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Subcutaneous Daratumumab + Bortezomib/Lenalidomide/Dexamethasone With Dara + Lenalidomide Maintenance in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma: Analysis of Sustained Minimal Residual Disease Negativity in the Phase 3 PERSEUS Trial

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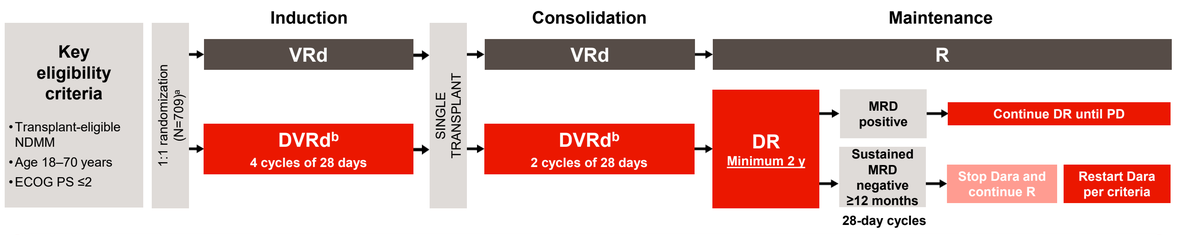
INTRODUCTION

- In PERSEUS, daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) induction/consolidation and daratumumab and lenalidomide (DR) maintenance improved **minimal residual disease (MRD) negativity and progression-free survival (PFS)** vs bortezomib, lenalidomide, and dexamethasone (VRd) induction/consolidation and lenalidomide (R) maintenance[1-3]
- Functionally high-risk patients (those experiencing relapse or progression within **18 months of treatment initiation**) often have poorer survival outcomes[4,5]
- **Sustained MRD negativity,** a key efficacy endpoint and prognostic marker, is linked to improved survival[6-8]
- This post hoc analysis explored 2 distinct aims in PERSEUS:
  - **Aim 1:** To determine whether DVRd + DR maintenance reduces the number of functionally high-risk patients
  - **Aim 2:** To explore the impact of sustained MRD negativity (10^{-5}) complete response (CR) or better on PFS

METHODS

- Patients were assigned to either DVRd induction/consolidation and DR maintenance, or VRd induction/consolidation and R maintenance (**Figure 1**)

Figure 1: PERSEUS study design



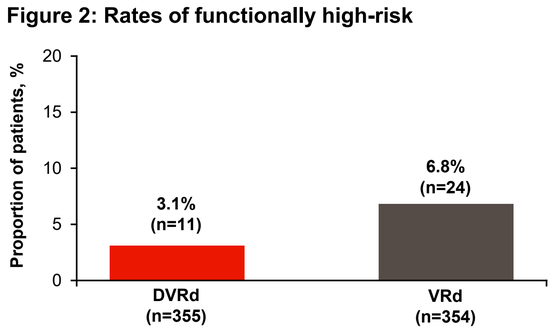
- MRD-negativity rate was defined as the proportion of patients achieving MRD negativity and ≥CR in the intent-to-treat (ITT) population
  - Patients who were not evaluable or had indeterminate results were considered MRD positive
  - MRD was evaluated post consolidation at the time of suspected CR or stringent complete response (sCR); at 12, 18, 24, 30, and 36 months after cycle 1 day 1; and yearly thereafter

[a]Stratified by ISS stage and cytogenetic risk. [b]Dara 1800 mg co-formulated with rHuPH20 (2000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA); VRd administered as in the VRd group. Dara, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; rHuPH20, recombinant human hyaluronidase PH20.

RESULTS

- Functionally high-risk incidence, defined as those experiencing relapse or progression within 18 months of treatment initiation, was halved with DVRd vs VRd (**Figure 2**)
  - When including preprogression deaths (patients who progressed or died within 18 months of treatment initiation), rates of functionally high-risk were lower with DVRd (5.4%; n=19) vs VRd (11.0%; n=39)

Figure 2: Rates of functionally high-risk



- Advanced disease, high cytogenetic risk, and CRAB criteria were more common in the functionally high-risk subgroup relative to the ITT population (**Table**)

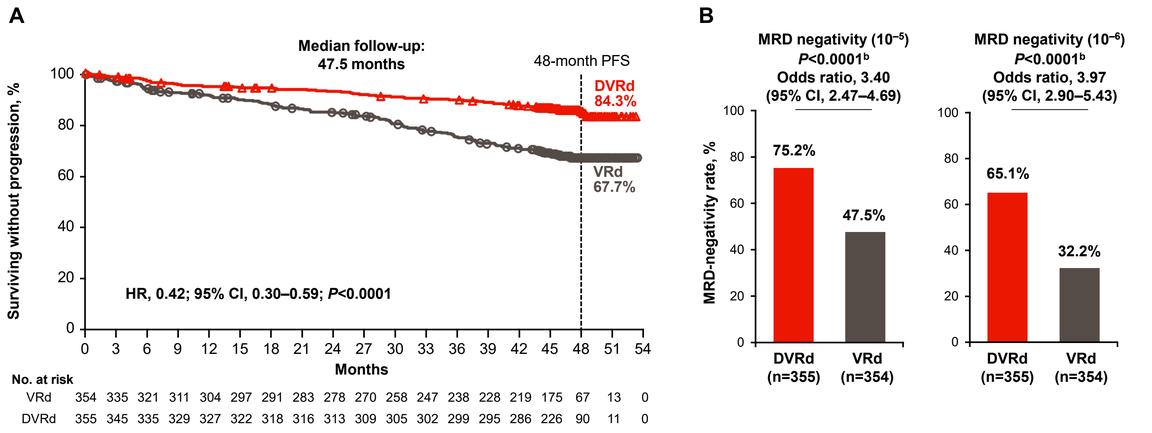
Table: Baseline demographics and clinical characteristics of functionally high-risk subgroup

Characteristic	Functionally high-risk subgroup (n=35)	ITT population (N=709)
Median age, years	60.0	60.0
ECOG PS, n (%)		
0	21 (60.0)	451 (63.6)
1	12 (34.3)	222 (31.3)
≥2	2 (5.7)	36 (5.1)
ISS staging,[a] n (%)		
I	13 (37.1)	364 (51.4)
II	13 (37.1)	239 (33.8)
III	9 (25.7)	105 (14.8)
Standard cytogenetic risk,[b] n (%)	14 (40.0)	530 (74.8)
High cytogenetic risk,[b] n (%)	20 (57.1)	154 (21.7)
del(17p)	13 (37.1)	70 (9.9)
t(4;14)	2 (5.7)	71 (10.0)
t(14;16)	7 (20.0)	25 (3.5)
CRAB criteria, n (%)	32 (91.4)	589 (83.1)

[a]Based on the combination of serum β_2-microglobulin and albumin levels. [b]Based on fluorescence in situ hybridization.
CRAB, calcium, renal, anemia, bone.

- DVRd and DR maintenance significantly improved PFS and overall MRD-negativity ≥CR rates vs VRd and R maintenance[2]
  - 58% reduction in the risk of progression or death in patients receiving DVRd (**Figure 3A**)
  - Deep and durable MRD negativity was achieved with DVRd (**Figure 3B**)

Figure 3: (A) PFS and (B) overall MRD-negativity ≥CR rate[a]

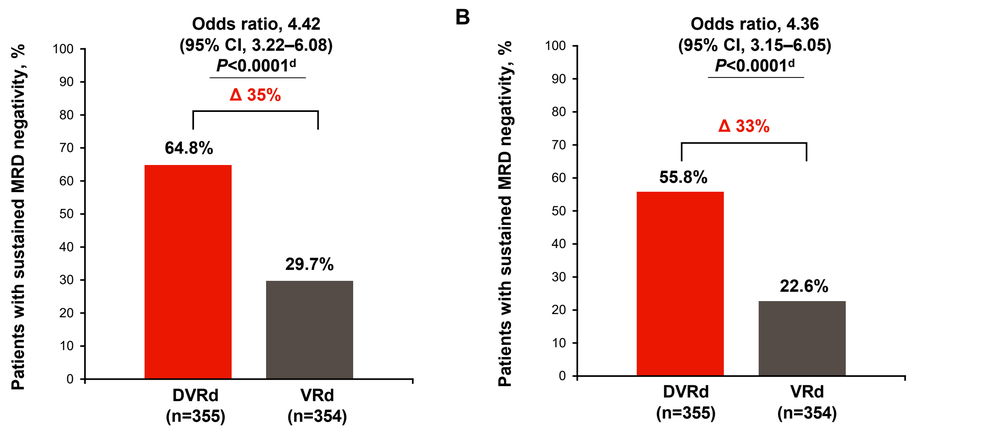


[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). [b]*P* values were calculated with the use of the stratified Cochran-Mantel-Haenszel chi-square test.
HR, hazard ratio; NGS, next-generation sequencing.

- DVRd more than doubled the rates of sustained MRD negativity for both ≥12 (**Figure 4A**) and ≥24 months vs VRd (**Figure 4B**)
- Among patients in the DVRd arm, those who achieved sustained MRD-negativity ≥CR for ≥12 months generally had less advanced disease and a lower incidence of high-risk cytogenetics compared with those who did not achieve sustained MRD-negativity ≥CR for ≥12 months

RESULTS (CONTINUED)

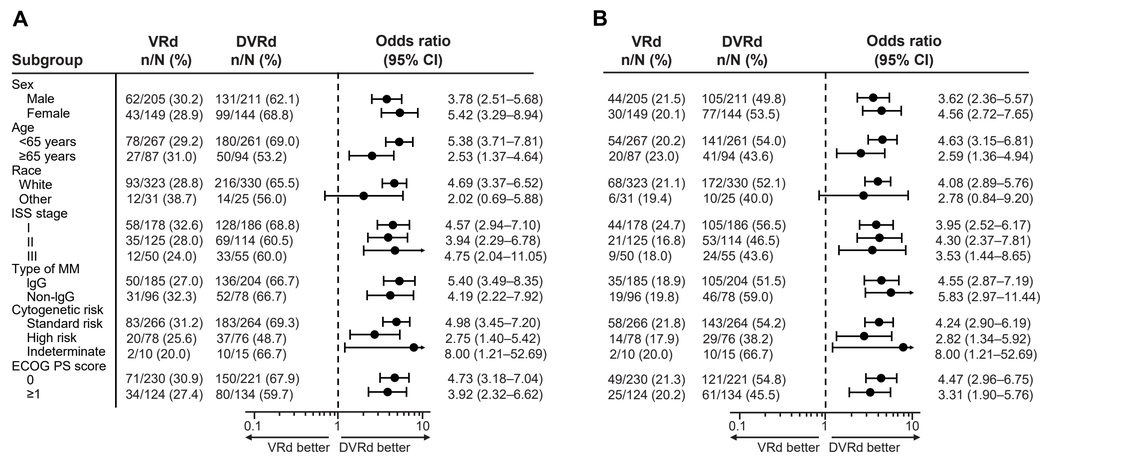
Figure 4: (A) Sustained MRD-negativity[a] (10^{-5}) ≥CR rate ≥12 months[b] and (B) sustained MRD-negativity[a] (10^{-5}) ≥CR rate ≥24 months[c]



[a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). [b]Sustained MRD negativity is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between. [c]Sustained MRD negativity is defined as 2 consecutive MRD-negative reads at least 24 months (–3) apart without MRD positive in between. [d]*P* value was calculated from the stratified Cochran-Mantel-Haenszel chi-squared test.

- DVRd led to higher rates of sustained MRD negativity (10^{-5}) ≥CR vs VRd across subgroups (**Figure 5**)

Figure 5: (A) Sustained MRD-negativity (10^{-5}) ≥CR rate ≥12 months[a] by subgroup and (B) sustained MRD-negativity (10^{-5}) ≥CR rate ≥24 months[b] by subgroup



[a]Sustained MRD negativity is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between. [b]Sustained MRD negativity is defined as 2 consecutive MRD-negative reads at least 24 months (–3) apart without MRD positive in between. MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR in the ITT population. Patients who were not evaluable or had indeterminate results were considered MRD positive. The subgroup analysis for type of MM was performed on data from patients who had measurable disease in serum. Cytogenetic risk was assessed by fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16). Ig, immunoglobulin; MM, multiple myeloma.

- Sustained MRD-negativity (10^{-5}) ≥CR rates for ≥12 months were twice as high with DVRd vs VRd (**Figure 6**)
- Among these patients, 48-month PFS rates were ~95% in both arms
- Sustained MRD-negativity (10^{-5}) ≥CR rates for ≥24 months were more than twice as high with DVRd vs VRd (**Figure 7**)
  - Among these patients, 48-month PFS rates exceeded 95% in both arms

Figure 6: PFS by sustained MRD-negativity (10^{-5}) ≥CR status at ≥12 months

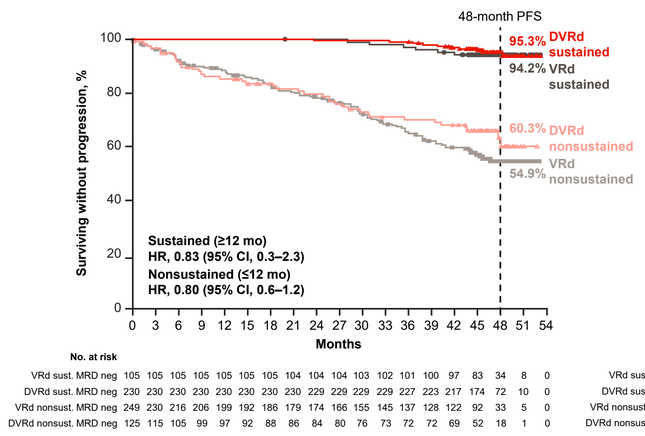
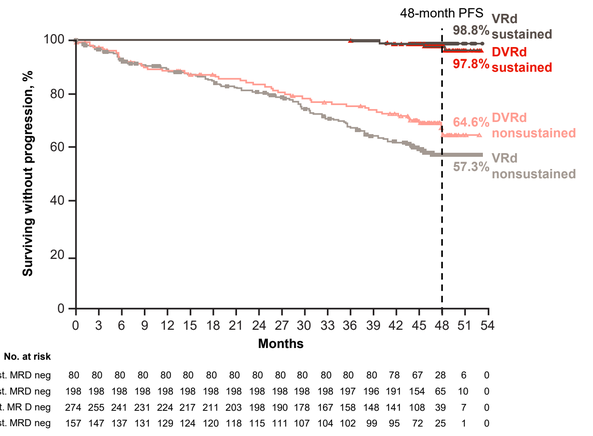


Figure 7: PFS by sustained MRD-negativity (10^{-5}) ≥CR status at ≥24 months



CONCLUSION

Key Takeaway

These results reinforce the consistent benefit of DVRd + DR maintenance and further support the PERSEUS regimen as standard of care for transplant-eligible NDMM

Conclusions

- Rates of relapse or progression **within 18 months** of treatment initiation (functionally high-risk disease) were lower than seen in other frontline trials[4] and were halved with **DVRd** (**3.1%**; n=11) vs VRd (6.8%; n=24)
- DVRd + DR maintenance led to deeper and more durable responses, and was associated with improved PFS
- Higher rates of sustained MRD negativity (10^{-5}) ≥CR were achieved with DVRd vs VRd, with nearly two-thirds of patients achieving sustained MRD negativity for ≥12 months and more than half achieving sustained MRD negativity for ≥24 months
- Sustained MRD negativity was associated with a PFS benefit, with >95% of patients with ≥12- or ≥24-month sustained MRD negativity remaining progression free at 48 months

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