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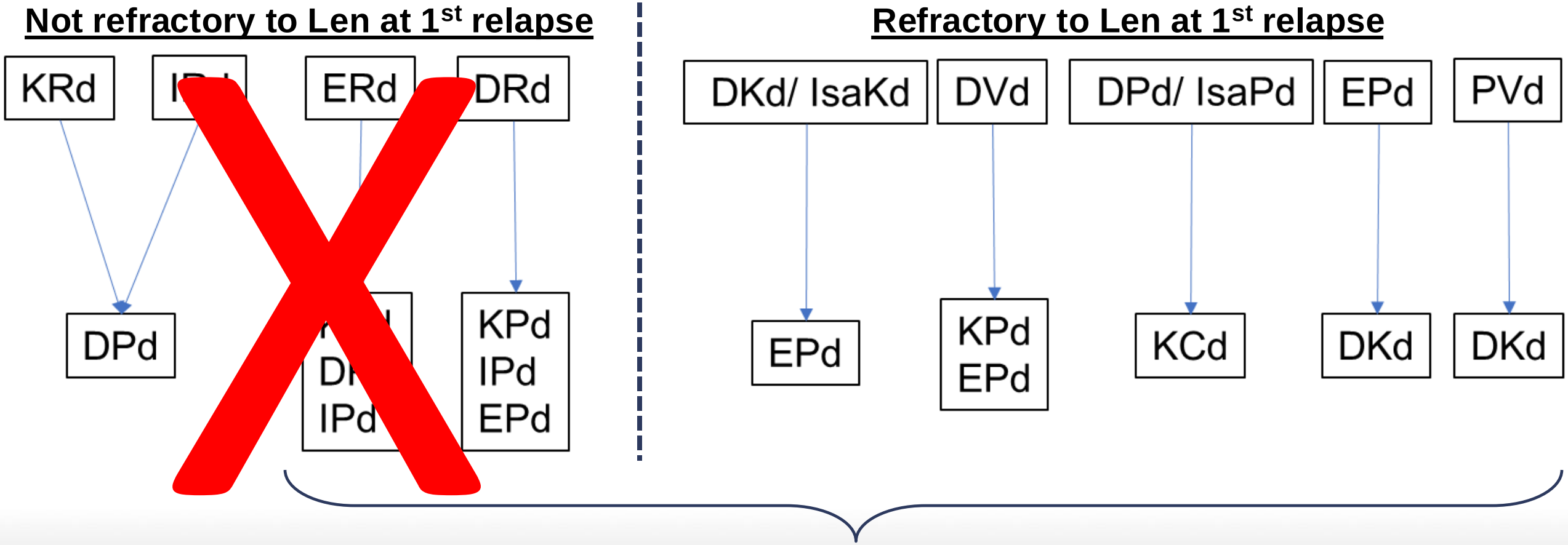
Relapsed Myeloma

Sagar Lonial, MD
Professor and Chair
Department of Hematology and Medical Oncology
Anne and Bernard Gray Professor in Cancer
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

General Principles

- Duration of initial response defines biology
- Triplet (two active classes + dex) preferred over doublet
  - At least one drug from a non-refractory class
- Consider PS, age, and comorbidities when selecting drug/doses
- Take into account prior toxicities/residual toxicities
- Treat to maximum response and maintain on one drug until progression or tolerability

Approach to First Relapse – and Later



Clinical trials OR repeat combinations of agents most remotely used

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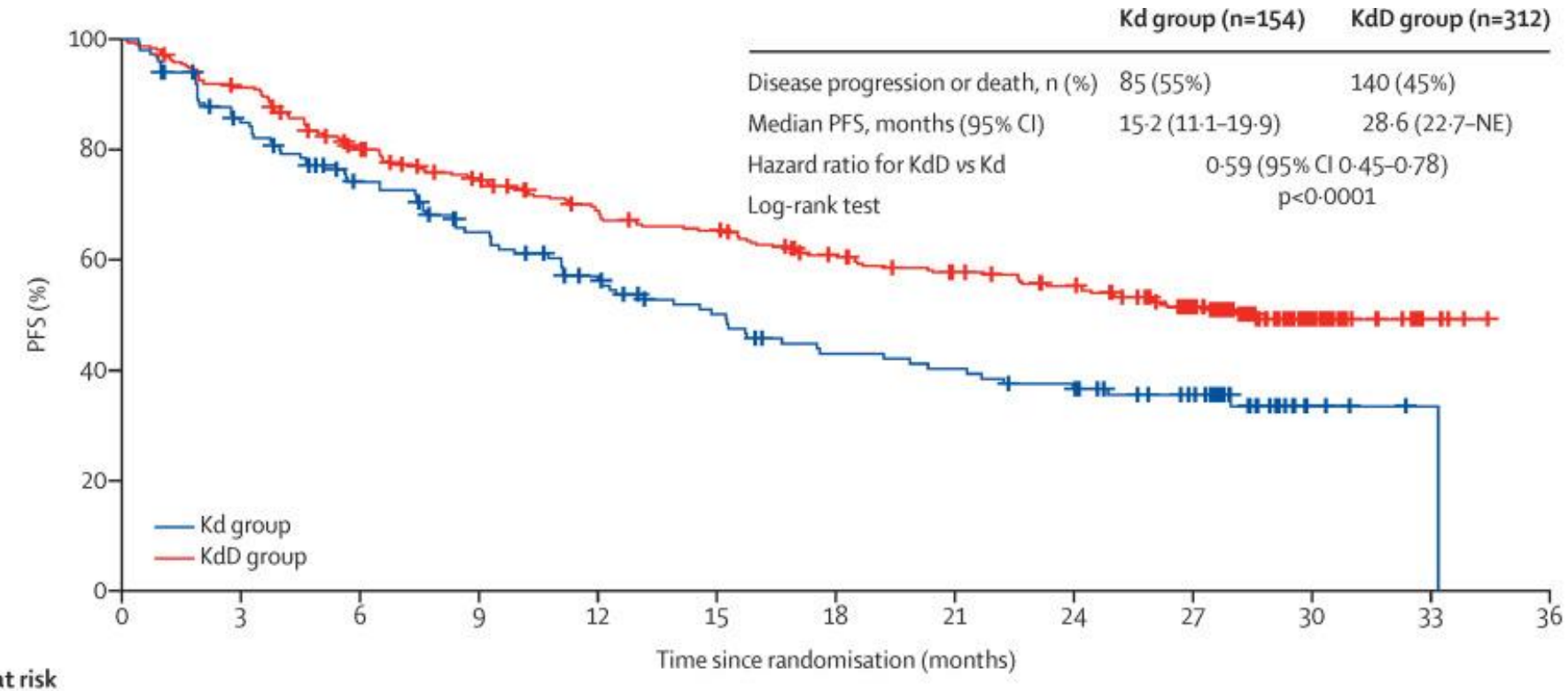
***Overall**: while triplets are preferred, lower dose triplets or doublets can be used in frail and older patients*

CANDOR: Dara-Kd Improved PFS vs Kd



Number at risk (number censored)													
Kd group	154 (0)	120 (12)	99 (18)	83 (22)	69 (26)	57 (30)	47 (32)	44 (32)	39 (33)	28 (43)	4 (66)	1 (69)	0 (69)
KdD group	312 (0)	279 (6)	235 (16)	210 (25)	189 (31)	178 (32)	159 (39)	146 (44)	136 (48)	105 (70)	30 (143)	6 (166)	0 (172)

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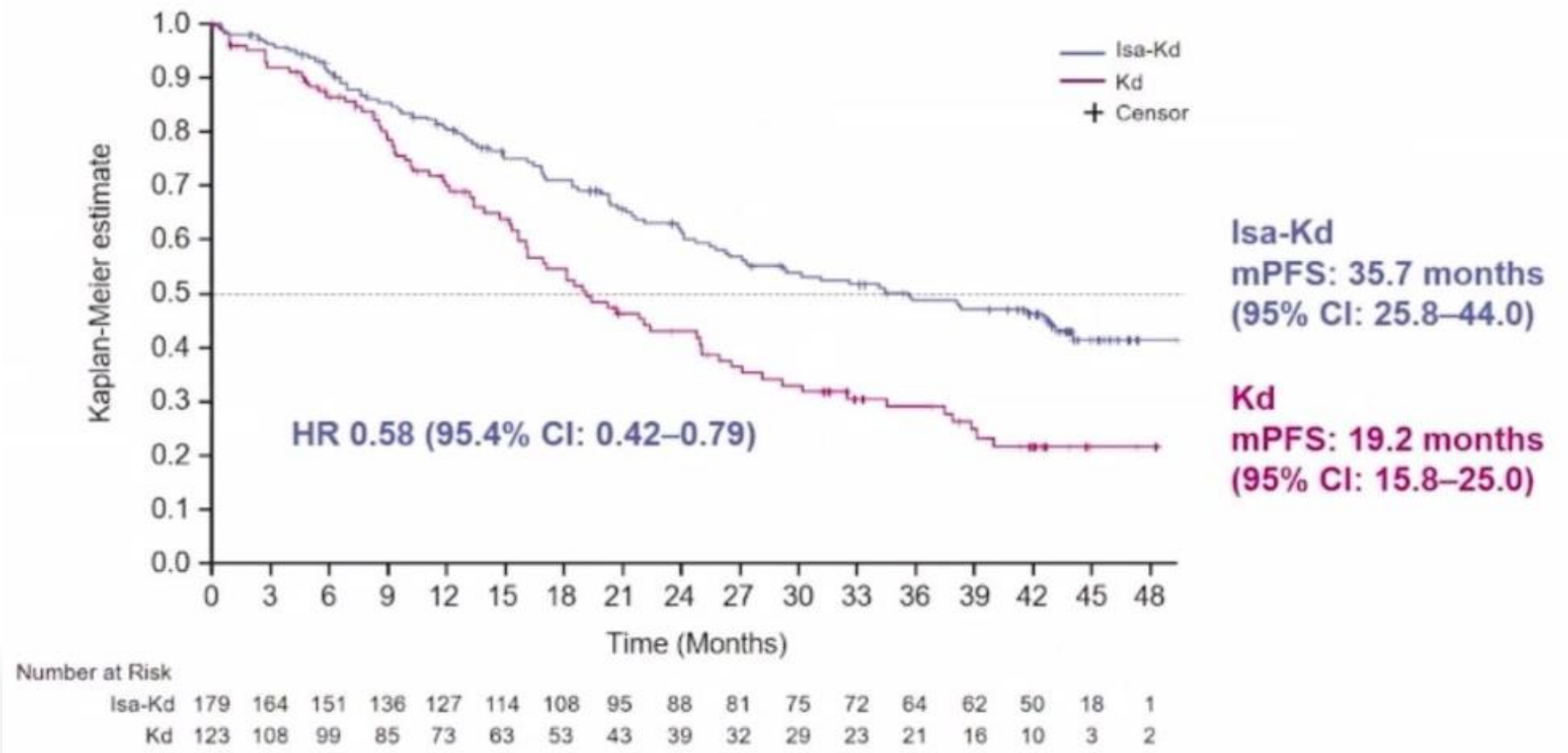
Usmani SZ et al. *Lancet Oncol*. 2022;23(1):65-76.

IKEMA: Isa-Kd Improved PFS vs Kd



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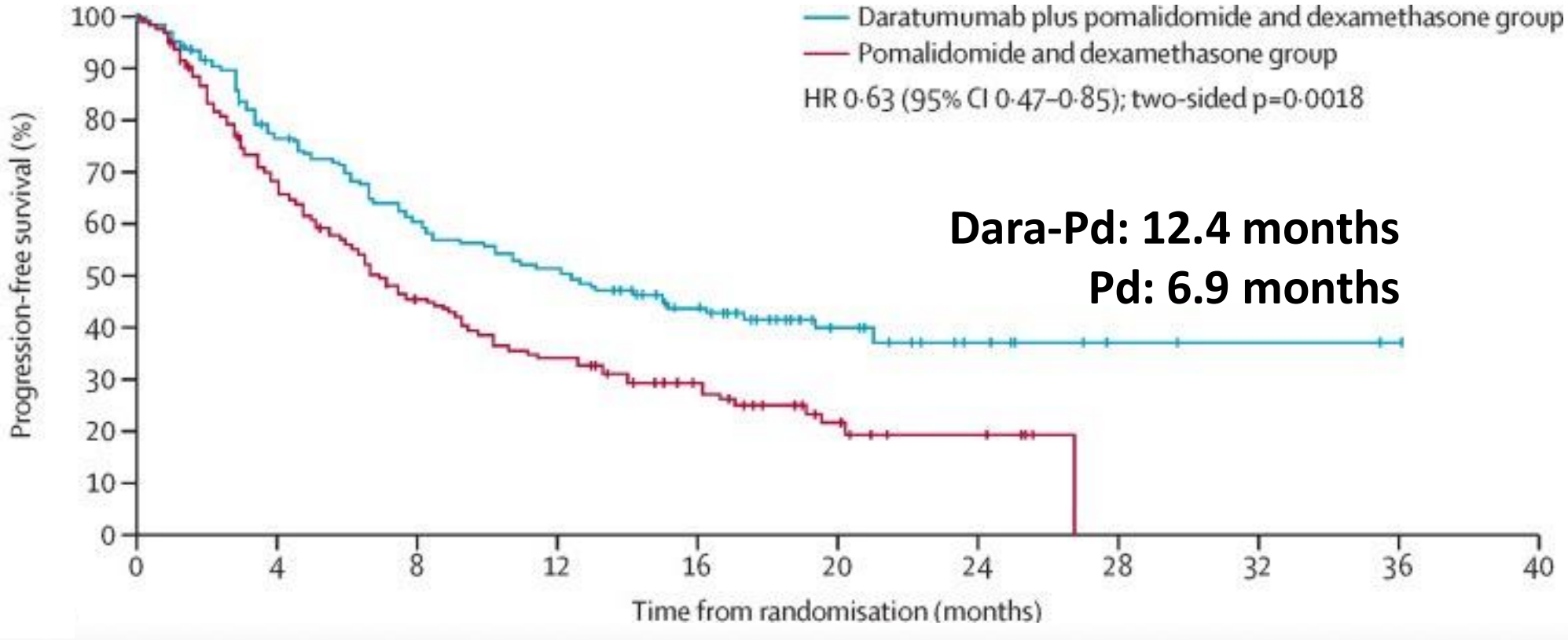
Moreau P et al. COMy 2022. Abstract VP5-2022.

APOLLO: Dara-Pd Improved PFS vs Pd



Dara-Pd: 12.4 months

Pd: 6.9 months

Median PFS among patients refractory to lenalidomide was 9.9 months for Dara-Pd and 6.5 months for Pd

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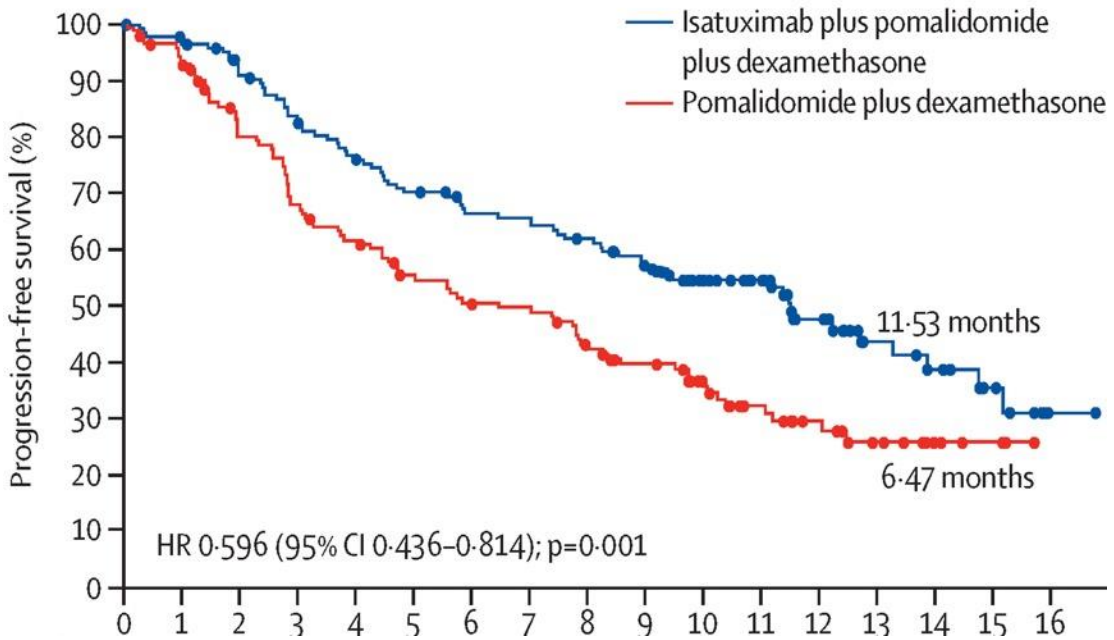
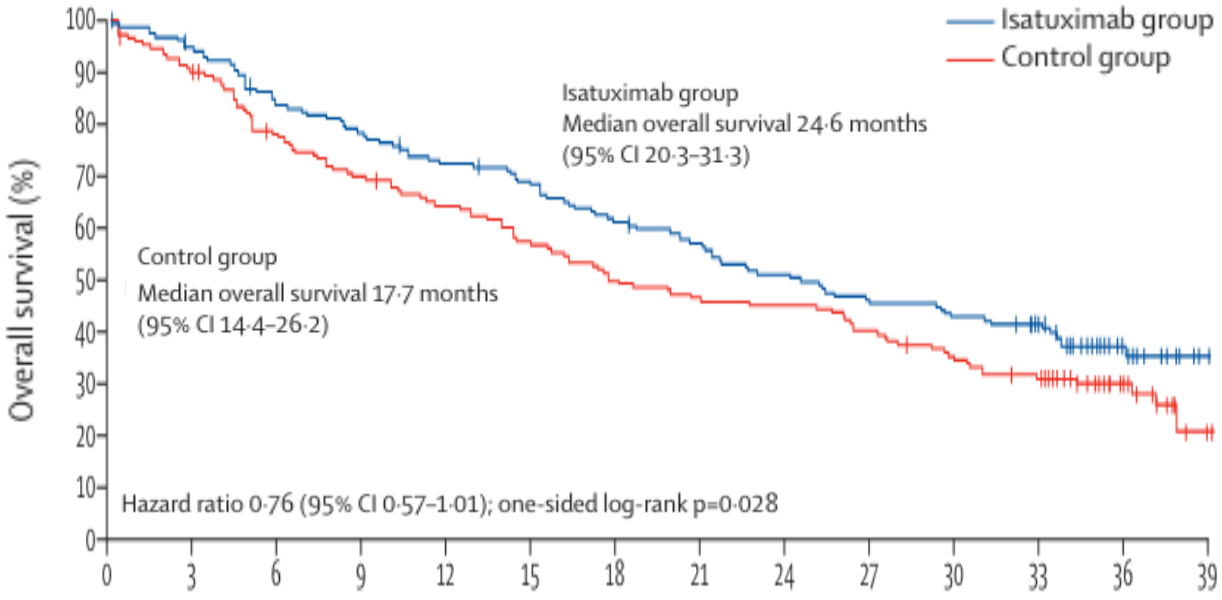
Dimopoulos MA et al. *Lancet Oncol*. 2021;22(6):801-812.

ICARIA-MM: Isa-Pd Improved PFS vs Pd





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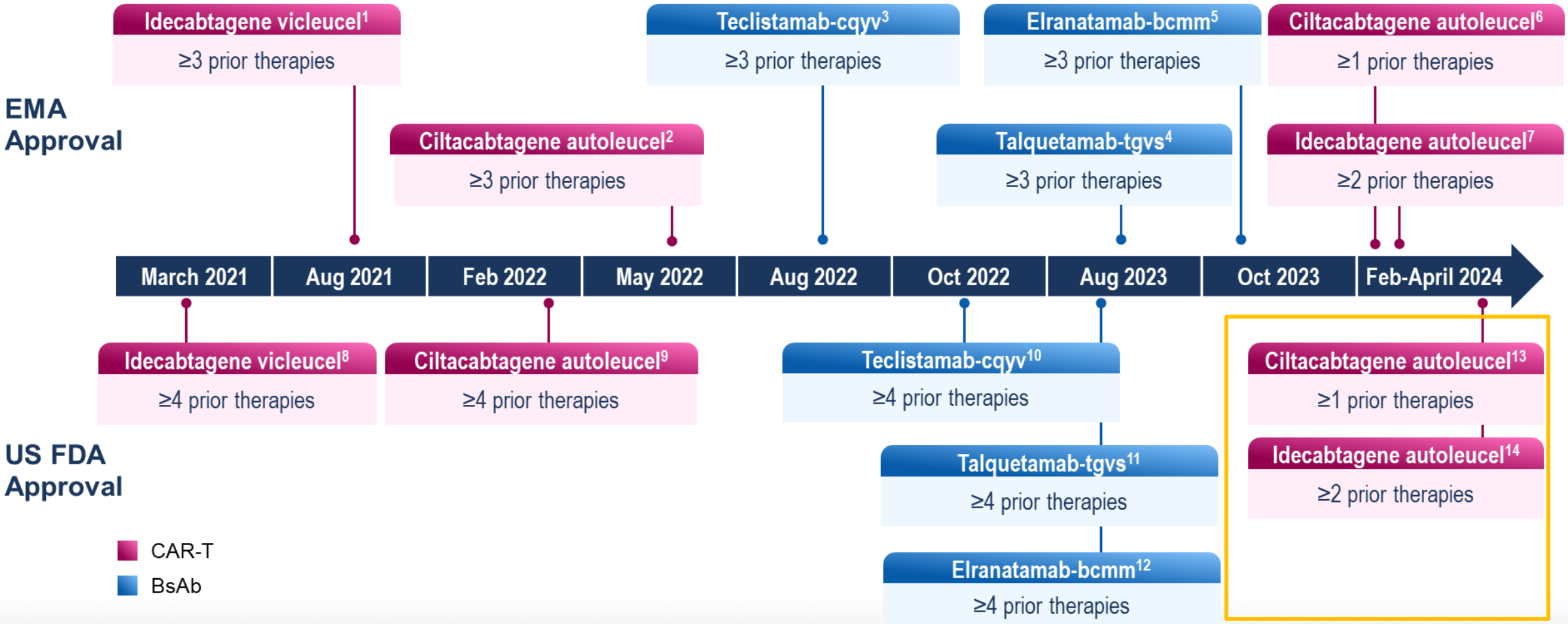
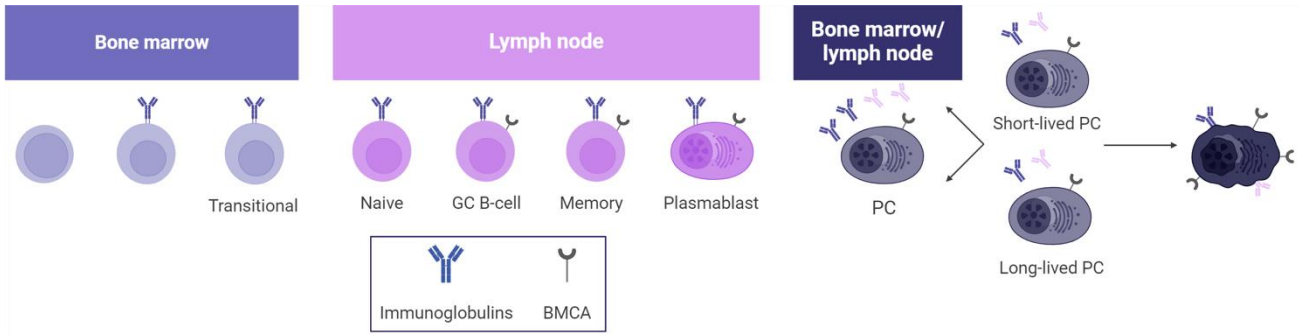
Attal M et al. *Lancet*. 2019;394(10214):2096-107.
Richardson PG et al. *Lancet Oncol*. 2022;23(3):416-427.

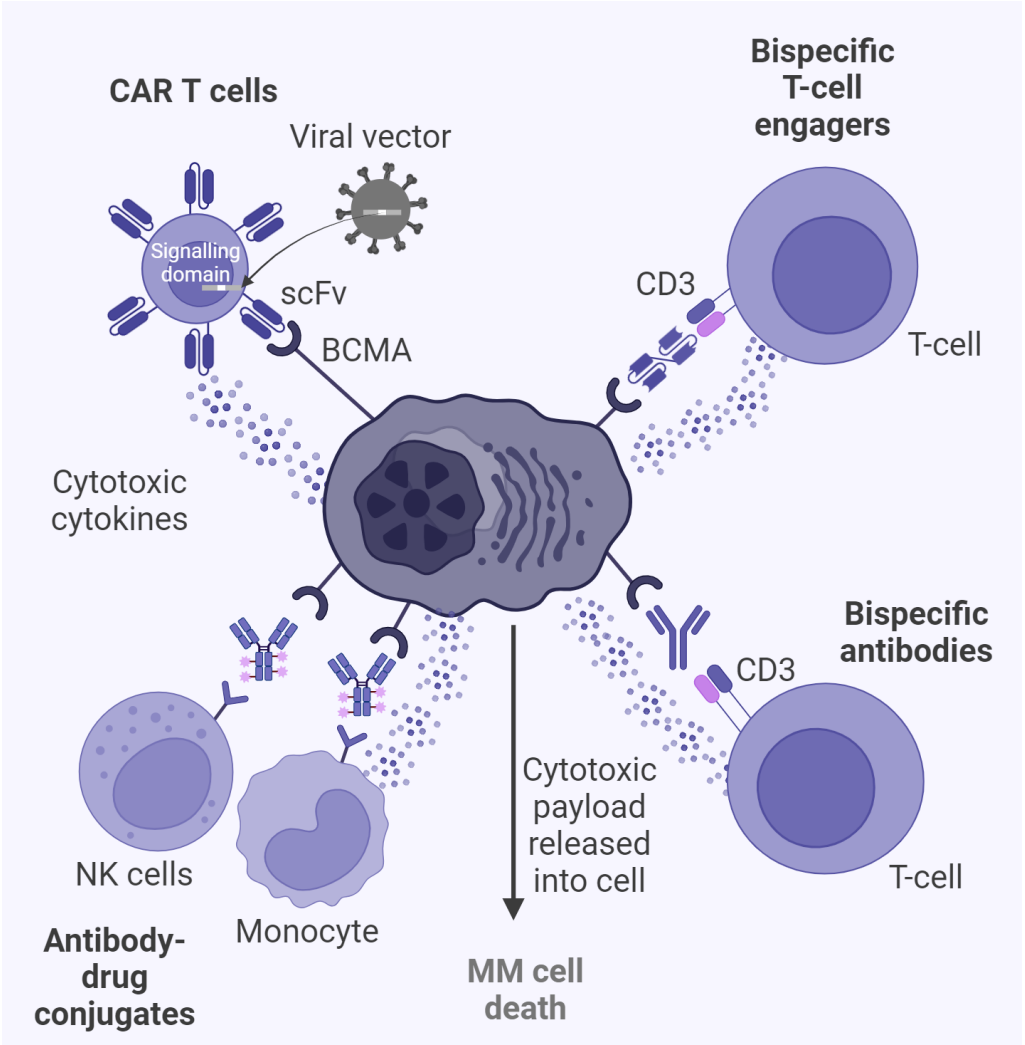
Recent Immunotherapy Advancements in R/R MM



BCMA engagement in RRMM[1]

- Bispecfic Abs simultaneously bind to myeloma-specific antigens on MM cells and CD3 on T-cells.
- MM antigens include BCMA, CD38, CS1/SLAMF7, GPRC5D, and FcRH5
- T-cell activation, proliferation, and differentiation into various memory subsets
- Increased levels of granzyme B, IFN-γ, IL2, IL6, IL8, IL10, and TNF-α





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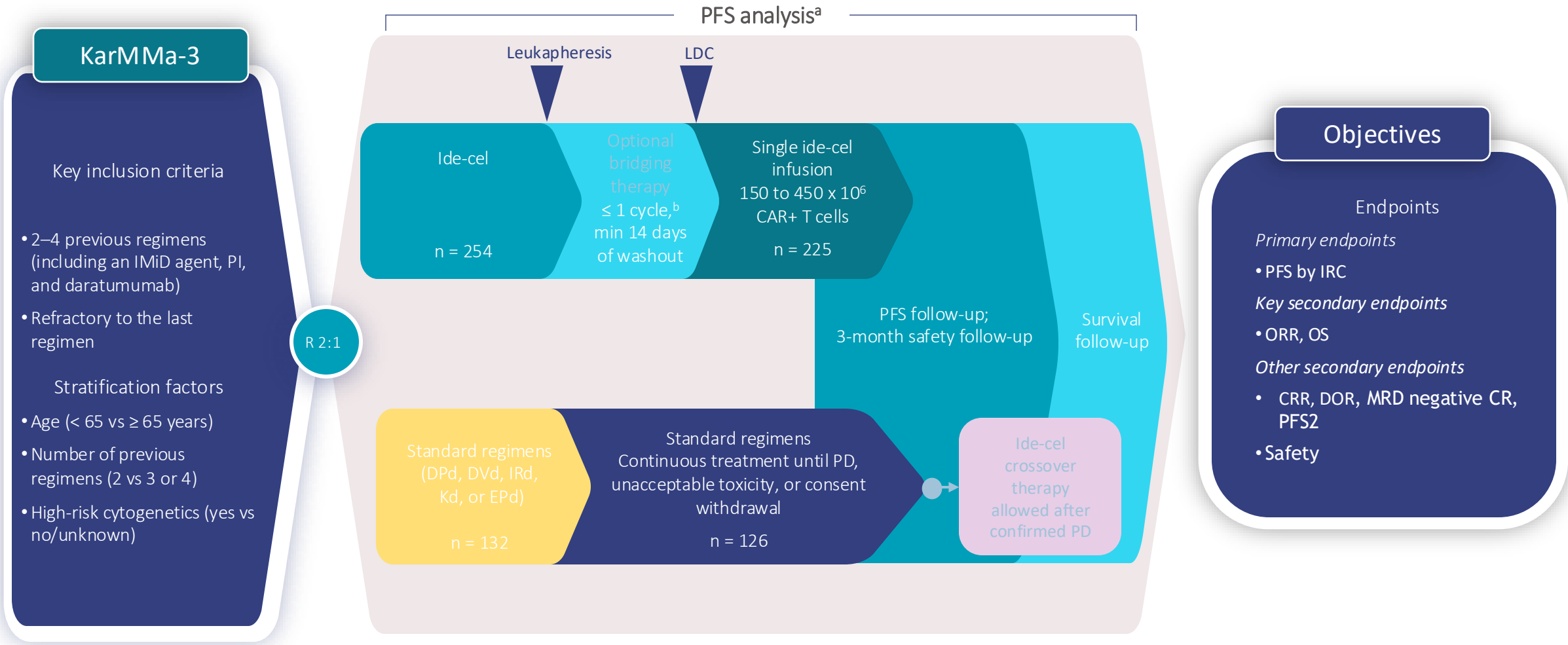
Ab, antibody; BCMA, B-cell maturation antigen; BM, bone marrow; CAR, chimeric antigen receptor; FcRH5, Fc receptor-homolog 5; GC, germinal center; GPRC5D, G protein–coupled receptor class C group 5 member D; IFN, Interferon; IL, interleukin; LN, lymph node; MM, multiple myeloma; NK, natural killer; PC, plasma cell; RRMM, relapsed/refractory multiple myeloma; scFv, single-chain fragment variable; SLAM, signaling lymphocytic activation molecule; TNF, tumor necrosis factor.

1. Cho SF, et al. *Front in Oncol*. 2022:12:1032775.

KarMMa-3 study design (NCT03651128)

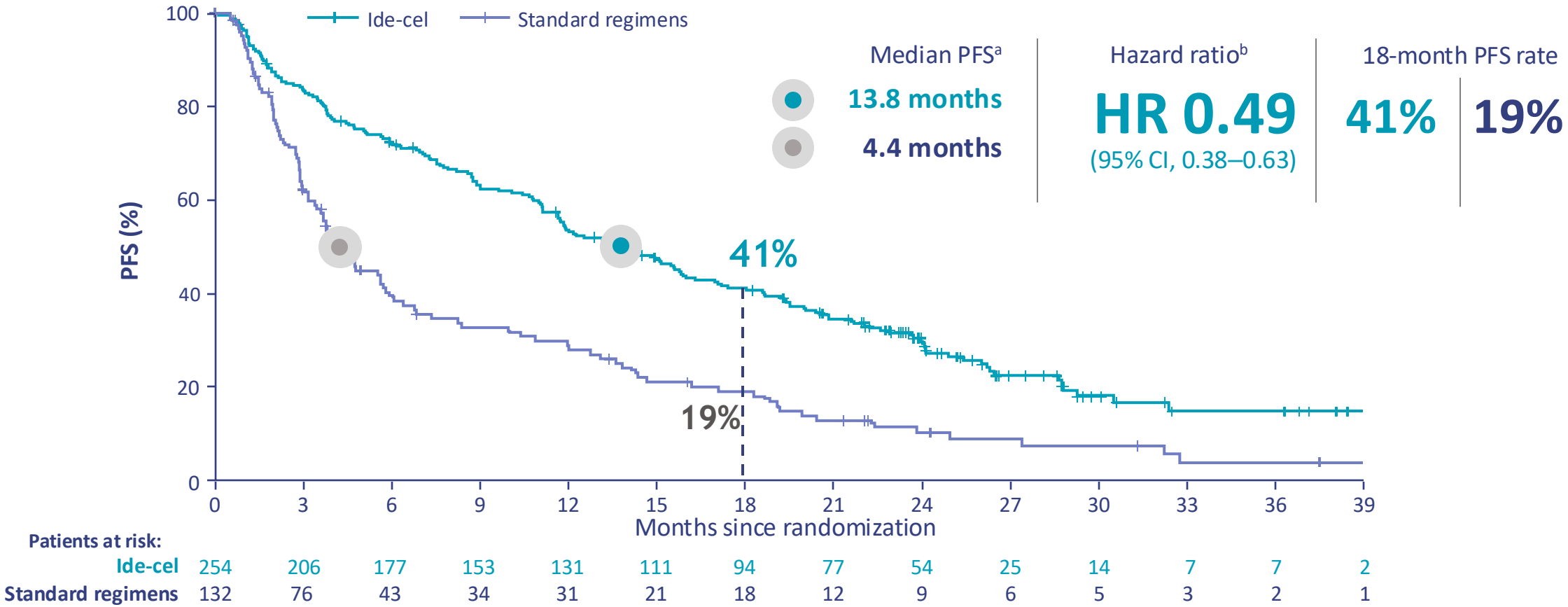
Animated slide



[a]Time from randomization to the first occurrence of disease progression or death from any cause according to IMWG criteria; [b]Up to 1 cycle of DPd, DVd, IRd, Kd, or EPd may be given as bridging
DPd, daratumumab/pomalidomide/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; EPd, elotuzumab/pomalidomide/dexamethasone; IRC, Independent Response Committee; IRd, ixazomib/lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; LDC, lymphodepleting chemotherapy; min, minimum; MRD, minimal residual disease; PD, progressive disease; PFS2, progression-free survival on next line of therapy; R, randomization.

Rodríguez-Otero P, et al. ASH 2023 Abstract 1028

Significant benefit with ide-cel at final PFS analysis (ITT population)



PFS was analyzed in the ITT population of all randomized patients in both arms and included early PFS events occurring between randomization and ide-cel infusion. PFS based on IMWG criteria per IRC. [a]Based on Kaplan–Meier approach; [b]Stratified HR based on univariate Cox proportional hazard model. CI is two-sided. IMWG, International Myeloma Working Group.

Rodríguez-Otero P, et al. ASH 2023 Abstract 1028

Phase III CARTITUDE-4 Clinical Trial: Study Design

Key Eligibility Criteria

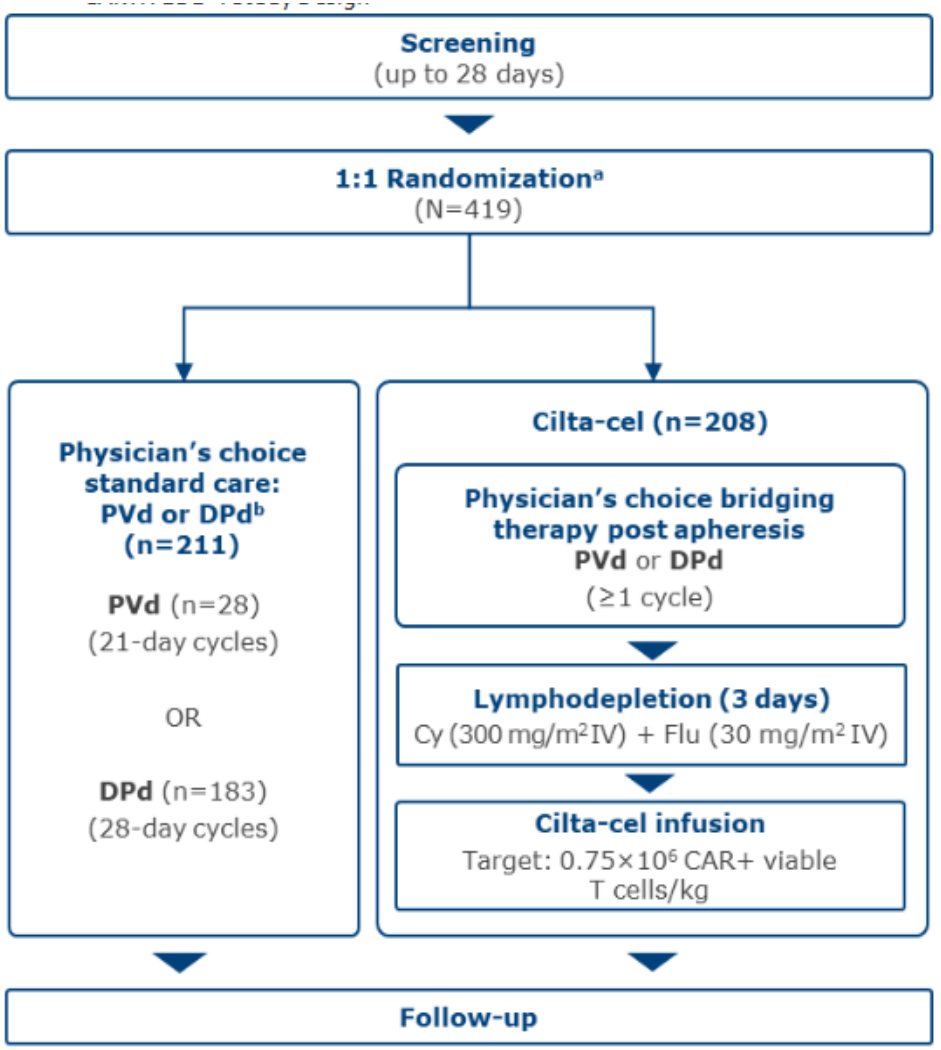
- Measurable disease
- Progressive MM per IMWG criteria or within 6 months of last regimen
- Received 1-3 prior lines of therapy including a PI and an immunomodulatory drug
- Refractory to lenalidomide
- No prior exposure to BCMA-targeting agents
- No prior treatment with CAR-T therapy
- ECOG performance status ≤1

Primary Outcome

- PFS

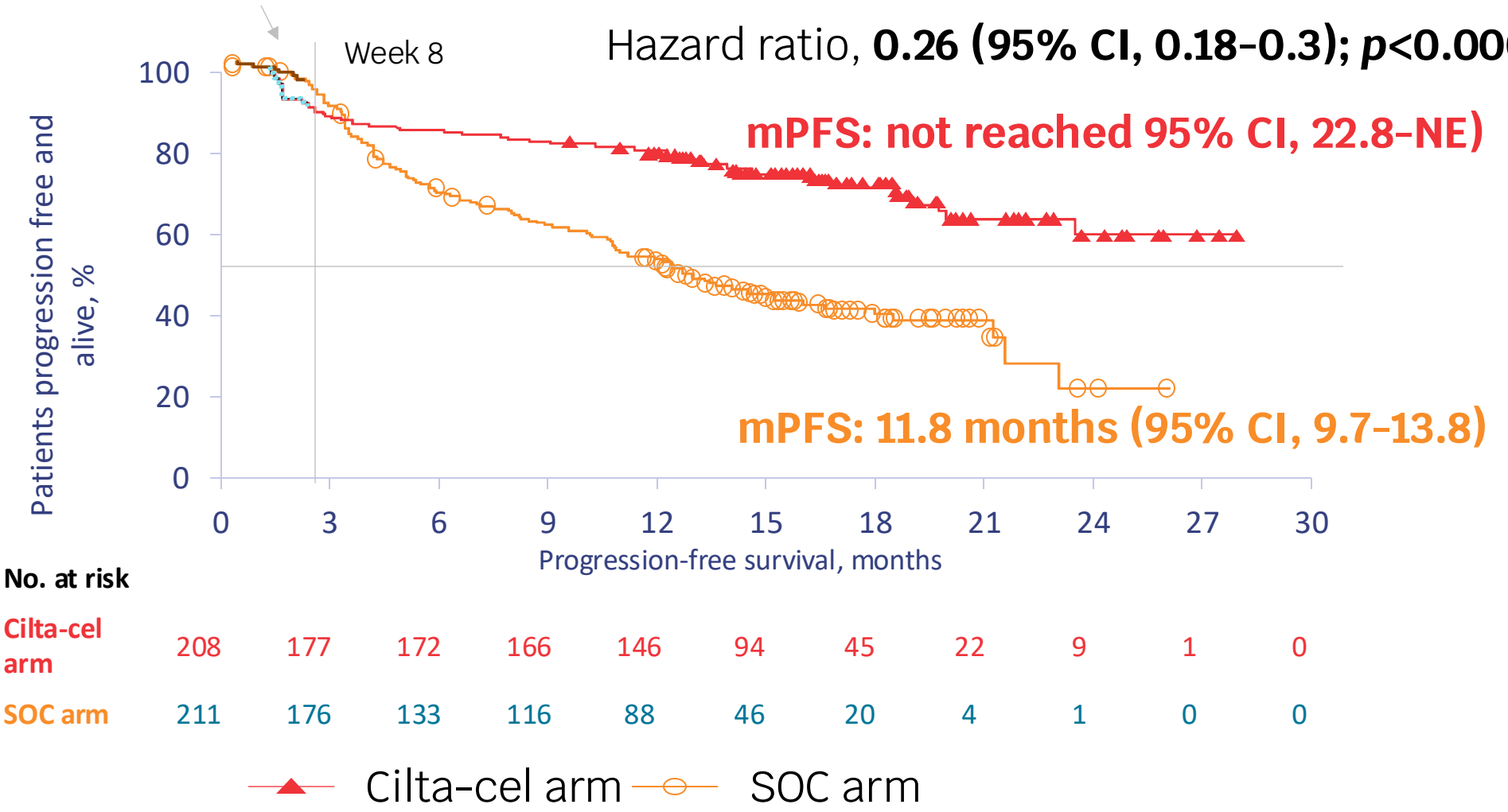
Key Secondary Outcomes[c]

- CR or better
- ORR
- Overall MRD negativity rate
- OS
- PROs
- Safety
- PK



San-Miguel J, et al. *N Engl J Med*. doi:10.1056/NEJMoa2303379
San-Miguel J, et al. *N Engl J Med*. Supplement .doi:10.1056/NEJMoa2303379..

CARTITUDE-4: Primary Endpoint- PFS



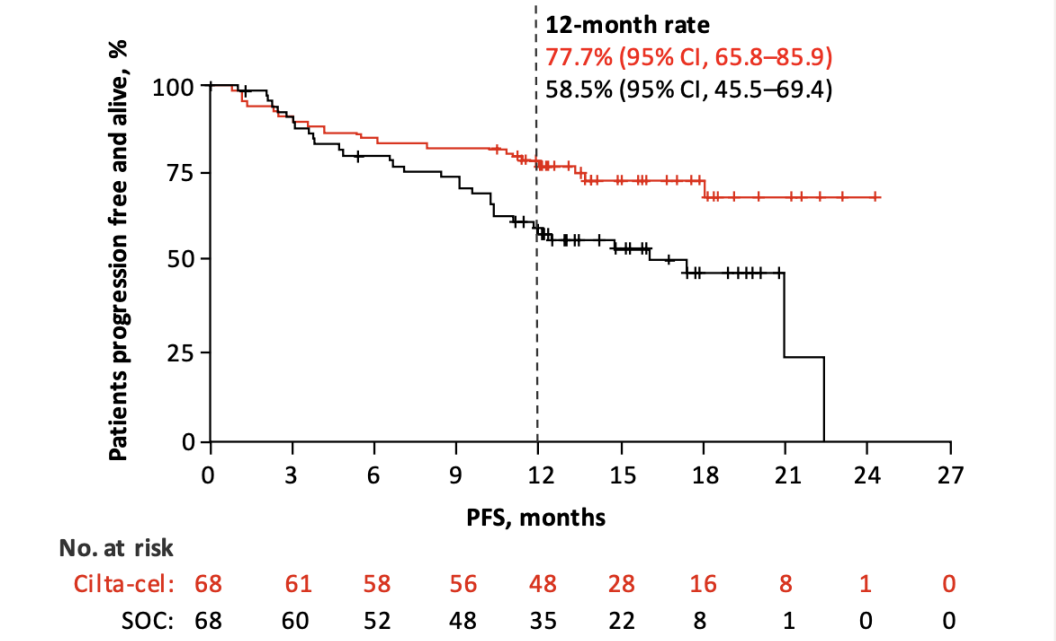
Cilta-cel vs SOC

- 12-month PFS rate: 76% vs 49%
- SOC performed as expected

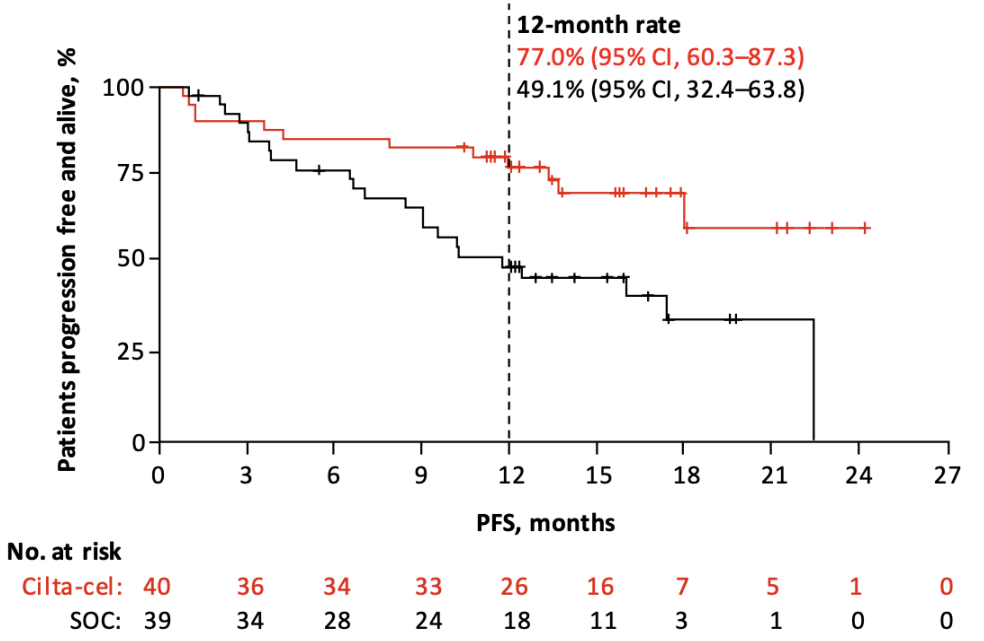
Dhakal et. al. ASCO 2023. J Clin Oncol 41, 2023 (suppl 17; abstr LBA106, San-Miguel J, Dhakal B, Yong K, et al: Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. New England Journal of Medicine 389:335-347, 2023

CART 4 updates, PFS by LOT

	Patients with 1 prior LOT	
	Cilta-cel (n=68)	SOC (n=68)
Median PFS (95% CI), months[a]	NR (NE–NE)	17.41 (11.10–NE)
HR (95% CI); *P* value[b,c]	0.35 (0.19–0.66); 0.0007	



	Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=40)	SOC (n=39)
Median PFS (95% CI), months[a]	NR (18.00–NE)	11.79 (8.44–NE)
HR (95% CI); *P* value[b,c]	0.27 (0.12–0.60); 0.0006	



Comparison of MM T-Cell Directed Therapies

Key characteristics		CAR-T cells		BsAbs		
		Idecabtagene vicleucel	Ciltacabtagene autoleucel	Teclistamab	Talquetamab	Elranatamab
Targets		BCMAxCD3			GPRC5DxCD3	BCMAxCD3
Line of therapy		**≥5th line or subsequent**				
Clinical trial		KarMMa	CARTITUDE-1	MajesTEC-1	MonumenTAL-1	MagnetisMM-3
		N=127	N=97	N=165	N=187	N=123
Efficacy	ORR, %	73	98	63	73	61
	CR, %	33	78	39	35	35
	DOR*, months	10.7	21.8	18.4 (14.9, NE)	9.5 (6.5, NE)	Not reached
Safety	CRS^, %	85 (9)	95 (5)	72 (0.6)	76 (1.5)	58 (0.5)
	Neurotoxicity^, %	28 (4)	26 (11)	57 (2.4)	55 (6)	59 (7)
	ICANS, %		23 (3)	6	9	3.3
Logistics	Drug route	IV		SC		
	Hospitalization	YES		YES – at therapy initiation		
	REMS	YES				

*median (95%CI); ^All grades (G3-4)

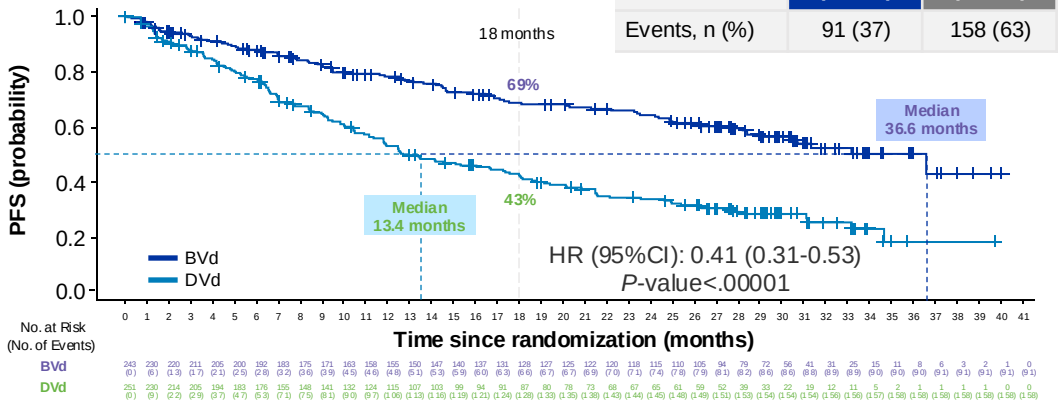
Idecabtagene vicleucel PI, 2021; Ciltacabtagene autoleucel PI 2023; Teclistamab PI, 2022; Elranatamab PI, 2023; Talquetamab PI, 2023

DREAMM-7: BVd DEMONSTRATED A STATISTICALLY SIGNIFICANT PFS BENEFIT VERSUS DVd IN 2L+ RRMM

DREAMM-7: phase III, open-label, randomized study of **BVd** versus **DVd** in **2L+ RRMM**

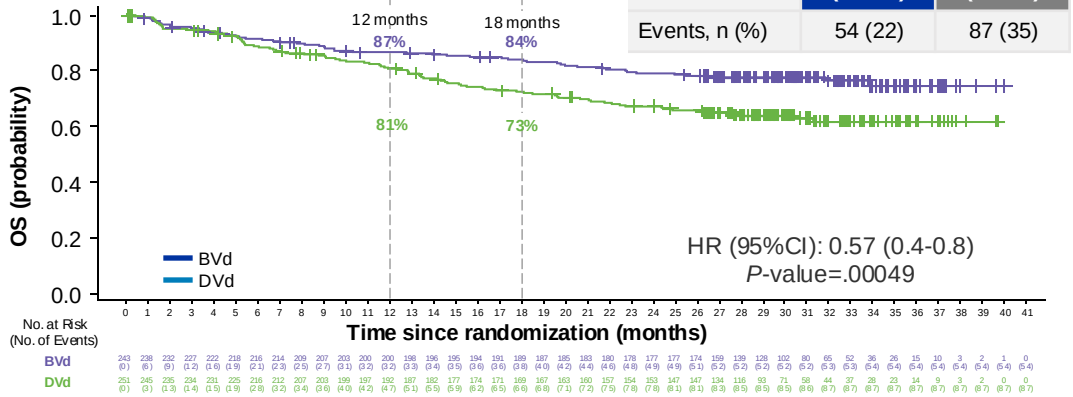
Progression-free survival

PFS*	BVd (n=243)	DVd (n=251)
Events, n (%)	91 (37)	158 (63)

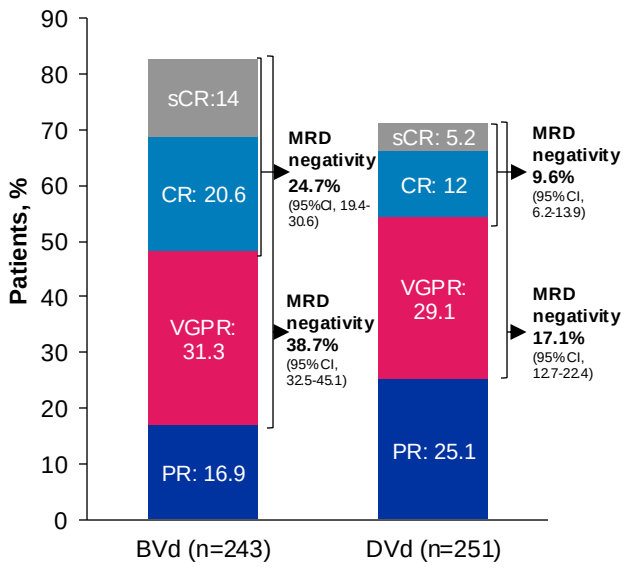


Overall survival

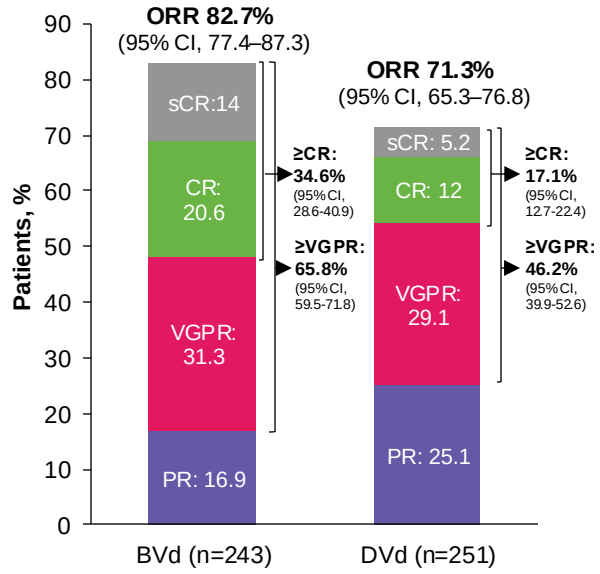
OS*	BVd (n=243)	DVd (n=251)
Events, n (%)	54 (22)	87 (35)



MRD negativity



Overall response rate



The **PFS benefit** of **BVd** versus DVd was also seen in patients who were **exposed/refractory** to **lenalidomide** and in those with **high-risk cytogenetic** features. BVd also demonstrated a **greater rate of MRD negativity** (38.7% versus 17.1%[II]) and an **early trend for OS benefit**[¶] compared with DVd

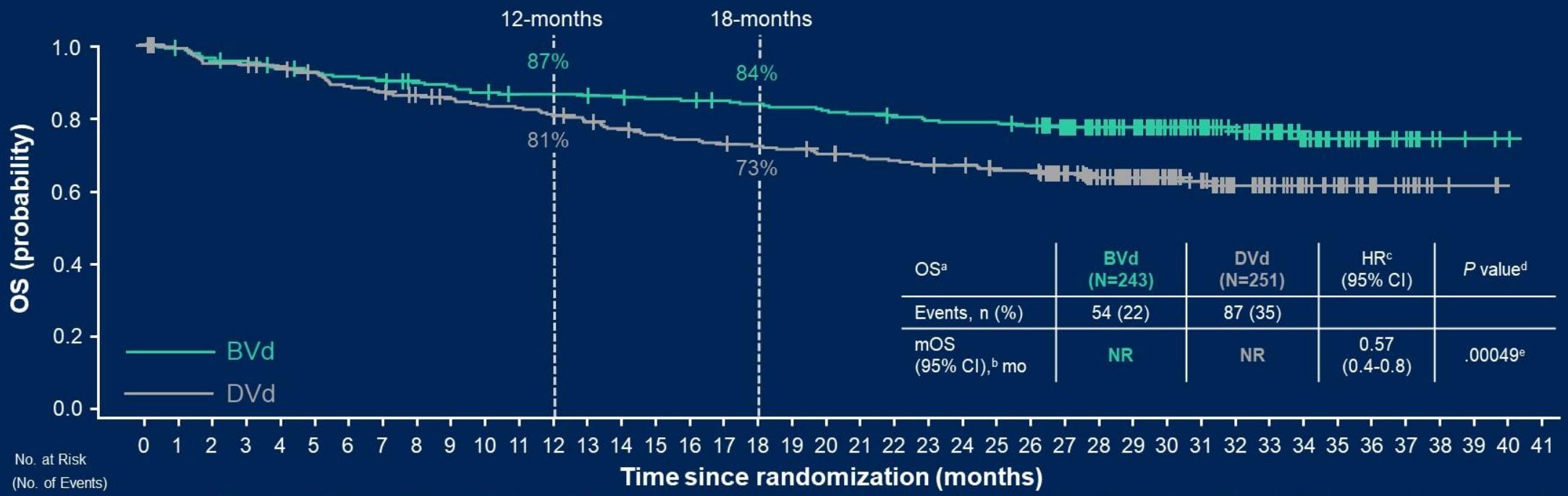
Median follow-up: 28.2 months. *Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as four unique patients in this output. †CIs estimated using the Brookmeyer-Crowley method. ‡HRs were estimated using a Cox proportional hazards model stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib, and R-ISS at screening (I vs II/III), with a covariate of treatment. §*P*-value from one-sided stratified log-rank test. IIIn patients who achieved ≥VGPR. ¶Additional OS follow-up ongoing.

2L, second line; BVd, belantamab mafodotin/bortezomib/dexamethasone; CI, confidence interval; CR, complete response; DVd, daratumumab/bortezomib/dexamethasone; HR, hazard ratio; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response.

Mateos MVM et al. Presented at the February American Society of Clinical Oncology Plenary Series. 2024 Abstract 439572.

SL

DREAMM-7: early OS trend favoring BVd vs DVd



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

No. at Risk (No. of Events)

BVd	243 (0)	238 (6)	232 (13)	227 (12)	222 (16)	218 (19)	216 (21)	214 (23)	209 (25)	207 (27)	203 (31)	200 (32)	200 (32)	198 (33)	196 (34)	195 (35)	194 (36)	191 (36)	189 (38)	187 (40)	185 (42)	183 (44)	180 (46)	178 (48)	177 (49)	177 (49)	174 (51)	159 (52)	139 (52)	128 (52)	102 (52)	80 (52)	65 (53)	52 (53)	36 (54)	26 (54)	15 (54)	10 (54)	3 (54)	2 (54)	1 (54)	0 (54)
DVd	251 (0)	245 (3)	236 (13)	234 (14)	231 (15)	225 (19)	216 (28)	212 (32)	207 (34)	203 (36)	199 (40)	197 (42)	192 (47)	187 (51)	182 (55)	177 (59)	174 (62)	171 (65)	169 (66)	167 (68)	163 (71)	160 (72)	157 (75)	154 (78)	153 (78)	147 (81)	147 (81)	134 (83)	116 (85)	93 (85)	71 (85)	58 (86)	44 (87)	37 (87)	28 (87)	23 (87)	14 (87)	9 (87)	3 (87)	2 (87)	0 (87)	0 (87)

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

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. [e] Has not yet reached criteria for statistical significance (*P* ≤.00037) at this interim analysis. Follow-up for OS is ongoing.

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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

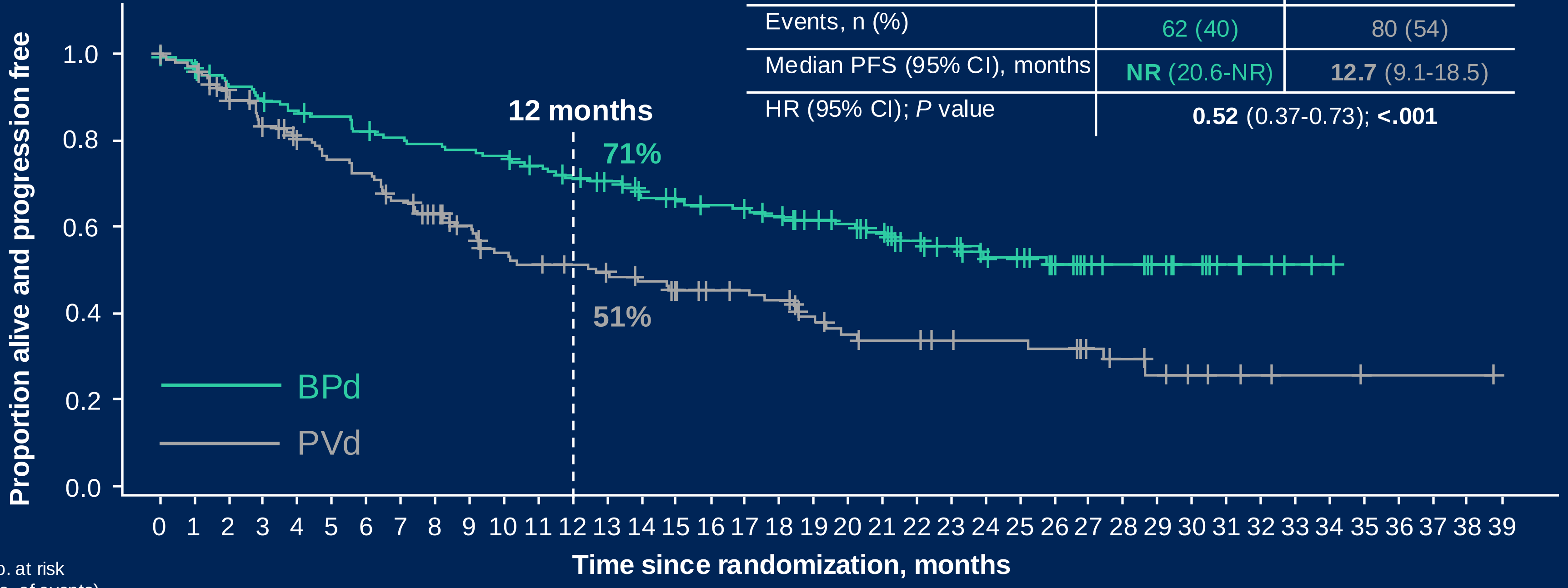
Additional secondary endpoints include:
ORR, CRR, ≥VGPR,TTBR, TTR, TTP, PFS2, AEs, ocular findings, HRQOL, and PROs

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)

BPd	155	143	135	130	125	122	117	113	111	109	107	102	97	93	82	80	77	75	72	67
	(0)	(5)	(10)	(15)	(19)	(21)	(26)	(28)	(30)	(32)	(34)	(37)	(41)	(42)	(47)	(47)	(49)	(50)	(52)	(53)
PVd	147	138	123	111	102	96	92	83	75	68	59	56	54	51	47	43	40	39	37	30
	(0)	(4)	(14)	(23)	(27)	(33)	(37)	(45)	(49)	(52)	(59)	(62)	(62)	(64)	(66)	(68)	(68)	(68)	(70)	(73)

BPd	64	59	50	45	38	36	28	23	21	16	13	8	4	2	1	0	0	0	0	0
	(54)	(56)	(58)	(59)	(61)	(61)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)
PVd	25	22	22	19	18	18	17	13	11	7	5	4	3	2	2	1	1	1	1	0
	(76)	(77)	(77)	(77)	(77)	(77)	(78)	(78)	(79)	(80)	(80)	(80)	(80)	(80)	(80)	(80)	(80)	(80)	(80)	(80)

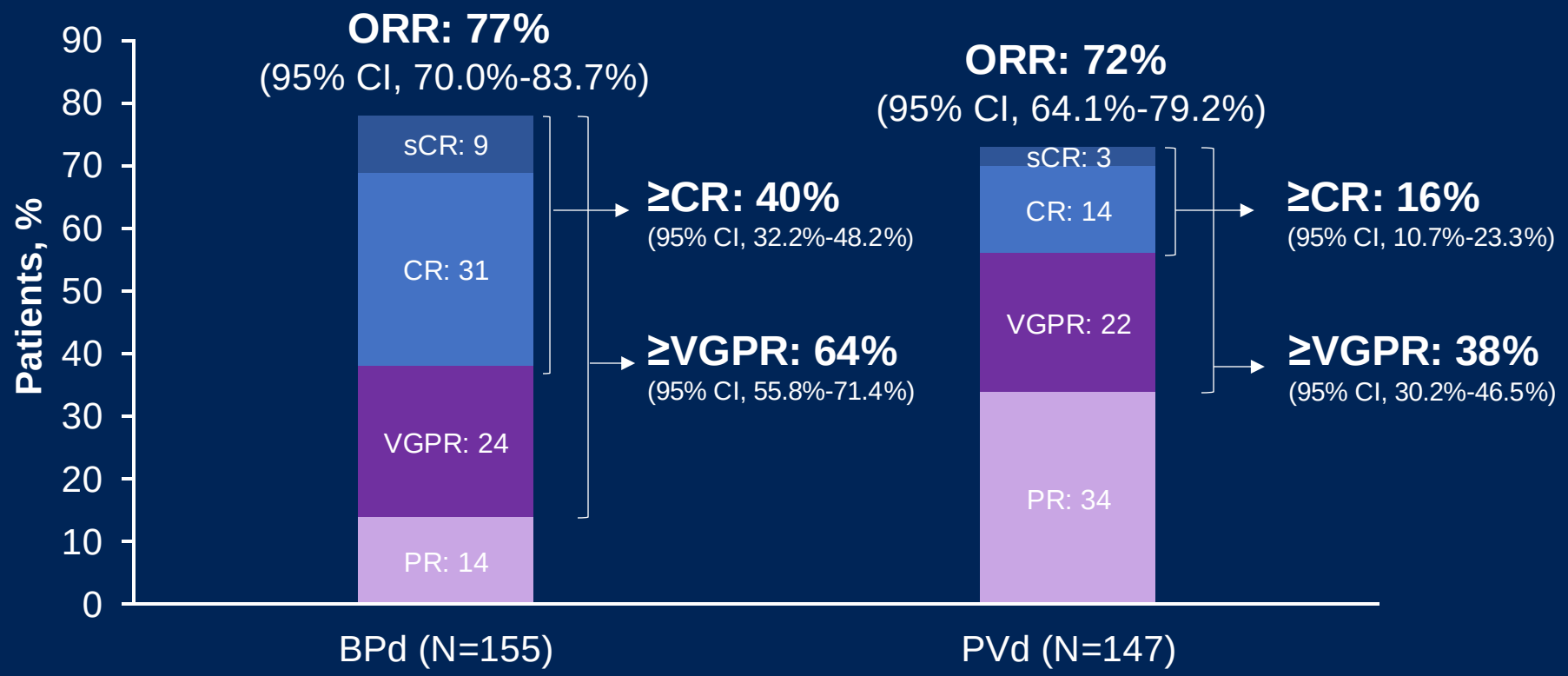
BPd led to a statistically significant and clinically meaningful reduction in risk of disease progression or death vs PVd (HR, 0.52; 95% CI, 0.37-0.73; *P*<.001)

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.

AEs of Clinical Interest

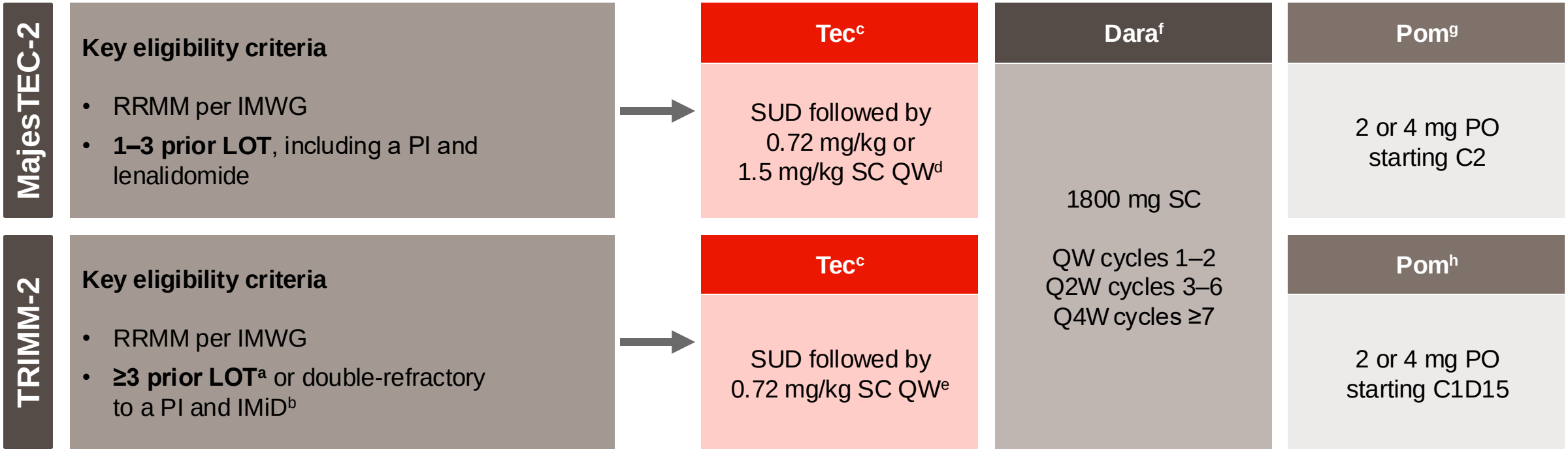
Grouped term, n (%)[a]	Safety population			
	BPd (N=150)		PVd (N=145)	
	n (%)	Patients/100-person years	n (%)	Patients/100-person years
Thrombocytopenia[b]				
Any event	82 (55)	40	60 (41)	44
Grade 3 or 4	57 (38)	28	42 (29)	31
Neutropenia[c]				
Any event	95 (63)	46	66 (46)	49
Grade ≥3	86 (57)	42	57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

Phase 1b MajesTEC-2 and TRIMM-2 Tec-Dara-Pom Cohorts



- **Key objectives:** Safety, antitumor activity, PK, PD, immunogenicity

MajesTEC-2: NCT04722146. TRIMM-2: NCT04108195. [a]Including a PI and an IMiD. [b]Including lenalidomide. [c]2 SUDs before first full dose; premedication included glucocorticoid, antihistamine, and antipyretic at SUD and first full dose. [d]Treatment doses of Tec could be adjusted from C3 onwards based on study safety evaluation team decision (eg, Q2W dosing). [e]Patients could switch to Q2W and then to Q4W dosing based on depth and duration of response. 1 patient in this cohort received Tec 0.75 mg/kg. [f]Given with 1-week (MajesTEC-2) or 2-week (TRIMM-2) corticosteroid taper (steroid-free administration). [g]Dexamethasone 40 mg PO given QW in C2–C4. [h]Dexamethasone 40 mg PO or IV given on D15 and D22 of C1, and QW in C2–C4. C, cycle; D, day; Dara, daratumumab; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IV, intravenous; LOT, line of therapy; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics; PO, orally; Pom, pomalidomide; PR, partial response; Q2W, every other week; Q4W, every 4 weeks; QW, weekly; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; SUD, step-up dose; Tec, teclistamab; VGPR, very good partial response.

Presented by A D'Souza at the 66th American Society of Hematology (ASH) Annual Meeting; December 7–10, 2024; San Diego, CA, USA

Tec-Dara-Pom in MajesTEC-2 and TRIMM-2: Infections

	MajesTEC-2 (1–3 prior LOT); n=17		TRIMM-2 (≥3 prior LOT); n=10		All patients; N=27	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any infection	16 (94.1)	11 (64.7)	9 (90.0)	6 (60.0)	25 (92.6)	17 (63.0)
Infections[a]						
Upper respiratory tract infection	8 (47.1)	0	4 (40.0)	0	12 (44.4)	0
Pneumonia	4 (23.5)	1 (5.9)	4 (40.0)	4 (40.0)	8 (29.6)	5 (18.5)
Sinusitis	4 (23.5)	0	4 (40.0)	1 (10.0)	8 (29.6)	1 (3.7)
COVID-19	3 (17.6)	1 (5.9)	4 (40.0)	1 (10.0)	7 (25.9)	2 (7.4)
COVID-19 pneumonia	4 (23.5)	4 (23.5)	1 (10.0)	1 (10.0)	5 (18.5)	5 (18.5)
Hypogammaglobulinemia						
Hypogammaglobulinemia[b]	16 (94.1)		10 (100)		26 (96.3)	
Received IVIG[c]	12 (70.6)		8 (80.0)		20 (74.1)	

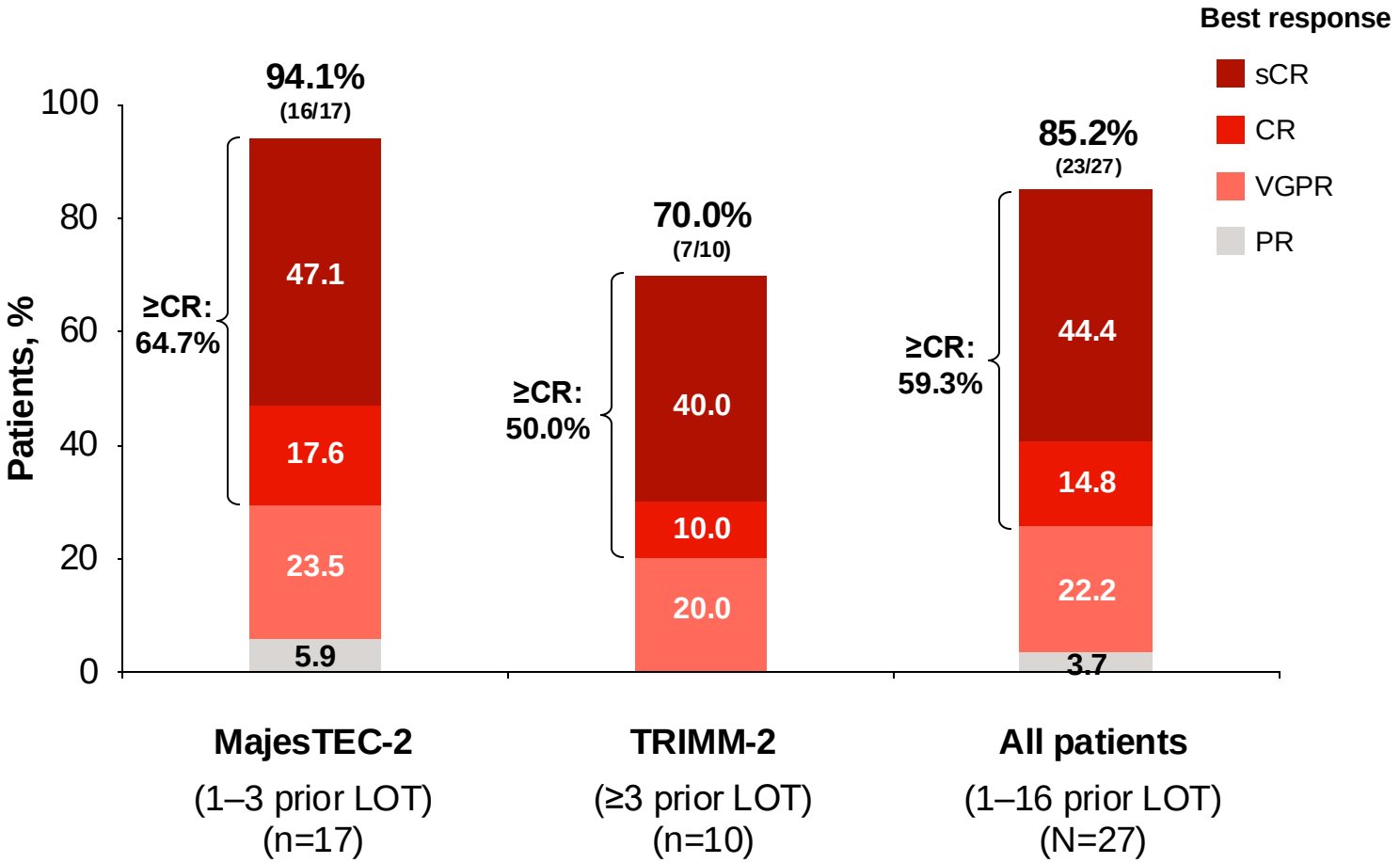
- 6 patients died due to infections
  - 4 due to COVID-19 pneumonia[d]
  - 1 due to pneumonia[e]
  - 1 due to pseudomonal bacteremia[f]
- 4 of these 6 patients had hypogammaglobulinemia at time of death and were not receiving Ig replacement before onset of the infection
- 1 additional patient died due to PD

No fatal infections occurred following implementation of intensified infection prophylaxis, including Ig replacement

[a]Infections in ≥15% of patients. [b]Hypogammaglobulinemia reported as an AE or postbaseline IgG <400 mg/dL. [c]Study enrollment began before IVIG was routinely recommended for patients treated with bispecific antibodies (MajesTEC-2, Mar 2021 to Aug 2021; TRIMM-2, Nov 2020 to Mar 2021). [d]MajesTEC-2, n=3; TRIMM-2, n=1. 1 case of COVID-19 death was reported as lung infection with COVID-19 as the causative pathogen; 2 of these 4 fatal COVID-19 pneumonia events qualified as TEAEs leading to treatment discontinuation. [e]TRIMM-2. [f]MajesTEC-2. AE, adverse event; Dara, daratumumab; Ig, immunoglobulin; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; LOT, line of therapy; PD, progressive disease; Pom, pomalidomide; TEAE, treatment-emergent adverse event; Tec, teclistamab.

Presented by A D'Souza at the 66th American Society of Hematology (ASH) Annual Meeting; December 7–10, 2024; San Diego, CA, USA

Tec-Dara-Pom in MajesTEC-2 and TRIMM-2: Response Rates



- Tec-Dara-Pom demonstrated rapid and deep responses across both cohorts
  - ORR: 85.2%
  - ORR: 72.7% in Dara-exposed patients[a]
- Deeper responses in 1–3 vs ≥3 prior LOT
  - ≥CR: 64.7% vs 50.0%
  - ≥VGPR: 88.2% vs 70.0%
- Median times to first and best response in all patients were 1.0 month and 3.2 months, respectively[b]

Response was assessed by investigators, based on International Myeloma Working Group criteria. Percentages were calculated with the number of patients in each group as the denominator. [a]n=8/11. [b]n=23.
CR, complete response; Dara, daratumumab; LOT, line of therapy; ORR, overall response rate; Pom, pomalidomide; PR, partial response; sCR, stringent complete response; Tec, teclistamab; VGPR, very good partial response.

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Tec-Dara-Pom in MajesTEC-2 and TRIMM-2: Treatment Duration in Responders

MajesTEC-2 (1–3 prior LOT)[a]

Median follow-up:
16.2 months (0.5–34.5)

Median DOR:
NE (9.7 months–NE)

24-month DOR:
59.8% (31.2–79.7)

24-month PFS:
59.8% (31.2–79.7)

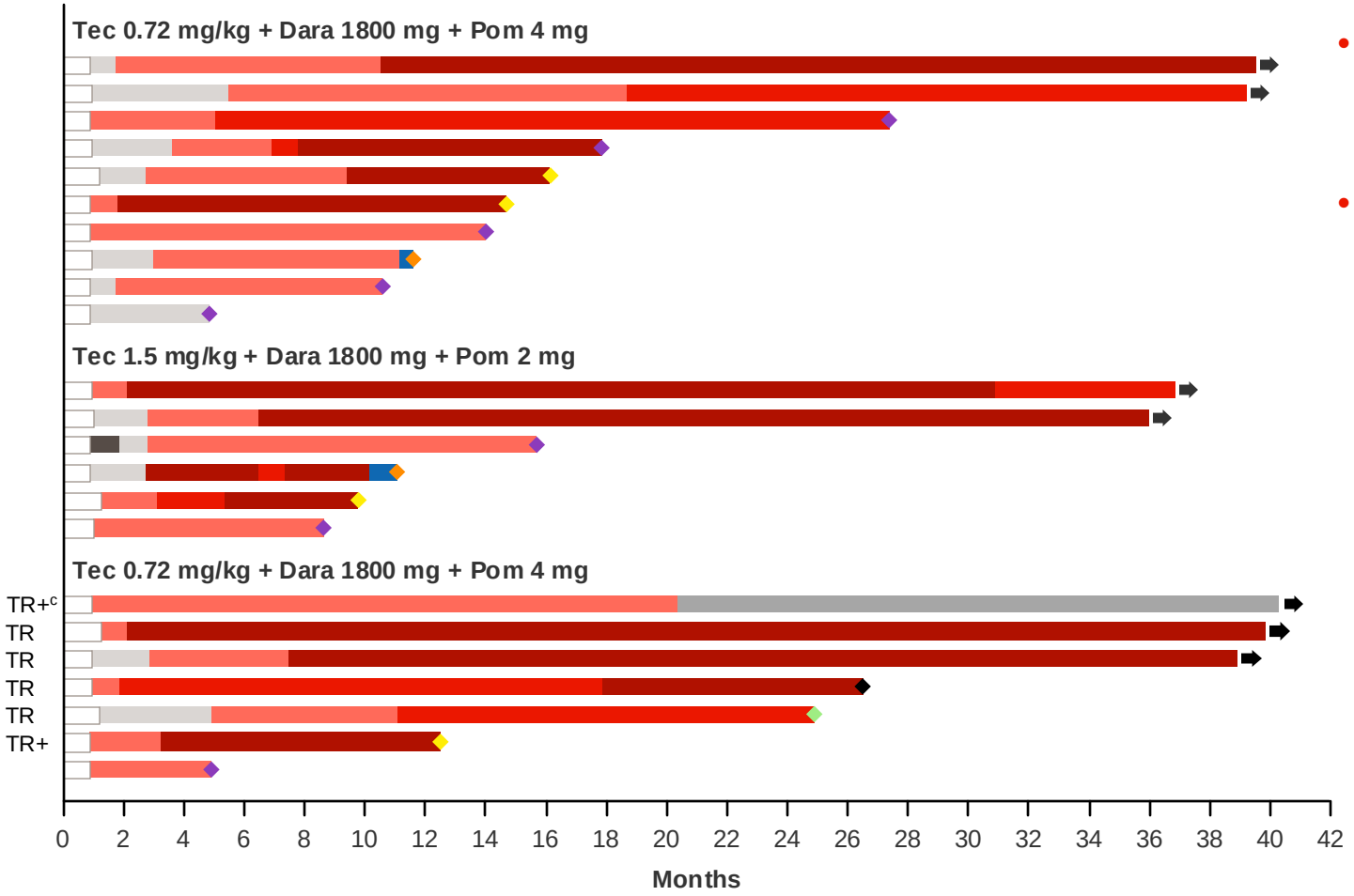
TRIMM-2 (≥3 prior LOT)[b]

Median follow-up:
38.3 months (1.2–39.6)

Median DOR:
25.6 months (12.5–NE)

24-month DOR:
66.7% (19.5–90.4)

24-month PFS:
46.7% (15.0–73.7)



- Tec-Dara-Pom demonstrated deepening responses over time across both studies
- In TRIMM-2, durable responses were observed in patients who were triple refractory

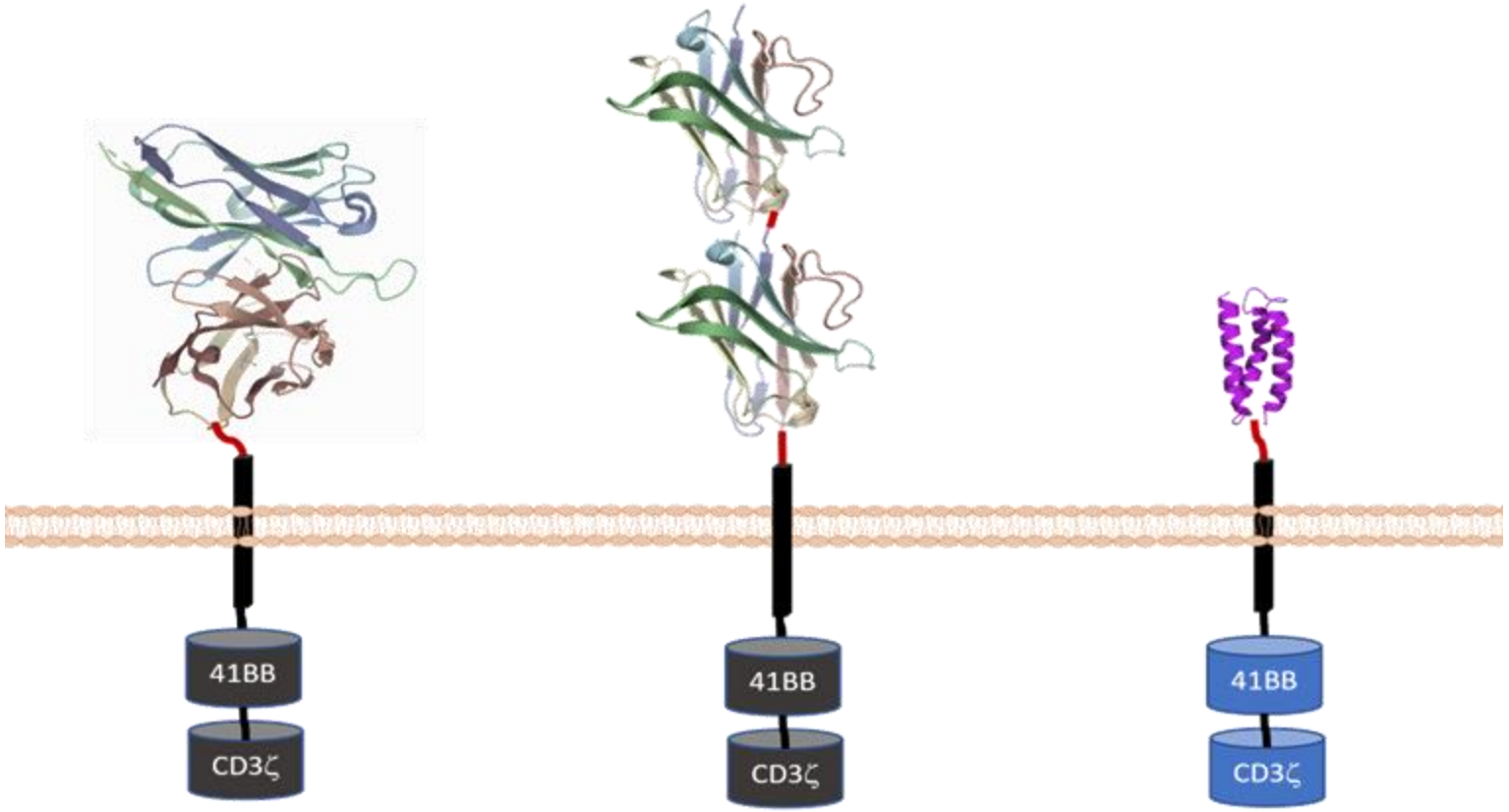
sCR · CR · VGPR · PR
MR · SD · PD
On treatment at clinical cut-off date
D/C - PD[d] · D/C - AE[e]
D/C - Other · D/C - Physician decision
Death[d]

Follow-up assessments will be conducted for up to 16 weeks after the last dose of study treatment. [a]n=16; clinical cut-off date Aug 22, 2024. [b]n=7; clinical cut-off date Apr 10, 2024. [c]Patient had PD per International Myeloma Working Group criteria (bone lesions) and remained on study treatment based on investigator decision following local radiation. [d]PD and deaths occurring beyond end of treatment are not represented in the figure. [e]Discontinuation due to AEs includes non–treatment-emergent events. +, penta-refractory; AE, adverse event; CR, complete response; D/C, discontinued (patients considered as discontinuing treatmentwhen all study drugs have been discontinued); Dara, daratumumab; DOR, duration of response; LOT, line of therapy; MR, minimal response; NE, not estimable; PD, progressive disease; PFS, progression-free survival; Pom, pomalidomide; PR, partial response; sCR, stringent complete response; SD, stable disease; Tec, teclistamab; TR, triple refractory (≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 monoclonal antibody); VGPR, very good partial response.

Presented by A D'Souza at the 66th American Society of Hematology (ASH) Annual Meeting; December 7–10, 2024; San Diego, CA, USA

Anitocabtagene autoleucel (anito-cel/CART-ddBCMA)

Autologous BCMA-directed CAR T-cell therapy using a novel, D-Domain binder[1,2]



scFv
(~25 kDa)

Bivalent camelid VHH
(~30 kDa)

D-Domain
(~8 kDa)

D-Domain Attributes:
Non-Antibody Derived Synthetic Protein[1,2]

Size	**Small D-Domain construct facilitates high transduction efficiency and CAR positivity[2-4] resulting in a low total cell dose**
Structure & Stability	**D-Domain CARs are stable and lack tonic signaling[4,6] due to the rapid folding, lack of disulfide bonds, and hydrophobic core[5,6] of the D-Domain**
Binding	**The D-Domain binder has a fast off-rate[4] and high CAR surface expression[4]. This combination may allow optimal tumor cell killing without prolonged inflammation**

[1]Rotte, et al. Immuno-Oncology Insights 2022; 3(1), 13–24; [2]Frigault, et al. Blood Adv. 2023; 7(5):768-777; [3]Cante-Barrett, et al. BMC Res. Notes 2016; 9:13; [4]Buonato, et al. Mol. Cancer Ther. 2022; 21(7):1171-1183; [5]Zhu, et al. Proc. Nat. Acad. Sci. 2003; 100(26): 15486-15491; [6]Qin, et al. Mol. Ther. 2019; 27(7): 1262-1274.

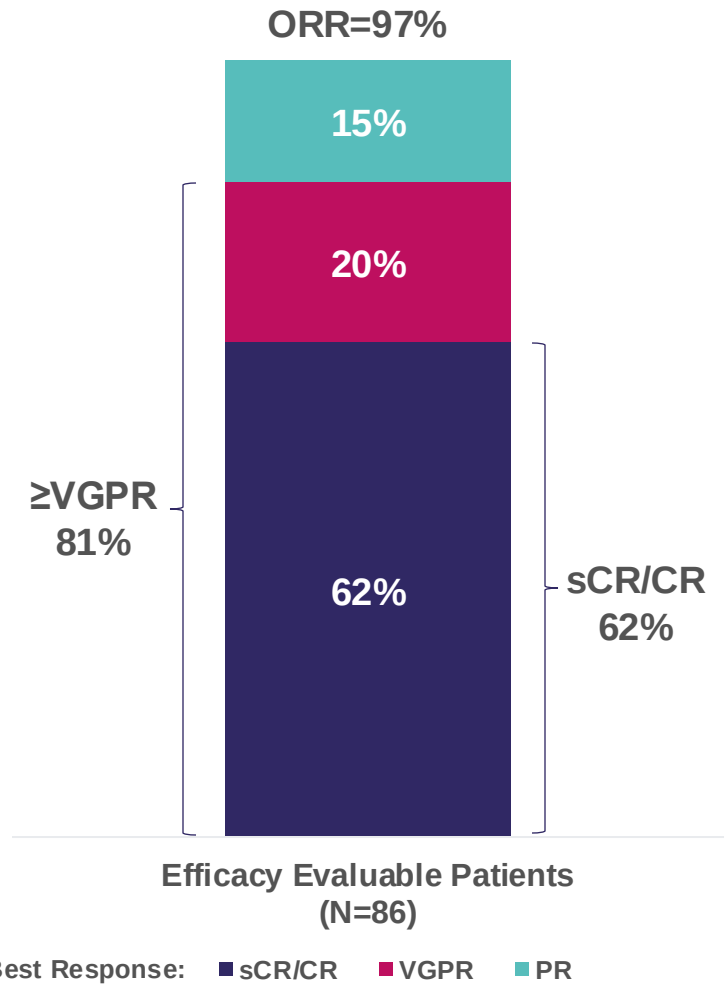
iMMagine-1: Patient and Disease Characteristics

Characteristics	Safety Evaluable (n=98)	Efficacy Evaluable (n=86)
Age (yrs), median (min - max)	65 (38 – 78)	65 (38 – 78)
Age ≥ 65	51 (52%)	47 (55%)
Age ≥ 75	10 (10%)	10 (12%)
Gender (male / female)	55 (56%) / 43 (44%)	48 (56%) / 38 (44%)
Race		
White	79 (81%)	70 (81%)
Black / African American	9 (9%)	8 (9%)
Asian / Other	10 (10%)	8 (9%)
ECOG PS 0 / 1	45 (46%) / 53 (54%)	39 (45%) / 47 (55%)
Extramedullary disease[a]	16 (16%)	13 (15%)
High Risk Cytogenetics[b]	39 (40%)	33 (38%)
Refractory to last line of therapy	98 (100%)	86 (100%)
Triple refractory	85 (87%)	74 (86%)
Penta refractory	41 (42%)	37 (43%)
Prior Lines of Therapy, median (min - max)	4 (3 – 8)	4 (3 – 8)
3 Prior LoT	45 (46%)	37 (43%)
Time since diagnosis (yrs), median (min-max)	7.2 (1 – 23)	7.5 (1 – 23)
Prior ASCT	73 (75%)	64 (74%)
Bridging therapy	65 (66%)	61 (71%)
Outpatient administration	8 (8%)	5 (6%)

a) Presence of a non-bone based plasmacytoma; b) Defined as the presence of Del 17p, t(14;16), or t(4;14).
ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LoT, line of therapy

iMMagine-1: Overall Response Rate and MRD Negativity

Efficacy Evaluable Patients (N=86)



- At a median follow-up of 9.5 months, ORR was 97% and sCR/CR rate was 62%
- 93.1% (n=54/58) of evaluable patients were MRD negative at minimum of 10^{-5} sensitivity

	Evaluable Patients	Months (min - max)
Median time to first response	83	1.0 (0.9 - 7.3)
Median time to MRD negativity of ≤10^{-5}	54	1.0 (0.9 - 6.4)

Responses are investigator assessed per IMWG criteria, ORR defined as partial response or better; MRD evaluable patients had an identifiable malignant clone in the baseline bone marrow sample and had a post-treatment bone marrow sample sufficient to assess MRD negativity
CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

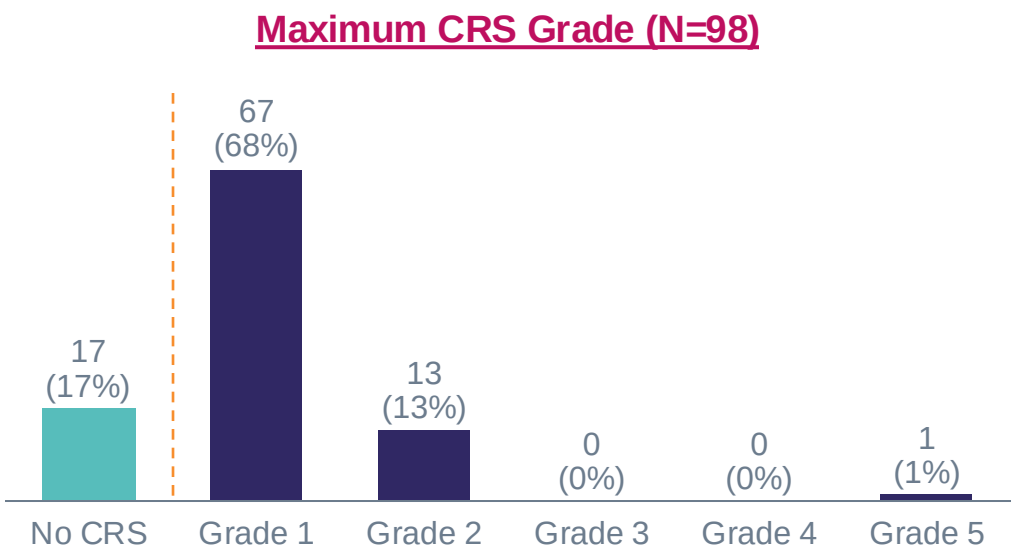
iMMagine-1: PFS and OS Rates Estimated by Kaplan-Meier

Efficacy Evaluable Patients (N=86)

	PFS Rate (%) (95% CI)	OS Rate (%) (95% CI)
6-Month	93.3% (84.4%, 97.2%)	96.5% (89.6%, 98.9%)
12-Month	78.5% (63.5%, 87.9%)	96.5% (89.6%, 98.9%)

Median follow-up of 9.5 months (range 2 to 23 months)
PFS, progression-free survival; OS, overall survival

iMMagine-1: Cytokine Release Syndrome



- 83% (81/98) of patients had CRS of any Grade; the median onset was 4 days
- 86% (84/98) of patients had CRS Grade 1 or less, including 17% (17/98) with no CRS
- % of patients with either no CRS or CRS that resolved by:
  - ≤7 days of anito-cel infusion: 63% (62/98)
  - ≤10 days of anito-cel infusion: 92% (90/98)
  - ≤14 days of anito-cel infusion: 98% (96/98)

Cytokine Release Syndrome (CRS) Per ASTCT criteria	Safety Evaluable Patients N=98
Median onset (min-max)	4 days (1-17 days)
Median duration (min-max)	3 days (1-9 days)
Supportive Measures	
Tocilizumab	72% (71/98)
Dexamethasone	65% (64/98)
Anakinra	8% (8/98)
Siltuximab	4% (4/98)
Vasopressor used	1% (1/98)
Intubation/mechanical ventilation	1% (1/98)

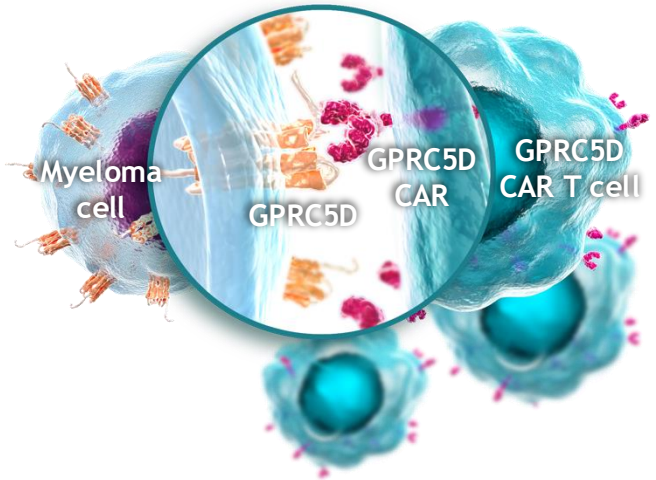
- CRS management per protocol was in line with standard medical practice with no prophylactic administration of tocilizumab or dexamethasone
  - For CRS onset in the first 48 hours, tocilizumab and dexamethasone were protocol recommended
  - For CRS onset after the first 48 hours, if tocilizumab was administered at investigator discretion, dexamethasone was also recommended
- Grade 5 CRS occurred in a 76-year-old patient who had rapidly progressive disease between screening and baseline and did not receive bridging therapy

ASTCT, American Society for Transplantation and Cellular Therapy

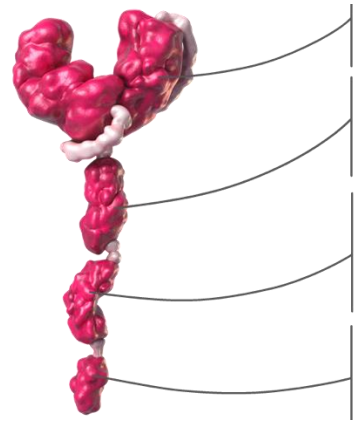
BMS-986393: a GPRC5D autologous CAR T-cell therapy

- In MM, CAR T-cell therapies have the potential for deep and durable responses and a unique safety profile compared with other T-cell redirecting therapies[1–3]
- GPRC5D is an emerging and validated target in MM, beyond IMiDs®, PIs, anti-CD38 antibodies, and BCMA-targeted therapies[1-5]
- BMS-986393 (CC-95266) is a potential first-in-class autologous CAR T-cell therapy targeting GPRC5D[5] that has been granted FDA RMAT designation for RRMM
- In the phase 1 CC-95266-MM-001 study of BMS-986393 in patients with RRMM (NCT04674813):
  - 150 × 10^6 CAR T cells has been selected as the BMS-986393 RP2D based on the totality of data[6,7]
  - High overall response rates, deepening of responses, and encouraging duration of response continue to be demonstrated in updated data

BMS-986393 mechanism of action



GPRC5D-targeted CAR construct

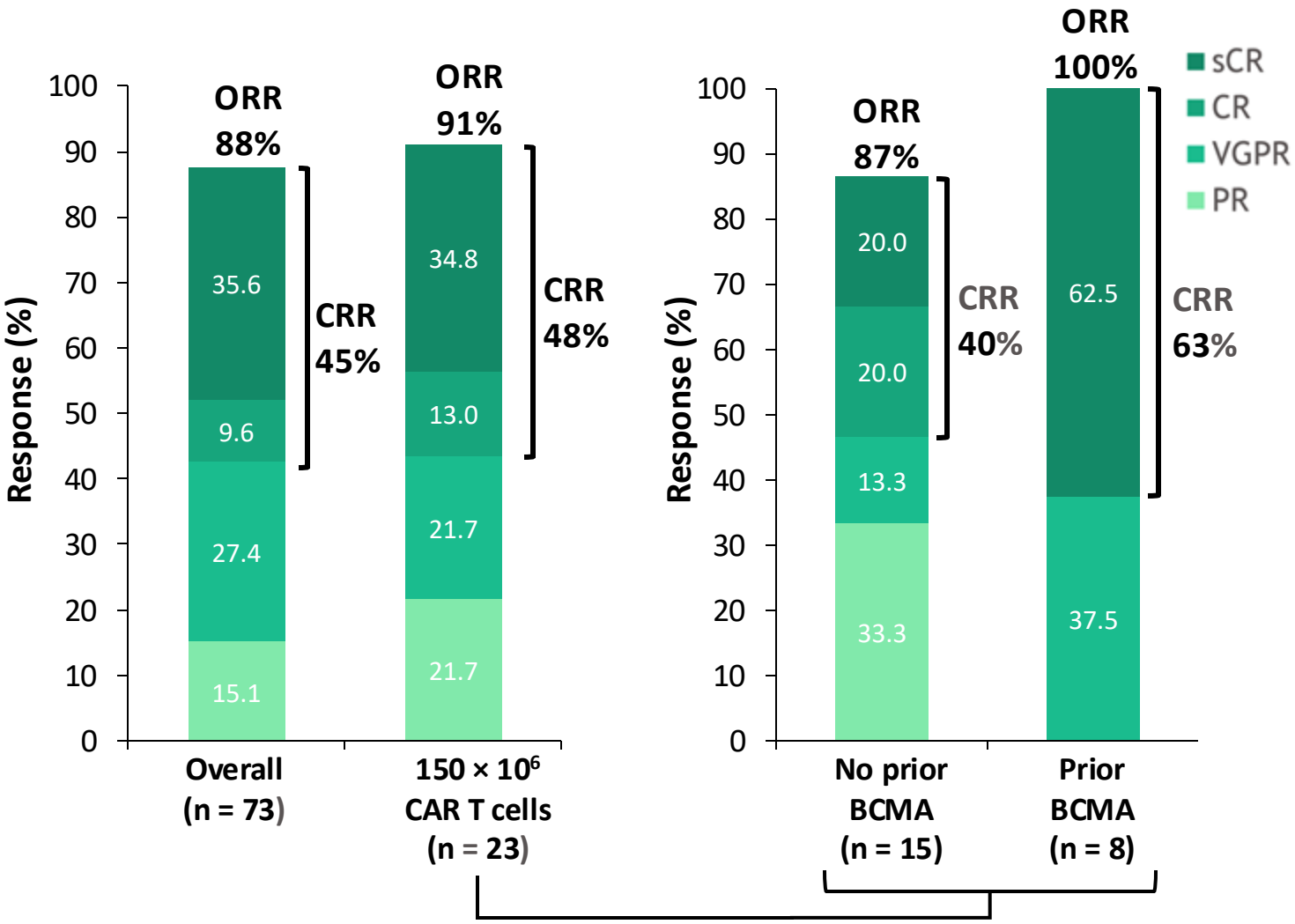


BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; GPRC5D, G protein–coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteosome inhibitor; RMAT, regenerative medicine advanced therapy; RP2D, recommended phase 2 dose; RRMM, relapsed and/or refractory multiple myeloma.

1. Berdeja JG, et al. *Lancet* 2021;398:314-324. 2. Munshi NC, et al. *N Engl J Med* 2021;384:705-716. 3. Rodriguez-Otero P, et al. *N Engl J Med* 2023;388:1002-1014.
4. Mailankody S, et al. *N Engl J Med* 2022;387:1196-1206. 5. Smith EL, et al. *Sci Transl Med* 2019;11:eaau7746. 6. Bal S, et al. *Blood* 2022;140(suppl 1):883.
7. Bal S, et al. *Hemasphere* 2023;7(suppl):e9863287. 8. Song D-G, et al. *Cancer Res* 2011;71:4617-4627.

Bal S, et al. ASH 2023 [Presentation 219]

BMS-986393 in RRMM: high response rates irrespective of prior BCMA-targeted therapy or high-risk features[a]



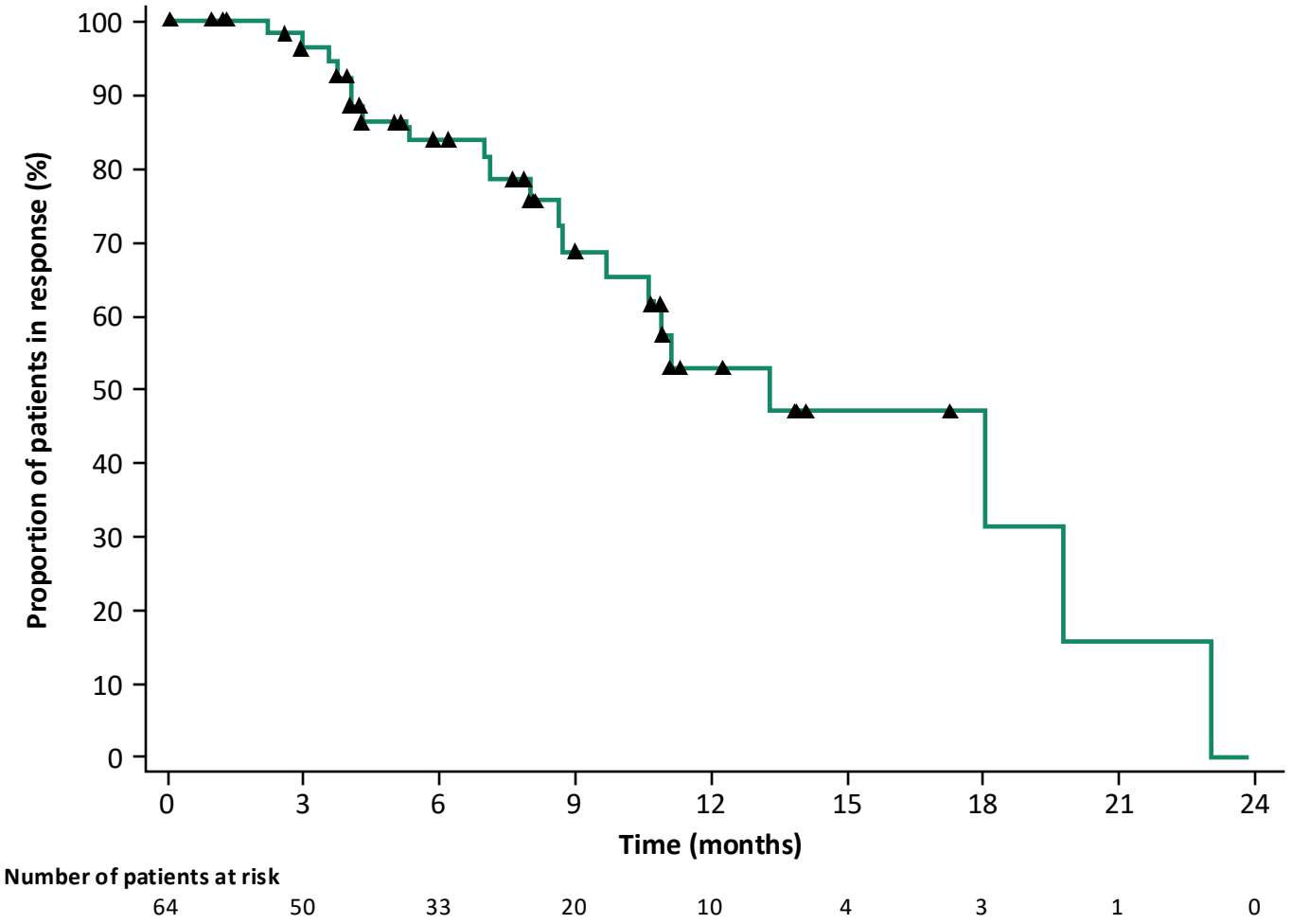
ORR in subgroups of interest (all dose levels)

Disease characteristic, % (n/N)	Present	Absent
Prior BCMA treatment	78% 25/32	95% 39/41
Extramedullary disease	84% 26/31	91% 38/42
High-risk cytogenetics[b]	83% 24/29	91% 40/44
Triple-class refractory	88% 50/57	88% 14/16

Data cutoff: September 11, 2023. [a]The efficacy-evaluable analysis set includes all patients who received conforming BMS-986393 cell product, had measurable disease at the last disease assessment prior to BMS-986393 infusion, and had ≥ 1 post-infusion disease response assessment. Responses were assessed per International Myeloma Working Group criteria.
[b]del(17p), t(4;14), and/or t(14;16).
CR, complete response; CRR, complete response rate; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Bal S, et al. ASH 2023 [Presentation 219]

BMS-986393 in RRMM: deep and durable responses[a]



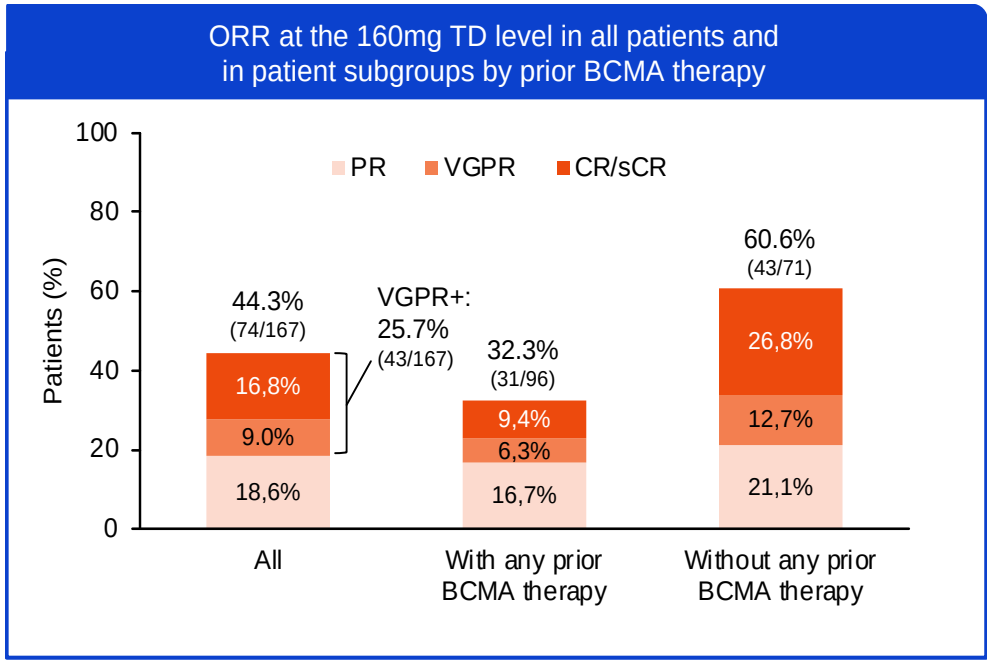
- Median duration of follow-up: 9 months (range, 1–25)
- 67% of responses are ongoing (43 of 64 efficacy-evaluable responders), yielding a median DOR of 13 months (95% CI, 10–20) at data cutoff
- 86% (12/14) of MRD-evaluable[b] patients with ≥ CR achieved MRD negativity

Data cutoff: September 11, 2023. [a]The efficacy-evaluable analysis set includes all patients who received conforming BMS-986393 cell product, had measurable disease at the last disease assessment prior to BMS-986393 infusion, and had ≥ 1 post-infusion disease response assessment. Responses were assessed per International Myeloma Working Group criteria. [b]Patients were MRD-evaluable if a dominant clone could be identified for tracking.
DOR, duration of response; MRD, minimal residual disease.

Bal S, et al. ASH 2023 [Presentation 219]

Cevostamab, a FCRh5 Bispecific monoclonal antibody in RRMM

- Aims: (1) present updated safety and efficacy data at the 160 mg target-dose (TD) level; (2) present CRS data with C1 0.3/1.2/3.6 triple-step (TS) dosing at the 160 mg target-dose
- 167 pts for the aim 1 after a median of 5PL and 30 pts for the aim 2 after a median of 7.5 PL
- Almost all pts were TCR and 57.5% for the aim 1 were BCMa-TT exposed and 75% for the aim 2 (including CAR-T, ADC and BsAb)



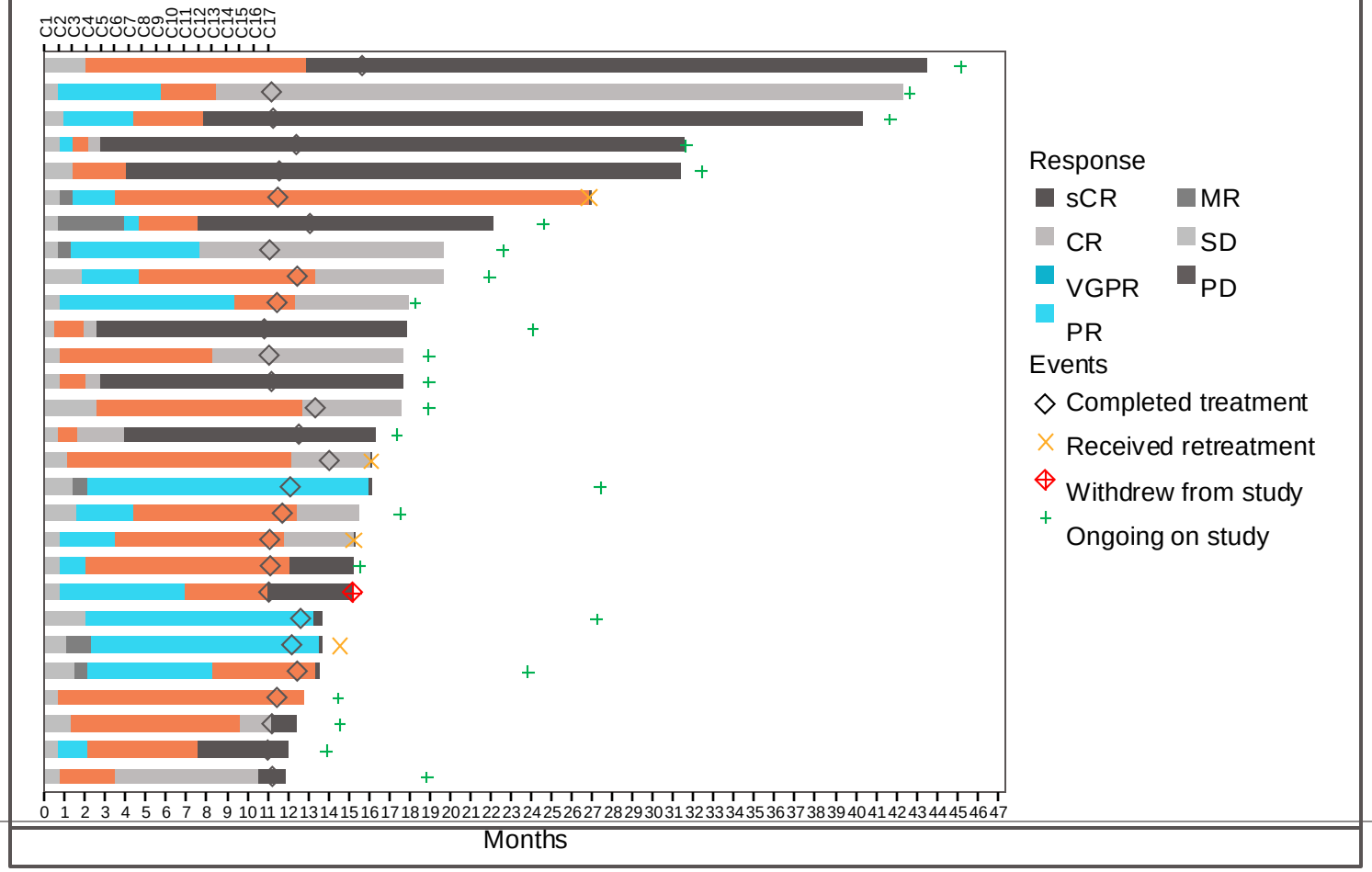
- mDoR in PR+ (n=74):
  10.4 months (95% CI: 6.2, 15.0)
- mDoR in VGPR+ (n=43):
  21.2 months (95% CI: 15.0, 36.4)*

Durability of response at the 160mg TD level after completion of treatment

- 28 patients completed 17 cycles of treatment at the 160mg TD level
- 9 patients had responses ≥6 months from completion (8/9 in CR/sCR at completion)
- 6 patients had ongoing responses of <6 months
- 1 patient in sCR withdrew from study

Responses continue after the completion of treatment, especially in patients who achieve CR/sCR

Treatment duration and response at the 160mg TD level among patients who completed 17 cycles (n=28)



Data cut-off: Aug 22, 2024

CONCLUSION

- Early relapse is the ‘New” ”newly diagnosed” in terms of outcomes
- Benefit from phase 3 trials of standard agents may be less in an era of quads
- Transplant remains a standard as part of induction, so less use in relapse
- Timing of CART remains an unanswered question, but clearly better than many standard treatments in early relapse
- How to consider ADC vs TCE vs CART in early relapse are ongoing questions

Patients and Families

Thanks to:

Jonathan Kaufman
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Nisha Joseph
Leon Bernal
Charise Gleason
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Donald Harvey
Amelia Langston
Y. Gu
S-Y Sun
Ben Barwick
Mala Shanmugan
Larry Boise
Bryan Burton

IMS

Golfers Against Cancer
T.J. Martell Foundation

And Many Others who
are part of the Myeloma clinical and
research team

sloni01@emory.edu