



# Puxando o desfecho para DRM no Mieloma: Justo?

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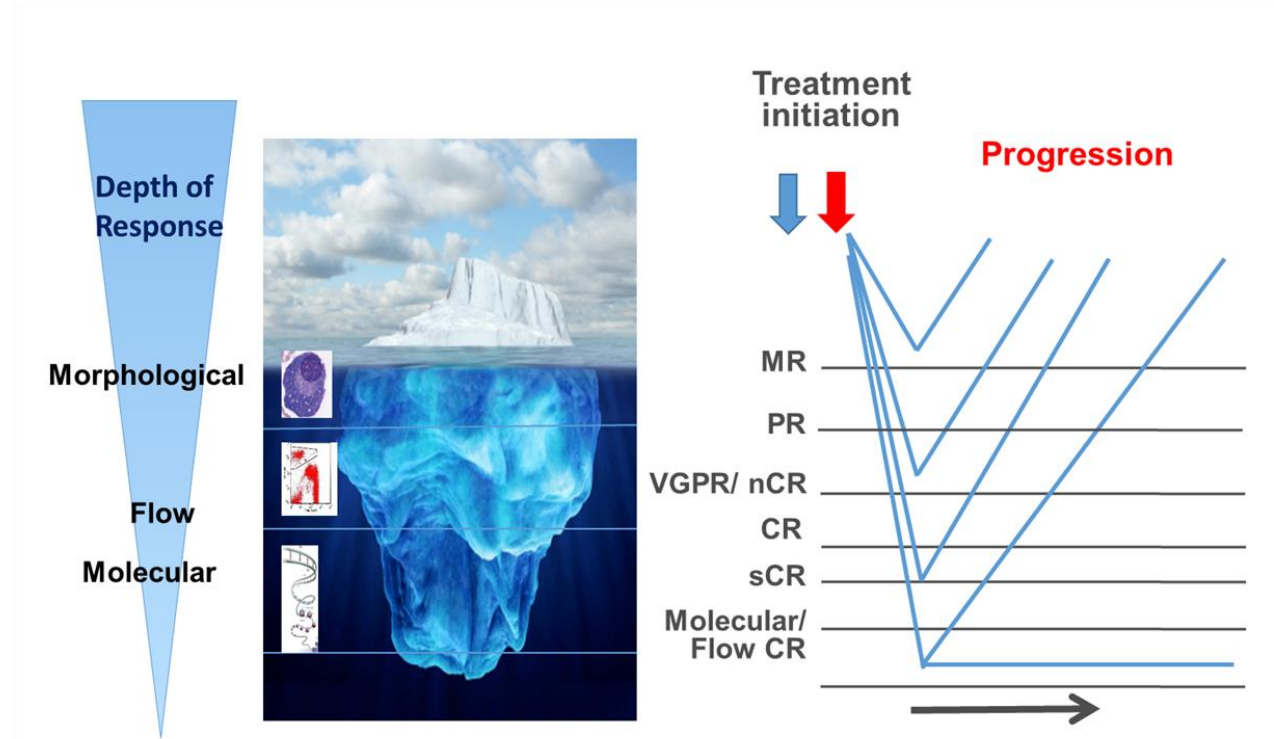


# Disclosures

I have the following financial relationships to disclosure

<b>Honorary for this lecture</b>	<b>no</b>
<b>Institution</b>	<b>UFRJ</b>
<b>Sponsored clinical research</b>	<b>Jansen, BMS, Sanofi</b>
<b>Patency &amp; Royalties</b>	<b>None</b>
<b>Speaker activity</b>	<b>Amgen, Janssen, BMS, Sanofi, Pfizer</b>
<b>Advisory Board</b>	<b>Amgen, Janssen, BMS, Sanofi, Pfizer</b>

# To achieve deeper and sustained responses, should be the goal of modern MM treatment?





## New 2016 IMWG Criteria for MRD in MM

IMWG MRD Negativity Criteria (Requires CR)

### Sustained MRD negative

- MRD negative in marrow (NGF or NGS) and by imaging as defined below, confirmed  $\geq 1$  year apart. Subsequent evaluations can be used to further specify duration of negativity (eg, MRD negative at 5 years)

### Imaging MRD negative

- MRD negative as defined below (NGF or NGS) PLUS disappearance of all areas of increased tracer uptake observed at baseline or previous PETs/CTs or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

### Flow MRD negative

- Absence of phenotypically aberrant clonal PCs by NGF on bone marrow aspirates using the **EuroFlow standard operating procedure** for MRD detection in MM (or equivalent validated method) with minimum sensitivity of 1 in  $10^5$  nucleated cells

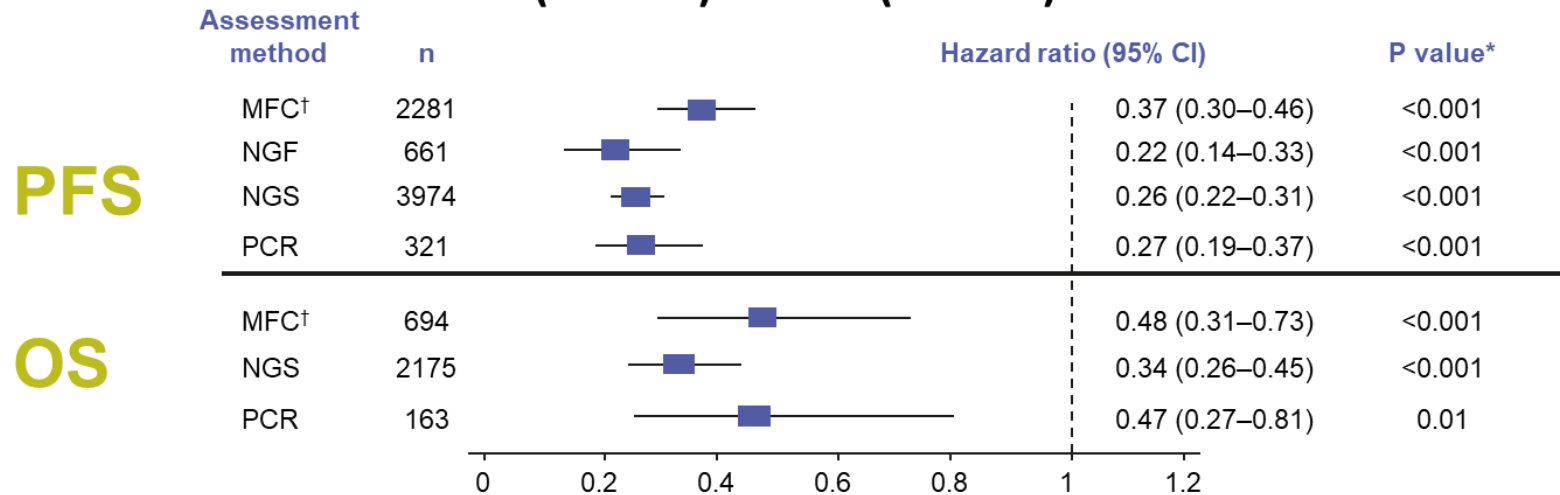
### Sequencing MRD negative

- Absence of clonal PCs by NGS on bone marrow aspirates where presence of a clone is defined as  $< 2$  identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the **LymphoSIGHT<sup>®</sup> platform** (or equivalent validated method) with minimum sensitivity of 1 in  $10^5$  nucleated cells

CR, complete response; CT, computed tomography; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; PC, plasma cell; PET, positron emission tomography; SUV, standardized uptake value. LymphoSIGHT<sup>®</sup> is a registered trademark of Sequentia, Inc.

# Does it matter which method is used to assess MRD?

- Meta-analysis of the prognostic value of MRD– for PFS (n=8098) and OS (n=4297) in MM



MRD– was associated with improved survival irrespective of the MRD assessment method used

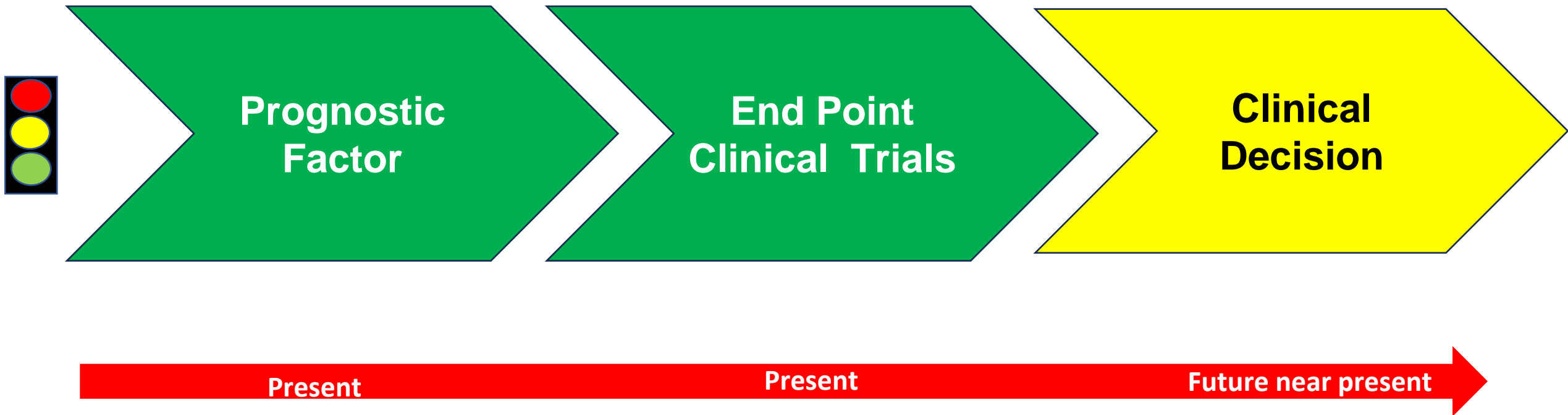


*International Harmonization guidelines: Results for MRD in scientific reports must state the method of detection and threshold utilized*

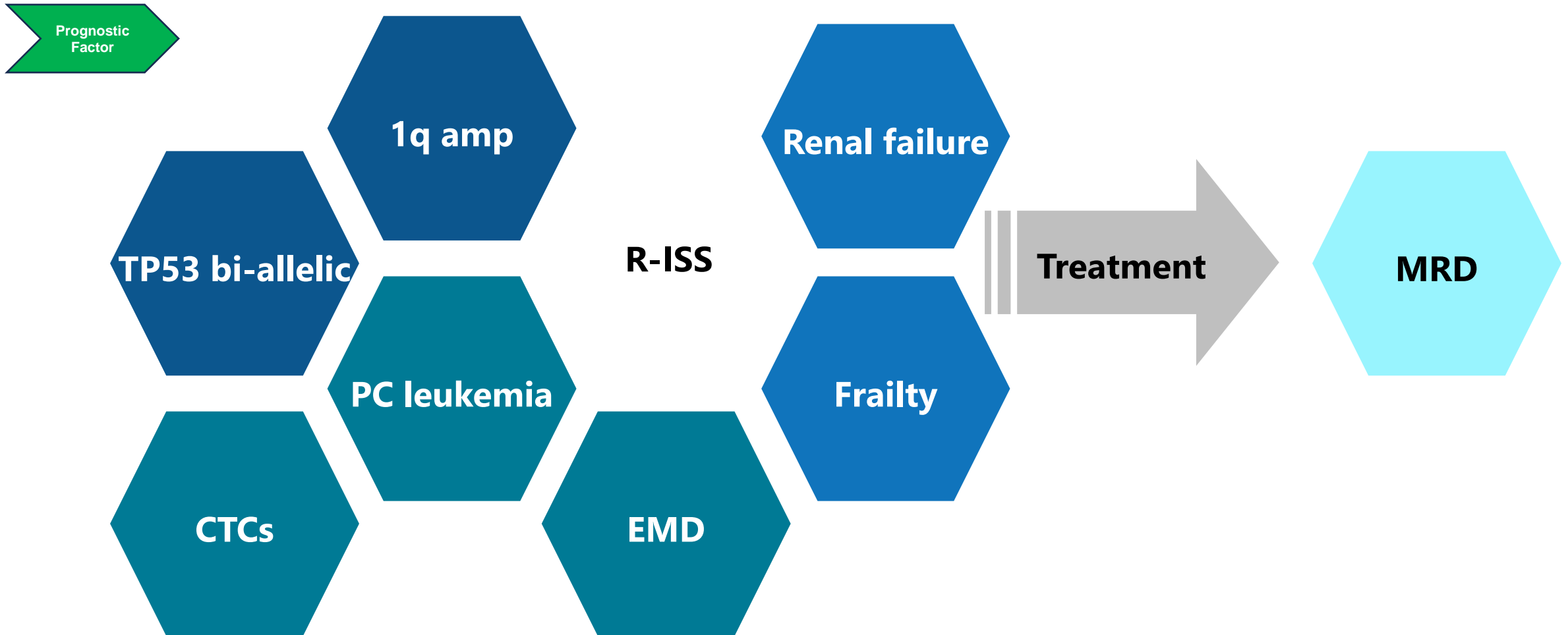
\*P versus MRD+; †Only includes studies with MRD sensitivity thresholds at 10<sup>-5</sup> and 10<sup>-6</sup>. MM, multiple myeloma; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival

# Mesurable Residual Disease (MRD) in Multiple Myeloma

## *Applications in 2024*



# MRD a dynamic prognostic factor

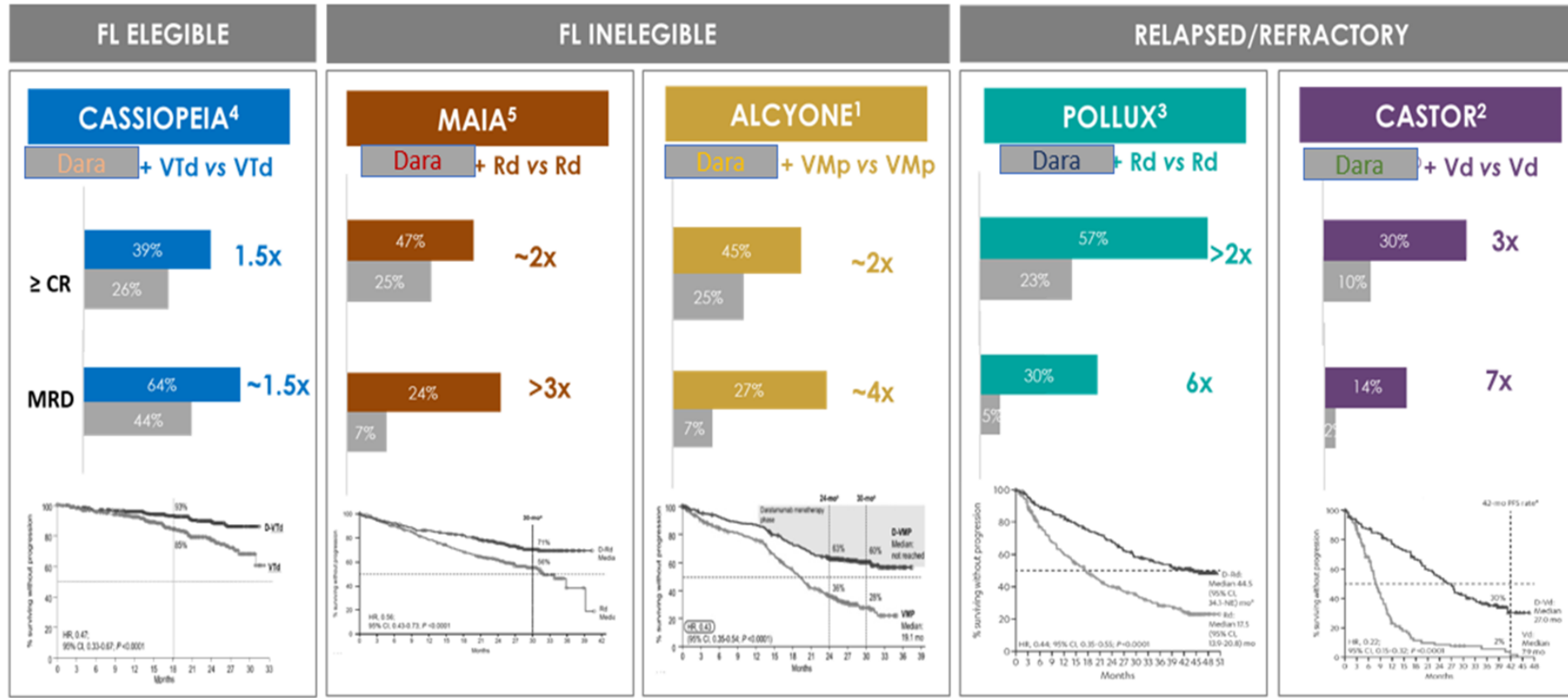


CTCs, circulating tumor cells; EMD, extramedullary disease; MRD, minimal residual disease; PC, plasma cell; R-ISS, Revised Multiple Myeloma International Staging System.



# MRD in Clinical trials

**No matter in first line or relapse ; transplant or ineligible patients, MRD is a powerful and relevant information and correlates with outcomes.**

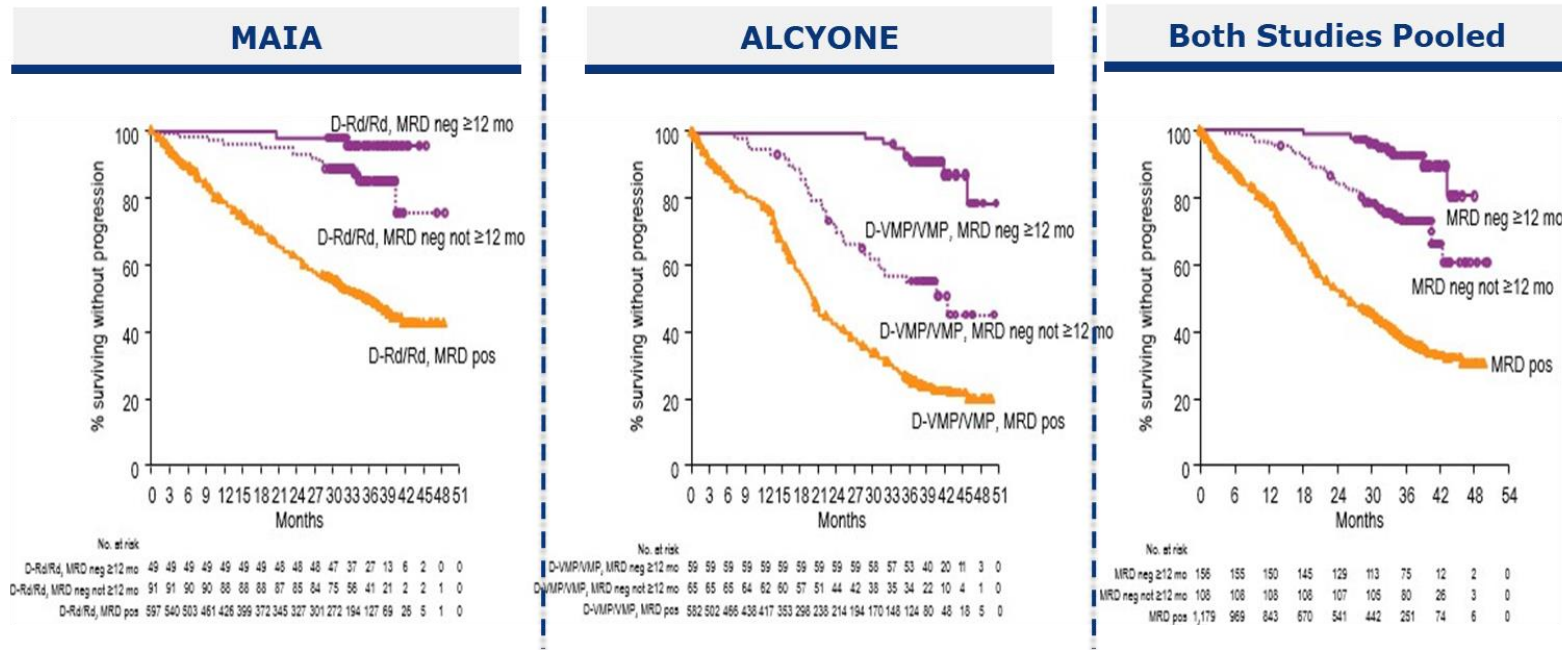


1. Dimopoulos MA et al. Oral presentation at ASH 2018, December 1-4, 2018; San Diego, California Abstract 156. 2. Mateos MV, et al. Presented at ASH 2018, December 1-4, 2018; San Diego, California P3270. 3. Bahlis NJ, et al. Presented at ASH 2018, December 1-4, 2018; San Diego, California P1996. 4. Moreau et al: Phase 3 randomized study of daratumumab (DARA) + bortezomib/thalidomide/dexamethasone (D-VTd) vs VTd in transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 1 results..2019 ASCO Annual Meeting, Chicago, IL, May 31th to June 4th, 2019. Abstract 8003. 5. Facon T; et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N ENGL J MED 380:22, 2019.



# A single MRD time point evaluation is not enough!

*PFS Based on Sustained MRD Negativity ( $10^{-5}$ )  
Lasting  $\geq 12$  Months*



PFS, progression-free survival; MRD, minimal residual disease; D-Rd, daratumumab plus lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; D-VMP, daratumumab plus bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone.

**MRD conversion from -ve to +ve (unsustained) is associated with impeding relapses!**

## Importance of whole body Imaging during treatment monitoring

	Newly Diagnostic	Relapse/Refractory
MRD <sup>-ve</sup> / imaging <sup>-ve</sup>	30 (36.1%)	8 (24.2%)
MRD <sup>-ve</sup> / imaging <sup>+ve</sup>	4 (4.8%)	8 (24.2%)
MRD <sup>+ve</sup> / imaging <sup>-ve</sup>	39 (47.0%)	10 (30.3%)
MRD <sup>+ve</sup> / imaging <sup>+ve</sup>	10 (8.4%)	7 (21.2%)
<b>Total (n)</b>	<b>83</b>	<b>33</b>

# What about MRD-NGF in a Real-World? Multiple Myeloma Transplanted Population in Brazil?

**cancers** **MDPI**

**Article**  
**Lenalidomide Maintenance and Measurable Residual Disease in a Real-World Multiple Myeloma Transplanted Population Receiving Different Treatment Strategies Guided by Access to Novel Drugs in Brazil**

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**Simple Summary:** Lenalidomide maintenance (M-Len) after autologous stem cell transplantation (ASCT) improved survival outcomes in multiple myeloma (MM). The present work found that M-Len and measurable residual disease detected by next-generation flow cytometry (NGF) were independent prognostic factors that could be used to discriminate patients at an earlier risk of relapse in a real-world study from Brazil.

**Abstract:** Despite recent advances in multiple myeloma (MM), the incorporation of novel agents and measurable residual disease (MRD) monitoring in the routine practice remains a challenge. Although lenalidomide maintenance (M-Len) after autologous stem cell transplantation (ASCT) has been associated with improved outcomes and MRD has refined the prognosis of complete response (CR) cases, until now, there have been no data on the benefits of these approaches in Latin America. Here, we evaluate the benefits of M-Len and MRD using next-generation flow cytometry (NGF-MRD) at Day +100 post-ASCT (n = 35). After ASCT, responses were evaluated based on the International Myeloma Working Group criteria and NGF-MRD. MRD was positive in 40% of patients with a median progression-free survival (PFS) of 31 months vs. not reached (NR) for MRD-negative cases (p = 0.05). The patients who received M-Len continuously had a significantly better PFS and overall survival (OS) than those without M-Len (median PFS: NR vs. 29 months, p = 0.007, with

**Keywords:** multiple myeloma; lenalidomide maintenance; measurable residual disease; next-generation flow cytometry

**1. Introduction**

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow, leading to the production of monoclonal immunoglobulin (Ig) and associated complications [1]. The standard of care for MM involves autologous stem cell transplantation (ASCT) followed by maintenance therapy [2]. Lenalidomide maintenance (M-Len) has emerged as a key component of the treatment strategy, significantly improving progression-free survival (PFS) and overall survival (OS) compared to no maintenance [3].

Measurable residual disease (MRD) is a critical prognostic factor in MM, reflecting the presence of residual clonal plasma cells after treatment [4]. MRD detection is typically performed using next-generation flow cytometry (NGF) [5]. MRD-positive patients are at a higher risk of relapse and shorter survival compared to MRD-negative patients [6].

The combination of M-Len and MRD monitoring offers a more comprehensive approach to patient management, allowing for earlier identification of high-risk patients and potentially more tailored treatment strategies [7]. However, the implementation of these advanced techniques in real-world settings, particularly in resource-limited regions like Brazil, remains a challenge [8].

This study aims to evaluate the impact of M-Len and MRD on PFS and OS in a real-world multiple myeloma transplanted population in Brazil, where access to novel drugs and advanced diagnostic tools may vary significantly [9].

**2. Materials and Methods**

**2.1. Study Design and Population**

This retrospective study included 100 multiple myeloma patients who underwent ASCT and were followed up in a tertiary care center in Brazil. The patients were divided into two groups based on their maintenance strategy: those who received M-Len (n = 50) and those who did not (n = 50). The study was approved by the local ethics committee.

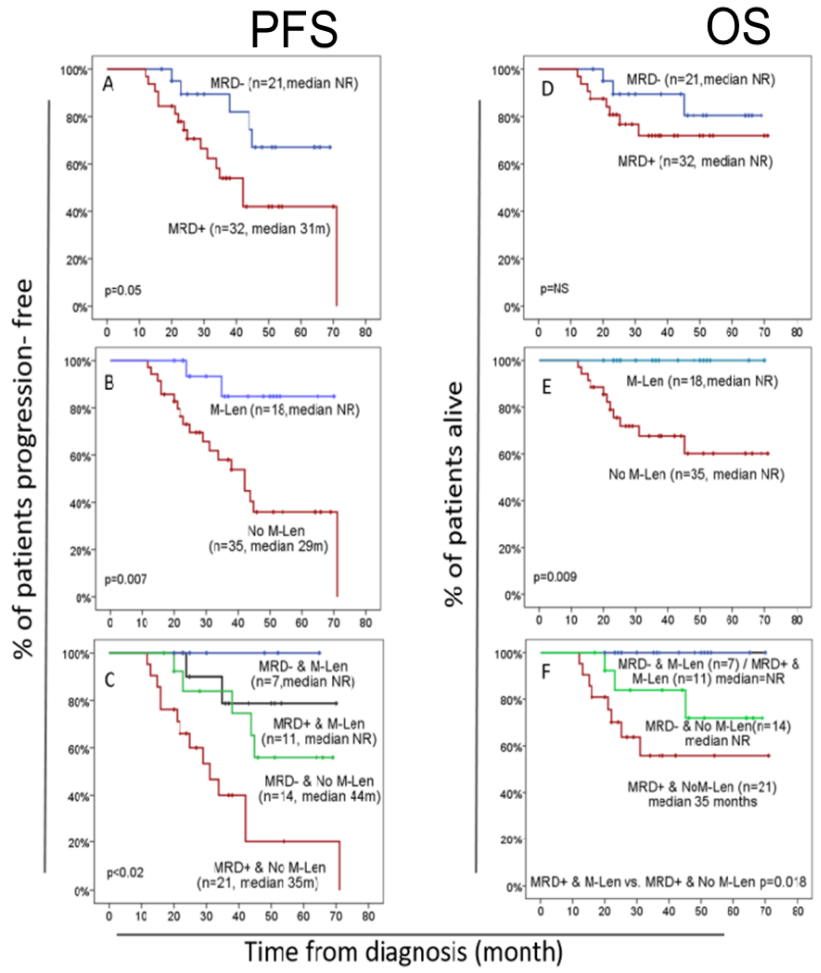
**2.2. Treatment and MRD Monitoring**

All patients received ASCT followed by lenalidomide maintenance (M-Len) at a dose of 15 mg daily, 7 days per week, for up to 24 months. For patients who did not receive M-Len, the reasons were documented. MRD was monitored using NGF-MRD at Day +100 post-ASCT. MRD was defined as the presence of clonal plasma cells at a sensitivity of 10<sup>-5</sup> to 10<sup>-6</sup> [10].

**2.3. Statistical Analysis**

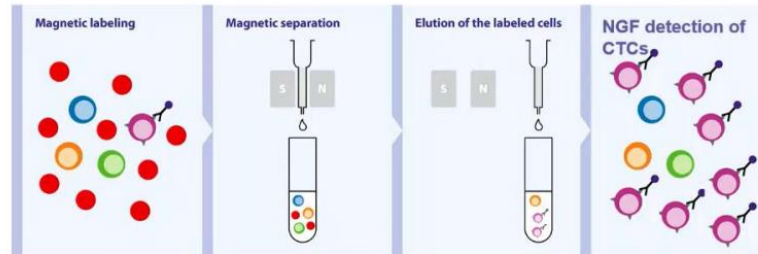
Statistical analysis was performed using the Kaplan-Meier method for survival curves. The log-rank test was used to compare PFS and OS between the M-Len and No M-Len groups. A p-value of less than 0.05 was considered statistically significant. The median was used to describe the central tendency of the survival data.

**Access to MM drugs for nations with constraints is a issue that always matter!**



## BloodFlow

### Immunomagnetic enrichment using MACS® MicroBeads prior NGF



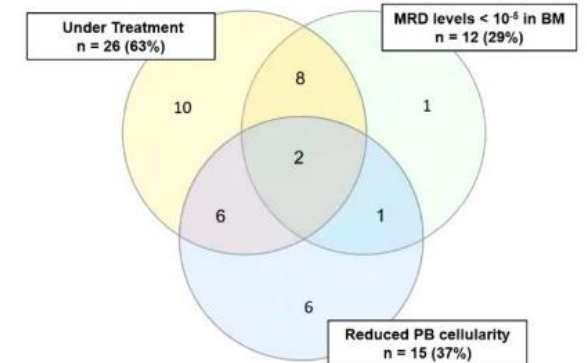
- A minimum **sensitivity of  $10^{-7}$**  requires analyzing  $\geq 2 \times 10^8$  cells (~50mL of PB)
- Large (~50mL) **PB volumes** were magnetically labeled and processed via MACS® columns, and ~100µL aliquots enriched with circulating PC were analyzed using EuroFlow NGF

## Performance of BloodFlow vs NGF in PB & BM (n = 199 paired samples)

BloodFlow showed a NPV of 77% when compared to NGF in BM

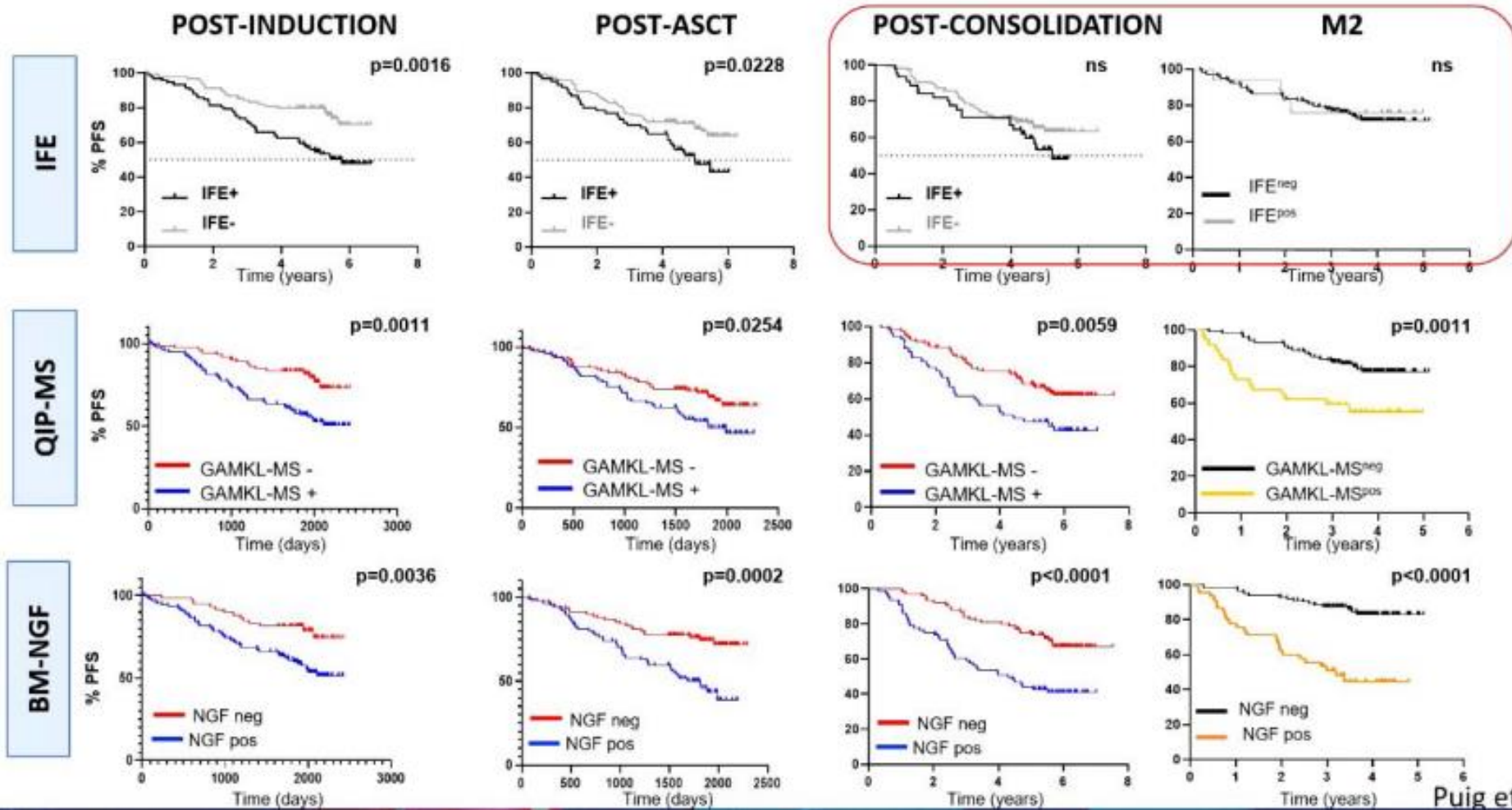
199 paired samples		BM	
		NGF-	NGF+
PB	BF-	137 (69%)	<b>41 (20.5%)</b>
	BF+	2 (1%)	19 (9.5%)

### Analysis of the 41 discordant cases



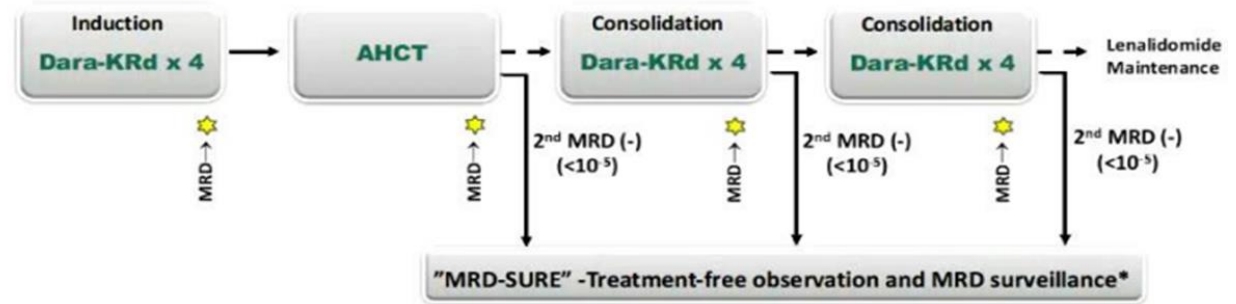


**As opposed to CR, MRD by NGF and quantitative immunoprecipitation mass spectrometry (QIP-MS) showed a significant prognostic value at all time-points**



## Phase 2 Master study: D-KRD -ASTC and MRD Adapted consolidation in NDMM

123 pts and 57% HR defined by gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)



- 84 patients achieved MRD-SURE
  - 0 HRCA – 62%
  - 1 HRCA – 78%
  - 2+ HRCA – 63%
- Median follow up in MRD-SURE: 14.2 mo.
- Risk of MRD resurgence or progression 12m after treatment cessation**
  - 0 HRCA – 4%
  - 1 HRCA – 0%
  - 2+ HRCA – 27%

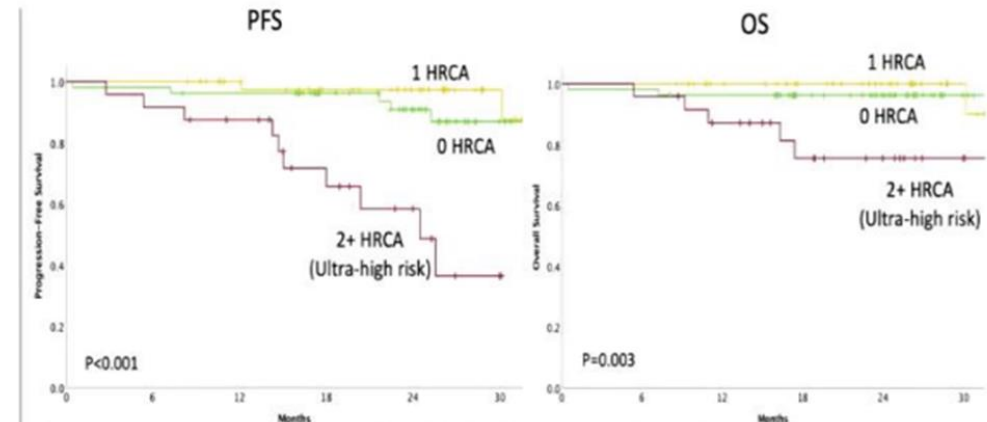
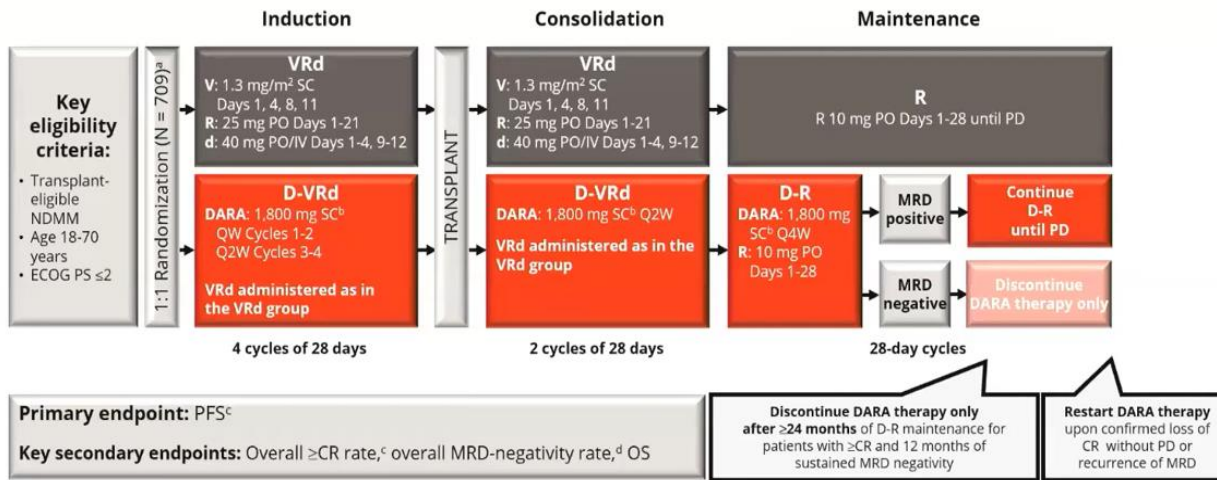


Figure 2 - PFS and OS according to number of high-risk cytogenetic abnormalities

## PERSEUS: Study Design

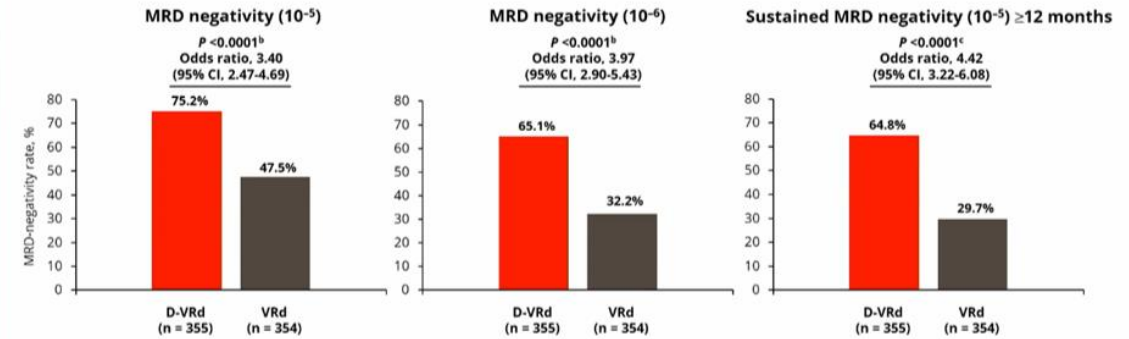


ECOG PS, Eastern Cooperative Oncology Group performance status; V, bortezomib; SC, subcutaneous; PO, oral; d, dexamethasone; IV, intravenous; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; Q4W, every 4 weeks; MRD, minimal residual disease; CR, complete response; OS, overall survival; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20; IMWG, International Myeloma Working Group; VGPR, very good partial response. <sup>a</sup>Stratified by ISS stage and cytogenetic risk. <sup>b</sup>DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE<sup>®</sup> drug delivery technology, Halozyme, Inc., San Diego, CA, USA). <sup>c</sup>Response and disease progression were assessed using a computerized algorithm based on IMWG response criteria. <sup>d</sup>MRD was assessed using the clonoSEQ assay (v.2.0; Adaptive Biotechnologies, Seattle, WA, USA) in patients with  $\geq$ VGPR post consolidation and at the time of suspected  $\geq$ CR. Overall MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity ( $10^{-5}$  threshold) and  $\geq$ CR at any time.

Presented by P. Sonneveld at American Society of Hematology Annual Meeting, December 9-12, 2023; San Diego, CA, USA.

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## PERSEUS: Overall and Sustained MRD-negativity Rates<sup>a</sup>



- Deep and durable MRD negativity was achieved with D-VRd
- 64% (207/322) of patients receiving maintenance in the D-VRd group discontinued DARA after achieving sustained MRD negativity per protocol<sup>d</sup>

<sup>a</sup>MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and  $\geq$ CR. MRD was assessed using bone marrow aspirates and evaluated via next-generation sequencing (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA). <sup>b</sup>P values were calculated with the use of the stratified Cochran-Mantel-Haenszel chi-squared test. <sup>c</sup>P value was calculated with the use of Fisher's exact test. <sup>d</sup>After  $\geq 24$  months of maintenance therapy, DARA was discontinued in patients who achieved  $\geq$ CR and sustained MRD negativity ( $10^{-5}$ ) for  $\geq 12$  months.

Presented by P. Sonneveld at the 65th American Society of Hematology (ASH) Annual Meeting, December 9-12, 2023; San Diego, CA, USA

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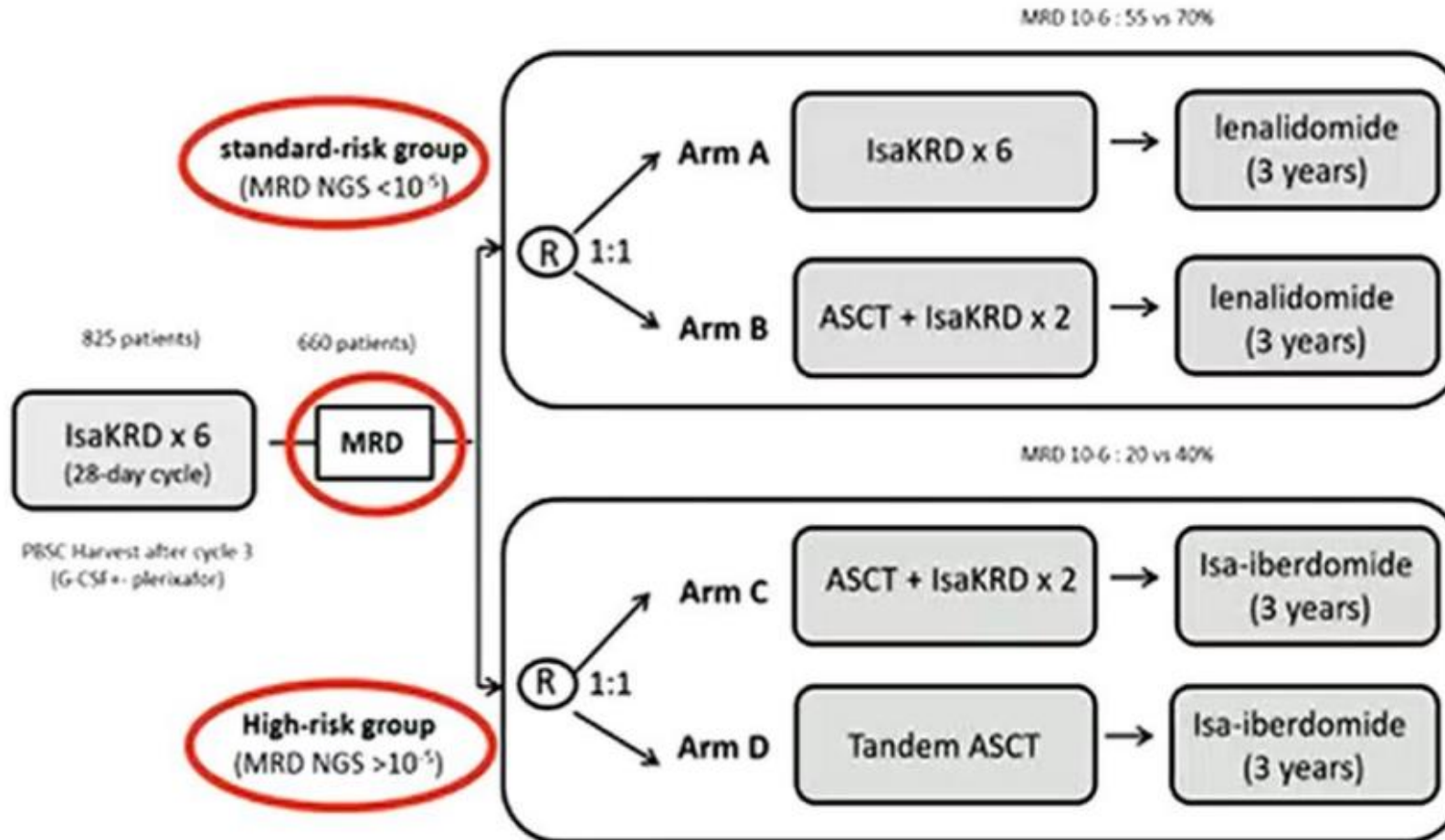




**MIDAS study : Minimal res Disease Adapted Strategy**

**Induction and PBSC harvest**

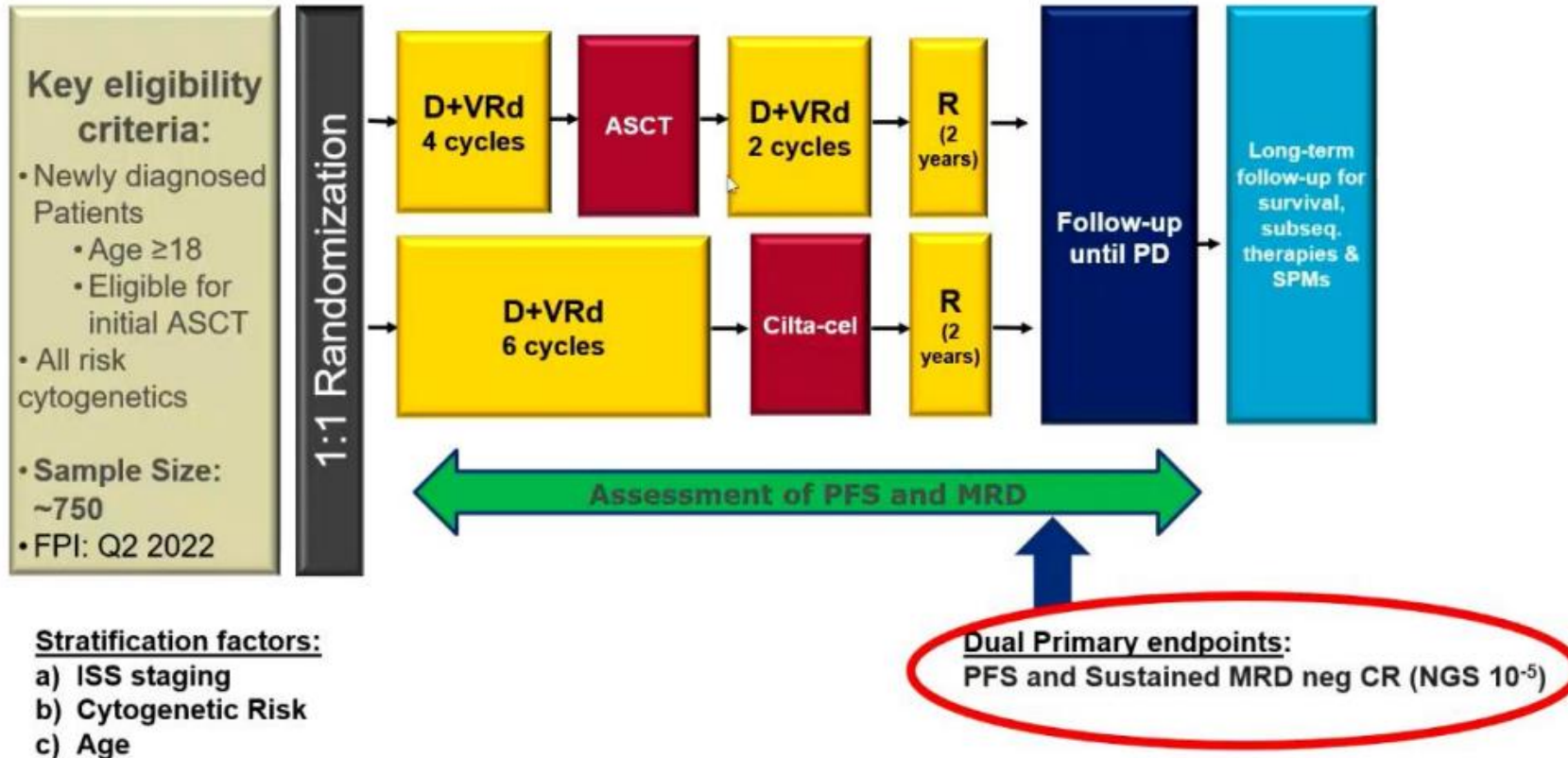
**Risk-adapted consolidation and maintenance**





# EMN28: Randomized trial of Cilta-cel vs ASCT in TE-NDMM

n=750





**Obrigado!**

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