Highlights from IMS 20th meeting 2023

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

MRD midollare e extramidollare

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Treatment paradigm for newly-diagnosed and R/R fit MM patients

- quickly reverse disease-related complications
- maximize the speed and depth of tumour burden reduction
- prolong disease control → **EXTEND OVERALL SURIVAL**

Importance of biological background:

- Genomic complexity of multiple myeloma
- Clonal evolution / development of drug-resistance

  Multiple clones with variable drug sensitivity

  Minor drug-resistant clones potentially lethal

Combination regimens + continuous suppressive therapy

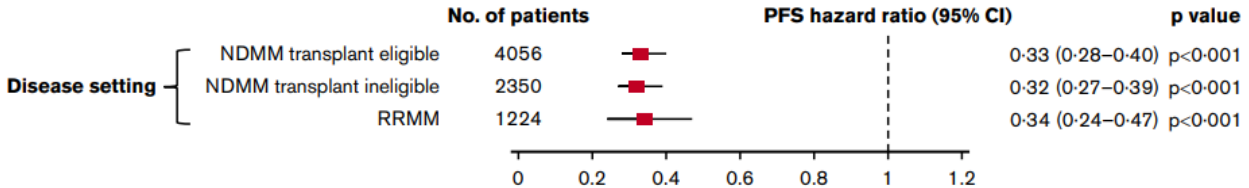
- Faster and deeper response
- Different mechanisms target multiple clones simultaneously
- Prevention of drug-resistant subclones emergence / eradication of all clones

Debulk and maintain disease at a level below detection (MRD)

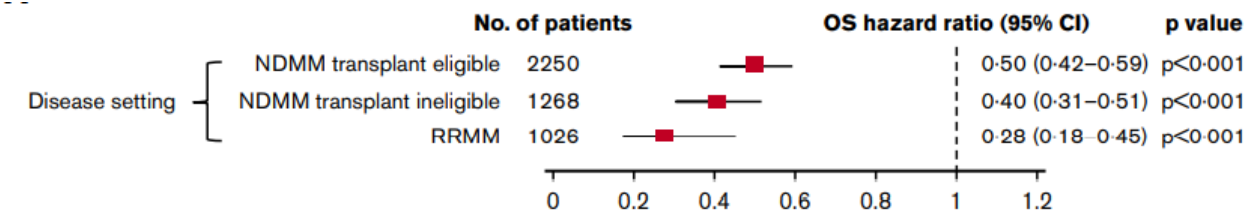
The literature evidence for the use of MRD in BM is strong

- 4 metanalysis published #, *
- ~ 100 publications supporting MRD on PFS/OS
- IMWG revised response criteria including MRD in CR patients * *

PFS



OS

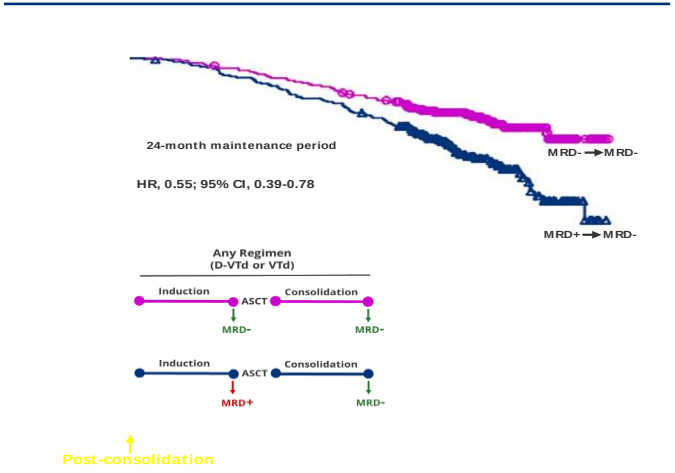


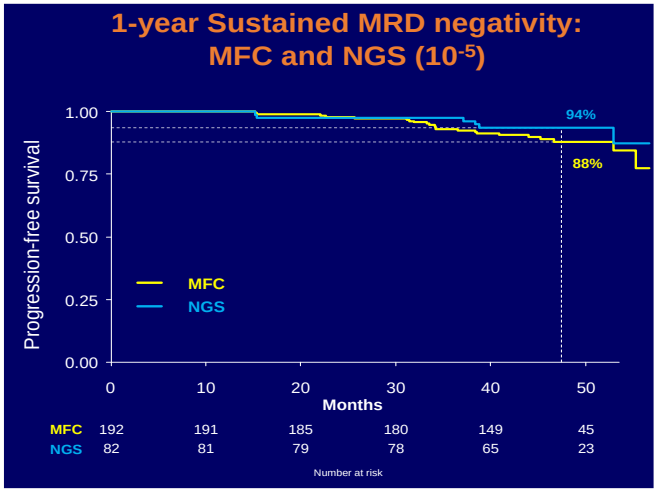
Landgren O et al Bone Marrow Transplant 2016; 51: 1565–1568, Munshi NC et al. JAMA Oncol. 2017 Jan 1;3(1):28-35; * Munshi NC et al. Blood Adv 2020; 4(23):5988–99; Avet-Loiseau H et al. Clinical Lymphoma, Myeloma & Leukemia, 2020.

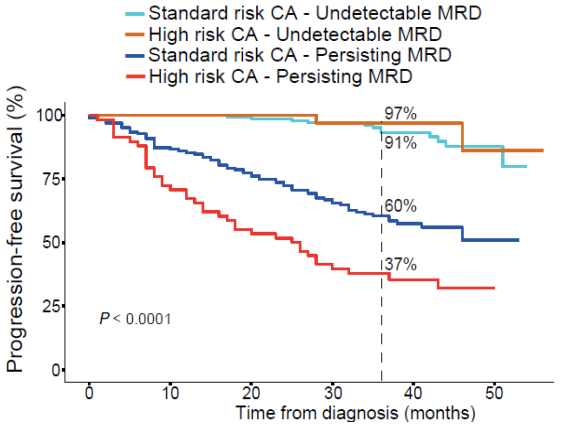
***** * Kumar S, et al. Lancet Oncol 2016;17(8):e328–46.

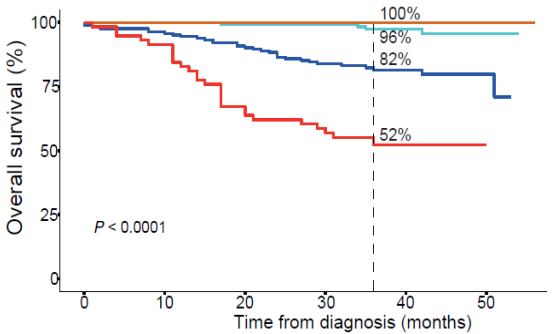
Sustained MRD is the "driver " of outcomes

ASCT patients



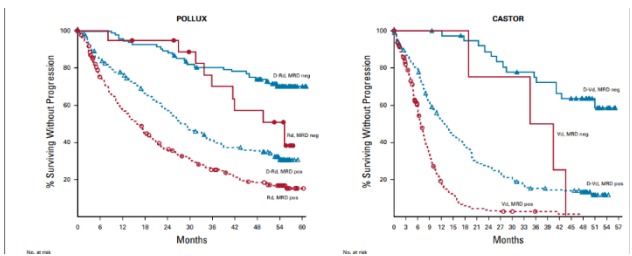






- Patients who achieve **1- or 2-years sustained MRD negativity**, show improved PFS over pts who did not, regardless of treatment
- This is true for all patients, but most importantly for **HR patients**

…regardless of BM techniques



…and in non-ASCT eligible and RRMM patients

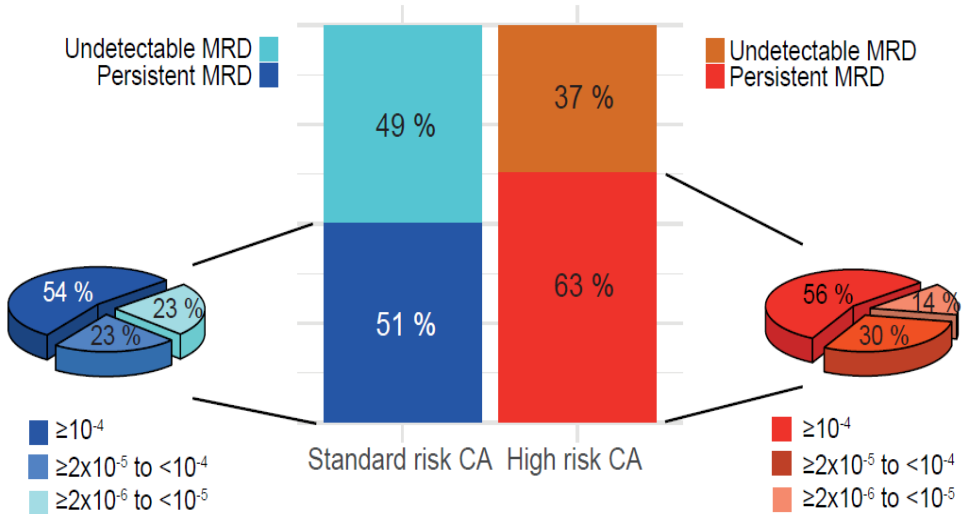
Avet Loiseau H et al. ASH 2021, oral presentation

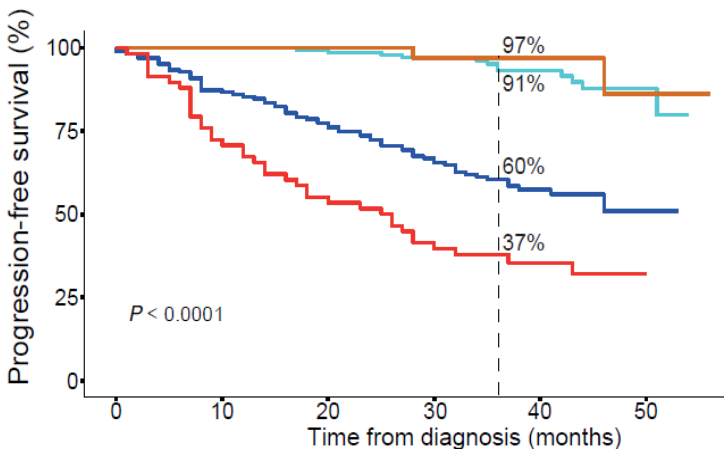
Oliva S et al. ASH 2020, oral presentation

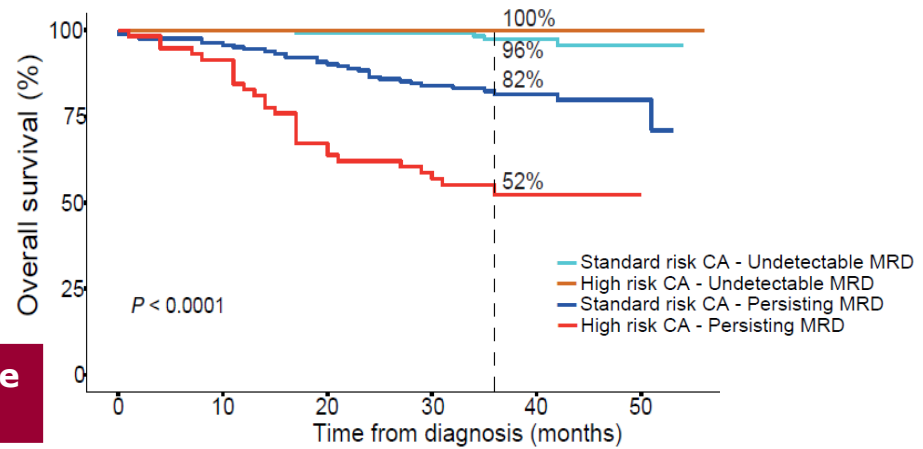
Avet Loiseu H et al. J Clin Oncol 2021 39:1139-1149
Goicoechea et al. Blood 2021;137(1):49–60

MRD and genetically high-risk patients

MRD status according to cytogenetic risk in the PETHEMA/GEM2012MENOS65 clinical trial







Sustained-undetectable MRD is the only way to try to overcome the dismal survival of patients with MM with high risk CA

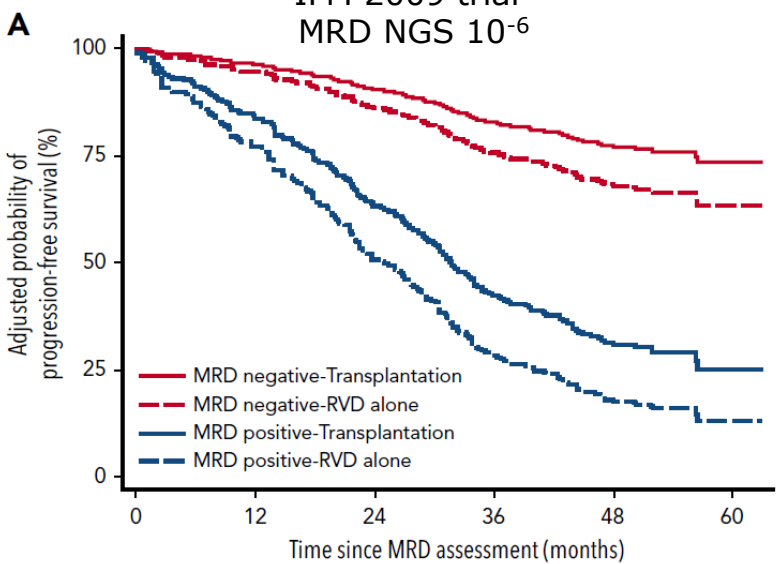
CA, cancer; MM, multiple myeloma; MRD, minimal residual disease

Goicoechea et al. Blood 2021;137(1):49–60

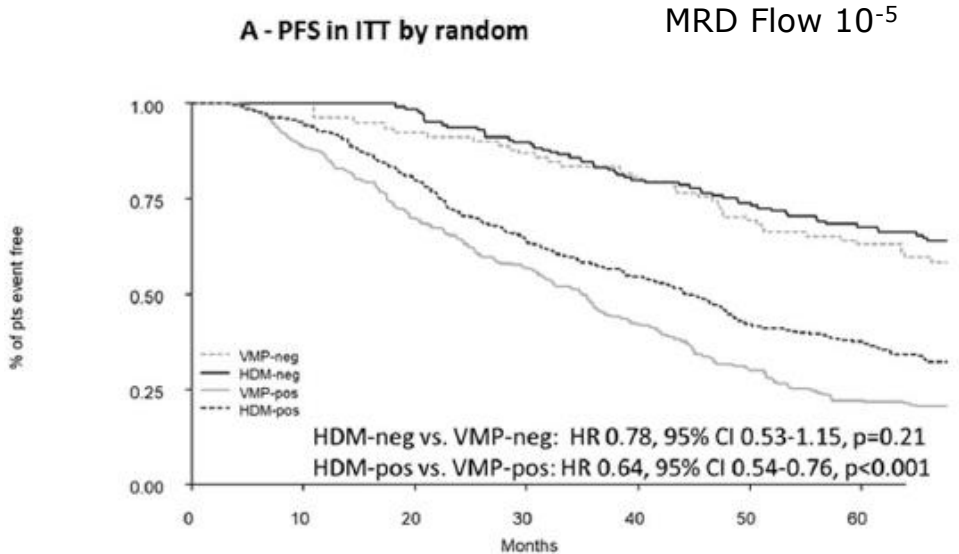
MRD more than the treatment arm is the key prognostic factor

The benefit of ASCT is questionable in patients achieving MRD negativity

IFM 2009 trial[1]
MRD NGS 10^{-6}



EMN-02 trial[2]
MRD Flow 10^{-5}



The preferred treatment for fit MM pts is currently the one pushing the higher percentage of them into sustained-MRD negativity

ASCT, autologous stem cell transplant; CI, confidence interval; EMN, European Migration Network; HDM, high-dose melphalan; HR, hazard ratio; IFM, international myeloma foundation; ITT, intent to treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; neg, negative; NGS, next-generation sequencing; PFS, progression-free survival; pos, positive; RVD, lenalidomide-bortezomib-dexamethasone; TE, transplant-eligible; VMP, bortezomib-melphalan-prednisone

1. Perrot et al. Blood 2018; ;132(23):2456–2464
2. Oliva et al. Blood Canc J 2021;11(6):106

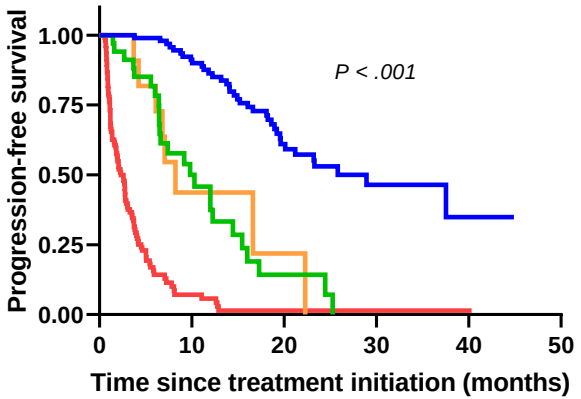
Achievement and maintainance of MRD negativity in NDMM

- MRD negativity in **newly diagnosed ASCT-eligible patients**:
  - In the range of 50-70% (sensitivity 10^{-5}) after triplet induction + ASCT (s) + consolidation + maintenance (first and second generation PIs, IMiDs and MoAbs); sustained MRD negativity @ 1 year 40-50%
  - MRD negativity, both pre-maintenance and post-induction, translates into prolonged PFS
- MRD negativity in **newly diagnosed non-ASCT-eligible patients**:
  - Possibility to obtain MRD negativity in the elderly population with combination of MoAbs and Pis/IMiDs, but significantly lower rate (30% in MAIA; sustained @ 1 year 11)%
  - Possibility to further improve with quadruplets/immunotherapies but unknown effect on survival outcomes

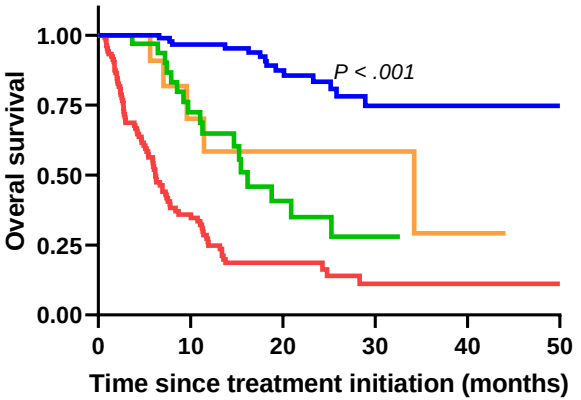
Achievement and maintainance of MRD negativity in RRMM

- Different percentage according to mechanism of action of the drugs, combinations and target, up to 70-80% with TCR therapies

Role of MRD in RRMM pts treated with CAR T cells and TCE



Number at risk						
CR/MRD-	102	78	33	11	1	0
CR/MRD+	11	4	1	0	0	0
No CR/MRD-	34	13	2	0	0	0
No CR/MRD+	105	5	1	1	1	0



Number at risk						
CR/MRD-	102	82	47	20	5	1
CR/MRD+	11	6	3	2	1	0
No CR/MRD-	34	20	7	2	0	0
No CR/MRD+	105	30	11	4	2	1

Group	Median PFS
CR/MRD-	29
CR/MRD+	8
No CR/MRD-	10
No CR/MRD+	2

Group	Median OS
CR/MRD-	NR
CR/MRD+	34
No CR/MRD-	16
No CR/MRD+	6

Prolonged survival in patients achieving CR and undetectable MRD

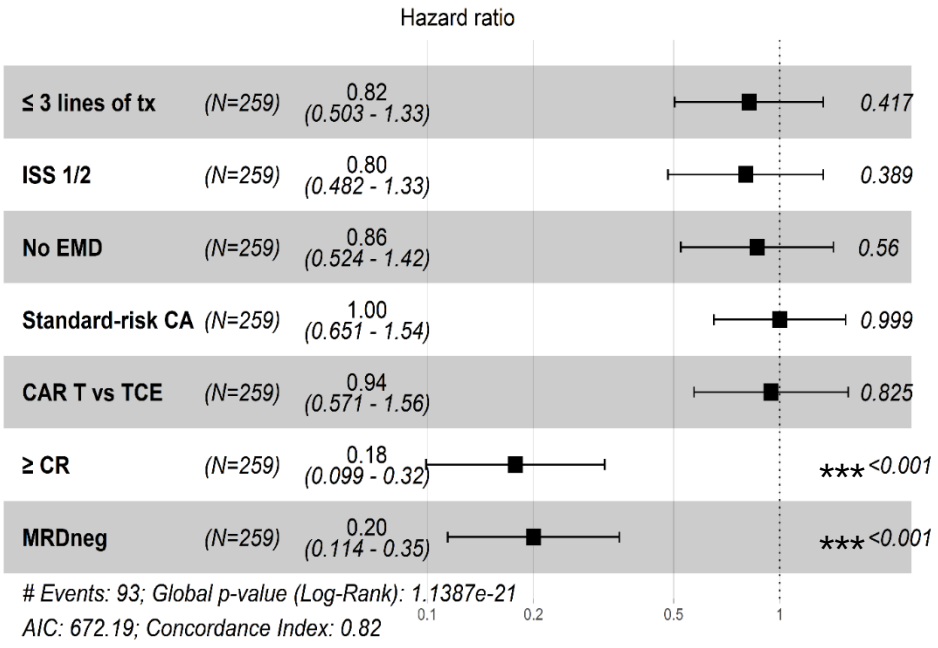
- Retrospective real-life analysis of 259 patients with RRMM treated with TCR therapies in Spain between 2017-203
- Median follow-up, 11 months

Zabaleta A et al, ASH 2023

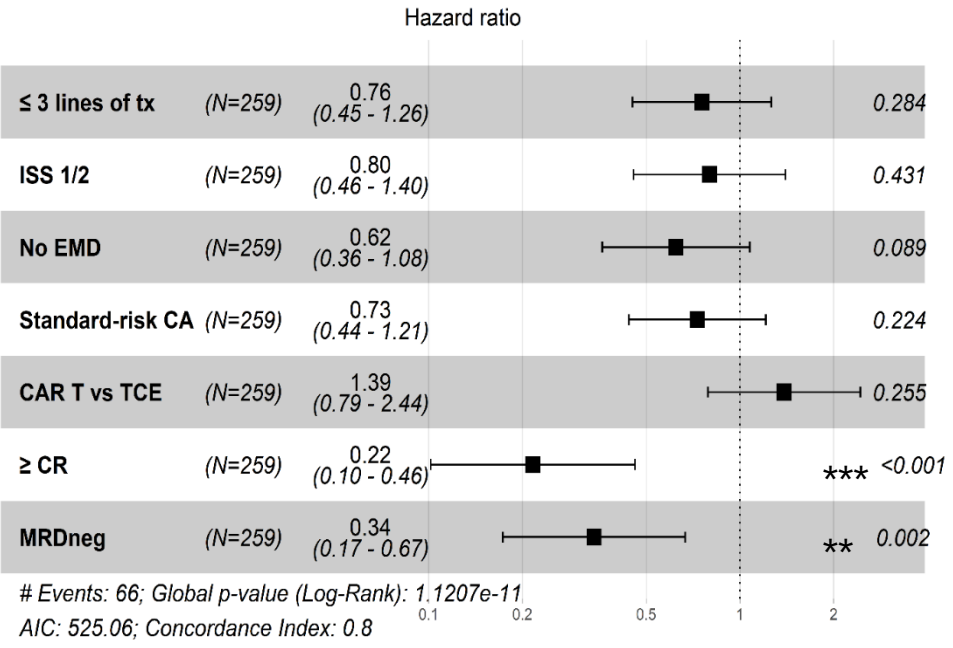
CR and MRD status are the most relevant prognostic factors

Multivariate analysis

Progression-free survival



Overall survival



- In contrast to newly-diagnosed MM, achieving CR does matter in MRD negative RRMM patients with respect to response durability after CAR T cells and TCE

Burning questions and different applications of MRD

- How should we evaluate MRD and when?
- MRD in clinical trials: trial end-point (primary, co-primary or secondary), MRD as driver of therapy
- Are we ready to use MRD outside clinical trials?
- Can we use MRD as a trial end-point, to accelerate drug approval and to provide inter-trials comparison?

Beyond conventional CR
MRD detection and novel response criteria

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Lancet Oncol 2016; 17: e328–46

Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé, Maria-Victoria Mateos, Meletios Dimopoulos, Efstathios Kastritis, Mario Boccadoro, Robert Orlowski, Hartmut Goldschmidt, Andrew Spencer, Jian Hou, Wee Joo Chng, Saad Z Usmani, Elena Zamagni, Kazuyuki Shimizu, Sundar Jagannath, Hans E Johnsen, Evangelos Terpos, Anthony Reiman, Robert A Kyle, Pieter Sonneveld, Paul G Richardson, Philip McCarthy, Heinz Ludwig, Wenming Chen, Michele Cavo, Jean-Luc Harousseau, Suzanne Lentzsch, Jens Hillengass, Antonio Palumbo, Alberto Orfao, S Vincent Rajkumar, Jesus San Miguel, Herve Avet-Loiseau

	Response criteria*
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates

Techniques currently used to detect MRD

Multiple features of disease biology inside and outside the bone marrow

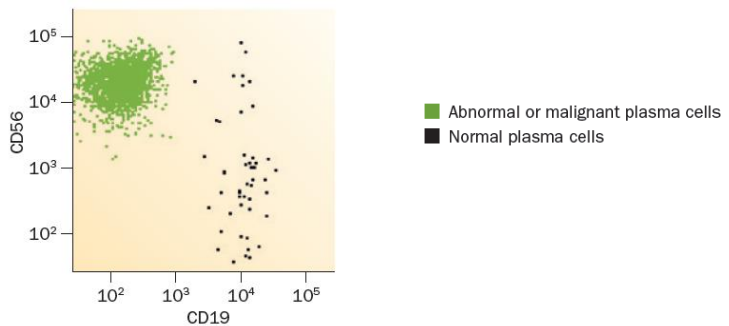
Techniques	Target	Serum	Peripheral Blood	Bone marrow	Intra- and extramedullary
NGF[2]	Aberrant cells	-	X	X	
NGS[3]	Clonotypic cells Unique patient barcode	-	X	X	
PET/CT or DWIMRI[4]	Active cells	-	-	-	X
Mass spec[1] /other peripheral blood techniques	M-protein/cfDNA	X	X	-	X

1. Dispenzieri A, et al. Blood Cancer J. 2020;10(2):20.
2. Sanoja-Flores L, et al. Blood. 2019;134(24):2218–2222.
3. Mazzotti C, et al. Blood Ad 2018;2(21):2811-2813.
4. Zamagni E, et al. J Clin Oncol. 2021;39(2):116-125; Belotti A et al Cancer Medicine 2021

MRD in BM by Flow cytometry

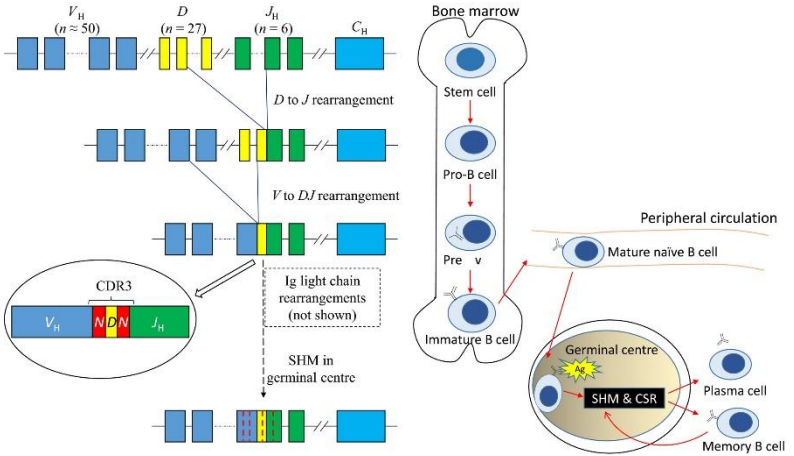
	Normal plasma cells	Normal plasma cells Less typical (<30%)	MM cells (all combinations are possible)
CD38	+ bright		+ low (80%)
CD138	+		+
CD19	+	-	- (96%)
CD45	+	-/low	- (73%)
CD27	+	low	-/low (40-68%)
CD81	+		-/low (55%)
CD56	-	+	+ (60-75%)
CD117	-		+ (30-32%)
cIgk/l	polyclonal		clonal

=> ***MFC*** (Multiparameter Flow Cytometry): a panel distinguishes MM cells from normal plasma cells



Mina R et al Cancer J 2021

MRD in BM by molecular biology



=> ***Molecular biology***: IGH rearrangement and somatic hypermutation (SHM) during B cell ontogeny generate a unique DNA sequence associated with clonal expansion of MM-PC

unique MM-PC "barcode"

Bai Y et al Br J Hematol 2018

PROS and CONS of NGF/MFC and NGS

Flow

PROS

- feasible in most pts
- does not require diagnostic sample
- widely available
- same day results
- affordable cost
- sensitivity 10^{-5}-10^{-6}

CONS

- fresh sample (<24-48h)
- PC die quickly outside BM
- operator-dependent
- Hemodiluition

NGS

PROS

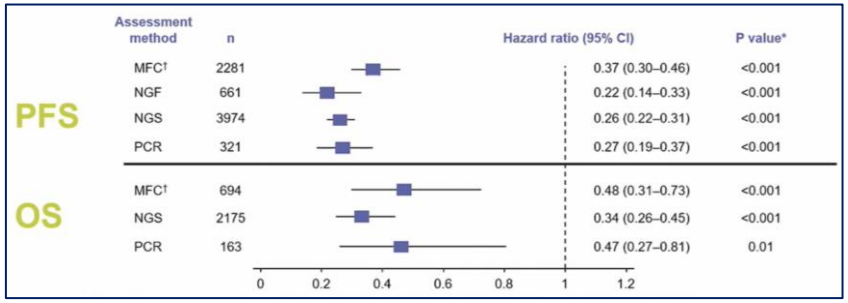
- sensitivity (up to 10^{-6})
- paraffin stored samples
- highly reproducible
- Clonal evolution

CONS

- requires diagnostic samples
- Commercial service only, few academic platforms
- turnaround time, complexity with bioinformatic support
- high cost

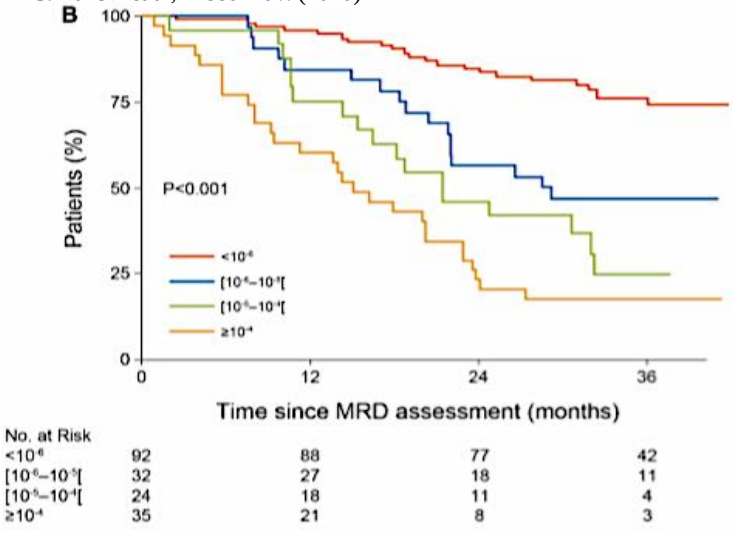
Stetler-Stevenson et al, Cytometry Part B 2016, Flores-Monteiro et al, Leukemia 2017, Oliva s et al Front. Oncol. 2020

Does it matter the Bone Marrow MRD method…and the threshold?



NC.Munshi et al, Blood Adv. (2020)

NGS

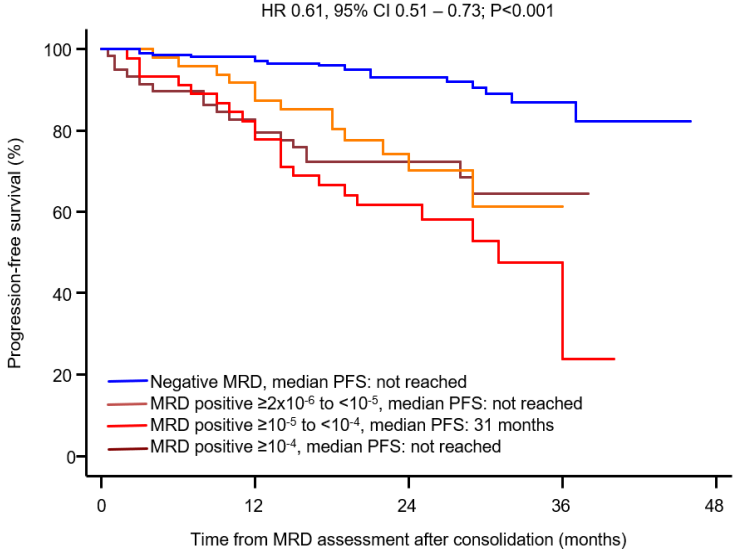


Perrot A, et al. Blood. 2018;132(23):2456-2464.

➔ ***REPORTS*** should state:

- the ***method*** of detection
- the ***threshold*** employed

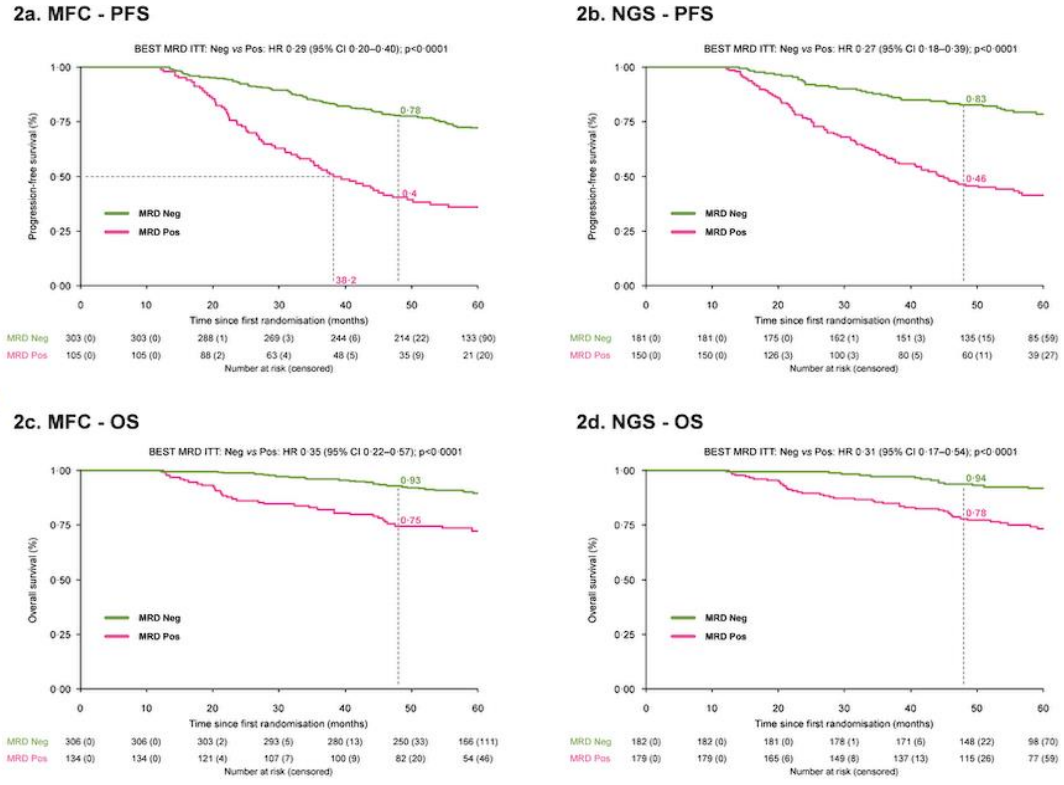
NGF



Paiva B, et al. JCO. 2020 Mar 10;38(8):784-792.

Similar prognostic value using NGF and NGS

Forte trial



Oliva S et al. eClin Med 2023

KarMMa trial (Ide-cel)

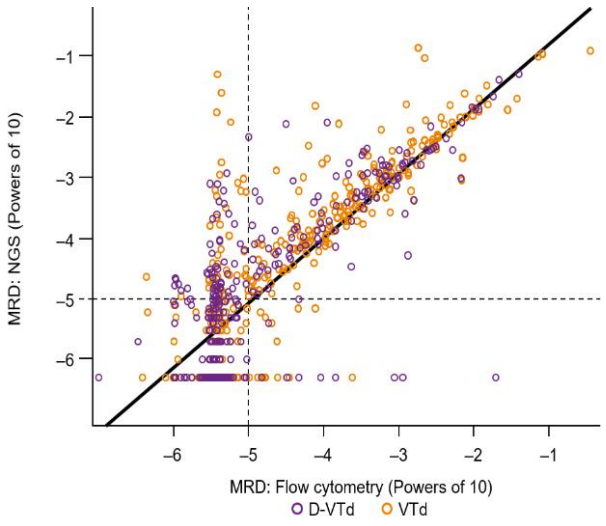
Hazard ratio for landmark PFS at each time point

	M1		M3		M6		M12	
	HR	P	HR	P	HR	P	HR	P
NGF	0.05	<.001	0.10	<.001	0.11	<.001	0.11	<.001
NGS	0.265	<.001	0.19	<.001	0.15	<.001	0.06	<.001

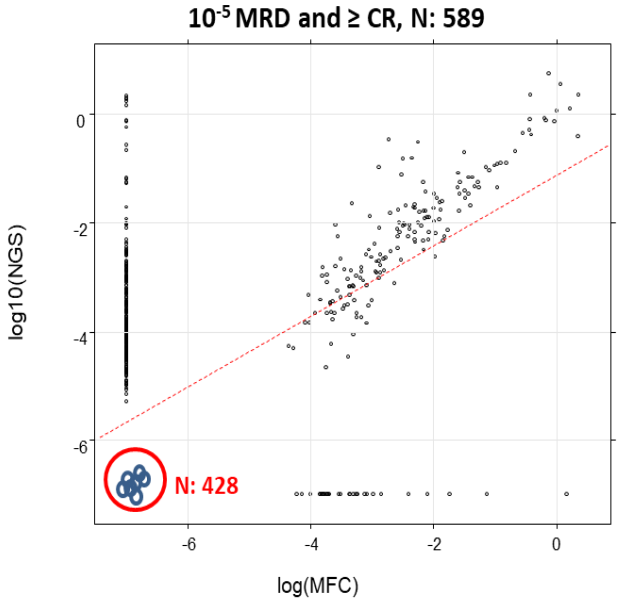
Paiva B et al ASH 2022 (oral presentation)

CONCORDANCE NGF/MFC and NGS

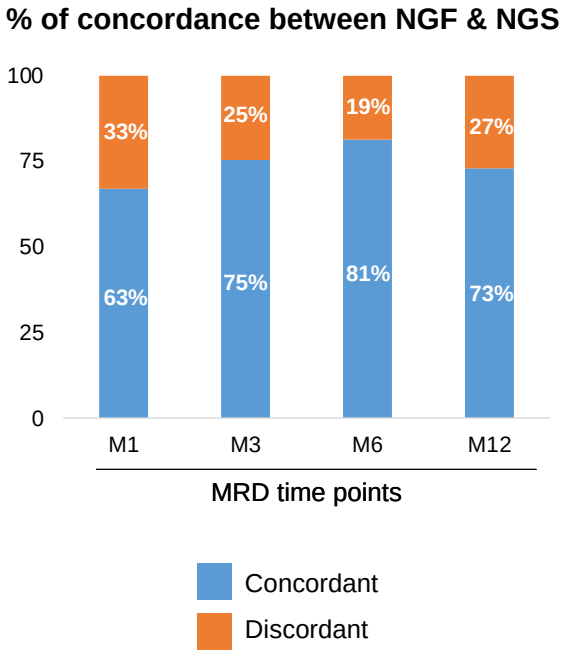
Cassiopeia trial



Forte trial



KarMMa trial (Ide-cel)



Good general agreement (> 80%) between MRD assessments was observed in the paired evaluation, with no differences between treatment arms

Avet Loiseau H et al. IMWG 2019.

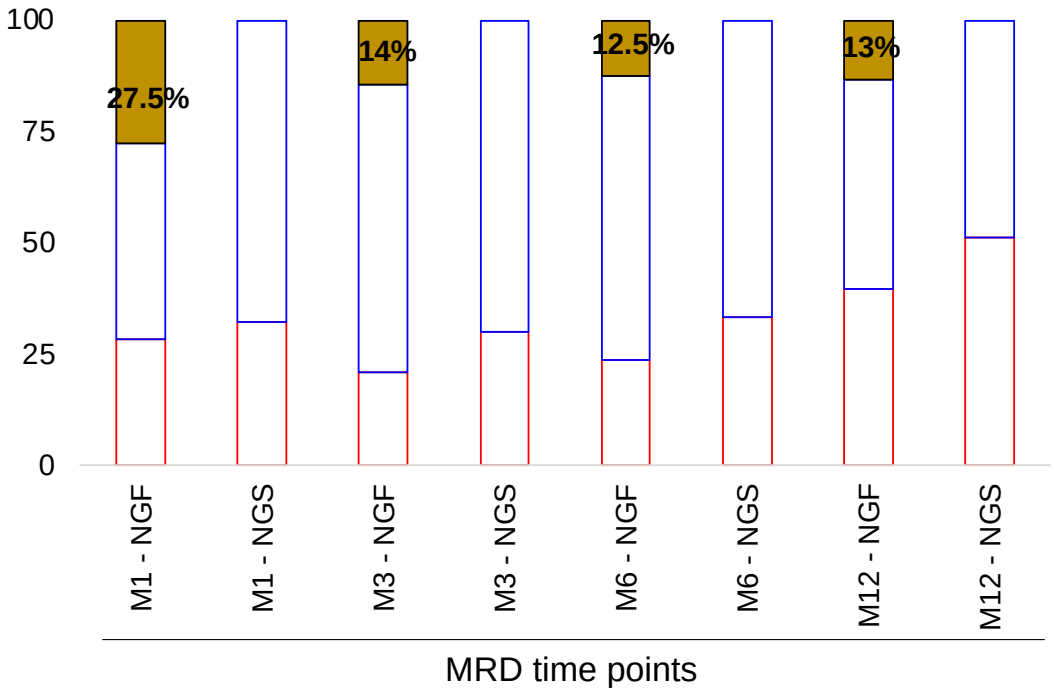
Oliva S et al. eClin Med 2023

Paiva B et al ASH 2022 (oral presentation)

Relatively high concordance between NGF and NGS

Most discordances are due to hemodiluted samples

MRD status according to NGF & NGS at each timepoint (%)



New Reference Values to Assess Hemodilution and Warn of Potential False-Negative MRD Results in Myeloma:

- Cellularity
- B-cell precursors
- Nucleated red blood cells
- Mast cells

Paiva B et al ASH 2022 (oral presentation) Puig N et al *Cancers* 2021

Reproducibility and harmonization of data

Leukemia (2021) 35:18–30
https://doi.org/10.1038/s41375-020-01012-4

REVIEW ARTICLE

Multiple myeloma gammopathies

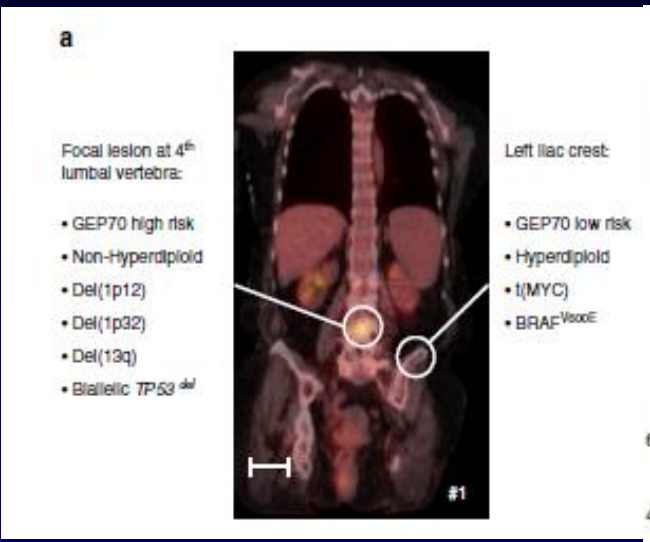
International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials

Luciano J. Costa[1] · Benjamin A. Derman[2] · Susan Bal[1] · Surbhi Sidana[3] · Saurabh Chhabra[4] · Rebecca Silbermann[5] · Jing C. Ye[6] · Gordon Cook[7] · Robert F. Cornell[8] · Sarah A. Holstein[9] · Qian Shi[10] · James Omel[11] · Natalie S. Callander[12] · Wee Joo Chng[13] · Vania Hungria[14] · Angelo Maiolino[15] · Edward Stadtmauer[16] · Sergio Giralt[17] · Marcelo Pasquini[4] · Andrzej J. Jakubowiak[2] · Gareth J. Morgan[18] · Amrita Krishnan[19] · Graham H. Jackson[20] · Mohamad Mohty[21] · Maria Victoria Mateos[22] · Meletious A. Dimopoulos[23] · Thierry Facon[24] · Andrew Spencer[25] · Jesus San Miguel[26] · Parameswaran Hari[4] Saad Z. Usmani[27] · Salomon Manier[28] · Phillip McCarthy[29] · Shaji Kumar[30] · Francesca Gay[31] · Bruno Paiva

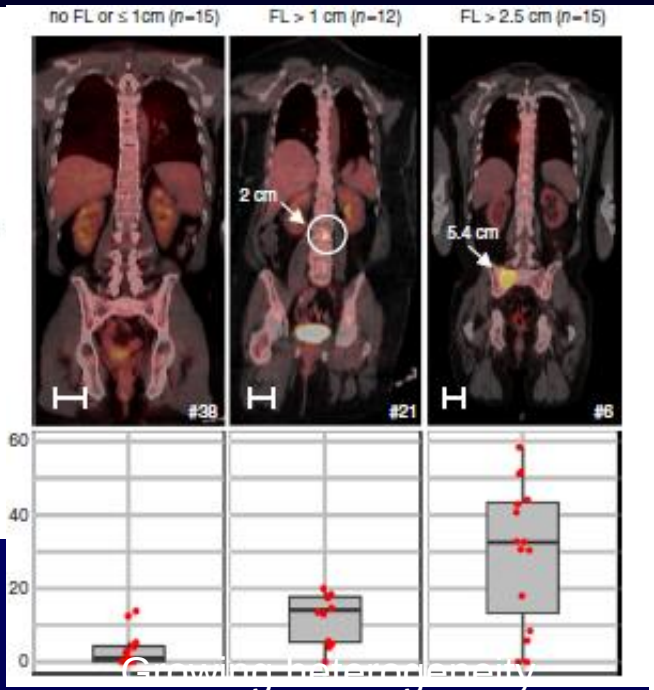
- to improve the quality and reproducibility of MRD dectection in future trials and ensure uniform reporting of MRD results ➡ better inter-trials comparison
- to validate MRD as a survival surrogate endpoint for accelerating drug approval

Functional imaging to evaluate response to therapy

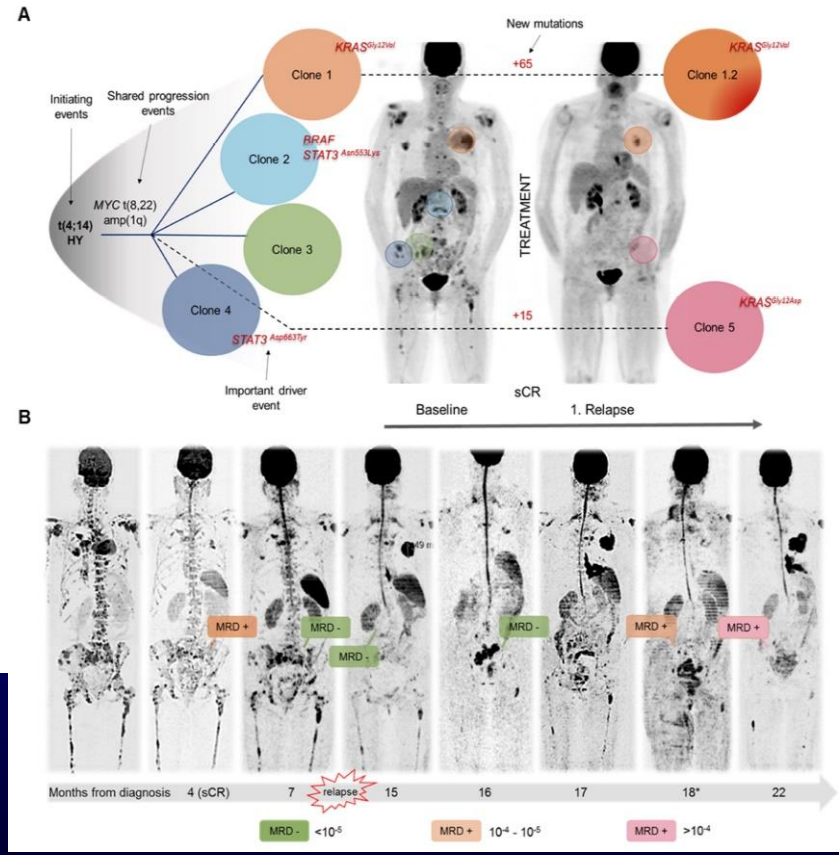
Discrepancy between BM MRD and imaging: need for Imaging MRD category



Different GEP profile between BM and FL



Growing heterogeneity with growing size of the lesions



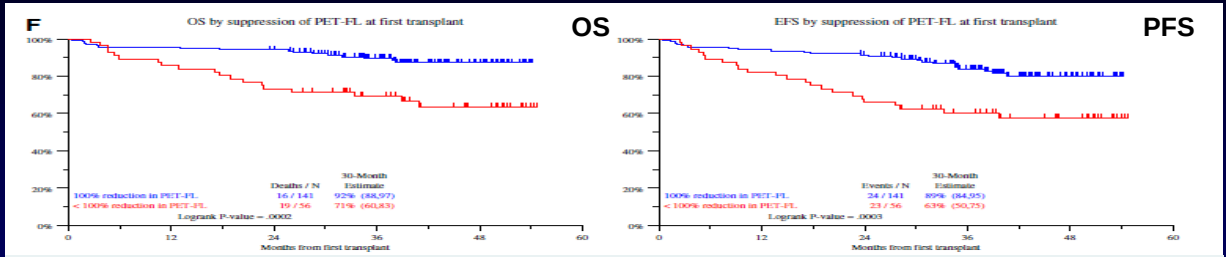
- **Patchy infiltration of the BM**
- **EMD**
- **Spatial heterogeneity**

Rasche L et at, Nature Comm 2017
Rasche L et al, Blood 2018
Rasche L et al, Leukemia 2018

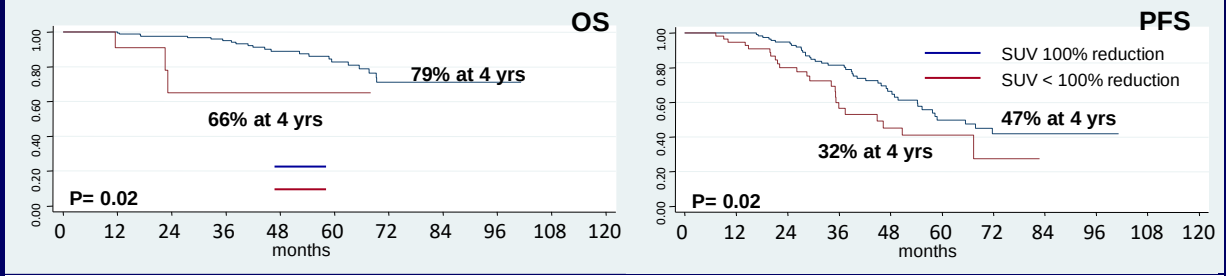
FDG PET/CT FOR EVALUATION OF METABOLIC RESPONSE TO THERAPY AND MRD

Prospective trials

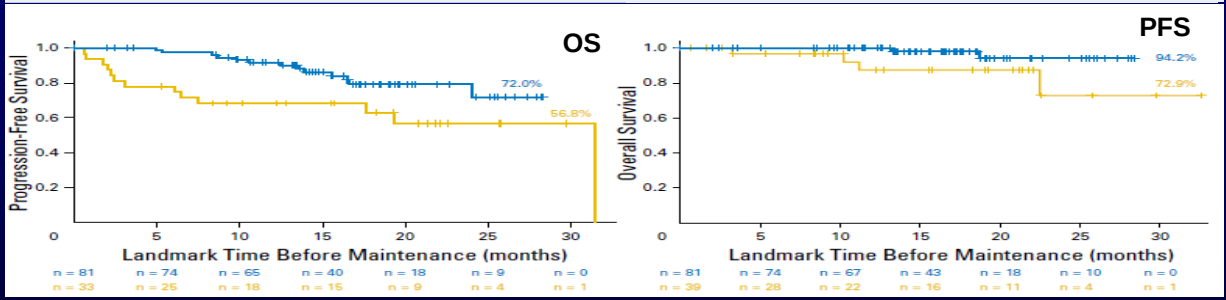
•65-80% of the patients after first-line treatment achieve a complete FDG suppression



BEFORE ASCT



AFTER ASCT



PRE-MAINTENANCE

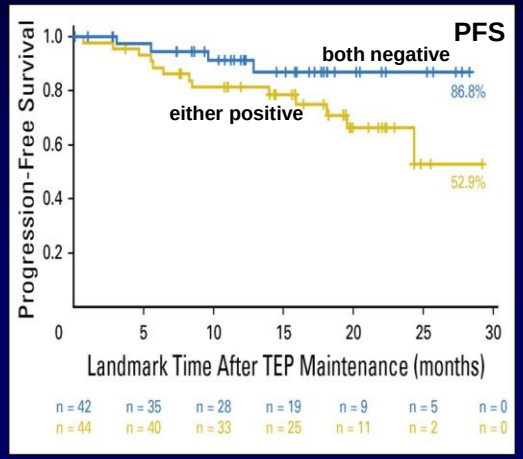
STANDARDIZED DEFINITION OF COMPLETE METABOLIC RESPONSE:

uptake ≤ liver activity in all localizations of the BM and FLs (including EMD and PMD) (DS 1-3)
Zamagni E et al, JCO 2021

Bartel. TB et al, Blood 2009
Usmani S.Z. et al, Blood 2013
Zamagni E. et al, Blood 2011
Moreau P. et al, JCO 2017
Pandit-Taskar N et al, Semin Hematol 2018

PET IMAGING TO EVALUATE RESPONSE TO THERAPY

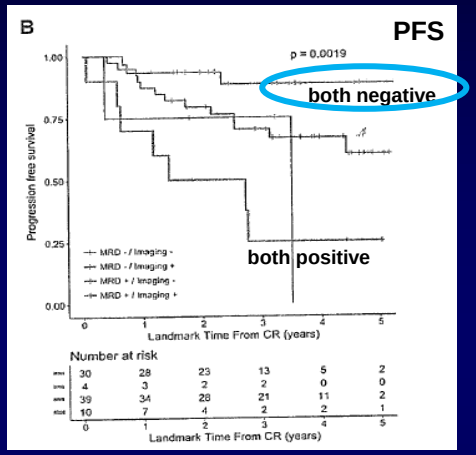
COMPLEMENTARITY BETWEEN PET/CT AND BM FLOW CYTOMETRY



86 patients, prospective study

- MFC (10^{-4}) and imaging + : 13%
- MFC and imaging - : 49%
- **Discrepancy MFC/imaging (38%):**
  - MFC+, imaging - : 23%
  - **MFC-, imaging + : 16%**

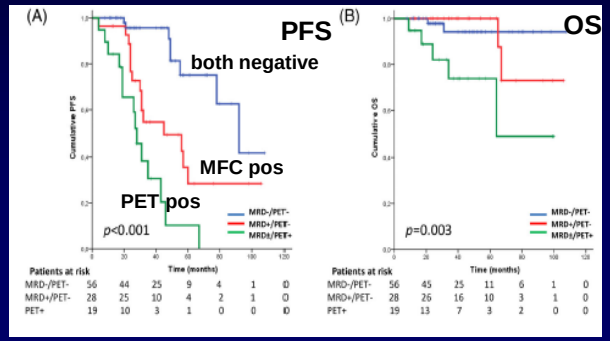
Moreau P. et al, JCO 2017



83 patients, prospective study

- MFC (10^{-5}) and imaging + : 12%
- MFC and imaging - : 36%
- **Discrepancy MRD/imaging (52%):**
  - MFC+, imaging - : 40%
  - **MFC-, imaging + : 12%**

Rasche L et al, Leukemia 2018



103 patients, retrospective study

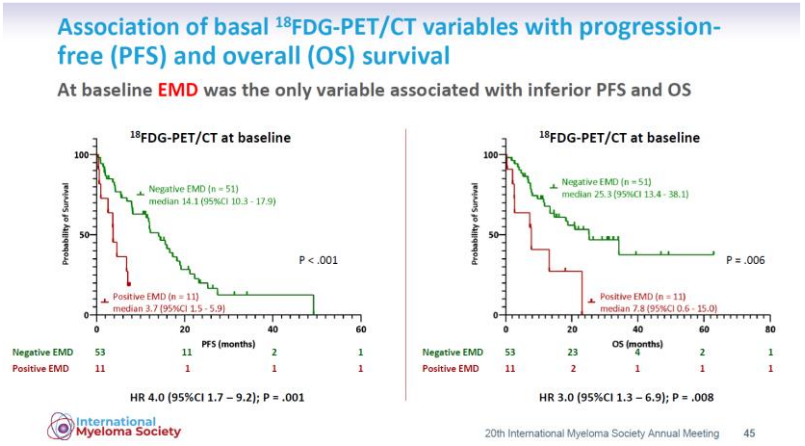
- MFC (10^{-4}) and imaging + : 6%
- MFC and imaging - : 54%
- **Discrepancy MRD/imaging (40%):**
  - MFC+, imaging - : 27%
  - **MFC-, imaging + : 12.6%**

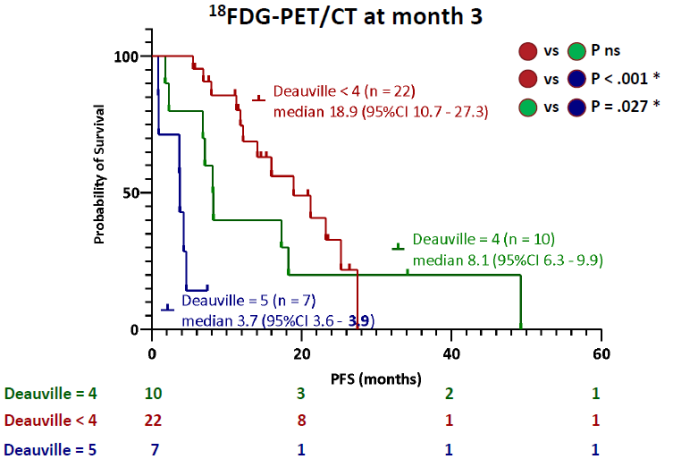
Alonso R et al, Am J Hematol 2019

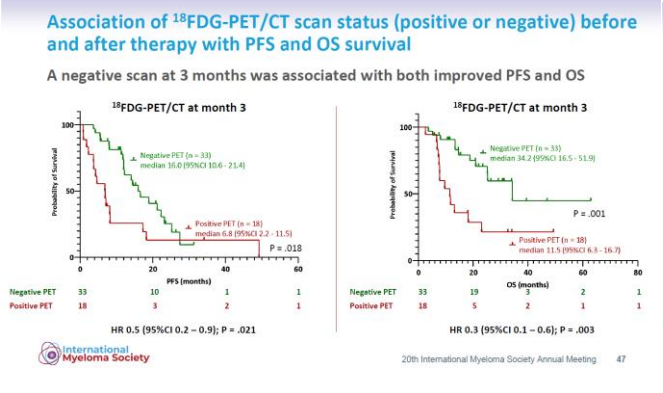
The discrepancy of imaging with BM techniques at $10^{-6}/10^{-7}$ sensitivity threshold in NDMM expected to be lower

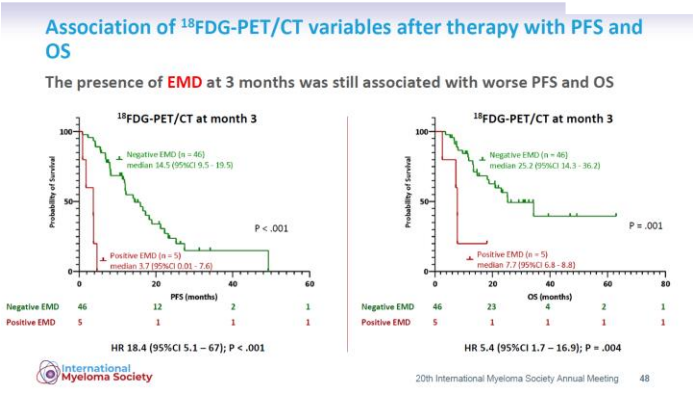
Imaging relapse while mantaining BM MRD negativity (MFC, $10^{-4}/10^{-5}$):
-higher risk in EMD/para-medullary disease
-up to 50% during relapse phases

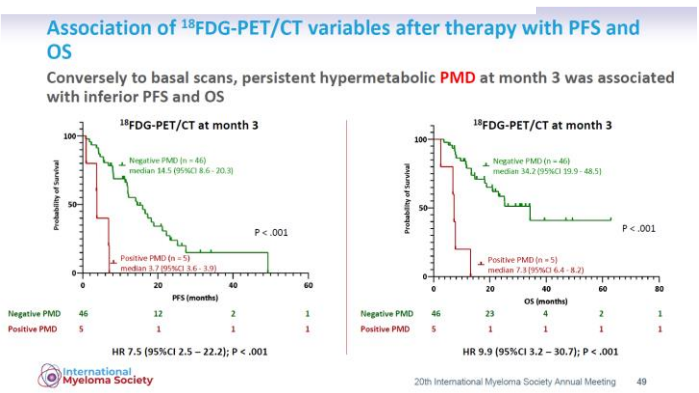
Definition of PET imaging response in patients receiving CARTs









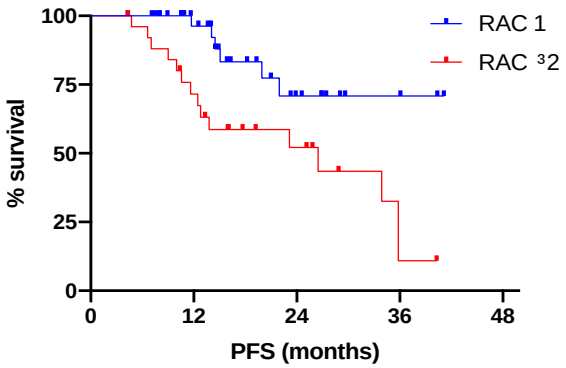


- Retrospective analysis on **62 pts** treated in Spain with anti-BCMA CARTs (2018-2023), studied by FDG PET/CT at **baseline, @ 1 mos (92%) and @ 3 mos (82%)**
- 79% PET pos baseline, 58% @ 1 mos, 35% @ 3 mos
- **No role on PFS of early 1 mos PET**

Tamariz-Amador LE et al, IMS Athens 2023

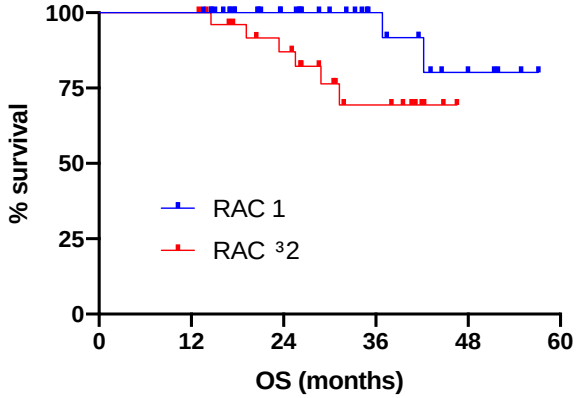
DWI-MRI to assess response after ASCT according to MY-RADS criteria

Post ASCT PFS according to imaging response



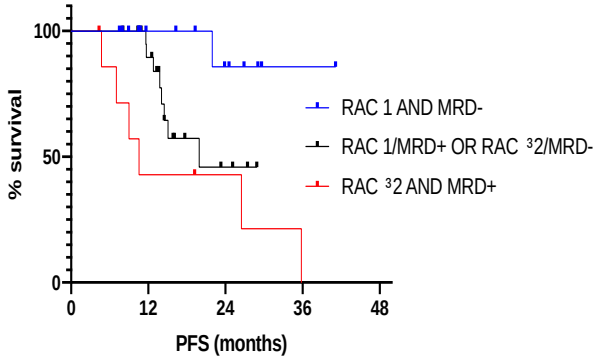
Median: NR vs 26.5 mos, HR 0.28, P= 0.004

Post ASCT OS according to imaging response



@ 3 yrs: 92% vs 69%, HR 0.24, P= 0.04

Post ASCT PFS according to MFC (10^{-5}) and imaging (46 pts)



Median PFS RAC1/MFC neg vs one pos vs both pos: NR vs 19.9 vs 10.6 mos, P= 0.007

MULTIVARIATE ANALYSIS

PFS	HR (95%CI)	P value
IMWG response: < CR	0,43 (0,17-1,03)	0,060
RAC ≥ 2	0,29 (0,11-0,75)	**0,011**
High Risk cytogenetic	0,39 (0,15- 0,99)	**0,048**

Retrospective analysis of 64 pts
Median follow-up 29 mos

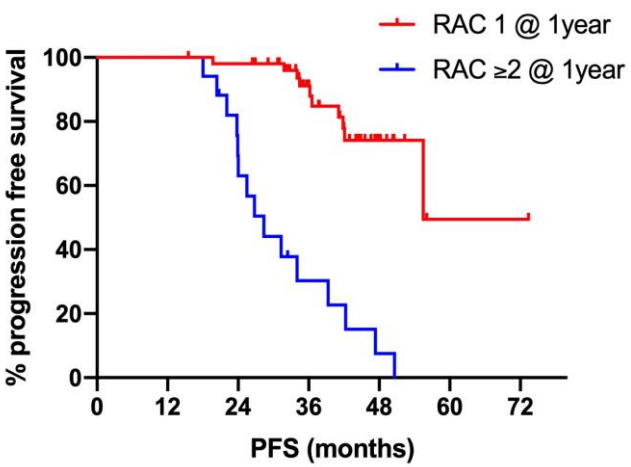
RAC 1 = complete imaging response
RAC 2 or higher = PR/stable/progressive imaging disease

Belotti A et al, Cancer Medicine 2021

DWI-MRI after 1 year len-maintenance post ASCT: «sustained» imaging MRD

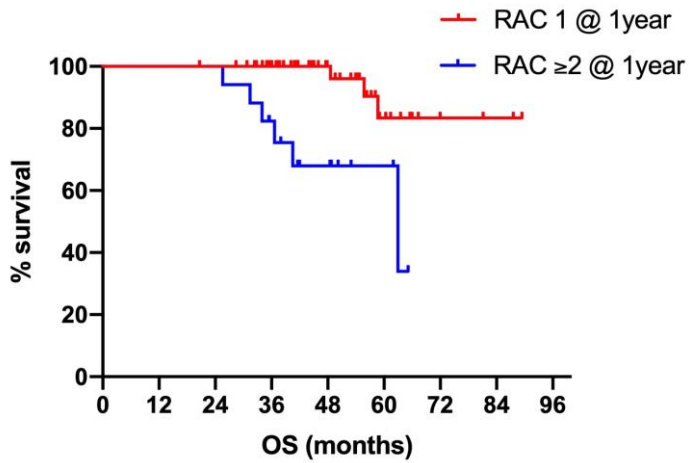
Questioning the role of imaging follow-up after therapy?

PF



HR 0.12 (95%CI: 0.04-0.35), p <0.0001

OS



HR 0.13 (95%CI: 0.03-0.66), p 0.0007

Multivariate analysis for PFS and OS

PFS	HR (95%CI)	P value
IMWG response after ASCT: < CR	0,82 (0,30-2,26)	0,700
ISS-3 stage	1,03 (0,42-2,48)	0,952
RAC ≥ 2 @1year	**0,12 (0,05-0,30)**	**<0,001**
High Risk cytogenetic	0,34 (0,15- 1,04)	0,060
OS	**HR (95%CI)**	**P value**
IMWG response after ASCT: < CR	1,44 (0,22-9,19)	0,701
ISS-3 stage	1,34 (0,26-7,01)	0,728
RAC ≥ 2 @1year	**0,20 (0,05-0,87)**	**0,032**
High Risk cytogenetic	0,26 (0,05- 1,38)	0,113

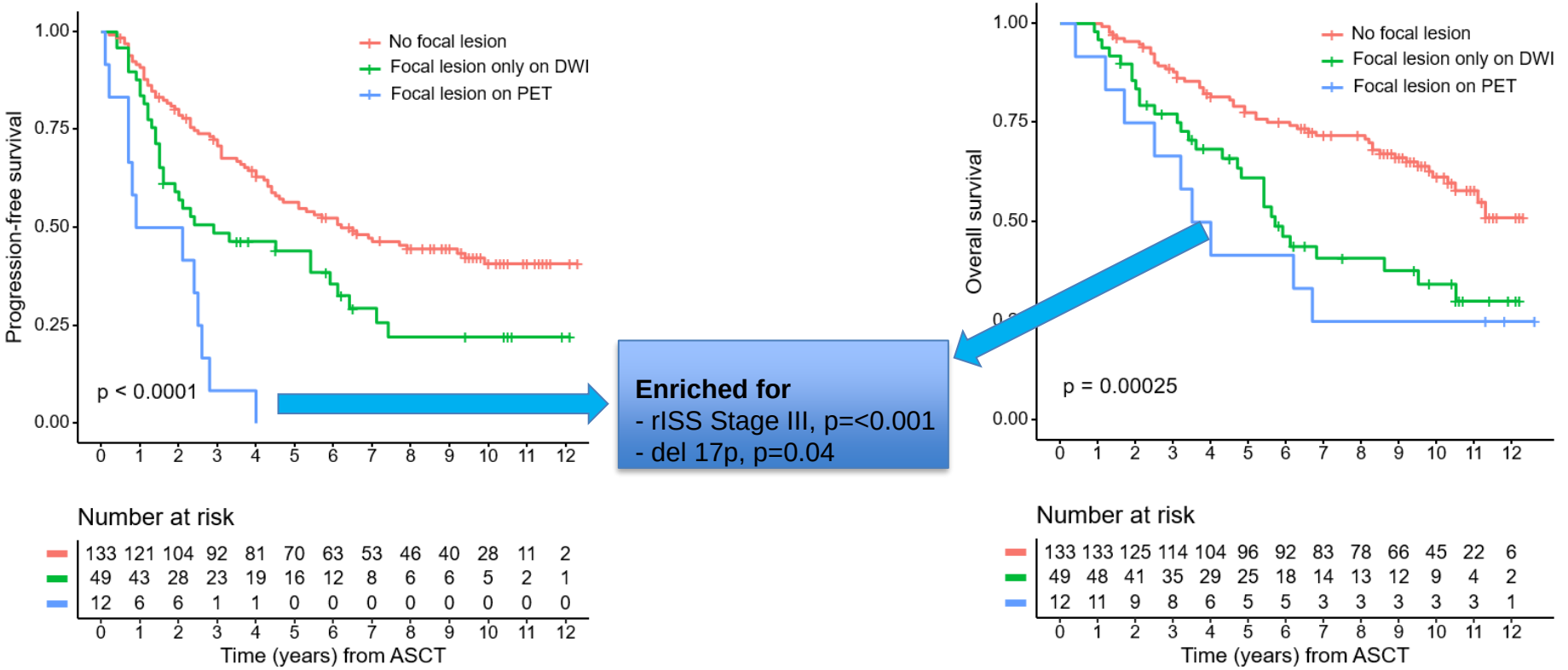
Median follow-up: 46 months

RAC 1 going **from 59%** +100 ASCT **to 76%** @ 1 year
NGF neg going from 64% +100 ASCT to 83% @ 1 year
Agreement NGF/MRI 85%, Cohen's kappa 0.46

Belotti A et al, ASH 2022, Am J Hematology 2023

PET and DWIMRI: is one of the two the winner or are they complementary/alternative?

Impact of persistent FLs post ASCT with different imaging techniques



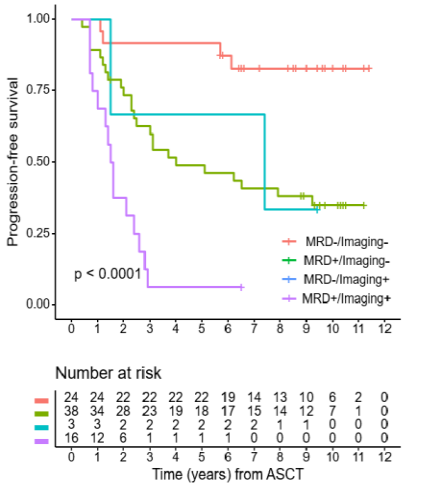
- 196 pts treated in the TT programs at UAMS
- Median follow-up: 85 mos

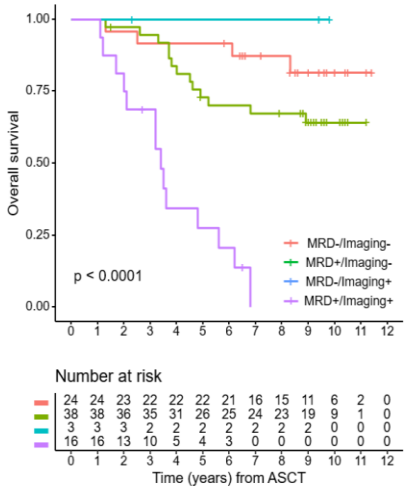
Schinke C et al, ASH 2023

Integration of imaging with BM techniques

Complementarity between BM and imaging MRD: uni and multivariate analysis

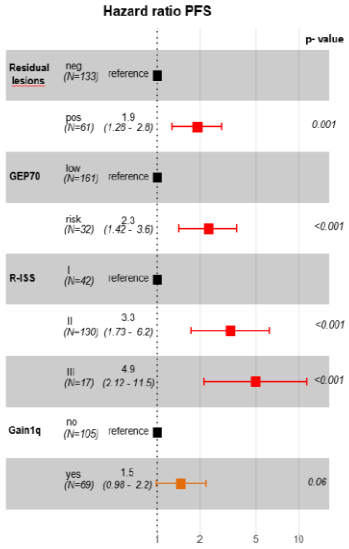
The combination of WBI and MRD assessment post ASCT improves prognostic impact

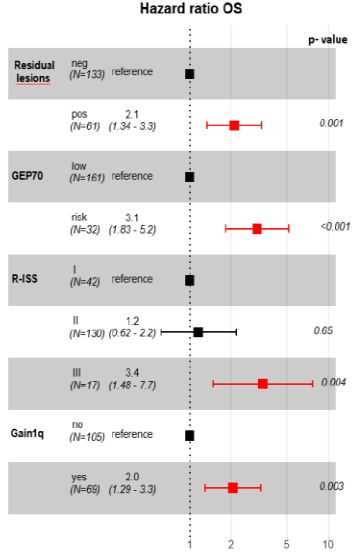




*MRD measured by 8 color flow cytometry with a sensitivity of 10^{-5}

Residual FLs post ASCT is an independent adverse risk factor for outcome





- 196 pts treated in the TT programs at UAMS
- Median follow-up: 85 mos

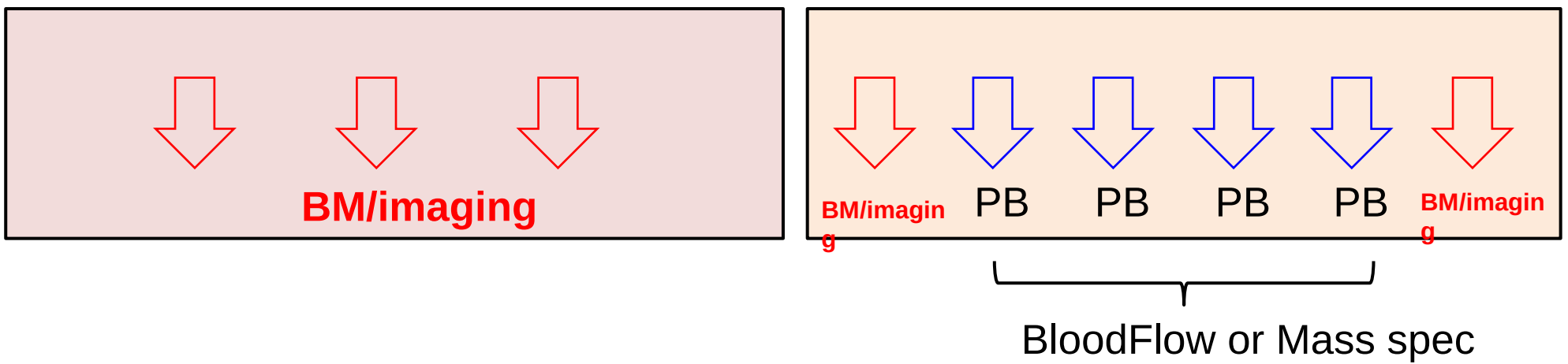
Schinke C et al, ASH 2023

Integration of imaging with BM/PB techniques

Hypothetical scenario to assess MRD by BM/PB and imaging

MRD assessment during induction/intensification

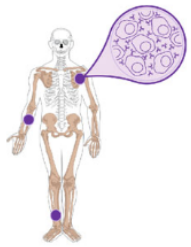
MRD assessment during maintenance/observation



Courtesy of Bruno Paiva, adapted

Tailoring MRD assessment on patient individuality

What technique in the future outside of clinical trials?



Baseline presentation

Patients with only **BM disease (no FL at PET/CT)**

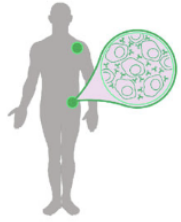
Initial MRD monitoring

PB MRD (MS or NGF/NGS)

If PB MRD neg: perform BM MRD

If BM MRD neg: need for sustained evaluation?

If BM MRD pos: repeat at later timepoint (after a clinical phase? After a fixed duration of time?)



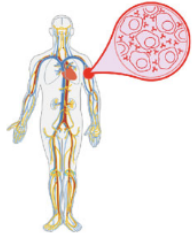
Patients with **EMD/focal lesions at PET/CT**

PB MRD (MS or NGF/NGS)

If PB MRD neg: perform PET/CT and BM MRD

If BM MRD and PET/CT neg: need for sustained MRD

If BM MRD pos: repeat at later time point (after a clinical phase? After a fixed duration of time?)



Patients with **circulating plasma cells**

PB MRD NGF (or MS/NGS)

If PB MRD neg: perform BM MRD and PET/CT

If BM MRD and PET/CT neg: need for sustained MRD? Only PB monitoring?

If BM MRD pos: repeat at later time point (after a clinical phase? After a fixed duration of time?)

For **high-risk patients**: high-risk CA, LDH, ISS II/III → consider multiple methods (imaging + BM)

Complementary multimodal methods

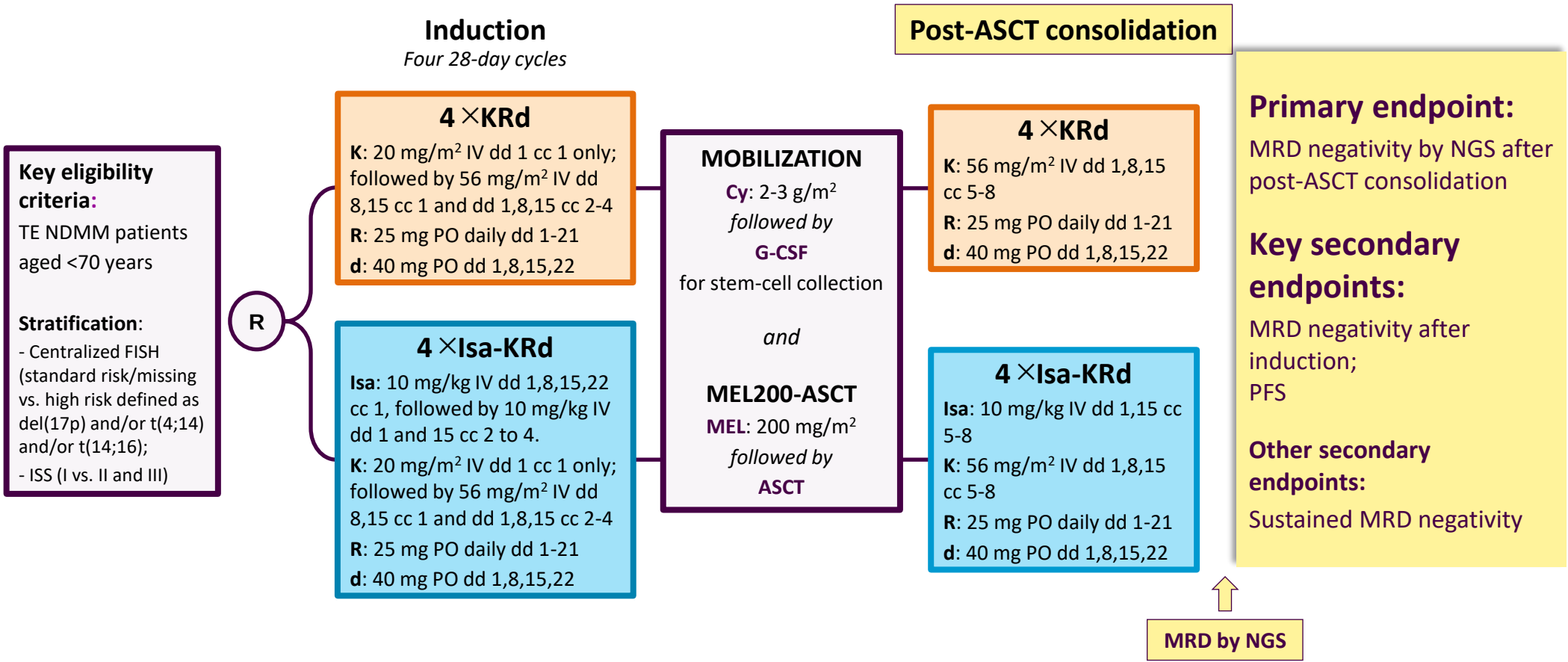
Bertamini L *et al* Current Hematologic Malignancy Reports 2021 16, pages 162–171 (2021)

Burning questions and different applications of MRD

- How should we evaluate MRD and when?
- MRD in clinical trials: trial end-point (primary, co-primary or secondary), MRD as driver of therapy (R. Mina)
- Are we ready to use MRD outside clinical trials?
- Can we use MRD as a trial end-point, to accelerate drug approval and to provide inter-trials comparison?

IsKia EMN24 Study Design

42 active sites; enrollment: Oct 7, 2020 – Nov 15, 2021



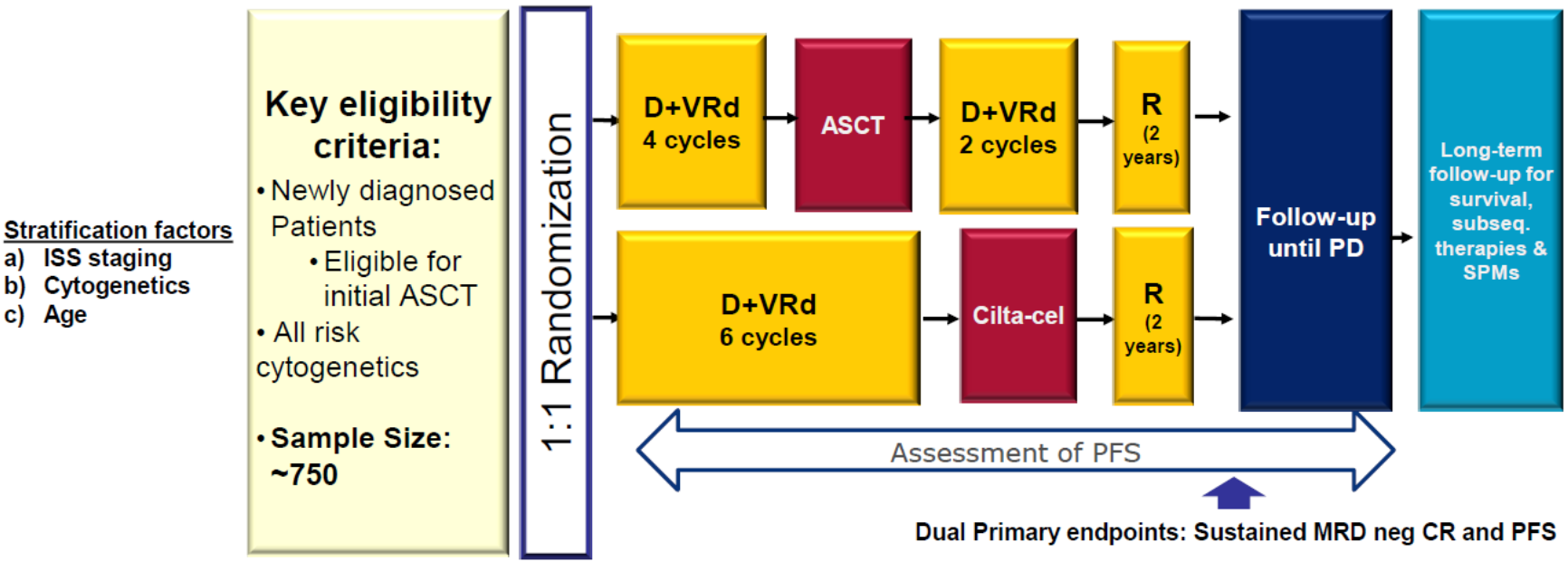
Gay F et al, ASH 2023

TE, transplant-eligible; NDMM, newly diagnosed multiple myeloma; FISH, fluorescence *in situ* hybridization; del, deletion; t, translocation; ISS, International Staging System stage; R, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenous; dd, days; cc, cycles; PO, orally; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MEL, melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival.

EMN 28- CARTITUDE 6 trial

Dual primary endpoints:

Sustained MRD-neg CR and PFS



ASCT, autologous stem cell transplant; CR, complete response; D, daratumumab; EMN, European Myeloma Network; ISS, international staging system; MRD, minimal residual disease; PD, progressive disease; PFS, progression-free survival; R, lenalidomide; SPM, second primary malignancies; VRd, bortezomib-lenalidomide-dexamethasone

1. NCT05257083. Available at: https://clinicaltrials.gov/ct2/show/NCT05257083. Accessed June 2022
2. Gay F et al. EMN 2022: (oral presentation)

Ongoing clinical trials including MRD status in patients' enrollment and/or MRD-driven interventions

Identifier	Phase	Regimen/Purpose	Subjects	MRD-driven decision	Primary endpoint	Status
NCT04108624 (MRD2STOP)	PO	Maintenance cessation	56 multimodality^{E}MRD^{neg} MM patients on a single-agent maintenance for ≥ 1year	Maintenance cessation	MRD conversion rate, PFS, OS	Not yet recruiting
NCT04221178	PO	Maintenance cessation	50 MRD^{neg} MM patients for ≥ 3 years while on continuous maintenance	Maintenance cessation	MRD negativity rate (10^{-5}) a year after enrolling	Recruiting
NCT03490344	2	Daratumumab effect on MRD^{pos} patients post induction	25 MRD^{pos} patients post induction with without consolidative HDT/ASCT	-	MRD negativity rate by MFC	Recruiting
NCT03992170 (DARAMM)	2	Daratumumab effect on MRD^{pos} patients	50 MRD^{pos} patients with ≥ VGPR after any previous therapy	All patients will receive Dara for 24 weeks MRD^{neg} (NGF): treatment cessation MRD^{pos}: Daratumumab every 4 weeks for 80 more weeks	MRD negativity rate	Recruiting
NCT03901963 (AURIGA)	3	DaraR vs. R alone as maintenance treatment	214 MRD^{pos} (≥10^{-5})patients post ASCT	-	MRD conversion rate tested by NGS (10^{-5})	Recruiting
NCT03697655 (PREDATOR)	2	Preventive role of Daratumumab (Dara vs. no intervention) in reappearance of MRD	274 MRD^{neg} patients after one or two prior lines of therapy	-	EFS	Recruiting
NCT02389517	2	Ixa-Rd vs. R alone as maintenance therapy	86 MRD^{pos} patients after ASCT	-	MRD negativity rate by MFC	Recruiting
NCT02969837	2	Elo-KRd as initial therapy	55 NDMM non-transplant or transplant eligible agreed to defer ASCT	All with receive Elo-KRD for 12 cycles and then: MRD^{neg}: Elo-Rd maintenance until PD MRD^{pos}: Elo-KRd for 6 more cycles and then Elo-Rd maintenance until PD	sCR rate, MRD negativity rate by NGS (clonoSIGHT)	Recruiting
NCT04071457 (DRAMMATIC)	3	DARArHuPH20 + R vs. R alone as maintenance therapyto direct therapy duration	1100 patients post ASCT	After 2 years of maintenance with each arm: MRD^{pos} >10^{-6}: Continue with assigned treatment MRD^{neg} (≤10^{-6}): Randomization to either stop or continue assigned treatment for up to 7 years	OS	Recruiting
NCT02659293	3	KRd vs. R alone after ASCT	180 post ASCT that received a maximum of 2 induction regimens and have ≥SD at d100 post ASCT	Carfilzomib cycles 5–8 for MRD- patients that have no risk factors at the end of cycle 6 Carfilzomib: cycles 5 - 36 for MRD^{pos} patients with high risk factors at the end of cycle 6	PFS	Recruiting
NCT04096066	3	KRd vs. Rd alone	340 elderly NDMM not eligible for ASCT	Patients with ≥VGPR & MRD^{neg} (10^{-5}) for ≥ 1 year in the KRD arm will stop K (after ≥ 2 years of treatment) and continue with RD until PD or intolerance	MRD negativity rate, PFS	Recruiting
NCT04140162	2	DaraRd induction ± DaraVRd consolidation + DaraR maintenance	50 NDMM eligible and not for ASCT	Only those with MRD positive status after 6 cycles of induction will receive consolidation	MRD negativity rate after induction and/or consolidation	Not yet recruiting
NCT03710603 (PERSEUS)	3	DaraVRd arm: DaraVRd for induction and consolidation, DaraR for maintenance VRd arm: VRd for induction and consolidation, R for maintenance	690 NDMM eligible for ASCT	Patients in DaraVRd group with sustained MRD negativity (10^{-5}) for 12 months and minimum 24 months of maintenance will stop Dara until PD or intolerance Upon recurrence of MRD or loss of CR, patients will restart Dara until PD or intolerance	PFS	Recruiting
NCT03224507 (MASTER)	2	DaraKRd for induction, ASCT ± DaraKRd consolidation ± R maintenance	82 NDMM eligible for ASCT	MRD (10^{-5}) is evaluated post induction, post ASCT and during each 4-cycle block of Dara-KRd consolidation MRD^{neg} patients after two consecutive evaluations will stop therapy and will be monitored for MRD resurgence (In 6 and 18 months. MRD^{pos} patients post ASCT will complete all cycles of consolidation and if MRD persists, they will receive R maintenance until PD or intolerance	MRD negativity rate by NGS (clonoSEQ)	Recruiting

Almost 50 phase III trials are currently enrolling with MRD as an end-point or using MRD-directed treatment assignment

Kostopoulous et al. Frontiers in Oncology 2021

Different possible uses of MRD in clinical practice

Treatment phase	Suggestion	Trials/Data
Post-Induction in NDTEMM	Be cautious!	Low rate of MRD neg post induction MIDAS trial on-going
Post- ASCT/consolidation in NDTEMM	Consider, in particular in HR pts	Trials on-going (Auriga, Commander, others)
During maintenance in NDTEMM	Consider, if sustained MRD neg, in SR pts	MRC XI data
ND NTEMM	Not yet	Low rate of MRD neg, few data
Resurgence of MRD	Consider strongly (> 1 log increase)	MASTER trial data, Diamond, Lancet Hemat 2021, Mohan, Blood Advances 2022, Remnant trial

Costa L, Comy Paris 2023, personal speach

Establishing MRD as a surrogate endpoint in clinical trials: i²TEAMM

Current requirements (EMA vs FDA)

- **FDA** provides extensive guidance on the meta-analysis required to validate MRD as a surrogate endpoint for MM but does not directly address approval based on MRD through its accelerated approval pathway – Jan 2020[1]
- **EMA** may consider product approvals based on MRD as primary endpoint on a 'case-by-case' basis – July 2018[2]
  - Confirmatory comprehensive data on PFS and OS from the same trial should be provided at a later stage[2]

Meeting with FDA on march 2024! EMA following…..

Criteria[1–3]	FDA	EMA
Acceptability of MRD as a validated surrogate endpoint for approval	Not acceptable yet; Agency open to discussing meta-analysis approaches	Might be acceptable on a case-by-case basis
MRD assay considerations	Analytically-validated platform	Analytically-validated platform
Measuring MRD	No specific mention of threshold	MRD will be considered undetectable if the proportion of malignant cells in the bone marrow is $<10^{-5}$
Timing of assessments	MRD should be assessed only in patients that are in CR	MRD measurement should be conducted after each treatment stage and at the time of suspected response (PR, VGPR, CR or sCR)
Duration/durability of response	No clear guidance	Sustained undetectable MRD as a secondary endpoint, defined as undetectable MRD in patients in CR and with normal imaging that has lasted a minimum of 1 year

CR, complete response; MRD, minimal residual disease; PR, partial response; sCR, stringent complete response; VGPR, very-good partial response

1. FDA https://www.fda.gov/media/134605/download; 2. EMA https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies_en.pdf; 3. Regulatory focus 2019 https://www.raps.org/news-and-articles/news-articles/2019/4/minimal-residual-disease-as-a-surrogate-endpoint-f

Conclusions

- MRD evaluation should be considered as the new key clinical end-point in MM
- NGS and NGF in BM are equivalent, if >10^{-5} sensitivity is reached; PET/CT and DWIMRI are the preferred imaging techniques to assess MRD outside the BM
- MRD in peripheral blood could be considered as a complementary method
- the samples' quality is of crucial importance : MRD results must be considered only if sample is representative of BM; the on-going MRD Italian network is essential for future patients' management
- MRD should be evaluated sequentially (=> to assess "sustained MRD"); sustained MRD negativity is crucial, in particular in high-risk patients
- Several clinical trials are currently addressing the issue of "MRD-driven" therapy; outside those trials, caution is needed to tailor treatment upon MRD
- Microenvironment, together with MM cell biology, play a role at MRD stages and drive the achievability of «cure»