GIORNATE EMATOLOGICHE VICENTINE

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Come definisco la malattia minima residua nel 2025

Mattia D'Agostino

Division of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino

Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

Disclosures of Mattia D'Agostino

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi						X	X
GSK						X	X
Janssen	X						X
BMS						X	
Adaptive biotechnology						X	

Let's dive deep into Measurable Residual Disease (MRD)

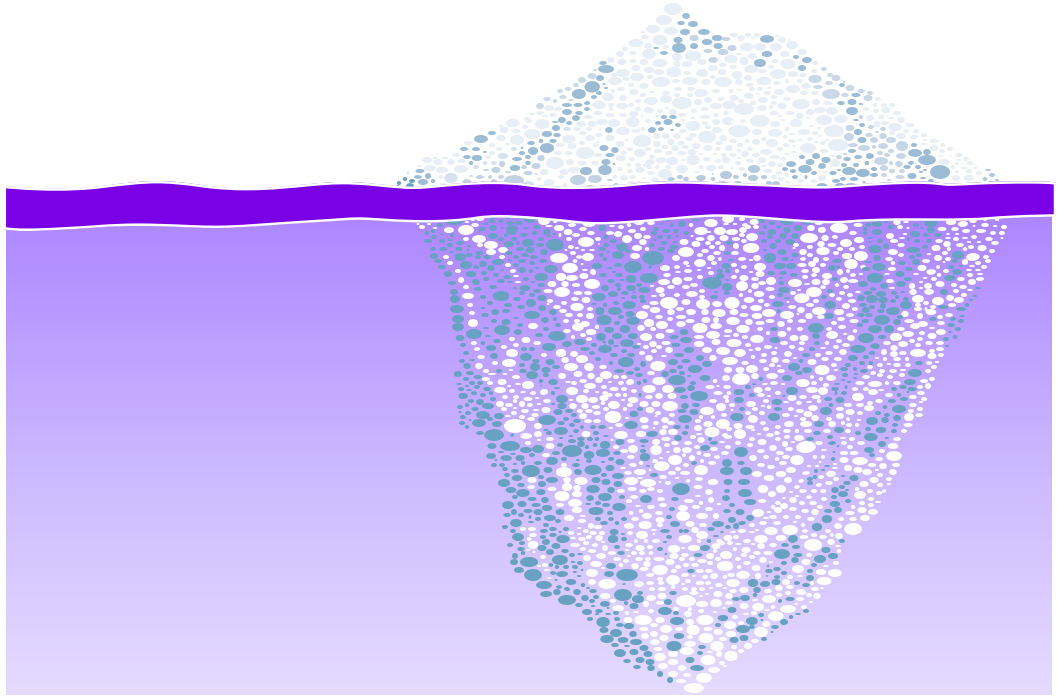
MRD: why we need it

MRD as a prognostic marker

MRD as an endpoint in clinical trials

MRD as an adaptive treatment tool

Integrating MRD in clinical practice



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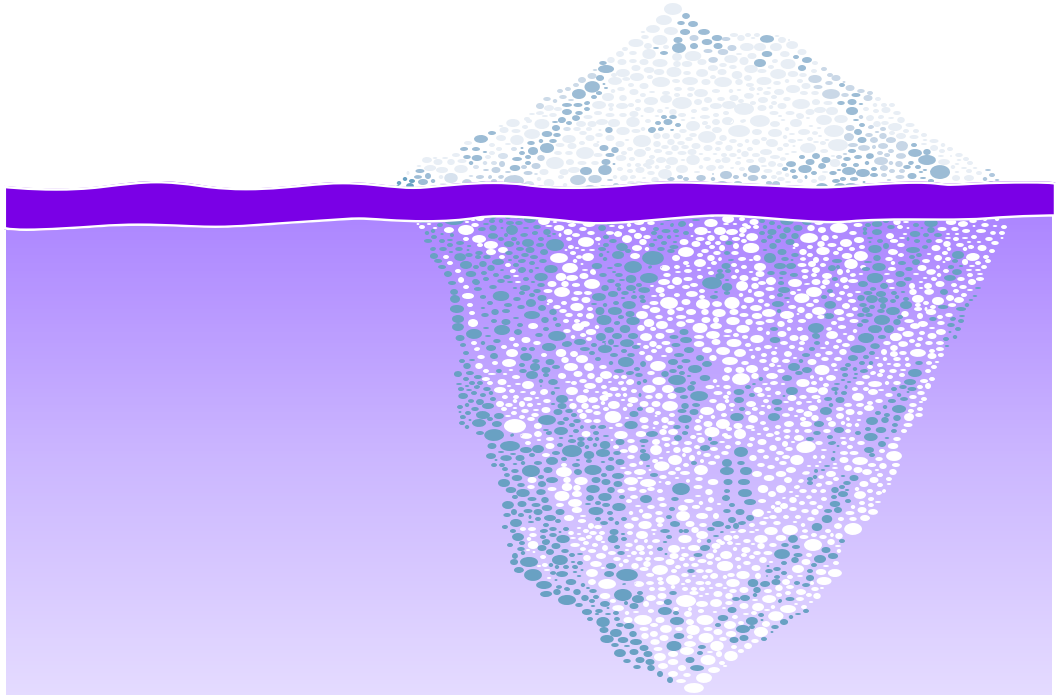
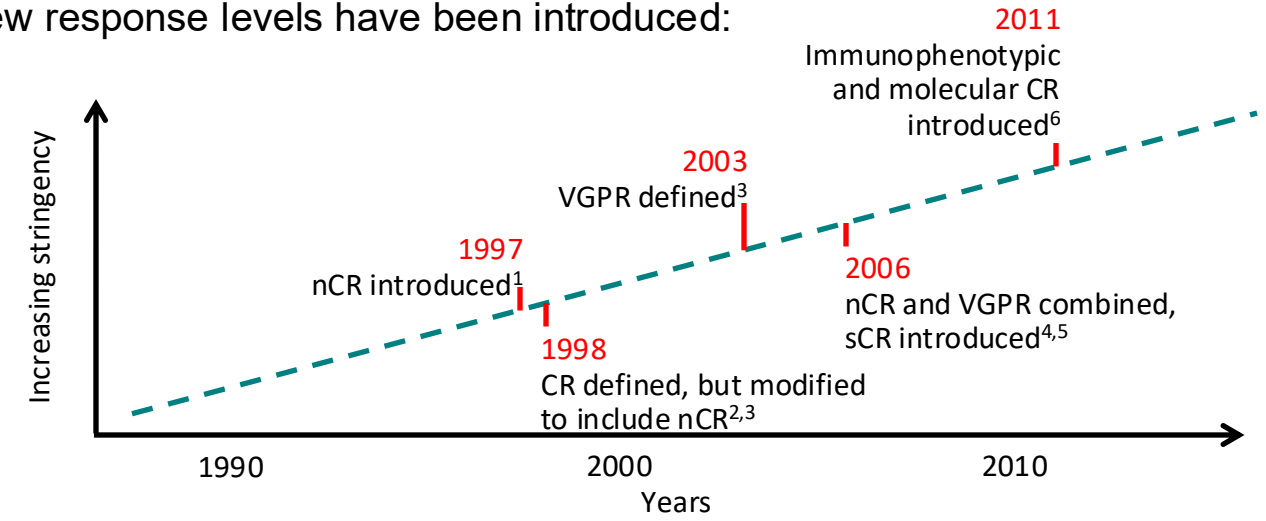


More ambitious treatment goals demand increasingly rigorous response criteria

- The treatment of MM has improved significantly: access to better drugs.

- Using combination of active agents, high response rates have been observed with significantly more CR, and longer PFS.

- Over time new response levels have been introduced:



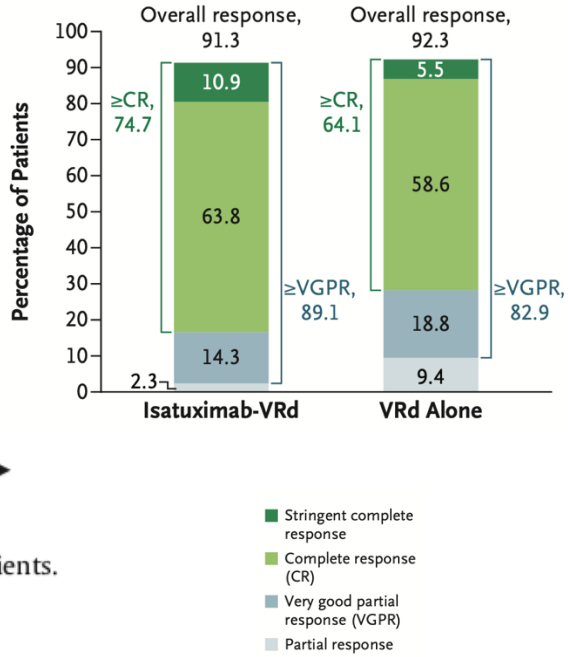
1. Ballester OF, et al. Br J Haematol 1997;96:746–748; 2. Bladé J. Br J Haematol 1998;102:1115–1123; 3. Richardson PG, et al. Oncology (Williston Park) 2005;19:1781–1792; 4. Durie BG, et al. Leukemia 2006;20:1467–1473; 5. Kyle RA, Rajkumar SV. Leukemia 2009;23:3–9; 6. Rajkumar SV, et al. Blood 2011;117:4691–4695.

More ambitious treatment goals demand increasingly rigorous response criteria

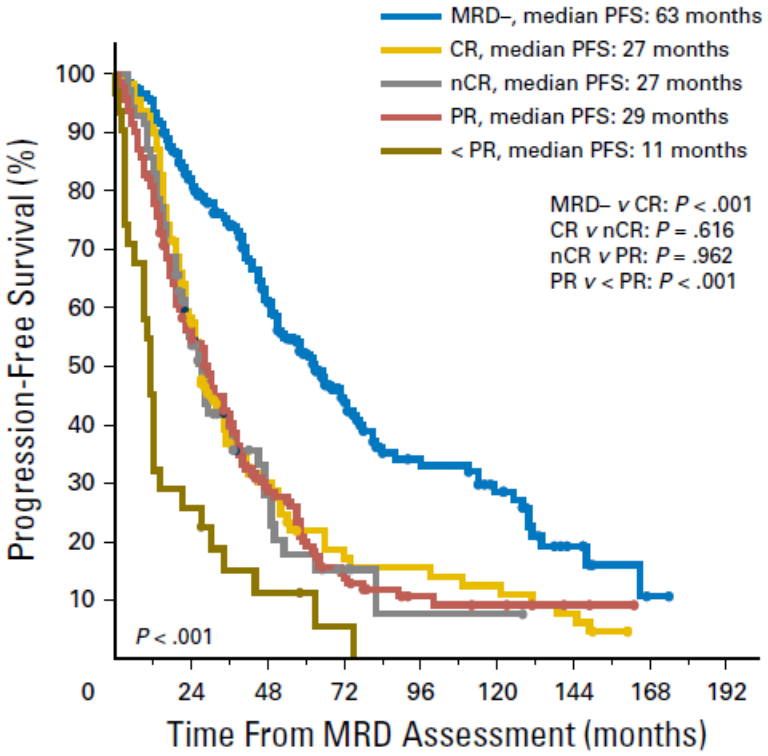
Therapy			
Older chemotherapy	VAD combination chemotherapy followed by transplant	Modern 3-drug combination therapy +/- transplant	Modern 3- or 4-drug combination therapy +/- transplant
Response to therapy			
Inferior responses	Very low rates of complete response (CR) due to toxic and inferior therapy	Starting to see MRD negativity in clinical trials; already up to 40-50% MRD negativity and rising (see Table 1)	Higher MRD rates: (when?) will MRD testing become a tool for clinical decision making in standard clinical practice?
	1950s-	Mid-1990s	2010s	2020-future

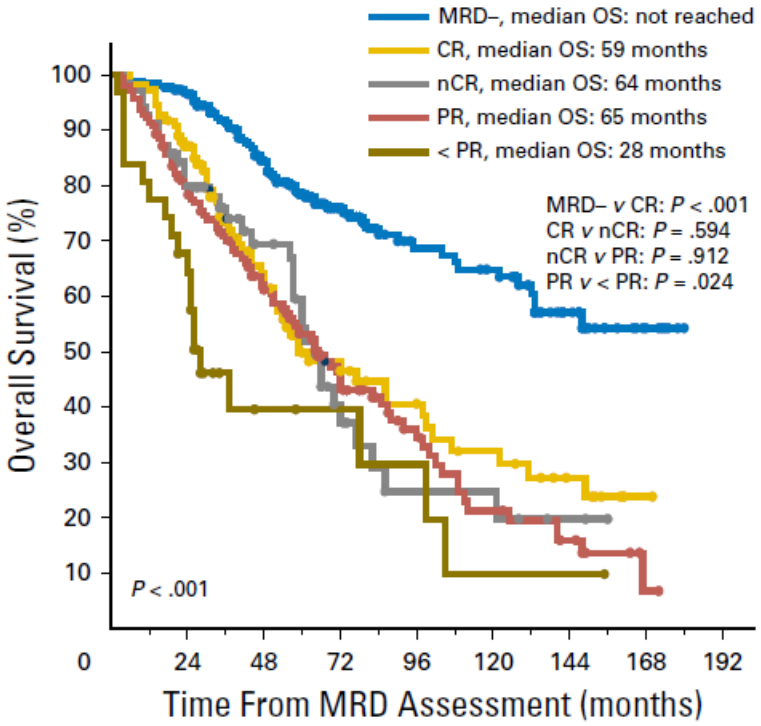
Fig. Evolution and future directions for therapy and MRD testing in newly diagnosed multiple myeloma patients.

IMROZ



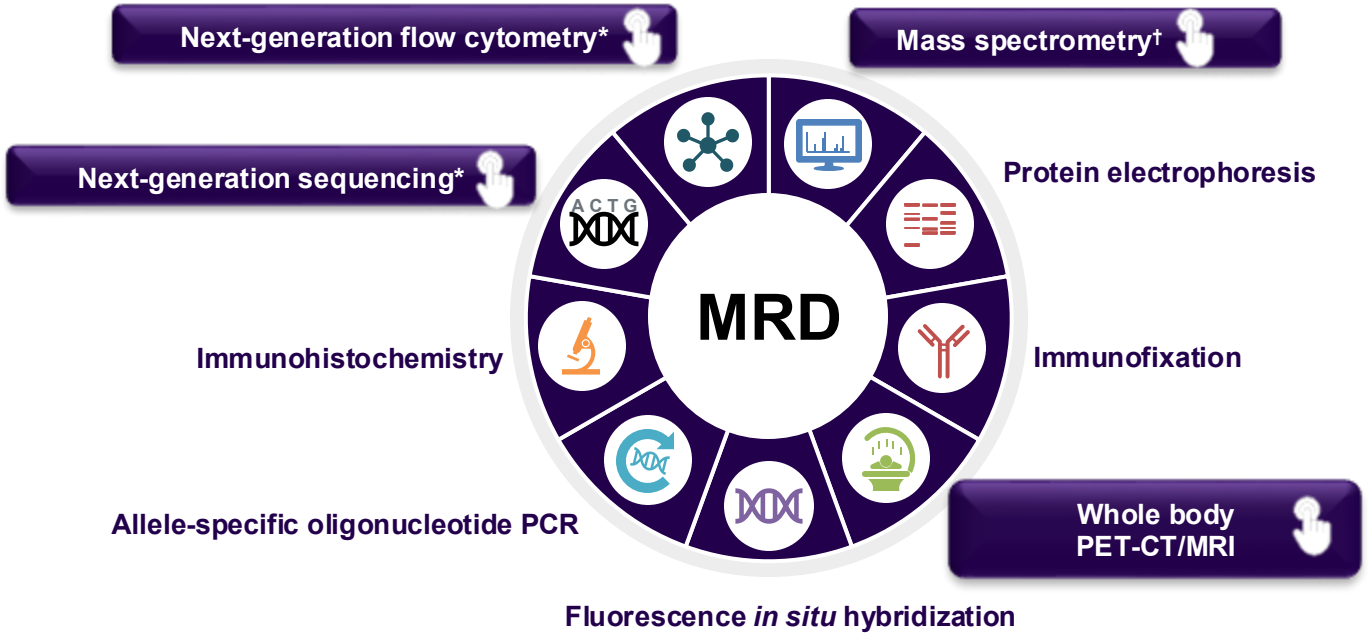
The value of CR relies in the MRD status
CR w/o MRD negativity is no better than PR





Lahuerta JJ et al. J. Clin Oncol. 2017

Techniques used to measure MRD[1–6]



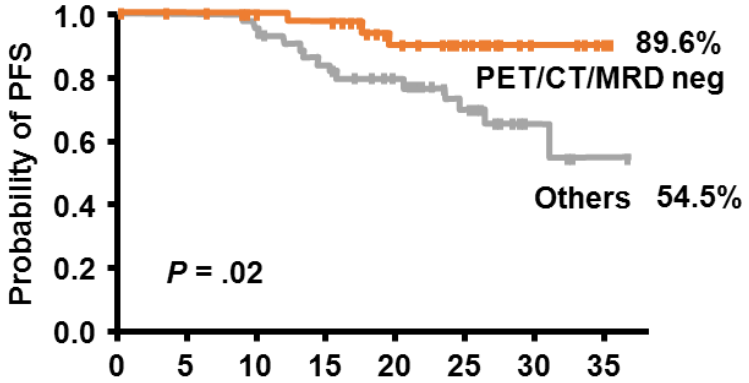
NGS and NGF are the most commonly used techniques to assess MRD status and are required as part of the IMWG definition for MRD response

*Required by IMWG to meet MRD response criteria[1] †Technique in development
IMWG, International Myeloma Working Group; MRD, minimal residual disease; MRI, magnetic resonance imaging; NGF, next-generation flow; NGS, next-generation sequencing; PCR, polymerase chain reaction; PET-CT, positron emission tomography-computed tomography

1. Kumar S, et al. Lancet Oncol 2016;17:e328–46;
2. Avet-Loiseau H, et al. Am Soc Clin Oncol Educ Book 2016;35:e425–30;
3. Flores-Montero J, et al. Leukemia 2017;31:2094–103;
4. Bolli N, et al. Front Oncol 2020;10:189;
5. Murray DL, et al. Blood Cancer J 2021;11:24;
6. Zamagni E, et al. J Clin Med 2020;9:3519

PET/CT and MRD Negativity as Predictor for PFS[1-2]

	PET/CT Positive	PET/CT Negative
MRD positive	11	20
MRD negative	14	41



IMPeTUs CRITERIA (Italian Myeloma Criteria for PET USe)

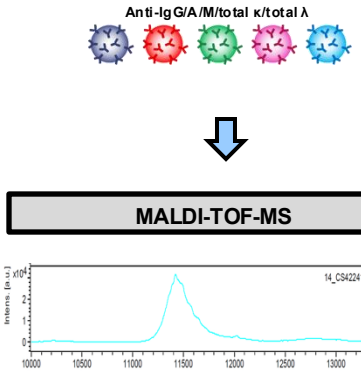
PET Response After Therapy	Response Criteria
Complete metabolic response	Uptake ≤ liver activity in BM sites and FLs previously involved (including extramedullary and paramedullary disease [DS score 1-3])
Partial metabolic response	Decrease in number and/or activity of BM/FLs present at baseline, but persistence of lesion(s) with uptake > liver activity (DS score 4 or 5)
Stable metabolic disease	No significant change in BM/FLs compared with baseline
Progressive metabolic disease	New FLs compared with baseline consistent with myeloma

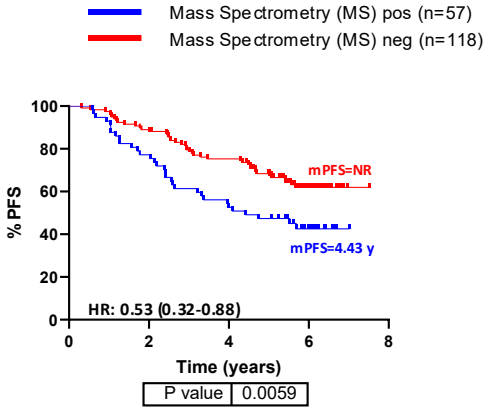
Abbreviations: BM, bone marrow; DS, Deauville scale; FL, focal lesion; PET, positron emission tomography.

Can we perform MRD on peripheral blood?

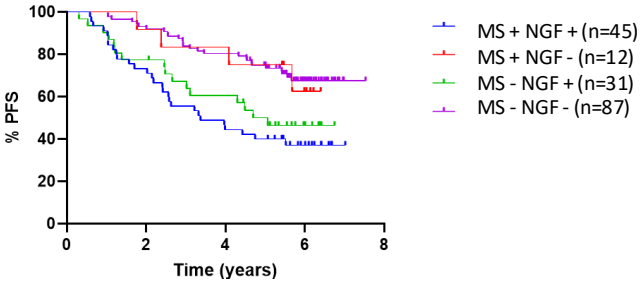
Mass spectrometry

Peripheral blood serum sample





P value	0.0059



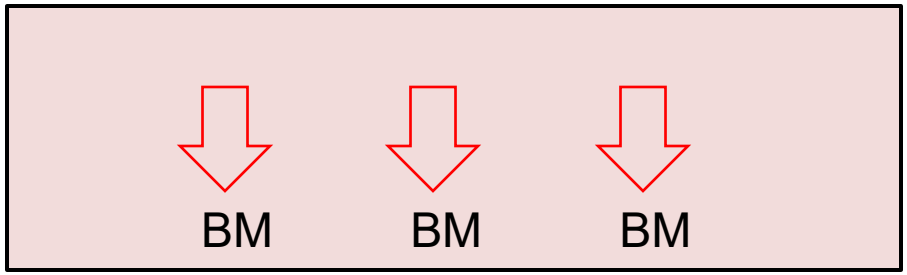
Test	Fisher's exact test	
P value	<0.0001	
Sensitivity	0.5921	0.4798 to 0.6956
Specificity	0.8788	0.8000 to 0.9293
Positive Predictive Value	0.7895	0.6671 to 0.8753
Negative Predictive Value	0.7373	0.6513 to 0.8083

N Puig et al IMS 2022

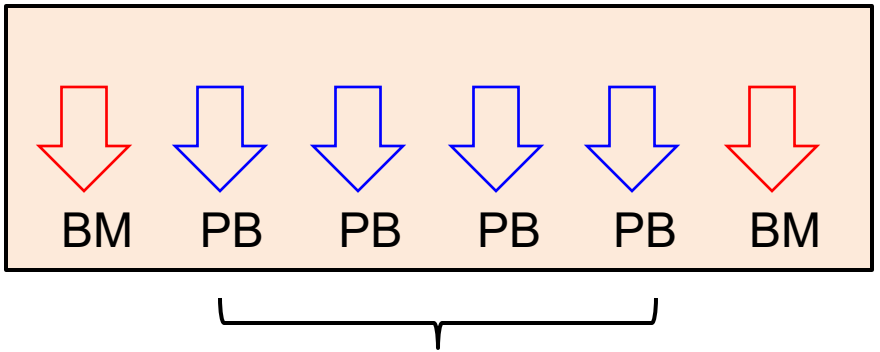
Minimally invasive MRD assessment at late time points

Hypothetical scenario to assess MRD in BM and PB

MRD assessment during induction/intensification



MRD assessment during maintenance/observation



...still BM win !!

Courtesy of Bruno Paiva

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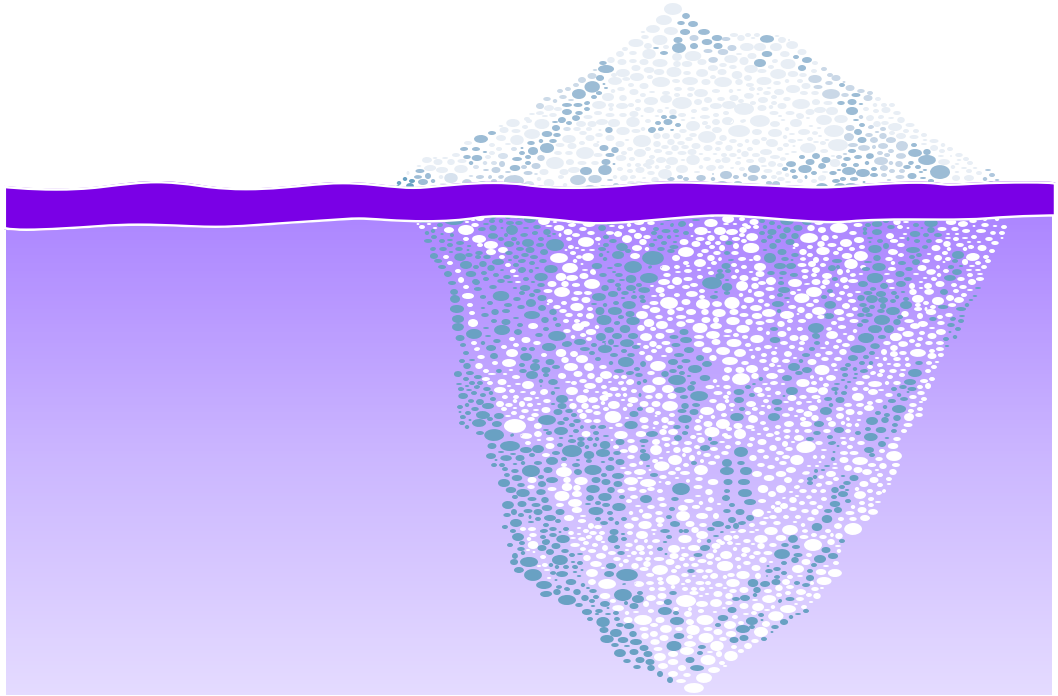
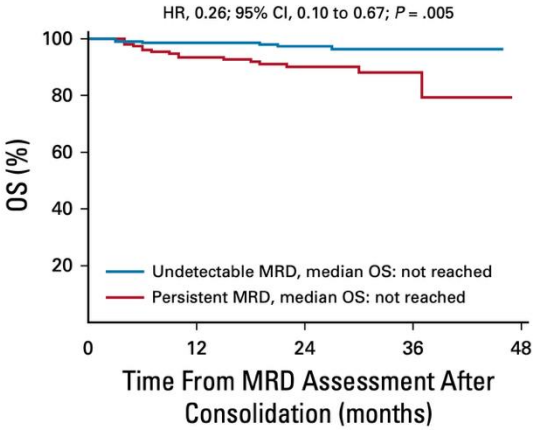
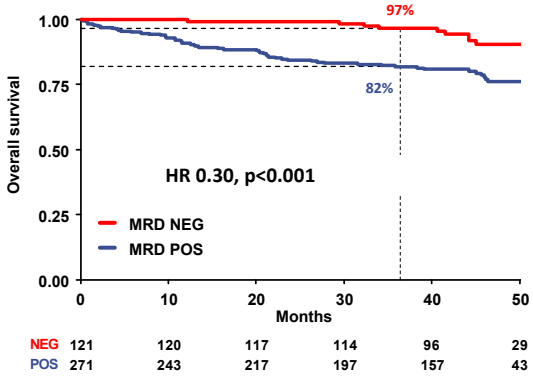


Bone Marrow MRD: NGF or NGS?

Next generation flow (NGF) EuroFlow Sensibility 10-5



Next generation sequencing (NGS) clonoSEQ® Sensibility 10-5



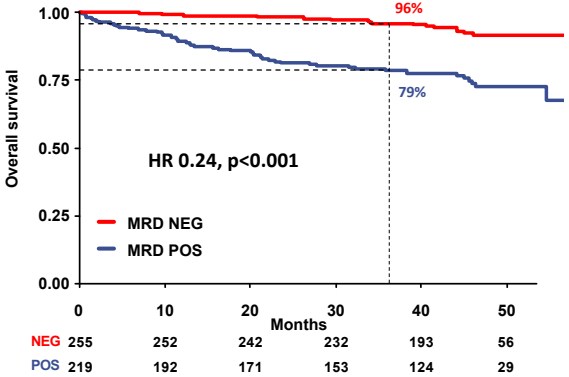
	Next-generation flow (NGF)	Next-generation sequencing (NGS)
Applicability	Nearly 100%	≥90%
Availability	Many laboratories with 4–6 colors; >8 colors restricted to more specialized centers	Commercial service only; ongoing efforts by academic platforms
Diagnostic sample	Not required	Required for identification of dominant clonotype
Number of cells required	10 million cells/tube	1–2 million cells/20 μg DNA
Sample processing	Requires a fresh sample; assessment within 24–48 h	Can use both fresh and stored samples
Standardization	EuroFlow consortium	Commercial companies (Adaptive Biothcnologies) Academic methodologies also available
Sample quality control	Possible to check by global bone marrow cell analysis	Not possible
Quantitative	Yes	Yes
Sensitivity	1 in 10^{-5}-10^{-6}	1 in 10^{-5}-10^{-6}
Turnaround and complexity	3–4 h. Requires flow cytometry skills. Automated software available	1 week. Academic methodologies require bioinformatics support
Clonal evolution	Not evaluable	Evaluable: can take into account all minor clones

MRD, minimal residual disease.

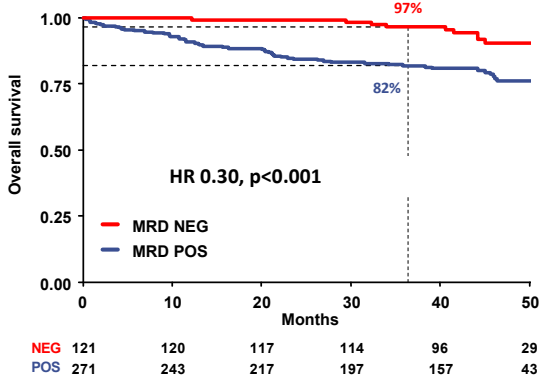
Bruno Paiva et al. J Clin Oncol 38:784-792 2019; Oliva S et al. ASH 2020, Oliva S et al, EClinicalMedicine 2023; Oliva s et al Front. Oncol. 2020

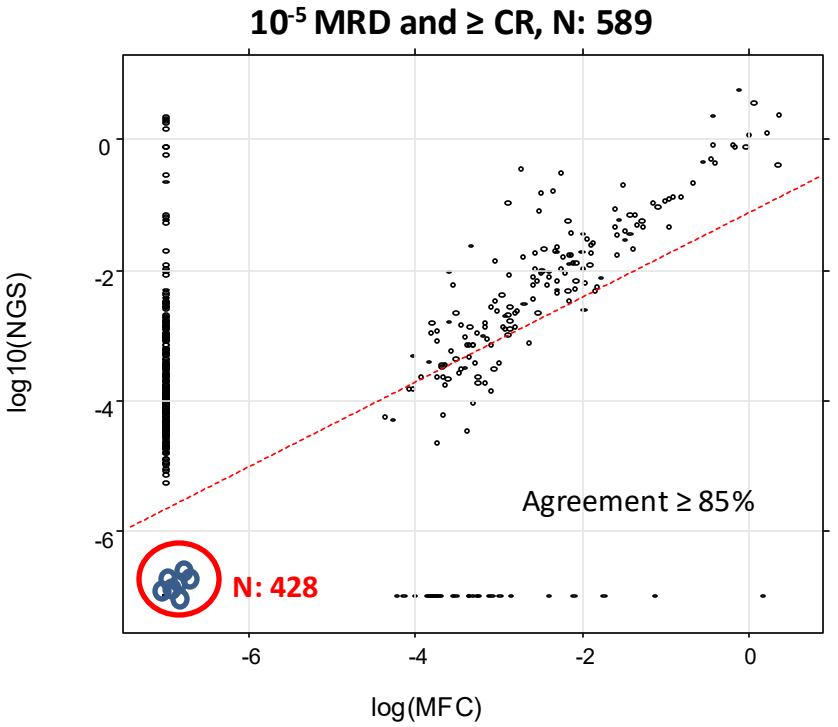
Good concordance between Flow and Sequencing MRD

Flow 10^{-5}



NGS 10^{-5}

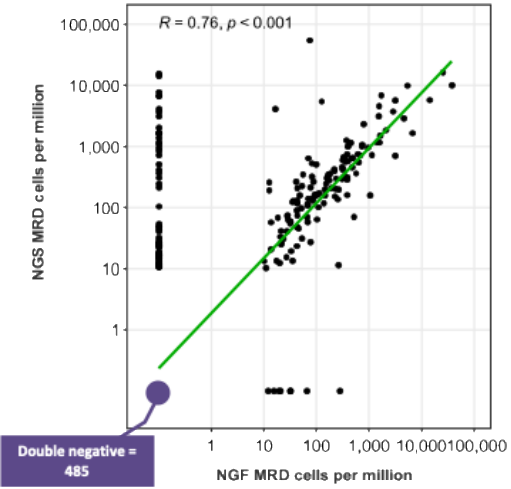




Oliva S et al, EClinicalMedicine 2023

NGF/NGS concordance at 10^{-5} vs $2*10^{-6}$ sensitivity

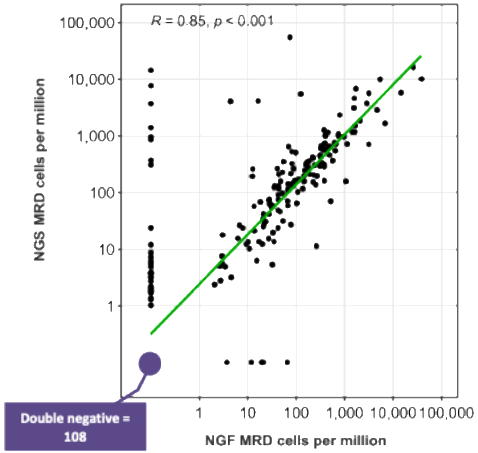
10^{-5}



Concordance: 89%
Cohen's κ: 0.70 (95% CI 0.64–0.76)
p<0.0001

NGF prediction of NGS status:
Sensitivity 65% (58–72%)
Specificity 98% (97–99%)
PPV 94% (89–97%)
NPV 88% (85–90%)

$2*10^{-6}$



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Cohen's κ: 0.80 (95% CI 0.73–0.87)
p<0.0001

NGF prediction of NGS status:
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Specificity 96% (91–99%)
PPV 97% (92–99%)
NPV 83% (75–89%)

D'Agostino et al IMS 2025

NGS, next-generation sequencing; NGF, next-generation flow; ASCT, autologous stem-cell transplantation; VGPR, very good partial response; CR, complete response; Pos, positive; Neg, negative; PPV, positive predictive value; NPV, negative preictive value.

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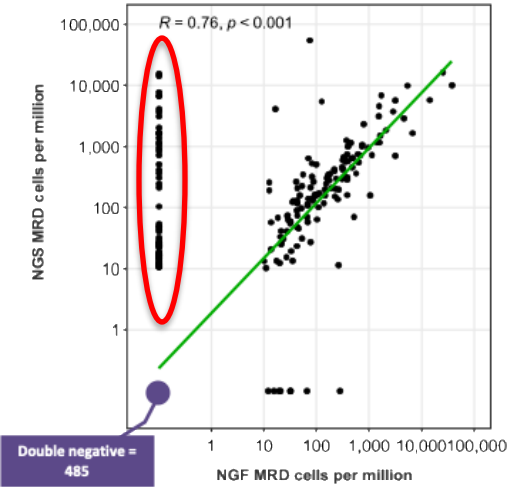
10^{-5}



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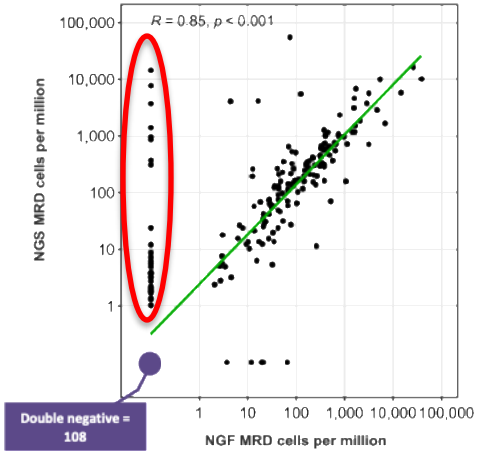

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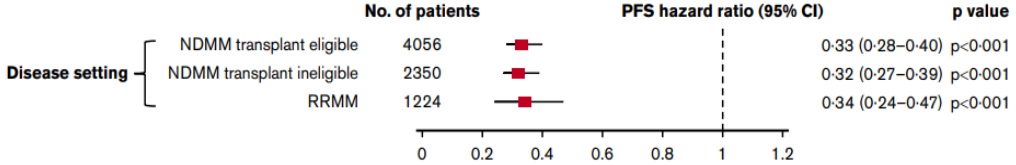
Overall effect of MRD status on PFS and OS

- 4 metanalysis published #, *

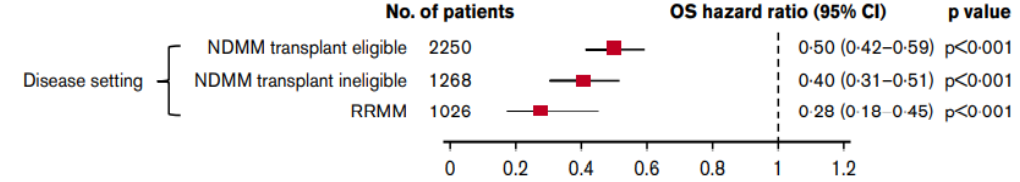
~ > 100 publications supporting MRD effect on PFS/OS

- Single strongest prognostic tool in Multiple Myeloma

PFS



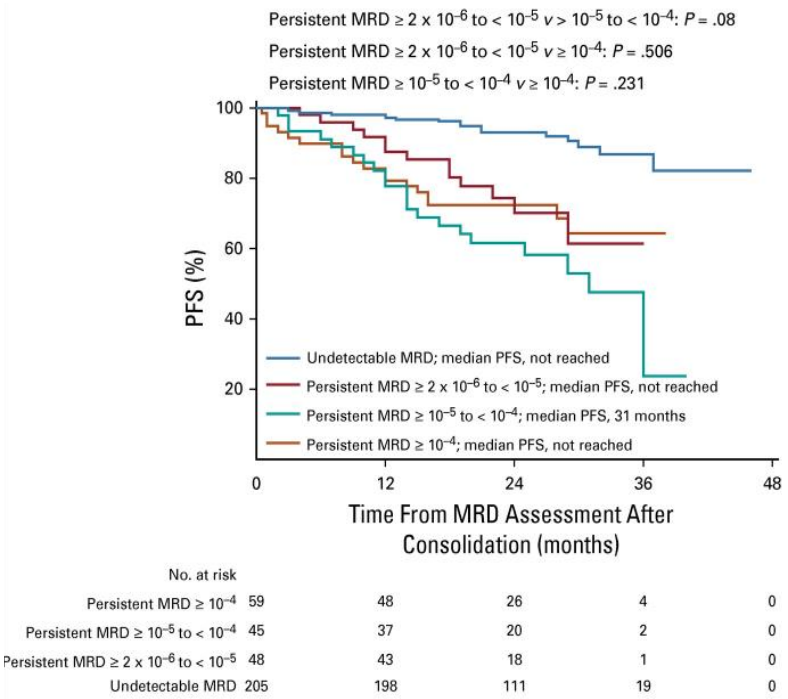
OS



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.

Positive MRD in the logarithmic range of 10^{-6} is clinically relevant

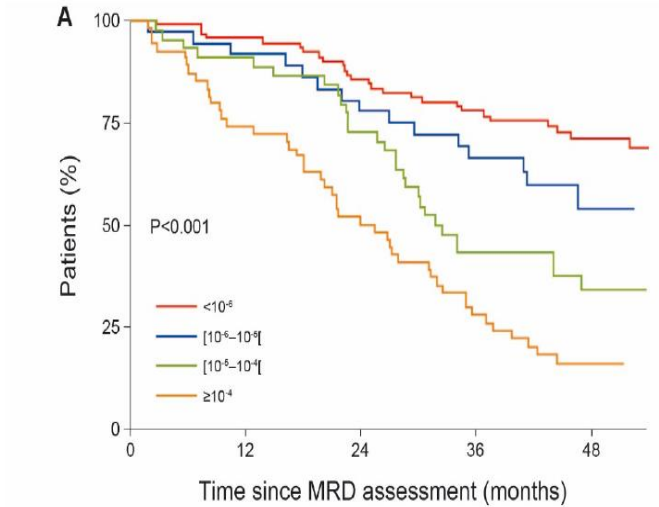
NGF



No. at risk					
Persistent MRD ≥ 10^{-4}	59	48	26	4	0
Persistent MRD ≥ 10^{-5} to < 10^{-4}	45	37	20	2	0
Persistent MRD ≥ 2 x 10^{-6} to < 10^{-5}	48	43	18	1	0
Undetectable MRD	205	198	111	19	0

Paiva B, et al. JCO. 2020

NGS

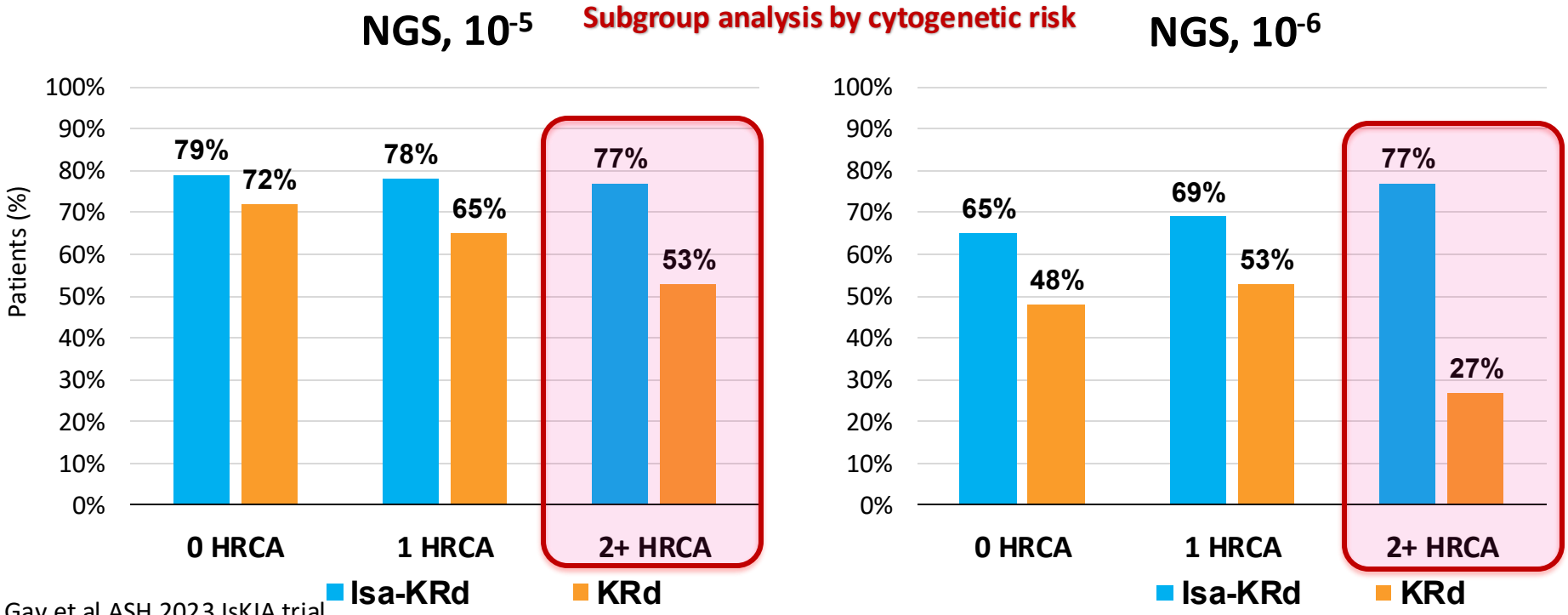


No. at Risk					
<10^{-6}	90	86	77	69	49
[10^{-6}–10^{-5}[	36	33	28	22	9
[10^{-5}–10^{-4}[	44	40	32	19	10
≥10^{-4}	54	40	27	15	7

Perrot A, et al. Blood. 2018

Positive MRD in the logarithmic range of 10^{-6} is clinically relevant

Post-consolidation MRD negativity by NGS
Subgroup analysis by cytogenetic risk



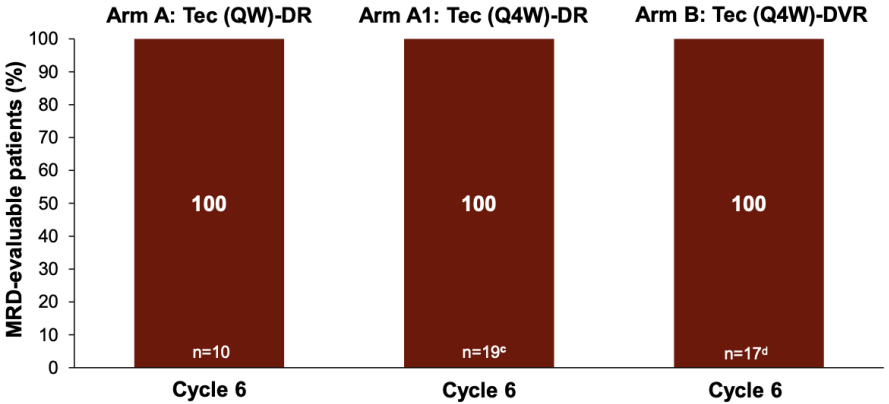
Gay et al ASH 2023 IsKIA trial

1 HRCA was defined as the presence of one of the following high-risk cytogenetic abnormalities: del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21); 2+ HRCA was defined as the presence of at least two high-risk cytogenetic abnormalities.

MRD, minimal residual disease; NGS, next-generation sequencing; HRCA, high-risk cytogenetic abnormalities; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; del, deletion; t, translocation; amp, amplification

Is 10^{-6} enough?

MajesTEC 5→100% MRD neg at 10^{-6} after induction



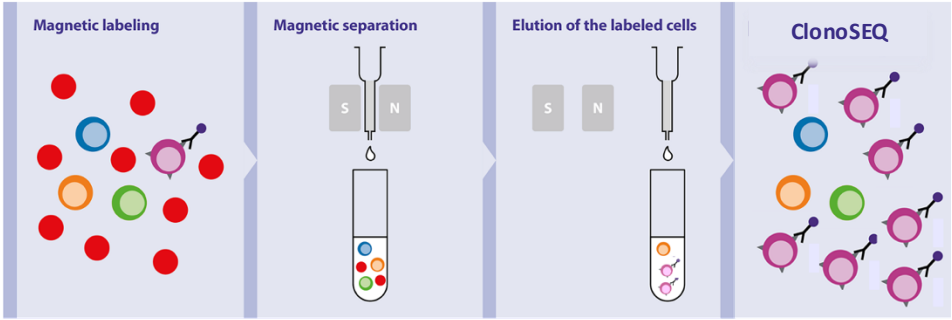
- When combining all patients across all arms (n=49), cumulative MRD-negativity rate[e] by end of induction in the efficacy analysis set was 98.0%
- 85.7% (42/49) of patients achieved ≥CR and MRD negativity at Cycle 6 (≤10^{-5})

100% of patients in the MRD-evaluable population,[b] regardless of depth of response, achieved MRD negativity (10^{-6}) at Cycle 6

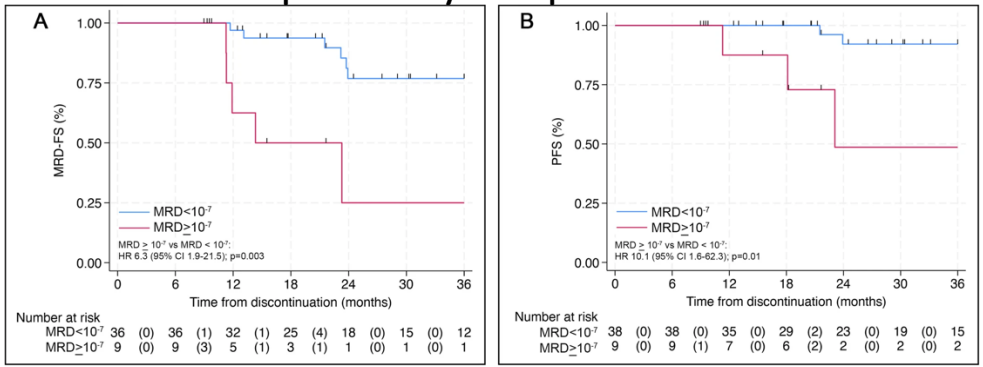
[a]MRD-negativity rate was defined as the proportion of patients who achieved MRD negativity (10^{-6}), regardless of response. [b]MRD-evaluable population defined as those patients with an available MRD test with a positive or negative result (excluding those who were not tested, were indeterminate, or had no baseline clone detected [NGS]). [c]One patient had discontinued after completing Cycle 3. [d]One patient had discontinued before completing Cycle 3, and 1 had no baseline clone detected for NGS. [e]Patients who achieved MRD negativity at 10^{-5} or 10^{-6} at any time on study (post-induction cycle 3 or cycle 6). D, daratumumab; DSMM, Deutsche Studiengruppe Multiples Myelom; GMMG, German-speaking Myeloma Multicenter Group; MRD, minimal residual disease; NGF, next-generation flow cytometry; NGS, next-generation sequencing; QW, weekly; Q4W, every 4 weeks; R, lenalidomide; Tec, teclistamab; V, bortezomib.

Presented by MS Raab at the 22nd International Myeloma Society (IMS) Annual Meeting; September 17-20, 2025; Toronto, Canada

Is 10^{-6} enough?
MRD2STOP trial

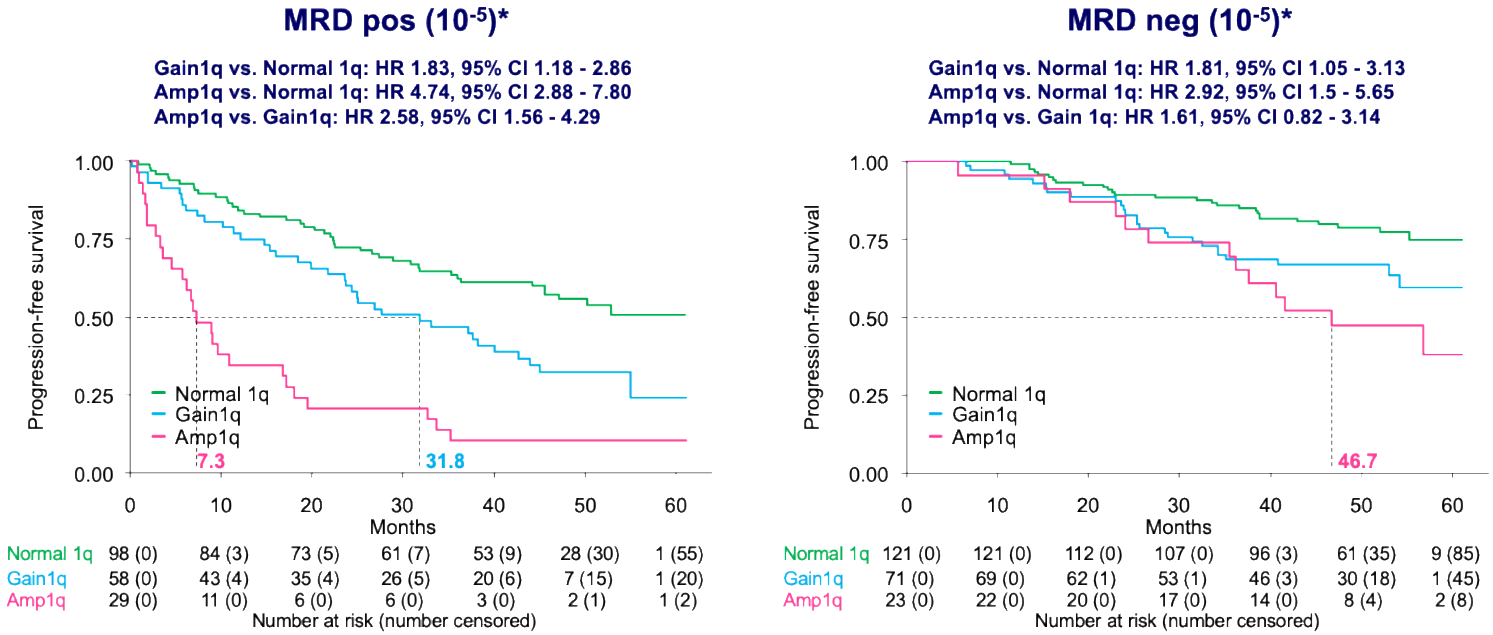


Exploratory endpoint: MRD 10-7



Derman B A et al BCJ 2024

MRD alone or MRD + baseline risk stratification?



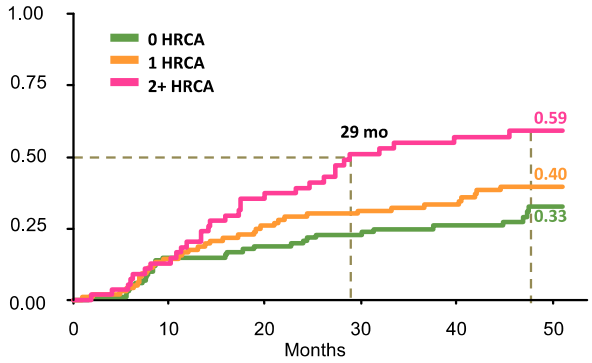
Analysis performed by multiparameter flow cytometry (MFC) before maintenance in the intention-to-treat population.

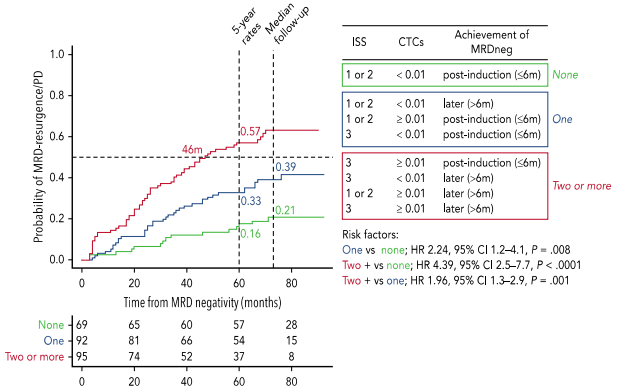
D'Agostino M. et al BCJ 2024

PFS: progression-free survival; HR, hazard ratio; MRD: minimal residual disease, POS, positivity; NEG, negativity.

Risk of losing MRD negativity over time

MRD resurgence from first MRD negativity





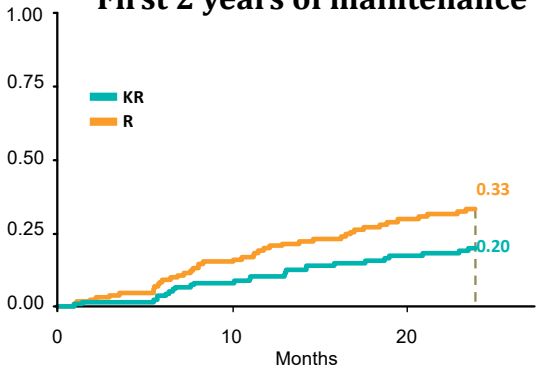
ISS	CTCs	Achievement of MRDneg	
1 or 2	< 0.01	post-induction (≤6m)	None
1 or 2	< 0.01	later (>6m)	One
1 or 2	≥ 0.01	post-induction (≤6m)	One
3	< 0.01	post-induction (≤6m)	One
3	≥ 0.01	post-induction (≤6m)	Two or more
3	< 0.01	later (>6m)	Two or more
1 or 2	≥ 0.01	later (>6m)	Two or more
3	≥ 0.01	later (>6m)	Two or more

Risk factors:
One vs none; HR 2.24, 95% CI 1.2–4.1, $P = .008$
Two + vs none; HR 4.39, 95% CI 2.5–7.7, $P < .0001$
Two + vs one; HR 1.96, 95% CI 1.3–2.9, $P = .001$

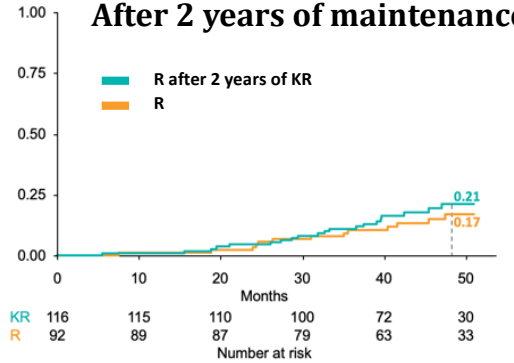
D'Agostino M et al, Blood 2024; Guerrero C et al, Blood 2024.
Abbreviations R; lenalidomide; K carfilzomib; HRCA: high-risk chromosomal abnormalities

FORTE trial: KR vs R maintenance

First 2 years of maintenance

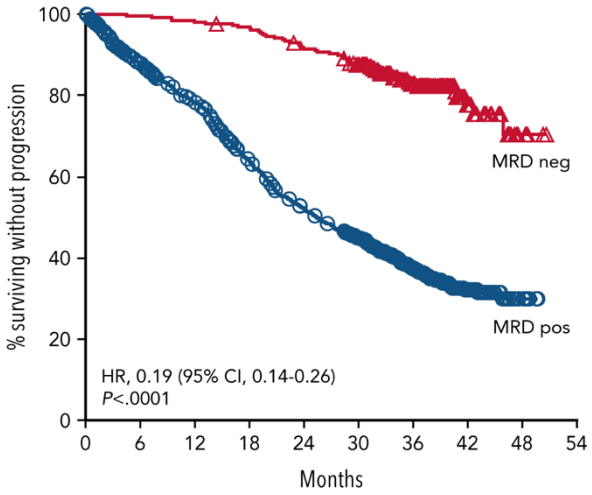


After 2 years of maintenance

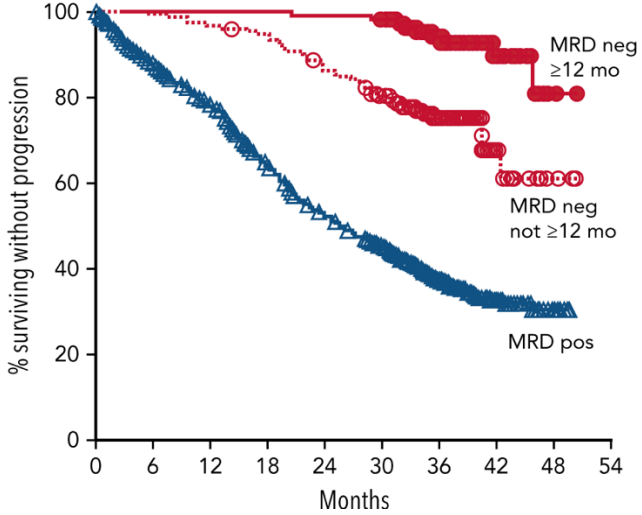


Sustained MRD negativity is clinically relavant

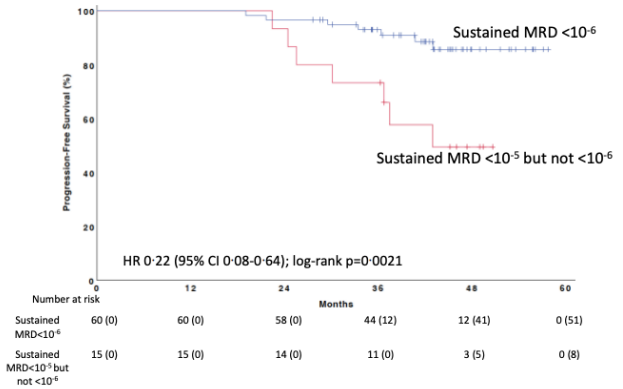
MRD negativity has prognostic impact



Sustained MRD negativity for 12 months has more powerful prognostic impact



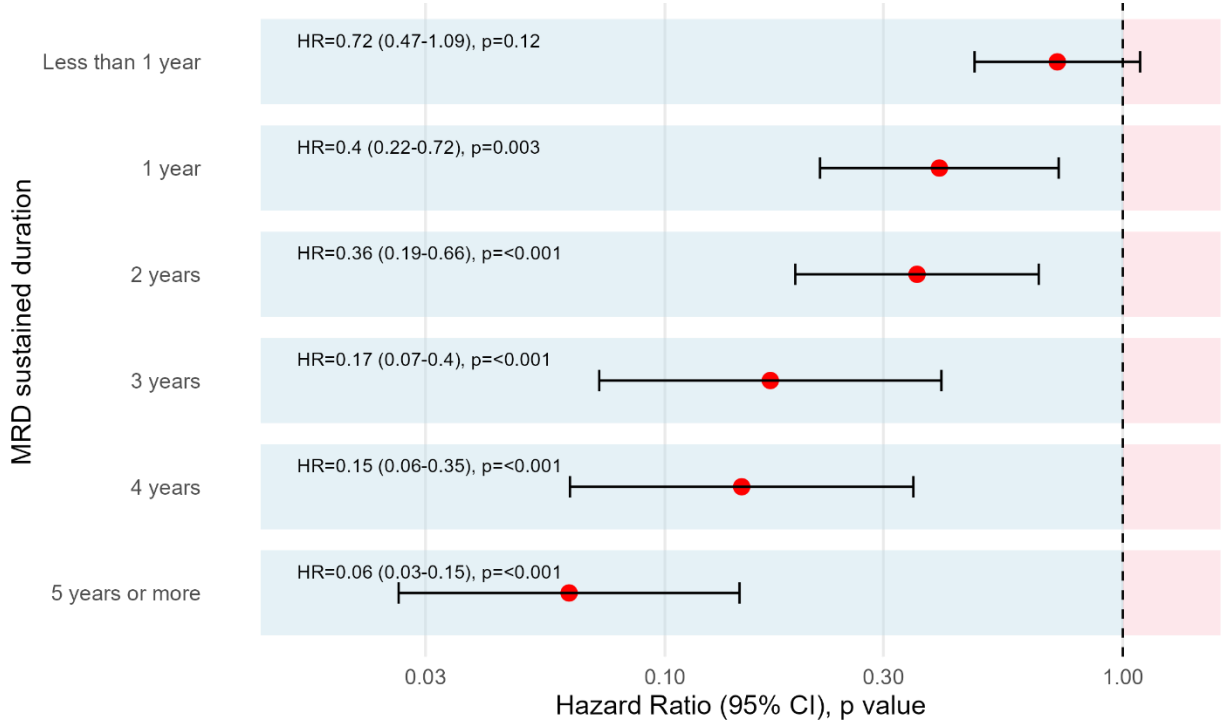
MASTER trial: sustained MRD negativity 10^{-6}



Maia and Alcyione trial, MRD by NGS at 10^{-5} San Miguel J et al. Blood (2022) 139 (4): 492–501. MASTER trial Costa L et al Lancet Haematol 2023; 10: e890–901

How many years of Sustained MRD negativity?

FORTE trial long term follow-up

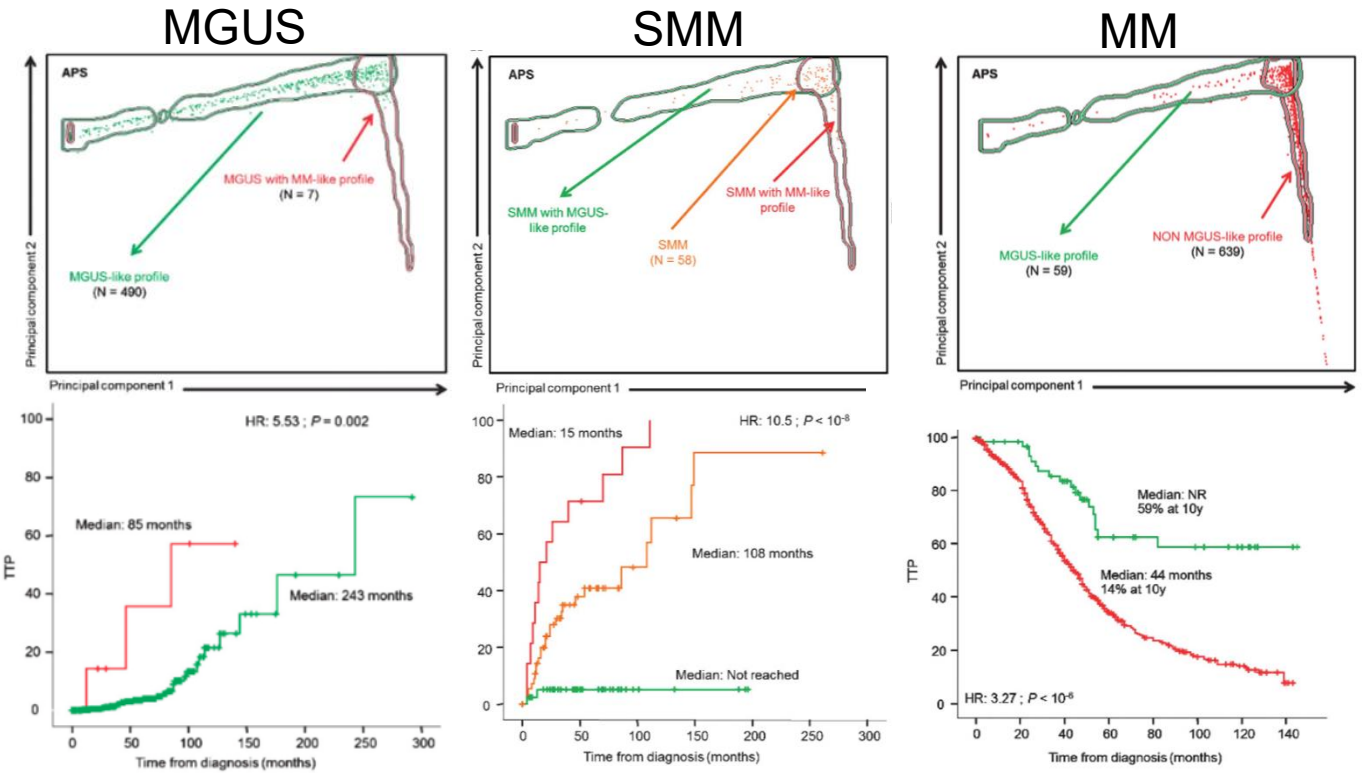


Manuscript in preparation

MGUS-like profile: Do we always need deep responses?

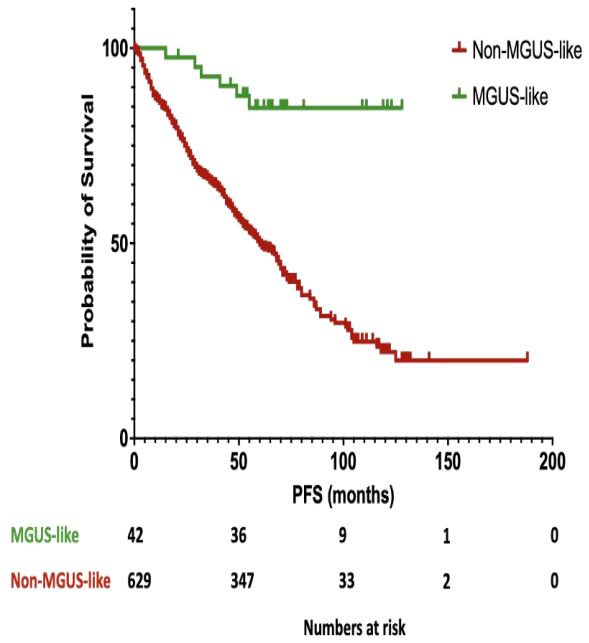
Degree of clonality of the bone marrow (BM) plasma-cell (PC) compartment at diagnosis

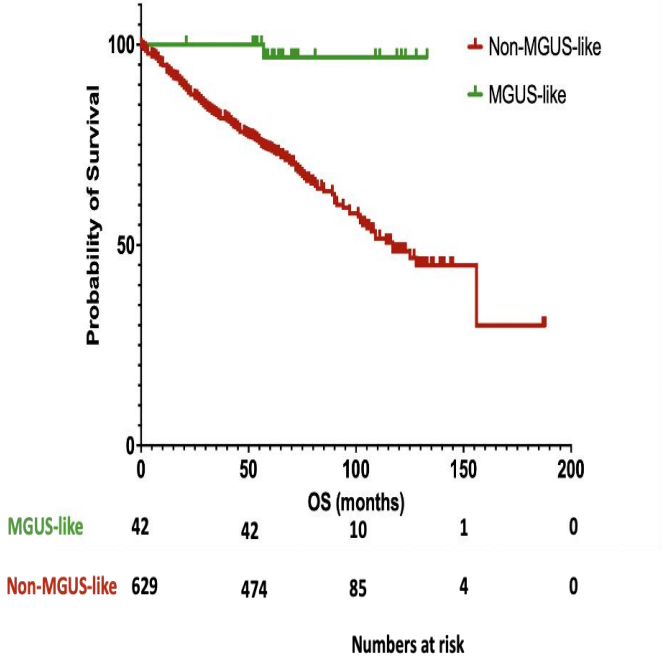
Outcome

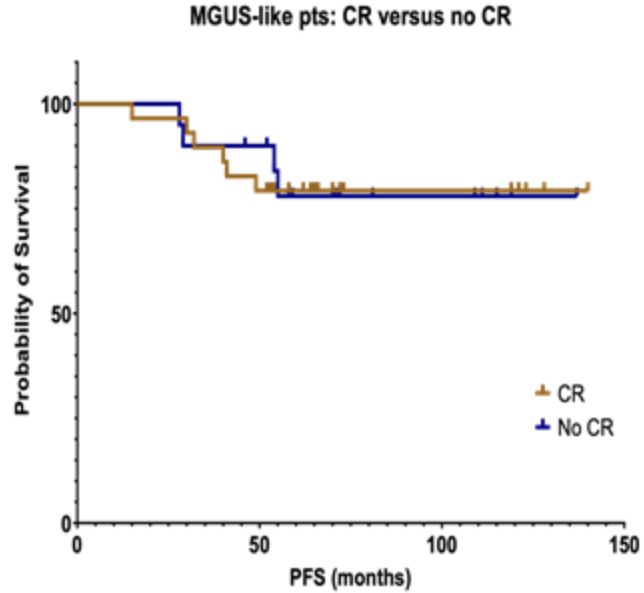


Paiva et al Leukemia (2013)

MGUS-like profile: Do we always need deep responses?







Burgos L et al ASH 2021

Let’s dive deep into Measurable Residual Disease (MRD)

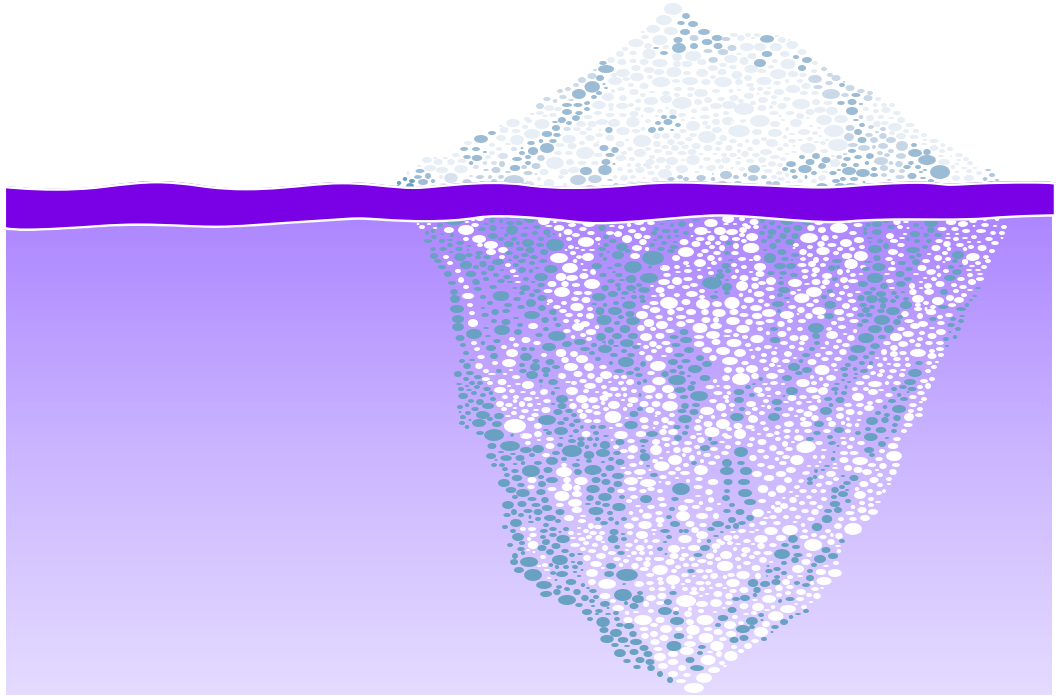
MRD: why we need it

MRD as a prognostic marker

MRD as an endpoint in clinical trials

MRD as an adaptive treatment tool

Integrating MRD in clinical practice

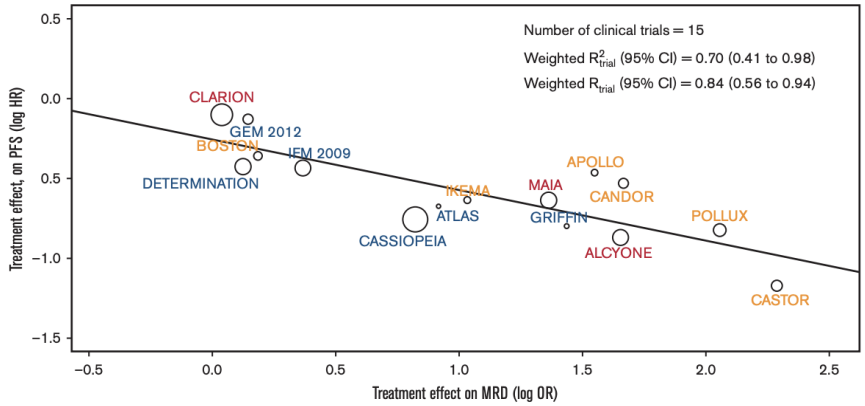


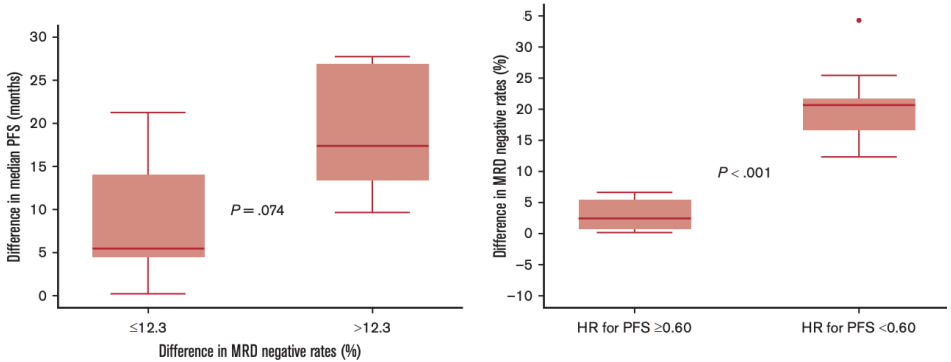
FDA ODAC voted 12-0 to recommend MRD as a MM Endpoint

On April 12, 2024, FDA ODAC voted 12-0 in favor of using minimal residual disease (MRD) as an accelerated approval endpoint in multiple myeloma clinical trials

Conclusion: The Applicants have worked with the broader MM community to develop a novel endpoint of MRD that has the potential to expedite drug development in MM. While there are still outstanding questions on how to best use MRD, the meta-analyses conducted **(University of Miami and IMF led i2TEAMM**) represent robust assessments of MRD that support its prognostic value, provide information regarding the appropriate timing of MRD assessment, and suggest that MRD may be appropriate to use as an intermediate clinical endpoint to support accelerated approval.

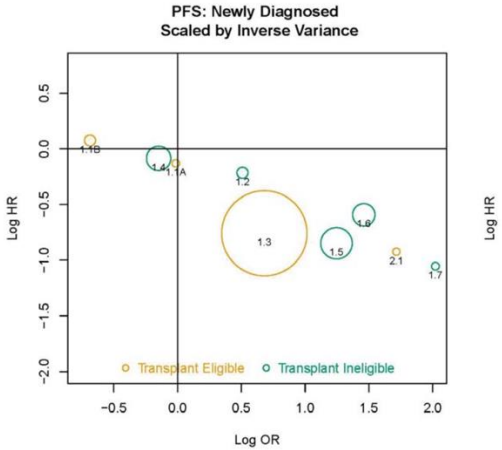
Treatment effect in PFS according to MRD-negative rates





Paiva B et al Blood Advances 2024

Correlation Between 12-months MRD negativity and PFS



Landgren O et al Blood 2024

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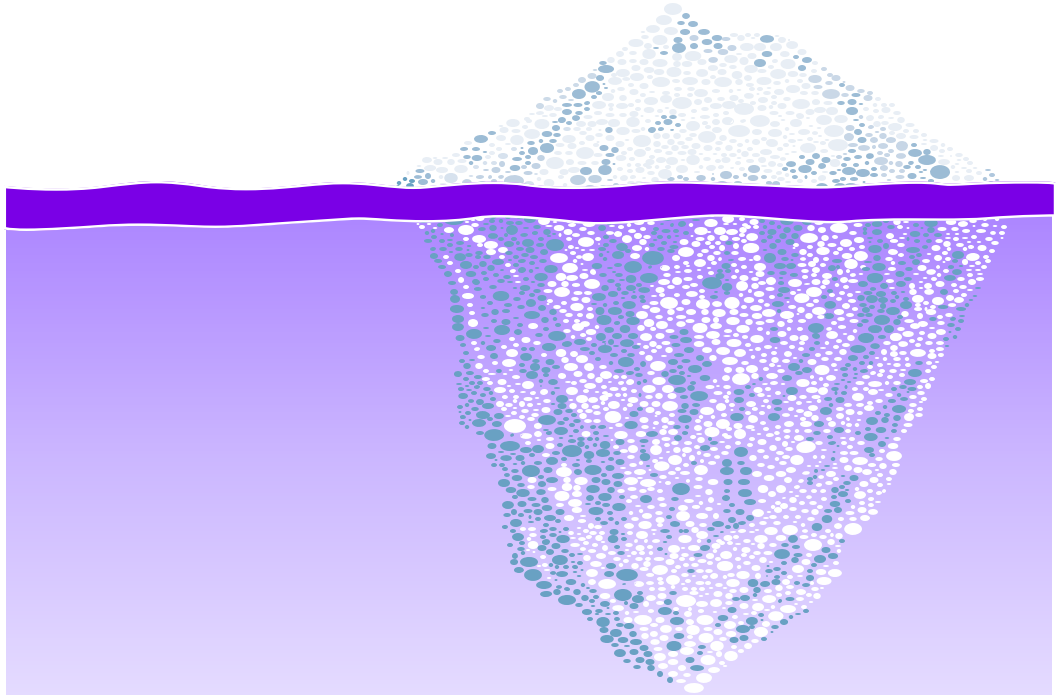
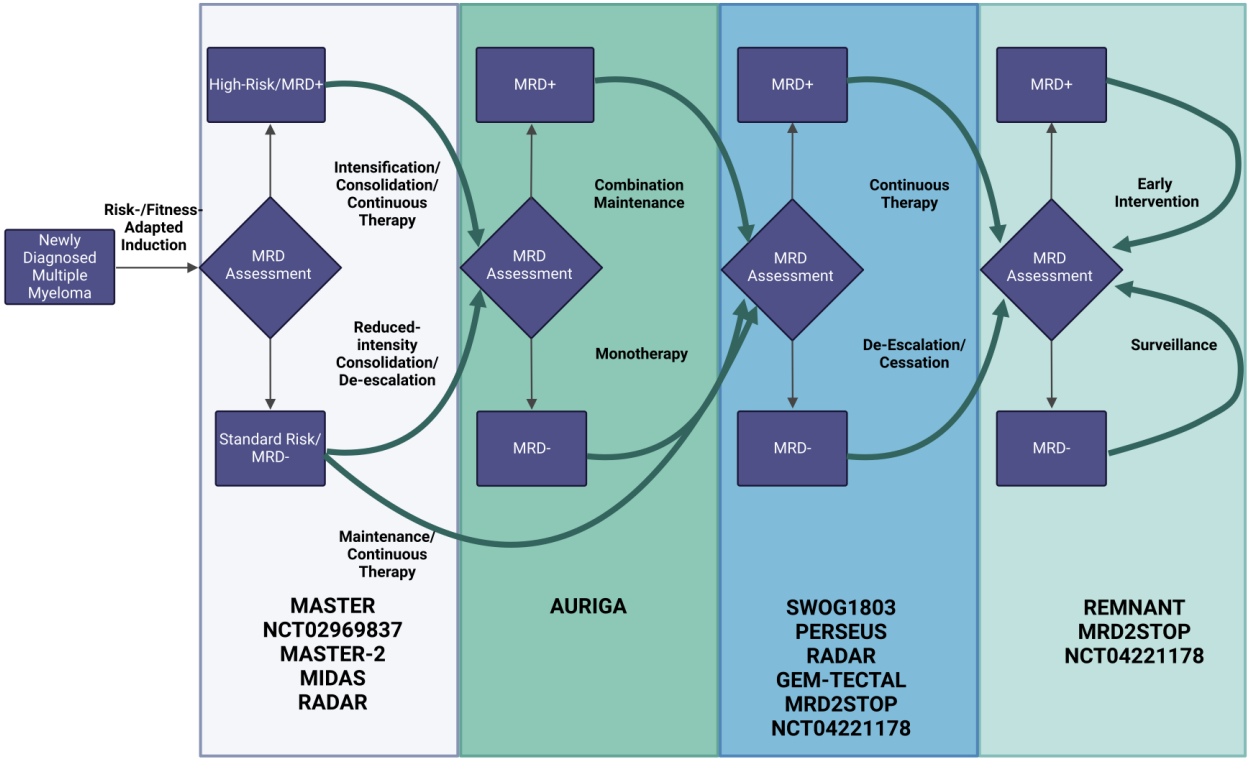


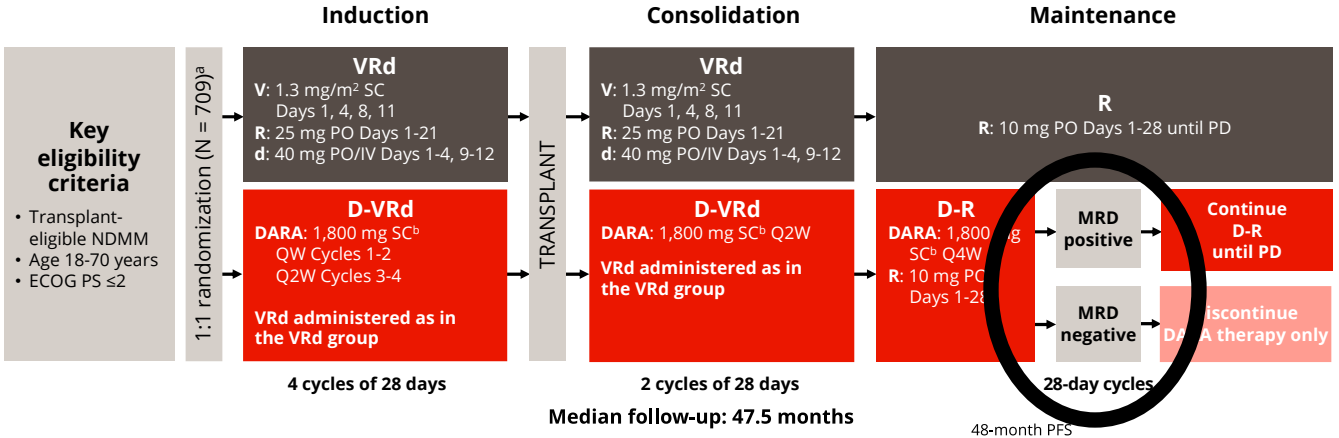
MRD driven strategies in NDMM

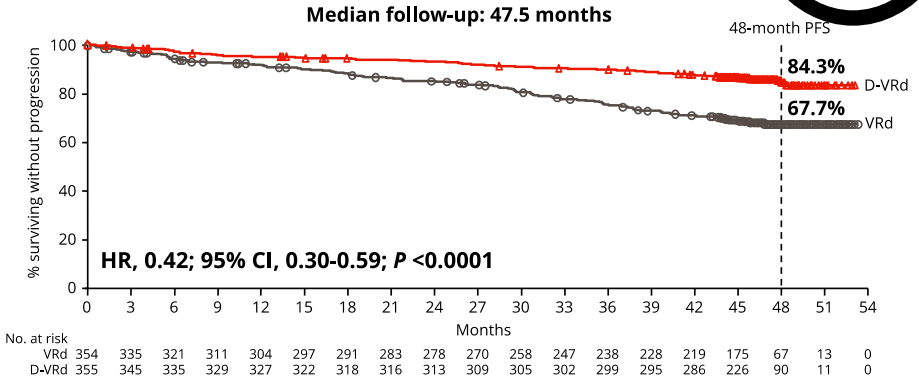


Meseha M et al Current Oncology Reports (2024) 26:679–690

Unanswered questions: How can we can exploit MRD to perform clinical decisions?

PERSEUS: STUDY DESIGN

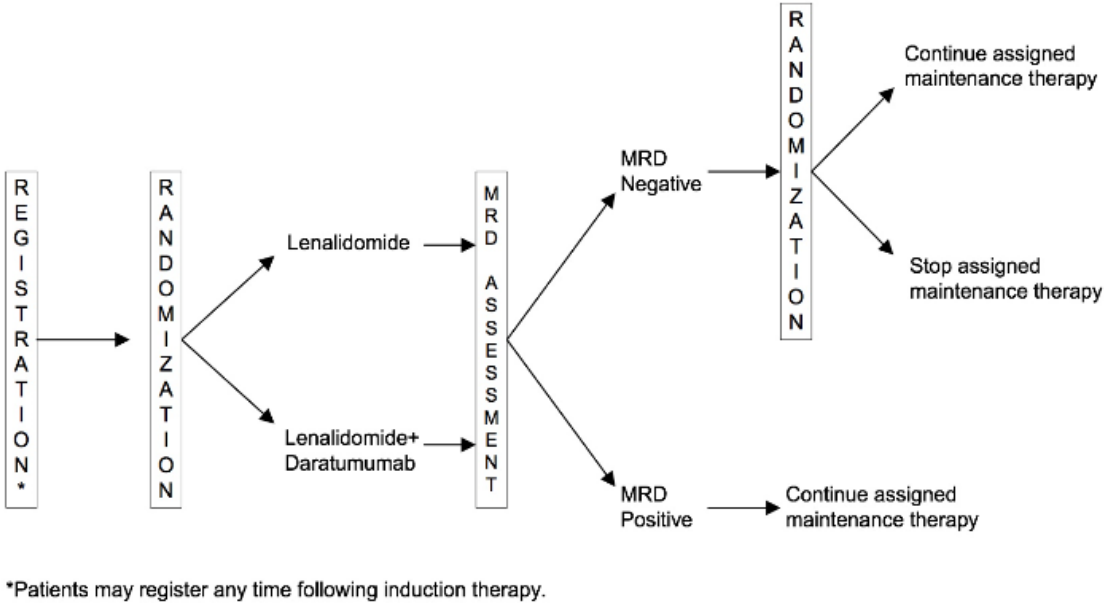




Sonneveld et al NEJM 2024 and ASH 2023; NDMM, newly diagnosed multiple myeloma; ISS, International Staging System stage; V, bortezomib; D, Daratumumab; R, lenalidomide; d, dexamethasone; IV intravenous; PO, orally; SC subcutaneous; PFS, progression-free survival. HR, hazard ratio; CI, confidence interval, MRD measurable residual disease, PD progressive disease, yr year; QW, weekly; Q2W, every 2 weeks.

Unanswered questions: How can we can exploit MRD to perform clinical decisions?

DRAMMATIC: STUDY DESIGN



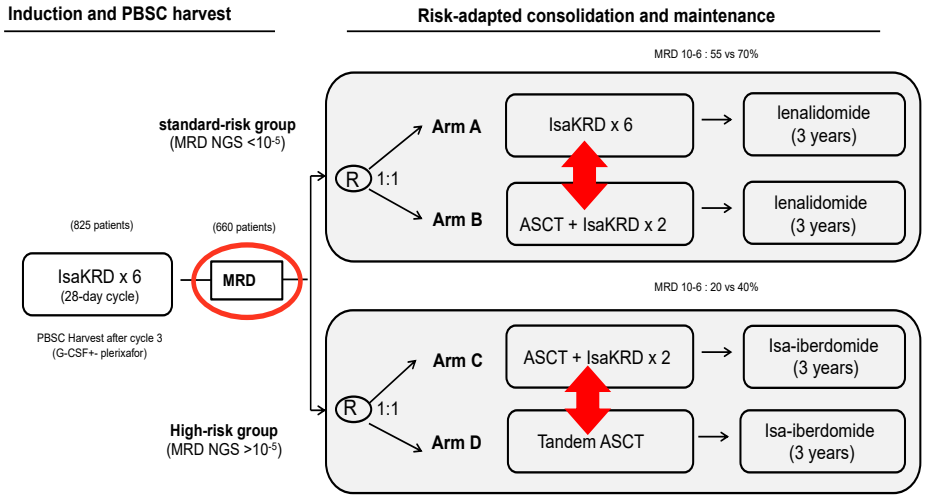
*Patients may register any time following induction therapy.

*MRD assessment after 2 years of maintenance

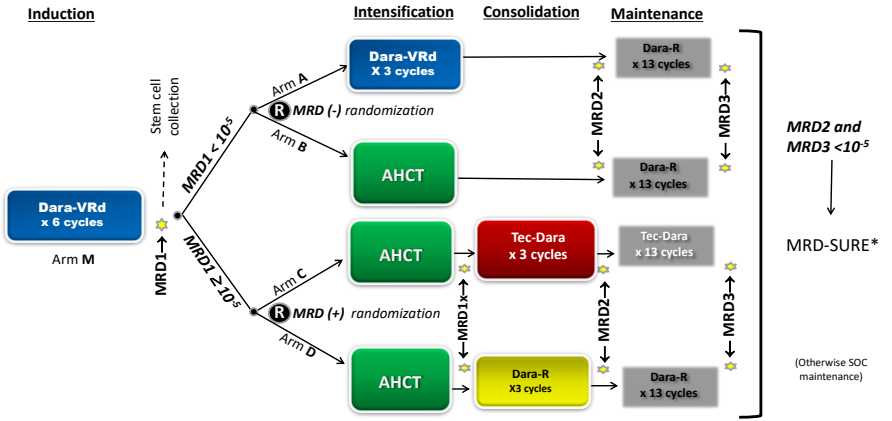
ClinicalTrials.gov Identifier: NCT04071457

Unanswered questions: How can we can exploit MRD to perform clinical decisions?

MIDAS



MASTER 2



ASCT, autologous stem cell transplant; Isa, isatuximab; KRD, carfilzomib, lenalidomide, dexamethasone; MRD, minimal residual disease; NGS, next-generation sequencing; PBSC, peripheral blood stem cell harvest

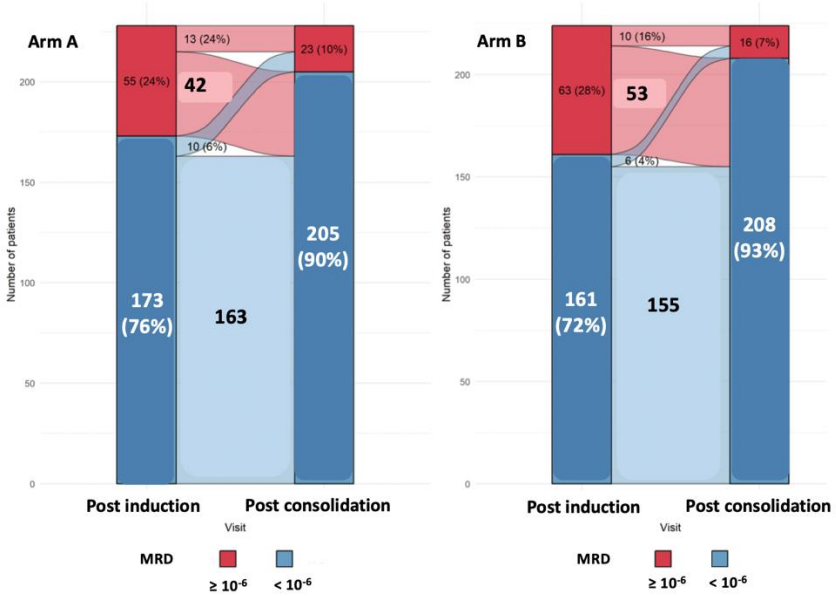
Clinicaltrials.gov/NCT04934475

MRD assessment by ClonoSEQ®

*MRD-SURE – Treatment-free observation and MRD surveillance

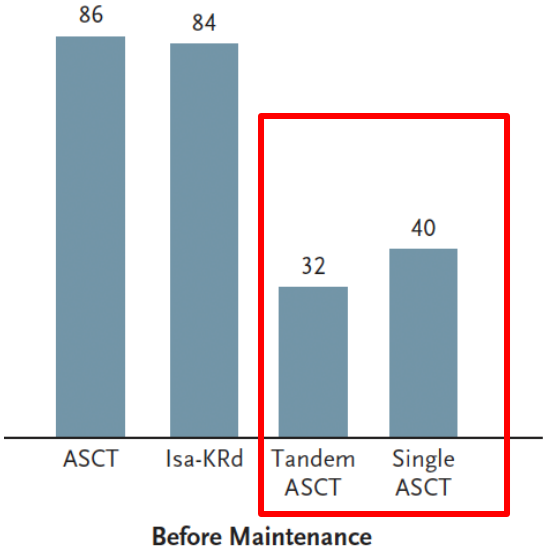
The randomised, Phase III IFM 2020-02 Minimal Residual Disease Adapted Strategy (MIDAS) study

Changes in MRD status (10-6, NGS) in Arms A & B



Per protocol analysis

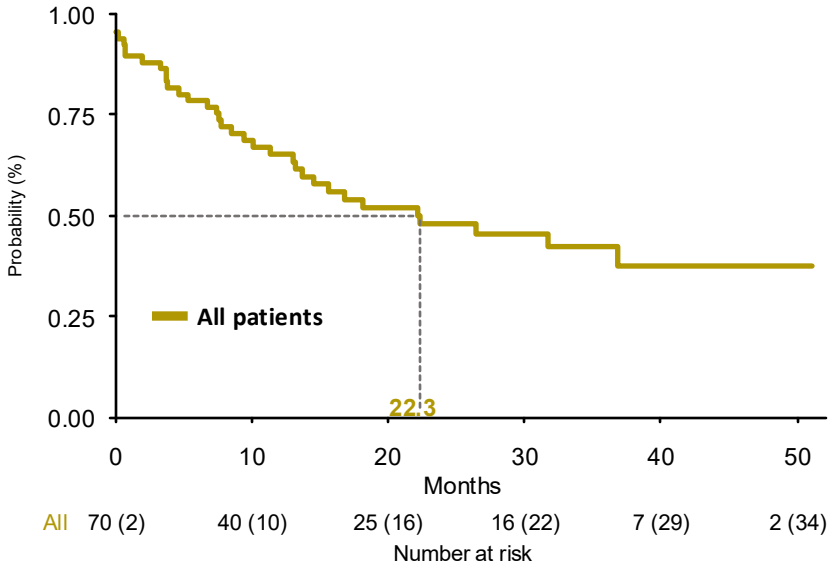
Changes in MRD status (10^{-5}, NGS) in Arms C & D



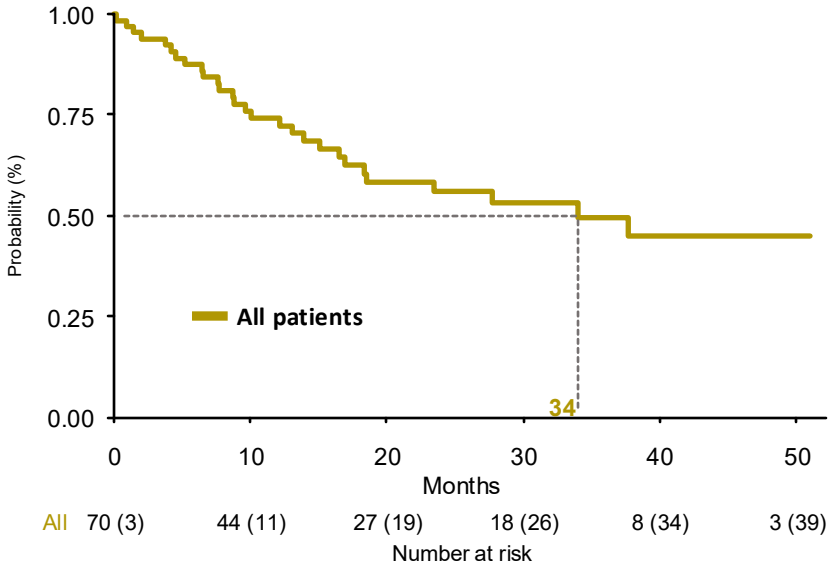
Perrot A. et al, NEJM 2025

MRD resurgence: what to do?

Median time from MRD-positivity to conventional PFS event



Median time from MRD-positivity to next treatment



D'Agostino M et al Blood 2024

MRD resurgence: what to do?

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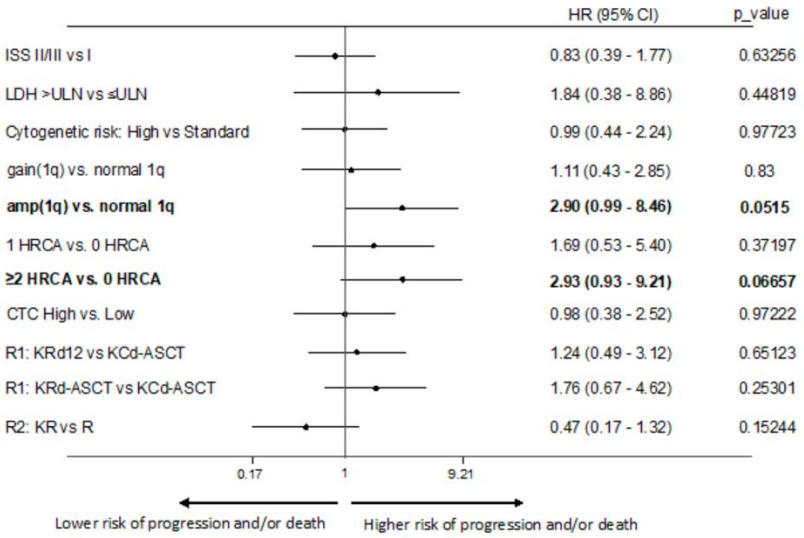
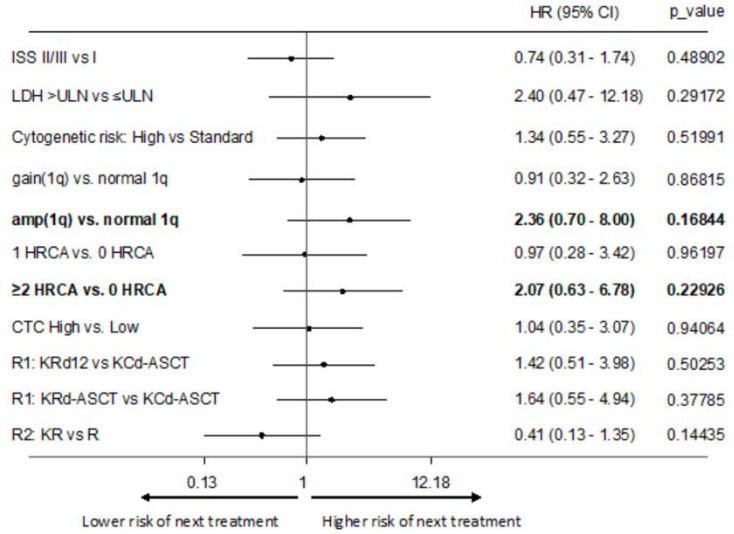


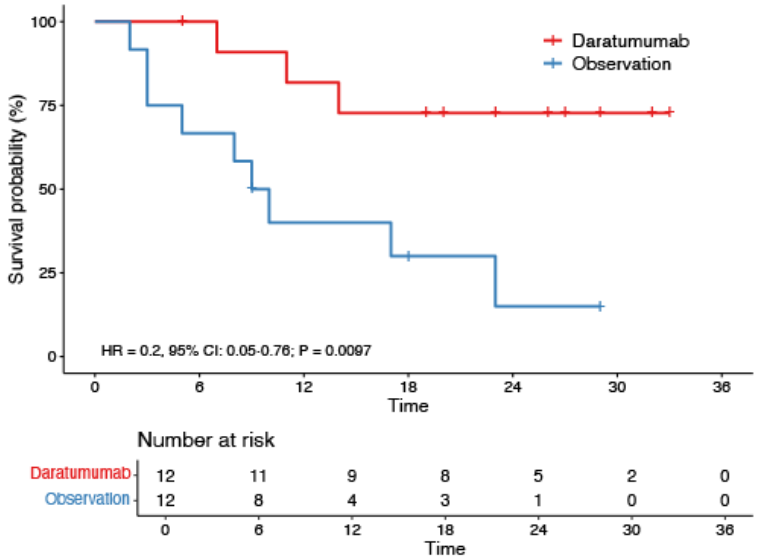
Median time from MRD-positivity to next treatment



D'Agostino M et al Blood 2024

MRD, minimal residual disease; PFS, progression-free survival.

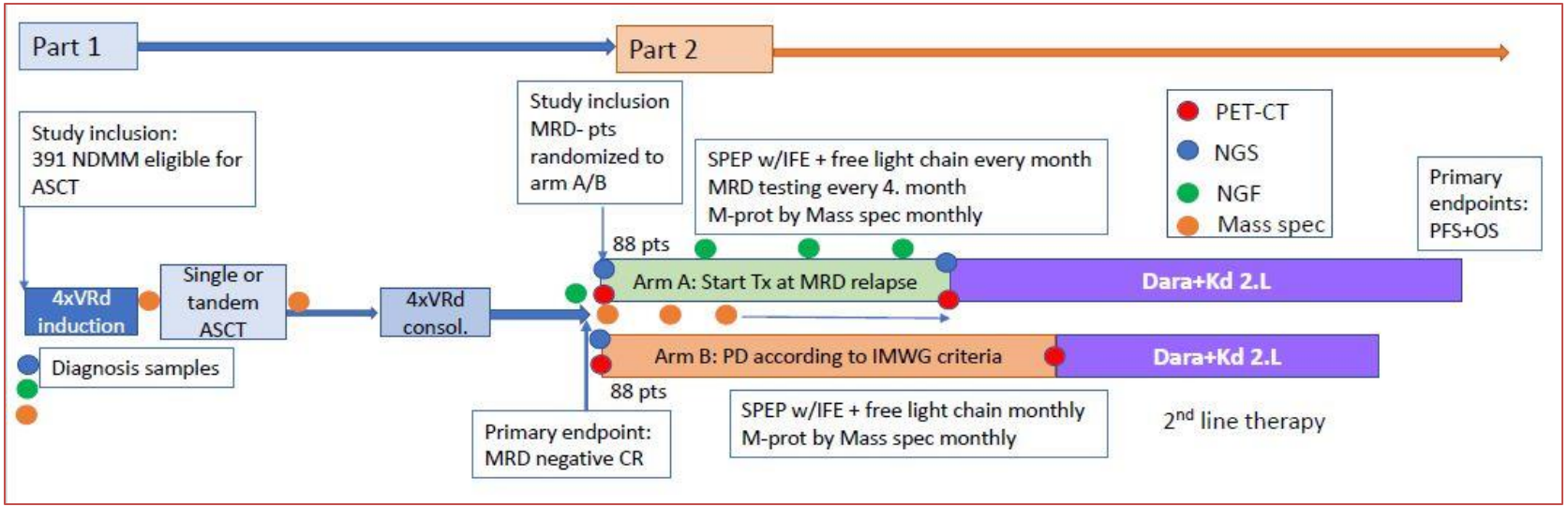
Treat at MRD resurgence: PREDATOR phase II trial



Krzysztof Jamroziak et al EHA 2025

Unanswered questions: How can we can exploit MRD to perform clinical decisions?

REMNANT: STUDY DESIGN



ClinicalTrials.gov Identifier:
NCT04513639

Rasmussen A. et al.,
Hemato 2020, *1*(2), 36-48

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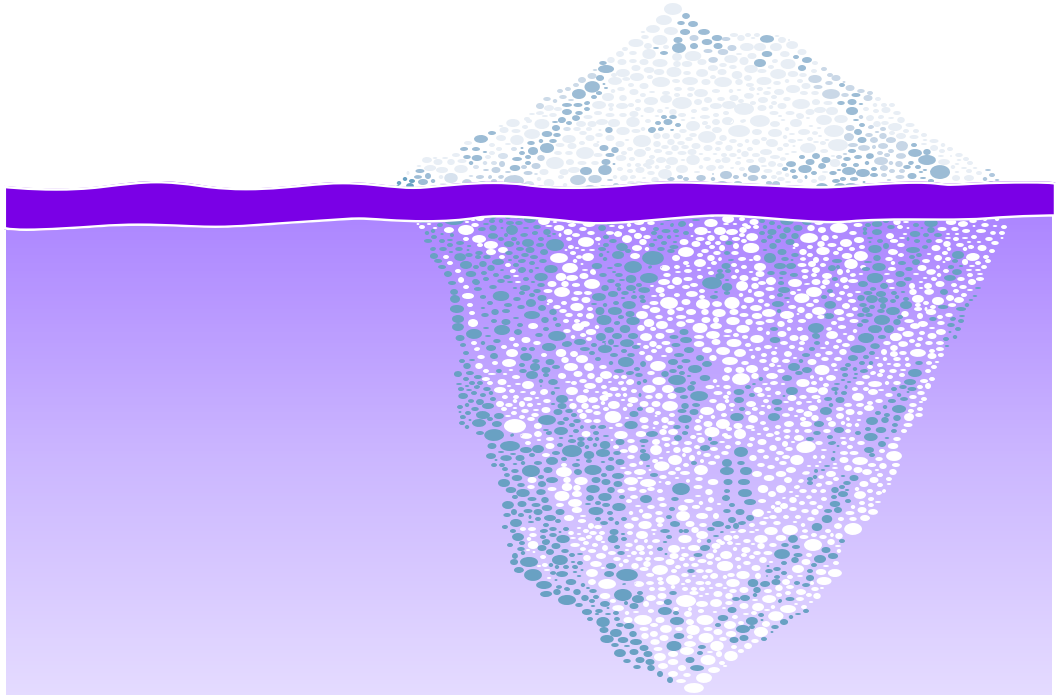
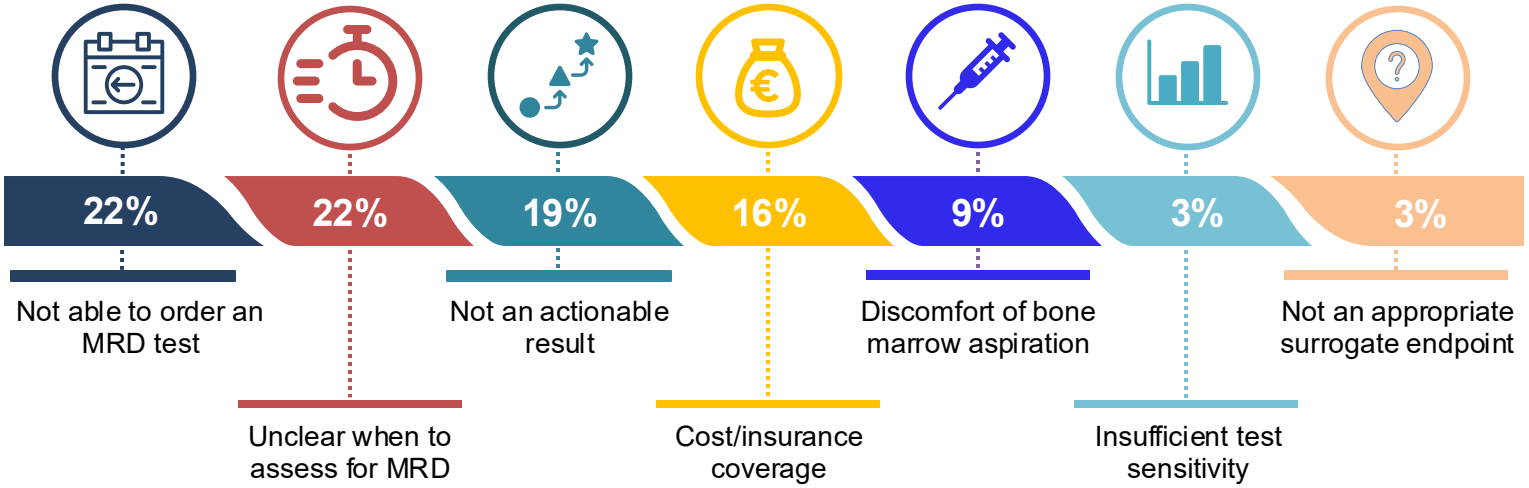


Physicians' attitudes to MRD assessment in the clinic vary

Reasons for not clinically assessing MRD

Global online survey of MM clinicians (n=32*)



In an online survey, 32 out of 89 physicians reported that they did not routinely assess MRD in clinical practice, due to a variety of factors

*Survey with up to 3 answers allowed
MM, multiple myeloma; MRD, minimal residual disease

1. Derman B, et al. Blood Cancer J 2022;12:108

Physicians' attitudes to MRD assessment in the clinic vary

NEXT GENERATION FLOW NEL MIELOMA MULTIPLO: DATI PRELIMINARI DI UN'ESPERIENZA MULTICENTRICA PER L'ARMONIZZAZIONE DELLA METODICA NELLA PRATICA CLINICA

E. Saraci, S. Oliva, V. Trimarco, M. Chiarini, N.L. Parrinello, R. Zambello, I. Cordone, S. Masi, G. Rossi, S. Marino, A.M. Triolo, A. Roccaro, A.M. Carella, F. Buccisano, A. Belotti, M.I. Consalvo, A. Romano, A. Tonini, S. Mercadante, B.Bruno, C. Terragna, E. Zamagni *(Torino, Padova, Brescia, Catania, Roma, San Giovanni Rotondo-FG, Bologna)*

SIES 2024

In an online survey, 61 out of 90 physicians reported that they did not routinely assess MRD in clinical practice, due to a variety of factors

*Survey with up to 3 answers allowed
MM, multiple myeloma; MRD, minimal residual disease

1. Derman B, et al. Blood Cancer J 2022;12:108

Summary

- MRD is the low level of malignant cells that persist even after a CR to myeloma treatment, and is associated with poor outcomes
- NGS and NGF are the most commonly used techniques to assess MRD status, but the role of other less invasive techniques such as peripheral blood based mass spectrometry are under ongoing investigation
- The prognostic value of MRD– surpasses that of CR achievement and is a strong prognostic marker for PFS and OS
- Achieving early and sustained MRD– is associated with the best outcomes, and may overcome poor survival in high-risk patients; while loss of MRD– is associated with poor outcomes
- MRD-adaptive approaches are being explored in clinical trials to understand the clinical utility of MRD-guided decisions at different stages in MM treatment
- Many clinical trials are now evaluating MRD as a primary endpoint in NDMM and RRMM
- The ability to use MRD as a surrogate endpoint could lead to reduced trial duration and cost, exposing fewer patients to potentially toxic treatment and lead to more rapid drug approvals
- MRD adaption in clinical practice is challenging, collaboration between laboratories is key to give clinicians reliable results

CR, complete response; FDA, Food and Drugs Administrations; EMA, European Medical Agency; Isa-RVd, isatuximab, lenalidomide, bortezomib, dexamethasone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma

Division of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino
Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
Prof . Benedetto Bruno

Clinical trial and multiple myeloma Unit
Prof. Francesca Gay
Prof. Alessandra Larocca
Prof. Roberto Mina
Dr. Giulia Benevolo
Dr. Stefania Oliva
Dr. Giuseppe Bertuglia
Dr. Lorenzo Cani
Dr. Andrea Casson
Dr. Tommaso Picardi
Dr. Edoardo Marchetti
Dr. Alessandro Di Nicola

Laboratory Staff

Transplant Unit
Nurses
Data Managing Staff