XIX CONGRESSO NAZIONALE SIES 2026

p53 isoform diversity in Multiple Myeloma: unexplored risk factor beyond TP53 mutation and del(17p)

Enrica Borsi

IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"

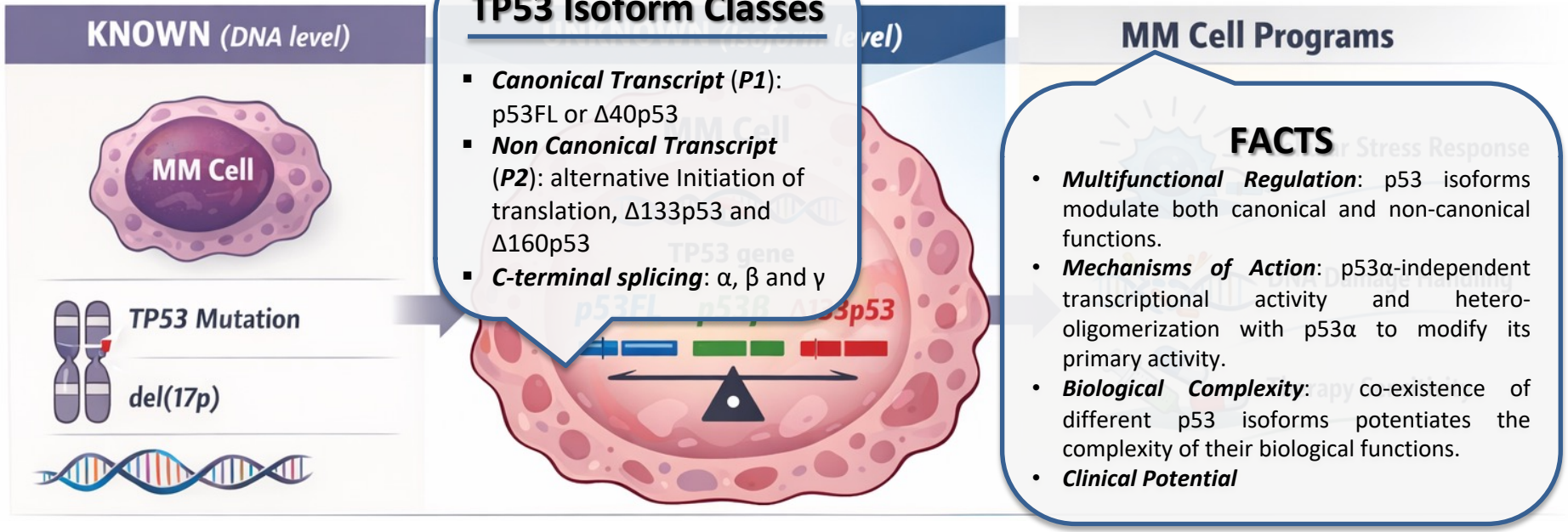
Firenze | 4-6 marzo 2026
Palazzo degli Affari

Disclosures of Name Surname

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

Nothing to Disclose

The p53 Isoform Landscape in Multiple Myeloma



TP53 Isoform Classes

- ***Canonical Transcript*** (***P1***): p53FL or Δ40p53
- ***Non Canonical Transcript*** (***P2***): alternative Initiation of translation, Δ133p53 and Δ160p53
- ***C-terminal splicing***: α, β and γ

FACTS

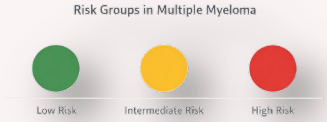
- ***Multifunctional Regulation***: p53 isoforms modulate both canonical and non-canonical functions.
- ***Mechanisms of Action***: p53α-independent transcriptional activity and hetero-oligomerization with p53α to modify its primary activity.
- ***Biological Complexity***: co-existence of different p53 isoforms potentiates the complexity of their biological functions.
- ***Clinical Potential***

p53 *isoform* expression represents an ***unexplored*** layer of biology in MM cells, modulating stress responses beyond ***TP53 DNA alterations***

Aims and Study Design

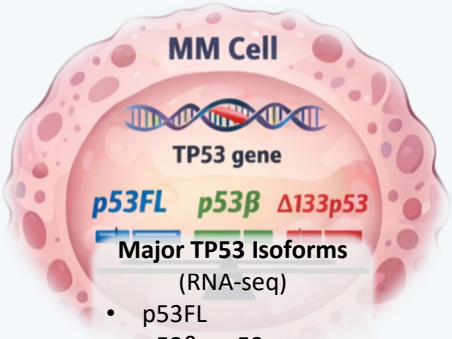
The «PROBLEM»

Current MM risk stratification relies on **TP53 DNA alterations**



The GAP

The clinical relevance of **TP53 isoform expression** remains unknown

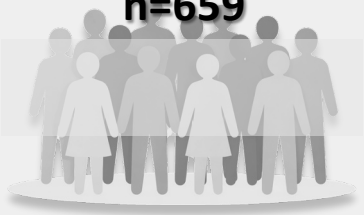


Patient

CoMMpass (AI22)

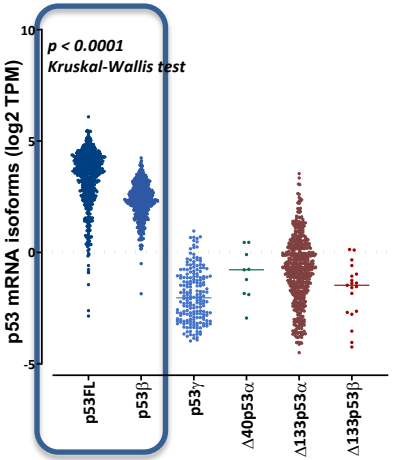
Patients with matched:

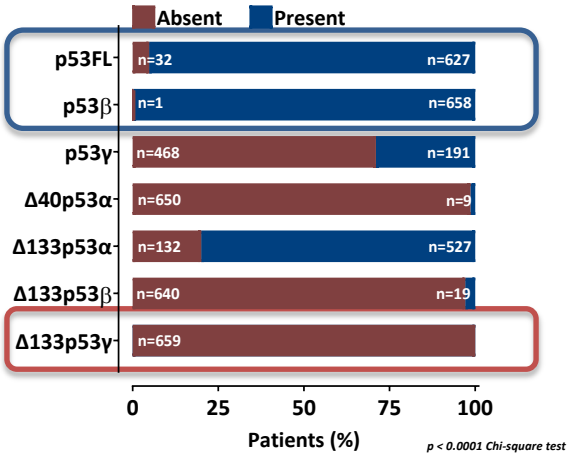
- Genomic profiling
- RNA-seq transcriptomics
- Clinical outcome data

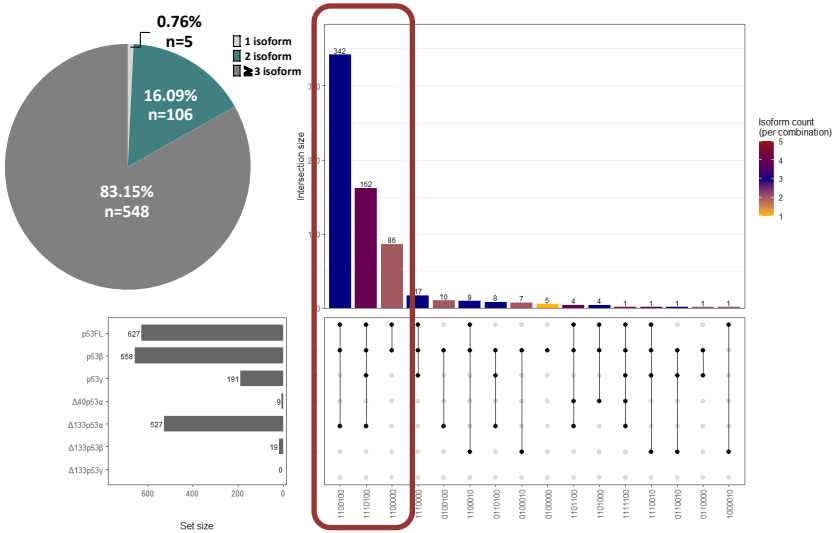


Aims: To assess whether ***TP53 isoform architecture*** adds prognostic value beyond DNA alterations

Expression landscape of major TP53 isoforms in MM (RNA-seq)





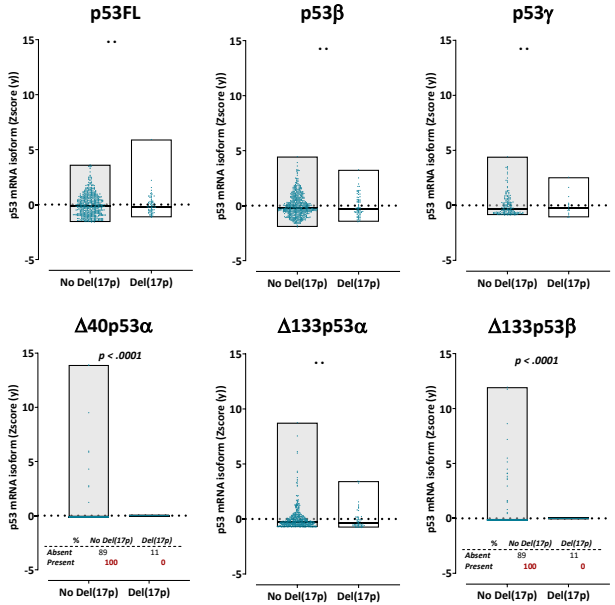


Canonical p53FL/β are ***broadly expressed***, whereas ***Δ isoforms*** define rarer expression patterns in MM

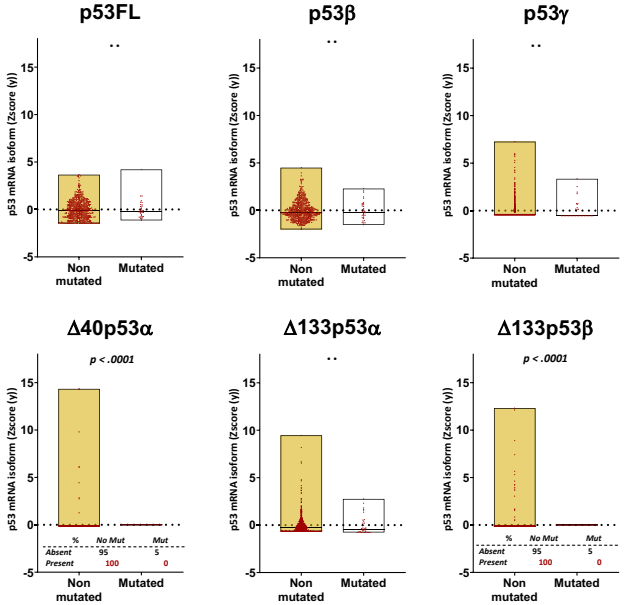
Most MM patients ***co-express*** multiple TP53 isoforms

p53 isoforms and TP53 DNA alterations

TP53 isoform distribution by del(17p)

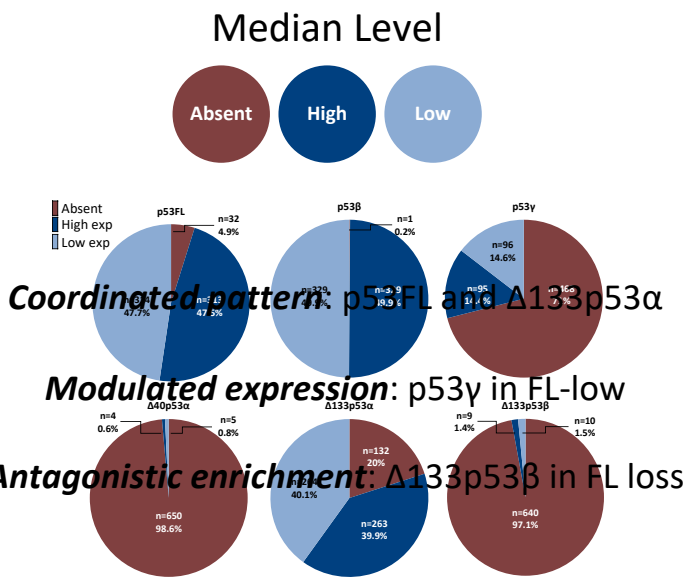


TP53 isoform distribution by mutation(s)



** Mann-Whitney test*

Non-random distribution of TP53 isoforms across p53FL expression levels

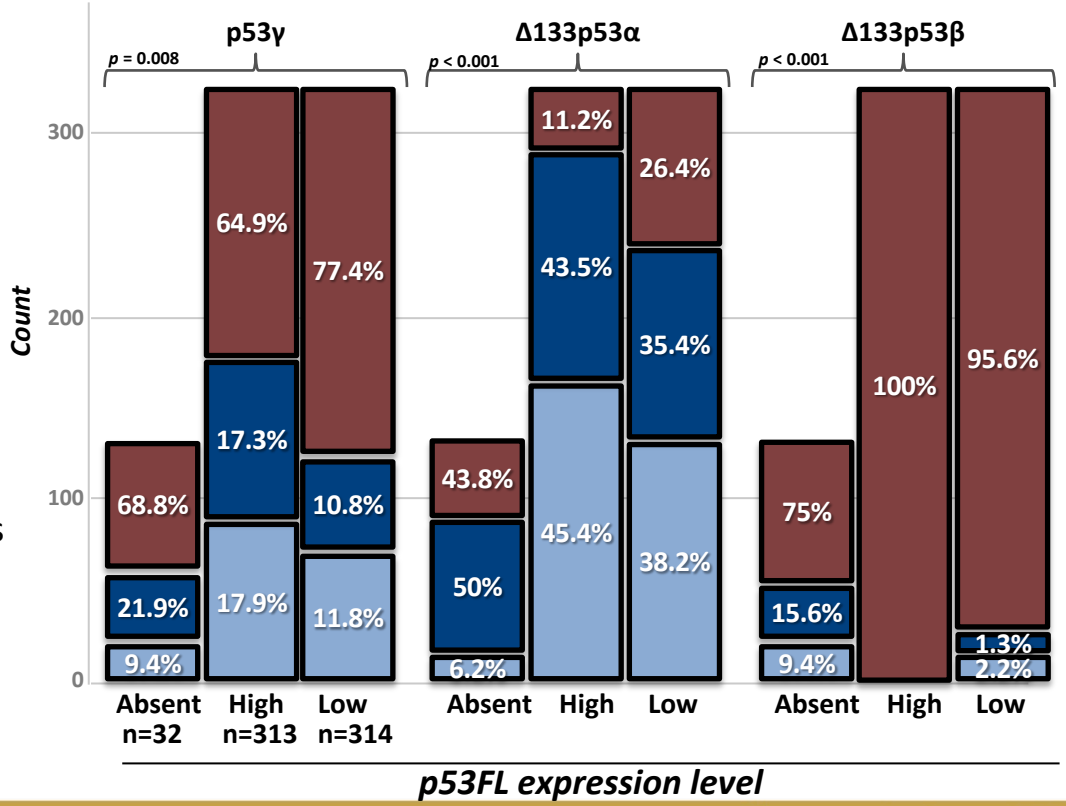


Coordinated pattern: p53FL and Δ133p53α

Modulated expression: p53γ in FL-low

Antagonistic enrichment: Δ133p53β in FL loss

p53FL status ***defines*** isoform-specific expression patterns



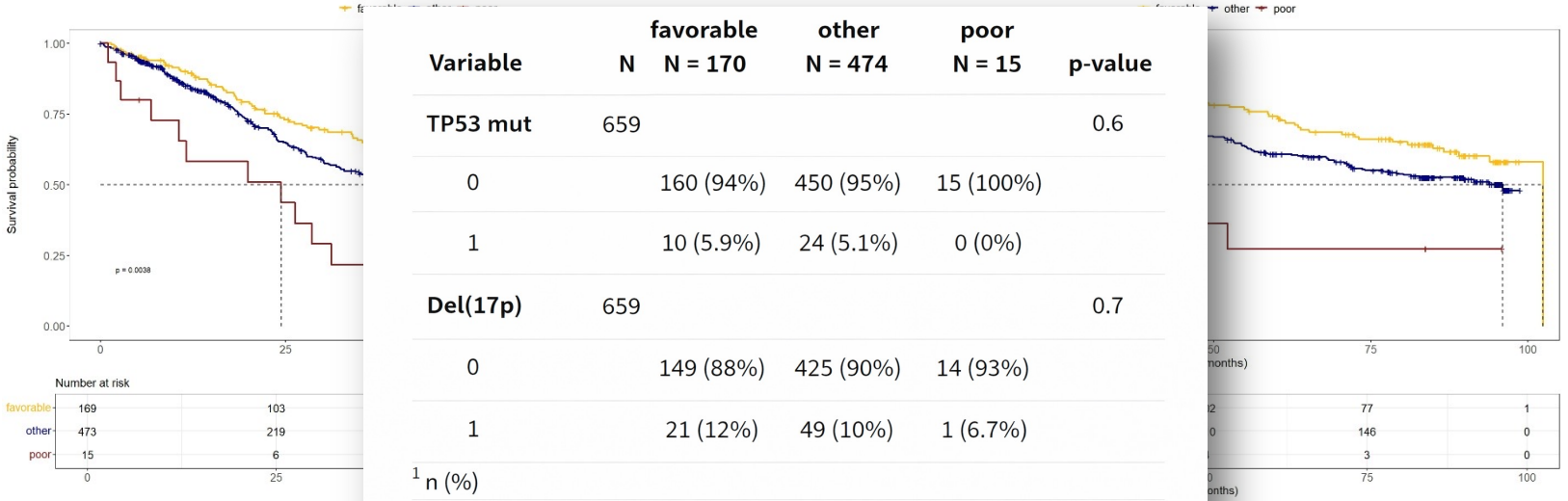
An isoform-driven risk classifier

Classifier Inputs

- **TP53 isoform expression** (p53FL, p53β, p53γ, Δ133p53β) → *Qualitative profile*
- **Isoform balance indicator** (Absent/high/low) → *Quantitative distribution*
- **Genomic and cytogenetics background** → *biological context*

We combined isoform expression and genomic/cytogenetics background to create a new prognostic model stratifying patients into three groups

TP53 Isoform-driven Stratifier Identifies Patients with Inferior Survival



Variable	N	favorable N = 170	other N = 474	poor N = 15	p-value
TP53 mut	659				0.6
0		160 (94%)	450 (95%)	15 (100%)	
1		10 (5.9%)	24 (5.1%)	0 (0%)	
Del(17p)	659				0.7
0		149 (88%)	425 (90%)	14 (93%)	
1		21 (12%)	49 (10%)	1 (6.7%)	

[1] n (%)

[2] Pearson's Chi-squared test

HR **2.55**, 95% CI 1 … 8–6.91, ***p*<0.001**

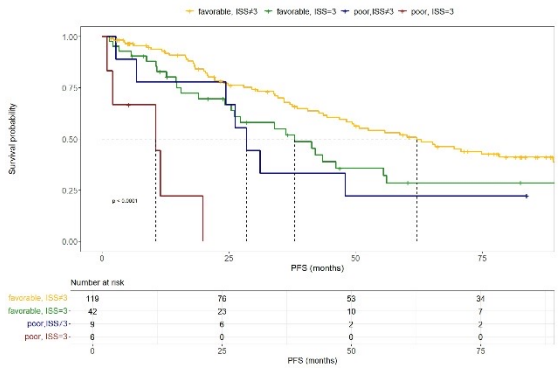
Median PFS: 50.7 *vs* 24.4 months

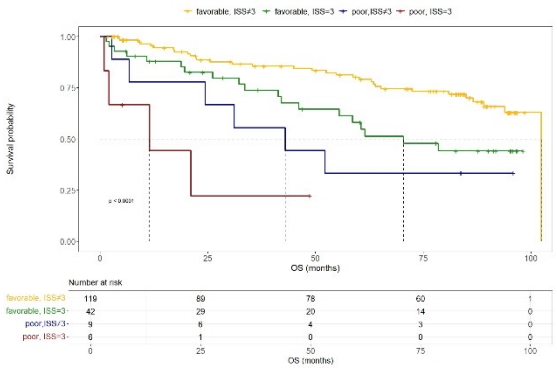
Median OS: 102 *vs* 31 months

Distribution of TP53 mutations and del(17p) across prognostic groups (N=659) → ***No significant association between TP53 status and prognostic categories***

TP53 isoform patterns alone define a high-risk subgroup with markedly worse outcomes

TP53 Isoform Stratification Provides Prognostic Value Beyond ISS and CGS





Interaction with ISS

High-risk subgroup with a median PFS of **10.5** months. A significant interaction with ISS was observed for PFS (***p* = 0.035**), whereas both factors independently impacted OS

Comparison with CGS

The TP53 isoform-based classifier identifies high-risk patients even within the CGS Low-Risk category (HR **2.46**, ***p* = 0.025**)

Summary

TP53 Isoform Architecture

The diversity of p53 isoforms in multiple myeloma represents an ***additional layer of biological complexity*** that can influence disease behavior beyond classical TP53 alterations.

Isoforms imbalance

The ***coexistence and expression*** patterns of specific isoforms, such as Δ133, are associated with a ***higher risk*** of disease progression and poorer survival outcomes.

Clinical Impact

Incorporating p53 isoform expression into risk models ***enhances the ability to identify high-risk patients***, even within established clinical and genetic stratifications.

Acknowledgments

IRCCS – Azienda Ospedaliero Universitaria di Bologna, Istituto di Ematologia “Seràgnoli”

Prof. Pier Luigi Zinzani

Molecular and cellular Biology Lab

Carolina Terragna
Ilaria Vigliotta
Alessia Varacalli
Silvia Armuzzi
Barbara Taurisano
Ignazia Pistis
Marina Martello
Enrica Borsi
Alessia Croce

Bio-informatics Unit

Vincenza Solli
Gaia Mazzocchetti
Viola Meixian Voung
Alessandra Vitale

Clinical Unit

Elena Zamagni
Paola Tacchetti
Lucia Pantani
Katia Mancuso
Ilaria Rizzello
Michele Puppi
Marco Talarico
Enrica Manzato
Ilaria Sacchetti
Simone Masci
Roberta Restuccia

Data Management

Simona Barbato
Francesca Trombetta
Nicola Parisi

Cytogenetic Lab

Carmen Baldazzi
Giulia Marzocchi