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Safety and Efficacy of Daratumumab Monotherapy in Patients With Heavily Pretreated Relapsed and Refractory Multiple Myeloma: Final Results From GEN501 and SIRIUS

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INTRODUCTION

- Daratumumab is a human CD38-targeting IgGκ monoclonal antibody with antimyeloma activity mediated by both on-tumor and immunomodulatory mechanisms of action[1-5]
- In 2 clinical studies (NCT00574288 [GEN501] and NCT01985126 [SIRIUS]), daratumumab monotherapy induced rapid, deep, and durable responses with a favorable safety profile in patients with heavily pretreated relapsed and refractory multiple myeloma[6,7]
  - Daratumumab monotherapy was approved by the US Food and Drug Administration in November 2015 and by the European Medicines Agency in May 2016 based on these studies
- A combined analysis of patients who received daratumumab 16 mg/kg in these studies at a median follow-up of 20.7 months was previously published[8]
  - Overall response rate (ORR) was 31.1%, including 13 patients with very good partial response (VGPR), 4 with complete response (CR), and 3 with stringent CR (sCR)
  - Median overall survival (OS) was 20.1 months
  - No new safety signals were identified
- Here we present the final safety and efficacy findings for the combined analysis of patients from the GEN501 and SIRIUS studies after a median follow-up of approximately 3 years

METHODS

Patients

- Data were pooled from 2 studies of single-agent daratumumab (GEN501 and SIRIUS) in patients treated with 16 mg/kg[6-8]
- In both studies, patients had documented multiple myeloma requiring systemic therapy and an Eastern Cooperative Oncology Group performance status ≤2
  - In GEN501, patients had relapsed from or were refractory to ≥2 prior lines of therapy, including proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs)
  - In SIRIUS, patients had received ≥3 prior lines of therapy, including a PI and an IMiD, or were double refractory to both a PI and an IMiD
- Key eligibility criteria for both GEN501 and SIRIUS were as follows:
  - Absolute neutrophil count ≥1,000/μL for GEN501 and >1,000/μL for SIRIUS
  - Hemoglobin ≥7.5 g/dL for GEN501 and >7.5 g/dL for SIRIUS
  - Platelet count
    - ≥75 x 10^9/L for GEN501
    - ≥50 x 10^9/L for SIRIUS
  - Alanine aminotransferase
    - ≤3.5 times the upper limit of normal for GEN501
    - <2.5 times the upper limit of normal for SIRIUS

Study Design and Treatment

- The methods of both studies are described in detail in previous reports[6-8]
- Briefly, GEN501 was a first-in-human, open-label, phase 1/2 study comprising a dose-escalation phase (Part 1) and a dose-expansion phase (Part 2)
  - In Part 2, patients received an initial infusion of daratumumab 16 mg/kg intravenously (IV), which was followed by a 3-week rest period, and then daratumumab infusions once weekly (QW) for 7 weeks, once every 2 weeks (Q2W) for 14 weeks, and once every 4 weeks (Q4W) thereafter until disease progression
- SIRIUS was an open-label phase 2 study
  - Patients received daratumumab 16 mg/kg IV QW for 8 weeks, Q2W for 16 weeks, and Q4W thereafter
- Patients treated with daratumumab 16 mg/kg IV in GEN501 Part 2 and in SIRIUS were included in this combined analysis

Statistical Analyses and Assessments

- The primary endpoint in GEN501 was safety, and efficacy was a secondary endpoint
- The primary endpoint in SIRIUS was ORR
- In both studies, responses were evaluated using the International Myeloma Working Group response criteria[9]
- ORR was calculated based on computerized algorithm results from both studies
  - Previously reported response results from SIRIUS were based on assessment by the Independent Review Committee, showing excellent agreement with the results of the computerized algorithm (kappa coefficient = 0.98)[7]
- The Kaplan-Meier method was used to analyze all time-to-event endpoints
- No formal statistical hypotheses were formulated or tested

RESULTS

- The combined analysis included 148 patients (GEN501 Part 2: n = 42; SIRIUS: n = 106) who were treated with daratumumab 16 mg/kg
- Patients were heavily pretreated, with 76% having received >3 prior therapies; 91% of patients were refractory to their last line of therapy, and 87% of patients were refractory to both a PI and an IMiD (**Table 1**)
- In the combined analysis set, the median duration of follow-up was 36.6 (range, 0.5-42.3) months

Table 1. Baseline Characteristics and Refractory Status: Combined Analysis of GEN501 Part 2 and SIRIUS

Characteristic	Daratumumab 16 mg/kg (N = 148)
Median (range) age, y	64 (31-84)
65 to <75 y, n (%)	52 (35)
≥75 y, n (%)	16 (11)
Female/male sex, %	47/53
ECOG score, n (%)	
0	41 (28)
1	97 (66)
2	10 (7)
Extramedullary plasmacytomas, n (%)	
0	130 (88)
≥1	18 (12)
Median (range) time since diagnosis, y	5.1 (0.8-23.8)
Renal function at baseline, CrCl, n (%)	
≥60 mL/min	89 (60)
≥30 to <60 mL/min	54 (37)
<30 mL/min	5 (3)
Bone marrow percent plasma cells at baseline, n (%)	(n = 146)
≤30	85 (58)
>30 to ≤60	26 (18)
>60	35 (24)
Median (range) number of prior lines of therapy	5 (2-14)
>3 prior lines of therapy, n (%)	113 (76)
Prior ASCT, n (%)	116 (78)
Prior PI, n (%)	148 (100)
Bortezomib	147 (99)
Carfilzomib	61 (41)
Prior IMiD, n (%)	146 (99)
Lenalidomide	145 (98)
Pomalidomide	82 (55)
Thalidomide	66 (45)
Refractory to last line of therapy, n (%)	135 (91)
Refractory to both a PI and an IMiD, n (%)	128 (87)
Refractory to PI + IMiD + alkylating agent, n (%)	100 (68)
Refractory to, n (%)	
Bortezomib	125 (85)
Carfilzomib	58 (39)
Lenalidomide	124 (84)
Pomalidomide	82 (55)
Thalidomide	41 (28)
Alkylating agent only	107 (72)

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

Safety

- The most common (≥20%) treatment-emergent adverse events (TEAEs) observed across the 2 studies are summarized in **Table 2**
  - No new safety signal was identified with longer follow-up
- The most common (≥5%) grade 3 or 4 TEAEs were anemia (18%), thrombocytopenia (14%), and neutropenia (10%; **Table 2**)
- Six (4%) patients discontinued treatment due to TEAEs
  - None were found related to daratumumab
- Three (2%) patients died due to TEAEs (viral H1N1 infection, pneumonia, and aspiration pneumonia)
  - None were found related to daratumumab
  - No new deaths due to TEAEs were observed with longer follow-up

Table 2. Most Common (≥20%) TEAEs: Combined Analysis of GEN501 Part 2 and SIRIUS

	Daratumumab 16 mg/kg (N = 148)		
Event, n (%)	All grades	Grade 3	Grade 4
Fatigue	62 (42)	3 (2)	0
Nausea	44 (30)	0	0
Anemia	42 (28)	26 (18)	0
Back pain	40 (27)	4 (3)	0
Cough	38 (26)	0	0
Upper respiratory tract infection	33 (22)	1 (1)	0
Thrombocytopenia	31 (21)	13 (9)	8 (5)
Neutropenia	31 (21)	11 (7)	4 (3)
Pyrexia	29 (20)	1 (1)	0
Nasal congestion	29 (20)	0	0

TEAE, treatment-emergent adverse event.

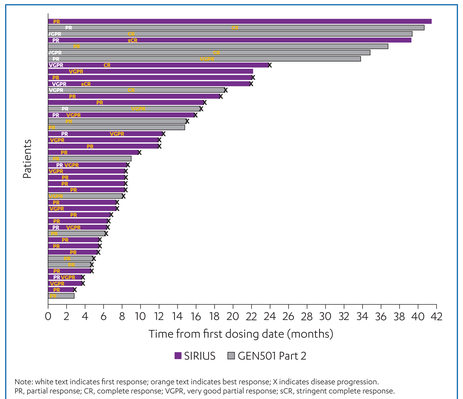
Efficacy

- ORR was 30.4% (95% confidence interval [CI], 23.1-38.5), with 20 (13.5%) patients achieving VGPR or better, and 7 (4.7%) patients achieving CR or better (**Table 3**)
- In both studies, deep responses were maintained over time (**Figure 1**)
  - Among responders, the median duration of response was 8.0 (95% CI, 6.5-14.7) months, and 19.6% (95% CI, 9.0-33.2) of responders remained progression free at 3 years
- Median OS was 20.5 months (95% CI, 16.6-28.1; **Figure 2**), and the 3-year OS rate was 36.5% (95% CI, 28.4-44.6)

Table 3. Best Overall Response Based on a Computerized Algorithm: Combined Analysis of GEN501 Part 2 and SIRIUS

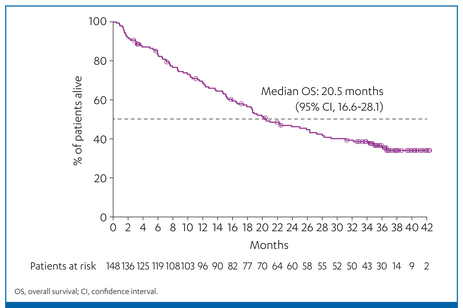
Response, n (%)	Daratumumab 16 mg/kg (N = 148)
Best response	
sCR	2 (1.4)
CR	5 (3.4)
VGPR	13 (8.8)
PR	25 (16.9)
Minimal response	9 (6.1)
Stable disease	70 (47.3)
Progressive disease	18 (12.2)
Not evaluable	6 (4.1)
ORR (sCR + CR + VGPR + PR)	45 (30.4)
VGPR or better (sCR + CR + VGPR)	20 (13.5)
CR or better (sCR + CR)	7 (4.7)

sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate.



Note: white text indicates first response; orange text indicates best response; X indicates disease progression.
PR, partial response; CR, complete response; VGPR, very good partial response; sCR, stringent complete response.

Figure 1. Swim-lane plot of responders: combined analysis of GEN501 Part 2 and SIRIUS (daratumumab 16 mg/kg).

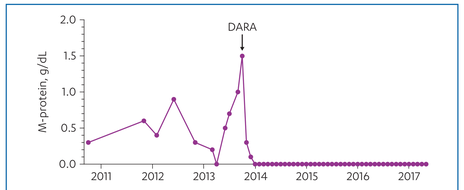


OS, overall survival; CI, confidence interval.

Figure 2. Overall survival: combined analysis of GEN501 Part 2 and SIRIUS (daratumumab 16 mg/kg).

Case Report

- A male patient initially diagnosed at 70 years of age with del17p, triple refractory myeloma was treated with daratumumab 16 mg/kg monotherapy in SIRIUS
  - Initial presentation with plasmacytoma in September 2010
    - The patient received local external radiotherapy and no active lesions were detected in January 2011
  - In October 2011, the patient was diagnosed with multiple myeloma (IgAκ)
  - The patient received 1 lenalidomide/dexamethasone induction cycle (minimal response) and 5 cycles of bortezomib/lenalidomide/dexamethasone (PR) between December 2011 and June 2012, prior to autologous stem cell transplantation in September 2012
  - The patient achieved VGPR and remained on maintenance bortezomib/lenalidomide until disease progression in March 2013
  - In April 2013, the patient received pomalidomide/bortezomib/dexamethasone and achieved PR before disease progression after 6 cycles
  - In October 2013, triple refractory 2 years following diagnosis, he was enrolled in SIRIUS
- The patient achieved PR at 28 days, VGPR at 56 days, and sCR at 194 days after the first daratumumab dose (**Figure 3**)
- Approximately 2 years after study enrollment, the patient showed no detectable minimal residual disease (MRD; 10^{-5} sensitivity threshold)
- The duration of the patient's clinical response is now over 3.5 years without relapse, including absence of MRD based on an assay developed by EuroFlow Consortium[10]
- The patient's immunophenotype revealed $CD8^+$ T-cell expansion, clonal expansion of the T-cell receptor repertoire, and decreases in regulatory T cells during daratumumab therapy, suggesting a robust adaptive immune response
  - Clonal T-cell expansion was sustained for 32 months



Note: M-protein levels were measured at the local laboratory and then centrally after the first dose of daratumumab.
sCR, stringent complete response; DARA, daratumumab.

Figure 3. M-protein levels over time in a patient with sCR in SIRIUS.

CONCLUSIONS

- **After 3 years of median follow-up, single-agent daratumumab continues to demonstrate a favorable safety profile with no new safety signals**
- **Deep and durable responses continue to be maintained in these heavily pretreated, highly refractory patients**
- **With over one-third of patients remaining alive after 3 years of study entry, these findings highlight the activity of single-agent daratumumab in this heavily pretreated, highly refractory multiple myeloma population**

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DISCLOSURES

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