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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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INTRODUCTION

- Daratumumab is a human IgG1κ monoclonal antibody targeting CD38 that exerts its antimyeloma activity through a direct (on-tumor) and indirect (immunomodulatory) mechanism of action[1-5]
- Daratumumab achieves rapid, deep, and durable responses with a favorable safety profile both as monotherapy[6] and in combination with standard of care regimens[7,8] in patients with relapsed and refractory (RR) multiple myeloma (MM)
- Based on the results of daratumumab monotherapy studies (GEN501 and SIRIUS)[6] and daratumumab combination therapy studies (POLLUX and CASTOR),[7,8] daratumumab is approved in the United States, European Union, and many other countries as monotherapy in heavily pretreated RRMM patients and in combination with the standard of care regimens lenalidomide/dexamethasone or bortezomib/dexamethasone in patients who relapsed after 1 prior therapy[9,10]
- In the United States, daratumumab plus pomalidomide/dexamethasone is indicated for patients with ≥2 prior therapies, including lenalidomide and a proteasome inhibitor[9,11]
- GEN503 was a 2-part, phase 1/2 study of daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed or RRMM[12]
  - At the primary analysis, conducted at a median follow-up of 15.6 months, overall response rate (ORR) in Part 2 (daratumumab 16 mg/kg in combination with lenalidomide/dexamethasone) was 81.3%, with 25.0% of patients achieving stringent complete response (sCR); rate of very good partial response (VGPR) or better was 62.5%[12]
  - The 18-month progression-free survival (PFS) rate was 72%, and the 18-month overall survival (OS) rate was 90%[12]
  - The combination was well tolerated, with a safety profile consistent with that of daratumumab alone or lenalidomide/dexamethasone alone[12]
- Here we provide the final safety and efficacy results of the GEN503 study of daratumumab in combination with lenalidomide and dexamethasone with a median follow-up of approximately 3 years in patients with relapsed or RRMM

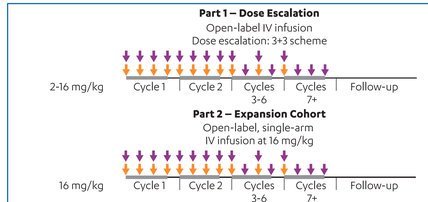
METHODS

Patients

- In Part 1 (dose-escalation phase), patients were ≥18 years of age, had an Eastern Cooperative Oncology Group performance status of ≤2, had measurable levels of M-component, and had relapsed MM after 2 to 4 prior lines of therapy
- In Part 2 (dose-expansion cohort), patients had received ≥1 prior line of MM therapy, achieved a partial response (PR) or better to ≥1 regimen, and had documented evidence of progressive disease on or after their last regimen, as defined by International Myeloma Working Group (IMWG) criteria
- Key exclusion criteria were as follows:
  - Patients who had previously received an allogeneic stem cell transplantation (SCT) at any time or an autologous SCT within 12 weeks of the first daratumumab infusion
  - Patients refractory or intolerant to lenalidomide (patients exposed to lenalidomide were permitted in the study)

Study Design and Treatment

- The methods for this study are described in detail in a previous report[12]
- Briefly, GEN503 was a phase 1/2, open-label, multicenter trial (**Figure 1**)
- Part 1 was a standard 3+3 dose-escalation study in which patients received 1 of 4 doses of daratumumab ranging from 2 to 16 mg/kg
- Part 2 was a cohort expansion study in which patients received the recommended phase 2 dose of daratumumab (16 mg/kg), which was selected based on the results of Part 1
- Daratumumab was administered weekly during Cycles 1 and 2, every 2 weeks during Cycles 3 to 6, and every 4 weeks thereafter until disease progression or unacceptable toxicity
- Lenalidomide 25 mg was administered orally on Days 1 to 21 of each cycle
- Dexamethasone 40 mg was administered weekly
- For OS assessment, patients were followed at 6-month intervals for 3 years after their final dose of lenalidomide
  - Patients were followed at 3-month intervals for secondary primary malignancies



IV, intravenous; PO, orally.
In Part 1, 4 cohorts were treated with daratumumab (2, 4, 8, and 16 mg/kg) and lenalidomide and dexamethasone in 28-day cycles.
In Part 2, daratumumab 16 mg/kg and lenalidomide and dexamethasone were administered using the same dosing schedule as Part 1.

Figure 1. GEN503 study design.

Statistical Analyses and Assessments

- The primary endpoint was safety
  - Adverse events (AEs) were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03
- After the primary analysis, data collection was limited to serious AEs, disease assessments, and second primary malignancies
- Secondary endpoints included ORR, duration of response, PFS, and OS
  - Responses were evaluated according to the IMWG uniform response criteria for myeloma[13]
  - PFS, OS, and duration of response were analyzed using the Kaplan-Meier method

RESULTS

Patients and Treatments

- The clinical cut-off date for the final analysis was February 14, 2017
- Thirteen patients were enrolled in Part 1 of the study and received 1 of 4 doses of daratumumab (2 mg/kg [n = 3], 4 mg/kg [n = 3], 8 mg/kg [n = 4], or 16 mg/kg [n = 3]) in combination with lenalidomide and dexamethasone (**Table 1**)
  - Median (range) number of prior lines of therapy was 3 (2-4), median (range) duration of follow-up was 39.9 (4.0-49.5) months, and median (range) number of treatment cycles received was 38 (4-53)
  - All 13 patients received a prior immunomodulatory drug (IMiD), and 77% had received prior lenalidomide
  - Eight patients discontinued treatment in Part 1 due to disease progression (n = 4) or AEs (n = 4)
- Thirty-two patients were enrolled in Part 2 of the study; median (range) number of prior lines of therapy was 2 (1-3), and 11 (34%) patients had received prior lenalidomide (**Table 1**)
  - Median (range) duration of follow-up was 32.5 (5.1-34.7) months, and median (range) number of treatment cycles received was 31 (1-39)
  - Sixteen patients discontinued treatment in Part 2 due to disease progression (n = 10), AEs (n = 4), or physician decision (n = 2)
- Some patients had a short duration of follow-up prior to implementation of protocol amendment 6, which revised the number of follow-up visits from 6 to indefinite until death or lost to follow-up

Safety

- As previously reported, no dose-limiting toxicities were observed in Part 1[12]
- The most common treatment-emergent AEs observed in Part 2 were neutropenia, diarrhea, cough, muscle spasms, and fatigue (**Table 2**)
- Neutropenia was the most common grade 3 or 4 AE (**Table 2**)
- No new infusion-related reactions were reported with longer follow-up
- In Part 1, 1 patient (daratumumab 8 mg/kg) acquired a second primary malignancy of Epstein-Barr virus–associated lymphoma
- In Part 2, second primary malignancies were observed in 4 patients: cutaneous squamous cell carcinoma in 3 patients (all of whom continued study treatment after their lesions were treated) and gastric adenocarcinoma in 1 patient

Table 1. Patient Demographics and Baseline Characteristics

	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 status, 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 (%)[a]	12 (92.3)	21 (65.6)
Prior bortezomib + lenalidomide[a]	9 (69.2)	9 (28.1)
Prior chemotherapy, n (%)[b]	13 (100.0)	32 (100.0)
Alkylating agents	13 (100.0)	29 (90.6)
Anthracyclines	8 (61.5)	15 (46.9)
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.
[a]Patients may have received these drugs in separate treatment regimens.
[b]Includes alkylating agents or ASCT.

Table 2. Most Common (≥25%) AEs in Part 2 (n = 32)

Event, n (%)	All grades	Grade 3/4
Neutropenia	29 (90.6)	27 (84.4)
Diarrhea	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)
Anemia	8 (25.0)	5 (15.6)
Leukopenia	8 (25.0)	4 (12.5)
Rhinitis	8 (25.0)	0 (0.0)
Peripheral edema	8 (25.0)	0 (0.0)
Back pain	8 (25.0)	0 (0.0)
Insomnia	8 (25.0)	0 (0.0)

AE, adverse event.

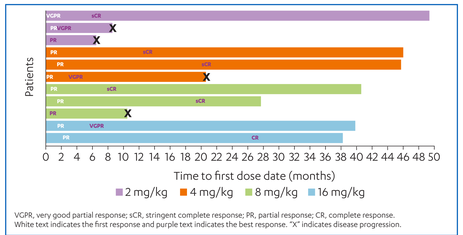
Efficacy

- In Part 1, ORR was 100% for patients treated with daratumumab 2 mg/kg or 4 mg/kg, 75% for patients treated with daratumumab 8 mg/kg, and 67% for patients treated with daratumumab 16 mg/kg in combination with lenalidomide and dexamethasone (**Table 3**)
- In Part 2, ORR was 81%, including 10 (31%) sCRs; rate of VGPR or better was 69%, and rate of complete response (CR) or better was 44% (**Table 3**)
  - While the ORR did not change since the primary analysis,[12] an increase in the number of patients who had a CR (4 versus 3 patients) or sCR (10 versus 8 patients) was observed, demonstrating a deepening of response over time with prolonged treatment
- A swim lane plot of responders in Part 1 is shown in **Figure 2**
- A swim lane plot of responders in Part 2 is shown in **Figure 3**
- In Part 2, the median duration of response was not reached (95% confidence interval [CI], 26.5 months-not estimable)
- Median PFS was not reached (95% CI, 16.6 months-not estimable); the 2-year PFS rate was 68.9% (95% CI, 48.5-82.5; **Figure 4**)

Table 3. Summary of Best Responses With Daratumumab Plus Lenalidomide and Dexamethasone

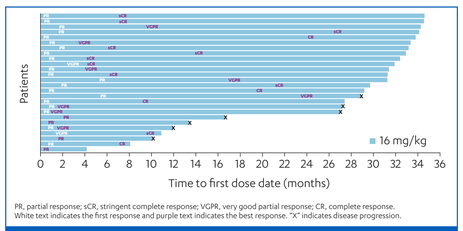
	Part 1				Part 2
Response, n (%)	DARA 2 mg/kg (n = 3)	DARA 4 mg/kg (n = 3)	DARA 8 mg/kg (n = 4)	DARA 16 mg/kg (n = 3)	DARA 16 mg/kg (n = 32)
Best response					
sCR	1 (33.3)	2 (66.7)	2 (50.0)	0 (0.0)	10 (31.3)
CR	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	4 (12.5)
VGPR	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	8 (25.0)
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)
ORR[a]	3 (100.0)	3 (100.0)	3 (75.0)	2 (66.7)	26 (81.3)
VGPR or better[b]	2 (66.7)	3 (100.0)	2 (50.0)	2 (66.7)	22 (68.8)
CR or better[c]	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, minor response; SD, stable disease; ORR, overall response rate.
[a]sCR + CR + VGPR + PR.
[b]sCR + CR + VGPR.
[c]sCR + CR.



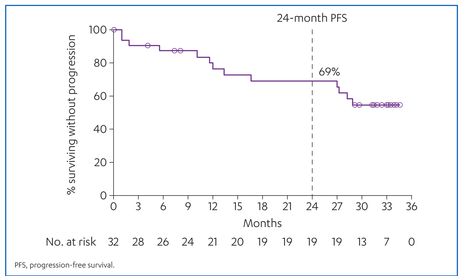
VGPR, very good partial response; sCR, stringent complete response; PR, partial response; CR, complete response.
White text indicates the first response and purple text indicates the best response. "X" indicates disease progression.

Figure 2. Swim lane plot of responders in Part 1.



PR, partial response; sCR, stringent complete response; VGPR, very good partial response; CR, complete response.
White text indicates the first response and purple text indicates the best response. "X" indicates disease progression.

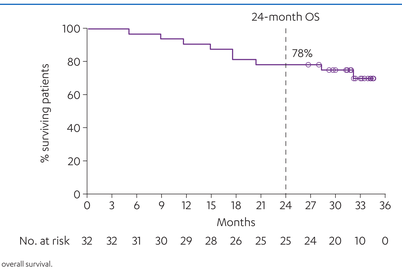
Figure 3. Swim lane plot of responders in Part 2.



PFS, progression-free survival.

Figure 4. PFS in patients receiving daratumumab 16 mg/kg plus lenalidomide and dexamethasone in Part 2.

- Median OS was not reached (95% CI, 32.2 months-not estimable); the 2-year OS rate was 78.1% (95% CI, 59.5-88.9; **Figure 5**)



OS, overall survival.

Figure 5. OS in patients receiving daratumumab 16 mg/kg plus lenalidomide and dexamethasone in Part 2.

CONCLUSIONS

- **The combination of daratumumab plus lenalidomide and dexamethasone induced deepening of responses that were maintained for over 2 years, with a favorable safety profile in patients with relapsed or RRMM**
  - **At a median follow-up of 32.5 months in Part 2 of the study, ORR was 81%, including 31% with sCR; rates of VGPR or better and CR or better were 69% and 44%, respectively**
  - **The 2-year PFS rate was 69%, and the 2-year OS rate was 78%**
  - **Patients achieving CR or better have not relapsed at the time of this final analysis**
- **Daratumumab was safely combined with lenalidomide and dexamethasone, with no additional safety signals**
- **The final results from this phase 1/2 study are consistent with and further support those from POLLUX, a phase 3 study of daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with RRMM who had received ≥1 prior line of therapy[8]**
- **Taken together, long-term treatment with daratumumab in combination with lenalidomide and dexamethasone achieves deep and durable responses and a manageable safety profile in patients with relapsed or RRMM**

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DISCLOSURES

FMG received honoraria from Takeda, Janssen, Amgen, Celgene, and Bristol-Myers Squibb; and served on an advisory committee for Takeda, Seattle Genetics, Roche, Mundipharma, Janssen, and Celgene. MCM served as a consultant for Amgen, Takeda, Celgene, Janssen, and Servier; and received research funding from Celgene. PM served on an advisory committee for Celgene, Janssen, Takeda, Novartis, Amgen, and Roche. JDC received honoraria from Janssen and served as a consultant for Celgene, Novartis, and Takeda. AP received honoraria from Janssen, Takeda, Celgene, Bristol-Myers Squibb, Sanofi, and Amgen; and served on an advisory committee for Janssen and Celgene. JL received research funding from Novartis, Takeda, Celgene, and Onyx; and served as a consultant for Novartis, Takeda, and Celgene. PR served as a consultant for Celgene, Takeda, and Jazz Pharmaceuticals; served on an advisory committee for Celgene, Jazz Pharmaceuticals, Janssen, and Millennium; and received research funding from Celgene, Takeda, and Jazz Pharmaceuticals. CdB, DC, CC, and JMS are employees of Janssen. JMS holds stock and/or stock options in Johnson & Johnson. TA is a former employee of Janssen and is a current employee of Genmab. All other authors report no conflicts.

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