Praxisrelevante Fortschritte bei nicht für eine Transplantation geeigneten PatientInnen

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Ziele der Myelomtherapie

Erzielen von Symptomfreiheit

Erzielen von Remission:

Unterschied ob
hohes oder niedriges Risiko

Verlängerung des PFS

Verlängerung des Gesamtüberlebens

Fortschritte in der Therapie der Behandlung von nicht für die Transplantation geeigneten Patienten mit multiplem Myelom

Immunmodulierende Substanzen:

Revlimid (Erstlinientherapie)

Pomalidomid

Proteasomeninhibitoren:

Carfilzomib

Ixozamib

HDAC-Inhibitoren

Vorinostat (Entwicklung gestoppt)

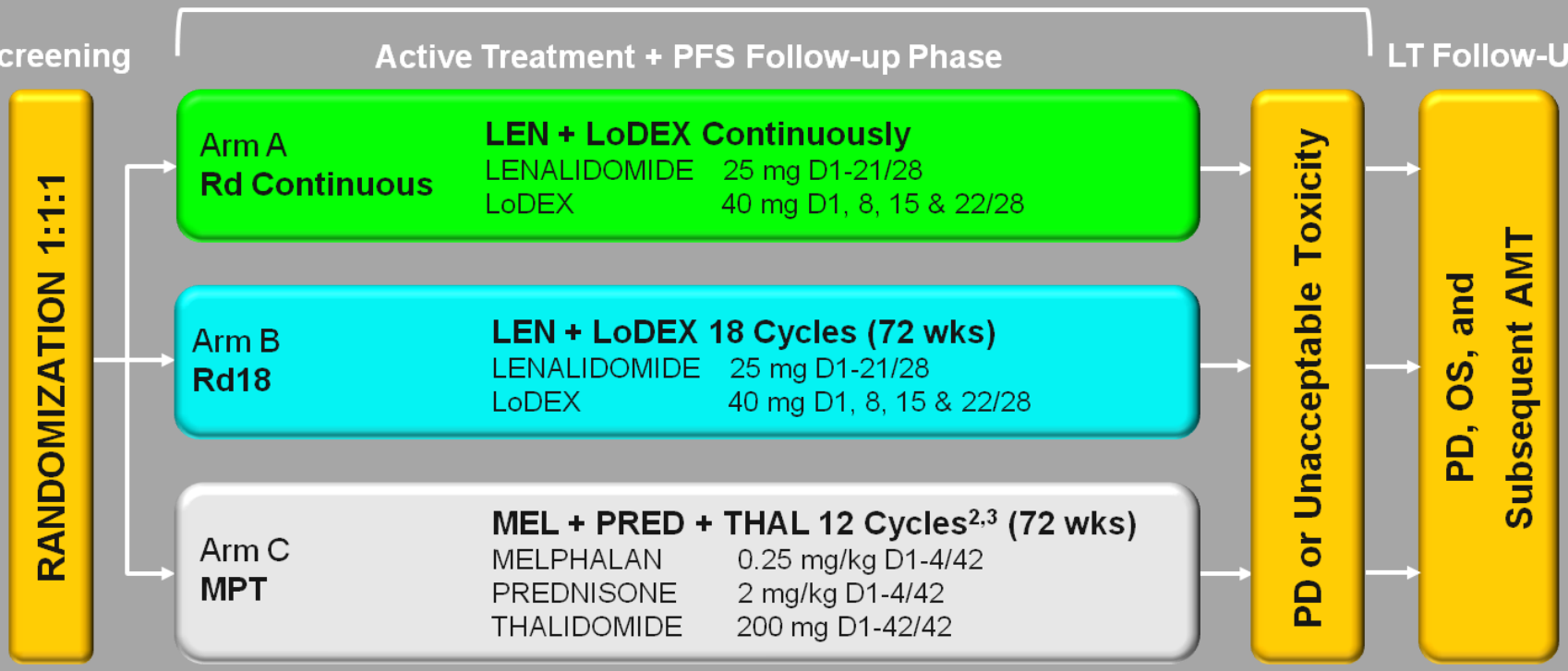
Panabinostat

Monoklonale Antikörper

Daratumumab

Elotuzumab

FIRST (MM-020): Impact of Cytogenetics
Study Design[1]



Pts aged > 75 yrs: LoDEX 20 mg D1, 8, 15 & 22/28; MEL 0.2 mg/kg D1-4; THAL 100 mg D1-42/42.
All pts received thromboprophylaxis.

- Stratification: age, country, and ISS stage
- Data cutoff: March 3, 2014

AMT, antimyeloma therapy; ISS, International Staging System; LEN, lenalidomide; LoDEX, low-dose dexamethasone; LT, long-term; MEL, melphalan; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRED, prednisone; pt, patient; THAL, thalidomide.

1. Benboubker L, et al. *N Engl J Med.* 2014;371:906-917. 2. Facon T, et al. *Lancet.* 2007;370:1209-1218. 3. Hulin C, et al. *J Clin Oncol.* 2009;27:3664-3670.
Avet-Loiseau H, et al. Impact of Cytogenetics on Outcomes of Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST (MM-020) Trial. *ASH 2015, abstract #730.*

FIRST (MM-020): Frailty Analysis
Frailty Algorithm

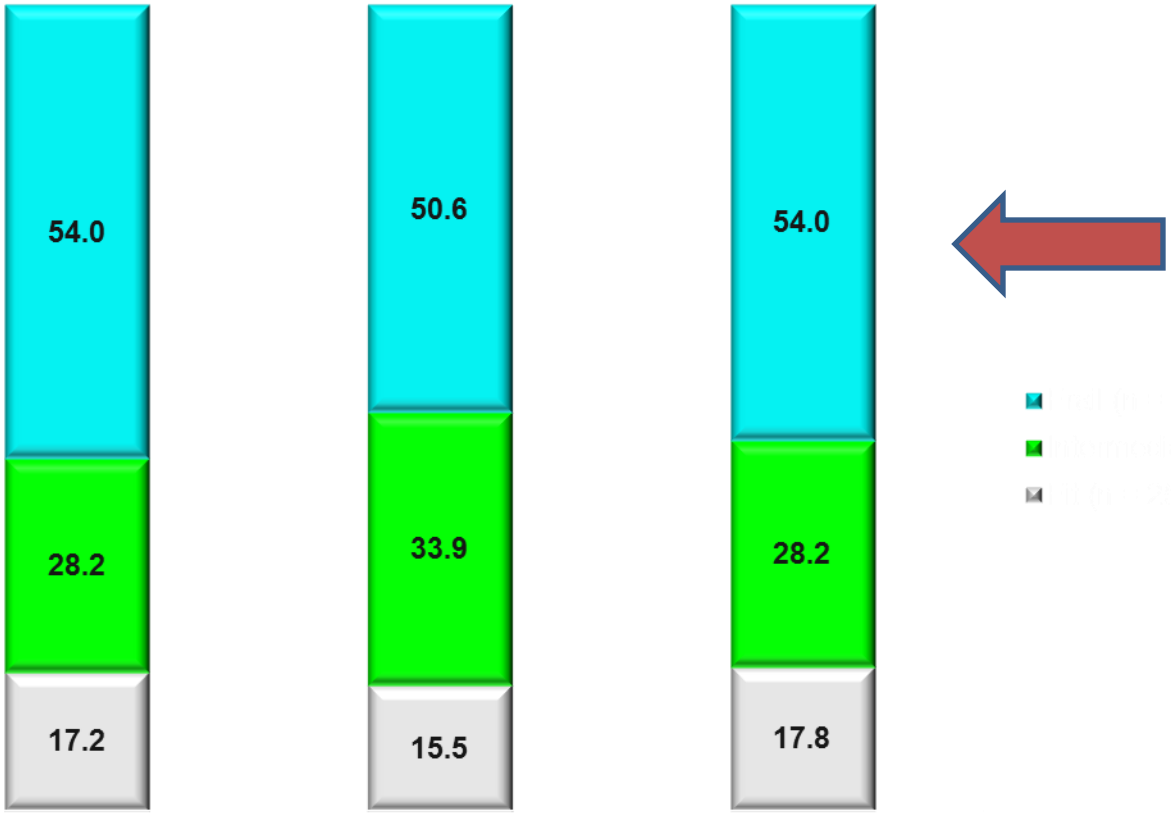
- Pts were categorized into 3 severity groups (fit, intermediate, or frail) as described by a proxy algorithm based on the IMWG frailty scale[1]

IMWG Frailty Scale[1]	Proxy for MM-020 Analysis	Score
Age	Age	
≤ 75 yrs	≤ 75 yrs	0
76-80 yrs	76-80 yrs	1
> 80 yrs	> 80 yrs	2
Activity of Daily Living score	EQ-5D: Self Care score	
> 4	1 (no problem)	0
≤ 4	2-3 (moderate or severe problem)	1
Instrumental Activity of Daily Living score	EQ-5D: Usual Activities score	
> 5	1 (no problem)	0
≤ 5	2-3 (moderate or severe problem)	1
Charlson Comorbidity Index score	Charlson Comorbidity Index score	
≤ 1	≤ 1	0
≥ 2	≥ 2	1
		Total
		0: Fit
		1: Intermediate
		≥ 2: Frail

1. Palumbo A, et al. *Blood.* 2015;125:2068-2074.
IMWG, International Myeloma Working Group; pt, patient.
Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. *ASH 2015, abstract 4239*.

Facon T et al, ASH 2015

FIRST (MM-020): Frailty Analysis
Breakdown of Severity Group by Treatment Arm

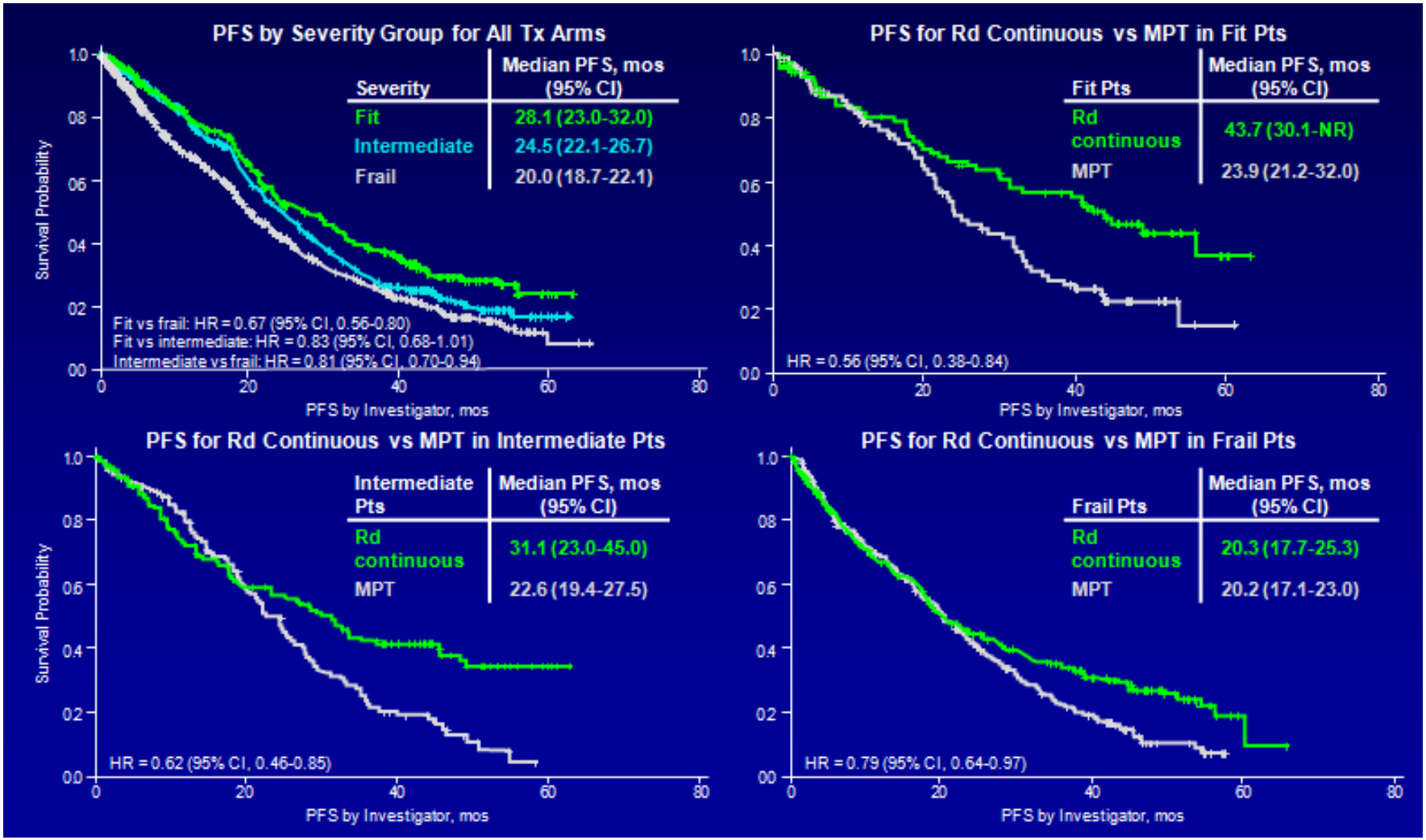


cont, continuous; MPT, melphalan, prednisone, and thalidomide; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles.

Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. *ASH 2015, abstract 4239*.

Facon T et al, ASH 2015

FIRST (MM-020): Frailty Analysis
PFS by Severity Group (Data Cutoff: March 3, 2014)

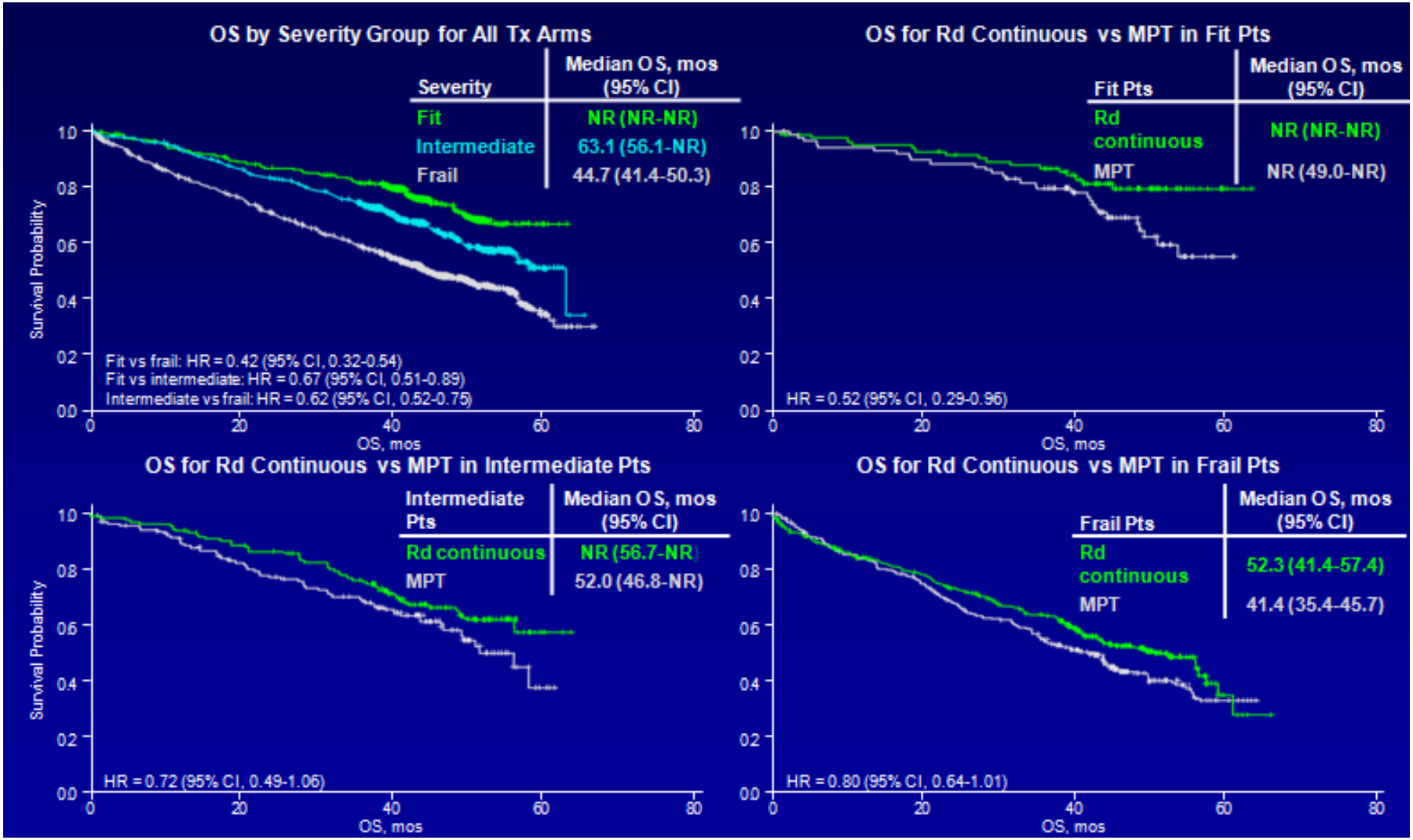


HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; NR, not reached; PFS, progression-free survival; pt, patient; Rd, lenalidomide and low-dose dexamethasone; Tx, treatment.

Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. *ASH 2015, abstract 4239*

Facon T et al, ASH 2015

FIRST (MM-020): Frailty Analysis
OS by Severity Group (Data Cutoff: March 3, 2014)

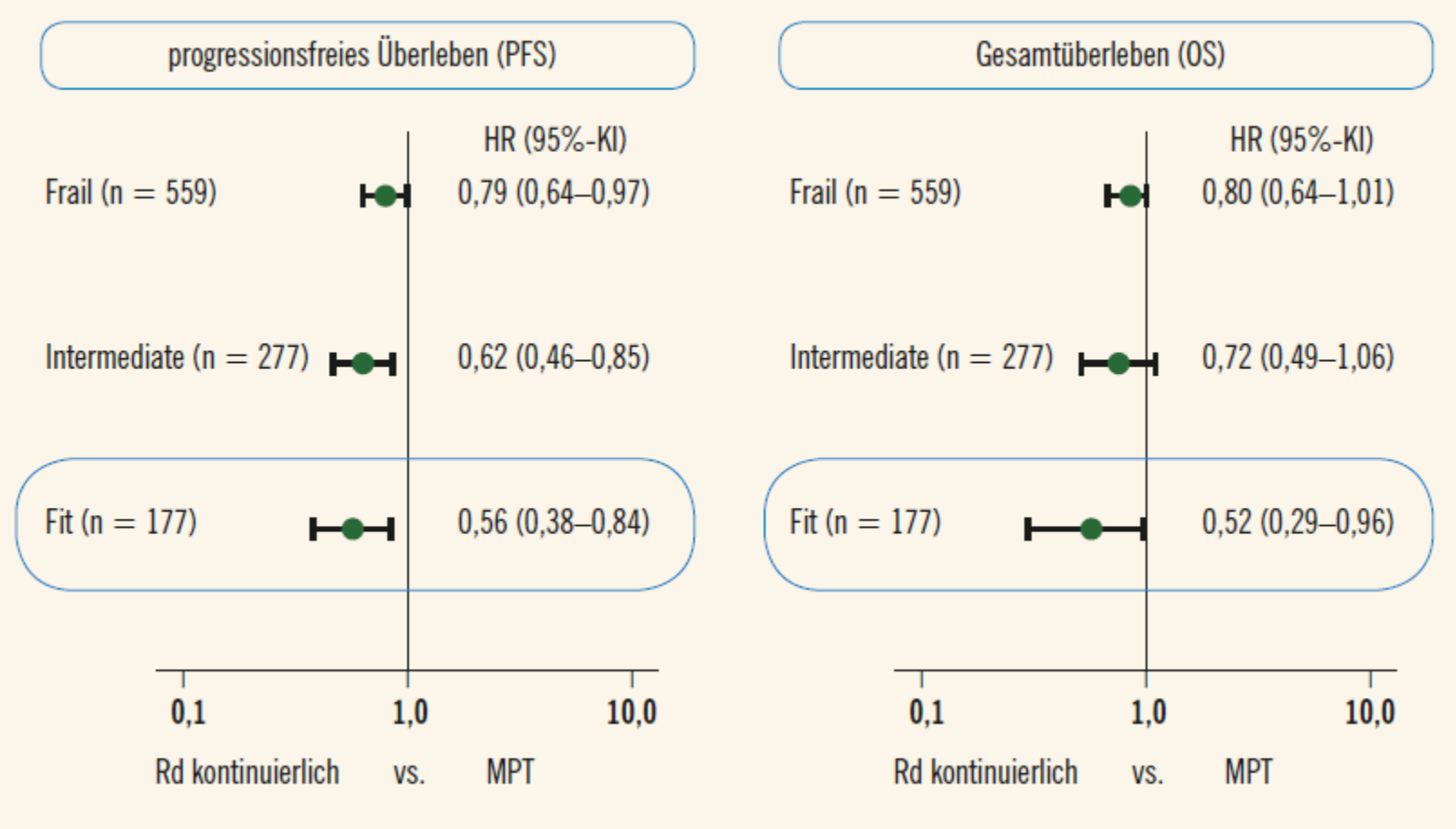


HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; NR, not reached; OS, overall survival; pt, patient; Rd, lenalidomide and low-dose dexamethasone; Tx, treatment.

Facon T. A Frailty Scale Predicts Outcomes in Patients With Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial. *ASH 2015, abstract 4239*

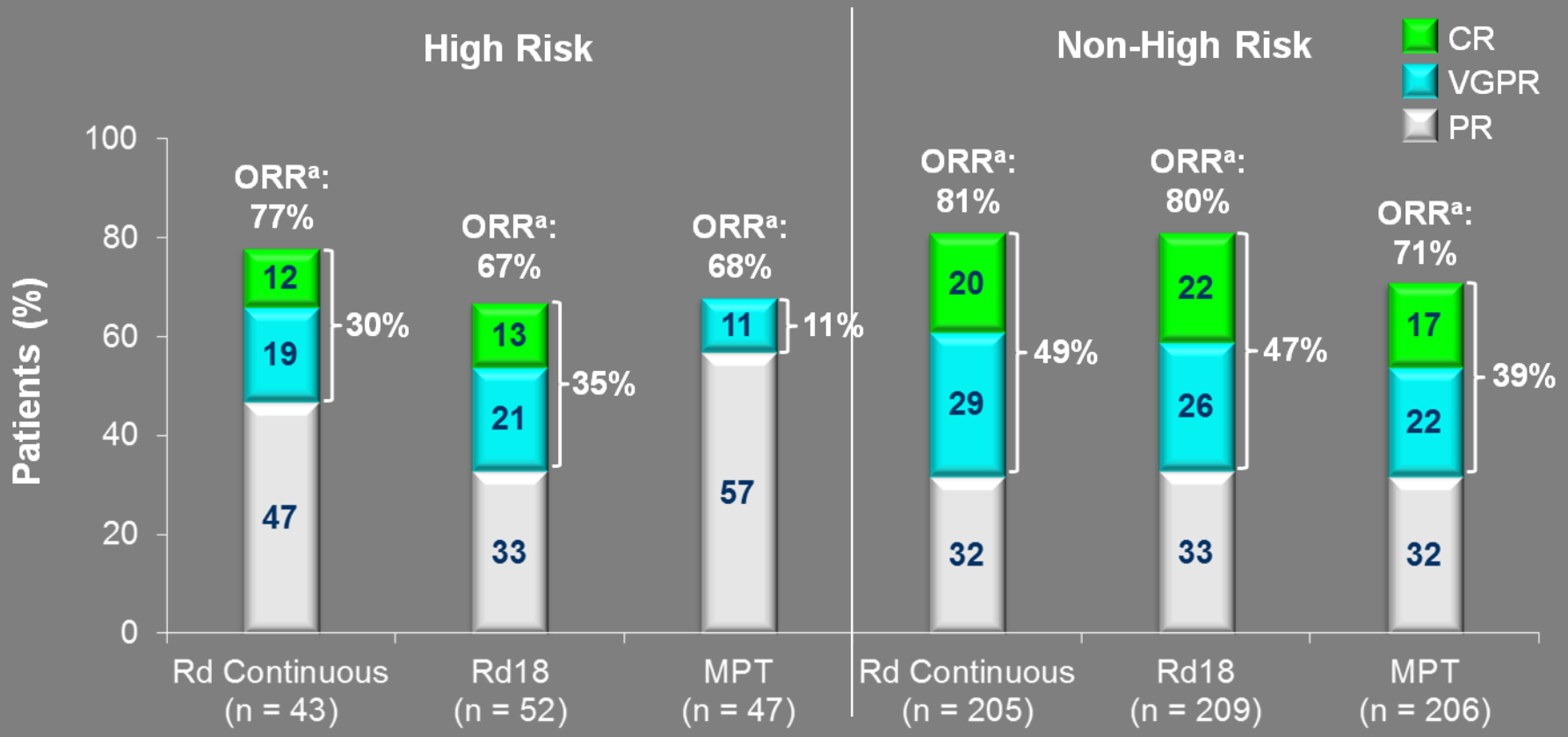
Facon T et al, ASH 2015

Kontinuierliche Therapie mit Revlimid + Dexamethason (Fortecortin) Unfitte vs. Fitte Patienten



Facon T et al, ASH 2015

FIRST (MM-020): Impact of Cytogenetics Response



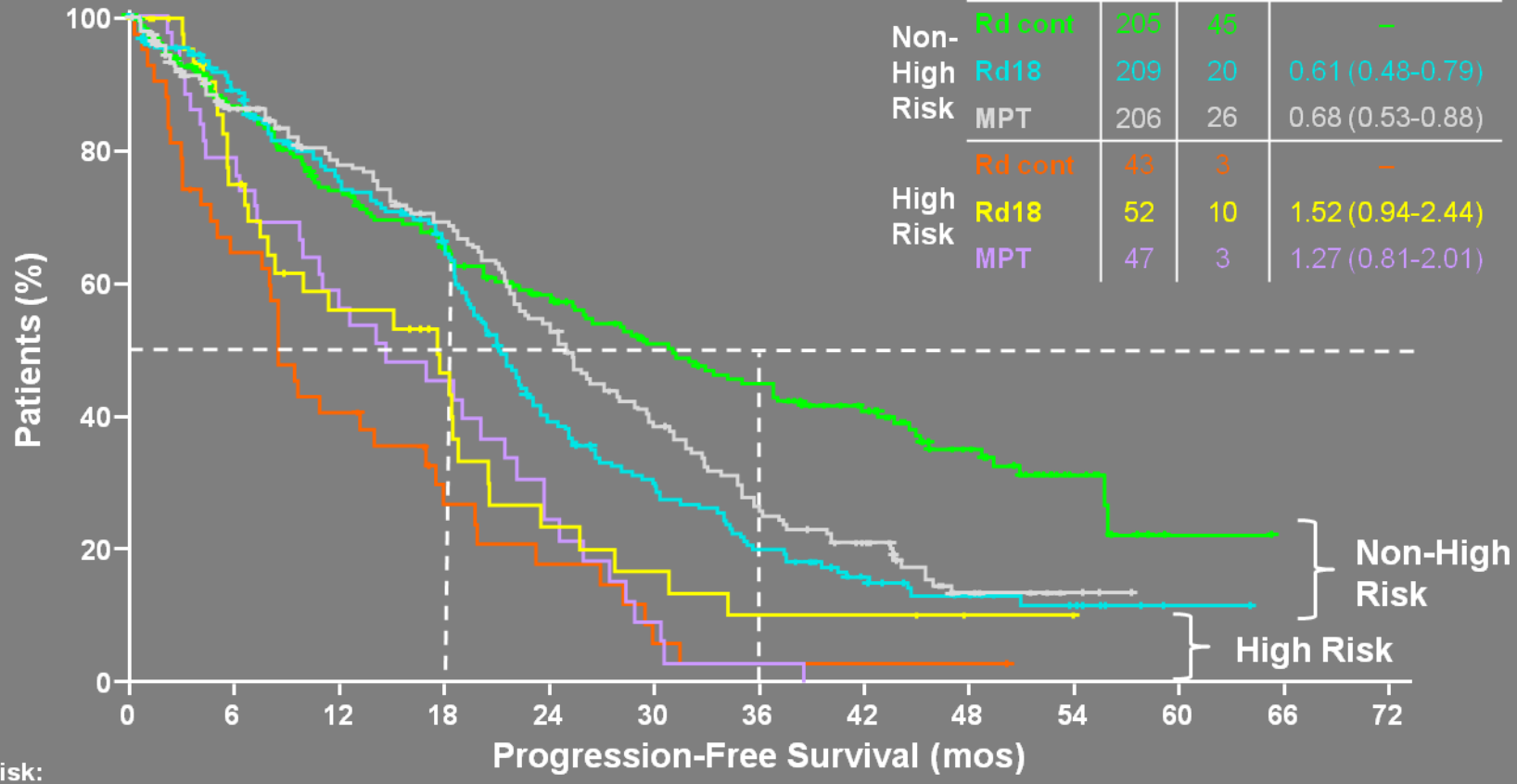
Odds Ratio (95% CI)	High Risk	Non-High Risk
Rd continuous vs MPT	1.55 (0.61-3.95)	1.75 (1.10-2.77)
Rd continuous vs Rd18	1.60 (0.64-4.00)	1.07 (0.66-1.74)

[a] Numbers may not sum due to rounding.

CR, complete response; MPT, melphalan, prednisone, and thalidomide; ORR, overall response rate; PR, partial response; Rd, lenalidomide plus low-dose dexamethasone; Rd18, Rd for 18 cycles; VGPR, very good partial response.

Avet-Loiseau H, et al. Impact of Cytogenetics on Outcomes of Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST (MM-020) Trial. *ASH 2015, abstract #730.*

FIRST (MM-020): Impact of Cytogenetics Progression-Free Survival



		n	3 Yr, %	HR (95% CI) (Rd cont vs)
Non-High Risk	Rd cont	205	45	–
	Rd18	209	20	0.61 (0.48-0.79)
	MPT	206	26	0.68 (0.53-0.88)
High Risk	Rd cont	43	3	–
	Rd18	52	10	1.52 (0.94-2.44)
	MPT	47	3	1.27 (0.81-2.01)

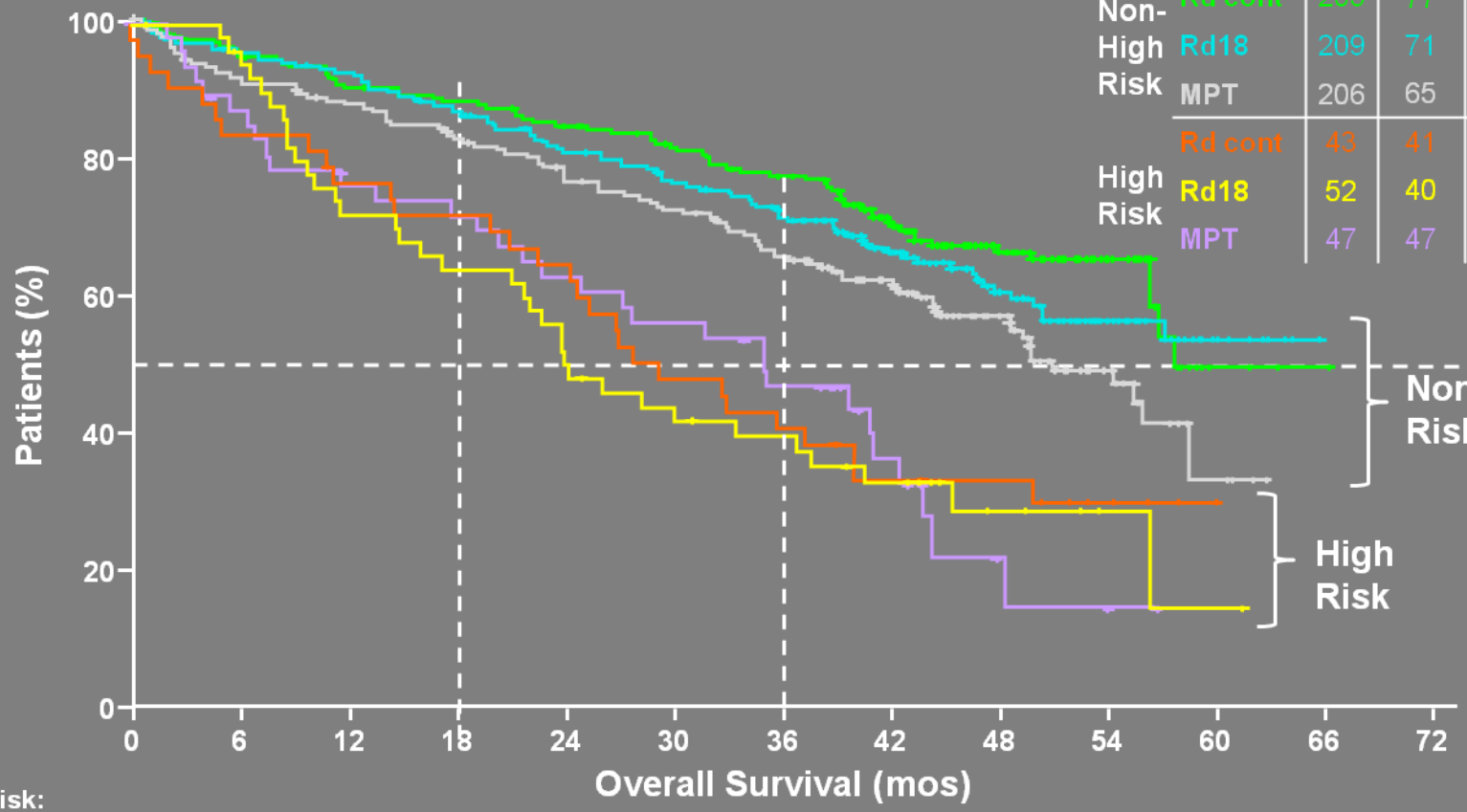
Pts at risk:

Non-High Risk	Rd cont	205	159	132	115	96	78	68	51	30	11	1	0
	Rd18	209	168	136	114	65	48	32	19	11	7	1	0
	MPT	206	152	127	108	84	58	38	27	10	4	0	
High Risk	Rd cont	43	27	17	9	6	2	1	1	1	0		
	Rd18	52	29	20	14	7	5	3	3	1	1	0	
	MPT	47	32	22	16	8	3	1	0				

cont, continuous; HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; pt, patient; Rd, lenalidomide plus low-dose dexamethasone; Rd18, Rd for 18 cycles.

Avet-Loiseau H, et al. Impact of Cytogenetics on Outcomes of Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST (MM-020) Trial. *ASH 2015, abstract #730.*

FIRST (MM-020): Impact of Cytogenetics
Overall Survival



		n	3 Yr, %	HR (95% CI) (Rd cont vs)
Non-High Risk	Rd cont	205	77	–
	Rd18	209	71	0.85 (0.62-1.18)
	MPT	206	65	0.66 (0.48-0.91)
High Risk	Rd cont	43	41	–
	Rd18	52	40	0.90 (0.55-1.47)
	MPT	47	47	0.95 (0.57-1.59)

Pts at risk:												
Non-High Risk	Rd cont	205	189	179	174	165	154	145	104	70	31	3	0
	Rd18	209	197	189	177	163	152	139	100	63	35	8	0
	MPT	206	182	174	162	148	139	122	97	58	25	4	0
High Risk	Rd cont	43	36	32	30	27	20	17	13	10	5	1	0
	Rd18	52	48	36	32	27	21	18	14	6	3	1	0
	MPT	47	40	34	33	28	25	20	10	4	2	0	

cont, continuous; HR, hazard ratio; MPT, melphalan, prednisone, and thalidomide; pt, patient; Rd, lenalidomide plus low-dose dexamethasone; Rd18, Rd for 18 cycles.

Avet-Loiseau H, et al. Impact of Cytogenetics on Outcomes of Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma Treated With Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST (MM-020) Trial. *ASH 2015, abstract #730.*

FIRST (MM-020): Frailty Analysis
Authors' Conclusions

- Das progressionsfreie- und Gesamtüberleben ist besser bei Patienten die mit Rev/Dex kontinuierlich behandelt werden im Vergleich zu jenen Patienten die in dieser Studie MPT bekommen haben.
- Die Bedeutung der IMWG Frailty Skala um das klinische Ansprechen vorauszusagen wurde durch diese Studie unterstrichen.
- Der Großteil der in die FIRST Studie eingebrachten Patienten bestand aus Patienten mit schlechterem Allgemeinzustand, sodass diese Studie eine für die klinische Praxis relevante Untersuchung darstellt.
- Patienten mit Niedrigrisiko – Zytogenetik profitieren durch diese Kombination mehr als Hochrisikopatienten.
- Die kontinuierliche Behandlung mit Rev/Dex kann daher als Standard zur Erstbehandlung älterer Patienten betrachtet werden.

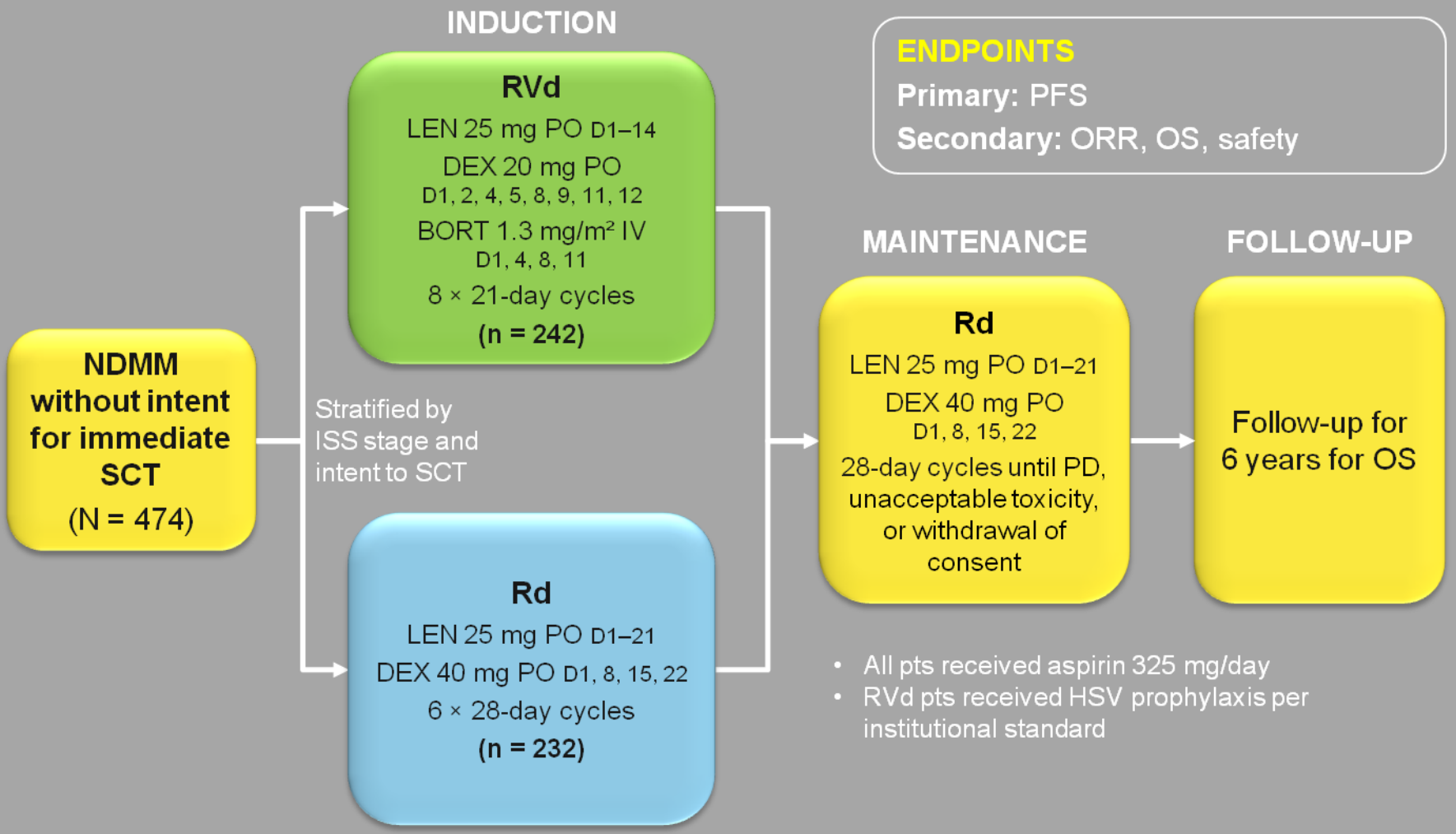
Facon T et al, ASH 2015

First-line therapy of multiple myeloma

Lenalidomide combinations

SWOG S077 (Durie) Abstract 25 – ASH 2015

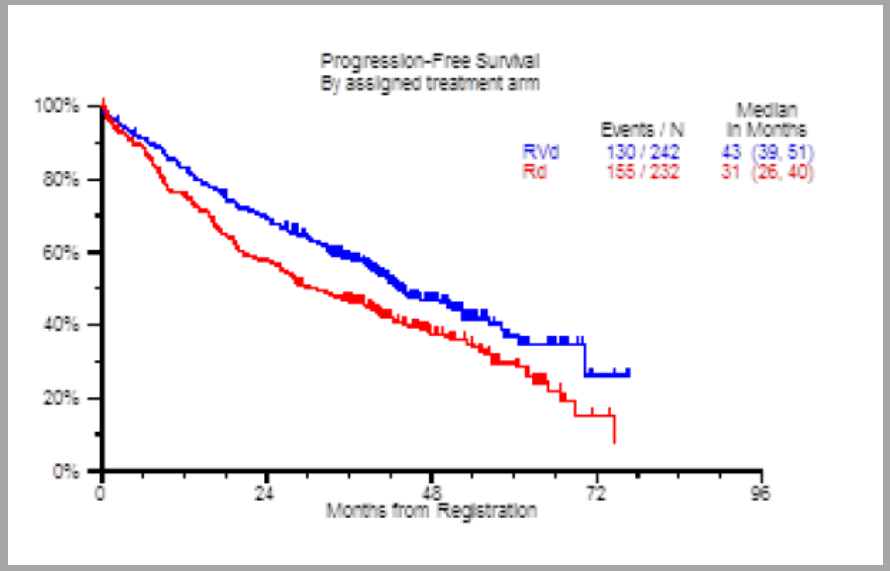
RVd vs Rd With Rd Maintenance: SWOG S0777 Study Design[1,2]

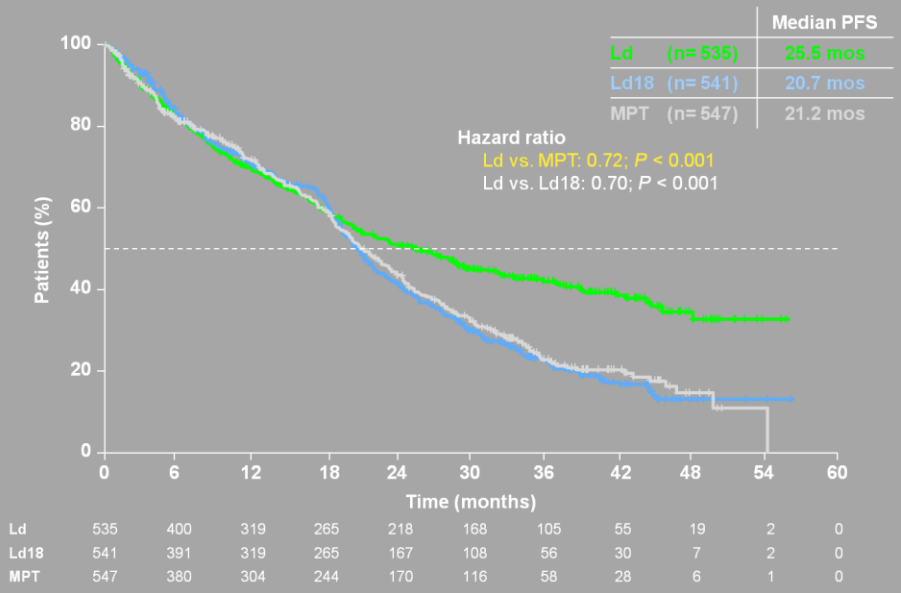


BORT, bortezomib; D, day; DEX, dexamethasone; HSV, herpes simplex virus; ISS, International Staging System; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral administration; pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone; SCT, stem cell transplant.

1. Durie B, et al. Bortezomib, Lenalidomide and Dexamethasone vs Lenalidomide and Dexamethasone in Patients (Pts) With Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777 *ASH 2015, abstract #25. 2.* https://clinicaltrials.gov/ct2/show/NCT00644228

Phase III Trial SWOG S0777: Results





ORR: RVD: 71% vs RD 64%

Durie:“…..dass in der SWOG0777 deutlich jüngere Patienten eingeschlossen waren als in der FIRST. „

RVd vs Rd With Rd Maintenance: SWOG S0777
Pt Characteristics

- Pt characteristics were similar between Tx arms, with two exceptions:
  - Fewer women received RVd vs Rd (37% vs 47%; *P* = 0.033)
  - Fewer pts ≥ 65 years received RVd vs Rd (38% vs 48%; *P* = 0.042)

Pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone; Tx, treatment.

Durie B, et al. Bortezomib, Lenalidomide and Dexamethasone vs Lenalidomide and Dexamethasone in Patients (Pts) With Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777 *ASH 2015, abstract #25.*

RVd vs Rd With Rd Maintenance: SWOG S0777 Survival Analyses

	RVd (n = 242)	Rd (n = 232)
Median PFS, mos (95% CI)	43 (39-51)	31 (26-40)
HR (96% Wald CI)	0.742 (0.579-0.951)	
1-sided stratified log-rank *P*-value	.0066[a]	
Median OS, mos (95% CI)	NR	63 (55-69)
HR	0.666	
2-sided log-rank *P*-value	.0114	

[a] This analysis reached the prespecified significance level of .02.

HR, hazard ratio; Rd, lenalidomide and low-dose dexamethasone; NR, not reached; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone.

Durie B, et al. Bortezomib, Lenalidomide and Dexamethasone vs Lenalidomide and Dexamethasone in Patients (Pts) With Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777 *ASH 2015, abstract #25.*

RVd vs Rd With Rd Maintenance: SWOG S0777 Authors' Conclusions

- The addition of BORT to Rd induction therapy provides a statistically significant and clinically meaningful improvement in PFS
  - OS is also extended with the addition of BORT to Rd
- The safety and tolerability of RVd is acceptable, although neurotoxicity is increased
- RVd represents a potential new standard of care for pts with NDMM

BORT, bortezomib; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone.

Durie B, et al. Bortezomib, Lenalidomide and Dexamethasone vs Lenalidomide and Dexamethasone in Patients (Pts) With Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777 *ASH 2015, abstract #25.*

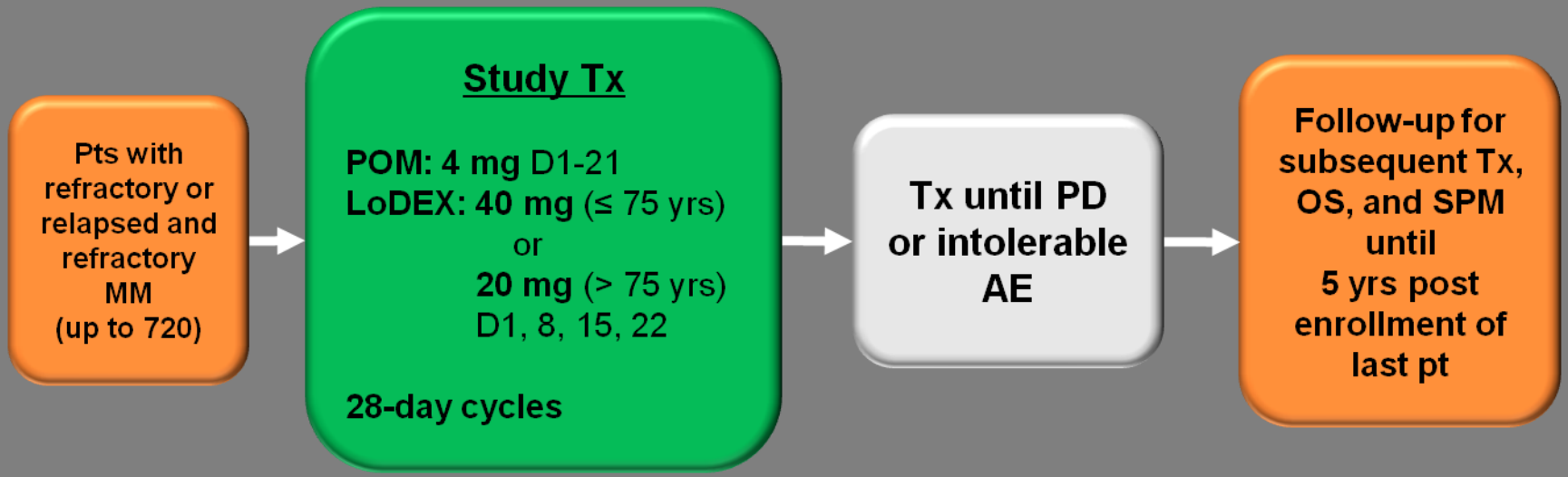
Therapy of relpased/refractory MM

Pomalidomide combinations

POM + LoDEX vs. HiDEX in Relapsed and Refractory MM

MM-010 (STRATUS): Trial Design

- Primary endpoint: Safety
- Key secondary endpoints: ORR (≥ PR by IMWG criteria), DOR, PFS, OS, and POM exposure
- Data cutoff: May 4, 2015



Thromboprophylaxis with low-dose aspirin, low-molecular-weight heparin, or equivalent was required for all pts

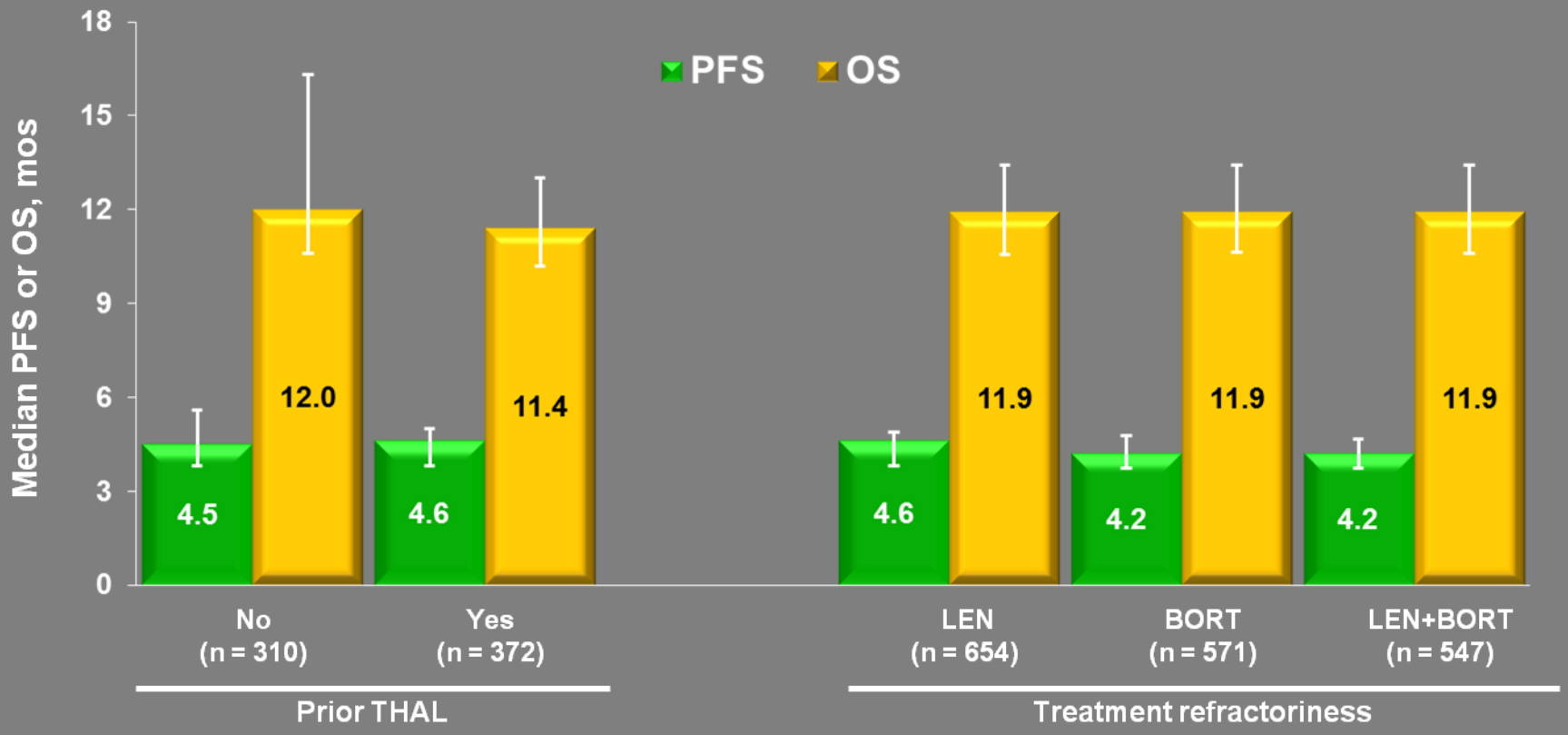
Registered at ClinicalTrials.gov as NCT01712789 and at EudraCT as 2012-001888-78.

AE, adverse event; DOR, duration of response; IMWG, International Myeloma Working Group; LoDEX, low-dose dexamethasone; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; POM, pomalidomide; PR, partial response; pts, patients; SPM, second primary malignancy, Tx, treatment.

Dimopoulos MA, et al. An Updated Analysis of the STRATUS Trial (MM-010): Safety and Efficacy of Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma. *ASH 2015, abstract #4225.*

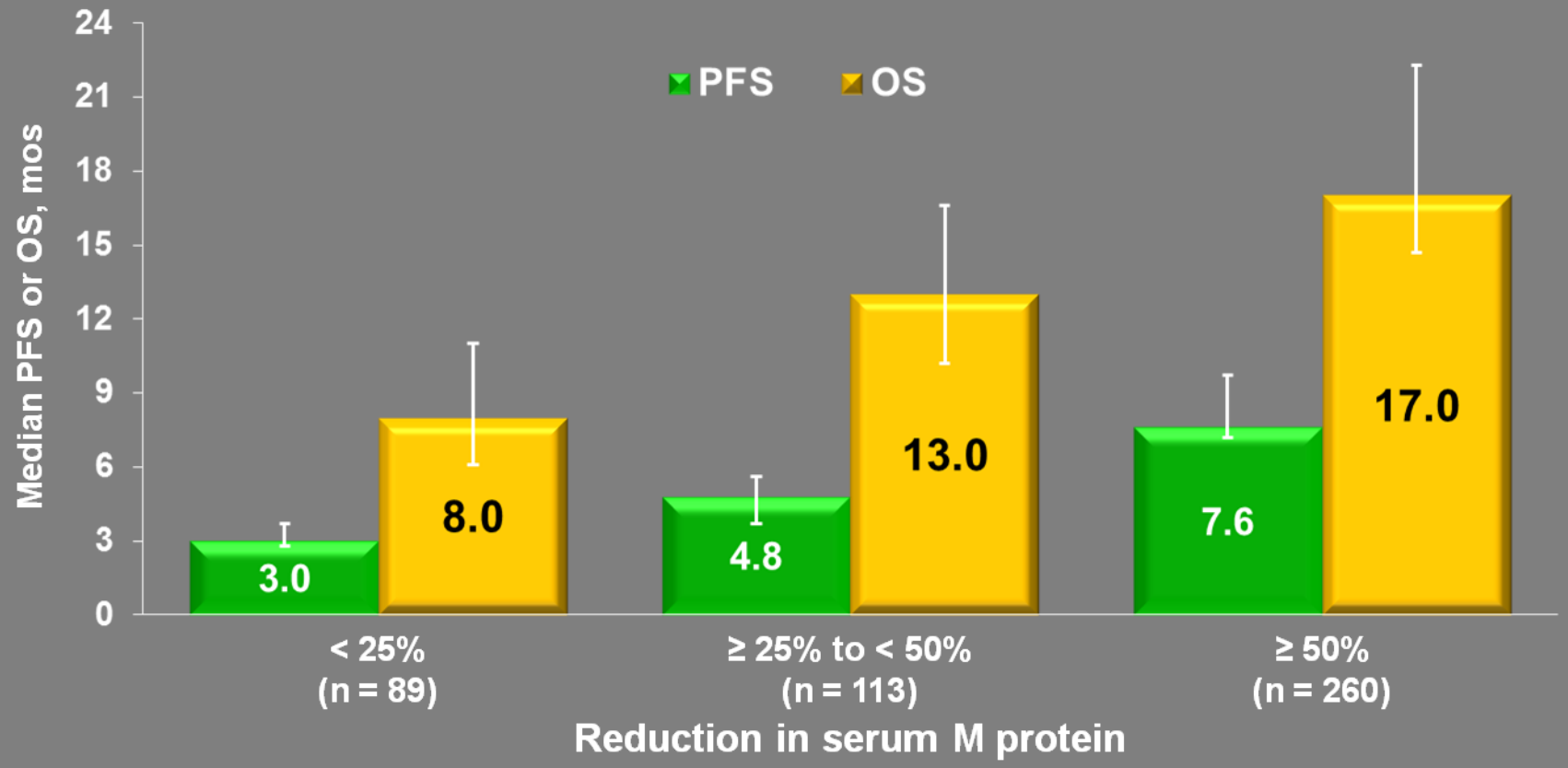
Moreau P, et al. Analysis of Patient Outcomes by Prior Treatment and Depth of Response in STRATUS (MM-010), a Phase 3b Study of Pomalidomide + Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma. *ASH 2015, abstract #1834.*

MM-010 (STRATUS): PFS and OS by Treatment History



Error bars show 95% confidence interval.
BORT, bortezomib; LEN, lenalidomide; OS, overall survival; PFS, progression-free survival; THAL, thalidomide.
Moreau P, et al. Analysis of Patient Outcomes by Prior Treatment and Depth of Response in STRATUS (MM-010), a Phase 3b Study of Pomalidomide + Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma. *ASH 2015, abstract #1834.*

MM-010 (STRATUS): PFS and OS by Depth of Response



Error bars show 95% confidence interval.
OS, overall survival; PFS, progression-free survival.
Moreau P, et al. Analysis of Patient Outcomes by Prior Treatment and Depth of Response in STRATUS (MM-010), a Phase 3b Study of Pomalidomide + Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma. *ASH 2015, abstract #1834.*

POM + LoDEX: Pooled Renal Analysis Efficacy

	With Moderate RI				Without Moderate RI			
	MM-002 (n = 37)	MM-003 (n = 93)	MM-010 (n = 225)	Overall (n = 355)	MM-002 (n = 68)	MM-003 (n = 205)	MM-010 (n = 440)	Overall (n = 713)
Median PFS (95% CI), mos	3.8 (2.8-7.9)	4.0 (2.8-4.8)	3.7 (2.8-4.6)	3.8 (2.9-4.6)	5.4 (3.7-6.8)	4.2 (3.7-5.6)	4.8 (4.1-5.5)	4.6 (4.1-5.5)
Median TTP (95% CI), mos	4.7 (3.1-9.3)	4.4 (2.9-6.5)	4.6 (3.7-5.4)	4.6 (3.8-4.9)	5.5 (3.7-7.2)	4.9 (3.9-6.7)	5.3 (4.6-6.0)	5.3 (4.6-5.8)
Median DOR (95% CI), mos	8.3 (5.8-14.1)	6.6 (3.9-9.7)	6.8 (4.6-9.5)	6.9 (5.8-8.8)	7.7 (3.7-12.5)	7.0 (5.6-12.4)	7.9 (6.5-9.2)	7.6 (6.5-8.8)
Median OS (95% CI), mos	13.4 (8.7-23.8)	10.4 (6.6-12.4)	9.8 (8.1-12.0)	10.5 (8.9-11.5)	16.9 (13.4-21.7)	14.6 (11.8-16.6)	12.9 (11.4-14.7)	14.0 (12.4-15.2)

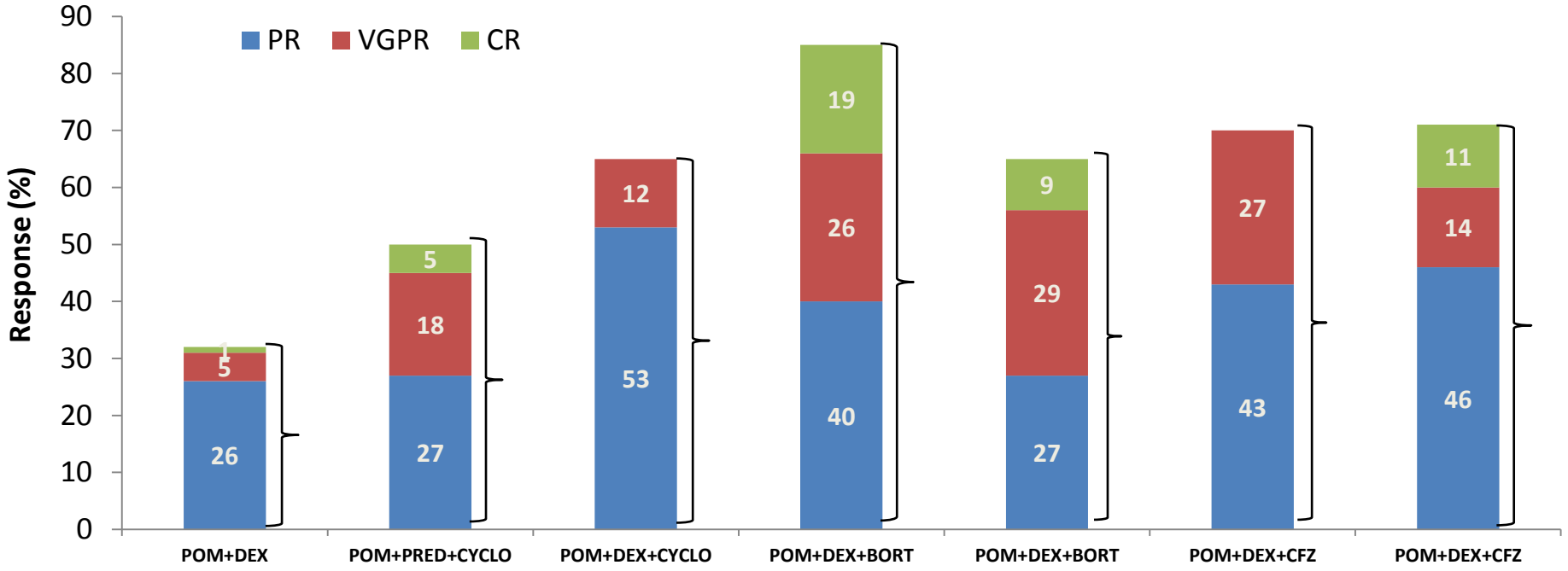
- ORR was similar in pts with moderate RI vs without RI (30.4% vs 33.8%; *P* = .299)
- Median PFS (*P* = .070), median TTP (*P* = .302), and median DOR (*P* = .435) were similar for both pt subgroups
- Pts with moderate RI had a significantly shorter median OS vs pts without RI (*P* = .004)

DOR, duration of response; LoDEX, low-dose dexamethasone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POM, pomalidomide; pt, patient; RI, renal impairment; TTP, time to progression.

Siegel DS, et al. Analysis of Pomalidomide Plus Low-Dose Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma With Vs Without Moderate Renal Impairment. *ASH 2015, abstract #3031.*

Overview Triplet Combination Pomalidomide rrMM new

Efficacy Results of Pomalidomide-based Triplet Therapies in Advanced rrMM

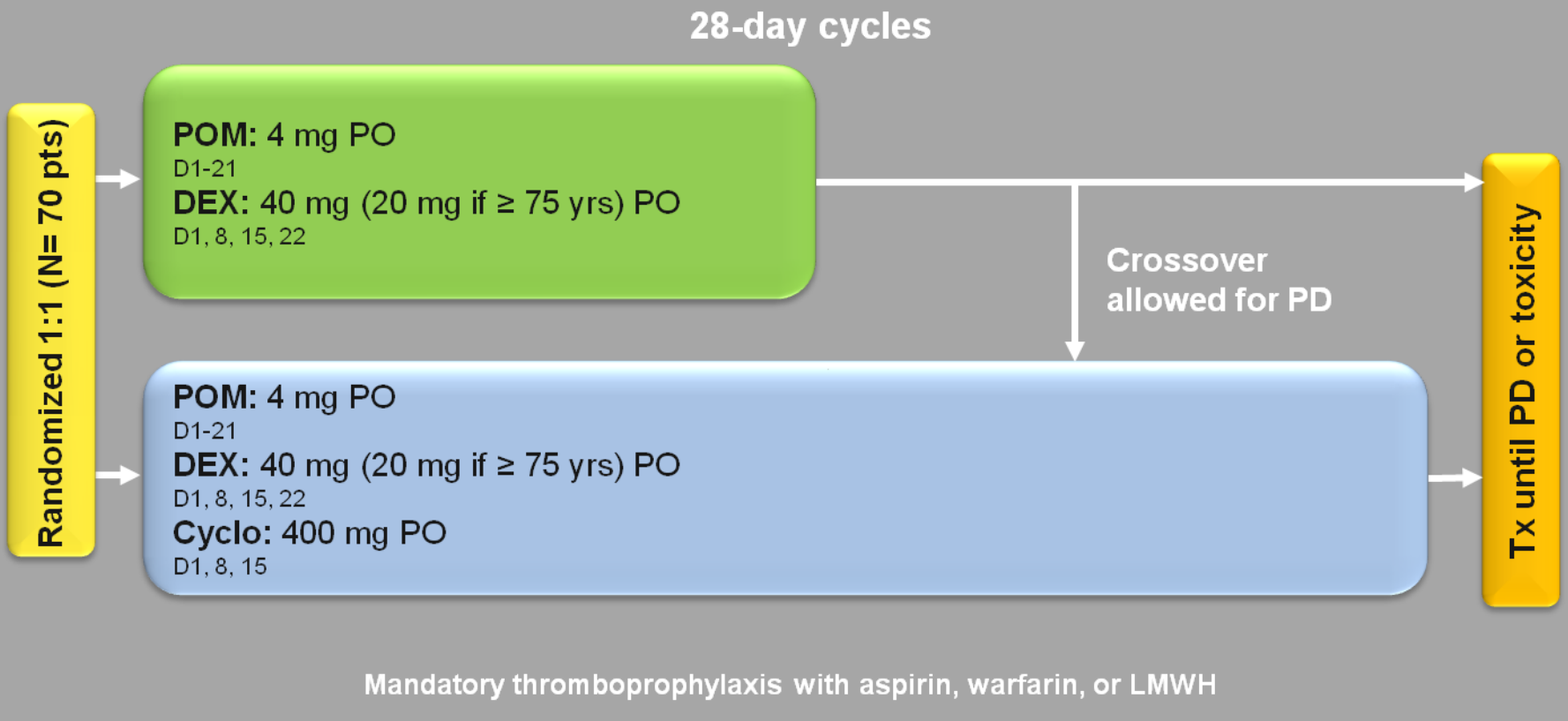


Study / Author / Phase	MM-003 / San-Miguel, 2013 / Phase III[1]	Larocca, 2013 / Phase I/II[2]	Baz, 2014 / Phase II[3]		MM-005 / Richardson, 2015 / Phase I[5]	Shah, 2013 / Phase I/II[6]	Rosenbaum, 2014 / Phase I/II[7]
N	302	55[a]	34[b]	47	34	79	28
Prior therapies	Range: 2-14 Median: 5	Range: 1-3 Median: 3	Range: 2-9 Median: 4	Range: 1-5 Median: 2	Range: 1-4 Median: 2	Range: 1-12 Median: 5	Range: 1-6 Median: 2
Inclusion criteria[c]	Previous LEN and BORT treatment	LEN-relapsed or/and refractory		Resistant or refractory to LEN	LEN-refractory, prior PI		
PFS	Median 4.0 mos	Median 10.4 mos	Median 9.5 mos	Median 10.7 mos	NR	Median 9.7 mos	Median 18.9 mos

[a] Data reported here for MTD and Phase II pts only; [b] CR not reported, [c] among others

BORT, bortezomib; CFZ, carfilzomib; CR, complete response; CYCLO, cyclophosphamide; DEX, dexamethasone; LEN, lenalidomide; ORR, overall response rate; POM, pomalidomide; PR, partial response; PRED, prednisone; VGPR, very good partial response; PFS, progression-free survival; NR, not reported.

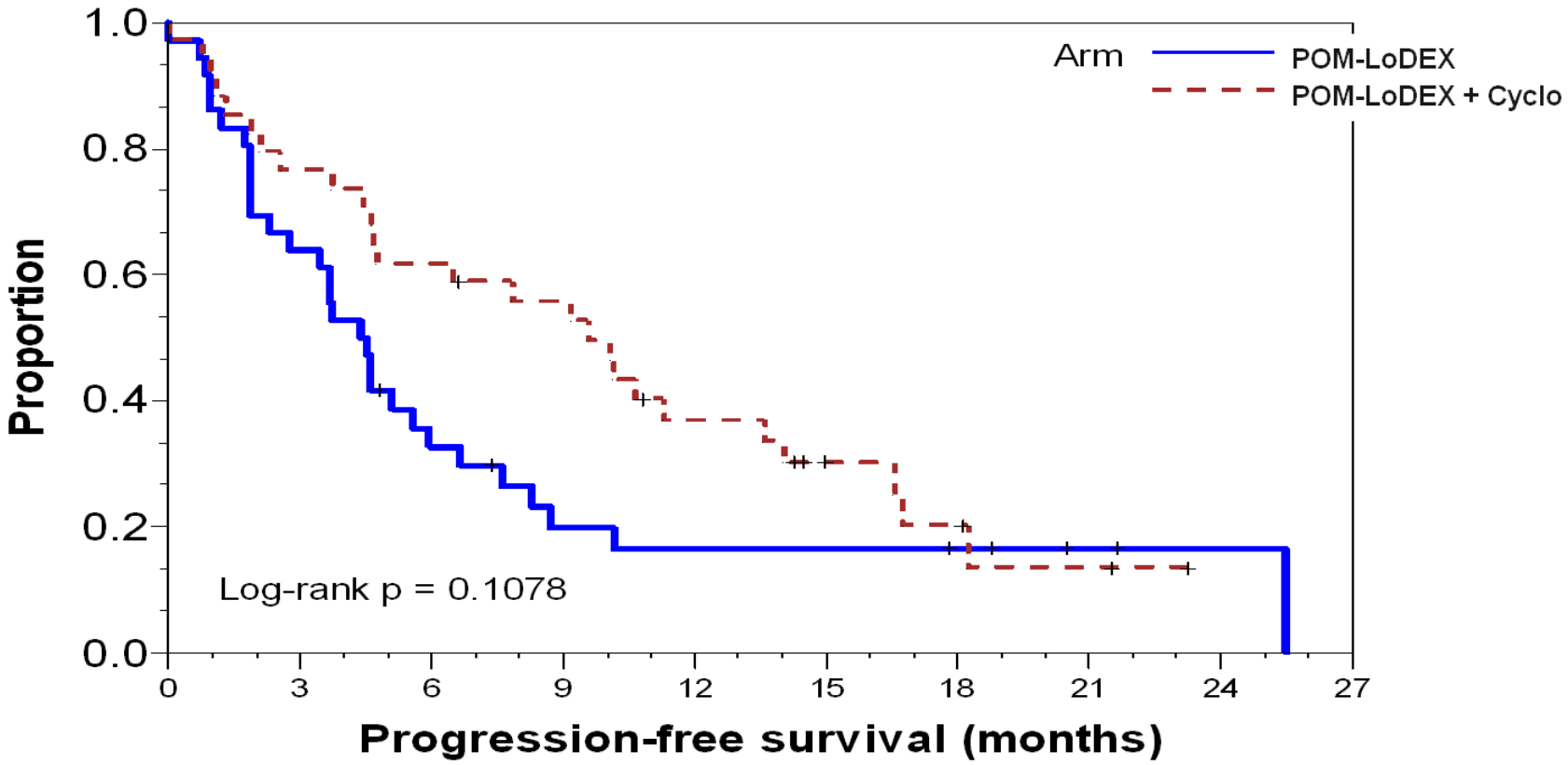
POM-LoDEX ± Cyclo: Study Design



Cyclo, cyclophosphamide; DEX, dexamethasone; LMWH, low-molecular weight heparin; LoDEX, low-dose dexamethasone; PD, progressive disease; PO, orally; POM, pomalidomide; Tx, treatment.

Baz R, et al. Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study. ASH 2014, abstract #303

POM-LoDEX ± Cyclo: PFS



Arm	N	Event	Censored	Median (95% CI)
POM-LoDEX	36	30 (83%)	6 (17%)	4.4(2.3, 6.0)
POM-LoDEX + Cyclo	34	26 (76%)	8 (24%)	9.5(4.6, 13.6)

Cyclo, cyclophosphamide; LoDEX, low-dose dexamethasone; PFS, progression free survival; POM, pomalidomide.

Baz R, et al. Pomalidomide, Cyclophosphamide, and Dexamethasone Is Superior to Pomalidomide and Dexamethasone in Relapsed and Refractory Myeloma: Results of a Multicenter Randomized Phase II Study. ASH 2014, abstract #303

Phase III studies in relapsed and refractory MM

	ASPIRE	PANORAMA	ELOQUENT	TOURMALINE-MM1
Regime	KRd vs Rd 27 mg/m^2 CFZ **K: max 18 cycles**	PAN+Vd vs Vd+Plb 20 mg oral **Max 12 cycles**	Elo+Rd vs Rd 10 mg/kg Elo **Until progression**	Ixa+Rd vs Rd+Plb 4 mg Ixa **Until progression**
ISS III (%)	43	22	21	12
ORR (%)	87.1 vs 66.7	60.7 vs 54.6	79 vs 66	78.3 vs 71.5
≥VGPR (%)	69.9 vs 40.4	27.6 vs 15.7	28 vs 21	48.1 vs 39
CR+sCR (%)	31.8 vs 9.3	11 vs 6	4 vs 7	11.7 vs 6.6
PFS (prim. EP)	26.3 vs 17.6 mo	12 vs 8.1 mo	19.4 vs 14.9 mo	20.6 vs 14.7 mo
OS (mo or %)	At 24 mo: 73.3 vs 65%	33.6 vs 30.4 mo	43.7 vs 39.6 mo	Not yet mature

Fortschritte in der Therapie der Behandlung von nicht für die Transplantation geeigneten Patienten mit multiplem Myelom

Immunmodulierende Substanzen:

- Revlimid (Erstlinientherapie)
- Pomalidomid

Proteasomeninhibitoren:

- **Carfilzomib**
- **Ixozamib**

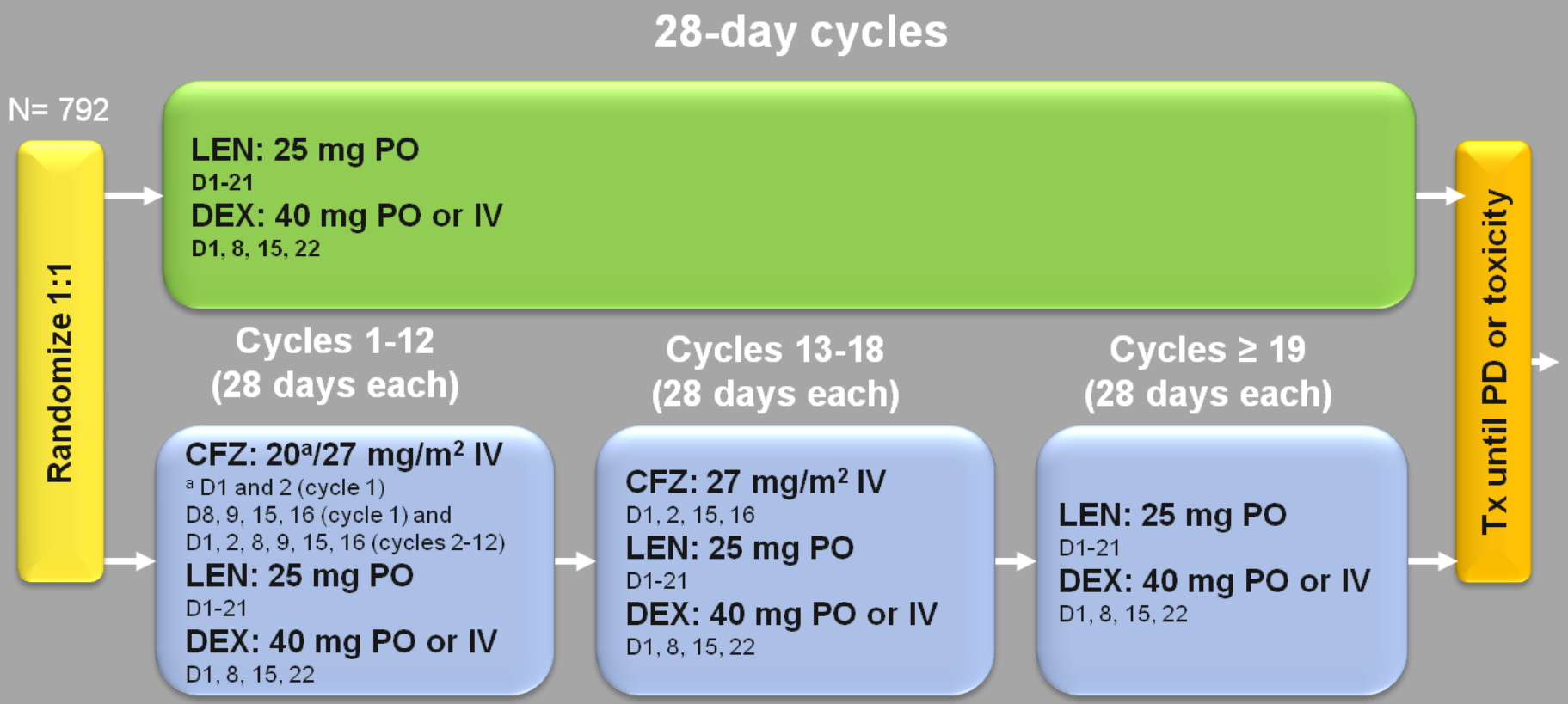
HDAC-Inhibitoren

- Vorinostat (Entwicklung gestoppt)
- Panabinostat

Monoklonale Antikörper

- Daratumumab
- Elotuzumab

ASPIRE Trial: Study Design[1]



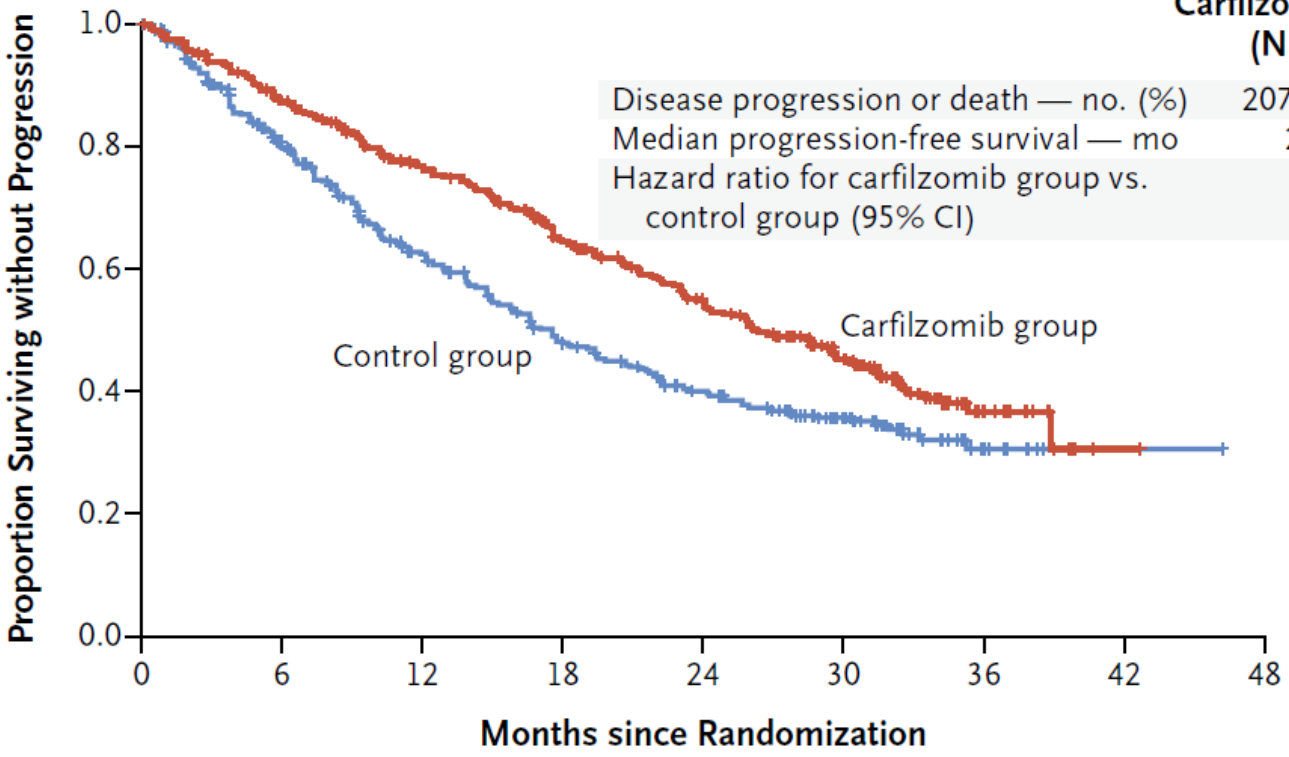
ASPIRE: CArfilzomib, Lenalidomide, and DexamethaSone versus Lenalidomide and Dexamethasone for the treatment of PatIents with Relapsed Multiple MyEloma; CFZ; carfilzomib; D: day; DEX: dexamethasone; IV: intravenous; LEN: lenalidomide; PD: progressive disease; PO: orally; Tx: treatment.

1. Moreau P. *J Clin Oncol*. 2011;29 [abstract TPS227, poster presentation].

Stewart AK, et al. *N Engl J Med*. 2014;371: DOI: 10.1056/NEJMoa1411321.

Primärer Endpunkt: Progressions-freies Überleben

ITT Population (n=792)



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	

P=0.0001

No. at Risk

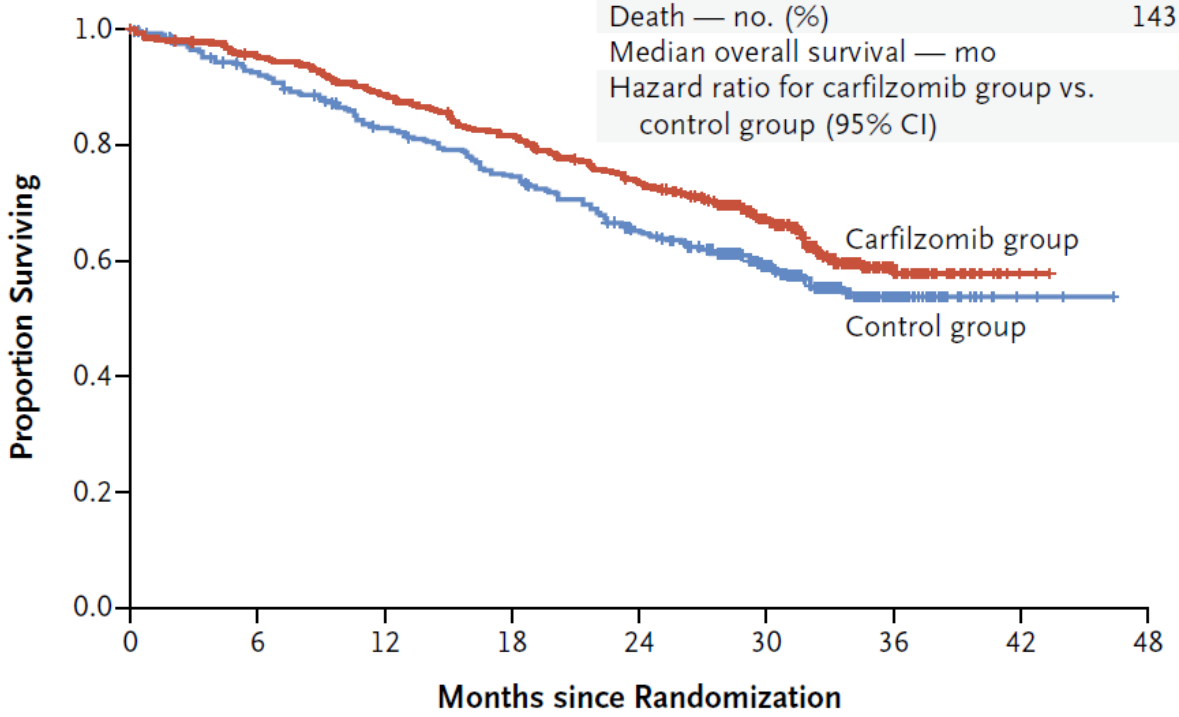
Carfilzomib group	396	332	279	222	179	112	24	1
Control group	396	287	206	151	117	72	18	1

Sekundärer Endpunkt: Gesamtüberleben - Interims-Analyse

Medianer Follow-up 32 Monate

	Carfilzomib Group (N=396)	Control Group (N=396)
Death — no. (%)	143 (36.1)	162 (40.9)
Median overall survival — mo	NE	NE
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.79 (0.63–0.99)	

P=0.04



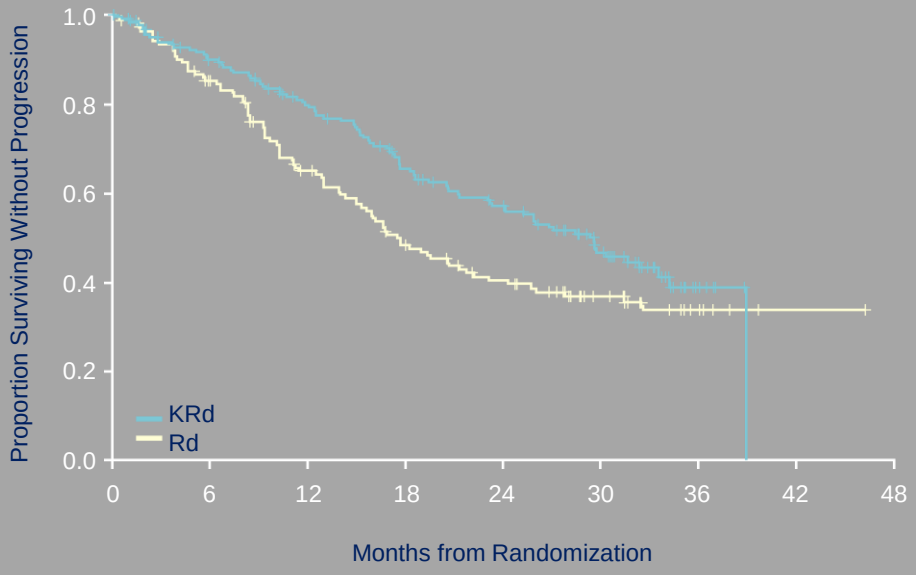
No. at Risk

Carfilzomib group	396	369	343	315	280	191	52	2
Control group	396	356	313	281	237	144	39	3

- Medianes Gesamtüberleben wurde nicht erreicht; die Ergebnisse haben die vorher bestimmte Abbruchsgrenze (P=0.005) bei der Interims-Analyse nicht erreicht

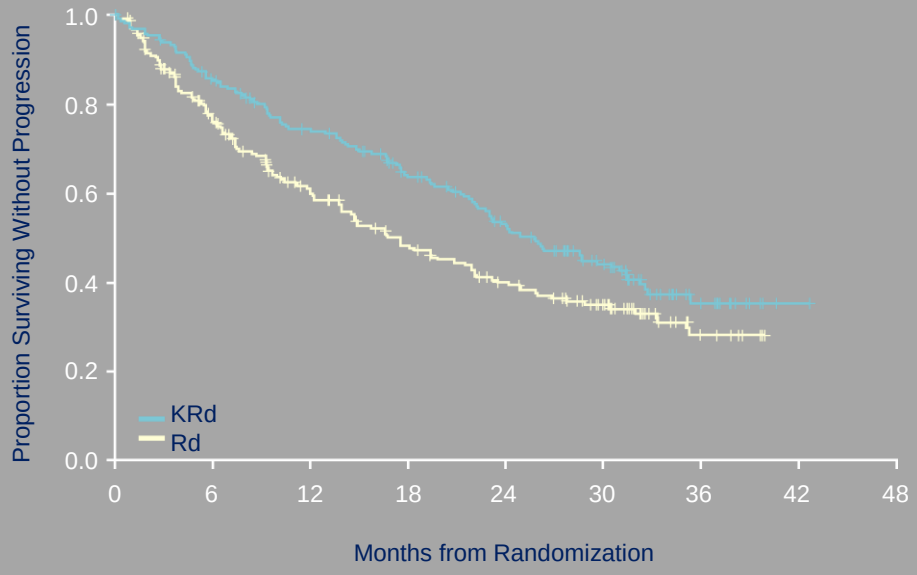
PFS by Prior Line of Therapy (1 vs ≥2)

1 prior line of therapy



	KRd (n=184)	Rd (n=157)
PFS, median months	29.6	17.6
Hazard ratio (95% CI)	0.69 (0.52–0.94)	
P value (one-sided)	.008	

≥2 prior lines of therapy

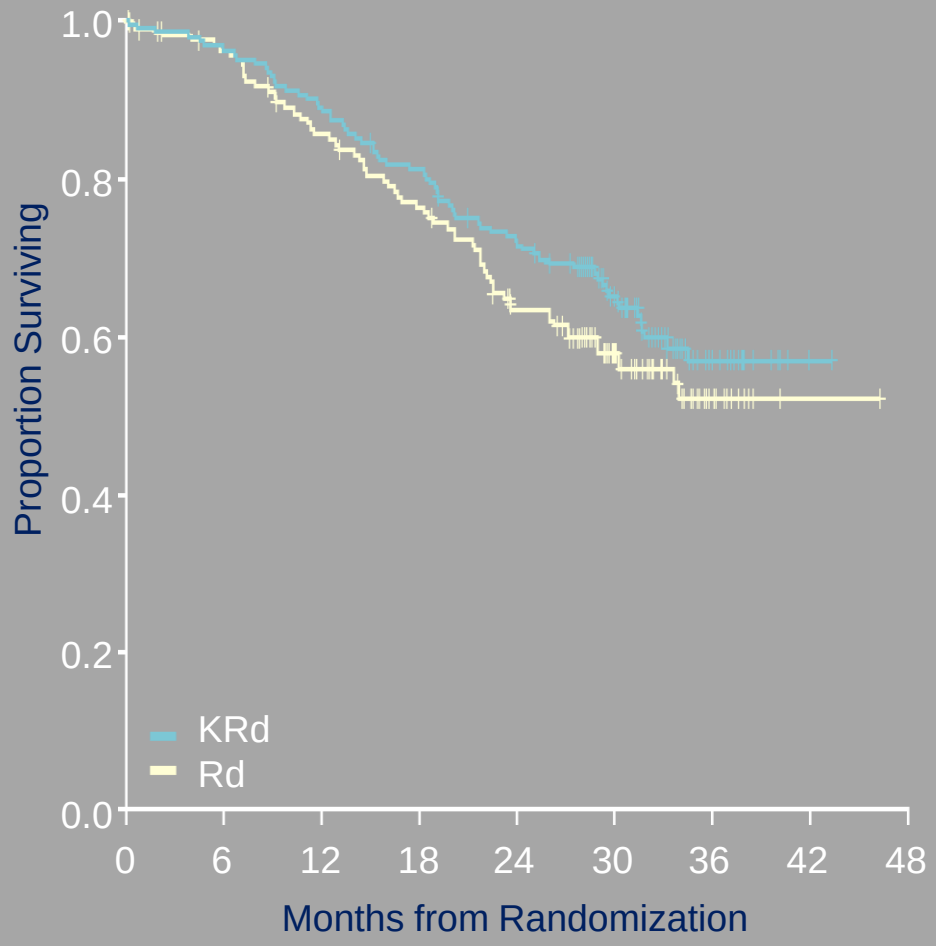


	KRd (n=212)	Rd (n=239)
PFS, median months	25.8	16.7
Hazard ratio (95% CI)	0.69 (0.54–0.89)	
P value (one-sided)	.002	

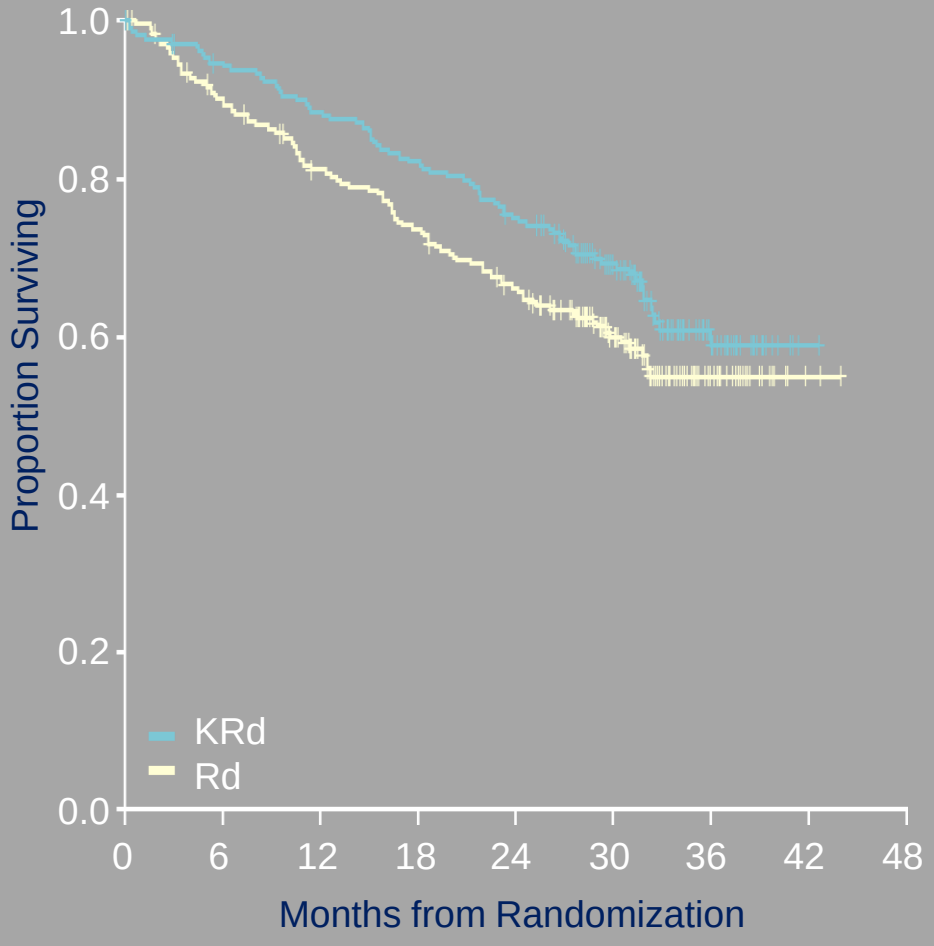
CI Confidence interval; KRd, carfilzomib, lenalidomide, and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

Overall Survival by Prior Line of Therapy (1 vs ≥2)

1 prior line of therapy



≥2 prior lines of therapy



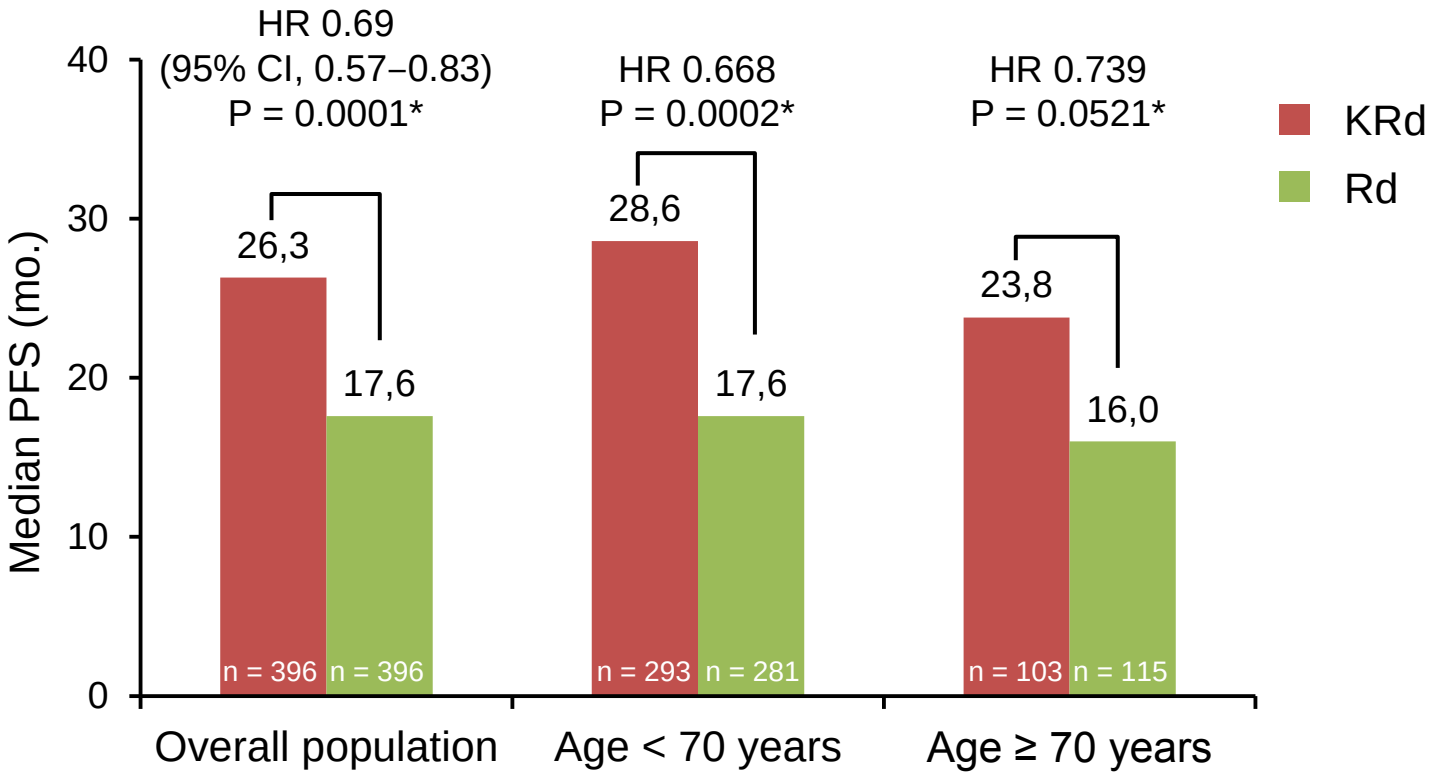
KRd, carfilzomib, lenalidomide, and dexamethasone; OS, overall survival; Rd, lenalidomide and dexamethasone.

Hematologic Grade ≥3 Adverse Events Reported in ≥3% of Patients in Any Subgroup

	1 prior line of therapy		≥2 prior lines of therapy	
	KRd (n=182)	Rd (n=154)	KRd (n=210)	Rd (n=235)
Hematologic grade ≥3 AEs (preferred terms), n (%)				
Neutropenia	48 (26.4)	34 (22.1)	68 (32.4)	69 (29.4)
Anemia	31 (17.0)	30 (19.5)	39 (18.6)	37 (15.7)
Thrombocytopenia	28 (15.4)	18 (11.7)	37 (17.6)	30 (12.8)
Leukopenia	6 (3.3)	5 (3.2)	6 (2.9)	11 (4.7)
Lymphopenia	6 (3.3)	3 (1.9)	5 (2.4)	5 (2.1)
Decreased platelet count	6 (3.3)	3 (1.9)	6 (2.9)	6 (2.6)
Decreased neutrophil count	4 (2.2)	1 (0.6)	8 (3.8)	10 (4.3)

AE, adverse event; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

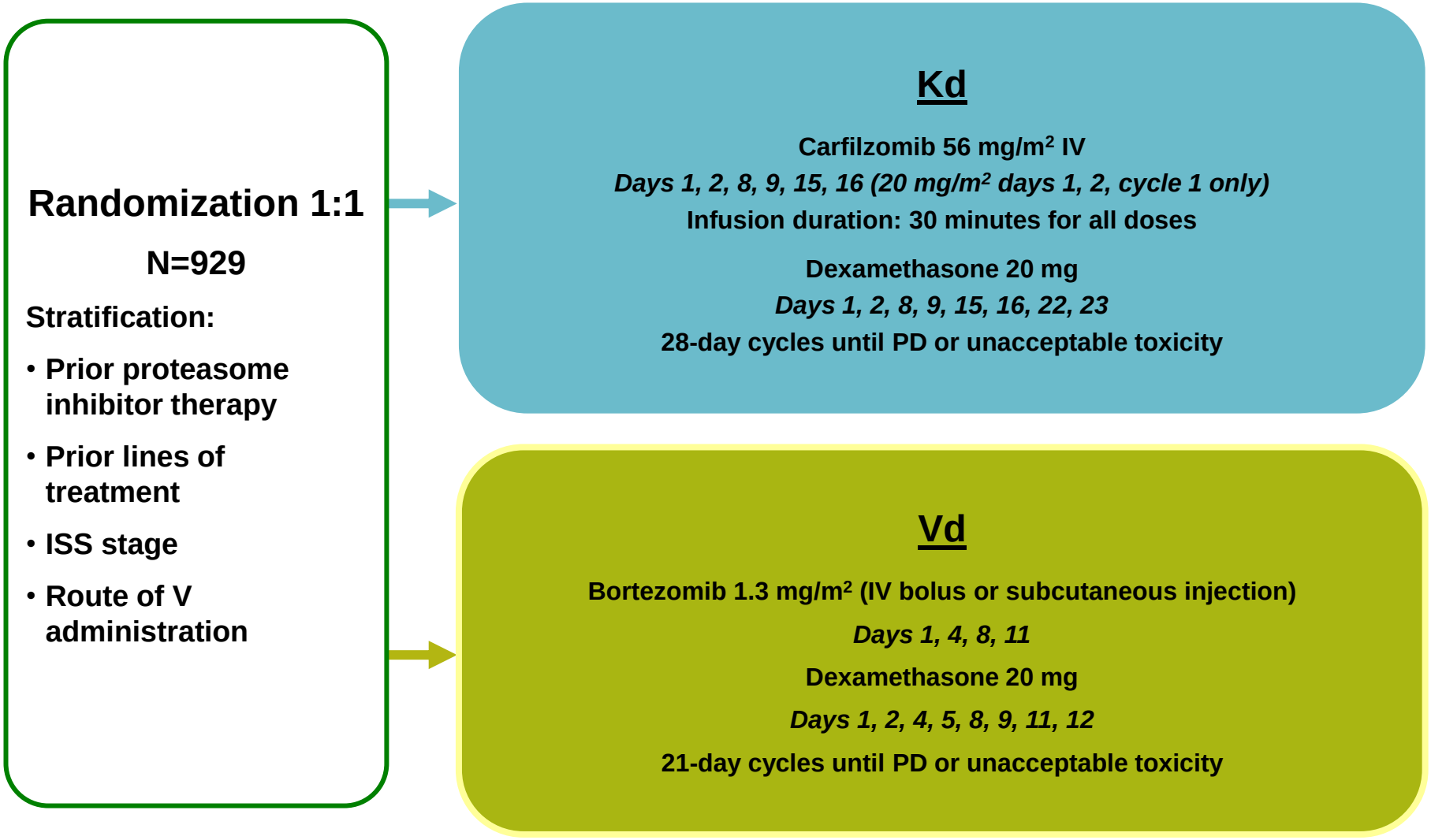
Median PFS



Stewart AK, et al. N Engl J Med 2015;372:142–52;
Palumbo A, et al. International Myeloma Workshop 2015: BP-051.

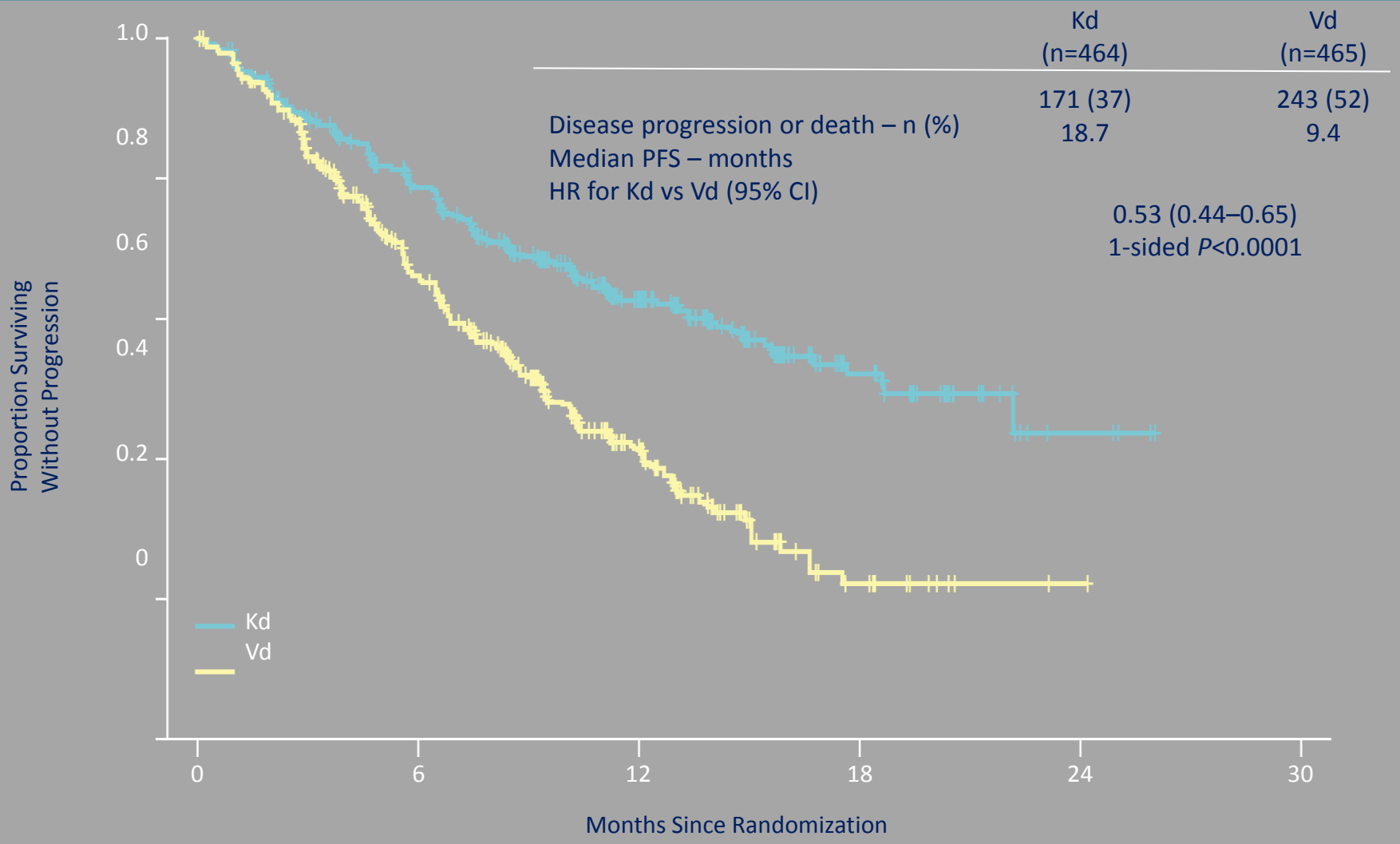
*Descriptive P-value.

ENDEAVOR Study Design



International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; PD, progressive disease; Vd, bortezomib and dexamethasone; V, bortezomib.

Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)

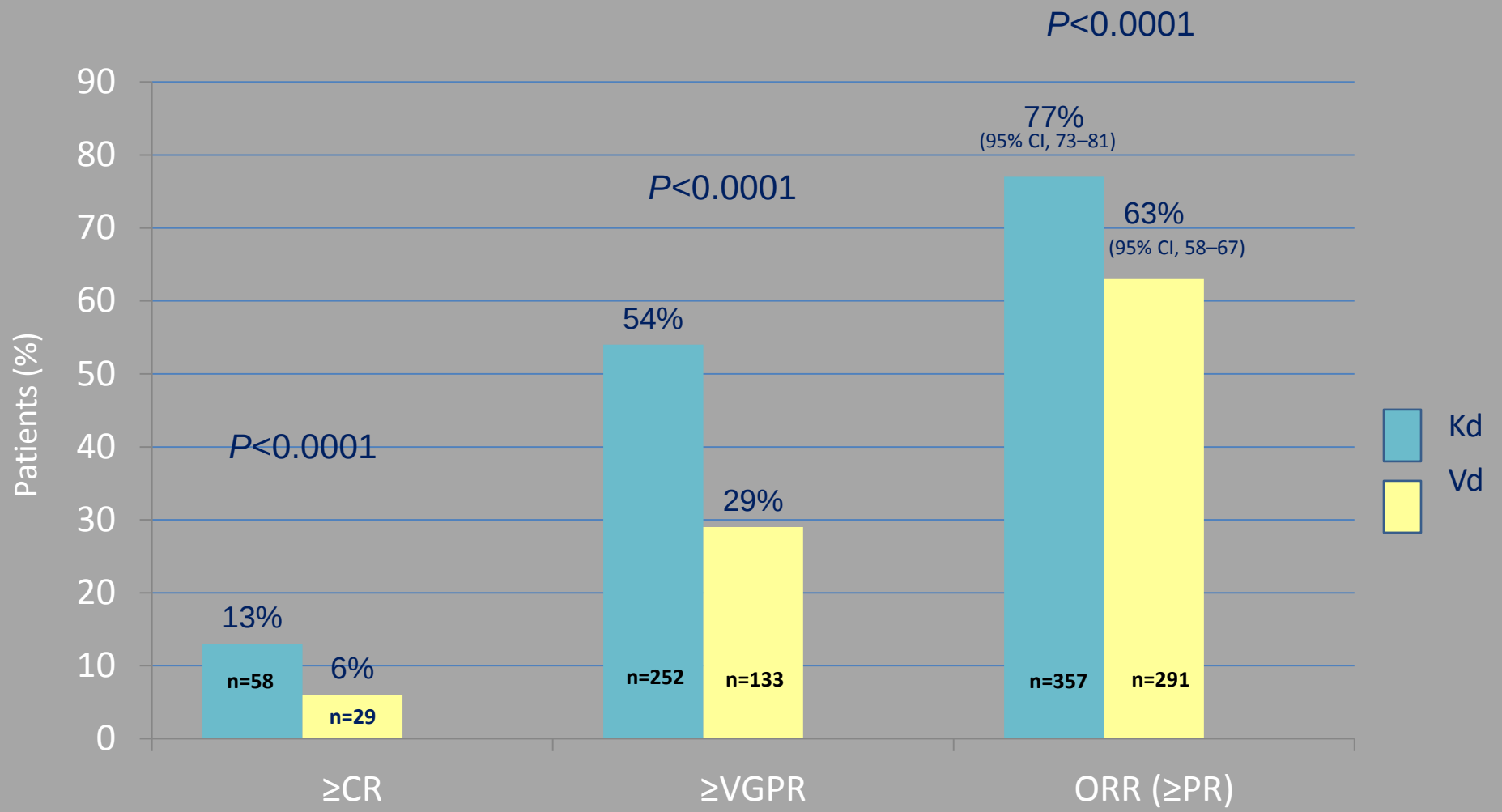


- **Median follow-up: 11.2 months**

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

Carfilzomib is not approved in EU

Secondary End Point: Response Rates

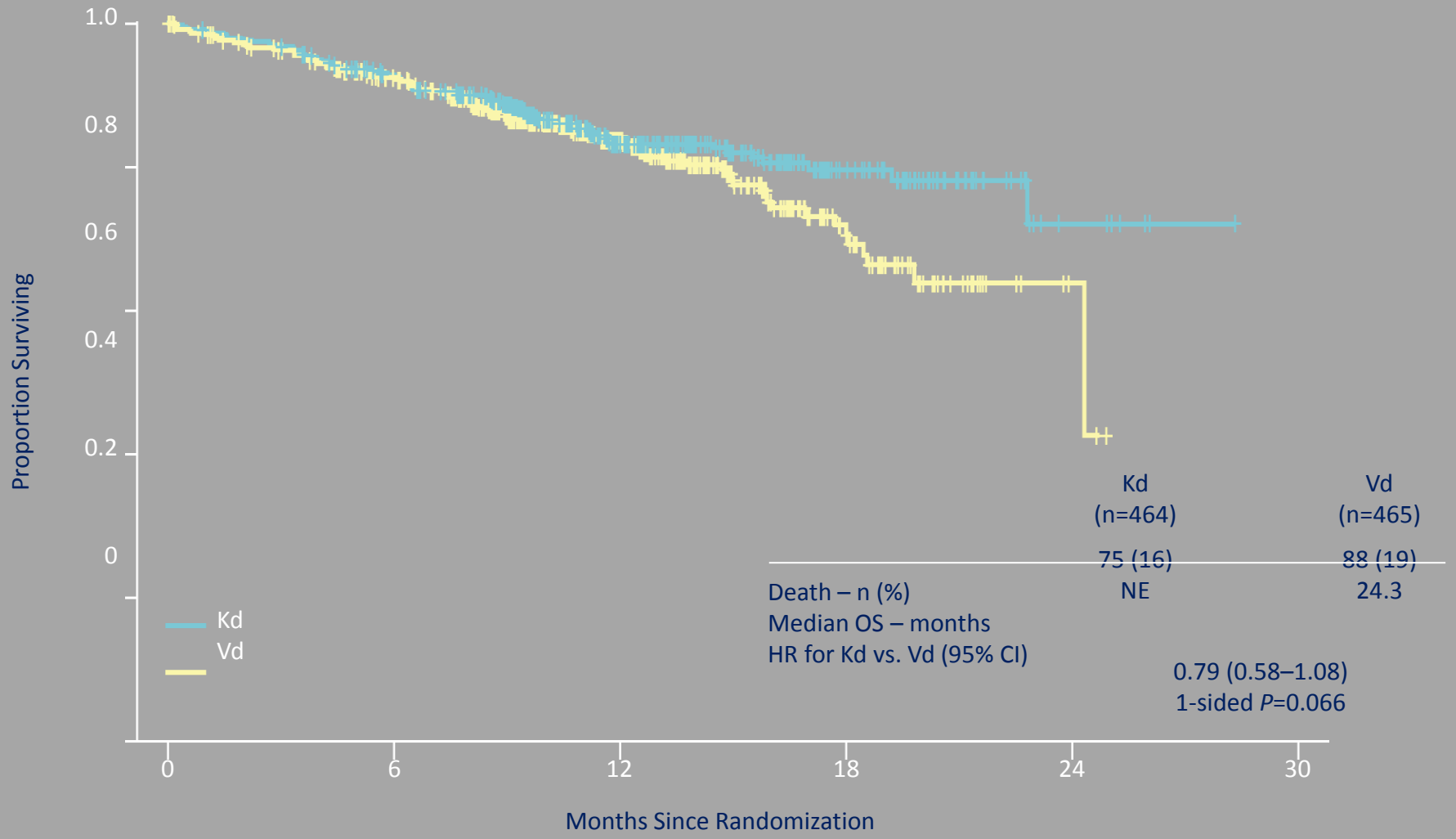


- **Median DOR: 21.3 months (95% CI, 21.3–NE) for Kd vs 10.4 months (95% CI, 9.3–13.8) for Vd**

CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; Kd, carfilzomib and dexamethasone; NE, not estimable; PR, partial response; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

Carfilzomib is not approved in EU

Secondary End Point: Overall Survival
Intent-to-Treat Population (N=929)



OS data were immature; the study will continue until the final OS analysis is performed

CI, confidence interval; HR, hazard ratio; ITT, intent to treat; Kd, carfilzomib and dexamethasone; NE, not estimable; OS, overall survival; Vd, bortezomib and dexamethasone.

Carfilzomib is not approved in EU

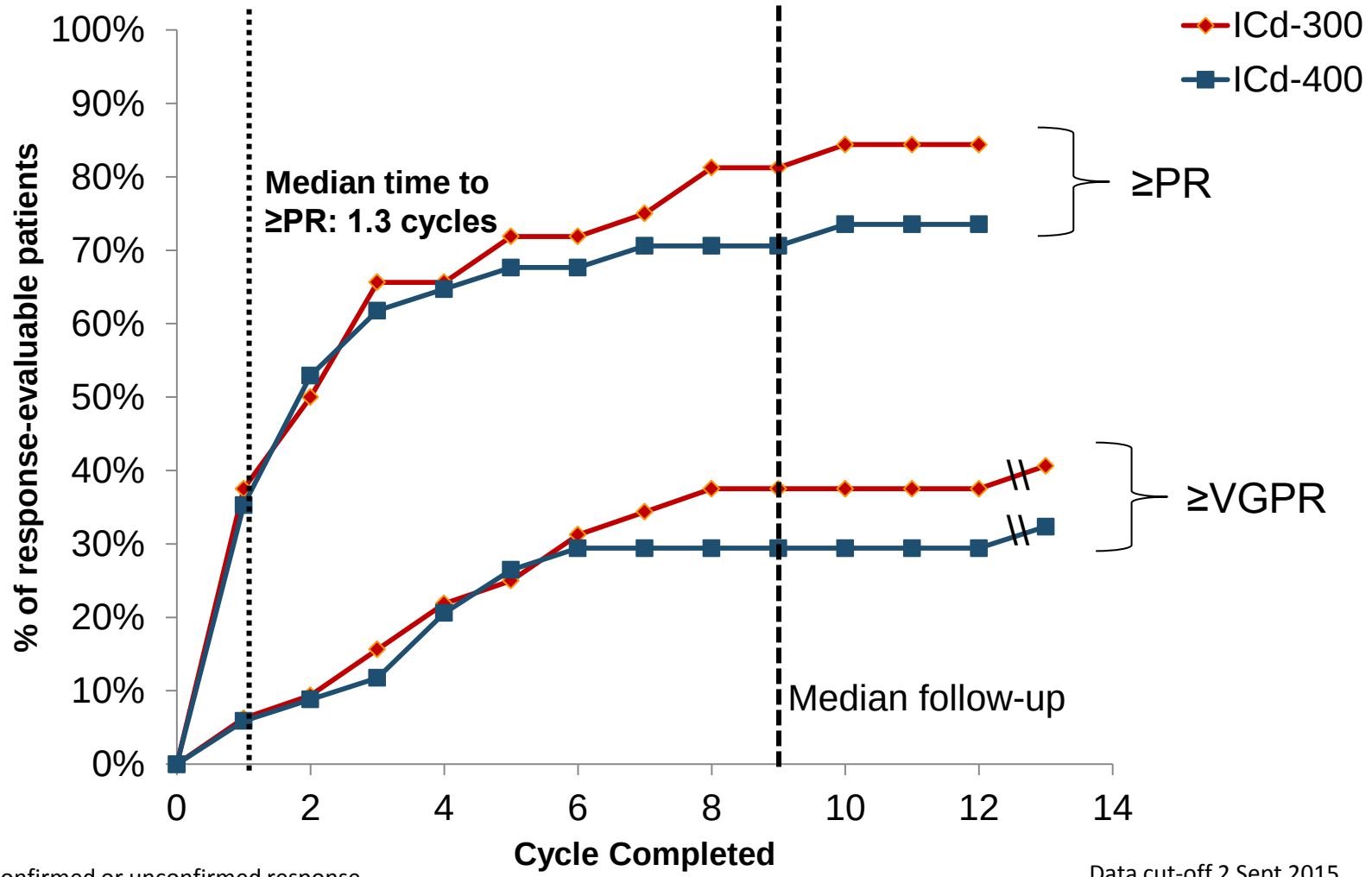
Ixazomib in transplant-ineligible patients
Best confirmed response

Confirmed response,* n (%)	ICd-300 (N=32)	ICd-400 (N=34)	All (N=66)
CR + VGPR	10 (28)	7 (21)	17 (26)
ORR (CR + VGPR + PR)	25 (78)	22 (65)	47 (71)
CR	3 (10)	3 (9)	6 (9)
sCR	1 (3)	0	1 (2)
PR	22 (69)	19 (56)	41 (62)
VGPR	7 (22)	4 (12)	11 (17)
SD	6 (16)	9 (26)	15 (23)

*response-evaluable patients

Dimopoulos, M et al. Presented at ASH 2015 (Abstract 26), oral presentation

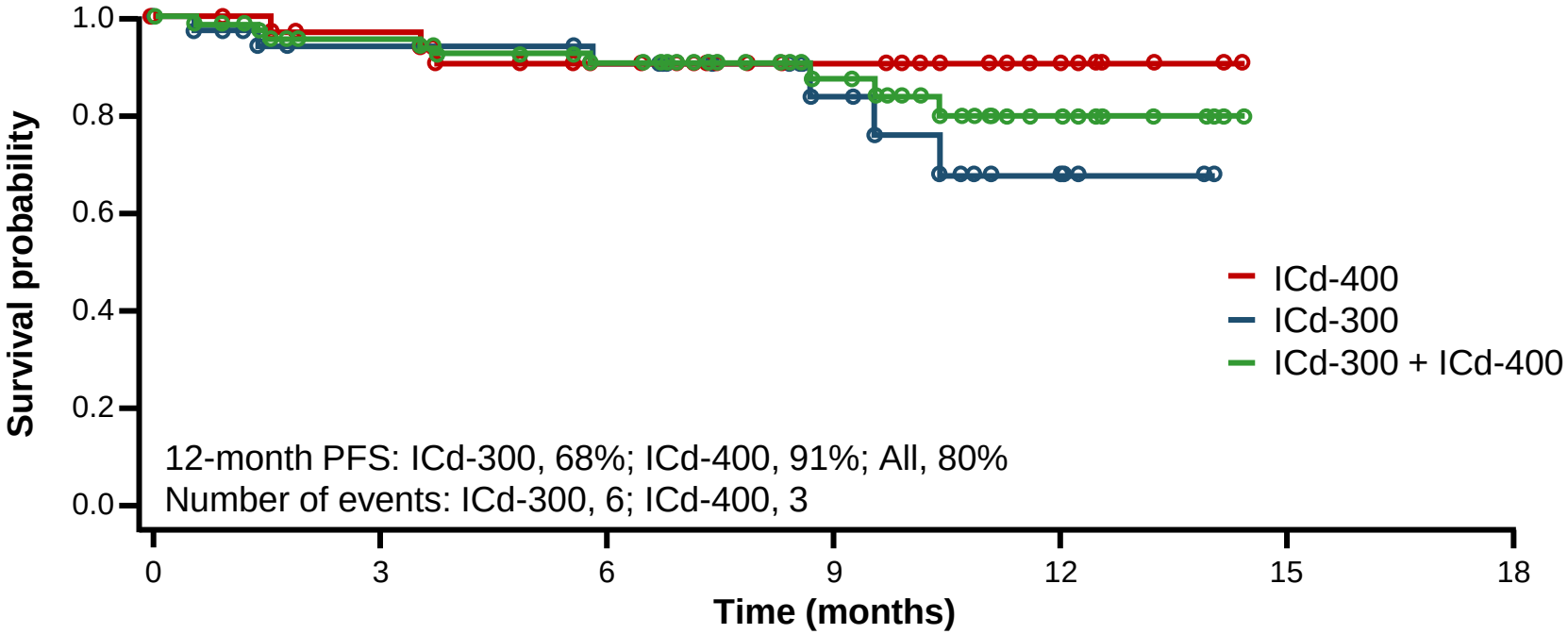
Ixazomib in transplant ineligible patients
Accumulated response rate over time*



*first confirmed or unconfirmed response

Data cut-off 2 Sept 2015

Ixazomib in transplant ineligible patients
Progression-free survival



Number of patients at risk:

ICd-300	36	30	26	12	4	0	0
ICd-400	34	31	25	15	6	0	0
ICd-300+ICd-400	70	61	51	27	10	0	0

- Median follow-up of 9.2 months

Data cut-off 2 Sept 2015

Dimopoulos, M et al. Presented at ASH 2015 (Abstract 26), oral presentation

Fortschritte in der Therapie der Behandlung von nicht für die Transplantation geeigneten Patienten mit multiplem Myelom

Immunmodulierende Substanzen:

- Revlimid (Erstlinientherapie)
- Pomalidomid

Proteasomeninhibitoren:

- Carfilzomib
- Ixozamib

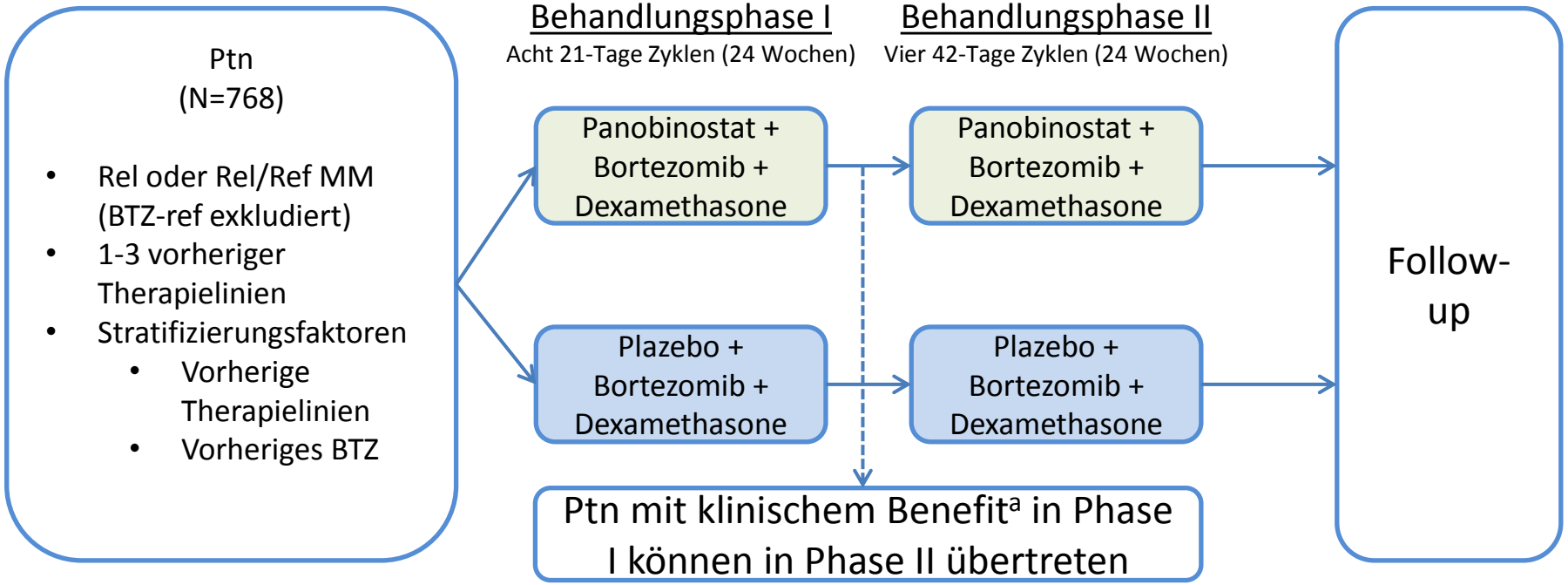
HDAC-Inhibitoren

- Vorinostat (Entwicklung gestoppt)
- Panabinostat

Monoklonale Antikörper

- Daratumumab
- Elotuzumab

PANORAMA 1 Studiendesign

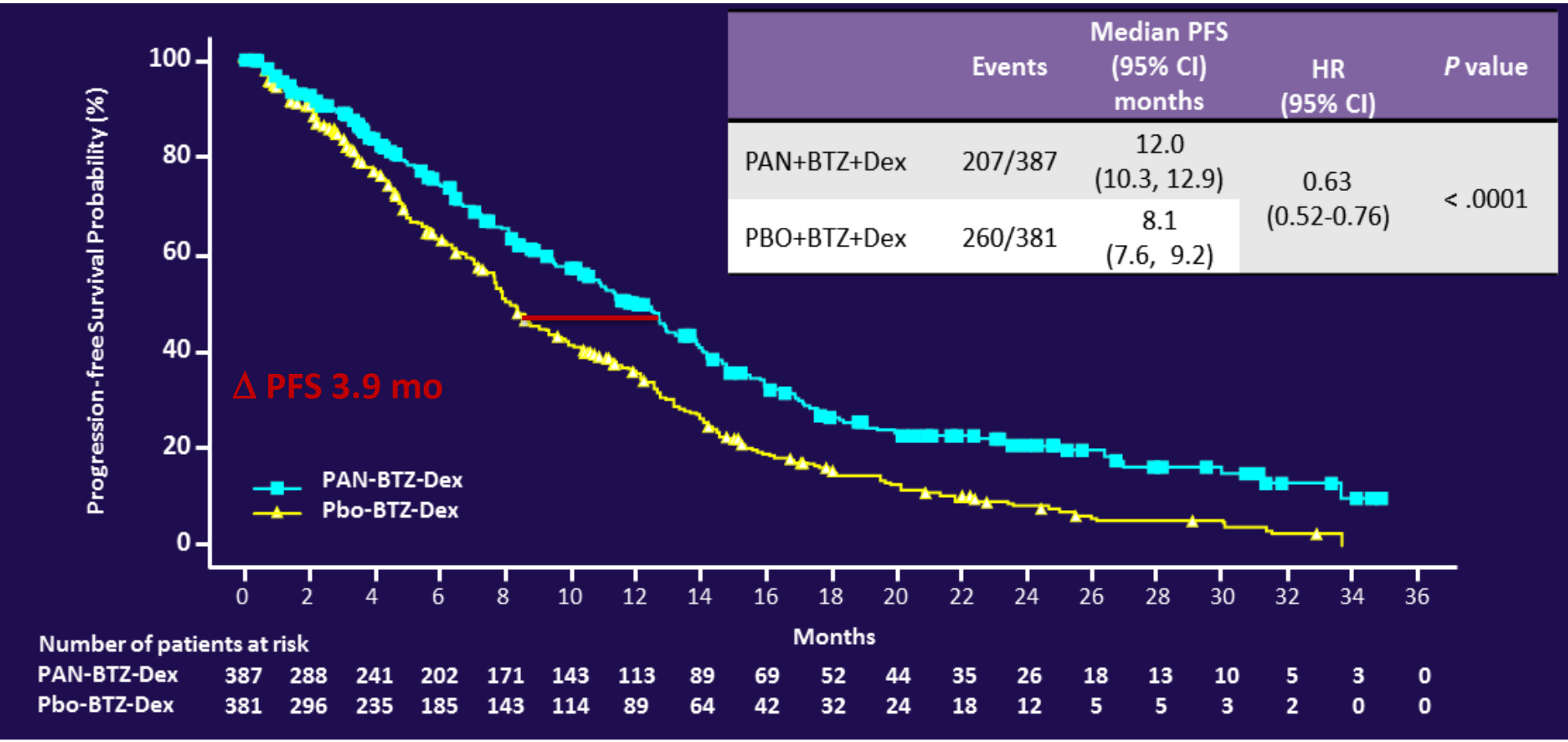


- Primärer Endpunkt: Progressions-freies Überleben
- Sekundärer Endpunkt: Gesamtüberleben
- Andere sekundäre Endpunkte: ORR, nCR/CR Rate,, DOR, TTR, TTP, QoL und Sicherheit

Studie wurde in 215 Zentren in 34 Ländern durchgeführt

[a] Erreichen von ≥ keine Veränderung nach den modifizierten EBMT Kriterien (SD oder besser)

Primary Endpoint (PFS) – overall study population



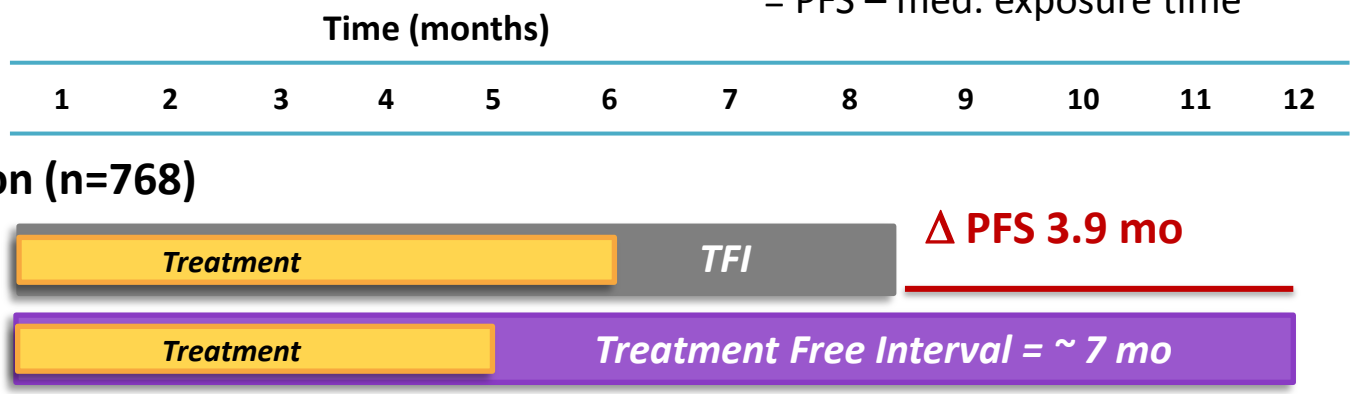
	Events	Median PFS (95% CI) months	HR (95% CI)	*P* value
PAN+BTZ+Dex	207/387	12.0 (10.3, 12.9)	0.63 (0.52-0.76)	< .0001
PBO+BTZ+Dex	260/381	8.1 (7.6, 9.2)		

- Primary endpoint met (*P* < .0001), with clinically relevant increase in median PFS of 3.9 months for PAN-BTZ-Dex arm
  - Updated IRC analysis demonstrated greater concordance with PFS by investigator per protocol assessment
  - The data cutoff date for the final analysis of PFS was September 10, 2013 *Richardson PG.2014.ASCO.Oral present. 8510*

Detailed Subgroup Analysis of PFS By Prior Treatment

Longer median PFS Linked With Longer "Treatment-free Interval"

Median duration of exposure Median PFS TFI ... Treatment-free interval = PFS – med. exposure time



Alternative Therapiemöglichkeiten für Zweit- und Mehrlinientherapien

Immunmodulierende Substanzen:

Pomalidomid

Proteasomeninhibitoren:

Carfilzomib

Ixozamib

HDAC-Inhibitoren

Vorinostat (Entwicklung gestoppt)

Panabinostat

Monoklonale Antikörper

Daratumumab

Elotuzumab

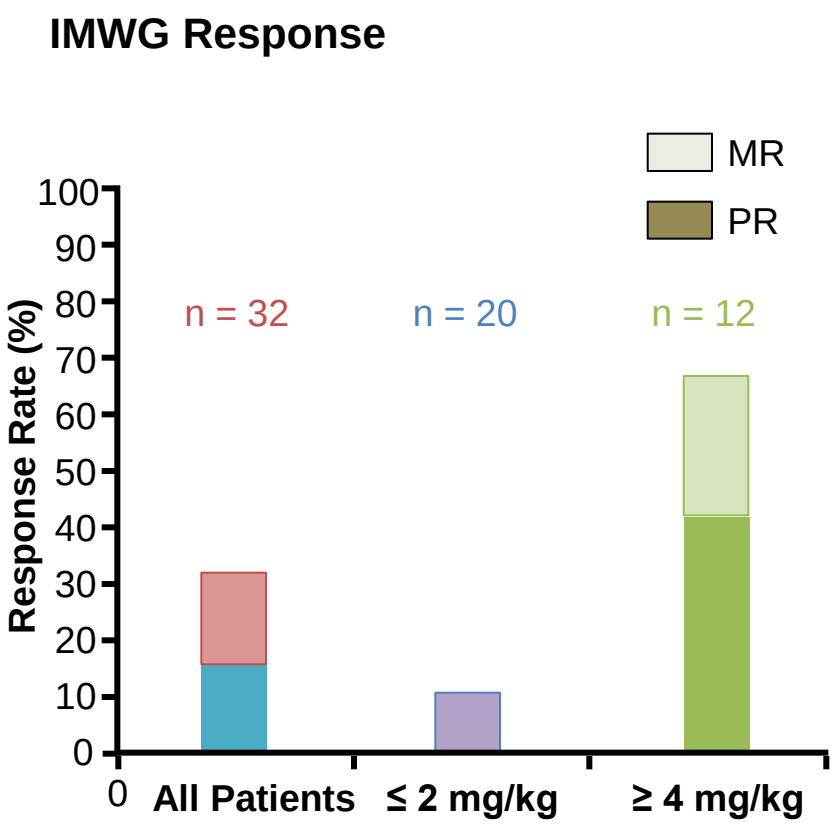
Monoklonaler Antikörper von Morphosys

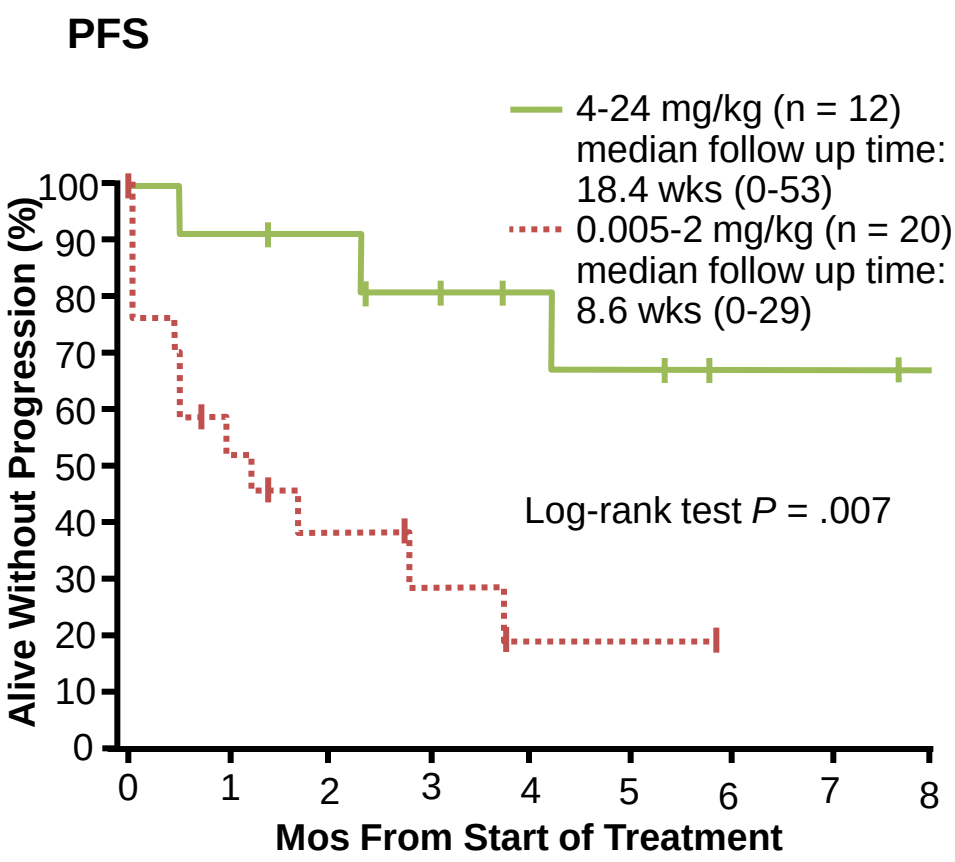
Myeloma targets and antibodies in development

Myeloma Target	mAb
CD30	Brentuximab vedotin
CD38	SAR650984, Daratumumab, MOR-202
CD40	Lucatumumab, Dacetuzumab
CD54 (ICAM-1)	BI-505
CD56	Lorvotuzumab
CD70	SGN-70
CD74	Milatuzumab (-doxorubicin)
CD138	BT062
CD200	Samalizumab
BCMA	GSK2857916
CXCR4	Ulocuplumab
FcRL5	Anti-FcRL5(hu10A8)-SPDB-DM4
SLamF7	Elotuzumab
Immune Targets	**mAb**
KIR	IPH2101
CD47	CC-90002
CD137	BMS-663513
PD-1	Pembrolizumab, nivolumab, pidilizumab
PD-L1	BMS-936559, MPDL3280A

IMW 2015

Phase I/II Daratumumab Monotherapy Study: IMWG Response and PFS





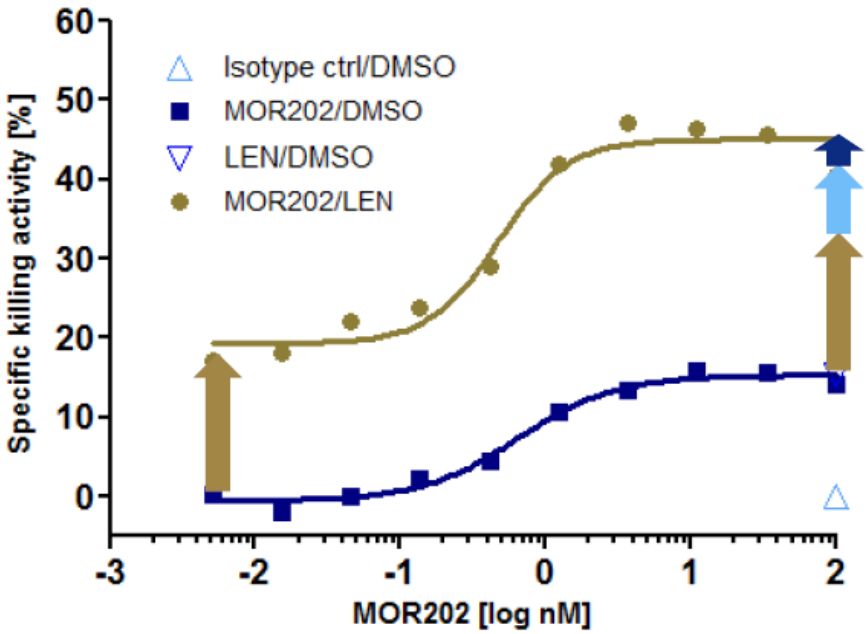
Lokhorst H J, et al. ASCO 2013. Abstract 8512.

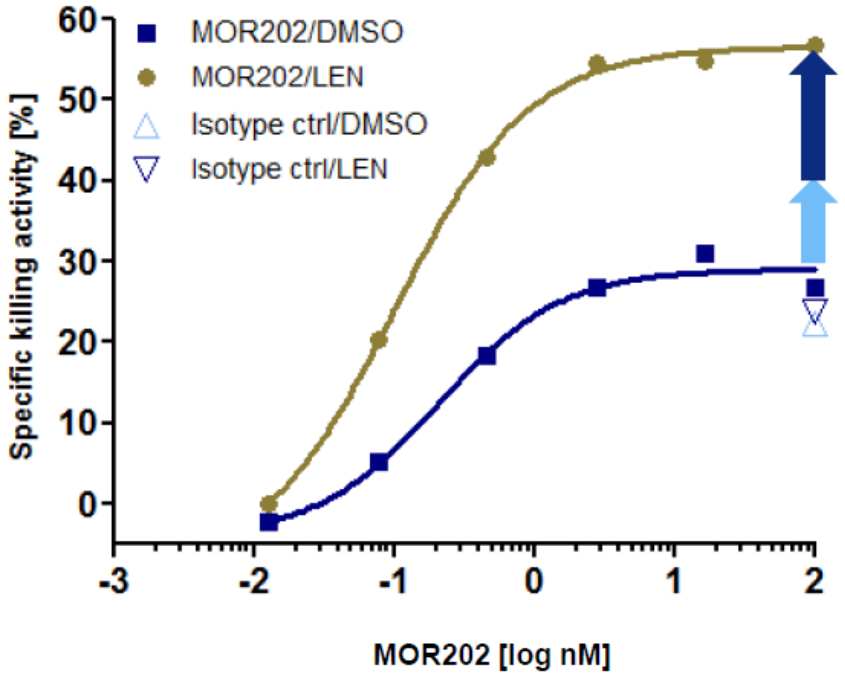
Lenalidomide on Effector and Target Cells: Enhanced ADCC Via NK Cell Activation & CD38 Upregulation

NCI-H929
(CD38 high, lenalidomide cytotoxicity sensitive)

AMO-1
(CD38 low, lenalidomide cytotoxicity insensitive)

- Lenalidomide added to effector cells and MM cell line
- MOR202 added to effector cells and MM cell line





- LEN-induced effector cell activation
- LEN-induced CD38 upregulation
- LEN-induced cytotoxic effect on target cells

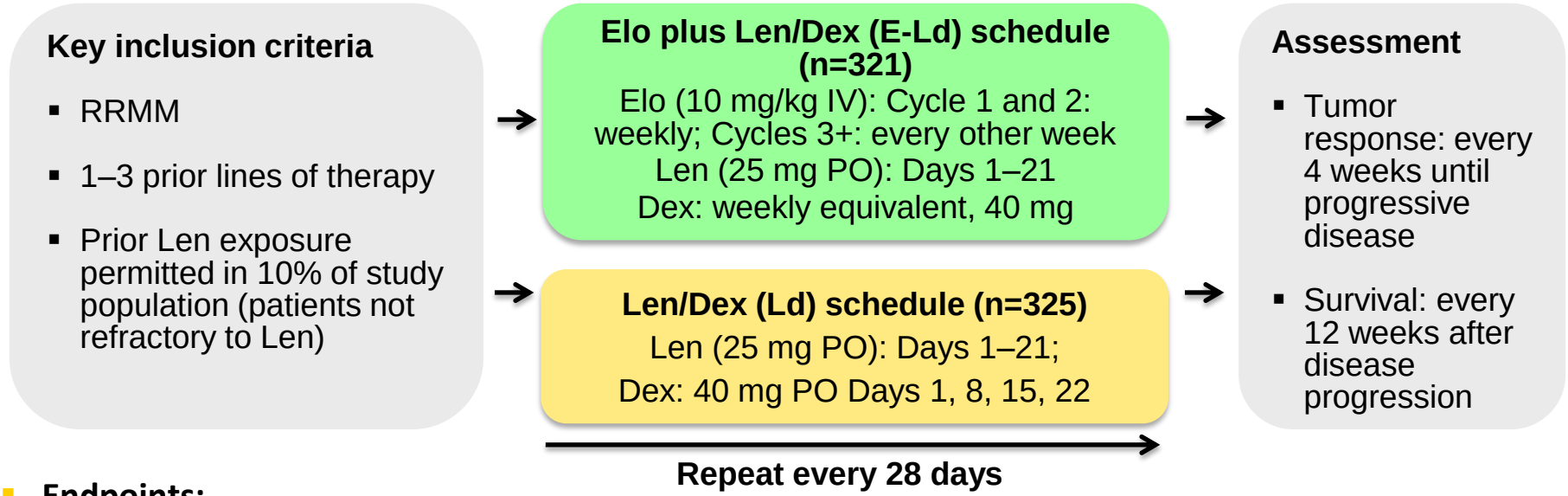
MOR 202: Clinical Benefit Rate (CBR)

Response, n (%)	Cohort 1 ibr 420 mg* (n=13)	Cohort 2 ibr 560 mg + dex (n=18)	Cohort 3 ibr 840 mg* (n=18)	Cohort 4 ibr 840 mg + dex (n=43)
CBR (MR or better)	1 (8)	1 (6)	0 (0)	10 (23)
PR	0 (0)	1 (6)	0 (0)	2 (5)
MR	1 (8)	0 (0)	0 (0)	8 (19)
SD $\geq$ 4 cycles	1 (8)	4 (22)	6 (33)	12 (28)

International Myeloma Workshop, 2015

ELOQUENT-2 Study Design

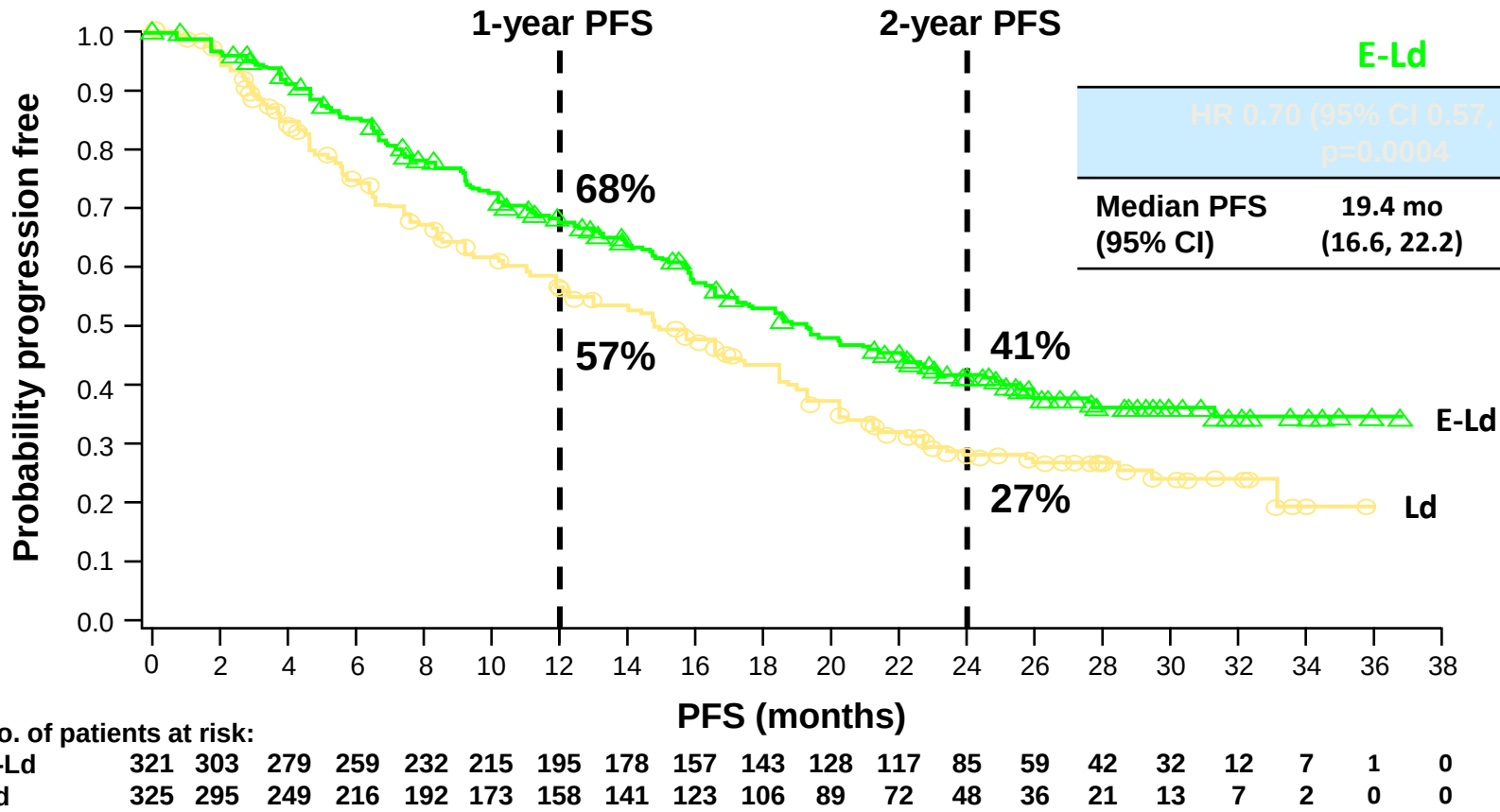
- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)



- **Endpoints:**
  - **Co-primary: PFS and ORR**
  - **Other: overall survival (data not yet mature), duration of response, quality of life, safety**
- **All patients received premedication to mitigate infusion reactions prior to elotuzumab administration**
- **Elotuzumab IV infusion administered ~ 2–3 hours**

Lonial et al, NEJM 2015

Co-primary Endpoint: Progression-Free Survival



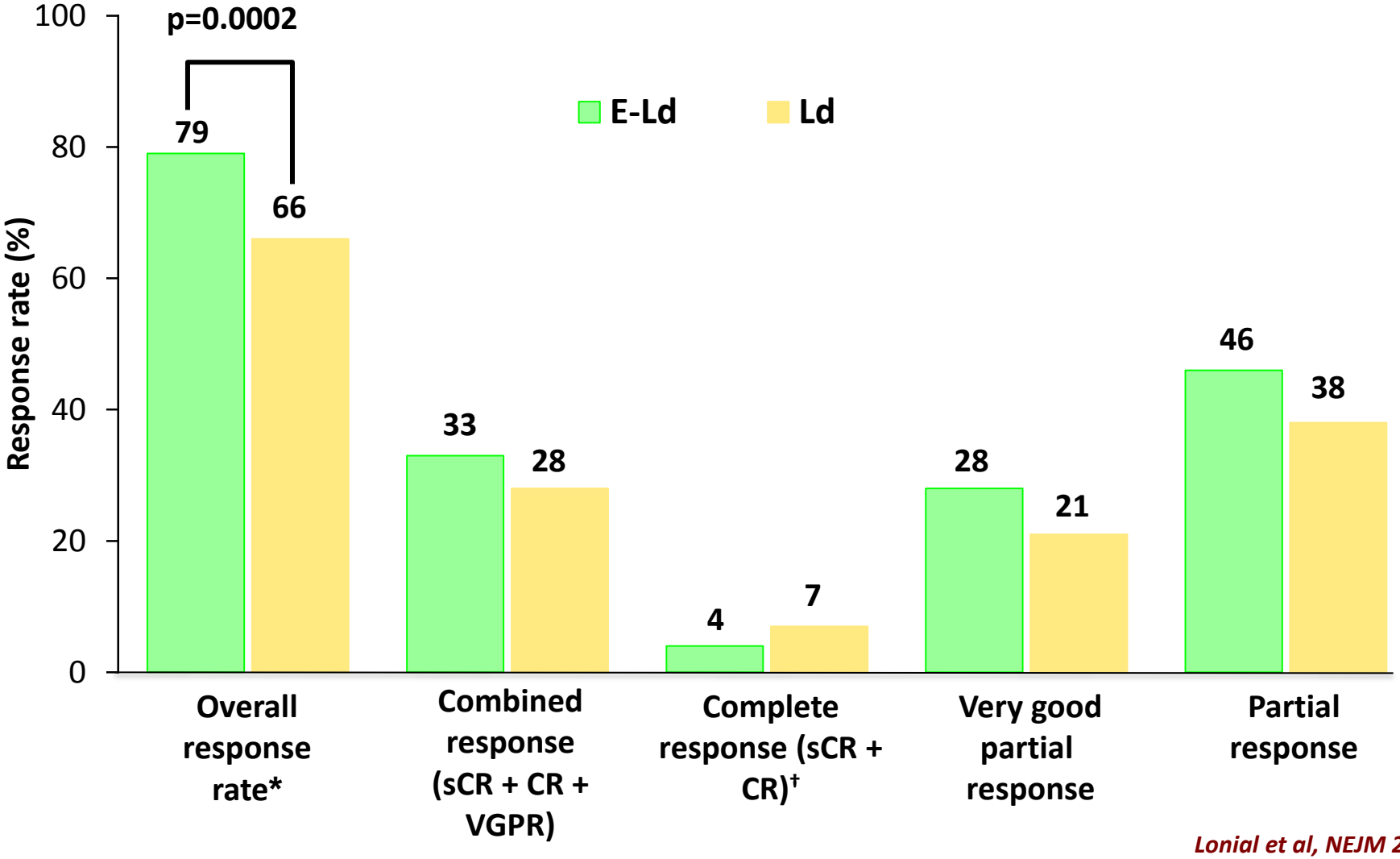
E-Ld–treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively

PFS analysis used the primary definition of PFS

Lonial et al, NEJM 2015

Co-primary Endpoint: Overall Response Rate

*Defined as partial response or better. †Complete response rates in the E-Ld group may be underestimated due to interference from therapeutic antibody in immunofixation and serum protein electrophoresis assay



Lonial et al, NEJM 2015

Danke für die Aufmerksamkeit