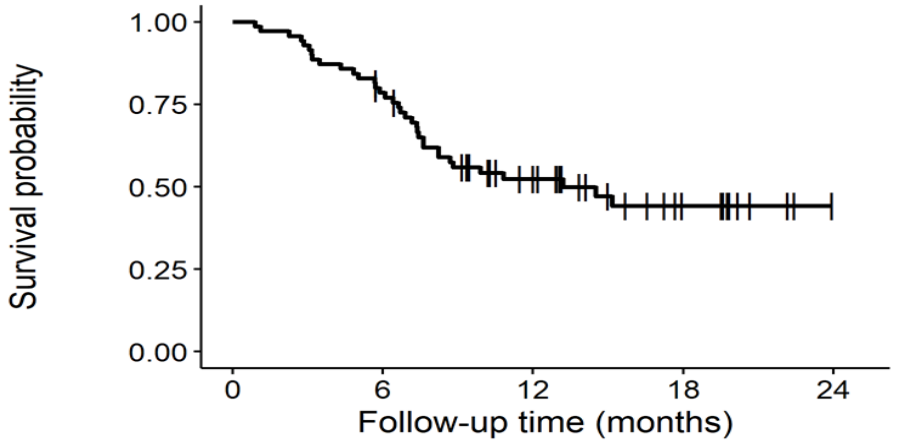


Subgroup analysis of ORR



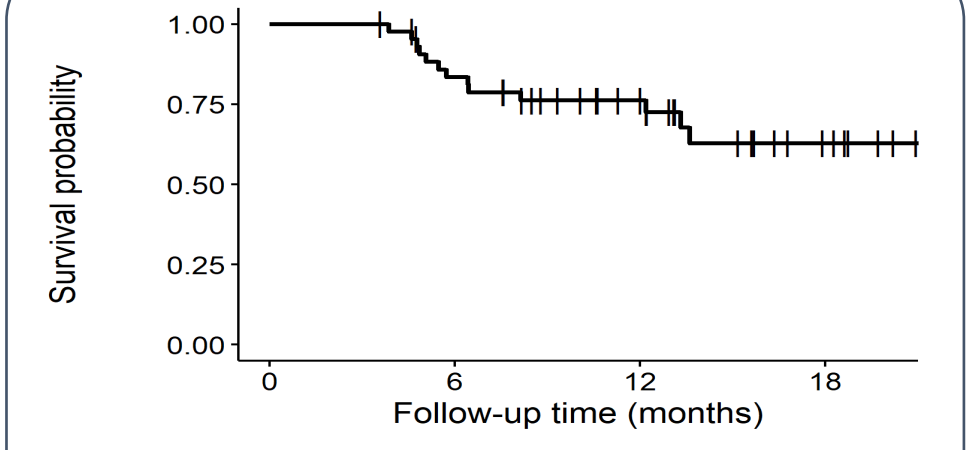
Progression-free survival and duration of response

Progression-free survival



12-month PFS : 52% (42% - 66%)

Duration of response

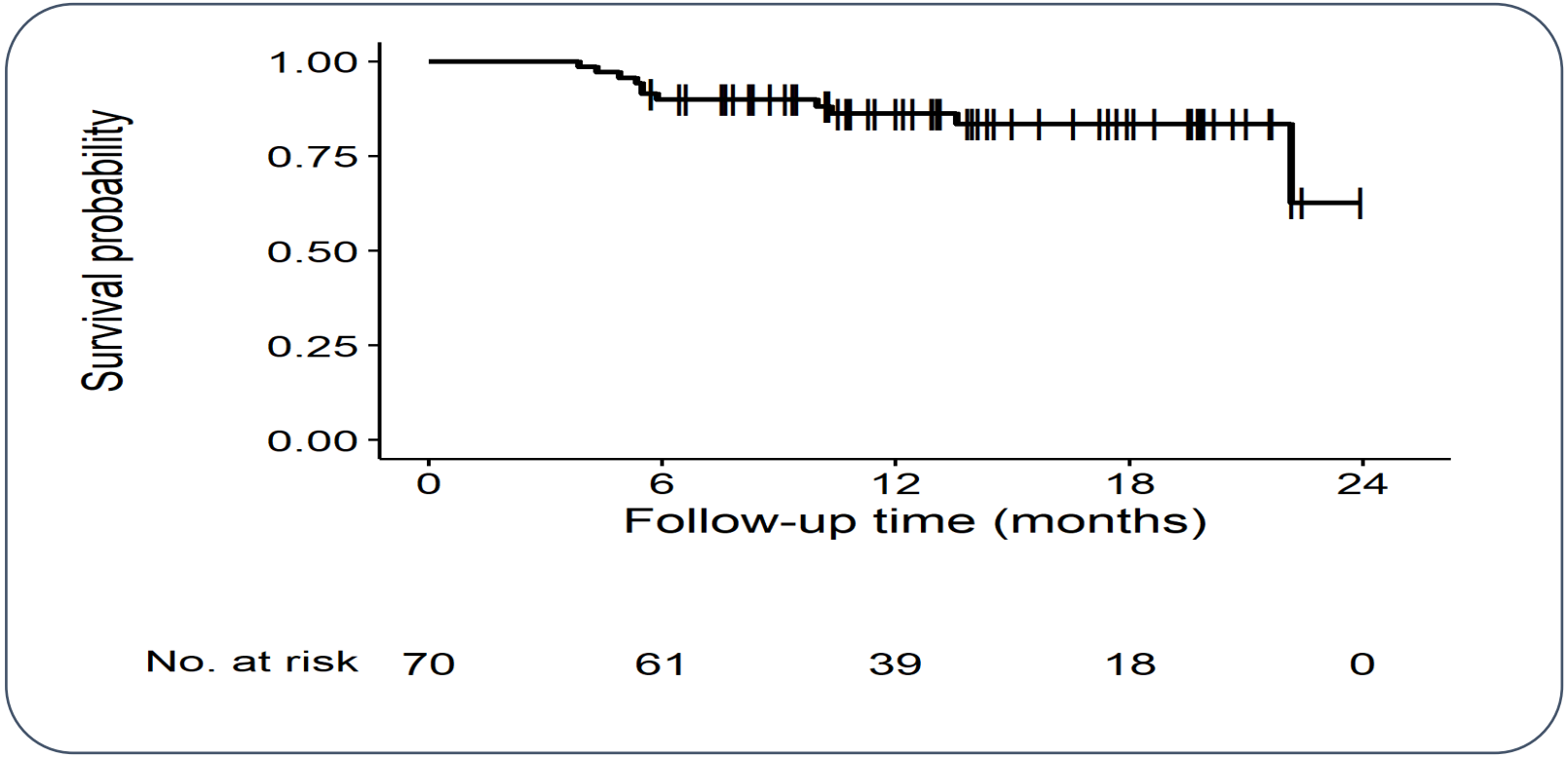


12-month DOR : 76% (64% - 90%)

Median follow-up: 14 months

Data cut-off: March 2024

I2D Overall survival



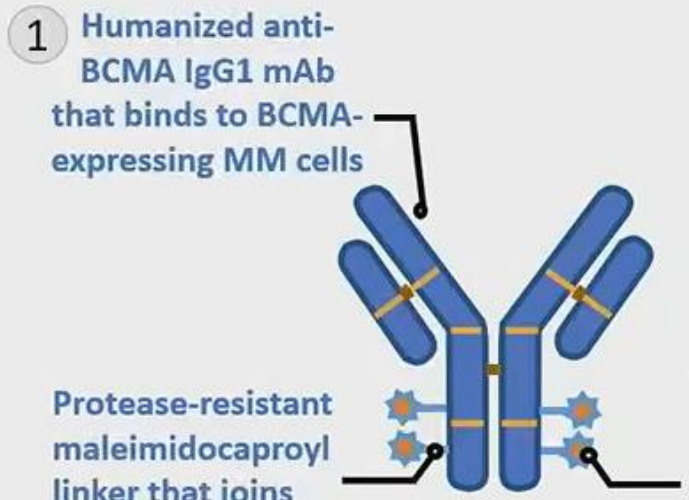
12-month OS : 86% (78% - 95%)

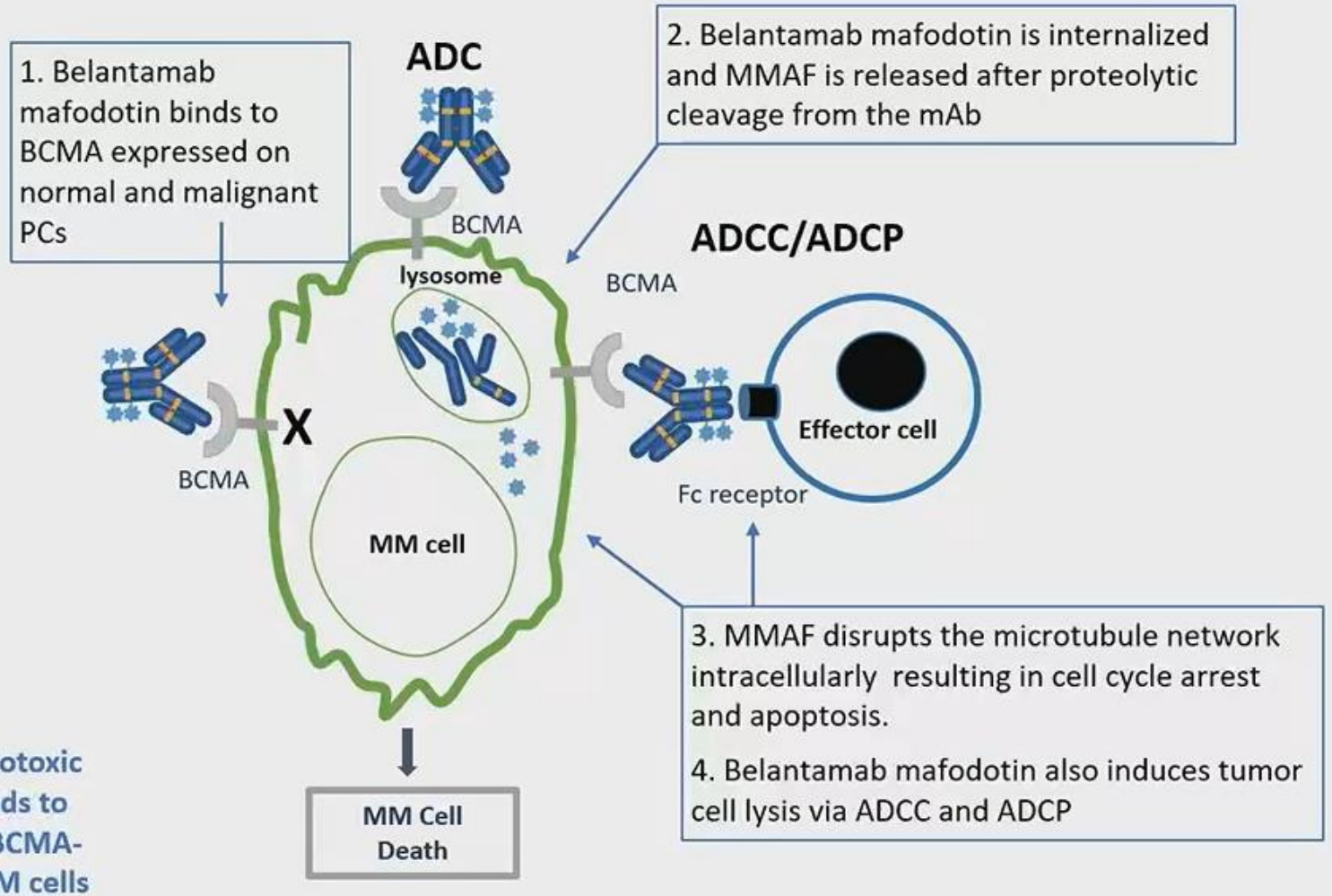
Median follow-up: 14 months

Data cut-off: March 2024

Belantamab Mafodotin: Overview

- **Belantamab mafodotin**: a BCMA-directed antibody and microtubule inhibitor conjugate, comprising 3 components

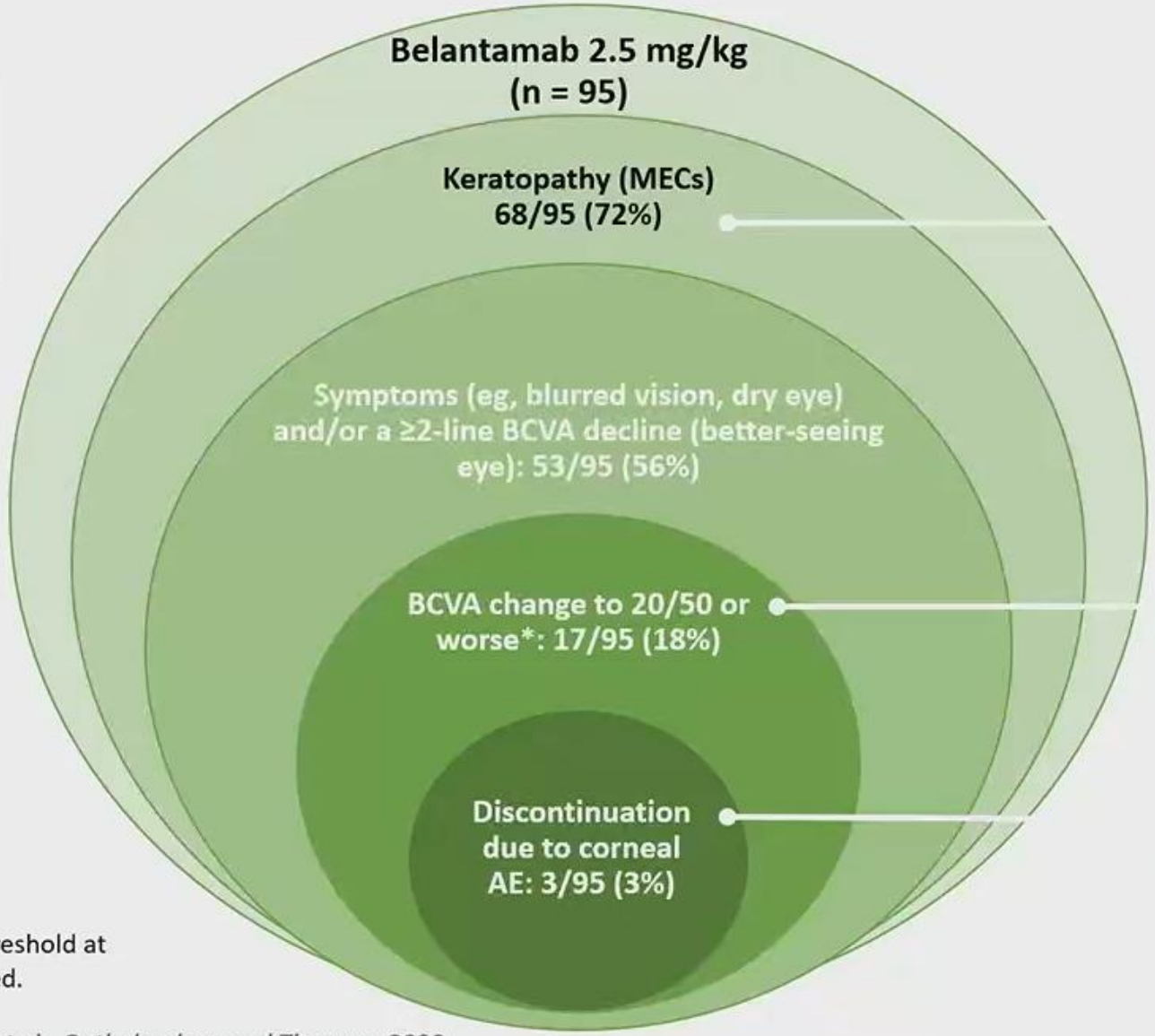




Tai. Blood. 2014;123:3128. Farooq. Ophthalmol Ther. 2020;9:889.

The unintended consequences of a payload

1 patient developed grade 4 corneal ulcer



In patients with keratopathy (MECs) events grade ≥2 per KVA, 48% (29/60) had >1 event

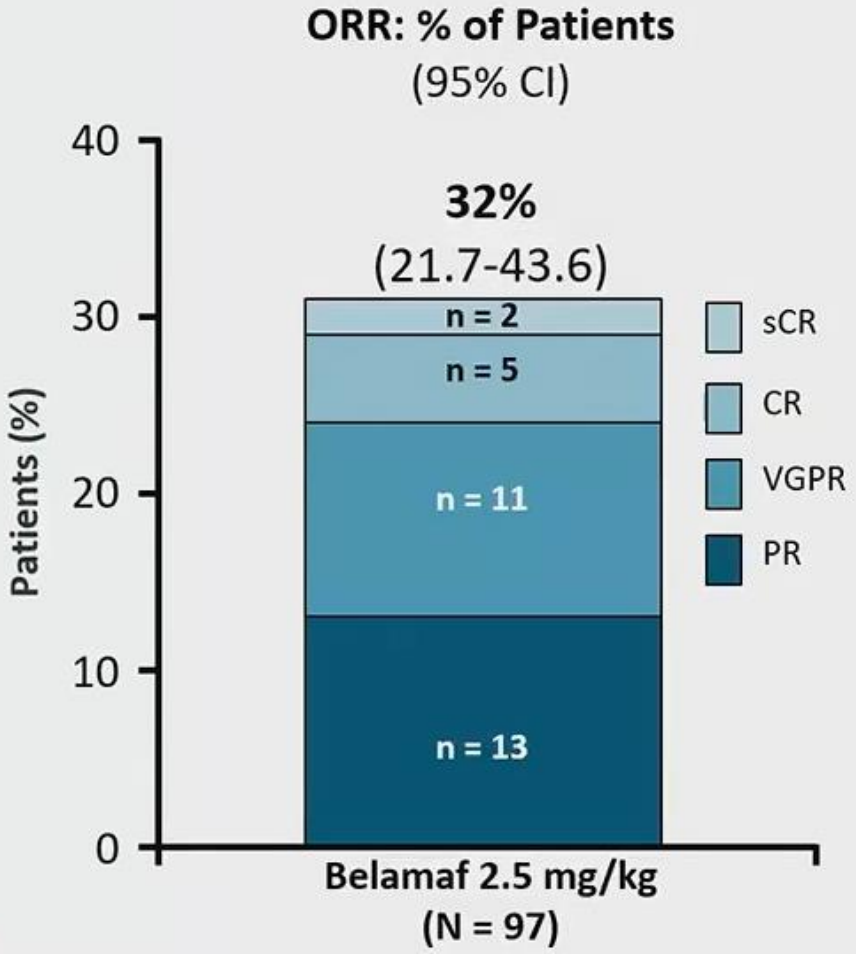
Of these patients, 76% (13/17) had 1 event and 24% (4/17) had 2 events (no patients had >2 events)

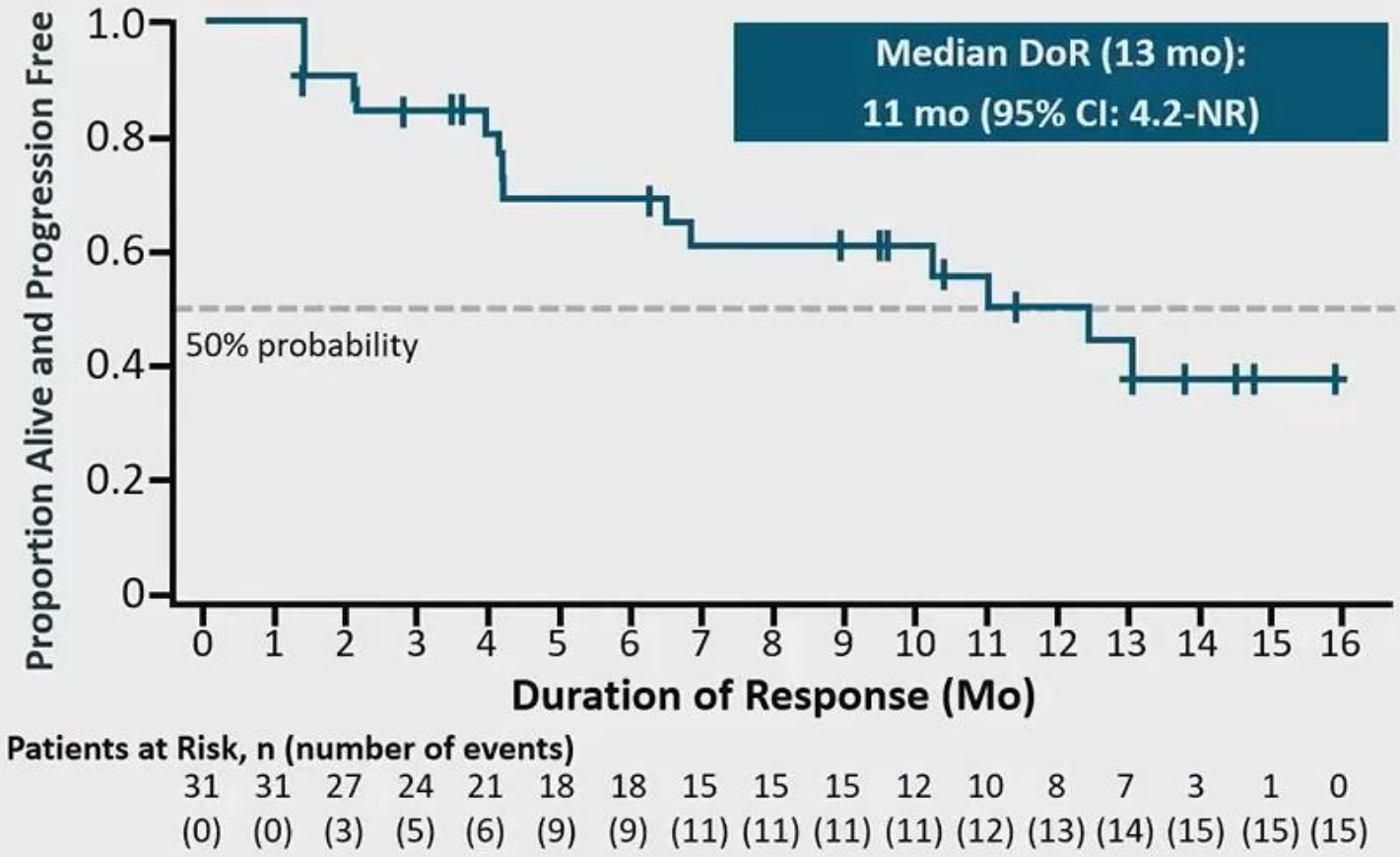
1 patient discontinued due to keratopathy (MECs), 1 due to blurred vision, and 1 due to reduced BCVA

*Better-seeing eye; represents threshold at which ADL (eg, driving) are affected.

Lonial. ASH 2020. Abstr 3224; Farooq et al, *Opthalmology and Therapy* 2020

Phase II DREAMM-2: Response and DoR at 13 Mo of Follow-up, Belantamab Mafodotin 2.5 mg/kg

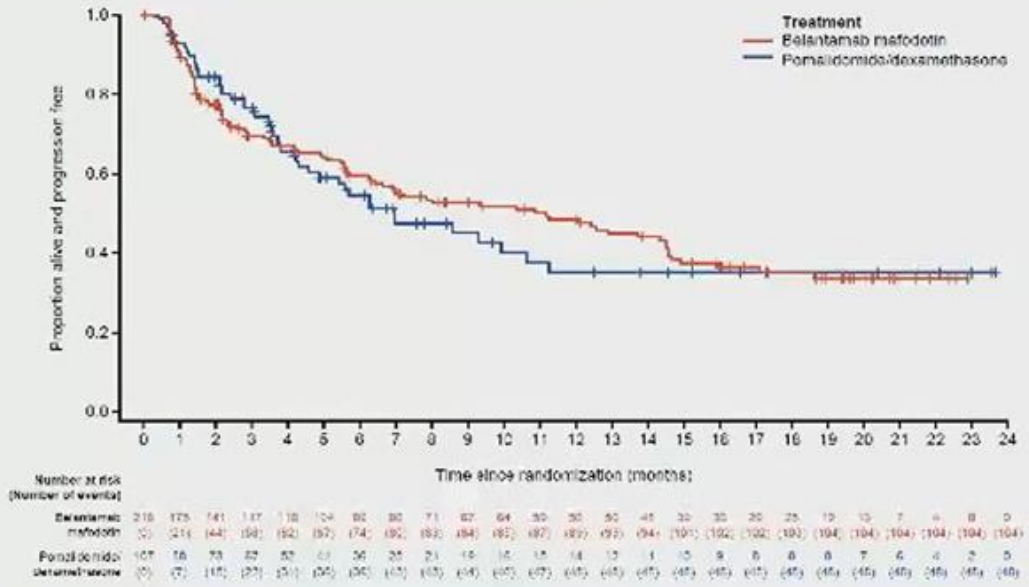




Lonial. Cancer 2021;[Epub].

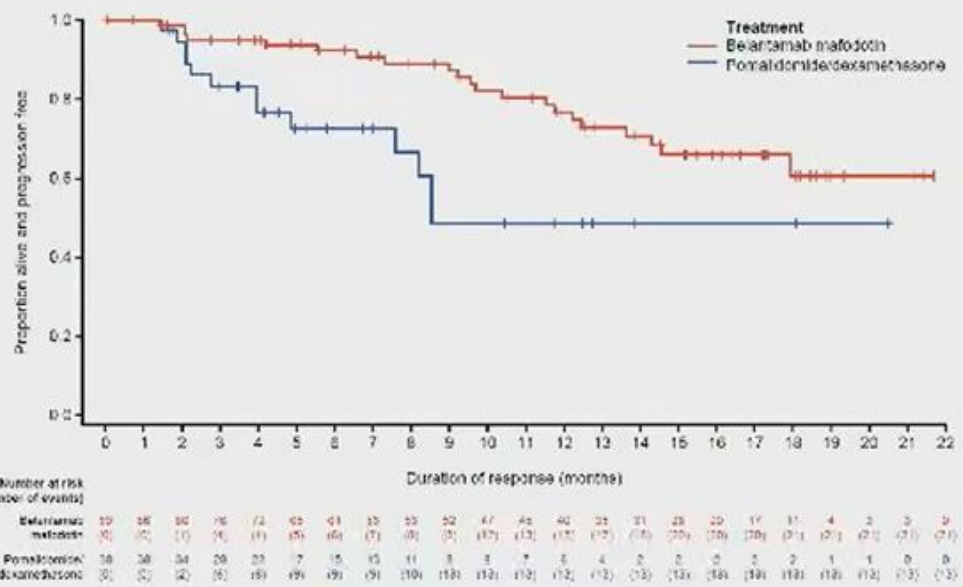
The DREAMM-3 (Bela vs PD in late relapse) did not meet its primary objective of superior PFS

PFS*



	Belantamab mafodotin	Pd
mPFS, months (95% CI)	11.2 (6.4-14.5)	7.0 (4.6-10.6)
HR (95% CI, p value)	1.03 (0.72-1.47, p=0.558)	

DOR*,†



	Belantamab mafodotin	Pd
mDOR, months (95% CI)	NR (17.9-NR)	8.5 (7.6-NR)

mPFS was longer for belantamab mafodotin than for Pd, but HR did not reach statistical significance

- *Median follow-up was 11.5 months for belamafab mafodotin and 10.8 months for Pd. † DOR was a secondary endpoint and was not tested for statistical significance.
- CI, confidence interval; DOR, duration of response; HR, hazard ratio; mDOR, median duration of response; mPFS, median progression-free survival; NR, not reached; Pd, pomalidomide/dexamethasone; PFS, progression-free survival.
- Weisel K et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2022; Chicago, IL. Presentation 8007.

2024 ASCO® ANNUAL MEETING

Results from the randomized phase 3 DREAMM-8 study of belantamab mafodotin plus pomalidomide and dexamethasone vs pomalidomide plus bortezomib and dexamethasone in relapsed/refractory multiple myeloma

Suzanne Trudel,[1] Meral Beksac,[2] Luděk Pour,[3] Sosana Delimpasi,[4] Hang Quach,[5] Vladimir I. Vorobyev,[6] Michele Cavo,[7] Kazuhito Suzuki,[8] Pawel Robak,[9] Kristin Morris,[10] Amy Phillips-Jones,[11] Xiaoou L. Zhou,[12] Giulia Fulci,[12] Neal Sule,[13] Brandon E. Kremer,[13] Joanna Opalinska,[13] Maria-Victoria Mateos Manteca,[14] Meletios A. Dimopoulos[15]

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Study Design

Recruitment period
October 2020 to December 2022

Treatment period
Until PD, death, unacceptable toxicity, end of study, or withdrawal of consent

Eligibility criteria

- Adults with MM
- ≥1 prior line of MM therapy including LEN
- Documented PD during or after their most recent therapy
- No prior treatment with anti-BCMA or pomalidomide; not refractory/intolerant to bortezomib

N=302

1:1 randomization

BPd (Q4W)

Belantamab mafodotin
2.5 mg/kg IV (cycle 1) then 1.9 mg/kg IV Q4W from cycle 2 onward
+
Pomalidomide 4 mg orally on days 1-21 (28-day cycles)
+
Dexamethasone 40 mg[a] on days 1, 8, 15, and 22

PVd (Q3W)

Bortezomib
1.3 mg/m^2 SC on days 1, 4, 8, and 11 of cycles 1-8 then days 1 and 8 (21-day cycles)
+
Pomalidomide 4 mg orally on days 1-14 (21-day cycles)
+
Dexamethasone 20 mg[a] on the day of and day after bortezomib

End-of-treatment visit

Primary endpoint:
PFS (IRC assessed per IMWG)

Key secondary endpoints:
OS, MRD negativity, DOR

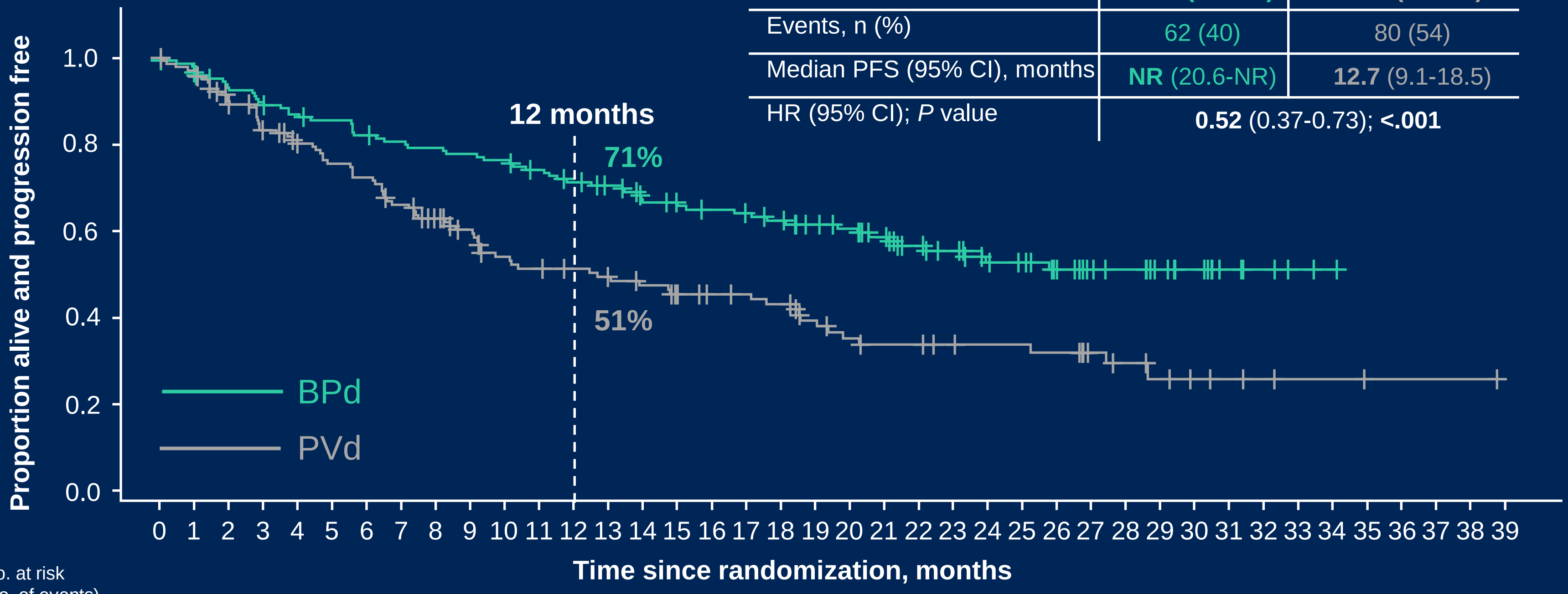
Additional secondary endpoints include:
ORR, CRR, ≥VGPR,TTBR, TTR, TTP, PFS2, AEs, ocular findings, HRQOL, and PROs

Stratification[b]:
- Prior lines of treatment (1 vs 2 or 3 vs ≥4)
- Prior bortezomib (yes vs no)
- Prior anti-CD38 therapy (yes vs no)

AE, adverse event; BCMA, B-cell maturation antigen; BPd, belamaf, pomalidomide, and dexamethasone; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; HRQOL, health-related quality of life; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; IV, intravenous; LEN, lenalidomide; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival on subsequent line of therapy; PRO, patient-reported outcome; PVd, pomalidomide, bortezomib, and dexamethasone; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous; TTBR, time to best response; TTP, time to progression; TTR, time to response; VGPR, very good partial response.
[a] Patients aged >75 years, with comorbidities, or intolerant to 40 mg dose in Arm A or 20 mg dose in Arm B could have dose level reduced to half per investigator discretion. [b] Some patients were stratified by ISS status (I vs II/III); the protocol was amended on 20 April 2021 to replace this randomization factor with prior anti-CD38 treatment (yes vs no).

BPd Led to a Significant PFS Benefit vs PVd

PFS	BPd (N=155)	PVd (N=147)
Events, n (%)	62 (40)	80 (54)
Median PFS (95% CI), months	**NR** (20.6-NR)	**12.7** (9.1-18.5)
HR (95% CI); *P* value	**0.52** (0.37-0.73); **<.001**	



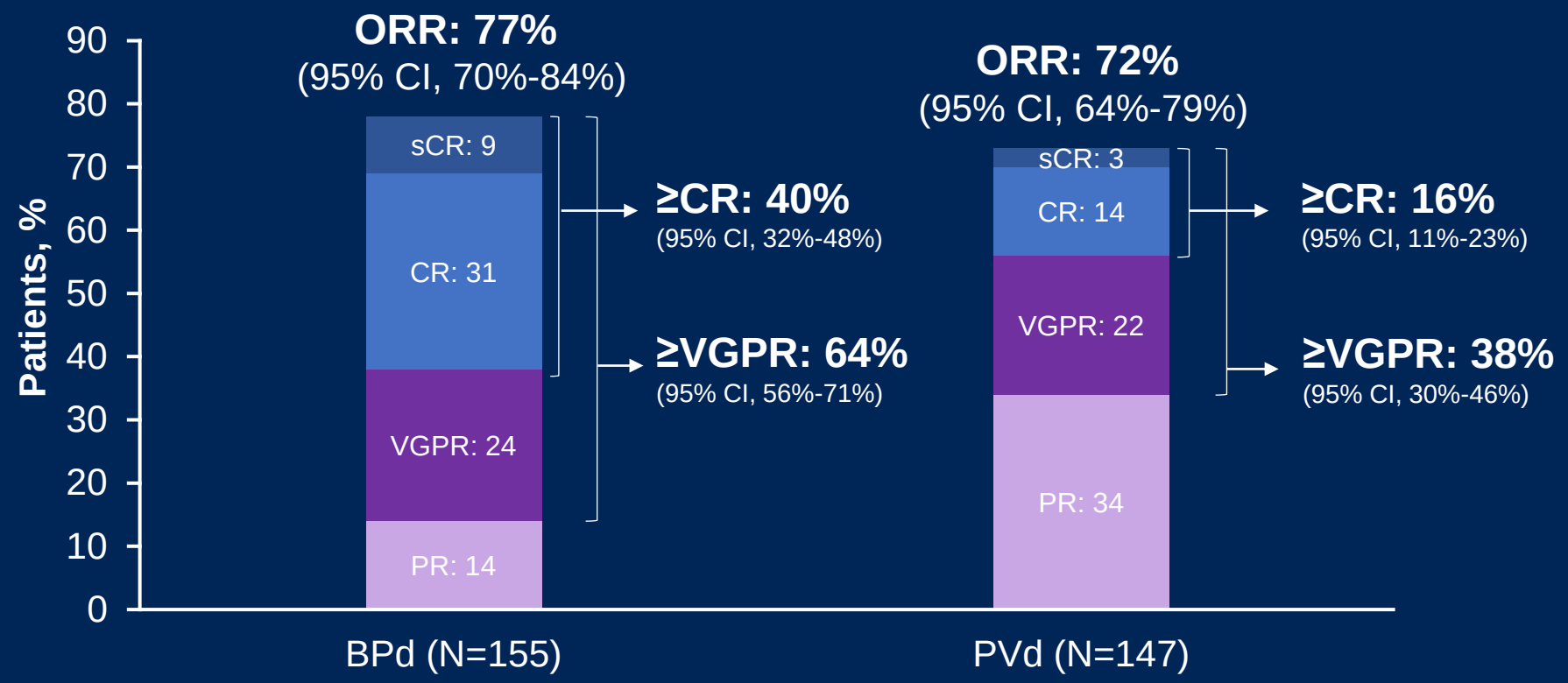
No. at risk (no. of events)

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
BPd	155 (0)	143 (5)	135 (10)	130 (15)	125 (19)	122 (21)	117 (26)	113 (28)	111 (30)	109 (32)	107 (34)	102 (37)	97 (41)	93 (42)	82 (47)	80 (47)	77 (49)	75 (50)	72 (52)	67 (53)	64 (54)	59 (56)	50 (58)	45 (59)	38 (61)	36 (61)	28 (62)	23 (62)	21 (62)	16 (62)	13 (62)	8 (62)	4 (62)	2 (62)	1 (62)	0 (62)	0 (62)	0 (62)	0 (62)	0 (62)
PVd	147 (0)	138 (4)	123 (14)	111 (23)	102 (27)	96 (33)	92 (37)	83 (45)	75 (49)	68 (52)	59 (59)	56 (62)	54 (62)	51 (64)	47 (66)	43 (68)	40 (68)	39 (68)	37 (70)	30 (73)	25 (76)	22 (77)	22 (77)	19 (77)	18 (77)	18 (77)	17 (78)	13 (78)	11 (79)	7 (80)	5 (80)	4 (80)	3 (80)	2 (80)	2 (80)	1 (80)	1 (80)	1 (80)	1 (80)	0 (80)

BPd led to a statistically significant and clinically meaningful reduction in risk of disease progression or death vs PVd (HR, 0.52; 95% CI, 0.37-0.73; *P*<.001)

Median follow-up, 21.8 months (range, 0.03-39.23 months)
The treatment effect (HR and corresponding 95% CIs) was estimated using the stratified Cox proportional hazards model, and the *P* value was produced based on the 1-sided stratified log-rank test. Stratified analyses were adjusted for number of prior lines of therapy and prior bortezomib use.
BPd, belamaf, pomalidomide, and dexamethasone; HR, hazard ratio; NR, not reported; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone.

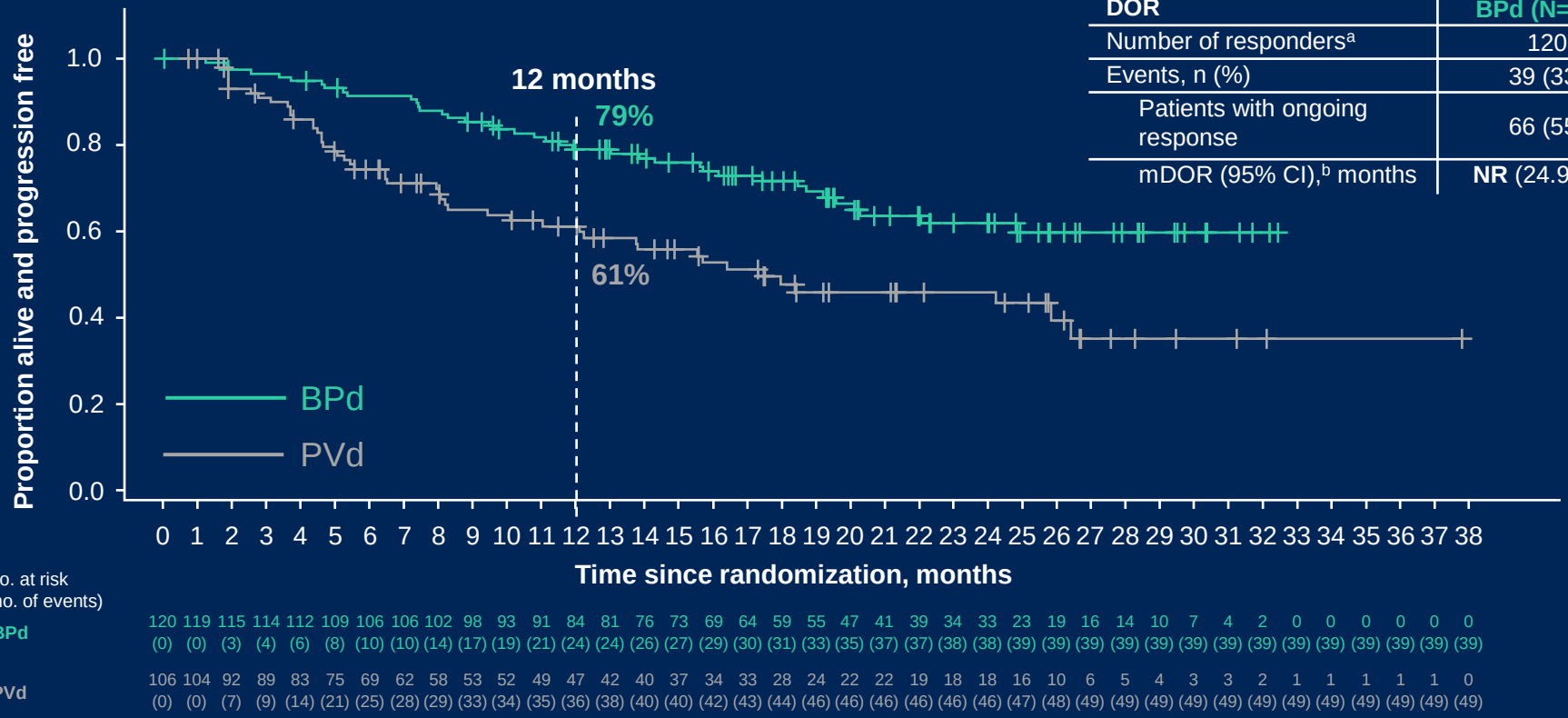
Deeper Responses With BPd vs PVd



The CR or better rate in the BPd arm was more than double that reported in the PVd arm

CIs were based on the exact method. All percents are based on the ITT population.
BPd, belamaf, pomalidomide, and dexamethasone; CR, complete response; ITT, intent to treat; ORR, objective response rate; PR, partial response; PVd, pomalidomide, bortezomib, and dexamethasone; sCR, stringent complete response; VGPR, very good partial response.

Longer Duration of Response With BPd vs PVd



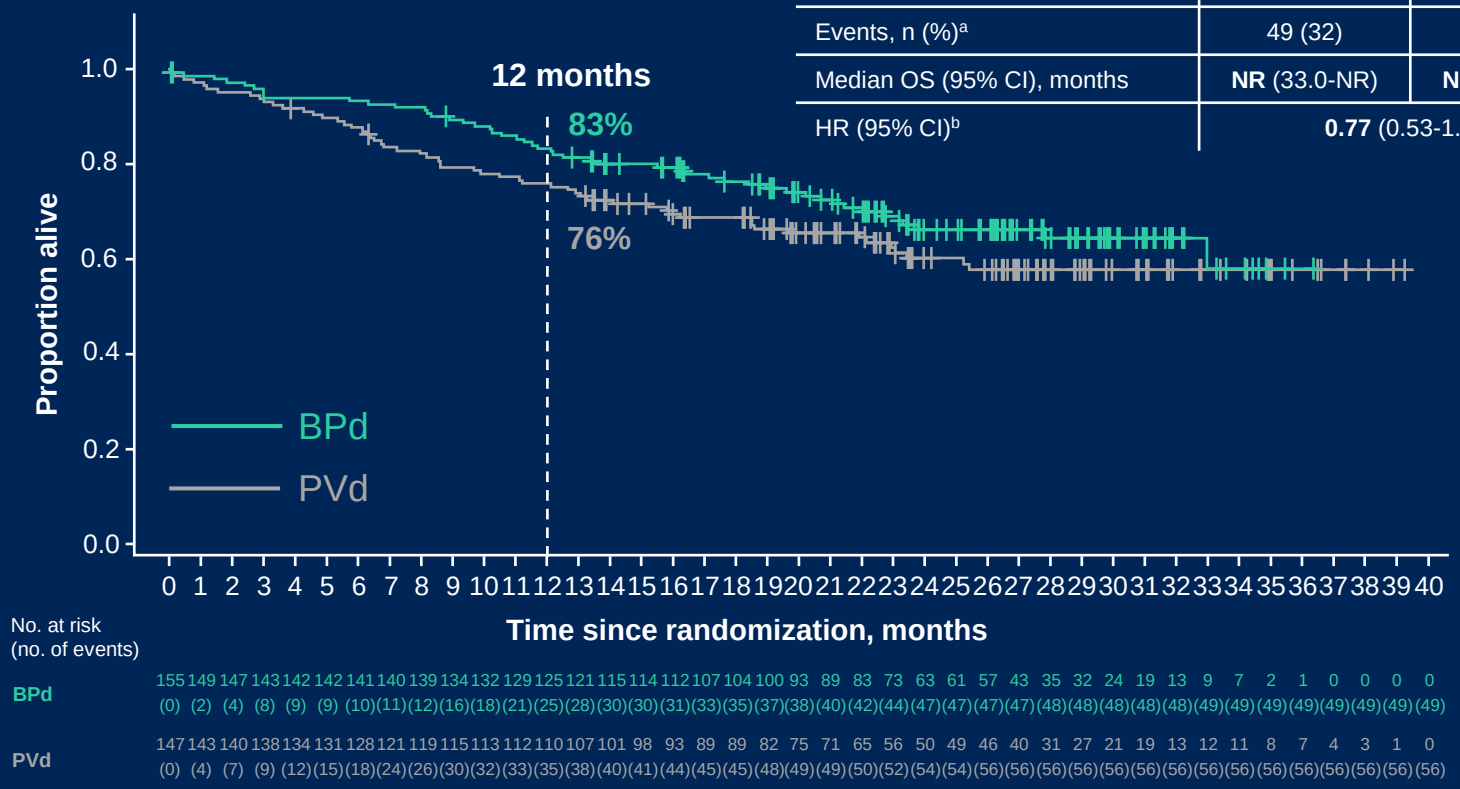
DOR	BPd (N=155)	PVd (N=147)
Number of responders[a]	120	106
Events, n (%)	39 (33)	49 (46)
Patients with ongoing response	66 (55)	33 (31)
mDOR (95% CI),[b] months	**NR** (24.9-NR)	**17.5** (12.1-26.4)

An early and consistent separation of DOR curves was observed favoring BPd vs PVd.
Follow-up for progression or death was ongoing in over half of the BPd responders at the data cutoff

Duration of response is defined as the time from first documented evidence of PR or better until progressive disease or death due to any cause.
BPd, belamaf, pomalidomide, and dexamethasone; DOR, duration of response, mDOR, median duration of response; NR, not reported; PR, partial response; PVd, pomalidomide, bortezomib, and dexamethasone.
[a] Percentages are based on the number of responders. [b] CIs estimated using the Brookmeyer-Crowley method.

Positive OS Trend Favoring BPd vs PVd

Interim OS	BPd (N=155)	PVd (N=147)
Events, n (%)[a]	49 (32)	56 (38)
Median OS (95% CI), months	**NR** (33.0-NR)	**NR** (25.2-NR)
HR (95% CI)[b]	**0.77** (0.53-1.14)	



Subsequent antimyeloma therapy, n (%)[c]	ITT population	
	BPd (N=155)	PVd (N=147)
Steroids	37 (24)	59 (40)
Anti-CD38 antibodies	**23 (15)**	**49 (33)**
Proteasome inhibitor	26 (17)	36 (24)
Immunomodulator	14 (9)	29 (20)
BCMA-targeting therapy[d,e]	**1 (<1)**	**20 (14)**
Chemotherapy	16 (10)	25 (17)
Transplant	1 (<1)	5 (3)

Positive OS trend favoring BPd was seen despite the use of effective anti-MM therapies after progression with PVd; additional OS follow-up is ongoing

Median follow-up, 21.8 months (range, 0.03-39.23 months). Minimum ongoing follow-up, 12.8 months.
BCMA, B-cell maturation antigen; BPd, belamaf, pomalidomide, and dexamethasone; HR, hazard ratio; ITT, intent to treat; NR, not reached; OS, overall survival; PVd, pomalidomide, bortezomib, and dexamethasone.
[a] Includes patients who died after study withdrawal when permitted per local laws. [b] The treatment effect (HR and corresponding 95% CIs) was estimated using the stratified Cox proportional hazards model. Stratified analyses were adjusted for number of prior lines of therapy and prior bortezomib use. [c] Includes any subsequent antimyeloma therapy. Selected categories of interest are included. [d] Identified by posthoc analysis. [e] Includes belamaf, teclistamab, elranatamab, REGN5458, and EMB-06.

Safety Overview

Event, n (%)	Safety population	
	BPd (N=150)	PVd (N=145)
Any AE	149 (>99)	139 (96)
Grade 3/4 AE[a]	136 (91)	106 (73)
Exposure adjusted, patients/100 person-years[b]	**66**	**78**
AEs leading to interruption/delay		
Exposure adjusted, patients/100		
Any ocular (CTCAE/KVA) event leading interruption/delay of any study treatme		
AEs leading to dose reduction		
Exposure adjusted, patients/100		
Any ocular (CTCAE/KVA) event leading any study treatment		
AEs leading to permanent discontin any study treatment		
Exposure adjusted, patients/100 person-years[b]	**11**	**13**
Any ocular (CTCAE/KVA) event leading to discontinuation of any study treatment	14 (9)	0
Any SAE	95 (63)	65 (45)
Exposure adjusted, patients/100 person-years[b]	**46**	**48**
Fatal SAEs	17 (11)[c]	16 (11)

Ocular events were managed by dose holds (83%) and reduction in dosing frequency[d] (59%) and led to treatment discontinuations **(9%)**

re-adjusted AE rates were
or lower in the BPd vs PVd

rates of AEs leading to
nt discontinuations were
l balanced between arms

Median treatment duration across all components was 16.54 months (range, 0.92-35.06 months) in the BPd group and 8.51 months (range, 0.26-39.85 months) in the PVd group.
AE, adverse event; BPd, belamaf, pomalidomide, and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; KVA, keratopathy and visual acuity; PVd, pomalidomide, bortezomib, and dexamethasone; SAE, serious adverse event.
[a] Includes any patient with a grade 3 or 4 AE. [b] posthoc analysis of exposure-adjusted incident rates were calculated as the total number of patients with an event divided by the total exposure time in person-years (per 100 person-years). Total person-years is the sum of all patient exposure calculated as (last dose − first dose + 1)/365.25. [c] Fatal SAEs of pneumonia, meningoencephalitis herpetic, and metastatic gastrointestinal cancer were considered related to treatment in one patient each in the BPd group. [d]Dose frequency was reduced Q4W to Q8W; 9 patients received 1.4 mg/kg Q8W

AEs of Clinical Interest

Grouped term, n (%)[a]	Safety population			
	BPd (N=150)		PVd (N=145)	
	n (%)	Patients/100-person years	n (%)	Patients/100-person years
Thrombocytopenia[b]				
Any event	82 (55)	40	60 (41)	44
Grade 3 or 4	57 (38)	28	42 (29)	31
Neutropenia[c]				
Any event	95 (63)	46	66 (46)	49
Grade 3 or 4	86 (57)	42	57 (39)	42
Infections[d]				
Any event	123 (82)	59	99 (68)	73
Grade ≥3	73 (49)	35	38 (26)	28

Ocular AESIs (by CTCAE) preferred terms, n (%) ≥30% of patients in either treatment group				
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any event	133 (89)	65 (43)	44 (30)	3 (2)
Vision blurred	119 (79)	26 (17)	22 (15)	0
Dry eye	91 (61)	12 (8)	14 (10)	0
Foreign body sensation in eye	91 (61)	9 (6)	9 (6)	0
Eye irritation	75 (50)	6 (4)	13 (9)	0
Photophobia	66 (44)	5 (3)	6 (4)	0
Eye pain	49 (33)	3 (2)	7 (5)	0

The safety profile of BPd was broadly consistent with the known profile of the individual components of the regimen

AE, adverse event; AESI, adverse event of special interest; BPd, belamaf, pomalidomide, and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; PVd, pomalidomide, bortezomib, and dexamethasone.
[a] posthoc analysis. [b] Thrombocytopenia includes events identified by site or preferred terms thrombocytopenia or platelet count decreased. [c] Neutropenia includes preferred terms febrile neutropenia, neutropenia, and neutrophil count decreased. [d] Infections are based on all preferred terms included in the system organ class of infections and infestations.

Bilateral Worsening in Best Corrected Visual Acuity

BPd	Bilateral worsening of BCVA in patients with normal baseline (20/25 or better in ≥1 eye)	
	20/50 or worse[a]	20/200 or worse[a]
Patients, n/N (%)	51/150 (34)	2/150 (1)
Time to onset of first event, median (range), days	112 (28-761)	351 (29-673)
Time to resolution of first event to normal baseline, median (range), days[b,c]	57 (14-451)	NA[d]
Time to improvement of first event, median (range), days[e]	29 (7-196)	25.5 (22-29)
First event resolved to normal baseline, n/N (%)[c]	43/51 (84)	1/2 (50)
First event improved, n/N (%)[e]	47/51 (92)	2/2 (100)
Follow-up ended with event ongoing, n/N (%)[c,f]	4/51 (8)	1/2 (50)

Visual acuity changes that could affect activities of daily living were reversible in most patients

BCVA, best corrected visual acuity; BPd, belamaf, pomalidomide, and dexamethasone; NA, not available.
[a] Only patients with baseline visual acuity of 20/25 or better in ≥1 eye with on-study worsening to 20/50 or 20/200 in each eye at the same visit. [b] Defined as time from onset to resolution to normal baseline. [c] posthoc analyses. [d] One event resolved to normal baseline after 57 days, while for the other event, patient follow-up ended prior to resolution; median not available. [e] "Improved" was defined as no longer 20/50 (or 20/200) or worse in both eyes. [f] Ongoing events were defined as events that had not resolved to normal baseline. Shi C, et al. *bioRxiv.* Published online May 22, 2018.

2024 ASCO ANNUAL MEETING

Results from the randomized phase 3 DREAMM-7 study of belantamab mafodotin plus bortezomib and dexamethasone vs daratumumab, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma

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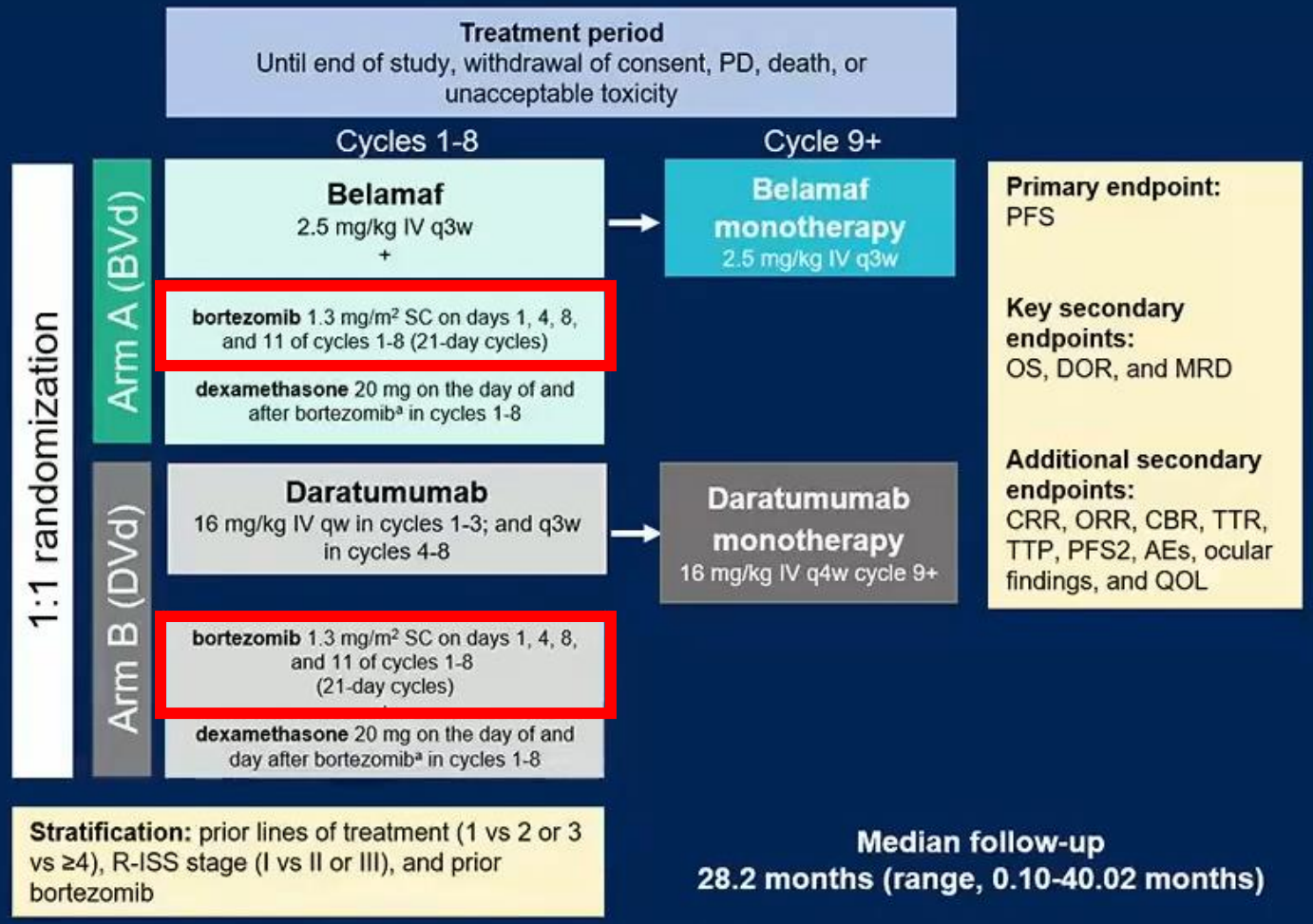
PRESENTED BY: María Victoria Mateos, MD, PhD

Introduction

- Patients with multiple myeloma often develop disease refractory to first-line triplet or quadruplet regimens and experience relapse, resulting in a need for efficacious second-line combinations that incorporate new therapy classes[1,2]
- Belamaf is a humanized, afucosylated, anti-BCMA monoclonal antibody conjugated to the microtubule inhibitor monomethyl auristatin-F by a protease-resistant cysteine linker[3,4]
- The DREAMM-7 trial (NCT04246047) evaluated BVd vs DVd in patients with RRMM who received ≥1 prior line of therapy



AE, adverse event; BCMA, B-cell maturation antigen; BVd, belantamab mafodotin, bortezomib, and dexamethasone; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; DVd, daratumumab, bortezomib, and dexamethasone; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival 2; q3w, every 3 weeks; q4w, every 4 weeks; QOL, quality of life; qw, once weekly; R-ISS, Revised International Staging System; RRMM, relapsed or refractory multiple myeloma; SC, subcutaneous; TTP, time to progression; TTR, time to response. [a]Reduce starting dose of dexamethasone to 10 mg for patients aged >75 years who have a body mass index of <18.5, previous unacceptable side effects associated with glucocorticoid therapy, or inability to tolerate the starting dose. 1. Gill SK, et al. *Blood Cancer J.* 2022;12:138. 2. Raje N, et al. *Blood Cancer J.* 2023;13:41. 3. Lassiter G, et al. *Curr Oncol.* 2021;28:640-660. 4. Tai YT, et al. *Blood.* 2014;123:3128-3138.

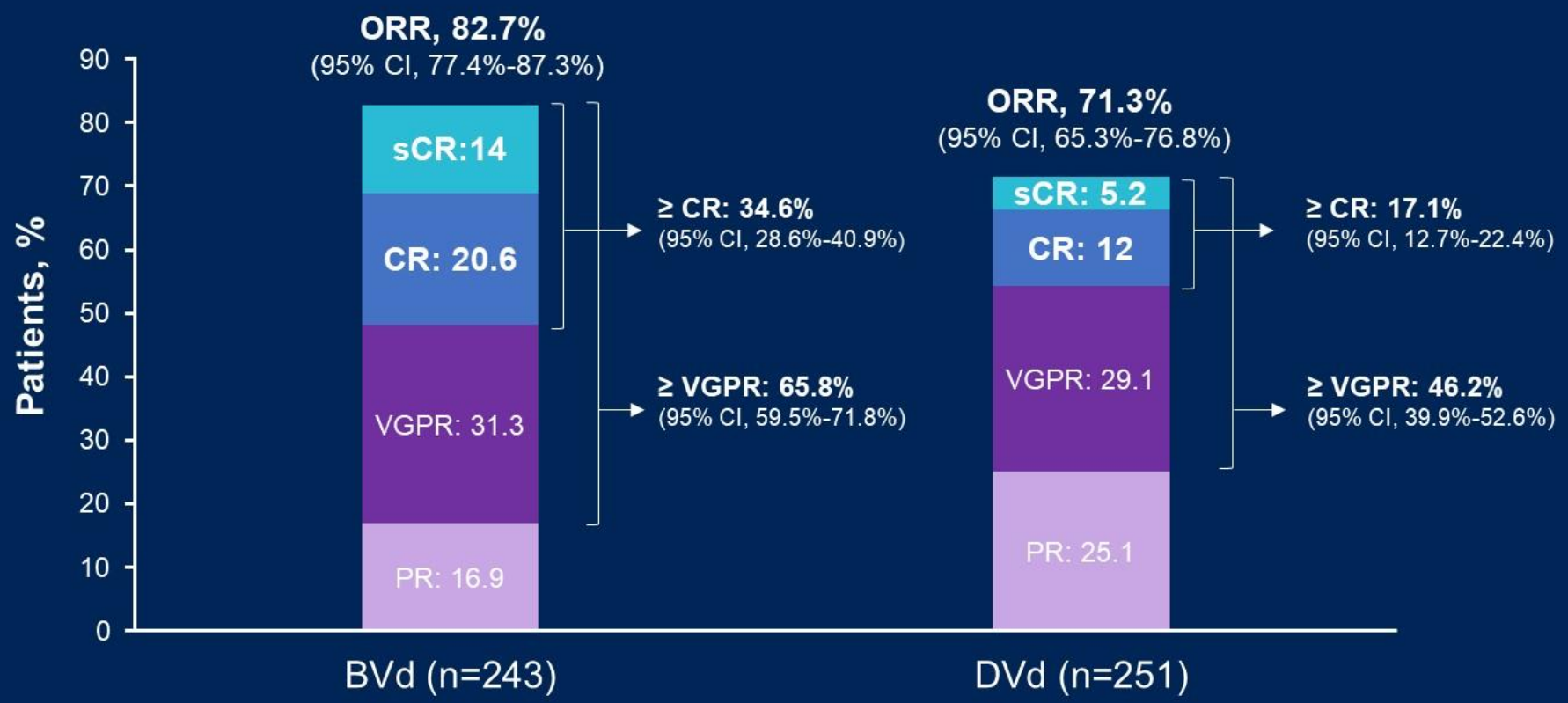
DREAMM-7: deeper responses with BVd vs DVd[a]

≥ CR MRD negativity[b]

24.7% (95% CI, 19.4%-30.6%) vs 9.6% (95% CI, 6.2%-13.9%)

≥ VGPR MRD negativity[b]

38.7% (95% CI, 32.5%-45.1%) vs 17.1% (95% CI, 12.7%-22.4%)



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

BVd, belantamab mafodotin, bortezomib, and dexamethasone; CR, complete response; DVd, daratumumab, bortezomib, and dexamethasone; ITT, intent to treat; MRD, minimal residual disease; NGS, next-generation sequencing; 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 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 (no vs yes), and R-ISS stage at screening (I vs II or III).

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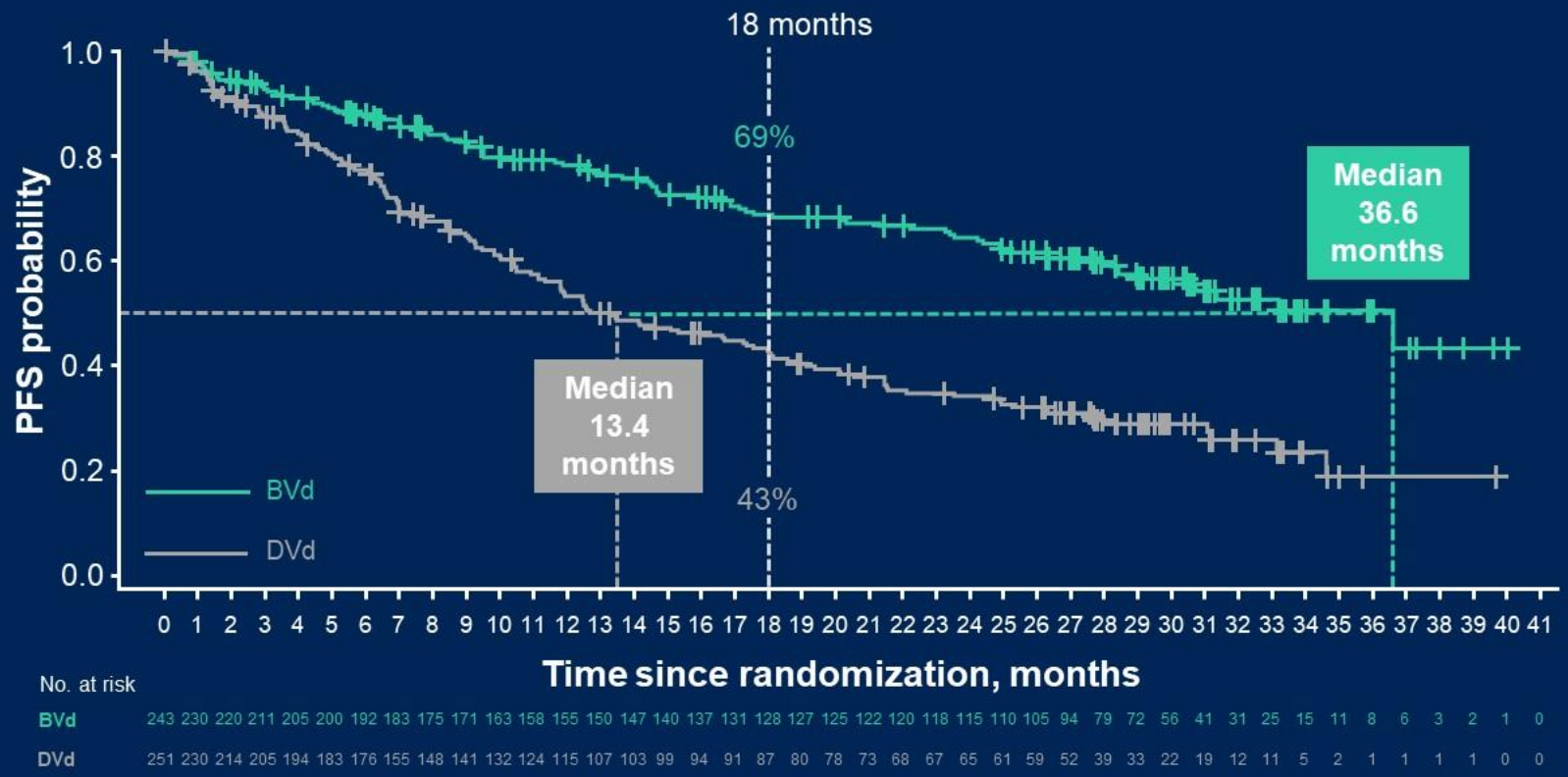
DREAMM-7: BVd led to a significant increase in PFS vs DVd

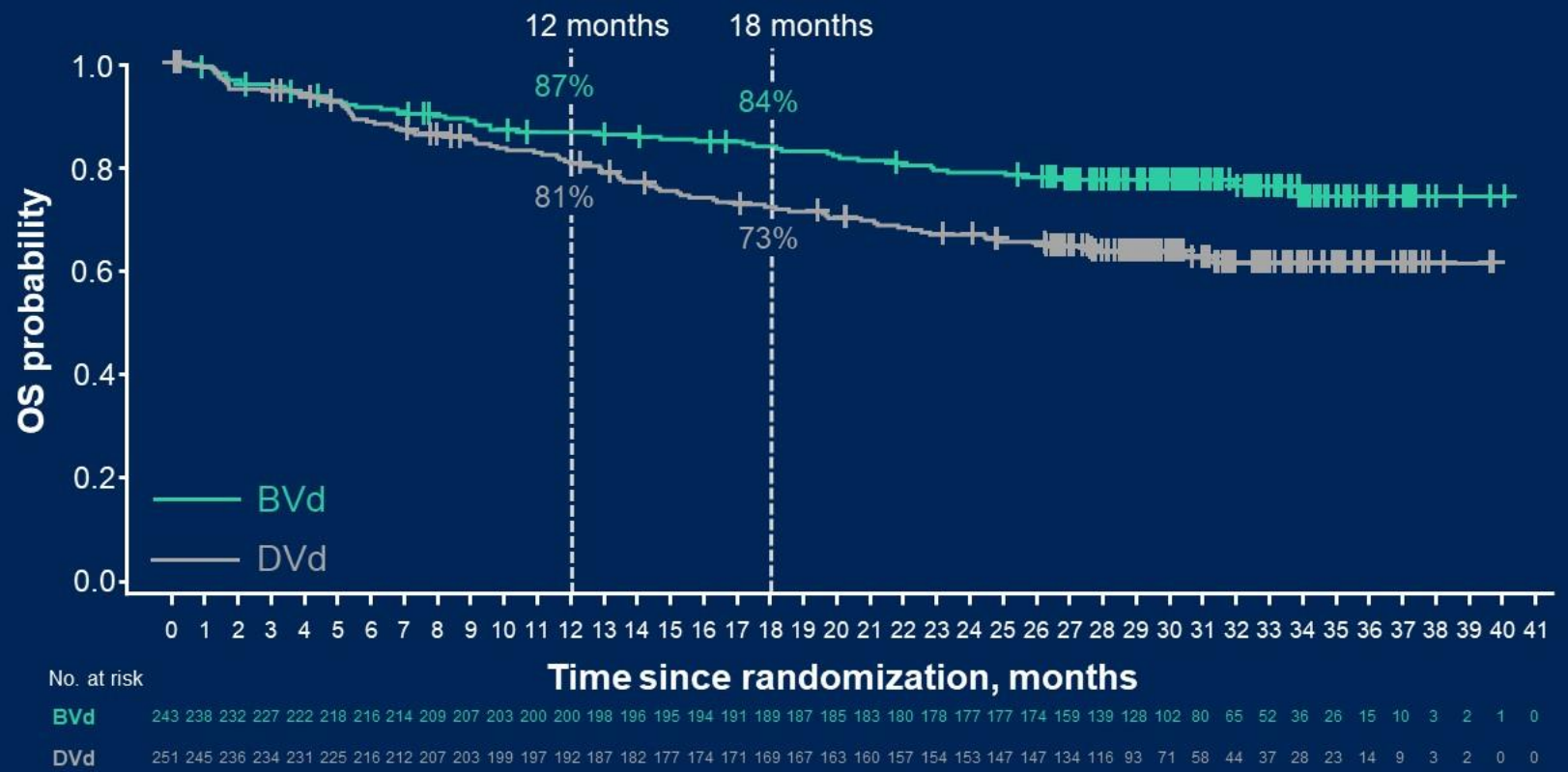


PFS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	91 (37)	158 (63)
PFS, median (95% CI), months[b]	36.6 (28.4-NR)	13.4 (11.1-17.5)
HR (95% CI)[c]	0.41 (0.31-0.53)	
P value[d]	<.00001	

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

BVd, belantamab mafodotin, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; HR, hazard ratio; ITT, intent to treat; NR, not reached; PFS, progression-free survival; PFS2, progression-free survival 2.
[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 (no vs yes), and R-ISS stage at screening (I vs II or III), with a covariate of treatment. [d] *P* value from 1-sided stratified log-rank test.

DREAMM-7: early OS trend favoring BVd vs DVd

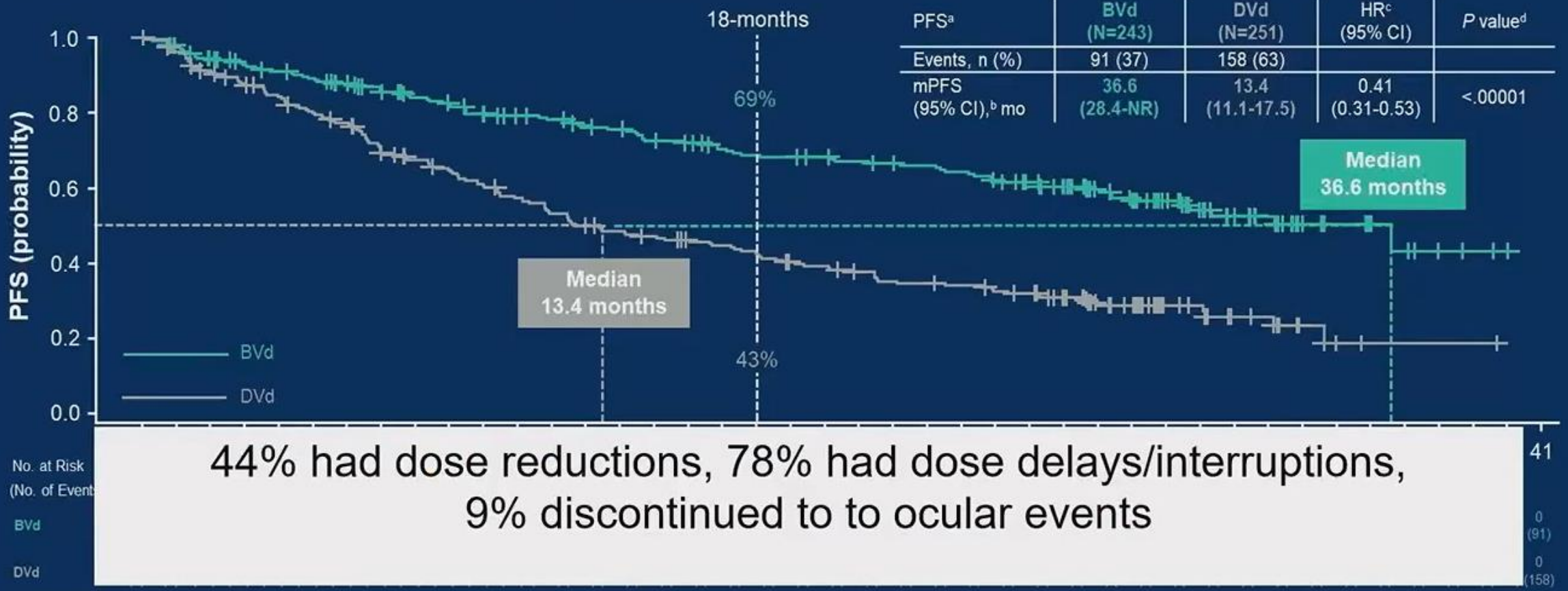


OS[a]	BVd (N=243)	DVd (N=251)
Events, n (%)	54 (22)	87 (35)
OS, median (95% CI), months[b]	NR	NR
HR (95% CI)[c]	0.57 (0.40-0.80)	
P value[d]	.00049[e]	

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

BVd, belantamab mafodotin, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; 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 (no vs yes), and R-ISS stage at screening (I vs II or 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: BVd led to a significant increase in PFS vs DVd



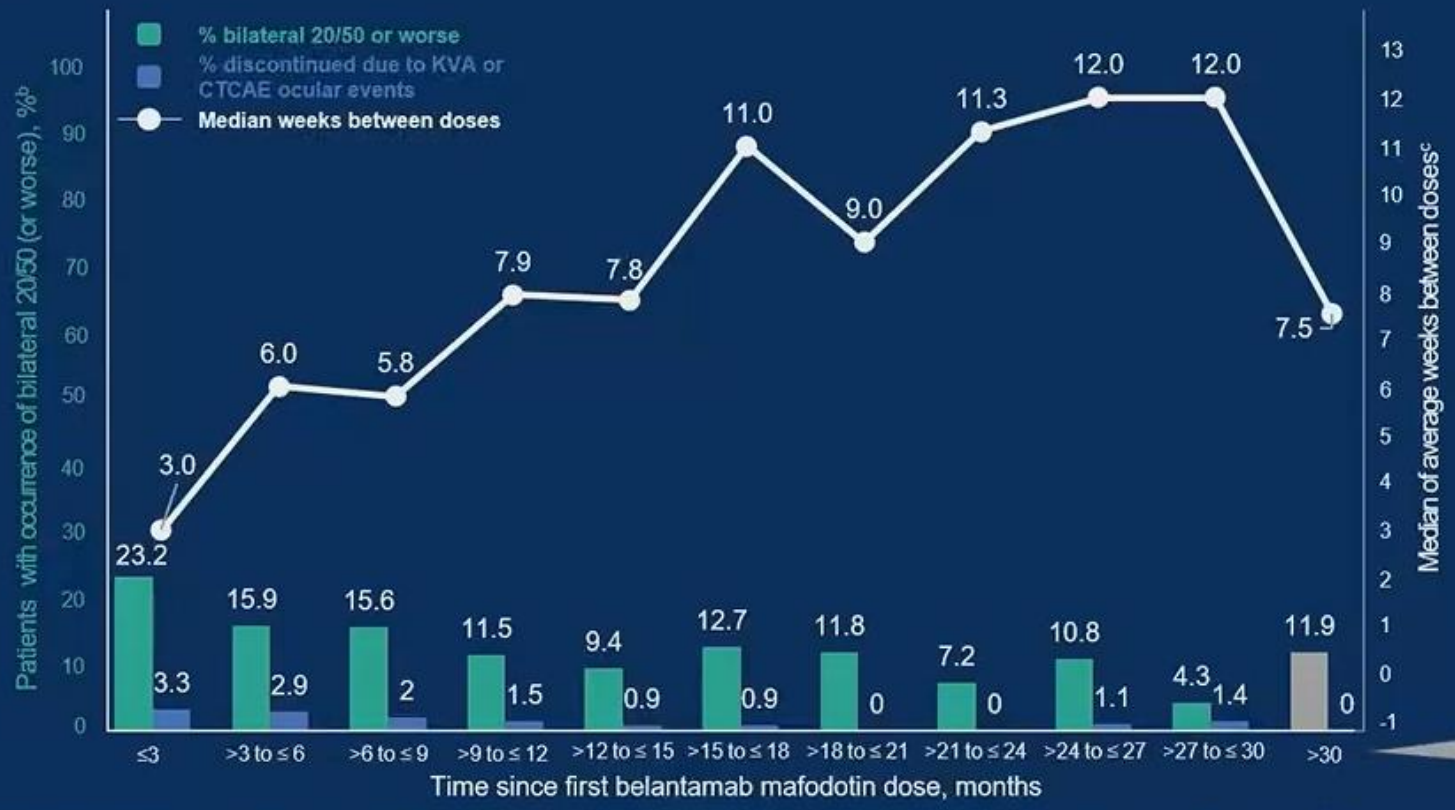
PFS[a]	BVd (N=243)	DVd (N=251)	HR[c] (95% CI)	*P* value[d]
Events, n (%)	91 (37)	158 (63)		
mPFS (95% CI),[b] mo	36.6 (28.4-NR)	13.4 (11.1-17.5)	0.41 (0.31-0.53)	<.00001

44% had dose reductions, 78% had dose delays/interruptions,
9% discontinued to to ocular events

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

HR, hazard ratio; IRC, independent review committee; mPFS, median PFS; NR, not reached.
[a] Two patients in the ITT population were randomized, not treated, re-screened, and re-randomized. 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 at screening (I vs II/III), with a covariate of treatment. [d] *P* value from 1-sided stratified log-rank test.

DREAMM-7: Impact of dose modifications on PFS and ocular management[a]

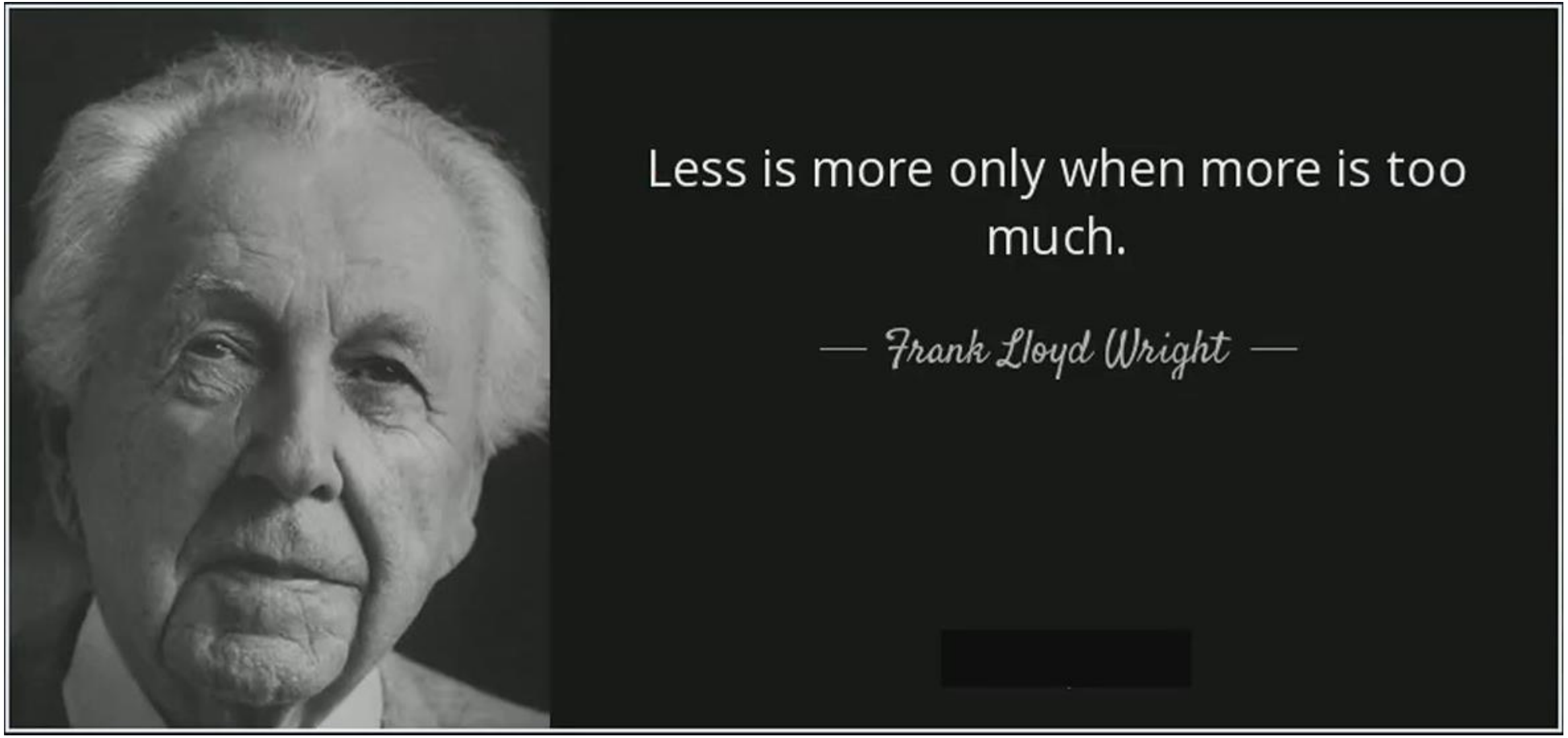


No. of patients on treatment	211	170	147	131	117	110	102	97	93	69	42
No. of patients with bilateral 20/50 or worse	49	27	23	15	11	14	12	7	10	3	5
Median days between doses	21	42	41	55	54	77	63	79	84	84	53
No. of patients who discontinued due to KVA or ocular CTCAE event	7	5	3	2	1	1	0	0	1	1	0

- Median time between doses increased the longer patients were on therapy
- **Dose delays did not have an impact on PFS**
  - BVd patients with ≥1 dose delay of ≥12 weeks (N= 126), **mPFS 36.6 months**
- 23% of patients experienced 20/50 or worse events in first 3 months; prevalence decreased thereafter
- Rate of treatment discontinuation due to ocular events were low

Data beyond 30 months is cumulative

[a] Only belantamab mafodotin treatment period considered. [b] Only patients with 20/25 or better in either or both eyes at baseline are considered. [c] Mean of days between doses, for each patient, per interval is used. [d] Only patients receiving ≥6 months of treatment included in analysis to exclude early discontinuations (e.g., rapid PDs)


Less is more only when more is too much.
— Frank Lloyd Wright —

Will I use Belantamab?

- Ocular side effects scare patients
- What are my other options?
  - CART
    - Vein-to-vein time has improved
    - Moved to 2nd LOT
  - Bispecifics

Multiple Myeloma Clinical trials at Ulowa

MULTIPLE MYELOMA

OPEN | ENROLLMENT HOLD | PENDING

SMOLDERING MYELOMA

Ecog-Acrin 173
Phase 3 Pre-emptive tx for high risk smoldering myeloma
Dara-Rd x2 years
Vs
Rd x 2 years

"High Risk" SMM = 2 of these:
- >2.0 g/dl m-protein
- Cyto: +1q, t[4;14], -17p, -13q
- >20% PCs in marrow
- Involved light chains 20x greater than uninvolved

Dx in last 1 year, no myeloma defining criteria

PI: Christopher Strouse

NCT: 03937635

NEWLY DIAGNOSED

CARTITUDE-6
Phase 3
DVRd->Cilta-cel vs DVRd->auto stem cell in first line

No prior treatment for MM

ASCT is part of intended treatment plan

PI: Christopher Strouse

NCT05257083

S2209
Phase 3 evaluation comparing up front 3 drug regimens with single or double agent maintenance

No prior treatment for MM

Myeloma Frailty Score= frail or intermediate risk regardless of age

PI: Hira Shaikh

NCT05561387

CARTITUDE-2 Cohort G
Phase 2 evaluation of anti-BCMA CARt cells in first line

Dara-RD->Cilta=cel-> no maintenance

Up to 2 cycles of Dara-Rd prior to enrollment is allowed (please call us before starting therapy)

Transplant deferred OR transplant ineligible patients

PI: Christopher Strouse

NCT: 04133636

POST SCT

S1803 Phase 3 evaluation of dara maintenance, and MRD based stopping decision
Dara-R vs R maintenance

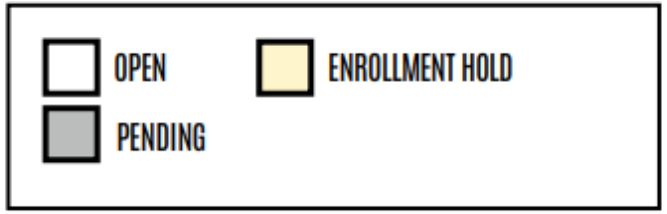
s/p Auto transplant

Enrollment within 180 days of transplant, and within 1 year of induction therapy

PI: Umar Farooq

NCT: 04071457

MULTIPLE MYELOMA (CONT'D)



RELAPSED/REFRACTORY

Ascorbic Acid + Melphalan High Dose Ascorbic Acid is hypothesized to have synergy with melphalan. This is a phase 1 dose escalation trial.	**C1071020 – Elranatamab + Carfilzomib / anti-CD47 antibody** Testing combinations with anti-BCMA bispecific antibody.	**P-BCMA-ALLO1** Allogeneic anti-BCMA CAR-T cells.	**QUINTESSENTIAL** Autologous anti-GPRC5d CAR-T cells	**LimiTEC** Limited duration therapy of teclistamab	**MonumenTAL-8** Combination anti-GPRC5d bispecific antibody + anti-BCMA CAR T cells for high risk myeloma
3+ prior lines of therapy Prior exposure to IMiD, PI, Anti-CD38 antibody required *PI: Christopher Strouse*	**Arm 1: Elra + Carf** 1-3 prior lines Prior carfilzomib is OK **Arm 2: Elra + anti-CD47** 3+ prior lines of therapy Refractory to IMiD, PI, anti-CD38 antibody *PI: Michael Tomasson*	EITHER - 2+ prior lines of therapy - Refractory to PI, IMiD, anti-CD38 antibody OR - 3+ prior lines of therapy - Exposure to PI, IMiD, anti-CD38 antibody *PI: Christopher Strouse*	3+ prior lines Prior treatment with anti-BCMA therapy is **required** *PI: Christopher Strouse*	Patients achieving VGPR or better after 6 cycles of teclistamab (less than 9). Telephone consenting and remote monitoring is possible (no need to visit Iowa City) *PI: Hira Shaikh*	3+ prior lines Exposure to IMiD, PI, anti-CD38 antibody "High Risk" myeloma = 1 of: - Cyto t[4;14, t[14;16], or -17p - Baseline ISS Stage III - Extramedullary plasmacytoma No prior anti-BCMA therapy *PI: Christopher Strouse*
NCT: 03602235	NCT: 05675449	NCT: 04960579	NCT: 06121843	NCT: pending	NCT: pending

Summary

- Consider quadruplets as upfront treatment in ‘transplant-ineligible’
  - With dose modifications
- All oral regimen as a second line therapy for frail?
- Belantamab may be coming back in R/R. But where will it fall with CART and bispecifics.