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Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone Alone for Relapsed or Refractory Multiple Myeloma Based on Prior Treatment Exposure: Updated Efficacy Analysis of CASTOR

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INTRODUCTION

- Daratumumab is a human monoclonal antibody that targets CD38 and has been shown to provide superior clinical benefit for the treatment of multiple myeloma in patients with ≥1 prior line of therapy (LOT)[1,2]
- Daratumumab-induced on-tumor activity occurs through several CD38 immune-mediated actions (eg, complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis), apoptosis, and modulation of CD38 enzymatic activity[3-6]
- Daratumumab has an immunomodulatory effect of increasing helper and cytotoxic T cells, T-cell functional responses, and T-cell clonality, while minimizing the immune-suppressive functions of CD38$^+$ myeloid-derived suppressor cells, regulatory T cells, and regulatory B cells[7]
- Single-agent daratumumab demonstrated an overall response rate (ORR) of 31% and median overall survival (OS) of 20.1 months in heavily pre-treated patients with relapsed or relapsed and refractory multiple myeloma[8]
- In a randomized phase 3 study (CASTOR), daratumumab in combination with bortezomib and dexamethasone (DVd) significantly prolonged progression-free survival (PFS) versus bortezomib and dexamethasone alone (Vd) in a prespecified interim analysis of patients with relapsed or refractory multiple myeloma[1]
  - Most patients in the CASTOR study (66%) previously received a bortezomib-containing regimen
  - 28% of patients were refractory to lenalidomide
- Retreatment with bortezomib has been shown to be effective, with manageable and predictable toxicity, in patients with relapsed or refractory multiple myeloma who responded to their initial bortezomib treatment[9-14]
- In this analysis using updated data, we examine subgroups from CASTOR to compare the efficacy of DVd versus Vd in bortezomib-naïve and bortezomib pre-treated patient populations and to evaluate the efficacy of DVd versus Vd in patients who were refractory to lenalidomide at their last prior LOT

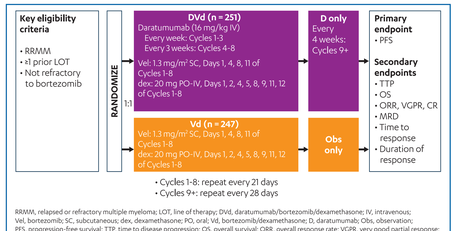
METHODS

Patients

- Patients were ≥18 years of age with an Eastern Cooperative Oncology Group (ECOG) status of ≤2
- Patients received ≥1 prior LOT and achieved at least a partial response (PR) to ≥1 of their prior therapies for multiple myeloma, and had documented progressive disease according to International Myeloma Working Group (IMWG) criteria on or after their last regimen
- All patients were required to have measurable disease in the serum and/or urine or serum free light chain at screening, as defined by the IMWG criteria
- Key exclusion criteria were as follows:
  - Patients refractory to or intolerant of bortezomib
  - Patients refractory to another proteasome inhibitor (after amendment 1)

Study Design and Treatment

- Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study of patients with relapsed or refractory multiple myeloma (**Figure 1**)
- Randomization was stratified by International Staging System (ISS; I, II, or III) at screening (based on central laboratory results), number of prior LOTs (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 for a total dose of 160 mg per cycle during 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 (Day 1) during Cycles 4 to 8, and every 4 weeks thereafter until withdrawal of consent, disease progression, or unacceptable toxicity
- For patients with suspected complete response (CR), and 6 and 12 months after first study dose, minimal residual disease (MRD) was assessed on bone marrow aspirate samples that were Ficolled and subjected to next-generation sequencing using ClonoSEQ™ assay (Adaptive Biotechnologies, Seattle, WA)
- In cases in which daratumumab interference with serum M-protein quantitation by electrophoresis or immunofixation assay was suspected in patients with possible CR, additional reflex testing using an anti-idiotype antibody was used to confirm CRs[8,15]



RRMM, relapsed or refractory multiple myeloma; LOT, line of therapy; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, 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.

Statistical Analyses and Assessments

- Approximately 480 patients with a total of 295 PFS events were hypothesized to provide 85% power to detect a 30% reduction in the risk of disease progression or death using a log-rank test, with an overall 2-sided significance level of 0.05
  - Following the positive primary analysis that occurred at 189 PFS events, efficacy and safety data were updated based on longer follow-up
- 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
- PFS was compared between treatment groups based on a stratified/unstratified log-rank test
  - Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by using a stratified/unstratified Cox regression model, with treatment as the sole explanatory variable
  - The Kaplan-Meier method was used to estimate the distributions
- A stratified Cochran-Mantel-Haenszel chi-square test/chi-square test was used to measure treatment differences in ORR, rate of very good PR (VGPR) or better, and rate of ≥CR
- Exploratory efficacy analyses were conducted within bortezomib pre-treated, bortezomib-naïve, and lenalidomide-refractory (in their last prior LOT) subgroups
- Proportions of MRD-negative patients between treatment arms were compared using the likelihood-ratio test
- MRD-negative rates were based on the ITT population
- PFS by MRD status was based on ITT/biomarker risk–evaluable population (had data for both DNA and RNA and had confirmed cytogenetic risk status)
- Cytogenetic analyses were based on next-generation sequencing

RESULTS

Patients and Treatments

- The clinical cut-off date was June 30, 2016, with a median follow-up of 13.0 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**)

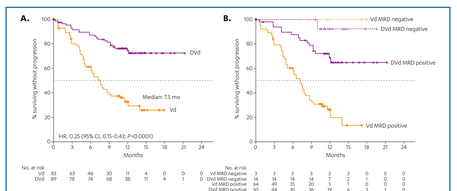
Efficacy in Bortezomib-naïve Patients

- In this subgroup of 172 patients (DVd, n = 89; Vd, n = 83), a total of 76 PFS events were observed (DVd, n = 22; Vd, n = 54)
  - Median PFS was not estimable (NE) for DVd versus 7.5 months for Vd (HR, 0.25; 95% CI, 0.15-0.43; P <0.0001; **Figure 2A**)
  - The estimated 12-month PFS rate was 74.6% for DVd versus 32.3% for Vd
- Rates of MRD negativity (10^{-5} sensitivity threshold) for DVd and Vd in bortezomib-naïve patients were 19.1% and 6.0%, respectively (P = 0.0084)
  - Patients who achieved MRD negativity demonstrated prolonged PFS (**Figure 2B**)
- The ORR was 90% for DVd versus 70% for Vd in the response-evaluable analysis set (P = 0.0019; **Figure 3A**)
- High response rates were observed in high-risk and standard-risk patients treated with DVd (**Figure 3B**)

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

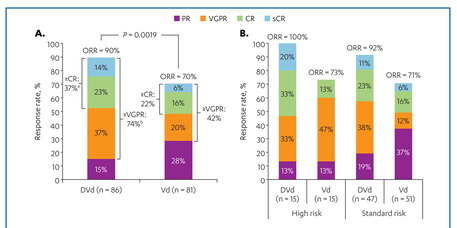
Characteristic	DVd (n = 251)	Vd (n = 247)
Age, y		
Median (range)	64 (30-88)	64 (33-85)
≥75, n (%)	23 (9)	35 (14)
ISS staging, n (%)		
I	98 (39)	96 (39)
II	94 (38)	100 (41)
III	59 (24)	51 (21)
Cytogenetic profile, n (%)[a]		
N	167	186
Standard risk	123 (74)	135 (73)
High risk	44 (26)	51 (27)
Time from diagnosis, y		
Median (range)	3.87 (0.7-20.7)	3.72 (0.6-18.6)
Prior LOTs, 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)
Previous bortezomib-containing regimen, n (%)	162 (65)	164 (66)
Bortezomib–naïve, n (%)	89 (36)	83 (34)
Prior IMiD, n (%)	179 (71)	198 (80)
Prior PI + IMiD, n (%)	112 (45)	129 (52)
Refractory to IMiD, n (%)	74 (30)	90 (36)
Refractory to last LOT, n (%)	76 (30)	85 (34)
Refractory to lenalidomide at last prior LOT, n (%)	45 (18)	60 (24)

ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; ISS, International Staging System; LOT, line of therapy; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
[a]Determined using centralized next-generation sequencing. High-risk cytogenetics were defined as having ≥1 of the following abnormalities: t(4;14), t(14;16), or del(17p.



PFS, progression-free survival; MRD, minimal residual disease; ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.

Figure 2. (A) Overall PFS and (B) PFS by MRD status (10^{-5}) in bortezomib-naïve patients.

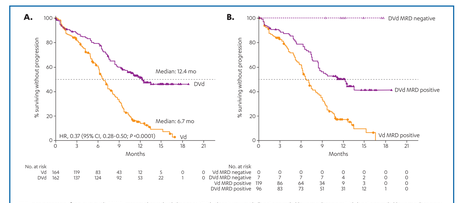


PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; ORR, overall response rate; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]P <0.05 for DVd vs Vd.
[b]P <0.0001 for DVd vs Vd.

Figure 3. Summary of (A) overall best confirmed response and (B) responses by cytogenetic status in bortezomib–naïve patients in CASTOR (response-evaluable analysis set).

Efficacy in Patients With Prior Bortezomib Exposure

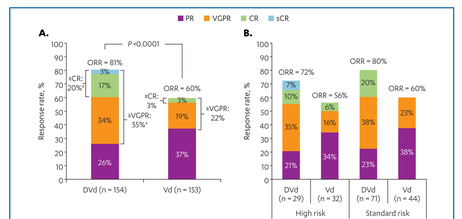
- In this subgroup of 326 patients (DVd, n = 162; Vd, n = 164 [ITT]), a total of 201 PFS events were observed (DVd, n = 78; Vd, n = 123)
  - Median PFS was 12.4 months for DVd versus 6.7 months for Vd (HR, 0.37; 95% CI, 0.28-0.50; P <0.0001; **Figure 4A**)
  - The estimated 12-month PFS rate was 51.3% for DVd versus 15.2% for Vd
- Rates of MRD negativity (10^{-5} sensitivity threshold) for DVd and Vd in bortezomib pre-treated patients were 5.6% and 0.6%, respectively (P = 0.0056)
  - Patients who achieved MRD negativity demonstrated prolonged PFS (**Figure 4B**)



PFS, progression-free survival; MRD, minimal residual disease; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval; ITT, intent-to-treat.
[a]No Vd patients achieved MRD negativity in the ITT/biomarker risk–evaluable population.

Figure 4. (A) Overall PFS and (B) PFS by MRD status (10^{-5})[a] in bortezomib–pre-treated patients.

- The ORR was 81% for DVd versus 60% for Vd in the response-evaluable analysis set (P <0.0001; **Figure 5A**)
- High response rates were observed in high-risk and standard-risk patients treated with DVd (**Figure 5B**)

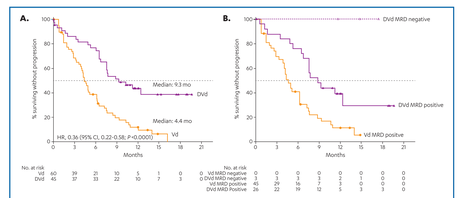


PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; ORR, overall response rate; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]P <0.0001 for DVd vs Vd.

Figure 5. Summary of (A) overall best confirmed response and (B) responses by cytogenetic status in bortezomib pre-treated patients in CASTOR (response-evaluable analysis set).

Efficacy in Patients Refractory to Lenalidomide at Last Prior LOT

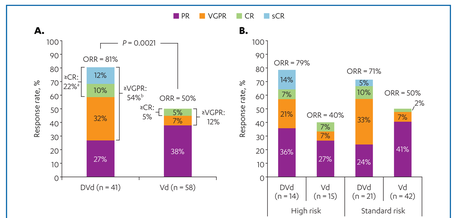
- In this subgroup of 105 patients (DVd, n = 45; Vd, n = 60 [ITT]), a total of 77 PFS events were observed (DVd, n = 25; Vd, n = 52)
  - Median PFS was 9.3 months for DVd versus 4.4 months for Vd (HR, 0.36; 95% CI, 0.22-0.58; P <0.0001; **Figure 6A**)
  - The estimated 12-month PFS rate was 43.5% for DVd versus 11.7% for Vd



PFS, progression-free survival; MRD, minimal residual disease; LOT, line of therapy; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval; ITT, intent-to-treat.
[a]No Vd patients achieved MRD negativity in the ITT/biomarker risk–evaluable population. P.S. received research funding from Janssen, Celgene, Amgen, Karyopharm, SkylineDx, Takeda, and Novartis; and received personal fees from Janssen, Celgene, and Amgen. S.L., J.-C.J., and H.-J.S. have no disclosures to report.

Figure 6. (A) Overall PFS and (B) PFS by MRD status (10^{-5})[a] in patients refractory to lenalidomide at last prior LOT.

- Rates of MRD negativity (10^{-5} sensitivity threshold) for DVd and Vd in patients refractory to lenalidomide at last prior LOT were 8.9% and 0%, respectively (P = 0.0082)
  - Patients who achieved MRD negativity demonstrated prolonged PFS (**Figure 6B**)
- The ORR was 81% for DVd versus 50% for Vd in the response-evaluable analysis set (P = 0.0021; **Figure 7A**)
- High response rates were observed in high-risk and standard-risk patients treated with DVd (**Figure 7B**)



LOT, line of therapy; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; ORR, overall response rate; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]P <0.05 for DVd vs Vd.
[b]P <0.0001 for DVd vs Vd.

Figure 7. Summary of (A) overall best confirmed response and (B) responses by cytogenetic status in patients refractory to lenalidomide at last prior LOT in CASTOR (response-evaluable analysis set).

CONCLUSIONS

- **DVd significantly improves outcomes for patients with relapsed or refractory multiple myeloma, regardless of prior treatment with bortezomib**
- **Importantly, the treatment benefit of DVd versus Vd was maintained in patients who were refractory to lenalidomide at their last prior LOT**
  - **These results suggest that DVd treatment can be sequenced after patients become refractory to lenalidomide**
- **Patients who achieved MRD negativity demonstrated prolonged PFS regardless of prior exposure to bortezomib or lenalidomide**
- **High rates of responses were observed in high-risk and standard-risk patients treated with DVd across all subgroups examined**
- **DVd should be considered a new standard of care for patients with myeloma who are currently receiving Vd alone and received ≥1 prior therapy**

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DISCLOSURES

A.C.-K. received research funding from the Mayo Clinic. H.Q. serves on the board of directors or advisory committees for Amgen, Janssen-Cilag, and Celgene. N.H. serves on the board of directors or advisory committees for Janssen. M.C. serves on a speakers bureau for Janssen. R.O. is a consultant for Janssen. M.Q., J.S., H.A., X.Q., W.D., T.C., C.C, and A.K.S. are employees of Janssen. M.Q., J.S., W.D., T.C., and A.K.S. have equity ownership of Janssen. P.S. received research funding from Janssen, Celgene, Amgen, Karyopharm, SkylineDx, Takeda, and Novartis; and received personal fees from Janssen, Celgene, and Amgen. S.L., J.-C.J., and H.-J.S. have no disclosures to report.

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