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& Myeloma Congress
October 13–16, 2026
New York City
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# Frontline Therapy in Newly Diagnosed Multiple Myeloma: Raising the Bar on Depth and Durability

**Suzanne Lentzsch, MD, PhD**
*Professor of Medicine*
*Director, Multiple Myeloma and Amyloidosis Program*
*Columbia University Irving Medical Center/NewYork-Presbyterian Hospital*
*New York City, New York*

**Cesar Rodriguez, MD**
*Associate Professor of Medicine (Hematology and Medical Oncology)*
*Icahn School of Medicine at Mount Sinai*
*New York City, New York*

This session is supported by an independent educational grant from Johnson & Johnson.

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# Disclosures

- **Suzanne Lentzsch, MD, PhD:** consultant—Sanofi, Pfizer, Johnson & Johnson, GSK, Kite, BMS, Alexion, Sanofi; royalties—Anselamimab
- **Cesar Rodriguez, MD:** Consultant—Sanofi, Johnson & Johnson, BMS, Pfizer, Regeneron, GSK, AbbVie

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# Learning Objectives

- Apply contemporary risk stratification, transplant eligibility, and MRD assessment to personalize frontline therapy selection and inform treatment sequencing in NDMM
- Interpret pivotal and emerging clinical trial data and guideline updates to optimize use of novel and frontline MM regimens
- Implement evidence-based strategies to proactively manage AEs and address treatment resistance in frontline MM therapy to improve QoL and long-term outcomes

MRD = measurable residual disease; NDMM = newly diagnosed multiple myeloma; AE = adverse event; QoL = quality of life.

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# Multiple Myeloma: Current Landscape and Clinical Challenges

**Suzanne Lentzsch, MD, PhD**

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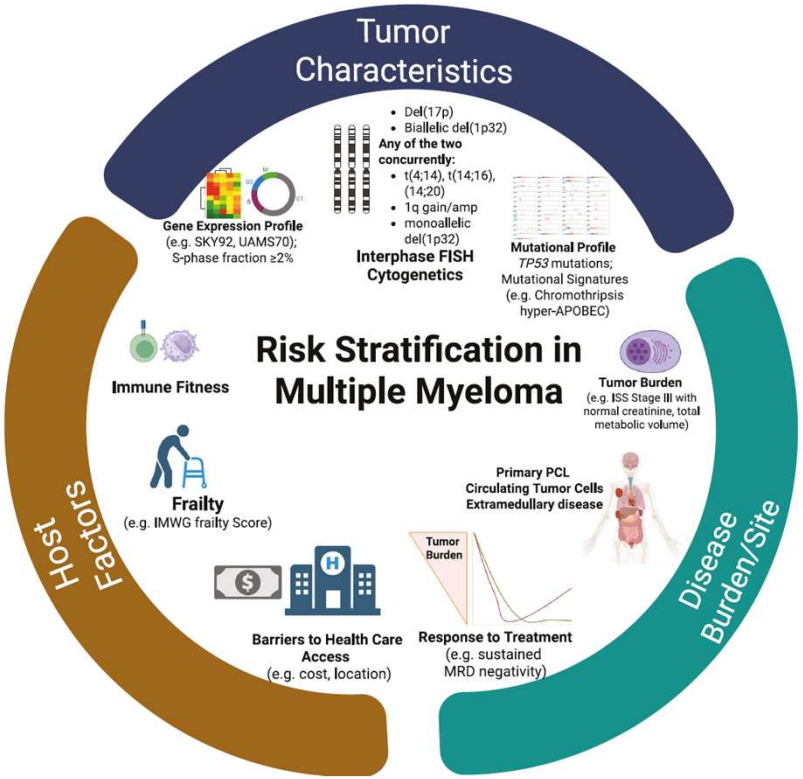
# Risk Assessment and Patient Stratification

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# Approach to NDMM

IMS-IMWG Consensus Genomic Staging (CGS), 2025—validated in real-world cohorts, 2026

- Deletion 17p and/or a TP53 mutation. Clonal cell fraction is 20%.
- IGH translocation—t(4;14), t(14;16), t(14;20)—with 1q gain and/or deletion of 1p
- A monoallelic deletion of 1p with 1q additional copies or a biallelic deletion of 1p
- Beta-2 microglobulin of at least 5.5 only when the creatinine is normal

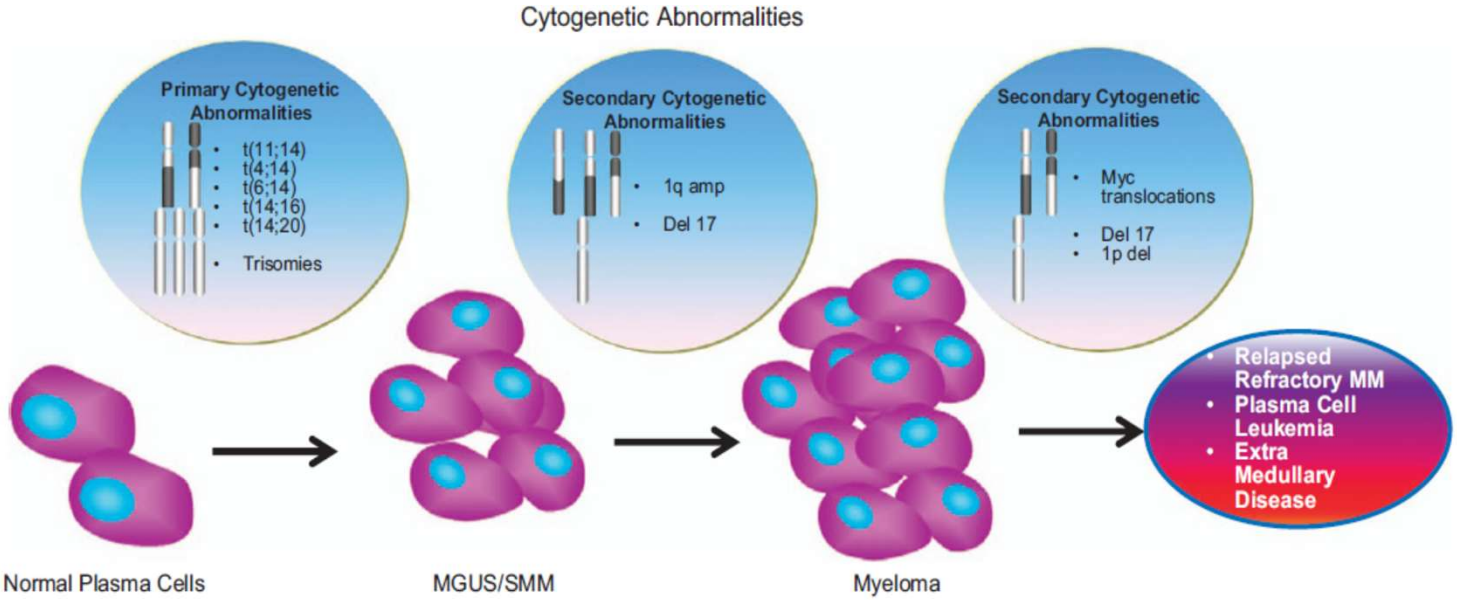



IMS-IMWG = International Myeloma Society International Myeloma Working Group; IGH = immunoglobulin heavy chain; FISH = fluorescence in situ hybridization; ISS = International Staging System; IMWG = International Myeloma Working Group; PCL = plasma cell leukemia.

Zanwar S, Rajkumar SV. *Leukemia*. 2025;39(11):2610-2617. Avet-Loiseau H, et al. *J Clin Oncol*. 2025;43(24):2739-2751.

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# High-Risk Cytogenetics in Myeloma



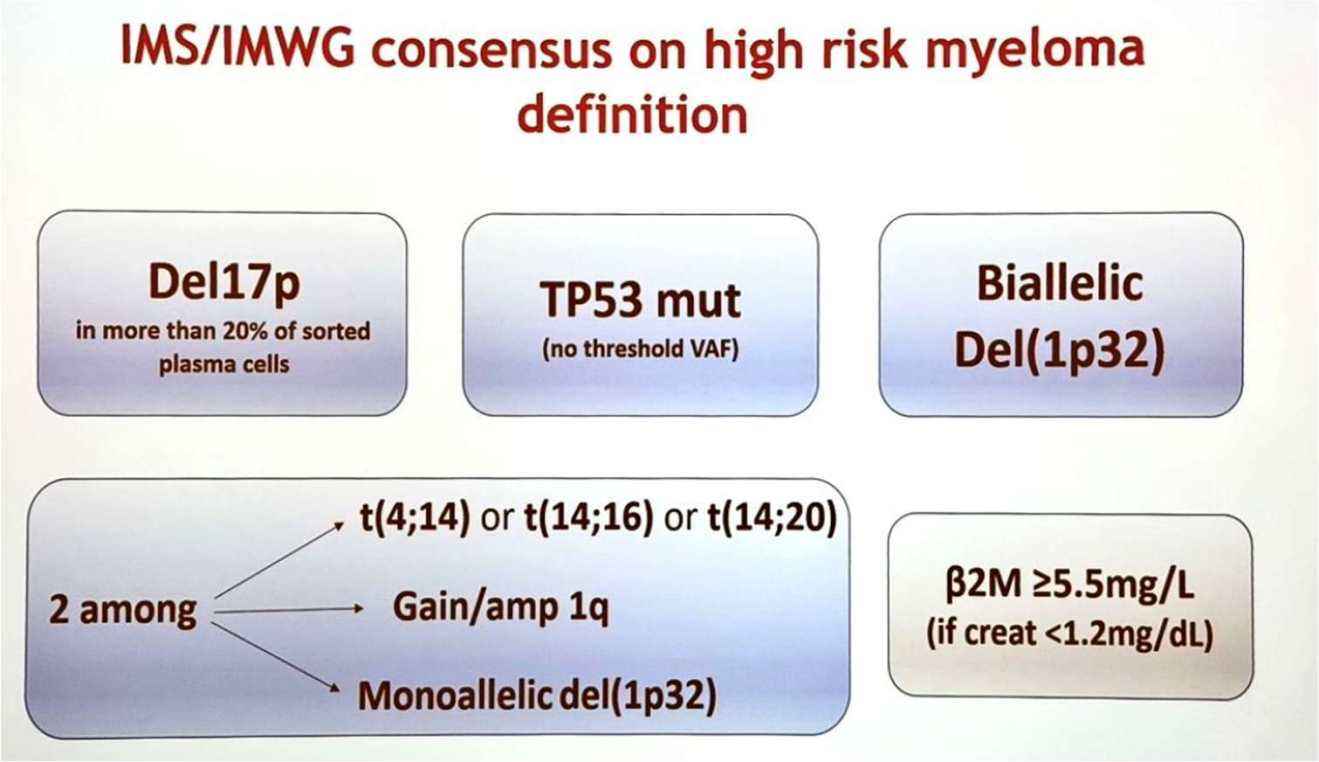

High-risk cytogenetic abnormalities on FISH

- t(4;14), t(14;16), del(17p), ??t(14;20)
- +1q (especially if ≥4 copies)
- del(1p)

MGUS = monoclonal gammopathy of undetermined significance; SMM = smoldering multiple myeloma.
Rajan AM, Rajkumar SV. *Blood Cancer J.* 2015;5(10):e365.

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# IMS-IMWG Consensus Genomic Staging (CGS)




- **IMS-IMWG CGS validated in independent real-world cohorts (Romanian, ANZ registries, 2026) → cytogenetic complexity, not single lesions, drives outcome**
- Will imaging, "tumor burden," and/or GEP be incorporated in the future?
- Most urgently: how to make NGS accessible in the clinic → implementation barriers remain the key gap

Requires NGS for full genomic assessment.
NGS = next-generation sequencing; ANZ = Australia and New Zealand; GEP = gene expression profile
Avet-Loiseau H, et al. *J Clin Oncol*. 2025;43(24):2739-2751.

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# mSMART 4.0: Classification of Active MM

## High-Risk Myeloma

- **High-risk cytogenetic abnormalities**
  - Del 17p[a] and/or *TP53* mutation
  - Biallelic del 1p
  - t(4;14), (14;16), or t(14;20) *plus* either Gain/amp 1q or Del 1p
  - Gain/amp 1q *plus* Del 1p
- **B2M >5.5 with normal renal function**
- **High plasma cell S-phase**
- **Primary plasma cell leukemia**
- **Newly diagnosed myeloma with extramedullary disease**

**Double-hit myeloma = Patients meeting criteria for high-risk myeloma with presence of two or more of the four high-risk qualifying cytogenetic abnormalities as listed above[b]**

## Standard-Risk Myeloma

MM with no high-risk abnormalities including isolated

- Trisomies
- t(11;14)
- t(6;14)

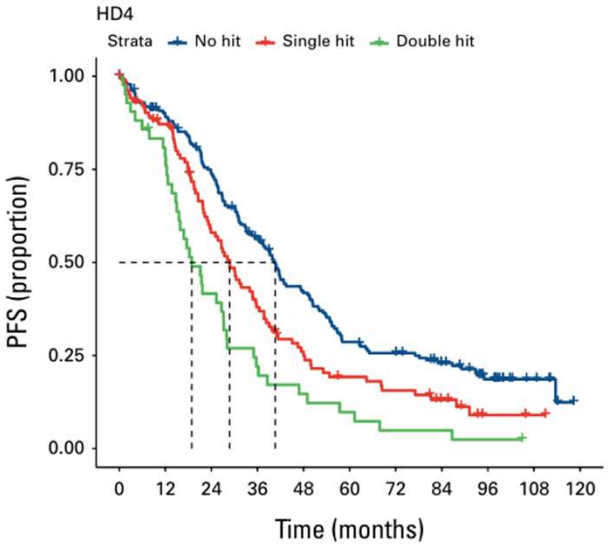
**@VincentRK**
**Mayo mSmart→ "goal is to be completely aligned with IMS-IMWG"**

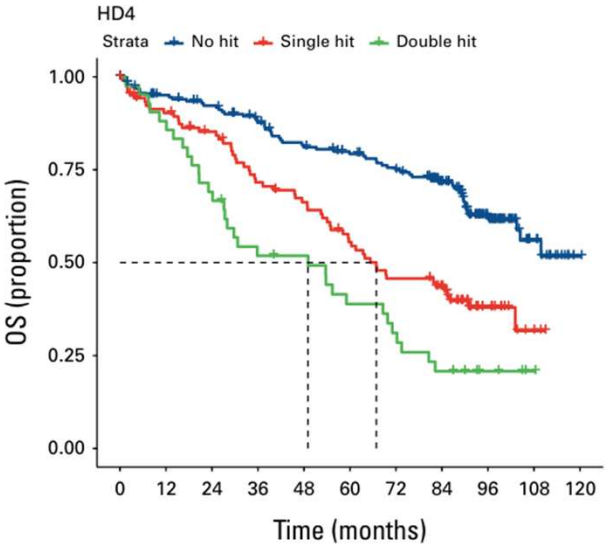
[a]del(17p) threshold to consider high risk is if the abnormality is detected in ≥20% of clonal plasma cells. [b]For example, presence of del 17p (high-risk qualifying cytogenetic abnormality) plus both t(4;14) and del 1p (second additional high-risk qualifying abnormality).
Rajkumar V [www.msmart.org]. Last updated October 2024. https://www.msmart.org/mm-treatment-guidelines.

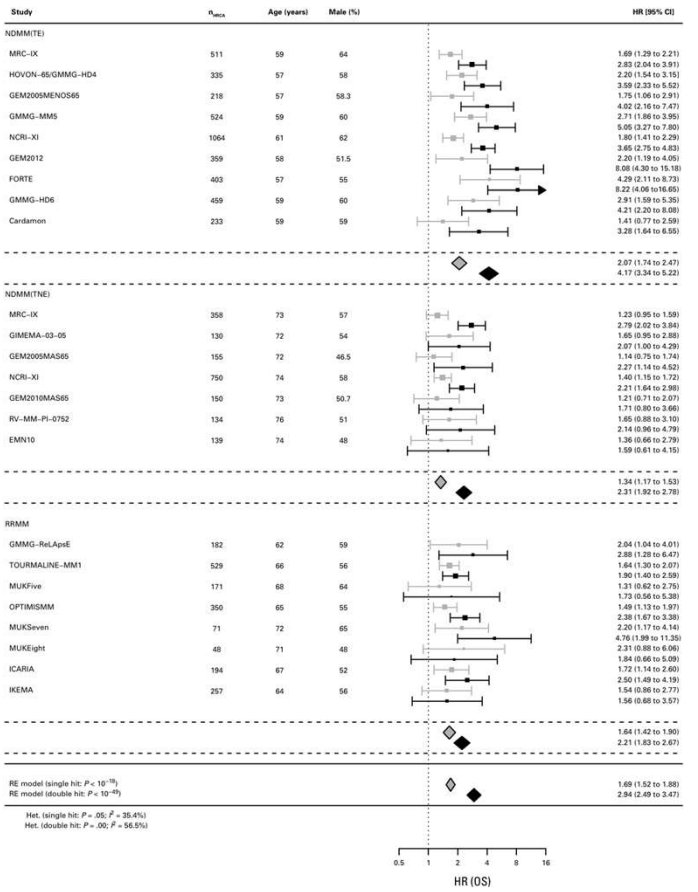
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# Single- vs Double-Hit MM

Consistent association with survival outcomes across TE NDMM, TNE NDMM, RRMM




**2+ HRCA = double hit = "ultra high-risk MM"**
**Consistent across (1) TE NDMM (2) TNE NDMM (3) RRMM**

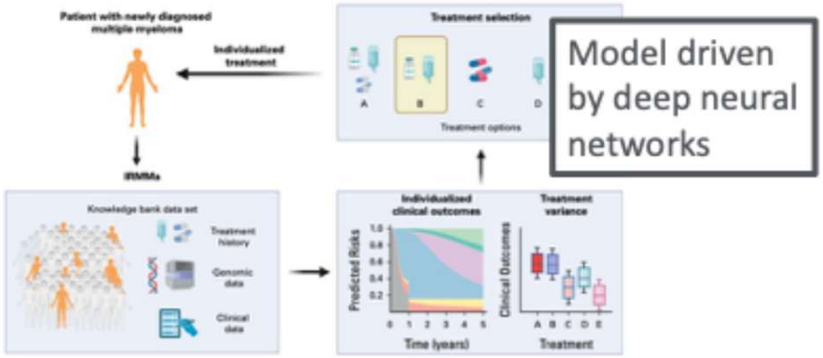
TE = transplant-eligible; TNE = transplant-non-eligible; HRCA = high-risk cytogenetic abnormalities.
Kaiser MF, et al. *J Clin Oncol*. 2025;43(24):2679-2691.

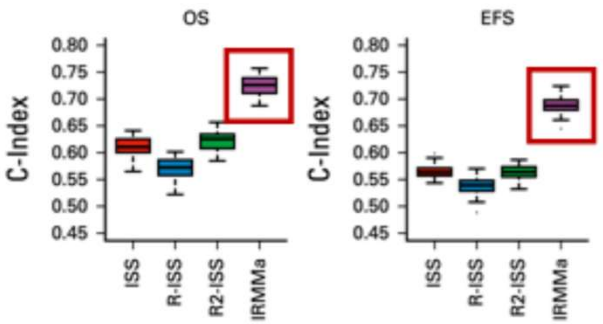
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# **Where the Future Is:** Individualized Risk Model for Multiple Myeloma (IRMMa)

- MMRF, N=1062
- Moffitt, N=177
- MPG, N=492
- MSKCC, N=109
- UAMS, N=93

- Clinical
- Demographic
- Ethnic
- Treatment
- Genomics (WES/WGS)



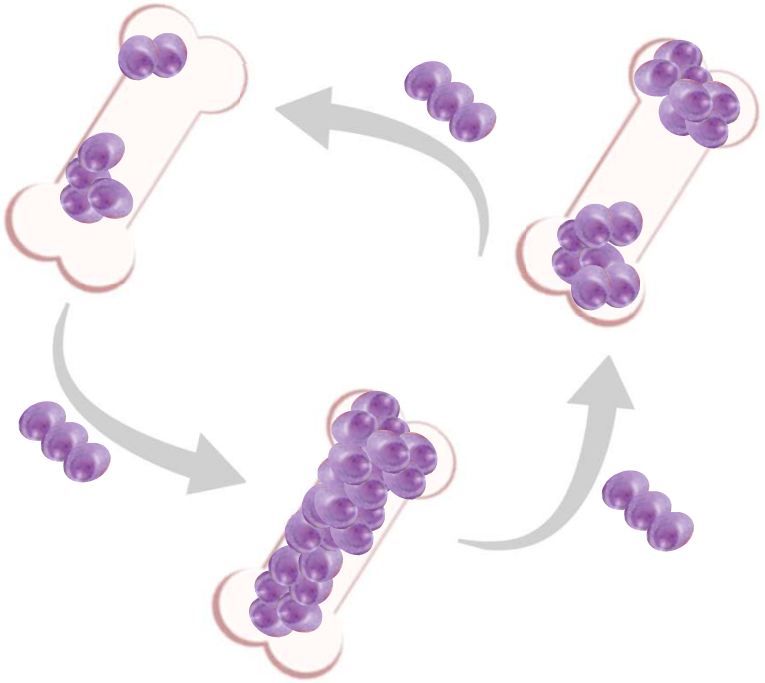

*A preview of replacing categorical labels like "ultra-high-risk" with individualized, patient-level scores.*

MMRF = Multiple Myeloma Research Foundation; MPG = Myeloma Genomics Pipeline; MSKCC = Memorial Sloan Kettering Cancer Center; UAMS = University of Arkansas for Medical Sciences; WES = whole exome sequencing; WGS = whole genome sequencing.

Maura F, et al. *J Clin Oncol*. 2024;42(11):1229-1240.

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# CTC: Surrogate of Tumor Burden



There are no unifying genetic events associated with tumor egress from the BM[1,2]

↓

Fully occupied hypoxic BM niches together with a pro-inflammatory tumor microenvironment force cancer cells to stop proliferating, recirculate in PB and seek other BM niches to continue growing[3]

↓

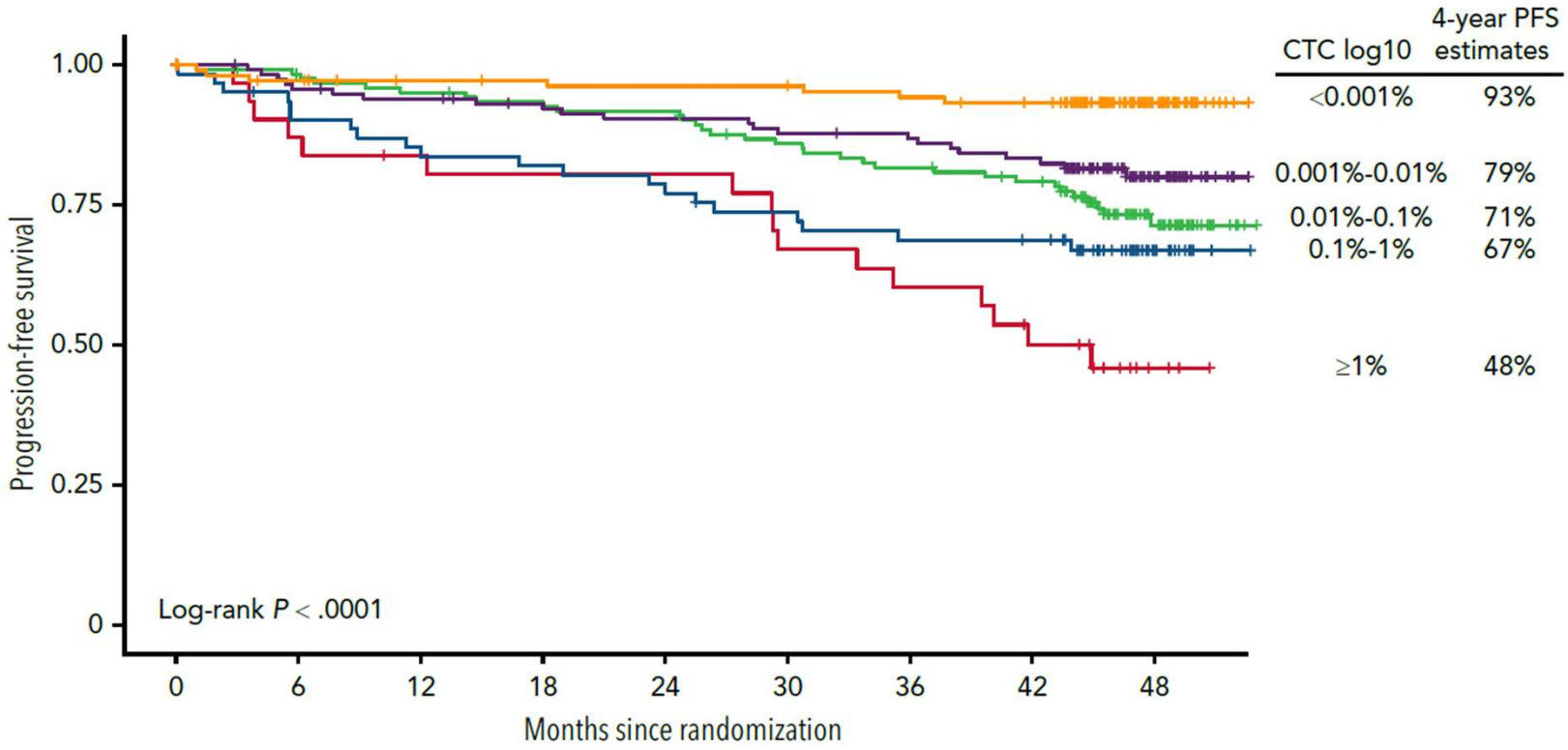
**The higher the CTC numbers the greater the risk of disease progression[4-12]**

CTC = circulating tumor cells; BM = bone marrow; PB = peripheral blood.

1. Garces JJ, et al. *Leukemia*. 2020;34(2):589-603. 2. Dutta AK, et al. *Cancer Discov*. 2023;13(2):348-363. 3. Garces JJ, et al. *Leukemia* 2020;34(11):3007-3018. 4. Sanoja-Flores L, et al. *Blood Cancer J*. 2018;8(12):117. 5. Sanoja-Flores L, et al. *Blood*. 2019;134(24):2218-2222. 6. Garces JJ, et al. *J Clin Oncol*. 2022;40(27):3151-3161. 7. Bertamini L, et al. *J Clin Oncol*. 2022;40(27):3120-3131. 8. Guerrero C, et al. *Clin Cancer Res*. 2022;28(12):2598-2609. 9. Termini R, et al. *Clin Cancer Res*. 2022;28(21):4771-4781. 10. Jelinek T, et al. *J Clin Oncol*. 2023;41(7):1383-1392. 11. Kostopoulos IV, et al. *J Clin Oncol*. 2023;41(3):708-710. 12. Lasa M, et al. *J Clin Oncol*. 2025;43(2):125-132.

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# Inferior PFS in NDMM According to Progressively Higher CTC Log Levels

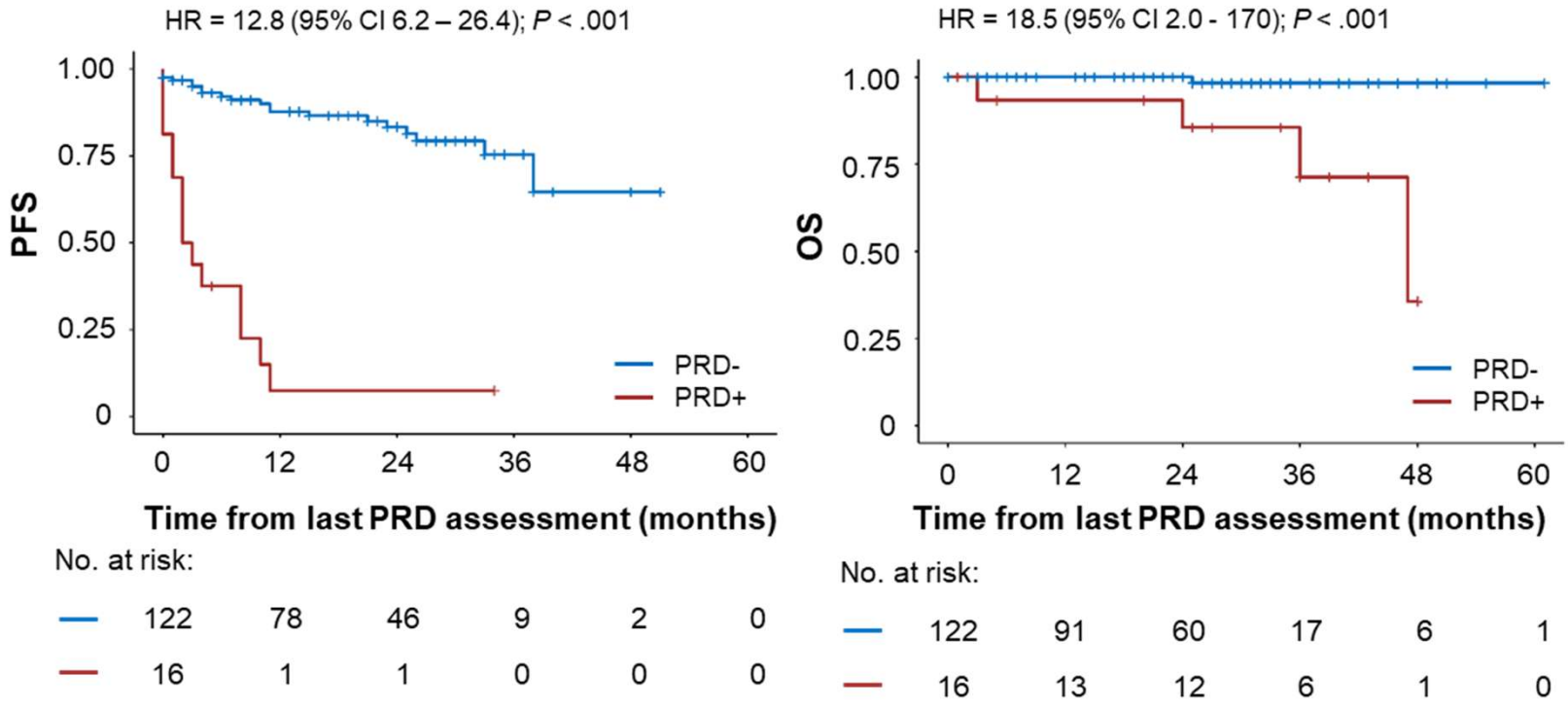



Bertamini L, et al. *Blood*. 2026;147(4):431-442.

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# Detection of CTCs by NGF as Prognostic Marker

## PETHEMA experience in the GEM2014MAIN clinical trial




NGF = next-generation flow cytometry; PRD = peripheral residual disease; PFS = progression-free survival; OS = overall survival.
Lasa M, et al. *J Clin Oncol*. 2025;43(2):125-132.

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# Key Learning Points



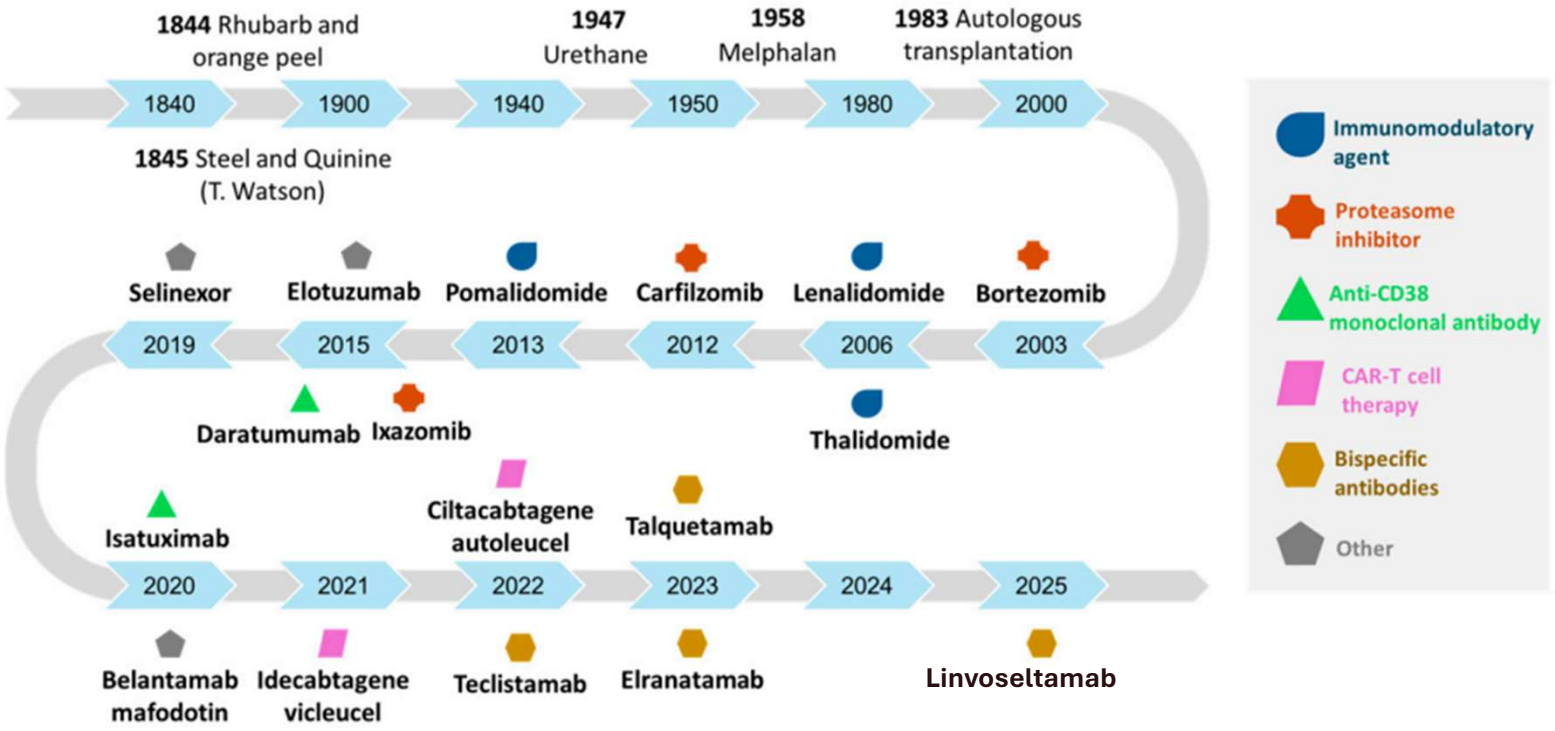
- The 2025 IMS-IMWG Consensus Genomic Staging (CGS) is the new standard for high-risk NDMM, validated in independent real-world cohorts (2026)
- Risk is driven by cytogenetic complexity (number of lesions) and functional response (MRD), not any single marker
- Prognostic markers should inform treatment intensity—quadruplets and intensified strategies for high-risk disease
- Most urgent implementation gap: making NGS-based genomic testing accessible in routine practice

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# Transplant-Eligible Patients: Induction Therapy and Consolidation

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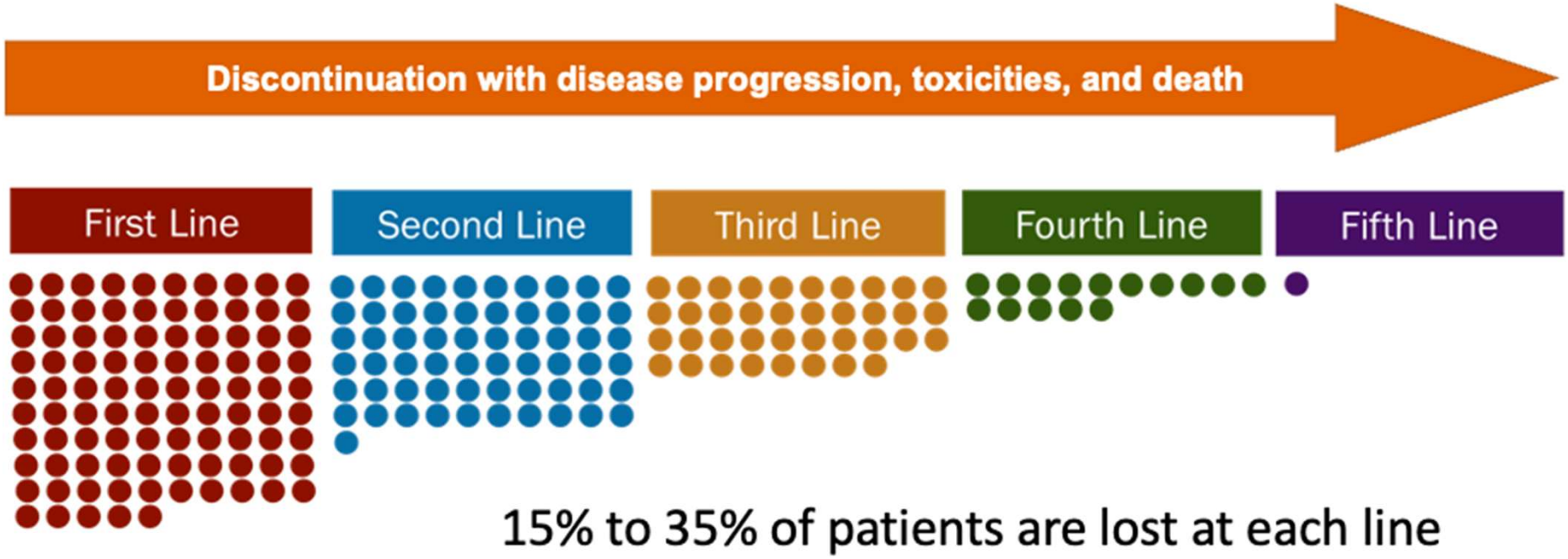
# MM Care Evolution: Drugs by Year of FDA Approval




Since 2025: belantamab mafodotin re-approval with Vd (Oct 2025, DREAMM-7) and teclistamab + daratumumab (Tec-Dara; Mar 2026, MajesTEC-3) for RRMM. FDA = US Food and Drug Administration.
Adapted from Besliu C, et al. *Cancers*. 2025;17(3):525.

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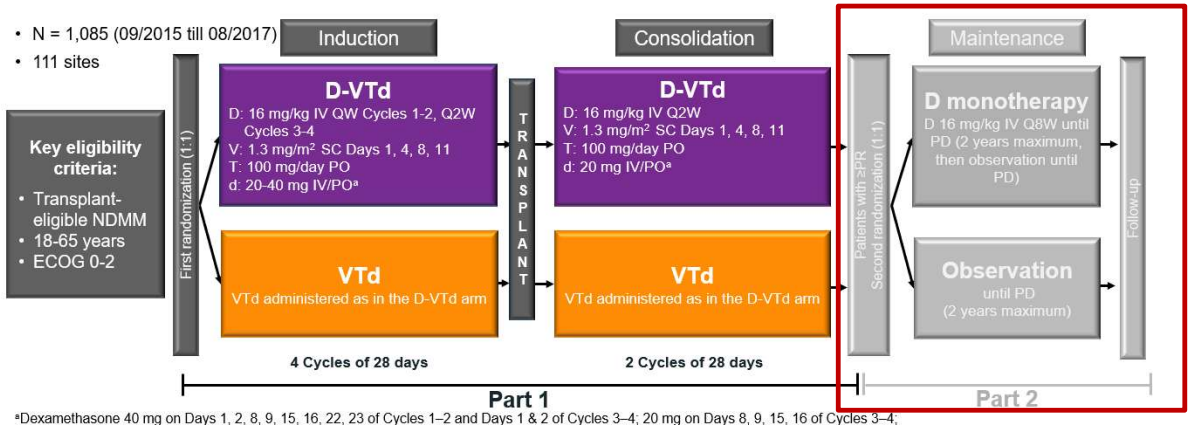
# Use Best Available Therapy in Every Line




Yong K, et al. *Br J Haematol*. 2016;175(2):252-264.

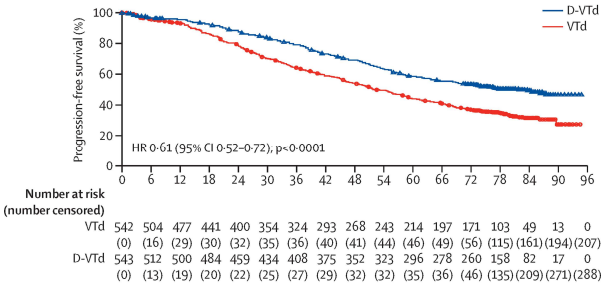
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# Where We Started: Dara-VTd vs VTd—CASSIOPEIA Trial (Phase 3, N=1,085 TE-NDMM)

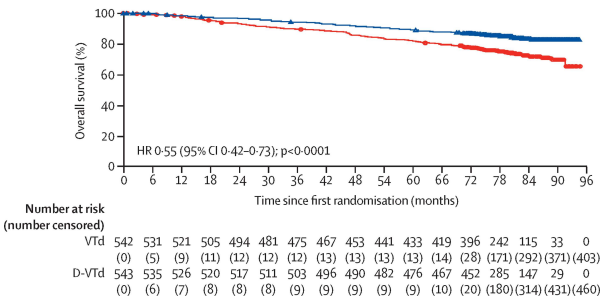



[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1–2 and Days 1 & 2 of Cycles 3–4; 20 mg on Days 8, 9, 15, 16 of Cycles 3–4.

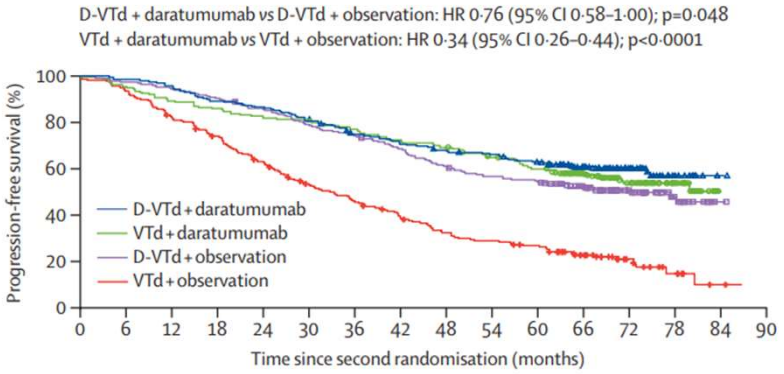
## PFS




## OS




## PFS from 2nd randomization




Update (2026): median follow-up 102.9 mo—PFS 87.8 vs 54.7 mo (HR 0.62); OS benefit confirmed (96-mo net survival 94.3% vs 80.7%).

CR = complete response; ECOG = Eastern Cooperative Oncology Group; OBS = observation; PD = progressive disease.

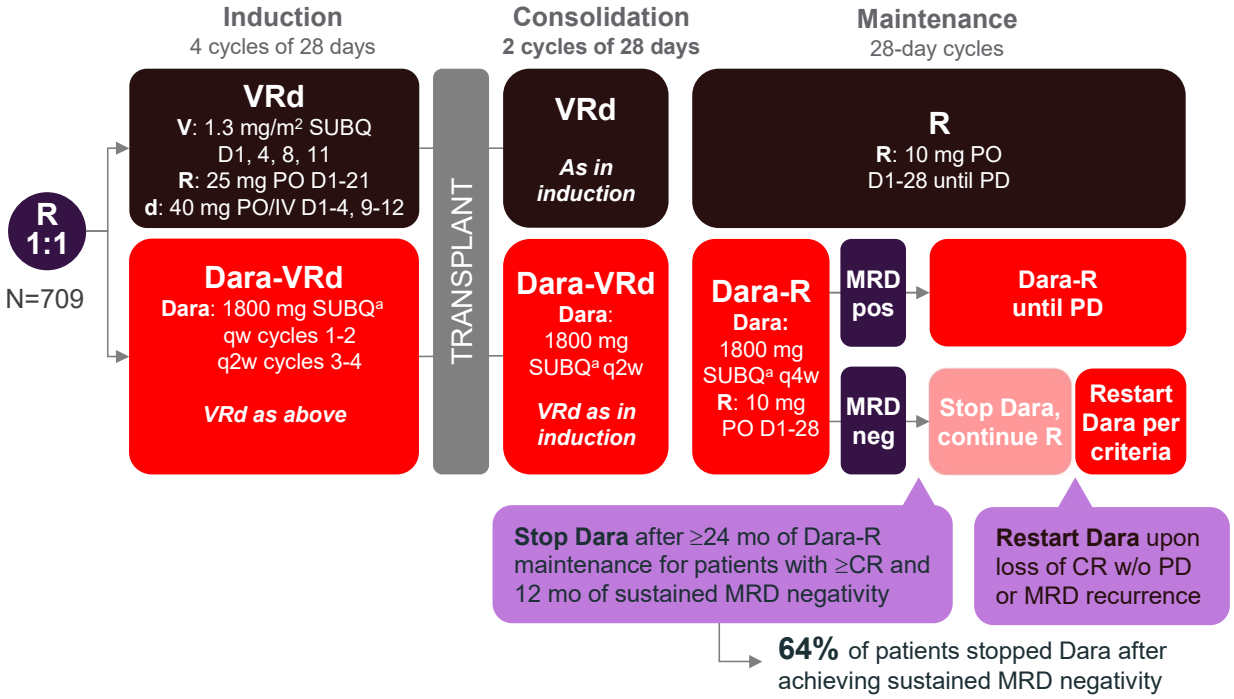
Moreau P, et al. *Lancet Oncol*. 2024;25(8):1003-1014. Magrangeas F, et al. *Blood Cancer J*. 2026;16:160. Avet-Loiseau H, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; 2021.

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# PERSEUS: Dara-VRd vs VRd

**Key Eligibility Criteria**

- Transplant-eligible NDMM; aged 18-70 years
- ECOG PS ≤2




**Primary endpoint**

- PFS

**Secondary endpoints**

- ≥CR, MRD negativity ($10^{-5}$), OS

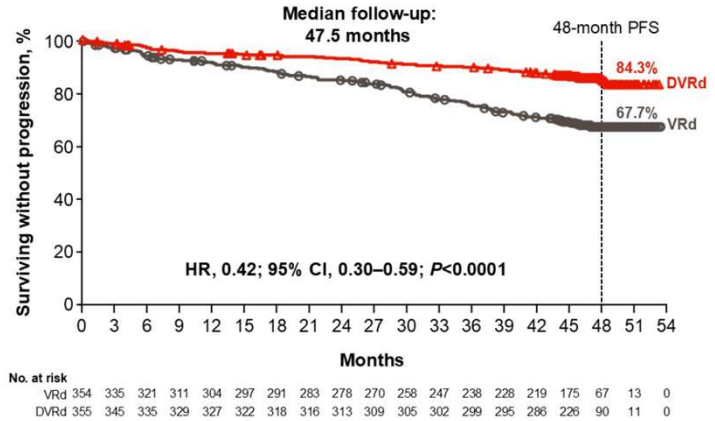
ECOG PS = ECOG performance status.

Sonneveld P, et al. Presented at: 23rd International Myeloma Society (IMS) Annual Meeting & Exposition; 2026. Abstract LBA-07.

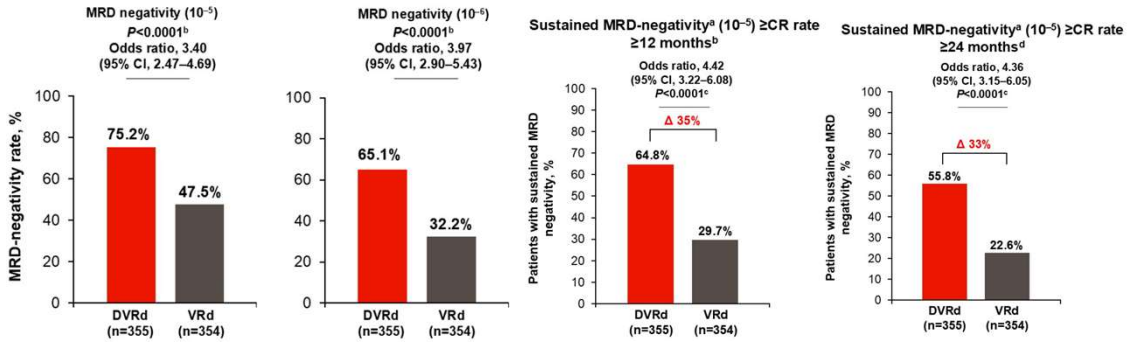
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# PERSEUS: Dara-VRd

## PFS by Treatment Arm




## Overall and Sustained MRD Negativity



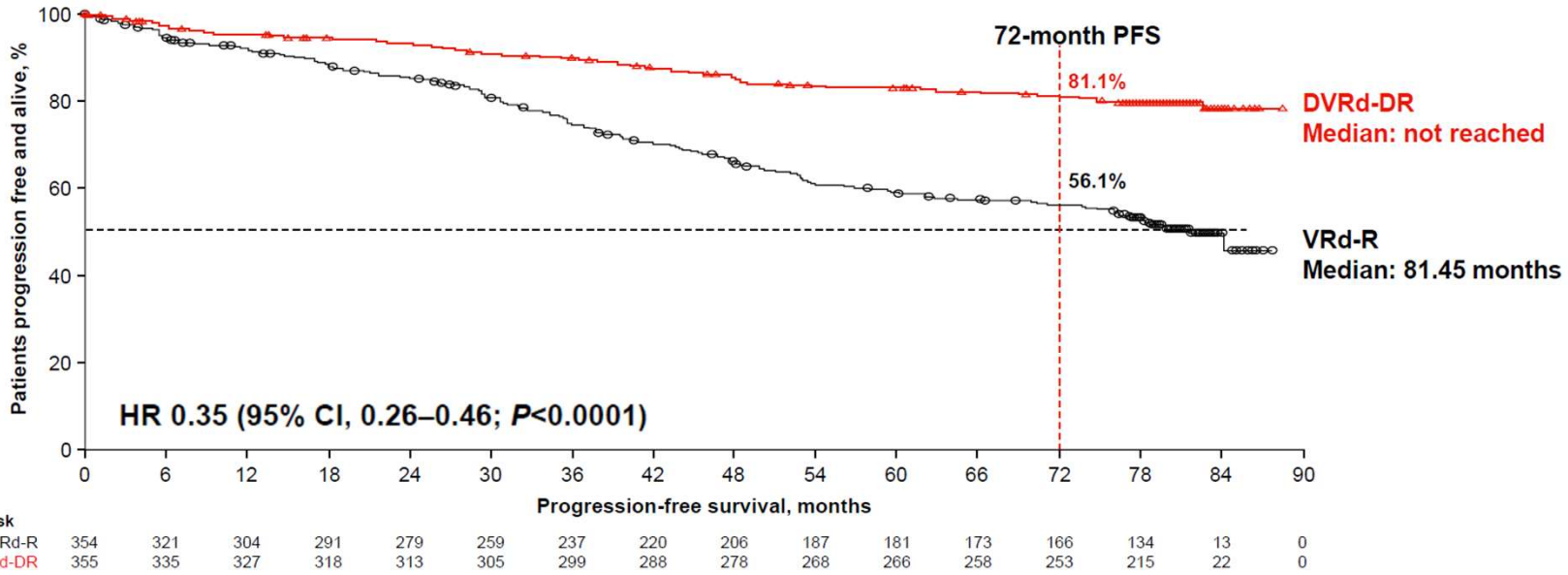

- Median follow-up: 47.5 months (ASCO/EHA 2025 update)
- Sustained MRD-neg ≥12 mo: 64.8% vs 29.7%; ≥24 mo: 55.8% vs 22.6% (Dara-VRd vs VRd)
- Maintenance: Dara-R may be discontinued after 24 months given CR + 12-month sustained MRD negativity

URTI = upper respiratory tract infection; ASCO = American Society of Clinical Oncology; EHA = European Hematology Association.
Sonneveld P, et al. Presented at: 29th EHA Congress; 2024.

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# Long-Term Outcomes from the Phase 3 PERSEUS Trial of Dara-VRd in TE NDMM

## Long-Term PFS



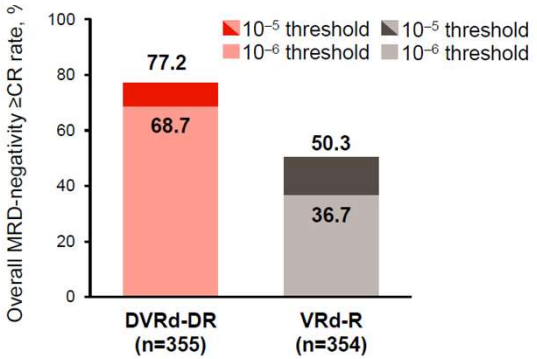

- Median follow-up: 81.3 months
- PFS benefit was consistent in clinically relevant subgroups, including by age and by risk categories

Data cutoff: June 1, 2026.
[a] High risk: ≥1 of del(17p), t(4;14), or t(14;16) by FISH.
Sonneveld P, et al. Presented at: 23rd IMS Annual Meeting & Exposition; 2026. Abstract LBA-07.

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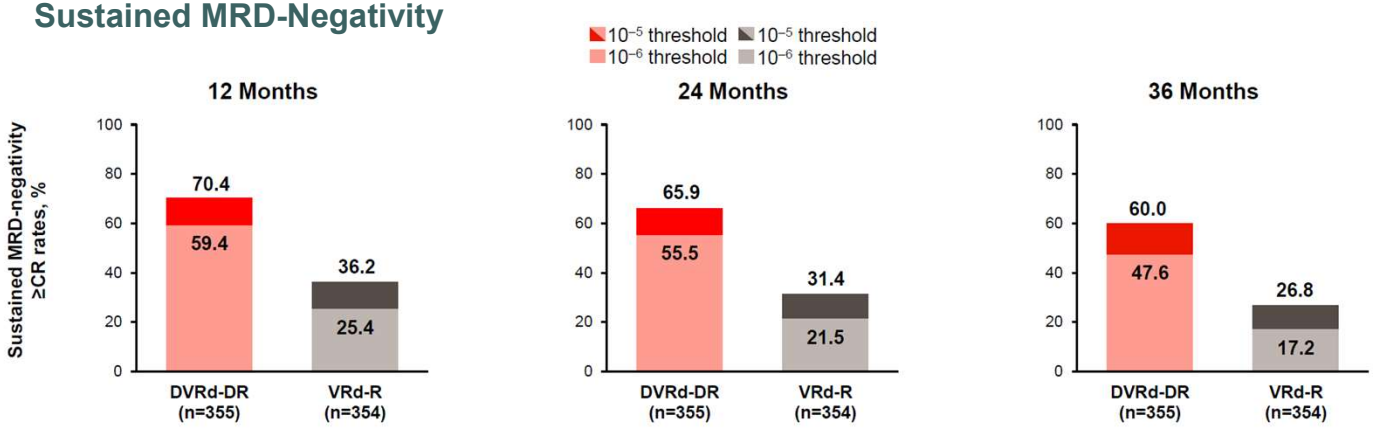
# Long-Term Outcomes from the Phase 3 PERSEUS Trial of Dara-VRd in TE NDMM: MRD Negativity and Guided Dara Stopping

## Overall MRD-Negativity ≥CR Rate




At $10^{-5}$: OR 3.41; 95% CI 2.46–4.73; *P*<0.0001
At $10^{-6}$: OR 3.88; 95% CI 2.83–5.31; *P*<0.0001

## Sustained MRD-Negativity




$10^{-5}$: OR 4.29; 95% CI 3.12–5.89; *P*<0.0001
$10^{-6}$: OR 4.40; 95% CI 3.19–6.08; *P*<0.0001

$10^{-5}$: OR 4.34; 95% CI 3.16–5.97; *P*<0.0001
$10^{-6}$: OR 4.69; 95% CI 3.36–6.55; *P*<0.0001

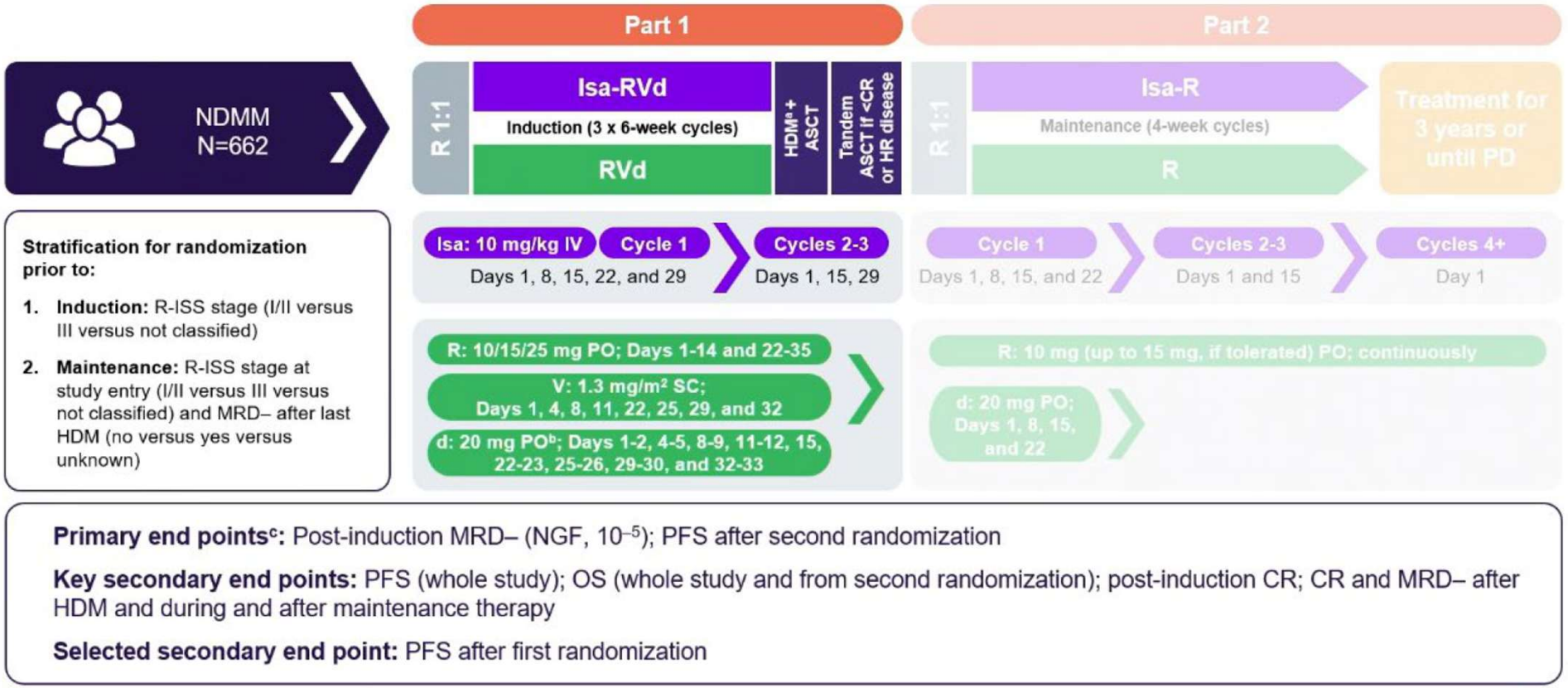
$10^{-5}$: OR 4.25; 95% CI 3.08–5.88; *P*<0.0001
$10^{-6}$: OR 4.47; 95% CI 3.15–6.34; *P*<0.0001

| MRD-Guided Dara Discontinuation, n (%) | DVRd-DR (n=351) |
|---|---|
| Subjects received maintenance treatment | 322 (91.7) |
| Subjects who have stopped daratumumab[a],[b] | 236 (73.3) |
| Subjects who have not restarted daratumumab[c],[d] | 175 (74.2) |
| Median duration of maintenance prior to stop[e], months (range) | 26.83 (24.5-68.5) |
| Median duration from daratumumab stop to CCO[f], months (range) | 44.06 (1.3-52.9) |

Data cutoff: June 1, 2026.
CCO = clinical cutoff.
Sonneveld P, et al. Presented at: 23rd IMS Annual Meeting & Exposition; 2026. Abstract LBA-07.

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# GMMG-HD7: Isa-VRd vs VRd



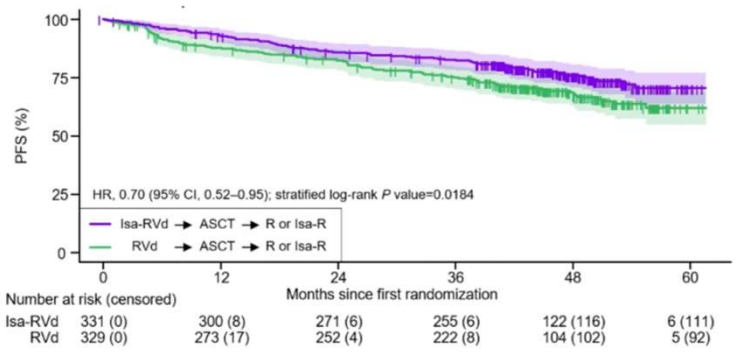

HDM = high-dose melphalan.

Goldschmidt H, et al. Presented at: 66th ASH Annual Meeting; 2024.

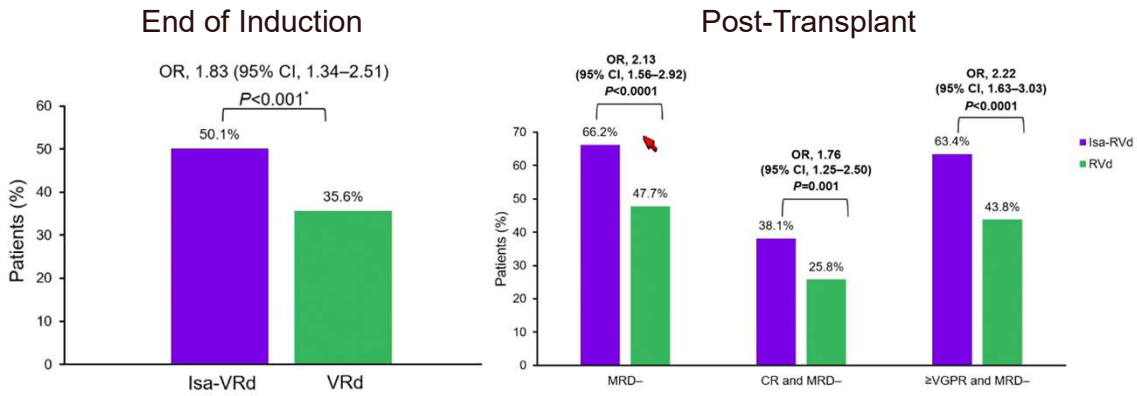
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# GMMG-HD7: Isa-VRd vs RVd

## PFS by Treatment Arm




## MRD Negativity ($10^{-5}$)

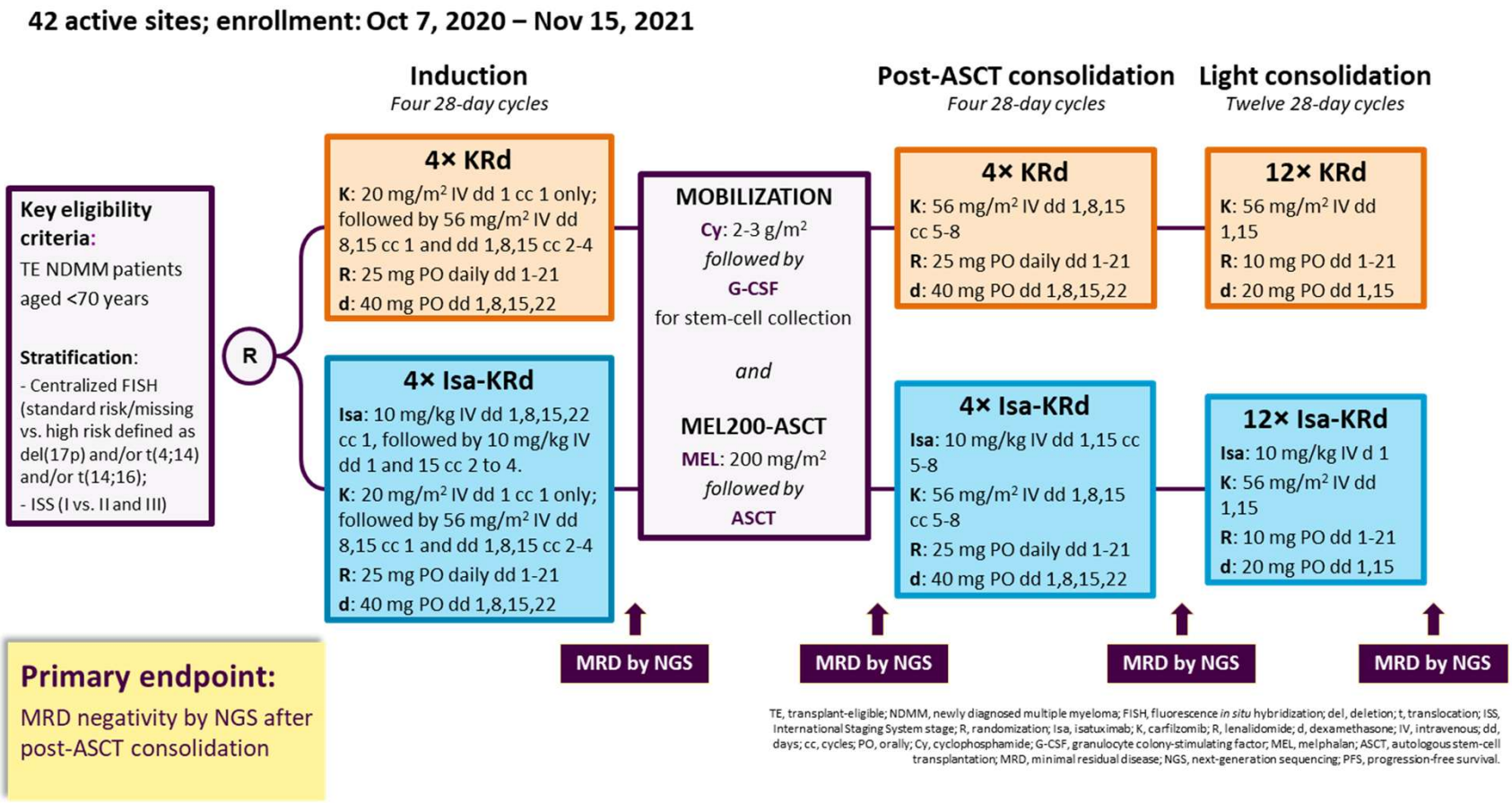



- Median follow-up: 48 months (phase 3, N=662, transplant-eligible NDMM)
- Final part 1 analysis: PFS HR 0.70 (Isa-RVd vs RVd); 3-/4-year PFS 83%/76% vs 75%/69%
- OS data not yet mature (per CHMP review, 2026); CHMP recommended EU approval of Isa-VRd for TE NDMM

CHMP = Committee for Medicinal Products for Human Use.
Goldschmidt H, et al. Presented at: 66th ASH Annual Meeting & Exposition; 2024.

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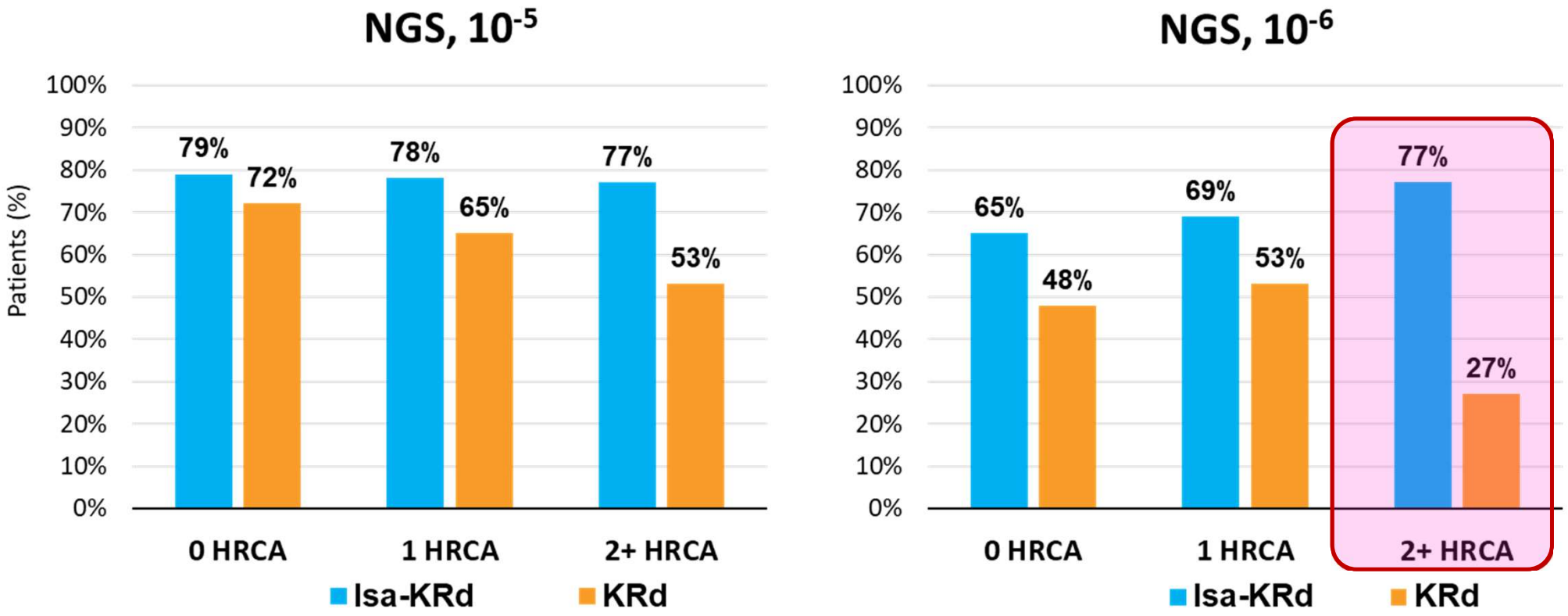
# Isa-KRd: Phase 3 ISKIA EMN24/HOVON Trial




Gay F, et al. Presented at: 65th ASH Annual Meeting & Exposition; 2023.

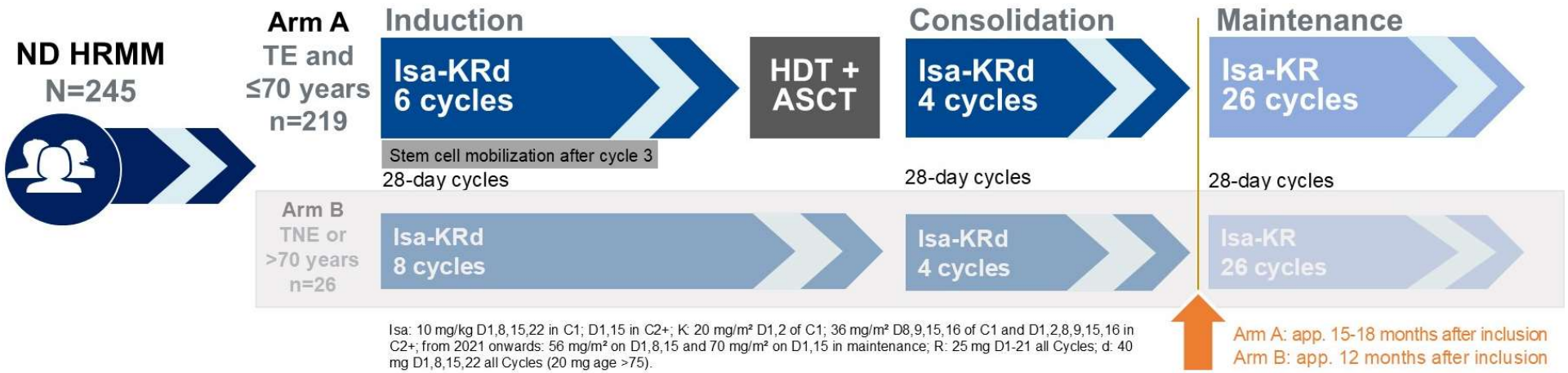
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# Post-Consolidation MRD Negativity by NGS: Subgroup Analysis by Cytogenetic Risk




1. HRCA was defined as the presence of one of the following high-risk cytogenetic abnormalities: del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21); 2+ HRCA was defined as the presence of at least two high-risk cytogenetic abnormalities.
**Update (ASCO/EHA 2025):** Phase 3, N=302 transplant-eligible NDMM. 1-year sustained MRD-neg (10-6): 52% Isa-KRd vs 38% KRd, retained across high-risk subgroups.
Gay F, et al. Presented at: 65th ASH Annual Meeting & Exposition; 2023. Gay F, et al. Presented at: EHA Congress; 2025.

# GMMG-Concept: Phase 2 Study of Isa-KRd in High-Risk NDMM



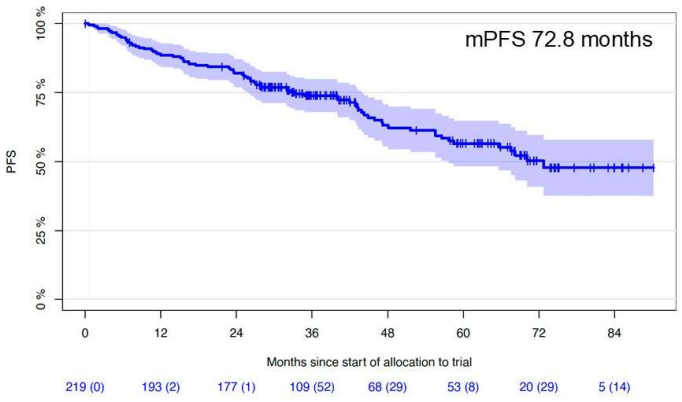

**HRMM criteria:** ISS stage II or III **PLUS** ≥1 of: del(17p), t(4;14), t(14;16) and/or ≥3 copies 1q21 (amp1q21)
Primary objective: MRD negativity after consolidation (NGF, $10^{-5}$)
Secondary objective: PFS; Selected tertiary objectives: ORR, OS

ORR = objective response rate.
Leypoldt L, et al. Presented at: ASCO Annual Meeting; 2025.

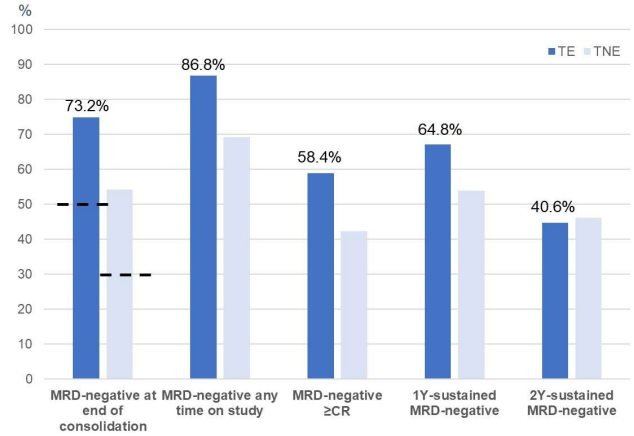
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# GMMG-Concept: Phase 2 Study of Isa-KRd in High-Risk NDMM

## PFS: TE NDMM




## MRD Negativity ($10^{-5}$)




- Median follow-up: 43 months. MRD-neg post-consolidation: 73.2% (58.4% also achieved ≥CR); PFS benefit with sustained MRD-neg (HR 0.15).
- Safety
  - Grade ≥3 infection: 28%
  - Grade ≥3 cardiac AEs: 2% (TE arm); 20% (TI arm)
- Carfilzomib dosing: once weekly (56 mg/m$^2$) vs twice weekly (36 mg/m$^2$) had more dose reductions but fewer carfilzomib discontinuations

mPFS = median PFS; TI = treatment-ineligible.
Leypoldt L, et al. Presented at: ASCO Annual Meeting; 2025.

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# Summary of Quad Induction in Transplant-Eligible NDMM

| | PERSEUS[1] | GMMG-HD7[2] | GRIFFIN[3,4] | MASTER[5] | GMMG-CONCEPT[6] | IsKia[7] | ADVANCE[8] |
|---|---|---|---|---|---|---|---|
| **Induction Maintenance** | **Dara-RVd vs RVd Dara-R vs R** | **Isa-RVd vs RVd Isa-R vs R** | **Dara-RVd vs RVd Dara-R vs R** | **Dara-KRd R/MRD surveillance** | **Isa-KRd Isa-KR** | **Isa-KRd vs KRd** | **Dara-KRd vs KRd** |
| **Total N** | 355 vs 354 | 331 vs 329 | 104 vs 103 | 123 | 99 (transplant eligible, high-risk disease) | 151 vs 151 | 153 vs 153 |
| **Median follow-up** | 47.5 mo | NA | 49.6 mo | 42.2 mo | 44 mo | 21 mo | 31.2 mo |
| **≥VGPR[a] ≥CR[a]** | NA 88% vs 70% | 83% vs 69% 44% vs 34% | 90% vs 73% 52% vs 42% | NA 72% | 91% 73% | 94% vs 94% 74% vs 72% | NA |
| **MRD-neg $10^{-5}$ [a]** | 75% vs 48% | 66% vs 48% | 50% vs 20% | 81% | 68% | 77% vs 67% | 59% vs 33% |
| **PFS[a]** | 4 year: 84% vs 68% | NA | 4 year: 87% vs 70% | NA | 3 year: 69% | 1 year: 95% vs 95% | 31.2 mo: 92% vs 83% |

The **ADVANCE** (Dara-KRd vs KRd) and **IsKia** trials are expected to further clarify the role of CD38 antibodies with carfilzomib-based induction, of high interest for patients with high-risk disease or intolerance to bortezomib

VGPR = very good partial response.

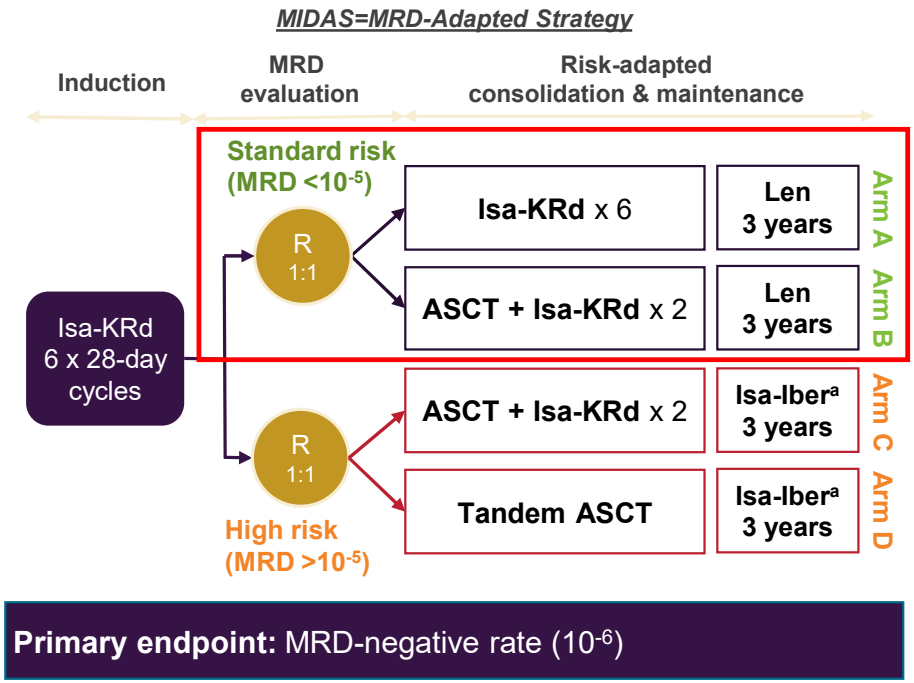
Table courtesy Vij R. Presented at: DAVA Oncology 12th Summit on Hematologic Malignancies; 2025. 1. Sonneveld P, et al. Presented at: ASH Annual Meeting; 2023. 2. Raab MS, et al. Presented at: EHA Congress; 2024. 3. Voorhees PM, et al. *Lancet Haematol*. 2023;10(10):e825-e837. 4. Sborov DW, et al. Presented at: IMS Annual Meeting; 2022. 5. Costa LJ, et al. *Lancet Haematol*. 2023;10(11):e890-e901. 6. Leypoldt LB, et al. *J Clin Oncol*. 2024;42(1):26-37. 7. Gay F, et al. Presented at: ASH Annual Meeting; 2023. 8. Landgren CO, et al. Presented at: ASCO Annual Meeting; 2025. Abstract 7503.

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# MIDAS = MInimal Residual Disease-Adapted Strategy

**Key Eligibility Criteria**

- Transplant eligible, NDMM, aged <66 years
- ECOG PS ≤2; no active cardiac disease

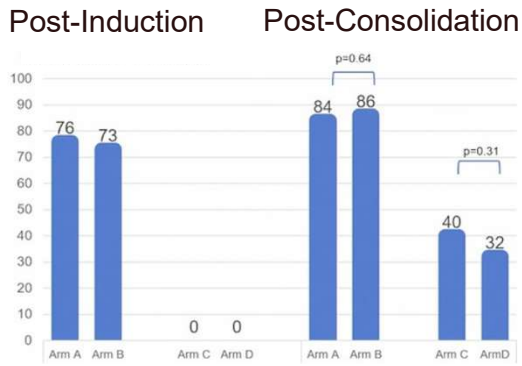



[a] Isa-Iber maintenance: isatuximab 10 mg/kg Q4W (initially IV, then SC) + iberdomide 1 mg QD on D1-21 of each 28-day cycle for up to 3 years.
Perrot A, et al. Presented at: 23rd IMS Annual Meeting & Exposition; 2026. Abstract OA-29.

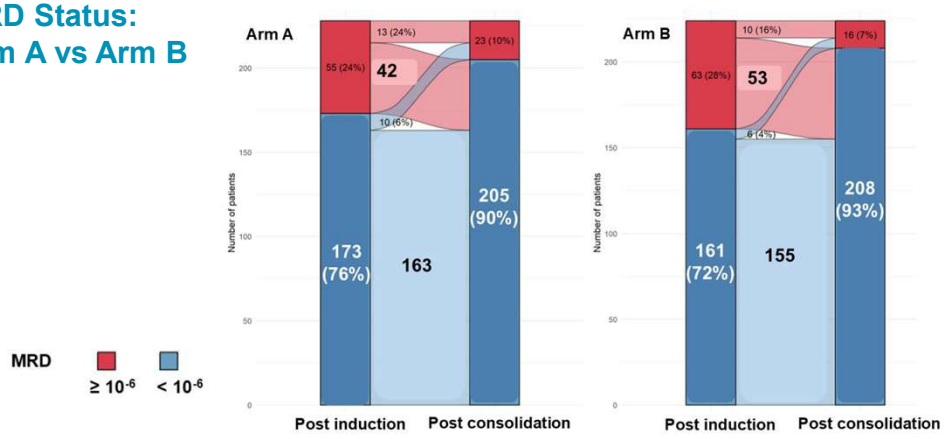
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# MIDAS = MInimal Residual Disease-Adapted Strategy

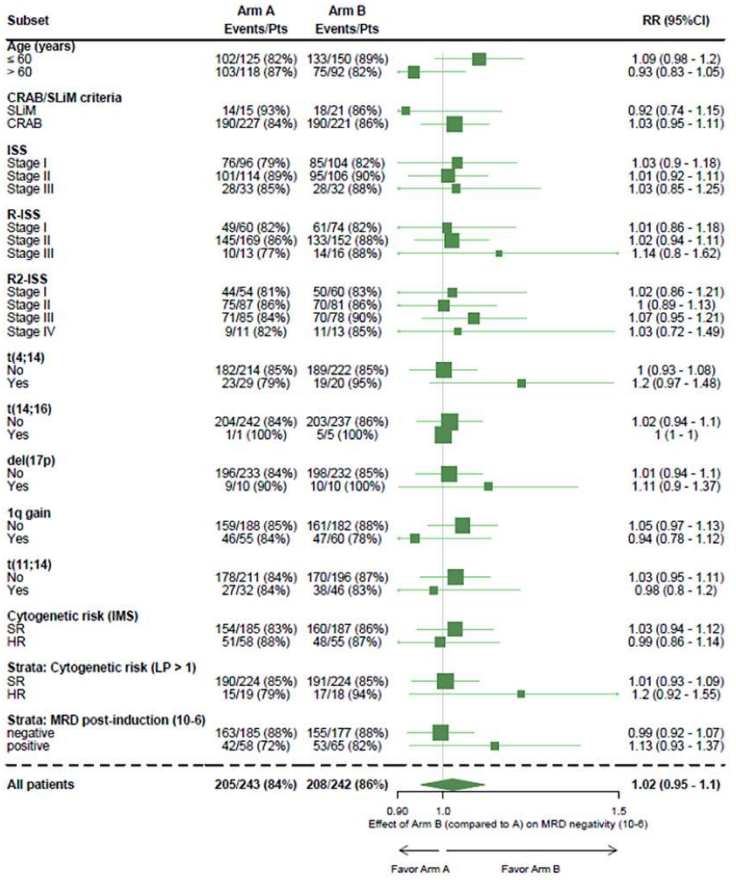
## MRD Negative ($10^{-6}$)




## MRD Status: Arm A vs Arm B




## MRD by Subgroups: Arm A vs B



| Subset | Arm A Events/Pts | Arm B Events/Pts | RR (95%CI) |
|---|---|---|---|
| **Age (years)** | | | |
| ≤ 60 | 102/125 (82%) | 133/150 (89%) | 1.09 (0.98 - 1.2) |
| > 60 | 103/118 (87%) | 75/92 (82%) | 0.93 (0.83 - 1.05) |
| **CRAB/SLiM criteria** | | | |
| SLiM | 14/15 (93%) | 18/21 (86%) | 0.92 (0.74 - 1.15) |
| CRAB | 190/227 (84%) | 190/221 (86%) | 1.03 (0.95 - 1.11) |
| **ISS** | | | |
| Stage I | 76/96 (79%) | 85/104 (82%) | 1.03 (0.9 - 1.18) |
| Stage II | 101/114 (89%) | 95/106 (90%) | 1.01 (0.92 - 1.11) |
| Stage III | 28/33 (85%) | 28/32 (88%) | 1.03 (0.85 - 1.25) |
| **R-ISS** | | | |
| Stage I | 49/60 (82%) | 61/74 (82%) | 1.01 (0.86 - 1.18) |
| Stage II | 145/169 (86%) | 133/152 (88%) | 1.02 (0.94 - 1.11) |
| Stage III | 10/13 (77%) | 14/16 (88%) | 1.14 (0.8 - 1.62) |
| **R2-ISS** | | | |
| Stage I | 44/54 (81%) | 50/60 (83%) | 1.02 (0.86 - 1.21) |
| Stage II | 75/87 (86%) | 70/81 (86%) | 1 (0.89 - 1.13) |
| Stage III | 71/85 (84%) | 70/78 (90%) | 1.07 (0.95 - 1.21) |
| Stage IV | 9/11 (82%) | 11/13 (85%) | 1.03 (0.72 - 1.49) |
| **t(4;14)** | | | |
| No | 182/214 (85%) | 189/222 (85%) | 1 (0.93 - 1.08) |
| Yes | 23/29 (79%) | 19/20 (95%) | 1.2 (0.97 - 1.48) |
| **t(14;16)** | | | |
| No | 204/242 (84%) | 203/237 (86%) | 1.02 (0.94 - 1.1) |
| Yes | 1/1 (100%) | 5/5 (100%) | 1 (1 - 1) |
| **del(17p)** | | | |
| No | 196/233 (84%) | 198/232 (85%) | 1.01 (0.94 - 1.1) |
| Yes | 9/10 (90%) | 10/10 (100%) | 1.11 (0.9 - 1.37) |
| **1q gain** | | | |
| No | 159/188 (85%) | 161/182 (88%) | 1.05 (0.97 - 1.13) |
| Yes | 46/55 (84%) | 47/60 (78%) | 0.94 (0.78 - 1.12) |
| **t(11;14)** | | | |
| No | 178/211 (84%) | 170/196 (87%) | 1.03 (0.95 - 1.11) |
| Yes | 27/32 (84%) | 38/46 (83%) | 0.98 (0.8 - 1.2) |
| **Cytogenetic risk (IMS)** | | | |
| SR | 154/185 (83%) | 160/187 (86%) | 1.03 (0.94 - 1.12) |
| HR | 51/58 (88%) | 48/55 (87%) | 0.99 (0.86 - 1.14) |
| **Strata: Cytogenetic risk (LP > 1)** | | | |
| SR | 190/224 (85%) | 191/224 (85%) | 1.01 (0.93 - 1.09) |
| HR | 15/19 (79%) | 17/18 (94%) | 1.2 (0.92 - 1.55) |
| **Strata: MRD post-induction (10-6)** | | | |
| negative | 163/185 (88%) | 155/177 (88%) | 0.99 (0.92 - 1.07) |
| positive | 42/58 (72%) | 53/65 (82%) | 1.13 (0.93 - 1.37) |
| **All patients** | **205/243 (84%)** | **208/242 (86%)** | **1.02 (0.95 - 1.1)** |



Premaintenance MRD-neg (10-6): 84% (Arm A) vs 86% (Arm B).
SLiM = greater than or equal to sixty percent clonal plasma cells in the bone marrow, involved/uninvolved free light chain (FLC) ratio of 100 or more with the involved FLC being greater than or equal 100 mg/L, magnetic resonance imaging (MRI) more than one focal marrow lesion; CRAB = increased calcium levels, renal insufficiency, anemia, presence of bone lesions.
Perrot A, et al. Presented at: ASCO Annual Meeting; 2025. Perrot A, et al. *N Engl J Med*. 2025;393(5):425-437.

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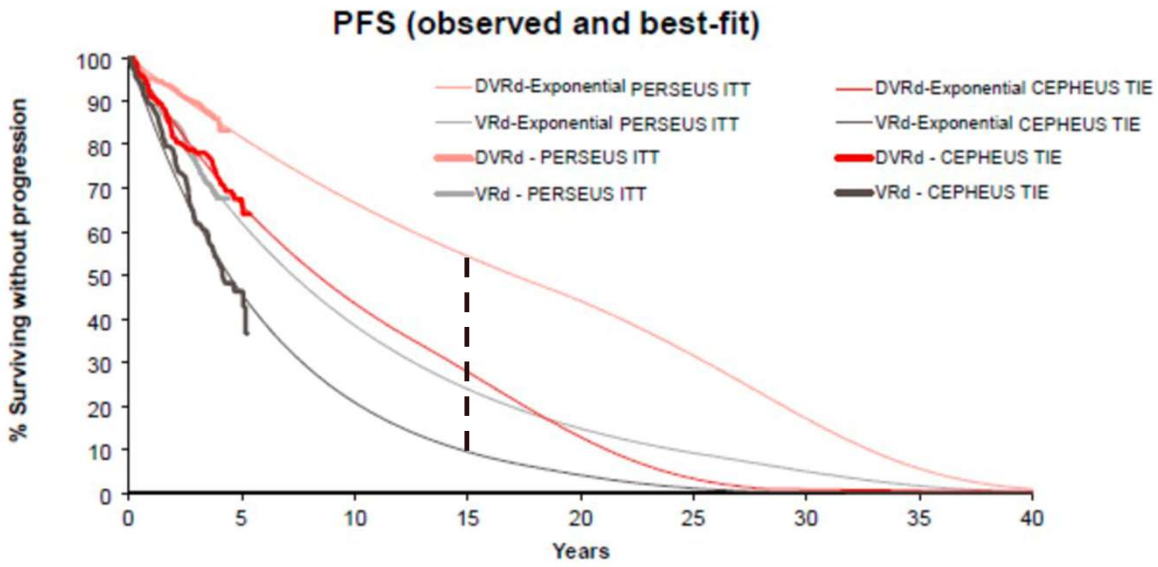
# MIDAS: Should We Stop HCT in MRD Neg?

- MIDAS—only one MRD time point; premaintenance MRD-neg rates similar with/without ASCT (84% vs 86%)
- PERSEUS—sustained MRD important; MIDAS PFS/OS follow-up still maturing
- MIDAS—high-risk cytogenetics still favor treatment intensification (tandem ASCT arm)

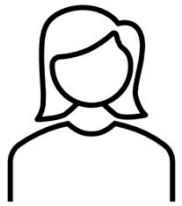
HCT = hematopoietic cell transplantation.

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# Myeloma Outcomes Are Changing Rapidly→Changing Perspectives for Physicians and Patients




Median estimated PFS PERSEUS: 17 years



**“Am I going to be on treatment the entire 17 years?”**

**“Will long-term treatment side effects risk my survivorship?”**

**“What are the long-term side effects of 17 years’ continuous treatment?”**

Sonneveld P, et al. Presented at: 6th European Myeloma Network (EMN) Meeting; 2025.

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# Transplant-Eligible Patients: Post-ASCT Maintenance Approaches

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# Ongoing Question: Should We Intensify Maintenance?

- Current state: deepens response, prolongs response, prolongs survival
- Lenalidomide until disease progression
- Future state
  - Single-agent antibody (Cd38, BisAb)
  - Doublet (CD38 + Len)
  - Triplet (CD38 + Len + PI)
  - Fixed duration; MRD guided

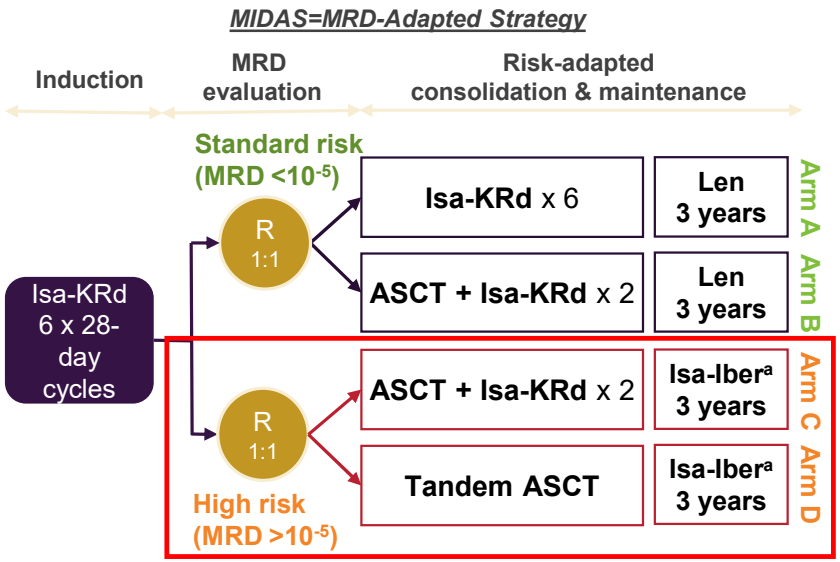
BisAb = bispecific antibody; PI = protease inhibitor.

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# First-Year Results of Isa-Iber Maintenance in MRD-Positive NDMM from the Phase 3 MIDAS Trial: Study Design and Patient Characteristics

**Key Eligibility Criteria**

- Transplant eligible, NDMM, aged <66 years
- ECOG PS ≤2; no active cardiac disease




**Primary endpoint:** MRD-negative rate ($10^{-6}$)

| Characteristic | Arm C (n=109) | Arm D (n=124) |
|---|---|---|
| Median age, years [range] | 57.5 [36-65] | 58.3 [33-65] |
| Age ≥60 years | 35 (32%) | 47 (38%) |
| Male sex | 58 (53%) | 75 (60%) |
| ECOG performance status 0-1 | 100 (91%) | 111 (90%) |
| ISS stage I-II | 100 (92%) | 113 (91%) |
| t(11;14) | 43 (41%) | 59 (49%) |
| High-risk cytogenetics (IMS/IMWG definition) | 18 (17%) | 29 (23%) |
| ≥VGPR after induction | 96 (88%) | 113 (91%) |

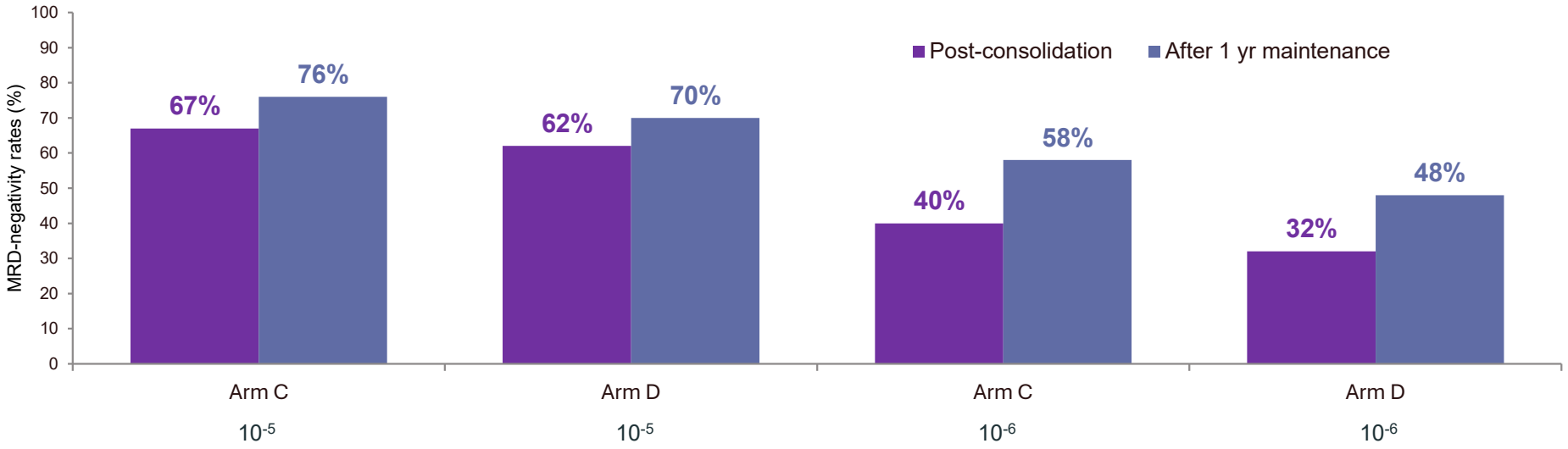
[a] Isa-Iber maintenance: isatuximab 10 mg/kg Q4W (initially IV, then SC) + iberdomide 1 mg QD on D1-21 of each 28-day cycle for up to 3 years.

Perrot A, et al. Presented at: 23rd IMS Annual Meeting & Exposition; 2026. Abstract OA-29.

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# First-Year Results of Isa-Iber Maintenance in MRD-Positive NDMM from the Phase 3 MIDAS Trial: MRD-Negativity Rates

## MRD-Negativity Rates of Post-Consolidation vs Year 1 of Maintenance



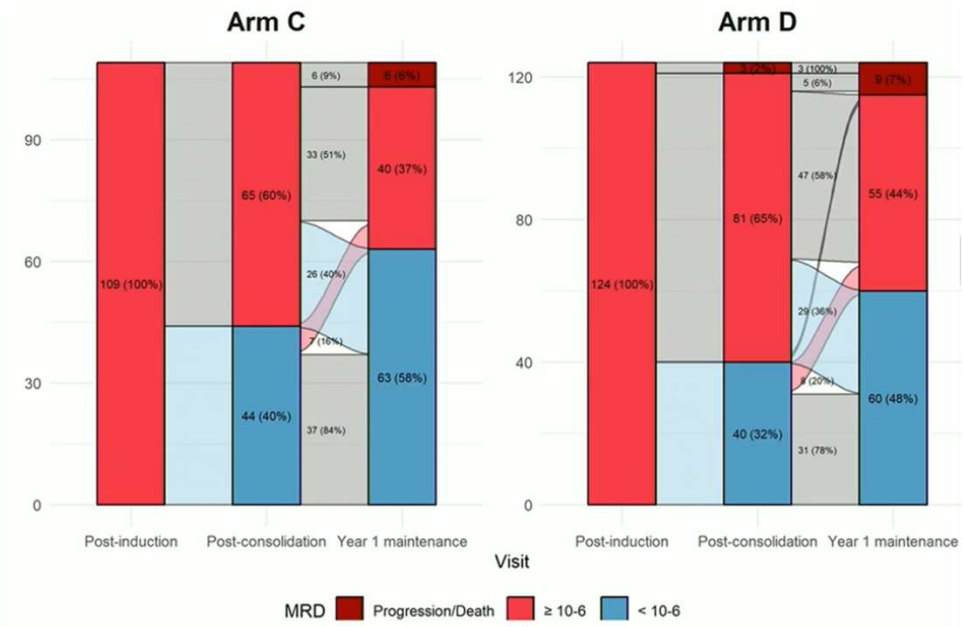

MRD negativity rates improved from post-consolidation to one year of Isa-Iber maintenance in both arms.

Perrot A, et al. Presented at: 23rd IMS Annual Meeting & Exposition; 2026. Abstract OA-29.

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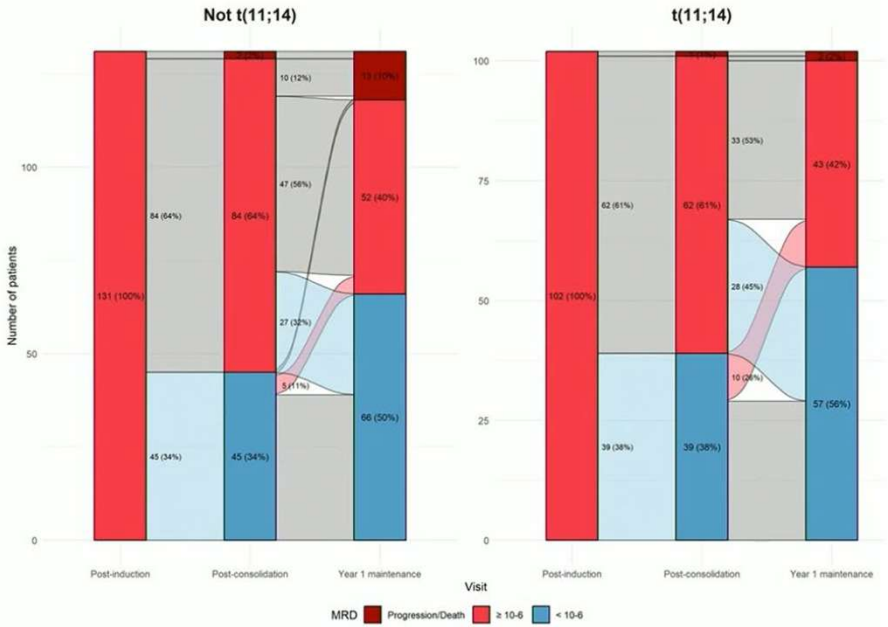
# First-Year Results of Isa-Iber Maintenance in MRD-Positive NDMM from the Phase 3 MIDAS Trial: MRD Conversion

## MRD Conversion




- Among 146 patients who remained MRD+ at $10^{-6}$ at the end of consolidation
  - **55 (37.7%) patients converted from MRD-positive to MRD-negative ($10^{-6}$) during the first year of Isa-Iber maintenance**
  - MRD conversion occurred in both arms
  - During first year of maintenance, 5 progressions + 1 death occurred in each arm

## MRD Conversion by t(11;14) Status



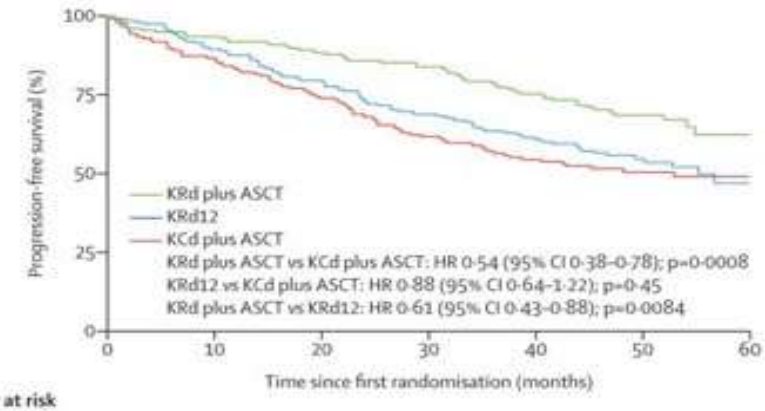

- Among 62 patients with t(11;14) who remained MRD+ after consolidation, 45% converted to MRD- ($10^{-6}$)
- Among 84 patients without t(11;14) who remained MRD+ after consolidation, 32% converted to MRD- ($10^{-6}$)

Perrot A, et al. Presented at: 23rd IMS Annual Meeting & Exposition; 2026. Abstract OA-29.

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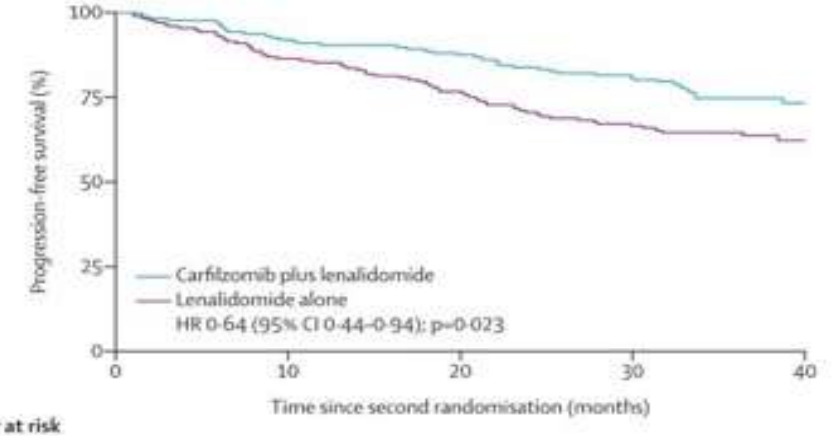
# FORTE Trial: PFS Doublet Maintenance

## PFS from 1st randomization




| Number at risk (number censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| KRd plus ASCT | 158 (0) | 147 (1) | 137 (3) | 129 (4) | 111 (9) | 61 (51) | 5 (103) |
| KRd12 | 157 (0) | 135 (6) | 120 (6) | 103 (7) | 90 (9) | 51 (39) | 5 (81) |
| KCd plus ASCT | 159 (0) | 137 (1) | 115 (3) | 94 (5) | 80 (8) | 46 (37) | 6 (76) |

## PFS from 2nd randomization

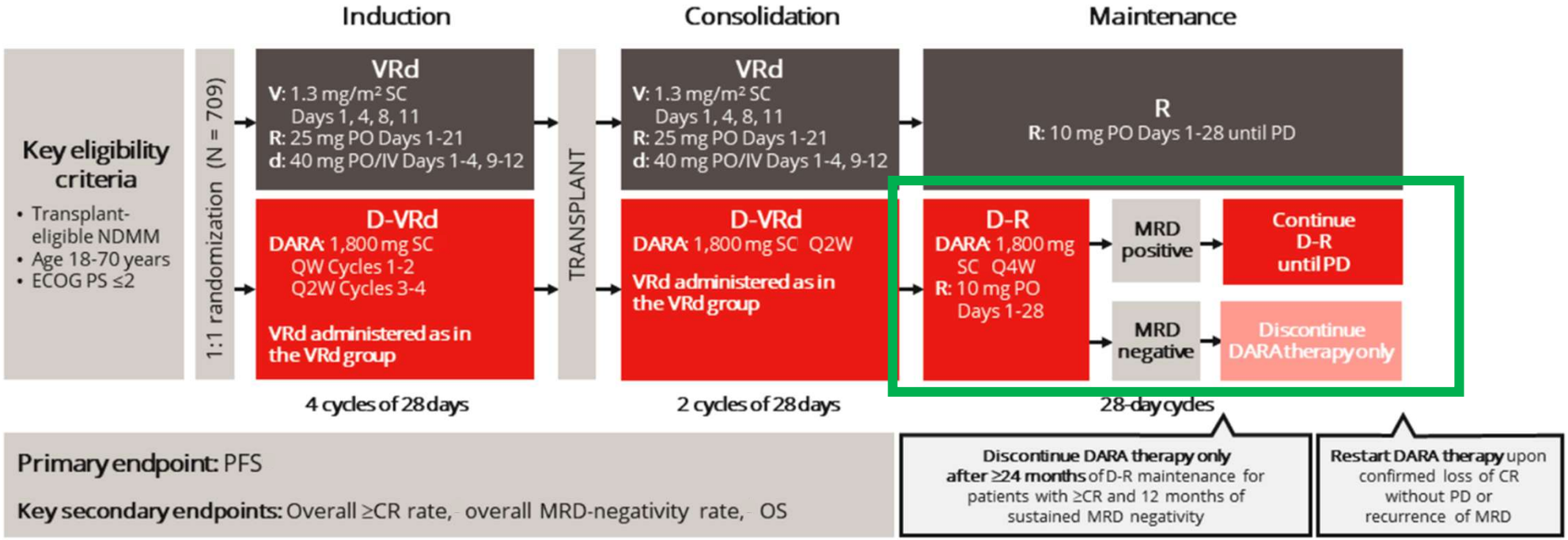



| Number at risk (number censored) | | | | | |
|---|---|---|---|---|---|
| Carfilzomib plus lenalidomide | 178 (1) | 162 (2) | 151 (5) | 123 (22) | 41 (95) |
| Lenalidomide alone | 178 (0) | 154 (0) | 135 (2) | 108 (11) | 39 (75) |

FORTE: Phase 2, N=474 transplant-eligible NDMM. Update: phase 3 ATLAS trial (2026) confirms KRd maintenance improves PFS and OS vs Rd alone, with high-risk cytogenetics deriving particular benefit.
Gay F, et al. *Lancet*. 2021;22(12):1705-1720. Dytfeld D, et al. *Lancet Haematol.* 2026;13(4):E241-E253.

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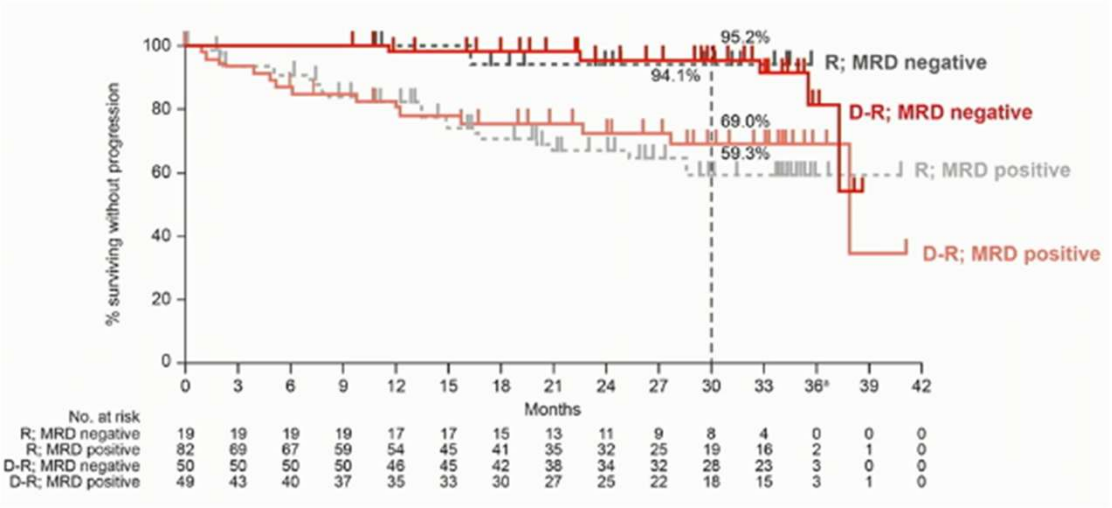
# Perseus: Double Maintenance in the D-VRd Arm!

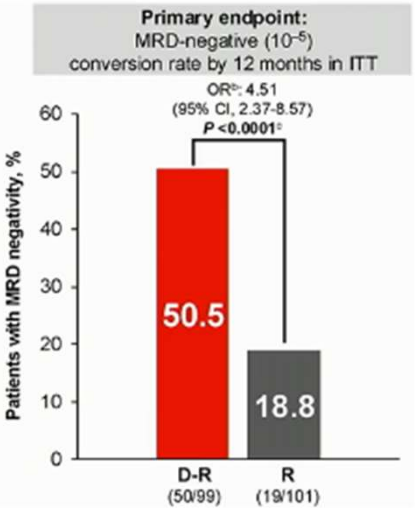


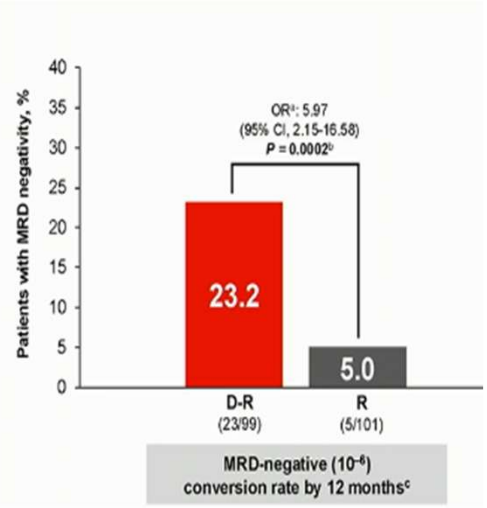

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated February 10, 2026. https://clinicaltrials.gov/study/NCT03710603.

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# AURIGA: MRD-Neg Conversion ($10^{-5}$ and $10^{-6}$) and PFS by MRD-Neg Conversion Status at 12 Months



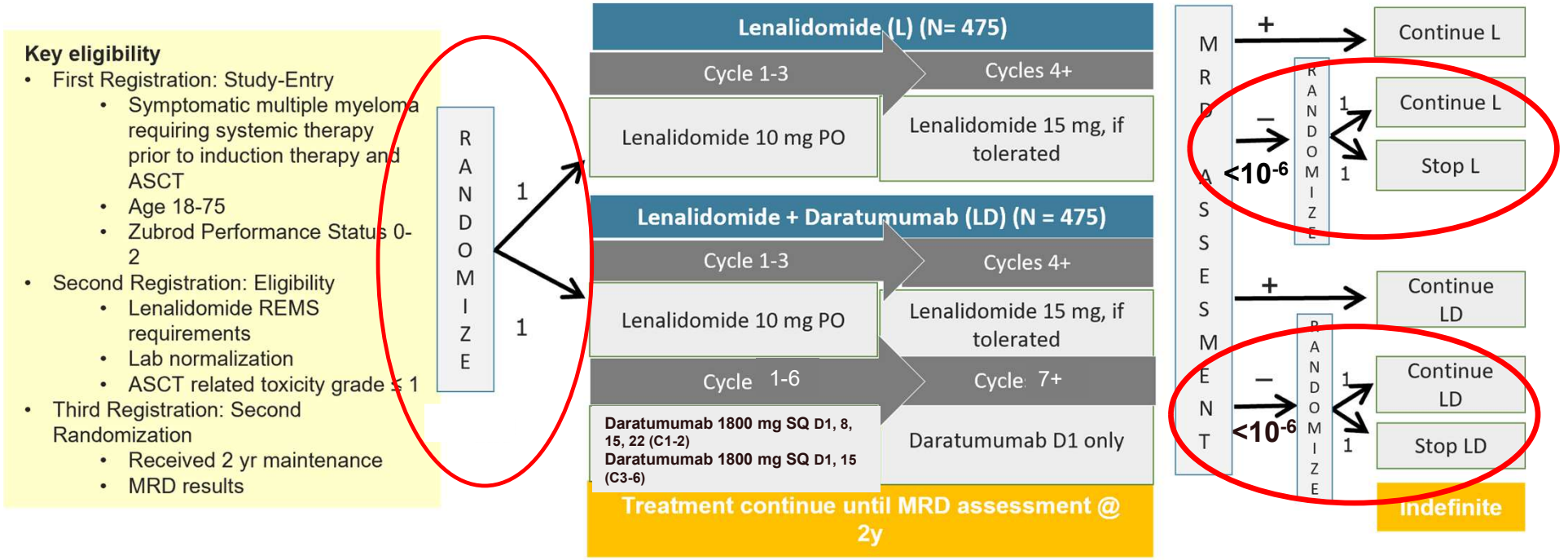




AURIGA: Phase 3, post-ASCT dara-R vs R maintenance in transplant-eligible NDMM.
Badros A, et al. *Blood*. 2025;145(3):300-310.

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# DRAMMATIC Trial Schema




- Registration Step 1: *baseline specimen for ID (B-cell clonality) mandatory
- Registration Step 2: within 180 days after ASCT (***1st randomization***)
- Registration Step 3: completed 24 months of maintenance and MRD-neg + ≥VGPR (*<$10^{-6}$) (***2nd randomization***)

REMS = risk evaluation and mitigation strategy.
Slide courtesy Krishnan A. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 17, 2026. https://clinicaltrials.gov/study/NCT04071457.

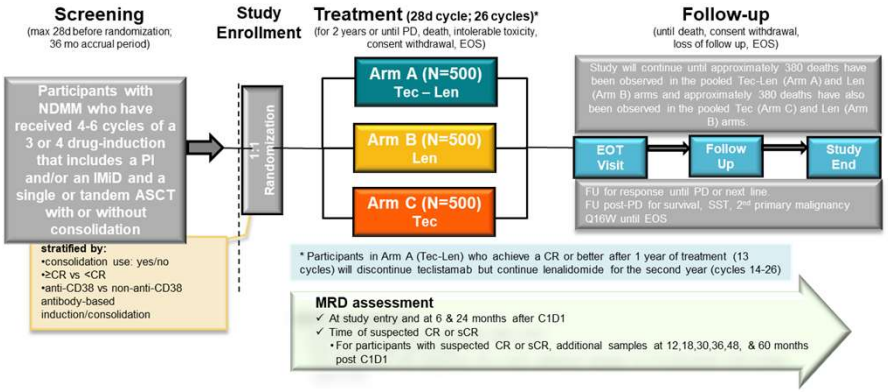
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# Transplant-Eligible Patients: Quadruplet and Emerging Combinations

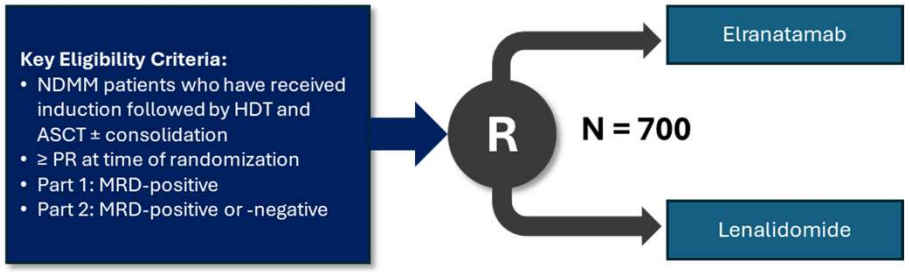
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# Frontline Immunotherapies for TE NDMM Patients

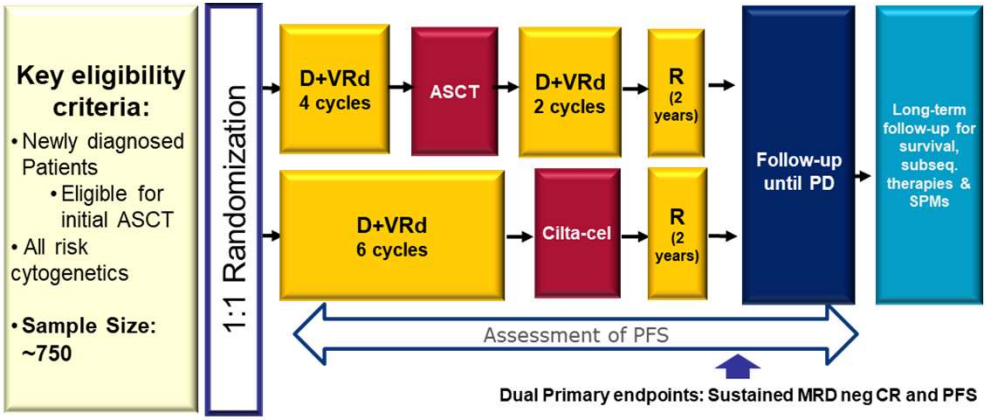
## MajesTEC-4




## MagnetisMM-7




## CARTITUDE-6

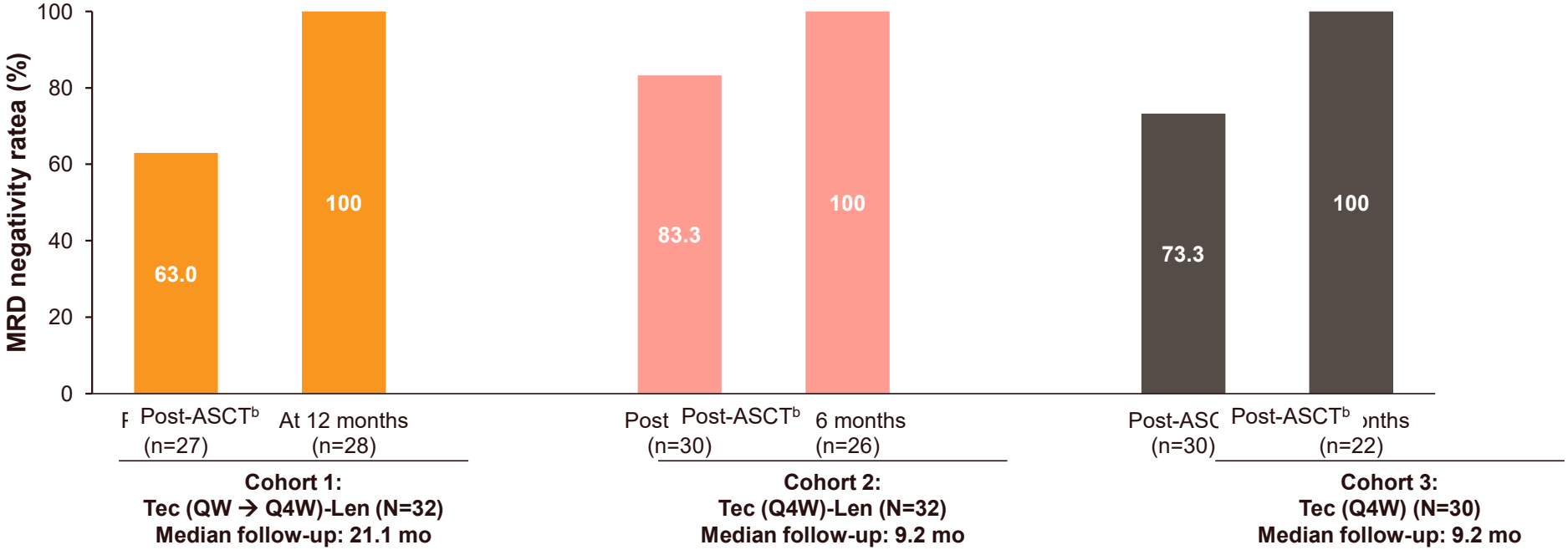



PI = proteasome inhibitor; IMiD = immunomodulatory drug; SPM = subsequent primary malignancy; EOS = end of study; FU = follow-up; SST = secondary solid tumor.

**Update (ASH 2025):** The phase 2 IMMUNOPLANT trial showed MRD-adaptive linvoseltamab consolidation converted persistent MRD positivity after quad induction to MRD negativity in all evaluable patients. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated August 17, 2025. Accessed August 6, 2024. https://clinicaltrials.gov/study/NCT05243797. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 10, 2025. Accessed August 6, 2024. https://clinicaltrials.gov/study/NCT05317416. ClinicalTrials.gov [www.clinicaltrials.gov]. Updated September 12, 2025. Accessed August 6, 2024. https://clinicaltrials.gov/study/NCT05257083. Kazandjian D, et al. *Blood*. 2025;146(Suppl 1):248.

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# EMN30/MajesTEC-4 SRI: MRD Negativity ($10^{-5}$) in Evaluable Patients Post-ASCT and during Maintenance




**100% of evaluable patients were MRD-negative during maintenance.**

Data cutoff date: September 9, 2024.

[a]MRD-negativity rate was defined as the proportion of patients who achieved MRD negativity ($10^{-5}$), regardless of response. Percentages are out of evaluable patients. Among 87 evaluable patients, 23 patients were MRD-positive at screening (cohort 1, n=10; cohort 2, n=5; cohort 3, n=8). All patients who were MRD-positive at study entry and had an assessment during treatment were MRD-negative during treatment. One patient in cohort 1 was MRD-positive at 18 months. [b]Post-ASCT ± consolidation. Update (EHA 2026, van de Donk, et al): Cohort 1 at 35.3-mo follow-up—100% MRD-negative CR rate on maintenance; estimated 18-/24-month PFS 94%-97% across cohorts, with only 3 progression events reported.

SRI = safety run-in.

Van de Donk NWCJ, et al. Presented at: EHA Congress; 2026.

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# Key Learning Points



- **Quadruplet induction** (dara- or isa-based) is now SOC in transplant-eligible NDMM—confirmed by mature PERSEUS, GMMG-HD7, and IsKia data
- Transplant remains a backbone for most patients; MIDAS suggests upfront ASCT may not be essential in MRD-negative patients, but longer follow-up and high-risk subgroup data are needed
- **MRD-guided**, intensified, and/or fixed-duration maintenance strategies (FORTE, CASSIOPEIA, AURIGA, PERSEUS, DRAMMATIC) are reshaping the post-transplant paradigm → **Double maintenance for MRD+?**
- Future SOC: T-cell-directed frontline immunotherapy (bispecifics, CAR T) and MRD-adaptive consolidation strategies for transplant-eligible NDMM

SOC = standard of care.

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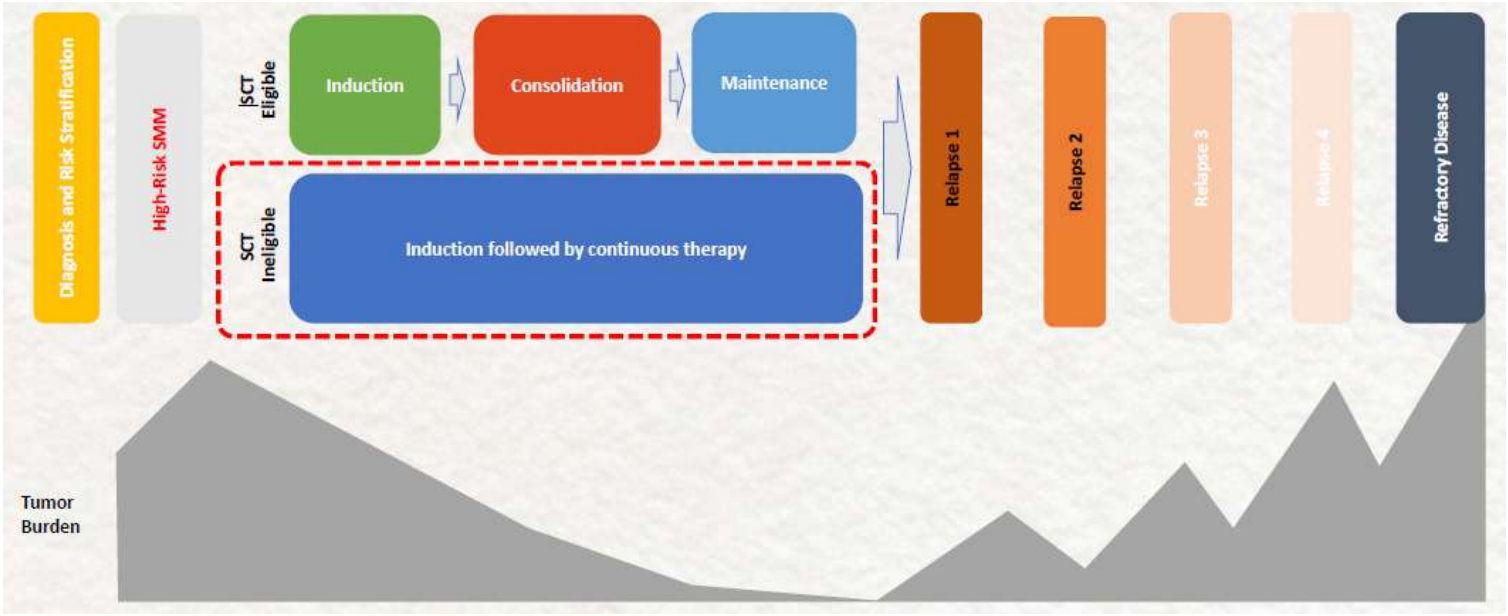
# Transplant-Ineligible or Deferred Patients

**Cesar Rodriguez, MD**

*Associate Professor of Medicine (Hematology and Medical Oncology)*
*Icahn School of Medicine at Mount Sinai*
*New York City, New York*

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# Initial Treatment of Myeloma




What factors make someone forego stem cell transplant?

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# Factors That Would Favor Omitting Transplant

- Comorbidities
- Frailty
- Limited social support
- Personal preference

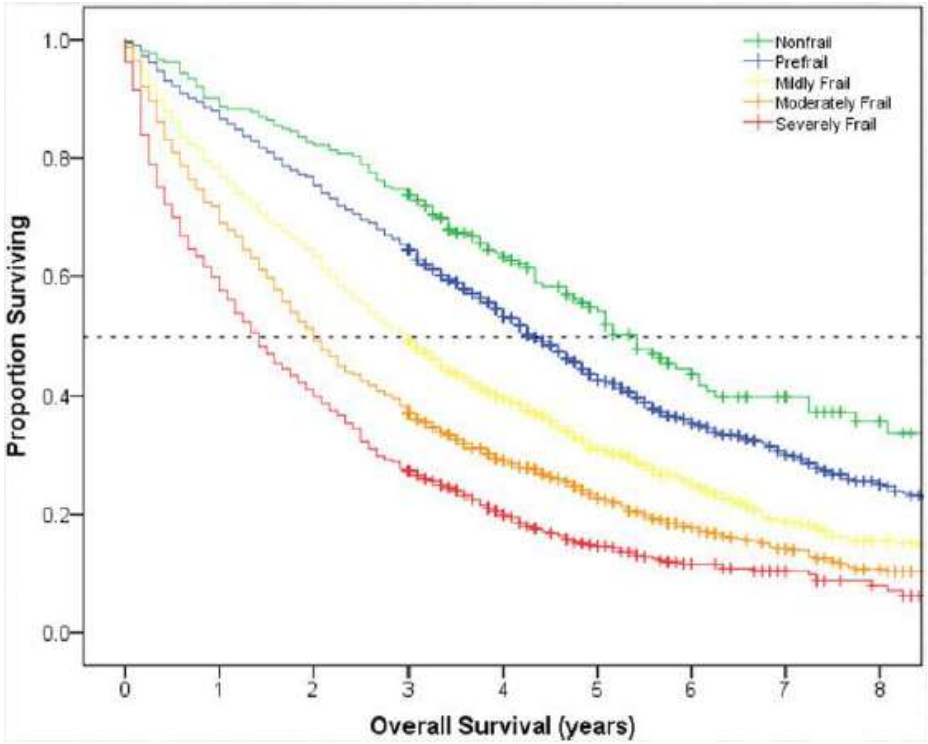
| Tool | Components | Stratification | Key Advantage | Limitation |
|---|---|---|---|---|
| **IMWG-FI** | Age, ADL, IADL, CCI | Fit, Int-Fit, Frail | Extensively validated, true geriatric focus | Time-consuming to administer in clinic. |
| **Simplified FI** | Age, ECOG, CCI | Non-Frail, Frail | Rapid, easiest for daily clinical use | Relies on subjective ECOG PS. |
| **MRP** | Age, ECOG, CRP, ISS | Low, Med, High Risk | Objective, captures tumor/inflammatory burden | Misses purely functional/geriatric deficits. |
| **Mayo Score** | Age, ECOG, NT-proBNP | Stages I - IV | Includes specific cardiac/renal biomarker | Requires specific lab draws (NT-proBNP). |

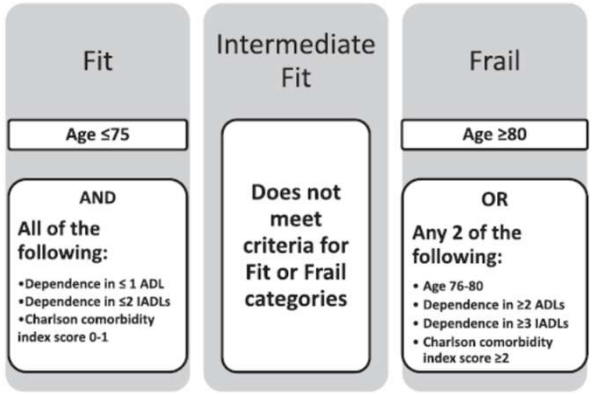
FI = frailty index; MRP = UK Myeloma Alliance Risk Stratification; ADL = activity of daily living; IADL = instrumental ADL; CCI = Charlson comorbidity index; NT-proBNP = aminoterminal pro B-type natriuretic peptide.

Sim S, et al. *Intern Med J.* 2023;53(5):819-824. Larocca A, et al. *Cancers (Basel).* 2023;15(10):2693.

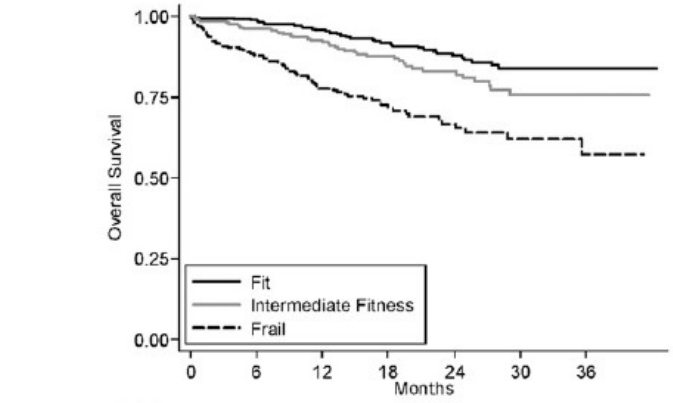
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# Impact of Frailty




*ADL, activities of daily living; IADLs, instrumental activities of daily living*



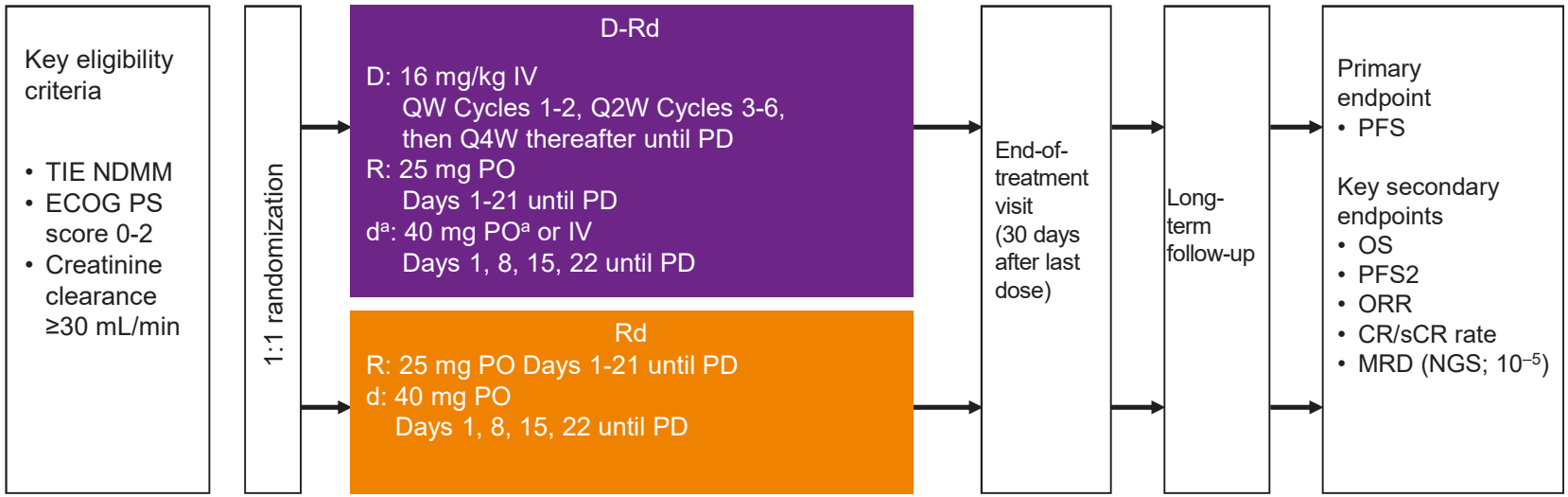

| At risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fit | 340 | 323 | 248 | 182 | 133 | 84 | 43 |
| Intermediate Fitness | 269 | 242 | 183 | 123 | 83 | 47 | 15 |
| Frail | 260 | 209 | 151 | 91 | 52 | 27 | 12 |

Mian H, et al. *Blood Cancer J.* 2023;13(1):76. Palumbo A, et al. *Blood*. 2015;125(13):2068-2074.

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# MAIA Study Design

Multicenter, randomized, open-label, active-controlled, phase 3 study



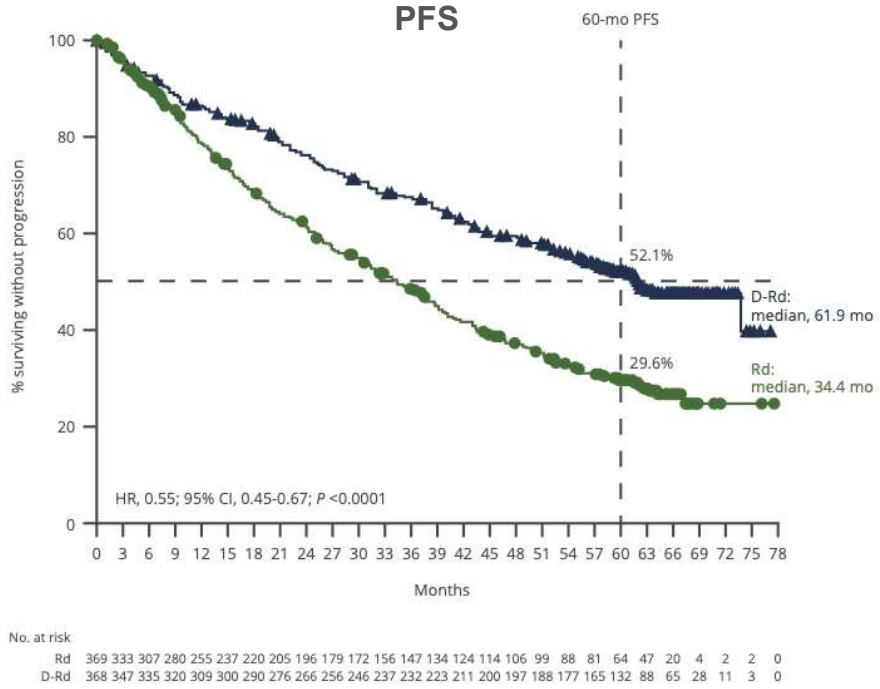

a. On days when daratumumab is administered, dexamethasone will be administered to patients in the D-Rd arm and will serve as the treatment dose of steroid for that day, as well as the required pre-infusion medication.
TIE = transplant-ineligible; sCR = stringent complete response; PFS2 = progression-free survival on next subsequent line of therapy.
Facon T, et al. Presented at: EHA Congress; 2024. Abstract P968.

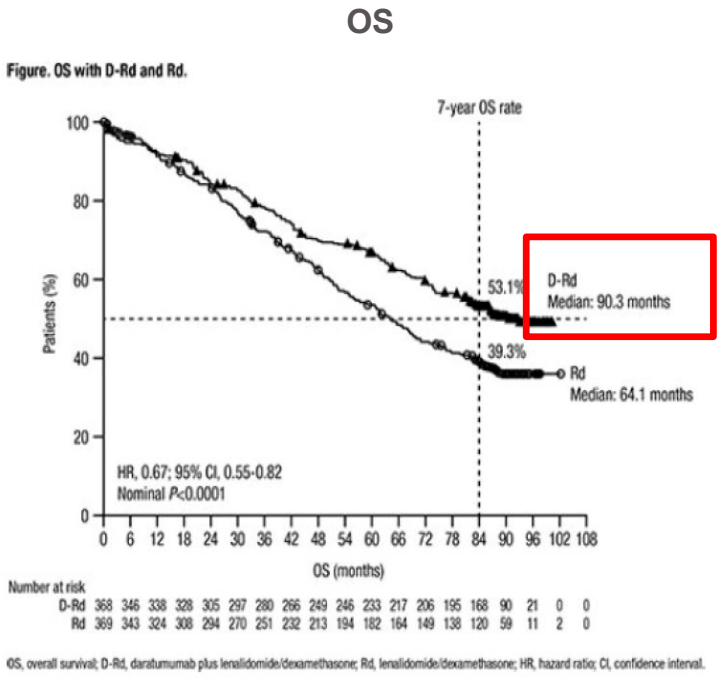
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# MAIA Updated Analysis: PFS

## Median follow-up of 64.5 months for PFS

**ORR: 93% vs 82% (SCR/CR rate: 51% vs 30%); MRD -ve rate: 32% vs 11%**



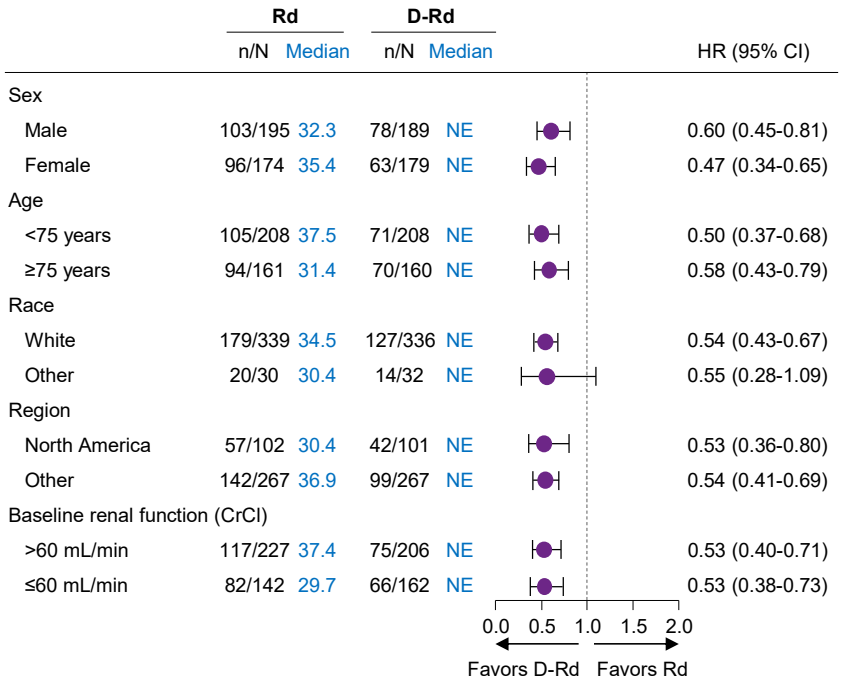



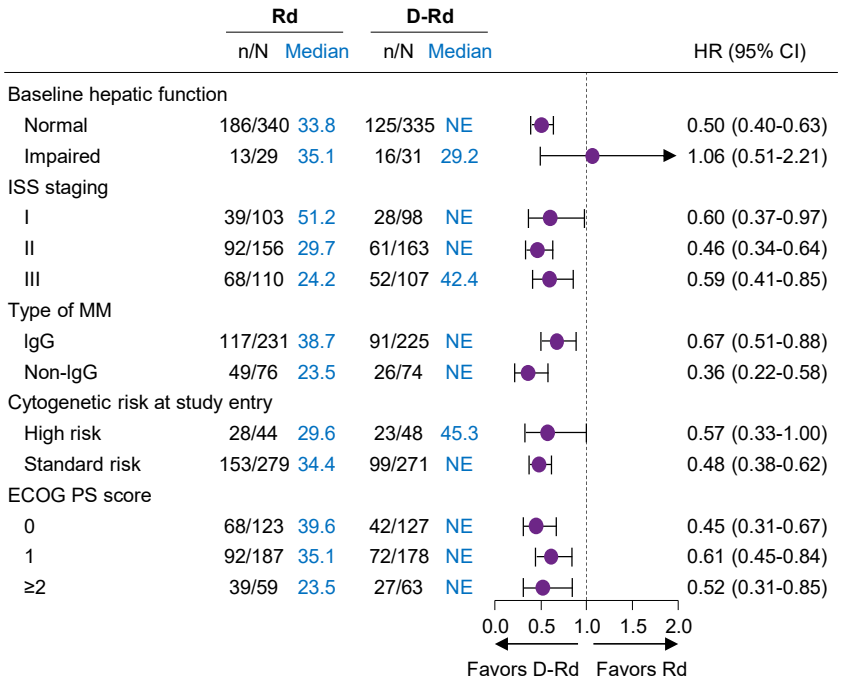

VMP = bortezomib, melphalan, prednisone.

Facon T, et al. Presented at: EHA Congress; 2024. Abstract P968.

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# Subgroup Analysis of PFS




NE = not estimable; CrCl = creatinine clearance.

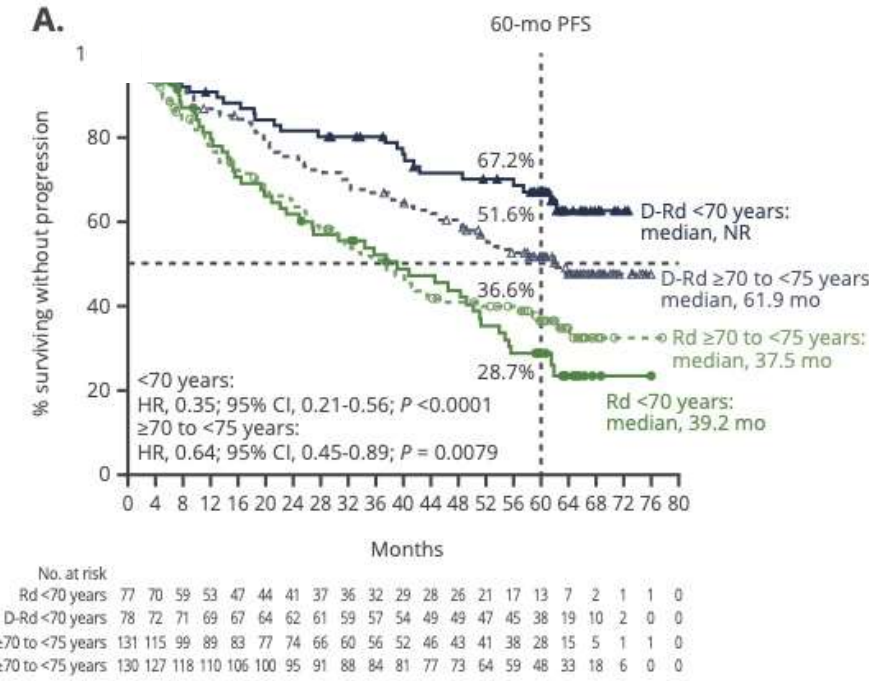
Facon T, et al. N Engl J Med. 2019;380(22):2104-2115. Facon T, et al. *Leukemia*. 2022;36(4):1066-1077.

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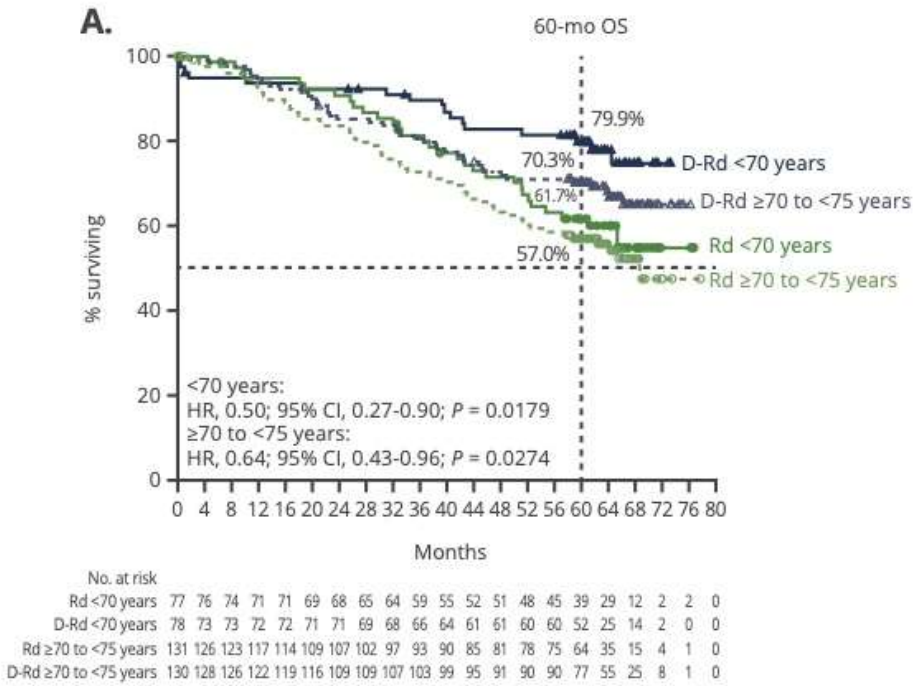
# MAIA Age Subgroups: PFS and OS

## Median follow-up of 64.5 months

PFS in patients aged <70 years and ≥70 and <75 years




OS in patients aged <70 years and ≥70 and <75 years



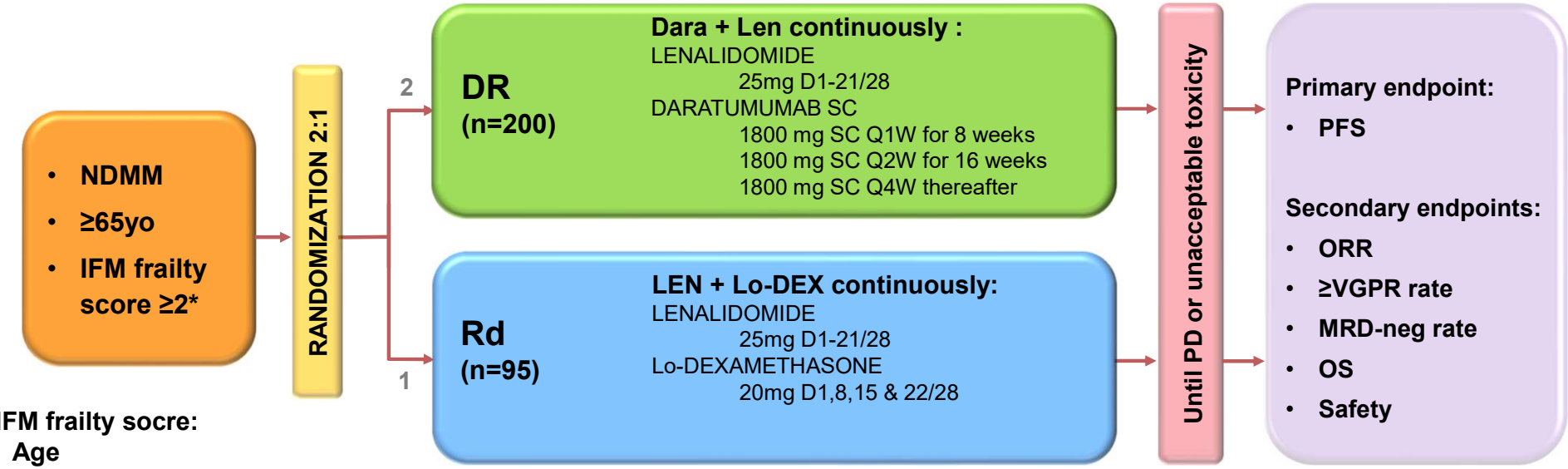

NR = not reached.

Facon T, et al. Presented at: 64th ASH Annual Meeting & Exposition; 2022. Abstract 4553.

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# IFM 2017-03—Study Design

**Phase 3 study of DR vs Rd in TNE frail NDMM (n=295)**




***IFM frailty socre:**
Age
ECOG
Charlson

Randomization stratified by ISS (I vs II vs III) and age (<80 vs ≥80)
In arm A low-dose dex (20 mg/week) during cycle 1 and 2 (with dara)

**Interim analysis:** 12-month data cut on response rates and safety

**Final analysis with primary endpoint:** PFS

Manier S, et al. *Blood*. 2024;144(Suppl 1):774.

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# IFM 2017-03—Patient Characteristics

| Characteristics | DR group (N=200) | Rd group (N=95) |
|---|---|---|
| **Median age (range) - yr** | 81 (68-92) | 81 (68-90) |
| **Age category—no. (%)** | | |
| **65 to <70 yr** | 2 (1%) | 2 (2%) |
| **70 to <75 yr** | 30 (15%) | 13 (14%) |
| **75 to <80 yr** | 49 (24%) | 19 (20%) |
| **≥80 yr** | 119 (60%) | 61(64%) |
| **Sex—no. (%)** | | |
| **Female** | 102 (51%) | 49 (52%) |
| **Male** | 98 (49%) | 46 (48%) |
| **ECOG—no. (%)** | | |
| **0** | 21 (10%) | 9 (10%) |
| **1** | 93 (46%) | 48 (50%) |
| **2** | 86 (44%) | 38 (40%) |
| **≥3** | 11 (6%) | 3 (3%) |
| **Charlson—no. (%)** | | |
| **≤1** | 117 (58%) | 57 (60%) |
| **>1** | 83 (42%) | 38 (40%) |
| **IFM frailty score—no. (%)** | | |
| **≤1** | 0 | 0 |
| **2** | 58 (29%) | 35 (37%) |
| **3** | 80 (40%) | 26 (28%) |
| **4** | 46 (23%) | 24 (25%) |
| **5** | 16 (8%) | 9 (9%) |

| Characteristics | DR group (N=200) | Rd group (N=95) |
|---|---|---|
| **ISS disease stage—no. (%)** | | |
| **I** | 33 (16%) | 19 (20%) |
| **II** | 103 (52%) | 49 (52%) |
| **III** | 64 (32%) | 27 (28%) |
| **NA** | 0 | 1 |
| **Type of measurable disease—no (%)** | | |
| **IgG** | 115 (57%) | 50 (53%) |
| **IgA** | 36 (18%) | 20 (21%) |
| **PBJ only** | 6 (3%) | 7 (7%) |
| **SFLC only** | 26 (13%) | 10 (11%) |
| **Cytogenetics profile*—no (%)** | | |
| **Standard risk** | 146 (84%) | 56 (77%) |
| **High risk** | 28 (16%) | 17 (23%) |
| **NA** | 26 | 22 |
| **del17p** | 16 (9%) | 11 (14%) |
| **t(4;14)** | 9 (5%) | 5 (6%) |
| **t(14;16)** | 5 (3%) | 2 (3%) |
| **Creatinine clearance—no. (%)** | | |
| **<30 mL/min** | 1 (1%) | 3 (3%) |
| **30 to <60 mL/min** | 120 (59%) | 50 (53%) |
| **≥60 mL/min** | 79 (40%) | 41 (44%) |

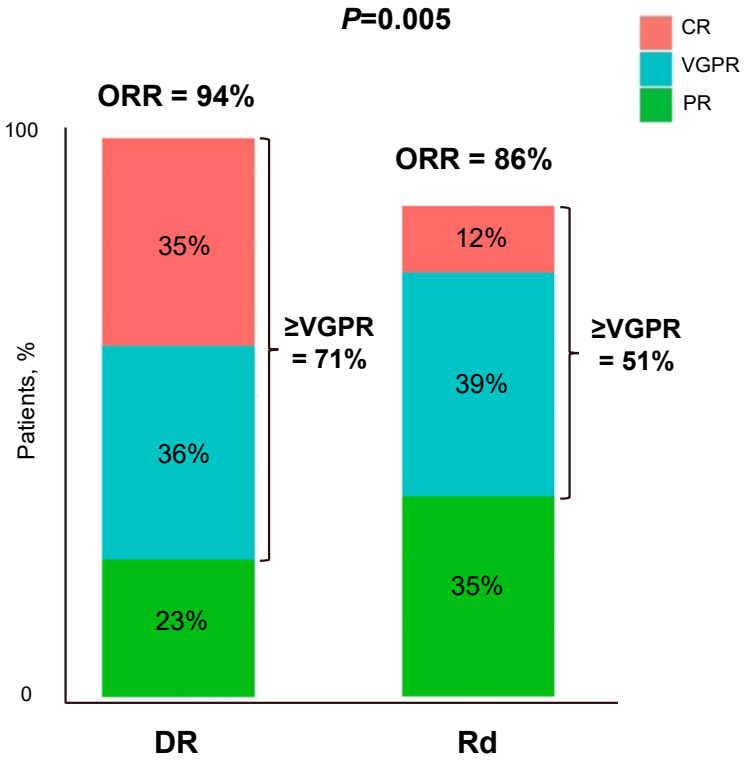
* HR defined as del17p and/or t(4;14) and/or t(14;16)

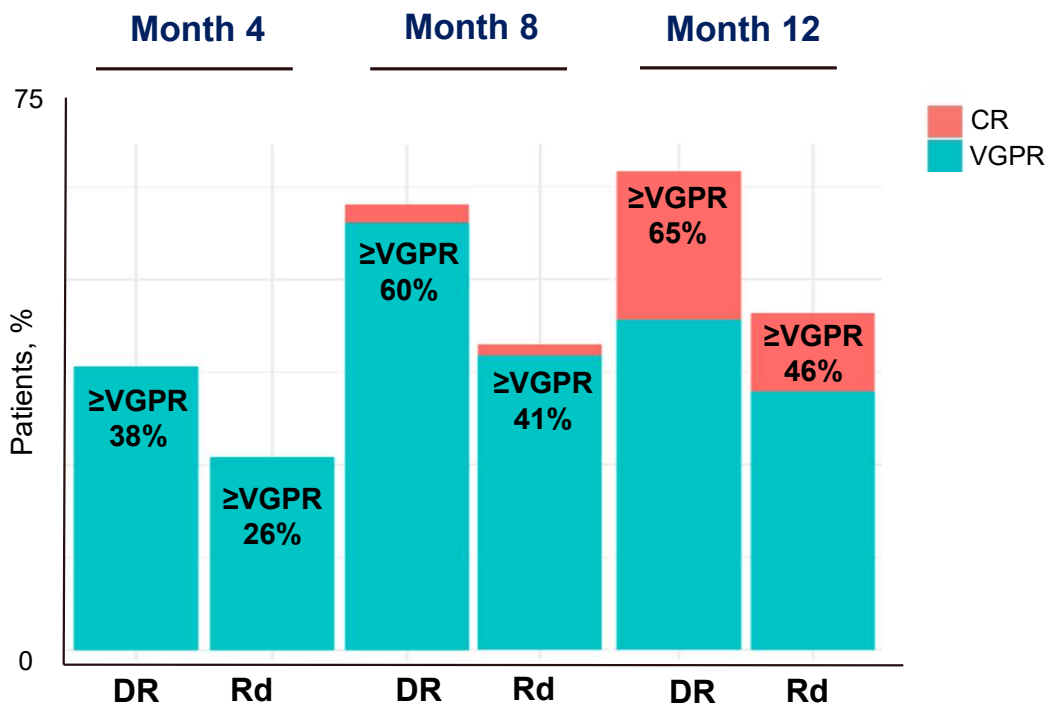
Ig = immunoglobulin; PBJ = Bence Jones proteinuria; SFLC = serum free light chain; IFM = Intergroupe Francophone du Myélome.

Manier S, et al. *Blood*. 2024;144(Suppl 1):774.

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# IFM 2017-03—Response Rates




**VGPR or better rate was significantly higher with DR**

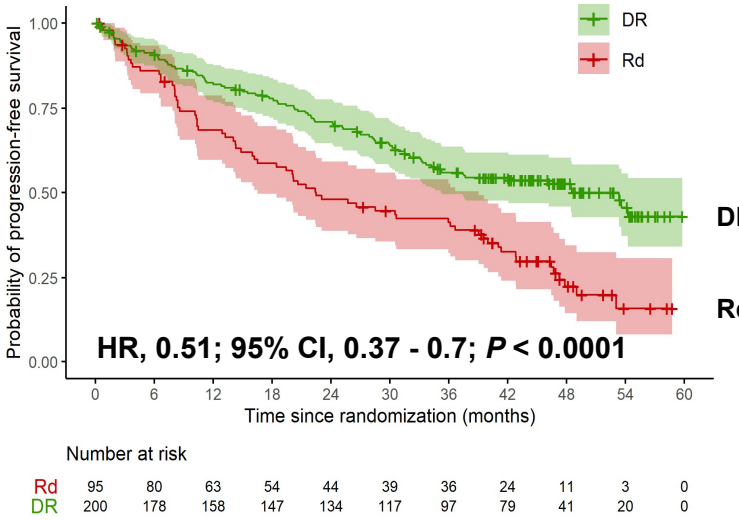
**Deeper responses were obtained with DR at all time points, including at early time points**

Manier S, et al. *Blood*. 2024;144(Suppl 1):774.

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# IFM 2017-03—Outcomes Data

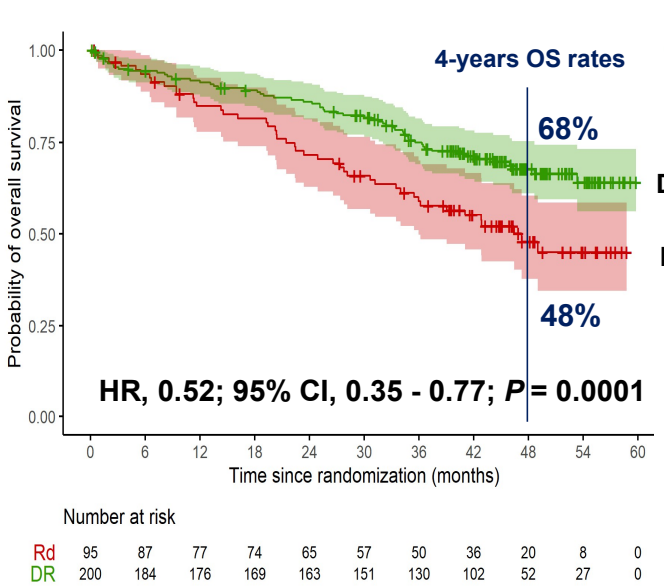
## Progression-free survival




**DR, median: 53.4 mo**

**Rd, median: 22.5 mo**

## Overall survival




**DR, median NR**

**Rd, median: 47.2 mo**

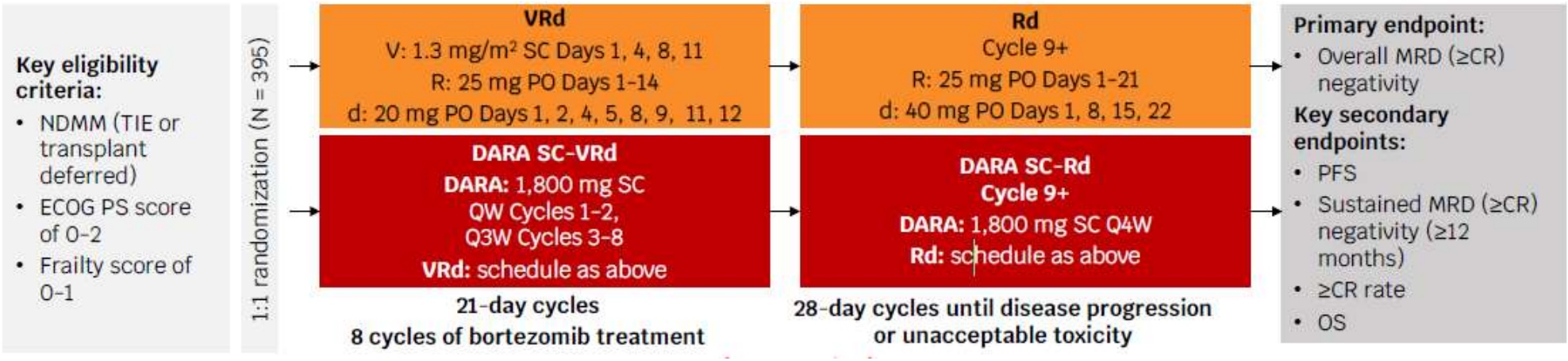
**Median follow-up time = 46.3 months**

**49% reduction in the risk of progression or death in patients receiving DR**

Manier S, et al. *Blood*. 2024;144(Suppl 1):774.

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# CEPHEUS Study Design




Usmani SZ, et al. Presented at: 21st IMS Annual Meeting; 2024.

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# Patient Characteristics

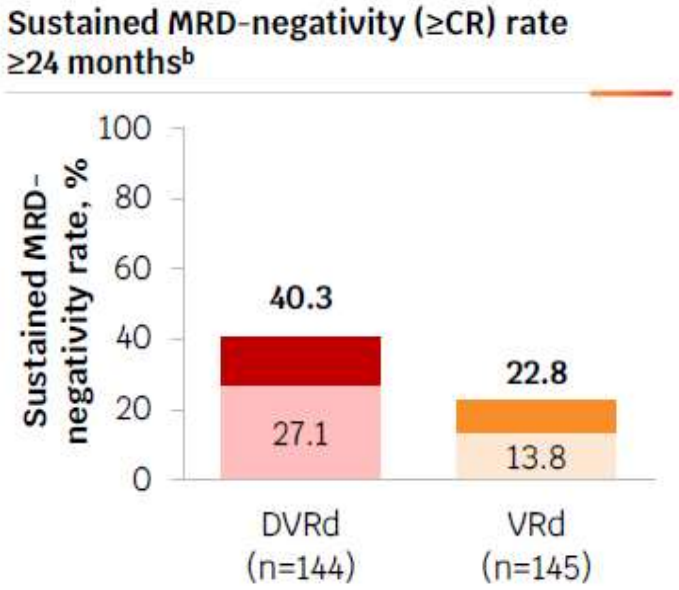
| Characteristic | DVRd (n=144) | VRd (n=198) |
|---|---|---|
| **Age** | | |
| Median (range), years | 72.0 (58-79) | 72.0 (51-80) |
| Age <70 years, n (%) | 35 (24.3) | 35 (24.1) |
| Age 70 to <75 years, n (%) | 68 (47.2) | 65 (44.8) |
| Age ≥75 years, n (%) | 41 (28.5) | 45 (31.0) |
| **Male, n (%)** | 65 (45.1) | 82 (56.6) |
| **ECOG PS score, n (%)[a]** | | |
| 0 | 52 (36.1) | 57 (39.3) |
| 1 | 75 (52.1) | 78 (53.8) |
| 2 | 17 (11.8) | 10 (6.9) |
| **IMWG frailty score, n (%)[b]** | | |
| 0 (fit) | 82 (56.9) | 88 (60.7) |
| 1 (intermediate fitness) | 62 (43.1) | 57 (39.3) |
| **IFM frailty score, n (%)** | | |
| Nonfrail (0-1) | 96 (66.7) | 110 (75.9) |
| Frail (≥2) | 48 (33.3) | 35 (24.1) |

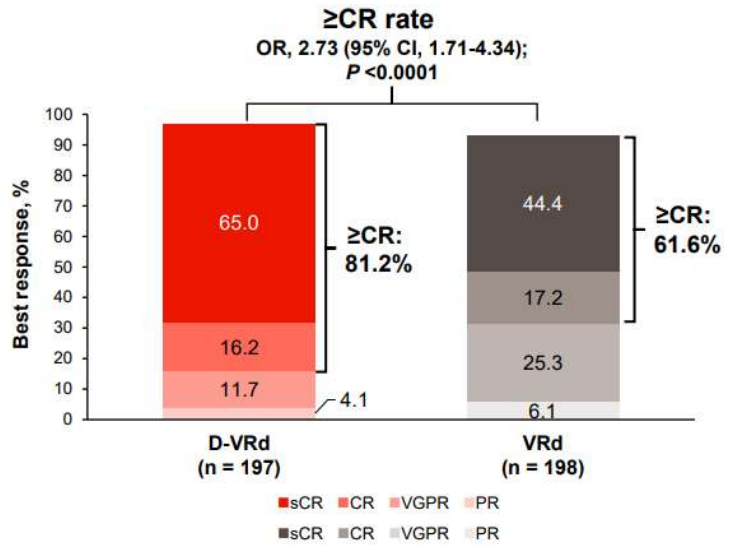
| Characteristic | DVRd (n=144) | VRd (n=198) |
|---|---|---|
| **Type of myeloma by immunofixation or serum FLC assay, n (%)** | | |
| IgG | 92 (63.9) | 78 (53.8) |
| IgA | 26 (18.1) | 42 (29.0) |
| IgD | 2 (1.4) | 2 (1.4) |
| Light chain | 20 (13.9) | 19 (13.1) |
| Biclonal | 4 (2.8) | 3 (2.1) |
| Unknown | 0 | 1 (0.7) |
| **Extramedullary plasmacytomas, n (%)** | 9 (6.3) | 12 (8.3) |
| **ISS staging, n (%)[c]** | | |
| I | 50 (34.7) | 48 (33.1) |
| II | 54 (37.5) | 57 (39.3) |
| III | 40 (27.8) | 40 (27.6) |
| **Cytogenetic risk, n (%)[d]** | | |
| Standard | 105 (72.9) | 111 (76.6) |
| High | 20 (13.9) | 18 (12.4) |
| Unevaluable or missing | 19 (13.2) | 16 (11.0) |

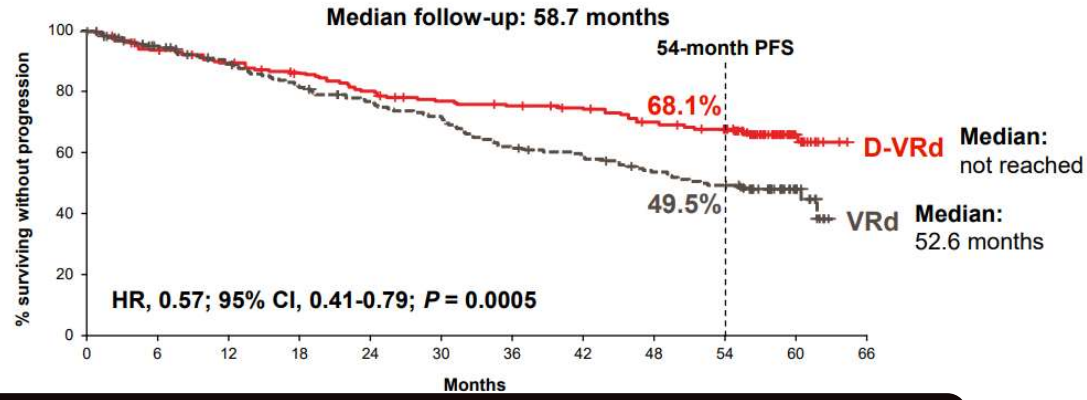
Usmani SZ, et al. Presented at: 21st IMS Annual Meeting; 2024

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# Primary Endpoint: MRD




**Estimated PFS, DVRd vs VRd**

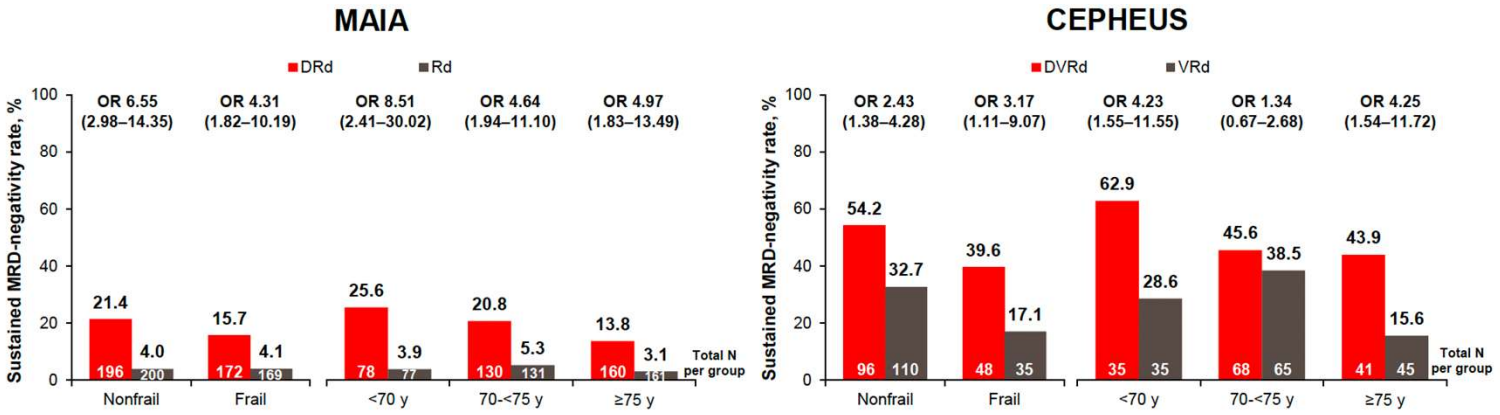
CEPHEUS: **100 months (8.3 yrs)** vs 53 months (4.4 yrs)

Usmani SZ, et al. Presented at: 21st IMS Annual Meeting; 2024

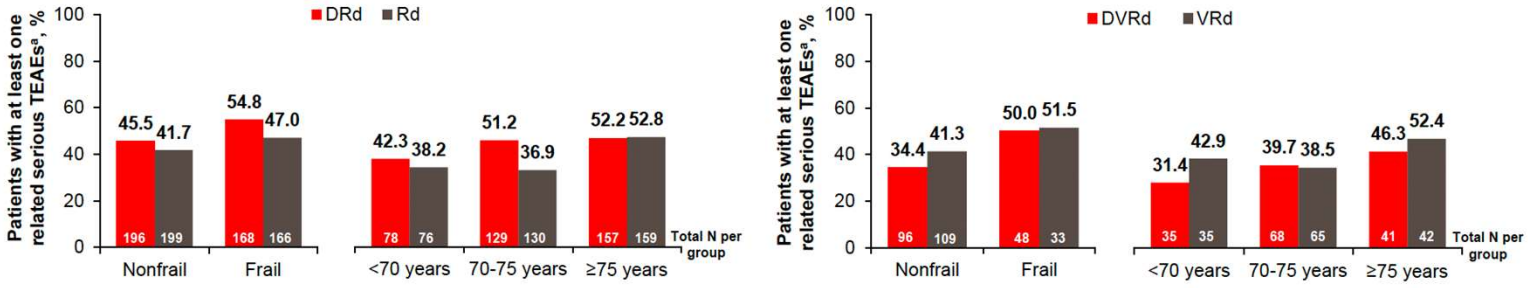
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# Frailty and Age Comparison between Studies

MRD negativity

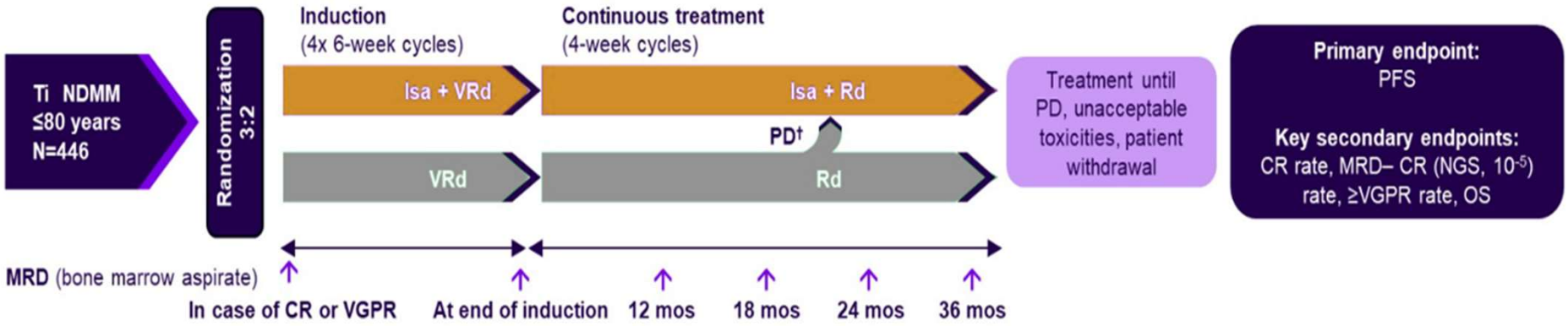



TEAEs




TEAE = treatment-emergent adverse event.
Venner CP, et al. Presented at: ASCO Annual Meeting; 2026.

# Phase 3 IMROZ: Isa-VRd vs VRd for Transplant-Ineligible NDMM




Facon T, et al. Presented at: ASCO Annual Meeting; 2024.

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# Patient Characteristics

| Characteristic, n (%) | Isatuximab + VRd (n=265) | VRd (n=181) |
|---|---|---|
| Median age, yr (range) | 72 (60-80) | 72 (55-80) |
| • <65 | 8 (3.0) | 9 (5.0) |
| • 65 to <70 | 73 (27.5) | 47 (26.0) |
| • 70 to <75 | 115 (43.4) | 68 (37.6) |
| • 75-80 | 69 (26.0) | 57 (31.5) |
| ECOG PS | | |
| • 0 or 1 | 235 (88.7) | 162 (89.5) |
| • >1 | 30 (11.3) | 19 (10.5) |
| eGFR <60 mL/min/1.73 $m^2$ | 66 (24.9) | 62 (34.3) |
| R-ISS stage | | |
| • I or II | 234 (88.3) | 157 (86.7) |
| • III | 29 (10.9) | 21 (11.6) |
| • Not classified | 2 (0.8) | 3 (1.7) |
| Extramedullary disease at study entry (per IRC) | 18 (6.8) | 6 (3.3) |

| Characteristic, n (%) | Isatuximab + VRd (n=265) | VRd (n=181) |
|---|---|---|
| Cytogenic risk | | |
| • Standard | 207 (78.1) | 140 (77.3) |
| • High* | 40 (15.1) | 34 (18.8) |
| • High-risk chromosomal abnormalities and 1q21+† | 19 (7.2) | 15 (8.3) |
| • Unknown | 18 (6.8) | 7 (3.9) |
| Chromosomal abnormality | | |
| • 1q21+‡ | 95 (35.8) | 70 (38.7) |
| • Amplification 1q21‡ | 32 (12.1) | 23 (12.7) |
| • del(17p) (50% cutoff) | 15 (5.7) | 9 (5.0) |

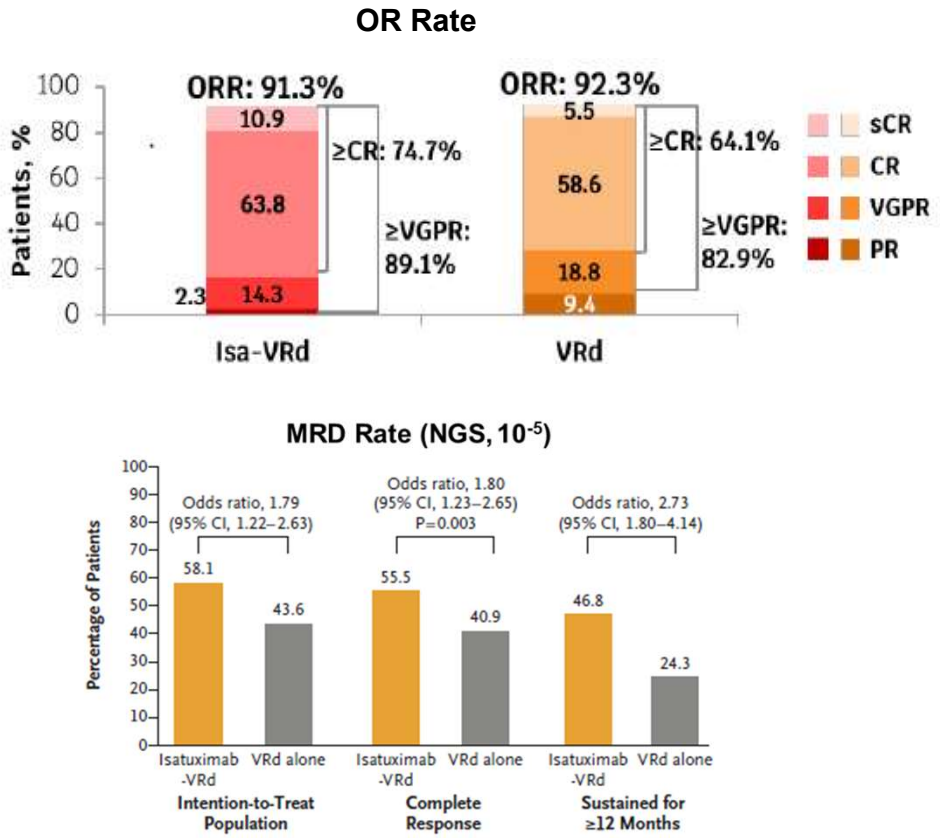
*High risk defined as presence of ≥1 of the following: del(17p), t(4;14), t(14;16).
†Abnormality defined as t(4;14), t(14:16), or 1q21+ (≥3 copies) present in ≥30% of abnormal bone marrow plasma cells and ≥50% abnormal plasma cells for del(17p). 1 patient in Isa-VRd arm had both del(17p) and t(4;14).
‡1q21+ defined as ≥3 copies of 1q21. Amplification 1q21 defined as ≥4 copies of 1q21.

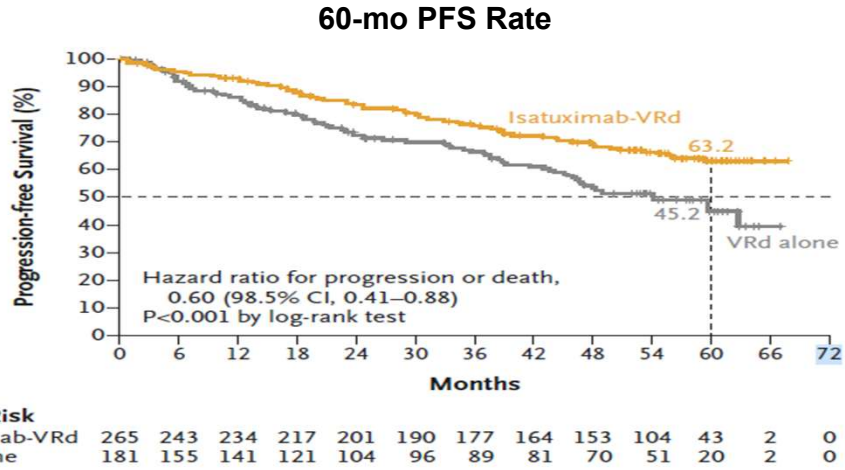
eGFR = estimated glomerular filtration rate.
Facon T, et al. Presented at: ASCO Annual Meeting; 2024.

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# IMROZ: Primary Endopoints

360 patients

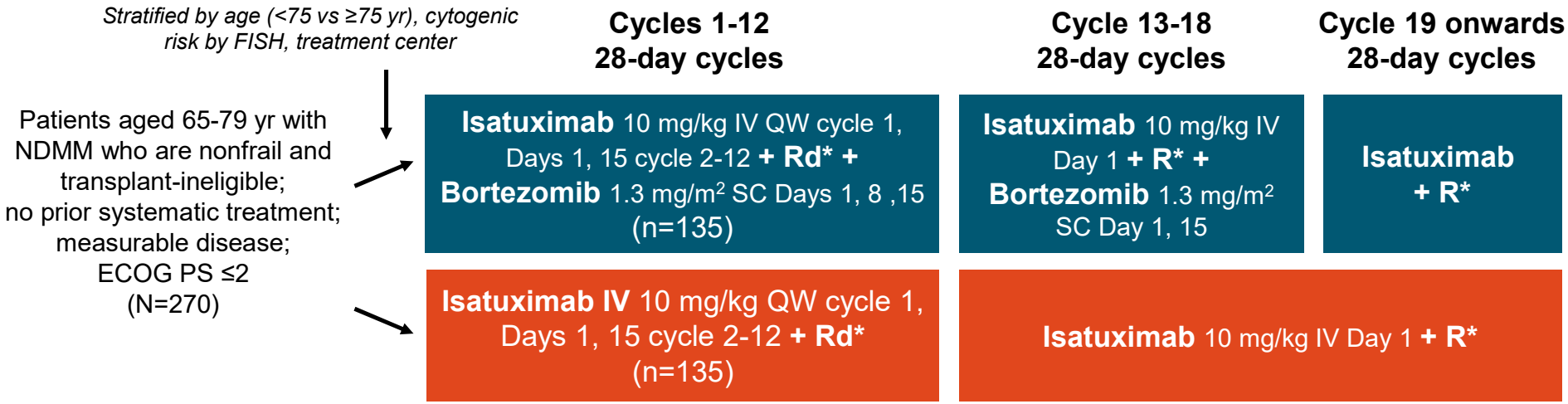



Facon T, et al. Presented at: ASCO Annual Meeting; 2024.

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# BENEFIT Phase 3 Trial of Isa-VRd vs Isa-Rd in Transplant-Ineligible NDMM




*R: lenalidomide 25 mg PO days 1-21, d: dexamethasone 20 mg IV QW.

**Primary endpoint:** MRD ($10^{-5}$) at 18 mo

**Key secondary endpoints:** ORR (CR, ≥ VGPR), MRD- CR ($10^{-5}$), PFS, OS, safety

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

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# Baseline Characteristics

| Characteristic, n (%) | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| Median age, yr (IQR) | 73 (71-76) | 74 (71-76) |
| • <70 | 28 (21) | 25 (19) |
| • 70-75 | 65 (48) | 62 (46) |
| • ≥75 | 42 (31) | 48 (36) |
| Male | 74 (55) | 71 (53) |
| ECOG PS, n (%) | | |
| • 0/1 | 125 (93) | 119 (88) |
| • >1 | 10 (7) | 16 (12) |
| eGFR <60 mL/min/1.73m$^2$ | 19 (14) | 28 (21) |

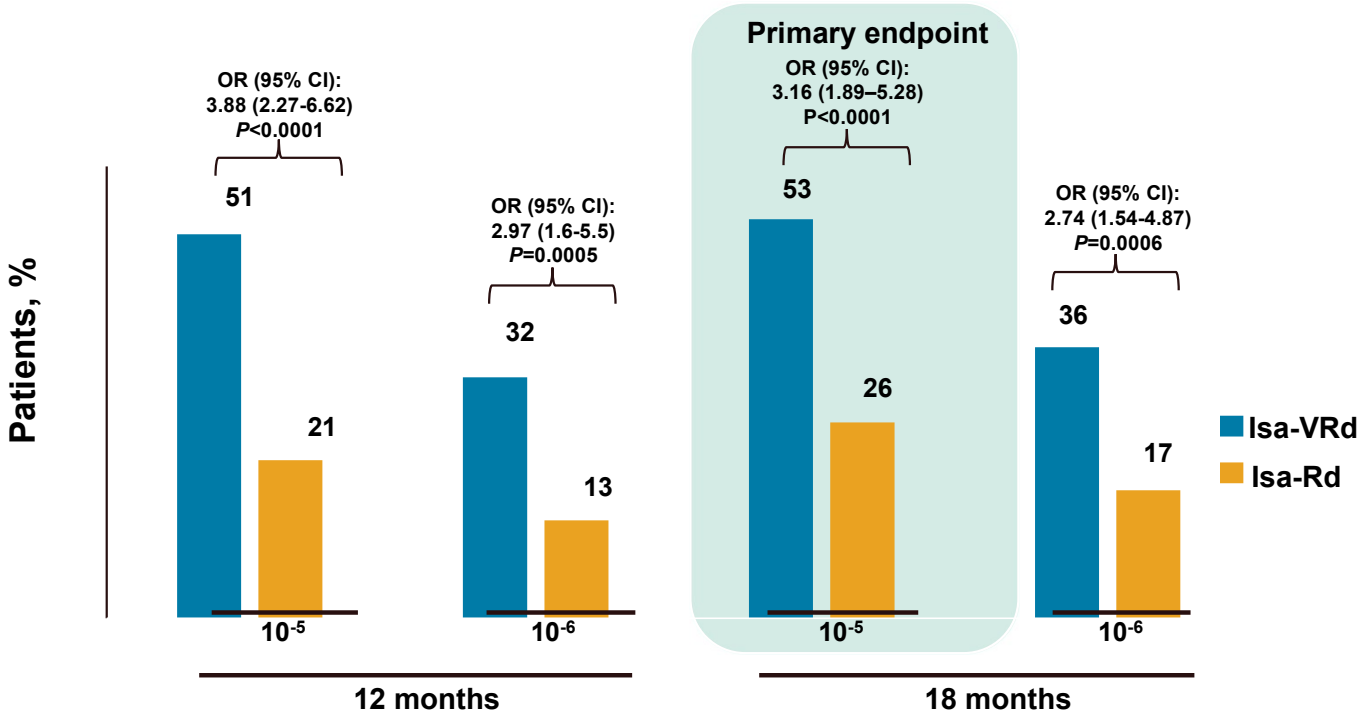
| Characteristic, n (%) | Isa-VRd (n=135) | Isa-Rd (n=135) |
|---|---|---|
| ISS stage | | |
| • I/II | 114 (84) | 108 (80) |
| • III | 21 (16) | 27 (20) |
| R-ISS stage | | |
| • I | 32 (24) | 35 (26) |
| • II | 92 (68) | 89 (66) |
| • III | 11 (8) | 11 (8) |
| Cytogenic risk | | |
| • Standard | 68 (53) | 75 (60) |
| • Intermediate | 48 (37) | 41 (33) |
| • High | 13 (10) | 10 (8) |

110 patients in Isa-VRd arm vs 102 in Isa-Rd arm were still on treatment at the time of this analysis

IQR = interquartile range.
Leleu X, et al. *Nat Med*. 2024;30(8):2235-2241.

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# BENEFIT Phase 3 Trial: MRD -ve Rate in the ITT




| Response at 18-Mo | Isa-VRd (n=135) | Isa-Rd (n=135) | *P* value |
|---|---|---|---|
| ORR, % | 85 | 78 | |
| • CR | 58 | 31 | <0.0001 |
| • VGPR | 24 | 39 | |
| ≥ VGPR, % | 82 | 70 | |

**A consistent MRD benefit was observed with Isa-VRd vs Isa-Rd across most subgroups. Survival benefit and PFS are still immature.**

ITT = intention-to-treat.

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

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# Proposed Regimen

## Hybrid Quadruplet in Fit/Unfit Patients

| Cycles 1-2<br>28-day cycles | Cycles 3-8<br>28-day cycles | Cycle 8 onwards<br>28-day cycles |
|---|---|---|
| Anti-CD38 +<br>Bortezomib 1.3 mg/m$^2$ SC days 1, 8, 15<br>Lenalidomide 15 mg 21 of 28 days<br>Dexamethasone 20 mg days 1, 8, 15 | Anti-CD38 +<br>Bortezomib 1.3 mg/m$^2$ SC days 1, 8 ,15<br>Lenalidomide 15 mg 21 of 28 days | **Anti-CD38<br>+ R** |

* Dexamethasone to be extended to 4 cycles in fit patients

## Hybrid Triplet in Frail Patients

| Cycles 1-2<br>28-day cycles | Cycles 3-8<br>28-day cycles | Cycle 8 onwards<br>28-day cycles |
|---|---|---|
| Anti-CD38 +<br>Lenalidomide 15 mg 21 of 28 days<br>Dexamethasone 20 mg days 1, 8, 15 | **Anti-CD38 +<br>Lenalidomide 10 mg 21 of 28 days** | **Anti-CD38<br>+ R** |

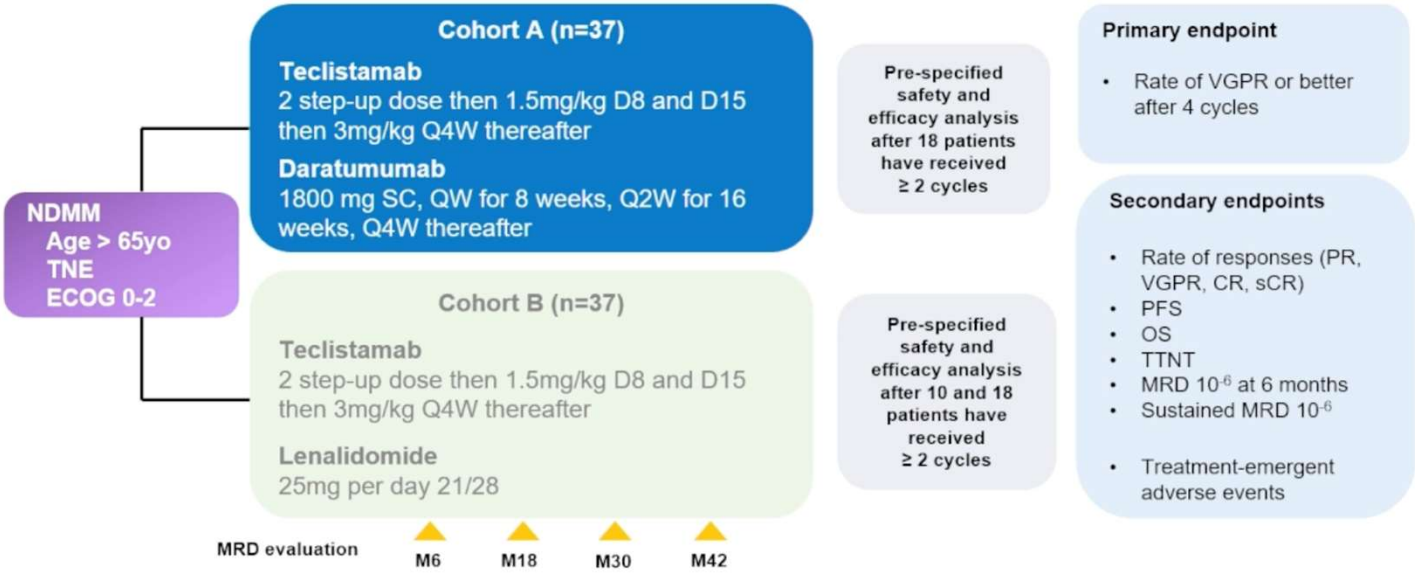
* Dexamethasone can be omitted after first cycle in frail patients

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# Emerging Approaches

# IFM 2021-01 TecLille—Study Design

**Phase 2 study of Tec-Dara and Tec-Len in TNE NDMM (n = 74)**




**Current amendment:**
**Teclistamab 3mg/kg Q8W after C13 if CR or better and treatment interruption if 2-years sustained MRD -**

TTNT = time to next treatment.

Manier S, et al. *Blood*. 2025;146(Suppl 1):367.

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# IFM 2021-01 TecLille—Cohort A: Tec-Dara Patients and Disease Characteristics

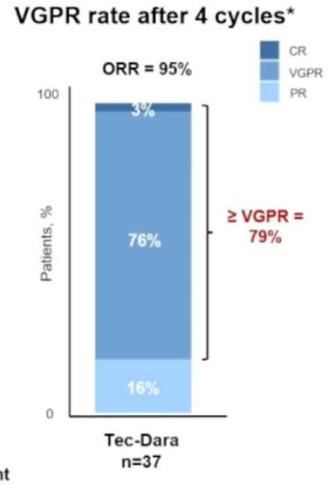
| Patients characteristics | Tec-Dara (n=37) |
|---|---|
| **Median age (range) - yr** | 73 (66-87) |
| **Age category – no. (%)** | |
| 65 to < 70 yr | 7 (19%) |
| 70 to < 75 yr | 18 (49%) |
| ≥ 75 yr | 12 (32%) |
| **Sex - no. (%)** | |
| Female | 20 (54%) |
| Male | 17 (46%) |
| **ECOG – no. (%)** | |
| 0 | 9 (24%) |
| 1 | 24 (65%) |
| 2 | 4 (11%) |
| **Frailty score (IMWG) – no. (%)** | |
| Fit | 16 (44%) |
| Intermediate | 12 (33%) |
| Frail | 8 (22%) |
| **Creatinine clearance – no. (%)** | |
| 30 to < 60mL/min | 14 (38%) |
| ≥ 60 mL/min | 23 (62%) |

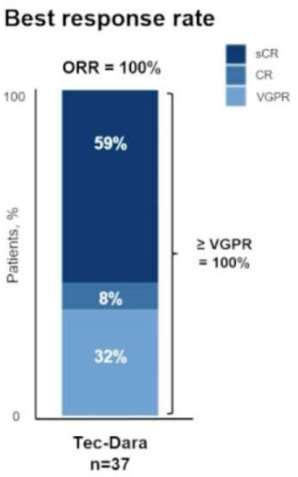
| Disease characteristics | Tec-Dara (n=37) |
|---|---|
| **Type of measurable disease – no (%)** | |
| IgG | 22 (59%) |
| IgA | 8 (22%) |
| SFLC only | 7 (19%) |
| **ISS disease stage – no. (%)** | |
| I | 13 (35%) |
| II | 19 (51%) |
| III | 5 (14%) |
| **Cytogenetic risk (IMWG/IMS) – no (%)** | |
| Standard risk | 25 (68%) |
| High risk | 12 (32%) |
| del17p | 4 (14%) |
| TP53 mutation | 3 (10%) |
| t(4;14) | 1 (3%) |
| t(14;16) | 1 (3%) |
| t(14;20) | 1 (3%) |
| gain 1q | 11 (38%) |
| del1p32 | 2 (7%) |
| **Extramedullary disease – no (%)** | |
| No | 35 (95%) |
| Yes | 2 (5%) |

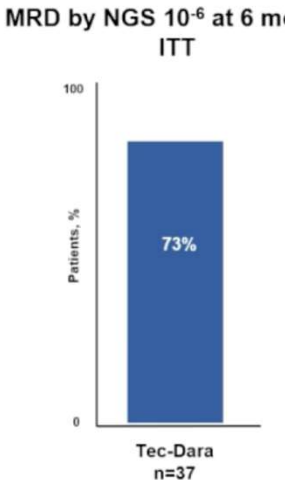
Manier S, et al. *Blood*. 2025;146(Suppl 1):367.

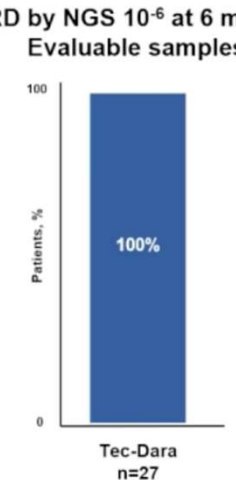
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# IFM 2021-01 TecLille—Cohort A: Tec-Dara Response Rates

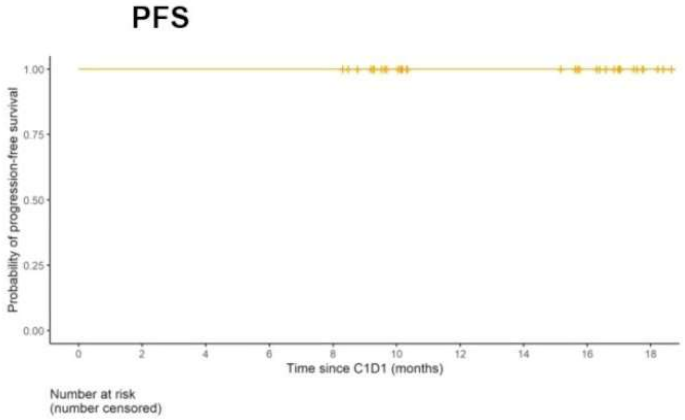


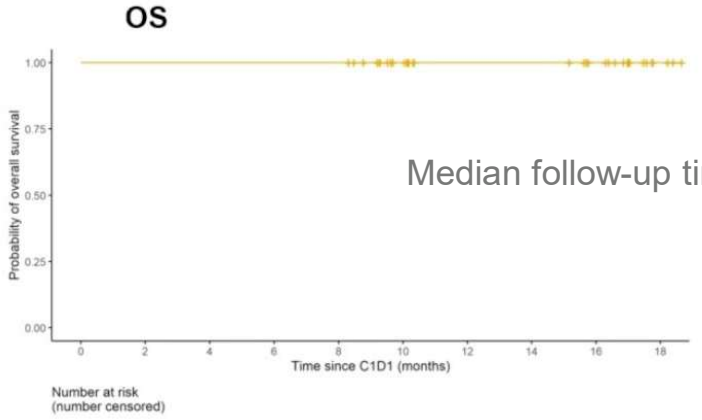




* primary endpoint



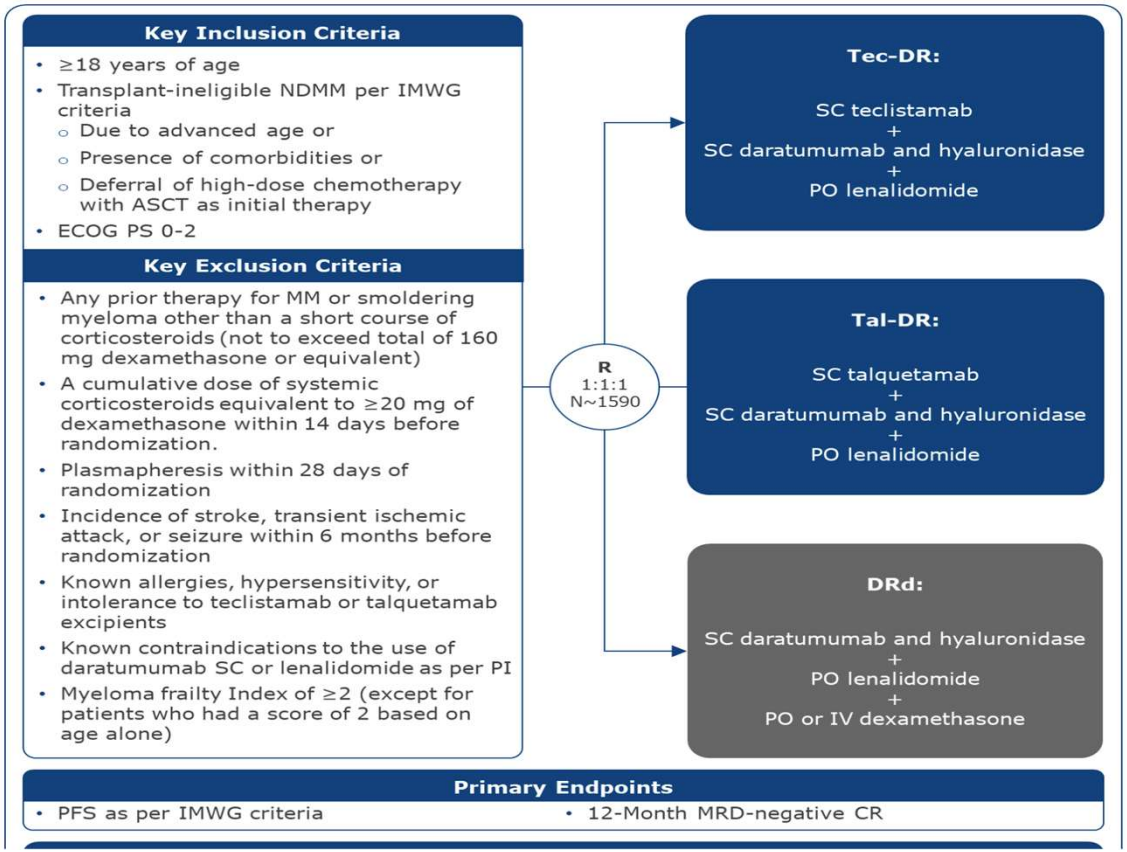

Median follow-up time = 10.3 months

Manier S, et al. *Blood*. 2025;146(Suppl 1):367.

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# MajesTEC-7

MajesTEC-7 Study Design (Randomized Phase)[1,2]




- 26 NDMM patients included in the safety run-in cohort with Tec-Dara-R
- 61.5% were fit
- ORR was 92.3% with 80.8% of CR or better
- Only 1 event in the PFS curve after a median f/u of 14 months
- Overal infection rate was 100% with 30.8% G3-4
- Cumulative incidence reported higher risk during the first 3 months

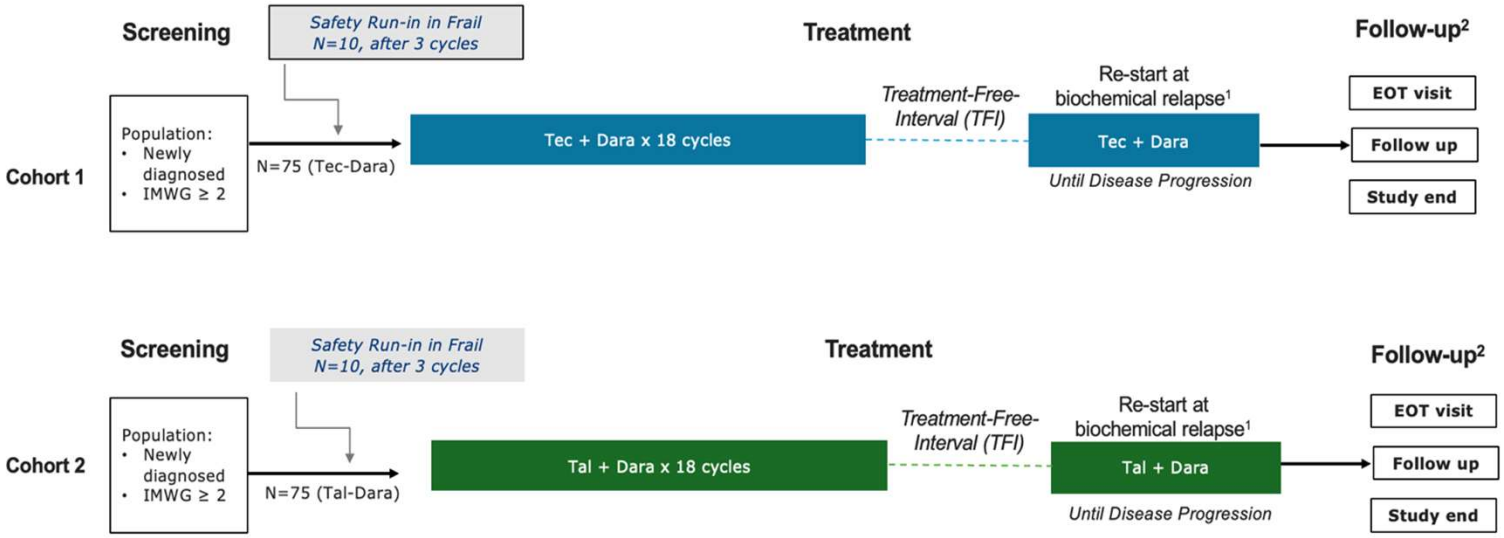
f/u = follow-up.

1. Dytfeld D, et al. Presented at: 63rd ASH Annual Meeting & Exposition; 2021. Abstract 1835. Manier S, et al. Presented at: ASCO Annual Meeting; 2024.

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# Optimizing the Use of BsAb in TIE NDMM

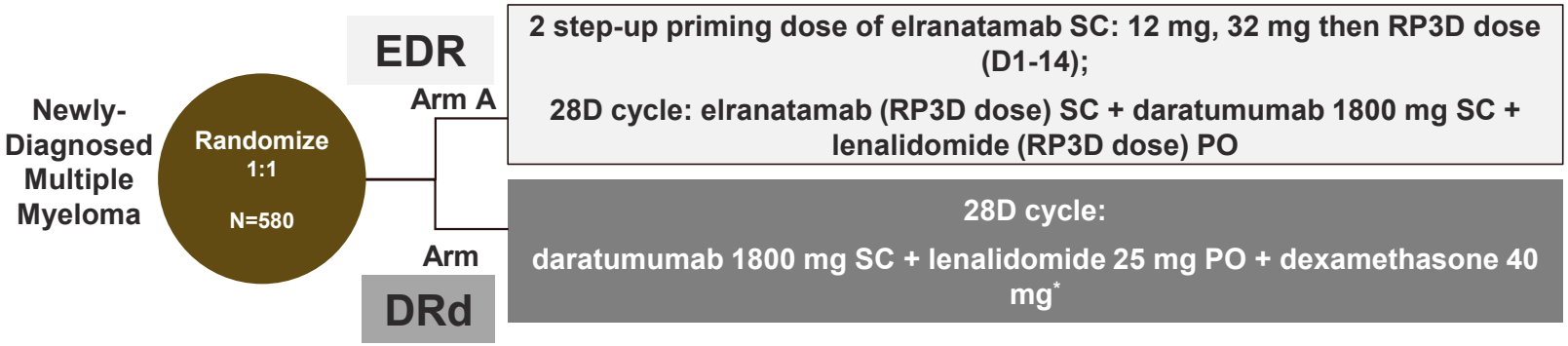
**EFficacy and Tolerability of FIXed-duration teclistamab and talquetamab FOR FRAIL patients with newly diagnosed multiple myeloma (2-cohort study)—EMN 37 FITFIX FOR FRAIL trial**




BsAb = bispecific antibody; EOT = end of treatment.
ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated April 4, 2026. https://clinicaltrials.gov/study/NCT07107529.

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# MM-6 Study Design for Part 2 (Phase III): ElraDR vs DRd




## Primary Objective

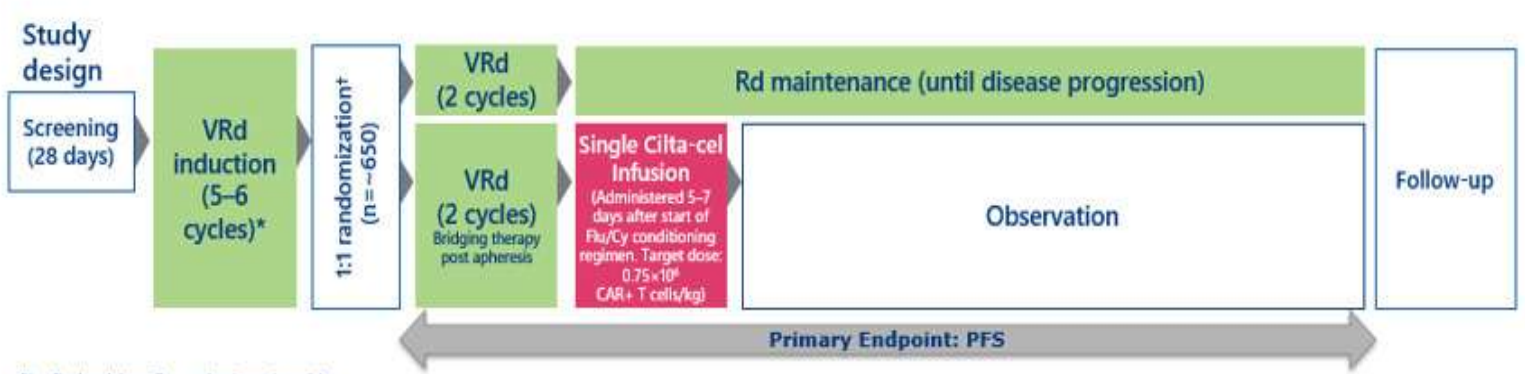
**To compare the efficacy of EDR vs DRd as measured by MRD status and PFS by BICR according the IMWG**

BICR = blinded independent central review.
ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 25, 2026. https://clinicaltrials.gov/study/NCT05623020

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# CARTITUDE-5

Figure: CARTITUDE-5 study design




Flu, fludarabine; Cy, cyclophosphamide
*1 cycle VRd allowed prior to screening
†Stratification factors: R-ISS (I,II,III); Age/transplant eligibility (≥70 years or <70 years and ASCT ineligible due to comorbidities or <70 years and ASCT deferred); Response to VRd induction (≥VGPR, ≤PR)

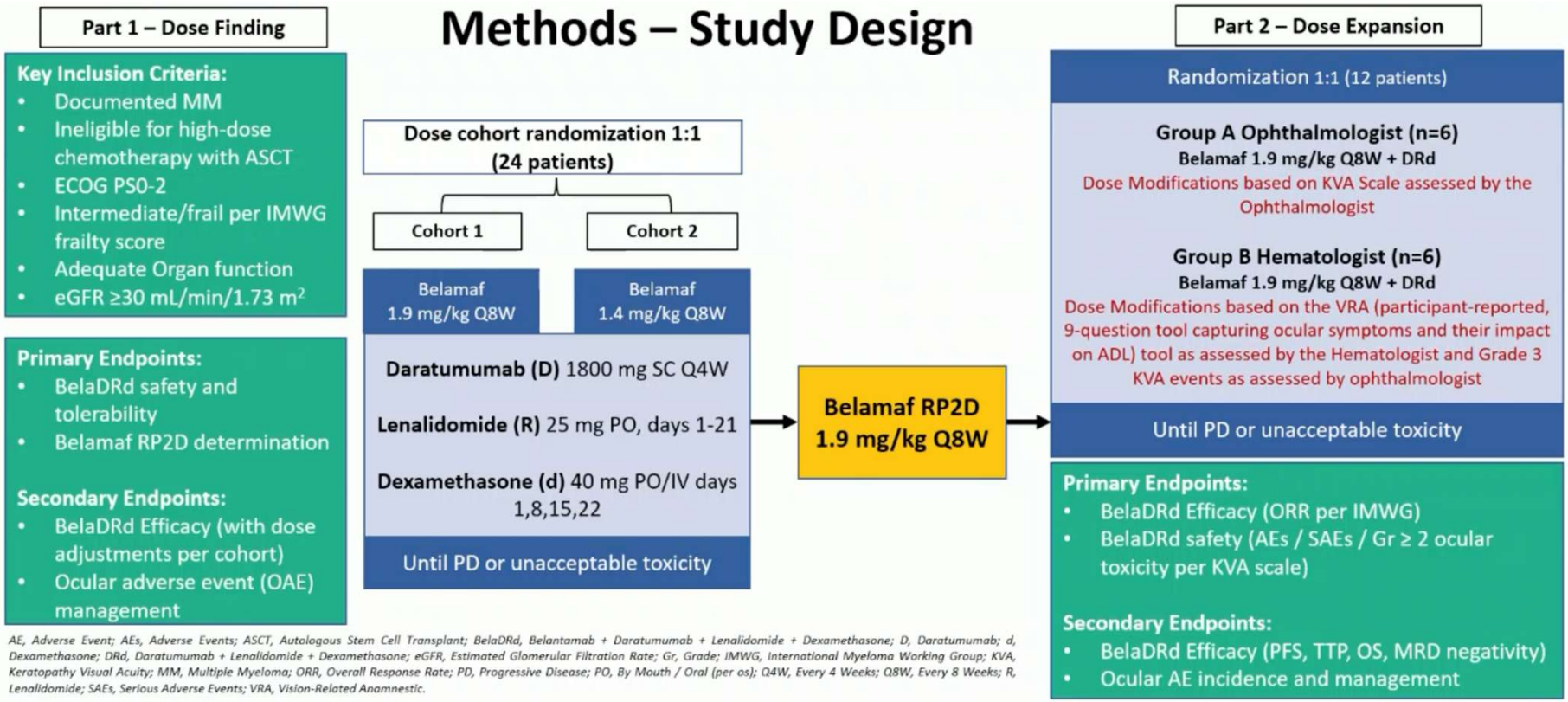
- Eligibility criteria include: Patients not eligible for ASCT because of age and/or comorbidities or patients who have decided to defer transplant
- IMWG-frailty score should be 0 or 1

1. Dytfeld D, et al. Presented at: 63rd ASH Annual Meeting & Exposition; 2021. Abstract 1835. 2. Touzeau C, et al. Presented at: ASCO Annual Meeting; 2024. Abstract 7605.
3. Grosicki S, et al. Presented at: ASCO Annual Meeting; 2023. Abstract TPS8065.

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# DREAMM-9 Bela-VRd Combination for TI-NDMM

## Methods – Study Design




*AE, Adverse Event; AEs, Adverse Events; ASCT, Autologous Stem Cell Transplant; BelaDRd, Belantamab + Daratumumab + Lenalidomide + Dexamethasone; D, Daratumumab; d, Dexamethasone; DRd, Daratumumab + Lenalidomide + Dexamethasone; eGFR, Estimated Glomerular Filtration Rate; Gr, Grade; IMWG, International Myeloma Working Group; KVA, Keratopathy Visual Acuity; MM, Multiple Myeloma; ORR, Overall Response Rate; PD, Progressive Disease; PO, By Mouth / Oral (per os); Q4W, Every 4 Weeks; Q8W, Every 8 Weeks; R, Lenalidomide; SAEs, Serious Adverse Events; VRA, Vision-Related Anamnestic.*

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 28, 2025. https://clinicaltrials.gov/study/NCT04091126.

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# Key Learning Points

- Addition of anti-CD38 improves outcomes and is well tolerated
- Quad vs triplet regimen will depend on frailty and comorbidities
- Future direction is to bring immunotherapies with finite duration of treatment

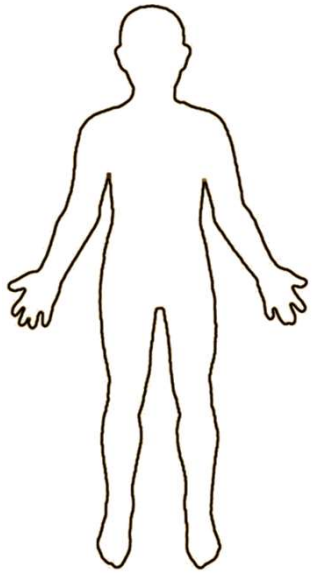
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# Personalizing Treatment Decisions

- MRD assessment
- Duration of maintenance
- Patient-centered care

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# Factors Influencing Treatment Decisions



- ISS stage
- High-risk disease
- Renal impairment
- ECOG performance status
- Prior treatments
- Goal of treatment
- Platelet and hemoglobin levels
- Vein access
- Extent of disease
- Comorbidities and comedications
- QoL and physical functioning
- Distance from center
- Support system
- Patient preference

NSCT = non-stem cell transplant eligible; QoL = quality of life.

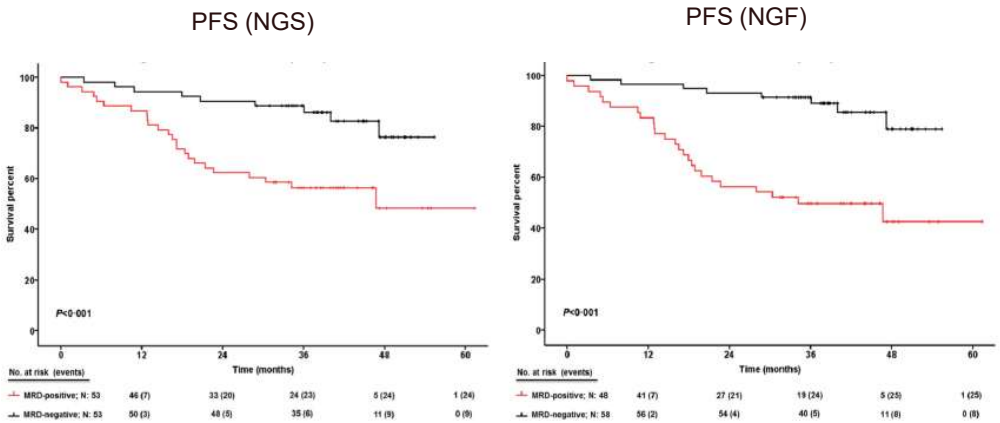
1. Keller J, et al. Presented at: 57th ASH Annual Meeting & Exposition; 2015. Abstract 3307. 2. Willan J, et al. *Clin Interv Aging.* 2016;11:423-435.

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# Features of NGF and NGS for MRD Detection

| | NGF | NGS |
|---|---|---|
| Applicability (% cases) | 99% | 90% |
| Sensitivity | 2-4 x $10^{-6}$ | $10^{-6}$ |
| Time to result | 2-3 h | ≥ 7 days |
| Number of cells required | 2 x $10^{7}$ | 2-3 x $10^{6}$ |
| Need for fresh sample | Yes (within 24h) | No |
| Need for diagnostic sample | No | Yes |
| Quantitative | Yes | Yes |
| Intrinsic quality control for hemodilution | Yes | No |
| Cell characterization | Yes | No |
| Molecular characterization | No | Yes |
| Availability | Wide | Limited |
| Reproducibility among centers | High | Not reported |
| Harmonization | Yes | Not reported |
| Cost | + | ++ |

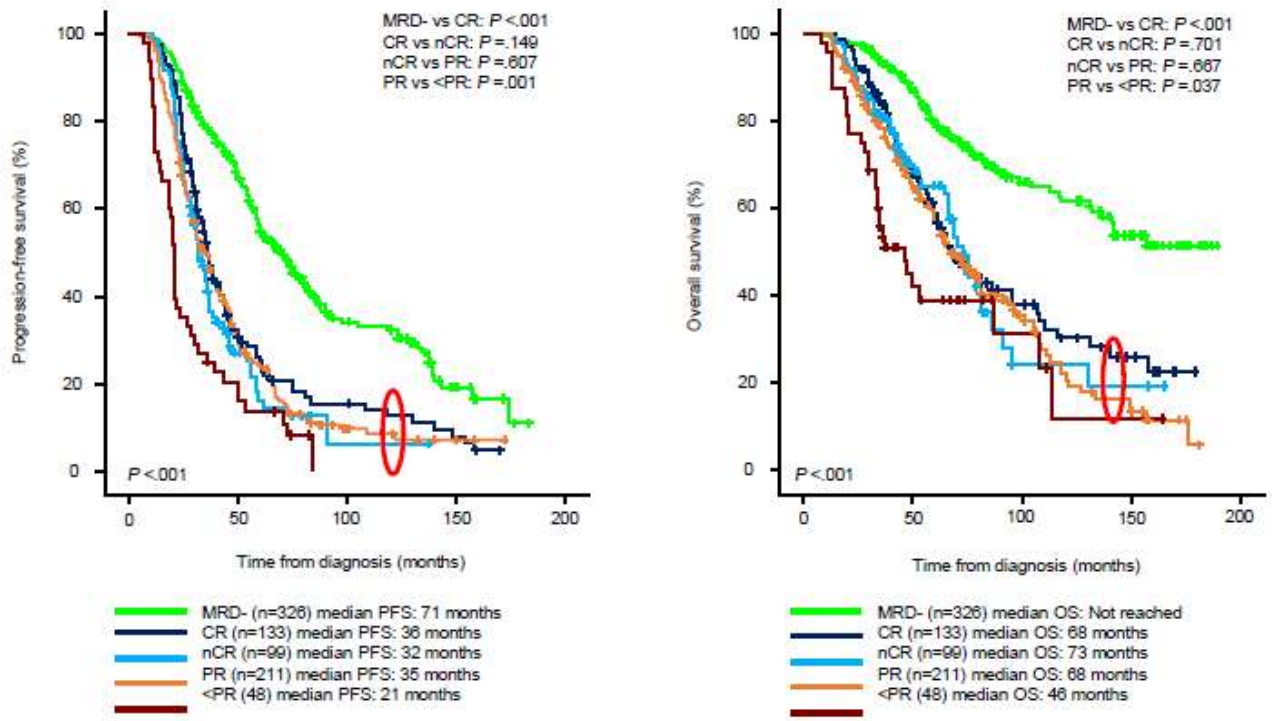
Concordance between MRD results and survival




Kostopoulos IV, et al. *Front Oncol*. 2020;10:860. Medina A, et al. *Blood Cancer J.* 2020;10(10):108.

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# The Value of CR Depends on MRD Status

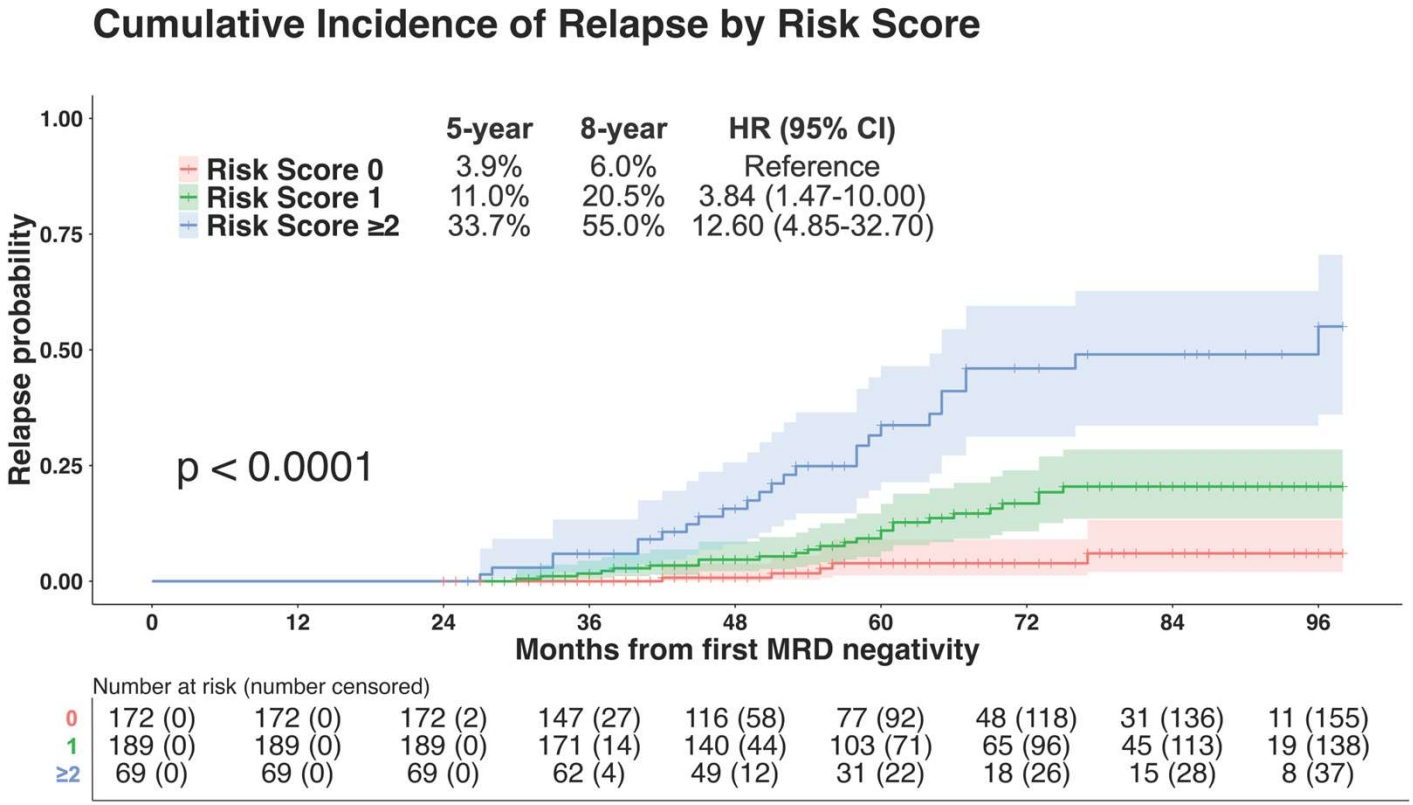



Patients in CR with persistent MRD had the same outcome as patients in nCR/VGPR and even PR

Lahuerta JJ, et al. *J Clin Oncol*. 2017;35(25):2900-2910.

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# sMRD24 and Risk of Relapse

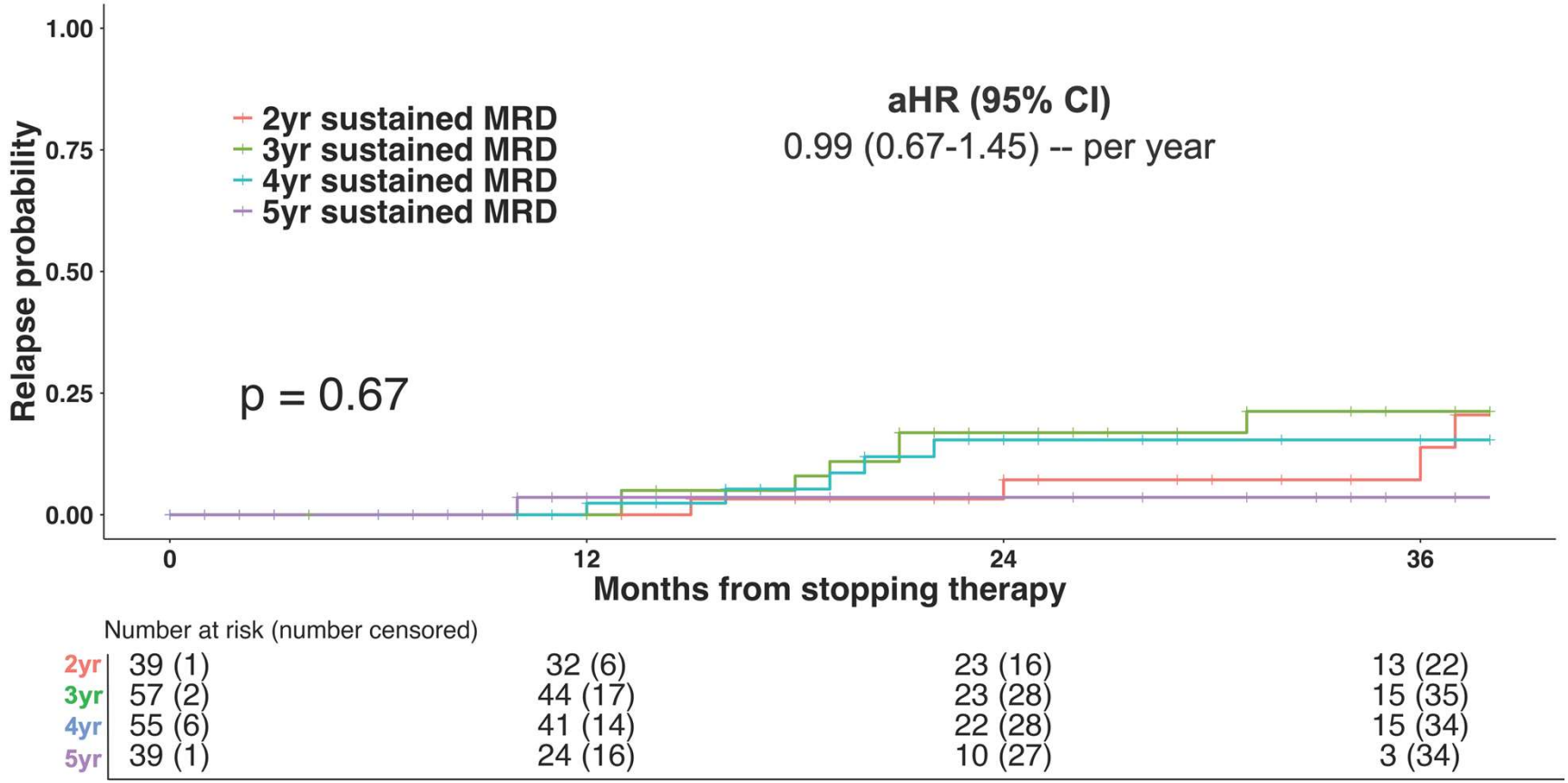



**Genomic SR, ISS 1/2, and MRD by NGS define ultra-low-risk subgroup with minimal relapse after sMRD24**

SR = standard risk; sMRD24 = sustained MRD-negative, imaging-negative remission lasting ≥24 months.
Avigan Z, et al. Presented at: 23rd IMS Annual Meeting; 2026.

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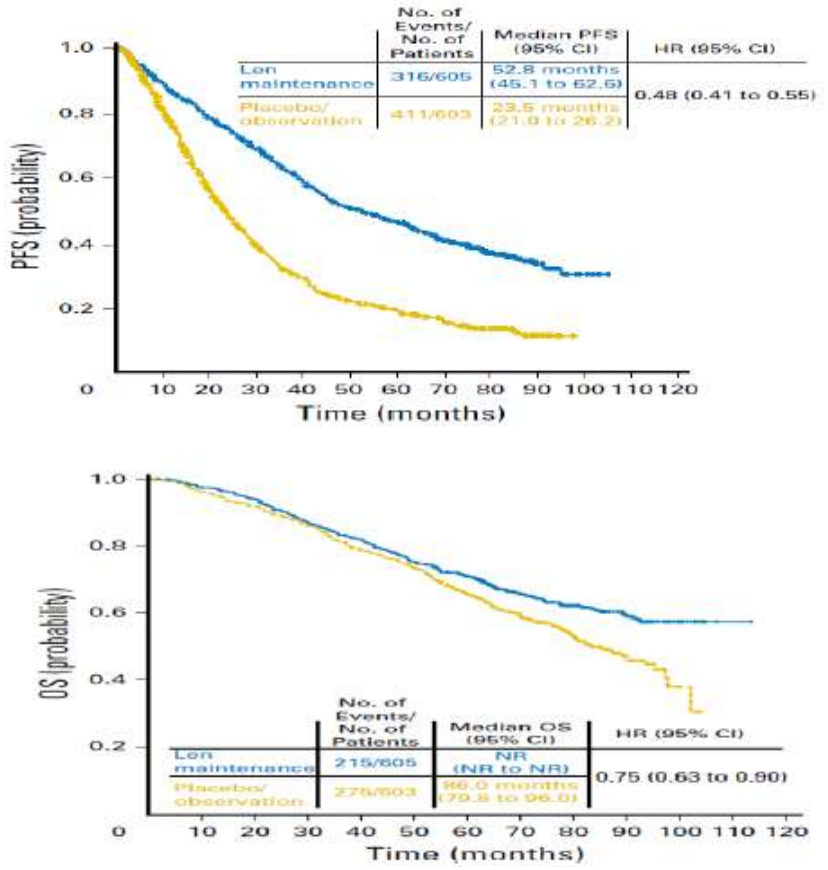
# Duration of Maintenance Therapy and Relapse Risk

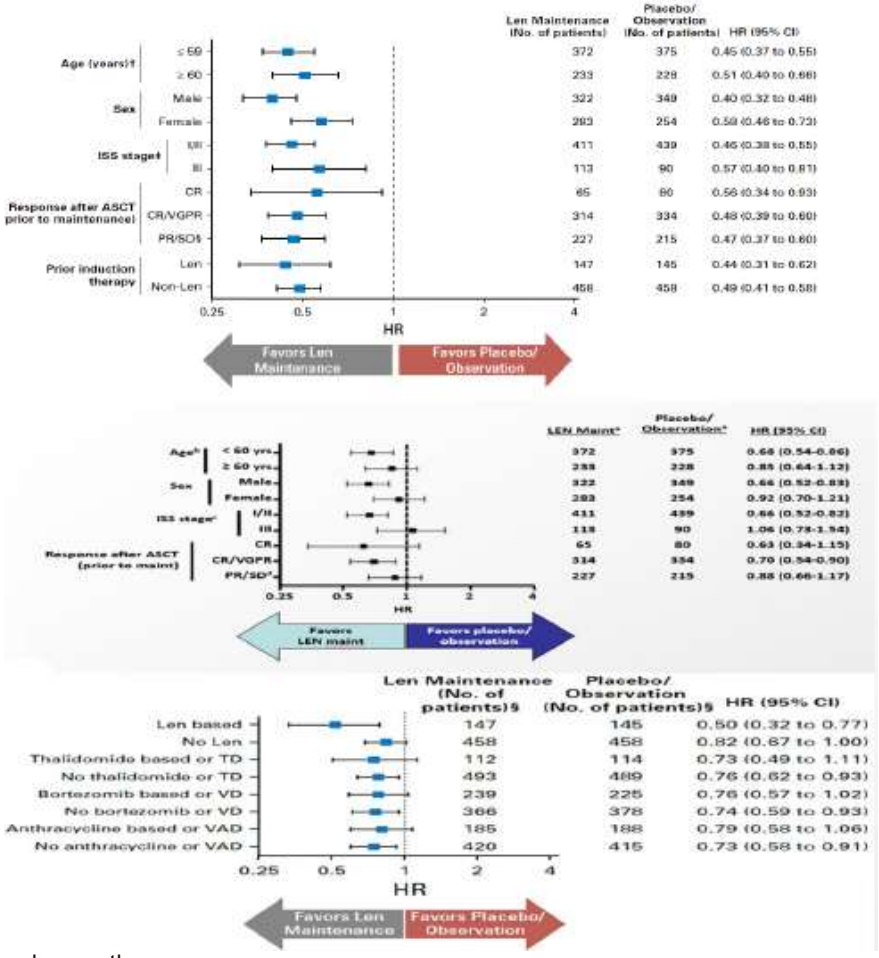



Avigan Z, et al. Presented at: 23rd IMS Annual Meeting; 2026.

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# Lenalidomide Maintenance after ASCT




SD = stable disease; TD = thalidomide, dexamethasone; VAD = vincristine, doxorubicin, dexamethasone

McCarthy PL, et al. *J Clin Oncol*. 2017;35(29):3279-3289.

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# Optimal Duration of Lenalidomide Maintenance

**Label use: lenalidomide at 10-15 mg daily until PD**

**Table 1.** Summary of randomized phase III trials evaluating lenalidomide maintenance after ASCT.

| Study | N | Induction Therapy | Dosing Schedule | Intended Duration of Maintenance | Reported Duration of Lenalidomide Maintenance | TTP or PFS (Maintenance vs. No) | OS (Maintenance vs. No) | SPMs |
|---|---|---|---|---|---|---|---|---|
| CALGB 100104 [7,8] | 460 | ≤2 regimens; 94% received a regimen containing Thal, Len, and/or Bor | 10 mg continuous, increase up to 15 mg | Until progression | 31 months (median) | Median TTP *: 57 vs. 29 months (HR, 0.57; $p < 0.0001$) | Median OS *: 114 vs. 84 months ($p = 0.0004$) | Len: 8% hematologic, 6% solid tumor, 5% noninvasive<br>Pbo: 1% hematologic, 4% solid tumor, 3% noninvasive |
| IFM 2005-02 [6,11] | 614 | 46% received vincristine, doxorubicin, Dex and 46% received Bor and Dex<br><br>21% received tandem transplant | All patients received 2 cycles of consolidation (25 mg/d, 21 out of 28 days)<br>Maintenance: 10 mg continuous, increase up to 15 mg | Stopped due to concerns regarding second primary malignancies at a median time of 2 years (range 1–3 years) | 25 months (mean) | Median PFS: 41 vs. 23 months (HR, 0.50; $p < 0.001$)<br><br>4-year PFS: 43 vs. 22% ($p < 0.001$) | Median follow-up 45 months: 74 vs. 76% ($p = 0.7$)<br><br>4-year OS: 73% vs. 75% ($p = 0.7$) | Len: 4% hematologic, 3% solid tumor, 2% nonmelanoma skin cancer<br>Pbo: 2% hematologic, 1% solid tumor, 1% nonmelanoma skin cancers |
| RV-MM-209 [9,11] | 402 | 4 cycles Len/Dex followed by either transplant or MPR | 10 mg (21 out of 28 days) | Until progression | 35 months (mean) (TE population) | Median PFS **: 42 vs. 22 months (HR, 0.47; $p < 0.001$) | 3-year OS **: 88% vs. 79% ($p = 0.14$) | 4.3% (Len) vs. 4.3% (Obs) |
| Myeloma XI [10] | 1247 *** | CTD vs. RCD followed by CVD if suboptimal response | 10 mg (21 out of 28 days) | Until progression | NR for TE population | Median PFS: 57 vs. 30 months (HR, 0.48; $p < 0.0001$) | 3-year OS: 88 vs. 80% (HR, 0.69; $p = 0.014$) | 3-year cumulative incidence: 5.3% (Len) vs. 3.1% (Obs) **** |

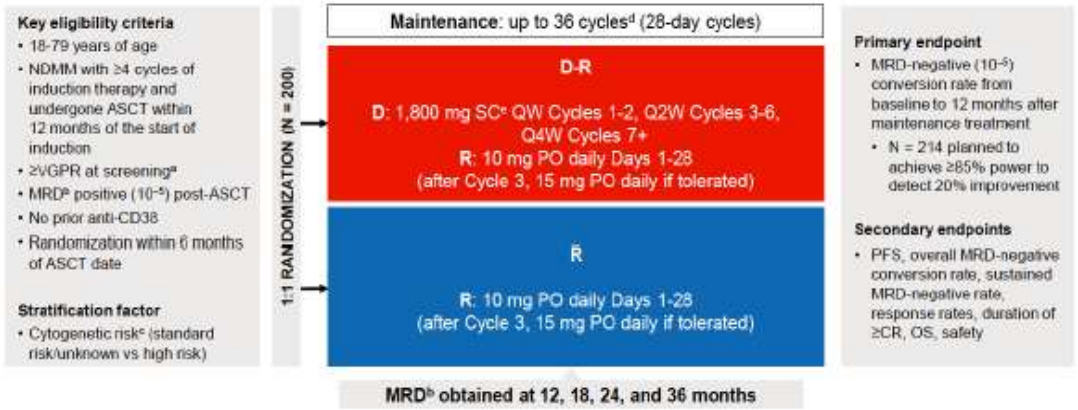
**Athough we plan continuous therapy, the median DoMaintenance is approx 2-3 years**

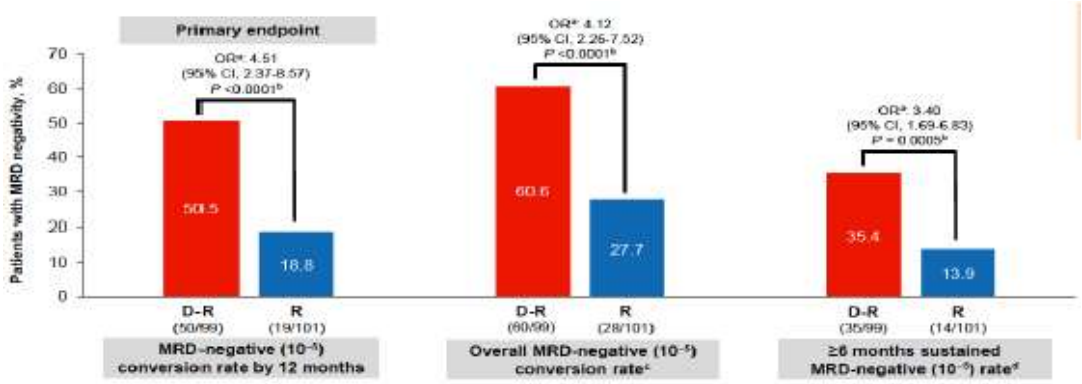
TTP = time to progression; SPM = secondary primary malignancy.
McCarthy PL, et al. *J Clin Oncol*. 2017;35(29):3279-3289.

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# Auriga Study: DaraR vs R as Maintenance

- Objective: To determine the impact of adding DARA to R maintenance on MRD-negative conversion

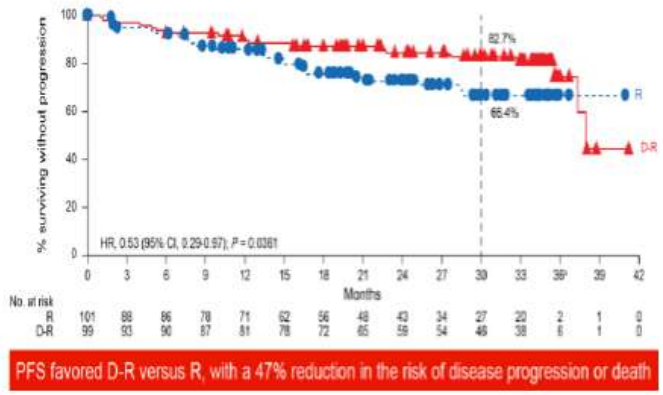



- 36-month maintenance duration
- All patients naïve for anti-CD38
- Suboptimal response after ASCT

Progression-free survival

- Median follow-up: 32.3 months



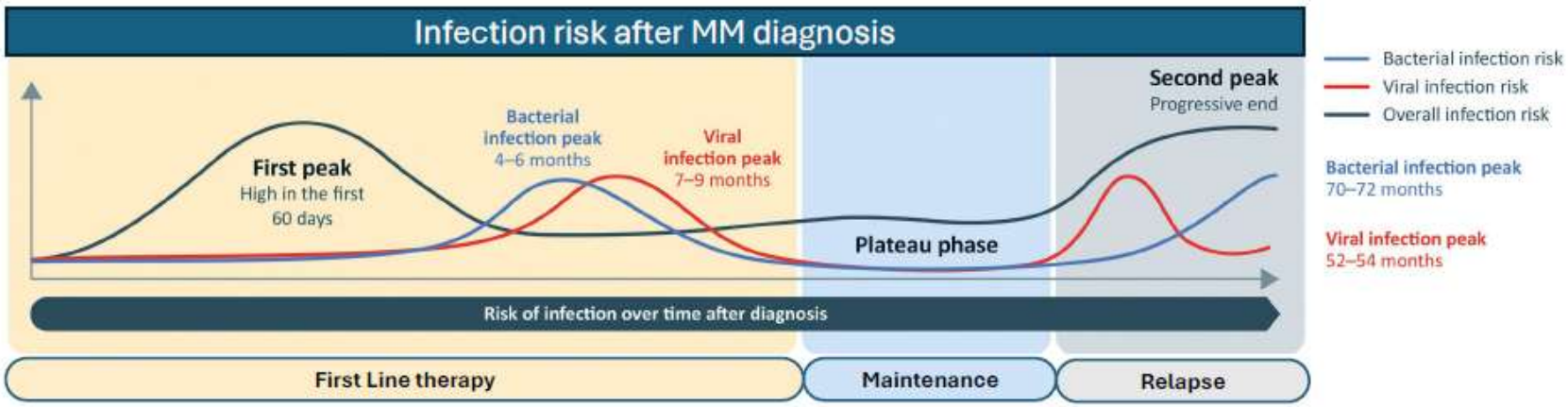

PFS favored D-R versus R, with a 47% reduction in the risk of disease progression or death

Badros A, et al. *Blood*. 2025;145(3):300-310.

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# Infections

MM patients have **5X risk of clinically significant infection** compared to matched controls without MM[1]




Blimark CH, et al. *Haematologica*. 2025;110(1):163-172. Giralt S, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23(10):719-732.

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# Supportive Care Approach

- **Acyclovir or valacyclovir**
  Reduce incidence of Zoster reactivation
  <2% vs13% bortezomib (APEX trial) or 2-4% daratumumab #

- **Sulfamethoxazole-Trimethoprim**
  *~90% reduction in PJP incidence with TMP-SMX in immunocompromised patients on high dose corticosteroids
  (prednisone ≥20 mg/day or dexamethasone at equivalent doses)

- **Without thromboprophylaxis,** risk of VTE about 14–26% in NDMM on IMiD-based regimens
- VTE calculators: **IMPEDE[1], SAVED[2], IMWG**

- **Recommendation:**
  - **Aspirin: low risk patients**
  - **Anticoagulation: high risk patients**

PJP = pneumocystis jiroveci pneumonia; TMP-SMX = sulfamethoxazole, trimethoprim; VTE = venous thromboembolism.
Green H, et al. *Mayo Clin Proc.* 2007;82(9):1052-1059.

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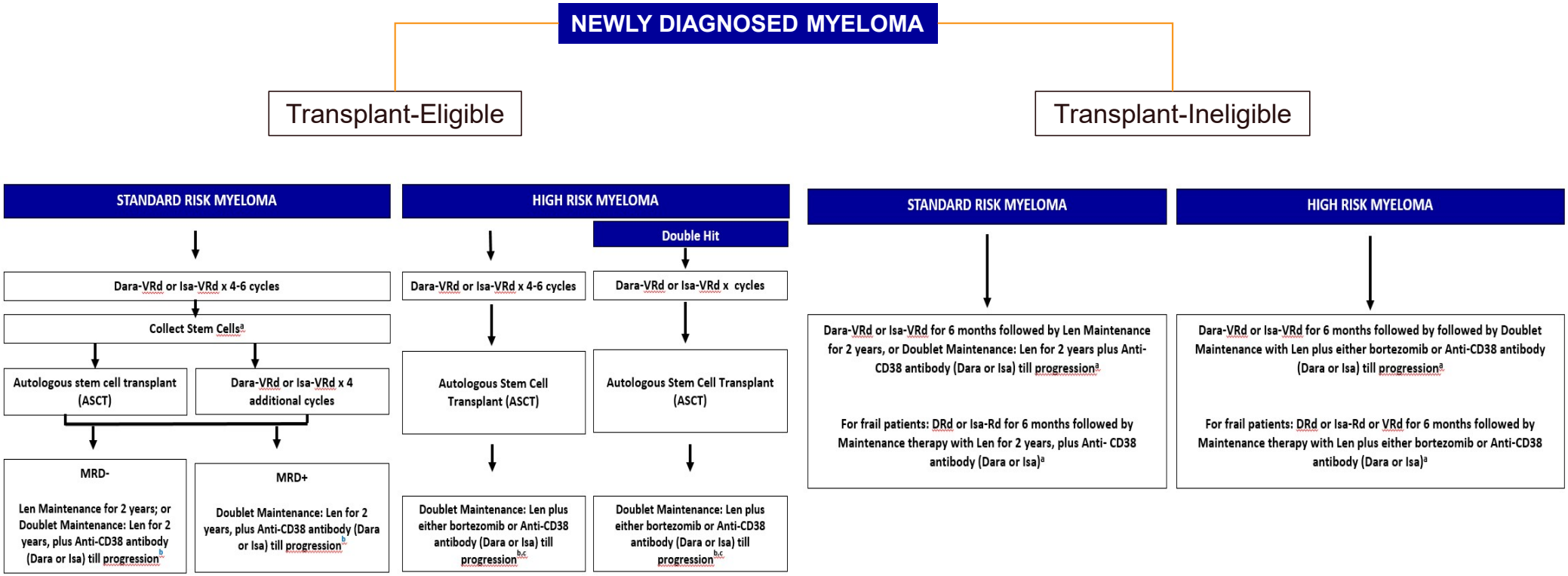
# Supportive Care after Stem Cell Transplant

- **Sulfamethoxazole trimethoprim:** First 100 days
  - Humoral and cellular immune compromise, PJP ppx
- **Acyclovir first 1 year**
  - Risk of zoster infection
- **Revaccination after 6 months**
- **No Live vaccines for first 2 years**
  - MEASLES OUTBREAK CONCERNS?
  - IVIG as post-exposure prophylaxis to exposed immunocompromised patients
  - 400 mg/kg IV within 6 days of exposure

Do LAH, Mulholland K. N Engl J Med. 2025;393(24):2447-2458.

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# Treatment Recommendation




Adapted from mSMART.org

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# Key Learning Points



- Treatment should be individualized and be designed to offer the best QoL
  - Patient factors, disease factors, social factors
- The use of anti-CD38 has become standard practice as part of induction and maintenance
- Supportive care is essential to reduce treatment interruptions and risks to patient

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# Q&A Session