

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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Key Words:	Daratumumab, monoclonal antibody, relapsed/refractory multiple myeloma, plasma cell disorders, MULTIPLE MYELOMA

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3 **Enduring efficacy and tolerability of daratumumab in combination with lenalidomide and**
4 **dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma**
5 **(GEN503): final results of an open-label, phase 1/2 study**
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12 **Running head: DARA-LEN-DEX phase 1/2 RRRM study: final results** (48 characters with
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14 spaces [limit 60])
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3 **Keywords:** Daratumumab, monoclonal antibody, multiple myeloma, relapsed/refractory
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ARTICLE

We present the final results of GEN503, a 2-part, phase 1/2 study of daratumumab plus lenalidomide/dexamethasone in patients with relapsed/refractory multiple myeloma. In Part 2, 32 patients received daratumumab 16 mg/kg plus lenalidomide/dexamethasone. The regimen continued to show favorable safety. In Part 2 (32.5-month median follow-up), 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, with 2-year PFS and OS rates of 69% and 78%, respectively. In GEN503, extended treatment had favorable safety and induced deep responses that were maintained for over 2 years.

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

Daratumumab was administered weekly for 8 weeks, then every 2 weeks for 16 weeks, followed by every 4 weeks until PD or unacceptable toxicity. Lenalidomide 25 mg was administered orally daily on Days 1 to 21 of each 28-day treatment cycle; dexamethasone 40 mg was administered weekly.

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3 The primary endpoint was safety. After the primary analysis, data collection was limited to
4 serious adverse events (AEs), disease assessments, and second primary malignancies (SPMs).
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6 Responses were evaluated using International Myeloma Working Group Uniform Response
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8 Criteria for myeloma (Rajkumar *et al*, 2011). PFS, OS, time to progression, and duration of
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10 response were analysed using the Kaplan-Meier method. To collect data on SPMs, all patients
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12 will be followed for 3 years following their last lenalidomide dose or from the end of the study,
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14 whichever comes first.
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21 The clinical cutoff was February 14, 2017, approximately 2.5 years after the last patient was first
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23 dosed. In Part 1 (n = 13), patients had received a median (range) of 3 (2-4) prior therapies. All 13
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25 patients had received a prior immunomodulatory drug (IMiD); 10 (76.9%) patients had received
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27 prior lenalidomide (**Table SI**). At a median (range) duration of follow-up of 39.9 (4.0-49.5)
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29 months, patients in Part 1 had received a median (range) of 38 (4-53) treatment cycles. Eight
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31 patients discontinued treatment due to PD (4 patients) or AEs (4 patients, including 2 patients
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33 since the primary analysis clinical cutoff). The remaining 5 patients remain on treatment.
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40 In Part 2 (n = 32), patients had received a median (range) of 2 (1-3) prior therapies. Twenty-three
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42 (71.9%) patients had received a prior IMiD, and 11 (34.4%) had received prior lenalidomide
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44 (**Table SI**). At a median (range) duration of follow-up of 32.5 (5.1-34.7) months, patients in Part
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46 2 had received a median (range) of 31 (1-39) treatment cycles. Since the primary analysis, an
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48 additional 6 patients discontinued treatment due to PD (5 patients) or AEs (1 patient). Sixteen
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50 patients remain on therapy.
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3 **Table I** shows the most common ($\geq 25\%$) treatment-emergent AEs (TEAEs) observed in Part 2.
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5 Since the primary analysis, additional patients reported neutropenia, diarrhoea, fatigue, muscle
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7 spasms, and cough, and 1 additional patient reported at least 1 grade ≥ 3 TEAE. Grade ≥ 3
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9 neutropenia was reported in 84.4% of patients (including 2 patients since the primary analysis)
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11 and was, by far, the most frequently reported grade ≥ 3 TEAE. No new infusion-related reactions
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13 were reported. Additionally, no patients tested positive for anti-daratumumab antibodies.
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19 One patient in Part 1 who received daratumumab 8 mg/kg acquired an SPM: Epstein-Barr virus
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21 associated lymphoma. Four patients in Part 2 acquired SPMs: cutaneous squamous cell
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23 carcinomas (3 patients, all of whom continued study treatment after their lesions were treated)
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25 and a gastric adenocarcinoma (1 patient). An SPM of myelodysplastic syndrome was reported in
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27 1 additional patient in Part 2 after the clinical cutoff for this analysis. Four patients in Part 1 died
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29 during the study, including 3 deaths after the primary analysis: 1 patient who received
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31 daratumumab 4 mg/kg, 2 patients who received 8 mg/kg, and 1 patient who received 16 mg/kg.
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33 All causes of death were PD except 1 patient who received 8 mg/kg and died within 30 days of
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35 the last dose, whose cause of death was unknown. Nine patients in Part 2 died during the study,
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37 including 6 patients after the primary analysis: 6 patients died due to PD, 2 due to AEs (septic
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39 shock and viral pneumonia), and 1 due to respiratory insufficiency resulting from polymorphic
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41 posttransplant lymphoproliferative disorder (association with Epstein-Barr virus unknown).
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49 Since the primary analysis, 1 additional patient in the 4 mg/kg group of Part 1 received a red
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51 blood cell transfusion. One additional patient in Part 2 received 1 red blood cell transfusion and 1
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53 platelet transfusion due to grade 3 anaemia and thrombocytopenia, both of which the investigator
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3 deemed possibly or probably related to daratumumab and lenalidomide. In total, patients in Part
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5 2 received an additional 7 red blood cell transfusions and 2 platelet transfusions since the
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7 primary analysis.
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12 **Table SII** shows response rates achieved in Part 1. One patient in the 16 mg/kg group had a
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14 response that deepened from very good partial response to complete response (CR) since the
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16 primary analysis. **Fig S1A** shows the timing and depth of response for each patient in Part 1 who
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18 achieved PR or better. Seven of the 11 responders remained progression free and alive for at
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20 least 28 months.
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26 In Part 2, the ORR was 81.3% (**Fig 1A, Table SII**). Since the primary analysis, the ORR has not
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28 changed, but more patients have achieved CR (4 versus 3 patients) or sCR (10 versus 8 patients)
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30 (Plesner *et al*, 2016). Thus, with prolonged treatment, responses deepened over time. The median
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32 (range) duration of response was not reached (95% confidence interval [CI], 26.5 months-not
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34 estimable [NE]). **Fig S1B** shows the timing and depth of response for each patient in Part 2 who
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36 achieved PR or better. Nineteen of the 26 responders remained progression free. Median PFS
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38 was not reached (95% CI, 16.62 months-NE); the 2-year PFS rate was 68.9% (95% CI, 48.5-
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40 82.5; **Fig 1B**). ORRs and 2-year PFS rates were similar in patients who were previously exposed
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42 to lenalidomide or IMiDs and patients who were lenalidomide or IMiD naïve (**Table SIII**).
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45 Median OS was not reached (95% CI, 32.2 months-NE); the 2-year OS rate was 78.1% (95% CI,
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47 59.5-88.9; **Fig 1C**).
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3 The results of this study are consistent with those of POLLUX, a phase 3 study of daratumumab
4 plus lenalidomide/dexamethasone versus lenalidomide/dexamethasone alone in patients with
5 relapsed/refractory multiple myeloma who received ≥ 1 prior line of therapy (Dimopoulos *et al*,
6 2016). In POLLUX, this triplet regimen significantly improved PFS and produced a higher ORR
7 compared with the control regimen. It also produced a higher minimal residual disease–negative
8 rate compared with the control regimen, demonstrating that daratumumab plus
9 lenalidomide/dexamethasone can drive responses even deeper than sCR. The safety profile
10 observed in the current study is also consistent with that observed in POLLUX; no new safety
11 signals were identified.
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26 The synergy between daratumumab and lenalidomide/dexamethasone may result from the fact
27 that daratumumab has, in addition to its immune-mediated activities, immunomodulatory effects
28 that include the depletion of immunosuppressive cell populations and the expansion of cytotoxic
29 and helper T cells (Krejci *et al*, 2016). In POLLUX, the addition of daratumumab to
30 lenalidomide/dexamethasone was associated with substantial increases in T-cell clonality and T-
31 cell fraction (number of T cells per nucleated cell) and reductions in T-cell richness (number of
32 clones with unique TCR β rearrangements) (Chiu *et al*, 2016). Additionally, in GEN503, T cell
33 changes towards a cytolytic, granzyme B+ phenotype indicate an adaptive immune response in
34 patients treated with daratumumab plus lenalidomide/dexamethasone and may contribute to the
35 depth of response in these patients (Adams *et al*, 2016).
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51 Neutropenia, the most common grade ≥ 3 AE in Part 2 of GEN503, is a known lenalidomide-
52 associated toxicity. The rate of grade ≥ 3 neutropenia observed in this study exceeded those
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3 reported previously for lenalidomide/dexamethasone alone (29.5%-41.2%) (Dimopoulos *et al*,
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5 2007; Weber *et al*, 2007). However, treatment interruptions, lenalidomide dose reductions, and
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7 growth factor administration were successful in managing neutropenia.
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12 In conclusion, long-term treatment with daratumumab plus lenalidomide/dexamethasone was
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14 associated with a manageable safety profile and displayed notable efficacy in patients with
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16 relapsed/refractory multiple myeloma. Responses to this regimen deepened over time and were
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18 maintained for more than 2 years. In Part 2 of this study, a remarkable number of patients (31%),
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20 including those with prior lenalidomide exposure, achieved sCR. Our results demonstrate that
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22 patients can be treated with daratumumab plus lenalidomide/dexamethasone for more than 2
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24 years, and that this regimen induces deep and durable responses.
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30 31 **ACKNOWLEDGEMENTS**

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36
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53 (ASH) Annual Meeting & Exposition, December 9-12, 2017, Atlanta, GA, USA.
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5 The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available
6 at <https://www.janssen.com/clinical-trials/transparency>. As noted on this site, requests for access
7
8 to the study data can be submitted through Yale Open Data Access (YODA) Project site at
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12 <http://yoda.yale.edu>.
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16 17 **DISCLOSURES**

18
19 TP received research funding from Roche, Novartis, Janssen, and Celgene and served on
20
21 advisory committees for Janssen, Celgene, and Genmab. FG received honoraria from Janssen
22
23 and Celgene and served on an advisory committee for Celgene. MCM received research funding
24
25 from Celgene and served on advisory committees for Celgene, Janssen, Amgen, Bristol-Myers
26
27 Squibb, and Takeda. PM received honoraria from and served on advisory boards for Celgene,
28
29 Takeda, and Janssen. JC received honoraria from Amgen, Celgene, Janssen, Novartis, and
30
31 Takeda. AP received research funding from Janssen, Amgen, Celgene, and Takeda and served on
32
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34
35 Novartis, Onyx Pharmaceuticals, Celgene, and Millennium Pharmaceuticals. TA is employed by
36
37 Genmab and is a former employee of Janssen. CdB, DC, CC, and JMS are employed by Janssen.
38
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42 PGR served on advisory committees for Bristol-Myers Squibb, Celgene, Novartis, Millennium
43
44 Takeda, and Johnson & Johnson. H-TA, MB, and JK have no conflicts to disclose.
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REFERENCES

- Adams, H., III, Stevenaert, F., Krejcik, J., Van der Borght, K., Casneuf, T., Smets, T., Bald, J., Abraham, Y., Ceulemans, H., Vanhoof, G., Ahmadi, T., Usmani, S.Z., Plesner, T., Lonial, S., van Kessel-Welmers, B., Lokhorst, H.M., Mutis, T., Van de Donk, N.W.C.J. & Sasser, A.K. (2016) High-parameter mass cytometry (CyTOF[®]) evaluation of relapsed/refractory multiple myeloma (MM) patients (Pts) treated with daratumumab supports immune modulation as a novel mechanism of action. *Presented at the 58th American Society of Hematology Annual Meeting; December 3-6, 2016; San Diego, CA*, Abstract 4521.
- Chiu, C., Casneuf, T., Axel, A., Lysaght, A., Bald, J., Khokhar, N.Z., Plesner, T., Usmani, S.Z., Goldschmidt, H., Ahmadi, T., Chan, K. & Sasser, A.K. (2016) Daratumumab in combination with lenalidomide plus dexamethasone induces clonality increase and T-cell expansion: results from a phase 3 randomized study (POLLUX). *Presented at the 58th American Society of Hematology Annual Meeting; December 3-6, 2016; San Diego, CA*, Abstract 4531.
- Dimopoulos, M., Spencer, A., Attal, M., Prince, H.M., Harousseau, J.L., Dmoszynska, A., San, M.J., Hellmann, A., Facon, T., Foa, R., Corso, A., Masliak, Z., Olesnyckyj, M., Yu, Z., Patin, J., Zeldis, J.B. & Knight, R.D. (2007) Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*, **357**, 2123-2132.
- Dimopoulos, M.A., Oriol, A., Nahi, H., San-Miguel, J., Bahlis, N., Usmani, S., Rabinovic, A., Orłowski, R.Z., Komarnicki, M., Suzuki, K., Plesner, T., Yoo, S.S., Yehuda, D.B., Richardson, P.G., Goldschmidt, H., Reece, D., Lisby, S., Khokhar, N.Z., O'Rourke, D.M., Chiu, C., Qin, X., Guckert, M., Ahmadi, T. & Moreau, P. (2016) Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*, **375**, 1319-1331.
- Krejci, J., Casneuf, T., Nijhof, I.S., Verbist, B., Bald, J., Plesner, T., Syed, K., Liu, K., van de Donk, N.W.C.J., Weiss, B.M., Ahmadi, T., Lokhorst, H.M., Mutis, T. & Sasser, A.K. (2016) Daratumumab depletes CD38⁺ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*, **128**, 384-394.
- Plesner, T., Arkenau, H.T., Gimsing, P., Krejcik, J., Lemech, C., Minnema, M.C., Lassen, U., Laubach, J.P., Palumbo, A., Lisby, S., Basse, L., Wang, J., Sasser, A.K., Guckert, M.E., de Boer, C., Khokhar, N.Z., Yeh, H., Clemens, P., Ahmadi, T., Lokhorst, H.M. & Richardson, P.G. (2016) Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. *Blood*, **128**, 1821-1828.
- Rajkumar, S.V., Harousseau, J.L., Durie, B., Anderson, K.C., Dimopoulos, M., Kyle, R., Blade, J., Richardson, P., Orłowski, R., Siegel, D., Jagannath, S., Facon, T., van Loiseau, H., Lonial, S., Palumbo, A., Zonder, J., Ludwig, H., Vesole, D., Sezer, O., Munshi, N.C. & San, M.J. (2011) Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*, **117**, 4691-4695.
- US Department of Health and Human Services, National Institutes of Health & National Cancer Institute (2010) Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed July 11, 2018).
- Weber, D.M., Chen, C., Niesvizky, R., Wang, M., Belch, A., Stadtmaier, E.A., Siegel, D., Borrello, I., Rajkumar, S.V., Chanan-Khan, A.A., Lonial, S., Yu, Z., Patin, J.,

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Olesnycky, M., Zeldis, J.B. & Knight, R.D. (2007) Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*, **357**, 2133-2142.

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

(A) Response rates. (A) Progression-free survival. At a median duration of follow-up of 32.5 months, median PFS was not reached (95% CI, 16.62 months-NE), and the 24-month PFS rate was 68.9% (95% CI, 48.5-82.5). (B) Overall survival. Median OS was not reached (95% CI, 32.2 months-NE), and the 24-month OS rate was 78.1% (95% CI, 59.5-88.9).

ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response; PFS, progression-free survival; CI, confidence interval; NE, not estimable; OS, overall survival.

Table I. Most Common ($\geq 25\%$) Adverse Events in Part 2 (N = 32)^a

Event, n (%)	All grades	Grade 3 or 4
Neutropenia	29 (90.6)	27 (84.4)
Diarrhoea	18 (56.3)	1 (3.1)
Cough	16 (50.0)	0 (0.0)
Muscle spasms	15 (46.9)	0 (0.0)
Fatigue	13 (40.6)	0 (0.0)
Thrombocytopenia	11 (34.4)	5 (15.6)
Nausea	11 (34.4)	0 (0.0)
Pyrexia	11 (34.4)	0 (0.0)
Hypertension	10 (31.3)	3 (9.4)
Nasopharyngitis	10 (31.3)	0 (0.0)
Bronchitis	9 (28.1)	1 (3.1)
Upper respiratory tract infection	9 (28.1)	1 (3.1)
Anaemia	8 (25.0)	5 (15.6)
Leucopenia	8 (25.0)	4 (12.5)
Rhinitis	8 (25.0)	0 (0.0)
Peripheral oedema	8 (25.0)	0 (0.0)
Back pain	8 (25.0)	0 (0.0)
Insomnia	8 (25.0)	0 (0.0)

AE, adverse event.

^aAEs were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (US Department of Health and Human Services *et al*, 2010).

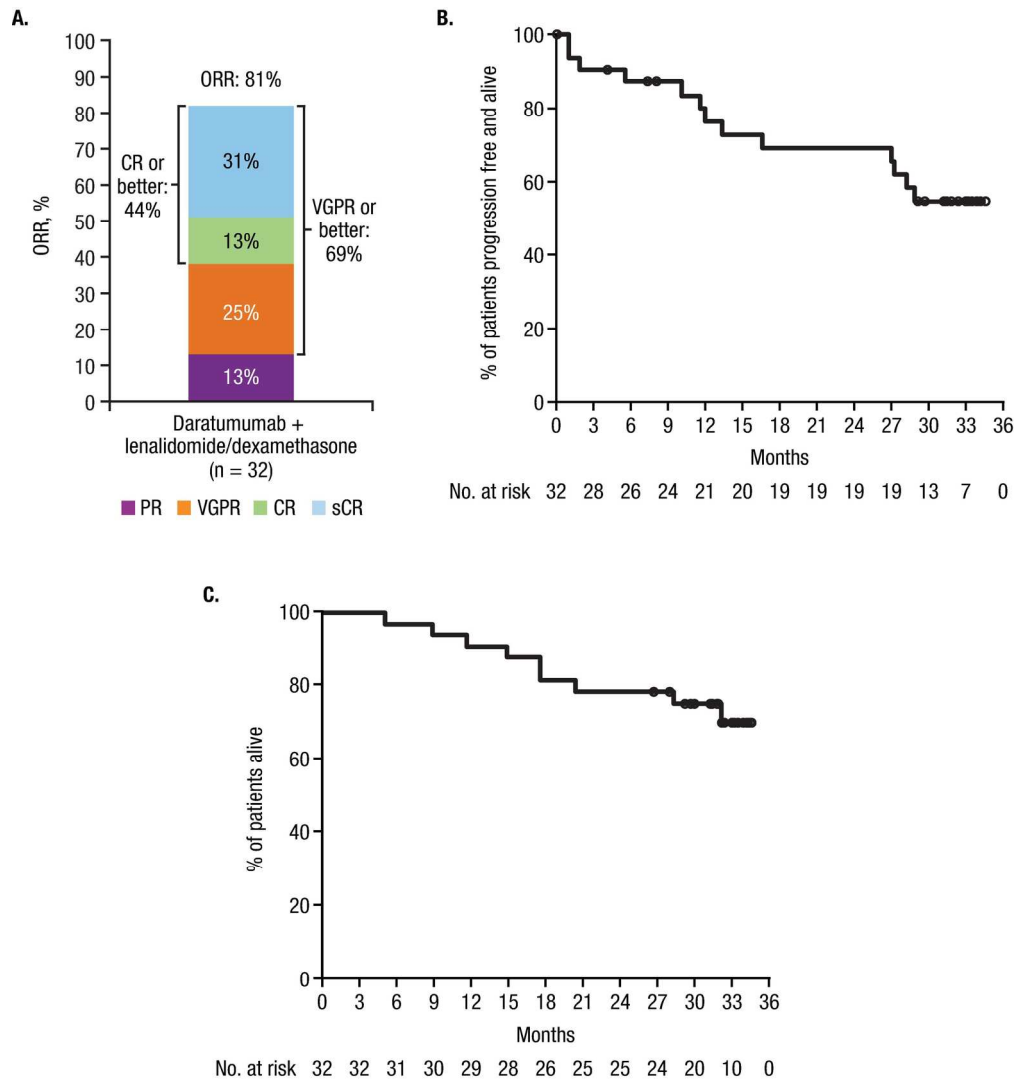


Fig 1. Response rates, progression-free survival, and overall survival of patients in Part 2. (A) Response rates. (A) Progression-free survival. At a median duration of follow-up of 32.5 months, median PFS was not reached (95% CI, 16.62 months-NE), and the 24-month PFS rate was 68.9% (95% CI, 48.5-82.5). (B) Overall survival. Median OS was not reached (95% CI, 32.2 months-NE), and the 24-month OS rate was 78.1% (95% CI, 59.5-88.9). ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response; PFS, progression-free survival; CI, confidence interval; NE, not estimable; OS, overall survival.

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Supplementary Information for Plesner et al. 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.

For Peer Review

Table SI. Baseline Characteristics of Patients in GEN503

	Part 1 (N = 13)	Part 2 (N = 32)
Median (range) age, y	62.0 (48-76)	59.5 (41-76)
Female/male sex, %	23/77	31/69
ECOG score, n (%)		
0	8 (61.5)	19 (59.4)
1	5 (38.5)	12 (37.5)
2	0 (0.0)	1 (3.1)
Median (range) time since diagnosis, y	3.8 (0.9-14.0)	3.2 (0.9-12.7)
Median (range) number of prior therapies	3.0 (2-4)	2.0 (1-3)
≥2 prior therapies, n (%)	13 (100.0)	17 (53.1)
Prior ASCT, n (%)	9 (69.2)	25 (78.1)
Prior IMiD, n (%)	13 (100.0)	23 (71.9)
Prior lenalidomide	10 (76.9)	11 (34.4)
Prior thalidomide	7 (53.8)	14 (43.8)
Prior PI, n (%)	12 (92.3)	29 (90.6)
Prior bortezomib	12 (92.3)	28 (87.5)
Prior PI + IMiD, n (%)*	12 (92.3)	21 (65.6)
Prior bortezomib + lenalidomide*	9 (69.2)	9 (28.1)
Prior steroids	12 (92.3)	32 (100)
Prior chemotherapy, n (%)**	13 (100.0)	32 (100.0)
Alkylating agents	13 (100.0)	29 (90.6)
Anthracyclines	8 (61.5)	15 (46.9)
Prior PI + IMiD + alkylating agents*,**	12 (92.3)	19 (59.4)
Refractory to last line of therapy, n (%)	5 (38.5)	7 (21.9)
Refractory to therapy containing, n (%)		
Lenalidomide	4 (30.8)	1 (3.1)
Bortezomib	6 (46.2)	5 (15.6)
Alkylating agents	3 (23.1)	3 (9.4)
PI only	2 (15.4)	5 (15.6)
IMiD only	2 (15.4)	1 (3.1)

ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplantation; IMiD, immunomodulatory drug; PI, proteasome inhibitor.

*Patients may have received these drugs in separate treatment regimens.

**Includes alkylating agents or ASCT.

Table SII. Summary of Best Responses

Response, n (%)	Part 1			Part 2	
	DARA 2 mg/kg (n = 3)	DARA 4 mg/kg (n = 3)	DARA 8 mg/kg (n = 4)	DARA 16 mg/kg (n = 3)	DARA 16 mg/kg (n = 32)
sCR	1 (33.3)	2 (66.7)	2 (50.0)	0 (0.0)	10 (31.3)
CR	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	4 (12.5)
VGPR	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	8 (25.0)
PR	1 (33.3)	0 (0.0)	1 (25.0)	0 (0.0)	4 (12.5)
MR	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (3.1)
SD	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	5 (15.6)
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ORR*	3 (100.0)	3 (100.0)	3 (75.0)	2 (66.7)	26 (81.3)
VGPR or better**	2 (66.7)	3 (100.0)	2 (50.0)	2 (66.7)	22 (68.8)
CR or better***	1 (33.3)	2 (66.7)	2 (50.0)	1 (33.3)	14 (43.8)

DARA, daratumumab; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

*sCR+CR+VGPR+PR.

**sCR+CR+VGPR.

***sCR+CR.

Table SIII. Summary of Best Responses and PFS in Patients in Part 2 Based on Prior Lenalidomide or IMiD Exposure

	Lenalidomide naive (n = 21)	Lenalidomide exposed (n = 11)	IMiD naive (n = 9)	IMiD exposed (n = 23)
Response, n (%)				
sCR	5 (23.8)	5 (45.5)	4 (44.4)	6 (26.1)
CR	3 (14.3)	1 (9.1)	1 (11.1)	3 (13.0)
VGPR	7 (33.3)	1 (9.1)	1 (11.1)	7 (30.4)
PR	2 (9.5)	2 (18.2)	1 (11.1)	3 (13.0)
MR	1 (4.8)	0 (0.0)	0 (0.0)	1 (4.3)
SD	3 (14.3)	2 (18.2)	2 (22.2)	3 (13.0)
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ORR*	17 (81.0)	9 (81.8)	7 (77.8)	19 (82.6)
VGPR or better**	15 (71.4)	7 (63.6)	6 (66.7)	16 (69.6)
CR or better***	8 (38.1)	6 (54.5)	5 (55.6)	9 (39.1)
24-month PFS rate, % (95% CI)	68.4 (42.4-84.5)	70.0 (32.9-89.2)	74.1 (28.9-93.0)	67.2 (43.1-82.8)

PFS, progression-free survival; IMiD, immunomodulatory drug; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CI, confidence interval; NE, not estimable.

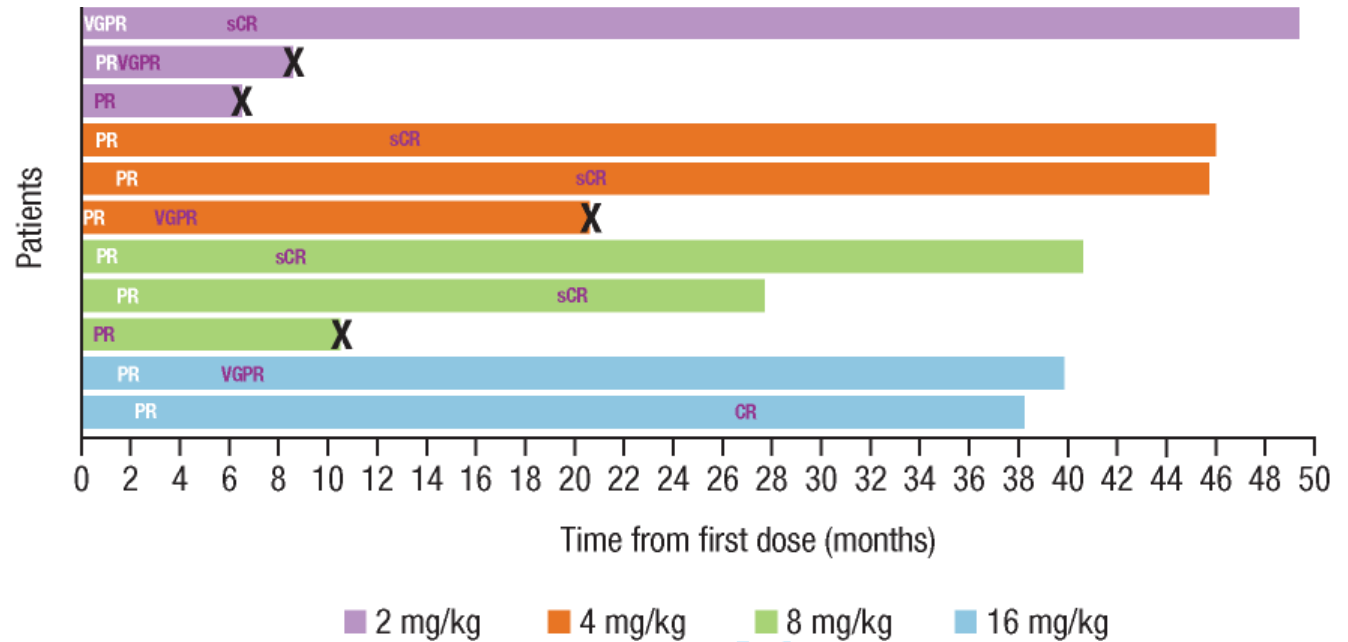
*sCR+CR+VGPR+PR.

**sCR+CR+VGPR.

***sCR+CR.

Fig S1. Timing and depth of response among responders. Swim lane plot of responders in **(A)** Part 1 and **(B)** Part 2. White text indicates the first response and purple text indicates the best response. “X” indicates disease progression. VGPR, very good partial response; sCR, stringent complete response; CR, complete response; PR, partial response; CR, complete response.

A.



B.

