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

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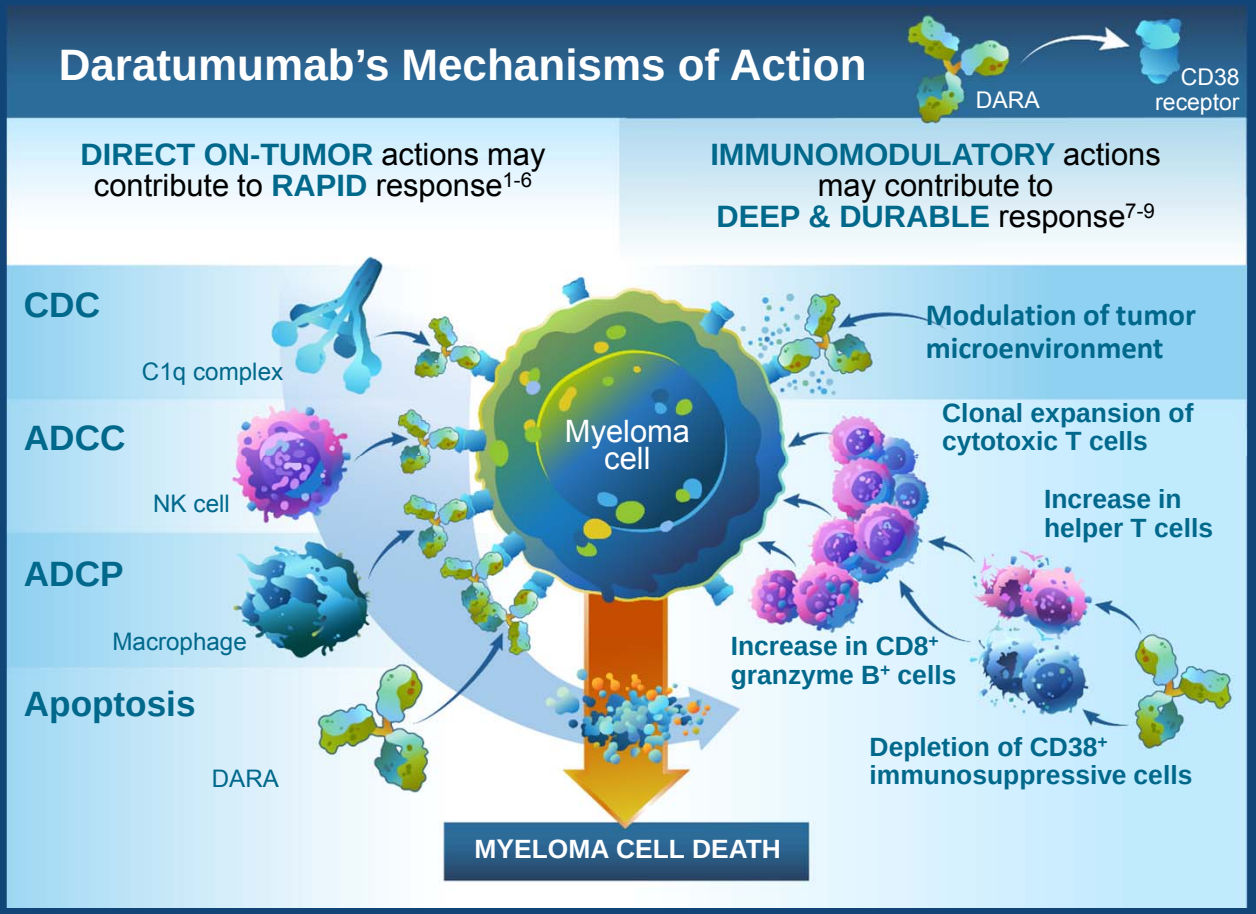
*ClinicalTrials.gov Identifier: NCT01998971.



- Daratumumab (DARA)
  - Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action
- Approved
  - As **monotherapy** and in **combination** with SOC regimens in RRMM in many countries
  - In **combination** with bortezomib, melphalan, and prednisone in non-transplant NDMM (USA and Brazil)
- Efficacy
  - DARA-based combinations significantly reduce risk of progression or death (by ≥50%) and induce rapid, deep, and durable responses in RRMM and NDMM[10-12]

1. DARZALEX US PI; 2018. 2. Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. 3. Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. 4. Overdijk MB, et al. *mABs*. 2015;7(2):311-321. 5. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. *Blood*. 2012;120:73. 7. Krejcik J, et al. *Blood*. 2016;128(3):384-394. 8. Adams H, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. 9. Chiu C, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. 10. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 11. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 12. Mateos MV, et al. *N Engl J Med*. 2018;378:518-528.

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; SOC, standard of care; RRMM, relapsed or refractory multiple myeloma; NDMM, newly diagnosed multiple myeloma.

Background: Len-refractory RRMM

- Many recent phase 3 RRMM studies were len-based and excluded len-refractory patients[1]
- The increasing adoption of len maintenance highlights a need for large studies in len-refractory RRMM[2]

Available Efficacy Data on Len-refractory RRMM Patients

Trial/Regimen	Analysis set	N	PFS	ORR	MRD neg. rate at 10^{-5}
CASTOR[3] D-Vd vs Vd	Len-refractory at last prior line of therapy	D-Vd: n = 45 Vd: n = 60	Median: **9.3 months vs 4.4 months** HR: 0.36; 95% CI, 0.21-0.63; *P* = 0.0002 18-mo PFS rate: 34% vs 2%	**81% vs 50%** *P* = 0.0021	**9% vs 0%** *P* = 0.0082
MMY1001[4] D-Pd	All treated (89% len-refractory)	n = 103	Median: **9.9 months** 24-month PFS rate: 31%	**66%**	**7%**
ENDEAVOR[5,6] Kd vs Vd	Len-refractory	Kd: n = 113 Vd: n = 122	Median**: 8.6 month vs 6.6 months**[5] HR: 0.80; 95% CI, 0.57-1.11[6]	N/R	N/R
MM-003[7] P-low d vs high d	Len-refractory	P-low d: n = 286 High d: n = 141	Median**: 3.9 months vs 1.9 months** HR: 0.50; 95% CI, 0.40-0.62; *P* <0.0001	**30% vs 9%** *P* <0.0001	N/R

Addition of DARA to SOC is effective in len-refractory RRMM

1. Harousseau JL, Attal M. *Blood.* 2017;130:963-973. 2. Sengsayadeth S, et al. *Blood Cancer J.* 2017;7(3):e545. 3. Lentzsch S, et al. Oral presentation at: Japanese Society of Hematology 79th Annual Meeting; October 20-22, 2017; Tokyo, Japan; Abstract OS3-12D-2. 4. Facon T, et al. Poster presented at ASH; December 9-12, 2017; Atlanta, GA; Abstract 1824. 5. Moreau P, et al. *Leukemia.* 2017;31:115-122. 6. Dimopoulos MA, et al. *Lancet Oncol.* 2016; 17(1):27-38. 7. San-Miguel J, et al. *Lancet Oncol.* 2013;14(11):1055-1066.

len, lenalidomide; D-Vd, daratumumab/bortezomid/dexamethasone; Vd, bortezomib/dexamethasone; PFS, progression-free survival; ORR, overall response rate; MRD, minimal residual disease; HR, hazard ratio; CI, confidence interval; Pd, pomalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; N/R, not reported; P, pomalidomide; d, dexamethasone.

Combining DARA With Carfilzomib

- Carfilzomib (K) is a PI approved for the treatment of RRMM patients[1]
  - In combination with dexamethasone, once-weekly dosing with K 20/70 mg/m^2 demonstrated superior efficacy and comparable safety to twice weekly dosing of K 20/27 mg/m^2 in RRMM[2]
- DARA plus SOC in RRMM and NDMM[3-7]
  - No new safety signals with triplet or quadruplet DARA-containing regimens, with excellent tolerability
  - Provides rationale for adding DARA to Kd for len-refractory patients
- In NDMM, DARA plus KRd was well tolerated and induced deep responses prior to elective ASCT[8]

Objective: Determine the safety, PK, and efficacy of DARA plus Kd in RRMM, including len-refractory patients

1. KYPROLIS® (carfilzomib) [package insert]. Thousand Oaks, CA: Onyx Pharmaceuticals, Inc; 2017. 2. Mateos MV, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 1-5, 2018; Chicago, IL; Abstract 8000. 3. Facon T, et al. Poster presented at ASH; December 9-12, 2017; Atlanta, GA; Abstract 1824. 4. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. 5. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14): 1319-1331. 6. Mateos MV, et al. *N Engl J Med*. 2018;378:518-528. 7. Mateos MV, et al. Presented at: 20th Congress of the European Hematology Association (EHA); June 11-14, 2015; Vienna, Austria; Abstract P275. 8. Jakubowiak AJ, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2017; Chicago, IL; Abstract 8000.

KRd, carfilzomib/lenalidomide/dexamethasone; PI, proteasome inhibitor; PK, pharmacokinetic; ASCT, autologous stem cell transplant.

Study Design: D-Kd Arm of MMY1001

- Open-label, non-randomized, multicenter, phase 1b study in RRMM patients
- Per protocol, DARA was administered as a **single first dose (n = 10)** or as a **split first dose (n = 75)**

Eligibility/treatment

- Relapsed MM
  - 1-3 prior lines of therapy, including bortezomib and an IMiD
  - Len-refractory patients allowed
- Carfilzomib-naïve
- ECOG status ≤2
- LVEF ≥40%
- ANC ≥1 × 10^9/L
- Platelet count ≥75 × 10^9/L

Dosing schedule (28-day cycles)

DARA:

- Split first dose[a]: 8 mg/kg Days 1-2 of Cycle 1
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

Carfilzomib[b]:

- 20 mg/m^2 IV Cycle 1 Day 1
- Escalated to 70 mg/m^2 Cycle 1 Day 8+; weekly (Days 1, 8, 15) until PD

Dexamethasone:

- 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR
- OS

Exploratory

- PFS
- MRD (NGS)[c]
- PK

[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.

D-Kd, daratumumab/carfilzomib/dexamethasone; IMiD, immunomodulatory drug; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ANC, absolute neutrophil count; IV, intravenous; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, oral; OS, overall survival; NGS, next-generation sequencing; IFE, immunofixation; CR, complete response; VGPR, very good partial response.

Baseline Characteristics and Prior Therapies

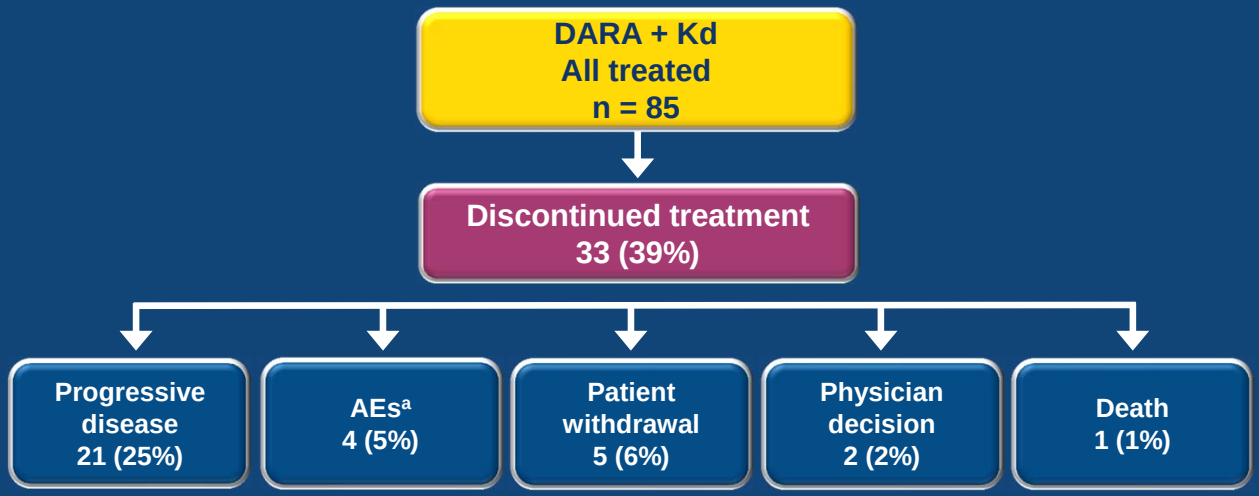
Characteristic	Len-refractory (n = 51)	All treated (n = 85)
Median (range) age, y	66 (38-85)	66 (38-85)
ECOG status, n (%)		
0-1	47 (92)	78 (92)
2	4 (8)	7 (8)
Prior lines of therapy, n (%)		
Median (range)	2 (1-4)	2 (1-4)
Prior ASCT, n (%)	33 (65)	62 (73)
Prior bortezomib, n (%)	51 (100)	85 (100)
Prior 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)

Demographics of len-refractory cohort are representative of the overall population

[a]Refractoriness was based on their most recent prior medication.

Patient Disposition

- Median (range) follow-up for overall population: 12.0 (0.5-23.2) months
  - Similar median follow-up (12.0 [0.5-22.8] months) observed for len-refractory population
- 83 (98%) patients escalated to carfilzomib 70 mg/m^2 within the first 2 cycles



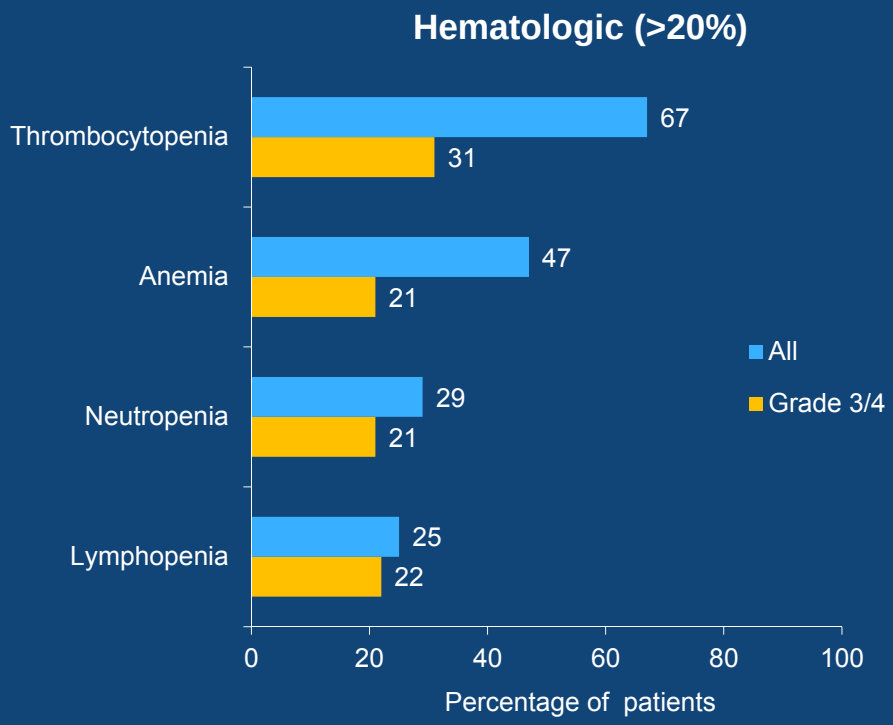
- Patient disposition for len-refractory patients was consistent with all-treated patients

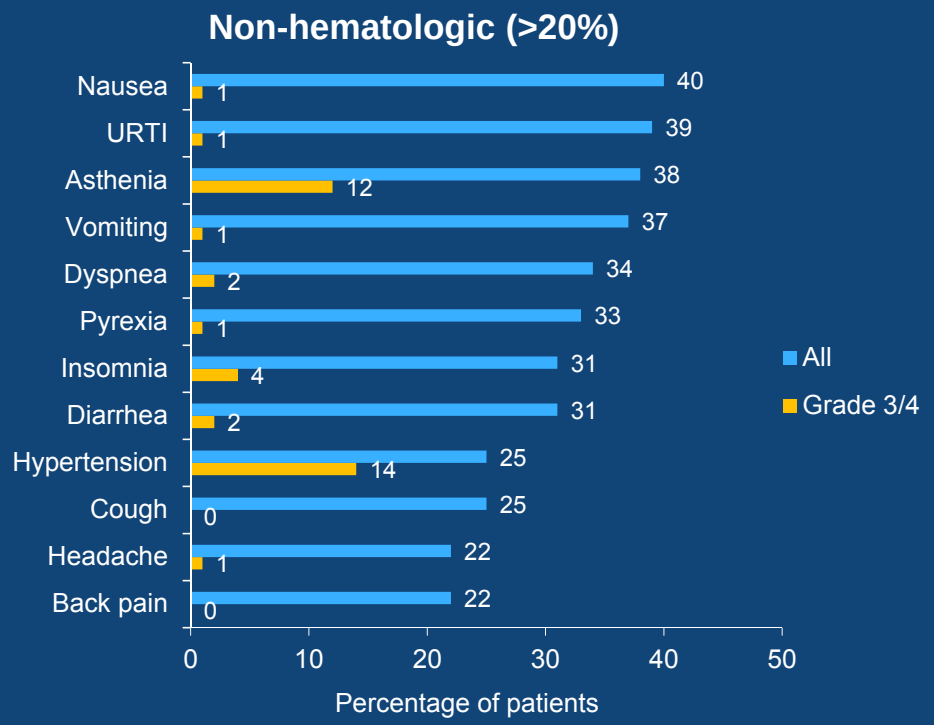
[a]AEs leading to discontinuation of study treatment included G4 thrombocytopenia, G3 asthenia, G3 prostate cancer, and G2 back pain.

Clinical cut-off date: January 29th, 2018

AE, adverse event; G, grade.

Most Common TEAEs (All Treated)





- **Low neutropenia rates with D-Kd in RRMM**
- **Similar safety profile observed for len-refractory patients**

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

Cardiac Function and TEAEs (All Treated)

Cardiac function

- No notable change from baseline over time in median LVEF[a]

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)

[a]Diastolic dysfunction not consistently assessed.

Cardiac TEAEs

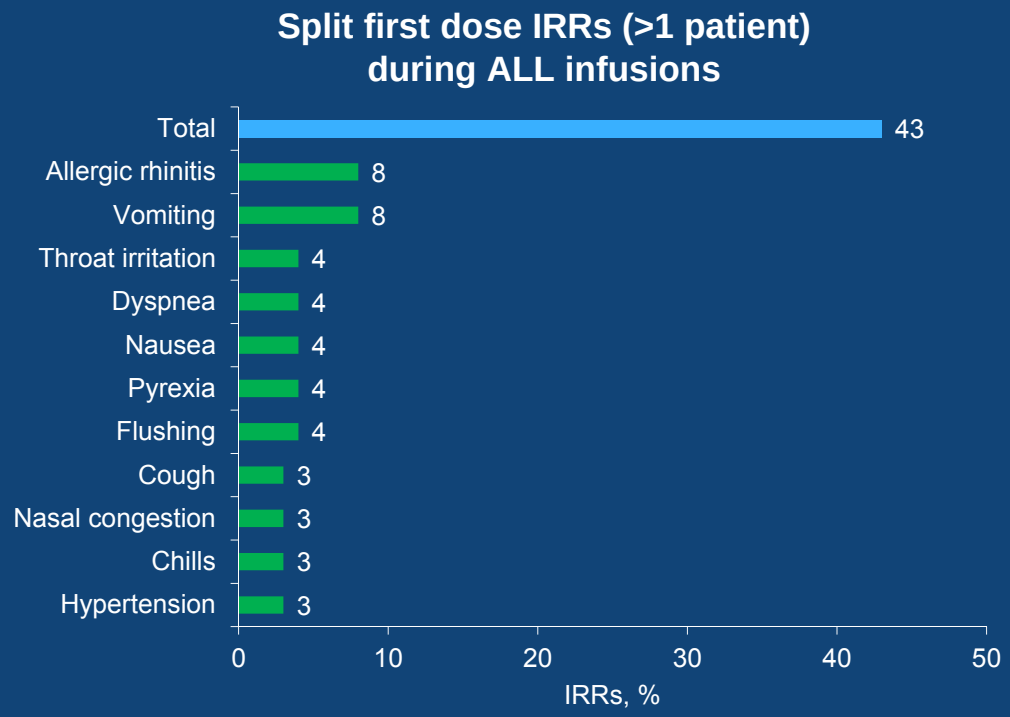
- Median (range) onset time: 191 (1-583) days
- One patient had a G4 AE (left ventricular failure; not related to DARA) that resolved
- Five (6%) patients had G3 cardiac AEs that resolved (systolic dysfunction [n = 2], cardiac failure, atrial fibrillation, and sinus tachycardia [n = 1 each])
- Two (2%) patients had unresolved G3 cardiac AEs (congestive cardiomyopathy and left ventricular dysfunction; not related to DARA)
- K was interrupted/withdrawn for all G3/4 cardiac AEs except for 1 case where only DARA was interrupted (G3 sinus tachycardia)
  - Cardiac AEs improved in grade when K was interrupted

Median LVEF remained stable with manageable cardiac toxicities

Infusion Rates and IRRs: Split First Dose DARA (All Treated)

	IRR, n (%)	Median (range) infusion time
Single first infusion (n = 10)		
Cycle 1 Day 1	5 (50.0%)	7.1 (6.5-8.9) h
Split first infusion (n = 75)		
Cycle 1 Day 1	27 (36.0%)	4.3 (3.9-10.6) h
Cycle 1 Day 2	3 (4.0%)	4.2 (3.9-8.6) h

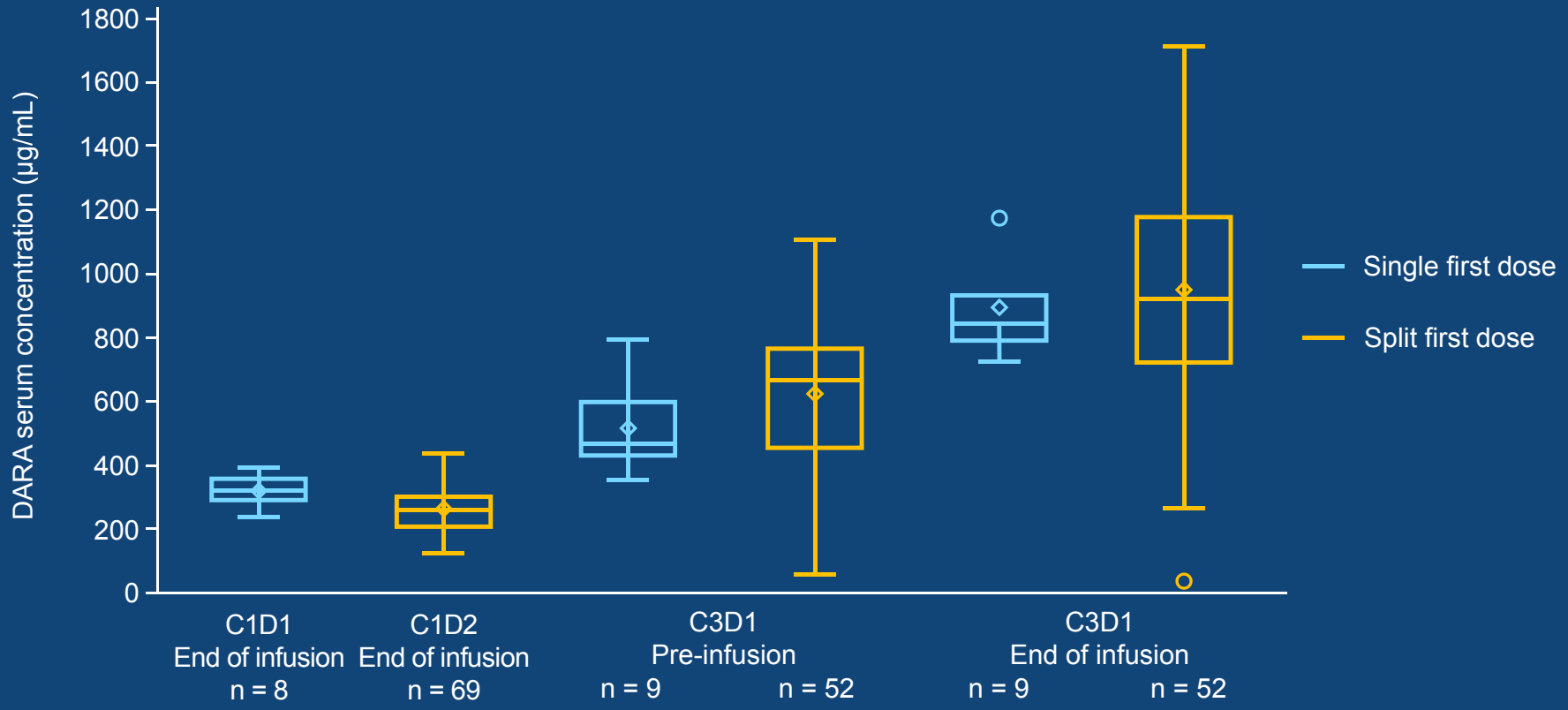
- IRR percentages and infusion times were consistent between single and split first dose for subsequent infusions



Split first dose of DARA is feasible and improves patient convenience

IRR, infusion-related reaction.

DARA PK: Single Versus Split First Dose (All Treated)

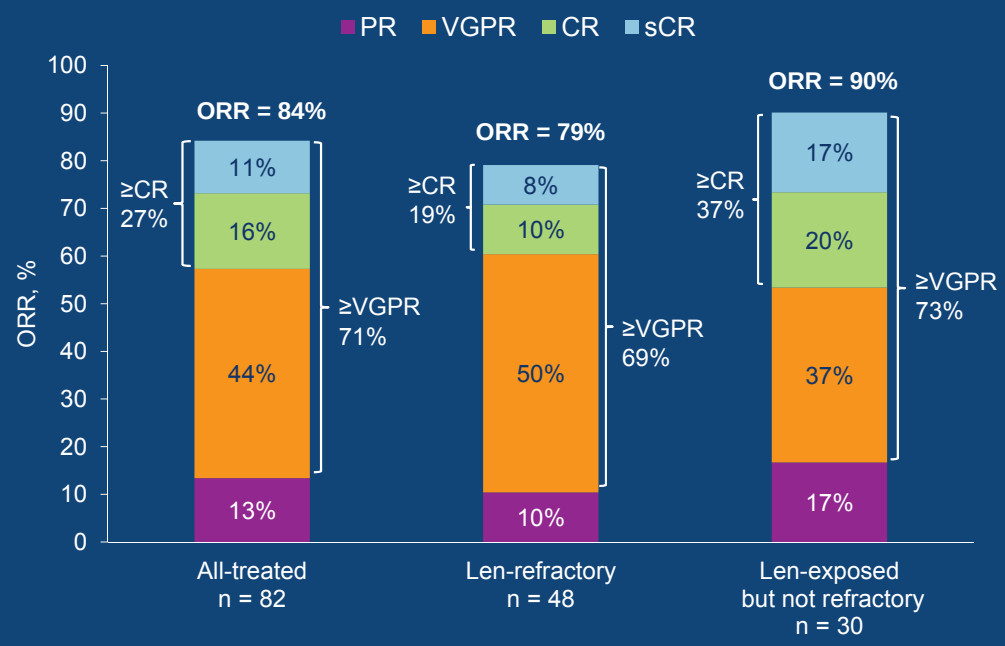


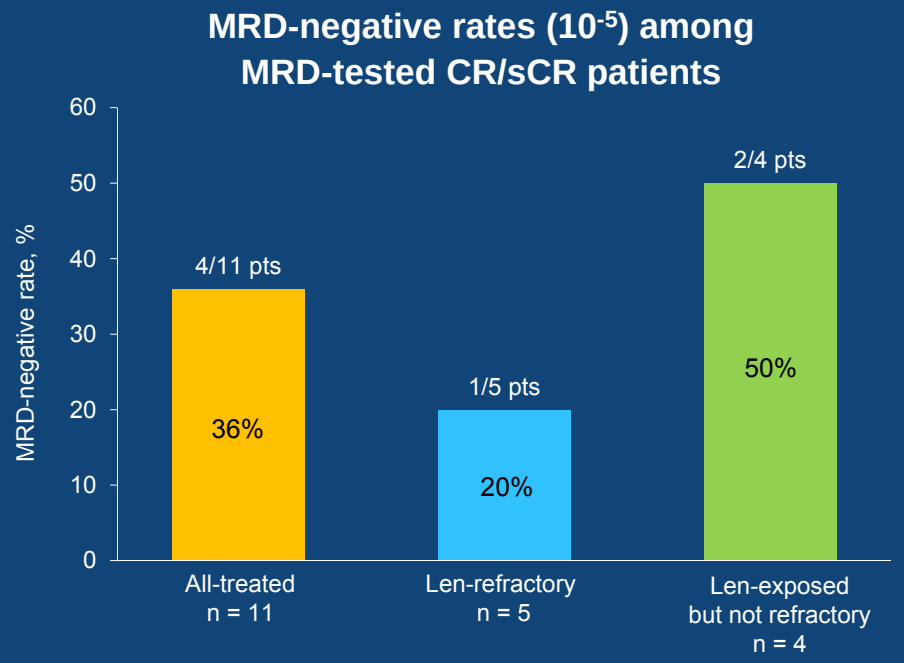
Split and single first DARA dosing have similar PK profiles

Note: diamonds represent the mean values.

Overall Response[a] and Confirmed MRD-negative Rates

- Median follow-up: 12.0 months
- Optional MRD testing in 11 patients with CR/sCR; 4 were MRD negative at 10^{-5}





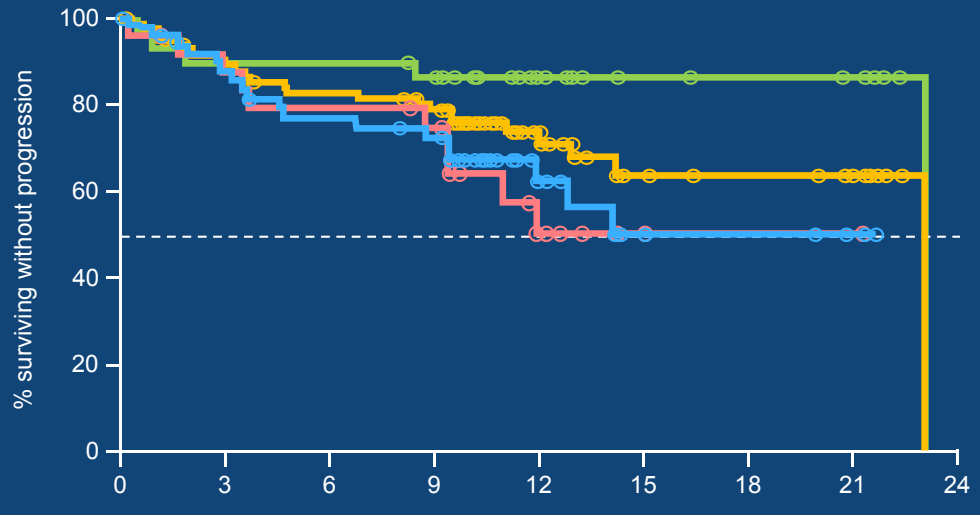
Responses are anticipated to deepen over longer follow-up

PR, partial response; sCR, stringent complete response.
[a]In response-evaluable patients (received at least 1 administration of any component of study treatment and have at least 1 post baseline disease assessment) who were treated more than 2 cycles or discontinued study treatment.

Progression-free Survival Across Subgroups

- Median follow-up: 12.0 months

	Median PFS, mo	12-month PFS, %
All-treated	NE	71%
Len-exposed but not refractory	NE	87%
Len-refractory	14.1 (95% CI, 12.0-NE)	62%
PI/IMiD-refractory	NE (95% CI, 9.4-NE)	51%



No. at risk									
All-treated	85	72	66	60	26	13	11	8	0
Len-refractory	51	41	35	32	12	6	5	3	0
Len-exposed	30	27	27	25	13	7	6	5	0
PI/IMiD-refractory	25	21	19	17	6	2	1	1	0

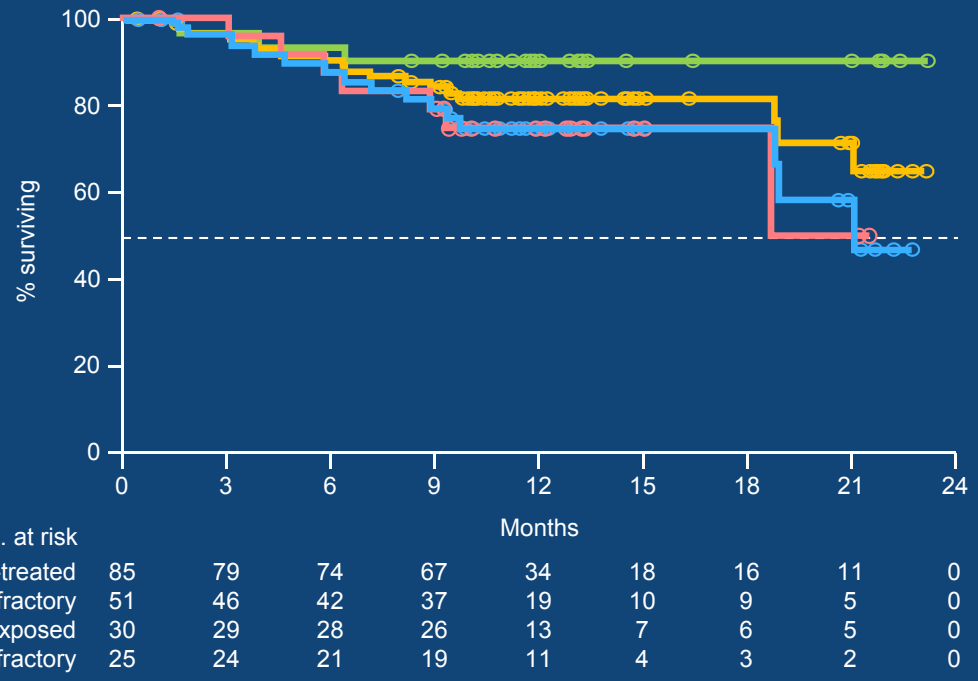
Encouraging PFS observed in lenalidomide- and PI/IMiD-refractory patients

NE, not estimable.

Overall Survival Across Subgroups

- Median follow-up: 12.0 months

	Median OS, mo	12-month OS, %
All-treated	NE	82%
Len-exposed but not refractory	NE	90%
Len-refractory	21.1 (95% CI, 18.8-NE)	75%
PI/IMiD-refractory	18.8 (95% CI, 18.8-NE)	75%



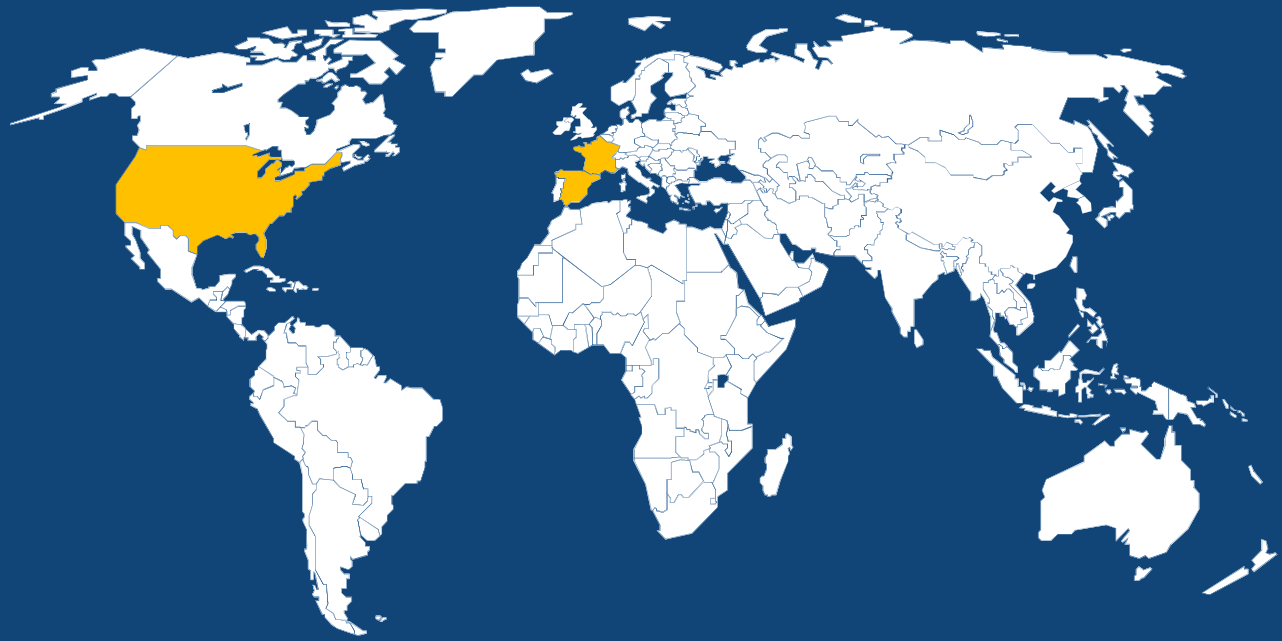
OS follow-up is ongoing

Conclusions

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

Acknowledgments

- Patients who participated in these studies
  - Staff members at the study sites
  - Data and safety monitoring committee
  - Staff members involved in data collection and analyses



This study was funded by Janssen Research & Development, LLC. Medical writing and editorial support were provided by Jason Jung, PhD (MedErgy) and were funded by Janssen Global Services, LLC.

Backup

Background: Len-exposed RRMM

Efficacy Data on Len-exposed RRMM Patients

Trial/Regimen	Analysis set	N	PFS	ORR	MRD neg. rate at 10^{-5}
CASTOR[1] D-Vd vs Vd	Len-exposed	D-Vd: n = 89 Vd: n = 120	Median: **9.5 months vs 6.1 months** HR: 0.38; 95% CI, 0.26-0.56; *P* <0.0001 18-mo PFS rate: 31% vs 4%	**78% vs 53%** *P* = 0.0002	**8% vs 2%** *P* = 0.0278
POLLUX[2] D-Rd vs Rd	Len-exposed	D-Rd: n = 50 Rd: n = 50	Median: **NR vs 18.6 months** HR: 0.35; 95% CI, 0.19-0.64; *P* = 0.0005 30-mo PFS rate: 59% vs 31%	**84% vs 64%** *P* = 0.0233	**26% vs 6%** *P* = 0.0049
MMY1001[3] D-Pd	All treated (100% len-exposed)	n = 103	Median: **9.9 months** **24-month PFS rate: 31%**	**66%**	**7%**
TOURMALINE-MM1[4] N-Rd vs Rd	Len-exposed	N-Rd: n = 44 Rd: n = 44	Median: **NR vs 17.5 months** HR: 0.58; 95% CI, 0.28-1.23	**77% vs 59%**	N/R
ENDEAVOR[5] Kd vs Vd	Len-exposed	Kd: n = 177 Vd: n = 177	Median**: 12.9 month vs 7.3 months** HR: 0.69; 95% CI, 0.52-0.92	**70% vs 59%**	N/R
ASPIRE[6] K-Rd vs Rd	Len-exposed	K-Rd: n = 79 Rd: n = 78	Median**: 19.4 months vs 13.9 months** HR: 0.80; 95% CI, 0.52-1.22; *P* = 0.145	**81% vs 50%**	N/R
OPTIMISMM[7] P-Vd vs Vd	All treated (100% len-exposed)	P-Vd: n = 281 Vd: n = 278	Median**: 11.2 months vs 7.1 months** HR: 0.61; 95% CI, 0.49-0.77; *P* <0.0001	**82% vs 50%**	N/R

1. Lentzsch S, et al. Oral presentation at: Japanese Society of Hematology 79th Annual Meeting; October 20-22, 2017; Tokyo, Japan; Abstract OS3-12D-2. 2. Moreau P, et al. Poster presented at ASH; December 9-12, 2017; Atlanta, GA; Abstract 1883. 3. Facon T, et al. Poster presented at ASH; December 9-12, 2017; Atlanta, GA; Abstract 1824. 4. Mateos MV, et al. *Haematologica*. 2017;102(10):1767-1775. 5. Moreau P, et al. *Leukemia.* 2017;31:115-122. 6. Dimopoulos MA, et al. *Blood Cancer J*. 2017;7(4):e554. 7. Richardson P, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 1-5, 2018; Chicago, IL; Abstract 8001.

len, lenalidomide; D-Vd, daratumumab/bortezomid/dexamethasone; Vd, bortezomib/dexamethasone; PFS, progression-free survival; ORR, overall response rate; MRD, minimal residual disease; HR, hazard ratio; CI, confidence interval; Pd, pomalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; N/R, not reported; d, dexamethasone.

Most Common TEAEs (>25%)

Any-grade TEAE, %	MMY3007 (ALCYONE) D-VMP (n = 346)	MMY3003 (POLLUX) D-Rd (n = 283)	MMY3004 (CASTOR) D-Vd (n = 243)	MMY1001 (EQUULEUS) D-KRd (n = 22)	MMY1001 (EQUULEUS) D-Kd (n = 85)
Hematologic					
Neutropenia	50	62	19	36	25
Anemia	28	38	29	50	48
Thrombocytopenia	49	29	60	55	64
Leukopenia	13	10	9	36	8
Lymphopenia	11	7	13	64	26
Non-hematologic					
Diarrhea	24	56	35	73	26
Upper respiratory tract infection	26	41	33	59	19
Viral upper respiratory tract infection	4	31	11	0	14
Fatigue	14	38	22	50	11
Cough	15	34	28	59	22
Constipation	18	31	22	50	13
Muscle spasms	2	29	10	41	11
Nausea	21	27	14	41	34
Insomnia	8	24	17	50	27
Back pain	14	23	20	41	20
Dyspnea	12	21	19	46	29
Vomiting	17	19	12	36	33
Asthenia	12	18	10	0	38
Rash	8	15	7	41	4
Peripheral sensory neuropathy	28	13	50	9	1
Pain in extremity	8	11	13	32	7
Hyperglycemia	6	10	10	32	2
Increased alanine aminotransferase	4	6	8	32	2