XIX CONGRESSO NAZIONALE SIES 2026

Identification of Outcome-Oriented Cut-Offs for Copy Number Alterations in Multiple Myeloma: Predictive Biomarkers with improved prognostic accuracy

Vincenza Solli

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
No disclosure							

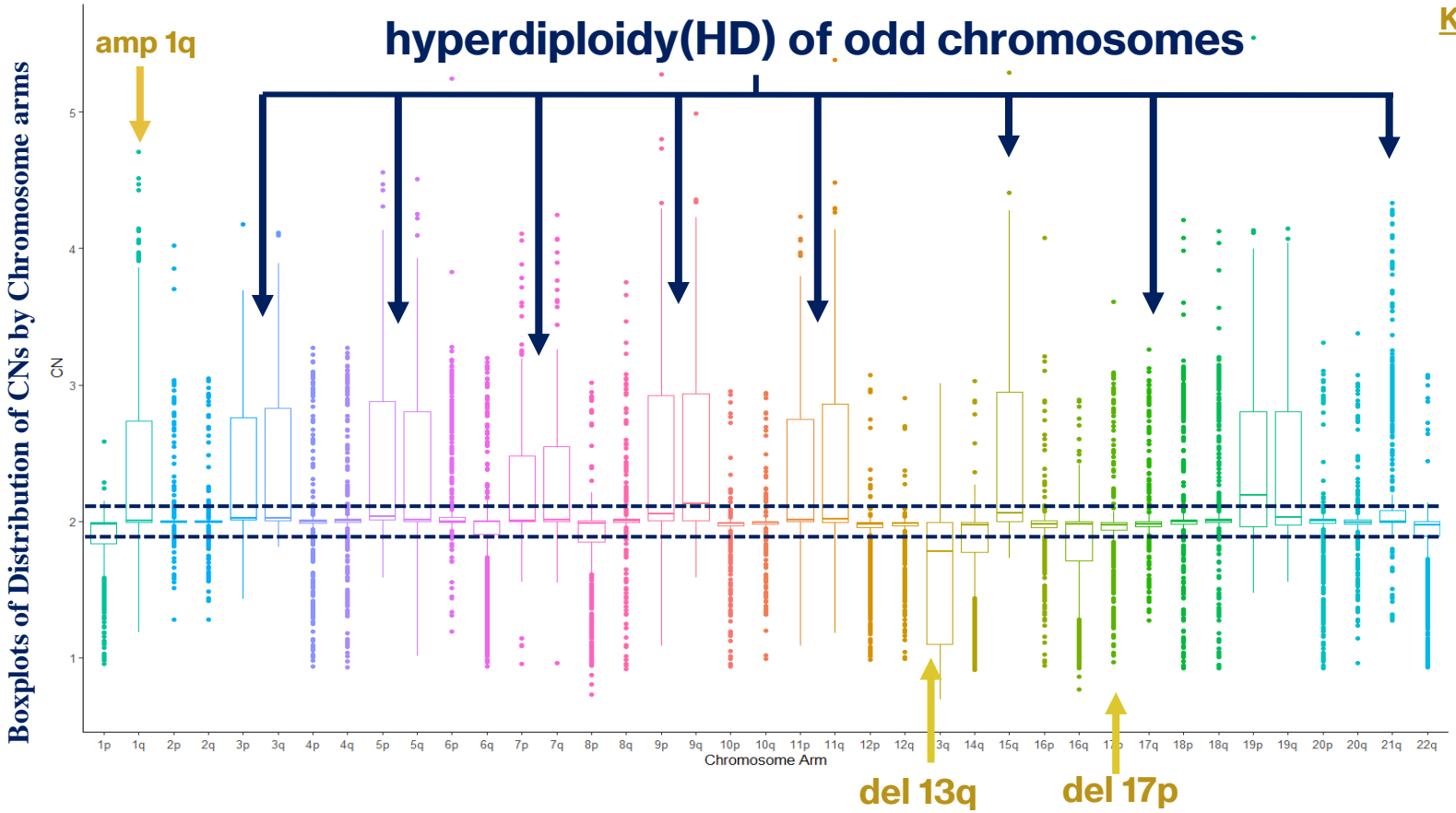
Failure of current risk stratification → FUNCTIONAL HR

System	Variables Included	Criteria / Cut-offs	Output
ISS (2005)	β2-microglobulin, Albumin	ISS I: β2M <3.5 mg/L & Alb ≥3.5 g/dL ISS II: neither I nor III ISS III: β2M ≥5.5 mg/L	I / II / III
R-ISS (2015)	ISS + LDH + FISH high-risk cytogenetics	HRCA: del(17p), t(4;14), t(14;16) R-ISS I: ISS I + normal LDH + no HRCA R-ISS II: neither I nor III R-ISS III: ISS III + elevated LDH and/or HRCA	I / II / III
R2-ISS (HARMONY, 2022)	ISS + HR-FISH + LDH + FLC ratio	Additive scoring system: +1 1q gain; +1 t(4;14); +1.5 del(17p); +1 FLC ratio ≥30; +1 elevated LDH; +1 ISS III; +1.5 ISS III (as defined in model) R2-ISS I = 0; R2-ISS II = 0.5–1.0; R2-ISS III = 1.5–2.5; R2-ISS IV ≥3.0	I / II / III / IV
Kaiser Score Double-Hit HRCA (2025)	Major HRCAs	≥2 HRCAs associated with poor prognosis in NDMM and RRMM Considered: 1q+, del(17p), t(4;14), t(14;16)	No hit / Single hit / Double hit (≥2)
CGS – Consensus Genomic Staging (IMS/IMWG 2025)	Genomically defined HRMM abnormalities	HR defined by ≥1 of the following: del(17p) with CCF ≥20% or TP53 mutation t(4;14), t(14;16), t(14;20) 1q gain or del(1p32) Biallelic abnormalities β2M ≥5.5 mg/L (with normal creatinine)	HR-MM if ≥1 criterion

Approximately 20% of NDMM patients experience recurrence within 18–24 months.

These patients often do not present classic high-risk genomic markers.

Copy Number Alterations



Kruskal Wallis Test, p-value < 0.001

Prognostic models use conventional thresholds **10%**

STUDY RATIONALE & AIM

743 newly diagnosed (ND) MM patients (pts)*, with Copy Number obtained by SNP array at chromosome arm level

AIM

To define outcome-oriented (OO) cut-offs for CNAs associated with early relapse, improving risk stratification and identification of functional high-risk MM.

To this end, we applied an outcome-oriented statistical approach based on maximising the log-rank statistic, using early recurrence within 18 months of the start of therapy as the clinical endpoint.

This approach allows for more accurate capture of the genomic heterogeneity of myeloma and improves patient stratification, identifying those with the highest probability of early relapse.

*26% Clinical Practice; 18% BO2005 Protocol; 54% EMN02 Protocol; 2% Forte Protocol

METHOD

1

Identification of Cut-offs:

Classification of alterations in terms of presence/absence (1/0), for amplifications and deletions

Classical Method (CL): 10% cutoffs, Amp > 2.10 , Del <1.90

Outcome Oriented Method (OO):

- Split analysis for amplification and deletions +/- 4% background noise
- identify the cutpoint with most significant relation with survival (Early Relapse) on **60/78** alterations

Exploratory analysis:

- Non-Metric Multidimensional Scaling (NMDS) for dimensionality reduction to highlight the position of each CNAs in space
- Cramer's V and Fisher's test
- Correlation Analysis

Univariate survival analysis:

- was preliminary carried out with relevant alterations defined by the new cut-offs), using the Kaplan-Meier curves and univariate Hazard Ratios (HR).

2

Validation:

Comparison between the Classical and Outcome-Oriented method

Comparison of univariate HRs and test of their differences (t-test)

Multivariate Cox Models of PFS compared with AIC:

- Complete models (CL vs OO)
- Reduced models, by LASSO selection

Bootstrap validation and stability of OO cut-offs

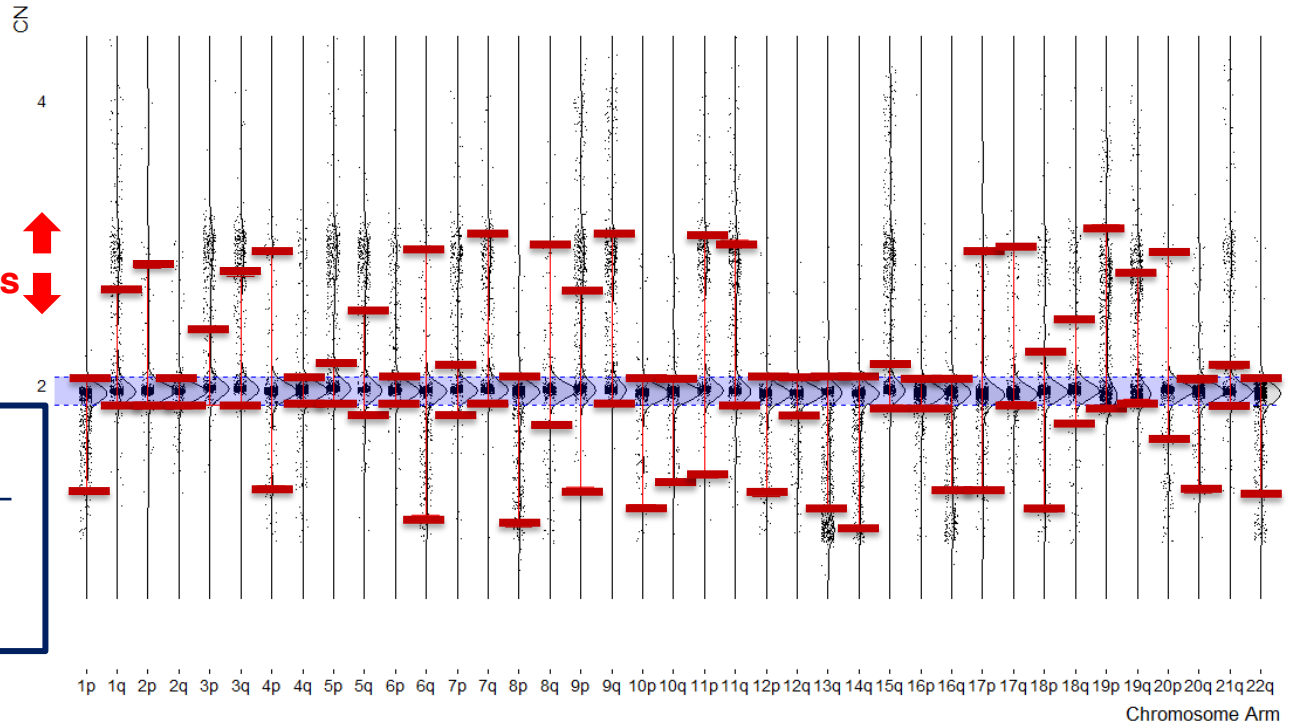
3

Identification of biomarkers predictive of early relapse

Results: Identification of Cut-offs

Distribution of CNs by Chromosome arms with Classical and Outcome Oriented method to Early Relapse Cut-offs.

The Outcome-oriented (OO) method identified 60 new cutoffs for 78 observable CNAs alterations



Clonality level
n. Observations

Classical Method (CL):
10% cut-off,
Amp > 2.10 ,
Del <1.90

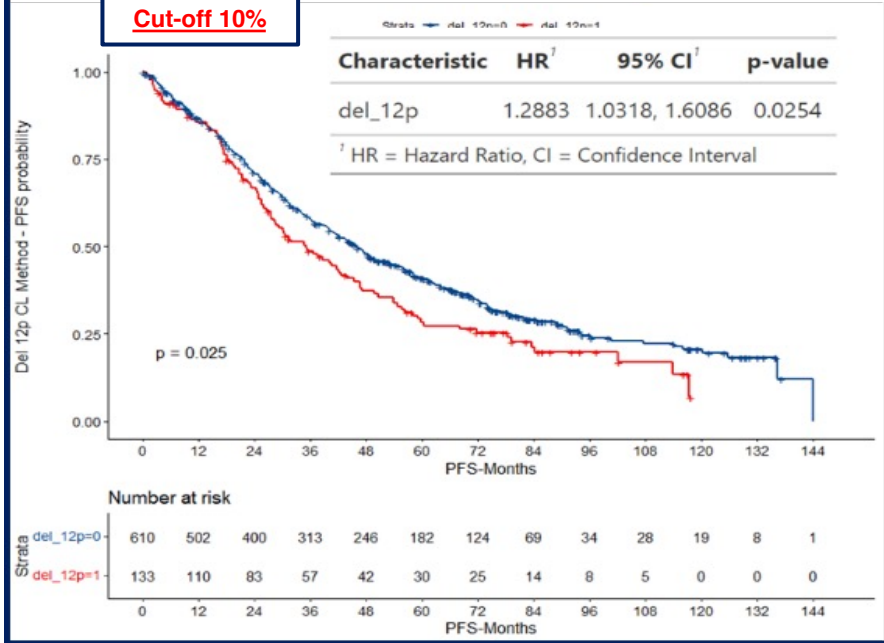
For low frequency alteration (18/78) the conventional cutoff (10%) was applyed

Validation: Comparison between the classic and Outcome-Oriented method

36/60 chromosomal alteration have a higher prognostic effect for early relapse

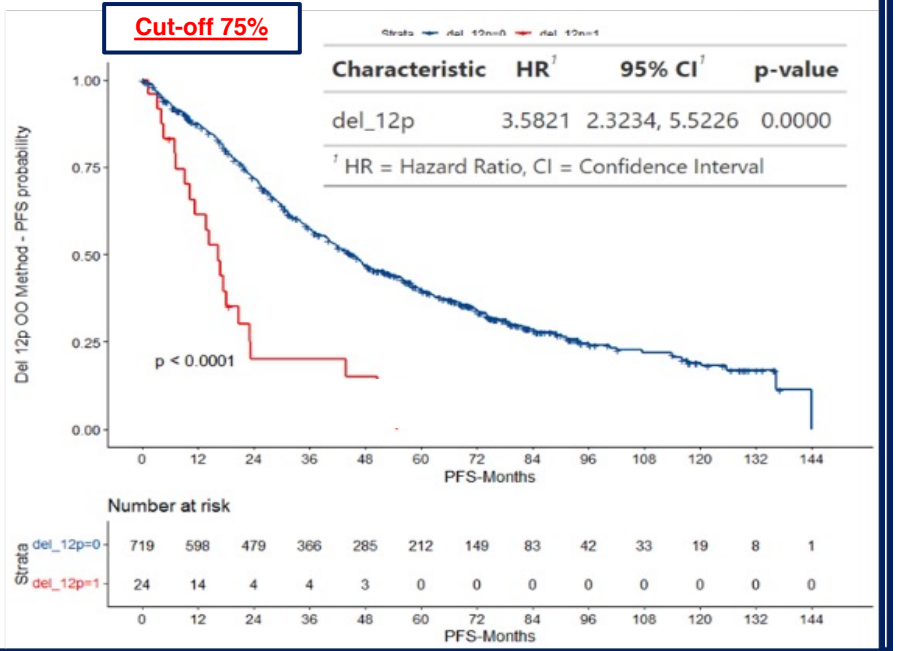
Classical Method

Cut-off 10%



Outcome Oriented Method

Cut-off 75%



Thakurta *et al.*, *Blood*, 2019
Martello *et al.*, *Blood Cancer Journal*, 2022

Results: Identification of biomarkers predictive of Early Relapse

AIM: Identification of a CNA-based signature predictive of early relapse

STEP 1: Association analysis

- Association between individual CNAs and ER vs. non-ER
- Statistical tests with FDR correction
- Selection of CNAs significantly associated with ER

Step 2: Evaluation of the multivariate model

- Reduced multivariate Cox model based on OO cut-offs
- 32 CNAs selected via LASSO
- Identification of CNAs independently associated with PFS

Step 3: Definition of the ER-CNA signature

Model	Classical Approach (CL)			Outcome Oriented Approach (OO)		
	df[a]	AIC[b]	C-index†	df[a]	AIC[b]	C-index†
Complete Model	78	5798.165	0.642	61	5670.010	0.672
Reduced model	5	5676.523	0.609	32	5624.78	0.665

[a] *The degree of freedom (df) indicates the number of variables considered in the model.*

[b] *AIC= Akaike Information Criterion.*

†C-index: Concordance Index

Intersection between:

- CNAs associated with ER (Step 1)
- Significant CNAs in the Cox model (Step 2)

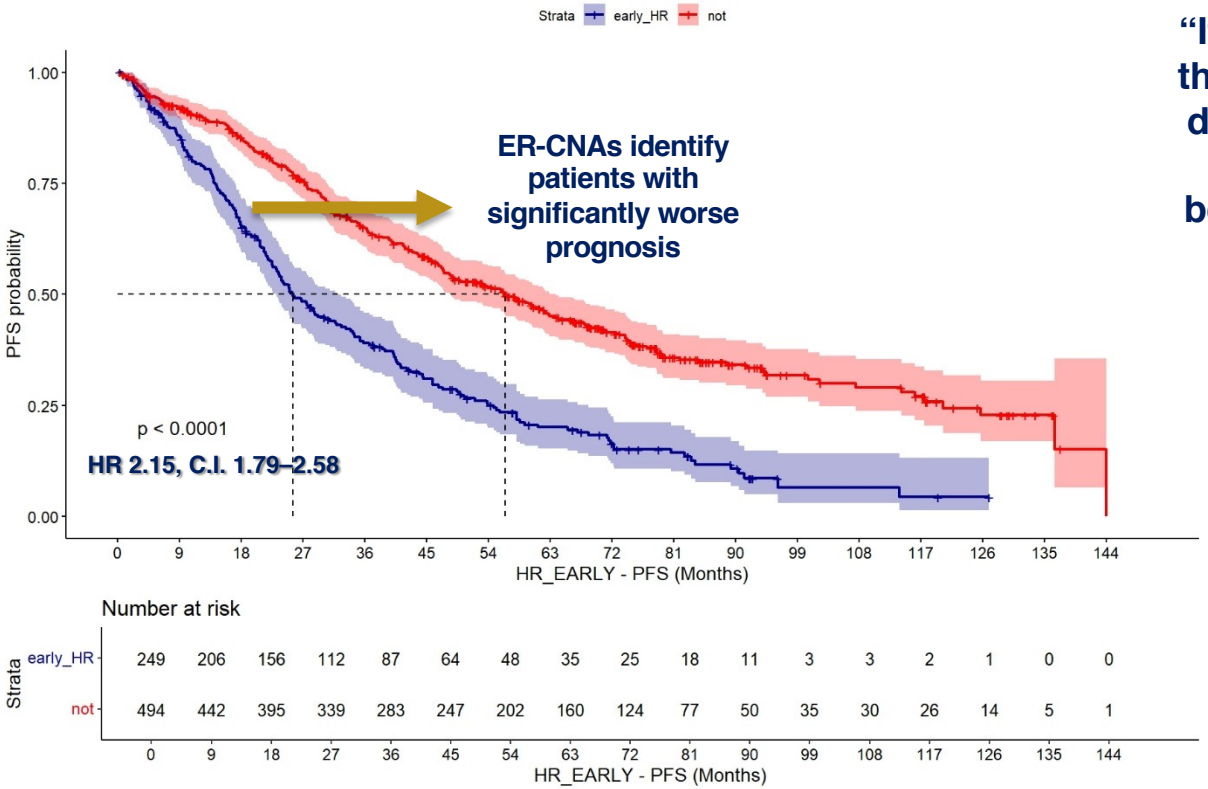
Inclusion of only CNAs with HR > 1

ER-CNA signature

(6 CNAs)

amp(1q), del(2p), amp(2p), del(12p), del(17p), del(19p)

Results: Univariate Analysis - Identification of biomarkers predictive of Early Relapse

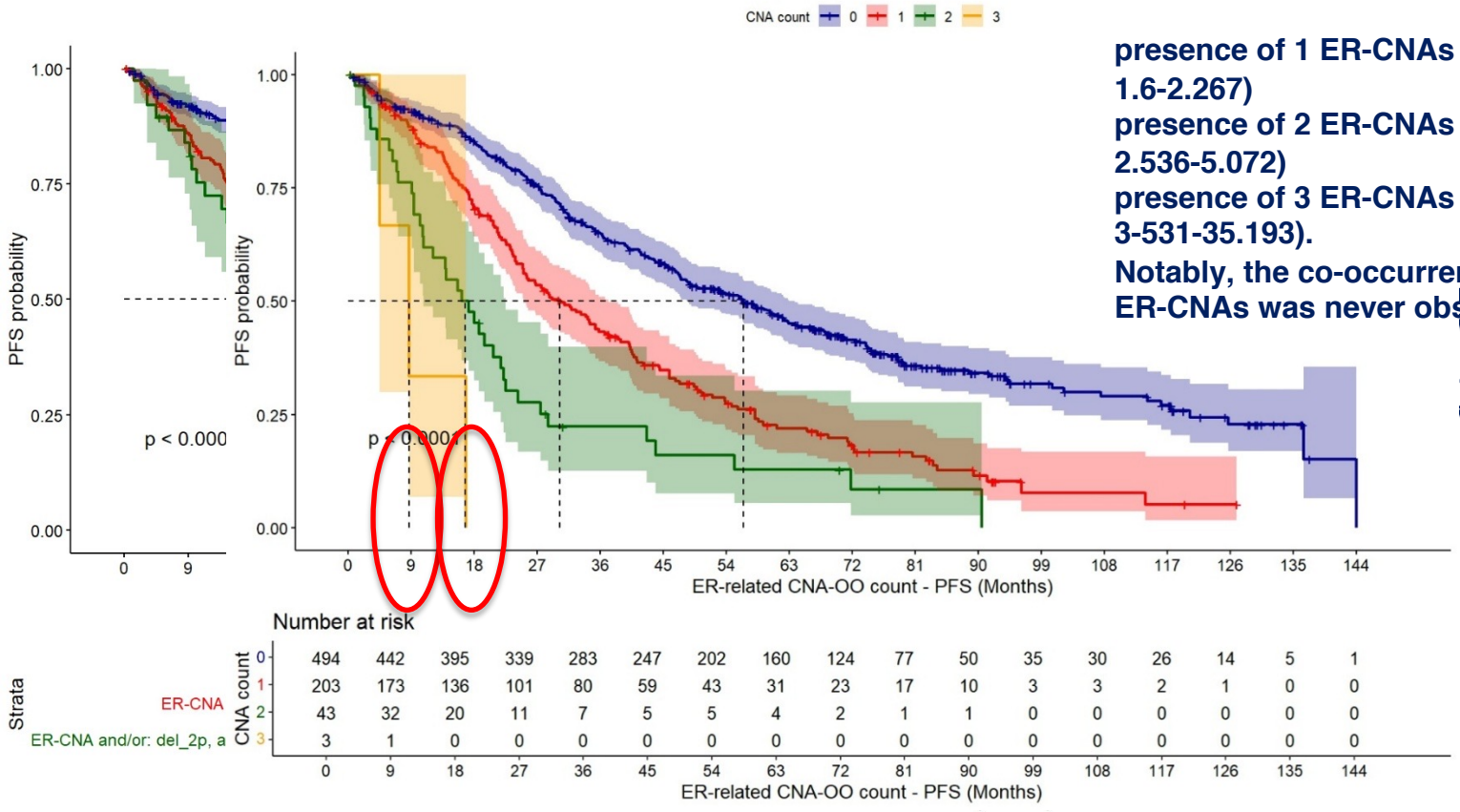


"It is important to notice that many of them are not classified as high risk at diagnosis according to traditional or genomic scores, but their clinical behaviour is that of aggressive MM.»

R-ISS	CGS/IMS*
16 (6%) I	48 (19%) SR
119 (48%) II	169 (68%) HR
40 (16%) III	32 (19%) nv
74 (30%) nv	//

Induction Response	Best Response
39 (16%) nCR, CR, sCR	81 (33%) nCR, CR, sCR
86 (35%) VGPR	101 (41%) VGPR

Results: Univariate Analysis - Identification of biomarkers predictive of Early Relapse



presence of 1 ER-CNAs has a HR= 1.946, (C.I. 1.6-2.267)

presence of 2 ER-CNAs has a HR= 3.586, (C.I. 2.536-5.072)

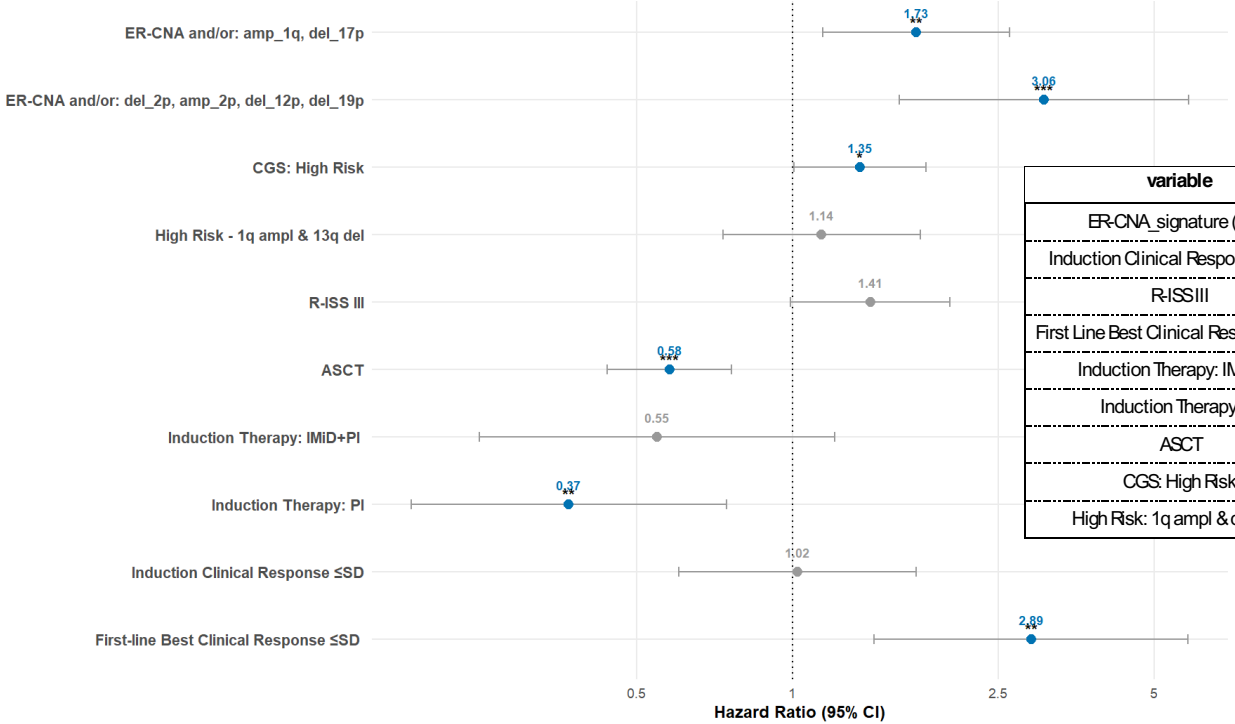
presence of 3 ER-CNAs has a HR=11.147, (C.I. 3-531-35.193).

Notably, the co-occurrence of more than three ER-CNAs was never observed.

r: del2p, amp2p, del12p,
, C.I. 1.79–3.70, p < 0.0001

: amp(1q) and/or del(17p):
'1–2.52, *p* < 0.0001

Results: Multivariate Analysis with clinical variables



variable	HR	P. VALUE	C.I. low	C.I high
ER-CNA_signature (pos)	1.97231	0.0000073 ***	1.362	2.851
Induction Clinical Response <= SD	1.10557	0.70083	0.6612	1.8491
R-ISS III	1.42623	0.04746 *	1.0034	2.0277
First Line Best Clinical Respone <= SD	2.65328	0.00511 **	1.3394	5.2549
Induction Therapy: IMID+PI	0.56022	0.1506	0.2537	1.2379
Induction Therapy: PI	0.38345	0.00721 **	0.1904	0.7724
ASCT	0.57602	0.0000851 ***	0.4374	0.7586
CGS: High Risk	1.31866	0.06461 .	0.9814	1.7714
High Risk: 1q ampl & del 13q	1.001527	0.994013	0.6723	1.492

The effect of ER-CNAs is not explained by other known factors.

Results: Validation in the CoMMpass dataset

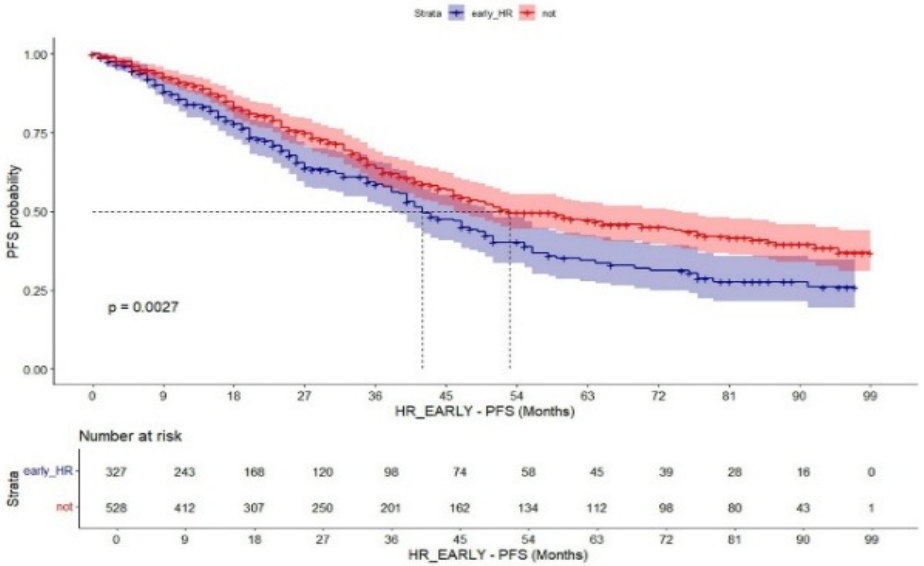
External validation of the ER-CNA signature in the CoMMpass cohort, (CoMMpass IA22, 855 NDMM patients with complete survival data)

Presence of ≥1 ER-CNA confirmed adverse prognosis:

- PFS: HR 1.65 (95% CI 1.34–2.04), p < 0.0001
- OS: HR 1.64 (95% CI 1.30–2.07), p < 0.0001

Patients with classical CNAs (amp(1q), del(17p)) **and"minor" CNAs** (del(2p), amp(2p), del(12p), del(19p)) **showed significantly worse outcomes vs controls**

Patients with only "minor" CNAs (n = 46) had reduced PFS and OS



SUMMARY

- In MM, which is characterized by high heterogeneity, CNAs' call have a prognostic effect on clinical outcomes, even though, to date, there is no agreement on the threshold for CN-specific call.
- Outcome-oriented CNA cut-offs overcome the limitations of classical cut-off–based approaches, which rely on fixed, one-size-fits-all thresholds applied uniformly across different CNAs.
- This approach enables the identification of patients with functional high-risk disease, characterized by early relapse, who are frequently missed by current risk stratification systems.
- Integrating clonal burden with clinical outcome represents a necessary step toward a more accurate and clinically meaningful prognostic stratification.

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