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Prof. Angelo Maiolino, M.D. PhD.

Mieloma Recidivado: Novos Mecanismos e Estratégias Terapêuticas Emergentes (ADCs, CELMoDs e Novos Alvos Terapêuticos)

GERENCIAMENTO
E PRODUÇÃO

RV+
EVENTOS

Mieloma Recidivado: Novos Mecanismos e Estratégias Terapêuticas Emergentes (ADCs, CELMoDs e Novos Alvos Terapêuticos)

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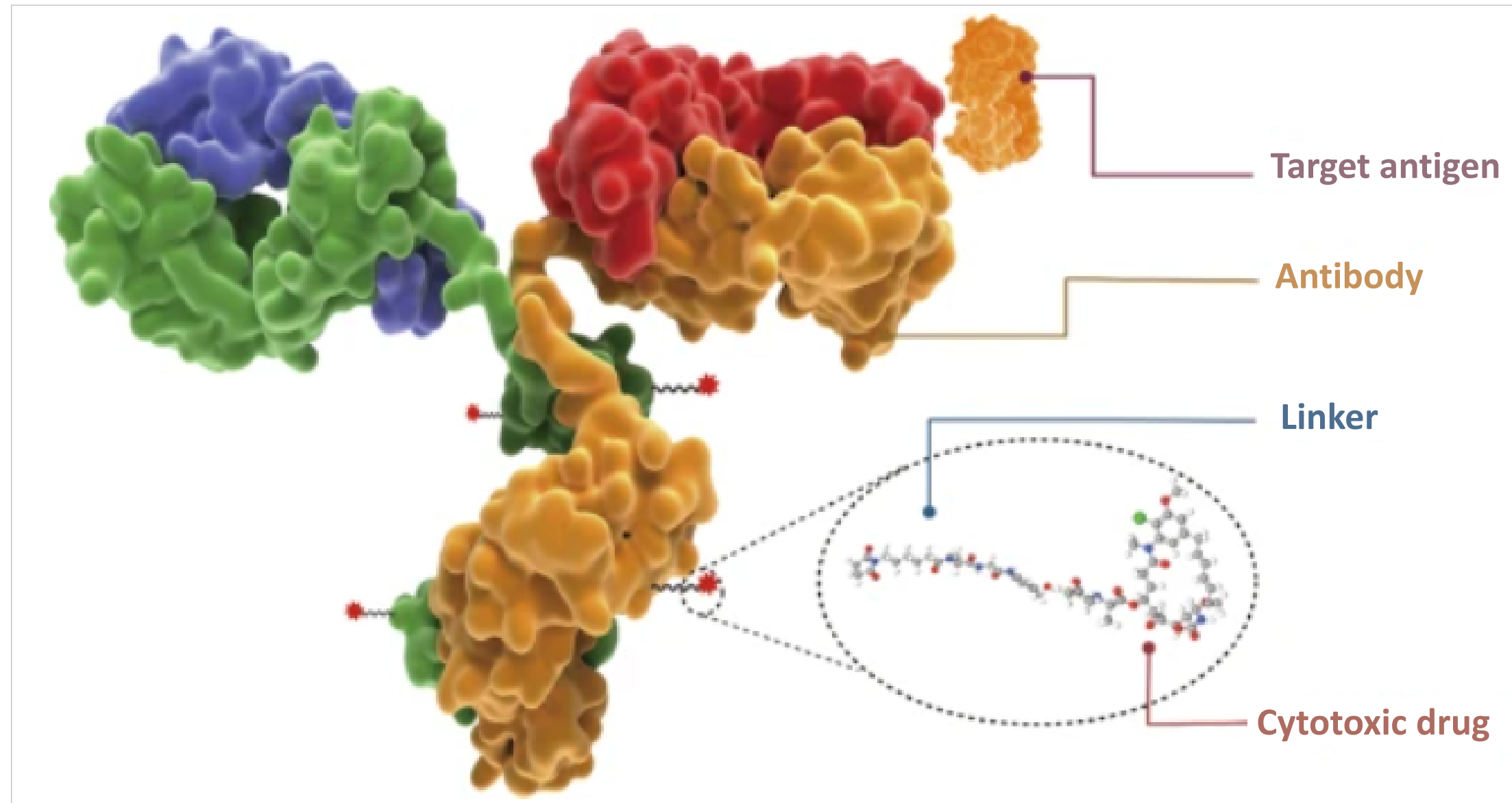
Member of the International Myeloma Working Group



Disclosure:

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 - Board of Directors Associação Brasileira de Hematologia e Hemoterapia
 - Member of International Myeloma Working Group
- Discussion of off-label drug use: not applicable

Structure and anti-tumor mechanism of ADCs



Key functions

Recognition of target cancer cells

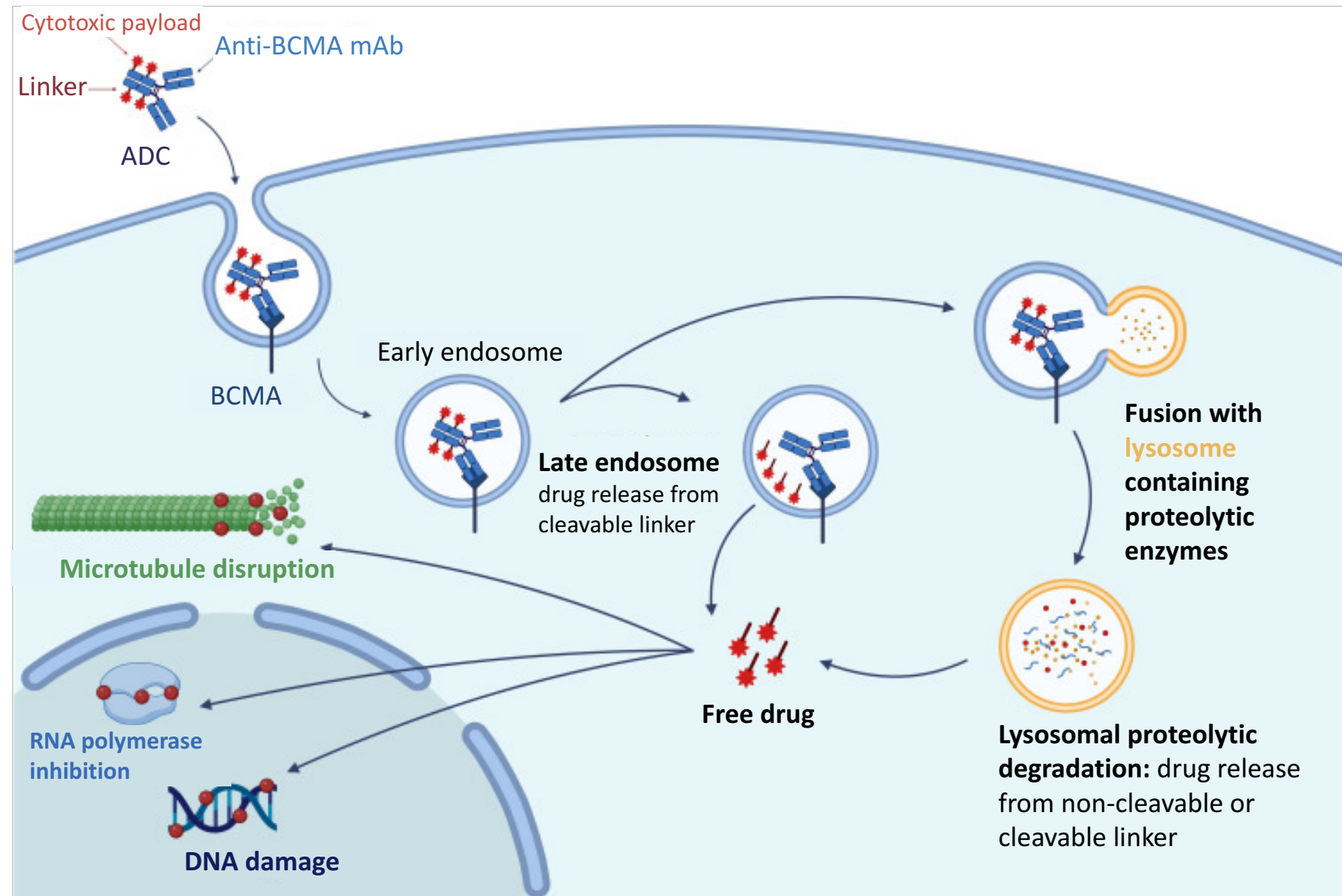
Guidance system for cytotoxic drugs

Bridge between antibody and drugs and to control the release of drugs inside cancer cells

Warhead for destroying cancer cells

The core components include target antigen, antibody, linker, cytotoxic drug

Mechanism of action of ADCs



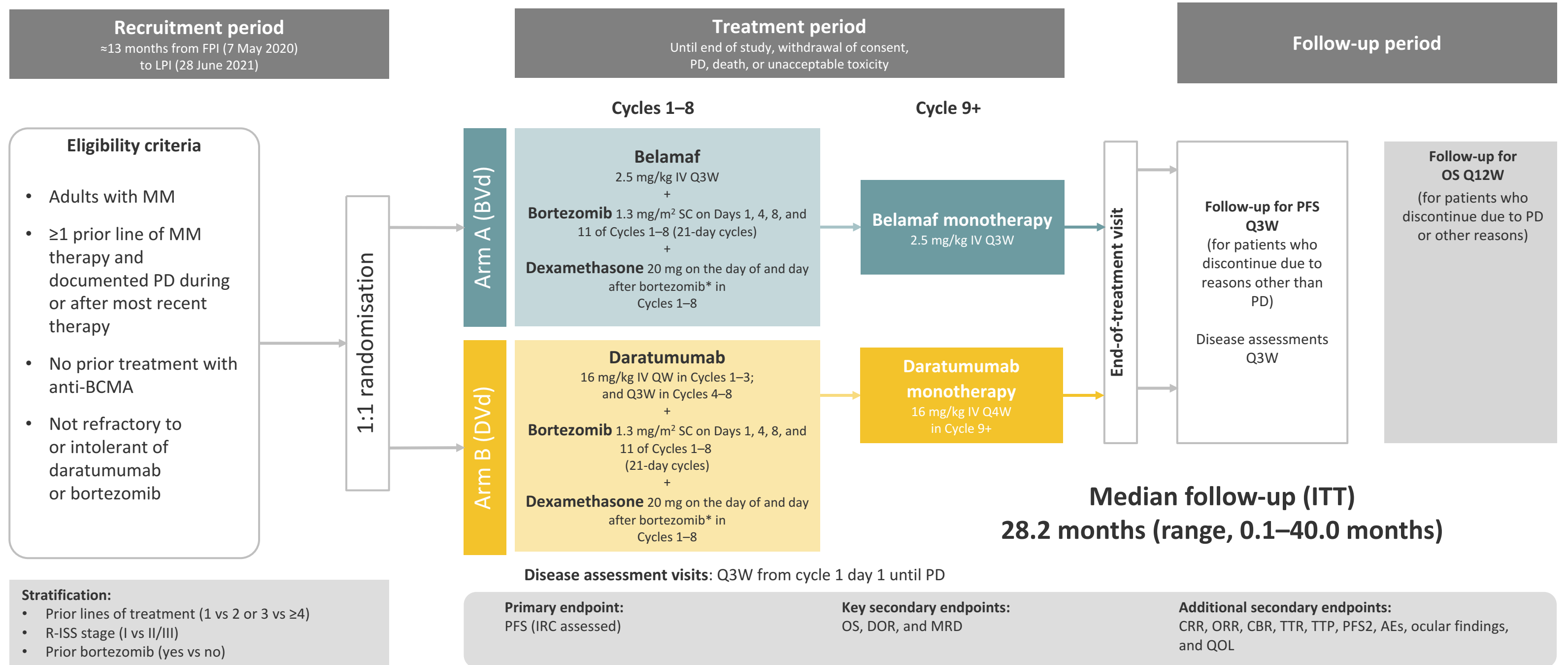
- Belantamab mafodotin is an ADC indicated for the treatment of MM in adult patients*¹
- Belantamab mafodotin binds to the BCMA receptor on the target cell which then takes up the ADC by endocytosis^{2,3}
- The cytotoxic payload of belantamab mafodotin, monomethyl auristatin F, is released, disrupting microtubule formation and causing cell death²
- The monoclonal antibody of belantamab mafodotin is afucosylated to enhance its binding affinity to effector cells²

*As monotherapy in patients who have received ≥ 4 prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

ADC, antibody-drug conjugate; BCMA, B cell maturation antigen; mAb, monoclonal antibody; MM, multiple myeloma.

1. EMA. Blenrep [SMPC]. 2. Morè S, et al. *Cancers (Basel)*. 2023;15:2948; 3. Diaz AAA, et al. *Blood Lymphat Cancer*. 2024;14:71–87.

DREAMM-7: Study design



*Starting dose of dexamethasone may be reduced to 10mg 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.
 AE, adverse event; BCMA, B-cell maturation antigen; Belamaf, belantamab mafodotin; BVD, belamaf, bortezomib, and dexamethasone; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; DVd, daratumumab, bortezomib, and dexamethasone; FPI, first patient in; IRC, independent review committee; ITT, intention 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; PFS2, progression-free survival on subsequent line of therapy; 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.
 Hungria V, et al. N Engl J Med. 2024;391:394–407 (supplement).

DREAMM-7: Baseline demographics and clinical characteristics

Baseline characteristics	ITT population	
	BVd (n=243)	DVd (n=251)
Age, median (range), years	65.0 (34–86)	64.0 (32–89)
Male, n (%)	128 (53)	144 (57)
ECOG PS ≤1, n/N (%)	232/242 (96)	235/246 (96)
R-ISS stage at screening, n (%) [*]		
I	102 (42)	103 (41)
II	130 (53)	132 (53)
III	9 (4)	14 (6)
Cytogenetic abnormalities, n (%)		
High risk [†]	67 (28)	69 (27)
Standard risk [‡]	175 (72)	175 (70)
Prior lines of therapy, n (%)		
1	125 (51)	125 (50)
2 or 3	88 (36)	99 (39)
4+	30 (12)	27 (11)
Prior proteasome inhibitor, n (%)	218 (90)	216 (86)
Prior bortezomib	210 (86)	211 (84)
Prior immunomodulatory drugs, n (%)	198 (81)	216 (86)
Prior lenalidomide	127 (52)	130 (52)
Refractory to lenalidomide	79 (33)	87 (35)
Prior daratumumab, n (%)	3 (1)	4 (2)

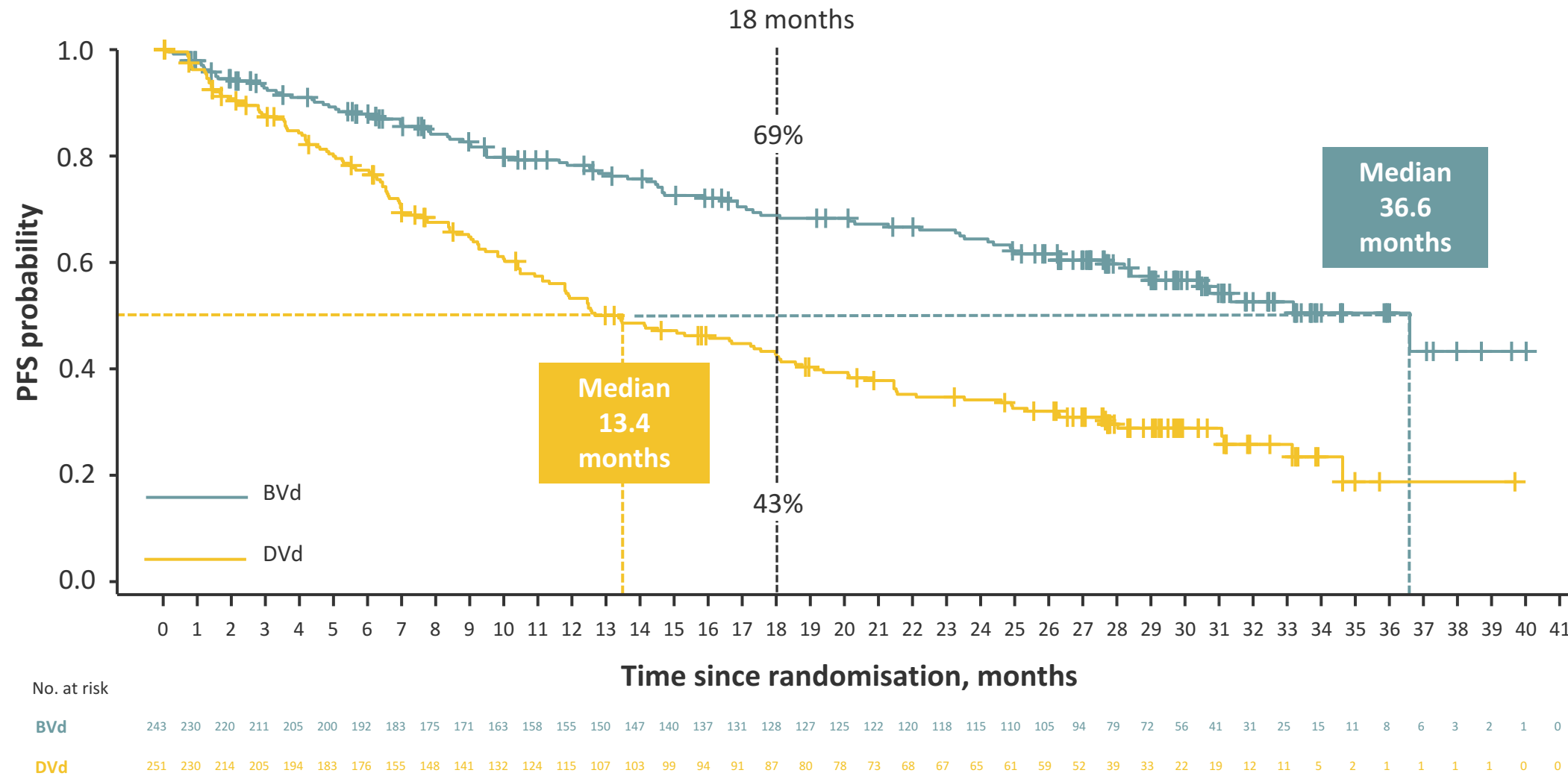
Baseline disease characteristics and prior treatments received were balanced across both treatment arms

^{*}R-ISS stage at baseline was unknown for two patients in each arm. Missing/nonevaluable cytogenetic abnormalities were reported in 1 and 7 patients in the BVd and DVd arms, respectively. [†]High-risk cytogenetic abnormalities were defined as the presence of ≥1 of the following: t(4;14), t(14;16), or del(17p13). [‡]Standard-risk cytogenetic abnormalities were defined as having negative results for all high-risk abnormalities: t(4;14), t(14;16), or del(17p13).

BVd, belantamab mafodotin, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention to treat; R-ISS, Revised International Staging System.

Hungria V, et al. N Engl J Med. 2024;391:394–407.

DREAMM-7: Primary endpoint (PFS)



PFS*	BVd (n=243)	DVd (n=251)
Events, n (%)	91 (37)	158 (63)
PFS, median (95% CI), months [†]	36.6 (28.4, NR)	13.4 (11.1, 17.5)
HR (95% CI) [‡]	0.41 (0.31, 0.53)	
P value [§]	<0.00001 ²	

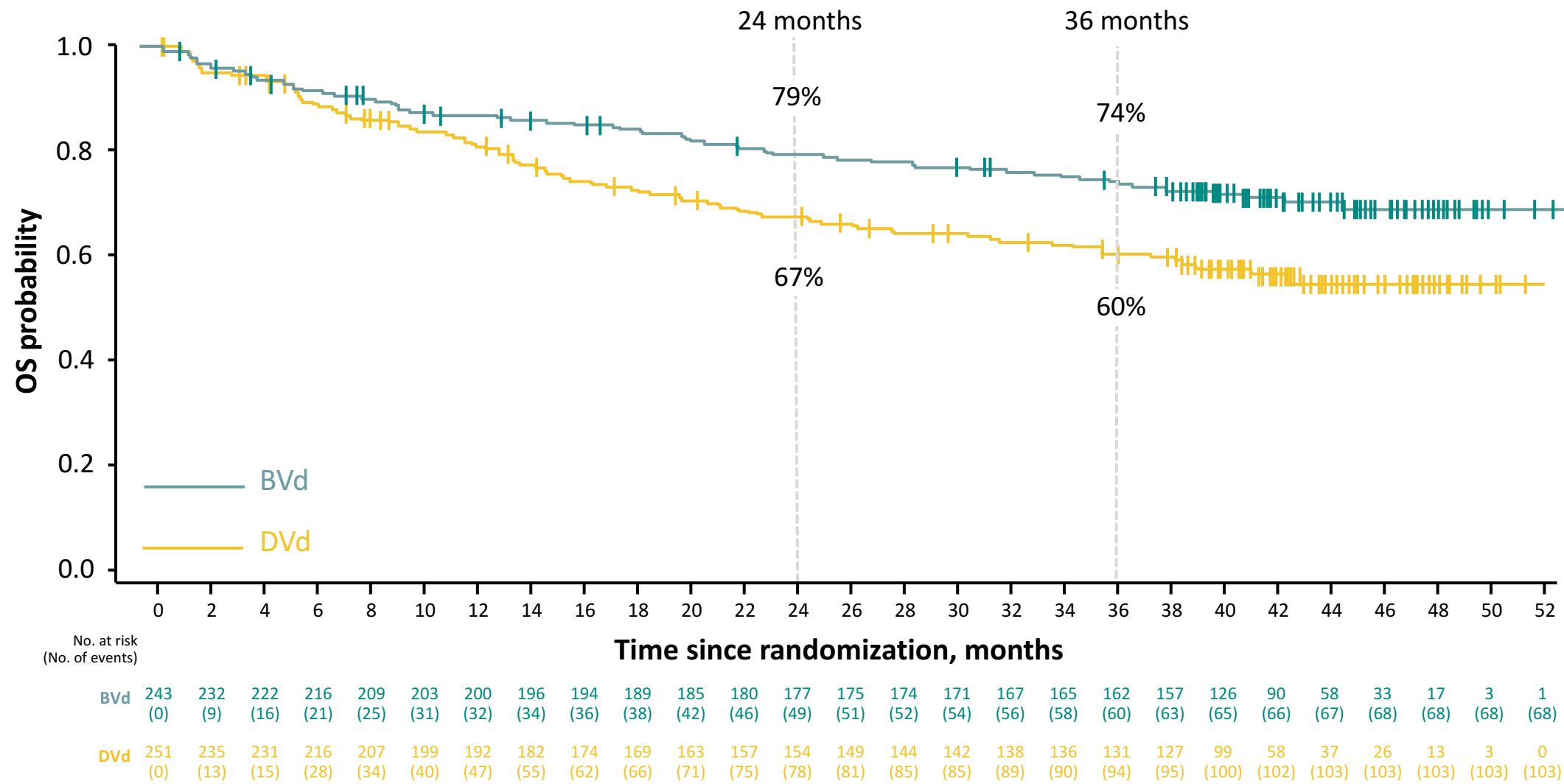
BVd demonstrated a statistically significant and clinically meaningful PFS benefit, with a median PFS that was 23 months longer than that with DVd¹

*Two patients in the ITT population were randomised, not treated, rescreened, and re-randomised. They are counted as four unique patients in this output. [†]CI were estimated using the Brookmeyer–Crowley method. [‡]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. [§]P value from 1-sided stratified log-rank test.

BVd, belantamab mafodotin, bortezomib, and dexamethasone; CI, confidence interval; DVd, daratumumab, bortezomib, and dexamethasone; HR, hazard ratio; ITT, intention to treat; NR, not reached; PFS, progression-free survival; PFS, progression-free survival.

1. Hungria V, et al. N Engl J Med. 2024;391:394–407; 2. Mateos MVM, et al. Presented at the American Society of Clinical Oncology Annual Meeting; 31 May-4 June 2024. Chicago, IL, USA. Updates on Abstract 439572.

DREAMM-7: Updated overall survival (OS)



OS ^a	BVd (n=243)	DVd (n=251)
Events, n (%)	68 (28)	103 (41)
OS, median (95% CI), months ^b	NR (NR, NR)	NR (41.0, NR)
HR (95% CI) ^c	0.58 (0.43, 0.79)	
P value ^d	0.00023	
24-month survival, % (95% CI)	79 (73–84)	67 (61–73)
36-month survival, % (95% CI)	74 (68–79)	60 (54–66)

Median OS was not reached

Predicted median OS based on modelling is 84 months with BVd and 51 months with DVd^e

BVd, belantamab mafodotin, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; HR, hazard ratio; ITT, intention 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 a 1-sided stratified log-rank test. At 171 actual events (48.2% OS information fraction), OS was declared significant if the P value was <.00112. ^e Post hoc analysis was performed with simulation using an exponential distribution to predict median OS values in each arm using the observed data at this interim analysis 2, with a 39.4-month median follow-up, to extrapolate time to death in ongoing censored patients. Predicted median OS values are subject to change as data mature. Hungria V, et al Presented at the American Society of Hematology Annual Meeting; December 7–10, 2024; San Diego, CA. Abstract 772.

DREAMM-7: Safety overview

n (%)	BVd (n=242)	DVd (n=246)
Any AE	242 (100)	246 (100)
Related to any study treatment*	242 (100)	234 (95)
Grade 3/4 AE	229 (95)	187 (76)
Related to any study treatment*	219 (90)	164 (67)
AEs leading to permanent discontinuation of any study treatment	75 (31)	46 (19)
Related to any study treatment leading to permanent discontinuation of any study treatment*	64 (26)	36 (15)
AEs leading to dose reduction	182 (75)	146 (59)
AEs leading to dose interruption/delay	228 (94)	185 (75)
Any SAE	121 (50)	90 (37)
Related to any study treatment*	47 (19)	30 (12)
Fatal SAEs	23 (10)	19 (8)
Related to any study treatment*	7 (3)	2 (<1)

Exposure-adjusted rate (per 100 person-years) [†]	BVd (n=242)	DVd (n=246)
Grade 3/4 AE	68.8	62.4
AEs leading to permanent discontinuation of any study treatment	22.5	15.4
AEs leading to dose reduction[‡]	54.7	48.7
AEs leading to dose interruption/delay[‡]	68.5	61.8
Any SAE	36.3	30.0

- The safety and tolerability of BVd were consistent with the known safety profiles of the individual agents
- In the BVd and DVd arms, exposure-adjusted rates of infections were 51.1 and 55.4 (all grades) and 22.5 and 16.4 (Grade ≥3), respectively

*Related to any study treatment includes responses of “yes” and missing responses to the following question: “Is there a reasonable possibility that the AE may have been caused by the study treatment?”. †Exposure-adjusted rates were calculated as the total number of patients with an event divided by the total exposure time in person-years (per 100 person-year). Total person-years is the sum of all patient exposure calculated as (last dose – first dose + 1) / 365.25. ‡Post hoc exposure-adjusted rates.

AE, adverse event; BVd, belantamab mafodotin, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; SAE, serious adverse event.

Hungria V, et al. N Engl J Med. 2024;391:394–407; Hungria V, et al. N Engl J Med. 2024;391:394–407 (supplement); Mateos MV et al. Presented at the ASCO Annual Meeting. May 31 – June 4, 2024; Abstract 439572.

DREAMM-7: Ocular AEs

Ocular events (CTCAE) in $\geq 30\%$ of patients in either treatment group by preferred term and maximum grade

Ocular AESIs (by CTCAE) preferred terms, n (%)	BVd (N=242)		DVd (N=246)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any event	191 (79)	82 (34)	72 (29)	7 (3)
Vision blurred	160 (66)	53 (22)	26 (11)	2 (<1)
Dry eye	123 (51)	17 (7)	17 (7)	0
Photophobia	114 (47)	5 (2)	6 (2)	0
Eye irritation	103 (43)	12 (5)	13 (5)	0
Foreign-body sensation in eye	106 (44)	8 (3)	10 (4)	0
Eye pain	77 (32)	2 (1)	8 (3)	1 (<1)

Ocular exams for patients in the BVd arm were assessed at screening/baseline and then every 3 weeks prior to dosing up to at least the sixth dose of belantamab mafodotin and then every three months if there were no significant ocular findings. For patients in the DVd arm, ocular exams were performed at screening/baseline with on treatment ocular exams performed at cycle 6 and then decreased to every 6 months.

DREAMM-7: Changes in BCVA

20/20



20/50



20/200



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BVd	Bilateral worsening of BCVA in patients with normal baseline 20/25 or better	
	20/50 or worse*	20/200 or worse*
Patients, n/N (%)	82/242 (34)	5/242 (2)
Time to onset of first event, median (range), days	73.5 (16–753)	105 (47–304)
Time to resolution of first event to baseline, median (range), days [†]	64 (8–908)	87 (22–194)
Time to improvement of first event, median (range), days [‡]	22 (6–257)	19 (8–26)
First event resolved, n/N (%) [†]	77/82 (94)	4/5 (80)
First event improved, n/N (%) [‡]	80/82 (98)	5/5 (100)
Follow-up ended with event ongoing, n/N (%)	2/82 (2)	0

Among all patients who received BVd, 44% had dose reductions, 78% had dose delays/interruptions, and 9% discontinued due to any ocular event

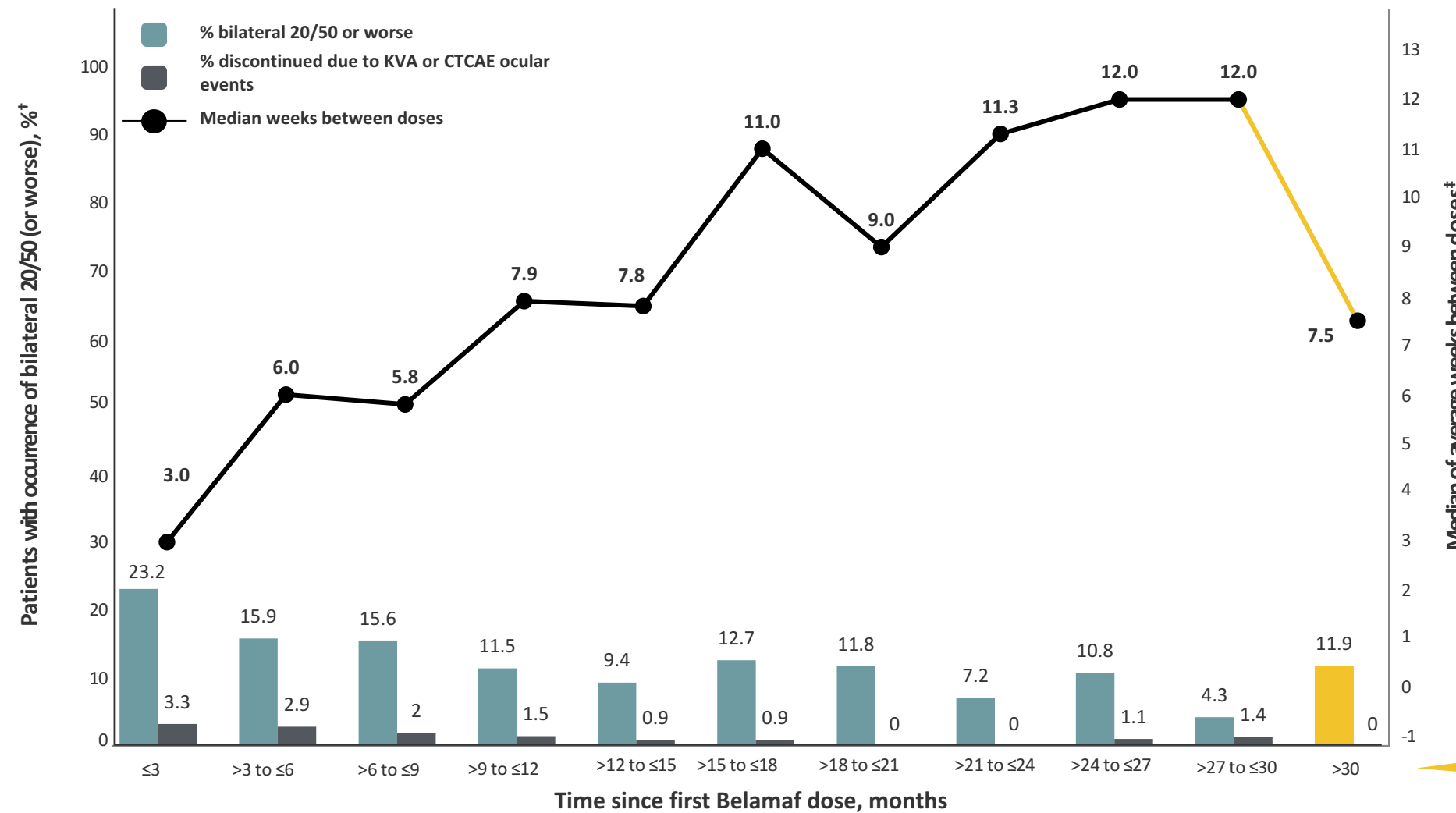
*Only patients with baseline visual acuity of 20/25 or better in ≥ 1 eye with on-trial worsening to 20/50 or 20/200 in each eye at the same visit. [†]Resolution (post hoc) was defined as returning to baseline visual acuity (20/25 or better in ≥ 1 eye).

[‡]Improvement was defined as bilateral improvement to better than 20/50 (or 20/200).

BCVA, best corrected visual acuity; BVd, belantamab mafodotin, bortezomib, and dexamethasone.

Hungria V, et al. N Engl J Med. 2024;391:394–407; Mateos MV et al. Presented at the ASCO Annual Meeting. May 31 – June 4, 2024; Abstract 439572.

DREAMM-7: Impact of dose modifications on PFS and ocular management*



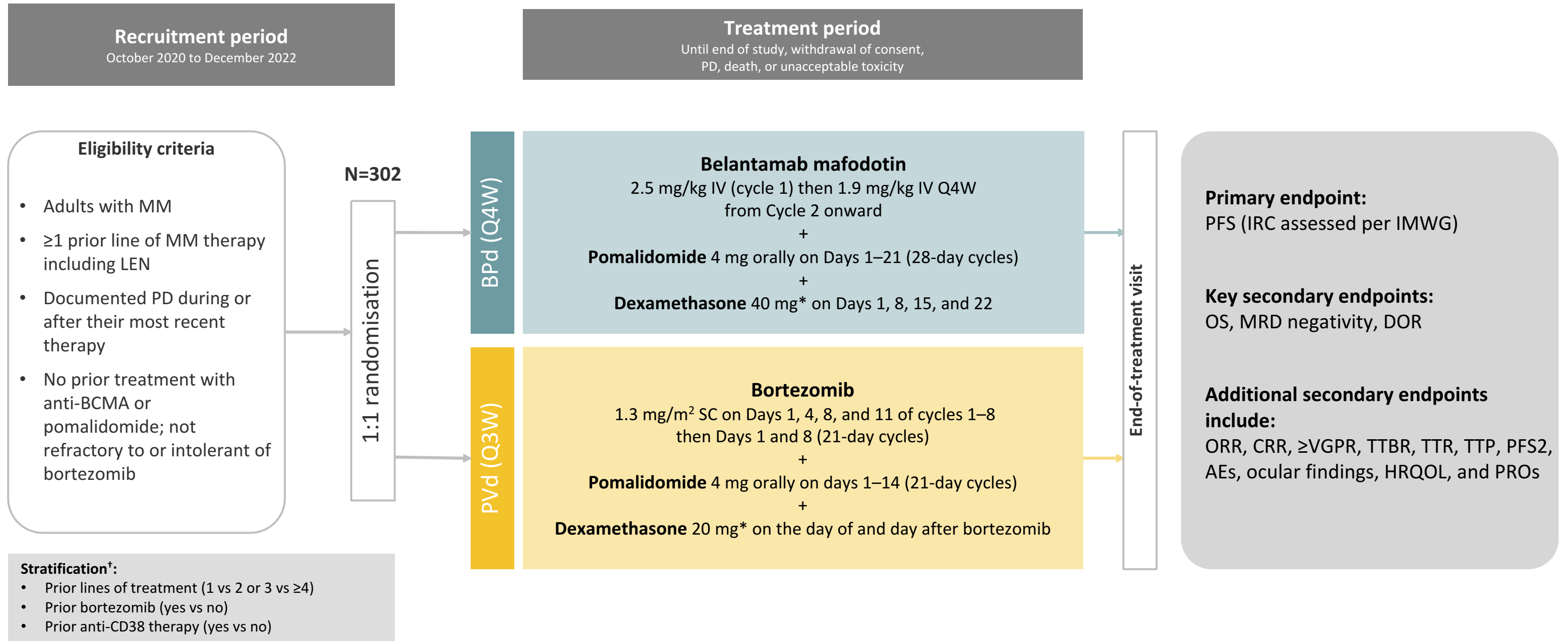
- Median time between doses increased the longer patients were on therapy
- **Dose delays did not have an impact on PFS[§]**
 - BVd patients with ≥1 dose delay of ≥12 weeks (n=126), **mPFS 36.6 months**
- 23% of patients experienced 20/50 or worse events in first 3 months; prevalence decreased thereafter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

Data beyond 30 months are cumulative

	≤3	>3 to ≤6	>6 to ≤9	>9 to ≤12	>12 to ≤15	>15 to ≤18	>18 to ≤21	>21 to ≤24	>24 to ≤27	>27 to ≤30	>30
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

*Only Belamaf treatment period considered in these post hoc analyses. †Only patients with 20/25 or better in either or both eyes at baseline are considered. ‡Mean of days between doses, for each patient, per interval is used. §Only patients receiving ≥6 months of treatment included in analysis to exclude early discontinuations (e.g., rapid PD). Belamaf, belantamab mafodotin; BVd, belamaf, bortezomib, and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; KVA, keratopathy and visual acuity; mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival. Hungria V et al. Presented at the IMS Annual Meeting. September 25–28, 2024; Poster P-396; Mateos MV et al. Presented at the ASCO Annual Meeting. May 31 – June 4, 2024; Abstract 439572.

DREAMM-8: Study design



*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. [†]Some patients were stratified by ISS status (I vs II/III); the protocol was amended on 20 April 2021 to replace this randomisation factor with prior anti-CD38 treatment (yes vs no).

AE, adverse event; BCMA, B-cell maturation antigen; BPd, belantamab mafodotin, 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.

Dimopoulos MA, et al. N Engl J Med. 2024;391:408–421 (supplement).

DREAMM-8: Baseline demographics and clinical characteristics

Baseline characteristics	ITT population	
	BPd (n=155)	PVd (n=147)
Age, median (range), years	67 (40–82)	68 (34–86)
18 to <65, n (%)	64 (41)	53 (36)
65 to <75, n (%)	72 (46)	59 (40)
≥75, n (%)	19 (12)	35 (24)
Male/female, n (%)	99 (64)/56 (36)	82 (56)/65 (44)
Asian/Black/Mixed race/White, n (%)*	133 (86)/0/20 (13)/1 (<1)	127 (87)/0/17 (12)/0
ECOG PS ≤1, n (%) [†]	146 (97)	140 (97)
ISS stage at screening, n (%)		
I	93 (60)	85 (58)
II	39 (25)	40 (27)
III	22 (14)	22 (15)
Unknown	1 (<1)	0
Years since diagnosis, median (range)	4.04 (0.4–16.7)	3.43 (0.4–17.7)
Cytogenetic abnormalities, n (%)		
Standard risk [‡]	72 (46)	75 (51)
High risk [§]	52 (34)	47 (32)
Missing or nonevaluable	31 (20)	25 (17)
Time to relapse after initiation of 1L treatment		
≤12 months	22 (14)	20 (14)
>12 months	133 (86)	127 (86)
Extramedullary disease, n (%)	20 (13)	11 (7)

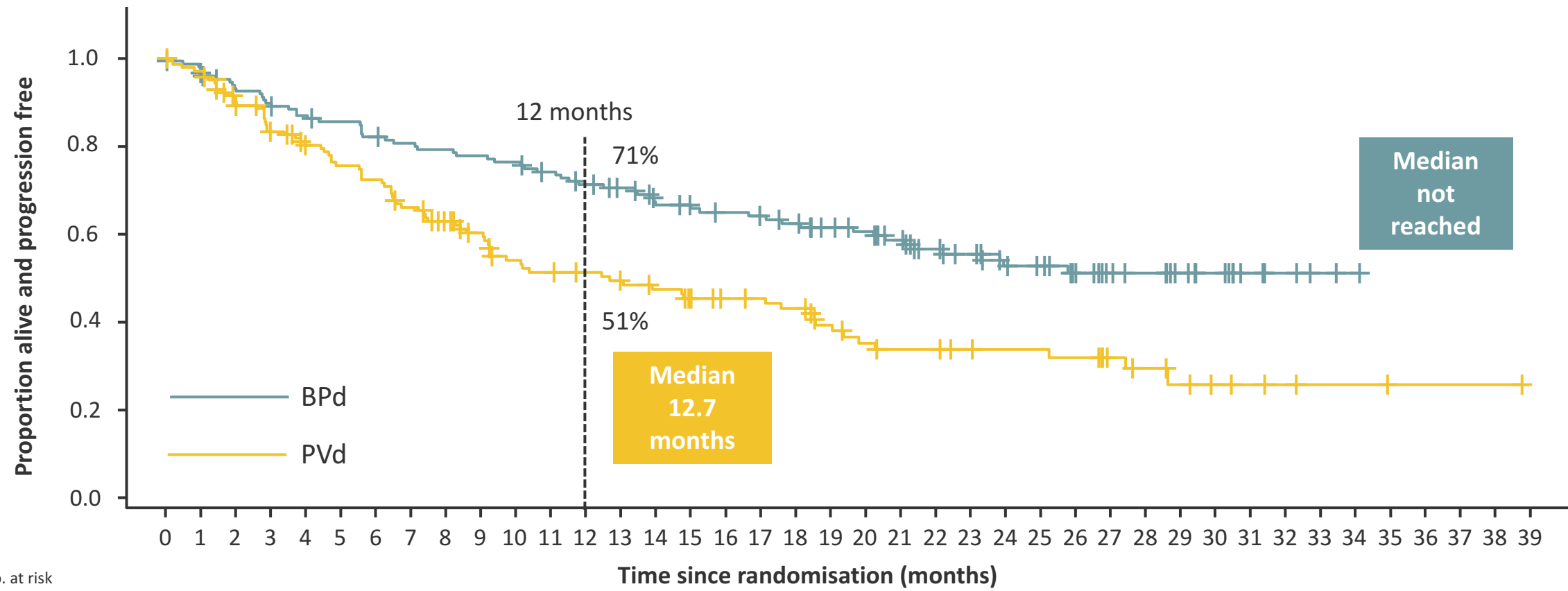
*Additionally, 1 patient (<1%) in the BPd arm and 2 patients (1%) in the PVd arm were Native Hawaiian or other Pacific Islander; 1 patient in the PVd arm had race missing and therefore percentage is out of 146. [†]Evaluated in the safety population (BPd, n=150; PVd, n=145).

[‡]Standard-risk cytogenetics were defined as having negative results for all high-risk abnormalities: t(4;14), t(14;16), or del(17p13). [§]High-risk cytogenetic abnormalities were defined as the presence of ≥1 of the following: t(4;14), t(14;16), or del(17p13).

1L, first line; BPd, belantamab mafodotin, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; ITT, intention to treat; PVd, pomalidomide, bortezomib, and dexamethasone.

Dimopoulos MA, et al. N Engl J Med. 2024;391:408–421.

DREAMM-8: Primary endpoint (PFS)



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

PFS	BPd (n=155)	PVd (n=147)
Events, ≈n (%)	62 (40)	80 (54)
PFS, median (95% CI), months	NR (20.6, NR)	12.7 (9.1, 18.5)
HR (95% CI)	0.52 (0.37, 0.73)	
P value	<0.00001	

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; $P < 0.001$)

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, belantamab mafodotin, pomalidomide, and dexamethasone; CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone.

Dimopoulos MA, et al. N Engl J Med. 2024;391:408–421.

DREAMM-8: Safety overview

N (%)	Safety population	
	BPd (n=150)	PVd (n=145)
Any AE	149 (>99)	139 (96)
Grade 3/4 AE*	136 (91)	106 (73)
Exposure adjusted, patients/100 person-years [†]	66	78
AEs leading to dose interruption/delay	136 (91)	109 (75)
Exposure adjusted, patients/100 person-years [†]	66	80
Any ocular (CTCAE/KVA) event leading to dose interruption/delay of any study treatment	124 (83)	2 (1)
AEs leading to dose reduction	92 (61)	88 (61)
Exposure adjusted, patients/100 person-years [†]	44	65
Any ocular (CTCAE/KVA) event leading to dose reduction of any study treatment	88 (59)	0
AEs leading to permanent discontinuation of any study treatment	22 (15)	18 (12)
Exposure adjusted, patients/100 person-years [†]	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 [†]	46	48
Fatal SAEs	17 (11) [‡]	16 (11)

- Exposure-adjusted AE rates were similar or lower in the BPd vs PVd arm
- Overall rates of AEs leading to treatment discontinuations were low and balanced between arms
- Ocular events were managed by dose holds (83%) and reduction in dosing frequency[§] (59%) and led to a low rate of treatment discontinuations (**9%**)

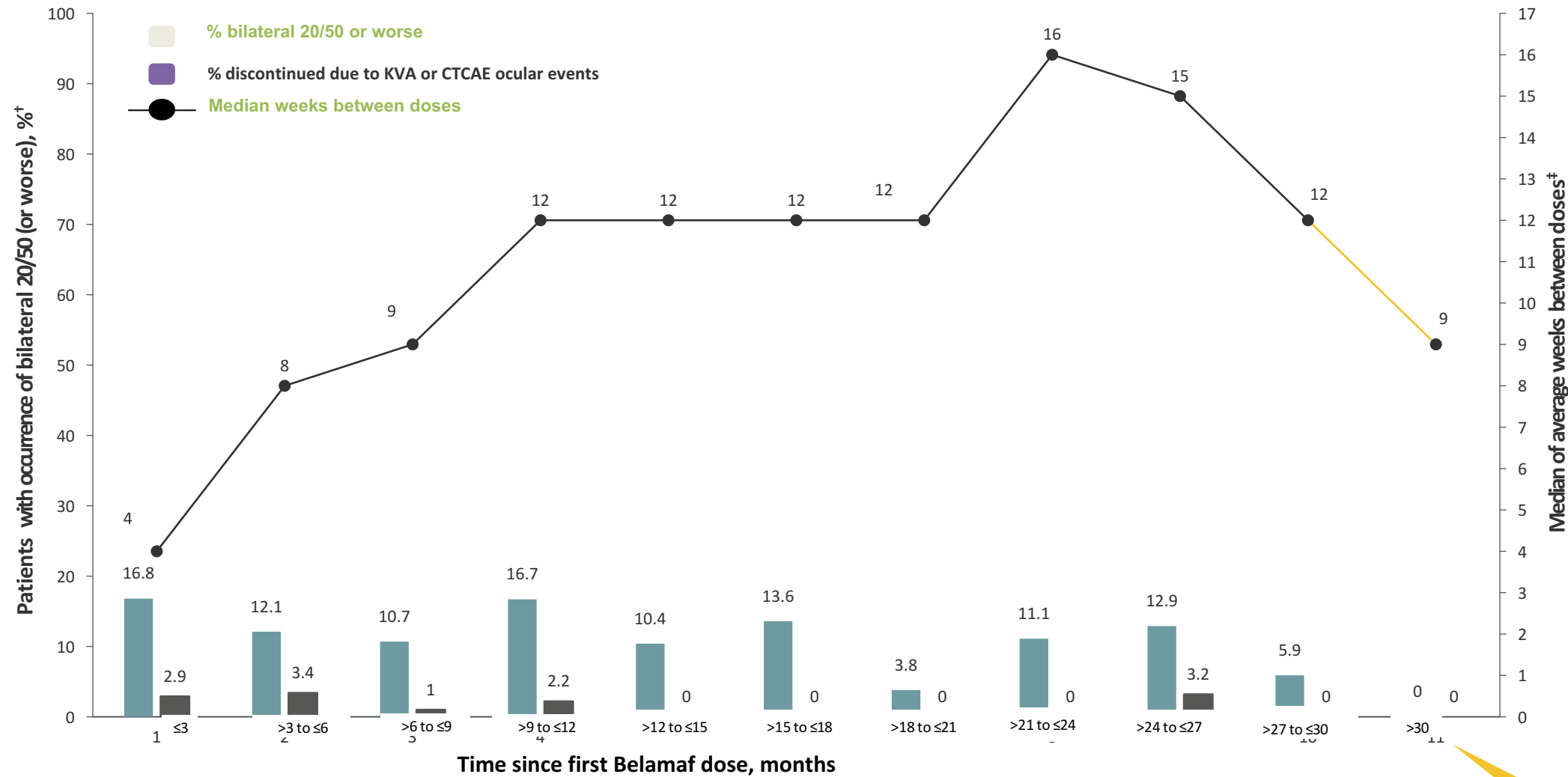
Median treatment duration across all components was 16.54 months (range, 0.92–35.06 months) in the BPd group and 8.51 months (range, 0.26–39.85 months) in the PVd group.

*Includes any patient with a Grade 3 or 4 AE. [†]Post hoc analysis of exposure-adjusted incident rates was 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. [‡]Fatal SAEs of pneumonia, meningoencephalitis herpetic, and metastatic gastrointestinal cancer were considered related to treatment in 1 patient each in the BPd group. [§]Dose frequency was reduced from Q4W to Q8W; 9 patients received 1.4 mg/kg Q8W.

AE, adverse event; BPd, belantamab mafodotin, pomalidomide, and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; KVA, keratopathy and visual acuity; PVd, pomalidomide, bortezomib, and dexamethasone; Q4W, every 4 weeks; Q8W, every 8 weeks; SAE, serious adverse event.

Dimopoulos MA, et al. N Engl J Med. 2024;391:408–421 (supplement).

DREAMM-8: Impact of dose modifications on PFS and ocular management*



- Median intervals between doses increased the longer patients were on therapy
- **Longer dosing intervals did not impact PFS[§]**
 - Median PFS was not reached in BPD-treated patients (n=93) with ≥1 dose delay of ≥12 weeks
- 16.8% of patients experienced BCVA 20/50 or worse within the first 3 months of treatment; prevalence remained low thereafter, generally decreasing with time
- Rates of treatment discontinuation due to ocular events were low

	1 ≤3	>3 to ≤6	>6 to ≤9	>9 to ≤12	>12 to ≤15	>15 to ≤18	>18 to ≤21	>21 to ≤24	>24 to ≤27	>27 to ≤30	>30
No. of patients on treatment	137	116	103	90	77	59	52	45	31	17	8
No. of patients with bilateral 20/50 or worse	23	14	11	15	8	8	2	5	4	1	0
Median days between doses	28.5	56	63.5	84	84	86	84	111	106	84	62.25
No. of patients who discontinued due to KVA or ocular CTCAE event	4	4	1	2	0	0	0	0	1	0	0

Data beyond 30 months are cumulative

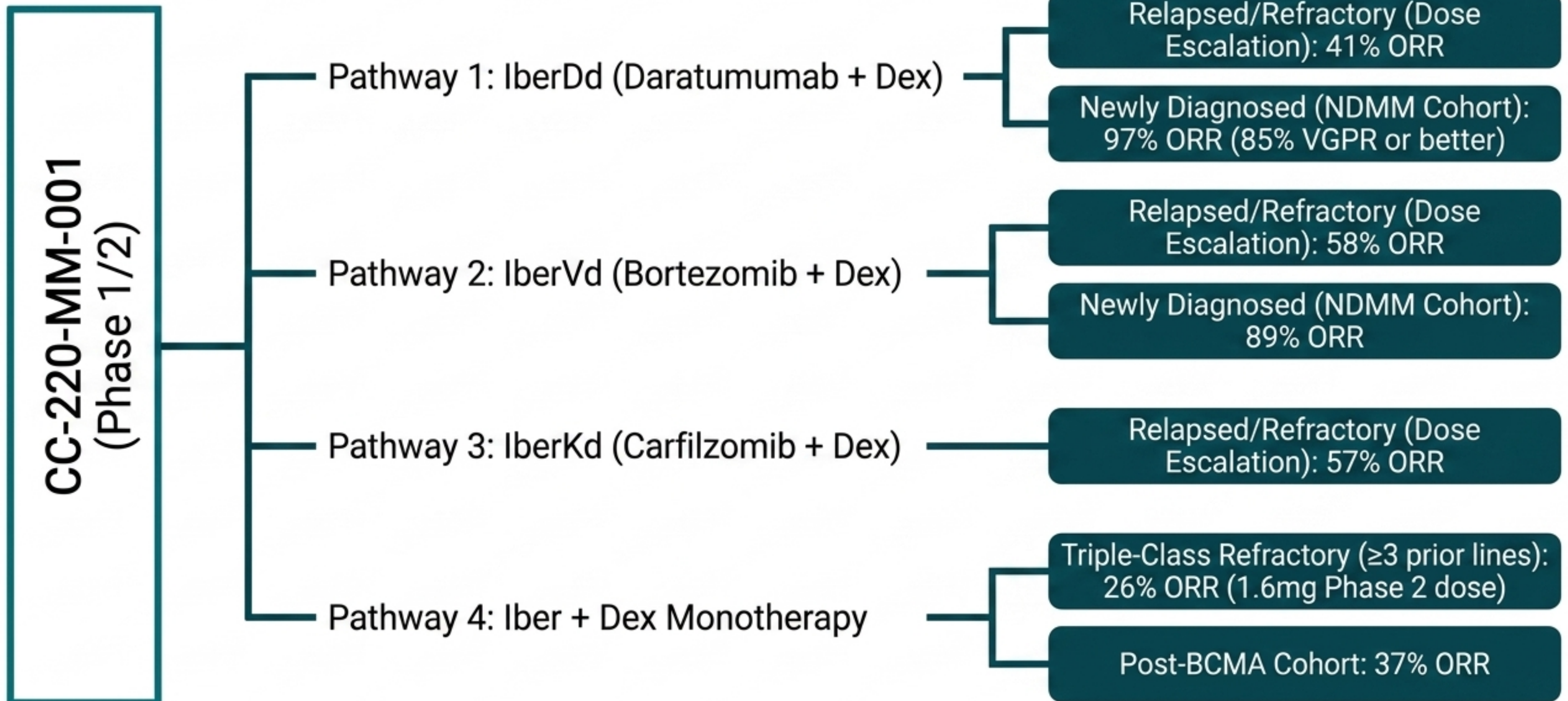
*Only Belamaf treatment period considered in these post hoc analyses. †Only patients with 20/25 or better in either or both eyes at baseline are considered. ‡Mean of days between doses, for each patient, per interval is used. §Only patients receiving ≥6 months of treatment included in analysis to exclude early discontinuations (e.g., rapid PDs). BCVA, best corrected visual acuity; Belamaf, belantamab mafodotin; BPD, belamaf, pomalidomide, and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; KVA, keratopathy and visual acuity; PD, progressive disease; PFS, progression-free survival.

THE CELMoD EVOLUTION: OVERCOMING IMiD RESISTANCE

	STANDARD IMiDs Lenalidomide / Pomalidomide	IBERDOMIDE (CELMoD)
TARGET BINDING	Binds CRBN	10 to 20-fold higher CRBN affinity
TRANSCRIPTION FACTOR DEGRADATION	Standard ubiquitination	Highly potent degradation of Ikaros and Aiolos (induces apoptosis)
IMMUNE CO-STIMULATION	Baseline T/NK cell activity	Enhanced IL-2 secretion, increased NK cell proliferation, and granzyme-B degranulation
RESISTANCE BYPASS	Loss of efficacy in dysregulated CRBN	Retains potent activity even in Pomalidomide-resistant cell lines

CC-220-MM-001: Efficacy Across Combinations and Disease Stages

IBERDOMIDE



EMN26: Deepening Responses in Post-ASCT Maintenance

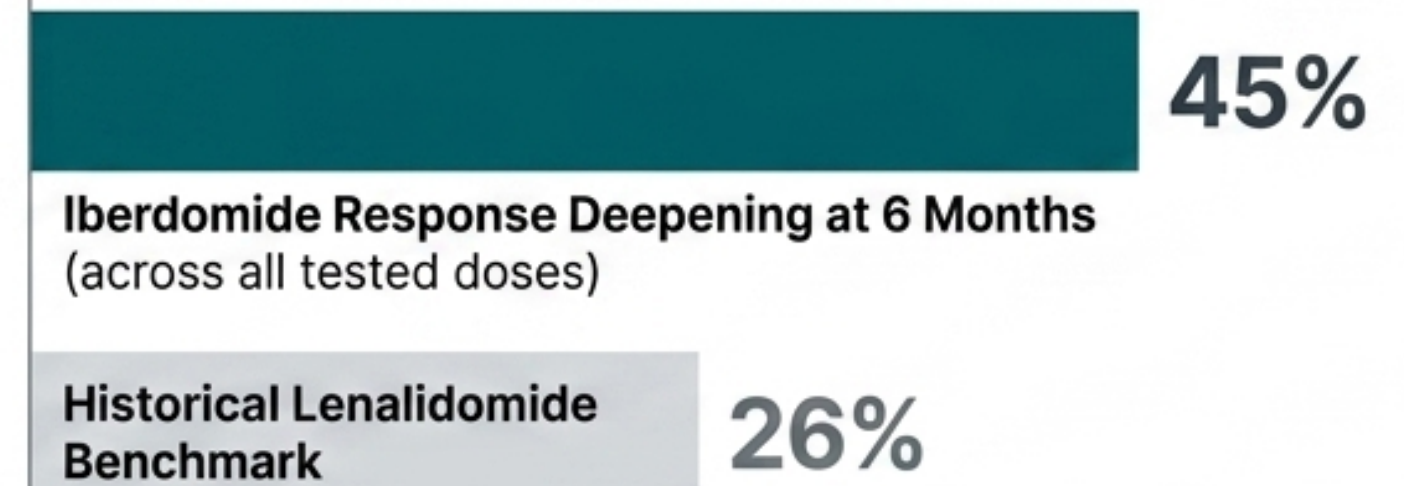
Trial Design

Phase 2, Multicohort.

Population: Newly diagnosed MM post-ASCT (single or double) with PR or better.

Doses tested: 0.75 mg, 1.0 mg, and 1.3 mg.

Efficacy & Tolerability



Safety Profile

Manageable toxicity. No occurrences of thrombocytopenia, anemia, or diarrhea. Primary AE: Neutropenia and fatigue.

The Path to Standard of Care: Phase 3 EXCALIBER Trials

EXCALIBER- RRMM (NCT04975997)

Setting: Early-line Relapsed/Refractory (1-2 prior lines).

Comparison: IberDd (Iberdomide + Dara + Dex) vs. DVd (Dara + Bortezomib + Dex).

Endpoints: PFS and MRD-negative CR at any time.

Completion target: March 2026.

EXCALIBER- Maintenance (NCT05827016)

Setting: Newly diagnosed MM post-ASCT.

Comparison: Head-to-head Iberdomide vs. Lenalidomide.

Endpoints: Defining the future of maintenance.

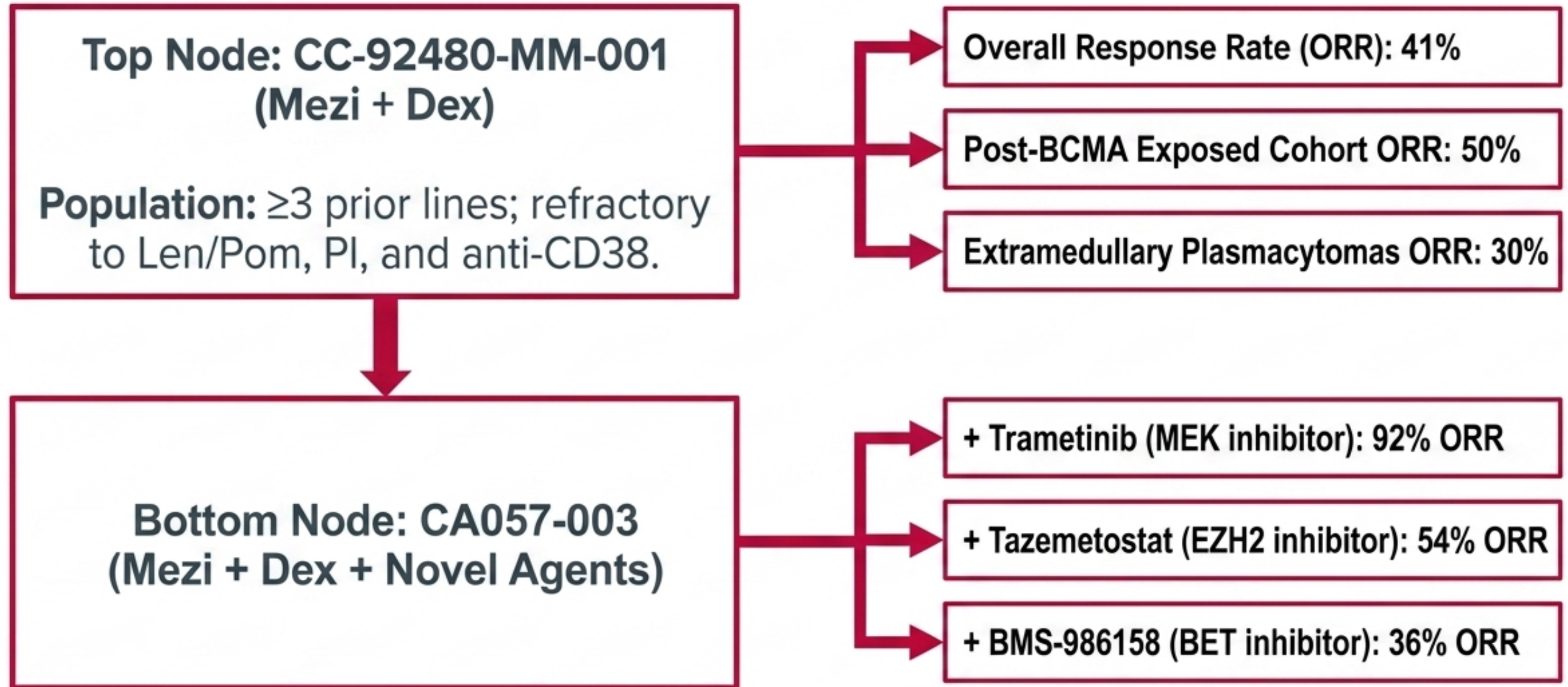
Completion target: March 2029.

Celgene. Available from: <https://clinicaltrials.gov/study/NCT04975997>. Accessed February 14, 2025.

Bristol Myers Squibb. Available from: <https://clinicaltrials.gov/study/NCT05827016>. Accessed February 14, 2025.24

Efficacy in Highly Refractory and Post-BCMA Populations

MEZIGOMIDE



Sandhu I, Richardson PG, Oriol A, et al.. *Blood*. 2024;144(Suppl 1):1025.

Costa LJ, Popat R, Siegel D, et al.. *Blood*. 2024;144(Suppl 1):677. doi:10.1182/blood-2024-198403

CC-92480-MM-002: Highly Potent Standard-of-Care Triplets

Quadrant 1: MeziDd
(Mezigdomide + Daratumumab)



Note: Zero patients refractory to Daratumumab in this arm.

Quadrant 2: MeziVd
(Mezigdomide + Bortezomib)



Note: Heavily pretreated population, all prior IMiD exposed.

Quadrant 3: MeziKd
(Mezigdomide + Carfilzomib)



Note: Highly refractory, robust synergy.

Quadrant 4: MeziEd
(Mezigdomide + Elotuzumab)



Richardson PG, Sandhu I, Hofmeister CC, et al. *Blood*. 2023;142(Suppl 1):1013.

Forcing the Next Line: The Phase 3 SUCCESSOR Trials

SUCCESSOR-1 (NCT05519085)

Setting: Relapsed/Refractory (1-3 prior lines). Prior lenalidomide exposure required; pomalidomide naïve.

Comparison: MeziVd (Mezigdomide + Bortezomib + Dex) vs. PomVd (Pomalidomide + Bortezomib + Dex).

Status: Stage 1 (dose selection) transitioning to Stage 2 (Efficacy).

SUCCESSOR-2 (NCT05552976)

Setting: Progressive disease (≥ 1 prior line). Prior lenalidomide and anti-CD38 exposure required; carfilzomib naïve.

Comparison: MeziKd (Mezigdomide + Carfilzomib + Dex) vs. Kd (Carfilzomib + Dex).

Status: Primary endpoint PFS, tracking MRD negativity.

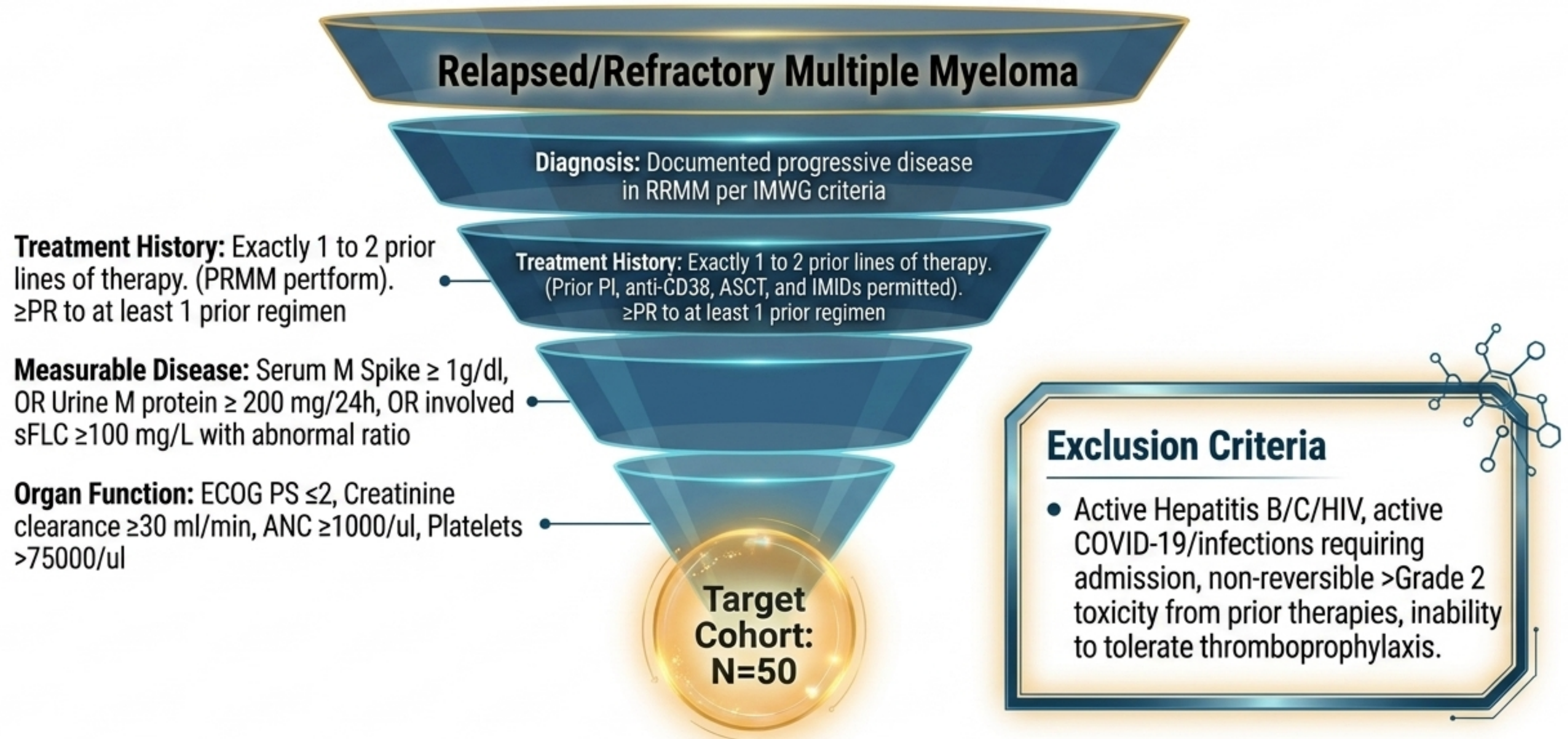
The LAMN Clinical Research Infrastructure

- **Rio de Janeiro, Brazil:**
Dr. Angelo Maiolino (PI) - Centro de Pesquisa, Instituto Americas
- **São Paulo, Brazil:**
Dr. Vania Hungría - Centro de Pesquisa Clinica São Germano
- **Bahia, Brazil:**
Dr. Edvan Crusoe - Centro de Pesquisa IDOR
- **Buenos Aires, Argentina:**
Dr. Dorotea Fantl & Dr. Natalia Schutz - Hospital Italiano
- **Santiago de Chile, Chile:**
Dr. Camila Peña - Hospital del Salvador



Study Scope: 50 total participants
Enrollment Period: 2 years

Isolating the Target Patient Cohort



An Optimized, All-Oral Dosing Regimen



28-Day Treatment Cycle

- **Iberdomide (CC-220):** 1.0 mg PO Once Daily (Days 1–21)
- **Dexamethasone:** 40 mg PO Once Weekly (Days 1, 8, 15, 22)
- **Age/Comorbidity Exception:** Dexamethasone reduced to 20 mg weekly for patients ≥ 75 years, BMI < 18.5 , or poorly controlled diabetes.

Mandatory Supportive Care:

- Venous thromboprophylaxis is mandatory continuously during treatment.
- G-CSF is encouraged to prevent neutropenia.

Conclusions & Limitations

Key Takeaways

- Iberdomide and mezigdomide expand druggable targets via cereblon modulation — active even in lenalidomide/pomalidomide-resistant disease
- Promising efficacy and manageable safety across multiple combination regimens in RRMM and NDMM
- Oral administration and synergy with anti-CD38, proteasome inhibitors, and T cell-redirecting therapies make them attractive backbone agents
- Phase 3 trials (EXCALIBER-RRMM, EXCALIBER-Maintenance, SUCCESSOR-1, SUCCESSOR-2) will provide definitive long-term efficacy and safety data



Thank you !

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Universidade Federal do Rio de Janeiro.



CNPq

MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E INOVAÇÕES

