MM-355

Daratumumab + Bortezomib/Lenalidomide/Dexamethasone (D-VRd) in Transplant-eligible (TE) Patients With Newly Diagnosed Multiple Myeloma (NDMM): Analysis of Minimal Residual Disease (MRD) in the Phase 3 PERSEUS Study

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Key Takeaway

These data further highlight the benefit of D-VRd and D-R maintenance as a new standard of care for TE patients with NDMM

Conclusions

- The potential for a cure in NDMM is predicated on reaching sustained MRD negativity at 10^{-6}
- In the PERSEUS study, for D-VRd followed by D-R, 47% of patients achieved sustained MRD negativity (10^{-6}) for 12 months versus 19% with VRd followed by R
- 58% of high-risk patients who received D-VRd followed by D-R achieved MRD negativity (10^{-6}) and 30% achieved sustained MRD negativity (10^{-6}) versus 31% and 14%, respectively, with VRd followed by R
- During D-R maintenance, the rate of MRD negativity (10^{-6}) increased by 30% versus 15% with R alone, and 31% versus 10% of MRD-positive patients, respectively, converted to sustained MRD negativity (10^{-6})

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Poster

Oral presentation

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Disclosure

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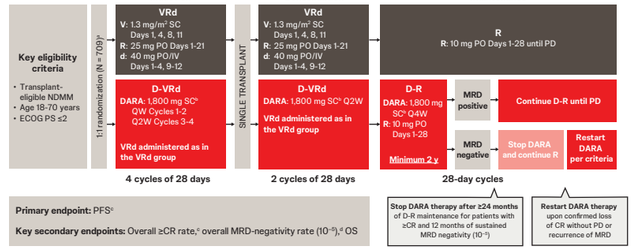
Introduction

- In newly diagnosed multiple myeloma (NDMM), minimal residual disease (MRD) negativity has been associated with longer progression-free survival (PFS) and overall survival (OS), and deeper responses (10^{-6}) have been associated with superior PFS compared with MRD negativity at 10^{-5} or 10^{-4} sensitivity[1,2]
- An increasing number of patients are achieving OS of 10 years or longer. Current MRD testing at a sensitivity level of 10^{-6} and sustained MRD at this level for over 5 years translates into very long survival and potentially a "cure" for patients with standard-risk features[3-5]
- In the primary analysis of PERSEUS (ClinicalTrials.gov Identifier: NCT03710603), daratumumab (DARA) plus bortezomib/lenalidomide/dexamethasone (D-VRd) induction/consolidation followed by daratumumab plus lenalidomide (D-R) maintenance improved depth of response and PFS versus VRd induction/consolidation followed by R maintenance in transplant-eligible (TE) NDMM[6]
  - 64% of patients receiving D-R maintenance stopped DARA after ≥2 years due to achieving sustained MRD negativity (10^{-5})
- Here, we report further results from PERSEUS on deepening of response and MRD negativity during maintenance therapy

Methods

- PERSEUS is a randomized, open-label, multicenter, phase 3 study comparing the efficacy and safety of D-VRd followed by D-R maintenance versus VRd followed by R maintenance in patients with TE NDMM (**Figure 1**)
- PERSEUS implemented an MRD response-adapted approach in maintenance:
  - After ≥24 months of D-R maintenance, DARA therapy was stopped in patients with complete response or better (≥CR) and 12 months of sustained MRD negativity (10^{-5} threshold). All patients continued R maintenance until disease progression
  - Patients restarted DARA therapy upon confirmed loss of CR without disease progression or recurrence of MRD
- The primary endpoint was PFS, which was assessed using a computerized algorithm based on International Myeloma Working Group response criteria
- Key secondary endpoints included overall ≥CR rate, overall MRD-negativity rate (10^{-5} threshold), and OS
- MRD was assessed using bone marrow aspirates and evaluated via next-generation sequencing using the clonoSEQ assay (v2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with very good partial response or better (≥VGPR) post-consolidation and at the time of suspected ≥CR
- Overall, MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity (10^{-5} threshold) and ≥CR at any time in the intent-to-treat (ITT) population. Patients who were not evaluable or had indeterminate results were considered MRD positive)

Figure 1: Study design



NDMM, newly diagnosed multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status; VRd, bortezomib/lenalidomide/dexamethasone; V, bortezomib; SC, subcutaneous; R, lenalidomide; PO, oral; d, dexamethasone; IV, intravenous; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; DARA, daratumumab; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; D-R, daratumumab plus lenalidomide; Q4W, every 4 weeks; MRD, minimal residual disease; PFS, progression-free survival; CR, complete response; OS, overall survival; rHuPH20, recombinant human hyaluronidase PH20; VGPR, very good partial response.
[a]Stratified by International Staging System 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 International Myeloma Working Group response criteria.
[d]MRD was assessed using the clonoSEQ assay (v2.0; 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.

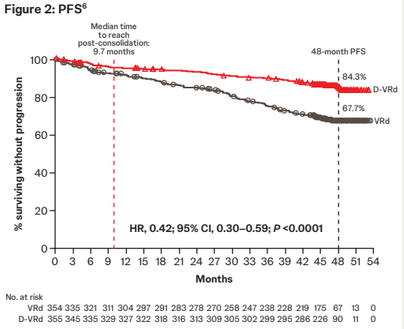
Results

- In total, 709 patients were randomized (D-VRd, n = 355; VRd, n = 354)

Progression-free survival

- After a median follow-up of 47.5 months, there was a 58% reduction in the risk of progression or death in patients receiving D-VRd (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.30–0.59; P <0.0001; **Figure 2**)

Figure 2: PFS[6]

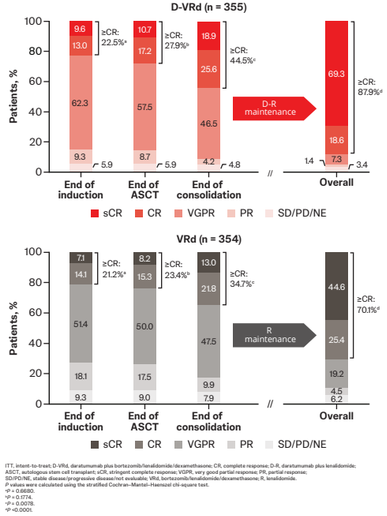


PFS, progression-free survival; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

Response rates

- In the ITT population, responses deepened to a greater extent with D-VRd followed by D-R versus VRd followed by R (**Figure 3**)

Figure 3: Responses over time (ITT population)

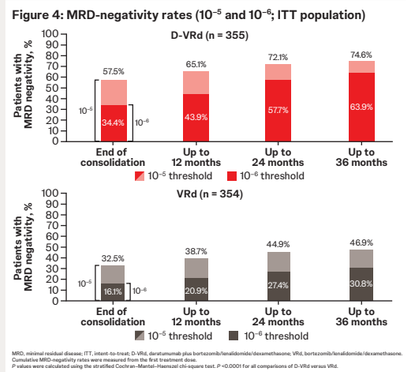


ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; CR, complete response; D-R, daratumumab plus lenalidomide; ASCT, autologous stem cell transplant; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; SD/PD/NE, stable disease/progressive disease/not evaluable; VRd, bortezomib/lenalidomide/dexamethasone; R, lenalidomide.
P values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test.
[a]P = 0.6680.
[b]P = 0.0774.
[c]P = 0.0078.
[d]P <0.0001.

MRD-negativity rates

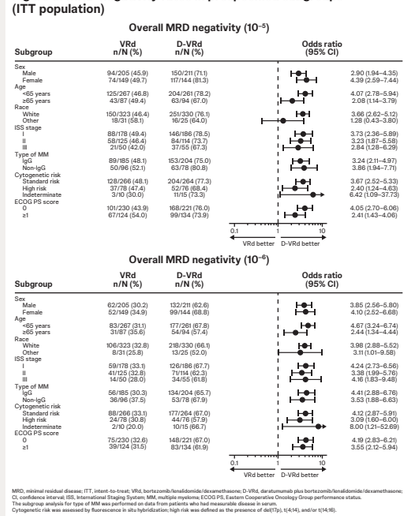
- D-VRd followed by D-R significantly improved the overall MRD-negativity rate at 10^{-5} versus VRd followed by R (75.2% vs 47.5%; odds ratio, 3.40; 95% CI, 2.47–4.69; P <0.0001) and doubled the rate of deeper MRD negativity at 10^{-6} (65.1% vs 32.2%; odds ratio, 3.97; 95% CI, 2.90–5.43; P <0.0001)[6]
  - MRD negativity at 10^{-6} increased by approximately 30% during maintenance with D-R (**Figure 4**)
  - Across prespecified subgroups, MRD-negativity rates were improved with D-VRd followed by D-R versus VRd followed by R (**Figure 5**)

Figure 4: MRD-negativity rates (10^{-5} and 10^{-6}; ITT population)



MRD, minimal residual disease; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone. Cumulative MRD-negativity rates were measured from the first treatment dose.
P values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test. P <0.0001 for all comparisons of D-VRd versus VRd.

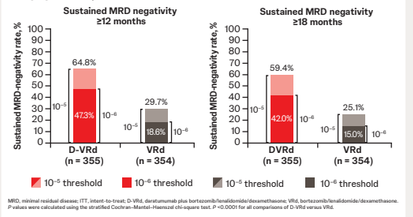
Figure 5: MRD-negativity rates in prespecified subgroups (ITT population)



MRD, minimal residual disease; ITT, intent-to-treat; VRd, bortezomib/lenalidomide/dexamethasone; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; CI, confidence interval; ISS, International Staging System; MM, multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status.
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).

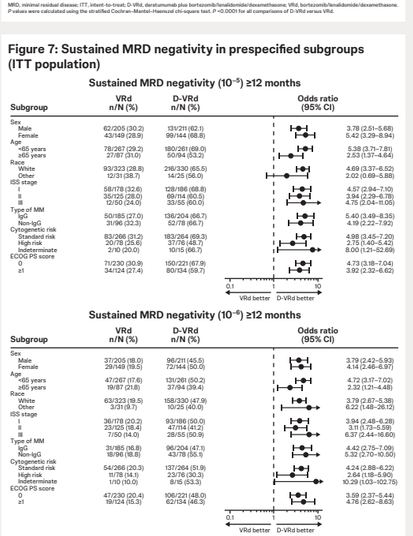
- Sustained MRD-negativity rates at 10^{-6} were 2.5-fold higher for D-VRd followed by D-R versus VRd followed by R, with >40% of patients having sustained MRD negativity at 10^{-6} for ≥18 months (**Figure 6**)
  - Sustained MRD-negativity rates were improved with D-VRd followed by D-R versus VRd followed by R across prespecified subgroups (**Figure 7**)

Figure 6: Sustained MRD-negativity rates (10^{-5} and 10^{-6}; ITT population)



MRD, minimal residual disease; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.
P values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test. P <0.0001 for all comparisons of D-VRd versus VRd.

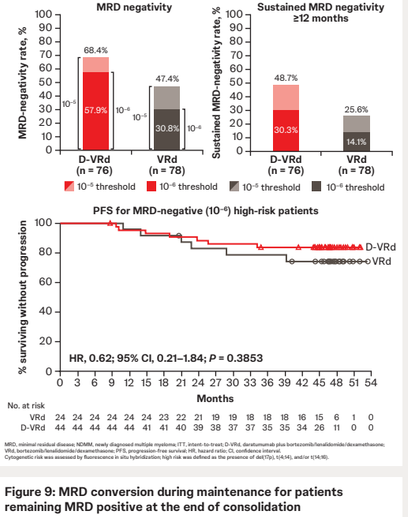
Figure 7: Sustained MRD negativity in prespecified subgroups (ITT population)



MRD, minimal residual disease; ITT, intent-to-treat; VRd, bortezomib/lenalidomide/dexamethasone; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; CI, confidence interval; ISS, International Staging System; MM, multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status.
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).

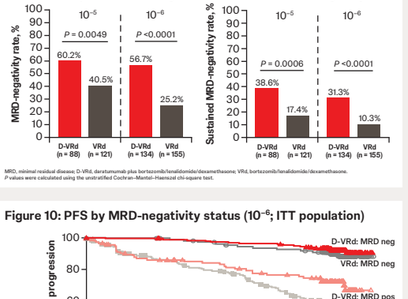
- In patients with high-risk NDMM, rates of MRD negativity at 10^{-6} and sustained MRD negativity ≥12 months were approximately doubled with D-VRd versus VRd; PFS was also improved with D-VRd versus VRd in MRD-negative patients with high-risk NDMM (**Figure 8**)
- During maintenance, conversion to MRD negativity (10^{-6}) was doubled and conversion to sustained MRD negativity was tripled with D-R versus R (**Figure 9**)
- Achievement of MRD negativity at 10^{-6} was associated with improved long-term outcomes (**Figure 10**)
  - Patients remaining MRD positive had improved PFS with D-R maintenance versus R alone

Figure 8: MRD negativity in patients with high-risk NDMM (ITT population)



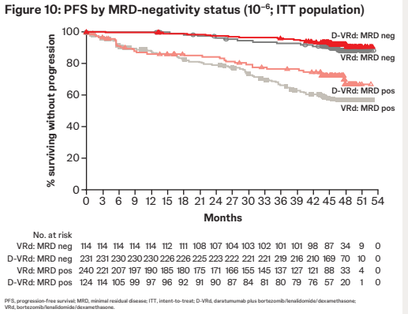
MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.
Cytogenetic risk was assessed by fluorescence in situ hybridization; high risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

Figure 9: MRD conversion during maintenance for patients remaining MRD positive at the end of consolidation



MRD, minimal residual disease; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.
P values were calculated using the unstratified Cochran–Mantel–Haenszel chi-square test.

Figure 10: PFS by MRD-negativity status (10^{-6}; ITT population)



PFS, progression-free survival; MRD, minimal residual disease; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.

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Multiple Myeloma

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