
# NUOVE TERAPIE NEI LINFOMI B AGGRESSIVI E NEL MIELOMA MULTIPLO

## *Ruolo della MRD: dagli studi clinici alla real life*

**Mariagrazia Michieli**

CRO Aviano (PN) - 9 ottobre 2024

# Convegno Regionale SIE

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|---|---|---|---|---|---|---|---|
| **Nessun conflitto di interesse** | | | | | | | |
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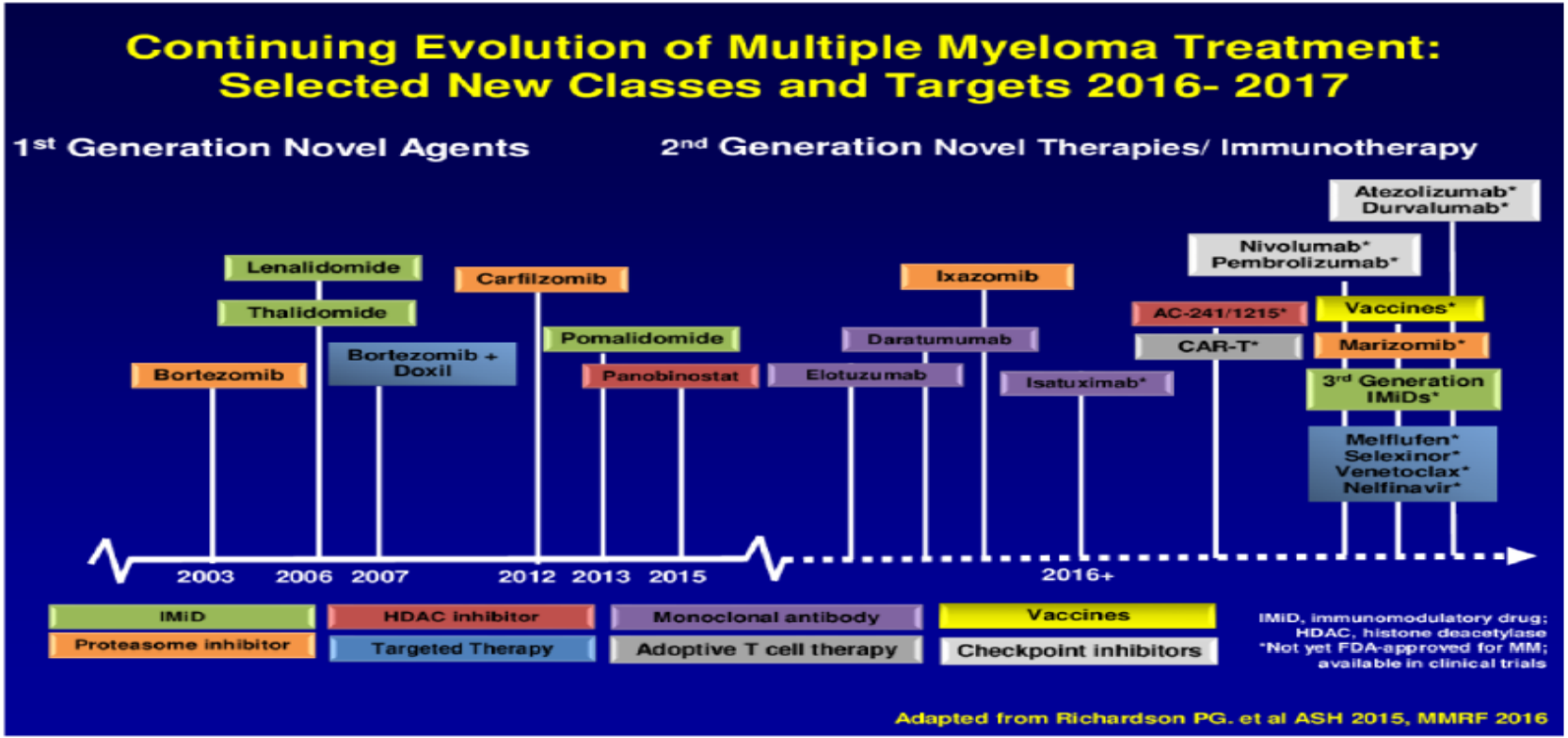
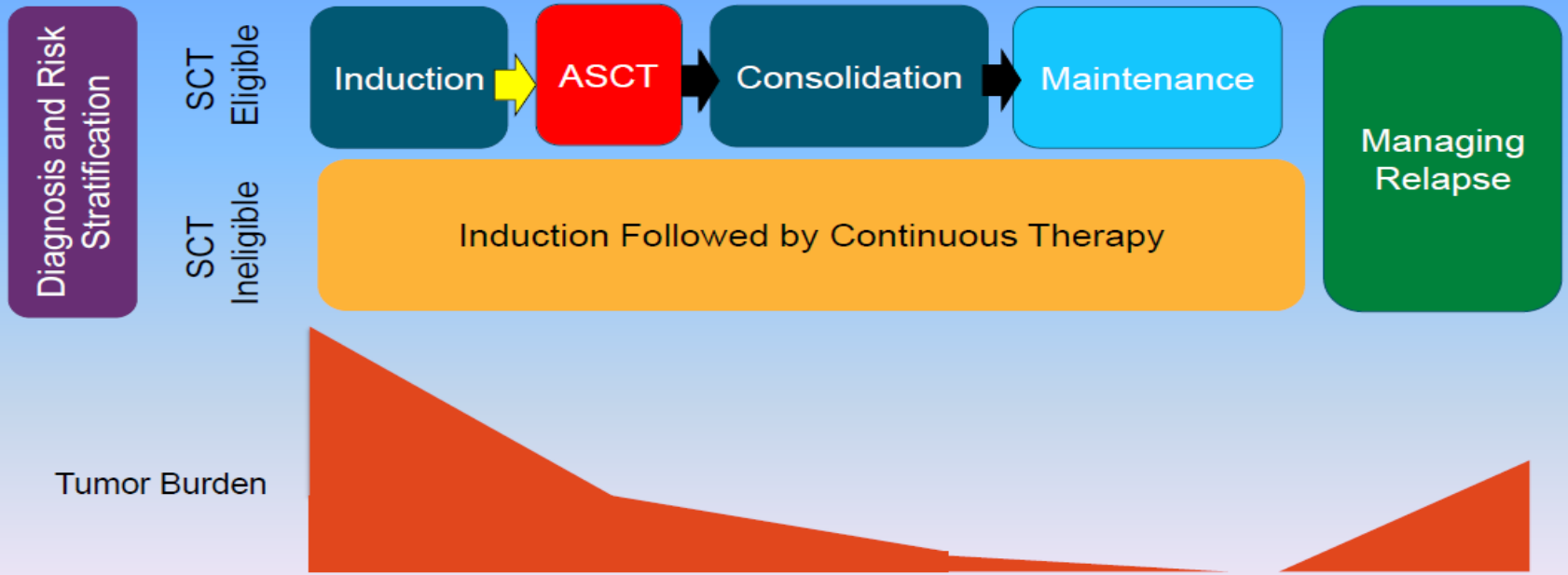
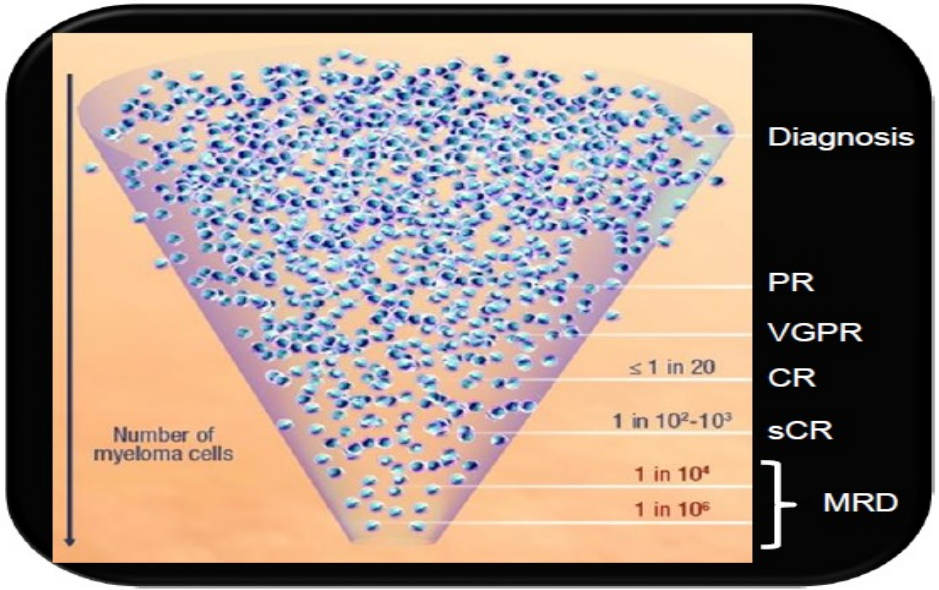



IMW 2017 New Dehli

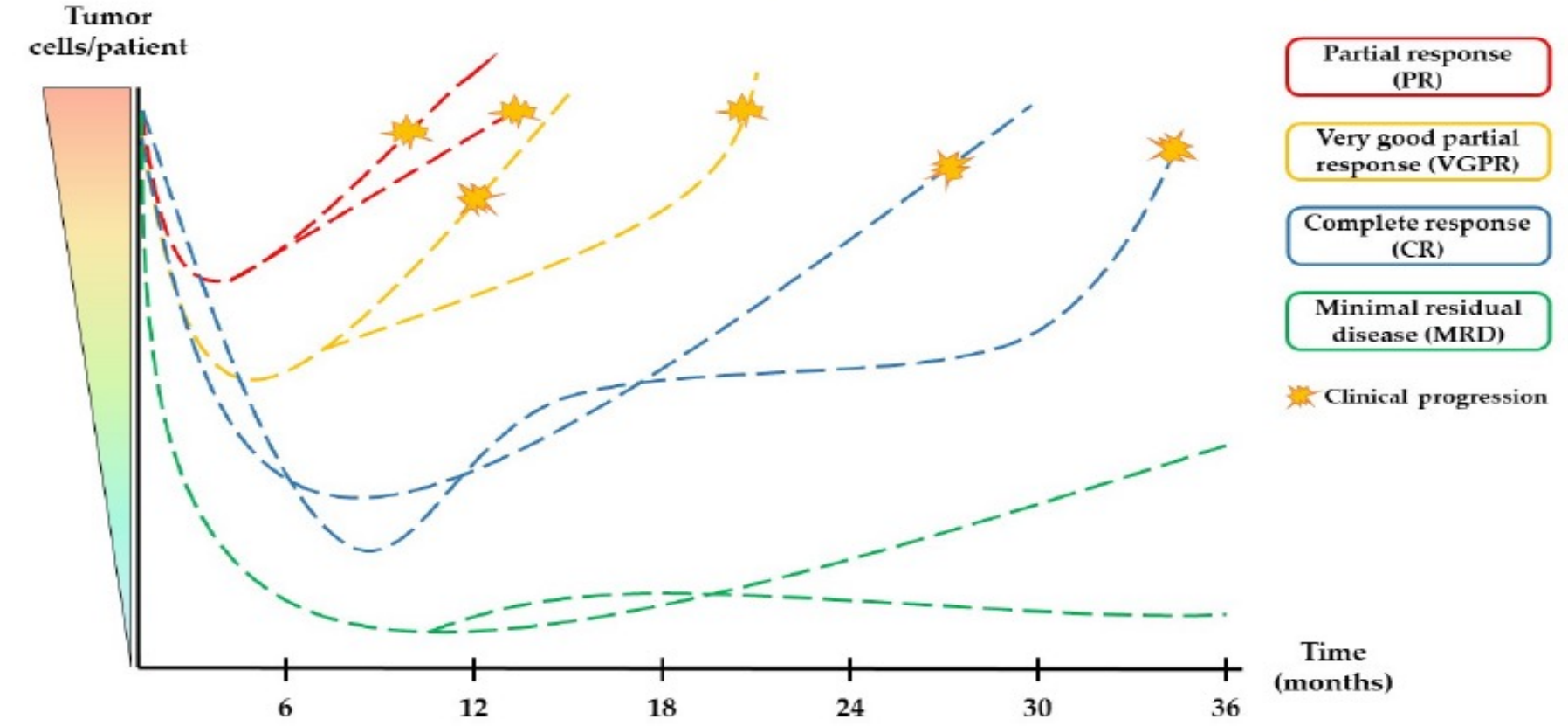
# Paradigma del Trattameto del Mieloma Multiplo



# Residual Disease is always present




- In multiple myeloma, relapse is characterized by the evolution and proliferation of residual tumor cells and decreased immune function[1-3]
- Achievement of a CR, by current IMWG criteria, does not eliminate all myeloma clones[4,5]
- Early and continuous suppression of residual disease may help improve disease control[6,7]


Tumor cells/patient
Partial response (PR)
Very good partial response (VGPR)
Complete response (CR)
Minimal residual disease (MRD)
Clinical progression
Time (months)
6
12
18
24
30
36

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

*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*

**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 |
| Very good partial response | Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h |
| Partial response | ≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h;<br>If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria;<br>If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required |
| Minimal response | ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required |
| Stable disease | Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease |
| Progressive disease ¶¶,‖‖ | Any one or more of the following criteria:<br>Increase of 25% from lowest confirmed response value in one or more of the following criteria:<br>Serum M-protein (absolute increase must be ≥0·5 g/dL);<br>Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL;<br>Urine M-protein (absolute increase must be ≥200 mg/24 h);<br>In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);<br>In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%);<br>Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis;<br>≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease |

(Table 4 and footnotes continue on the next page)

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| | 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 $10^6$ 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 $10^6$ 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¶ |

**Ricerca di MRD va fatta solo nei casi che hanno già raggiunto > VGPR**

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*Review*

# Minimal Residual Disease in Multiple Myeloma: Past, Present, and Future

Alejandro Medina-Herrera, María Eugenia Sarasquete *, Cristina Jiménez, Noemí Puig and Ramón García-Sanz

| | Standard MFC | NGF | ASOqPCR | NGS | ddPCR |
|---|---|---|---|---|---|
| Applicability | 90–100% | 90–100% | 40–75% | ~90% | Comparable to qPCR |
| Sensitivity | $10^{-4}$–$10^{-5}$ | $10^{-5}$–$10^{-6}$ | $10^{-4}$–$10^{-5}$ | $10^{-5}$–$10^{-6}$ | At least $10^{-5}$ |
| Standardization | No | EuroFlow | EuroMRD | ClonoSEQ * | Ongoing |
| Turnaround time | 1 day | 1 day | ≥1 week | 4 days–1 week | ≥1 week |
| Specific primers/probes | Not applicable | Not applicable | Yes | No | Yes |
| Standard curve | Not applicable | Not applicable | Yes | No | No |
| Influenced by SHM | No | No | Yes | Yes | Yes |
| Baseline BM | No | No | Yes | Yes | Yes |
| Fresh sample (processing time) | Yes (24–48 h) | Yes (24 h) | No | No | No |

## Blood-based minimal residual disease assessment

### Circulating plasma cells

The presence of circulating plasma cells (CPC) in peripheral blood (PB) can be detected in most MM patients and is associated with poor prognosis. Different methods have been used to assess the presence of CPC. The standard EuroFlow NGF is reliable and requires a small volume of blood. Other methods are available that use a plasma cell enrichment method, which requires a larger blood sample, and is more sensitive but also more complex. NGF has been used to identify and track CPC in MM patients with interesting results. However, while CPC detection appears to be a powerful prognostic factor, CPC is unlikely to be a good MRD marker. Indeed, a comparison between NGF in BM and PB after therapy in a real-world case series of 137 patients showed that 40% of patients achieving blood-based MRD negativity had BM MRD-positive disease, strongly suggesting that blood NGF-based MRD evaluation is a less sensitive MRD marker than BM MRD.[22,25,26]

**Less Sentitive in PB**

**Role of minimal residual disease assessment in multiple myeloma**

Raphael E. Szalat,[1] Kenneth C. Anderson[2] and Nikhil C. Munshi[2]

# LIQUID BIOPSY - Genomic Aberration

## Circulating cell-free DNA for minimal residual disease assessment

Circulating cell-free DNA (cfDNA)-based methods, often referred to as 'liquid biopsy', allow tracking genomic aberrations such as tumor mutations, copy number aberration or translocation present in circulating cfDNA isolated from blood plasma.[27-29] Multiple studies showed a high concordance of somatic mutations and copy-number alterations between BM and cfDNA of patients with MM.[30-33] However, the low level of circulating tumor DNA is a significant challenge and most current methods are not sensitive enough. Ultradeep targeted sequencing has significantly improved the detection of cfDNA, but its sensitivity relates to the number of tumor mutations available to track and has so far only been evaluated in few clinical studies. In a study which compared blood and BM evaluation with NGS and cfDNA in 42 patients, there was only 49% consistency and poor correlation between the two methods. Similar to CPC detection, BM MRD was more often positive and suggested lack of sensitivity of the cfDNA approach.[34] Novel and more sensitive methods are needed before cfDNA can be utilized as a standard approach.

**Single-cell RNA sequencing**

Single-cell RNA sequencing (scRNA-seq) is another powerful technology widely used in research. It allows transcriptomic analysis at a single cell level and can detect rare malignant cells.[35] Ongoing research is investigating whether this approach could even allow the selection of therapy based on transcriptomic features and clonal heterogeneity.[36,37] However, its availability, its relative complex workflow, reproducibility and cost are significant challenges that need to be addressed before it can be considered for use in clinical practice.[38] This approach is also limited by the fact that it can currently only evaluate a certain number of cells, far fewer than with flow- or NGS MRD-based assessment methods. Therefore, the lack of detection of malignant cells would not necessarily correspond to negative MRD, and scRNAseq appears more as a potential complimentary method that may help tailor therapy to target MRD positive cells rather than to determine MRD status.

## Role of minimal residual disease assessment in multiple myeloma

Raphael E. Szalat,[1] Kenneth C. Anderson[2] and Nikhil C. Munshi[2]

**Table 1**
**Mass spectrometry methods for minimal (measurable) residual disease detection in multiple myeloma**

| Mass Spectrometry Method | Alternative Names | Limit of Detection | Advantages | Disadvantages |
|---|---|---|---|---|
| MALDI-TOF | MASS-FIX EXENT | 0.015 g/dL | • Quick (10 s)<br>• Can be automated | • Not as sensitive as other MS assays |
| Liquid chromatography | miRAMM | 0.005 g/dL | • Higher sensitivity than MALDI | • Time-consuming (20 min per sample)<br>• M-spike lags significantly behind tumor lysis |
| Clonotypic peptide | EasyM M-InSight | 0.00001–0.00005 g/dL | • Highest sensitivity<br>• No interference from polyclonal background | • Expensive<br>• Time-consuming<br>• M-spike lags significantly behind tumor lysis |

Somatic recombination and hypermutation leading to an unique Heavy and light chain genes

Discordant cases with NGS

The protein is first digested

**Measurable Residual Disease and Decision-Making in Multiple Myeloma**

Benjamin A. Derman, MD[a,*], Rafael Fonseca, MD[b]

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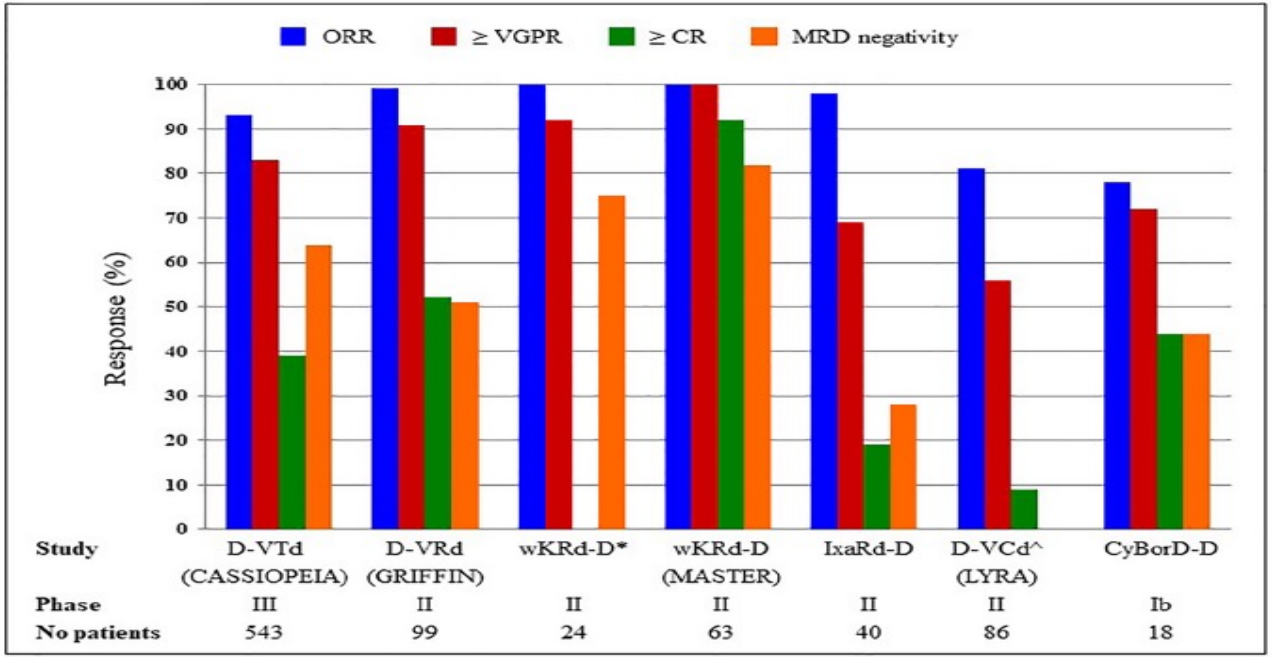


**FIGURE 1** | D-VTd, daratumumab, bortezomib, thalidomide, dexamethasone; D-VRd, daratumumab, bortezomib, lenelidomide, dexamethasone; wKRd_D, weekly carfilzomib, lenalidomide, dexamethasone, daratumumab; IxaRd-D, ixazomib, lenalidomide, dexamethasone, daratumumab; D-VCd and CyBorD-D, daratumumab, cyclophosphamide, bortezomib, dexamethasone. *≥ CR not available; ^MRD status not available.

REGULAR ARTICLE

blood advances

# A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma

Nikhil C. Munshi,[1,2] Herve Avet-Loiseau,[3] Kenneth C. Anderson,[1] Paola Neri,[4] Bruno Paiva,[5] Mehmet Samur,[1] Meletios Dimopoulos,[6] Margarita Kulakova,[7] Annette Lam,[8] Mahmoud Hashim,[7] Jianming He,[8] Bart Heeg,[7] Jon Ukropec,[9] Jessica Vermeulen,[9] Sarah Cote,[8] and Nizar Bahlis[4]

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**Key Points**

- This meta-analysis establishes the role of MRD negativity in improving long-term survival in a heterogeneous cohort of patients with MM.
- The strong prognostic value of MRD negativity sets the stage to adopt MRD as a clinically valid surrogate biomarker for PFS and OS in MM.

The prognostic value of minimal residual disease (MRD) for progression-free survival (PFS) and overall survival (OS) was evaluated in a large cohort of patients with multiple myeloma (MM) using a systematic literature review and meta-analysis. Medline and EMBASE databases were searched for articles published up to 8 June 2019, with no date limit on the indexed database. Clinical end points stratified by MRD status (positive or negative) were extracted, including hazard ratios (HRs) on PFS and OS, *P* values, and confidence intervals (CIs). HRs were estimated based on reconstructed patient-level data from published Kaplan-Meier curves. Forty-four eligible studies with PFS data from 8098 patients, and 23 studies with OS data from 4297 patients were identified to assess the association between MRD status and survival outcomes. Compared with MRD positivity, achieving MRD negativity improved PFS (HR, 0.33; 95% CI, 0.29-0.37; $P < .001$) and OS (HR, 0.45; 95% CI, 0.39-0.51; $P < .001$). MRD negativity was associated with significantly improved survival outcomes regardless of disease setting (newly diagnosed or relapsed/refractory MM), MRD sensitivity thresholds, cytogenetic risk, method of MRD assessment, depth of clinical response at the time of MRD measurement, and MRD assessment premaintenance and 12 months after start of maintenance therapy. The strong prognostic value of MRD negativity and its association with favorable outcomes in various disease and treatment settings sets the stage to adopt MRD as a treatment end point, including development of therapeutic strategies. This large meta-analysis confirms the utility of MRD as a relevant surrogate for PFS and OS in MM.

## Introduction

44 studi per PFS
23 studi per OS

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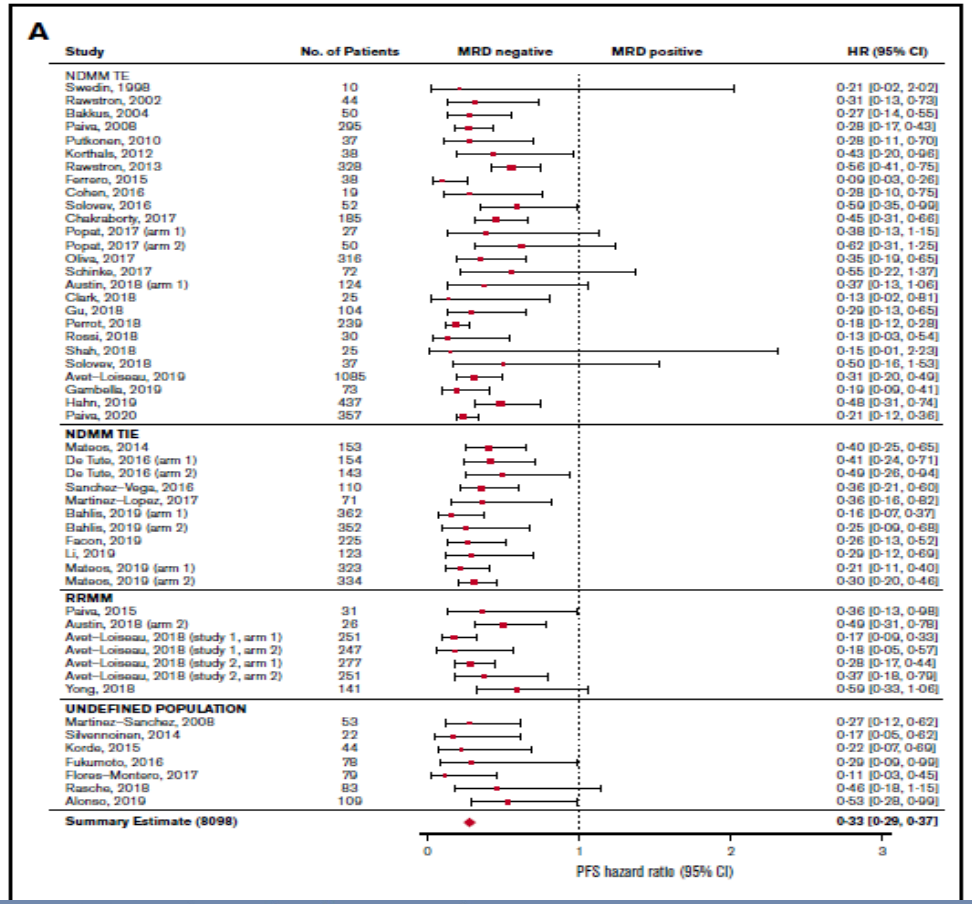


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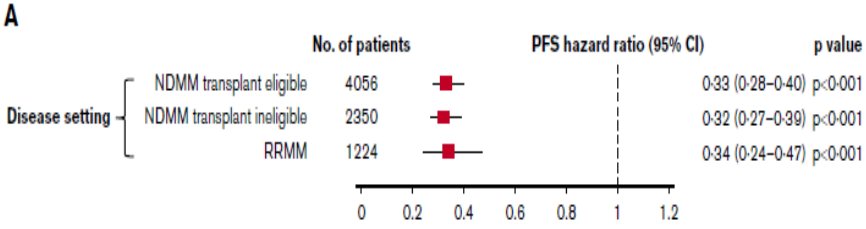


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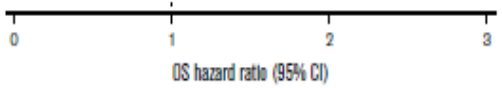
B

| Study | No. of Patients | HR (95% CI) |
|---|---|---|
| **NDMM TE** | | |
| Rawstron, 2002 | 44 | 0·53 [0·16, 1·75] |
| Bakkus, 2004 | 50 | 0·59 [0·21, 1·65] |
| Paiva, 2008 | 295 | 0·50 [0·38, 0·64] |
| Putkonen, 2010 | 37 | 0·23 [0·05, 0·97] |
| Korthals, 2012 | 38 | 0·67 [0·26, 1·70] |
| Rawstron, 2013 | 287 | 0·63 [0·43, 0·90] |
| Ferrero, 2015 | 38 | 0·32 [0·10, 1·02] |
| Ludwig, 2015 | 42 | 0·27 [0·08, 0·97] |
| Chakraborty, 2017 | 185 | 0·55 [0·32, 0·93] |
| Schinke, 2017 | 72 | 0·84 [0·30, 2·39] |
| Gu, 2018 | 104 | 0·23 [0·09, 0·59] |
| Perrot, 2018 | 239 | 0·26 [0·10, 0·68] |
| Shah, 2018 | 25 | 0·25 [0·03, 2·22] |
| Hahn, 2019 | 437 | 0·77 [0·35, 1·67] |
| Paiva, 2020 | 357 | 0·26 [0·10, 0·67] |
| **NDMM TIE** | | |
| Mateos, 2014 | 153 | 0·48 [0·27, 0·88] |
| De Tute, 2016 (arm 1) | 154 | 0·41 [0·27, 0·62] |
| Sanchez-Vega, 2016 | 110 | 0·36 [0·18, 0·72] |
| Martinez-Lopez, 2017 | 71 | 0·27 [0·07, 1·02] |
| Li, 2019 | 123 | 0·13 [0·02, 0·96] |
| Mateos, 2019 (arm 1) | 323 | 0·24 [0·08, 0·76] |
| Mateos, 2019 (arm 2) | 334 | 0·44 [0·25, 0·79] |
| **RRMM** | | |
| Avet-Loiseau, 2018 (study 1, pooled arms) | 498 | 0·07 [0·02, 0·30] |
| Avet-Loiseau, 2018 (study 2, arm 1) | 277 | 0·35 [0·21, 0·59] |
| Avet-Loiseau, 2018 (study 2, arm 2) | 251 | 0·23 [0·06, 0·94] |
| **Summary Estimate (4297)** | | **0·45 [0·39, 0·51]** |

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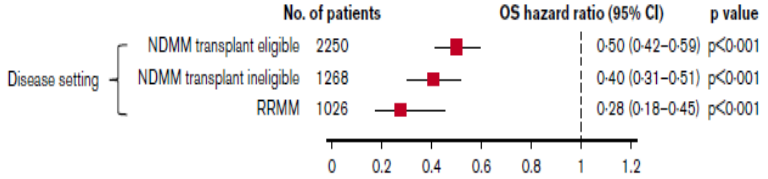


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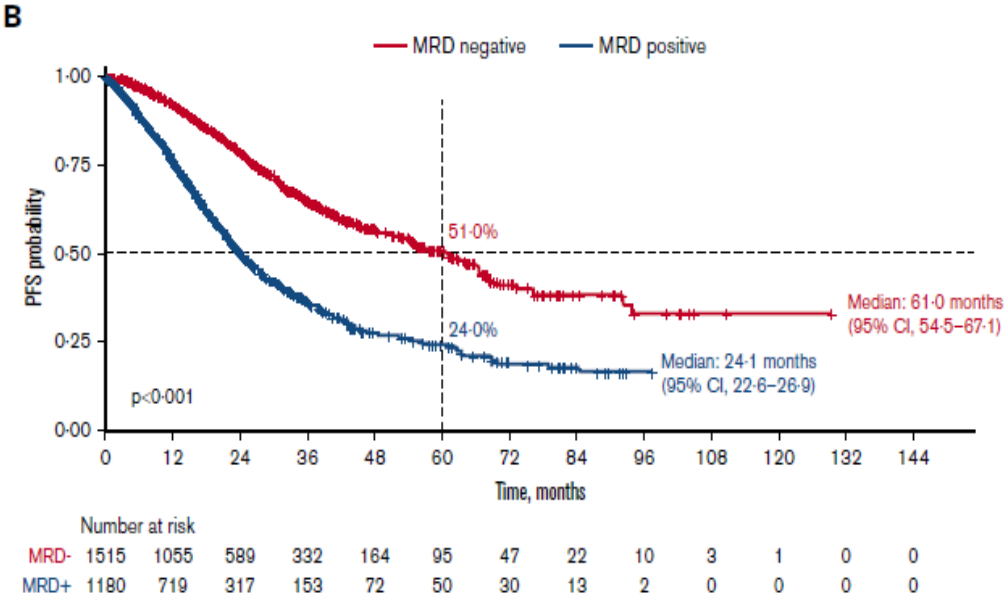


MEDIAN PFS
NDMM TE

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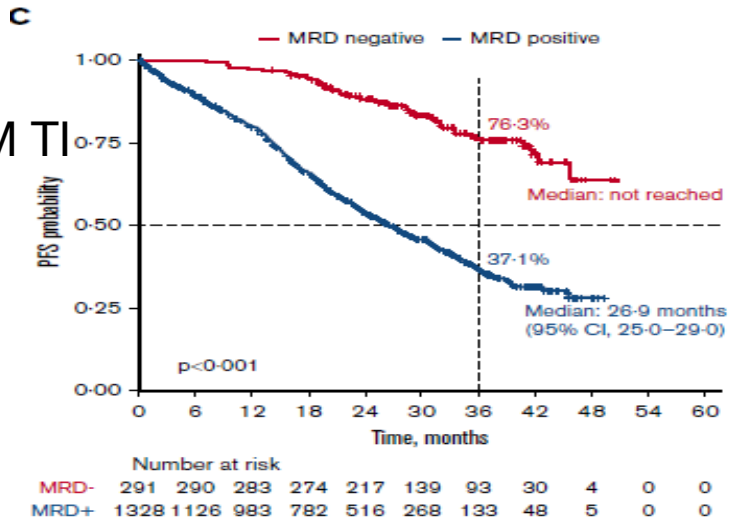
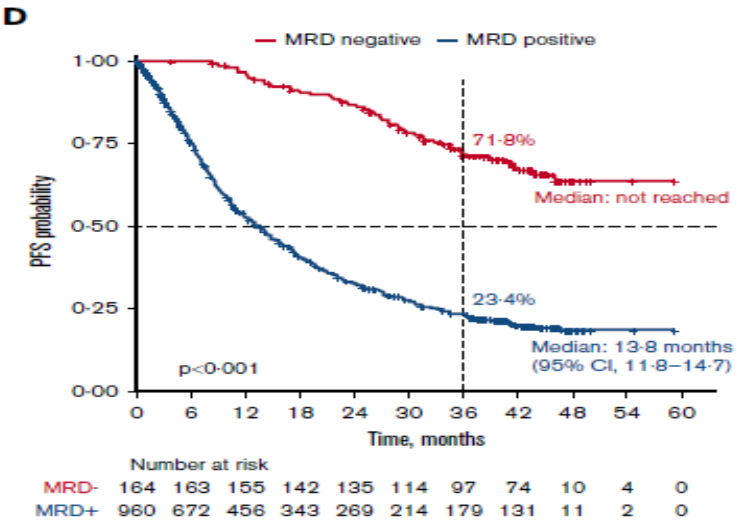
PFS
NDMM TI




PFS
RRMM

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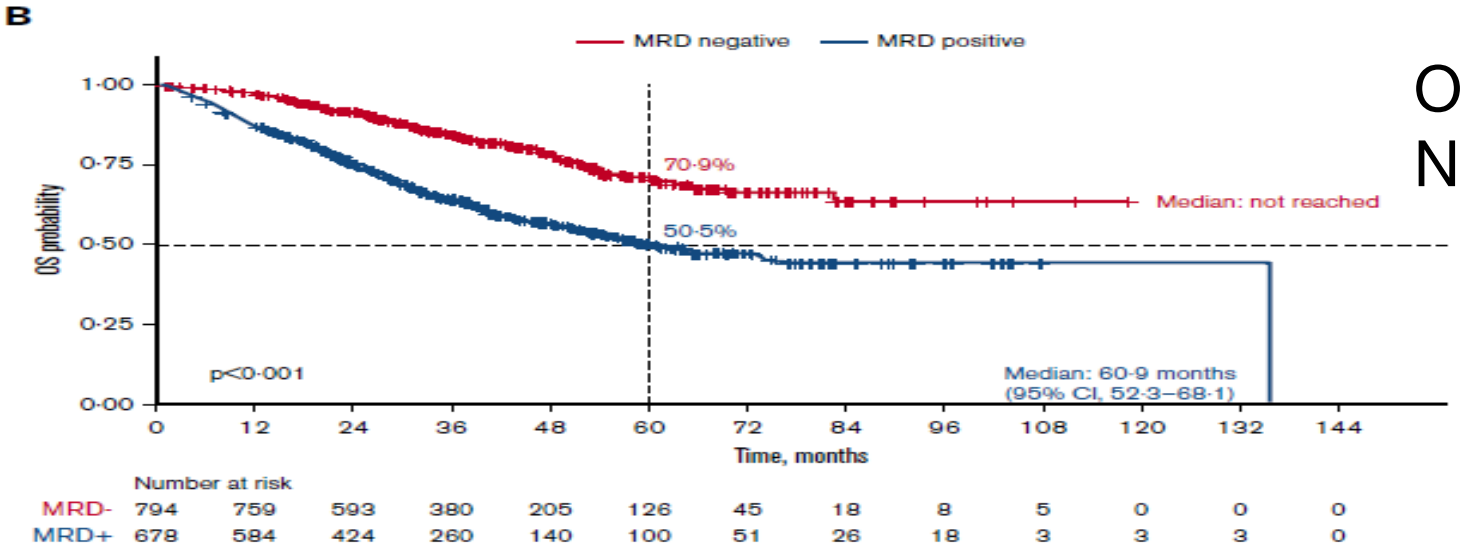


OS
NDMM TE

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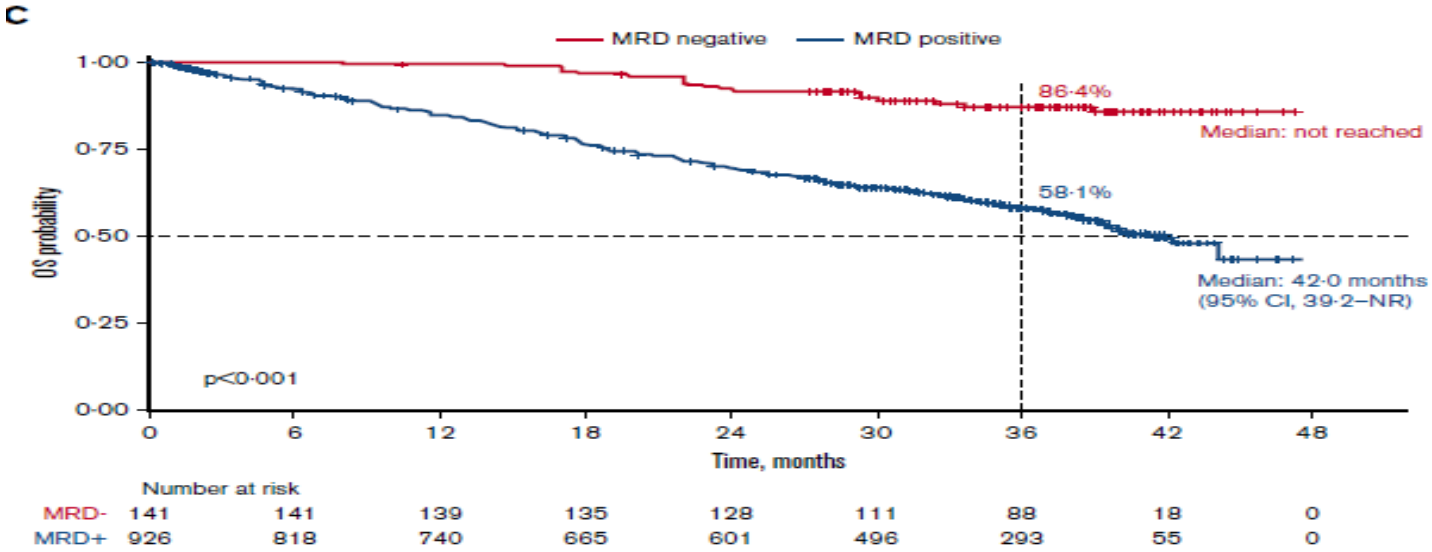


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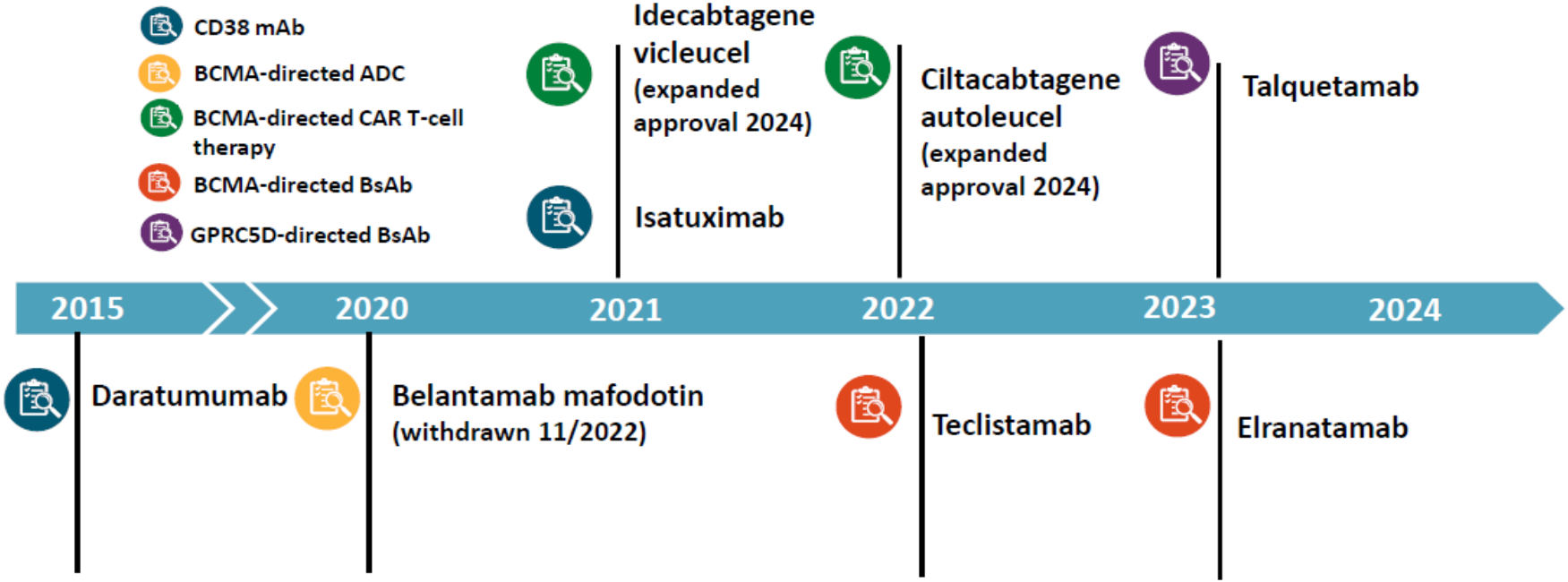
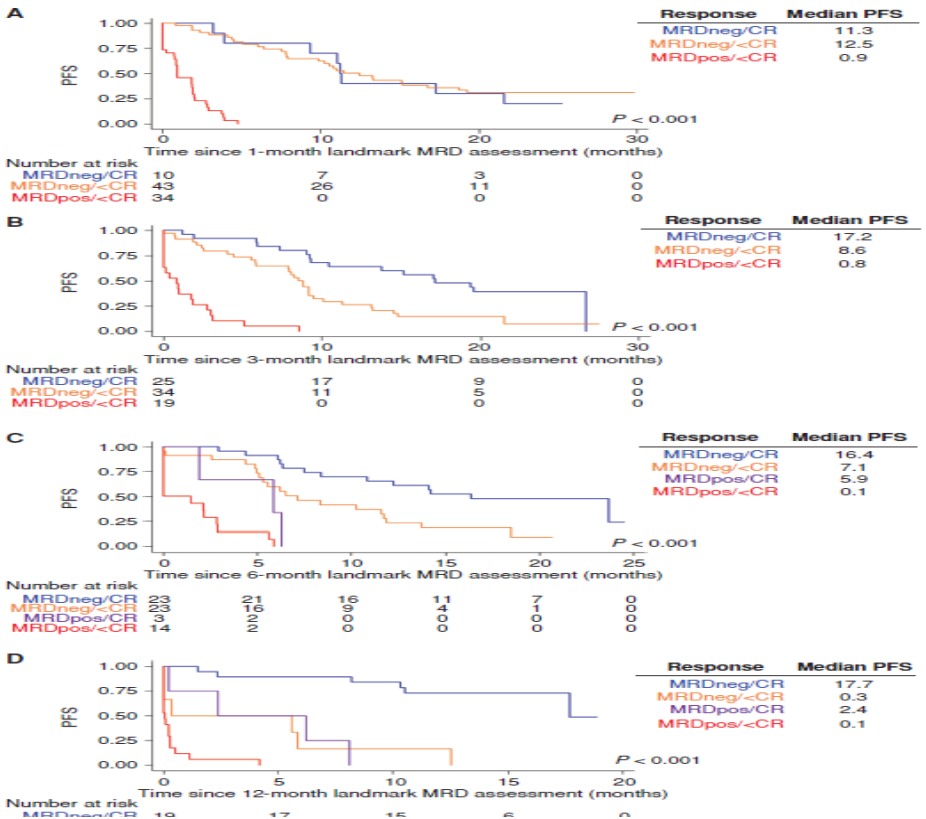
# Novel Therapies in Multiple Myeloma



RESEARCH BRIEF

# Time-Dependent Prognostic Value of Serological and Measurable Residual Disease Assessments after Idecabtagene Vicleucel

Bruno Paiva[1], Irene Manrique[1], Julie Rytlewski[2], Timothy Campbell[3], Christian C. Kazanecki[2], Nathan Martin[2], Larry D. Anderson Jr.[4], Jesús G. Berdeja[5], Sagar Lonial[6], Noopur S. Raje[7], Yi Lin[8], Philippe Moreau[9], Jesús F. San-Miguel[1], Nikhil C. Munshi[10], and Shari M. Kaiser[2]



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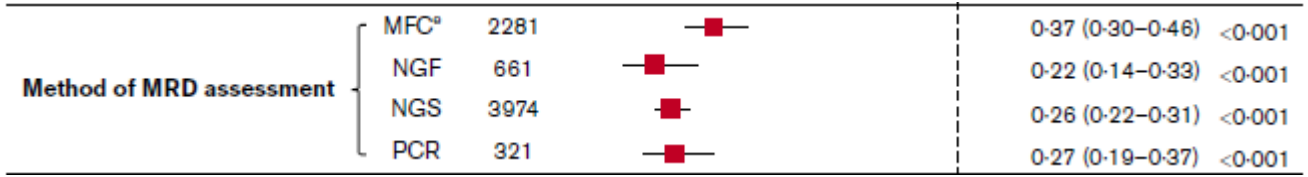


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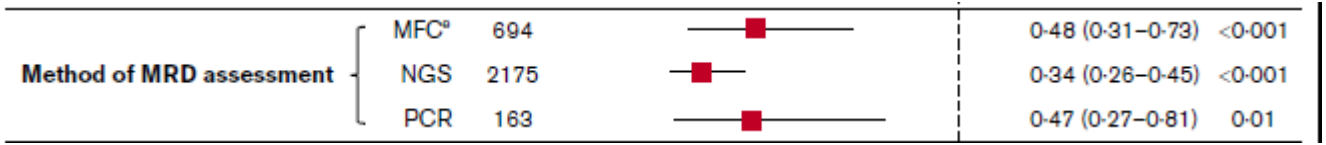


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https://doi.org/10.1038/s41408-020-00377-0

Blood Cancer Journal

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# Comparison of next-generation sequencing (NGS) and next-generation flow (NGF) for minimal residual disease (MRD) assessment in multiple myeloma

Alejandro Medina[1], Noemi Puig[1], Juan Flores-Montero[2], Cristina Jimenez[1], M.-Eugenia Sarasquete[1], María García-Alvarez[1], Isabel Prieto-Conde[1], Carmen Chillon[1], Miguel Alcoceba[1], Norma C. Gutierrez[1], Albert Oriol[3], Laura Rosinol[4], Joan Bladé[4], Mercedes Gironella[5], Miguel T. Hernandez[6], Veronica Gonzalez-Calle[1], Maria-Teresa Cedena[7], Bruno Paiva[8], Jesus F. San-Miguel[8], Juan-Jose Lahuerta[7], Maria-Victoria Mateos[1], Joaquin Martinez-Lopez[7], Alberto Orfao[2], Marcos Gonzalez[1] and Ramon Garcia-Sanz[1]

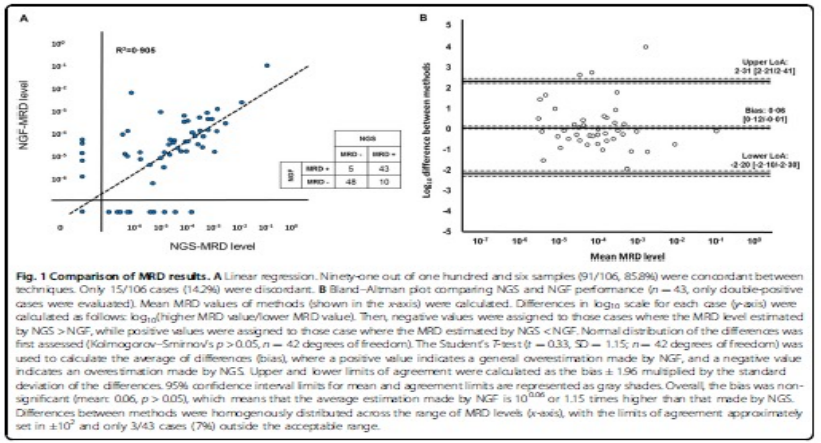


**Fig. 1 Comparison of MRD results. A** Linear regression. Ninety-one out of one hundred and six samples (91/106, 85.8%) were concordant between techniques. Only 15/106 cases (14.2%) were discordant. **B** Bland–Altman plot comparing NGS and NGF performance ($n = 43$, only double-positive cases were evaluated). Mean MRD values of methods (shown in the *x*-axis) were calculated. Differences in $\log_{10}$ scale for each case (*y*-axis) were calculated as follows: $\log_{10}$(higher MRD value/lower MRD value). Then, negative values were assigned to those cases where the MRD level estimated by NGS > NGF, while positive values were assigned to those case where the MRD estimated by NGS < NGF. Normal distribution of the differences was first assessed (Kolmogorov–Smirnov's $p > 0.05$, $n = 42$ degrees of freedom). The Student's *T*-test ($t = 0.33$, $SD = 1.15$; $n = 42$ degrees of freedom) was used to calculate the average of differences (bias), where a positive value indicates a general overestimation made by NGF, and a negative value indicates an overestimation made by NGS. Upper and lower limits of agreement were calculated as the bias ± 1.96 multiplied by the standard deviation of the differences. 95% confidence interval limits for mean and agreement limits are represented as gray shades. Overall, the bias was non-significant (mean: 0.06, $p > 0.05$), which means that the average estimation made by NGF is $10^{0.06}$ or 1.15 times higher than that made by NGS. Differences between methods were homogeneously distributed across the range of MRD levels (*x*-axis), with the limits of agreement approximately set in $\pm 10^2$ and only 3/43 cases (7%) outside the acceptable range.

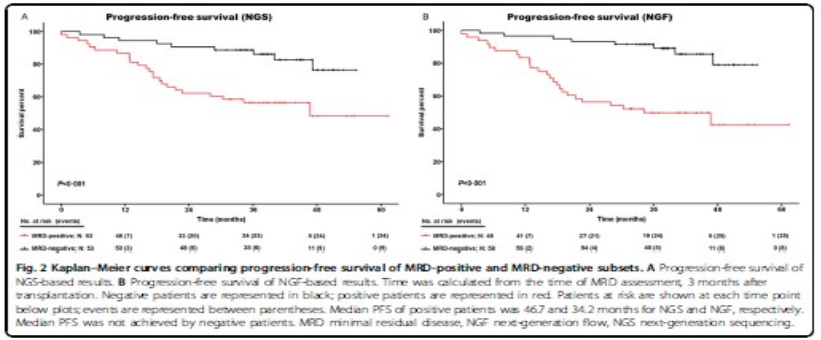


**Fig. 2 Kaplan–Meier curves comparing progression-free survival of MRD-positive and MRD-negative subsets. A** Progression-free survival of NGS-based results. **B** Progression-free survival of NGF-based results. Time was calculated from the time of MRD assessment, 3 months after transplantation. Negative patients are represented in black; positive patients are represented in red. Patients at risk are shown at each time point below plots; events are represented between parentheses. Median PFS of positive patients was 46.7 and 34.2 months for NGS and NGF, respectively. Median PFS was not achieved by negative patients. MRD minimal residual disease, NGF next-generation flow, NGS next-generation sequencing.

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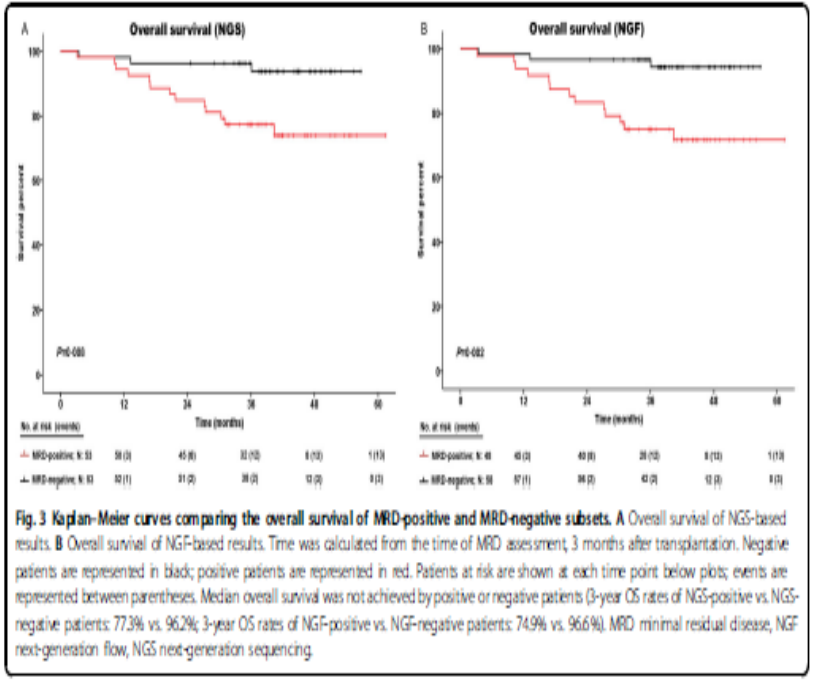


**Fig. 3 Kaplan-Meier curves comparing the overall survival of MRD-positive and MRD-negative subsets. A** Overall survival of NGS-based results. **B** Overall survival of NGF-based results. Time was calculated from the time of MRD assessment, 3 months after transplantation. Negative patients are represented in black; positive patients are represented in red. Patients at risk are shown at each time point below plots; events are represented between parentheses. Median overall survival was not achieved by positive or negative patients (3-year OS rates of NGS-positive vs. NGS-negative patients: 77.3% vs. 96.2%; 3-year OS rates of NGF-positive vs. NGF-negative patients: 74.9% vs. 96.6%). MRD minimal residual disease, NGF next-generation flow, NGS next-generation sequencing.

# A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma

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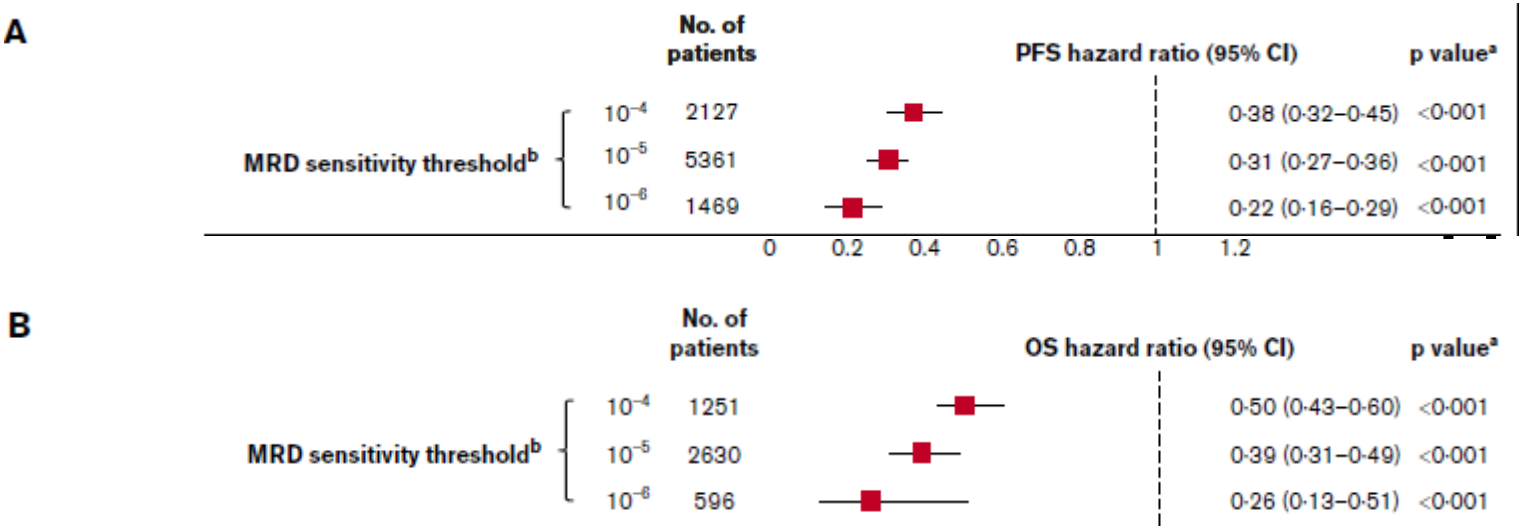


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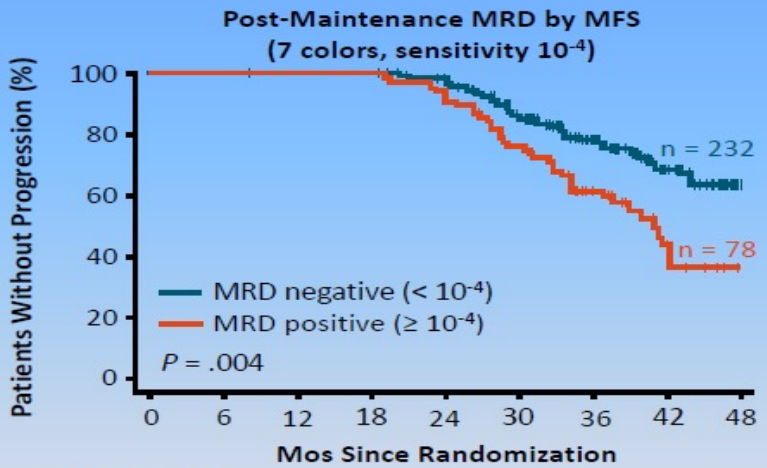
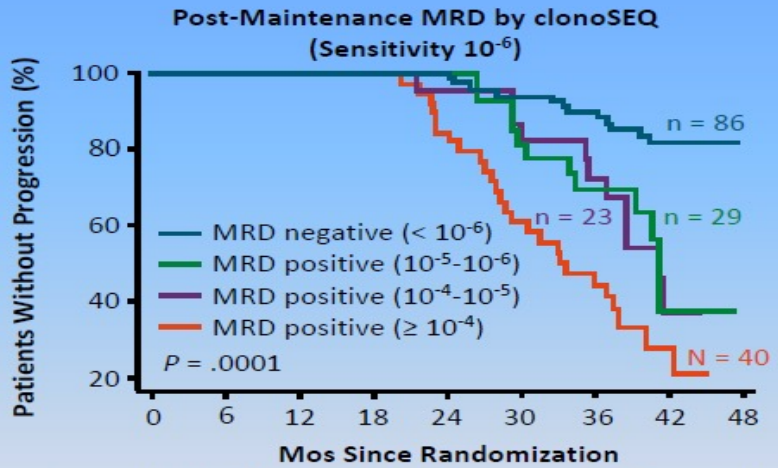
# Comparison of NGS and Flow Cytometry in DFCI IFM 2009 Post Maintenance: Sensitivity Matters




- Of 163 MRD-negative patients by flow cytometry (sensitivity $10^{-4}$), 84 (51%) were MRD positive by clonoSEQ (sensitivity $10^{-6}$)
- Patients that were MRD negative by flow and MRD positive by clonoSEQ (NGS) had worse outcomes

Avet-Loiseau. ASH 2015. Abstr 191.

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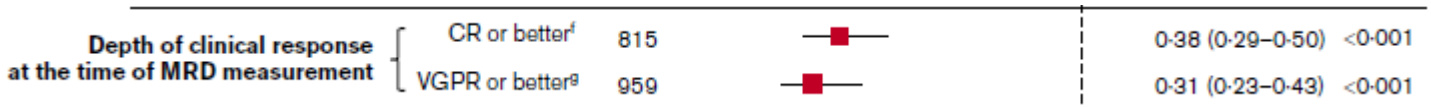


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# MRD in multiple myeloma: does CR really matter?

Bruno Paiva,[1] Jesus San-Miguel,[1] and Hervé Avet-Loiseau[2,3]

[1]Clinica Universidad de Navarra, Centro de Investigacion Medica Aplicada, Centro de Cáncer Universidad de Navarra, Instituto de Investigacion Sanitaria de Navarra, Pamplona, Spain; [2]Myeloma Genomics Laboratory, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France; and [3]Cancer Research Center of Toulouse, INSERM 1037, Toulouse, France

**Multiple myeloma embodies the paradigm of the deeper the response, the longer the survival. However, results are conflicting regarding achievement of complete remission (CR) and minimal residual disease (MRD) negativity; some patients with persistent M protein have undetectable MRD. We reviewed the frequency of this discordance and outcomes of these patients. We spotlight possible explanations for and consequences of conflicting response criteria and suggest that MRD be assessed in patients achieving very good partial response or better in clinical trials.**

# MRD in multiple myeloma: does CR really matter?

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| Study | Method | Sensitivity | Patients with undetectable MRD | | Outcome |
|---|---|---|---|---|---|
| | | | CR (%) | Less than CR (%) | |
| GEM2000 | Flow cytometry | $10^{-4}$ | 94/125 (75) | 31/125 (25) | Median PFS, 71 vs 65 mo |
| GEM2005MAS65 | Flow cytometry | $10^{-4}$ | 24/31 (77) | 7/31 (23) | Median PFS not reached in either* |
| PETHEMA/GEM† | Flow cytometry | $10^{-4}$ to $10^{-5}$ | 177/259 (68) | 82/259 (32) | Median PFS, 63 vs 62 mo |
| MRC Myeloma IX | Flow cytometry | $10^{-4}$ | 183/246 (74) | 63/246 (26) | Not reported‡ |
| NCT00861250 | Flow cytometry | $6 \times 10^{-6}$ | 56/91 (61.5) | 35/91 (38.5) | Not reported |
| NCT01402284 | Flow cytometry | $10^{-6}$ | 29/34 (85) | 5/34 (25) | Not reported |
| NCT01816971 | Flow cytometry | $10^{-4}$ to $10^{-5}$ | 34/45 (75.5) | 11/45 (24.5) | Not reported |
| GEM2012MENOS65 | NGF | $3 \times 10^{-6}$ | 182/205 (89) | 23/205 (11) | 4-y rate, 87% vs 78.5%; $P = .35$ |
| GMMG-HD6 | NGF | $6 \times 10^{-6}$ | 37/54 (68.5) | 17/54 (31.5) | Not reported |
| Tschautscher et al | NGF | $10^{-5}$ to $2 \times 10^{-6}$ | 116/204 (57) | 88/204 (43) | Median PFS not reached in either§ |
| GEM2000 | F-PCR | Not reported | 19/26 (73) | 7/26 (27) | Not reported |
| GEM2000 | ASO qRT-PCR | $10^{-6}$ | 6/7 (86) | 1/7 (14) | Not reported |
| NCT00861250 | ASO qRT-PCR | $4 \times 10^{-6}$ | 37/60 (62) | 23/60 (38) | Not reported |
| PETHEMA/GEM‖ | NGS | $10^{-6}$ | 26/30 (87) | 4/30 (13) | Not reported |
| NCT01402284 | NGS | Not reported | 22/23 (96) | 1/23 (4) | Not reported |
| IFM-2009 | NGS | $10^{-6}$ | 54/90 (60) | 36/90 (40) | Not reported |

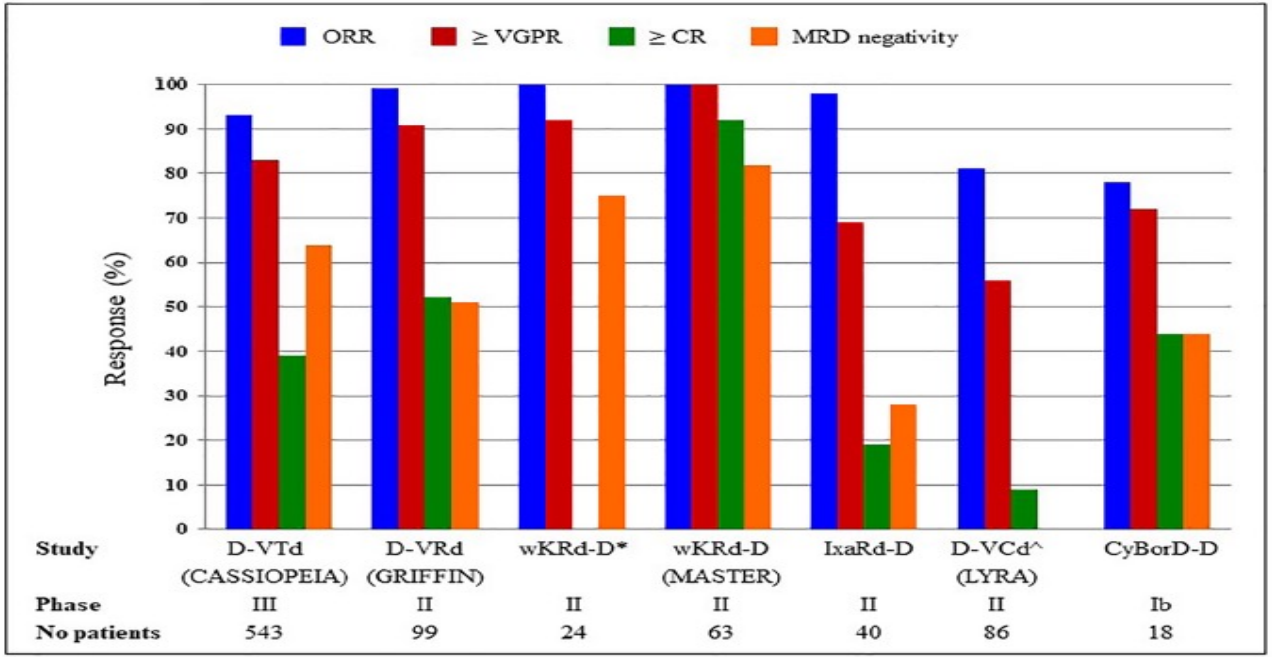


**FIGURE 1** | D-VTd, daratumumab, bortezomib, thalidomide, dexamethasone; D-VRd, daratumumab, bortezomib, lenelidomide, dexamethasone; wKRd_D, weekly carfilzomib, lenalidomide, dexamethasone, daratumumab; IxaRd-D, ixazomib, lenalidomide, dexamethasone, daratumumab; D-VCd and CyBorD-D, daratumumab, cyclophosphamide, bortezomib, dexamethasone. *≥ CR not available; ^MRD status not available.

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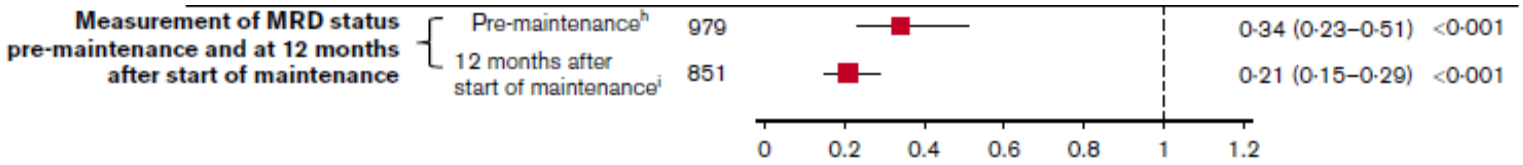


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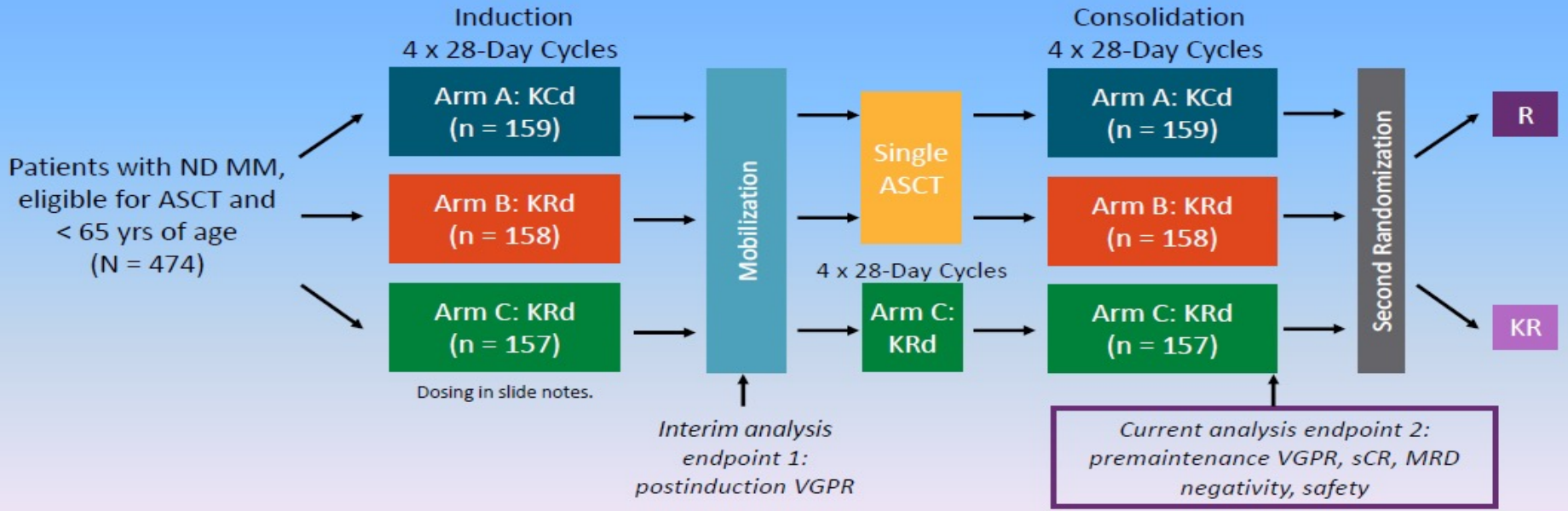
# FORTE Premaintenance Analysis: Study Design

- Multicenter, randomized, open-label phase II study




Gay. ASH 2018. Abstr 121.

Slide credit: clinicaloptions.com

# Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial

Francesca Gay*, Pellegrino Musto*, Delia Rota-Scalabrini, Luca Bertamini, Angelo Belotti, Monica Galli, Massimo Offidani, Elena Zamagni, Antonio Ledda, Mariella Grasso, Stelvio Ballanti, Antonio Spadano, Michele Cea, Francesca Patriarca, Mattia D'Agostino, Andrea Capra, Nicola Giuliani, Paolo de Fabritiis, Sara Aquino, Angelo Palmas, Barbara Gamberi, Renato Zambello, Maria Teresa Petrucci, Paolo Corradini, Michele Cavo, Mario Boccadoro

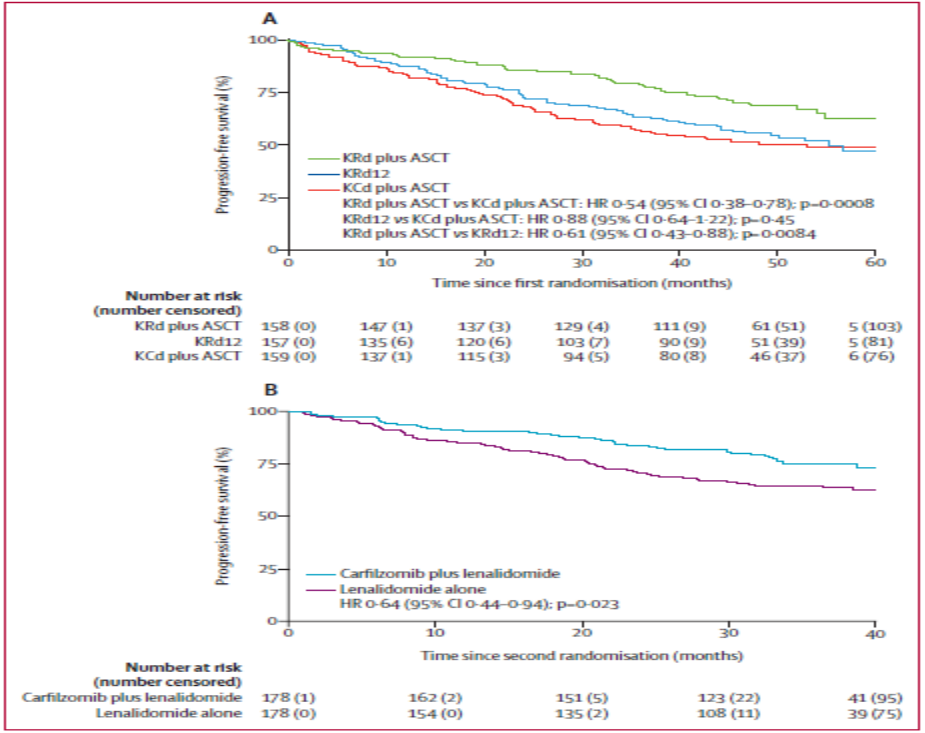
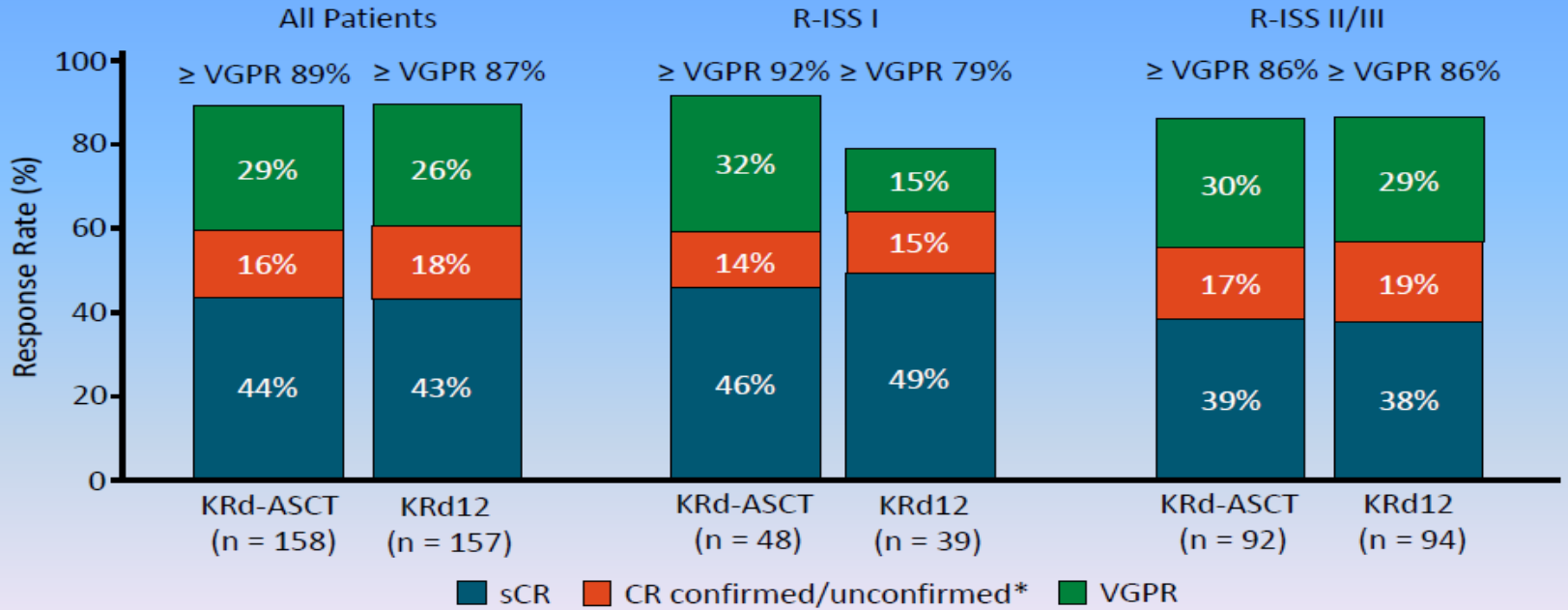



***Figure 2:*** **Survival outcomes according to first and second randomisation**
(A) Kaplan-Meier estimates of progression-free survival from first randomisation. (B) Kaplan-Meier estimates of progression-free survival from second (maintenance) randomisation. HR=hazard ratio. KRd=carfilzomib plus lenalidomide plus dexamethasone. ASCT=autologous stem-cell transplantation. KCd=carfilzomib plus cyclophosphamide plus dexamethasone. MEL200=melphalan at 200 mg/m². KRd plus ASCT=four KRd induction cycles, MEL200-ASCT, and four KRd consolidation cycles. KRd12=12 KRd cycles. KCd plus ASCT=four KCd induction cycles, MEL200-ASCT, and four KCd consolidation cycles.

# FORTE: Premaintenance Response Rates by Risk Status




*Unconfirmed patients missing immunofixation/sFLC analysis.

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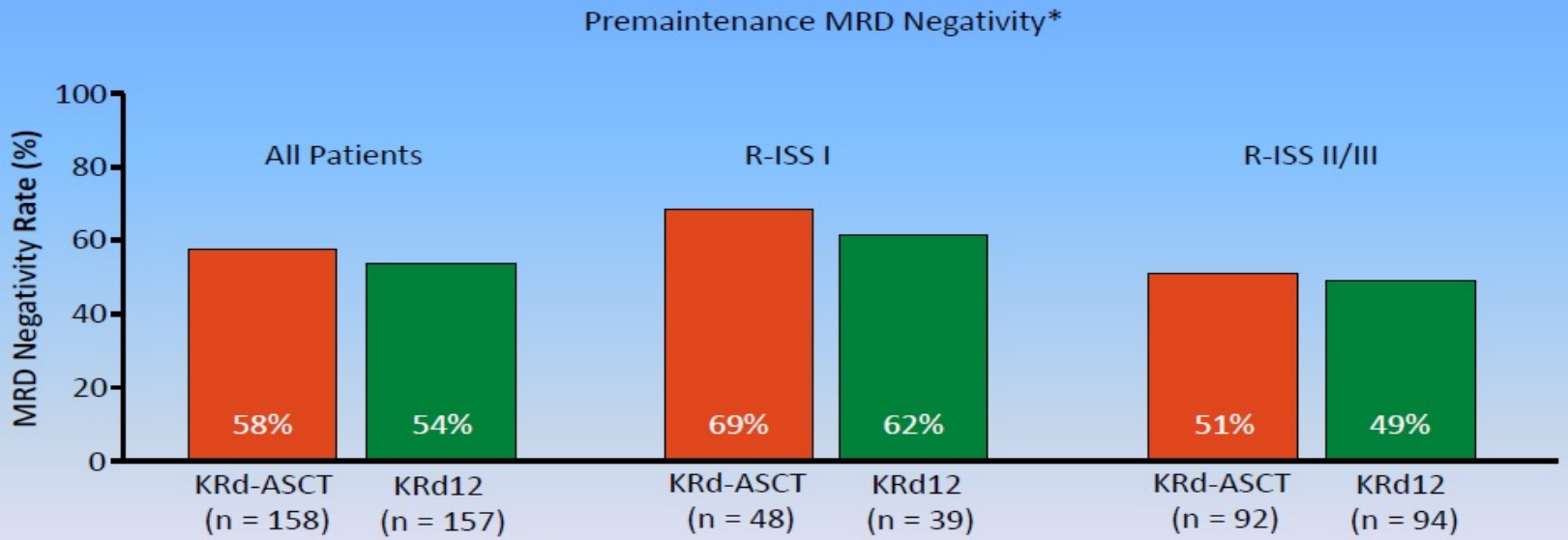
# FORTE: Premaintenance MRD Negativity by Risk Status




*MRD negativity was assessed by second-generation flow cytometry (sensitivity $10^{-5}$); Patients whose samples were not available for MRD analysis (~ 10%) were considered as positive; 13% of MRD-negative patients in KRd-ASCT arm and 17% in KRd12 arm had no available R-ISS data.

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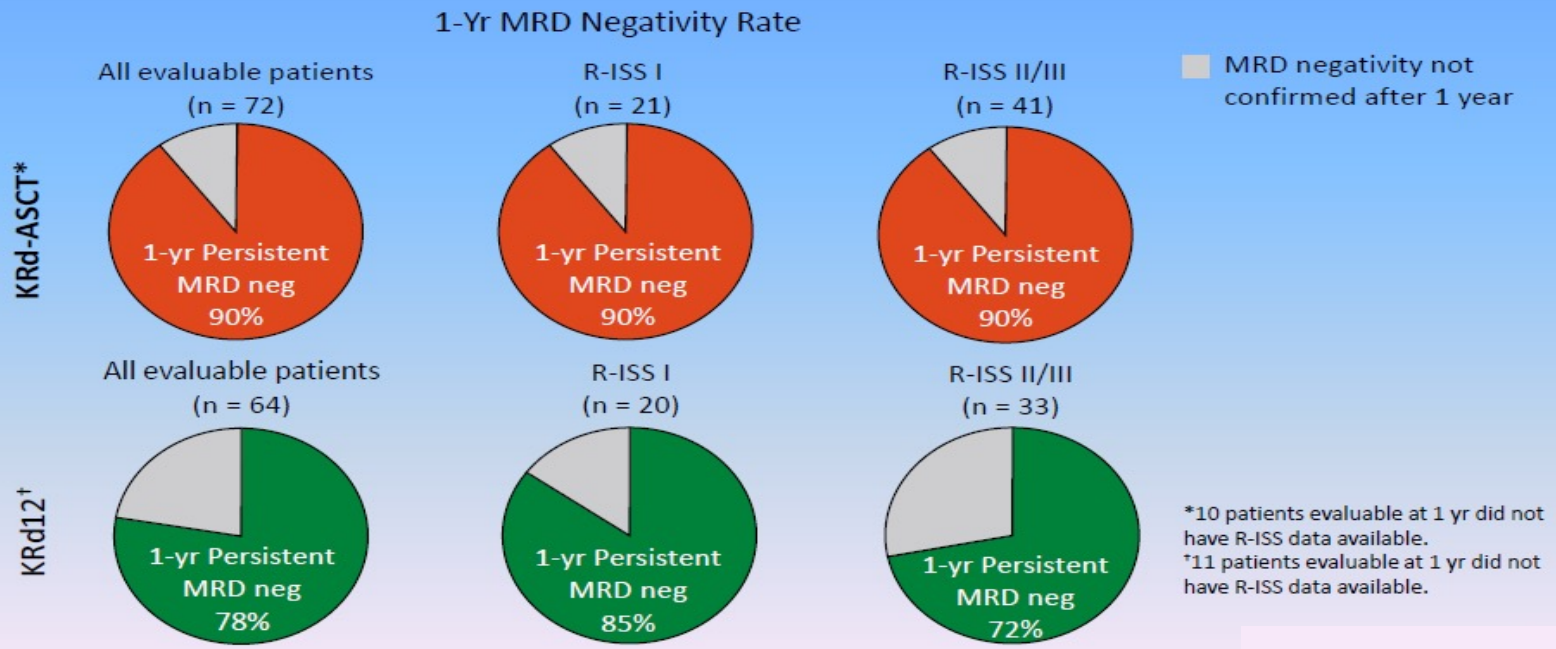
# FORTE: 1-Yr MRD Negativity Rate by Risk Status

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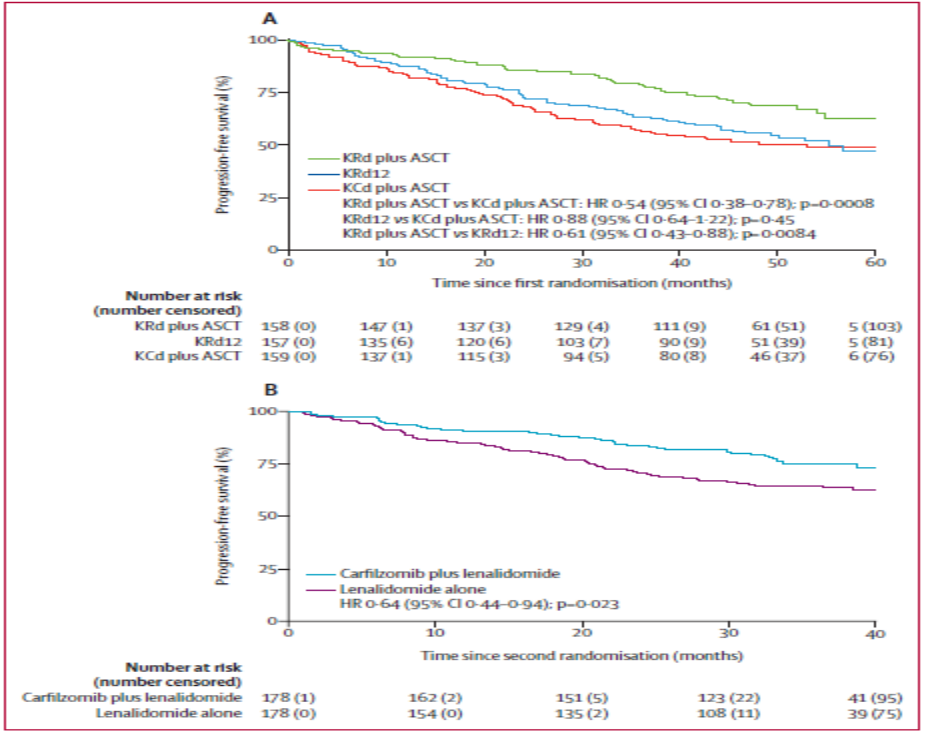


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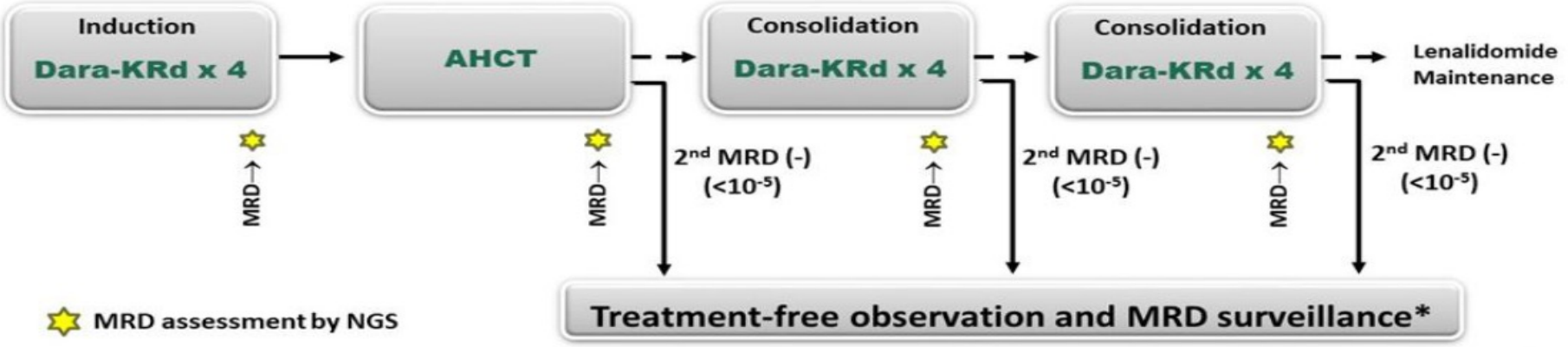
## MASTER trial: Daratumumab + KRD in transplant eligible patients

Primary endpoint: MRD-negative remission (< $10^{-5}$) on NGS assay

### Dara-KRd

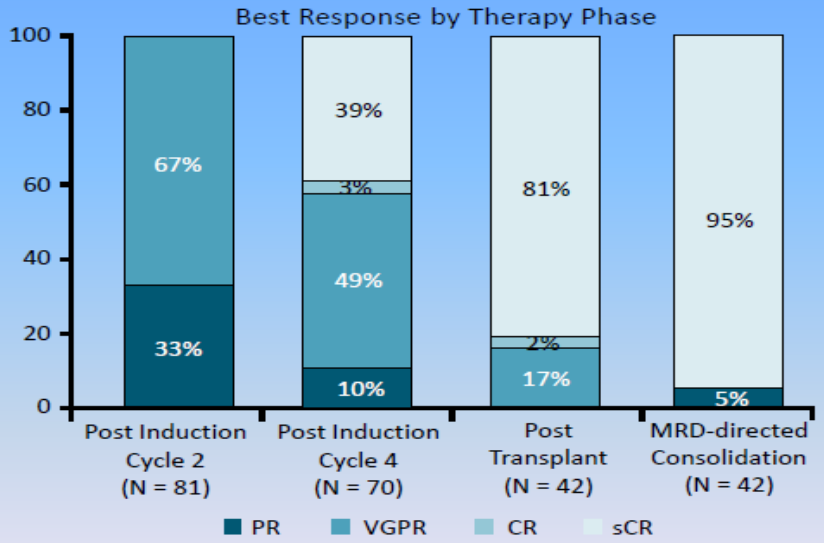
- Daratumumab 16 mg/m$^2$ days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m$^2$ Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22




*24 and 72 weeks after completion of therapy

MASTER trial

# MASTER: Best Response by Treatment Phase




| sCR, % (n) | Post Induction | Post Transplant | MRD-Based Consolida-tion |
|---|---|---|---|
| All patients | 39 (70) | 81 (42) | 95 (42) |
| Standard-risk patients | 44 (50) | 79 (29) | 97 (29) |
| High-risk patients [t(4;14), t(14;16) or del17p] | 25 (20) | 85 (13) | 91 (13) |

- n = 27 (n= 19 standard risk, n = 7 high risk) achieved MRD-negative status and entered observation phase; no relapse or MRD positivity at median median follow-up of 4.9 mos

Costa. ASH 2019. Abstr 860.

# Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): final report of the multicentre, single-arm, phase 2 trial

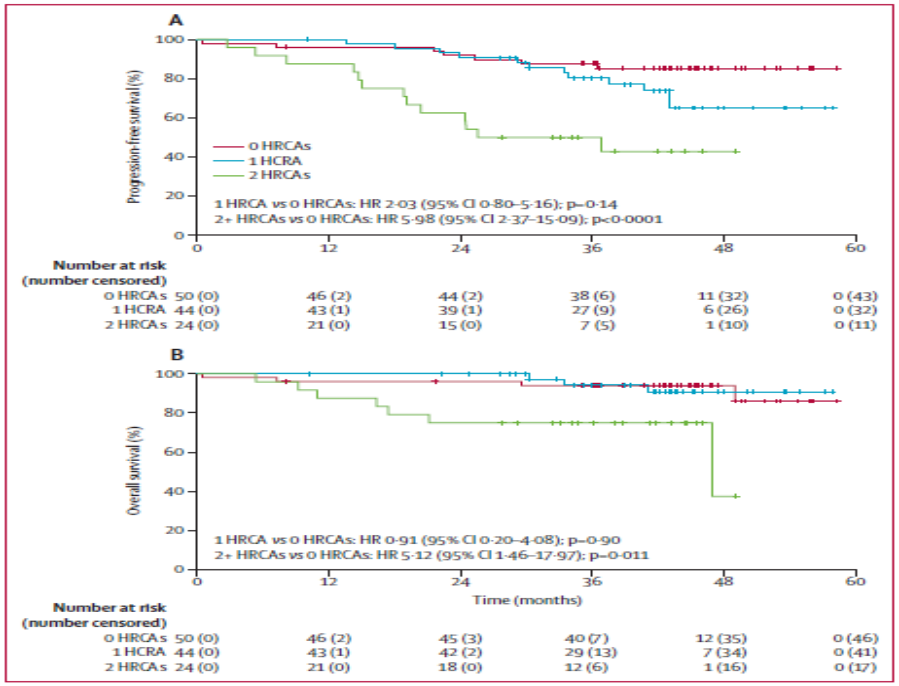



*Figure 2:* **Survival data for participants for whom MRD was evaluable, by cytogenetic risk group**
Progression-free survival (A) and overall survival (B) for the 118 participants for whom MRD was evaluable, according to cytogenetic risk group. HRCA=high-risk chromosome abnormality. MRD=minimal residual disease.

96/118
Reached
MDR neg

PFS 36 months
88% in 0 HRCAs
79% in 1 HRCAs
50% in 2 HRCAs

# Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): final report of the multicentre, single-arm, phase 2 trial

84/118
MDR SURE

PFS 36 months
88% in 0 HRCAs
85% in 1 HRCAs
60% in 2 HRCAs

24 months
cumulative incidence of progression
9% in 0 HRCAs
9% in 1 HRCAs
47% in 2 HRCAs

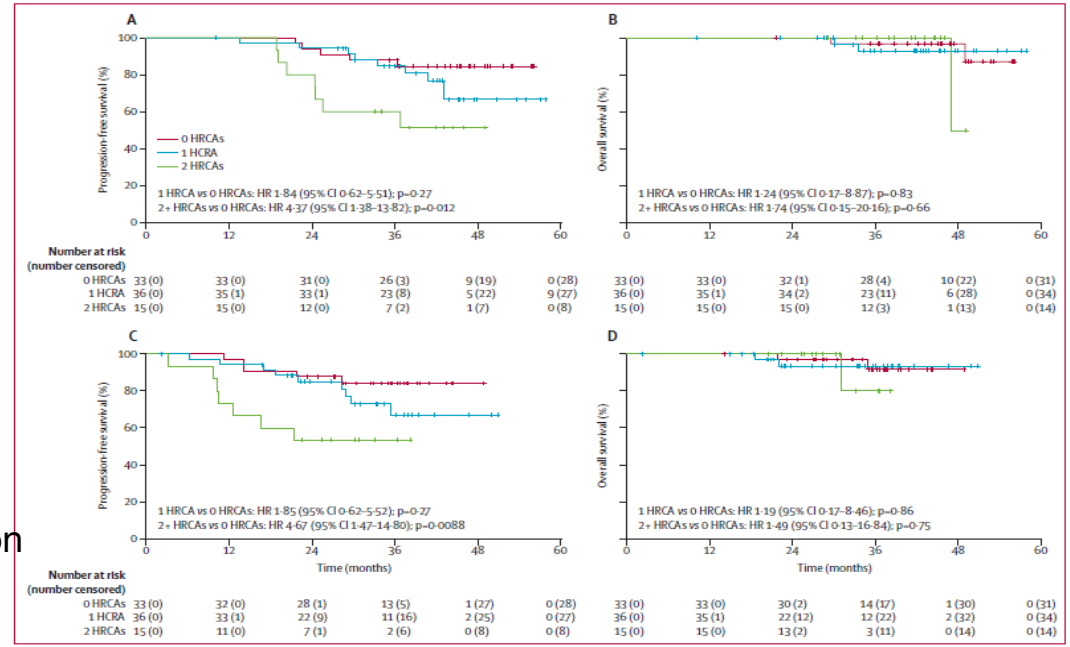



*Figure 3:* Survival data for participants who transitioned to MRD-SURE, by cytogenetic risk group
Progression-free survival (A, C) and overall survival (B, D) for the 84 participants who transitioned to MRD-SURE, according to cytogenetic risk group. In panels (C) and (D), the analysis is landmarked at the onset of MRD-SURE. HRCA=high-risk chromosome abnormality. MRD=minimal residual disease. MRD-SURE=treatment-free observation with MRD surveillance.

From CT cessation

27% Resumed Therapy

| Clinical trial | Patient population | Treatment scheme |
|---|---|---|
| UMCC 2018.056 (NCT04140162) | Phase 2 Study With Minimal Residual Disease (MRD) Driven Adaptive Strategy in Treatment for Newly Diagnosed Multiple Myeloma (MM) With Upfront Daratumumab-based Therapy | This phase 2 trial will test whether the combination of DaraRd (daratumumab + lenalidomide + dexamethasone) as induction therapy, followed by DRVd (daratumumab + lenalidomide + bortezomib + dexamethasone) consolidation therapy, if needed, will result in more patients achieving minimal residual disease (MRD)-negative status, relative to the standard of care. Consolidation therapy will be administered only to those patients with MRD-positive status after induction therapy. |
| MIDAS NCT04934475 | MInimal Residual Disease Adapted Strategy (MIDAS)<br><br>Phase 3 clinical trials in newly diagnosed MM patients | IFM 2020-02 will enroll patients eligible for ASCT less than 66 years. All patients will receive induction based on 6 cycles (28-day) of KRD-Isatuximab (Isa-KRD), in order to achieve deep responses and high MRD negativity rates. Patients will be classified at diagnosis according to cytogenetics (standard vs high-risk cytogenetics defined by the LP score including 17p deletion, t(4;14), del(1p32), gain 1q, trisomy 21 and trisomy 5. |
| PERSEUS (NCT03710603) | Phase 3 clinical trial Daratumumab, VELCADE (Bortezomib), Lenalidomide and Dexamethasone Compared to VELCADE, Lenalidomide and Dexamethasone in Subjects With Previously Untreated Multiple Myeloma | A Phase 3 Study Comparing Daratumumab, VELCADE (Bortezomib), Lenalidomide, and Dexamethasone (D-VRd) vs VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Previously Untreated Multiple Myeloma Who Are Eligible for High-dose Therapy. MRD-negative subjects will stop daratumumab after sustained MRD negativity for 12 months & after a min. of 24 months of maintenance. Daratumumab should be restarted at recurrence of MRD or confirmed loss of CR without disease progression. |
| DRAMMATIC (NCT04071457) | Phase 3 clinical trial Lenalidomide +/- Daratumumab/rHuPh20 as Post-ASCT Maintenance for MM w/MRD to Direct Therapy Duration (DRAMMATIC) | In this trial, patients who received HDCSCT are randomized between Lenalidomide for 2 years and Lenalidomide + Daratumumab. After 2 years of Maintenance, MRD is assessed to guide further therapy. MRD-positive patients will continue with the assigned treatment. MRD-negative patients will be further randomized to either continue or discontinue the assigned treatment. |

| | | |
|---|---|---|
| **EMN20 (NCT04096066)** | Phase 3 clinical trial. A Trial That Compares Two Treatments in Newly Diagnosed Myeloma Patients Not Eligible for Transplant (KRd vs Rd) | This protocol is a randomized, multicenter study designed to determine the MRD negativity and the PFS of KRd treatment regimen. Patients will be randomized in a 1:1 ratio to receive carfilzomib-lenalidomide-dexamethasone (KRd - Arm A) or lenalidomide-dexamethasone (Rd - Arm B). Patients will be stratified basing on international staging system (ISS) and fitness status using a web-based procedure completely concealed to study participants. Patients will be treated until disease progression or intolerance to the therapy. The only exception is for patients enrolled in KRd arm who achieve at least a VGPR during the first year of treatment and in sustained MRD negativity (MRD negative at least at 10-5 after one and two years of therapy): these patients will stop carfilzomib administration after 2 years, whereas treatment with lenalidomide and dexamethasone will be continued. |
| **MASTER-2 (NCT05231629)** | Phase 2 clinical trial. Sequential Therapy in Multiple Myeloma Guided by MRD Assessments (MASTER-2) | This research study will determine the proportion of patients with lowest minimal residual disease (MRD) response obtainable after receiving 6 cycles of study treatment. Minimal residual disease is multiple myeloma cells below the level of 1 cancer cell out of 100,000 in the bone marrow. For patients who become MRD "negative" (i.e. less than 1 cancer cell out of 100,000) at the end of 6 cycles of therapy, this study will study if that good response can be maintained with 3 additional cycles of treatment instead of use of autologous hematopoietic cell transplantation (AHCT). For patients who are MRD "positive" at the end of 6 cycles of therapy, this study will answer whether more patients can become and remain MRD "negative" with AHCT plus teclistamab in combination with daratumumab when compared with patients who undergo AHCT followed by lenalidomide (an established anti-myeloma drug) plus daratumumab. |
| **RADAR (EudraCT 2019-001258-25)** | Phase 3 clinical trial. Risk-Adapted therapy Directed According to Response comparing treatment escalation and de-escalation strategies in newly diagnosed patients with multiple myeloma (NDMM) suitable for stem cell transplant. | All participants will receive the same initial induction treatment and during this time will have genetic tests to determine whether they have 'standard-risk' or 'high-risk' disease. Following this chemotherapy treatment participants will receive AHCT. After induction treatment participants will be allocated to a second stage treatment group based on their genetic risk, high-risk or standard-risk, and on how well the myeloma has responded to the initial treatment. Each treatment group will then receive different combinations of medication to investigate their benefit. Treatment will comprise of combinations of isatuximab, bortezomib, cyclophosphamide, lenalidomide and dexamethasone. |

Discover Oncology

Research

# Real-world prognostic significance of attaining minimal residual disease negativity in newly diagnosed multiple myeloma

Jing Wang[1] · Jing Li[1] · Run Zhang[1] · Jianyong Li[1] · Lijuan Chen[1] · Yuanyuan Jin[1]

Received: 9 September 2023 / Accepted: 11 February 2024
Published online: 17 February 2024

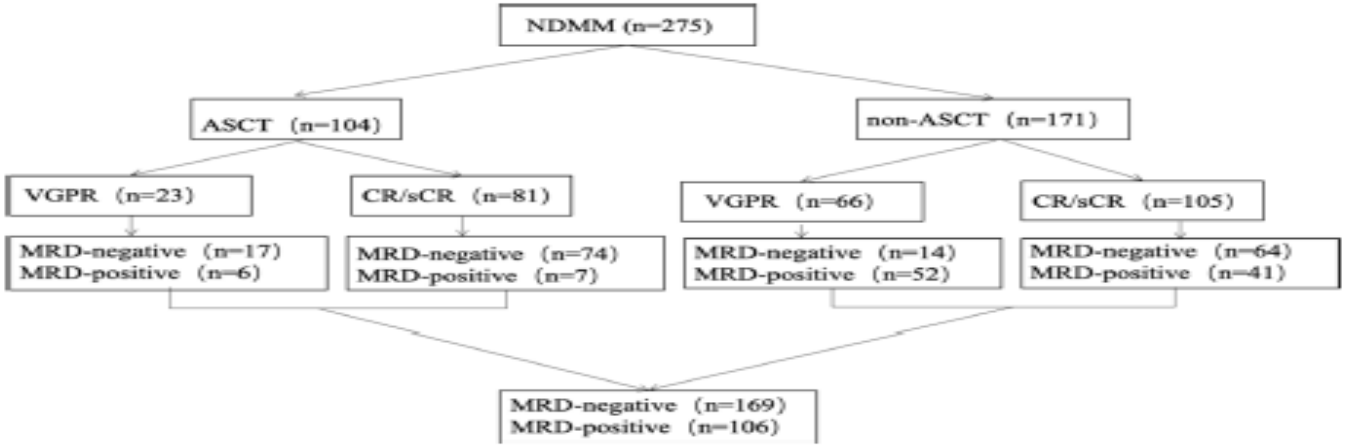




Fig. 1 Study flow chart

Discover Oncology

Research

# Real-world prognostic significance of attaining minimal residual disease negativity in newly diagnosed multiple myeloma

Jing Wang[1] · Jing Li[1] · Run Zhang[1] · Jianyong Li[1] · LiJuan Chen[1] · Yuanyuan Jin[1]

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Discover Oncology (2024) 15:38 | https://doi.org/10.1007/s12672-024-00891-8 Research

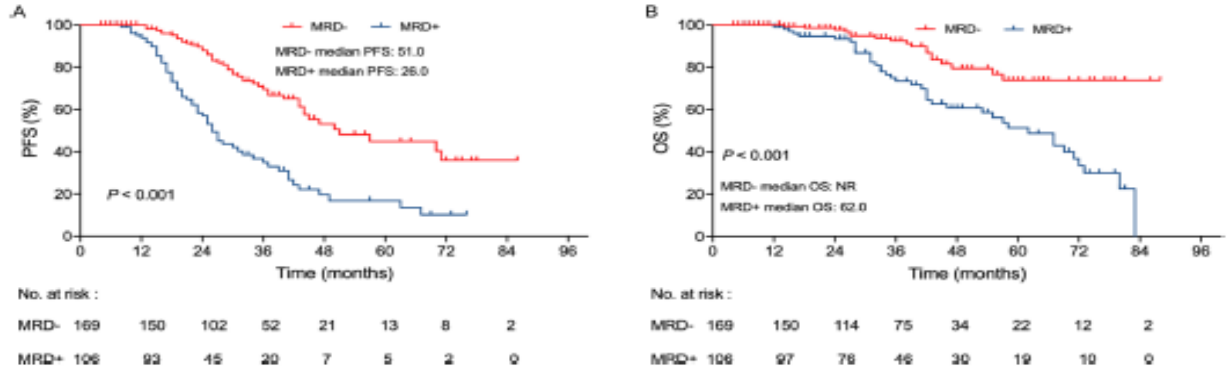



Fig. 3 Kaplan-Meier survival curves for PFS (**A**) and OS (**B**) according to MRD status

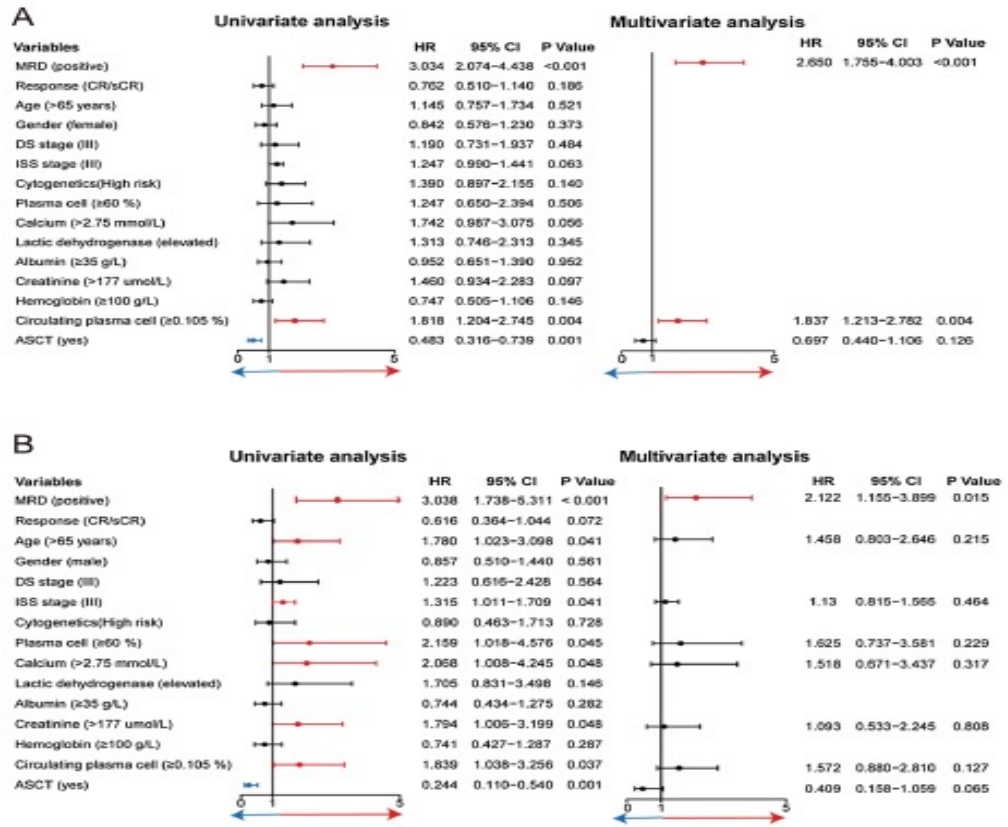



Fig. 4 Univariate and multivariate Cox proportional hazards regressions for PFS (**A**) and OS (**B**)

PFS

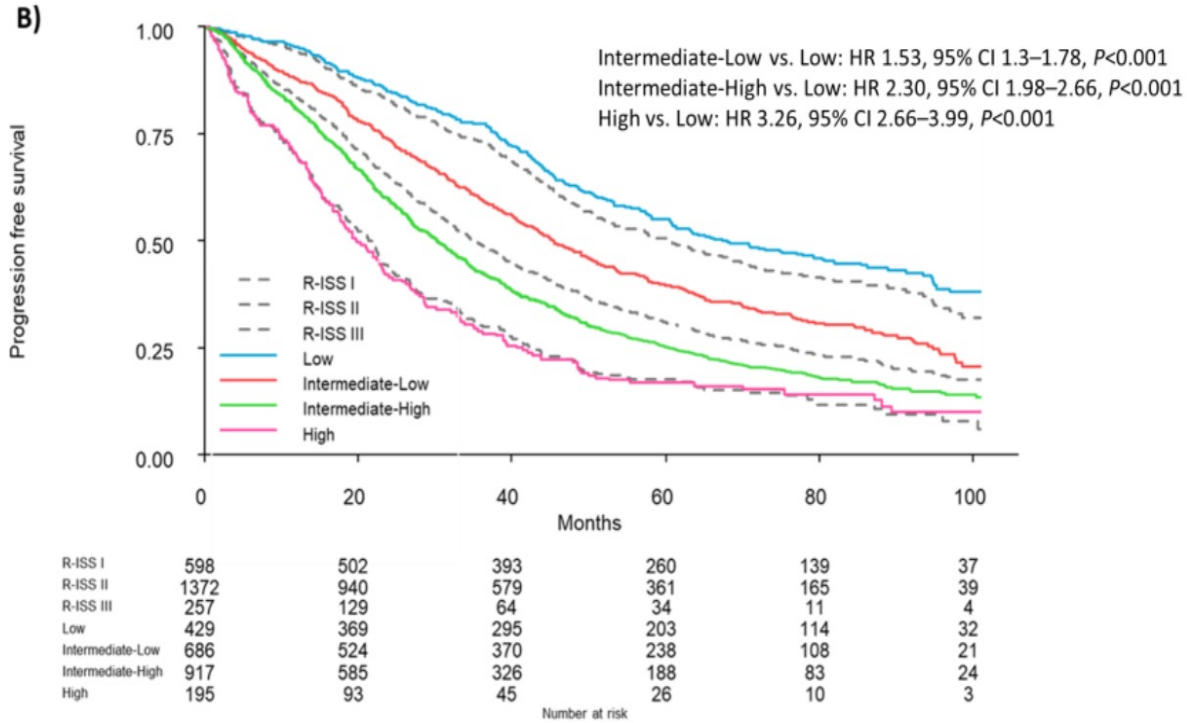
OS

- Measurable (minimal) residual disease (MRD) is one of the most powerful prognostic factors for progression-free survival and overall survival.
- There are several ways to assess for MRD; bone marrow methods such as next-generation sequencing and next-generation flow cytometry can achieve sensitivity thresholds of $10^{-6}$.
- Each increase in MRD sensitivity threshold is associated with improved prognostication, and sustained MRD negativity carries greater significance than a single instance of MRD negativity.
- Peripheral blood techniques, chiefly mass spectrometry, to assess for MRD are quickly moving from research only to clinical use.
- MRD-adapted clinical decision-making is controversial, but there is mounting evidence that MRD-guided de-escalation of therapy is feasible and may not compromise clinical outcomes.

**Measurable Residual Disease and Decision-Making in Multiple Myeloma**

Benjamin A. Derman, MD[a,*], Rafael Fonseca, MD[b]

Hematol Oncol Clin N Am 38 (2024) 477–495
https://doi.org/10.1016/j.hoc.2023.12.009




**Abbreviations**. OS, overall survival; PFS, progression-free survival; pts, patients; R-ISS, Revised International Staging System stage; HR, hazard ratio; CI, confidence interval; *P*, p-value.

## PFS according to the R2-ISS risk score

D'Agostino M et al. ASH 2020;Abstract 1329

| High-risk features | Definition |
|---|---|
| Patient-based factors | |
| Frailty status | IMWG frailty score<br>Modified IMWG frailty score<br>R-MCI<br>GAH |
| Disease-based factors | |
| Aggressiveness in the clinical presentation | Extramedullary disease (no bone-related plasmacytomas)<br>Plasma cell leukemia<br>LDH elevated |
| Cytogenetic abnormalities | del(17p), t(4;14), t(14;16), amp1q, del(1p) |
| Mutations | *TP53* |
| Biochemical abnormalities | LDH elevated<br>β2-microglobulin ≥5.5mg/L<br>Albumin levels ≤3.5mg/L |
| Prognostic scores | |
| R-ISS | R-ISS III: beta2-microglobulin ≥5.5mg/L plus either LDH elevated or high-risk CA (del(17p), t(4;14), or t(14;16)) |

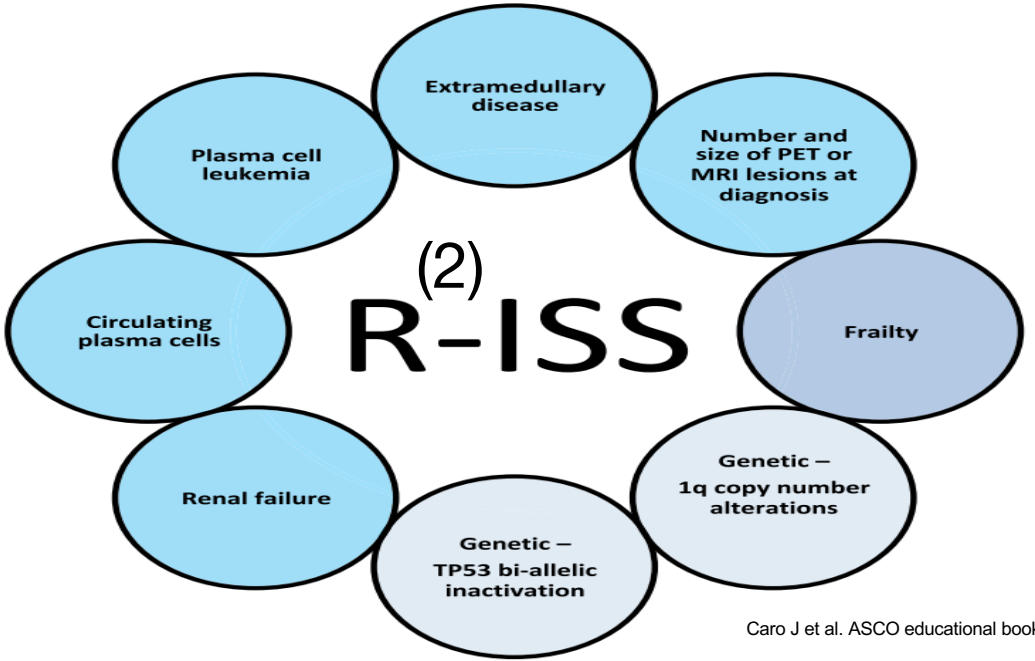
GAH, geriatric assessment in hematology; R-MCI, Revised Myeloma Comorbidity Index.

## Patient- and disease-based factors for the identification of high-risk MM



Mateos MV et al. ASH Education Program. Hematology 2021

# Proposed modifications to R-ISS to incorporate additional high risk features




Caro J et al. ASCO educational book 2021

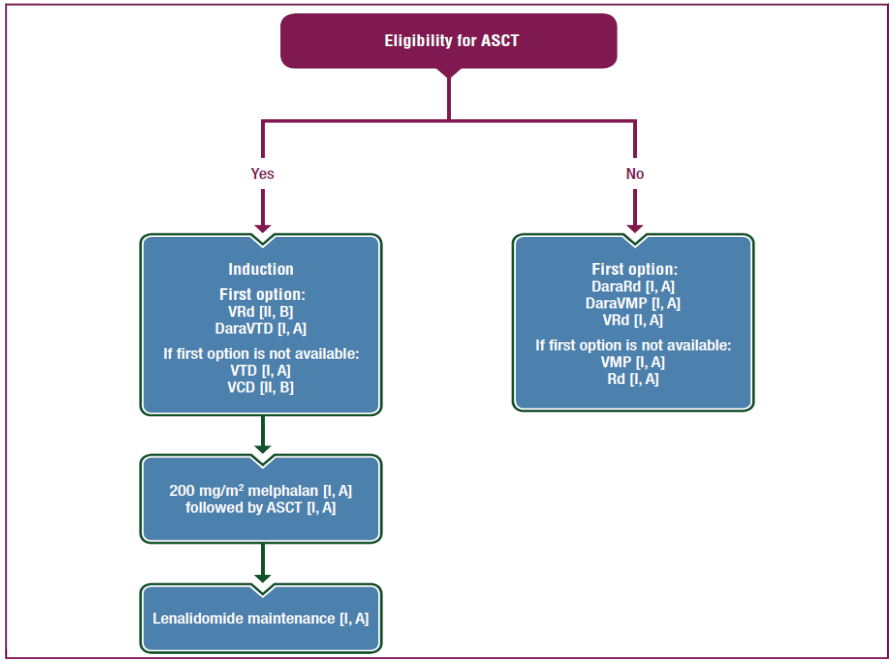



**Figure 1. Recommendations for MM front-line therapy.**
ASCT, autologous stem cell transplantation; DaraRd, daratumumab/lenalidomide/dexamethasone; DaraVMP, daratumumab/bortezomib/melphalan/prednisone; DaraVTD, daratumumab/bortezomib/thalidomide/dexamethasone; MM, multiple myeloma; Rd, lenalidomide/dexamethasone; VCD, bortezomib/cyclophosphamide/dexamethasone; VMP, bortezomib/melphalan/prednisone; VRd, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

# Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. A. Dimopoulos[1], P. Moreau[2], E. Terpos[1], M. V. Mateos[3], S. Zweegman[4], G. Cook[5], M. Delforge[6], R. Hájek[7], F. Schjesvold[8,9], M. Cavo[10], H. Goldschmidt[11], T. Facon[12], H. Einsele[13], M. Boccadoro[14], J. San-Miguel[15], P. Sonneveld[16] & U. Mey[17], on behalf of the EHA Guidelines Committee* and ESMO Guidelines Committee*

[1]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Hematology, University Hospital Hôtel-Dieu, Nantes, France; [3]University Hospital of Salamanca, IBSAL, Cancer Research Center, Salamanca, Spain; [4]Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [5]Leeds Cancer Centre and University of Leeds, Leeds, UK; [6]Department of Hematology, University Hospital Leuven, Leuven, Belgium; [7]Faculty of Medicine, University Hospital Ostrava, Ostrava, Czech Republic; [8]Oslo Myeloma Center, Oslo University Hospital, Oslo; [9]KG Jebsen Center for B Cell Malignancies, University of Oslo, Oslo, Norway; [10]Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [11]University Hospital Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany; [12]Hôpital Claude Huriez, Lille University Hospital, Lille, France; [13]Department of Internal Medicine II, University Hospital Wurzburg, Wurzburg, Germany; [14]Division of Hematology, University of Torino, AOU Città della Salute e della Scienza di Torino, Torino, Italy; [15]Clinica Universidad de Navarra, CIMA, IDISNA, CIBERONC, Pamplona, Spain; [16]Erasmus Medical Center Cancer Institute, Rotterdam, Netherlands; [17]Department of Oncology and Hematology, Kantonsspital Graubünden, Chur, Switzerland

Available online 3 February 2021

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

*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*

(Continued from previous page)

| | |
|---|---|
| Clinical relapse | Clinical relapse requires one or more of the following criteria:<br>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;<br>Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);<br>Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion;<br>Hypercalcaemia (>11 mg/dL);<br>Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions;<br>Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;<br>Hyperviscosity related to serum paraprotein |
| Relapse from complete response (to be used only if the end point is disease-free survival) | Any one or more of the following criteria:<br>Reappearance of serum or urine M-protein by immunofixation or electrophoresis;<br>Development of ≥5% plasma cells in the bone marrow;<br>Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above) |
| Relapse from MRD negative (to be used only if the end point is disease-free survival) | Any one or more of the following criteria:<br>Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);<br>Reappearance of serum or urine M-protein by immunofixation or electrophoresis;<br>Development of ≥5% clonal plasma cells in the bone marrow;<br>Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia) |

# Fattori prognostici nel mieloma

## Therapy-related

- Response/Refractoriness to previous therapy
- Prior stem cell transplant
- Toxicity: myelosuppression, neuropaty, thrombosis, GI tolerance
- Single agent vs combination therapies
- Mode af administration (PO, SQ, IV)
- Cost
- Risk of second primary malignancy

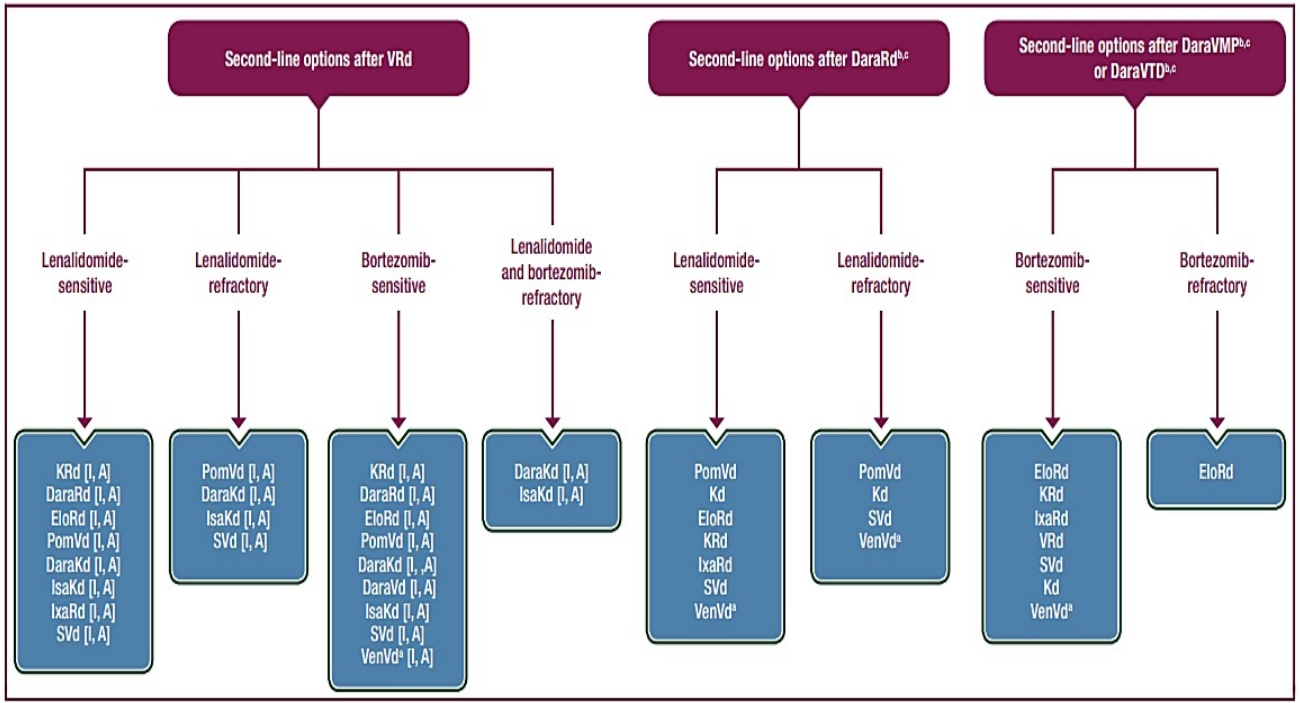
## Disease-related

- Risk status (high, intermediate, standard)
- Depth and duration of response to previous therapy
- Aggressiveness of relapse (rapid M protein growth, organ damage, plasma cell leukemia)
- Chromosomal abnormalities

## Patient-related

- Age
- Performance status
- Comorbidities (renal insufficiency, preexisting neuropaty, diabetes, cardiac)
- Poor BM reserve (previous myelosuppression)
- Social factors (support system, accessibility to treatment center)

patients who received a front-line therapy

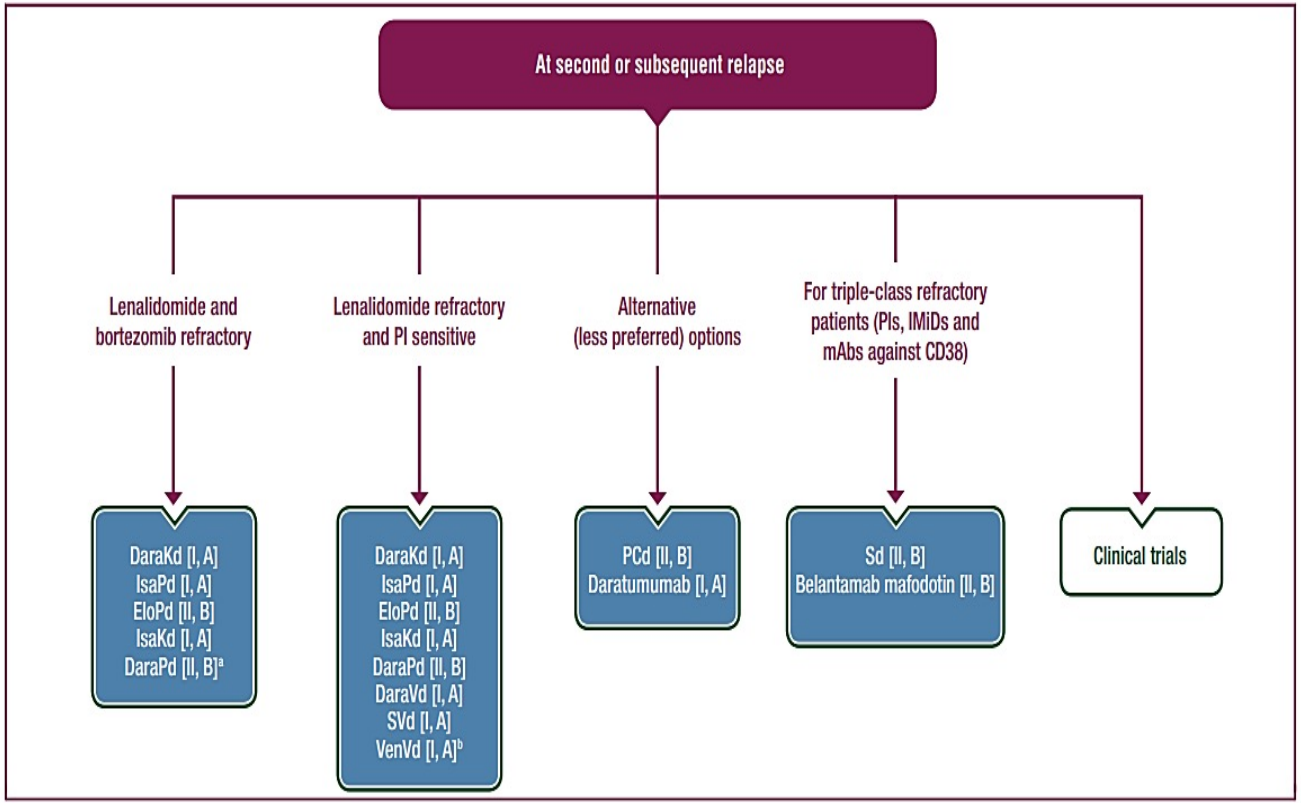




Dimopoulos et al, annals of OncologY, VOLUME 32, ISSUE 3, P309-322, MARCH 01, 2021

# ESMO 2021

## patients who receive a third or subsequent line of therapy






Dimopoulos et al, annals of OncologY, VOLUME 32, ISSUE 3, P309-322, MARCH 01, 2021

# How Do (Should) We Use MRD in the Clinic Today?

| Flow Cytometry | Next-Gen Sequencing | Imaging |
|---|---|---|
| ▪ Defined: absence of clonal plasma cells in bone marrow aspirate using next-gen flow cytometry | ▪ Defined: absence of clonal plasma cells in BM aspirate with < 2 identical DNA sequence reads | ▪ Defined: disappearance of areas of tracer uptake at baseline PET/CT or decrease to < normal surrounding tissue |
| ▪ Sensitivity: $10^{-4}$ to $10^{-6}$ | ▪ Sensitivity: $10^{-4}$ to $10^{-6}$ | ▪ Sensitivity: high (?) |
| ▪ Need for specialized, validated equipment | ▪ Sent to lab for evaluation (clonoSEQ) | ▪ Can be used as monitoring along with other assays |

- ClonoSEQ FDA approved for MRD testing in acute lymphoblastic leukemia or myeloma
- **BUT there are currently no data on altering length of induction therapy, need for ASCT and/or consolidation, or maintenance based on MRD results**

# Convegno Regionale SIE

CRO Aviano (PN) - 9 ottobre 2024

MMR

COSTI 250 E/determinazione (costo kit impiegato)

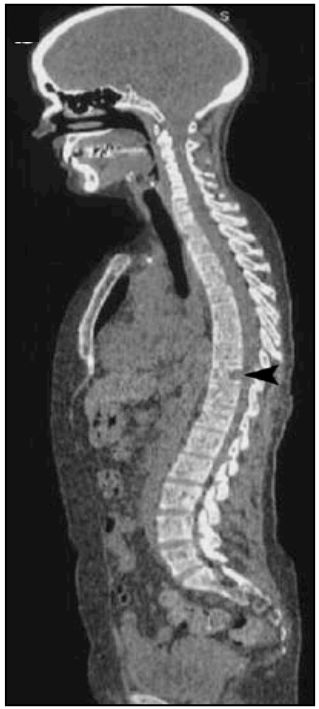
TEMPI DI ESECUZIONE

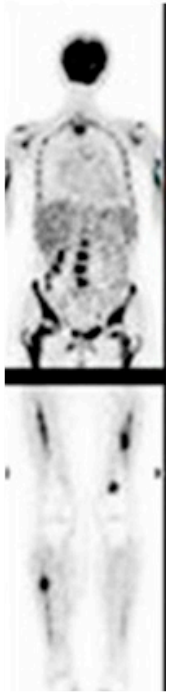
| | | |
|---|---|---|
| processazione del campione | 2 ore | > 3 ore |
| acquisizione al citofluorimetro | variabile (10-15 m) | |
| analisi dei risultati | 45 m | |
| refertazione | 5 m | |

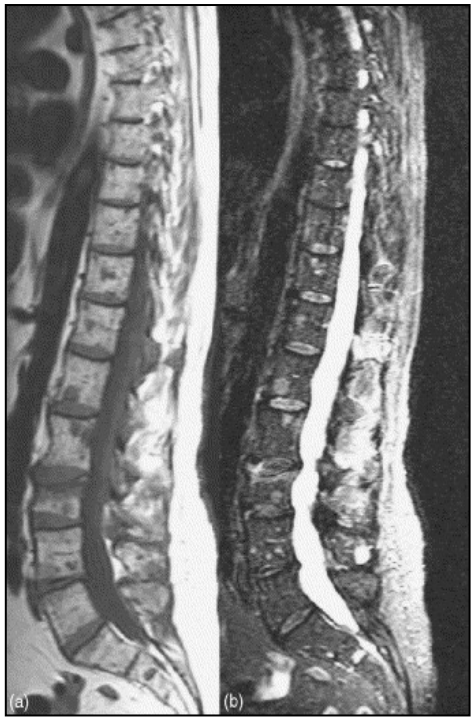
1-2 OPERATORE ESPERTO

# Diagnostic Imaging in MM

- Low-dose whole-body CT (LDWBCT) or MRI recommended for diagnosis and monitoring bone damage
- ≥ 1 site of osteolytic bone destruction (≥ 5 mm) seen on CT (including LDWBCT) or PET/CT indicative of active myeloma
- Absence of bone disease on skeletal survey is not








Rajkumar. Multiple myeloma: 2015 update on diagnosis, risk-stratification, and management. Am J Hematol 2015; 90:29, 2015.

# Multiple myeloma: Every year a new standard?

MM

Both criteria must be met:

- Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma
- Any one or more of the following myeloma-defining events:
  - Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically
    - Hypercalcemia: serum calcium > 0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L (>2 mg/dL)
    - Anemia: hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value < 10 g/dL
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, computerized tomography (CT), or positron emission tomography–CT (PET-CT)
  - Clonal bone marrow plasma cell percentage ≥ 60%
  - Involved:uninvolved serum free light chain (FLC) ratio ≥ 100 (involved FLC level must be ≥ 100 mg/L)
  - >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

**How to cite this article:** Rajkumar SV. Multiple myeloma: Every year a new standard? *Hematological Oncology*. 2019;37(S1):62–65. https://doi.org/10.1002/hon.2586

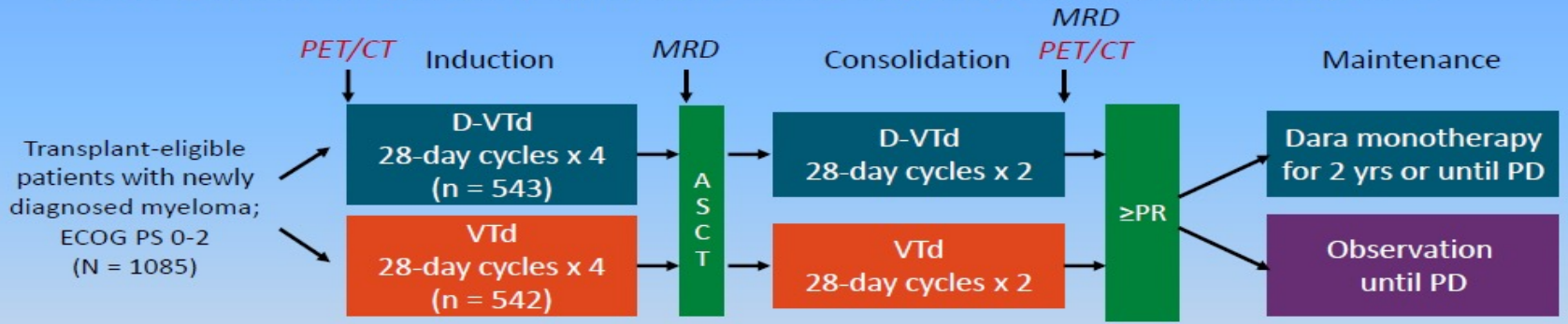
# FORTE Premaintenance Analysis: Background

- Current standard of care for newly diagnosed MM defined as induction with a triplet regimen including a **PI and an IMiD, typically VRd**, followed by ACST ± **consolidation** and **maintenance therapy**
- Several regimens evaluated as pretransplant induction for newly diagnosed MM
  - ≥ VGPR post transplant: KRd, 96%[1]; VTD, 60%[2]; VRd, 58%[3]
- Current study compared safety, efficacy of KRd induction–ASCT–KRd consolidation vs 12 cycles of KRd vs KCd induction–ASCT–KCd consolidation
  - Interim analysis: ≥ VGPR postinduction, KCd vs KRd: 61% vs 74% ($P$ = .01)[4]
  - Current analysis reports data from follow-up through post consolidation[5]

1. Jakubowiak. EHA 2015. Abstr S787. 2. Rosiñol. Blood. 2012;120:1589. 3. Roussel. J Clin Oncol. 2014;32:2712. 4. Gay. ASCO 2017. Abstr 8003. 5. Gay. ASH 2018. Abstr 121.

# CASSIOPEIA Phase III Trial

- CASSIOPEIA showed significantly higher rates of MRD negativity with D-VTd, and longer PFS[1]




- CASSIOPET companion study conducted in 268 patients from CASSIOPEIA (median f/u: 29.2 mos)[2]
- PET/CT images interpreted by blinded independent team of nuclear medicine physicians using IMAGYS platform
  - Baseline assessments: BM diffuse uptake, bone focal lesions, EMD, PMD, most-intense FDG uptake, $SUV_{max}$
  - Responses defined by Deauville score of most intense lesion at Day 100
    - CR: lesion uptake < MBP
    - uCR: lesion uptake between MPB and liver

1. Moreau. Lancet. 2019;394:29 2. Moreau. ASH 2019. Abstr 692.

LETTER TO THE EDITOR

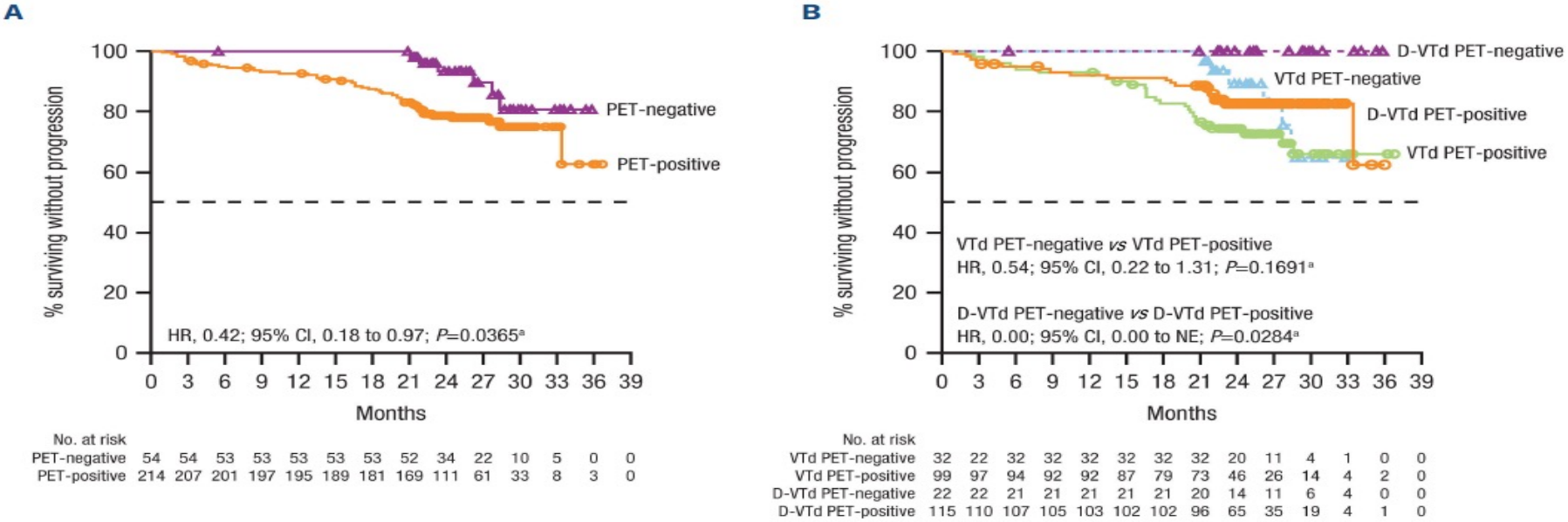



**Figure 2. Progression-free survival outcomes by baseline positron emission tomography/computed tomography status in CASSIOPET.** (A) Progression-free survival (PFS) for baseline positron emission tomography (PET)-negative patients *versus* PET-positive patients and (B) PFS for baseline PET-negative patients *versus* PET-positive patients by treatment group. Baseline PET assessments were performed prior to the first dose of study drug, and PFS was based on time from first randomization. CI: confidence interval; D-VTd: daratumumab plus bortezomib/thalidomide/dexamethasone; HR: hazard ratio; NE: not estimable; VTd: bortezomib/thalidomide/dexamethasone. [a]Based on a log-rank test.

**Table 1.** Univariable and multivariable analyses of the prognostic value of baseline positron emission tomography (PET) characteristics on progression-free survival based on all patients with PET measurements at baseline (54/268 progression-free survival events).

| Baseline characteristics | PFS events (n/N) | Univariable analysis | | Analysis adjusted for treatment group and r-ISS | | Multivariable analysis adjusted for treatment group, r-ISS, and all baseline PET/CT characteristics | |
|---|---|---|---|---|---|---|---|
| | | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| PET status | | | | | | | |
| Positive | 48/214 | 1.00 | 0.037 | 1.00 | 0.039 | 1.00 | 0.372 |
| Negative | 6/54 | 0.42 (0.18-0.97) | | 0.41 (0.17-0.95) | | 0.55 (0.15-2.04) | |
| Presence of FL | | | | | | | |
| No | 12/88 | 1.00 | 0.047 | 1.00 | 0.051 | 1.00 | 0.753 |
| Yes | 42/180 | 1.90 (1.00-3.60) | | 1.90 (1.00-3.62) | | 0.84 (0.29-2.44) | |
| Presence of diffuse BM infiltration[a] | | | 0.220 | | 0.234 | | 0.922 |
| No | 24/139 | 1.00 | | 1.00 | | 1.00 | |
| Yes | 30/129 | 1.40 (0.82-2.39) | | 1.39 (0.81-2.39) | | 1.03 (0.54-1.96) | |
| Presence of PMD | | | | | | | |
| No | 36/221 | 1.00 | <0.001 | 1.00 | <0.0001 | 1.00 | 0.001 |
| Yes | 18/47 | 2.81 (1.59-4.98) | | 3.82 (2.11-6.92) | | 3.16 (1.60-6.28) | |
| Presence of EMD | | | | | | | |
| No | 46/247 | 1.00 | 0.034 | 1.00 | 0.012 | 1.00 | 0.041 |
| Yes | 8/21 | 2.21 (1.04-4.69) | | 2.68 (1.24-5.77) | | 2.32 (1.04-5.19) | |
| FL hottest $SUV_{max}$[b,c] | | 1.03 (1.00-1.06) | 0.043 | 1.06 (1.02-1.10) | 0.002 | 0.96 (0.85-1.08) | 0.479 |
| Bone $SUV_{max}$[c] | | 1.04 (1.01-1.07) | 0.021 | 1.06 (1.03-1.10) | <0.001 | 1.07 (0.96-1.19) | 0.223 |
| LDH | | | | | | | |
| <Upper limit | 24/155 | 1.00 | 0.017 | —[d] | — | — | — |
| ≥Upper limit | 28/103 | 1.92 (1.11-3.31) | | —[d] | | — | |
| Cytogenetic risk | | | | | | | |
| Standard | 41/219 | 1.00 | 0.158 | —[d] | — | — | — |
| High | 13/49 | 1.56 (0.84-2.92) | | —[d] | | — | |
| Serum $\beta_2$ microglobulin | | | | | | | |
| <3.5 mg/L | 27/167 | 1.00 | 0.009 | —[d] | — | — | — |
| 3.5-5.4 mg/L | 13/62 | 1.43 (0.74-2.78) | | —[d] | | — | |
| >5.4 mg/L | 14/39 | 2.68 (1.40-5.12) | | —[d] | | — | |
| ISS stage | | | | | | | |
| I | 18/118 | 1.00 | 0.010 | — | — | — | — |
| II | 22/111 | 1.34 (0.72-2.50) | | —[d] | | — | |
| III | 14/39 | 2.80 (1.39-5.65) | | —[d] | | — | |

BM: bone marrow; CI: confidence interval; EMD: extramedullary disease; FL: focal lesion; HR: hazard ratio; ISS: IMWG International Staging System; IMWG: International Myeloma Working Group; LDH: lactate dehydrogenase; PET: positron emission tomography; PFS: progression-free survival; PMD: paramedullary disease; r-ISS: IMWG revised International Staging System; $SUV_{max}$: maximum standardized uptake value. [a]Diffuse BM infiltration is considered to be present if visual analysis (Deauville scale) of BM uptake indicates the residual uptake to be > liver activity (4) or >> liver activity (5); otherwise, the diffuse BM infiltration is considered to be absent. [b]Imputed to 1 for patients with no presence of FL. [c]Highest result among FL hottest $SUV_{max}$, BM uptake $SUV_{max}$, PMD hottest $SUV_{max}$. Imputed FL hottest $SUV_{max}$ to 1 for patients with no presence of FL. [d]Covariates not included in the adjusted analysis.

LETTER TO THE EDITOR

# Prognostic value of positron emission tomography/computed tomography in transplant-eligible newly diagnosed multiple myeloma patients from CASSIOPEIA: the CASSIOPET study

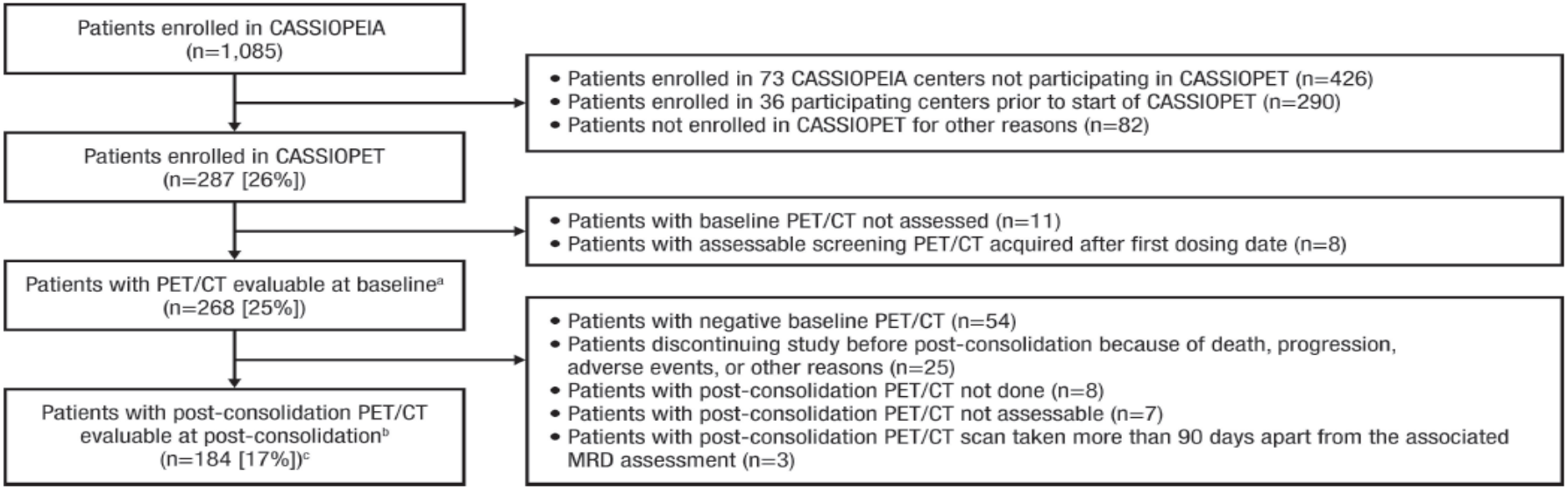



**Figure 1. STROBE flow chart for CASSIOPET.** ASCT: autologous stem cell transplant; MRD: minimal residual disease; PET: positron emission tomography; PET/CT: positron emission tomography/computed tomography. [a]Baseline PET–evaluable patients were defined as patients with assessable baseline PET acquired before the first dosing date. [b]Post-consolidation PET–evaluable patients included patients with assessable day 100 post-ASCT PET data and positive baseline PET but excluded patients with a date of PET/CT post-consolidation >±90 days from the date of the day 100 MRD assessment. [c]13 patients had unevaluable baseline PET/CT but evaluable post-consolidation PET/CT and were included in the post-consolidation analysis.

Table 1. Staging and risk stratification systems for MM with their prognostic factors and implications for survival.

| Staging System or Stratification model | Year | Staging (prognostic) criteria: Tumor mass (clinical) and/or other parameters | Staging (prognostic) criteria: Tumor mass/ biological (mixed) | Staging (prognostic) criteria: Biological | Median OS (months) or 5-year survival rate (%) based on stages or risk stratification: I | II | III | IV | Reference |
|---|---|---|---|---|---|---|---|---|---|
| DSS | 1975 | Bone lesions, hemoglobin, calcium, M protein | - | - | 191[a]<br>- | 54[a]<br>11[b] | 34[a]<br>5[b] | - | [1] |
| ISS | 2005 | albumin | B2-microglobulin | - | 62 | 45 | 29 | - | [2] |
| DSS PLUS | 2006 | DSS+MRI | PET/CT scan | - | - | - | - | - | [5] |
| R-ISS | 2015 | albumin | B2-micloglobulin, LDH | del(17p), and/or t(4;14) and/or t (14;16) | 82%<br>Not reached | 62%<br>83 | 40%<br>43 | - | [7] |
| SKY-RISS | 2020 | albumin | B2-microgobulin, LDH | del(17p), t(4;14) and 1q+ | 88[c] | 66[c] | 26[c] | - | [14] |
| R-ISS+PET/CT | 2021 | albumin | B2-microglobulin, LDH PET/CT scan | Del(17), t(4;14) and t(14;16) | 97%[d] | 90%[d] | 75%[d] | 50%[d] | [12] |
| Modified Risk Staging | 2021 | Age, albumin, calcium, glomerular filtration rate, hemoglobin | B2-microglobulin | - | 86% | 62% | 49% | - | [17] |
| Mayo Additive Staging system (MASS) | 2022 | albumin | B2-micloglobulin, LDH | High-risk IgH translocations, 1q gain/amplification and chromosome 17 abnormalities | 132 | 84 | 54 | - | [13] |
| R2-ISS (2nd revision ISS) | 2022 | albumin | LDH | del(17p), and/or t(4;14) and/or t (14;16) | Not reached | 109 | 69 | 38 | [11] |
| Prognostic stratification model (IAC-50) | 2022 | albumin | B2-microglobulin | 46-gene expression signature | n/a[e] | n/a[e] | n/a[e] | n/a[e] | [15] |

[a]Excluding patients with abnormal renal function; [b]patients with abnormal kidney function; [c]3-year survival rate; [d]2-year survival rate; [e]overall survival was predicted at 6, 12, 18, 24, 48, and 60 months using time-dependent areas under the curve (AUCs).

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

*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*

**Treatment of multiple myeloma has substantially changed over the past decade with the introduction of several classes of new effective drugs that have greatly improved the rates and depth of response. Response criteria in multiple myeloma were developed to use serum and urine assessment of monoclonal proteins and bone marrow assessment (which is relatively insensitive). Given the high rates of complete response seen in patients with multiple myeloma with new treatment approaches, new response categories need to be defined that can identify responses that are deeper than those conventionally defined as complete response. Recent attempts have focused on the identification of residual tumour cells in the bone marrow using flow cytometry or gene sequencing. Furthermore, sensitive imaging techniques can be used to detect the presence of residual disease outside of the bone marrow. Combining these new methods, the International Myeloma Working Group has defined new response categories of minimal residual disease negativity, with or without imaging-based absence of extramedullary disease, to allow uniform reporting within and outside clinical trials. In this Review, we clarify several aspects of disease response assessment, along with endpoints for clinical trials, and highlight future directions for disease response assessments.**

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# Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. A. Dimopoulos[1], P. Moreau[2], E. Terpos[1], M. V. Mateos[3], S. Zweegman[4], G. Cook[5], M. Delforge[6], R. Hájek[7], F. Schjesvold[8,9], M. Cavo[10], H. Goldschmidt[11], T. Facon[12], H. Einsele[13], M. Boccadoro[14], J. San-Miguel[15], P. Sonneveld[16] & U. Mey[17], on behalf of the EHA Guidelines Committee* and ESMO Guidelines Committee*

**Table 1.** Recommendations on examinations at diagnosis, response assessment, during follow-up and at relapse of MM

| | Tool | Diagnosis | At response | At follow-up | At relapse |
|---|---|---|---|---|---|
| Blood | Blood count and blood smear | Obligatory | Obligatory | Obligatory | Obligatory |
| | Serum electrophoresis and IF | Obligatory | Obligatory (IF for CR confirmation) | Obligatory (IF for CR patients) | Obligatory |
| | Serum-free light chain | Obligatory | Obligatory to confirm sCR | Obligatory | Obligatory |
| | Serum immunoglobulin levels | Obligatory | Obligatory | Obligatory | Obligatory |
| | Renal and liver function tests | Obligatory | Obligatory | Obligatory | Obligatory |
| | Calcium | Obligatory | Obligatory | Obligatory | Obligatory |
| | Lactate dehydrogenase | Obligatory | Obligatory | Obligatory | Obligatory |
| | Albumin, $\beta$2m | Obligatory | Not required | Optional | Obligatory |
| | Flow cytometry | Optional | Not required | Not required | Optional |
| Urine | Urine sample from 24 h urine collection to check for proteinuria and light-chain proteinuria | Obligatory | Obligatory | Obligatory | Obligatory |
| | Urine electrophoresis and IF electrophoresis | Obligatory | Obligatory (IF for CR confirmation) | Obligatory (IF for CR patients) | Obligatory |
| Bone marrow | BM cytology and biopsy to confirm plasmacytosis and monoclonality | Obligatory | Obligatory to confirm CR or for non-secretory MM | Not required | Optional (obligatory for non-secretory disease) |
| | NGF or NGS to detect clonal plasma cells | Obligatory | Obligatory to confirm MRD negativity in CR or sCR patients | Every 12 months in CR and/or MRD-negative patients[a] | Optional |
| | Cytogenetics: karyotype and FISH for detection of del17p, t(4;14), t(14;16), ampl 1q/ gain 1q, t(11;14) | Obligatory | Not required | Not required | Obligatory for del17p, ampl 1q/ gain 1q and t(11;14) |
| | Advanced techniques: GEP, NGS | For clinical trials use only | For clinical trials use only | For clinical trials use only | For clinical trials use only |
| Imaging | WBLD-CT | Obligatory | Not required | When symptomatic (or CT of the symptomatic area) | Obligatory |
| | PET-CT | Optional (it may be carried out instead of WBLD-CT if available) | Obligatory to confirm imaging MRD | Every 12 months in bone marrow MRD-negative patients[b] | Optional |
| | Whole-body MRI | Obligatory in WBLD-CT-negative cases and if PET-CT is not carried out | Not required | When symptomatic | Optional |

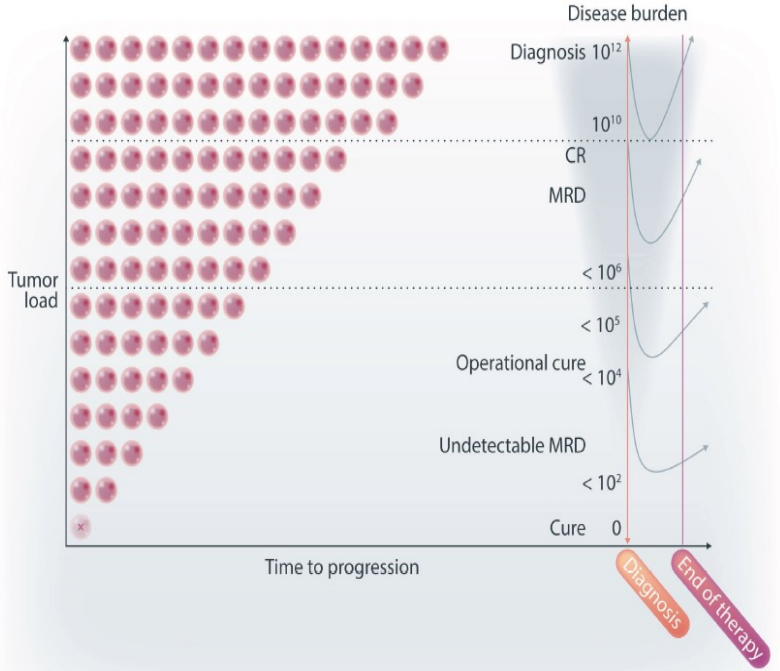


**Figure 1. Correlation of depth of response and survival.** CR: complete remission; MRD: measurable residual disease.

Haematologica | 109 August 2024

REVIEW ARTICLE

# Functional cure and long-term survival in multiple myeloma: how to challenge the previously impossible

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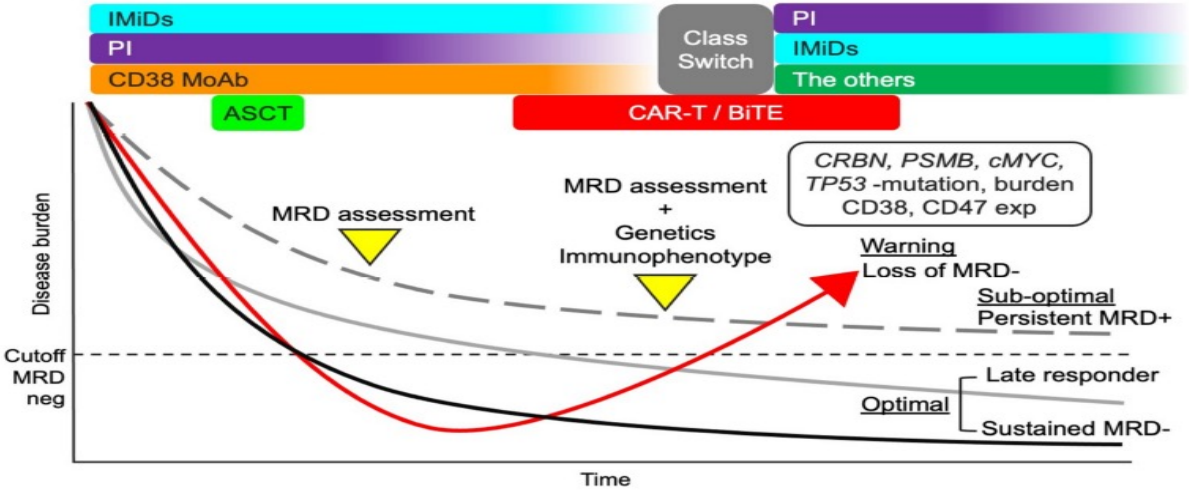


**Figure 3.** Treatment strategy considering MRD status. A total therapy approach combining IMiDs, PIs, anti-CD38 MoAb, and ASCT may be suitable for MM patients considering the efficacy against myeloma cells and improved microenvironment. MRD status after the total therapy approach can be useful in further treatment decisions. If the MRD status is negative, the current treatment should continue (optimal). However, if the MRD status is positive, the genetic and immunophenotypic characteristics of residual myeloma cells should be analyzed to optimize treatment. Loss of MRD negativity can lead to aggressive recurrence (warning). The clinical outcome of persistent MRD positivity is better than that of loss of MRD-negativity (sub-optimal). Repeated MRD assessment may be necessary for patients with persistent MRD positivity to identify late responders and detect early-phase recurrence. MM, multiple myeloma; MRD, minimal residual disease; IMiDs, immunomodulatory drugs; PIs, proteasome inhibitors; MoAbs, monoclonal antibodies; ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptor T cell; CRBN, cereblon; PSMB5, proteasome 20S subunit beta 5; and exp, expression.

*Review*

# Treatment Strategy for Multiple Myeloma to Improve Immunological Environment and Maintain MRD Negativity

Kazuhito Suzuki [1,2,*], Kaichi Nishiwaki [1,2] and Shingo Yano [2]

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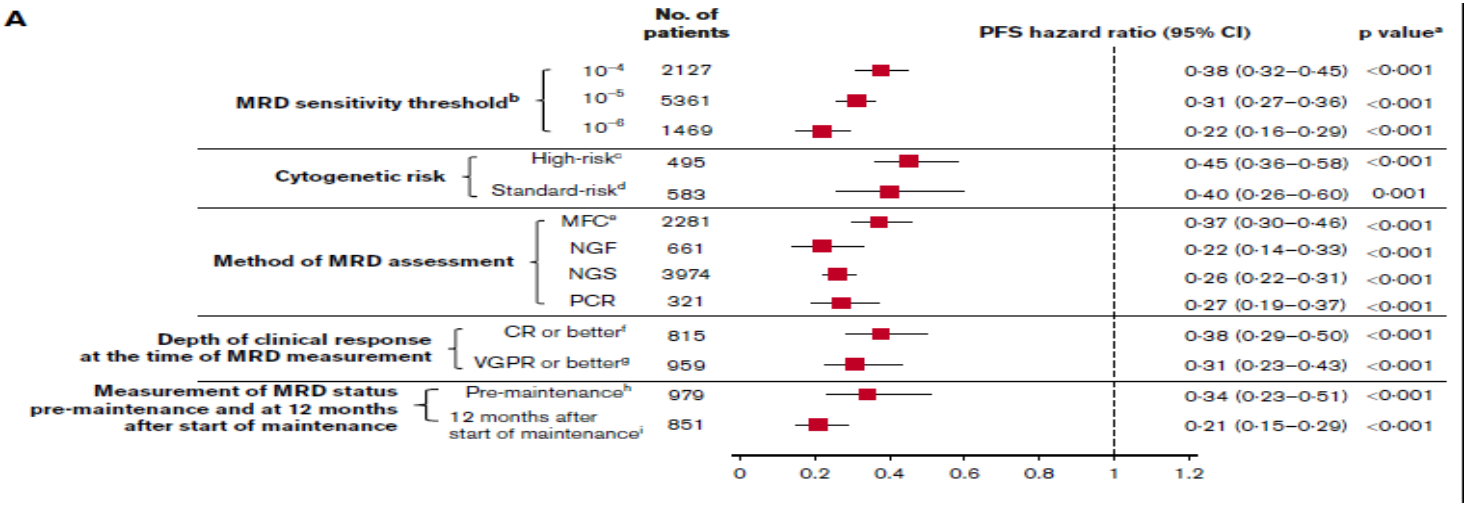
# A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma

Nikhil C. Munshi,[1,2] Herve Avet-Loiseau,[3] Kenneth C. Anderson,[1] Paola Neri,[4] Bruno Paiva,[5] Mehmet Samur,[1] Meletios Dimopoulos,[6] Margarita Kulakova,[7] Annette Lam,[8] Mahmoud Hashim,[7] Jianming He,[8] Bart Heeg,[7] Jon Ukropec,[9] Jessica Vermeulen,[9] Sarah Cote,[8] and Nizar Bahlis[4]




**PFS**

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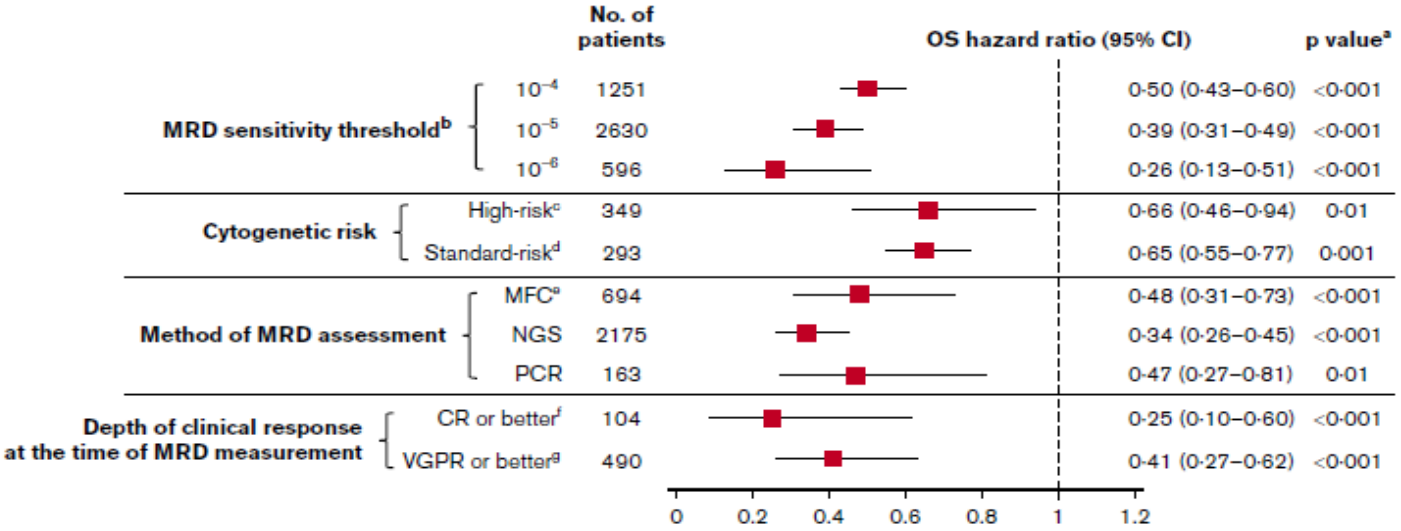


OS

blood advances 8 DECEMBER 2020 · VOLUME 4, NUMBER 23

# METABOLIC RESPONSE ASSESSMENT BY PET_CT

Table 2. Metabolic response and MRD assessment by FDG-PET/CT.

| Reference | Study design | Number of patients | Treatment | Time of assessment | Parameter | End point |
|---|---|---|---|---|---|---|
| Bartel et al. [37] | Prospective | 239 | CHT + novel agents + double ASCT | Pre-ASCT | Normalization vs. persistence of FDG uptake | PFS: 63% vs. 89% at 30 months from first ASCT |
| Dimitrakopoulou-Strauss et al. [41] | Prospective | 19 | CHT | Post first CHT cycle | SUV > 4 | PFS at 18 months: worse |
| Zamagni et al. [9] | Prospective | 192 | TD + double ASCT | Post TD | SUV > 4-2 vs. ≤4-2 | PFS at 4 years: 44% vs. 69% (p = .007) |
| | | | | Post double ASCT | SUV > 4-2 vs. ≤4-2 | PFS at 4 years: 47% vs. 32% (p = .02)<br>OS at 4 years: 79% vs. 66% (p = .02) |
| Usmani et al. [32] | Prospective | 302 | CHT + novel agents + double ASCT | Post treatment day 7 | FLs 0 vs. 1–3 vs. >3 | PFS: 84% vs. 78% vs. 56% (p < .0003)<br>OS: 87% vs. 82% vs. 63% (p < .0001) |
| Beksac et al. [38] | Retrospective | 139 | CHT + ASCT | After ASCT | SUV > 4.2<br>SUV > 3.35 | PFS at 3 years: worse (p = .05)<br>OS at 3 years: worse (p = .037) |
| Patriarca et al. [39] | Retrospective | 54 | Allo-SCT | 6 months after Allo-SCT | PET/CT positive vs. negative | PFS at 2 years from Allo-SCT: 25% vs. 51% (p = .03)<br>OS at 2 years from Allo-SCT: 81 vs. 47 (p = .001) |
| Moreau et al. [37] | Prospective | 134 | VRD ± ASCT, | After VRD | PET/CT positive vs. negative | PFS at 30 months: 60% vs. 79% (p = .04) |
| | | | | Prior to maintenance | PET/CT positive vs. negative | PFS at 30 months: 54.4% vs. 75.9% (p = .0004) |
| Zamagni et al. [42] | Retrospective | 189 | CHT, novel agents ± ASCT | 3 months after therapy | PET/CT positive vs. negative | PFS: median 38 vs. 52 months, (p = .0319)<br>OS at 5 years: 71% vs. 90% (p = .00014) |
| Korde et al. [29] | Prospective | 45 | CRD | After CRD | PET/CT positive/partial vs. negative/decreased | PFS at 18 months: 82% vs. 89% (p = ns) |

CHT: chemotherapy; ASCT: autologous stem cell transplantation; FDG: $^{18}$Fluorine-fluoro-deoxyglucose; PFS: progression free survival; SUV: standardized uptake value; TD: thalidomide-dexamethasone; OS: overall survival; FLs: focal lesions; PET: positron emission tomography; CT: computed tomography; TTP: time to progression; allo-SCT: allogenic stem cell transplantation; MTV: metabolic tumor volume; VRD: bortezomib-lenalidomide-dexamethasone; PTs: patients; CRD: carfilzomib-lenalidomide-dexamethasone.

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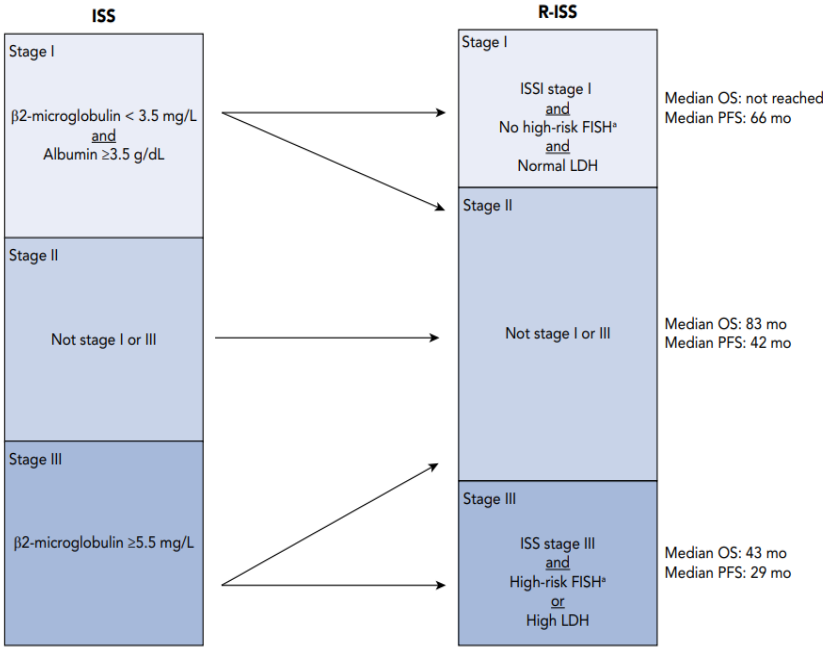
## R-ISS is the currently validated score to define the high risk MM patient




Costa L & Usmani S. J Natl Compr Canc Netw 2020;18(12):1730–1737

## Validated genetic abnormalities associated with worse prognosis

- t(4;14)
- t(14;16)
- del(17p)

All together account for approximately 25% of patients with newly diagnosed MM (NDMM)

The revised ISS (R-ISS) acknowledges the impact of t(4;14), t(14;16), and del(17p) and the presence of elevated lactate dehydrogenase level on MM prognosis, defining a subset of approximately 15% of patients with R-ISS stage III disease and very poor prognosis.

Costa L & Usmani S. J Natl Compr Canc Netw 2020;18(12):1730–1737

# Role of minimal residual disease assessment in multiple myeloma

by Raphael Szalat, Kenneth Anderson, and Nikhil Munshi

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*Role of minimal residual disease assessment in multiple myeloma.*
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| Whole body imaging methods | PETCT | Whole Body MRI |
|---|---|---|
| Bone marrow evaluation | No | No |
| Standardization | Yes | Yes |
| Require evaluation at diagnosis | Not required* Negative in ~10% of MM patients | Not required* |
| Cost | ++ | ++ |
| Applicability | ++ | + |
| Sensitivity | ++ | +++ |

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*Review*

# Minimal Residual Disease in Multiple Myeloma: Past, Present, and Future

Alejandro Medina-Herrera, María Eugenia Sarasquete *, Cristina Jiménez, Noemí Puig and Ramón García-Sanz

| Study | Sensitivity (Median) | Treatment Algorithm | MRDneg Rates |
|---|---|---|---|
| *ASCT-eligible* **Myeloma XI** (NCT01554852) [55] | $4 \times 10^{-5}$ | ASCT + R vs. no maintenance | 65.6% 34.4% |
| **GEM2012MENOS65** (NCT01916252) [52,53] | $3 \times 10^{-6}$ | VRd + ASCT + VRd | 50.2% |
| **CASSIOPEIA** (NCT02541383) [57] | $10^{-5}$ | Part 1: Dara − VTd + ASCT + Dara − VTd vs. VTd + ASCT + VTd | 64% 44% |
| | $10^{-5}$ | Part 2: Maintenance with Dara vs. observation | 66% 55.2% |
| **EMN02/HO95** (NCT01208766) [54] | $10^{-5}$ | Consolidation with VRd vs. No consolidation | 9.8% 8.2% |

**MCF**

*Review*

# Minimal Residual Disease in Multiple Myeloma: Past, Present, and Future

Alejandro Medina-Herrera, María Eugenia Sarasquete *, Cristina Jiménez, Noemí Puig and Ramón García-Sanz

| Study | Sensitivity (Median) | Treatment Algorithm | Mrdneg Rates |
|---|---|---|---|
| *ASCT-eligible* | | | |
| **IFM2009** (NCT01191060) [89] | $10^{-6}$ | VRd, 8 cycles vs.<br>VRd + ASCT | 20%<br>30% |
| **CASSIOPEIA** (NCT02541383) [57] | $10^{-5}$ | Part 1: Dara — VTd + ASCT + Dara — VTd vs.<br>VTd + ASCT + VTd | 57%<br>37% |
| | $10^{-6}$ | Part 2: Maintenance with Dara vs.<br>observation | 49.5%<br>36.7% |
| **GRIFFIN** (NCT02874742) [96] | $10^{-5}$ | Dara — VRd + ASCT + Dara — VRd vs.<br>VRd + ASCT + VRd | 51%<br>20.4% |
| *ASCT-non-eligible* | | | |
| **ALCYONE** (NCT02195479) [97,98] | $10^{-5}$ | Dara — VMP vs.<br>VMP | 22%<br>6% |
| **MAIA** (NCT02252172) [98,99] | $10^{-5}$ | Dara — Rd vs.<br>Rd | 24.2%<br>7.3% |
| *Relapsed/refractory* | | | |
| **CASTOR** (NCT02136134) [100] | $10^{-5}$ | Dara — Vd vs.<br>Vd | 15%<br>1.6% |
| **POLLUX** (NCT02076009) [101] | $10^{-5}$ | Dara — Rd vs.<br>Rd | 33.2%<br>6.7% |
| **IKEMA** (NCT03275285) [102] | $10^{-5}$ | Isa–Kd vs.<br>Kd | 29.6%<br>13% |

**NGS**

**Table 2.**

Primary Molecular Cytogenetic Classification of Multiple Myeloma

| Subtype | Gene(s)/chromosomes affected | Approximate Percentage of myeloma patients |
|---|---|---|
| **Hyperdiploid multiple myeloma** | Recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21 | ***45*** |
| **IgH translocated multiple myeloma** | | ***40*** |
| t(11;14) (q13;q32) | *CCND1* (cyclin D1) | 20 |
| t(6;14)(p21;q32) | *CCND3* (cyclin D3) | 5 |
| t(4;14) (p16;q32) | *NSD2* | 10 |
| t(14;16) (q32;q23) | *C-MAF* | 4 |
| t(14;20) (q32;q11) | *MAFB* | <1 |
| **Other IgH translocations, other cytogenetic abnormalities, or normal** | | ***5*** |

Modified from Kumar S et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. Blood 2012; 119:2100. © American Society of Hematology.

* Requires absence of an immunoglobulin heavy chain translocation. If an immunoglobulin heavy chain translocation is present, classification will be based on that abnormality.

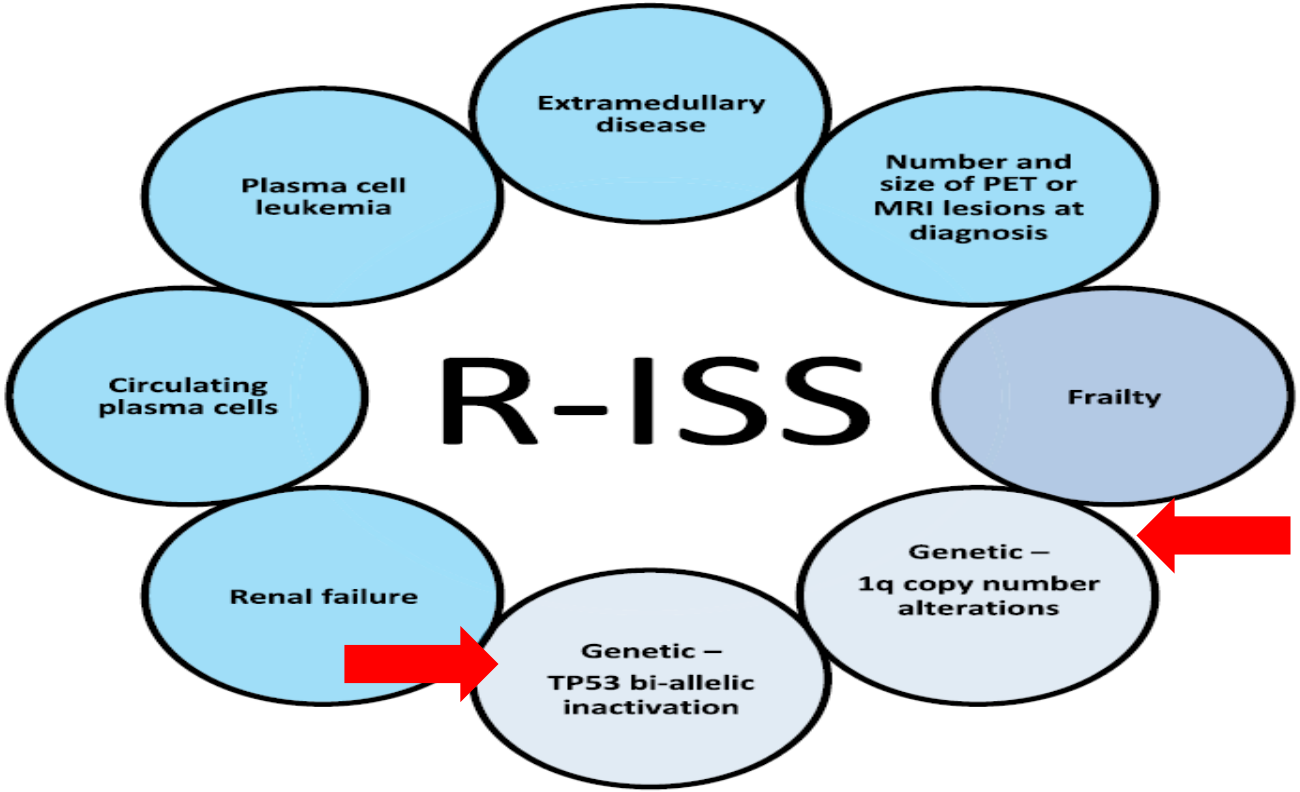
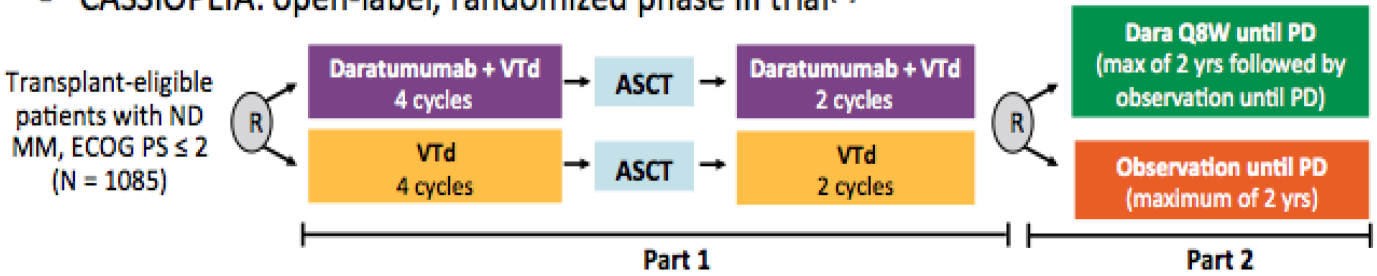


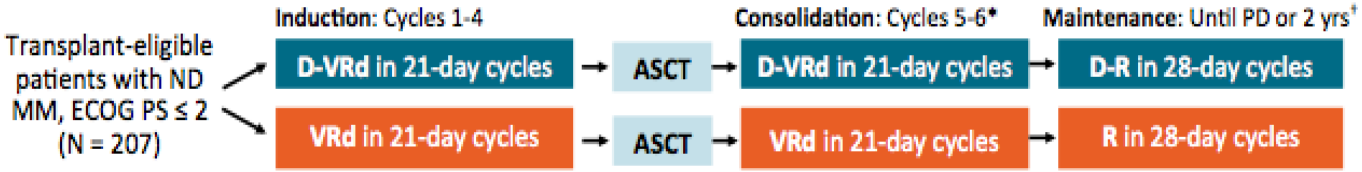

**FIGURE 1.** Proposed Modifications to Revised International Scoring System to Incorporate Additional High-Risk Features

# Clinical Trials With Quad Therapy in Newly Diagnosed MM

- CASSIOPEIA: open-label, randomized phase III trial[1]




- GRIFFIN: open-label, randomized phase II trial[2]




*Consolidation began 60-100 days after ASCT. †Patients completing maintenance were permitted to continue single-agent len.

1. Moreau. Lancet. 2019;394:29. 2. Voorhees. Blood. 2020;[Epub].

original reports

# Evaluation of Sustained Minimal Residual Disease Negativity With Daratumumab-Combination Regimens in Relapsed and/or Refractory Multiple Myeloma: Analysis of POLLUX and CASTOR

Hervé Avet-Loiseau, MD[1]; Jesus San-Miguel, MD[2]; Tineke Casneuf, PhD[3]; Shinsuke Iida, MD[4]; Sagar Lonial, MD[5]; Saad Z. Usmani, MD[6]; Andrew Spencer, MD[7]; Philippe Moreau, MD[8]; Torben Plesner, MD[9]; Katja Weisel, MD[10]; Jon Ukropec, PhD[11]; Christopher Chiu, PhD[12]; Sonali Trivedi, PhD[12]; Himal Amin, BS[13]; Maria Krevvata, PhD[12]; Priya Ramaswami, MSPH[14]; Xiang Qin, MS[12]; Mia Qi, PhD[13]; Steven Sun, PhD[13]; Ming Qi, MD[12]; Rachel Kobos, MD[13]; and Nizar J. Bahlis, MD[15]

abstract

**PURPOSE** In relapsed and/or refractory multiple myeloma, daratumumab reduced the risk of progression or death by > 60% in POLLUX (daratumumab/lenalidomide/dexamethasone [D-Rd]) and CASTOR (daratumumab/bortezomib/dexamethasone [D-Vd]). Minimal residual disease (MRD) is a sensitive measure of disease control. Sustained MRD negativity and outcomes were evaluated in these studies.

**METHODS** MRD was assessed via next-generation sequencing ($10^{-5}$) at suspected complete response (CR), 3 and 6 months following confirmed CR (POLLUX), 6 and 12 months following the first dose (CASTOR), and every 12 months post-CR in both studies. Sustained MRD negativity (≥ 6 or ≥ 12 months) was evaluated in the intention-to-treat (ITT) and ≥ CR populations.

**RESULTS** The median follow-up was 54.8 months in POLLUX and 50.2 months in CASTOR. In the ITT population, MRD-negativity rates were 32.5% versus 6.7% for D-Rd versus lenalidomide and dexamethasone (Rd) and 15.1% versus 1.6% for D-Vd versus bortezomib and dexamethasone (Vd; both $P < .0001$). Higher MRD negativity rates were achieved in ≥ CR patients in POLLUX (D-Rd, 57.4%; Rd, 29.2%; $P = .0001$) and CASTOR (D-Vd, 52.8%; Vd, 17.4%; $P = .0035$). More patients in the ITT population achieved sustained MRD negativity ≥ 6 months with D-Rd versus Rd (20.3% *v* 2.1%; $P < .0001$) and D-Vd versus Vd (10.4% *v* 1.2%; $P < .0001$), and ≥ 12 months with D-Rd versus Rd (16.1% *v* 1.4%; $P < .0001$) and D-Vd versus Vd (6.8% *v* 0%). Similar results for sustained MRD negativity were observed among ≥ CR patients. More patients in the daratumumab-containing arms achieved MRD negativity and sustained MRD negativity, which were associated with prolonged progression-free survival.

**CONCLUSION** Daratumumab-based combinations induce higher rates of sustained MRD negativity versus standard of care, which are associated with durable remissions and prolonged clinical outcomes.

J Clin Oncol 39:1139-1149. 

# Evaluation of Sustained Minimal Residual Disease Negativity With Daratumumab-Combination Regimens in Relapsed and/or Refractory Multiple Myeloma: Analysis of POLLUX and CASTOR

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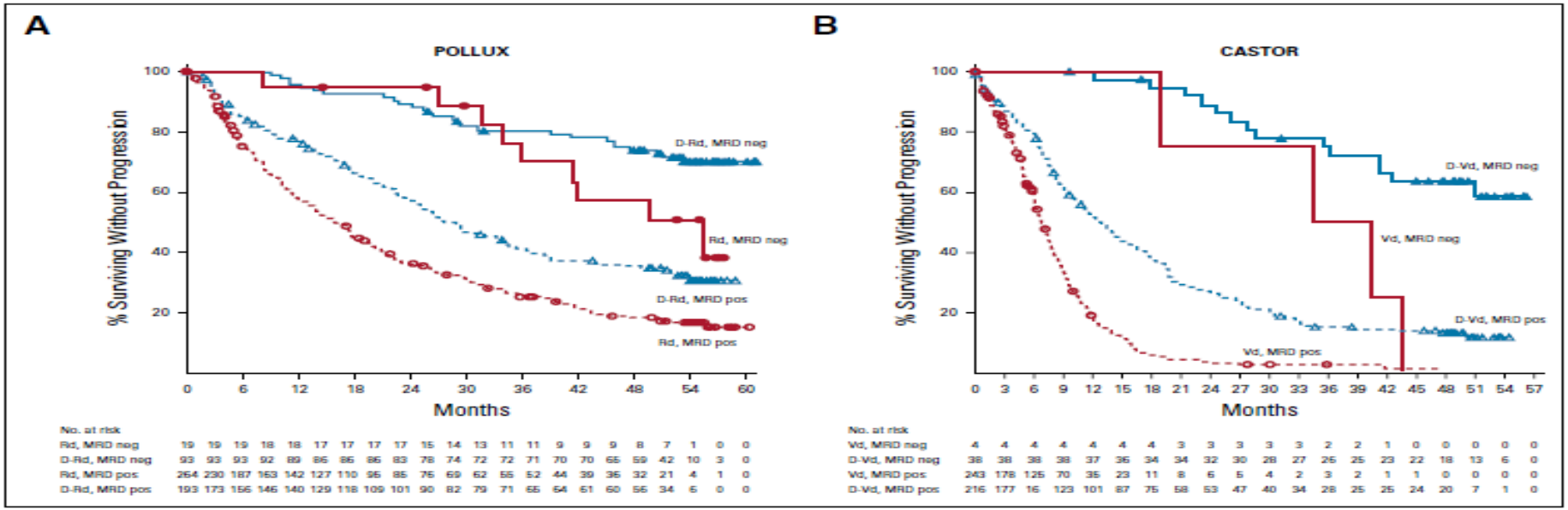



**FIG 1.** PFS based on MRD status ($10^{-5}$) in POLLUX (A) and CASTOR (B). Shown are the results of the Kaplan-Meier estimates of PFS among patients in the ITT population based on the absence of MRD at a threshold of one tumor cell per $10^5$ white cells. Blue lines show regimens containing daratumumab; red lines show standard-of-care regimens. D-Rd, daratumumab plus lenalidomide and dexamethasone; D-Vd, daratumumab plus bortezomib and dexamethasone; ITT, intention-to-treat; MRD, minimal residual disease; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.

# COMPARISON OF DIFFERENT TECHNIQUES

Table 3. Comparison of different techniques to assess MRD in MM.

| Parameter | NGF | ASO qPCR | NGS | PET/CT |
|---|---|---|---|---|
| **Quantitative assessment** | Yes | Yes | Yes | Yes |
| **Applicability** | ~100% | 60–70% | ≥90% | 75% |
| **Baseline sample** | Not mandatory | Mandatory | Mandatory | Not mandatory |
| **Cost** | Intermediate | High | High | High |
| **Sensitivity** | ≥1 in $10^5$ | ≥1 in $10^5$ | ≥1 in $10^5$ | Lesions ≥5 mm |
| **Patchy BM infiltration and/or EMD** | Impact | Impact | Impact | Not impact |
| **Standardization** | Ongoing | Yes | Ongoing | Ongoing |
| **Prognostic value of MRD status** | Improvements in PFS and OS | Improvements in PFS and OS | Improvements in PFS and OS | Improvements in PFS and OS |

NGF: next-generation-flow; ASO qPCR: allele specific oligonucleotide polymerase chain reaction; NGS: next generation sequencing; PET/CT: positron emission tomography/computerized tomography scanning.

EXPERT REVIEW OF HEMATOLOGY, 2016
VOL. 9, NO. 9, 831–837
http://dx.doi.org/10.1080/17474086.2016.1212654

# » DEFINIZIONE DI MRD

**ABSTRACT**

Precise assessment of response to therapy is of high importance in every phase of multiple myeloma (MM). In addition to the well-established role of monoclonal protein for clinical monitoring, several methods of minimal residual disease evaluation, both inside and outside the bone marrow (BM), are to date available. Next generation flow cytometry and sequencing are probably the best approaches at the BM level, being highly sensitive and uniformly applied. FDG PET/CT is the best imaging technique for evaluating and monitoring response to therapy outside the BM. Functional whole-body MRI techniques (DCE and DWI) seem promising for response evaluation and need further studies. Standardization of most of these techniques is in progress.

# Minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma (MASTER): final report of the multicentre, single-arm, phase 2 trial

*Luciano J Costa, Saurabh Chhabra, Eva Medvedova, Bhagirathbhai R Dholaria, Timothy M Schmidt, Kelly N Godby, Rebecca Silbermann, Binod Dhakal, Susan Bal, Smith Giri, Anita D'Souza, Aric C Hall, Pamela Hardwick, James Omel, Robert F Cornell, Parameswaran Hari, Natalie S Callander*

# MASTER: Study Design

**MRD- SURE**
**2 neg in 2 consecutive Phases**

- Multicenter, single-arm phase II trial

Untreated* patients with NDMM and measurable disease, ECOG PS 0-2, CrCl ≥ 40 mL/min, without significant cardiopulmonary disease or current/prior malignancy (N = 81)†

→ Induction Dara-KRd x 4 cycles → AHCT → Consolidation Dara-KRd x 4 cycles → Consolidation Dara-KRd x 4 cycles → *Lenalidomide maintenance*

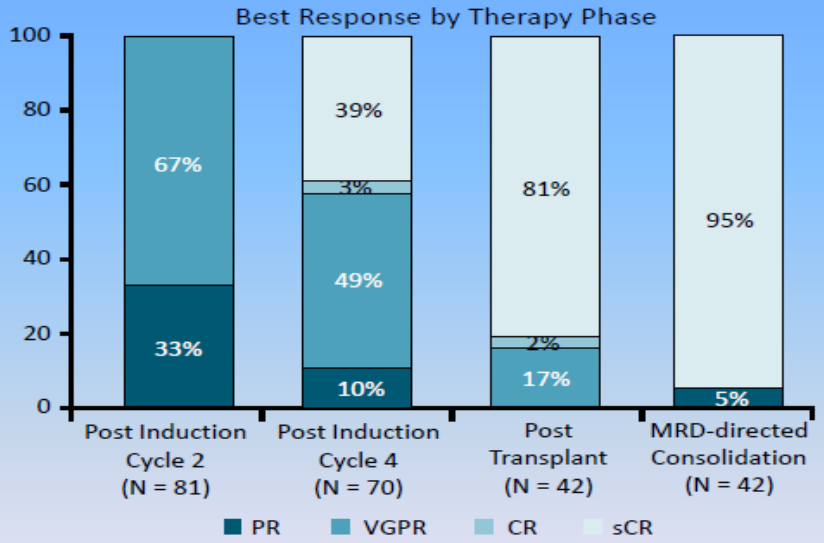
MRD assessment after each treatment phase; pts with confirmed (2nd) MRD-negative status (< $10^{-5}$) entered treatment-free observation phase with MRD assessment at 24 and 72 wks after EOT.

Dara-KRd dosing: daratumumab 16 mg/m² on Days 1,8,15,22 (Days 1,15 of Cycles 3-6; Day 1 Cycle > 6); carfilzomib 56 mg/m² Days 1,8,15; lenalidomide 25 mg Days 1-21; dexamethasone 40 mg PO Days 1,8,15,22. *1 VCD cycle permitted. †Planned recruitment N = 123.

- Primary endpoint: MRD-negative remission (< $10^{-5}$) on NGS assay in pts receiving induction, AHCT, and response-adapted consolidation
- Secondary endpoints: safety, imaging frequency plus remission, MRD status post-AHCT, IMWG response, loss of MRD negativity in pts with no maintenance therapy
- Exploratory endpoint: MRD-negative rates on NGS assay (threshold < $10^{-6}$)

Costa. ASH 2019. Abstr 860.

# MASTER: Best Response by Treatment Phase




| sCR, % (n) | Post Induction | Post Transplant | MRD-Based Consolida-tion |
|---|---|---|---|
| All patients | 39 (70) | 81 (42) | 95 (42) |
| Standard-risk patients | 44 (50) | 79 (29) | 97 (29) |
| High-risk patients [t(4;14), t(14;16) or del17p] | 25 (20) | 85 (13) | 91 (13) |

- n = 27 (n= 19 standard risk, n = 7 high risk) achieved MRD-negative status and entered observation phase; no relapse or MRD positivity at median median follow-up of 4.9 mos

Costa. ASH 2019. Abstr 860.

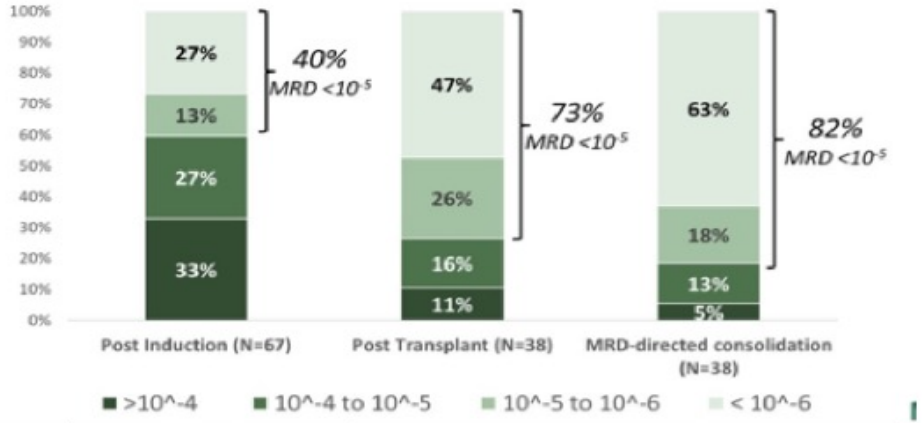
## Conclusions

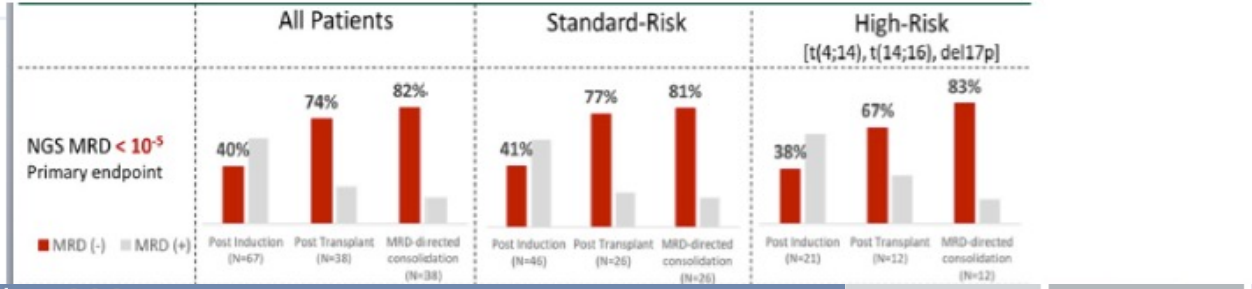
- Use of Dara-KRd induction with AHCT and **Dar-KRd consolidation** was effective and tolerable in untreated patients with NDMM
  - **39% achieved sCR post induction and 95% at MRD-based consolidation**
  - **High level of response observed in both high-risk and standard-risk patients**
  - Few patients discontinued for toxicity
- **Investigators concluded that delivery of NGS MRD-based, response adapted therapy feasible in clinical setting**
- Study ongoing

Costa. ASH 2019. Abstr 860.

# MASTER trial

- MRD trackable by NGS clonoSEQ® in 78/81 patients (96%)
- 100% of datapoints obtained in patients with trackable MRD



# FORTE Premaintenance Analysis: Response Rates

| Response Rate | KCd–ASCT–KCd (n = 159) | KRd–ASCT–KRd (n = 158) | KRd x 12 cycles (n = 157) |
|---|---|---|---|
| After ASCT or 8 KRd cycles (ITT), % | | | |
| ▪ ≥ VGPR | 66 | 81 | 85 |
| ▪ sCR | 15 | 23 | 30 |
| ▪ CR* | 9 | 11 | 4 |
| ▪ VGPR | 42 | 47 | 51 |
| Premaintenance, % | | | |
| ▪ ≥ VGPR | 76 | 89 | 87 |
| ▪ sCR | 32 | 44 | 43 |
| ▪ CR* | 15 | 16 | 18 |
| ▪ VGPR | 29 | 29 | 26 |
| MRD negativity† premaintenance, % | 42 | 58 | 54 |

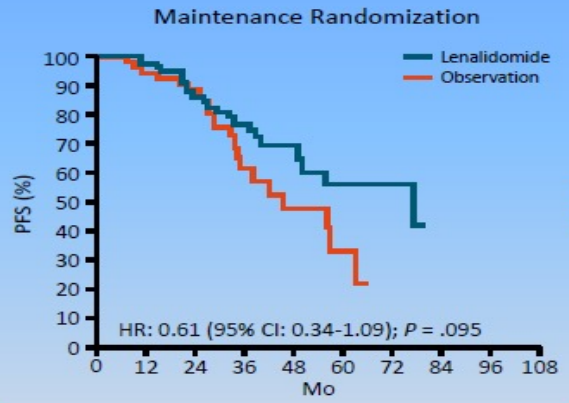
*Confirmed or unconfirmed. †MRD assessed by 2nd generation flow cytometry, with sensitivity of $10^{-5}$.

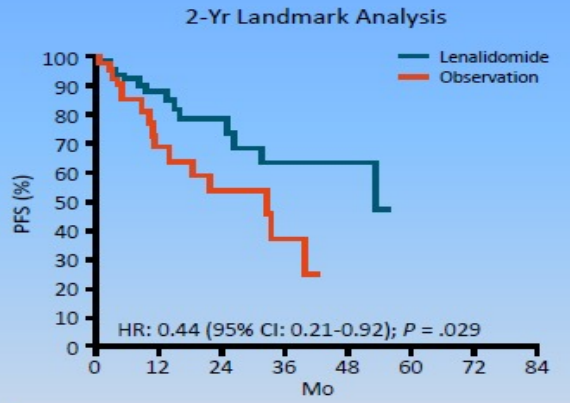
| Likelihood of Premaintenance Response | OR | *P* Value |
|---|---|---|
| ≥ VGPR | | |
| ▪ KRd–ASCT–KRd vs KCd–ASCT–KCd | 2.53 | .004 |
| ▪ KRd12 vs KCd–ASCT–KCd | 2.11 | .015 |
| sCR | | |
| ▪ KRd–ASCT–KRd vs KCd–ASCT–KCd | 1.65 | .035 |
| ▪ KRd12 vs KCd–ASCT–KCd | 1.69 | .048 |
| MRD negativity† | | |
| ▪ KRd–ASCT–KRd vs KCd–ASCT–KCd | 2.02 | .009 |
| ▪ KRd12 vs KCd–ASCT–KCd | 1.73 | .042 |

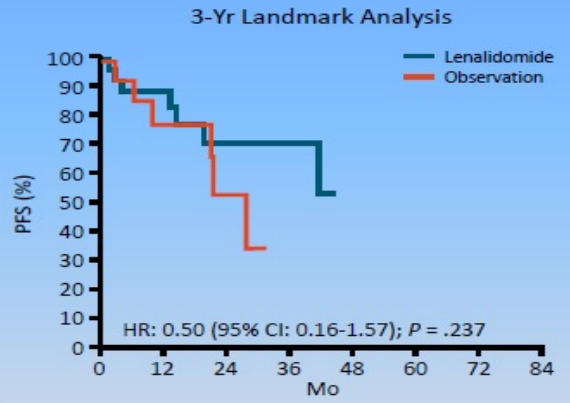
- Results replicated across most subgroups evaluated

Gay F, et al. ASH 2018. Abstract 121.

# Myeloma XI Trial: PFS by Sustained MRD Negativity and Yr of Treatment (Landmark Analyses)




| Median PFS, Mo (95% CI) | Lenalidomide | Observation |
|---|---|---|
| Maintenance | 77 (50-NE) | 46 (35-64) |

| Median PFS, Mo (95% CI) | Lenalidomide | Observation |
|---|---|---|
| 2 yr | 53 (27-NE) | 33 (11-NE) |

| Median PFS, Mo (95% CI) | Lenalidomide | Observation |
|---|---|---|
| 3 yr | NE (20-NE) | 28 (10-NE) |

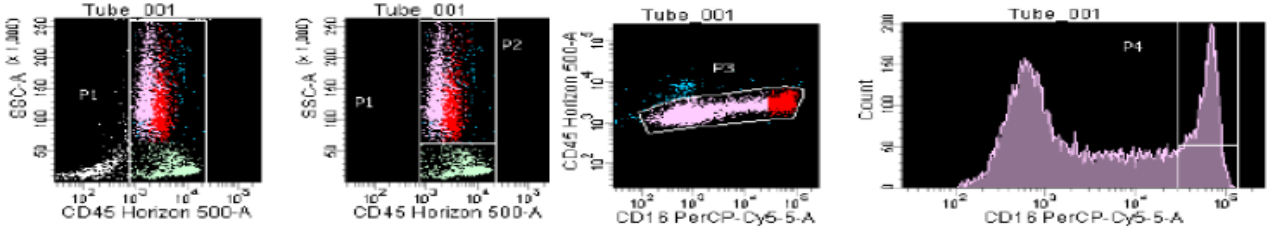
Includes patients with sustained MRD negativity at 6 mo after maintenance began

Pawlyn. ASH 2022. Abstr 570. Reproduced with permission.

MMR

# EMODILUIZIONE

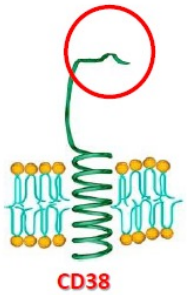
**Preliminarmente in tutti i casi è necessario valutare il grado di contaminazione di sangue periferico determinando la quota di elementi mieloidi maturi (CD16$^{bright}$ ) *(Loken et al Cytometry 2009).***

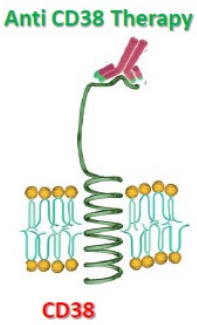


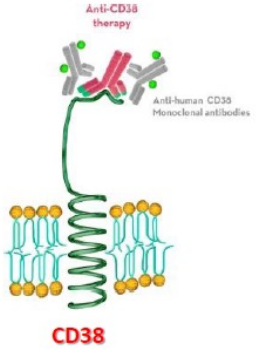

| | MINIMA | MODERATA | SIGNIFICATIVA |
|---|---|---|---|
| CD16$^{bright}$ | < 30% | 30%-60% | > 60% |

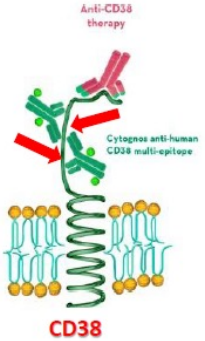
MMR

CRITICITA'



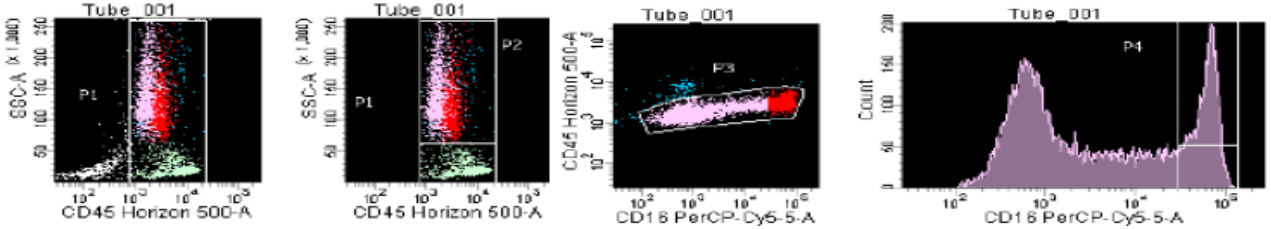



MMR

# EMODILUIZIONE

**Preliminarmente in tutti i casi è necessario valutare il grado di contaminazione di sangue periferico determinando la quota di elementi mieloidi maturi (CD16$^{bright}$ ) *(Loken et al Cytometry 2009).***




| | MINIMA | MODERATA | SIGNIFICATIVA |
|---|---|---|---|
| CD16$^{bright}$ | < 30% | 30%-60% | > 60% |

MMR

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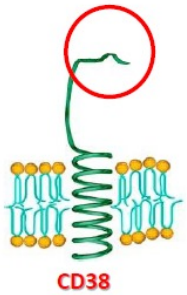


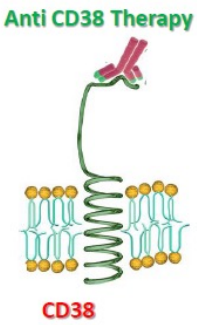


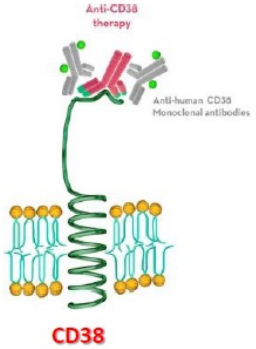


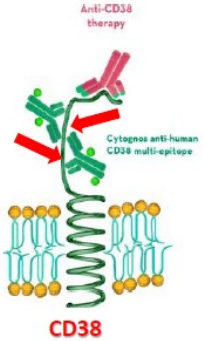

# MRD ASSESSMENT IN BM (MCF)

Table 1. MRD assessment by MFC.

| Study | Treatment | N° of patients | MFC | Results |
|---|---|---|---|---|
| Paiva et al. [5] | GEM2000 trial: VBMCP/VBAD plus ASCT | 295 | 4-color | MRD– at day 100 after ASCT was predictive of superior PFS and OS, both among whole patient population and among patients who achieved CR |
| Paiva et al. [13] | GEM2005 > 65y trial: VMP vs. VTP | 102 | 4-color | MRD– after 6 cycles of induction translated into superior PFS and TTP compared with CR or CR plus normal sFLCR |
| Paiva et al. [20] | GEM2000 trial: VBMCP/VBAD plus ASCT | 241 | 4-color | MRD+ at day 100 after ASCT, and presence of baseline high-risk cytogenetics by FISH were the only independent factors that predicted unsustained CR |
| | GEM2005 < 65y trial: VBMCP/VBAD plus V in the last 2 cycles or TD or VTD, plus ASCT | | | |
| Rawstron et al. [6] | MRC Myeloma IX trial: | 378 | 6-color | Intensive-pathway: MRD– at day 100 after ASCT was predictive of favorable PFS and OS. |
| | Intensive pathway: CTD vs. CVAD plus ASCT | 245 | | Nonintensive-pathway: MRD assessment after induction therapy did not seem to be predictive of outcome |
| | Non-intensive pathway: MP vs. CTDa | | | |
| Roussel et al. [21] | Phase II trial: VRD plus ASCT | 31 | 7-color | Estimated 3-year PFS: 100% in MRD– vs. 23% in MRD+ |
| Paiva et al. [22] | PETHEMA/GEM2010MAS65 study: sequential vs. alternating scheme VMP/Rd | 162 | 8-color | MRD– at cycle 9 correlated better with prolonged TTP and OS than did patients in CR but MRD+ and those in less than CR |

MFC: multiparameter flow cytometry; VBMCP: vincristine, carmustine, melphalan, cyclophosphamide, prednisone; VBAD: vincristine, carmustine, doxorubicin, dexamethasone; ASCT: autologous stem cell transplantation; PFS: progression-free survival; OS: overall survival; CR: complete response; VMP: bortezomib-melphalan-prednisone; VTP: bortezomib-thalidomide-prednisone; VT: bortezomib-thalidomide; VP: bortezomib-prednisone; TTP: time to progression; sFLCR: serum free light chain k/λ ratio; V: bortezomib; TD: thalidomide-dexamethasone; VTD: bortezomib-thalidomide-dexamethasone; FISH: fluorescence *in situ* hybridization; CTD: cyclophosphamide-thalidomide-dexamethasone; CVAD: cyclophosphamide-vincristine-doxorubicin-dexamethasone; MP: melphalan-prednisolone; CTDa: attenuated CTD; VRD: bortezomib-lenalidomide-dexamethasone; Rd: lenalidomide-dexamethasone.

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# MOLECULAR Approaches

***Next-Generation Sequencing***

NGS MRD testing for MM identifies and quantifies rearranged immunoglobulin heavy chain (IgH) variable, diversity, and joining (VDJ) and diversity and joining (DJ) rearrangements and kappa and lambda rearrangements.[5] An initial high tumor burden sample is needed to identify clonotypic sequences (clone identification [ID]) for tracking on subsequent assessments. Close to 95% of patients will have an identifiable clone ID at the time of diagnosis.[6,7] MRD by NGS can be performed using the FDA-cleared clonoSEQ assay (Adaptive Biotechnologies), though other similar assays exist as well. With the maximum input of 20 μg of DNA (which equates to approximately 2–3 million cellular equivalents), clonoSEQ has the highest sensitivity of the assays with an LoD of $6.8 \times 10^{-7}$ and an LoQ of $1.76 \times 10^{-6}$.

MRD negativity by NGS has been shown on a number of occasions to be associated with longer PFS and OS, regardless of International Staging System (ISS) staging, cytogenetic risk, or treatment.[8–11] Although NGS offers a standardized way to achieve $10^{-6}$ sensitivity with fewer cells than next generation flow (NGF), it requires a baseline high tumor burden sample and offers no way to determine if samples are hemodiluted.

Blood Cancer Journal

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# Prognostic value of early bone marrow MRD status in CAR-T therapy for myeloma

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Bone marrow (BM) assessment of minimal residual disease (MRD) is prognostic for survival in multiple myeloma (MM). BM is still hypocellular at month 1 post CAR-T, thus the value of MRD negative (MRDneg) status at this timepoint is unclear. We examined the impact of month 1 BM MRD status in MM patients who received CART at Mayo Clinic between 8/2016 and 6/2021. Among 60 patients, 78% were BM-MRDneg at month 1; and 85% (40/47) of these patients also had decreased to less than normal level of both involved and uninvolved free light chain (FLC < NL). Patients who achieved CR/sCR had higher rates of month 1 BM-MRDneg and FLC < NL. The rate of sustained BM-MRDneg was 40% (19/47). Rate of conversion from MRDpos to MRDneg was 5%(1/20). At month 1, 38%(18/47) of the BM-MRDneg were hypocellular. Recovery to normal cellularity was observed in 50%(7/14) with a median time to normalization at 12 months (range: 3–Not reached). Compared to Month 1 BM-MRDpos patients, patients who were BM-MRDneg had longer PFS irrespective of BM cellularity [PFS: 2.9 months (95% CI, 1.2-NR) vs. 17.5 months (95% CI, 10.4-NR), $p < 0.0001$]. Month 1 BM-MRDneg and FLC below normal were associated with prolonged survival. Our data support the continued evaluation of BM early post-CART infusion as a prognostic tool.

*Blood Cancer Journal* (2023)13:47; https://doi.org/10.1038/s41408-023-00820-y

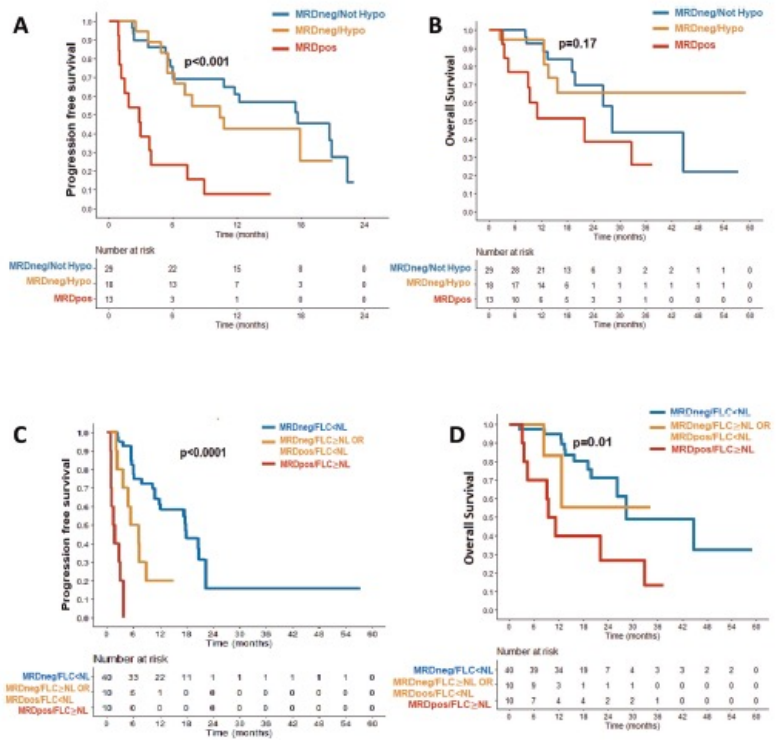
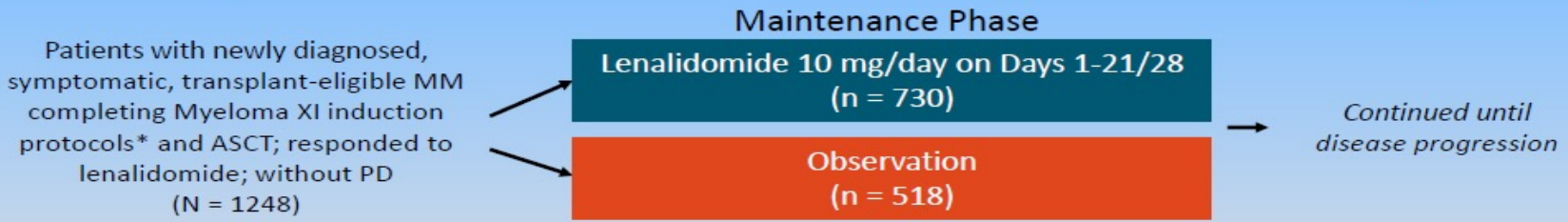



**Fig. 2 Bone marrow MRD status and correlation with clinical outcome for patients with myeloma who received CAR-T. A** Kaplan-Meier curve for progression free survival (PFS) between patients with month 1 BM MRDpos and MRDneg stratified by BM cellularity (top left). Kaplan-Meier curve for overall survival (OS) between patients with month 1 BM MRDpos and MRDneg stratified by BM cellularity (top right panel). **C** Kaplan-Meier curve) for PFS among patients with month 1 BM MRDneg/FLC < NL, MRDneg/FLC > = NL or MRDpos/FLC < NL and MRDpos/FLC > = NL(bottom right). **D** Kaplan-Meier curve for OS among patients with month 1 BM MRDneg/FLC < NL, MRDneg/FLC > = NL or MRDpos/FLC < NL and MRDpos/FLC > = NL (bottom left).

# Myeloma XI Trial: Study Design

- Open-label, randomized phase III study with 3 randomizations: induction (allocation by ASCT eligibility), intensification (allocation by response to induction therapy), and maintenance treatment
  - **Current analysis: maintenance with lenalidomide monotherapy vs observation following ASCT**




*Cyclophosphamide/thalidomide/dexamethasone or cyclophosphamide/lenalidomide/dexamethasone or carfilzomib/cyclophosphamide/lenalidomide/dexamethasone.

- Median follow-up: 44.7 mo (IQR: 32.4-62.7); median duration of lenalidomide therapy: 28 cycles (range: 1-96) with 45% of patients (330/730) still on therapy
- **Endpoints**: Overall PFS, PFS2; landmark PFS by genetic risk subgroups and MRD status

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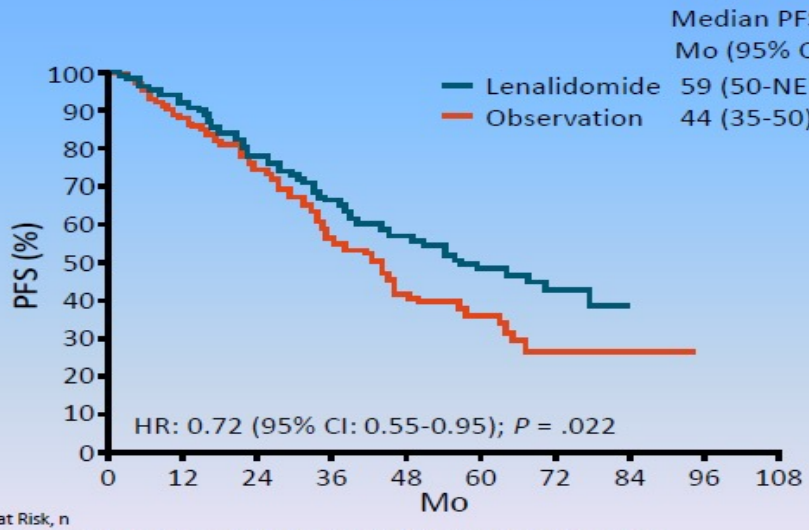
# Myeloma XI Trial: PFS From Maintenance Randomization by MRD Negativity Status

## MRD Negative




| Patients at Risk, n | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lenalidomide | 299 (3) | 273 (4) | 213 (24) | 127 (83) | 63 (132) | 35 (153) | 19 (106) | 0 (184) | |
| Observation | 175 (0) | 154 (1) | 125 (7) | 53 (45) | 35 (59) | 19 (72) | 9 (78) | 2 (85) | 0 (87) |

*MRD assessed by flow cytometry with median sensitivity of 4 x $10^5$.

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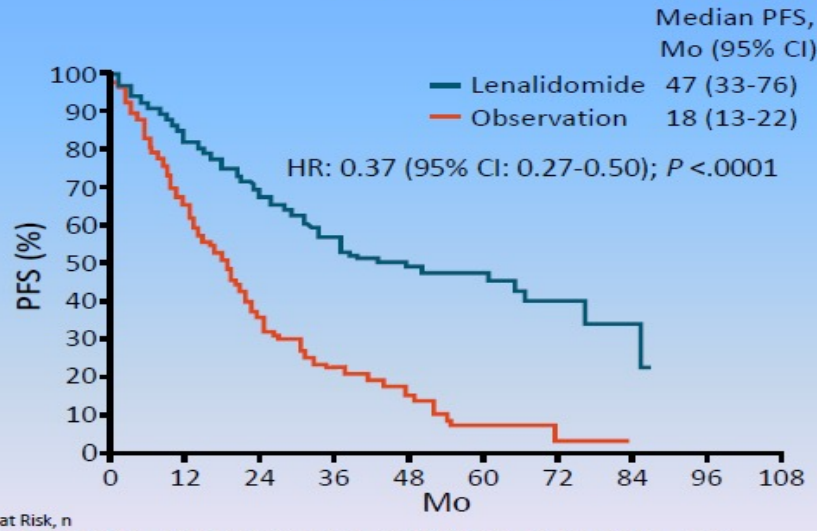
## MRD Positive




| Patients at Risk, n | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lenalidomide | 153 (0) | 120 (5) | 92 (13) | 60 (31) | 39 (45) | 23 (50) | 13 (67) | 3 (76) | 0 (78) |
| Observation | 122 (0) | 79 (1) | 39 (5) | 23 (8) | 9 (14) | 3 (17) | 1 (18) | 0 (19) | |

# Myeloma XI Trial: PFS by Risk Status and MRD Status by Yr of Treatment (Landmark Analyses)

| Outcome | Lenalidomide (n = 730) | Observation (n = 518) | HR (95% CI) | *P* |
|---|---|---|---|---|
| Median PFS by risk status, mo (95% CI) | | | | |
| ▪ Standard risk | | | | |
| – 2 yr | 53 (42-NE) | 29 (22-43) | 0.44 (0.26-0.74) | .032 |
| – 3 yr | NE (31-NE) | 28 (11-NE) | 0.46 (0.25-0.68) | .019 |
| – 4 yr | NE (26-NE) | 31 (16-NE) | 0.71 (0.29-1.75) | .462 |
| – 5 yr | NE (17-NE) | 19 (5-NE) | 0.46 (0.13-1.62) | .227 |
| ▪ High risk or ultra-high risk | | | | |
| – 2 yr | 48 (30-NE) | 20 (10-33) | 0.44 (0.24-0.80) | .008 |
| – 3 yr | NE (26-NE) | 21 (8-NE) | 0.59 (0.21-1.65) | .314 |
| – 4 yr | NE (16-NE) | NE (1-NE) | 0.54 (0.14-2.09) | .372 |
| Median PFS by MRD status, mo (95% CI) | | | | |
| ▪ MRD negative | | | | |
| – 2 yr | 53 (40-NE) | 33 (22-NE) | 0.63 (0.43-0.94) | .025 |
| – 3 yr | NE (41-NE) | 31 (21-NE) | 0.65 (0.36-1.15) | .140 |
| – 4 yr | NE (29-NE) | NE (17-NE) | 0.68 (0.27-1.69) | .403 |
| – 5 yr | NE (NE-NE) | NE (7-NE) | 0.43 (0.11-1.72) | .232 |
| ▪ MRD positive | | | | |
| – 2 yr | 61 (41-NE) | 20 (10-28) | 0.34 (0.15-0.51) | <.0001 |
| – 3 yr | 49 (40-NE) | 16 (8-35) | 0.28 (0.11-0.58) | .001 |
| – 4 yr | 37 (28-NE) | 6 (0-NE) | 0.14 (0.04-0.48) | .002 |

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# Myeloma XI Trial: Investigators' Conclusions

- Long-term results from Myeloma XI phase III trial demonstrated ongoing PFS improvement with continuing lenalidomide maintenance beyond 4-5 yr in patients with newly diagnosed MM after response to protocol-specified induction and ASCT
  - **Continuing lenalidomide maintenance for ≥3 yr benefited patients with sustained MRD negativity, but benefit of additional lenalidomide maintenance is unclear**
  - **In MRD-positive patients, results support continuing lenalidomide until disease progression**
- No evidence of cumulative hematologic toxicity observed with long-term lenalidomide maintenance
- Investigators concluded that additional data from ongoing studies needed to determine optimal duration of lenalidomide maintenance

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# Measurable Residual Disease and Decision-Making in Multiple Myeloma

Benjamin A. Derman, MD[a,*], Rafael Fonseca, MD[b]

**KEYWORDS**

• Multiple myeloma • MRD • Minimal residual disease • Measurable residual disease

**KEY POINTS**

- Measurable (minimal) residual disease (MRD) is one of the most powerful prognostic factors for progression-free survival and overall survival in multiple myeloma (MM).
- There are several ways to assess for MRD in MM; bone marrow methods such as next-generation sequencing and next-generation flow cytometry can achieve sensitivity up to $10^{-6}$.
- Each increase in MRD sensitivity threshold is associated with improved prognostication, and sustained MRD negativity carries greater significance than a single instance of MRD negativity.
- Peripheral blood techniques (ie, mass spectrometry) to assess for MRD are quickly moving from research only to clinical use.
- MRD-adapted clinical decision-making is controversial, but there is mounting evidence that MRD-guided de-escalation of therapy is feasible and may not compromise clinical outcomes.

Research Discover Oncology (2024) 15:38 | https://doi.org/10.1007/s12672-024-00891-8

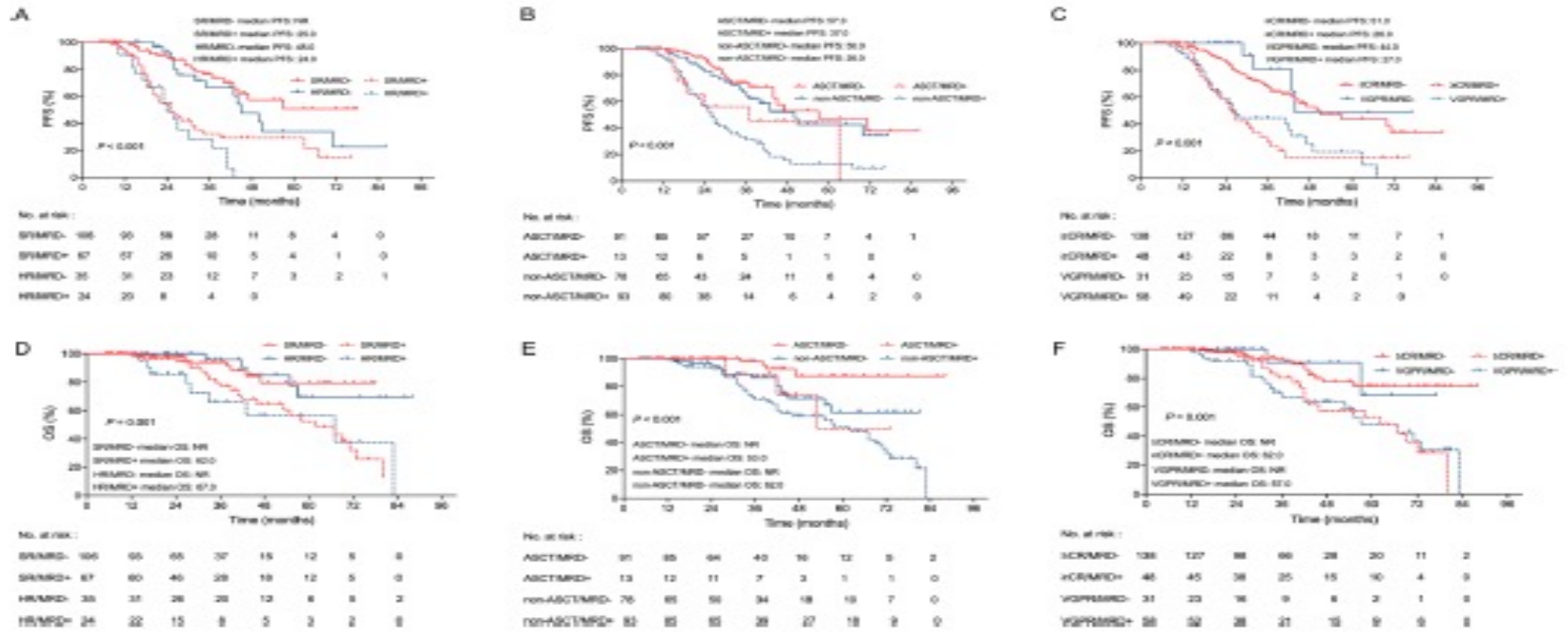


Fig. 2 PFS (**A**) and OS (**D**) in MM patients according to combined cytogenetic risk and MRD status. PFS (**B**) and OS (**E**) in MM patients according to combined ASCT and MRD status. PFS (**C**) and OS (**F**) in MM patients according to combined clinical response and MRD status