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Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone for Relapsed/Refractory Multiple Myeloma (RRMM) Patients: An Update of Overall Survival in CASTOR

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INTRODUCTION

- Daratumumab is a human CD38 IgGκ monoclonal antibody that has both direct on-tumor and immunomodulatory mechanisms 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 had received ≥1 prior line of therapy
  - Based on these pivotal studies, daratumumab in combination with Vd (DVd) or with Rd was approved by the US Food and Drug Administration for the treatment of patients with MM who have received ≥1 prior therapy[9]
- After a median follow-up of 19.4 months, median progression-free survival (PFS) was 16.7 months in the DVd group versus 7.1 months in the Vd group (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[10]
- 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)[10]
- Minimal residual disease (MRD) is a more sensitive measure of disease burden than traditional definitions of clinical response[11,12]
  - MRD-negative status is associated with prolonged PFS and overall survival (OS) in newly diagnosed patients with MM,[11,12] and may be a primary endpoint for clinical studies in the future
  - International Myeloma Working Group (IMWG) guidelines recommend an MRD sensitivity threshold of ≥10^{-5} using next-generation sequencing (NGS) or next-generation flow cytometry[13]
  - After a median of 19.4 months of follow-up, MRD-negative rates were >4-fold higher at all 3 sensitivity thresholds in patients receiving DVd versus Vd (12% vs 2% at a 10^{-5} sensitivity threshold; clonoSEQ® assay V1.3)[10]
  - MRD-negative patients demonstrated prolonged PFS compared with MRD-positive patients[10]
- Based on the significant clinical benefit associated with adding daratumumab to Vd, we hypothesized that the prolonged PFS and higher rates of deeper responses would translate to long-term benefit for DVd versus Vd

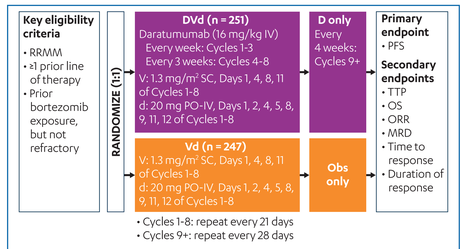
METHODS

Patients

- Patients received ≥1 prior line of therapy and achieved at least a partial response to ≥1 of their prior therapies for MM, and had documented progressive disease according to IMWG 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 (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
  - At the interim analysis, the Independent Data and Safety Monitoring Committee recommended unblinding the study early and allowing patients in the Vd treatment group with disease progression to receive daratumumab monotherapy[7]



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; 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 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 with an available sample
- Patients were considered to be MRD positive if they had an MRD-positive test result or had no MRD assessment
- The entire intent-to-treat (ITT) population was evaluated to allow for a stringent and unbiased evaluation of MRD
- The rate of MRD negativity per treatment arm was determined as the proportion of patients with MRD-negative status at any time point following the first treatment dose

Cytogenetic Risk

- Cytogenetic risk was determined by NGS
- 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

Statistical Analyses and Assessments

- Unless otherwise specified, efficacy analyses were based on the 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
- 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 log-rank test was used to compare PFS2 between the DVd and Vd treatment groups
  - HRs and 95% CIs were estimated by using a stratified Cox proportional hazards model, with treatment as the sole explanatory variable

RESULTS

Patients and Treatments

- The clinical cutoff date was August 30, 2017, with a median follow-up (range) of 26.9 (0-35.1) 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
  - The median (range) number of daratumumab infusions for DVd was 23 (1-45)
  - Among 191 patients who went on to single-agent daratumumab maintenance, median duration of treatment was 14.8 months

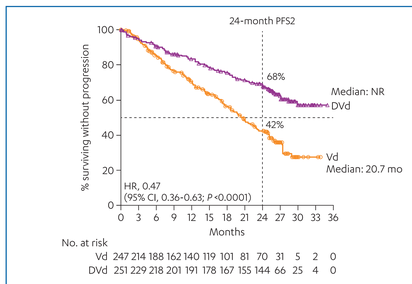
Table 1. Patient Demographic, Baseline Disease, and Clinical Characteristics (ITT)

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)
Creatinine clearance, mL/min, n (%)		
N	243	233
>30-60	49 (20)	59 (25)
>60	186 (77)	163 (70)
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 ASCT, n (%)	156 (62)	149 (60)
Prior PI, n (%)	169 (67)	172 (70)
Bortezomib	162 (65)	164 (66)
Prior IMiD, n (%)	179 (71)	198 (80)
Lenalidomide	89 (36)	120 (49)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to IMiD only, n (%)	74 (30)	90 (36)
Refractory to last line of therapy, n (%)	76 (30)	85 (34)

ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; ISS, International Staging System; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
[a]ISS staging was derived based on the combination of serum ß2-microglobulin and albumin.

PFS2 in ITT and Subgroup Populations

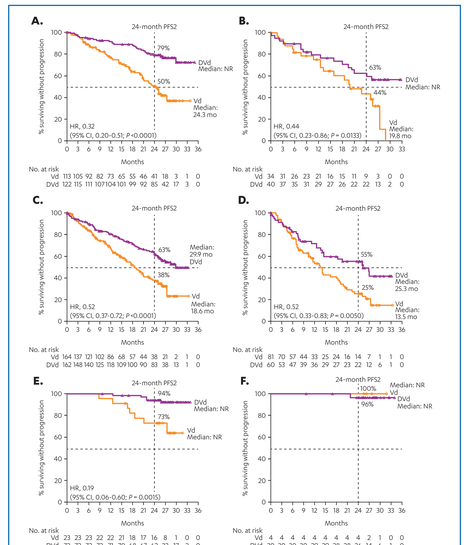
- In the ITT population, PFS2 was significantly prolonged with DVd compared with Vd (median not reached [NR] vs 20.7 months; HR, 0.47; 95% CI, 0.36-0.63; P <0.0001; **Figure 2**)



PFS2, progression-free survival with subsequent line of therapy; ITT, intent-to-treat; NR, not reached; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.

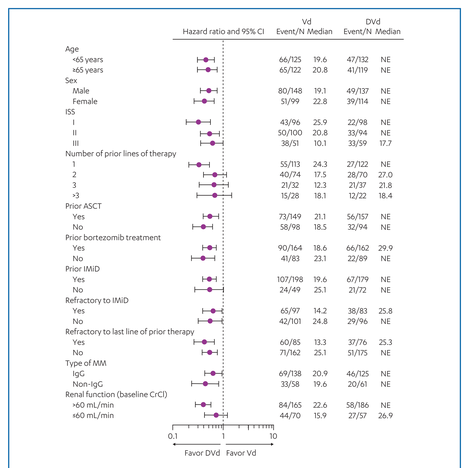
Figure 2. PFS2 in the ITT population.

- PFS2 subgroup analyses demonstrated superiority of DVd versus Vd among patients:
  - With 1 prior line of therapy (median NR vs 24.3 months; HR, 0.32; 95% CI, 0.20-0.51; P <0.0001; **Figure 3A**)
  - With high cytogenetic risk (median NR vs 19.8 months; HR, 0.44; 95% CI, 0.23-0.86; P = 0.0133; **Figure 3B**)
  - Previously treated with bortezomib (median 29.9 vs 18.6 months; HR, 0.52; 95% CI, 0.37-0.72; P <0.0001; **Figure 3C**)
  - Refractory to lenalidomide (median 25.3 vs 13.5 months; HR, 0.52; 95% CI, 0.33-0.83; P = 0.0050; **Figure 3D**)
  - Achieving ≥CR (median NR vs NR; HR, 0.19; 95% CI, 0.06-0.60; P = 0.0015; **Figure 3E**)
- Follow-up of PFS2 in patients achieving MRD negativity at a 10^{-5} sensitivity threshold is ongoing (**Figure 3F**)
- PFS2 subgroup analyses by other baseline and clinical characteristics are summarized in **Figure 4**



PFS2, progression-free survival with subsequent line of therapy; CR, complete response; MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; NR, not reached; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.

Figure 3. PFS2 for patients (A) with 1 prior line of therapy; (B) with high cytogenetic risk; (C) previously treated with bortezomib; (D) refractory to lenalidomide; (E) achieving ≥CR; and (F) by MRD negativity at a 10^{-5} sensitivity threshold.

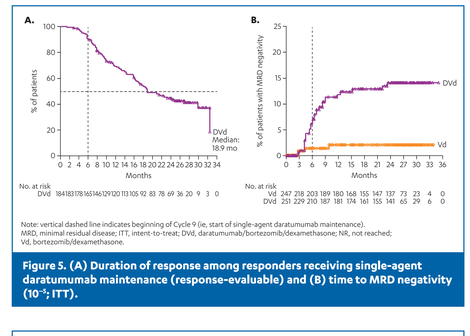


PFS2, progression-free survival with subsequent line of therapy; CI, confidence interval; Vd, bortezomib/dexamethasone; DVd, daratumumab/bortezomib/dexamethasone; NE, not evaluable; ISS, International Staging System; ASCT, autologous stem cell transplantation; IMiD, immunomodulatory drug; MM, multiple myeloma; IgG, immunoglobulin G; CrCl, creatinine clearance.

Figure 4. Forest plot for subgroup analyses of PFS2.

Single-agent Daratumumab Maintenance

- Among responders who received single-agent daratumumab as maintenance after completing 8 cycles of DVd (n = 184 in the response-evaluable population), median duration of response was 18.9 (95% CI, 16.8-24.7) months (**Figure 5A**)
- Patients in the DVd treatment arm continued to achieve MRD negativity (10^{-5}) while receiving single-agent daratumumab (**Figure 5B**)



Note: vertical dashed line indicates beginning of Cycle 9 (ie, start of single-agent daratumumab maintenance).
MRD, minimal residual disease; ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; NR, not reached; Vd, bortezomib/dexamethasone.

Figure 5. (A) Duration of response among responders receiving single-agent daratumumab maintenance (response-evaluable) and (B) time to MRD negativity (10^{-5}; ITT).

CONCLUSIONS

- **Patients continue to benefit from prior daratumumab treatment, as demonstrated by significant PFS2 benefit in the ITT and subgroup populations**
  - **Patients with deep responses and those with 1 prior line of therapy most benefitted from DVd treatment**
- **Responses were durable among responders receiving maintenance treatment with single-agent daratumumab, and MRD-negative rates continued to accumulate in the DVd arm during this treatment period**
- **These findings highlight the prolonged benefit of adding daratumumab to a standard of care regimen in relapsed or refractory MM**
- **Per study protocol, long-term survival follow-up will continue until 320 deaths have been observed in both arms (ie, when two-thirds of the randomized patients have died)**
  - **OS data currently remain immature**

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DISCLOSURES

SL consulted for Bristol-Myers Squibb, Celgene, and Janssen; served on speakers bureaus for Takeda; and holds equity in Caelum BioSciences. HQ consulted for and received honoraria from Amgen, Janssen, Takeda, and Celgene; and received research funding from Amgen and Celgene. MC served on a speakers bureau for Janssen. PT, HA, TC, and JMS are employed by Janssen. JMS holds equity in Johnson & Johnson. PS consulted for and received honoraria and research funding from Amgen, Celgene, Janssen, Karyopharm, and Takeda. VH received honoraria from Amgen, Celgene, Janssen, Roche, and Takeda. AC-K, NH, RO, J-CJ, and H-JS have no relationships to disclose.

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