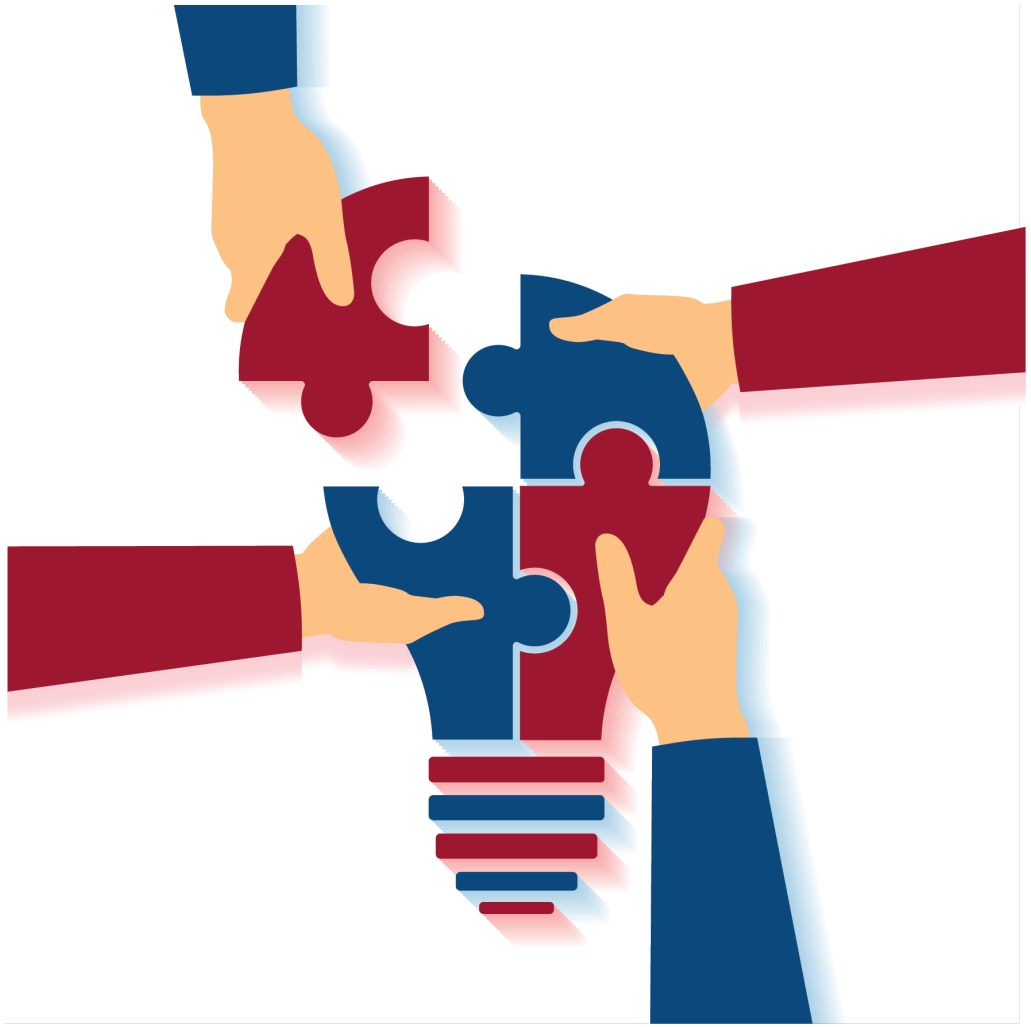

‘Four’ Every Patient: Maximizing Outcomes in Newly Diagnosed Multiple Myeloma Care With Anti-CD38 Monoclonal Antibody–Based Quadruplet Therapies

Faculty Speakers

Caitlin Costello, MD
Clinical Professor of Medicine
Director, Multiple Myeloma Program
University of California, San Diego
La Jolla, California

Paul G. Richardson, MD
RJ Corman Professor of Medicine, Harvard Medical School
Director of Clinical Research, Clinical Program Leader
Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute
Boston, Massachusetts

Faculty Disclosures

Caitlin Costello, MD, has relevant financial relationship(s) with ineligible companies in the form of:

Grant/Research Support from AstraZeneca; Bristol Myers Squibb; Janssen; Kite Pharmaceuticals; Pfizer; and Takeda.

Honoraria from AstraZeneca; Bristol Myers Squibb; Genentech; Janssen; Karyopharm; Kite Pharmaceuticals; Pfizer; and Takeda.

Paul G. Richardson, MD, has relevant financial relationship(s) with ineligible companies in the form of:

Consultant and/or Advisor for Celgene/Bristol Myers Squibb; GSK; Karyopharm; Oncopeptides AB; Regeneron Pharmaceuticals; and Sanofi.

Grant/Research Support from Karyopharm and Oncopeptides AB.

All relevant financial relationships have been mitigated prior to the commencement of the activity.

Educational Objectives

Upon completion of this activity, participants should be better able to:

- Identify the rationale for anti-CD38 monoclonal antibody–based quadruplet regimens in the treatment of patients with newly diagnosed multiple myeloma (NDMM)
- Evaluate the clinical implications of evidence on anti-CD38 monoclonal antibody–containing quadruplet therapies in patients with NDMM
- Review strategies to optimize anti-CD38 monoclonal antibody–containing quadruplet therapies, including in the community setting

About This Activity

- This activity is supported by an educational grant from Sanofi.
- Answers in CME is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians

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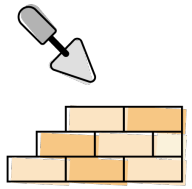
- Complete the evaluation form to let us know what educational topics you would find most useful in the future

‘Four’ Every Patient: Maximizing Outcomes in NDMM Care With Anti-CD38 Monoclonal Antibody–Based Quadruplet Therapies



Laying the Groundwork: How Quadruplet Regimens Fit Into NDMM Care

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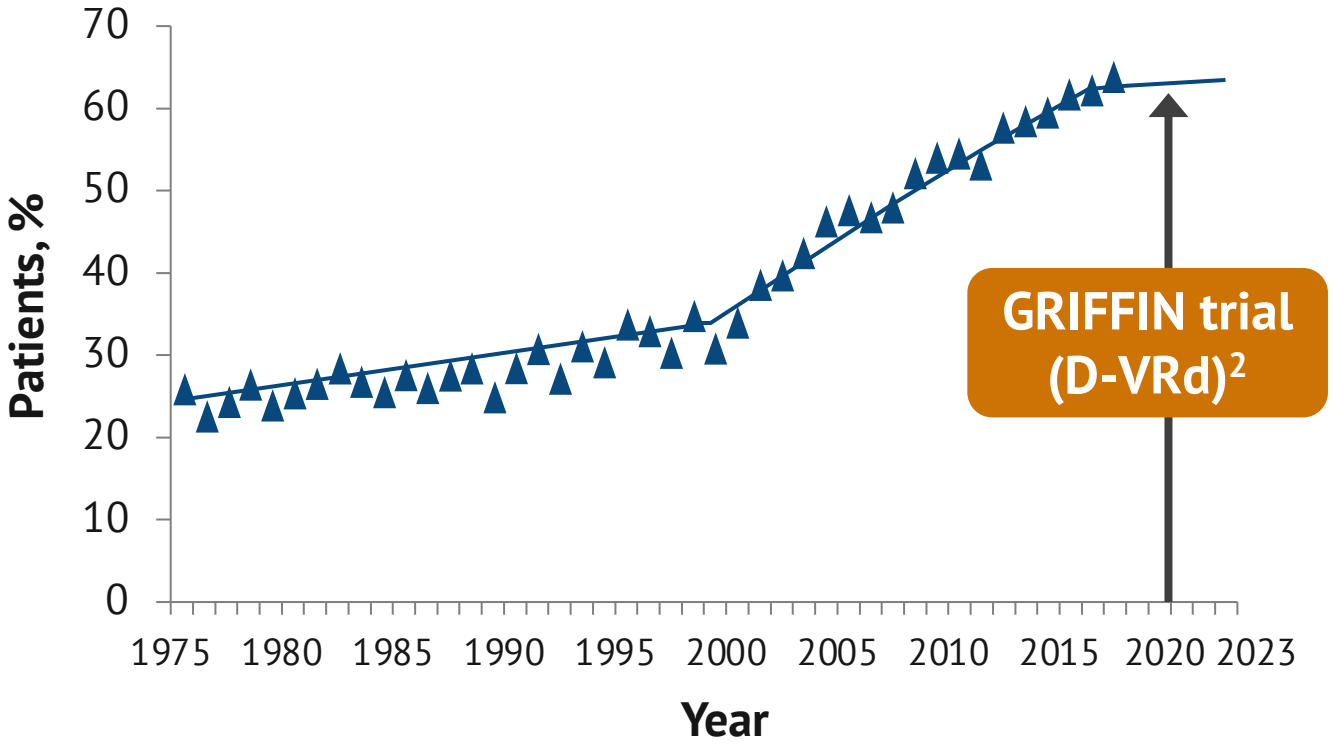
Safety by the Numbers: Managing Adverse Effects in Quadruplet Regimens

Individualized Care: Personalizing Quadruplet Therapies in NDMM

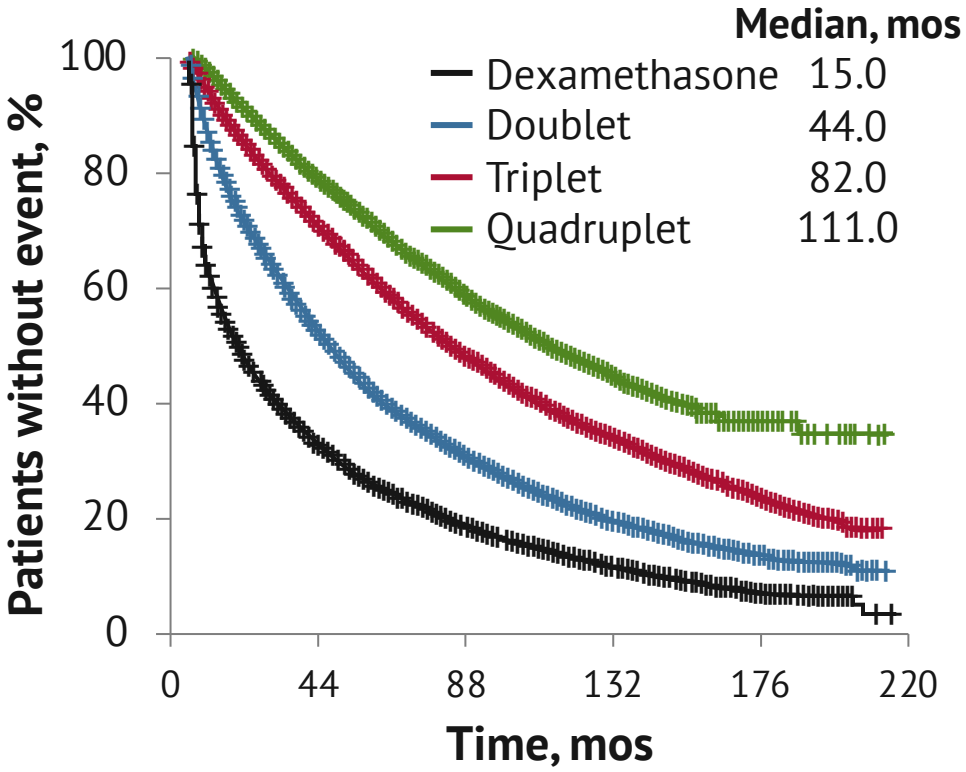
Strategies “Four” Success: Optimizing Outcomes With Quadruplet Therapies

The Treatment Landscape for Multiple Myeloma: Where We've Been

SEER 5-year survival rates, 1975 to 2017[1]



MM survival by therapy[3]



Abbreviation(s): d: dexamethasone; D: daratumumab; MM: multiple myeloma; R: lenalidomide; SEER: surveillance, epidemiology, and end results; V: bortezomib.

Reference(s): 1. National Cancer Institute: SEER Program. Accessed November 25, 2025. https://seer.cancer.gov/statfacts/html/mulmy.html; 2. Voorhees PM et al. *Blood*. 2020;136:936-945; 3. Saba L et al. *Clin Lymphoma Myeloma Leuk*. 2025;25:e1-e10. doi:10.1016/j.clml.2024.10.006.

Goals of Initial Therapy in Patients With NDMM[1-4]

- Control symptoms
- Obtain deep and durable responses
- Minimize toxicity

High attrition rates in subsequent lines of therapy underscore the need for the most effective treatment regimens upfront

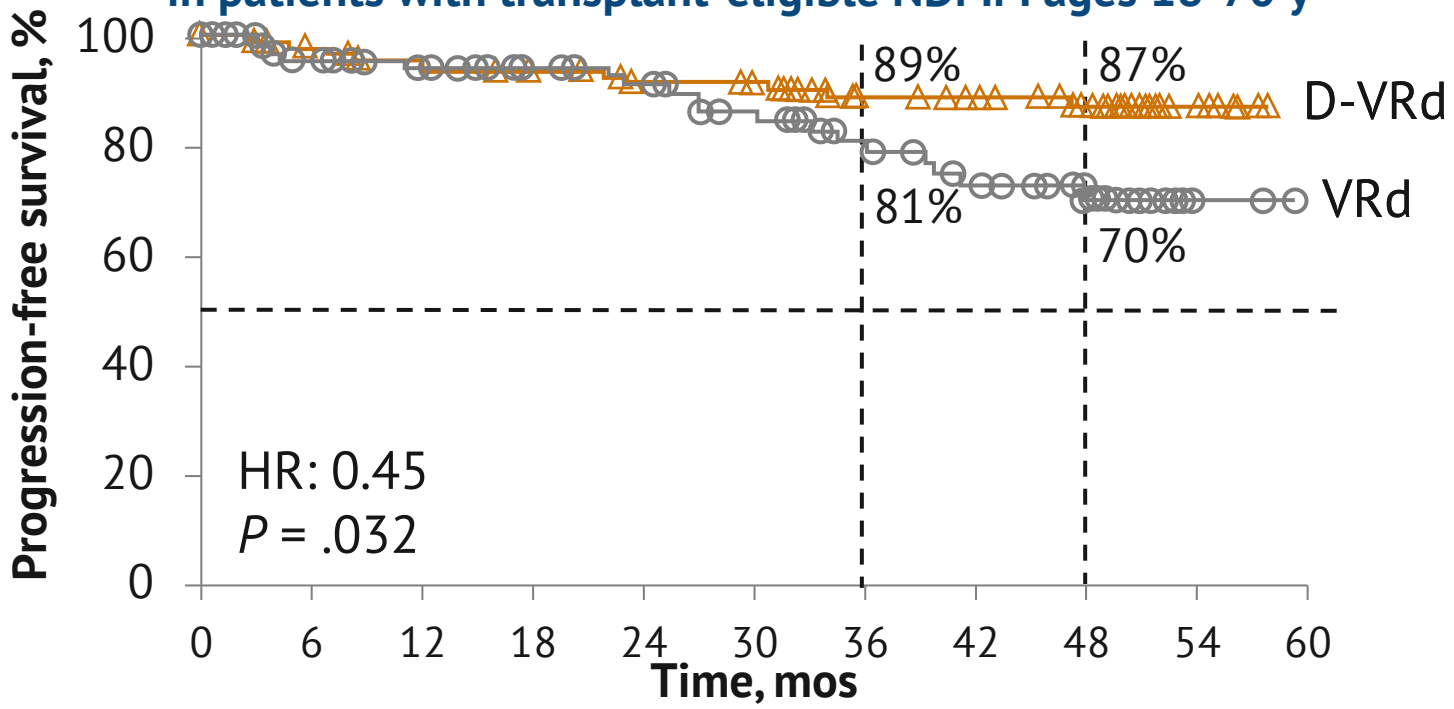
Early treatments have the greatest impact in myeloma care

Abbreviation(s): NDMM: newly diagnosed MM.

Reference(s): 1. Kumar SK. *Hematology Am Soc Hematol Educ Program.* 2024;1:551-560; 2. Fonseca R et al. *BMC Cancer.* 2020;20:1087. doi:10.1186/s12885-020-07503-y; 3. Facon T et al. *N Engl J Med.* 2024;391:1597-1609; 4. Bonello F et al. *Front Oncol.* 2022;12:830922. doi:10.3389/fonc.2022.830922

Why "Four Is Better Than Three" in Patients With NDMM: Rationale for Quadruplet Therapies[1-5]

GRIFFIN: Randomized, active-controlled, phase 2 trial in patients with transplant-eligible NDMM ages 18-70 y[1,a]



Adding upfront anti-CD38 mAB to triplet regimen adds another MoA

Enables deeper responses and longer disease control in patients with NDMM

[a] Patients were randomized to D-VRd or VRd induction, autologous HSCT, D-VRd or VRd consolidation, and lenalidomide ± daratumumab maintenance for 2 y.

Abbreviation(s): HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; mAB: monoclonal antibody; MoA: mechanism of action.

Reference(s): 1. Voorhees PM et al. *Lancet Haematol.* 2023;10:e825-e837. doi:10.1016/S2352-3026(23)00217-X; 2. Facon T et al. *N Engl J Med.* 2024;391:1597-1609; 3. Ebraheem MS et al. *Blood Adv.* 2024;8:5993-6002; 4. Sonneveld P et al. *N Engl J Med.* 2024;390:301-313; 5. Ocio EM et al. *Leukemia.* 2023;37:1521-1529.

Key Factors That Guide Initial Therapy in NDMM

Patient factors

- Age
- PS/frailty
- Goals/expectations
- Caregiver status
- Financial impact

Disease factors

- Symptoms
- Risk category
- Prior therapy
- Aggressiveness of presentation

Treatment factors

- Exposure/refractoriness to anti-myeloma regimens
- Residual symptom burden
- Expected efficacy/toxicity
- Logistics

Abbreviation(s): PS: performance status.

Reference(s): Cerchione C et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e390202. doi:10.1200/EDBK_390202

Prognostic Risk Stratification in MM[1-3]

Disease-related factors may be used to risk-stratify patients

Recommended tools include:

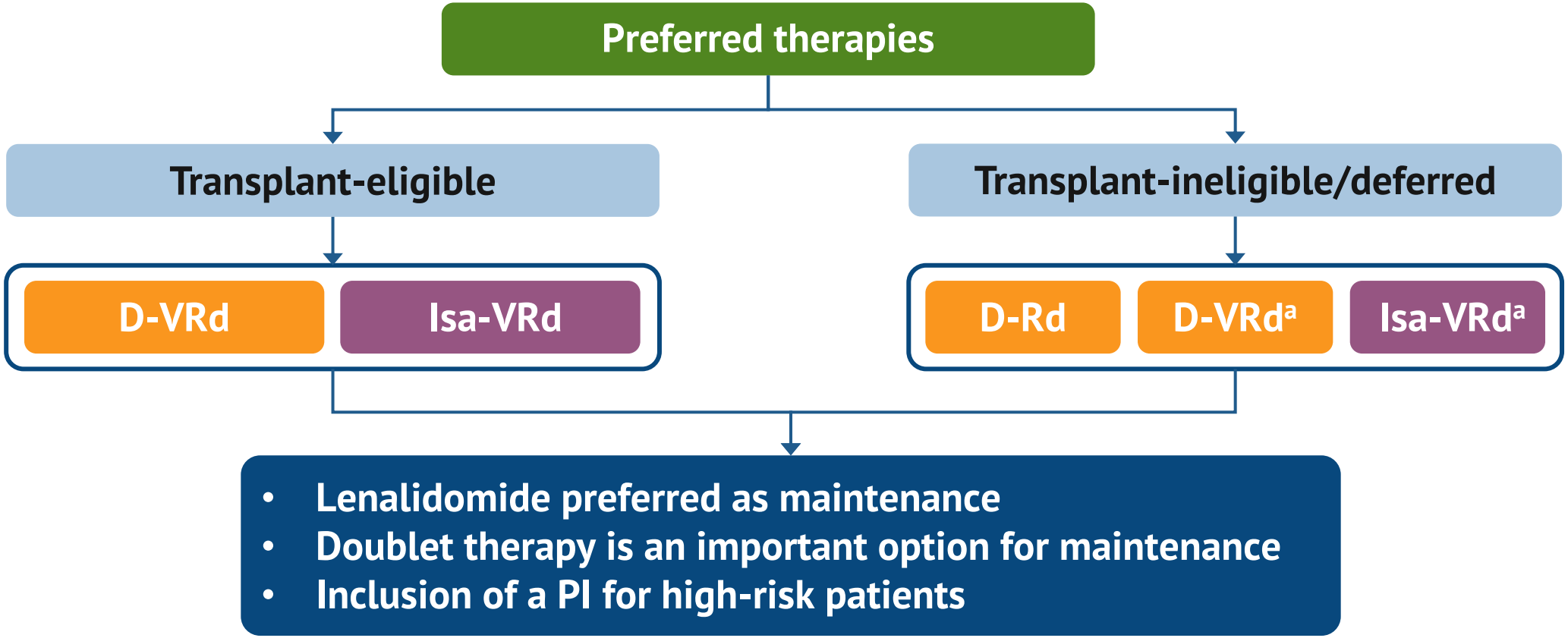
- ISS
- R-ISS
- IMS-IMWG CGS

Prognostic risk stratification is important for tailoring treatment

Abbreviation(s): CGS: Consensus Genomic Staging; IMS-IMWG: International Myeloma Society–International Myeloma Working Group; ISS: international staging system; R-ISS: revised ISS.

Reference(s): 1. National Comprehensive Cancer Network (NCCN). Multiple Myeloma (Version 1.2025). Accessed November 11, 2024. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf; 2. International Myeloma Foundation. Accessed November 11, 2024. https://www.myeloma.org/imwg/imwg-consensus-risk-stratification-multiple-myeloma; 3. Rajkumar SV. *Am J Hematol.* 2022;97:1086-1107.

Guideline-Recommended Therapies in NDMM: Induction Therapy



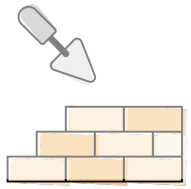
[a] Non-frail patients <80 y of age.

Abbreviation(s): Isa: isatuximab; PI: protease inhibitor.

Reference(s): NCCN. Multiple Myeloma (Version 3.2026). Accessed November 25, 2025. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

How may academic and community clinics collaborate to enhance access and uptake of these therapies?

‘Four’ Every Patient: Maximizing Outcomes in NDMM Care With Anti-CD38 Monoclonal Antibody–Based Quadruplet Therapies



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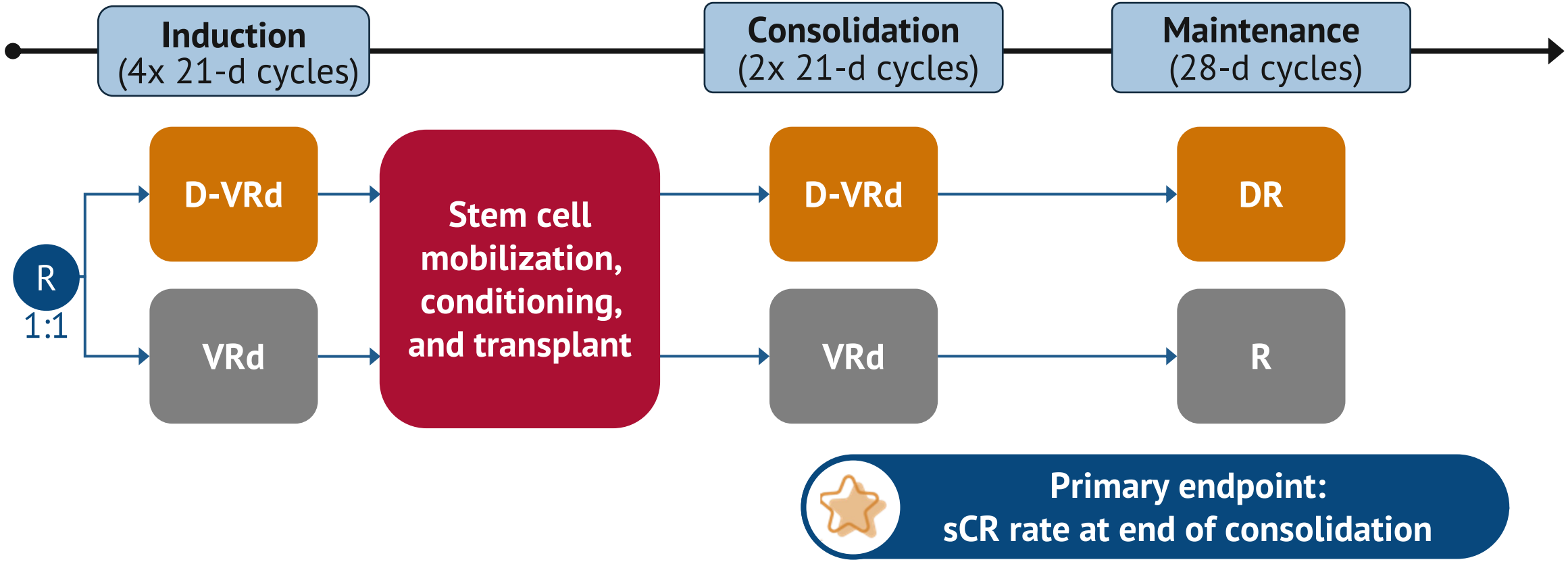
Quadruplet Regimens in Transplant-Eligible Patients With NDMM

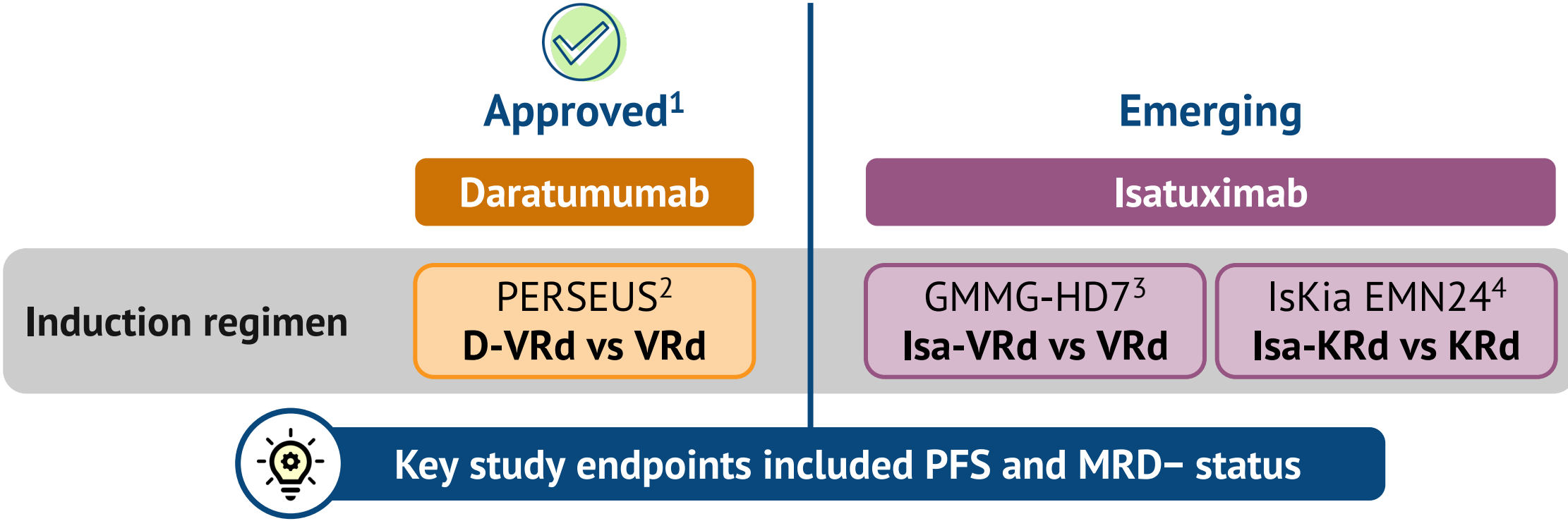
Quadruplet Regimens in Transplant-Eligible Patients With NDMM: GRIFFIN Phase 2 Study Design



Abbreviation(s): sCR: stringent complete response.

Reference(s): Voorhees PM et al. *Blood*. 2020;136:936-945.

Quadruplet Regimens in Key Phase 3 Trials in Transplant-Eligible Patients With NDMM

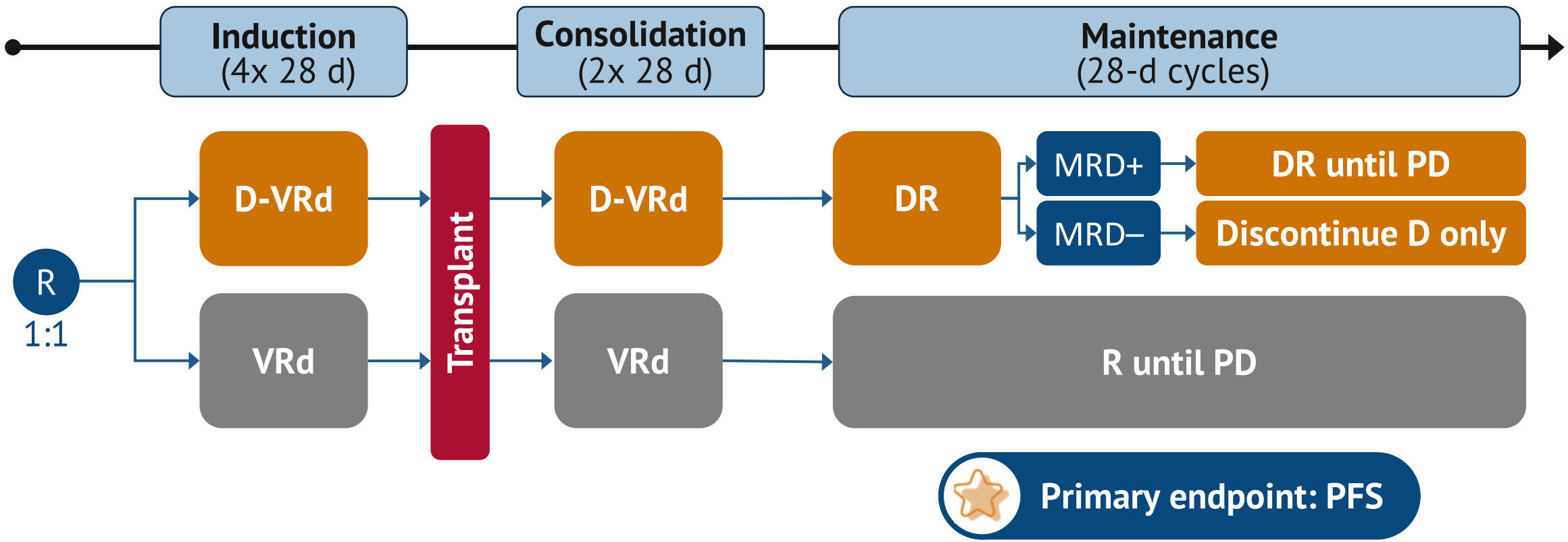


Abbreviation(s): K: carfilzomib; MRD: minimal residual disease; PFS: progression-free survival.

Reference(s): 1. US Food and Drug Administration (FDA). Accessed November 25, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-daratumumab-and-hyaluronidase-fihj-bortezomib-lenalidomide-and-dexamethasone-multiple; 2. Sonneveld P et al. *N Engl J Med.* 2024;390:301-313; 3. Goldschmidt H et al. *Blood.* 2024;144(suppl 1):769. doi:10.1182/blood-2024-193308; 4. Gay F et al. American Society of Hematology 2023 Annual Meeting (ASH 2023). Plenary Scientific Session 4. Accessed November 25, 2025. https://ash.confex.com/ash/2023/webprogram/Paper177546.html

PERSEUS Trial: Study Design

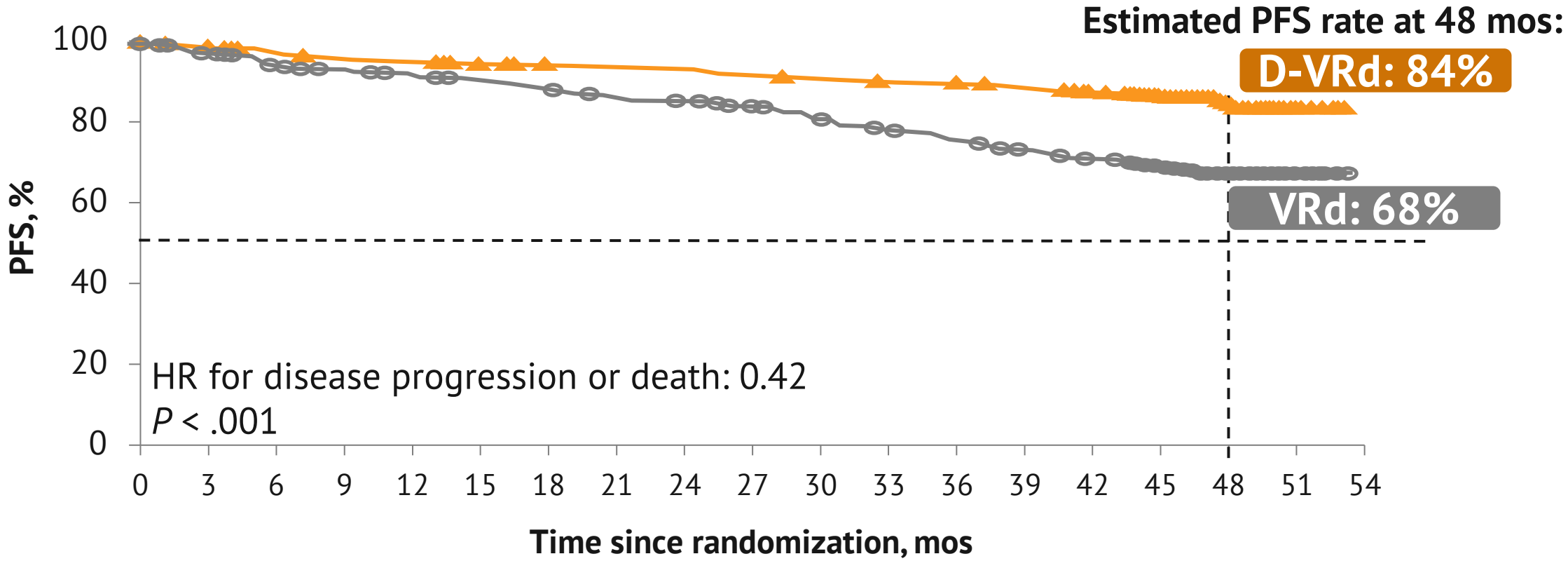
Key eligibility: NDMM, eligible for transplant, age 18-70 y, ECOG PS ⩽2 (N = 709)



Abbreviation(s): ECOG: Eastern Cooperative Oncology Group; PD: progressive disease.
Reference(s): Sonneveld P et al. ASH 2023. Abstract LBA-1.

Efficacy of Quadruplet Regimen in Transplant-Eligible NDMM: PERSEUS Trial

Primary endpoint: PFS (N = 709; mFU: 47.5 mos)



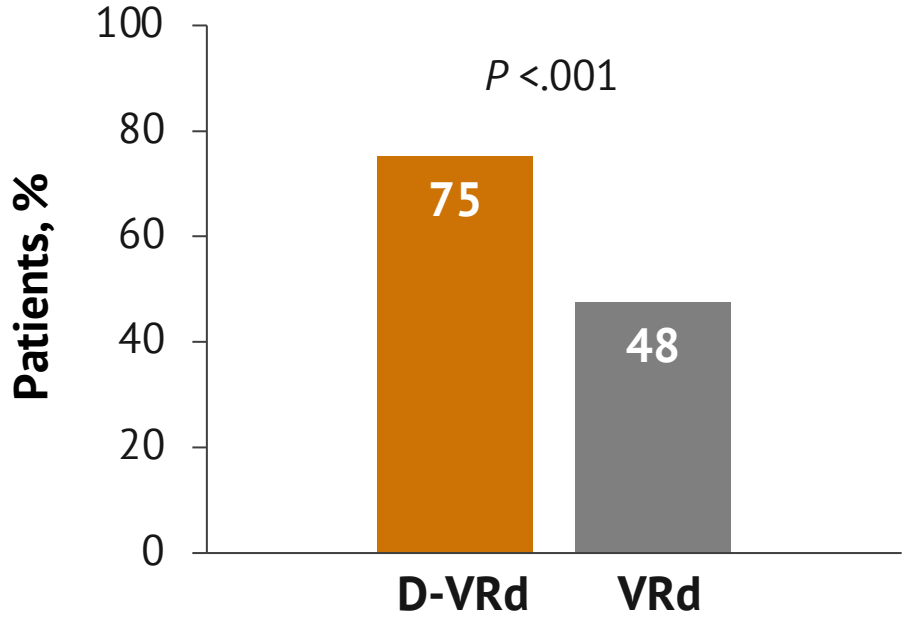
Abbreviation(s): mFU: median follow-up.

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

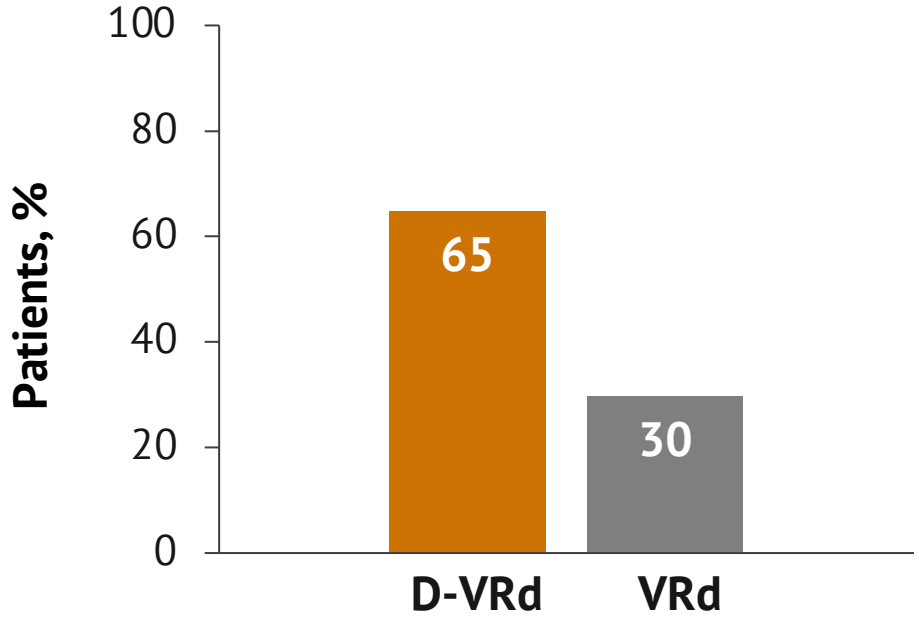
Efficacy of Quadruplet Regimen in Transplant-Eligible NDMM: PERSEUS Trial

Key secondary endpoint: MRD– status (N = 709; mFU: 47.5 mos)

Overall MRD– (10^{-5})



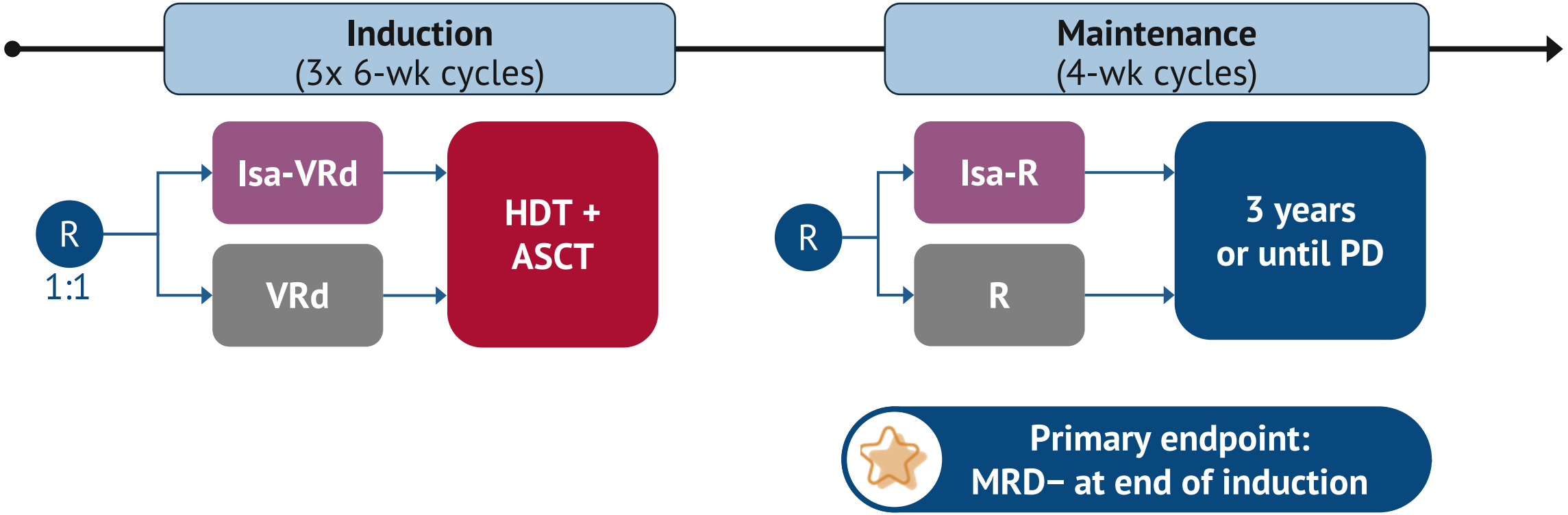
Sustained MRD– (10^{-5}), ≥12 mos



Reference(s): 1. Sonneveld P et al. *N Engl J Med*. 2024;390:301-313; 2. Rodríguez-Otero P. 2024 American Society of Clinical Oncology Annual Meeting (ASCO 2025). Abstract 7502.

GMMG-HD7 Trial: Study Design

Key eligibility: NDMM, eligible for transplant, age 18-70 (N = 662)[1,2]

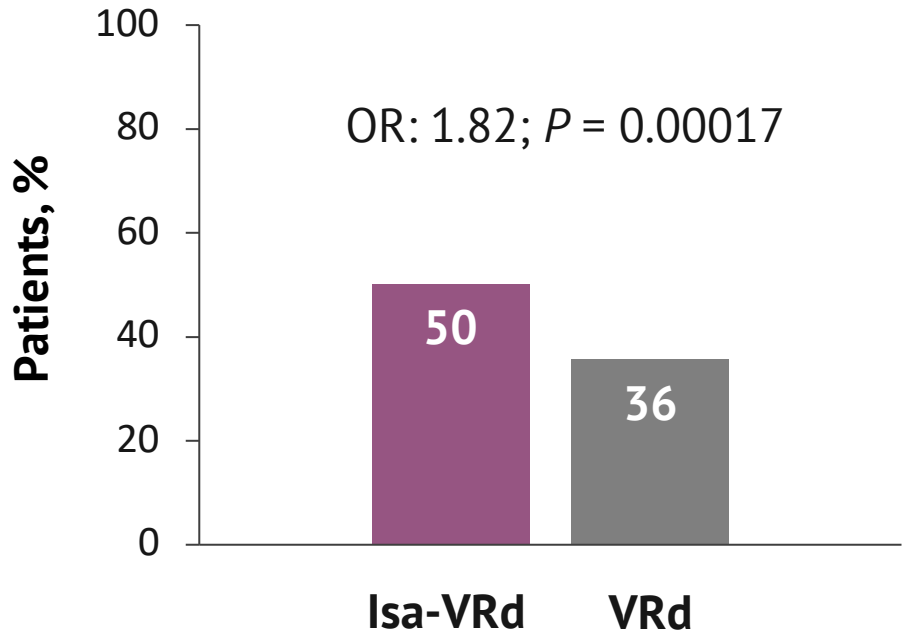


Abbreviation(s): ASCT: autologous stem cell transplant; HDT: high-dose therapy.

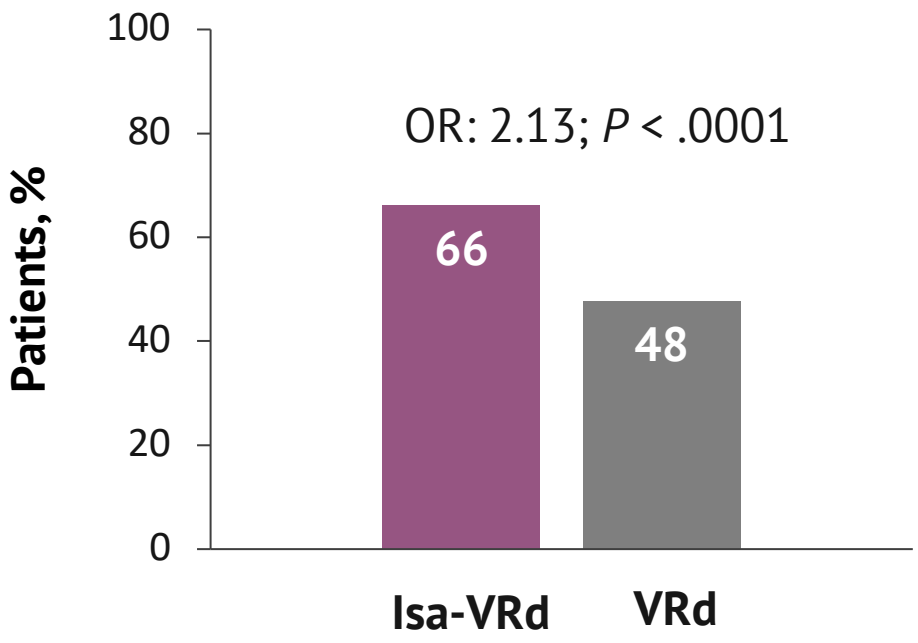
Reference(s): 1. Mai EK et al. ASH 2024. Abstract 364; 2. Goldschmidt H et al. ASH 2024. Abstract 769.

Efficacy of Quadruplet Regimen in Transplant-Eligible NDMM: GMMG-HD7 Trial[1-3]

Primary endpoint: Post-induction MRD– (mFU: 4 mos [125 d]; part 1)



Post-transplant MRD– (mFU: 47 mos)

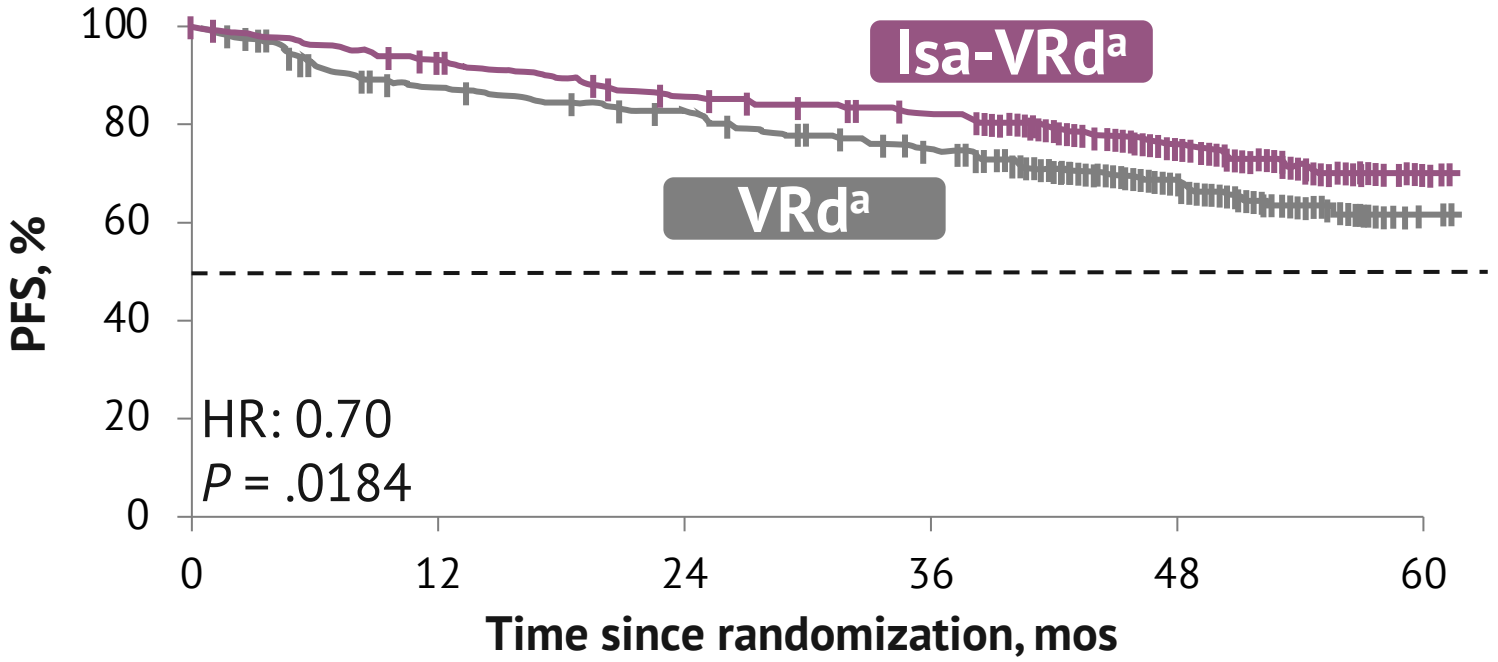


Abbreviation(s): OR: odds ratio.

Reference(s): 1. Mai EK et al. *J Clin Oncol*. 2025;43:1279-1288; 2. Goldschmidt H et al. *Blood*. 2024;144(suppl 1):769. doi:10.1182/blood-2024-193308; 3. Goldschmidt H et al. *Lancet Haematol*. 2022;9:e810-e821. doi:10.1016/S2352-3026(22)00263-0

Efficacy of Quadruplet Regimen in Transplant-Eligible NDMM: GMMG-HD7 Trial

Secondary endpoint of part 1: PFS from first randomization (mFU: 48 mos)[1-3]



↓30%

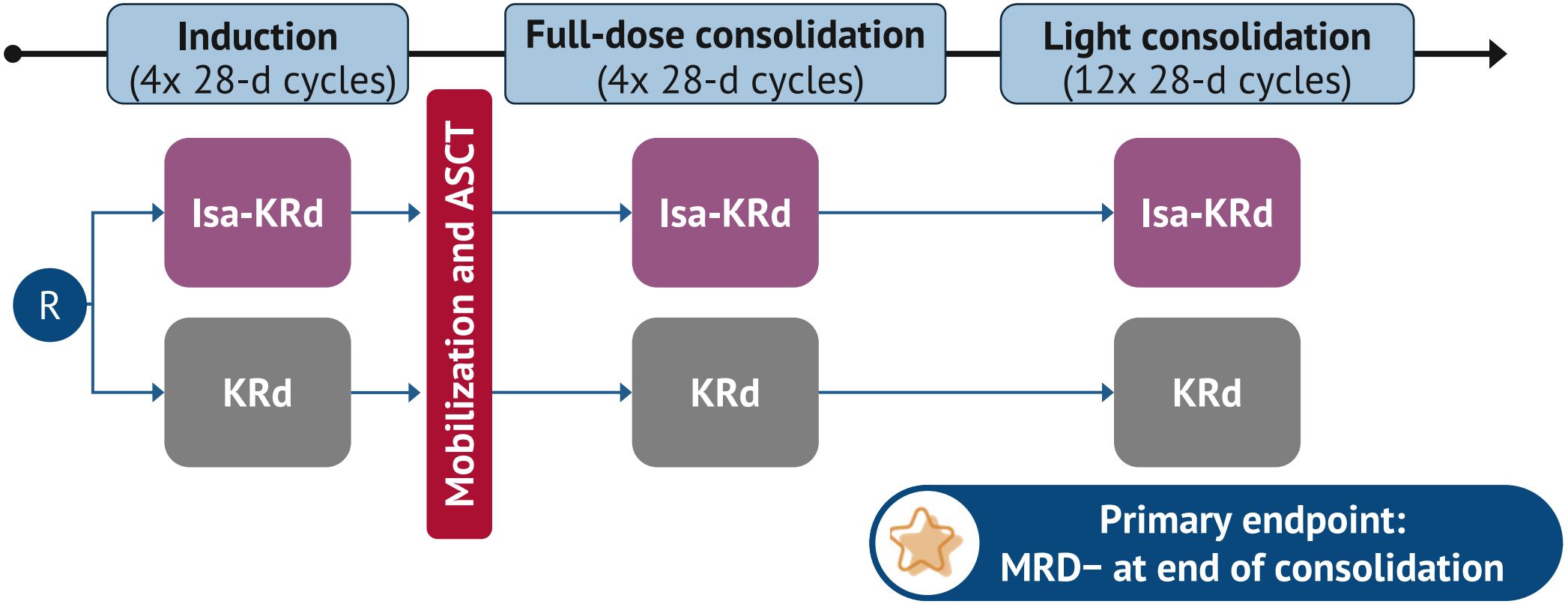
Risk of progression or death vs VRd with 18 wks of induction with Isa-VRd

[a] Treatment arm → ASCT → R or Isa-R.

Reference(s): 1. Mai EK et al. *J Clin Oncol*. 2025:43:1279-1288; 2. Goldschmidt H et al. *Blood*. 2024;144(suppl 1):769. doi:10.1182/blood-2024-193308; 3. Goldschmidt H et al. *Lancet Haematol*. 2022;9:e810-e821. doi:10.1016/S2352-3026(22)00263-0

IsKiA Trial: Study Design

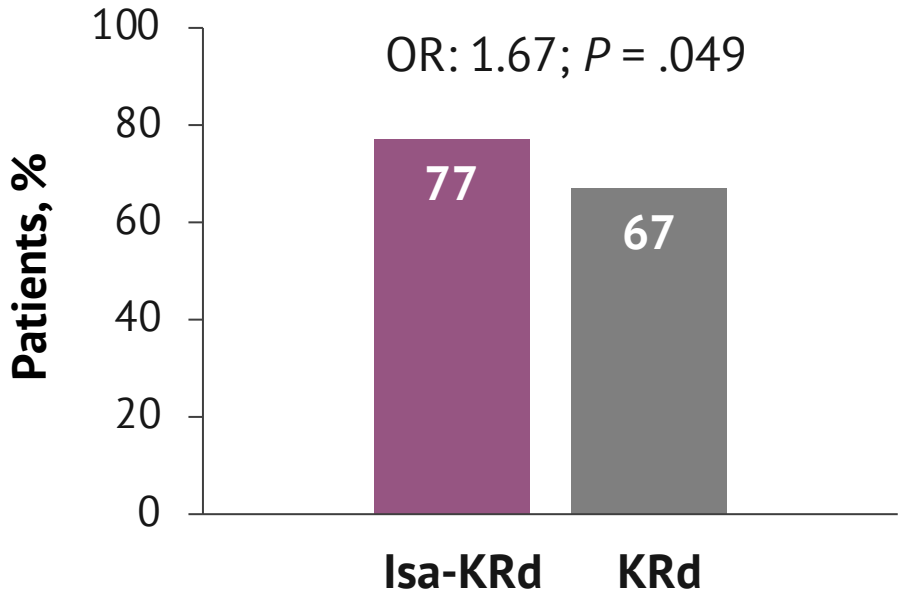
Key eligibility: NDMM, eligible for transplant, age <70 y (N = 302)



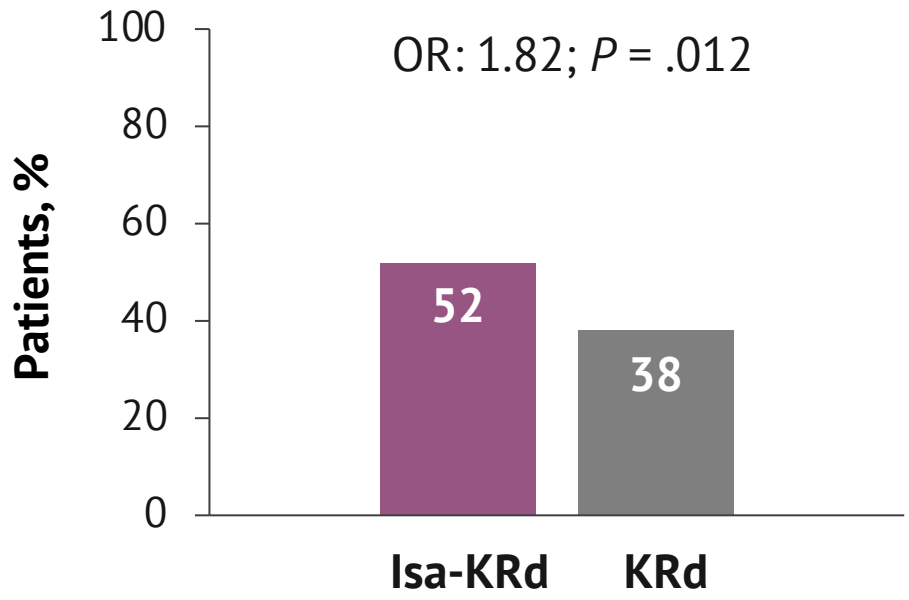
Reference(s): Gay F et al. ASH 2023. Plenary Scientific Session 4. Accessed November 25, 2025. https://ash.confex.com/ash/2023/webprogram/Paper177546.html

Efficacy of Quadruplet Regimen in Transplant-Eligible NDMM: IsKiA Trial

Primary endpoint: Post-consolidation MRD– (10^{-5}; mFU: 20 mos)[1]



Post-light consolidation MRD– (1-yr sustained MRD–, 10^{-6}; mFU: 35 mos)[2]

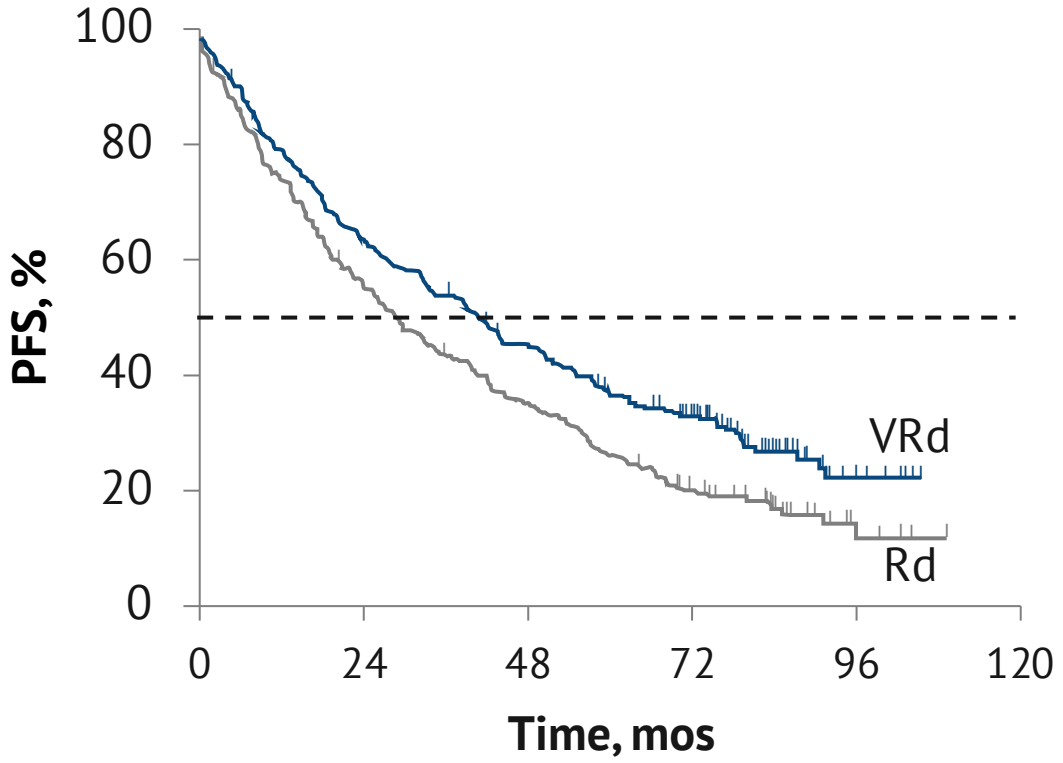


Reference(s): 1. Gay F et al. ASH 2023. Plenary Scientific Session 4. Accessed November 25, 2025. https://ash.confex.com/ash/2023/webprogram/paper177546.html; 2. Gay F et al. *J Clin Oncol*. 2025;46(suppl 16):7502.

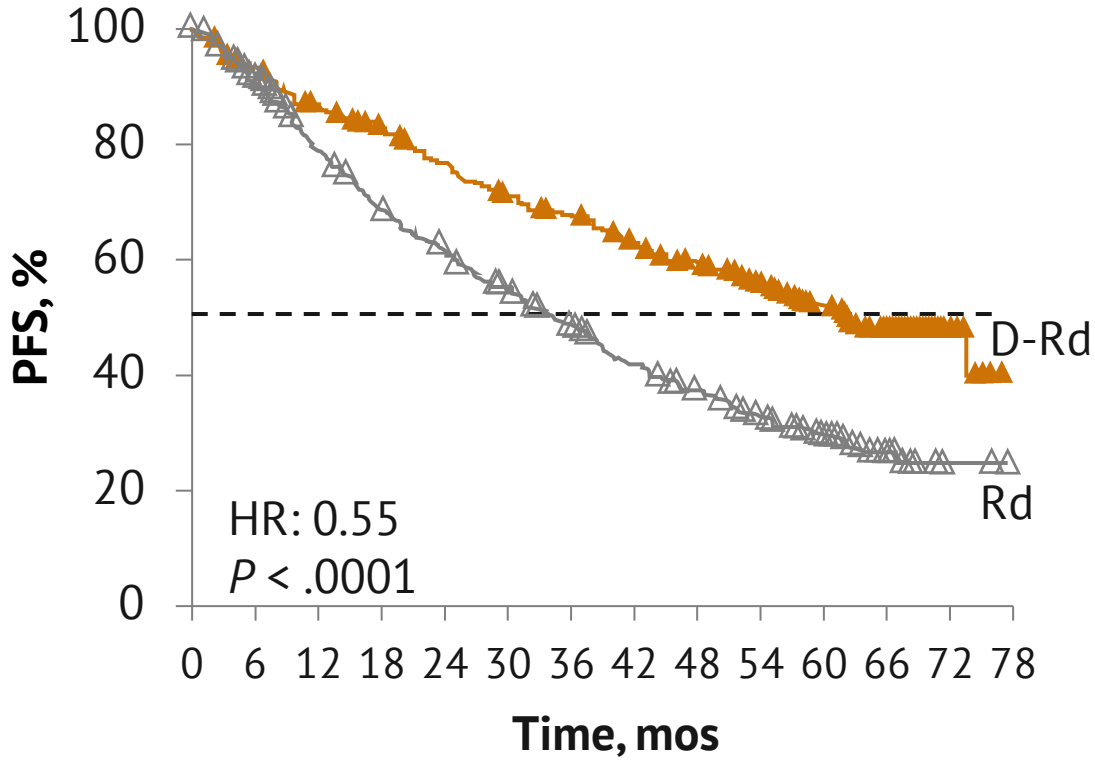
Quadruplet Regimens in Transplant-Ineligible Patients With NDMM

Triplet Regimens in Transplant-Ineligible or -Deferred Patients With NDMM: SWOG S0777 and MAIA Trials

SWOG S0777: VRd vs Rd (N = 460; mFU: 84 mos)



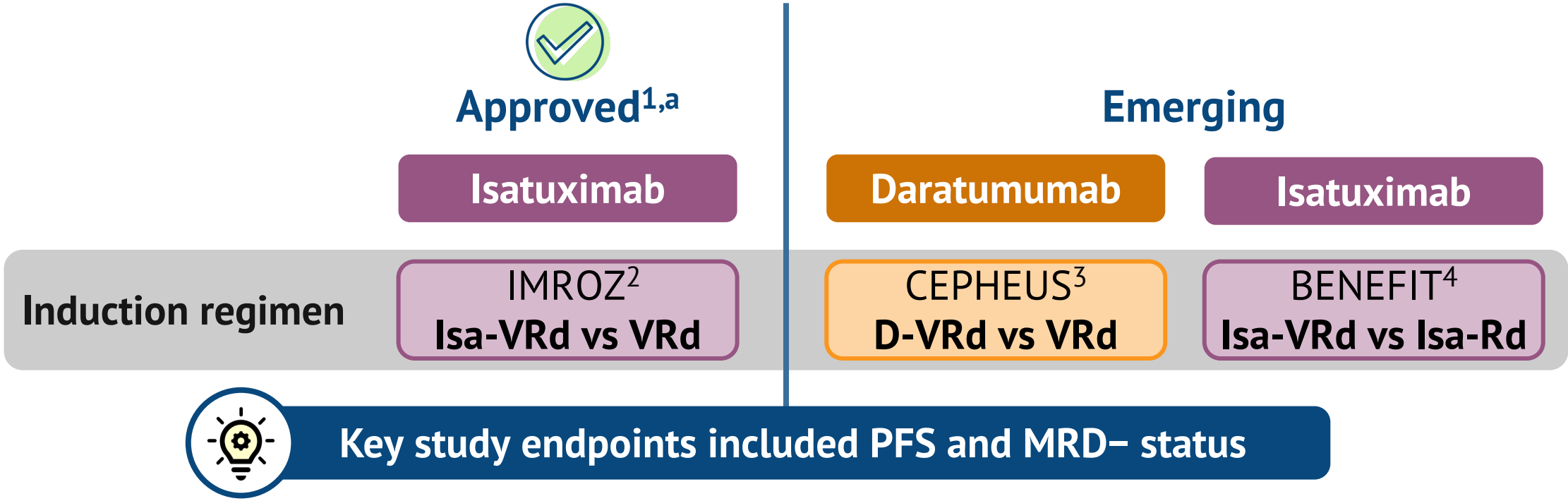
MAIA: D-Rd vs Rd (N = 737; mFU: 64.5 mos)



Data are from unrelated trials and should not be directly compared.

Reference(s): 1. Durie BGM et al. *Blood Cancer J.* 2020;10:53. doi:10.1038/s41408-020-0311-8; 2. Facon T et al. *Leukemia.* 2025;39:942-950.

Quadruplet Regimens in Key Phase 3 Trials in Transplant-Ineligible or -Deferred Patients With NDMM

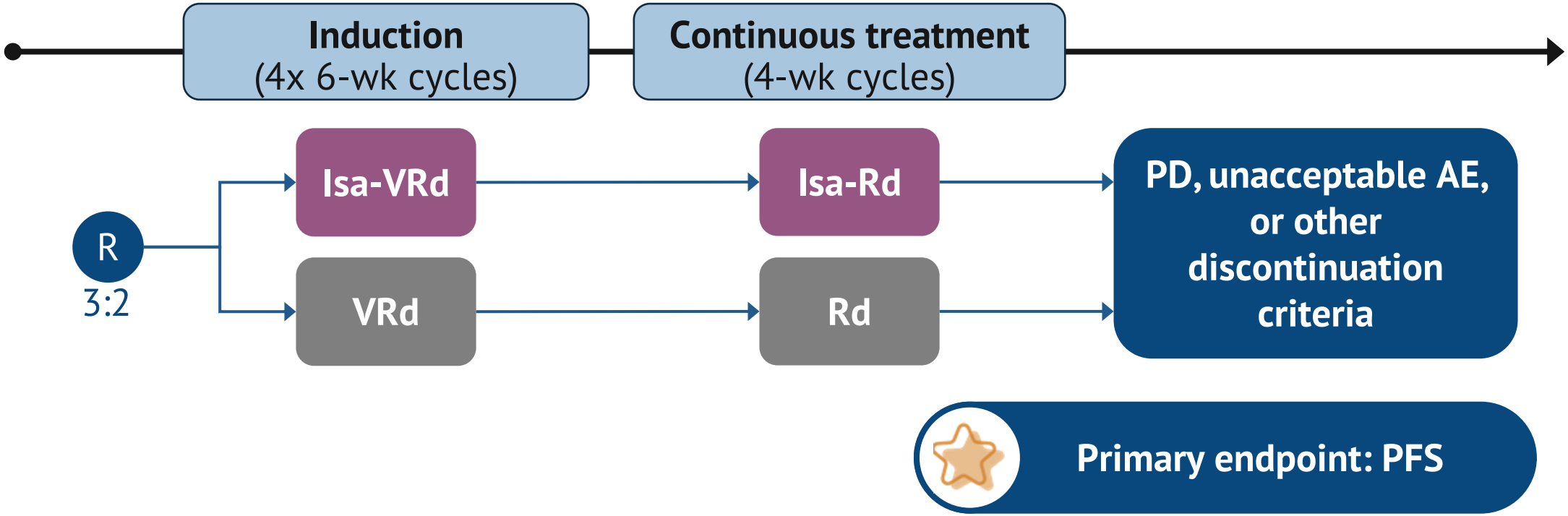


[a] Approved for adult patients with NDMM who are not eligible for ASCT.

Reference(s): 1. FDA. Accessed November 25, 2025, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-isatuximab-irfc-bortezomib-lenalidomide-and-dexamethasone-newly-diagnosed-multiple; 2. Facon T et al. *N Engl J Med*. 2024;391:1597-1609; 3. Usmani SZ et al. *Nat Med*. 2025;31:1195-1202; 4. Leleu X et al. *Nat Med*. 2024;30:2235-2241.

IMROZ Trial: Study Design

Key eligibility: NDMM, ineligible for transplant, age ≤80 y (N = 446)

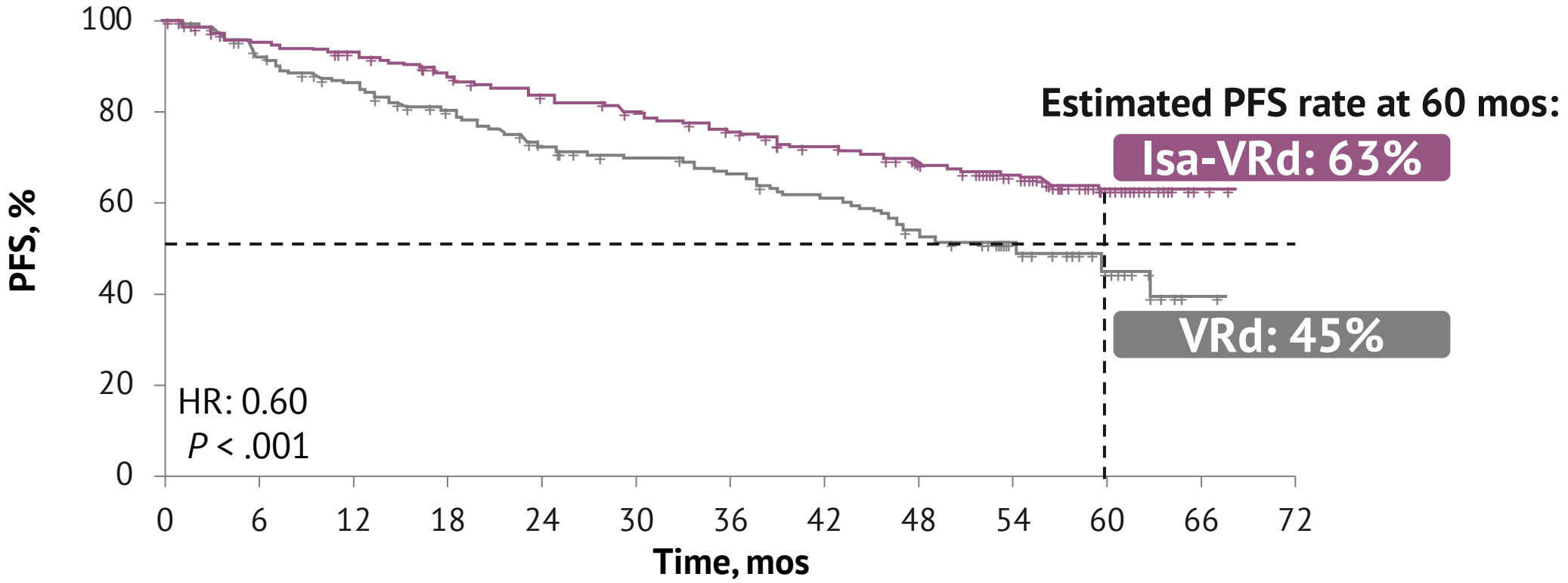


Abbreviation(s): AE: adverse event.

Reference(s): Facon T et al. ASCO 2024. Abstract 7500.

Efficacy of Quadruplet Regimen in Transplant-Ineligible NDMM: IMROZ Trial

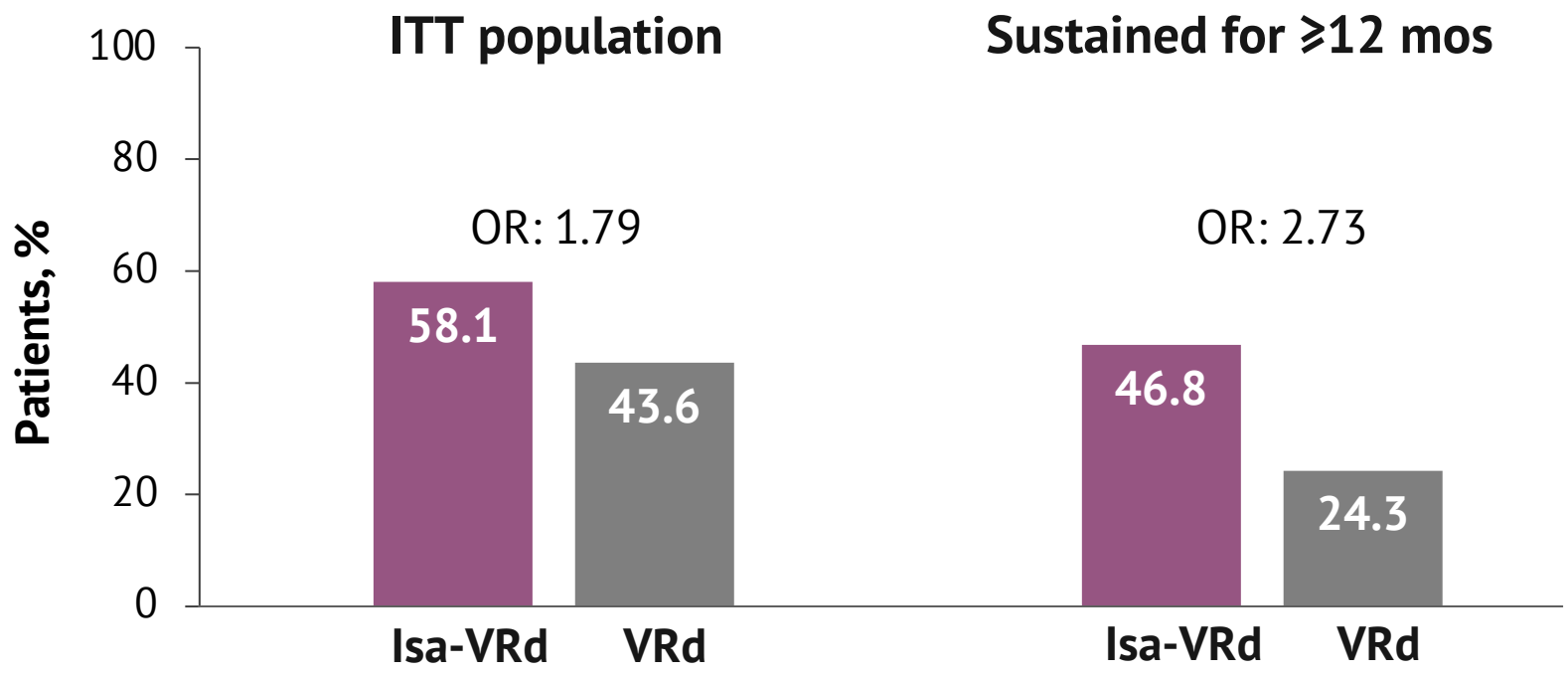
Primary endpoint: PFS (N = 446; mFU: 59.7 mos)



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

Efficacy of Quadruplet Regimen in Transplant-Ineligible NDMM: IMROZ Trial

Key secondary endpoint: MRD– (N = 446; mFU: 59.7 mos)

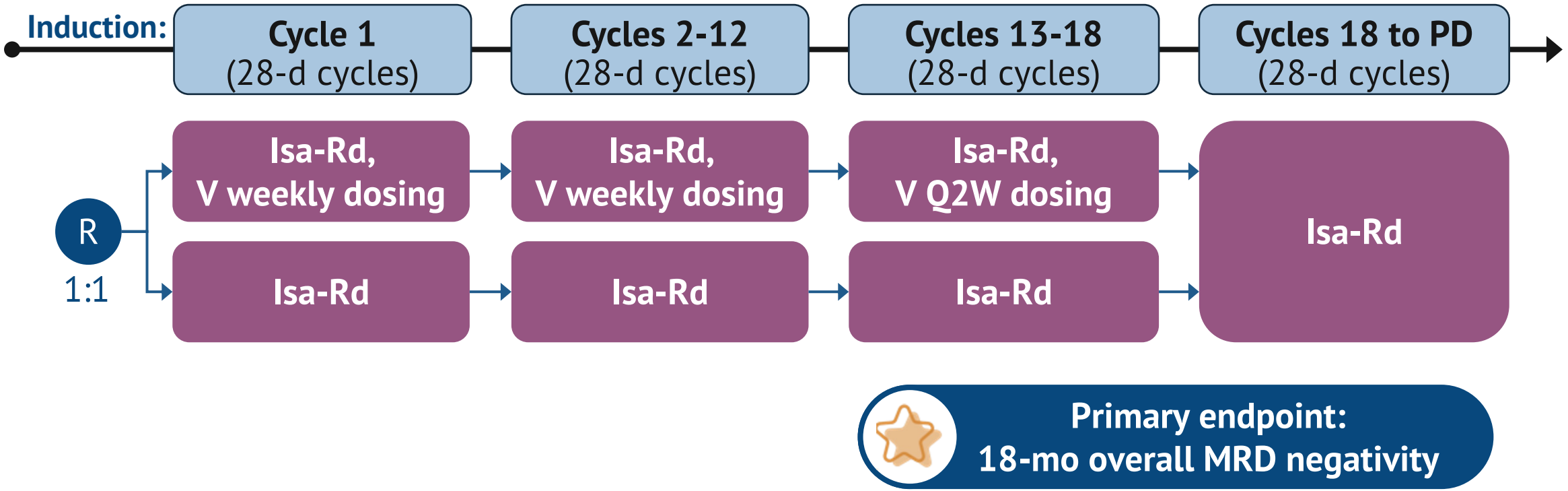


Abbreviation(s): ITT: intention-to-treat.

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

BENEFIT Trial: Study Design

Key eligibility: NDMM, ineligible for transplant, ECOG PS ⩽2, age 65-79 y (N = 270)[1,2]



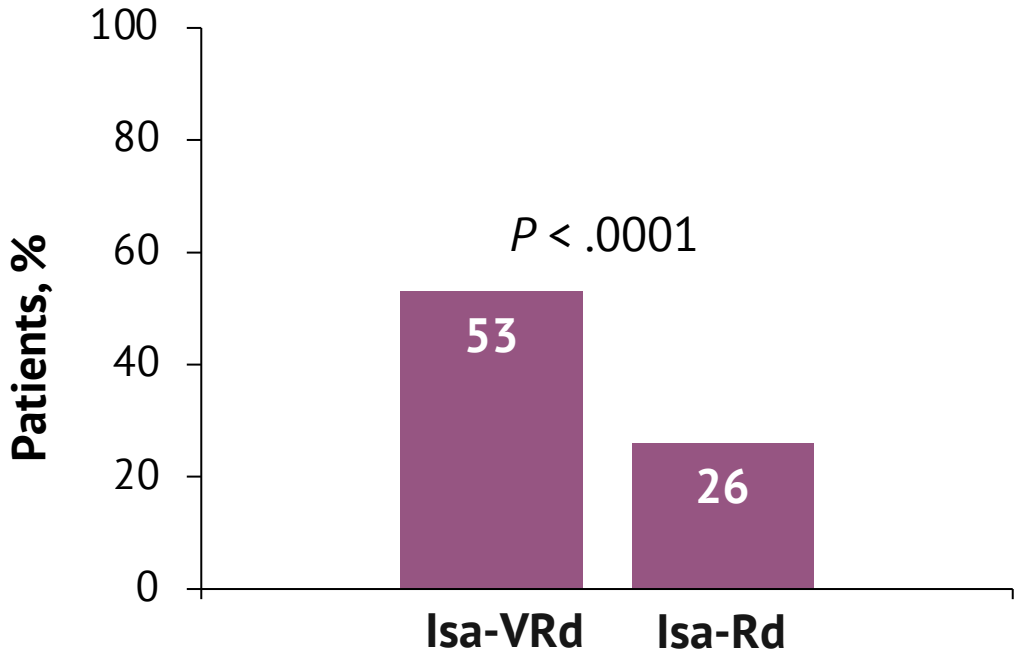
Abbreviation(s): Q2W: every 2 weeks.

Reference(s): 1. Leleu X et al. *Nat Med.* 2024;30:2235-2241; 2. ClinicalTrials.gov Identifier: NCT04751877. Accessed December 2, 2025. https://clinicaltrials.gov/study/NCT04751877

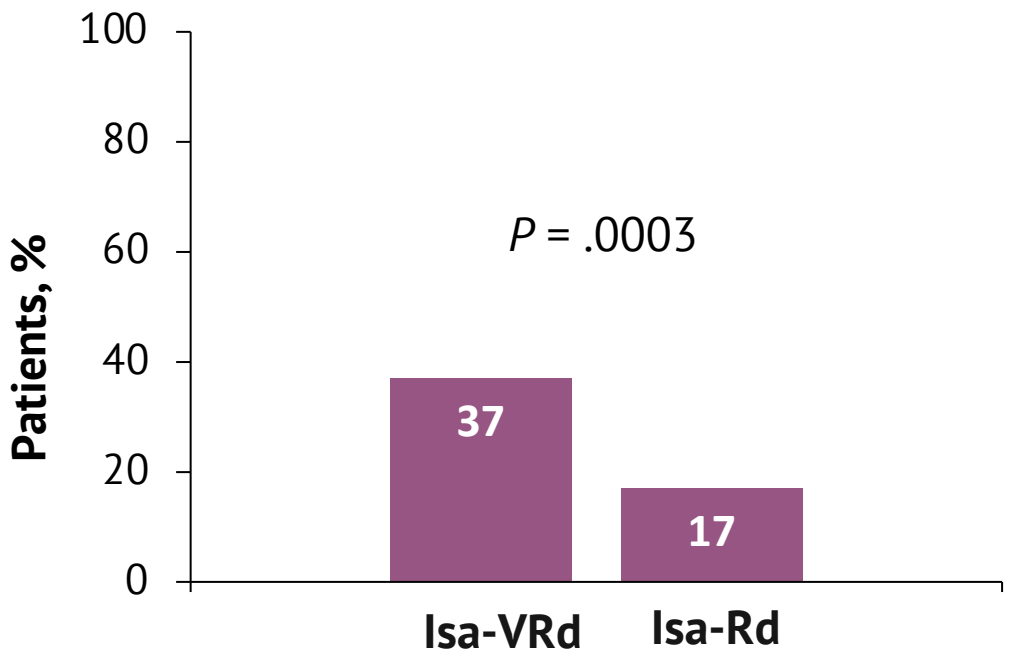
Efficacy of Quadruplet Regimen in Transplant-Ineligible NDMM: BENEFIT Trial

N = 270; mFU: 23.5 mos[a]

Primary endpoint: 18-mo overall MRD– (10^{-5})



18-mo rate of MRD– and CR (10^{-5})



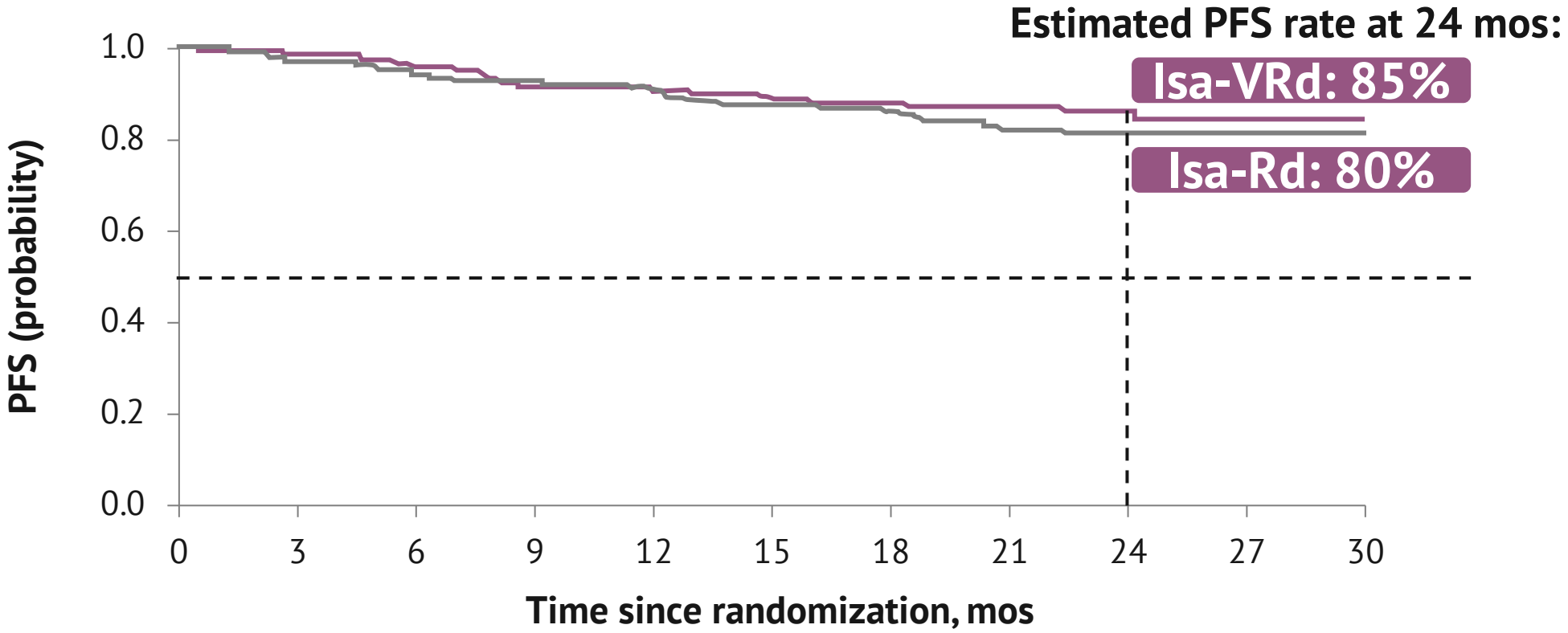
[a] At an mFU of 23.5 months, no difference was observed for survival times (immature data).

Abbreviation(s): CR: complete response.

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

Efficacy of Quadruplet Regimen in Transplant-Ineligible NDMM: BENEFIT Trial

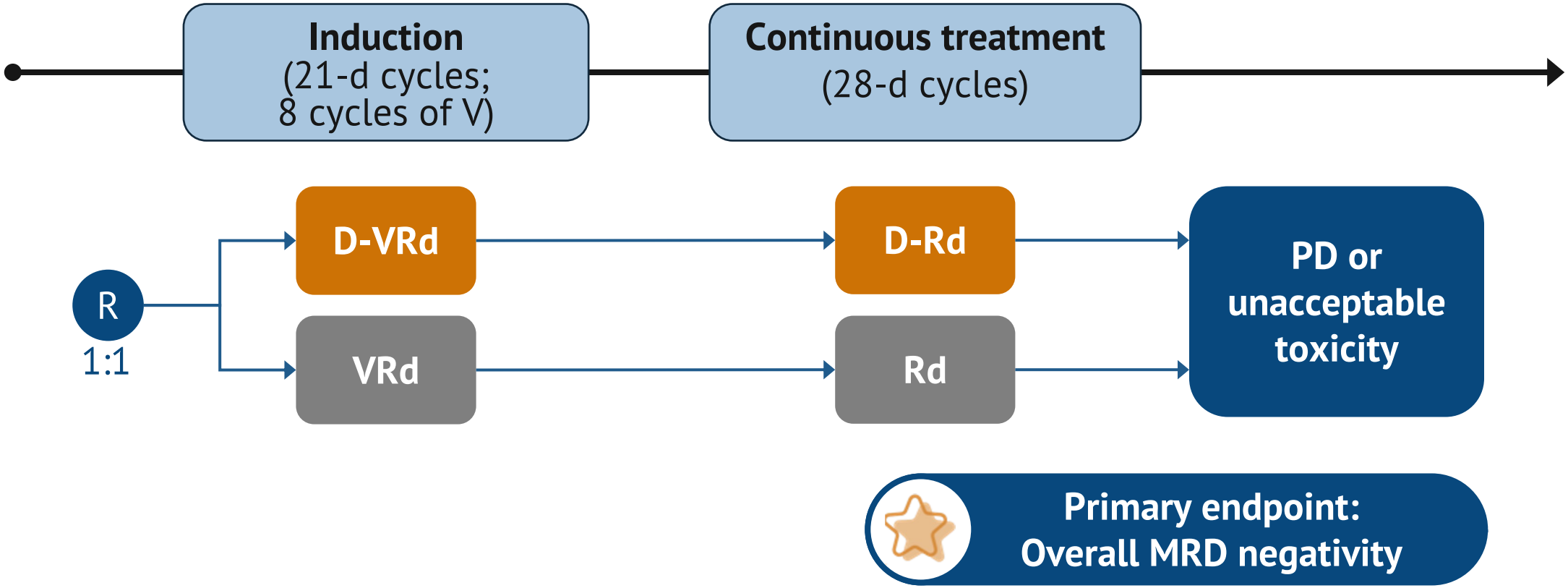
Key secondary endpoint: PFS



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

CEPHEUS Trial: Study Design

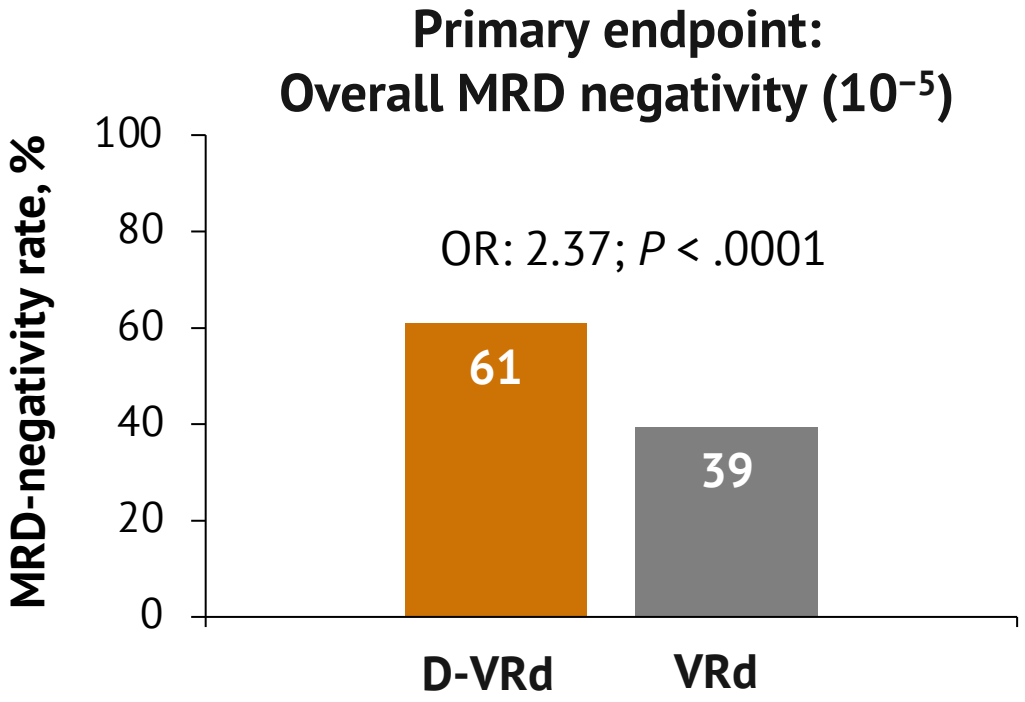
Key eligibility: NDMM, transplant-ineligible or -deferred patients, ECOG PS 0-2, Frailty index 0-1 (N = 395)

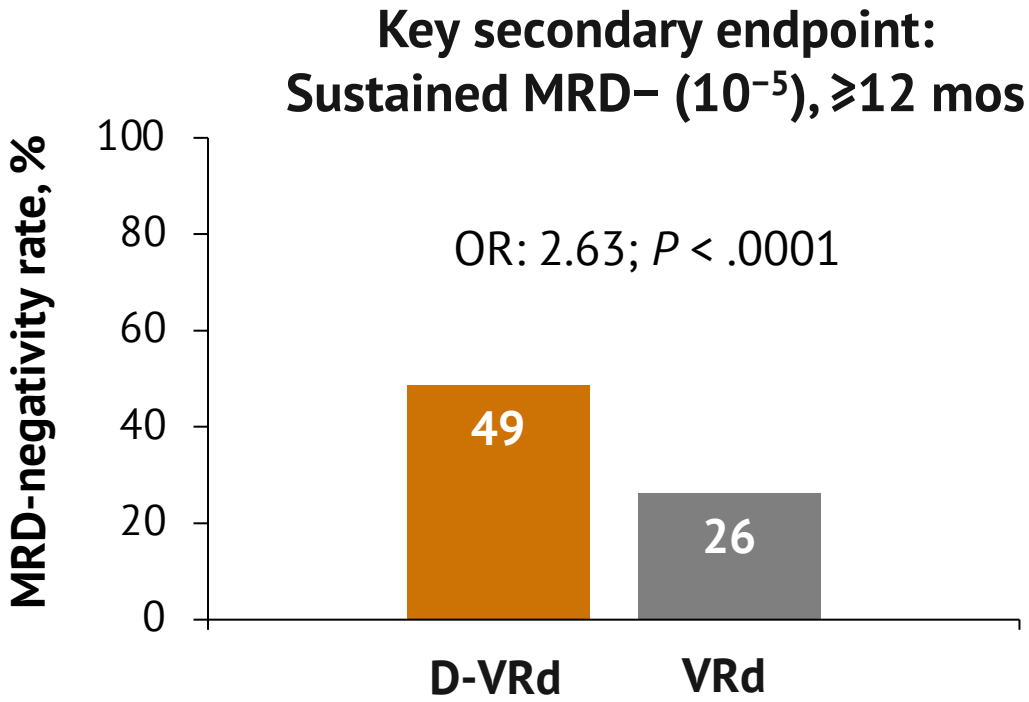


Reference(s): Zweegman S. ASH 2024. Abstract 362.

Efficacy of Quadruplet Regimen in Transplant-Ineligible NDMM: CEPHEUS Trial[1,2]

N = 395; mFU: 58.7 mos

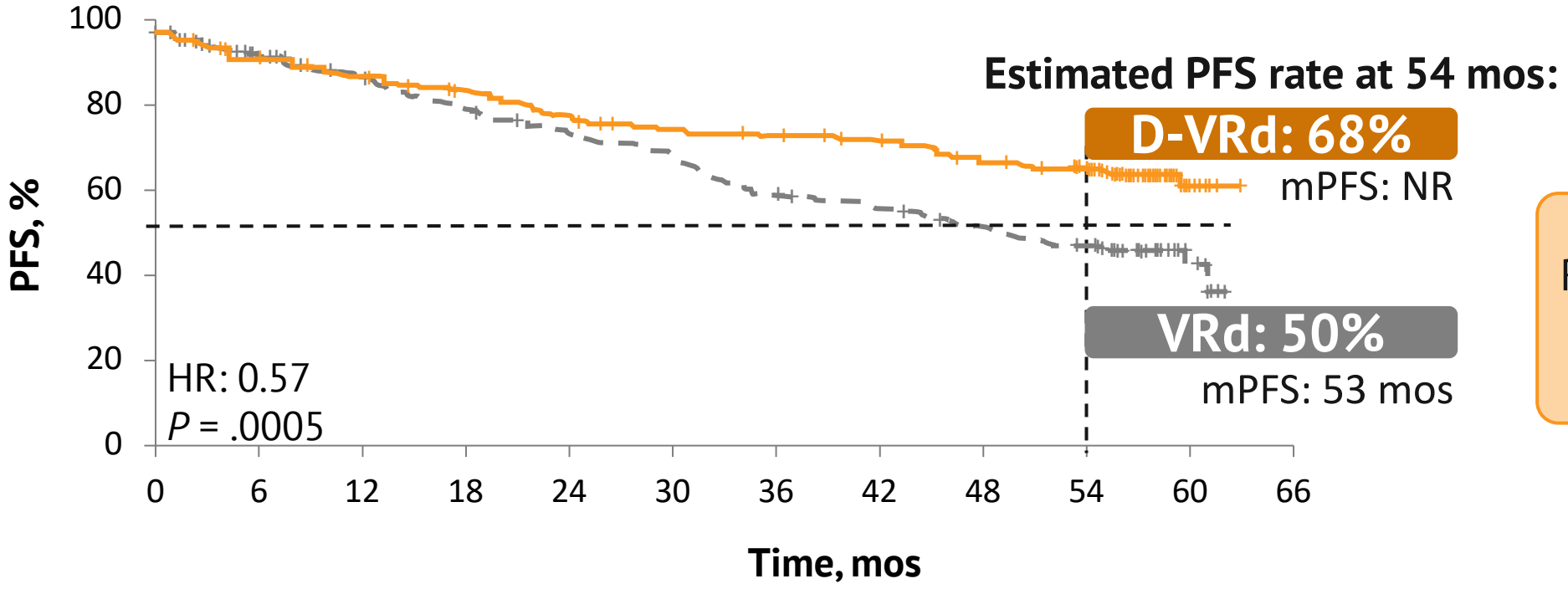




Reference(s): 1. Usmani SZ et al. *Nat Med.* 2025;31:1195-1202; 2. Usmani SZ et al. 21st International Myeloma Society Annual Meeting (IMS 2024).

Efficacy of Quadruplet Regimen in Transplant-Ineligible NDMM: CEPHEUS Trial

Key secondary endpoint: PFS (mFU is 58.7 mo)[1,2]



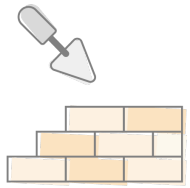
↓43%

Risk of progression or death with D-VRd

Abbreviation(s): NR: not reached.

Reference(s): 1. Usmani SZ et al. *Nat Med*. 2025;31:1195-1202; 2. Usmani SZ et al. IMS 2024.

‘Four’ Every Patient: Maximizing Outcomes in NDMM Care With Anti-CD38 Monoclonal Antibody–Based Quadruplet Therapies



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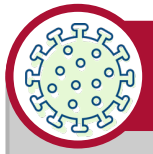
Overview of Safety Profiles

Key AEs Observed With Quadruplet Regimens in Phase 3 Clinical Trials[1-7]

Cytopenias

- Anemia
- Neutropenia
- Thrombocytopenia



Infections

- Respiratory infections, such as pneumonia
- Other infections, such as VZV and HSV

GI issues

- Diarrhea
- Constipation
- Nausea

Other nonhematological AEs

- Peripheral neuropathy: Needs to be limited using appropriate strategies
- Infusion-related reactions

Abbreviation(s): GI: gastrointestinal; HSV: herpes simplex virus; VZV: varicella zoster virus.

Reference(s): 1. Facon T et al. *N Engl J Med.* 2024;391:1597-1609; 2. Usmani SZ et al. *Nat Med.* 2025;31:1195-1202; 3. Leleu X et al. *Nat Med.* 2024;30:2235-2241; 4. Goldschmidt H et al. *Lancet Haematol.* 2022;9:e810-e821. doi:10.1016/S2352-3026(22)00263-0; 5. Sonneveld P et al. *N Engl J Med.* 2024;390:301-313; 6. Gay M et al. *Blood.* 2023;142(suppl 1):4. doi:10.1182/blood-2023-177546; 7. Raje NS et al. *Lancet Haematol.* 2022;9:e143-e161. doi:10.1016/S2352-3026(21)00283-0

Rates of Treatment Discontinuations With Quadruplets in Transplant-Eligible Patients

	PERSEUS[1]		GMMG-HD7[2,3]		IsKia[4,a]	
	D-VRd (n = 351)	VRd (n = 347)	Isa-VRd (n = 331)	VRd (n = 329)	Isa-KRd (n = 151)	KRd (n = 151)
AEs leading to discontinuation, %	**9**	21	**3**	3	**3**	2
mFU, mos	48		~48		35	

Trials are not head-to-head and should not be directly compared.

[a] Post light consolidation.

Reference(s): 1. Sonneveld P et al. *N Engl J Med.* 2024;390:301-313. 2. Raab M. 29th European Hematology Association Congress (EHA 2024). Abstract S202; 3. Mai EK et al. *J Clin Oncol.* 2025;43:1279-1288; 4. Gay F et al. *J Clin Oncol.* 2025;46(suppl 16):7502.

Rates of Treatment Discontinuations With Quadruplets in Transplant-Ineligible Patients

	IMROZ[1]		CEPHEUS[2,a]		BENEFIT[3,b]	
	Isa-VRd (n = 265)	VRd (n = 181)	D-VRd (n = 197)	VRd (n = 195)	Isa-VRd (n = 135)	Isa-Rd (n = 135)
AEs leading to discontinuation, %	**23**	26	**8**	16	**15**	22
mFU, mos	60		59		24	

Trials are not head-to-head and should not be directly compared.

[a] Discontinuation of all study drugs. [b] All-cause discontinuation.

Reference(s): 1. Facon T et al. *N Engl J Med.* 2024;391:1597-1609; 2. Usmani SZ et al. IMS 2024; 3. Leleu X et al. *Nat Med.* 2024;30:2235-2241;

Key AE Management Strategies

Safety Considerations With Quadruplet Therapies in NDMM[1-7]

Cytopenias

- Growth factors
- Dose-reduce IMiDs

Risk of high-grade infection

- Consider prophylactic anti-microbials in first few cycles
- Prophylactic IVIG
- Use appropriate vaccinations

Peripheral neuropathy

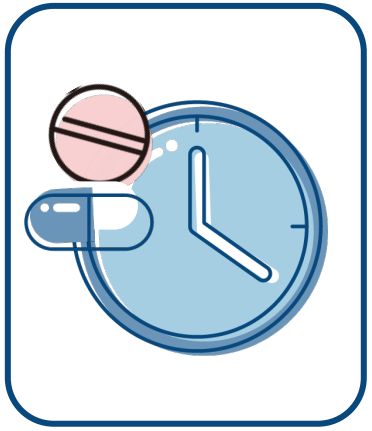
- Supportive care
- Dose-reduce bortezomib
- Discontinuation

Dose reductions are not recommended for anti-CD38 mABs.

Abbreviation(s): IMiD: immunomodulatory drug; IVIG: intravenous immunoglobulin.

Reference(s): 1. Raje NS et al. *Lancet Haematol*. 2022;9:143-161; 2. FDA website. Daratumumab prescribing information (PI). Published April 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761036s054lbl.pdf; 3. European Medicines Agency (EMA). Daratumumab Summary of Product Characteristics (SmPC). Revised October 2025. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf; 4. Lenalidomide PI. Revised March 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021880s067lbl.pdf; 5. Lenalidomide SmPC. Revised September 2025. https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf; 6. Bortezomib PI. Revised November 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021602s046lbl.pdf; 7. Bortezomib SmPC. Revised May 2025. https://www.ema.europa.eu/en/documents/product-information/bortezomib-hospira-epar-product-information_en.pdf; 8. Facon T et al. *N Engl J Med*. 2024;391:1597-1609.

Safety Considerations With Quadruplet Therapies in NDMM



IMiD dosing

- **Dose-reduce lenalidomide** in cases of comorbidities, such as renal impairment[1]

Corticosteroid dosing

- **Dose-reduce dexamethasone** in patients who are older/frailer or in case of toxicities[2]
- Common toxicities include hyperglycemia and insomnia[3]

Consider VTE prophylaxis for all patients treated with IMiDs and dexamethasone[4]

Abbreviation(s): VTE: venous thromboembolism.

Reference(s): 1. Lenalidomide PI. Revised March 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021880s067lbl.pdf; 2. NCCN. Multiple Myeloma (Version 1.2025). Accessed November 11, 2024. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf; 3. Banerjee R et al. *Blood*. 2025;145:75-84; 4. Frenzel L et al. *Thromb Res*. 2024;233:153-164.

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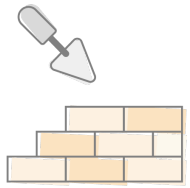

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Patient Selection Considerations

Patients Included in Pivotal Trials of Quadruplet Therapies in Transplant-Eligible NDMM

Patient characteristics[1,2]

- Newly diagnosed multiple myeloma
- Age 18-70 y
- Eligibility to undergo transplant
- ECOG PS ⩽2

Reference(s): 1. Sonneveld P et al. *N Engl J Med.* 2024;390:301-313; 2. ClinicalTrials.gov. Trial Identifiers: NCT03617731, NCT04483739. Accessed November 26, 2025.

Patients Included in Pivotal Trials of Quadruplet Therapies in Transplant-Ineligible NDMM

Patient characteristics[1,2]

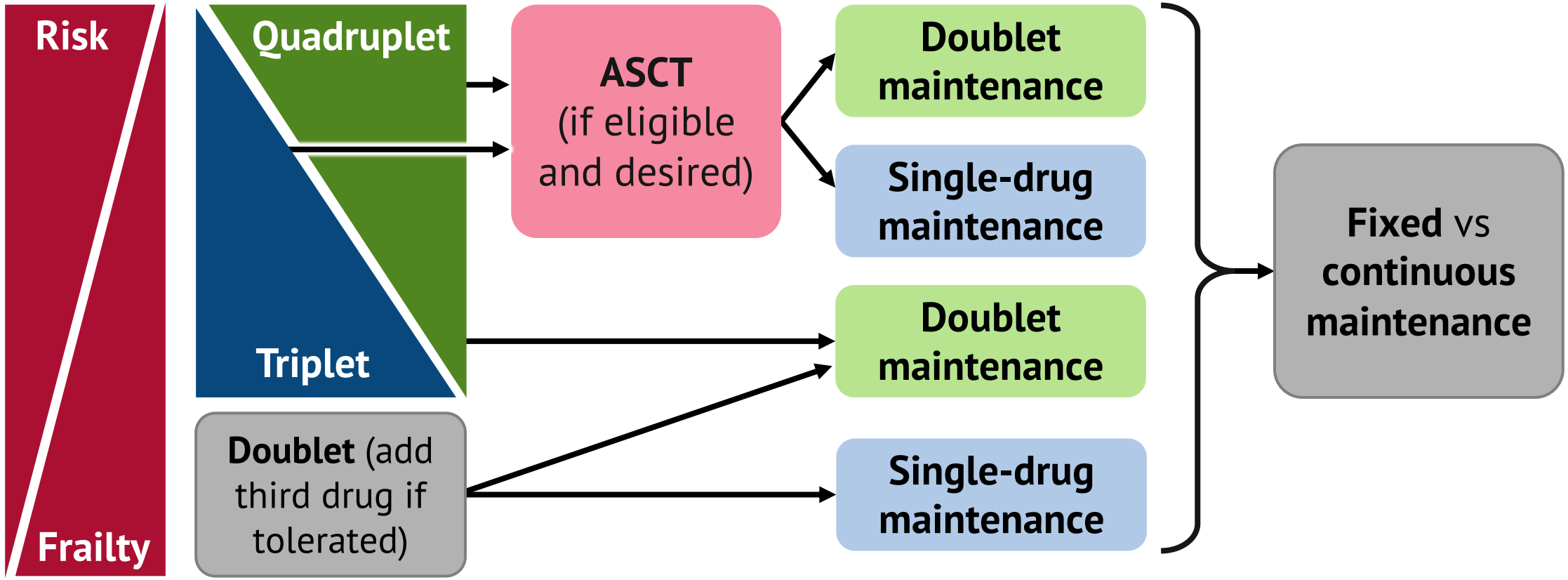
- Newly diagnosed multiple myeloma
- Ineligibility for transplant due to age or comorbidity
- Frailty index <2 per Myeloma Geriatric Assessment score (CEPHEUS)
- ECOG PS ⩽2
- Adequate organ function

Key exclusion criterion: Age >80 y[1,2]

Clinical guidelines recommend against quadruplet therapy for these patients[3]

Reference(s): 1. Facon T et al. *N Engl J Med*. 2024;391:1597-1609; 2. ClinicalTrials.gov. Trials Identifiers NCT03319667, NCT03652064, NCT04751877; 3. NCCN. Multiple Myeloma (Version 1.2025). Accessed November 11, 2024. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

Individualizing the Treatment Approach in NDMM Based on Risk Status and Frailty[1,2]



Reference(s): 1. Kumar SK. *Hematology Am Soc Hematol Educ Program.* 2024;1:551-560; 2. Mian H et al. *Am J Hematol.* 2025;100:1483-1485.

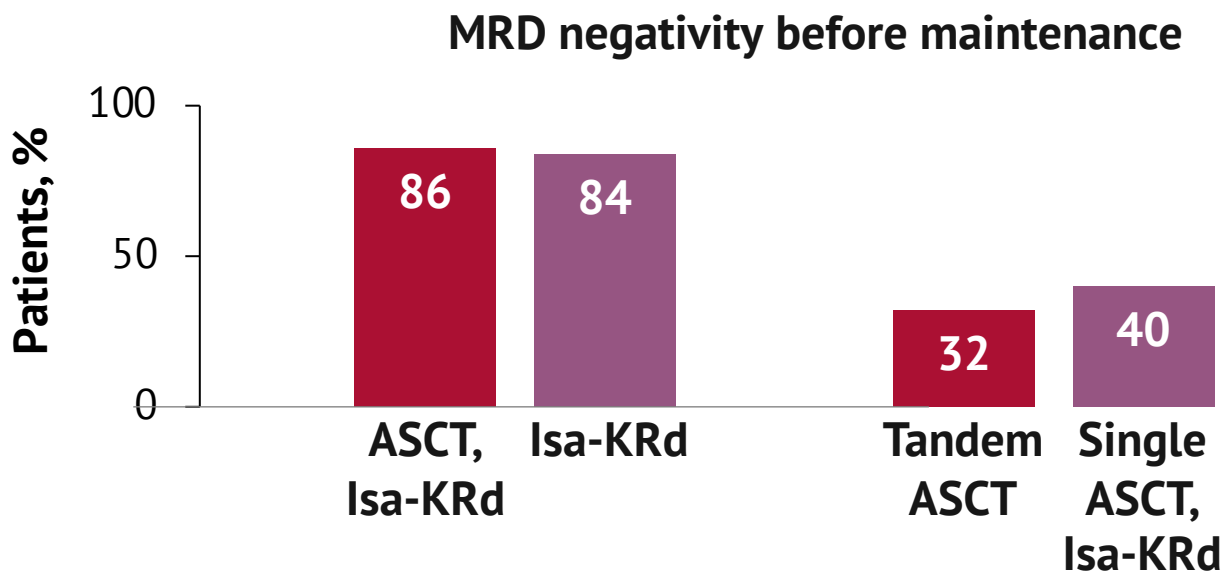
What are the implications of these data for clinical practice in community settings?

Are quadruplet therapies appropriate for clinically relevant patient subgroups (eg, ISS stage 3, high cytogenic risk)?

Emerging Perspectives in Quadruplet Therapy

Emerging Perspectives: MRD-Guided Therapy in NDMM

MIDAS: Phase 3 trial in TE patients with NDMM who completed induction therapy with Isa-KRd to receive consolidation therapy per MRD status
(N = 485; mFU 16.8 mos in ASCT and Isa-KRd groups, 16.3 mos in tandem and single ASCT groups)[1]



MASTER-2:
Phase 2 trial with a response-adaptive design to evaluate if transplant can be deferred in patients with NDMM achieving MRD− after D-VRd induction[2]

Abbreviation(s): TE: transplant-eligible.

Reference(s): 1. Perrot A et al. *N Engl J Med*. 2025;393:425-437; 2. Dhakal B et al. *Blood*. 2024;144(suppl 1):2000.1. doi:10.1182/blood-2024-200210

Emerging Perspectives: Quadruplet Therapies in Patients With High-Risk NDMM

Phase 2 trials in pts with NDMM with high cytogenetic risk (del(17p), t(4;14), t(14;16), gain or amplified 1q21)

Trial name (phase, N)	Patient population	Treatment	Results
GMMG-Concept[1] **Phase 2** (N = 219 TE, 26 TNE)	**HRCA ≥1 + ISS stage II/III**	• **Induction:** Isa-KRd, then ASCT (TE) or Isa-KRd (TNE) • **Consolidation:** Isa-KRd • **Maintenance:** Isa-KR	Met primary endpoint: **MRD− after consolidation**
MASTER[2] **Phase 2** (N = 123)	**HRCA 0, 1, 2+; 20% R-ISS**	• **Induction:** D-KRd, then ASCT • **Consolidation:** D-KRd • **Maintenance:** MRD surveillance if confirmed MRD−; otherwise R	In pts with 0, 1, and 2+ HRCA: • **3-y PFS:** 88%, 79%, 50% • **3-y OS:** 94%, 92%, 75%

Abbreviation(s): HCRA: high-risk cytogenetic abnormalities; OS: overall survival; TNE: transplant-ineligible.

Reference(s): 1. Leypoldt et al. EHA 2025 Abstract S209; 2. Costa L et al. *HemaSphere* 2023;7:e1332195. doi:10.1097/01.HS9.0000967724.13321.95

Emerging Perspectives: Limited Dexamethasone Dosing in Older and Frailer Patients

REST: Phase 2, single-arm trial of Isa-VRd with both weekly V and dexamethasone omitted after 2 cycles in adults with NDMM with ECOG PS 0-3 (N = 51; median age 77 y)

Response	Patients, n (%)
Overall response	51 (100% [93-100])
Best overall response	
MRD− CR (primary endpoint)	19 (37% [25-51])

Supports use of Isa-VRd with limited dexamethasone in transplant-ineligible patients with NDMM who are older and frailer than those in IMROZ trial

Reference(s): Askeland FB et al. *Lancet Haematol.* 2025;12:e120-e127. doi:10.1016/S2352-3026(24)00347-8

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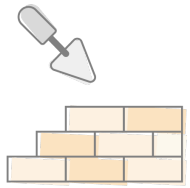

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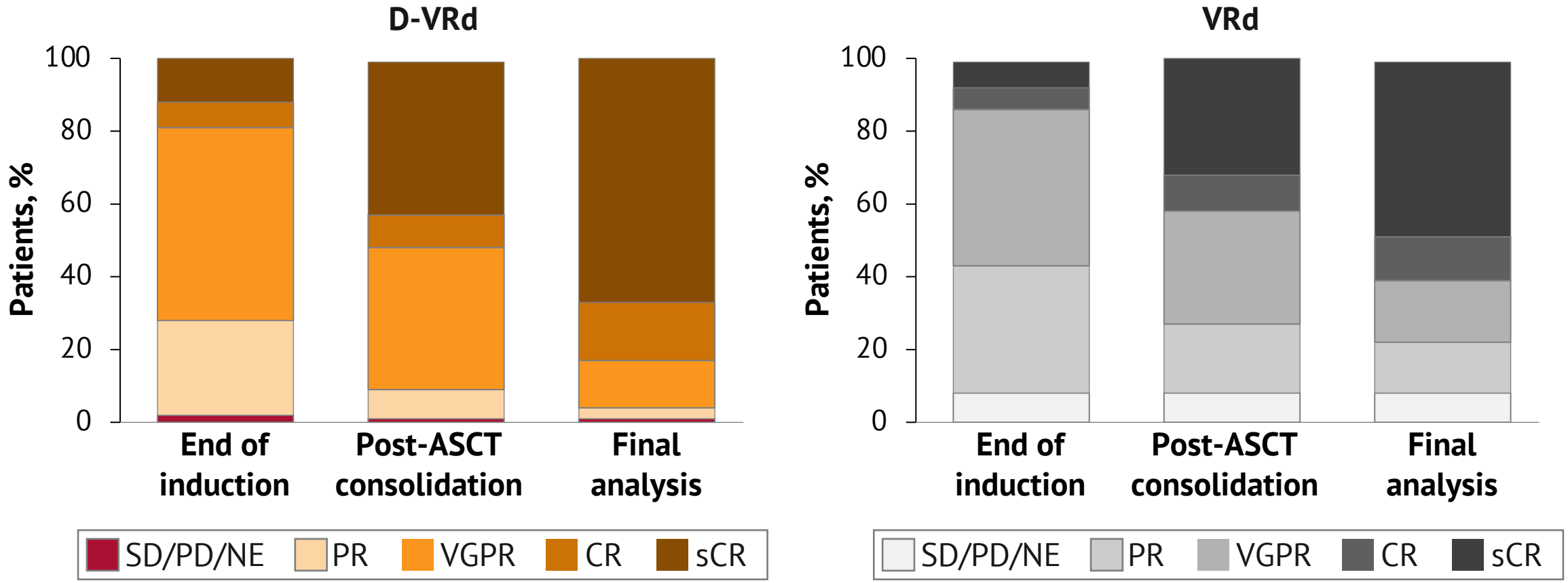
Deepening of Responses Over Time With Quadruplet Therapies

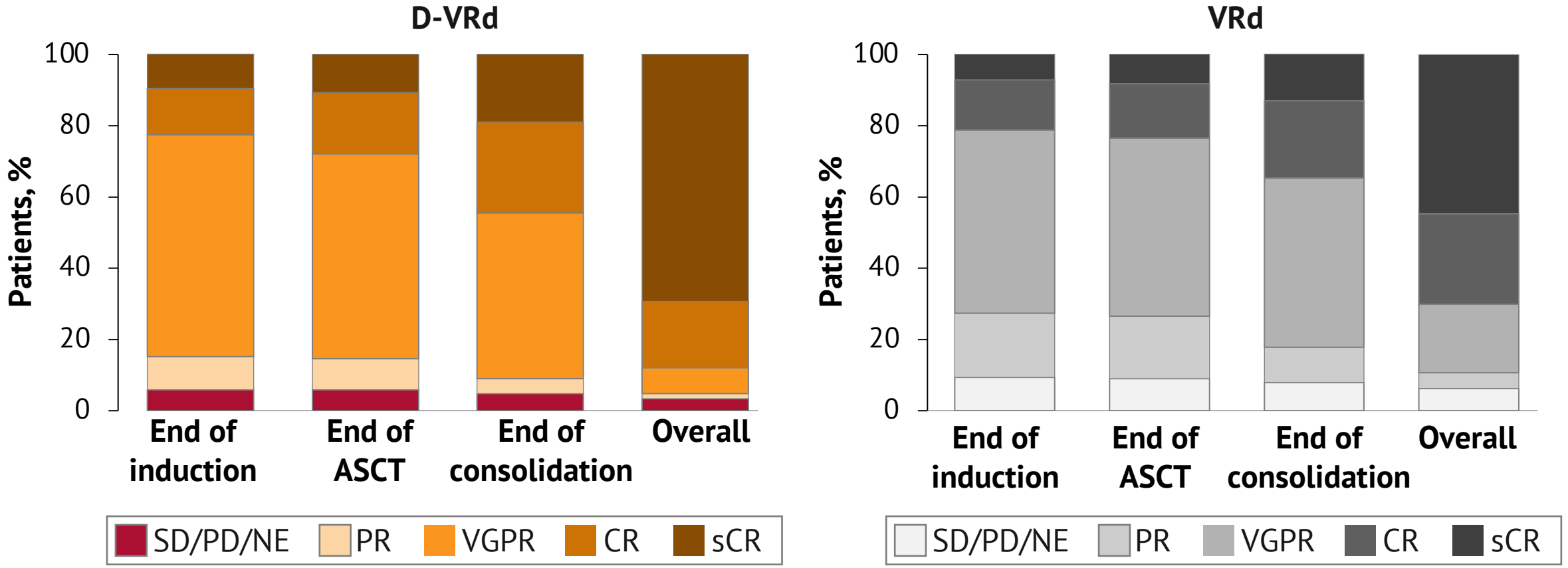
GRIFFIN: Deepening of Responses Over Time



Abbreviation(s): NE: not evaluable; PR: partial response; SD: stable disease; VGPR: very good PR.

Reference(s): Voorhees PM et al. *Lancet Haematol.* 2023;10:e825-e837. doi:10.1016/S2352-3026(23)00217-X

PERSEUS: Deepening of Responses Over Time

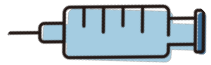


Reference(s): Rodríguez-Otero P et al. ASCO 2024. Abstract 7502.

As patients achieve deeper responses in the “age of the quadruplets,” how is the role of transplantation evolving?

Optimizing Outcomes for All Patients With NDMM

Considerations Around Route of Administration: Patient Preferences



Route of administration may contribute to patient preference

Daratumumab: SC administration[1]

Isatuximab: IV administration[2]
(SC under investigation)[3]

Subcutaneous administration is associated with:

- Lower incidence of infusion reactions[1,3-5]
- More convenient and efficient administration[3]

May enable:

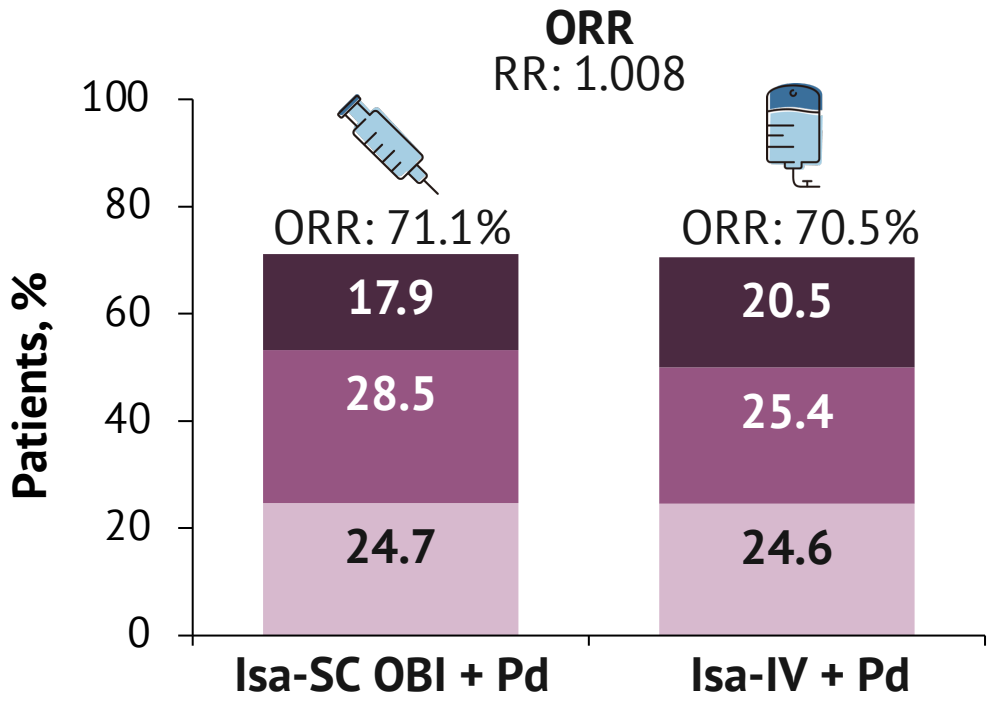
- Treatment persistence[3]
- Future at-home administration[3]

Abbreviation(s): SC: subcutaneous.

Reference(s): 1. Daratumumab and hyaluronidase-fihj PI: FDA website. Revised November 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761145s032lbl.pdf; 2. Isatuximab PI: FDA website. Revised October 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761113s012lbl.pdf; 3. Ailawadhi S et al. *J Clin Oncol.* 2025;43:2527-2537; 4. Sonneveld P et al. *N Engl J Med.* 2024;390:301-313; 5. Daratumumab PI: FDA website. Revised April 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761036s054lbl.pdf

Emerging Perspectives: Subcutaneous Administration of Isatuximab

Phase 3 IRAKLIA Trial: SC isatuximab delivered via on-body injector (N = 531)



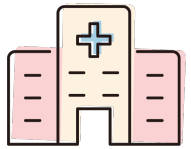
	Isa SC	Isa IV
Incidence of infusion reactions, %	2	25
Satisfaction[a], %	70	53

[a] Satisfied or very satisfied on cycle 5, day 15 on patient experience and satisfaction questionnaire.

Abbreviation(s): OBI: on-body injector; ORR: objective response rate; P: pomalidomide; RR: relative risk.

Reference(s): Ailawadhi S et al. *J Clin Oncol.* 2025;43:2527-2537.

Fostering Inclusiveness in Myeloma Care: Care Barriers in the Community



Patients in rural/underserved areas may have:

- Limited access to large medical centers
- Lower insurance rates
- Lower rates of cancer screening
- Poor access to standard care
- Less opportunity to enroll in clinical trials

Increased collaboration between community oncologists and academic centers is vital to better outcomes

Reference(s): Unger JM et al. *CA Cancer J Clin*. 2025;75:341-361.

Fostering Inclusiveness: Strategies to Overcome Care Disparities in All Patients With MM[1-3]

Build trust with patient	By using shared decision-making
Create disease awareness through education	Use culturally appropriate language and tools, include community and caregivers
Expand eligibility criteria in clinical trials	Improve referral to trials, consider implicit bias training
Improve time to diagnosis	To prevent delays in receipt of treatment
Support access to quality care	by providing resources to offset medical/ ancillary costs, and improving telemedicine

Reference(s): 1. Bhutani M et al. *Blood Cancer J.* 2023;13:189. doi:10.1038/s41408-023-00961-0; 2. Banerjee R et al. *Blood Cancer J.* 2024;14:149. doi:10.1038/s41408-024-01129-0; 3. Hartley-Brown M et al. *Clin Lymphoma Myeloma Leuk.* 2024;24:32-39.

The Treatment Landscape for NDMM: Where We're Going[1,2]

Anti-CD38 mAB and CAR T-cell therapy

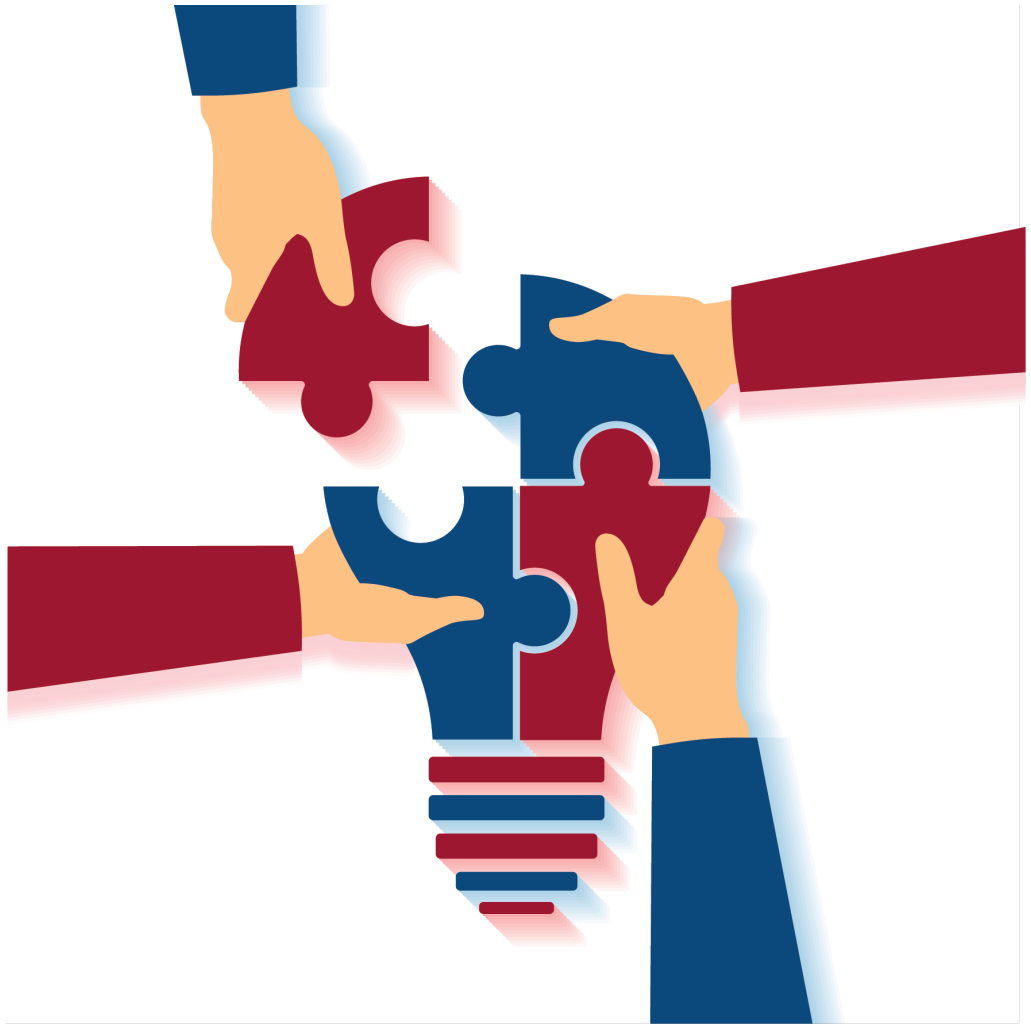
- **CARTITUDE-6:** D-VRd followed by ASCT vs D-VRd followed by cilta-cel
- **GEM-AnitoFIRST:** D-VRd/Isa-VRd followed by anito-cel

Anti-CD38 mAB and bispecific antibodies

- **MajesTEC-2:** Teclistamab in combinations of anti-CD38 mAB, IMiDs, and PIs
- **MajesTEC-5:** Teclistamab/talquetamab in combinations of anti-CD38 mAB, IMiDs, and PIs
- **MajesTEC-7:** Teclistamab + daratumumab + lenalidomide
- **MonumenTAL-2:** Talquetamab in combinations of anti-CD38 mAB, IMiDs, and PIs

Abbreviation(s): anito-cel: anitocabtagene autoleucel; CAR: chimeric antigen receptor; cita-cel: ciltacabtagene autoleucel.

Reference(s): 1. Besliu C et al. *Cancers (Basel).* 2025;17:525. doi:10.3390/cancers17030525; 2. ClinicalTrials.gov Identifiers: NCT05257083, NCT07045909, NCT04722146, NCT05695508, NCT05552222, NCT05050097. Accessed November 26, 2025.



Audience Q&A