Biology of high-risk multiple myeloma or the role of minimal residual disease in multiple myeloma

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EuroFlow Consortium

Disclosures

Name of Company	Research support	Employee	Consultant	Major Stockholder	Speakers' Bureau	Scientific Advisory Bd.	Honoraria
Adaptive							X
Amgen	X						X
Beigene	X						
Becton Dickinson	X						X
Bristol-Myers Squibb	X		X			X	X
GlaxoSmithKline	X		X			X	X
Janssen			X			X	X
Roche	X		X			X	
Sanofi	X		X				X
Takeda			X				X

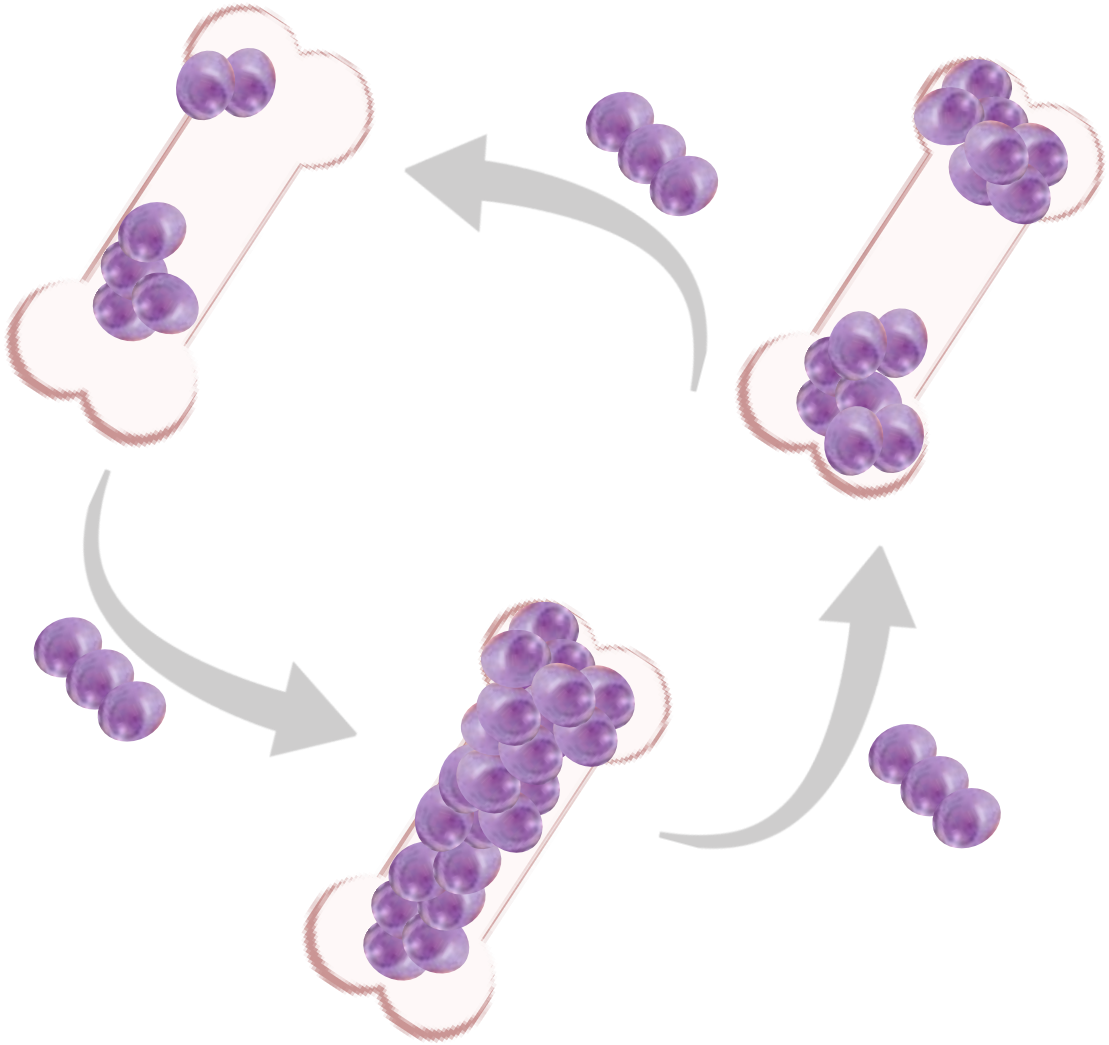
High-risk clones

- ~~CSCs~~
- CTCs
- MRD

Clinical significance of monitoring high-risk clones

Author´s Opinion

CTC numbers are a potential surrogate of tumor burden, proliferation, niche occupancy and dissemination



There are no unifying genetic events associated with tumor egress from the BM[1]

Fully occupied hypoxic BM niches together with a pro-inflammatory tumor microenvironment force cancer cells to stop proliferating, recirculate in PB and seek other BM niches to continue growing[2]

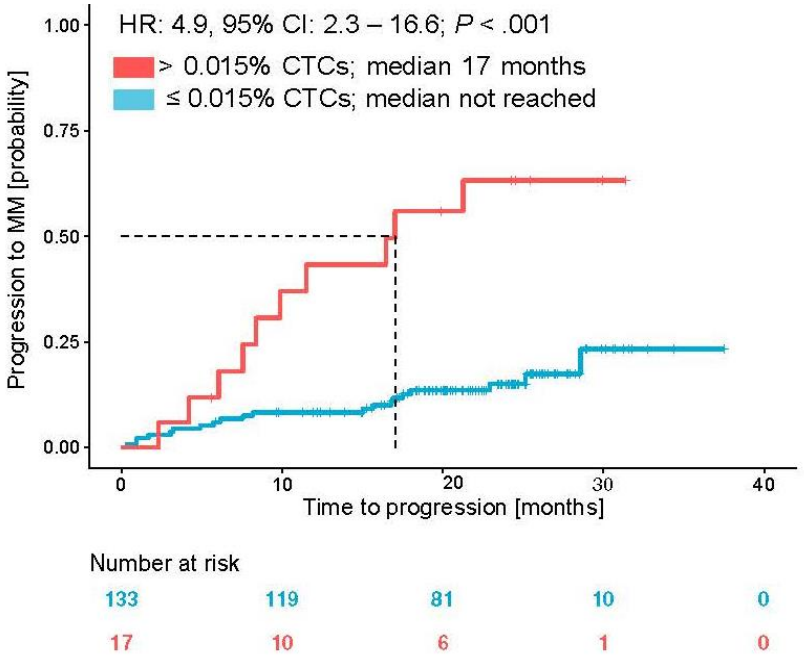
CTCs are a powerful prognostic factor[3-4]

1. Garces JJ, et al. Leukemia. 2020;34(2):589-603.
2. Garces JJ, et al. Leukemia 2020;34(11):3007-3018.
3. Garces JJ, et al. J Clin Oncol. 2022;40(27):3151-3161.
4. Termini R, et al. Clin Cancer Res. 2022;28(21):4771-4781.

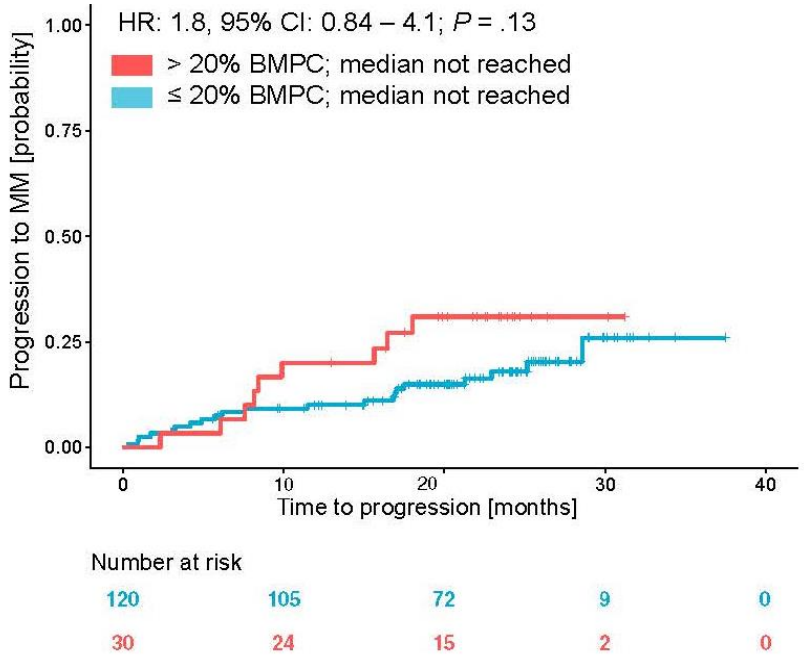
CTCs outperform BM PCs to predict TTP in SMM

Paving the way for minimally-invasive models

>0.015% CTCs



>20% BM PC

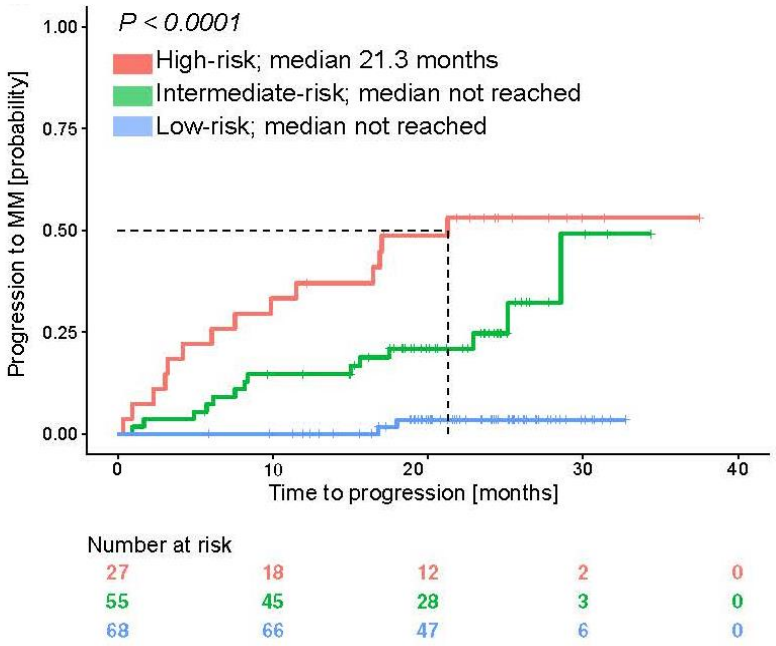


Termini R, et al. Clin Cancer Res. 2022;28(21):4771-4781.

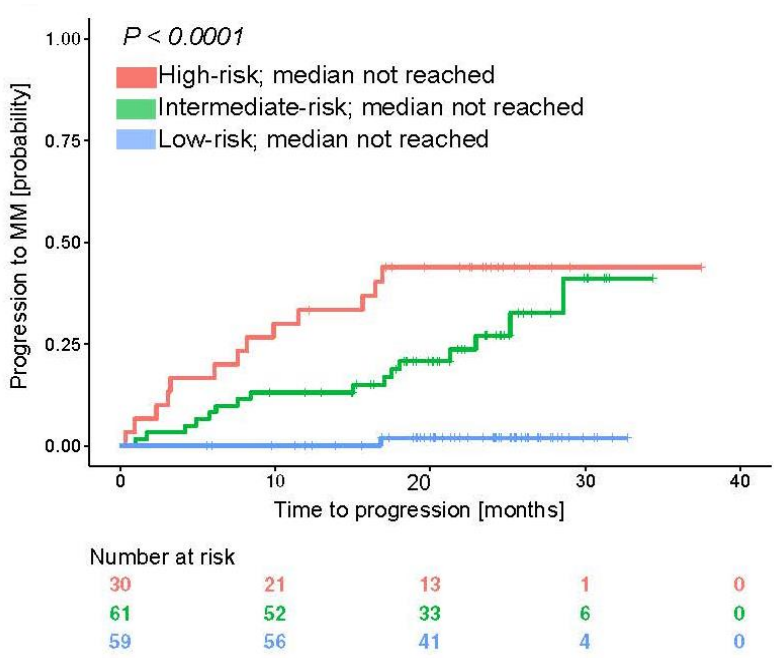
CTCs can replace BM PCs in the IMWG risk model for SMM

Similar performance between minimally and partially invasive models

2/20/0.015 Model (>0.015% CTCs)



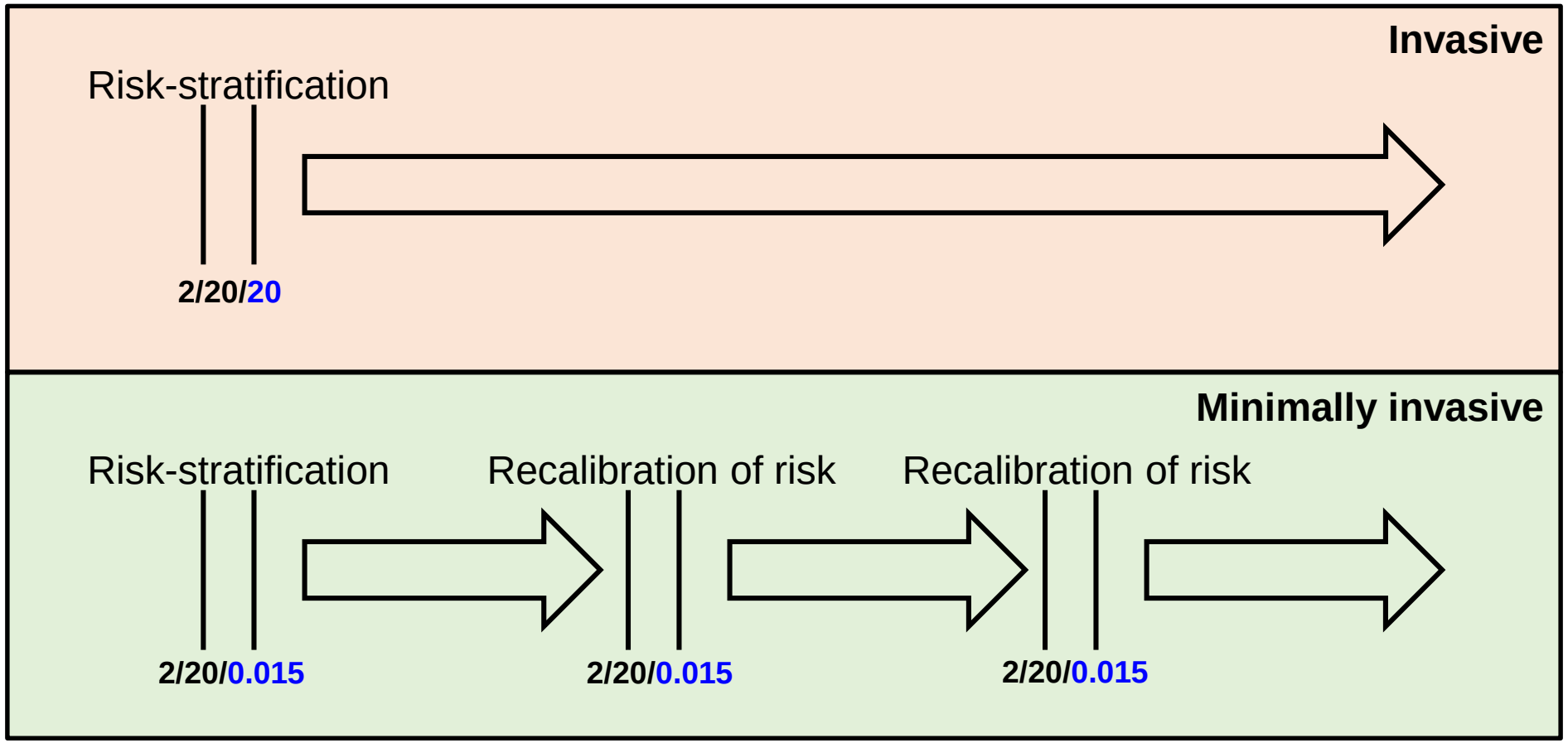
2/20/20 Model (>20% BMPC)



Termini R, et al. Clin Cancer Res. 2022;28(21):4771-4781.

Possible added value of dynamic risk-stratification in SMM[1]

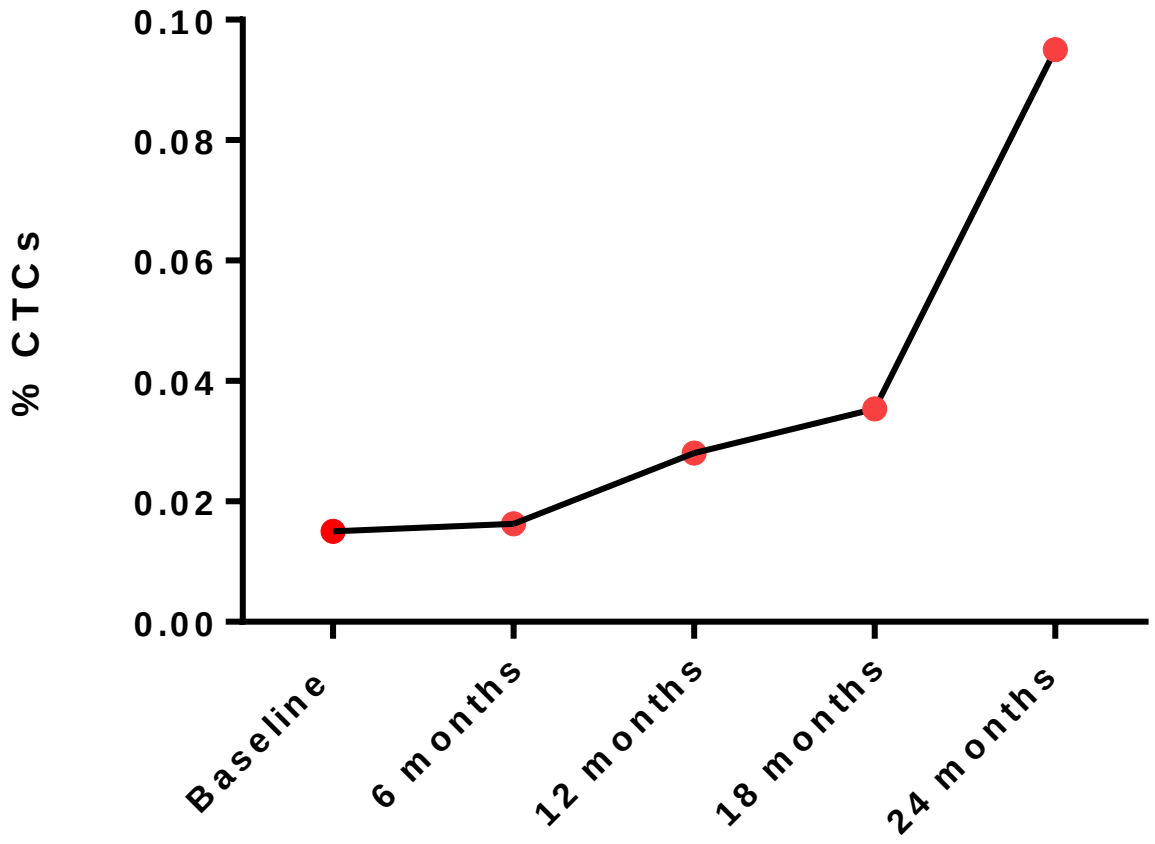
Replacing invasive by minimally invasive tumor burden assessment in the model



1. Visram A, et al. Blood Cancer J. 2021;11(11):186.

Periodic assessment of CTCs

Patient example



At baseline:

- High-risk per 20/2/20
- 0.015% CTCs

Progressed 32 months after enrollment

Prognostic value of CTCs in newly diagnosed active MM

5 independent studies published in 2022 at the J Clin Oncol

More Than 2% of Circulating Tumor Plasma Cells Defines Plasma Cell Leukemia–Like Multiple Myeloma

Tomas Jelinek, MD, PhD[1]; Renata Bezdekova, PhD[2]; David Zihala, PhD[1]; Tereza Sevcikova, PhD[1,3]; Anjana Anilkumar Sithara, MSc[1,3]; Lenka Pospisilova, MSc[4]; Sabina Sevcikova, PhD[5]; Petra Polackova, MSc[2]; Martin Stork, MD, PhD[6]; Zdenka Knechtova, MCs[6]; Ondrej Venglar, MSc[3]; Veronika Kapustova, MSc[1]; Tereza Popkova, MD[1]; Ludmila Muronova, MD[1]; Zuzana Chyra, PhD[1]; Matous Hrdinka, PhD[1]; Michal Simicek, PhD[1]; Juan-Jose Garcés, PhD[7]; Noemi Puig, MD, PhD[8]; Maria-Teresa Cedena, MD, PhD[9]; Artur Jurczyszyn, MD, PhD[10]; Jorge J. Castillo, MD, PhD[11]; Miroslav Penka, MD[2]; Jakub Radocha, MD, PhD[12]; Maria Victoria Mateos, MD[8]; Jesús F. San-Miguel, MD, PhD[7]; Bruno Paiva, PhD[7]; Ludek Pour, MD, PhD[5]; Lucie Rihova, PhD[2]; and Roman Hajek, MD, PhD[1]

High Levels of Circulating Tumor Plasma Cells as a Key Hallmark of Aggressive Disease in Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma

Luca Bertamini, MD[1]; Stefania Oliva, MD, PhD[1]; Delia Rota-Scalabrini, MD[2]; Laura Paris, MD[3]; Sonia Morè, MD[4]; Paolo Corradini, MD[5]; Antonio Ledda, MD[6]; Massimo Gentile, MD[7]; Giovanni De Sabbata, MD[8]; Giuseppe Pietrantuono, MD[9]; Anna Pascarella, MD[10]; Patrizia Tosi, MD[11]; Paola Curci, MD[12]; Milena Gilestro, BSc[1]; Andrea Capra, MScEng[1]; Piero Galieni, MD[13]; Francesco Pisani, MD[14]; Ombretta Annibali, MD, PhD[15]; Federico Monaco, MD[16]; Anna Marina Liberati, MD[17]; Salvatore Palmieri, MD[18]; Mario Luppi, MD, PhD[19]; Renato Zambello, MD[20]; Francesca Fazio, MD[21]; Angelo Belotti, MD[22]; Paola Tacchetti, MD, PhD[23]; Pellegrino Musto, MD[12,24]; Mario Boccadoro, MD[1]; and Francesca Gay, MD, PhD[1]

Circulating Tumor Cells for the Staging of Patients With Newly Diagnosed Transplant-Eligible Multiple Myeloma

Juan-Jose Garcés, MSc[1]; Maria-Teresa Cedena, MD[2]; Noemi Puig, MD, PhD[3]; Leire Burgos, PhD[1]; Jose J. Perez, PhD[3]; Lourdes Cordon, PhD[4]; Juan Flores-Montero, MD, PhD[5,6]; Luzalba Sanoja-Flores, PhD[7]; Maria-Jose Calasanz, PhD[1]; Albert Ortiol, MD[8]; María-Jesús Blanchard, MD[9]; Rafael Rios, MD, PhD[10]; Jesus Martin, MD[7]; Rafael Martínez-Martinez, PhD[11]; Joan Bargay, MD, PhD[12]; Anna Sureda, MD, PhD[8,13]; Javier de la Rubia, MD[4,14,15]; Miguel-Teodoro Hernandez, MD, PhD[16]; Paula Rodriguez-Otero, MD, PhD[1]; Javier de la Cruz, MD[2]; Alberto Orfao, MD, PhD[5,6]; Maria-Victoria Mateos, MD, PhD[3]; Joaquin Martinez-Lopez, MD[2,17]; Juan-Jose Lahuerta, MD[2]; Laura Rosiñol, MD, PhD[18]; Joan Blade, MD, PhD[18]; Jesus F. San-Miguel, MD, PhD[1]; and Bruno Paiva, PhD[1]

Identification of High-Risk Multiple Myeloma With a Plasma Cell Leukemia-Like Transcriptomic Profile

Davine Hofste op Bruinink, MD, MSc[1,2]; Rowan Kuiper, PhD[1,3]; Mark van Duin, PhD[1]; Tom Cupedo, PhD[1]; Vincent H.J. van der Velden, PhD[2]; Remco Hoogenboezem, MSc[1]; Bronno van der Holt, PhD[4]; H. Berna Beverloo, PhD[5]; Erik T. Valent, PhD[3]; Michael Vermeulen, BSc[1]; Francesca Gay, MD, PhD[6]; Annemiek Broijl, MD, PhD[1]; Hervé Avet-Loiseau, MD, PhD[7]; Nikhil C. Munshi, MD, PhD[8]; Pellegrino Musto, MD[9]; Philippe Moreau, MD[10]; Sonja Zweegman, MD, PhD[11]; Niels W.C.J. van de Donk, MD, PhD[11]; and Pieter Sonneveld, MD, PhD[1]

Circulating Plasma Cells in Newly Diagnosed Multiple Myeloma: Prognostic and More

CTCs are one of the most relevant prognostic factors in MM

Independent of treatment-related and other risk factors

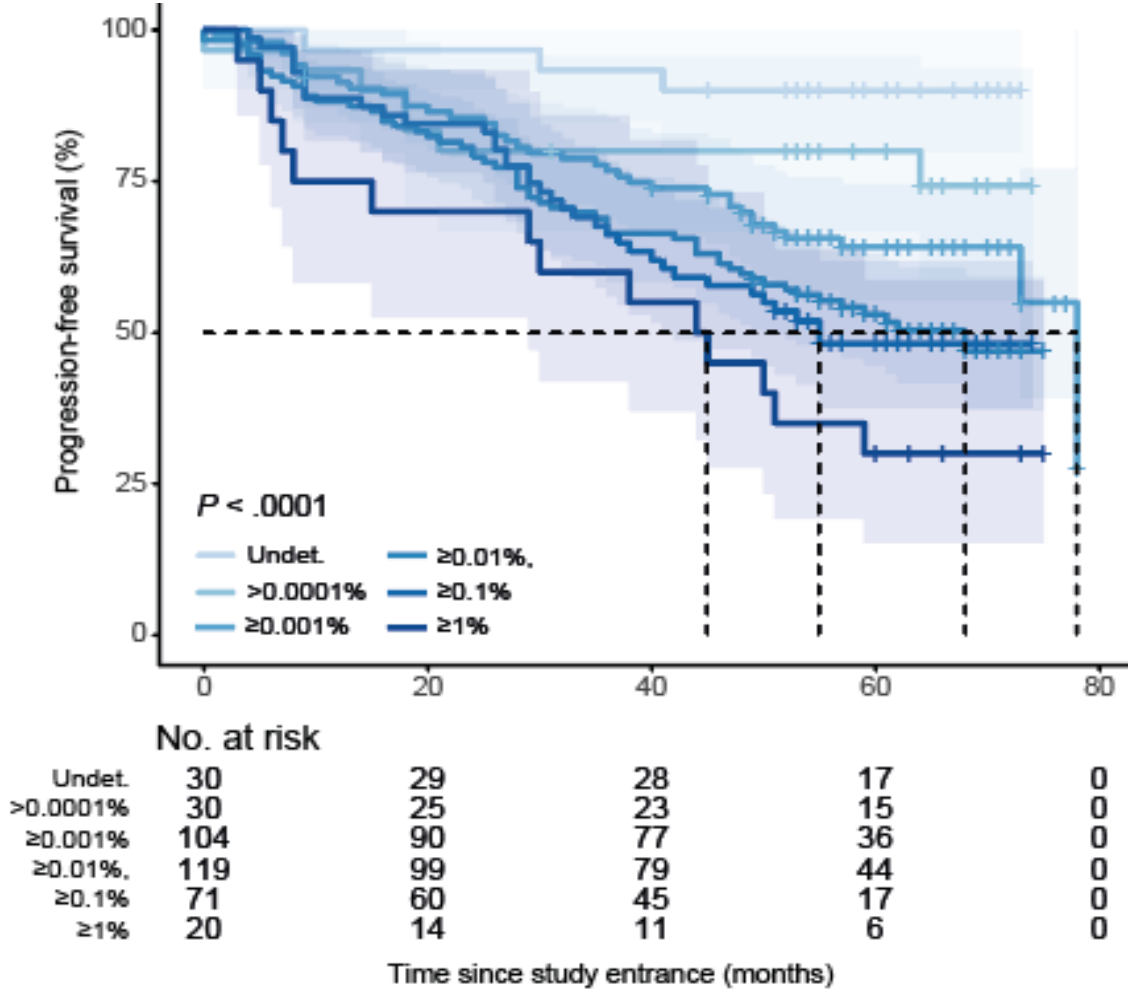
	HR (95% CI)	sig.
<0.2% CTCs (vs undet.)	2.61 (1.15-5.94)	0.022*
≥0.2% CTCs (vs undet.)	4.44 (1.87-10.55)	0.001**
ISS II (vs ISS I)	1.01 (0.72-1.43)	0.943
ISS III (vs ISS I)	1.12 (0.77-1.62)	0.552
Elevated LDH	1.56 (1.1-2.22)	0.013*
HR cytogenetics	1.64 (1.21-2.24)	0.002**
Transplant-eligibility	3.0 (2.13-4.21)	<0.001***

- The detection of **high-CTC** levels resulted in 4-fold increment in the risk of progression and/or death

Garces JJ, et al. ASH 2021; abstract 76

Identification of unique patient subgroups based on CTCs

Hidden plasma cell leukemia and macrofocal disease (undetectable CTCs)

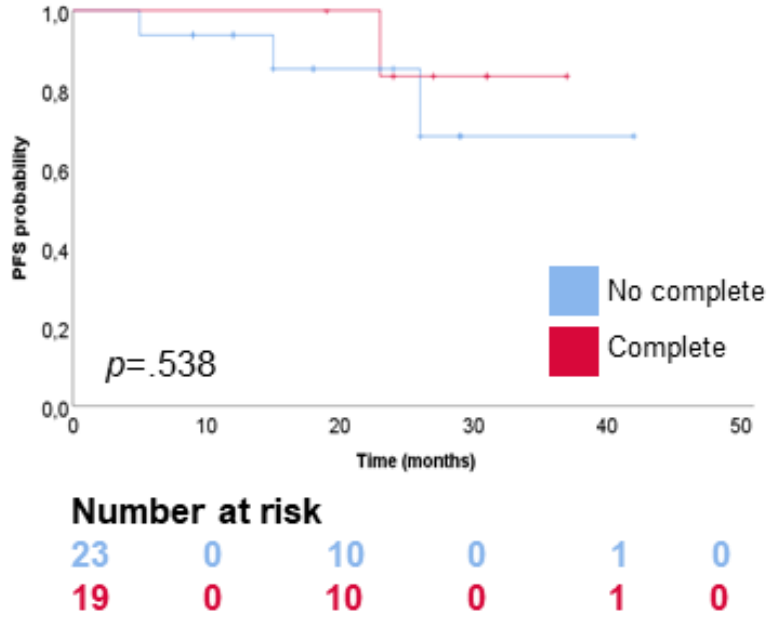


Garces JJ, et al. J Clin Oncol. 2022;40(27):3151-3161.

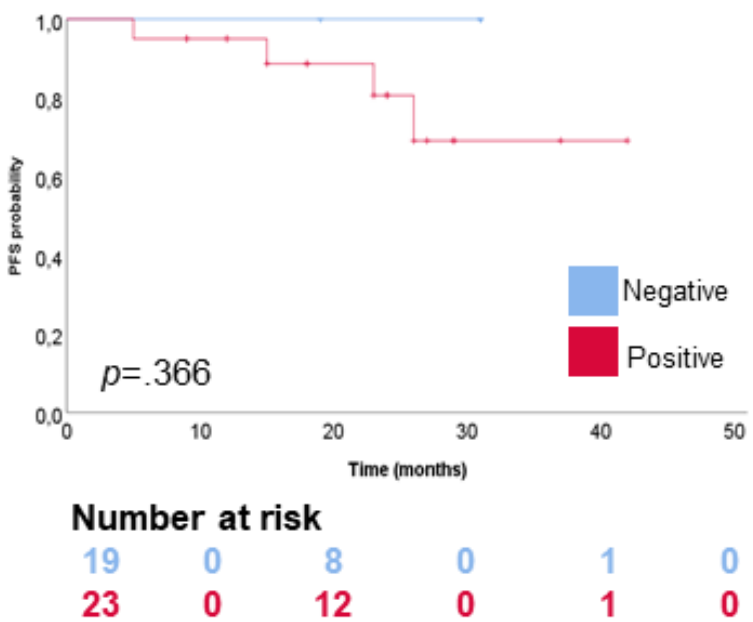
Undetectable CTCs defines a unique subgroup in active MM

Favorable outcome regardless of the depth of response

CR status



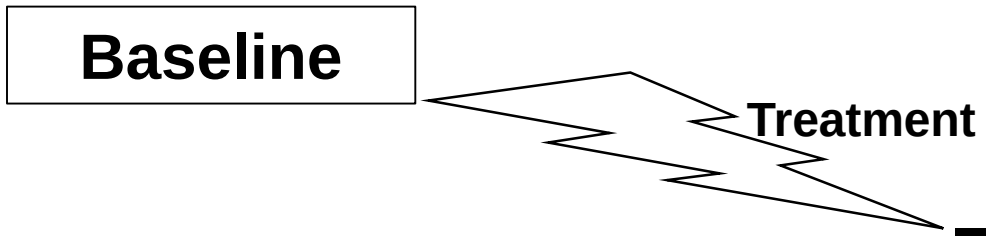
MRD status



Garces JJ, et al. *Manuscript in preparation*

Putative role of MRD to understand treatment resistance

Biology of residual clones: black box



- Performance status
- Frailty
- Disease aggressiveness
- Tumor biology
- Intratumor heterogeneity
- Tolerability
- Sensitivity vs resistance

MRD

- Why only a few tumor cells are empowered to survive?
- Is it clonal selection or adaptation?
- Common mechanisms of resistance or patient-specific?
- Can we study MRD cells?
- Is their biology meaningful?

Author´s Opinion

Putative role of MRD to understand treatment resistance

Biology of residual clones: black box

Baseline

Treatment

- Performance status
- Frailty
- Disease aggressiveness
- Tumor biology
- Intratumor heterogeneity
- Tolerability
- Sensitivity vs resistance

MRD

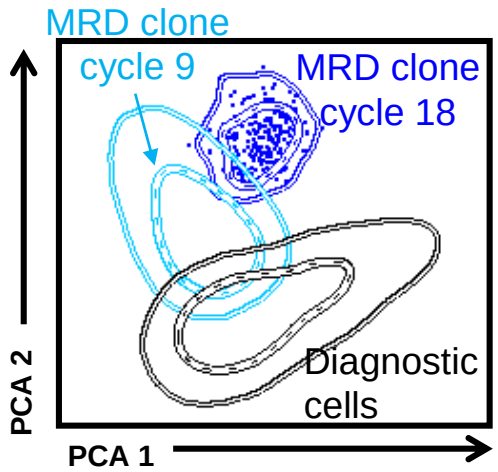
- Why only a few tumor cells are empowered to survive?
- Is it clonal selection or adaptation?
- Common mechanisms of resistance or patient-specific?
- Can we study MRD cells?
- Is their biology meaningful?

The persistence of MRD withholds prolonging patients survival

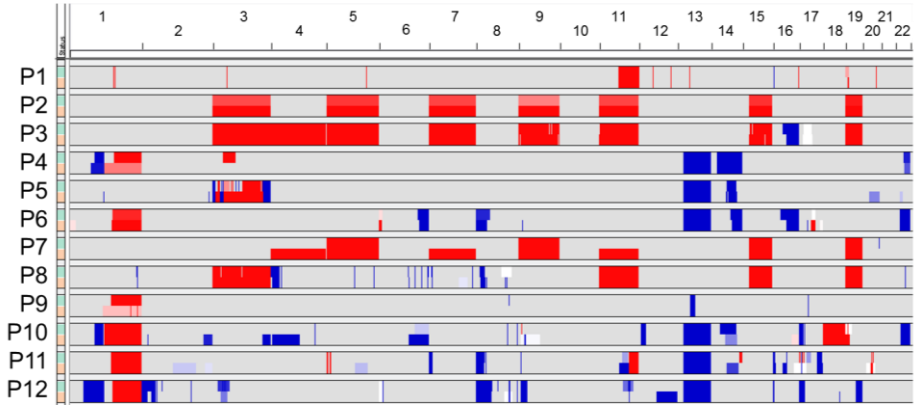
Author´s Opinion

It is possible to isolate and characterize MRD cells

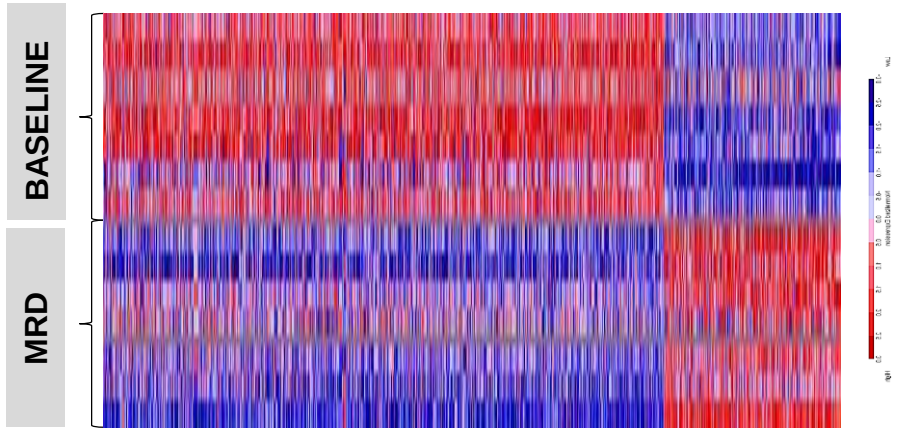
Clonal selection at MRD stages [1]
(in 20% of cases with more immature cells [2])



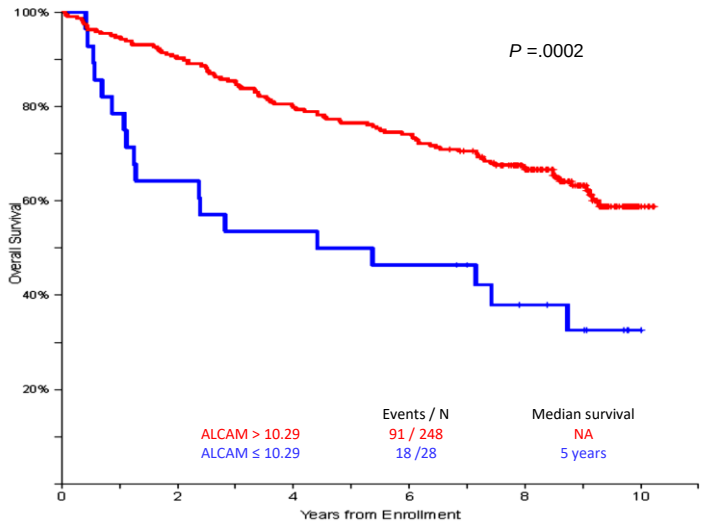
Different genetic profiles [3]

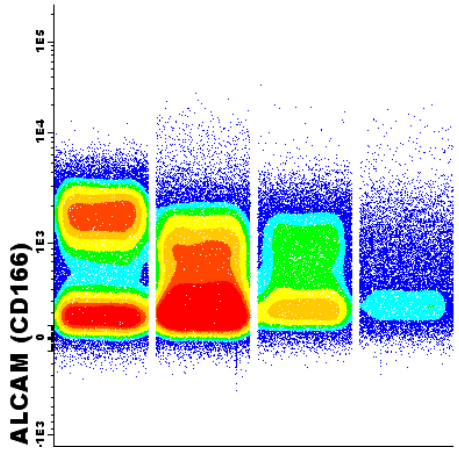


Different transcriptome [3]



Validation of putative markers of resistance [3]

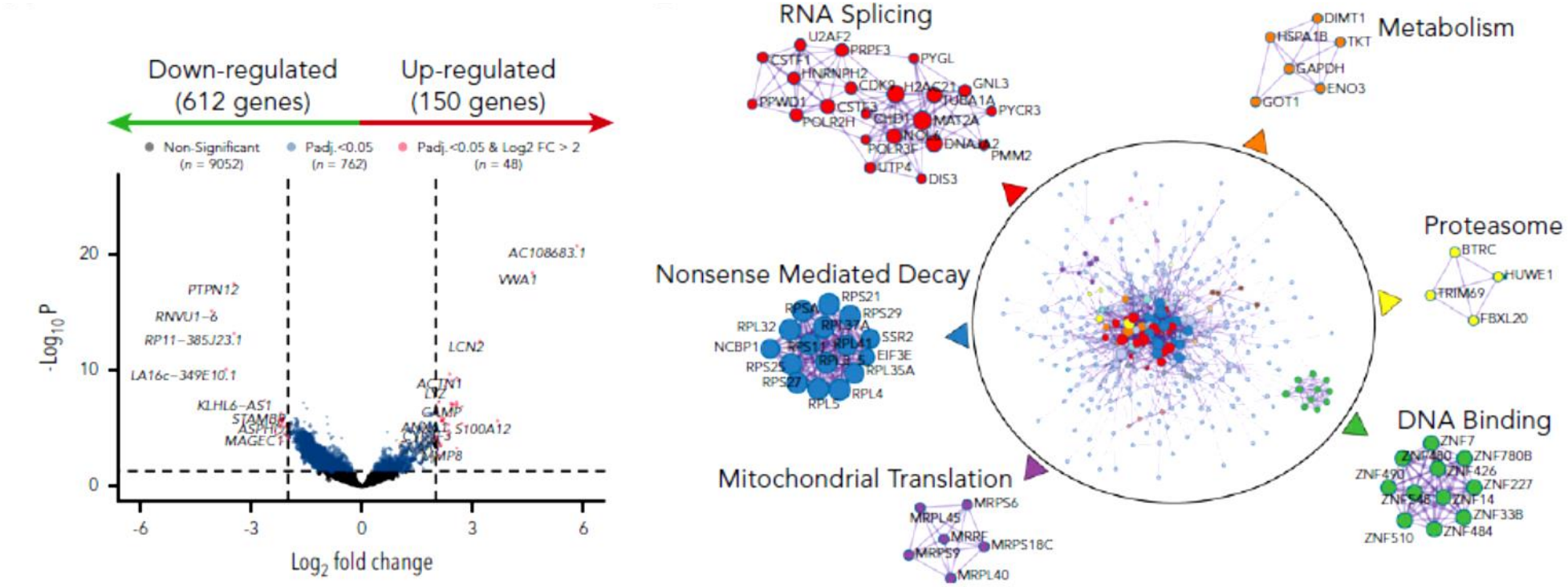




1. Paino T, et al. Leukemia. 2015;29(5):1186-94
2. Paiva B, et al. Leukemia 2017;31(2):382-392.
3. Paiva B, et al. Blood. 2016;127(15):1896-906.

Mechanisms of MRD resistance

Reprogramming of rare tumor cells with unrelated genetic background



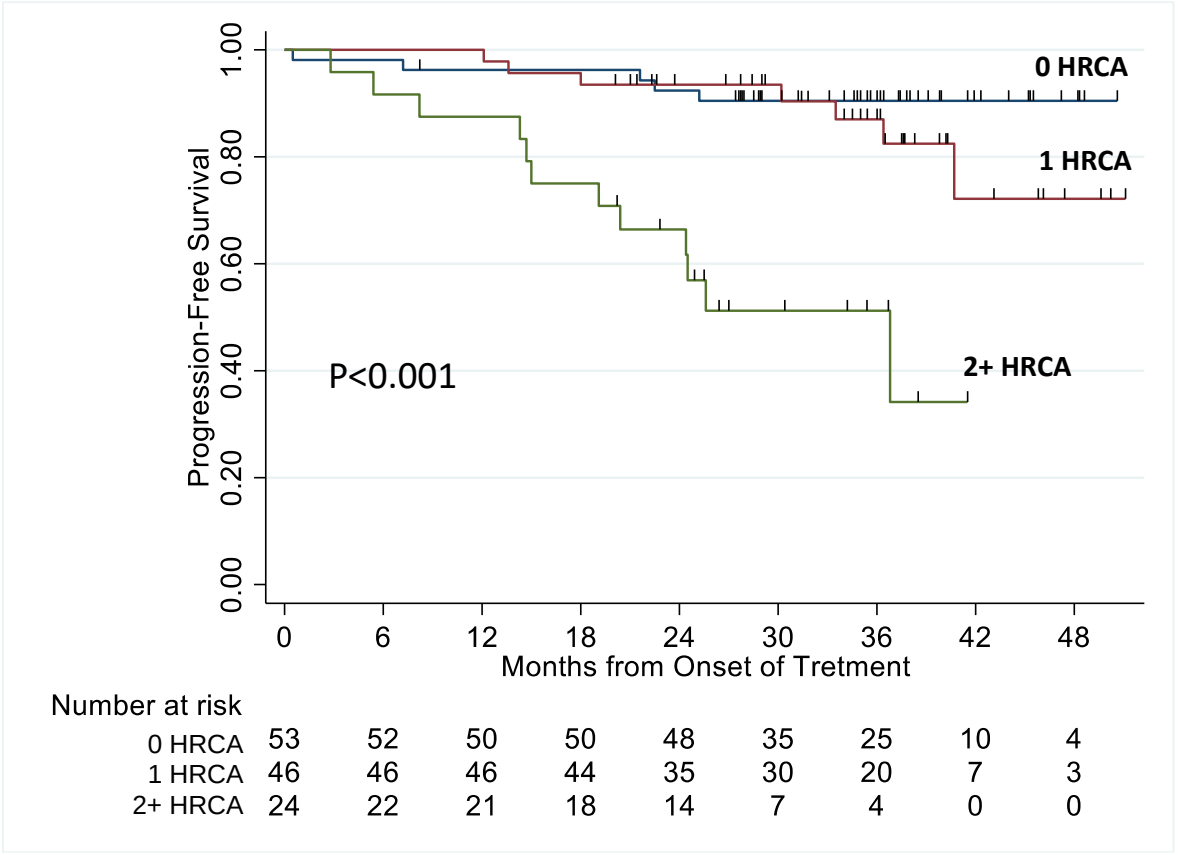
Goicoechea I, et al. Blood. 2021;137(1):49-60.

The case for undetectable MRD in patients with high-risk cytogenetics

Can uMRD abrogate the poor prognosis of high risk cytogenetics?

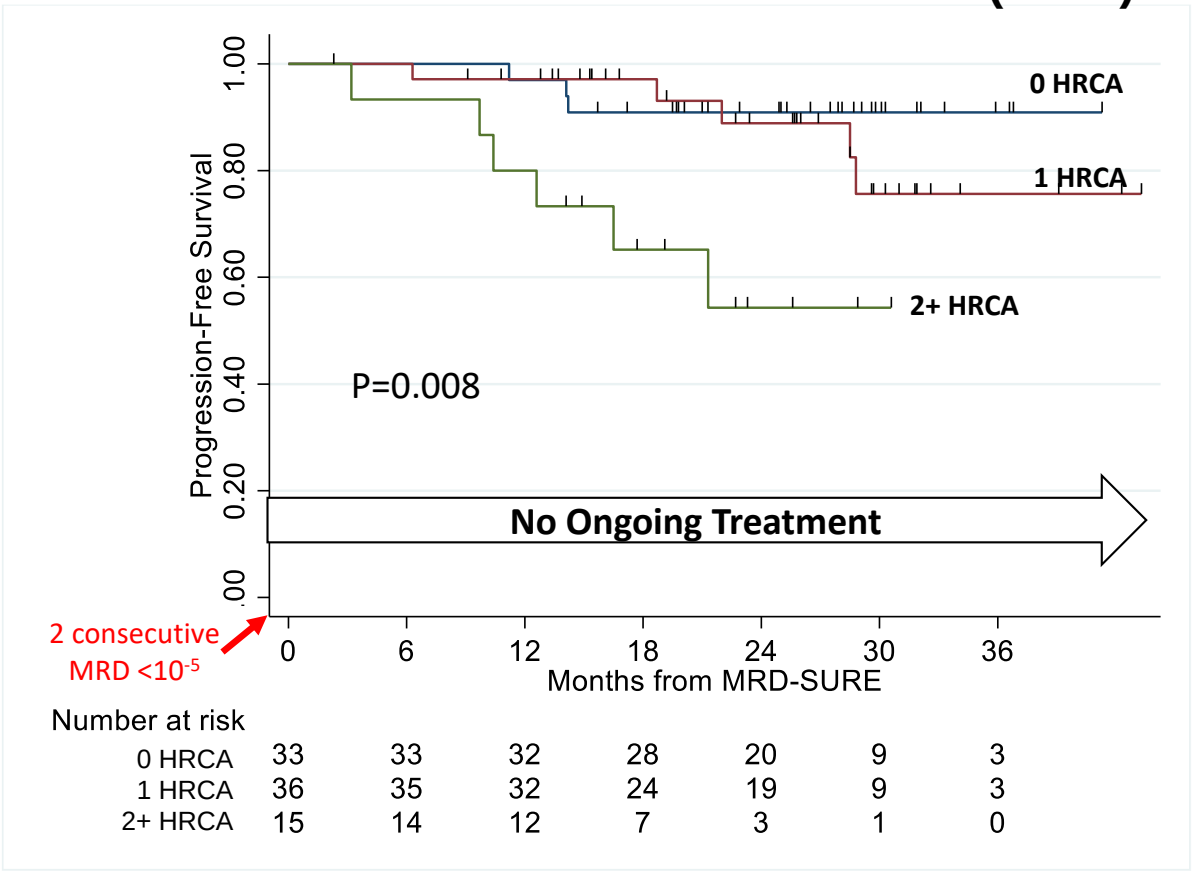
Results from the MASTER (10^{-5}, stop treatment)

PFS – All Patients (N=123)



Number at risk									
0 HRCA	53	52	50	50	48	35	25	10	4
1 HRCA	46	46	46	44	35	30	20	7	3
2+ HRCA	24	22	21	18	14	7	4	0	0

PFS – Patients in MRD-SURE (N=84)



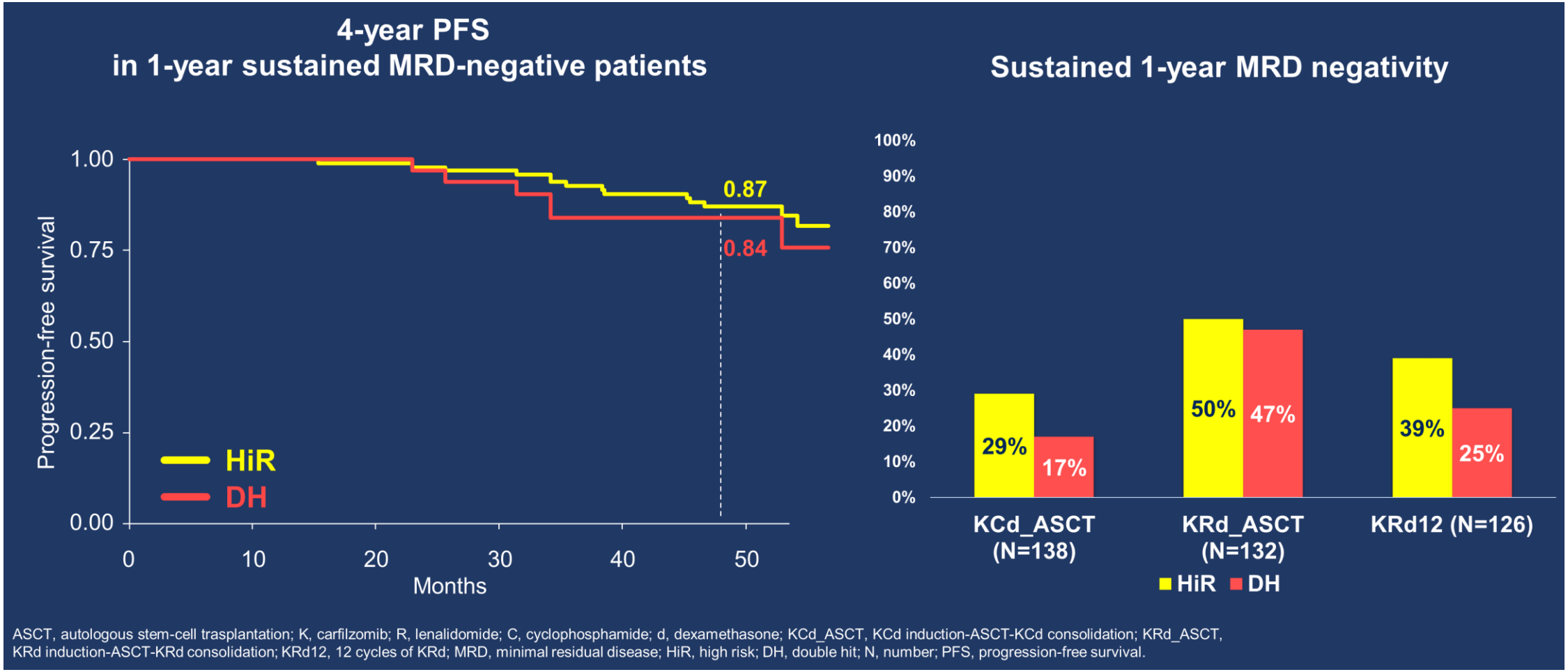
Number at risk							
0 HRCA	33	33	32	28	20	9	3
1 HRCA	36	35	32	24	19	9	3
2+ HRCA	15	14	12	7	3	1	0

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) and/or del(17p)

Costa LJ, et al. J Clin Oncol. 2022;40(25):2901-2912.

Can uMRD abrogate the poor prognosis of high risk cytogenetics?

Results from the FORTE (10^{-5}, continuous therapy)



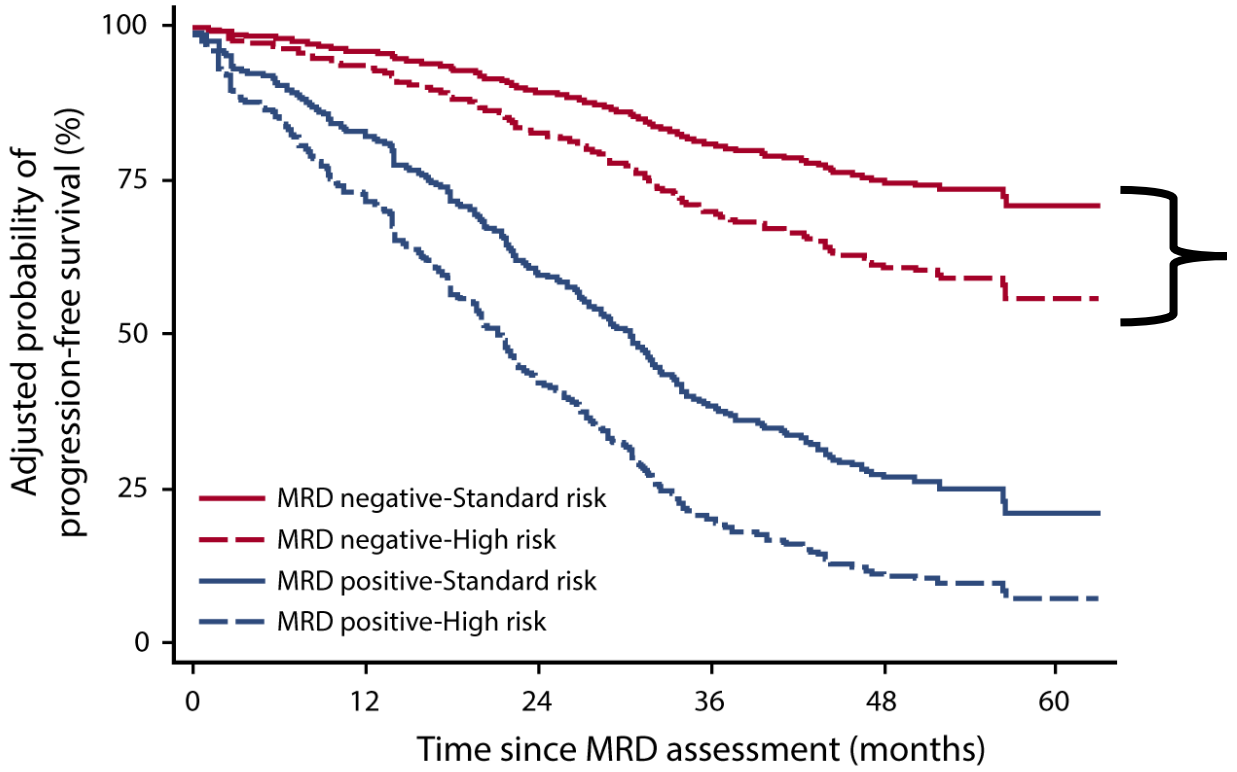
ASCT, autologous stem-cell trasplantation; K, carfilzomib; R, lenalidomide; C, cyclophosphamide; d, dexamethasone; KCd_ASCT, KCd induction-ASCT-KCd consolidation; KRd_ASCT, KRd induction-ASCT-KRd consolidation; KRd12, 12 cycles of KRd; MRD, minimal residual disease; HiR, high risk; DH, double hit; N, number; PFS, progression-free survival.

HRCA = gain/amp 1q, t(4;14), t(14;16), and/or del(17p)

Gay F, et al. ASCO 2021; Abstract #8002

Can uMRD abrogate the poor prognosis of high risk cytogenetics?

Results from the IFM-2009 (10^{-6}, 1y maintenance)

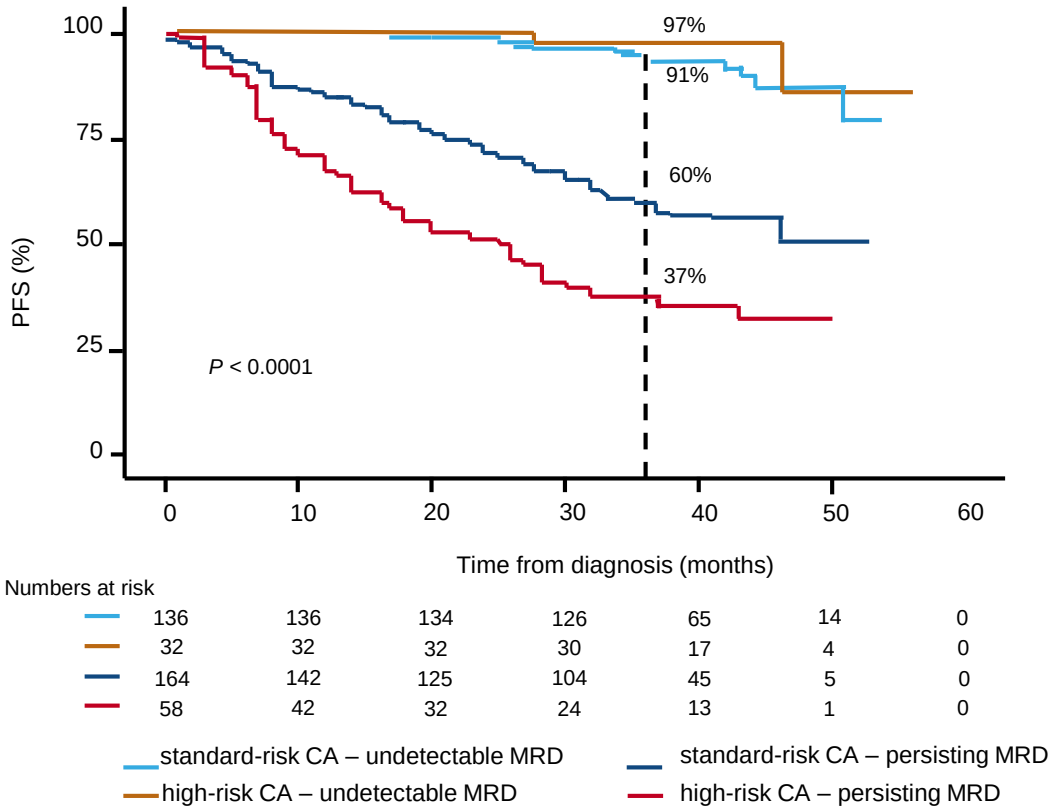


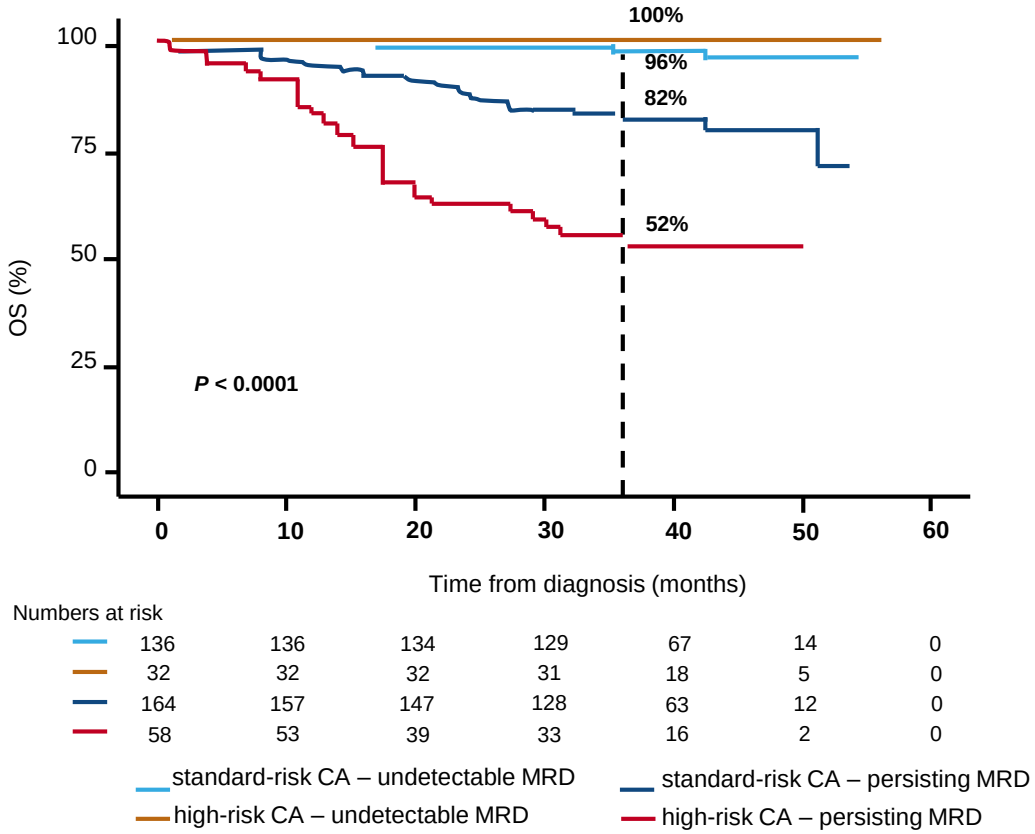
HRCA = t(4;14), t(14;16), and/or del(17p)

Perrot A, et al. Blood. 2018;132(23):2456-2464.

Can uMRD abrogate the poor prognosis of high risk cytogenetics?

Results from the GEM2012MENOS65 (10^{-6}, 2y maintenance, LenDex)





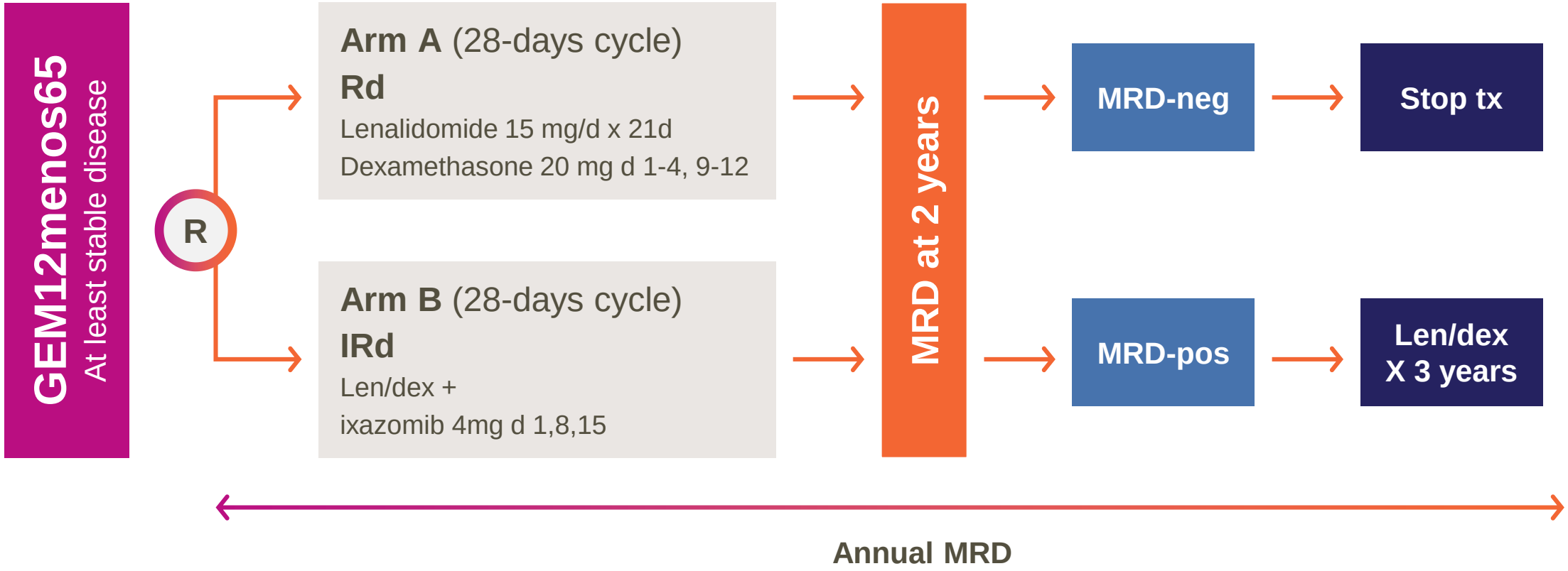
HRCA = t(4;14), t(14;16), and/or del(17p)

Goicoechea I, et al. Blood. 2021;137(1):49-60.

Can treatment be stopped in some MRD negative patients?

Can MRD be used to interrupt or prolong treatment?

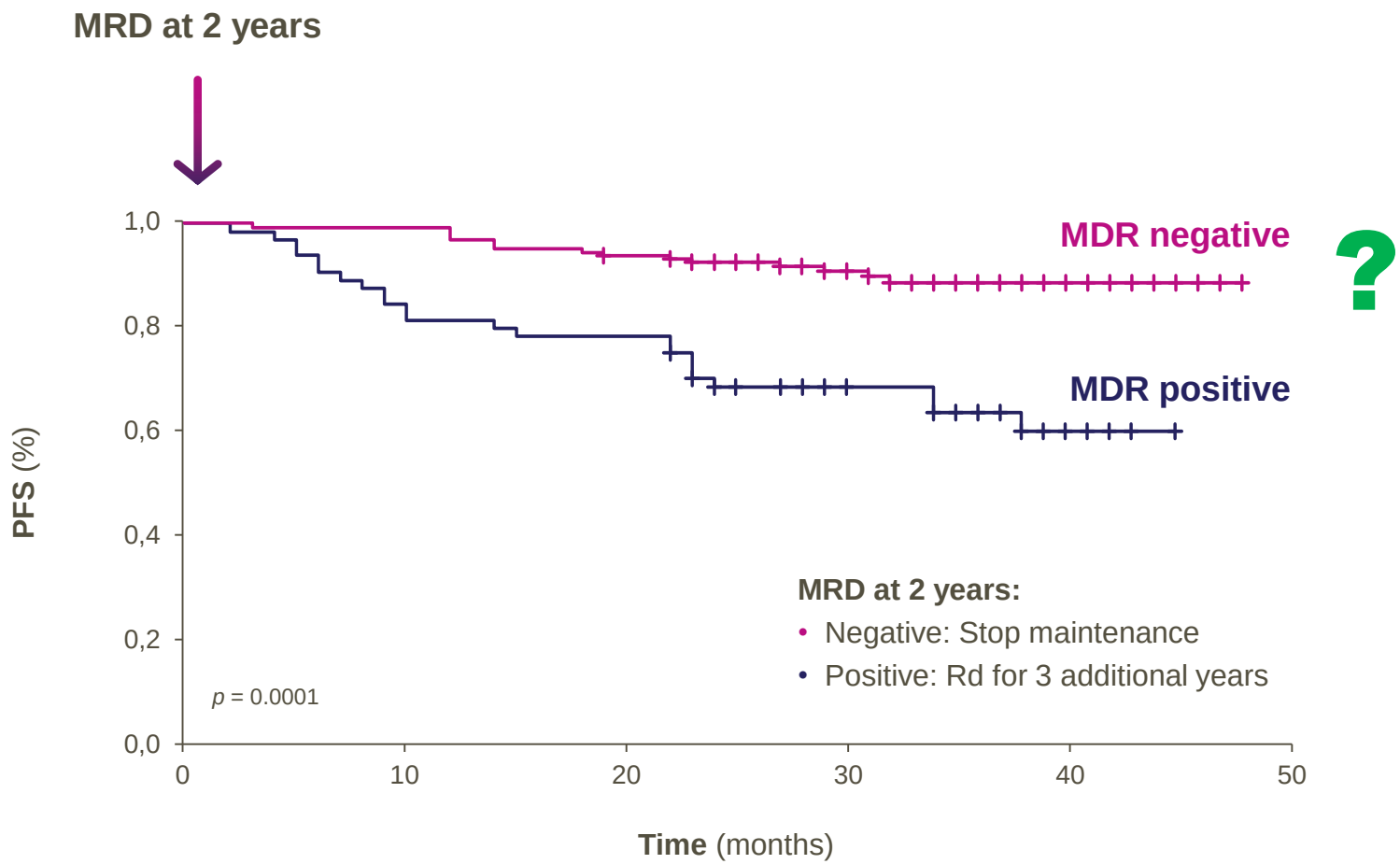
Results from the GEM2014MAIN trial



Rosiñol L, et al. Blood. 2023:blood.2022019531.

Can MRD be used to interrupt treatment?

Results from the GEM2014MAIN trial

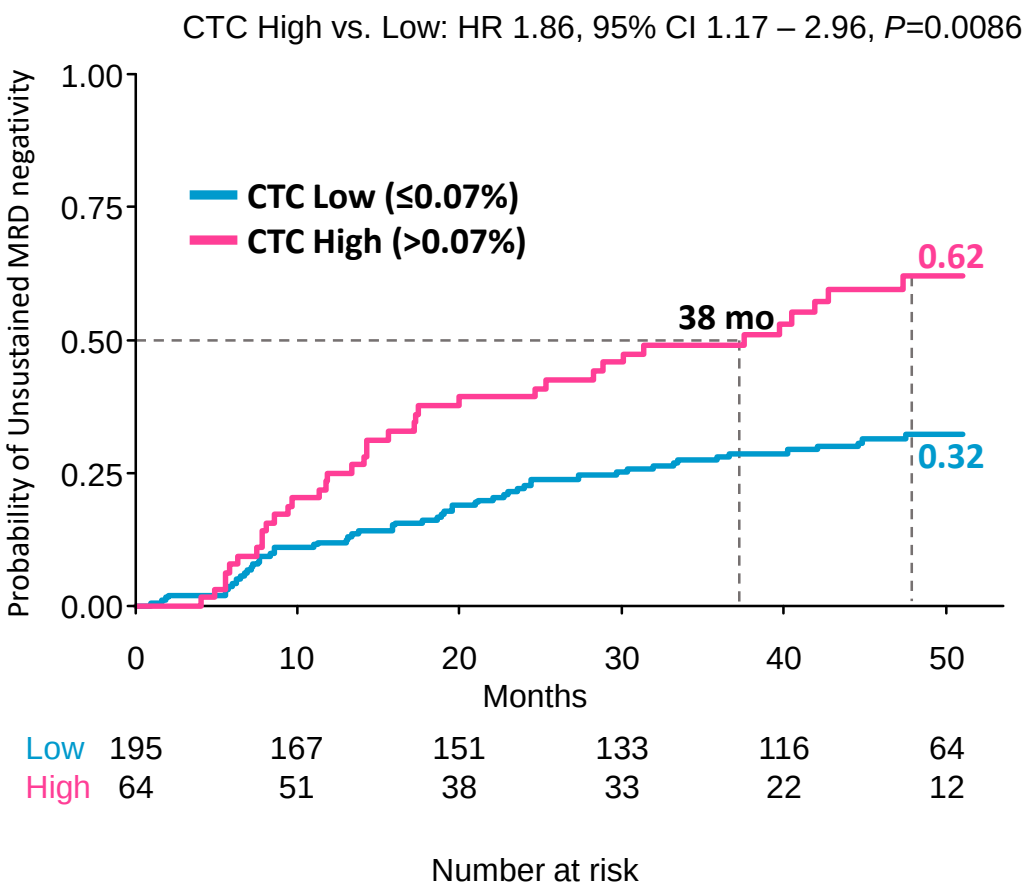


Rosiñol L, et al. Blood. 2023:blood.2022019531.

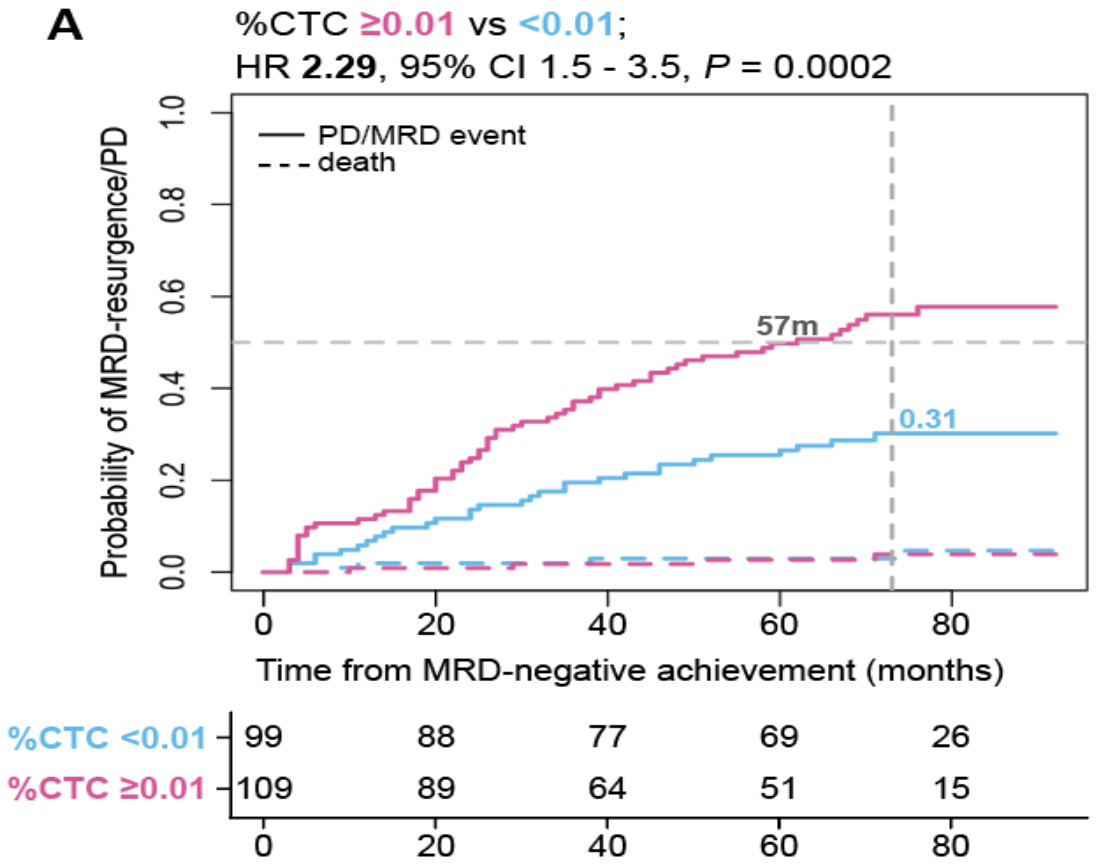
High CTC levels at diagnosis predict unsustained negative MRD

Potentially valuable information before treatment interruption

FORTE[1]



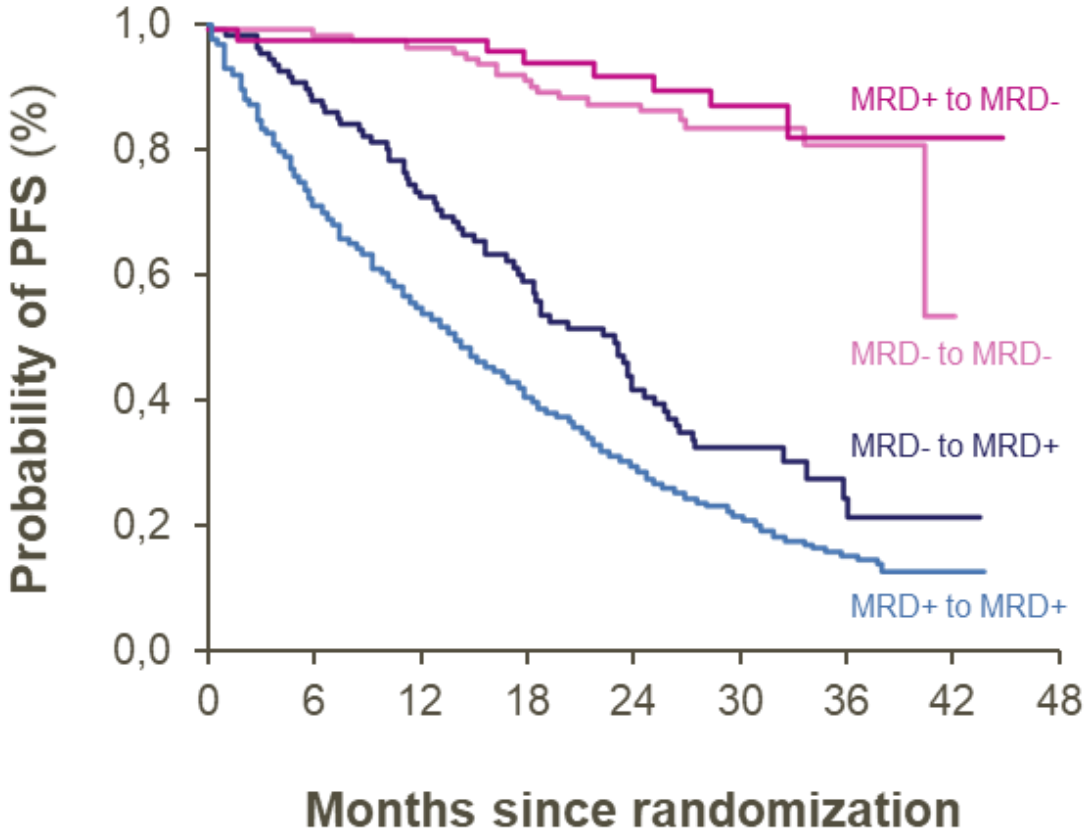
GEM2014MAIN[2]



1. D'Agostino M, et al. IMS 2022;OAB-11
2. Guerrero C, et al. IMS 2023

The problem of MRD is that a single “snapshot” is not enough!

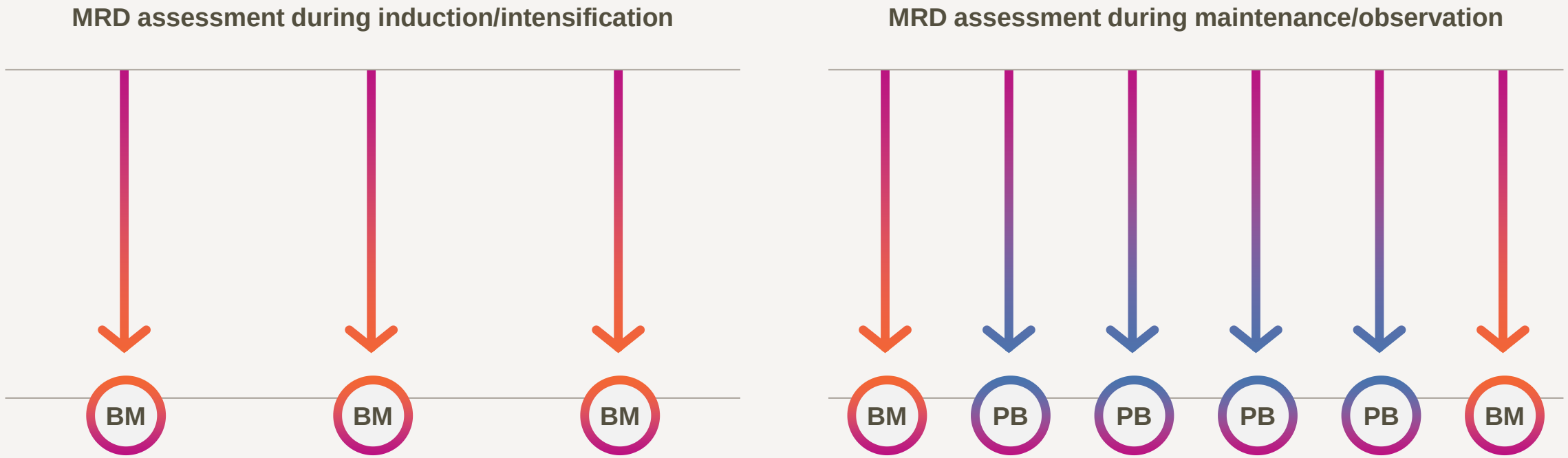
MRD status is dynamic and must be reassessed periodically



Paiva B, et al. Blood. 2023;141(6):579-591.

Hypothetical scenario to assess MRD in BM and PB

Imaging, Mass-spec and BloodFlow for minimally invasive MRD

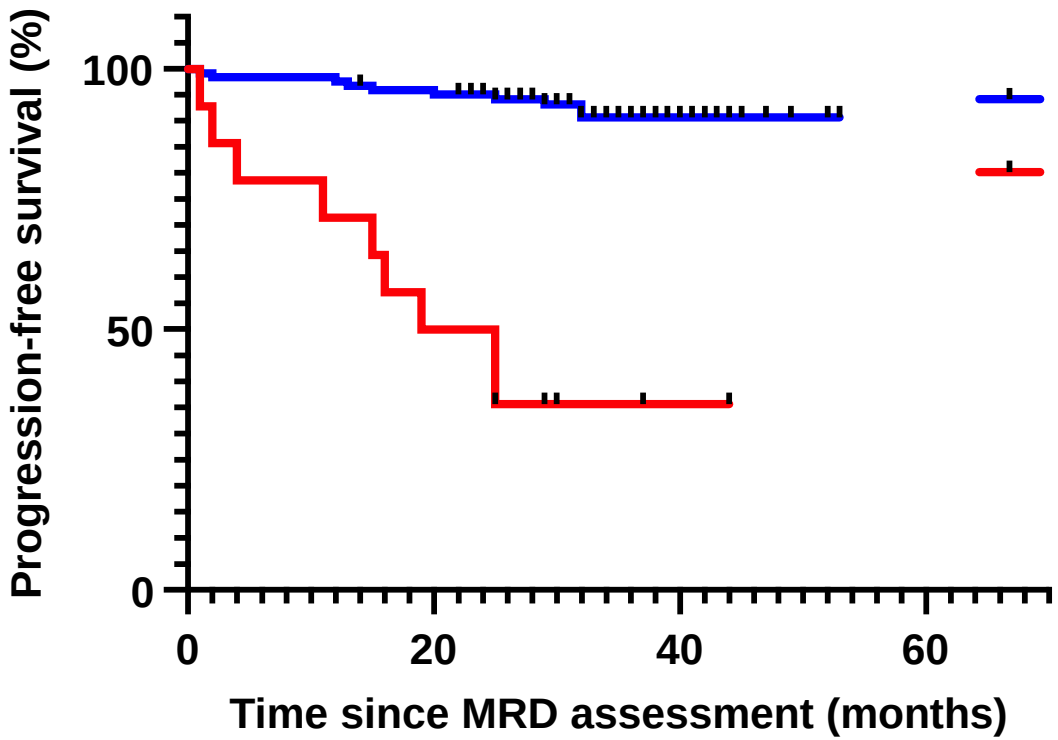


BM, bone marrow; MRD, minimal residual disease; PB, peripheral blood.

Author´s Opinion

Prognostic value of MRD assessment in PB using NGF

GEM2014MAIN trial (n = 138)



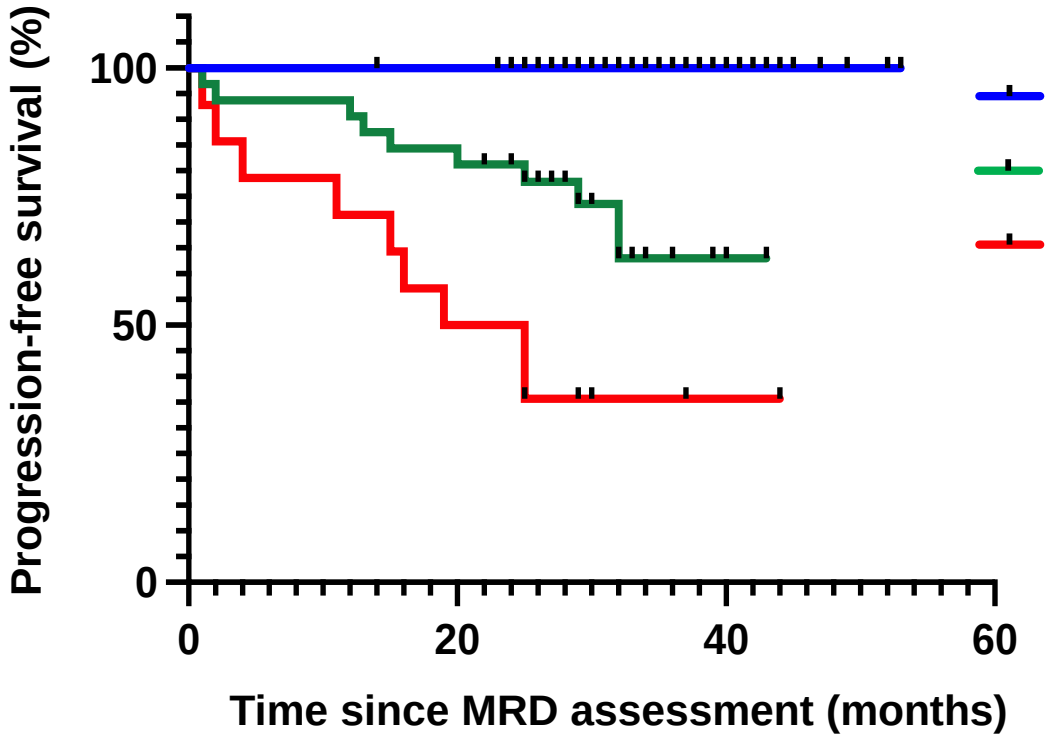
MRD	No.	Median PFS	PFS @2y	Hazard ratio
Negative	123	NR	98%	11.7 (*P* < .0001)
Positive	15	22 mo	50%	

PB, peripheral blood; BM, bone marrow; NGF, next-generation flow

Notarfranchi L, et al. Blood 2022;140 (Supplement 1): 2095–2097

Prognostic value of MRD assessment in PB & BM using NGF

GEM2014MAIN trial (n = 138)



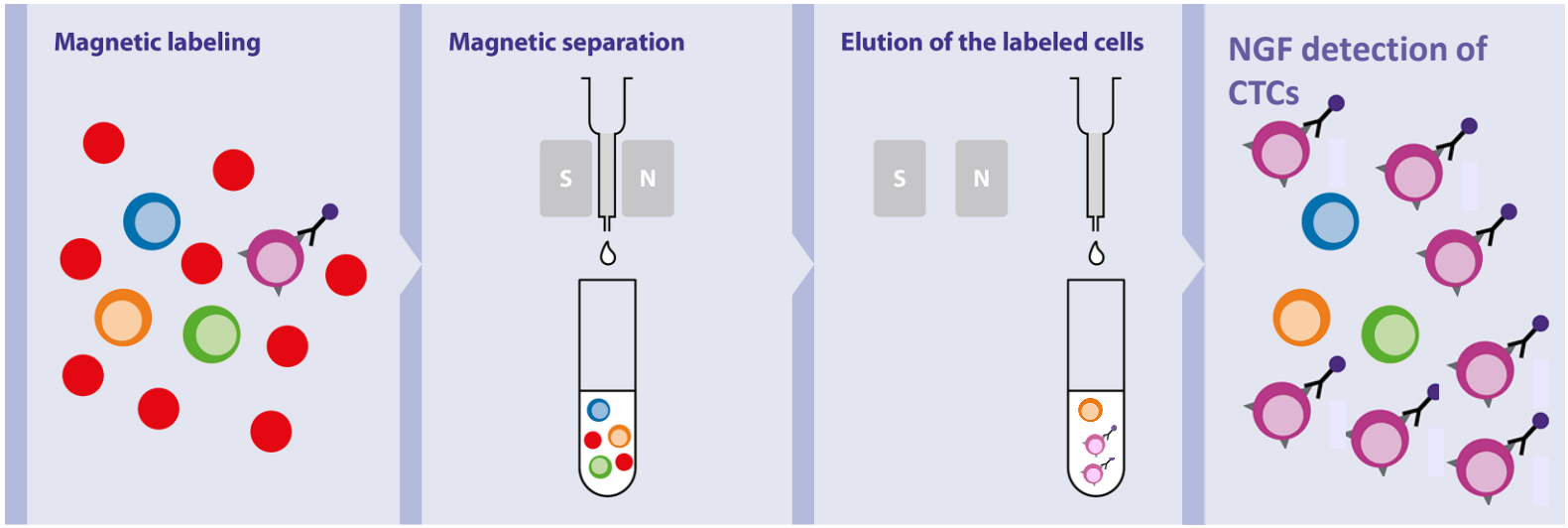
MRD PB / BM	No.	Median PFS	PFS @2y	Hazard ratio
- / -	90	NR	100%	
- / +	33	NR	80%	*P* < .0001
+ / +	15	22 mo	50%	

PB, peripheral blood; BM, bone marrow; NGF, next-generation flow

Notarfranchi L, et al. Blood 2022;140 (Supplement 1): 2095–2097

BloodFlow

Immunomagnetic enrichment using MACS® MicroBeads prior NGF



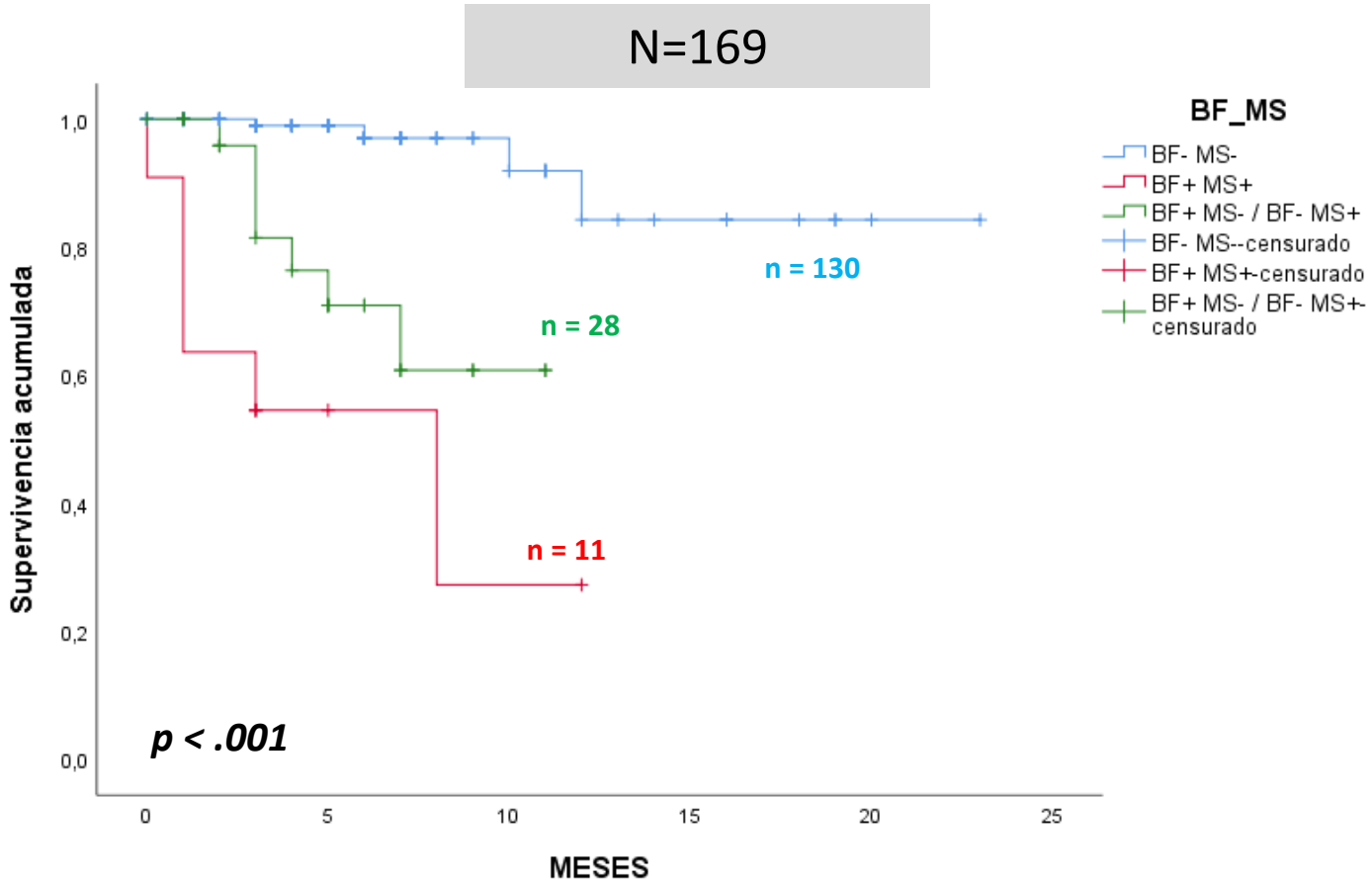
- A minimum sensitivity of 10^{-7} requires analyzing ≥ $2x10^8$ cells (~50mL of PB)
- Large (~50mL) PB volumes were magnetically labeled and processed via MACS® columns, and ~100µL aliquots enriched with circulating PC were analyzed using EuroFlow NGF

PB, peripheral blood; PC, plasma cells; NGF, next-generation flow

Notarfranchi L, et al. Blood 2022;140 (Supplement 1): 2095–2097

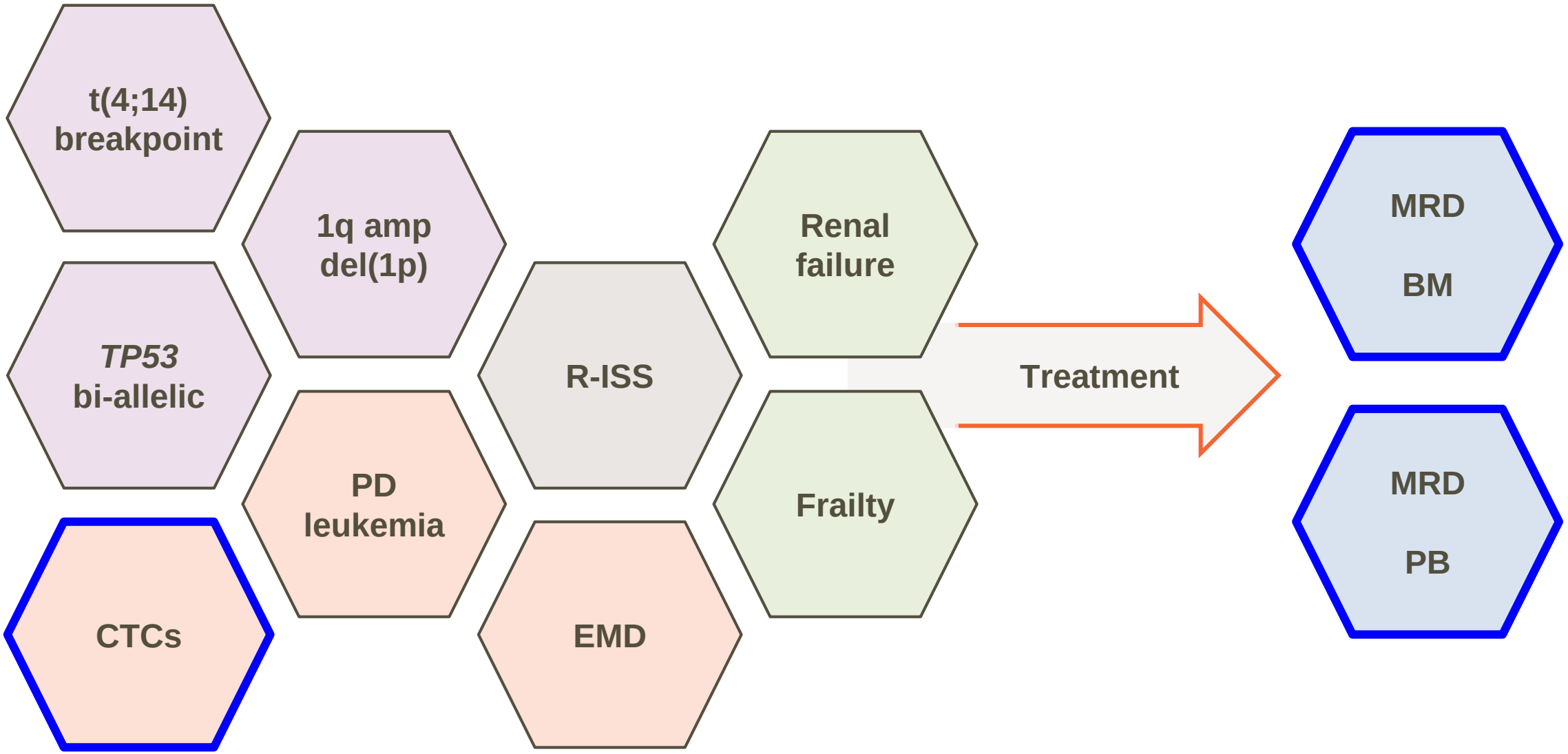
Prognostic value of minimally invasive MRD assessment

BloodFlow and QIP-MS



Lasa M, et al. Manuscript in preparation

There is no precision medicine without precision diagnostics



Author´s Opinion