1824

Daratumumab in Combination With Pomalidomide and Dexamethasone for Relapsed and/or Refractory Multiple Myeloma (RRMM) Patients With ≥2 Prior Lines of Therapy: Updated Analysis of MMY1001

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INTRODUCTION

- Daratumumab is a human IgG1κ monoclonal antibody targeting CD38 that has a direct on-tumor and 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[7-9] in patients with relapsed and/or 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[10,11]
- In a randomized, phase 3 study, patients relapsed from or refractory to previous treatment with bortezomib or lenalidomide who received pomalidomide plus low-dose dexamethasone achieved an overall response rate (ORR) of 31%, with a median progression-free survival (PFS) and overall survival (OS) of 4.0 months and 12.7 months, respectively[12]
- Pomalidomide increases CD38 expression in a time- and dose-dependent fashion in MM cells[13]
- Based on these observations, the addition of pomalidomide to daratumumab was hypothesized to enhance the efficacy of daratumumab and to improve patient outcomes
- MMY1001 is a multiarm phase 1b study (ClinicalTrials.gov Identifier: NCT01998971) that is evaluating daratumumab in combination with various backbone therapies, including pomalidomide/dexamethasone (pom-dex)
- Primary results from the daratumumab plus pom-dex treatment arm of MMY1001 were recently published and reported safety and efficacy results at a median follow-up of 13.1 months[9]
  - The safety profile of daratumumab plus pom-dex was similar to pom-dex alone, but with increased neutropenia
  - ORR was 60%, with a stringent complete response (sCR) of 8%; median PFS and OS were 8.8 months and 17.5 months, respectively
- Based on the results of the MMY1001 study, daratumumab plus pom-dex was approved in the United States for RRMM patients with ≥2 prior therapies, including lenalidomide and a proteasome inhibitor (PI)[9,10]
- Here we provide updated safety and efficacy results from the daratumumab plus pom-dex treatment arm of MMY1001 with >1 year of additional follow-up

METHODS

Patients

- Key eligibility criteria were as follows:
  - Refractory to last line of therapy
  - ≥2 prior lines of therapy, including ≥2 consecutive cycles that included lenalidomide and bortezomib
  - Pomalidomide naïve
  - Eastern Cooperative Oncology Group performance status of ≤2
  - Absolute neutrophil count ≥1 × 10^9/L
  - Platelet count ≥75 × 10^9/L for patients with <50% plasma cells
  - Calculated creatinine clearance ≥45 mL/min/1.73 m^2

Study Design and Treatment

- The methods for this study are described in detail in a previous report[9]
- Briefly, MMY1001 was an open-label, multicenter, phase 1b study that evaluated daratumumab in combination with a variety of backbone regimens
  - The study design for the daratumumab plus pom-dex arm is shown in **Figure 1**

Eligibility/treatment	Dosing schedule (28-day cycles)	Endpoints
• RRMM • ≥2 prior lines of therapy, including lenalidomide and bortezomib • Pomalidomide naïve • ECOG status ≤2 • CrCl ≥45 mL/min • ANC ≥1.0×10^9/L • Platelets ≥75×10^9/L	**Daratumumab:** • 16 mg/kg IV QW on Cycles 1-2 • Q2W on Cycles 3-6 • Q4W thereafter **Pomalidomide:** • 4 mg PO on Days 1-21 **Dexamethasone:** • 40 mg/week[a]	**Primary** • Safety, tolerability **Secondary** • ORR • Duration of response • Time to response • PFS • OS

pom-dex, pomalidomide/dexamethasone; RRMM, relapsed/refractory multiple myeloma; ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; ANC, absolute neutrophil count; IV, intravenously; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; PO, orally; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.
[a]20 mg if >75 years of age. On daratumumab dosing days, dexamethasone 20 mg IV was administered as premedication on the infusion day and 20 mg PO the day after infusion. On weeks when no daratumumab infusion was administered, dexamethasone 40 mg PO was given as a single dose on Day 1.

Figure 1. MMY1001 study design: daratumumab plus pom-dex.

- Six patients were initially treated with daratumumab plus pom-dex and, because ≤1 patient experienced dose-limiting toxicity, 97 additional patients were enrolled in an expansion cohort
- Daratumumab 16 mg/kg was administered intravenously (IV) in 28-day cycles weekly during Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and every 4 weeks thereafter until disease progression
  - All patients also received an antihistamine and acetaminophen prior to each daratumumab infusion to reduce the risk for infusion-related reactions (IRRs)
- Pomalidomide 4 mg was administered orally (PO) on Days 1 to 21 of each cycle
- Dexamethasone 40 mg was administered IV/PO every week

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
- Efficacy endpoints included ORR, duration of response, PFS, and OS
  - Responses were analyzed in the response-evaluable population, which included patients who have a confirmed diagnosis of MM and measurable disease at baseline or screening visit, have received ≥1 administration of study treatment, and have adequate post-baseline disease assessments
  - Responses were evaluated by a computerized algorithm according to the International Myeloma Working Group uniform response criteria for myeloma[14]
  - For daratumumab interference on serum immunofixation (IFE), a second reflex assay using an anti-idiotype monoclonal antibody was used to confirm daratumumab migration on the IFE[15]
  - PFS, OS, and duration of response were analyzed using the Kaplan-Meier method based on all treated patients
- Bone marrow aspirates at screening were used to assess cytogenetic risk status via fluorescence in situ hybridization or karyotyping
  - High-risk cytogenetic status was defined as having ≥1 of the following abnormalities: t(4;14), t(14;16), or del17p
- Minimal residual disease (MRD) was assessed via next-generation sequencing using the clonoSEQ® assay (Version 1.3; Adaptive Biotechnologies, Seattle, WA) at sensitivities of 0.01% (1 cancer cell per 10,000 nucleated cells or 10^{-4}), 0.001% (10^{-5}), and 0.0001% (10^{-6})

RESULTS

Patients and Treatments

- The clinical cutoff date for the updated analysis was October 12, 2017
- A total of 103 patients received ≥1 dose of daratumumab plus pom-dex
- Baseline demographic and clinical characteristics are summarized in **Table 1**
  - Median (range) age was 64 (35-86) years
  - Median (range) number of prior therapies was 4 (1-13), and 52% of patients had received >3 prior therapies
  - The majority (89%) of patients were refractory to lenalidomide, and 71% were refractory to both a PI and an immunomodulatory drug
  - Of the 87 patients with an available cytogenetic profile, 25% were high risk
- Median (range) duration of follow-up was 28.1 (0.2-39.8) months
- At the clinical cutoff date, 85% of patients discontinued treatment due to progressive disease (53%), AEs (17%), physician decision (4%), death (4%), other reasons (4%), or patient withdrawal (3%)

Table 1. Patient Demographics and Baseline Characteristics

	Daratumumab + pom-dex (N = 103)
Age, y	
Median (range)	64 (35-86)
Category, n (%)	
<65	52 (51)
65-<75	43 (42)
≥75	8 (8)
Female/male sex, %	45/55
ECOG status, n (%)	
0	28 (27)
1	63 (61)
2	12 (12)
Cytogenetic profile, n (%)[a]	n = 87
Standard risk	65 (75)
High risk	22 (25)
del17p	16 (18)
t(4;14)	6 (7)
t(14;16)	1 (1)
Median (range) time since diagnosis, y	5.1 (0.4-16.0)
Prior lines of therapy, n (%)	
Median (range)	4 (1-13)
1	3 (3)
2	22 (21)
3	25 (24)
>3	53 (52)
Prior ASCT, n (%)	76 (74)
Prior PI, n (%)	102 (99)
Prior bortezomib	101 (98)
Prior carfilzomib	34 (33)
Prior lenalidomide, n (%)	103 (100)
Prior PI + IMiD, n (%)	102 (99)
Refractory to therapy containing, n (%)	
Lenalidomide	92 (89)
Bortezomib	73 (71)
Carfilzomib	31 (30)
Refractory to PI + IMiD, n (%)	73 (71)

pom-dex, pomalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
[a]Based on fluorescence in situ hybridization or karyotyping; percentages based on n = 87 as the denominator.

Safety

- A total of 44% of patients had baseline grade 1 or 2 neutropenia
- The most common (≥25%) treatment-emergent adverse events (TEAEs) are shown in **Table 2**
- The most common grade 3 or 4 AEs were neutropenia (79% [febrile neutropenia 8%]), anemia (28%), and leukopenia (24%; **Table 2**)
- Other than neutropenia, rates of grade 3 or 4 AEs were similar to those observed historically with pom-dex alone[12]
- Serious AEs occurred in 57% of patients; 19%, 22%, and 19% were related to daratumumab, pomalidomide, and dexamethasone, respectively
- A total of 19% of patients discontinued treatment (any components) due to a TEAE; 4% were reasonably related to daratumumab
- TEAEs leading to death occurred in 9% of patients, none of which were related to daratumumab
- Only 1 patient reported a secondary primary malignancy

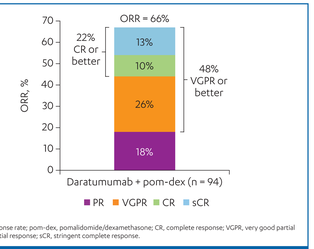
Table 2. Most Common (≥25%) AEs With Daratumumab Plus Pom-dex (N = 103)

Event, n (%)	All grades	Grade ≥3
Neutropenia	83 (80.6)	81 (78.6)
Anemia	57 (55.3)	29 (28.2)
Fatigue	54 (52.4)	13 (12.6)
Diarrhea	51 (49.5)	5 (4.9)
Thrombocytopenia	44 (42.7)	20 (19.4)
Cough	42 (40.8)	0
Leukopenia	40 (38.8)	25 (24.3)
Constipation	37 (35.9)	0
Nausea	36 (35.0)	0
Dyspnea	34 (33.0)	8 (7.8)
Pyrexia	34 (33.0)	2 (1.9)
Back pain	33 (32.0)	6 (5.8)
Upper respiratory tract infection	33 (32.0)	3 (2.9)
Muscle spasms	30 (29.1)	1 (1.0)
Vomiting	29 (28.2)	2 (1.9)
Arthralgia	28 (27.2)	2 (1.9)

AE, adverse event; pom-dex, pomalidomide/dexamethasone.

Efficacy

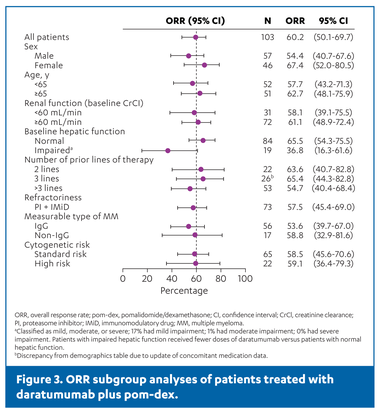
- ORR was 66% (95% confidence interval [CI], 55.5-75.4), including 12 (13%) sCRs and 9 (10%) complete responses (CRs; **Figure 2**)
  - Rate of very good partial response (VGPR) or better was 48%, and rate of CR or better was 22% (**Figure 2**)
- High response rates were maintained across clinically relevant patient subgroups, including double refractory and high cytogenetic risk patients (**Figure 3**)



ORR, overall response rate; pom-dex, pomalidomide/dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response.

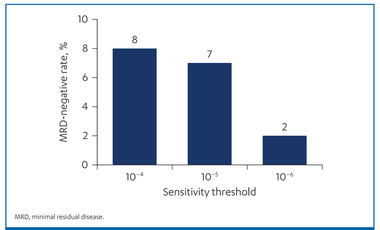
Figure 2. ORR in the response-evaluable population in patients treated with daratumumab plus pom-dex.

- Among responders, the median duration of response was 21.5 (95% CI, 13.6-not estimable) months
- In the total study population, MRD-negative rates were 8%, 7%, and 2% at sensitivity thresholds of 10^{-4}, 10^{-5}, and 10^{-6}, respectively (**Figure 4**)
- Median PFS was 9.9 (95% CI, 5.4-15.4) months, and the 24-month PFS rate was 30.8% (95% CI, 21.3-40.8; **Figure 5A**)
- Median OS was 25.1 (95% CI, 15.6-not estimable) months, and the estimated 24-month OS rate was 52.4% (95% CI, 41.9-61.8; **Figure 5B**)
- Patients with stable disease/minimal response derived a survival benefit with daratumumab plus pom-dex compared with those with progressive disease or who were not estimable (**Figure 6**)



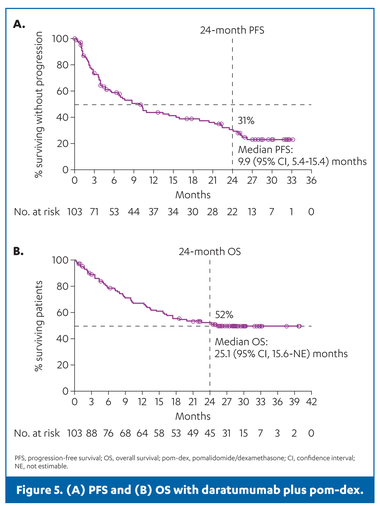
ORR, overall response rate; pom-dex, pomalidomide/dexamethasone; CI, confidence interval; CrCl, creatinine clearance; PI, proteasome inhibitor; IMID, immunomodulatory drug; MM, multiple myeloma.
[a]Classified as mild, moderate, or severe; 17% had mild impairment; 1% had moderate impairment; 0% had severe impairment. Patients with impaired hepatic function received fewer doses of daratumumab versus patients with normal hepatic function.
[b]Discrepancy from demographics table due to update of concomitant medication data.

Figure 3. ORR subgroup analyses of patients treated with daratumumab plus pom-dex.



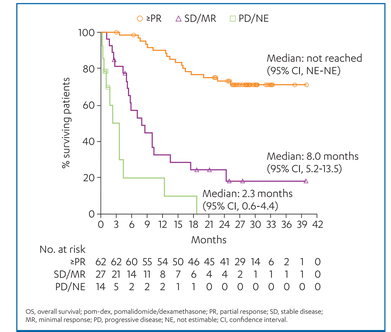
MRD, minimal residual disease.

Figure 4. MRD-negative rates.



PFS, progression-free survival; OS, overall survival; pom-dex, pomalidomide/dexamethasone; CI, confidence interval; NE, not estimable.

Figure 5. (A) PFS and (B) OS with daratumumab plus pom-dex.



OS, overall survival; pom-dex, pomalidomide/dexamethasone; PR, partial response; SD, stable disease; MR, minimal response; PD, progressive disease; NE, not estimable; CI, confidence interval.

Figure 6. OS by response category in patients treated with daratumumab plus pom-dex.

CONCLUSIONS

- **Adding daratumumab to pom-dex resulted in a safety profile consistent with that of the individual therapies, with the exception of higher rates of neutropenia**
- **Deep, durable responses were achieved, including MRD negativity, and the regimen was associated with encouraging OS in a heavily pretreated patient population**
  - **At a median follow-up of 28.1 months, ORR was 66%, including 13% with sCR; rates of VGPR or better and CR or better were 48% and 22%, respectively**
  - **MRD-negative rate was 7% at 10^{-5}**
  - **Median PFS was 9.9 months, and the 24-month PFS rate was 31%**
  - **Median OS was 25.1 months, and the 24-month OS rate was 52%**
- **Daratumumab plus pom-dex is approved in the United States for use in RRMM patients with ≥2 prior therapies, including lenalidomide and a PI[10]**
- **A phase 3 study evaluating daratumumab plus pom-dex versus pom-dex alone in RRMM patients is ongoing (APOLLO; NCT03180736)**

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DISCLOSURES

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