HOW TO NAVIGATE A PATIENT WITH RELAPSED REFRACTORY MYELOMA

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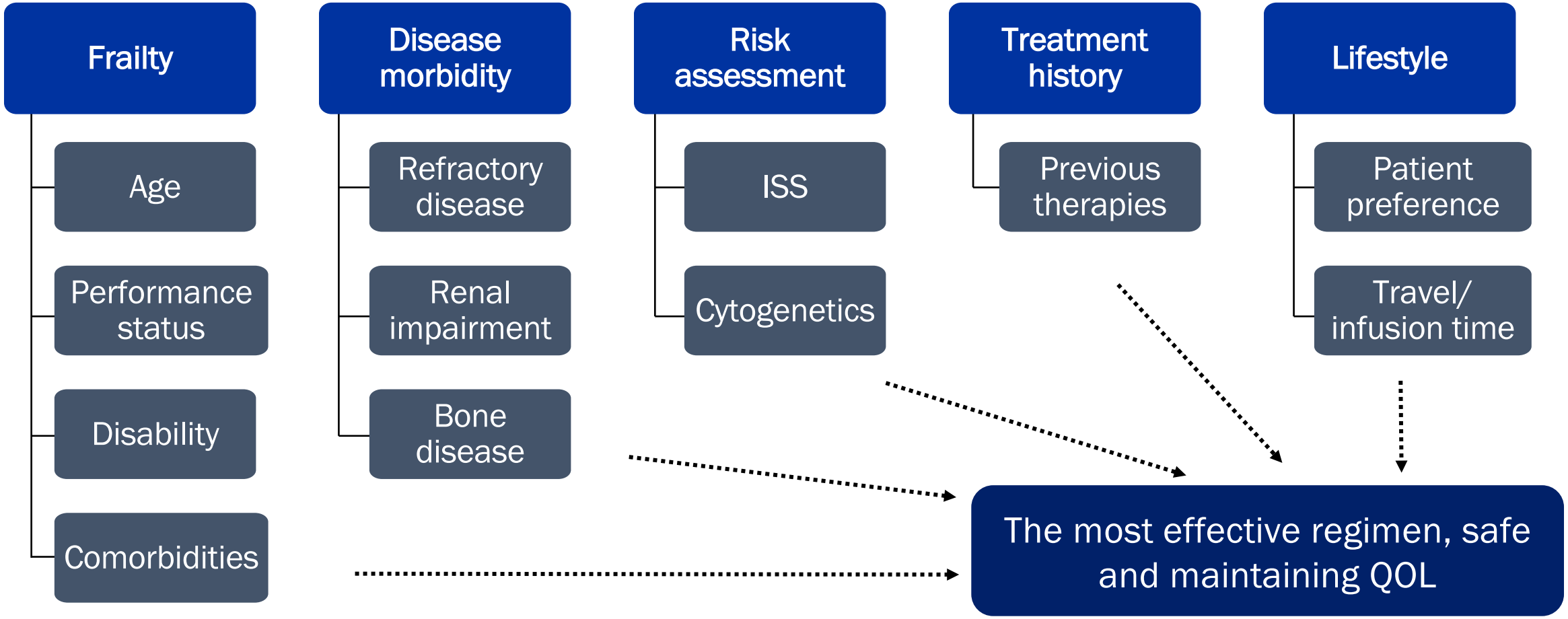
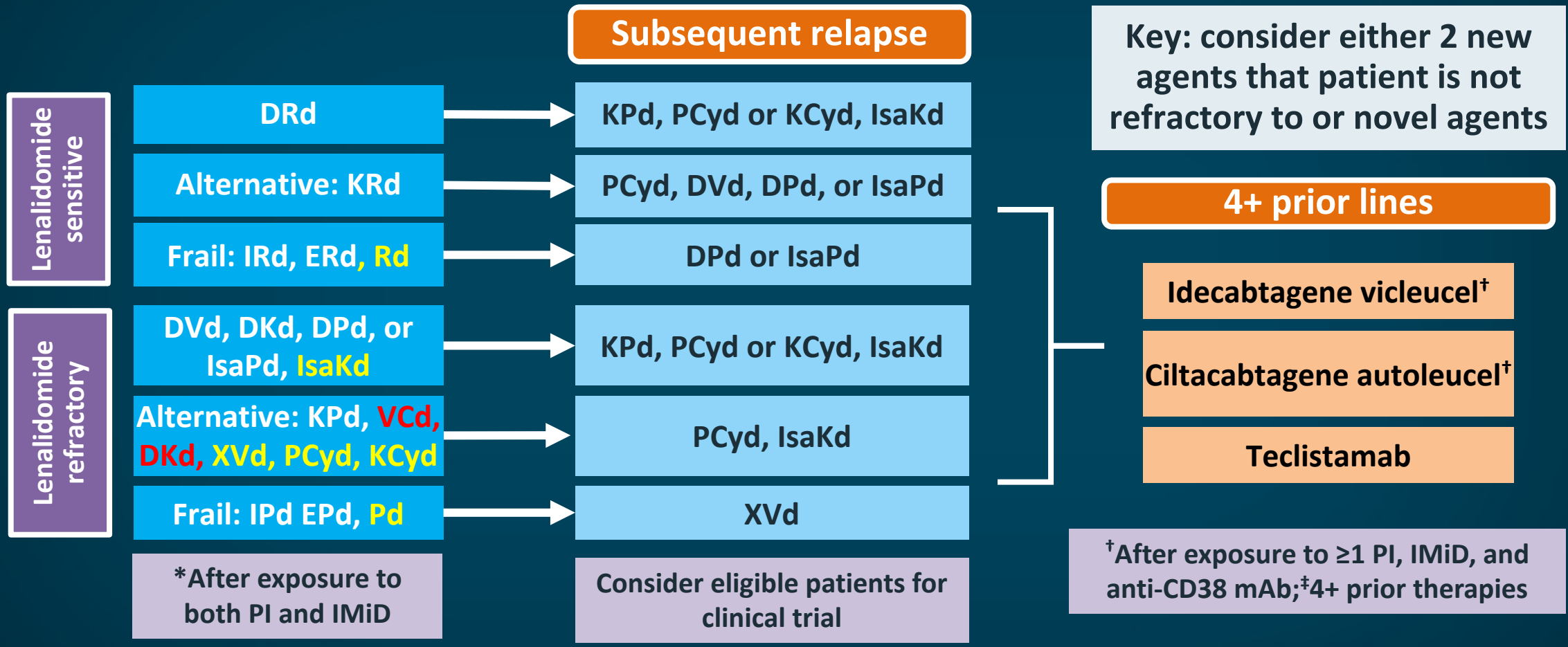
DISEASE AND PATIENT FACTORS INFLUENCE TREATMENT CHOICES IN RELAPSED/REFRACTORY MM



Treatment Algorithms, No One Size Fits All R/R MM
Review and Discussion



Cy = cyclophosphamide; D = daratumumab; d = dexamethasone; E = elotuzumab; I = ixazomib; Isa = isatuximab; K = carfilzomib; P = pomalidomide; R = lenalidomide; V = bortezomib; X = selinexor; PI = proteasome inhibitor; IMiD = immunomodulatory drug; CD = cluster of differentiation; mAb = monoclonal antibody.

Modified from Rajkumar SV, Kumar S. *Blood Cancer J*. 2020;10:94.

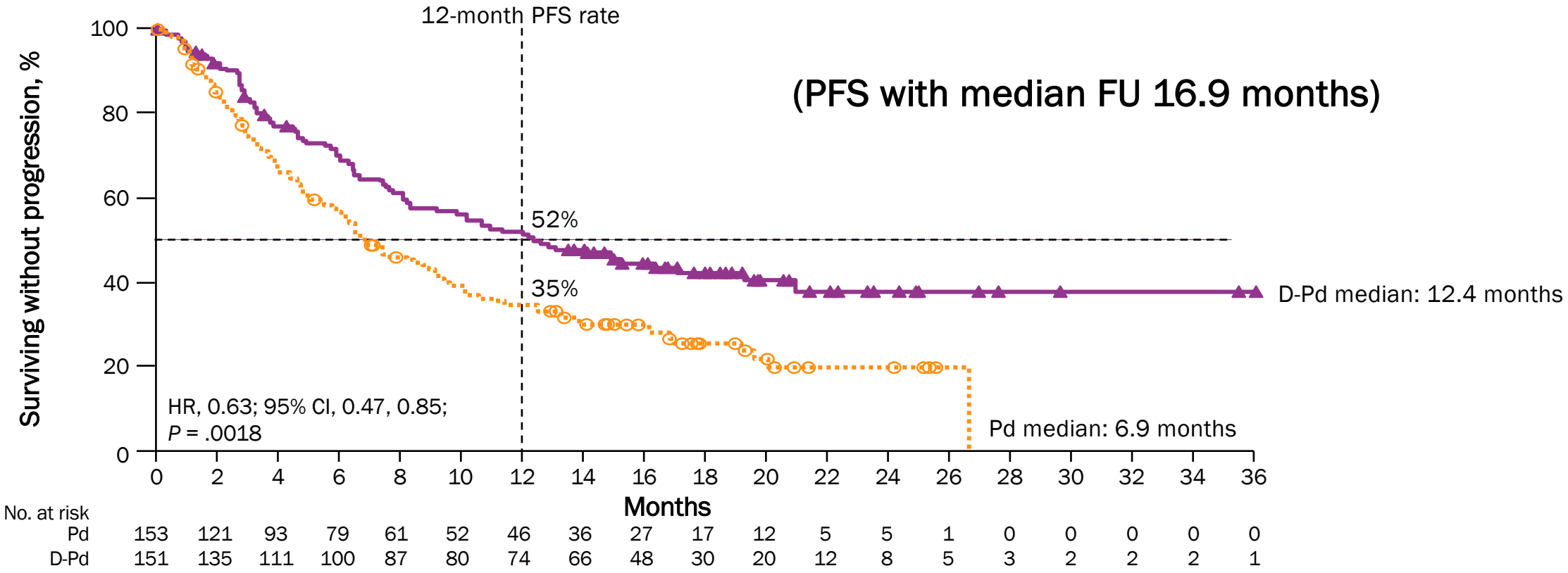
Result	dara/len/dex[1] vs len/dex	dara/car/dex[2] vs car/dex	dara/pom/dex[3] vs pom/dex
Prior line of therapy median in months	1 (1-11, range) 1 (1-8, range)	2 (1-2, IQR) 2 (1-2, IQR)	2 (2-3, IQR; 1-5 range) 2 (2-3, IQR; 1-5 range)
First relapse (%)	52.1 51.6	46 45	11 12
Len non refractory (%)	100 100	68 64	21 20
PFS (median in months)	44.5 (HR 0.44) 17.5	28.6 (0.59) 15.2	12.4 (HR 0.63) 6.9
PFS, not refractory to len	44.5 (HR 0.44) 17.5	28.6 (HR 0.63) 19.9	NE (HR 0.36) 10.6
PFS, 1st relapse	NR (HR 0.42) 19.6	NE (HR 0.66) 21.3	14.1 (HR 0.70) 12.6
1st relapse len refractory (%)	0 0	6 4	≤ 11 ≤ 12

1. Leukemia. 2020 Jul;34(7):1875-1884. doi: 10.1038/s41375-020-0711-6. Epub 2020 Jan 30.
2. Lancet Oncol. 2021 Dec 3:S1470-2045(21)00579-9. doi: 10.1016/S1470-2045(21)00579-9.
3. Lancet Oncol. 2021 Jun;22(6):801-812. doi: 10.1016/S1470-2045(21)00128-5. PMID: 34087126

Result	dara/len/dex[1] vs len/dex	isa/car/dex[2] vs car/dex	isa/pom/dex[3] vs pom/dex
Prior line of therapy median in months	1 (1-11, range) 1 (1-8, range)	2 (1-2, IQR) 2 (1-3, IQR)	3 (2-4, range) 2 (2-4range)
First relapse (%)	52.1 51.6	44 45	0 0
Len non refractory (%)	100 100	68 66	6 8
PFS (median in months)	44.5 (HR 0.44) 17.5	NE (HR 0.53) 19.15	11.5 (HR 0.60) 6.5
PFS, not refractory to len	44.5 (HR 0.44) 17.5	NC (HR 0.48) NC	1/10* (HR 0.18) 7/13*
PFS, 1st relapse	NR (HR 0.42) 19.6	NC (HR 0.59) NC	N/A N/A
1st relapse len refractory (%)	0 0	NR NR	0 0

1. Leukemia. 2020 Jul;34(7):1875-1884. doi: 10.1038/s41375-020-0711-6.
2. Lancet. 2021 Jun 19;397(10292):2361-2371. doi: 10.1016/S0140-6736(21)00592-4.
3. Lancet. 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5.

APOLLO: Phase III Trial of SC Daratumumab, Pomalidomide, and Dexamethasone (D-Pd) vs Pd in R/R MM



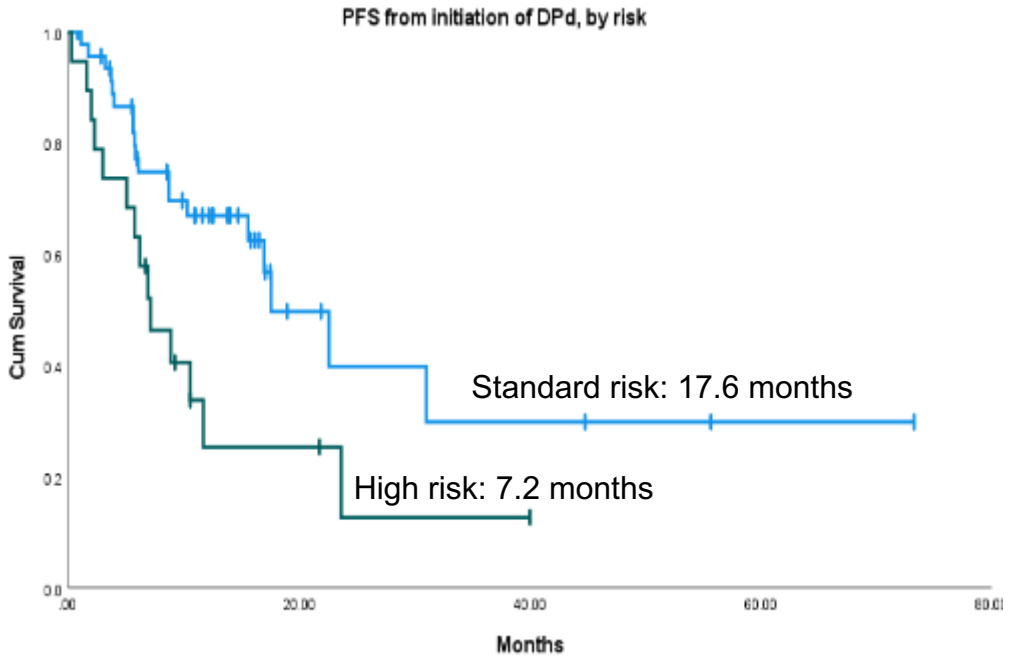
Median PFS among patients refractory to lenalidomide was 9.9 months for D-Pd and 6.5 months for Pd.

Addition of DARA SC to Pd improved PFS; 37% reduction in the risk of progression or death.

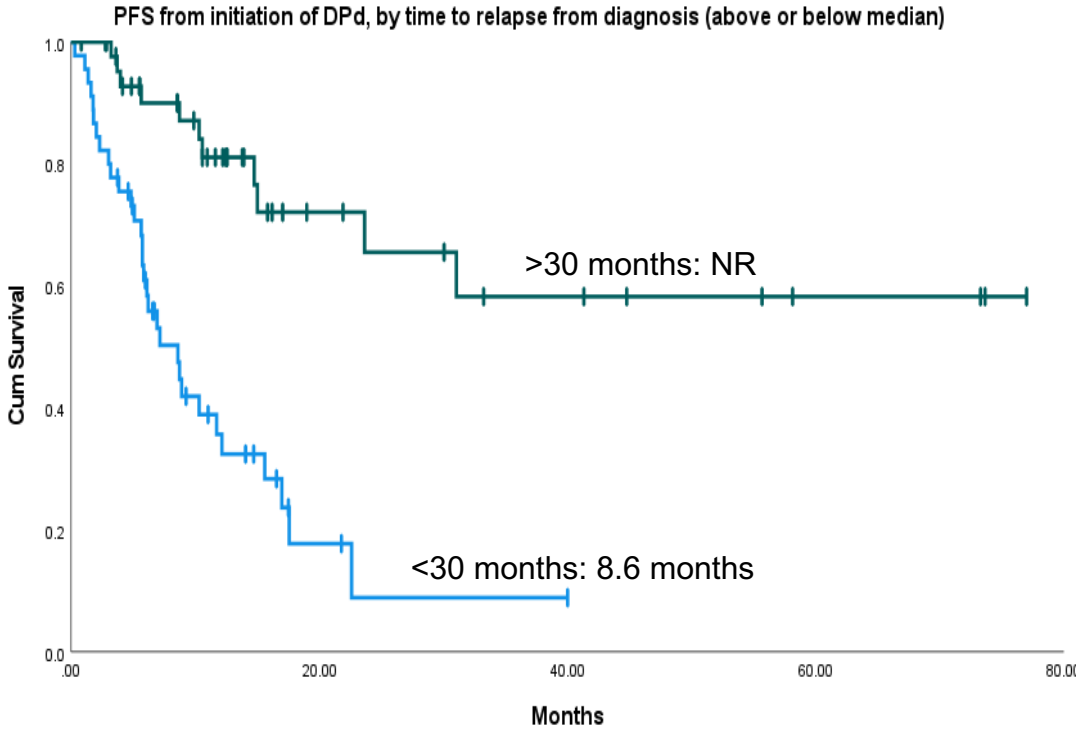
Dimopoulos MA, et al. *Blood.* 2020;136(Suppl 1): abstract 412.

DPD in First Relapse: Emory Experience

Median progression-free survival in standard-risk vs high-risk patients treated with DPD at first relapse



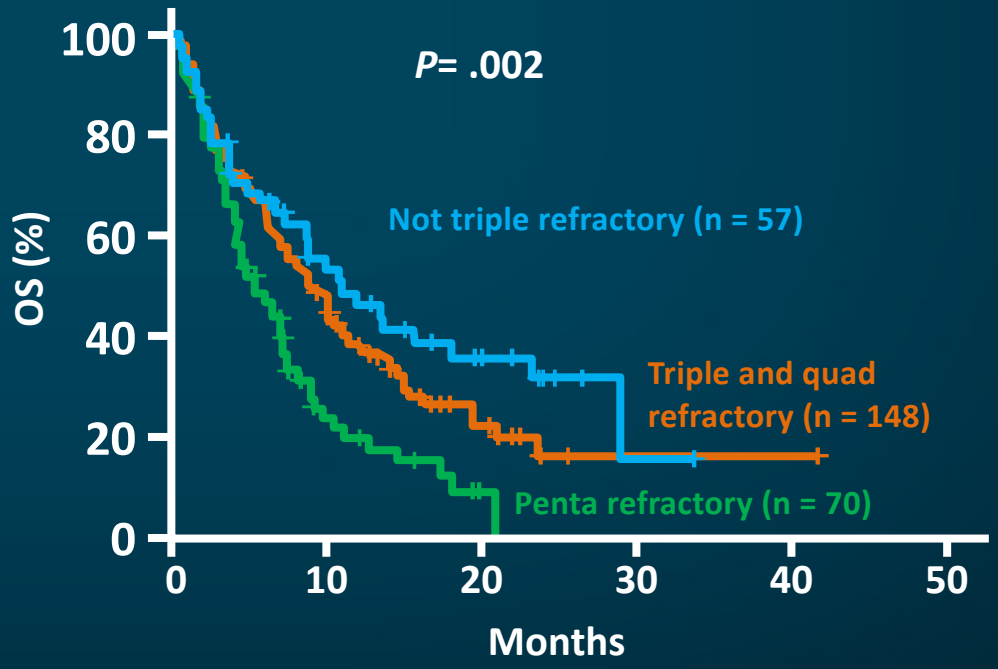
Median progression-free survival by time to first relapse from diagnosis (<30 months vs >30 months)



Patients With R/R MM With Late Relapses (>3 Prior Therapies)

- Fitness and stability of the patient is increasingly important to assess
- Always see if a clinical trial with new drugs or CAR-T is available
- If never transplanted and cells available, strongly consider autologous PBSCT
- Consider other regimens, eg, ide-cel, cilta-cel, bispecific antibody, salvage transplant, and novel agents

Key messages:
Patients with triple-class exposed (TCE) MM have a poor prognosis (median OS = 1–4 months)
New therapies are needed for this population



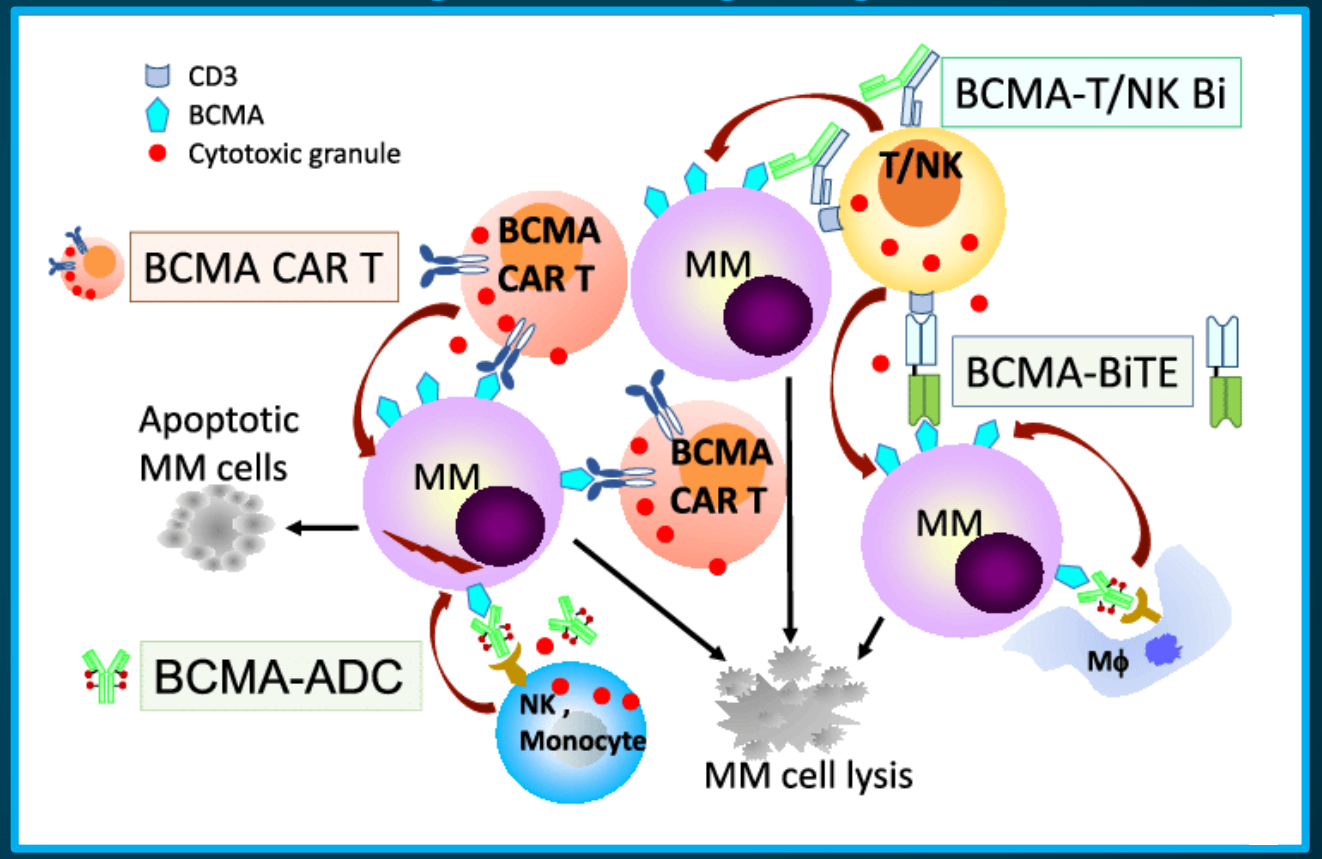
PBSCT = peripheral blood stem cell transplant

Gandhi UH, et al. Leukemia. 2019;33:2266-2275.

BCMA as Therapeutic Target

- BCMA is highly and specifically expressed on plasma blasts and plasma cells
- Anti-BCMA antibodies are detected in patients in remission after donor lymphocyte infusion with graft-vs-tumor response
- BCMA mRNA and protein are more highly expressed on malignant than normal plasma cells

Strategies for Targeting BCMA



BCMA = B cell maturation antigen; mRNA = messenger ribonucleic acid; ADC = antibody drug conjugate; Bi = bispecific full-length immunoglobulin; BiTE = bispecific T-cell engager; NK = natural killer (cell); Mϕ = macrophage.

Cho SF, et al. *Front Immunol.* 2018;9:1821.

BCMA-Targeted Therapies for Multiple Myeloma

Myeloma cell

BCMA

Antibody-drug conjugates

Belantamab mafodotin (discontinued)
MEDI2228
CC-99712

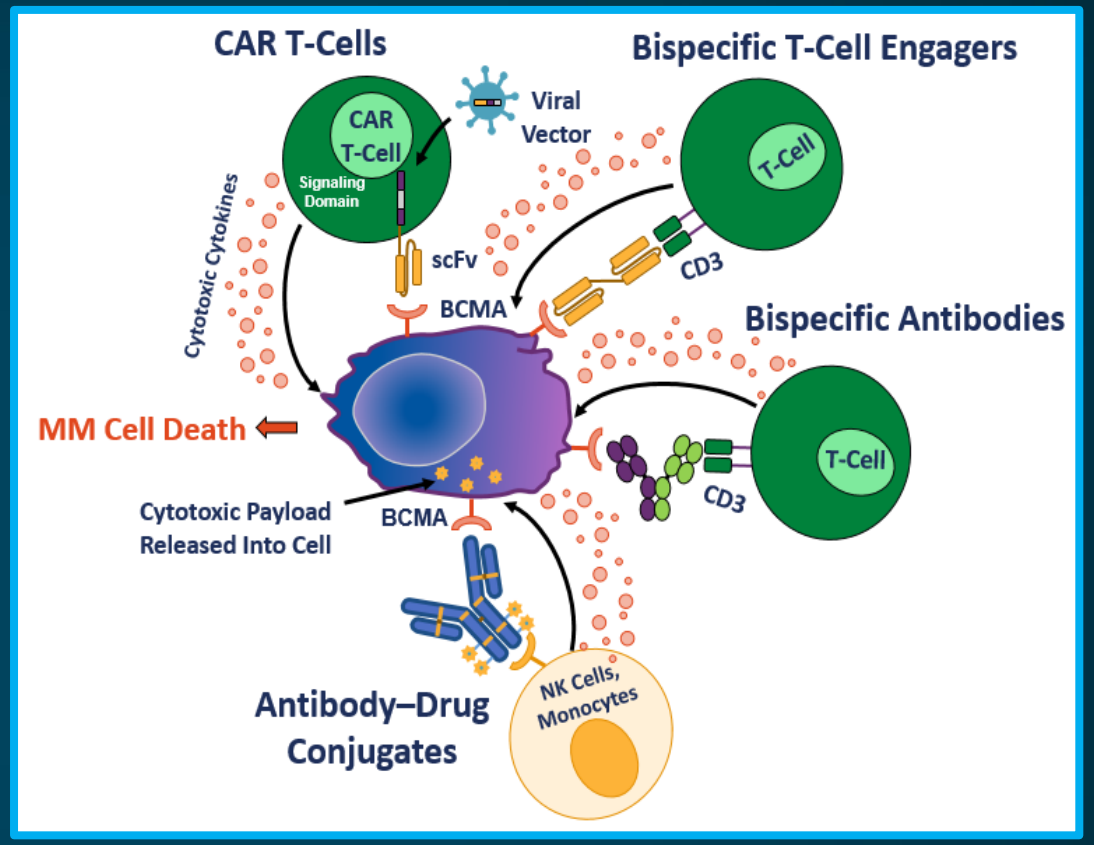
Bispecific antibodies/BiTEs

Teclistamab*
Linvoseltamab
Alnuctamab (cc-93269)
Elranatamab
TNB-383B
RO7297089
Pavurutamab (discontinued)

CAR-T therapies

Idecabtagene vicleucel*
Ciltacabtagene autoleucel*
Zevorcabtagene autoleucel
Orvacabtagene autoleucel (discontinued)

ALLO-715
P-BCMA-ALLO1
CT103A
C-CAR088
PHE885
CART-ddBCMA



*FDA-Approved for MM
BiTEs = bispecific T-cell engagers.

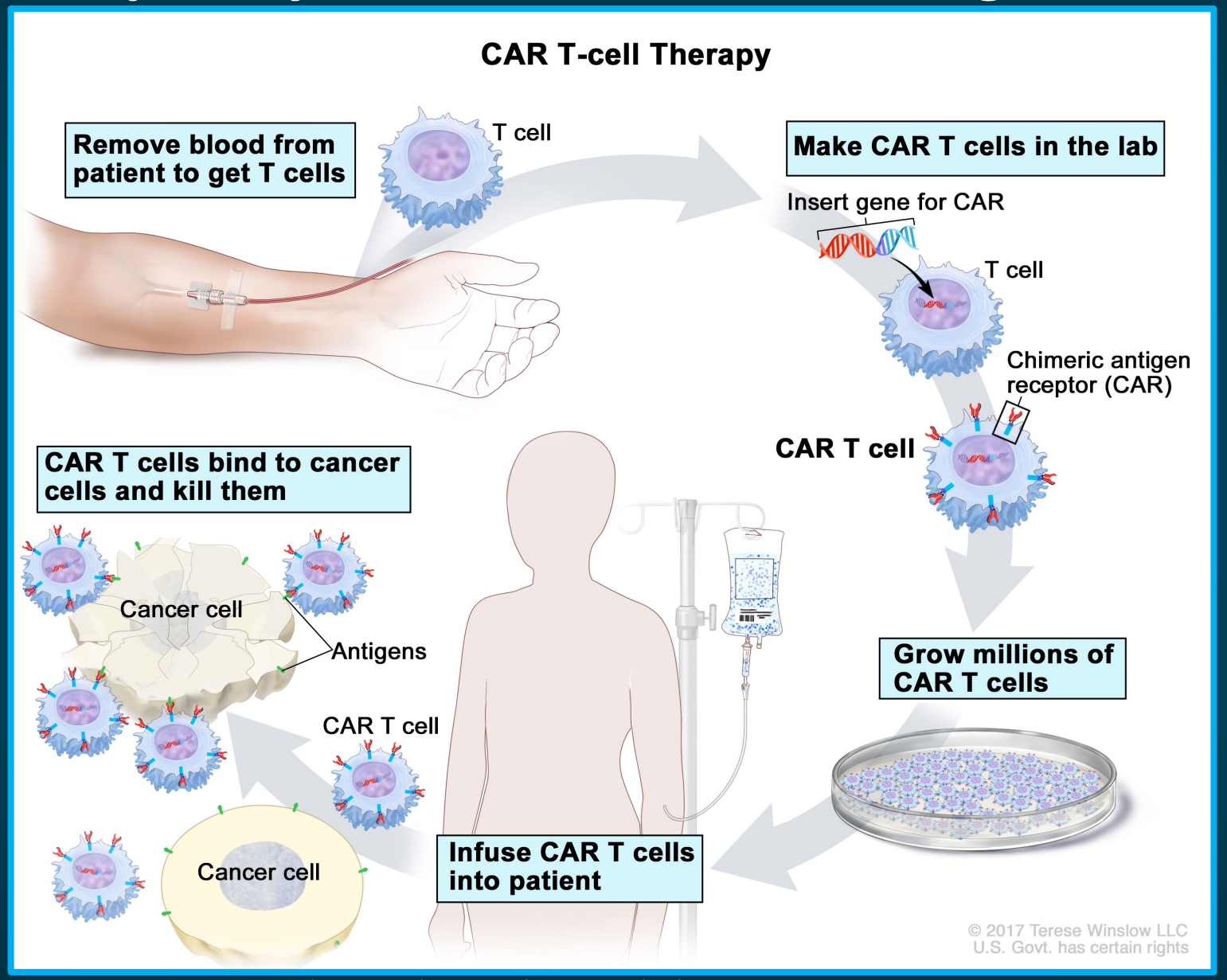
Currently Available Therapies Targeting BCMA

Current therapies for MM targeting BCMA		
Treatment	**Initial US approval**	**Mechanism of action**
Belantamab mafodotin[1]	2020 see below[2]	B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate
Idecabtagene vicleucel[3]	2021	BCMA-directed and genetically modified autologous T cell immunotherapy
Ciltacabtagene autoleucel[4]	2022	BCMA-directed and genetically modified autologous T cell immunotherapy
Teclistamab[5]	2022	Bispecific BCMA-directed CD3 T-cell engager

R/R = relapsed or refractory; REMS = Risk Evaluation and Mitigation Strategy.

1. Belantamab mafodotin-blmf (Blenrep®) prescribing information (PI), 2/2022 (https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Blenrep/pdf/BLENREP-PI-MG.PDF). 2. Dear health care provider letter (Blenrep) (www.blenrep.com/content/dam/cf-pharma/dsa-blenrepv3/en_US/pdf/Blenrep-(belantamab-mafodotin-blmf)DearHCPLetterNov2022.pdf). 3. Idecabtagene vicleucel (Abecma®) PI, 3/2021 (https://packageinserts.bms.com/pi/pi_abecma.pdf). 4. Ciltacabtagene autoleucel (Carvykti™) PI, 3/2022 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/CARVYKTI-pi.pdf). 5. Teclistamab-cqyv (Tecvayli™) PI, 10/2022 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TECVAYLI-pi.pdf).

Complexity of CAR-T Manufacturing Process



National Institutes of Health (NIH)/NCI. CAR T-cell therapy (www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy).

Idecabtagene Vicleucel

Indication	Pivotal Study(s)	Adverse Events

Adults with R/R MM after ≥4 prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb	**KarMMa**
	• 135 patients with R/R MM
	• 100 patients in efficacy population had:
	  ○ ORR of 72%
	  ○ sCR rate of 28%
	• Median DoR:
	  ○ 11.1 mos for patients with VGPR
	  ○ 4.0 mos for patients with PR
		Most common AEs (>20%):
		• CRS, infections (pathogen unspecified), fatigue, musculoskeletal pain, hypogammaglobulinemia, diarrhea, URTI, nausea, viral infections, encephalopathy, edema, pyrexia, cough, headache, and decreased appetite
		Black box warning:
		• CRS, neurologic toxicity, HLH/MAS, and prolonged cytopenias
		Available only through REMS program

CR = complete response; sCR = stringent CR; PR = partial response; VGPR = very good partial response; CRS = cytokine release syndrome; URTI = upper respiratory tract infection; HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome; NE = not estimatable.

Idecabtagene vicleucel (Abecma®) PI, 3/2021 (https://packageinserts.bms.com/pi/pi_abecma.pdf).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

P. Rodriguez-Otero, S. Ailawadhi, B. Arnulf, K. Patel, M. Cavo, A.K. Nooka, S. Manier, N. Callander, L.J. Costa, R. Vij, N.J. Bahlis, P. Moreau, S.R. Solomon, M. Delforge, J. Berdeja, A. Truppel-Hartmann, Z. Yang, L. Favre-Kontula, F. Wu, J. Piasecki, M. Cook, and S. Giralt

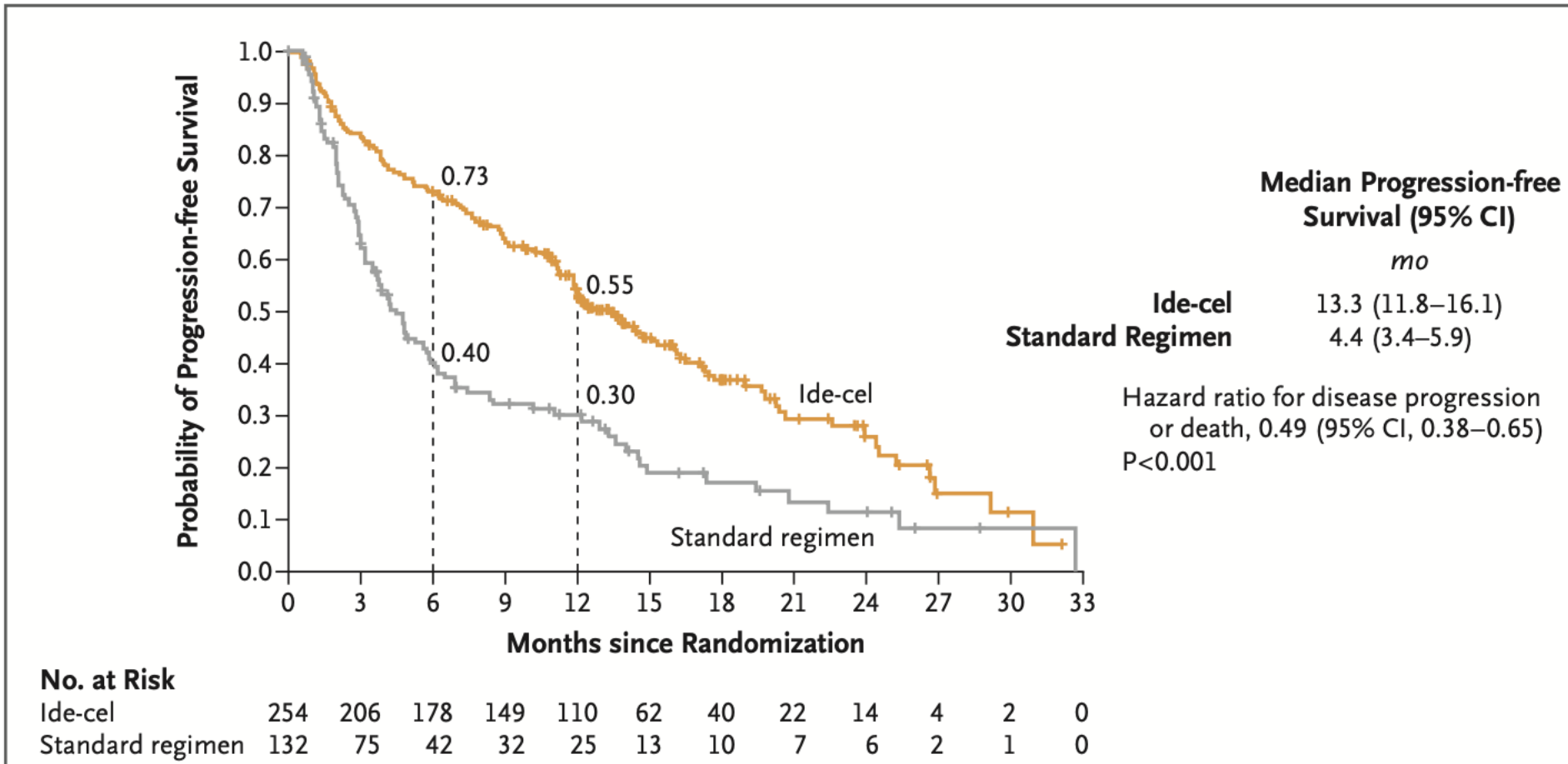


Figure 2. Progression-free Survival (Intention-to-Treat Population).

Progression-free survival was assessed by the independent response committee on the basis of International Myeloma Working Group criteria.[23] The P value was based on a stratified two-sided log-rank test. Data at the dashed lines show the probability of progression-free survival at 6 months and 12 months. Tick marks indicate censored data.

Ciltacabtagene Autoleucel

Indication	Pivotal Study(s)	Adverse Events

Adults with R/R MM after ≥4 prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb	**CARTITUDE-1**
	• 113 patients with R/R MM
	• 97 patients in efficacy population had:
	  ○ ORR of 97.9%
	  ○ sCR rate of 78.4%
	• Median time to response: 1 mo
	• DoR: 21.8 mos
		Most common AEs (>20%)
		• Pyrexia, CRS, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections (pathogen unspecified), cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, URTI, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting
		Black box warning:
		• CRS, neurologic toxicity, HLH/MAS, and prolonged/recurrent cytopenia
		Available only through REMS program

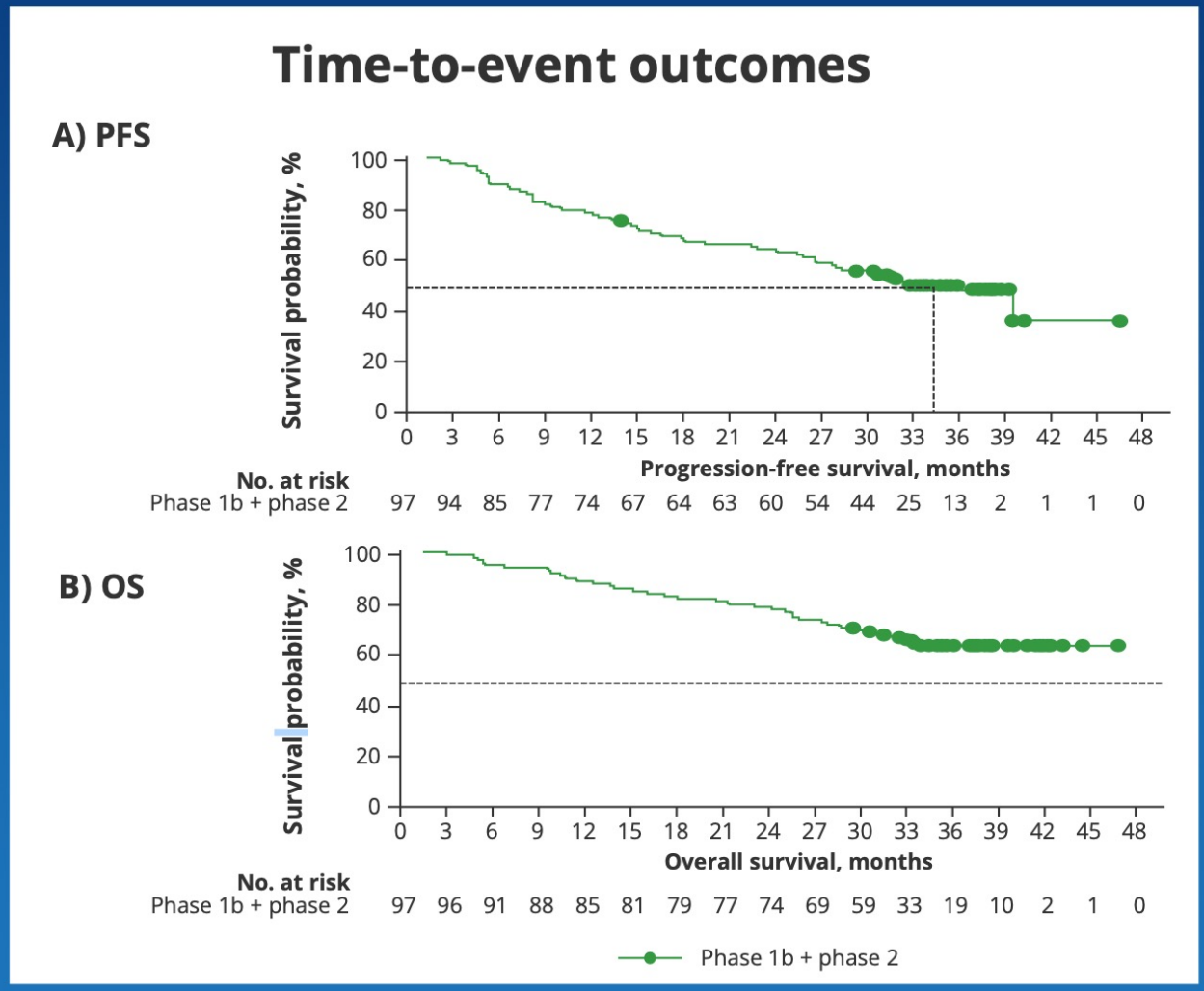
CR = complete response; sCR = stringent CR; PR = partial response; VGPR = very good partial response; CRS = cytokine release syndrome; URTI = upper respiratory tract infection; HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome; NE = not estimatable.

Ciltacabtagene autoleucel (Carvykti™) PI, 3/2022 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/CARVYKTI-pi.pdf).

CARTITUDE-1 Final Results: Efficacy
(~3-Year Follow-Up)

At study closeout:

- Median DOR was 33.9 months (95% CI, 25.5–NE)
- Median PFS was 34.9 months (95% CI, 25.2–NE)
- Median OS was not reached
  - An estimated 62.9% of patients were alive at ~3-year follow-up



Phase 3 Results From CARTITUDE-4: Cilta-cel Versus Standard of Care (PVd or DPd) in Lenalidomide-Refractory Multiple Myeloma

Binod Dhakal[1], Kwee Yong[2], Simon Harrison[3], María-Victoria Mateos[4], Philippe Moreau[5], Niels WCJ van de Donk[6], Surbhi Sidana[7], Rakesh Popat[8], Nikoletta Lendvai[9], Carolina Lonardi[10], Ana Slaughter[11], Jordan M Schecter[9], Katherine Li[12], Enrique Zudaire[12], Diana Chen[13], Jane Gilbert[14], Lida Pacaud[15], Nitin Patel[15], Jesús San-Miguel[16], Hermann Einsele[17]

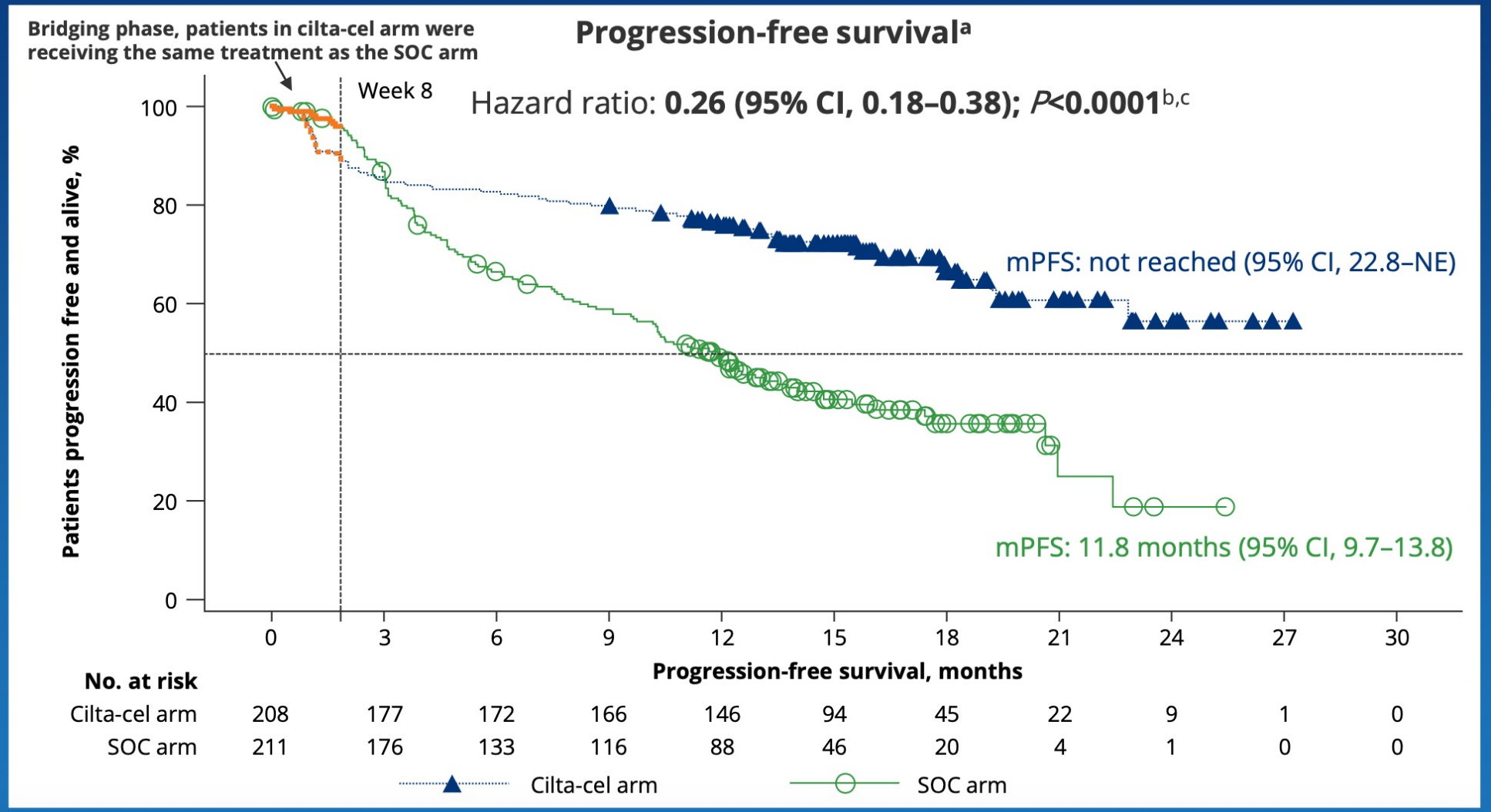
[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]Univiersity College London Cancer Institute, London, UK; [3]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia; [4]University Hospital of Salamanca/IBSAL/CIC/CIBERONC, Salamanca, Spain; [5]Hematology Clinic, University Hospital Hotel-Dieu, Nantes, France; [6]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [7]Department of Medicine, Stanford University School of Medicine Stanford, CA, USA; [8]University College London Hospitals, NHS Foundation Trust, London, UK; [9]Janssen Research & Development, Raritan, NJ, USA; [10]Janssen, Buenos Aires, Argentina; [11]Cilag GmbH International, Zug, Switzerland; [12]Janssen Research & Development, Springhouse, PA, USA; [13]Janssen Research & Development, Shanghai, China; [14]Janssen Research & Development, High Wycombe, UK; [15]Legend Biotech USA Inc., Somerset, NJ, USA; [16]Clinica University of Navarra, CCUN, CIMA; IDISNA, CIBERONC, Pamplona, Spain; [17]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany

Presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA & Virtual

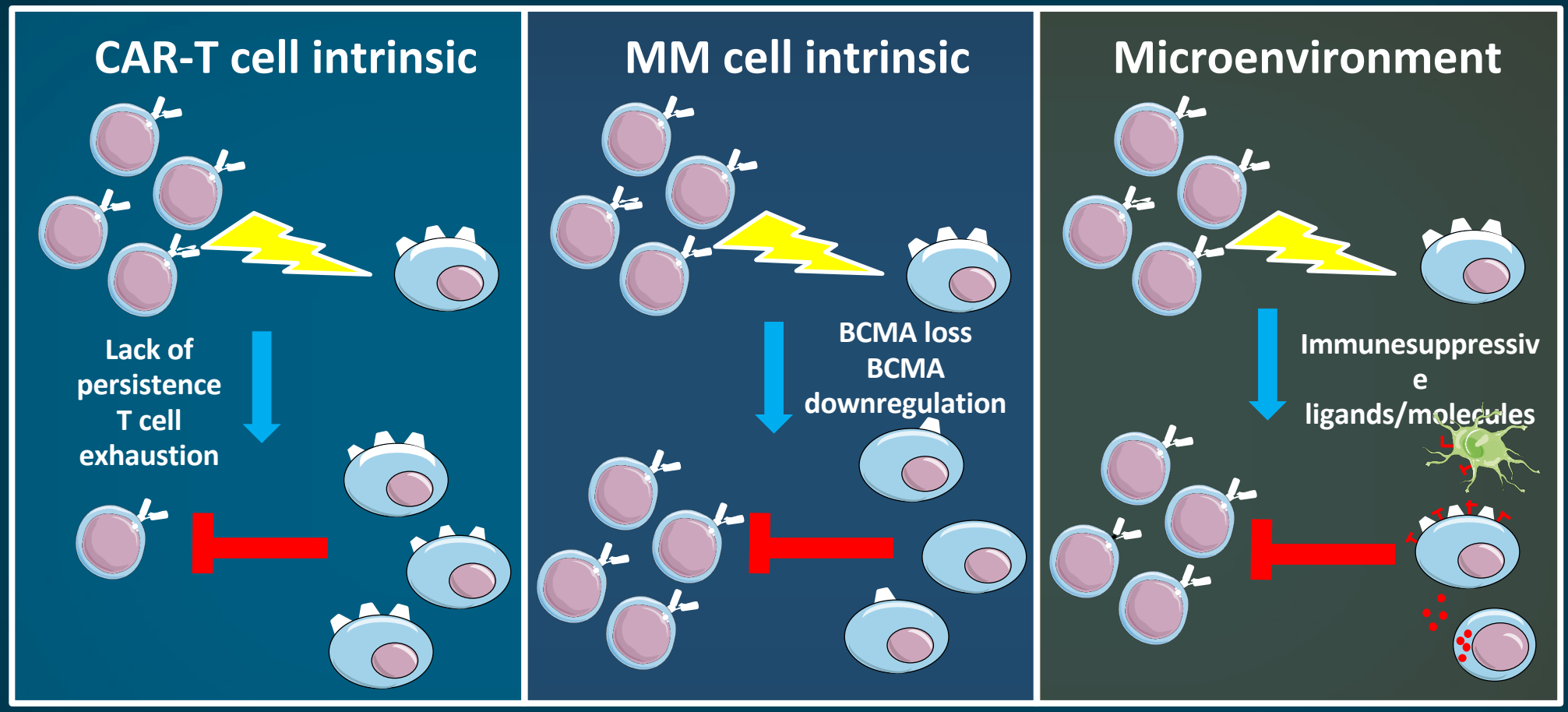
CARTITUDE-4: Primary Endpoint – PFS (ITT Population)

Cilta-cel vs SOC

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



Mechanisms of Resistance to Anti-BCMA CAR-T Therapy



- Humoral and/or cellular immune responses
- Antigen loss or downregulation
- Impaired CAR-T expansion or persistence
- Immunosuppression by TME

BCMA = B-cell maturation antigen; TME = tumor microenvironment.

D'Agostino M, Raje N. *Leukemia*. 2020;34:21-34.

Teclistamab

- Indication: RRMM in patients who received ≥4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
- MajesTEC-1 study (n = 165): median age of 64 yrs who previously received ≥3 prior therapies (not including prior BCMA-targeted therapy) and median of 5 prior therapies
- Step-up dosing (SQ) on days 1 (0.06 mg/kg), 4 (mg/kg) and 7 (1.5 mg/kg) (hospitalization for at least 48 hours required for each step-up dose) followed by outpatient weekly administration (1.5 mg/kg)

Most Common AEs (≥20%)
• Pyrexia
• Cytokine release syndrome
• Musculoskeletal pain
• Injection site reaction
• Fatigue
• URTI
• Nausea
• Headache
• Pneumonia
• Diarrhea
Boxed Warning: • CRS and neurologic toxicity   • Available via REMS program

Teclistamab-cqyv (Tecvayli™) PI, 10/2022 (www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TECVAYLI-pi.pdf). Moreau P, et al. *N Engl J Med.* 2022;387:495-505. van de Donk N, et al. *J Clin Oncol*. 2023;41(suppl 16):abstract 8011.

Teclistamab: Efficacy

2023 ASCO Update

- Phase 1/2 MajesTEC-1: teclistamab resulted in high rate of deep and durable response in patients with triple-class exposure

Data Highlights from MajesTEC-1	
ORR	63%
≥CR (median time to CR)	45% (4.6 mo)
MRD negativity rate by day 100	81%
Duration of response *All* *≥CR*	 22 mo 27 mo
Median PFS *All* *≥CR*	 11 mo 20 mo
Median OS *All* *≥CR*	 22 mo Not reached

van de Donk N, et al. *J Clin Oncol*. 2023;41(suppl 16):abstract 8011.

Teclistamab: Safety

2023 ASCO Update

AE Profile		
	Any Grade	Grade 3/4
Infections	78%	52%
CRS	72%	1%
Neutropenia	72%	65%
Anemia	54%	38%
Thrombocytopenia	42%	22%
Lymphopenia	35%	33%
ICANS	3% (all grade 1/2)	--

van de Donk N, et al. *J Clin Oncol*. 2023;41(suppl 16):abstract 8011.

Investigational Bispecific Antibodies in Multiple Myeloma

Elranatamab: Efficacy

2023 ASCO Update

- Humanized bispecific mAb targeting BCMA/CD3
- Doses were 80, 130, 215, 360, 600, and 1000 µg/kg, given SC
- Eligible pts received at least 1 PI, 1 IMiD, 1 anti-CD38 antibody, and 1 BCMA (ADC and/or CAR-T).

Highlights from Pooled MagnetisMM Studies (10 mo; n=86)	
ORR *All* *Prior BCMA therapy (ADC)* *Prior BCMA therapy (CAR-T)*	 45.3% 41.4% 52.8%
Median time to OR	1.9 mo
≥CR	17.4%
Duration of response rate* *All* *Prior BCMA therapy (ADC)* *Prior BCMA therapy (CAR-T)*	 72.4% 67.3% 78.9%
Median PFS	4.8 mo
Median OS	Not reached

***Rate at 9 months, not 10, as DOR not reached at 10mo**

Nooka A, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 8008.

Elranatamab (PF-06863135): Safety

2023 ASCO Update

AE Profile		
	Any Grade	Grade 3/4
CRS	65%	1%
Anemia	59%	47%
Neutropenia	44%	41%
Thrombocytopenia	41%	29%
Diarrhea	34%	0%
Lymphopenia	33%	30%
ICANS	6%	2%

Nooka A, et al. *J Clin Oncol.* 2021;39(15 suppl): abstract 8008.

Novel Bispecific Antibody Targets: GPRC5D and FcRH5

GPRC5DxCD3

- Targeted by bispecific antibody talquetamab (JNJ-64407564)[1,2,3]
- Phase 2 MonumenTAL-1 (N=288)[4]
  - (1) QW dosage: 74% ORR; 59% with ≥VGPR
  - (2) Q2W dosage: 73% ORR; 57% with ≥VGPR
  - (3) Prior T-cell therapy cohort: 63% ORR; 53% with ≥VGPR
- Common AEs (range for three cohorts above)
  - CRS: 75-79%; skin-related: 56-71%; nail-related: 54-61%; dysgeusia: 48-61%; infections: 58-71%; ICANS: 3-11%; most were grade 1/2 and clinically manageable.

FcRH5xCD3

- Targeted by bispecific antibody cevostamab (BFCR4350A)[1,5]
- ORR in phase 1 was 51.7% (15/29 patients); patients receiving treatment at doses of ≥3.6 mg on day 1 followed by 20 mg with subsequent doses[5]
- CRS was most common AE; most were grade 1 (39.2) or grade 2 (33.3%) severity; with 1 case of grade 3 CRS (2%); most resolved within 2 days; 47.3% of patients received tocilizumab and/or steroids[5]
- Severe AEs (grade 3 or higher) reported include lymphocyte count decreased (11.8%), neutropenia (9.8%), anemia (5.9%), and decreased platelet count (5.9%)[5]

GPRC5D = G protein-coupled receptor class C group 5 member D; Fc = crystallizable fragment (of immunoglobulin); FcRH5 = Fc receptor-homolog 5.

1. Lancman G, et al. *Blood Cancer Discov*. 2021;2:423-433. 2. Chari A, et al. *New Engl J Med*. 2022;387:2232-44. 3. Janssen press release (www.jnj.com/janssen-announces-u-s-fda-breakthrough-therapy-designation-granted-for-talquetamab-for-the-treatment-of-relapsed-or-refractory-multiple-myeloma). 4. Schinke C, et al. ASCO 2023 Annual Meeting. *J Clin Oncol*. 2023;41(suppl 16):abstr 8036. https://meetings.asco.org/abstracts-presentations/220369 5. Cohen AD, et al. *Blood*. 2020;136(suppl 1): 42-43 (abstract 292).

Relapsed/Refractory Myeloma

- Treatment of relapsed disease depends on multiple factors: prior therapy response and tolerance; patient characteristics and preference; disease biology
- When you choose second line therapy, you are choosing second and third line
- Once a patient is on third line therapy, start thinking about CAR T and bispecific
- CAR T and bispecific therapy will move earlier in the course of treatment
- Optimal sequencing remains an area of investigation