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Daratumumab Plus Bortezomib, Lenalidomide, and Dexamethasone in Transplant-eligible Patients With Multiple Myeloma: A Pooled Analysis of Patients Aged ≥65 Years From Both PERSEUS and GRIFFIN Studies

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Key Takeaway

This post hoc analysis of pooled data from the phase 3 PERSEUS and phase 2 GRIFFIN studies supports D-VRd followed by D-R maintenance as a standard of care and highlights the benefit of DARA during induction, consolidation, and maintenance for all TE patients with NDMM, irrespective of age

Conclusions

The limited PFS benefit previously seen in PERSEUS in patients aged ≥65 years[1,2] was due to a contribution of several factors, including a small number of events, imbalances in cytogenetic risk, and censoring of PFS events

After pooling data for patients aged ≥65 years from both PERSEUS and GRIFFIN to perform a more robust analysis and correct for the above imbalances, the addition of DARA to VRd induction/consolidation and R maintenance led to a PFS benefit versus VRd followed by R alone

Quadruplet therapy with D-VRd followed by D-R maintenance in patients aged ≥65 years also resulted in deeper IMWG responses and greater MRD-negativity rates versus VRd followed by R alone

In patients aged ≥65 years, treatment with D-VRd led to an adequate amount of stem cells to perform ASCT and achieve rapid engraftment

No new safety concerns were identified when patients aged ≥65 years were treated with D-VRd followed by D-R maintenance

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Poster

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Disclosure

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Introduction

- Daratumumab (DARA), a human IgGκ monoclonal antibody targeting CD38 with direct on-tumor[3-6] and immunomodulatory[7-9] mechanisms of action, is approved as a monotherapy for relapsed/refractory multiple myeloma and in combination with other standard-of-care therapies for newly diagnosed multiple myeloma (NDMM) and relapsed/refractory multiple myeloma[10-12]
- The addition of DARA to bortezomib, lenalidomide, and dexamethasone (D-VRd) induction/consolidation and lenalidomide (D-R) maintenance has been shown to significantly improve patient outcomes versus VRd followed by R maintenance alone[1,13,14]
  - In the phase 2 GRIFFIN (ClinicalTrials.gov Identifier: NCT02874742)[13,14] and phase 3 PERSEUS (NCT03710603)[1] studies, D-VRd followed by D-R maintenance improved progression-free survival (PFS) and deepened both response and minimal residual disease (MRD)–negativity rates compared with VRd followed by R alone in transplant-eligible (TE) patients with NDMM
- Older adults are at a higher risk of poor prognosis and are a population of particular interest[15]
- In PERSEUS, in an unstratified PFS subgroup analysis among patients aged ≥65 years, PFS hazard ratios (HRs) were 0.97 by computerized algorithm and 0.87 by independent review committee (IRC) assessment[1,2]
  - The less pronounced PFS benefit seen in older adults may have been due to the small number of PFS events, a cytogenetic risk imbalance between treatment groups (high risk: D-VRd, 25.5%; VRd, 19.5%), and an imbalance in censoring patients for PFS after ≥2 missing consecutive disease evaluations (US Food and Drug Administration–mandated censoring rule; events censored: D-VRd, 0; VRd, 3), which impacted the PFS HRs in favor of the VRd group
- In contrast, an unstratified PFS subgroup analysis among patients aged ≥65 years in GRIFFIN showed a PFS benefit favoring D-VRd followed by D-R maintenance versus VRd followed by R maintenance alone (HR, 0.29),[16] comparable to that seen in older adults across other studies of DARA combination regimens[17-21]
- Here, we present a post hoc, pooled analysis of data from the PERSEUS and GRIFFIN studies that increases sample size to provide a more robust analysis and to better understand the impact of DARA in combination with VRd in TE patients aged ≥65 years with NDMM

Methods

Study design

- In PERSEUS and GRIFFIN, patients aged 18 to 70 years with NDMM[22] who were candidates for high-dose therapy and autologous stem cell transplant (ASCT) were randomized (1:1) to receive D-VRd or VRd
- In both studies, all patients received 4 induction cycles (PERSEUS, 28-day cycles; GRIFFIN, 21-day cycles) of VRd and 2 post-ASCT consolidation cycles of VRd followed by R maintenance
- Patients randomized to D-VRd also received DARA subcutaneous, co-formulated with recombinant human hyaluronidase (Halozyme, Inc.) in PERSEUS or DARA intravenous in GRIFFIN during induction, consolidation, and maintenance

Endpoints and assessments

- Endpoints analyzed and reported in this post hoc, pooled analysis include the following: PFS (defined as time from randomization to disease progression or death due to any cause), response rates (per International Myeloma Working Group [IMWG] criteria[22]), MRD-negativity rate (10^{-5} threshold; in patients who achieved complete response or better [≥CR] by next-generation sequencing), sustained MRD-negativity rate (10^{-5} threshold; lasting ≥12 months), stem cell mobilization, ASCT rates, and safety

Statistical analysis

- Data from the primary analysis of PERSEUS (median follow-up, 47.5 months) and final analysis of GRIFFIN (median follow-up, 49.6 months) were pooled for patients aged ≥65 years
- PFS was estimated using the Kaplan–Meier method
  - HRs and 95% confidence intervals (CIs) were estimated using a Cox regression model with treatment as the sole explanatory variable, stratified by International Staging System (ISS) disease stage (I vs II vs III) and cytogenetic risk (high risk [del(17p), t(4;14), and/or t(14;16)] vs standard/unknown risk)
  - PFS was based on IRC assessment for PERSEUS and computerized algorithm for GRIFFIN; patients were not censored after ≥2 missing consecutive disease evaluations
- A Mantel–Haenszel estimate of the common odds ratio (OR), stratified by ISS disease stage and cytogenetic risk, was used to compare response and MRD-negativity rates

Results

Patients

- A total of 237 patients aged ≥65 years were included in the pooled intent-to-treat population (D-VRd, n = 122; VRd, n = 115)
  - Patients aged ≥65 years represented 25.5% of patients in PERSEUS (D-VRd, n = 94/355; VRd, n = 87/354) and 27.1% of patients in GRIFFIN (D-VRd, n = 28/104; VRd, n = 28/103)
- Baseline characteristics were balanced between groups (**Table 1**)

Table 1: Baseline demographic and disease characteristics in patients aged ≥65 years in the pooled PERSEUS/GRIFFIN ITT population[a]

Characteristic	D-VRd (n = 122)	VRd (n = 115)
Age, median (range), years	67 (65-70)	67 (65-70)
Male, n (%)	76 (62.3)	67 (58.3)
ECOG PS score, n (%)		
n	122	114
0	66 (54.1)	66 (57.9)
1	47 (38.5)	40 (35.1)
2	9 (7.4)	8 (7.0)
ISS disease stage,[b] n (%)		
I	51 (41.8)	39 (33.9)
II	32 (26.2)	33 (28.7)
III	11 (9.0)	15 (13.0)
Missing	28 (23.0)	28 (24.3)
Cytogenetic risk,[c] n (%)		
n	119	114
Standard risk	88 (73.9)	91 (79.8)
High risk	27 (22.7)	22 (19.3)
del(17p)	17 (14.3)	12 (10.5)
t(4;14)	10 (8.4)	7 (6.1)
t(14;16)	2 (1.7)	5 (4.4)
Indeterminate	4 (3.4)	1 (0.9)

ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System.
[a]Pooled ITT population included all patients aged ≥65 years who were randomized in PERSEUS or GRIFFIN.
[b]ISS staging was derived based on the combination of serum β2-microglobulin and albumin.
[c]High risk was defined as ≥1 of the following cytogenetic abnormalities: del(17p), t(4;14), and/or t(14;16) by fluorescence in situ hybridization. Standard risk was defined by the absence of these cytogenetic abnormalities.

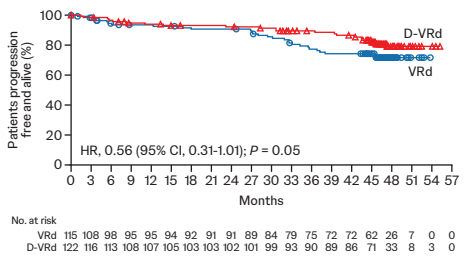
Treatment exposure and modifications

- Median (range) duration of treatment was 37.4 (0.5-52.5) months in the D-VRd group and 32.6 (0.1-53.0) months in the VRd group
- Median relative dose intensities were comparable between groups for bortezomib (D-VRd, 92.9%; VRd, 93.5%) and dexamethasone (95.5%; 100%) but were slightly lower in the D-VRd group for lenalidomide (75.5%; 87.7%); median relative dose intensity for DARA in the D-VRd group was 99.7%
- Discontinuation rates were comparable between groups for bortezomib (D-VRd, 12.5%; VRd, 12.3%) and dexamethasone (3.3%; 3.5%) but were higher in the D-VRd group for lenalidomide (23.3%; 17.5%)

PFS

- At a median follow-up of 47.5 months for PERSEUS and 49.6 months for GRIFFIN, median PFS was not reached in either treatment group
- D-VRd resulted in a 44% reduction in the risk of disease progression or death versus VRd (HR, 0.56 [95% CI, 0.31-1.01]; $P = 0.05$; **Figure 1**)
- Estimated 48-month PFS rates were 79.1% for D-VRd versus 71.6% for VRd

Figure 1: PFS by treatment group in patients aged ≥65 years in the pooled PERSEUS/GRIFFIN ITT population[a]

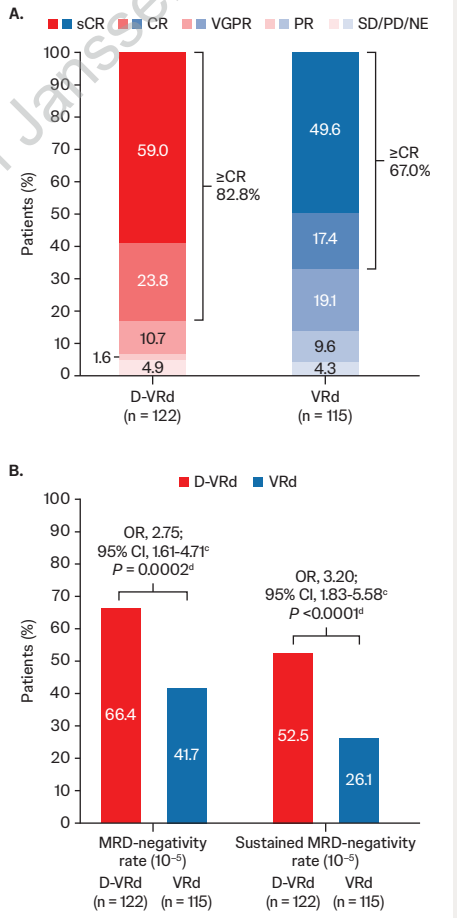


PFS, progression-free survival; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; IRC, independent review committee; ISS, International Staging System.
PFS was based on IRC assessment for PERSEUS and computerized algorithm for GRIFFIN, stratified by ISS disease stage (I vs II vs III) and cytogenetic risk (high risk vs standard/unknown risk), and not censored for death or disease progression after ≥2 missing consecutive disease evaluations.
[a]Pooled ITT population included all patients aged ≥65 years who were randomized in PERSEUS or GRIFFIN.

Response and MRD-negativity rates

- Higher response rates with D-VRd versus VRd (**Figure 2A**)
  - ≥CR: 82.8% vs 67.0% (OR, 2.37 [95% CI, 1.28-4.39]; $P = 0.005$)
  - sCR: 59.0% vs 49.6% (OR, 1.49 [95% CI, 0.88-2.53]; $P = 0.14$)
- Higher overall MRD-negativity rate (10^{-5}) with D-VRd versus VRd (66.4% vs 41.7%; OR, 2.75 [95% CI, 1.61-4.71]; $P = 0.0002$; **Figure 2B**)
- Higher sustained MRD-negativity rate (≥12 months) with D-VRd versus VRd (52.5% vs 26.1%; OR, 3.20 [95% CI, 1.83-5.58]; $P < 0.0001$; **Figure 2B**)

Figure 2: Summary of (A) response rates and (B) overall and sustained (≥12 months) MRD-negativity rates (10^{-5})[a] in patients aged ≥65 years in the pooled PERSEUS/GRIFFIN ITT population[b]



MRD, minimal residual disease; ITT, intent-to-treat; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; OR, odds ratio; CI, confidence interval; ISS, International Staging System.
[a]MRD-negativity rates were for patients who also achieved ≥CR. MRD was assessed using bone marrow aspirate and evaluated by next-generation sequencing (clonoSEQ assay Version 2.0; Adaptive Biotechnologies). Sustained MRD negativity was defined as 2 consecutive MRD measurements ≥12 months apart without an MRD-positive measurement in between.
[b]Pooled ITT population included all patients aged ≥65 years who were randomized in PERSEUS or GRIFFIN.
[c]Mantel–Haenszel estimates of the common ORs for stratified tables were used. The stratification factors were ISS disease stage (I vs II vs III) and cytogenetic risk (high risk vs standard/unknown risk).
[d]P value from the stratified Cochran–Mantel–Haenszel chi-squared test.

Stem cell mobilization and transplant

- Among patients aged ≥65 years in the pooled safety population who received ≥1 dose of study treatment (D-VRd, n = 120; VRd, n = 114), the majority in both treatment groups (93.3%; 84.2%) underwent stem cell mobilization (**Table 2**)
  - Median number of CD34+ cells collected was sufficient for ASCT in both treatment groups
  - Only 2 patients in the D-VRd group and 1 patient in the VRd group had <2 × 10^6/kg CD34+ stem cells collected
- Similar proportions of patients in each treatment group proceeded to ASCT (D-VRd, 86.7%; VRd, 82.5%)
  - Median time to engraftment was similar between treatment groups (D-VRd, 14 days; VRd, 13 days)

Safety and tolerability

- The overall safety profile in patients aged ≥65 years was generally comparable to that of all pooled patients irrespective of age, with no new safety concerns (**Table 3**)
- The incidence of grade 3/4 infections was higher with D-VRd than VRd, with slightly higher rates in patients aged ≥65 years (D-VRd, 36.3%; VRd, 24.8%) than in all patients (29.5%; 22.5%)
- The frequency of treatment-emergent adverse events leading to discontinuation of ≥1 study drug was similar between treatment groups both in patients aged ≥65 years and in all patients

Table 2: Stem cell mobilization and ASCT outcomes in patients aged ≥65 years in the pooled PERSEUS/GRIFFIN safety population[a]

	D-VRd (n = 120)	VRd (n = 114)
Patients proceeded to stem cell mobilization, n (%)	112 (93.3)	96 (84.2)
Mobilization medication/therapy used, n (%)		
n	112	96
G-CSF[b]	110 (98.2)	91 (94.8)
Cyclophosphamide	71 (63.4)	51 (53.1)
Plerixafor	59 (52.7)	32 (33.3)
Chemotherapy	2 (1.8)	0
Other	1 (0.9)	2 (2.1)
Patients with stem cells collected, n (%)	108 (90.0)	95 (83.3)
Total CD34+ stem cells collected, median (range), × 10^6/kg	4.22 (1.80-13.50)	5.76 (1.12-49.50)
Patients who completed melphalan conditioning therapy, n	104	94
Total dose of melphalan conditioning therapy, median (range), mg/m²	193 (59-385)	192 (52-371)
Patients who proceeded to ASCT, n (%)	104 (86.7)	94 (82.5)
Patients with hematopoietic reconstitution, n	103	93
Time to achieve ANC ≥0.5 × 10^9/L,[c] median (range), days	13 (0-28)	12 (0-34)
Time to achieve platelets ≥20 × 10^9/L without transfusion,[c] median (range), days	13 (0-33)	12 (1-48)
Time to engraftment,[c,d] median (range), days	14 (0-33)	13 (1-48)

ASCT, autologous stem cell transplant; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; G-CSF, granulocyte colony-stimulating factor; ANC, absolute neutrophil count.
[a]Pooled safety population included all patients aged ≥65 years who were randomized in PERSEUS or GRIFFIN and received ≥1 dose of study treatment.
[b]Grade 3/4 TEAEs that occurred in ≥10% of patients aged ≥65 years in either treatment group.
[c]Serious TEAEs that occurred in ≥5% of patients aged ≥65 years in either treatment group.
[d]Fatal TEAEs were considered related to daratumumab in 1 patient aged ≥65 years (squamous cell carcinoma) and in 1 patient aged <65 years (sepsis).

Table 3: Summary of TEAEs in patients aged ≥65 years and all patients irrespective of age in the pooled PERSEUS/GRIFFIN safety population[a]

	Aged ≥65 years		All patients	
n (%)	D-VRd (n = 120)	VRd (n = 114)	D-VRd (n = 450)	VRd (n = 449)
Grade 3/4 TEAEs	113 (94.2)	99 (86.8)	406 (90.2)	378 (84.2)
Most common[b]				
Neutropenia/febrile neutropenia	71 (59.2)	49 (43.0)	282 (62.7)	214 (47.7)
Thrombocytopenia	46 (38.3)	22 (19.3)	118 (26.2)	69 (15.4)
Diarrhea	17 (14.2)	12 (10.5)	44 (9.8)	32 (7.1)
Pneumonia	13 (10.8)	7 (6.1)	49 (10.9)	35 (7.8)
Serious TEAEs	81 (67.5)	60 (52.6)	246 (54.7)	224 (49.9)
Most common[c]				
Pneumonia	15 (12.5)	9 (7.9)	55 (12.2)	35 (7.8)
Febrile neutropenia	8 (6.7)	5 (4.4)	19 (4.2)	17 (3.8)
Pyrexia	8 (6.7)	2 (1.8)	24 (5.3)	26 (5.8)
Diarrhea	7 (5.8)	4 (3.5)	11 (2.4)	11 (2.4)
Sepsis	6 (5.0)	3 (2.6)	9 (2.0)	10 (2.2)
Fatal TEAEs[d]	6 (5.0)	4 (3.5)	14 (3.1)	17 (3.8)
Discontinuation of ≥1 study drug due to TEAEs	49 (40.8)	52 (45.6)	149 (33.1)	136 (30.3)

TEAE, treatment-emergent adverse event; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.
[a]Pooled safety population included all patients who were randomized in PERSEUS or GRIFFIN and received ≥1 dose of study treatment.
[b]Grade 3/4 TEAEs that occurred in ≥10% of patients aged ≥65 years in either treatment group.
[c]Serious TEAEs that occurred in ≥5% of patients aged ≥65 years in either treatment group.
[d]Fatal TEAEs were considered related to daratumumab in 1 patient aged ≥65 years (squamous cell carcinoma) and in 1 patient aged <65 years (sepsis).

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Multiple Myeloma

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