

# Therapie des Multiplen Myeloms

## Alles im Fluss ?

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Newly Diagnosed Multiple Myeloma – Transplant Eligible

**NDMM – TE**

Eligibility for autologous stem cell transplantation (ASCT)

Yes

No

Induction:  
3 drug regimens  
VTD  
VCD  
PAD  
RVD

First option:  
VMP or Rd or VRd

Second option:  
MPT or VCD

Other options:  
CTD, MP, bendamustine  
prednisone

200 mg/m<sup>2</sup>  
melphalan followed  
by ASCT

Lenalidomide  
maintenance

- VCD is preferable to PAD,  
*Mai, Leukemia 2015*
- VTD is superior to VCD,  
*Cavo, Leukemia 2015*
- Len-dex is better than Thal-dex,  
*Gay F Blood 2010*

## ESMO guidelines 2017

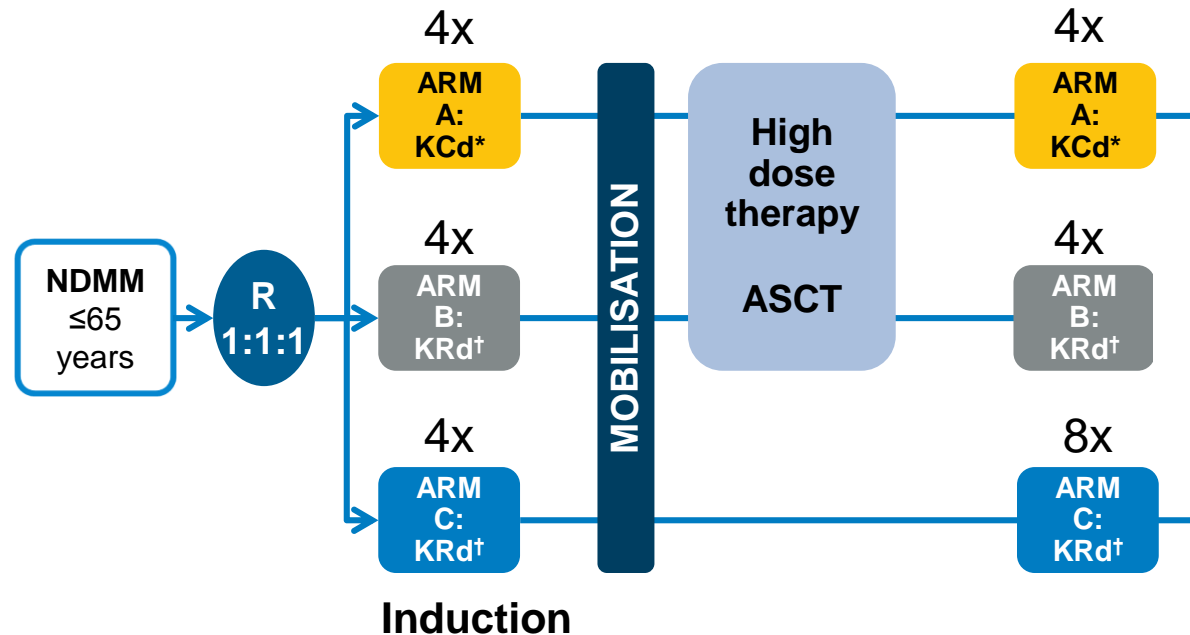
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## **A Randomized Study of Carfilzomib-Lenalidomide-Dexamethasone vs Carfilzomib-Cyclophosphamide-Dexamethasone Induction in Newly Diagnosed Myeloma Patients Eligible for Transplant: High Efficacy in High- and Standard-risk Patients – FORTE**

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Gay F, Rota Scalabrini D, Musto P, Belotti A, Galli M, Offidani M, Gambella M, Coha V, Montefusco V, Zamagni E, Zambello R, Ledda A, Grasso M, Aquino S, Esma F, Ribolla R, Tosi P, Pisani F, Annibali O, Liberati A.M, Oliva S, Paris L, Baraldi A, Galieni P, Specchia G, Pescosta N, Palumbo A, Cavo M and Boccadoro M

# FORTE: KRd vs KCd in newly diagnosed MM



- **Post-induction response rates and minimal residual disease<sup>‡</sup>** were evaluated
  - For this analysis, data of the two KRd groups (Arms B and C) were pooled
- **Primary objective:** compare **efficacy** of **KRd** vs **KCd** **induction** in patients eligible for transplantation
- **Secondary objective:** evaluate the **efficacy** of **KRd** vs **KCd** in **different subgroups** according to prognostic features, focusing specifically on high-risk patients

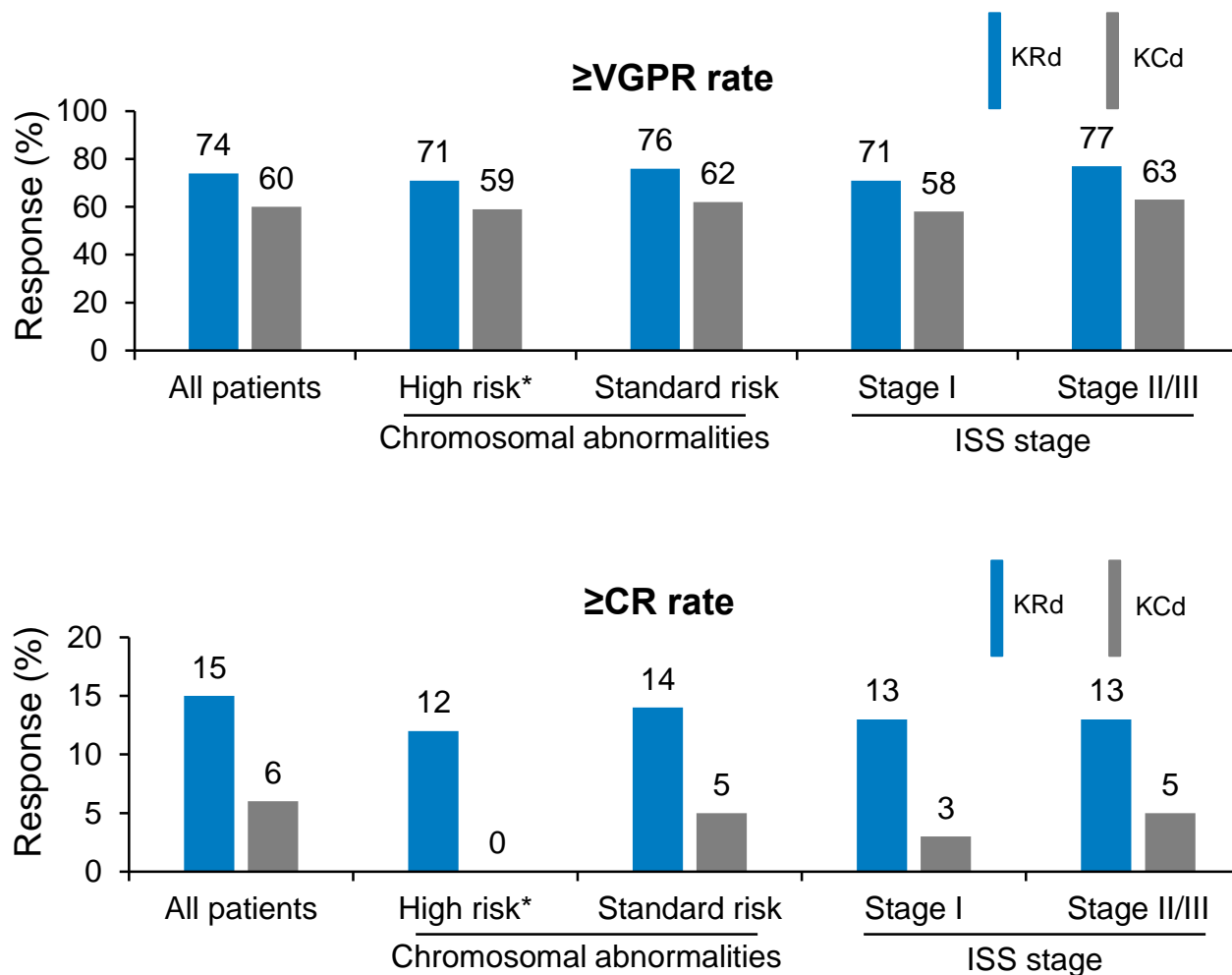
\*Carfilzomib: 20/36 mg/m<sup>2</sup> IV d 1, 2, 8, 9, 15, 16; cyclophosphamide 300 mg/m<sup>2</sup> d 1, 8, 15; dexamethasone: 20 mg d 1, 2, 8, 9, 15, 16.

†Carfilzomib and dexamethasone as above; lenalidomide: 25 mg d 1-21.

‡by multiparameter flow cytometry (8 colours, sensitivity 10<sup>-5</sup>)

ASCT, autologous stem cell transplant; KCd, carfilzomib, cyclophosphamide and dexamethasone; KRd, carfilzomib, lenalidomide and dexamethasone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma.

# KRd achieved higher response rates vs KCd in subgroup analyses



\* High risk: del(17p) or t(4;14) or t(14;16).

CR, complete response; ISS, International Staging System; KCd, carfilzomib, cyclophosphamide and dexamethasone; KRd, carfilzomib, lenalidomide and dexamethasone; , very good partial response.

# Autologous SCT remains up-front SoC

**N Engl J Med 2017;376:1311-20.**

## Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Cyrille Hulin, M.D., Xavier Leleu, M.D., Denis Caillot, M.D., Martine Escoffre, M.D., Bertrand Arnulf, M.D., Margaret Macro, M.D., Karim Belhadj, M.D., Laurent Garderet, M.D., Murielle Roussel, M.D., Catherine Payen, M.D., Claire Mathiot, M.D., Jean P. Fermand, M.D., Nathalie Meuleman, M.D., Sandrine Rollet, M.S., Michelle E. Maglio, B.S., Andrea A. Zeytoonjian, B.S., Edie A. Weller, Ph.D., Nikhil Munshi, M.D., Kenneth C. Anderson, M.D., Paul G. Richardson, M.D., Thierry Facon, M.D., Hervé Avet-Loiseau, M.D., Jean-Luc Harousseau, M.D., and Philippe Moreau, M.D., for the IFM 2009 Study\*

# IFM/DFCI 2009 Phase 3 Trial

newly diagnosed MM pts  $\leq 65$  years (ASCT candidates)

1 cycle RVD

Randomize, stratification  
ISS & FISH

ARM B: Early transplant arm

ARM A: Late transplant arm

RVD, cycles 2, 3

CY ( $3\text{g}/\text{m}^2$ ) + G-CSF  
MOBILIZATION  
Goal:  $5 \times 10^6$  cells/kg

Melphalan  
 $200\text{ mg}/\text{m}^2$  + ASCT

RVD  $\times 2$

Lenalidomide 12 mos (IFM)  
Lenalidomide until relapse (DFCI)

PBSC collection

Consolidation

Maintenance

RVD, cycles 2, 3

CY ( $3\text{g}/\text{m}^2$ ) + G-CSF  
MOBILIZATION  
Goal:  $5 \times 10^6$  cells/kg

RVD  $\times 5$

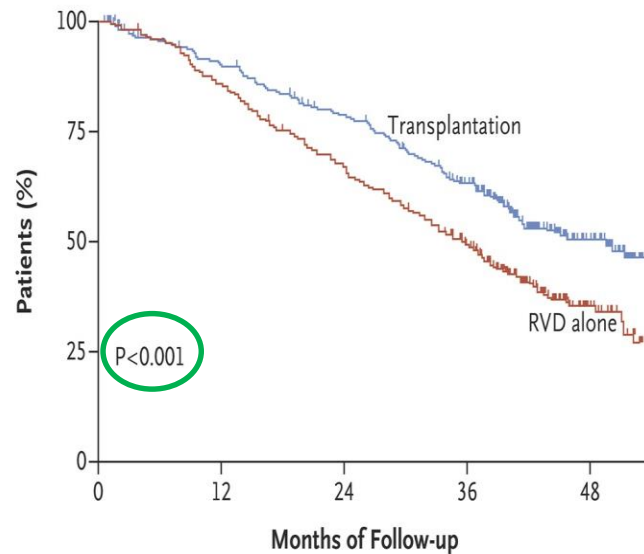
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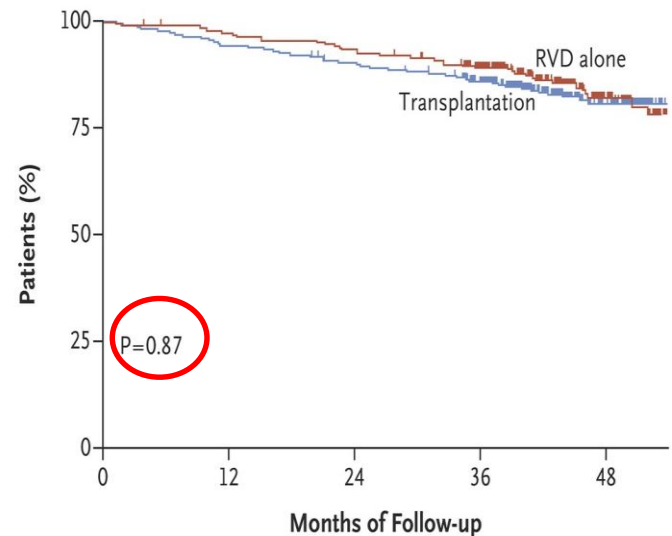
**A** Progression-free Survival



**No. at Risk**

RVD alone	350	294	228	157	32
Transplantation	350	308	264	196	50

**B** Overall Survival

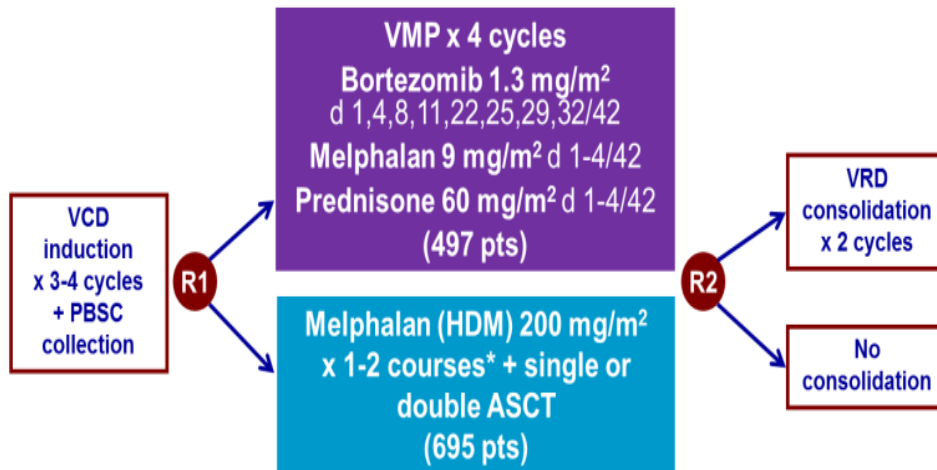


**No. at Risk**

RVD alone	350	339	325	293	95
Transplantation	350	330	313	281	89

# European Myeloma Network

## EMN02/HO95 MM trial: study design



All pts received lenalidomide maintenance until PD

Stratification: ISS I vs. II vs. III

Randomization to VMP or HDM was 1:1 in centers with a fixed single ASCT policy

Randomization to VMP or HDM-1 or HDM-2 was 1:1:1 in centers with a double ASCT policy

- median PFS **NE** vs **44mo**
- 3-year estimate of PFS **64%** vs **57%**, (HR=0.76; p=0.002)
- MRD neg ( $10^{-5}$ ) **64%** vs **36%**
- Pts with high-risk cytogenetics benefit from **double ASCT**  
3-yr PFS for ASCT-2 vs ASCT-1: **69.2% vs 44.2%**  
(HR: 0.42; P = .014)

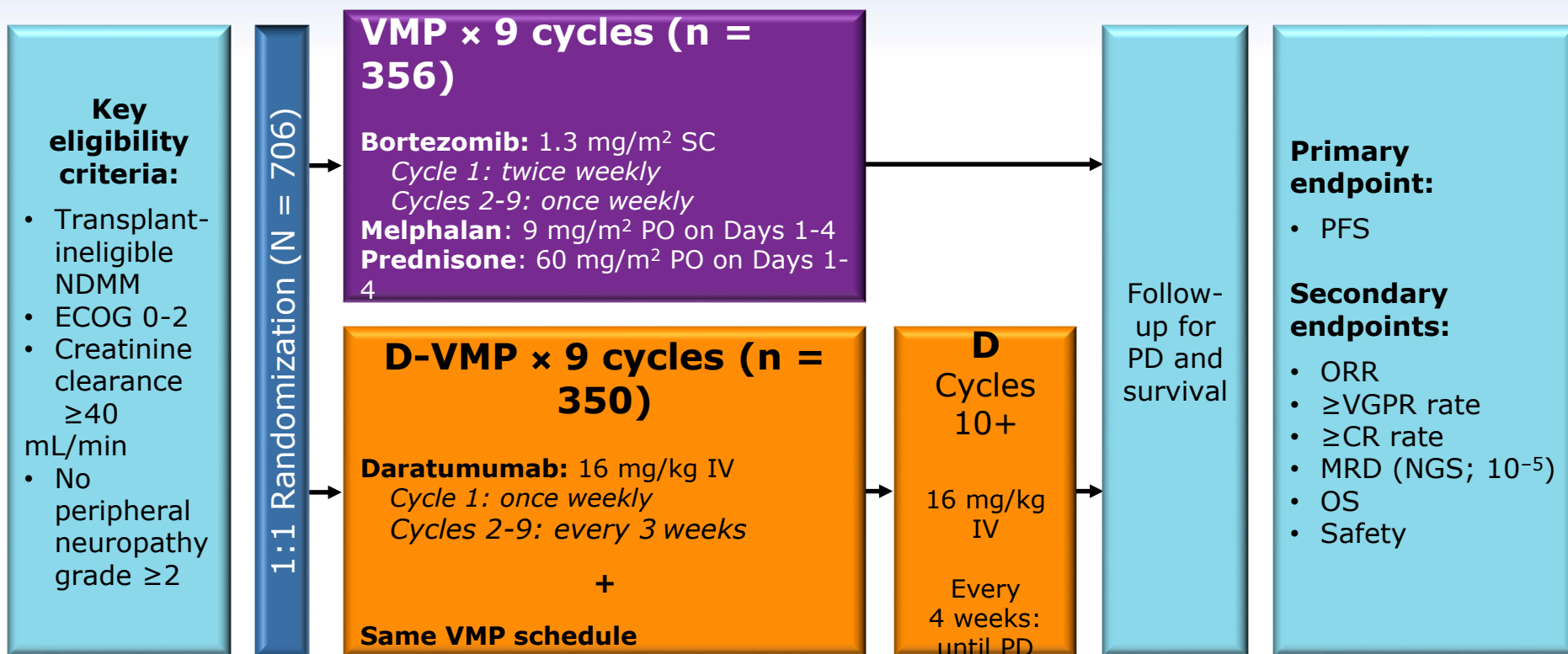
Newly Diagnosed Multiple Myeloma – Transplant Ineligible

**NDMM - TI**

# **Phase 3 Randomized Study of Daratumumab Plus Bortezomib, Melphalan, and Prednisone (D-VMP) Versus Bortezomib, Melphalan, and Prednisone (VMP) in Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible for Transplant (ALCYONE)**

# ALCYONE phase 3 study of daratumumab + VMP in NDMM

## Study Design



### Stratification factors

- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs  $\geq 75$  years)

- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

### Statistical analyses

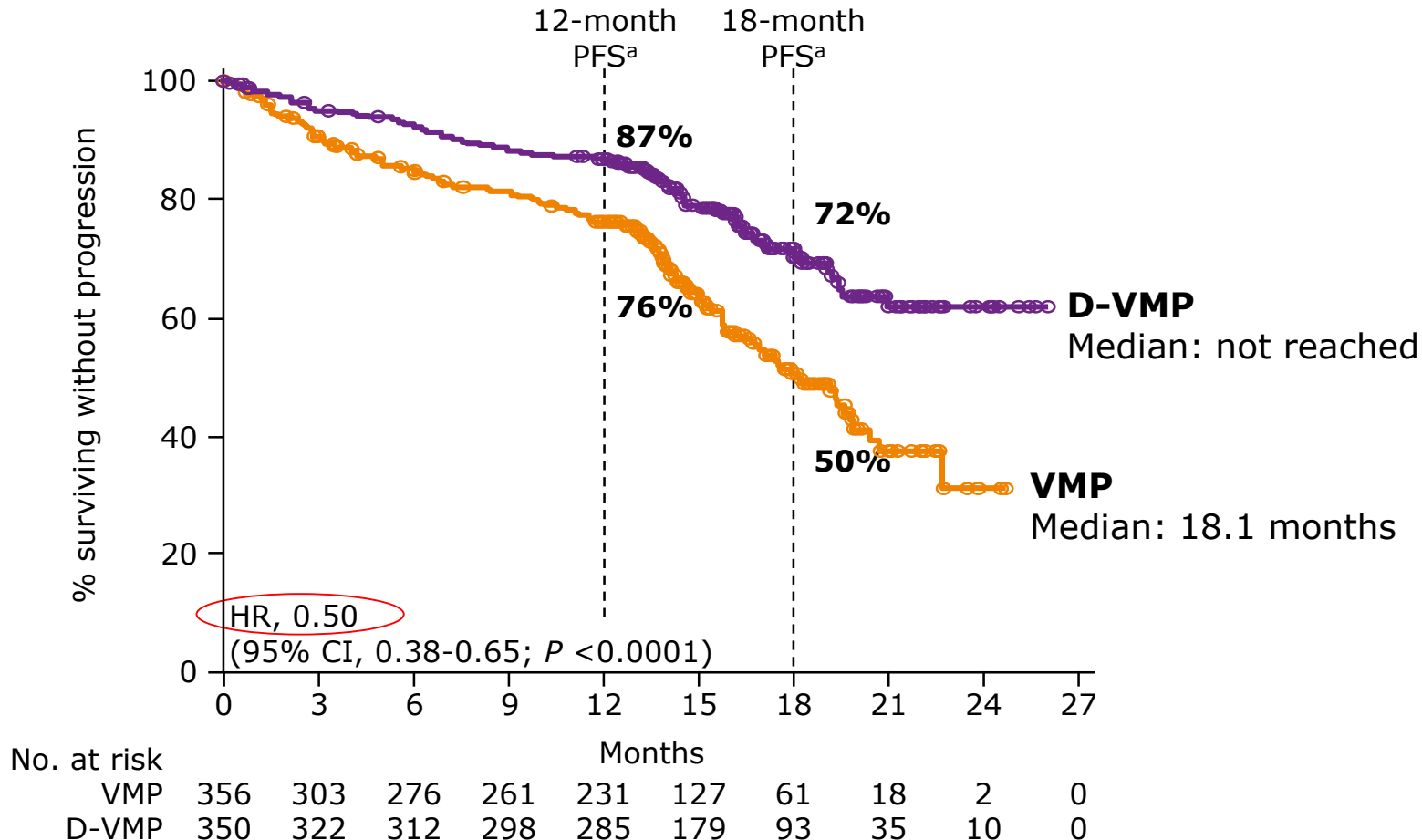
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; VMP, bortezomib/melphalan/prednisone; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.

# ALCYONE: PFS

Pre-specified interim analysis after 231 PFS events

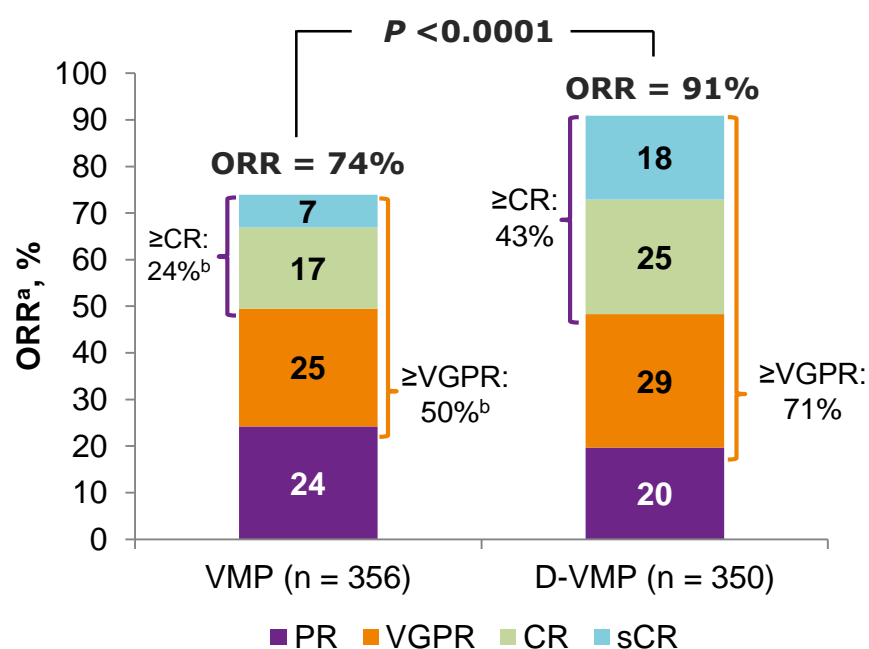
Median (range) follow-up: 16.5 (0.1-28.1) months



**50% reduction in the risk of progression or death in patients receiving D-VMP**

# ALCYONE: Response Rates

- Median duration of response: 21.3 months in VMP versus not reached in D-VMP



Response	VMP (n = 263) <sup>c</sup>	D-VMP (n = 318) <sup>c</sup>
Median (range) time to first response, months	0.82 (0.7-12.6)	0.79 (0.4-15.5)
Median (range) time to best response, months	4.11 (0.7-20.5)	4.93 (0.5-21.0)

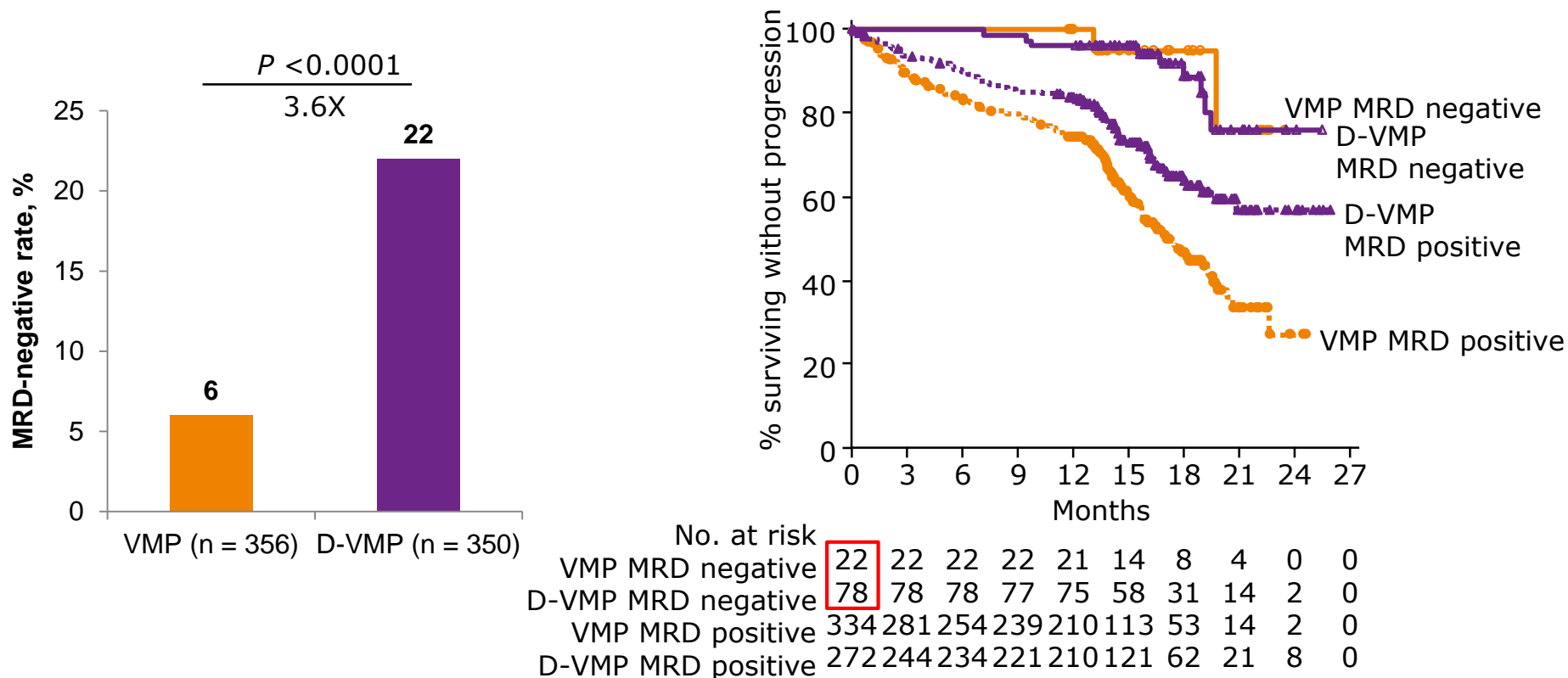
**Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP;  
>2-fold increase in rate of sCR with D-VMP**

PR, partial response; sCR, stringent complete response.

<sup>a</sup>ITT population. <sup>b</sup>P < 0.0001; P value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test. <sup>c</sup>Responders in response-evaluable population.

# ALCYONE Efficacy: MRD<sup>a</sup> (NGS; 10<sup>-5</sup> Sensitivity Threshold)

- Median (range) follow-up: 16.5 (0.1-28.1) months



**>3-fold higher MRD-negativity rate with D-VMP;  
Lower risk of progression or death in all MRD-negative patients**

MRD, minimal residual disease; NGS, next-generation sequencing using clonoSEQ version 2.0 (Adaptive); VMP, bortezomib/melphalan/prednisone; D, daratumumab; CR, complete response; sCR stringent complete response.

<sup>a</sup>Assessed at time of confirmation of CR/sCR, and if confirmed, 12, 18, 24, and 30 months after first dose.



Relapsed/Refractory Multiple Myeloma

**RRMM**

**Autologous SCT for relapse/progression**

# Recommendations for salvage ASCT in RRMM

**ESMO:** In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT and had a PFS of more than **24 months**

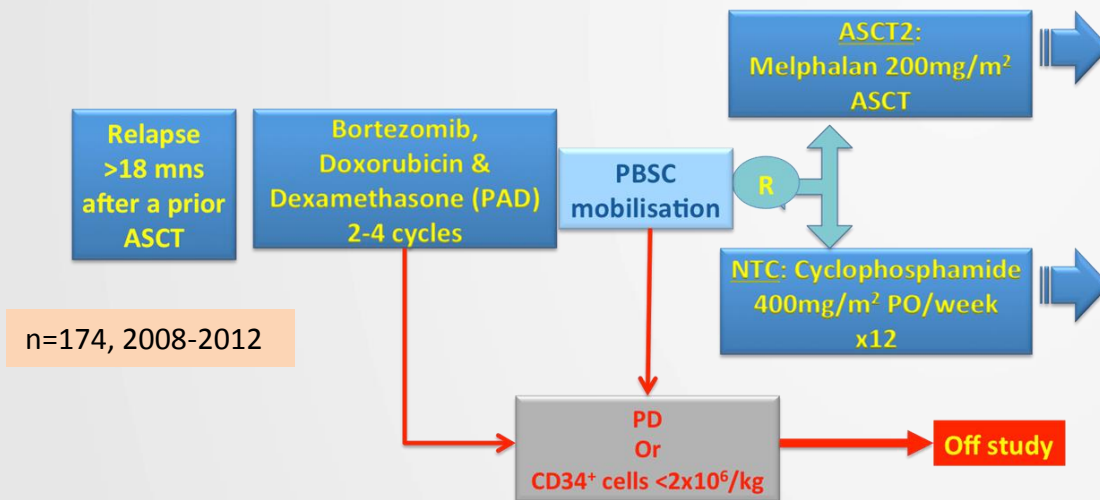
**EBMT/ASBMT:** High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than **18 months**.

**NCCN 2018:** RETROSPECTIVE STUDIES SUGGEST A MINIMUM LENGTH OF **2-3 YEARS** OF REMISSION FOR CONSIDERATION OF A SECOND ASCT

# High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial

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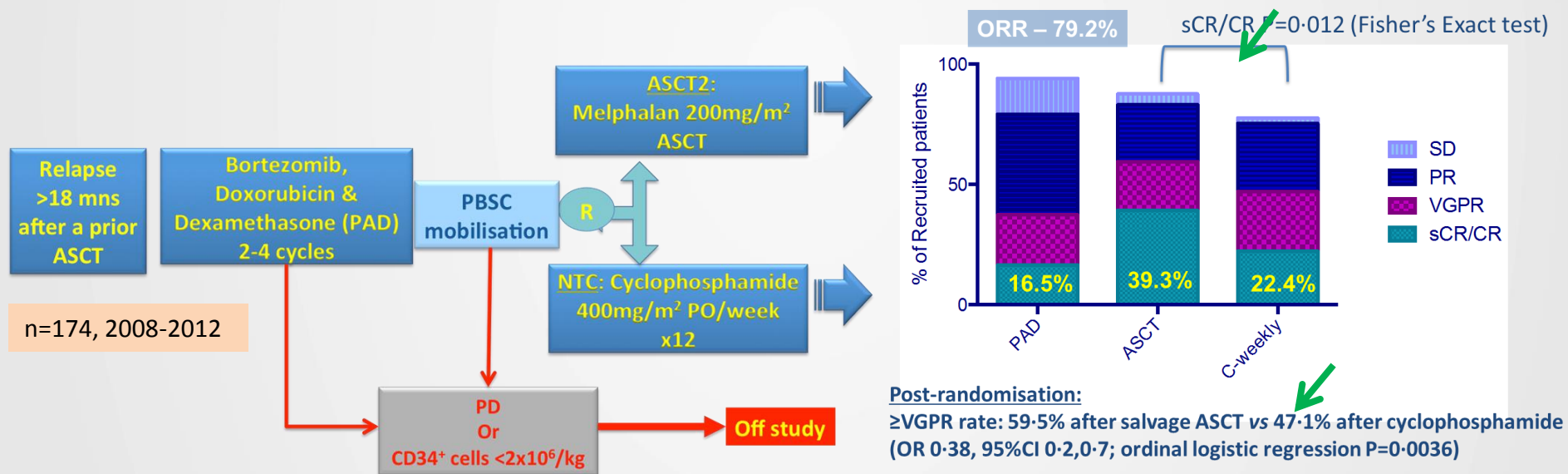
*Lancet Oncol* 2014; 15: 874–85



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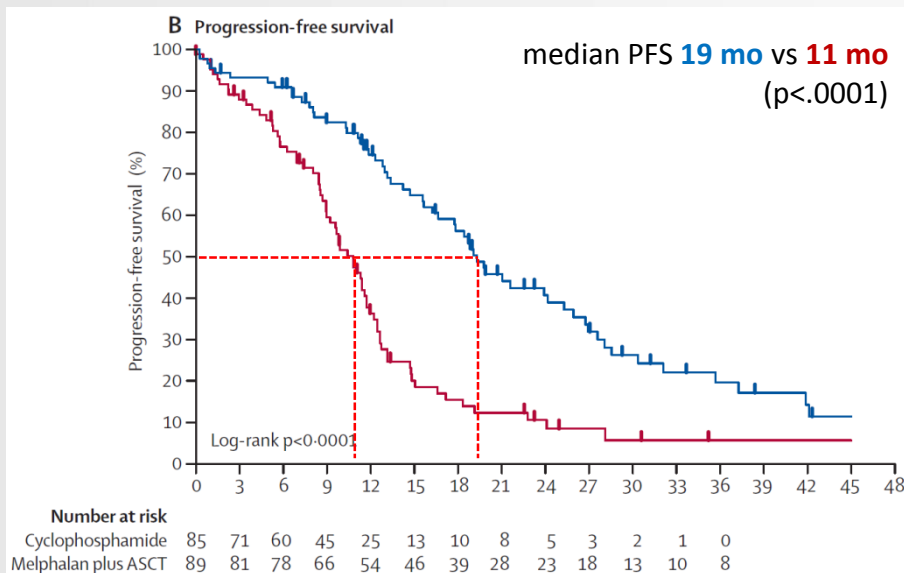
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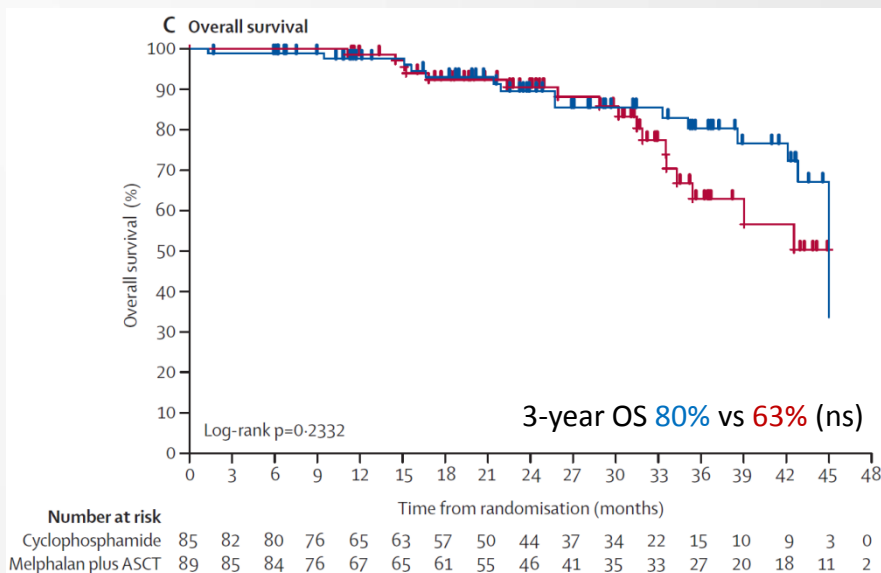
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G Cook, Leeds

NRM **1%** vs **0%**



## Multiple retrospective salvage ASCT studies

Patients (n)	High Dose therapy	Interval (months)	CTX lines (numbers)	TRM (%)	ORR (%)	PFS (%)	OS (%)	PFS cut-off (months)	References
83	MEL200	31.2	—	—	—	15.6	34.8	18.0†	Alvares <i>et al</i> (2006)
83	MEL200, MEL <200	35.4	—	7.2	—	15.5	31.5	21.5†	Auner <i>et al</i> (2013)
66	MEL100	22.2	0.0	0.0	62.1	8.5	24.0	22.2†	Blimark <i>et al</i> (2011)
25	MEL200, MEL140	39.0	2.0	8.0	64.0	12.0	19.0	—	Burzynski <i>et al</i> (2009)
30	MEL200, MEL <200, MEL200+BOR, MEL+BU	30.2	1.5	3.0	80.0	22.0	45.0	36.0	Chow <i>et al</i> (2013)
106	—	19.0	0.0	—	63.0	—	37.0	18.0*†	Cook <i>et al</i> (2011)
26	MEL120+BU	20.4	—	0.0	69.2	14.8	38.1	—	Elice <i>et al</i> (2006)
55	MEL200, MEL140+BU, MEL200+BOR	28.0	2.0	5.9	75.0	14.0	52.0	12.0*†	Fenk <i>et al</i> (2011)
98	MEL200, MEL140	46.0	3.0	4.1	86.7	10.3	33.0	12.0*†	Gonsalves <i>et al</i> (2013)
81	MEL200, MEL140	—	1.0	2.6	97.4	16.4	53.0	24.0*†	Jimenez-Zepeda <i>et al</i> (2012)
11	—	—	—	6.0	27.3	—	—	—	Johnsen <i>et al</i> (1996)
31	MEL100	12.0	1.0	0.0	58.1	5.0	8.0	6.0*†	Krejci <i>et al</i> (2010)
32	MEL200	—	—	3.1	75.0	12.9	79.1	—	Krivanova <i>et al</i> (2004)
50	BEAM, BU+CY, MEL200, MEL140+TBI, MEL 110+TBI-MEL	—	—	14.0	54.0	4.0	9.0	n.s.	Lee <i>et al</i> (2002)
81	MEL220, MEL200, MEL140, MEL+BU	47.0	—	0.0	92.6	18.0	48.0	24.0*†	Lemieux <i>et al</i> (2013)
18	CY+CP+ET	—	4.0	22.2	28.6	—	—	—	Mehta <i>et al</i> (1997)
41	MEL200, MEL <200, MEL+TBI, BU+CY	37.0	3.0	7.3	55.3	8.5	20.7	12.0*	Olin <i>et al</i> (2009)
14	MEL200, MEL140+TBI, MEL+TO+CY, THIO+BU+CY	25.0	6.0	14.3	64.3	6.8	29.0	—	Qazilbashi <i>et al</i> (2006)
44	MEL200, MEL+BU, MEL+TO+CY, MEL+TBI, THIO+BU+CY	30.0	2.0	2.3	90.0	12.3	31.7	—	Shah <i>et al</i> (2012)

Interval, median time between initial autologous stem cell transplantation (ASCT) and salvage ASCT. CTX lines, the median numbers of lines of chemotherapy (CTX) given between first and second ASCT. PFS cut-off, the effect of progression-free survival (PFS) after initial ASCT on \* PFS or † overall survival (OS) after salvage ASCT. —: categories that were not investigated or reported in the respective study. n.s., not significant, MEL, melphalan, BU, busulfan, BOR, bortezomib, BEAM, carmustine + etoposide + cytarabine + melphalan, CY, cyclophosphamide, CP, carboplatin, ET, etoposide, IMC, idarubicin + melphalan + cyclophosphamide, TBI, total body irradiation, TO, topotecan, THIO, thiotepa. The study by Tricot *et al* (1995) was not included because it did not distinguish between patients receiving autologous and allogeneic transplants.

# Multiple retrospective salvage ASCT studies

~3-5%

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# Multiple retrospective salvage ASCT studies

~15 mo

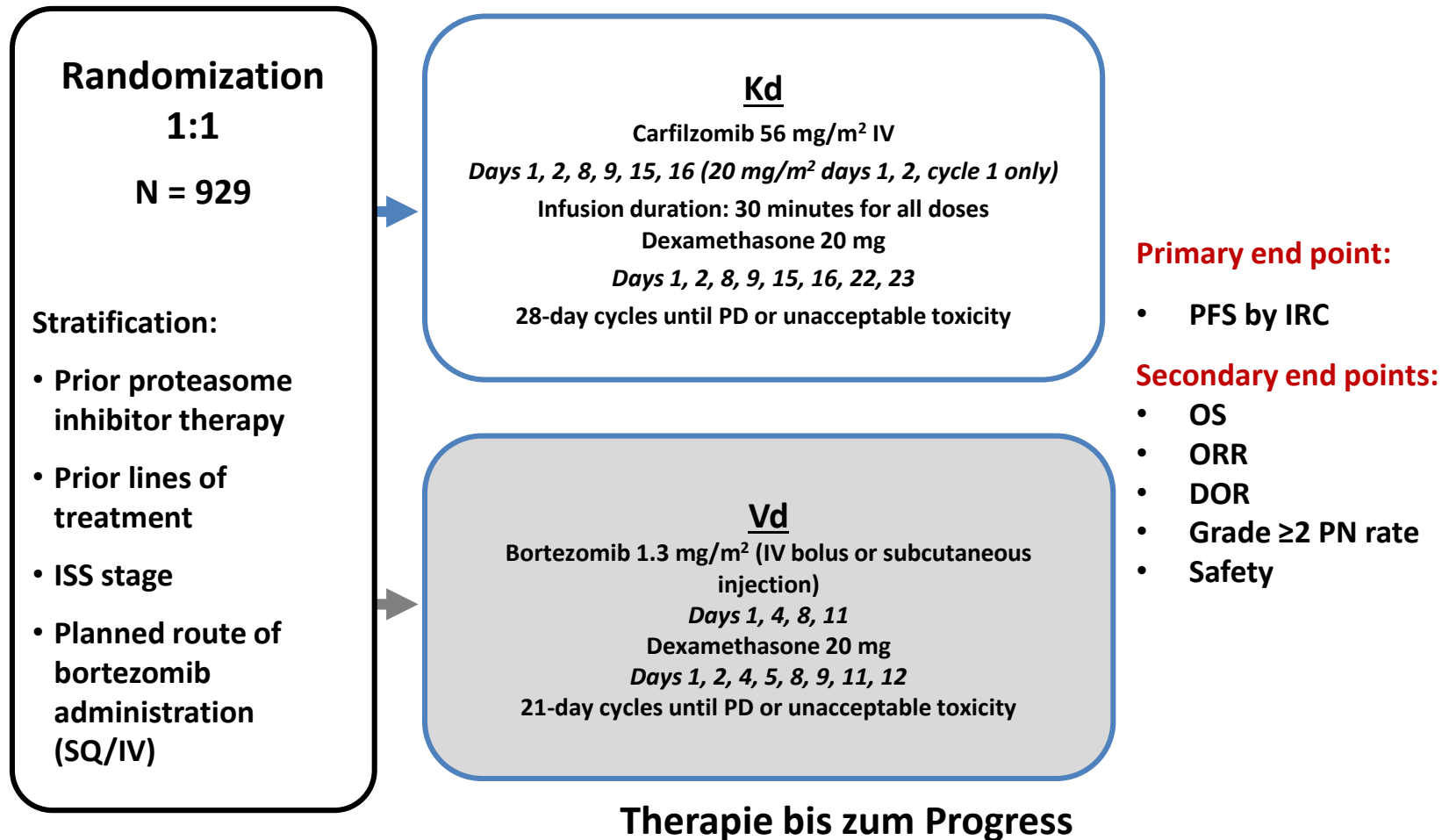
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81	MEL200, MEL140	—	1.0	2.6	97.4	16.4	53.0	24.0*†	Jimenez-Zepeda <i>et al</i> (2012)
11	—	—	—	6.0	27.3	—	—	—	Johnsen <i>et al</i> (1996)
31	MEL100	12.0	1.0	0.0	58.1	5.0	8.0	6.0*†	Krejci <i>et al</i> (2010)
32	MEL200	—	—	3.1	75.0	12.9	79.1	—	Krivanova <i>et al</i> (2004)
50	BEAM, BU+CY, MEL200, MEL140+TBI, MEL 110+TBI-MEL	—	—	14.0	54.0	4.0	9.0	n.s.	Lee <i>et al</i> (2002)
81	MEL220, MEL200, MEL140, MEL+BU	47.0	—	0.0	92.6	18.0	48.0	24.0*†	Lemieux <i>et al</i> (2013)
18	CY+CP+ET	—	4.0	22.2	28.6	—	—	—	Mehta <i>et al</i> (1997)
41	MEL200, MEL <200, MEL+TBI, BU+CY	37.0	3.0	7.3	55.3	8.5	20.7	12.0*	Olin <i>et al</i> (2009)
14	MEL200, MEL140+TBI, MEL+TO+CY, THIO+BU+CY	25.0	6.0	14.3	64.3	6.8	29.0	—	Qazilbashi <i>et al</i> (2006)
44	MEL200, MEL+BU, MEL+TO+CY, MEL+TBI, THIO+BU+CY	30.0	2.0	2.3	90.0	12.3	31.7	—	Shah <i>et al</i> (2012)

Interval, median time between initial autologous stem cell transplantation (ASCT) and salvage ASCT. CTX lines, the median numbers of lines of chemotherapy (CTX) given between first and second ASCT. PFS cut-off, the effect of progression-free survival (PFS) after initial ASCT on \* PFS or † overall survival (OS) after salvage ASCT. —: categories that were not investigated or reported in the respective study. n.s., not significant, MEL, melphalan, BU, busulfan, BOR, bortezomib, BEAM, carmustine + etoposide + cytarabine + melphalan, CY, cyclophosphamide, CP, carboplatin, ET, etoposide, IMC, idarubicin + melphalan + cyclophosphamide, TBI, total body irradiation, TO, topotecan, THIO, thiotepa. The study by Tricot *et al* (1995) was not included because it did not distinguish between patients receiving autologous and allogeneic transplants.

**What to expect from non-transplant relapse treatments ?**

**Phase III studies**

# ENDEAVOR – Phase III: Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd)



ISS, International Staging System; IV, intravenous; PD, progressive disease; SQ, subcutaneous.

# ENDEAVOR:

## Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd)

### Key inclusion criteria:

- Relapsed multiple myeloma
- 1–3 prior treatments
- ECOG PS 0–2
- Prior treatment with bortezomib or carfilzomib was allowed if:
  - $\geq$  PR to prior treatment
  - $\geq$  6 month proteasome inhibitor treatment-free interval
  - Not discontinued due to toxicity
- LVEF  $\geq$  40%
- Creatinine clearance  $\geq$  15 mL/min
- Len refraktäre Patienten durften eingeschlossen werden

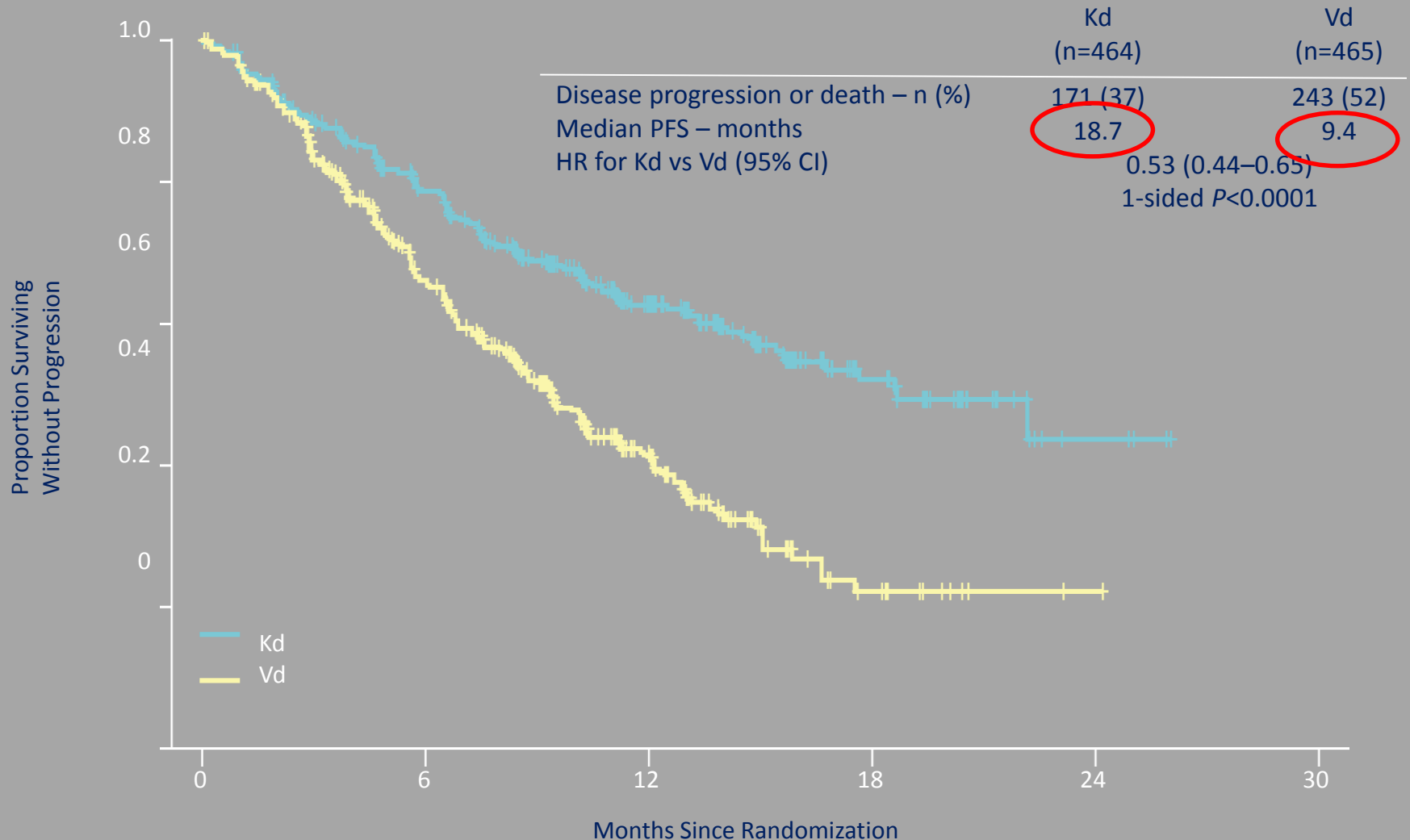
### Key exclusion criteria:

- Grade 3 or 4 peripheral neuropathy (or grade 2 with pain) within 14 days prior to randomization
- Myocardial infarction within 4 months prior to randomization
- New York Heart Association class III or IV heart failure

ECOG PS, Eastern Cooperative Oncology Group performance status; LVEF, left ventricular ejection fraction; PR, partial response.

# Primary End Point: Progression-Free Survival

## *Intent-to-Treat Population (N=929)*



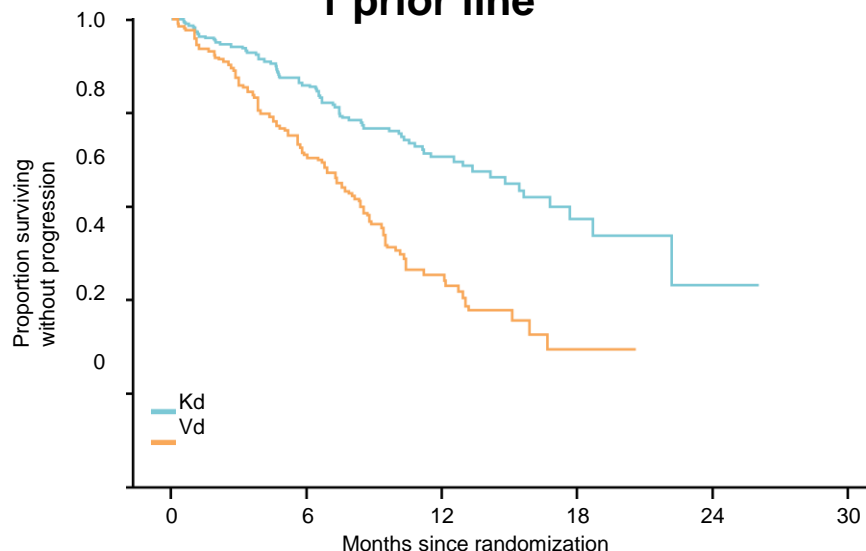
- **Median follow-up: 11.2 months**

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

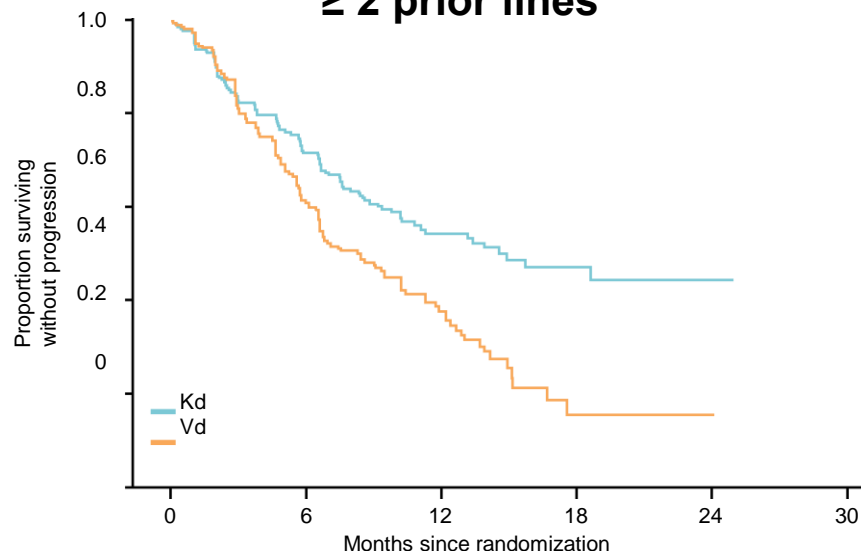
# Progression-Free Survival by Prior Lines of Therapy

## *Intent-to-Treat Population (N=929)*

**1 prior line**



**≥ 2 prior lines**



	<b>Kd (n = 232)</b>	<b>Vd (n = 232)</b>
<b>Median PFS, months</b>	<b>22.2</b>	<b>10.1</b>
<b>HR (95% CI)</b>	<b>0.45 (0.33–0.61)</b>	
<b>P-value (one sided)*</b>	<b>&lt; 0.0001</b>	

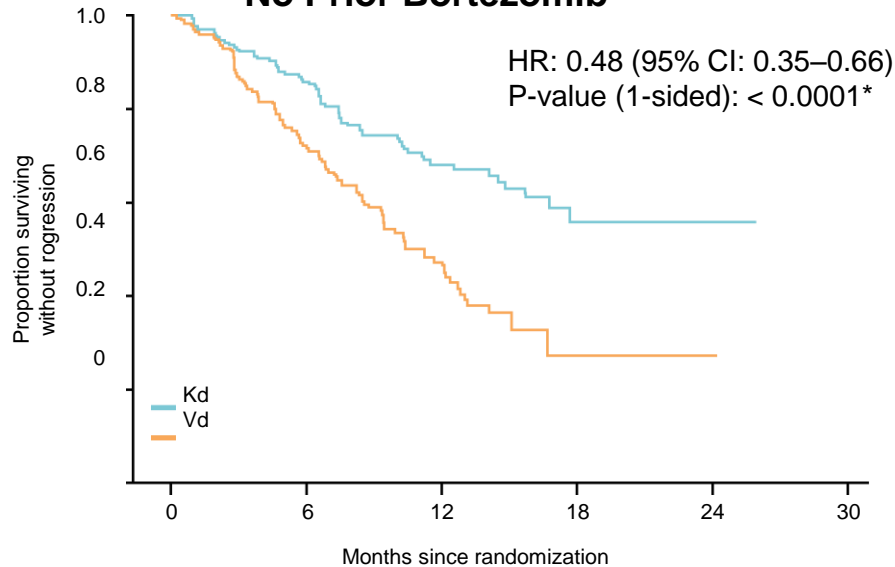
	<b>Kd (n = 232)</b>	<b>Vd (n = 233)</b>
<b>Median PFS, months</b>	<b>14.9</b>	<b>8.4</b>
<b>HR (95% CI)</b>	<b>0.60 (0.47–0.78)</b>	
<b>P-value (one sided)*</b>	<b>&lt; 0.0001</b>	

\*Descriptive; unadjusted for multiplicity.  
CI, confidence interval

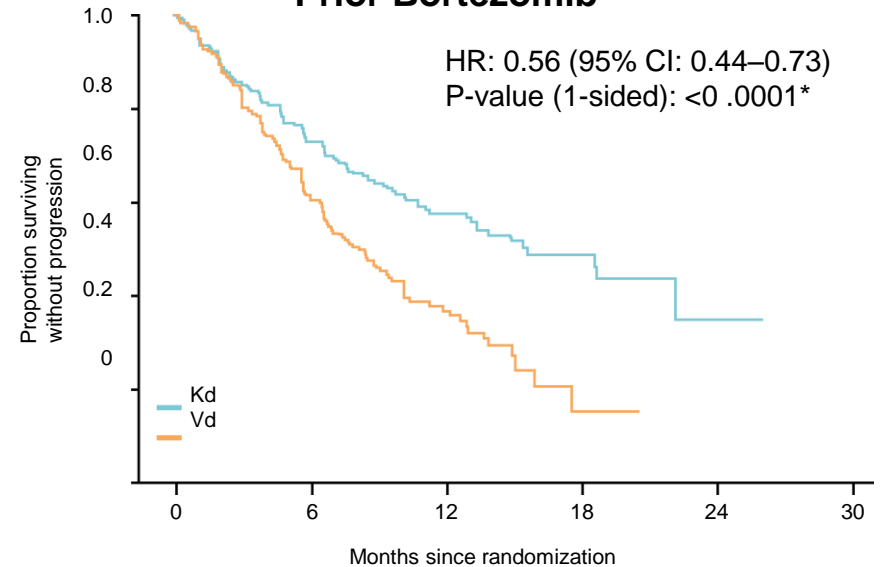
# PFS and ORR by Prior Bortezomib Exposure

## *Intent-to-Treat Population (N = 929)*

**No Prior Bortezomib**



**Prior Bortezomib**

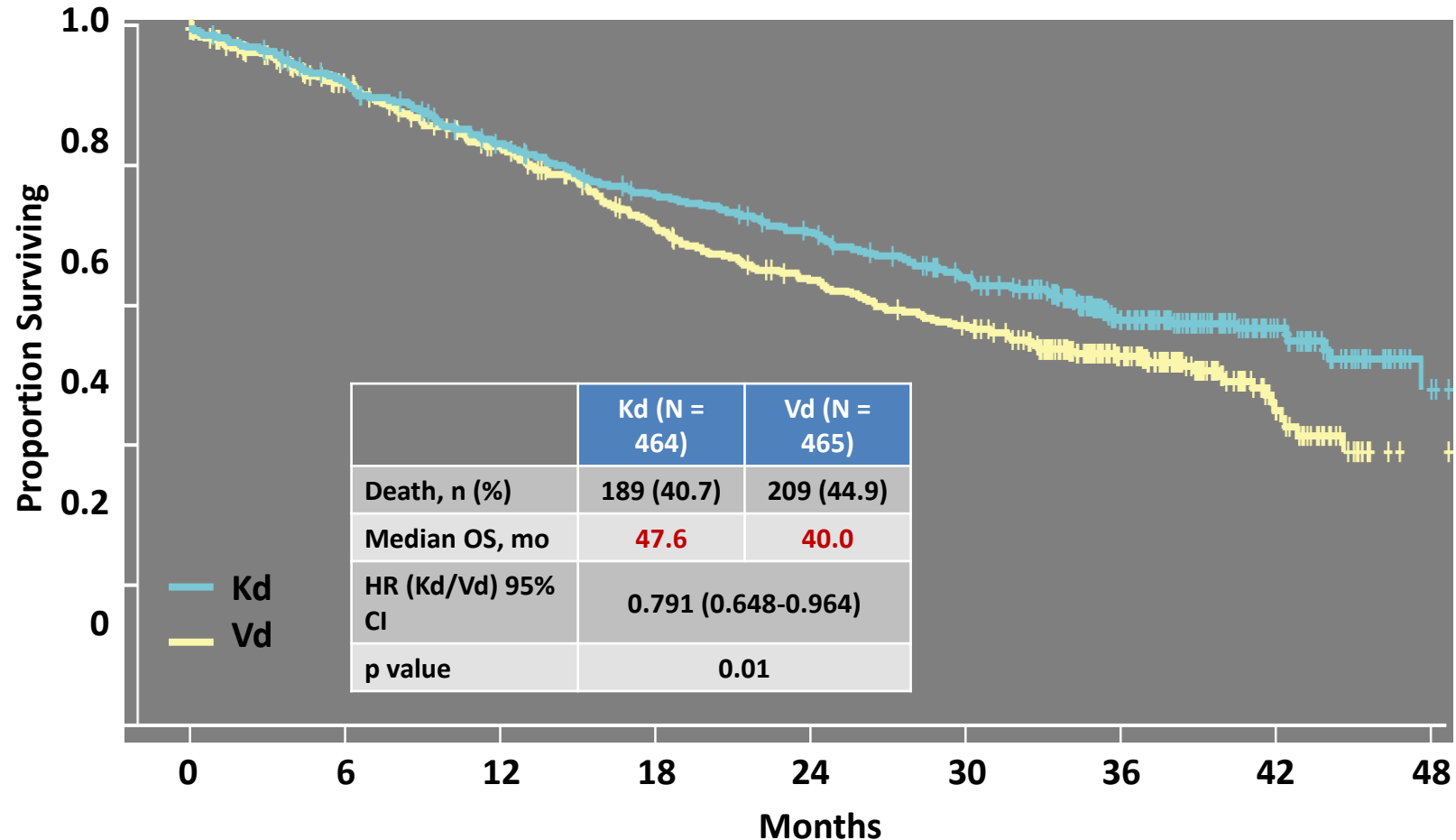


	Kd (n = 214)	Vd (n = 213)
Median PFS, months	NE	11.2
ORR, %	83.6	65.3
P-value (one sided)*	<.0001	

	Kd (n = 250)	Vd (n = 252)
Median PFS, months	15.6	8.1
ORR, %	71.2	60.3
P-value (one sided)*	0.0051	

\*Descriptive; unadjusted for multiplicity.

# Overall survival was significant increased: 21% risk reduction

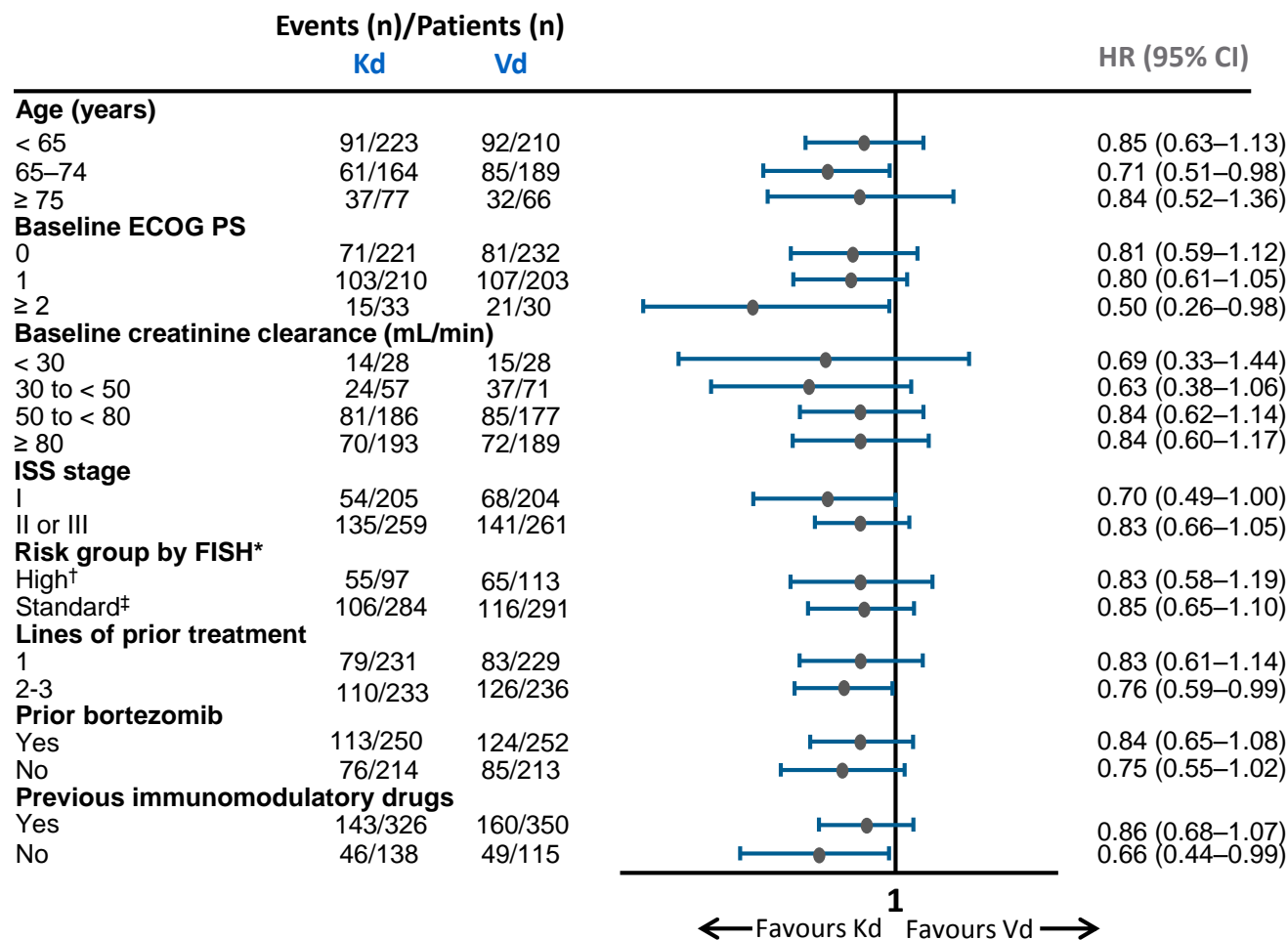


Number at risk:

Kd	464	423	373	335	308	270	162	66	10
Vd	465	402	351	293	256	228	140	39	5



# Overall Survival according to subgroups: all subgroups benefit from Kd



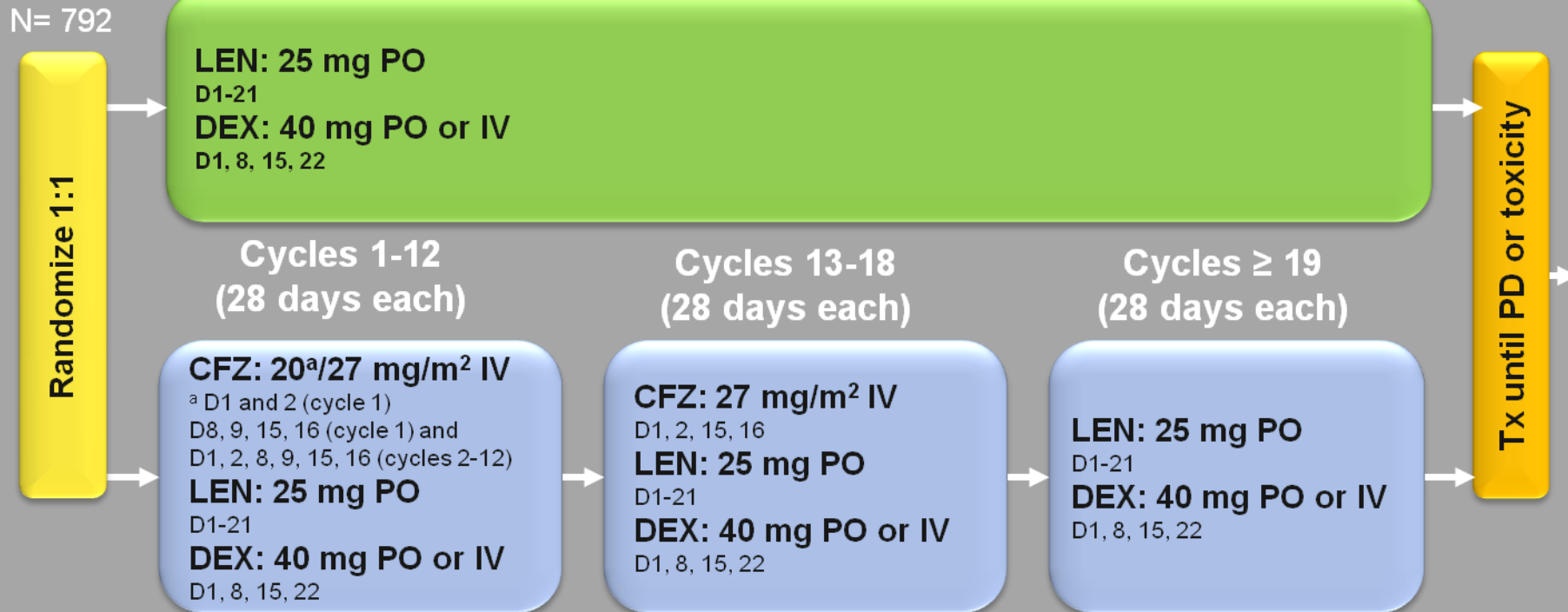
\*Excludes patients with missing or unknown results. <sup>†</sup>High-risk FISH is defined as detection of ≥ 10% t(4;14) or t(14;16) genetic subtypes in screened plasma cells, or ≥ 20% 17p deletions in screened plasma cells at study entry. <sup>‡</sup>Standard-risk patients were those in whom chromosomal abnormalities were not detected.

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence in situ hybridization;

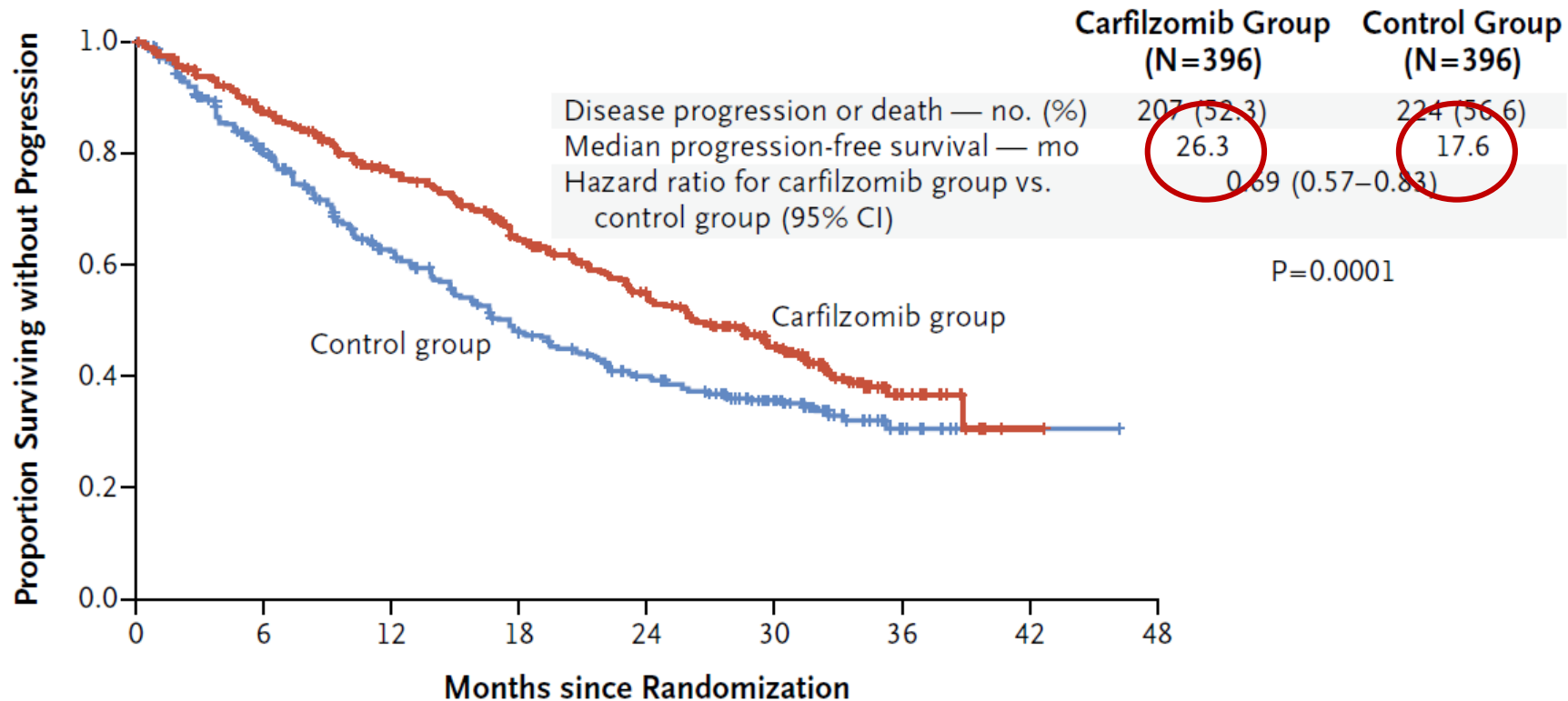
HR = hazard ratio; ISS = International Staging System; Kd = carfilzomib and dexamethasone; Vd = bortezomib and dexamethasone.

# ASPIRE - Phase III Study design

28-day cycles



# Primary endpoint: Progression-free survival ITT Population (n=792)

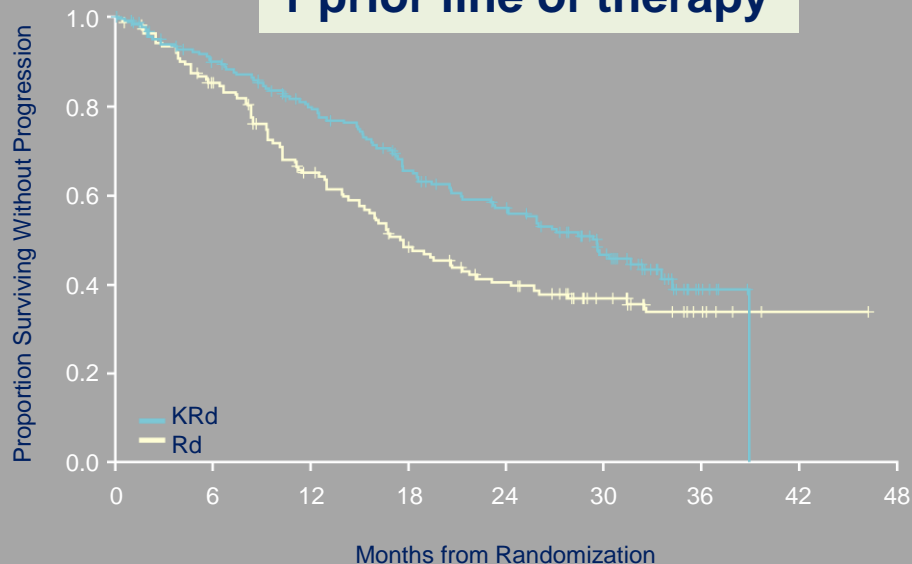


## No. at Risk

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

# PFS by Prior Line of Therapy (1 vs $\geq 2$ )

**1 prior line of therapy**



	KRd (n=184)	Rd (n=157)
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**PFS, median months**

**29.6**

**17.6**

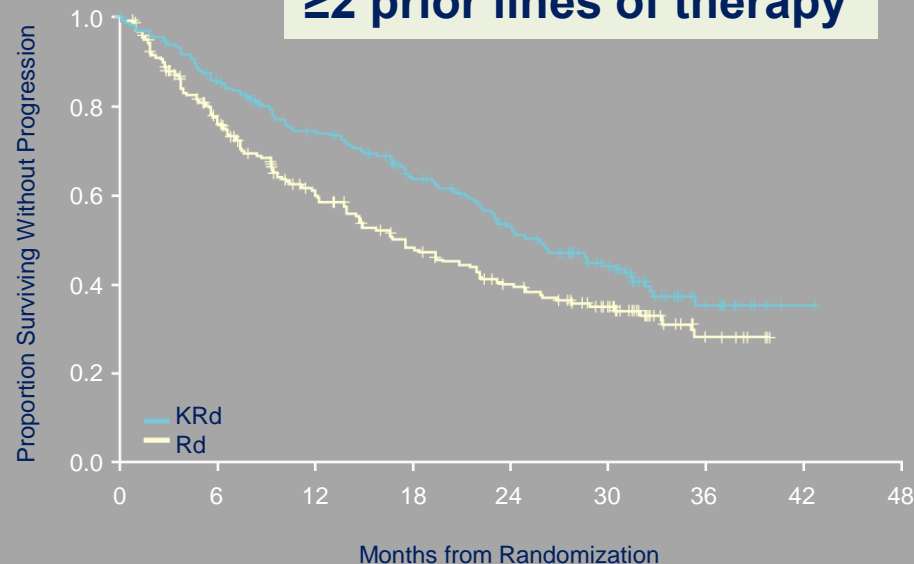
**Hazard ratio  
(95% CI)**

**0.69  
(0.52–0.94)**

**P value  
(one-sided)**

**.008**

**$\geq 2$  prior lines of therapy**



	KRd (n=212)	Rd (n=239)
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**PFS, median months**

**25.8**

**16.7**

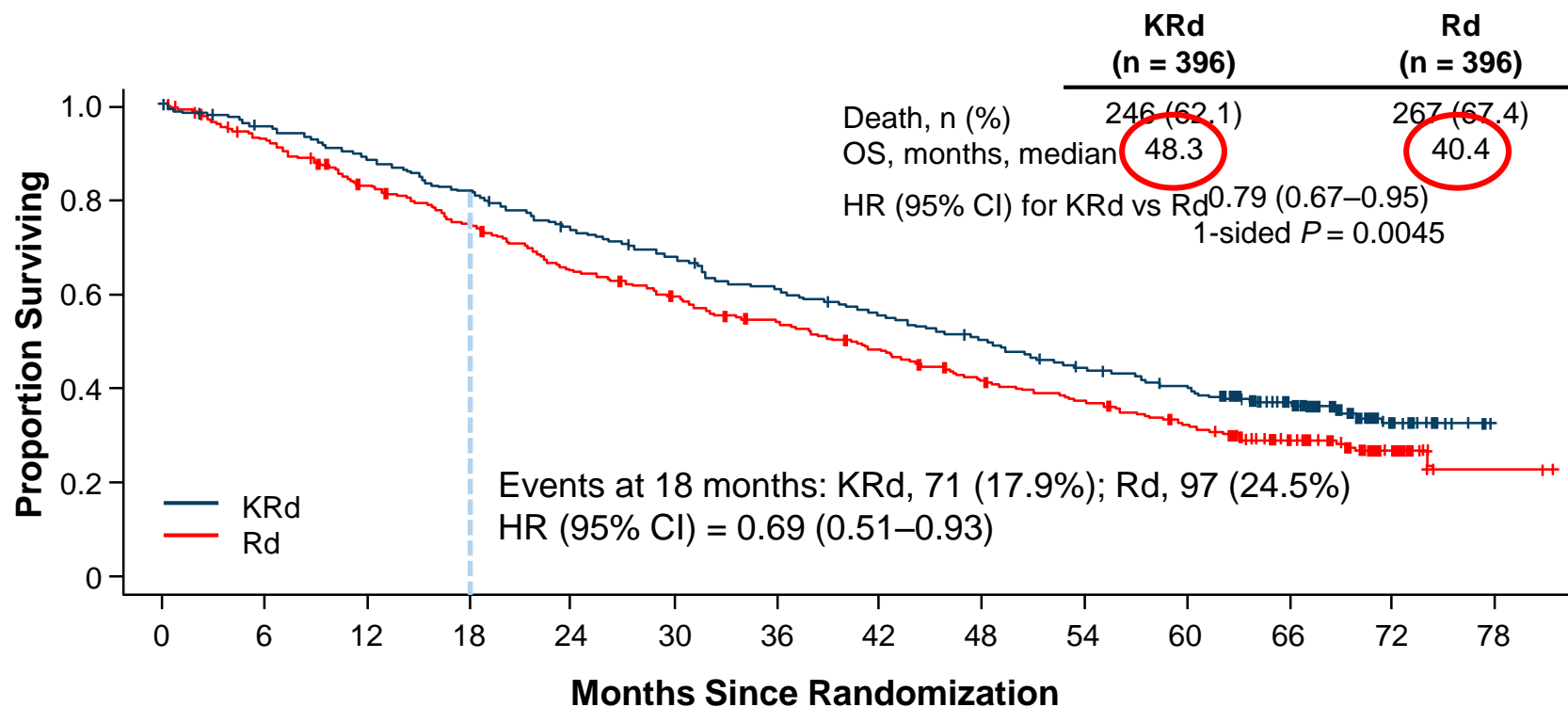
**Hazard ratio  
(95% CI)**

**0.69  
(0.54–0.89)**

**P value  
(one-sided)**

**.002**

# KRd Extended Median Overall Survival by 7.9 Months vs Rd



## Number of patients at risk:

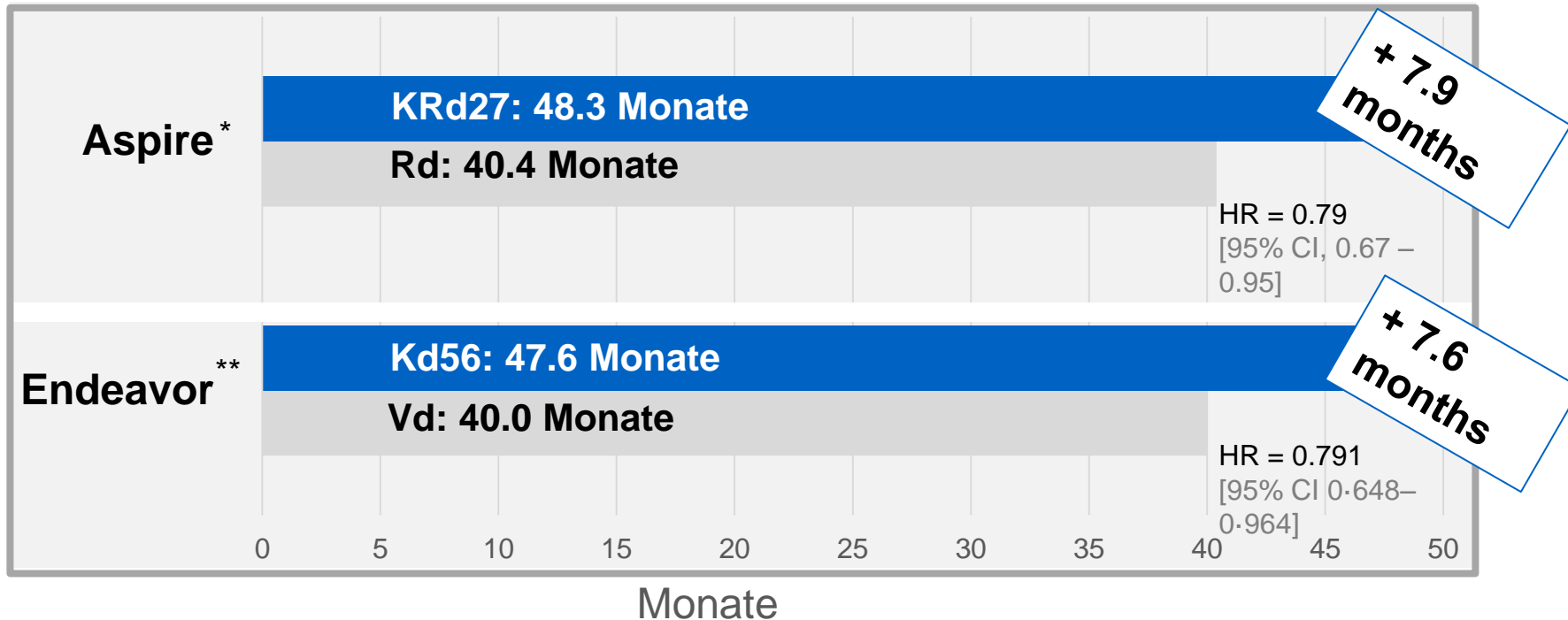
KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

CI = confidence interval; HR = hazard ratio; KRd = carfilzomib, lenalidomide, and dexamethasone; OS = overall survival; Rd = lenalidomide and dexamethasone.

Siegel DS, et al; [published online ahead of print January 17, 2018]. *J Clin Oncol*. doi: 10.1200/JCO.2017.76.5032.

Stewart AK, et al. Slides presented at: Annual Meeting of the American Society of Hematology; December 9-12, 2017; Atlanta, GA.

# Carfilzomib is currently the only myeloma drug that has demonstrated significant OS benefit in 2 phase III trials in relapsed/ refractory setting compared to SoC



\*Kyprolis® was given –as defined in study protocol – for a maximum of 18 cycles, Rd was continued until progression in both arms

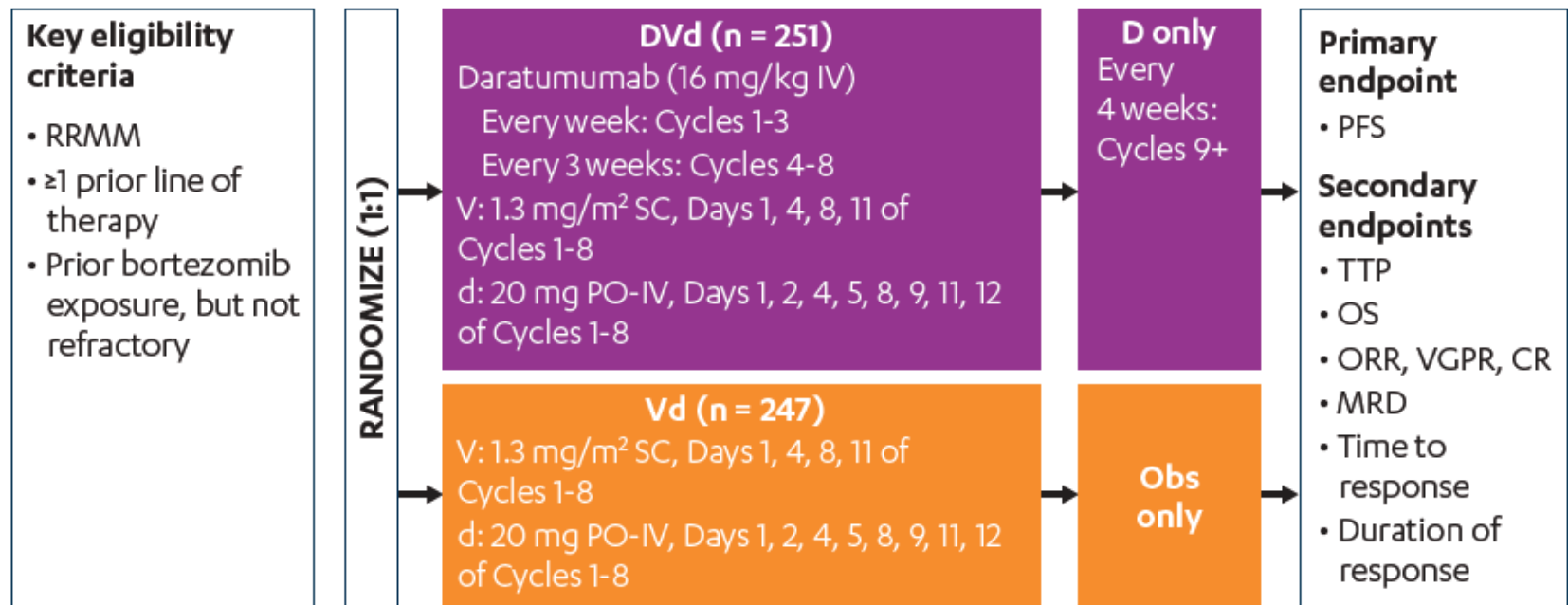
\*\* In der post hoc Analyse nach 3 Jahren (FDA gefordertes Marketing Requirement) konnte eine **Reduktion des Mortalitätsrisikos um 24%** und eine **Verlängerung des Gesamtüberlebens um 9 Monate** im Vergleich zum Vd Arm gezeigt werden. (OS 47,8 Monate für Kd versus 38,8 Monate für Vd, HR=0,76; 95 % CI, 0,63-0,92; p=0,0017)

# **Daratumumab, Bortezomib, and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of CASTOR**

# CASTOR phase 3 study of DVd vs Vd in RRMM

## Study Design

- Clinical cutoff date: 30 August 2017
- Median duration of follow-up: 26.9 months
- Median duration of treatment: DVd, 13.4 months; Vd, 5.2 months



- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

**Premedication for the DVd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine**

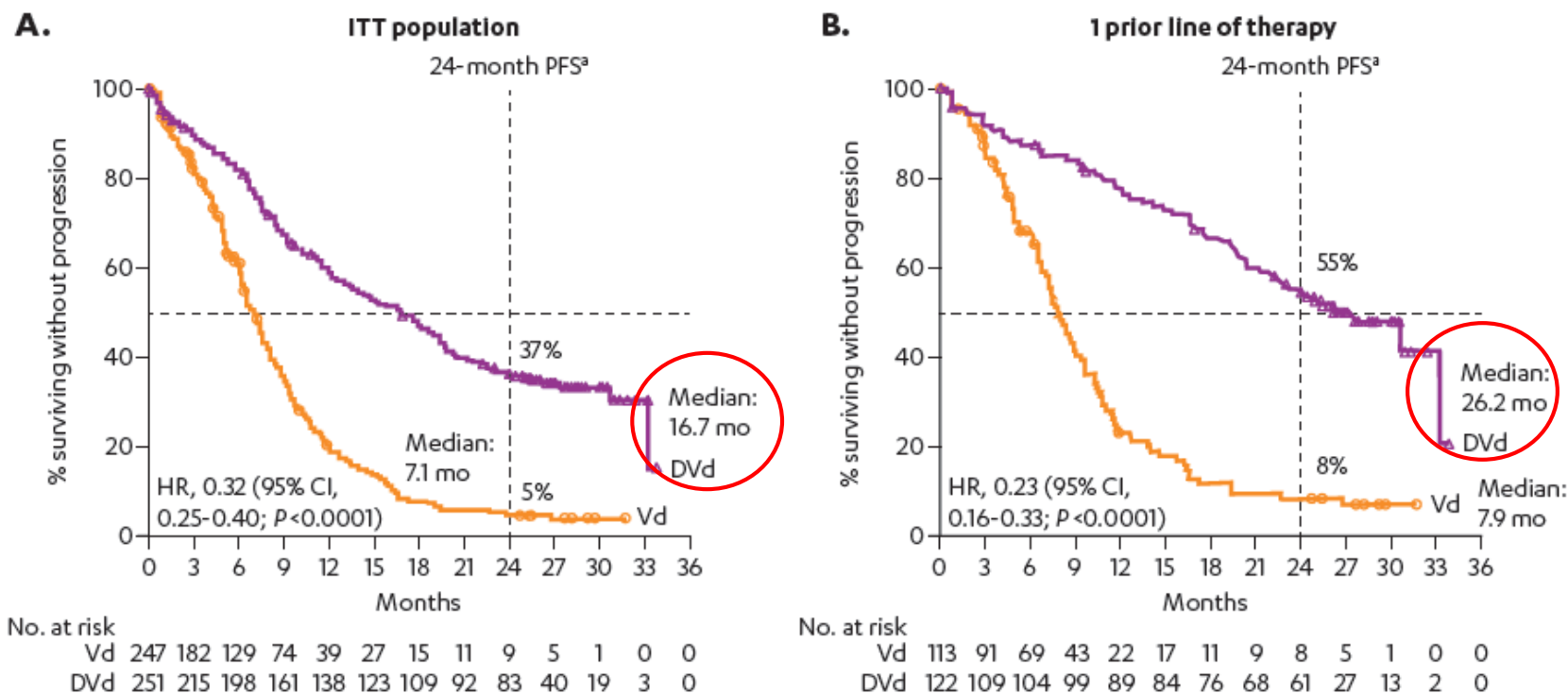
DVd, daratumumab, bortezomib and dexamethasone; IV, intravenous; V, bortezomib; SC, subcutaneously; d, dexamethasone; PO, orally; VD, bortezomib and dexamethasone; D, daratumumab; Obs, observation; PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; ISS, International Staging System.



# CASTOR updated analysis

## PFS: ITT and Prior Lines of Therapy

PFS (A) in the ITT population and (B) based on prior lines of therapy

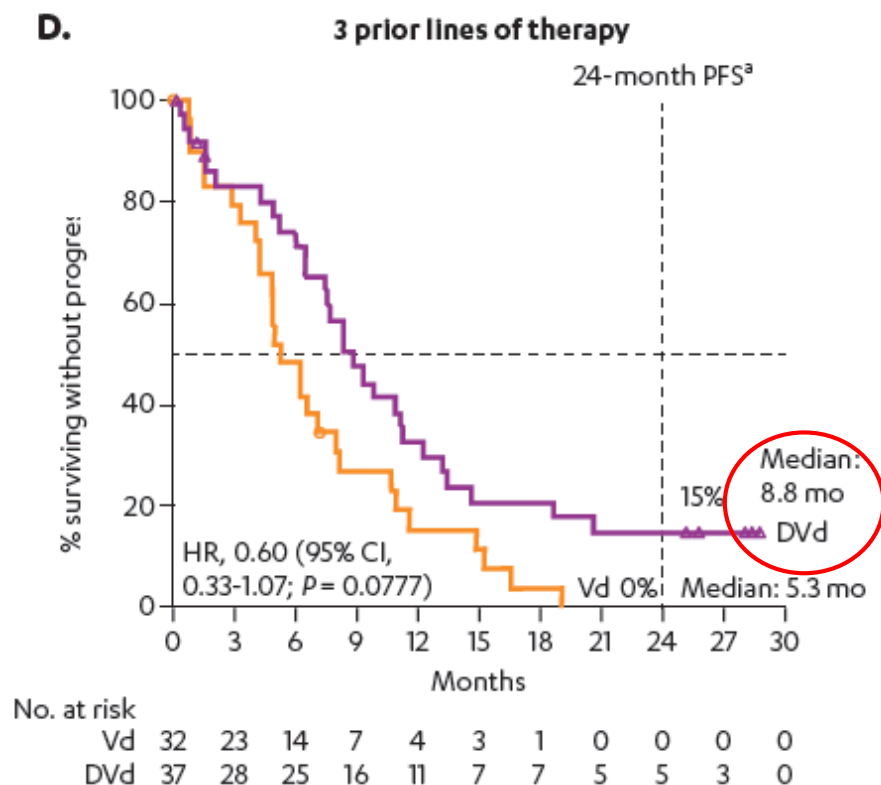
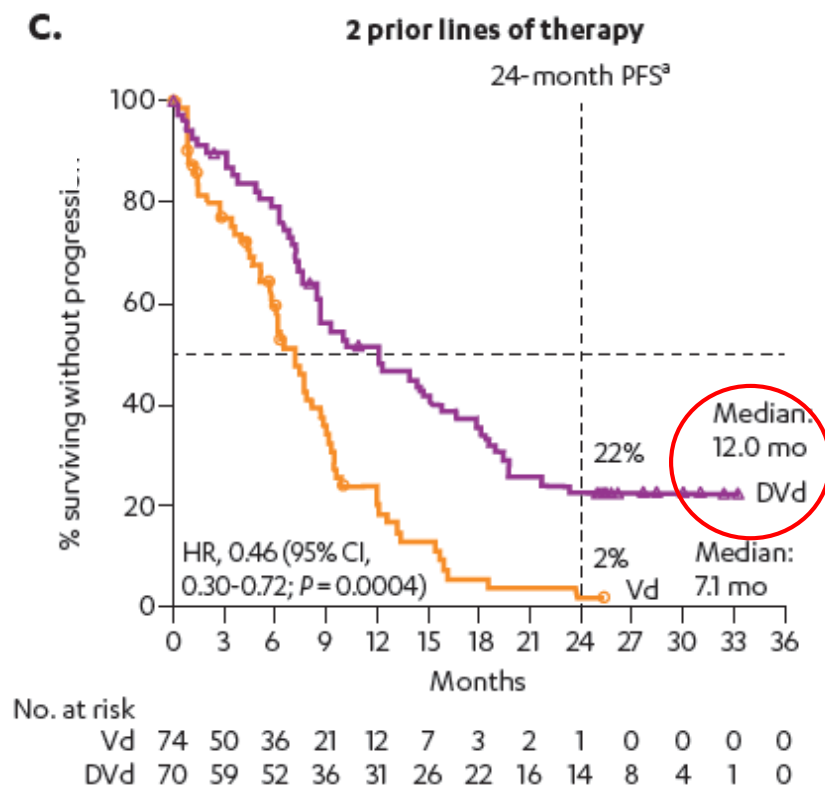


■ Median duration of follow-up: 26.9 months

- Addition of daratumumab to Vd continues to significantly prolong PFS with longer follow-up.
- Patients who received 1 prior line of therapy benefitted the most from DVd

# CASTOR updated analysis: PFS by prior lines of therapy

## PFS based on prior lines of therapy



■ Median duration of follow-up: 26.9 months

■ DVd improved PFS regardless of the number of prior lines of therapy

# **Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Lenalidomide and Dexamethasone (Rd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of POLLUX**

# POLLUX Study Design

## Key eligibility criteria

- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure allowed, but not if lenalidomide refractory
- Creatinine clearance ≥30 mL/min

## Stratification factors

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

R  
A  
N  
D  
O  
M  
I  
Z  
E

1:1

## DRd (n = 286)

**Daratumumab 16 mg/kg IV**  
Every week in Cycles 1-2  
Every 2 weeks in Cycles 3-6  
Every 4 weeks  
**Lenalidomide 25 mg PO**  
Days 1-21 of each cycle  
**Dexamethasone 40 mg PO<sup>a</sup>**  
Every week  
**Treatment until PD**

## Rd (n = 283)

**Lenalidomide 25 mg PO**  
Days 1-21 of each cycle  
**Dexamethasone 40 mg PO**  
Every week  
**Treatment until PD**

Cycles: 28 days

## Primary endpoint

- PFS

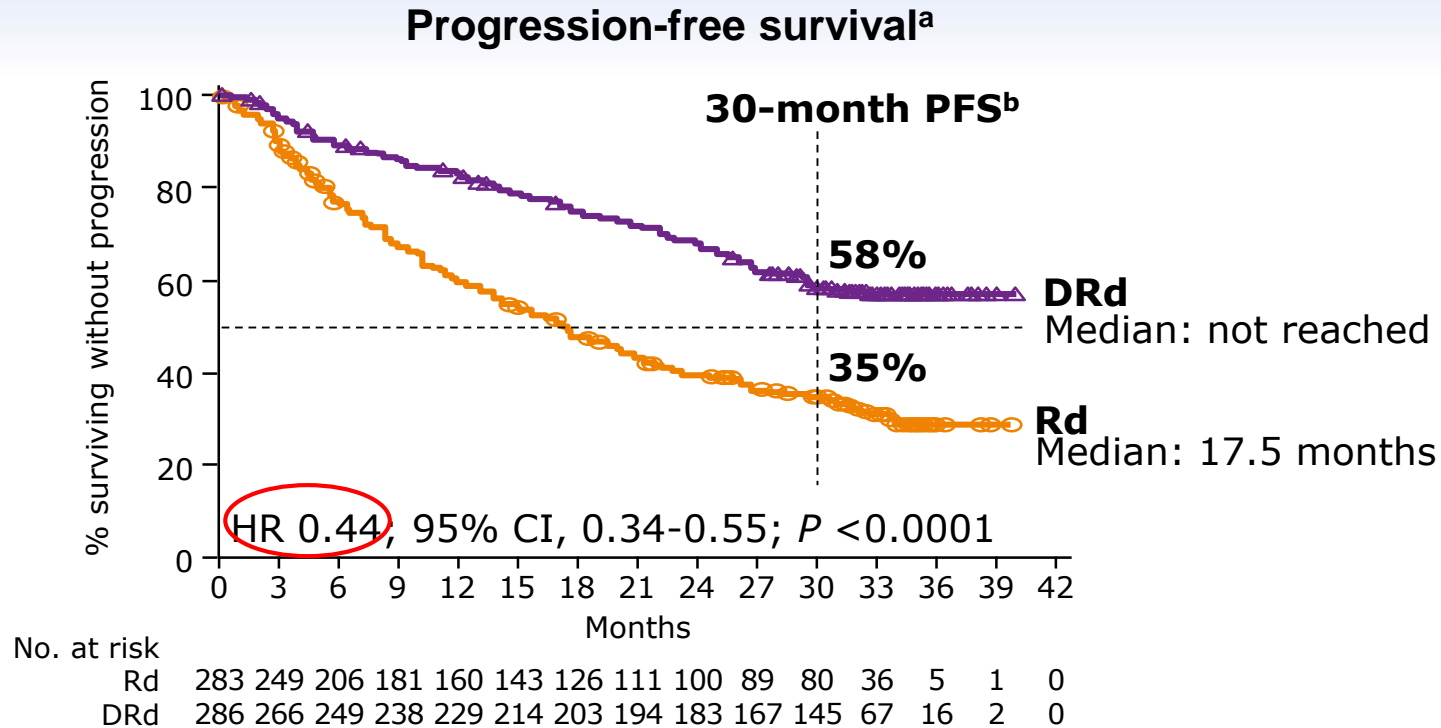
## Secondary endpoints

- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

## Statistical analyses

- Final OS analysis at 330 OS events

# POLLUX updated analysis: PFS



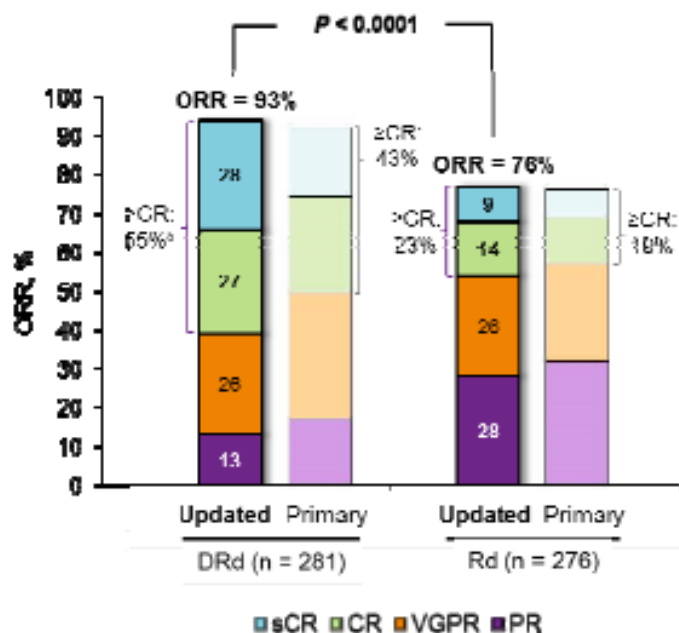
Median follow-up: 32.9 months (range, 0 - 40.0 months)

**56% reduction in risk of progression/death for DRd versus Rd**

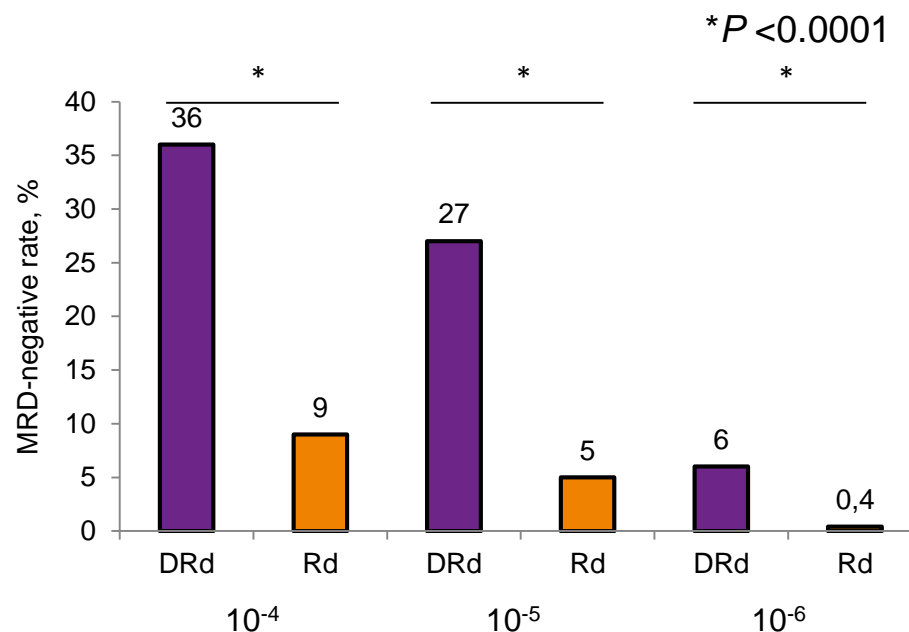
# POLLUX updated analysis: ORR and MRD-negative rates<sup>a</sup>

Median follow-up: 32.9 months (range, 0 - 40.0 months)

## Overall Response Rate<sup>a</sup>



## MRD-negative Rate



- MRD assessed using clonoSEQ<sup>®</sup> assay V2.0

**Responses continued to deepen in the DRd group**  
**Significantly higher (>3-fold) MRD-negative rates for DRd versus Rd**

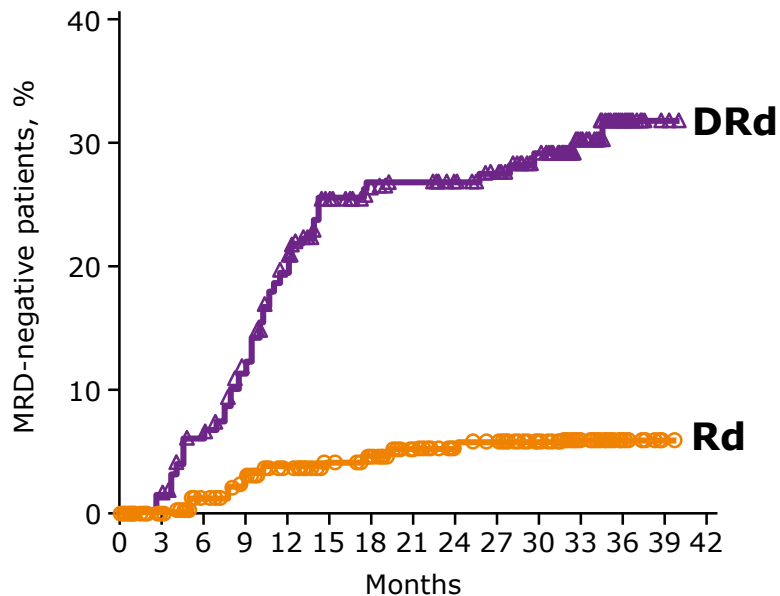
sCR, stringent complete response; PR, partial response.

Primary analysis reported in Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331.

<sup>a</sup>Exploratory analyses based on clinical cutoff date of October 23, 2017; <sup>b</sup> $P < 0.0001$  for DRd versus Rd.

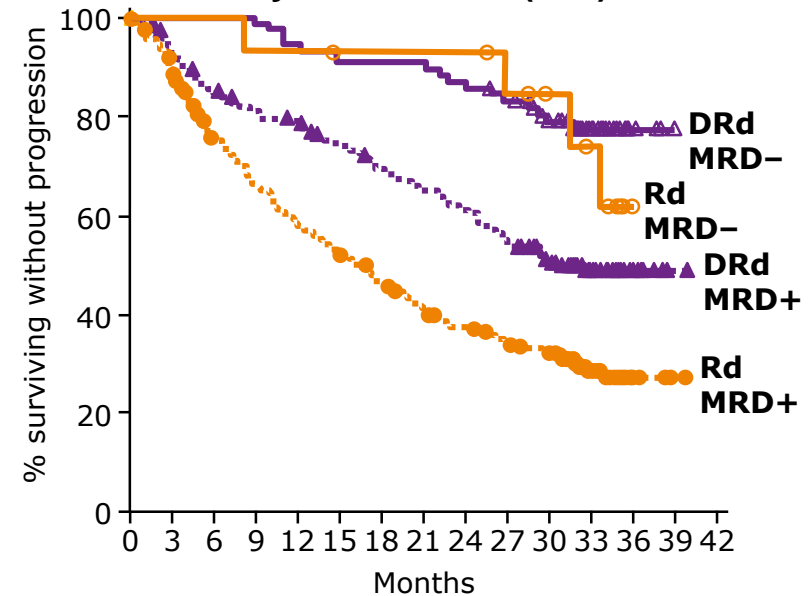
# POLLUX: Time to MRD Negativity and PFS by MRD Status

**Time to MRD Negativity ( $10^{-5}$ )**



No. at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	
Rd	28	32	27	22	25	22	24	22	29	21	20	9	19	31	18	1	0
DRd	28	6	27	1	25	5	23	5	20	8	16	7	15	11	5	3	0

**PFS by MRD Status ( $10^{-5}$ )**

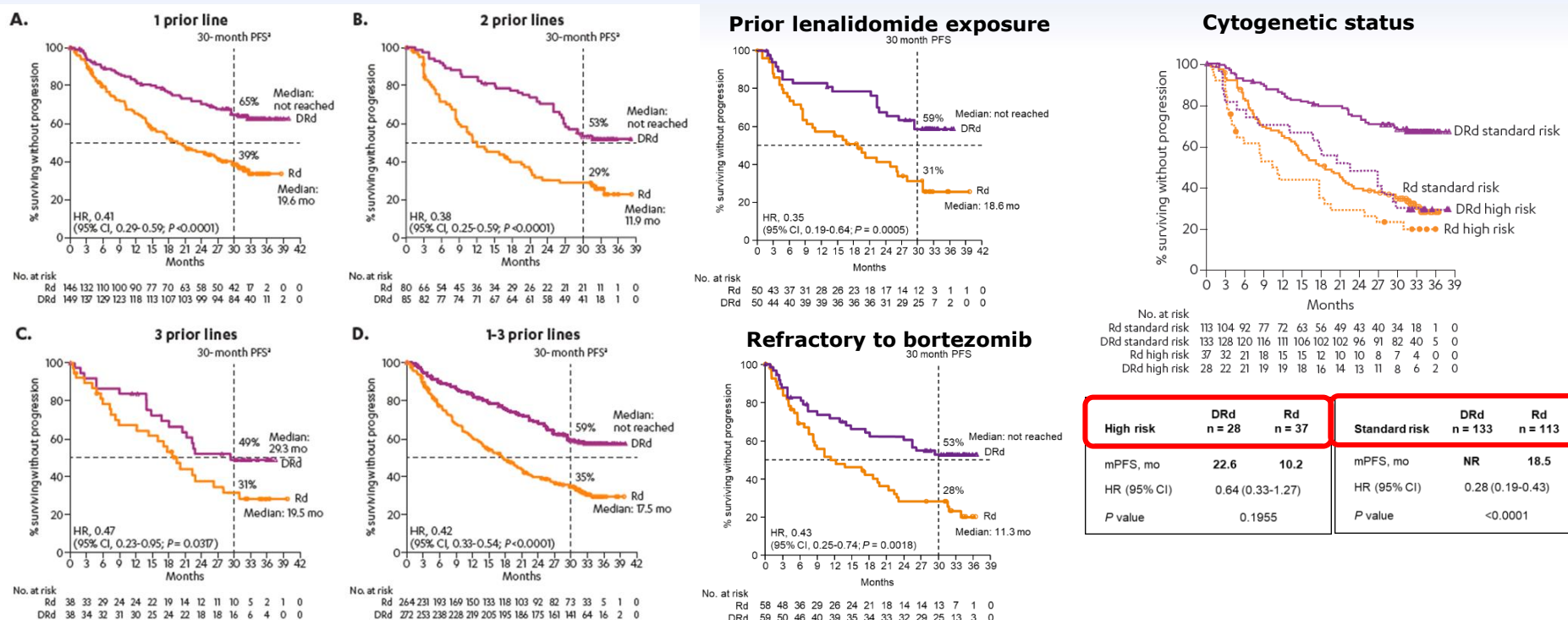


No. at risk		Time (months)																	
		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42			
Rd MRD negative	14	14	14	13	13	12	12	12	12	10	8	6	0	0	0	0			
DRd MRD negative	76	76	76	75	72	69	69	69	66	62	54	26	7	1	0	0			
Rd MRD positive	26	9	23	5	19	2	16	8	14	7	13	11	4	9	8	1	0		
DRd MRD positive	21	0	19	0	17	3	16	3	15	7	14	5	13	4	17	10	5	1	0

**MRD negativity occurs more rapidly with DRd and increases over time**  
**Achievement of MRD negativity was associated with prolonged PFS**

# POLLUX updated analysis: Subgroup analyses

## Progression-free survival



Median follow-up: 32.9 months

**DRd improved PFS, ORR, sCR and MRD –ve rates versus Rd regardless of prior treatment, cytogenetic risk or moderate renal impairment**



# Treatment for relapse post / prior AutoSCT - PFS expectations

- Doublet (Rd, Vd) : ~12-18 months
- K-doublet or triplet (Kd, KRd) : ~ >24 months
- Dara-triplet (DRd) : ~**2-3 years**
- AE/treatment-related deaths ~5% (<10%)

Versus

- salvage ASCT : 15 -19 months

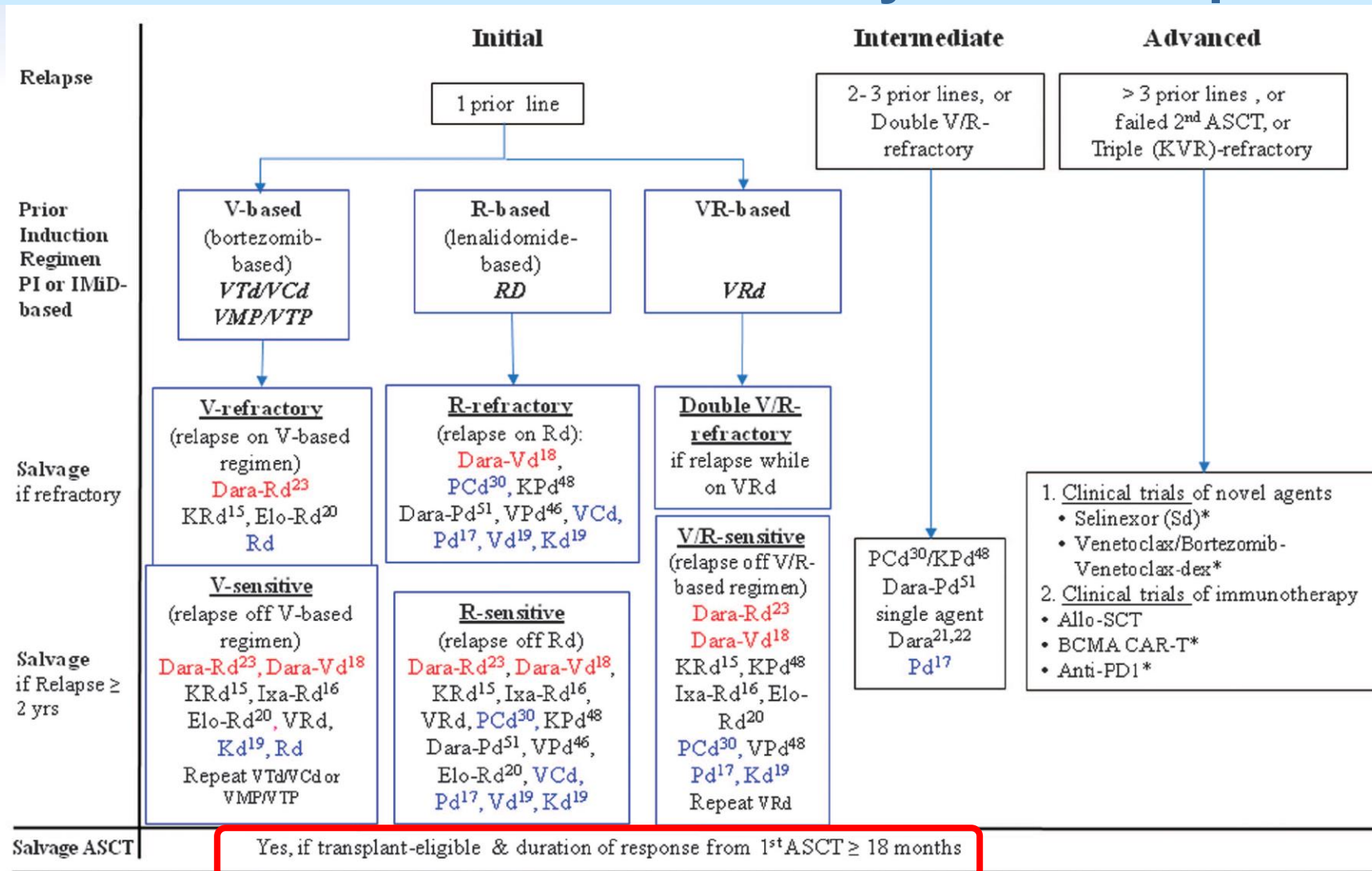
# Conclusions: 2nd/salvage AutoSCT for relapse

- **safe** (NRM<5%, minimal SPM effect)
- **straight-forward** (outpatient basis, cells stored)
- **effective** (PFS > 2years with modern re-induction and maintenance?)

## Open Questions:

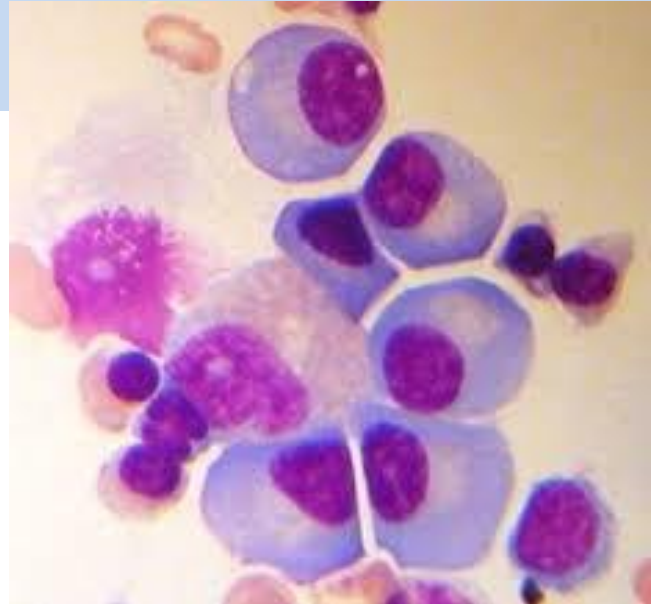
- Superior to non-SCT approaches (triple therapies)?
- Maintenance?
- Conditioning?
- PFS1 (18mo – 36mo) or response-to-reinduction ‘cut-off’?
- Molecular risk?

# Proposed algorithm for the treatment of 'initial', 'intermediate' or 'advanced' myeloma relapses



**Red: most potent // blue: less expensive**

***VIELEN DANK FÜR DIE  
AUFMERKSAMKEIT***





**CANDOR: A Randomized, Open-label, Phase 3 Study comparing  
Carfilzomib, Dexamethasone and Daratumumab to Carfilzomib  
and Dexamethasone for the Treatment of Patients with Relapsed  
or Refractory Multiple Myeloma**

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*EudraCT number 2016-003554-33*

**Currently enrolling....**

# ALCYONE:

## Baseline Demographics and Disease Characteristics

### Baseline Characteristics

	VMP (N = 356)	D-VMP (N = 350)
Age		
Median (range), years	71.0 (50-91)	71.0 (40-93)
Distribution, n (%)		
<65 years	24 (7)	36 (10)
65-74 years	225 (63)	210 (60)
≥75 years	107 (30)	104 (30)
Male, n (%)	167 (47)	160 (46)
Race, n (%)		
White	304 (85)	297 (85)
Others	52 (15)	53 (15)
ECOG status <sup>a</sup> , n (%)		
0	99 (28)	78 (22)
1	173 (49)	182 (52)
2	84 (24)	90 (26)

### Disease Characteristics

	VMP (N = 356)	D-VMP (N = 350)
Type of multiple myeloma <sup>b</sup> , n (%)		
IgG	229 (64)	224 (64)
IgA	82 (23)	73 (21)
ISS stage <sup>c</sup> , n (%)		
I	67 (19)	69 (20)
II	160 (45)	139 (40)
III	129 (36)	142 (41)
Median (range) time from multiple myeloma diagnosis, months	0.82 (0.1-25.3)	0.76 (0.1-11.4)
Cytogenetic profile <sup>d</sup> , n (%)	N = 302	N = 314
Standard risk	257 (85)	261 (83)
High risk	45 (15)	53 (17)

<sup>a</sup>ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. <sup>b</sup>Determined by immunofixation or serum free light chain assay. <sup>c</sup>Based on the combination of serum  $\beta$ 2-microglobulin and albumin. <sup>d</sup>Based on fluorescence in situ hybridization/karyotype testing performed at local sites.

# ALCYONE Safety: Most Common TEAEs<sup>a</sup>

	VMP (n = 354)		D-VMP (n = 346)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic, n (%)				
Neutropenia	186 (53)	137 (39)	172 (50)	138 (40)
Thrombocytopenia	190 (54)	133 (38)	169 (49)	119 (34)
Anemia	133 (38)	70 (20)	97 (28)	55 (16)
Nonhematologic, n (%)				
Peripheral sensory neuropathy	121 (34)	14 (4)	98 (28)	5 (1)
Upper respiratory tract infection	49 (14)	5 (1)	91 (26)	7 (2)
Diarrhea	87 (25)	11 (3)	82 (24)	9 (3)
Pyrexia	74 (21)	2 (1)	80 (23)	2 (1)
Nausea	76 (22)	4 (1)	72 (21)	3 (1)
Pneumonia	17 (5)	14 (4)	53 (15)	39 (11)

- 1 patient in each arm discontinued treatment due to pneumonia
- 1.4% and 0.9% of patients receiving VMP and D-VMP, respectively, discontinued treatment due to infection

	VMP (n = 354)	D-VMP (n = 346)
Deaths due to TEAEs, n (%)	19 (5)	19 (6)

TEAE, treatment-emergent adverse event; VMP, bortezomib/melphalan/prednisone; D, daratumumab.

<sup>a</sup>Any grade TEAEs in ≥20% of patients and grade 3 or 4 TEAEs in ≥10% of patients in either treatment group.



# Subsequent anti-myeloma therapies were balanced

	Kd (n = 391)	Vd (n = 413)
<b>Number of patients treated with at least one therapy</b>	<b>262 (67%)</b>	<b>291 (70%)</b>
<b>Systemic corticosteroids</b>		
<b>Dexamethasone</b>	<b>189 (48%)</b>	<b>220 (53%)</b>
<b>Prednisone</b>	<b>20 (5%)</b>	<b>32 (8%)</b>
<b>Prednisolone</b>	<b>19 (5%)</b>	<b>15 (4%)</b>
<b>Proteasome inhibitors</b>		
<b>Bortezomib</b>	<b>98 (25%)</b>	<b>51 (12%)</b>
<b>Carfilzomib</b>	<b>3 (1%)</b>	<b>33 (8%)</b>
<b>Immunomodulatory drugs</b>		
<b>Lenalidomide</b>	<b>125 (32%)</b>	<b>152 (37%)</b>
<b>Pomalidomide</b>	<b>64 (16%)</b>	<b>99 (24%)</b>
<b>Thalidomide</b>	<b>36 (9%)</b>	<b>55 (13%)</b>
<b>Monoclonal antibodies</b>		
<b>Daratumumab</b>	<b>14 (4%)</b>	<b>18 (4%)</b>

Data are n (%) of patients for therapies for which 2% or more of patients were given subsequent therapies. On completion of Kd or Vd therapy, 391 patients in the Kd group (of 397 completing therapy) and 413 patients in the Vd group (of 418 completing therapy) entered long-term follow-up.

# Subsequent anti-myeloma therapies were well balanced

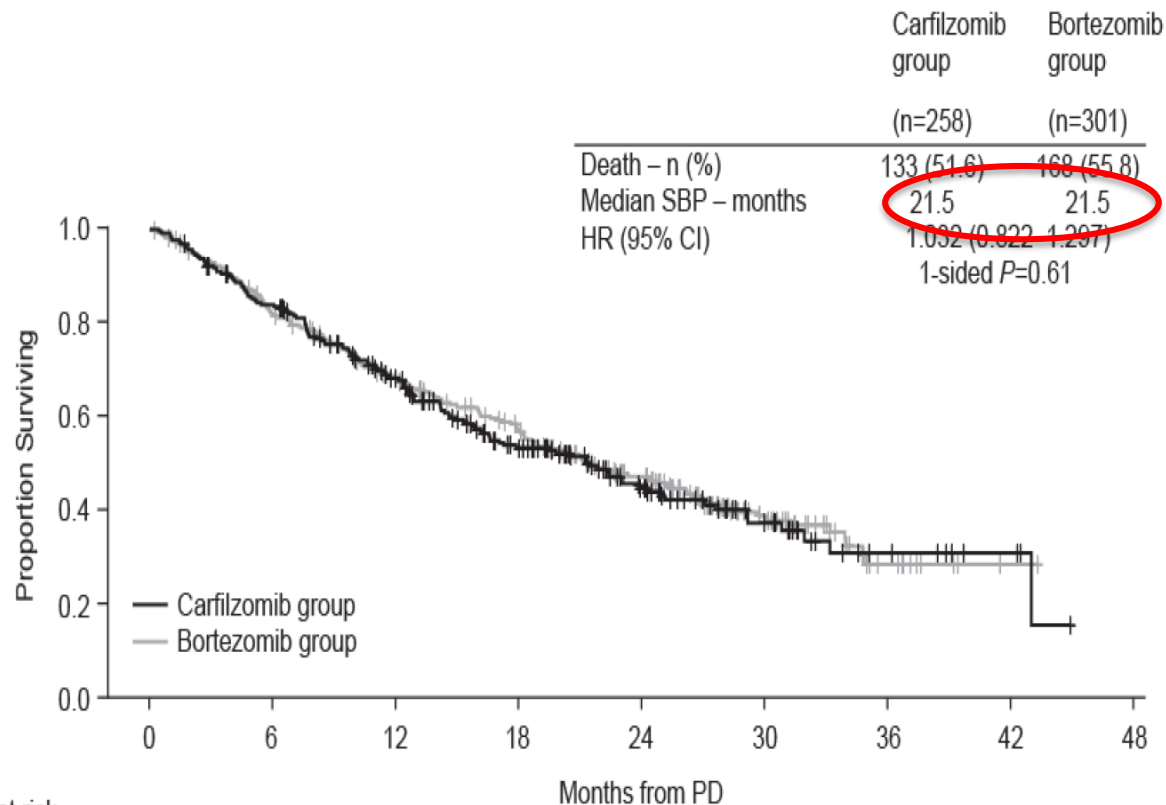
	Kd (n = 391)	Vd (n = 413)
<b>Antineoplastic agents</b>		
<b>Cyclophosphamide</b>	<b>85 (22%)</b>	<b>102 (25%)</b>
<b>Melphalan</b>	<b>50 (13%)</b>	<b>53 (13%)</b>
<b>Bendamustine</b>	<b>20 (5%)</b>	<b>35 (8%)</b>
<b>Doxorubicin</b>	<b>25 (6%)</b>	<b>21 (5%)</b>
<b>Etoposide</b>	<b>14 (4%)</b>	<b>15 (4%)</b>
<b>Cisplatin</b>	<b>12 (3%)</b>	<b>15 (4%)</b>
<b>Vincristine</b>	<b>11 (3%)</b>	<b>7 (2%)</b>
<b>Other therapeutic products</b>		
<b>Investigational drug</b>	<b>7 (2%)</b>	<b>11 (3%)</b>

Data are n (%) of patients for therapies for which 2% or more of patients were given subsequent therapies. On completion of Kd or Vd therapy, 391 patients in the Kd group (of 397 completing therapy) and 413 patients in the Vd group (of 418 completing therapy) entered long-term follow-up.

Note: Data on response were not collected for subsequent treatment and thus are not available

# Post-hoc „Landmark-Analysis“: OS from time of progression is identical

OS from time of progression is 21.5 months in both arms



- Both curves are identical thus indicating that the PFS benefit gained under Kd treatment is responsible for the OS benefit in the Kd arm.

Number at risk (number censored):									
Carfilzomib group	258 (0)	211 (6)	155 (24)	99 (49)	56 (80)	26 (103)	9 (117)	4 (122)	0 (125)
Bortezomib group	301 (0)	240 (8)	191 (18)	149 (29)	100 (54)	42 (98)	11 (122)	1 (132)	

## Aspire Conclusions

- KRd demonstrated a statistically significant and clinically meaningful reduction in the risk of death vs Rd, **improving the median OS by 7.9 months (48.3 vs 40.4 months; HR = 0.79;  $P = 0.0045$ )**
- Median OS at first relapse improved by 11.4 months with KRd (47.3 vs 35.9 months; HR = 0.81)

• **Treatment with KRd did not compromise overall survival after relapse**

# CASTOR: Overview of safety profile

	All grades ≥25%		Grades 3/4 ≥5%	
TEAE	DVd	Vd	DVd	Vd
Hematologic (%)				
Thrombocytopenia	59.7	44.3	45.7	32.9
Anemia	28.4	31.6	15.2	16.0
Neutropenia	18.9	9.7	13.6	4.6
Lymphopenia	13.2	3.8	9.9	2.5
Nonhematologic (%)				
Pneumonia	15.6	13.1	10.3	10.1
Peripheral sensory neuropathy	49.8	38.0	4.5	6.8
Hypertension	9.9	3.4	6.6	0.8
Upper respiratory tract infection	32.9	18.1	2.5	0.4
Diarrhea	35.4	22.4	3.7	1.3
Cough	28.0	12.7	0	0

- The safety profile was consistent with previous analyses of CASTOR
- TEAE-related treatment discontinuations occurred in 9.5% and 9.3% of patients in the DVd and Vd arms, respectively
- With longer follow-up, secondary primary malignancies were reported in 10 (4.1%) and 3 (1.3%) patients who received DVd and Vd, respectively

The safety profile of DVd remains consistent with previous studies and no new safety signals were reported

## CASTOR updated analysis: OS

- Per study protocol, long-term survival follow-up will continue until 320 deaths have been observed in both arms (i.e, when two-thirds of the randomized patients have died)
- OS data currently remain immature

# CASTOR: Efficacy Summary Table

	Primary Analysis <sup>1</sup>		ASH 2016 <sup>2</sup>		ASCO 2017 <sup>3</sup>		ASH 2017 <sup>4</sup>	
	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Vd
Median follow-up (range)	7.4		13.0		19.4		26.9	
Median PFS <sup>a</sup> , mo	NE	7.2	NE	7.1	16.7	7.1	16.7	7.1
HR (95% CI) <i>P</i> value	0.39 (0.28-0.53) <i>P</i> <0.001		0.33 (0.26-0.43) <i>P</i> <0.0001		0.31 (0.24-0.39) <i>P</i> <0.0001		0.32 (0.25-0.40) <i>P</i> <0.0001	
ORR <sup>b</sup> , %	83	63	84	63	84	63	85	63
≥CR, %	19	9	26	10	29	10	30	10
MRD-negative (10 <sup>-5</sup> ) <sup>a</sup> , %	N/A	N/A	10	2	12	2	12	2

<sup>a</sup>ITT population.

<sup>b</sup>Response evaluable population.

<sup>1</sup>Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766. <sup>2</sup>Mateos MV, et al. Oral presentation at ASH 2016. Abstract: 1150. <sup>3</sup>Lentzsch S, et al. Poster presentation at ASCO 2017. Abstract: 8036. <sup>4</sup>Spencer A, et al. Poster presentation at ASH 2017. Abstract: 3145.

# CASTOR updated analysis

## ORR and MRD-negative rate ( $10^{-5}$ )

	ITT Population		1 prior LOT		2 prior LOT		3 prior LOT		1-3 prior LOT	
	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Vd	DVd	Rd
ORR <sup>a</sup>										
N	240	234	119	109	64	71	35	29	218	209
%	85	63	92	74	84	65	69	41	86	67
P value	<0.0001		0.0007		0.0563		0.0487		<0.0001	
≥VGPR, %	63	29	77	42	61	18	34	28	65	32
P value	<0.0001		<0.0001		<0.0001		0.6999		<0.0001	
≥CR, %	30	10	43	15	25	9	11	3	33	11
P value	<0.0001		<0.0001		0.0118		0.3009		<0.0001	
sCR, %	10	3	14	5	6	1	6	0	11	3
MRD-negative rate ( $10^{-5}$ ) <sup>b</sup>										
N	251	247	122	113	70	74	37	32	229	219
%	12	2	16	3	11	0	5	3	13	2
P value	<0.0001		0.0002		0.0005		0.64		<0.0001	

- DVd improved ORR regardless of the number of prior lines of therapy
- Higher MRD-negative rates were observed with DVd

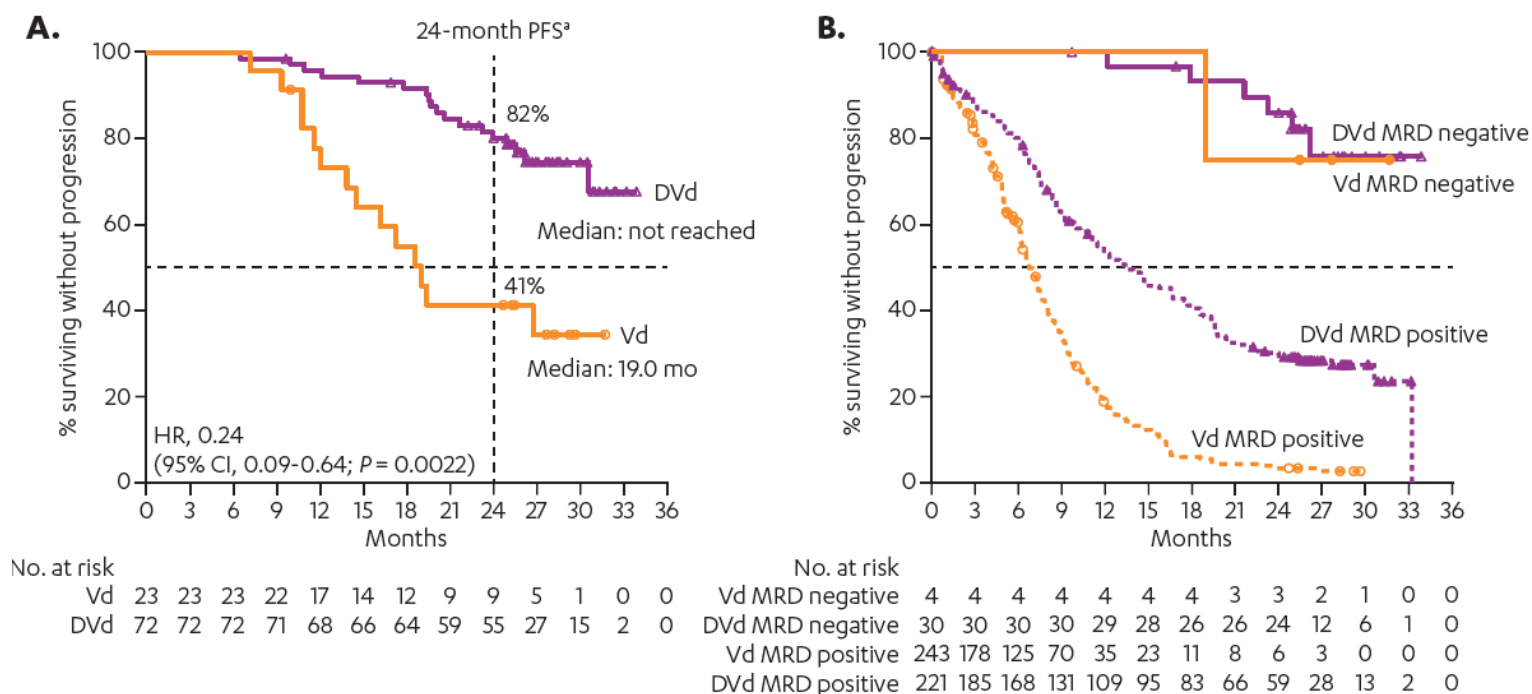
<sup>a</sup>Response-evaluable population.

<sup>b</sup>ITT population.



# CASTOR updated analysis: PFS by response and MRD status

**PFS in patients who achieved (A)  $\geq$ CR and (B) MRD negativity at  $10^{-5}$  (clonoSEQ V2.0)**

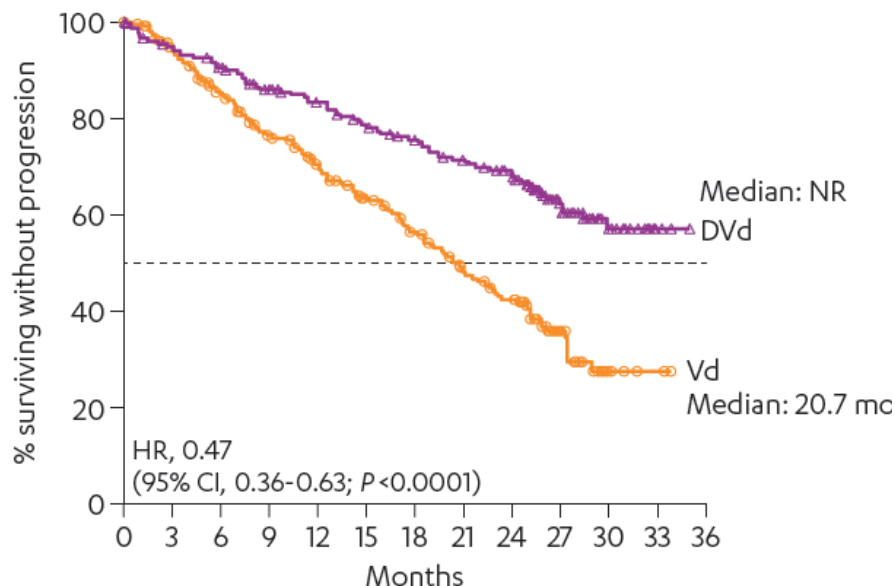


- PFS among patients who achieved deep responses was prolonged with DVd versus Vd.
- MRD negativity was associated with prolonged PFS

# CASTOR updated analysis: PFS2

## PFS2 in (A) the ITT Population and in (B) Patients Who Received 1 Prior Line of Therapy

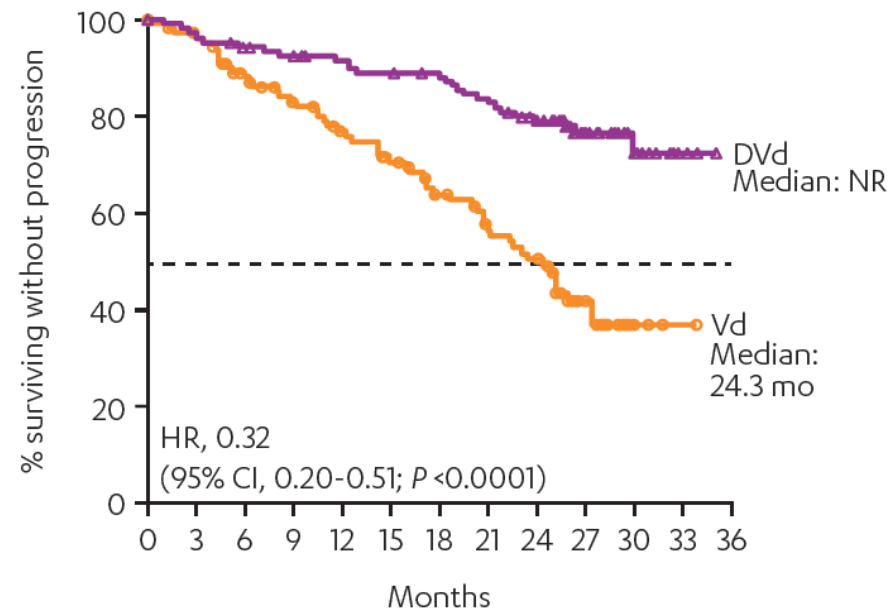
**A.**



No. at risk

Vd	247	214	188	162	140	119	101	81	70	31	5	2	0
DVd	251	229	218	201	191	178	167	155	144	66	25	4	0

**B.**



No. at risk

Vd	113	105	92	82	73	65	55	46	41	18	3	1	0
DVd	122	115	111	107	104	101	99	92	85	42	17	3	0

- PFS2 is defined as the time from randomization to PD after the next line of subsequent therapy or death

Addition of daratumumab to Vd leads to persistent benefit after next line of therapy

# POLLUX: Overview of Safety profile

	All grades (≥25%) <sup>a</sup>		Grade 3/4 (≥5%) <sup>a</sup>	
TEAE, %	DRd (n = 283)	Rd (n = 281)	DRd (n = 283)	Rd (n = 281)
Hematologic				
Neutropenia	62	47	54	41
Febrile neutropenia	6	3	6	3
Anemia	38	41	16	22
Thrombocytopenia	29	31	14	16
Lymphopenia	7	6	6	4
Nonhematologic				
Diarrhea	56	34	7	4
Upper respiratory tract infection	41	27	1	1
Viral upper respiratory tract infection	31	19	0	0
Fatigue	38	31	6	4
Cough	34	15	0.4	0
Constipation	31	27	1	0.7
Muscle spasms	29	21	1	1
Nausea	27	18	2	0.7
Pneumonia	24	16	14	10
Hypokalemia	17	11	5	3

- Median duration of treatment: 30.4 months for DRd versus 16.0 months for Rd
- Discontinuations due to TEAEs were similar (13% in both arms)
- Rate of grade 3/4 infections: 39% for DRd versus 26% for Rd
- No differences in rates of SPMs between treatment groups (7% of patients in both groups)
  - Most common SPM in both arms was cutaneous, non-invasive SCC (2% each)

**Safety profile remains unchanged with longer follow-up**

TEAE, treatment-emergent adverse event; SPM, secondary primary malignancy; SCC, squamous cell carcinoma. <sup>a</sup>Common TEAEs listed are either ≥25% all grade OR ≥5% grade 3/4.

# POLLUX: Efficacy Summary Table

	Primary Analysis <sup>1</sup>		ASH 2016 <sup>2</sup>		ASCO 2017 <sup>3</sup>		ASH 2017 <sup>4</sup>	
	DRd	Rd	DRd	Rd	DRd	Rd	DRd	Rd
Median follow-up (range)	13.5		17.3		25.4		32.9	
Median PFS <sup>a</sup> , mo	NE	18.4	NE	17.5	NE	17.5	NE	17.5
HR (95% CI) <i>P</i> value	0.37 (0.27-0.52) <i>P</i> <0.001		0.37 (0.28-0.50) <i>P</i> <0.0001		0.41 (0.31-0.53) <i>P</i> <0.0001		0.44 (0.34-0.55) <i>P</i> <0.0001	
ORR <sup>b</sup> , %	93	76	93	76	93	76	93	76
≥CR <sup>b</sup> , %	43	19	46	20	51	21	55	23
MRD-negative (10 <sup>-5</sup> ) <sup>a</sup> , %	22	5	25	6	26	6	27	5

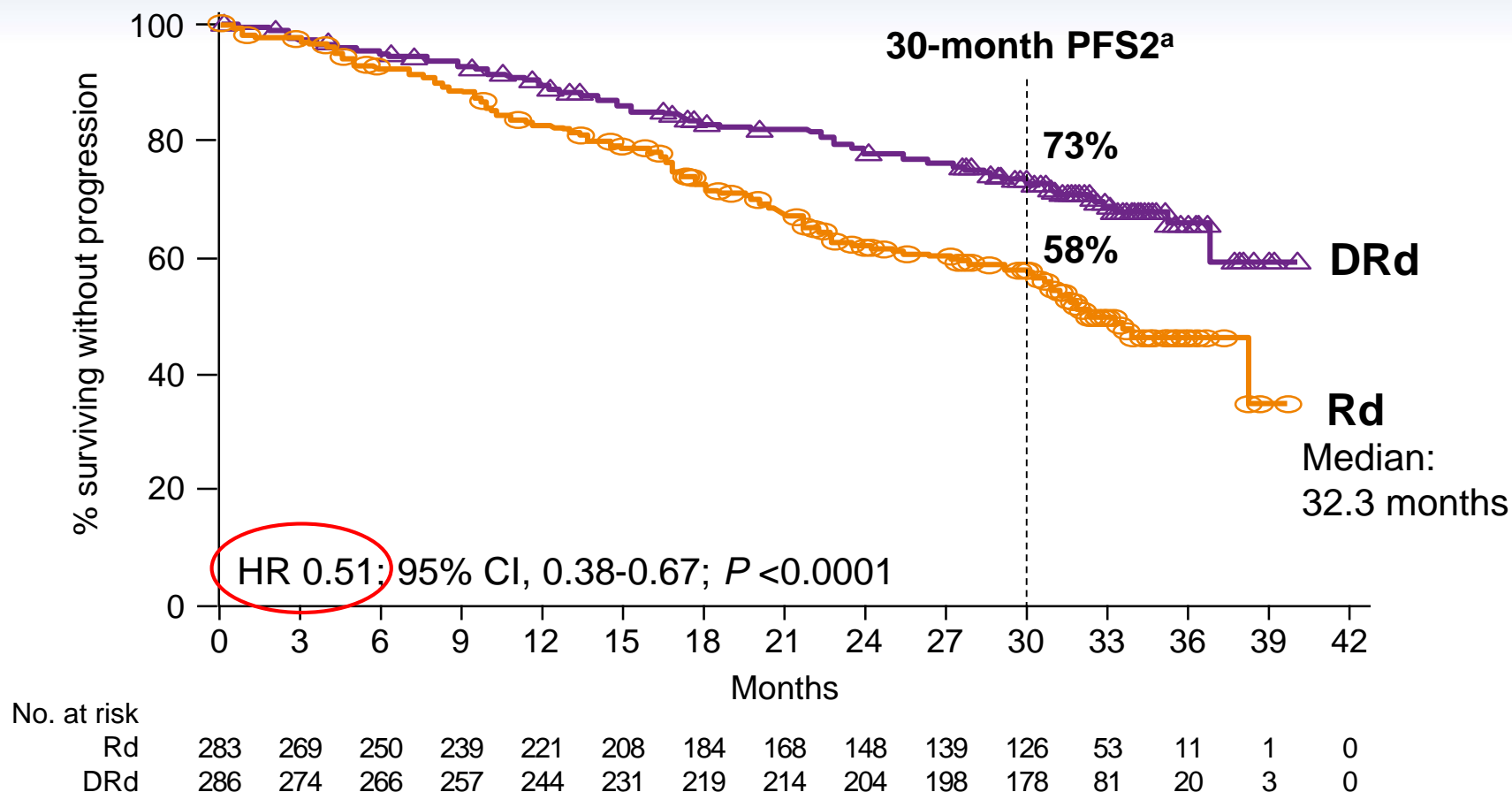
- OS data are immature; long term follow-up will continue until 330 events are observed

<sup>a</sup>ITT population.

<sup>b</sup>Response evaluable population.

<sup>1</sup>Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. <sup>2</sup>Usmani SZ, et al. Oral presentation at ASH 2016. Abstract: 1151. <sup>3</sup>Bahlis NJ, et al. Poster presentation at ASCO 2017. Abstract: 8025. <sup>4</sup>Dimopoulos MA, et al. Oral presentation at ASH 2017. Abstract: 739.

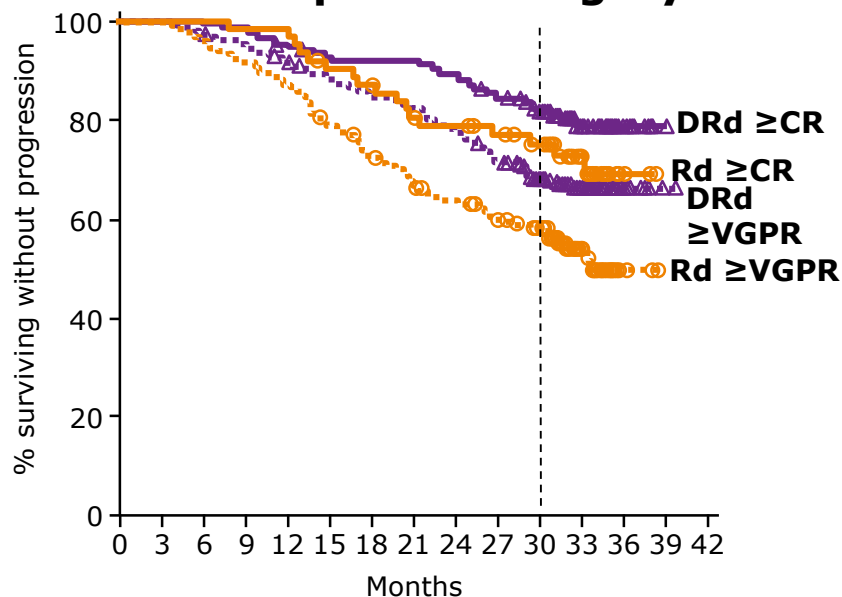
# POLLUX: PFS with Subsequent Line of Therapy (PFS2)



**DRd does not negatively impact outcomes of subsequent therapy**

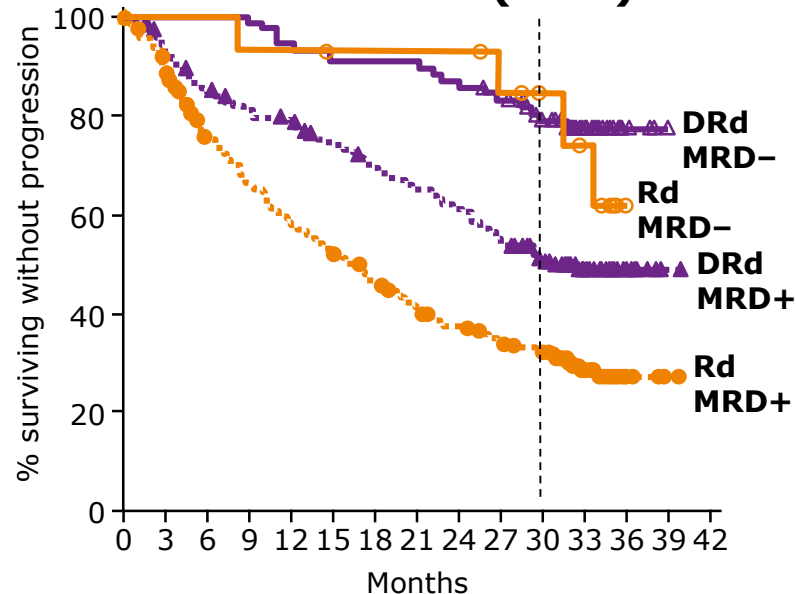
# POLLUX: PFS by Depth of Response

## Response Category



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
DRd ≥ CR	154	154	154	151	146	141	140	140	136	127	115	53	12	1	0
Rd ≥ CR	62	62	62	61	61	56	53	48	46	43	39	22	3	0	0
DRd ≥ VGPR	226	226	226	202	142	061	951	891	831	731	581	137	62	14	2
Rd ≥ VGPR	134	134	129	123	117	106	96	87	80	73	66	31	4	0	0

## MRD Status ( $10^{-5}$ )



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Rd MRD negative	14	14	14	13	13	12	12	12	12	10	8	6	0	0	0
DRd MRD negative	76	76	76	75	72	69	69	69	66	62	54	26	7	1	0
Rd MRD positive	269	235	192	168	147	131	114	99	88	79	72	30	5	1	0
DRd MRD positive	210	190	173	163	157	145	134	125	117	105	91	41	9	1	0

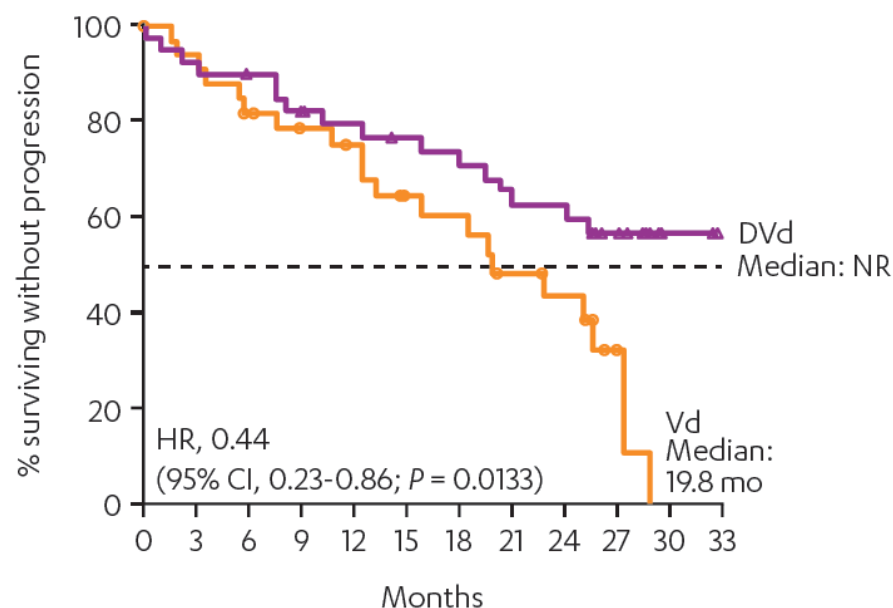
Deeper responses were more common on DRd and were associated with longer PFS  
MRD negativity was associated with longer PFS

# CASTOR updated analysis

## PFS2 Based on Cytogenetic Risk and MRD-negativity

PFS2 in (A) patients with high cytogenetic risk and (B) patients achieving MRD-negativity at  $10^{-5}$

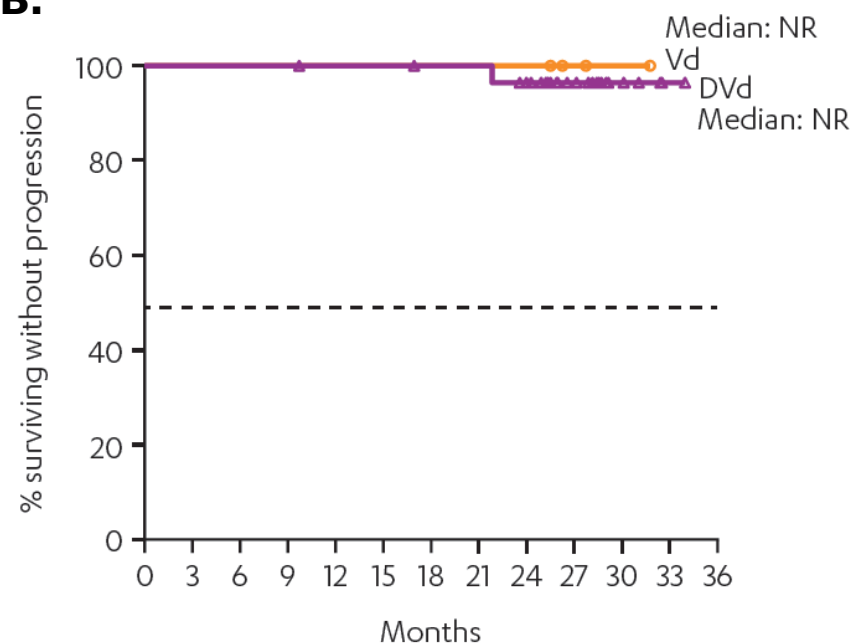
**A.**



No. at risk

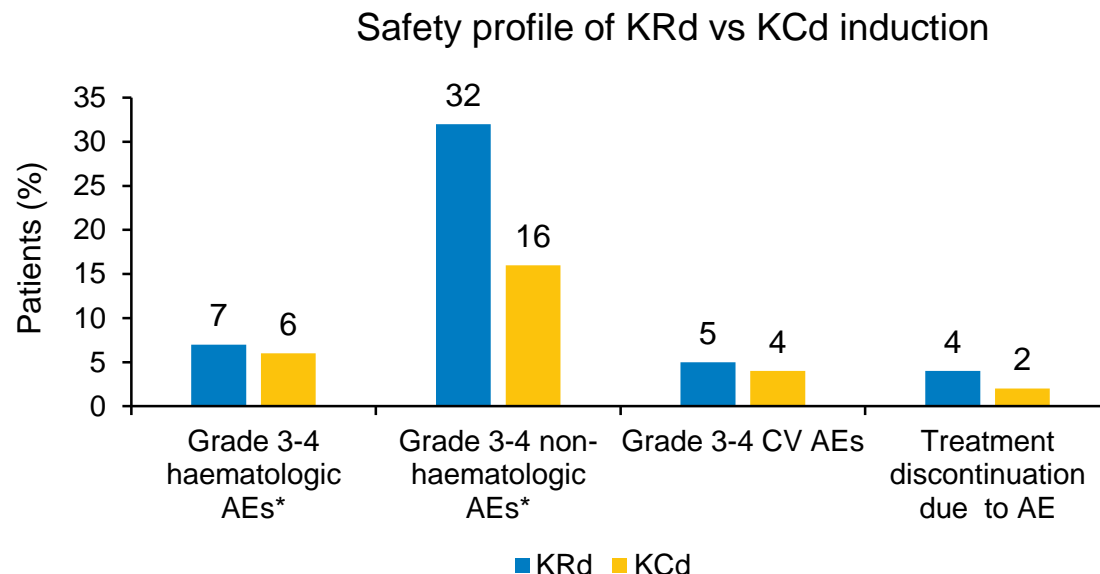
Vd	34	31	26	23	21	16	15	11	9	3	0	0
DVd	40	37	35	31	29	27	26	22	22	13	2	0

**B.**



No. at risk													
Vd	4	4	4	4	4	4	4	4	4	2	1	0	0
DVd	30	30	30	30	29	29	28	28	26	14	6	1	0

# KRd induction had an acceptable safety profile



- The most frequent grade 3-4 haematologic AE was neutropenia (KRd 6% vs KCd 5%)
- The most frequent grade 3-4 non-haematologic AEs were manageable cutaneous toxicity (KRd 8% vs KCd 1%,  $p < 0.001$ ) and reversible increase in liver enzymes (KRd 8% vs KCd 1%,  $p < 0.001$ )
- Treatment discontinuation due to AEs was reported in 4% of KRd and 2% of KCd patients

\*Rate of  $\geq 1$  AE.

AE, adverse events; CV, cardiovascular; KCd, carfilzomib, cyclophosphamide and dexamethasone; KRd, carfilzomib, lenalidomide and dexamethasone.