Oncology Learning Network

Novel Therapeutics and Essential Strategies for Optimized Outcomes in Relapsed/Refractory Multiple Myeloma

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HMP Education

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Faculty Disclosures

- **Ajay K. Nooka, MD, MPH**: Honoraria/Advisory Board—Adaptive Biotechnologies, Amgen, AstraZeneca, Bristol Myers Squibb, Cellectar Biosciences, GlaxoSmithKline, Janssen, K36 Therapeutics, ONK Therapeutics, Pfizer, Sanofi, Sebia, Takeda; Grant/Research Support—Aduro Biotech, Amgen, Arch Oncology, Bristol Myers Squibb, Cellectis, Genentech, GlaxoSmithKline, Janssen, Karyopharm, Kite Pharma, Merck, Pfizer, Takeda
- **Christopher A. Fausel, PharmD, MHA, BCOP** has disclosed no relevant financial relationship with any ineligible company (commercial interest)

This presentation will discuss the unapproved use of drugs for the treatment of multiple myeloma.

Program Information

- This program is provided by HMP Education, an HMP Global company
- Supported by an educational grant from Janssen Biotech, Inc.

Learning Objectives

- Evaluate the mechanisms of action, clinical rationale, and most recent clinical trial and real-world data associated with novel and emerging monotherapies and combination strategies in R/R MM
- Describe the latest recommendations for treatment selection and sequencing as well as strategies to mitigate potential toxicities associated with novel and emerging therapies for R/R MM
- Implement multidisciplinary team strategies to address AEs, treatment resistance, care coordination, and overall outcomes

R/R MM = relapsed/refractory multiple myeloma; AE = adverse event.

Overview, Standard of Care, and Emerging Role of BCMA in R/R MM

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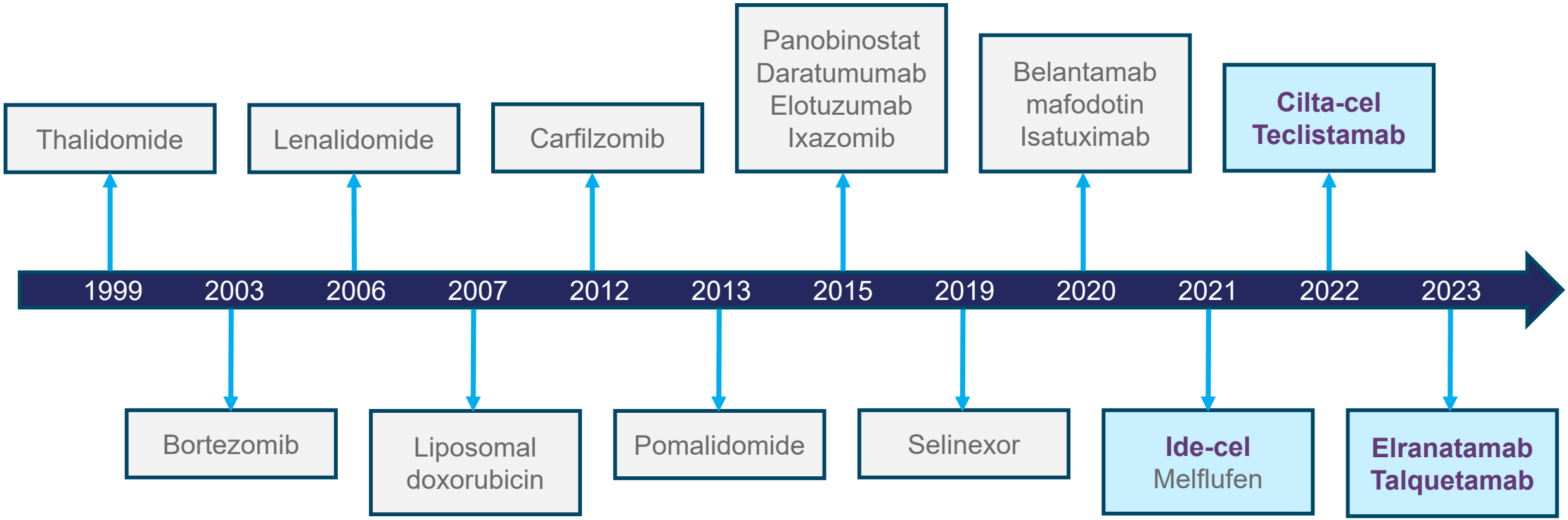
Epidemiology of Myeloma

- In 2024, 35,780 new cases will be diagnosed (19,520 in men and 16,260 in women) and 12,540 deaths are expected to occur (7020 in men and 5520 in women)
- In 2021, there were an estimated 179,063 people living with myeloma in the United States (5-year survival rate is 61.1%, median age at diagnosis is 69 years, and median age of death is 76 years)
- Prognosis has significantly improved, with median survival estimated at 12 years
- Disease is sensitive to treatment, but curable only in a small subset

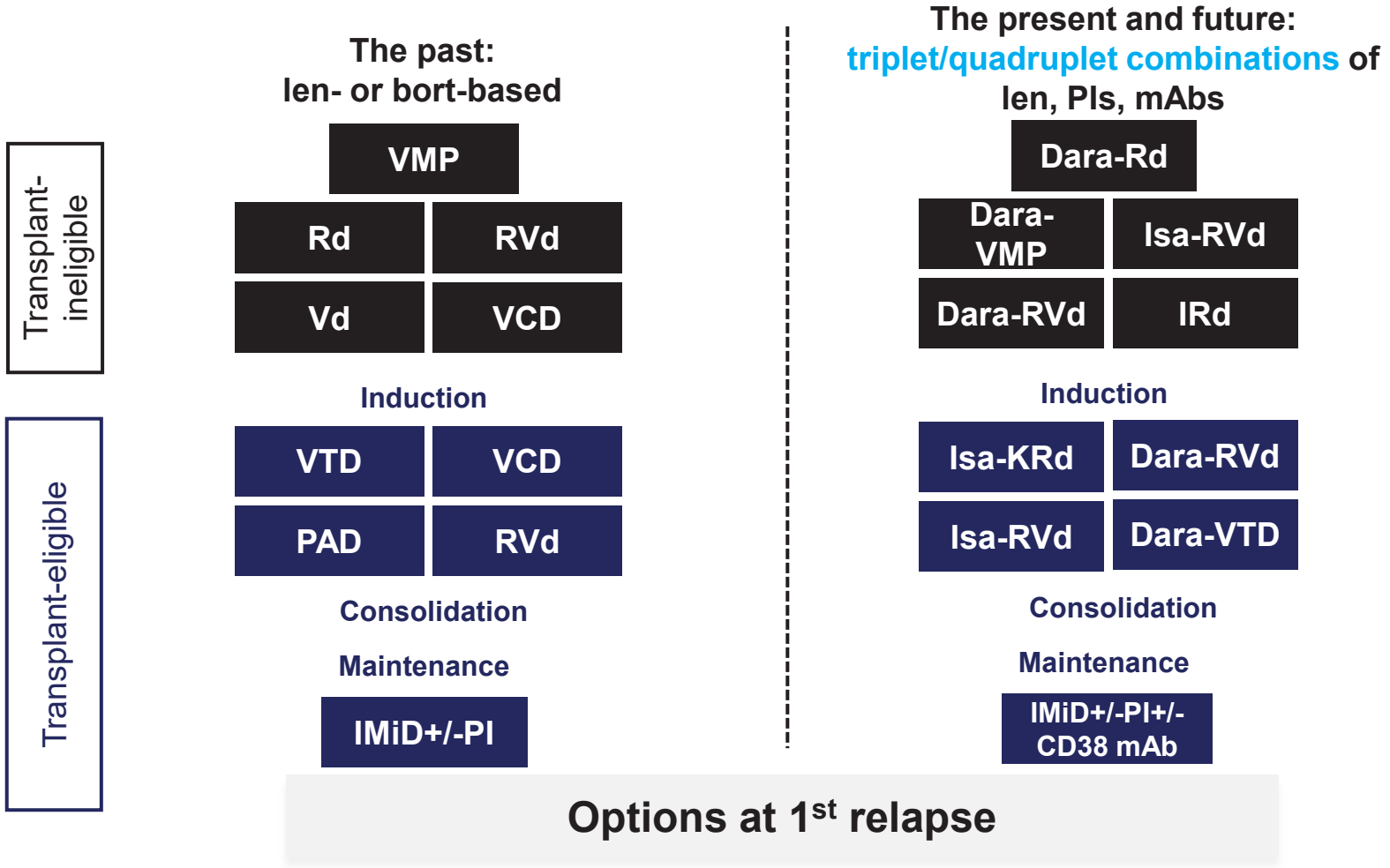
American Cancer Society. Accessed October 24, 2024. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acs.pdf. NCI. Accessed October 24, 2024. https://seer.cancer.gov/statfacts/html/mulmy.html. Parikh, R et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, Illinois. Abstract 8061.

Evolution of Modern Multiple Myeloma Therapy



US Food and Drug Administration (FDA). Accessed October 28, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20785lbl.pdf; 2003/021602lbl.pdf; 2005/021880lbl.pdf; 2007/050718s029lbl.pdf; 2012/202714lbl.pdf; 2013/204026lbl.pdf; 2015/205353s000lbl.pdf; 2015/761036Orig1s000lbledt.pdf; 2015/761035s000lbl.pdf; 2015/208462lbl.pdf; 2019/212306s000lbl.pdf; 2020/761158s000lbl.pdf; 2020/761113s000lbl.pdf; 2021/214383s000lbl.pdf; 2022/761291s000lbl.pdf; 2023/761345Orig1s000lbl.pdf; 2023/761342s000lbl.pdf; https://www.fda.gov/media/147055/download?attachment; https://www.fda.gov/media/156560/download.

Landscape of Myeloma at First Relapse



mAb = monoclonal antibody; V = bortezomib; M = melphalan; P = prednisone; R = lenalidomide; d/D = dexamethasone; C = cyclophosphamide; T = thalidomide; PAD = PS-341 (bortezomib), doxorubicin, dexamethasone; A = doxorubicin; I = ixazomib; K = carfilzomib; IMiD = immunomodulatory drugs; PI = proteasome inhibitor.

NCCN Guidelines

NCCN Guidelines Version 1.2025 Multiple Myeloma

Relapsed/Refractory Disease After 1–3 Prior Therapies

Order of regimens does not indicate comparative efficacy

Anti-CD-38 Refractory	Bortezomib-Refractory	Lenalidomide-Refractory
• Carfilzomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Pomalidomide/bortezomib/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone	• Carfilzomib/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone
CAR T-Cell Therapy ***After one prior line of therapy including IMiD and a PI, and refractory to lenalidomide*** ▸ Ciltacabtagene autoleucel (category 1) ***After two prior lines of therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI*** ▸ Idecabtagene vicleucel (category 1)		

* For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Relapsed/Refractory Disease After 1–3 Prior Therapies, see MYEL-G 4 of 5

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[l] Regimens included under 1–3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] In order to maximize benefit of systemic therapy, agents/regimens may be reconsidered or repeated if relapse is after at least 6 months of stopping therapy.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.

NCCN Guidelines Version 1.2025 Multiple Myeloma

Relapsed/Refractory Disease After 3 Prior Lines of Therapy

Preferred Regimens

▸ ***CAR T-cell Therapy:***
◊ Ciltacabtagene autoleucel
◊ Idecabtagene vicleucel

After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD
▸ *Bispecific Antibodies:*
◊ Elranatamab-bcmm
◊ Talquetamab-tgvs
◊ Teclistamab-cqyv

Other Recommended Regimens

• Bendamustine
• Bendamustine/bortezomib/dexamethasone
• Bendamustine/carfilzomib/dexamethasone
• Bendamustine/lenalidomide/dexamethasone
• High-dose or fractionated cyclophosphamide

After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody
• Selinexor/dexamethasone

Useful in Certain Circumstances[q]

After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD
• Belantamab mafodotin-blmf (if available through compassionate use program)

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
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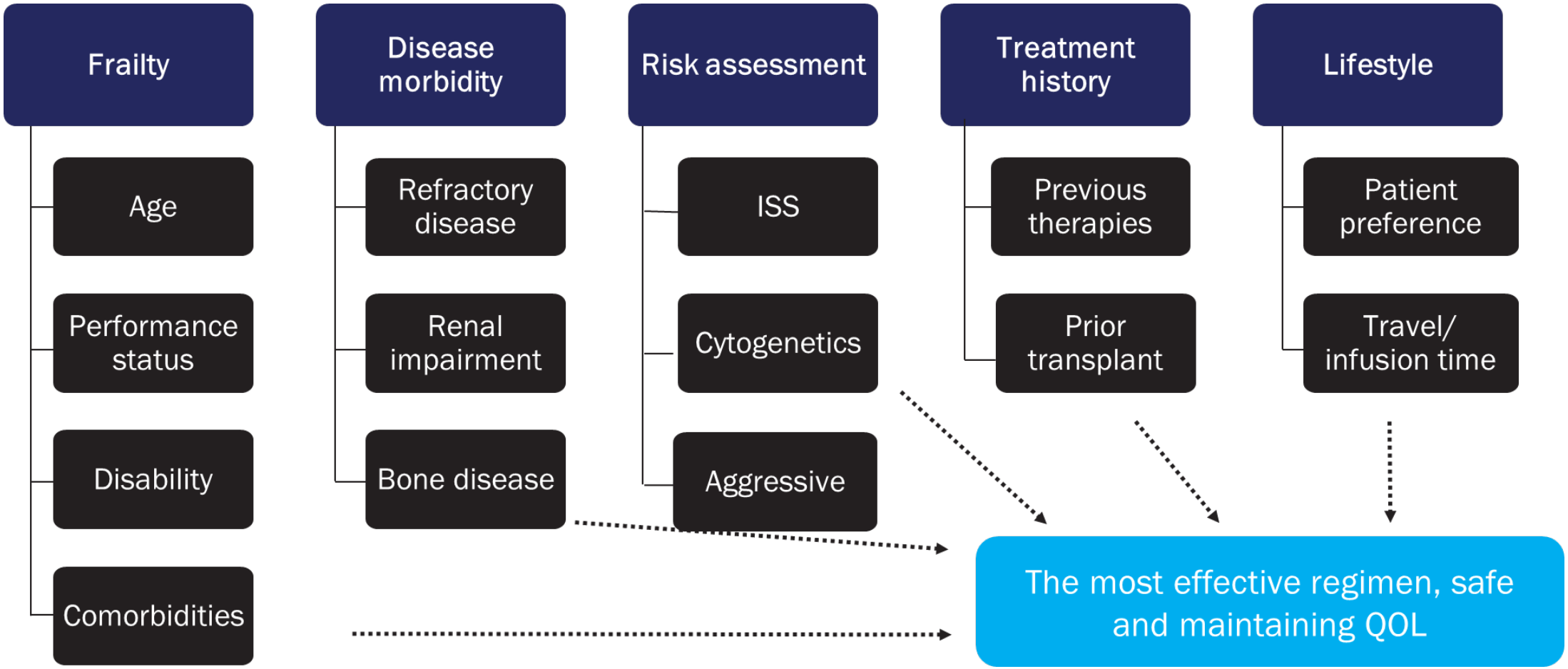
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] In order to maximize benefit of systemic therapy, agents/regimens may be reconsidered or repeated if relapse is after at least 6 months of stopping therapy.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.
[q] Patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy. Optimal sequencing of sequential BCMA targeted therapies is not known; however accumulated data suggests immediate follow on with second BCMA directed therapy after relapse may be associated with lower response rates

National Comprehensive Cancer Network (NCCN). Accessed October 24, 2024. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1445.

Factors in Selecting Treatment for Early Relapsed Myeloma



ISS = International Staging System; QOL = quality of life.

Framework to Choose the Best First Relapse Regimen

IMiDs	PIs
Lenalidomide/dexamethasone back bone	Bortezomib/dexamethasone back bone
Pomalidomide/dexamethasone back bone	Carfilzomib/dexamethasone back bone

Randomized Studies with Lenalidomide-Dex Control Arms

Efficacy	Carfilzomib KRd vs Rd (n=792)		Ixazomib IRd vs Rd (n=722)		Elotuzumab ERd vs Rd (n=646)		Daratumumab DRd vs Rd (n=569)	
	Tx	Control	Tx	Control	Tx	Control	Tx	Control
Median FU, mo	67.1		85		70.6		79.7	
ORR, %	87.1%	66.7%	78.3%	71.5%	79%	66%	92.9%	76.4%
CR, %	31.8%	9.3%	12%	7%	4%	7%	56.6%	23.2%
Median PFS, mo	26.1	**16.6**	20.6	**14.7**	19.4	**14.9**	45	**17.5**
PFS HR (95% CI)	0.66 (0.55-0.78, *P*<.001)		0.74 (0.59-0.94, *P*=.01)		0.70 (0.57-0.85, *P*<.001)		0.44 (0.35-0.54, *P*=.0001)	
Median OS, mo	48.3	40.4	53.6	51.6	48.3	39.6	67.6	51.8
OS HR (95% CI)	0.79 (0.67-0.95, *P*=.005)		0.94 (0.78-1.13, *P*=.5)		0.82 (0.68-1.00, *P*=.05)		0.73 (0.58-0.91, *P*=.0044)	
IMiD refractory, %	21		21		-		3.5	

D = daratumumab; E = elotuzumab; FU = follow-up; ORR = overall repsonse rate; CR = complete response; PFS = progression-free survial; OS = overall survival; HR = hazard ratio; CI = confidence interval.

Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152. Siegel DS, et al. *J Clin Oncol*. 2018;36(8):728-734. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634. Richardson PG, et al. *J Clin Oncol*. 2021;39(22):2430-2442. Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631. Dimopoulous MA, et al. *Blood Cancer J*. 2020;10(9):91. Bahlis NJ, et al. *Leukemia*. 2020;34(7):1875-1884. Dimopoulous MA, et al. *J Clin Oncol*. 2023;41(8):1590-1599.

Randomized Studies with Bortezomib-Dex Control Arms Including Lenalidomide-Refractory MM

Efficacy	Pomalidomide PVd vs Vd (n=559)		Daratumumab* DVd vs Vd (n=498)		Carfilzomib Kd vs Vd (n=929)		Selinexor SVd vs Vd (n=402)		Venetoclax VenVD vs VD (n=194 vs n=97)	
	Tx	Control	Tx	Control	Tx	Control	Tx	Control	Tx	Control
Median FU, mo	64.5		72.6		44.3		28		45.6	
ORR, %	82	50	84	63	77	63	76	62	84	70
CR, %	13	3	29	10	13	6	17	11	29	7
Median PFS, mo	11.7	**6.9**	16.7	**7.1**	18.7	**9.4**	13.2	**9.5**	23.4	**11.4**
PFS HR (95% CI)	0.56 (0.49-0.77, *P*<.001)		0.31 (0.24-0.39, *P*<.001)		0.53 (0.44-0.65, *P*<.0001)		0.71 (0.54-0.93, *P*<.006)		0.58 (0.43, 0.78)	
Median OS, mo	35.6	31.6	49.6	38.5	47.8	38.8	36.7	30.2	33.5	NR
OS HR (95% CI)	0.94 (0.77-1.15, *P*=.571)		0.74 (0.59-0.92, *P*=.0075)		0.76 (0.63-0.92, *P*=.0017)		0.84 (0.60-1.17, *P*=.147)		0.74 (0.59-0.92, *P*=.0075)	

Daratumumab-refractory patients excluded in CASTOR, not represented in others

t(11;14):
PFS HR 0.12
OS HR 0.61

***Vd: 8, 21-day cycles.**

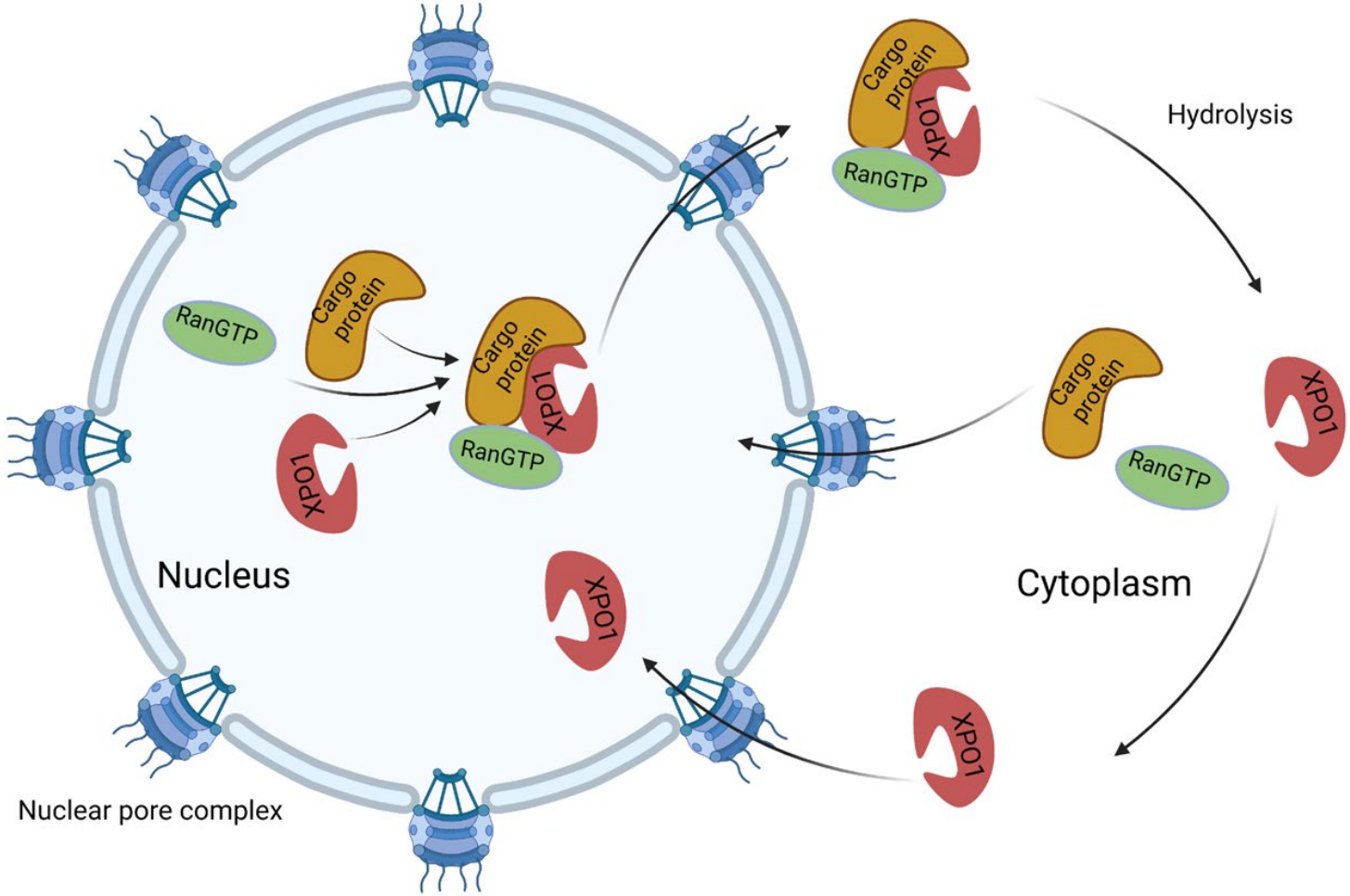
Richardson PG, et al. *Lancet Oncol*. 2019;20(6):781-794. Beksac M, et al. Presented at: International Myeloma Society Annual Meeting; September 27-30, 2023; Athens, Greece. Abstract OA-52. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. Sonneveld P, et al. *J Clin Oncol*. 2023;41(8):1600-1609. Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38. Orlowski RZ, et al. *Clin Lymphoma Myeloma Leuk*. 2019;19(8):522-530.e1. Mateos M-V, et al. *Eur J Haematol*. 2024;113(2):242-252. Kumar S, et al. *HemaSphere*. 2020;4(S1):Abstract EP939.

Randomized Studies with Carfilzomib and Pomalidomide-Dex Control Arms Including Lenalidomide-Refractory MM

Efficacy	Daratumumab DKd vs Kd (n=569)		Isatuximab IKd vs Kd (n=341)		Daratumumab DPd vs Pd (n=304)		Isatuximab IPd vs Pd (n=307)		Elotuzumax EPd vs Pd (n=117)	
	Tx	Control	Tx	Control	Tx	Control	Tx	Control	Tx	Control
Median FU, mo	50		56.6		39.6		52.4			
ORR, %	84.3%	72.7%	86.6%	83.7%	69%	46%	60%	35%	53%	26%
Median PFS, mo	28.4	**15.2**	35.7	**19.2**	12.4	**6.9**	11.5	**6.5**	10.3	**4.7**
PFS HR (95% CI)	0.64 (0.49-0.83, *P*<.0027)		0.58 (0.42-0.79, *P*<.05)		0.63 (0.47-0.85, *P*<.0018)		0.59 (0.44-0.81, *P*=.001)		0.54 (0.34-0.86, *P*=.008)	
Median OS, mo	50.8	43.6	NR	50.6	34.4	23.7	24.6	17.7	29.8	17.4
OS HR (95% CI)	0.78 (0.60-1.03, *P*<.042)		0.86 (0.61-1.2, *P*<.184)		0.82 (0.61-1.11, *P*<.2)		0.78 (0.59-1.02, *P*<.03)		0.59 (0.37-0.93, *P*=.0217)	
PFS HR, Len Non-Refractory	0.74 (0.49-1.11)		0.48 (0.28-0.82)		0.36 (0.15-0.83)		0.18 (0.02-1.49)		0.51 (0.21-1.19)	
PFS HR, Len Refractory	0.47 (0.29-0.78)		0.60 (0.34-1.06)		0.66 (0.49-0.90)		0.59 (0.43-0.82)		0.59 (0.33-0.97)	

Dimopoulos MA, et al. *Lancet Oncol*. 2020;396(10245):186-197. Usmani SZ, et al. *Blood Adv.* 2023;7(14):3739-3748. Martin T, et al. *Blood Cancer J*. 2023;13(1):72. Yong K, et al. Presented at: International Myeloma Society Annual Meeting; September 27-30, 2023; Athens, Greece. Dimopoulos MA, et al. *Lancet Oncol*. 2021;22(6)801-812. Dimopoulos MA, et al. *Lancet Haematol*. 2023;10(10):e813-e824. Attal M, et al. *Lancet.* 2019;394(10214):2096-2107. Richardson PG, et al. *Haematologica*. 2024;109(7):2239-2249. Dimopoulos MA, et al. *N Engl J Med*. 2018;379(19):1811-1822. Dimopoulos MA, et al. *J Clin Oncol.* 2023;41(3):568-578.

Selinexor MOA



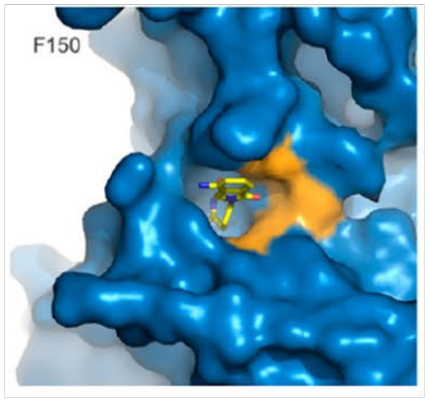
MOA = mechanism of action.

Nooka AK, et al. *Clin Lymphoma Myeloma Leuk.* 2022;22(7):e526-e531

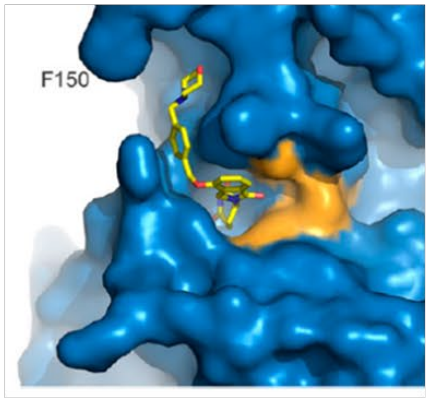
Newer Compounds: Iberdomide MOA

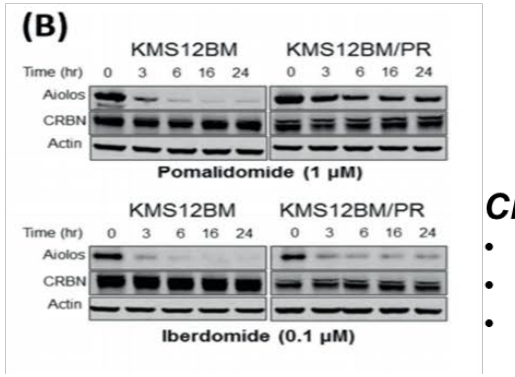
IBER enhances in vitro immune stimulatory activity vs LEN and POM

LEN

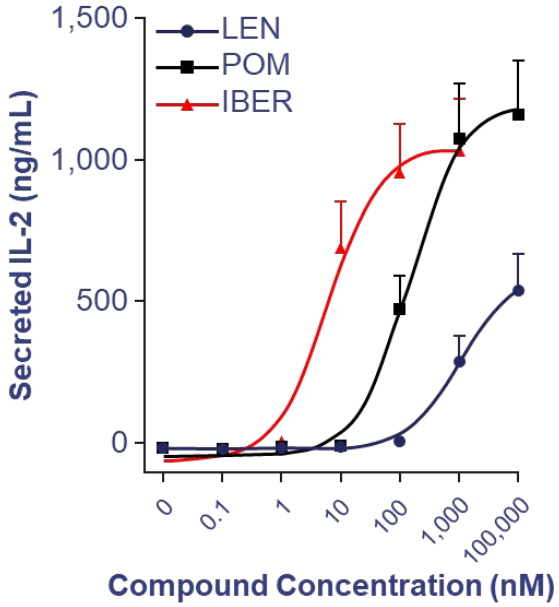


IBER

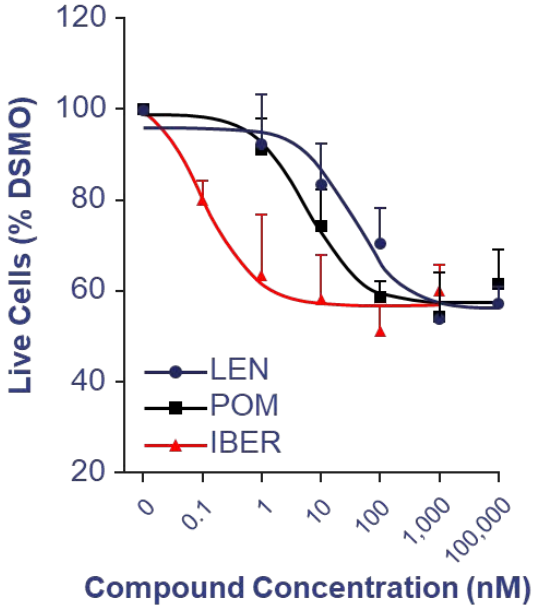




IL-2 Secretion by Treated PBMCs



MM Cell Survival in Co-Culture With Treated PBMCs



***CRBN* binding IC_{50}**

- CC-220: 0.06 uM
- Pomalidomide: 1.20 uM
- Lenalidomide: 1.50 uM

Aiolos degradation (5 hrs) EC_{50}

- CC-220: 0.5 nM
- Pomalidomide: 22.0 nM
- Lenalidomide: 87.0 nM

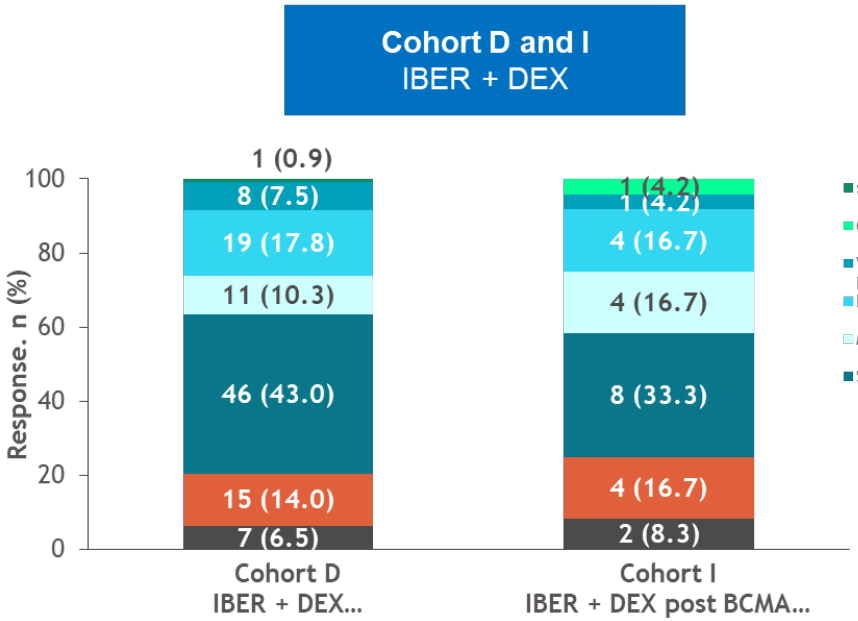
Ikaros degradation (5 hrs) EC_{50}

- CC-220: 1.0 nM
- Pomalidomide: 24.0 nM
- Lenalidomide: 67.0 nM

PBMC = peripheral blood mononuclear cell; IL = interleukin; EC_{50} = half-maximal effective concentration; IC_{50} = half-maximal inhibitory concentration; DSMO = dimethylsulfoxide.

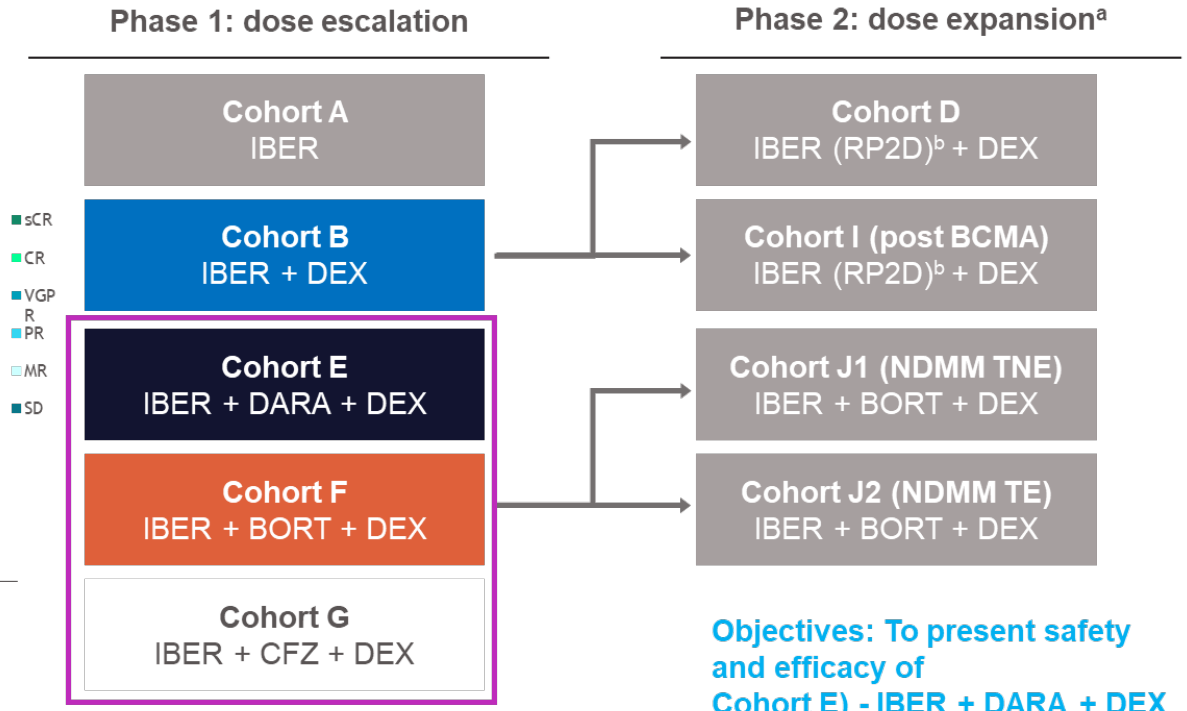
Bjorklund CC, et al. *Leukemia*. 2020;34(4):1197-1201. Adapted with permission from: Matyskiela ME, et al. *J Med Chem*. 2018;61(2):535-542.

CC-220-MM-001 Study Design and Objectives



Key eligibility criteria (Cohorts E, F, and G)

- RRMM ≥ 2 prior regimens (≥ 1 in Cohort F) including Len/Pom and PI
- PD on or within 60 days of last antimyeloma therapy



Study endpoints

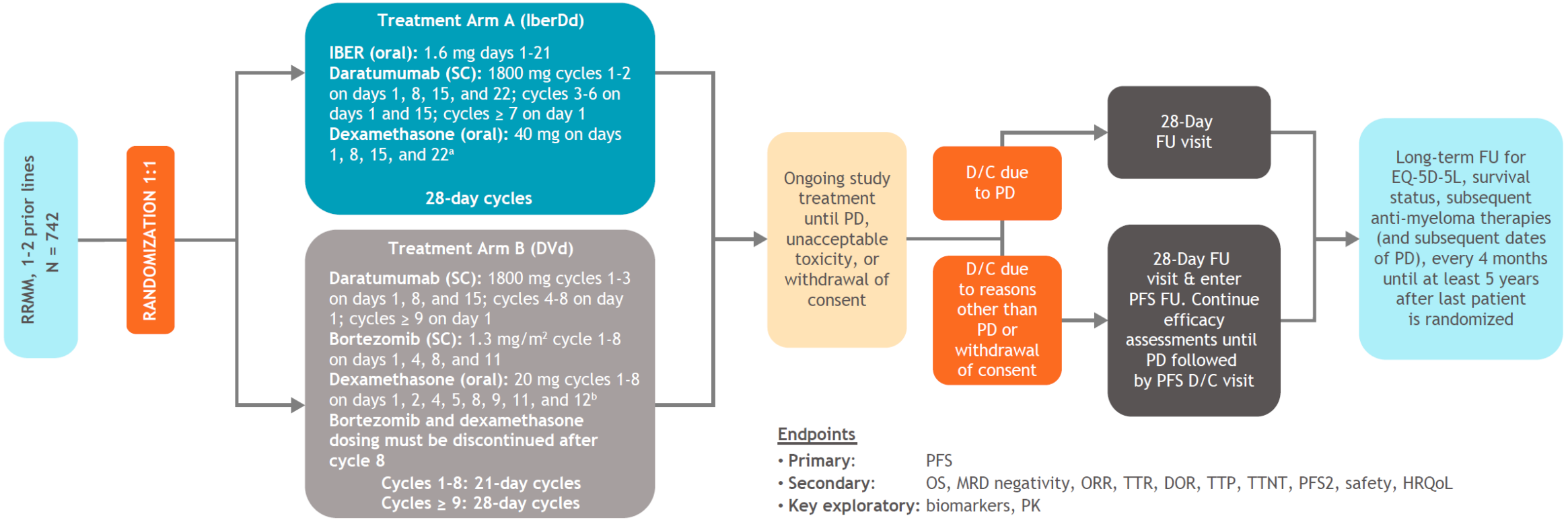
- Primary: to determine MTD/RP2D
- Secondary: to assess safety and preliminary efficacy

Objectives: To present safety and efficacy of
Cohort E) - IBER + DARA + DEX
Cohort F) - IBER + BORT + DEX
Cohort G) - IBER + CFZ + DEX

[a]Cohort C (IBER monotherapy expansion) was planned, but not opened; [b]1.6 mg q.d.
BCMA = B-cell maturation antigen; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; TE = transplant eligible; TNE = transplant non-eligible.

Lonial S, et al. Presented at: Congress of the European Haematology Association; June 9, 2021; virtual. Abstract S187. National Institutes of Health (NIH). Accessed October 25, 2024. https://clinicaltrials.gov/ct2/show/NCT02773030. EU Clinical Trials Register. Accessed October 25, 2024. www.clinicaltrialsregister.eu/ctr-search/search?query=2016-000860-40.

EXCALIBER Study

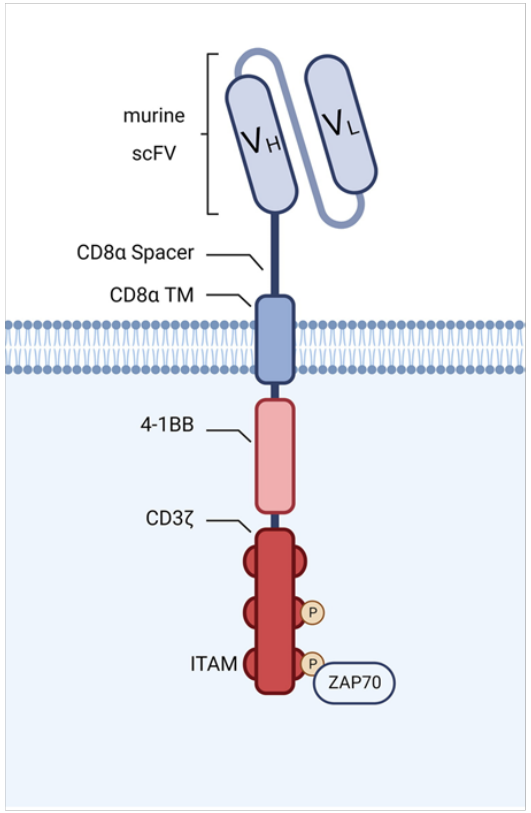


PD = progressive disease; D/C = discontinue; MRD = minimal residual disease; TTR = time in therapeutic range; DOR = duration of response; TTP = time to progression; TTNT = time to next treatment; PFS2 = time to second disease progression; HRQoL = health-related quality of life; PK = pharmacokinetics.

NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04975997. Lonial S, et al. Presented at: International Myeloma Workshop; September 8, 2021; Vienna, Austria. Presentation 1087040.

BCMA-Directed CAR-T in Multiple Myeloma

Ide-cel



FDA Approved: Mar 26, 2021

KarMMa Trial

Phase II (N=128)

ORR: 72%
- 95% CI, 63.2-80.8
- ORR = sCR + VGPR + PR

mDOR: 11.3 months
- 95% CI, 10.3-15.3

mPFS: 22.6 months
- 95% CI, 14.39-NE

mOS: 24.0 months
- 95% CI, 18.96-NE

Cilta-cel

FDA Approved: Feb 28, 2022

CARTITUDE-1 Trial

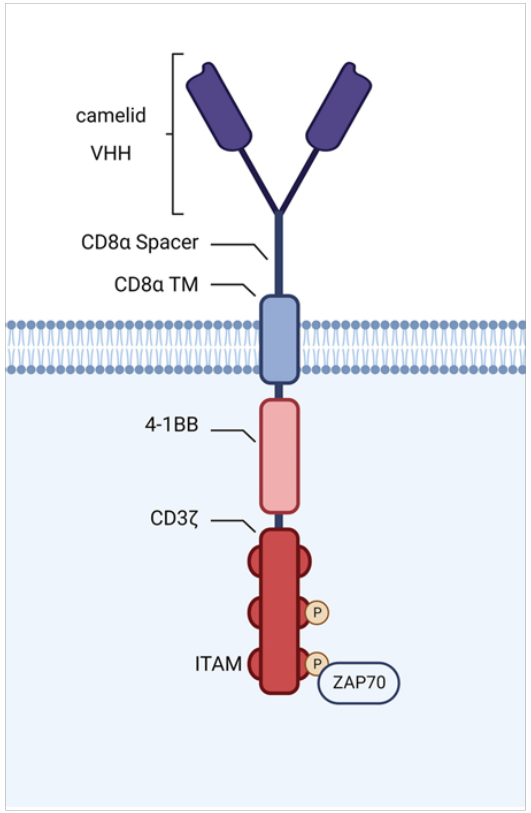
Phase Ib/II (N=97)

ORR: 98%
- 95% CI, 92.7-99.7
- ORR = sCR + VGPR + PR

mDOR: 33.9 months
- 95% CI, 25.5-NE

mPFS: 34.9 months
- 95% CI, 25.2-NE

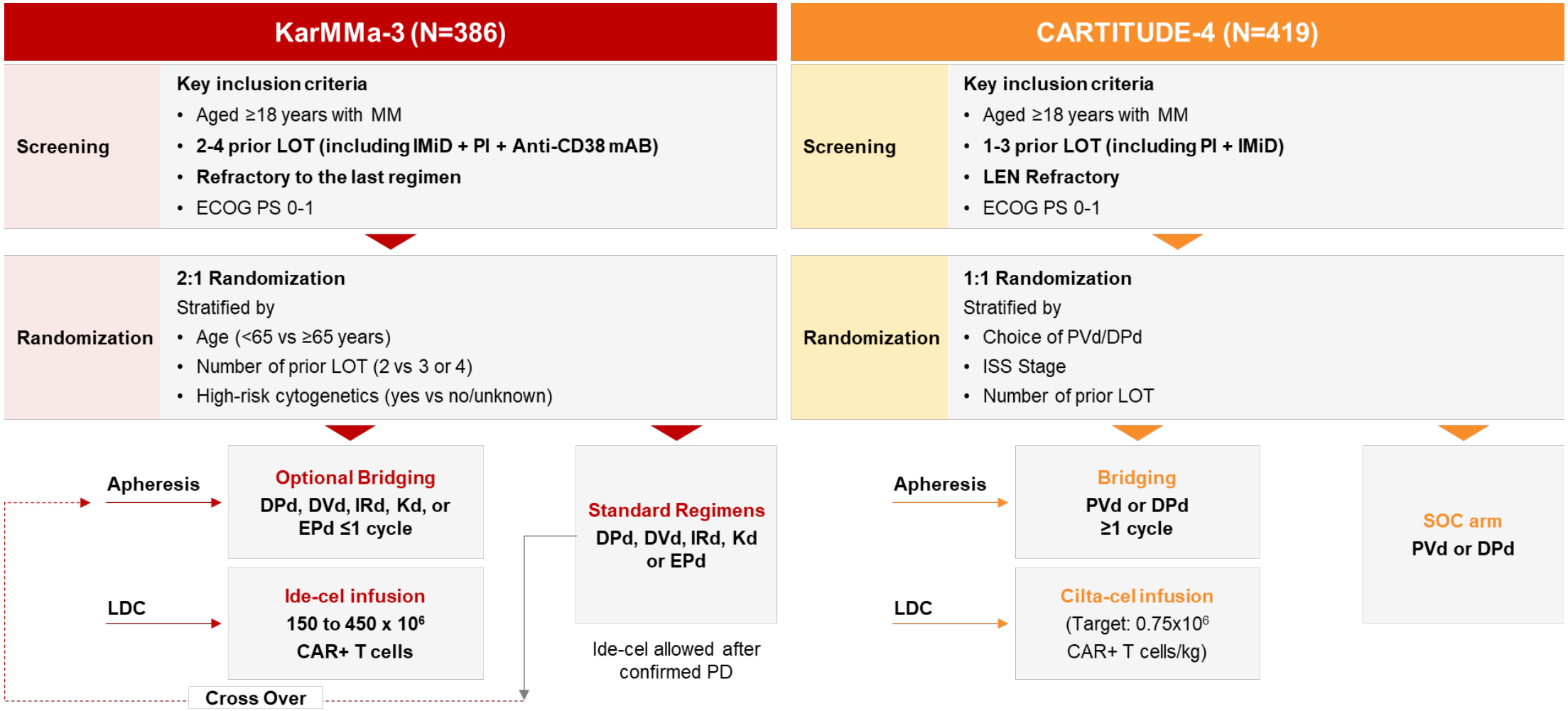
mOS: NR
- 62.9% OS at 36 months



CAR-T = chimeric antigen receptor T cell; mDOR = median duration of response; mPFS = median progression-free survival; mOS = median overall survival; sCR = stringent complete response; VGPR = very good partial response; PR = partial response; NE = not estimable; NR = not reached.

NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT03361748; NCT03548207. Lin Y, et al. *J Clin Oncol.* 2023;41(Suppl 16):8009. Scheller L, et al. *Leuk Lymphoma*. 2024;65(2):143-157.

Earlier Line CAR-T Is HERE!



LOT = line of therapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LDC = lymphodepleting chemotherapy; SOC = standard of care.

Rodriguez-Otero P, et al. *N Engl J Med.* 2023;389(11):1002-1014. San-Miguel J, et al. *N Engl J Med.* 2023;389(4):335-347. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT03651128; NCT04181827.

Study Designs: Key Differences

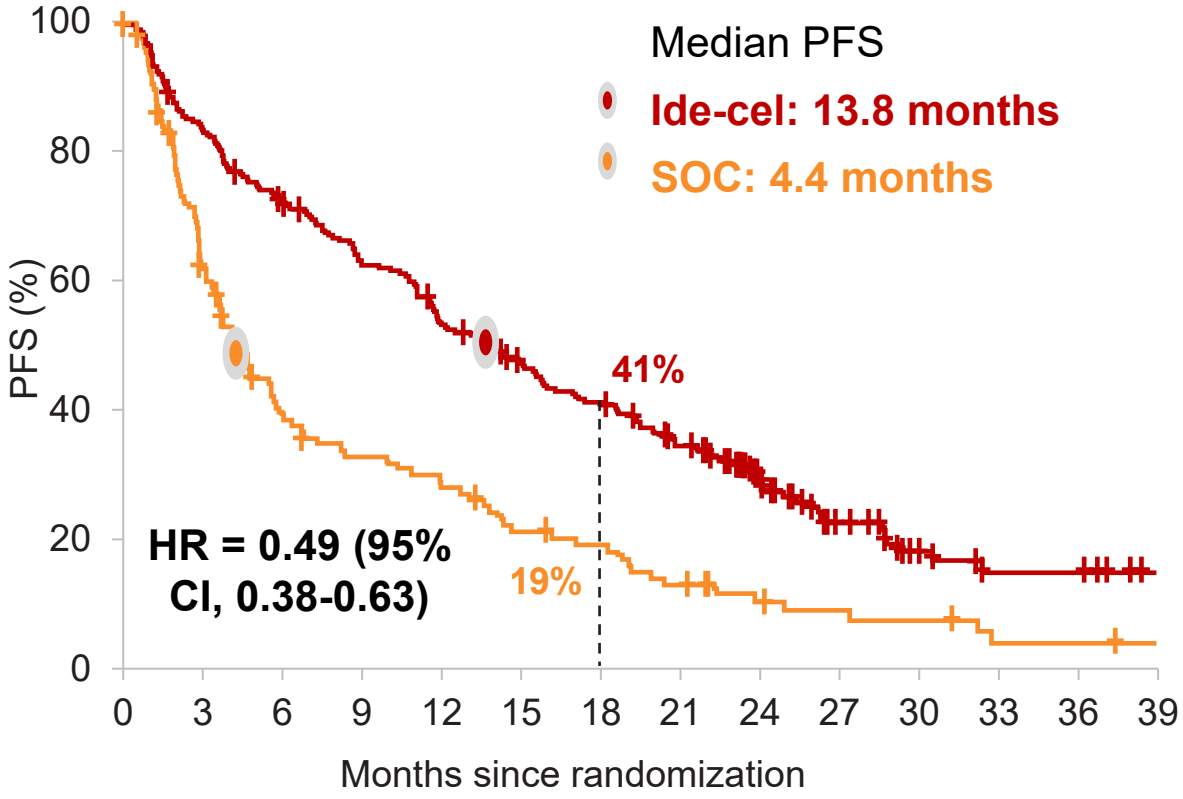
KarMMa-3		CARTITUDE-4
2-4	Prior Lines of Therapy	1-3
Triple-class exposed	Prior Treatment Exposure	PI, IMiD exposed, LEN refractory
Not required; only 1 cycle allowed	Bridging Requirement	Required per protocol; 80% received 2 or 3 cycles
PFS in ITT, including patients who were apheresed but not infused with ide-cel	Primary Endpoint Analysis Methodology	PFS HR excludes any events within the first 8 weeks of randomization
Allowed; 56% in SR arm went on to receive Ide-cel	Cross-Over	Not permitted per protocol

ITT = intention-to-treat; SR = standard regimens.

Rodriguez-Otero P, et al. *N Engl J Med.* 2023;389(11):1002-1014. San-Miguel J, et al. *N Engl J Med.* 2023;389(4):335-347. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT03651128; NCT04181827.

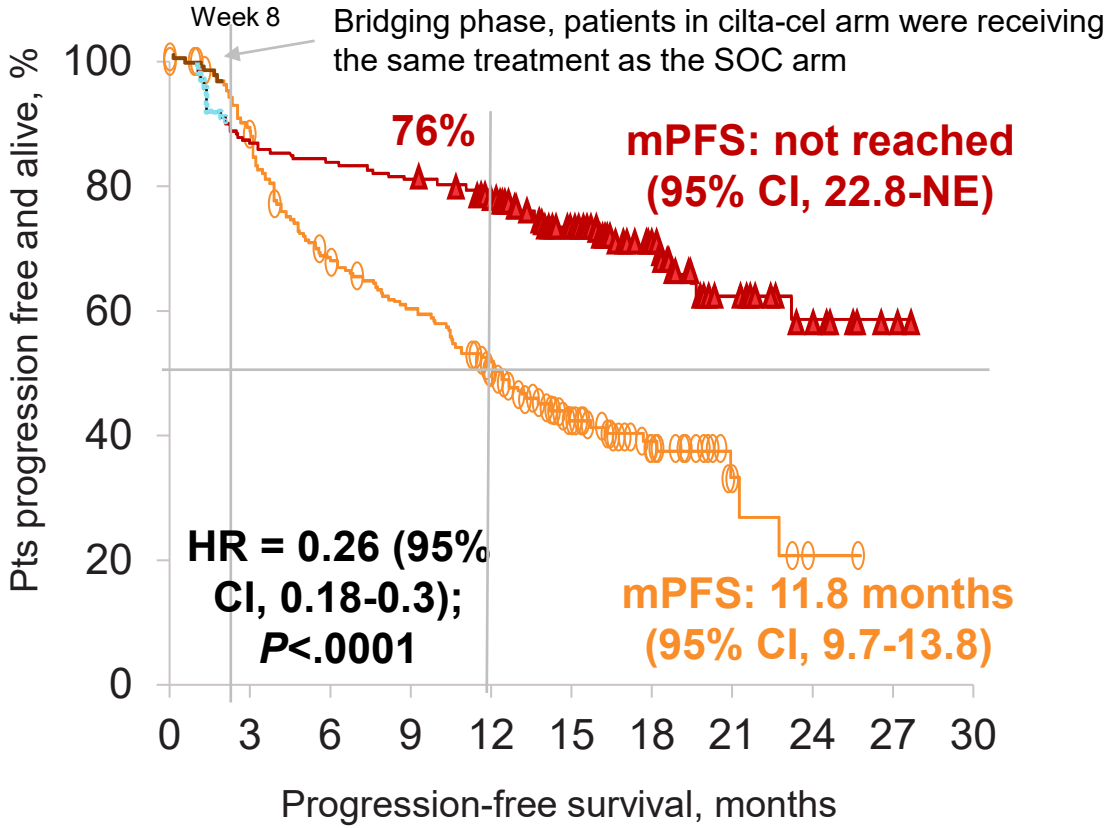
Efficacy of CAR-T as an Earlier LOT

KarMMa-3 Primary Endpoint: PFS analysis (ITT)



FDA APPROVED in 3L as of 4/5/24

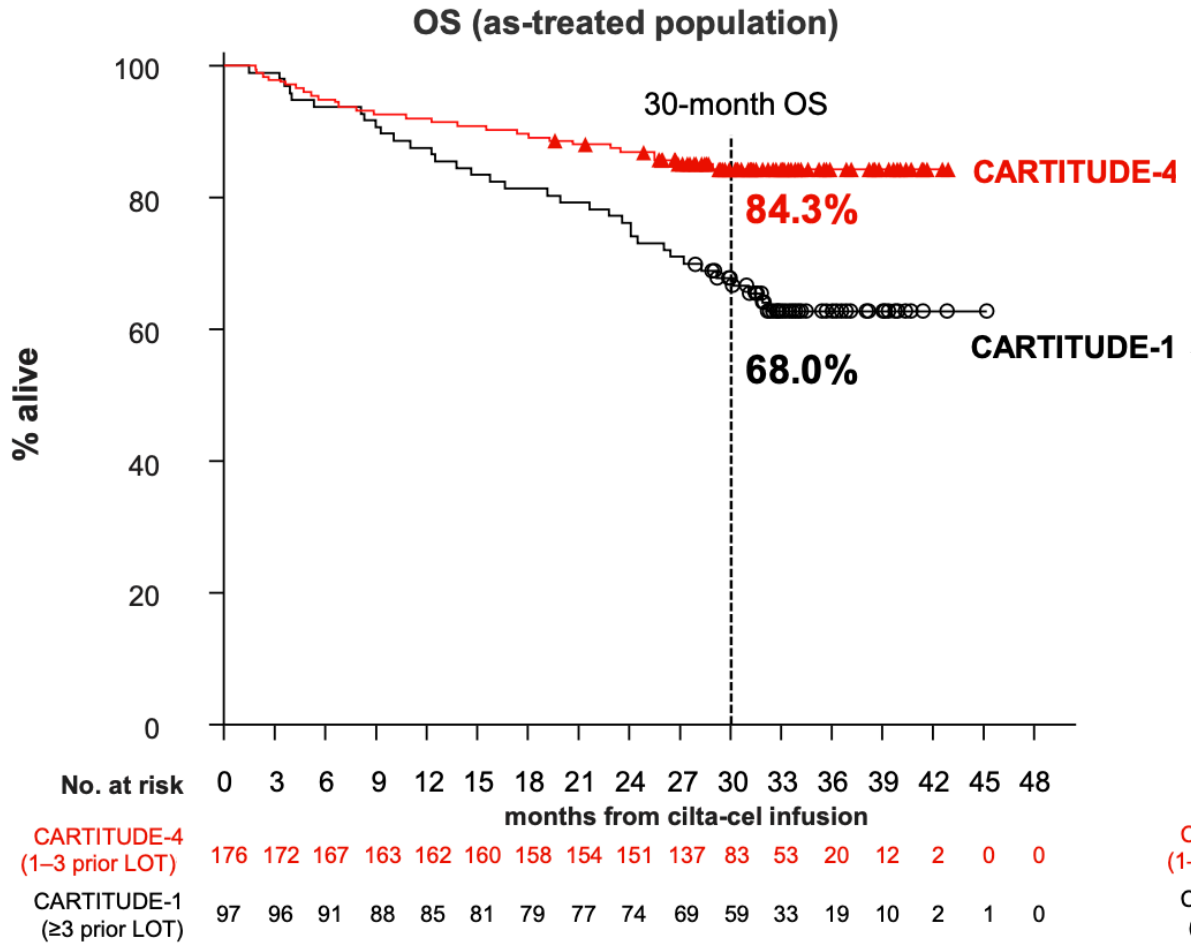
CARTITUDE-4 Primary Endpoint: PFS (ITT Population)

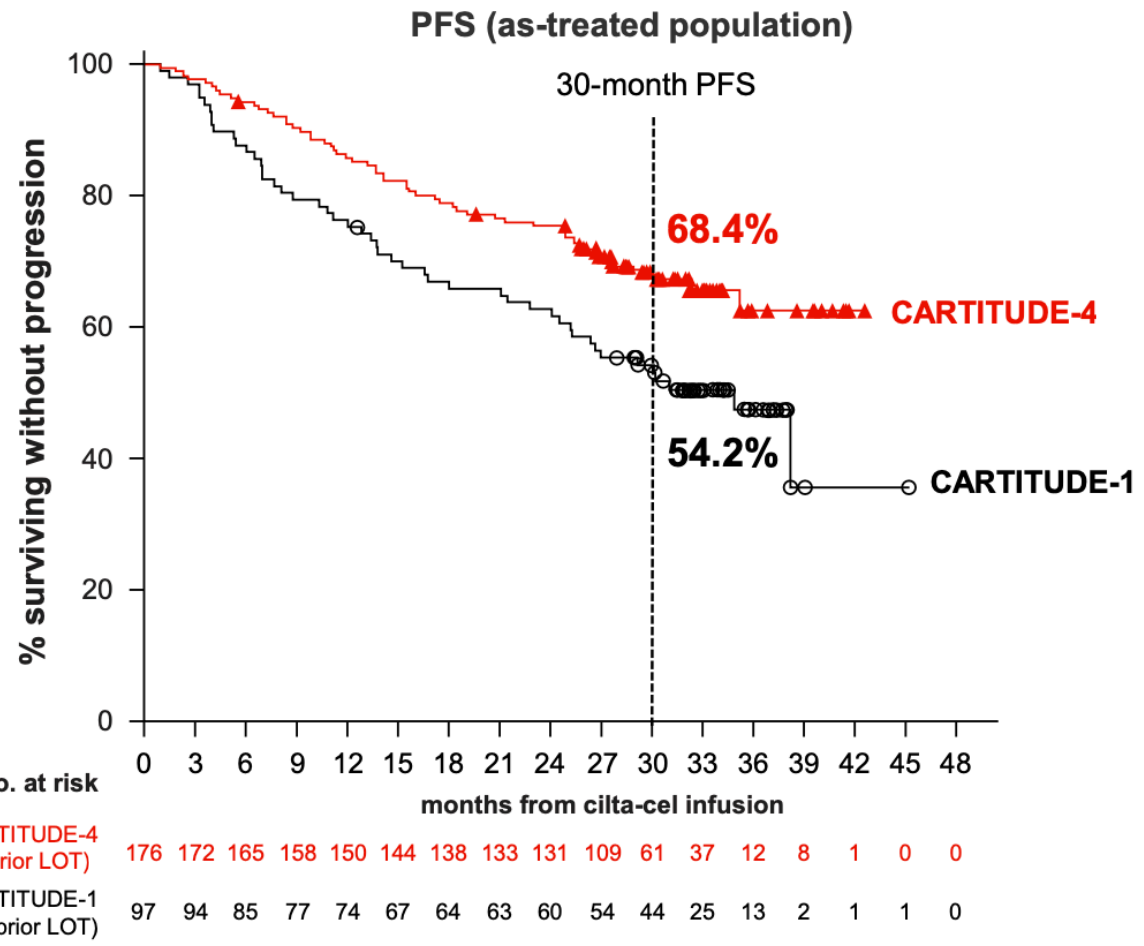


FDA APPROVED in 2L as of 4/5/24

Dhakal B, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023. Abstract LBA106. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT03651128; NCT04181827.

CARTITUDE-4 PFS and OS vs CARTITUDE-1

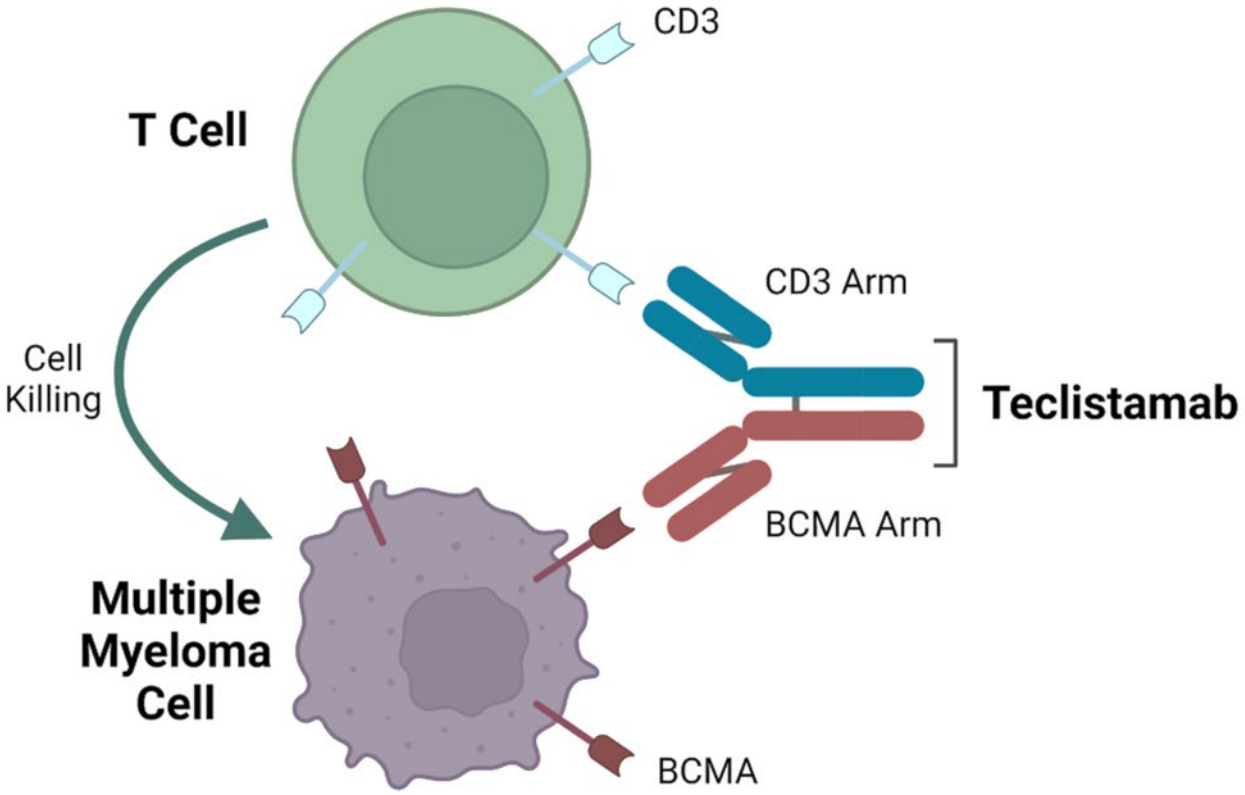




Cilta-cel use in earlier lines demonstrated numerically higher rates of overall and progression-free survival

Mateos MV, et al. Presented at: International Myeloma Society Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Abstract OA-65. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04181827; NCT03548207.

Overview of Teclistamab



Key eligibility criteria:

- RRMM[7]
- ECOG PS 0 or 1
- Triple-class exposed (PI, IMiD, anti-CD38 mAb)
- No prior BCMA-directed therapy

Phase 1

Dose escalation

- IV cohorts
- SC cohorts

Dose expansion

- RP2D 1.5 mg/kg SC QW

Phase 2

- Cohort A

Primary endpoint: ORR

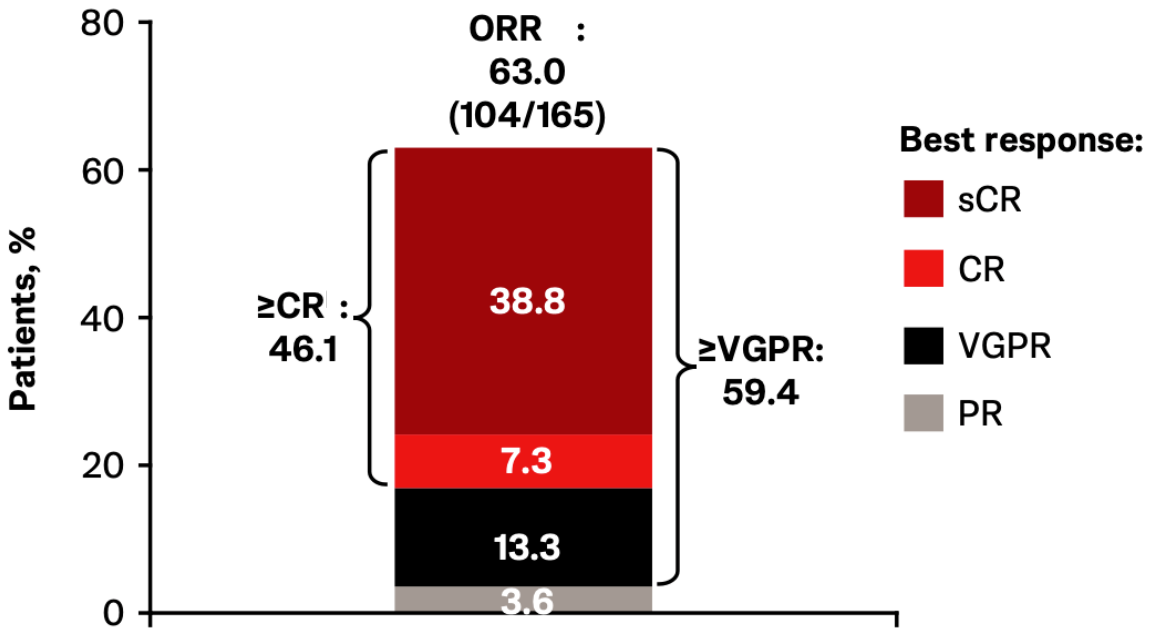
Key secondary endpoints:

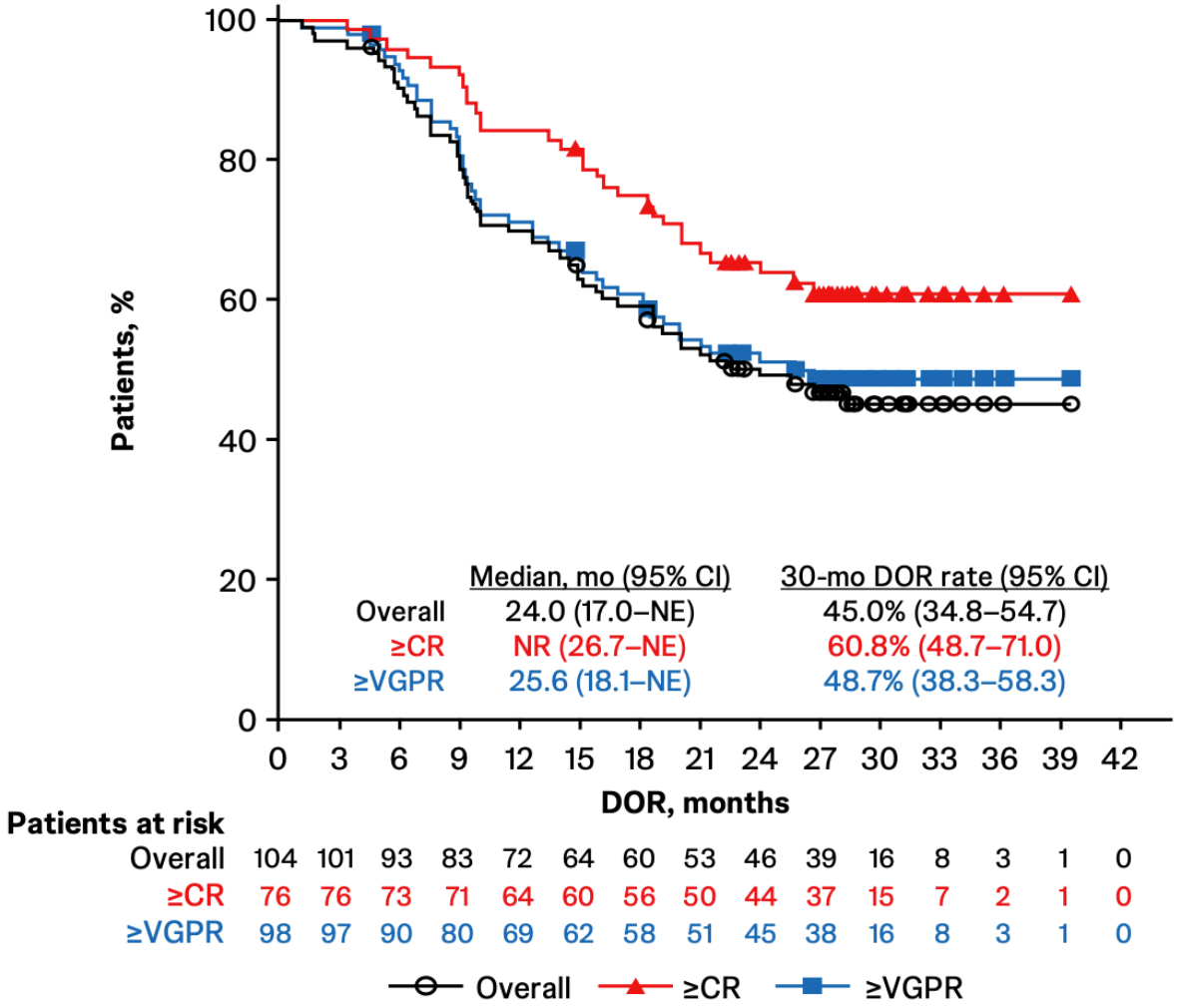
- PK/PD
- DOR
- PFS
- OS
- MRD negativity
- AEs
- HRQoL

PD = pharmacodynamics; AE = adverse event.

Adapted from: Pillarisetti K, et al. *Blood Adv.* 2020;4(18):4538-4549. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04557098.

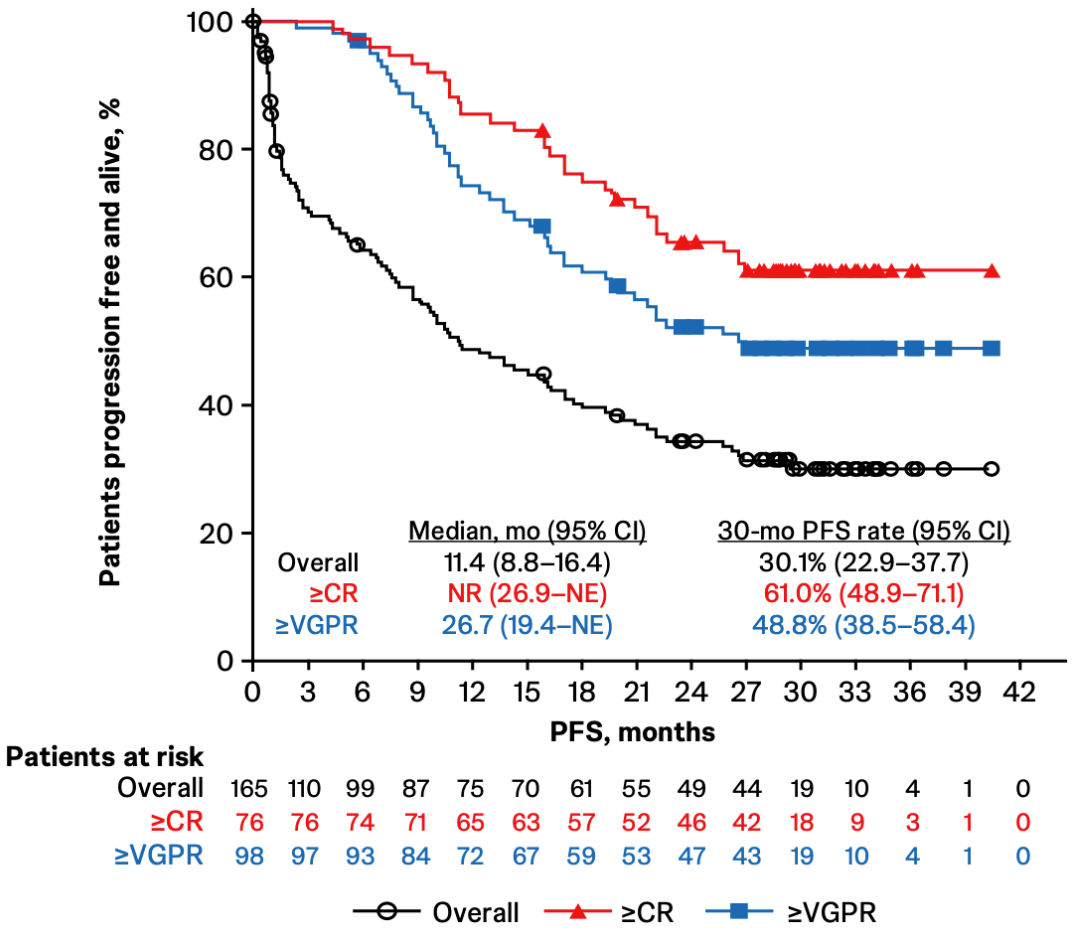
MajesTEC-1 ORR and DOR





Oriol A, et al. Presented at: European Haematology Association Congress; June 13, 2024; Madrid, Spain. Abstract P942. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04557098.

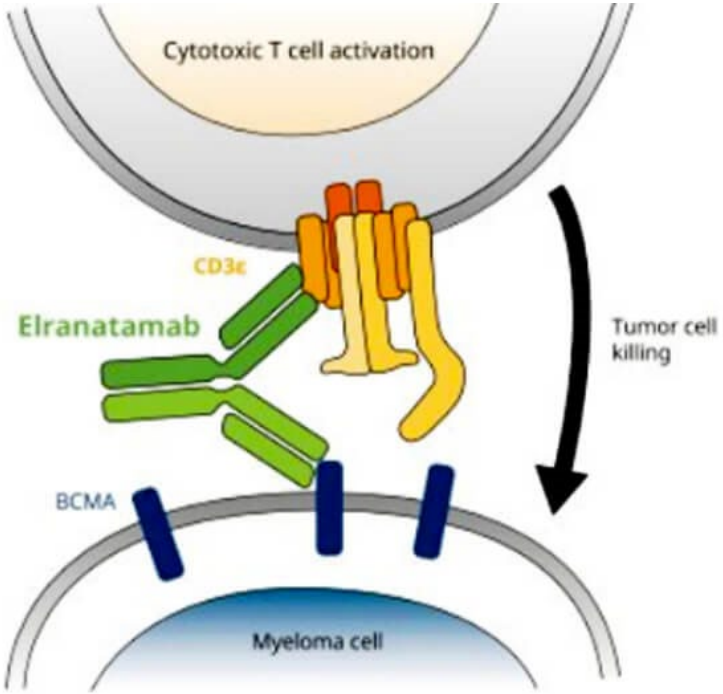
MajesTEC-1 PFS and OS



	mDOR, mo (95% CI)	mPFS, mo (95% CI)	mOS, mo (95% CI)
All RP2D (N=165)	24.0 (17.0–NE)	11.4 (8.8–16.4)	22.2 (15.1–29.9)
≥CR (n=76)	NR (26.7–NE)	NR (26.9–NE)	NR (35.5–NE)
≥VGPR (n=98)	25.6 (18.1–NE)	26.7 (19.4–NE)	NR (31.0–NE)
MRD-neg (n=48)	NR (19.2–NE)	NR (21.0–NE)	NR (29.9–NE)
≤3 pLOT (n=43)	24.0 (14.0–NE)	21.7 (13.8–NE)	NR (18.3–NE)
>3 pLOT (n=122)	22.4 (14.9–NE)	9.7 (6.4–13.1)	17.7 (12.2–29.7)
Phase 2 efficacy (USPI) (n=110)	22.4 (14.9–NE)	10.8 (7.4–16.4)	21.7 (12.7–29.9)
≥CR (n=51)	NR (21.6–NE)	NR (22.8–NE)	NR (NE–NE)

Oriol A, et al. Presented at: European Haematology Association Congress; June 13, 2024; Madrid, Spain. Abstract P942. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04557098.

Overview of Elranatamab



- MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study
  - Interim analysis data-cut off: March 23, 2022

Patients with RRMM

Key inclusion criteria:
- Refractory to at least 1 each of the following: proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody
- ECOG performance status ≤2
- Creatinine clearance ≥30 mL/min
- Platelets ≥25 x 10^9/L
- ANC ≥1.0 x 10^9/L
- Hemoglobin ≥8 g/dL

Cohort A (n = 123)
No prior BCMA-directed treatment

Cohort B (n = 64)
Prior BCMA-directed ADC or CAR-T

- Patients will be followed for ~2 y from enrollment

Elranatamab 76 mg SC QW on a 28-d cycle

Interim analysis of Cohort A
First 94 patients who received ≥1 dose of elranatamab

Primary endpoint
- ORR by BICR

Secondary endpoints
- Duration of response
- CR rate
- ORR
- ORR by baseline extramedullary disease status
- Duration of CR
- Time-to-response
- PFS
- MRD-negativity rate
- OS
- Safety
- Pharmacokinetics

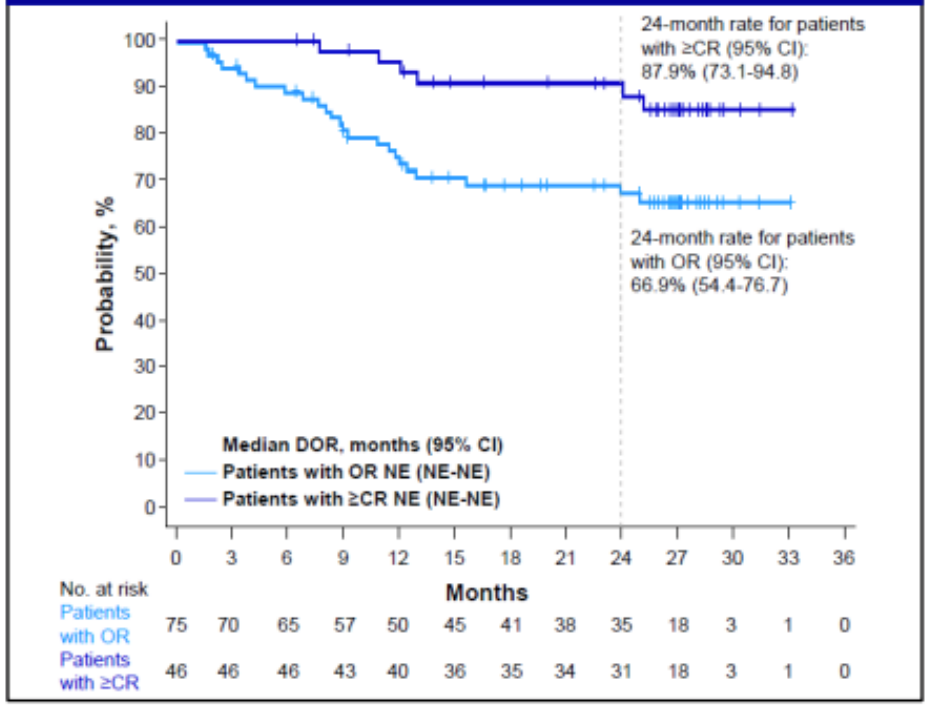
ANC = absolute neutrophil count; ADC = antibody-drug conjugate.

NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04649359.

MagnetisMM-3 ORR and DOR

- With extended follow-up, ORR per BICR remained at 61.0% (≥CR rate, 37.4%)
  - sCR, 16.3%; CR, 21.1%; VGPR, 18.7%; PR, 4.9%
- MRD negativity rate was 90.3% in patients with ≥CR who were evaluable for MRD (n=31) at the threshold of 10^{-5}
- Median DOR was not reached (**Figure**)
- The probability of maintaining a response at 2 years was:
  - 66.9% (95% CI, 54.4-76.7) among all responders, and
  - 87.9% (95% CI, 73.1-94.8) in patients with ≥CR

Figure: DOR

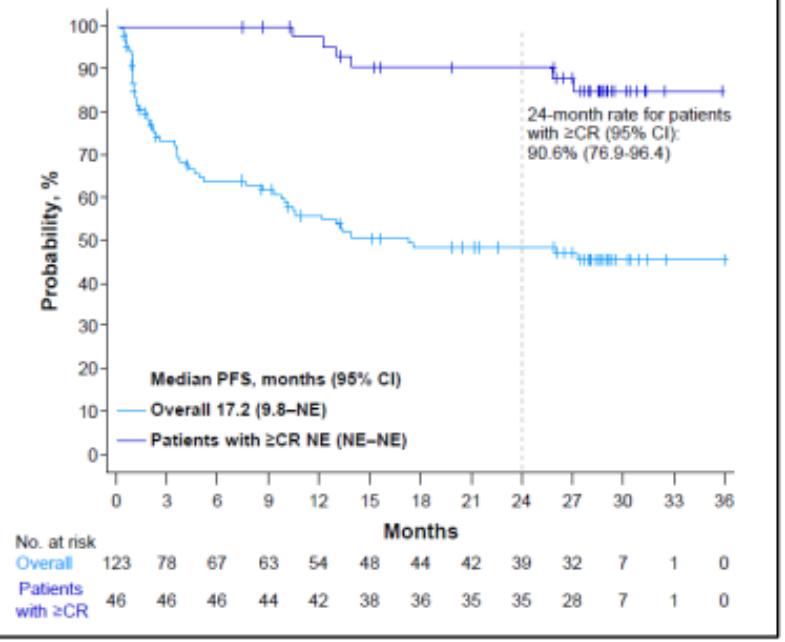


BICR = blinded independent central review.

Mohty M, et al. Presented at: European Haematology Association Congress; June 13, 2024; Madrid, Spain. Abstract P932. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04649359.

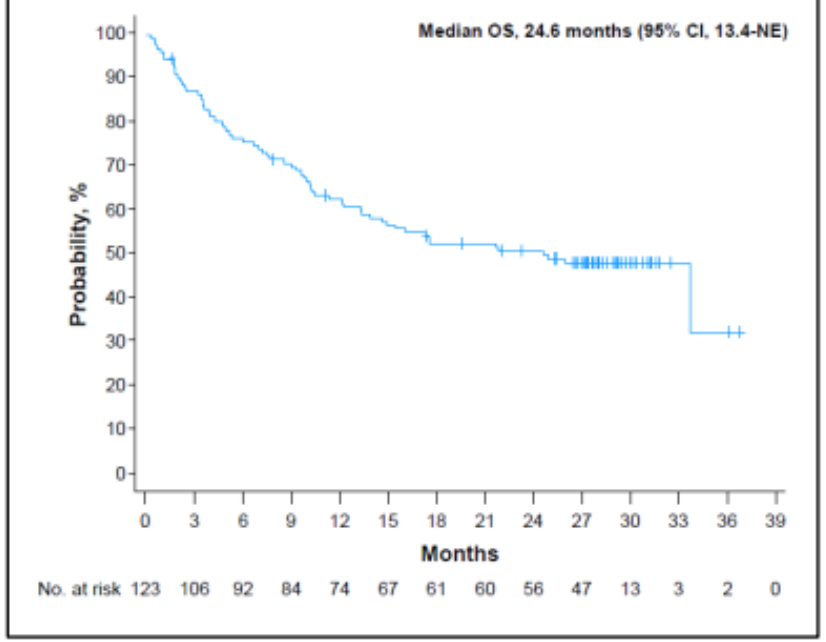
MagnetisMM-3 PFS and OS

Figure 1: PFS



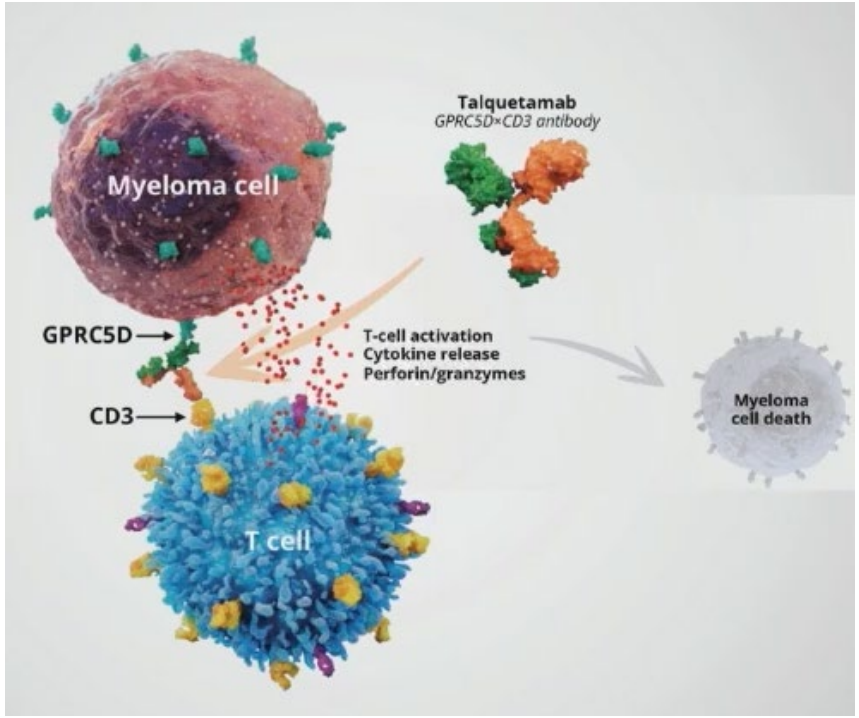
- Median PFS was 17.2 (95% CI, 9.8-NE) months (**Figure 1)**
  - In patients with ≥CR, median PFS was not reached and the probability of being progression-free at 2 years was 90.6% (95% CI, 76.9-96.4)
- Median OS was 24.6 (95% CI, 13.4-NE) months (**Figure 2**)

Figure 2: OS



Mohty M, et al. Presented at: European Haematology Association Congress; June 13, 2024; Madrid, Spain. Abstract P932. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04649359.

Overview of Talquetamab



Eligibility Criteria

Phase 1
- Measurable MM
- Intolerant to or progressed on established therapies
- ECOG PS ≤1

Phase 2
- Measurable MM
- ≥3 prior LOT
- ECOG PS ≤2

0.4 mg/kg SC QW (TCR naïve) → Prior anti-BCMA ADC allowed

0.8 mg/kg SC Q2W (TCR naïve) → Prior anti-BCMA ADC allowed

0.4 mg/kg SC QW or 0.8 mg/kg SC Q2W (PRIOR TCR) → Prior anti-BCMA CART, or BsAb allowed

Endpoints

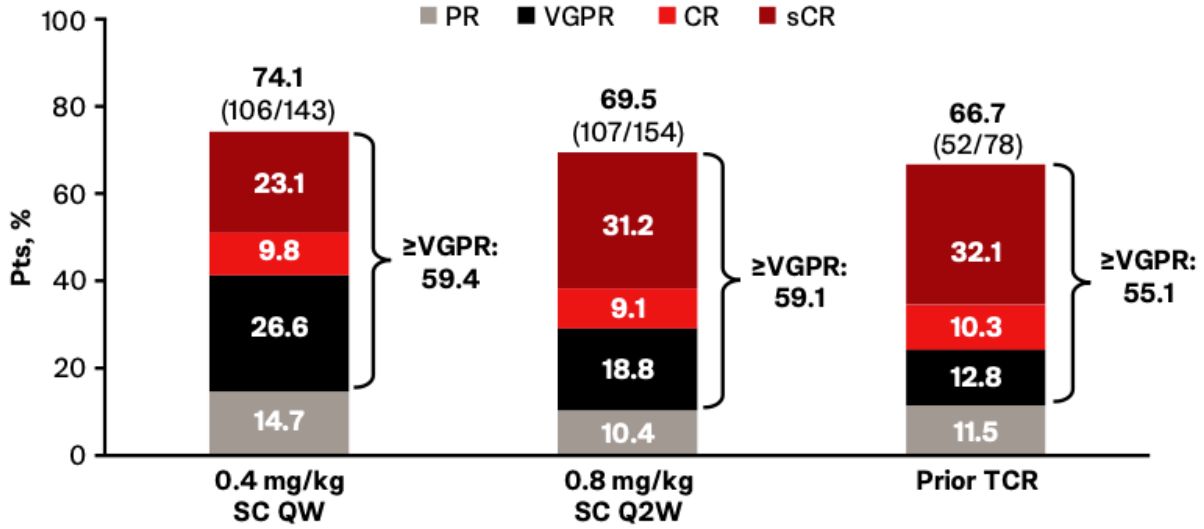
Primary Endpoint
- ORR

Secondary Endpoint
- DOR
- PFS
- OS
- Safety
- Immunogenicity
- Pharmacodynamics

TCR = triple-class refractory; BsAb = bispecific antibody.

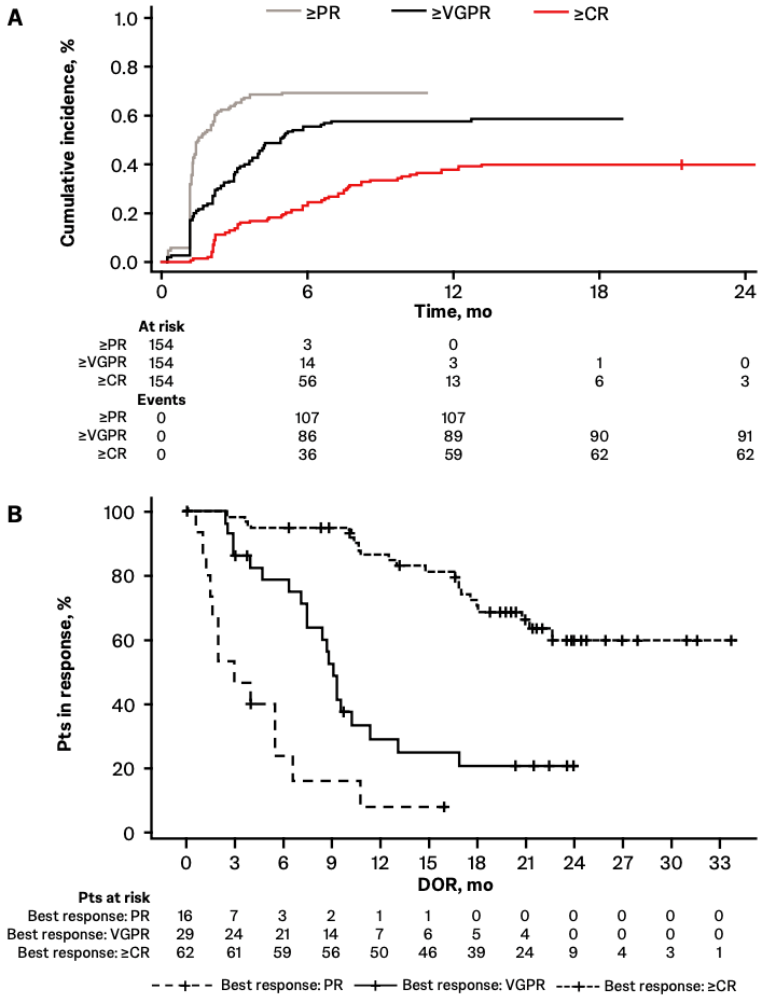
NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04634552.

MonumenTAL-1 Long-Term Follow-Up



Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
mFU, mo	29.8	23.4	20.5
mDOR (95% CI), mo	9.5 (6.7–13.4)	17.5 (12.5–NE)	N/A
mDOR in pts with ≥CR (95% CI), mo	28.6 (19.4–NE)	NR (21.2–NE)	N/A
mPFS (95% CI), mo	7.5 (5.7–9.4)	11.2 (8.4–14.6)	7.7 (4.1–14.5)
24-mo OS rate (95% CI), %	60.6 (51.7–68.4)	67.1 (58.3–74.4)	57.3 (43.5–68.9)

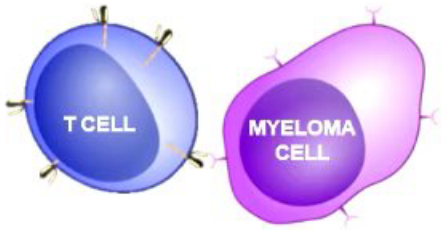
Figure 3: Time to first confirmed response per IRC (A) and DOR by depth of response (B) in the Q2W cohort



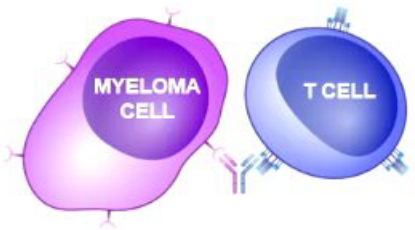
IRC = independent review committee.

Rasche L, et al. Presented at: European Haematology Association Congress; June 13, 2024; Madrid, Spain. Abstract P915.
NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04634552.

Potential Mechanisms of Resistance to T-Cell Directing Therapies



CAR T



BsAb

CAR T		BsAb
Target antigen loss Expression of immunosuppressive molecules Adverse genomic features	***Tumor intrinsic***	Target antigen loss MHC downregulation Tumor biology (eg, EMD, stage) Adverse genomic features
T-cell exhaustion Activation-induced cell death T-cell subset/phenotype or CAR design	***T-cell dependent***	BCMA binding domain mutation T-cell exhaustion
Immunosuppressive cell types and soluble molecules	***Microenvironment***	Soluble BCMA sink (for BCMA-directed BsAbs) Immunosuppressive cells/cytokines

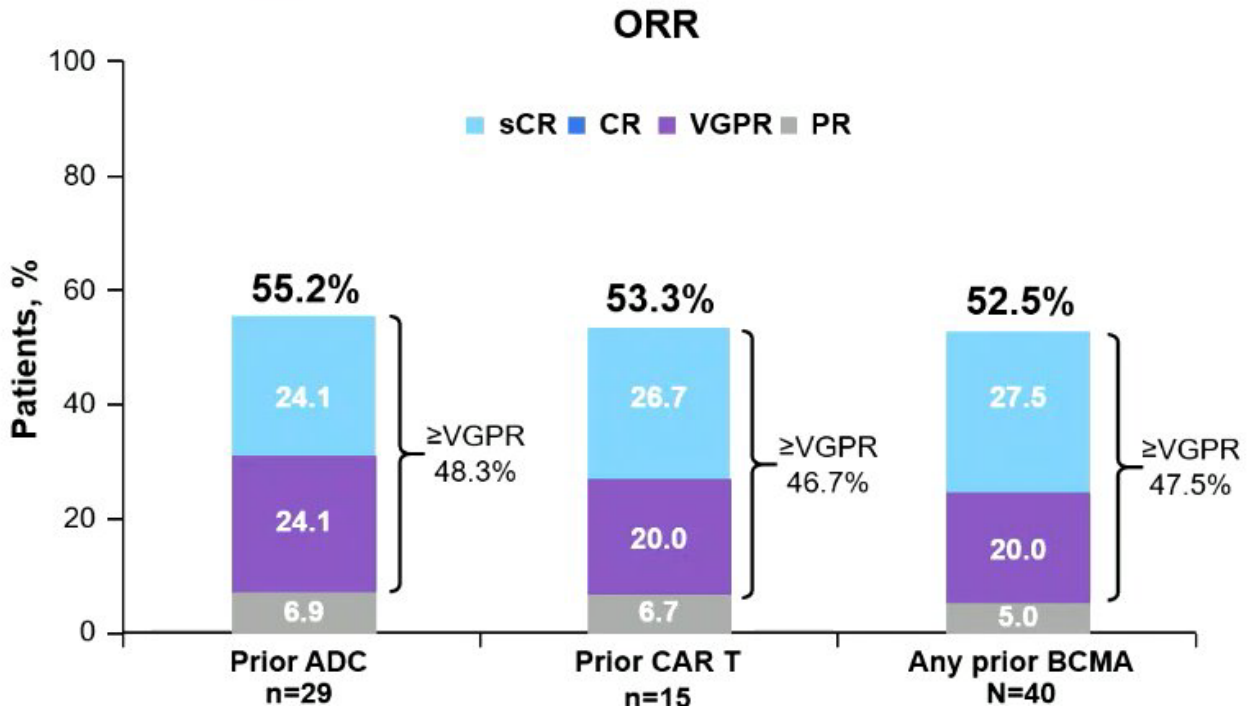
EMD = extramedullary disease.

Lee H, et al. *Nat Med.* 2023;29(9):2295-2306.

Sequencing: Teclistamab following Prior Anti-BCMA Therapy

MajesTEC-1: RRMM with ≥3 prior LoT including PI, IMiD, anti-CD38 mAb
N=40

BCMA ADC or CAR T → BCMA BsAb



Median Duration of Therapy, mo (range)

5.2 (0.2–13.6)

mDOR, mo (95% CI)

Not reached (10.5–NE)

MRD negativity rate (10^{-5})

17.5%

Median follow-up: 12.5 mo (range, 0.7–14.4)

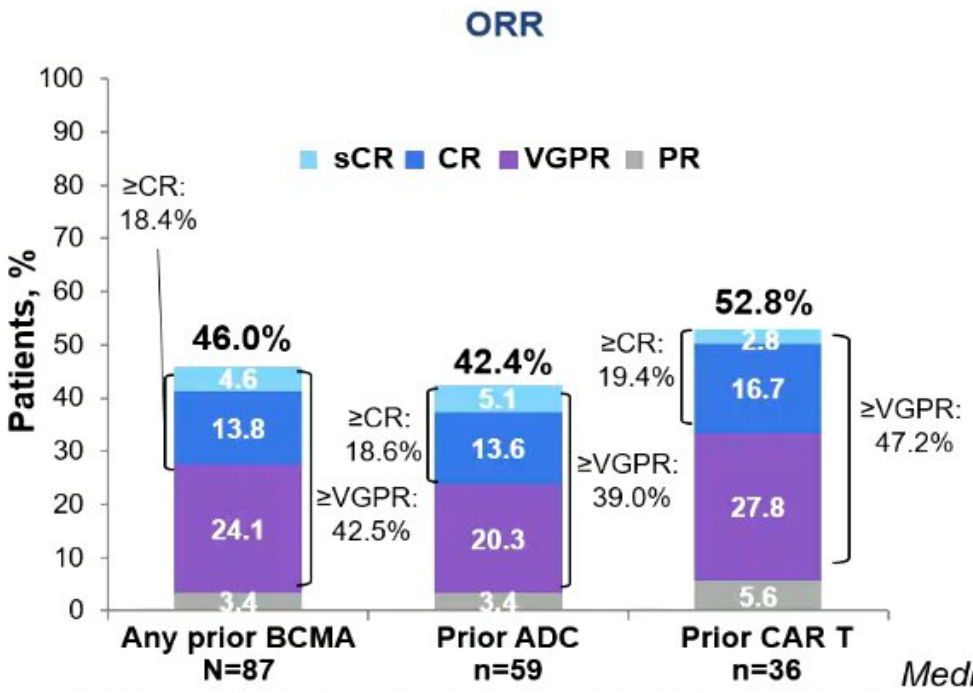
Touzeau C, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2, 2022; Chicago, Illinois. Abstract 8013.

Sequencing: Elranatamab following Prior Anti-BCMA Therapy

MagnetisMM-1 (n=13), MagnetisMM-2 (n=1), MagnetisMM-3 (n=64), and MagnetisMM-9 (n=9)

BCMA ADC or CAR T → BCMA BsAb

Prior BCMA Pooled Analysis (N=87)
Any prior ADC (n=59) | Any prior CAR T (n=36)

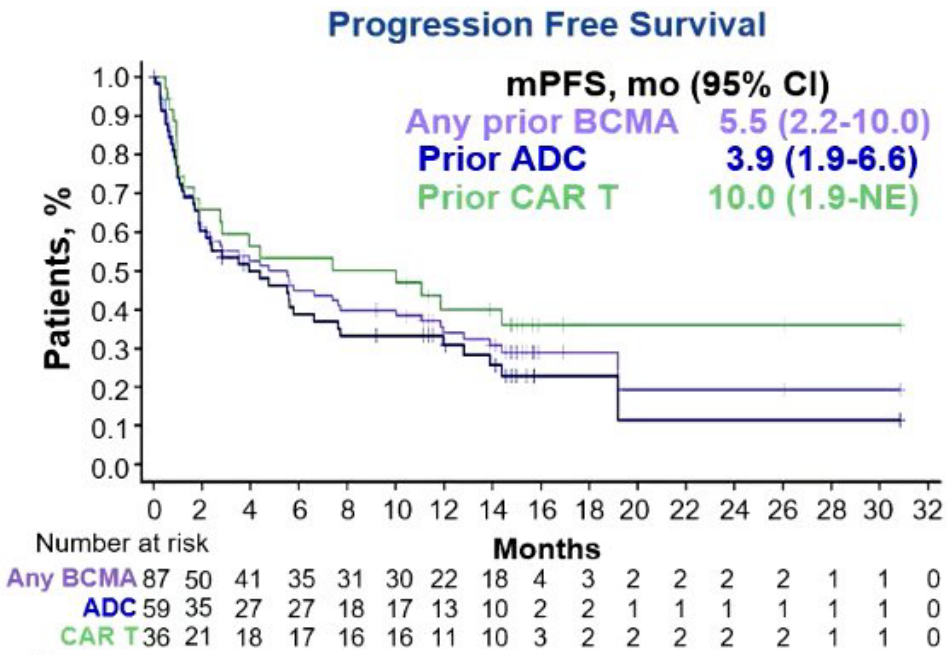


mDOR, mo* (95% CI)

Any prior BCMA
17.1 (9.8–NE)

Prior ADC
13.6 (6.8–NE)

Prior CAR T
NE (9.8–NE)



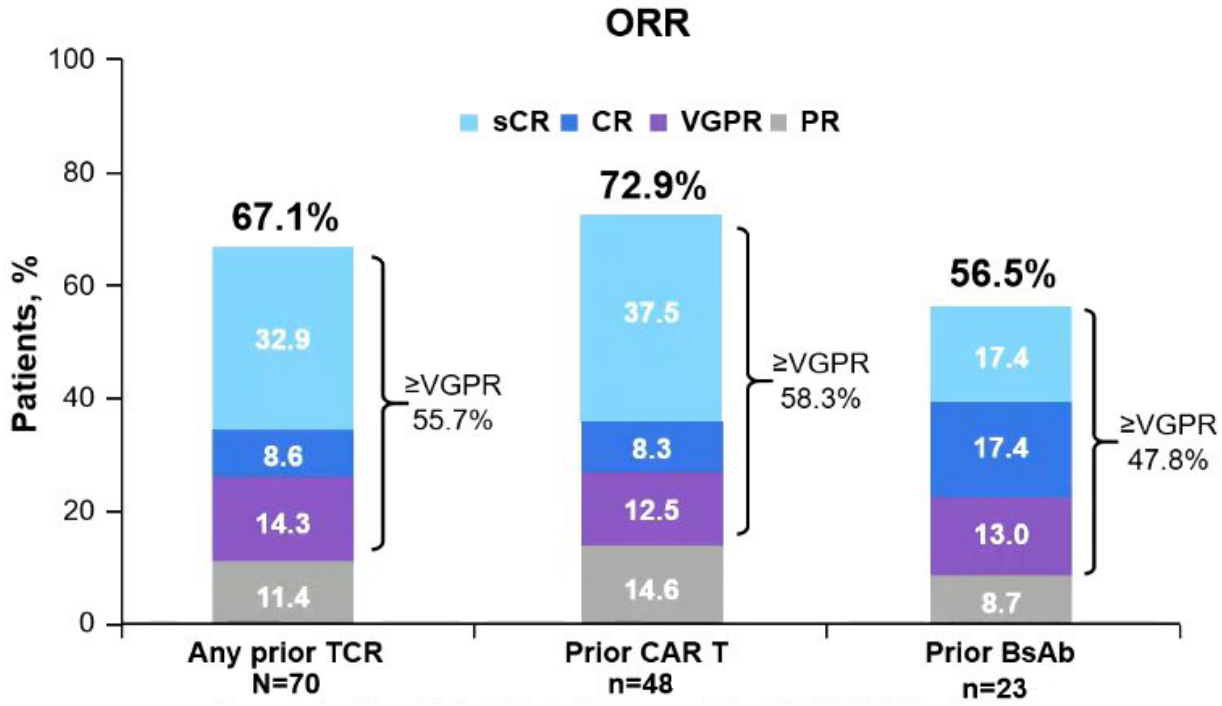
Median follow-up: 11.3 months

Nooka A, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois. Abstract 8008.

Sequencing: Talquetamab following Prior Anti-BCMA Therapy

MonumenTAL-1: RRMM with ≥3 prior LoT including PI, IMiD, anti-CD38 mAb
N=70

BCMA CAR T / BsAb → GPRC5D BsAb



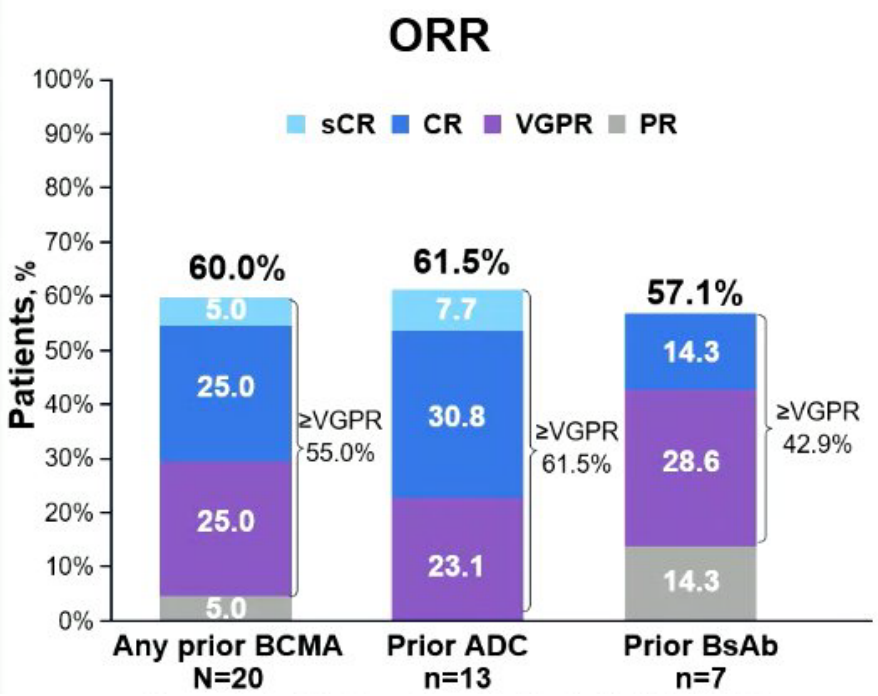
Efficacy Outcomes	Any prior BCMA N=70	Prior CAR T n=48*	Prior BsAb n=23*
Median follow-up, mo	**18.4**	18.4	16.3
12-mo PFS rate, % (95% CI)	**44.1 (32.1–55.4)**	50.0 (34.9–63.4)	30.4 (13.5–49.3)
12-mo DOR rate, % (95% CI)	**55.2 (39.3–68.5)**	54.7 (36.0–70.0)	43.3 (16.3–67.9)

Nooka A, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois. Abstract 8008.
Jakubowiak AJ, et al. Presented at: American Society of Hematology Annual Meeting & Exposition; December 10, 2023; San Diego, California. Abstract P3377. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04634552.

Sequencing: Cilta-Cel following Prior Anti-BCMA Therapy

CARTITUDE-2: Phase 2 study of cilta-cel in RRMM
N=20

BCMA ADC / BsAb → CAR T

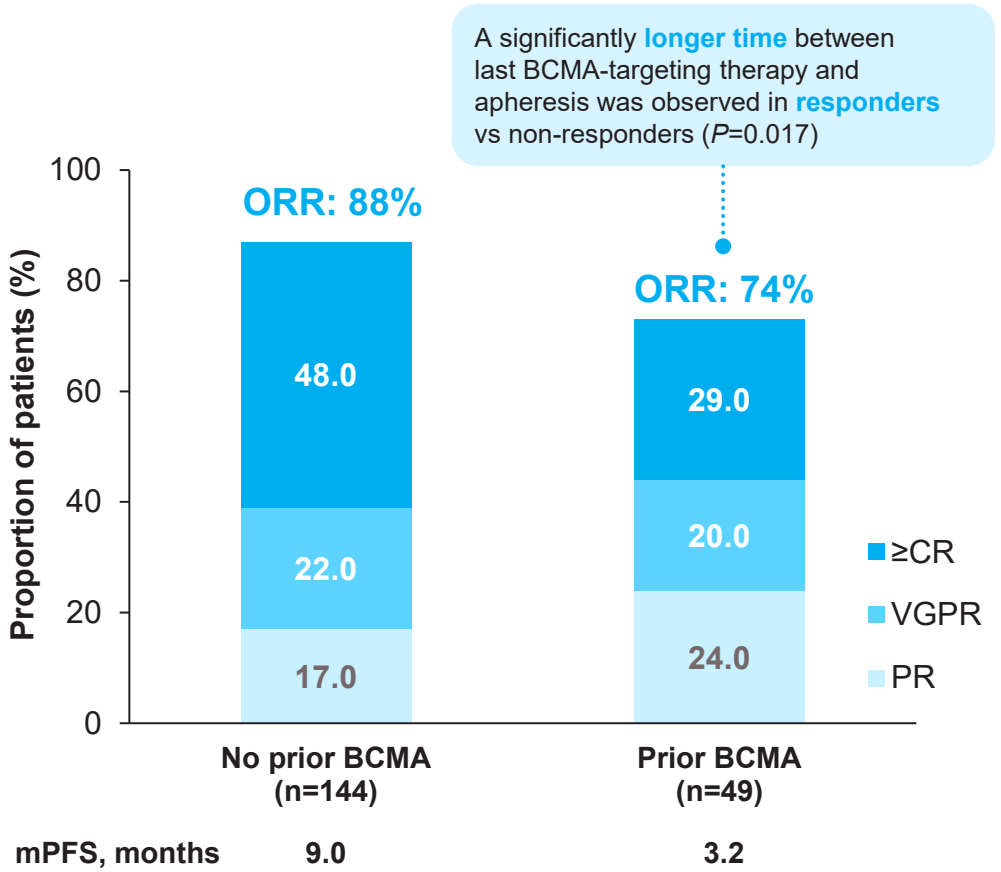


Efficacy outcomes	Any prior BCMA N=20	Prior ADC n=13	Prior BsAb n=7
mDoR, mo (95% CI)	**11.5** (7.9-NE)	11.5 (7.9-NE)	8.2 (4.4-NE)
mTTR (range), mo	**0.95** (0.9-6.0)	0.97 (0.9-5.1)	0.92 (0.9-6.0)
Median time to best response (range), mo	**2.22** (0.9-9.9)	2.58 (0.9-9.9)	1.41 (0.9-7.0)
MRD negativity, %	**70.0** (7/10)	71.4 (5/7)	66.7 (2/3)

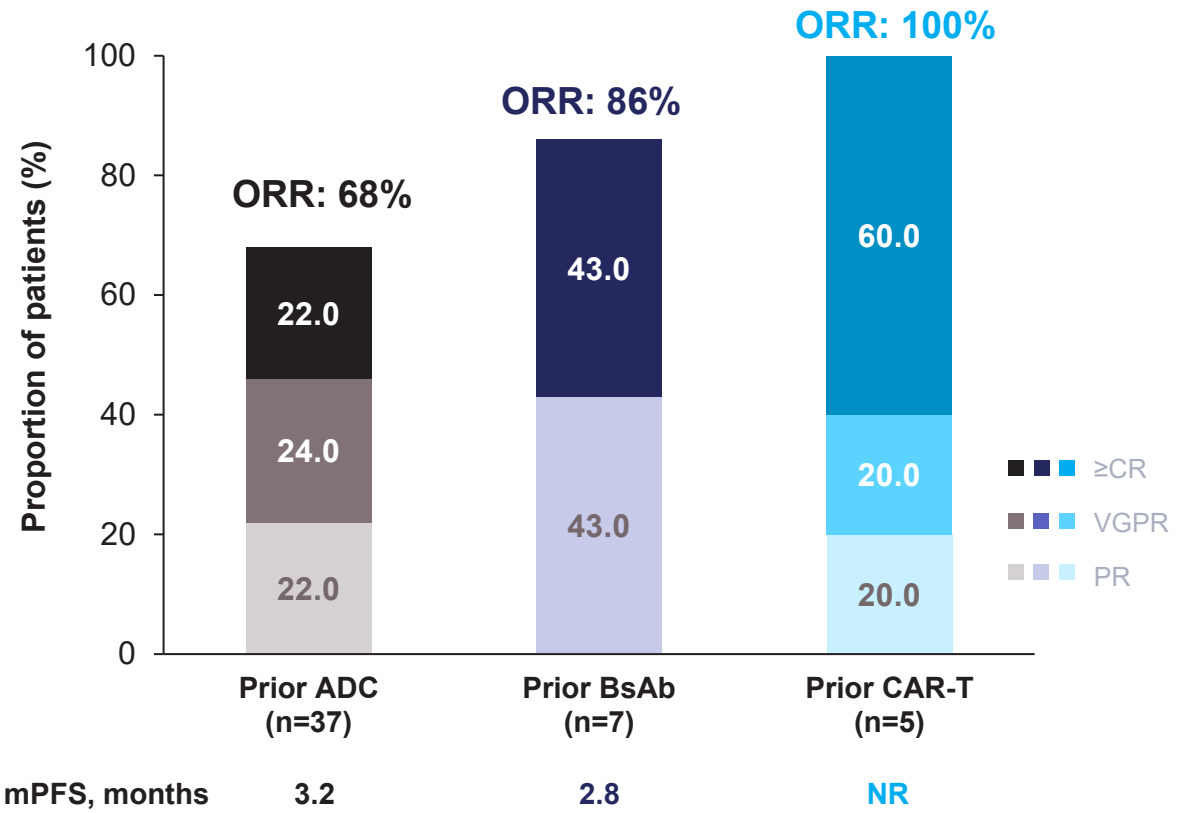
Nooka A, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois. Abstract 8008.
Cohen AD, et al. *Blood*. 2023;141(3):219-230.

Sequencing: Ide-Cel following Prior Anti-BCMA Therapy

RWE: Ide-cel ORR (prior vs no prior anti-BCMA)



RWE: Ide-cel ORR post-anti-BCMA ADC/BsAb/CAR-T

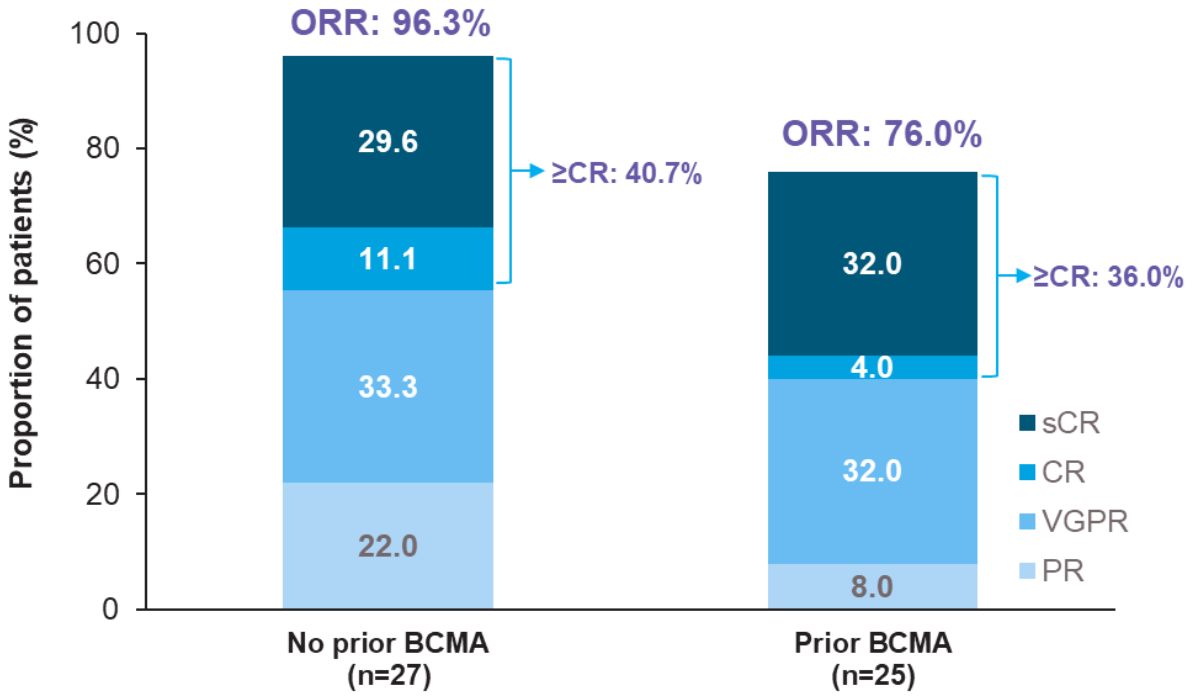


RWE = real-world evidence.

Ferreri CJ, et al. *Blood Cancer J*. 2023;13(1):117.

Non-Anti-BCMA (GPRC5D) CAR T Therapy (BMS-986393) after Various Anti-BCMA Therapies

Phase II study of BMS-986393 after BCMA-targeted therapy



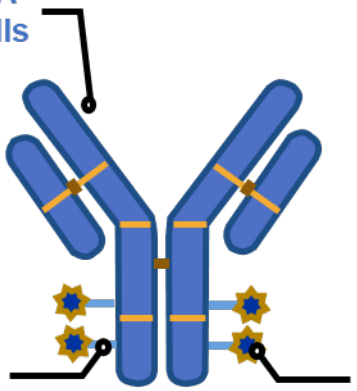
Prior Anti-BCMA Therapy, n (%)	Total (N=25)
CAR-T cell therapy (cilta-cel, ide-cel, orva-cel, ALLO 715, others not specified)	**19 (76.0%)**
Non-CAR-T cell therapy (ADC, BsAb)	**8 (32.0%)**

NIH. Accessed October 28, 2024. https://www.clinicaltrials.gov/study/NCT06297226.

Belantamab Mafodotin MOA

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

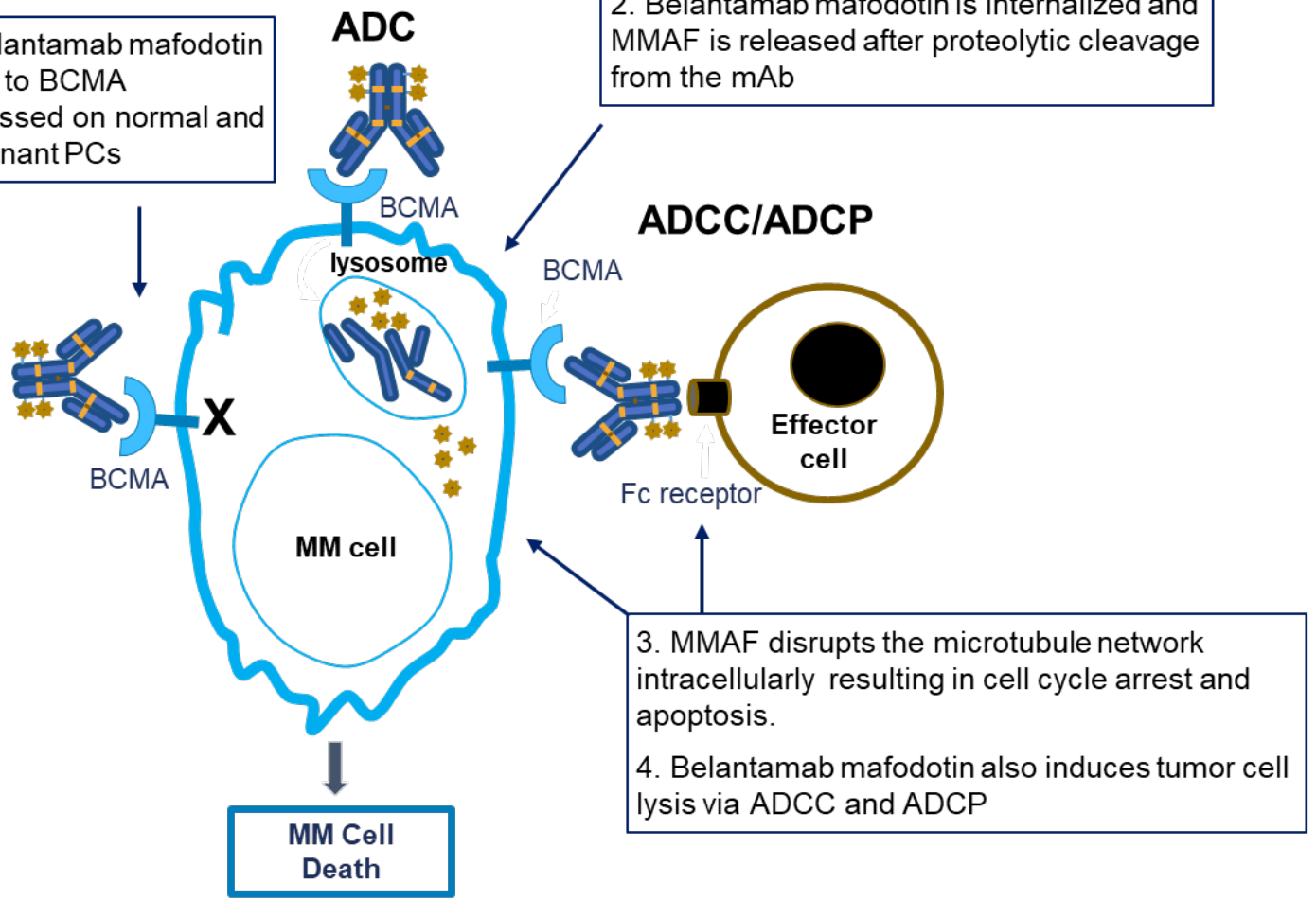
1 Humanized anti-BCMA IgG1 mAb that binds to BCMA-expressing MM cells



Protease-resistant maleimidocaproyl linker that joins MMAF to mAb and releases payload only in target cell

3

2 MMAF: microtubule-disrupting cytotoxic agent that leads to apoptosis of BCMA-expressing MM cells

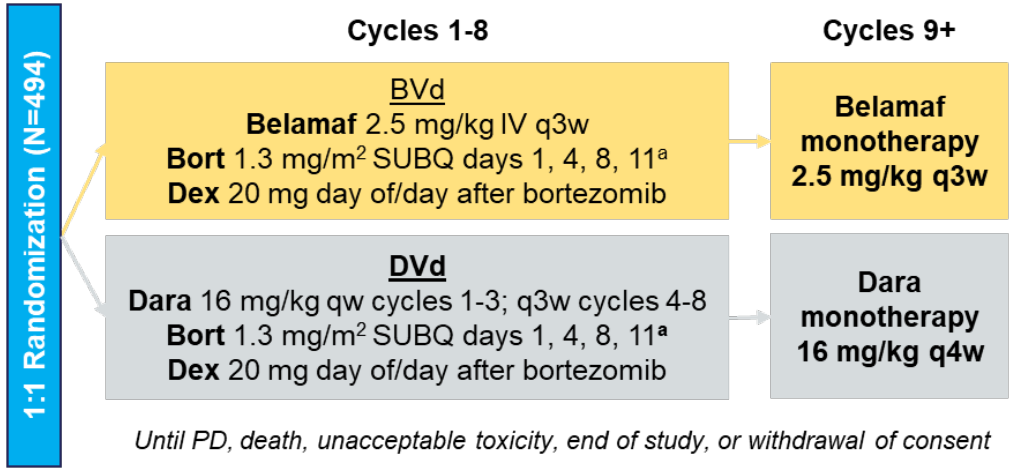


MMAF = monomethylauristatin F; ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; PC = plasma cell.

Tai YT, et al. *Blood*. 2014;123(20):3128-3138. Farooq AV, et al. *Ophthalmol Ther*. 2020;9(4):889-911.

DREAMM-7 Phase 3 Trial of BVd vs DVd in R/R MM: Will Belantamab Mafodotin Be Back?

Key Eligibility Criteria
- RRMM with ≥1 prior LOT; PD during or after most recent therapy
- No prior anti-BCMA
- Not refractory to or intolerant of daratumumab or bortezomib



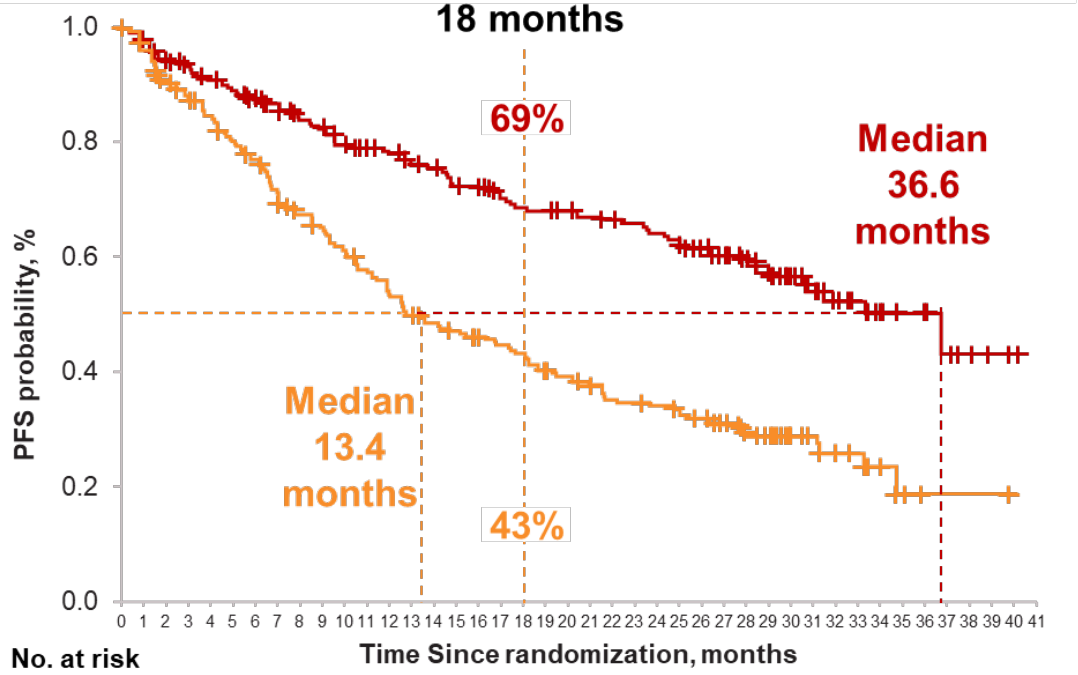
Primary endpoint: PFS (IRC)
Key secondary endpoints: OS, DOR, MRD

Patient Characteristics[b]		BVd (n=243)	DVd (n=251)
Median age (range), years		65.0 (34-86)	64.0 (32-89)
ECOG PS ≤1, n/N (%)		232/242 (96)	235/246 (96)
R-ISS stage I at screening, n (%)		102 (42)	103 (41)
High-risk cytogenetics, n (%)		67 (28)	69 (27)
t(4;14)		41 (61)	42 (61)
t(14;16)		8 (12)	6 (9)
del(17p13)		30 (45)	35 (51)
Prior LOT, n (%)	1	125 (51)	125 (50)
	2 or 3	88 (36)	99 (39)
	≥4	30 (12)	27 (11)
Prior treatment, n (%)	Bortezomib	210 (86)	211 (84)
	Daratumumab	3 (1)	4 (2)
	Lenalidomide	127 (52)	130 (52)
Refractory to Len, n (%)		79 (33)	87 (35)
Refractory (n=79/87) or not (n=164/164) by prior LOT, n (%)[c]	1	22 (28) / 103 (63)	27 (31) / 98 (60)
	2	24 (30) / 30 (18)	21 (24) / 42 (26)
	3+	33 (42) / 31 (19)	39 (45) / 24 (15)

[a]21-day cycles; [b]Subgroup analyses by high- vs standard-risk cytogenetics and Len-refractory vs not Len-refractory are noted by the blue shading; [c]Post hoc analysis.
R-ISS = Revised International Staging System.
Mateos MV, et al. Presented at: American Society of Clinical Oncology Annual Meeting; May 31–June 4, 2024; Chicago, Illinois. Abstracts 7503 and 439572.
Mateos MV, et al. Presented at: Congress of the European Haematology Association; June 13, 2024; Madrid, Spain. Abstract S214. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04246047.

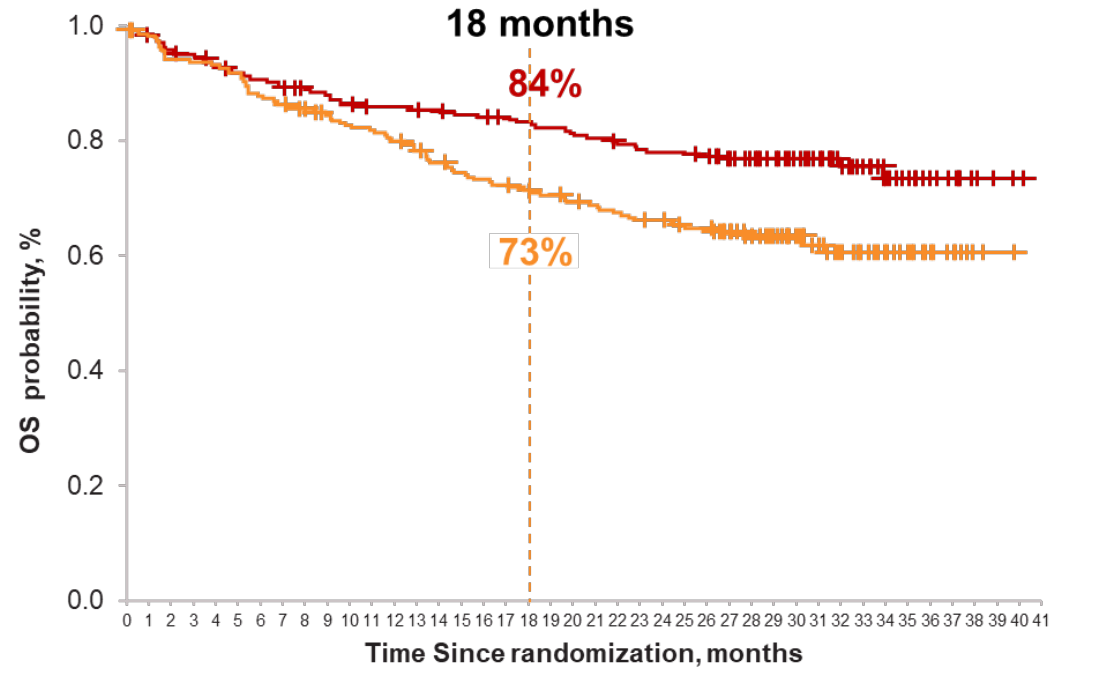
DREAMM-7 PFS and OS in the ITT

PFS



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

OS



OS	BVd (n=243)	DVd (n=251)
Events, n(%)	54 (22)	87 (35)
OS, median (95% CI), mo	NR	NR
HR (95% CI)	0.57 (0.4-0.8)	
P value	.00049	

Reference.

DREAMM-8 Phase 3 Trial of BPd vs PVd in R/R MM: Study Design and Patients

Key Eligibility Criteria
- RRMM with ≥1 prior LOT including Len
- PD during or after most recent therapy
- No prior anti-BCMA, Pom; not refractory/intolerant to Bort

1:1 Randomization (N=302)

BPd (q4w)
Belantamab mafodotin 2.5 mg/kg IV (cycle 1), then 1.9 mg/kg IV (cycle 2+)
Pom 4 mg PO, days 1-21 (28-day cycles)
Dex 40 mg[a], days 1, 8, 15, 22

PVd (q3w)
Bortezomib 1.3 mg/m^2 SUBQ, days 1, 4, 8, 11 cycles 1-8, then days 1, 8 (21-day cycles)
Pom 4 mg PO, days 1-14 (21-day cycles)
Dex 20 mg[a], on the day of and day after Bort

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

Primary endpoint: PFS (IRC per IMWG)
Key secondary endpoints: OS, MRD negativity, DOR

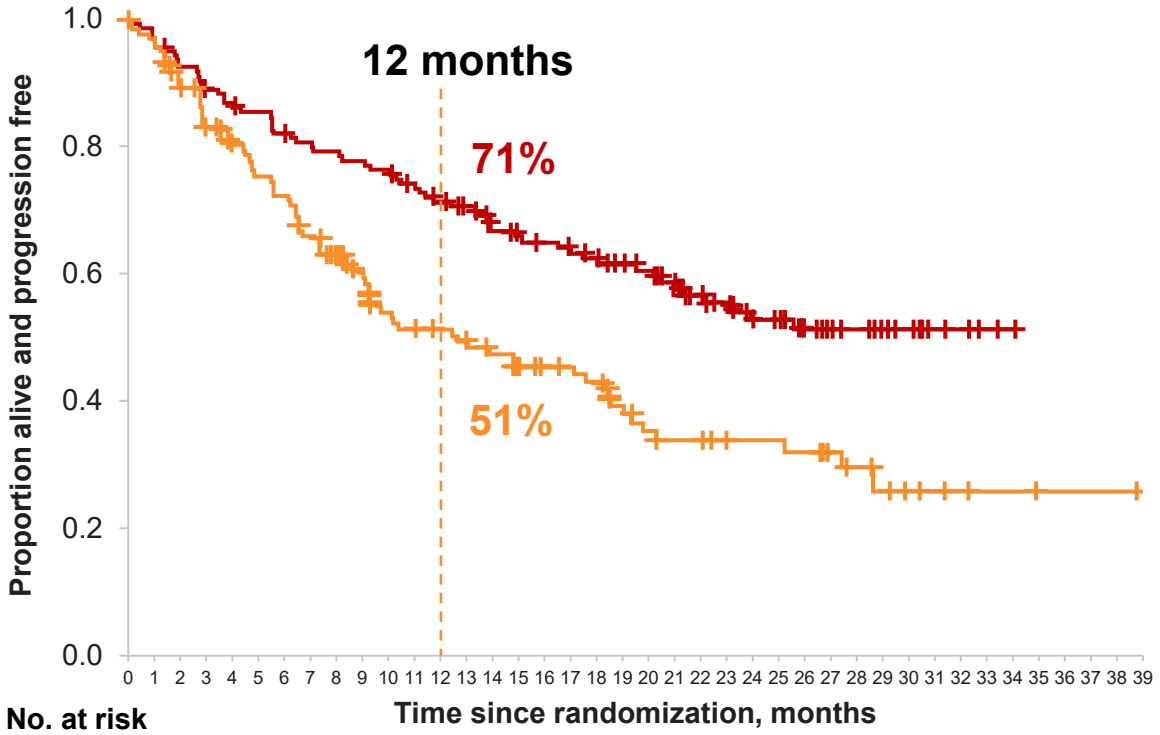
Patient Characteristics		BPd (n=155)	PVd (n=147)
Median age (range), years		67 (40-82)	68 (34-86)
Age ≥75 years, n (%)		19 (12)	35 (24)
ECOG PS ≤1, n (%)		146 (97)	140 (97)
ISS stage I at screening, n (%)		93 (60)	85 (58)
Extramedullary disease, n (%)		20 (13)	11 (7)
High-risk cytogenetics,[b] n (%)		52 (34)	47 (32)
Relapse >12 months after 1L initiation, n (%)		133 (86)	127 (86)
Prior LOT, n (%)	1	82 (53)	77 (52)
	2 or 3	54 (35)	48 (33)
	≥4	19 (12)	22 (15)
Prior ASCT, n (%)		99 (64)	82 (56)
Bortezomib, n (%)	Exposed	134 (86)	130 (88)
	Refractory	16 (10)	8 (5)
Lenalidomide, n (%)	Exposed	155 (100)	147 (100)
	Refractory	125 (81)	111 (76)
Anti-CD38 mAb, n (%)	Exposed	38 (25)	42 (29)
	Refractory	35 (23)	36 (24)

[a]Patients aged >75 years, with comorbidities, or intolerant to 40 mg in arm A or 20 mg in arm B could have dose level reduced to half per INV discretion; [b]High-risk cytogenetics defined as the presence of ≥1 of: t(4;14), t(14,16), or del(17p13).
ASCT = autologous stem cell transplantation; INV = investigator.
Trudel S, et al. Presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2024; Chicago, Illinois. Abstract LBA105. Dimopoulos M, et al. Presented at: European Haematology Association Congress; June 13, 2024; Madrid, Spain. Abstract LB3440. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04484623.

DREAMM-8 Efficacy

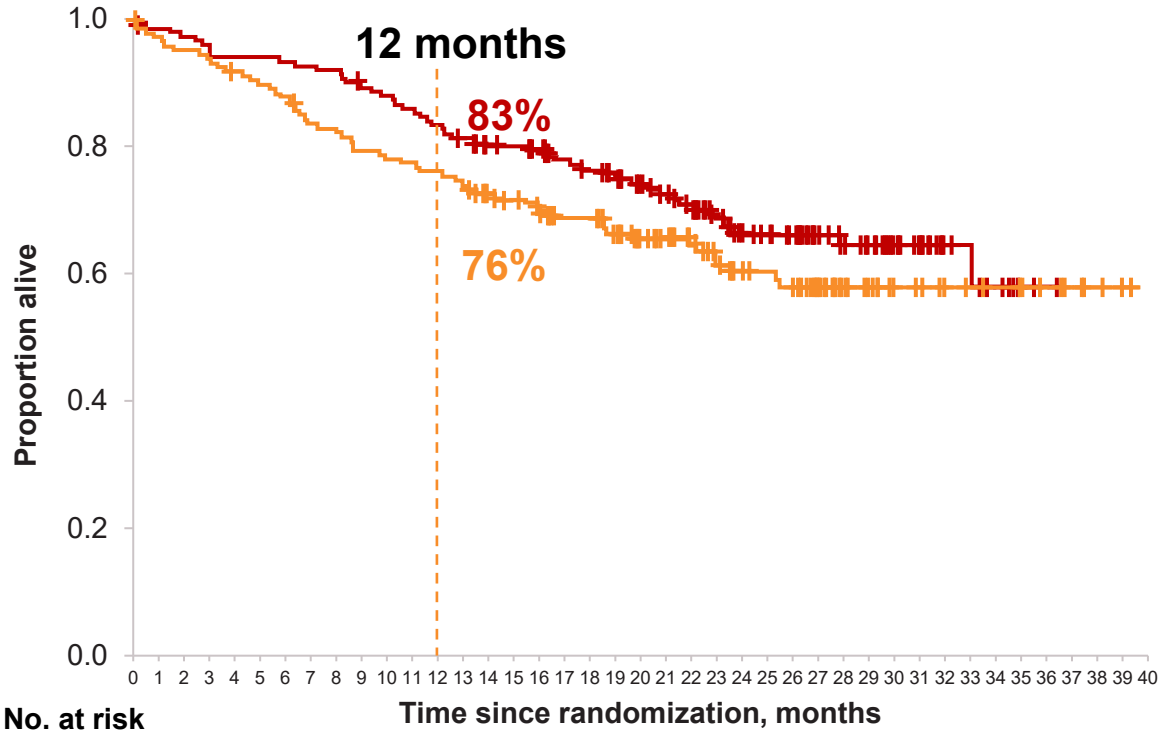
BPd PVd

PFS



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**	

Positive OS Trend Favoring BPd vs PVd



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

Trudel S, et al. Presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2024; Chicago, Illinois. Abstract LBA105. NIH. Accessed October 25, 2024. https://www.clinicaltrials.gov/study/NCT04484623.

Ocular Issues with Q 8-Week Dosing

	Cohort 1 2.5 mg/kg q8w N=216	Cohort 2 1.9 mg/kg q8w N=244	Cohort 3 1.4 mg/kg q8w N=207
Total N of OAE[a] /Total N of ocular assessments (%) Grade 0-1 Grade 2 Grade 3-4	 86 (39.3) 91 (43.9) 39 (18.1)	 130 (55.7) 81 (31.1) 33 (13.5)	 115 (56.5) 66 (31.4) 26 (12.6)
Total N of BCVA decline assessments/Total N of ocular assessments (%) Grade 0-1 Grade 2 Grade 3-4[b]	 90 (41.7) 93 (43) 33 (15.3)	 139 (57) 73 (30) 32 (13)	 119 (57.5) 63 (30.4) 25 (12.1)
Total N of keratopathy assessments/Total N of ocular assessments (%) Grade 0-1 Grade 2 Grade 3-4	 179 (82.9) 28 (13.0) 9 (4.2)	 214 (87.3) 30 (12.2) 1 (0.4)	 185 (89.4) 21 (10.1) 1 (0.5)
N of assessments with meaningful BCVA decline[c] with at least 3 lines drop in the better seeing eye/Total N of ocular assessments (%)	21/216 (9.7)	24/244 (9.8)	17/201 (8.5)
Time to resolution of BCVA decline in months, median (range)	2.1 (0.3-6.3)	1.9 (0.9-6.2)	1.9 (0.9-8.6)
Time to resolution[d] of meaningful BCVA decline with at least 3 lines drop in better seeing eye in months, median (range)	1.2 (1.0-4.5)	1.4 (0.8-2.0)	1.55 (0.9-5.5)
Time to resolution[d] of OAE in months, median (range)	2.1 (0.3-6.3)	1.9 (0.9-6.2)	1.9 (0.9-8.6)
Time to resolution[d] of BCVA decline in months, median (range)	2.1 (0.3-6.3)	1.9 (0.9-6.2)	1.9 (0.9-8.6)
Time to resolutiond of keratopathy in months, median (range)	1.0 (0.5-7.4)	1.4 (0.9-2.8)	1.0 (0.9-3.7)

Bortezomib is associated with a high risk of grade 3 or higher infections.

OAE = ocular adverse evento; BCVA = best-corrected visual acuity.

Terpos E, et al. *Haematologica*. 2024;109(8):2594-2605.

Real-World Considerations Are Vital in Selecting Treatment

	CAR-T cell therapies (autologous)	Bispecific antibodies	Small molecules	ADC-based
Treatment availability	Cell manufacturing takes **~4 weeks**	**Little to no wait** time is required prior to administration; limited **resourceutilization**	**Little to no wait** time is required prior to administration	**Little to no wait** time is required prior to administration
Administration setting	Usually administered in **specialized medical center** and/or **hospitals**	Usually administered in **specialized medical centers** and/or **hospitals**; outpatient administration approaches are being explored	**Outpatient** (no hospitalization required)	**Outpatient** (no hospitalization required)
Post-administration monitoring	Post treatment monitoring for CRS/neurotoxicity requires patients to remain **within proximity to an administration center for ≥4 weeks** following administration	Must remain **within proximity to a healthcare facility for 48 hours** after step-up dosing	--*	Regular visits with an **ophthalmologist(Q3W)** ***Or less frequently with new approaches***

***Specific monitoring requirements are currently unknown.**
CELMoD = cereblon E3 ligase modulator; CRS = cytokine release syndrome.
Herrera AF, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(7):452-468.e4. Morè S, et al. *Cancers (Basel).* 2023;15(11):2948. Barilà G, et al. *Pharmaceuticals (Basel).* 2021;14(1):40. Varshavsky-Yanovsky AN, et al. *Hemasphere*. 2023;7(Suppl):e605007f. Hartley-Brown MA, et al. *Cancers (Basel).* 2024;16(6):1166. FDA. Accessed October 25, 2024. https://www.fda.gov/media/147055/download?attachment; https://www.fda.gov/media/156560/download?attachment; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761291s000lbl.pdf.

Questions?

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Novel and Emerging Therapies and Overcoming Challenges in R/R MM Management

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Idecabtagene Vicleucel—Grade III/IV Toxicity

Event	Idecabtagene Vicleucel (n=128)
Neutropenia	89%
Anemia	60%
Thrombocytopenia	52%
Leukopenia	39%
Lymphopenia	27%
Febrile neutropenia	16%
Cytokine release syndrome	5% (84% all grades)
Neurotoxicity	3% (18% all grades)
Hypophosphatemia	16%
Hypocalcemia	8%
Hyponatremia	5%
Hypoalbuminemia	3%

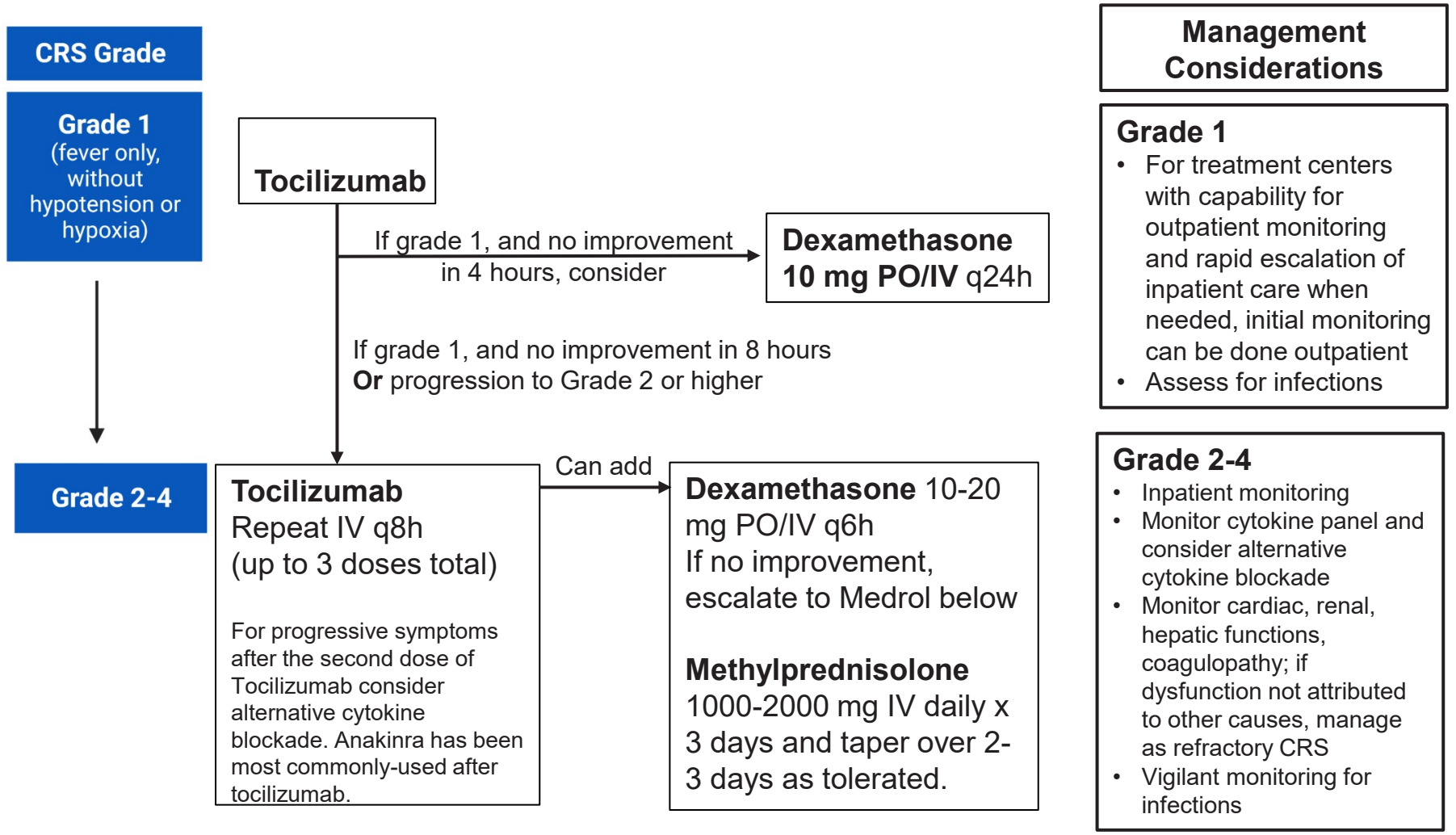
Munshi NC, et al. *N Engl J Med*. 2021;384:705-716.

Ciltacabtagene Autoleucel—Grade III/IV Toxicity

Treatment-Emergent Adverse Event	Grade III/IV Toxicity (n=97)	Grade V Toxicity (n=97)
Fatigue	95%	
Anemia	68%	
Thrombocytopenia	60%	
Leukopenia	61%	
Lymphopenia	51%	
Cytokine release syndrome	4% (95% all grades)	1%
Neurotoxicity	11% (22% all grades)	1%
Neutropenia	5%	
AST increased	5%	
ALT increased	3%	
Hypocalcemia	3%	
Hypophosphatemia	7%	
Hyponatremia	4%	
Hypokalemia	2%	

AST = aspartate transaminase; ALT = alanine transaminase.
Martin T, et al. *J Clin Oncol.* 2023;41(6):1265-1274.

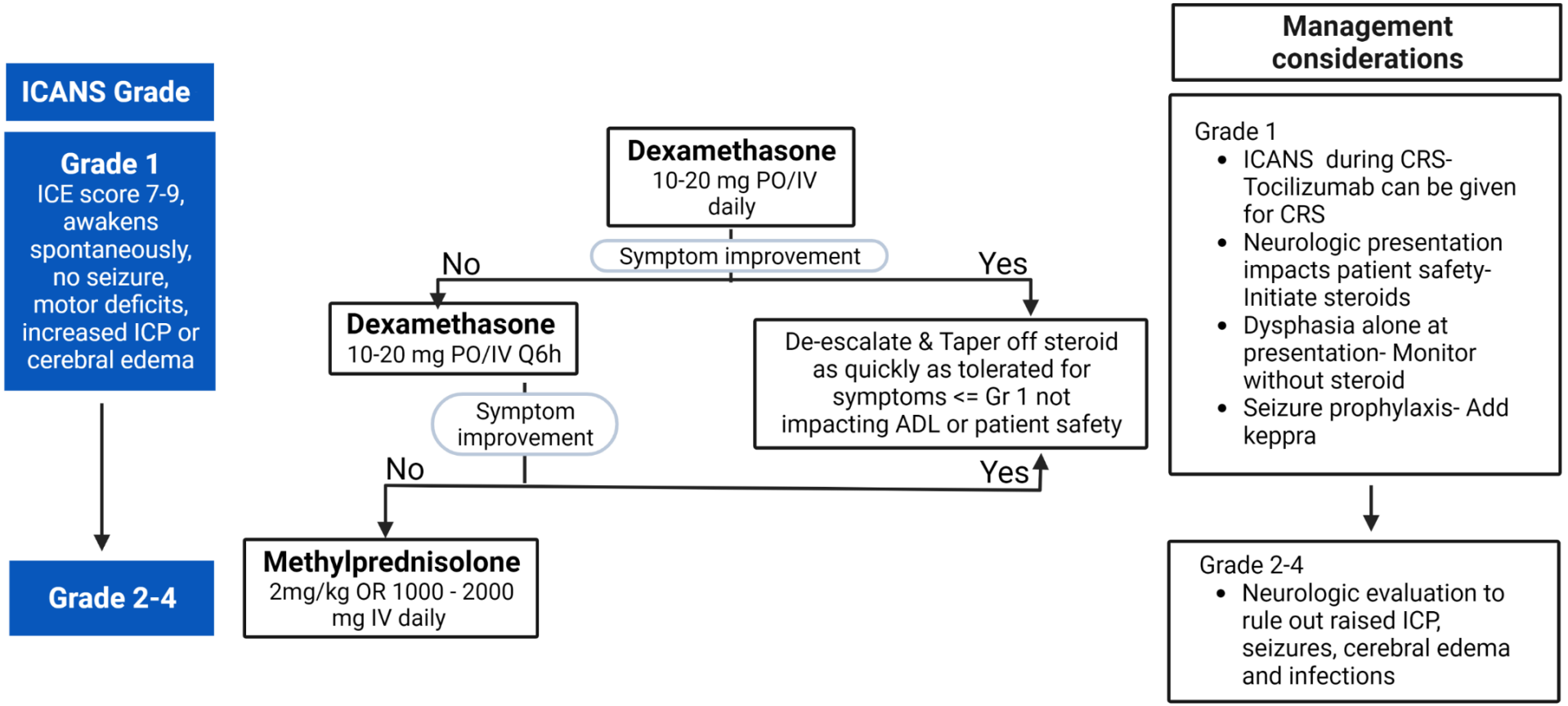
Management of CAR T-Associated CRS



- Consider disease debulking during CAR-T manufacturing whenever possible to reduce CRS risk
- Proactive intervention should be given early in the onset of CRS to reduce the likelihood of progression to higher grade
- Prophylactic cytokine blockade is being studied and not standard of care at this time

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Management of ICANS Associated with CAR T



Cerebral edema should be co-managed with neurology ICU specialists.
Consider adding mannitol and lymphotoxic agents.

ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell encephalopathy; ICP = intracranial pressure; ADL = activity of daily living; ICU = intensive care unit.

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

Management of Post-CAR T Cytopenia

	Evaluations	Management
Month 1 Grade 3 or higher cytopenia can be common depending on cytopenia prior to CAR-T and CRS severity	Rule out persistent or recurrent inflammation • CRP, ferritin, bone marrow biopsy Rule out nutritional deficiencies • Iron studies, pernicious anemia eval, copper, zinc Rule out infection • PCR for CMV, EBV, parvovirus B19, HHV6	• If IEC-HS identified, consider anakinra, add steroid if refractory. Escalate immunosuppressive agents if refractory. • If nutritional deficiencies or infections identified, treat as appropriate • Continue blood count monitoring and transfusion support • Variable success with growth factor and thrombopoietin mimetics
Month 3 Anticipate cytopenia improvement to grade 2 or less	Rule out nutritional deficiencies and infections as above if not tested earlier Rule out persistent or recurrent inflammation • CRP, ferritin Rule out MDS, T-MN • Bone marrow biopsy with cytogenetic testing	• If MDS and T-MN is ruled out, consider stem cell boost in patients with grade 3 or higher cytopenia and who have stem cells available

- Antibacterial prophylaxis should be given during prolonged neutropenia
- Antifungal prophylaxis should be given in month 1 post-CAR T and continued if patient is receiving chronic immunosuppressive medications
- Antiviral prophylaxis and PJP prophylaxis should be continued until CD4 T cells count is persistent >200 (this can take 1 year or longer)
- Prophylactic IVIG, 400 mg/kg IV, should be given monthly for IgG<400 mg/dL, or for patients with IgG<600 mg/dL who have frequent infections

CRP = C-reactive protein; PCR = polymerase chain reaction; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HHV6 = human herpesvirus 6; MDS = myelodysplastic syndromes; T-MN = therapy-related myeloid neoplasms; IEC-HS = immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; PJP = pneumocystis jirovecii pneumonia; IVIG = intravenous immunoglobulin.

Teclistamab—Grade III/IV Toxicity

Event	Teclistamab (n=156)
Neutropenia	64%
Anemia	37%
Thrombocytopenia	21%
Lymphopenia	33%
Leukopenia	7%
Diarrhea	4%
Fatigue	2%
Nausea	1%
Pyrexia	1%
Headache	1%
Arthralgia	1%
Pneumonia	13%
COVID-19	12%
Bone pain	4%
Back pain	2%
Cytokine release syndrome	1%
Neurotoxic event	1%

Moreau P, et al. *New Engl J Med.* 2022;387(6):495-505.

Talquetamab—Grade III/IV Toxicity

Adverse Event	Talquetamab Sub-Q 405 mcg/week (n=30)	Talquetamab Sub-Q 800 mcg/week (n=44)
Anemia	30%	23%
Neutropenia	60%	32%
Lymphopenia	40%	39%
Thrombocytopenia	23%	11%
Leukopenia	30%	14%
Cytokine release syndrome	3% (77% all grades)	0% (80% all grades)
Skin-related event	0%	2%
Rash-related event	0%	16%
Fatigue	3%	0%
Increased alanine aminotransferase	3%	7%
Increased aspartate aminotransferase	0%	7%
Hypophosphatemia	17%	7%
Decreased appetite	3%	0%
Increased glutamyltransferase	3%	7%

Chari A, et al. *New Engl J Med*. 2022;387:2232-2244.

Elranatamab—Grade III/IV Toxicity

Treatment-Emergent Adverse Event	Elranatamab (n=123)
Anemia	37%
Neutropenia	49%
Thrombocytopenia	24%
Lymphopenia	25%
Cytokine release syndrome	0 (58% all grades)
Diarrhea	2%
Fatigue	3%
Decreased appetite	1%
Pyrexia	4%
COVID-19 related	15%
Hypokalemia	11%

Lesokhin A, et al. *Nat Med*. 2023;29(9):2259-2267.

Options for Management of Severe CRS and IEC-HS

Additional medications have been used to manage CAR T-associated severe CRS, IEC-HS.
Use may be off-label usage and not covered by insurance.

Medication	Starting Dose	Comment(s)
Anakinra	100 mg subQ BID	• IV doses can be given if concerns for subQ absorption • Doses up to 48 mg/kg/day and 3500 mg/day IV for 3 days have been tolerated in infection and COVID-19 • Max dose: 100 mg bolus, 2 mg/kg/hr IV
Siltuximab	11 mg/kg IV over 1-hour x 1	• If cytokine blockade in IL-6 strongly consider
Basiliximab	20 mg IV x1	• If cytokine blockade in IL-2 strongly consider • Assess response after 6 to 8 hours; for robust responses additional doses can be given 4 days after the first
Etoposide	150 mg/m^2 IV twice a week	• Not exceeding a cumulative dose of 2 g
Ruxolitinib	5 mg po BID with a max of 20 mg po BID	
Etanercept	25 mg subQ 2 times a week	
Cyclosporine	Trough of 200 to 250	
Emapalumab	1 mg/kg IV 2 times a week	• Non-formulary treatment and may increase administration time • If cytokine blockade in IFN-γ strongly consider • Max dose: 10 mg/kg IV 2 times a week
Cyclophosphamide**	1000 mg/m^2 IV	
ATG (rabbit)**	2 mg/kg/day IV	

****For refractory, potentially fatal severe CRS or IEC-HS where high expansion of CAR T is detected, lymphotoxic agents such as high-dose cyclophosphamide or anti-thymocyte globulin (ATG) may be considered.**

Hines MR, et al. *Transplant Cell Ther*. 2023;29(7):438.e1-438.e16.

Venetoclax—Grade III/IV Toxicity

Event	Venetoclax (n=66)
Neutropenia	21%
Anemia	14%
Thrombocytopenia	26%
Leukopenia	14%
Lymphopenia	15%
Nausea	3%
Diarrhea	3%
Fatigue	5%
Back pain	8%
Vomiting	3%

The investigators noted “serious adverse events” occurred in <10%, with pneumonia, sepsis, cough, hypotension, pain, and pyrexia.

Kumar S, et al. *Blood*. 2017;130(22):2401-2409.

Selinexor/Dexamethasone—Grade III/IV Toxicity

Event	Selinexor/Dexamethasone (n=123)
Thrombocytopenia	58%
Anemia	44%
Neutropenia	21%
Leukopenia	14%
Lymphopenia	11%
Fatigue	25%
Hyponatremia	22%
Nausea	10%
Pneumonia	9%
Diarrhea	7%
Hypoglycemia	7%
Hypokalemia	7%
Mental status changes	6%
Decreased appetite	5%
Dyspnea	4%
Vomiting	3%

Chari A, et al. *N Engl J Med*. 2019;381(8):727-738.

Key Learning Points

- In R/R MM patients who received a median of four prior lines of therapy in the RedirecTT-1 study, combination talquetamab + teclistamab exhibited a manageable safety profile consistent with each of the monotherapies
- The combination of daratumumab + carfilzomib with dexamethasone is approved for the treatment of adult patients with R/R MM in an effort to overcome drug resistance
- Bortezomib is associated with a high risk of grade 3 or higher infections

Thank you