Highlights from EHA

Mieloma Multiplo

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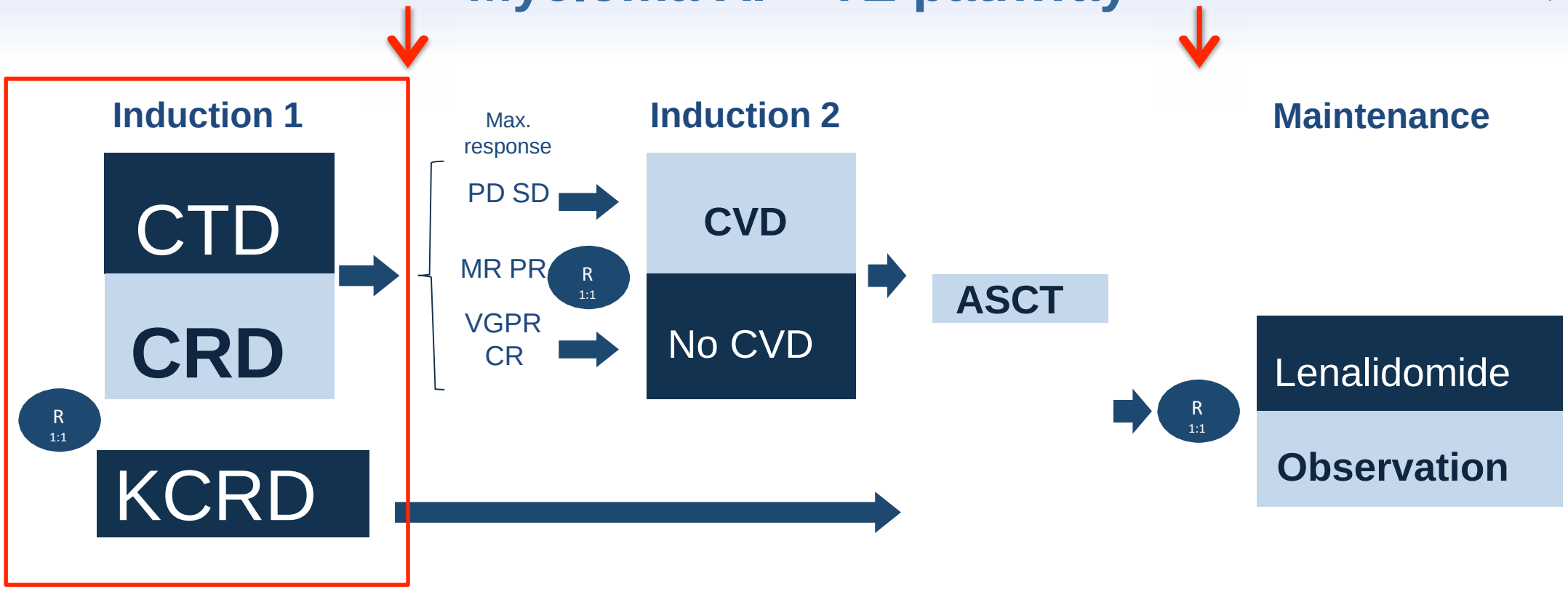
Myeloma XI – TE pathway

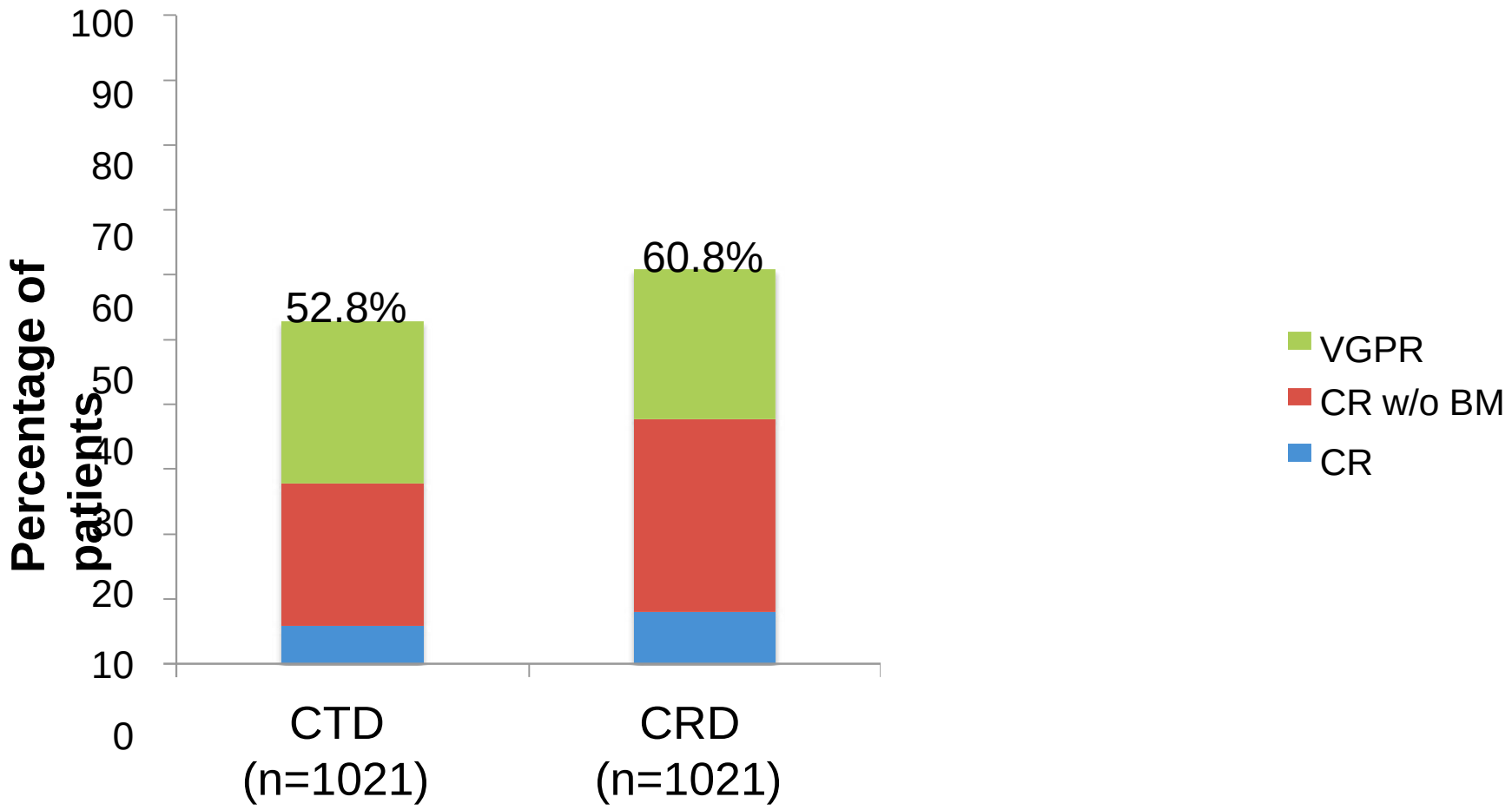


This analysis compares toxicity and response to KCRD vs triplets pre and post - ASCT

Patients were ineligible for the CVD randomisation if they had achieved a CR or VGPR to induction (went straight to ASCT if eligible or maintenance if not) or had PD or SD to induction (all primary refractory received CVD). Patients were ineligible for the maintenance randomisation if they failed to respond to lenalidomide as their induction IMiD or failed to respond to all trial induction treatment, had PD or had previous or concurrent active malignancies. Dose adjustments for renal impairment and following AEs were permitted.

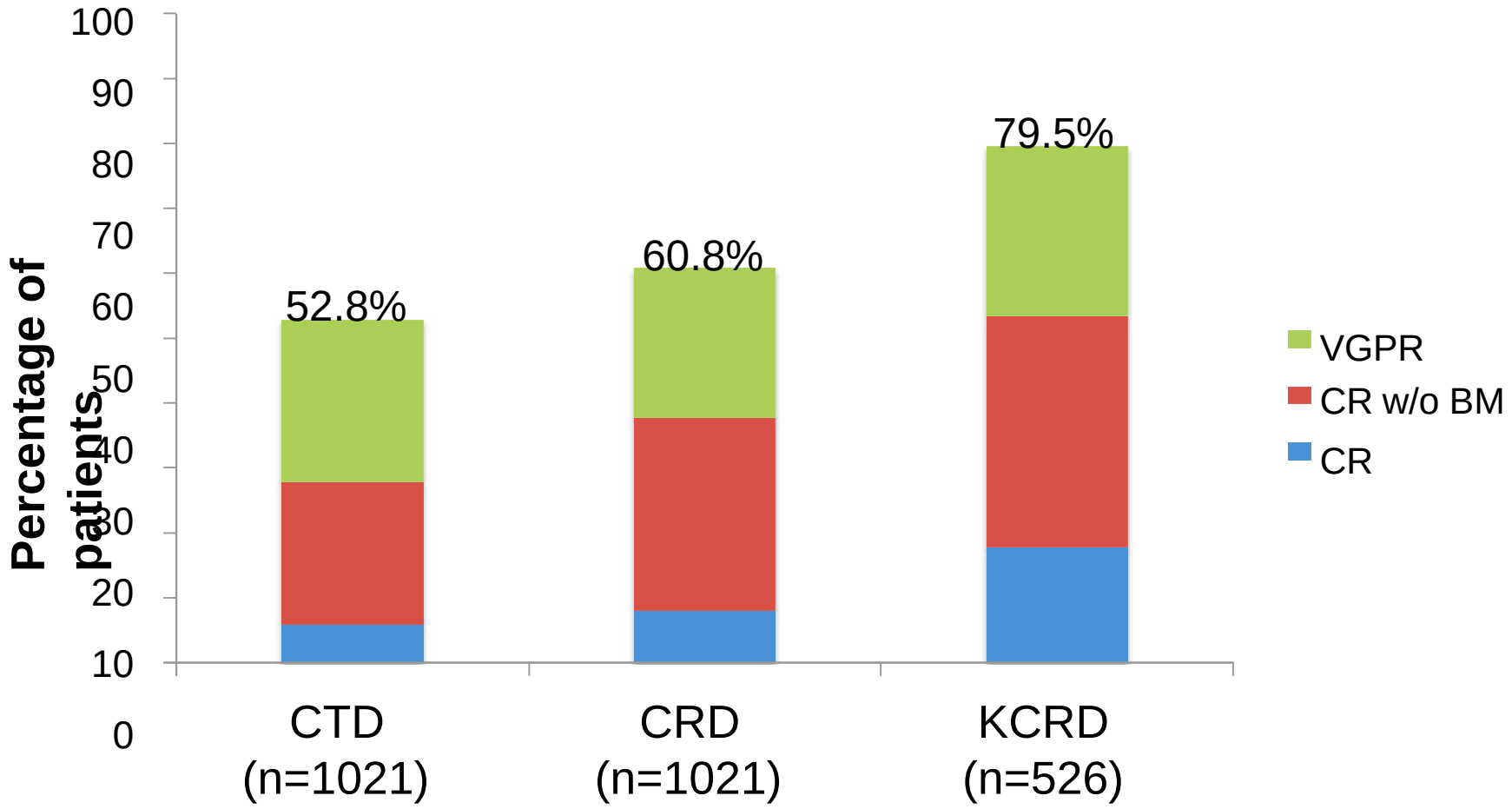
Response to initial induction

Lenalidomide led to deeper responses than thalidomide

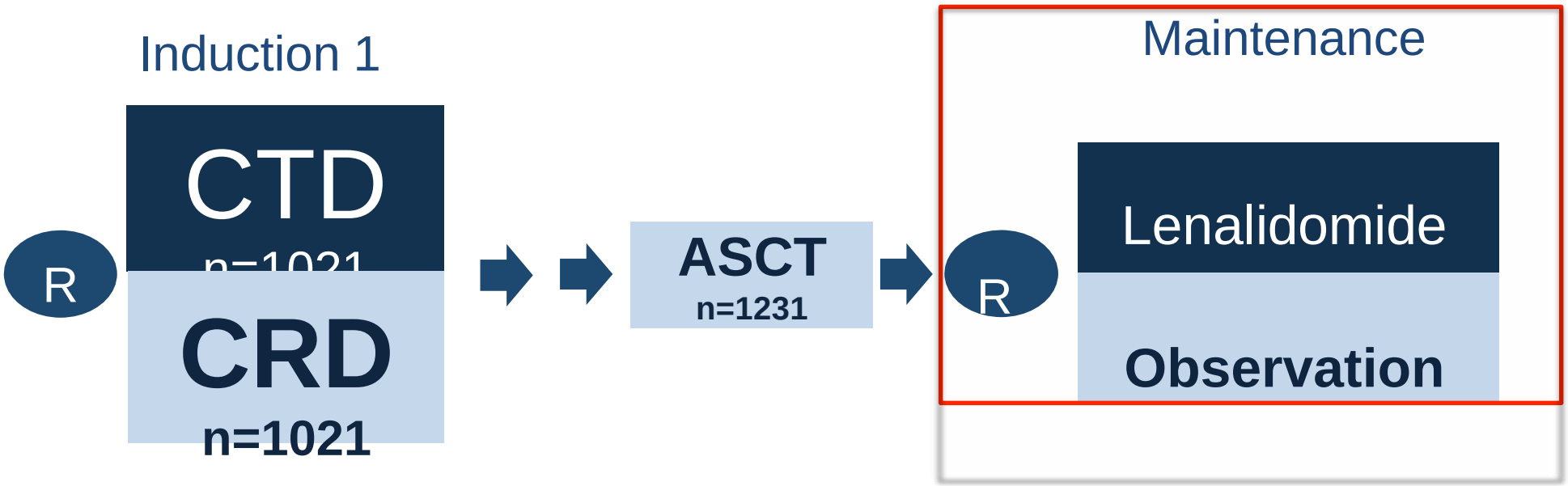


Response to initial induction

Quadruplet KCRD led to deeper responses than either triplet



Myeloma XI – trial outline, TE pathway

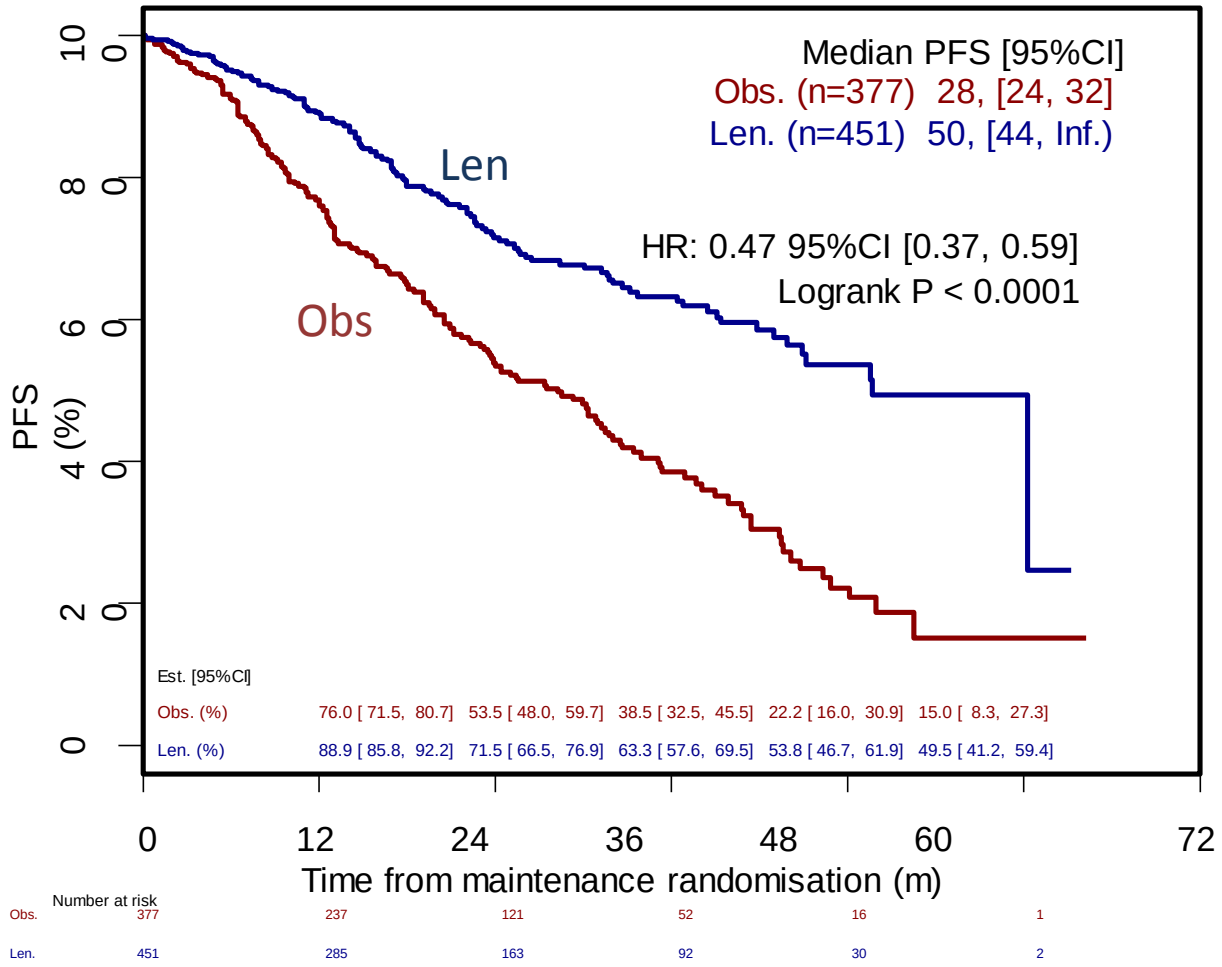


- Primary endpoints: PFS and OS for each randomisation
- Median follow up 36.3 months

Patients with a suboptimal response to Induction 1 (<VGPR) were eligible for Induction 2. Patients with PR/MR were randomised to CVD (cyclophosphamide, bortezomib and dexamethasone) or no further therapy prior to ASCT. Patients with NC/PD all received CVD. Patients were ineligible for the CVD randomisation if they had achieved a CR or VGPR to induction (went straight to ASCT) or had PD or SD to induction. Patients were ineligible for the maintenance randomisation if they failed to respond to lenalidomide as their induction IMiD or failed to respond to all trial induction treatment, had PD or had previous or concurrent active malignancies. Dose adjustments for renal impairment and following AEs were permitted.

Maintenance randomisation

Significant improvement in PFS from 28 to 50 months, HR 0.47

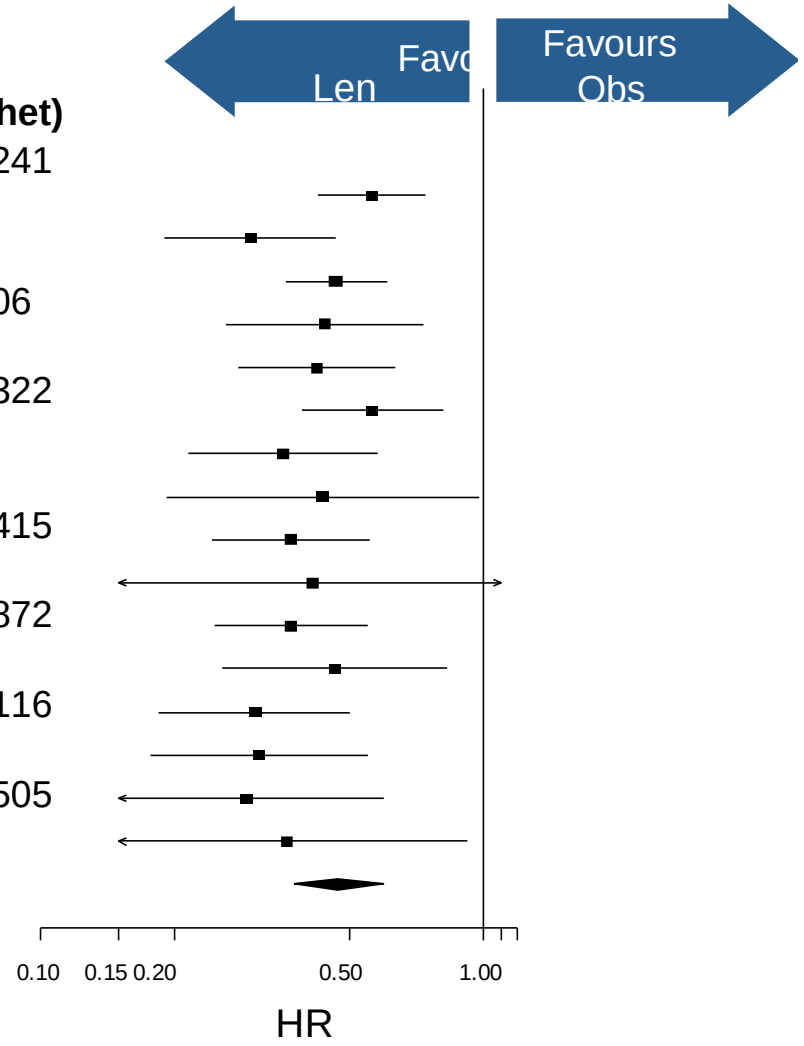


GH Jackson et al ASH 2016 (abstract no. 1143)

Maintenance randomisation

Significant improvement in PFS from 28 to 50 months, HR 0.47

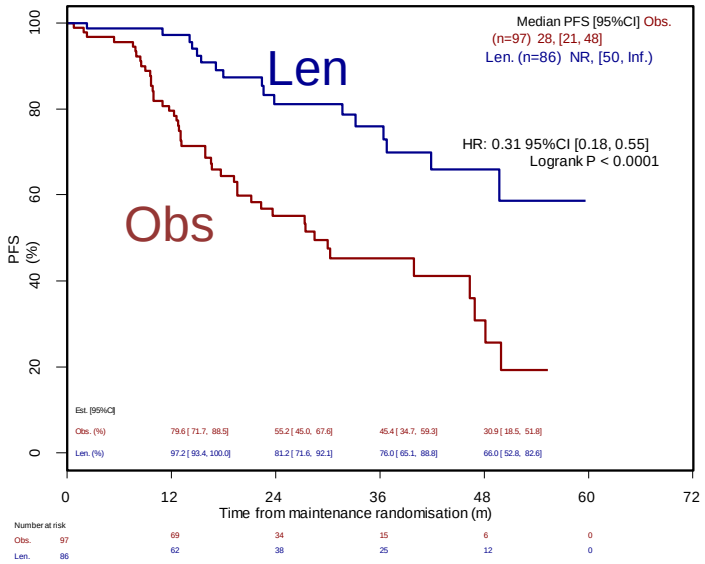
Subgroup	Level	No treat. n/N	Len. n/N	HR [95%CI]	P. (het)
Gender	Male	113/235	91/294	0.56 (0.42, 0.74)	0.0241
	Female	72/142	27/157	0.30 (0.19, 0.47)	
Age	<=65 years	149/306	90/364	0.47 (0.36, 0.61)	0.906
	>65 years	36/71	28/87	0.44 (0.26, 0.74)	
ISS	Stage I	62/137	37/149	0.42 (0.28, 0.64)	0.3322
	Stage II	69/148	49/168	0.57 (0.39, 0.82)	
	Stage III	45/71	25/97	0.35 (0.22, 0.58)	
t(4,14)	Present	14/17	11/29	0.44 (0.19, 0.98)	0.8415
	Absent	70/138	35/149	0.37 (0.24, 0.55)	
del(17p)	Present	8/9	9/17	0.41 (0.14, 1.25)	0.9872
	Absent	76/146	37/161	0.37 (0.25, 0.55)	
1q gain	Present	26/44	24/69	0.46 (0.26, 0.83)	0.3116
	Absent	58/111	22/109	0.30 (0.18, 0.50)	
Cytogenetic Risk	SR	46/97	17/86	0.31 (0.18, 0.55)	0.8505
	HiR	23/41	13/66	0.29 (0.15, 0.59)	
	UHiR	15/17	16/26	0.36 (0.14, 0.92)	
Overall		**185/377**	**118/451**	**0.47 (0.37, 0.60)**	



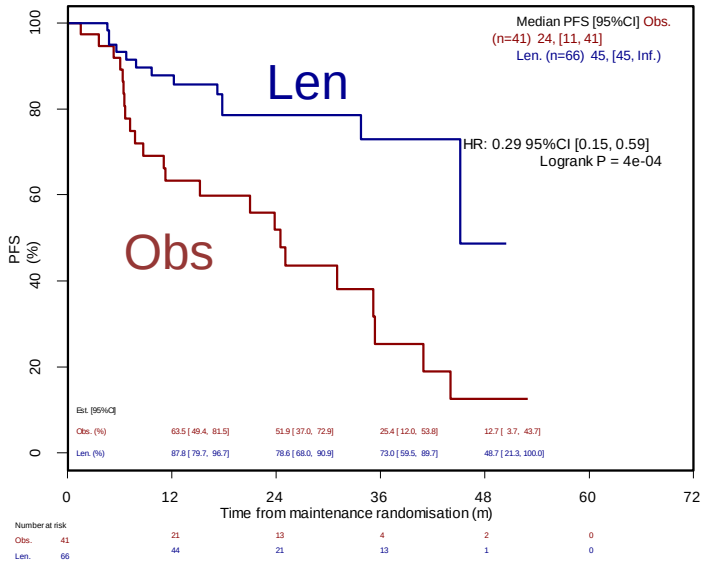
Maintenance randomisation

Lenalidomide improved PFS irrespective of cytogenetic risk

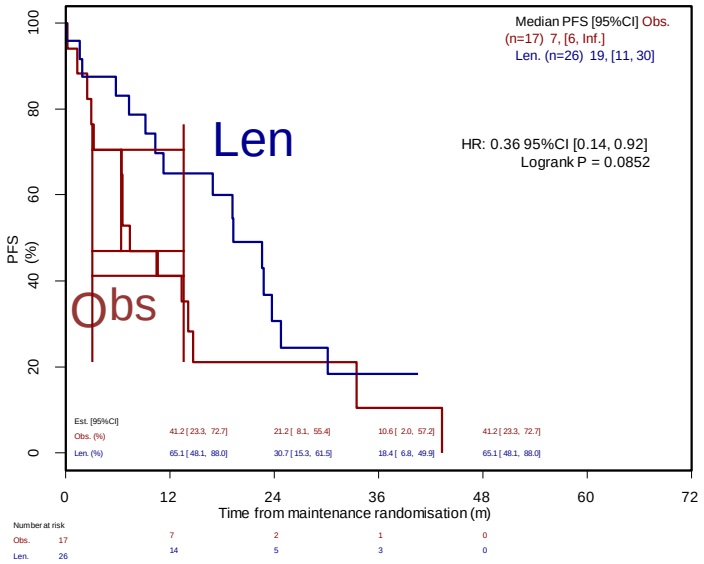
Standard risk



High risk



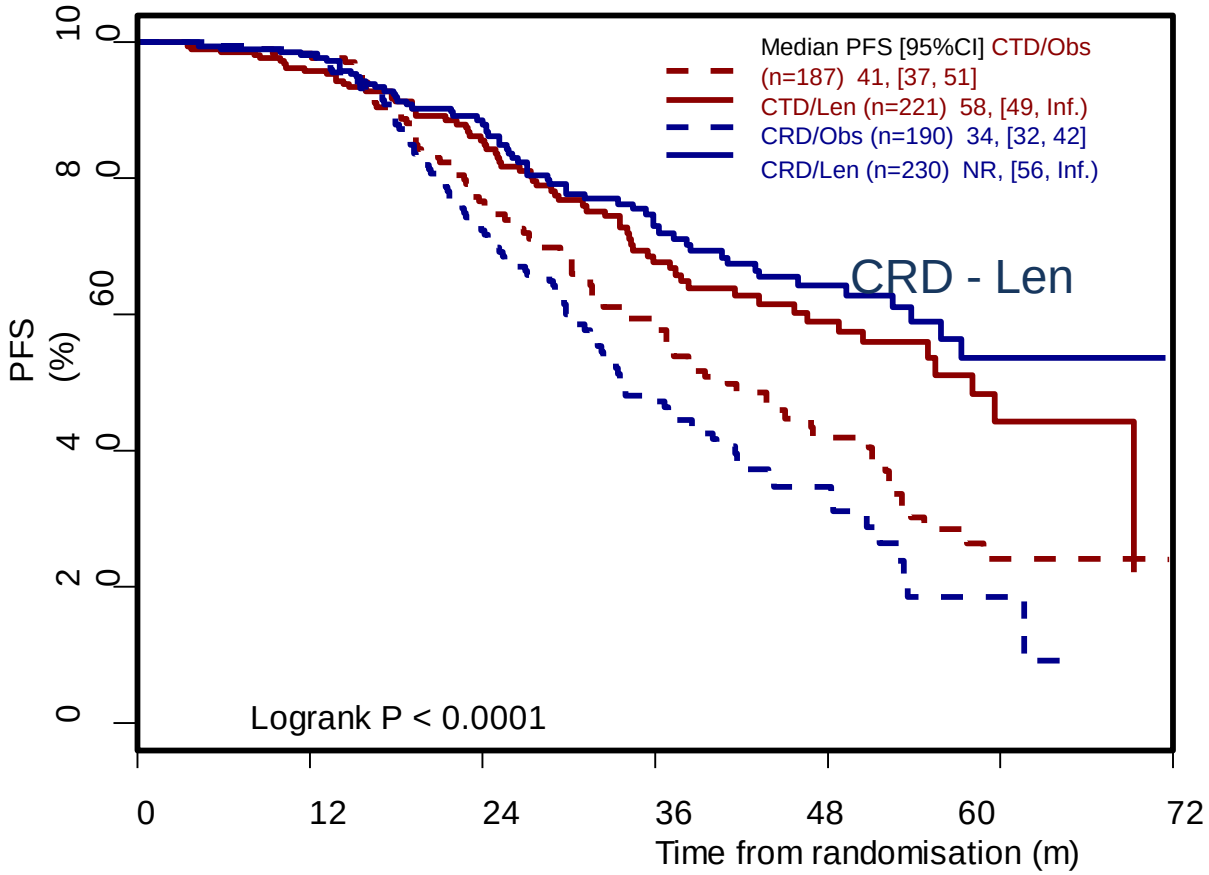
Ultra--high risk



- High risk (HiR) - presence of any one of t(4;14), t(14;16), t(14;20), del(17p), or gain(1q).
- Ultra-high risk (UHiR) - presence of more than one lesion.
- Standard risk (SR) - absence of any of the above lesions.

Interaction between induction and maintenance

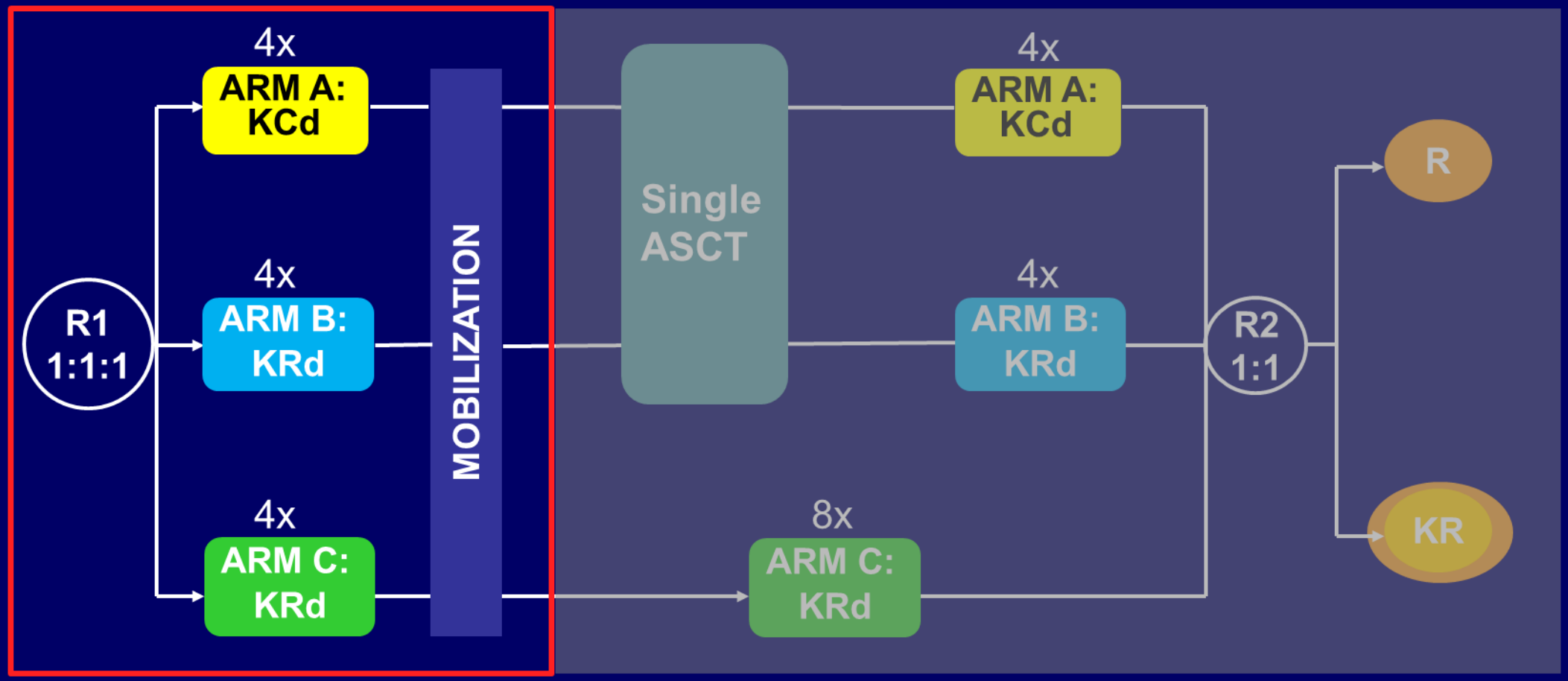
The best outcomes are associated with lenalidomide induction and maintenance



CTD/Obs = CTD induction, randomised to observation. CTD/Len = CTD induction, randomised to lenalidomide maintenance. CRD/Obs = CRD induction, randomised to observation. CRD/Len = CRD induction, randomised to lenalidomide maintenance.

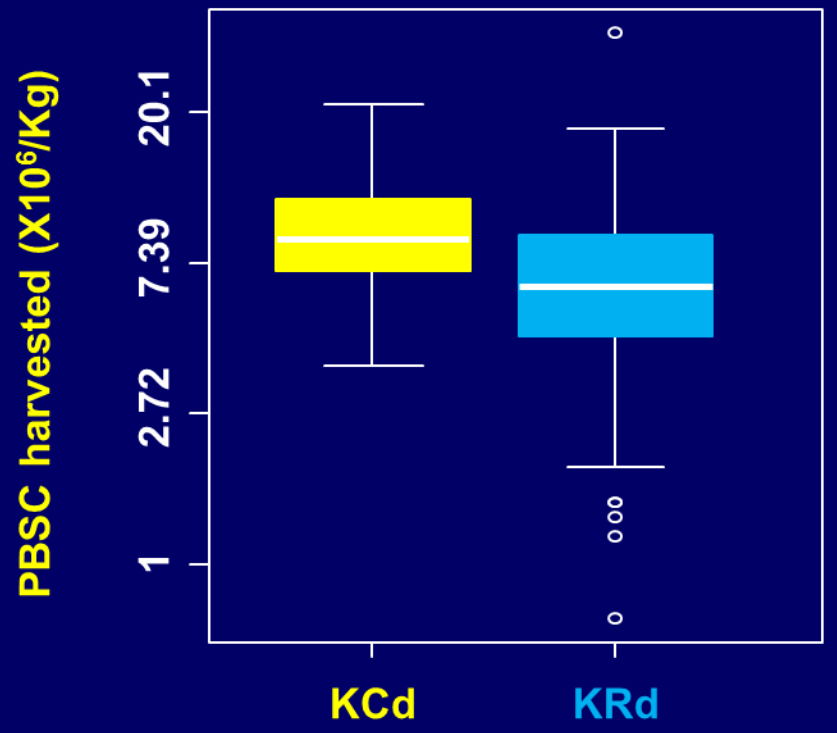
Treatment schema

- 477 NDMM patients enrolled in 46 Italian sites, last patients enrolled in March 2017
- Data cut-off March 31st, 2017

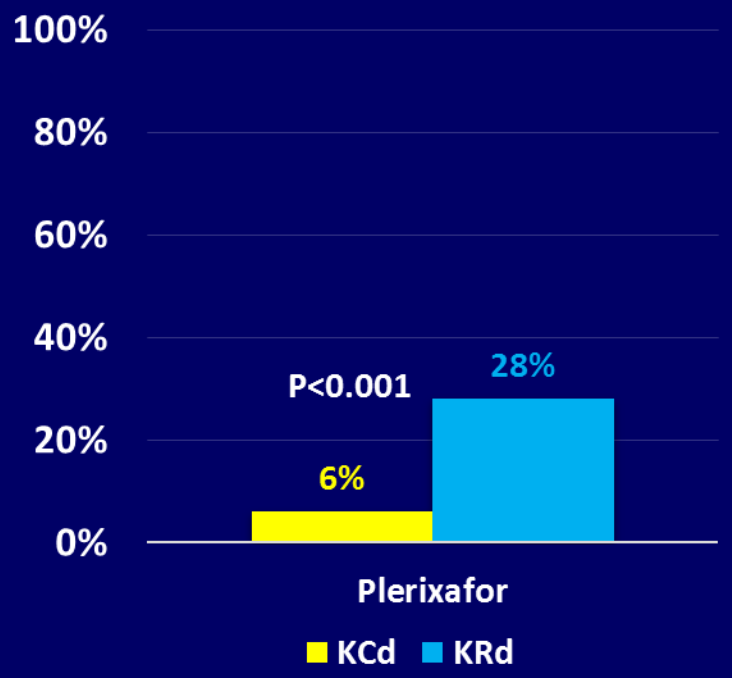


R1: randomization1; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; ASCT: Autologous Stem Cell Transplant; R2: randomization2; R: Lenalidomide; KR: Carfilzomib, Lenalidomide. NDMM, newly diagnosed multiple myeloma.

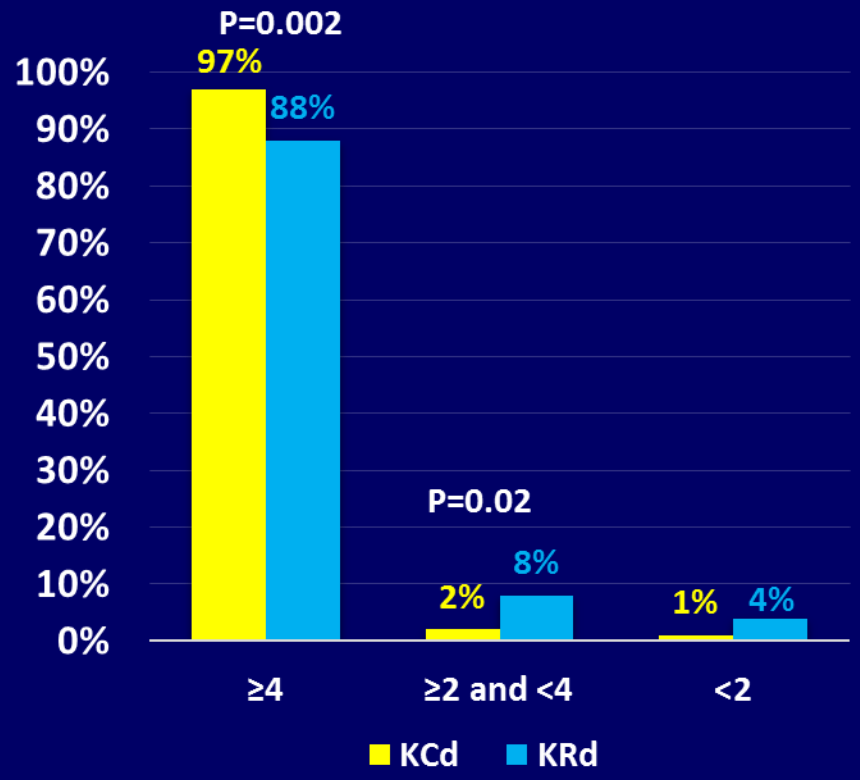
PBSC mobilization



Patients requiring Plerixafor



PBSC harvest

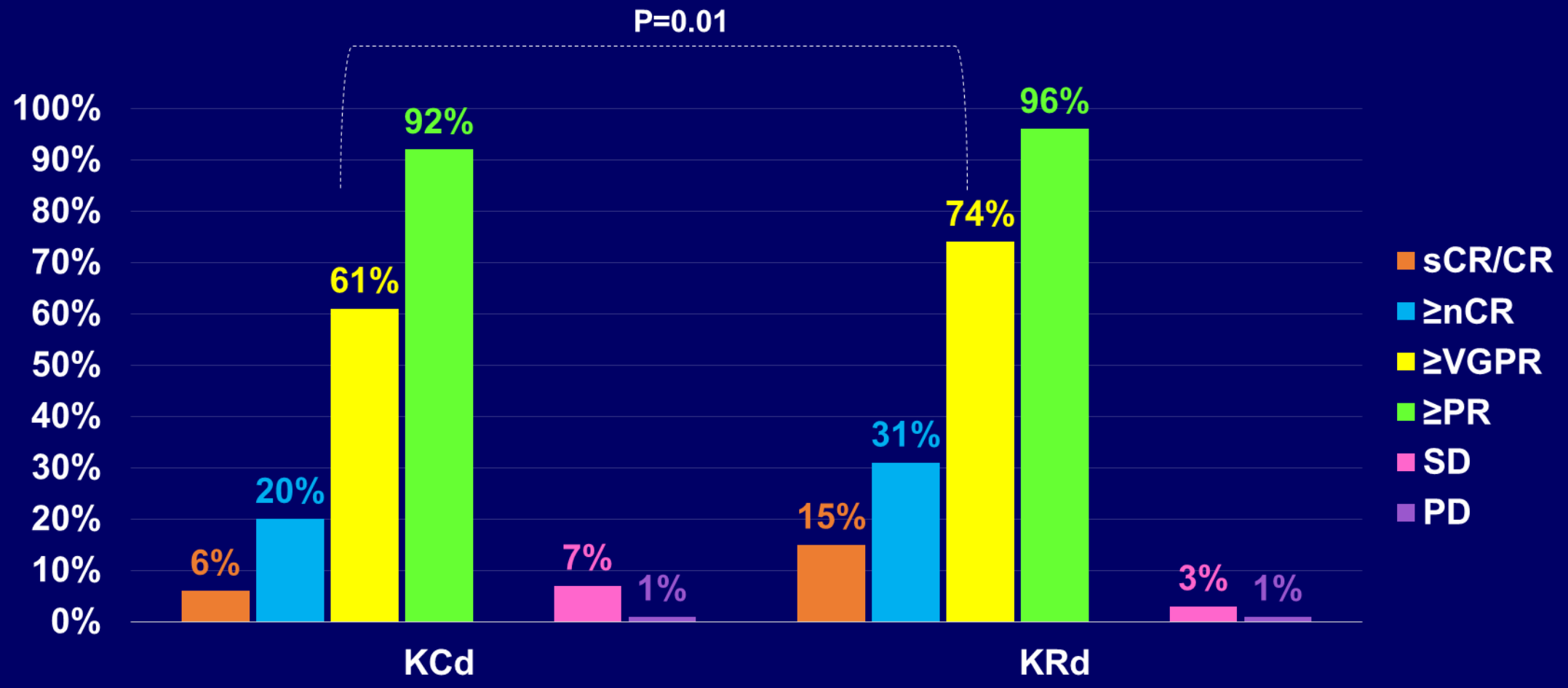


	KCd	KRd	P value
PBSC Median	8.6x10⁶/Kg	6.3x10⁶/Kg	<0.001
PBSC IQR	7.0-11.3	4.5-8.8	

In logistic regression analysis, KRd was the factor presenting the highest risk of poor mobilization.

PBSC: peripheral blood stem cell; KRd: Carfilzomib, Lenalidomide, dexamethasone; KCd: Carfilzomib, Cyclophosphamide, dexamethasone; IQR, interquartile range; CTX: cyclophosphamide

Best Responses

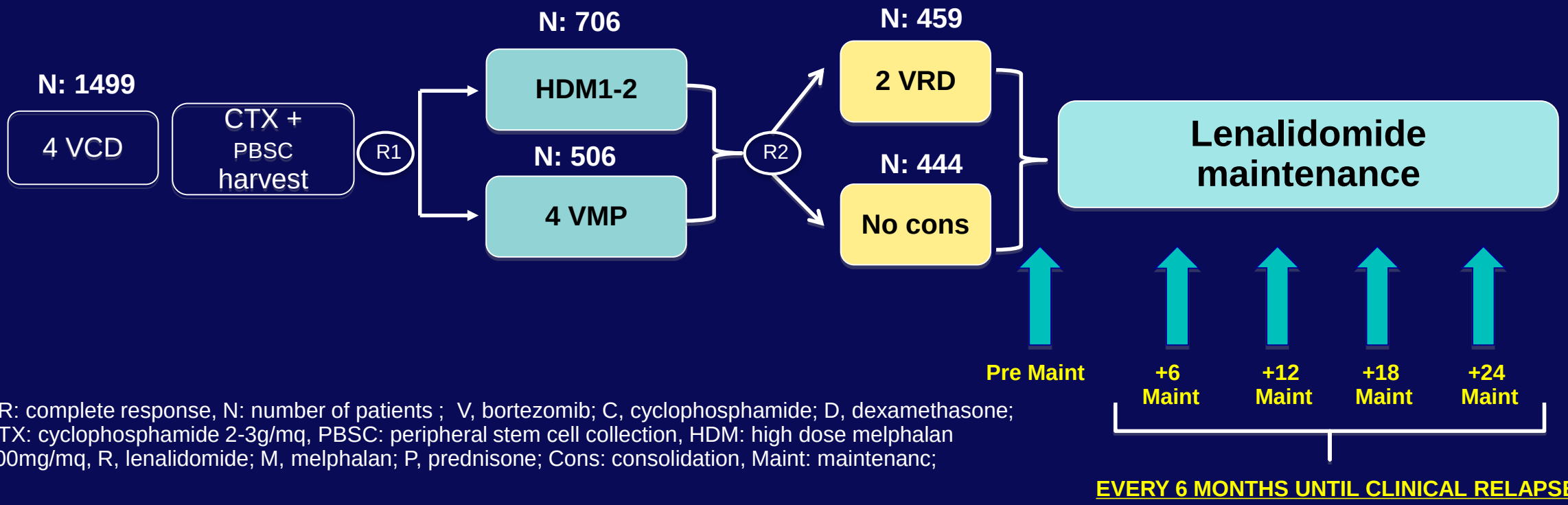


KCd: Carfilzomib, Cyclophosphamide, dexamethasone; KRd: Carfilzomib, Lenalidomide, dexamethasone; sCR: stringent Complete Response nCR: near Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

Methods

MM patients enrolled in the RV-MM-COOP-0556 (EMN02/HO95 MM; NCT01208766)

- Newly diagnosed ≤ 65 years
- MRD assessement in patients achieving suspected CR before lenalidomide maintenance



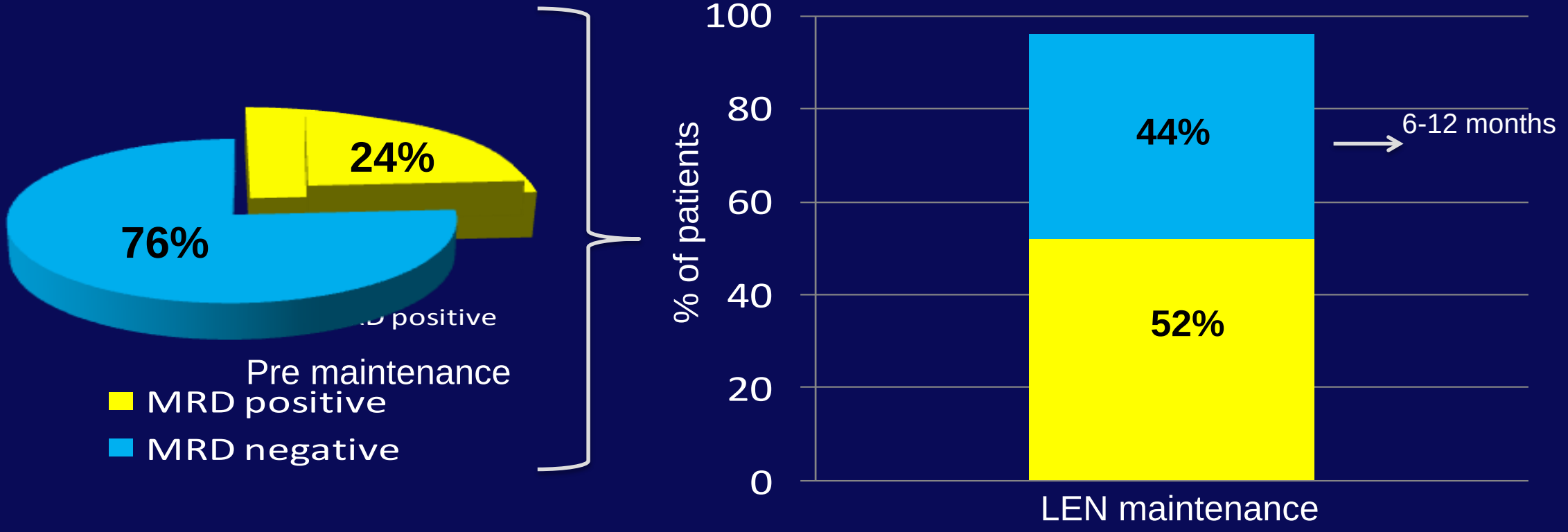
CR: complete response, N: number of patients ; V, bortezomib; C, cyclophosphamide; D, dexamethasone; CTX: cyclophosphamide 2-3g/mq, PBSC: peripheral stem cell collection, HDM: high dose melphalan 200mg/mq, R, lenalidomide; M, melphalan; P, prednisone; Cons: consolidation, Maint: maintenanc;

Cavo M et al. ASH 2016; Abstract 673. Sonneveld P. et al. ASH 2016; Abstract 292

Results

MRD status at pre-maintenance

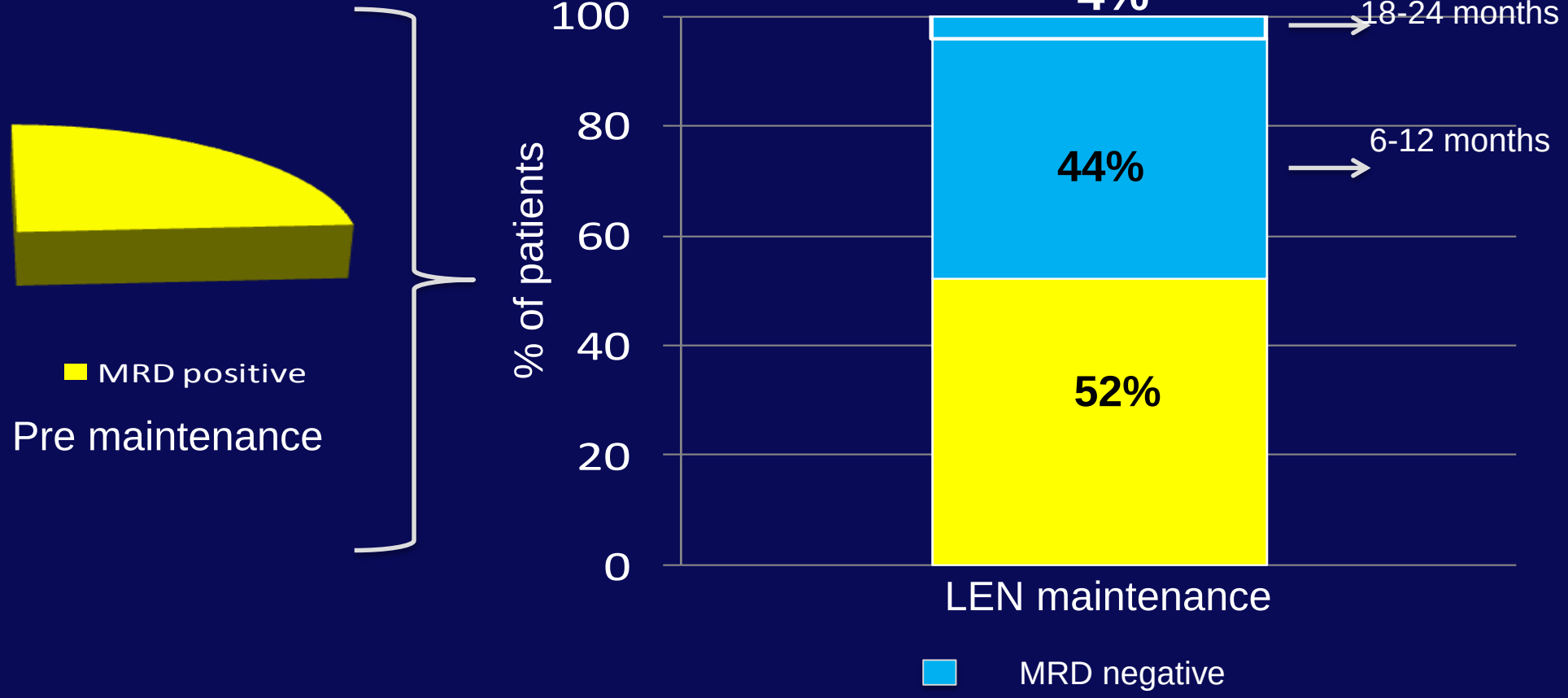
Sub-analysis on MRD positive patients at pre-maintenance who had a second MRD evaluation >1 year of Lenalidomide



Results

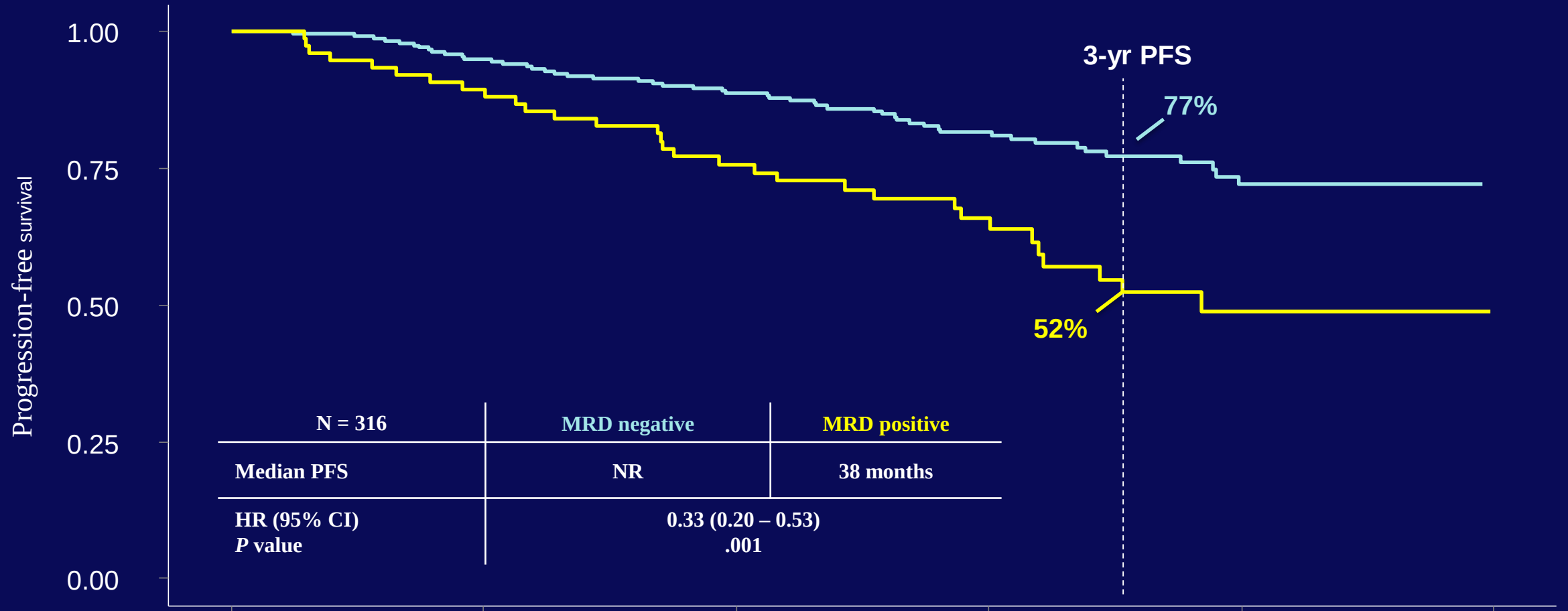
MRD status during maintenance

Sub-analysis on MRD positive patients at pre-maintenance who had a second MRD evaluation >1 year of Lenalidomide



Results

Progression free Survival: Median Follow-Up from MRD enrollement of 33 Months



Numbers at risk

MRD Negative	239	222	192	131	53	13
MRD Positive	77	68	52	33	14	4

ELOQUENT-2: Study Design

ELOQUENT-2 (NCT01239797): international, open-label, randomized, multicenter, Phase 3 trial

Patients

- RRMM
- 1–3 prior lines of therapy
- Prior lenalidomide permitted in 10% of patients (if sensitive)

ELd: n=321

Elo (10 mg/kg IV): Cycles 1 and 2 weekly, Cycle 3+ every other week
Len (25 mg PO): Days 1–21
Dex (40 mg): Weekly equivalent

Ld: n=325

Len (25 mg PO): Days 1–21
Dex (40 mg PO): Weekly

Repeat every 28 days

Endpoints

Co-primary

- Progression-free survival (PFS)
- Overall response rate (ORR)

Secondary

- Overall survival (OS)

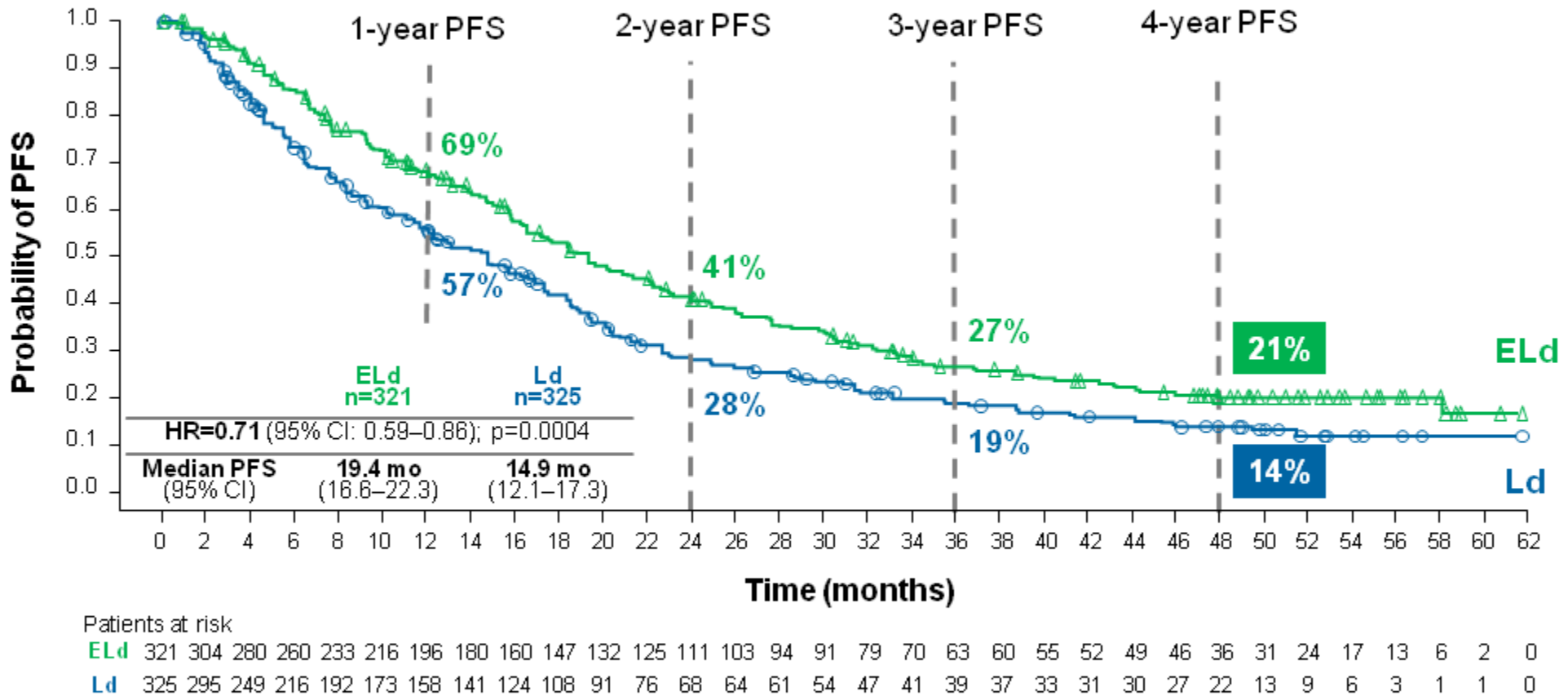
Exploratory

- Safety
- Duration of response (DOR)

Start	Primary analysis	Extended analyses	
Jun 2011	2-y PFS (minFU: 24 mo)	3-y PFS (minFU: 33 mo) Interim OS (minFU: 36 mo)	**4-y PFS[a] (minFU: 48 mo)** Data cut-off: Oct 18, 2016

minFU, minimum follow-up; RRMM, relapsed/refractory multiple myeloma
[a]P-values provided are descriptive and were not adjusted for multiplicity

Progression-Free Survival – All Randomized Patients

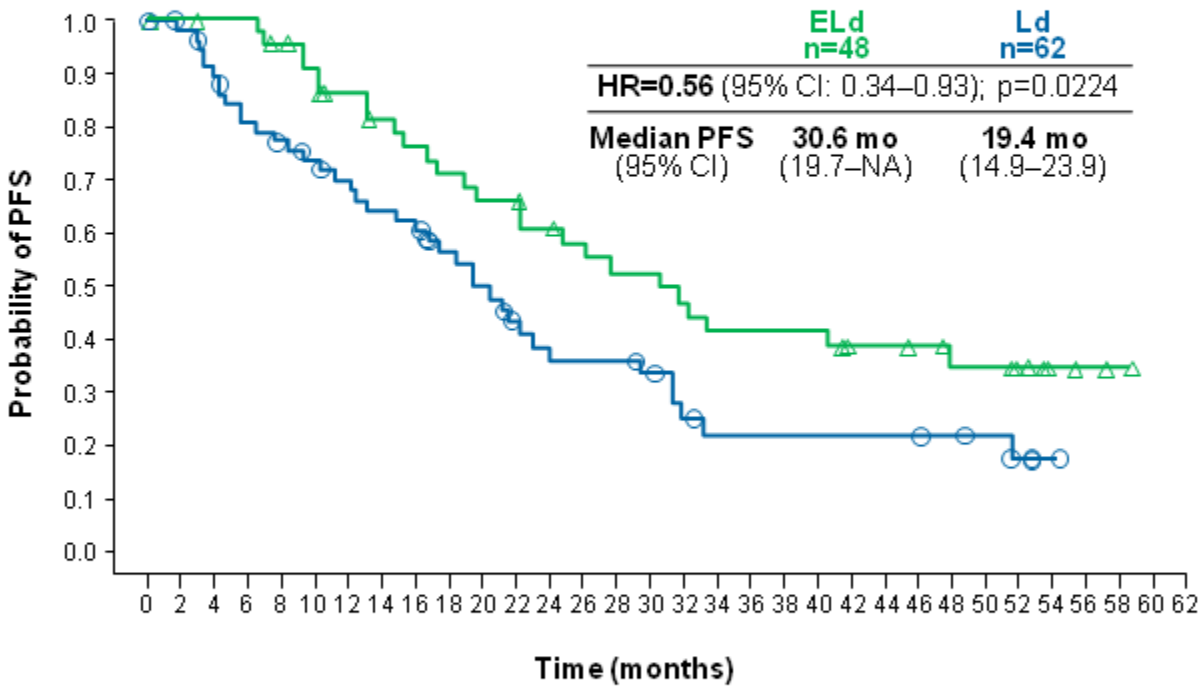


- At 4 years, ELOQUENT-2 has the longest follow-up for PFS in RRMM
- 29% reduction in the risk of progression or death (sustained over time)
- 50% relative improvement in the PFS rate at 4 years (21% vs 14%) in favor of ELd

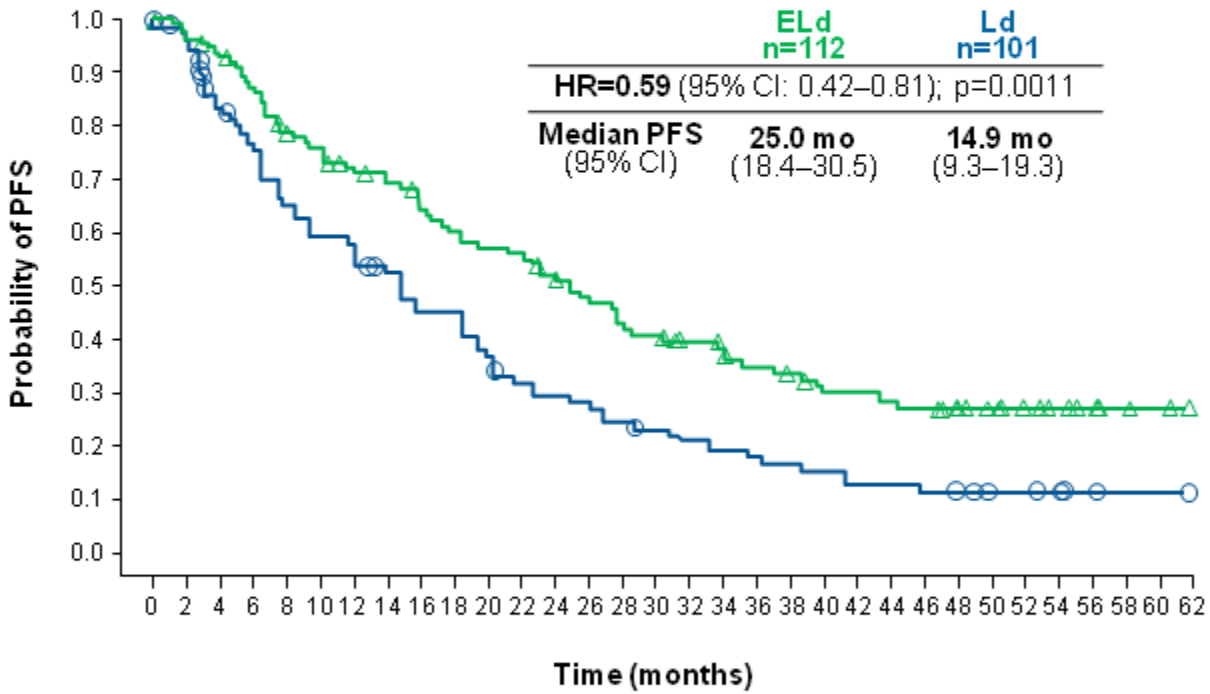
Progression-Free Survival – Median Time Since Diagnosis (3.5 years) and Prior Lines of Therapy

≥Median time from diagnosis

1 prior line of therapy



>1 prior line of therapy

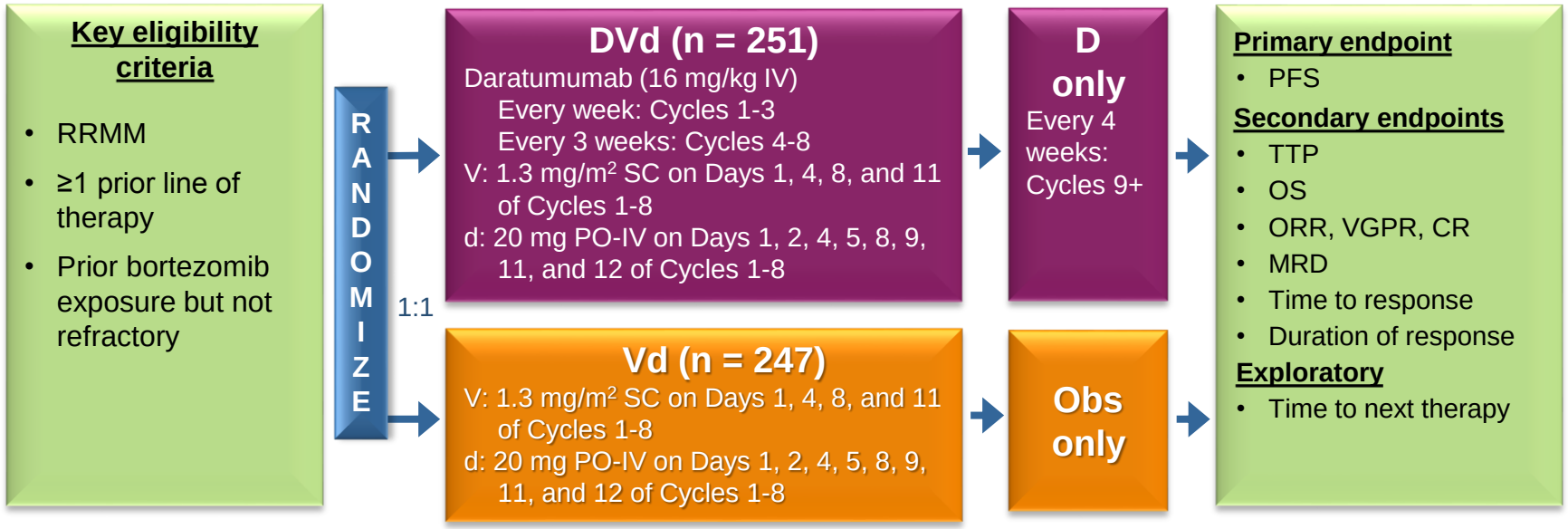


- Greatest benefit in patients with ≥3.5 years (median time) since diagnosis and 1 prior line of therapy
- 44% reduction in the risk of progression or death

NA, not available

Study Design

Multicenter, randomized, open-label, active-controlled, phase 3 study



Stratification factors

- ISS (I, II, and III)
- Number of prior lines (1 vs 2 or 3 vs >3)
- Prior bortezomib (no vs yes)

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

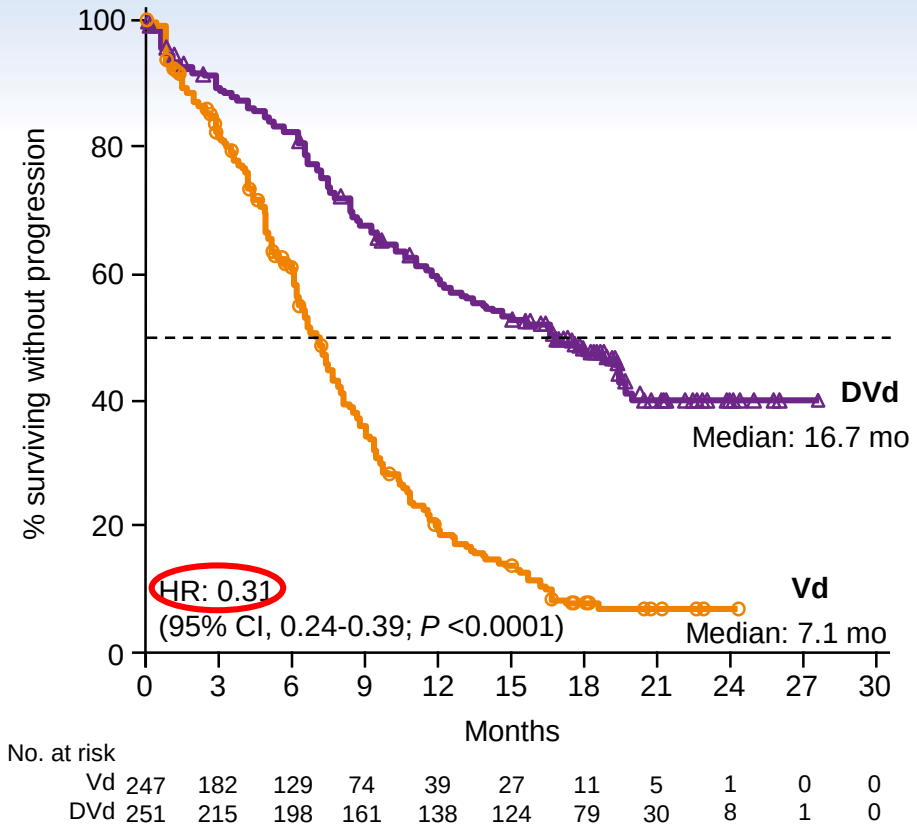
Premedication for the DVd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine

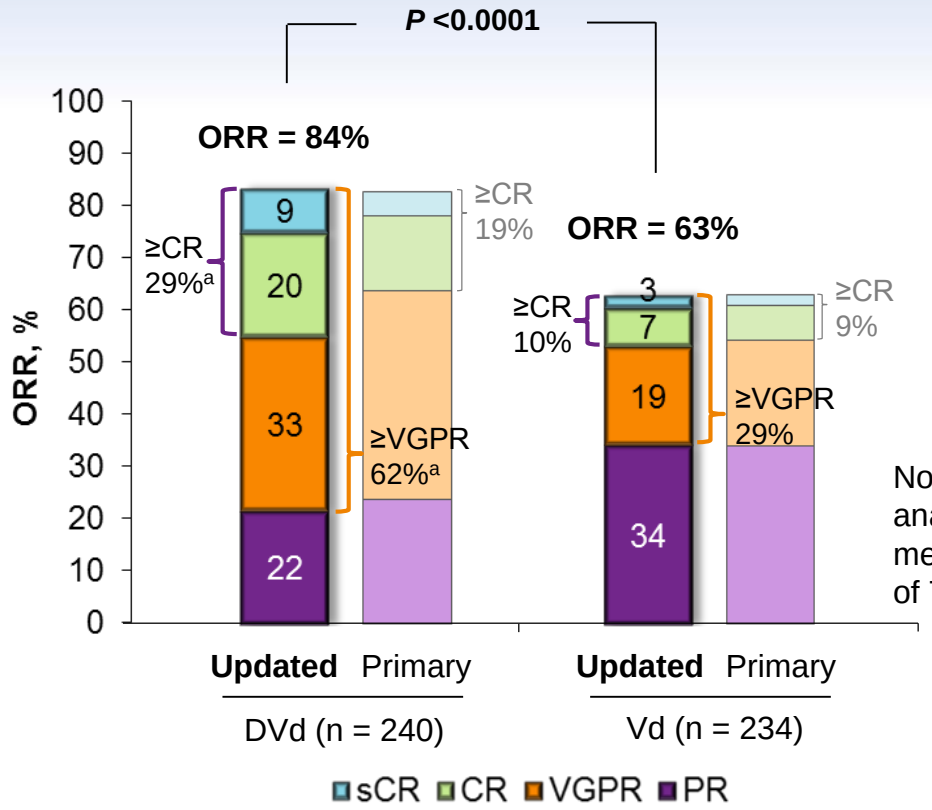
MRD evaluation

- Assessed at suspected CR and at 6 and 12 months following the first treatment dose for patients who maintain CR

ISS, International Staging System; 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.

Updated Efficacy: ITT





Note: Primary analysis based on median follow-up of 7.4 months[1]

Duration of response: 18.9 months for DVd versus 7.6 months for Vd

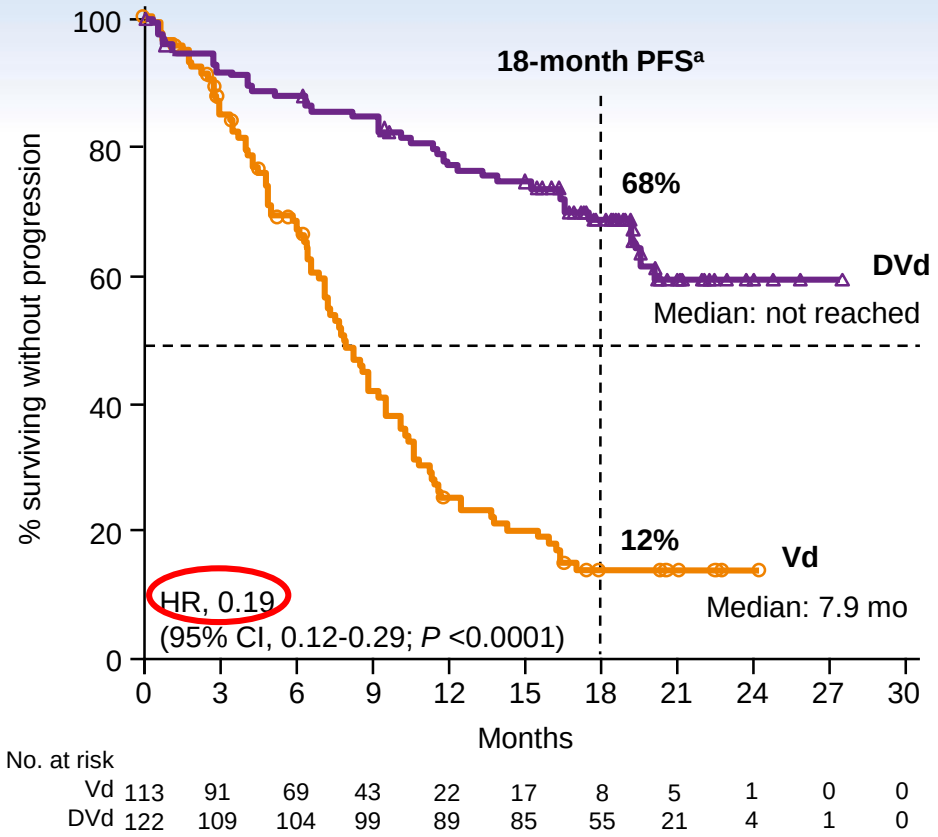
- 69% reduction in risk of progression for DVd versus Vd
- 9.6-month improvement in median PFS for DVd versus Vd
- Responses continue to deepen

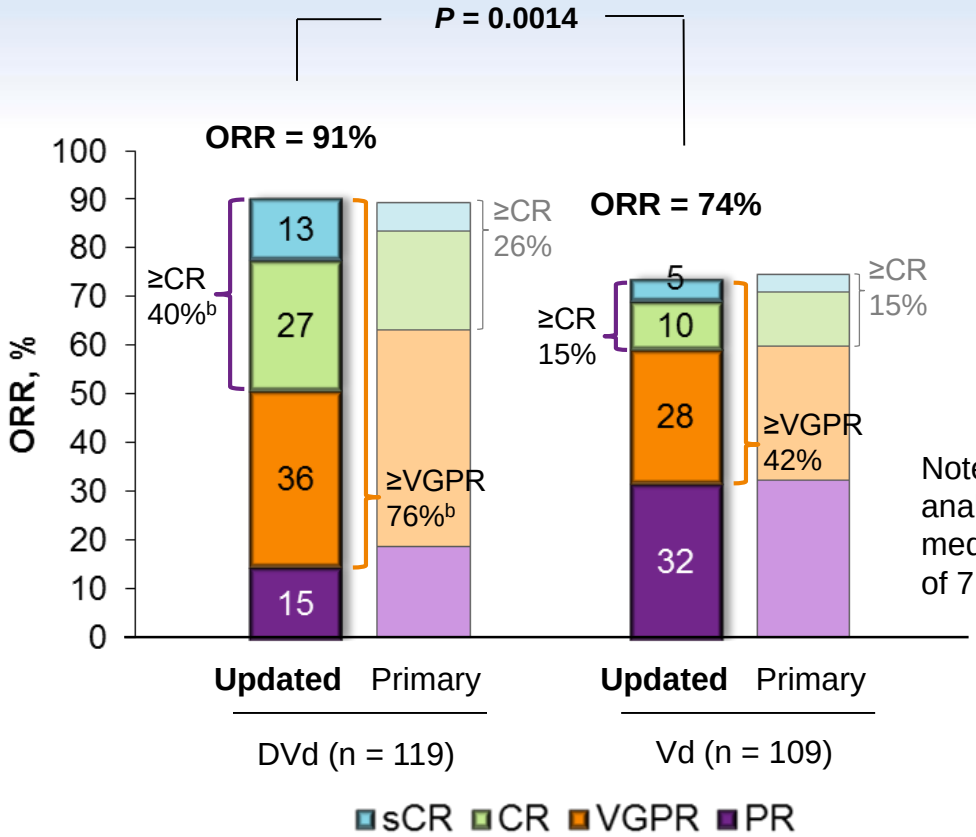
HR, hazard ratio; CI, confidence interval; PR, partial response; sCR, stringent complete response.

1. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

[a]*P* <0.0001 for DVd versus Vd.

Updated Efficacy: 1 Prior Line



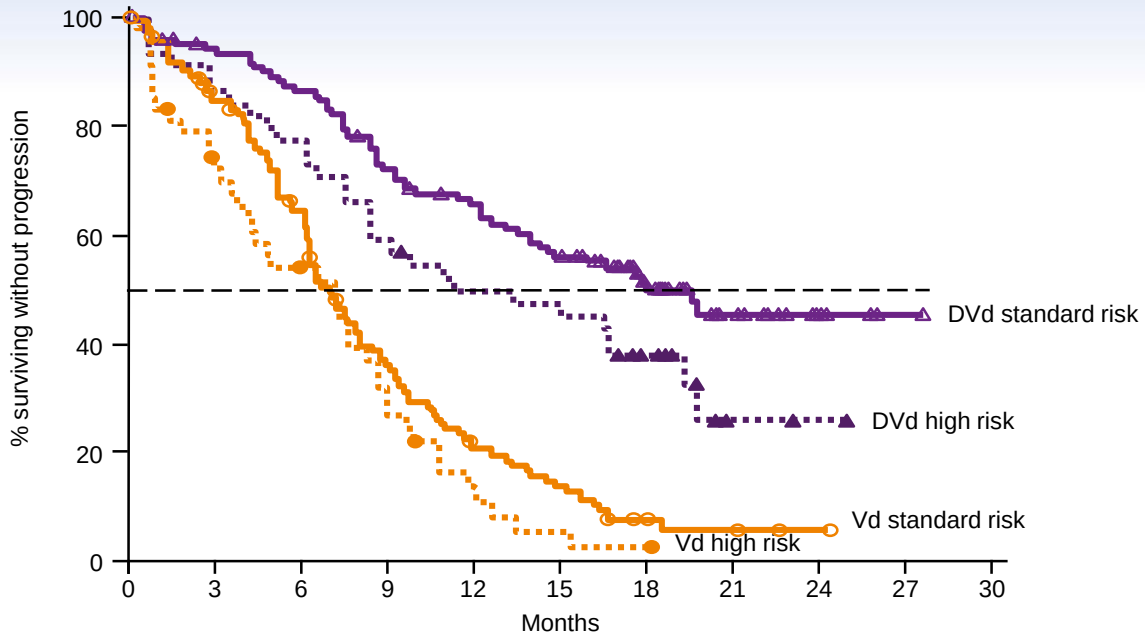


Note: Primary analysis based on median follow-up of 7.4 months[1]

- 81% reduction in risk of progression/death for DVd versus Vd
- Deeper responses with longer follow-up

[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.
1. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

CASTOR: PFS by Cytogenetic Risk Status[a]



No. at risk											
Vd standard risk	135	106	79	44	25	16	5	3	1	0	0
DVd standard risk	123	110	101	83	74	63	36	15	5	1	0
Vd high risk	51	32	23	13	4	2	1	0	0	0	0
DVd high risk	44	38	34	26	21	20	11	2	1	0	0

High risk	**DVd** n = 44	**Vd** n = 51
mPFS, mo	**11.2**	**7.2**
HR (95% CI)	0.45 (0.25-0.80)	
P value	0.0053	

Standard risk	**DVd** n = 123	**Vd** n = 135
mPFS, mo	**19.6**	**7.0**
HR (95% CI)	0.26 (0.18-0.37)	
P value	<0.0001	

Adding DARA to standard of care prolongs PFS regardless of cytogenetic risk

[a]ITT/biomarker-risk-evaluable analysis set: patients in the ITT population with both RNA and DNA results available.

POLLUX: Study Design

Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

Key eligibility criteria

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

Stratification factors

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

RANDOMIZE

1:1

DRd (n = 286)

Daratumumab 16 mg/kg IV
- Qw in Cycles 1-2, q2w in Cycles 3-6, then q4w until PD

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Rd (n = 283)

R 25 mg PO
- Days 1-21 of each cycle until PD

d 40 mg PO
- 40 mg weekly until PD

Cycles: 28 days

Primary endpoint

- PFS

Secondary endpoints

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

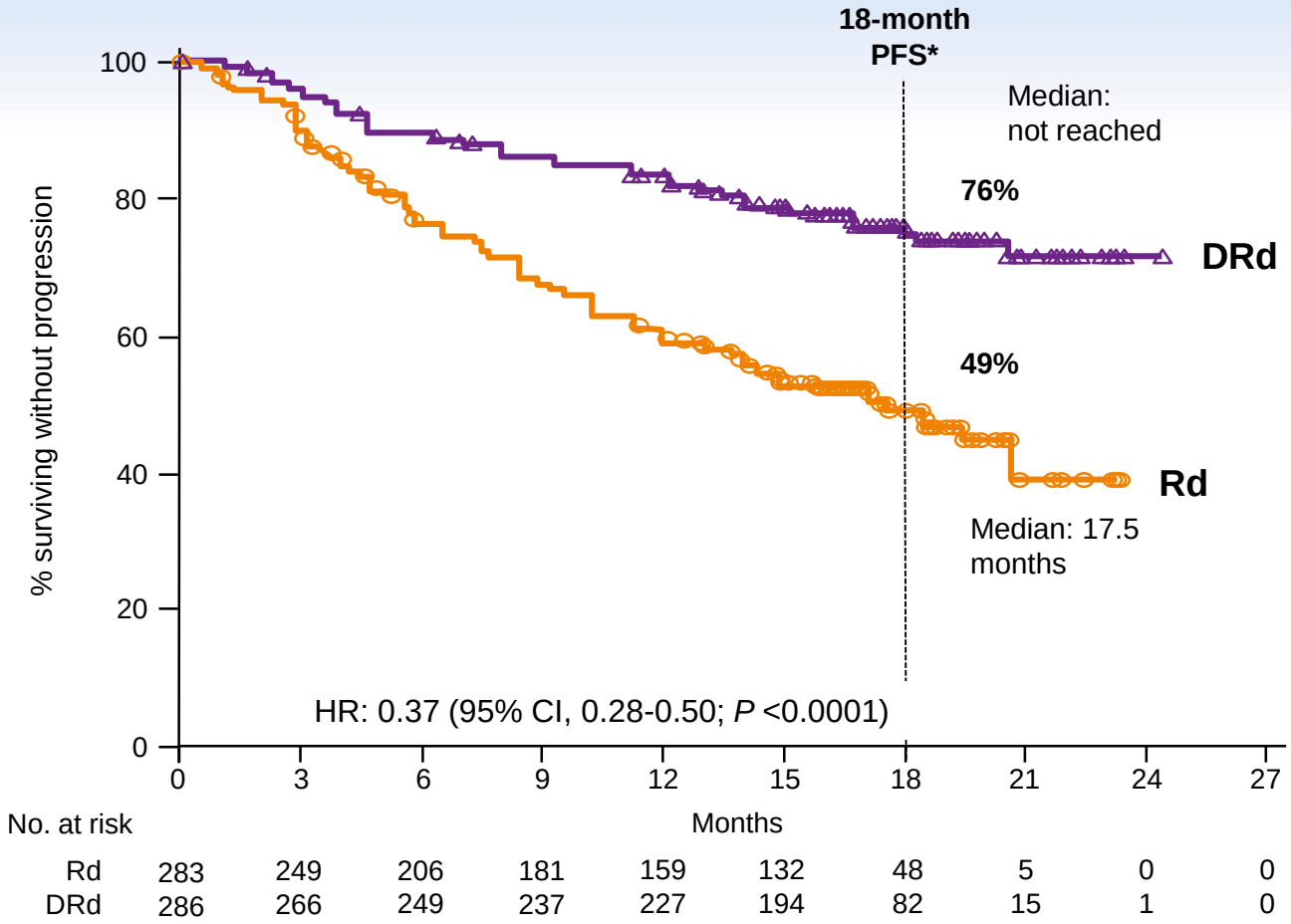
Statistical analyses

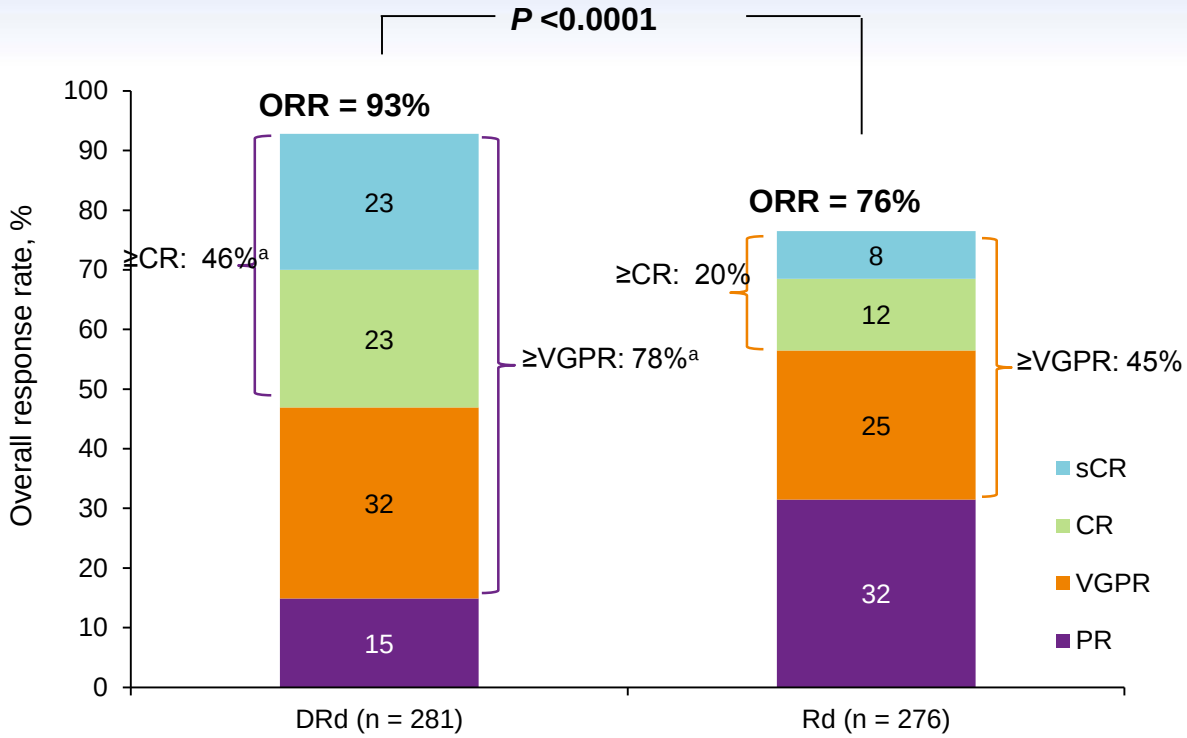
- Primary analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg[a], acetaminophen, and an antihistamine

[a]On daratumumab dosing days, dexamethasone was administered 20 mg premed on Day 1 and 20 mg on Day 2.
RRMM, relapsed and/or refractory multiple myeloma; ISS, international staging system; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; R, lenalidomide; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; 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.

Updated Efficacy

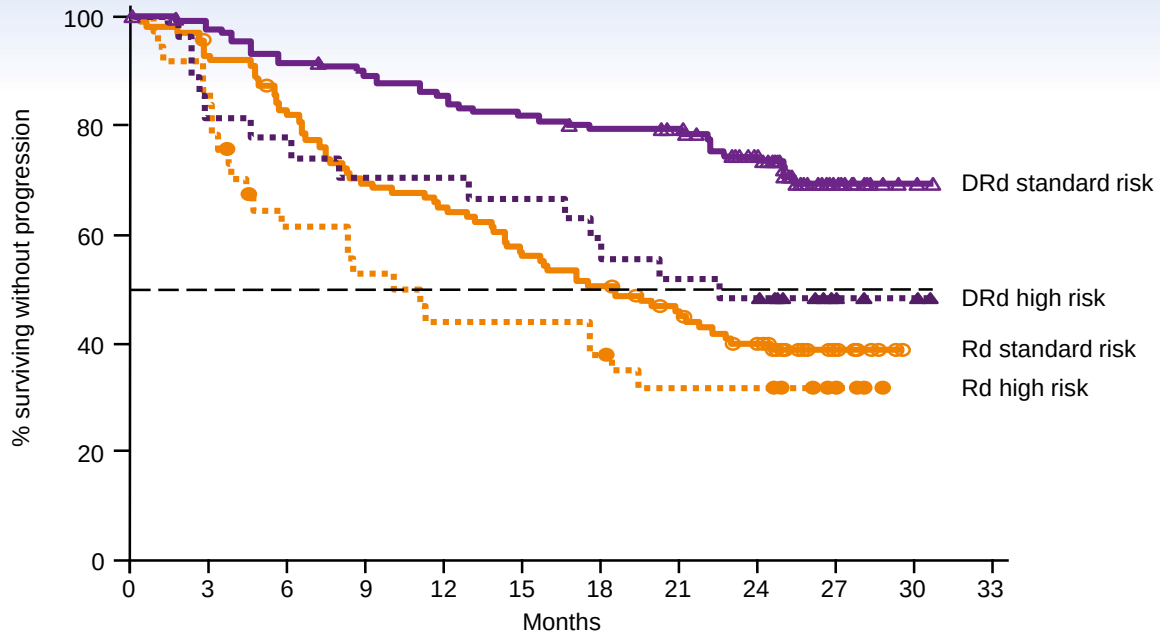




- **Median follow-up: 17.3 (range, 0-24.5) months**
- Responses continue to deepen in the DRd group with longer follow-up

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

POLLUX: PFS by Cytogenetic Risk Status[a]



Patients at risk												
Rd standard risk	113	104	92	77	72	63	56	47	36	10	0	0
DRd standard risk	133	128	120	116	111	106	102	99	76	19	2	0
Rd high risk	37	32	21	18	15	15	13	10	10	4	0	0
DRd high risk	28	22	21	19	19	18	16	14	13	4	2	0

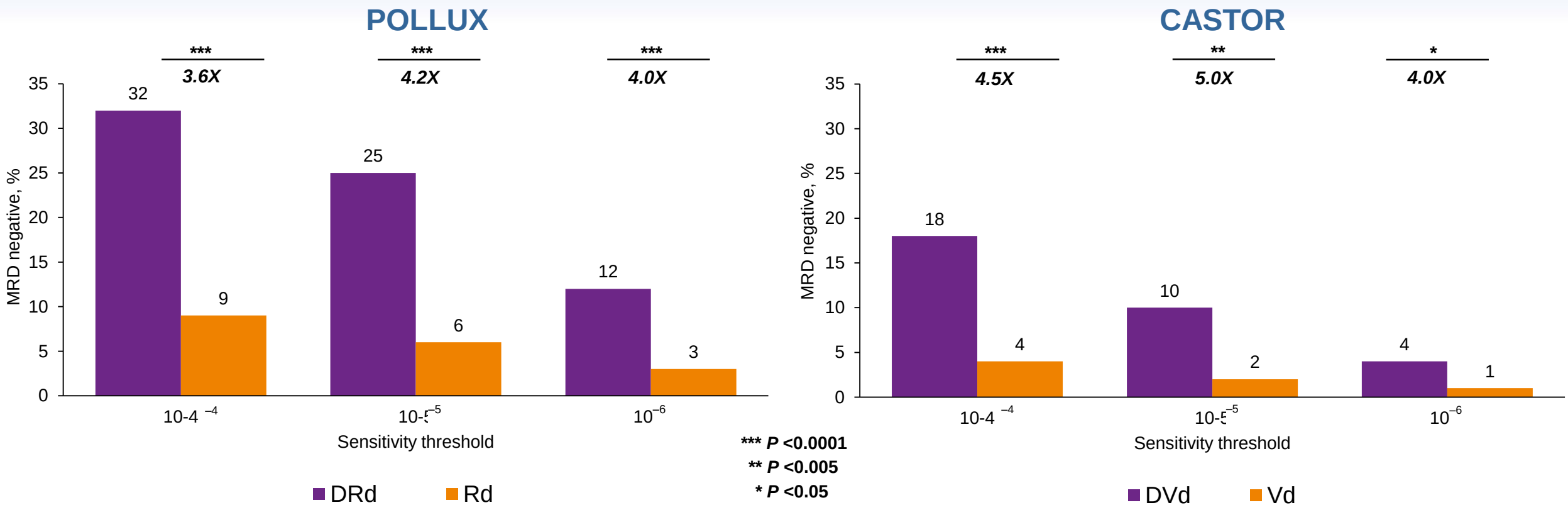
High risk	**DRd** n = 28	**Rd** n = 37
mPFS, mo	**22.6**	**10.2**
HR (95% CI)	0.53 (0.25-1.13)	
P value	0.0921	

Standard risk	**DRd** n = 133	**Rd** n = 113
mPFS, mo	**NR**	**18.5**
HR (95% CI)	0.30 (0.20-0.47)	
P value	<0.0001	

Adding DARA to Rd prolongs PFS regardless of cytogenetic risk

mPFS, median PFS; NR, not reached.
[a]ITT/biomarker-risk-evaluable analysis set: patients in the ITT population with both RNA and DNA results available.

Proportion of MRD-negative Patients at 10^{-4}, 10^{-5}, and 10^{-6} Thresholds

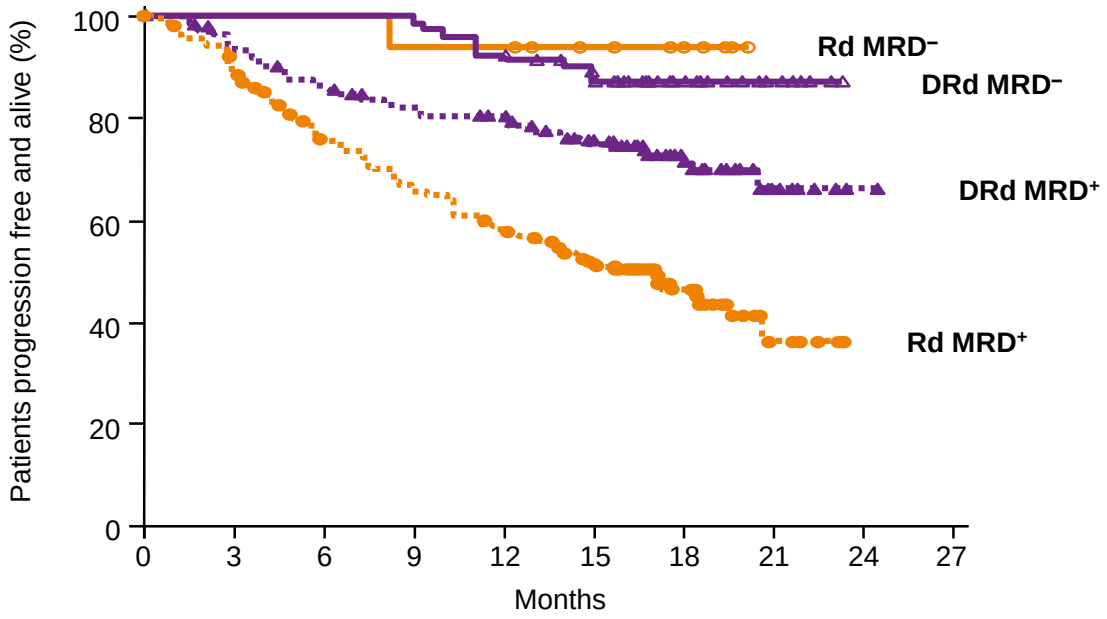


- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds

P values calculated using likelihood-ratio chi-square test.

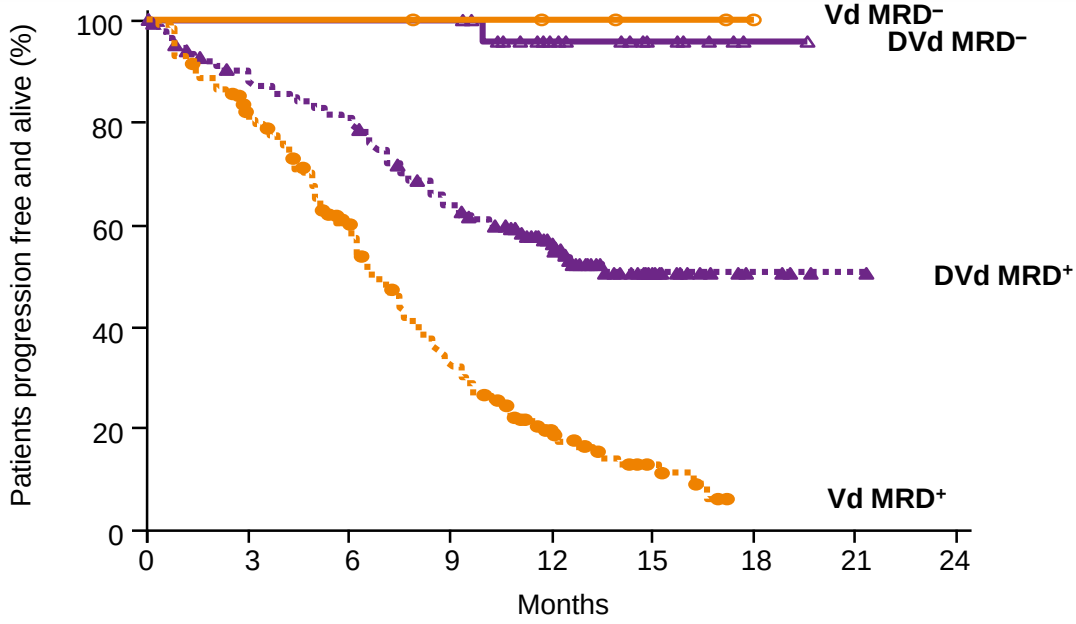
PFS According to MRD Status at 10^{-5}

POLLUX



Patients at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0

CASTOR

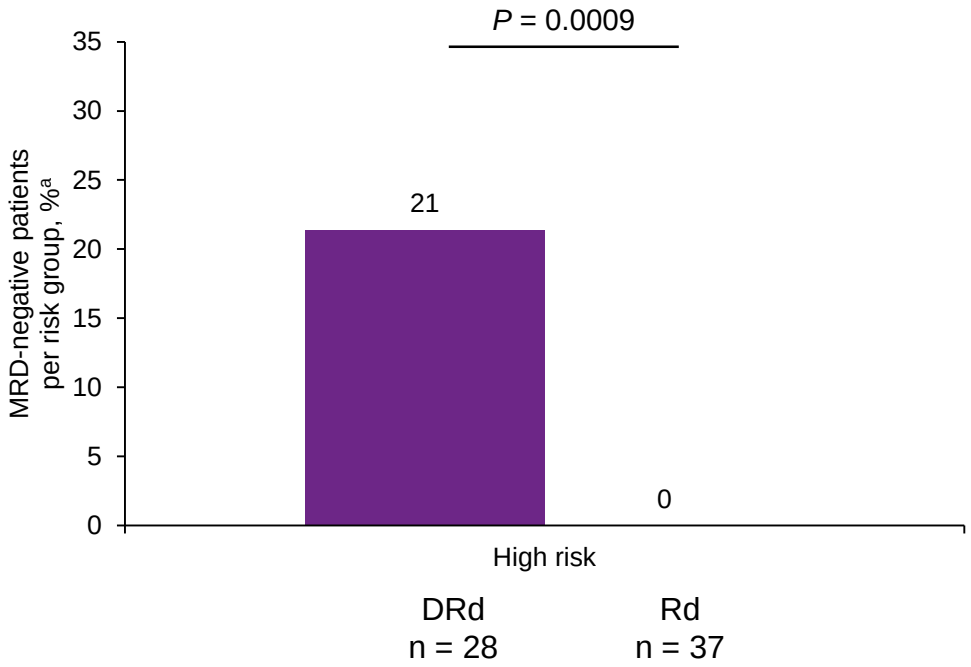


Patients at risk									
Vd MRD negative	6	6	6	5	3	2	0	0	0
DVd MRD negative	26	26	26	26	15	7	1	0	0
Vd MRD positive	241	176	123	68	20	7	0	0	0
DVd MRD positive	225	189	172	134	76	26	4	1	0

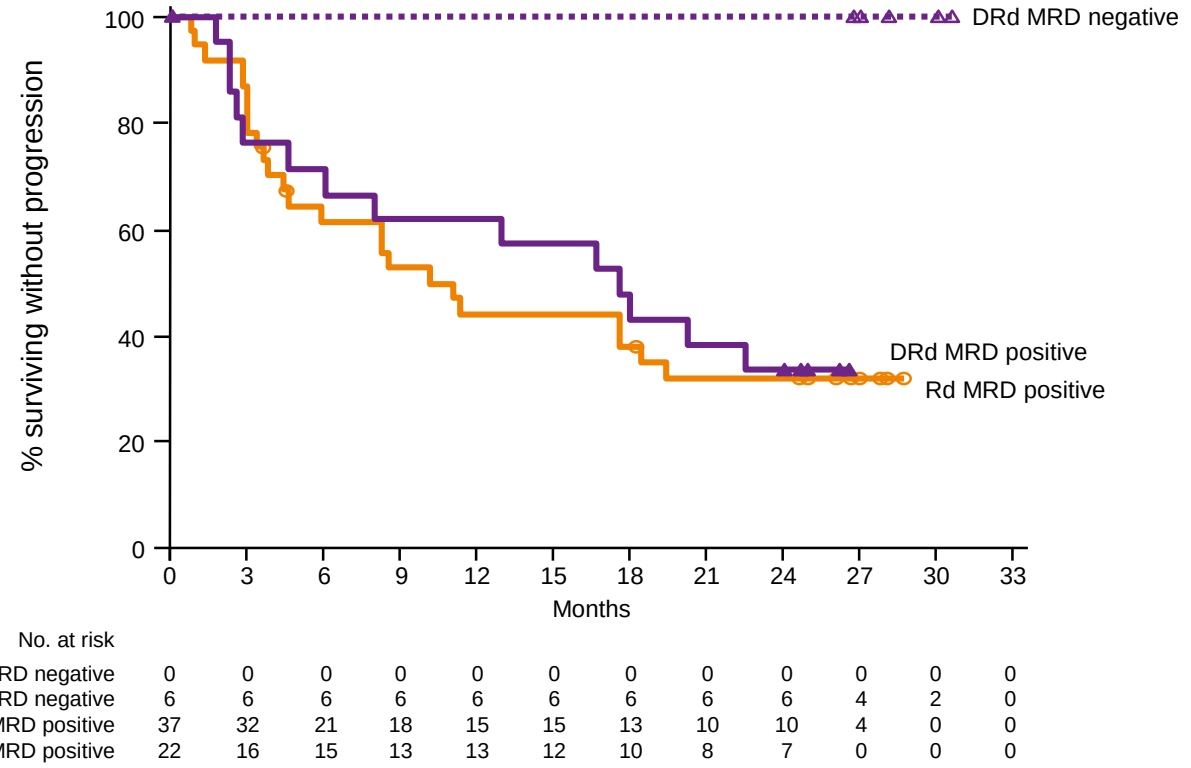
- Lower risk of progression in MRD-negative patients
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

POLLUX: MRD in Patients of High Cytogenetic Risk Status (10^{-5})

MRD-negative rates



PFS



No. at risk

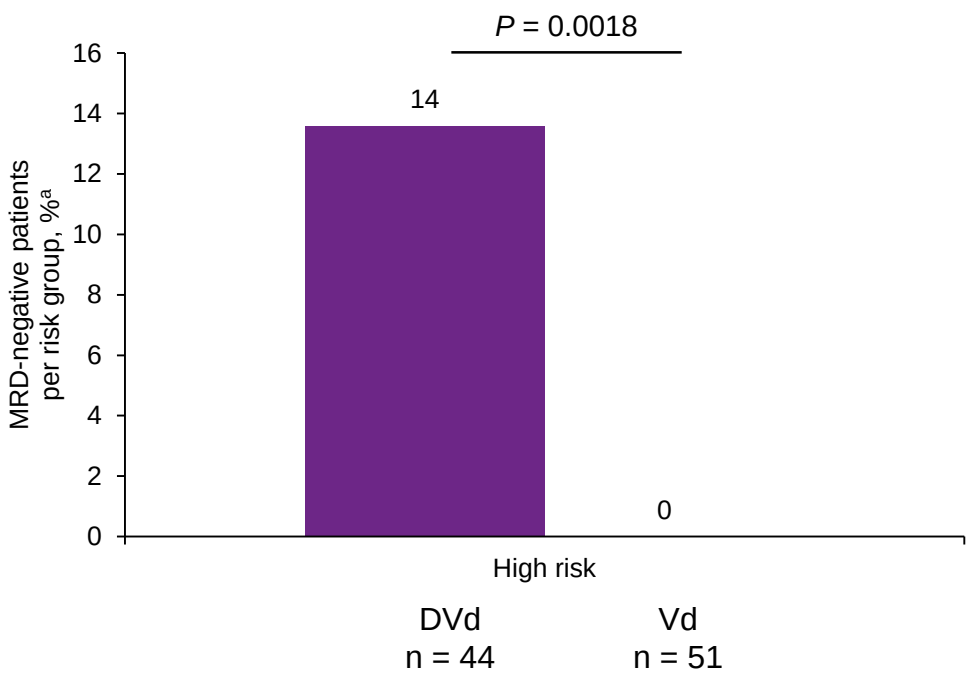
Rd MRD negative	0	0	0	0	0	0	0	0	0	0	0	0
DRd MRD negative	6	6	6	6	6	6	6	6	6	4	2	0
Rd MRD positive	37	32	21	18	15	15	13	10	10	4	0	0
DRd MRD positive	22	16	15	13	13	12	10	8	7	0	0	0

In POLLUX, high-risk patients treated with DARA who were MRD negative remained progression free

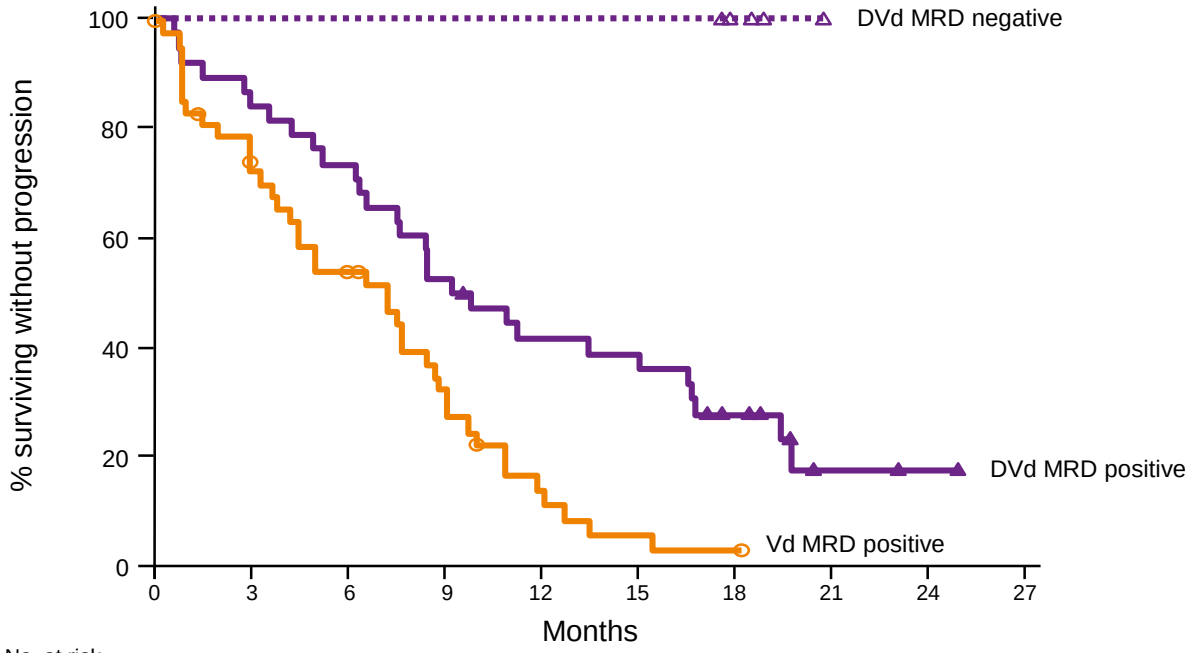
[a]Percentage of patients within a given risk group and treatment arm.

CASTOR: MRD in Patients of High Cytogenetic Risk Status (10^{-5})

MRD-negative rates



PFS



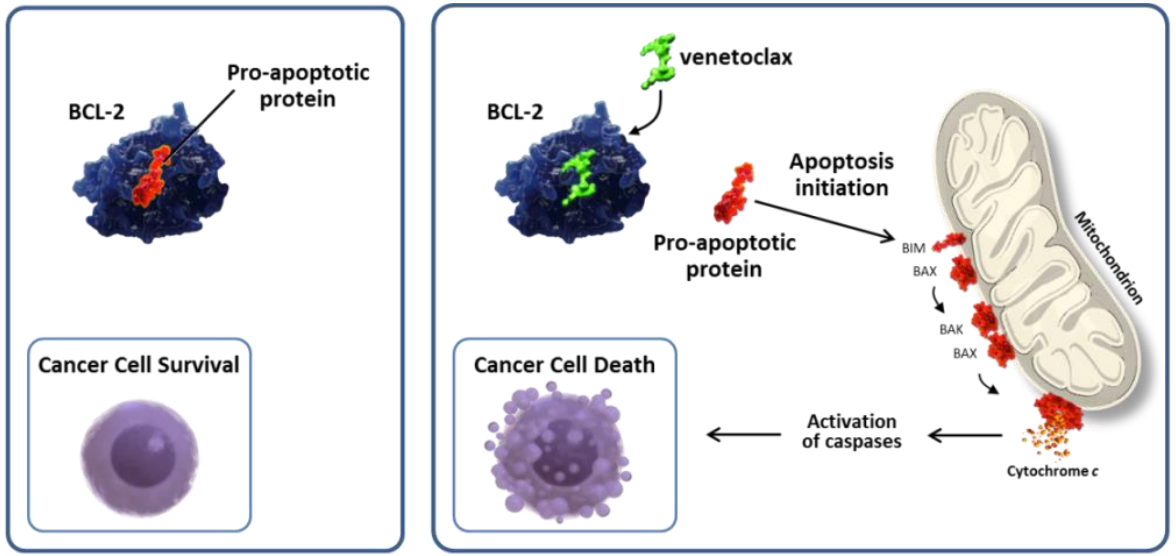
No. at risk										
Vd MRD negative	0	0	0	0	0	0	0	0	0	0
DVd MRD negative	6	6	6	6	6	6	3	0	0	0
Vd MRD positive	51	32	23	13	4	2	1	0	0	0
DVd MRD positive	38	32	28	20	15	14	8	2	1	0

In CASTOR, high-risk patients treated with DARA who were MRD negative remained progression free

[a]Percentage of patients within a given risk group and treatment arm.

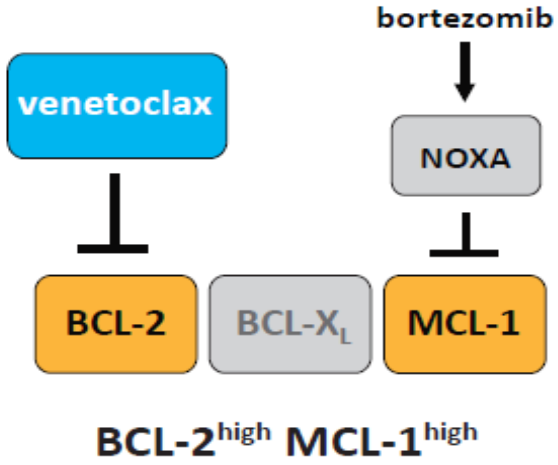
Background

- Anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival
- Venetoclax is a selective, orally available small molecule BCL-2 inhibitor[1] and bortezomib can indirectly inhibit MCL-1[2]
- When combined, venetoclax can enhance the activity of bortezomib in MM cell lines and xenograft models[2]



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

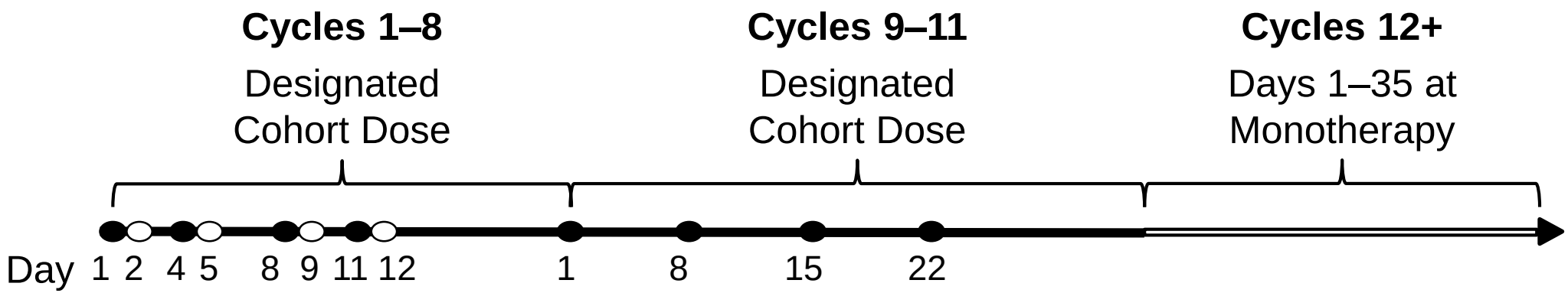


1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296.
4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

1. Roberts AW et al. *N Eng J Med* 2015; 374:311-22
2. Punnoose E et al. *Mol Cancer Ther* 2016;15(5):1132-44

Dosing and Enrollment

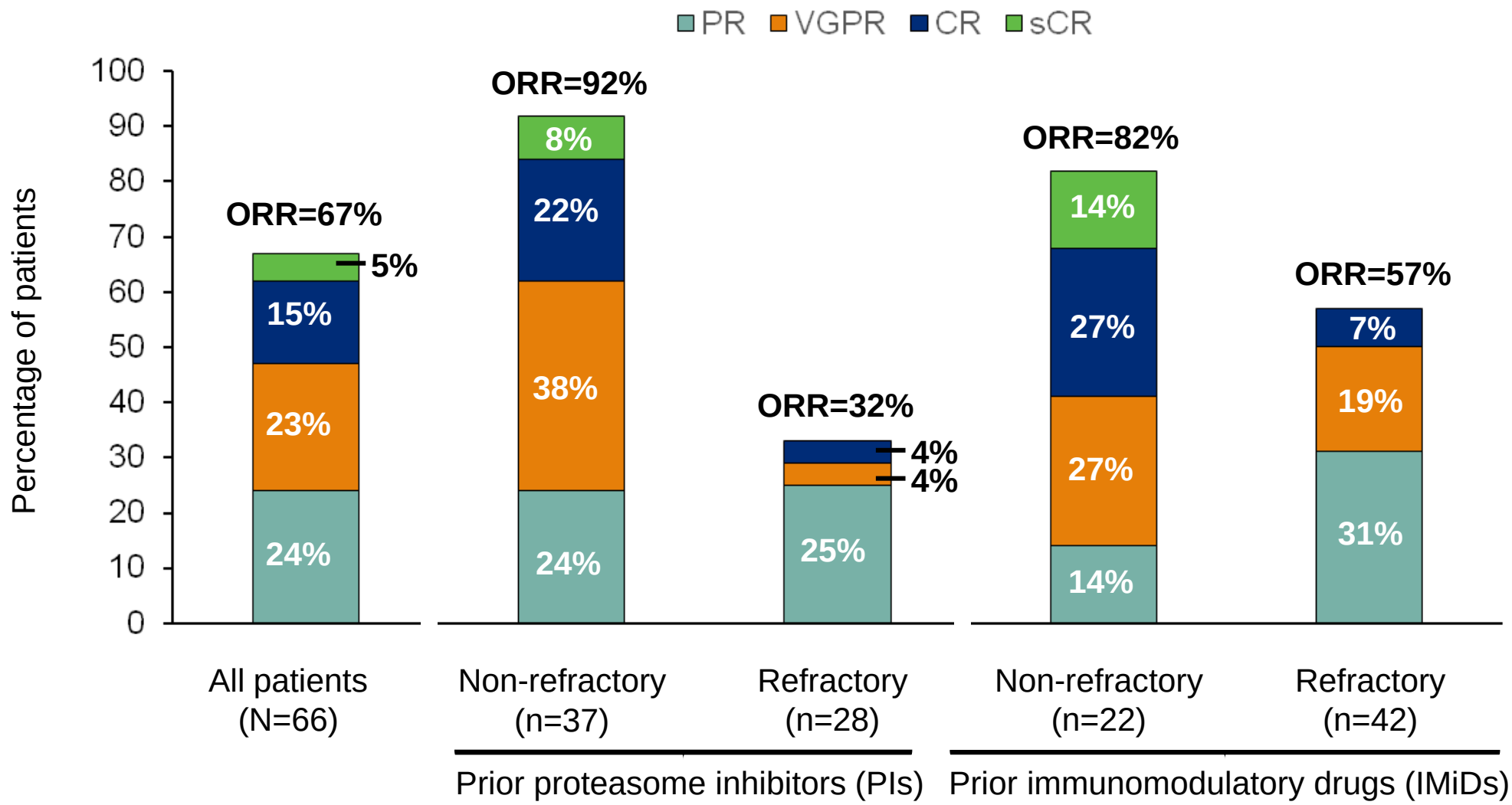
- Patients received 50–1200 mg venetoclax per designated dose escalation cohorts



Enrollment by Dose Cohort													
Dose (mg)	50	100	200	300	400	500	600	800	1000	1200	Total DE	SE	Total DE + SE
n	3	6	5	7	6	7	5	3	3	9	**54**	12	**66**

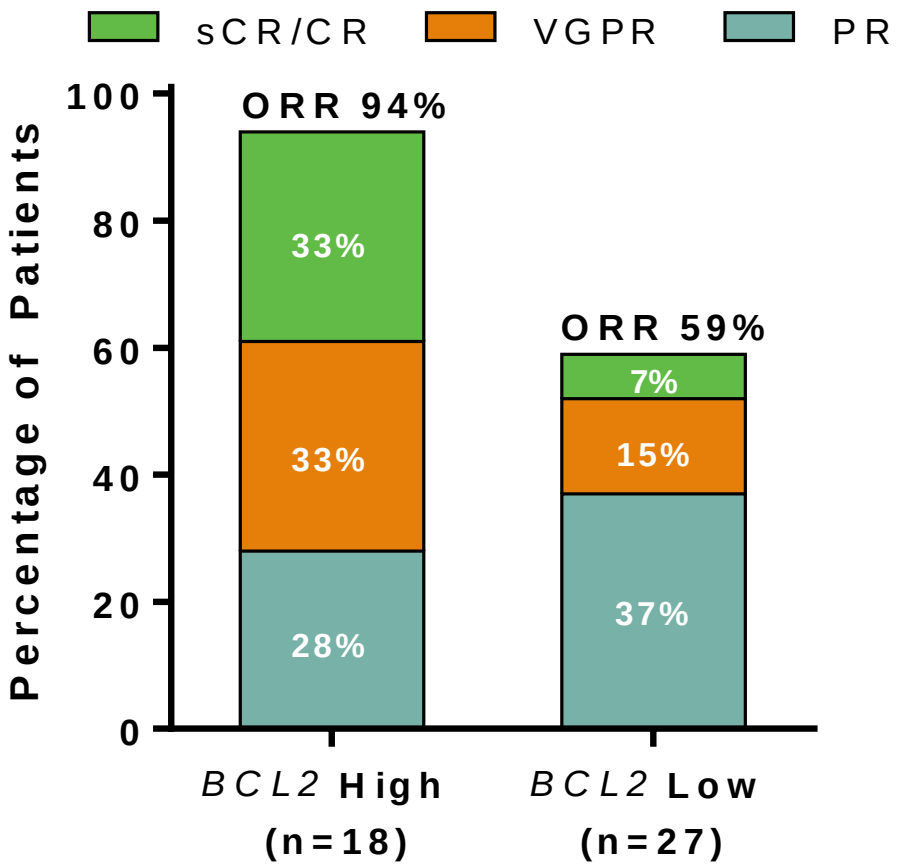
DE, dose escalation cohorts; SE, safety expansion cohort (800 mg)

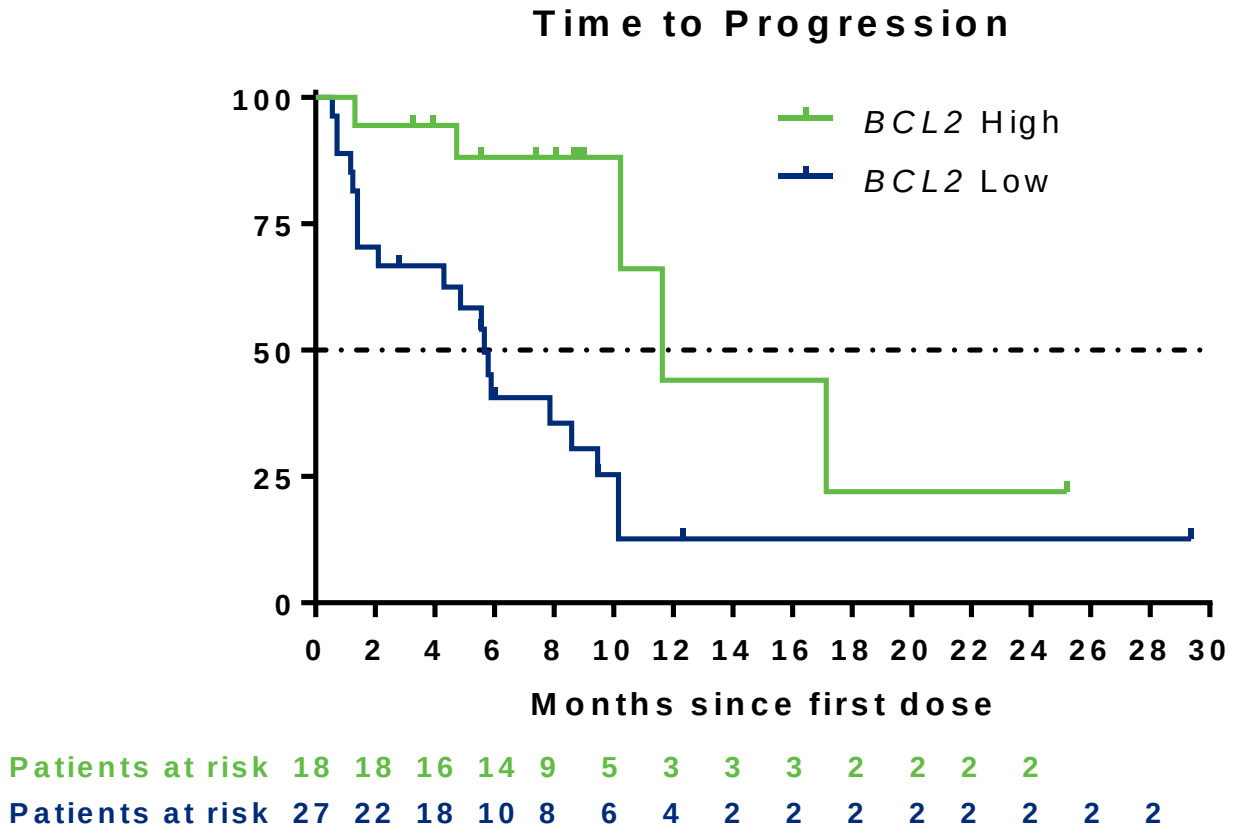
Objective Responses in All Patients and Those Non-Refractory and Refractory to PIs and IMiDs



As of 19Aug2016

BCL2 Gene Expression and Clinical Response





BCL2 quantitation using ddPCR performed on CD138-selected bone marrow mononuclear cells collected at baseline. BATTing was used to estimate a threshold of *BCL2* to provide optimum selection of patients likely to have a response.