Minimal Residual Disease assessment in Multiple Myeloma by Next-Generation Sequencing

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MRD Meta-Analysis in Myeloma

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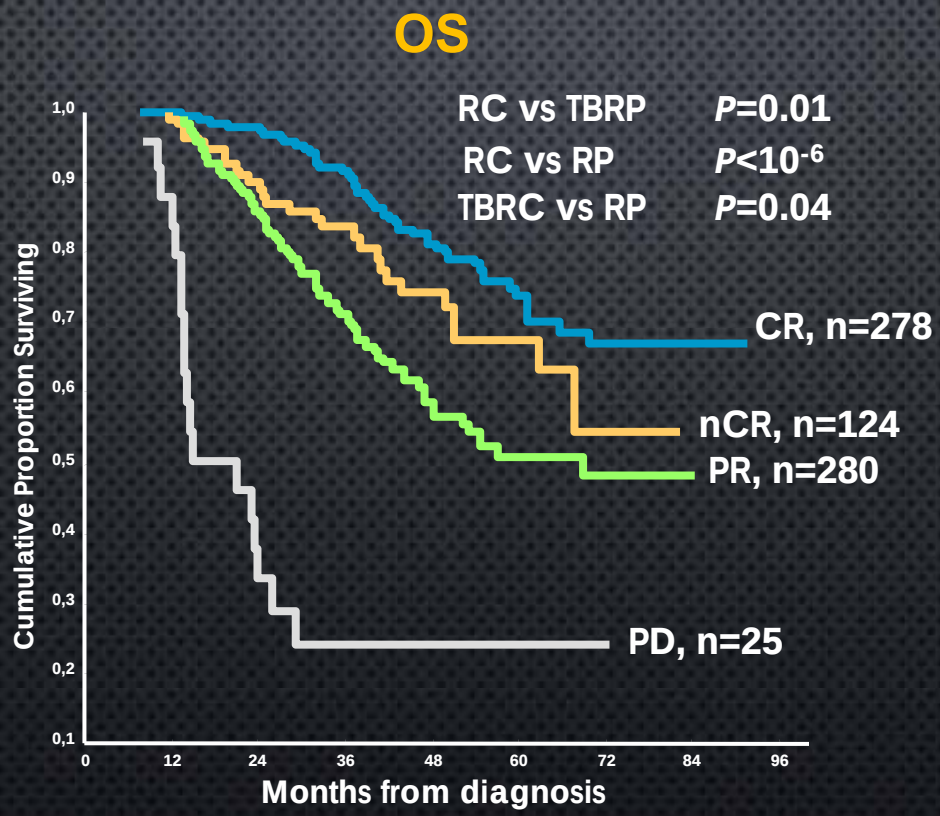
Why to assess MRD in Myeloma?

The main rationale is the correlation response/outcome

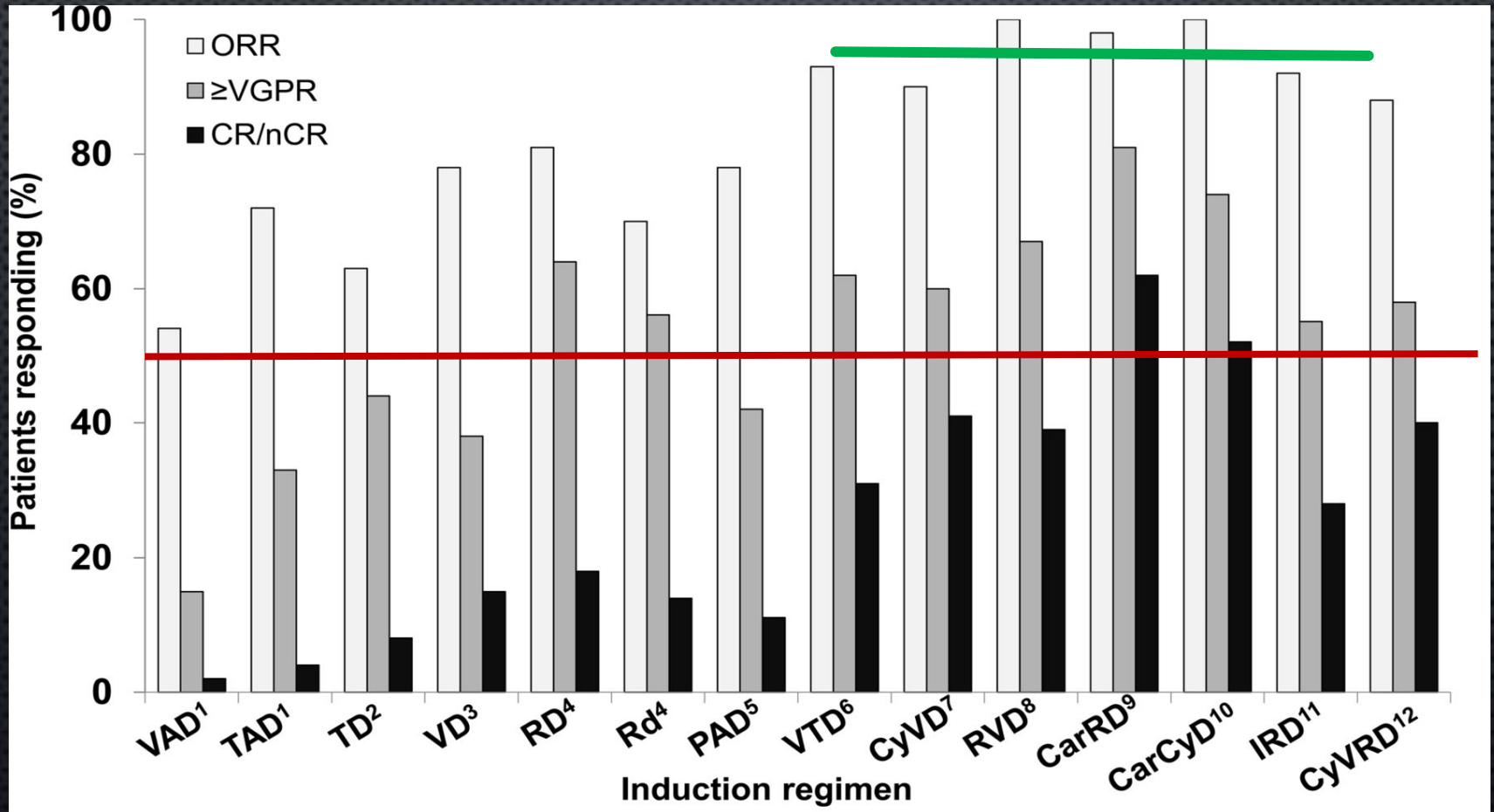


	CR	nCR	PR	PD
Medians EFS, months	61	40	34	13
Medians OS, months	NR	NR	61	15

Lahuerta *et al*. *JCO* 2008

Why to assess MRD in Myeloma?

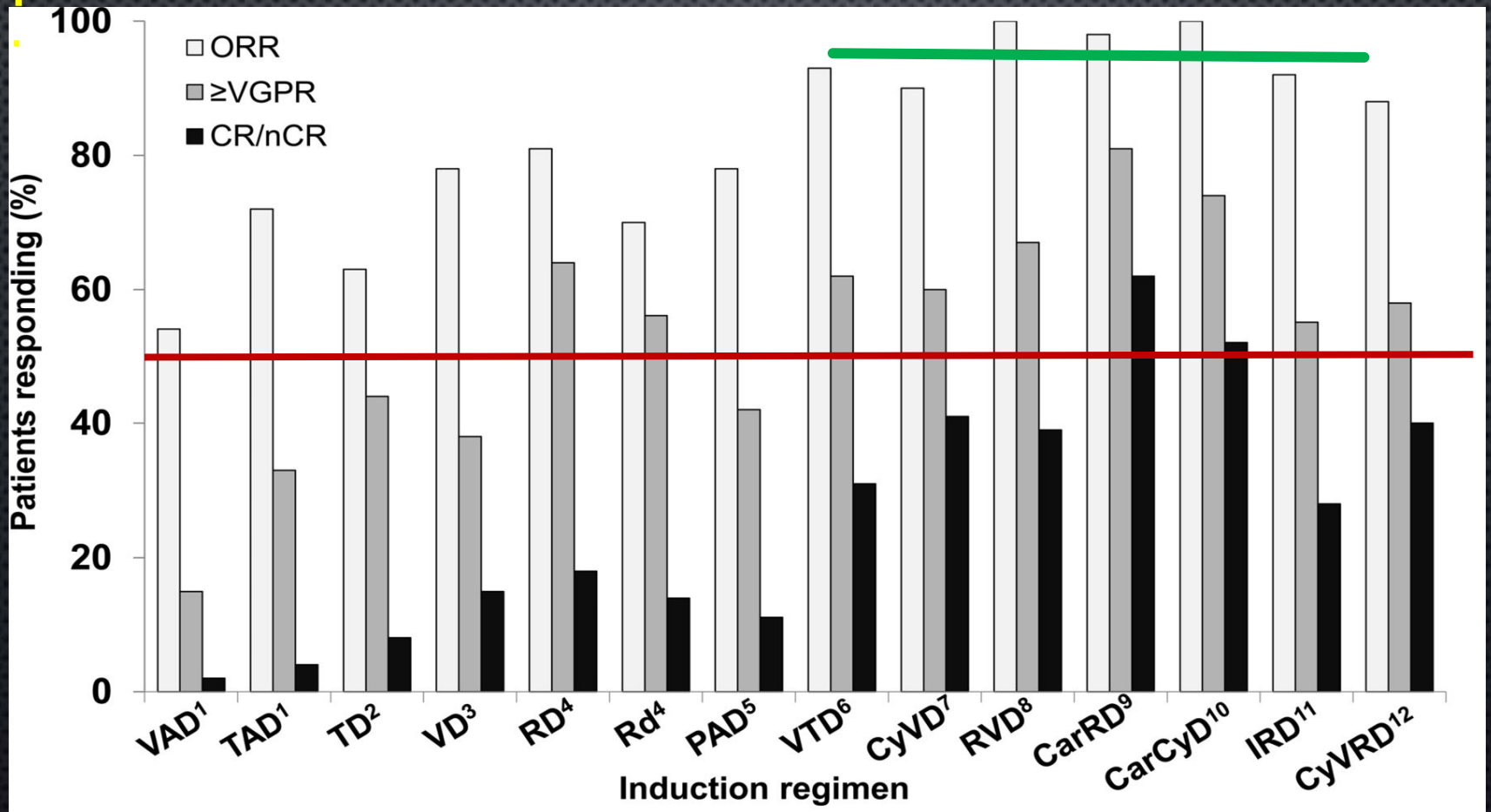
Treatment advances have increased the likelihood of achieving CR.



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.

Why to assess MRD in Myeloma?

However, a large majority of pts with CR eventually relapse, suggesting that undetectable, but clinically meaningful MRD may be present

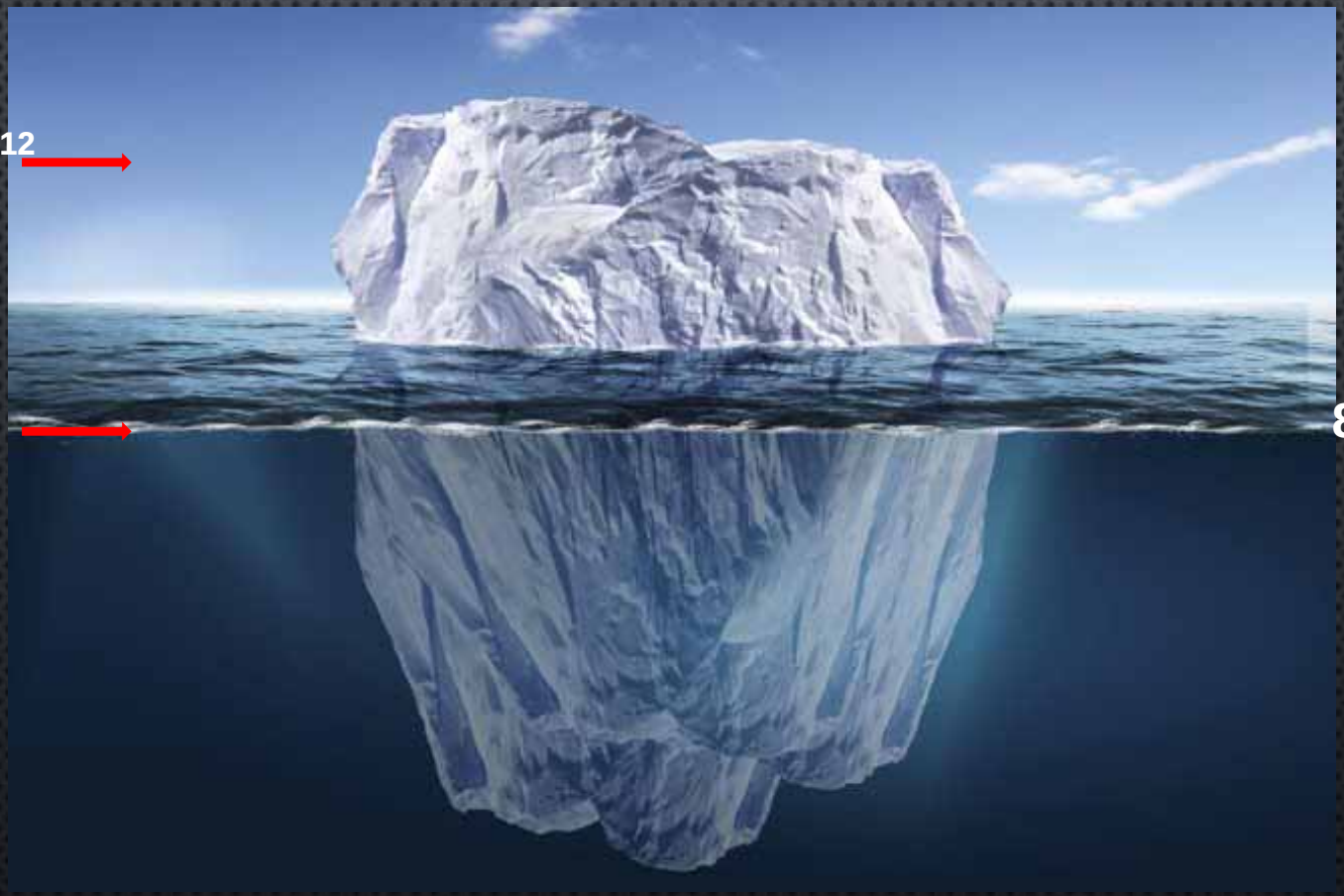


1. Lokhorst HM, et al. Haematologica. 2008;93:124-7. 2. Rajkumar SV, et al 2008 J Clin Oncol 26:2171-77. 3. Harousseau JL, et al 2010 J Clin Oncol 28:4621-4629. 4. Rajkumar SV, et al Lancet Oncol 2010; 11: 29–37. 5. Sonneveld P, et al J Clin Oncol 2012; 30:2946-55. 6. Cavo M, et al Lancet 2010; 376: 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.

Why to assess MRD in Myeloma?

Diagnosis 10^{12}

CR 10^{10}



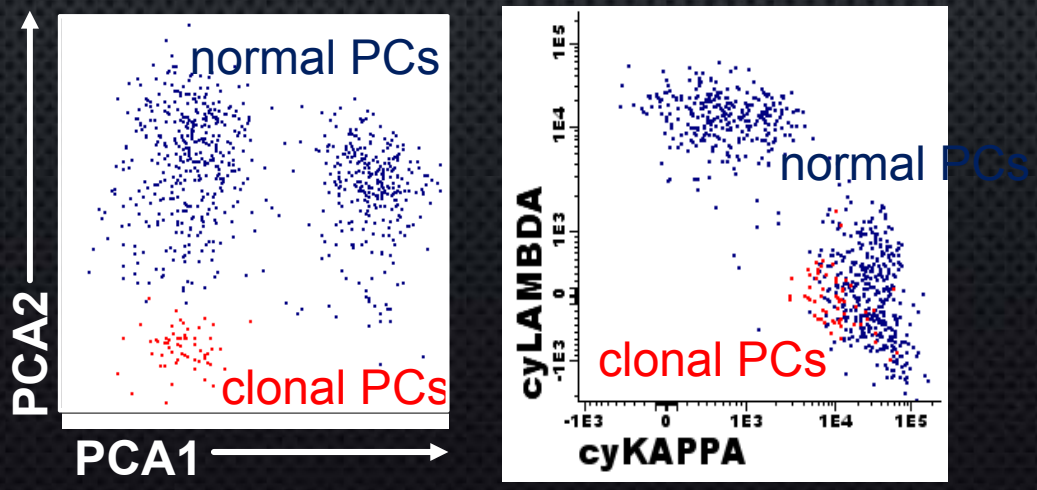
80% HD trial

MRD: What are the techniques?

(Old) Gold Standard: Multiparametric Flow Cytometry

Myeloma cells present a specific phenotype / normal PC

This phenotype is stable during evolution



MRD: What are the techniques?

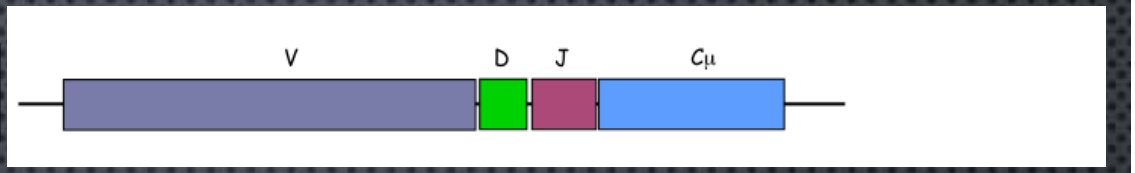
Next-Generation Sequencing

Myeloma cells present unique Ig gene rearrangements

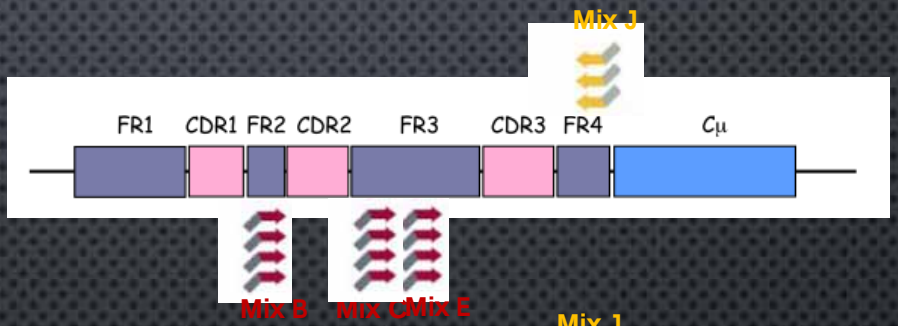
These clonal rearrangements are stable during evolution

NGS: Technical principles

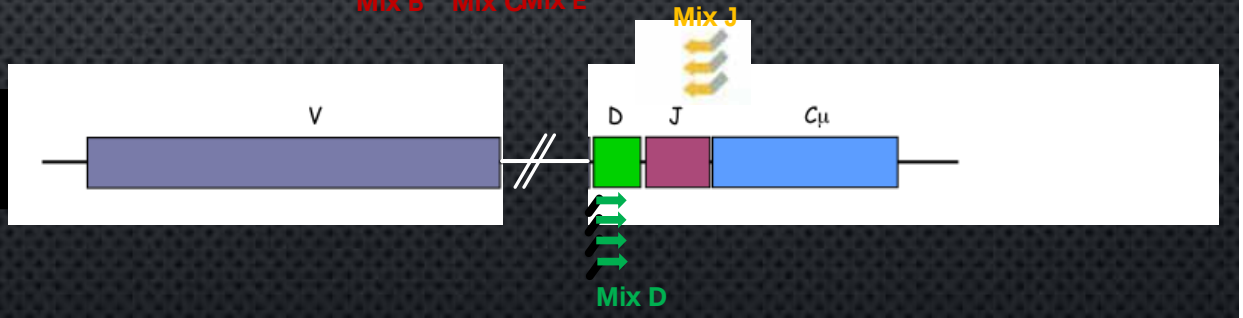
Functional Allele



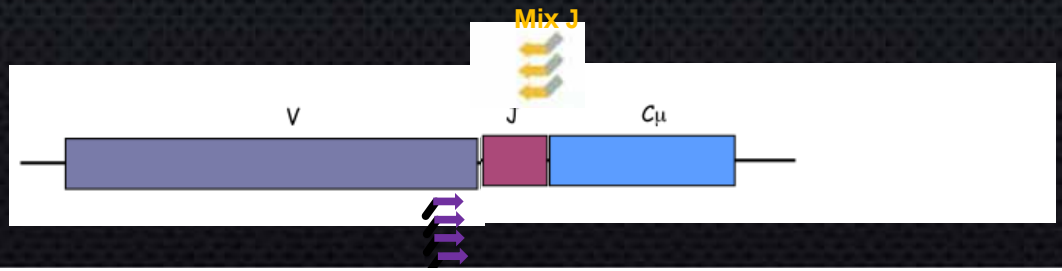
Locus IGH 14q32



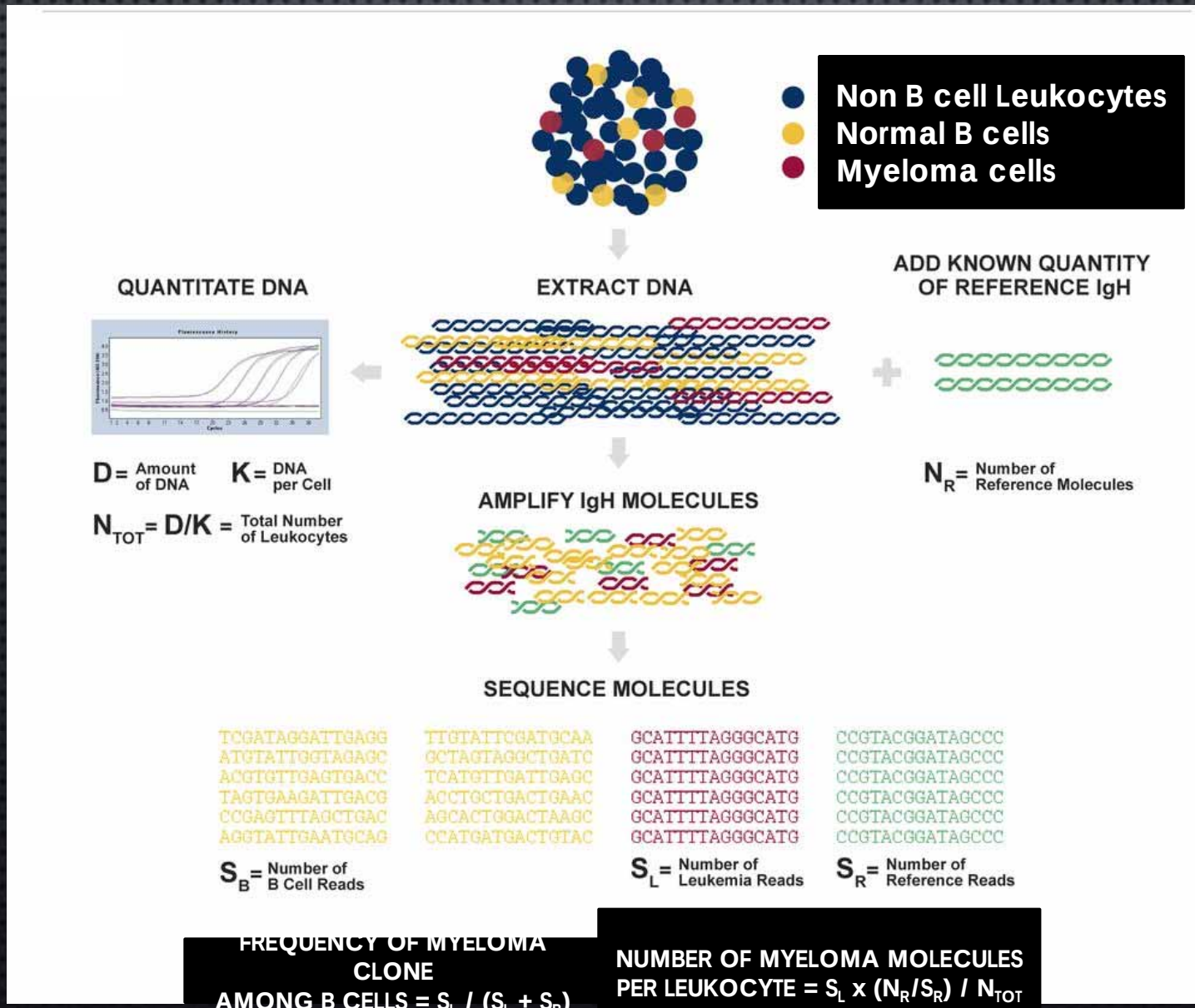
Non-Functional allele



Locus IGK 2p11



NGS: Technical principles



Is MRD clinically pertinent?

British Journal of Haematology, 1998, 103, 1145–1151

Clinical utility of immunoglobulin heavy chain gene rearrangement identification for tumour cell detection in multiple myeloma

Agneta Swedin,[1] Stig Lenhoff,[1] Tor Olofsson,[2] Britt Thuresson[2] and Jan Westin[1]
[1]Division of Haematology, Department of Medicine, and [2]Blood Centre, University Hospital, Lund, Sweden

BLOOD, 19 JANUARY 2012 - VOLUME 119, NUMBER 3

High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma

Bruno Paiva,[1,2] Norma C. Gutiérrez,[1,2] Laura Rosiñol,[3] María-Belén Vidriales,[1,2] María-Ángeles Montalbán,[4] Joaquín Martínez-López,[4] María-Victoria Mateos,[1,2] María-Teresa Cibeira,[3] Lourdes Cordón,[3] Albert Oriol,[5] María-José Terol,[7] María-Asunción Echeveste,[8] Raquel de Paz,[9] Felipe de Arriba,[10] Luis Palomera,[11] Javier de la Rubia,[5] Joaquín Díaz-Mediavilla,[12] Anna Sureda,[13] Ana Gorosquieta,[14] Adrian Alegre,[15] Alejandro Martín,[16] Miguel T. Hernández,[17] Juan-José Lahuerta,[4] Joan Bladé,[3] and Jesús F. San Miguel,[1,2] on behalf of the PETHEMA/GEM (Programa para el Estudio de la Terapéutica en Hemopatías Malignas/Grupo Español de Mieloma) Cooperative Study Groups

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Minimal Residual Disease Assessed by Multiparameter Flow Cytometry in Multiple Myeloma: Impact on Outcome in the Medical Research Council Myeloma IX Study

Andy C. Rawstron, J. Anthony Child, Ruth M. de Tute, Faith E. Davies, Walter M. Gregory, Sue E. Bell, Alexander J. Szubert, Nuria Navarro-Coy, Mark T. Drayson, Sylvia Feyler, Fiona M. Ross, Gordon Cook, Graham H. Jackson, Gareth J. Morgan, and Roger G. Owen

Biol Blood Marrow Transplant 19 (2013) 1109–1115

Molecular Monitoring of Minimal Residual Disease in the Peripheral Blood of Patients with Multiple Myeloma

Mark Korthals [1,2], Nina Sehnke [1], Ralf Kronenwett [1,†], Thomas Schroeder [1], Tobias Strapatsas [1], Guido Kobbe [1], Rainer Haas [1], Roland Fenk [1,*]
[1] Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine-University, Duesseldorf, Germany
[2] Department of Functional Genomics and Medical Toponomics, University Magdeburg, Magdeburg, Germany

VOLUME 28 · NUMBER 12 · APRIL 20 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Major Tumor Shrinking and Persistent Molecular Remissions After Consolidation With Bortezomib, Thalidomide, and Dexamethasone in Patients With Autografted Myeloma

Marco Ladetto, Gloria Pagliano, Simone Ferrero, Federica Cavallo, Daniela Drandi, Loredana Santo, Claudia Crippa, Luca De Rosa, Patrizia Pregno, Mariella Grasso, Anna Marina Liberati, Tommaso Caravita, Francesco Pisani, Tommasina Guglielmelli, Vincenzo Callea, Pellegrino Musto, Clotilde Cangialosi, Roberto Passera, Mario Boccadoro, and Antonio Palumbo

BLOOD, 15 MAY 2014 - VOLUME 123, NUMBER 20

Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma

Joaquín Martínez-López,[1] Juan J. Lahuerta,[1] François Pepin,[2] Marcos González,[3] Santiago Barrio,[1] Rosa Ayala,[1] Noemí Puig,[3] María A. Montalbán,[1] Bruno Paiva,[4] Li Weng,[2] Cristina Jiménez,[3] María Sopena,[1] Martin Moorhead,[2] Teresa Cedena,[1] Inmaculada Rapado,[1] María Victoria Mateos,[3] Laura Rosiñol,[5] Albert Oriol,[6] María J. Blanchard,[7] Rafael Martínez,[8] Joan Bladé,[5] Jesús San Miguel,[4] Malek Faham,[2] and Ramón García-Sanz[3]
[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Sequenta, Inc., San Francisco, CA; [3]Hospital Universitario de Salamanca-IBSAL, IBMCC-CSIC, Salamanca, Spain; [4]Clínica Universitaria de Navarra, Centro de Investigación Médica Aplicada (CIMA), Pamplona, Spain; [5]Hospital Clínic i Provincial de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [6]Hospital Germans Trias i Pujol, Barcelona, Spain; [7]Hospital Ramón y Cajal, Madrid, Spain; and [8]Hospital Clínico de Madrid, Madrid, Spain

Significant Impact of Minimal Residual Disease (MRD) Status On Survival Outcomes In pts (pts) With Multiple Myeloma (MM) Who Achieve Complete Response (CR): A Meta-Analysis

- A total of 405 published articles with MRD
  - 25 articles recently published articles
- Of these, 21 reported overall survival (OS) or progression-free survival (PFS) results, as well as MRD status
- Overall, 2,208 pts were evaluated for MRD
- Nine publications reported conventional CR at the time of MRD measurement. Six represented unique data sets.

Munshi N et al., JAMA Oncol, in press

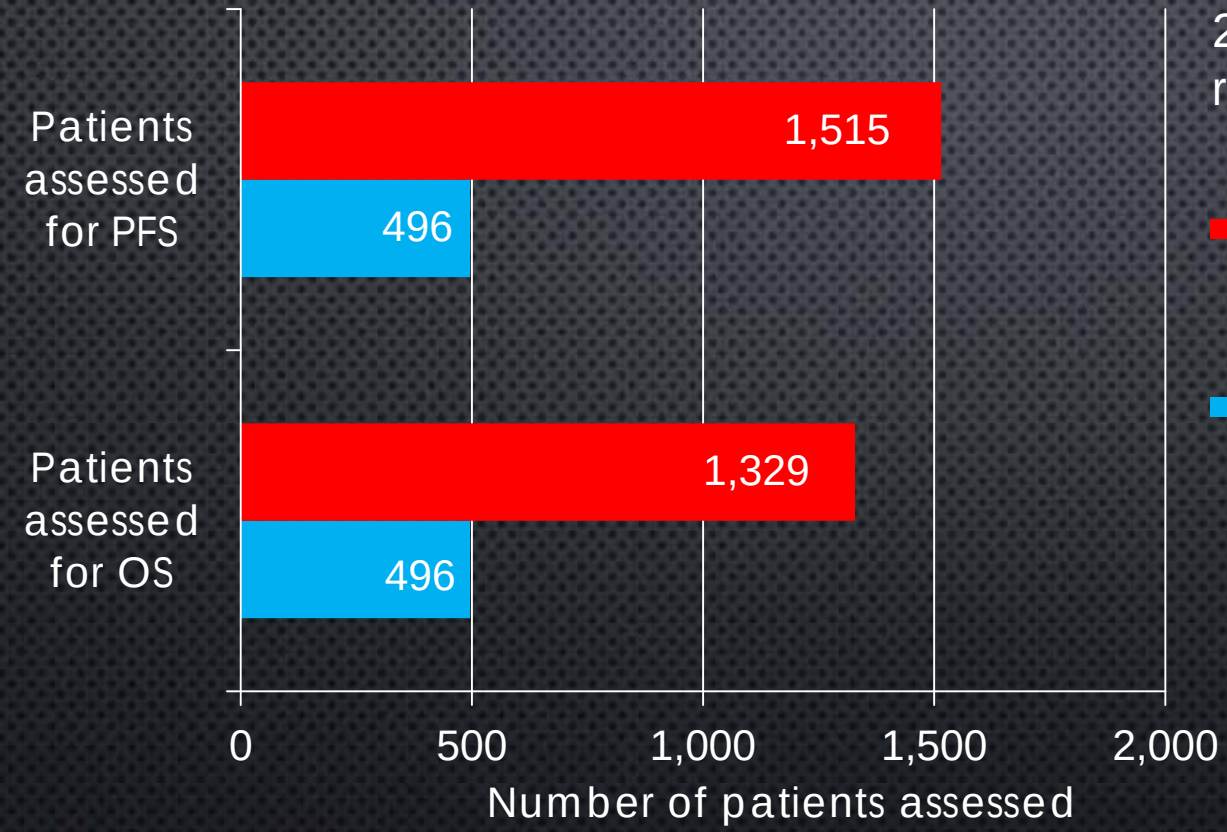
Refining the literature search

Exclusion criteria

- Publications were excluded if they:
  - Only included patients with relapsed and/or refractory MM
  - Included patients who had undergone allogenic SCT
  - Assessed MRD in apheresis product
  - Reported on the same study population used in an already-included trial
- Analysis was restricted to techniques with a detection limit of ≤ 0.01%

MM, multiple myeloma; MRD, minimal residual disease; SCT, stem cell transplant.

Number of patients with PFS and OS data allowing for analysis

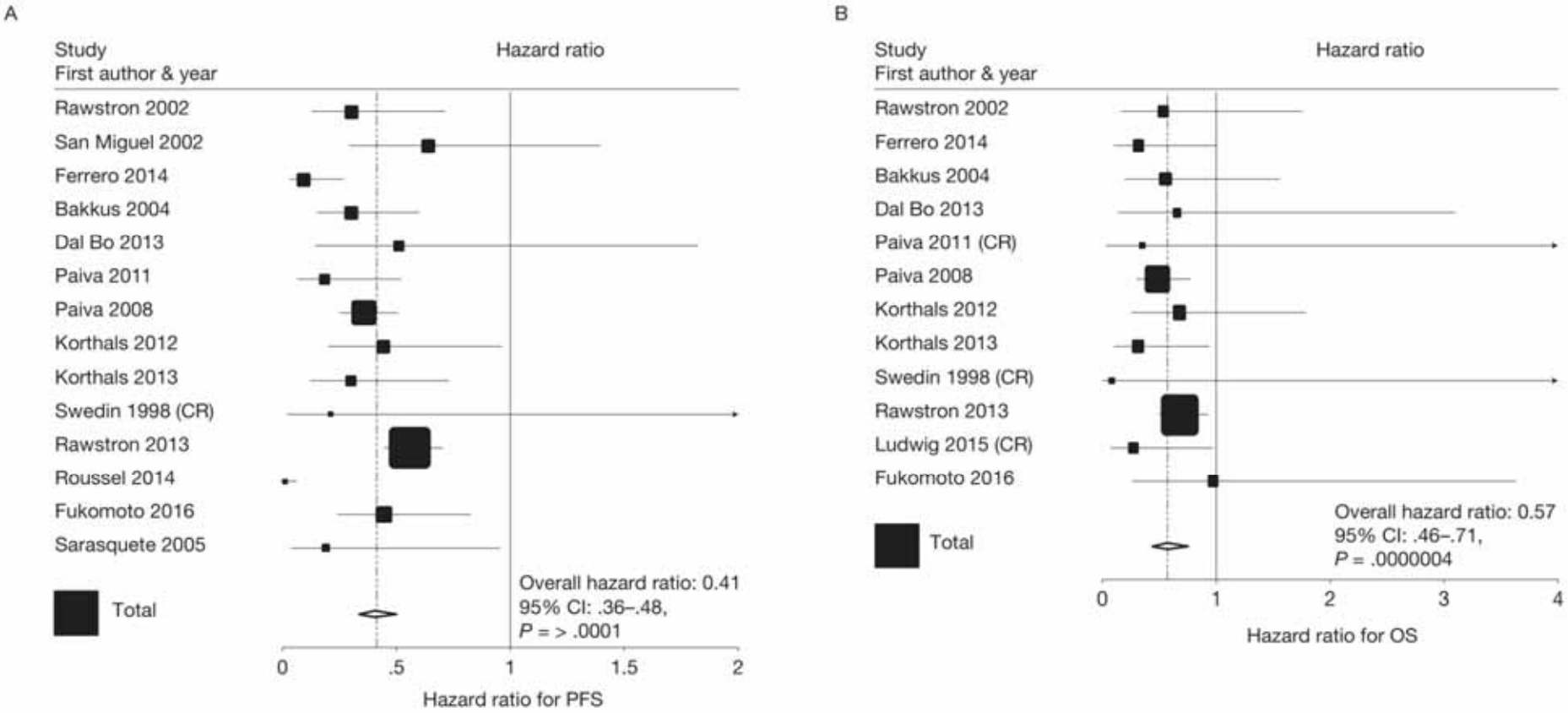


OS, overall survival; PFS, progression-free survival.

1. Paiva B, et al. J Clin Oncol. 2011;29:1627-33.
2. Paiva B, et al. Blood. 2012;119:687-91.
3. Rawstron AC, et al. J Clin Oncol. 2013;31:2540-7.
4. Swedin A, et al. Br J Haematol. 1998;103:1145-51.

Munshi N et al., JAMA Oncol, in press

The effect of MRD status on PFS and OS (All patients)



Munshi N et al., JAMA Oncol, in press

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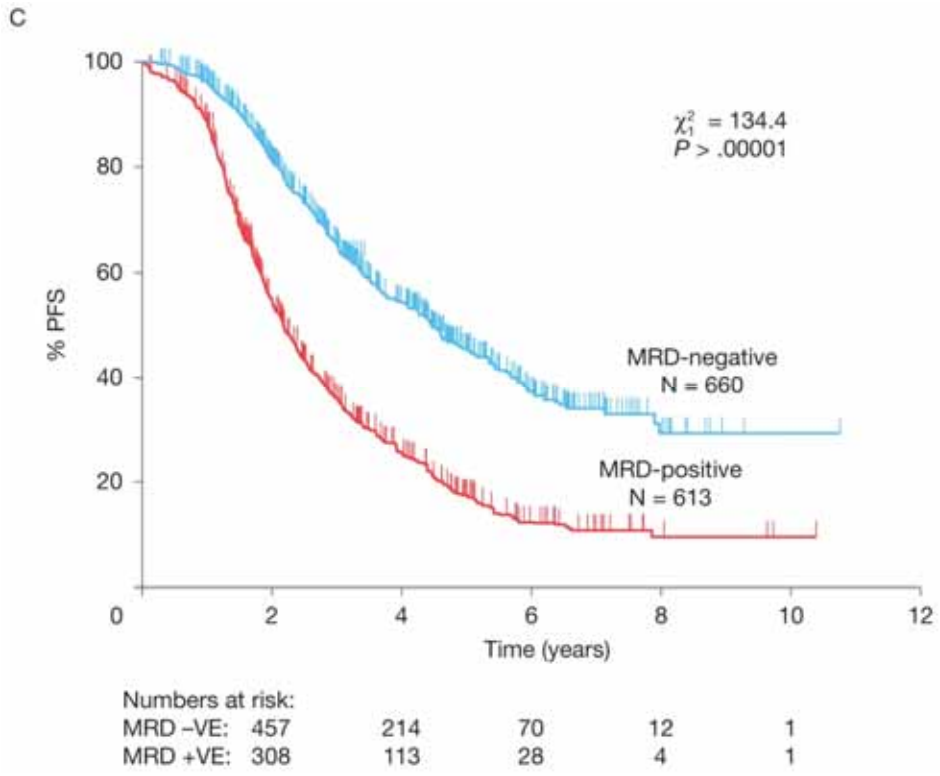
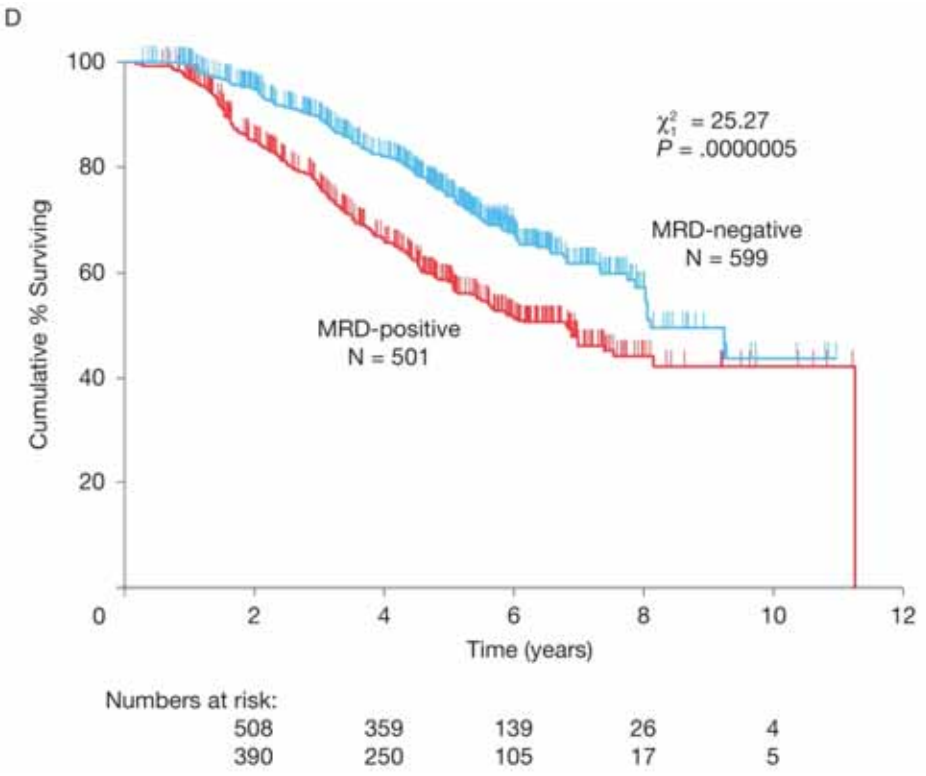
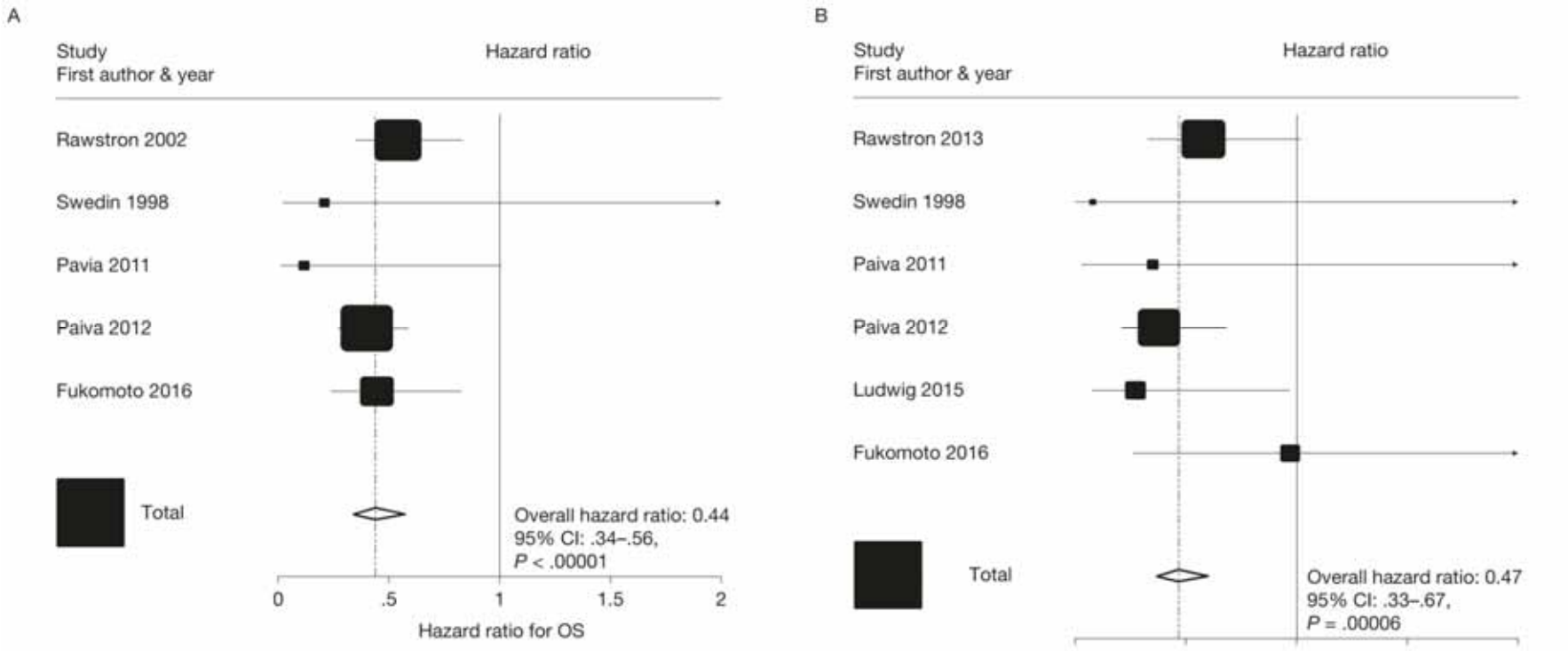




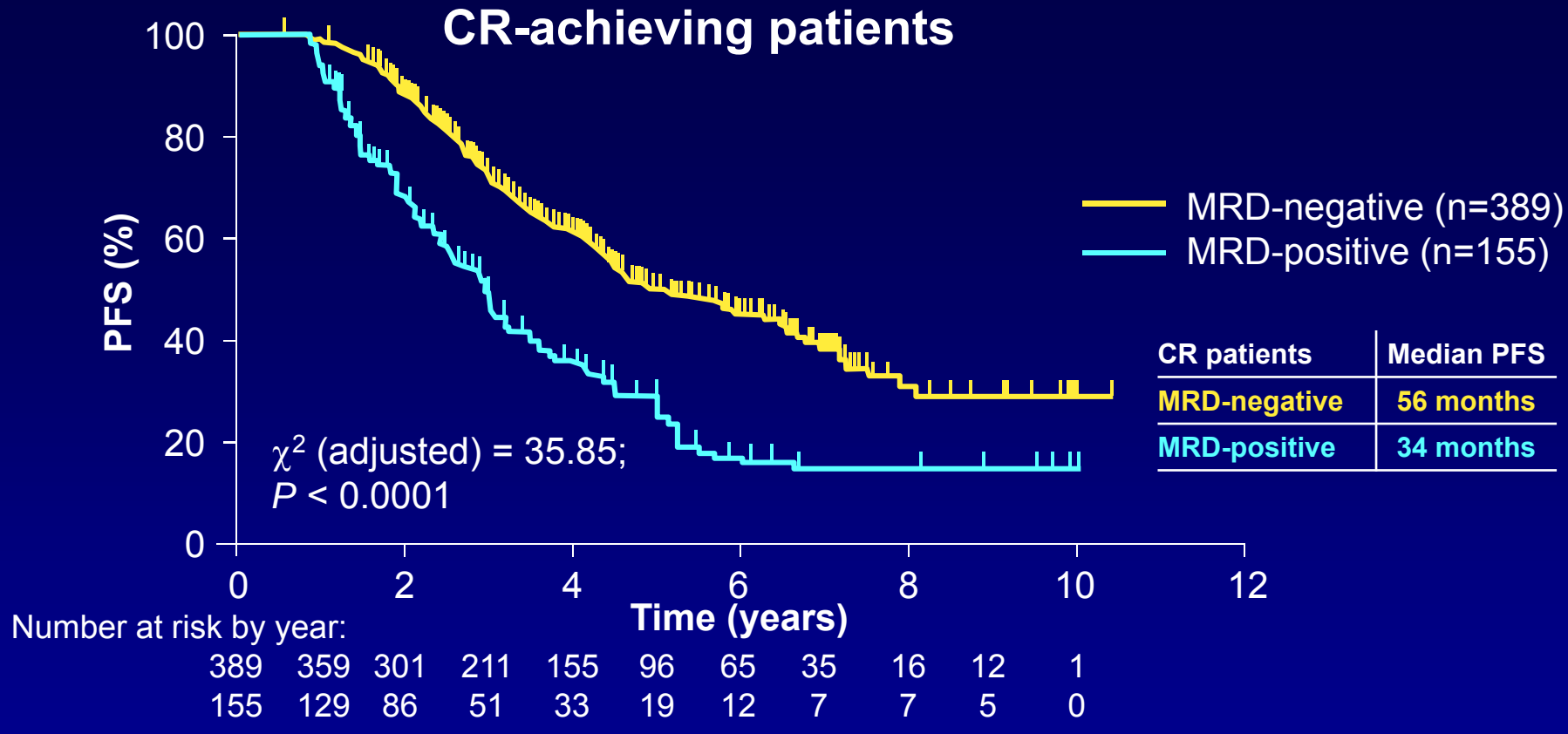
Munshi N et al., JAMA Oncol, in press

The effect of MRD status on PFS and OS (CR patients)



Munshi N et al., JAMA Oncol, in press

The effect of MRD status on PFS (CR patients)



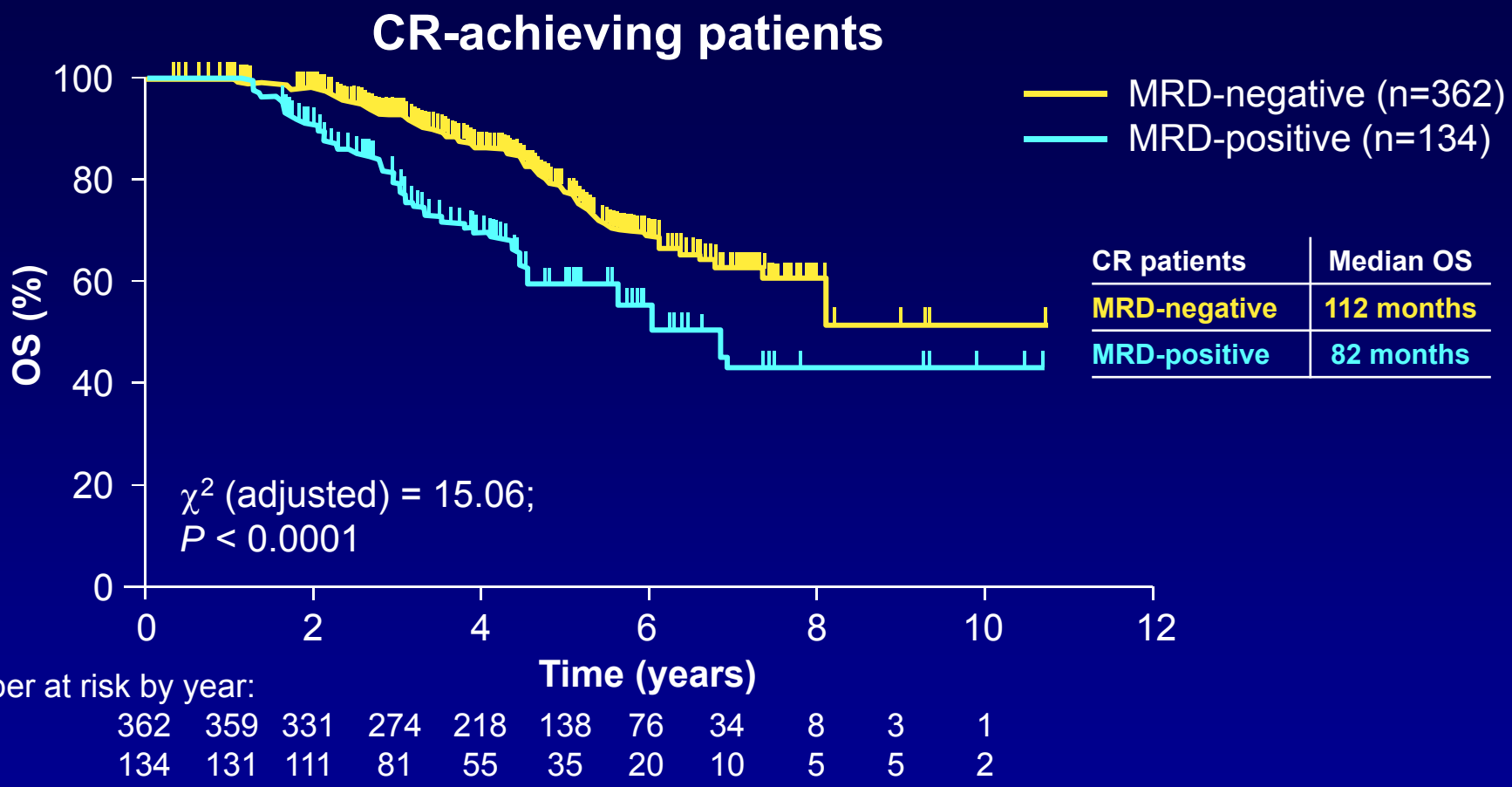
CR patients	Median PFS
MRD-negative	56 months
MRD-positive	34 months

Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

- **3-year PFS: 70% (MRD⁻) vs. 46% (MRD+)**
- **5-year PFS: 48% (MRD⁻) vs. 27% (MRD+)**
- **Majority of MRD-positive patients progressed by 6 years; nearly 50% of MRD-negative patients progression free**

Munshi N et al., JAMA Oncol, in press

The effect of MRD status on OS (CR patients)



CR patients	Median OS
MRD-negative	112 months
MRD-positive	82 months

Data are adjusted for different proportions of patients being MRD-positive and MRD-negative by study.

- **Median OS was not reached for MRD-negative pts versus 82 months for MRD-positive pts)**
- **OS @ 3-years, 94% versus 80%** **OS @ 7-years, 67% versus 47%**
- **OS @ 5-years, 80% versus 61%**

CR, complete response; MRD, minimal residual disease; NR, not reached; OS, overall survival.

Munshi N, et al. IMW 2015, abstract 0394.

Conclusions of the meta-analysis

MRD is definitely predictive of both longer PFS and OS

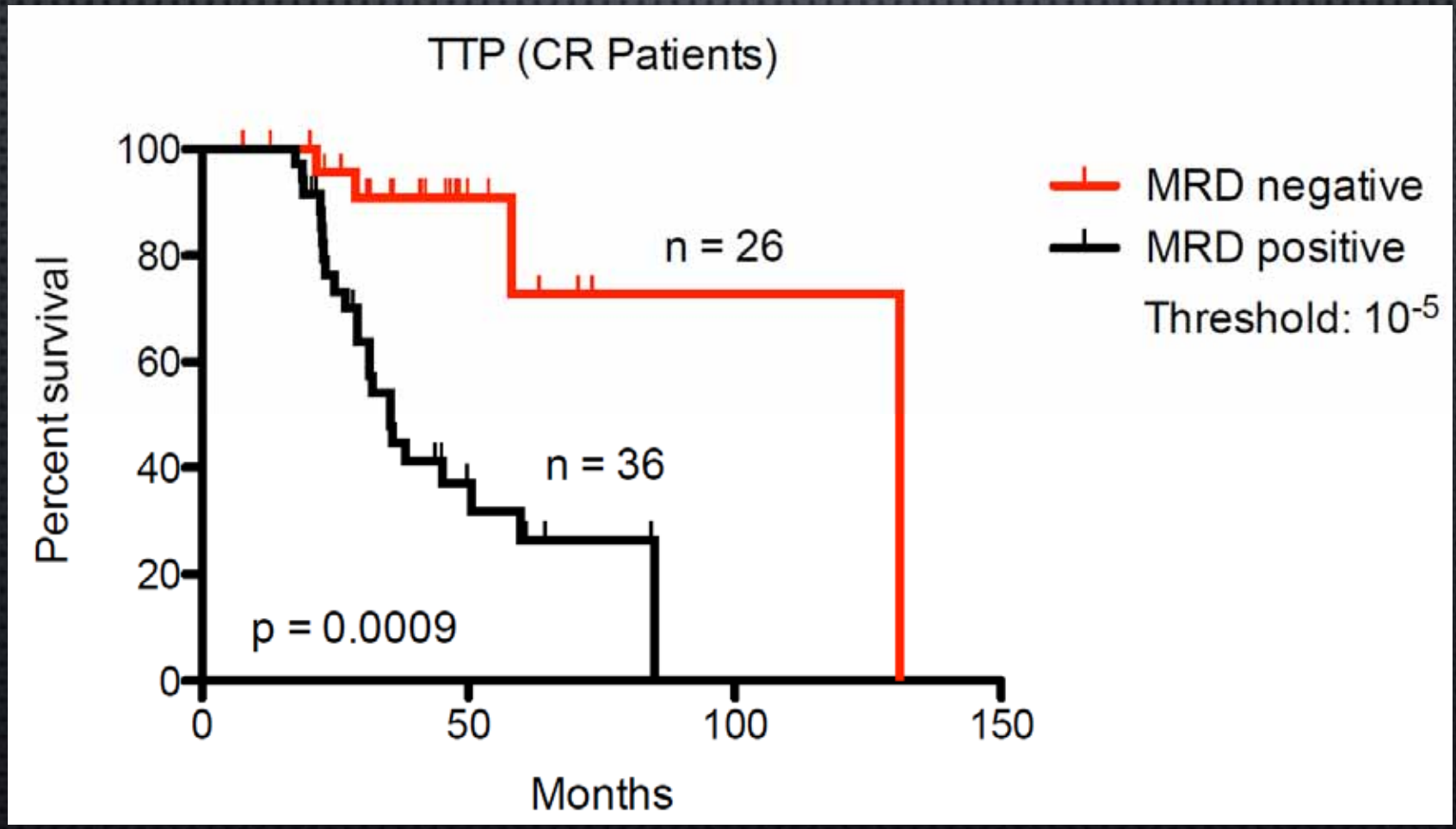
Most of the available results are from MFC

MFC has a quite low sensitivity (10^{-4})

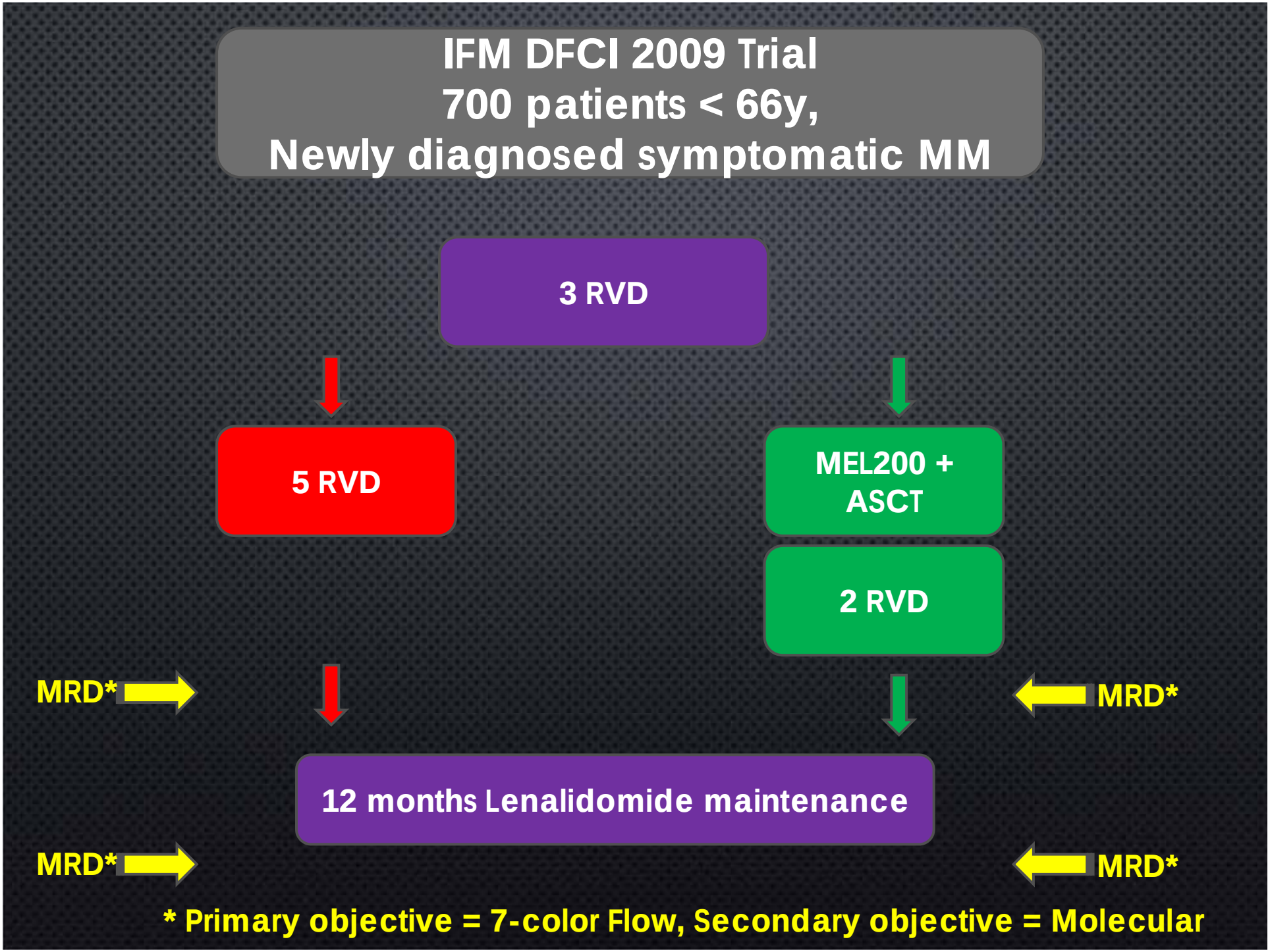
Following question:

→ Would a higher sensitivity have a better predictivity?

Higher sensitivity: NGS



Martinez-Lopez J et al., Blood 2014;123:3073


IFM DFCI 2009 Trial
700 patients < 66y,
Newly diagnosed symptomatic MM
3 RVD
5 RVD
MEL200 + ASCT
2 RVD
MRD*
MRD*
12 months Lenalidomide maintenance
MRD*
MRD*
* Primary objective = 7-color Flow, Secondary objective = Molecular

IFM 2009 trial

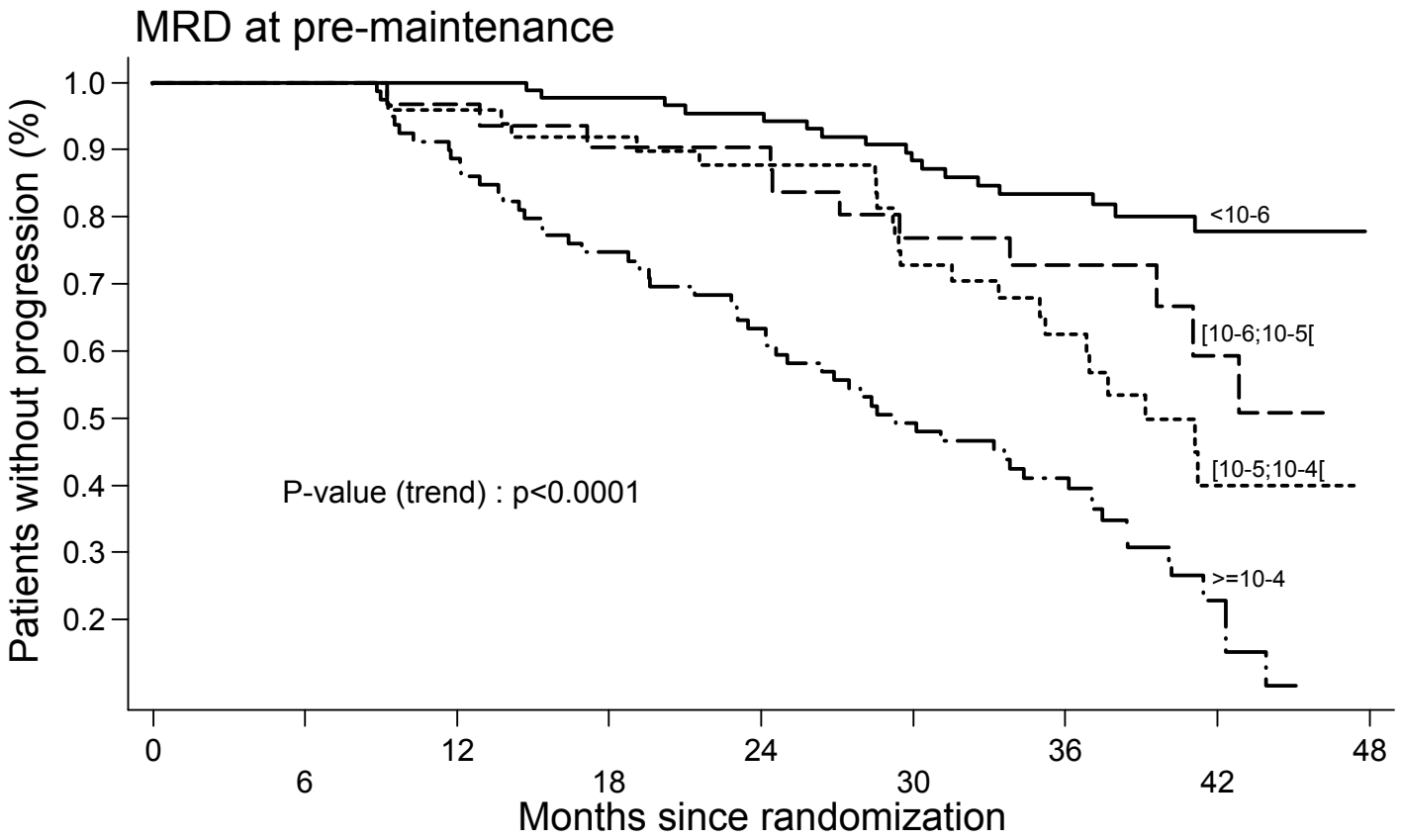
54% Conventional CR

289 patients analyzed by NGS

Applicability of NGS: 92% (8% clone ID failure)

Median follow-up: 44 months

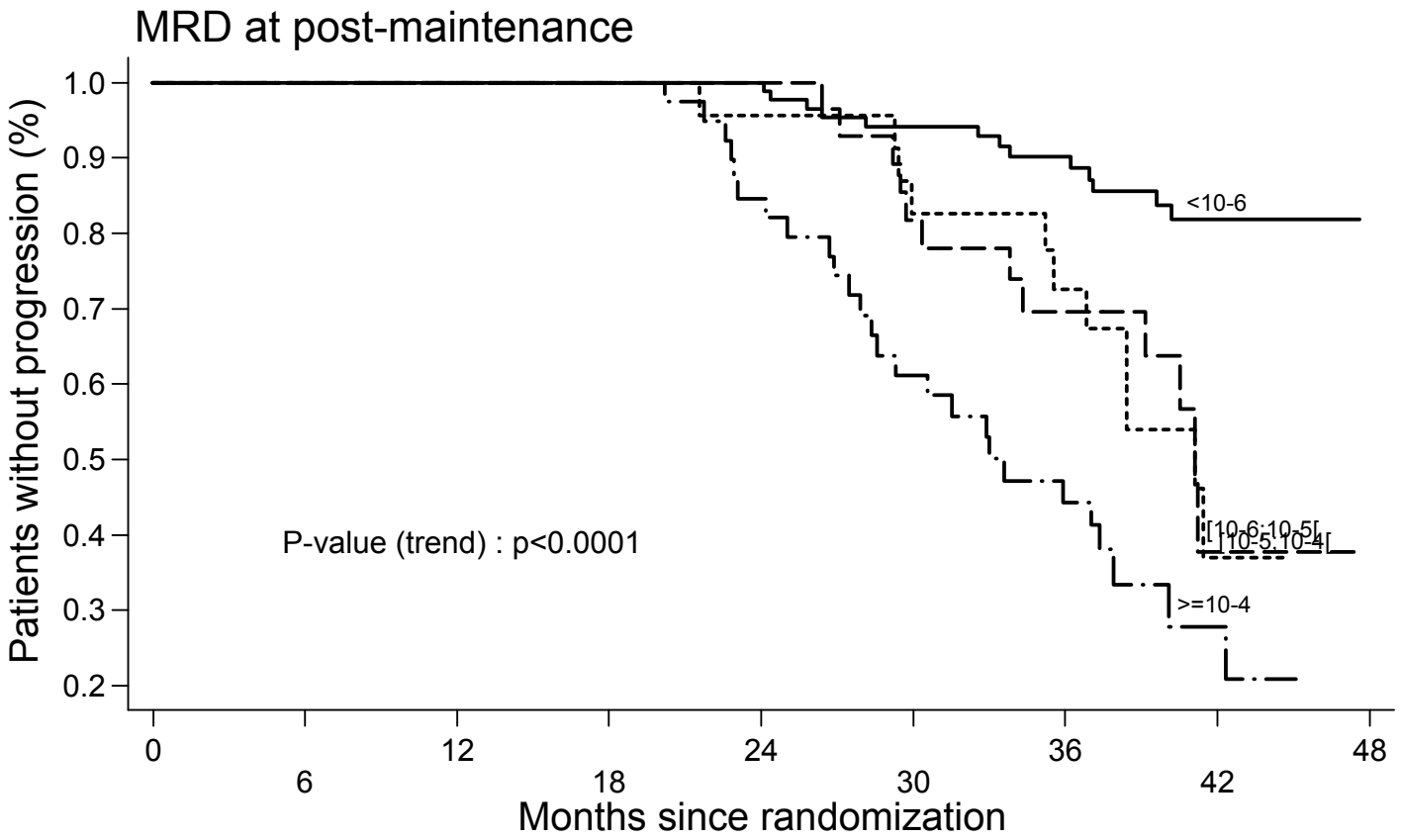
IFM 2009 trial



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

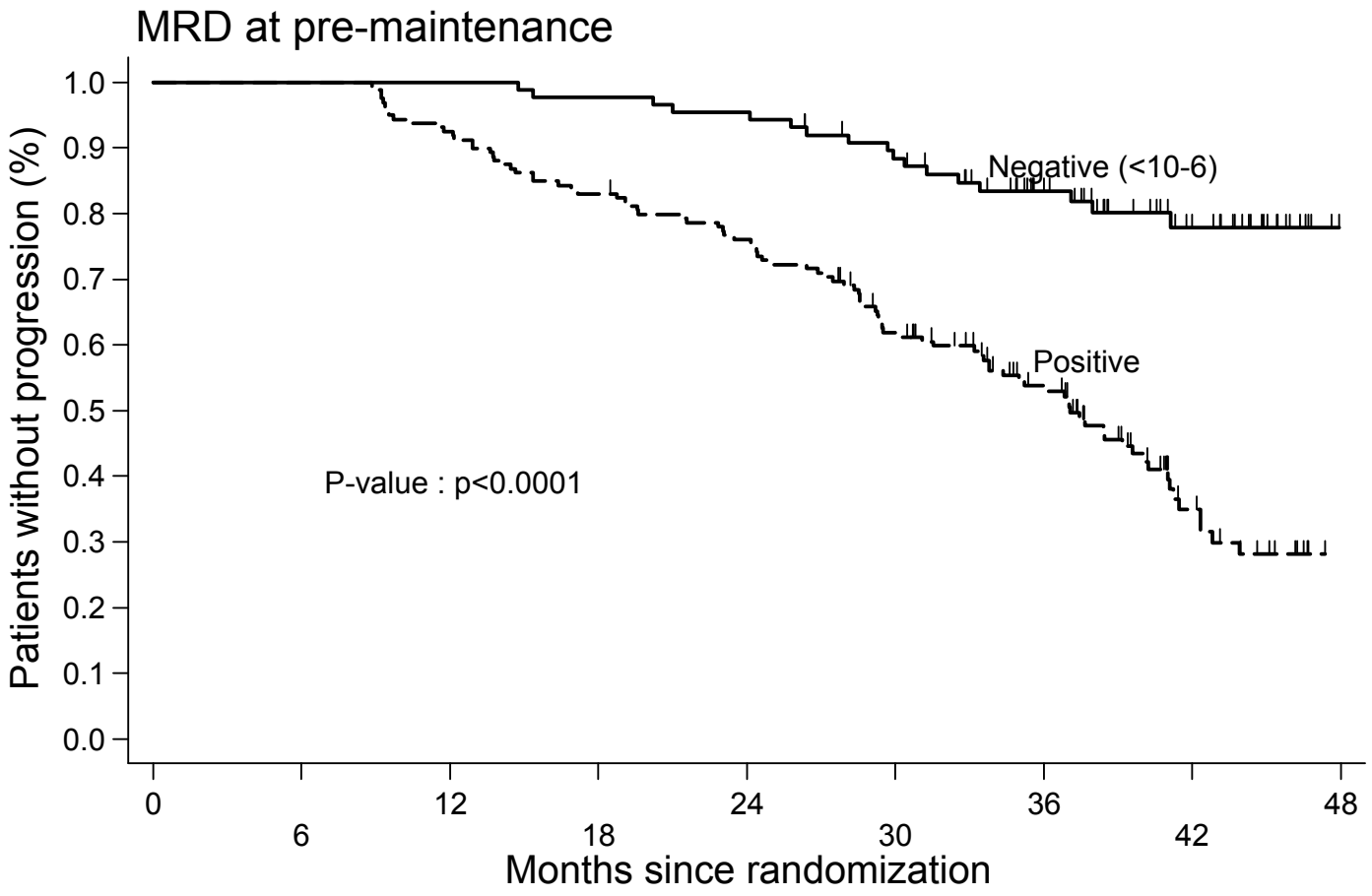
IFM 2009 trial



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

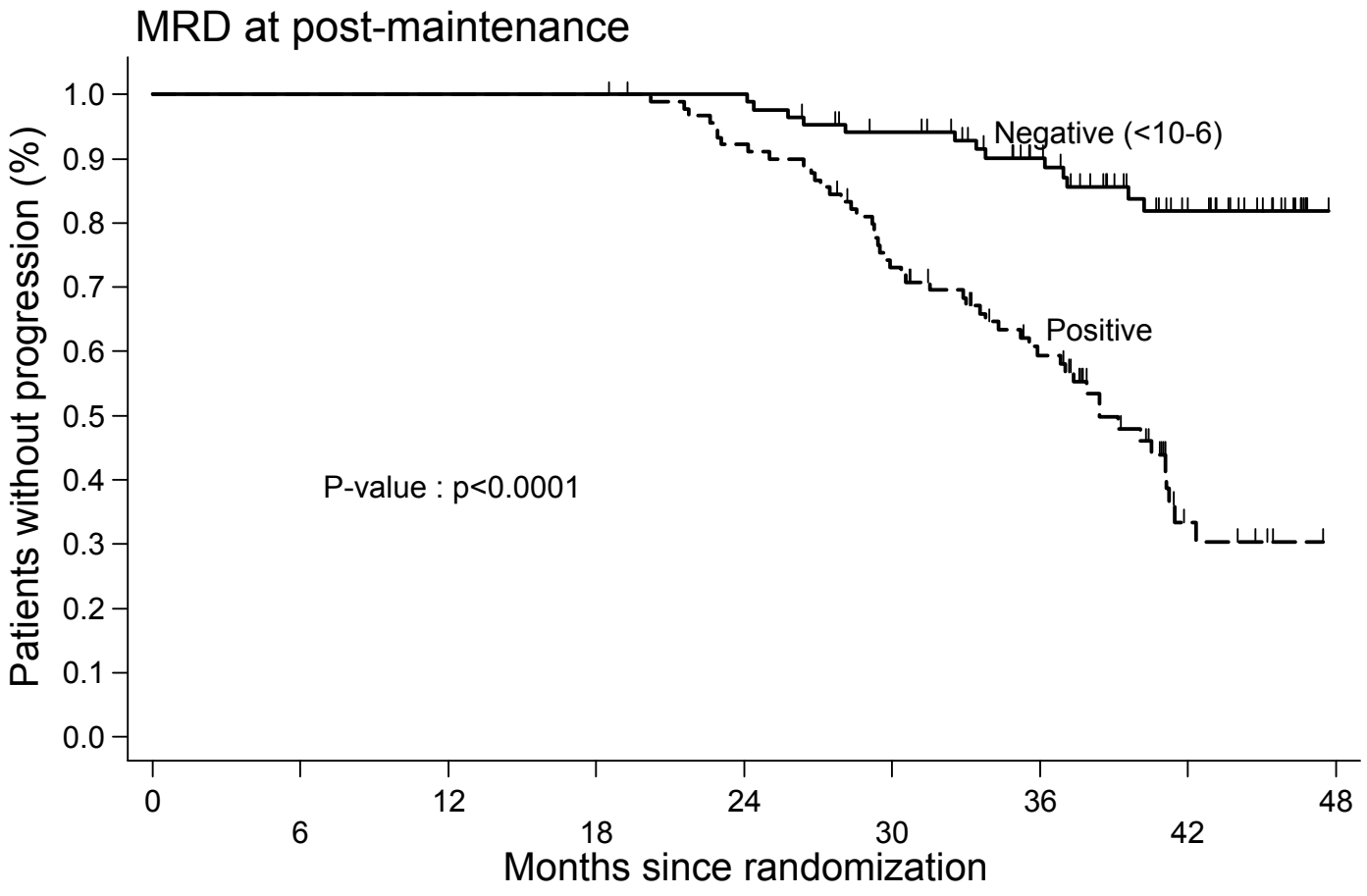
IFM 2009 trial
FCM Negative Patients



N at risk (events)

MRD neg ($<10^{-6}$)	87	(0)	87	(0)	87	(2)	85	(2)	83	(6)	74	(4)	54	(3)	31	(0)	8
MRD positive	159	(0)	159	(12)	147	(15)	132	(11)	120	(22)	94	(11)	67	(17)	22	(4)	6

IFM 2009 trial
FCM Negative Patients



N at risk (events)

MRD neg ($<10^{-6}$)	86	(0)	86	(0)	86	(0)	86	(0)	86	(5)	77	(3)	61	(5)	36	(0)	10
MRD positive	92	(0)	92	(0)	92	(0)	92	(7)	83	(17)	64	(11)	45	(13)	11	(1)	5

MRD by NGS vs MFC

NGS

- Highly sensitive (> 10^{-6})
- Standardized
- Informative in 92% of pts
- Frozen samples

FCM

- Less sensitive (10^{-5})
- Many different panels
- Informative in 100% of pts
- Fresh samples

Conclusions

The highest sensitivity is the most discriminant
→ 10^{-6} is required

NGS is probably the technique of choice

MFC should be used in case of clone ID failure

MRD could (should?) be the main objective of future trials

MRD could identify cured patients

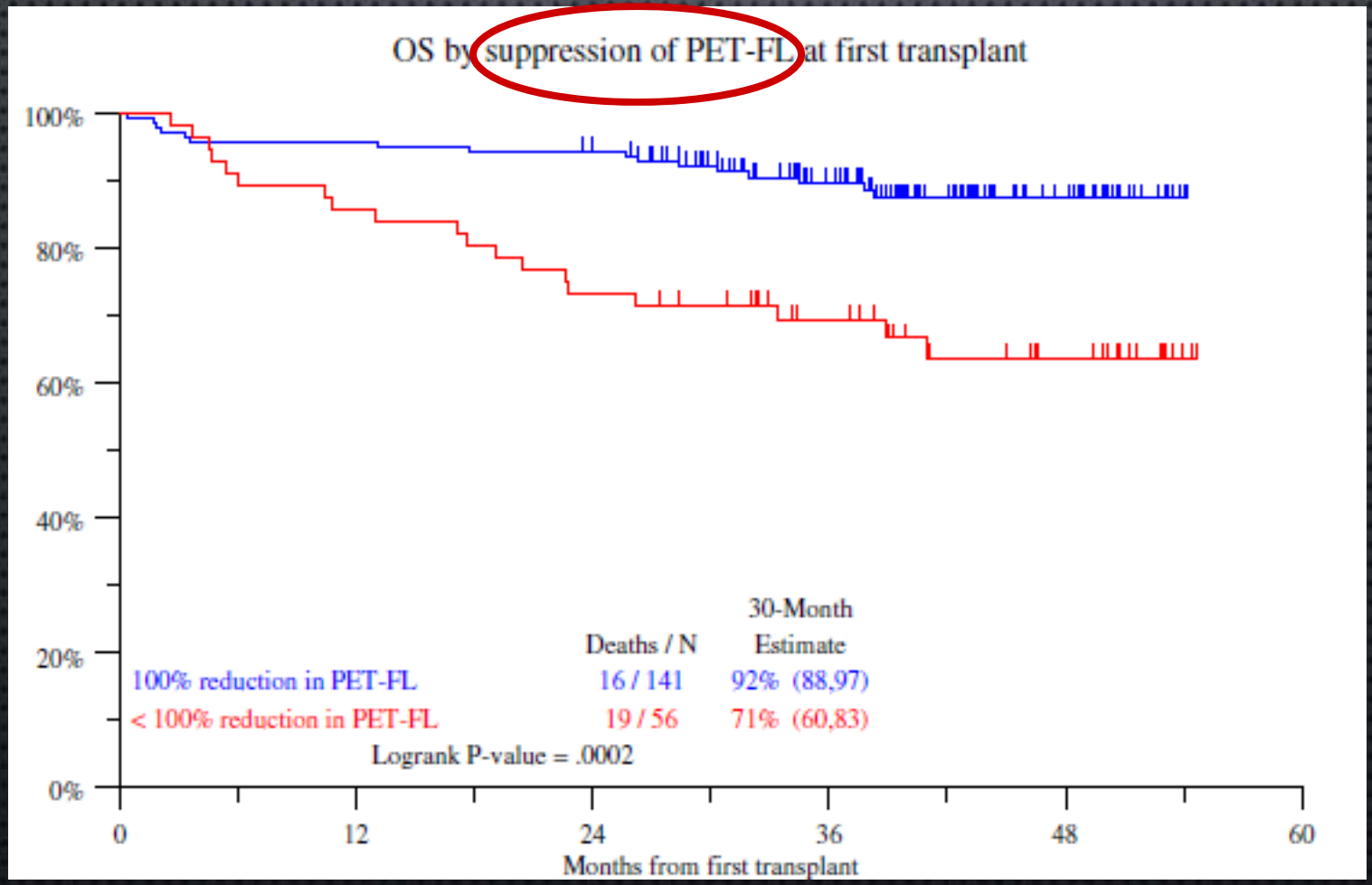
Conclusions

Limitations: MRD evaluates MM in one BM region

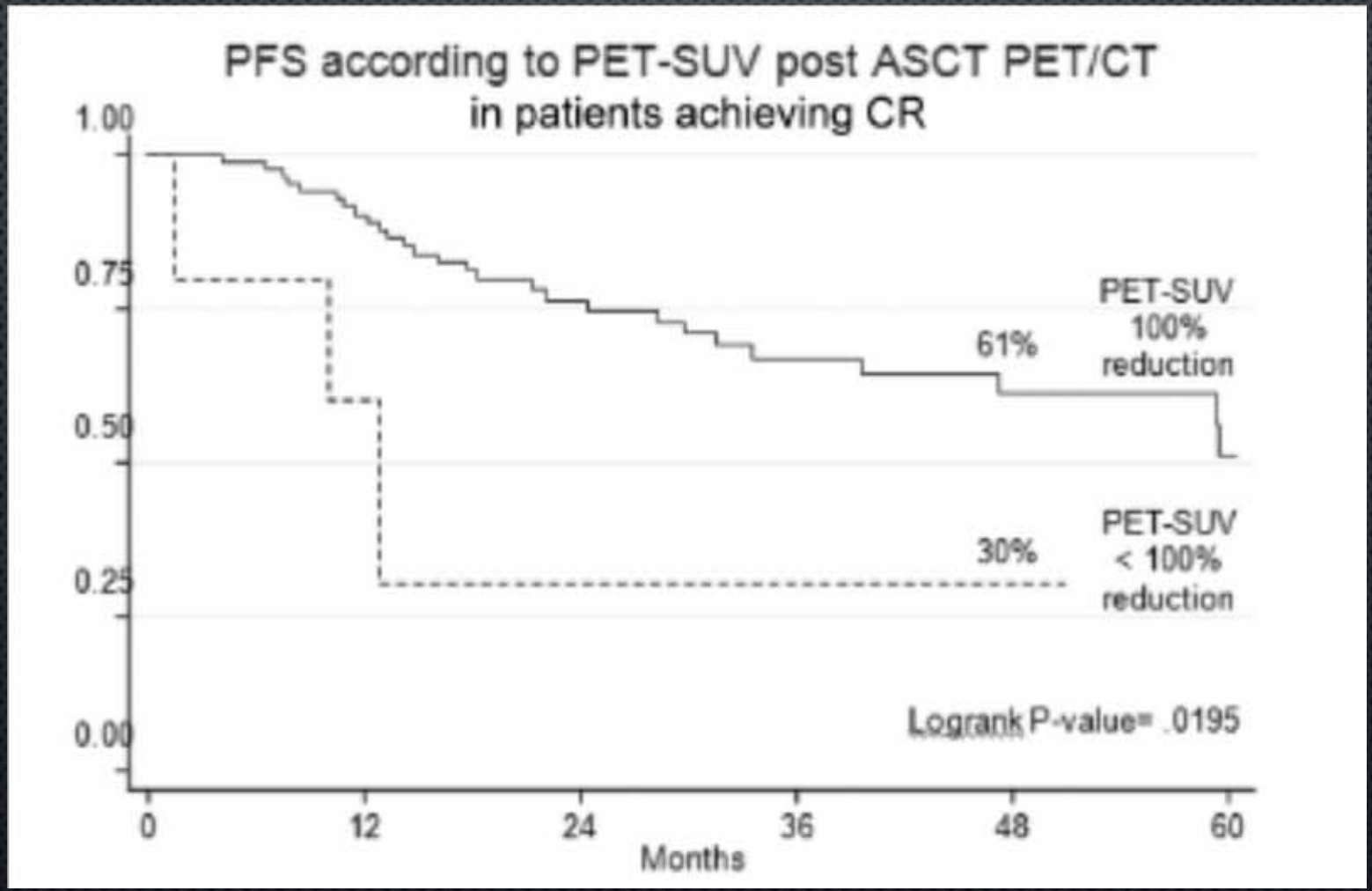
→ What about other regions?

Solutions:

- **cfDNA sequencing analyses? → ongoing**
- **Imaging techniques: PET-TDM+++**



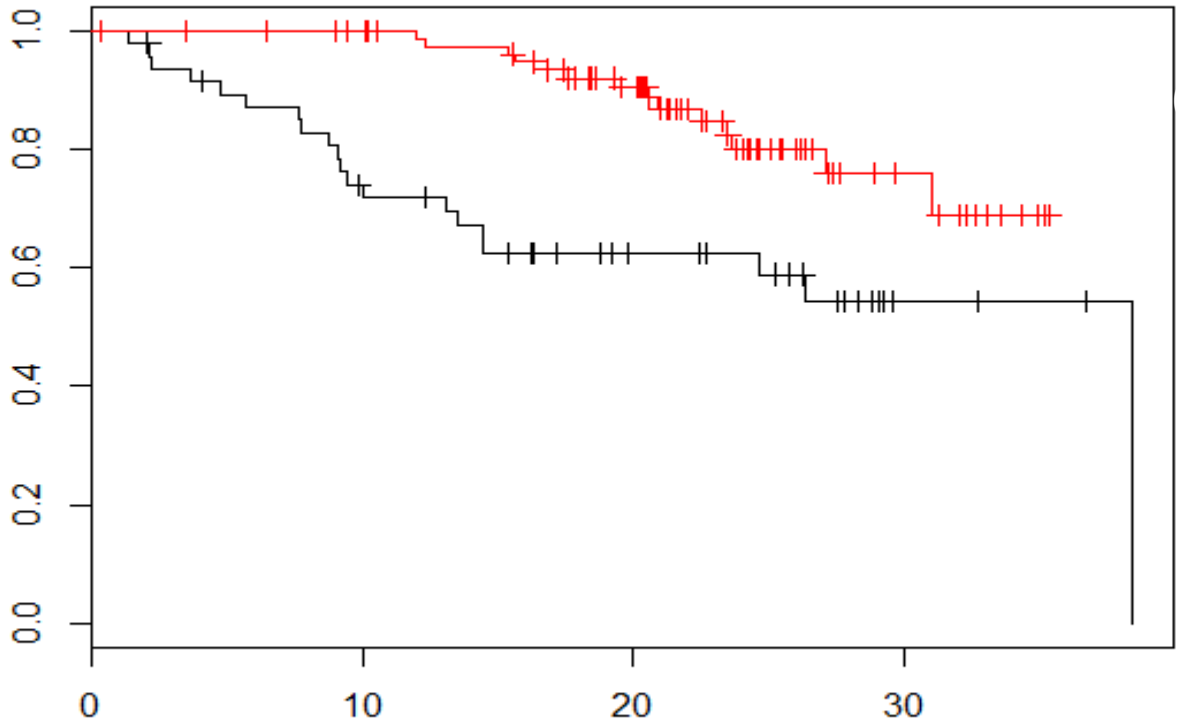
Bartel et al. Blood 2009;114:2068-2076



Zamagni et al, Blood 2011;118:5989-5995

IFM 2009 trial

PET-CT normalisation before maintenance
Impact on PFS (62% normalised)



Conclusions

New concepts in assessment of response in MM

→ IMWG consensus (Kumar S et al., Lancet Oncol, in press)

- MRD in BM with the most sensitive technique
- PET-TDM