New IMS/IMWG Risk Criteria by Next-Generation Sequencing (NGS): Analysis of Daratumumab Benefit in Both High- and Standard-Risk Patients in the PERSEUS/EMN017 Study

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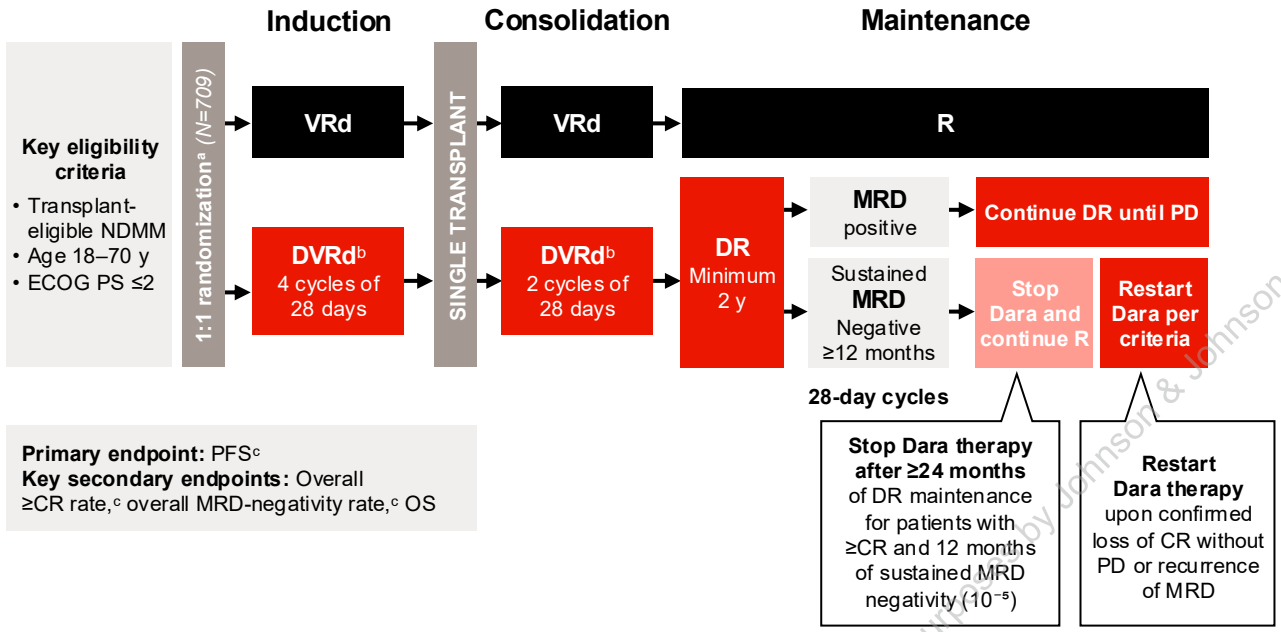
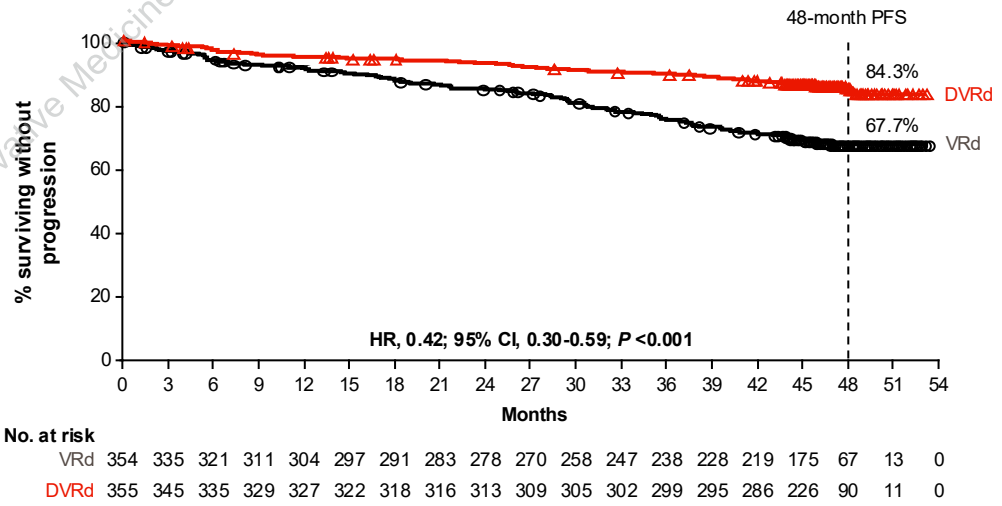
PERSEUS: IMS/IMWG CGS – Key Takeaways

- DVRd improved PFS, overall MRD-negativity, and sustained MRD-negativity rates versus VRd in both standard- and high-risk subgroups as defined by the new IMS/IMWG CGS criteria
- The UMA-NGS panel successfully stratified risk according to the new IMS/IMWG CGS criteria, identifying more high-risk patients in the PERSEUS study (35%) compared with those previously identified using PP-FISH (22%)
- Achieving 12-month sustained MRD-negativity removes the negative prognostic impact of an IMS/IMWG CGS high-risk classification at diagnosis
- These post hoc results expand the benefit of DVRd induction/consolidation followed by DR maintenance as standard of care for TE-NDMM, regardless of cytogenetic risk or risk classification system
- This study is the first to re-stratify patients with TE-NDMM from a phase III trial using IMS/IMWG CGS

CGS, Consensus Genomic Staging; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; MRD, minimal residual disease; PFS, progression-free survival; PP-FISH, per protocol fluorescence in situ hybridization; SOC, standard of care; TE-NDMM, transplant-eligible newly diagnosed multiple myeloma; UMA-NGS, Unique Molecular Assay-next generation sequencing.

PERSEUS: DVRd-ASCT-DR as Standard of Care





58% reduction in the risk of progression or death in patients receiving DVRd

[a]Stratified by ISS stage and cytogenetic risk. [b]Dara 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [c]Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. [d]MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with ≥VGPR post-consolidation and at the time of suspected ≥CR. Overall, the MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time. ≥CR, complete response or better; Dara, daratumumab; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; ISS, International Staging System; IV, intravenous; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; ≥VGPR, very good partial response or better; VRd, bortezomib, lenalidomide, and dexamethasone; y, years.

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

PERSEUS: IMS/IMWG CGS High-Risk Criteria

The IMS/IMWG recently proposed novel CGS high-risk criteria for NDMM, including genetic alterations not identifiable by FISH but by NGS (eg, *TP53* mutations)[1]

Risk subgroup	Definition
PP-FISH high risk	Defined per protocol as ≥1 del17p, t(4;14), and/or t(14;16)
IMS/IMWG CGS high risk[1]	Defined as the presence of at least one of the following: • del17p[a] and/or *TP53* mutation[b] • t(4;14) or t(14;16) or t(14;20) with additional amp1q or biallelic del1p • Monoallelic del1p with additional amp1q, or biallelic del1p[b] • High β2M with normal renal function

[a]CCF ≥20%, by analyses conducted on CD138+/purified cells. [b]Assessed using an NGS-based method.
β2M, β2-microglobulin; CCF, cancer cell fraction; CGS, consensus genomic staging; FISH, fluorescence in situ hybridization; PP, per protocol; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; PP-FISH, per-protocol fluorescence in situ hybridization; UMA, Unique Molecular Assay.

1. Avet-Loiseau H, et al. *J Clin Oncol. 2025;*43:2739-51. 2. Poletti A, et al. *Haematologica*. 2025;110(10):2436-2450.

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Study aim

This expanded post hoc analysis investigated clinical outcomes based on the presence of high-risk disease as defined by the new IMS/IMWG CGS risk criteria utilizing the recently developed NGS-based UMA target panel[2]

[a]CCF ≥20%, by analyses conducted on CD138+/purified cells. [b]Assessed using an NGS-based method.
β2M, β2-microglobulin; CCF, cancer cell fraction; CGS, consensus genomic staging; FISH, fluorescence in situ hybridization; PP, per protocol; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; PP-FISH, per-protocol fluorescence in situ hybridization; UMA, Unique Molecular Assay.
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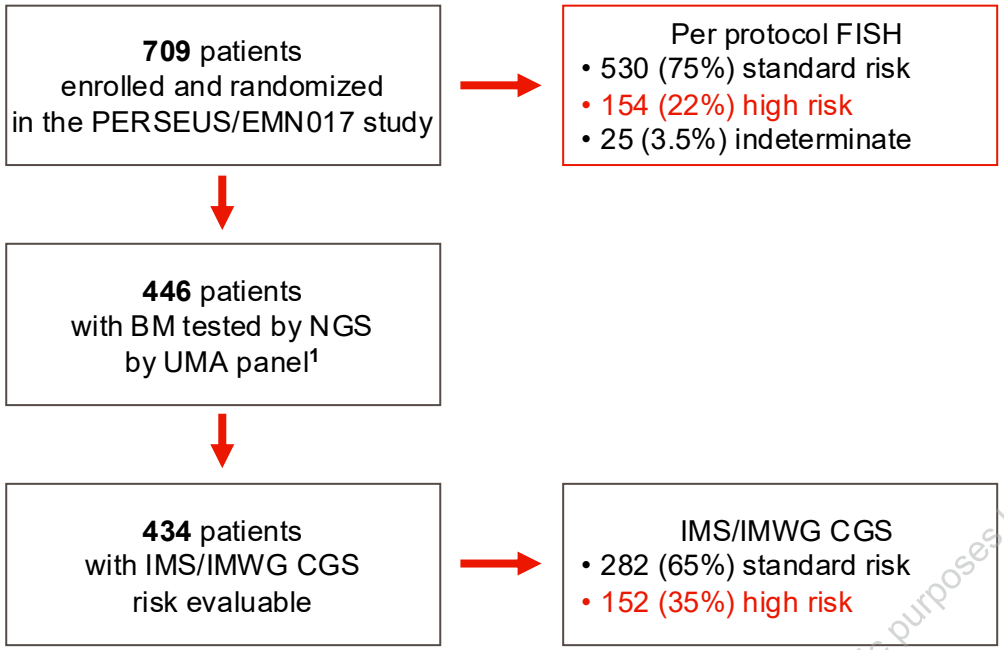
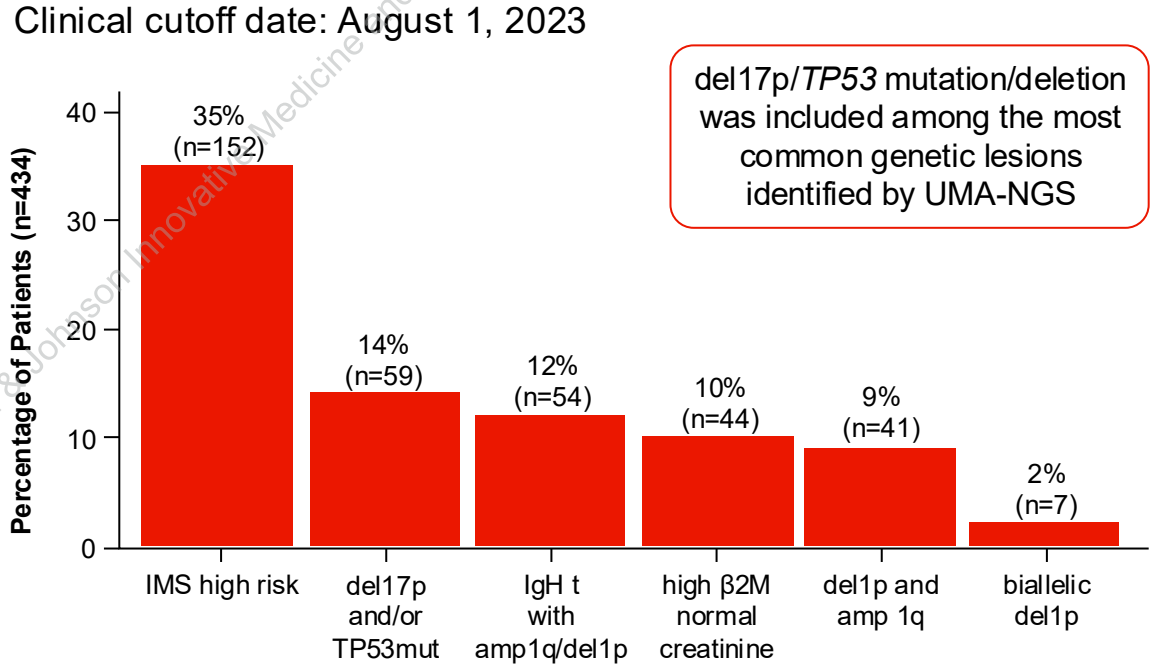
PERSEUS: IMS/IMWG CGS – Risk Classification Results





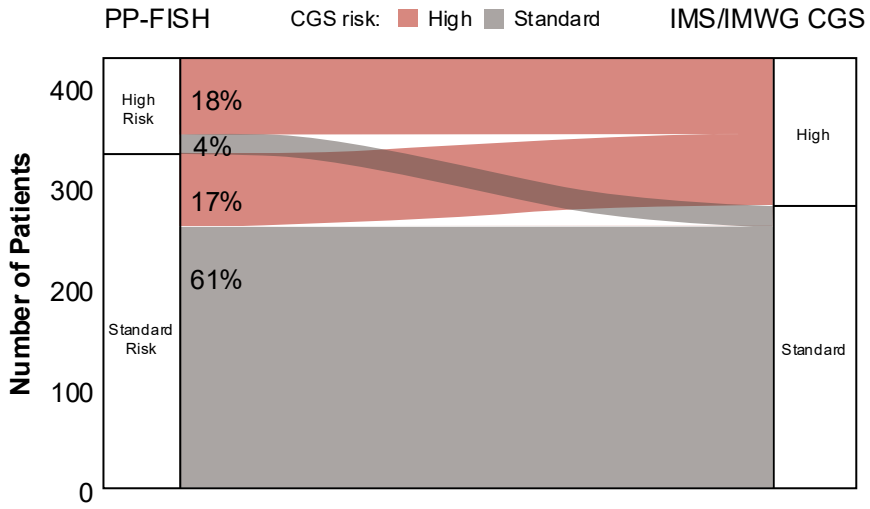
UMA-NGS panel successfully stratified risk according to CGS criteria, identifying at least 12% more high-risk patients in the PERSEUS study versus those identified using PP-FISH

BM, bone marrow; CGS, Consensus Genomic Staging, DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; ITT, intent-to-treat; NGS, next-generation sequencing; PP-FISH, per-protocol fluorescence in-situ hybridization; UMA-NGS, Unique Molecular Assay next-generation sequencing; VRd, bortezomib, lenalidomide, and dexamethasone.

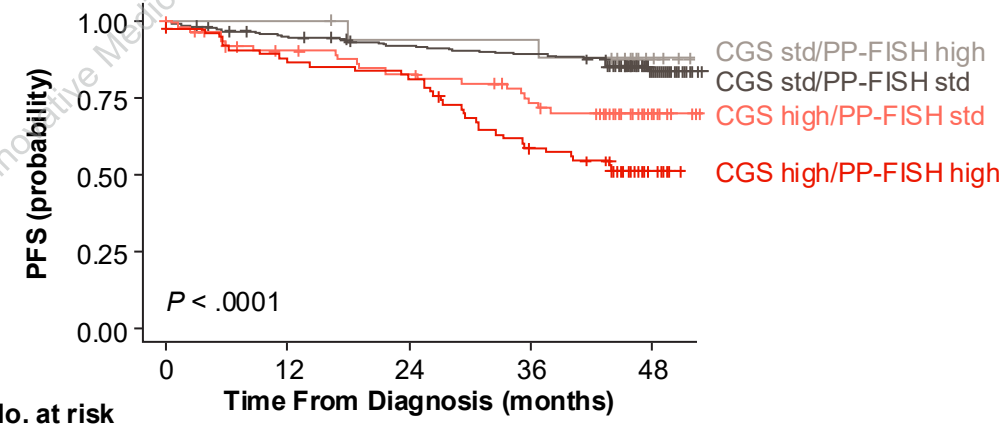
1. Poletti A, et al. *Haematologica*. 2025;110(10):2436-2450.

PERSEUS: IMS/IMWG CGS – Risk Re-classification

Re-classification of patient risk from PP-FISH criteria to IMS/IMWG CGS



PFS in patients with re-classified risk status based on PP-FISH and IMS/IMWG CGS



No. at risk					
CGS std/PP-FISH high	17	17	15	15	4
CGS std/PP-FISH std	258	237	225	218	65
CGS high/PP-FISH std	73	61	55	46	11
CGS high/PP-FISH high	76	64	60	41	12

IMS/IMWG CGS reclassified 17% of patients from standard to high risk[a], with only 4% being reclassified from high to standard risk with improved risk classification. In patients re-classified from PP-FISH high risk to IMS/IMWG CGS standard risk, PFS outcomes did not differ from those observed in patients classified as standard risk by both methods

[a]IMS/IMWG reclassified patients from standard-risk to high-risk mainly due to *TP53* mutations not detectable by PP-FISH or inclusion of amp1q and del1p.
CGS, Consensus Genomic Staging; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; NA, not available; PFS, progression-free survival; PP-FISH, per-protocol fluorescence in-situ hybridization; std, standard risk.

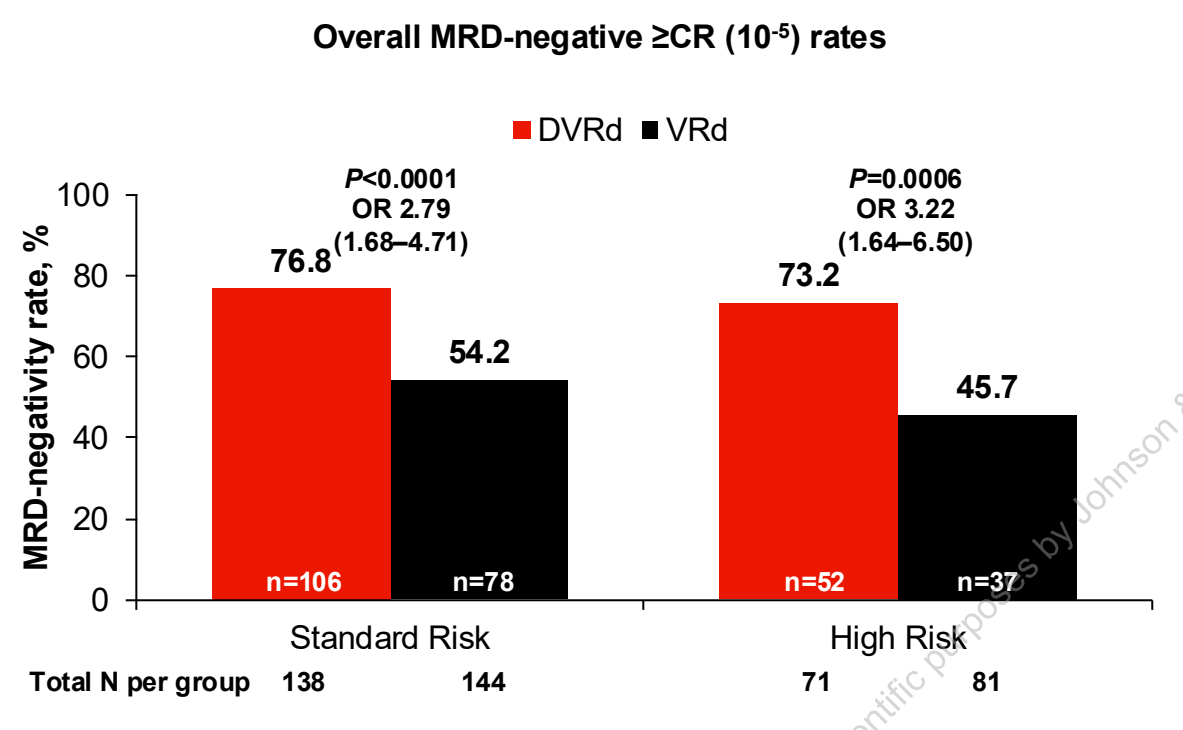
PERSEUS: IMS/IMWG CGS – Baseline Characteristics in UMA-Evaluable Patients

Variable	DVRd (n=209)	VRd (n=225)	*P* value
IMS/IMWG CGS, high risk, n (%)	69 (33.0)	81 (36.0)	.581
Sex, female, n (%)	86 (41.1)	95 (42.2)	.897
Age, years, median (IQR)	61 (53-65)	60 (54-65)	.840
ISS, n (%)			
ISS I	105 (50.2)	113 (50.2)	.747
ISS II	69 (33.0)	79 (35.1)	
ISS III	35 (16.7)	32 (14.2)	
PP-FISH cytogenetics, high risk, n (%)	49 (23.4)	44 (19.6)	.432

Baseline characteristics were generally balanced across treatment arms, and were comparable to those not evaluated by UMA-NGS (n=275) and to the PERSEUS ITT population (N=709), suggesting sample availability did not bias the results

CGS, Consensus Genomic Staging; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; IQR, interquartile range; ISS, International Staging System; ITT, intent-to-treat; PP-FISH, per-protocol fluorescence in-situ hybridization; UMA-NGS, Unique Molecular Assay next-generation sequencing; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: IMS/IMWG CGS – Overall MRD-Negative ≥CR Rates (10^{-5} and 10^{-6})



DVRd was associated with increased MRD-negativity rates compared with VRd in both IMS/IMWG CGS standard-risk and high-risk patients

Bone marrow MRD was assessed using NGS (clonoSEQ®). Overall MRD-negativity rate was defined as the proportion of patients who achieved both ≥CR and MRD-negative status.
CGS, Consensus Genomic Staging; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; MRD, minimal residual disease; OR, odds ratio; VRd, bortezomib, lenalidomide, and dexamethasone.

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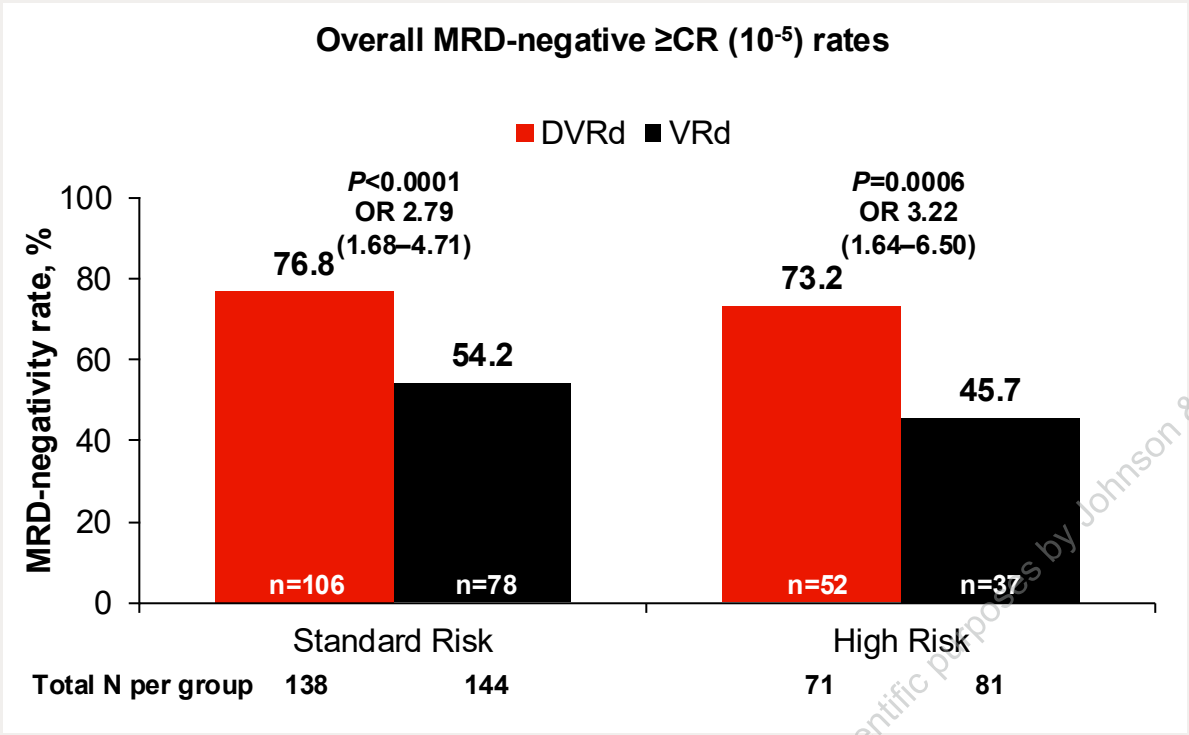

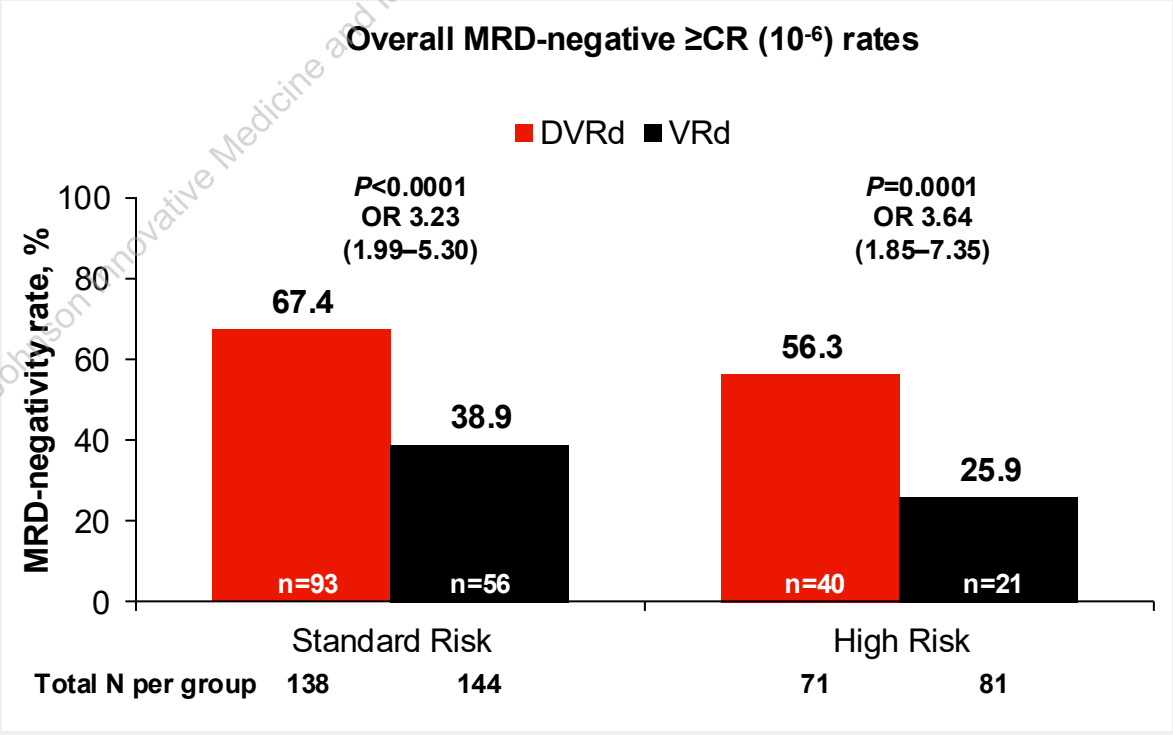

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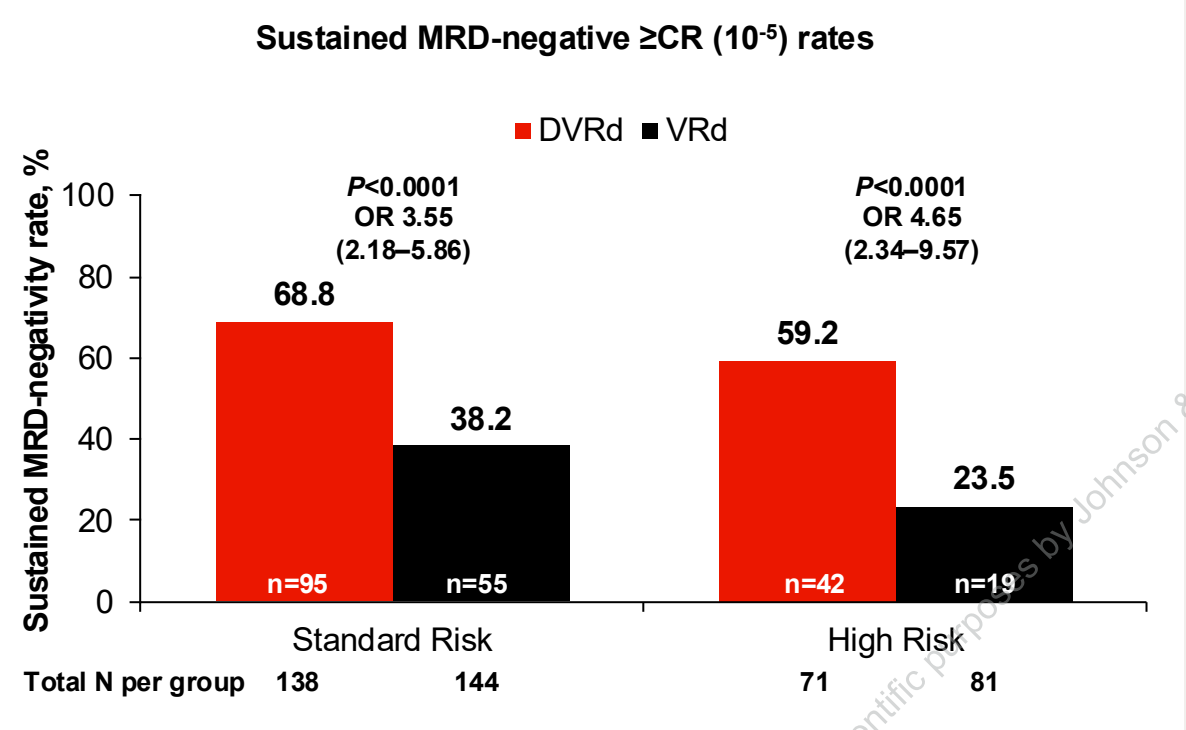
Bone marrow MRD was assessed using NGS (clonoSEQ®). Overall MRD-negativity rate was defined as the proportion of patients who achieved both ≥CR and MRD-negative status.
CGS, Consensus Genomic Staging; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; MRD, minimal residual disease; OR, odds ratio; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: IMS/IMWG CGS Sustained MRD-Negative ≥CR Rates (10^{-5} and 10^{-6}) for ≥12 months



Sustained MRD-negativity rates for ≥12 months were higher with DVRd vs VRd for both IMS/IMWG CGS standard-risk and high-risk patients

Bone marrow MRD was assessed using NGS (clonoSEQ®). Sustained MRD negativity was defined, in patients with ≥CR, as confirmed MRD negativity ≥12 ± 1 months apart without any MRD positivity in between.
CGS, Consensus Genomic Staging; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; MRD, minimal residual disease; OR, odds ratio; VRd, bortezomib, lenalidomide, and dexamethasone.

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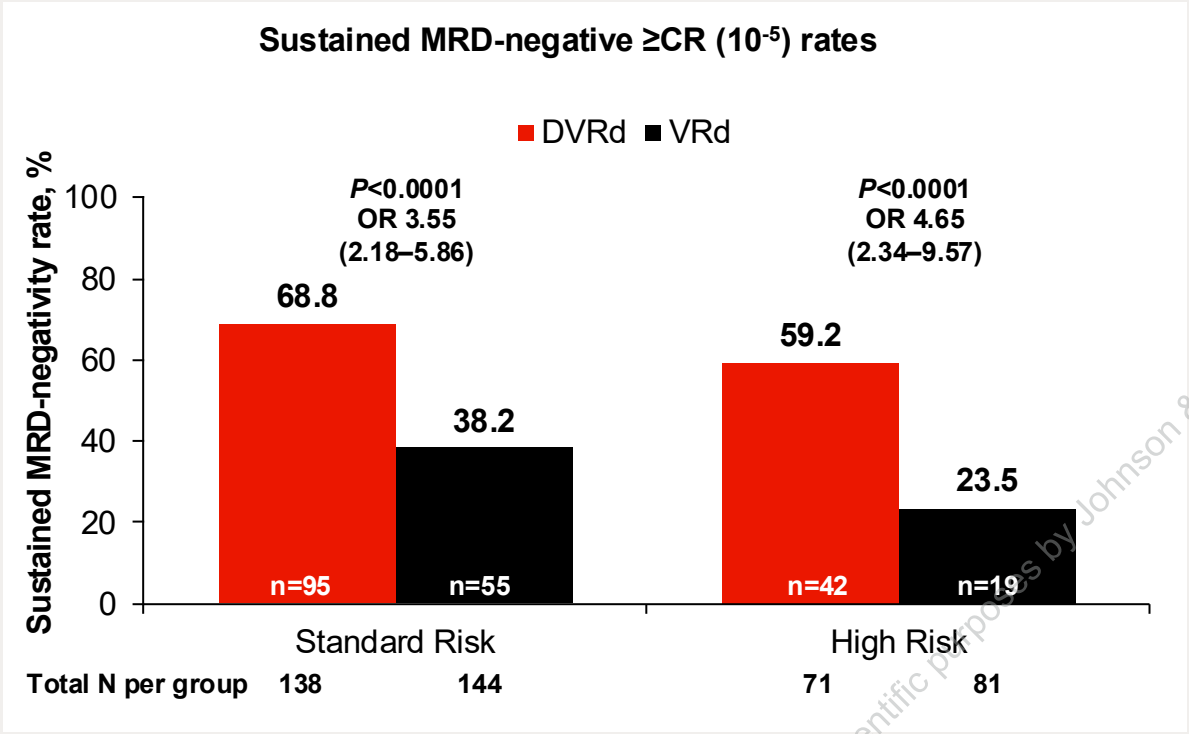

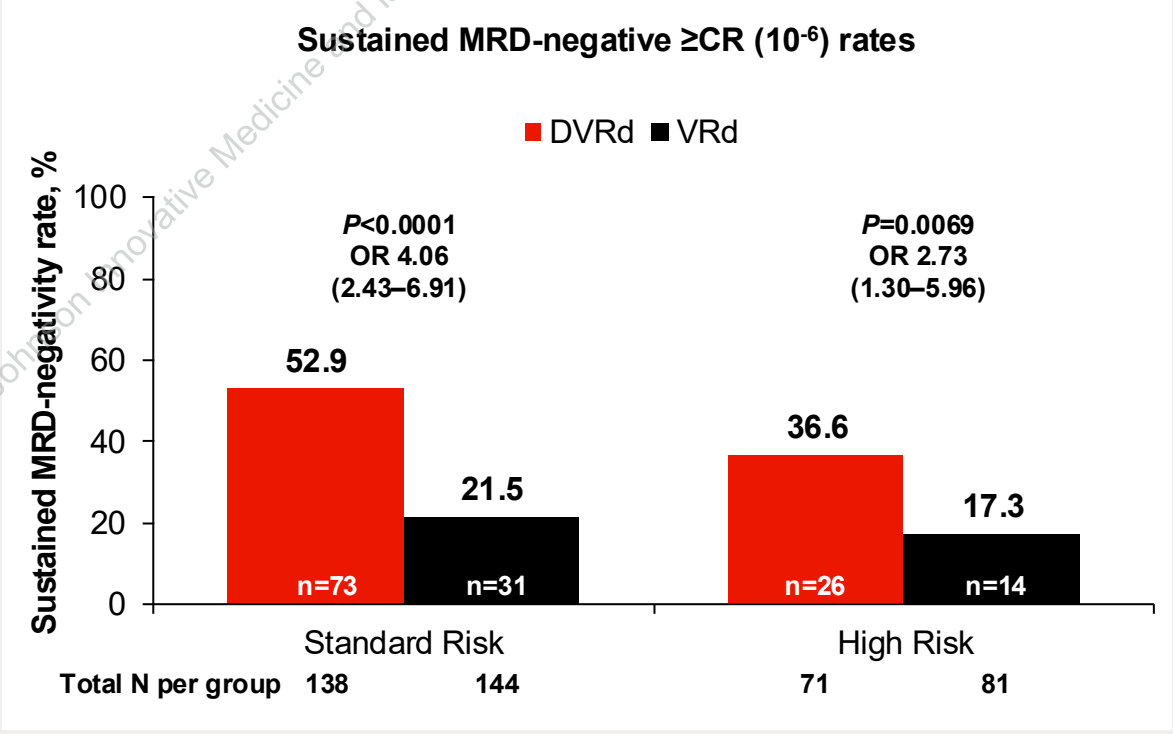

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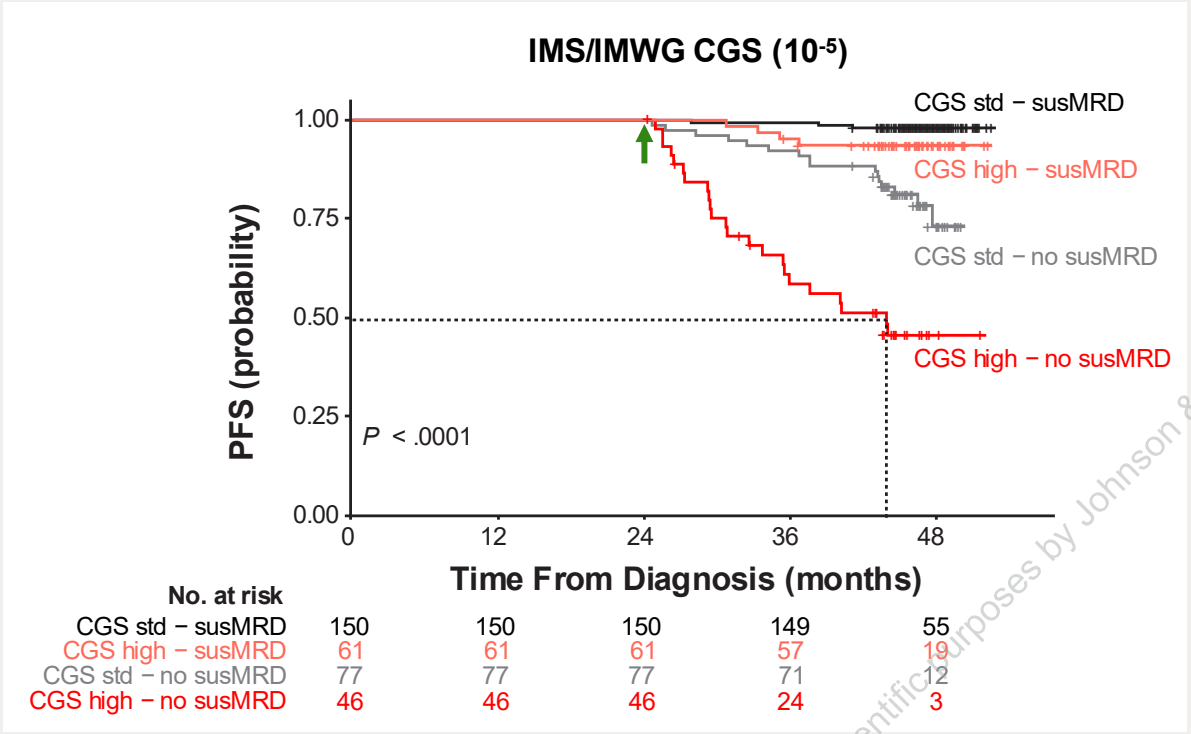
Bone marrow MRD was assessed using NGS (clonoSEQ®). Sustained MRD negativity was defined, in patients with ≥CR, as confirmed MRD negativity ≥12 ± 1 months apart without any MRD positivity in between.
CGS, Consensus Genomic Staging; CR, complete response; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; MRD, minimal residual disease; OR, odds ratio; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: IMS/IMWG CGS – PFS Landmark Analysis From 24 Months in Patients Achieving Sustained MRD-Negativity (10^{-5} and 10^{-6})



Achieving 12-month sustained MRD-negativity removes the negative prognostic impact of an IMS/IMWG CGS high-risk classification at diagnosis, highlighting a promising treatment goal

CGS, Consensus Genomic Staging; ≥CR, complete or better response; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; MRD, minimal residual disease; MRD neg, MRD negative; MRD pos, MRD positive; OR, odds ratio; PFS, progression-free survival; std, standard; susMRD, sustained MRD-negativity.

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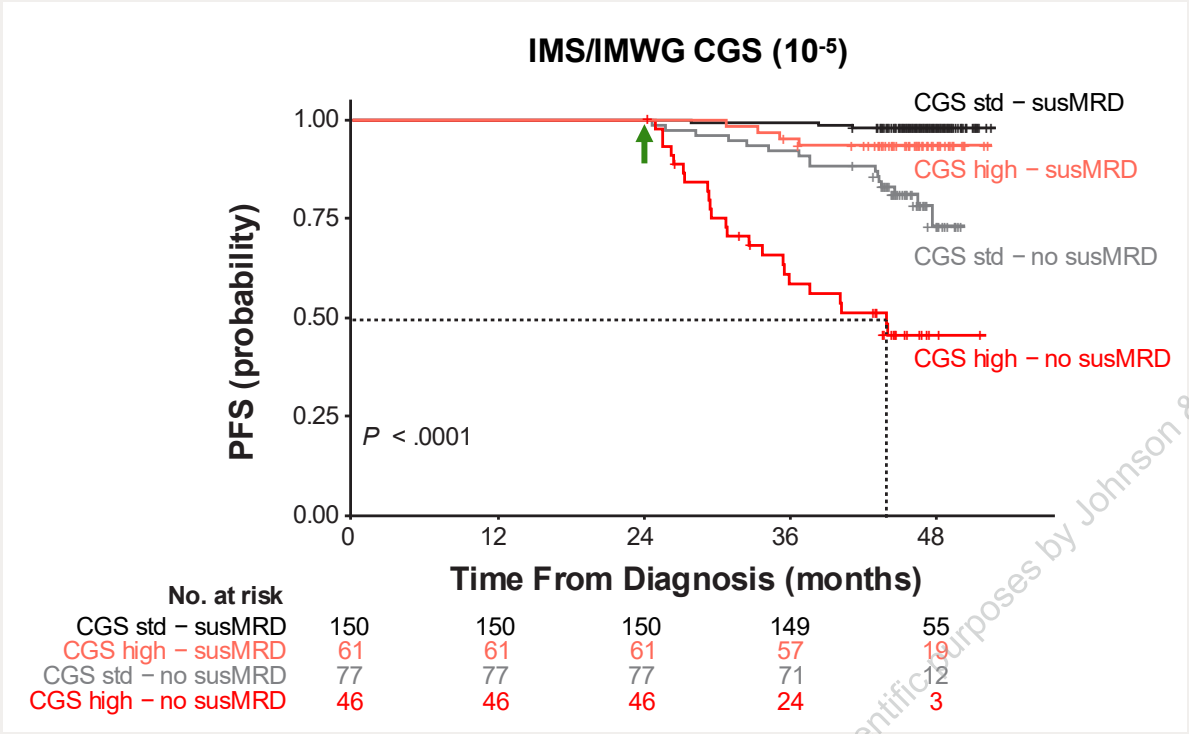

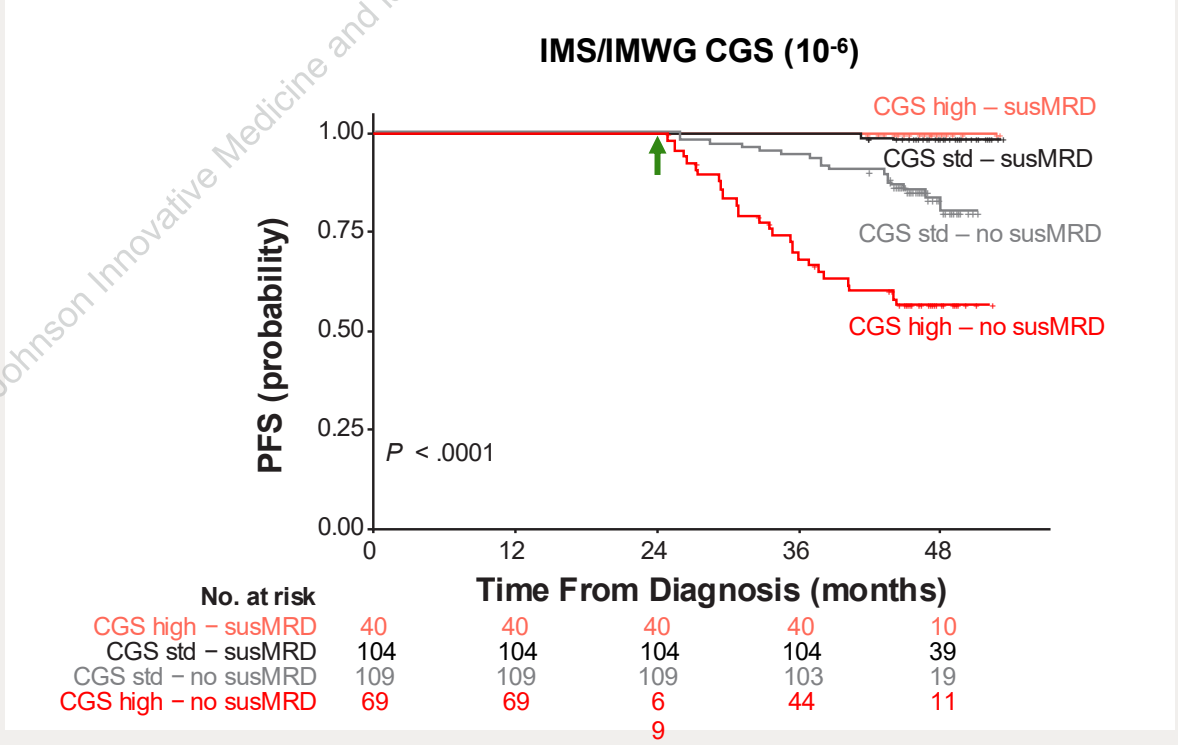

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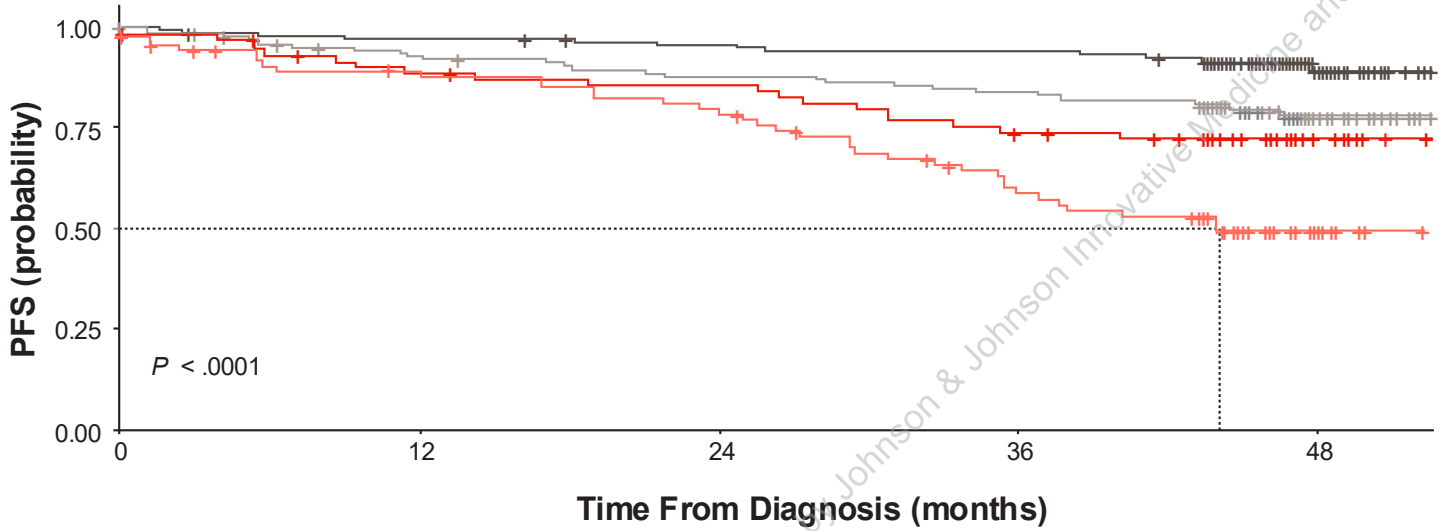
PERSEUS: IMS/IMWG CGS PFS



DVRd std risk
VRd std risk
DVRd high risk
VRd high risk

OR, 0.38 (95% CI 0.20–0.74; *P*=0.005)

OR, 0.54 (95% CI 0.31–0.95; *P*=0.03)

No. at risk

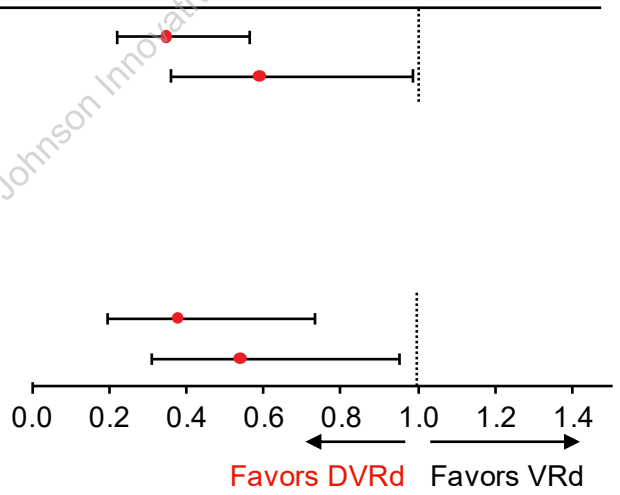
DVRd standard risk	138	133	128	126	43
VRd standard risk	144	126	117	112	28
DVRd high risk	71	61	58	49	15
VRd high risk	81	67	60	41	8

DVRd led to improved PFS in both IMS/IMWG CGS standard-risk and high-risk patients

CGS, Consensus Genomic Staging; CI, confidence interval; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; OR, odds ratio; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone; std, standard.

PERSEUS: IMS/IMWG CGS – PFS Based on Cytogenetic Risk by PP-FISH and IMS/IMWG CGS Risk by UMA-NGS

Criteria		DVRd N/n	DVRd Median PFS (mo)	VRd N/n	VRd Median PFS (mo)	OR (95% CI)	*P* value
PP-FISH							
PP-FISH	Standard risk	25/264	NE	62/266	NE	0.35 (0.22 to 0.56)	< .0001
PP-FISH	High risk	24/76	NE	38/78	44.1	0.59 (0.36 to 0.99)	.0439
IMS/IMWG CGS							
IMS/IMWG	Standard risk	13/138	NE	29/144	NE	0.38 (0.20 to 0.74)	.005
IMS/IMWG	High risk	19/71	NE	36/81	NE	0.54 (0.31 to 0.95)	.03



DVRd improved PFS versus VRd, for both standard- and high-risk defined by PP-FISH or IMS/IMWG CGS, in patients with TE-NDMM

CGS, Consensus Genomic Staging; CI, confidence interval; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; OR, odds ratio; PFS, progression-free survival; PP-FISH, per-protocol fluorescence in situ hybridization; TE-NDMM, transplant-eligible newly diagnosed multiple myeloma; VRd, bortezomib, lenalidomide, and dexamethasone.

PERSEUS: IMS/IMWG CGS – Conclusions

- The UMA-NGS panel[1] successfully stratified cytogenetic risk according to the new IMS/IMWG CGS criteria in the PERSEUS study, improving risk stratification
- In both standard-risk and high-risk patients according to the IMS/IMWG CGS, DVRd compared with VRd was associated with:
  - Increased MRD-negativity rates (≥CR; 10^{-5} and 10^{-6})
  - Increased sustained MRD-negativity rates for ≥12 months (≥CR; 10^{-5} and 10^{-6})
  - Improved PFS
- **DVRd improved PFS versus VRd, for both standard- and high-risk defined by PP-FISH or IMS/IMWG CGS, in patients with TE-NDMM**

These data further support DVRd induction/consolidation and DR maintenance as standard of care for TE-NDMM, regardless of risk status

CGS, Consensus Genomic Staging; CR, complete response; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; MRD, minimal residual disease; PFS, progression-free survival; PP-FISH, per-protocol fluorescence in situ hybridization; TE-NDMM, transplant-eligible newly diagnosed multiple myeloma; UMA-NGS, Unique Molecular Assay next-generation sequencing; VRd, bortezomib, lenalidomide, and dexamethasone. 1. Poletti A, et al. *Haematologica*. 2025;110(10):2436-2450.