Carfilzomib, Lenalidomide, and Dexamethasone vs Lenalidomide and Dexamethasone in Patients With Relapsed Multiple Myeloma: Interim Results From ASPIRE, a Randomized, Open-Label, Multicenter Phase III Study

Abstract #79

Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, Hájek R, Rosiñol L, Siegel DS, Mihaylov GG, Goranova-Marinova, V, Rajnics P, Suvorov A, Niesvizky R, Jakubowiak A, San Miguel JF, Ludwig H, Zojwalla N, Tonda ME, Xing B, Moreau P, and Palumbo A

Background

- Lenalidomide plus high-dose dexamethasone (RD) is a reference treatment for relapsed multiple myeloma (MM)
- Lenalidomide plus weekly dexamethasone (Rd) is less toxic than RD, while yielding similar response rates
- Carfilzomib is an epoxyketone proteasome inhibitor approved in the United States as a single agent in relapsed and refractory MM
- Carfilzomib, lenalidomide, and weekly dexamethasone (KRd) was well tolerated in phase I/II trials with clinical activity in newly diagnosed and relapsed MM

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ASPIRE: KRd vs Rd

- **Primary endpoint:** progression-free survival (PFS)
- **Secondary endpoints:** overall survival (OS), overall response rate (ORR), duration of response, health-related quality of life, safety

Key inclusion criteria

- Symptomatic MM
- Measurable disease
- 1-3 prior treatments
- Relapsed or progressive disease
- Partial response or better to at least 1 prior regimen

Key exclusion criteria

- Creatinine clearance <50 mL/min
- Progressive disease (PD) on bortezomib*
- If previously treated with Rd:
  - PD during the first 3 months of treatment
  - PD at any time if Rd was the most recent treatment
- Lenalidomide or dexamethasone intolerance

*If a patient progressed during any bortezomib-containing regimen, they were eligible to enroll if the progression date occurred after discontinuation of bortezomib.

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ASPIRE Study Design

28-day cycles

Randomization

N = 792

Stratification:

- **β_2-microglobulin**
- **Prior bortezomib**
- **Prior lenalidomide**

KRd

Carfilzomib 27 mg/m^2 IV (10 min)

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Lenalidomide 25 mg *days 1–21*

Dexamethasone 40 mg *days 1, 8, 15, 22*

After cycle 12, carfilzomib given on days 1, 2, 15, 16

After cycle 18, carfilzomib discontinued

Rd

Lenalidomide 25 mg *days 1–21*

Dexamethasone 40 mg *days 1, 8, 15, 22*

IV, intravenously

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Patient and Disease Characteristics at Baseline Intent-to-Treat (ITT) Population (N = 792)

Characteristic	KRd (n = 396)	Rd (n = 396)
Median age, years (range)	64 (38–87)	65 (31–91)
≥65 years, %	46.7	52.5
ECOG performance status, %		
0–1	89.9	91.2
2	10.1	8.8
Cytogenetic risk category by FISH, %		
High	12.1	13.1
Standard	37.1	42.9
Unknown	50.8	43.9
Mean creatinine clearance, mL/min (SD)	85.0 (28.9)	85.9 (30.2)
≥50 mL/min, %	93.4	90.4
Serum β_2-microglobulin		
≥2.5 mg/L, %	80.6	80.6

ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence *in situ* hybridization; SD, standard deviation

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Patient and Disease Characteristics at Baseline (continued) ITT Population (N = 792)

Characteristic	KRd (n = 396)	Rd (n = 396)
Presence of neuropathy at baseline, %	36.4	34.6
Number of prior regimens, median (range)	2 (1–3)	2 (1–3)
Prior therapies, %		
Transplant	54.8	57.8
Bortezomib	65.9	65.7
Refractory to prior bortezomib in any prior regimen*	15.2	14.6
Lenalidomide	19.9	19.7
Any IMiD	58.8	57.8
Refractory to prior IMiD in any prior regimen*	21.5	22.2
Bortezomib and IMiD	36.9	35.1
Refractory to prior bortezomib and IMiD in any prior regimen*	6.1	6.8

*Refractory is defined as less than minimal response to or progression during therapy or within 60 days after completion of therapy. If a patient progressed during any bortezomib-containing regimen, they were eligible to enroll if the progression date occurred after discontinuation of bortezomib.

IMiD, immunomodulatory agent

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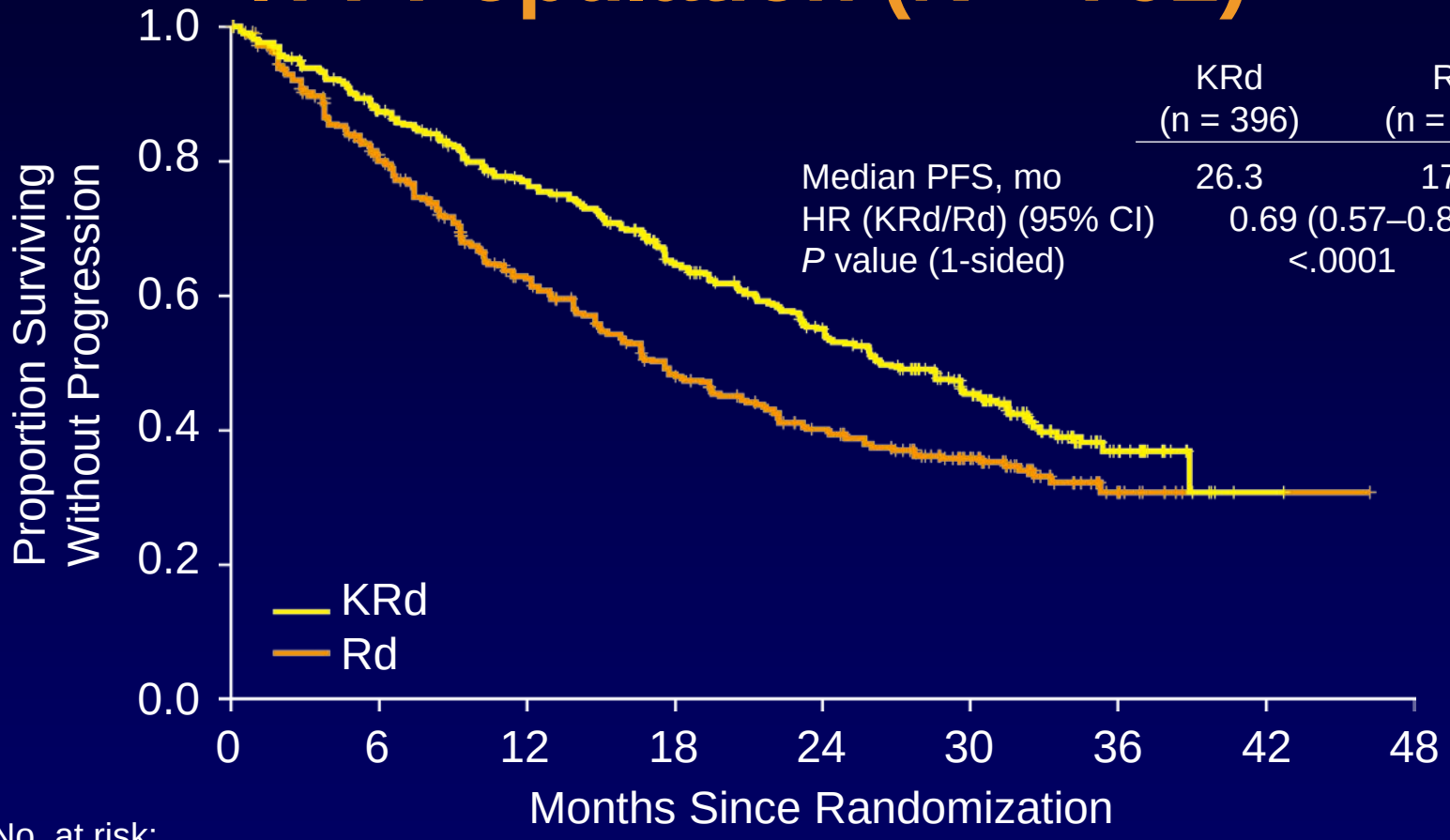
Primary Endpoint: PFS ITT Population (N = 792)



	KRd (n = 396)	Rd (n = 396)
Median PFS, mo	26.3	17.6
HR (KRd/Rd) (95% CI)	0.69 (0.57–0.83)	
P value (1-sided)	<.0001	

No. at risk:

KRd	396	332	279	222	179	112	24	1
Rd	396	287	206	151	117	72	18	1

- **Median duration of response was 28.6 months in the KRd group and 21.2 months in the Rd group**

CI, confidence interval; HR, hazard ratio.

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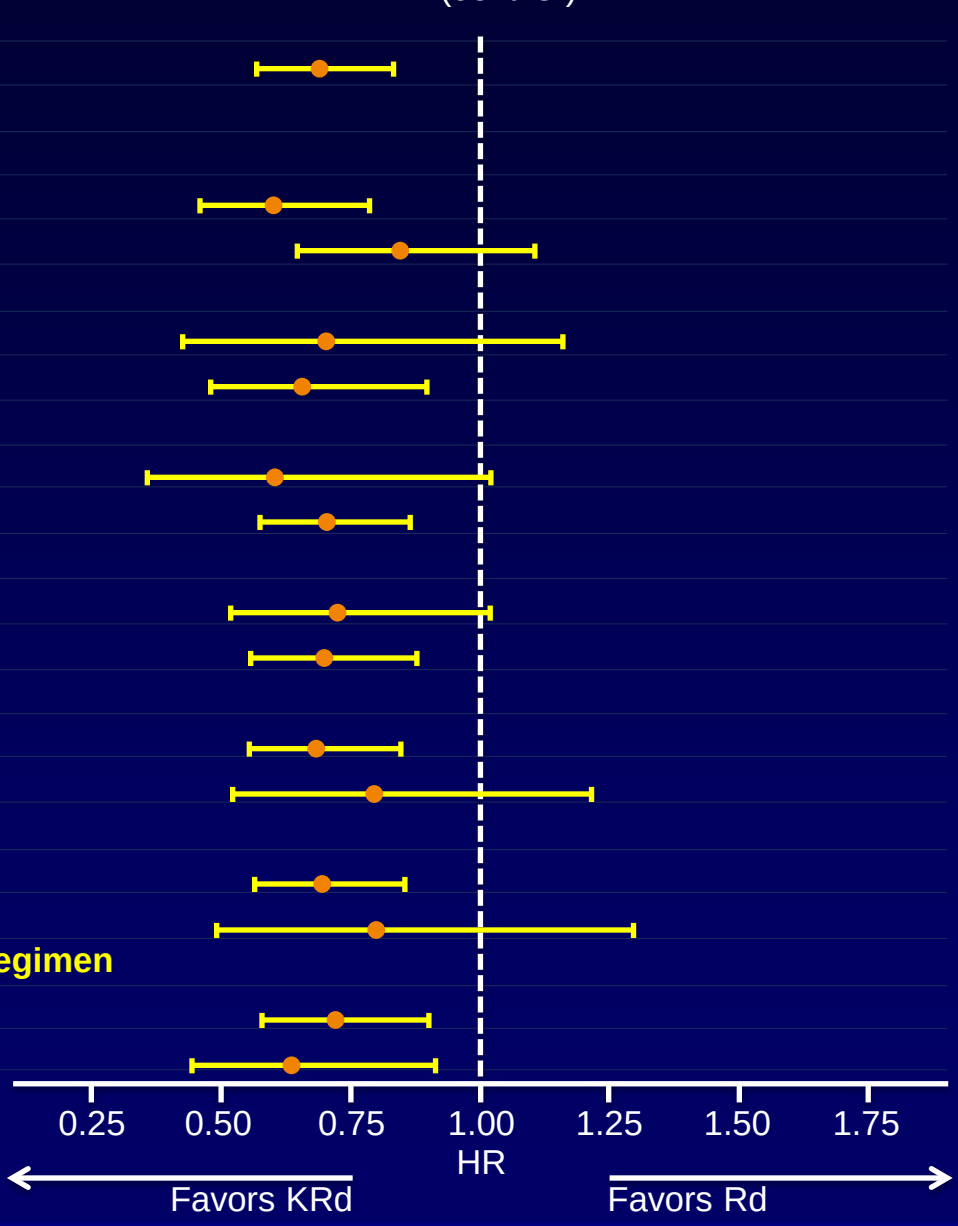
Primary Endpoint: PFS by Subgroup

Intent-to-treat group	KRd (n)	Rd (n)
Overall	396	396
Subgroup		
Age, years		
18–64	211	188
≥65	185	208
Risk group by FISH		
High risk	48	52
Standard risk	147	170
$ß_2$ microglobulin, mg/L		
<2.5	68	71
≥2.5	324	319
Prior treatment with bortezomib		
No	135	136
Yes	261	260
Prior treatment with lenalidomide		
No	317	318
Yes	79	78
Refractory to bortezomib in any prior regimen		
No	336	338
Yes	60	58
Refractory to immunomodulatory agent in prior regimen		
No	311	308
Yes	85	88



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PFS by Risk Group

	KRd (n = 396)		Rd (n = 396)			
Risk group by FISH	N	Median, months	N	Median, months	HR	*P* value (1-sided)
High	48	23.1	52	13.9	0.703	.0829
Standard	147	29.6	170	19.5	0.656	.0039

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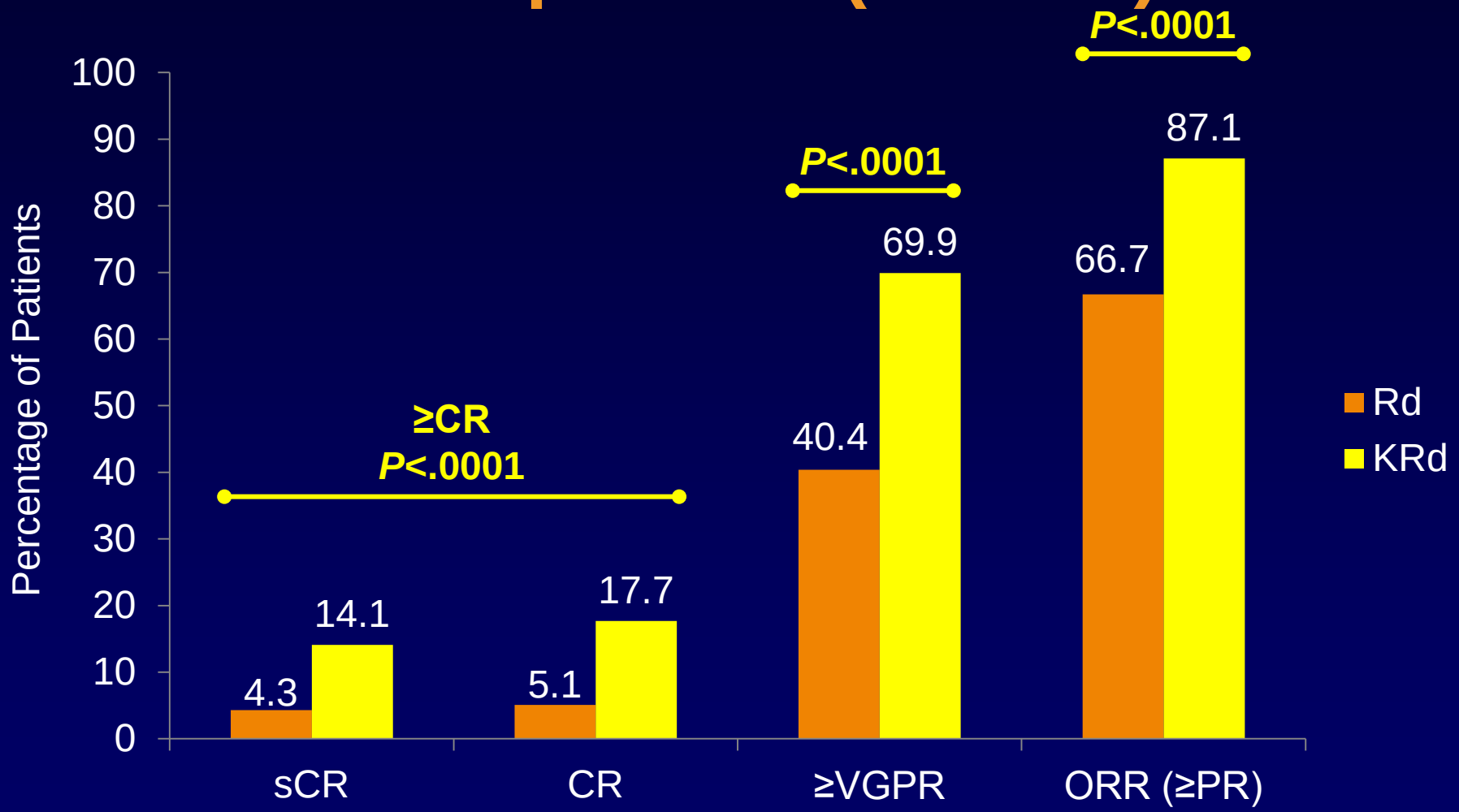
Secondary Endpoints: Response ITT Population (N = 792)



- **Mean time to response was 1.6 months in the KRd group and 2.3 months in the Rd group**

CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

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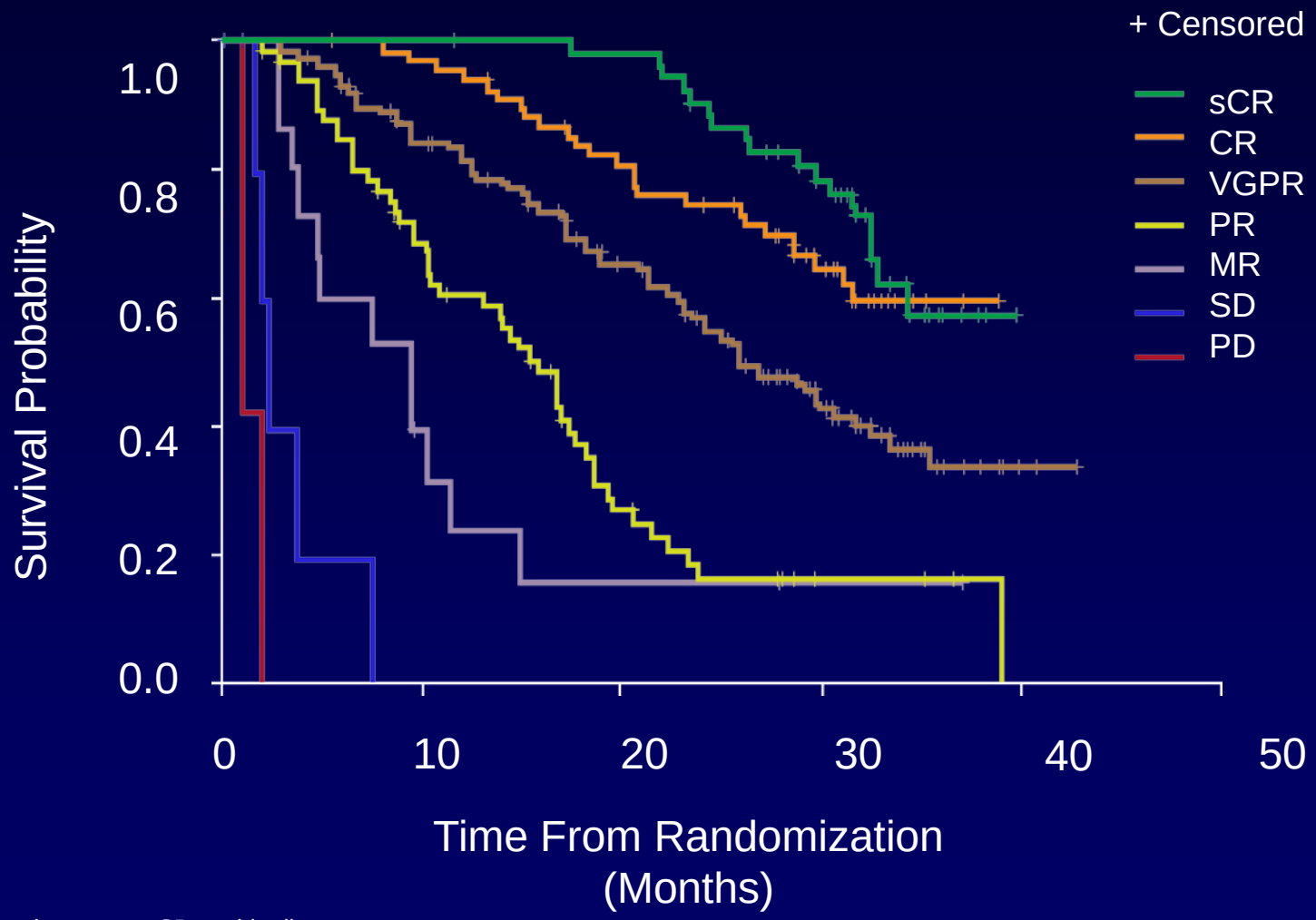
PFS by Response Category, in the KRd Group



MR, minimal response; SD, stable disease

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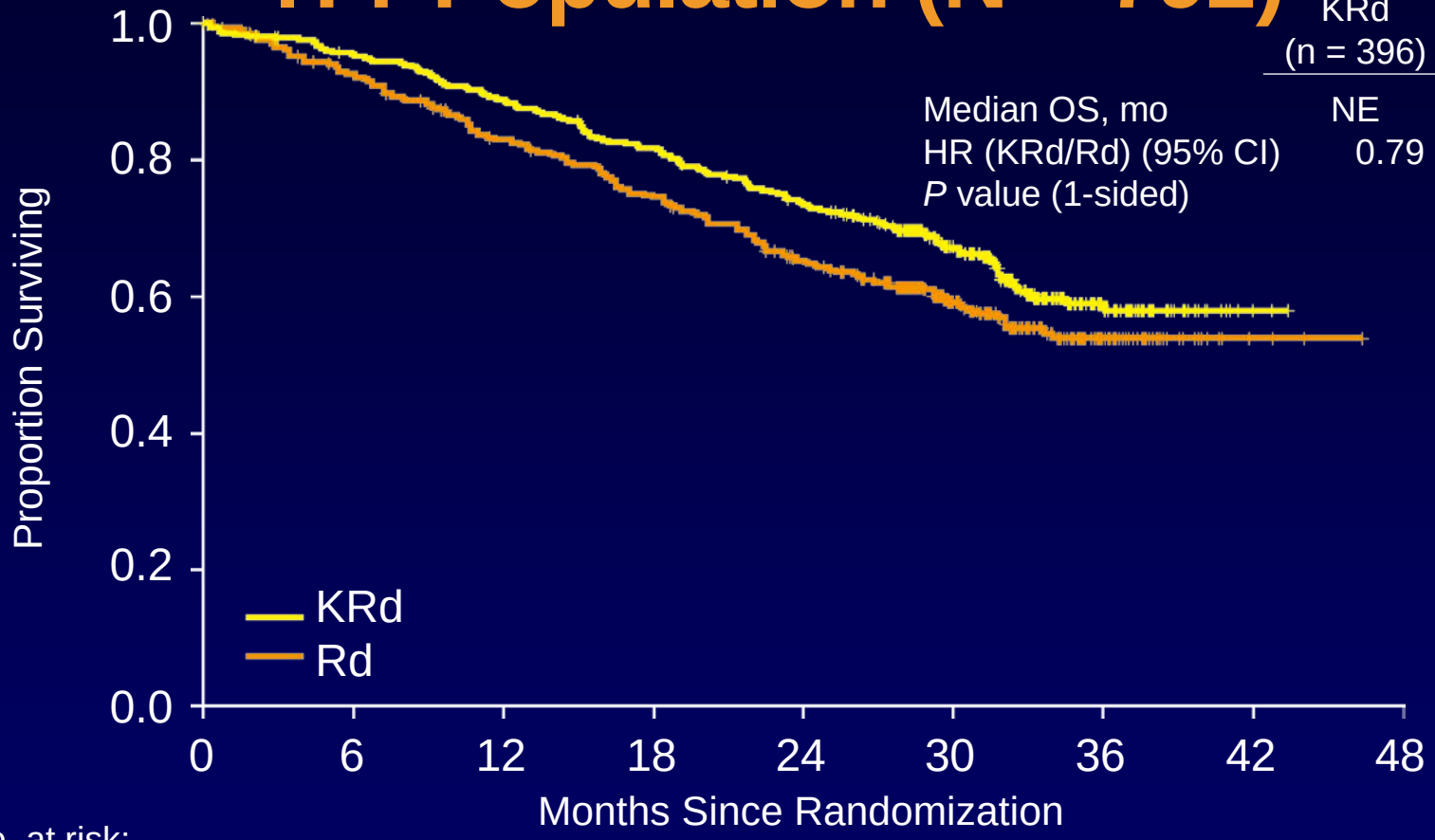
Secondary Endpoints: OS ITT Population (N = 792)



	KRd (n = 396)	Rd (n = 396)
Median OS, mo	NE	NE
HR (KRd/Rd) (95% CI)	0.79 (0.63–0.99)	
P value (1-sided)	.018	

No. at risk:

KRd	396	369	343	315	280	191	52	2
Rd	396	356	313	281	237	144	39	3

- **Median OS was not reached; results did not cross the prespecified stopping boundary at the interim analysis**
- **Kaplan-Meier 24-month OS rates were 73.3% with KRd and 65.0% with Rd**

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Adverse Events (AEs), Treatment Discontinuations, and Deaths Safety Population (n = 781)

Category	KRd (n = 392)	Rd (n = 389)
Any AE, %	96.9	97.2
Grade ≥3 treatment-emergent AE	83.7	80.7
Deaths within 30 days of last dose, %	7.7	8.5
Deaths due to disease progression	0.5	1.3
Deaths due to AEs	6.9	6.9
Serious AE, %	59.7	53.7
Median treatment duration, weeks	88.0	57.0
Treatment discontinuations, %	69.9	77.9
Discontinuation due to disease progression	39.8	50.1
Discontinuation due to AE	15.3	17.7

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AEs Occurring in ≥25% of Patients in Either Arm Safety Population (n = 781)

AE, %	KRd (n = 392)		Rd (n = 389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic AEs				
Anemia	42.6	17.9	39.8	17.2
Neutropenia	37.8	29.6	33.7	26.5
Thrombocytopenia	29.1	16.6	22.6	12.3

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AEs Occurring in ≥25% of Patients in Either Arm (continued) Safety Population (n = 781)

AE, %	KRd (n = 392)		Rd (n = 389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Nonhematologic AEs				
Diarrhea	42.3	3.8	33.7	4.1
Fatigue	32.9	7.7	30.6	6.4
Cough	28.8	0.3	17.2	0
Pyrexia	28.6	1.8	20.8	0.5
Upper respiratory tract infection	28.6	1.8	19.3	1.0
Hypokalemia	27.6	9.4	13.4	4.9
Muscle spasms	26.5	1.0	21.1	0.8

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Other AEs of Interest Safety Population (n = 781)

AE, %	KRd (n = 392)		Rd (n = 389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Dyspnea	19.4	2.8	14.9	1.8
Peripheral neuropathy*	17.1	2.6	17.0	3.1
Hypertension	14.3	4.3	6.9	1.8
Acute renal failure*	8.4	3.3	7.2	3.1
Elevated creatinine	6.6	1.0	4.6	0.3
Cardiac failure*	6.4	3.8	4.1	1.8
Deep vein thrombosis	6.6	1.8	3.9	1.0
Ischemic heart disease*	5.9	3.3	4.6	2.1
Pulmonary embolism	3.6	3.1	2.3	2.3
Second primary malignancy*	2.8	2.3	3.3	2.8

*Grouped term

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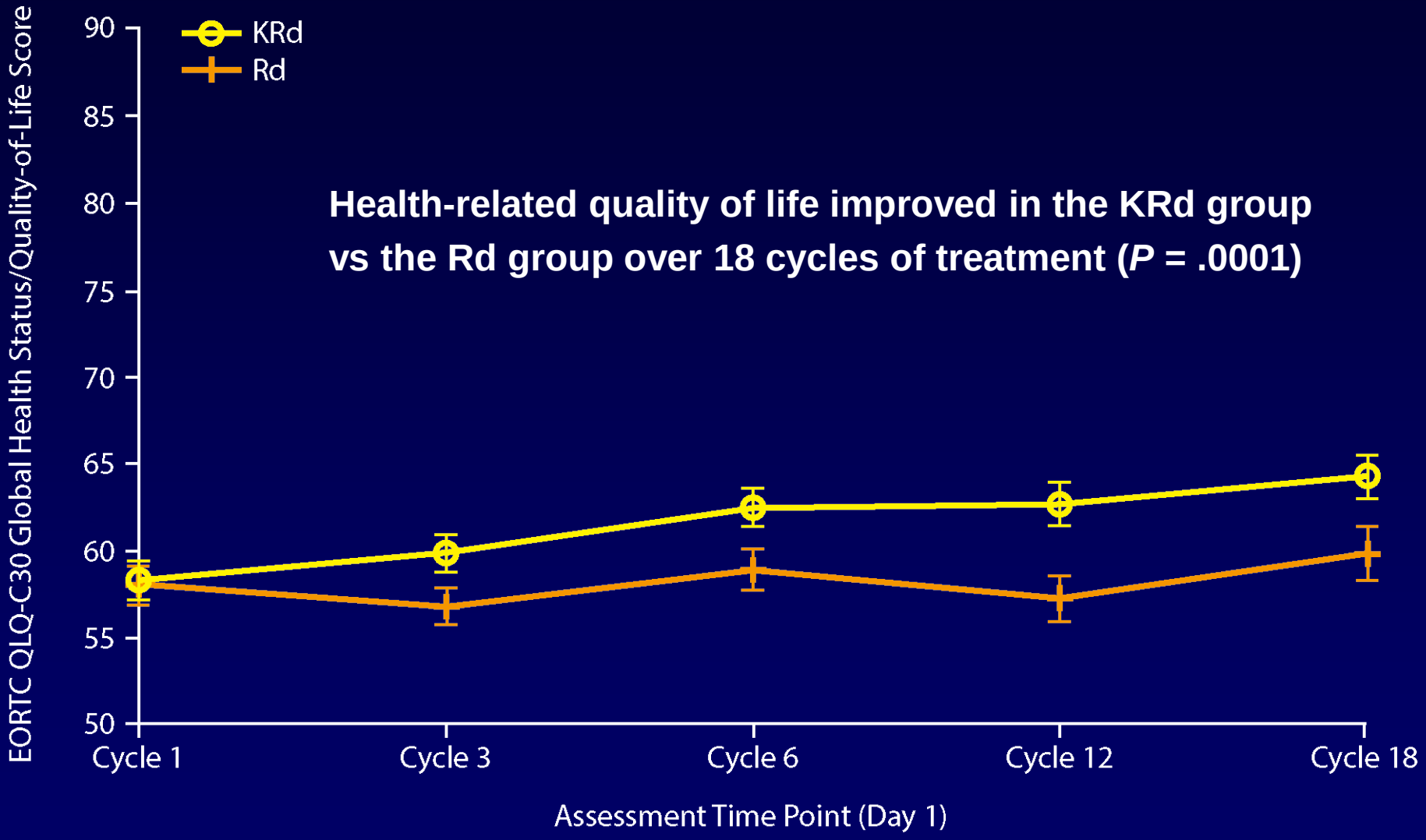
Health-Related Quality of Life



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Conclusions

- PFS was significantly improved with KRd (hazard ratio, 0.69; *P*<.0001)
  - An unprecedented median PFS of 26.3 months with KRd
- Trend in OS favoring the KRd group: Kaplan–Meier 24-month OS rates of 73.3% (KRd) vs 65.0% (Rd)
- ORR was higher with KRd (87.1% vs 66.7%); significantly more patients achieved a complete response or better (31.8% vs 9.3%)

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Conclusions (continued)

- AEs led to fewer discontinuations in the KRd group, and patients remained on study treatment longer
  - Cardiac and renal events were reported at rates consistent with or lower than prior studies of
    - single-agent carfilzomib
- KRd consistently improved health-related quality of life compared with Rd over 18 cycles of treatment
- KRd represents a potential new standard of care in relapsed MM

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