Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): an Open-label, Phase 1b Study

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Background

- Triplet regimens with proteasome inhibitor (PI) and/or immunomodulatory drug (IMiD), with or without ASCT, are now established as standard of care for newly diagnosed myeloma.

- Among triplets, extended treatment with KRd emerged as highly active in newly diagnosed myeloma\(^1,2\)

- The KRd results appear to be improved by incorporation of ASCT\(^3-5\)
  - sCR rate 51% w/o ASCT and 74% with ASCT
  - 3-year PFS 80% w/o ASCT and 86% with ASCT

- We hypothesized that KRd activity can alternatively be improved by incorporating daratumumab into KRd treatment regimen.
Daratumumab (DARA)

- Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory MoA\(^1\)
- Approved as **monotherapy** in many countries for heavily pretreated RRMM
- Approved in **combination** with standard of care regimens in RRMM after ≥1 prior therapy in the USA, EU, and other countries
- DARA induces rapid, deep and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM\(^2,3\)

MoA, mechanism of action; RRMM, relapsed/refractory multiple myeloma; CDC, cellular dependent cytotoxicity; ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; MDSC, myeloid-derived suppressor cell.

These studies provided rationale for evaluation of DARA + KRd in this phase 1b study.

**POLLUX (ITT)**
Median follow-up: 25.4 months

- **24-month PFS**
  - DRd: 68%
  - Rd: 41%
  - Median: 17.5 mo

- **HR, 0.41**
  - (95% CI, 0.31-0.53; \(P < 0.0001\))

**CASTOR (1 prior line)**
Median follow-up: 19.4 months

- **18-month PFS**
  - DVd: 68%
  - Vd: 12%
  - Median: 7.9 mo

- **HR, 0.19**
  - (95% CI, 0.12-0.29; \(P < 0.0001\))

**SOC, standard of care; ITT, intent-to-treat; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.**

**aKaplan-Meier estimates.**

Exploratory analyses based on clinical cut-off: January 11, 2017 for CASTOR; March 7, 2017 for POLLUX.

Study Design

Open-label, Multicenter, Phase 1b Study (N = 22)

Endpoints

Primary
- Safety, tolerability

Secondary
- ORR, duration of response, time to response, IRR

Exploratory
- PFS

Eligibility/Treatment
- NDMM
- Transplant eligible and non-eligible
- Treatment duration: ≤13 cycles or until elective discontinuation for ASCT
- No clinically significant cardiac disease; echo required at screening

Dosing Schedule (28-d cycles)

Daratumumab:
- **Split dose: 8 mg/kg Days 1-2 of Cycle 1**
- 16 mg/kg QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter

Carfilzomib:
- 20 mg/m² C1D1
- Escalated to 70 mg/m² C1D8+; **weekly (Days 1, 8, 15)**

Lenalidomide:
- 25 mg; Days 1-21 of each cycle

Dexamethasone: 40 mg/week

Pre- and post-infusion medications:
- Dexamethasone 20 mg
- Diphenhydramine 25-50 mg
- Paracetamol 650-1,000 mg
- Montelukast 10 mg

Echo, echocardiogram; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C1D1, Cycle 1 Day 1; C1D8, Cycle 1 Day 8; IRR, infusion-related reaction; C1D3, Cycle 1 Day 3.

-20 mg if >75 y. **On daratumumab dosing days, dexamethasone 20 mg IV was administered as pre-medication on infusion day and 20 mg PO the day after infusion; for DARA, split first dose dexamethasone 20 mg IV was administered as a pre-medication on C1D1 and C1D2, on C1D3, administration of low-dose methylprednisolone (≤20 mg PO) was optional.** Required before first daratumumab dose, optional for subsequent doses.
### Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DARA + KRd (N = 22)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age, years, n (%)</strong></td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>59.5 (34-74)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>15 (68)</td>
</tr>
<tr>
<td>65 - &lt;75</td>
<td>7 (32)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (46)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19 (86)</td>
</tr>
<tr>
<td>African American</td>
<td>1 (5)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (5)</td>
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<tr>
<td><strong>ECOG score, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (55)</td>
</tr>
<tr>
<td>1</td>
<td>9 (41)</td>
</tr>
<tr>
<td>2</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.
Patient Disposition

- Median follow-up:
  - 10.8 (range, 4.0-12.5) months
- Median number of treatment cycles:
  - 11.5 (range, 1.0-13.0)
- Except for 3 patients, all escalated to carfilzomib 70 mg/m² by C2D1
  - 1 discontinued treatment before C2D1
  - 1 dose reduction to 56 mg/m² at C2D1
  - 1 escalated to 70 mg/m² at C3D8

DARA + KRd

N = 22

Discontinued treatment
8 (36%)

AE
1 (5%)

Progressive disease
1 (5%)

ASCT
6 (27%)

Clinical cut-off date: March 24th, 2017

Presented by: Andrzej Jakubowiak

C2D1, Cycle 2 Day 1; C3D8, Cycle 3 Day 8; AE, adverse event.
Most Common (≥30%) Hematologic TEAEs (N = 22)

- Lymphopenia: All 64%, Grade 3/4 68%
- Thrombocytopenia: All 55%, Grade 3/4 9%
- Anemia: All 46%, Grade 3/4 9%
- Leukopenia: All 41%, Grade 3/4 9%
- Neutropenia: All 32%, Grade 3/4 14%

TEAE, treatment emergent adverse event.

Presented by: Andrzej Jakubowiak
Most Common (≥30%) Nonhematologic TEAEs (N = 22)

Safety profile is consistent with previous reports for DARA or KRd

ALT: alanine aminotransferase.
### Serious TEAEs (N = 22)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
</tr>
<tr>
<td>Influenza</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
</tr>
<tr>
<td>Dermatitis allergic</td>
<td>1</td>
</tr>
<tr>
<td>Presyncope</td>
<td>1</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
</tr>
<tr>
<td>Lobular pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia bacterial</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Serious TEAEs**: 10 of 22 patients (46%)
- **Number (%) of patients with a serious TEAE reasonably related to study drug**
  - Daratumumab: 3 (14%)
  - Carfilzomib: 5 (23%)
  - Lenalidomide: 5 (23%)
  - Dexamethasone: 2 (9%)
- 1 (5%) treatment discontinuation due to pulmonary embolism; unrelated to daratumumab or carfilzomib
- All patients were on aspirin prophylaxis

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*Consistent with previous reports from KRd studies*

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* Bilateral deep vein thrombosis and pulmonary embolism was reported in 1 patient.
* Independent Data and Safety Monitoring Board was notified of serious TEAEs on a regular basis.
Echocardiogram Assessment

- Median left ventricular ejection fraction: no change from baseline over time
- 1 patient had a transient grade 3 SAE of cardiac failure; possibly related to daratumumab or carfilzomib
  - Patient resumed treatment on C2D1 with reduced carfilzomib dose (56 mg/m²)
  - Patient elected ASCT on study Day 113 and ended treatment with VGPR

<table>
<thead>
<tr>
<th>Time point</th>
<th>Left Ventricular Ejection Fraction</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>60 (55-77)</td>
<td></td>
</tr>
<tr>
<td>Cycle 3</td>
<td>60 (55-78)</td>
<td></td>
</tr>
<tr>
<td>Cycle 6</td>
<td>59 (50-70)</td>
<td></td>
</tr>
<tr>
<td>Cycle 9</td>
<td>60 (50-69)</td>
<td></td>
</tr>
<tr>
<td>Cycle 12</td>
<td>62 (56-75)</td>
<td></td>
</tr>
</tbody>
</table>

No apparent adverse impact on cardiac function

SAE, serious adverse event; VGPR, very good partial response.
Infusion Times and Reactions (N = 22)

Infusion Times

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Median (range) infusion time, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td></td>
</tr>
<tr>
<td>C1D1</td>
<td>4.15 (4.0-6.0)</td>
</tr>
<tr>
<td>C1D2</td>
<td>4.15 (3.9-6.0)</td>
</tr>
<tr>
<td>Second</td>
<td>4.18 (3.6-7.1)</td>
</tr>
<tr>
<td>Subsequent</td>
<td>3.38 (1.4-6.1)</td>
</tr>
</tbody>
</table>

Infusion-related reactions (IRR), %

- No grade 3/4
- Occurrence
  - First infusion: 5 (23%) patients
  - Second infusion: 1 (5%) patient
  - Subsequent infusions: 1 (5%) patient

Lower rates of IRRs observed with split first dosing
Response Rate\textsuperscript{a,b}

- Median number of treatment cycles: 11.5 (range, 1.0-13.0)

Depth of response improved with duration of treatment

\begin{itemize}
  \item After 4 cycles:
    \begin{itemize}
      \item n = 21
      \item ≥PR: 100%
      \item ≥VGPR: 71%
      \item ≥CR: 5%
      \item sCR: 5%
    \end{itemize}

  \item After 8 cycles:
    \begin{itemize}
      \item n = 15*\textsuperscript{a}
      \item ≥PR: 100%
      \item ≥VGPR: 87%
      \item ≥CR: 27%
      \item sCR: 27%
    \end{itemize}

  \item Best response:
    \begin{itemize}
      \item n = 21
      \item ≥PR: 100%
      \item ≥VGPR: 91%
      \item ≥CR: 43%
      \item sCR: 29%
    \end{itemize}
\end{itemize}

\textsuperscript{a}5 patients who proceeded to ASCT before C8 and 1 patient who discontinued due to PD at C7 were excluded.

\textsuperscript{b}PR, partial response; CR, complete response.

\textsuperscript{a}Response-evaluable population. \textsuperscript{b}Response rate (≥PR) evaluated by IMWG criteria; M-protein measurements by central lab assessment.
DARA (16 mg/kg) + KRd

- Median follow-up: 10.8 (range, 4.0-12.5) months
- Overall survival = 100%

12-month PFS rate\(^a\) = 94%

\(^a\)Kaplan-Meier estimate.
Stem Cell Harvest and ASCT\textsuperscript{a}

- Median number of CD34\textsuperscript{+} cells collected from patients: \(10.4 \times 10^6\) cells/kg (\(n = 19\))
- Median 5 treatment cycles prior to stem cell harvest
- 14 (74\%) patients had \(\geq VGPR\) prior to stem cell harvest

\textbf{Stem cell yield is consistent with previous KRd studies}

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stem cell mobilization</th>
<th>Total CD34\textsuperscript{+} cells (x10\textsuperscript{6}/kg body weight)</th>
<th>Treatment cycle at ASCT</th>
<th>Best response\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Plerixafor and Filgrastim</td>
<td>30</td>
<td>9</td>
<td>sCR</td>
</tr>
<tr>
<td>2</td>
<td>Plerixafor and Filgrastim</td>
<td>12</td>
<td>5</td>
<td>VGPR</td>
</tr>
<tr>
<td>3</td>
<td>Plerixafor and Filgrastim</td>
<td>28</td>
<td>4</td>
<td>VGPR</td>
</tr>
<tr>
<td>4</td>
<td>Filgrastim</td>
<td>38</td>
<td>4</td>
<td>VGPR</td>
</tr>
<tr>
<td>5</td>
<td>Plerixafor and Filgrastim</td>
<td>10.4</td>
<td>5</td>
<td>VGPR</td>
</tr>
<tr>
<td>6</td>
<td>Filgrastim</td>
<td>6.5</td>
<td>4</td>
<td>VGPR</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Per protocol, patients who continued to ASCT discontinued study treatment.
\textsuperscript{b}Best response among patients who elected ASCT.
Conclusions

- **DARA + KRd was well tolerated**
  - Safety is consistent with previous reports of DARA and KRd
  - Low IRR rates associated with split first dose; no grade 3/4

- **Highly effective with 100% ORR**
  - 91% ≥VGPR and 43% ≥CR
  - Depth of response improved with duration of treatment

- **No adverse impact on stem cell collection (10.4 x 10^6 cells/kg)**
  - DARA is feasible as part of induction therapy

Data from this study support further investigation of DARA-KRd in NDMM
Ongoing Phase 3 Studies

- **NDMM (transplant-ineligible)**
  - ALCYONE (DARA + VMP)
  - MAIA (DARA + Rd)

- **NDMM (transplant-eligible)**
  - CASSIOPEIA (DARA + VTd)

- **RRMM**
  - CANDOR (DARA + Kd)
  - APOLLO (DARA + Pd)
Acknowledgments

- Patients who participated in these studies
- Staff members at the study sites
- Data and safety monitoring committee
- Staff members involved in data collection and analyses

This study was funded by Janssen Research & Development, LLC. Medical writing and editorial support was provided by Kristin Runkle, PhD (MedErgy) and was funded by Janssen Global Services, LLC.
Backup
Adverse Event of Interest

- 61 year old male diagnosed with multiple myeloma
  - History of ongoing grade 2 coronary artery disease with stent placement, ongoing grade 1 intermittent chest pain, and grade 1 hypertension
- Grade 3 SAE of cardiac failure reported on study Day 11, which lasted for 4 days while study treatment was interrupted
  - Considered possibly related to daratumumab and carfilzomib
- Patient resumed treatment on Cycle 2 Day 1 with reduced carfilzomib dose (56 mg/m²)
- No additional cardiac TEAEs or dose reductions were reported
- Patient elected ASCT on study Day 113 and ended study treatment with a clinical response of VGPR

SAE, serious adverse event; TEAE, treatment emergent adverse event; ASCT, autologous stem cell transplant; VGPR, very good partial response.
## Carfilzomib Dose Escalation

<table>
<thead>
<tr>
<th>Patient</th>
<th>C1D1</th>
<th>D1D8</th>
<th>C1D15</th>
<th>C2D1</th>
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<tr>
<td>Patient 1</td>
<td>20</td>
<td>70</td>
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<td>Patient 2</td>
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<tr>
<td>Patient 3</td>
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<tr>
<td>Patient 4</td>
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<td>Patient 5</td>
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<td>Patient 6</td>
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<td>Patient 10</td>
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<td><strong>56</strong></td>
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<table>
<thead>
<tr>
<th>Patient</th>
<th>C1D1</th>
<th>D1D8</th>
<th>C1D15</th>
<th>C2D1</th>
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<td>Patient 12</td>
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<td>Patient 13</td>
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<td>Patient 14</td>
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