Evaluation of Minimal Residual Disease (MRD) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Treated With Daratumumab in Combination With Lenalidomide Plus Dexamethasone or Bortezomib Plus Dexamethasone

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Daratumumab

- Human monoclonal antibody that targets CD38
- Direct on-tumor and immunomodulatory mechanisms of action

Daratumumab is approved by the FDA as monotherapy and in combination with standard of care regimens for patients with multiple myeloma (MM) with ≥1 prior line of treatment

Daratumumab + standard of care regimens
- Resulted in a >60% reduction in the risk of disease progression or death
- The immunomodulatory effects of daratumumab may drive deep responses

Minimal Residual Disease

- Minimal residual disease (MRD) is a more sensitive measure of disease burden than traditional definitions of clinical response\(^1,2\)
- MRD-negative status is associated with prolonged progression-free survival (PFS) and overall survival (OS) in newly diagnosed MM patients\(^1,2\)
  - In the future, MRD may be a primary endpoint for clinical studies
- International Myeloma Working Group guidelines recommend an MRD-sensitivity threshold of at least \(10^{-5}\) using next-generation sequencing (NGS) or next-generation flow cytometry\(^3\)
- This study is the first evaluation of MRD in relapsed and refractory (RR) MM using a randomized, controlled, and prospective analysis

POLLUX and CASTOR

- Multicenter, randomized (1:1), open-label, active-controlled, phase 3 studies in ≥1 prior line of therapy for MM

### POLLUX

- **DRd (n = 286)**
  - D 16 mg/kg IV
    - Every week: Cycles 1-2
    - Every 2 weeks: Cycles 3-6
    - Every 4 weeks until PD
  - R 25 mg PO (similar to Rd alone)
  - d 40 mg

- **Rd (n = 283)**
  - R 25 mg PO
    - Days 1-21 of each cycle until PD
  - d 40 mg weekly until PD

#### MRD assessments
- At suspected CR
- 3 & 6 months after CR

### CASTOR

- **DVd (n = 251)**
  - D 16 mg/kg IV
    - Every week: Cycles 1-3
    - Every 3 weeks: Cycles 4-8
    - Every 4 weeks: Cycles 9+
  - V 1.3 mg/m² SC (similar to Vd alone)
  - d 20 mg

- **Vd (n = 247)**
  - V 1.3 mg/m² SC on Days 1, 4, 8, and 11 for 8 cycles
  - d 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 for 8 cycles

#### MRD assessments
- At suspected CR
- 6 & 12 months after first study dose

### Patient characteristics

- **POLLUX**
  - Median (range) prior lines: 1 (1-11)
  - Prior V: 84%
  - Prior R: 18%

- **CASTOR**
  - Median (range) prior lines: 2 (1-10)
  - Prior V: 66%
  - Prior R: 42%

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DRd, daratumumab, lenalidomide, and dexamethasone; D, daratumumab; IV, intravenous; PD, progressive disease; R, lenalidomide; PO, orally; Rd, lenalidomide and dexamethasone; d, dexamethasone; CR, complete response; DVd, daratumumab, bortezomib, and dexamethasone; V, bortezomib; SC, subcutaneously; Vd, bortezomib and dexamethasone.
Updated PFS: POLLUX and CASTOR

POLLUX

Median (range) follow-up: 17.3 (0-24.5) months

- Median PFS
  - DRd: not reached; Rd: 17.5 months
  - HR: 0.37 (95% CI, 0.28-0.50; P <0.0001)

CASTOR

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

- Median PFS
  - DVd: not reached; Vd: 7.1 months
  - HR: 0.33 (95% CI, 0.26-0.43; P <0.0001)

HR, hazard ratio; CI, confidence interval.
ClonoSEQ™ MRD Assay

Collect fresh or archived non-decalcified bone marrow

Targeted IgH-VDJ sequencing library

Sequence ~1M 100 bp reads

- MRD was assessed at suspected CR using bone marrow aspirate samples and evaluated by ClonoSEQ™ NGS-based assay

MRD, minimal residual disease; BP, base pair; IgH, immunoglobulin H; 1M, 1 million.

aVersion 1.3; Adaptive Biotechnologies.
Criteria for MRD Negativity

- MRD was evaluated at 3 sensitivity thresholds: $10^{-4}$, $10^{-5}$, and $10^{-6}$
- MRD-negativity rate = proportion of patients with negative MRD test results at any time during treatment
- A stringent, unbiased MRD evaluation was applied
  - MRD-negativity counts were evaluated against the intent-to-treat (ITT) population
  - Any patient in the ITT population not determined to be MRD negative was scored as MRD positive
  - A minimum cell input equivalent to the given sensitivity threshold was required to determine MRD negativity
    - i.e., MRD at $10^{-6}$ required that $\geq$1 million cells were evaluated
Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds.

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

*** P <0.0001
** P <0.005
* P <0.05
MRD Negativity Among Patients With ≥CR

- Values refer to the percentage of MRD-negative patients among those who achieved ≥CR in a given treatment arm.

Consistently higher MRD-negative rates in patients with ≥CR treated with a daratumumab-containing regimen

*P* values calculated using likelihood-ratio chi-square test.
Rapid accumulation of MRD-negative events in patients treated with daratumumab-containing regimens versus standard of care

MRD-negative patients continued to accumulate over time in both studies

Majority of patients maintain MRD negativity; patients will continue to be followed annually

Only 1 MRD-negative sample counted per patient.
No high-risk MRD negative patients have progressed or converted to MRD positive
- High risk = any of t(4;14), t(14;16), del17p
- Standard risk = conclusive absence of all 3 markers

In high-risk patients, MRD-negative status was achieved only in those treated with daratumumab-containing regimens

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

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<tr>
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<th>CASTOR</th>
<th>POLLUX</th>
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<tbody>
<tr>
<td></td>
<td>MRD-negative patients per risk group, %a</td>
<td>MRD-negative patients per risk group, %a</td>
</tr>
<tr>
<td>High risk</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Standard risk</td>
<td>0</td>
<td>30</td>
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- DRd (17% high riskb)  
- Rd (25% high riskb)  
- DVd (26% high riskb)  
- Vd (27% high riskb)
- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care
Conclusions

- Daratumumab induced MRD negativity in over 3 times as many patients as standard of care regimens
- Daratumumab led to rapid and durable achievement of MRD negativity
  - Patients continued to achieve MRD negativity over time
- Daratumumab allowed high-risk patients to achieve MRD-negative status
- MRD-negative status was associated with a lower risk of progression
- The high rate of MRD negativity and deep clinical responses induced by daratumumab may lead to improved long-term clinical benefit
The magnitude of daratumumab-induced MRD negativity in the RRMM setting is unprecedented

The potential benefit of MRD-negative status induced by daratumumab in newly diagnosed MM is being explored in ongoing studies
Acknowledgments

- Patients who participated in these studies
- Investigators
- Data and safety monitoring committee
- Staff members involved in data collection and analyses
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Backup
Baseline bone marrow plasma cell percentages of the 238 samples that successfully calibrated were significantly higher than the 75 samples that failed to calibrate (median of 25% vs 11%, respectively; \( P < 0.0001 \))

NDMM, newly diagnosed multiple myeloma.
Calibration using ClonoSEQ™ Version 1.3
MRD Threshold

- Samples with input cell equivalents below the MRD-sensitivity level were considered MRD positive in the analysis of MRD-negativity rate.
Ficoll enrichment removes the granulocytic cell population that makes up 25-50% of nucleated cells in the sample.

- Calculations of MRD-negative rate in Ficoll-enriched samples are more stringent than those using RBC lysates, which would include all of the leukocytes in the sample.
MRD assessment is a more sensitive measure of disease burden than traditional definitions of clinical response\textsuperscript{1,2}

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ORR by Cytogenetic Risk\textsuperscript{a}: POLLUX

\begin{itemize}
  \item \textbf{High risk} (DRd, n = 27) ORR = 85\% \quad \text{ORR = 67\%} \quad \text{ORR = 82\%}
  \item \textbf{Std risk} (Rd, n = 36) ORR = 95\%
\end{itemize}

\textbf{P values calculated using Mantel-Haenszel estimate of common odds ratios.}

\textbf{aCentral NGS.} High-risk patients had any of t(4;14), t(14;16), del17p. Standard-risk patients had an absence of high-risk abnormalities.
ORR by Cytogenetic Risk\(^a\): CASTOR

\(P = 0.039\)

\(P = 0.0003\)

\textbf{High risk} (n = 47)

\textbf{Std risk} (n = 131)

\(\text{ORR} = 82\%\)
\(\text{ORR} = 62\%\)
\(\text{ORR} = 85\%\)
\(\text{ORR} = 64\%\)

\(P\) values calculated using Mantel-Haenszel estimate of common odds ratios.

\(^a\)Central NGS. High-risk patients had any of t(4;14), t(14;16), del17p. Standard-risk patients had an absence of high-risk abnormalities.