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

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Key Takeaway

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

Conclusions

- DVRd improved PFS versus VRd, for both standard- and high-risk defined by PP-FISH or IMS/IMWG CGS, in patients with TE-NDMM
- In both standard- 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}), and improved PFS
- The UMA-NGS panel successfully stratified cytogenetic risk according to the new IMS/IMWG CGS criteria in the PERSEUS study, improving risk stratification

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Disclosures

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Introduction

- International Myeloma Society/International Myeloma Working Group (IMS/IMWG) recently proposed Consensus Genomic Staging (CGS) risk criteria for 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 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 Unique Molecular Assay (UMA) target panel[2]

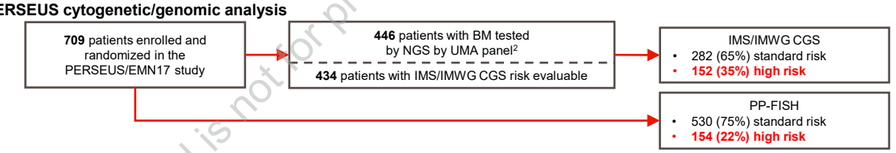
Risk subgroup	Definition
PP-FISH high risk	Defined per protocol as ≥1 del17p, t(4;14), and/or t(14;16)
IMS/IMWG CGS high risk[1]	Defined as the presence of at least one of the following: • del17p[a] and/or *TP53* mutation[b] • t(4;14) or t(14;16) or t(14;20) with additional amp1q or biallelic del1p •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

Methods

- PERSEUS is a phase 3, randomized clinical trial[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 (CR) in the intent-to-treat [ITT] population) was one of the key secondary endpoints. Bone marrow (BM) MRD was assessed using NGS (clonoSEQ®)
- Sustained MRD negativity was defined as MRD negativity with ≥CR at least 12 months apart and without MRD positivity in between
- 709 patients with NDMM were randomized 1:1 to daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) vs VRd. UMA-NGS target panel was used on DNA extracted from CD138+ BM cells (**Figure 1**)

Figure 1: PERSEUS cytogenetic/genomic analysis

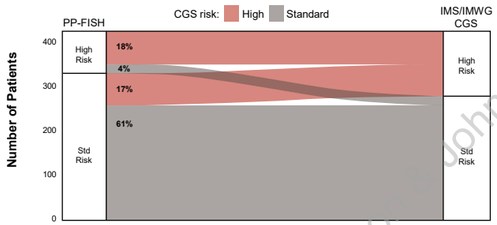


Results

Risk classification

- 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 (**Figure 1**)
- The most common genetic lesions were del17p/TP53 (n=59, 14%), IgH translocation with amp1q/del1p (12%), and del1p with amp1q (9%); 2% had biallelic focal del1p
- IMS/IMWG CGS reclassified 17% of patients from standard to high risk, with only 4% being reclassified from high to standard risk with improved risk classification (**Figure 2**)

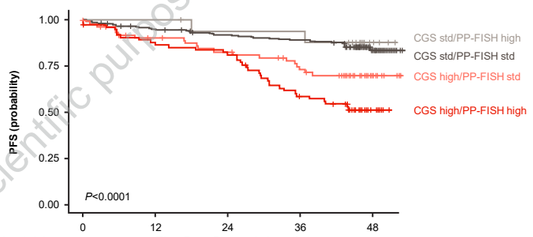
Figure 2: IMS/IMWG CGS – Risk classification results



IMS/IMWG CGS – PFS in re-classified patients

- 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 (**Figure 3**)

Figure 3: 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

Std, standard.

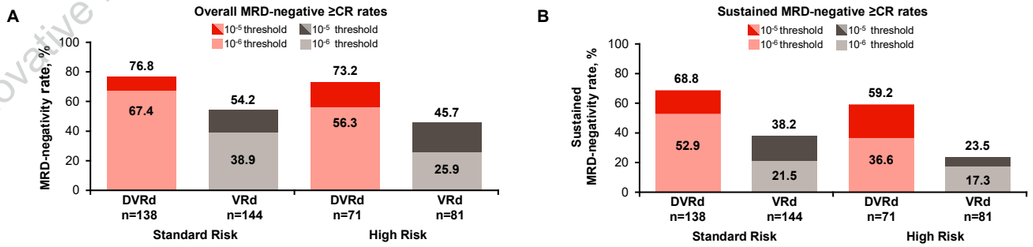
MRD negativity and PFS

- DVRd was associated with increased overall (**Figure 4A**) and sustained (**Figure 4B**) MRD-negativity rates compared with VRd in both IMS/IMWG CGS standard-risk and high-risk patients at sensitivity thresholds of 10^{-5} and 10^{-6}

MRD negativity and PFS (continued)

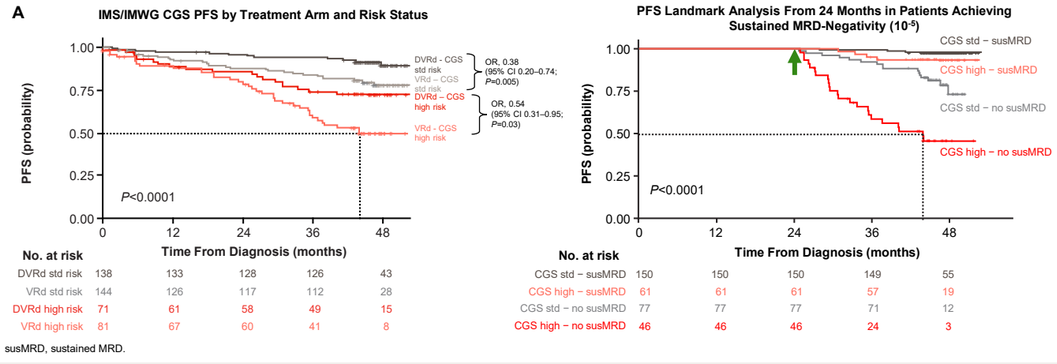
- DVRd led to improved PFS in both IMS/IMWG CGS standard- and high-risk patients (**Figure 5A**); notably, achieving 12-month sustained MRD-negativity removes the negative prognostic impact of an IMS/IMWG CGS high-risk classification at diagnosis (**Figure 5B**)
- DVRd improved PFS versus VRd, for both standard- and high-risk defined by PP-FISH or IMS/IMWG CGS, in patients with transplant-eligible (TE)-NDMM (**Figure 6**)

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



OR, odds ratio.

Figure 5: PFS Stratified by Risk and Treatment Arm and Sustained MRD Negativity (10^{-5})



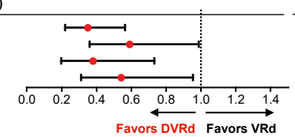
No. at risk					
DVRd std risk	138	133	128	126	43
VRd std risk	144	126	117	112	28
DVRd high risk	71	61	58	49	15
VRd high risk	81	67	60	41	8

No. at risk					
CGS std – susMRD	150	150	150	149	55
CGS high – susMRD	61	61	61	57	19
CGS std – no susMRD	77	77	77	71	12
CGS high – no susMRD	46	46	46	24	3

susMRD, sustained MRD.

Figure 6: 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	Standard risk	25/264	NE	62/266	NE	0.35 (0.22 to 0.56)	<0.0001
PP-FISH	High risk	24/76	NE	38/78	44.1	0.59 (0.36 to 0.99)	0.0439
IMS/IMWG	Standard risk	13/138	NE	29/144	NE	0.38 (0.20 to 0.74)	0.005
IMS/IMWG	High risk	19/71	NE	36/81	NE	0.54 (0.31 to 0.95)	0.03



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Multiple Myeloma

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