XIX CONGRESSO NAZIONALE SIES 2026

Describing the heterogeneity of disease distribution in multiple myeloma patients through a liquid biopsy approach

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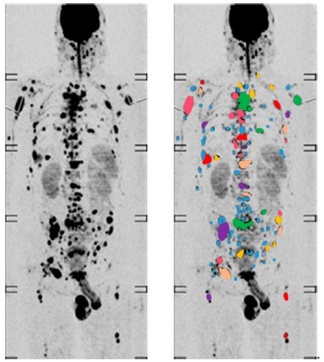
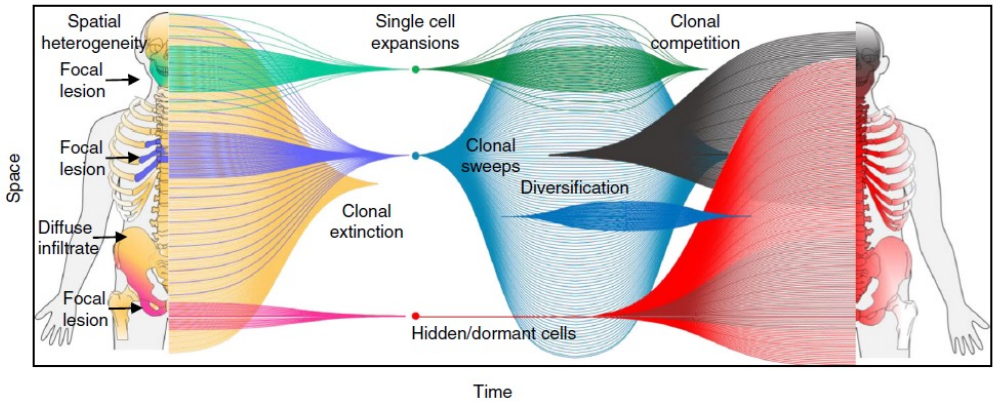
Disclosures of Silvia Armuzzi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Background





Disease Dissemination

- Multifocal bone marrow involvement
- Possible extramedullary disease
- Dynamic evolution over time

Spatial Heterogeneity

- Variability among BM lesions
- Coexistence of distinct subclones
- Risk of disease underestimation from single-site sampling

Genomic Heterogeneity

- Cytogenetic and molecular complexity
- Presence of subclonal genetic alterations
- Clonal evolution during the clinical course

CONSEQUENCE

Multiple myeloma is a systemic, dynamic, and biologically heterogeneous disease, difficult to accurately represent with a single diagnostic assessment.

Rasche, L., et al., Nat Commun 2022; Rasche L., et al., Int. J. Mol. Sci. 2019

Multimodal MRD: A New Paradigm in Monitoring ?

AIMS

1. to explore the use of liquid biopsy approach to measure the spread of the disease

2. to investigate the prognostic significance of diffuse disease distribution correlated to the quality response to therapy

Patients' cohort

Inclusion criteria:

140 MM newly diagnosed patients

- diagnosis of MM, according to the IMWG
- patients with ≤70 years, transplant-eligibility, or fit patients
- evidence of diffuse disease and/or lesions positive at the 18F-FDG PET/CT.

Median age: 62 years old (range 26-81)
- "Young" pts 116/140 (83%)
- "Elderly-fit" pts 24/140 (17%)

Sex:
- Male: 75/140 (53%)
- Female: 65/140 (47%)

R_ISS: 127/140
- Stage 1: 59/127 (46%)
- Stage 2: 56/127 (44%)
- Stage 3: 11/127 (10%)

CSG IMS/IMWG Criteria: 83/140
- Non-high risk: 41/83 (51%)
- High risk: 42/83 (49%)

Imaging Data: 134/140
- BM DS≥4: 39/134 (29%)
- PM DS≥2: 36/134 (26%)

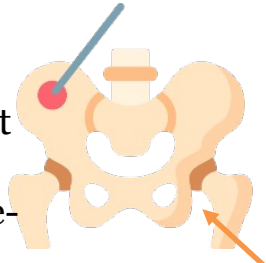
Induction Therapy
- DARA-based: 63/140 (45%)
- Conventional triplet: 77/140 (55%)

Pts evaluated at pre-maintenance (MRD): 84/140 (60%)

Materials and Methods

Bone Marrow site:

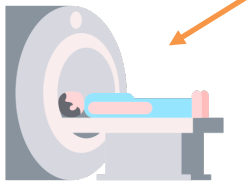
- CD138+ PCs BM for clonotype assessment and FISH
- MRD Monitoring pre- and during maintenance



Peripheral Blood (liquid biopsy)

- cfDNA (TF) analyzed by ULP-WGS
- CPCs evaluations by flow cytometry

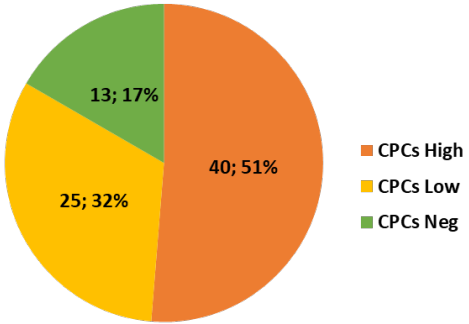
Imaging data collected at the diagnosis (PET/CT)



Baseline **clinical data** (routine biochemical analysis),therapy and response to therapy.

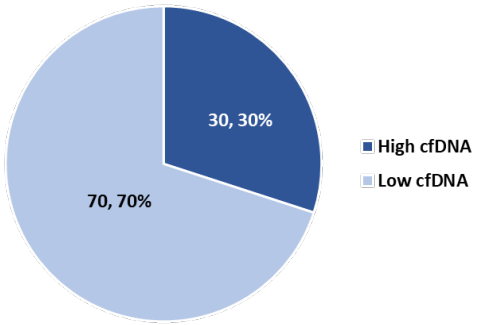
Results – Diagnosis Analysis

CPCs 78/140 pts



Cut-off: 0,02%*
CPCs High>0.02%
CPCs Low<0,02%

Tumor Fraction – cfDNA 100/140 pts



Cut-off: 12%**
High cfDNA>12%
Low cfDNA<12%

High levels of circulating elements are associated with:

- Higher disease diffusion, assessed by imaging;
- High risk score (ISS, R-ISS, IMS-Criteria);
- Adverse biochemical parameters (albumin, clearance, creatine, anaemia, higher B2M levels…)

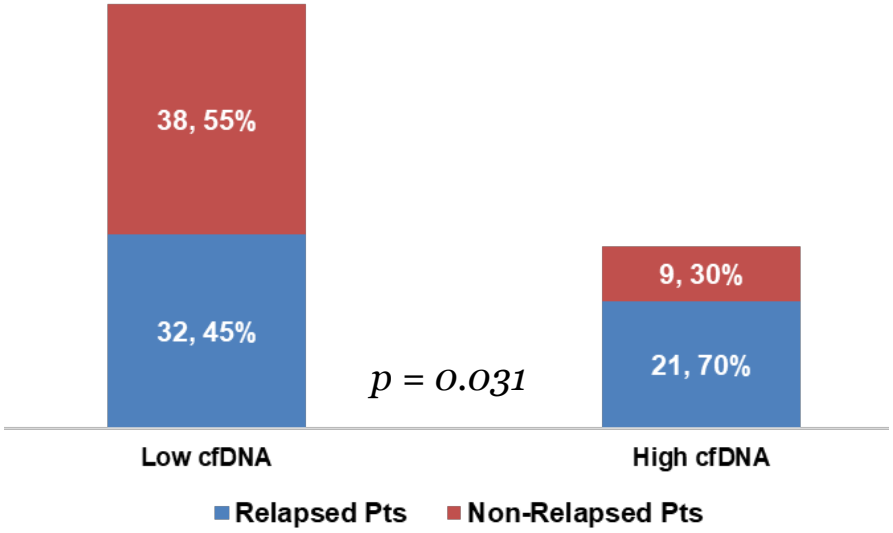
**Vigliotta I., et al., Cancers (Basel), 2024; **Martello M., et al., Blood Cancer Journal, 2024.*

Can cfDNA TF predict clinical outcomes?

Low TF cfDNA group (70/100 pts)

STANDARD RISK MM PTS

Median follow up: 29m (range 3-58)



High TF cfDNA group (30/100 pts)

HIGH RISK MM PTS

Median follow up: 12m (range 2-56)

Early endpoint: MRD pre-maintenance (~12 months)

Method: NGS (sensitivity at 10^{-5})

MRD Dynamic

High TF cfDNA group
HIGH RISK MM PTS

15 patients with MRD evaluation pre-maintenance

3 POS | **12 NEG**

20% MRD POSITIVE

Low TF cfDNA group
STANDARD RISK MM PTS

43 patients with MRD evaluation pre-maintenance

15 POS | **28 NEG**

34% MRD POSITIVE

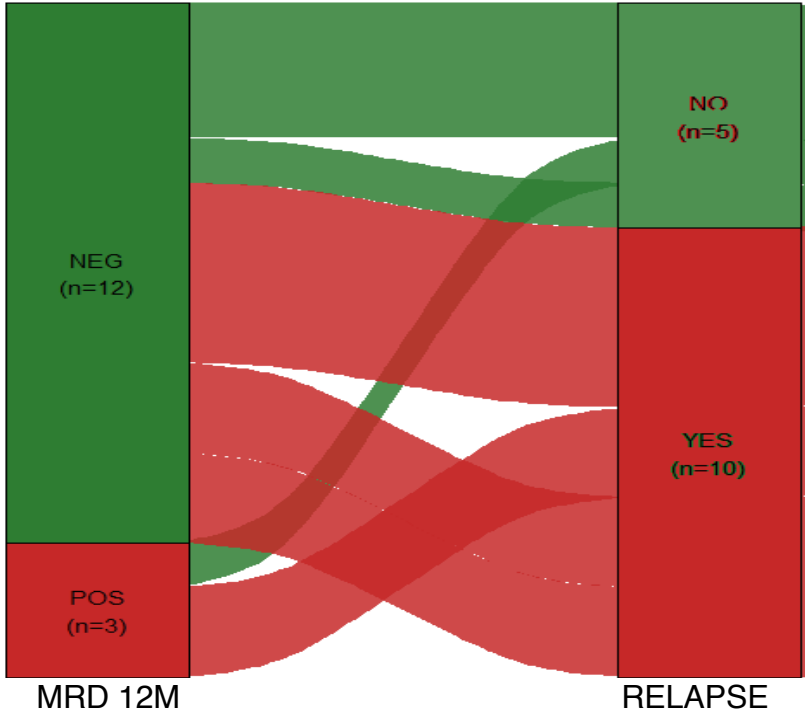
Could ***BM-MRD*** be *more reliable* in patients with low level of circulating elements and a standard risk profile?

MRD Dynamic

High TF cfDNA group
HIGH RISK MM PTS

10/15 (66%) -> relapse

! 8/12 (67%) neg at MRD 12M have relapsed, even though 2/8 (25%) had a sustained MRD



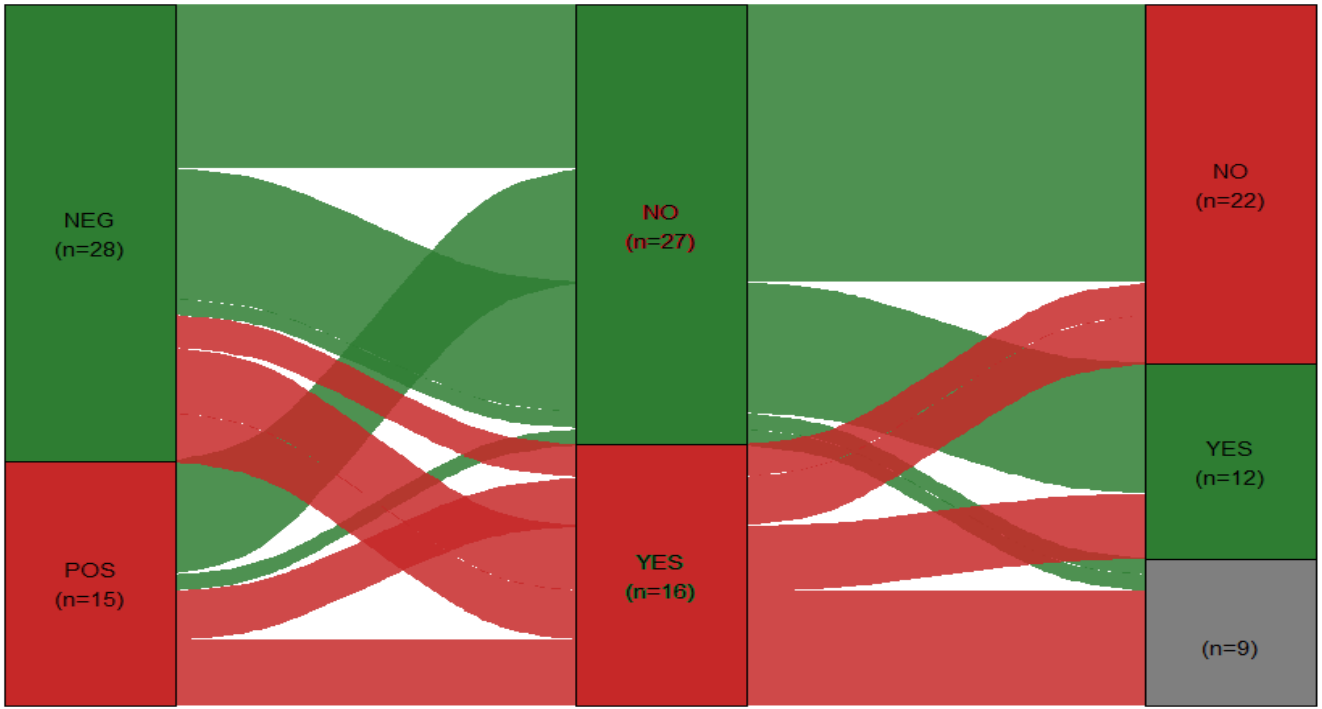
MRD Dynamic

Low TF cfDNA group

STANDARD RISK MM PTS

16/43 (37%) -> relapse

! 9/28 (32%) neg at MRD 12M have relapsed



Conclusions

At diagnosis presence of:

- Diffuse disease in BM
- PM lesions
- High level of TF cfDNA
- High level of CPCs

→

- ***High risk score***
- ***Worse outcome (relapse)***
- ***Advanced/aggressive disease***

BM-MRD may not completely mirror the status of the disease at early time-point in patients with high level of circulating elements

Integration of liquid biopsy as informative tool to describe patients' disease

Key Message

"In a biologically heterogeneous and spatially distributed disease such as multiple myeloma, a multimodal MRD approach represents a crucial tool for a truly comprehensive assessment of residual disease."

Thank You!

IRCCS – Azienda Ospedaliero Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" – **Prof. Pier Luigi Zinzani**

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