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

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Key Takeaway

These data further support D-VRd induction/consolidation followed by D-R maintenance as standard of care for transplant-eligible patients with NDMM regardless of risk status

Conclusions

- D-VRd improved PFS versus VRd for both standard- and high-risk patients, as defined by PP-FISH or IMS/IMWG CGS criteria
- In both standard- and high-risk patients according to IMS/IMWG CGS criteria, D-VRd increased the rates of MRD negativity (≥CR; 10^{-5} and 10^{-6}) and sustained MRD negativity lasting ≥12 months (≥CR; 10^{-5} and 10^{-6}) and improved PFS compared with VRd
- The UMA-NGS panel successfully stratified cytogenetic risk according to the new IMS/IMWG CGS criteria in the PERSEUS/EMN017 study, improving risk stratification

Acknowledgments

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Disclosure

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Introduction

- The International Myeloma Society/International Myeloma Working Group (IMS/IMWG) recently proposed Consensus Genomic Staging (CGS) risk criteria for newly diagnosed multiple myeloma (NDMM), including genetic alterations not identifiable by fluorescence in situ hybridization (FISH), by utilizing next-generation sequencing (NGS; eg, *TP53* mutations)[1]
- This expanded post hoc analysis of the PERSEUS/EMN017 study investigated clinical outcomes in patients based on the presence of high-risk disease, as defined by the new IMS/IMWG CGS risk criteria utilizing the recently developed NGS-based Unique Molecular Assay (UMA) target panel[2]

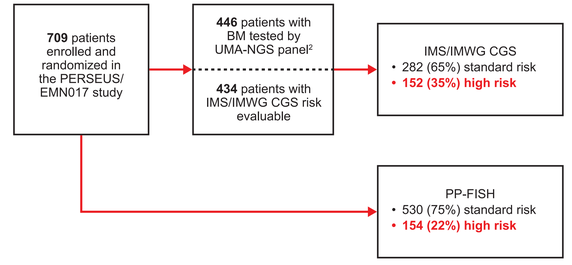
Risk subgroup	Definition
PP-FISH high risk	Defined per protocol as ≥1 del17p, t(4;14), and/or t(14;16)
IMS/IMWG CGS high risk[1]	Defined as the presence of ≥1 of the following: • del17p[a] and/or *TP53* mutation[b] • t(4;14), t(14;16), and/or t(14;20) with additional amp1q or biallelic del1p • Monoallelic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

PP-FISH, per-protocol fluorescence in situ hybridization; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; CGS, Consensus Genomic Staging; β2M, β2 microglobulin; CCF, cancer cell fraction; NGS, next-generation sequencing.
[a]CCF ≥20%, by analyses conducted on CD138+purified cells.
[b]Assessed using an NGS-based method.

Methods

- In the phase 3 PERSEUS/EMN017 study (ClinicalTrials.gov Identifier: NCT03710603), 709 transplant-eligible patients with NDMM were randomized 1:1 to daratumumab plus bortezomib, lenalidomide, and dexamethasone (D-VRd) induction/consolidation followed by daratumumab and lenalidomide (D-R) maintenance or VRd induction/consolidation followed by lenalidomide maintenance[3]
- The primary endpoint was progression-free survival (PFS)
- Minimal residual disease (MRD)–negativity rate, defined as the proportion of patients who achieved both MRD negativity and complete response or better (≥CR) in the intent-to-treat population, was a key secondary endpoint. Bone marrow MRD was assessed using NGS (clonoSEQ®)
- Sustained MRD negativity was defined as MRD negativity with ≥CR ≥12 months apart and without MRD positivity in between
- For cytogenetic/genomic analyses, the UMA-NGS target panel was used on DNA extracted from CD138+ bone marrow cells (**Figure 1**)

Figure 1: PERSEUS cytogenetic/genomic analysis



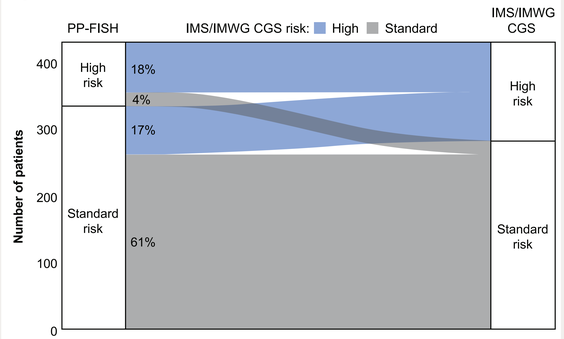
BM, bone marrow; UMA, Unique Molecular Assay; NGS, next-generation sequencing; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; CGS, Consensus Genomic Staging; PP-FISH, per-protocol fluorescence in situ hybridization.

Results

Risk classification

- The UMA-NGS panel successfully stratified risk according to IMS/IMWG CGS criteria, identifying ≥12% more high-risk patients in the PERSEUS/EMN017 study versus those identified using per-protocol FISH (PP-FISH; **Figure 1**)
- The most common genetic lesions were del17p/*TP53* (14%), IgH translocation with amp1q/del1p (12%), and del1p with amp1q (9%); 2% of patients had biallelic focal del1p
- IMS/IMWG CGS reclassified 17% of patients from standard to high risk, with only 4% reclassified from high to standard risk with improved risk classification (**Figure 2**)

Figure 2: IMS/IMWG CGS risk classification results[a]

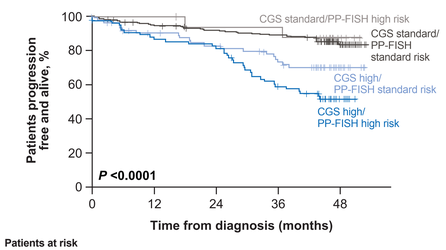


IMS/IMWG, International Myeloma Society/International Myeloma Working Group; CGS, Consensus Genomic Staging; PP-FISH, per-protocol fluorescence in situ hybridization.
[a]IMS/IMWG CGS reclassified patients from standard risk to high risk mainly due to *TP53* mutations not detectable by PP-FISH or inclusion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

IMS/IMWG CGS: PFS in reclassified patients

- In patients reclassified 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 (**Figure 3**)

Figure 3: PFS in patients with reclassified risk status based on PP-FISH and IMS/IMWG CGS criteria[a]



Patients at risk

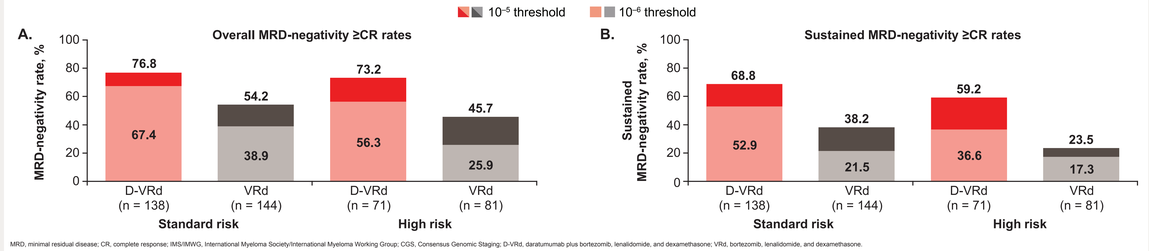
CGS standard/PP-FISH high risk	17	17	15	15	4
CGS standard/PP-FISH standard risk	258	237	225	218	65
CGS high/PP-FISH standard risk	73	61	55	46	11
CGS high/PP-FISH high risk	76	64	60	41	12

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

MRD negativity and PFS

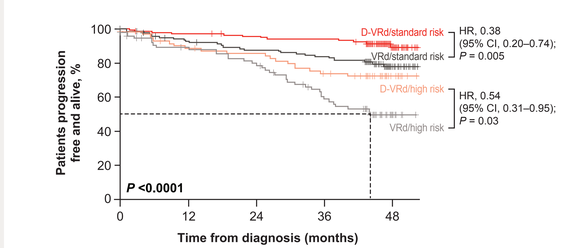
- D-VRd was associated with increased overall (**Figure 4A**) and sustained (**Figure 4B**) MRD-negativity rates compared with VRd in both IMS/IMWG CGS standard- and high-risk patients at sensitivity thresholds of 10^{-5} and 10^{-6}
- D-VRd led to improved PFS in both IMS/IMWG CGS standard- and high-risk patients (**Figure 5**)
- Notably, achieving ≥12-month sustained MRD negativity removes the negative prognostic impact of an IMS/IMWG CGS high-risk classification at diagnosis (**Figure 6**)
- D-VRd improved PFS versus VRd for both standard- and high-risk patients classified by PP-FISH or IMS/IMWG CGS criteria (**Figure 7**)

Figure 4: Overall and sustained (≥12 months) MRD-negativity ≥CR rates (10^{-5} and 10^{-6}) by IMS/IMWG CGS risk



MRD, minimal residual disease; CR, complete response; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; CGS, Consensus Genomic Staging; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

Figure 5: PFS stratified by IMS/IMWG CGS risk and treatment arm

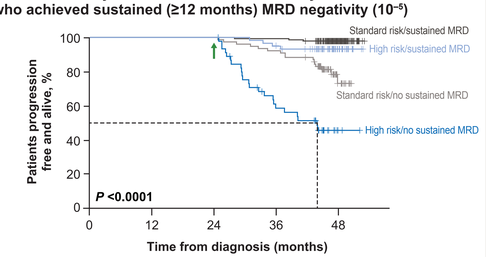


Patients at risk

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

PFS, progression-free survival; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; CGS, Consensus Genomic Staging; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; CI, confidence interval.

Figure 6: Landmark analysis of PFS from 24 months by IMS/IMWG CGS risk in patients who achieved sustained (≥12 months) MRD negativity (10^{-5})



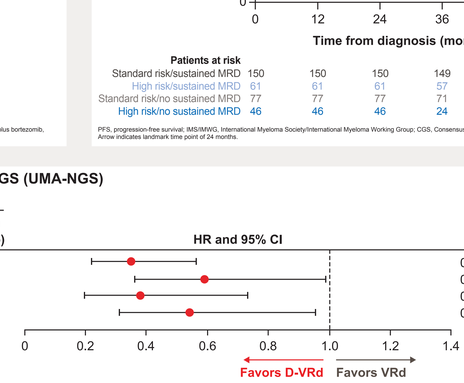
Patients at risk

Standard risk/sustained MRD	150	150	150	149	55
High risk/sustained MRD	61	61	61	57	19
Standard risk/no sustained MRD	77	77	77	71	12
High risk/no sustained MRD	46	46	46	24	3

PFS, progression-free survival; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; CGS, Consensus Genomic Staging; MRD, minimal residual disease. Arrow indicates landmark time point of 24 months.

Figure 7: PFS based on cytogenetic risk by PP-FISH and IMS/IMWG CGS (UMA-NGS)

		D-VRd		VRd			
Criteria		Event/N	Median PFS (mo)	Event/N	Median PFS (mo)	HR and 95% CI	HR (95% CI)	*P* value
PP-FISH	Standard risk	25/264	NR	62/266	NR		0.35 (0.22–0.56)	<0.0001
PP-FISH	High risk	24/76	NR	38/78	44.1		0.59 (0.36–0.99)	0.0439
IMS/IMWG CGS	Standard risk	13/138	NR	29/144	NR		0.38 (0.20–0.74)	0.005
IMS/IMWG CGS	High risk	19/71	NR	36/81	NR		0.54 (0.31–0.95)	0.03



PFS, progression-free survival; PP-FISH, per-protocol fluorescence in situ hybridization; IMS/IMWG, International Myeloma Society/International Myeloma Working Group; CGS, Consensus Genomic Staging; UMA, Unique Molecular Assay; NGS, next-generation sequencing; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached.

References

1. Avet-Loiseau H, et al. *J Clin Oncol.* 2025;43(24):2739–2751. 2. Poletti A, et al. *Haematologica.* 2025;110(10):2436–2450. 3. Sonneveld P, et al. *N Engl J Med.* 2024;390(4):301–313.

Multiple Myeloma

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