An Open-label, Randomised, Phase 3 Study of Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Lenalidomide and Dexamethasone (Rd) in Relapsed or Refractory Multiple Myeloma (RRMM): POLLUX*

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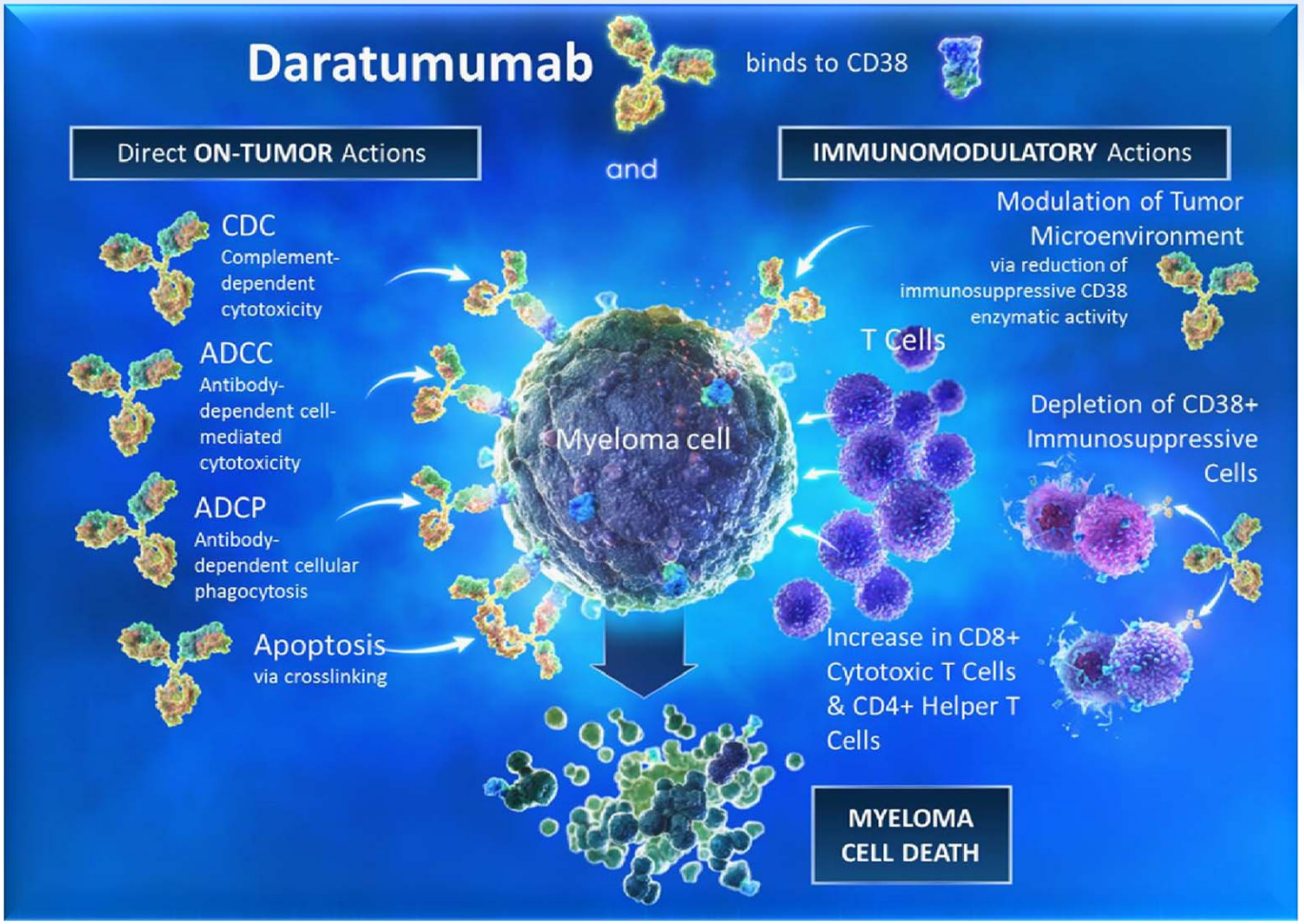
*NCT02076009

Daratumumab: Mechanism of Action

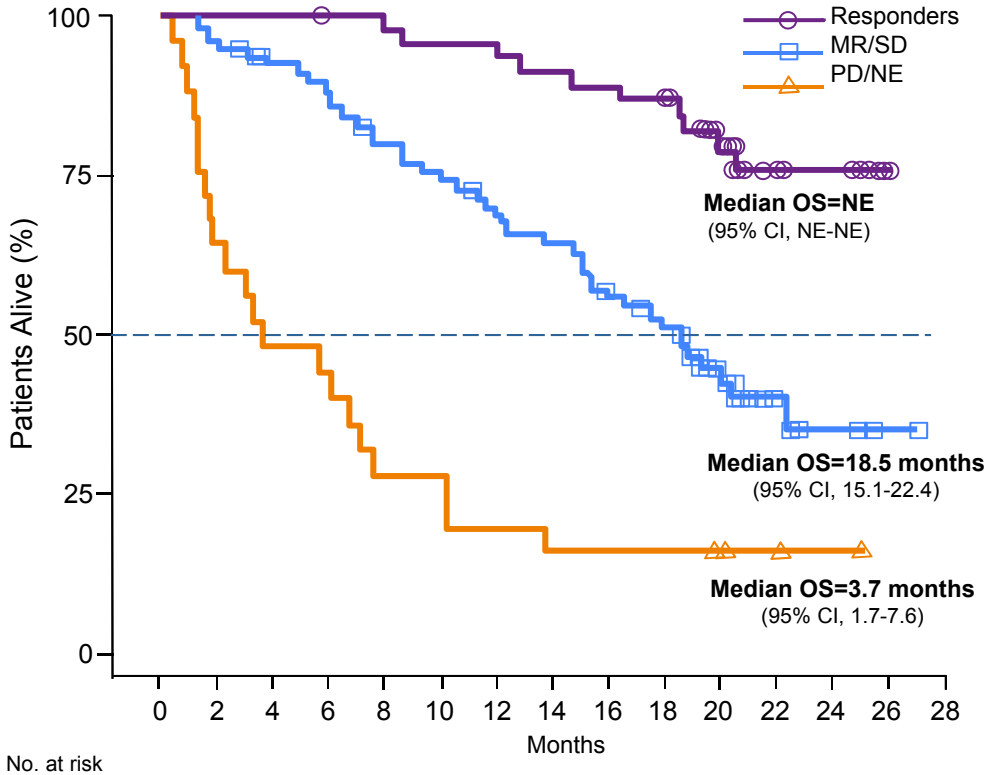
- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]



1. Lammerts van Bueren J, et al. *Blood*. 2014;124:Abstract 3474.
2. Jansen JMH, et al. *Blood*. 2012;120:Abstract 2974.
3. de Weers M, et al. *J Immunol*. 2011;186:1840-8.
4. Overdijk MB, et al. *MAbs*. 2015;7:311-21.
5. Krejcik J, et al. *Blood*. 2016. Epub ahead of print.

Daratumumab: Single-agent Activity

- **Daratumumab as a single agent[1,2]**
  - Approved by FDA and conditionally approved by EMA in relapsed/refractory multiple myeloma
- **Patients received a median of 5 prior lines of therapy**
  - 86.5% of patients were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)[3]
- **Combined overall response rate (ORR):31%[3]**
- **Median overall survival (OS) of 20.1 months[3]**
  - 2-year OS was ~75% in responders
  - Median OS was 18.5 months in MR/SD patients

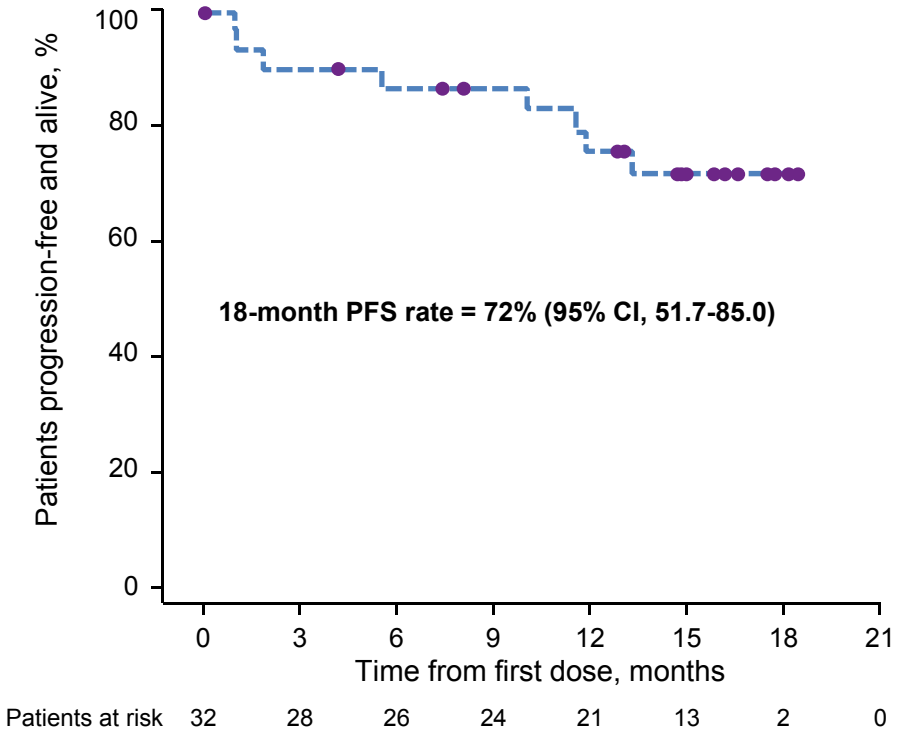


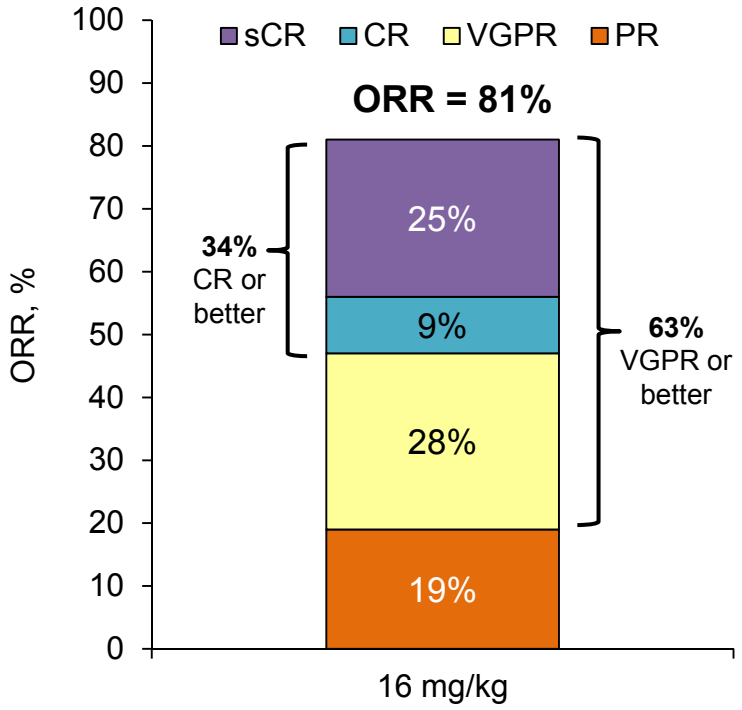
MR, minimal response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval; NE, not evaluable.

1. Lokhorst HM, et al. *N Engl J Med*. 2015;373:1207-19.
2. Lonial S, et al. *Lancet*. 2016;387:1551-60.
3. Usmani SZ, et al. *Blood*. 2016. Epub ahead of print.

Daratumumab (D) With Lenalidomide and Dexamethasone (Rd)[1]

- In a phase 1/2 study, 32 patients with relapsed or refractory multiple myeloma were treated with daratumumab 16 mg/kg and lenalidomide/dexamethasone
- DRd induced rapid, deep, and durable responses
- Safety profile was manageable
  - Neutropenia, the most common adverse event (AE), was managed with treatment interruptions, lenalidomide dose reduction, and growth factor administrations



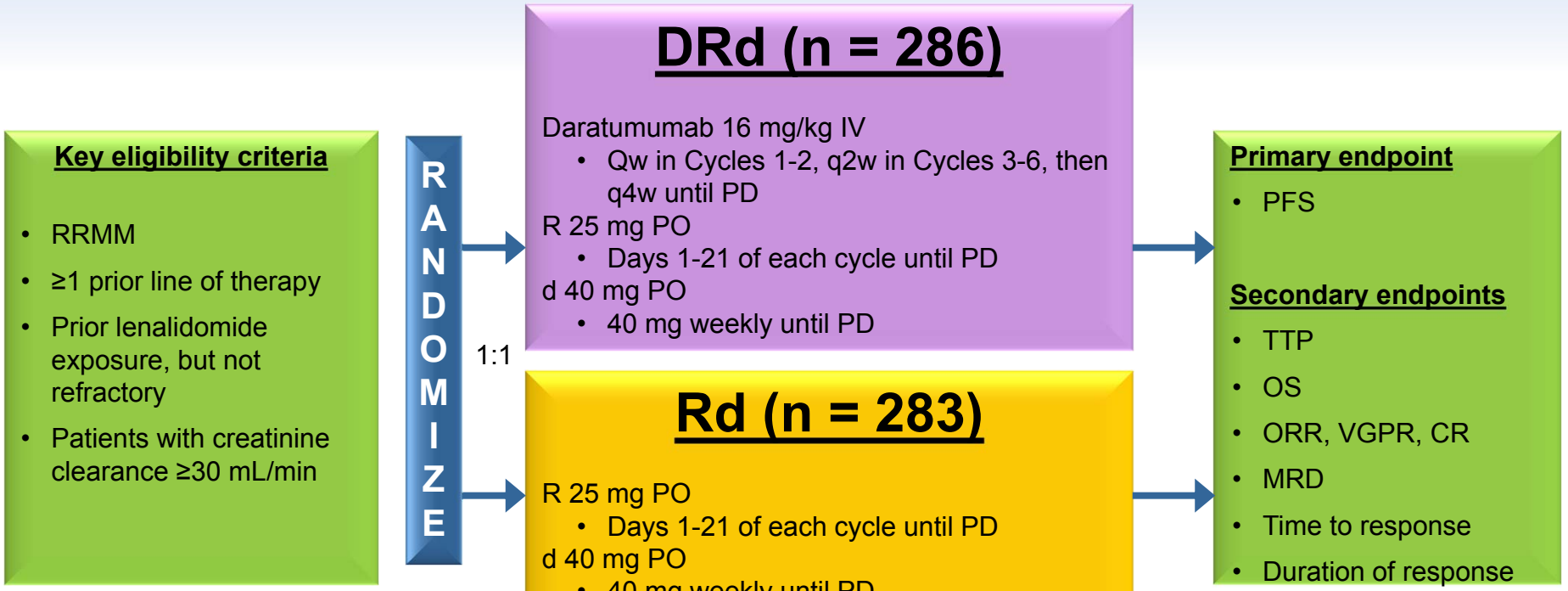


PFS, progression-free survival; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response.

1. Plesner T, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 507.

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study



Stratification factors

- No. prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

Cycles: 28 days

Statistical analyses

- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], paracetamol, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2; RRMM, relapsed or refractory multiple myeloma; ISS, international staging system; R, lenalidomide; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; TTP, time to progression; MRD, minimal-residual disease.

Baseline Demographics and Clinical Characteristics

Characteristic	DRd (n = 286)	Rd (n = 283)
Age, yr		
Median (range)	65 (34-89)	65 (42-87)
≥75, %	10	12
ISS stage, %[a]		
I	48	50
II	33	30
III	20	20
Median (range) time from diagnosis, yr	3.48 (0.4-27.0)	3.95 (0.4-21.7)
Creatinine clearance (mL/min)		
N	279	281
>30-60	28	23
>60	71	77
Prior lines of therapy, %		
Median (range)	1 (1-11)	1 (1-8)
1	52	52
2	30	28
3	13	13
>3	5	7

[a]ISS stage is derived based on the combination of serum β2-microglobulin and albumin.

Baseline Demographics and Clinical Characteristics (cont.)

Characteristic	DRd (n = 286)	Rd (n = 283)
Prior ASCT, %	63	64
Prior PI, %	86	86
Prior IMiD, % Prior lenalidomide, %	55 18	55 18
Prior PI + IMiD, %	44	44
Refractory to PI, %	20	16
Refractory to last line of therapy, %	28	27

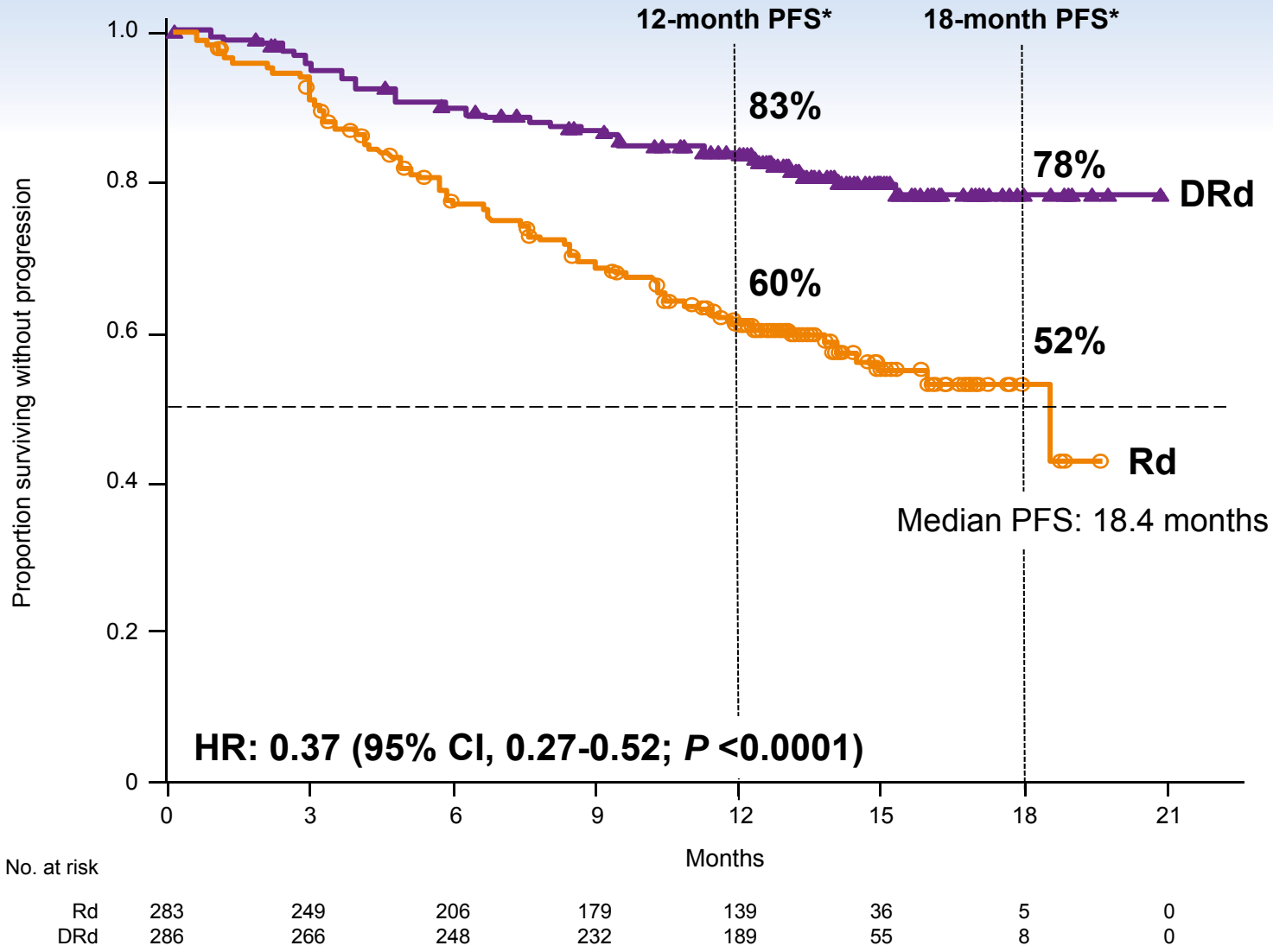
ASCT, autologous stem cell transplant.

Patient Disposition

- Randomization: June 2014 – July 2015
- Clinical cut-off date: March 7, 2016; 198 patients discontinued treatment
- Median follow-up: 13.5 months

	DRd (n = 286)	Rd (n = 283)
Patients treated, n	283	281
Patients who discontinued treatment, %	23	47
Reasons for discontinuation		
Progressive disease	14	34
Adverse event	7	8
Non-compliance with study drug	0.4	2
Withdrawal by patient	0.4	2
Physician decision	1	0.7
Death	0.7	0.4

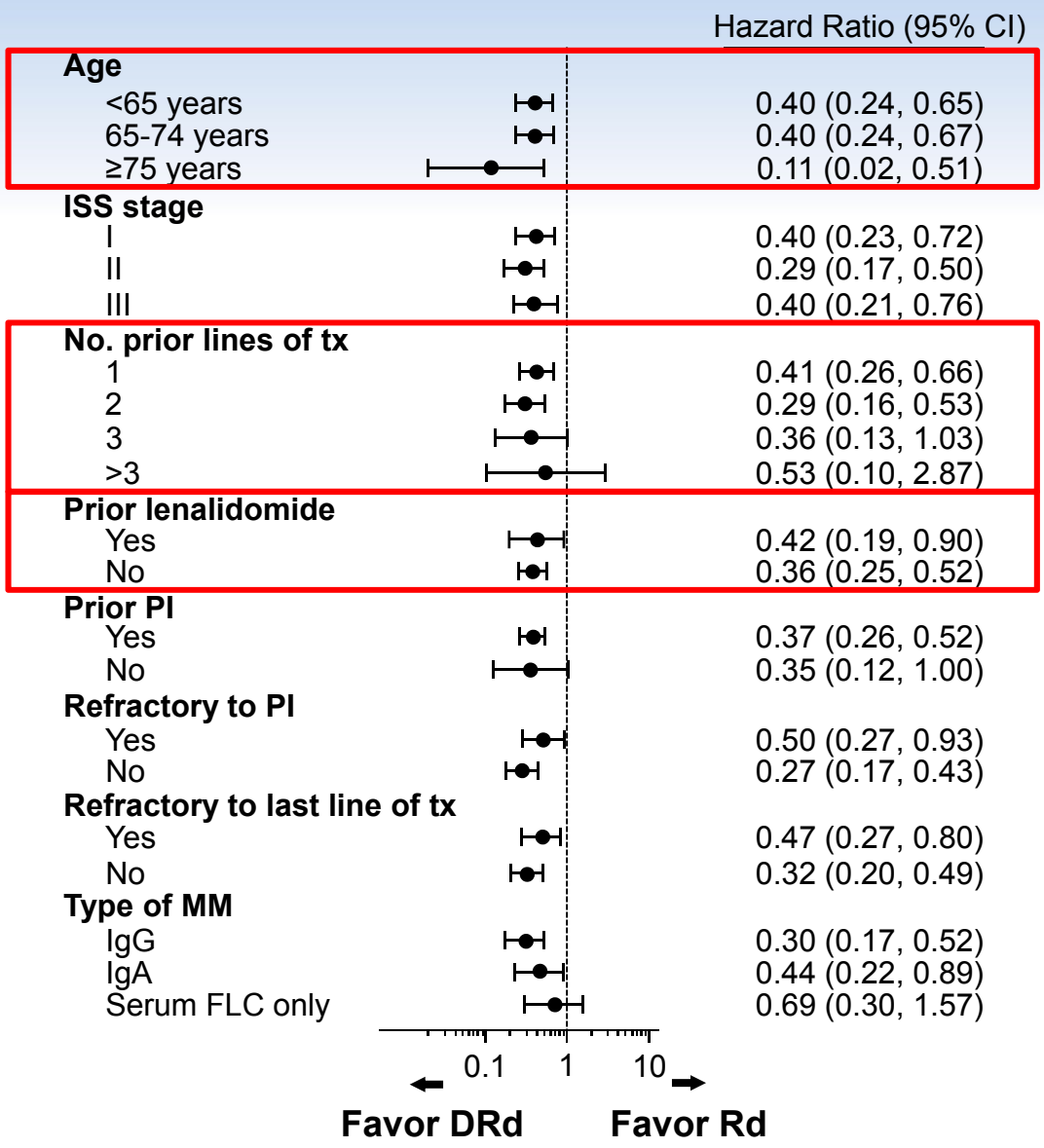
Progression-free Survival



63% reduction in the risk of disease progression or death for DRd vs Rd

*KM estimate; HR, hazard ratio.

PFS: Subgroup Analysis

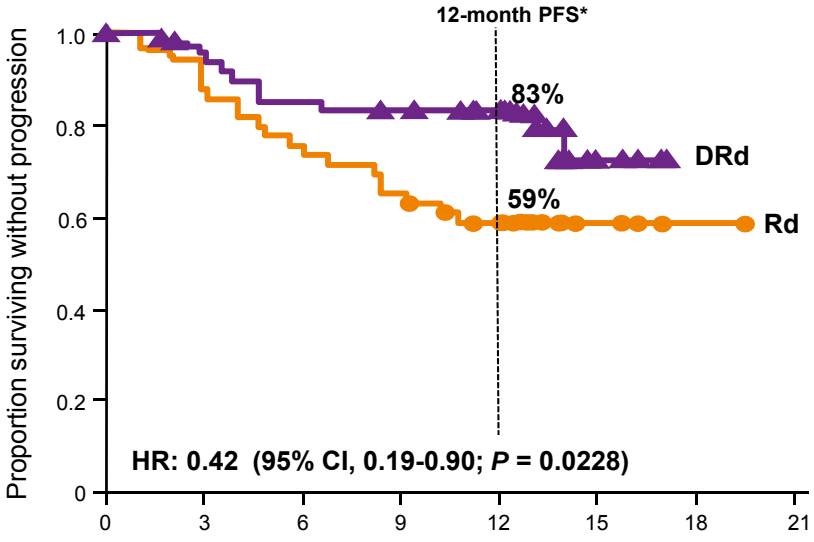


Higher efficacy was observed for DRd versus Rd across all subgroups

Tx, treatment; MM, multiple myeloma; IgG, immunoglobulin G; IgA, immunoglobulin A; FLC, free light chain.

PFS: Prior Lenalidomide Treatment

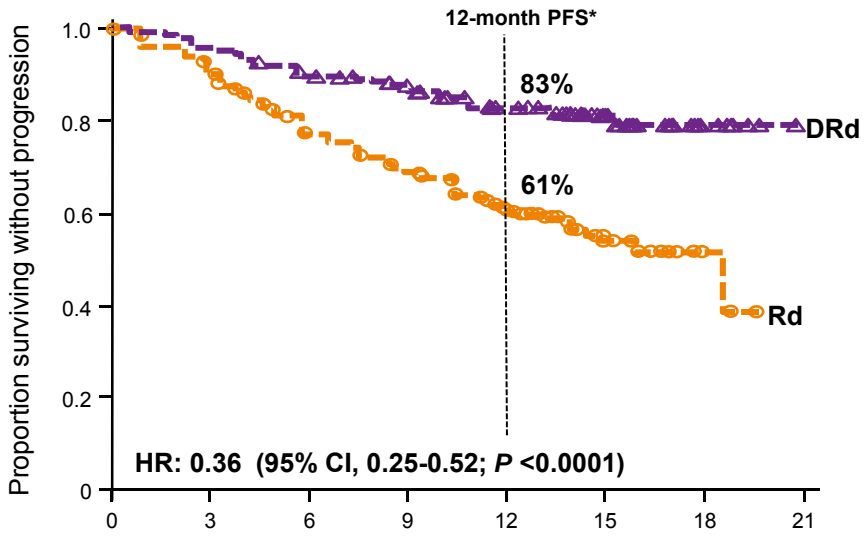
Prior Lenalidomide Treatment



No. at risk

Rd	50	43	37	31	23	5	1	0
DRd	50	44	40	38	28	5	0	0

No Prior Lenalidomide Treatment



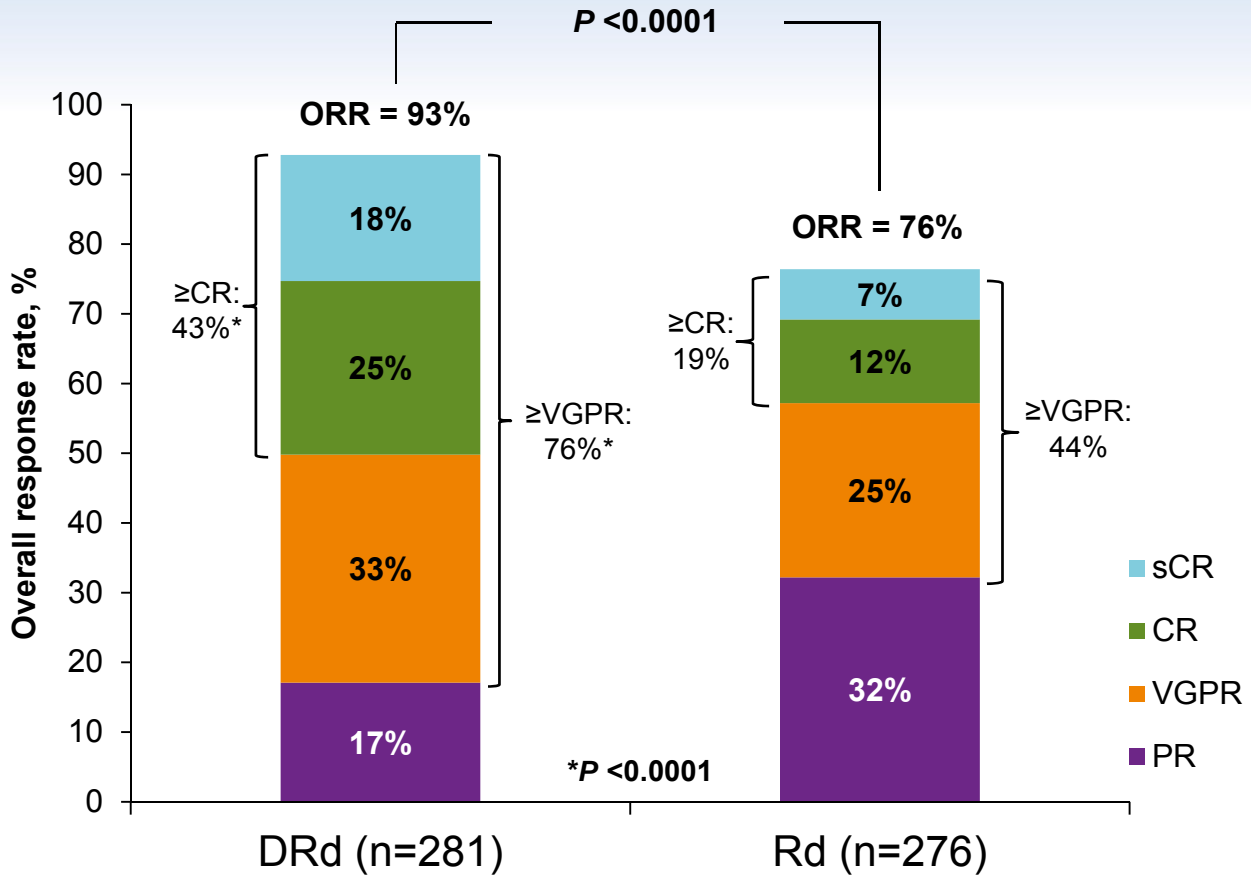
No. at risk

Rd	233	206	169	148	116	31	4	0
DRd	236	222	208	194	161	50	8	0

Treatment effect is consistent regardless of prior lenalidomide exposure

*KM estimate.

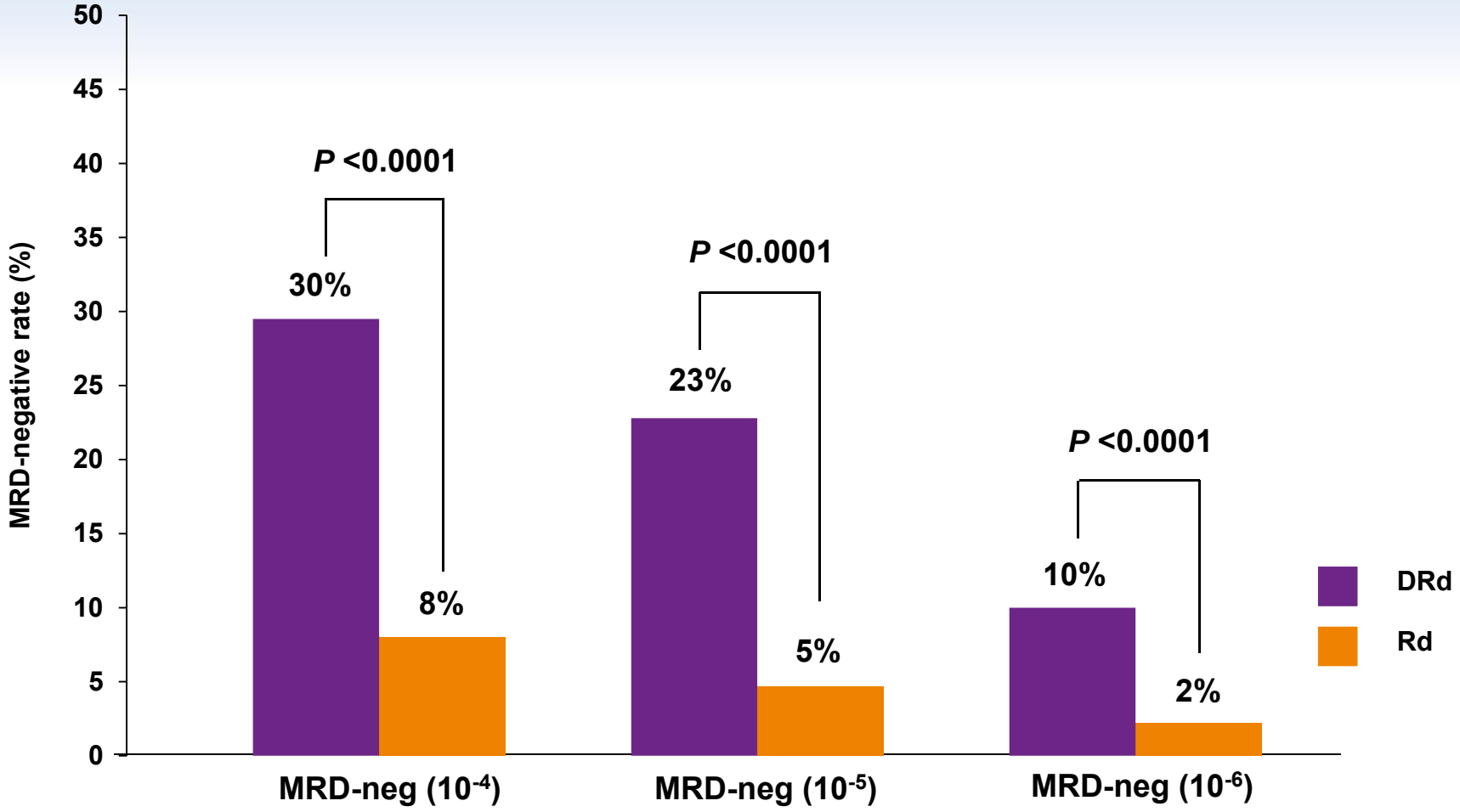
Overall Response Rate[a]



- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

[a]When serum interference was suspected, CR was confirmed using the daratumumab interference reflex assay.

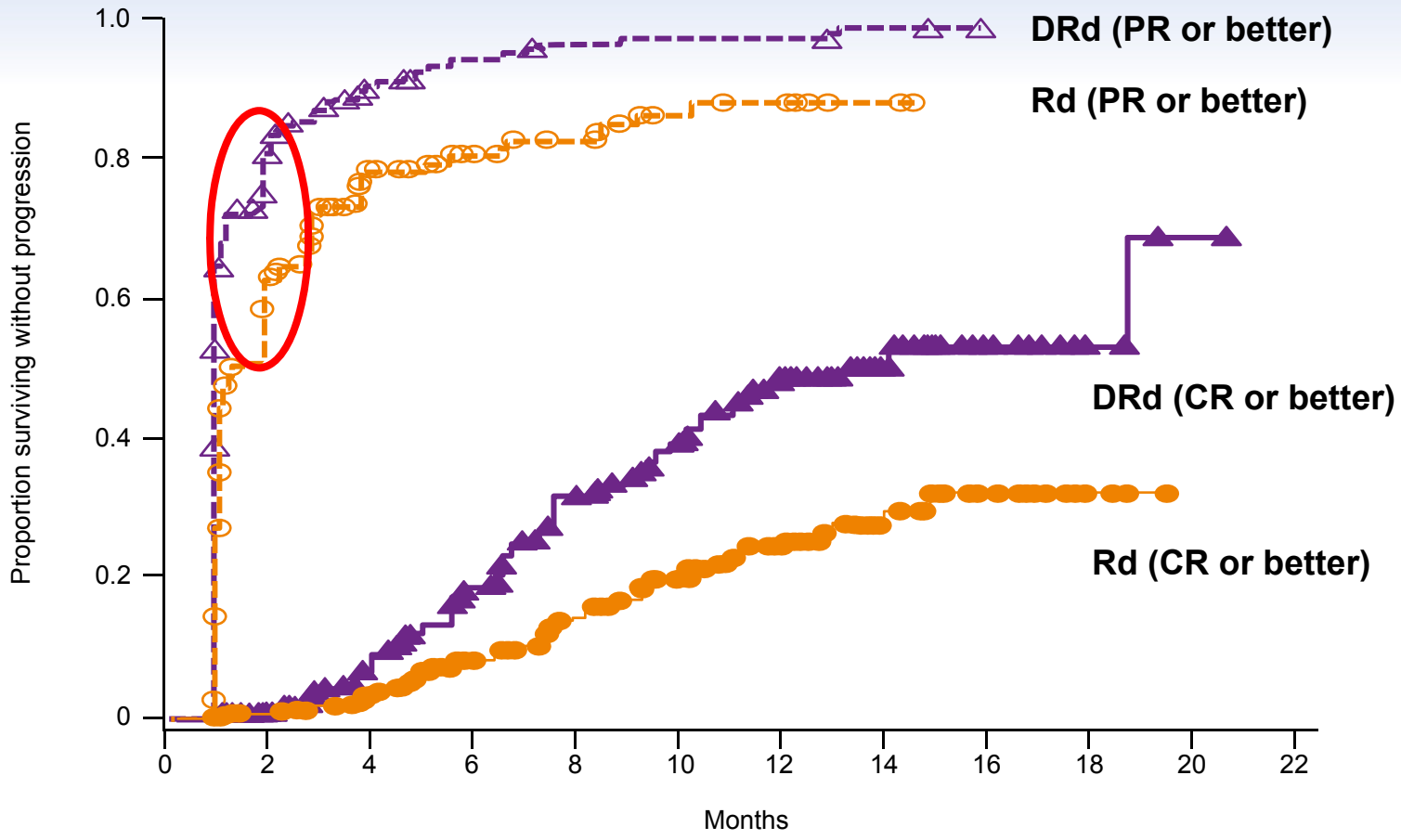
MRD-negative Rate



Significantly higher MRD-negative rates for DRd vs Rd

Response-evaluable set. Assessed by next generation sequencing in bone marrow.

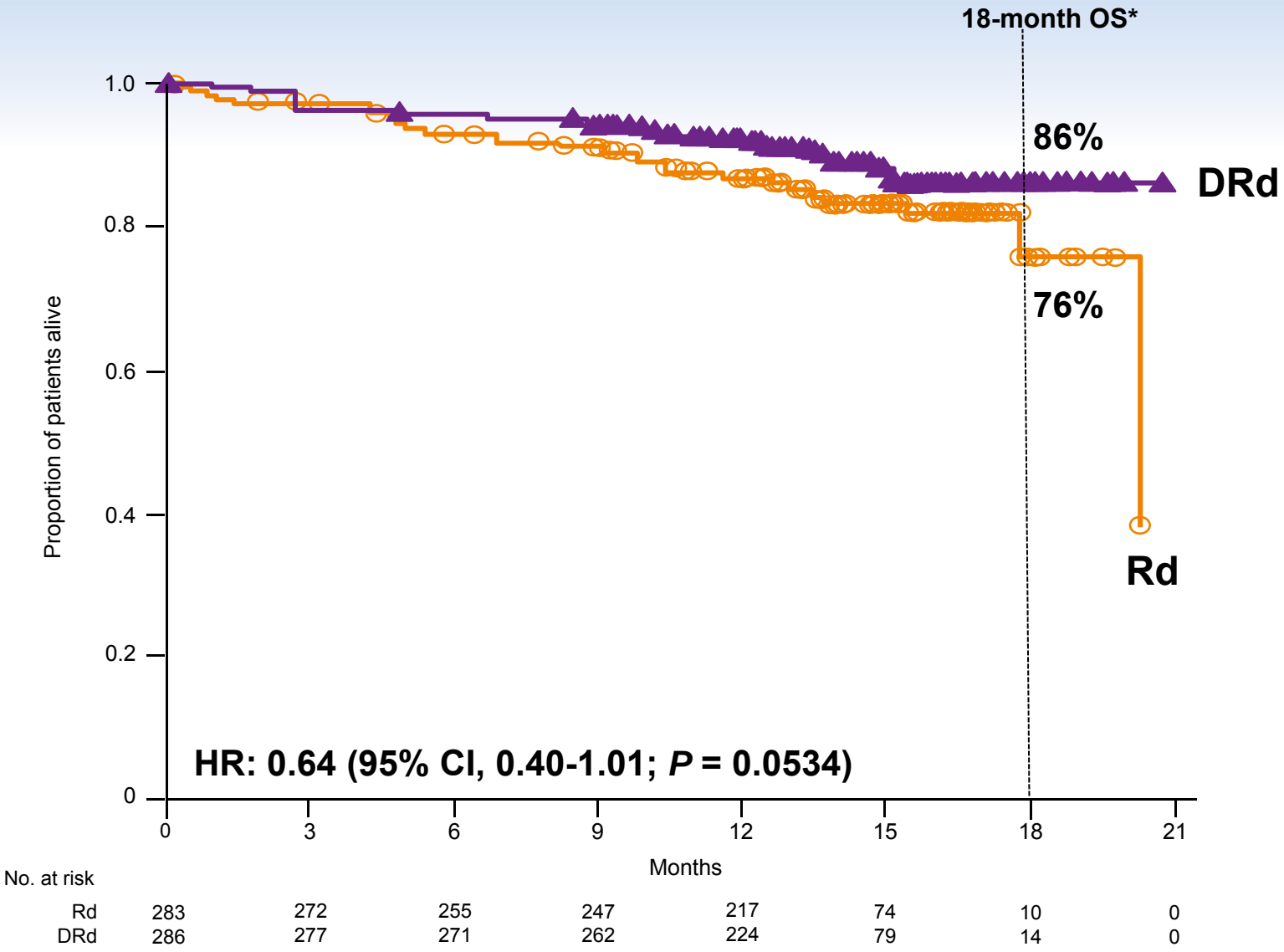
Time to Response



No. at risk

Rd (PR or better)	276	95	35	23	16	8	6	2	0	0	0	0
DRd (PR or better)	281	46	19	10	6	5	5	2	0	0	0	0
Rd (CR or better)	276	262	220	187	159	133	100	36	14	3	0	0
DRd (CR or better)	281	271	237	201	162	132	100	37	12	4	1	0

Overall Survival



18-month overall survival: 86% in DRd versus 76% in Rd

*KM estimate.

Infusion-related Reactions (IRRs)

IRRs ≥2%	Safety Analysis Set (n = 283)	
	All grades (%)	Grade 3 (%)
Patients with IRRs	48	5
Cough	9	0
Dyspnea	9	0.7
Vomiting	6	0.4
Nausea	5	0
Chills	5	0.4
Bronchospasm	5	0.4
Pruritus	3	0.4
Throat irritation	3	0
Headache	3	0
Nasal congestion	3	0
Wheezing	2	0.7
Laryngeal edema	2	0.4
Rhinorrhea	2	0
Pyrexia	2	0

- No grade 4 or 5 IRRs were reported
- 92% of all IRRs occurred during the first infusion
- 1 patient discontinued daratumumab due to an IRR

Most Common AEs

	DRd (n = 283)		Rd (n = 281)	
Hematologic AEs	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%	All-grade (%) ≥25%	Grade 3/4 (%) ≥5%
Neutropenia	59	52	43	37
Febrile neutropenia	6	6	3	3
Anemia	31	12	35	20
Thrombocytopenia	27	13	27	14
Lymphopenia	6	5	5	4
Non-hematologic AEs				
Diarrhea	43	5	25	3
Fatigue	35	6	28	3
Upper respiratory tract infection	32	1	21	1
Constipation	29	1	25	0.7
Cough	29	0	13	0
Muscle spasms	26	0.7	19	2
Pneumonia	14	8	13	8

Infections and infestations:

- Grade 3 or 4: 28% patients in DRd vs 23% patients in Rd
- The most common grade 3 or 4 infections/infestations AE was pneumonia (8% vs 8%)

Lenalidomide-based Studies

	POLLUX DRd vs Rd	ASPIRE KRd vs Rd[1]	ELOQUENT-2 ERd vs Rd[2,3]	TOURMALINE-MM1 NRd vs Rd[4]
PFS HR (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	93%	87%	79%	78%
≥VGPR	76%	70%	33%	48%
≥CR	43%	32%	4%	14%
Duration of response, mo	NE	28.6	20.7	20.5
OS HR (95% CI)	0.64 (0.40-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

1. Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152.
2. Lonial S, et al. *N Engl J Med*. 2015;373(7):621-631.
3. Dimopoulos MA, et al. *Blood*. 2015;126(23):Abstract 28.
4. Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.

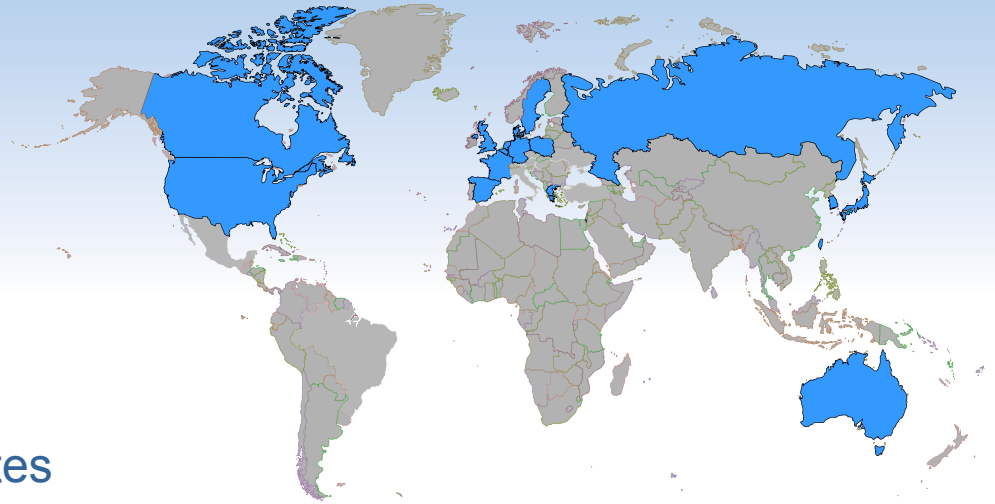
K, carfilzomib; E, elotuzumab; N, ixazomib.

Conclusions

- Daratumumab-Rd significantly improved PFS in comparison with Rd alone
  - DRd was associated with a 63% reduction in the risk of progression or death
- Treatment benefit of DRd versus Rd was consistent across subgroups
- DRd doubled CR/sCR rates and quadrupled MRD-negative rates
- DRd has a manageable safety profile consistent with the known safety profile of daratumumab or Rd alone

Daratumumab combined with Rd potentially represents a new standard of care for myeloma patients after ≥1 prior treatment

Acknowledgments



18 countries

- Patients who participated in this study
  - 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 was provided by Jason Jung, PhD (MedErgy) and was funded by Janssen Global Services, LLC