Stato dell'arte: dalle opzioni terapeutiche alla strategia terapeutica nel 2017

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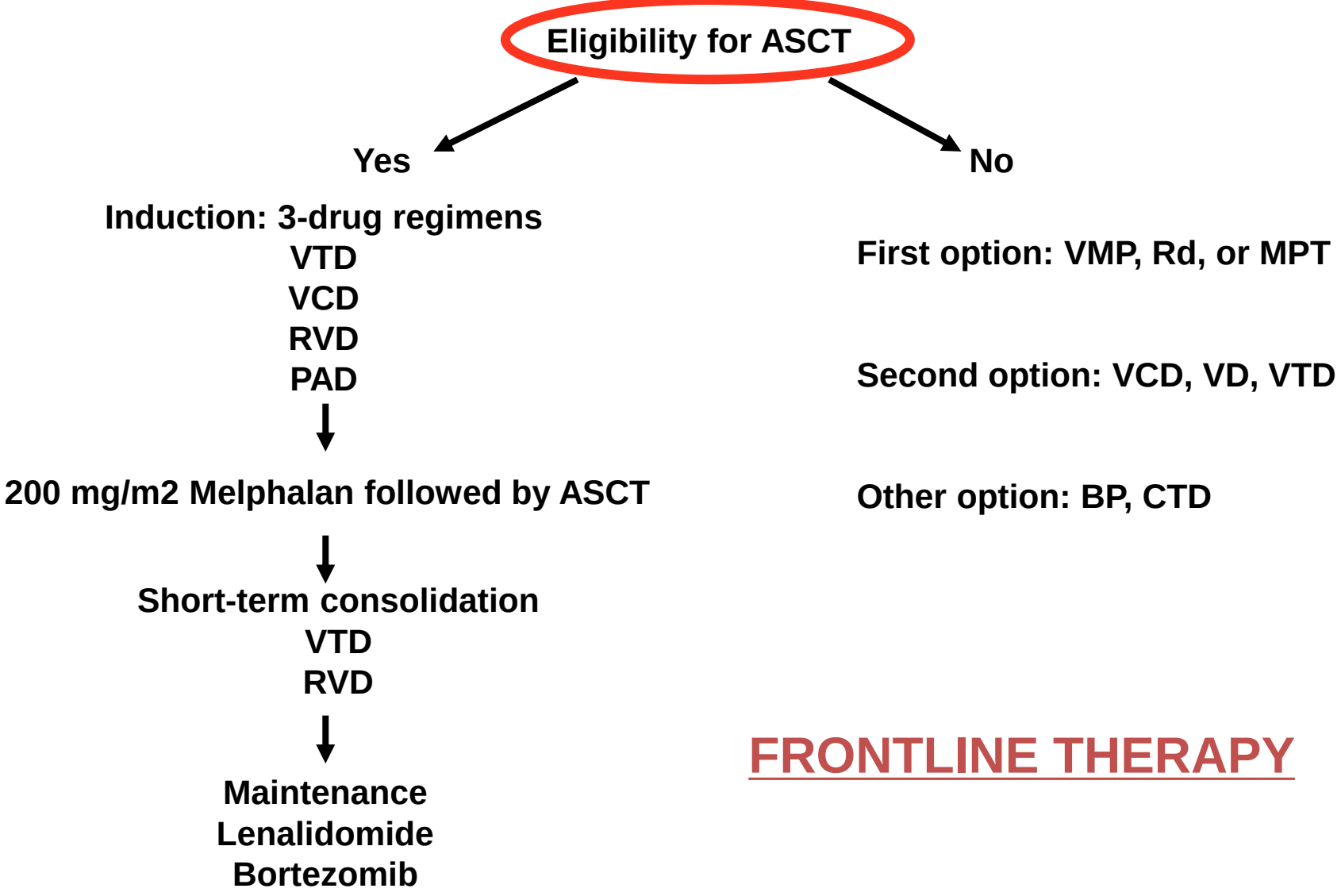
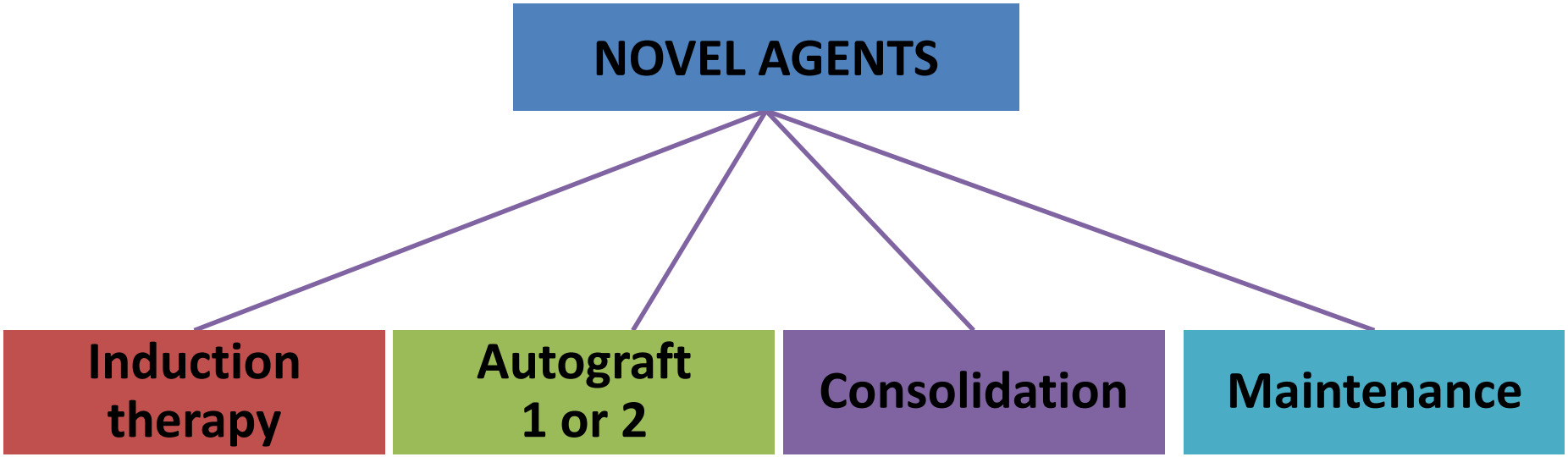


FRONTLINE THERAPY

Frontline therapy of multiple myeloma.
Moreau P, Attal M, Facon T.
Blood. 2015 May 14;125(20):3076-3084. Epub 2015 Apr 2. Review

Actual treatment paradigm for patients who are eligible for ASCT



- Maximize the depth of response
- Minimize the burden of residual tumor cells

Cavo M et al. Blood 2011;117(23):6063-73; Cavo et al. Blood 2012;120(1):9-19.

Meta-analysis: Bortezomib-based versus non-bortezomib-based induction prior to ASCT

- Integrated analysis (n=1572) of 3 randomized trials: Bortezomib-based versus non-bortezomib-based induction regimens

Response rate	Bortezomib-based induction (n=775)	Non-bortezomib-based induction (n=772)	OR	95% CI	P
Post-transplant (%)					
CR+nCR	38	24	2.05	1.64–2.56	< 0.001

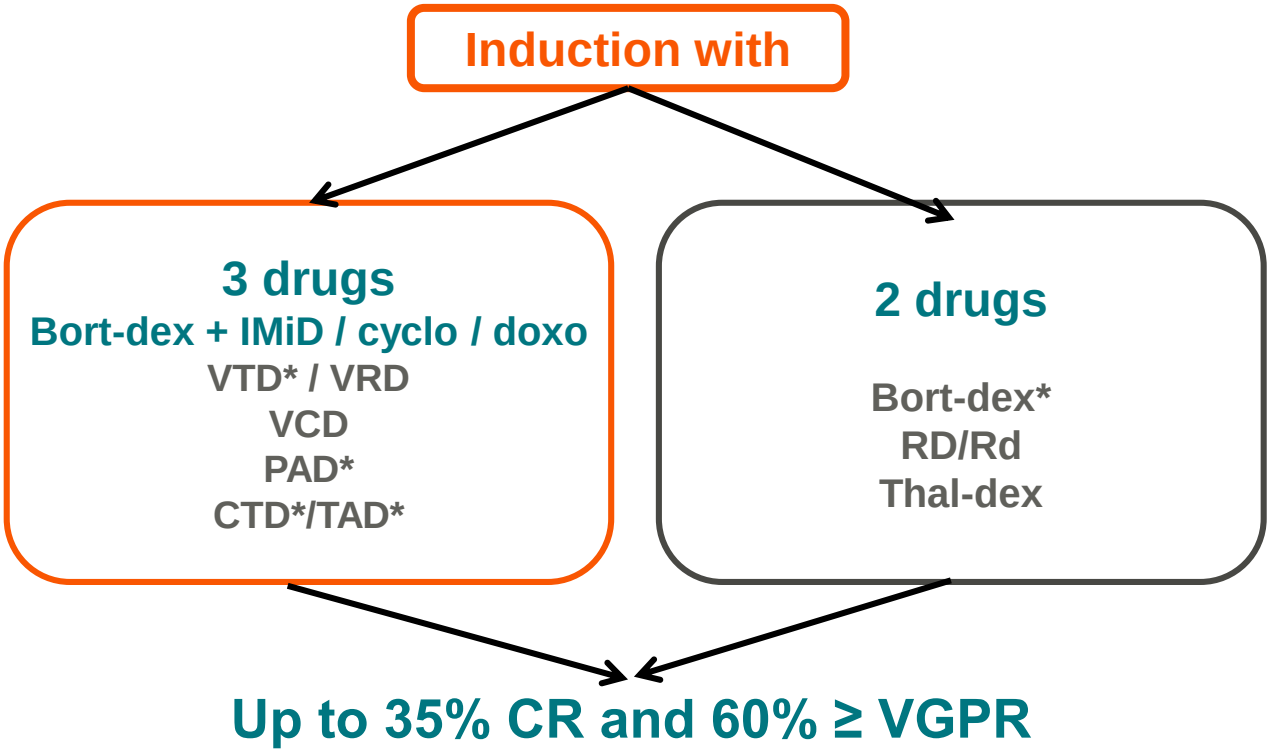
- Median follow-up ~37 months

	Bortezomib-based induction	Non-bortezomib-based induction	HR	95% CI	P
Median PFS, mos	35.9	28.6	0.75	0.65–0.85	< 0.001
3-yr PFS, %	50.0	41.1			

Primary end point: Post transplant CR+nCR and PFS

Sonneveld et al. J Clin Oncol 2013;31(26):3279-87

Current standard induction regimens



How to choose? Very few phase 3 comparisons

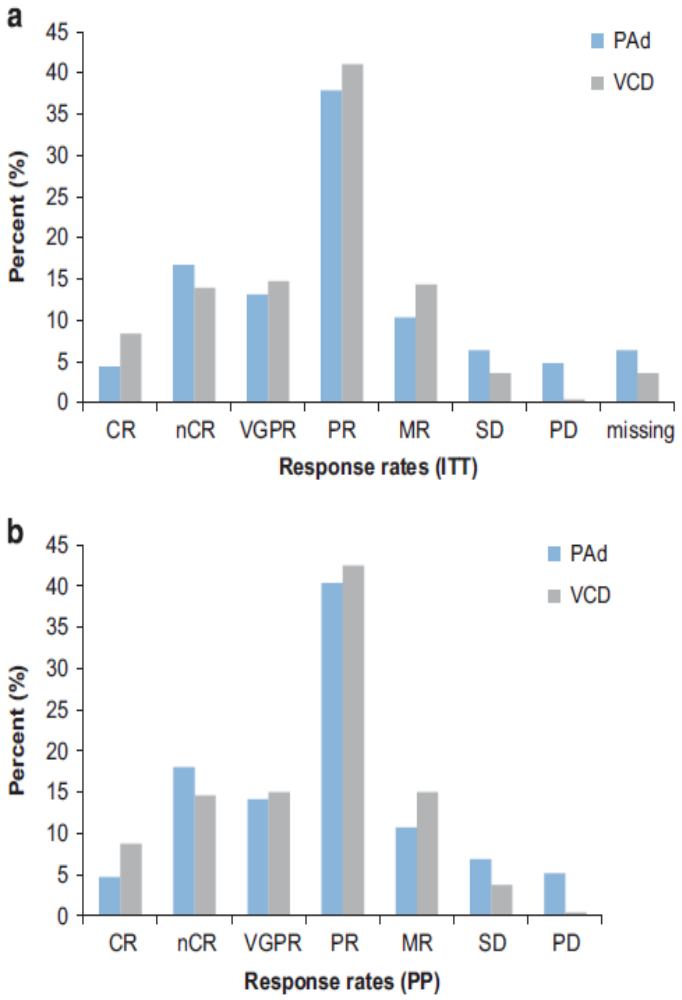
- VTD and VD have been approved by the EMA for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for transplant

Cavo M et al. Blood 2011;117(23):6063-73.

VCD vs PAD induction

GMMG-MM5 phase 3 trial

- 504 patients
- Comparable VGPR rate: 37% vs 34%
- SAE: 24% vs 33% (P= 0.04)



Mai EK, et al. Leukemia. 2015;29:1721-9

VTD vs VCD induction: Response

IFM 2013-04 trial (prospective, intent-to-treat analysis)[1]

	VTD (4-cycles)* N = 169	VCD (4-cycles)† N = 169	p-value
≥ CR	13.0%	8.9%	0.22
≥ VGPR	66.3%	56.2%	0.05

*Bortezomib 1.3 mg/m^2/day SC D1,4,8,11 + Thalidomide 100 mg/day PO D1–21 + Dexamethasone 40 mg/day PO D1–4, D9–12
†Bortezomib 1.3 mg/m^2 /day SC D1,4,8,11 + Cyclophosphamide 500 g/m^2 /day PO D1,8,15 + Dexamethasone 40 mg/day PO D1–4, D9–12

GIMEMA MMY-3006 and EMN-02 studies (retrospective, case-matched analysis)[2]

	VTD (3-cycles)‡ N = 236	VCD (3-cycles)§ N = 236	p-value
≥ CR	19%	6%	< 0.001
≥ VGPR	64%	37%	< 0.001

‡ Bortezomib 1.3mg/m^2 twice weekly + Thalidomide 100➔200mg/day + Dexamethasone 320mg/cycle (3 X 21-day cycles)
§ Bortezomib 1.3mg/m^2 SC D1,4,8,11 + Cyclophosphamide 500 g/m^2/day IV D1,8 + Dexamethasone 40 mg/day PO D 1, 2, 4, 5,8, 9,11, 12 (3 X 21-day cycles)

1. Moreau, P et al. Blood 2016;127:2569-74;
2. Cavo et al. Leukemia 2015;29(12):2429-31.

VTD vs VCD induction: Toxicity

IFM 2013-04 trial (prospective, intent-to-treat analysis)[1]

%	VTD, N = 169	VCD, N = 169	p-value
Any grade 3 or 4 AEs	63.9	68.2	0.40
Hematologic toxicities, grade 3 or 4			
Anemia	4.1	9.5	0.05
Neutropenia	18.9	33.1	0.003
Thrombocytopenia	4.7	10.6	0.04
Non-hematologic toxicities, grade 3 or 4			
Peripheral neuropathy	7.7	2.9	0.05

GIMEMA MMY-3006 and EMN-02 studies (retrospective, case-matched analysis)[2]

	VTD, N = 236	VCD, N = 236	p-value
Any grade 3 or 4 AE	27%	26%	0.754
Hematologic toxicities, grade 3 or 4			
Anemia	0	7%	<0.001
Neutropenia	2%	8%	0.003
Thrombocytopenia	<1%	4%	0.006
Non-hematologic toxicities, grade 3 or 4			
Peripheral neuropathy	7%	2%	0.009

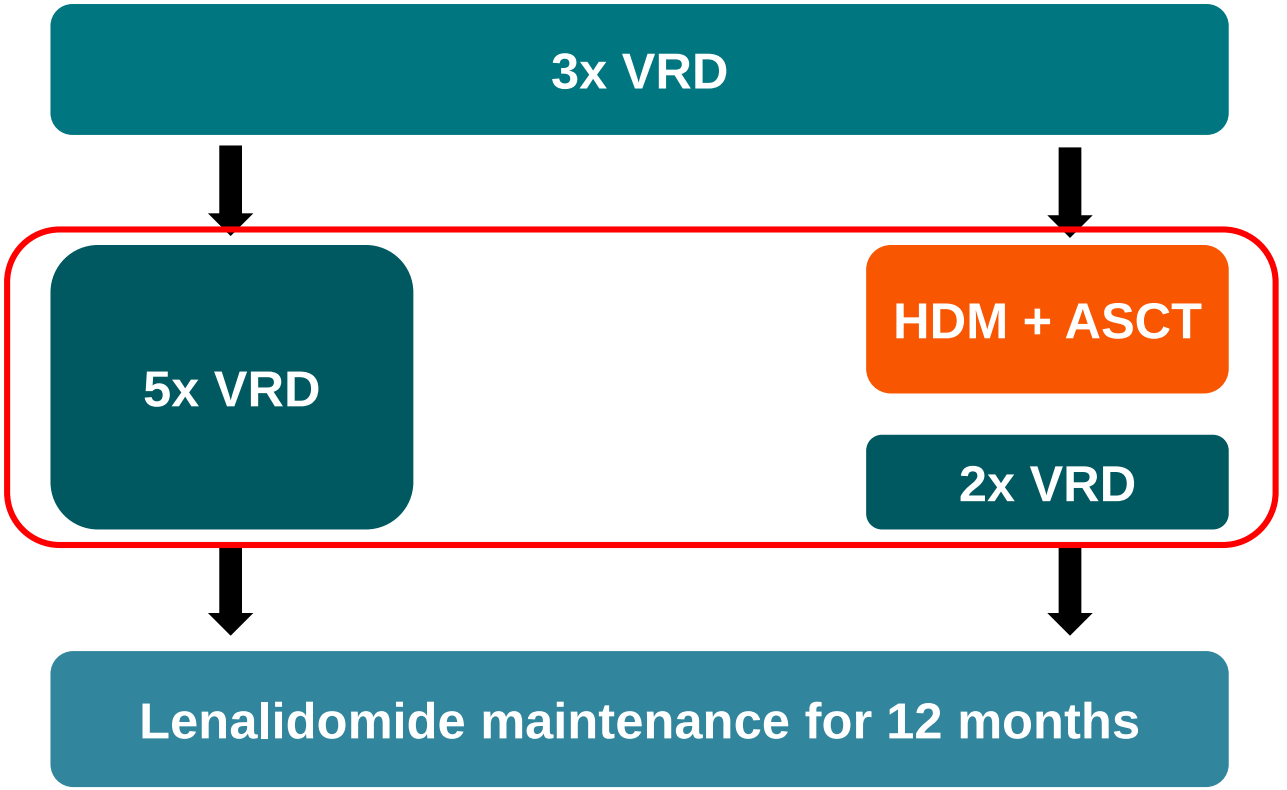
Toxicities assessed according to NCI CTCAE, version 4.0.

1. Moreau, P et al. Blood 2016;127:2569-74;
2. Cavo et al. Leukemia 2015;29(12):2429-31.

ASCT vs VRD

IFM 2009 phase 3 trial

700 patients < 66 years old with newly diagnosed, symptomatic MM



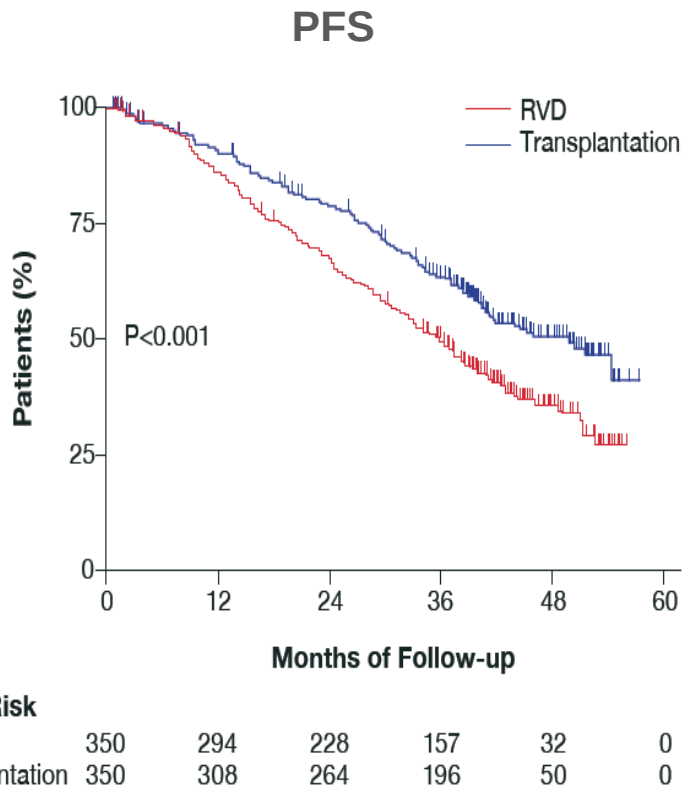
HDM, high-dose melphalan; IFM, Intergroupe Francophone Du Myelome.

Attal M, et al. Blood. 2015;126:391.

ASCT vs VRD: Best response and PFS

Second interim analysis of IFM DFCI 2009 study

	VRD (N=350)	ASCT (N=350)	P-value
CR, %	49	59	
VGPR, %	29	29	0.02
PR, %	20	11	
< PR, %	2	1	
At least VGPR, %	78	88	0.001
MRD –ve by FCM, n (%)	228 (65)	280 (80)	0.001

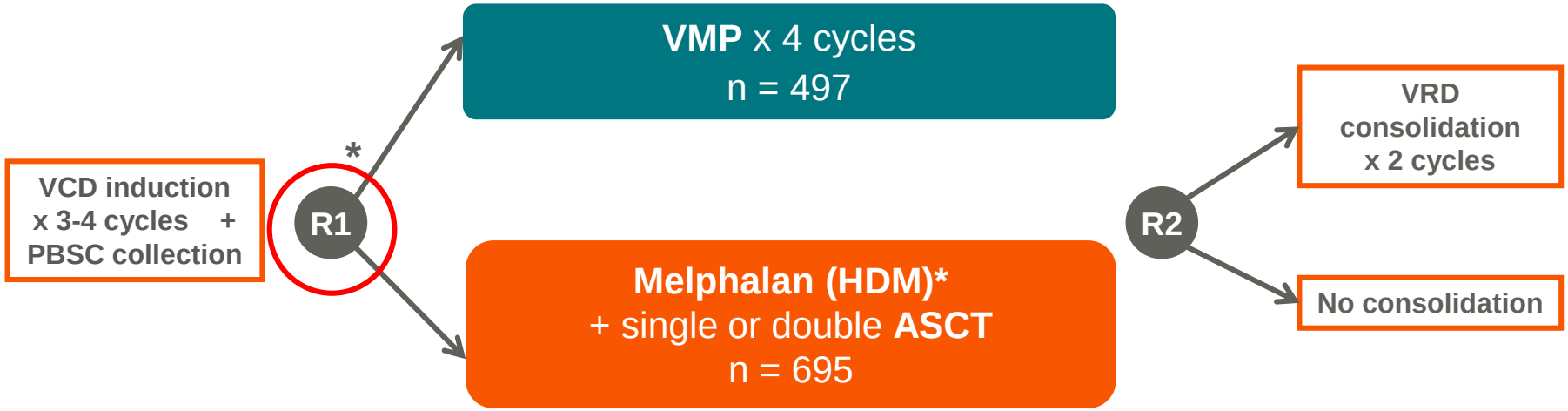


FCM, flow cytometry.

Attal M, et al. N Engl J Med. 2017; in press.

ASCT vs VMP

EMN02/HO95 MM phase 3 trial



All pts received lenalidomide maintenance until relapse/progression

*** Randomization was to VMP vs HDM-1 (1:1) in centers with a single ASCT policy and to VMP vs HDM-1 vs HDM 1-2 (1:1:1) in centers with a double ASCT policy**

Stratification: ISS I vs II vs III

Primary endpoint: PFS from R1 (VMP vs ASCT)

Cavo M, et al. Blood. 2016;128:673; as presented at ASH 2016.
Cavo M, et al. J Clin Oncol. 2016;34 (suppl; abstr 8000); as presented at ASCO 2016.

ASCT vs VMP: Best response and PFS

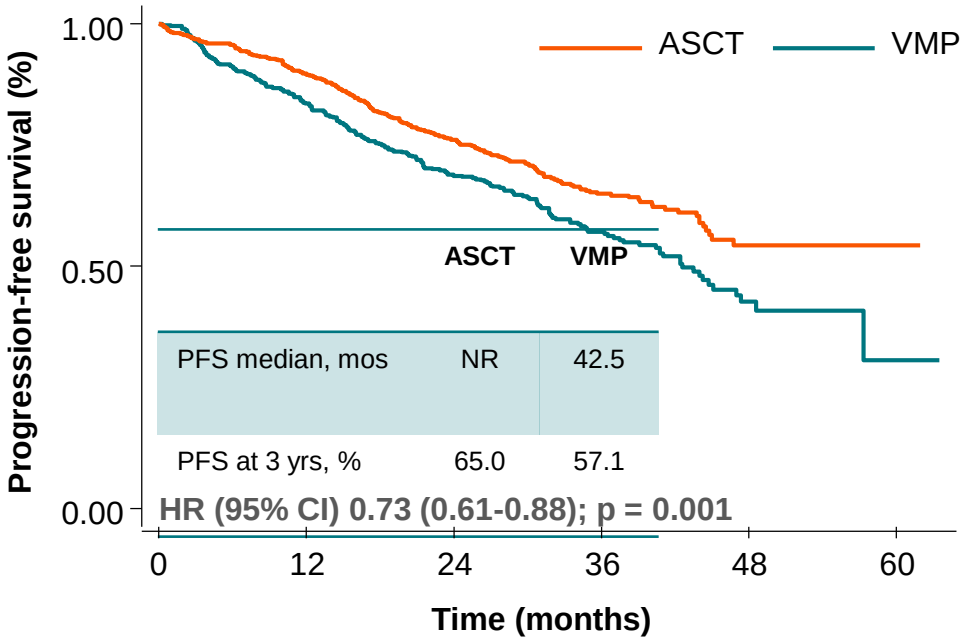
EMN02/HO95 MM phase 3 trial

EMN02/HO95 MM trial

Best response

	ASCT (N=695)	VMP (N=497)	P-value
sCR, %	17.0	18.2	
CR, %	25.3	25.3	
VGPR, %	43.2	30.4	
PR, %	11.2	14.9	
< PR, %	3.3	11.3	
≥ VGPR, %	85.5	73.8	<.0001

PFS

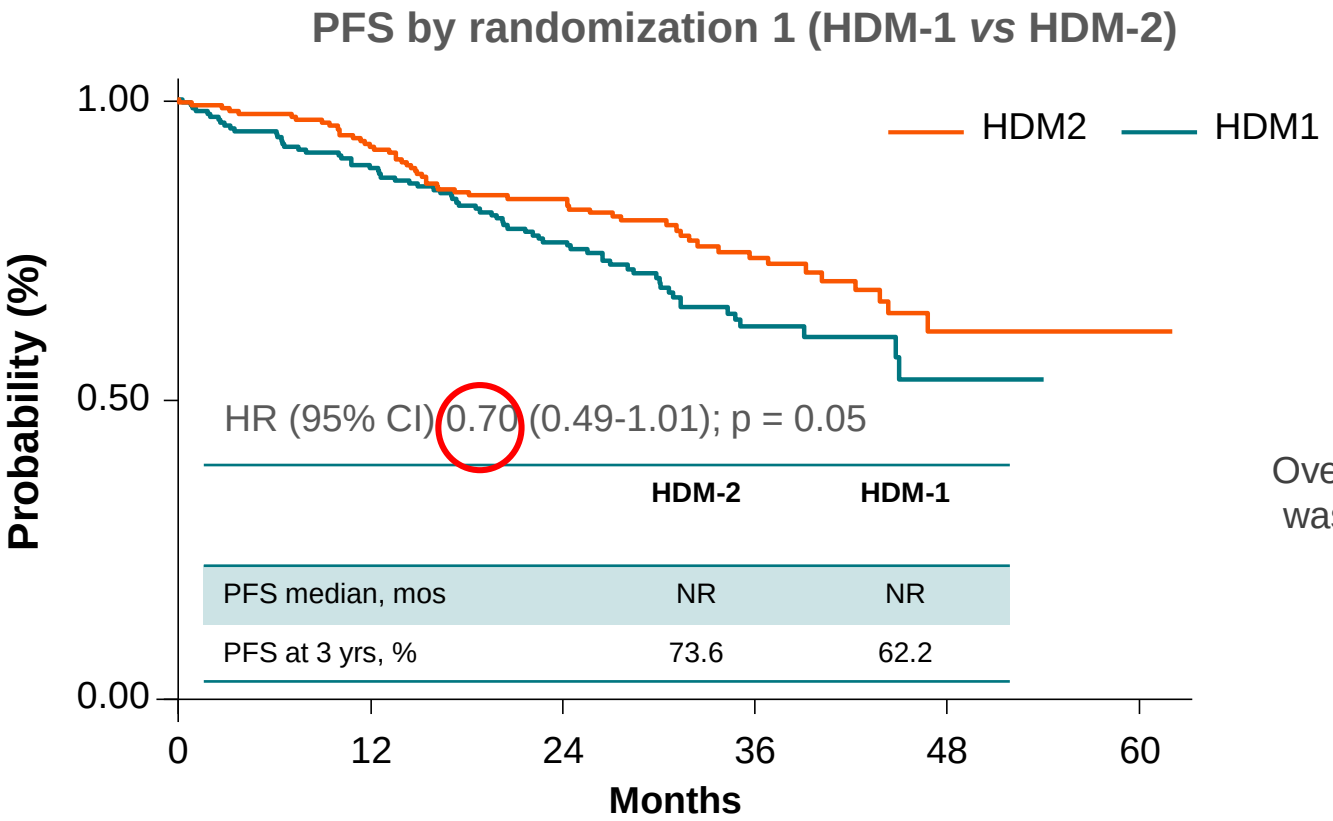


Number at risk

ASCT 695	596	449	192	39	2
VMP 497	400	298	142	27	1

Cavo M, et al. Blood. 2016;128:673; as presented at ASH 2016.
Cavo M, et al. J Clin Oncol. 2016;34 (suppl; abstr 8000); as presented at ASCO 2016.

Upfront single vs double ASCT:
EMN02/HO95 MM phase 3 trial



Overall survival data was not yet mature

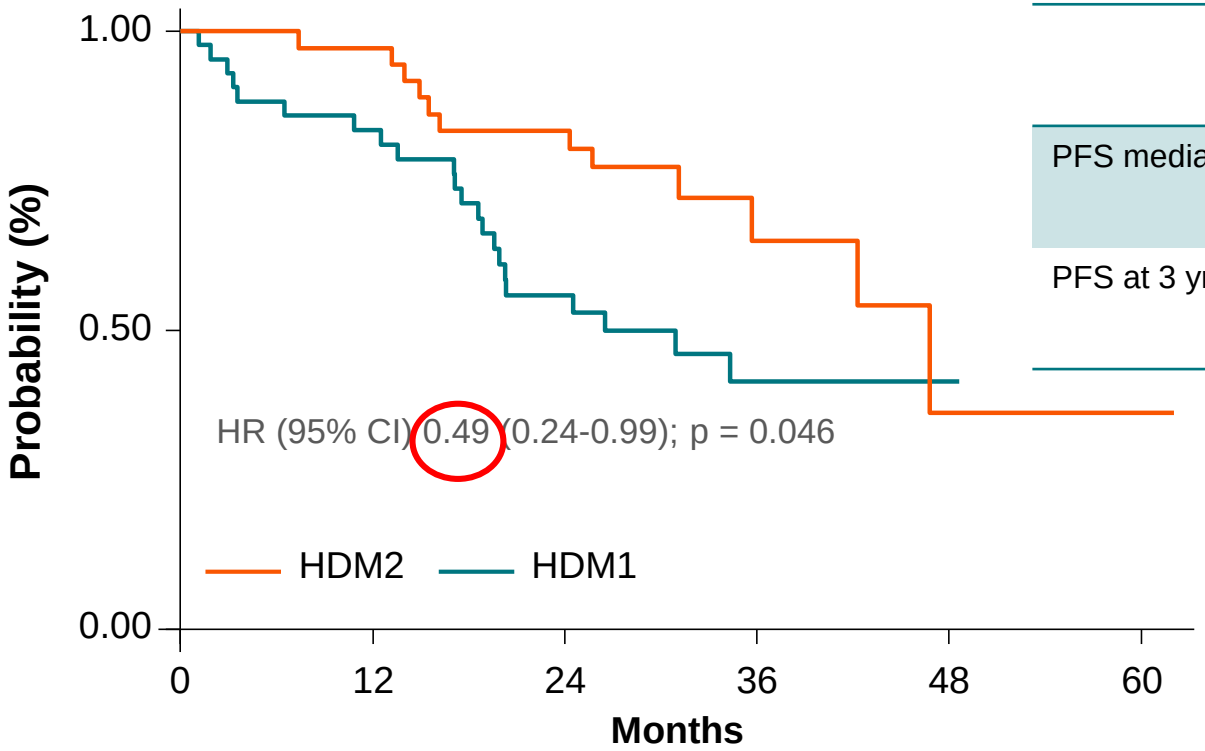
Median follow-up: 32 months (IQR 26-41)

Cavo M, et al. Blood. 2016;128:991; as presented at ASH 2016.

Upfront single vs double ASCT in patients with high-risk cytogenetics

EMN02/HO95 MM trial

PFS by randomization 1 (HDM-1 *vs* HDM-2)



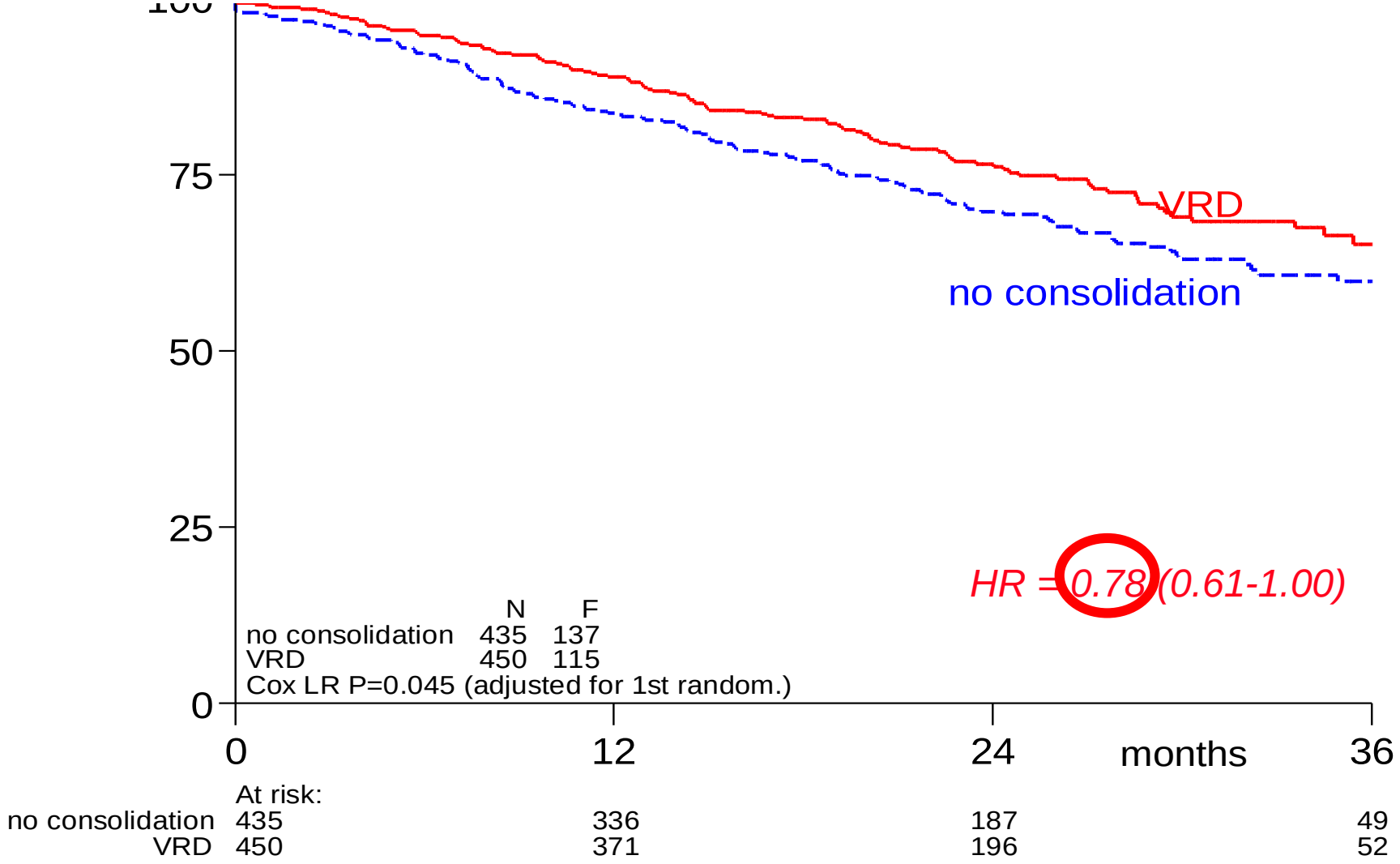
	HDM-2	HDM-1
PFS median, mos	46.8	26.5
PFS at 3 yrs, %	64.9	41.4

Number at risk

HDM2	38	35	28	9	2	1
HDM1	43	34	20	7	1	0

Cavo M, et al. Blood. 2016;128:991; as presented at ASH 2016.

Progression-free survival

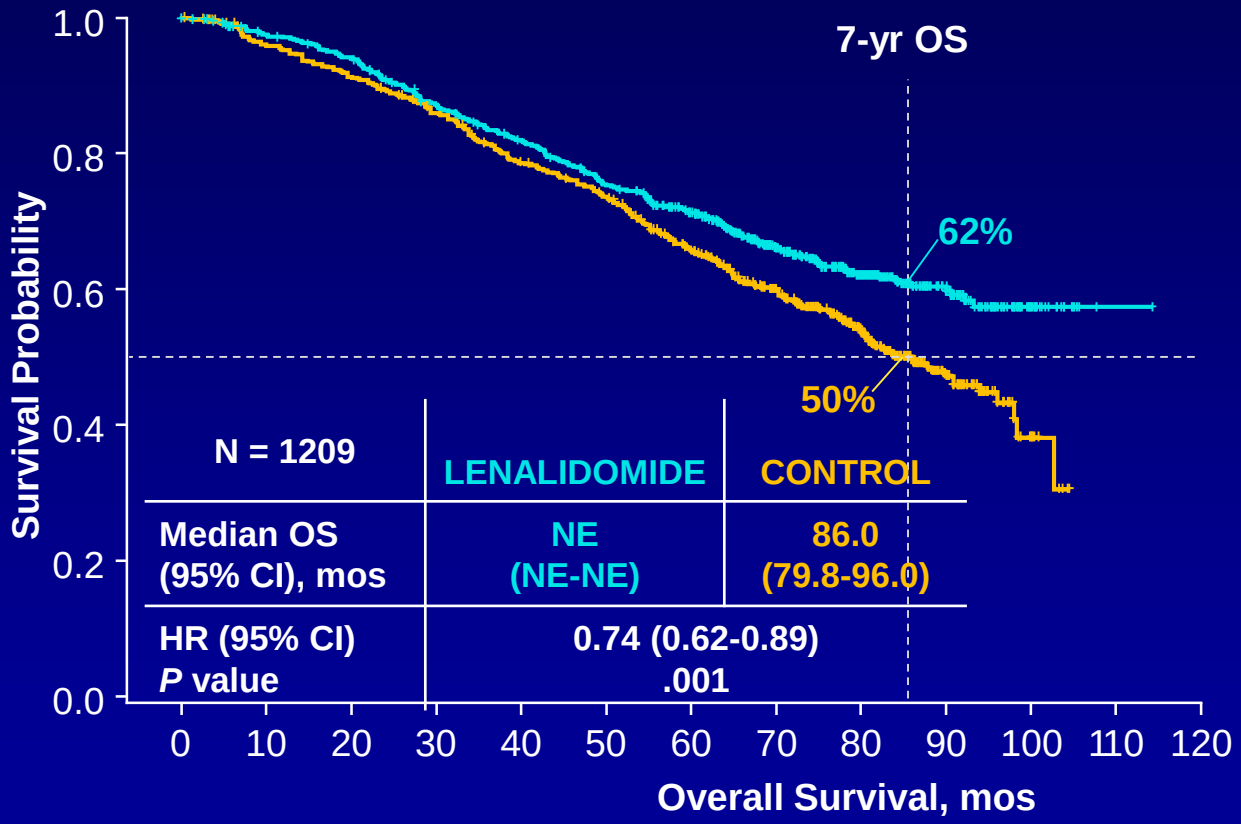


Sonneveld P et al. ASH 2016

METANALYSIS OF LENALIDOMIDE MAINTENANCE RADOMIZED STUDIES

OS: Median Follow-Up of 80 Months

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival



Problemi aperti:

- Ruolo del doppio trapianto autologo (dati contrastanti studio EMN02 e STaMINA (BMT-CTN)
- Ruolo del consolidamento (dati contrastanti studio EMN02 e STaMINA)
- Disponibilità e durata ottimale della terapia di mantenimento
- Terapia modellata sul rischio

AVAILABLE FRONTLINE THERAPY IN NEWLY DIAGNOSED MM PATIENTS NOT ELIGIBLE FOR ASCT

- **First option: VMP (EMA approved 2008), Ld (EMA approved 2015), or MPT (EMA approved 2008)**
- **Second option: VCD, VD, VTD**
- **Other options: BP, CTD**

Fayers et al. *Blood* 2011
San Miguel JF, et al. *N Engl J Med* 2008;359:906-17
Mateos MV, *J Clin Oncol* 2010, April 5

Rajkumar SV, et al. *Lancet Oncol* 2010;11:29-37
Benboubker et al. N Engl J Med. 2014 Sep 4;371(10):906-17
Mateos MV et al. *Haematologica* 2015

VMP modifications:

- **Bi weekly, VISTA** (San Miguel, N Engl J Med 2008)

- **Once a week** (Mateos, Lancet Oncol 2010)

- **Maintenance** (Mateos, Blood 2012 & Blood 2014)

- **Bortezomib sc** (Moreau, Lancet Oncol 2011)

Future

MP based :

Daratumumab- VMP vs VMP: Alcyone

Ld based :

VRD: SWOG SO777 study (Durie B et al, Lancet 2017)

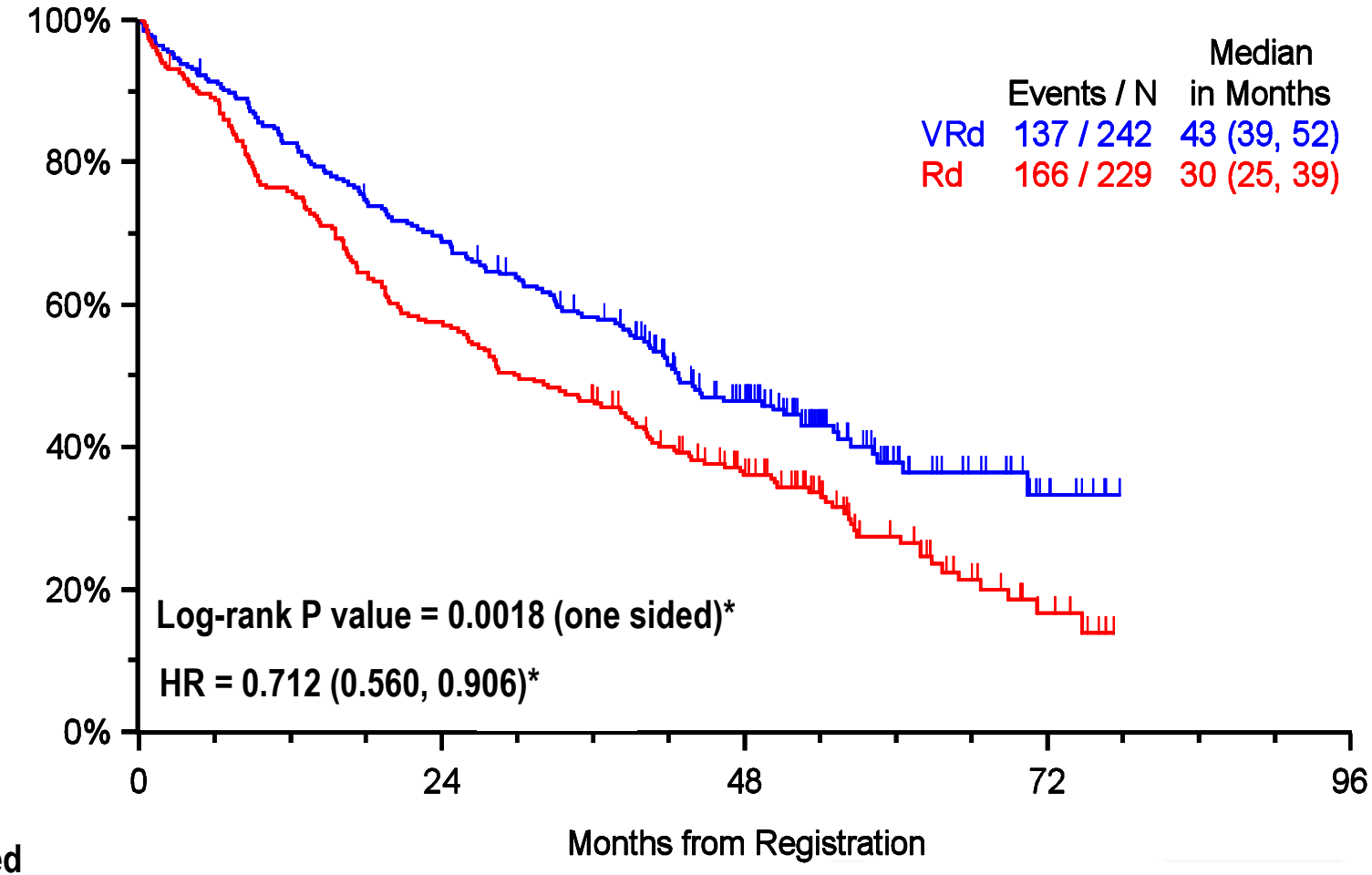
Ixazomib-Ld vs Ld: Tourmaline 2

Elotuzumab-Ld vs Ld: Eloquent 1

Daratumumab-Ld vs Ld: Maia

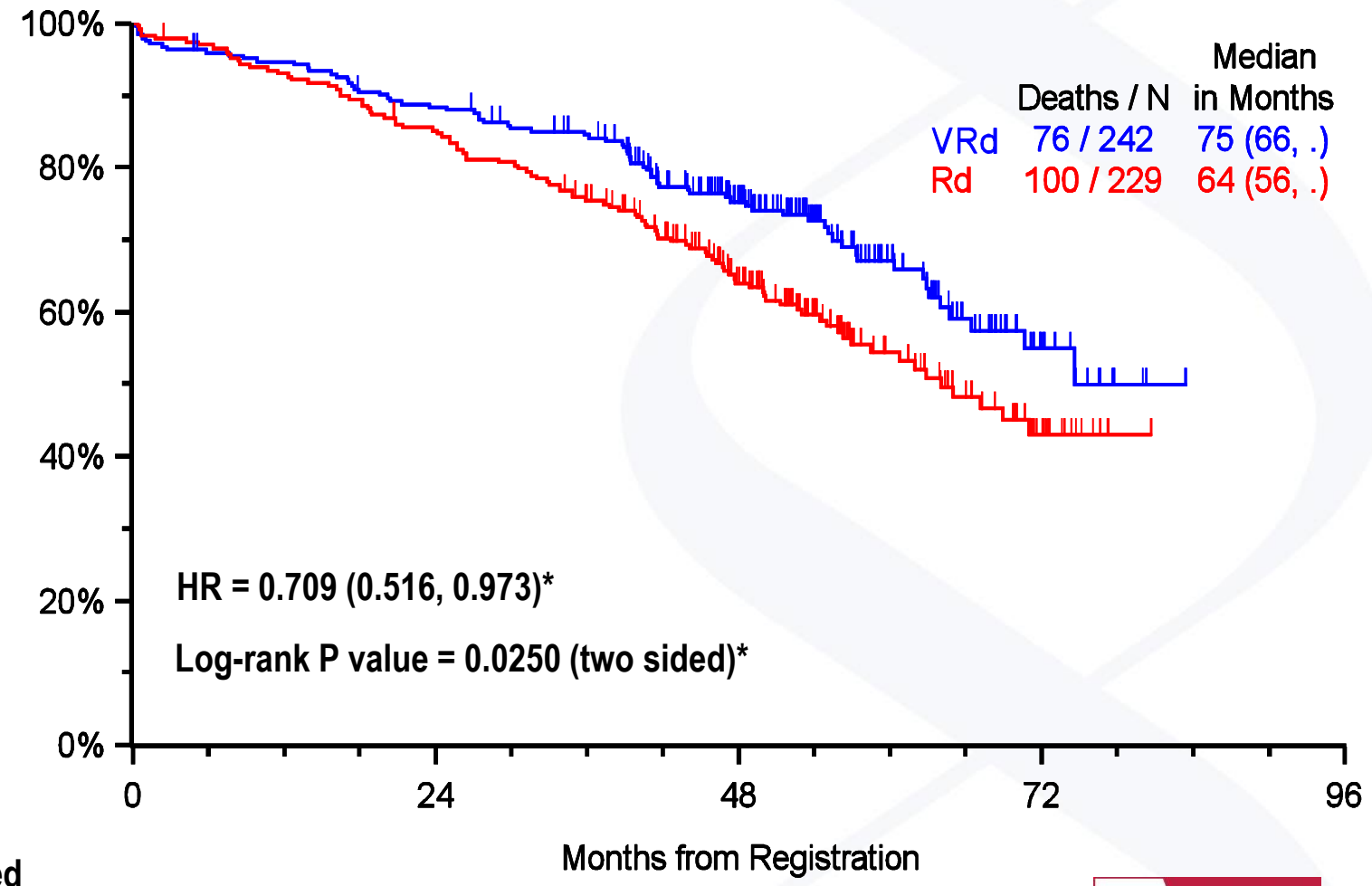
Pembrolizumab-Ld vs Ld: MK 3475

SWOG SO777 trial: VRd vs Rd
PFS



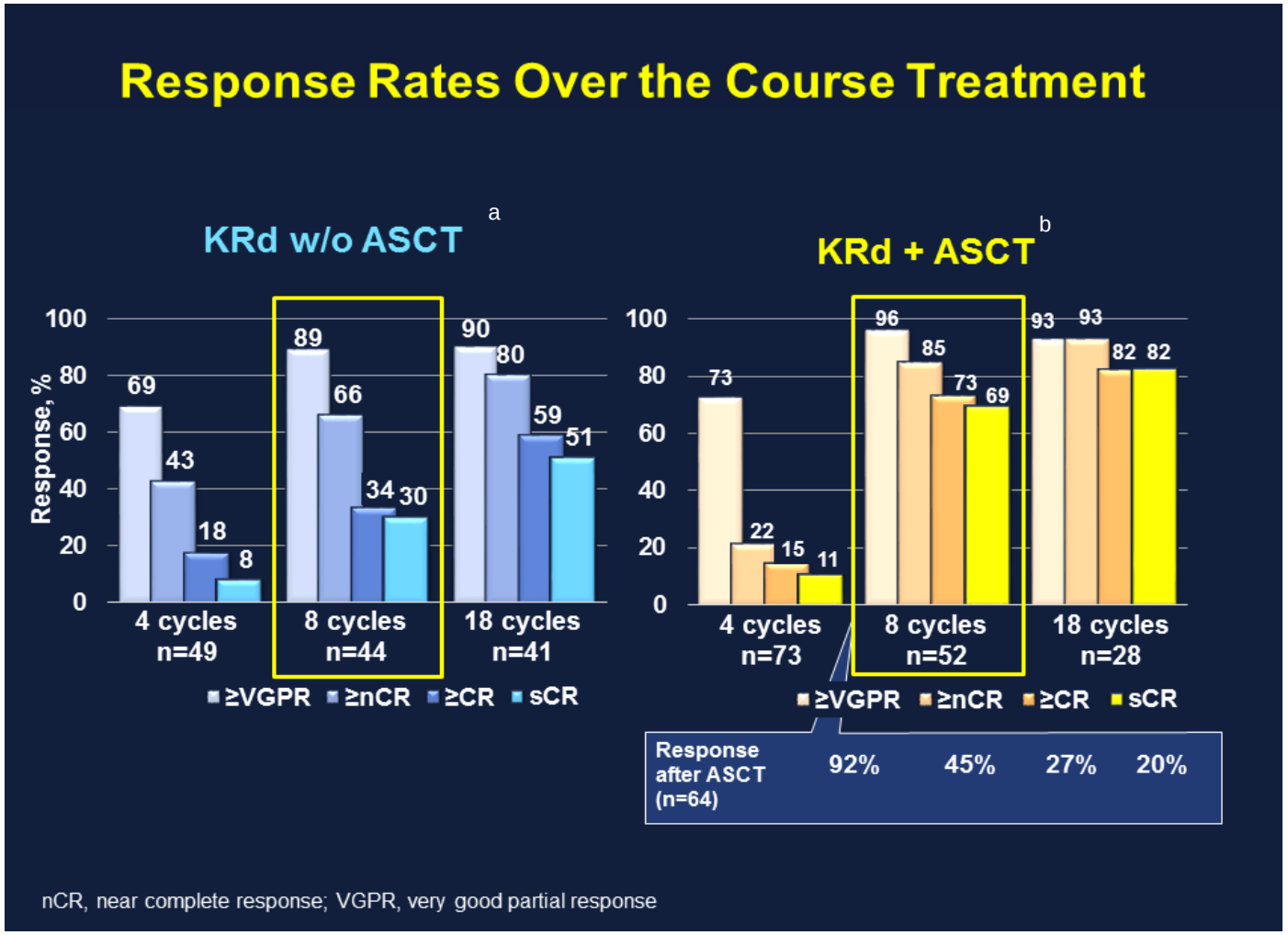
*Stratified

SWOG SO777 trial: VRd vs Rd
OS



*Stratified

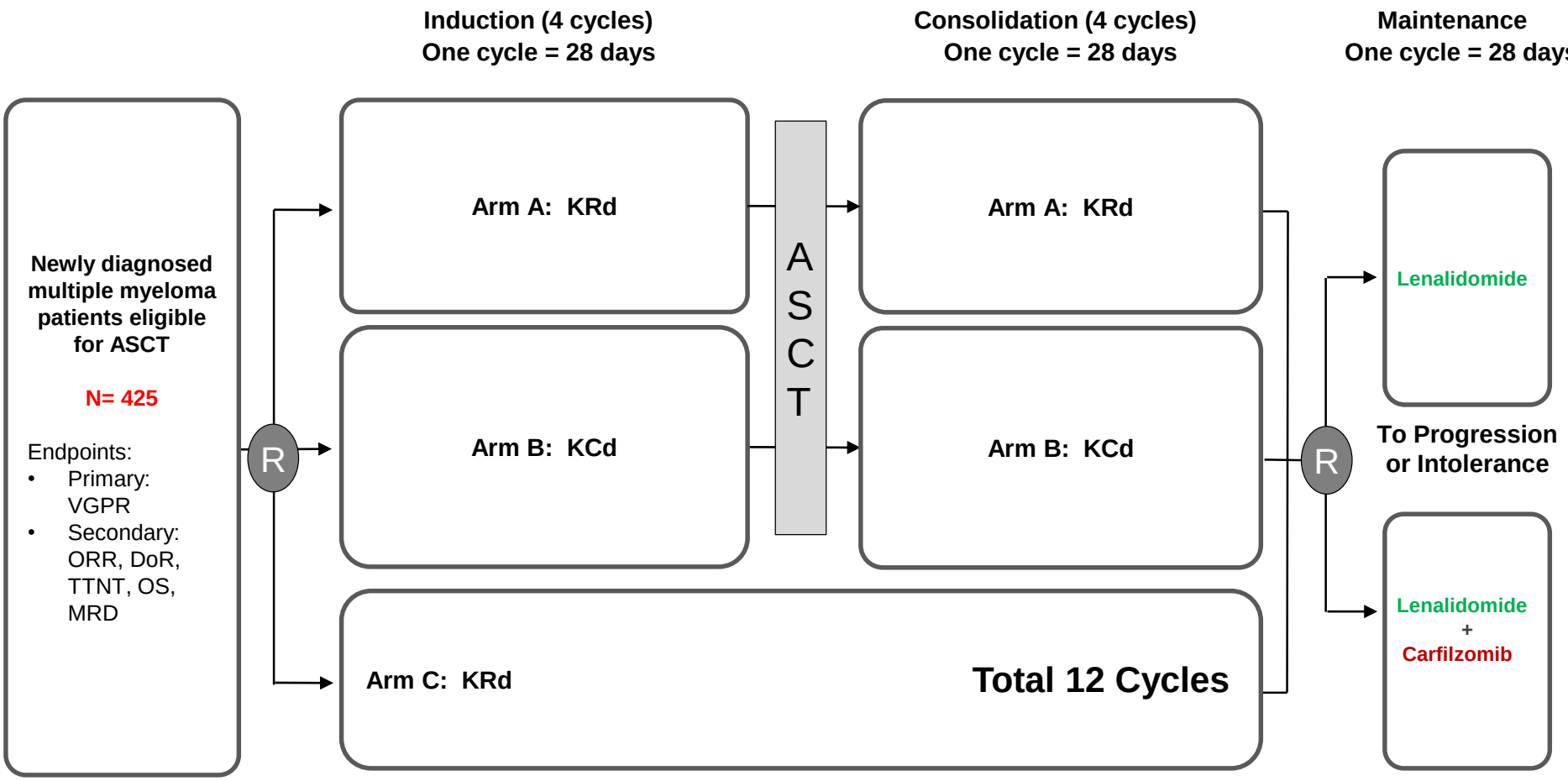
KRd induction followed by ASCT



a Phase 1/2 trial (N=53); extended treatment with KRd without (w/o) ASCT
b Phase 2 trial (N=72), extended KRd followed by ASCT

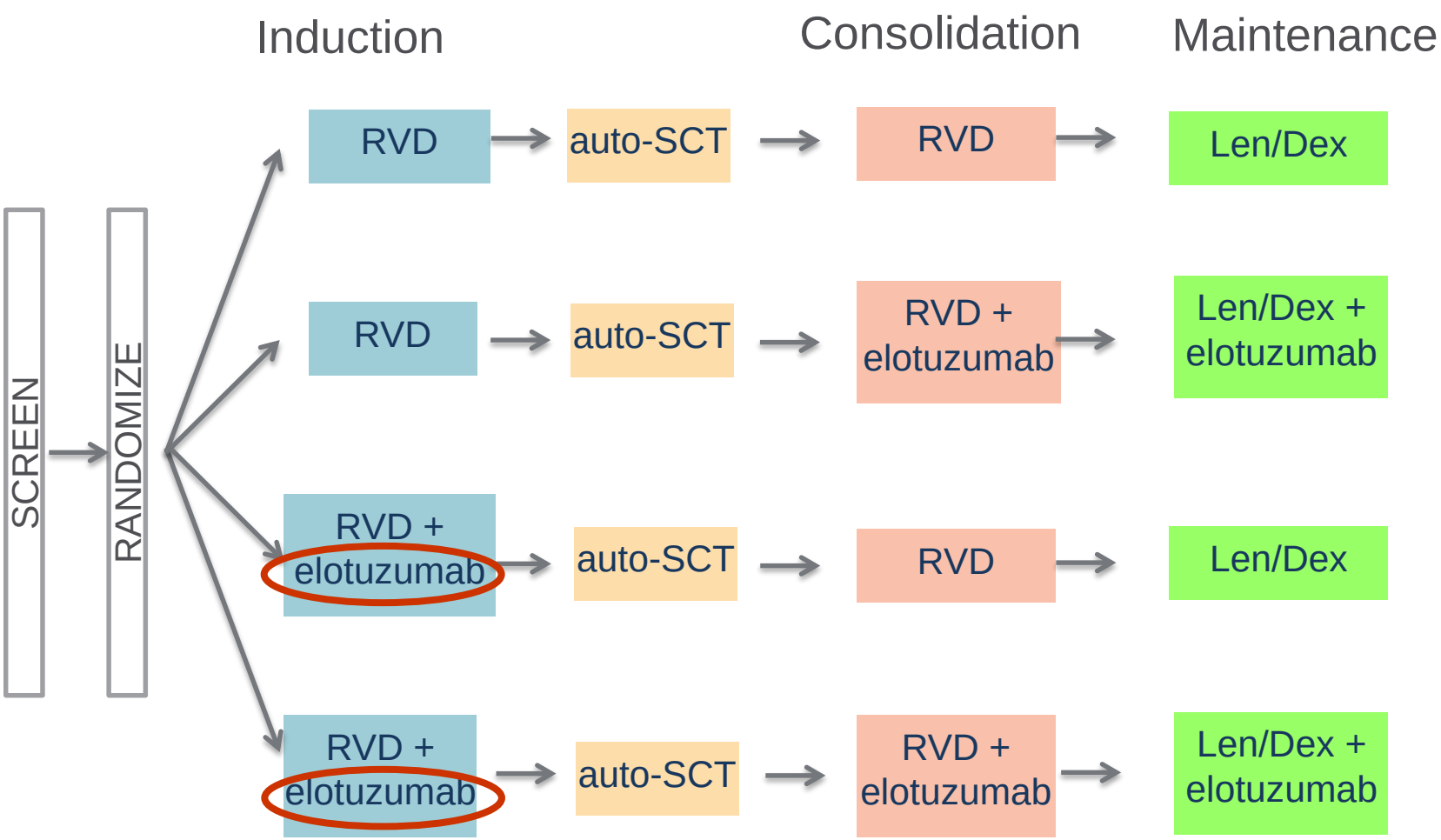
Jakubowiak A, et al. As presented at EHA 2016; abstract S101.

KRd vs KCd induction therapy
FORTE study

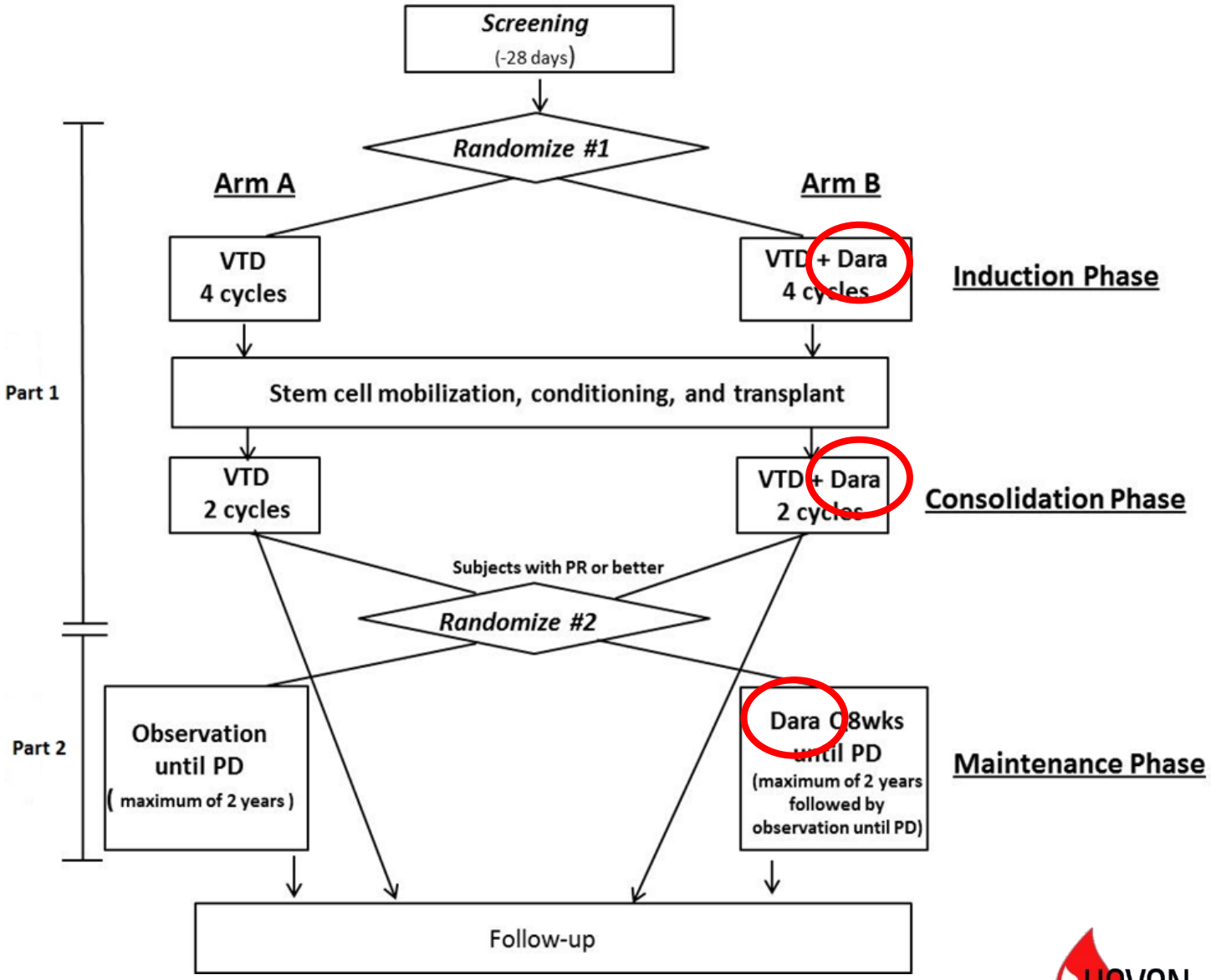


www.clinicaltrials.gov; NCT02203643.

Phase 3: Elotuzumab + VRD induction/consolidation + Lenalidomide maintenance in newly diagnosed MM (GMMG-HD6)



Study Scheme



TREATMENT AT RELAPSE:

DISEASE AND PATIENT RELATED FACTORS

The challenge when treating patients with relapsed or refractory disease is to select the optimal treatment by **BALANCING EFFICACY, TOXICITY and SEVERITY OF RELAPSE.**

It is necessary to consider:

❖ **DISEASE RELATED FACTORS**: quality and duration of response to initial therapy, class of agent used, indolent or aggressive relapse, high risk features such as cytogenetic abnormalities (del17p, t(4;14), ampl1q21), extramedullary disease (EMD), plasma cell leukemia;

❖ **PATIENT RELATED FACTORS**: age, performance status (PS), comorbidities, quality of life, renal function, hematopoietic reserve, prior drug exposure, ongoing toxicities from prior therapies, peripheral neuropathy (PN), venous thromboembolism (VTE).

Mohty B et al, Leukemia 2012; Ludwig H et al, Leukemia Research 2012; Castelli R et al, Oncology 2013

Main randomized trials in R/R MM until 2015

Regimen	ORR, %	CR, %	TTP/PFS, mo	OS
Bortezomib vs Dexamethasone[1]	38 vs 18	6 vs 1	6.2 vs 3.5	80% vs 66% @ 1 year
Bortezomib+Doxil vs Bortezomib[2]	44 vs 41	4 vs 2	9.3 vs 6.5	76% vs 65% @ 15 mo
Lenalidomide-dexamethasone vs Dexamethasone[3,4]	61/60.2 vs 19./24	14.1/15.9 vs 0.6/3.4	11.1/11.3 vs 4.7/4.7	29.6/NR vs 20.2/20.6 mo
Pomalidomide – dexamethasone vs Dexamethasone[5]	31 vs 10	1 vs 0	4 vs 1.9	12.7 vs 8.1 mo

1.Richardson PG, et al. N Engl J Med. 2005; 352:2487-2498 2.Orlowski RZ, et al J Clin Oncol. 2007: 3892-3901. 3.Weber DM, et al N Engl J Med. 2007; 357: 2133-2142 4. Dimopoulous M, et al. N Engl J med,. 2007; 357: 2123-2132, 5. San Miguel et al, Lancet Oncol 2013; 14(11): 1055-66

Treatment options for R/R MM

Transplant Eligible Patients

Bortezomib-based Induction

↓

ASCT

Transplant Inelegible Patients

VMP/MPT

FIRST RELAPSE

Second Transplant

- **Lenalidomide-dexamethasone**
- **Bortezomib-dexamethasone/Doxil**

SECOND RELAPSE

- **Lenalidomide-dexamethasone**
- **Bortezomib-dexamethasone/Doxil**
- **Pomalidomide-Dexamethasone***

*at second or subsequent relapse in pts previously treated with both lenalidomide and bortezomib

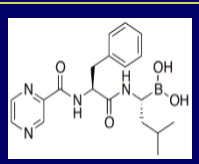
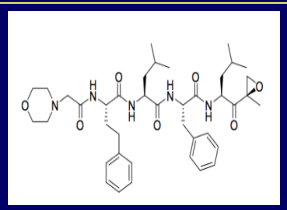
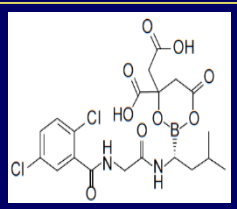
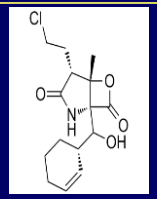
RETREATMENT WITH BORTEZOMIB

META-ANALYSIS of the efficacy and safety of Bortezomib retreatment in patients with multiple myeloma

	ORR, %	TTP, months	OS, months	PN G 3-4, %
All patients (n = 1051)	39	7,5	16,6	3
Prior therapies: ≤ 4 > 4	 43 29	 8,2 7,1	 13,3 20,0	
Therapy: - Bortezomib ± Dex (5 studies) - Combination (18 studies)	 51 36	 7,9 7,1	 19,2 16,1	
Only relapsed not refractory to Bortezomib	57	8,5	19,7	

Knopf K et al, ASH 2012

Proteasome inhibitors

	Bortezomib	Carfilzomib	Ixazomib	Marizomib
Structure & chemical class				
	Boronate[3]	Epoxyketone	Boronate[3]	Lactam/β-lactone[3]
Type of Inhibition	Reversible[4]	**Irreversible**[4]	Reversible[4]	**Irreversible**[4]
Mechanism of Action	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of tetrahedral intermediate with side-chain hydroxyl groups (with proteasome and other classes of proteases)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2] •Formation of covalent adduct with N-terminal threonine active site (exclusively within the proteasome)[6]	•Inhibits preferentially **β5**, but also **β1** and **β2**[2]	•Inhibits **all three** proteolytic activities, with **IC50 values** in the **nM range**[5]
Route of Administration	Intravenous, subcutaneous[4]	Intravenous[3]	Oral[4]	Intravenous[4]

Proteasome inhibitors vary by chemical class, mechanism of action, type of inhibition[1-6]

[1] Mujtaba and Dou. Discov Med 2011;12(67):471-80; [2] Muz et al., Drug Des Devel Ther 2016;10:217-26; [3] Wang. Oncology (Williston Park) 2011; 25 Suppl 2:19-24; [4] Kurtin and Bilotti. J Adv Pract Oncol 2013;4(5):307-21; [5] Potts et al., Curr Cancer Drug Targets 2011;11(3):254-84; [6] Arastu-Kapur et al. Clin Cancer Res 2011;17:2734-43.

Monoclonal antibodies

Target	Antibody	Mechanism of action	Activity as single agent	Activity/under evaluation in combo
CS1 (SLAM F7)	**Elotuzumab (Humanized IgG1k)**	ADCC Enhance NK activity Interference with cell interaction	-	+ VD + Rd
CD38	**Daratumumab (Fully human IgG1k)**	ADCC CDC ADCP	+	+ V-based + Rd + Pd
	Isatuximab (SAR650984; chimeric IgG1k)	Direct induction of apopotosis Modulation CD38 function	+	+ VCD + Rd
	MOR202 (fully human IgG1λ)		+	

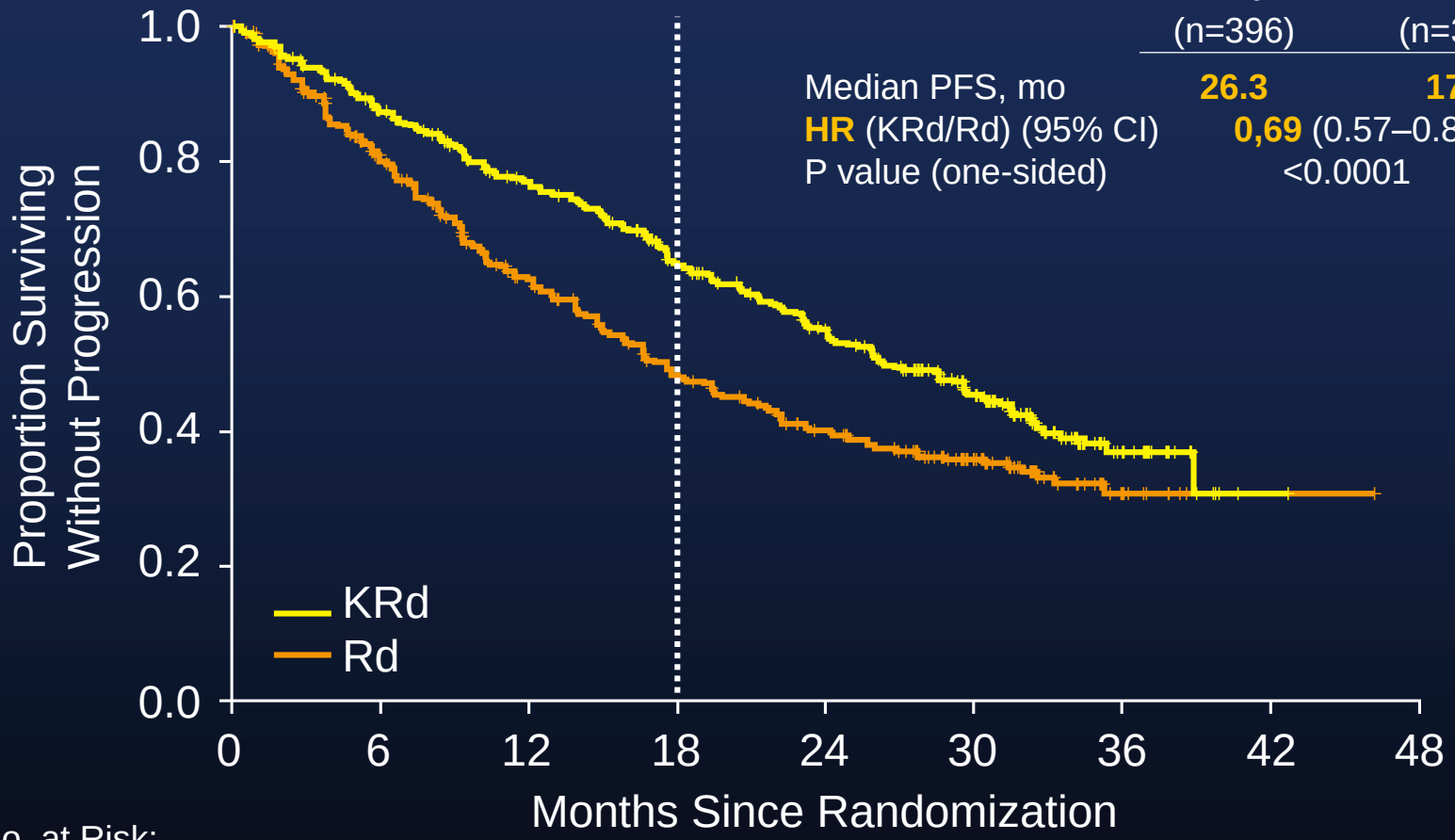
MM: multiple myeloma; ADCC: antibody depandent cell-mediated cytotoxicity; ADCP: antibody depedent cell-mediated phagocytosis; CDC; complement dependent cytotoxicity; VD: bortezomib-dexamethasone; Rd: lenalidomide;dexamethasone; Pd: pomalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone; V: bortezomib

Relapse following VMP or VTD/VCD based ASCT

- Lenalidomide-dex

- Lenalidomide-dex + third agent
  - Carfilzomib (ASPIRE)
  - Elotuzumab (ELOQUENT)
  - Ixazomib (TOURMALINE)
  - Daratumumab (POLLUX)

ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd) PFS



No. at Risk:

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

Stewart K et al, NEJM 2015

Safety: KRd vs Rd

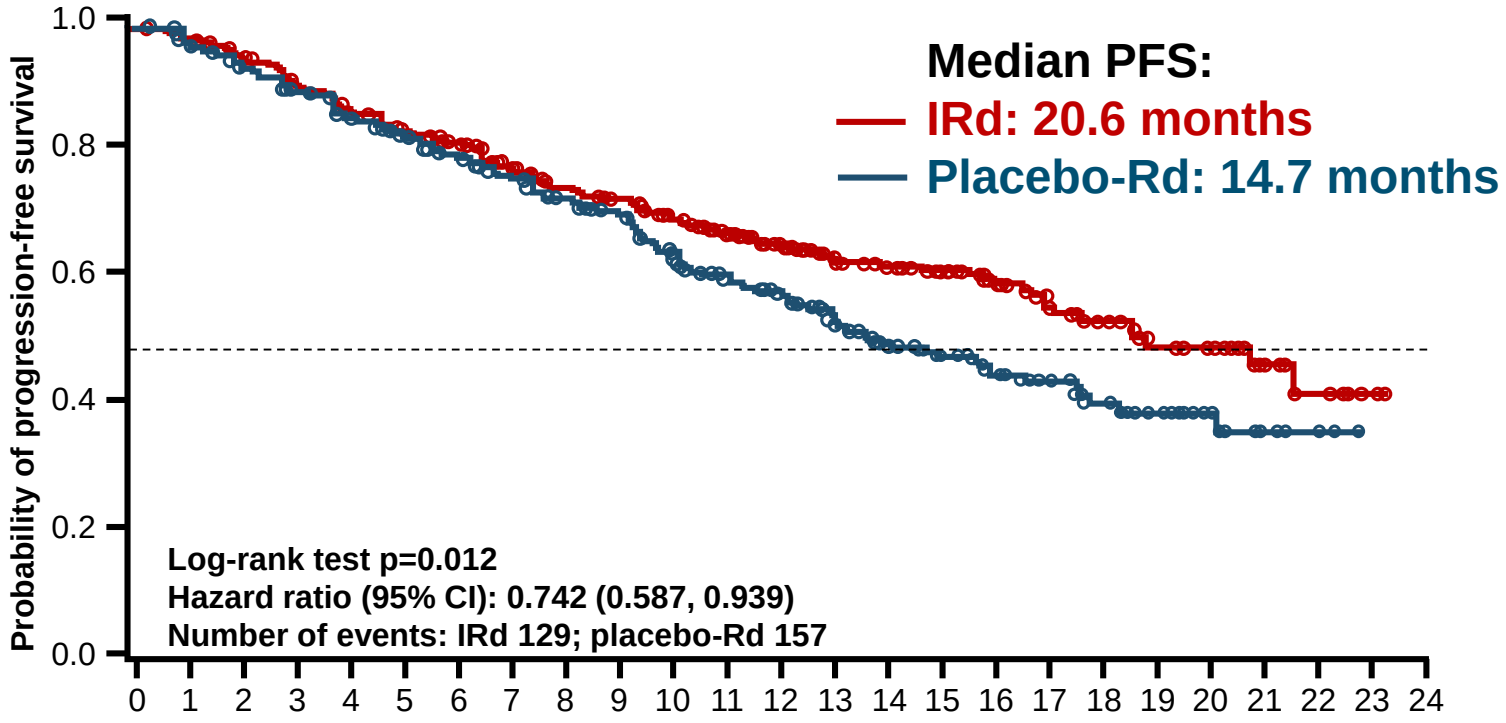
Category	KRd (n=392)	Rd (n=389)
Median treatment duration, weeks	88.0	57.0
Any AE, % Grade ≥3 treatment-emergent AE	96.9 83.7	97.2 80.7
Treatment discontinuations, % PD AE	69.9 39.8 15.3	77.9 50.1 17.7
Serious AE, %	59.7	53.7
Deaths within 30 days of last dose, % PD Aes	7.7 0.5 6.9	8.5 1.3 6.9

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

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

Stewart AK, et al. N Engl J Med 2015;372:142–52.

Final PFS analysis(median fup: 23 mos): A significant, 35% improvement in PFS with IRd vs placebo-Rd



Number of patients at risk:																								
IRd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0
Placebo-Rd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0

Median follow-up: ~15 months

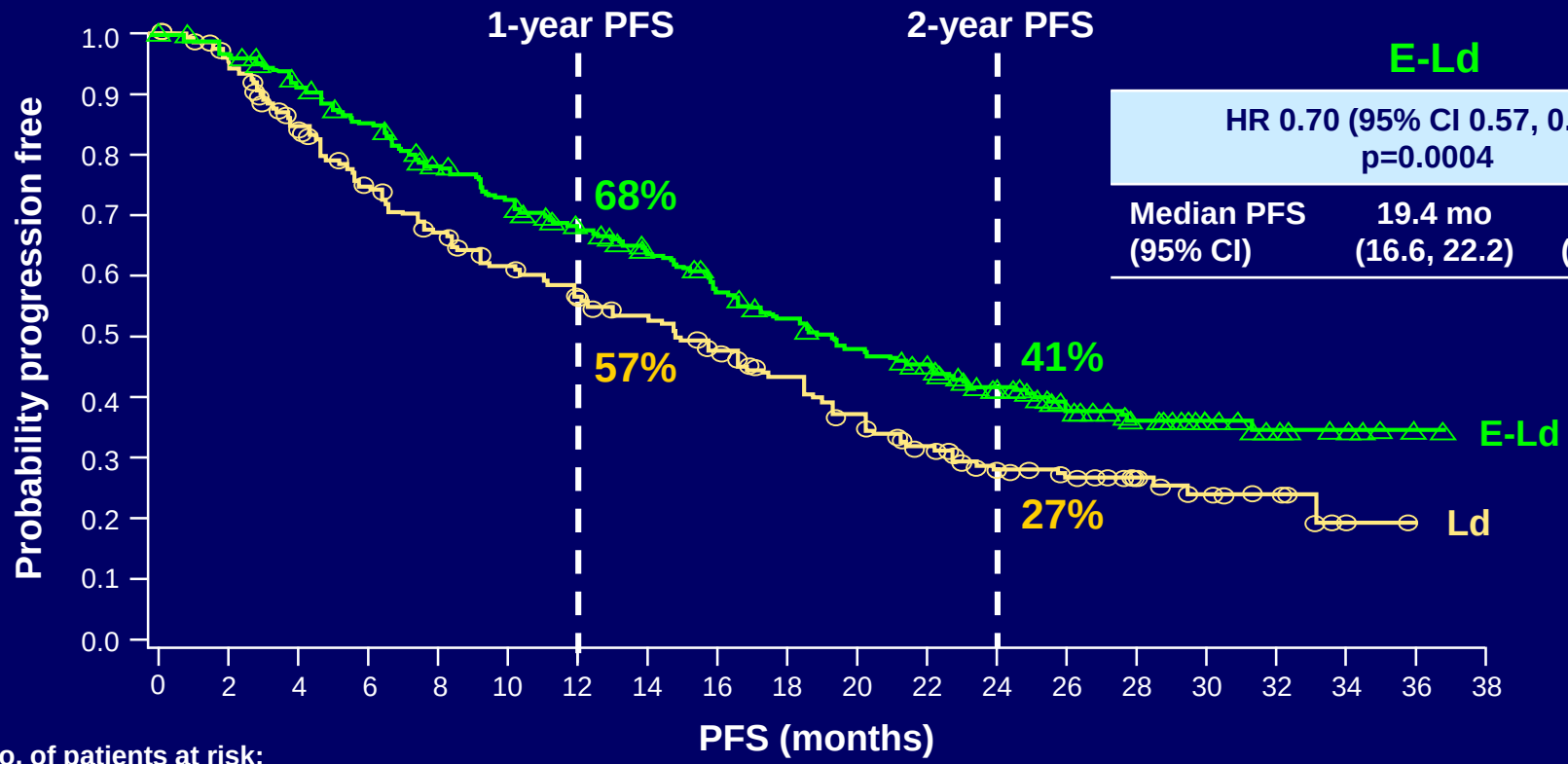
Moreau P et al, NEJM 2016

AEs after median follow-up of 23 months: increased rates with IRd driven by low-grade events

	IRd (N=361), %			Placebo-Rd (N=359), %		
Preferred terms	All-grade	Grade 3	Grade 4	All-grade	Grade 3	Grade 4
AEs overlapping with lenalidomide						
Diarrhea	45	6	0	39	3	0
Constipation	35	<1	0	26	<1	0
Nausea	29	2	0	22	0	0
Vomiting	23	1	0	12	<1	0
Rash	36	5	0	23	2	0
Back pain	24	<1	0	17	3	0
Upper respiratory tract infection	23	<1	0	19	0	0
Thrombocytopenia	31	12	7	16	5	4
AEs with proteasome inhibitors						
Peripheral neuropathy	27	2	0	22	2	0
Peripheral edema	28	1	0	20	1	0
AEs with lenalidomide						
Thromboembolism	8	2	<1	11	3	<1
Neutropenia	33	18	5	31	18	6

Moreau P et al, NEJM 2016

ELOQUENT-2: Elo Rd vs Rd Progression-Free Survival



	E-Ld	Ld
HR 0.70 (95% CI 0.57, 0.85); p=0.0004		
Median PFS (95% CI)	19.4 mo (16.6, 22.2)	14.9 mo (12.1, 17.2)

No. of patients at risk:

E-Ld	321	303	279	259	232	215	195	178	157	143	128	117	85	59	42	32	12	7	1	0
Ld	325	295	249	216	192	173	158	141	123	106	89	72	48	36	21	13	7	2	0	0

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

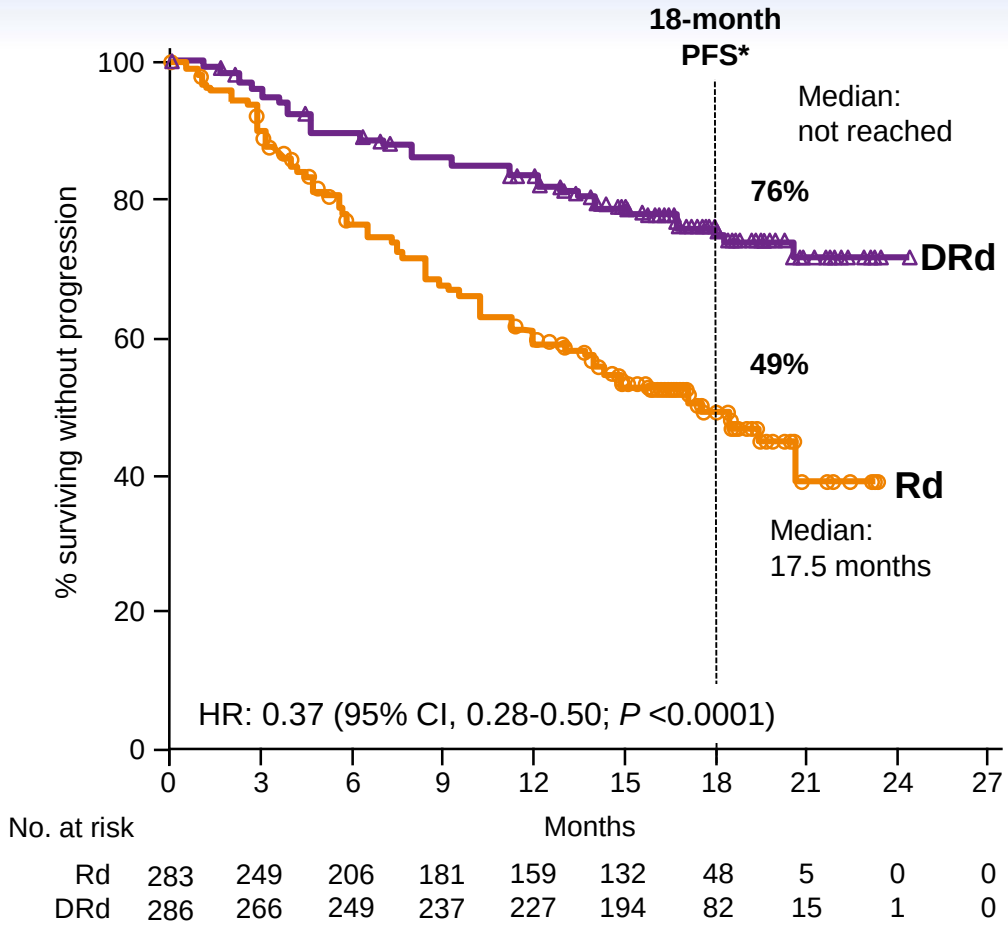
PFS analysis used the primary definition of PFS

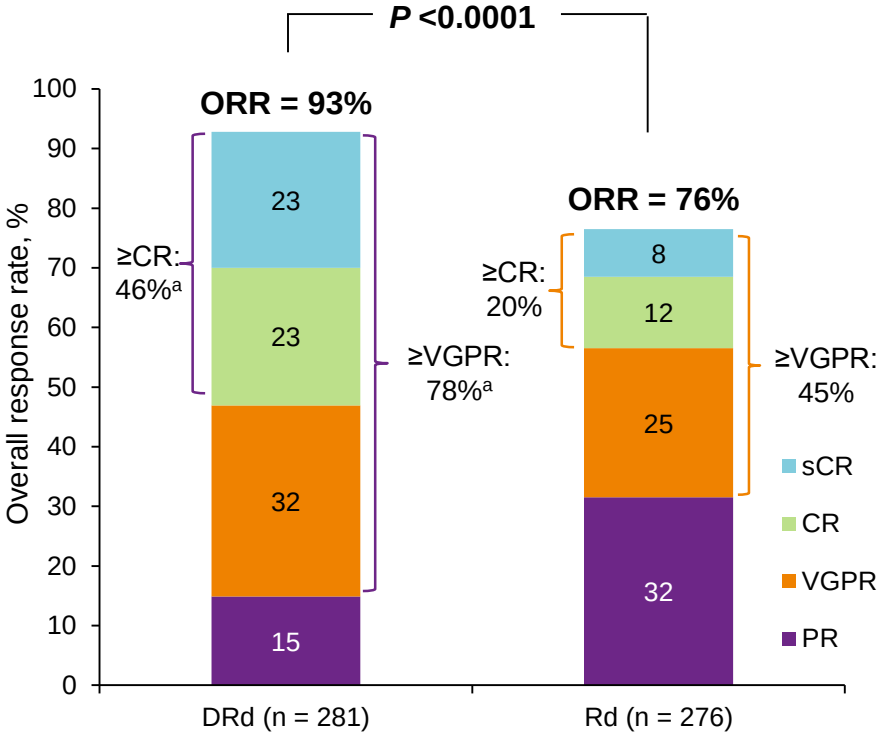
Infusion Reactions

Events, n (%)	E-Ld (n=318)		
	Grade 1/2	Grade 3	Grade 4/5
Infusion reaction	**29 (9)**	**4 (1)**	**0**
Pyrexia	10 (3)	0	0
Chills	4 (1)	0	0
Hypertension	3 (1)	1 (<1)	0

- **Infusion reactions occurred in 10% of patients**
- **70% of infusion reactions occurred with the first dose**
- **No Grade 4 or 5 infusion reactions**
- **Elotuzumab infusion was interrupted in 15 (5%) patients due to an infusion reaction (median interruption duration 25 minutes)**
- **2 (1%) patients discontinued the study due to an infusion reaction**

POLLUX: Dara Rd vs Rd (ASH 2016)





- **Median follow-up: 17.3 (range, 0-24.5) months**
- Responses continue to deepen in the DRd group with longer follow-up

Note: PFS: ITT population; ORR: response-evaluable population.
*Kaplan-Meier estimate;
a*P* <0.0001 for DRd vs Rd.

Lenalidomide-Based Studies

	POLLUX DRd [1]	ASPIRE KRd [2]	ELOQUENT-2 ERd [3,4]	TOURMALINE-MM1 IxaRd[5]
PFS HR vs Rd (95% CI)	0.37 (0.27-0.52)	0.69 (0.57-0.83)	0.73 (0.60-0.89)	0.74 (0.59-0.94)
ORR	93%	87%	79%	78%
≥ VGPR	76%	70%	34%	48%
≥ CR	43%	32%	5%	14%
Duration of response, mos	NE	28.6	20.7	20.5
OS HR vs Rd (95% CI)	0.64 (0.40-1.01)	0.79 (0.63-0.99)	0.77 (0.61-0.97)	NE

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

Not only efficacy!!!!

Lenalidomide-Based Studies

	POLLUX DRd[1]	ASPIRE KRd[2]	ELOQUENT-2 ERd[3,4]	TOURMALINE-MM1 IxaRd[5]
N° Median lines	1 (1-11) 82% 1-2	2	2	59% 1-2
Prior Len (%)	18	20	5	12
Prior Bort (%)	86 (PI)	66	68	69
Refractory pop. (%)	28	UK	35	12 (7% primary)
Bort-refractory (%)	20	15	22	NA
HR cyto (%)	9	12	31	21

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

Lenalidomide-Based Studies: sub-groups analysis of PFS advantage over Rd of the triplet combination

	POLLUX DRd [1]	ASPIRE KRd [2]	ELOQUENT-2 ERd [3,4]	TOURMALINE-MM1 IxaRd [5]
HR overall population	0,37	0,69	0,73	0,74
Higher Age	**HR 0,11** (> 75 yr)	HR 0,87 (> 65 yr)	0,65 (≥ 65 yr)	
HR cyto	@18 mos: 66% vs 85%	Med PFS 23 vs 29 mos	**0,65**	Med PFS 21 vs 20,6 mos
Moderate renal impairment (Crea Cl 30-60)	UK	UK (93% crea clear > 50)	**0,56** (Crea Clear < 60)	UK
Refractory population	HR 0,47	UK	**0,56**	0,71
Bort exposure	=	=	=	=
Bort refractory	HR 0,50	HR 0,79 vs 0,69	UK	UK

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

Burden on Healthcare System and Patients

	Ixazomib-Rd	Carfilzomib-Rd	Elotuzumab-Rd	Dara-Rd
Route of administration	**PO**	IV	IV	IV
Dosing schedule	Days 1, 8, and 15 of 28-day cycle	Days 1, 2, 8, 9, 15, and 16 of 28-day cycle	Days 1, 8, 15, 22 of 28-day of cycles 1-2 then Days 1 and 15, cycle 3+	Days 1, 8, 15, 22 of cycles 1-2 Days 1, 15 of cycles 3-6 Day 1 of cycle 7+
Hospital/clinic visit	Every 4 ks	Twice a k	Weekly x 8 then twice montly	Weekly x 8 then twice monthly
Minimum clinic visits based on 18 cycles	**18**	96	44	28
Administration time in clinic/ hospital per visit	**0 hours**	Over 2 hrs	About 2- 5 hrs	3-6 hrs
Premedication	N	N	Y	Y
Prehydration	N	Additional IV hydration needed especially before each dose in cycle 1, may be in other cycles	N	N

Which regimen to choose with Ld?

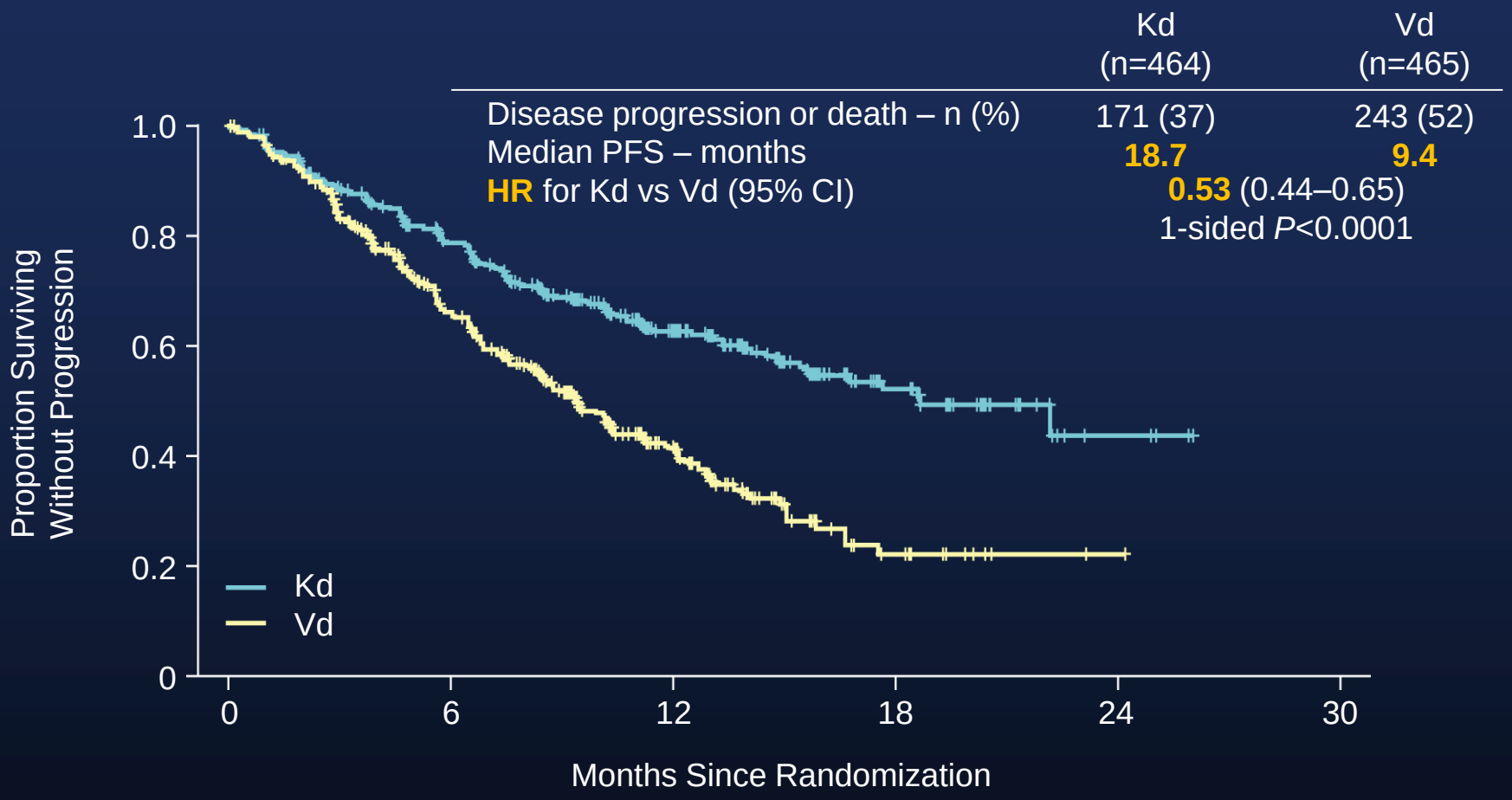
Young patient, no cardiac co-morbidities, aggressive relapse, need to achieve MRD negativity (HR cyto) → **KRd**, **Dara-Rd**

Elderly patient, indolent disease, biochemical relapse, RI?, del 17p? → **Elo-Rd**

Elderly patient, difficulties of access to the hospital → **Ixa-Rd**

Relapse following Ld or lena maintenance

ENDEAVOR: Carfilzomib and Dexamethasone (Kd) vs Bortezomib and Dexamethasone (Vd): PFS

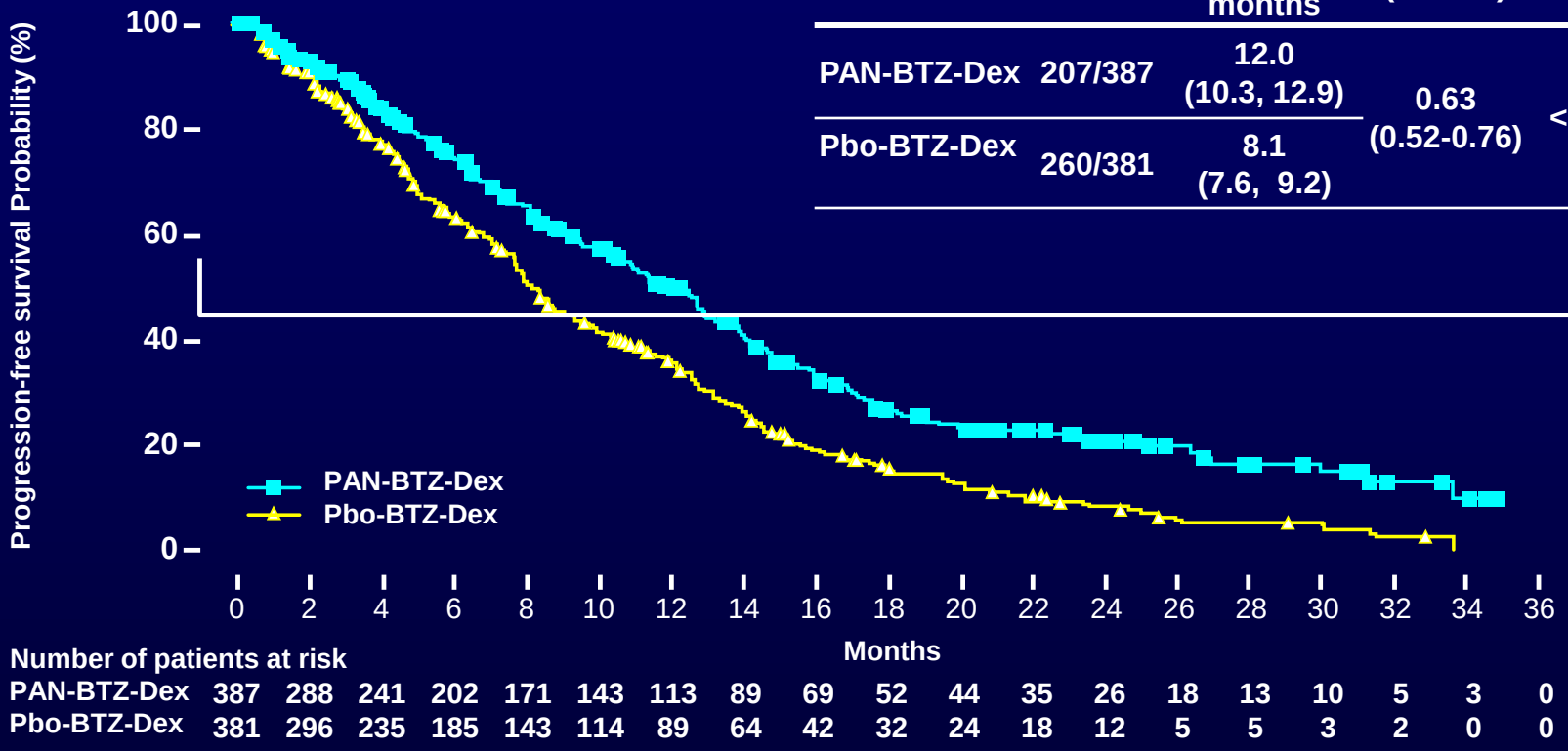


- **Median follow-up: 11.2 months**
- **OS advantage with extended FUP (IMW New Delhi 2017)**

Dimopoulos D et al, Lancet Oncology 2016

Panorama 1 : VD vs VD-panobinostat, PFS

	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)		



Number of patients at risk

PAN-BTZ-Dex	387	288	241	202	171	143	113	89	69	52	44	35	26	18	13	10	5	3	0
Pbo-BTZ-Dex	381	296	235	185	143	114	89	64	42	32	24	18	12	5	5	3	2	0	0

San Miguel et al. Lancet Oncology 2014

Non-Hematologic AEs

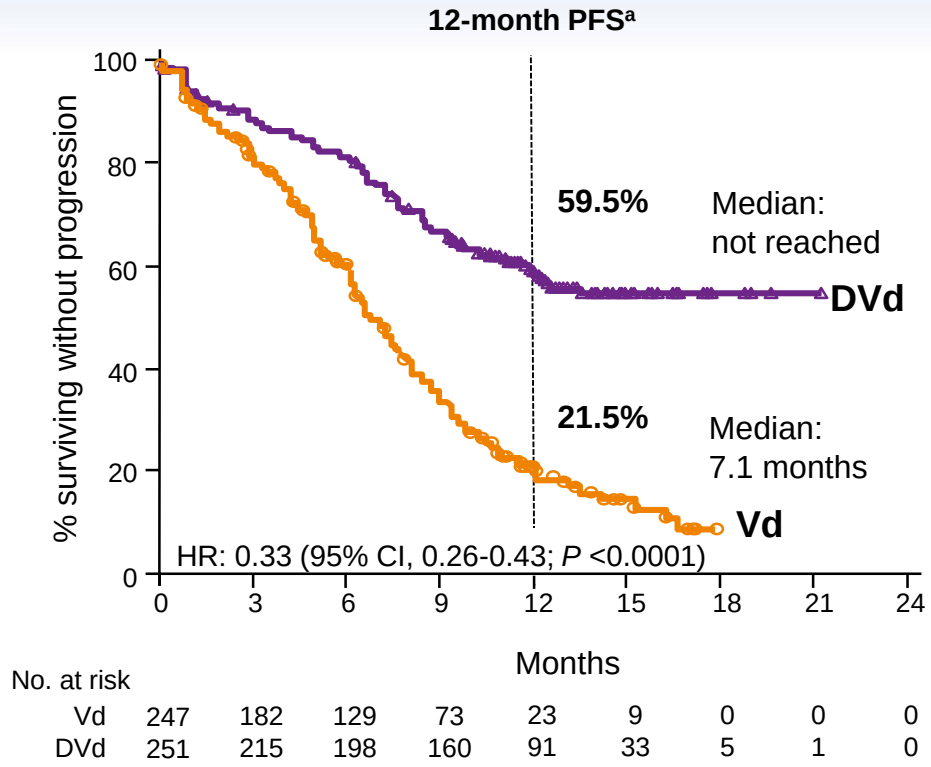
Grade 3/4 Diarrhea and Asthenia/Fatigue Observed

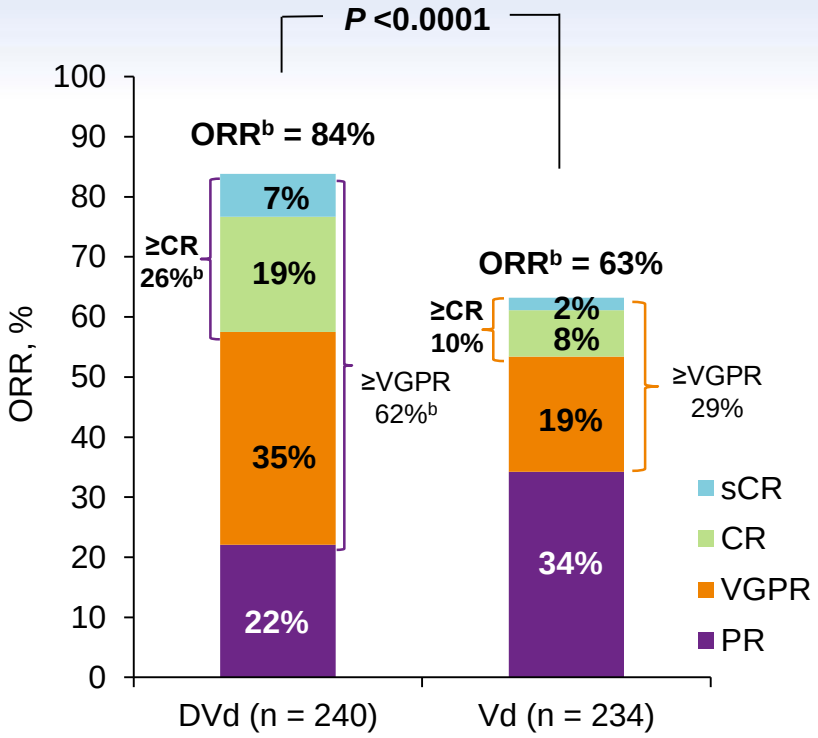
	PAN-BTZ-Dex (n = 381)		Pbo-BTZ-Dex (n = 377)	
Preferred term – %	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	68.2	25.5	41.6	8.0
Peripheral neuropathy[a]	60.6	17.6	67.1	14.6
Asthenia/fatigue	57.0	23.9	40.6	11.9
Nausea	36.2	5.5	20.7	0.5
Peripheral edema	28.6	2.1	19.1	0.3
Decreased appetite	28.1	3.1	12.5	1.1
Constipation	26.8	1.0	32.6	1.1
Pyrexia	26.0	1.3	14.9	1.9
Vomiting	25.7	7.3	13.0	1.3
Cough	21.3	1.0	18.6	0

- Discontinuation due to diarrhea (4.5%) and fatigue (2.9%) on PAN arm

[a]Combined incidence of hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy.

CASTOR: Dara Vd vs Vd (ASH 2016)





- Median (range) follow-up: 13.0 (0-21.3) months
- Responses continue to deepen in the DVd group with longer follow-up
  - An additional 7% achieved ≥CR with longer follow-up

ITT, intent to treat.
Note: PFS: ITT population; ORR: response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.

PI-Based Studies

	Daratumumab DVd vs Vd [5]	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
PFS HR (95% CI)	0.39 (0.28-0.53)	0.53 (0.44-0.65)	0.63 (0.52-0.76)	0.72 (0.59-0.88)
PFS Median mo	NE	18.7	12.0	9.7
≥ VGPR	59%	54%	28%	36%
≥ CR	19%	13%	11%	4%
Duration of response, mos	NE	21.3	13.1	11.4
OS HR (95% CI)	0.77 (0.47, 1.26)	0.79 (0.58-1.08)	0.94 (0.78-1.14)	0.61 (0.32-1.15)

1. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38.
2. San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206.
3. San-Miguel JF, et al. Blood. 2015;126:Abstract 3026.
4. Jakubowiak A, et al. Blood. 2016;[Epub ahead of print].
5, Palumbo A et al, NEJM 2016

Palumbo et al. Presented at ASCO 2016 (Abstract LBA4), oral presentation

PI-Based Studies

	Daratumumab DVd vs Vd [5]	Carfilzomib Kd vs Vd[1]	Panobinostat PVd vs Vd[2,3]	Elotuzumab EVd vs Vd[4]
N° Median lines	2	2	1	1
Prior Len (%)	71	38	19	50
Prior PIs (%)	67	54	44	49
Refractory pop. (%)	30	UK	35	UK
Len-refractory (%)	30	24	UK	UK
HR cyto (%)	16 (del 17p) 8 (t 4;14)	21	5	NA

1. Dimopoulos MA, et al. Lancet Oncol. 2016;17:27-38.
2. San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206.
3. San-Miguel JF, et al. Blood. 2015;126:Abstract 3026.
4. Jakubowiak A, et al. Blood. 2016;[Epub ahead of print].
5, Palumbo A et al, NEJM 2016

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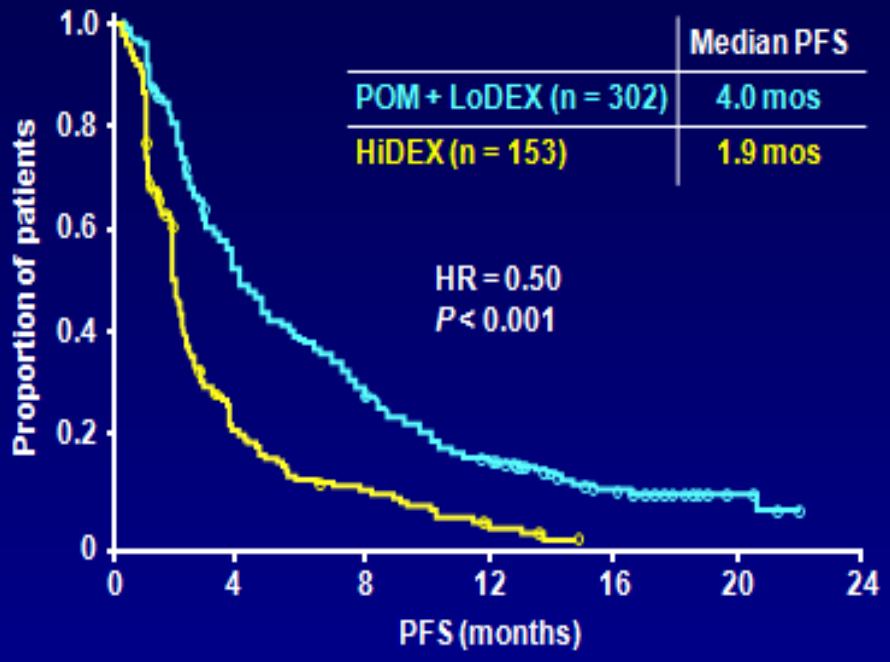
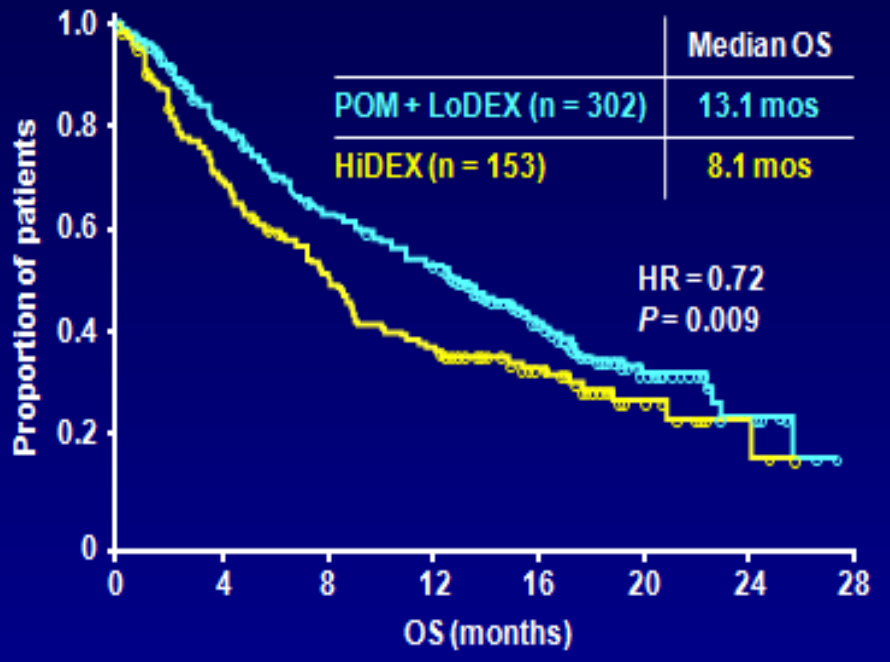
Adverse events

	COMBINATION	GRADE 3 / 4 (%)
ASPIRE	Rd + Carfilzomib	HYPERTENSION (4) CARDIAC FAILURE (4) ACUTE RENAL FAILURE (3)
ELOQUENT	Rd + Elotuzumab	INFUSION REACTION (1)
TOURMALINE	Rd + Ixazomib	RASH (5)
POLLUX	Rd + Daratumumab	INFUSION REACTION (5)
PANORAMA	Vd + Panobinostat	DIARRHEA (25) FATIGUE (24) VOMITING (7)
ENDEAVOR	Kd	HYPERTENSION (9) DYSPNEA (5) CARDIAC FAILURE (5)
POLLUX	Vd + Daratumumab	INFUSION REACTION (9) HYPERTENSION (7)

Beyond 1 – 3 prior lines

MM-003 trial: Pom-dex vs Dex

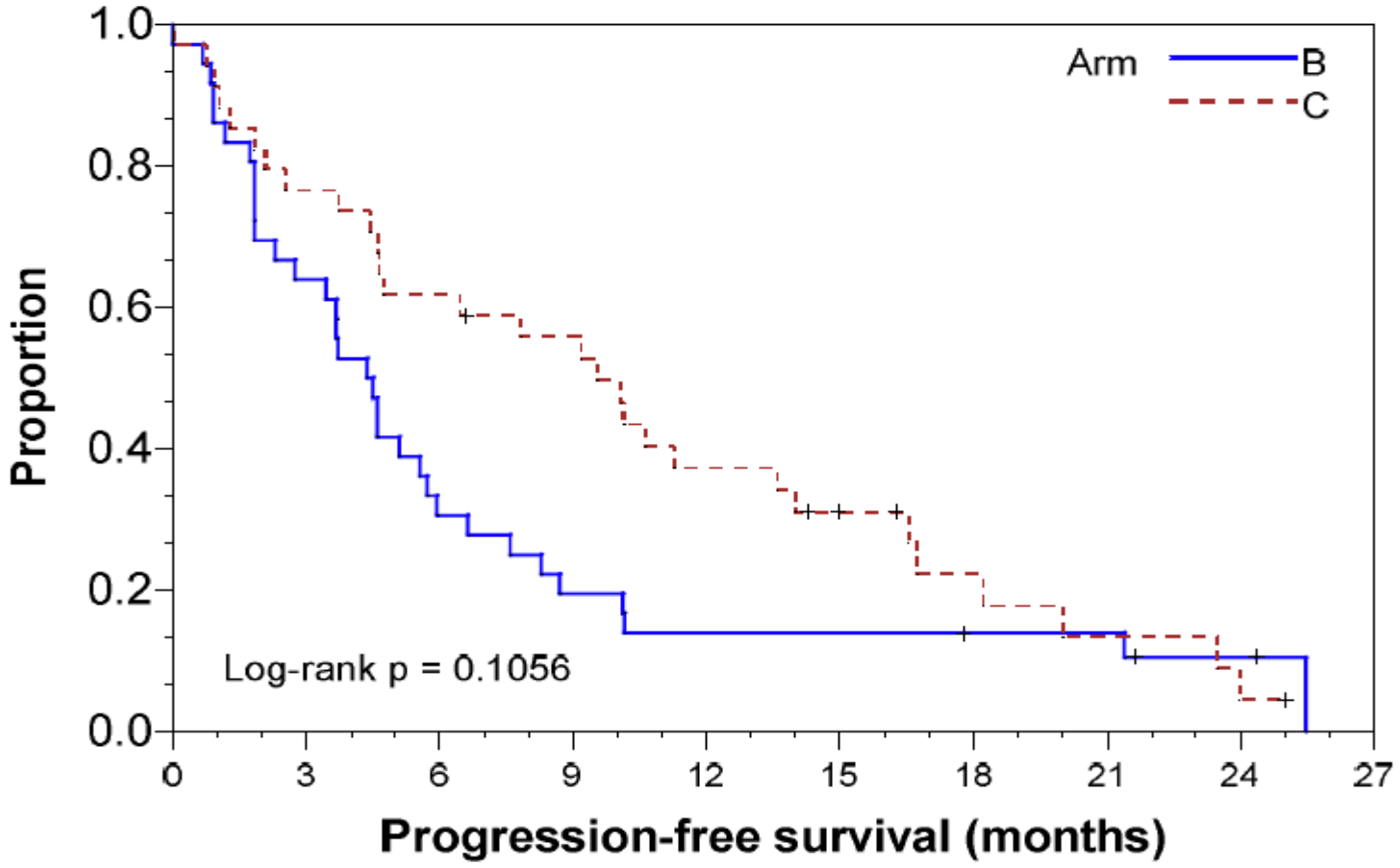




- Compared with HiDEX, POM + LoDEX significantly improved PFS (4.0 vs 1.9 months; P < 0.001) and OS (13.1 vs 8.1 months; *P* = 0.009)
- 85 patients (56%) in the HiDEX arm received subsequent POM

San Miguel et al, Lancet Oncol 2013;14:1055-66
Dimopoulos et al, Blood 2013 (suppl,abstr 408)

Phase II randomized trial of Pom-dex vs Cyclo-Pom-dex: PFS



Arm	N	Event	Censored	Median (95% CI)
B	36	33 (92%)	3 (8%)	4.4(2.3, 5.7)
C	34	29 (85%)	5 (15%)	9.5(4.6, 14.0)

Baz RC et al, Blood 2016

Cyclophosphamide : 400 mg oral D1, D8, D15

DARATUMUMAB SINGLE AGENT

Patients received a median of **5 prior lines** of therapy

86.5% of patients were double refractory to a PI and IMiD

	16 mg/kg (N = 148)	
Response	n (%)	95% CI
ORR	46 (31.1)	23.7-39.2
Clinical benefit (ORR + MR)	55 (37.2)	29.4-45.5
VGPR or better (sCR+CR+VGPR)	20 (13.5)	8.5-20.1
CR or better (sCR+CR)	7 (4.7)	1.9-9.5
sCR	3 (2.0)	0.4-5.8
CR	4 (2.7)	0.7-6.8
VGPR	13 (8.8)	4.8-14.6
PR	26 (17.6)	11.8-24.7
MR	9 (6.1)	2.8-11.2
SD	68 (45.9)	37.7-54.3
PD	18 (12.2)	7.4-18.5
NE	7 (4.7)	1.9-9.5

CI, confidence interval; ORR, overall response rate; MR, minimal response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

- Median DOR = 7.6 (95% CI, 5.6-NE) months
- Median (range) time to response = 0.95 (0.5-5.6) months
- Of 10 patients with an initial PR, 7 went to on to achieve VGPR with further treatment and 3 patients with an initial PR achieved deeper responses of CR (1 patient) and sCR (2 patients)
- Responses in 4 patients with an initial VGPR continued to deepen to CR (3 patients) and sCR (1 patient)

1. Lokhorst HM, et al. *N Engl J Med*. 2015;373:1207-19.
2. Lonial S, et al. *Lancet*. 2016;387:1551-60.
3. Usmani SZ, et al. *Blood*. 2016;128:37-44.

Treatment options for R/R MM

Transplant Eligible Patients

Bortezomib-based Induction

↓

Autologous Transplant

Transplant Inelegible Patients

VMP/MPT
Rd

FIRST RELAPSE

Second Transplant

Rd, KRd, ERd,IRd, Dara-Rd

Vd, EVd, Kd, Dara-Vd

SECOND RELAPSE

Rd,KRd,ERd,Ird, Dara-Rd

Kd

Vd,EVd,Kd, Dara-Vd

Pomalidomide-Dexamethasone

Daratumumab Single Agent

Clinical trials
(MoAbs, check-point inhibitors, venetoclax, selinexor, anti BCMA…)

Conclusions

- Availability of newer combos in R/R MM and of newer class of agents
- High response rates, extended TTP, PFS and TTNT
- Favorable safety profile
- Warning for cardiac toxicity of Carfilzomib
- Infusion reactions for MoAbs
- Similarity but also differences in between studies (previous drugs exposure/refractoriness, drugs duration, cytogenetic high-risk cut off)
- **Need to identify sub-groups of patients mostly benefiting from each combo**
- **Need to identify from the very beginning a long-term treatment strategy**