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Daratumumab in Combination With Carfilzomib and Dexamethasone in Patients (Pts) With Relapsed Multiple Myeloma (MMY1001): An Open-label, Phase 1b Study

Sagar Lonial,[1,*] Jesus San-Miguel,[2] Joaquín Martinez-Lopez,[3] Maria-Victoria Mateos,[4] Joan Bladé,[5] Lotfi Benboubker,[6] Albert Oriol,[7] Bertrand Arnulf,[8] Ajai Chari,[9] Luis Pineiro,[10] Kaida Wu,[11] Jianping Wang,[12] Parul Doshi,[11] Jordan M. Schecter,[12] Philippe Moreau[13]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]Clínica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Pamplona, Spain; [3]Hospital-12-de-Octubre, Madrid, Spain; [4]University Hospital of Salamanca/IBSAL, Salamanca, Spain; [5]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; [6]Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; [7]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; [8]Hôpital Saint Louis, Paris, France; [9]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [10]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [11]Janssen Research & Development, LLC, Spring House, PA, USA; [12]Janssen Research & Development, LLC, Raritan, NJ, USA; [13]University Hospital Hôtel-Dieu, Nantes, France.

*Presenting author.

INTRODUCTION

- Daratumumab (DARA) is a human IgGκ monoclonal antibody targeting CD38 with direct on-tumor and immunomodulatory mechanisms of action[1-5]
- Based on the results of DARA monotherapy studies (GEN501 and SIRIUS)[6] and DARA combination therapy studies (POLLUX and CASTOR),[7,8] DARA is approved in the United States, European Union, and many other countries, as monotherapy in heavily pretreated relapsed or refractory (RR) multiple myeloma (MM) patients, and in combination with the standard of care regimens lenalidomide/dexamethasone (Rd) or bortezomib/dexamethasone (Vd) in patients who have received ≥1 prior therapy[9,10]
  - A pooled analysis of the DARA monotherapy studies, GEN501 and SIRIUS, identified an overall response rate (ORR) of 30.4% with a median overall survival of 20.5 months[11]
  - In POLLUX, with a median follow-up of 25.4 months, DARA in combination with Rd reduced the risk of disease progression or death by 59% versus Rd alone; median progression-free survival (PFS) was not reached with DARA in combination with Rd versus 17.5 months with Rd (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.31-0.53; P <0.0001)[12]
  - In CASTOR, with a median follow-up of 19.4 months, DARA in combination with Vd reduced the risk of disease progression or death by 69% versus Vd alone; median PFS was 16.7 versus 7.1 months (HR, 0.31; 95% CI, 0.24-0.39; P <0.0001), respectively[13]
- In the multi-arm MMY1001 study, with a median follow-up of 13.1 months, the ORR was 60.2% and the median overall survival was 17.5 months with DARA in combination with pomalidomide/dexamethasone (pom-dex)[14]
  - In the United States, DARA plus pom-dex is indicated for patients with ≥2 prior therapies, including lenalidomide and a proteasome inhibitor[9,14]
- Carfilzomib (20/27 mg/m^2 or 20/56 mg/m^2) is a proteasome inhibitor that is approved for the treatment of patients with RRMM[15]
  - As a single agent for patients who have received ≥1 line of therapy
  - In combination with dexamethasone (Kd) or with Rd (KRd) for patients who have received 1 to 3 lines of therapy
- Recent results from the ARROW phase 3 trial demonstrated superiority of the once weekly carfilzomib 70 mg/m^2 dose with dexamethasone compared with the twice weekly carfilzomib 27 mg/m^2 dose with dexamethasone[16]
- In newly diagnosed MM patients, the addition of DARA to the carfilzomib-based regimen KRd was well tolerated and highly effective[17]
  - The safety profile was consistent with DARA and KRd alone
  - ORR was 100% and deep responses (91% ≥very good partial response [VGPR] and 43% ≥complete response [CR]) were achieved after only 10.8 months of median follow-up
  - DARA did not adversely impact stem cell collection
- We hypothesized that the addition of DARA to Kd would provide additional clinical benefit for relapsed MM patients as well

OBJECTIVE

- The aim of this study was to determine the tolerability and efficacy of DARA in combination with Kd in patients with relapsed MM

METHODS

Patients

- Key inclusion criteria were as follows:
  - Carfilzomib-naïve
  - Eastern Cooperative Oncology Group status ≤2
  - Measurable MM disease
  - 1 to 3 prior lines of therapy, including bortezomib and an immunomodulatory drug
  - 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 DARA in combination with Kd for the treatment of patients with relapsed MM (**Figure 1**)

Eligibility/treatment	Dosing schedule (28-day cycles)	Endpoints
• Relapsed MM – 1-3 prior lines of therapy, including bortezomib and an IMiD • Carfilzomib-naïve • ECOG status ≤2 • LVEF ≥40% • ANC ≥1 × 10^9/L • Platelet count ≥75 × 10^9/L	**DARA:** • Single dose: 16 mg/kg QW on Cycles 1-2; Q2W on Cycles 3-6; and Q4W thereafter • Split dose: 8 mg/kg on Days 1-2 of Cycle 1, then 16 mg/kg QW thereafter during Cycle 1 and Cycle 2, Q2W on Cycles 3-6, and Q4W thereafter **Carfilzomib:** • 20 mg/m^2 Cycle 1 Day 1 • Escalated to 70 mg/m^2 Cycle 1 Day 8+; weekly (Days 1, 8, 15) **Dexamethasone:** 40 mg/week[a]	**Primary** • Safety, tolerability **Secondary** • ORR • Duration of CR • Duration of response • OS

DARA, daratumumab; Kd, carfilzomib and dexamethasone; MM, multiple myeloma; IMiD, immunomodulatory drug; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; ORR, overall response rate; CR, complete response; OS, overall survival; IV, intravenous; PO, oral; IRR, infusion-related reaction.
[a]20 mg if ≥75 years of age. On DARA dosing days, dexamethasone 20 mg IV was administered as premedication on infusion day and 20 mg PO the day after infusion; for DARA as a split first dose, dexamethasone 20 mg IV was administered as a premedication on Cycle 1 Day 1 and Cycle 1 Day 2; on Cycle 1 Day 3, administration of low-dose methylprednisolone (40 mg PO) was optional. On weeks when no DARA infusion was administered, dexamethasone was given as a single dose on Day 1; if dexamethasone was reduced to 20 mg, methylprednisolone (≤20 mg PO) was administered the day after DARA infusion to prevent delayed IRRs. Montelukast was required before first DARA dose and was optional for subsequent doses.

Figure 1. Study design: DARA plus Kd.

- All patients were treated in 28-day cycles until disease progression
  - DARA (16 mg/kg intravenous) 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 standard first DARA dose (16 mg/kg) on Cycle 1 Day 1 (Cycle 1 was 29 days)
    - Per protocol, the remaining patients received the first dose of DARA as a split dose over 2 days per protocol (8 mg/kg on Days 1 and 2 of Cycle 1) to collect safety data with split dosing
  - Carfilzomib was administered weekly on Days 1, 8, and 15 of each 28-day cycle as a 30-minute infusion
    - Patients received an initial dose of 20 mg/m^2 on Cycle 1 Day 1 and escalated to 70 mg/m^2 on 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 daratumumab 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 per 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 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}

Statistical Analyses and Assessments

- Patients who received ≥1 administration of study treatment were included in the safety and PFS analysis (N = 85)
- The primary endpoint was safety and tolerability of DARA in combination with Kd
- PFS was estimated using the Kaplan-Meier method and was based on all treated patients
- ORR was a secondary endpoint and was based on the response-evaluable population
  - Patients in the response-evaluable population had a confirmed diagnosis of MM and had measurable disease at the baseline or screening visit, received ≥1 study treatment, and had adequate post-baseline disease assessment
  - Response was assessed by a computerized algorithm,[18] based on International Myeloma Working Group Consensus Criteria
- The rate of MRD negativity was determined as the proportion of all treated patients with MRD-negative status at any time point following the first treatment dose
- Patients with positive, ambiguous, missing, or unevaluable MRD status were considered MRD positive

RESULTS

Patients and Treatments

- A total of 85 patients were enrolled in the study
  - Median (range) age was 66 (38-85) years, and the median (range) number of prior therapies received was 2 (1-4; **Table 1**)
    - Two patients received 4 prior lines of therapy and were categorized as protocol deviations
  - Other baseline patient characteristics and prior treatments received are summarized in **Table 1**

Table 1. Baseline Characteristics and Prior MM Therapies Received

Characteristic	DKd (N = 85)
Age, y	
Median (range)	66 (38-85)
≥75 y, n (%)	8 (9)
ECOG status, n (%)	
0	32 (38)
1	46 (54)
2	7 (8)
Prior lines of therapy, n (%)	
Median (range)	**2 (1-4)**
1	21 (25)
2	39 (46)
3	23 (27)
>3	2 (2)
Prior ASCT, n (%)	62 (73)
Prior PI, n (%)	84 (99)
Bortezomib	84 (99)
Ixazomib	7 (8)
Prior IMiD, n (%)	84 (99)
Lenalidomide	80 (94)
Pomalidomide	13 (15)
Thalidomide	21 (25)
Prior PI + IMiD, n (%)	83 (98)
Prior PI + IMiD + ALKY, n (%)	79 (93)
Refractory to, n (%)	
Lenalidomide	51 (60)
Pomalidomide	11 (13)
PI	27 (32)
PI + IMiD	25 (29)

MM, multiple myeloma; DKd, daratumumab/carfilzomib/dexamethasone; ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug; ALKY, alkylator.

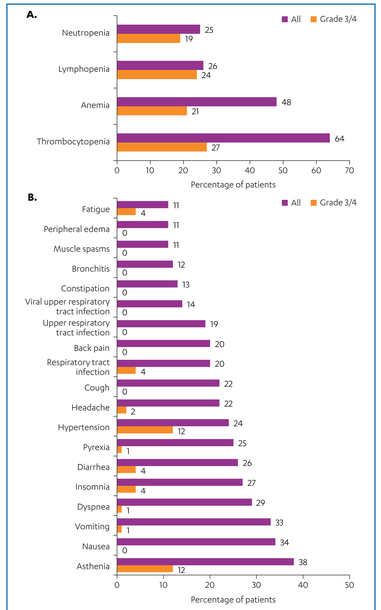
- The clinical cut-off date was October 12, 2017, with a median (range) follow-up of 8.5 (0.5-19.5) months
  - Patients received a median (range) of 9 (1.0-21.0) treatment cycles
- A total of 83 (98%) patients escalated to carfilzomib 70 mg/m^2 within the first 2 cycles

Patient Disposition

- Twenty-six (31%) patients discontinued study treatment
  - Eighteen (21%) patients discontinued treatment due to progressive disease; 3 (4%) due to adverse events; 3 (4%) due to patient withdrawal; 1 (1%) due to physician decision (this patient was also categorized under patient withdrawal); and 1 (1%) due to other

Adverse Events

- The most common hematologic treatment-emergent adverse event (TEAE) was thrombocytopenia, occurring in 54 (64%) patients (**Figure 2A**)
- Asthenia was the most common nonhematologic TEAE, occurring in 32 (38%) patients (**Figure 2B**)
- Grade 3/4 infections were observed in 15 (18%) patients
  - Pneumonia was the most common grade 3/4 infection (7%)



TEAE, treatment-emergent adverse event.

Figure 2. Most common (≥10%) (A) hematologic and (B) nonhematologic TEAEs.

- Serious adverse events (SAEs) were reported in 34 (40%) patients, with pneumonia (7 [8%] patients) being the most common SAE
  - Among patients with SAEs, 6 (7%) events were reasonably related to DARA, 13 (15%) to carfilzomib, and 11 (13%) to dexamethasone
- Eight (9%) patients discontinued treatment (any components) due to TEAEs
- One death due to TEAE occurred (general health deterioration related to disease progression) and was unrelated to any of the study treatments

Cardiac Function

- No notable change from baseline over time was observed for median LVEF (**Table 2**)
- A transient grade 3 cardiac adverse event (cardiac failure, atrial fibrillation, systolic dysfunction, and sinus tachycardia) was reported in 4 (5%) patients; 1 patient reported a grade 4 event (left ventricular failure) not related to DARA, which was resolved
- One (1%) patient reported grade 3 congestive cardiomyopathy not related to DARA, which remained unresolved

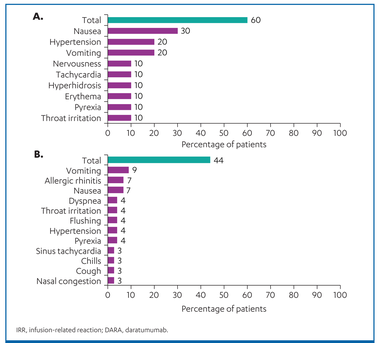
Table 2. Echocardiogram Assessment

Time point	LVEF, median (range)
Baseline (n = 84)	64 (44-83)
Cycle 3 (n = 55)	61 (25-80)
Cycle 6 (n = 52)	62 (46-77)
Cycle 9 (n = 31)	63 (48-80)
Cycle 12 (n = 16)	61 (50-76)

LVEF, left ventricular ejection fraction.

Infusion Times and Related Reactions

- Median (range) infusion time for the first split-dose infusion was 4.25 (3.9-10.6) hours on Cycle 1 Day 1 and 4.17 (3.9-8.6) hours on Cycle 1 Day 2
  - Median infusion durations were similar for the second (4.02 [3.2-9.6] hours) and subsequent (3.42 [2.3-5.9] hours) infusions
- Infusion-related reactions (IRRs) occurred in 6 (60%) patients who received the single-dose infusion and in 33 (44%) patients who received the split-dose infusion (**Figure 3**)
  - IRRs occurred primarily during the first infusion: 5 (50%) patients who received the single dose of DARA and 28 (37%) patients who received the split dose of DARA
  - IRRs occurred in 2 (20%) patients during the second infusion and in 1 (10%) patient during a subsequent infusion for those who received the single dose, and in 1 (1%) patient and 8 (11%) patients, respectively, who received the split-dose infusion

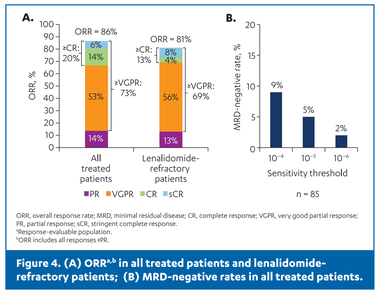


IRR, infusion-related reaction; DARA, daratumumab.

Figure 3. IRRs (any grade) in patients receiving (A) a single-dose infusion (all reported IRRs); (B) a split-dose infusion of DARA (in >1 patient).

Efficacy Results

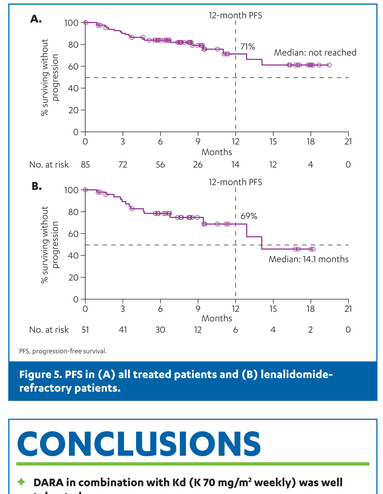
- The ORR was 86.4%, with 6.2% stringent CR, 13.6% CR, 53.1% VGPR, and 13.6% partial response (**Figure 4A**)
- The MRD-negative rate was:
  - 9% for 10^{-4} sensitivity threshold (**Figure 4B**)
  - 5% for 10^{-5} sensitivity threshold (**Figure 4B**)
  - 2% for 10^{-6} sensitivity threshold (**Figure 4B**)
- Similar response rates were observed in lenalidomide-refractory patients (**Figure 4A**)



ORR, overall response rate; MRD, minimal residual disease; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response.
[a]Response-evaluable population.
[b]ORR includes all responses ≥PR.

Figure 4. (A) ORR[a,b] in all treated patients and lenalidomide-refractory patients; (B) MRD-negative rates in all treated patients.

- Median duration of response was not reached (95% CI, 13.1 months-not estimable)
- Median PFS was not reached (95% CI, 12.9 months-not estimable; **Figure 5A**)
  - 12-month PFS rate was 71% (95% CI, 55-83)
- In lenalidomide-refractory patients, median PFS was 14.1 (95% CI, 9.4-not estimable) months (**Figure 5B**)
  - 12-month PFS rate was 69% (95% CI, 49-82)



PFS, progression-free survival.

Figure 5. PFS in (A) all treated patients and (B) lenalidomide-refractory patients.

CONCLUSIONS

- **DARA in combination with Kd (K 70 mg/m^2 weekly) was well tolerated**
  - **The safety profile is consistent with previous reports of DARA and Kd**
- **Split first dosing of DARA is feasible and may improve patient convenience**
- **Despite short follow-up, deep responses were achieved in RRMM patients who were previously treated with standard of care agents**
  - **With a median follow-up of only 8.5 months, DARA plus Kd was highly effective, with an 86% ORR, including 73% of patients with ≥VGPR and 20% of patients with ≥CR**
  - **MRD negativity was achieved by 5% of patients at 10^{-5} sensitivity**
  - **Based on experience with daratumumab plus standard of care regimens,[12,13] we anticipate the responses to continue to deepen with longer follow-up**
- **Deep responses were maintained in lenalidomide-refractory patients who demonstrated a median PFS of 14.1 months**
- **Phase 3 randomized studies of DARA in combination with Kd (CANDOR; NCT03158688) or pom-dex (APOLLO; NCT03180736) for patients with RRMM are ongoing**

REFERENCES

1. de Weers M, et al. *J Immunol.* 2011;186(3):1840-1848.
2. Overdijk MB, et al. *MAbs.* 2015;7(2):311-321.
3. Overdijk MB, et al. *J Immunol.* 2016;197(3):807-813.
4. Lammerts van Bueren J, et al. *Blood.* 2014;124(21):3474.
5. Krejcik J, et al. *Blood.* 2016;128(3):384-394.
6. Usmani SZ, et al. *Blood.* 2016;128(1):37-44.
7. Dimopoulos MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.
8. Palumbo A, et al. *N Engl J Med.* 2016;375(8):754-766.
9. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2017.
10. European Medicines Agency. Summary of opinion (post authorisation). Darzalex (daratumumab). 2017.
11. Usmani SZ, et al. Presented at: American Society of Hematology (ASH) Annual Meeting & Exposition; December 9-12, 2017; Atlanta, GA. Abstract 3107.
12. Bahlis NJ, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2017; Chicago, IL. Abstract 8025.
13. Weisel K, et al. Presented at: 22nd Congress of the European Hematology Association (EHA); June 22-25, 2017; Madrid, Spain. Abstract 1459.
14. Chari A, et al. *Blood.* 2017;130(10):974-981.
15. Kyprolis® (carfilzomib) [package insert]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc; 2015.
16. Amgen Press Release. https://www.amgen.com/media/news-releases/2017/10/phase-3-arrow-study-of-onceweekly-kyprolis-carfilzomib-regimen-meets-primary-endpoint-of-progression-free-survival-in-relapsed-and-refractory-multiple-myeloma-patients/. Accessed Nov 22, 2017.
17. Jakubowiak AJ, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2017; Chicago, IL. Abstract 8000.
18. Lonial S, et al. *Lancet Oncol.* 2016;387(10027):1551-1560.

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