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Enduring efficacy and tolerability of daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma (GEN503): final results of an open-label, phase 1/2 study

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ARTICLE
We present the final results of GEN503, a 2 part, phase 1/2 study of daratumumab plus lenalidomide/dexamethasone (D-Rd) in relapsed/refractory multiple myeloma (RRMM). In Part 2, 32 patients received daratumumab 16 mg/kg (approved schedule) plus lenalidomide (25 mg/day, days 1-21)/dexamethasone (40 mg per week) in 28-day cycles. After a median follow-
up of 32.5 months, the overall response rate (ORR) was 81%, with 10 (31.3%) stringent complete responses (sCRs). Median progression-free survival (PFS) and overall survival (OS) were not reached (NR); 2-year PFS and OS rates were 69% and 78%. Extended treatment had favourable safety and induced deep responses that were maintained for ≥2 years.

The detailed methods for GEN503 were described previously (Plesner et al., 2016). In Part 1 (3+3 dose-escalation), patients received 1 of 4 daratumumab doses (2 mg/kg, 4 mg/kg, 8 mg/kg or 16 mg/kg). In Part 2 (cohort expansion), patients received the recommended phase 2 daratumumab dose (16 mg/kg). Patients in Part 2 had ≥1 prior line of therapy, had achieved ≥partial response (PR) to ≥1 regimen and had documented evidence of progressive disease (PD) (Rajkumar et al., 2011) during or after their last regimen. Prior exposure to, but not refractoriness to, lenalidomide was permitted. The primary endpoint was safety. The Supplementary Information details additional methods.

The clinical cut-off date was 14 February 2017, ~2.5 years after the last patient was first dosed. In Part 1 (n = 13), patients had received a median (range) of 3 (2-4) prior therapies. All patients had received a prior immunomodulatory drug (IMiD); 10 (76.9%) patients had received prior lenalidomide (Table SI). At a median (range) follow-up of 39.9 (4.0-49.5) months, patients had received a median (range) of 38 (4-53) treatment cycles. Eight patients discontinued treatment due to PD (4 patients) or adverse events (AEs; 4 patients, including 2 patients since the primary analysis clinical cut-off). Five patients remain on treatment.

In Part 2 (n = 32), patients had received a median (range) of 2 (1-3) prior therapies. Twenty-three (71.9%) patients had received a prior IMiD; 11 (34.4%) had received prior lenalidomide (Table SI). At a median (range) follow-up of 32.5 (5.1-34.7) months, patients had received a median (range) of 31 (1-39) treatment cycles. Since the primary analysis, 6 additional patients discontinued treatment due to PD (5 patients) or AEs (1 patient). Sixteen patients remain on therapy.

Table I shows the most common treatment-emergent AEs (TEAEs) in Part 2. Since the primary analysis, additional patients reported neutropenia, diarrhoea, fatigue, muscle spasms and cough;
1 additional patient reported ≥1 grade ≥3 TEAE. Grade ≥3 neutropenia, reported in 84.4% of patients (including 2 patients since the primary analysis), was, by far, the most common grade ≥3 TEAE. There were no new infusion-related reactions and no patients had anti-daratumumab antibodies.

Four patients in Part 1 died during the study, including 3 deaths after the primary analysis: 1 patient who received daratumumab 4 mg/kg, 2 who received 8 mg/kg and 1 who received 16 mg/kg. All deaths were due to PD except 1 patient (8 mg/kg) with an unknown cause who died within 30 days of the last dose. Of 9 patients who died in Part 2 (6 after the primary analysis), 6 deaths were due to PD, 2 due to AEs (septic shock, viral pneumonia) and 1 due to respiratory insufficiency resulting from polymorphic post-transplant lymphoproliferative disorder (unknown Epstein-Barr virus association). Data on second primary malignancies and blood transfusions are described in the Supplementary Information.

Table SII shows response rates in Part 1. One patient’s response (16 mg/kg) deepened, from very good PR to complete response (CR) since the primary analysis. Fig S1A shows the timing and depth of response for each patient in Part 1 who achieved ≥PR. Seven of 11 responders remained progression-free and alive for ≥28 months.

In Part 2, the ORR was 81.3% (Fig 1A, Table SII). Since the primary analysis, the ORR was unchanged, but more patients achieved CR (4 versus 3 patients) or sCR (10 versus 8 patients) (Plesner et al, 2016). The median (range) duration of response was NR (95% confidence interval [CI], 26.5 months-not estimable [NE]). Fig S1B shows the timing and depth of response for each patient in Part 2 who achieved ≥PR. Nineteen of 26 responders remained progression-free. Median PFS was NR (95% CI, 16.62 months-NE); the 2-year PFS rate was 68.9% (95% CI, 48.5-82.5; Fig 1B). ORRs and 2-year PFS rates were similar in patients who were previously exposed to lenalidomide or IMiDs and patients who were lenalidomide or IMiD naïve (Table SIII). Median OS was NR (95% CI, 32.2 months-NE); the 2-year OS rate was 78.1% (95% CI, 59.5-88.9; Fig 1C).
The results of GEN503 are consistent with POLLUX, a phase 3 study of D-Rd versus Rd alone in patients with RRMM who received ≥1 prior line of therapy (Dimopoulos et al, 2016). In POLLUX, this triplet regimen significantly improved PFS and produced a higher ORR compared with the control regimen. It also produced a higher minimal residual disease–negative rate, demonstrating that D-Rd can drive responses even deeper than sCR. The safety profile observed in GEN503 is also consistent with that observed in POLLUX; no new safety signals were identified.

Neutropenia, the most common grade ≥3 AE in Part 2 of GEN503, is a known lenalidomide-associated toxicity. The rate of grade ≥3 neutropenia observed in this study exceeded those reported previously for Rd alone (29.5%-41.2%) (Dimopoulos et al, 2007; Weber et al, 2007). However, treatment interruptions, lenalidomide dose reductions and growth factor administration were successful in managing neutropenia. Granulocyte colony-stimulating factor support is recommended in order maintain lenalidomide dose intensity.

Long-term D-Rd treatment was associated with a manageable safety profile and displayed notable efficacy in patients with RRMM. Responses to this regimen deepened over time and were maintained for ≥2 years. In Part 2 of GEN503, a remarkable number of patients (31%), including those with prior lenalidomide exposure, achieved sCR. Our results demonstrate that patients can receive D-Rd for ≥2 years, and that this regimen induces deep and durable responses.

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All authors developed the manuscript, provided final submission approval, and confirmed that the protocol was followed and that the data were accurate and complete. This study was sponsored by Janssen Research and Development. Medical writing and editorial support were provided by Kimberly Carmony, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

The authors thank the patients who participated in this study and their families, as well as the study co-investigators, research nurses, and coordinators at each of the clinical sites.
Results of this analysis were presented, in part, at the 59th American Society of Hematology (ASH) Annual Meeting & Exposition, December 9-12, 2017, Atlanta, GA, USA.

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

DISCLOSURES
TP received research funding from Roche, Novartis, Janssen and Celgene and served on advisory committees for Janssen, Celgene and Genmab. FG received honoraria from Janssen and Celgene and served on an advisory committee for Celgene. MCM received research funding from Celgene and served on advisory committees for Celgene, Janssen, Amgen, Bristol-Myers Squibb and Takeda. PM received honoraria from and served on advisory boards for Celgene, Takeda and Janssen. JC received honoraria from Amgen, Celgene, Janssen, Novartis and Takeda. AP received research funding from Janssen, Amgen, Celgene, and Takeda and served on advisory boards for Janssen, Amgen, Celgene and Sanofi. JPL received research funding from Novartis, Onyx Pharmaceuticals, Celgene and Millennium Pharmaceuticals. TA is employed by Genmab and is a former employee of Janssen. CdB, DC, CC and JMS are employed by Janssen. PGR served on advisory committees for Bristol-Myers Squibb, Celgene, Novartis, Millennium Takeda and Johnson & Johnson. H-TA, MB, and JK have no conflicts to disclose.

REFERENCES


### Table 1. Most Common Adverse Events (≥25%) and Infusion-related Reactions in Part 2 (N = 32)

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>29 (90.6)</td>
<td>27 (84.4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>18 (56.3)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (50.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>15 (46.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (40.6)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>11 (34.4)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (34.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (34.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (31.3)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (31.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>9 (28.1)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9 (28.1)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>8 (25.0)</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>8 (25.0)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>8 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>8 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (25.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>18 (56.3)</td>
<td>2 (6.3)</td>
</tr>
</tbody>
</table>

*Adverse events were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf."

**FIGURE LEGEND**

**Fig 1. Response rates, progression-free survival, and overall survival of patients in Part 2.**

(A) Response rates. (B) Progression-free survival. At a median duration of follow-up of 32.5 months, median PFS was NR (95% CI, 16.62 months-NE), and the 24-month PFS rate was 68.9% (95% CI, 48.5-82.5). (C) Overall survival. Median OS was NR (95% CI, 32.2 months-NE), and the 24-month OS rate was 78.1% (95% CI, 59.5-88.9).

CI, confidence interval; CR, complete response; NE, not estimable; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
A. Daratumumab + lenalidomide/dexamethasone (n = 32)

- ORR: 81%
- CR or better: 44%
- VGPR or better: 69%
- 25%
- 13%
- 13%

B. % of patients progression free and alive

C. % of patients alive

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