PF579

Daratumumab, Carfilzomib, and Dexamethasone (D-Kd) in Lenalidomide-refractory Patients With Relapsed Multiple Myeloma (MM): Subgroup Analysis of MMY1001

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INTRODUCTION

- Many recent phase 3 studies in relapsed or refractory multiple myeloma (RRMM) patients were lenalidomide (len)-based and excluded len-refractory patients[1]
  - The increasing adoption of len maintenance highlights a need for large studies in len-refractory RRMM patients[2]
  - Based on subgroup analyses, several regimens have demonstrated varying degrees of efficacy in len-refractory patients[3-7]
- Daratumumab (DARA) is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action[8-12]
- DARA is approved in many countries as a monotherapy for heavily pre-treated patients with RRMM and in combination with standard-of-care regimens in patients with RRMM who have received ≥1 prior therapy[13,14]
- Recently, DARA 16 mg/kg intravenously in combination with bortezomib, melphalan, and prednisone was approved for the treatment of patients with newly diagnosed multiple myeloma (MM) who are ineligible for autologous stem cell transplant (ASCT)[13]
- Carfilzomib (K) is a proteasome inhibitor (PI) approved for the treatment of RRMM patients[15]
  - In combination with dexamethasone, once-weekly dosing with K 70 mg/m^2 demonstrated superior efficacy and comparable safety to twice-weekly dosing of K 27 mg/m^2 in RRMM patients[16]
  - In newly diagnosed MM patients, DARA plus K/len/dexamethasone (KRd) was well tolerated and induced deep responses prior to elective ASCT[17]
- We examined the safety, pharmacokinetics, and efficacy of DARA in combination with K and dexamethasone (D-Kd) in len-refractory RRMM patients in MMY1001

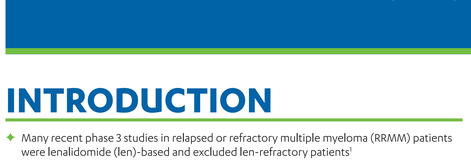
METHODS

Patients

- Key inclusion criteria were as follows:
  - K-naïve
  - Eastern Cooperative Oncology Group status ≤2
  - Measurable MM disease
  - 1 to 3 prior lines of therapy, including bortezomib and an immunomodulatory drug
    - Len-refractory patients were eligible
  - Disease progression after last therapy
  - Left ventricular ejection fraction (LVEF) ≥40%
  - Absolute neutrophil count ≥1.0 × 10^9/L
  - Creatinine clearance ≥20 mL/min/1.73 m^2
  - Bilirubin ≤2.0 mg/dL
  - Platelet count ≥75 × 10^9/L

Study Design and Treatment

- This was an open-label, nonrandomized, multicenter, phase 1b study of D-Kd for the treatment of patients with relapsed MM (**Figure 1**)



D-Kd, daratumumab/carfilzomib/dexamethasone; MM, multiple myeloma; IMiD, immunomodulatory drug; len, lenalidomide; K, carfilzomib; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; DARA, daratumumab; IV, intravenous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, oral; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; MRD, minimal residual disease; NGS, next-generation sequencing; PK, pharmacokinetic; CR, complete response; IFE, immunofixation; VGPR, very good partial response.
[a]In 500 mL dilution volume.
[b]Both 20 mg/m^2 and 70 mg/m^2 were administered as 30-minute IV infusions.
[c]Among patients evaluated for MRD, MRD was assessed using NGS at time of suspected CR and at 12 and 18 months after initial dose. In cases where DARA is suspected of interfering with IFE and preventing clinical CR response calls, subjects with VGPR may also be evaluated for MRD.

Figure 1. Study design: D-Kd in MMY1001.

- All patients were treated in 28-day cycles until disease progression
  - DARA (16 mg/kg intravenously) was administered weekly (Days 1, 8, 15, and 22) during Cycles 1 and 2, every 2 weeks (Days 1 and 15) during Cycles 3 to 6, and every 4 weeks thereafter
    - Ten patients received a single first dose of DARA (16 mg/kg) on Cycle 1 Day 1 (Cycle 1 was 29 days)
    - The remaining patients (n = 75) received a split first dose of DARA over 2 days: 8 mg/kg on Days 1 and 2 of Cycle 1
  - K was administered weekly on Days 1, 8, and 15 of each 28-day cycle
    - Patients received an initial dose of K 20 mg/m^2 on Cycle 1 Day 1 and escalated to K 70 mg/m^2 at Cycle 1 Day 8+, if deemed tolerable
  - Dexamethasone was administered at a dose of 40 mg per week in patients aged ≤75 years and at a dose of 20 mg per week in patients >75 years of age
    - During weeks when patients received DARA, dexamethasone 20 mg was administered before the infusion and the day after the infusion
    - During weeks when patients did not receive DARA, dexamethasone was administered as a single dose
- Pre-infusion medications included diphenhydramine 25 mg to 50 mg, paracetamol 650 mg to 1,000 mg, and montelukast 10 mg
  - Montelukast was required before the first dose and was optional for subsequent doses
  - Patients receiving a split first dose of DARA on Cycle 1 Day 2 also received diphenhydramine and paracetamol on this day
- Post-infusion medications included methylprednisolone ≤20 mg if dexamethasone was reduced to 20 mg/week due to toxicity and was given as pre-infusion medication prior to DARA

Minimal Residual Disease (MRD) Evaluation

- MRD was assessed at the time of suspected complete response (CR) and at 12 and 18 months following the first treatment dose
- MRD was assessed on bone marrow aspirate or whole blood samples that were ficolled and evaluated by the clonoSEQ™ assay V2.0 (Adaptive Biotechnologies, Seattle, WA) at sensitivity thresholds of 10^{-4} (1 cancer cell per 10,000 nucleated cells), 10^{-5}, and 10^{-6}

RESULTS

Patients and Treatment

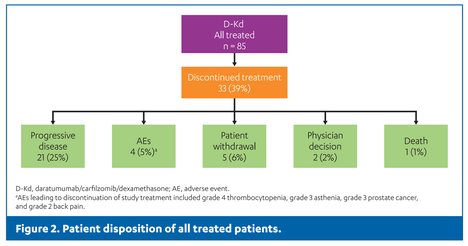
- A total of 85 patients were enrolled in the study, including 51 patients who were len-refractory (**Table 1**)
  - Two patients received 4 prior lines of therapy and were categorized as protocol deviations
  - Demographics and clinical characteristics of len-refractory patients were representative of all treated patients

Table 1. Baseline and Disease Characteristics

Characteristic	Len-refractory (n = 51)	All treated (n = 85)
Median (range) age, y	66 (38-85)	66 (38-85)
ECOG status, n (%)		
0-1	47 (92)	78 (92)
2	4 (8)	7 (8)
Prior lines of therapy, median (range)	2 (1-4)	2 (1-4)
Prior ASCT, n (%)	33 (65)	62 (73)
Prior bortezomib, n (%)	51 (100)	85 (100)
Prior IMiD, n (%)	51 (100)	85 (100)
Lenalidomide	51 (100)	81 (95)
Pomalidomide	9 (18)	13 (15)
Thalidomide	11 (22)	21 (25)
Prior PI + IMiD, n (%)	51 (100)	85 (100)
Refractory to, n (%)[a]		
Lenalidomide	51 (100)	51 (60)
Pomalidomide	9 (18)	11 (13)
Bortezomib	21 (41)	26 (31)
PI + IMiD	22 (43)	25 (29)

ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplant; IMiD, immunomodulatory drug; PI, proteasome inhibitor.
[a]Refractoriness was based on most recent prior medication.

- January 29, 2018 was the clinical cut-off date
- Median (range) follow-up for the overall population was 12.0 (0.5-23.2) months
  - Similar median follow-up (12.0 [0.5-22.8] months) was observed for the len-refractory population
  - 83 (98%) patients escalated to K 70 mg/m^2 within the first 2 cycles
- Patient disposition for all treated patients is summarized in **Figure 2**
  - Patient disposition for len-refractory patients was consistent with all treated patients

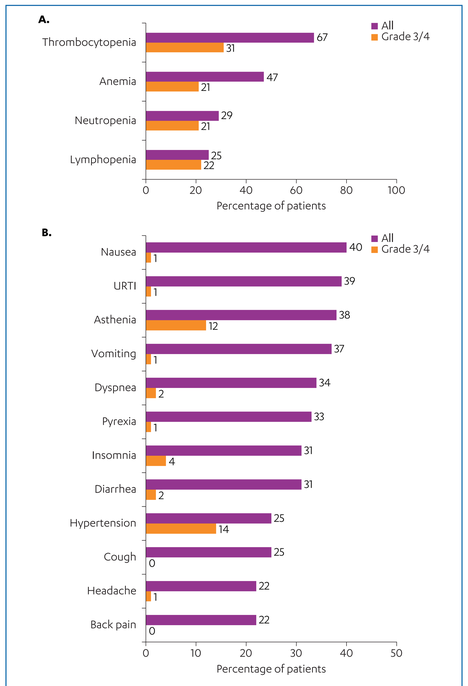


D-Kd, daratumumab/carfilzomib/dexamethasone; AE, adverse event.
[a]AEs leading to discontinuation of study treatment included grade 4 thrombocytopenia, grade 3 asthenia, grade 3 prostate cancer, and grade 2 back pain.

Figure 2. Patient disposition of all treated patients.

Adverse Events (AEs; All Treated)

- The most common (>20%) hematologic and nonhematologic treatment-emergent adverse events (TEAEs) reported among all treated patients are summarized in **Figure 3**
  - Thrombocytopenia was the most common TEAE (67% any grade; 31% grade 3/4)
  - Low neutropenia rates were observed with D-Kd (29% any grade; 21% grade 3/4)
  - Len-refractory patients treated with D-Kd demonstrated a similar safety profile to that of all treated patients



TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Figure 3. Most common (A) hematologic and (B) nonhematologic TEAEs in all treated patients.

Cardiac Function and TEAEs (All Treated)

- No notable change in median LVEF was observed from baseline over time (**Table 2**)
  - Diastolic dysfunction was not consistently assessed
- Median (range) onset time of cardiac TEAEs was 191 (1-583) days
- One grade 4 AE (left ventricular failure; not related to DARA) was resolved
- Grade 3 cardiac AEs were observed in 5 (6%) patients that resolved (systolic dysfunction [n = 2], cardiac failure, atrial fibrillation, and sinus tachycardia [n = 1 each])
- Unresolved grade 3 cardiac AEs were observed in 2 (2%) patients (congestive cardiomyopathy and left ventricular dysfunction [n = 1 each]; not related to DARA)
- K was interrupted/withdrawn for all grade 3/4 cardiac AEs except for 1 case where only DARA was interrupted (grade 3 sinus tachycardia)
  - Cardiac AEs improved in grade when K was interrupted

Table 2. Echocardiogram Assessment in All Treated Patients

Echocardiogram assessment time point	All treated patients LVEF, median (range)
Baseline (n = 84)	**64 (44-83)**
Cycle 6 (n = 53)	62 (46-77)
Cycle 12 (n = 36)	60 (50-76)
Cycle 18 (n = 8)	60 (52-74)
Cycle 24 (n = 3)	60 (53-66)

LVEF, left ventricular ejection fraction.

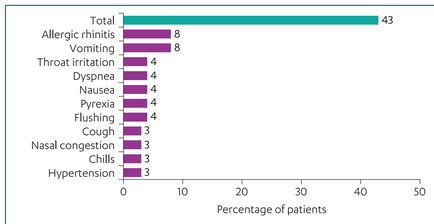
Infusion-related Reactions (IRRs) and Infusion Rates (All Treated)

- Median infusion time and IRR rates for single and split first infusion cohorts during the first infusion are summarized in **Table 3**
  - IRR rates and infusion times were consistent between single and split first dose for subsequent infusions
- The most common (>1 patient) IRRs for the split first dose cohort during all infusions are listed in **Figure 4**

Table 3. IRRs and Infusion Rates During Cycle 1 Day 1 and Cycle 1 Day 2 in All Treated Patients

	IRR, n (%)	Median (range) infusion time, hours
Single first infusion (n = 10)		
Cycle 1 Day 1	5 (50)	7.1 (6.5-8.9)
Split first infusion (n = 75)		
Cycle 1 Day 1	27 (36)	4.3 (3.9-10.6)
Cycle 1 Day 2	3 (4)	4.2 (3.9-8.6)

IRR, infusion-related reaction.

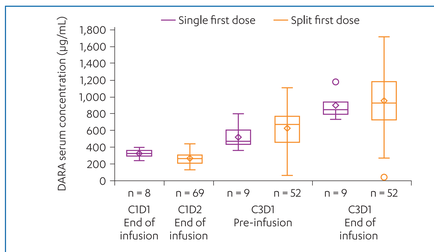


IRR, infusion-related reaction.

Figure 4. Most common (>1 patient) IRRs in the split first dose cohort during all infusions.

Pharmacokinetics

- Split and single first DARA dosing schedules demonstrated similar pharmacokinetic profiles based on DARA serum concentrations over time (**Figure 5**)



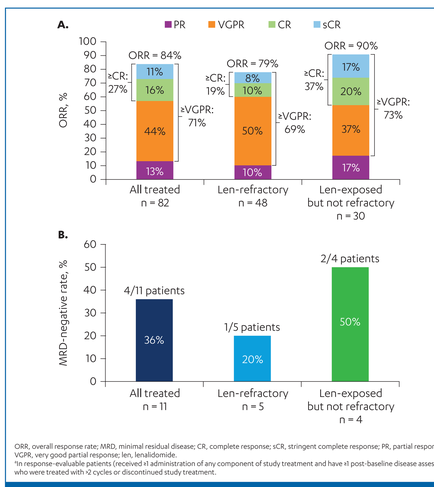
DARA, daratumumab; C, Cycle; D, Day.

Figure 5. DARA serum concentrations in split and single first dose cohorts among all treated patients.

Efficacy

Overall Response and MRD-negative Rates

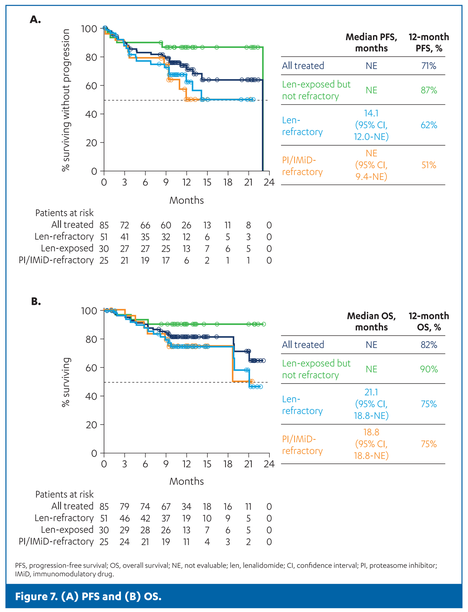
- Deep responses were observed with D-Kd in all treated, len-refractory, and len-exposed patients (**Figure 6A**)
- Optional MRD testing was conducted in 11 patients who achieved CR or stringent CR; 4 patients achieved MRD negativity at 10^{-5} (**Figure 6B**)



ORR, overall response rate; MRD, minimal residual disease; CR, complete response; sCR, stringent complete response; PR, partial response; VGPR, very good partial response; len, lenalidomide.
[a]In response-evaluable patients (received ≥1 administration of any component of study treatment and have ≥1 post-baseline disease assessment) who were treated with ≥2 cycles or discontinued study treatment.

Figure 6. (A) ORR[a] and (B) MRD-negative rates at 10^{-5} in MRD-tested patients who achieved CR/sCR.

- After a median follow-up of 12.0 months, the median progression-free survival (PFS) for all treated, len-exposed, and PI/IMiD-refractory patients was not reached, with median PFS for len-refractory patients being 14.1 months (**Figure 7A**)
- Median overall survival (OS) was not reached for all treated and len-exposed patients; median OS was 21.1 months and 18.8 months for len-refractory and PI/IMiD-refractory patients, respectively (**Figure 7B**)



PFS, progression-free survival; OS, overall survival; NE, not evaluable; len, lenalidomide; CI, confidence interval; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

Figure 7. (A) PFS and (B) OS.

CONCLUSIONS

- **D-Kd is safe and efficacious regardless of prior len exposure or refractoriness**
  - **D-Kd was well tolerated with low neutropenia rates**
  - **D-Kd induced deep and durable responses**
- **Median PFS was not reached with D-Kd for all treated patients with 12 months of median follow-up**
  - **14-month median PFS was encouraging for len-refractory patients**
- **Split first DARA dosing is feasible and may improve patient convenience for initial dosing**
- **Phase 3 randomized studies of D-Kd (CANDOR; NCT03158688) or pomalidomide plus dexamethasone (APOLLO; NCT03180736) for len-exposed RRMM patients are ongoing**

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DISCLOSURES

PM consulted for and received honoraria from Celgene, Takeda, and Janssen. JM-L consulted for Janssen and Celgene; and served on speakers bureaus for Janssen, Celgene, BMS, and Novartis. M-VM received honoraria from and consulted for Celgene, Janssen, Takeda, and Amgen. JB received honoraria from Janssen, Celgene, Amgen, and Takeda; received research funding from Janssen and Celgene; and received travel expenses from Janssen, Celgene, Amgen, and Takeda. SL consulted for Millennium, Celgene, Novartis, BMS, Janssen, Amgen, GSK, and Merck; and received research funding from Janssen, Millennium, and Celgene. LB consulted for and received honoraria from Takeda, Celgene, Amgen, and Janssen; and received travel expenses from Janssen, Celgene, and Amgen. AO consulted for and received honoraria from Amgen, Takeda, and consulted for AbbVie, Amgen, BMS, Celgene, Janssen, Karyopharm, SkylineDx, and Takeda. CdB, JW, and JMS are employees of Janssen. JS holds stock and/or stock options in J&J. AC consulted for Amgen, Array BioPharma, Celgene, Janssen, Millennium, Takeda, and Novartis; and received research funding from Amgen, Array BioPharma, Celgene, Janssen, Millennium, Takeda, Novartis, and Pharmacyclics. PR-O has no conflicts of interest to disclose.

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