Efficacy of Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma Based on Prior Lines of Therapy: Updated Analysis of CASTOR

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ClinicalTrials.gov Identifier: NCT02136134
Background

- Daratumumab
  - Human monoclonal antibody targeting CD38
  - Direct on-tumor and immunomodulatory MoA\(^1\)-\(^5\)

- Approved
  - As monotherapy for heavily pretreated RRMM by the FDA, EMA, Health Canada, Mexico, and Singapore
  - Combo with standard of care regimens for RRMM after ≥1 prior therapy (POLLUX and CASTOR) by the FDA

- Early phase study of daratumumab in combination with bortezomib\(^6\)
  - Deep and durable responses
  - Well tolerated with manageable adverse events

MoA, mechanism of action; RRMM, relapsed or refractory multiple myeloma; FDA, Food and Drug Administration; EMA, European Medicines Agency; CDC, complement-mediated cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cell-mediated phagocytosis.

Study Design
Multicenter, randomized, open-label, active-controlled, phase 3 study

N = 498

Key eligibility criteria
• RRMM
• ≥1 prior line of therapy
• Prior bortezomib exposure, but not refractory

Stratification factors
• ISS (I, II, and III)
• Number of prior lines (1 vs 2 or 3 vs >3)
• Prior bortezomib (no vs yes)

DVd (n = 251)
Daratumumab (16 mg/kg IV)
Every week: Cycles 1-3
Every 3 weeks: Cycles 4-8
V: 1.3 mg/m² SC on Days 1, 4, 8, and 11 of Cycles 1-8
d: 20 mg PO-IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1-8

D only
Every 4 weeks: Cycles 9+

Vd (n = 247)
V: 1.3 mg/m² SC on Days 1, 4, 8, and 11 of Cycles 1-8
d: 20 mg PO-IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1-8

Obs only

Primary endpoint
• PFS

Secondary endpoints
• TTP
• OS
• ORR, VGPR, CR
• MRD

Statistical analyses
• Planned to enroll 480 patients
• Primary analysis: ~177 PFS events

Premedication for the DVd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine

DVd, daratumumab, bortezomib and dexamethasone; IV, intravenous; V, bortezomib; SC, subcutaneously; d, dexamethasone; PO, orally; VD, bortezomib and dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; ISS, International Staging System.
Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DVd (n = 251)</th>
<th>Vd (n = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>64 (30-88)</td>
<td>64 (33-85)</td>
</tr>
<tr>
<td>≥75, n (%)</td>
<td>23 (9)</td>
<td>35 (14)</td>
</tr>
<tr>
<td><strong>ISS staging, n (%)</strong>^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>98 (39)</td>
<td>96 (39)</td>
</tr>
<tr>
<td>II</td>
<td>94 (38)</td>
<td>100 (41)</td>
</tr>
<tr>
<td>III</td>
<td>59 (24)</td>
<td>51 (21)</td>
</tr>
<tr>
<td><strong>Creatinine clearance (mL/min), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>243</td>
<td>233</td>
</tr>
<tr>
<td>&gt;30-60</td>
<td>49 (20)</td>
<td>59 (25)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>186 (77)</td>
<td>163 (70)</td>
</tr>
<tr>
<td><strong>Median time from diagnosis, y (range)</strong></td>
<td>3.87 (0.7-20.7)</td>
<td>3.72 (0.6-18.6)</td>
</tr>
<tr>
<td><strong>Cytogenetic profile, n (%)</strong>^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>167</td>
<td>186</td>
</tr>
<tr>
<td>Standard risk</td>
<td>123 (74)</td>
<td>135 (73)</td>
</tr>
<tr>
<td>High risk</td>
<td>44 (26)</td>
<td>51 (27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DVd (n = 251)</th>
<th>Vd (n = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior lines of therapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2 (1-9)</td>
<td>2 (1-10)</td>
</tr>
<tr>
<td>1</td>
<td>122 (49)</td>
<td>113 (46)</td>
</tr>
<tr>
<td>2</td>
<td>70 (28)</td>
<td>74 (30)</td>
</tr>
<tr>
<td>3</td>
<td>37 (15)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>22 (9)</td>
<td>28 (11)</td>
</tr>
<tr>
<td><strong>1-3</strong>^c</td>
<td>229 (91)</td>
<td>219 (89)</td>
</tr>
<tr>
<td><strong>Prior ASCT, n (%)</strong></td>
<td>156 (62)</td>
<td>149 (60)</td>
</tr>
<tr>
<td><strong>Prior PI, n (%)</strong></td>
<td>169 (67)</td>
<td>172 (70)</td>
</tr>
<tr>
<td><strong>Prior IMiD, n (%)</strong></td>
<td>179 (71)</td>
<td>198 (80)</td>
</tr>
<tr>
<td><strong>Prior PI + IMiD, n (%)</strong></td>
<td>112 (45)</td>
<td>129 (52)</td>
</tr>
<tr>
<td><strong>Refractory to IMiD only, n (%)</strong></td>
<td>74 (30)</td>
<td>90 (36)</td>
</tr>
<tr>
<td><strong>Refractory to last line of therapy, n (%)</strong></td>
<td>76 (30)</td>
<td>85 (34)</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

^aISS staging is derived based on the combination of serum β2-microglobulin and albumin.

^bCentralized analysis using next-generation sequencing. Patients with high risk had t(4;14), t(14;16), or del17p abnormalities.

^cExploratory.
Primary Analysis Results

- The primary endpoint was met at the primary analysis (7.4 months of median follow-up)
  - Hazard ratio (HR): 0.39; 61% reduction in the risk of progression or death with DVd versus Vd
- Significantly higher and deeper responses for DVd versus Vd
- At the primary analysis, the independent data and safety monitoring committee recommended that Vd patients with progressive disease receive daratumumab monotherapy

CI, confidence interval; sCR, stringent complete response; PR, partial response.

Objectives

- Updated outcome of the total patient cohort with longer-term follow-up
- Outcome in different subgroups of patients according to:
  - Number of prior lines of therapy
  - Minimal residual disease status
  - Cytogenetic abnormalities
- Updated safety profile
Updated Efficacy

Median (range) follow-up: 13.0 (0-21.3) months

An additional 7% of patients receiving DVd achieved ≥CR with longer follow up

Responses continue to deepen in the DVd group with longer follow-up

ITT, intent to treat.
Note: PFS: ITT population; ORR: response-evaluable population.
*Kaplan-Meier estimate.
*bP <0.0001 for DVd versus Vd.
PFS: Prior Lines of Treatment

DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line.

DVd is superior to Vd regardless of prior lines of therapy, with greatest benefit observed in 1 prior line.

Kaplan-Meier estimate.
PFS by Prior Bortezomib Exposure: 1 Prior Line Population

DVd provides treatment benefit regardless of prior bortezomib exposure
Time From Last Line of Therapy to Study Treatment of > or ≤12 Months

>12 Months

HR: 0.27 (95% CI, 0.17-0.43; \( P < 0.0001 \))

Kaplan-Meier estimate.

12-month PFS\(^a\)

% surviving without progression

\[ \begin{array}{cccccccc}
0 & 3 & 6 & 9 & 12 & 15 & 18 & 21 & 24 \\
\hline
0 & 21 & 90 & 118 & 104 & 109 & 74 & 48 & 16700
\end{array} \]

Vd

Median: 9.4 months

Dvd

Median: 10.3 months

≤12 Months

HR: 0.34 (95% CI, 0.24-0.48; \( P < 0.0001 \))

Kaplan-Meier estimate.

12-month PFS\(^a\)

% surviving without progression

\[ \begin{array}{cccccccc}
0 & 3 & 6 & 9 & 12 & 15 & 18 & 21 & 24 \\
\hline
0 & 0 & 0 & 0 & 0 & 0 & 0
\end{array} \]

Vd

Median: 5.2 months

Dvd

Median: 10.3 months

Dvd is superior to Vd regardless of time since last therapy

\(^a\)Kaplan-Meier estimate.
More patients achieve a deeper response with DVd after 1 prior line of treatment

**ORR by Prior Lines**

<table>
<thead>
<tr>
<th>Prior Lines</th>
<th>Response-Evaluable Population</th>
<th>ORR (%)</th>
<th>≥ CR (%)</th>
<th>≥ VGPR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 prior line</td>
<td>Response-evaluable population</td>
<td>91%</td>
<td>36%</td>
<td>75%</td>
</tr>
<tr>
<td>2 to 3 prior lines</td>
<td>Response-evaluable population</td>
<td>74%</td>
<td>15%</td>
<td>42%</td>
</tr>
</tbody>
</table>
MRD rates by prior lines of therapy

**ITT (N = 498)**

**1 prior line (n = 235)**

<table>
<thead>
<tr>
<th>Sensitivity threshold</th>
<th>DVd</th>
<th>Vd</th>
<th>DVd</th>
<th>Vd</th>
<th>DVd</th>
<th>Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>10^{-4}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-5}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-6}</td>
<td></td>
<td></td>
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</tbody>
</table>

- MRD was evaluated by ClonoSEQ-NGS-based assay in a central lab at three sensitivity thresholds, for patients with suspected CR and also for patients who maintain CR at C9 and C15

**MRD-negative rates for DVd were ≥3-fold higher across all thresholds**

***P<0.0001; **P<0.01; NS, not significant.**

P values calculated using likelihood-ratio chi-square test.

MRD-negativity rate = proportion of patients with negative MRD test results at any time during treatment.
PFS: MRD Status (10^{-5})

MRD negativity is associated with better outcomes
PFS: Cytogenetic Risk in All Evaluable Patients\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
High risk\textsuperscript{b} & DVd & Vd \\
\hline
Median PFS, mo & 11.2 & 7.2 \\
HR (95\% CI) & 0.49 (0.27-0.89) & \\
\textit{P} value & 0.0167 & \\
\hline
n = 44 & n = 47 & \\
\hline
ORR, \% & 82 & 62 \\
\textit{P} value & 0.039 & \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
Standard risk & DVd & Vd \\
\hline
Median PFS, mo & NR & 7.0 \\
HR (95\% CI) & 0.29 (0.20-0.43) & \\
\textit{P} value & <0.0001 & \\
\hline
n = 118 & n = 131 & \\
\hline
ORR, \% & 85 & 64 \\
\textit{P} value & 0.0003 & \\
\hline
\end{tabular}
\end{table}

\textbf{DVd improves outcomes regardless of cytogenetic risk}

NR, not reached.

\textsuperscript{a}ITT/Biomarker risk–evaluable analysis set.

\textsuperscript{b}Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.
OS

- **OS events**
  - 37 (15%) in DVd
  - 58 (24%) in Vd

- **OS HR for DVd versus Vd by prior lines:**
  - 1 prior line = HR: 0.42
    (95% CI, 0.19-0.93)
  - 1-3 prior line = HR: 0.54
    (95% CI, 0.34-0.84)

Curves are beginning to separate, but OS data are immature

Median OS was not reached; results did not cross the prespecified stopping boundary.
### Most Common TEAEs (All Patients): Updated Analysis

<table>
<thead>
<tr>
<th></th>
<th>DVd (n = 243)</th>
<th>Vd (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-grade ≥25%&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4 ≥5%&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>145 (60)</td>
<td>110 (45)</td>
</tr>
<tr>
<td>Anemia</td>
<td>67 (28)</td>
<td>36 (15)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>45 (19)</td>
<td>32 (13)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>32 (13)</td>
<td>24 (10)</td>
</tr>
<tr>
<td><strong>Nonhematologic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>120 (49)</td>
<td>90 (38)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>83 (34)</td>
<td>53 (22)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>72 (30)</td>
<td>43 (18)</td>
</tr>
<tr>
<td>Cough</td>
<td>66 (27)</td>
<td>30 (13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>53 (22)</td>
<td>58 (25)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>33 (14)</td>
<td>28 (12)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (9)</td>
<td>8 (3)</td>
</tr>
</tbody>
</table>

- Grade 3/4 TEAEs: 79% of DVd patients versus 63% of Vd patients
- Discontinuations due to TEAEs: 9% of DVd patients versus 9% of Vd patients<sup>b</sup>
- No new IRRs; incidence remains stable with longer follow up (45%)

**Notes:**
- TEAE, treatment-emergent adverse event; IRR, infusion-related reaction.
- Common TEAEs listed are either ≥25% all grade OR ≥5% grade 3/4.<sup>a</sup>
- Vd arm treated for 8 cycles and DVd arm treated until progressive disease, per protocol.<sup>b</sup>
Conclusions

- PFS benefit continues to be maintained with DVd over time
- DVd is superior to Vd regardless of prior lines of therapy
- Largest magnitude of benefit with DVd is observed in patients with 1 prior line of therapy
  - 78% reduction in risk of progression or death for DVd versus Vd
- More patients in DVd achieved deeper responses with longer follow-up
  - Higher CR and MRD-negative rates
  - MRD negativity translated into longer PFS
- DVd is superior to Vd regardless of cytogenetic risk or time since last therapy
- No new safety signals were reported

These data further support the use of this newly approved regimen of DVd in RRMM, with most benefit in patients with 1 prior line of therapy
Acknowledgments

- Patients who participated in this study
- Investigators
- Data and safety monitoring committee
- Staff members involved in data collection and analyses
  - David Soong and Christopher Velas

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16 countries