Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): an Open-label, Phase 1b Study

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Background

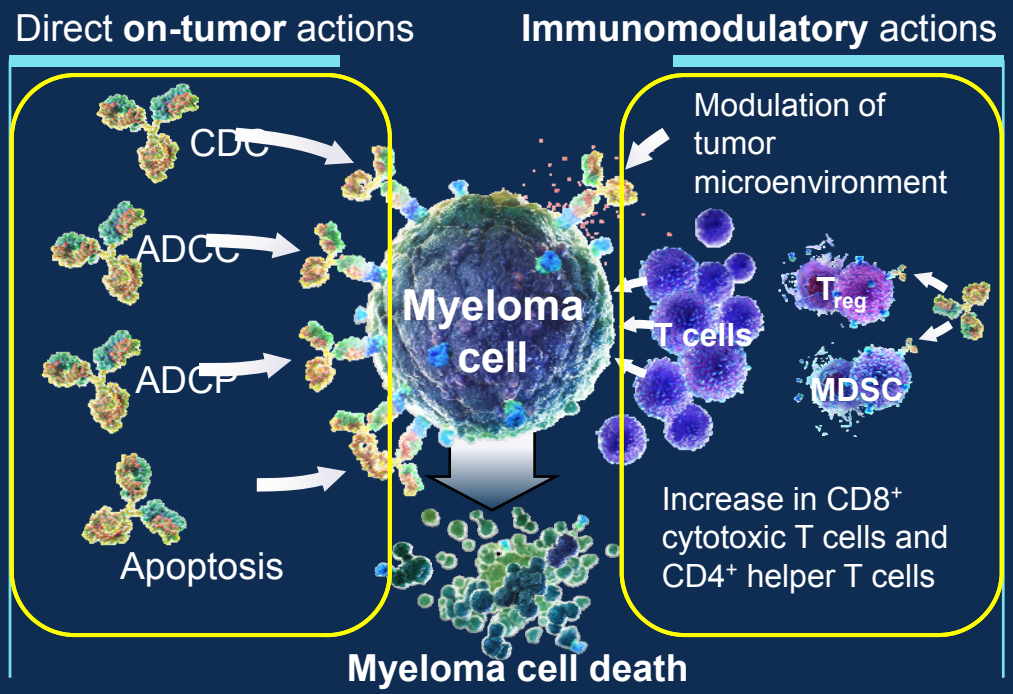
- Triplet regimens with proteasome inhibitor (PI) and/or immunomodulatory drug (IMiD), with or without ASCT, are now established as standard of care for newly diagnosed myeloma
- Among triplets, extended treatment with KRd emerged as highly active in newly diagnosed myeloma[1,2]
- The KRd results appear to be improved by incorporation of ASCT[3-5]
  - sCR rate **51% w/o ASCT** and **74% with ASCT**
  - 3-year PFS **80% w/o ASCT** and **86% with ASCT**
- We hypothesized that KRd activity can alternatively be improved by incorporating daratumumab into KRd treatment regimen

ASCT, autologous stem cell transplant; sCR, stringent complete response; PFS, progression-free survival.

1. Jakubowiak AJ, et al. *Blood* 2012;120(9):1801-1809.
2. Korde N, et al. *JAMA Oncol* 2015;1(6):746-754.
3. Jakubowiak A, et al. Oral presentation at the 21st EHA Annual Congress, June 9-12, 2016. Copenhagen, Denmark; Abstract: S101.
4. Zimmerman TM, et al. Oral presentation at the 58th ASH Annual Meeting and Exposition, December 3-6, 2016. San Diego, CA; Abstract: 675.
5. Roussel M, et al. Oral presentation at the 58th ASH Annual Meeting and Exposition, December 3-6, 2016. San Diego, CA; Abstract: 1142.

Daratumumab (DARA)

- Human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory MoA[1]
- Approved as monotherapy in many countries for heavily pretreated RRMM
- Approved in combination with standard of care regimens in RRMM after ≥1 prior therapy in the USA, EU, and other countries
- DARA induces rapid, deep and durable responses in combination with a PI (bortezomib) or an IMiD (lenalidomide) in RRMM[2,3]



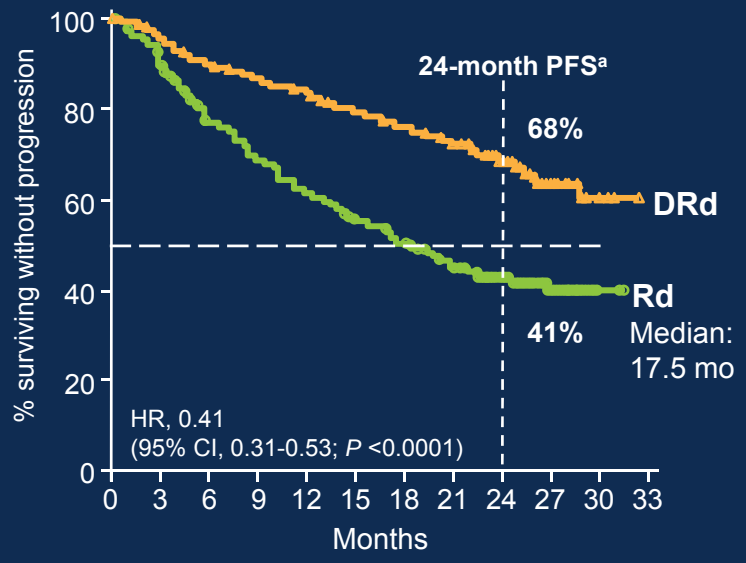
MoA, mechanism of action; RRMM, relapsed/refractory multiple myeloma; CDC, cellular dependent cytotoxicity; ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; MDSC, myeloid-derived suppressor cell.

1. Touzeau C, Moreau P. *Expert Opin Biol Ther*. 2017. Epub ahead of print.
2. Mateos MV, et al. Oral presentation at the 58th ASH Annual Meeting and Exposition, December 3-6, 2016. San Diego, CA; Abstract 1150.
3. Usmani SZ, et al. Oral presentation at the 58th ASH Annual Meeting and Exposition, December 3-6, 2016. San Diego, CA; Abstract 1151.

DARA Plus SOC in RRMM: Updated PFS

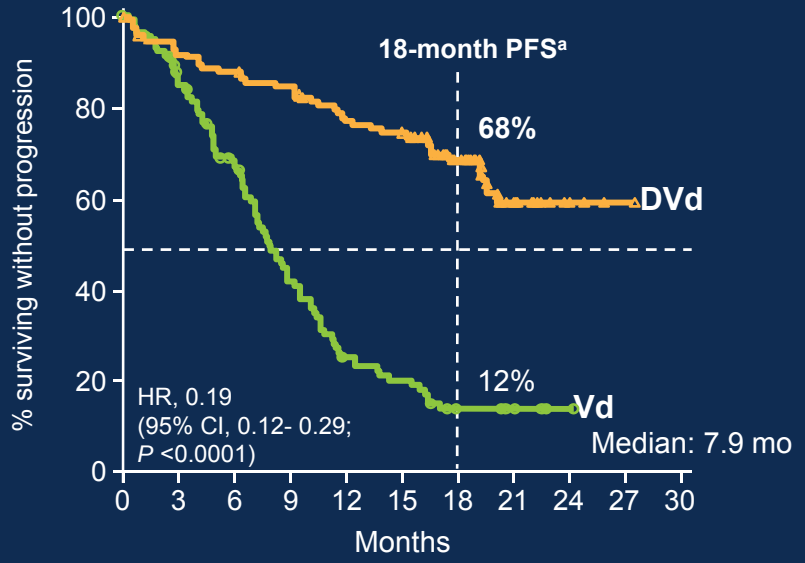
POLLUX (ITT)

Median follow-up: 25.4 months[1]



CASTOR (1 prior line)

Median follow-up: 19.4 months[2]



These studies provided rationale for evaluation of DARA + KRd in this phase 1b study

SOC, standard of care; ITT, intent-to-treat; DRd, daratumumab/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone.
[a]Kaplan-Meier estimates.
Exploratory analyses based on clinical cut-off: January 11, 2017 for CASTOR; March 7, 2017 for POLLUX.

1. Bahlis NZ, et al. Poster presentation at the ASCO 2017 Annual Meeting, June 2-6 , 2017. Chicago, IL; Abstract 8025.
2. Lentzsch S, et al. Poster presentation at the ASCO 2017 Annual Meeting, June 2-6 , 2017. Chicago, IL; Abstract 8036.

Study Design

Open-label, Multicenter, Phase 1b Study (N = 22)

Eligibility/Treatment

- NDMM
- Transplant eligible and non-eligible
- Treatment duration: ≤13 cycles or until elective discontinuation for ASCT
- No clinically significant cardiac disease; echo required at screening

Dosing Schedule (28-d cycles)

Daratumumab:

- Split dose: 8 mg/kg Days 1-2 of Cycle 1
- 16 mg/kg QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter

Carfilzomib:

- 20 mg/m^2 C1D1
- Escalated to 70 mg/m^2 C1D8+; weekly (Days 1, 8, 15)

Lenalidomide:

- 25 mg; Days 1-21 of each cycle

Dexamethasone: 40 mg/week[a]

Endpoints

Primary

- Safety, tolerability

Secondary

- ORR, duration of response, time to response, IRR

Exploratory

- PFS

Pre- and post-infusion medications:

Dexamethasone 20 mg[b]; Diphenhydramine 25-50 mg; paracetamol 650-1,000 mg; montelukast 10 mg[c]

Echo, echocardiogram; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C1D1, Cycle 1 Day 1; C1D8, Cycle 1 Day 8; IRR, infusion-related reaction; C1D3, Cycle 1 Day 3.
[a]20 mg if >75 y. [b]On daratumumab dosing days, dexamethasone 20 mg IV was administered as pre-medication on infusion day and 20 mg PO the day after infusion; for DARA, split first dose dexamethasone 20 mg IV was administered as a pre-medication on C1D1 and C1D2; on C1D3, administration of low-rose methylprednisolone (≤20 mg PO) was optional. [c]Required before first daratumumab dose, optional for subsequent doses.

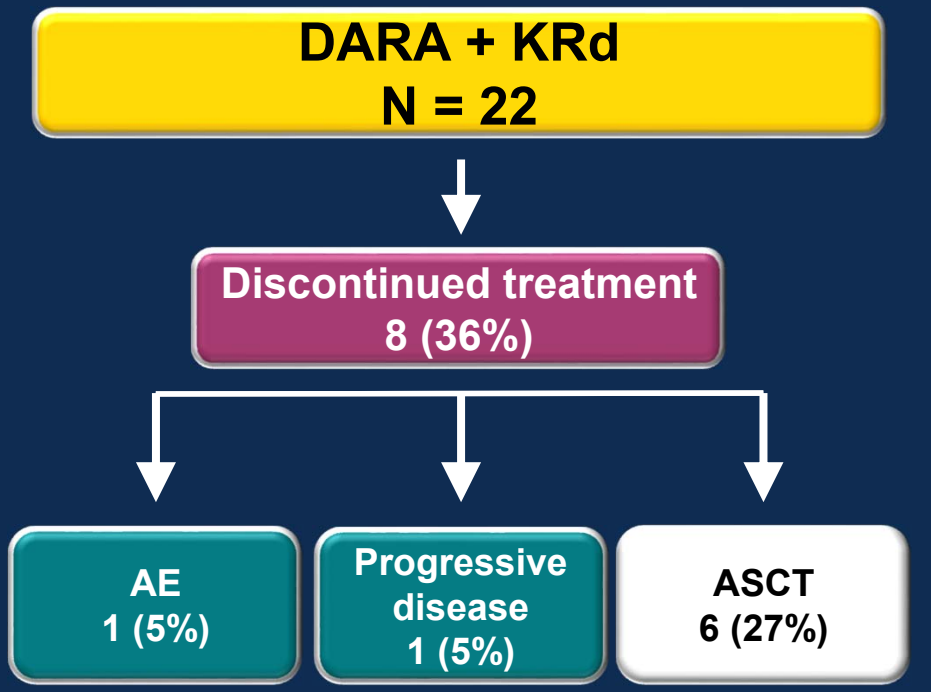
Baseline Demographics

Characteristic	DARA + KRd (N = 22)
Age, years, n (%)	
Median (range)	59.5 (34-74)
<65	15 (68)
65 - <75	7 (32)
Gender, n (%)	
Male	12 (55)
Female	10 (46)
Race, n (%)	
White	19 (86)
African American	1 (5)
American Indian or Alaska Native	1 (5)
Not reported	1 (5)
ECOG score, n (%)	
0	12 (55)
1	9 (41)
2	1 (5)

ECOG, Eastern Cooperative Oncology Group.

Patient Disposition

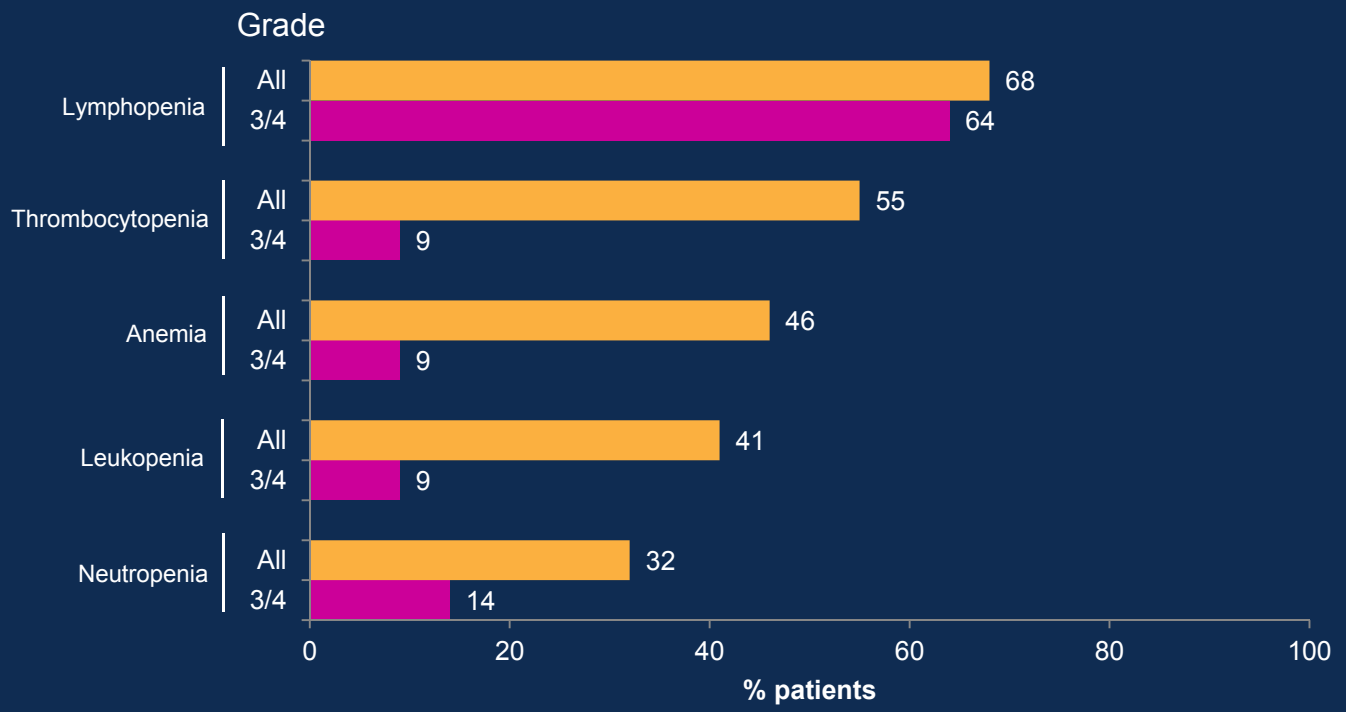
- Median follow-up:
  - 10.8 (range, 4.0-12.5) months
- Median number of treatment cycles:
  - 11.5 (range, 1.0-13.0)
- Except for 3 patients, all escalated to carfilzomib 70 mg/m^2 by C2D1
  - 1 discontinued treatment before C2D1
  - 1 dose reduction to 56 mg/m^2 at C2D1
  - 1 escalated to 70 mg/m^2 at C3D8



Clinical cut-off date: March 24th, 2017

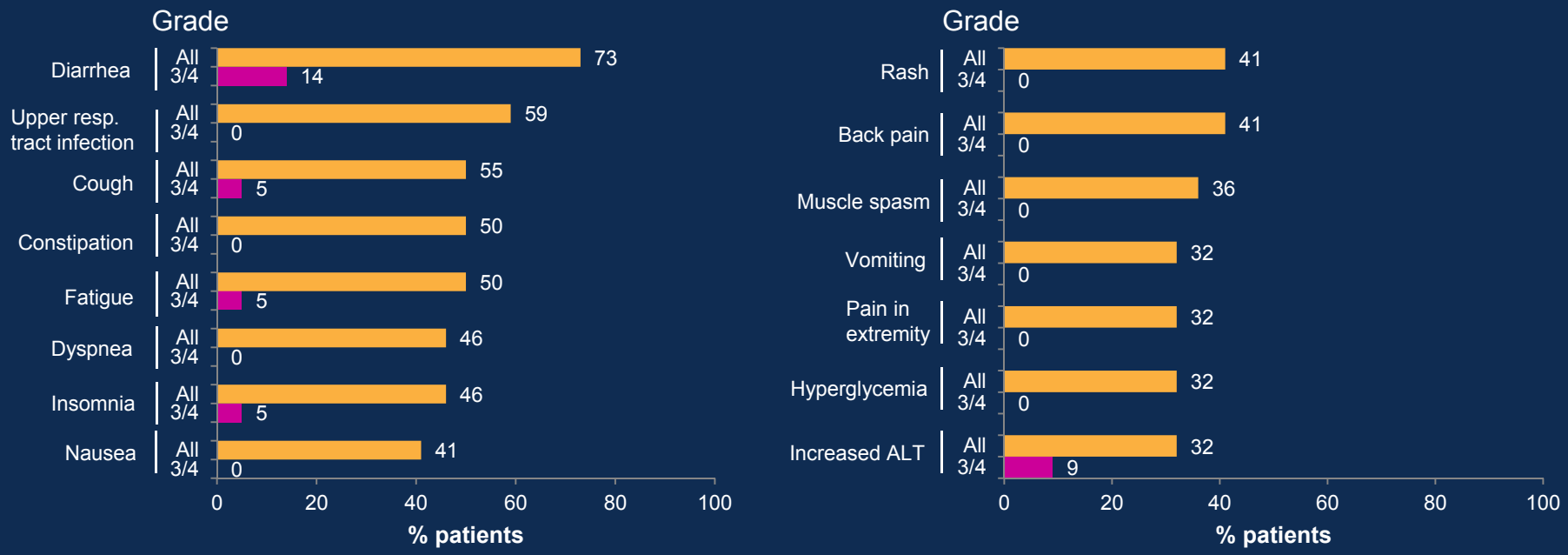
C2D1, Cycle 2 Day 1; C3D8, Cycle 3 Day 8; AE, adverse event.

Most Common (≥30%) Hematologic TEAEs (N = 22)



TEAE, treatment emergent adverse event.

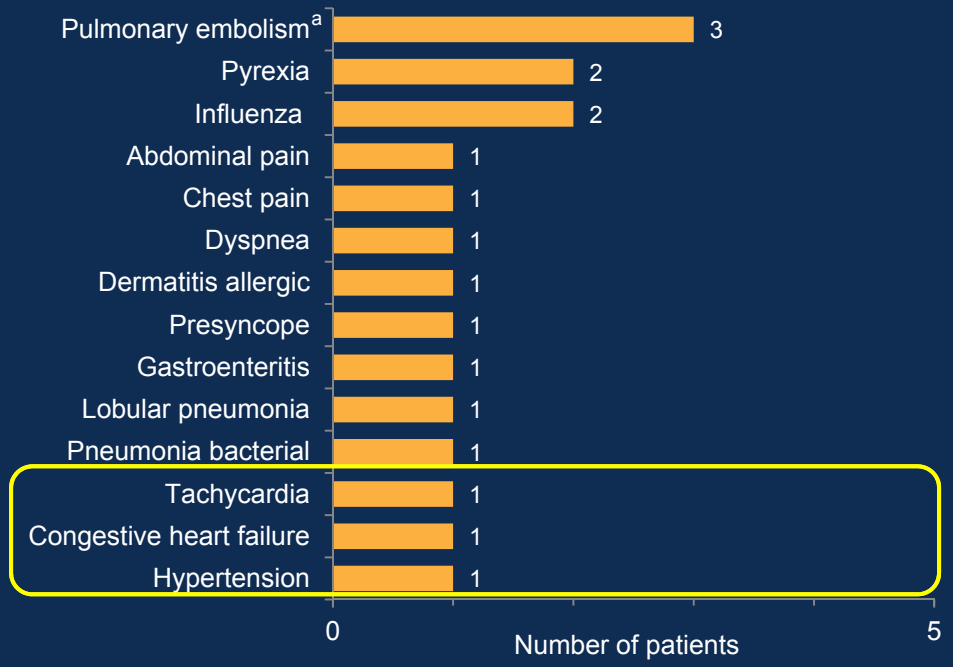
Most Common (≥30%) Nonhematologic TEAEs (N = 22)



Safety profile is consistent with previous reports for DARA or KRd

ALT, alanine aminotransferase.

Serious TEAEs (N = 22)



- Serious TEAEs: 10 of 22 patients (46%)
- Number (%) of patients with a serious TEAE reasonably related to study drug[b]
  - Daratumumab: 3 (14%)
  - Carfilzomib: 5 (23%)
  - Lenalidomide: 5 (23%)
  - Dexamethasone: 2 (9%)
- 1 (5%) treatment discontinuation due to pulmonary embolism; unrelated to daratumumab or carfilzomib
- All patients were on aspirin prophylaxis

Consistent with previous reports from KRd studies

[a]Bilateral deep vein thrombosis and pulmonary embolism was reported in 1 patient.
[b]Independent Data and Safety Monitoring Board was notified of serious TEAEs on a regular basis.

Echocardiogram Assessment

Time point	Left Ventricular Ejection Fraction
	Median (range)
Baseline	60 (55-77)
Cycle 3	60 (55-78)
Cycle 6	59 (50-70)
Cycle 9	60 (50-69)
Cycle 12	62 (56-75)

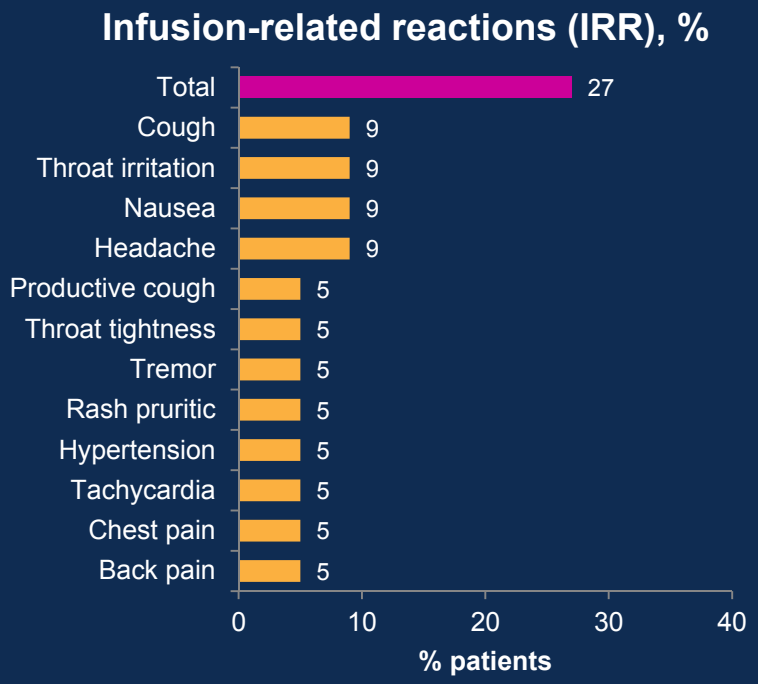
- Median left ventricular ejection fraction: no change from baseline over time
- 1 patient had a transient grade 3 SAE of cardiac failure; possibly related to daratumumab or carfilzomib
  - Patient resumed treatment on C2D1 with reduced carfilzomib dose (56 mg/m^2)
  - Patient elected ASCT on study Day 113 and ended treatment with VGPR

No apparent adverse impact on cardiac function

SAE, serious adverse event; VGPR, very good partial response.

Infusion Times and Reactions (N = 22)

Infusion Times	
Infusion	**Median (range) infusion time, h**
First **C1D1** **C1D2**	 **4.15 (4.0-6.0)** **4.15 (3.9-6.0)**
Second	**4.18 (3.6-7.1)**
Subsequent	**3.38 (1.4-6.1)**

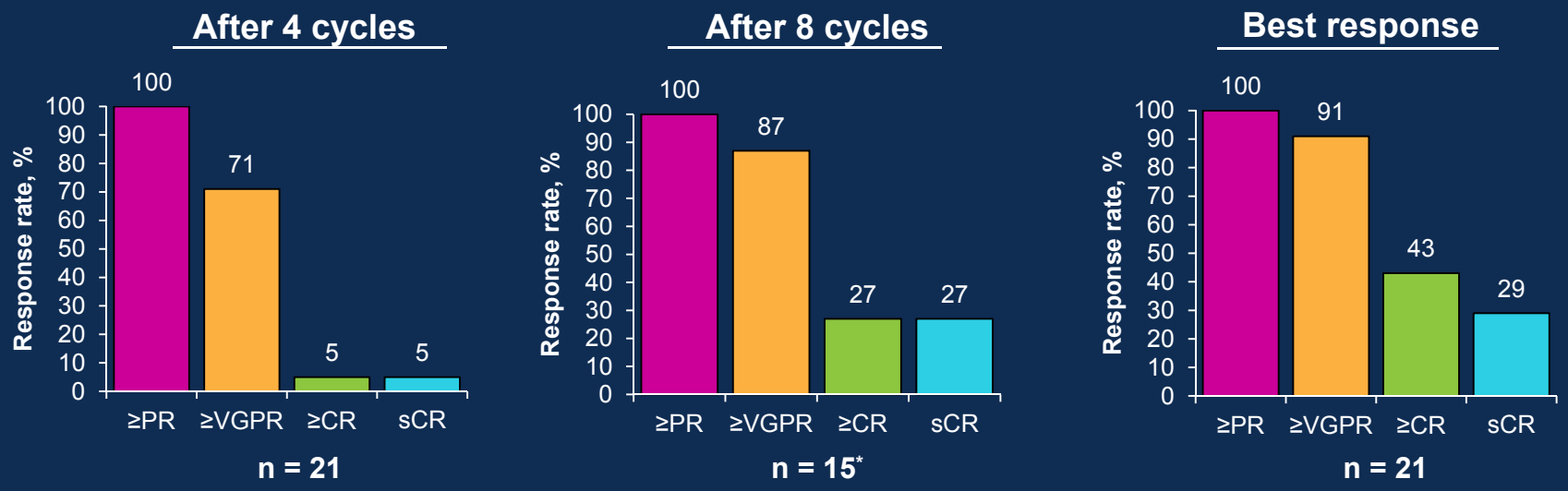


- No grade 3/4
- Occurrence
  - First infusion: 5 (23%) patients
  - Second infusion: 1 (5%) patient
  - Subsequent infusions: 1 (5%) patient

Lower rates of IRRs observed with split first dosing

Response Rate[a,b]

- Median number of treatment cycles: 11.5 (range, 1.0-13.0)



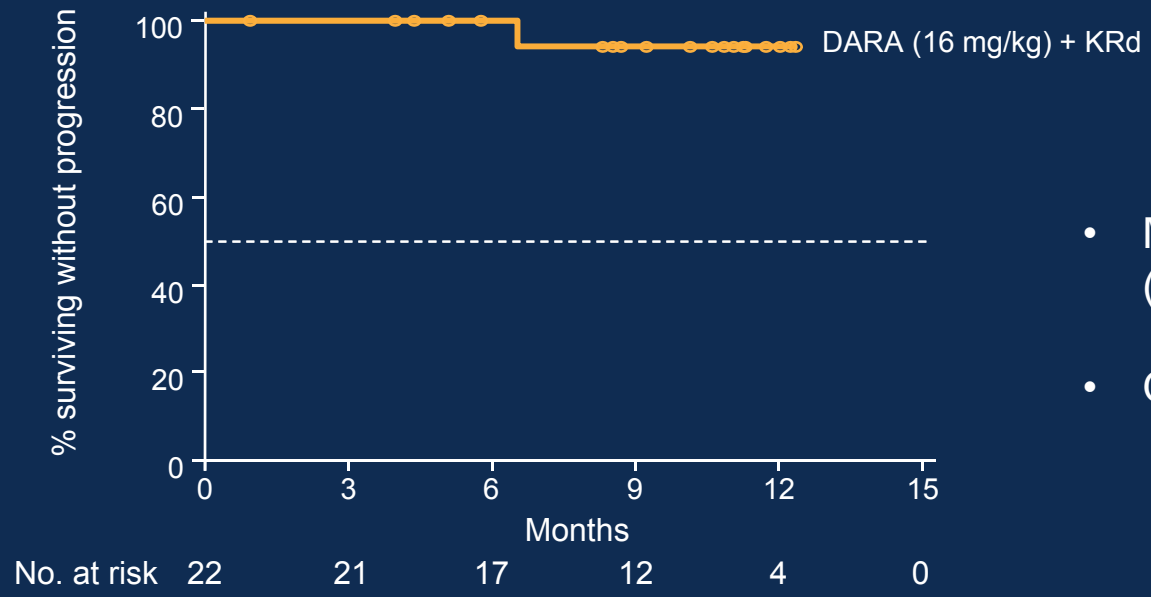
Depth of response improved with duration of treatment

*5 patients who proceeded to ASCT before C8 and 1 patient who discontinued due to PD at C7 were excluded.

PR, partial response; CR, complete response.

[a]Response-evaluable population. [b]Response rate (≥PR) evaluated by IMWG criteria; M-protein measurements by central lab assessment.

PFS



- Median follow-up: 10.8 (range, 4.0-12.5) months
- Overall survival = 100%

12-month PFS rate[a] = 94%

[a]Kaplan-Meier estimate.

Stem Cell Harvest and ASCT[a]

- Median number of $CD34^+$ cells collected from patients: 10.4 x 10^6 cells/kg (n = 19)
- Median 5 treatment cycles prior to stem cell harvest
- 14 (74%) patients had ≥VGPR prior to stem cell harvest

Patient	Stem cell mobilization	Total $CD34^+$ cells ($x10^6$/kg body weight)	Treatment cycle at ASCT	Best response[b]
1	Plerixafor and Filgrastim	30	9	sCR
2	Plerixafor and Filgrastim	12	5	VGPR
3	Plerixafor and Filgrastim	28	4	VGPR
4	Filgrastim	38	4	VGPR
5	Plerixafor and Filgrastim	10.4	5	VGPR
6	Filgrastim	6.5	4	VGPR

Stem cell yield is consistent with previous KRd studies

[a]Per protocol, patients who continued to ASCT discontinued study treatment .
[b]Best response among patients who elected ASCT.

Conclusions

- **DARA + KRd was well tolerated**
  - Safety is consistent with previous reports of DARA and KRd
  - Low IRR rates associated with split first dose; no grade 3/4
- **Highly effective with 100% ORR**
  - 91% ≥VGPR and 43% ≥CR
  - Depth of response improved with duration of treatment
- **No adverse impact on stem cell collection (10.4×10^6 cells/kg)**
  - DARA is feasible as part of induction therapy

Data from this study support further investigation of DARA-KRd in NDMM

Ongoing Phase 3 Studies

- NDMM (transplant-ineligible)
  - ALCYONE (DARA + VMP)
  - MAIA (DARA + Rd)
- NDMM (transplant-eligible)
  - CASSIOPEIA (DARA + VTd)
- RRMM
  - CANDOR (DARA + Kd)
  - APOLLO (DARA + Pd)

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

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Backup

Adverse Event of Interest

- 61 year old male diagnosed with multiple myeloma
  - History of ongoing grade 2 coronary artery disease with stent placement, ongoing grade 1 intermittent chest pain, and grade 1 hypertension
- Grade 3 SAE of cardiac failure reported on study Day 11, which lasted for 4 days while study treatment was interrupted
  - Considered possibly related to daratumumab and carfilzomib
- Patient resumed treatment on Cycle 2 Day 1 with reduced carfilzomib dose (56 mg/m^2)
- No additional cardiac TEAEs or dose reductions were reported
- Patient elected ASCT on study Day 113 and ended study treatment with a clinical response of VGPR

SAE, serious adverse event; TEAE, treatment emergent adverse event; ASCT, autologous stem cell transplant; VGPR, very good partial response.

Carfilzomib Dose Escalation

	Carfilzomib (mg/m^2)			
	C1D1	D1D8	C1D15	C2D1
Patient 1	20	70	70	70
Patient 2	20	70	70	70
Patient 3	20	70	70	70
Patient 4	20	70	70	70
Patient 5	20	70	70	70
Patient 6	20	70	70	70
Patient 7	20	70	0	Off Study
Patient 8	20	70	70	70
Patient 9	20	70	70	70
Patient 10	20	70	0	56
Patient 11	20	70	70	70

	Carfilzomib (mg/m^2)			
	C1D1	D1D8	C1D15	C2D1
Patient 12	20	56	70	70
Patient 13	20	36	70	70
Patient 14	20	70	70	70
Patient 15	20	70	70	70
Patient 16	20	70	70	70
Patient 17	20	0	0	20
Patient 18	20	70	70	70
Patient 19	20	70	70	70
Patient 20	20	70	70	70
Patient 21	20	36	70	70
Patient 22	20	70	70	70