The 7th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

Daratumumab SC + SOC in MM Across Lines of Therapy in Phase-2 PLEIADES: Initial Results for Daratumumab SC + Carfilzomib/Dexamethasone and Updated Results for Daratumumab SC + Bortezomib/Melphalan/Prednisone or Lenalidomide/Dexamethasone

Cyrille Touzeau[1], Ajai Chari[2], Mathias Hänel[3], Albert Oriol[4], Paula Rodriguez-Otero[5], Helen McCarthy[6], Kenshi Suzuki[7], Vania T. M. Hungria[8], Anna Sureda Balari[9], Lauriane Clement-Filliatre[10], Cyrille Hulin[11], Hila Magen[12], Shinsuke Iida[13], Vladimir Maisnar[14], Lionel Karlin[15], Luděk Pour[16], Philippe Moreau[1], Shiyi Yang[17], Michele Kosh[17], Maria Delioukina[17], Christoph Heuck[17], Hartmut Goldschmidt[18]

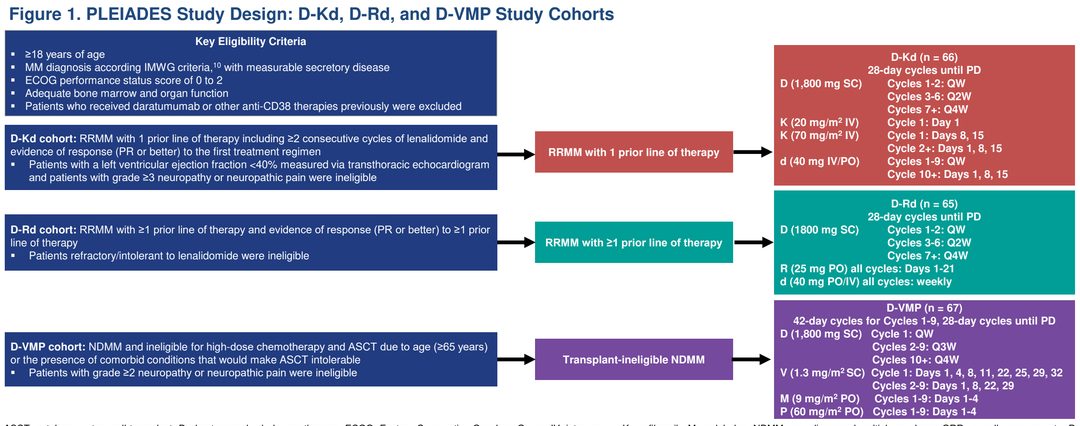
[1]Hematology, University Hospital Hôtel-Dieu, Nantes, France; [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Klinikum Chemnitz, Chemnitz, Germany; [4]Institut Català d'Oncologia i Institut Josep Carreras, Hospital Germans Trias i Pujol, Barcelona, Spain; [5]Clínica Universidad de Navarra, Pamplona, Spain; [6]Royal Bournemouth Hospital, Bournemouth, UK; [7]Japanese Red Cross Medical Center, Department of Hematology, Tokyo, Japan; [8]Clinica Medica São Germano, São Paulo, Brazil; [9]Hematology Department, Institut Català d'Oncologia - Hospitalet, IDIBELL, University of Barcelona, Barcelona, Spain; [10]Department of Hematology, CHRU Nancy Brabois, Vandoeuvre les Nancy, France; [11]Department of Hematology, Hôpital Haut Lévêque, University Hospital, Pessac, France; [12]Department of Hematology Chaim Sheba Medical Center, Ramat-Gan, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [13]Department of Hematology and Oncology, Nagoya City University Institute of Medical and Pharmaceutical Sciences, Nagoya, Japan; [14]4th Department of Medicine - Haematology, Charles University Hospital, Hradec Králové, Czech Republic; [15]Department of Hematology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France; [16]University Hospital Brno, Brno, Czech Republic; [17]Janssen Research & Development, LLC, Spring House, PA, USA; [18]University Clinic Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany.

INTRODUCTION

- Daratumumab (DARA, a human IgGκ CD38-targeting monoclonal antibody) intravenous (IV) is approved across multiple lines of therapy for multiple myeloma (MM), including patients with relapsed and/or refractory MM (RRMM) or newly diagnosed MM (NDMM)[1]
- A formulation of DARA for subcutaneous administration (DARA SC) was developed (1800 mg DARA co-formulated with recombinant human hyaluronidase PH20 [rHuPH20]; ENHANZE® drug delivery technology, Halozyme, Inc.) and approved by the FDA in 2020[2-4]
  - Advantages of DARA SC include reduced administration time and lower rates of infusion-related reactions (IRRs)
- In phase 3 clinical studies, DARA IV in combination with lenalidomide/dexamethasone (Rd) for RRMM (POLLUX), in combination with bortezomib/melphalan/prednisone (VMP) for transplant-ineligible (TIE) NDMM (ALCYONE), and in combination with carfilzomib/dexamethasone (Kd) for RRMM (CANDOR) reduced the risk of disease progression or death by ≥37%[5-7]
- The phase 2 PLEIADES study is evaluating the safety and efficacy of DARA SC combined with standard of care for MM, including DARA SC plus bortezomib/lenalidomide/dexamethasone (D-VRd) for transplant-eligible NDMM, D-Kd for RRMM, D-Rd for RRMM, and D-VMP for TIE NDMM[8,9]
  - In the primary analysis of D-VRd, D-Rd, and D-VMP cohorts in PLEIADES, D-VRd, D-Rd, and D-VMP demonstrated clinical activity and safety comparable to corresponding DARA IV regimens, with low rates of IRRs
- The primary analysis of the D-Kd cohort and updated data for the D-Rd and D-VMP cohorts of PLEIADES are reported here

METHODS

Figure 1. PLEIADES Study Design: D-Kd, D-Rd, and D-VMP Study Cohorts



ASCT, autologous stem cell transplant; D, daratumumab; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; K, carfilzomib; M, melphalan; NDMM, new diagnosed multiple myeloma; ORR, overall response rate; P, prednisone; PD, progressive disease; PO, orally; PR, partial response; QW, once weekly; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; SC, subcutaneous; V, bortezomib.

Endpoints and Statistical Analyses

- **Primary endpoint (for each cohort):** overall response rate (ORR)
- **Secondary endpoints included:** very good partial response (VGPR) or better rate, complete response (CR) or better rate, minimal residual disease (MRD)–negativity rate, and IRR rate
- Safety evaluations were performed throughout the study as measured by adverse events (AEs), laboratory test results, echocardiograms, vital sign measurements, physical examinations, SC injection-site assessments, and assessment of Eastern Cooperative Oncology Group performance status score
- Descriptive statistics were used to summarize data; the number of observations, mean, standard deviation, median, and range were used for continuous parameters, and frequency was summarized for discrete parameters
- Two-sided 90% Clopper–Pearson exact CIs are also presented for ORR, the rate of VGPR or better, the rate of CR or better, and MRD negativity

RESULTS

Patients

- Baseline demographics and clinical characteristics of patients in each cohort were consistent with studies evaluating corresponding DARA IV regimens in similar patient populations[5-7] (**Table 1**)

Patient Disposition and Drug Exposure

- Median duration of follow-up was 9.2 months for D-Kd (primary analysis), 25.7 months for D-Rd, and 25.2 months for D-VMP cohorts
- 38% of patients in the D-Kd, 37% of patients each in the D-Rd and D-VMP cohorts have discontinued treatment (**Table 2**). A summary of patient drug exposure is provided in **Table 3**
- The median duration of treatment administration of DARA SC was 5 minutes during the first, second, and all subsequent infusions across all cohorts

Table 1. Demographic and Baseline Clinical Characteristics[a]

	D-Kd (n=66) RRMM with 1 prior line of therapy	D-Rd (n=65) RRMM with ≥1 prior line of therapy	D-VMP (n=67) Transplant-ineligible NDMM
Age, years			
Median (range)	61 (42-84)	69 (33-82)	75 (66-86)
18 to <65, n (%)	39 (59)	22 (34)	0 (0)
65 to <75, n (%)	23 (35)	29 (45)	33 (49)
≥75, n (%)	4 (6)	14 (22)	34 (51)
Male, n (%)	34 (52)	45 (69)	31 (46)
Body weight, median (range), kg	74 (48-114)	81 (54-143)	66 (45-100)
Race, White, n (%)	48 (73)	45 (69)	46 (69)
ECOG PS score, n (%)			
0	40 (61)	36 (55)	25 (37)
1	23 (35)	29 (45)	38 (57)
2	3 (5)	0 (0)	4 (6)
ISS disease stage, n (%)[b]			
n	66	64	67
I	45 (68)	27 (42)	22 (33)
II	12 (18)	19 (30)	30 (45)
III	9 (14)	18 (28)	15 (22)
Time since initial diagnosis, median (range), months	32.3 (6.9-132.2)	35.0 (3.6-384.5)	1.2 (0.5-5.3)
Prior ASCT, n (%)	52 (79)	34 (52)	–
Prior lines of therapy, median (range)	1 (1-1)	1 (1-5)	–
Refractory to, n (%)			
Last prior line of therapy	41 (62)	20 (31)	–
PI and IMiD	9 (14)	1 (2)	–
Lenalidomide	41 (62)	–	–
Bone marrow % plasma cells, n (%)			
n	65	65	67
<10	21 (32)	15 (23)	3 (5)
10-30	23 (35)	28 (43)	31 (46)
>30	21 (32)	22 (34)	33 (49)
Cytogenetic profile[c]			
n	44	31	41
Standard risk, n (%)	28 (64)	20 (65)	33 (81)
High risk, n (%)	16 (36)	11 (36)	8 (20)
t(4;14)	9 (20)	6 (19)	2 (5)
t(14;16)	9 (20)	3 (10)	2 (5)
del17p	2 (5)	4 (13)	4 (10)

D-Kd, daratumumab subcutaneous plus carfilzomib/dexamethasone; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; RRMM, relapsed or refractory multiple myeloma; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem cell transplant; PI, proteasome inhibitor; IMiD, immunomodulatory drug. [a]All-treated population, defined as patients who received ≥1 dose of study treatment. [b]Based on the combination of serum β2-microglobulin and albumin. [c]Based on fluorescence in situ hybridization/karyotype testing.

Table 2. Patient Disposition Across All DARA SC Combination Therapy Cohorts[a]

	D-Kd (n=66) RRMM with 1 prior line of therapy	D-Rd (n=65) RRMM with ≥1 prior line of therapy	D-VMP (n=67) Transplant-ineligible NDMM
Patients who are still on treatment, n (%)	41 (62)	41 (63)	42 (63)
Patients who discontinued treatment, n (%)	25 (38)	24 (37)	25 (37)
Reason for discontinuation, n (%)			
Progressive disease	19 (29)	13 (20)	16 (24)
Patient withdrawal	2 (3)	2 (3)	2 (3)
Death	2 (3)	1 (2)	2 (3)
Adverse event	1 (2)	7 (11)	4 (6)
Other	1 (2)	0 (0)	0 (0)
Protocol deviation	0 (0)	1 (2)	0 (0)
Physician decision	0 (0)	0 (0)	1 (1)

DARA SC, daratumumab subcutaneous; D-Kd, daratumumab subcutaneous plus carfilzomib/dexamethasone; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma. [a]All-treated population, defined as patients who received ≥1 dose of study treatment

Table 3. Patient Drug Exposure With D-Kd, D-Rd, and D-VMP Therapies[a]

	D-Kd (n=66) RRMM with 1 prior line of therapy	D-Rd (n=65) RRMM with ≥1 prior line of therapy	D-VMP (n=67) Transplant-ineligible NDMM
Median (range) number of treatment cycles	9.0 (1-19)	27.0 (1-31)	23.0 (1-26)
Median (range) duration of treatment, months	8.3 (0-17)	25.6 (0-28)	24.9 (0-28)
Relative dose intensity, median %			
Daratumumab	100.0	100.0	100.0
Carfilzomib	95.2	–	–
Dexamethasone[b]	89.5	59.7	–
Lenalidomide	–	77.8	–
Bortezomib	–	–	95.2
Melphalan	–	–	97.5
Prednisone	–	–	98.0

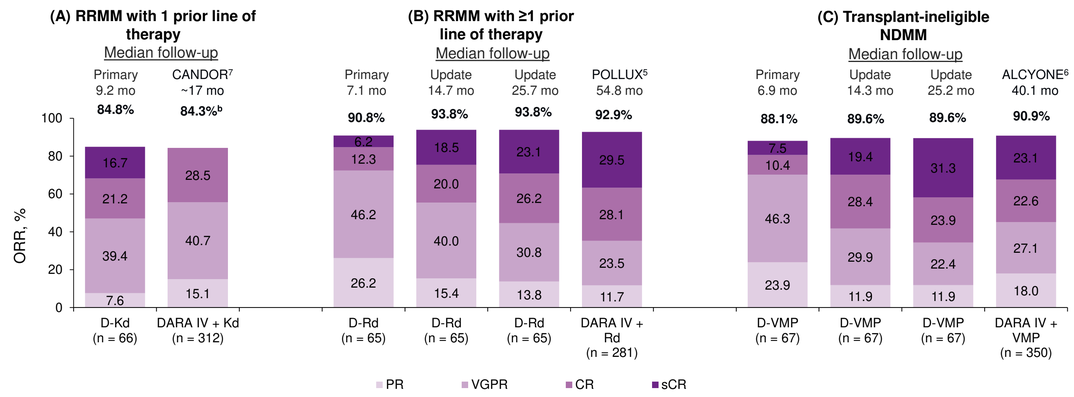
D-Kd, daratumumab subcutaneous plus carfilzomib/dexamethasone; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma. [a]All-treated population, defined as patients who received ≥1 dose of study treatment. [b]Dexamethasone dose intensity was affected by dose modifications due to the COVID-19 pandemic.

RESULTS (CONTD.)

Efficacy

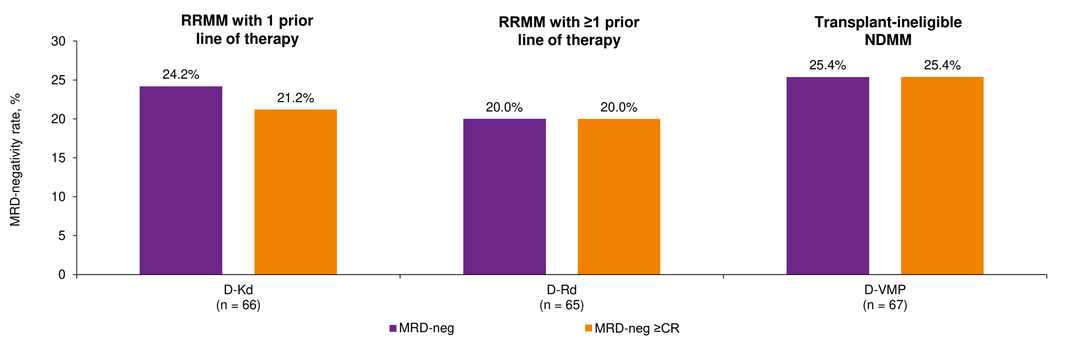
- The ORR in the D-Kd, D-Rd, and D-VMP cohorts remained consistent with DARA IV studies at the time of the efficacy and safety analysis (**Figure 2**)
- The primary ORR for D-Kd was 84.8% (90% CI, 75.7-91.5) and response rates were consistent with DARA IV plus Kd in CANDOR[7] (**Figure 2A**)
- Updated analysis of D-Rd cohort: ORR: 93.8% (90% CI, 86.5-97.9); response rates were consistent with DARA IV plus Rd in POLLUX[5] (**Figure 2B**)
- Updated analysis of D-VMP cohort: ORR: 89.6% (90% CI, 81.3-95.0), response rates were consistent with DARA IV plus VMP in ALCYONE[6] (**Figure 2C**)
- MRD-negative ≥CR rates were higher in the D-Kd cohort versus those reported in CANDOR (14%)[7]; MRD-negative rates in the D-Rd and D-VMP cohorts were lower compared with those reported in POLLUX (33%),[5] and ALCYONE (28%)[6] (**Figure 3**)

Figure 2. ORR (A) in D-Kd, (B) in D-Rd, and (C) D-VMP Cohorts: Comparison to DARA IV Studies[a]



CR, complete response; DARA IV, daratumumab intravenous; D-Kd, daratumumab subcutaneous plus carfilzomib/dexamethasone; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; Kd, carfilzomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PR, partial response; Rd, lenalidomide/dexamethasone; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response; VMP, bortezomib/melphalan/prednisone. [a]All-treated population, defined as patients who received ≥1 dose of study treatment. [b]In CANDOR, sCR could not be differentiated due to lack of kappa/lamda ratio by immunohistochemistry.

Figure 3. MRD-negative and MRD-negative ≥CR (10^{-5}) Rates[a,b,c] in D-Kd, D-Rd, and D-VMP Cohorts



CR, complete response; DARA IV, daratumumab intravenous; D-Kd, daratumumab subcutaneous plus carfilzomib/dexamethasone; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma [a]All-treated population, defined as patients who received ≥1 dose of study treatment. [b]MRD negativity was assessed by next-generation sequencing. [c]MRD-negative CR was defined by achievement of a CR and MRD negativity at any time during the study.

Safety (Table 4)

- DARA SC combination therapies were well-tolerated, and no new safety concerns were identified
- All patients in all treatment cohorts experienced ≥1 any-grade treatment-emergent AE (TEAE)
- Grade 3/4 TEAEs occurred in 71% of patients in the D-Kd cohort, 94% of patients in the D-Rd cohort, and 78% of patients in the D-VMP cohort
  - The most common grade 3/4 TEAE reported was hypertension in the D-Kd cohort, neutropenia in the D-Rd cohort, and thrombocytopenia in the D-VMP cohort.
  - Cardiac toxicities were infrequent (<5%) in all cohorts
- Serious TEAEs were reported in 27%, 55%, and 45% of patients in the D-Kd, D-Rd, and D-VMP cohorts, respectively
- Any-grade IRRs occurred in 6% (12/198) of patients across all cohorts
  - Most patients with IRRs experienced them on the first administration (D-Kd, 100%; D-Rd, 100%; D-VMP, 83%)
  - IRRs were mild (grade 1/2); only 2 patients in the D-Kd had a grade 3 IRR and no patients had a grade 4 IRR
- Median (range) time to onset of IRRs: 65 (4-75) minutes, 330 (254-330) minutes, and 411 (121-534) minutes in the D-Kd, D-Rd, and D-VMP cohorts, respectively
- Local injection-site reactions occurred in 6% (11/198) of patients across all cohorts (grade 1/2)

Table 4. Summary of TEAEs across All DARA SC Combination Therapy Cohorts[a]

	D-Kd (n=66) RRMM with 1 prior line of therapy	D-Rd (n=65) RRMM with ≥1 prior line of therapy	D-VMP (n=67) Transplant-ineligible NDMM
Any-grade TEAE, n (%)	66 (100)	65 (100)	67 (100)
Grade 3/4 TEAE, n (%)	47 (71)	61 (94)	52 (78)
Most common (≥5% in any cohort)			
Hypertension	14 (21)	8 (12)	6 (9)
Thrombocytopenia	13 (20)	9 (14)	30 (45)
Lymphopenia	8 (12)	7 (11)	15 (22)
Anemia	7 (11)	6 (9)	13 (19)
Neutropenia	7 (11)	36 (55)	25 (37)
Insomnia	4 (6)	3 (5)	2 (3)
Pneumonia	2 (3)	10 (15)	5 (7)
Leukopenia	2 (3)	6 (9)	4 (6)
Hyperglycemia	1 (2)	6 (9)	1 (1)
Hypokalemia	0	4 (6)	2 (3)
Diarrhea	0	4 (6)	2 (3)
Lower respiratory tract infection	0	4 (6)	0
Grade 5 TEAEs, n (%)	2 (3)	2 (3)	3 (4)
Serious TEAEs, n (%)	18 (27)	36 (55)	30 (45)
TEAEs leading to treatment discontinuation, n (%)[b]	1 (2)	6 (9)	4 (6)
Any-grade IRR, n (%)	3 (5)	3 (5)	6 (9)

D-Kd, daratumumab subcutaneous plus carfilzomib/dexamethasone; D-Rd, daratumumab subcutaneous plus lenalidomide/dexamethasone; D-VMP, daratumumab subcutaneous plus bortezomib/melphalan/prednisone; IRR, infusion-related reaction; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma; SC, subcutaneous; TEAEs, treatment-emergent adverse events. [a]All-treated population, defined as patients who received ≥1 dose of study treatment. [b]D-Kd cohort: fatigue (n=1); D-Rd cohort: pneumonia (n=2), diverticulitis (n=1), Enterobacter infection (n=1), myocardial infarction (n=1), and face edema (n=1); D-VMP cohort: neutropenic sepsis (n=1), hepatic neoplasm (n=1), cognitive disorder (n=1), and pneumonitis (n=1).

CONCLUSIONS

- The primary analysis of the D-Kd cohort compared favorably with DARA IV plus Kd in CANDOR[7]
  - The D-Kd cohort demonstrated higher rates of ≥CR and MRD negativity with decreased rates of serious TEAEs, grade 5 TEAEs, and TEAEs leading to discontinuation compared to DARA IV plus Kd[7]
- With extended follow-up in the D-Rd and D-VMP cohorts, clinical activity was comparable to corresponding DARA IV–containing regimens at half the median follow-up[5,6]
  - The D-VMP cohort demonstrated higher rates of ≥CR compared to DARA IV plus VMP[5]
- The rates of IRRs and injection-site reactions were comparable to those observed with DARA SC monotherapy in the COLUMBA study[11]
- Overall, these results provide additional support for the use of DARA SC 1,800 mg flat dose in combination with standard treatment regimens across lines of therapy in MM

References

1. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc. 2020. **2.** Usmani SZ, et al. *Blood.* 2019;134(8):668-677. **3.** San-Miguel J, et al. *Haematologica.* April 30, 2020; doi: 10.3324/haematol.2019.243790. Epub ahead of print. **4.** DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use [package insert]. Horsham, PA: Janssen Biotech, Inc; 2020. **5.** Kaufman JL, et al. Presented at: 61st American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2019; Orlando, FL. Abstract 1866. **6.** Mateos MV, et al. *Lancet.* 2020;395(10218):132-141. **7.** Dimopoulos M, et al. *Lancet.* 2020;396(10245):186-197. **8.** Chari A, et al. *Clin Lymphoma Myeloma Leuk.* 2019;19(10):e16-e17. **9.** Chari A, et al. *Clin Lymphoma Myeloma Leuk.* 2019;19:e144. **10.** Rajkumar SV, et al. Lancet Oncol. 2014;15(12):e538-e548. **11.** Mateos MV, et al. *Lancet Haematol.* 2020;7(5):e370-e380.

Acknowledgments

The authors would like to acknowledge the patients participating in this study and their families, the staff members at the study sites, the data and safety monitoring committees, and the staff members who were involved in data collection and analyses. Medical writing and editorial support were provided by Grace Wang, PharmD, of MedErgy, and was funded by Janssen Global Services, LLC.

https://comylive.cme-congresses.com/

This poster was supported by Janssen Global Services, LLC

Previously presented at the 62nd American Society of Hematology (ASH) Annual Meeting & Exposition 2020. Poster #1380.

Presented at the *7th World Congress on Controversies in Multiple Myeloma (COMy) E-Conference, May 07-09, 2021;* Poster #18