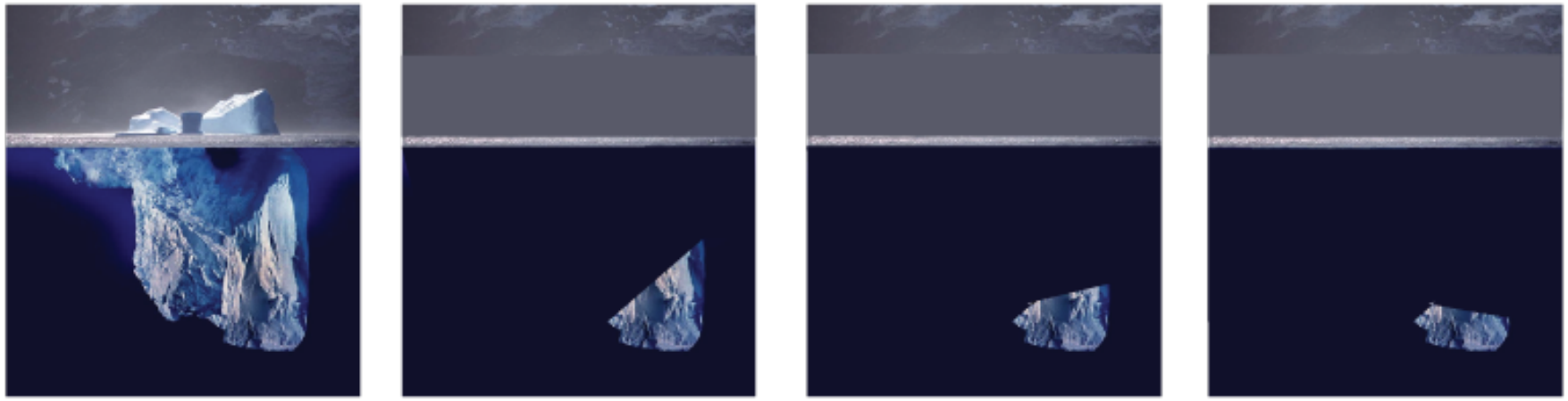
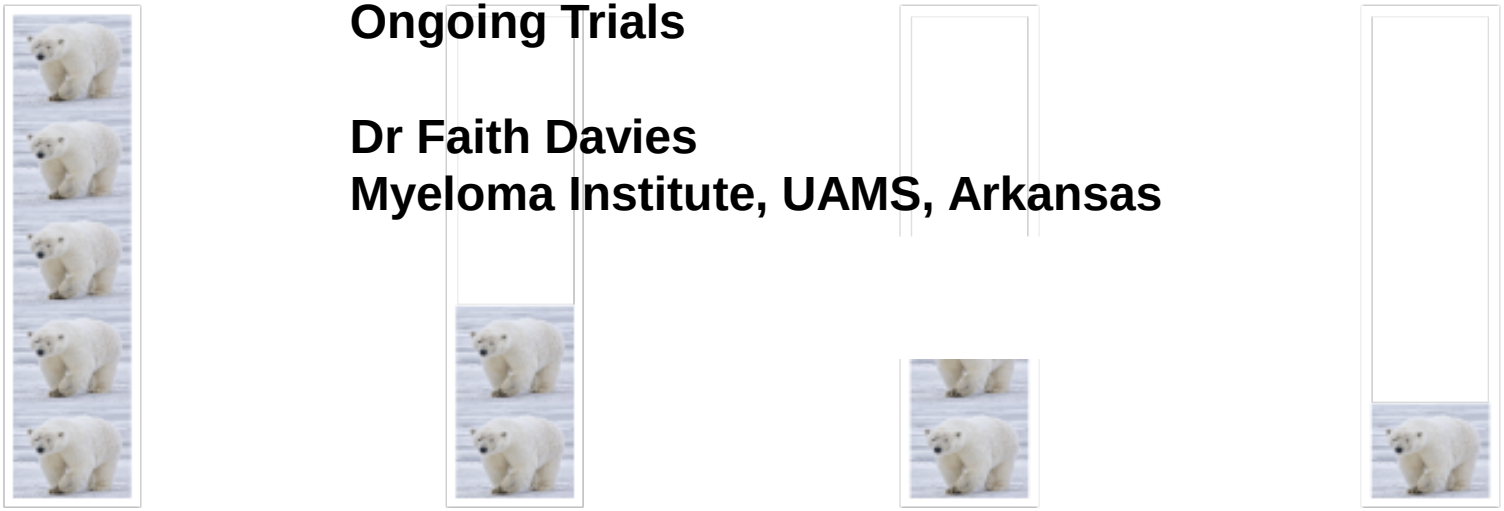


Induction → Transplant → Consolidation

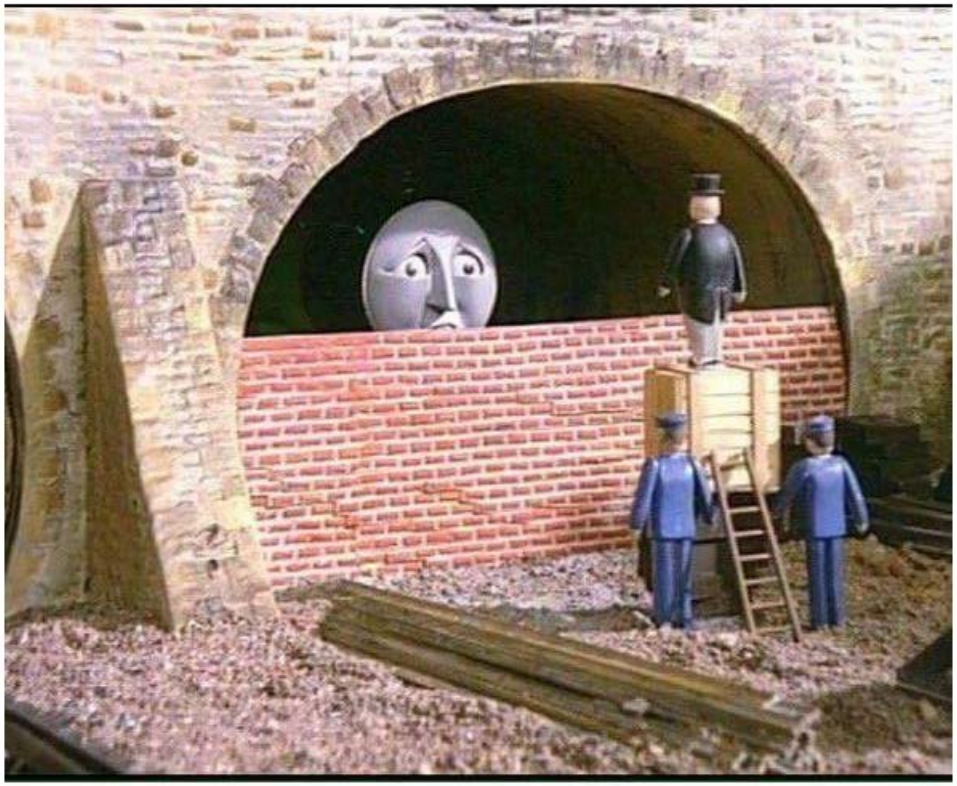
Overall disease bulk:



Ongoing Trials

Dr Faith Davies
Myeloma Institute, UAMS, Arkansas

This just in from the channel tunnel...
#WhatHaveWeDone



MRD studies in Clinical Trials.Gov

June 20 2016 Search terms – Myeloma MRD = 41 studies
Review – 28 studies

NDMM	20	RRMM	8	
IST	16	company	12	(3 phase 1)
Primary EP	4	Secondary EP	21	UKN 3
TE	18	NTE	10	
NGS	4	Flow 3	Both 4	UKN 17

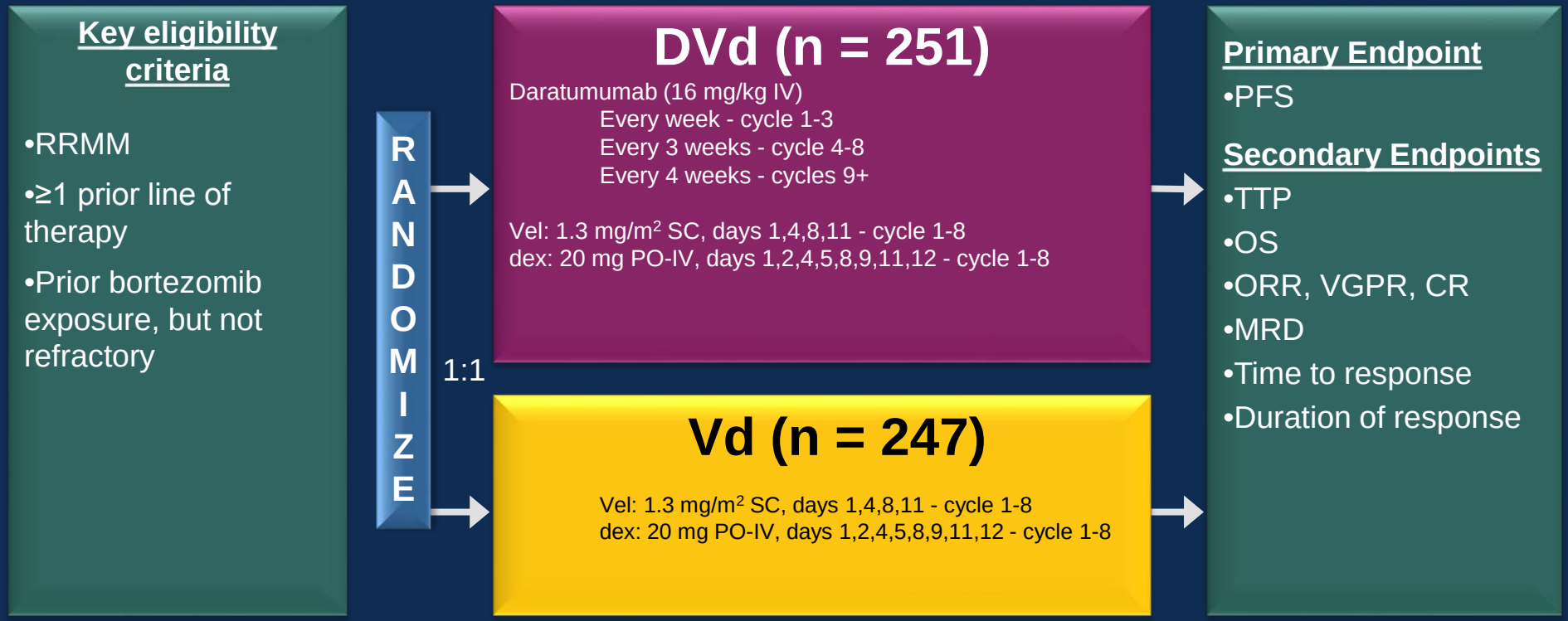
little detail about the timing of MRD, or whether studies are powered for the end points

Recent Data

- MRD response rate with novel treatments
  - FCM
  - NGS
- MRD and outcome
  - FCM
  - NGS
- NDMM and RMM

CASTOR: Study Design

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

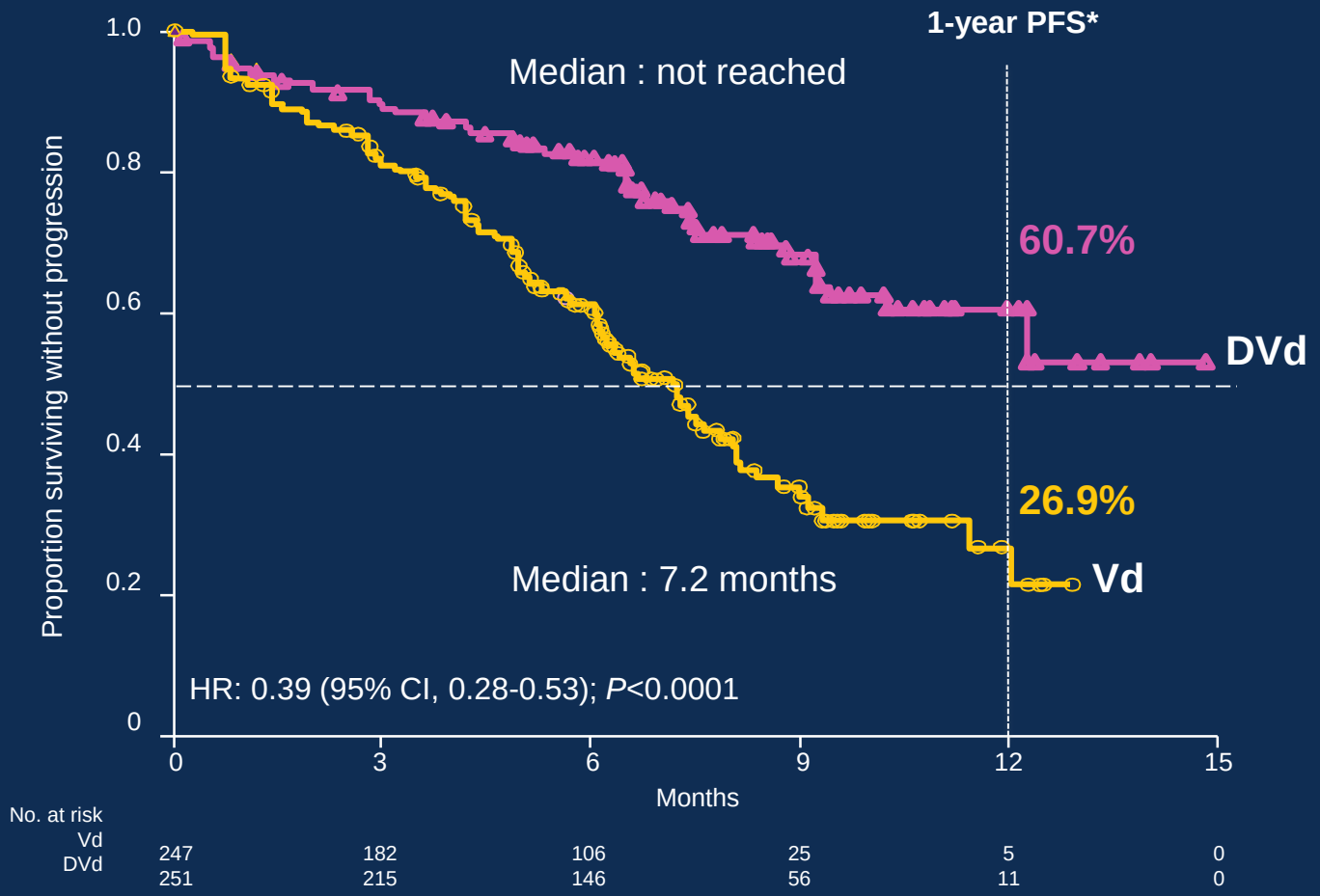


- Cycles 1-8: repeat every 21 days
- Cycles 9+: repeat every 28 days

Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/min permitted

RRMM, relapsed or refractory multiple myeloma; DVd, daratumumab/bortezomib/dexamethasone; IV, intravenous; Vel, bortezomib; SC, subcutaneous; dex, dexamethasone; PO, oral; Vd, bortezomib/dexamethasone; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

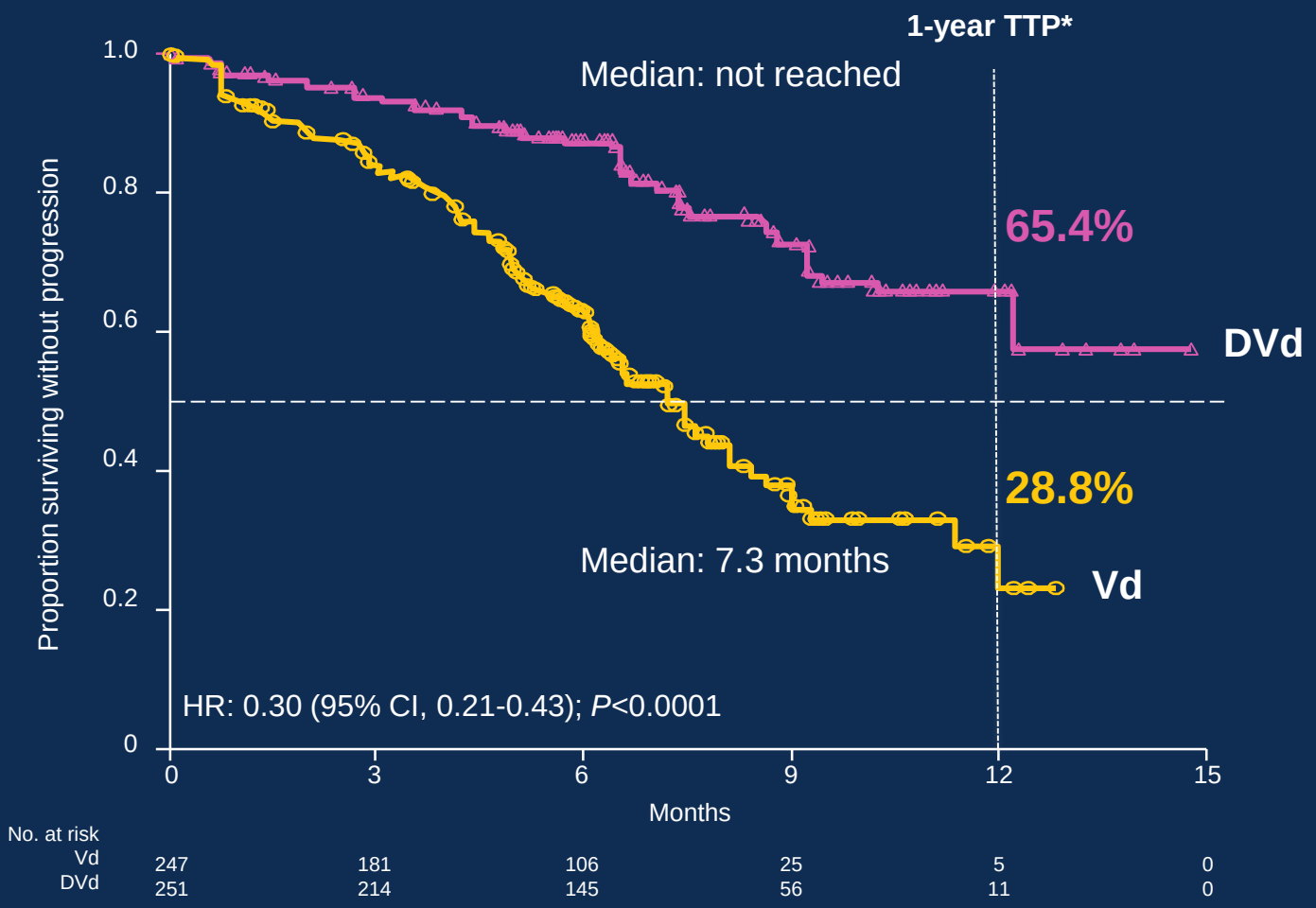
Progression-free Survival



61% reduction in the risk of disease progression or death for DVd vs Vd

*KM estimate; HR, hazard ratio.

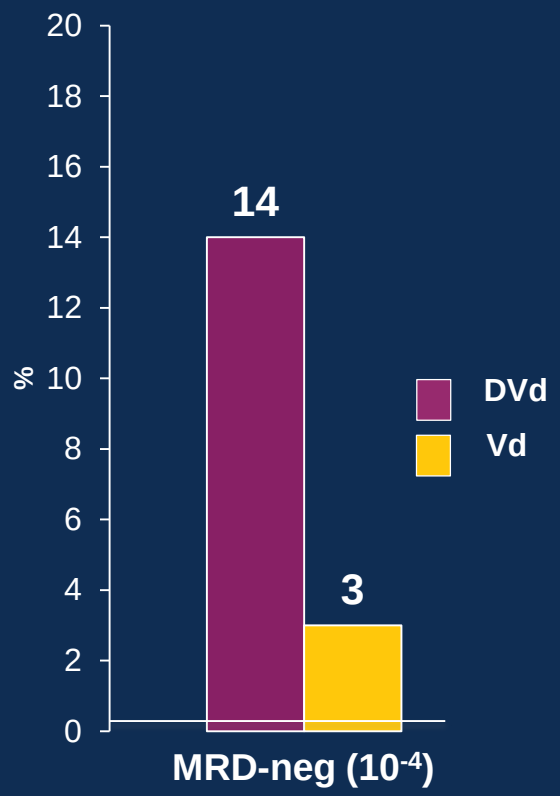
Time to Progression



70% reduction in the risk of disease progression for DVd vs Vd

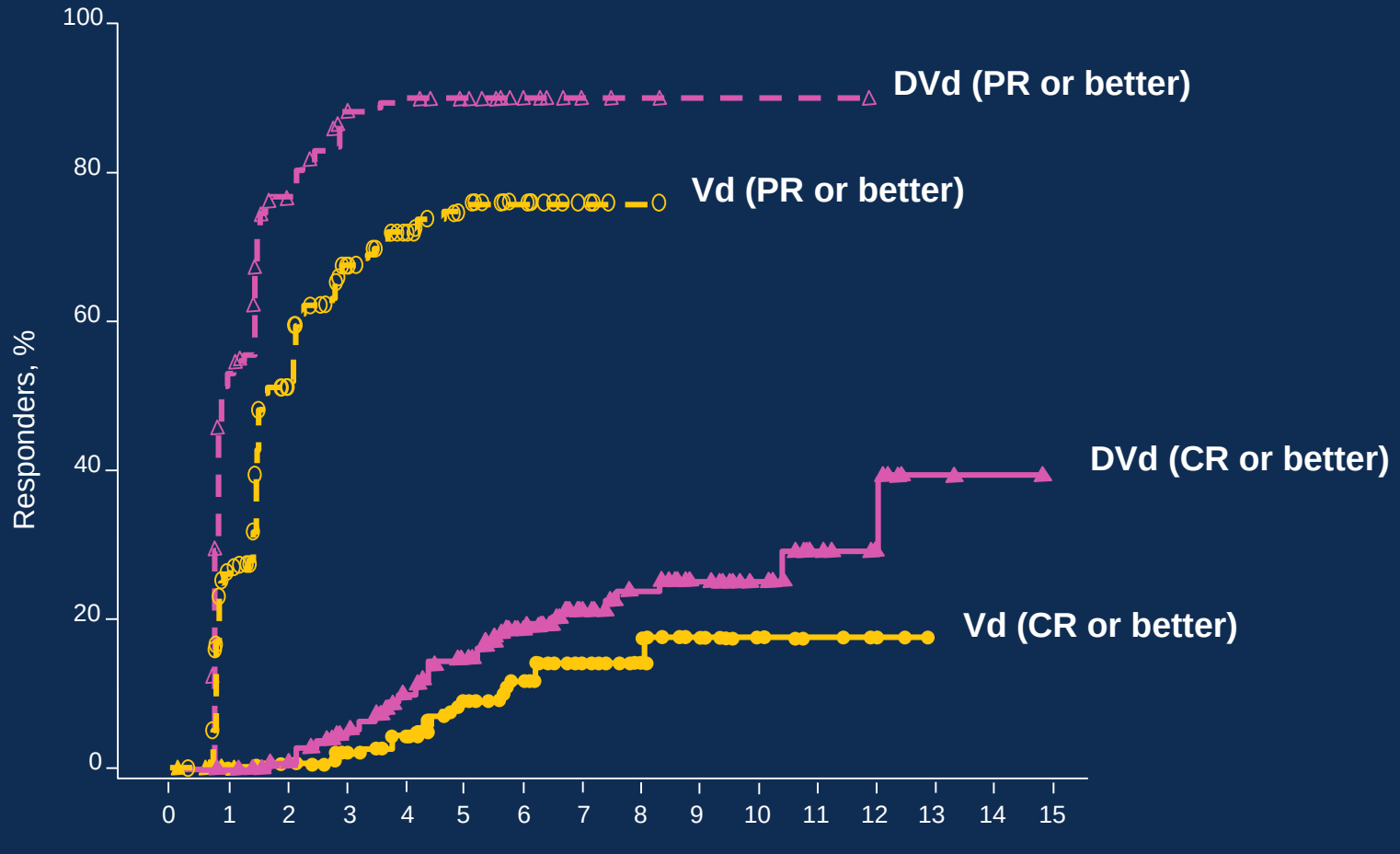
*KM estimate

Overall Response Rate[a]



[a]Response-evaluable population.

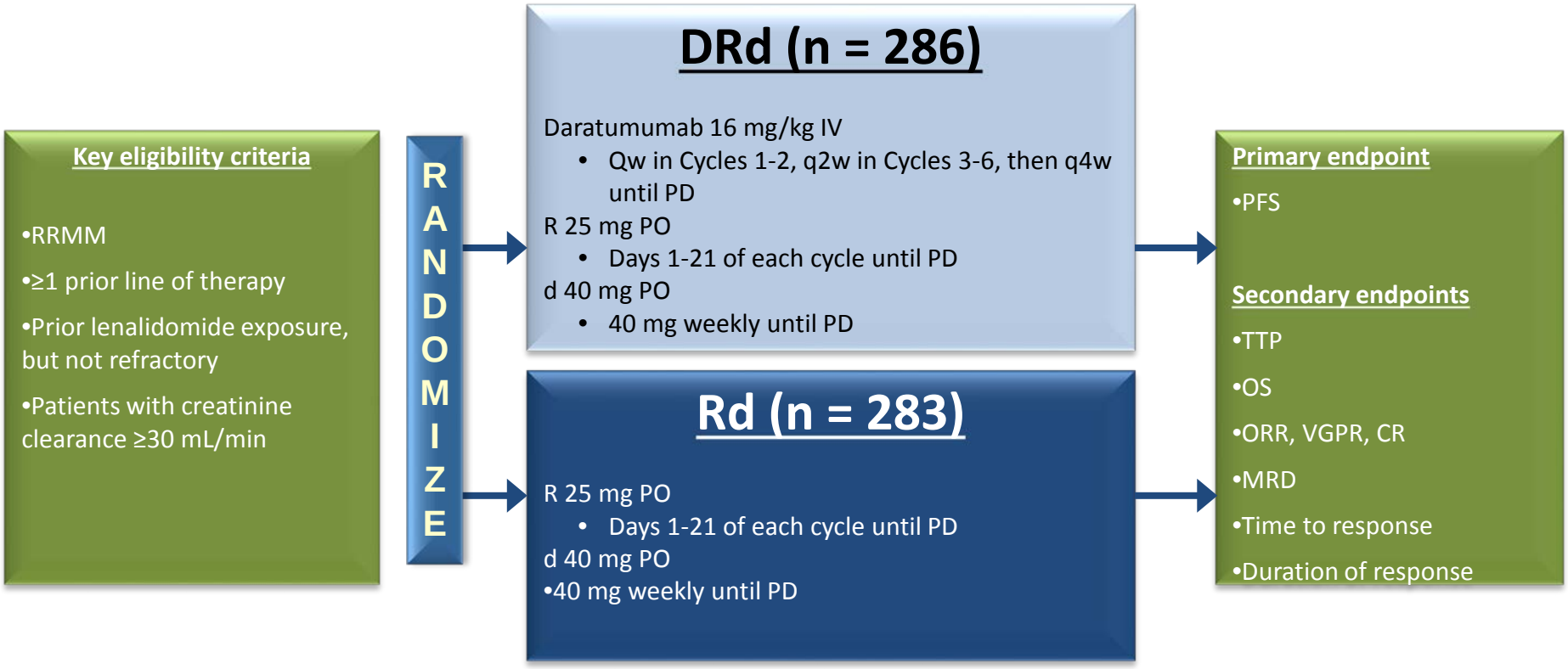
Time to Response



No. at risk

Vd (PR or better)	234	155	89	49	35	21	14	4	1	0	0	0	0	0	0	0
DVd (PR or better)	240	108	48	22	17	14	9	4	2	1	1	1	0	0	0	0
Vd (CR or better)	234	215	197	177	161	121	91	48	27	17	8	5	3	0	0	0
DVd (CR or better)	240	229	220	203	185	163	116	76	55	40	27	13	7	2	1	0

POLLUX: Study Design

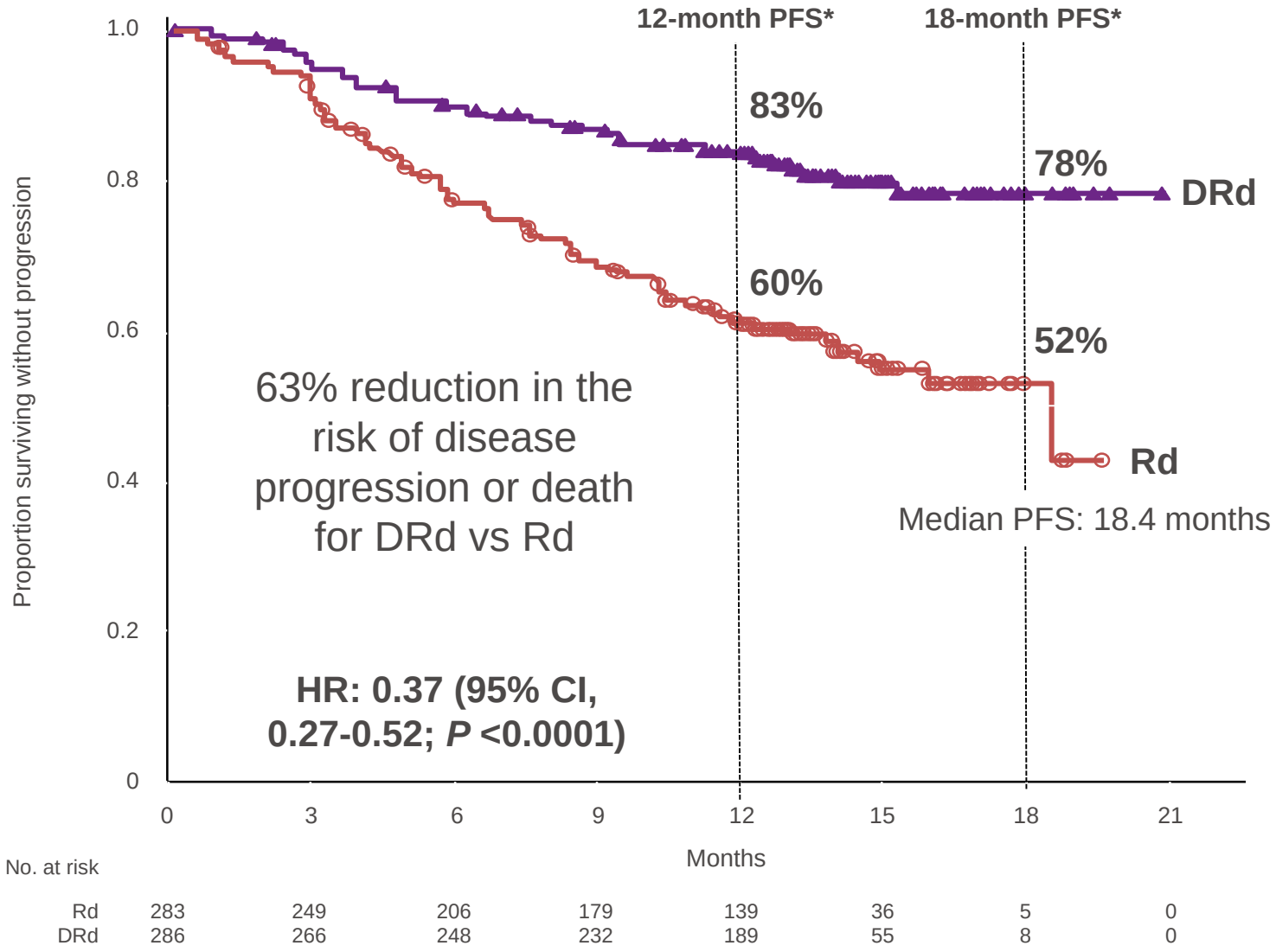


Multicenter, randomized (1:1), open-label, active-controlled phase 3 study

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

Dimopoulos MA, et al. EHA 2016

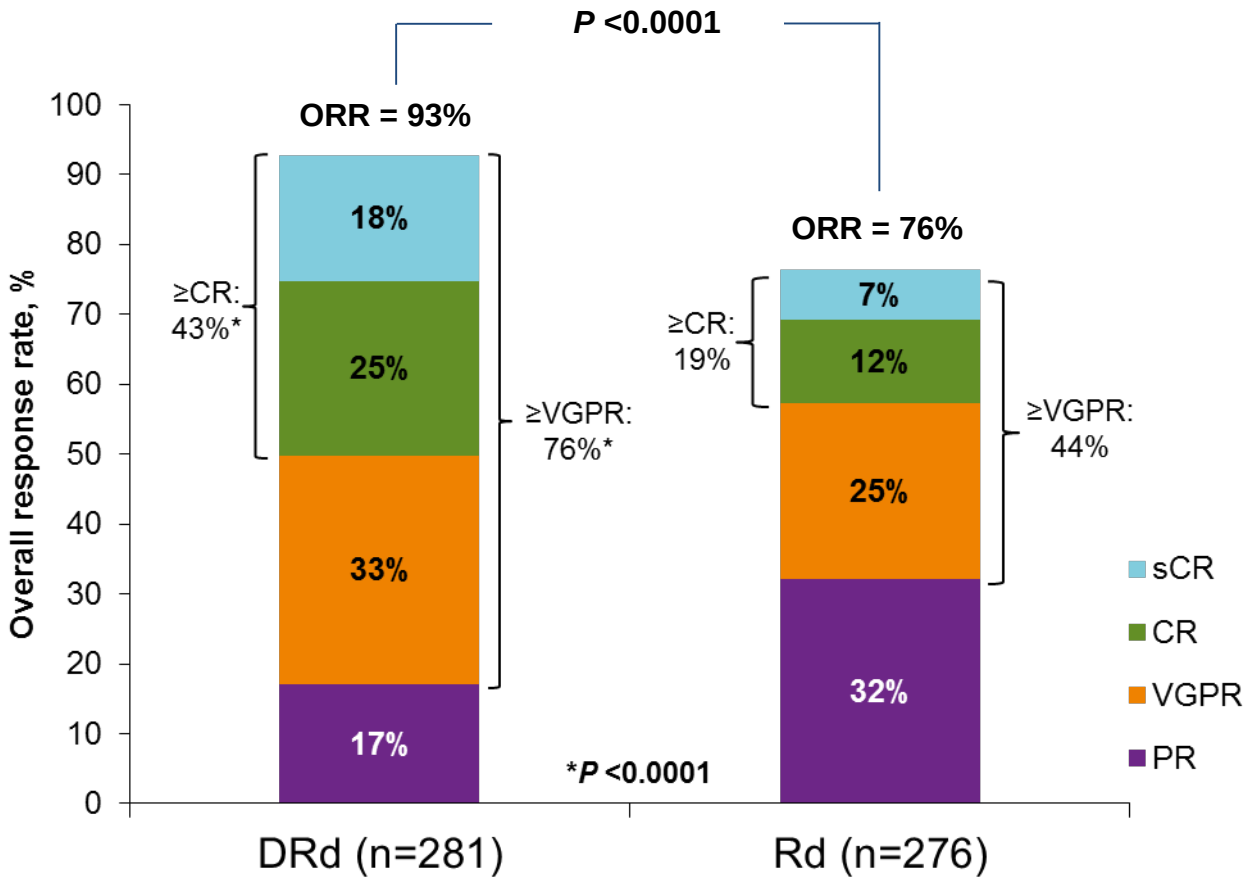
POLLUX: Progression-free Survival



Dimopoulos MA, et al. EHA 2016

11

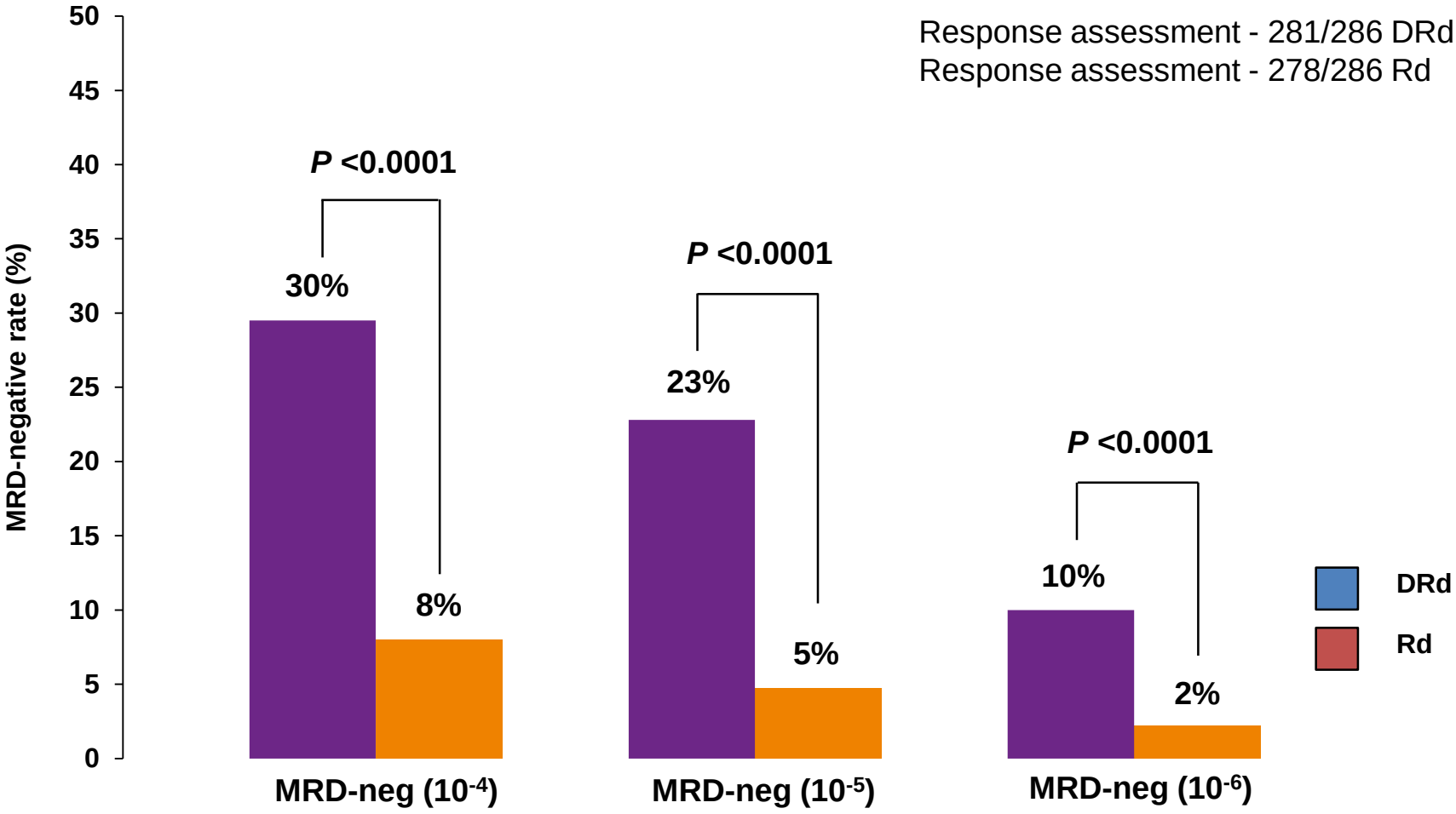
POLLUX: Overall Response Rate



- Median duration of response: Not reached for DRd vs 17.4 months for Rd
- Median time to response: 1.0 month for DRd vs 1.3 months for Rd

Dimopoulos MA, et al. EHA 2016

POLLUX: MRD-negative Rate

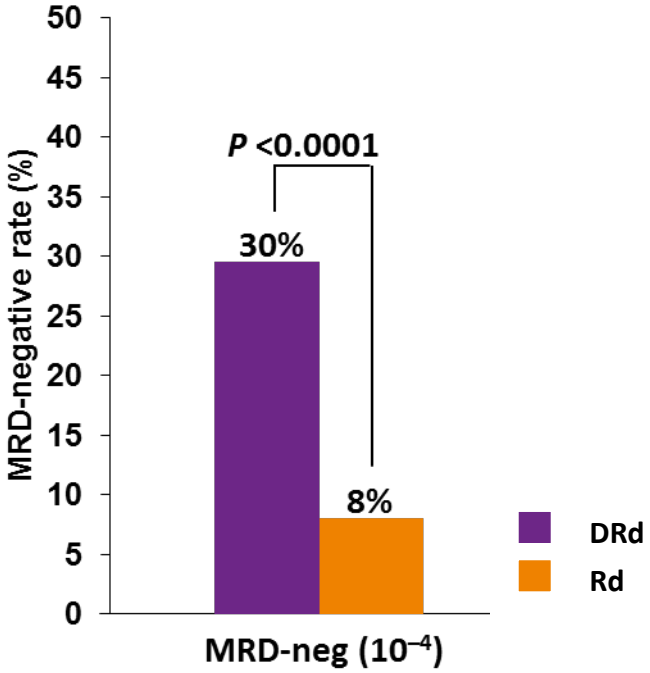


Significantly higher MRD-negative rates for DRd vs Rd

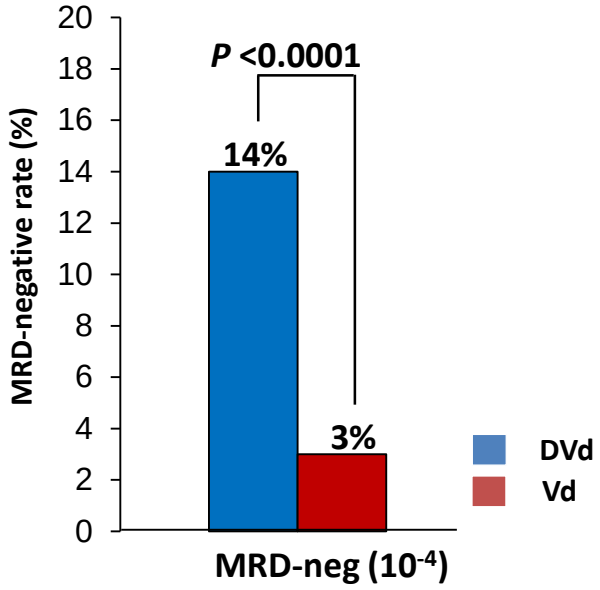
Dimopoulos MA, et al. EHA 2016

MRD by NGS

Pollux (MMY3003)
Rd vs. DRd



Castor (MMY3004)
Vd vs. DVd



- MRD testing using ClonoSIGHT™
- MRD thresholds of 10^{-5} and 10^{-6} were also evaluated
- Evaluated in those suspected of CR (ie VGPR and CR)

Dimopoulos et al.; EHA 2016
Palumbo et al.; ASCO 2016 and EHA 2016

Does the threshold matter?

Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction

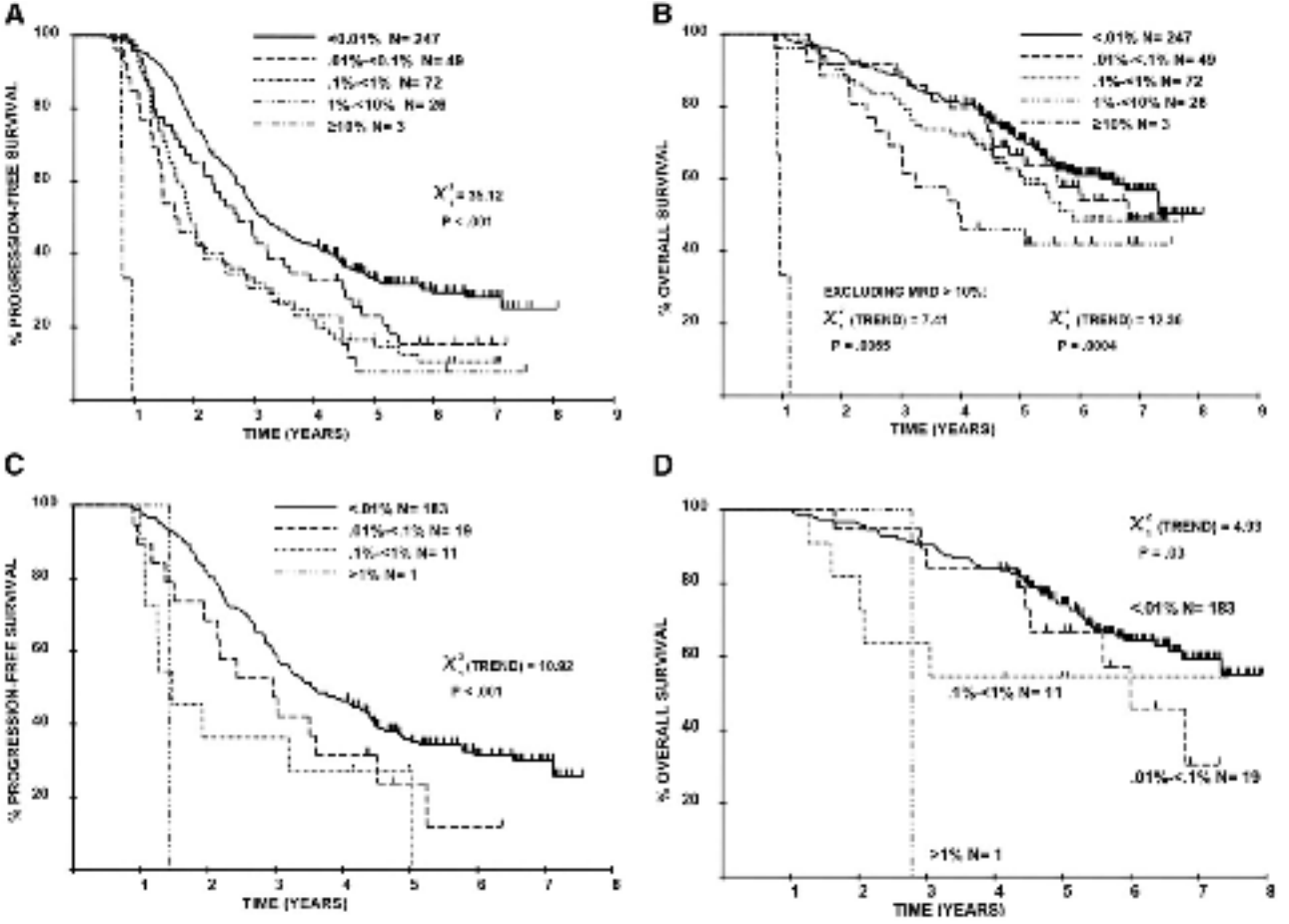


Figure 1. Sequential improvements in PFS and OS for each log depletion in MRD level, as assessed by multiparameter flow cytometry. This effect is demonstrable in all patients ([A] PFS; [B] OS) as well as those achieving conventional CR ([C] PFS; [D] OS).

Rawstron et al Blood 2015

Phase III IFM 2009: RVD ± ASCT in Newly Diagnosed Younger MM Pts

- Primary objective: PFS
- Secondary objectives
  - Response rate
  - MRD
  - Time to progression
  - OS
  - Toxicity

Stratified by ISS stage and cytogenetics

Pts 65 yrs old of age or younger with symptomatic NDMM; ECOG PS < 2 with organ damage and measurable disease*; treated with 1 cycle RVD† (N = 700)

RVD† Cycles 2, 3
PBSC collection
Cyclophosphamide 3 g/m² + **G-CSF**
RVD† Cycles 4-8
(n = 350)

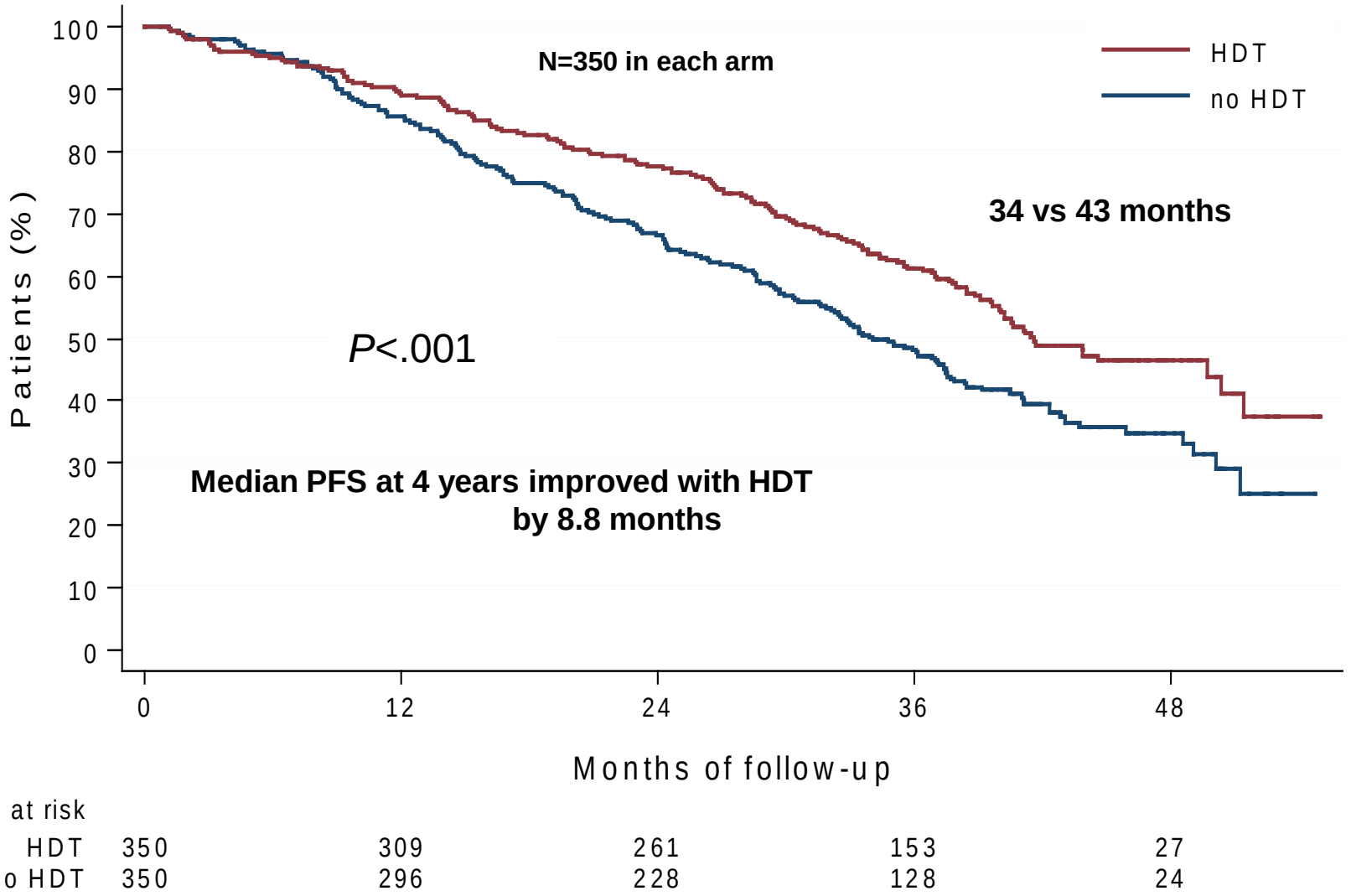
RVD† Cycles 2, 3
PBSC collection
Cyclophosphamide 3 g/m² + **G-CSF**
ASCT with **MEL200**
RVD† Cycles 4, 5
(n = 350)

Lenalidomide Maintenance
10-15 mg/day for 12 mos

*Serum M-protein > 10 g/L and/or urine M-protein > 200 mg/24 hrs and/or serum FLC > 100 mg/L if serum FLC ratio is abnormal.
†Lenalidomide 25 mg/day on Days 1-14; bortezomib 1.3 mg/m² on Days 1, 4, 8, 11; dexamethasone 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11, 12.

Attal M, et al. ASH 2015. Abstract 391.

IFM 2009: PFS (9/2015)



Median follow up 41 months
31% reduced risk of progression or death (P < .001)

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

IFM 2009: Responses

Response, %	RVD (n = 350)	Transplantation (n = 350)	*P* Value
CR	49	59	.02
VGPR	29	29	
PR	20	11	
< PR	2	1	
≥ VGPR	78	88	.001
Negative MRD by FCM	65	80	.001

- important that MRD performed at a number of different time points

Attal M, et al. ASH 2015. Abstract 391.

IFM 2009: PFS Prognostic Factors

PFS Prognostic Factor	Multivariate Analysis: Adjusted HR	*P* Value
Treatment arm: no transplant vs transplant	0.80	.02
ISS stage		
▪ II vs I	1.33	.02
▪ III vs I	1.45	.01
FISH	2.22	< .001
▪ High risk vs standard risk		
CR	0.58	< .001
Negative MRD by flow cytometry	0.39	< .001

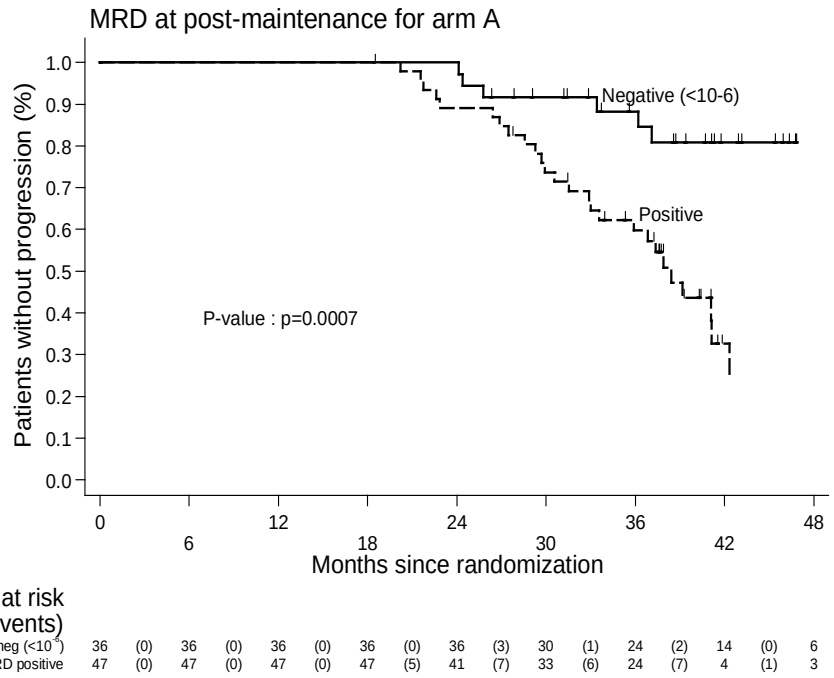
- Median PFS with negative MRD significantly longer in each arm ($P < .001$)
- TTP significantly different between arms ($P < .001$)

Attal M, et al. ASH 2015. Abstract 391.

IFM/DFCI 2009: PFS According to MRD Post Maintenance

NGS

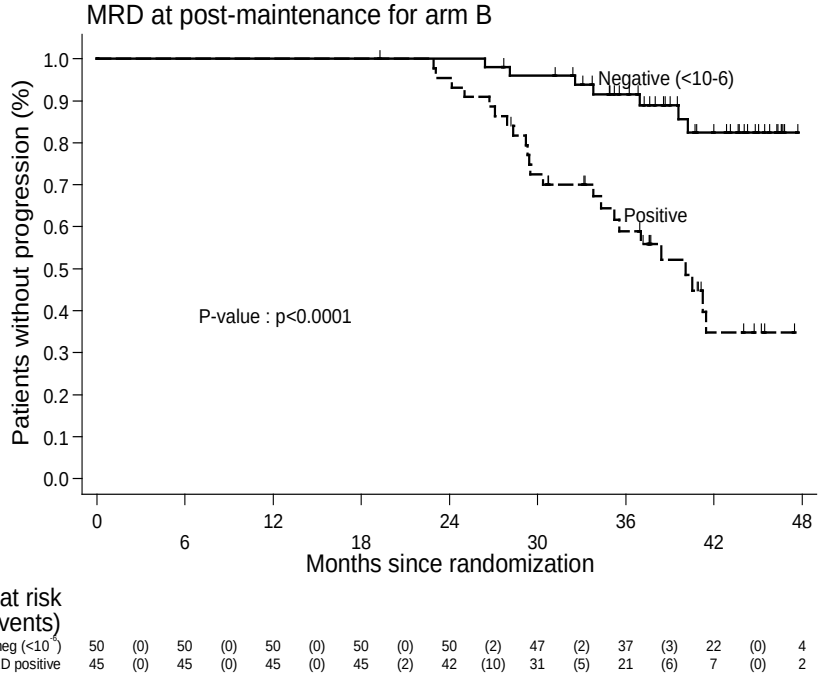
RVD Arm



N at risk (events)

MRD neg (<10^{-6})	36	(0)	36	(0)	36	(0)	36	(0)	36	(3)	30	(1)	24	(2)	14	(0)	6
MRD positive	47	(0)	47	(0)	47	(0)	47	(5)	41	(7)	33	(6)	24	(7)	4	(1)	3

Transplant Arm

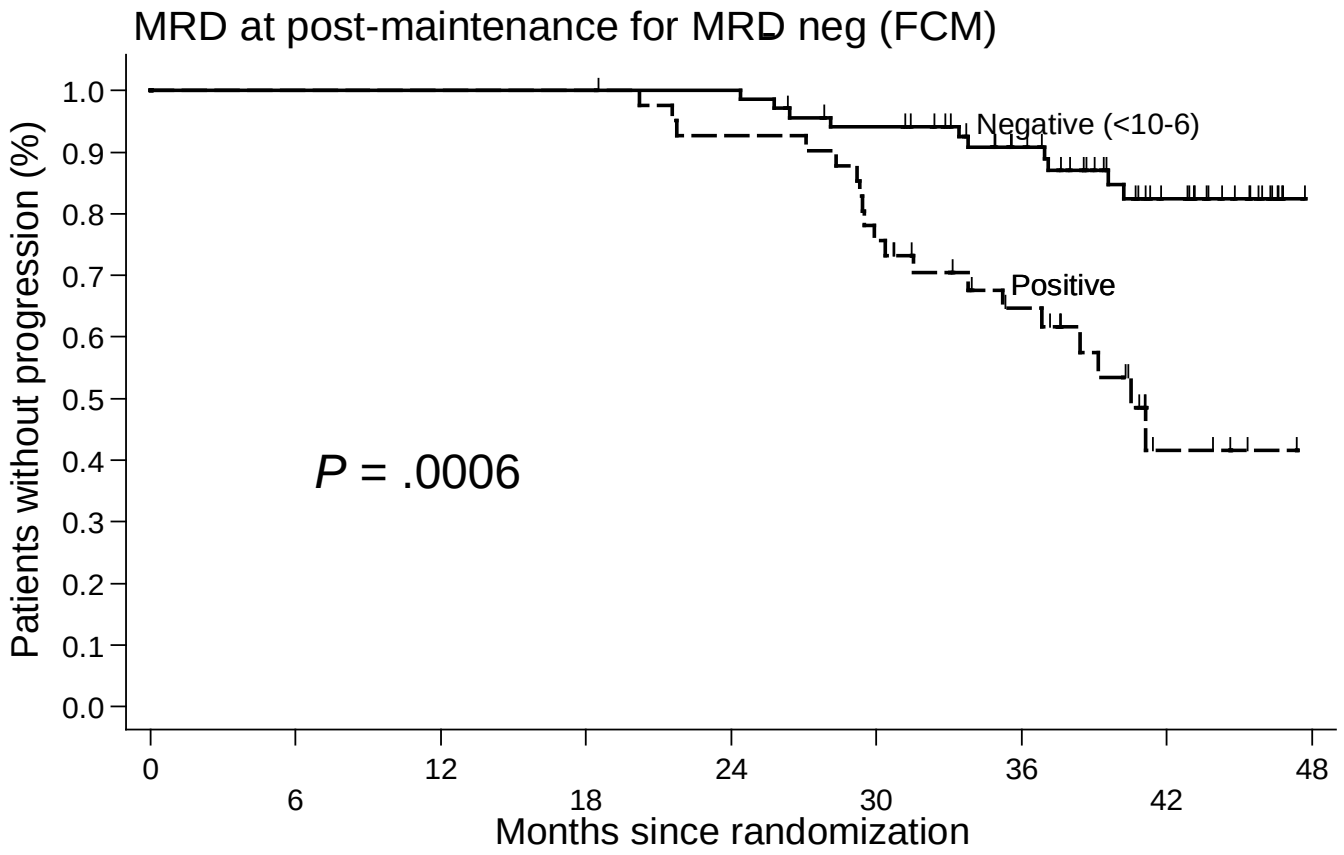


N at risk (events)

MRD neg (<10^{-6})	50	(0)	50	(0)	50	(0)	50	(0)	50	(2)	47	(2)	37	(3)	22	(0)	4
MRD positive	45	(0)	45	(0)	45	(0)	45	(2)	42	(10)	31	(5)	21	(6)	7	(0)	2

Avet-Loiseau H, et al. *Blood.* 2015;126: Abstract 191.

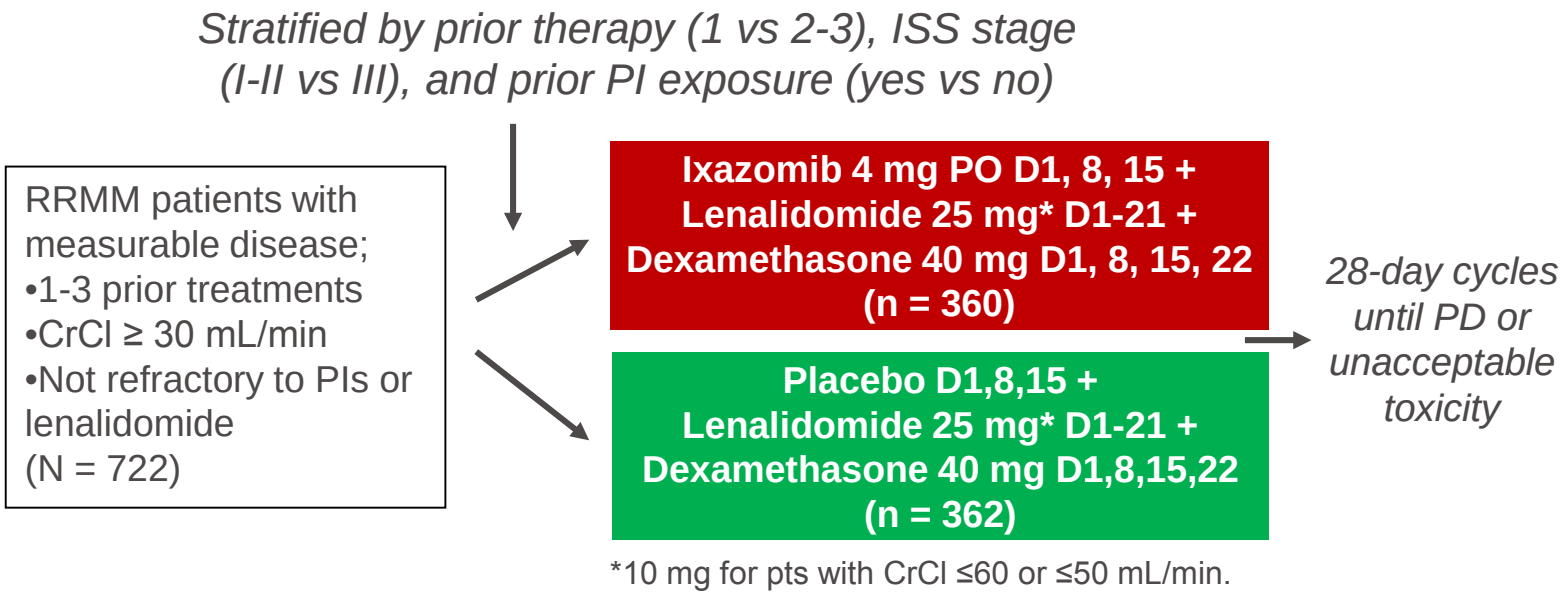
IFM/DFCI 2009: In Flow-Based MRD-Negative Patients Molecular MRD Status Predicts Survival Post Maintenance



Avet-Loiseau H, et al. *Blood.* 2015;126: Abstract 191.

TOURMALINE-MM1: Study Design

- Randomized, double-blind, placebo-controlled phase III trial[1]

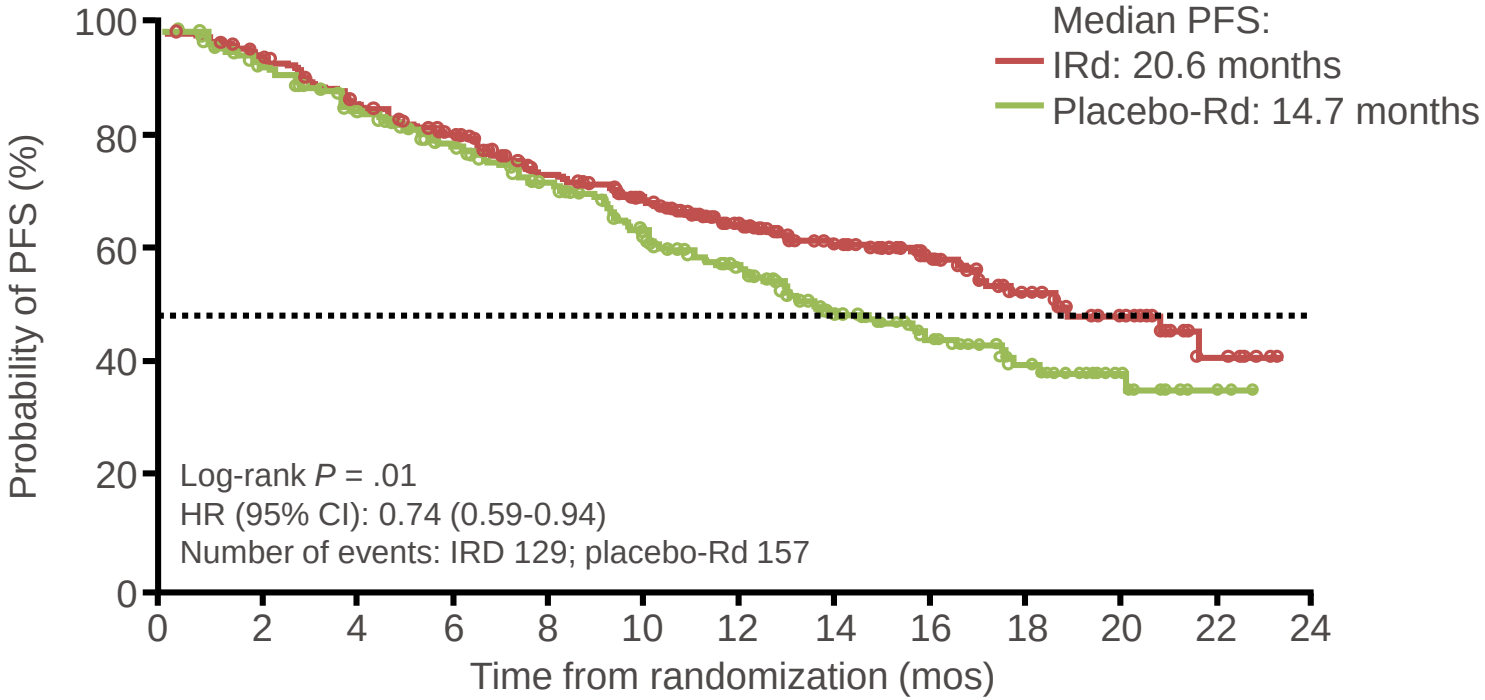


- Primary endpoint: PFS by IRC per IMWG criteria[2]
- Secondary endpoints (data not yet mature): OS, OS in del(17p) patients

1. Moreau P, et al. *N Engl J Med.* 2016;374(17):1621-1634. 2. Rajkumar SV, et al. *Blood.* 2011;117(18):4691-4695.

TOURMALINE-MM1: PFS

- Addition of ixazomib to Rd resulted in 35% improvement in PFS vs Rd alone



- PFS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high risk, PI and IMiD exposed

Moreau P, et al. *N Engl J Med.* 2016;374(17):1621-1634.

TOURMALINE-MM1: Outcomes by Cytogenetic Risk Group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543*
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

*$P < .05$ for comparison between regimens. †Alone or in combination with t(4;14) or t(14;16)
Data not included on patients with t(14;16) alone due to small numbers (n = 7)

- Median OS was not reached in either arm
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

Moreau P, et al. *Blood.* 2015;126: Abstract 727. Moreau P, et al. *N Engl J Med.* 2016;374(17):1621-1634.

MRD measurements in Tourmaline MM trials

- **Tourmaline MM2**
  - **NDMM (Ixazomib/Rd vs Placebo/Rd) [enrollment complete]**
  - **MRD measurement done in Bone Marrow using flow. Samples taken from patient achieving CR and at cycle 18**

- **Tourmaline MM3**
  - **NDMM post-SCT - maintenance trial (Ixazomib vs Placebo) [enrollment complete]**
  - **MRD measurements done in Bone Marrow using flow and NGS, and in blood using NGS. Samples taken from all CR and VGPR patients at screening and after 1 and 2 years of therapy. Patients entering the trial with a PR, and upgrading their response to CR, will be also assessed for MRD**
  - **Genomic characterization of MRD positive samples, if available**

- **Tourmaline MM4**
  - **NDMM no-SCT - maintenance trial (Ixazomib vs Placebo) [currently enrolling]**
  - **MRD measurements done in Bone Marrow using flow and NGS. Samples taken from all CR patients at screening and after 1 and 2 years of therapy. Patients entering the trial with a PR, and upgrading their response to CR, will be also assessed for MRD**
  - **Genomic characterization of MRD positive samples, if available**

Venetoclax (ABT-199) + Vd in R/R MM: Background

- Venetoclax: potent, selective inhibitor of BCL2 that promotes apoptosis[1]
  - Resistance likely mediated via MCL-1
- Bortezomib: MCL-1 inhibitor, active by promoting expression of NOXA, which neutralizes MCL-1 and induces degradation
- Addition of venetoclax to bortezomib enhanced tumor growth inhibition and DoR in MM xenograft models[2]
- Current study evaluated safety, activity of adding venetoclax to Vd in R/R MM pts[3]

1. Roberts AW, et al. N Engl J Med. 2016;374:311-322. 2. Punnoose EA, et al. Mol Cancer Ther. 2016;15:1132-1144. 3. Moreau P, et al. ASCO 2016. Abstract 8011.

Venetoclax + Vd in R/R MM: Study Design

- Multicenter, open-label phase Ib study of venetoclax in combination with Vd; dose escalation and expansion cohorts planned
  - Venetoclax 50-1200 mg PO for cycles 1-12+
  - Bortezomib 1.3 mg/m^3 SC on Days 1, 4, 8, 11 for cycles 1-8 and Days 1, 8, 15, and 22 for cycles 9-11
  - Dexamethasone 20 mg PO on Days 1, 2, 4, 5, 8, 9, 11, 12 for cycles 1-8 and Days 1, 2, 8, 9, 15, 16, 22, 23 for cycles 9-11
  - Dosing cycle: 21 days for cycles 1-8, 35 days subsequently
- Primary objectives: safety and tolerability, MTD, RP2D, PK
- Secondary/exploratory objectives: ORR, TTP, DoR, biomarkers

Moreau P, et al. ASCO 2016. Abstract 8011.

Venetoclax + Vd in R/R MM: Phase 3

- Encouraging safety and response rates observed in phase 1b
  - 58% ORR in overall cohort
  - Higher ORRs in pts not refractory to bortezomib (84%) and those who had received only 1-3 prior lines of therapy (84%)
  - Higher *BCL2* expression associated with improved response
- planned phase III trial of this regimen in R/R MM pts
- V-Vel Dex vx placebo Vel Dex
- MRD secondary endpoint in patients who potentially achieve CR by NGS

Moreau P, et al. ASCO 2016. Abstract 8011.

Conclusions

- Numerous Commercial and Investigator led studies with MRD as secondary end point
  - Multi-centre
  - Can be measured
  - FCM and NGS
  - QA/QC

Outstanding Questions

Is MRD the same in a high risk patient
eg IFM 700 patient study – if looking at FCM negative patients and splitting by NGS result = 100 pts ……is there enough power to look at HRMM?

Who should we be measuring it in……..
All patients or just those that achieve a CR
Needs to be clearly stated

Timing
Potentially easier in TE patients (defined disease phases)
When is appropriate in NTE
One time point or multiple