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Daratumumab, Bortezomib, and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of CASTOR

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INTRODUCTION

- Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action[1-6]
  - The on-tumor activity of daratumumab occurs through several CD38 immune-mediated actions, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, apoptosis, and modulation of CD38 enzymatic activity[3-5]
  - The immunomodulatory effect of daratumumab increases T-cell clonality and induces lysis of immune-suppressive CD38$^+$ myeloid-derived suppressor cells, regulatory B cells, and regulatory T cells[6]
- In 2 randomized, open-label, active-controlled, phase 3 studies, daratumumab demonstrated superior clinical benefit when combined with standard of care regimens (bortezomib and dexamethasone [Vd; CASTOR[7]] or lenalidomide and dexamethasone [Rd; POLLUX[8]]) for the treatment of patients with multiple myeloma (MM) who received ≥1 prior line of therapy
  - Based on these pivotal studies, daratumumab in combination with Vd (DVd) or Rd (DRd) was approved in the United States and Europe for the treatment of patients with MM who have received ≥1 prior therapy[9,10]
- In CASTOR, after a median follow-up of 19.4 months, DVd prolonged progression-free survival (PFS) (median: 16.7 versus 7.1 months; hazard ratio [HR], 0.31; 95% confidence interval [CI], 0.24-0.39; *P* <0.0001), conferring a 69% lower risk of disease progression or death[11]
  - Daratumumab also significantly improved the overall response rate (ORR) compared with the control group (84% vs 63%; *P* <0.0001), as well as the rates of complete response (CR) or better (29% vs 10%; *P* <0.0001) and very good partial response (VGPR) or better (62% vs 29%; *P* <0.0001)[11]
  - Deeper responses with DVd translated to higher rates of minimal residual disease (MRD)–negativity versus Vd at a sensitivity threshold of 10^{-5} (12% vs 2%; *P* <0.0001) using clonoSEQ™ assay V1.3[11]
- This poster provides updated safety and efficacy data for DVd versus Vd after a median follow-up of 26.9 months in CASTOR

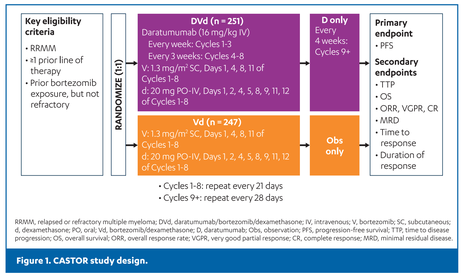
METHODS

Patients

- Patients received ≥1 prior line of therapy and achieved at least a partial response (PR) to ≥1 of their prior therapies for MM, and had documented progressive disease according to International Myeloma Working Group criteria on or after their last regimen
- Key exclusion criteria were as follows:
  - Creatinine clearance ≤20 mL/min/1.73 m^2
  - Patients refractory to or intolerant of bortezomib
  - Patients refractory to another proteasome inhibitor (after amendment 1)
  - Grade ≥2 peripheral neuropathy or neuropathic pain

Study Design and Treatment

- This was a multicenter, randomized (1:1), open-label, active-controlled, phase 3 study of patients with relapsed or refractory MM (**Figure 1**)
- Randomization was stratified by International Staging System (ISS; I, II, or III) at screening (based on central laboratory results), number of prior lines (1 vs 2 or 3 vs >3), and prior bortezomib (no vs yes)
- All patients received up to 8 cycles (21 days/cycle) of Vd
  - Bortezomib was administered subcutaneously at a dose of 1.3 mg/m^2 on Days 1, 4, 8, and 11 of Cycles 1 to 8
  - Dexamethasone was administered orally or intravenously (IV) at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1 to 8
  - For patients assigned to DVd, daratumumab 16 mg/kg IV was administered weekly (Days 1, 8, and 15) during Cycles 1 to 3, every 3 weeks of Cycles 4 to 8, and every 4 weeks thereafter until progressive disease
    - Following the primary analysis, patients who progressed on Vd had the option to receive daratumumab monotherapy
  - PFS was the primary endpoint



RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; V, bortezomib; SC, subcutaneous; d, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to disease progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

Figure 1. CASTOR study design.

MRD Evaluation

- MRD was assessed at the time of suspected CR (blinded to treatment group) and at 6 and 12 months following the first treatment dose, which occurred at the end of Vd background therapy and 6 months later, respectively
- MRD was assessed via next-generation sequencing on bone marrow aspirate samples that were ficolled and evaluated by the clonoSEQ® assay V2.0 (Adaptive Biotechnologies, Seattle, WA) at sensitivity thresholds of 10^{-4} (1 cancer cell per 10,000 nucleated cells), 10^{-5}, and 10^{-6}
  - clonoSEQ® assay V2.0 demonstrates increased calibration rates compared to V1.3 (86% vs 73%, respectively) in patients with a confirmed response of CR or greater with an available sample
- Patients were considered to be MRD positive if they had an MRD-positive test result or had no MRD assessment

Cytogenetic Risk

- Cytogenetic risk was determined by next-generation sequencing
- High-risk patients had t(4;14), t(14;16), and/or del17p cytogenetic abnormalities
  - For del17p detection using exome-seq, a >50% deletion cutoff of the 17p region was utilized
- Standard-risk patients were confirmed negative for these abnormalities

Statistical Analyses and Assessments

- Unless otherwise specified, efficacy analyses were based on the intent-to-treat (ITT) population
- The response-evaluable analysis set included patients with measurable disease at the baseline or screening visit who received ≥1 study treatment and had ≥1 post-baseline disease assessment
- A stratified log-rank test was used to compare PFS between the DVd and Vd treatment groups
  - HRs and 95% CIs were estimated by using a stratified Cox regression model, with treatment as the sole explanatory variable
- The Kaplan-Meier method was used to estimate the distributions
- PFS on the subsequent line of therapy (PFS2) was defined as the time from randomization to progressive disease after the next line of subsequent therapy or death
- A stratified Cochran-Mantel-Haenszel chi-square test was used to measure treatment differences in ORR, rate of VGPR or better, and rate of CR or better
- The entire ITT population was evaluated to allow for a stringent and unbiased evaluation of MRD
- The rate of MRD negativity was determined as the proportion of patients who achieved MRD-negative status at any time point following the first treatment dose
- MRD-negative rates for each treatment group were compared using the likelihood-ratio test

RESULTS

Patients and Treatments

- The clinical cutoff date was August 30, 2017, with a median follow-up of 26.9 months
- A total of 498 patients were enrolled (DVd, n = 251; Vd, n = 247)
- Demographic, baseline disease, and clinical characteristics were well balanced (**Table 1**)
- The median (range) number of prior lines of therapy was 2 (1-10)
- Median duration of treatment was 13.4 months for DVd and 5.2 months for Vd
  - Among 191 patients who went on to single-agent daratumumab maintenance, median duration of treatment was 14.8 months

Table 1. Patient Demographic, Baseline Disease, and Clinical Characteristics (ITT)

Characteristic	DVd (n = 251)	Vd (n = 247)
Age, y		
Median (range)	64 (30-88)	64 (33-85)
≥75 y, n (%)	23 (9)	35 (14)
ISS, n (%)[a]		
I	98 (39)	96 (39)
II	94 (38)	100 (41)
III	59 (24)	51 (21)
Time from diagnosis, y		
Median (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)
Prior lines of therapy, n (%)		
Median (range)	2 (1-9)	2 (1-10)
1	122 (49)	113 (46)
2	70 (28)	74 (30)
3	37 (15)	32 (13)
>3	22 (9)	28 (11)
Prior bortezomib	162 (65)	164 (66)
Prior lenalidomide	89 (36)	120 (49)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to lenalidomide at last prior line of therapy, n (%)	45 (18)	60 (24)

ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; ISS, International Staging System; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
[a]ISS staging was based on the combination of serum β2-microglobulin and albumin.

Updated Efficacy Results

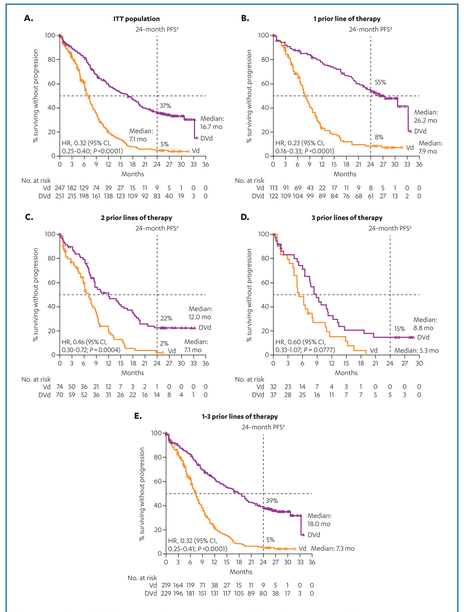
- After a median follow-up of 26.9 months, PFS was significantly prolonged with DVd compared with Vd in the ITT population (16.7 vs 7.1 months; HR, 0.32; 95% CI, 0.25-0.40; *P* <0.0001; **Figure 2A**), with 24-month PFS rates of 37% versus 5%, respectively
- A higher ORR was observed with DVd versus Vd (85% vs 63%; *P* <0.0001), with significantly higher rates of VGPR or better (63% vs 29%; *P* <0.0001) and CR or better (30% vs 10%; *P* <0.0001), respectively, in the response-evaluable population (**Table 2**)

Number of Prior Lines of Therapy

- In patients with 1 prior line of therapy, PFS was significantly prolonged with DVd compared with Vd (26.2 vs 7.9 months; HR, 0.23; 95% CI, 0.16-0.33; *P* <0.0001; **Figure 2B**), with 24-month PFS rates of 55% versus 8%, respectively
  - Higher ORR was observed in patients with 1 prior line of therapy treated with DVd versus Vd (92% vs 74%; *P* = 0.0007), with significantly higher rates of VGPR or better (77% vs 42%; *P* <0.0001) and CR or better (43% vs 15%; *P* <0.0001), respectively (**Table 2**)
- PFS and ORR by 2 prior lines of therapy, 3 prior lines of therapy, and 1-3 prior lines of therapy are summarized in **Figure 2C** to **2E** and **Table 2**
- PFS among patients who achieved deep responses (≥CR) was prolonged with DVd versus Vd (not reached vs 19.0 months; HR, 0.24; 95% CI, 0.09-0.64; *P* = 0.0022; **Figure 3A**)

MRD Negativity

- MRD-negative rates were significantly higher at 10^{-5} threshold for DVd versus Vd in the ITT population (**Table 2**)
- Except for patients with 3 prior lines of therapy, significantly higher MRD-negative rates at 10^{-5} were observed in all subgroups (**Table 2**)
- MRD negativity was associated with prolonged PFS (**Figure 3B**)



PFS, progression-free survival; ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.
*Kaplan-Meier estimate.

Figure 2. PFS in the (A) ITT population and in patients with (B) 1 prior line of therapy, (C) 2 prior lines of therapy, (D) 3 prior lines of therapy, and (E) 1 to 3 prior lines of therapy.

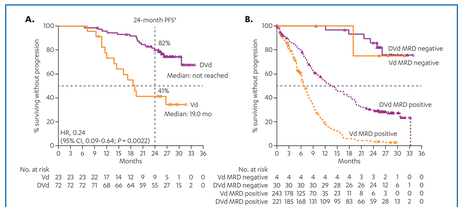
PFS2

- PFS2 was significantly prolonged with DVd compared with Vd in the ITT population (median not reached vs 20.7 months; HR, 0.47; 95% CI, 0.36-0.63; *P* <0.0001; **Figure 4**)
- The PFS2 benefit of DVd was maintained in patients who received 1 prior line of therapy (median not reached vs 24.3 months; HR, 0.32; 95% CI, 0.20-0.51; *P* <0.0001; **Figure 4**) or 1 to 3 prior lines of therapy (median not reached vs 20.9 months; HR, 0.45; 95% CI, 0.33-0.61; *P* <0.0001)

Table 2. Response and MRD-negative Rates of DVd Based on the Number of Prior Lines of Therapy

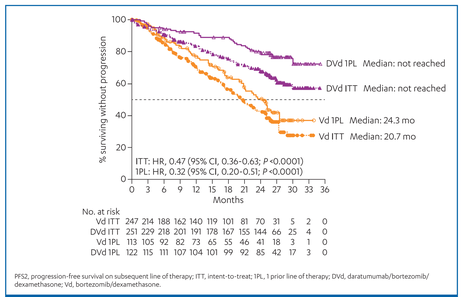
	Study population		1 prior line of therapy		2 prior lines of therapy		3 prior lines of therapy		1 to 3 prior lines of therapy	
	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Vd
ORR[a]										
N	240	234	119	109	64	71	35	29	218	209
%	85	63	92	74	84	65	69	41	86	67
P value	<0.0001		0.0007		0.0563		0.0487		<0.0001	
≥VGPR, %	63	29	77	42	61	18	34	28	65	32
P value	<0.0001		<0.0001		<0.0001		0.6999		<0.0001	
≥CR, %	30	10	43	15	25	9	11	3	33	11
P value	<0.0001		<0.0001		0.0118		0.3009		<0.0001	
sCR, %	10	3	14	5	6	1	6	0	11	3
MRD-negative rate (10^{-5})[b]										
N	251	247	122	113	70	74	37	32	229	219
%	12	2	16	3	11	0	5	3	13	2
P value	<0.0001		0.0002		0.0005		0.64		<0.0001	

MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; ITT, intent-to-treat; Vd, bortezomib/dexamethasone; ORR, overall response rate; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.
[a]Response-evaluable population.
[b]ITT population.



PFS, progression-free survival; CR, complete response; MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.
*Kaplan-Meier estimate.

Figure 3. PFS in patients who achieved (A) ≥CR and (B) MRD negativity at 10^{-5}.



PFS2, progression-free survival on subsequent line of therapy; ITT, intent-to-treat; 1PL, 1 prior line of therapy; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

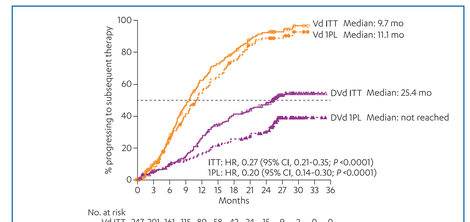
Figure 4. PFS2 in the ITT population and in patients who received 1PL.

Time to Next Therapy (TTNT)

- TTNT was significantly prolonged with DVd versus Vd in the ITT population (25.4 vs 9.7 months; HR, 0.27; 95% CI, 0.21-0.35; *P* <0.0001; **Figure 5**)
- TTNT was significantly prolonged in patients who received 1 prior line of therapy (not reached vs 11.1 months; HR, 0.20; 95% CI, 0.14-0.30; *P* <0.0001; **Figure 5**)
- TTNT was also significantly prolonged with DVd in patients with high cytogenetic risk (25.2 vs 9.7 months; HR, 0.29; 95% CI, 0.16-0.54; *P* <0.0001)

Updated Safety Results

- The most common treatment-emergent adverse events (TEAEs; ≥25% patients) and most common grade 3 and 4 TEAEs (≥5% patients) are summarized in **Table 3**
- 9.5% of patients in the DVd arm and 9.3% of patients in the Vd arm discontinued treatment due to TEAEs
- With longer follow-up, secondary primary malignancies were reported in 10 (4.1%) patients who received DVd (no new cases since previous analysis) versus 3 (1.3%) patients who received Vd (2 new cases since previous analysis, consisting of squamous cell carcinoma of the skin and acute myeloid leukemia [n = 1 patient each])



TTNT, time to next therapy; ITT, intent-to-treat; 1PL, 1 prior line of therapy; Vd, bortezomib/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone.

Figure 5. TTNT in the ITT population and in patients who received 1PL.

Table 3. Most Common (≥25% of Patients) and Grade 3 and 4 (≥5% of Patients) TEAEs

	All grades ≥25%		Grade 3 and 4 ≥5%	
TEAE	DVd	Vd	DVd	Vd
Hematologic (%)				
Thrombocytopenia	59.7	44.3	45.7	32.9
Anemia	28.4	31.6	15.2	16.0
Neutropenia	18.9	9.7	13.6	4.6
Lymphopenia	13.2	3.8	9.9	2.5
Nonhematologic (%)				
Pneumonia	15.6	13.1	10.3	10.1
Peripheral sensory neuropathy	49.8	38.0	4.5	6.8
Hypertension	9.9	3.4	6.6	0.8
Upper respiratory tract infection	32.9	18.1	2.5	0.4
Diarrhea	35.4	22.4	3.7	1.3
Cough	28.0	12.7	0	0

TEAE, treatment-emergent adverse event; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.

CONCLUSIONS

- **Addition of daratumumab to Vd continues to significantly prolong PFS with longer follow-up**
- **DVd improved PFS and ORR regardless of the number of prior lines of therapy**
  - **Patients who received 1 prior line of therapy benefited the most from DVd**
- **Higher MRD-negative rates (6-fold) were observed with DVd at 10^{-5} in the ITT population**
- **Durable responses in the DVd arm translated into longer PFS2 and TTNT**
- **The safety profile of daratumumab remains consistent with previous analyses of CASTOR,[7,11] and no new safety signals were reported with longer follow-up**
- **The high rate of deep clinical responses induced by daratumumab supports the use of DVd in relapsed or refractory MM patients and suggests that patients achieve the greatest benefit at first relapse**

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DISCLOSURES

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