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Stem Cell (SC) Yield and Transplant With Daratumumab + Bortezomib, Lenalidomide, and Dexamethasone in Transplant-eligible Newly Diagnosed Multiple Myeloma Patients in the Phase 3 PERSEUS Study

Pieter Sonneveld[1], Meletios A Dimopoulos[2], Mario Boccadoro[3], Hang Quach[4], P Joy Ho[5], Meral Beksac[6], Cyrille Hulin[7], Elisabetta Antonioli[8], Xavier Leleu[9], Silvia Mangiacavalli[10], Aurore Perrot[11], Michele Cavo[12], Angelo Belotti[13], Annemiek Broijl[1], Francesca Gay[14], Roberto Mina[14], Niels WCJ van de Donk[15], Yanfang Liu[16], Jianping Wang[17], Anna Sitthi-Amorn[17], Carla J de Boer[18], Robin Carson[17], Paula Rodriguez-Otero[19], Joan Bladé[20], Philippe Moreau[21]

[1]Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [2]National and Kapodistrian University of Athens, Athens, Greece; [3]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; [4]University of Melbourne, St Vincent's Hospital, Melbourne, Australia; [5]Institute of Haematology, Royal Prince Alfred Hospital and University of Sydney, Camperdown, NSW, Australia; [6]Ankara University, Ankara, Turkey; [7]Department of Hematology, Hôpital Haut Lévêque, University Hospital, Pessac, France; [8]Department of Hematology, Careggi Hospital and University of Florence, Firenze, Italy; [9]University of Poitiers, CHU and Inserm 1313, Poitiers, France; [10]Hematology Division, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; [11]CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France; [12]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [13]Department of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; [14]Division of Hematology 1, AOU Città della Salute e della Scienza di Torino and Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy; [15]Department of Hematology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [16]Janssen Research & Development, LLC, Beijing, China; [17]Janssen Research & Development, LLC, Spring House, PA, USA; [18]Janssen Research & Development, LLC, Leiden, The Netherlands; [19]Department of Hematology, Cancer Center Clínica Universidad de Navarra, Pamplona, Navarra, Spain; [20]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain, and GEM/PETHEMA; [21]Hematology Department, University Hospital Hôtel-Dieu, Nantes, France

Key Takeaway

In the PERSEUS phase 3 randomized trial of transplant-eligible NDMM patients, the addition of subcutaneously administered daratumumab to VRd during induction did not impair the feasibility of stem cell mobilization and harvesting and achieved comparable transplant outcomes versus standard-of-care VRd therapy

Conclusions

Despite numerically lower stem cell yields with D-VRd induction compared to VRd, stem cell mobilization and collection remained feasible with D-VRd induction

Successful ASCT was achieved in transplant-eligible NDMM patients when combining daratumumab with VRd induction and when performed after Cycle 6

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Poster

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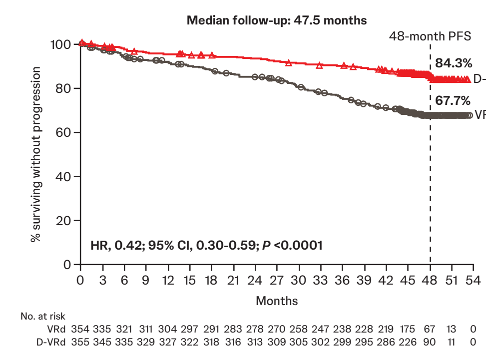
Disclosure

PS served in a consulting or advisory role for Bristol Myers Squibb, Janssen, Pfizer, and SkylineDx; serves as president of the board for the European Myeloma Network; and is a professor, hematologist, and trial lead at Erasmus Medical Center.

Introduction

- Recommended treatment for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM) includes induction therapy followed by high-dose therapy (HDT) with autologous stem cell transplant (ASCT) and lenalidomide maintenance therapy[1-4]
- Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with direct on-tumor[5-8] and immunomodulatory[9-11] mechanisms of action
- In the primary analysis of the phase 3 PERSEUS trial (ClinicalTrials.gov Identifier: NCT03710603), transplant-eligible NDMM patients received subcutaneous daratumumab plus bortezomib, lenalidomide, and dexamethasone (D-VRd) followed by D-R maintenance, which resulted in improved progression-free survival (PFS) and increased rates of deep and durable responses compared to VRd alone followed by R maintenance[12]
  - At a median follow-up of 47.5 months, PFS was significantly improved with D-VRd versus VRd (hazard ratio [HR], 0.42; 95% confidence interval, 0.30-0.59; *P* <0.0001; **Figure 1**)
    - Median PFS was not reached in either group; estimated 48-month PFS rate was 84.3% for D-VRd versus 67.7% for VRd
  - Minimal residual disease (MRD)–negativity rates at a threshold of 10^{-5} were higher for D-VRd versus V-Rd (75.2% vs 47.5%; *P* <0.001)
  - Sustained MRD negativity at a threshold of 10^{-5} for ≥12 months was higher for D-VRd versus VRd (64.8% vs 29.7%)
  - Rates of complete response or better (≥CR) were higher for D-VRd versus VRd (87.9% vs 70.1%; *P* <0.001)
  - Overall survival (OS) was descriptive due to a low number of events, with 78 total deaths (D-VRd, 34; VRd, 44); however, descriptive results indicated a trend toward a beneficial treatment effect (HR, 0.73)
- Here, we report stem cell yield and ASCT results for transplant-eligible NDMM patients who received D-VRd versus VRd induction prior to HDT/ASCT in the PERSEUS trial

Figure 1: PFS



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

Methods

Patients

- Eligible patients had NDMM and were candidates for HDT and ASCT
- Patients were aged 18 to 70 years with an Eastern Cooperative Oncology Group performance status score of 0 to 2

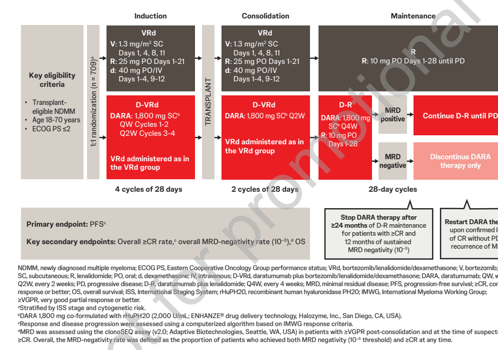
Study design and treatment

- PERSEUS was an open-label, multicenter, randomized, phase 3 trial of D-VRd versus VRd in transplant-eligible NDMM patients (**Figure 2**)
- Patients were randomized 1:1 to receive 4 induction cycles (28 days) and 2 post-ASCT consolidation cycles (28 days) of D-VRd or VRd
  - After induction (Cycle 4), patients underwent stem cell mobilization per local standard of care
  - Per institutional practice, plerixafor use, in addition to the standard agents cyclophosphamide and granulocyte colony-stimulating factor (GCSF), was recommended to aid mobilization
  - If impacted by COVID-19 site closures, stem cells were collected after Cycle 4 and transplanted immediately after completion of Cycle 6
  - Melphalan was given as HDT prior to ASCT
- Patients received maintenance therapy (28-day cycles) consisting of D-R or R alone

Assessments and analyses

- The primary endpoint of PERSEUS was PFS
- Key secondary endpoints included the rate of ≥CR, MRD negativity with a ≥CR, and OS
- Descriptive statistics are used herein to describe patient characteristics, stem cell mobilization outcomes, and stem cell transplant outcomes

Figure 2: Study design

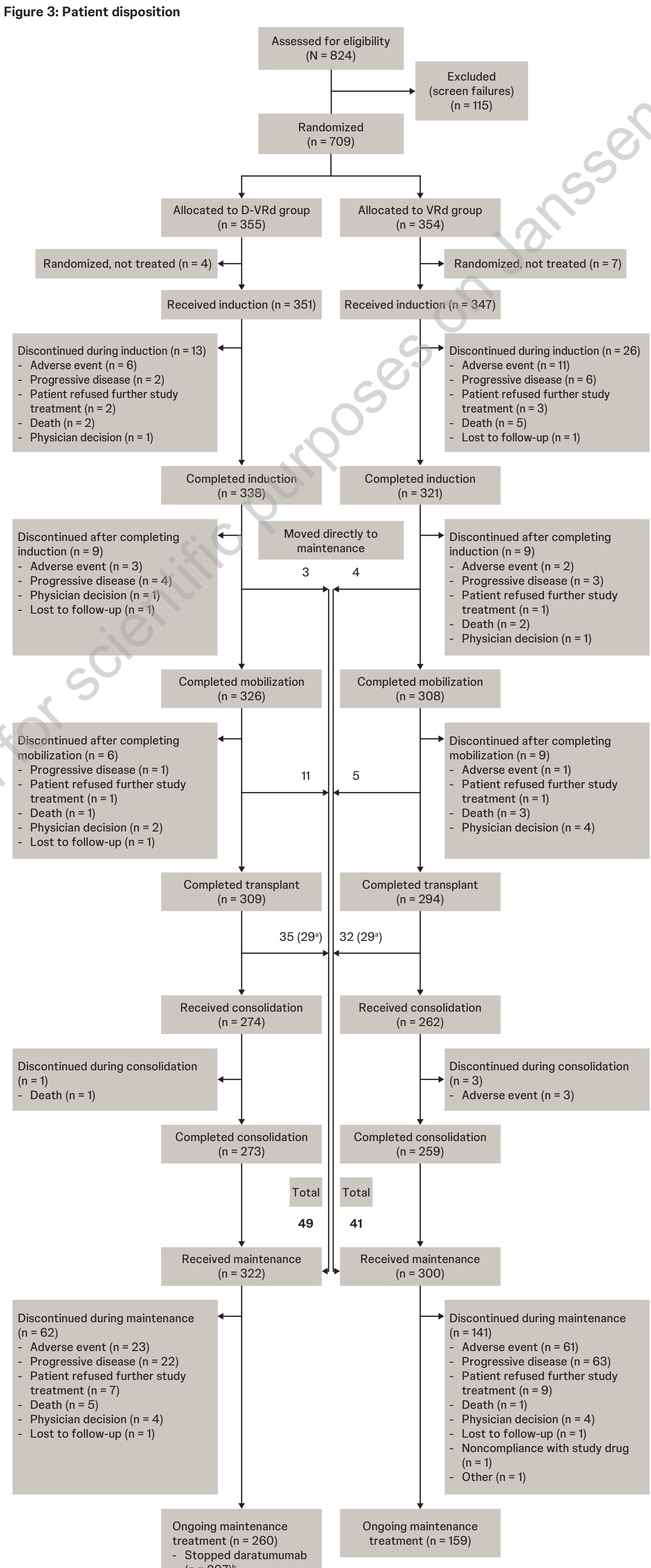


NDMM, newly diagnosed multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status; VRd, bortezomib/lenalidomide/dexamethasone; V, bortezomib; SC, subcutaneous; R, lenalidomide; PO, oral; d, dexamethasone; IV, intravenous; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; 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 or better; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; ≥VGPR, very good partial response or better.
[a]Stratified by ISS 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 IMWG 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 PERSEUS, at the time of the data cutoff (August 1, 2023), a total of 709 patients were randomized to D-VRd (n = 355) or VRd (n = 354)
  - Baseline demographic and disease characteristics were generally well balanced between D-VRd and VRd
    - Median age (range): 60 (31-70) years
    - International Staging System (ISS) stage III disease: 14.8% of patients
    - High cytogenetic risk (t[4;14], t[14;16], and/or del[17p]): 21.7% of patients
- Of the 698 treated patients (D-VRd, n = 351; VRd, n = 347), a total of 652 underwent mobilization (D-VRd, n = 335; VRd, n = 317; **Figure 3**)

Figure 3: Patient disposition



D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; ≥CR, complete response or better; MRD, minimal residual disease.
[a]Patients who received Cycles 5 and 6 consecutive to induction therapy due to the COVID-19 pandemic.
[b]After ≥24 months of maintenance therapy, daratumumab was discontinued in patients who achieved ≥CR and sustained MRD negativity (at or below a sensitivity threshold of 10^{-5}) for 12 months; patients continued lenalidomide maintenance therapy until disease progression or unacceptable toxicity.

- Results for stem cell mobilization and harvesting are presented in **Table 1**
  - In total, 134 (40.0%) patients in the D-VRd group and 72 (22.7%) patients in the VRd group received plerixafor during stem cell mobilization
  - The median time from last induction dose to first mobilization agent was 22 days
  - Among patients who underwent stem cell collection (D-VRd, n = 326; VRd, n = 314), the percentage of patients who had a sufficient number of stem cells collected for ASCT (≥2 × 10^6/kg cells) was high in both groups (D-VRd, n = 320 [98.2%]; VRd, n = 312 [99.4%])
  - While the median number of collected CD34⁺ stem cells was numerically lower for the D-VRd group versus the VRd group (5.52 × 10^6/kg vs 7.44 × 10^6/kg), the percentage of patients who underwent ASCT was similar between groups (89.7% vs 87.0%)

Table 1: Stem cell mobilization and harvesting (safety analysis set)

	D-VRd (n = 351)	VRd (n = 347)
PBSC mobilizing agents, n (%)[a]		
n	335	317
Cyclophosphamide	261 (77.9)	235 (74.1)
G-CSF[b]	324 (96.7)	307 (96.8)
Plerixafor	134 (40.0)	72 (22.7)
Total number of CD34⁺ stem cells collected[a] (10^6/kg) among patients with stem cells collected[c,d]		
n	326	314
Mean (SD)	6.236 (3.3243)	8.317 (5.0732)
Median (range)	5.52 (1.00-26.00)	7.44 (0.74-49.50)
≥2 × 10^6/kg, n (%)	320 (98.2)	312 (99.4)
≥5 × 10^6/kg, n (%)	193 (59.2)	242 (77.1)

D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; PBSC, peripheral blood stem cell; G-CSF, granulocyte colony-stimulating factor; SD, standard deviation.
[a]Percentages were calculated with the number of patients with available data in the related subgroup as the denominator.
[b]Includes standardized medications of filgrastim, G-CSF, and lenograstim.
[c]Percentages were calculated with the number of patients in each group as the denominator.
[d]The stem cells were collected by PBSC apheresis or bone marrow harvest.

- Stem cell transplant results are presented in **Table 2**
  - The median number of CD34⁺ stem cells transplanted was 3.25 × 10^6/kg for the D-VRd group and 3.98 × 10^6/kg for the VRd group
  - Hematopoietic reconstitution rates were high in both the D-VRd (314/315 [99.7%]) and VRd (300/302 [99.3%]) groups
  - To obtain sustained absolute neutrophil counts (≥0.5 × 10^9/L), a median (range) of 13 (1-67) days versus 13 (1-38) days was needed for the D-VRd group and the VRd group, respectively
  - To obtain sustained platelet counts (≥20 × 10^9/L) without transfusion, a median (range) of 14 (1-94) days versus 12 (1-137) days was needed for the D-VRd group and the VRd group, respectively
  - A total of 58 patients (29 per treatment group) underwent ASCT after Cycle 6 completion, with 100% hematopoietic reconstitution and similar time to engraftment (D-VRd, 14 [1-67] days; VRd, 14 [12-137] days) in both groups

Table 2: Stem cell transplant (safety analysis set)

	D-VRd (n = 351)	VRd (n = 347)
Transplant, n (%)[a]	315 (89.7)	302 (87.0)
CD34⁺ stem cells transplanted (10^6/kg)		
n	315	302
Mean (SD)	4.07 (2.628)	4.87 (3.601)
Median (range)	3.25 (0.8-26.0)	3.98 (1.0-38.7)
Transplanted patients with hematopoietic reconstitution, n (%)[b]		
n	315	302
Yes	314 (99.7)	300 (99.3)
No	1 (0.3)	2 (0.7)
Days to achieve sustained ANC ≥0.5 × 10^9/L		
n	314	300
Mean (SD)	13.5 (5.47)	13.0 (4.88)
Median (range)	13 (1-67)	13 (1-38)
Days to achieve sustained platelets ≥20 × 10^9/L without transfusion[c]		
n	314	300
Mean (SD)	14.4 (7.79)	13.0 (9.44)
Median (range)	14 (1-94)	12 (1-137)
Days to engraftment post-ASCT[c,d]		
n	314	300
Mean (SD)	15.7 (7.68)	14.9 (9.37)
Median (range)	14.0 (1-94)	14.0 (1-137)

D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; SD, standard deviation; ANC, absolute neutrophil count; ASCT, autologous stem cell transplant.
[a]Percentages were calculated with the number of patients in each group as the denominator.
[b]Percentages were calculated with the number of patients with available data in the related subgroup as the denominator.
[c]Number of days from the transplant date, excluding patients whose counts did not reach nadir below the set threshold.
[d]The date of engraftment post-ASCT is defined as the latest date of ANC ≥0.5 × 10^9/L and platelet count ≥20 × 10^9/L. Patients with hematopoietic reconstitution are included.

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Multiple Myeloma

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