Are We Integrating Biologic Advances in Multiple Myeloma Into Clinical Practice?

Minimal Residual Disease: A Measurable and Relevant Endpoint in Treatment

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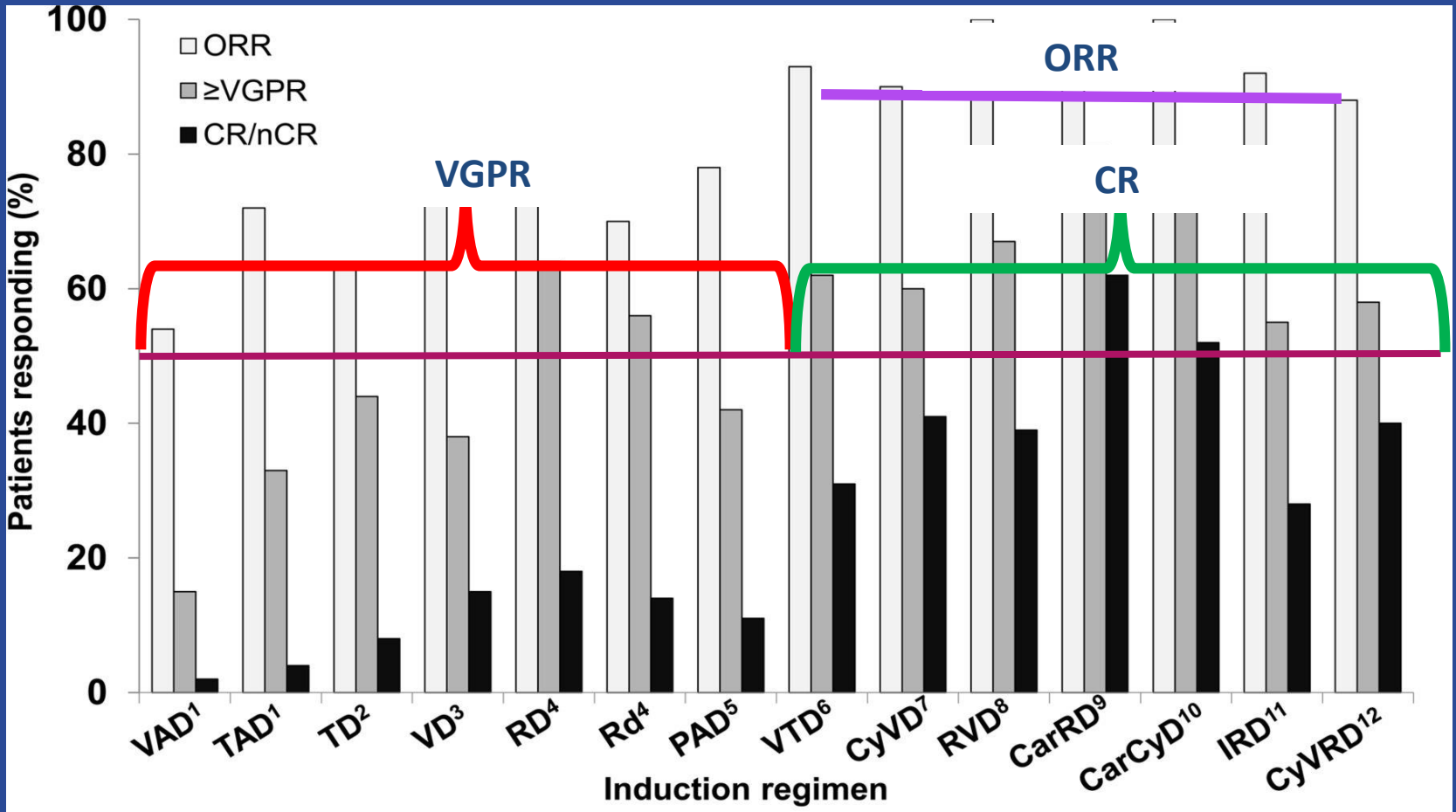
MRD: A Measurable and Relevant Endpoint in Treatment

- Depth of response in Myeloma
  - Are all CR the same
- What is MRD
  - Techniques: NGF vs NGS
  - Is it just about prolongation of PFS as a surrogate for OS
- Prognostic role of MRD
  - MRD impacts OS
- MRD Rate and relevance in current treatment options and strategies
  - MRD in NDMM
  - MRD in RRMM
  - MRD Including high risk MM
- Depth of MRD matters
- Work to do
- Conclusion

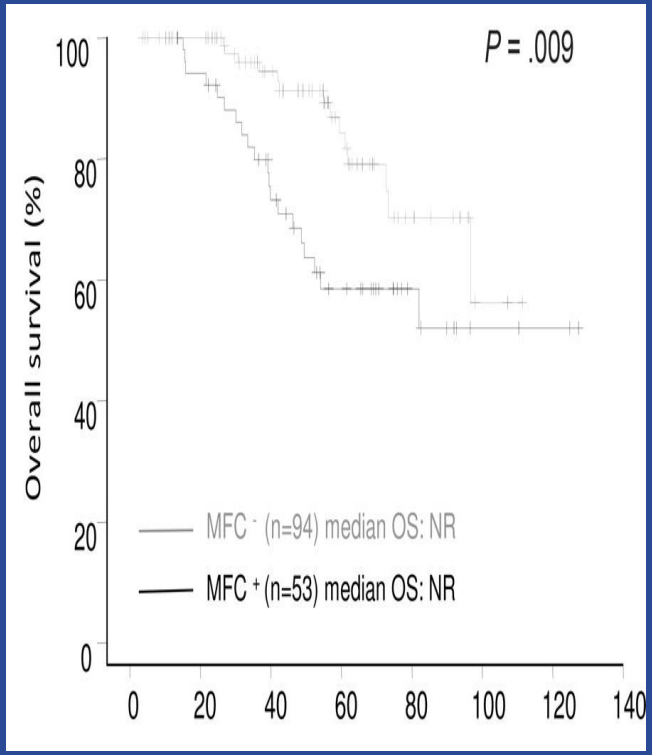
Treatment advances have increased the likelihood of achieving CR



1. Lokhorst HM, et al. Haematologica. 2008;93:124-7. 2. Rajkumar SV, et al 2008 J Clin Oncol 26:2171-77. 3. Harousseau JL, et al 2010 J Clin Oncol 28:4621-4629. 4. Rajkumar SV, et al Lancet Oncol 2010; 11: 29–37. 5. Sonneveld P, et al J Clin Oncol 2012; 30:2946-55. 6. Cavo M, et al Lancet 2010; 376: 2075–85. 7. Reeder CB, et al. Blood. 2010; 115:3416-7. 8. Richardson et al. Blood 2010;116:679-686. 9. Jakubowiak AJ, et al Blood. 2012 30;120:1801-9. 10. Palumbo A, et al. Blood. 2012;120:[abstract 730]. 11. Kumar S, et al . Blood. 2012;120:[abstract 332]. 12. Kumar S, et al. Blood 2012 119: 4375-82.

The prognostic impact to CR comes from MRD

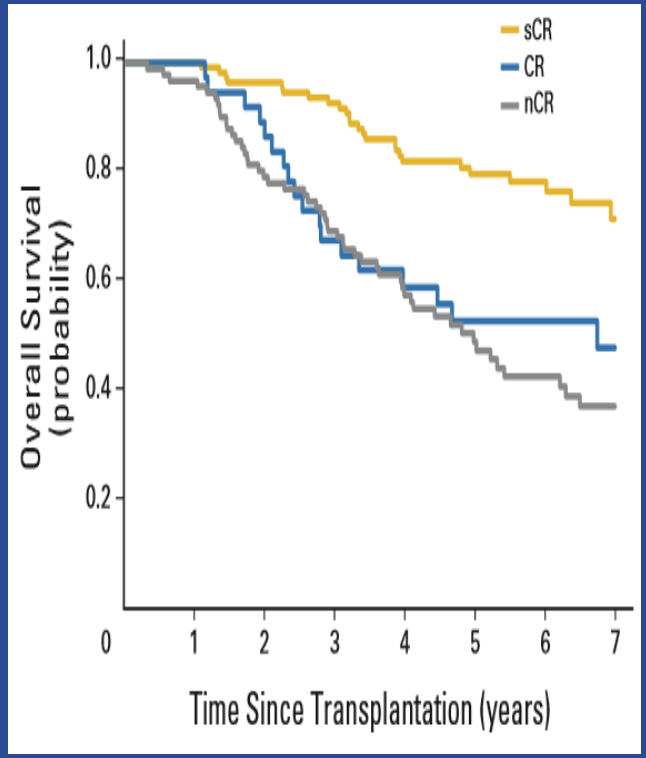
Multicentric, prospective study of 445 NDMM, post ASCT, 1/3 ≥CR



Not reached vs 81 months

Kapoor *et al*., JCO, 2010

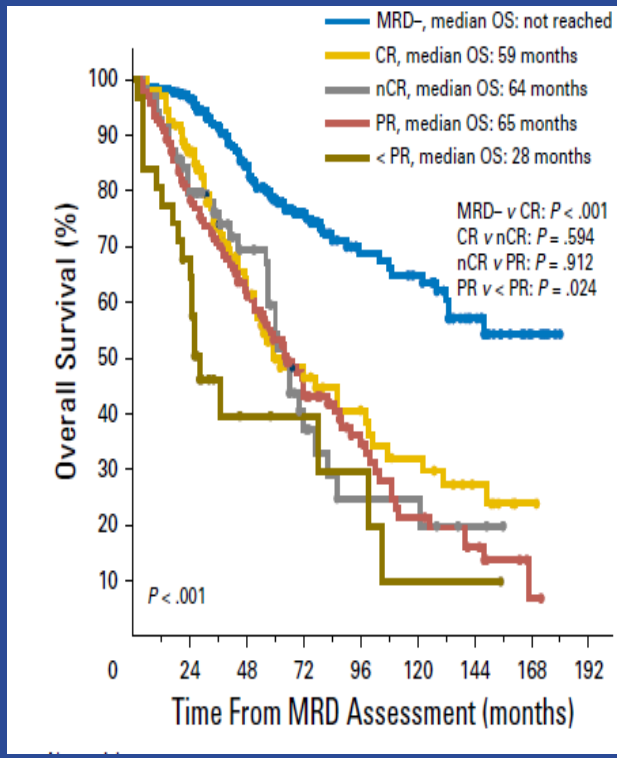
147/295 NDMM (GEM2000) in CR post ASCT. MRD by MFC at day 100 after ASCT.



5-year OS rates 87% vs 59%

Paiva *et al*., Blood, 2008

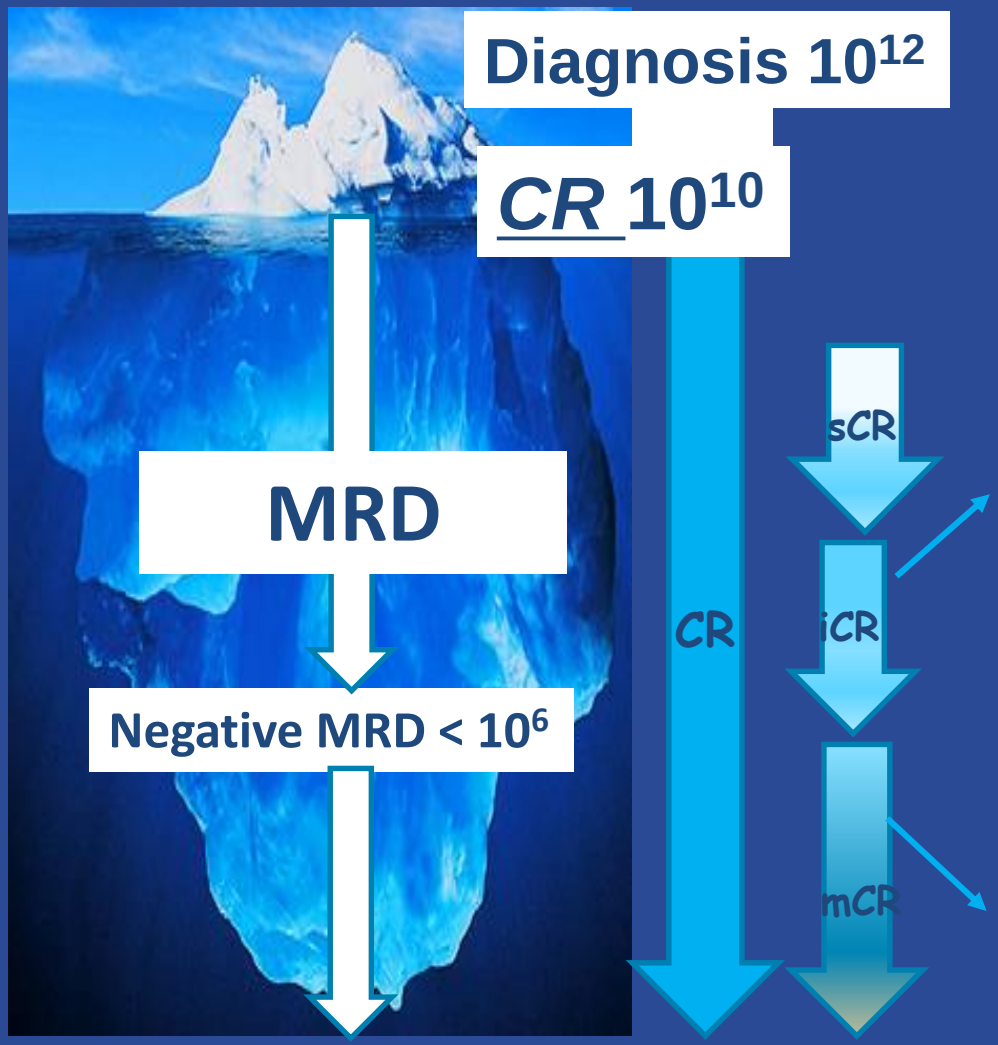
609 NDMM, GEM2000/GEM2005/GEM5010, MRD assessment 9 months after enrolment



Not reached vs 59 months

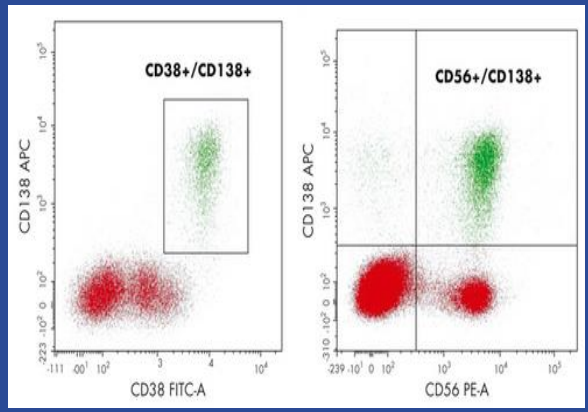
Lahuerta *et al*., JCO, 2017

Minimal Residual Disease, MRD



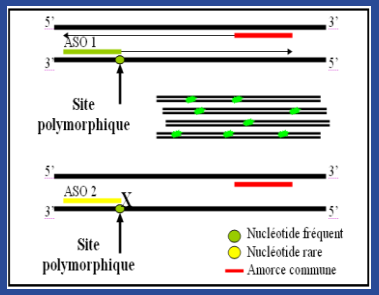
Immunophenotypic CR.

CMF (Sensibilité de 10^{-4} à 10^{-8} selon le nombre de couleurs (2 à 10 couleurs))



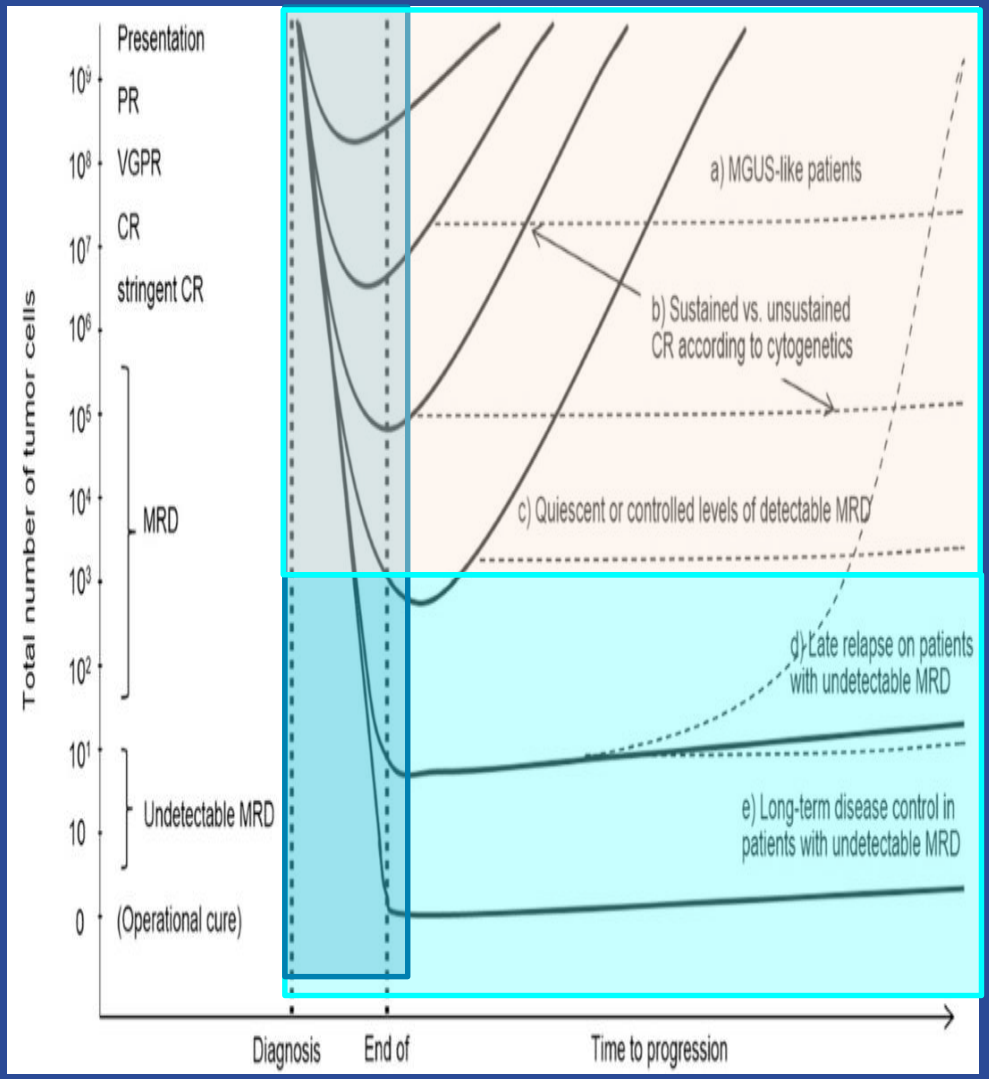
Molecular CR.

ASO-PCR (Se 10^{-5}), NGS

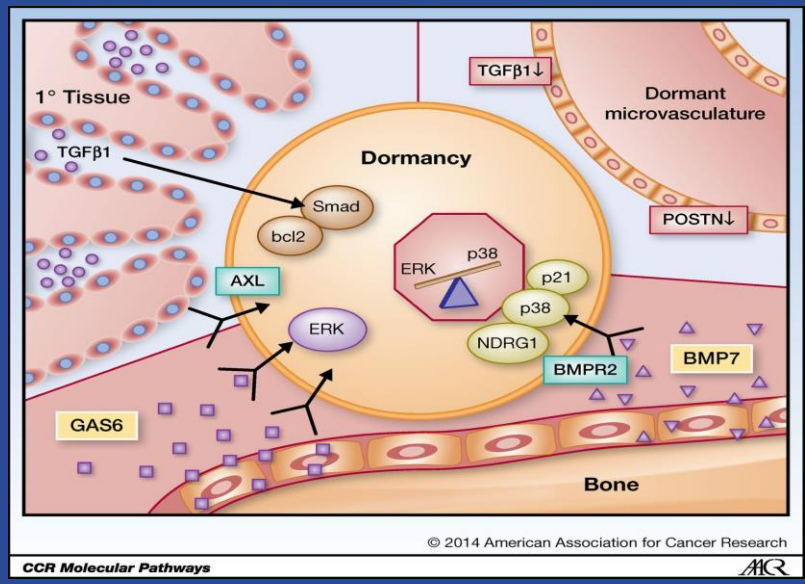


MRD is about

Prolongs PFS as a surrogate for OS



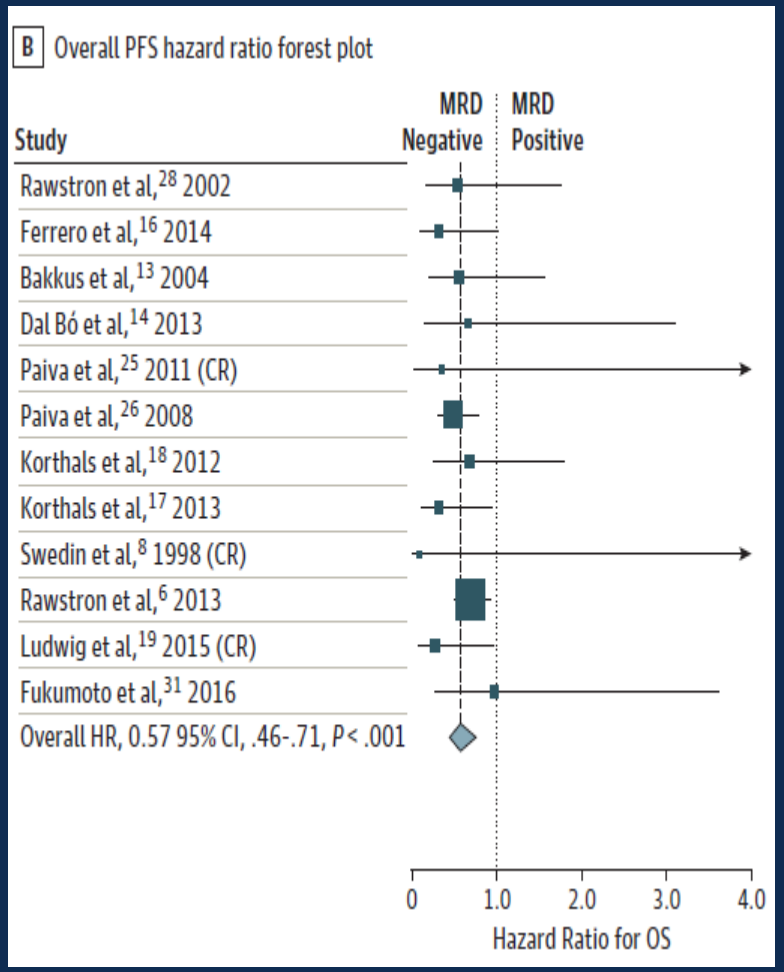
Tumor dormancy, the ultimate objective for 'cure'

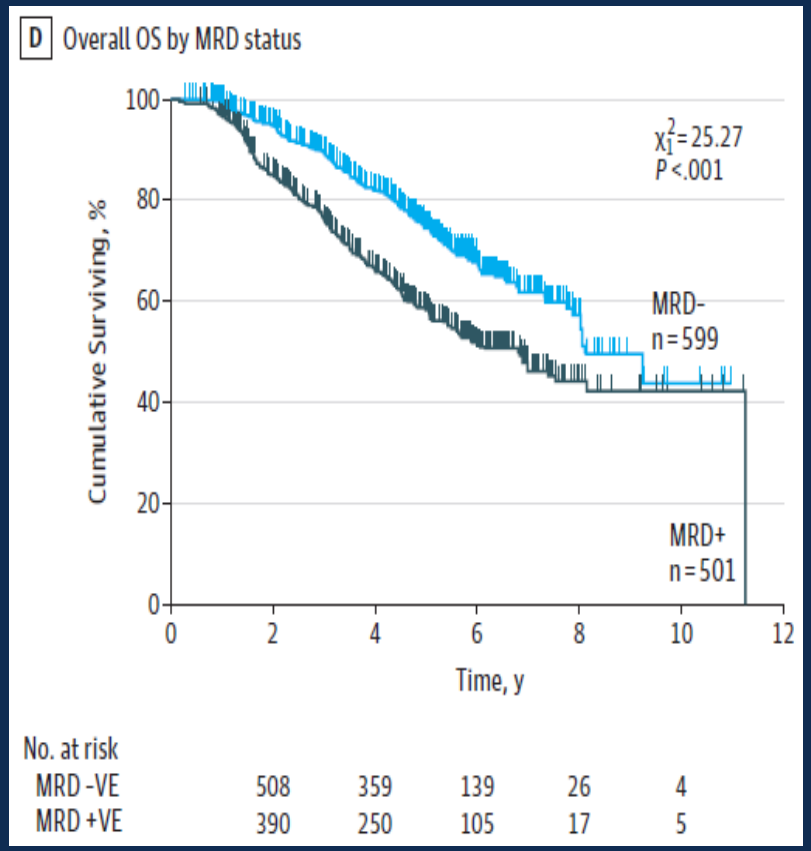


Paiva *et al.*, Blood, 2015

Overall effect of MRD on OS

MRD-negative status was associated with significantly better OS overall (HR, 0.57; 95%CI, 0.46-0.71; P < .001)

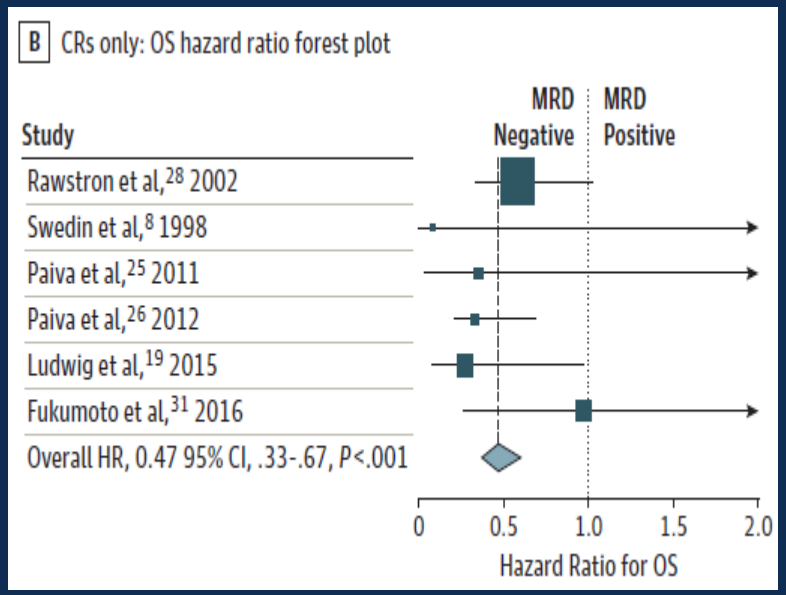


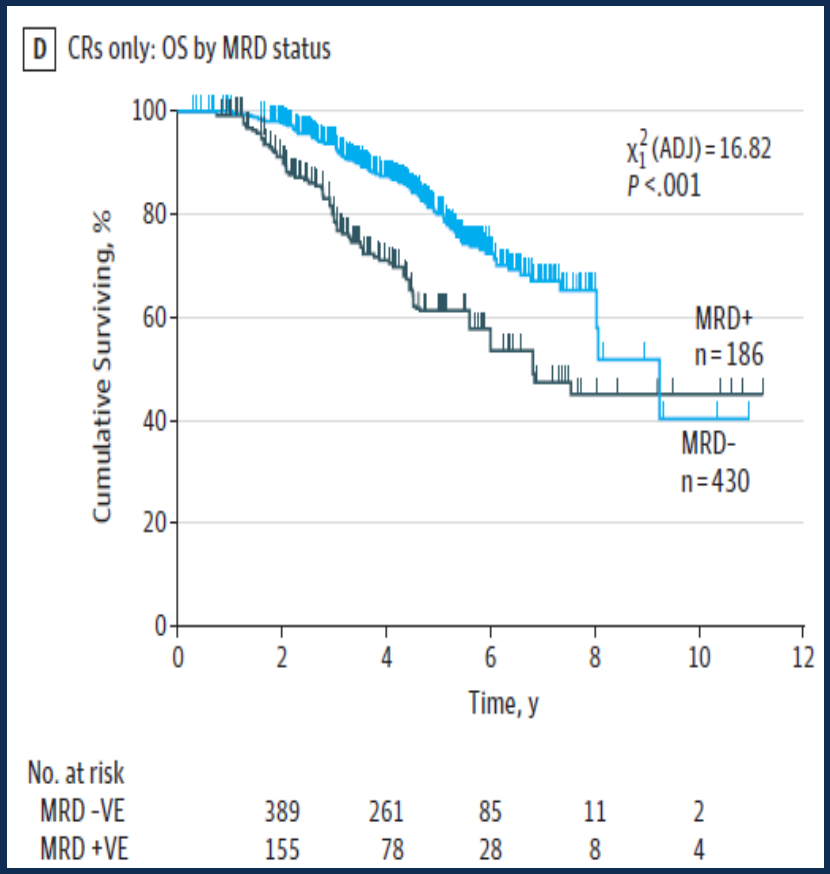


Munshi et al. JAMA Oncol 2017;3:28-35.

Effect of MRD status on OS in CR patients

MRD-negative status was associated with significantly better OS in CR patients (HR, 0.47; 95%CI, 0.33-0.67; *P* < .001)





Munshi et al. JAMA Oncol 2017;3:28-35.

IFM 2008

Phase 2. 31 NDMM, VRD x 3 - Transplant - VRD x 2 - Rev 1 year

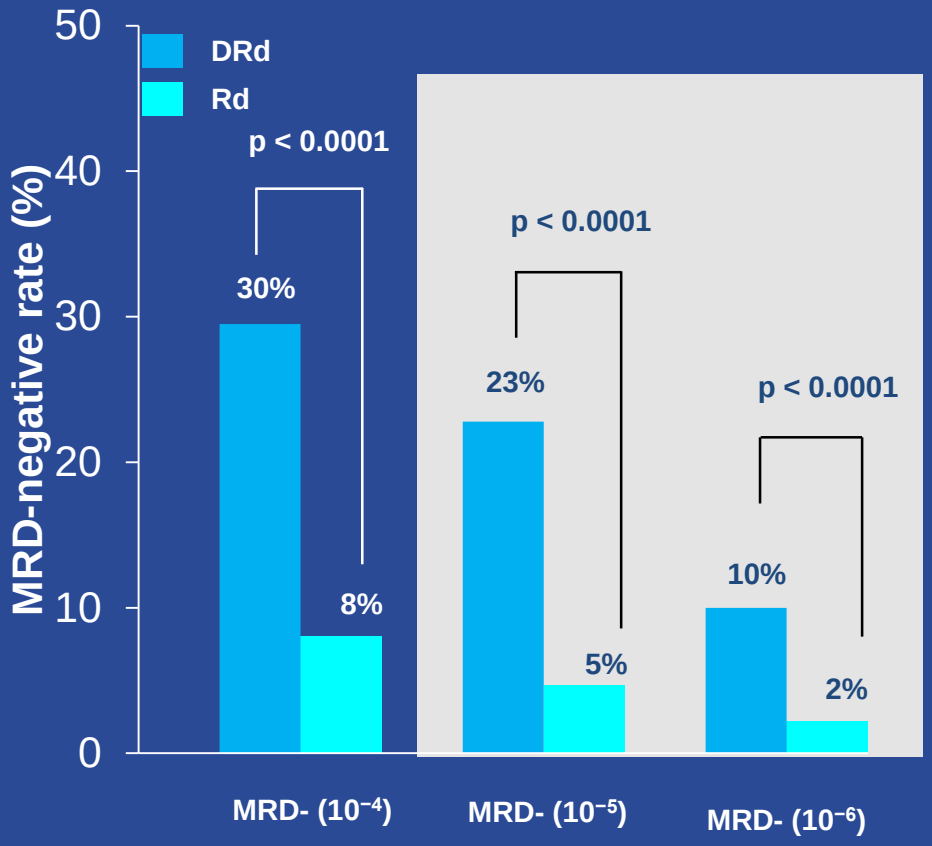
	After induction	After ASCT	After consolidation	Completed Therapy
n (%)	n=31	n=31	n=31	n=31
Negative MRD	4/25 (16)	14/26 (54)	15/26 (58)	21/30 (70)
sCR + CR	7 (23)	14 (45)	15 (48)	18 (58)
≥ VGPR	18 (58)	21 (68)	26 (84)	26 (84)

MRD at 10^{-4}-10^{-5}

Roussel et al. JCO 2014

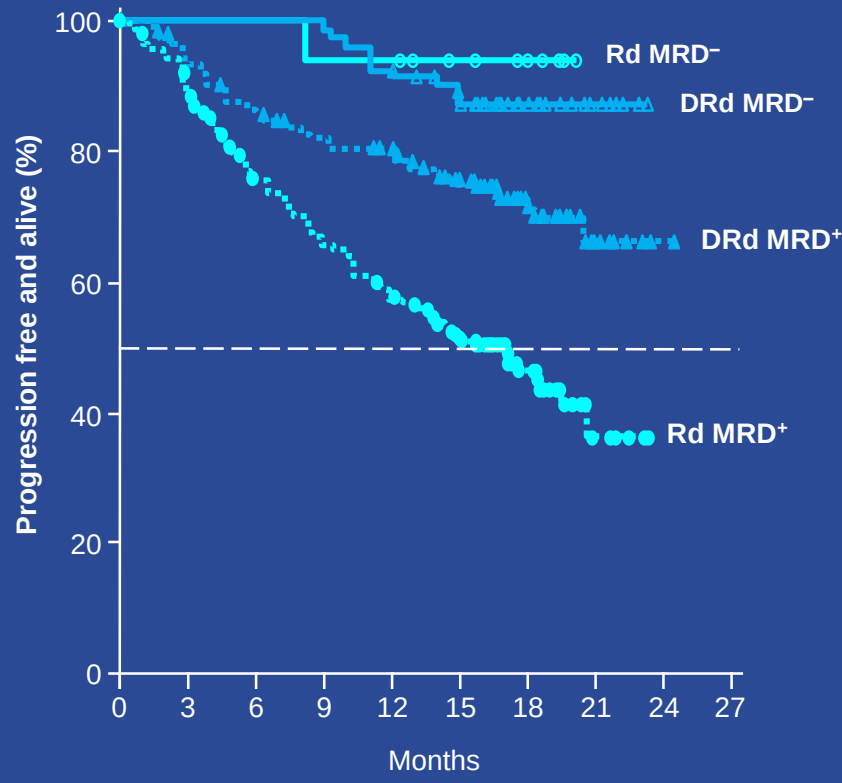
POLLUX: DRd vs Rd - *MRD-negative rate*

Phase 3 multicenter, early RRMM



Response-evaluable set. Assessed by next generation sequencing (NGS) in bone marrow.

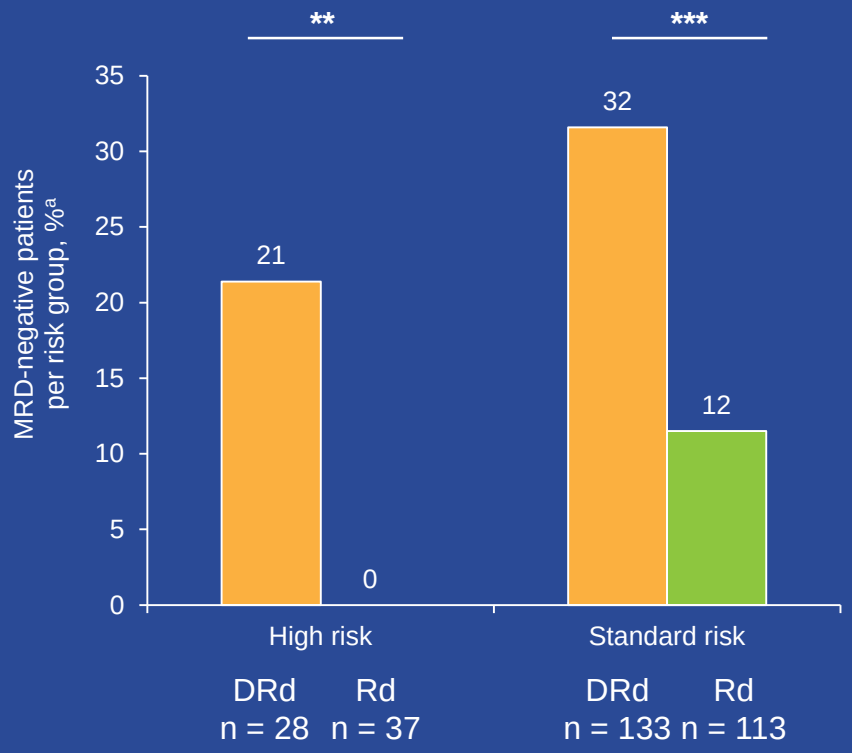
PFS



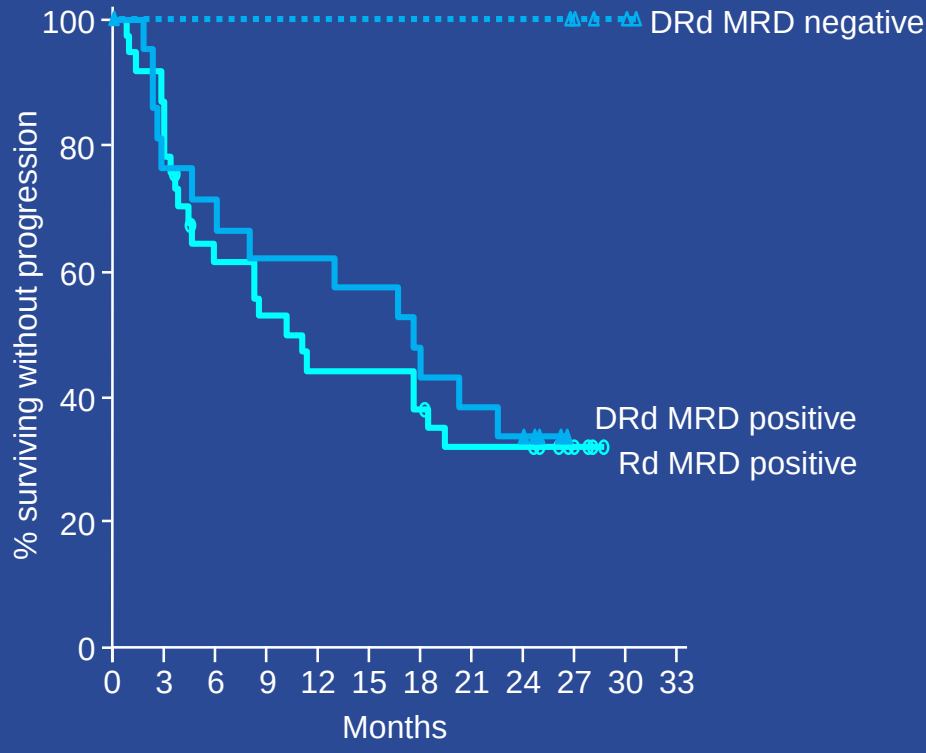
Avet-Loiseau H. Oral presentation at IMW 2017. New Delhi, India.

POLLUX: MRD by Cytogenetic Risk Status (10^{-5})

MRD-negative rates



PFS in high-risk patients



In POLLUX, high-risk patients treated with daratumumab achieve MRD negativity and remain progression free

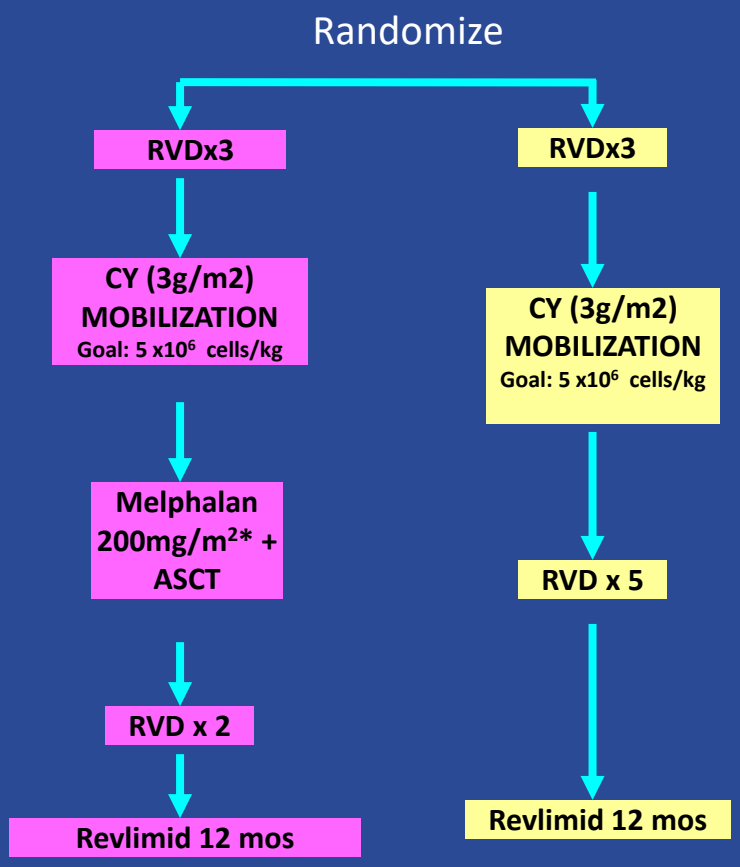
***P* = 0.0009. ****P* = 0.0001.

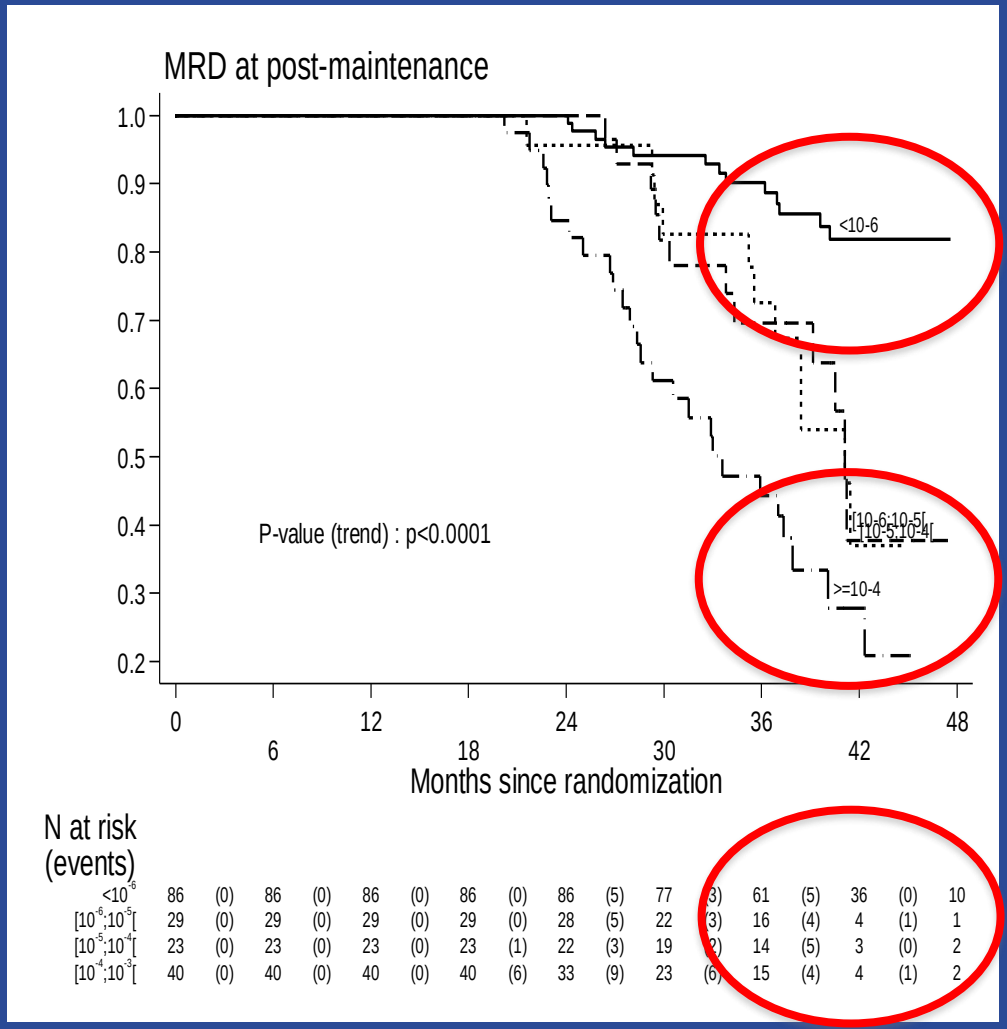
[a]Percentage of patients within a given risk group and treatment arm.

ClinicalTrials.gov Identifiers: NCT02136134

Depth of MRD matters

Phase 3 multicenter, IFM/DFCI 2009, NDMM

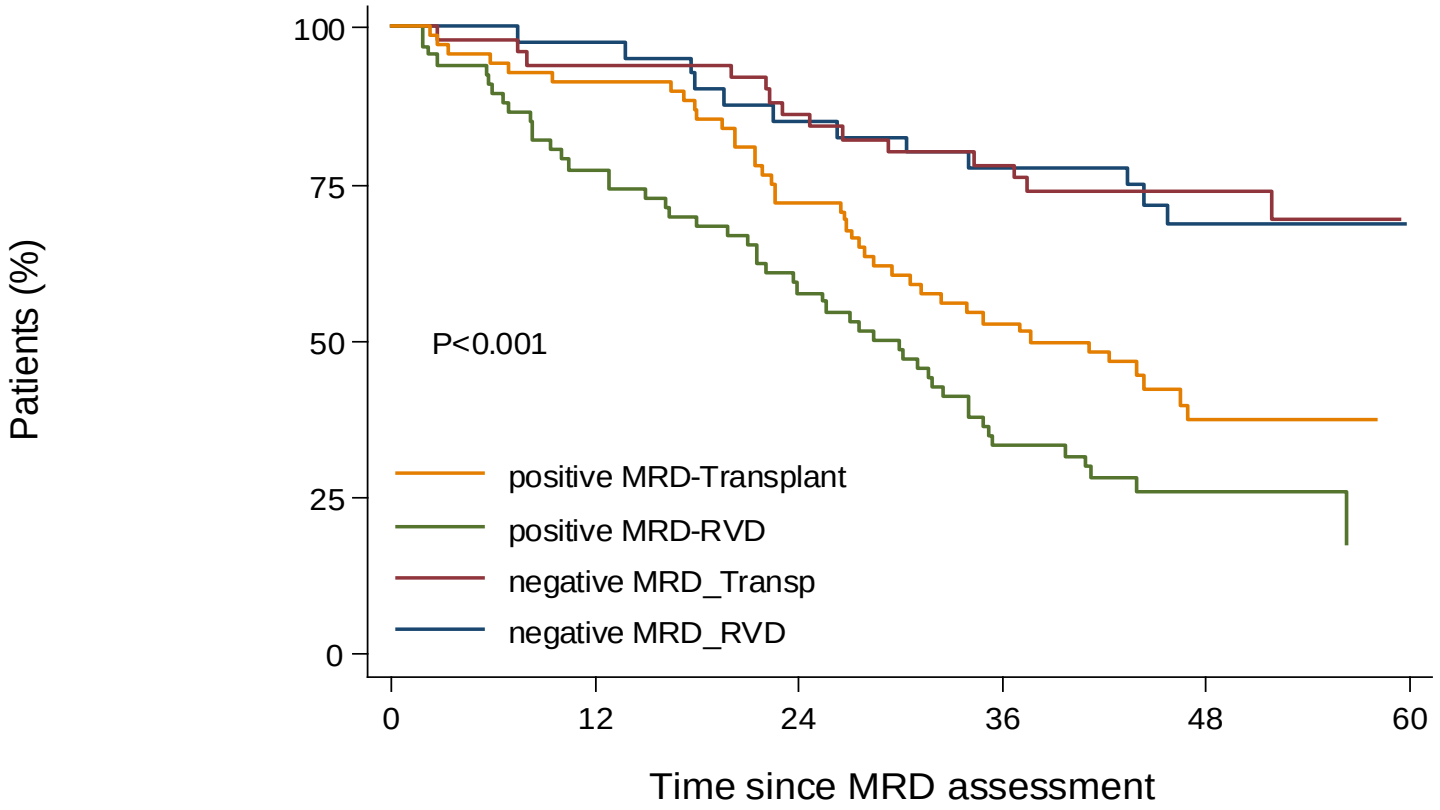




Avet-Loiseau H. Oral presentation at IMW 2017. New Delhi, India.

IFM 2009 trial

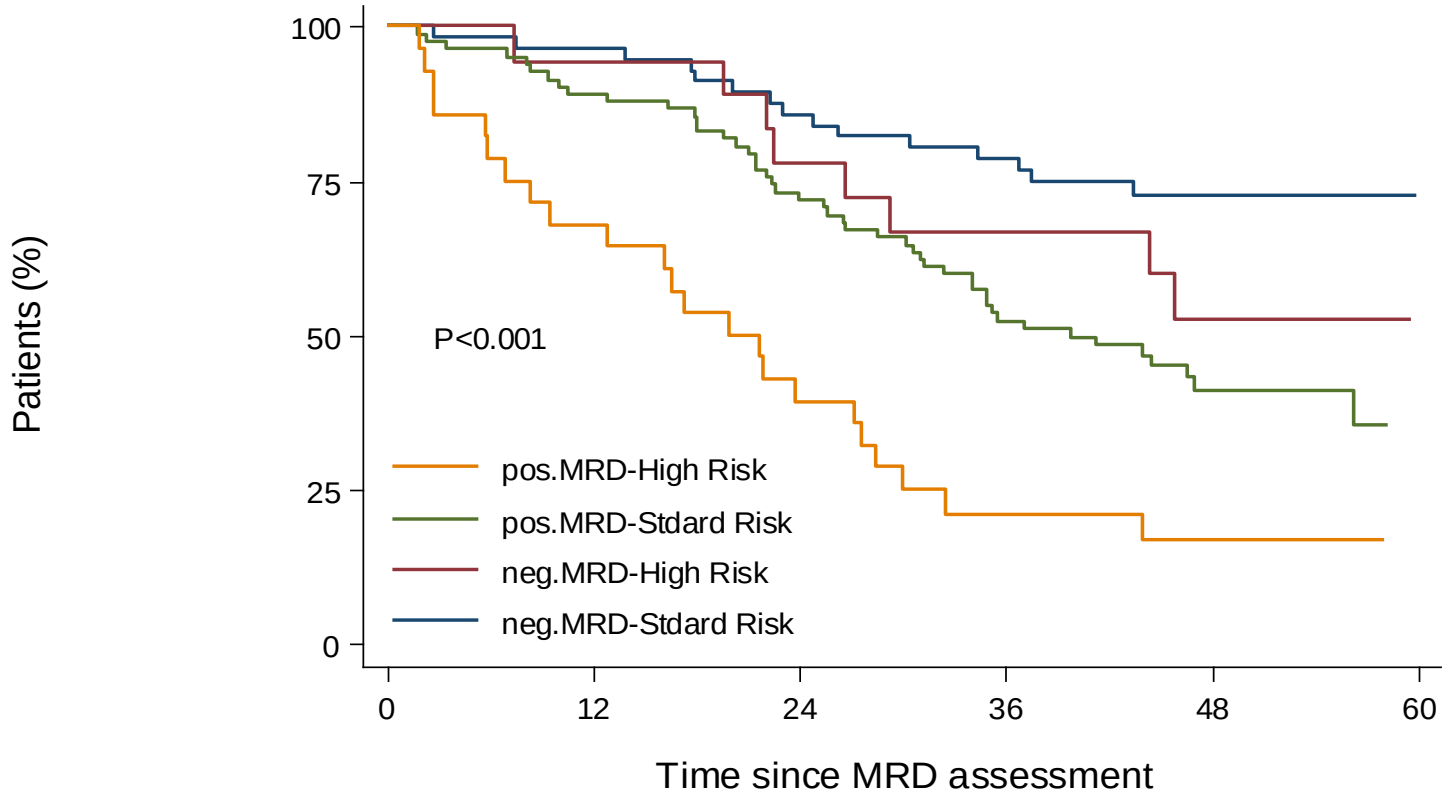
Role of treatment



N at risk						
positive MRD-Transplant	68	62	49	35	15	1
positive MRD-RVD	66	51	38	21	11	2
negative MRD_Transp	50	47	43	38	23	4
negative MRD_RVD	40	39	34	31	17	1

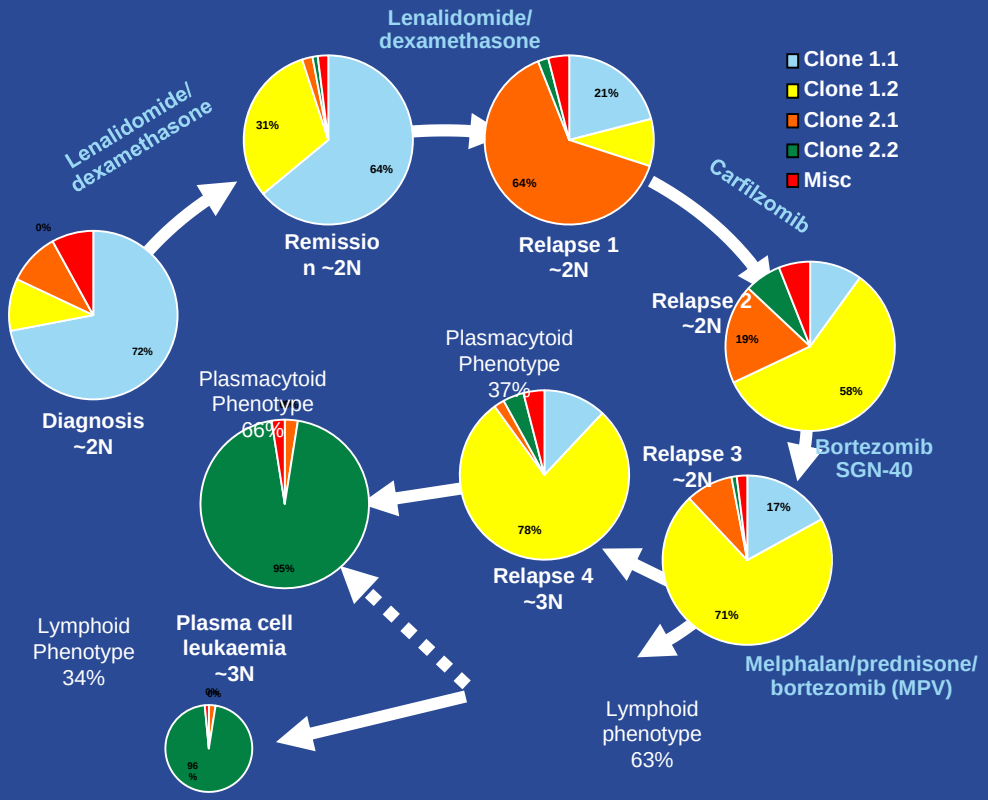
IFM 2009 trial

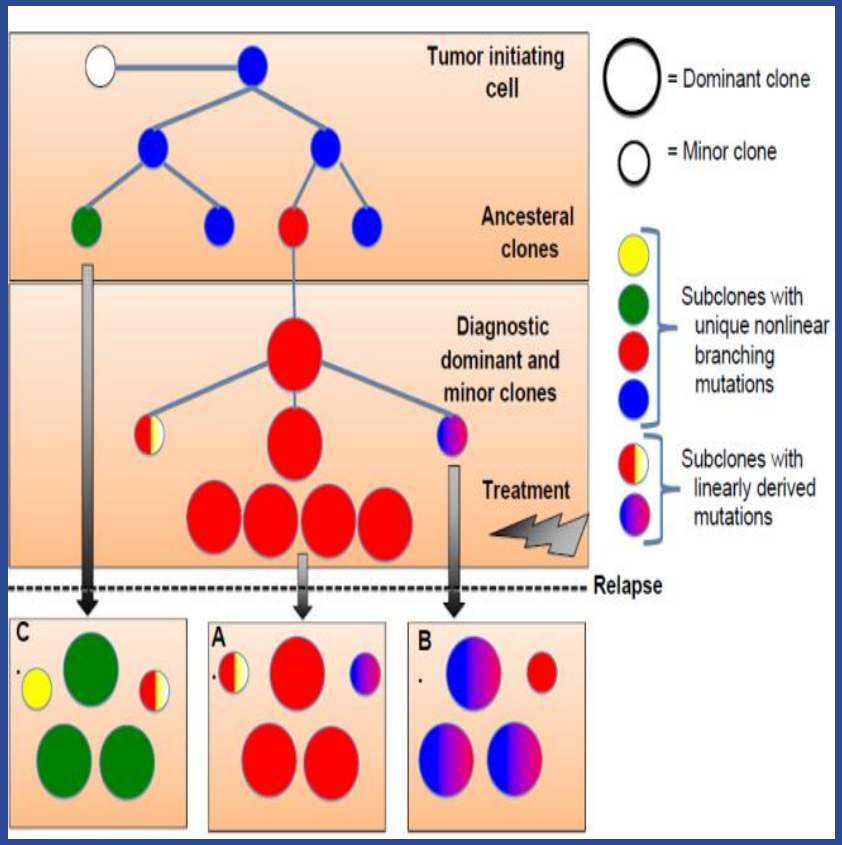
Role cytogenetics



N at risk						
pos.MRD-High Risk	28	19	11	5	4	0
pos.MRD-Stdard Risk	82	73	59	42	21	3
neg.MRD-High Risk	18	17	14	12	5	1
neg.MRD-Stdard Risk	56	54	48	43	25	4

Work to do (1), MRD and – Clonal selection

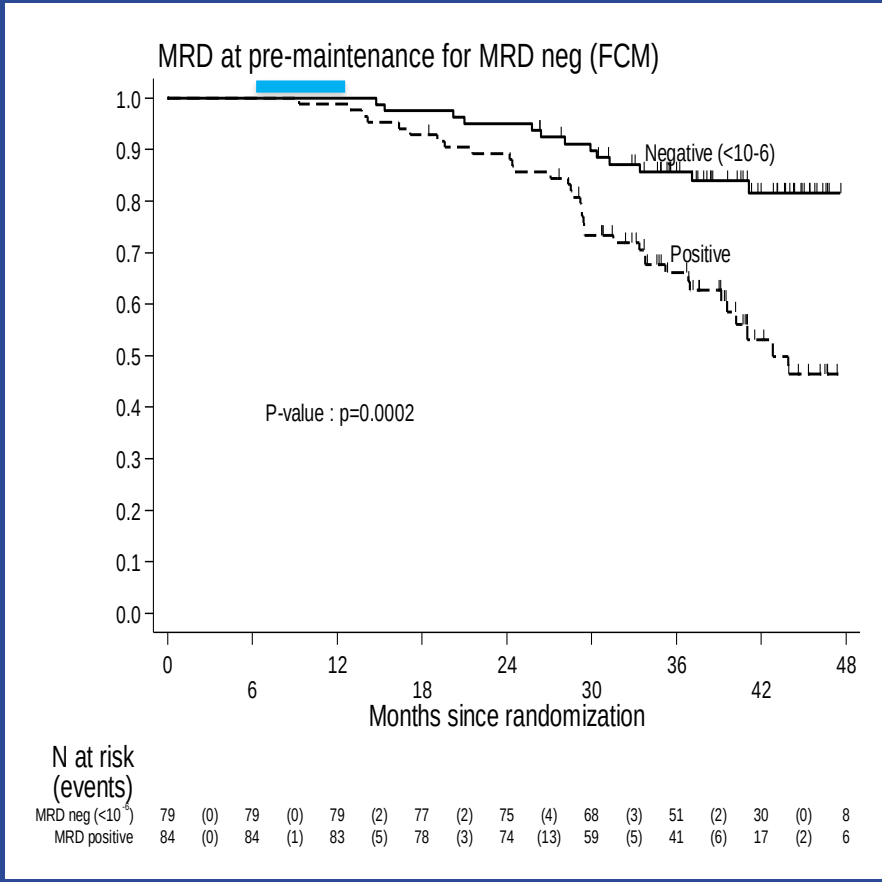


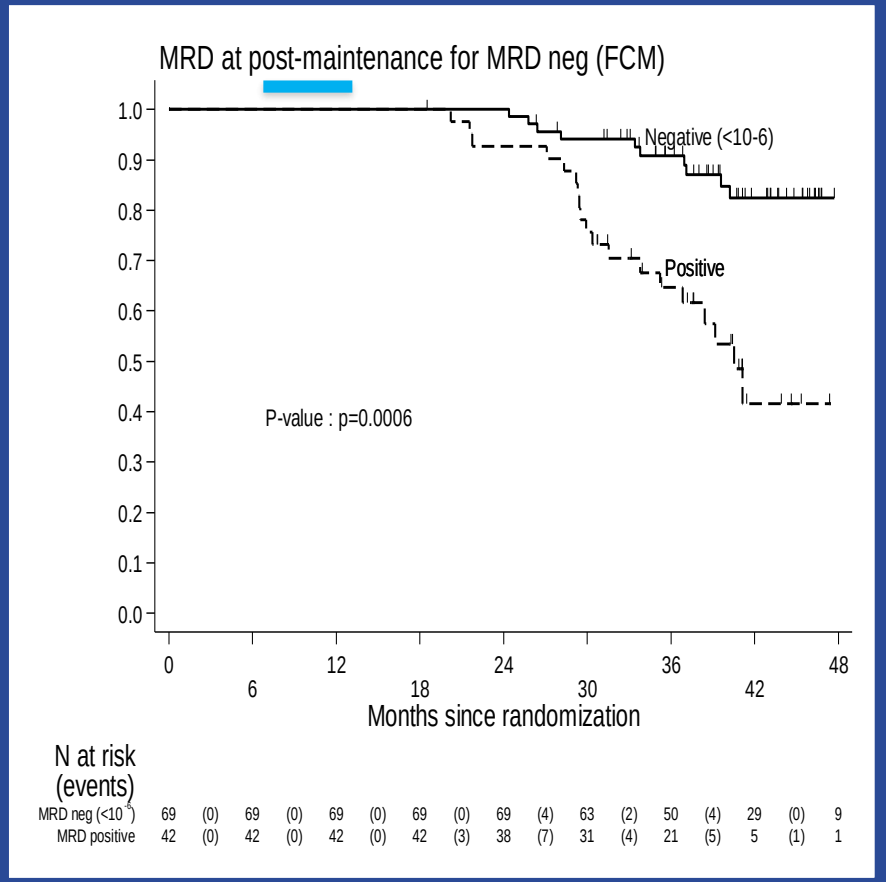


Keats *et al.*, Blood, 2012

Morgan *et al.*, Oral communication

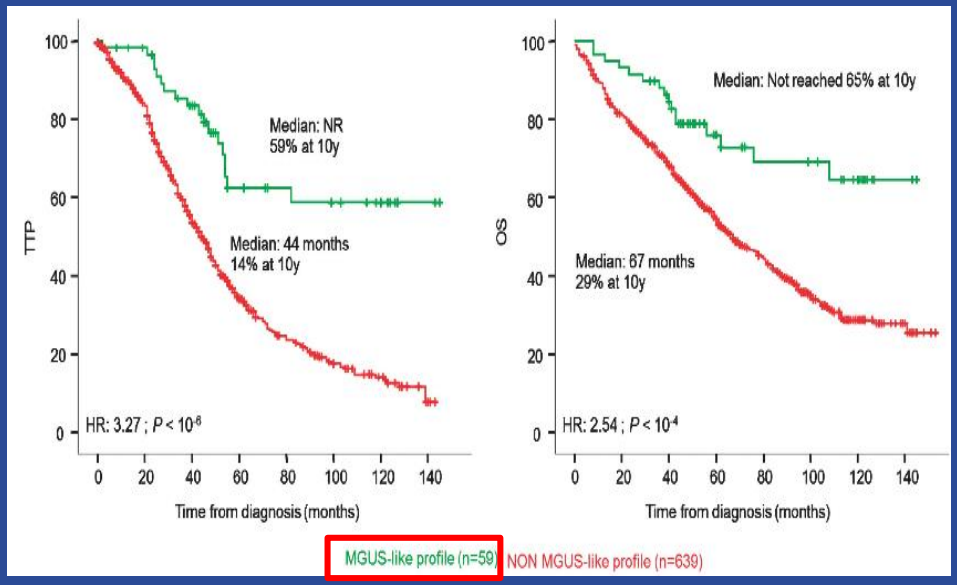
Work to do (2) MRD and – Best timing

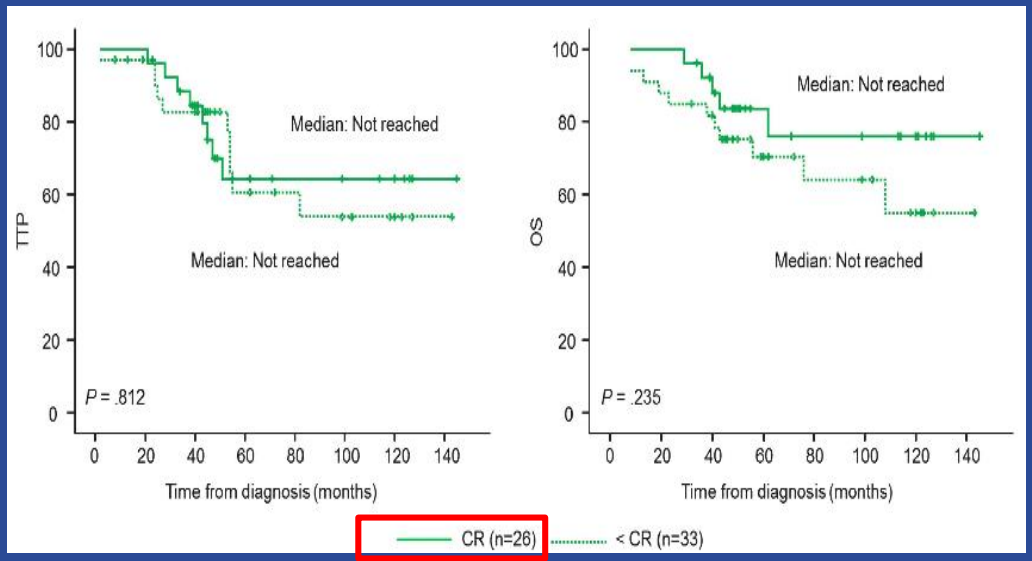




Avet-Loiseau H. Oral presentation at IMW 2017. New Delhi, India.

Work to do (3) MRD and – MGUS like profile



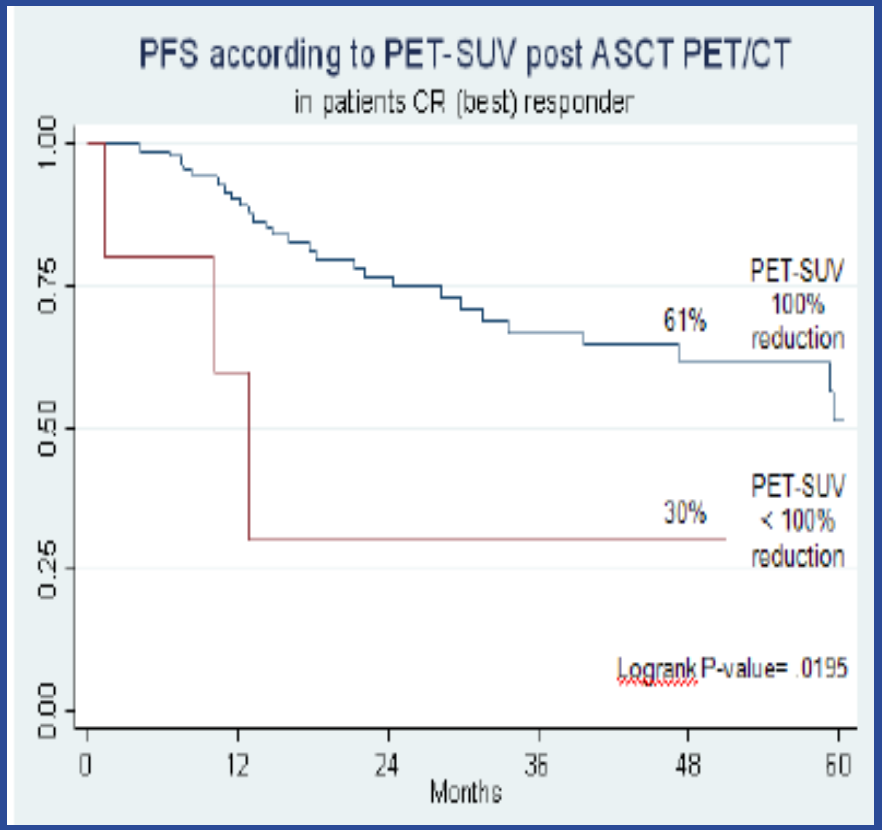


Paiva *et al.*, Leukemia, 2013

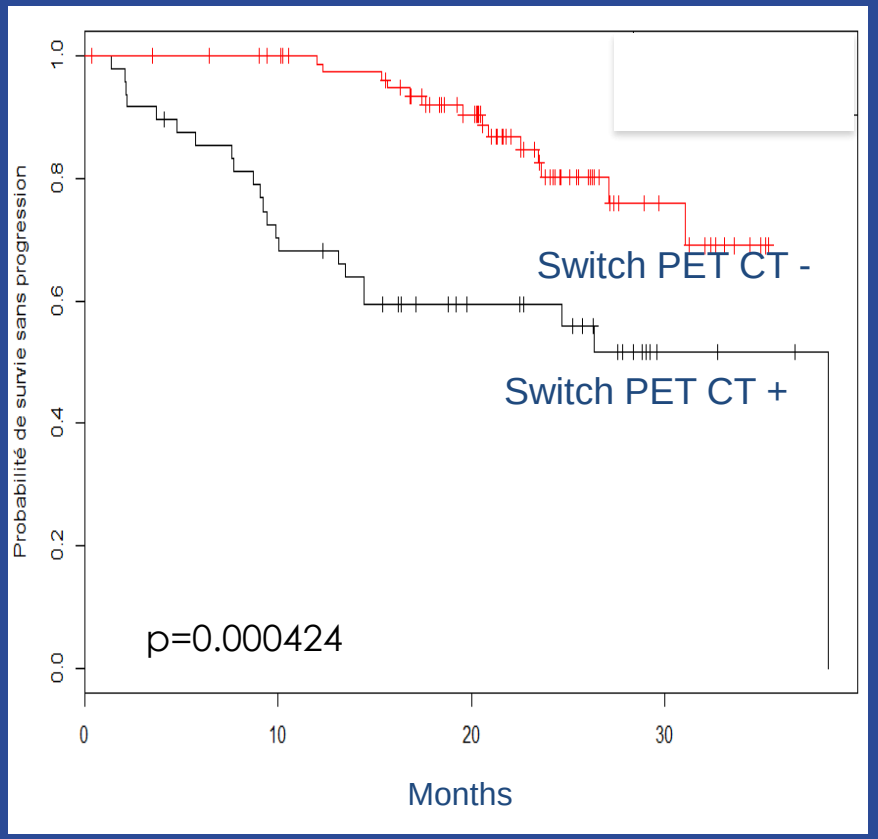
Work to do (4) MRD study

Various ways to study the BM, BM sampling, PET CT ….

Thal/dex followed by tandem ASCT



IFM 2009/DFCI - Imajem



Zamagni et al, Blood 2011

Moreau et al, Oral communication

Work to do (5) MRD and – treatment decision

IFM 2018

	MRD1		MRD2	
<u>Standard Risk</u> PI⁺ImidsD-MoAB x6	- R ↗ ↘	HDT1 + PI⁺ImidsD-MoAB X4 PI⁺ImidsD-MoAB x7	→	R ↗ Maint A ↘ Maint B
PI⁺ImidsD-MoAB x6	+	HDT1 + PI⁺ImidsD-MoAB* x6 *diff PI, Imids,..	+ HDT2	→ R ↗ Maint C ↘ Maint D
			- R	↗ Maint A ↘ Maint B
<u>High Risk</u> PI⁺ImidsD-MoAB x6	→	HDT1 + PI⁺ImidsD-MoAB* x6 *diff PI, Imids,..	→ HDT2	→ Maint C or D

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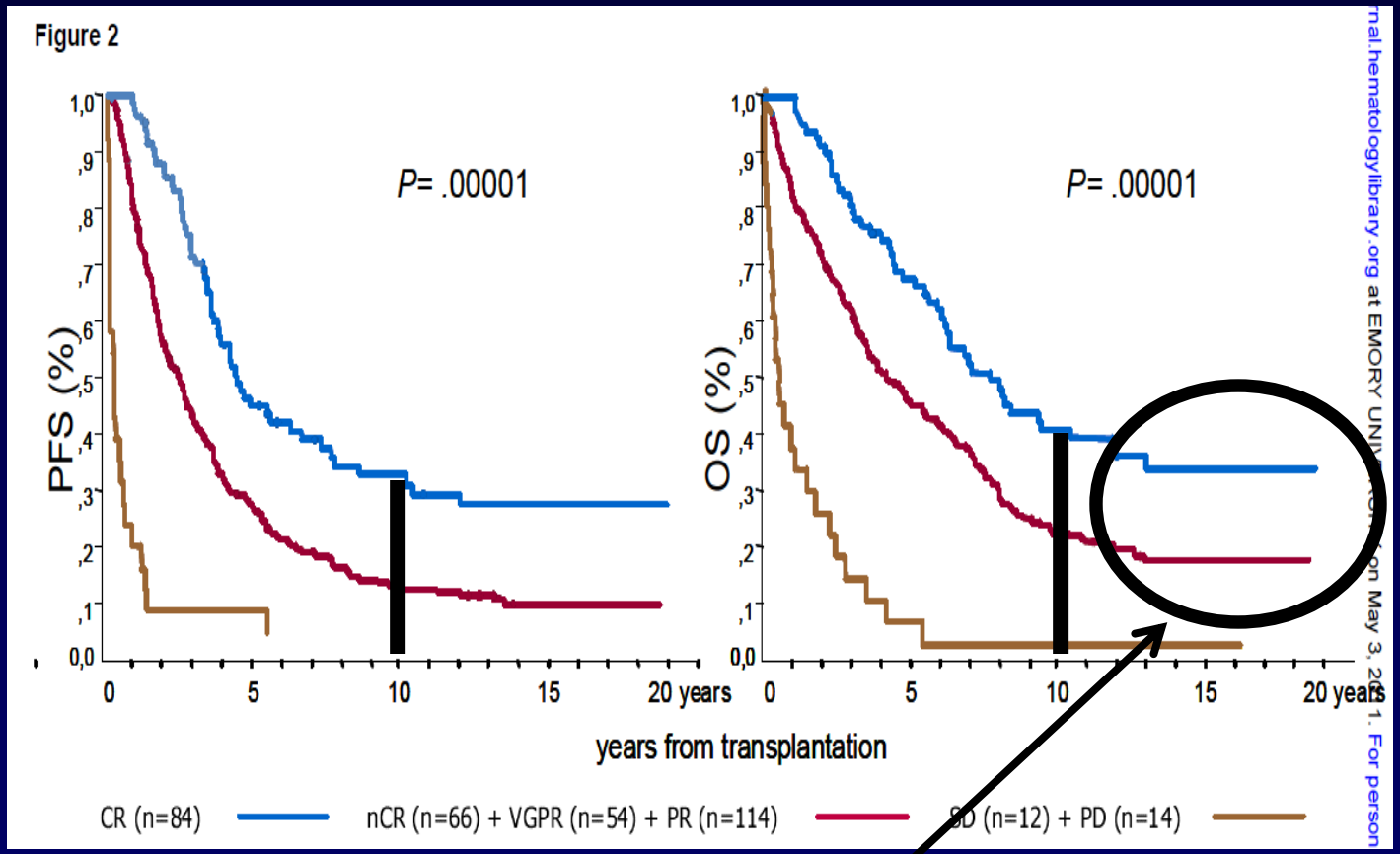
Minimal Residual Disease Assessment: Not Relevant for Clinical Practice Yet

Sagar Lonial, MD
Chair and Professor
Department of Hematology and Medical Oncology
Chief Medical Officer, Winship Cancer Institute
Emory University School of Medicine

There are patients with old drugs and old tests that do well..



Functional cure?

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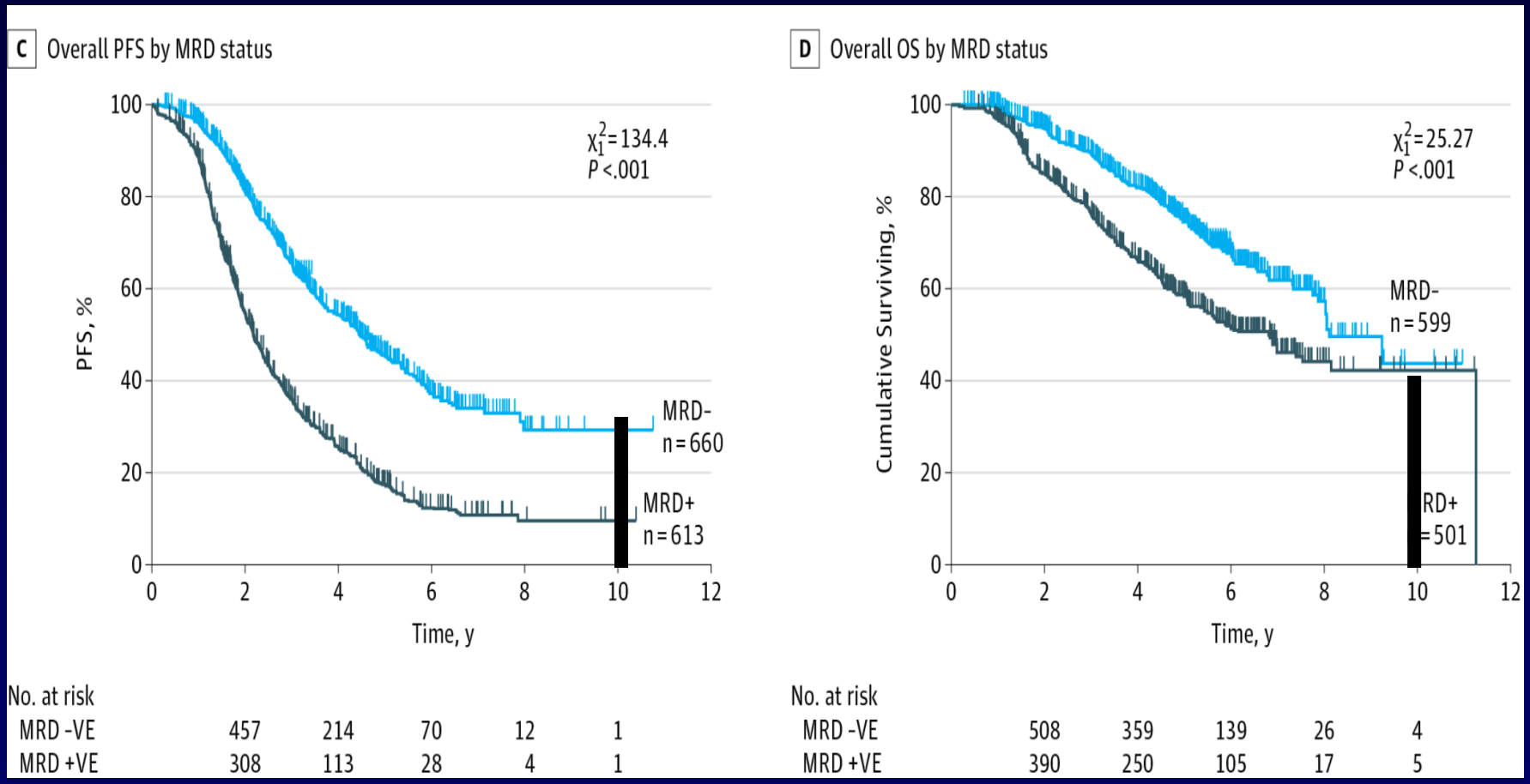
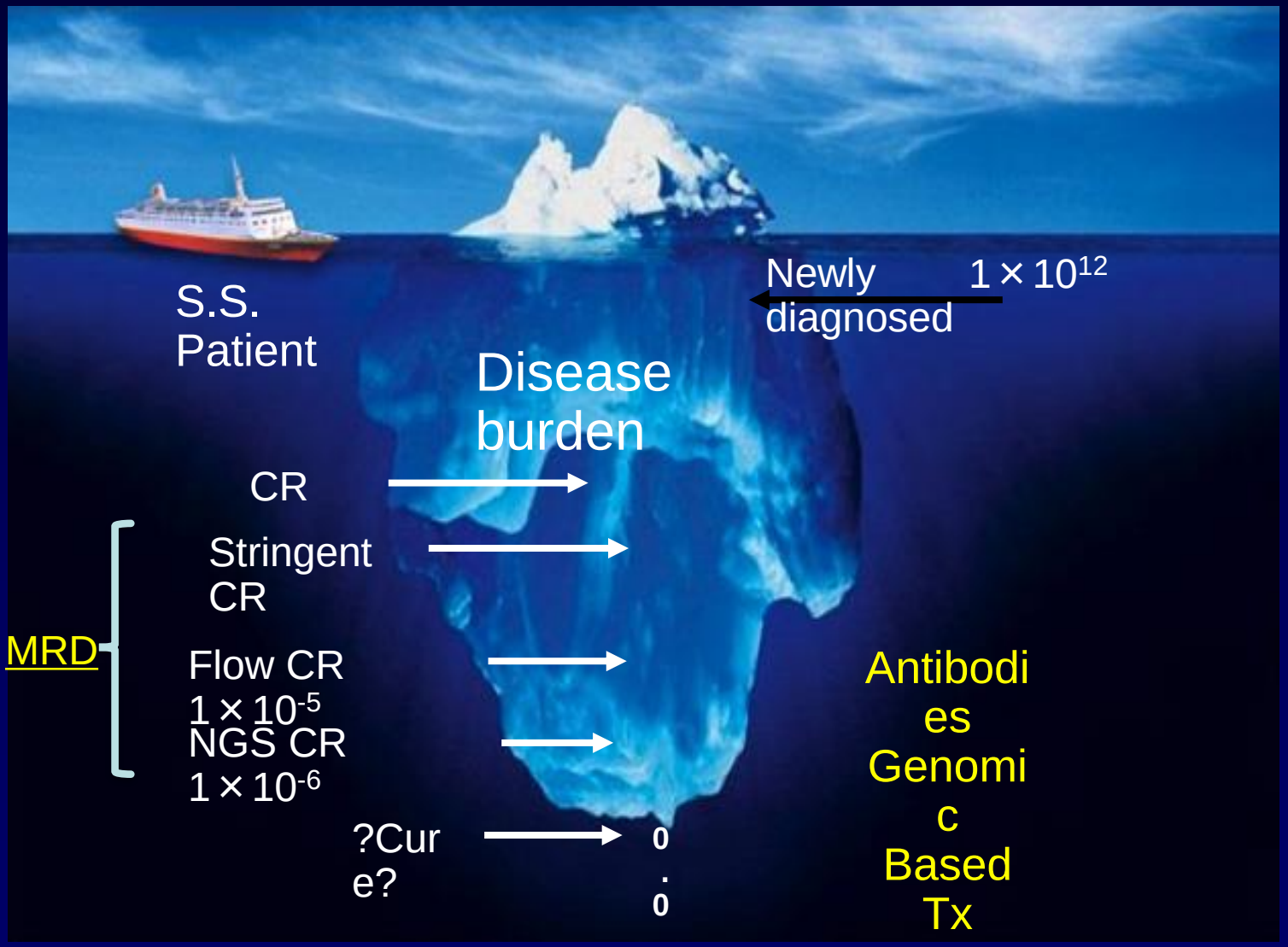
Martinez-Lopez et al, Blood 2011

Impact of MRD: Meta-analysis
Are these the same patients?



Munshi et al, JAMA Oncol. 2017;3(1):28-35.

Getting to Minimal Residual Disease (MRD): New Definitions for CR



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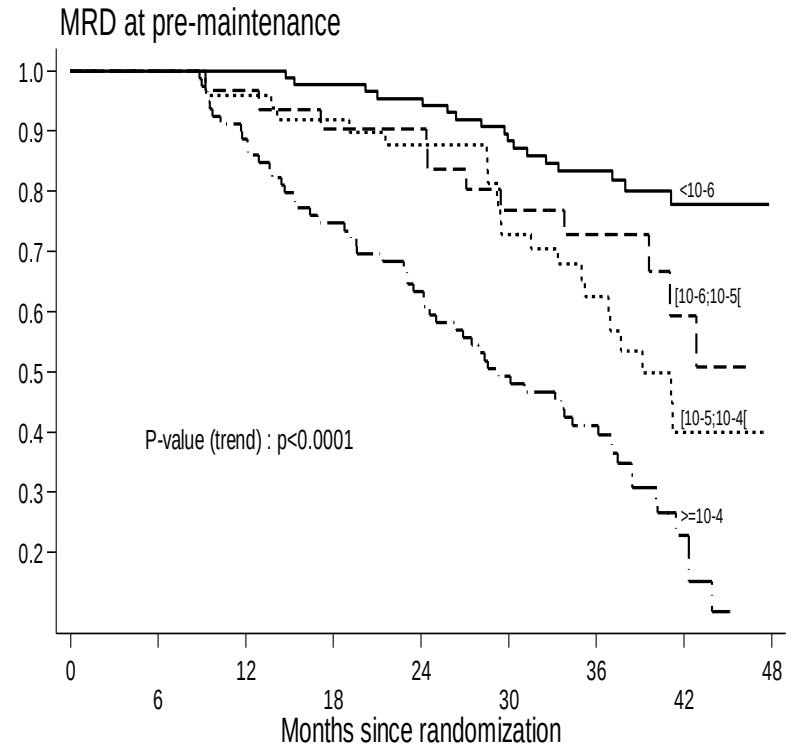
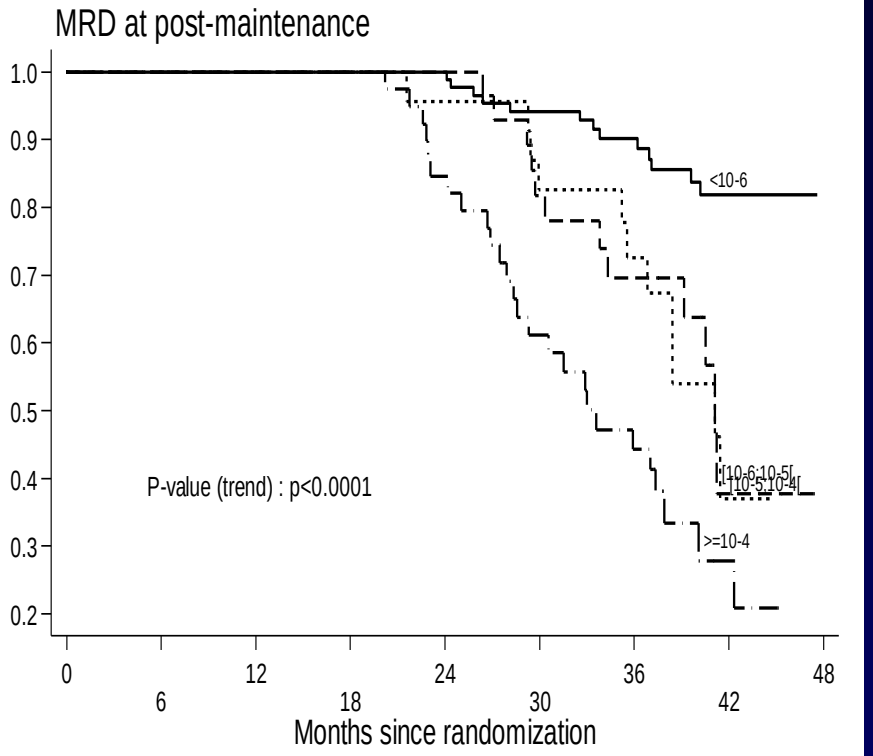
How you measure MRD impacts the results



N at risk (events)

$<10^{-6}$	87	(0)	87	(0)	87	(2)	85	(2)	83	(6)	74	(4)	54	(3)	31	(0)	8
$[10^{-6};10^{-5}[$	31	(0)	31	(1)	30	(2)	28	(0)	27	(4)	22	(1)	17	(2)	8	(1)	4
$[10^{-5};10^{-4}[$	49	(0)	49	(2)	47	(2)	45	(2)	43	(7)	34	(4)	22	(6)	8	(0)	2
$[10^{-4};10^{-3}[$	79	(0)	79	(9)	70	(11)	59	(9)	50	(11)	38	(6)	28	(9)	6	(3)	0



N at risk (events)

$<10^{-6}$	86	(0)	86	(0)	86	(0)	86	(0)	86	(5)	77	(3)	61	(5)	36	(0)	10
$[10^{-6};10^{-5}[$	29	(0)	29	(0)	29	(0)	29	(0)	28	(5)	22	(3)	16	(4)	4	(1)	1
$[10^{-5};10^{-4}[$	23	(0)	23	(0)	23	(0)	23	(1)	22	(3)	19	(2)	14	(5)	3	(0)	2
$[10^{-4};10^{-3}[$	40	(0)	40	(0)	40	(0)	40	(6)	33	(9)	23	(6)	15	(4)	4	(1)	2

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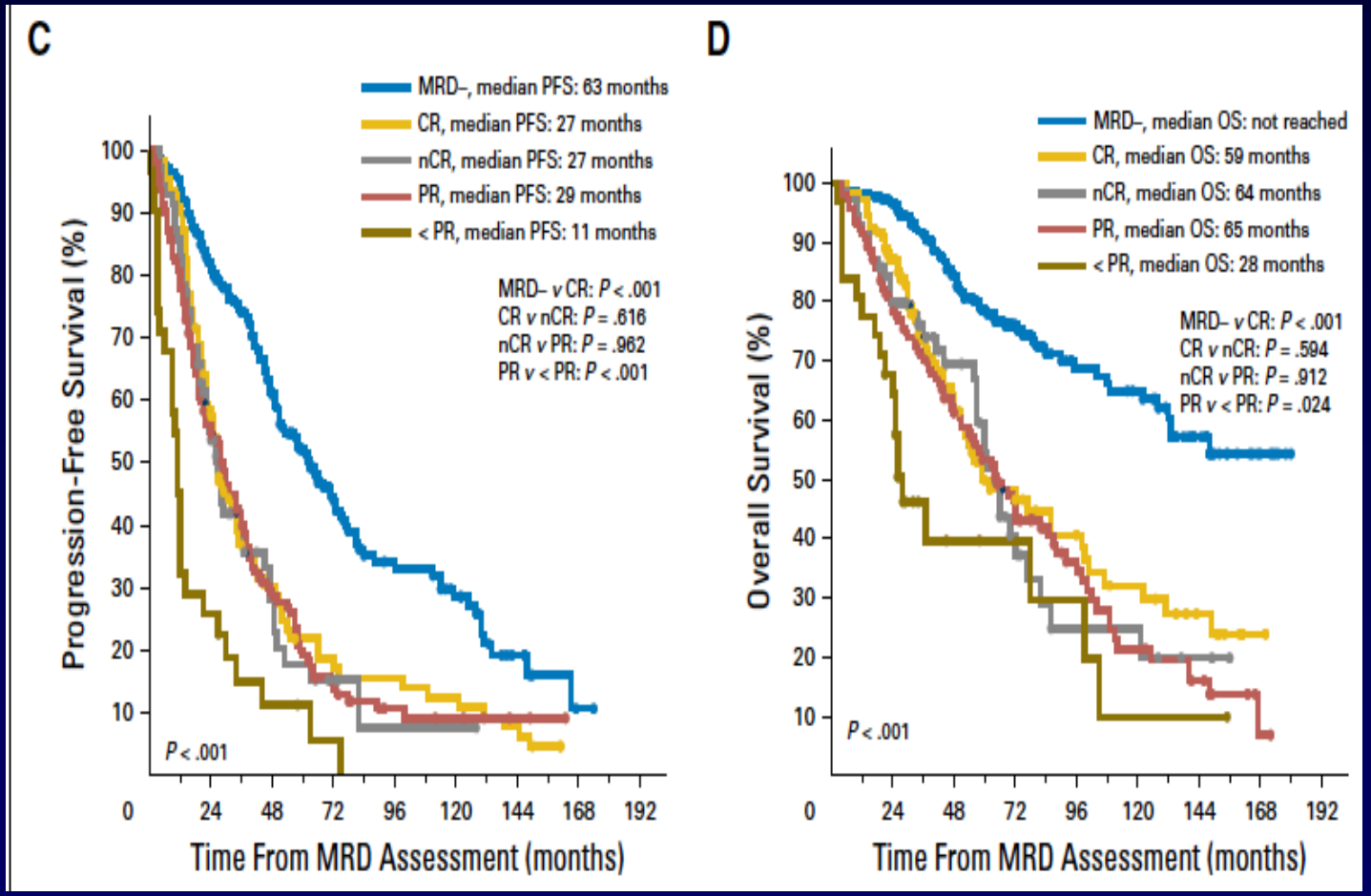
Avet-Loiseau et al, ASH 2015

MRD testing is not a surrogate for Cure



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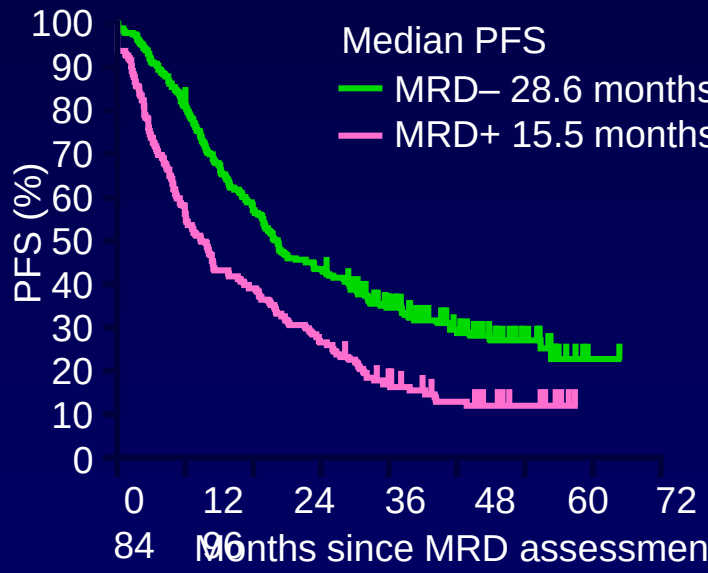
Lahuerta et al, JCO 201

MRC Myeloma IX: PFS and OS Do Not Plateau

- **MRD negativity at Day 100 post-ASCT was associated with improved PFS (P<0.0001) and OS (P=0.0183)**

PFS

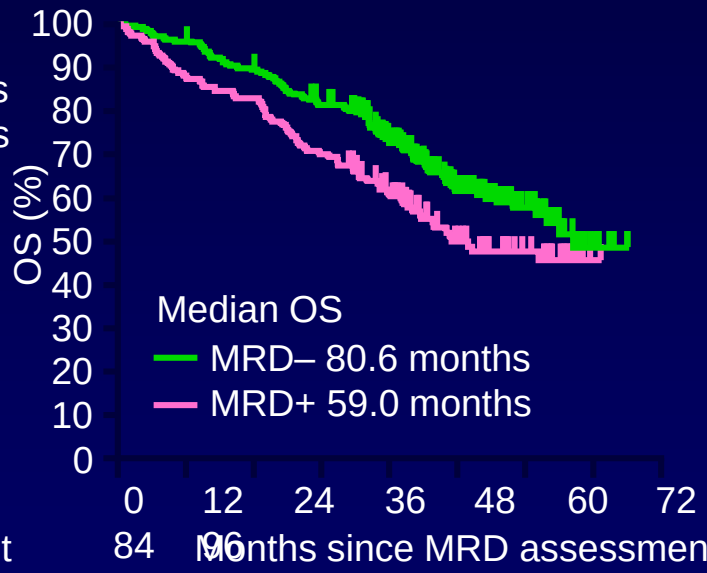


Numbers at risk:

MRD–	200	145	107	73	41	20	2
MRD+	87	59	42	24	14	7	0

0

OS



Numbers at risk:

MRD–	237	220	197	157	92	43	9
MRD+	132	124	105	83	46	25	1

0

MRD status at Day 100 post-ASCT: MRD– n=247; MRD+ n=150

1. Rawstron AC, et al. J Clin Oncol)

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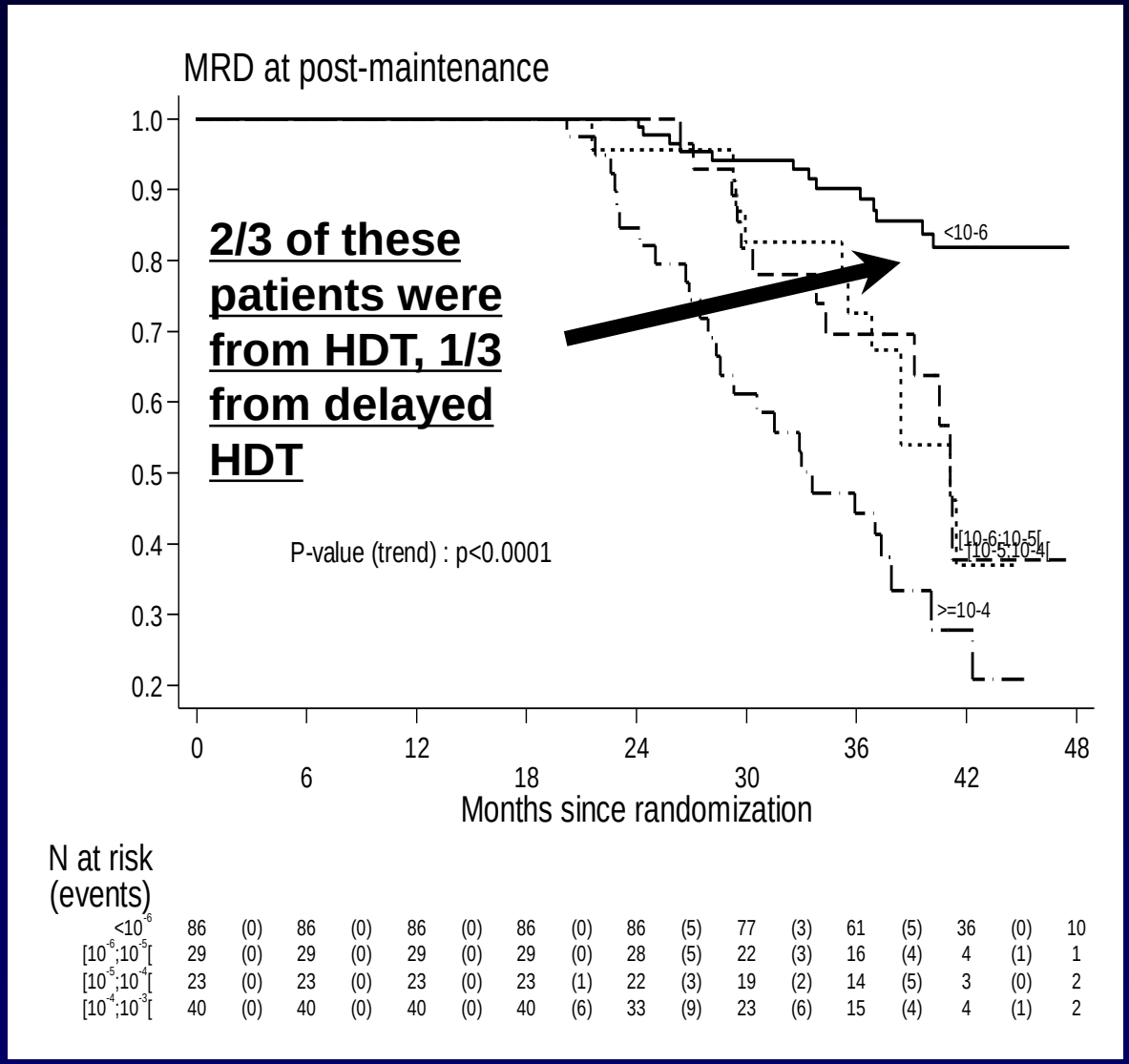
Cannot use MRD to decide who gets a transplant



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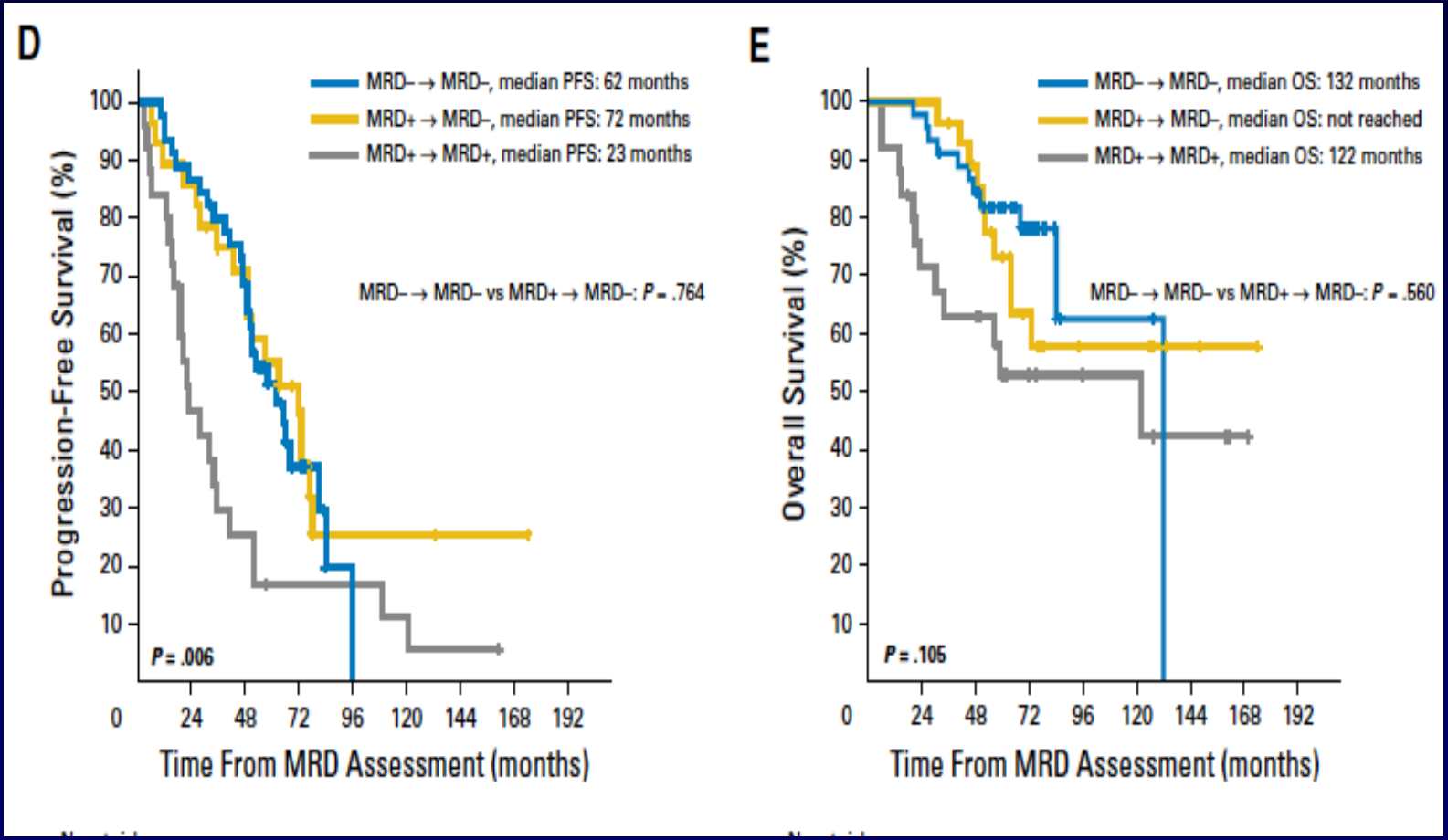
Avet-Loiseau et al, ASH

MRD changes post transplant do not impact OS



EMORY WINSHIP CANCER INSTITUTE

Lahuerta et al, JCO 201

Conclusion

YES. Minimal Residual Disease is
A Measurable and Relevant Endpoint in Treatment

- Is manageable in most countries
- Has demonstrated a prognostic role, PFS and OS
- You already have implemented depth of response in your practice for treatment decision
  - You decide a treatment strategy based on known depth of response
  - You optimize a treatment scheme to improve depth of response, ASCT, consolidation, maintenance…
- Time for the next step, MRD-based treatment choice decision making

Summary (Fallacies) of MRD testing

- MRD is a surrogate for cure
- If you are MRD negative, you can stop treatment
- If you are MRD positive after transplant, you need to change from standard treatment
- MRD is the only predictor of good long term outcomes
- If you convert from MRD negative to MRD positive, you need to change therapy
- MRD assessment in the marrow is enough to declare victory

What can MRD testing be used for

- Comparing across clinical trials
- Assessing efficacy of new treatment approaches
- Prognosis

But **not** for current clinical decision making

There are too many unknowns that will be addressed by ongoing trials

Never give up!

Thank you for your attention