Treating Myeloma Relapse

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Disclosures

Amgen, BMS, Celgene, Ionis, Jannsen

Amanda

- 31 years old previously healthy presented with cord compression
- Recent history of Left axillary thrombosis and Brachial plexopathy
- Tumor Left Humerus and infiltrating T4-T8
- Surgery – sheets of CD138+ve Lambda plasma cells
- Marrow – 90% MM, complex karyotype, High proliferation, hyperdiploid flow, Dup1q by FISH, IDH2 mutant (47%), B2M high, Albumin 3.3, LDH 366
- Blurred vision Left Eye – Biopsy shows intravitreal Plasma cells

Amanda

- Rads to humerus and T spine, CyborD x 1
- VRd for 5 cycles, Rads to left eye
- ASCT – Revlimid and Velcade maintenance
- 12 months later Marrow, Labs negative, concern for possible relapse L arm = radiated

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Considerations in Early Relapsing MM

- SCT versus not
- Coming off of maintenance versus not?
- Aggressive versus indolent relapse?
- Carfilzomib, Daratumumab or both?
- What about ixazomib and elotuzumab ?

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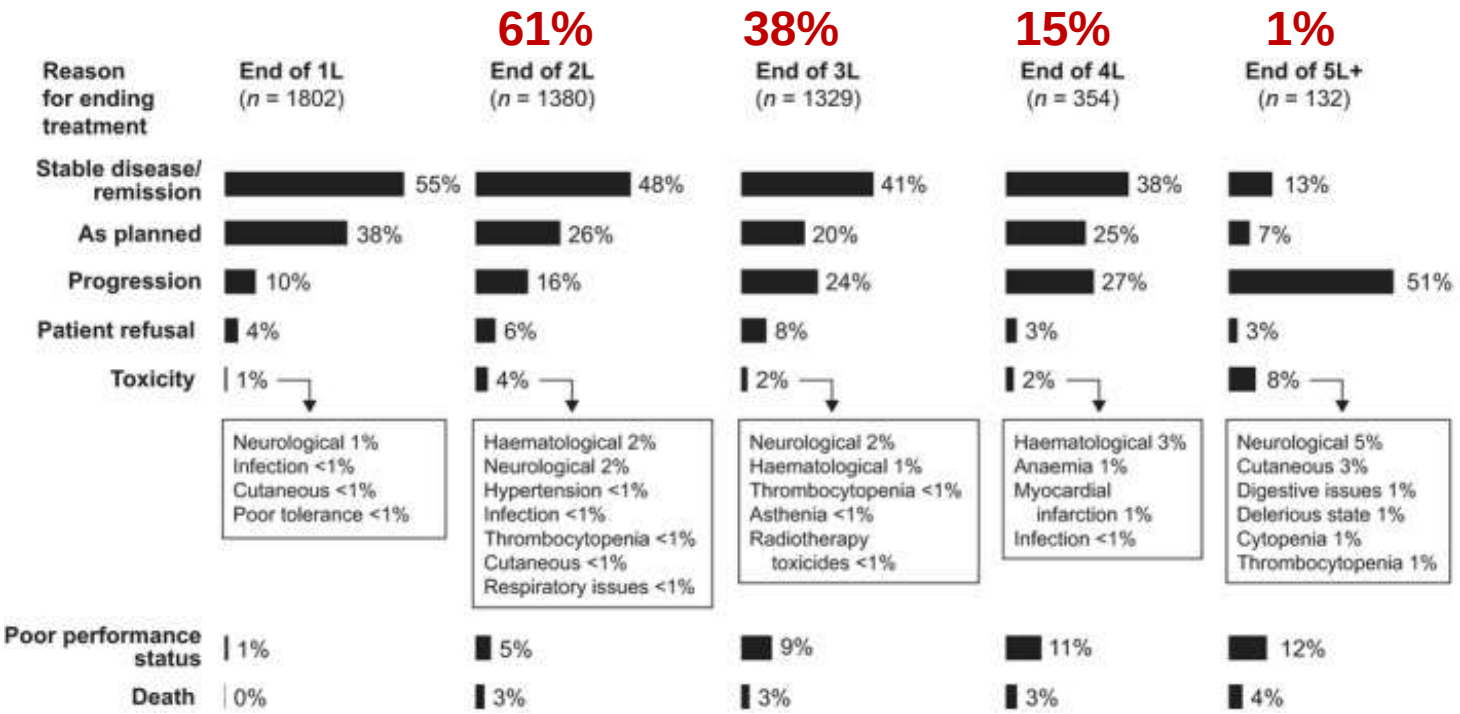
High rate of attrition



Br J Haematol. 2016 Oct;175(2):252-264

MAYO CLINIC

Randomized Trials at Relapse

✓	ASPIRE:	KRd vs Rd
✓	TOURMALINE-MM1:	IRd vs Rd
✓	ELOQUENT-2:	ERd vs Rd
✓	POLLUX	DaraRd vs Rd
✓	PANORAMA:	PanVd vs Vd
✓	CASTOR	DaraVd vs Vd
✓	ENDEAVOR	Kd vs Vd
✓	OPTIMMISM	PVd vs Vd
✓	ELOQUENT- 3	EPd vs Pd
✓	ARROW	K weekly vs K biweekly

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First Relapse Off-Study

On maintenance		Off-therapy/ Unmaintained*	
Fit Patients*	Indolent Relapse* or Frail patients	Fit Patients*	Indolent Relapse* or Frail patients
↓	↓	↓	↓
KPd or DVd if Rev maintenance DRd if Vel maintenance	DVd or ICd if Rev maintenance IRd or DRd if Vel maintenance	KRd or DRd	IRd or ERd

*Consider salvage auto SCT in patients eligible for ASCT who have not had transplant before; Consider 2nd auto SCT if eligible and >18 months unmaintained or >36 months maintained response to first auto

v5 //last reviewed March 2017; Dingli et al. Mayo Clin Proc 2017;92(4):578-59

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CASTOR Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma

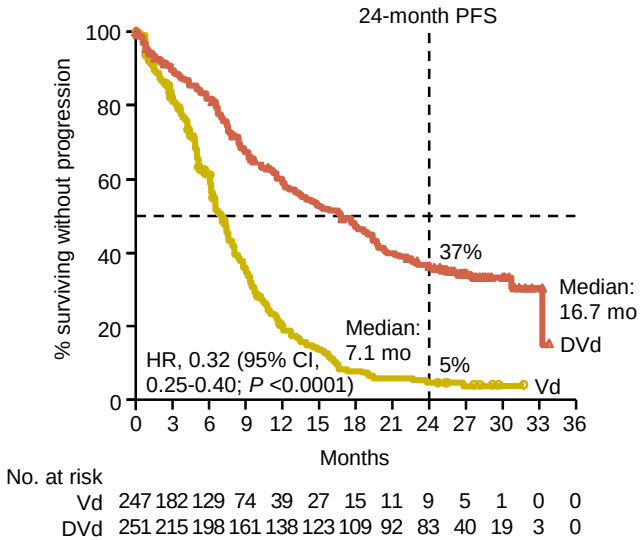
Antonio Palumbo, M.D., Asher Chanan-Khan, M.D., Katja Weisel, M.D., Ajay K. Nooka, M.D., Tamas Masszi, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Vania Hungria, M.D., Markus Munder, M.D., Maria V. Mateos, M.D., Tomer M. Mark, M.D., Ming Qi, M.D., Jordan Schecter, M.D., Himal Amin, B.S., Xiang Qin, M.S., William Deraedt, Ph.D., Tahamtan Ahmadi, M.D., Andrew Spencer, M.D., and Pieter Sonneveld, M.D., for the CASTOR Investigators*

Palumbo et al , et al. N Engl J Med 2016

MAYO CLINIC

Updated PFS in the ITT Population

- **PFS was significantly prolonged with DVd compared with Vd (median: 16.7 vs 7.1 months; HR, 0.32; 95% CI, 0.25-0.40; *P* <0.0001; Figure)**



PFS, progression-free survival; ITT, intent-to-treat; DVd, daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone; HR, hazard ratio; CI, confidence interval.

MAYO CLINIC

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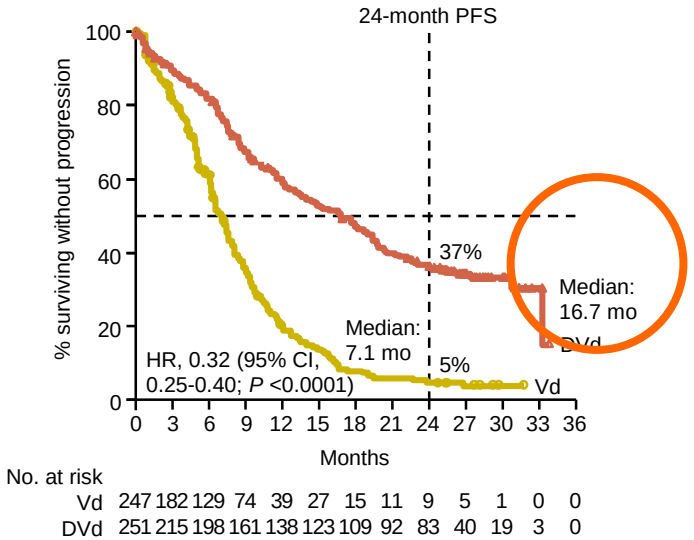

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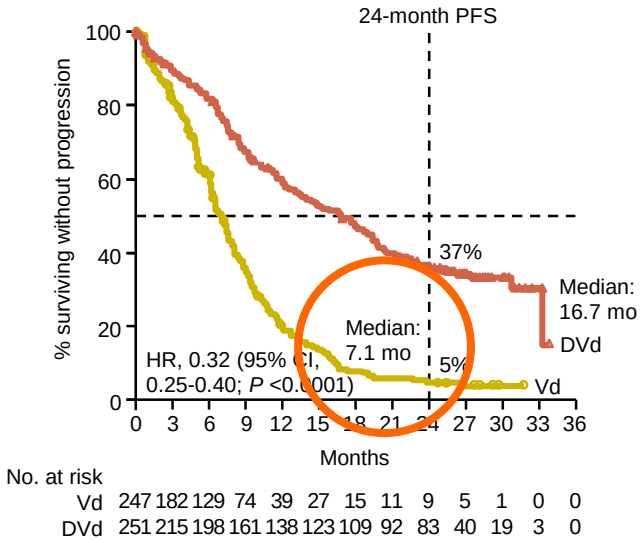

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Pollux Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

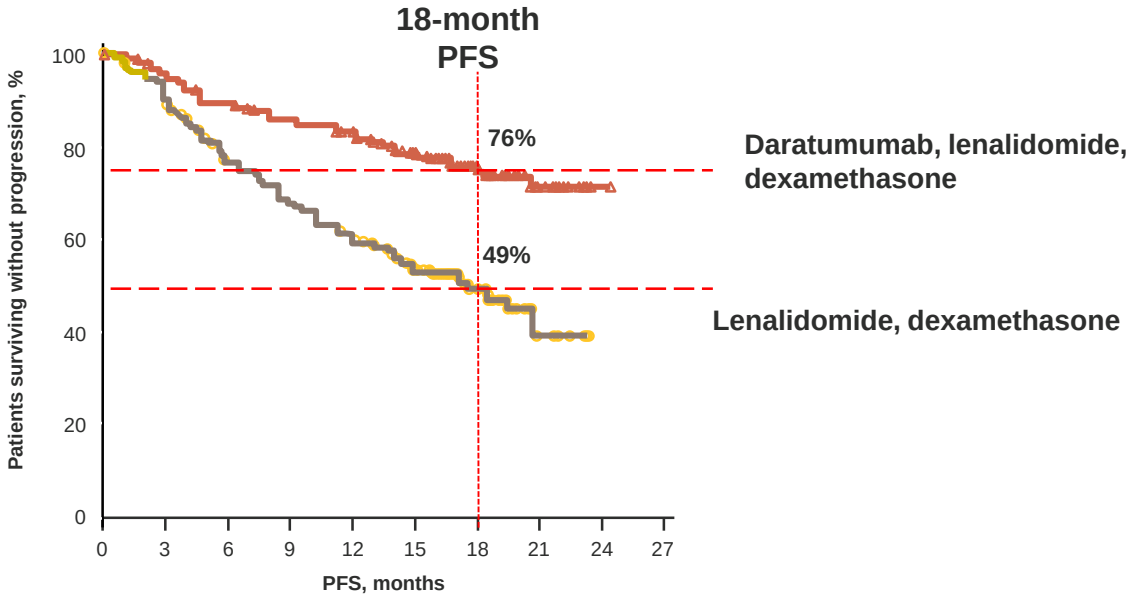
M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*

@rfonsi1, fonseca.rafael@mayo.edu

Dimopoulos et al , et al. N Engl J Med 2016;375:1319-31.

MAYO CLINIC

Updated PFS for POLLUX Trial



HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimates.
Clinical cut-off: June 30, 2016.

Median (range) follow-up:
17.3 (0-24.5) months

Median PFS

DRd: not reached; Rd: 17.5 months

HR: 0.37 (95% CI, 0.28-0.50; *P* <0.0001)

Dimopoulos et al N Engl J Med 2016; 375:1319-1331

Amanda

- Switched to Dara Pom Dex
- 6 months later presented with Tamponade - Myeloma cells in pericardial effusion
- Marrow still negative, Labs and PET scan still negative

ENDEAVOR: Study Design

Randomization 1:1

N=929

Stratification:

- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of V administration

Kd

Carfilzomib* 56 mg/m^2 IV

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

Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg

Days 1, 2, 8, 9, 15, 16, 22, 23

28-day cycles until PD or unacceptable toxicity

Treat to progression

Vd

Bortezomib 1.3 mg/m^2 (3–5 second IV bolus or subcutaneous injection)

Days 1, 4, 8, 11

Dexamethasone 20 mg

Days 1, 2, 4, 5, 8, 9, 11, 12

21-day cycles until PD or unacceptable toxicity

Treat to progression

Primary end point:
PFS by IRC

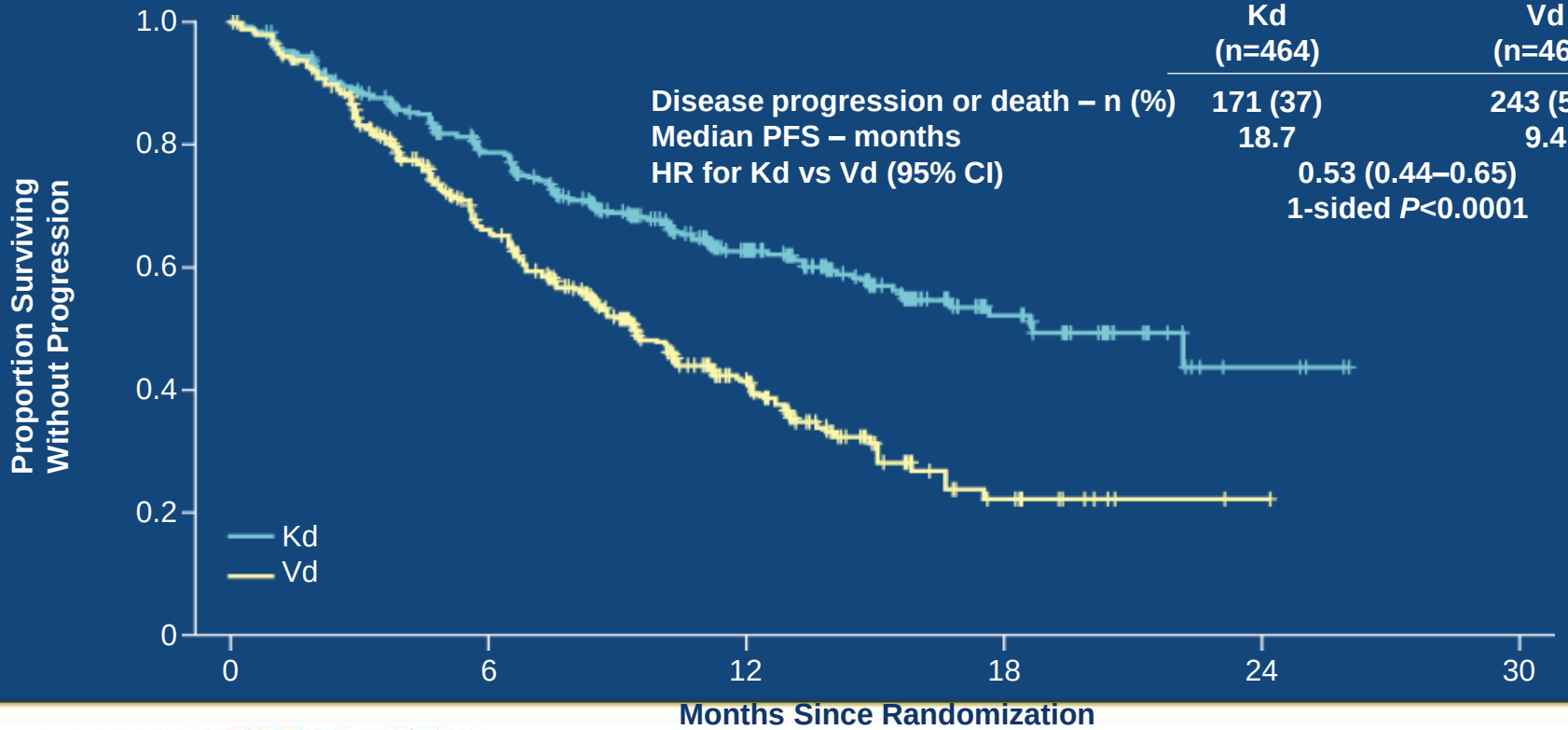
Secondary end points:

- OS
- ORR
- DOR
- Grade ≥2 PN rate
- Safety

*Carfilzomib was administered for 3 weeks out of 4

Dimopoulos MA, et al. Presented at: 16th International Myeloma Workshop; March 1-4, 2017; New Delhi, India.

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



	Kd (n=464)	Vd (n=465)
Disease progression or death – n (%)	171 (37)	243 (52)
Median PFS – months	18.7	9.4
HR for Kd vs Vd (95% CI)	0.53 (0.44–0.65)	
	1-sided *P*<0.0001	

PRESENTED AT: 2018 ASCO ANNUAL MEETING
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PRESENTED BY:

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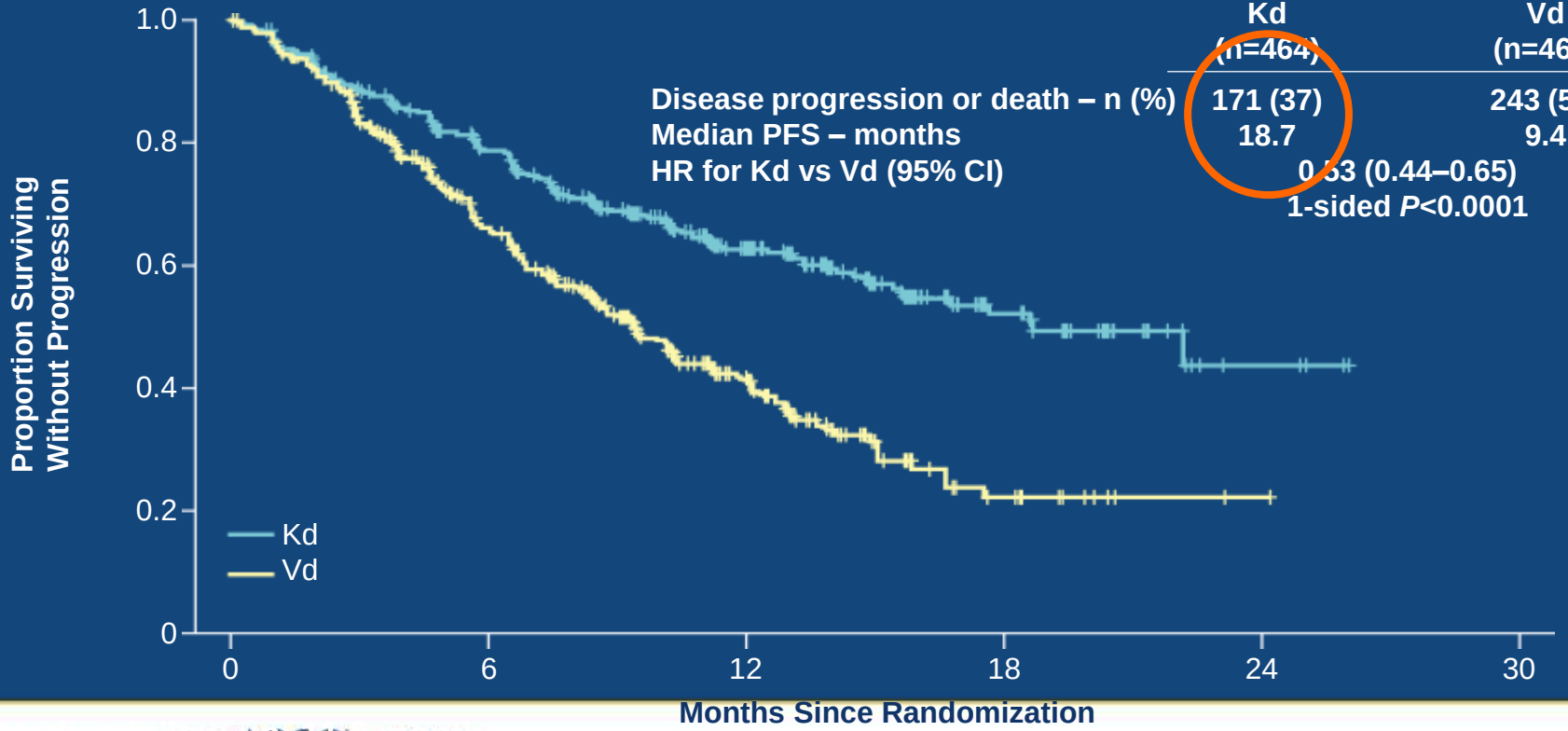

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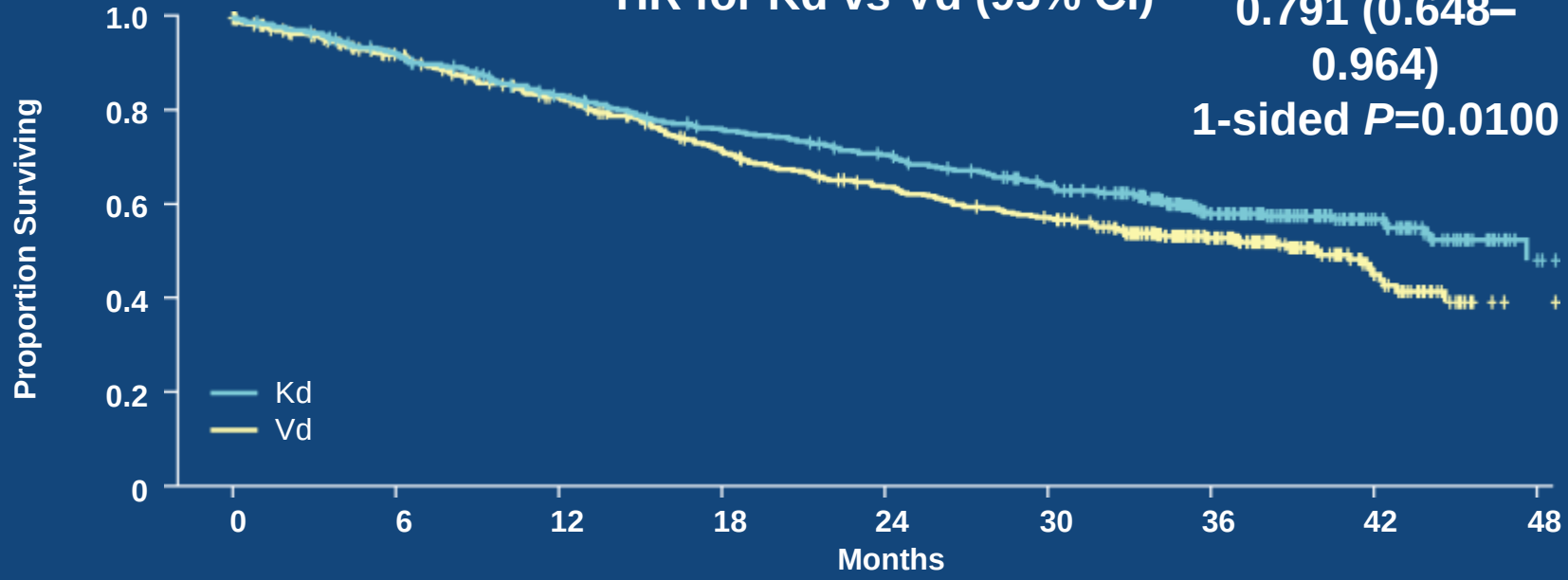
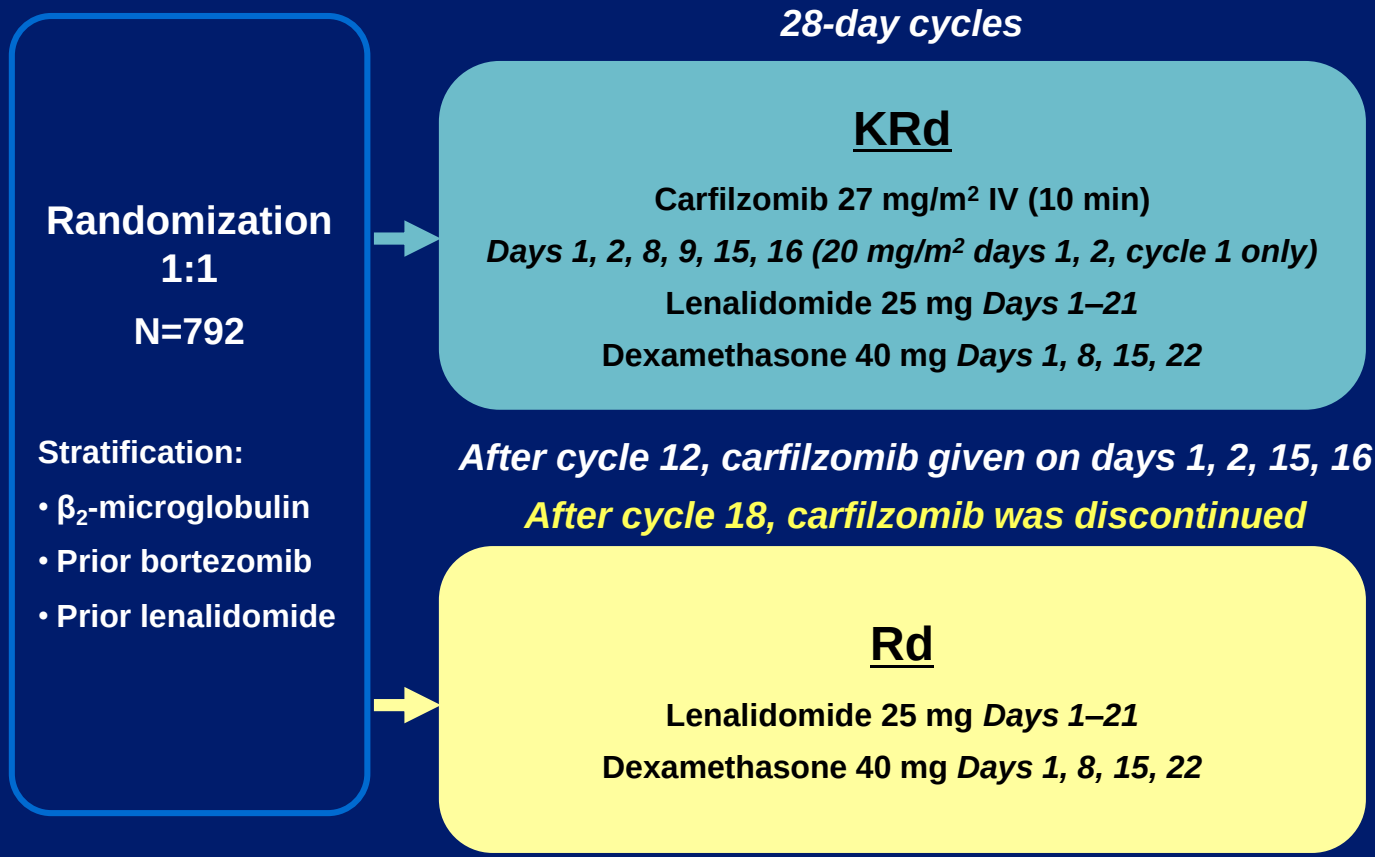
Dimopoulos MA, et al. Presented at: 16th International Myeloma Workshop; March 1-4, 2017; New Delhi, India.

Overall Survival

	Kd (n=464)	Vd (n=465)
Death – n (%)	189 (40.7)	209 (44.9)
Median OS – months	47.6	40.0
HR for Kd vs Vd (95% CI)	0.791 (0.648–0.964)	
	1-sided *P*=0.0100	



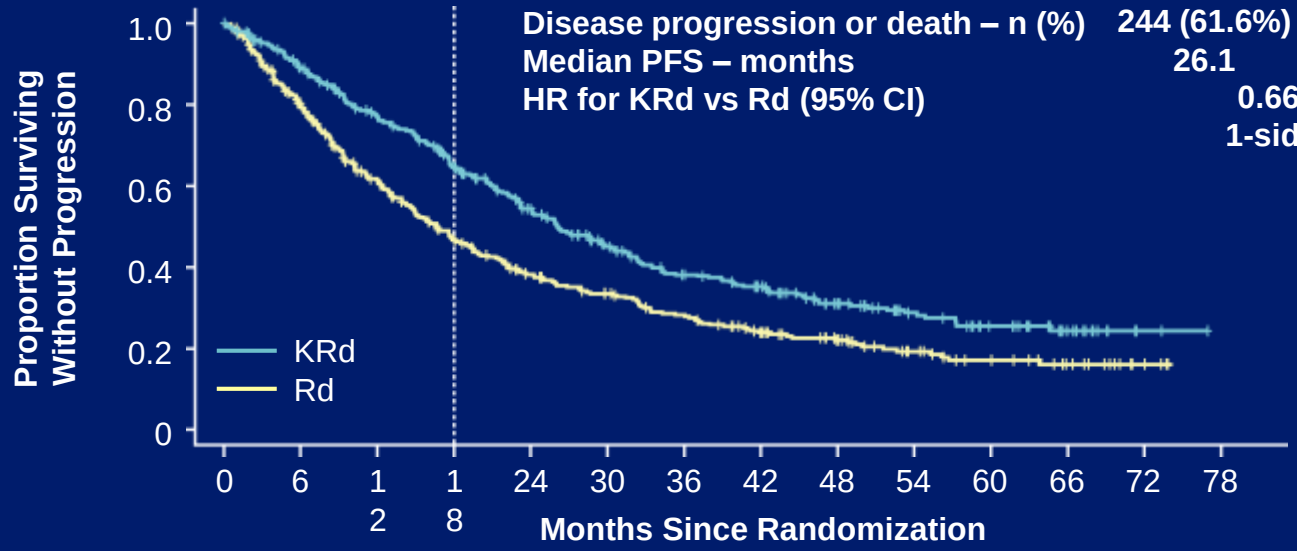
ASPIRE: Study Design



Updated Investigator-Assessed Progression-Free Survival

ITT Population (N=792): 9.5 month improvement

	KRd (n=396)	Rd (n=396)
Disease progression or death – n (%)	244 (61.6%)	272 (68.7)
Median PFS – months	26.1	16.6
HR for KRd vs Rd (95% CI)	0.66 (0.55–0.78)	
	1-sided *P*<0.0001	



Number of patients at risk:

KRd	396	337	282	227	178	136	109	94	65	45	32	17	2	0
Rd	396	291	211	154	118	99	81	61	45	30	21	13	4	0

- **Data cutoff date: April 28, 2017; Median follow-up: 48.8 (KRd) and 48.0 (Rd) months**
- **Carfilzomib discontinued after 18 cycles**

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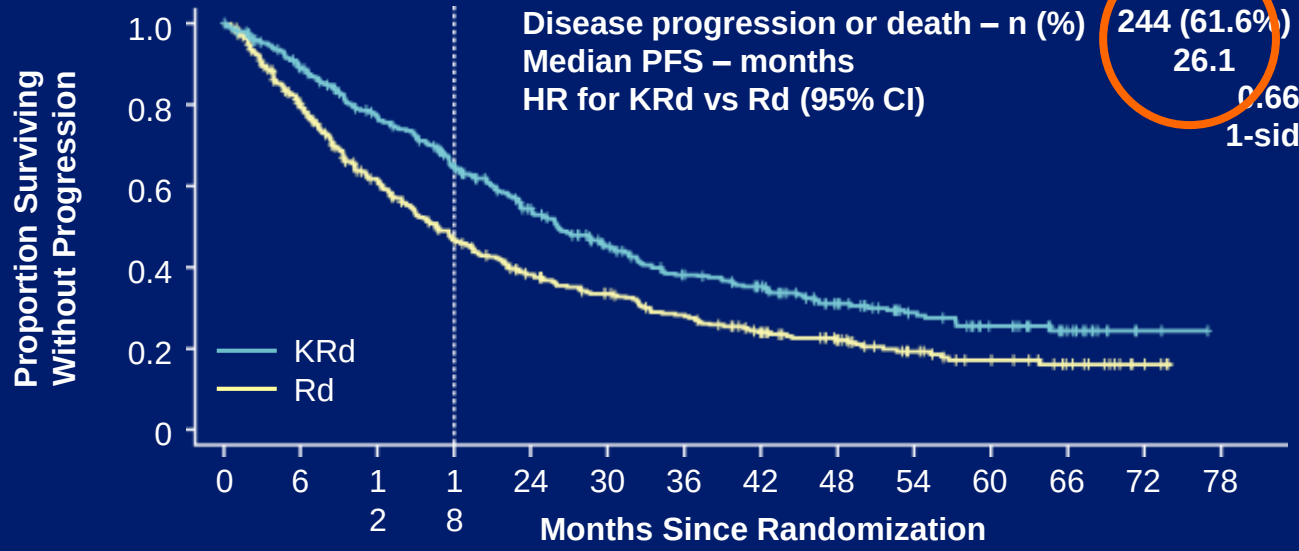

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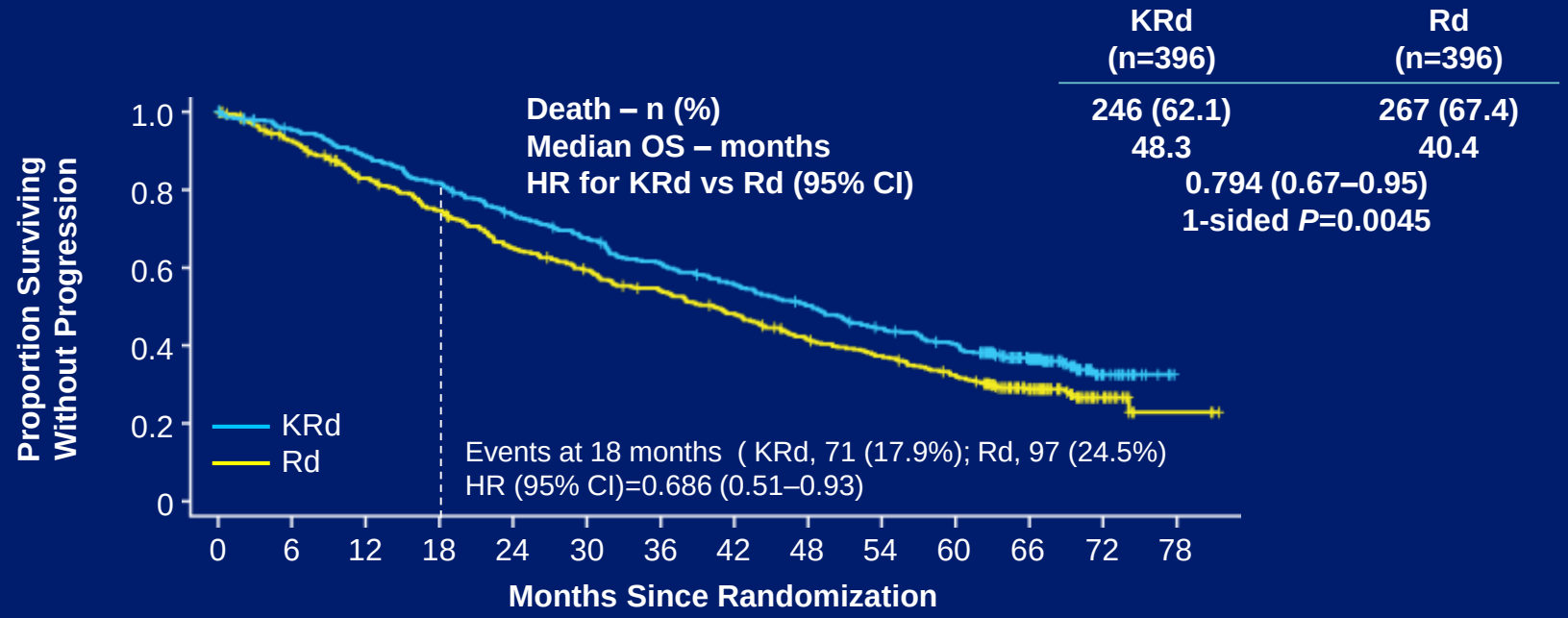
Overall Survival: 7.9 month median improvement



Siegel et al. J Clin Oncol. 2018 Mar 10;36(8):728-734

Carfilzomib and Cyclophosphamide

- VCD vs KCD Randomized Ph2 (1:2 ratio) in 300 first relapse or primary refractory patients

- K 20/36 mg/m^2 , V day 1,4,9,11 s/c

Overall response was 84.0% and 68.1% (OR 2.72; 90% CI (1.62, 4.55); p=0.0014).

MRD negativity (n=134 KCD, n=48 VCD) at 24 weeks was 16.4% for KCD and 12.5% for VCD.

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Kwee Yong et al: ASH abstracts 2017

MUK FIVE: KCd vs VCd at first relapse

- Only 53.5% of patients completed all 24 weeks of treatment with VCd, vs 81.6% of KCd patients
- Reasons for early discontinuation with KCd and VCd were:
  - Toxicity (7% vs 19.2%)
  - PD (6.5% vs 6.1%)
  - Consent withdrawal (2.5% vs 11.1%)

After 24 weeks, response to KCd was non-inferior to VCd
Overall response rate for KCd was superior to VCd

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Yong et al. Abstract 835

Carfilzomib and Cyclophosphamide

Grade 3 and 4	KCD	VCD
Proportion of SAEs categorized as:		
Neurological	0.7%	8.1%
Cardiac	4.2%	1.4%
Proportion of patients with each AR type:		
Grade ≥3 neutropenia	11.3%	21.9%
Grade ≥3 thrombocytopenia	11.8%	36.5%

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Kwee Yong et al: ASH abstracts 2017

A.R.R.O.W. Study Design

1:1 Randomization

N = 478

- Relapsed and Refractory MM
- 2-3 prior lines
- Prior exposure to IMiD & PI (except carfilzomib or oprozomib)
- PS 0-1
- CrCl of ≥30 mL/min

<u>Stratification:</u>

- ISS stage
- Refractory to bortezomib
- Age (<65 vs. ≥65)

Arm A: Once-weekly carfilzomib + dex

(30 min infusion of K)

Carfilzomib 20 mg/m^2 IV D1 (Cycle 1)
Carfilzomib 70 mg/m^2 IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

28-day cycles

Arm B: Twice-weekly carfilzomib + dex

(10 min infusion of K)

Carfilzomib 20 mg/m^2 IV D1, 2 (Cycle 1)
Carfilzomib 27 mg/m^2 IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Follow-up for Disease Status until Confirmed PD

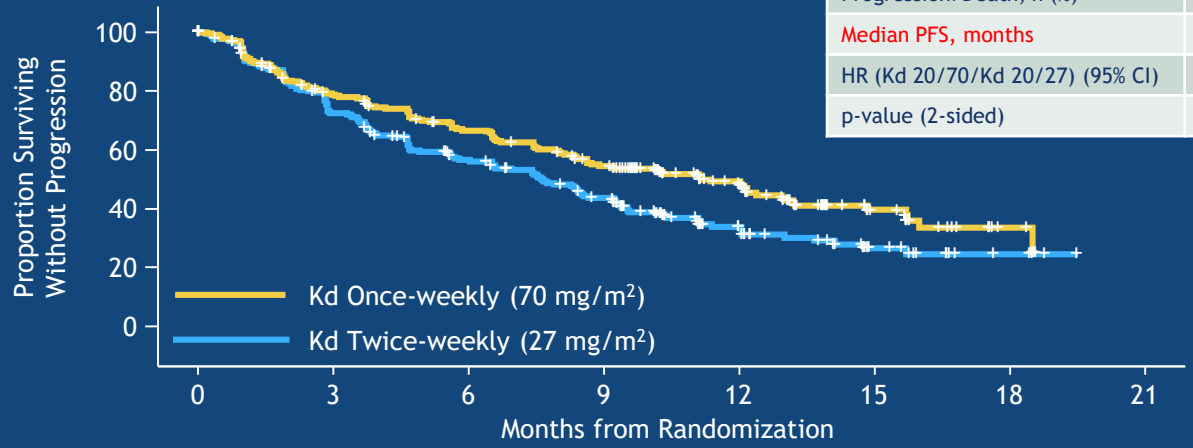
Long-term Follow-up for Survival

Primary end point: PFS

CrCl, creatinine clearance; D, day; IMiD, immunomodulator; ISS, international staging system; IV, intravenous; K, carfilzomib; PD, progressive disease; PI, proteasome inhibitor; PO, by mouth

Primary Endpoint: PFS

	Once-weekly Kd 20/70 mg/m² (n=240)	Twice-weekly Kd 20/27 mg/m² (n=238)
Progression/Death, n (%)	126 (53%)	148 (62%)
Median PFS, months	11.2	7.6
HR (Kd 20/70/Kd 20/27) (95% CI)	0.693 (0.544, 0.883)	
p-value (2-sided)	0.0029	



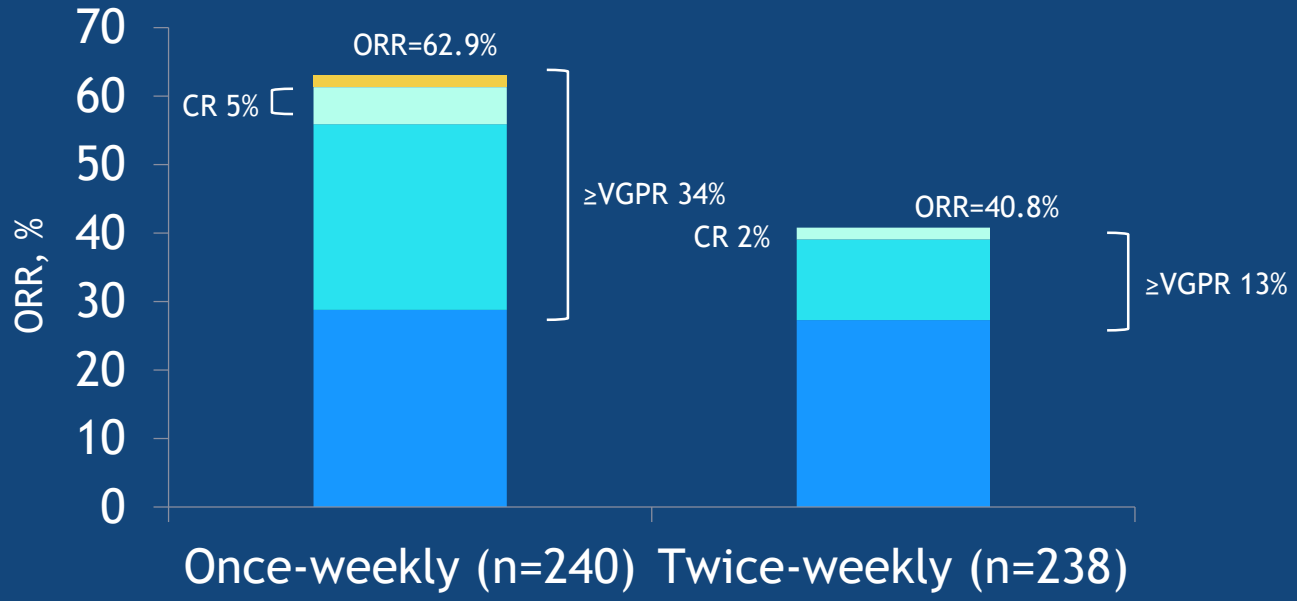
Number of Patients at Risk:

Kd 20/70	240	178	145	114	69	24	5	0
Kd 20/27	238	164	119	86	41	15	4	0

Data cutoff date: June 15, 2017; Median follow-up: 12.6 (once-weekly) and 12.0 (twice-weekly) months

CI, confidence interval; HR, hazard ratio

Overall Response Rates



Stringent complete response

Complete response

Very good partial response

OR (95% CI); p-value (2-sided): 2.49 (1.72, 3.60); p<0.0001

CI, confidence interval; CR, complete response; OR, odds ratio; VGPR, very good partial response.

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Adverse Events of Interest

AE, % (SMQN)	Once-weekly Kd (n=238)		Twice-weekly Kd (n=235)	
	All grades	Grade ≥3	All grades	Grade ≥3
Peripheral neuropathy	4	0	7	<1
Acute renal failure	7	4	7	6
Cardiac failure	4	3	5	4
Ischemic heart disease	2	1	1	1
Pulmonary hypertension	2	0	1	<1

- Safety findings were consistent with the known safety profile of carfilzomib, and no new risks were identified.

AE, adverse event; SMQN, standardized MedDRA Query, narrow scope

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Amanda

- Started KweeklyCd therapy
- Serial Echocardiograms
- Planned Second Auto
- Repeat MRD testing – likely continue K weekly