What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Multiple Myeloma

A CME Friday Satellite Symposium Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Professor Philippe Moreau, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Sagar Lonial, MD

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Faculty

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Head of the Translational Research Program
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Prof Moreau — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Amgen Inc, Bristol Myers Squibb, Celgene Corporation, GSK, Janssen Biotech Inc, Pfizer Inc, Sanofi

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Dr Orlowski — Disclosures
Faculty

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Contracted Research	Bristol Myers Squibb, CARsgen Therapeutics, Exelixis Inc, Heidelberg Pharma, Janssen Biotech Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Laboratory Research Funding	Asylia Therapeutics Inc, Biotheryx, Heidelberg Pharma
Patent	Asylia Therapeutics Inc

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Dr Raje — Disclosures
Faculty

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Consulting Agreements	AbbVie Inc, Amgen Inc, Bristol Myers Squibb, Janssen Biotech Inc, Pfizer Inc, Sanofi, Takeda Pharmaceuticals USA Inc
Contracted Research	bluebird bio

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Dr Richardson — Disclosures
Faculty

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Contracted Research	Oncopeptides

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Dr Lonial — Disclosures
Moderator

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Stock Options/Stock — Public Company	TG Therapeutics Inc

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Commercial Support

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Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Breast Cancer

A 3-Part CME Hybrid Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

HER2-Low and HER2-Ultralow Breast Cancer

Tuesday, December 10, 2024

7:15 PM – 8:45 PM CT

New Developments in Endocrine Treatment for Breast Cancer

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT

Management of Metastatic Breast Cancer

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT

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Save The Date

Fourth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, February 28 to March 2, 2025

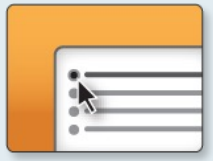
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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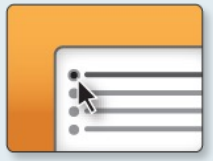
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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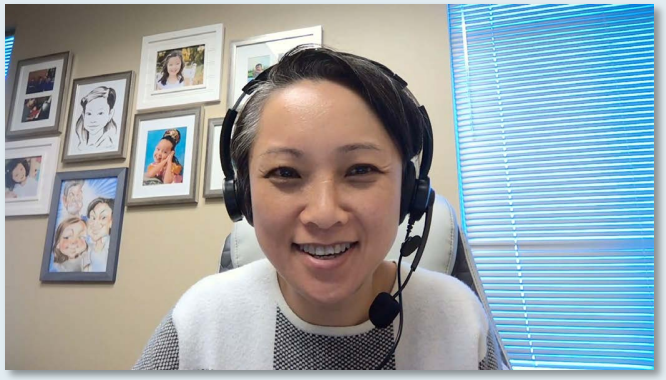
Contributing General Medical Oncologists

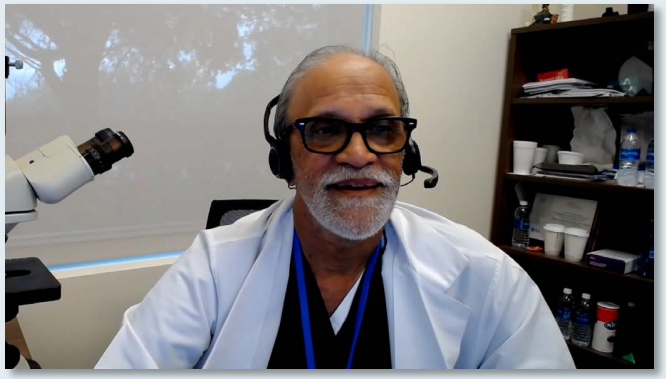
Susmitha Apuri, MD
Florida Cancer Specialists
& Research Institute
Inverness and Lecanto,
Florida

Eric H Lee, MD, PhD
Los Angeles Cancer
Network
Fountain Valley, California

Shams Bufalino, MD
Advocate Lutheran
General Hospital
Park Ridge, Illinois



Yanjun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee



Kapisthalam (KS) Kumar, MD
Florida Cancer Specialists
& Research Institute
Trinity, Florida

Henna Malik, MD
Texas Oncology
Houston, Texas

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Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Orlowski

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory MM — Dr Richardson

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies for the Treatment of MM — Prof Moreau

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Lonial

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Case Presentation: 61-year-old African American man with high-risk del(1q) MM (TP53 mutation) receives D-RVd induction

Dr Eric Lee (Fountain Valley, California)

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QUESTIONS FOR THE FACULTY

What is your approach to induction treatment for younger transplant-eligible patients with standard-risk disease? What about those with high-risk disease, and how do you define high risk? Are there any situations in which an anti-CD38 monoclonal antibody should not be used?

What is your general approach to maintenance therapy for transplant-eligible patients who have received an anti-CD38-containing induction regimen?

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QUESTIONS FOR THE FACULTY

In which situations, if any, do you offer ixazomib as maintenance treatment?

What is your current approach to the use of ASCT, and does this differ for African American patients?

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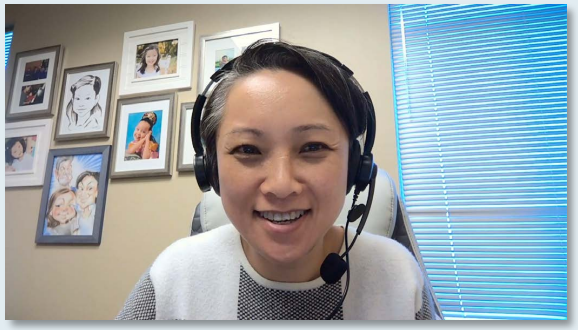
Dr Susmitha Apuri
(Inverness and Lecanto, Florida)

Case Presentation: 80-year-old woman with a history of ER/PR-positive, HER2-positive breast cancer is diagnosed with lambda-restricted plasma cell MM



Dr Yanjun Ma
(Murfreesboro, Tennessee)

Question and Comments: Integrating bortezomib-based induction therapy for elderly patients with MM

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QUESTIONS FOR THE FACULTY

What is your approach to induction treatment for elderly and "very elderly" (eg, older than age 90) transplant-ineligible patients with standard-risk disease? What about those with high-risk disease?

Provided they are fit enough, should all transplant-ineligible patients receive an anti-CD38 monoclonal antibody as part of their induction regimen? If so, how do you select between a doublet and triplet partner? Are you comfortable using daratumumab/RVd for transplant-ineligible patients?

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QUESTIONS FOR THE FACULTY

What is your general approach to maintenance therapy for transplant-ineligible patients who have received an anti-CD38-containing induction regimen?

How do you modify the dose/schedule of commonly employed induction/maintenance strategies for elderly patients? How do you modify corticosteroid dosing?

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Management of Newly Diagnosed Multiple Myeloma

Robert Z. Orlowski, M.D., Ph.D.

Deputy Chair, Department of Lymphoma/Myeloma & Vice Chair, Myeloma Translational Research

Florence Maude Thomas Cancer Research Professor

Principal Investigator, MD Anderson SCOR in High Risk Plasma Cell Dyscrasias

Chair, SWOG Myeloma Committee

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

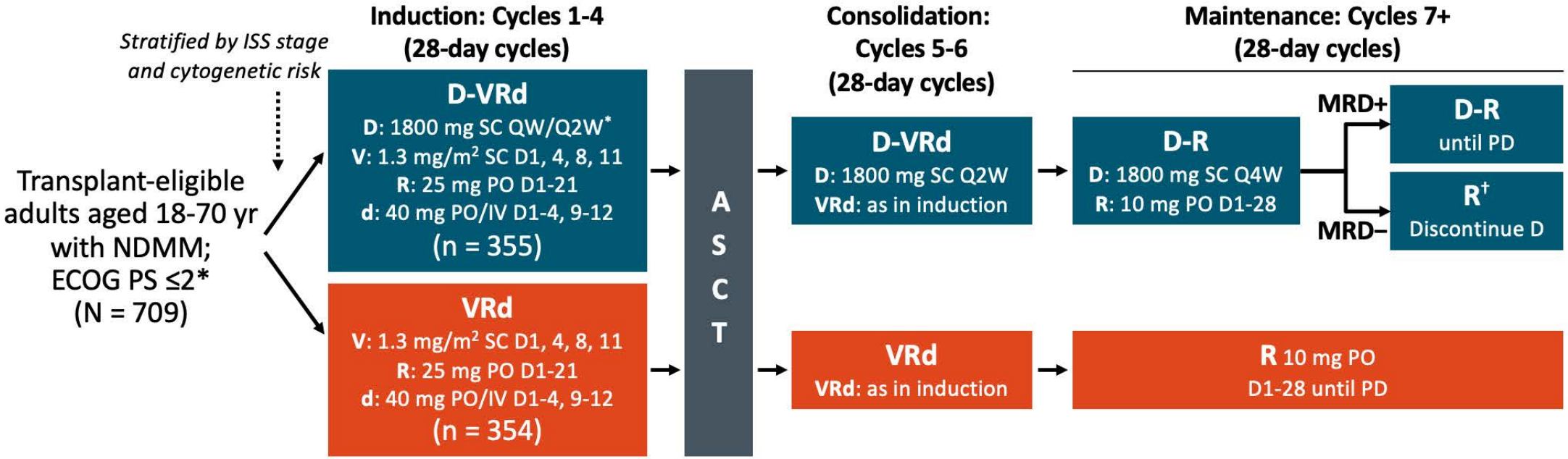
Induction for Transplant-Eligible Patients

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES[a-d]
Preferred Regimens • Daratumumab/lenalidomide/bortezomib/dexamethasone (category 1)
Other Recommended Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/lenalidomide/dexamethasone • Isatuximab-irfc/bortezomib/lenalidomide/dexamethasone
Useful In Certain Circumstances • Bortezomib/cyclophosphamide/dexamethasone[e] • Carfilzomib/cyclophosphamide/dexamethasone[e,f] • Daratumumab/bortezomib/cyclophosphamide/dexamethasone • Daratumumab/carfilzomib/lenalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/ bortezomib[g] (VTD-PACE) • Isatuximab-irfc/carfilzomib/lenalidomide/dexamethasone

NCCN Guidelines for Multiple Myeloma; Version 1.2025

PERSEUS Study

- Multicenter, open-label, randomized phase III trial; current analysis median f/u: 47.5 mo

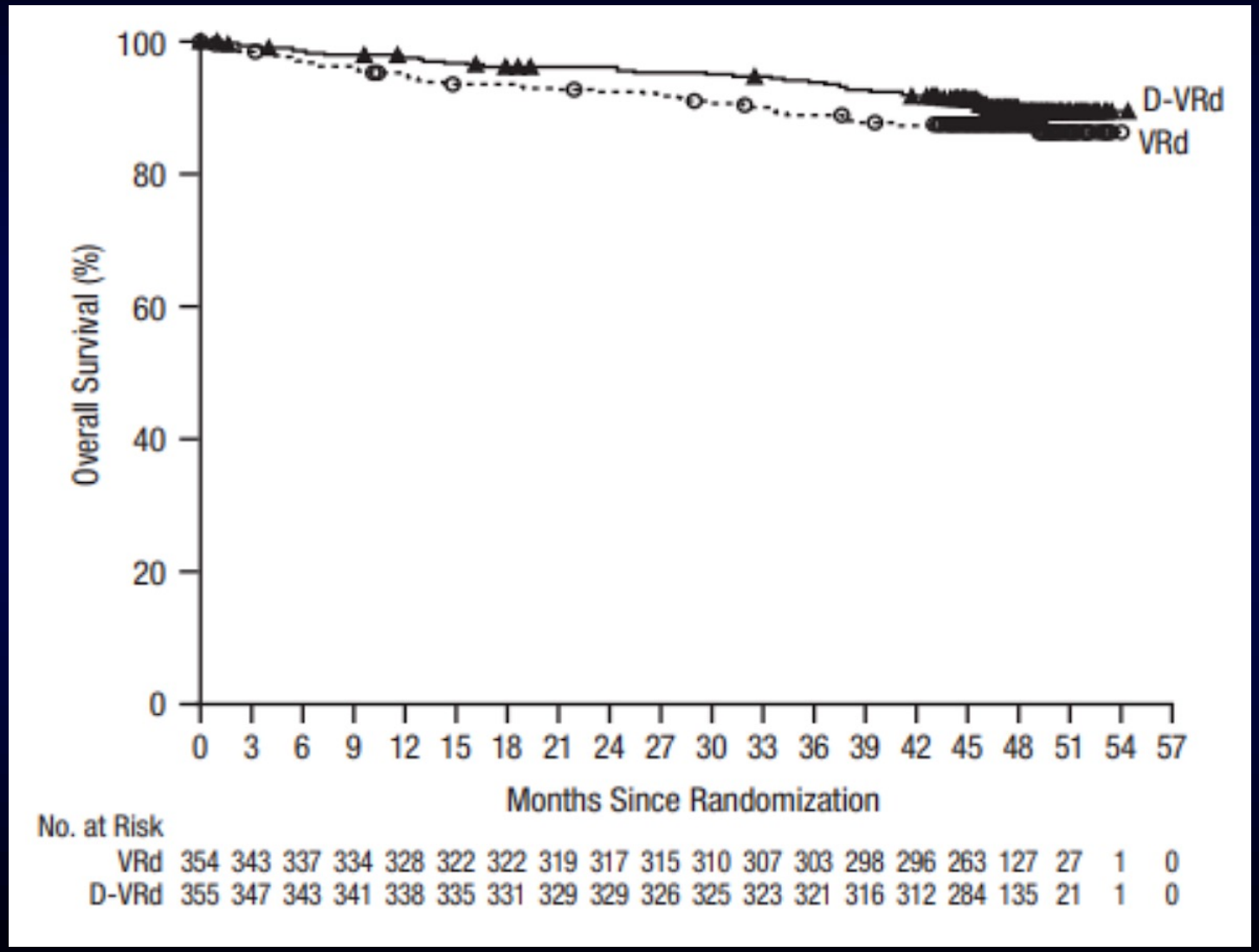


*QW during cycles 1-2, Q2W during cycles 3-4. †D discontinued after ≥24 mo in patients with ≥CR and 12 mo sustained MRD negativity; D restarted upon confirmed loss of CR without PD or MRD recurrence.

- **Primary endpoint:** PFS
- **Key secondary endpoints:** ≥CR rate, MRD negativity rate, OS

Sonneveld P et al. N Engl J Med. 2024;390(4):301-313.

Response & Durability Data



Sonneveld P et al. N Engl J Med. 2024;390(4):301-313.

Common AEs

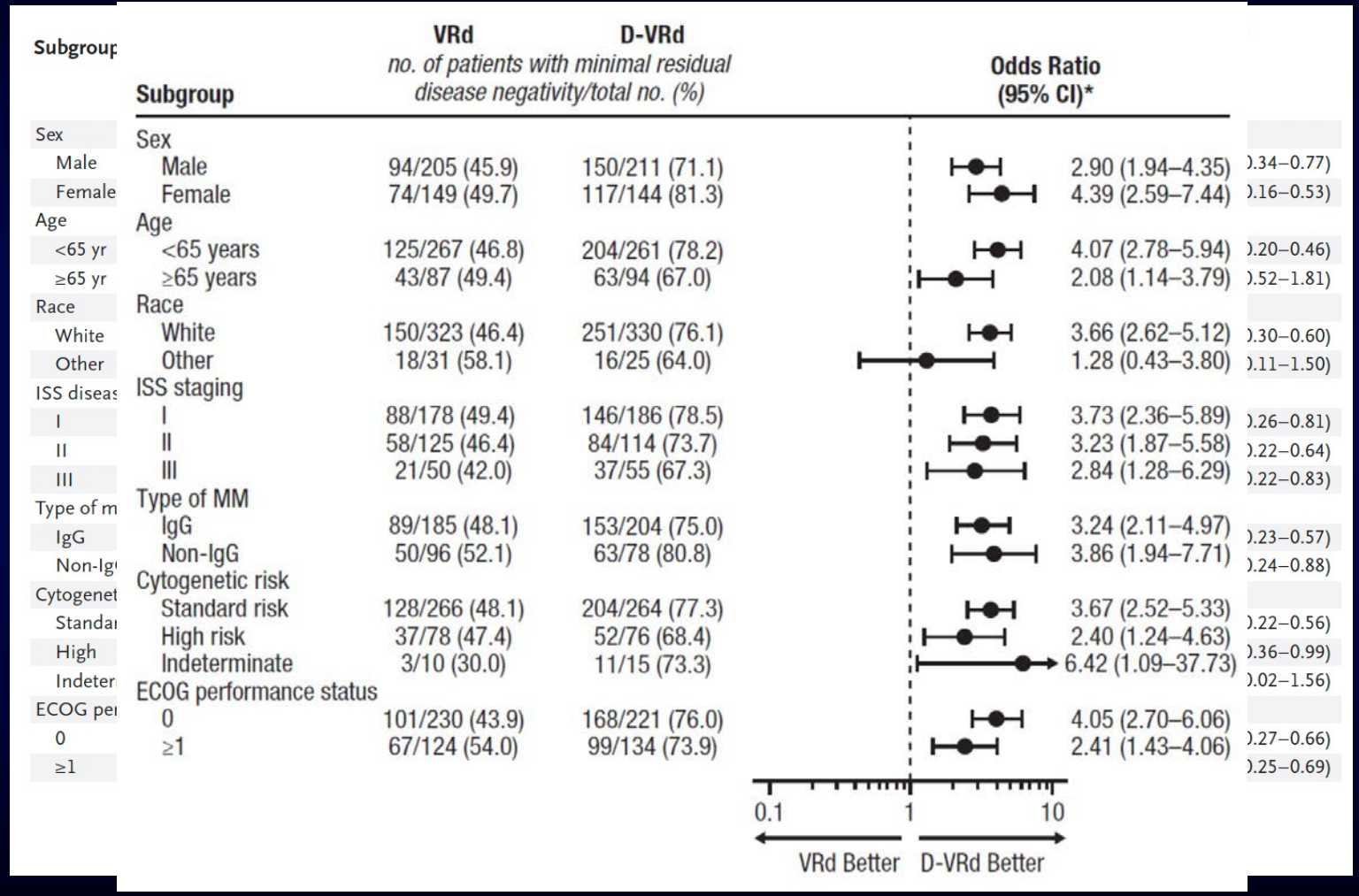
Table 3. Most Common Adverse Events (Safety Population).*

Event	D-VRd (N=351)		VRd (N=347)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	349 (99.4)	321 (91.5)	344 (99.1)	297 (85.6)
Hematologic adverse event				
Neutropenia	243 (69.2)	218 (62.1)	204 (58.8)	177 (51.0)
Thrombocytopenia	170 (48.4)	102 (29.1)	119 (34.3)	60 (17.3)
Anemia	78 (22.2)	21 (6.0)	72 (20.7)	22 (6.3)
Febrile neutropenia	34 (9.7)	33 (9.4)	38 (11.0)	35 (10.1)
Nonhematologic adverse event				
Diarrhea	214 (61.0)	37 (10.5)	188 (54.2)	27 (7.8)
Peripheral sensory neuropathy	188 (53.6)	15 (4.3)	179 (51.6)	14 (4.0)
Constipation	119 (33.9)	8 (2.3)	118 (34.0)	6 (1.7)
Pyrexia	111 (31.6)	8 (2.3)	109 (31.4)	9 (2.6)
Insomnia	95 (27.1)	8 (2.3)	61 (17.6)	6 (1.7)
Asthenia	94 (26.8)	12 (3.4)	89 (25.6)	9 (2.6)
Cough	85 (24.2)	1 (0.3)	51 (14.7)	0
Fatigue	84 (23.9)	10 (2.8)	92 (26.5)	18 (5.2)
Rash	82 (23.4)	9 (2.6)	94 (27.1)	17 (4.9)
Back pain	80 (22.8)	2 (0.6)	66 (19.0)	1 (0.3)
Peripheral edema	72 (20.5)	4 (1.1)	74 (21.3)	1 (0.3)
Nausea	71 (20.2)	2 (0.6)	58 (16.7)	2 (0.6)
Infection	305 (86.9)	124 (35.3)	266 (76.7)	95 (27.4)
Coronavirus disease 2019	123 (35.0)	12 (3.4)	83 (23.9)	4 (1.2)
Upper respiratory tract infection	111 (31.6)	2 (0.6)	87 (25.1)	6 (1.7)
Pneumonia	64 (18.2)	37 (10.5)	38 (11.0)	21 (6.1)
Second primary cancer	37 (10.5)	NA	25 (7.2)	NA
Any infusion-related reaction	21 (6.0)	3 (0.9)	NA	NA

* The safety population included patients who had received at least one dose of the assigned treatment. Adverse events of any grade that were reported in at least 20% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 10% of patients in either treatment group are listed. NA denotes not applicable.

Sonneveld P et al. N Engl J Med. 2024;390(4):301-313.

Subgroup Analyses



Sonneveld P et al. N Engl J Med. 2024;390(4):301-313.

FDA Approval

FDA approves daratumumab and hyaluronidase-fihj with bortezomib, lenalidomide, and dexamethasone for multiple myeloma

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On July 30, 2024, the Food and Drug Administration approved daratumumab and hyaluronidase-fihj in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (ASCT).

Full prescribing information will be posted on Drugs@FDA.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-daratumumab-and-hyaluronidase-fihj-bortezomib-lenalidomide-and-dexamethasone-multiple

Induction for Transplant-Ineligible Patients

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES[a-d,j]	
In general, continue primary therapy until progression with de-escalation of therapy (modification of dose and duration) as needed.	
Preferred Regimens • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/bortezomib/lenalidomide/dexamethasone (for patients <80 years old who are not frail)(category 1) • Lenalidomide/bortezomib/dexamethasone (category 1)	
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone	
Useful In Certain Circumstances • Lenalidomide/low-dose dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[e] • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone (VRD-lite) for patients assessed as being frail	• Carfilzomib/cyclophosphamide/dexamethasone[e,f] • Daratumumab/cyclophosphamide/bortezomib/dexamethasone[k] • Isatuximab-irfc/carfilzomib/lenalidomide/dexamethasone (category 2B) • Lenalidomide/cyclophosphamide/dexamethasone

NCCN Guidelines for Multiple Myeloma; Version 1.2025

IMROZ Study

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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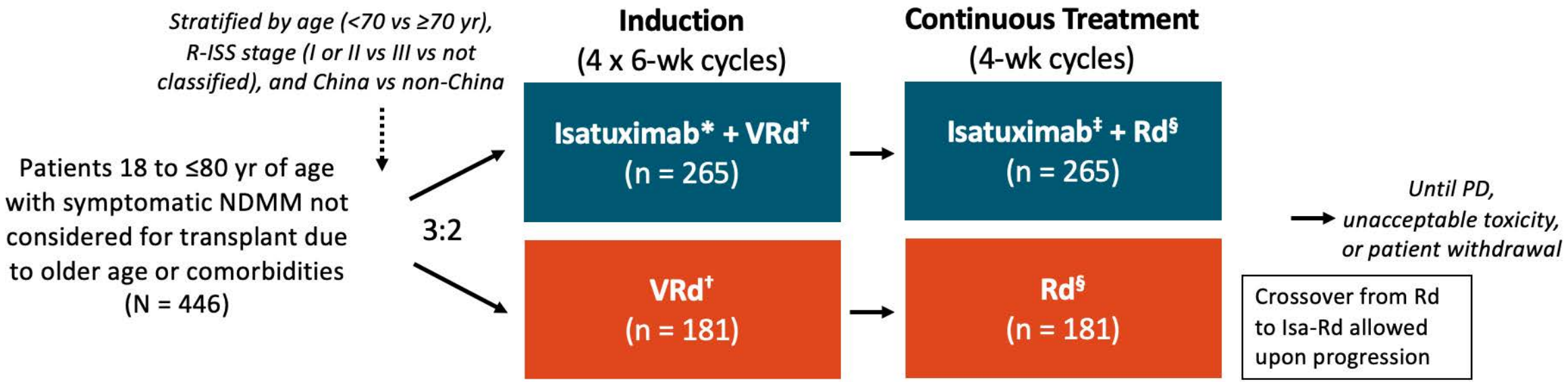
- International, randomized, open-label phase III trial

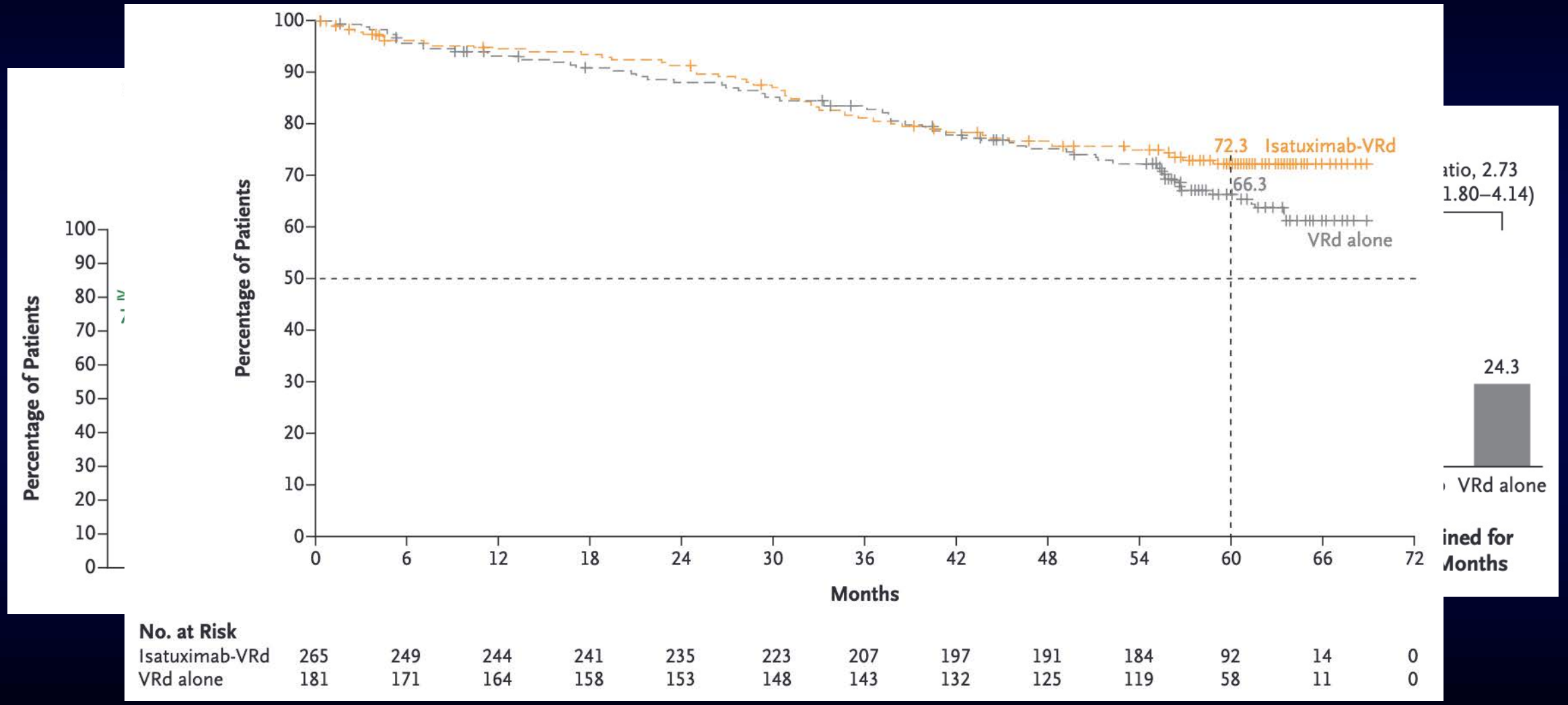


*Isa IV (C1 only) 10 mg/kg Q1W; Isa IV (C2-4) 10 mg/kg Q2W. †V: SC 1.3 mg/m^2 on D1,4,8,11,22,25,29,32; R: PO 25 mg on D1-14 and 22-35; d: IV/PO 20 mg on D1,2,4,5,8,9,11,12,15,22,23,25,26,29,30,32,33. ‡Isa IV (C5-17) 10 mg/kg Q2W; Isa IV (C18+) 10 mg/kg monthly. §R: PO 25 mg on D1-21; d: IV/PO 20 mg on Q1W.

- **Primary endpoints:** PFS
- **Secondary endpoints:** CR rate, MRD– CR (NGS 10^{-5}) rate, ≥ VGPR rate, OS

Facon T et al. N Engl J Med. 2024;391(17):1597-1609.

Response & Durability Data



Facon T et al. N Engl J Med. 2024;391(17):1597-1609.

Common AEs

- No un-expected AEs given known profile of α-CD38s

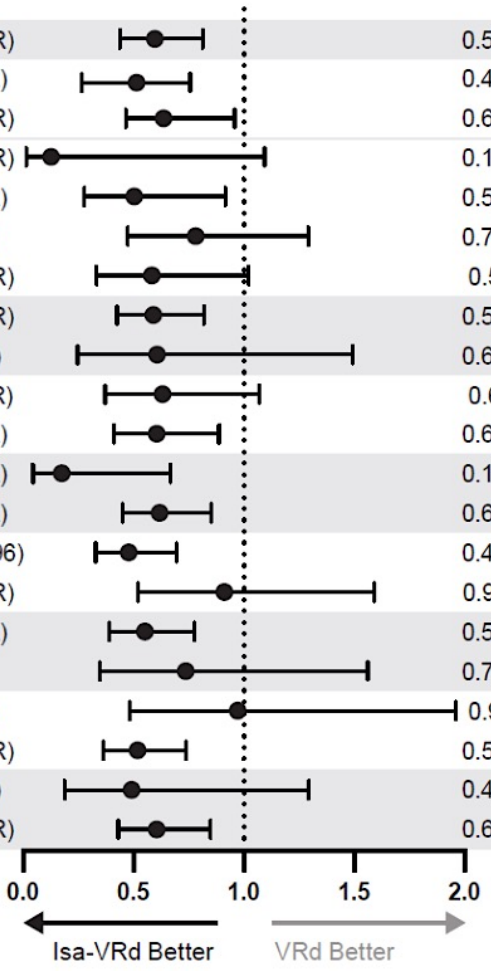
Table 2. Hematologic Laboratory Abnormalities, Adverse Events of Any Grade, and Second Primary Cancers (Safety Population).*

Event	Isatuximab-VRd (N=263)		VRd (N=181)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Hematologic laboratory abnormalities†				
Anemia	260 (98.9)	46 (17.5)	177 (97.8)	29 (16.0)
Lymphopenia	251 (95.4)	158 (60.1)	167 (92.3)	96 (53.0)
Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Leukopenia	256 (97.3)	83 (31.6)	160 (88.4)	30 (16.6)
Thrombocytopenia	251 (95.4)	79 (30.0)	153 (84.5)	50 (27.6)
Nonhematologic adverse events				
Infection‡				
Pneumonia	79 (30.0)	53 (20.2)	35 (19.3)	23 (12.7)
Bronchitis	58 (22.1)	7 (2.7)	32 (17.7)	3 (1.7)
Upper respiratory tract infection	90 (34.2)	2 (0.8)	61 (33.7)	2 (1.1)
Diarrhea	144 (54.8)	20 (7.6)	88 (48.6)	15 (8.3)
Peripheral sensory neuropathy	143 (54.4)	19 (7.2)	110 (60.8)	11 (6.1)
Cataract	100 (38.0)	41 (15.6)	46 (25.4)	20 (11.0)
Constipation	94 (35.7)	6 (2.3)	74 (40.9)	3 (1.7)
Fatigue	91 (34.6)	21 (8.0)	48 (26.5)	12 (6.6)
Peripheral edema	86 (32.7)	0	59 (32.6)	2 (1.1)
Infusion-related reaction	62 (23.6)	1 (0.4)	2 (1.1)	0
Covid-19§	78 (29.7)	23 (8.7)	37 (20.4)	12 (6.6)
Insomnia	59 (22.4)	10 (3.8)	44 (24.3)	4 (2.2)
Back pain	58 (22.1)	9 (3.4)	31 (17.1)	3 (1.7)
Asthenia	57 (21.7)	7 (2.7)	44 (24.3)	4 (2.2)
Invasive second primary cancer¶				
Solid tumor‖	22 (8.4)	14 (5.3)	8 (4.4)	6 (3.3)
Hematologic cancer	3 (1.1)	1 (0.4)	2 (1.1)	2 (1.1)

Facon T et al. N Engl J Med. 2024;391(17):1597-1609.

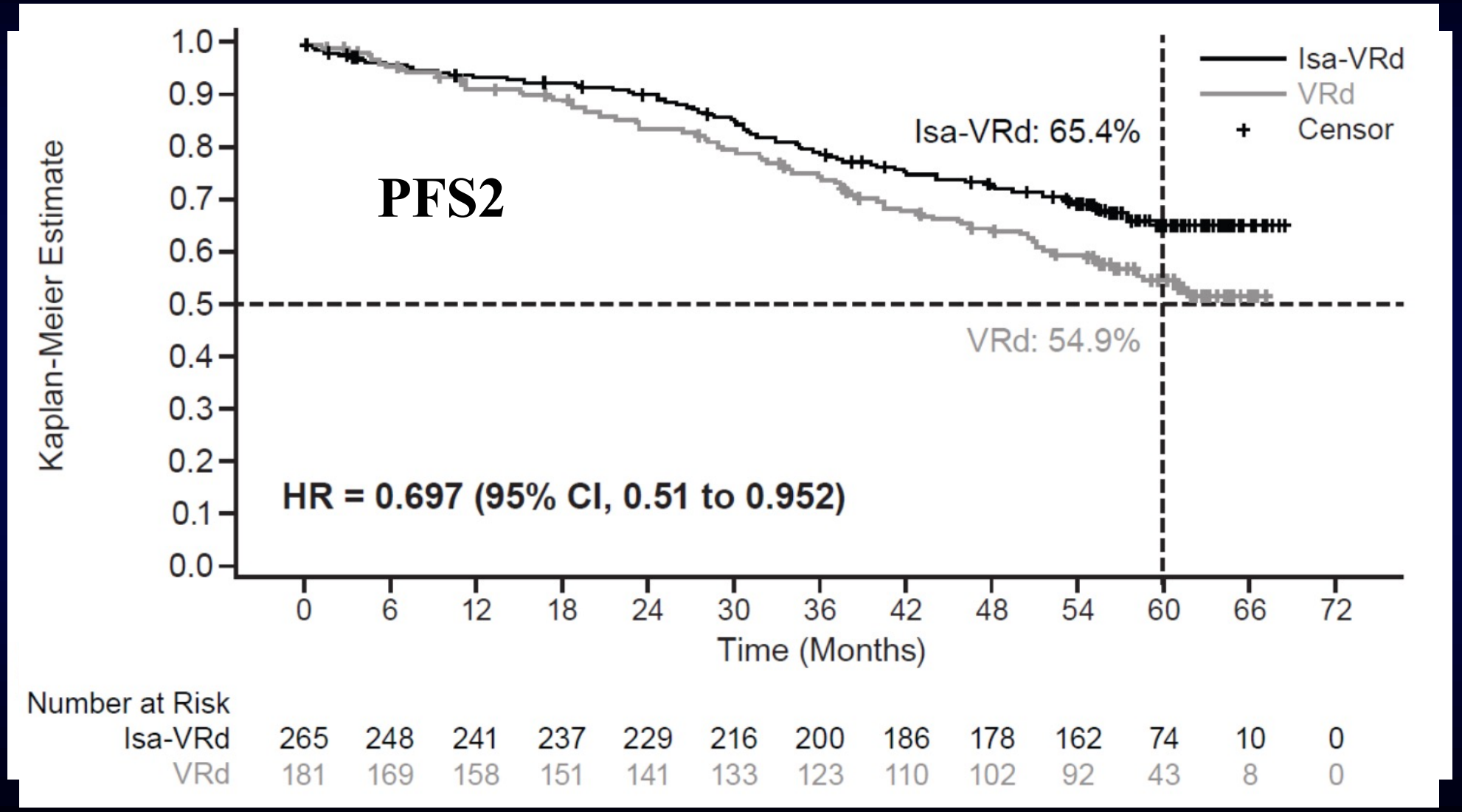
Subgroup Analyses

	Subgroup	Isa-VRd Events/total	Median PFS (95% CI)	VRd Events/total	Median PFS (95% CI)	Hazard ratio (95% CI)
All patients		84/265	NR (NR–NR)	78/181	54.341 (45.207–NR)	0.596 (0.438–0.812)
Age*	<70 years	22/80	NR (NR–NR)	27/56	53.914 (37.52–NR)	0.441 (0.251–0.775)
	≥70 years	62/185	NR (NR–NR)	51/125	54.341 (43.598–NR)	0.671 (0.463–0.972)
	<65 years	1/8	NR (48.066–NR)	5/9	31.524 (12.189–NR)	0.126 (0.014–1.095)
	65-<70 years	21/73	NR (NR–NR)	22/47	59.663 (37.52–NR)	0.503 (0.276–0.915)
	70-<75 years	39/115	NR (56.214–NR)	25/68	NR (45.207–NR)	0.781 (0.472–1.291)
	75-80 years	23/69	NR (53.06–NR)	26/57	45.864 (23.819–NR)	0.582 (0.331–1.02)
Baseline ECOG PS	0 or 1	74/235	NR (NR–NR)	69/162	54.341 (45.864–NR)	0.589 (0.424–0.818)
	>1	10/30	NR (29.503–NR)	9/19	43.598 (5.29–NR)	0.606 (0.246–1.493)
Baseline eGFR (MDRD)	<60 mL/min/1.73 m^2	25/66	NR (48.066–NR)	31/62	43.598 (33.117–NR)	0.63 (0.371–1.068)
	≥60 mL/min/1.73 m^2	59/197	NR (NR–NR)	47/119	59.663 (46.62–NR)	0.604 (0.412–0.887)
Extramedullary disease at baseline	Yes	6/19	NR (35.91–NR)	5/7	17.873 (2.825–NR)	0.174 (0.045–0.666)
	No	78/246	NR (NR–NR)	73/174	59.663 (46.16–NR)	0.618 (0.449–0.851)
Type of myeloma at study entry	IgG	54/171	NR (NR–NR)	56/115	46.62 (37.454-59.696)	0.478 (0.328–0.695)
	Non-IgG	30/93	NR (NR–NR)	22/65	62.752 (48.953–NR)	0.911 (0.521–1.591)
R-ISS stage at study entry	I or II	67/234	NR (NR–NR)	65/157	59.663 (46.62–NR)	0.551 (0.391–0.776)
	III	16/29	45.602 (21.027–NR)	12/21	37.52 (4.6–NR)	0.736 (0.347–1.561)
Cytogenetic risk at baseline	High	18/40	NR (30.259–NR)	14/34	NR (37.454–NR)	0.971 (0.481–1.96)
	Standard	61/207	NR (NR–NR)	62/140	53.914 (43.006–NR)	0.517 (0.363–0.737)
HRCA and 1q21+†	Yes	8/19	NR (22.998–NR)	9/15	37.52 (5.782–NR)	0.491 (0.187–1.293)
	No	70/227	NR (NR–NR)	65/157	59.696 (45.864–NR)	0.604 (0.431–0.847)



Facon T et al. N Engl J Med. 2024;391(17):1597-1609.

Other Notable Findings



Facon T et al. N Engl J Med. 2024;391(17):1597-1609.

FDA Approval

FDA approves isatuximab-irfc with bortezomib, lenalidomide, and dexamethasone for newly diagnosed multiple myeloma

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On September 20, 2024, the Food and Drug Administration approved isatuximab-irfc with bortezomib, lenalidomide, and dexamethasone for adults with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant (ASCT).

Full prescribing information will be posted on Drugs@FDA.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-isatuximab-irfc-bortezomib-lenalidomide-and-dexamethasone-newly-diagnosed-multiple

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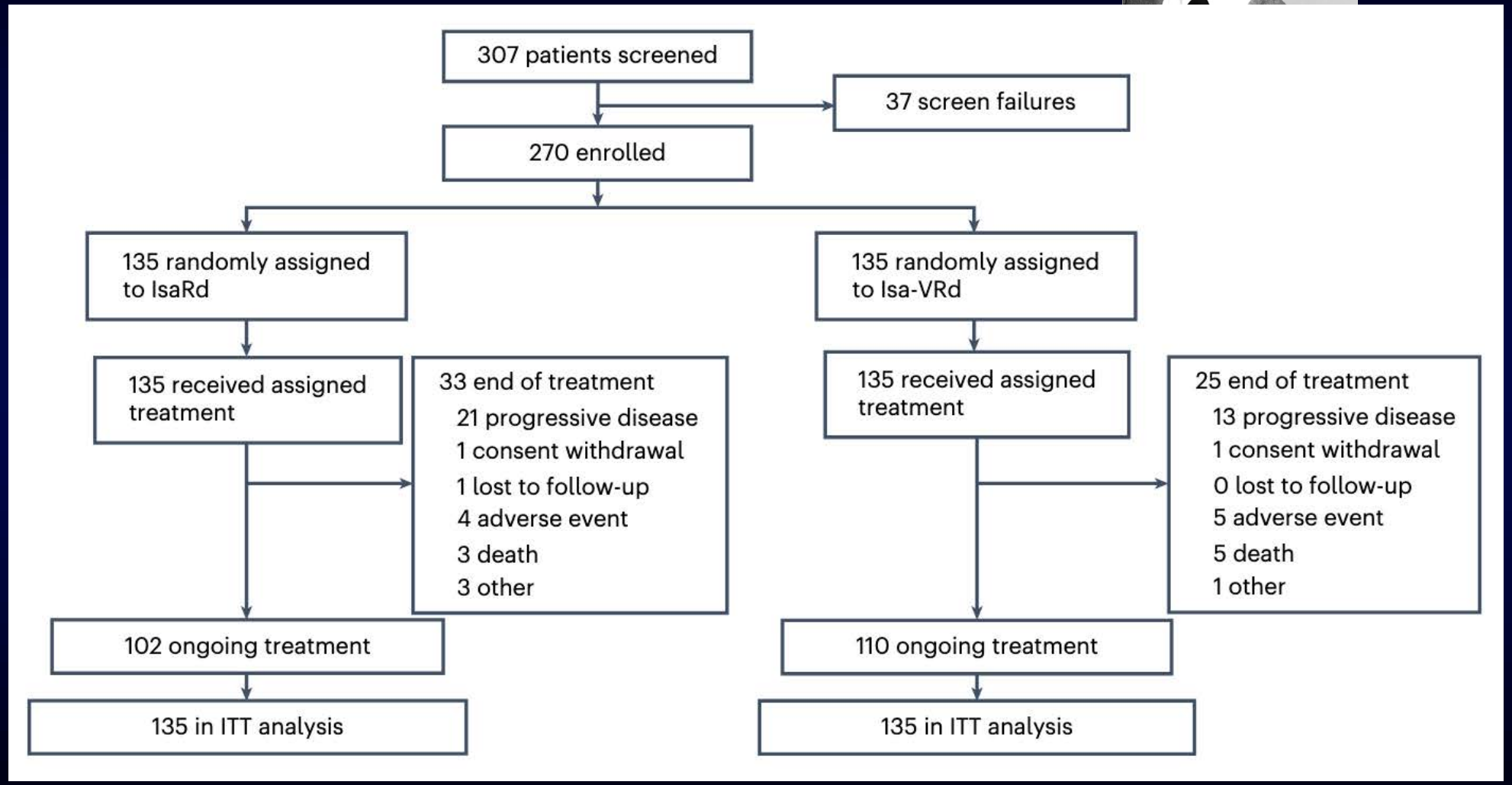
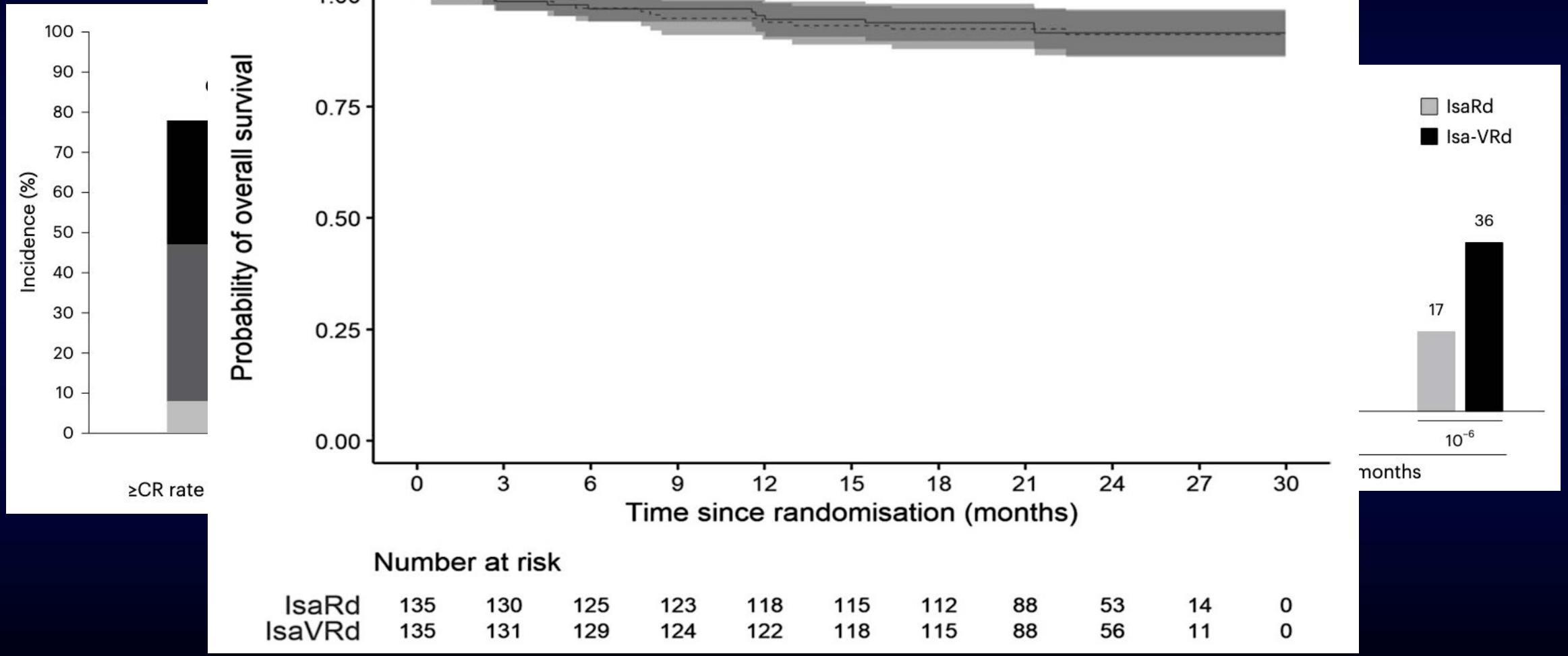
BENEFIT Study



Leleu X et al. Nat Med. 2024;30(8):2235-2241.

Response & Durability Data



Leleu X et al. Nat Med. 2024;30(8):2235-2241.

Common AEs

Event, no. of patients (%)	IsaRd(*N*=135)		Isa-VRd(*N*=135)	
	Any grade	≥Grade 3	Any grade	≥Grade 3
Hematologic AE				
Neutropenia	82 (61)	61 (45)	77 (57)	53 (40)
Nervous system disorders				
Peripheral neuropathy	38 (28)	13 (10)	70 (52)	37 (27)
Other	41 (30)	17 (13)	38 (28)	19 (14)
Psychiatric disorders	32 (24)	17 (13)	33 (24)	22 (16)
Eye disorders	19 (14)	12 (8)	20 (15)	10 (7)
Hepatobiliary disorders	19 (14)	13 (9)	—	—
Renal and urinary disorders	18 (13)	14 (9)	24 (18)	16 (12)
Cardiac disorders	—	—	15 (11)	11 (8)
Vascular disorders	34 (25)	23 (17)	36 (27)	21 (15)
Hypokalemia	15 (11)	11 (8)	16 (12)	11 (8)
Muscle spasms	28 (21)	9 (7)	27 (20)	7 (5)
Peripheral Edema	27 (20)	10 (7)	48 (36)	18 (14)
Pyrexia	17 (13)	9 (7)	—	—
Weight decreased	26 (19)	12 (9)	21 (16)	12 (9)
Dyspnea	16 (12)	9 (7)	—	—
Cough	—	—	16 (12)	5 (4)
Insomnia	14 (10)	6 (5)	14 (10)	6 (4)

Shown are listed AEs of any grade and ≥grade 3 for hematologic AEs, and any grade and ≥grade 2 for nonhematologic AEs that were reported in at least 10% of patients in either treatment group. [a]The safety population included all patients who received at least one dose of study treatment.

Leleu X et al. Nat Med. 2024;30(8):2235-2241.

CEPHEUS Study

LATE BREAKING ABSTRACTS

Key eligibility criteria:

- NDMM (TIE or transplant deferred)
- ECOG PS score of 0-2
- Frailty score of 0-1

1:1 randomization (N = 395)

VRd

V: 1.3 mg/m^2 SC Days 1, 4, 8, 11
R: 25 mg PO Days 1-14
d: 20 mg PO Days 1, 2, 4, 5, 8, 9, 11, 12

Rd
Cycle 9+

R: 25 mg PO Days 1-21
d: 40 mg PO Days 1, 8, 15, 22

DARA SC-VRd

DARA: 1,800 mg SC QW Cycles 1-2, Q3W Cycles 3-8
VRd: schedule as above

DARA SC-Rd
Cycle 9+

DARA: 1,800 mg SC Q4W
Rd: schedule as above

Primary endpoint:

- Overall MRD (≥CR) negativity

Key secondary endpoints:

- PFS
- Sustained MRD (≥CR) negativity (≥12 months)
- ≥CR rate
- OS

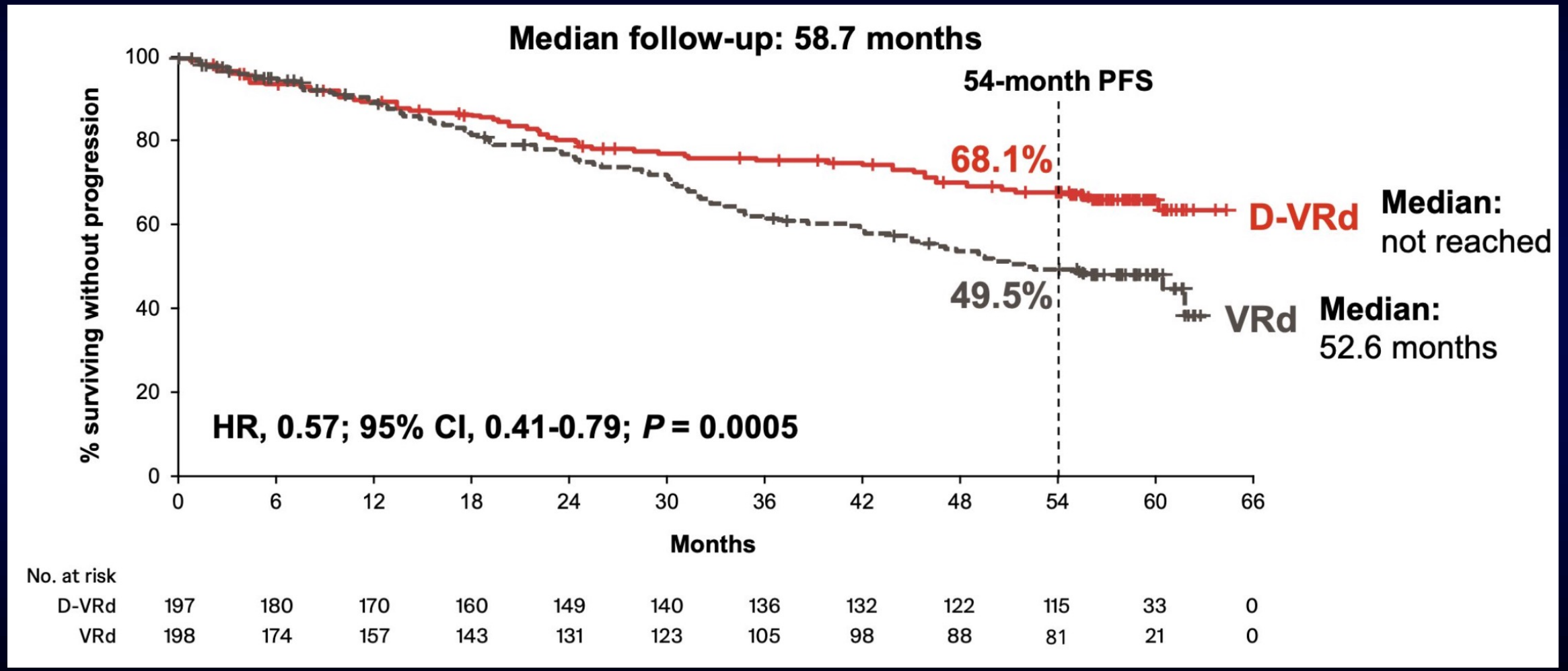
21-day cycles
8 cycles of bortezomib treatment

28-day cycles
until disease progression or unacceptable toxicity

Lorena Lopez-Masi[20], Jodi Carey[19], Melissa Rowe[21], Robin Carson[19], Sonja Zweegman[22]

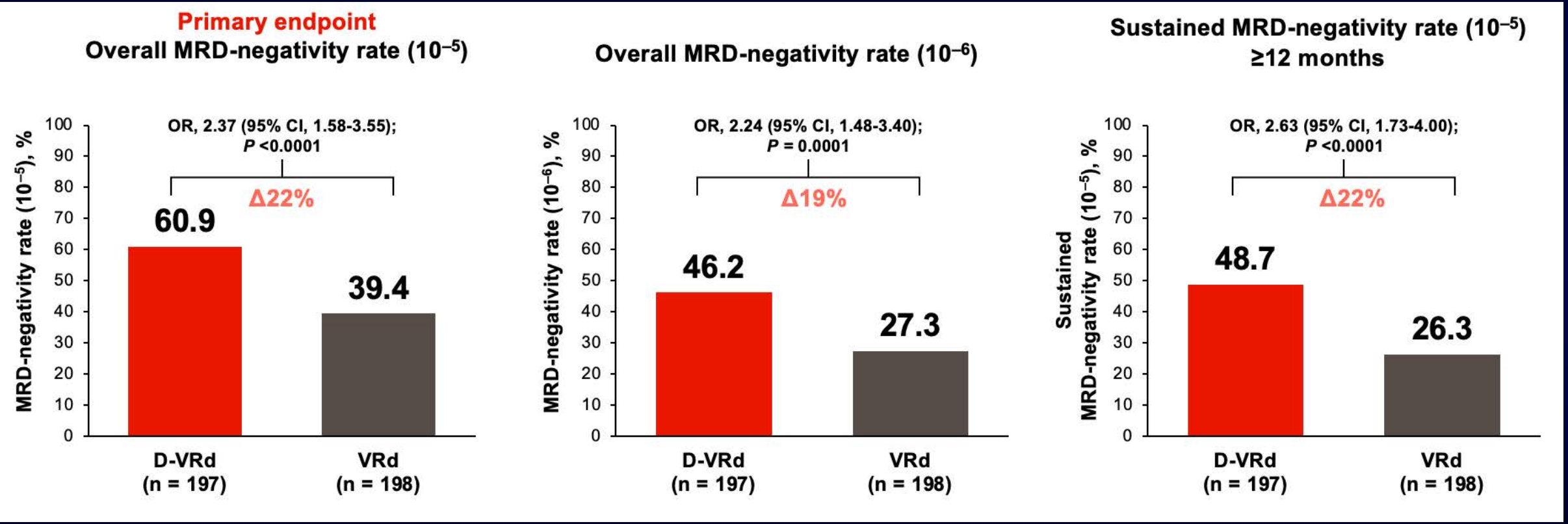
Usmani SZ et al. IMS 2024

Primary Endpoint, Response & Durability Data



Usmani SZ et al. IMS 2024

Other Notable MRD Findings



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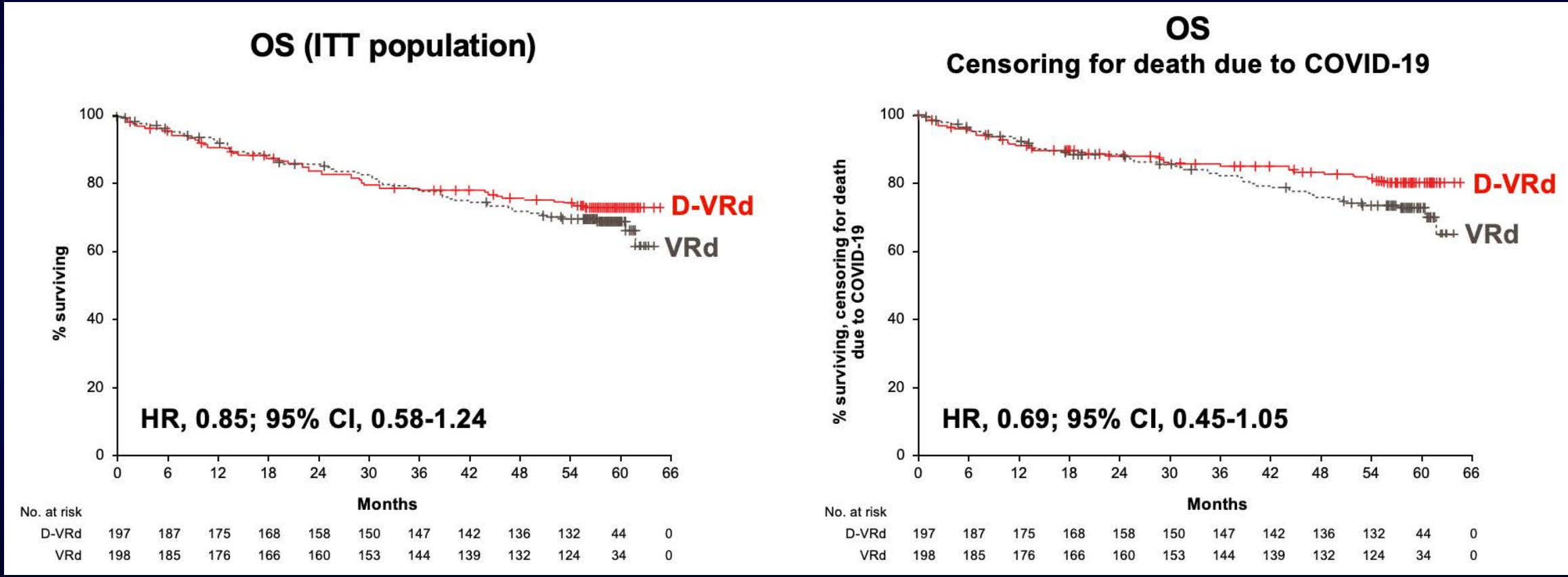
Longer Term Follow-Up



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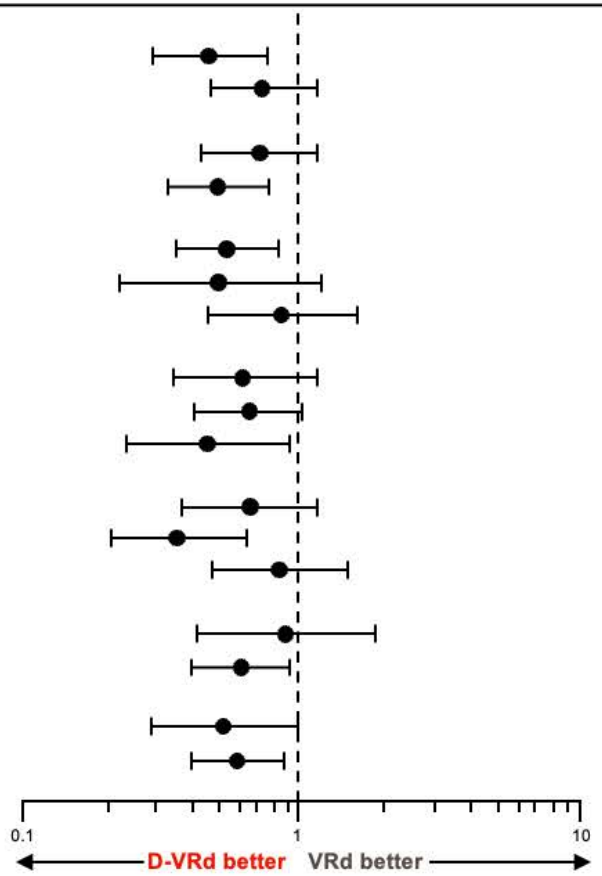
Subgroup Analyses

Subgroup	Disease progression or death, n/N		Median PFS, months		HR (95% CI)
	D-VRd	VRd	D-VRd	VRd	
Sex					
Male	24/87	53/111	NE	49.2	0.46 (0.29-0.75)
Female	39/110	38/87	NE	NE	0.73 (0.47-1.15)
Age					
<70 years	30/88	38/88	NE	NE	0.72 (0.44-1.16)
≥70 years	33/109	53/110	NE	49.4	0.50 (0.33-0.78)
Region					
Europe	37/120	54/116	NE	51.1	0.54 (0.36-0.82)
North America	10/37	13/31	NE	50.2	0.51 (0.22-1.17)
Other	16/40	24/51	NE	NE	0.87 (0.46-1.64)
Weight					
≤65 kg	17/58	24/63	NE	NE	0.62 (0.34-1.16)
>65-85 kg	34/101	40/88	NE	51.1	0.65 (0.41-1.02)
>85 kg	12/38	27/47	NE	41.9	0.46 (0.23-0.91)
ISS disease stage					
I	21/68	28/68	NE	60.6	0.66 (0.37-1.16)
II	18/73	37/75	NE	45.6	0.36 (0.21-0.64)
III	24/56	26/55	NE	49.2	0.84 (0.48-1.46)
Cytogenetic risk					
High risk	13/25	17/27	39.8	31.7	0.88 (0.42-1.84)
Standard risk	43/149	60/149	NE	60.6	0.61 (0.41-0.91)
ECOG PS score					
0	16/71	30/84	NE	NE	0.53 (0.29-0.97)
≥1	47/126	61/114	NE	43.8	0.59 (0.40-0.86)



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Safety & Common AEs

TEAE, n (%)	D-VRd (n = 197)		VRd (n = 195)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
HEMATOLOGIC				
Blood and lymphatic system disorders	163 (82.7)	126 (64.0)	126 (64.6)	98 (50.3)
Neutropenia	110 (55.8)	87 (44.2)	76 (39.0)	58 (29.7)
Thrombocytopenia	92 (46.7)	56 (28.4)	66 (33.8)	39 (20.0)
Anemia	73 (37.1)	26 (13.2)	62 (31.8)	23 (11.8)
NONHEMATOLOGIC				
Gastrointestinal disorder	157 (79.7)	41 (20.8)	159 (81.5)	40 (20.5)
Diarrhea	112 (56.9)	24 (12.2)	115 (59.0)	18 (9.2)
Constipation	75 (38.1)	4 (2.0)	82 (42.1)	5 (2.6)
General disorders and administration-site conditions	159 (80.7)	40 (20.3)	147 (75.4)	28 (14.4)
Peripheral edema	83 (42.1)	4 (2.0)	76 (39.0)	1 (0.5)
Fatigue	63 (32.0)	18 (9.1)	60 (30.8)	16 (8.2)
Psychiatric disorders	91 (46.2)	10 (5.1)	96 (49.2)	10 (5.1)
Insomnia	63 (32.0)	4 (2.0)	63 (32.3)	2 (1.0)
Infections	181 (91.9)	79 (40.1)	167 (85.6)	62 (31.8)
Upper respiratory tract infection	78 (39.6)	1 (0.5)	64 (32.8)	1 (0.5)
COVID-19	75 (38.1)	22 (11.2)	48 (24.6)	9 (4.6)
Second primary malignancies	15 (7.6)	–	18 (9.2)	–

	Any grade	Grade 2	Grade 3 or 4	Any grade	Grade 2	Grade 3 or 4
Peripheral sensory neuropathy	110 (55.8)	60 (30.5)	16 (8.1)	119 (61.0)	70 (35.9)	16 (8.2)

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Maintenance Therapy & α-CD38s

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[h] (category 1)
Other Recommended Regimens • Carfilzomib/lenalidomide[i,h] • Daratumumab/lenalidomide[i,h]
Useful In Certain Circumstances • Bortezomib ± lenalidomide[i,h] • Ixazomib (category 2B)

NCCN Guidelines for Multiple Myeloma; Version 1.2025

AURIGA Study

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Key Inclusion Criteria

- Age 18-79 years
- NDMM with ≥4 cycles of induction therapy
- ≥VGPR at screening[a]
- MRD positive (10^{-5}) post-ASCT[b] at the time of screening
- Randomization within 6 months of ASCT date
- HDT and ASCT within 12 months of the start of the induction treatment
- ECOG PS ≤2

Key Exclusion Criteria

- Prior anti-CD38 antibody exposure

1:1 Randomization (N = 200)

28-day cycles

Maintenance: up to 36 cycles[c] (28-day cycles)

D-R
D: 1800 mg SC[d] QW in cycles 1-2, Q2W in cycles 3-6, Q4W in cycles 7+
+
R: 10 mg PO QD[e] on days 1-28

R
10 mg PO QD[e] on days 1-28

Continue until unacceptable toxicity, disease progression, consent withdrawal, or for a maximum of 36 cycles

Primary Endpoint

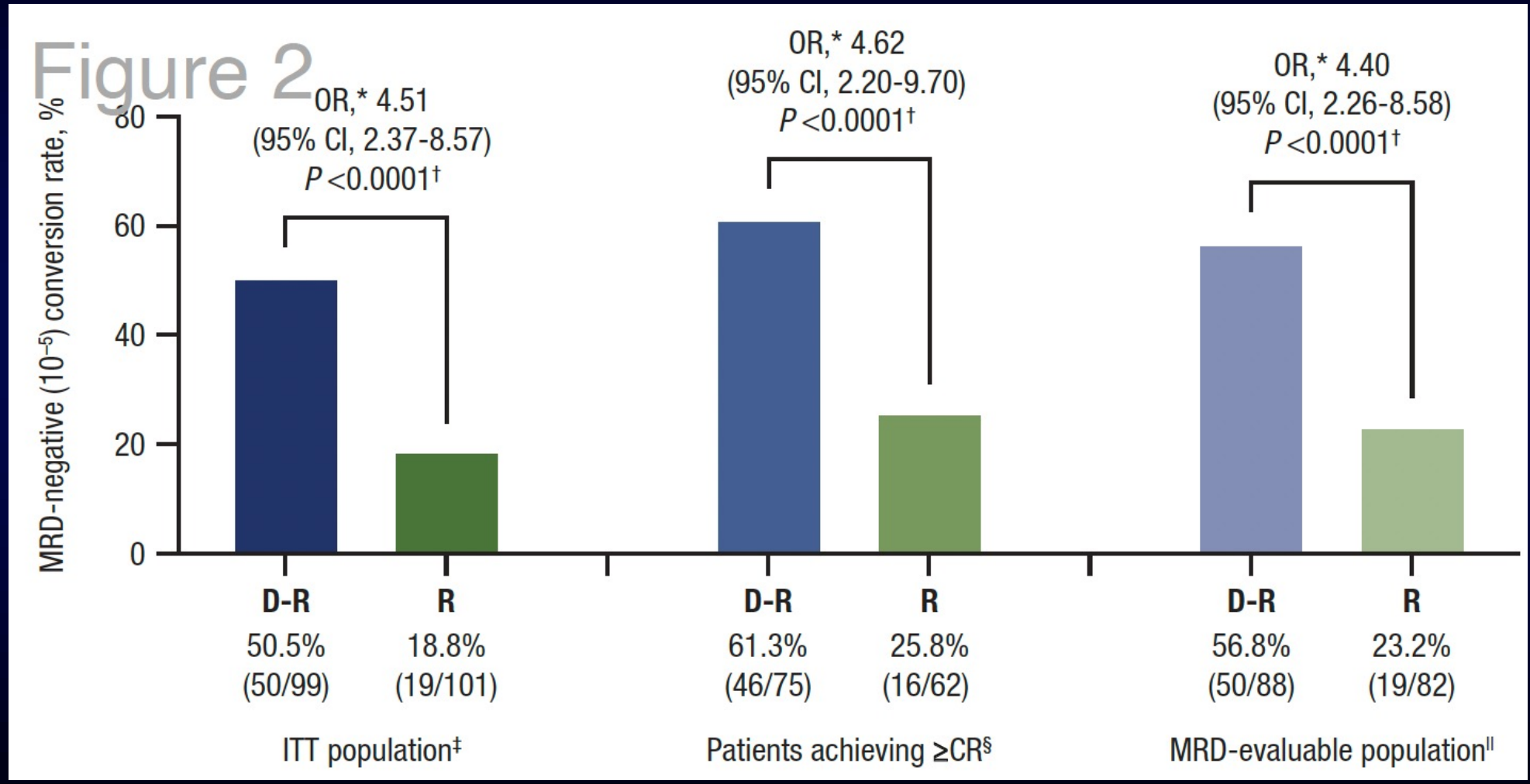
- MRD-negativity (10^{-5}) conversion rate from baseline to 12 months[e]
  - MRD assessed at 12, 18, 24, and 36 months

Key Secondary Endpoints

- Safety
- PFS
- Overall MRD-negativity conversion rate
- Sustained MRD-negativity rate (≥6 months)
- Response rates including CR/sCR[a]
- Duration of ≥CR
- OS
- HRQoL changes based on PROs

Badros AZ et al. Blood. Published online September 27, 2024.

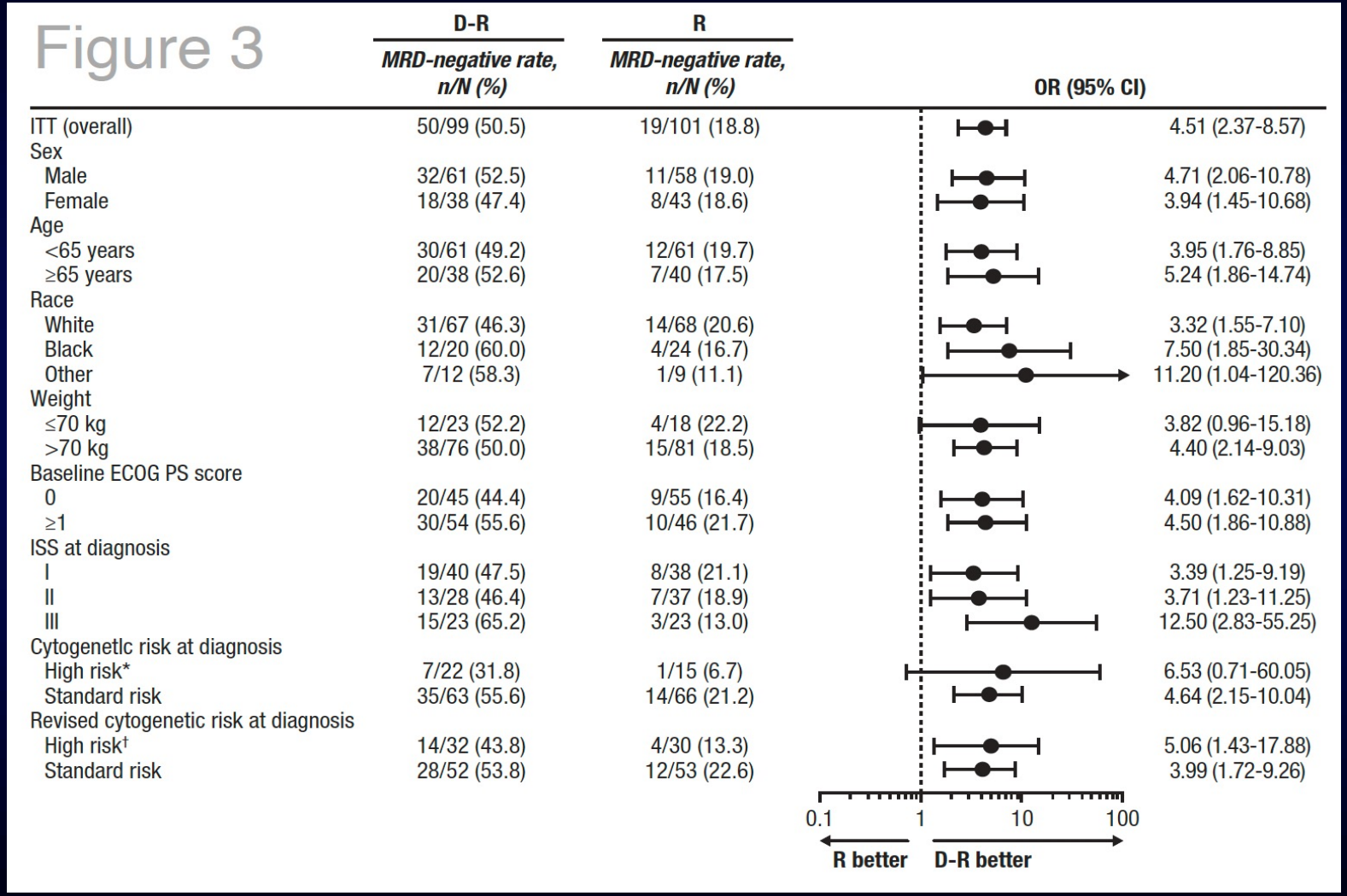
MRD Conversion Rate



Badros AZ et al. Blood. Published online September 27, 2024.

Subgroup Analyses

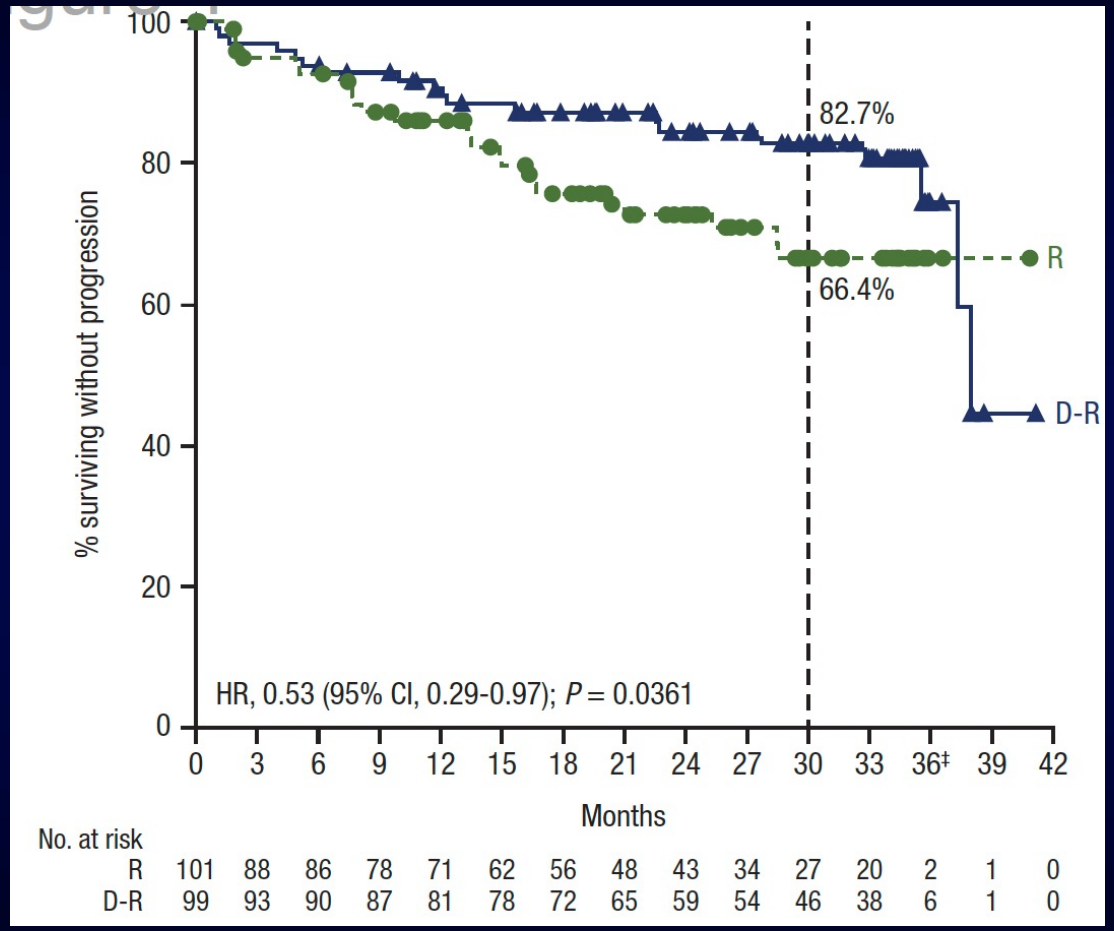
Figure 3

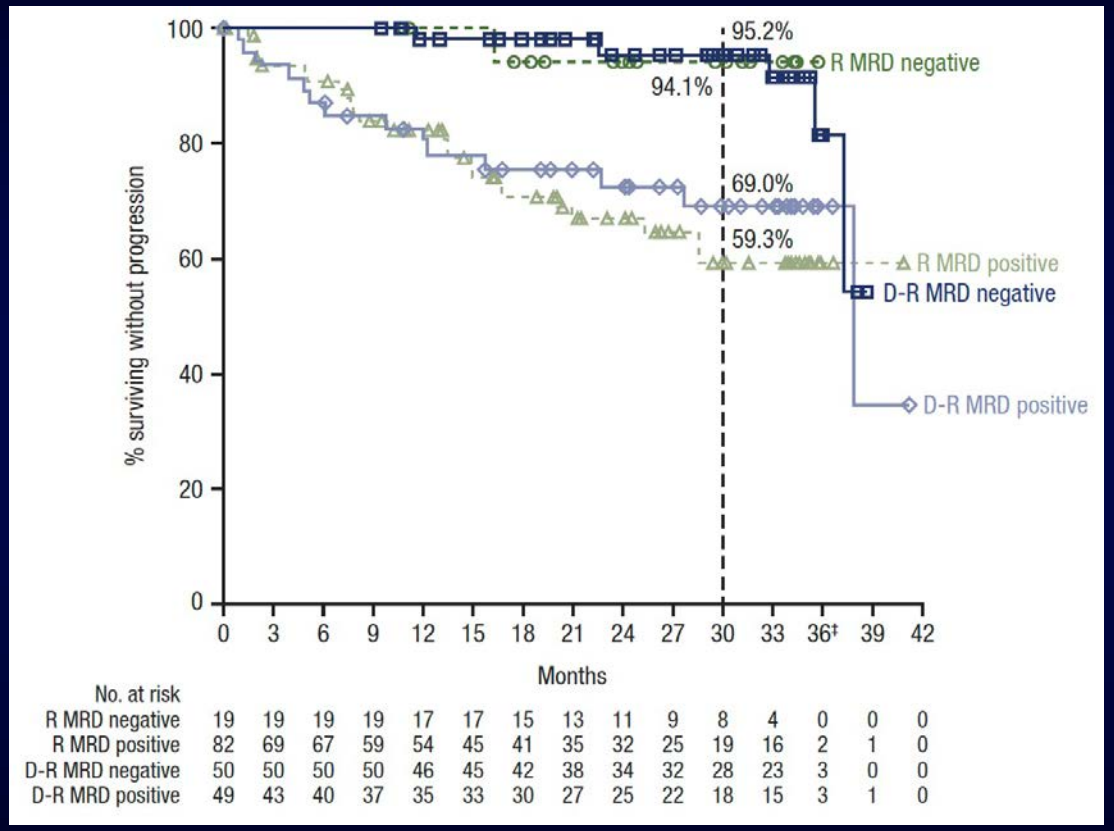


	D-R MRD-negative rate, n/N (%)	R MRD-negative rate, n/N (%)	OR (95% CI)
ITT (overall)	50/99 (50.5)	19/101 (18.8)	4.51 (2.37-8.57)
Sex			
Male	32/61 (52.5)	11/58 (19.0)	4.71 (2.06-10.78)
Female	18/38 (47.4)	8/43 (18.6)	3.94 (1.45-10.68)
Age			
<65 years	30/61 (49.2)	12/61 (19.7)	3.95 (1.76-8.85)
≥65 years	20/38 (52.6)	7/40 (17.5)	5.24 (1.86-14.74)
Race			
White	31/67 (46.3)	14/68 (20.6)	3.32 (1.55-7.10)
Black	12/20 (60.0)	4/24 (16.7)	7.50 (1.85-30.34)
Other	7/12 (58.3)	1/9 (11.1)	11.20 (1.04-120.36)
Weight			
≤70 kg	12/23 (52.2)	4/18 (22.2)	3.82 (0.96-15.18)
>70 kg	38/76 (50.0)	15/81 (18.5)	4.40 (2.14-9.03)
Baseline ECOG PS score			
0	20/45 (44.4)	9/55 (16.4)	4.09 (1.62-10.31)
≥1	30/54 (55.6)	10/46 (21.7)	4.50 (1.86-10.88)
ISS at diagnosis			
I	19/40 (47.5)	8/38 (21.1)	3.39 (1.25-9.19)
II	13/28 (46.4)	7/37 (18.9)	3.71 (1.23-11.25)
III	15/23 (65.2)	3/23 (13.0)	12.50 (2.83-55.25)
Cytogenetlc risk at diagnosis			
High risk*	7/22 (31.8)	1/15 (6.7)	6.53 (0.71-60.05)
Standard risk	35/63 (55.6)	14/66 (21.2)	4.64 (2.15-10.04)
Revised cytogenetic risk at diagnosis			
High risk†	14/32 (43.8)	4/30 (13.3)	5.06 (1.43-17.88)
Standard risk	28/52 (53.8)	12/53 (22.6)	3.99 (1.72-9.26)

Badros AZ et al. Blood. Published online September 27, 2024.

Longer-Term Data

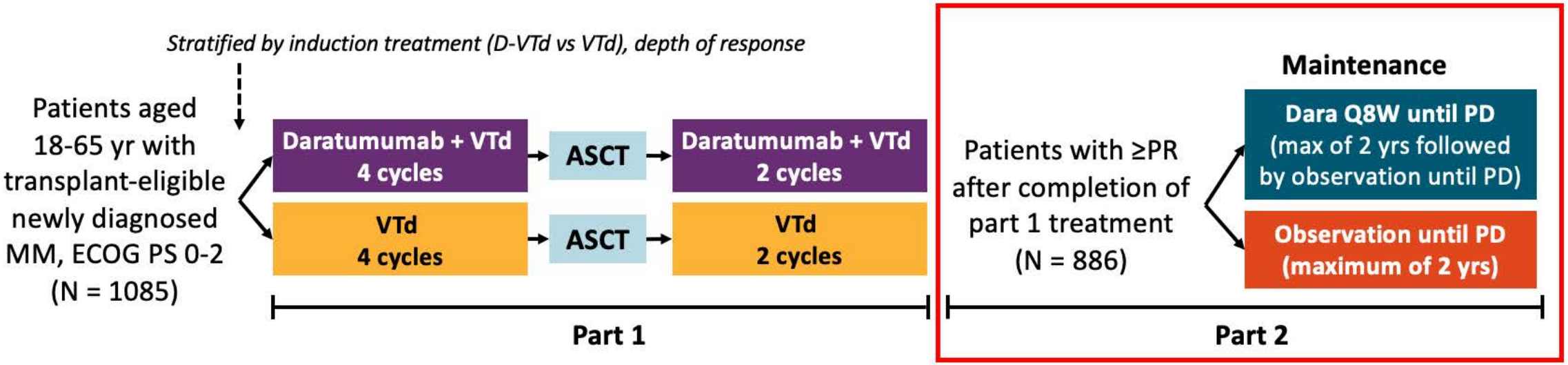




Badros AZ et al. Blood. Published online September 27, 2024.

Updated CASSIOPEIA Data

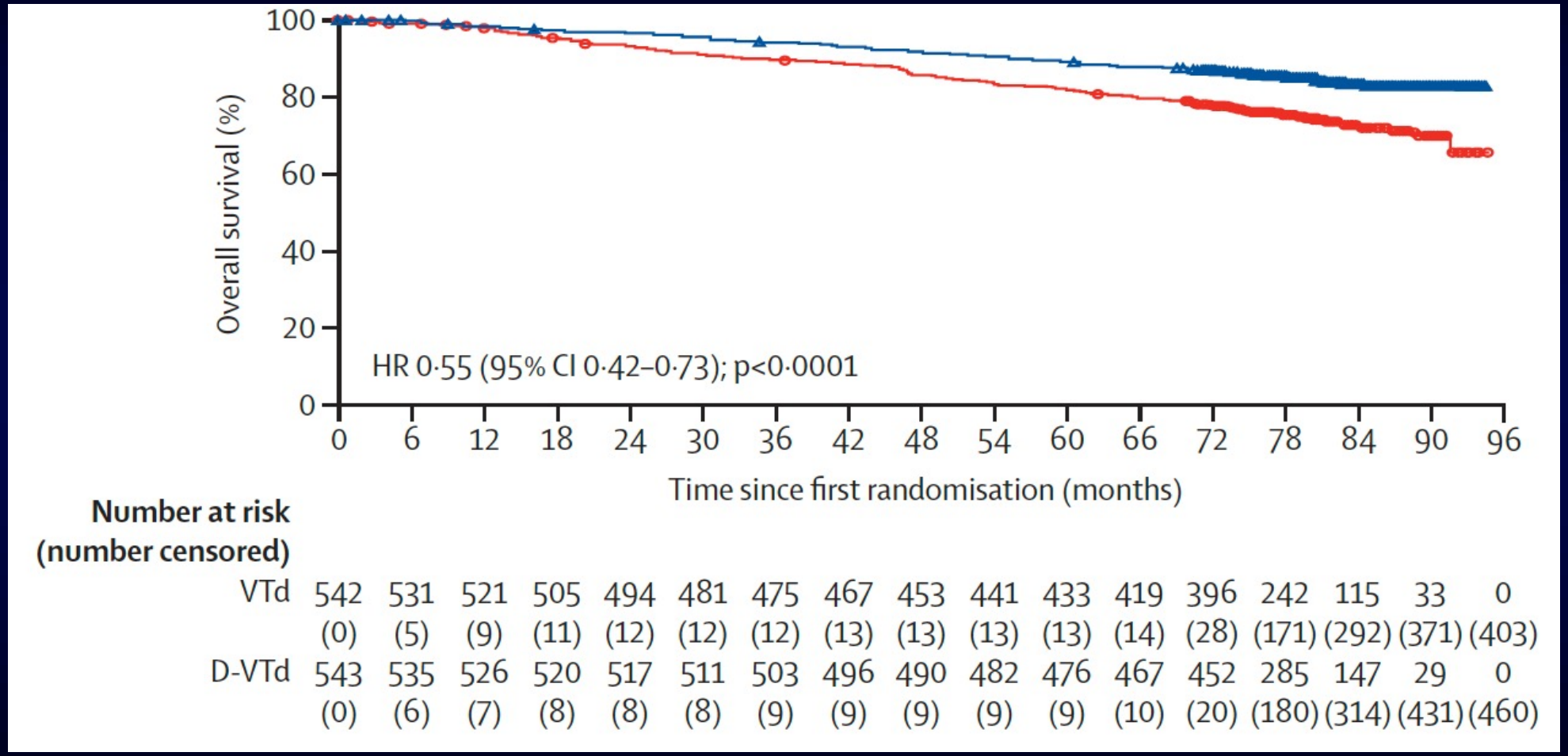
- Open-label, global, multicenter, randomized phase III trial



- **Primary endpoint (part 2):** PFS (after second randomization)
- **Key secondary endpoints (part 2):** TTP (after second randomization), rates of ≥CR, MRD negativity rates (in ≥CR at a threshold of 10^{-5} by NGS), OS

Moreau P et al. Lancet Oncol. 2024;25(8):1003-1014.

PFS & OS From Randomization #1

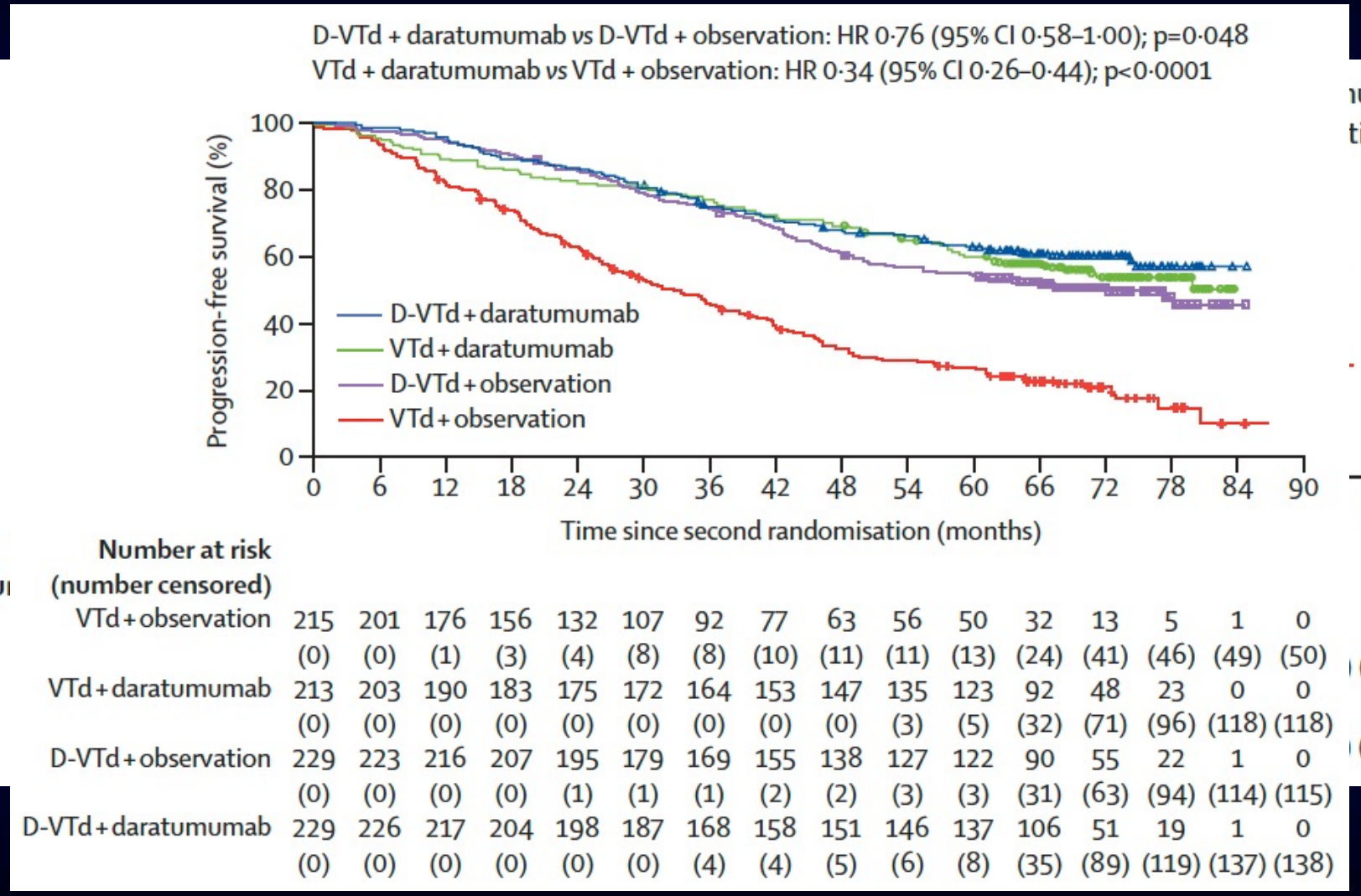


Number at risk (number censored)

VTd	542	531	521	505	494	481	475	467	453	441	433	419	396	242	115	33	0
	(0)	(5)	(9)	(11)	(12)	(12)	(12)	(13)	(13)	(13)	(13)	(14)	(28)	(171)	(292)	(371)	(403)
D-VTd	543	535	526	520	517	511	503	496	490	482	476	467	452	285	147	29	0
	(0)	(6)	(7)	(8)	(8)	(8)	(9)	(9)	(9)	(9)	(9)	(10)	(20)	(180)	(314)	(431)	(460)

Moreau P et al. Lancet Oncol. 2024;25(8):1003-1014.

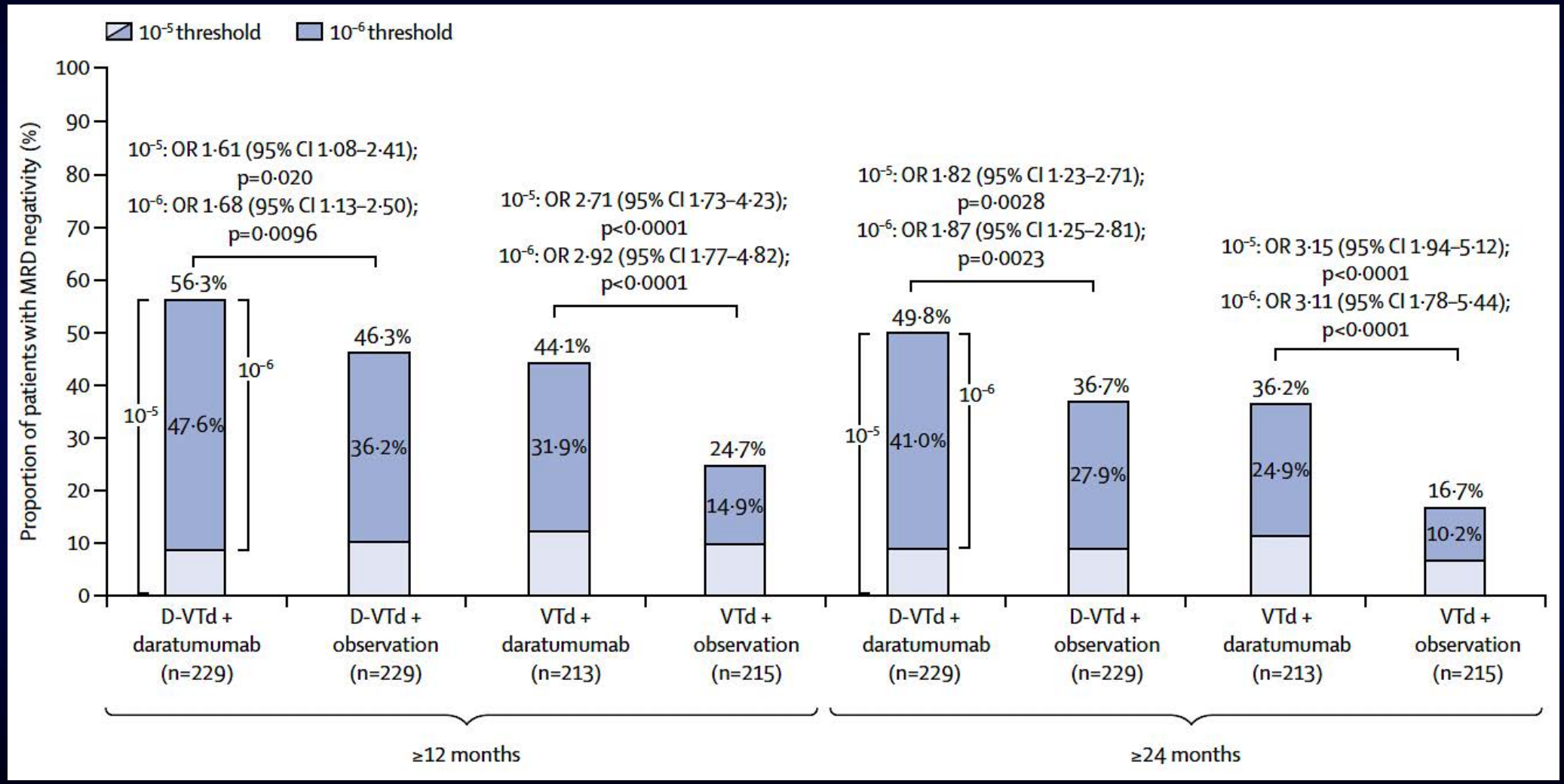
PFS From Randomization #2



Number at risk (number censored)																
VTd + observation	215 (0)	201 (0)	176 (1)	156 (3)	132 (4)	107 (8)	92 (8)	77 (10)	63 (11)	56 (11)	50 (13)	32 (24)	13 (41)	5 (46)	1 (49)	0 (50)
VTd + daratumumab	213 (0)	203 (0)	190 (0)	183 (0)	175 (0)	172 (0)	164 (0)	153 (0)	147 (0)	135 (3)	123 (5)	92 (32)	48 (71)	23 (96)	0 (118)	0 (118)
D-VTd + observation	229 (0)	223 (0)	216 (0)	207 (0)	195 (1)	179 (1)	169 (1)	155 (2)	138 (2)	127 (3)	122 (3)	90 (31)	55 (63)	22 (94)	1 (114)	0 (115)
D-VTd + daratumumab	229 (0)	226 (0)	217 (0)	204 (0)	198 (0)	187 (0)	168 (4)	158 (4)	151 (5)	146 (6)	137 (8)	106 (35)	51 (89)	19 (119)	1 (137)	0 (138)

Moreau P et al. Lancet Oncol. 2024;25(8):1003-1014.

Post-hoc MRD Analysis



Moreau P et al. Lancet Oncol. 2024;25(8):1003-1014.

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Induction Conclusions

- Quadruplet induction regimens are the standards of care for both TE and TIE patients
  - α-CD38s + PI + IMiD + dex
- Triplets remain reasonable in some scenarios
  - Severe neuropathy / other drug tolerance
  - Frailty or significant comorbid medical challenges & access

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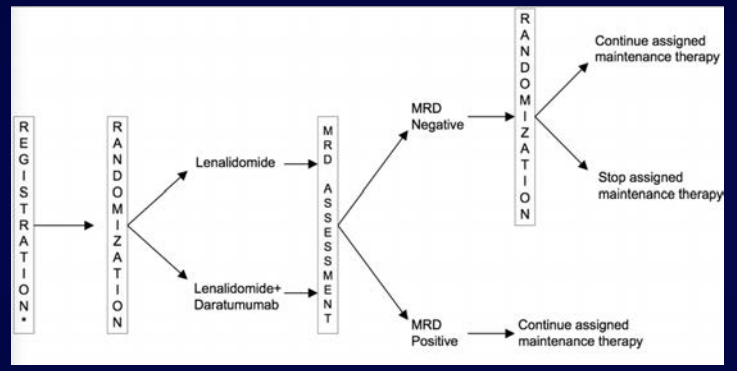
Maintenance Conclusions

- Continuation of Len/α-CD38 after prior quadruplet regimen seems reasonable
  - Higher MRD$^-$ rates and likely PFS
  - SWOG-S1803 trial
- Landscape remains unclear in some areas
  - Frail patients: Len vs. Dara/len
  - High-risk patients: Len/α-CD38 vs. Len/PI vs. triplet?



Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Orlowski

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory MM — Dr Richardson

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies for the Treatment of MM — Prof Moreau

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Lonial

RTP
RESEARCH
TO PRACTICE

Case Presentation: 60-year-old woman with multiple regimen-relapsed MM and poor tolerance of IMiDs and proteasome inhibitors receives CAR-T therapy

Dr Susmitha Apuri (Inverness and Lecanto, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you approach sequencing of systemic therapies for patients with poor tolerance of IMiDs and proteasome inhibitors?

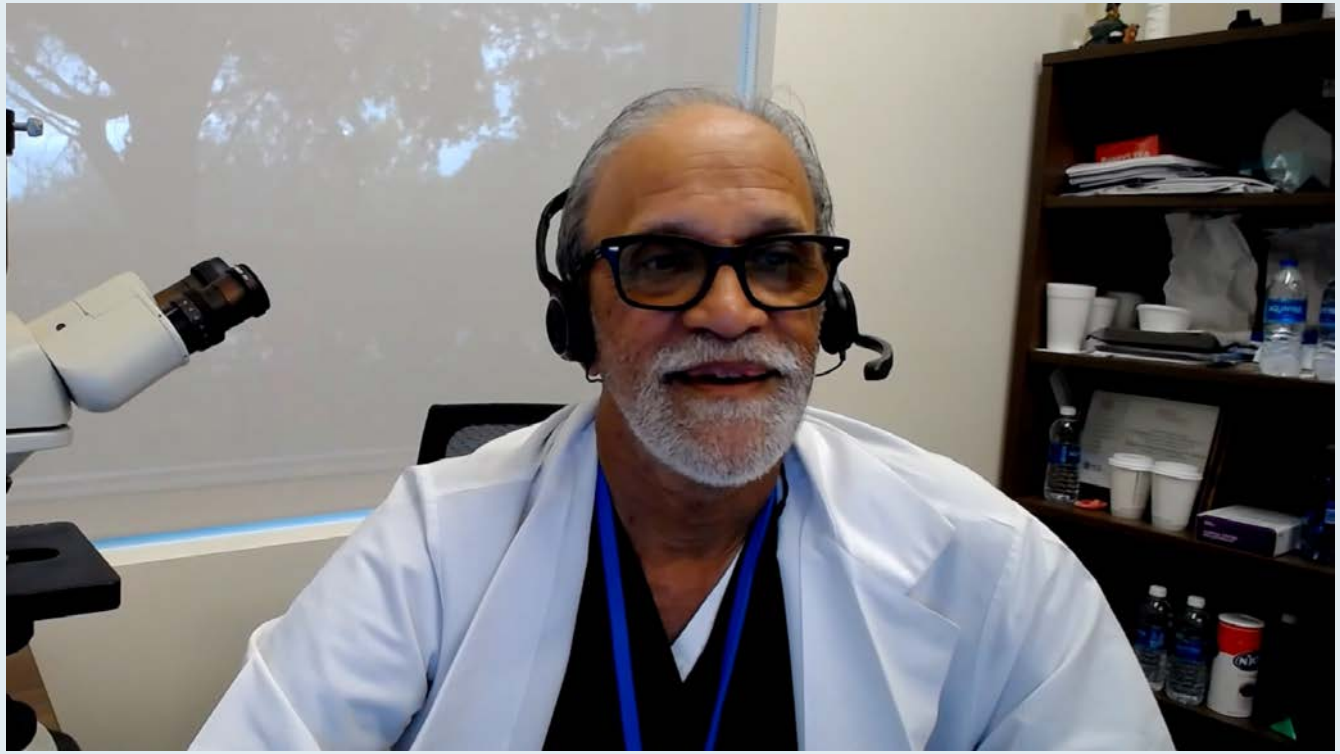
In which situations do you recommend selinexor, and what do you partner it with?

What starting dose and schedule of selinexor do you generally recommend, and how do you approach dose modification for patients experiencing toxicity?

What preemptive medications do you recommend for patients about to begin treatment with selinexor?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 64-year-old man with acute renal insufficiency, large lytic lesion in the skull and newly diagnosed standard-risk MM



Dr KS Kumar (Trinity, Florida)

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QUESTIONS FOR THE FACULTY

What is your usual induction treatment for patients with acute renal insufficiency, including those on dialysis?

How would you approach the care of a patient with a large area of radiation-related necrosis in the skull? What has been your experience with the use of titanium implants?

What is your experience with kyphoplasty for patients with vertebral lesions, and what innovative local strategies are you using for the management of bone lesions in MM?

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Integration of Novel Therapies into the Management of Relapsed/Refractory (R/R) MM

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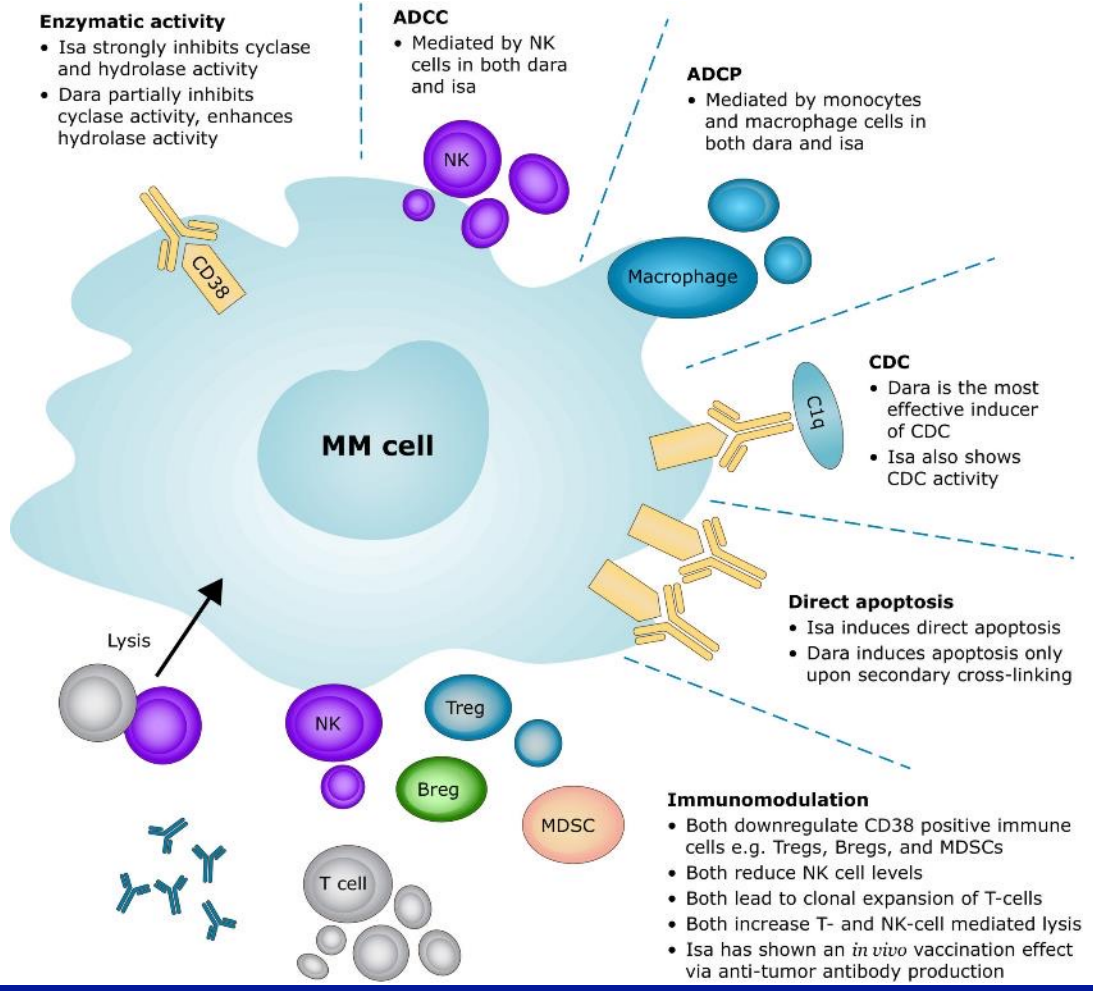
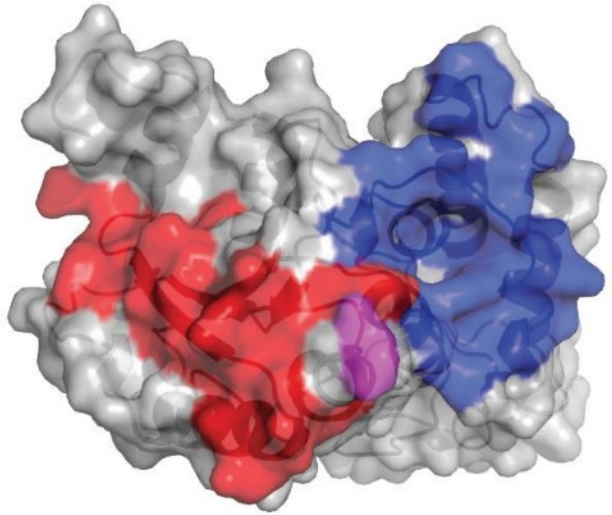
DANA-FARBER CANCER INSTITUTE

VE RI TAS

Isatuximab: a distinct CD38 mAb

Differing relative contributions to mechanisms of action of daratumumab and isatuximab[1–3]





Distinct epitopes on human CD38 interact with daratumumab (red) and isatuximab (blue), potentially contributing to distinct mechanisms of action[3]

Isatuximab epitope includes catalytic domain of CD38 – isatuximab inhibits NAD+ substrate and thus the production of immune-suppressing adenosine[4]

Distinct characteristics[3,5-7]

Isatuximab saturates membrane CD38 and can be internalized – different membrane dynamics vs daratumumab	ADCC, ADCP, CDC with isatuximab triggered at threshold of surface CD38	Isatuximab inhibits CD38 enzymatic features	Isatuximab can directly induce cell death without crosslinking[7]	Isatuximab induces NK cell activation and NK cell-mediated cytotoxicity through CD38 and CD16 crosslinking[3]

Daratumumab and isatuximab potentially valuable as complementary / alternative therapies[5]

1. Bisht K, et al. Cancer Med 2023;12(20):20332–52 (left-hand figure reproduced under Creative Commons BY 4.0 license). 2. van de Donk NWCJ, et al. Blood 2018;131(1):13–29.
3. Zhu C, et al. Front Immunol 2020;11:1771. 4. Martin TG, et al. Cells 2019;8(12):1522 (right-hand figure reproduced under Creative Commons BY 4.0 license).
5. Malavasi F, Faini AC. Clin Cancer Res 2019;25(10):2946–8. 6. Moreno L, et al. Clin Cancer Res 2019;25(10):3176–87. 7. Martino EA, et al. Expert Opin Biol Ther 2023;23(4):315–8.

Isa-based standard-of-care triplet regimens for early-relapse RRMM

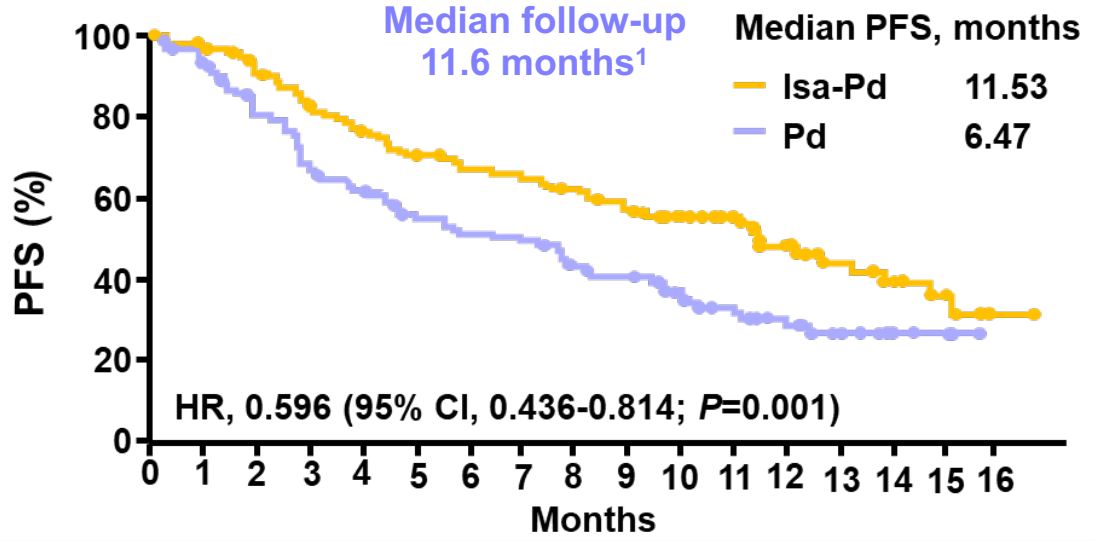
Isa-Pom-dex (ICARIA-MM)[1–3]

Phase 3 ICARIA-MM trial: Isa-Pom-dex (N=154) vs Pom-dex (N=153)

- Median age 68 vs 66 years; 21% vs 19% aged ≥75 years
- Median (IQR) 3 (2–4) prior lines of treatment in both arms
- ISS stage III at study entry: 22% vs 28%; high-risk cytogenetics: 16% vs 24%
- 100% PI- and lenalidomide-exposed in both arms
- 94% v 92% lenalidomide-refractory (60% vs 58% in last line); 77% vs 75% PI-refractory; 72% vs 70% double-refractory
- CD38 mAb-refractory patients excluded

Response[1]	Isa-Pom-dex	Pom-dex
ORR, %	60	35
≥VGPR	32	9
sCR	0	<1
CR	5	1
VGPR	27	7
PR	29	27
Median TTR, days	35	58
Median DOR, months	13.3	11.1

Safety, %[3]	Isa-Pom-dex	Pom-dex
Grade ≥3 AEs, %	91	76
Neutropenia	51	35
Pneumonia	23	21
Thrombo-cytopenia	13	12
SAEs	74	61
Fatal AEs	15	13
Discontinuation due to AEs	13	15
SPMs	7	2



PFS HR (95% CI)		
R-refractory	R-refractory in last line	R/PI-refractory
0.59 (0.43-0.82)	0.50 (0.34-0.76)	0.58 (0.40-0.84)

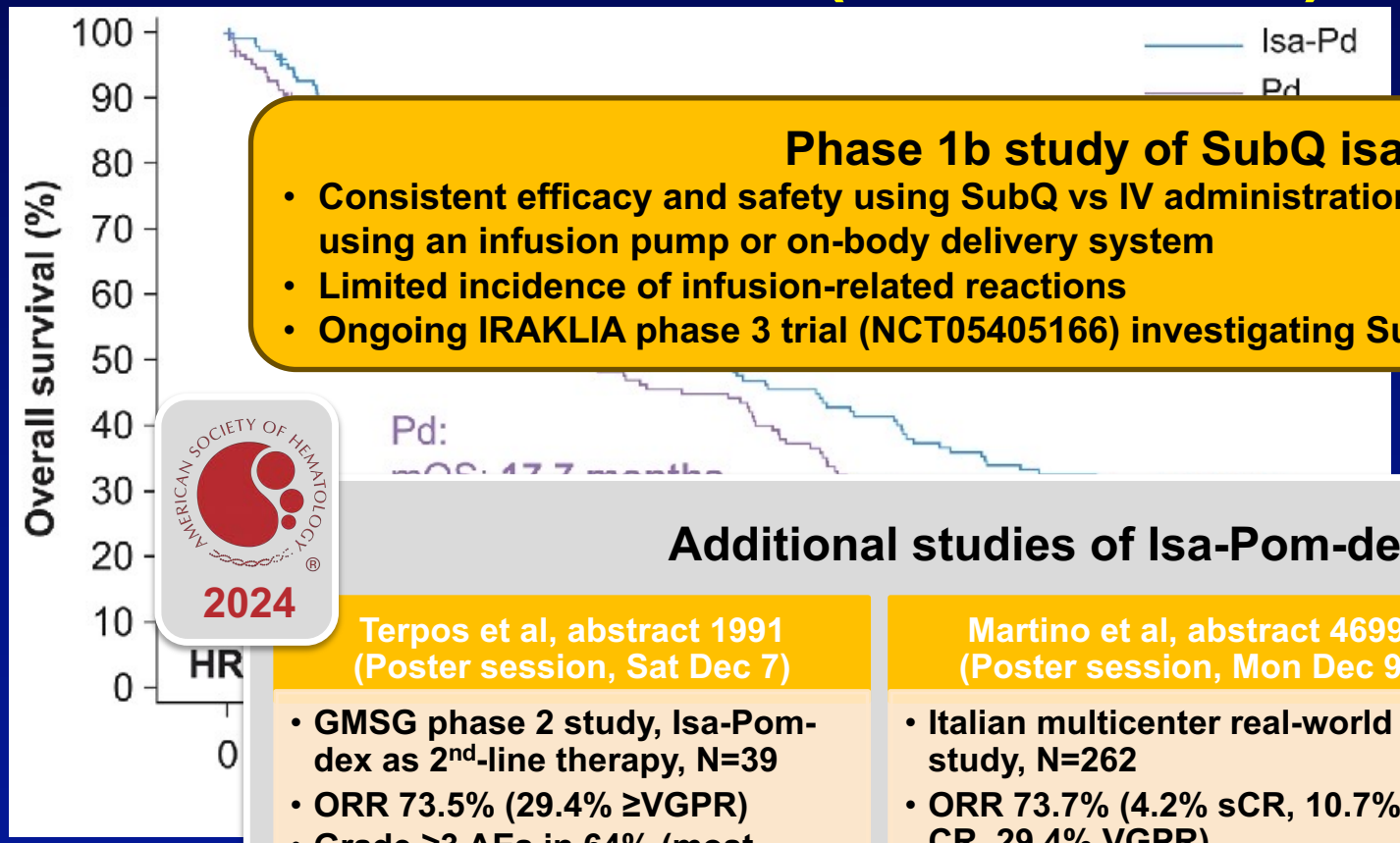
Benefit of Isa-Pom-dex vs Pom-dex seen in multiple subgroup analyses:

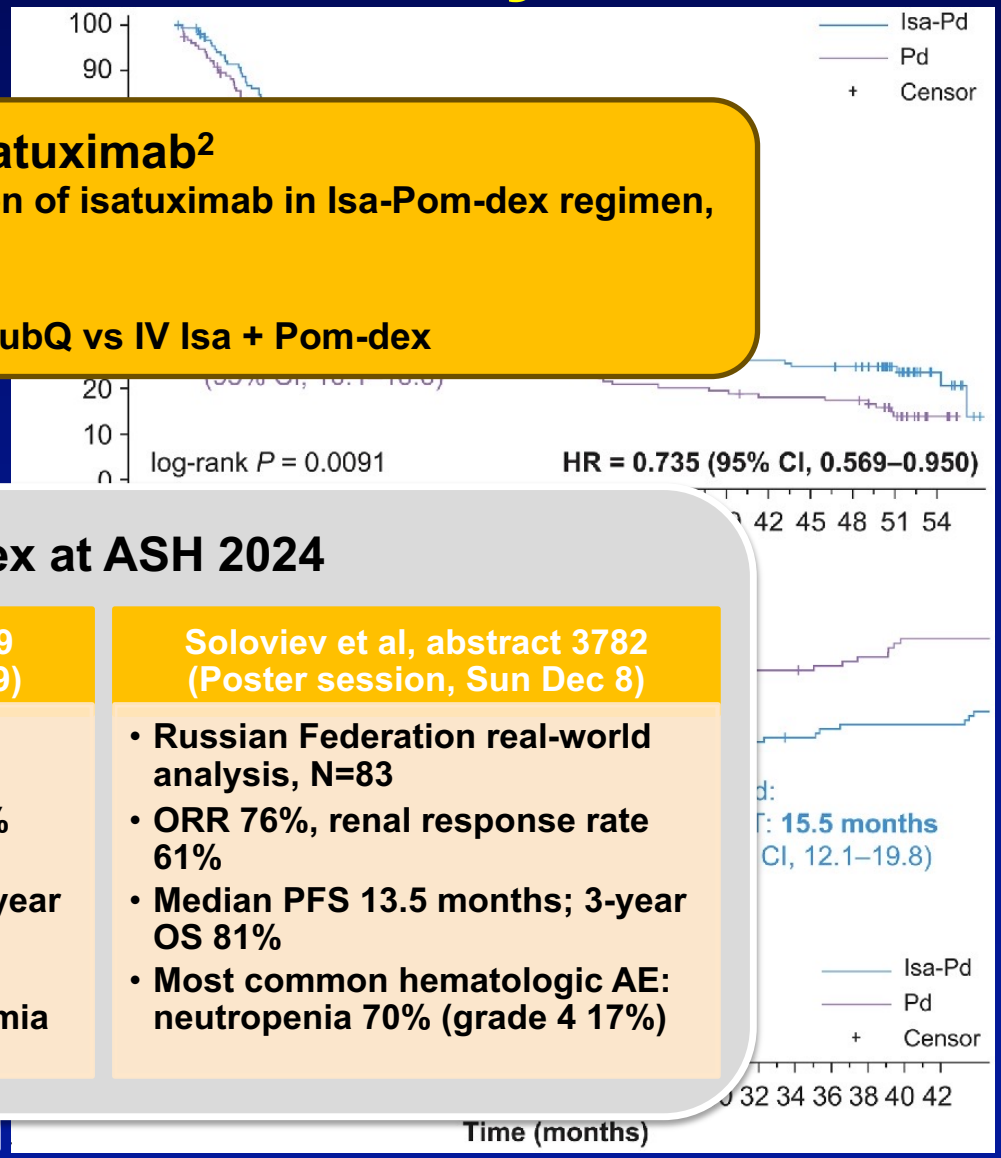
- Renal impairment: median PFS 9.5 vs 3.7 months (HR 0.50)[4]
- High-risk cytogenetics: median PFS 7.3 vs 3.7 months (HR 0.66)[5]
- Age ≥75 years: median PFS 11.4 vs 4.5 months (HR 0.48)[6]
- Frail pts: median PFS 9.0 vs 4.5 months (HR 0.81)[7]
- East Asian pts: median PFS NR vs 7.9 months (HR 0.52)[8]

1. Attal M, et al. Lancet 2019;394(10214):2096–107. 2. Richardson PG, et al. Lancet Oncol 2022;23(3):416–27. 3. Richardson PG, et al. Haematologica 2024;109(7):2239–49.
4. Dimopoulos MA, et al. Leukemia 2021;35(2):562–72. 5. Harrison SJ, et al. Br J Haematol 2021;194(1):120–31. 6. Schjesvold FH, et al. Haematologica 2021;106(4):1182–7.
7. Schjesvold FH, et al. Am J Hematol 2021;96(11):E423–7. 8. Sunami K, et al. Clin Lymphoma Myeloma Leuk 2022;22(8):e751–61.

Isa-based standard-of-care triplet regimens for early-relapse RRMM

Isa-Pom-dex (ICARIA-MM): final OS analysis[1]





Phase 1b study of SubQ isatuximab[2]

- Consistent efficacy and safety using SubQ vs IV administration of isatuximab in Isa-Pom-dex regimen, using an infusion pump or on-body delivery system
- Limited incidence of infusion-related reactions
- Ongoing IRAKLIA phase 3 trial (NCT05405166) investigating SubQ vs IV Isa + Pom-dex

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Additional studies of Isa-Pom-dex at ASH 2024

Terpos et al, abstract 1991 (Poster session, Sat Dec 7)

- GMSG phase 2 study, Isa-Pom-dex as 2nd-line therapy, N=39
- ORR 73.5% (29.4% ≥VGPR)
- Grade ≥3 AEs in 64% (most common: neutropenia in 46%)

Martino et al, abstract 4699 (Poster session, Mon Dec 9)

- Italian multicenter real-world study, N=262
- ORR 73.7% (4.2% sCR, 10.7% CR, 29.4% VGPR)
- Median PFS 15.4 months; 2-year OS 66.3%
- Grade 3/4 neutropenia 56%, thrombocytopenia 16%, anemia 14%

Soloviev et al, abstract 3782 (Poster session, Sun Dec 8)

- Russian Federation real-world analysis, N=83
- ORR 76%, renal response rate 61%
- Median PFS 13.5 months; 3-year OS 81%
- Most common hematologic AE: neutropenia 70% (grade 4 17%)

- Median OS
- Median PF
- Median TNT

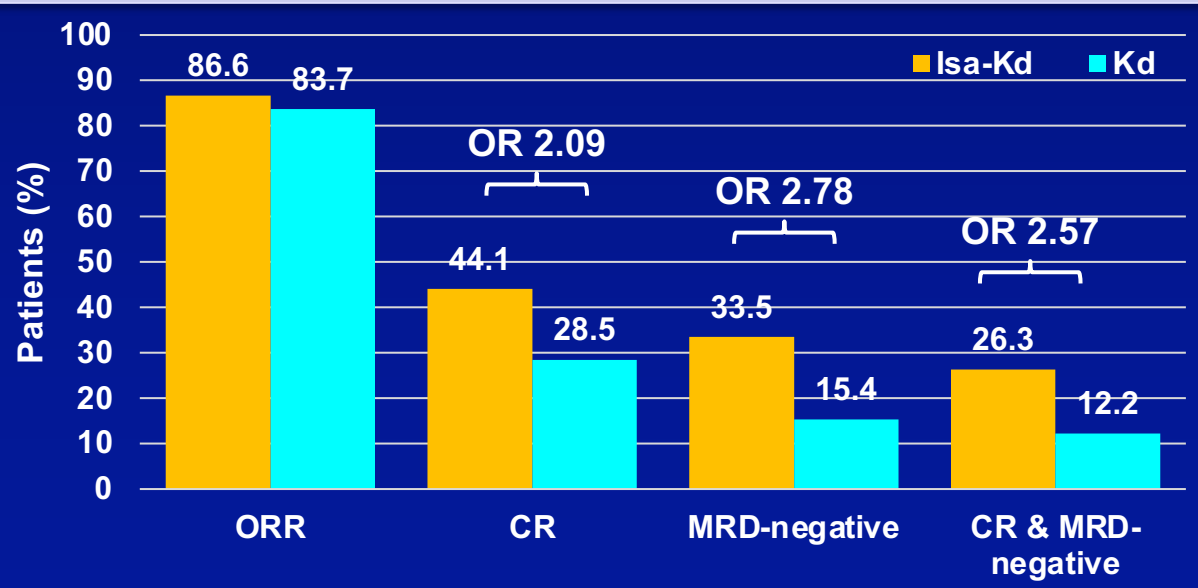
1. Richardson PG, et al. Haematologica 2024;109(7):2239–49. 2. Quach H, et al. Haematologica 2024;doi:10.3324/haematol.2023.284730.

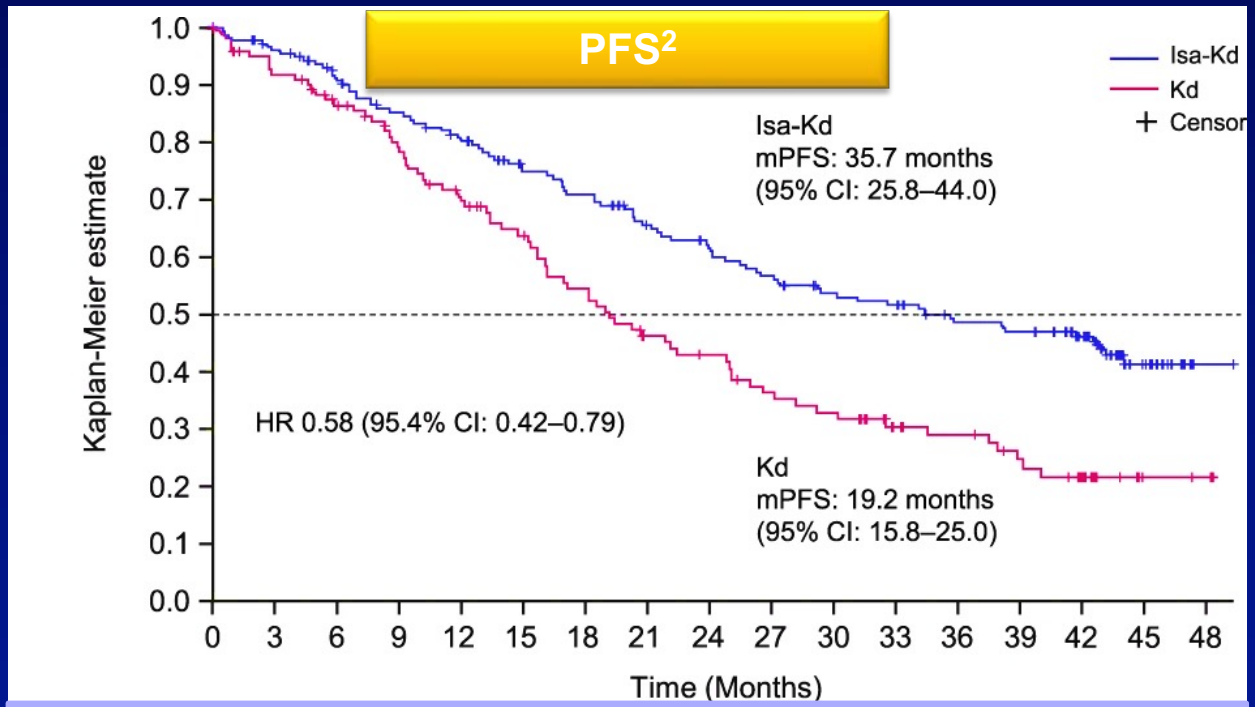
Isa-based standard-of-care triplet regimens for early-relapse RRMM

Isa-Kd (IKEMA)

Phase 3 IKEMA trial: Isa-Kd (N=179) vs Kd (N=123)[1,2]

- Median age 65 vs 63 years; 9.5% vs 8.1% aged ≥75 years
- Median (range) 2 (1–4) prior lines of treatment in both arms
- ISS stage III at baseline: 14.5% vs 16.3%; high-risk cytogenetics: 23.5% vs 25.2%
- 92.7% vs 85.4% prior PI; 76.0% vs 81.3% prior IMiDs
- 43.6% v 47.2% IMiD-refractory; 31.8% vs 34.1% lenalidomide-refractory; 31.3% vs 35.8% PI-refractory
- Patients with prior carfilzomib excluded





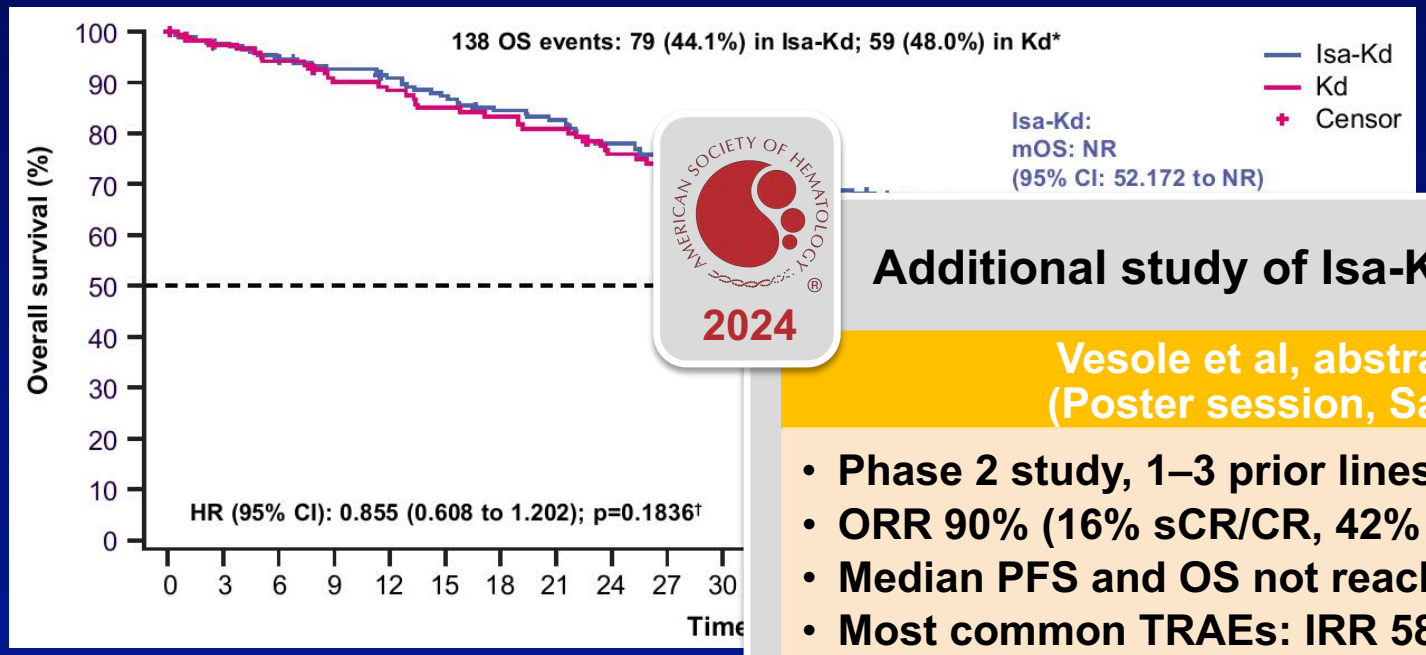
PFS benefit of Isa-Kd vs Kd seen in multiple subgroup analyses:

- MRD-neg (HR 0.58) and MRD-pos (HR 0.67) patients[3]
- Renal impairment: median NR vs 13.4 months (HR 0.27)[4]
- Elderly (≥70 years) patients: median NR vs 16.2 months (HR 0.36)[5]
- Prior ASCT: median NR vs 19.15 months (HR 0.60)[6]
- In pts with 1 prior line (HR 0.59) or >1 prior line (HR 0.48),[7] pts refractory to bortezomib (HR 0.62) or lenalidomide (HR 0.60)[7]
- Pts with 1q21+: median 25.8 vs 16.2 months (HR 0.58)[8]
- East Asian pts: median NR vs 18.5 months (HR 0.58)[9]

1. Moreau P, et al. Lancet 2021;397(10292):2361–71. 2. Martin T, et al. Blood Cancer J 2023;13(1):72. 3. Martin T, et al. Blood Adv 2022;6(15):4506–15. 4. Capra M, et al. Haematologica 2022;107(6):1397–409. 5. Facon T, et al. Hematol Oncol 2022;40(5):1020–9. 6. Martin TG, et al. Transplant Cell Ther 2023;29(2):134.e1–134.e7. 7. Dimopoulos MA, et al. Am J Hematol 2023;98(1):E15–19. 8. Facon T, et al. Hematol Oncol 2024;42(2):e3258. 9. Kawano Y, et al. Clin Lymphoma Myeloma Leuk 2023;23(10):e360–7.

Isa-based standard-of-care triplet regimens for early-relapse RRMM

Isa-Kd (IKEMA): updated analysis and safety



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Additional study of Isa-Kd at ASH 2024

Vesole et al, abstract 1982
(Poster session, Sat Dec 7)

- Phase 2 study, 1–3 prior lines of therapy, N=50
- ORR 90% (16% sCR/CR, 42% VGPR, 32% PR)
- Median PFS and OS not reached
- Most common TRAEs: IRR 58%, hypertension 52%, nausea 50%, cough 42%, fatigue 40%, dyspepsia 40%

Updated analysis

- Median follow-up 56.6 months
- Median OS NR vs 50.6 months, 48-month OS 59.7% vs 52.2%, HR 0.855
- Median PFS2 47.2 vs 32.4 months, HR 0.663
- Median TNT 44.0 vs 25.0 months, HR 0.583

Safety, %[1–3]	Isa-Kd	Kd
Grade ≥3 AEs[1,2]	84.2	73.0
SAEs[1,2]	71.2	60.7
	6.8	4.9
Es[1,2]	13.6	18.0
ic		
	22.6	23.0
	18.6	12.3
	6.2	2.5
	5.6	0.8
	5.6	0.8
Cardiac failure SMQ[1,2]	8.5	8.2
Grade ≥3	4.5	4.1

Matching adjusted indirect comparison analysis, IKEMA vs Dara-Rd (POLLUX), suggested significant PFS benefit and trend for OS benefit with Isa-Kd[4]

1. Yong K, et al. IMS 2023, abstract OA-48. 2. Yong K, et al. Lancet Haematol 2024;11(10):e741–50. 3. Martin T, et al. Blood Cancer J 2023;13(1):72.
4. Richter J, et al. Blood 2023;142(suppl 1):abstract 6734.

Ongoing studies of isa-based quadruplet regimens and novel combinations in RRMM

Study	Regimen	Phase	ClinicalTrials.gov	N	Setting	Primary endpoint	Initial completion
Quadruplet regimens							
IMPEDE[1]	Isa + Elo-Pom-dex	2	NCT04835129	~53	• ≥2 prior lines; prior R and a PI • Refractory to most recent line	Response rates	January 2025
IFM 2018-03[2]	Isa + K-Pom-dex	2	NCT04287855	82	• 1 or 2 prior lines, including R	MRD-neg	April 2025
NCI-2021-03406	Isa + K-Pom-dex	2	NCT04883242	~37	• ≥1 prior line, prior R	ORR	December 2029
ISABELA	Isa + Belamaf-Pom-dex	2	NCT05922501	~50	• ≥1 prior line	ORR	December 2025

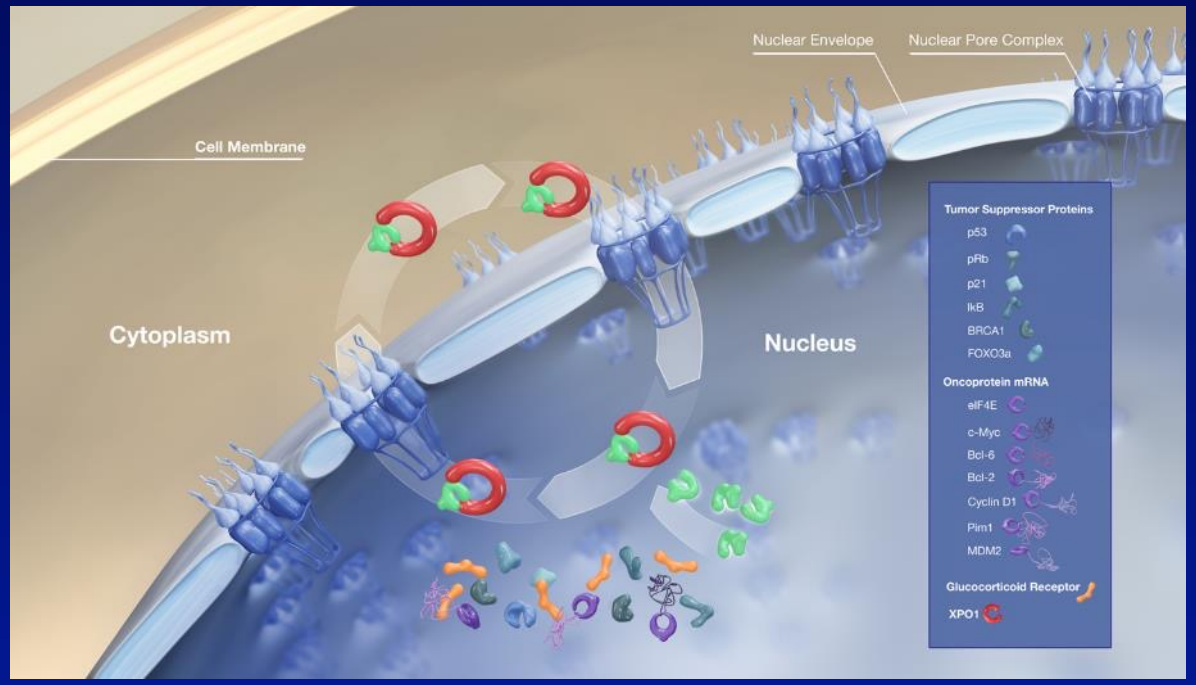
ClinicalTrials.gov, November 14, 2024. 1. Dhakal B, et al. Blood 2023;142(suppl 1):abstract 3379. 2. Bobin A, et al. Blood 2023;142(suppl 1):abstract 6742.

Novel targeted therapies for RRMM

Selinexor: Mechanism of action – inhibition of XPO1[1–4]

XPO1 overexpression

1. Enables cancer cells to escape tumor suppressor proteins (TSPs) mediated cell cycle arrest and induction of apoptosis
2. Correlates with poor prognosis and drug resistance



Inhibition of XPO1 impacts tumor cells via 3 core mechanisms

1. Increases nuclear levels and activation of TSPs
2. Traps oncoprotein mRNA in the nucleus leading to reduced oncoprotein levels
3. Retains activated glucocorticoid receptor in the nucleus

Selinexor is an oral selective XPO1 inhibitor; preclinical data demonstrate that, in MM models, selinexor:

- Reactivates multiple TSPs relevant to MM, inhibits NF-kB signaling and reduces c-Myc levels
- Reactivates GR signaling in combination with dexamethasone
- Demonstrates synergistic activity in combination with bortezomib, pomalidomide, and lenalidomide in vitro and in vivo
- Enhanced NK cell activity against MM cells[5]

1. Gupta A, et al. J Thorac Oncol 2017;12(9):1446–50. 2. Sun Q, et al. Signal Transduct Target Ther 2016;1:16010.
3. Gandhi UH, et al. Clin Lymphoma Myeloma Leuk 2018;18(5):335–45. 4. Gravina GL, et al. J Hematol Oncol 2014;7:85.

Selinexor + dexamethasone for RRMM

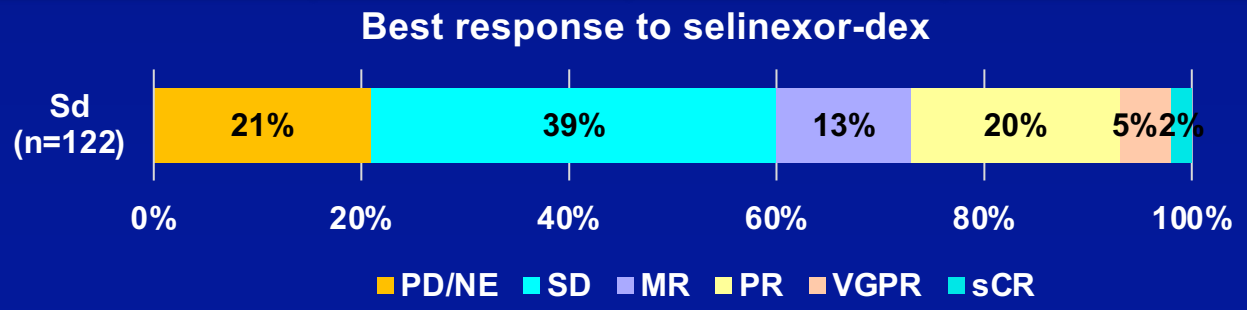
STORM phase 2b trial: selinexor BIW + dex

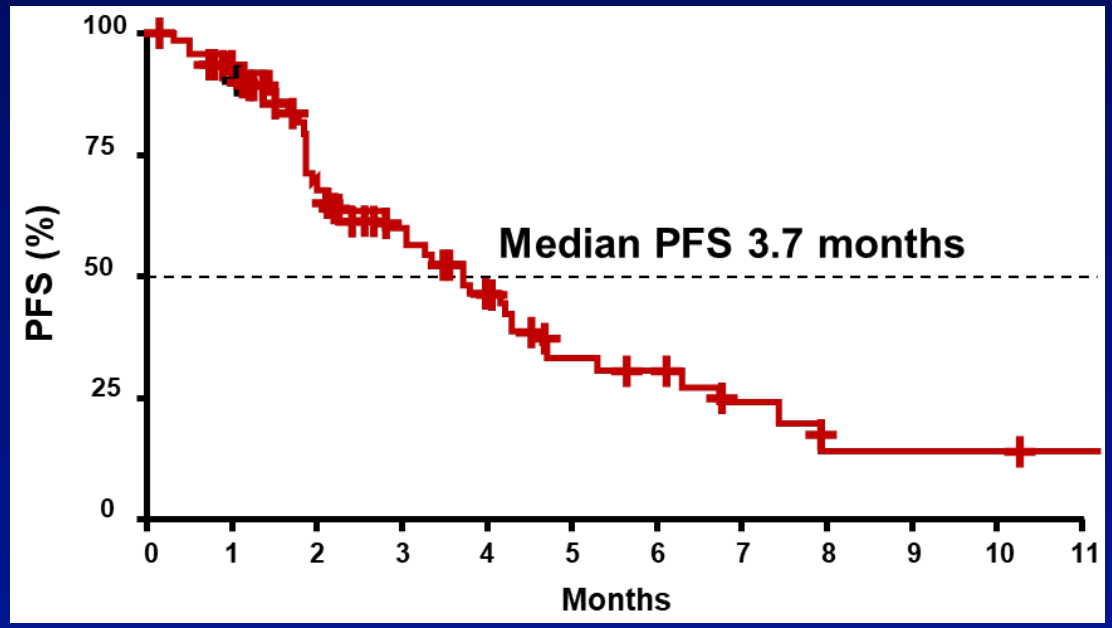
STORM part 2: 122 patients with RRMM

- Median age 65 years; 15% aged >75 years
- 53% high-risk cytogenetics, including 26% del17p/p53
- 33% gain 1q
- Median (range) 7 (3–18) previous treatment regimens
- 100% triple-class (PI, IMiD, CD38 mAb) refractory
- 68% penta-refractory
- 84% prior ASCT, 2% prior CAR T-cell therapy

Efficacy

ORR (≥PR) 26% ≥MR 39% 7% ≥VGPR	Median DOR 4.4 months	Median PFS 3.7 months	Median OS 8.6 months





Safety

- Grade 3/4 AEs: thrombocytopenia 59%, anemia 44%, fatigue 25%, hyponatremia 22%, neutropenia 21%, nausea 10%, pneumonia 9%, diarrhea 7%
- AEs leading to dose modification/interruption: 80%
- Related AEs leading to discontinuation: 18%
- SAEs: 63% (pneumonia 11%, sepsis 9%)

Chari A, et al. N Engl J Med. 2019;381(8):727–38.

Selinexor + dexamethasone for RRMM

Additional studies of selinexor + dex[1–4]

Phase 2: STORM part 1[1]

- Selinexor BIW + dex, N=79; median 7 prior lines; 100% quad-refractory, 39% penta-refractory
- CBR (≥MR) 33%; ORR 21%; ≥VGPR 5%
- Median DOR 5 months; median PFS 2.3 months; median OS 9.3 months
- Grade 3/4 AEs: thrombocytopenia 57–61%, anemia 18–33%, neutropenia 21–24%, hyponatremia 20–25%, nausea 6–11%

Phase 2: MARCH[2]

- Selinexor BIW + dex, N=82; median 5 prior therapies; 24% triple-class refractory
- CBR (≥MR) 42%; ORR 29%; ≥VGPR 5%
- Median DOR 4.7 months; median PFS 3.7 months; median OS 13.2 months
- Grade 3/4 AEs: thrombocytopenia 51%, anemia 57%, neutropenia 39%, hyponatremia 29%, nausea 7%

Phase 1 study[3]

- Selinexor BIW/TIW + dex, N=81 MM patients; median 6 prior therapies
- CBR (≥MR) 25%; ORR 10%; CR 1%
- Median DOR 5 months
- Grade 3/4 AEs: thrombocytopenia 45%, anemia 23%, neutropenia 23%, hyponatremia 26%, diarrhea 5%

1. Vogl DT, et al. J Clin Oncol 2018;36(9):859–66. 2. Qiu L, et al. BMC Med 2022;20(1):108. 3. Chen C, et al. Blood 2018;131(8):855–63. 4. Mo CC, et al. EJHaem 2023;4(3):792–810.

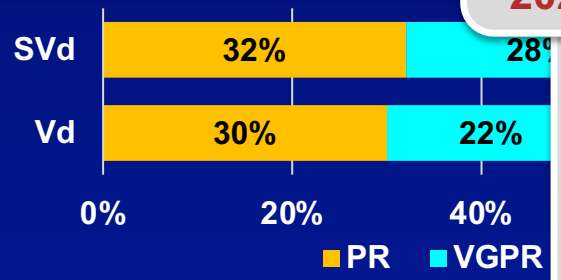
Selinexor + bortezomib-dexamethasone for RRMM

BOSTON phase 3 trial: selinexor QW + Vd vs Vd

BOSTON phase 3 trial (N=402)

- 195 SVd vs 207 Vd, median of 2 prior therapies (range 1–3)
- Median age 66 vs 67 year
- 11% vs 8% del(17p); 41% q21 amp
- 69% vs 70% prior bortez

Efficacy

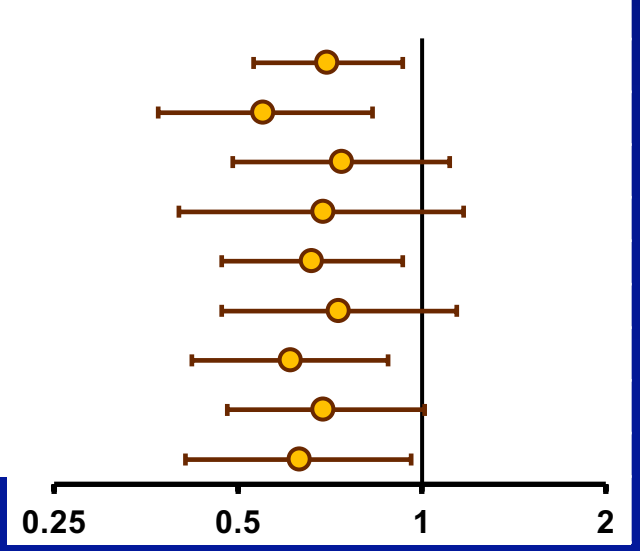


- Median DOR 20.3 vs 12.9 mor

Safety

- Higher rates of grade 3-4 thro anemia (16% vs 10%), neutrop vs 1%), and cataracts (9% vs
- Significantly lower rate of PN (3 (21% vs 34%)
- Grade ≥3 PN: 4.6% vs 8.8%

≥2 prior lines[4]	11.8	9.4	0.69
1 prior line[4]	16.6	10.7	0.63



Additional study of selinexor-Vd at ASH 2024

Lu et al, abstract 4748
(Poster session, Mon Dec 9)

- Phase 3 randomized BENCH study, Chinese patients with 1–3 prior lines of therapy, Selinexor-Vd (N=101) vs Vd (N=53)
- ORR 72% vs 62% (46% vs 23% ≥VGPR)
- Median DOR 9.7 vs 7.2 months
- Median PFS 8.1 vs 6.3 months (HR 0.74); median OS not reached in either arm
- Most common grade 3/4 AEs: thrombocytopenia 55.0% vs 28.8%, anemia 25% vs 17.3%, neutropenia 17.0% vs 3.8%, pneumonia 14.0% vs 13.5%, cataract 13.0% vs 0%, diarrhea 6.0% vs 15.4%, and hypokalemia 8.0% vs 11.5%

1. Grosicki S, et al. Lancet 2020;396:1563–73. 2. Auner HW, et al. Am J Hematol 2021;96(6):708–18. 3. Richard S, et al. Am J Hematol 2021;96(9):1120–30. 4. Mateos MV, et al. J Hematol Oncol 2021;14(1):59.

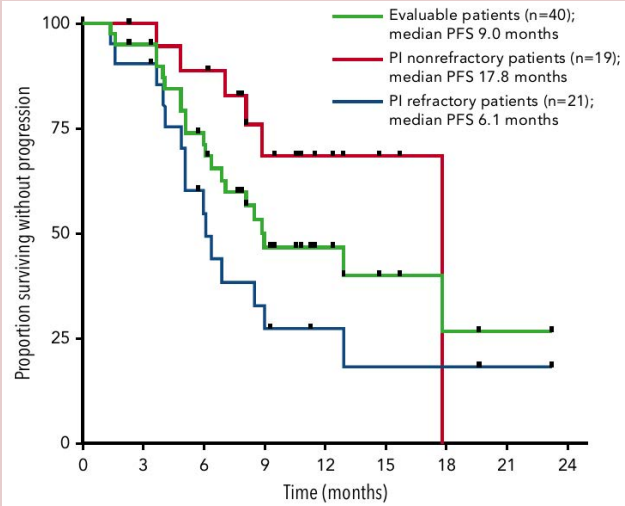
PN, peripheral neuropathy, SVd, Selinexor, bortezomib, dexamethasone.

Selinexor + bortezomib/carfilzomib-dexamethasone for RRMM

STOMP: selinexor + Vd/Kd

Selinexor BIW/QW + Vd[1]

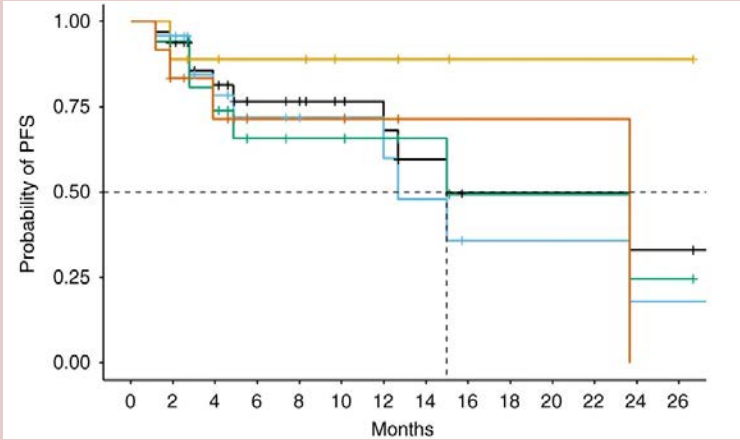
- STOMP selinexor + Vd arm: 42 patients
  - Median age 64 years; 9% high-risk cytogenetics
  - Median 3 prior therapies; 81% IMiD-refractory, 50% PI-refractory, 12% CD38 mAb-refractory
- ORR (≥PR) 63%; 30% ≥VGPR



- Median PFS: all patients, 9.0 months, PI-refractory 6.1 months, PI-non-refractory 17.8 months
- Grade 3/4 thrombocytopenia 46%, neutropenia 23%, fatigue 14%, diarrhea 7%, nausea 5%

Selinexor QW + Kd[2]

- STOMP selinexor + Kd arm: 32 patients
  - Median age 69.5 years; 53.1% high-risk cytogenetics
  - Median 4 prior therapies; 37.5% triple-class refractory
- ORR (≥PR) 78.1%; 43.8% ≥VGPR



- Median PFS (curve color):
  - All (black) 15.0 months, 1-2 prior lines (yellow) NR, triple-class refractory (orange) 23.7 months
- Median DOR 22.7 months; median OS NR
- Grade 3/4 thrombocytopenia 47%, anemia 19%, fatigue 9%, nausea 6%, hyperglycemia 6%

1. Bahlis NJ, et al. Blood 2018;132(24):2546–54.
2. Gasparetto C, et al. Br J Cancer 2022;126(5):718–25.

Selinexor + PI-dexamethasone for RRMM

Additional studies of selinexor + Kd/Ixa-dex[1–4]

Phase 1: Derman et al[1]

- Selinexor QW + Kd, N=30; median 5 prior lines; 30% K-refractory, 20% prior CAR T-cell therapy
- CBR (≥MR) 83%; ORR 70%; ≥VGPR 27%
- Median PFS 5.3 months; median OS 23.3 months
- Grade 3/4 AEs: thrombocytopenia 43%, anemia 27%, neutropenia 17%, fatigue 23%, anorexia 23%, nausea 10%

Phase 1: Jakubowiak et al[2]

- Selinexor BIW + Kd, N=21; median 4 prior therapies; triple-class refractory, 5% penta-exposed
- CBR (≥MR) 71%; ORR 48%; VGPR 14%
- Median PFS 3.7 months; median OS 22.4 months
- Grade 3/4 AEs: thrombocytopenia 71%, anemia 33%, neutropenia 33%, infection 24%, fatigue 14%, diarrhea 10%

Phase 1: Salcedo et al[3]

- Selinexor BIW/QW + Ixa-dex, N=18; median 5 prior lines, 83% PI-refractory
- ORR 22%; VGPR 14%; outcomes data not reported
- Grade 3/4 AEs: thrombocytopenia 61%, neutropenia 28%, anemia 17%, nausea 11%, vomiting 11%, fatigue 11%

1. Derman BA, et al. Eur J Haematol 2023;110(5):564–70. 2. Jakubowiak AJ, et al. Br J Haematol 2019;186(4):549–60.
3. Salcedo M, et al. Clin Lymphoma Myeloma Leuk 2020;20(3):198–200. 4. Mo CC, et al. EJHaem 2023;4(3):792–810.

Selinexor combinations for RRMM

STOMP: additional selinexor combinations under study

Regimen	N	RRMM population	Responses	Outcomes	Grade 3/4 AEs
Selinexor BIW/QW + Rd[1]	24	Median 2 prior lines	CBR 70% ORR 60% ≥VGPR 25%	NR	Thrombocytopenia 63%, neutropenia 63%, anemia 17%, fatigue 17%, decreased appetite 8%, weight decreased 8%
Selinexor BIW/QW + Dara-dex[2]	34	Median 3 prior therapies; 6% Dara-refractory	CBR 81% ORR 69% VGPR 34%	Median DOR: 5.3 mos Median PFS: 12.5 mos	Thrombocytopenia 47%, anemia 32%, neutropenia 27%, fatigue 18%, hyponatremia 12%, nausea 9%
Selinexor QW + Kd / Pom-dex[3]	46 (23/23)	Median 4 prior regimens; prior CD38 mAb; 63% TCR, 11% penta-refractory	CBR 74%/70% ORR 65%/52%	Median DOR: 13.1/7.9 mos Median PFS: 15.0/8.7 mos Median OS: 33.0/9.6 mos	Thrombocytopenia 39%/30%, anemia 22%/39%, neutropenia 4%/52%, hypertension 17%/0, hyponatremia 4%/9%, fatigue 4%/4%, decreased appetite 4%/4%
Multiple combinations with selinexor[4]	11	Median 6 prior lines; prior anti-BCMA therapy	CBR 82% ORR 64% VGPR 18%	6-mo PFS: 75.0%	Thrombocytopenia 64%, neutropenia 46%, anemia 27%

1. White DJ, et al. Blood 2020;136(Suppl 1):18–19. 2. Gasparetto C, et al. EJHaem 2021;2(1):56–65.
3. Schiller GJ, et al. Clin Lymphoma Myeloma Leuk 2023;23(9):e286–96. 4. Baljevic M, et al. EJHaem 2022;3(4):1270–6.

Selinexor + pomalidomide-dexamethasone for RRMM

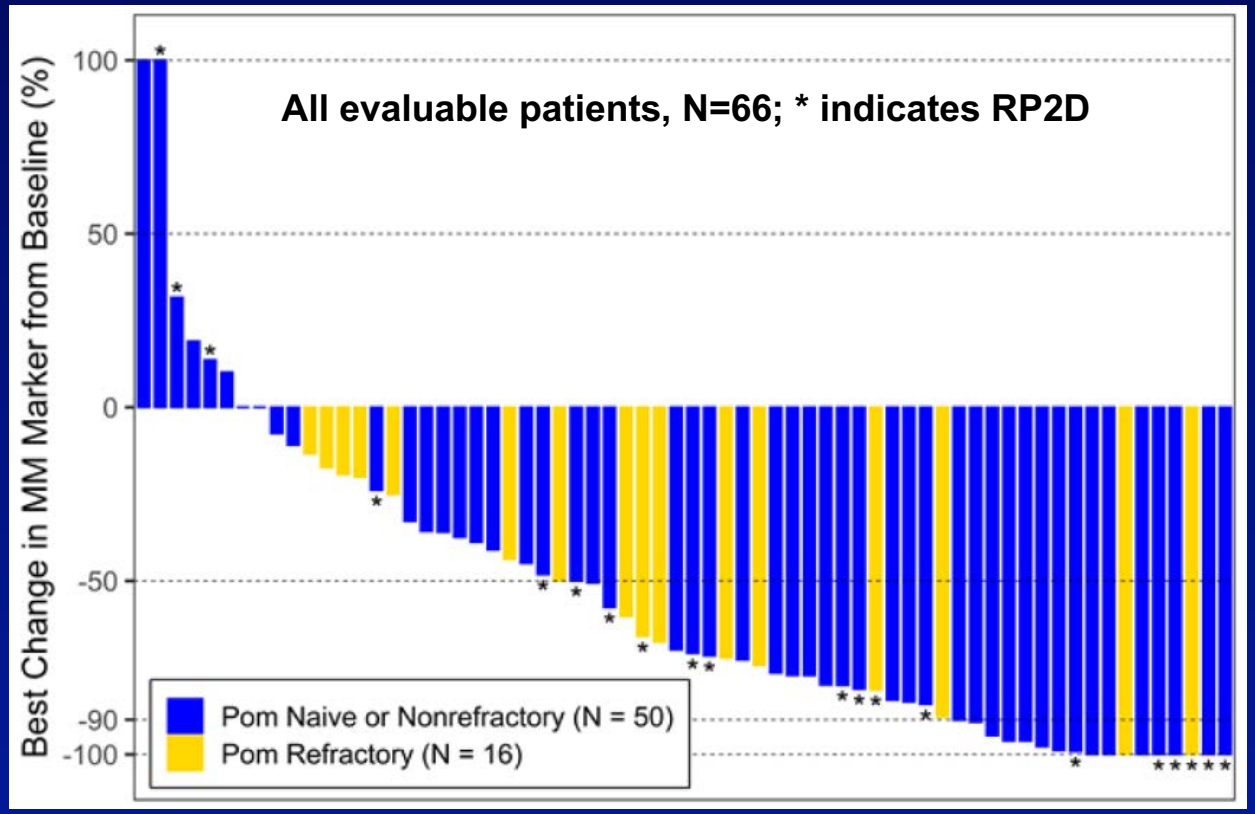
STOMP: XPd dose-escalation

Phase 1b/2 trial (N=72 / n=20 at RP2D)

- Median age 64.0 / 65.5 years
- ISS stage III 13.9% / 15.0%
- Median prior regimens (range) 4 (1–12) / 3.5 (1–12)
- Lenalidomide-refractory 80.6% / 80.0%
- Pomalidomide-refractory 26.4% / 15.0%
- Bortezomib-refractory 50.0% / 45.0%
- Carfilzomib-refractory 37.5% / 50.0%
- CD38 mAb-refractory 27.8% / 25.0%
- Prior ASCT 80.6% / 70.0%

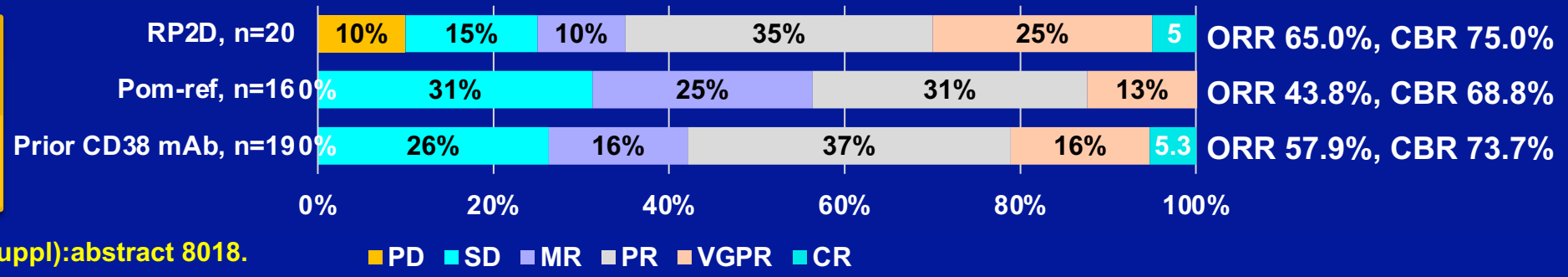
Safety (N=72 / n=20 at RP2D)

- Grade 3/4 neutropenia 52.8% / 60.0%, anemia 29.2% / 25.0%, thrombocytopenia 27.8% / 25.0%
- Any-grade nausea 61.1% / 70.0%, decreased appetite 41.7% / 30.0%, diarrhea 29.2% / 25.0%, vomiting 22.2% / 20.0%



Best response in evaluable patients

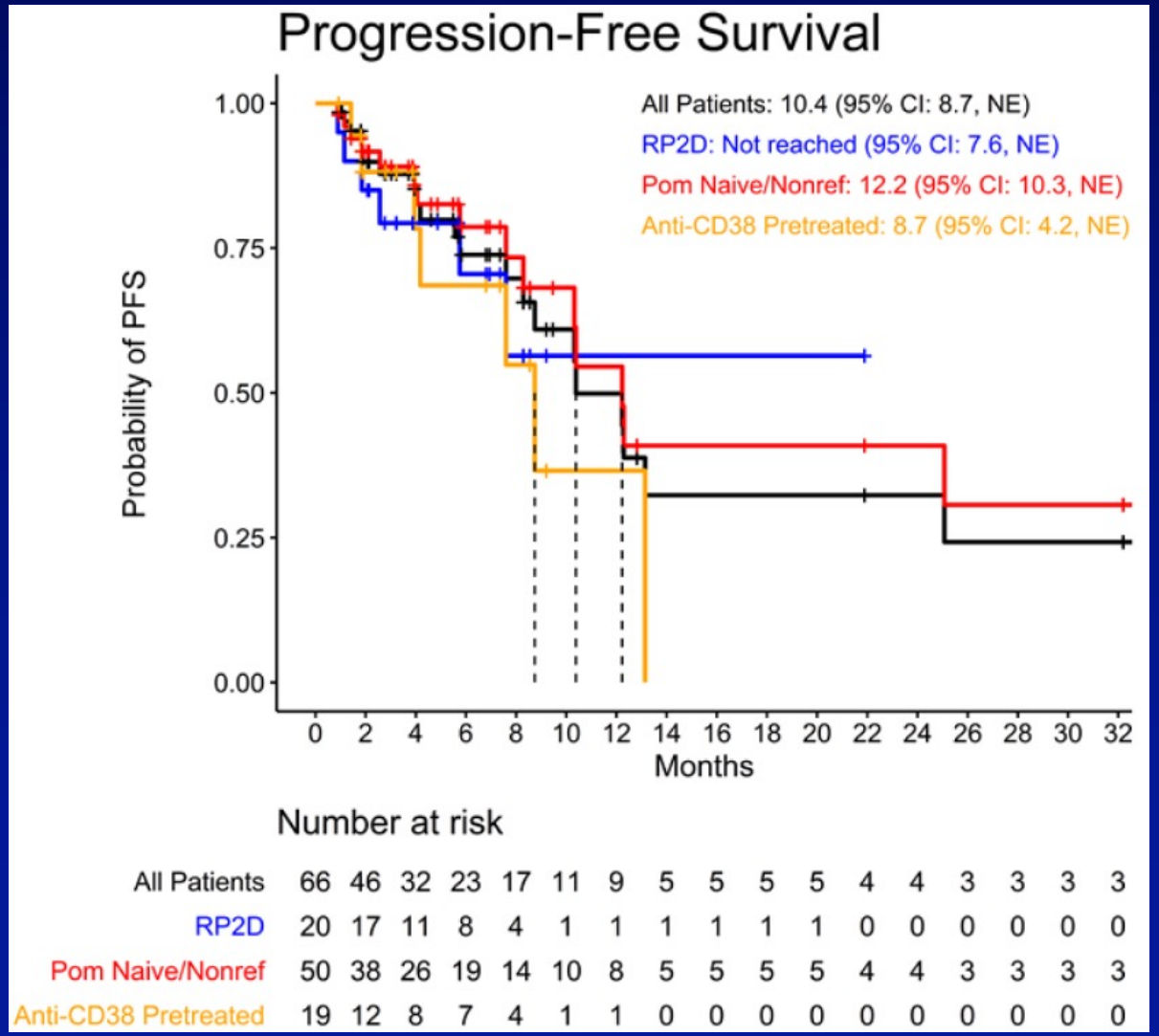
RP2D = Selinexor 60 mg QW, pomalidomide 4 mg	Pom-ref = pomalidomide-refractory patients

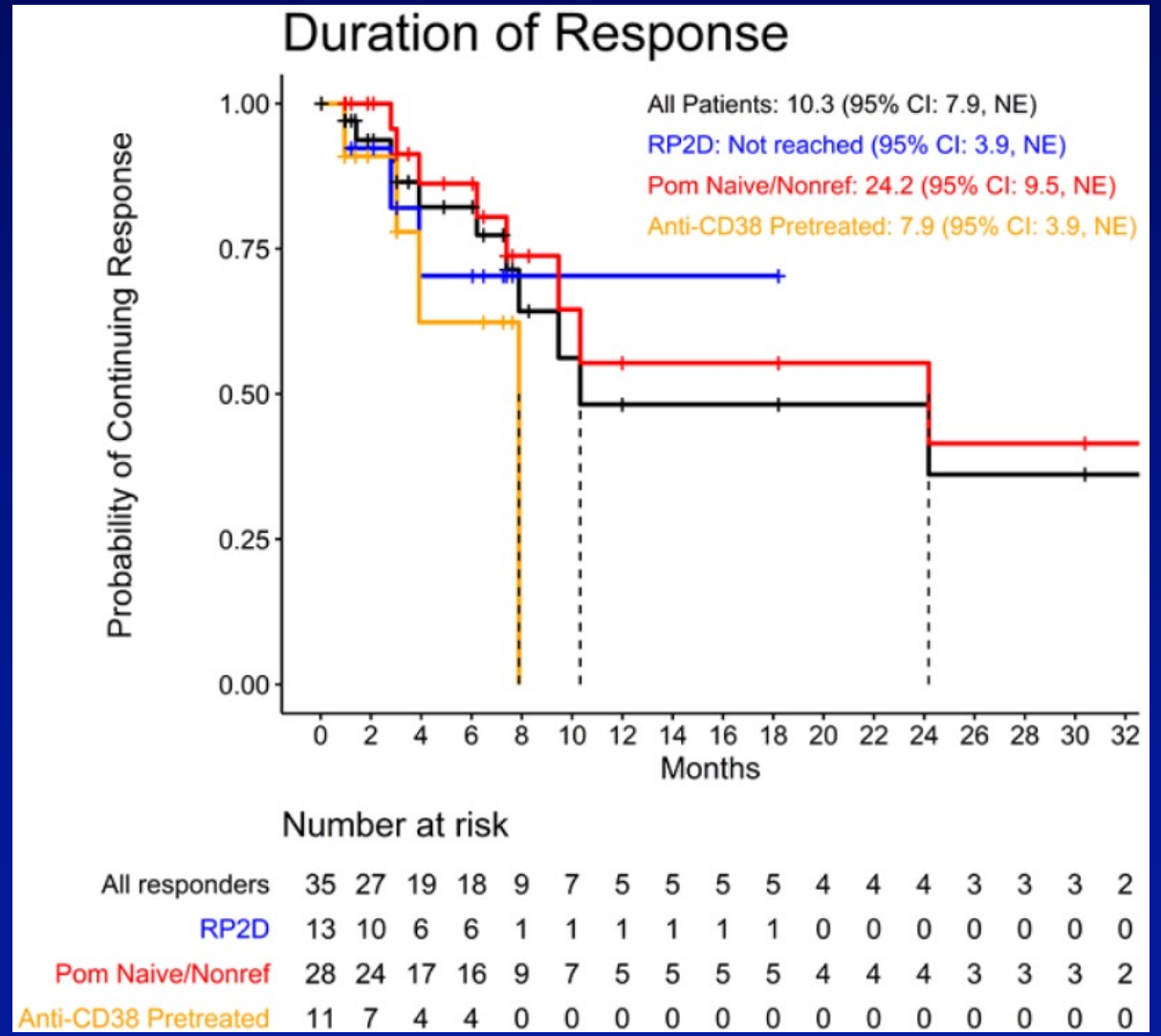


White DJ, et al. J Clin Oncol 2021;13(15_suppl):abstract 8018.

Selinexor + pomalidomide-dexamethasone for RRMM

STOMP: XPd dose-escalation





White DJ, et al. J Clin Oncol 2021;13(15_suppl):abstract 8018.

Selinexor + pomalidomide-dexamethasone for RRMM

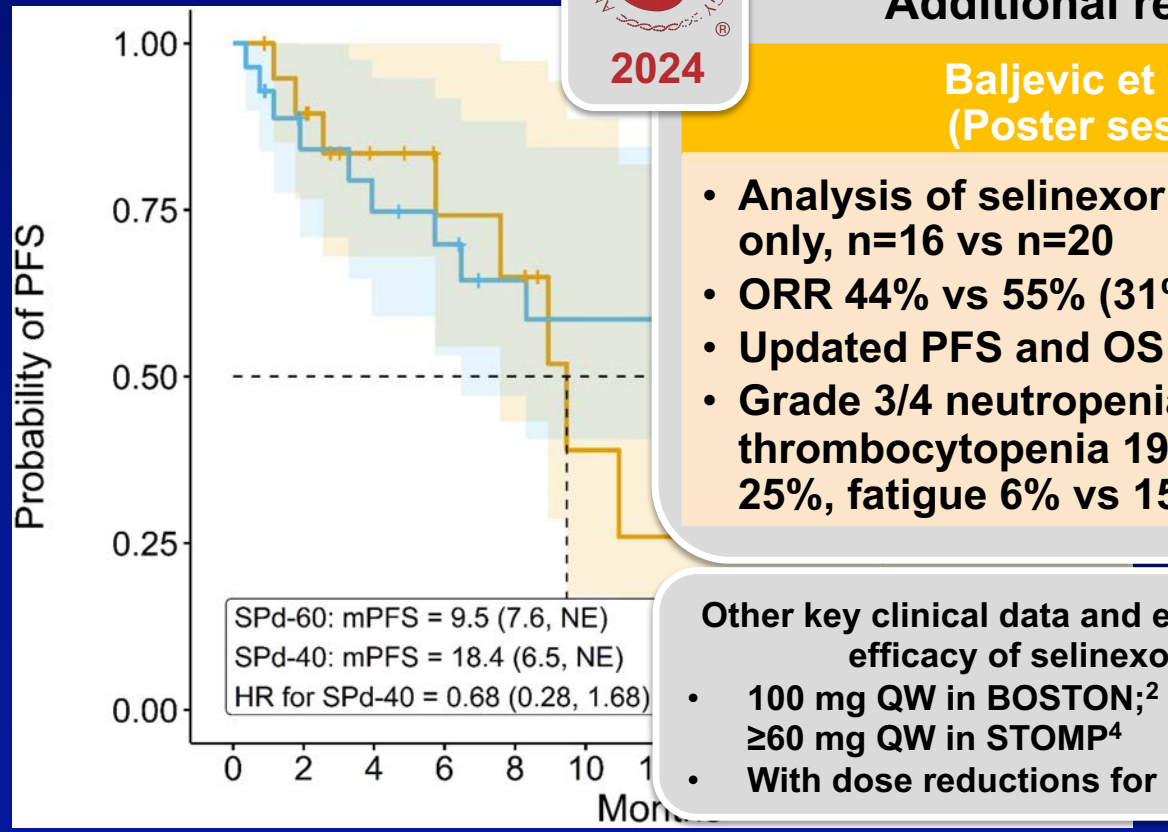
STOMP/XPORT-MM-028: XPd – selinexor 40 vs 60 mg[1]

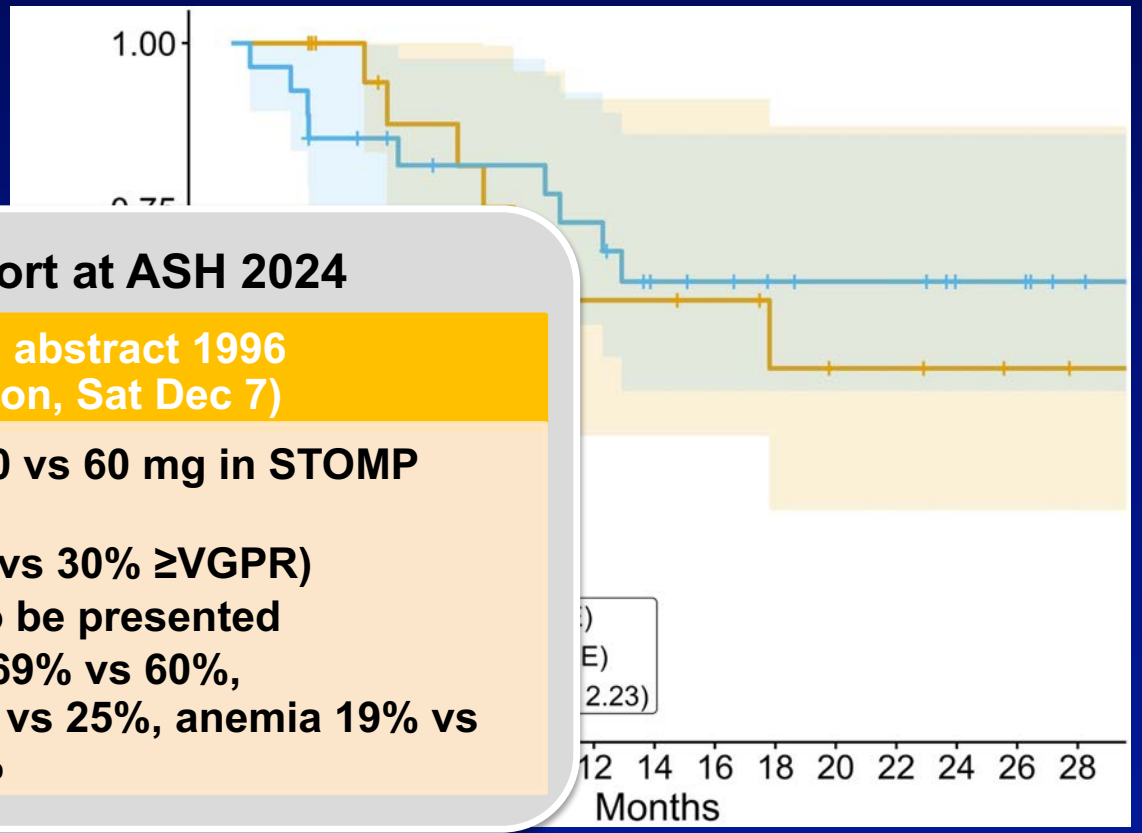
Selinexor 40 mg (n=28) vs 60 mg (n=20) + Pom-dex

- Median age 67.5 vs 65.5 years; high-risk cytogenetics 14% vs 15%
- Median 2 vs 2 prior lines; 43% vs 20% triple-class refractory

Efficacy

- ORR 50% vs 65%; CBR 68% vs 75%
- DOR NR vs 8.6 months
- PFS 18.4 vs 9.5 months





2024

Additional report at ASH 2024

Baljevic et al, abstract 1996 (Poster session, Sat Dec 7)

- Analysis of selinexor 40 vs 60 mg in STOMP only, n=16 vs n=20
- ORR 44% vs 55% (31% vs 30% ≥VGPR)
- Updated PFS and OS to be presented
- Grade 3/4 neutropenia 69% vs 60%, thrombocytopenia 19% vs 25%, anemia 19% vs 25%, fatigue 6% vs 15%

Other key clinical data and experience supportive of safety and efficacy of selinexor starting doses ≥60 mg[2–4]

- 100 mg QW in BOSTON;[2] 80 mg BIW in STORM;[3] ≥60 mg QW in STOMP[4]
- With dose reductions for management of toxicities[5,6]

ety

thrombocytopenia 25% vs 25%, 15%, nausea 7% vs 0
25% vs 15%)
40 mg regimen in this study (n=28)

1. White D, et al. Front Oncol 2024;14:1352281. 2. Grosicki S, et al. Lancet 2020;396:1563–73. 3. Chari A, et al. N Engl J Med 2019;381(8):727–38. 4. Schiller GJ, et al. Clin Lymphoma Myeloma Leuk 2023;23(9):e286–96. 5. XPOVIO® US Prescribing Information, July 2022. 6. Mo CC, et al. EJHaem 2023;4(3):792–810.

Selinexor + pomalidomide-dexamethasone for RRMM

EMN29/XPORT-MM-031 phase 3 trial: XPd vs Elo-Pom-dex

Part 1, N=~60 — 1:1:1 → Selinexor 40 mg QW + Pom-dex vs Selinexor 60 mg QW + Pom-dex vs Elo-Pom-dex

Based on findings from STOMP/XPORT-MM-028 analysis, selinexor 40 mg QW selected for Part 2*

Part 2, N=~222

- RRMM, 1–4 prior lines, including ≥2 cycles of R + PI, plus CD38 mAb as part of last prior treatment
- ECOG PS ≤2
- Adequate hematologic, hepatic, renal function

1:1

- Selinexor 40 mg QW + Pom-dex
- Elo-Pom-dex

28-day cycles

Randomization stratified by:
- Prior lines (1–2 vs 3–4)
- R-ISS stage (III vs I or II)
- Triple-class refractory (yes vs no)

Primary endpoint
- PFS

Key secondary endpoints
- ORR
- OS

Other secondary endpoints
- DOR, TNT, PFS2
- Safety, tolerability
- HRQoL

Weisel K, et al. IMS 2023, poster 1552200.
European Myeloma Network: https://www.myeloma-europe.org/trials/emn29/
ClinicalTrials.gov: NCT05028348
*Potential expansion cohort also planned at selinexor 60 mg dose level.

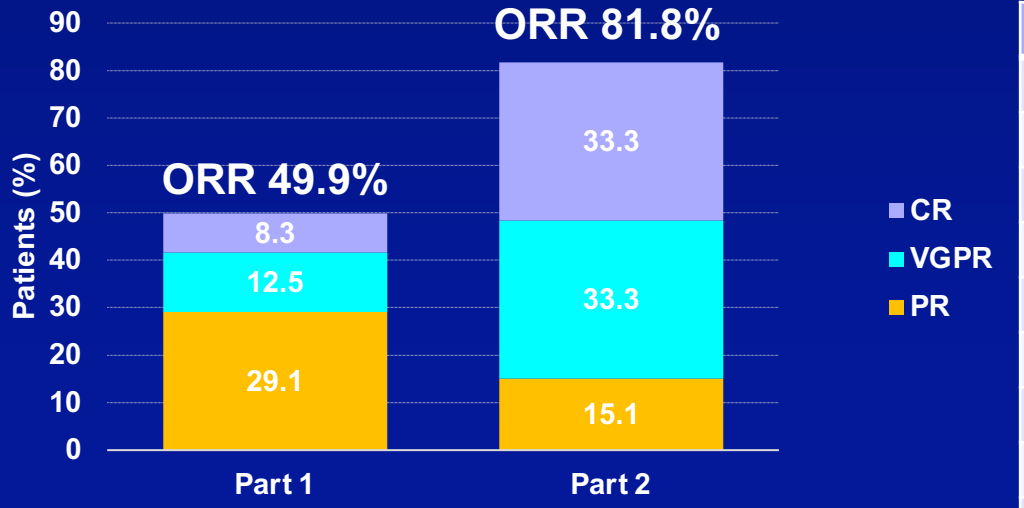
Estimated primary completion: March 2026

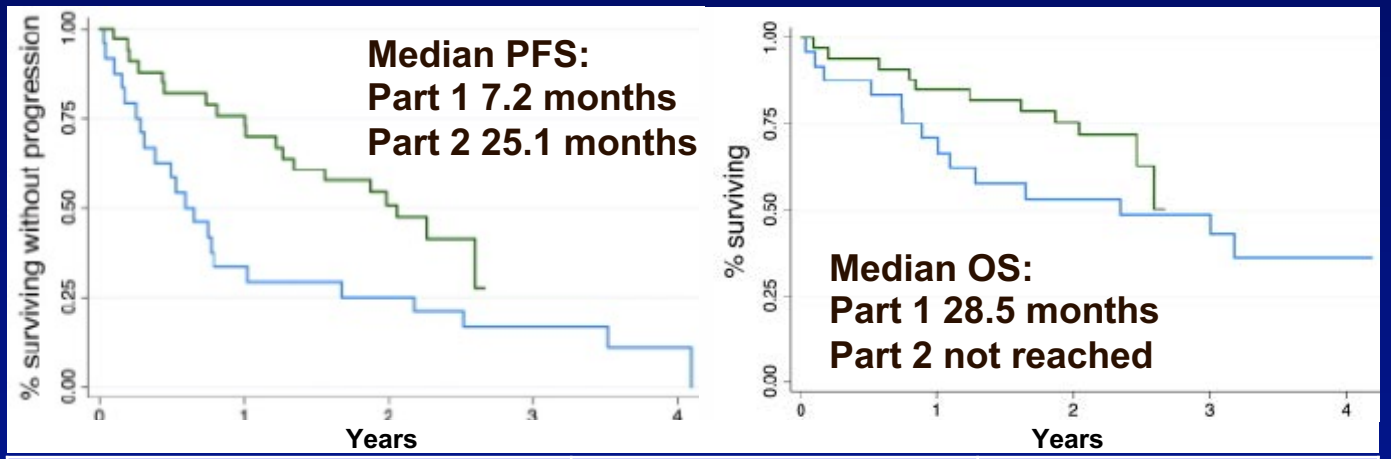
Selinexor combinations for RRMM

GEM-SELIBORDARA: Selinexor-based quadruplet therapy

Phase 2 study: selinexor + Dara-Vd in patients with RRMM

Part 1	Part 2
• 24 patients	• 33 patients
• Median age 66 years	• Median age 69 years
• Median 3 prior lines	• Median 1 prior line
• R-ISS III 16%	• R-ISS III 16%
• High-risk cytogenetics 26%	• High-risk cytogenetics 19%
• R-refractory 96%	• R-refractory 46%
• PI-refractory 71%	• PI-refractory 15%
• R/PI-refractory 71%	• R/PI-refractory 12%





Common TRAEs, %	All grade	Grade ≥3
Any hematologic TRAE	82	60
Thrombocytopenia	70	46
Neutropenia	39	30
Anemia	30	12
Non-hematologic TRAEs		
Infection	74	32
Fatigue/asthenia	44	14
Diarrhea	39	4
Nausea or vomiting	35	9

González-Calle V, et al. Haematologica 2024;109(7):2219–28.

Selinexor combinations for RRMM

Novel selinexor combinations under investigation in RRMM

Study	Regimen	Phase	ClinicalTrials.gov	N	Setting	Primary endpoint	Initial completion
STOMP (Arm 12)	Selinexor + Mezigdomide-dex[1]	1/2	NCT02343042	NR	• ≥2 prior lines, including a PI, an IMiD, and a CD38 mAb • Progressed on or ineligible for T-cell redirecting therapy	Safety, PK, ORR, DOR, CBR	April 2027
NCI-2020-13697	Selinexor + Dara-Kd	2	NCT04756401	~52	• 1–3 prior lines	MRD-neg rate	September 2024
SCOPE	Selinexor + K-Pom-dex	1/2	NCT04764942	~81	• ≥3 prior lines, including a PI and an IMiD	MTD ORR	March 2025
SELVEDge[2]	Selinexor + Venetoclax-dex	2	NCT05530421	~33	• t(11;14)-positive RRMM • ≥2 prior lines, and refractory to, ineligible for, or intolerant of a PI, an IMiD, and a CD38 mAb	ORR	March 2026
NCI-2020-09704	Selinexor + choline salicylate	1	NCT04640779	~39	• Penta-refractory RRMM • ≥4 prior lines	MTD	August 2026
KPT-IST-391	Selinexor + Ruxolitinib (JAK1/2 inhibitor) + Methylprednisolone	1	NCT06225310	~30	• ≥3 prior lines	MTD/RP2D	April 2027

ClinicalTrials.gov, November 14, 2024

1. Richardson PG, et al. N Engl J Med 2023;389(11):1009–22. 2. Kazandjian D, et al. Blood 2023;142(suppl 1):abstract 6740.

Selinexor for RRMM

Safety profile

Common toxicities

- GI AEs – nausea and vomiting potentially mediated by CNS due to selinexor crossing blood–brain barrier
- Hematologic AEs
- Fatigue

Grade ≥3 thrombocytopenia

- Due to inhibition of thrombopoietin signalling early during megakaryopoiesis
- Mechanistically distinct for bortezomib-mediated thrombocytopenia
- Associated bleeding events are rare

QW vs BIW selinexor

- Distinct safety profile
- Lower rates of GI, hematologic AEs, fatigue
- Lower rates of infections, hyponatremia

Toxicities manageable with supportive care

- Toxicity management guidelines developed for both BIW and QW regimens

Mo CC, et al. EJHaem 2023;4(3):792–810. Midha S, et al. Expert Opin Drug Saf 2023;22(11):1049–71.

Selinexor for RRMM

Prophylaxis and management of GI toxicity[1–3]

	US prescribing information[2]	Expert recommendations (selinexor QW)[3]
Prophylaxis	• Provide prophylactic antiemetics; 5-HT3 receptor antagonist and other anti-nausea agents prior to treatment	• Combination of olanzapine, 5-HT3 receptor antagonists (ondansetron, granisetron) ± neurokinin 1 receptor antagonists (aprepitant, rolapitant, casopitant, fosaprepitant) • Low-dose olanzapine (2.5–5 mg), evenings, prior to/for 3 days post selinexor
Supportive care	• Administer 5-HT3 receptor antagonist and other anti-nausea agents during treatment • Provide standard anti-diarrheal agents • Provide IV fluids to prevent dehydration; replace electrolytes as clinically indicated • Monitor weight, nutritional status, and volume status throughout treatment, more frequently during first 3 months	• Comprehensive metabolic panel weekly (cycle 1) then at start of every cycle • Combination of olanzapine, 5-HT3 receptor antagonists ± neurokinin 1 receptor antagonists • Low-dose olanzapine (2.5–5 mg), evenings, prior to/for 3 days post selinexor • Taper anti-nauseants after cycle 2 as needed • Maintain hydration (2 L daily) – water, salt-containing drinks • IV fluids as required, for example, IV normal saline • Nutritional consultation, appetite stimulants • Consider dronabinol 2.5–5 mg PO BID for grade ≥2/3 anorexia • Initiate anti-diarrhoeal treatment for grade 1 diarrhea

1. Mo CC, et al. EJHaem 2023;4(3):792–810. 2. Karyopharm Therapeutics. XPOVIO (selinexor) United States Prescribing Information, accessed November 14, 2024. 3. Nooka AK, et al. Clin Lymphoma Myeloma Leuk 2022;22(7):e526–31. 4. Midha S, et al. Expert Opin Drug Saf 2023;22(11):1049–71.

Selinexor for RRMM

Management of other key toxicities[1–3]

	US prescribing information[2]	Expert recommendations (selinexor QW)[3]
Fatigue	–	• Consider methylphenidate 5 mg PO BID for grade 4 fatigue
Thrombocytopenia	• Monitor platelet counts throughout treatment, more frequently during first 3 months • Platelet transfusion and/or other treatments as clinically indicated	• Complete blood count weekly (cycle 1) then at start of every cycle • Romiplostim 10 µg/kg weekly for grade 3/4 toxicity
Neutropenia / Serious infections	• Monitor white blood cell counts with differential throughout treatment, more frequently during first 3 months • Consider antimicrobials and growth factors (e.g., G-CSF) • Monitor for signs and symptoms of infection, evaluate and treat promptly	• Complete blood count weekly (cycle 1) then at start of every cycle • Grade 4 or febrile neutropenia: G-CSF until ANC >1.0 × 10^9/L
Hyponatremia	• Monitor sodium level throughout treatment, more frequently during first 2 months • Correct sodium levels for concurrent hyperglycemia and high serum paraprotein levels • Manage per clinical guidelines, including IV saline and/or salt tablets as appropriate and dietary review	• Maintain hydration (2 L daily) – water, salt-containing drinks • Consider addition of salt tablets, salty foods to diet
Neurologic toxicity	• Optimize hydration, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status • Institute fall precautions	–

1. Mo CC, et al. EJHaem 2023;4(3):792–810. 2. Karyopharm Therapeutics. XPOVIO (selinexor) United States Prescribing Information, accessed November 14, 2024. 3. Nooka AK, et al. Clin Lymphoma Myeloma Leuk 2022;22(7):e526–31. 4. Midha S, et al. Expert Opin Drug Saf 2023;22(11):1049–71.

Isatuximab for RRMM

Conclusions and future directions

Isa triplets established standards of care in the early relapse RRMM setting[1]

- Based on demonstrated benefit overall and across patient subgroups in ICARIA-MM and IKEMA

However, Dara quadruplets established and Isa quadruplets emerging as new standards of care for NDMM[2]

- Impact of quadruplets in NDMM, plus CD38 mAb-R maintenance, on early-relapse RRMM treatment efficacy remains to be determined

Evaluation of optimal sequencing and positioning in treatment algorithm, and of efficacy following prior CD38-directed therapy, is key

- Feasibility of CD38 retreatment?[3]
- Sequencing in context of T-cell redirecting therapies also of emerging importance[4] – CAR T therapies and bispecific antibodies are moving into the NDMM and early relapse RRMM settings

Multiple Isa-based quadruplet regimens under investigation in RRMM

- Feasibility post first-line quadruplet regimens?

Multiple novel Isa-based combinations under investigation

- Including with immune-based therapies – ADC (belantamab mafodotin), bispecific antibody (linvoseltamab), TGFβ mAb and NK cells
- Importance of sequencing and avoiding immune exhaustion – long-term strategic considerations

1. Kumar SK, et al. J Natl Compr Cancer Netw 2023;21(12):1281–301 (updated per V1.2025; https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf). 2. Richardson PG. HASEK (Hematology Association of South Eastern Korea) meeting, September 2024, Busan, South Korea. 3. Perez de Acha O, et al. *Blood Adv.* 2023;7(21):6430-40. 4. Razzo B, et al. Hematology Am Soc Hematol Educ Program 2023;2023(1):450–8.

Selinexor for RRMM

Conclusions and future directions

Selinexor and other small molecules/targeted therapies – important treatment options for RRMM

- Selinexor approved in combination with Vd after ≥1 prior therapy and with Dex after ≥4 prior therapies (penta-refractory disease)[1]
- Selinexor combination strategies to improve therapeutic index under investigation
- Potential specific benefit for patients with high-risk cytogenetics including del(17p)[2]

Selinexor demonstrating activity in evolving settings in treatment algorithm[2]

- Value of novel mechanism of action in context of quadruplet therapies for NDMM and early relapse RRMM – e.g. in triple-class refractory and penta-refractory settings
- Activity post T-cell redirection therapy (CAR T-cell therapy, bispecific antibody therapy)
- Importance in the context of T-cell exhaustion

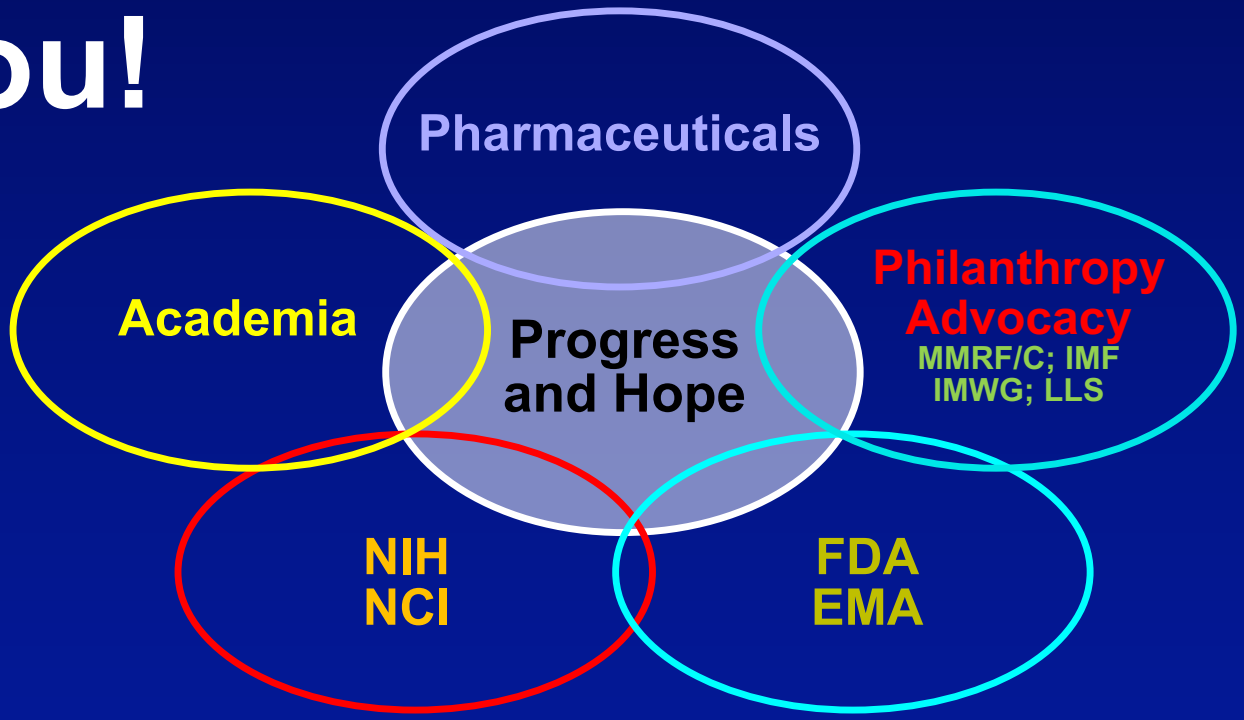
Novel combination strategies – e.g. with mezigdomide[3]

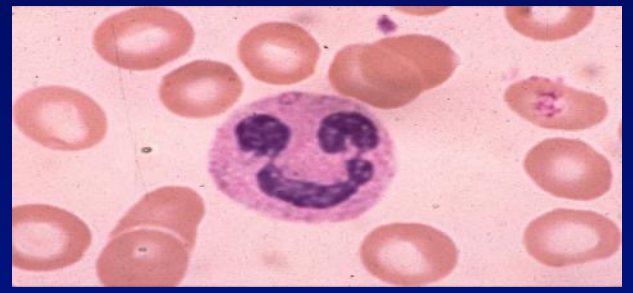
- Non-immune-based triplet treatment options
- Emerging quadruplet treatment options utilizing novel mechanism of action with standard-of-care agents
- Importance of optimizing the use of all available and emerging treatment options and novel targets to improve patient outcome[4]

1. Karyopharm Therapeutics. XPOVIO (selinexor) United States Prescribing Information, accessed November 14, 2024. 2. Mo CC, et al. EJHaem 2023;4(3):792–810.
3. Richardson PG, et al. N Engl J Med 2023;389(11):1009–22. 4. Richardson PG. 15th Freiburg Myeloma Workshop 2024, October 2024, Freiburg, Germany.

Ongoing MM collaborative model for rapid translation of novel therapeutics from bench to bedside 2003–2024

Thank you!





Courtesy of Phil McCarthy MD

19 novel drugs and >34 new FDA-approved drug combos/indications in last 21 years

INTERNATIONAL MYELOMA FOUNDATION
BRIGHAM AND WOMEN'S HOSPITAL
Dana-Farber Cancer Institute
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK
Alliance for Clinical Trials in Oncology
AMERICAN SOCIETY OF HEMATOLOGY

Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Orlowski

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory MM — Dr Richardson

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies for the Treatment of MM — Prof Moreau

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Lonial

RTP
RESEARCH
TO PRACTICE

Case Presentation: 67-year-old woman with multiple regimen-refractory MM is referred for CAR T-cell therapy

Dr Susmitha Apuri (Inverness and Lecanto, Florida)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What therapies do you most commonly employ as a bridge to CAR T-cell therapy? Have you administered selinexor prior to CAR T-cell therapy? In addition to tumor reduction, do you believe this agent potentiates T-cell activity?

Where in the treatment sequence are you typically integrating BCMA-directed CAR T-cell therapy? Is this form of treatment more effective when used earlier?

How would you compare the potential benefits and complications of the available BCMA-directed CAR T-cell products in MM? In general, do you prefer one product over the other?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 51-year-old woman with MM and suboptimal disease response to autoSCT enters a trial of CAR T-cell therapy followed by lenalidomide maintenance

Dr Yanjun Ma (Murfreesboro, Tennessee)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Have deepening responses over time been observed in patients after CAR T-cell therapy in MM?

What is the role of MRD assessment after CAR T-cell therapy, and do you have a preferred assay?

How accurate is copy number as a reflection of disease status in current MRD assessment?

RTP
RESEARCH
TO PRACTICE

Chimeric Antigen Receptor (CAR) T-Cell Therapy for Multiple Myeloma

Noopur Raje, MD
Center for Multiple Myeloma
MGH Cancer Center

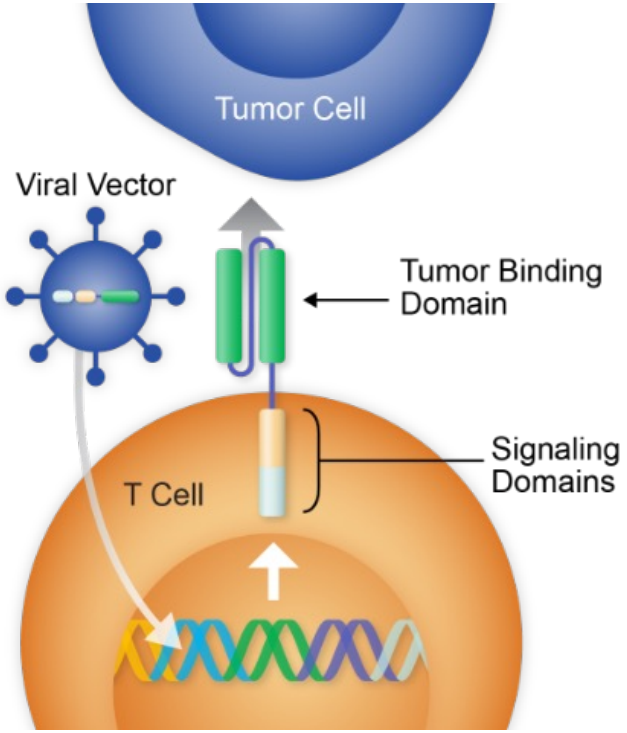
Professor of Medicine
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Ide-cel and Cilta-cel Constructs

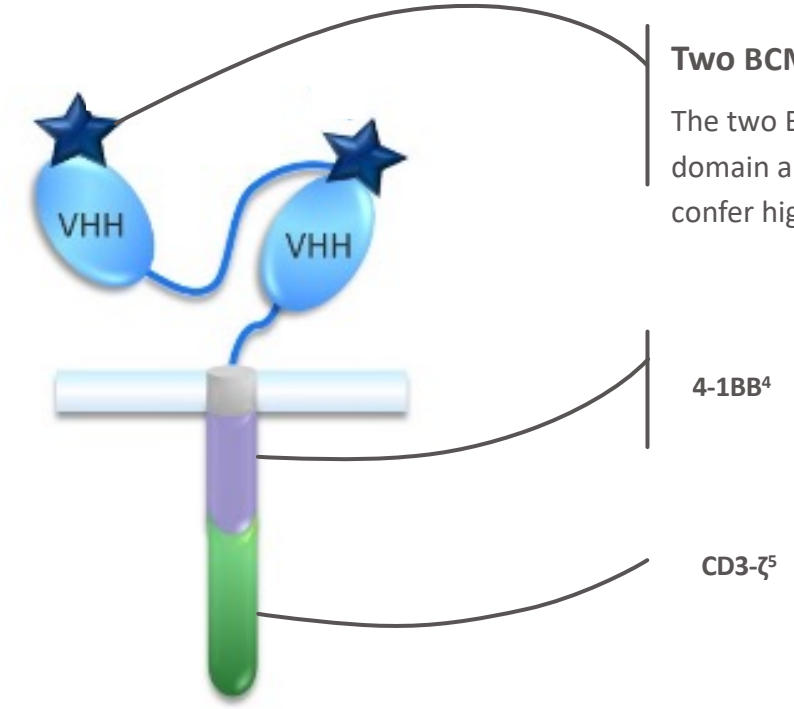
Idecabtagene Vicleucel (ide-cel) CAR T



Second-generation CAR construct[1]

Murine scFv

Ciltacabtagene Autoleucel (cilta-cel) CAR T



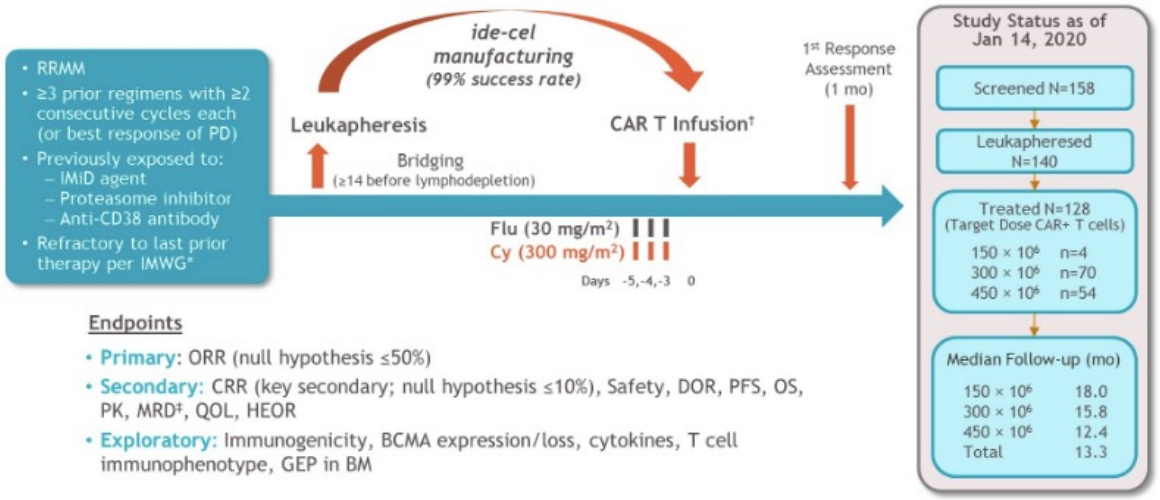
Dual epitope-binding CAR construct[1,2]

Llama 2xVhH

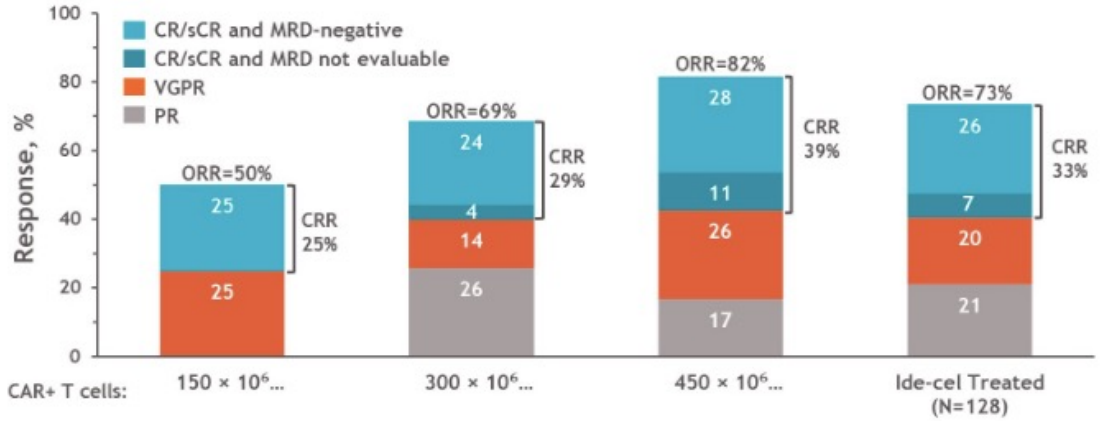
- BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; ide-cel, idecabtagene vicleucel; MM, multiple myeloma; MND, murine leukemia-derived promoter; scFv, single-chain variable fragment.
- 1. Raje N et al. *N Engl J Med*. 2019;380(18):1726-1737. 2. Friedman KM et al. *Hum Gene Ther*. 2018;29(5):585-601. 3. Song DG et al. *Cancer Res*. 2011;71(13):4617-4627. 4. Zhao WH et al. *J Hematol Oncol*. 2018;11(1):141. 5. Berdeja JG et al. ASCO 2020. Abstract 8505.

KarMMa: Ide-cel Registration Study

Trial design



Response

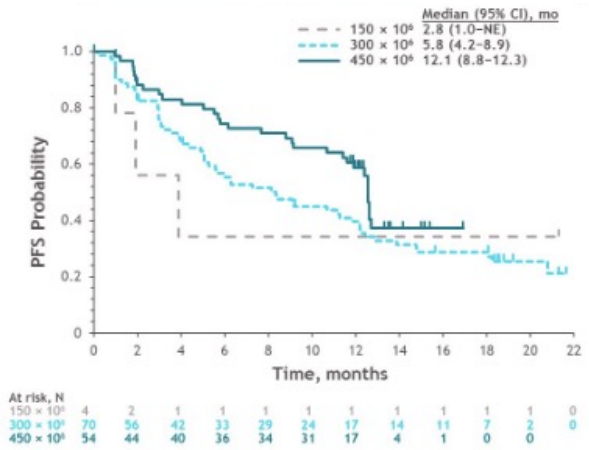


- Primary (ORR > 50%) and key secondary (CRR >10%) endpoints met in the Ide-cel treated population
  - *ORR of 73% (95% CI, 65.8-81.1; P<0.0001)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7-40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5-8.8); median time to CR of 2.8 mo (range, 1.0-11.8)
- Median follow-up of 13.3 mo across target dose levels

Munshi et al. N Engl J Med 2021;384:705-16.

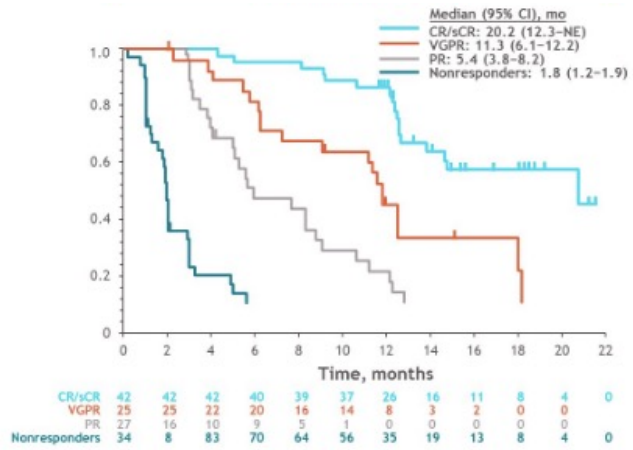
KarMMa: PFS and MRD-negativity

PFS by Target Dose



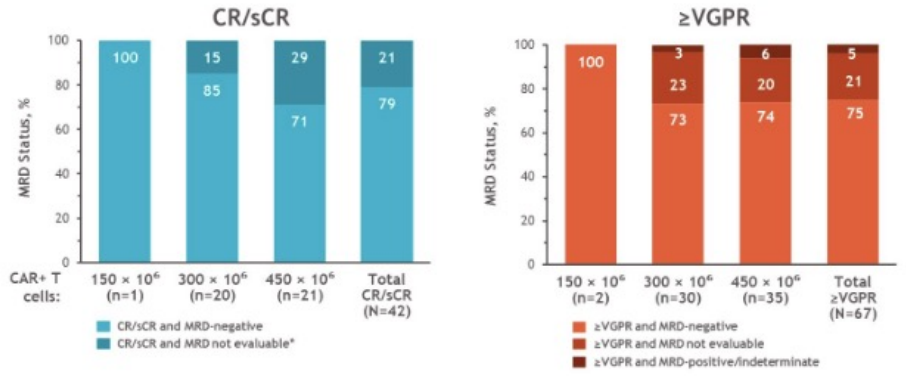
- PFS increased with higher target dose
- Median PFS was 12 mo at 450 x 10^6 CAR+ T cells

PFS by Best Response



- PFS increased by depth of response
- Median PFS was 20 mo in patients with CR/sCR

MRD-negativity by target dose



Target Dose, CAR+ T cells	150 x 10^6	300 x 10^6	450 x 10^6	Total
All ide-cel treated	N=4	N=70	N=54	N=128
MRD-negative and >CR, n(%) [95% CI]	1 (25) [0.6-80.6]	17 (24) [14.8-36.0]	15 (28) [16.5-41.6]	33 (26) [18.5-34.3]
MRD-negative and >VGPR, n(%) [95% CI]	2 (50) [6.8-93.2]	22 (31) [20.9-43.6]	26 (48) [34.4-62.2]	50 (39) [30.6-48.1]

- mOS 24.8 months (95% CI: 19.9-31.2) among all treated patients

CARTITUDE-1: Cilta-cel Registration Study

Trial design

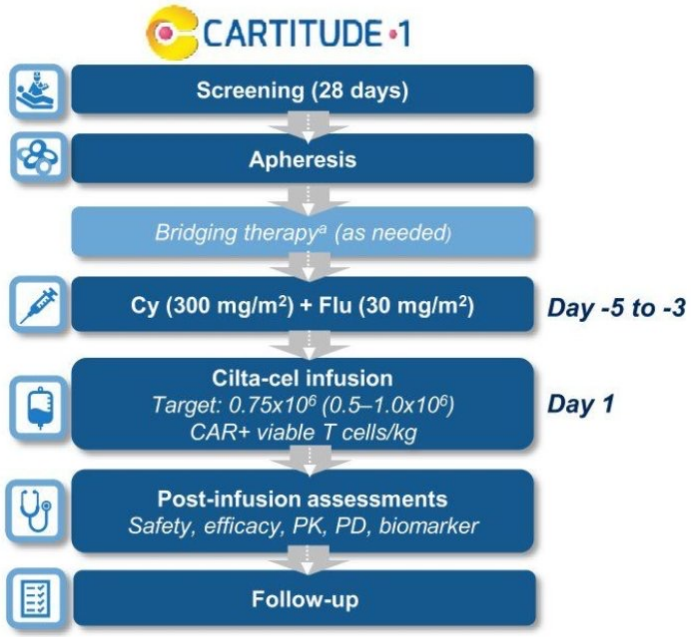
Primary objectives

- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel by ORR

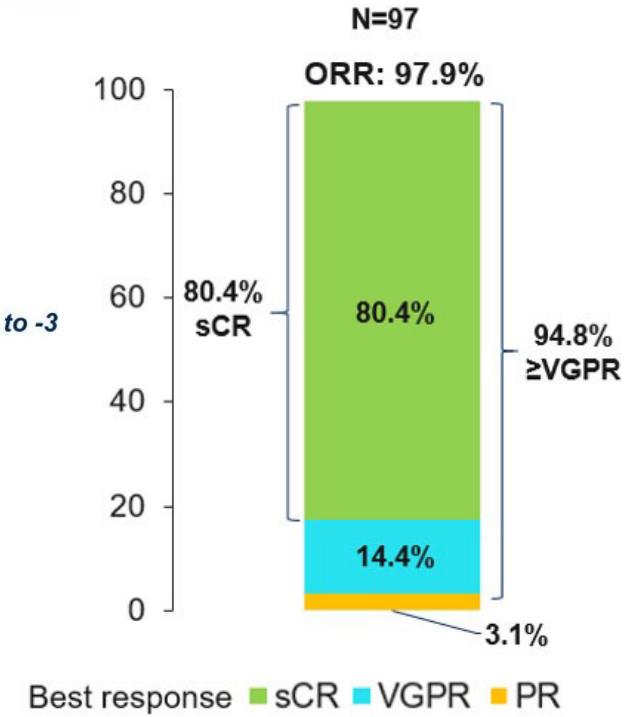
Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 therapy

- Median administered dose: 0.71×10^6 ($0.51–0.95 \times 10^6$) CAR+ viable T cells/kg



Response



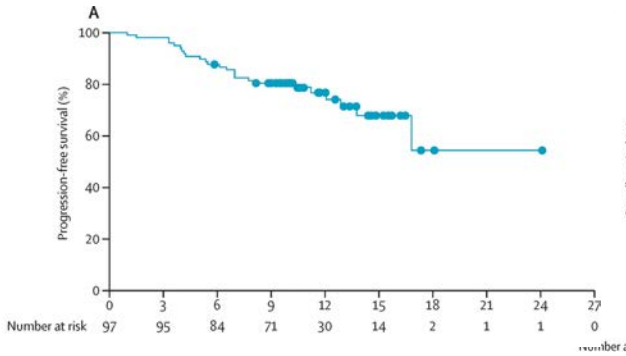
Berdeja et al. Lancet 2021; 398: 314–24

CARTITUDE-1 Follow Up

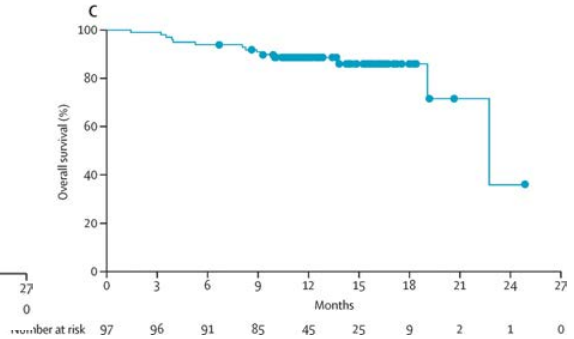
~27 months

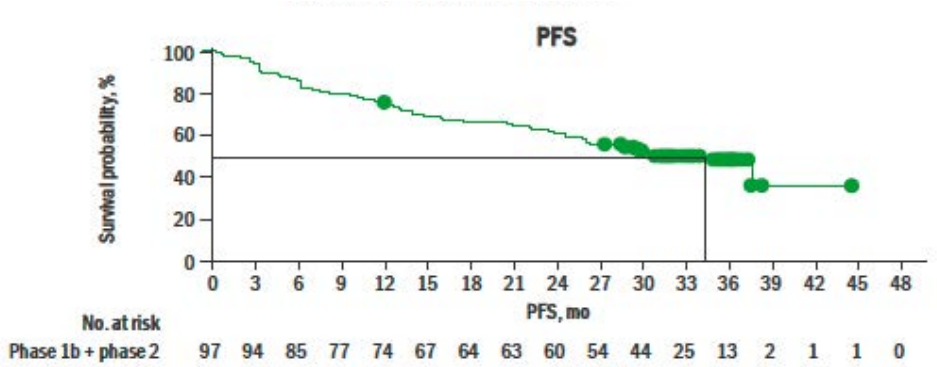
~3 years

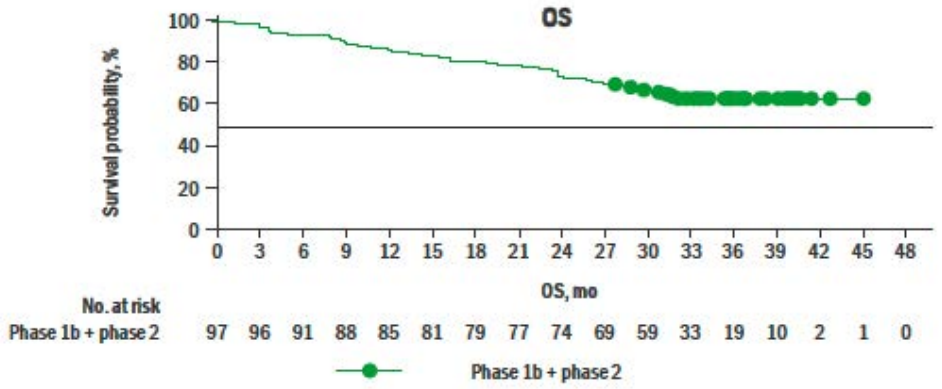
PFS



OS







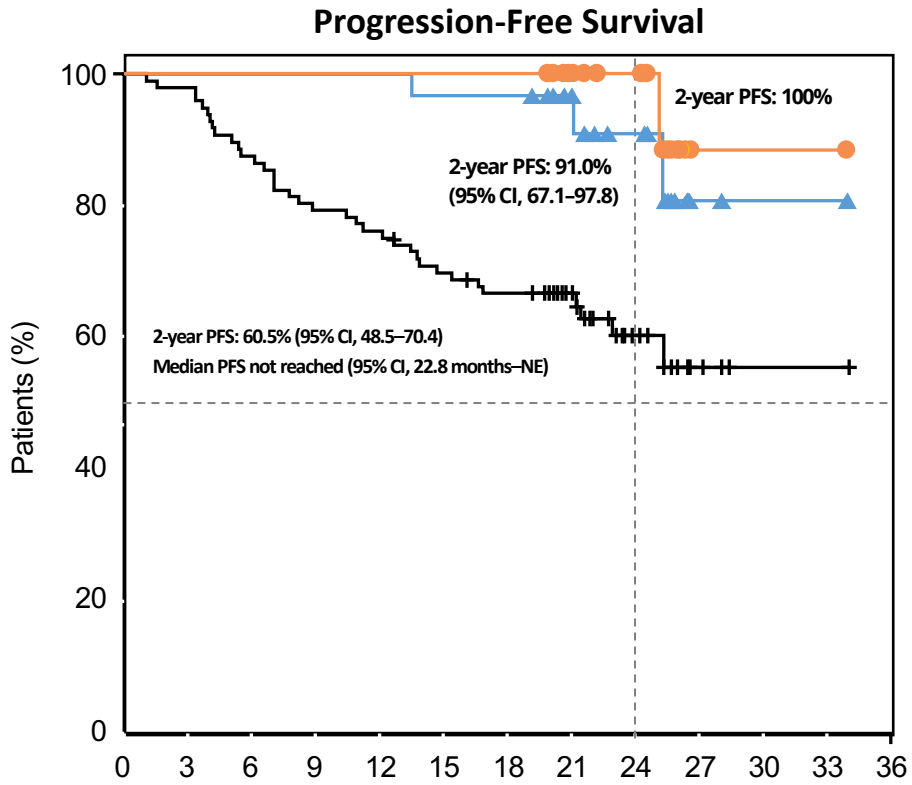
PFS by CR and sustained MRD negativity

Subgroups	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All patients	34.9 (25.2–NE)	54.2%	47.5%
≥CR[a]	38.2 (34.9–NE)	66.8%	59.8%
12-mo sustained MRD negativity[b]	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative ≥CR[b]	NR (NE–NE)	78.5%	NE

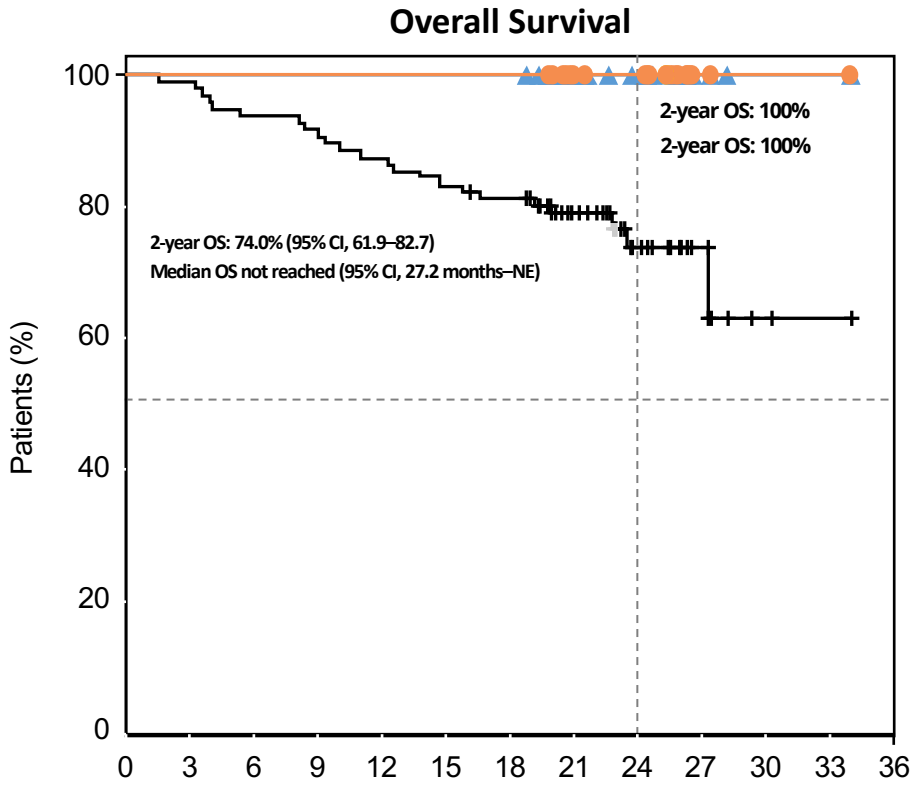
Berdeja et al. Lancet 2021; 398: 314–24

CARTITUDE-1: Progression-Free Survival and Overall Survival by MRD Negativity (10^{-5}) sustained for ≥ 6 and 12 months

- Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})



Patients at risk													
All patients	97	95	85	77	74	67	63	36	19	4	1	1	0
MRD negativity ≥6 months	30	30	30	30	30	29	29	17	12	2	1	1	0
MRD negativity ≥12 months	18	18	18	18	18	18	18	12	10	1	1	1	0



Patients at risk													
All patients	97	96	91	88	85	81	78	46	23	8	2	1	0
MRD negativity ≥6 months	30	30	30	30	30	30	30	17	13	3	1	1	0
MRD negativity ≥12 months	18	18	18	18	18	18	18	12	11	2	1	1	0

All patients MRD negativity sustained ≥6 months MRD negativity sustained ≥12 months

KarMMa and CARTITUDE-1 CRS and NT

	Ide-cel	Cilta-cel
FDA approval Trial, Reference Publication	KarMMa (n=124) Munshi NEJM 2021	CARTITUDE-1 (n=97) Berdeja Lancet 2021
Safety		
CRS (all; grades 3–4)	84% (5%)	95% (5%)
Median onset of CRS	1 day	7 days
ICANS (all; grades 3–4)	18% (3%)	17% (2%)
Delayed neurotoxicity (all; grades 3-4)	None	12% (9%)
Infections (all; grades 3–4)	69% (22%)	58% (20%)
Grades 3–4 neutropenia > 1 month Grades 3–4 thrombocytopenia > 1 month	41% 48%	10% 25%

Berdeja et al. Lancet 2021; 398: 314–24
Munshi et al. N Engl J Med 2021;384:705-16.

CARTITUDE-1: Safety

- **No new treatment-related deaths**
- **A total of 20 SPMs were reported in 16 patients**
  - Nine patients with hematologic malignancies (1 low-grade B-cell lymphoma, 6 MDS, 3 fatal AML[one patient had both MDS and fatal AML])
  - One patient each with malignant melanoma, adenocarcinoma, myxofibrosarcoma, and prostate cancer
  - Six non-melanoma skin cancers
- **One new case of signs and symptoms of parkinsonism (previously termed movement and neurocognitive TEAEs) (total n=6)**
  - On day 914, patient experienced cognitive slowing, gait instability, and neuropathy (all grade 1), and tremor (grade 3); he is currently stable and functioning, and remains in sCR with no steroids or anticytokine therapies given
  - Work-up is ongoing, including a differential diagnosis as post-encephalitis syndrome
  - Had 2 risk factors for parkinsonism (grade 2 CRS and grade 3 ICANS) after cilta-cel[5,6]
- **Outcomes in the previously reported 5 patients with parkinsonism[1,2]**
  - 3 have died (two from other underlying causes [sepsis and lung abscess] and one related to parkinsonism)
  - One patient has recovered, and one is recovering (ongoing grade 2 symptoms) at the time of the data cut
- **Following implementation of patient management strategies, the incidence of parkinsonism has decreased from 6% in CARTITUDE-1 to <0.5% across the CARTITUDE program**

Deaths

	Total (N=97)	Time of death post cilta-cel infusion (days)
Total deaths during the study	30	45–917
Due to progressive disease	14	253–746
AEs unrelated to treatment (n=9)		
Pneumonia	1	109
Acute myeloid leukemia[a]	3	418, 582, 718
Ascites[b]	1	445
Myelodysplastic syndrome	1	803
Respiratory failure	3	733, 793, 829
Septic shock	1	917
AEs related to treatment (n=6)		
Sepsis and/or septic shock	2	45, 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

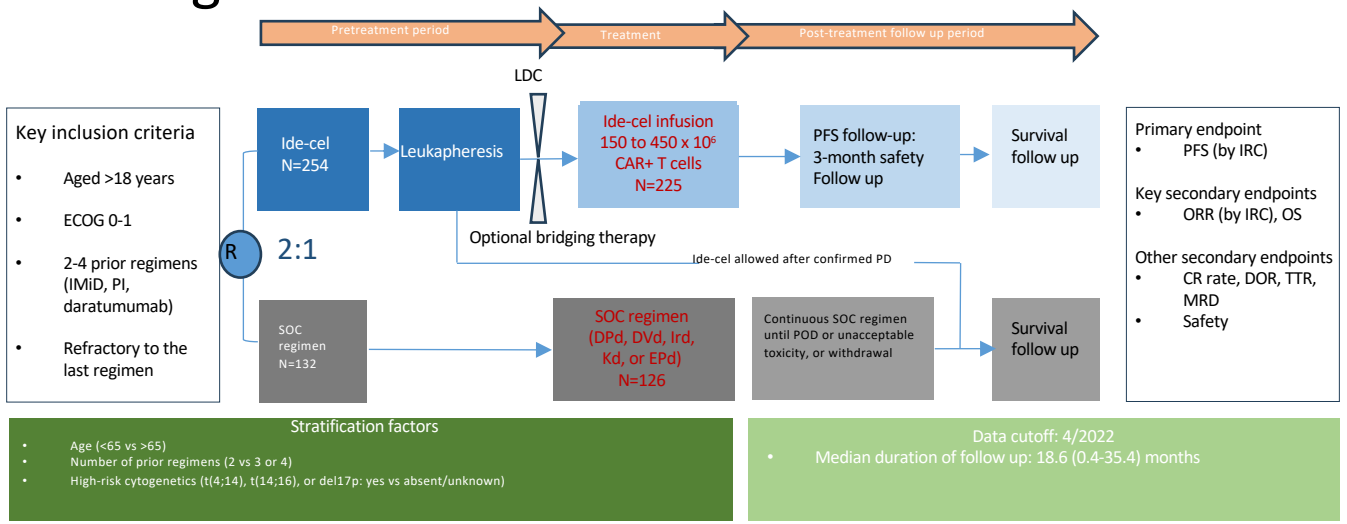
[a]One patient with AML also had MDS and a cytogenetic profile consistent with MDS (del20q [present before cilta-cel infusion], loss of 5q); another patient who died from AML had both prostate cancer and squamous cell carcinoma of the scalp. [b]Patient died from ascites unrelated to cilta-cel as assessed by the investigator due to noncirrhotic portal fibrosis and nonalcoholic steatosis that was present for many years preceding the study.
AML, acute myelogenous leukemia; AEs, adverse events; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; MDS, myelodysplastic syndrome; sCR, stringent complete response; SPM, secondary primary malignancies; TEAE, treatment-emergent AE

1. Berdeja JG, et al. *Lancet* 2021; 398:314-24. 2. Cohen AD, et al. *Blood Cancer J* 2022; 12:32.

CAR T-cell therapy in earlier lines

KarMMa-3: Ide-cel vs SOC After 2-4 Lines

Trial design



Baseline characteristics

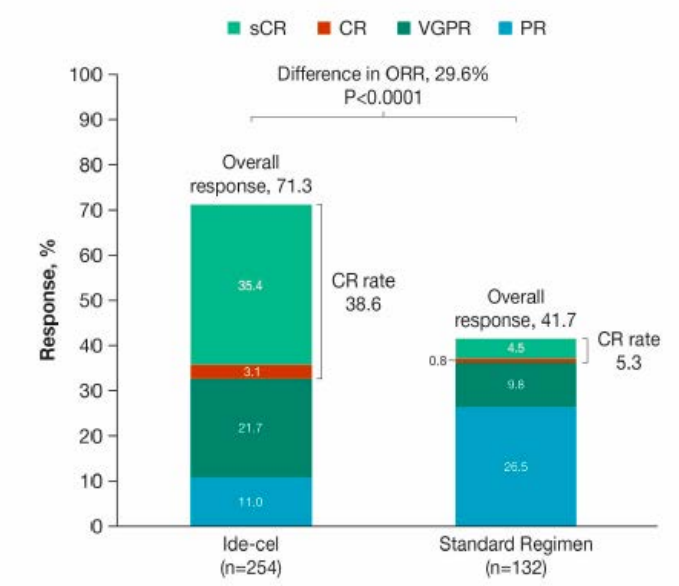
Median age	63 yrs
Median time since diagnosis	4.1 yrs
Median prior therapies	N=3
Triple-class refractoriness	66%
Daratumumab refractoriness	95%
High-risk cytogenetics	44%

Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

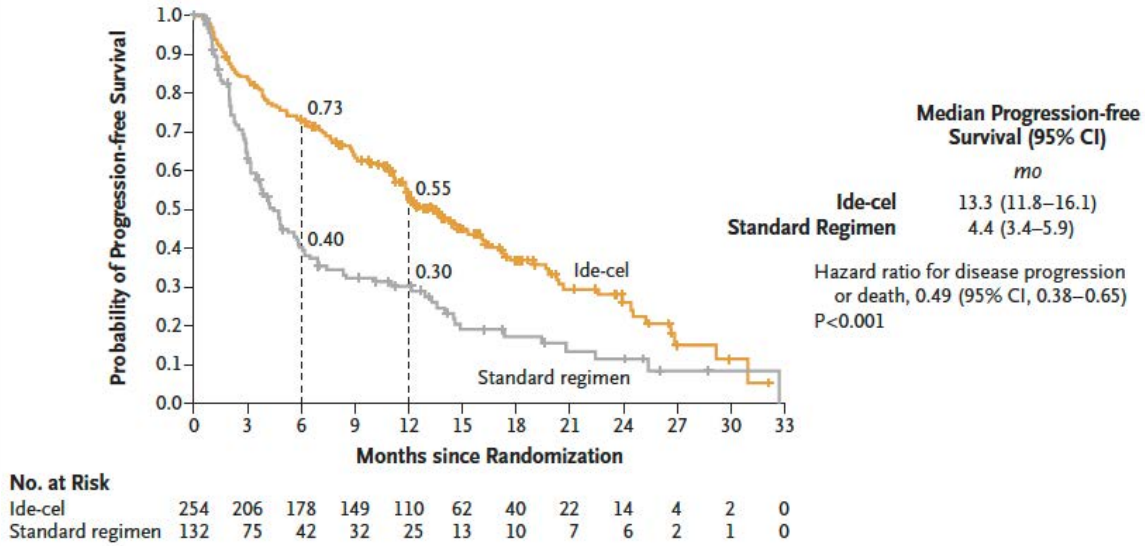
Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

KarMMa-3: Response and PFS

Response



PFS

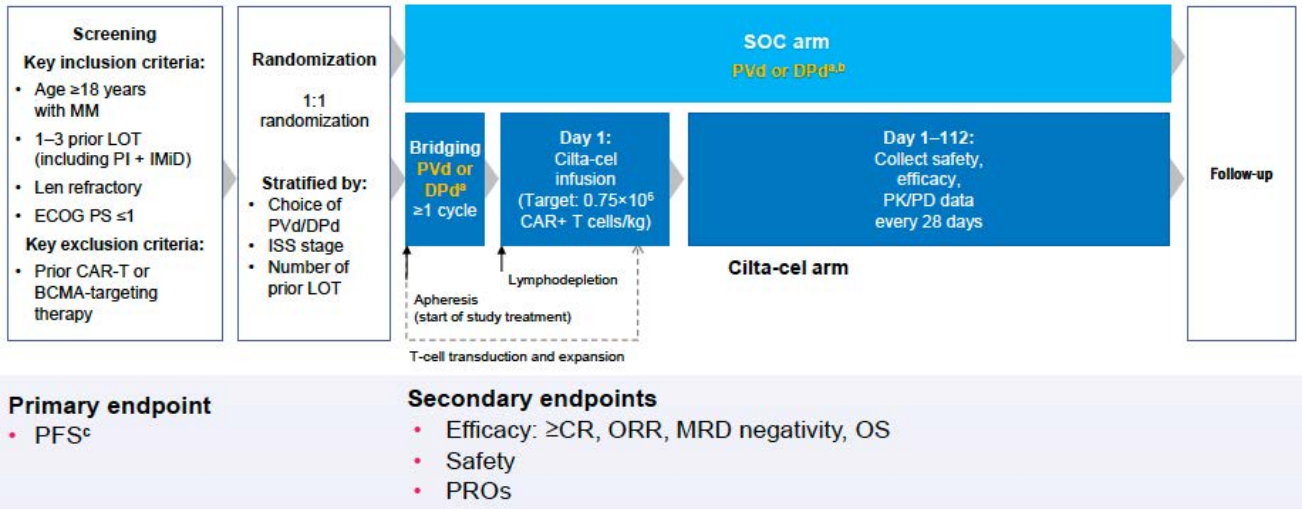


Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014

CARTITUDE-4: Cilta-cel vs DPd/PVd After 1-3 Lines

Trial design



Baseline characteristics

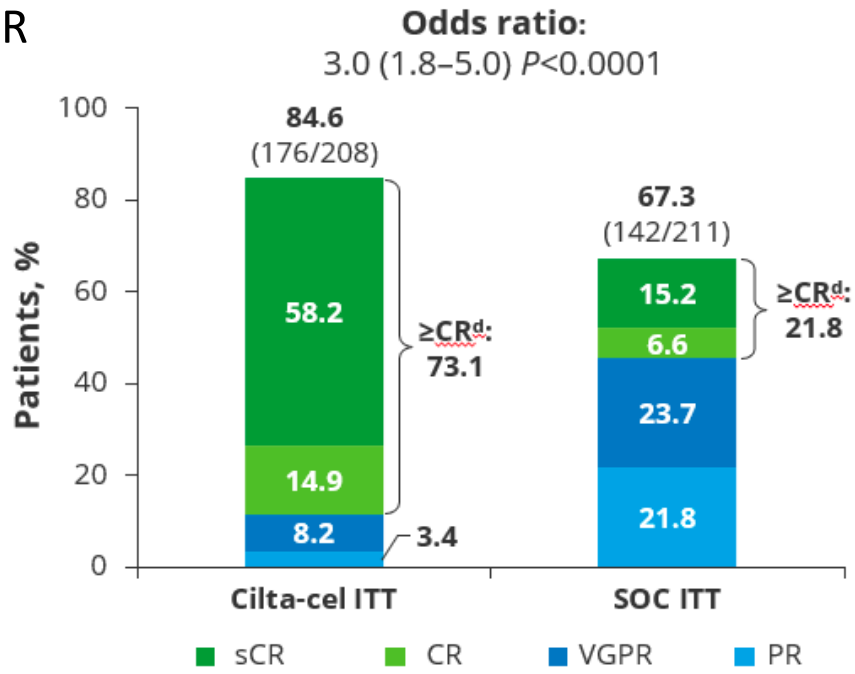
Median age	61.5 yrs
Median time since diagnosis	3 yrs
Median prior therapies	N=2
Triple-class refractoriness	14.4%
Daratumumab refractoriness	23.1%
High-risk cytogenetics	59.4%

Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

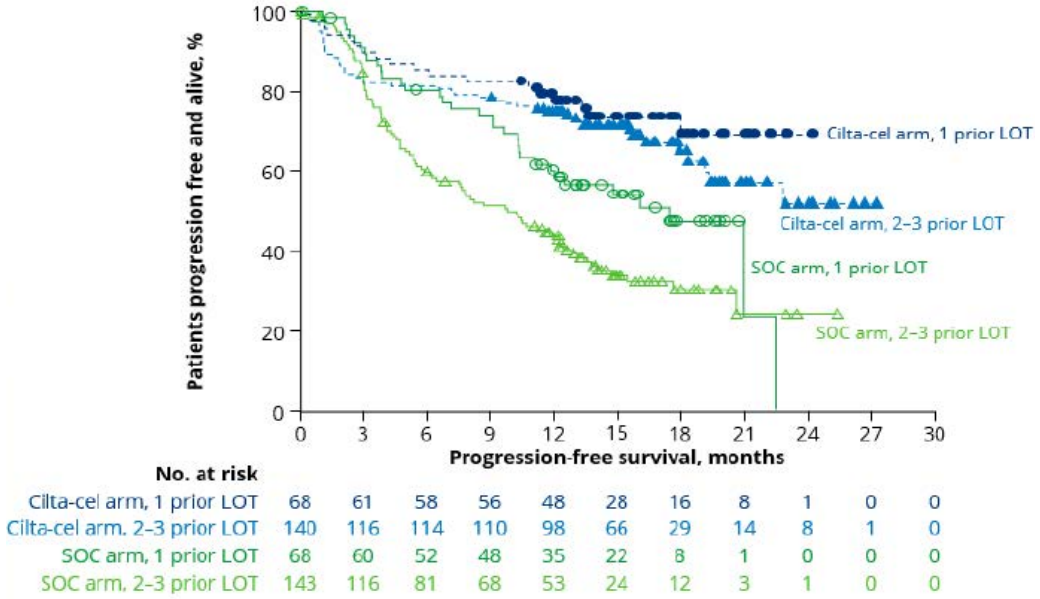
Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

CARTITUDE-4: Response and PFS

ORR



PFS by treatment and number of prior lines



No. at risk											
Cilta-cel arm, 1 prior LOT	68	61	58	56	48	28	16	8	1	0	0
Cilta-cel arm, 2–3 prior LOT	140	116	114	110	98	66	29	14	8	1	0
SOC arm, 1 prior LOT	68	60	52	48	35	22	8	1	0	0	0
SOC arm, 2–3 prior LOT	143	116	81	68	53	24	12	3	1	0	0

Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

KarMMa-3 / CARTITUDE-4: CRS and NT

KarmMMa-3

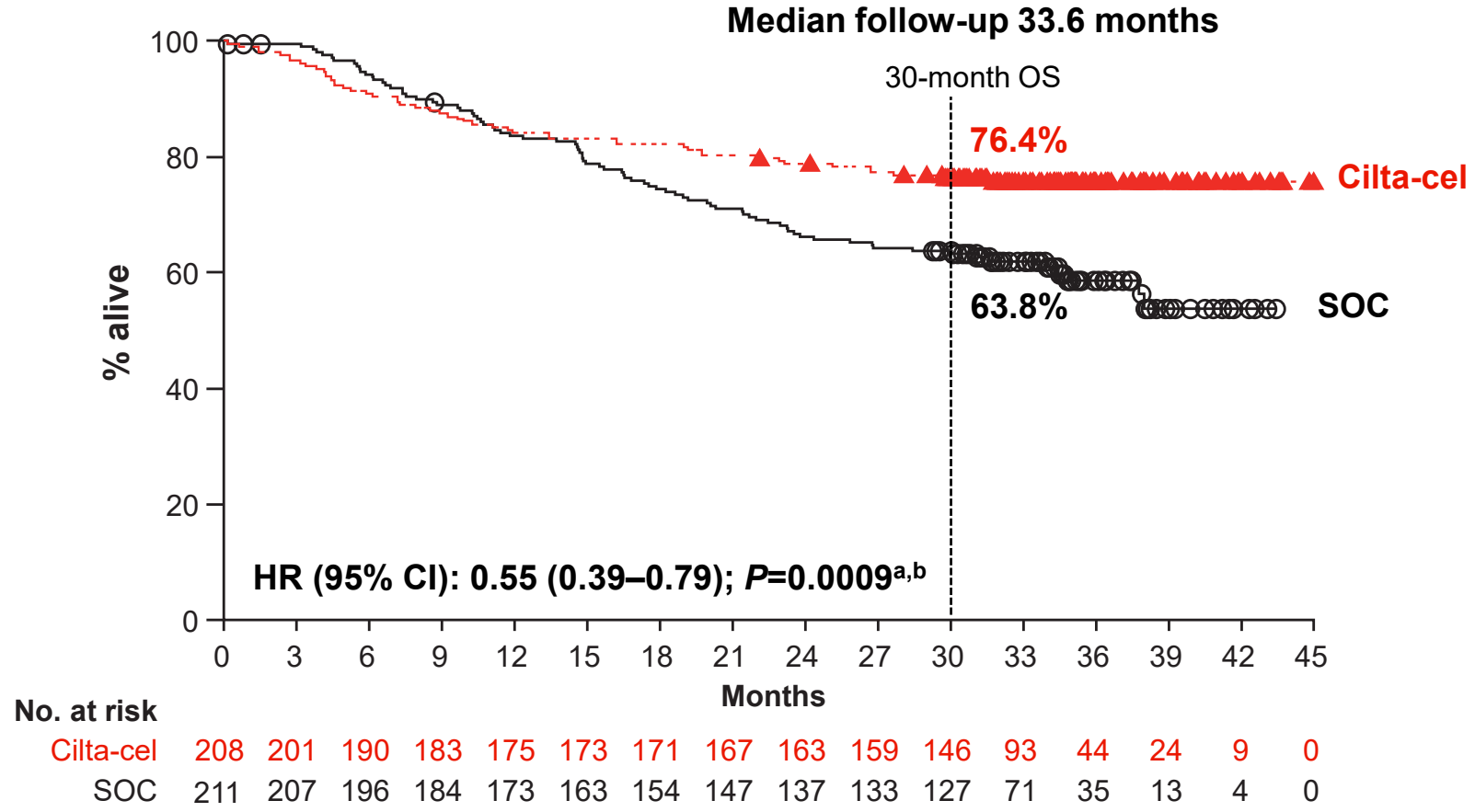
	Ide-cel (n = 225)
CRS,[a] n (%)	
Any grade	197 (88)
Grade 3/4	9 (4)
Grade 5	2 (1)
Median (range) time to first onset, days[b]	1.0 (1.0–14.0)
Median (range) duration, days	3.5 (1.0–51.0)
iiNT,[c] n (%)	
Any grade	34 (15)
Grade 3/4	7 (3)
Grade 5	0
Median (range) time to first onset, days[b]	3.0 (1.0–317.0)
Median (range) duration, days	2.0 (1.0–37.0)

CARTITUDE-4

AEs, n (%)	As-treated patients (n=176)				
	Any grade	Grade 3/4	Median time to onset, days	Median duration, days	Resolved, n
CRS	134 (76.1)	2 (1.1)	8	3	134
Neurotoxicity[a]	36 (20.5)	5 (2.8)			
ICANS	8 (4.5)	0[b]	10	2	8
Other[c]	30 (17.0)	4 (2.3)			
Cranial nerve palsy[d]	16 (9.1)	2 (1.1)	21	77	14
Peripheral neuropathy	5 (2.8)	1 (0.6)	63	201	3
MNT	1 (0.6)	0	85	–	0

Paula Rodriguez-Otero et al. N Engl J Med 2023; 388:1002-1014
Jesús San-Miguel et al. N Engl J Med 2023; 389:335-347

Long-Term CARTITUDE-4 Update (34 Months): Cilta-cel Significantly Improved Overall Survival

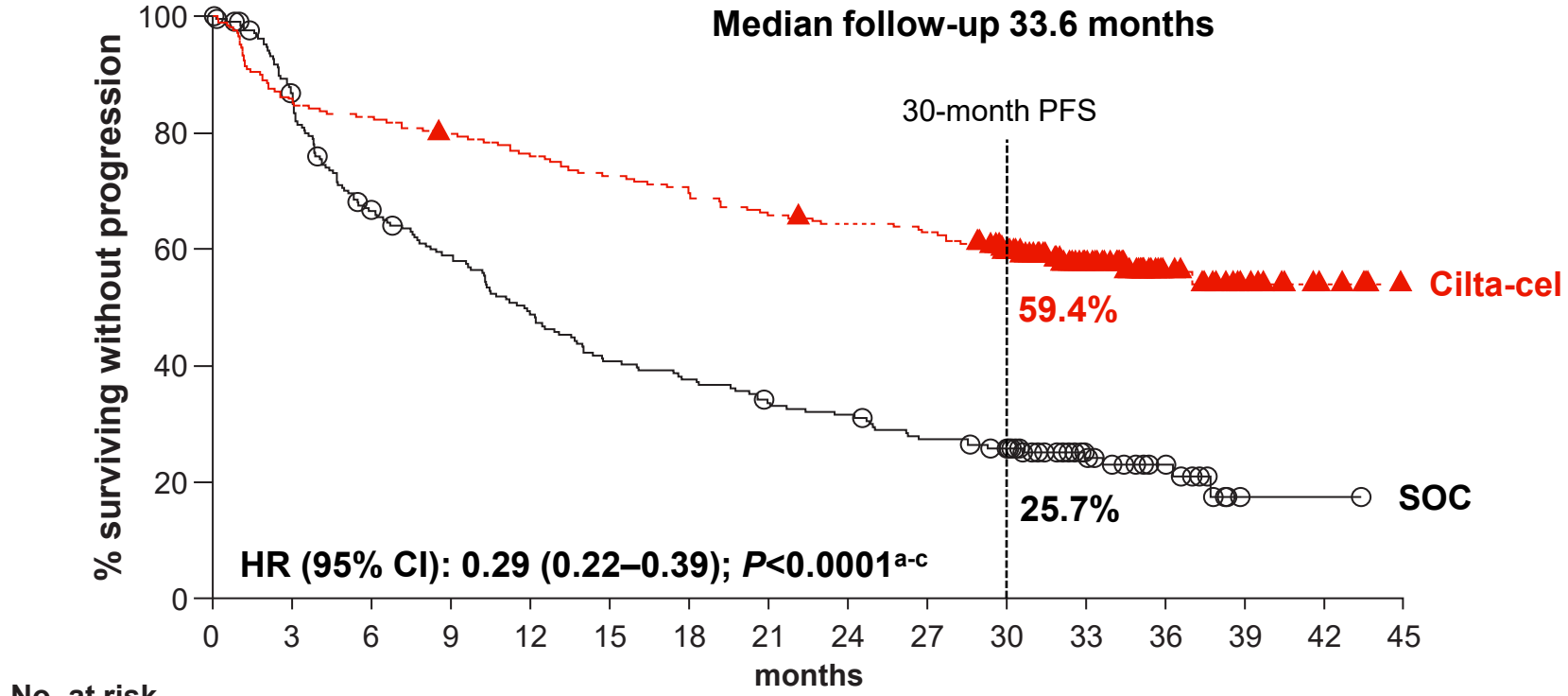


First CAR-T to demonstrate overall survival benefit in multiple myeloma

[a]Log-rank test. *P*-value, 0.0009, crossed the prespecified boundary of 0.0108 as implemented by the Kim-DeMets spending function with parameter=2. [b]Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.
CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; OS, overall survival; SOC, standard of care.

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Long-Term CARTITUDE-4 Update (34 Months): Cilta-cel Maintained Significant Improvement in Progression-Free Survival

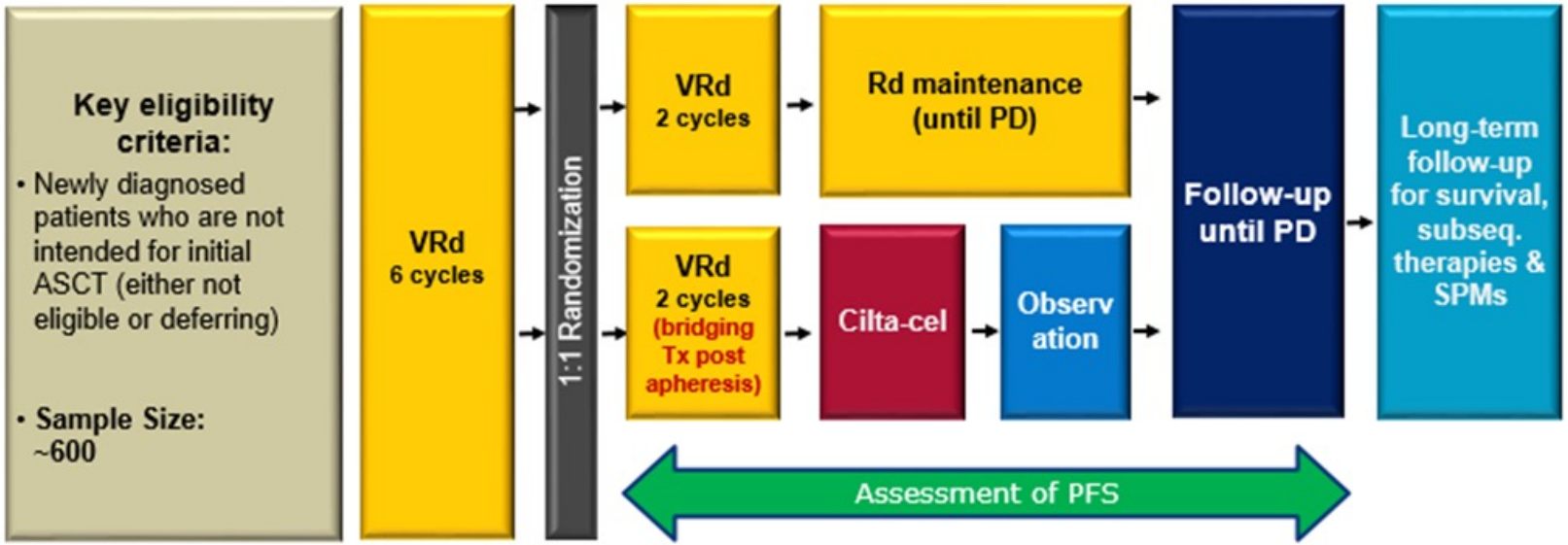


~70% reduction in the risk of progression or death in patients who received cilta-cel and mPFS has not been reached

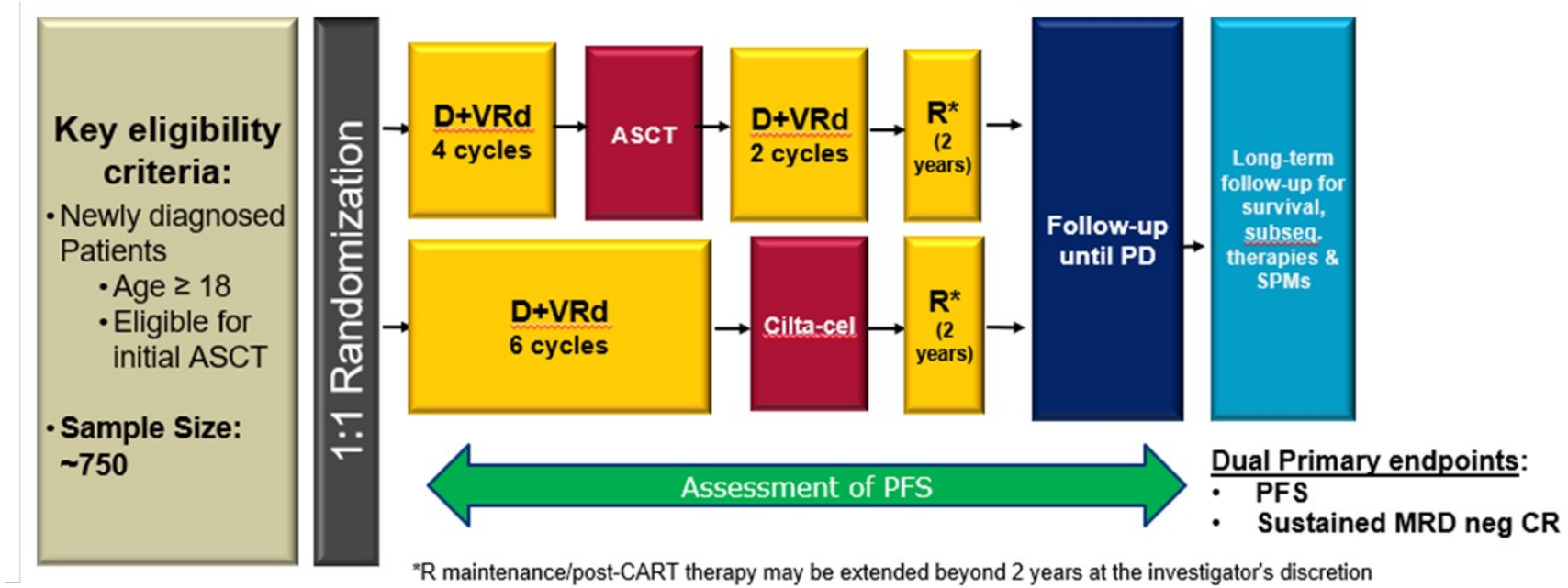
[a]Constant piecewise weighted log-rank test. [b]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization.
[c]Nominal *P* value.
Cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival; SOC, standard of care.

Presented by M-V Mateos at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

CARTITUDE-5: Randomized, phase 3 in NDMM, not intended for transplant



CARTITUDE-6: Randomized, phase 3 in NDMM, transplant eligible

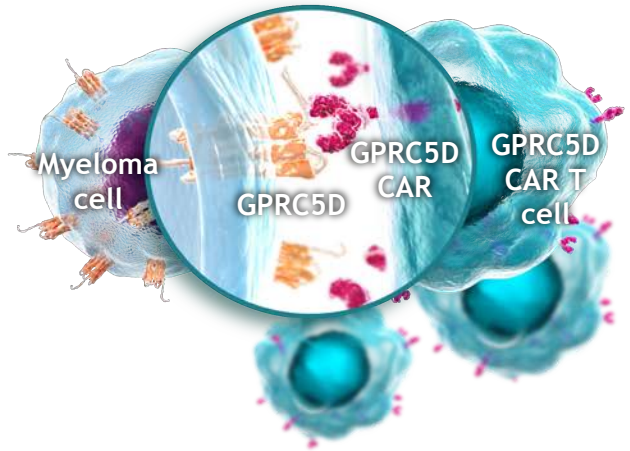


Emerging CAR-T therapies in R/R myeloma

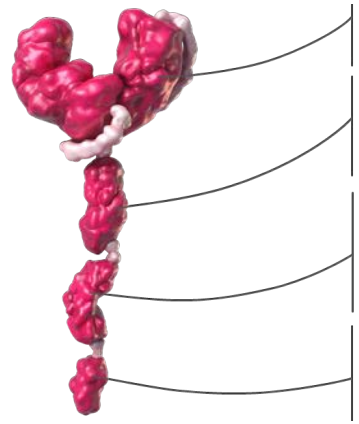
BMS-986393: a GPRC5D autologous CAR T-cell therapy

- 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

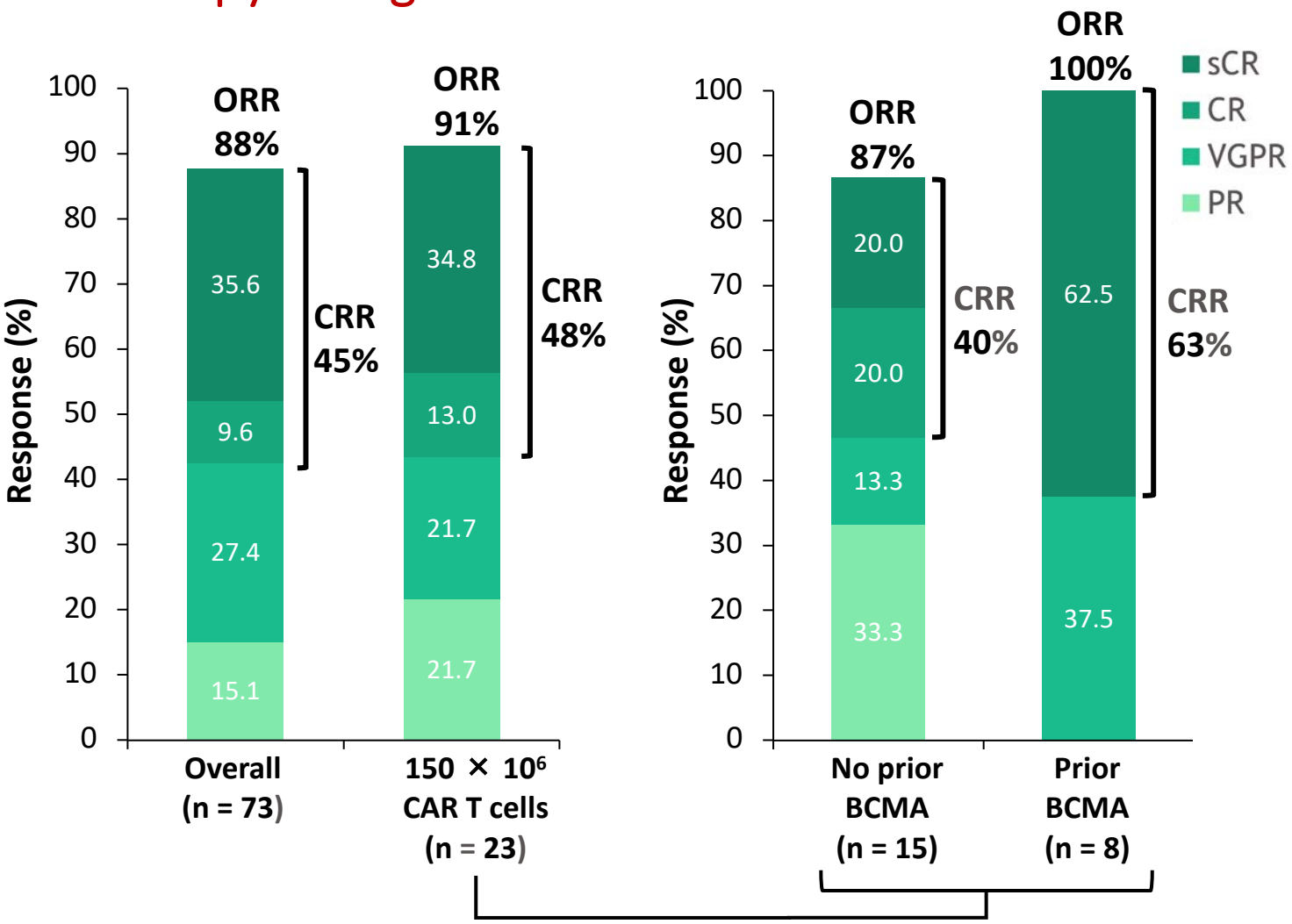


BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; GPRC5D, G protein-coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteosome inhibitor; RMAT, regenerative medicine advanced therapy; RP2D, recommended phase 2 dose; RRMM, relapsed and/or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



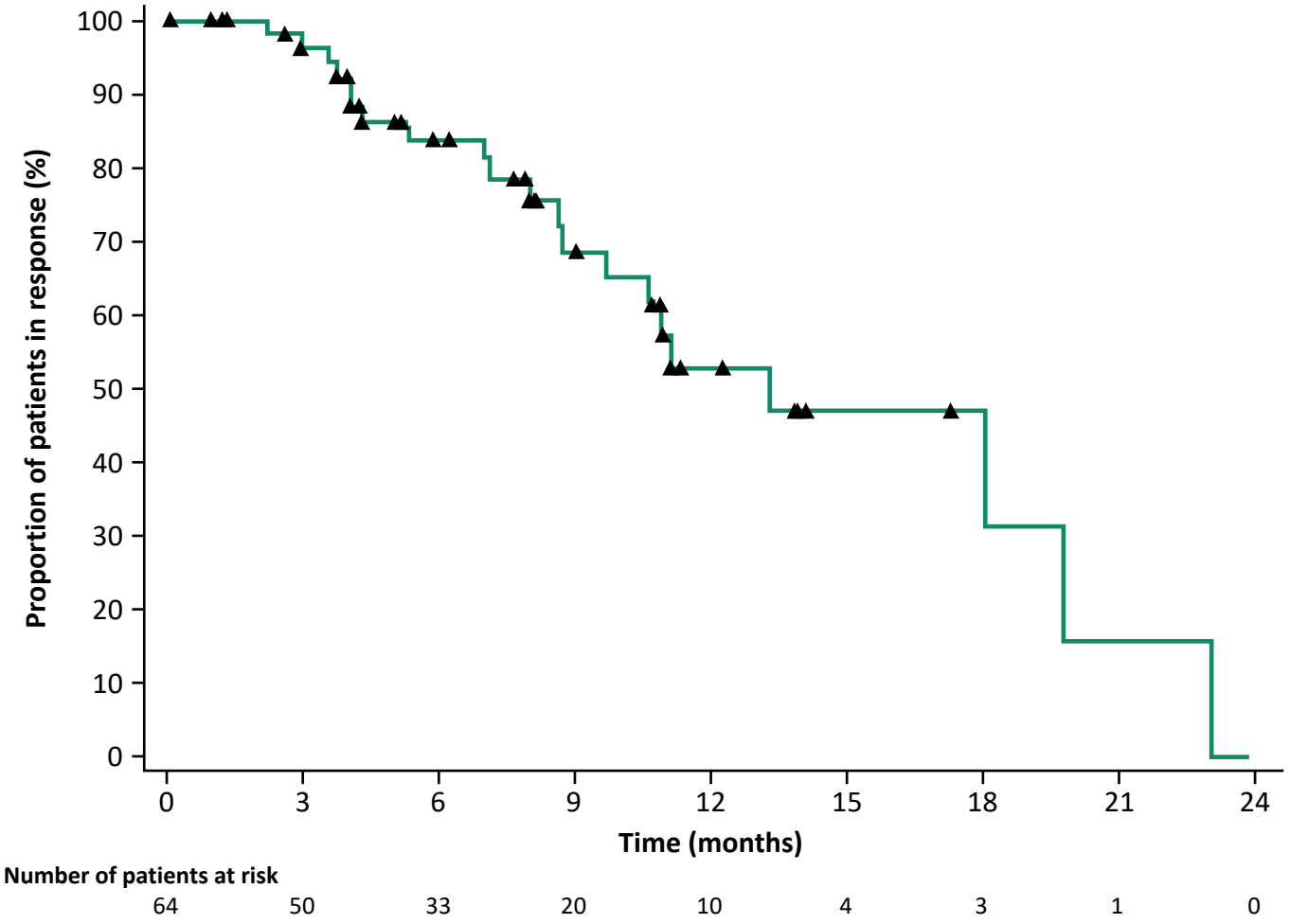
ORR in subgroups of interest (all dose levels)

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]

FDA warns of secondary cancer risk tied to CAR-T therapies that treat cancer

By Jacqueline Howard, CNN

5 minute read · Updated 4:36 PM EST, Wed January 24, 2024

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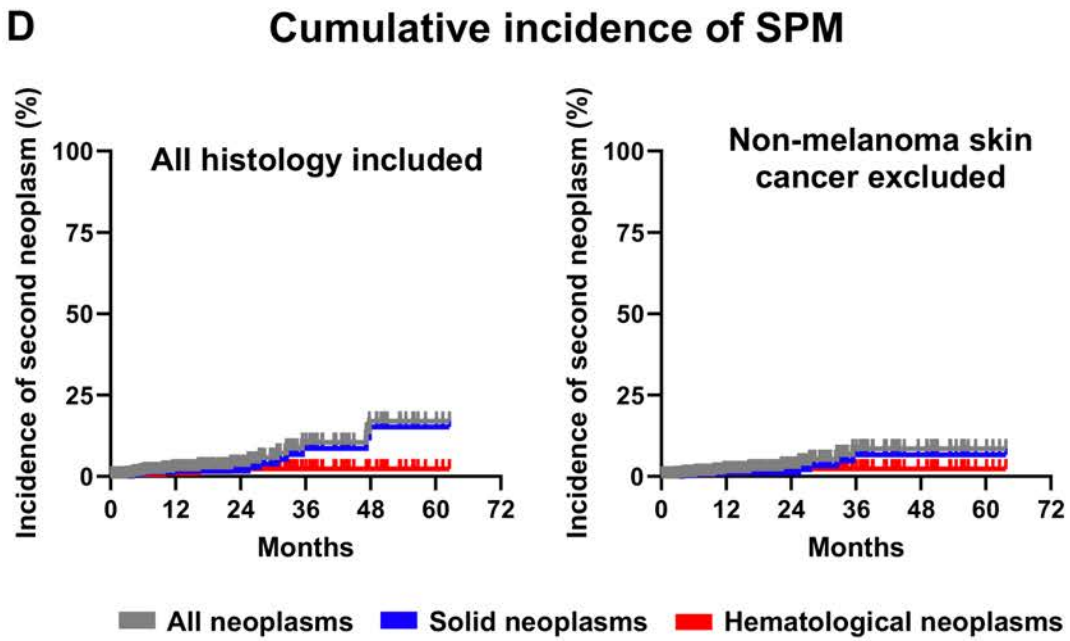
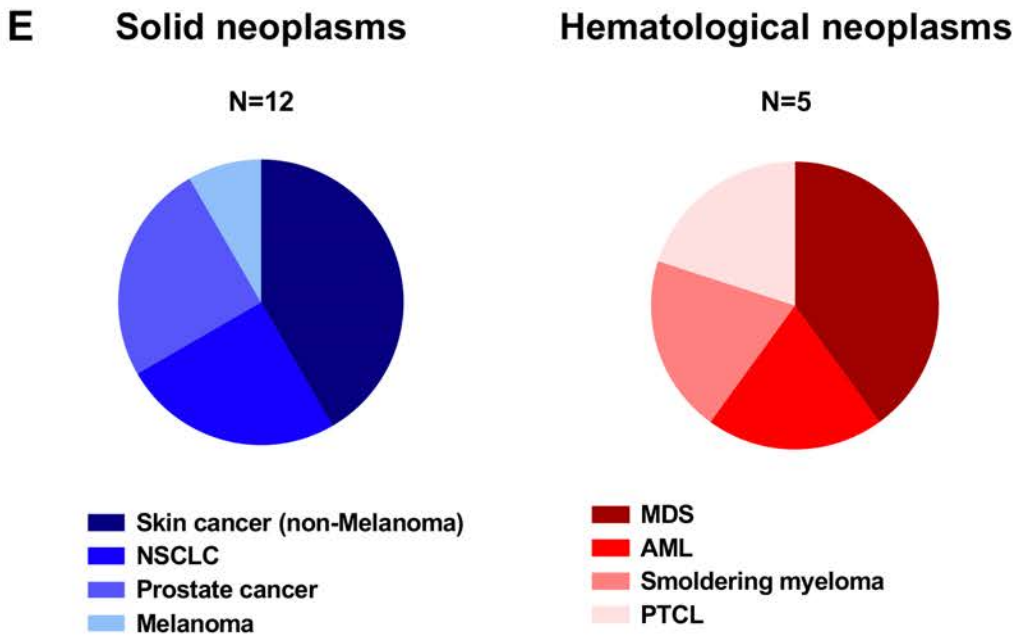
Second Primary Cancers after CAR T Cells





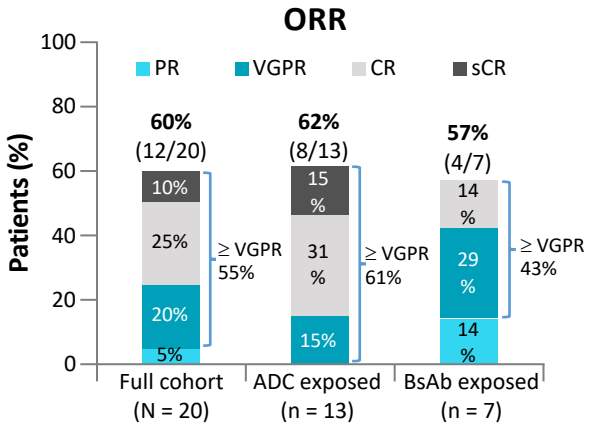
Ghilardi et al Nat Medicine 2024

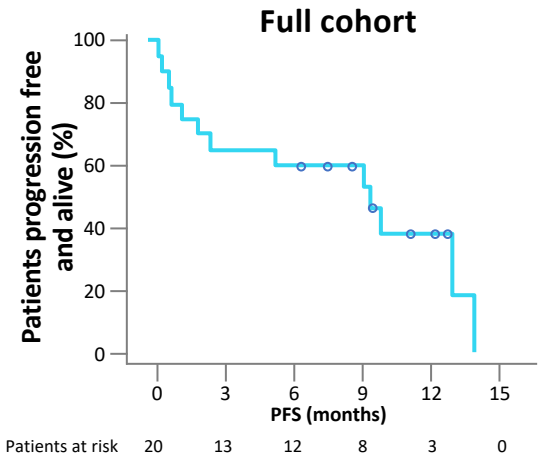
Questions and Challenges

- Moving therapies early
- Sequencing
- Duration
- Combinations

Sequencing: CAR-T Cell Therapy After BCMA-Targeted Therapy

CARTITUDE-2, Cohort C: Cilta-cel
Patients with RRMM with previous exposure to PI, IMiD agent, anti-CD38 mAb, and a non-cellular BCMA-targeting therapy[1]

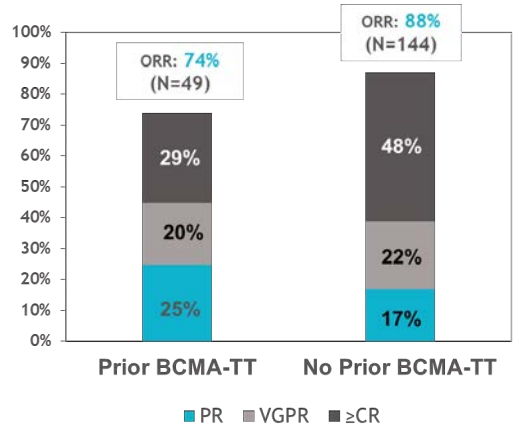


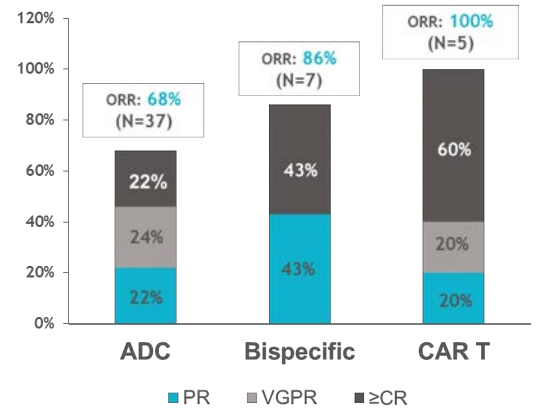


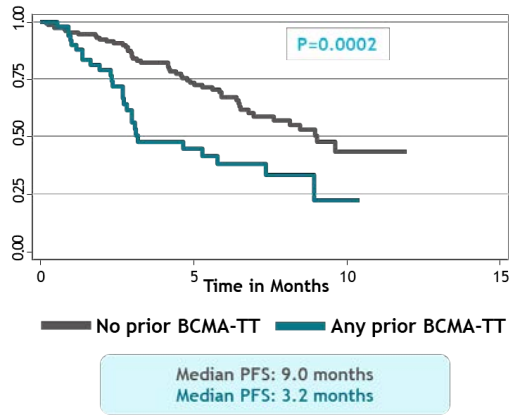
Median PFS

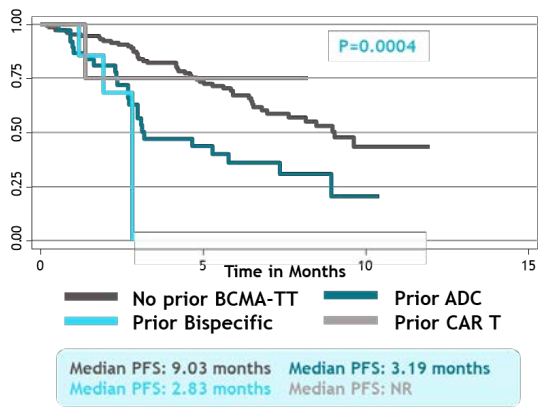
	Full cohort (N = 20)	ADC exposed (n = 13)	BsAb exposed (n = 7)
PFS, mo (95% CI)	9.1 (1.5-13.2)	9.5 (1.0-15.2)	5.3 (0.6-NE)

Real-world experience of patients with multiple myeloma receiving ide-cel after a prior BCMA-targeted therapy[2]



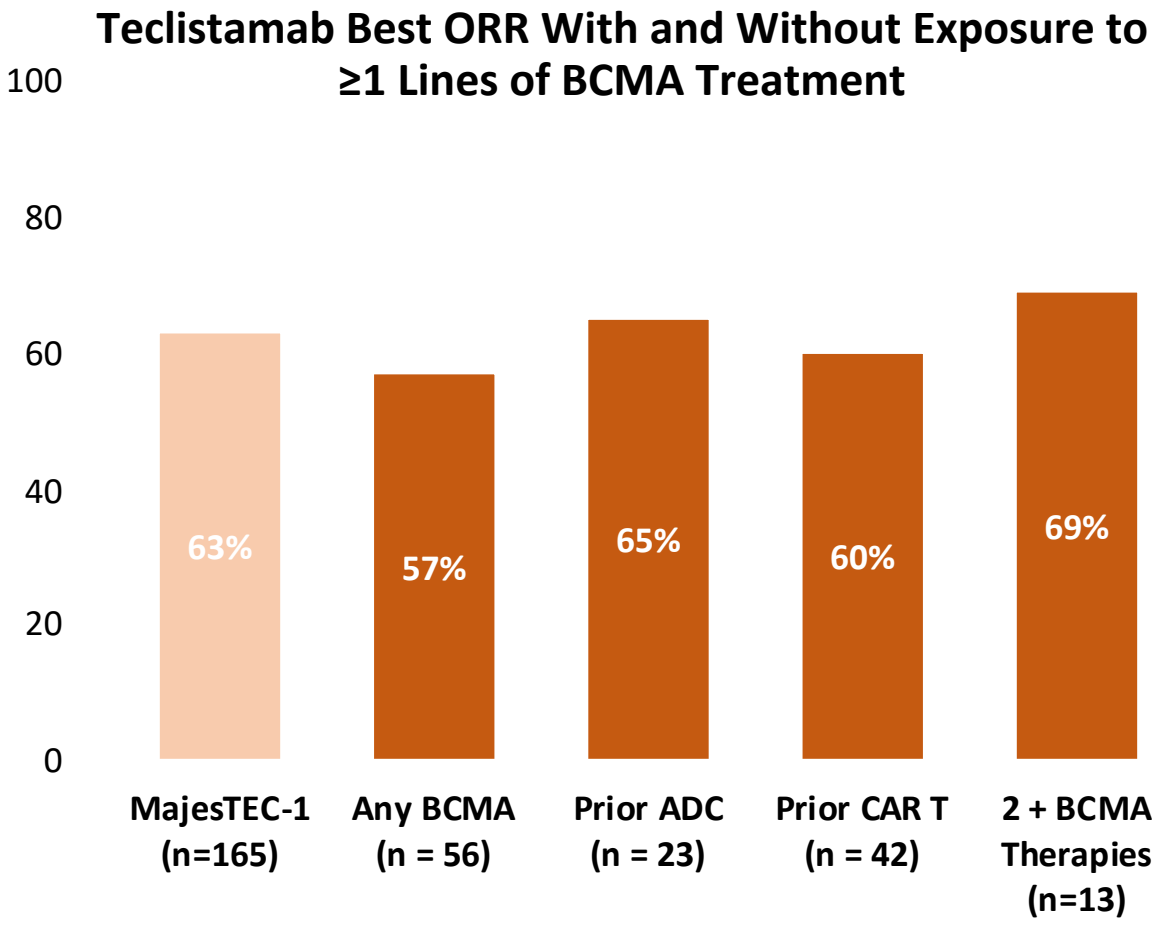


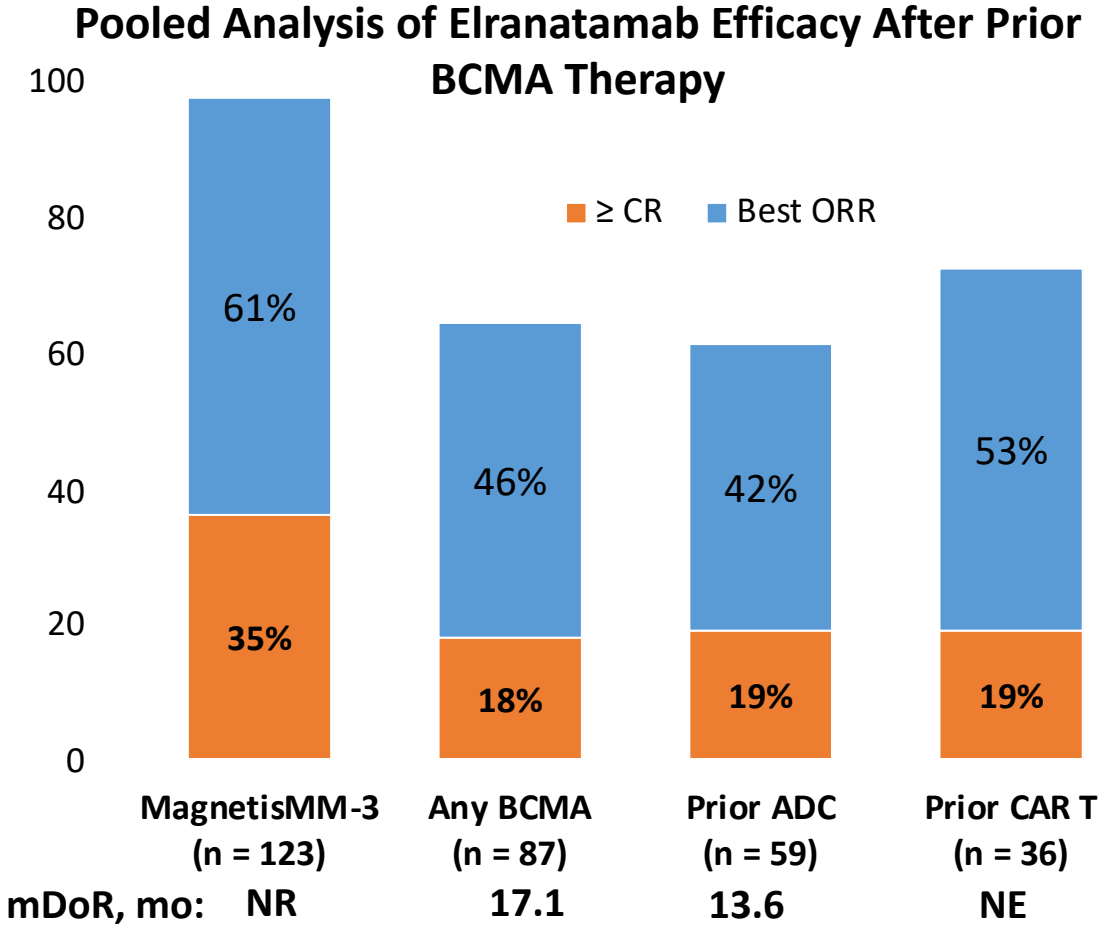




1. Cohen et al. *Blood*. 2023;141(3):219-230. 2. Ferreri CJ et al. *Blood Cancer J*. 2023;13:117; abstract 766.

Outcomes With Bispecific Antibodies After Prior BCMA-Directed Therapy





Moreau. NEJM. 2022;387:495. Dima. ASH 2023. Abstr 91.
Lesokhin. Nat Med. 2023;29;2259-2267. Nooka. ASCO 2023. Abstr 8008

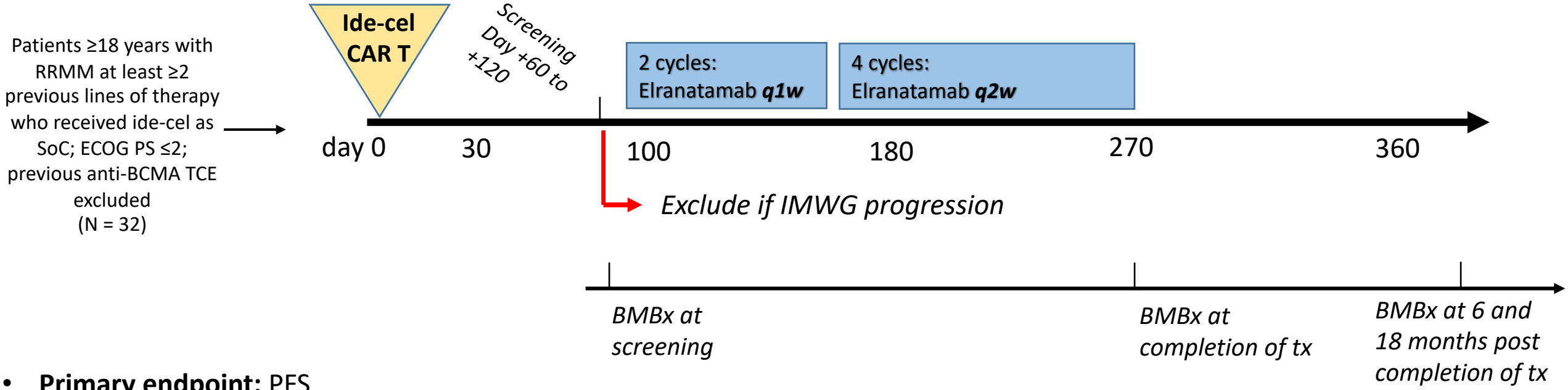
Challenges

- Moving therapies early can impact later therapies
- Sequencing and maintenance?
- With early—no more one and done?
- ? Combinations

Bispecific Consolidation after CAR T cells

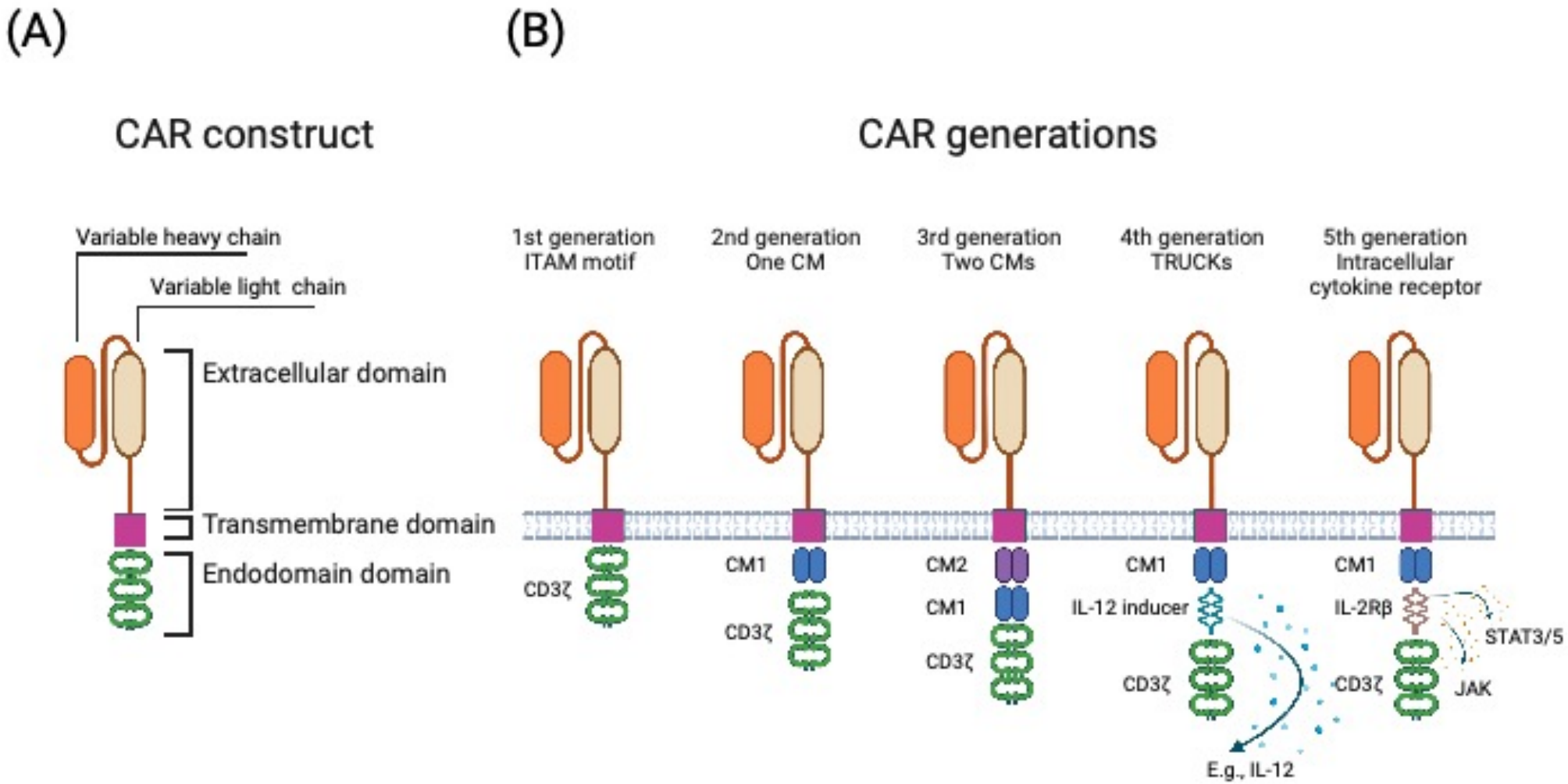
A Phase 2 Study of Idecabtagene vicleucel followed by Elranatamab consolidation in Relapsed/Refractory Multiple Myeloma

- Single center, investigator-sponsored, phase II study

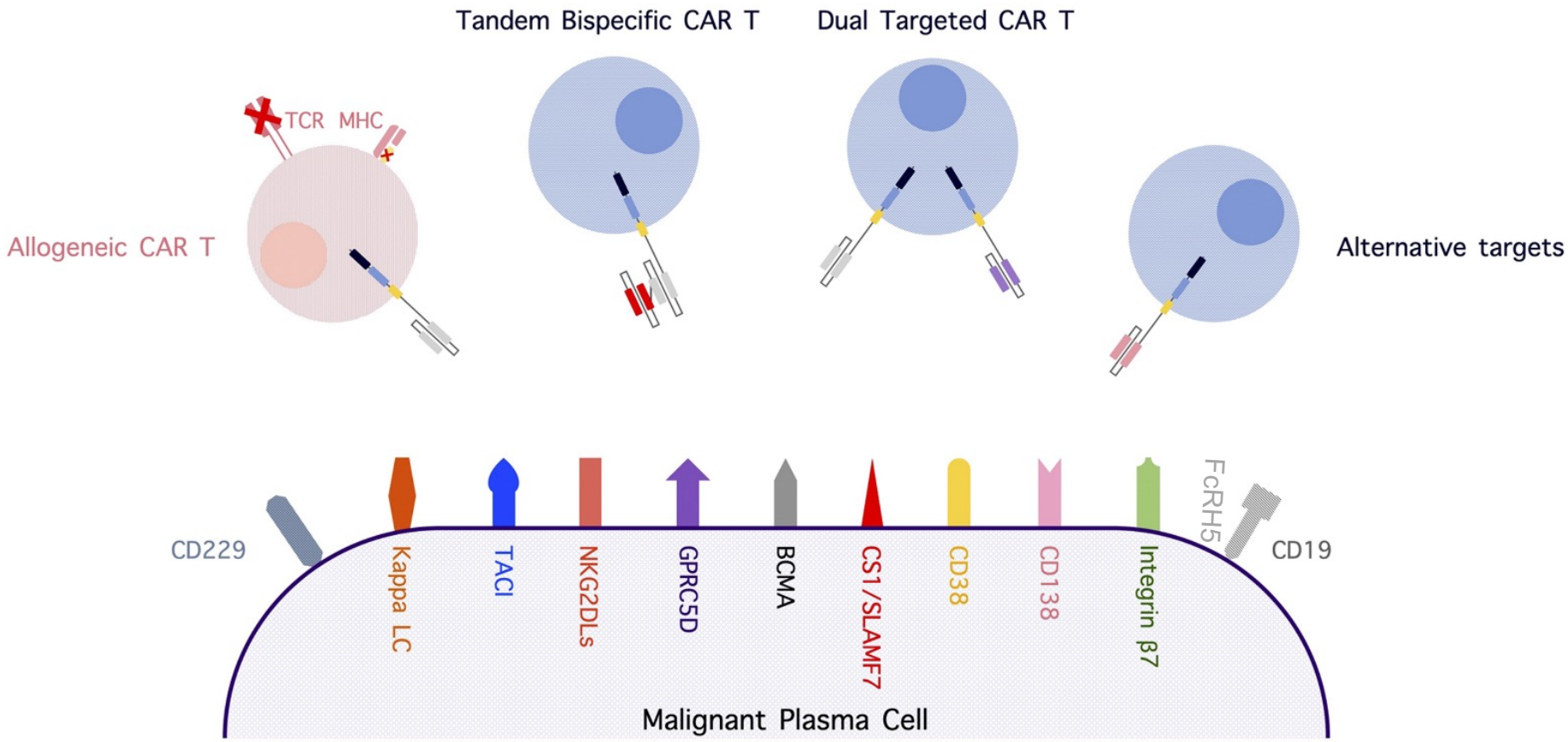


- **Primary endpoint:** PFS
- **Secondary endpoints** included safety, OS, ORR, DOR time to MRD negative status and sustained MRD negative status of ≥6 or ≥12 months

The Future of CAR Constructs



Future of CAR T cells and/or BiTES in Multiple Myeloma



Kitsada Wudhikarn,Sham Mailankody,Eric L. Smith, Future of CAR T cells in multiple myeloma, Hematology Am Soc Hematol Educ Program, 2020, Figure 1.

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Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Orlowski

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory MM — Dr Richardson

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies for the Treatment of MM — Prof Moreau

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Lonial

RTP
RESEARCH
TO PRACTICE

Case Presentation: 72-year-old woman experiences disease relapse 7 years after induction RVd followed by autotransplant and maintenance

Dr Henna Malik (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How often do you encounter patients who cannot tolerate lenalidomide maintenance, and what do you do in that situation?

In which situations, if any, do you recommend a second ASCT, particularly for patients with a prolonged response to initial transplant?

Are there any reliable predictors of treatment benefit after ASCT?

RTP
RESEARCH
TO PRACTICE

Dr Shams Bufalino
(Park Ridge, Illinois)

Case Presentation: 56-year-old morbidly obese man with atrial fibrillation and heart failure is not considered a candidate for CAR-T therapy because of comorbidities

Dr Shams Bufalino
(Park Ridge, Illinois)

Case Presentation: 64-year-old woman with multiple regimen-refractory MM receives teclistamab

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you typically sequence bispecific antibodies vis-à-vis CAR T-cell therapy in MM?

For a patient who has experienced disease progression on BCMA-directed CAR T-cell therapy, would you be more inclined to treat with a BCMA- or non-BCMA-directed bispecific antibody? Will you administer a non-BCMA bispecific antibody immediately after a BCMA-targeted agent?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What tolerability issues have you encountered with teclistamab, and how do you prevent and ameliorate these?

What tolerability issues have you encountered with talquetamab, and how do you prevent and ameliorate these?

RTP
RESEARCH
TO PRACTICE

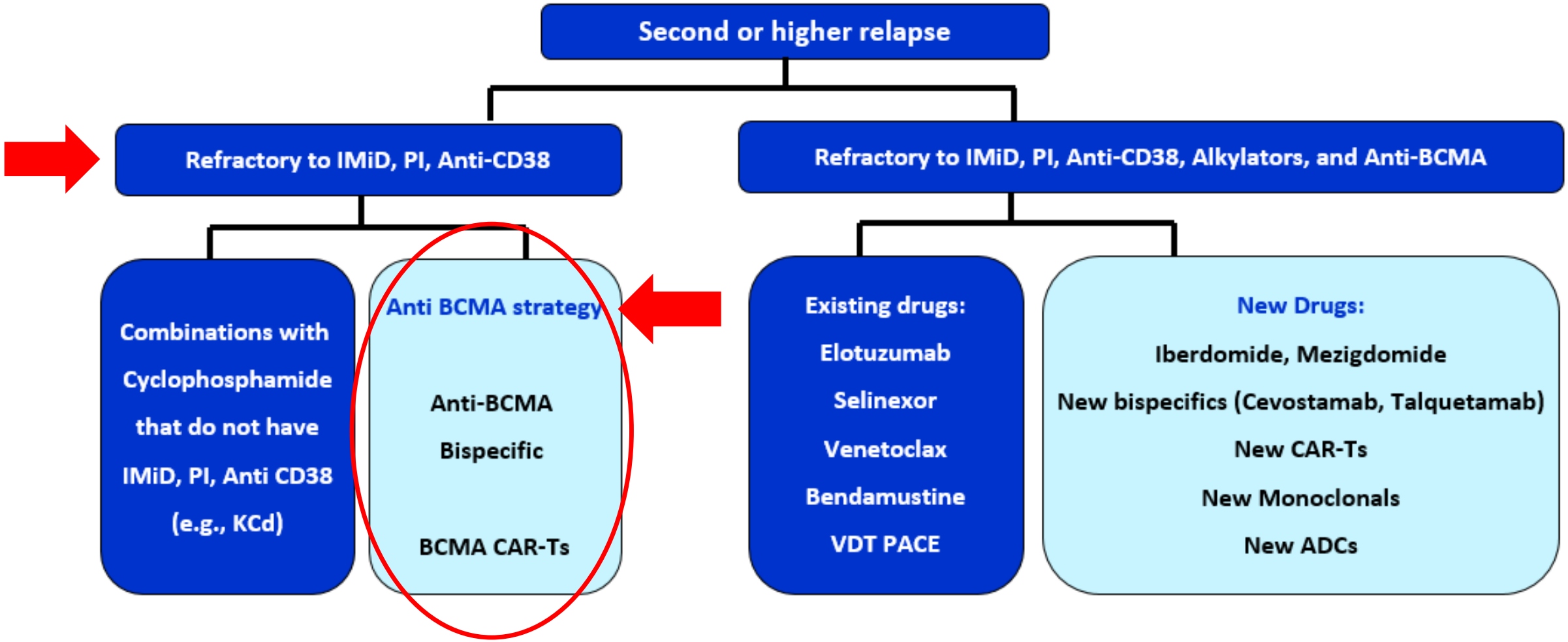
Bispecific antibodies (BsAb) in MM
What are the differences?
Which targeted BsAb to start with?

Pr Philippe Moreau

CHU Hôtel-Dieu, Nantes, France

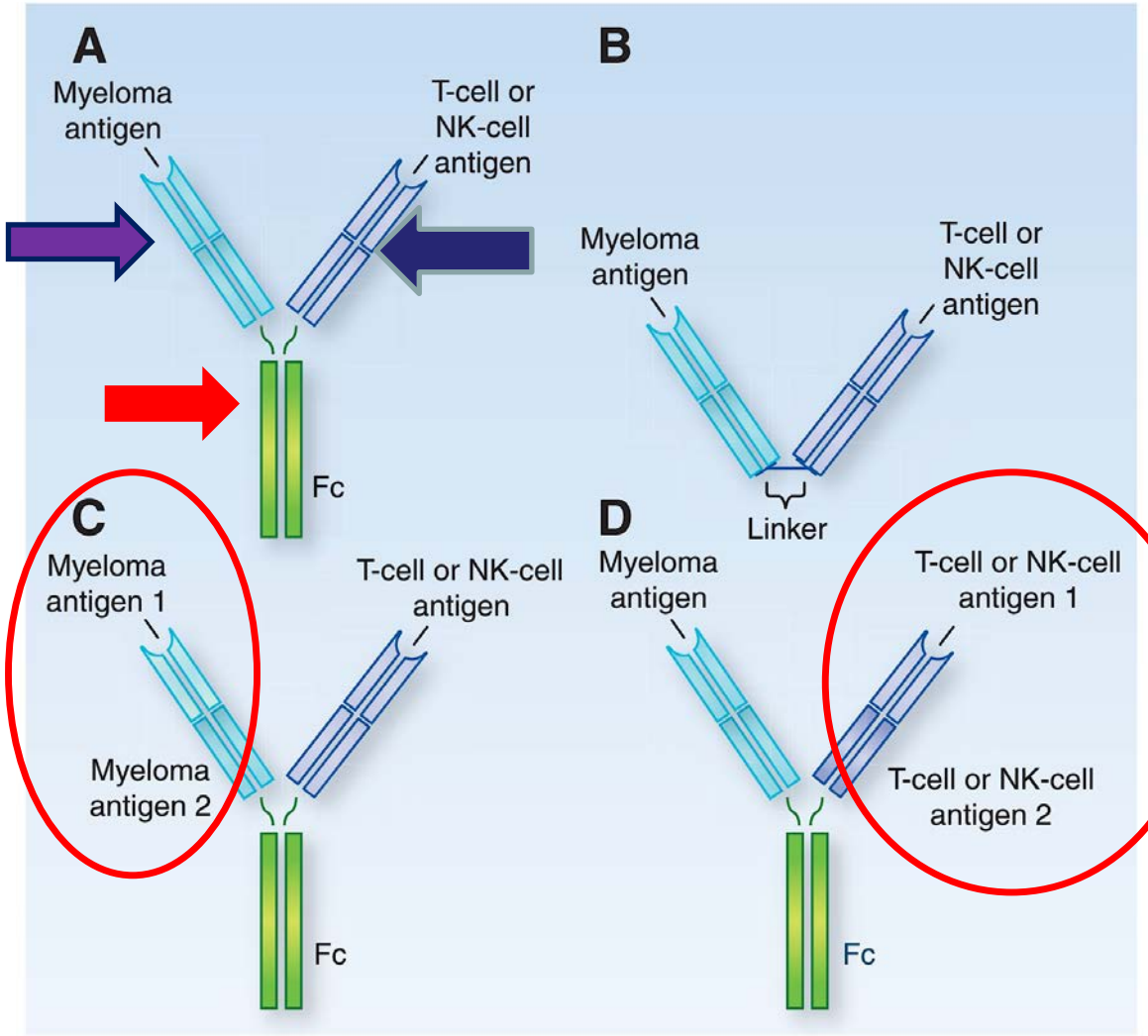
CENTRE HOSPITALIER
UNIVERSITAIRE DE NANTES

Myeloma: Second or higher relapse



Bispecific Antibodies in Multiple Myeloma: Present and Future

Guido Lancman[1], Dahniel L. Sastow[2], Hearn J. Cho[1], Sundar Jagannath[1], Deepu Madduri[1], Samir S. Parekh[1], Shambavi Richard[1], Joshua Richter[1]. Larvsa Sanchez[1]. and Aiai Chari[1]



NK, natural killer

Lancman G et al. Blood Cancer Disc 2021;2(5):423-33

Bispecific Antibodies in Multiple Myeloma: Present and Future

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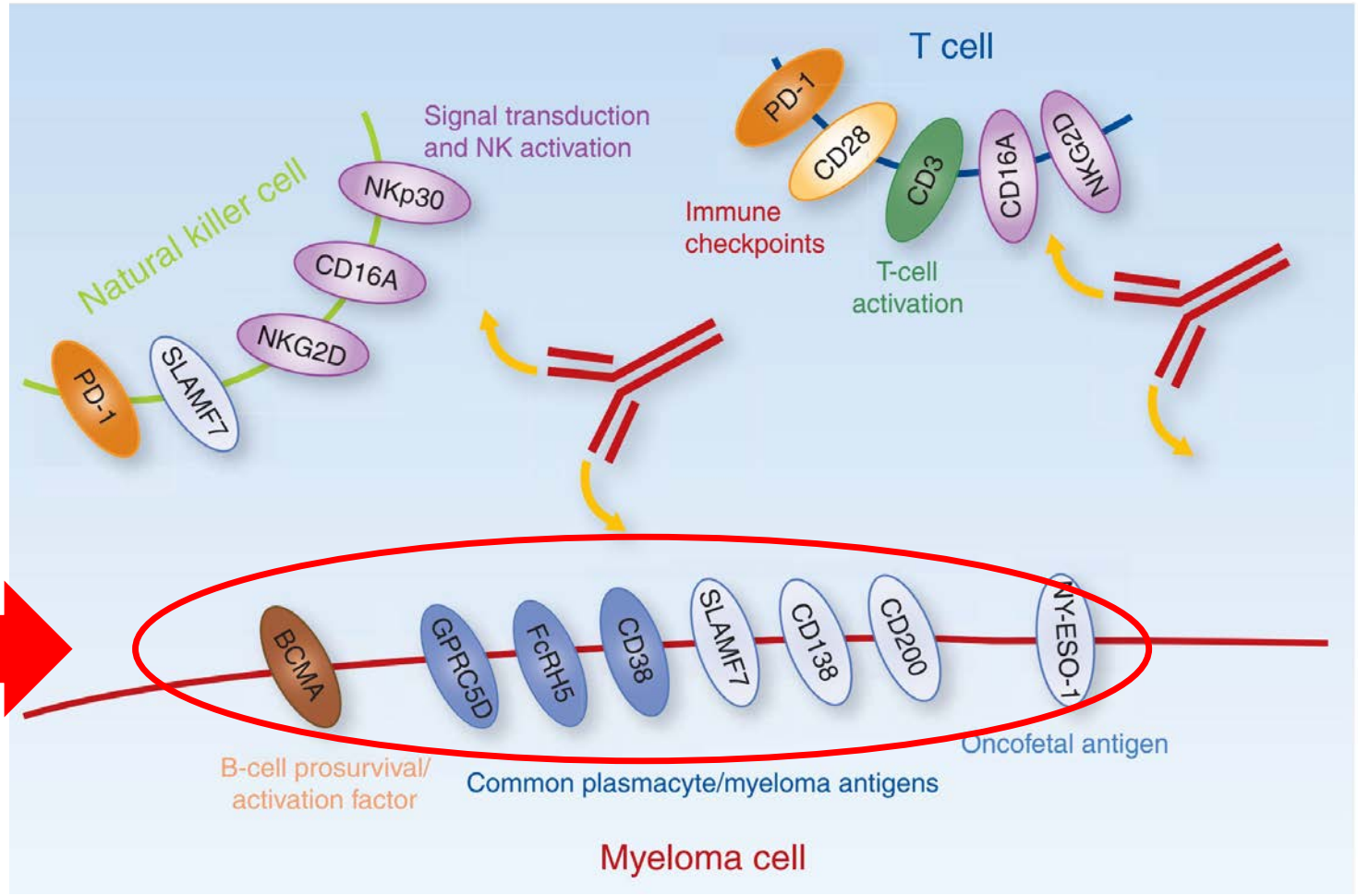
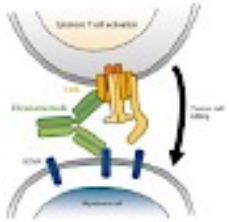


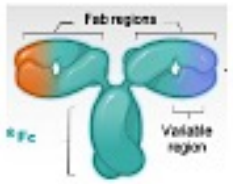
BCMA, B-cell maturation antigen; NK, natural killer; PD-1, Programmed cell death protein 1;

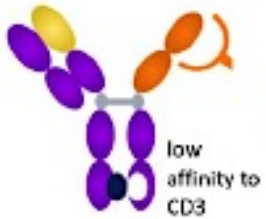
Lancman G et al. Blood Cancer Disc 2021;2(5):423-33

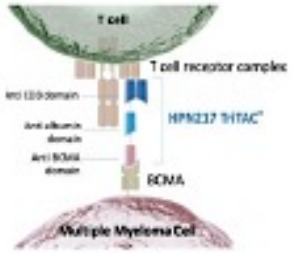
BCMA-targeting bispecific antibodies

	Approved BsAb		2:1 binding	IV infusion		Trispecifics
	Teclistamab MajesTEC-1[1] (n=165)	Elranatamab MagnetisMM-3 (n=123)	Alnuctamab[5] CC-93269 (n=68) *	ABBV-383[3] * (n=118)	Linvoseltamab LINKER-MM1[4] (n=117) *	HPN217[7] * (n=62)
Phase	I/II	I/II	I/II	I	II	I
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3-Albumin
scFv	Humanized	Humanized	Humanized	Human	Human	Humanized
Ig	IgG4	IgG2a	IgG1-based	IgG4	IgG4	Small globular protein
Administration	SC	SC	SC	IV	IV	IV
# prior lines	5 (2-14)	5 (2-12)	4 (3-11)	5 (1-15)	5 (2-14)	6 (2-19)
Age	64 (33-84)	69 (44-89)	64 (36-79)	68 (35-88)	70 (37-91)	69 (38 – 85)









*Not approved in EMA yet

[1]Nooka et al. ASCO 2022; [2]Bahlis et al. ASH 2022; [3]Voorhees et al. IMS 2022; [4]Hans L. et al. ASCO 2023; [5]Wong et al. ASH 2019; [6]Suvannasankha et al. AACR 2023; [7]Abdallah et al. ASH 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

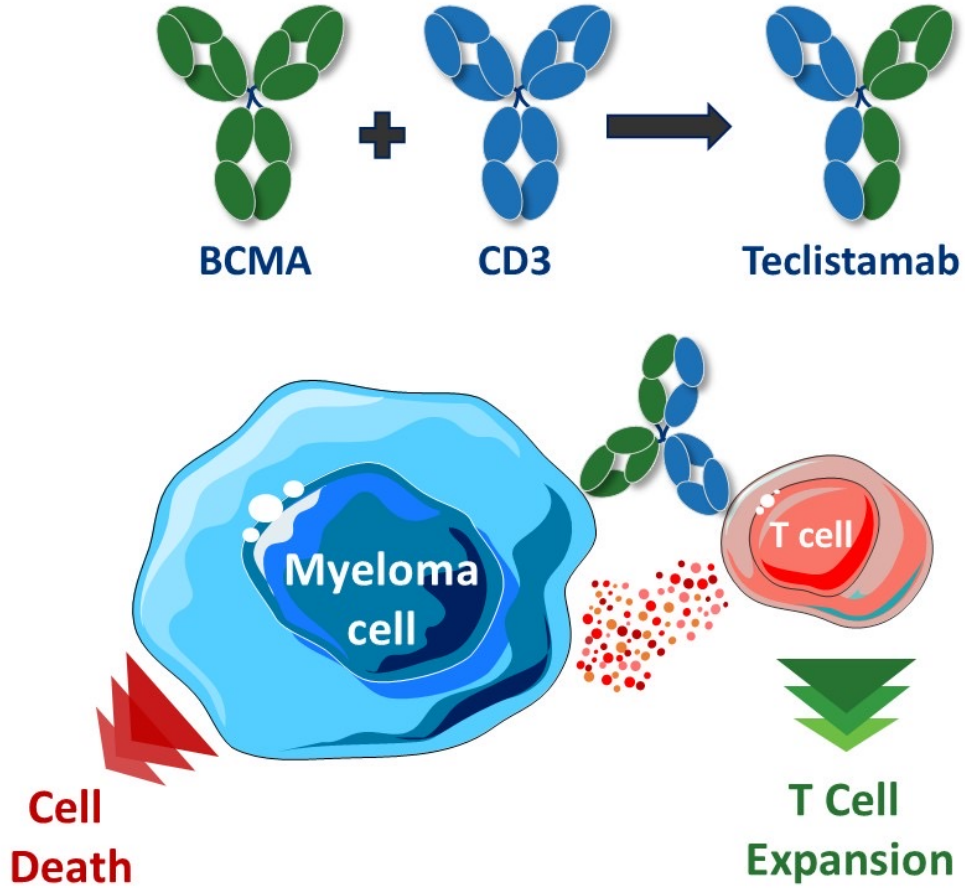
P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

This article was published on June 5, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2203478

Teclistamab: BCMA x CD3 Bispecific Antibody

- Teclistamab (JNJ-64007957) is a humanized IgG-4 bispecific DuoBody® antibody that binds to BCMA and CD3
- Teclistamab redirects $CD3^+$ T cells to BCMA-expressing myeloma cells to induce cytotoxicity of the targeted cells in preclinical studies[1,2]
- Teclistamab potently kills myeloma cell lines and primary myeloma cells from heavily pretreated patients[2]
- A Phase 1 first-in-human study is underway to evaluate safety and antitumor activity of teclistamab in patients with RRMM (NCT03145181)



Teclistamab includes technology licensed from GenMab. [1]Labrijn AF et al. *Proc Natl Acad Sci USA*. 2013;110:5145. [2]Frerichs KA et al. *Clin Cancer Res*. 2020; doi: 10.1158/1078-0432.CCR-19-2299. BCMA=B-cell maturation antigen; MM=multiple myeloma; RR=relapsed or refractory

MajesTEC-1 study design

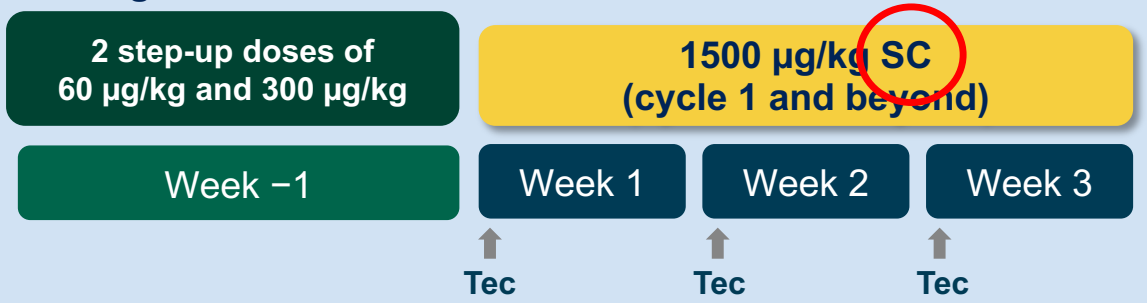
Key Objectives

- Part 1: Identify RP2D
- Part 2: Safety and tolerability at RP2D
- Antitumor activity, pharmacokinetics, pharmacodynamics

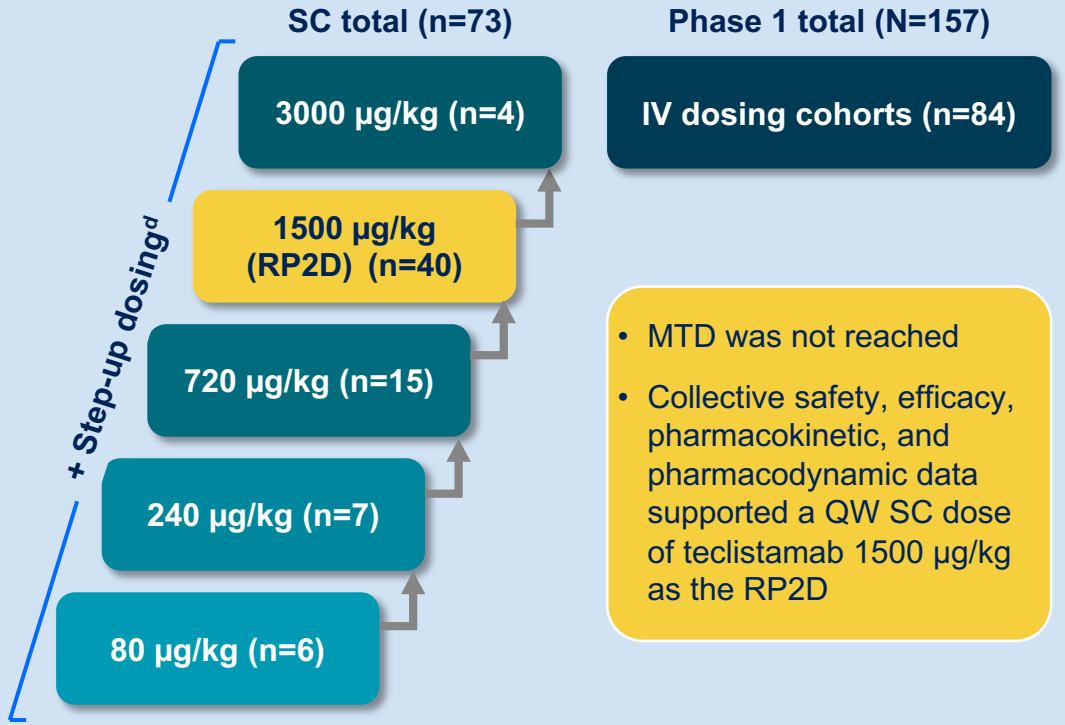
Key Eligibility Criteria

- Adults with measurable MM
- RR or intolerant to established MM therapies
- Hemoglobin ≥8 g/dL, platelets ≥75 × 10^9/L, ANC ≥1.0 × 10^9/L
- No prior BCMA-targeted therapy

Dosing Schedule at RP2D



- Premedications were limited to step-up doses and first full dose
  - No steroid requirement after first full dose

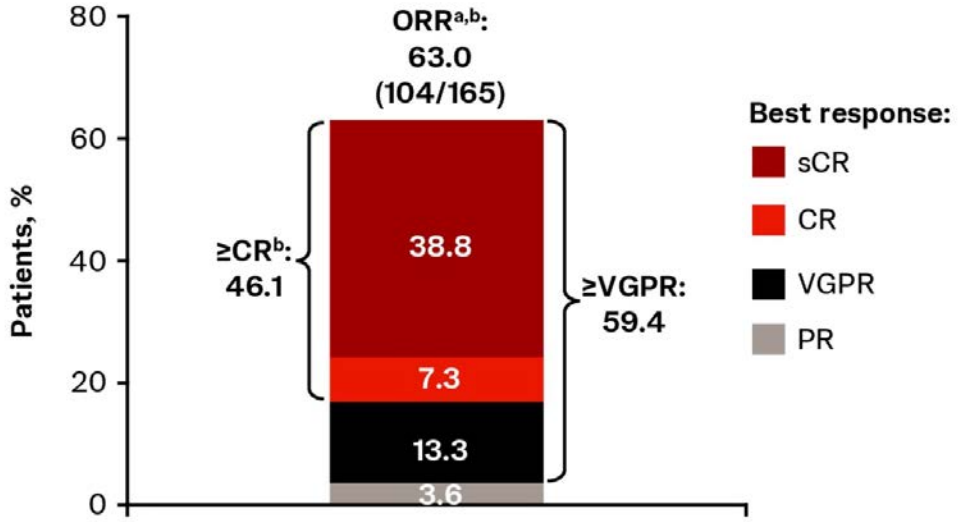


- MTD was not reached
- Collective safety, efficacy, pharmacokinetic, and pharmacodynamic data supported a QW SC dose of teclistamab 1500 µg/kg as the RP2D

ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; MTD, maximum tolerated dose; QW, weekly; RP2D, recommended phase 2 dose; SC, subcutaneous

Nooka A et al. ASCO 2022;abstract 8007 (oral presentation)

MajesTEC-1:
Overall response rate for teclistamab monotherapy



[a]Response assessed by independent review committee. [b]At 30-month mFU of the phase 2 efficacy population (patients enrolled in cohort A on or before March 18, 2021; n=110 patients supporting the USPI[1]): ORR, 61.8%; ≥CR, 46.4% (n=51). sCR, stringent complete response; USPI, United States prescribing information.

- ORR was 63.0% (≥CR, 46.1%); responses continued to deepen and remained durable (**Figures 2** and **3**)
- 85.7% (48/56) of minimal residual disease (MRD)-evaluable patients achieved MRD negativity (10^{-5} threshold), sustained for ≥6 months in 56.1% (23/41) and for ≥12 months in 38.9% (14/36); 30-month DOR, PFS and OS rates were ≥80% for patients with sustained MRD negativity for ≥6 months (**Table 1** and **Supplemental Figure 2**)
- DOR, PFS, and OS were further improved for patients who achieved very good partial response (VGPR) or better, ≥CR, or MRD negativity, and for those with ≤3 vs >3 prior lines of therapy (LOT) (**Figure 4** and **Table 1**)
  - No notable differences in baseline characteristics were observed between patients with ≤3 vs >3 prior LOT

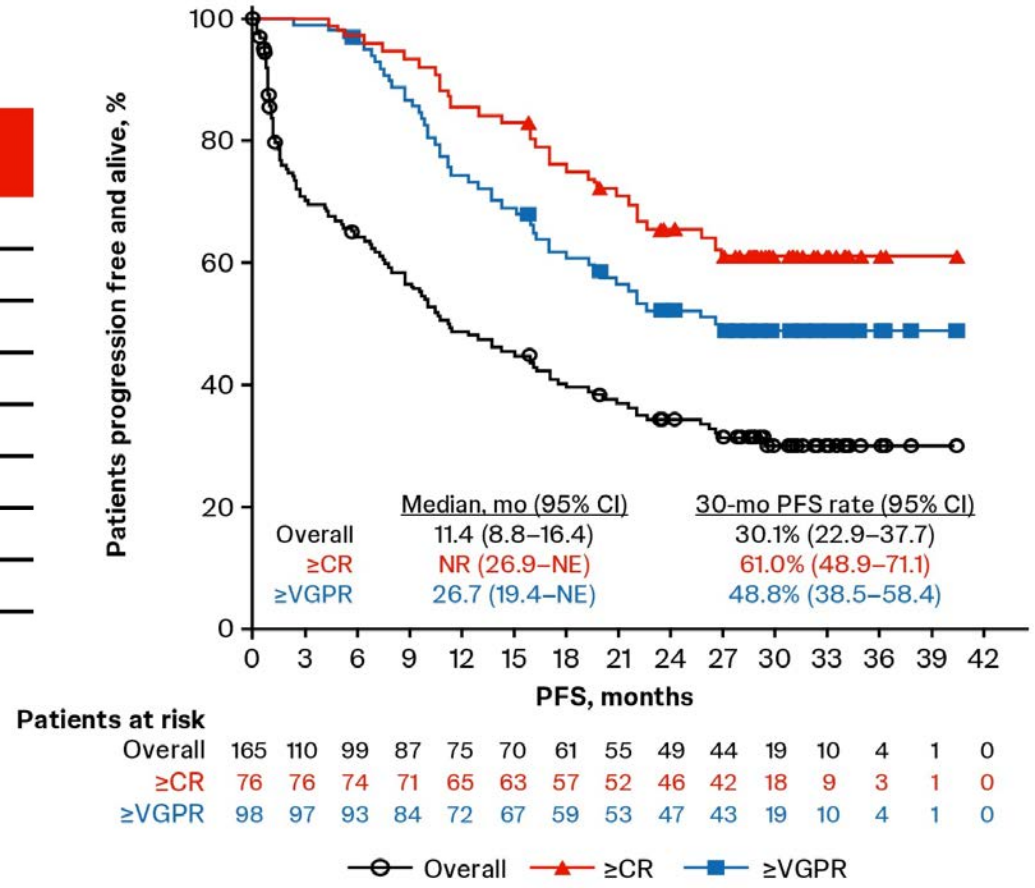
Garfall AL et al. ASCO 2024; Abstract 7540.

MajesTEC-1: Updated DOR, PFS, and OS

Table 1: DOR, PFS, and OS in patient subgroups

	mDOR, mo (95% CI)	mPFS, mo (95% CI)	mOS, mo (95% CI)
All RP2D (N=165)[a]	24.0 (17.0–NE)	11.4 (8.8–16.4)	22.2 (15.1–29.9)
≥CR (n=76)[a]	NR (26.7–NE)	NR (26.9–NE)	NR (35.5–NE)
≥VGPR (n=98)[a]	25.6 (18.1–NE)	26.7 (19.4–NE)	NR (31.0–NE)
MRD-neg (n=48)[b]	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)[c]	22.4 (14.9–NE)	10.8 (7.4–16.4)	21.7 (12.7–29.9)
≥CR (n=51)[c]	NR (21.6–NE)	NR (22.8–NE)	NR (NE–NE)

Figure 4: PFS



Garfall AL et al. ASCO 2024; Abstract 7540.

MajesTEC-1: Safety Profile

Table 2: TEAEs occurring in ≥20% of patients in MajesTEC-1

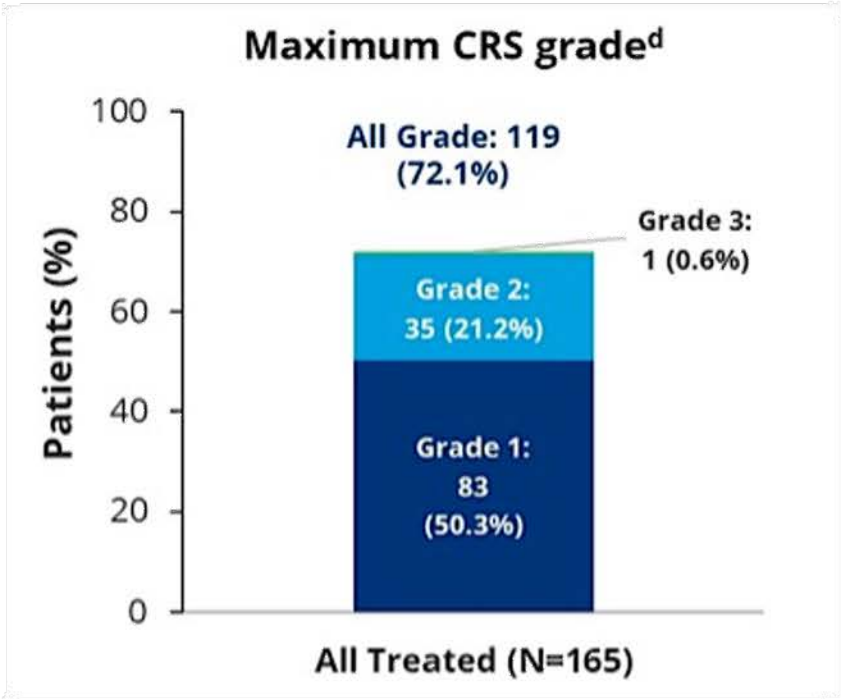
TEAEs, n (%)	N=165	
	Any Grade	Grade 3/4
Any TEAE	**165 (100)**	**156 (94.5)**
Hematologic		
Neutropenia	118 (71.5)	108 (65.5)
Anemia	91 (55.2)	62 (37.6)
Thrombocytopenia	69 (41.8)	38 (23.0)
Lymphopenia	60 (36.4)	57 (34.5)
Leukopenia	33 (20.0)	15 (9.1)
Nonhematologic		
Infections	130 (78.8)	91 (55.2)
COVID-19	48 (29.1)	35 (21.2)
CRS	119 (72.1)	1 (0.6)
Diarrhea	57 (34.5)	6 (3.6)
Pyrexia	51 (30.9)	1 (0.6)
Fatigue	50 (30.3)	4 (2.4)
Cough	46 (27.9)	0
Nausea	45 (27.3)	1 (0.6)
Injection site erythema	44 (26.7)	0
Arthralgia	42 (25.5)	2 (1.2)
Headache	40 (24.2)	1 (0.6)
Constipation	37 (22.4)	0
Hypogammaglobulinemia	36 (21.8)	3 (1.8)
Back pain	33 (20.0)	4 (2.4)

- The most common treatment-emergent adverse events (TEAEs) remained cytopenias and infections (**Table 2**)
- No changes in cytokine release syndrome (CRS) or immune effector cell–associated neurotoxicity syndrome at 30.4-month mFU
- Infections occurred in 78.8% of patients (grade 3/4, 55.2%)
  - Of grade 5 infections, 18/22 were due to COVID-19
    - No new grade 5 COVID-19 TEAEs at 30.4-month mFU
  - Onset of new grade ≥3 infections continued to generally decline over time
    - Factors such as transitioning to Q2W dosing and increasing use of immunoglobulin replacement may contribute to this trend
- TEAEs leading to dose reduction (n=1 [0.6%]) or discontinuation (n=8 [4.8%]; 5 due to infection) were infrequent
- No new safety signals were reported

Garfall AL et al. ASCO 2024; Abstract 7540.

MajesTEC-1: Cytokine release syndrome

Parameter	N=165
Patients with CRS, n (%)	119 (72.1)
Patients with ≥2 CRS events	55 (33.3)
Time to onset[a] (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Received supportive measures[a] for CRS, n (%)	110 (66.7)
Tocilizumab[b]	60 (36.4)
Low-flow oxygen by nasal cannula[c]	21 (12.7)
Corticosteroids	14 (8.5)
Single vasopressor	1 (0.6)



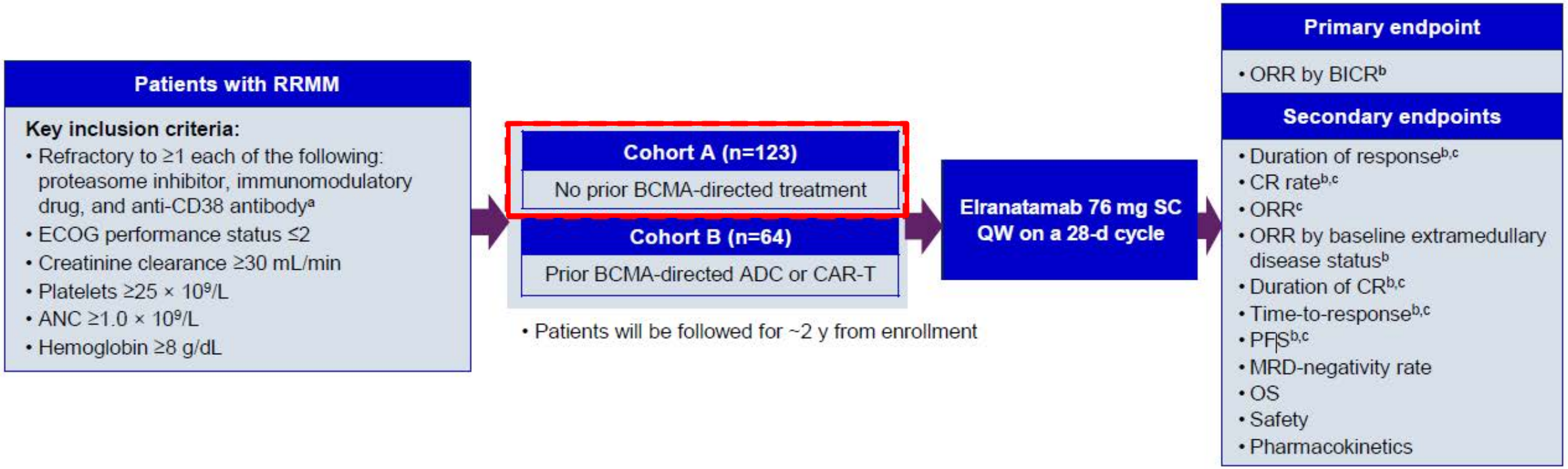
- Most CRS events were confined to step-up and first full treatment doses
- All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that occurred in the context of concurrent pneumonia (resolved in 2 days)
- All CRS events fully resolved without treatment discontinuation or dose reduction

Analysis cutoff date: March 16, 2022.
[a]A patient could receive >1 supportive therapy. [b]Tocilizumab was administered at physician discretion. [c]≤6 L/min. [d]CRS was graded using Lee et al *Blood* 2014 in the phase 1 portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al *Blood* 2014 criteria were mapped to ASTCT criteria for patients in the phase 1 portion.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome

ELRANATAMAB

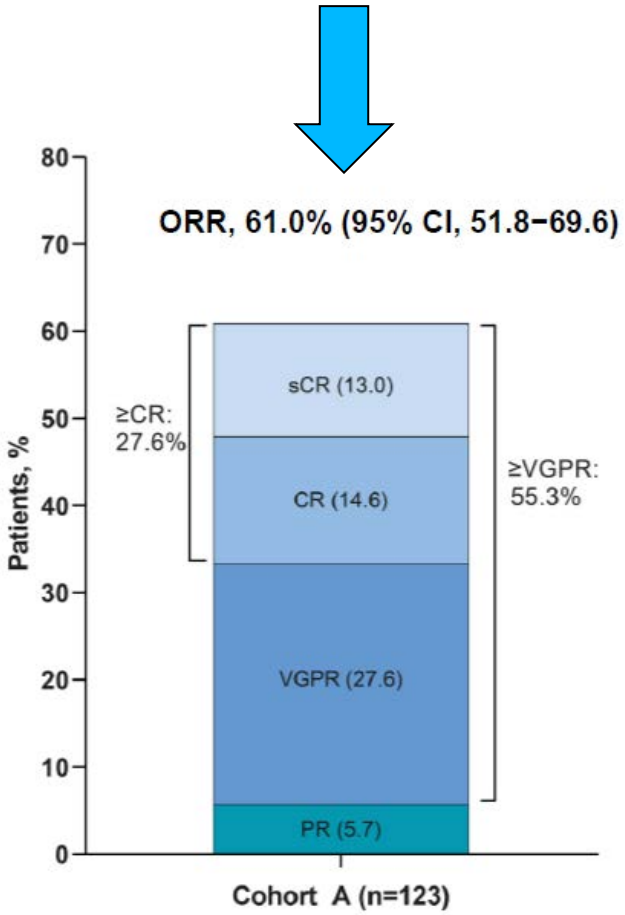
MagnetisMM-3 Study

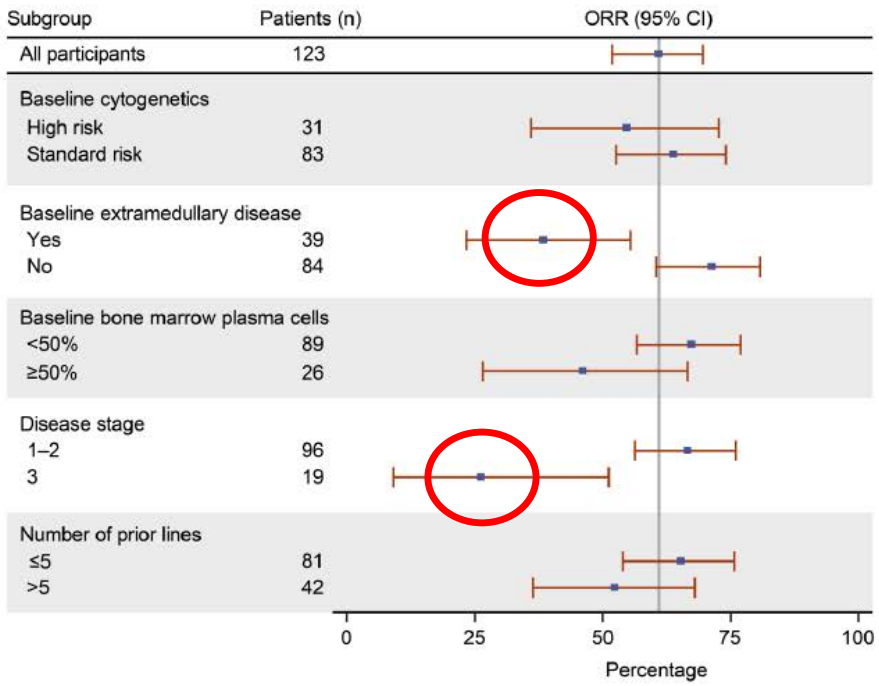
- MagnetisMM-3 is an open-label, multicenter, non-randomized, phase 2 study

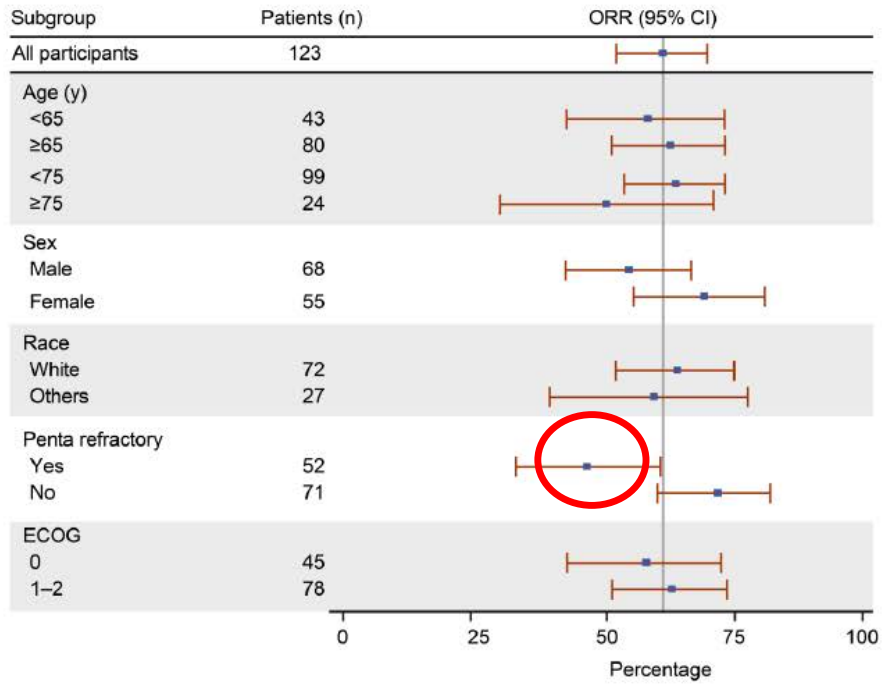


Bahlis N et al. ASH2022. **Leshokin et al. Nat Med 2023**

Objective Response Rate per BICR Across Subgroups







Bahlis N et al. ASH2022. Leshokin et al. Nat Med 2023

Received: 26 March 2024 | Accepted: 4 July 2024

DOI: 10.1002/hem3.136

HemaSphere EHA EUROPEAN HEMATOLOGY ASSOCIATION

LETTER

Long-term survival and safety of elranatamab in patients with relapsed or refractory multiple myeloma: Update from the MagnetisMM-3 study

Michael H. Tomasson[1] | Shinsuke Iida[2] | Ruben Niesvizky[3] | Mohamad Mohty[4] | Nizar J. Bahlis[5] | Joaquin Martinez-Lopez[6] | Guenther Koehne[7] | Paula Rodriguez-Otero[8] | H. Miles Prince[9] | Andrea Viqueira[10] | Eric Leip[11] | Umberto Conte[12] | Sharon T. Sullivan[13] | Alexander M. Lesokhin[14]

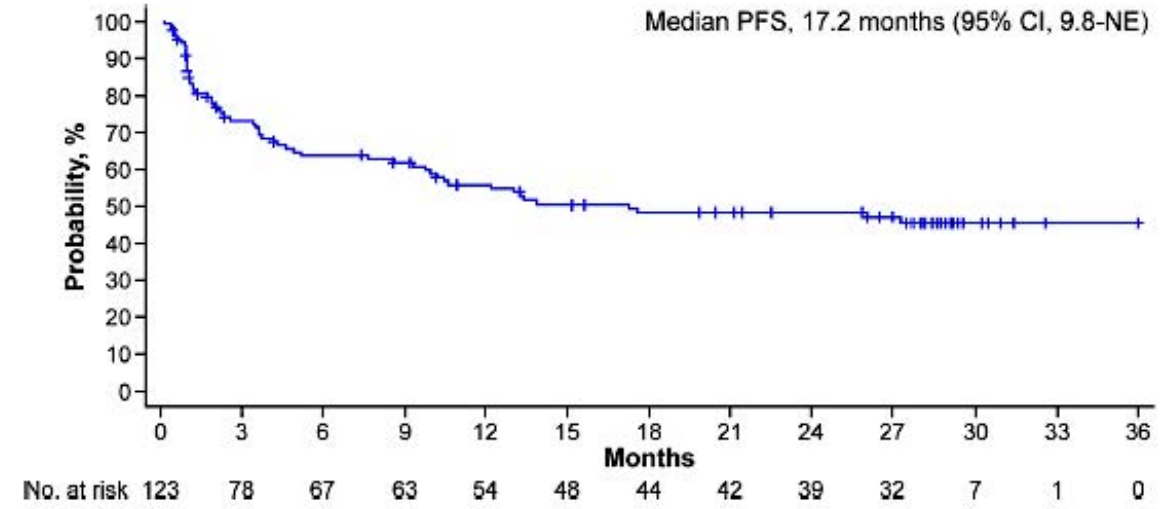


FIGURE 1 Kaplan–Meier analysis of progression-free survival. Progression-free survival in B-cell maturation antigen–naive patients with relapsed or refractory multiple myeloma in the MagnetisMM-3 study. Tick marks indicate censored data.

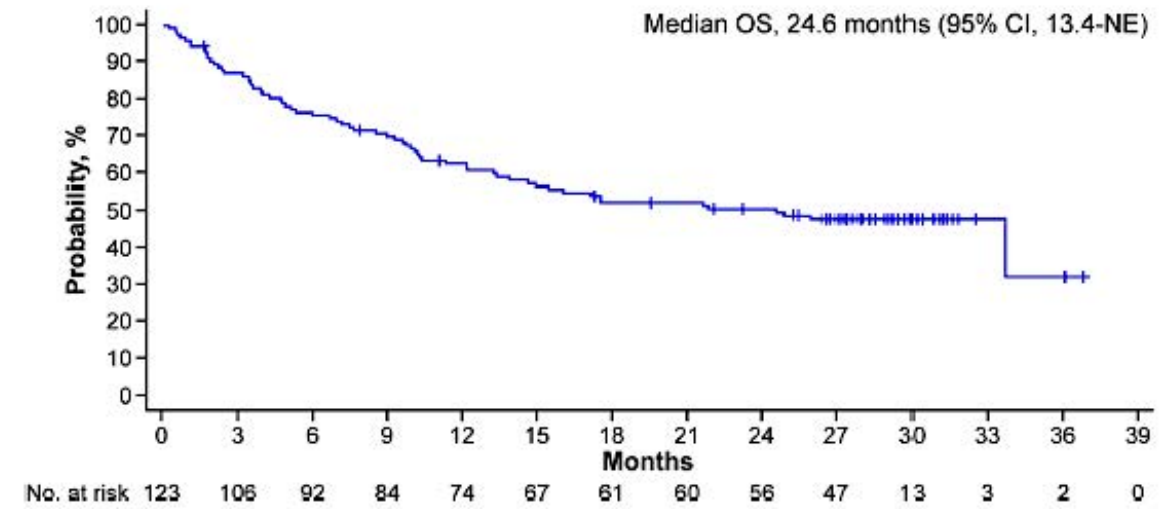
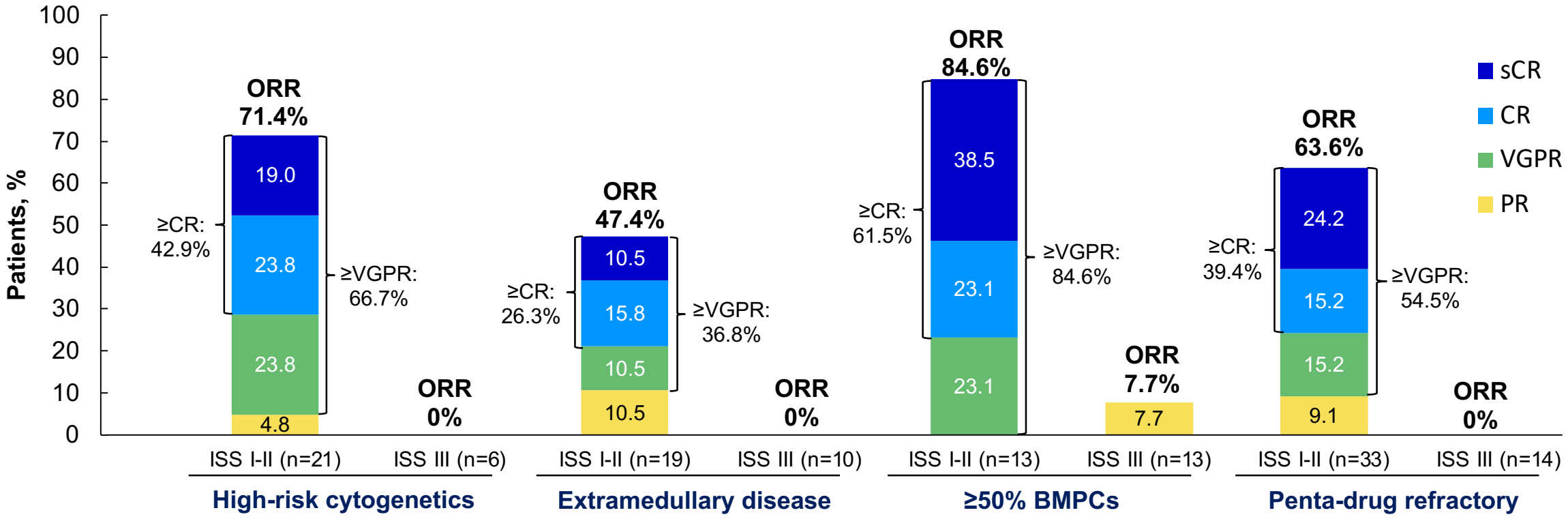


FIGURE 2 Kaplan–Meier analysis of overall survival. Overall survival in B-cell maturation antigen–naive patients with relapsed or refractory multiple myeloma in the MagnetisMM-3 study. Tick marks indicate censored data.

MagnetisMM-3 – high-risk subgroups



Tomasson et al. ASH 2023

Elranatamab: the MagnetisMM-3 trial

FDA approved in 2023

EMA approved in 2023

TEAEs in ≥20% of patients, n (%)	Cohort A (N=123) Any grade	Grade 3/4
Hematologic		
Anemia	59 (48.0)	45 (36.6)
Neutropenia	59 (48.0)	59 (48.0)
Thrombocytopenia	37 (30.1)	27 (22.0)
Lymphopenia	32 (26.0)	30 (24.4)
Non-hematologic		
CRS	71 (57.7)	0
Diarrhea	48 (39.0)	2 (1.6)
Fatigue	42 (34.1)	4 (3.3)
Decreased appetite	40 (32.5)	1 (0.8)
Injection site reaction	32 (26.0)	0
Nausea	32 (26.0)	0
COVID-19 related[a]	31 (25.2)	14 (11.4)
Hypokalemia	29 (23.6)	12 (9.8)
Pyrexia	29 (23.6)	4 (3.3)
Cough	27 (22.0)	0
Headache	27 (22.0)	0

Table 3: AEs of special interest: Infections

Patients, n (%)	Cohort A (N=123) Any grade	Grade 3/4	Grade 5
Infection TEAEs in ≥5% of patients			
COVID-19–related[a]	36 (29.3)	19 (15.4)	2 (1.6)
Upper respiratory tract infection	20 (16.3)	0	0
Pneumonia	20 (16.3)	10 (8.1)	0
Sinusitis	13 (10.6)	2 (1.6)	0
Urinary tract infection	12 (9.8)	4 (3.3)	0
Sepsis	8 (6.5)	8 (6.5)	0
Bacteremia	7 (5.7)	2 (1.6)	0
CMV infection reactivation	7 (5.7)	2 (1.6)	0

Infections were reported in 69.9% (grade 3/4, 39.8%; grade 5, 6.5%)

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DOI: 10.1111/bjh.19148

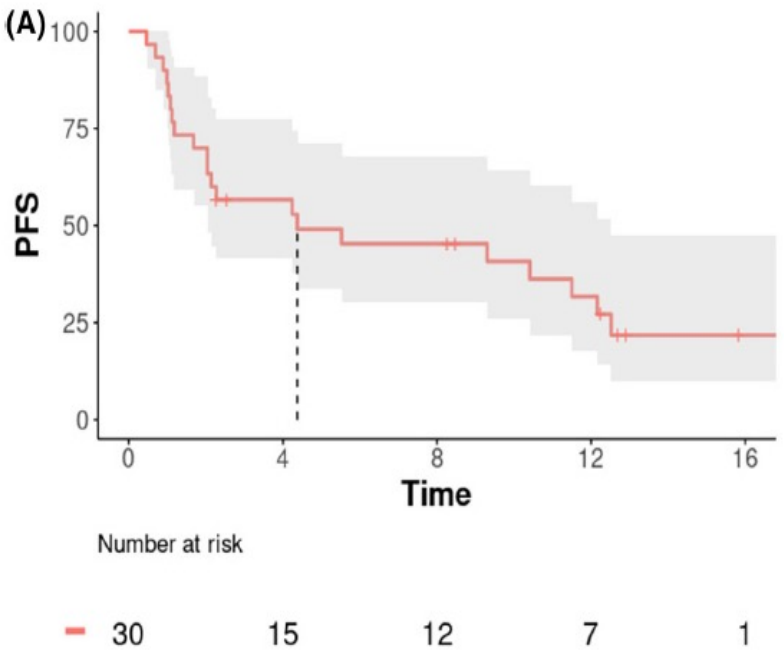
BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

SHORT REPORT

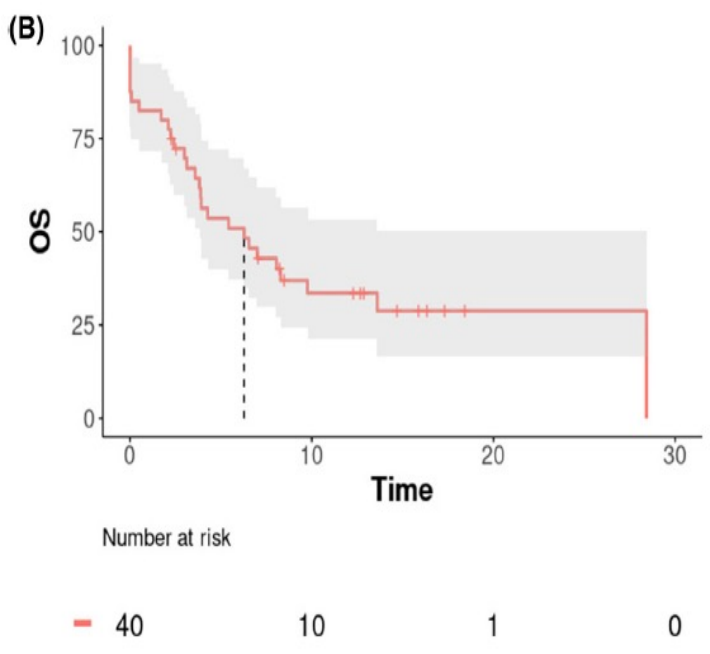
Quad-class exposed/refractory myeloma is associated with short survival

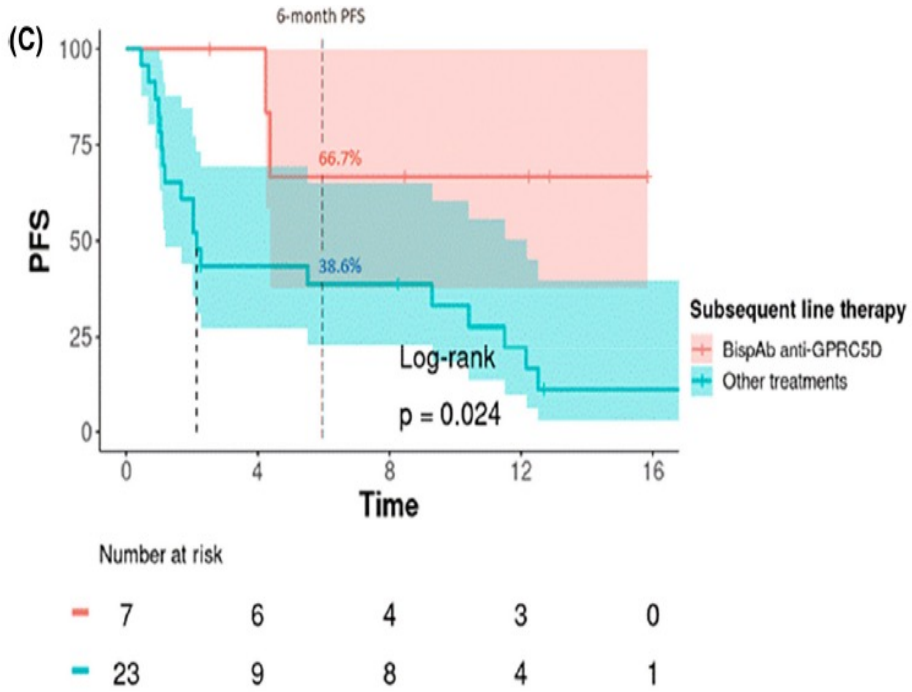
Bénédicte Piron[1] | Domitille Costes-Tertrais[1] | Thomas Gastinne[1] | Aude Marie Fourmont[1] | Viviane Dubruille[1] | Nicolas Blin[1] | Philippe Moreau[1,2,3] | Cyrille Touzeau[1,2,3] | Benoit Tessoulin[1,2]

PFS 4.4 months

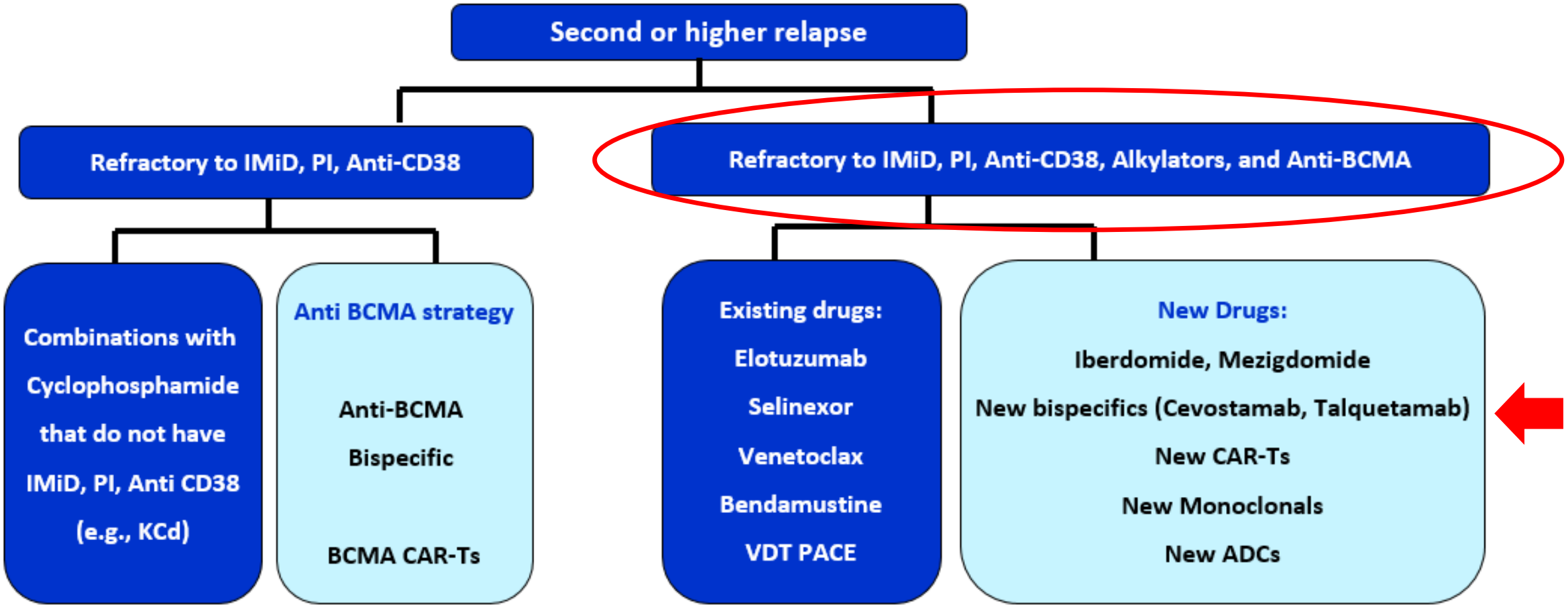


OS 6.3 months



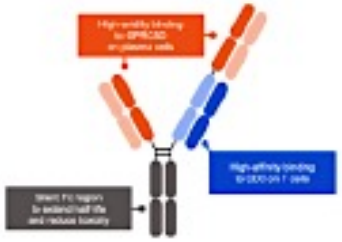


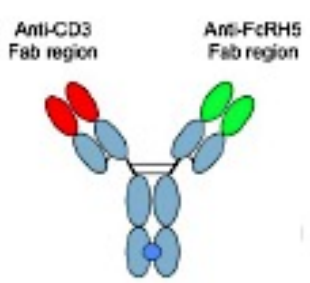
Myeloma: Second or higher relapse



Other targets for bispecific antibodies

	GPRC5D		FCRH5
	MonumenTAL-1 Talquetamab[1] (n=145)	GRACE[2] Forimtamig (n=57)*	GO39775[3] Cevostamab * (n=249)
Target	GPRC5D-CD3	GPRC5D-CD3	FcRH5–CD3
Administration	SC (800 Q2W)	SC	IV
Age (range)	67 (38-84)	63 (46–79)	64 (33–84)
# lines (range)	5 (2-17)	4 (2–14)	6 (2–18)
HR cytog, n (%)	37 (29)	18/38 (47)	53/157 (34)
EMD, n (%)	39 (27)	18 (32)	59 (23.7)
Triple-R, %	100 (69)	41 (72)	213 (86)





*Not approved in EMA yet

[1] Chari et al. ASH 2022; [2] Carlo-Stella et al. ASH 2022; [3] Lesokhin et al. ASH 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

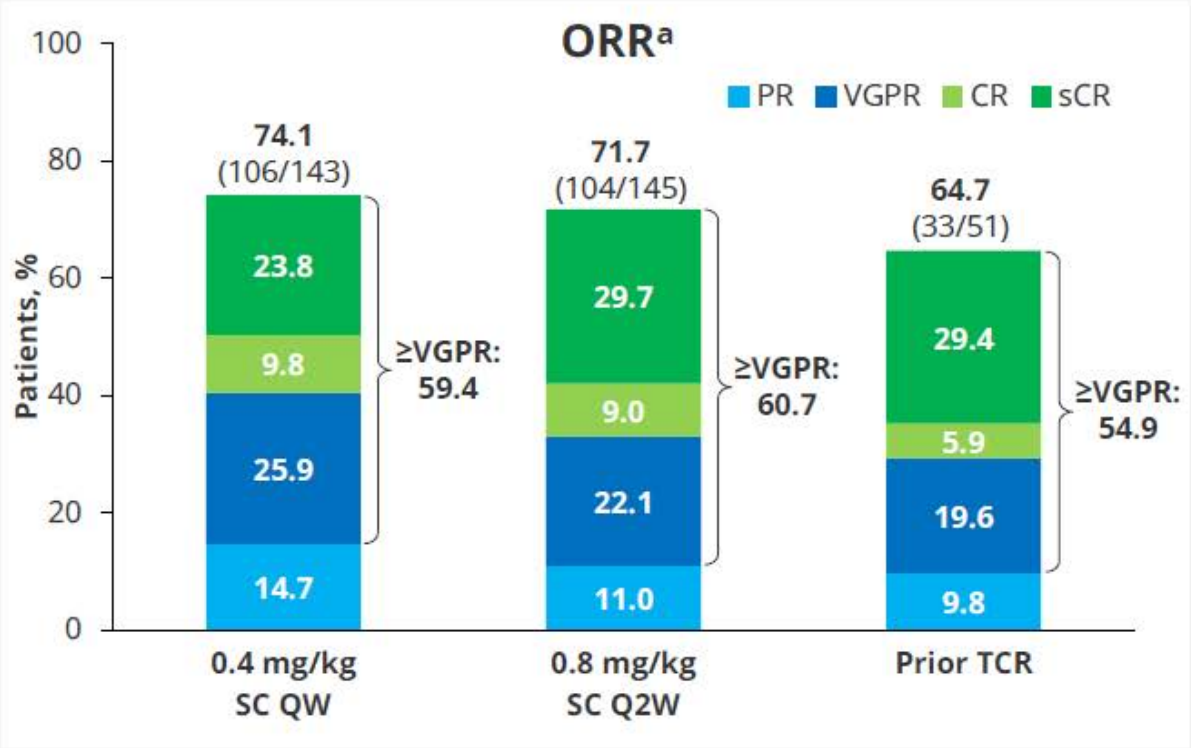
Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma

Ajai Chari, M.D., Monique C. Minnema, M.D., Jesus G. Berdeja, M.D., Albert Oriol, M.D., Ph.D., Niels W.C.J. van de Donk, M.D., Ph.D., Paula Rodríguez-Otero, M.D., Ph.D., Elham Askari, M.D., María-Victoria Mateos, M.D., Ph.D., Luciano J. Costa, M.D., Ph.D., Jo Caers, M.D., Ph.D., Raluca Verona, Ph.D., Suzette Girgis, Ph.D., Shiyi Yang, Ph.D., Rachel B. Goldsmith, Ph.D., Xiang Yao, Ph.D., Kodandaram Pillarisetti, M.Sc., Brandi W. Hilder, Ph.D., Jeffery Russell, M.D., Ph.D., Jenna D. Goldberg, M.D., and Amrita Krishnan, M.D.

December 10, 2022

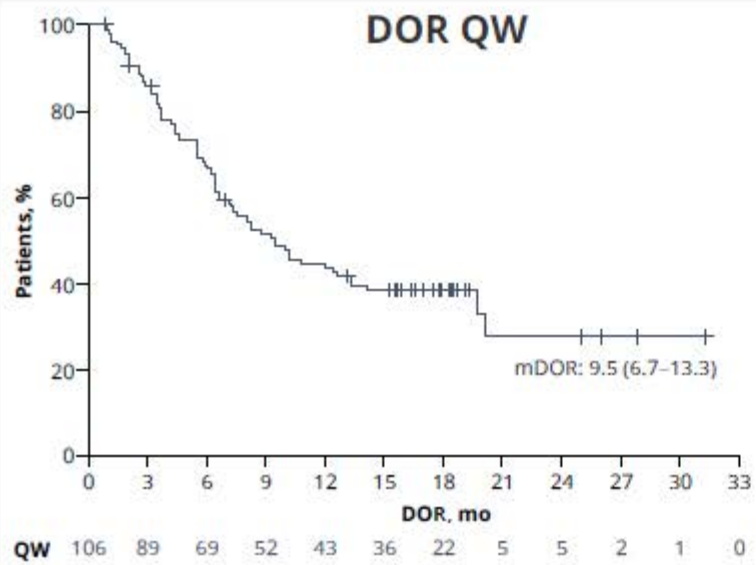
MonumenTAL-1: Deep Responses Across Cohorts

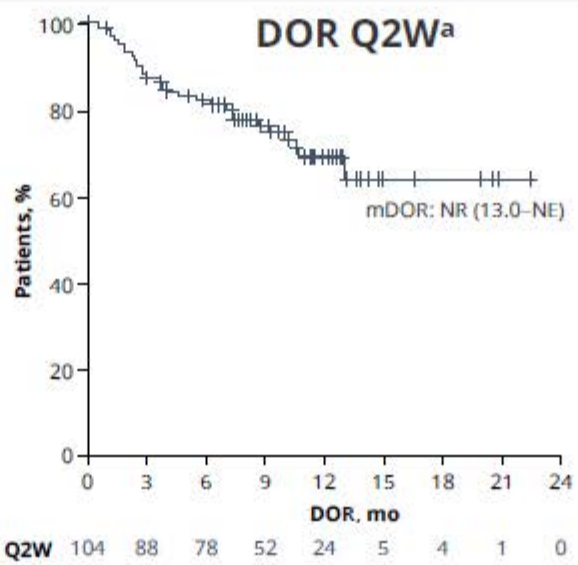
- In the prior TCR cohort, ORR was:
  - 75.0% (n=27/36) with prior CAR-T therapy
  - 44.4% (n=8/18) with prior BsAb
- ORR was consistent across traditionally high-risk subgroups:
  - Cytogenetic risk, ISS stage III disease, ≥4 prior LOT, refractoriness,[b] and prior belantamab
- Patients with EMD had lower ORR:
  - 31–49% with EMD
  - 80–82% without EMD

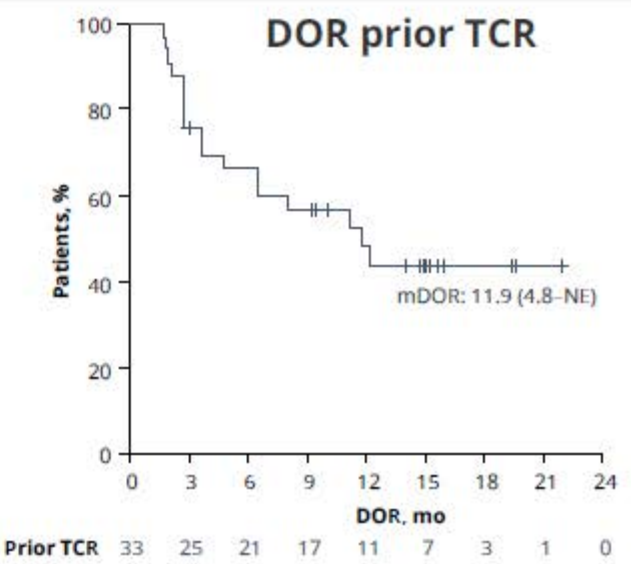


Schinke CD et al. ASCO 2023; Abstract 8036.

MonumenTAL-1: Durable Responses Across Cohorts







Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=145)	Prior TCR (n=51)
mFU, mo	18.8	12.7	14.8
12-mo DOR rate in patients with ≥CR, %	78.9	90.5	80.5
mPFS, mo (95% CI)	7.5 (5.7–9.4)	14.2 (9.6–NE)[b]	5.1 (3.4–12.3)
12-mo PFS rate, %	34.9	54.4	38.1
12-mo OS rate, %	76.4	77.4	62.9

Schinke CD et al. ASCO 2023; Abstract 8036.

Talquetamab: SAFETY

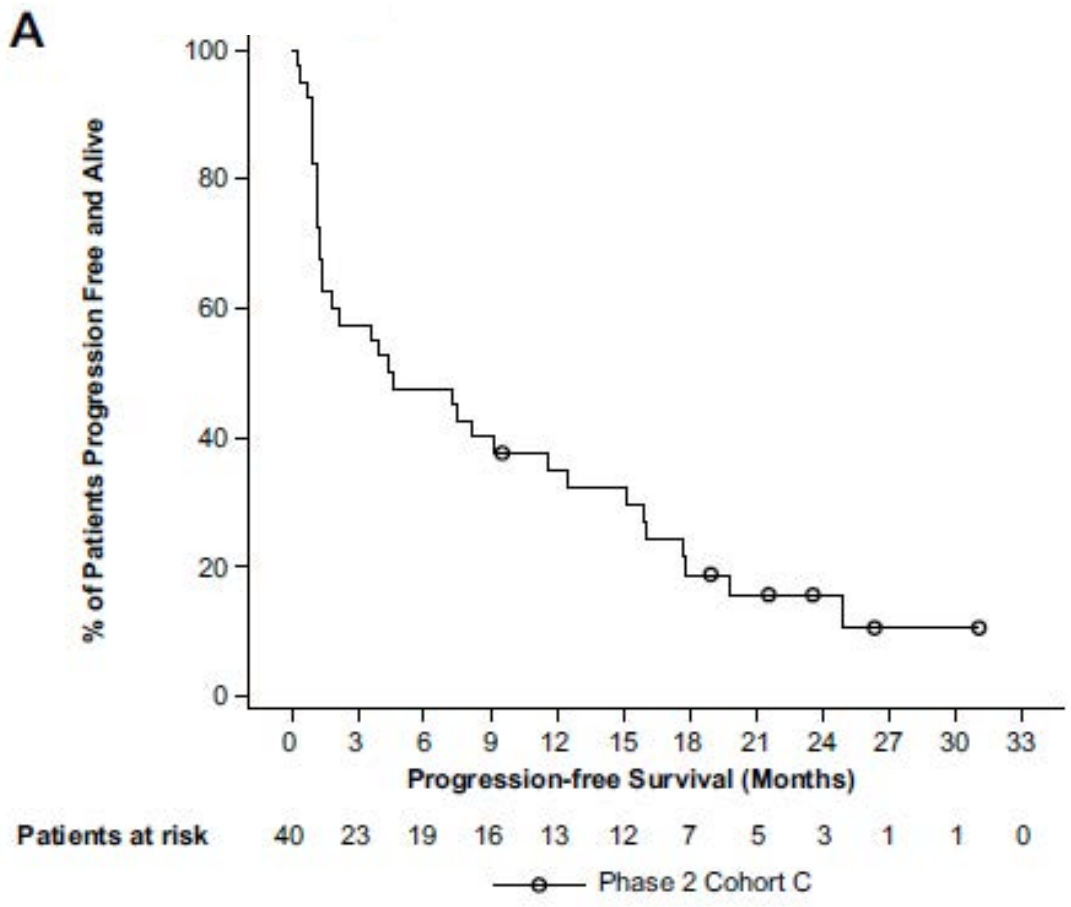
FDA approved in 2023
EMA approved in 2023

AEs (≥20% of any RP2D cohort), n (%)	0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	Any Grade	Grade 3/4
CRS	105 (72.4)	1 (0.7)
Skin-related AEs[d]	98 (67.6)	1 (0.7)
Dysgeusia[f]	67 (46.2)	NA
Nail-related AEs[e]	63 (43.4)	0
Dry mouth	53 (36.6)	0
Weight decreased	47 (32.4)	2 (1.4)
Rash-related AEs[g]	39 (26.9)	8 (5.5)
Pyrexia	35 (24.1)	1 (0.7)
Dysphagia	33 (22.8)	3 (2.1)
Diarrhea	32 (22.1)	0
Fatigue	29 (20.0)	1 (0.7)
Decreased appetite	29 (20.0)	2 (1.4)

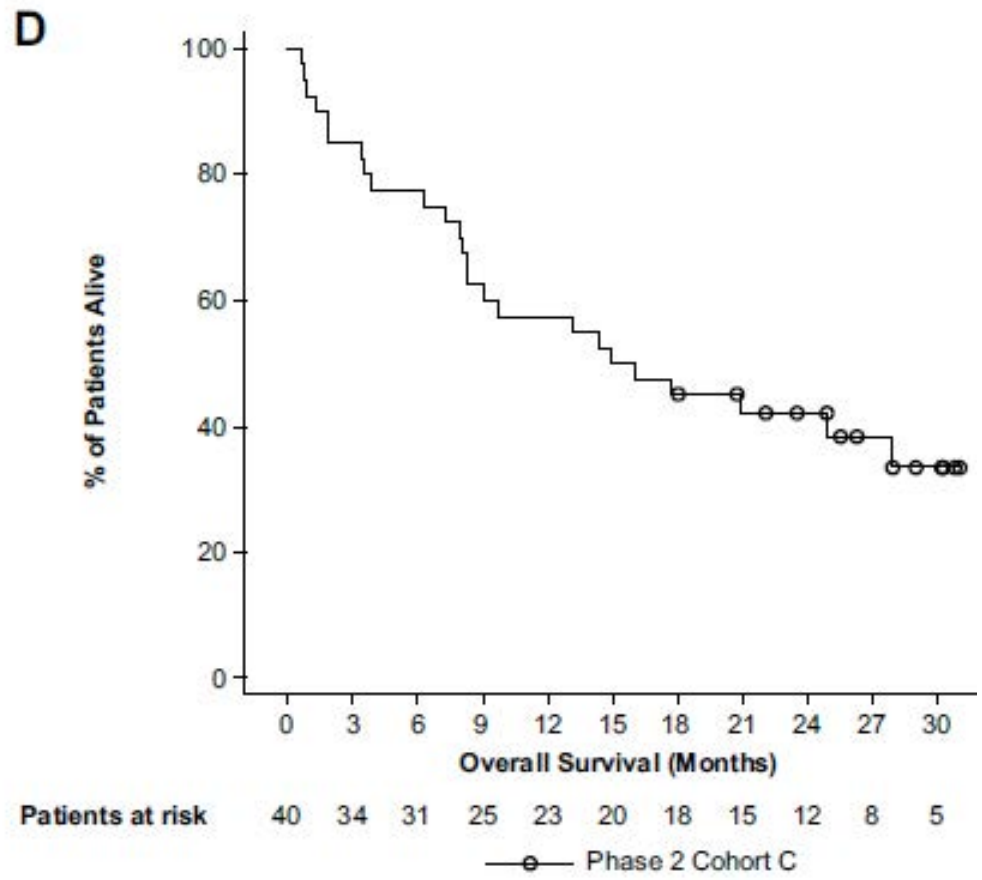
Schinke CD et al. ASCO 2023; Abstract 8036.

Sequencing

Teclistamab post BCMA-immunotherapies



Median PFS was 4.5 months



Median OS was 15.5 months

Touzeau et al. Blood 2024

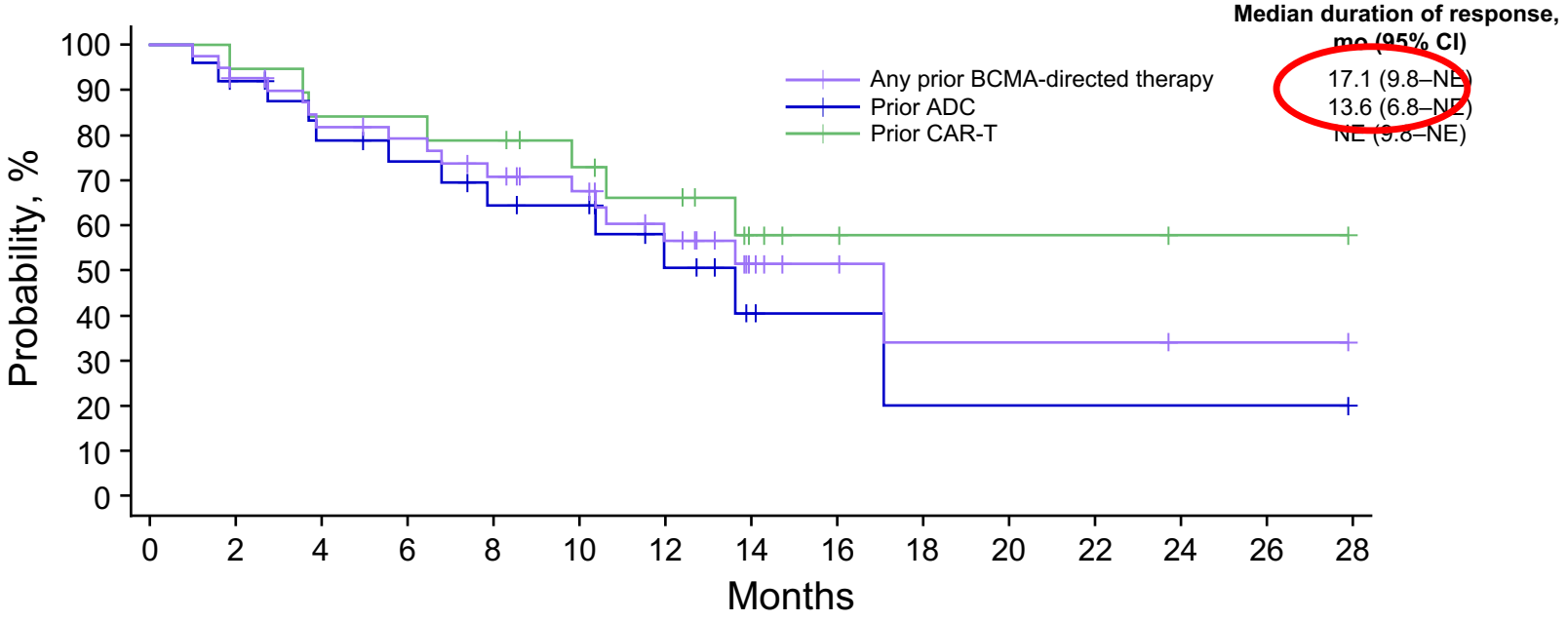
Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma and prior B-cell maturation antigen (BCMA)-directed therapies: A pooled analysis from MagnetisMM studies

Ajay K. Nooka, MD[1], Alexander M. Lesokhin, MD[2], Mohamad Mohty, MD[3], Ruben Niesvizky, MD[4], Christopher Maisel, MD[5], Bertrand Arnulf, MD[6], Sarah M. Larson, MD[7], Asya Nina Varshavsky-Yanovsky, MD, PhD[8], Xavier Leleu, MD[9], Lionel Karlin, MD[10], David H. Vesole, MD, PhD[11], Nizar J. Bahlis, MD[12], Carlos Fernández de Larrea, MD[13], Noopur Raje, MD[14], Eric Leip, PhD[15], Umberto Conte, PharmD[16], Mohamed Elmeliegy, PhD[17], Andrea Viqueira, MD[18], Salomon Manier, MD[19]

[1]Winship Cancer Institute, Atlanta, GA, USA; [2]Division of Hematology and Oncology, Memorial Sloan Kettering Cancer Center/Weill Cornell Medical College, New York, NY, USA; [3]Sorbonne University, Hôpital Saint-Antoine, and INSERM UMRs938, Paris, France; [4]Weill Cornell Medical College - New York Presbyterian Hospital, New York, NY, USA; [5]Baylor University Medical Center, Dallas, TX, USA; [6]Hôpital Saint-Louis, Paris, France; [7]University of California Los Angeles Medical Center, Los Angeles, CA, USA; [8]Fox Chase Cancer Center, Philadelphia, PA, USA; [9]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [10]Centre Hospitalier Lyon, Lyon, France; [11]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA; [12]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; [13]Hospital Clinic de Barcelona, Barcelona, Spain; [14]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [15]Pfizer Inc, Cambridge, MA, USA; [16]Pfizer Inc, New York, NY, USA; [17]Pfizer Inc, San Diego, CA, USA; [18]Pfizer SLU, Madrid, Spain; [19]Lille University Hospital, Lille, France

Nooka et al. ASCO 2023 Abstract 8008

Duration of Response (Responders Only)



No. at risk															
Any prior BCMA-directed therapy:	40	36	31	29	25	21	15	7	4	2	2	2	1	1	0
Prior ADC:	25	22	18	16	13	12	7	3	2	1	1	1	1	1	0
Prior CAR-T:	19	18	16	16	15	12	10	5	3	2	2	2	1	1	0

- Median duration of response was not yet mature after censoring data for 23 (57.5%) patients

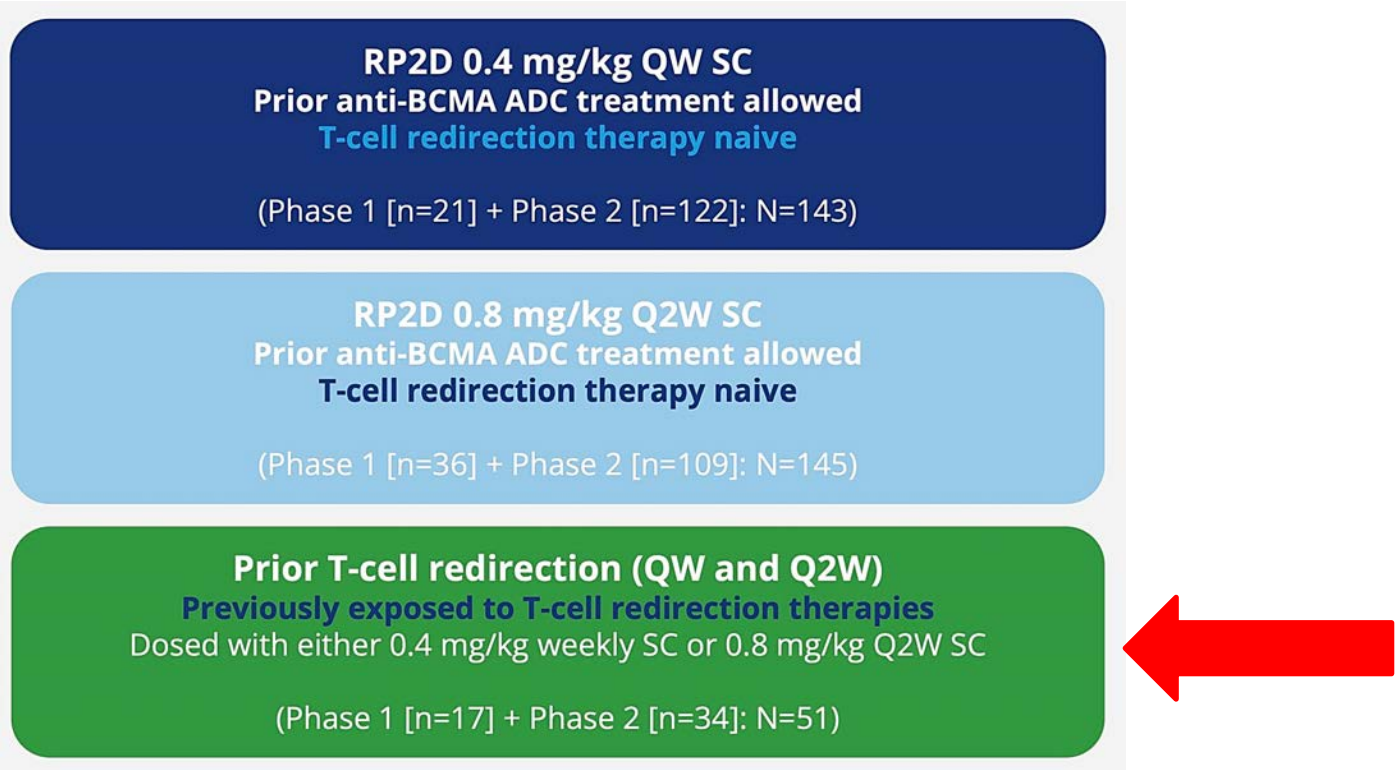
ADC=antibody drug conjugate; BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; NE=not evaluable

Sequencing

BCMA → GPRC5D

MonumenTAL-1: Talquetamab cohorts and baseline characteristics

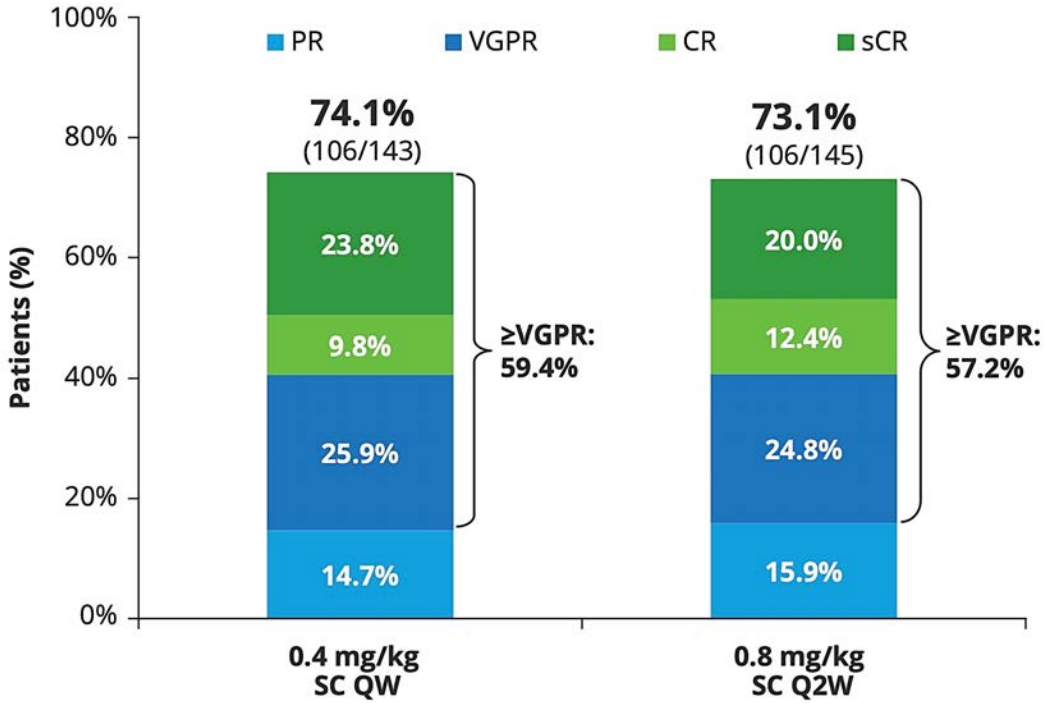
Study cohorts



Chari A et al. ASH 2022;abstract 157 (oral presentation); **Schinke et al ASCO 2023 abstract 8036**

MonumenTAL-1: Response rates with talquetamab

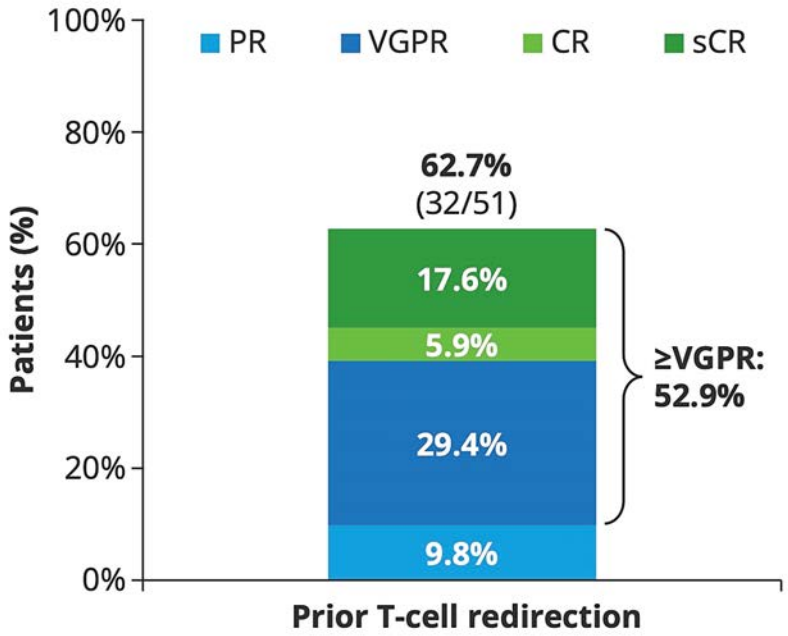
ORR in all patients[a]



- **Median follow-up:** 14.9 and 8.6 months for QW and Q2W cohorts
- **ORR in triple-class refractory: 72.6%** (95% CI, 63.1–80.9) and **71.0%** (95% CI, 61.1–79.6)
- **ORR in penta-drug refractory: 71.4%** (95% CI, 55.4–84.3) and **70.6%** (95% CI, 52.5–84.9)

>70% ORR with talquetamab in patients with heavily pretreated RRMM

ORR in patients with prior T-cell redirecting therapies[a]



- **Median follow-up**: 11.8 months
- **Median duration of response**: 12.7 months
- **72.2% ORR** (26/36; 95% CI, 54.8–85.8%) in patients with **prior CAR-T cell therapy**
- **44.4% ORR** (8/18; 95% CI, 21.5–69.2%) in patients with **prior bispecific antibody treatment**
- **Median PFS : 5.1 mos**

Chari A et al. ASH 2022;abstract 157**, Schinke et al ASCO 2023 abstract 8036**

Combination trials

RedirecTT-1 Tal + Tec: Study Design

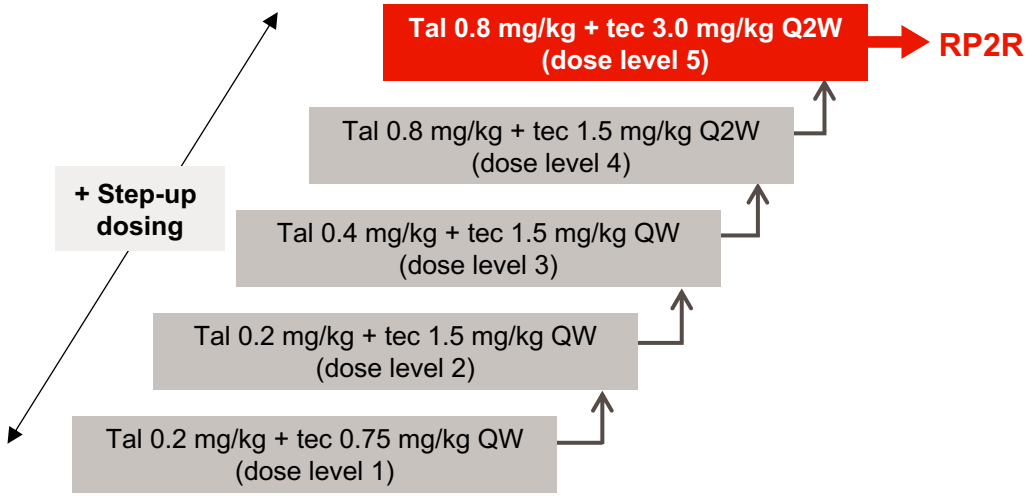
Key eligibility criteria

- Measurable MM
- EMD permitted (≥1 nonradiated, bone-independent lesion ≥2 cm)
- RR or intolerant to established therapies, including last LOT
- Triple-class exposed (prior PI, IMiD, anti-CD38)

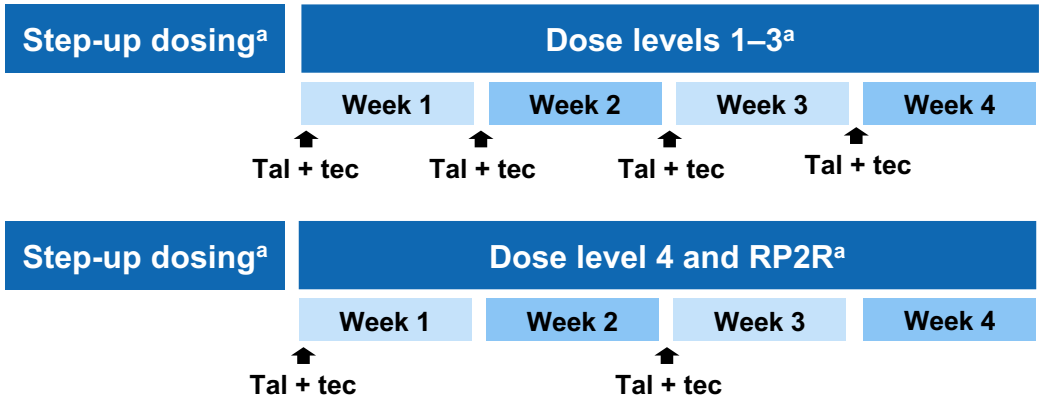
Key objectives

- Safety, including DLTs
- Identify RP2R(s)
- ORR, DOR, time to response, PK, immunogenicity
- PFS

Phase 1 dose escalation



Dosing schedule

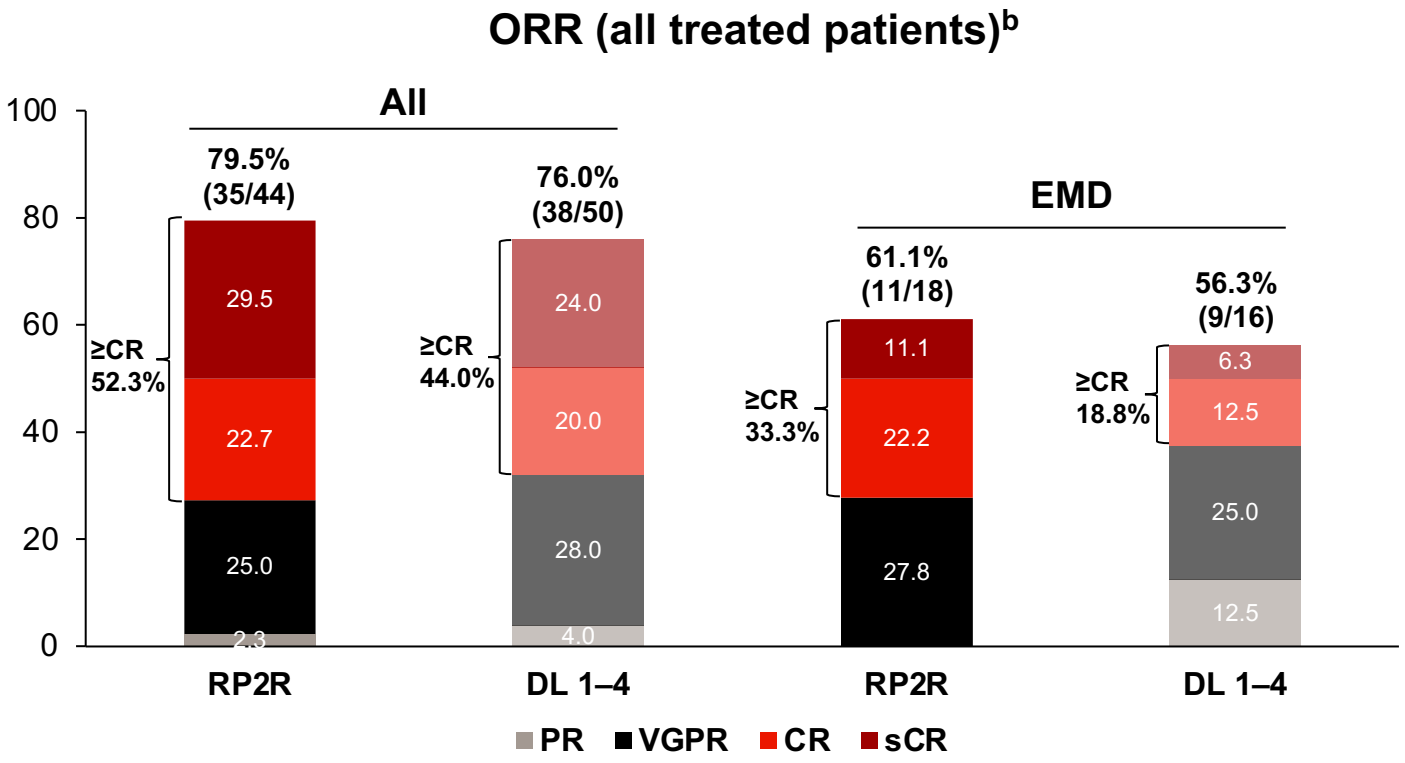


Patients could transition from QW to Q2W and from Q2W to Q4W dosing after achieving a ≥PR after cycle 4

[a]Tal and tec administered on the same day, 30 (±10) minutes apart, for all step-up and full treatment doses. DLT, dose-limiting toxicity; DOR, duration of response; EMD, extramedullary disease; IMiD, immunomodulatory drug; LOT, line of therapy; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; PK, pharmacokinetics; PR, partial response; Q4W, monthly, Q2W, every other week; QW, weekly; RP2R, recommended phase 2 regimen; RR, relapsed/refractory.

Presented by YC Cohen at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

RedirecTT-1 Tal + Tec: High ORR and Deep Responses, Including in EMD[a]



All patients	RP2R (n=44)	DL 1–4 (n=50)
Median (range) follow-up, mo	18.2 (0.7–27.0)	29.0 (0.5[c]–37.1)
Median (range) time to first response, mo	1.4 (0.3–5.1)	2.1 (1.1–7.7)

Patients with EMD	RP2R (n=18)	DL 1–4 (n=16)
Median (range) follow-up, mo	13.6 (0.7–25.9)	18.7 (0.5[c]–33.8)
Median (range) time to first response, mo	3.0 (1.4–5.1)	2.6 (2.1–3.8)

ORR 79.5% (61.1% in EMD) at RP2R with rapid and deep responses

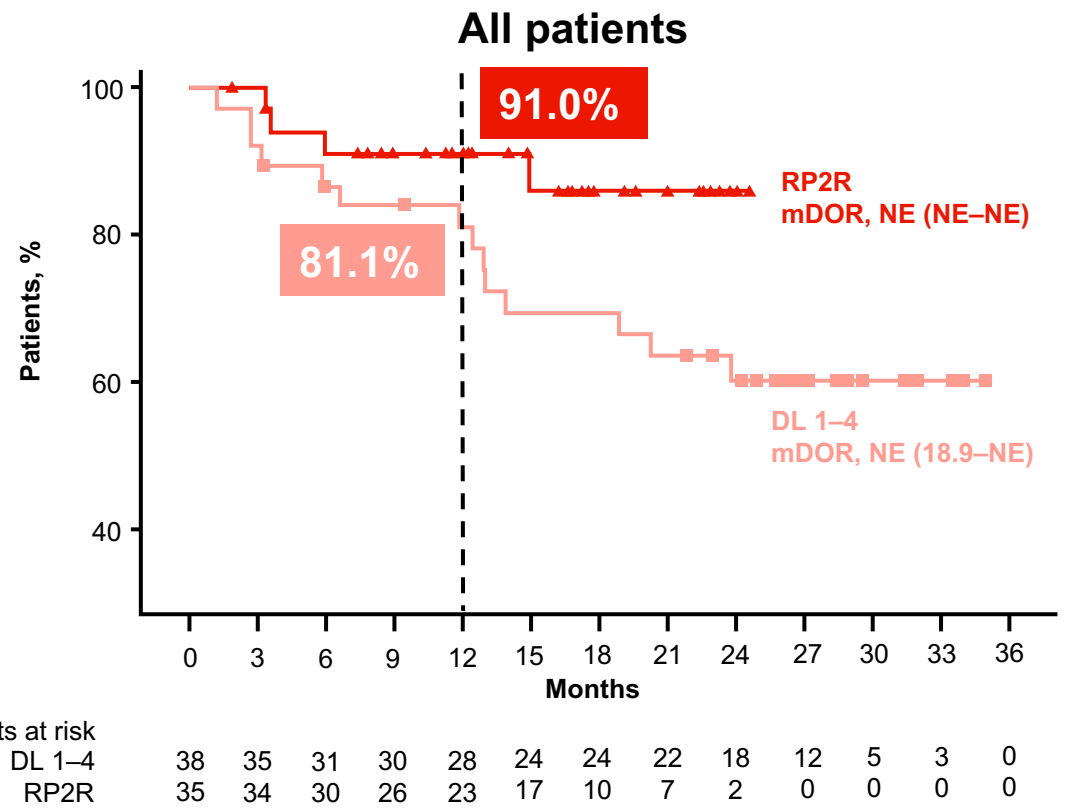
Data cut-off date: March 15, 2024.

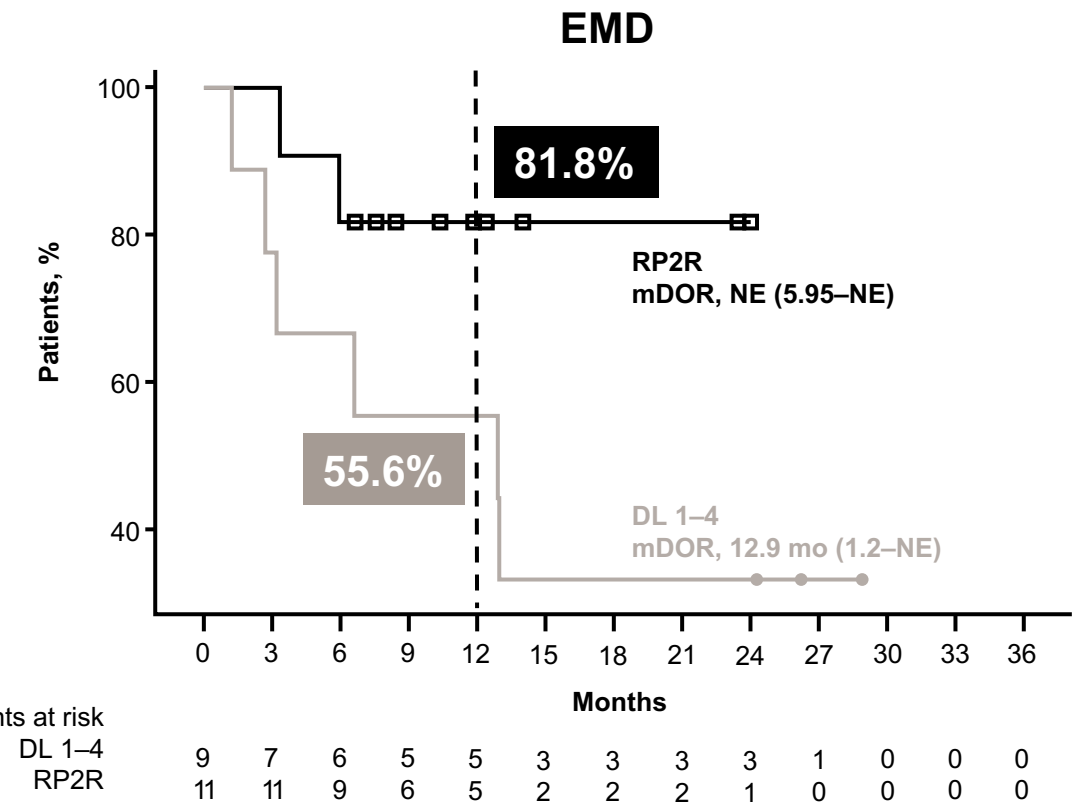
[a]EMD defined as ≥1 nonradiated, bone-independent lesion ≥2 cm. [b]Responses were investigator-assessed per IMWG 2016 criteria. Data shown are confirmed responses and calculated in all treated patients. [c]Denotes patients who died. CR, complete response; DL, dose level; EMD, extramedullary disease; IMWG, International Myeloma Working Group; ORR, overall response rate; PR, partial response; RP2R, recommended phase 2 regime; sCR, stringent complete response; VGPR, very good partial response.

Presented by YC Cohen at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

RedirecTT-1 Tal + Tec: Highly Durable Responses, Including in EMD[a]

Duration of response (DOR)





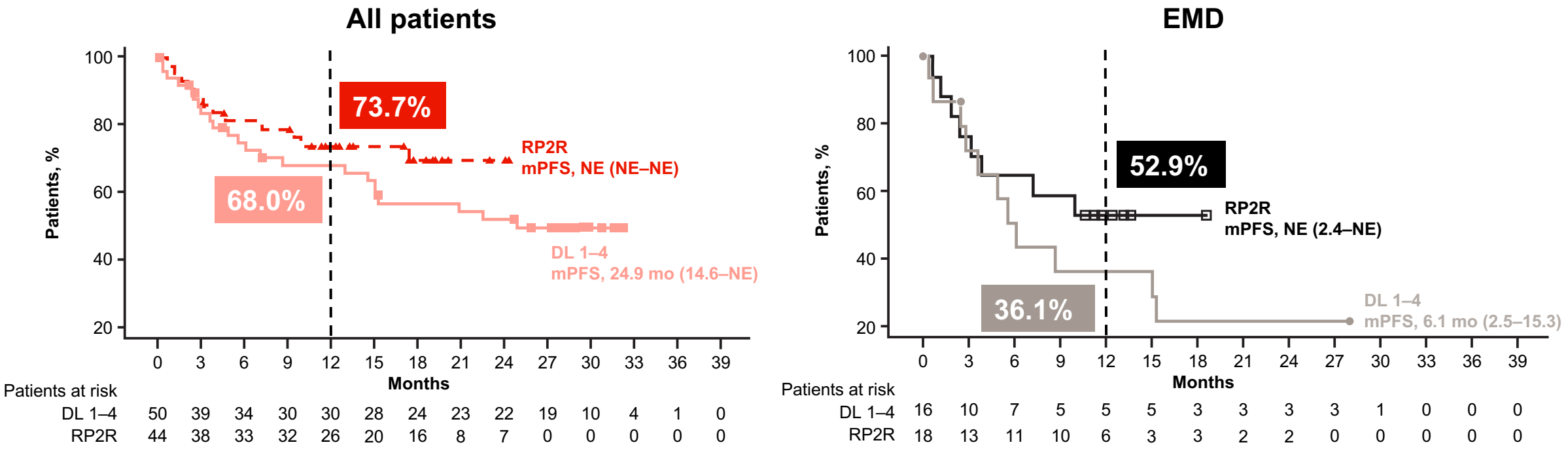
Longest DOR at RP2R (81.8% 12-mo rate in EMD)

Data cut-off date: March 15, 2024. Median follow-up: 18.2 months (RP2R) and 29.0 months (dose levels 1–4). Eighteen-month DOR rates at the RP2R were 85.9% (all patients) and 81.8% (EMD patients).
[a]EMD defined as ≥1 nonradiated, bone-independent lesion ≥2 cm. DL, dose level; EMD, extramedullary disease; mDOR, median duration of response; NE, not evaluable; RP2R, recommended phase 2 regimen.

Presented by YC Cohen at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

RedirecTT-1 Tal + Tec: Promising Early PFS, Including in EMD[a]

Progression-free survival (PFS)



Longest PFS at RP2R (52.9% 12-mo rate in EMD)

Data cut-off date: March 15, 2024. Median follow-up: 18.2 months (RP2R) and 29.0 months (dose levels 1–4). Eighteen-month PFS rates at the RP2R were 69.8% (all patients) and 52.9% (EMD patients).
[a]EMD defined as ≥1 nonradiated, bone-independent lesion ≥2 cm. DL, dose level; EMD, extramedullary disease; mPFS, median progression-free survival; NE, not evaluable; RP2R, recommended phase 2 regimen.

Presented by YC Cohen at 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

Bispecific antibodies

- Off the shelf, ORR: 60-70% in triple class refractory MM
- PFS: 1.5 year
- Community hospital, outpatient
- Combinations / sequencing
- Use in earlier lines
- A revolution ?…

Agenda

Module 1: Management of Newly Diagnosed Multiple Myeloma (MM) — Dr Orlowski

Module 2: Integration of Novel Therapies into the Management of Relapsed/Refractory MM — Dr Richardson

Module 3: Chimeric Antigen Receptor (CAR) T-Cell Therapy for MM — Dr Raje

Module 4: Bispecific Antibodies for the Treatment of MM — Prof Moreau

Module 5: Other Novel Agents and Strategies Under Investigation for MM — Dr Lonial

RTP
RESEARCH
TO PRACTICE

Case Presentation: 59-year-old man diagnosed with high-risk light chain MM experiences suboptimal response to D-RVd but wishes to avoid hospitalization to provide care for his elderly mother

Dr Eric Lee (Fountain Valley, California)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What do you see as the potential new role for belantamab mafodotin in MM? If belantamab mafodotin were to return to the market, when in the treatment sequence would you most likely administer it?

Would you be comfortable recommending this agent to a patient who has experienced disease progression on another BCMA-directed approach? What about 2 forms of BCMA-directed treatment?

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What agents would you most likely combine with belantamab mafodotin? What regimen/dose/schedule do you believe is optimal?

How much of a challenge is ophthalmic toxicity with belantamab mafodotin, and how do you believe this can best be mitigated? Is this any different in the context of combination regimens?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 80-year-old man with MM receives the combination of daratumumab with iberdomide on a clinical trial

Dr Yanjun Ma (Murfreesboro, Tennessee)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What do you see as the future role of CELMoDs in MM?

How would you compare the efficacy and tolerability of iberdomide and mezigdomide?

Would you like to have access to either or both of these agents at the current time, and if so, where would you likely employ them in the treatment sequence?

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A Cancer Center Designated by
the National Cancer Institute

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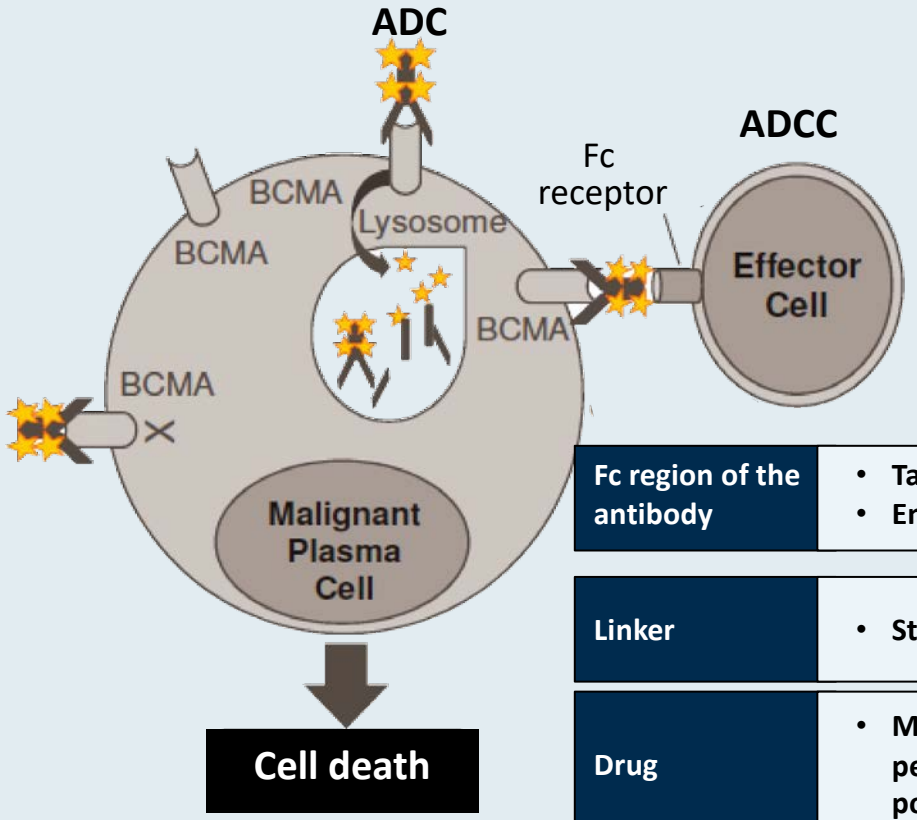
Other Novel Agents

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

Belantamab Mafodotin: Anti-BCMA Antibody-Drug Conjugate (ADC)

- B-cell maturation factor (BCMA) expression is restricted to B cells at later stages of differentiation and is required for survival of plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker



Fc region of the antibody	• **Target specific** • **Enhanced ADCC**
Linker	• **Stable in circulation**
Drug	• **MMAF (non cell permeable, highly potent auristatin)**

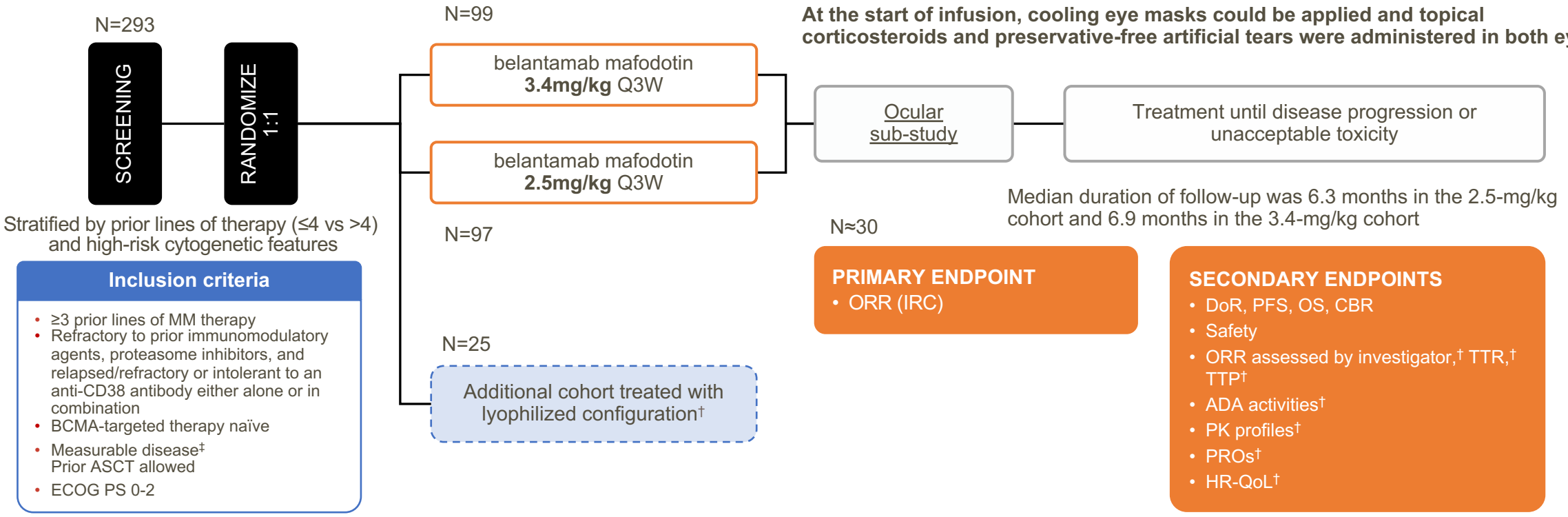
Mechanisms of action:
- ADC mechanism
- ADCC mechanism (antibody-dependent cellular cytotoxicity)
- Immunogenic cell death
- BCMA receptor signaling inhibition

Tai YT et al. *Blood* 2014;123(20):3128-38.

RTP RESEARCH TO PRACTICE

Study design

A phase II, open-label, randomized, 2-dose study in RRMM patients who were refractory to an immunomodulatory drug, proteasome inhibitor, and refractory/intolerant to an anti-CD38 monoclonal antibody



Screening occurred between June 18, 2018, and Jan 2, 2019. *Presence or absence of t(4;14), t(14;16) or 17p13del, or 1q21+. †Will be reported separately. ‡Measurable disease defined as serum myeloma protein (M-protein) ≥0.5 g/dL; urine M-protein ≥200 mg/24h; serum FLC assay: involved FLC level ≥10 mg/dL and an abnormal serum FLC ratio (<0.26 or >1.65).

ADA, anti-drug antibody; ASCT, autologous stem cell transplant; CBR, clinical benefit rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; FLC, free light chain; HR-QoL, health-related quality of life; IRC, independent review committee; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcome; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; TTR, time to response.

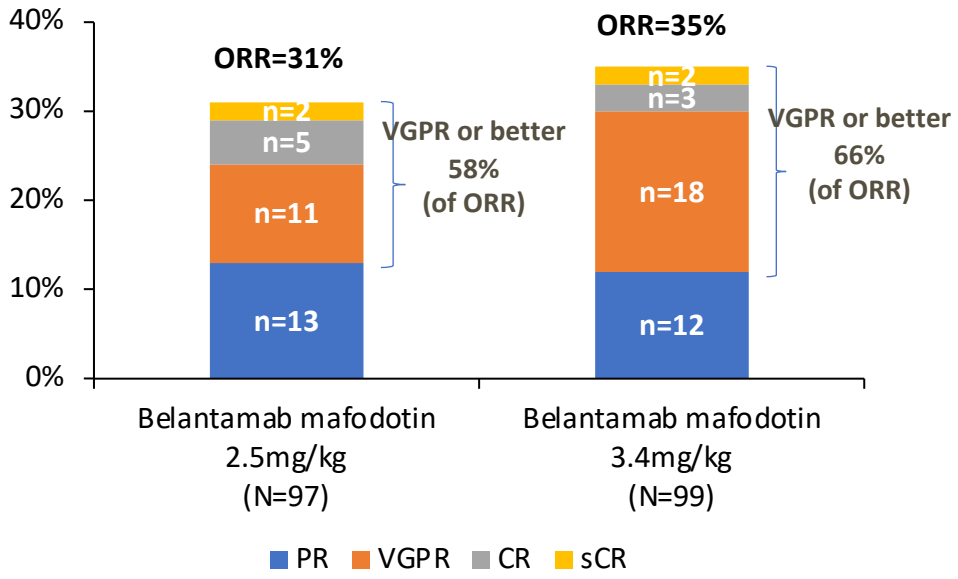
1. Lonial S et al. *Lancet Oncol.* 2020;21(2):207-221. **2**. Lonial S et al. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual Format, USA. Poster 436.

Belantamab mafodotin demonstrated a mOS of 14.9 months and a mDOR of 11.0 months in the heavily pretreated 2.5-mg/kg cohort

	belantamab mafodotin 2.5mg/kg (n=97)	belantamab mafodotin 3.4mg/kg (n=99)
mOS	14.9 months (95% CI: 9.9-NR)	14.0 months (95% CI: 10-NR)
mDOR	11.0 months (95% CI: 4.2-NR)	6.2 months (95% CI: 4.8-NR)
mPFS	2.8 months (95% CI: 1.6-3.6)	3.9 months (95% CI: 2.0-5.8)
ORR*	31% (97.5% CI: 21.7-43.6)	35% (97.5% CI: 24.8-47.0)

Duration of follow-up was 13 months in the 2.5-mg/kg and 3.4-mg/kg cohorts

Belantamab mafodotin demonstrated a meaningful ORR



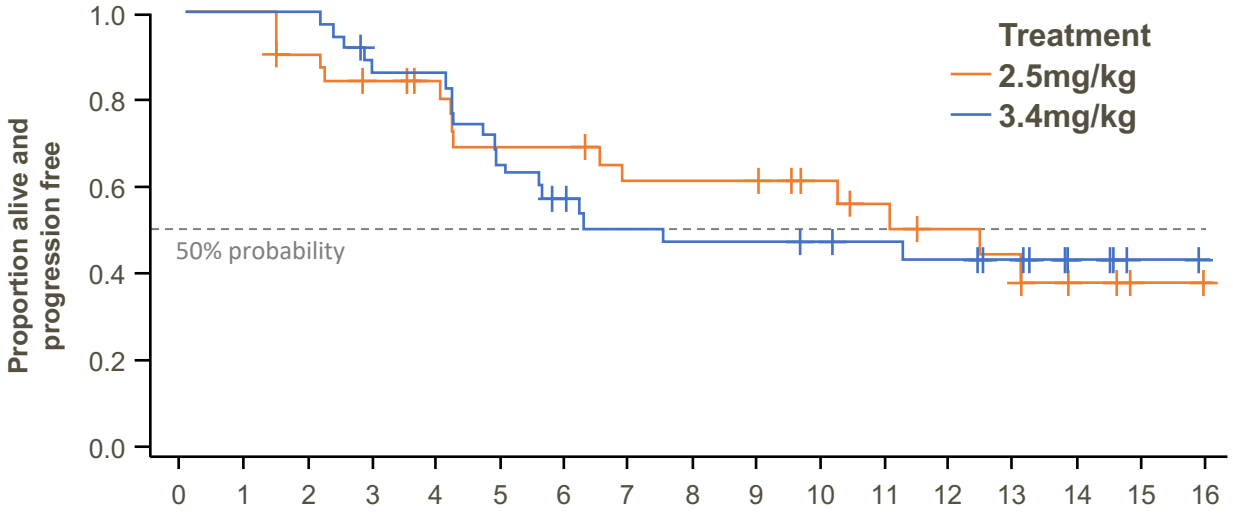
*Best response as assessed by independent review committee using 2016 IMWG criteria. Intent-to-treat population (all randomly assigned patients, regardless of treatment administration). All patients who received ≥2 doses of belantamab mafodotin and completed at ≥1 disease assessment after the second dose were evaluable for response. For response-rate analyses, patients with unknown or missing data were treated as non-responders.

CI, confidence interval; CR, complete response; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; OS, overall survival; VGPR, very good partial response.

Lonial S et al. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual Format, USA. Poster 436.

Belantamab mafodotin demonstrated deep and durable responses in patients who achieved a response

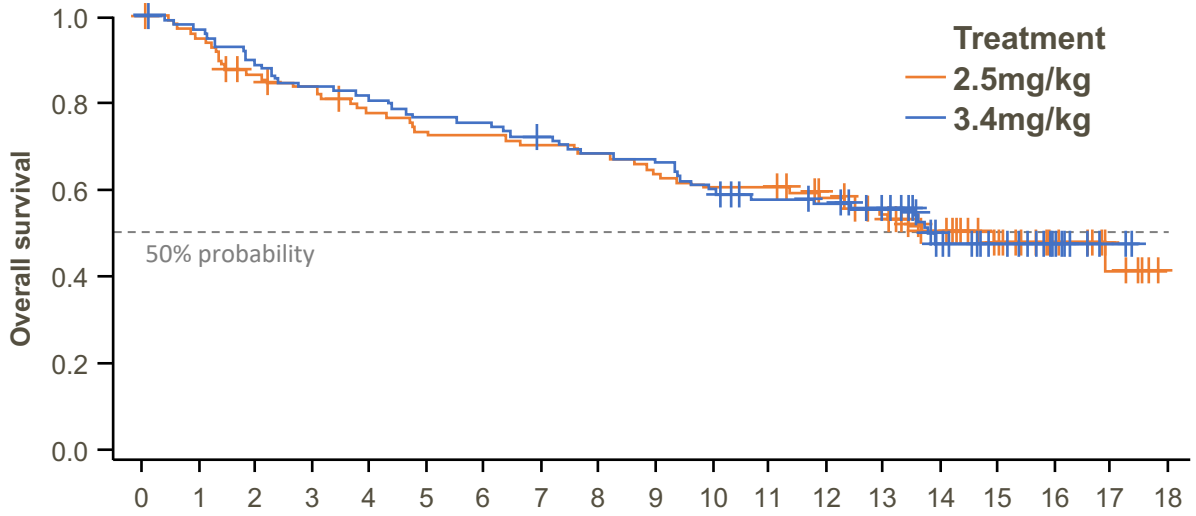
Duration of response



Number at risk (Number of events)

2.5mg/kg	31 (0)	31 (0)	27 (3)	24 (5)	21 (6)	18 (9)	18 (9)	15 (11)	15 (11)	15 (11)	12 (11)	10 (12)	8 (13)	7 (14)	3 (15)	1 (15)	0 (15)
3.4mg/kg	35 (0)	35 (0)	35 (0)	29 (5)	29 (5)	22 (12)	18 (15)	15 (17)	14 (18)	14 (18)	13 (18)	12 (18)	11 (19)	9 (19)	4 (19)	1 (19)	0 (19)

Overall survival

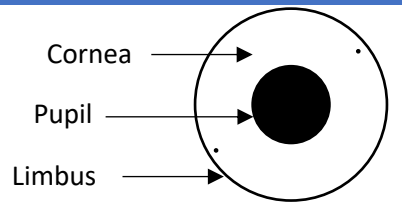
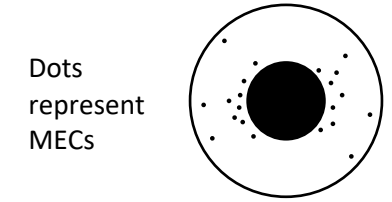
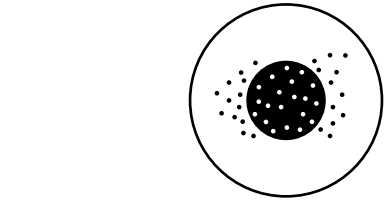


Number at risk (Number of events)

2.5mg/kg	97 (0)	91 (5)	81 (13)	77 (16)	71 (21)	67 (25)	66 (26)	64 (28)	62 (30)	59 (33)	55 (37)	55 (37)	49 (39)	43 (42)	31 (45)	22 (46)	13 (46)	6 (47)	0 (47)
3.4mg/kg	99 (0)	95 (3)	88 (10)	82 (16)	80 (18)	75 (23)	74 (24)	70 (27)	66 (31)	65 (32)	58 (39)	53 (41)	51 (42)	46 (43)	32 (48)	20 (49)	10 (48)	2 (49)	0 (49)

Lonial S et al. Pivotal DREAMM-2 study: single-agent belantamab mafodotin (GSK2857916) in patients with relapsed/refractory multiple myeloma (RRMM) refractory to proteasome inhibitors (PIs), immunomodulatory agents, and refractory and/or intolerant to anti-CD38 monoclonal antibodies (mAbs). Poster presented at: American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual Format, USA. Poster 436.

Grading Corneal Adverse Events per the Keratopathy and Visual Acuity (KVA) Scale to Inform Doing Decisions for the US PI

Corneal Adverse Reaction			Presentation of microcyst-like epithelial changes (MECs)[b]	
	Change in BCVA due to treatment-related corneal findings	**Corneal examination finding(s)**	**Evaluate based on density and location**	**Example schematics by severity**
Grade 1	Decline from baseline of 1 line on Snellen Visual Acuity	**Mild superficial keratopathy**[a] (documented worsening from baseline), with or without symptoms	**Mild** **Density**: Non-confluent **Location**: Predominantly (≥80%) peripheral *Few, if any, microcysts observed*	
Grade 2	Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200	**Moderate superficial keratopathy**[a] with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity	**Moderate** **Density**: Semi-confluent **Location**: Predominantly (≥80%) paracentral	
Grade 3	Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200	**Severe superficial keratopathy**[a] with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity	**Severe** **Density**: Confluent **Location**: Predominantly (≥80%) central	
Grade 4	Snellen Visual Acuity worse than 20/200	**Corneal epithelial defect** such as corneal ulcers	***The worst severity for microcyst-like epithelial change density or location should be used in grading. Grading is based on the worst finding in the worst affected eye.***	

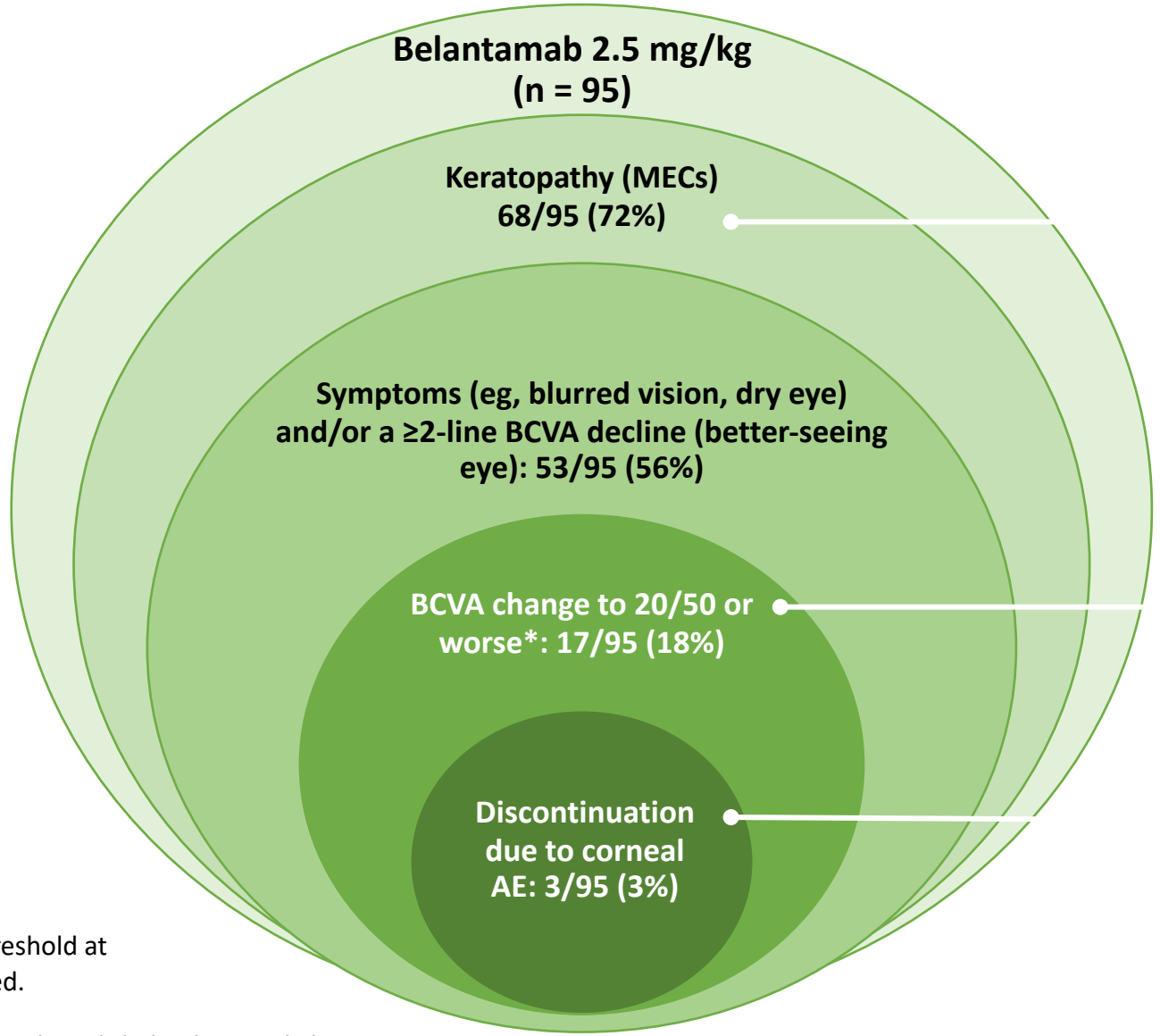
[a] Patients may have superficial punctate keratopathy, microcyst-like epithelial changes, or both. Keratopathy refers to superficial punctate keratopathy (revealed by fluorescein staining) or microcyst-like epithelial changes (not stained by fluorescein). Fluorescein staining should be part of each eye exam, including baseline examination. The worst grade for the keratopathy and the change in BCVA should be used to determine the grade of the corneal adverse event.

[b] These evaluations and examples do not apply to, or include, superficial punctate keratopathy.

Lonial S, et al. *Blood Cancer Journal 2021*; 11:103.

The unintended consequences of a payload

1 patient developed grade 4 corneal ulcer



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

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

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

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

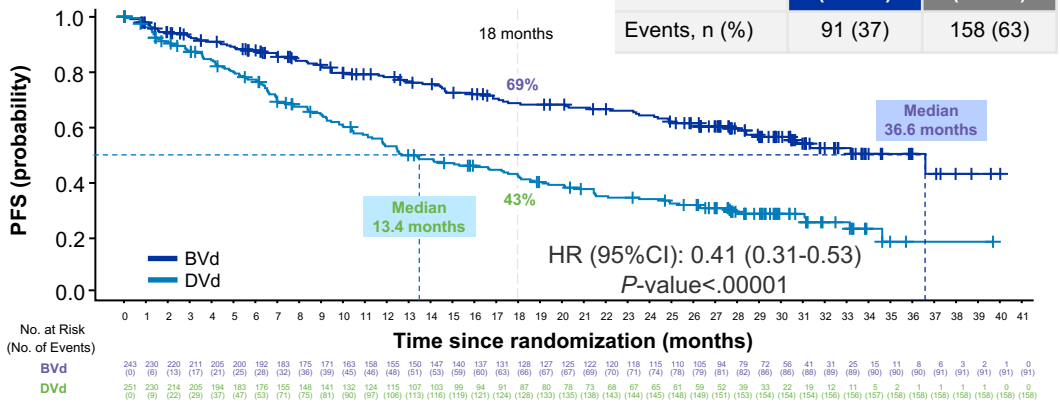
Lonial. ASH 2020. Abstr 3224; Farooq et al, *Ophthalmology and Therapy* 2020

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**

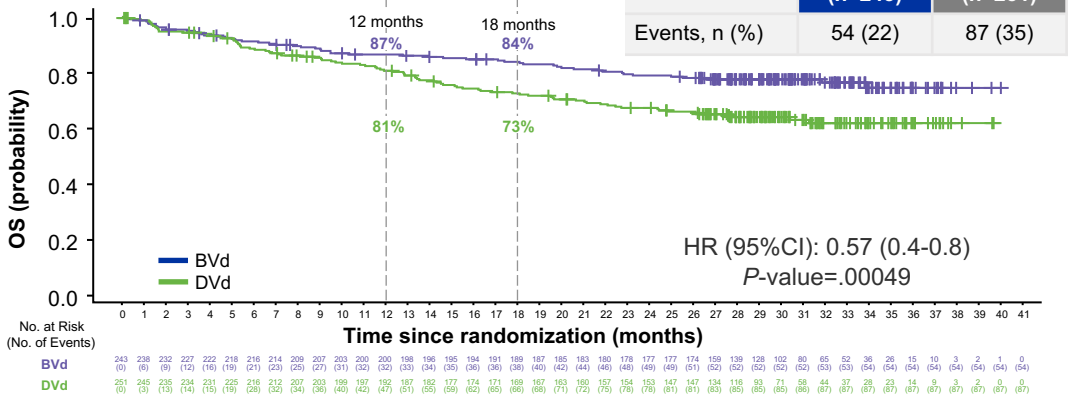
Progression-free survival

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

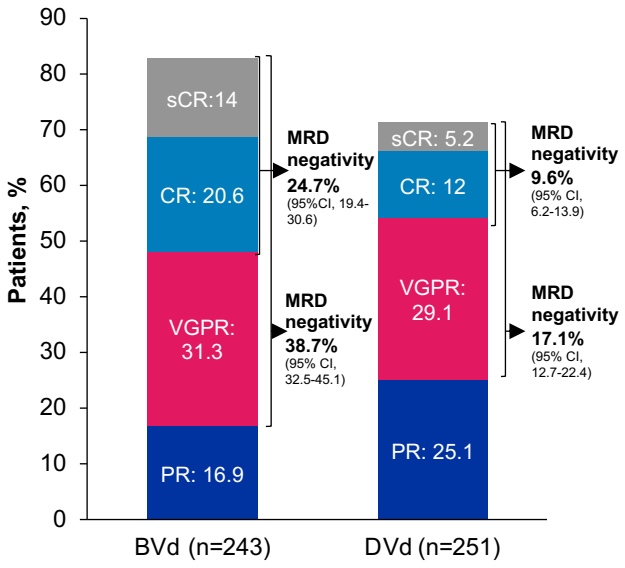


Overall survival

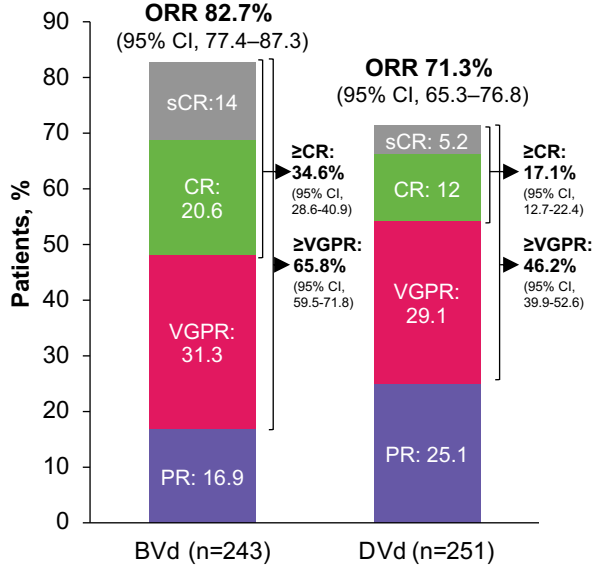
OS*	BVd (n=243)	DVd (n=251)
Events, n (%)	54 (22)	87 (35)



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

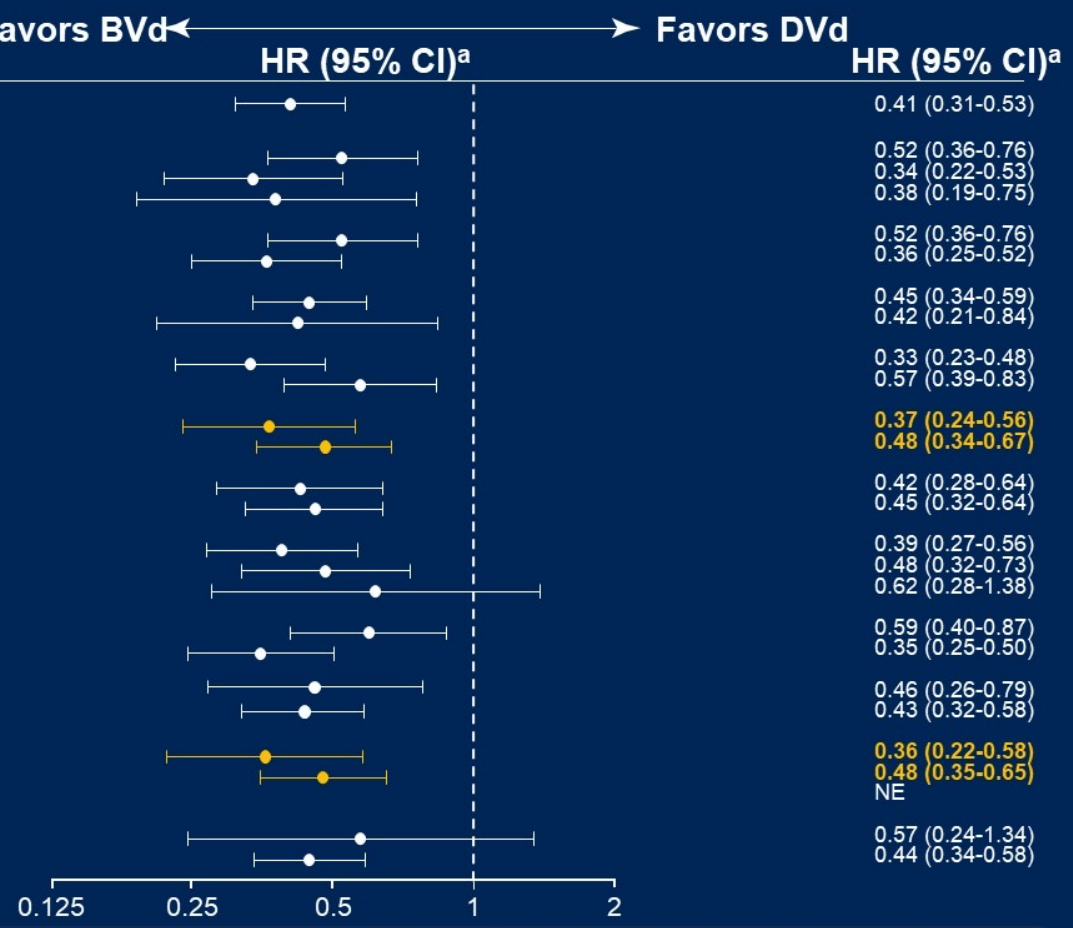
Median follow-up: 28.2 months. *Two patients in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as four unique patients in this output. †CIs estimated using the Brookmeyer-Crowley method. ‡HRs were estimated using a Cox proportional hazards model stratified 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. ||In 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.

Hungria V et al. *N Engl J Med* 2024 Aug 1;391(5):393-407; Mateos MVM et al. American Society of Clinical Oncology Plenary Series 2024;Abstract 439572.

SL

DREAMM-7: prespecified subgroup analysis of IRC-assessed PFS

Categories	BVd n/N	DVd n/N	HR (95% CI)[a]
All Subjects (Stratified)[b]	91/243	158/251	0.41 (0.31-0.53)
Number of Prior LOT (1 vs 2 or 3 vs ≥4)			
1	46/125	76/125	0.52 (0.36-0.76)
2 or 3	30/88	62/99	0.34 (0.22-0.53)
≥4	15/30	20/27	0.38 (0.19-0.75)
Number of Prior LOT (1 vs >1)			
1	46/125	76/125	0.52 (0.36-0.76)
>1	45/118	82/126	0.36 (0.25-0.52)
Prior Bortezomib			
Yes	79/210	132/211	0.45 (0.34-0.59)
No	12/33	26/40	0.42 (0.21-0.84)
Prior Lenalidomide			
Yes	44/127	88/130	0.33 (0.23-0.48)
No	47/116	70/121	0.57 (0.39-0.83)
Refractory to Lenalidomide			
Yes	**33/79**	**64/87**	**0.37 (0.24-0.56)**
No	**58/164**	**94/164**	**0.48 (0.34-0.67)**
Revised ISS Staging at Screening			
I	37/102	64/103	0.42 (0.28-0.64)
II/III	53/139	94/146	0.45 (0.32-0.64)
Age			
<65 years	42/121	84/126	0.39 (0.27-0.56)
65-<75 years	37/85	61/95	0.48 (0.32-0.73)
≥75 years	12/37	13/30	0.62 (0.28-1.38)
Gender			
Female	48/115	59/107	0.59 (0.40-0.87)
Male	43/128	99/144	0.35 (0.25-0.50)
Time to Relapse After Completion of 1L Treatment			
≤12 months	23/49	31/50	0.46 (0.26-0.79)
>12 months	68/194	127/201	0.43 (0.32-0.58)
Cytogenetics Risk			
High Risk[c]	**26/67**	**48/69**	**0.36 (0.22-0.58)**
Standard Risk[d]	**65/175**	**106/175**	**0.48 (0.35-0.65)**
Missing or Not Evaluable	0/1	4/7	NE
Extramedullary Disease at Baseline			
Yes	8/13	18/25	0.57 (0.24-1.34)
No	83/230	140/226	0.44 (0.34-0.58)

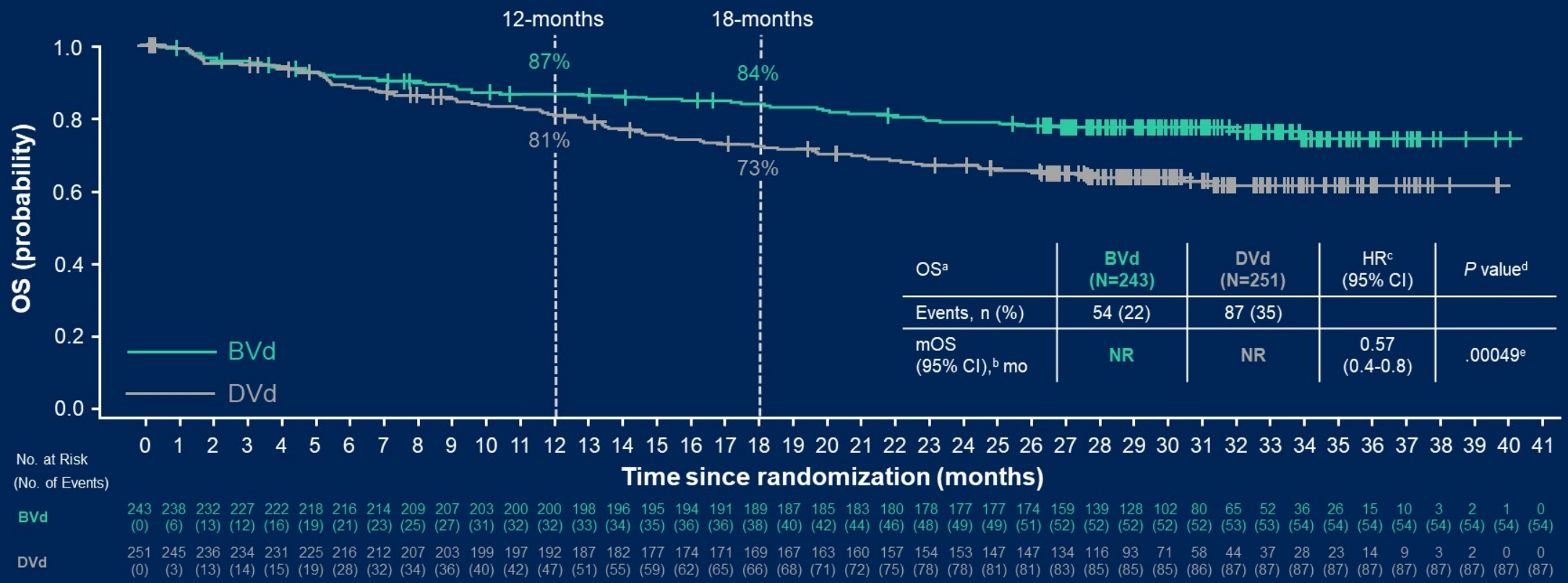


PFS benefit consistently favored BVd vs DVd across prespecified subgroups, including patients with lenalidomide refractory or high-risk cytogenetic MM

IVRS, interactive voice response system; NE, not evaluable.
[a] HRs for subgroups were only plotted if number of the events was ≥20 in total across both treatments. HRs for subgroups were estimated using Cox proportional hazards model, without adjustment for stratification variables. [b] Stratified by the number of lines of prior therapy (1 vs 2 or 3 vs ≥4), prior bortezomib (no, yes) and R-ISS at screening (I vs II/III) according to IVRS strata, with a covariate of treatment. [c] A patient was considered as high risk if the subject had any of the following cytogenetics: t(4;14), t(14;16) or del(17p13). [d] A patient was considered standard risk if the subject has negative results for all high-risk abnormalities: t(4;14), t(14;16) or del(17p13).

Hungria V et al. *N Engl J Med* 2024 Aug 1;391(5):393-407;
Mateos MVM et al. ASCO Plenary Series 2024;Abstract 439572.

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.

Hungria V et al. *N Engl J Med* 2024 Aug 1;391(5):393-407;
Mateos MVM et al. ASCO Plenary Series 2024;Abstract 439572.

Belantamab Mafodotin, Bortezomib, and Dexamethasone vs Daratumumab, Bortezomib, and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Overall Survival Analysis and Updated Efficacy Outcomes of the Phase 3 DREAMM-7 Trial

Hungria V et al.

ASH 2024;Abstract 772.

ORAL ABSTRACTS | MONDAY, DECEMBER 9 | 11:15 AM PT

RTP
RESEARCH
TO PRACTICE

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)

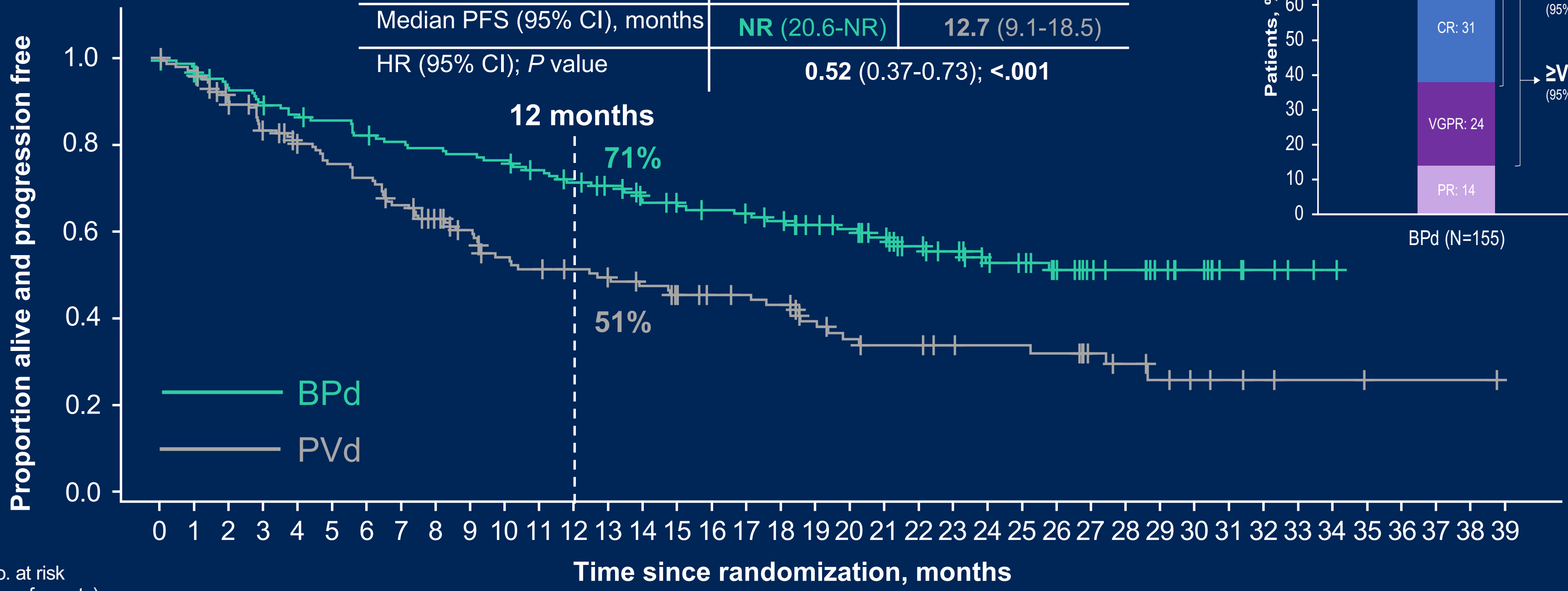
AE, adverse event; BCMA, B-cell maturation antigen; BPd, belamaf, pomalidomide, and dexamethasone; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; HRQOL, health-related quality of life; IMWG, International Myeloma Working Group; IRC, independent review committee; 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).

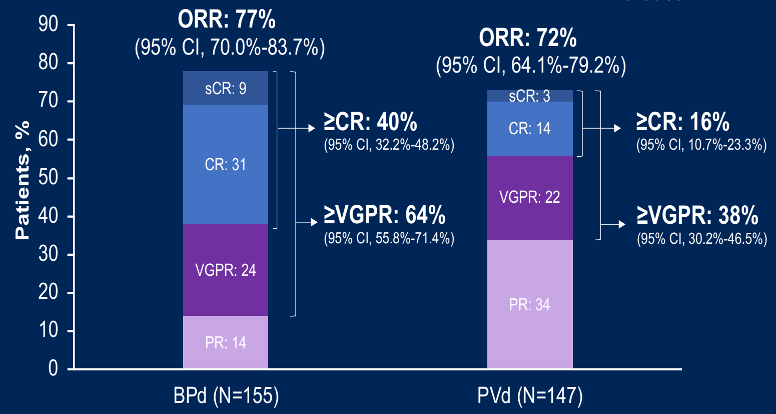
Dimopoulos MA et al. *N Engl J Med* 2024 Aug 1;391(5):408-21;
Trudel S et al. ASCO 2024;Abstract LBA105.

DREAMM-8
Belantamab Mafodotin + Pd

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)

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

Month	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
BPd	64 (54)	59 (56)	50 (58)	45 (59)	38 (61)	36 (61)	28 (62)	23 (62)	21 (62)	16 (62)	13 (62)	8 (62)	4 (62)	2 (62)	1 (62)	0 (62)	0 (62)	0 (62)	0 (62)	0 (62)
PVd	25 (76)	22 (77)	22 (77)	19 (77)	18 (77)	18 (77)	17 (78)	13 (78)	11 (79)	7 (80)	5 (80)	4 (80)	3 (80)	2 (80)	2 (80)	1 (80)	1 (80)	1 (80)	1 (80)	0 (80)

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

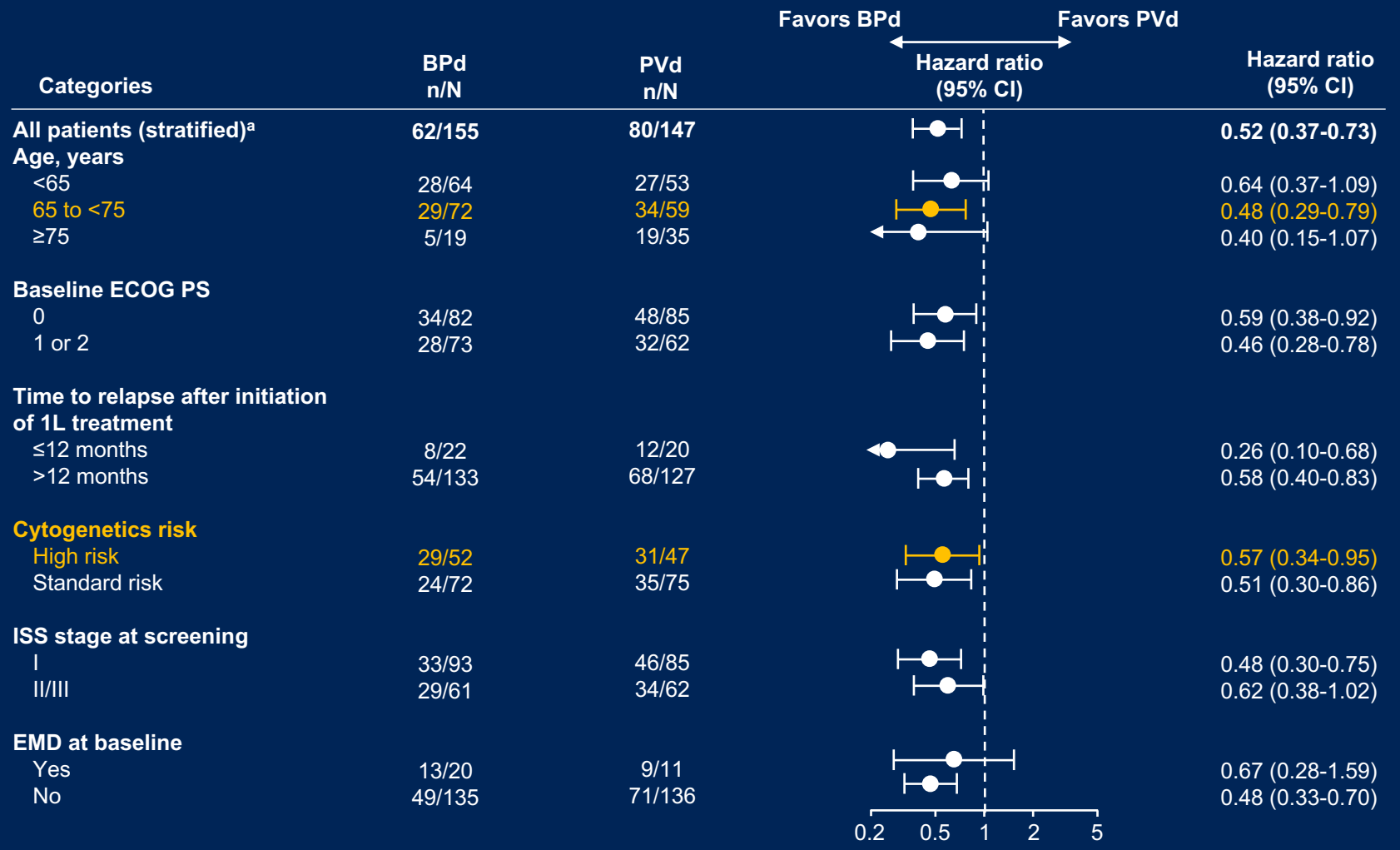
Median follow-up, 21.8 months (range, 0.03-39.23 months)

The treatment effect (HR and corresponding 95% CIs) was estimated using the stratified Cox proportional hazards model, and the *P* value was produced based on the 1-sided stratified log-rank test. Stratified analyses were adjusted for number of prior lines of therapy and prior bortezomib use.

BPd, belamaf, pomalidomide, and dexamethasone; HR, hazard ratio; NR, not reported; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone.

Dimopoulos MA et al. *N Engl J Med* 2024 Aug 1;391(5):408-21;
Trudel S et al. ASCO 2024;Abstract LBA105.

PFS Benefit Was Seen Consistently Across All Prespecified Subgroups



HRs for subgroups were only plotted if the number of events was ≥20 in total across both treatments and were estimated using Cox proportional hazards models, without adjustments for stratification variables. A patient was considered high risk if they had any of the following cytogenetics: t(4;14), t(14;16), or del(17p13) and considered standard risk if they had negative results for all high-risk cytogenetics listed above.

[a] HR for all patients was stratified by the number of lines of prior therapy (1 vs 2/3 vs ≥4) and prior bortezomib (yes or no) according to interactive voice response system strata with a covariate of treatment.

1L, first line; BPd, belamaf, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; EMD, extramedullary disease; HR, hazard ratio; ISS, International Staging System; LOT, line of therapy; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone.

Dimopoulos MA et al. *N Engl J Med* 2024 Aug 1;391(5):408-21;
Trudel S et al. ASCO 2024;Abstract LBA105.

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

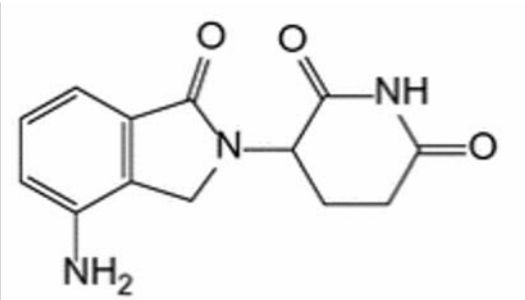
AE, adverse event; AESI, adverse event of special interest; BPd, belamaf, pomalidomide, and dexamethasone; CTCAE, Common Terminology Criteria for Adverse Events; PVd, pomalidomide, bortezomib, and dexamethasone.
[a] Post-hoc analysis. [b] Thrombocytopenia includes events identified by site or preferred 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.

Dimopoulos MA et al. *N Engl J Med* 2024 Aug 1;391(5):408-21;
Trudel S et al. ASCO 2024;Abstract LBA105.

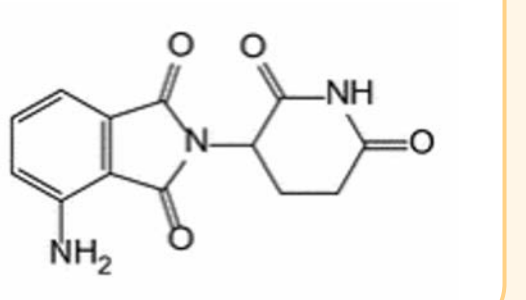
Novel cereblon E3 ligase modulators (CELMoD® agents) in development

LEN and **POM**
(a subgroup of CELMoD® agents)
helped to **transform therapy and drive survival** in MM[1-3]

LEN



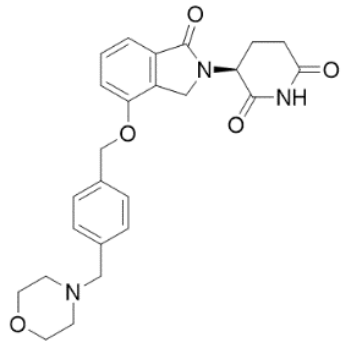
POM



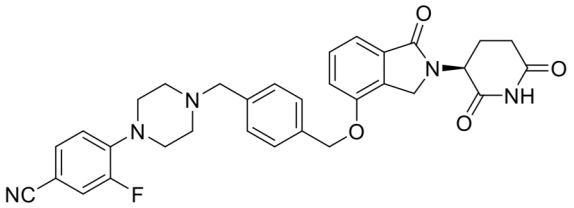
Rational selection of molecules based on **deep scientific understanding of CRBN and MM biology: iberdomide (IBER; CC-220) and mezigdomide (CC-92480)**[4-6]

2019 and 2020: First clinical data for IBER and CC-92480 in MM

IBER



CC-92480



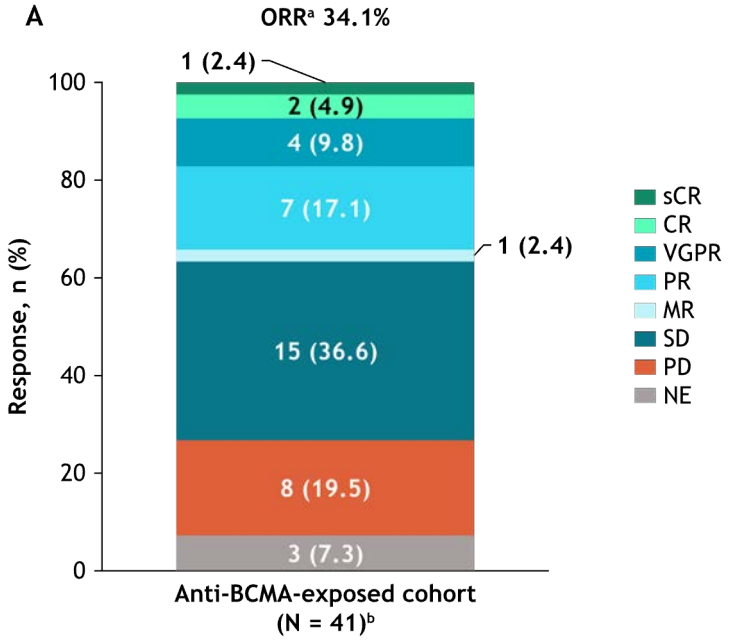
Iberdomide (IBER; CC-220) and mezigdomide (CC-92480) are investigational products, currently not approved by any regulatory agency.

CRBN, cereblon; IBER, iberdomide; LEN, lenalidomide; MM, multiple myeloma; POM, pomalidomide.

1. Rajkumar SV, et al. Lancet Oncol. 2010;11:29-37. 2. Facon T, et al. Blood. 2018;131:301-10. 3. Durie BGM, et al. Blood Cancer J. 2020;10:53. 4. Ito T, Handa H. Int J Hematol. 2016;104:293-9.
5. Matyskiela ME, et al. J Med Chem. 2018;61:535-42. 6. Hansen JD, et al. J Med Chem. 2020;63:6648-67.

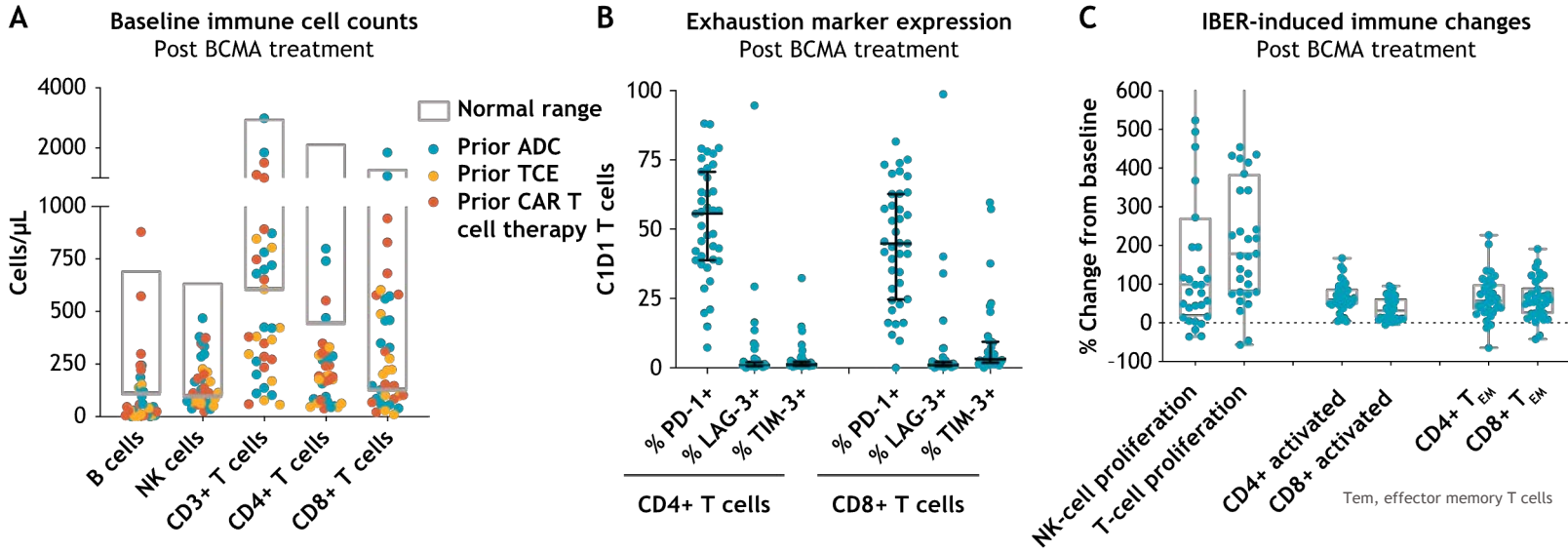
CC-220-MM-001 IBER+DEX (Cohort I) efficacy and safety in patients with heavily pretreated, anti-BCMA-exposed RRMM

Efficacy (ORR) and safety of IBER+DEX in anti-BCMA-exposed patients with RRMM



[a]PR or better; [b]Data cutoff: August 1, 2022; [c]Includes viral pneumonia, bacterial pneumonia, COVID-19 pneumonia, *Pneumocystis jirovecii* pneumonia, and pseudomonal pneumonia.
COVID-19, coronavirus disease 2019; MR, minimal response; NE, not evaluable; SD, stable disease; TEAE, treatment-emergent adverse event.

IBER is immune-stimulatory post-BCMA therapy

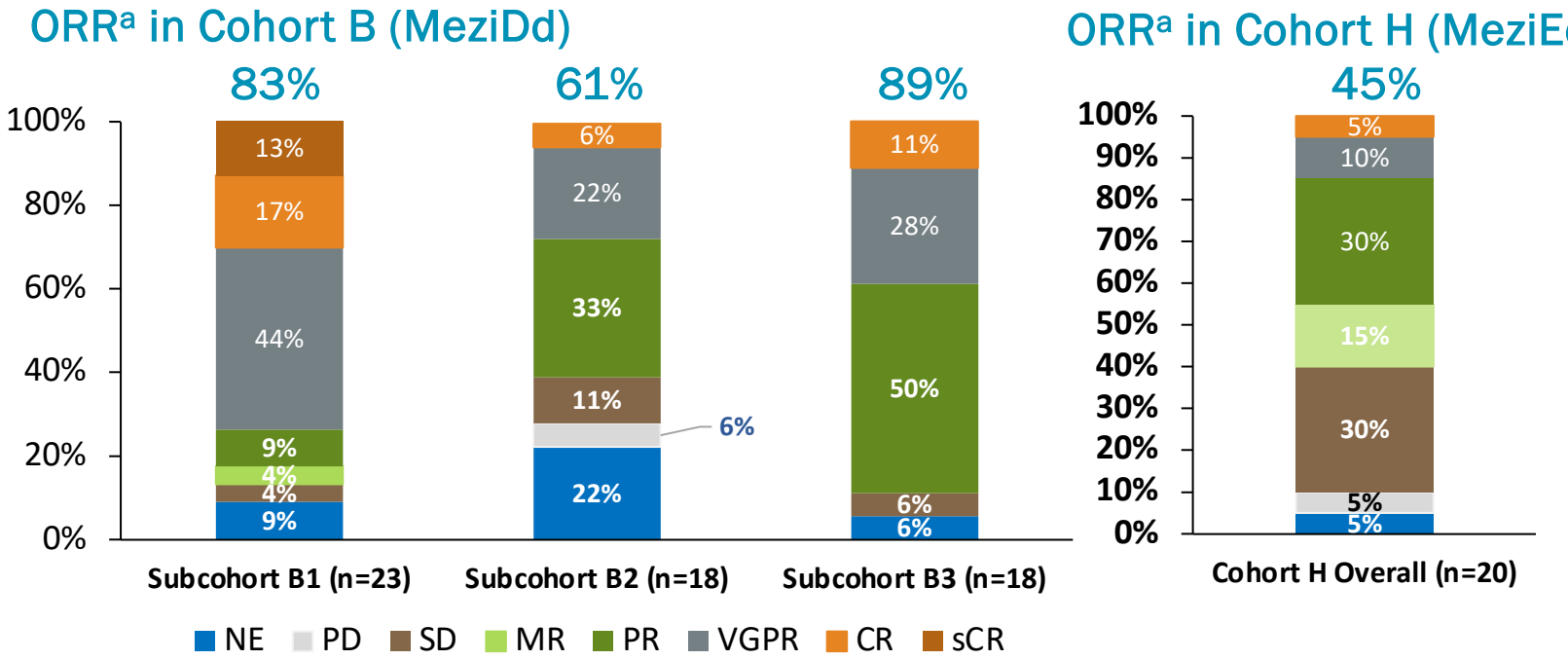


Most frequent (≥ 20% all grade) TEAEs and events of interest,[b] n (%)	Anti-BCMA-exposed cohort IBER + DEX (N = 41)		
	All grades	Grade 3	Grade 4
Hematologic TEAEs			
Neutropenia	23 (56.1)	11 (26.8)	10 (24.4)
Febrile neutropenia	1 (2.4)	1 (2.4)	0
Anemia	15 (36.6)	11 (26.8)	0
Thrombocytopenia	12 (29.3)	4 (9.8)	4 (9.8)
Leukopenia	12 (29.3)	6 (14.6)	4 (9.8)
Lymphopenia	9 (22.0)	2 (4.9)	6 (14.6)
Non-hematologic TEAEs			
Fatigue	15 (36.6)	2 (4.9)	0
Diarrhea	10 (24.4)	1 (2.4)	0
Constipation	10 (24.4)	0	0

[a]PR or better; [b]Data cutoff: August 1, 2022; [c]Includes viral pneumonia, bacterial pneumonia, COVID-19 pneumonia, *Pneumocystis jirovecii* pneumonia, and pseudomonal pneumonia.
COVID-19, coronavirus disease 2019; MR, minimal response; NE, not evaluable; SD, stable disease; TEAE, treatment-emergent adverse event.

Lonial S, et al. ASH 2022; CC-220-MM-001 Study

Results From the Phase 1/2 Study of Mezigdomide + Dex and Dara or Elo in RRMM: Efficacy



- Combined ORR for cohort B (MeziDd) was 78%
- Lower ORR to date in Subcohort B2 might be explained by the median follow-up time of only 3 mo
- Among the efficacy-evaluable population in Subcohort B2, only 1 PD was reported
- Importantly, dose exposure per cycle was highest in patients receiving Mezi for 3 out of 4 weeks and lowest in patients receiving Mezi for 1 out of 2 weeks, suggesting that Subcohort B2 is not yet mature for ORR

	Cohort B (MeziDd)			Cohort H (MeziEd)
	Subcohort B1	Subcohort B2	Subcohort B3	
Median time to first response[b] (range), mo	1.18 (0.9-4.6)	0.89 (0.7-2.8)	1.61 (0.9-4.6)	0.95 (0.9-2.8)
Median DOR (95% CI), mo	NR (23.3-NR)	NR (4.6-NR)	9.5 (9.5-NR)	5.0 (3.7-NR)
Median follow-up[c] (range), mo	22.6 (0.7-39.6)	3.1 (0.5-15.2)	6.6 (2.8-14.1)	7.1 (2.0-21.7)

[a]PR or better. [b]Data derived from the safety population. [c]Data derived from the full analysis population.
Data cut-off: July 6, 2023
Richardson P, et al. ASH 2023. Abstract 1013.

Venetoclax Versus Bortezomib, in Combination with Daratumumab and Dexamethasone, in Patients With t(11;14)-Positive Relapsed or Refractory Multiple Myeloma

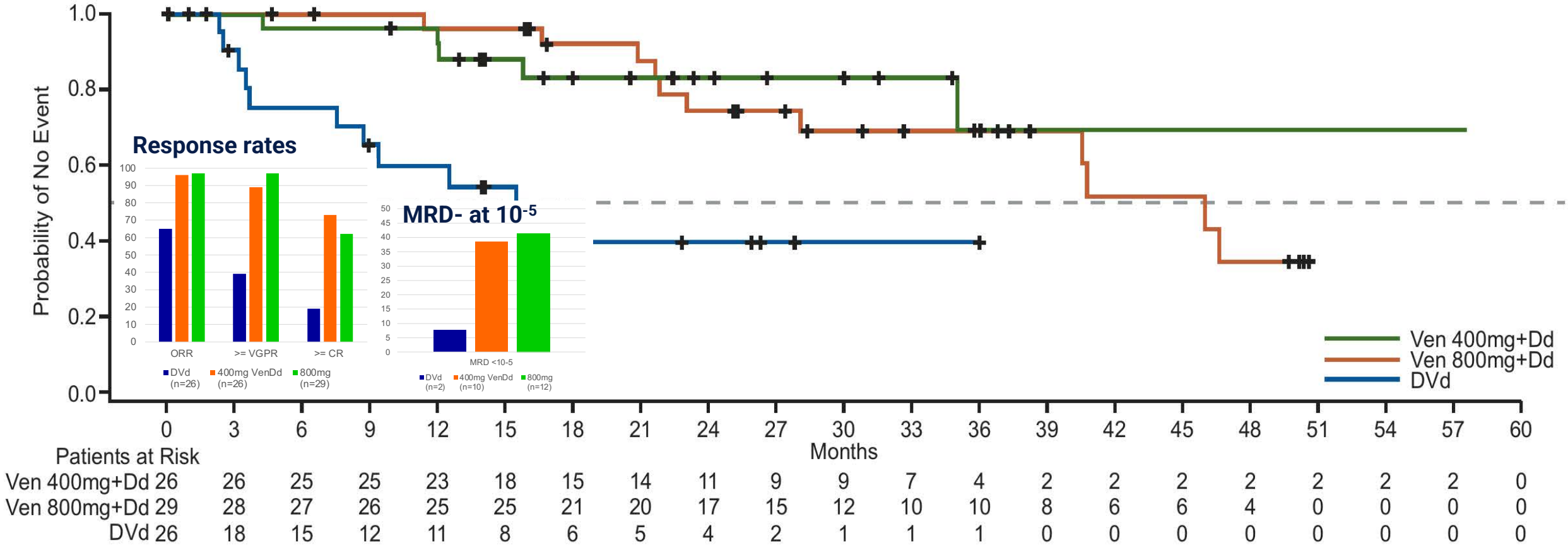
Jonathan L. Kaufman[1], Hang Quach[2], Rachid Baz[3], Annette Juul Vangsted[4], Shir-Jing Ho[5], Niels Abildgaard[6], Jacob Laubach[7], Vincent Ribrag[8], Simon Gibbs[9], Eva Medvedova[10], Peter Voorhees[11], Muhammad Jalaluddin[12], Jiewei Zeng[12], Jeremy A. Ross[12], Xifeng Wang[12], Leanne Lash Fleming[12], Orlando F. Bueno[12], Yan Luo[12], Nizar J. Bahlis[13]

[1]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA; [2]St.Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia; [3]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [4]Department of Haematology, Rigshospitalet,Copenhagen, Denmark; [5]St George Hospital, University of NSW, Sydney, Australia; [6]Haematology Research Unit, Department of Haematology, Odense University Hospital, and Department of Clinical Research, University of Southern Denmark, Odense, Denmark; [7]Dana-Farber/Partners CancerCare, Harvard Medical School,Boston, MA, USA; [8]Department of Hematology, Gustave Roussy, Université Paris-Saclay, Villejuif, France; [9]Department of Haematology, Eastern Health, Melbourne, Victoria and Monash University, Melbourne, Victoria; [10]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [11]Levine Cancer Institute, Atrium Health Wake Forest School of Medicine, Charlotte, NC, USA; [12]AbbVie, Inc. North Chicago, IL, USA; [13]Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, Canada; Tom Baker Cancer Center, Department of Hematology and Oncology, Calgary, Canada.

Objective

To report updated safety and efficacy from a Phase 1/2 trial of venetoclax (Ven) plus daratumumab and dexamethasone (VenDd) at 400 mg and 800 mg Ven dose levels, versus bortezomib plus Dd (DVd) in patients with t(11;14)+ relapsed or refractory multiple myeloma (RRMM)

The 33-month progression-free survival estimate was numerically higher for patients treated with VenDd when compared with patients treated with DVd



Group	Follow-up time, median (range), months	33-month PFS estimate, % (95% CI)
400 mg VenDd (n=26)	24.2 (4.2-57.6)	83.2 (61.0-93.4)
800 mg VenDd (n=29)	32.6 (1.0-50.6)	69.1 (45.6-84.1)
DVd (n=26)	17.8 (0.0-36.0)	39.7 (17.0-61.8)

Data set includes both non-randomized Part 1 patients and randomized Part 3 patients. No statistical comparisons were performed.
Dd, daratumumab and dexamethasone; DVd, bortezomib, daratumumab, and dexamethasone; PFS; progression-free survival; Ven, Venetoclax.

First Results From the Randomized Portion of a Phase 2 Study of Venetoclax Plus Carfilzomib-Dexamethasone vs Carfilzomib-Dexamethasone in Patients With t(11;14)-Positive Relapsed/Refractory Multiple Myeloma

Jonathan L. Kaufman, MD[1]; Cristina Gasparetto, MD[2]; Tibor Kovacsovics, MD[3]; Gabor Mikala, MD, PhD[4]; Tamás Masszi, MD, PhD[5]; Laura Rosiñol, MD, PhD[6]; Wojciech Janowski, MBBS[7]; Albert Oriol, MD, PhD[8]; Maika Onishi, MD, MAS[9]; Zhuangzhuang Liu, PhD[10]; Mohamed Badawi, PhD[10]; Jeremy A. Ross, PhD[10]; Rajvineeth K. Pothacamury, MD[10]; Orlando F. Bueno, MD, PhD[10]; Edyta Dobkowska, MD[11]; Edward A. Stadtmauer, MD[12]*; and Luciano J. Costa, MD, PhD[13]*

*Authors contributed equally

[1]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, USA; [2]Division of Hematologic Malignancies and Cellular Therapy, Department of Medicine, Duke University School of Medicine, Durham, NC, USA; [3]Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; [4]Department of Hematology and Stem Cell Transplantation, South Pest Central Hospital, National Institute for Hematology and Infectious Diseases, Budapest, Hungary; [5]Department of Haematology and Stem Cell Transplantation, St. István and St. László Hospital, Department of Internal Medicine and Hematology, Semmelweis University, Budapest, Hungary; [6]Amyloidosis and Myeloma Unit, Department of Hematology, Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain; [7]Department of Haematology, Calvary Mater Newcastle, Waratah, New South Wales, Australia; [8]Catalan Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [9]Genentech, Inc, South San Francisco, CA, USA; [10]AbbVie, Inc, North Chicago, IL, USA; [11]Pharmacyclics Switzerland GmbH, An AbbVie Company, Schaffhausen, Switzerland; [12]Division of Hematology and Oncology, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA, USA; [13]Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

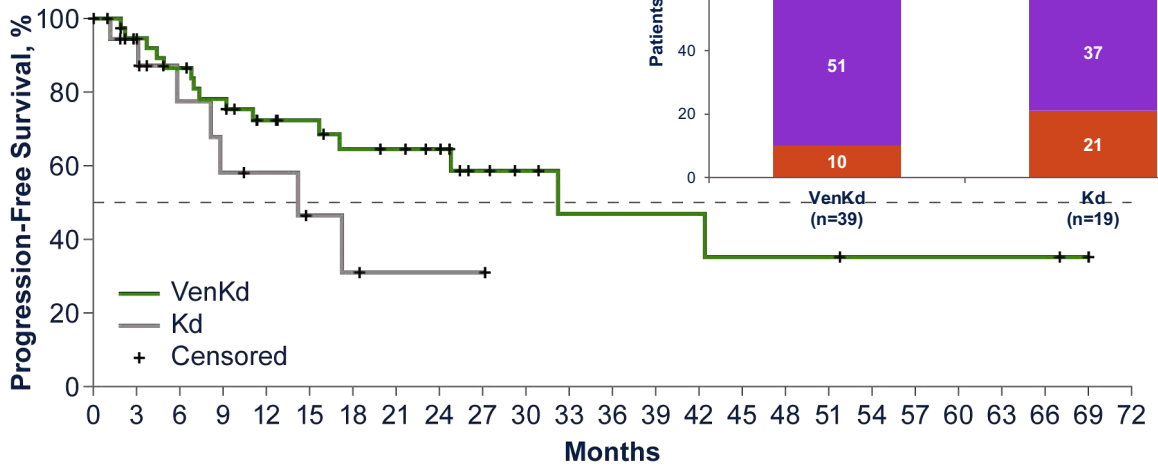
International Myeloma Society Annual Meeting, September 27-30, 2023, Athens, Greece

abbvie

Addition of venetoclax to Kd resulted in longer median PFS vs Kd alone, and median OS has not yet been reached in any group

Investigator-Assessed PFS in All Patients

PFS	VenKd	Kd
Median, months	32.2	14.2
HR (95% CI)	0.490 (0.193–1.243)	

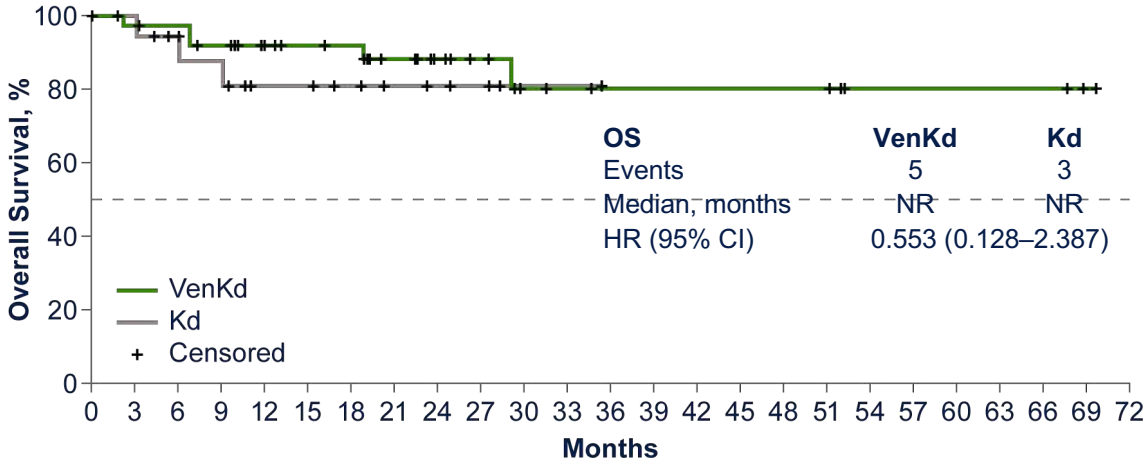


Patients at Risk

39	35	32	28	22	19	16	15	13	8	6	4	4	4	4	3	3	3	2	2	2	2	2	1	0
19	14	8	6	5	3	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

OS in All Patients

OS	VenKd	Kd
Events	5	3
Median, months	NR	NR
HR (95% CI)	0.553 (0.128–2.387)	



Patients at Risk

39	37	36	33	28	26	25	20	15	12	8	7	6	6	6	6	6	6	3	3	3	3	3	1	0
19	18	15	13	9	9	7	5	4	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0

	VenKd (n=39)	Kd (n=19)
Median follow-up, months (range)	22.6 (1.8–69.7)	16.8 (0.0–35.4)
Median DOR, months (95% CI)	41.5 (23.9–NE)	16.3 (6.5–NE)
Median TTR, months (95% CI)	1.0 (1.0–1.1)	1.3 (1.0–4.2)
Median TTP, months (95% CI)	32.2 (17.1–NE)	17.2 (5.8–NE)

DOR, duration of response; HR, hazard ratio; Kd, carfilzomib + dexamethasone; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; TTP, time to progression; TTR, time to response; VenKd, venetoclax + carfilzomib + dexamethasone.

Patients and Families

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