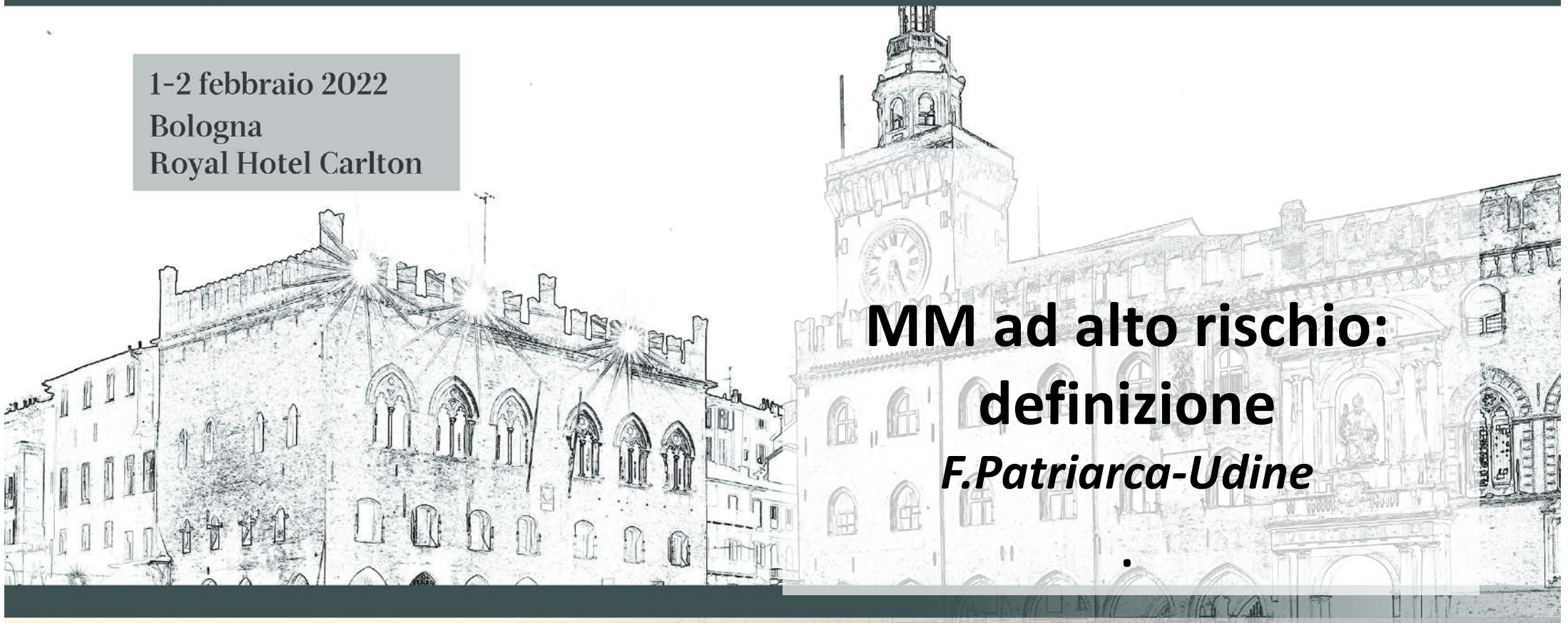
Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton



MM ad alto rischio: definizione

F.Patriarca-Udine

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Coordinatore Scientifico
Michele **CAVO**

Comitato Scientifico
Michele **CAVO**
Maria Teresa **PETRUCCI**

Disclosures of Francesca Patriarca

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen						X	
Celgene-BMS					X		
Roche						X	
Amgen						X	
Clinigen						X	
Glaxo						**X**	

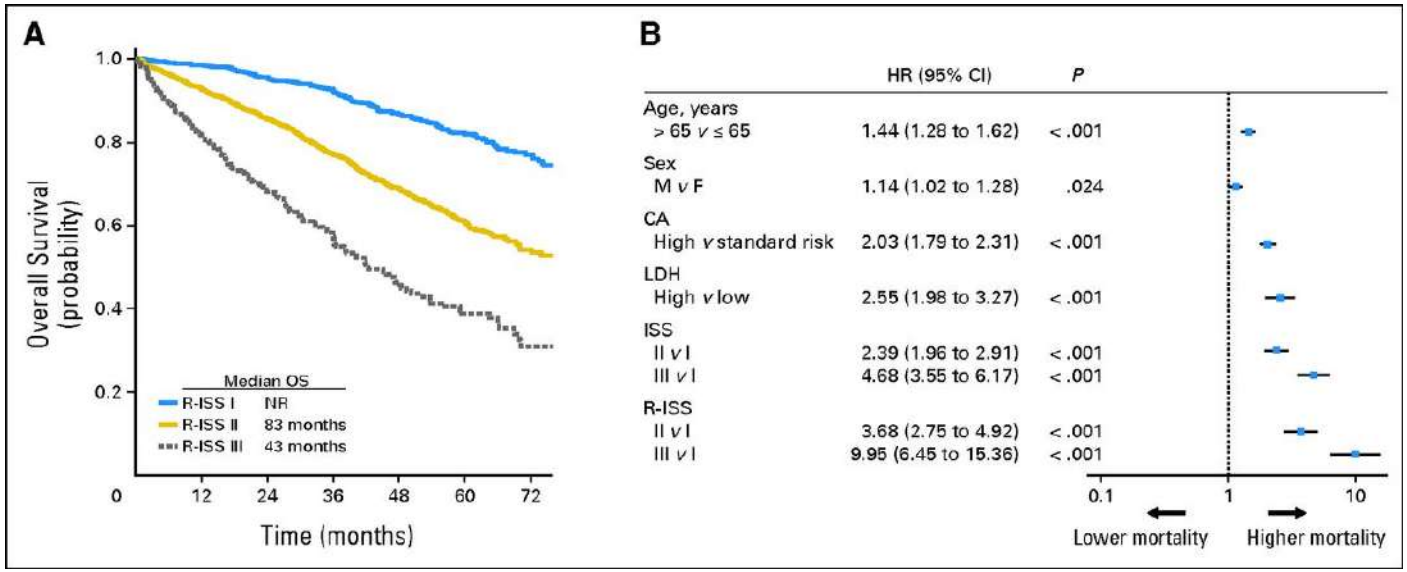
Grazie

Prof. Baccarani!

Prognostic factors in MM

Patient characteristics	Disease characteristics	Tumor burden	Response
Age	ISS stage	D-S stage	CR *vs* other
PS	FISH cytogenetics	PET scan	MRD
Frailty	GEP	MRI	
Comorbidity index	LDH	FLC + HLC	
	High LI		
	Extramedullary disease		
	Renal failure		
	Circulating plasma cells		

R-ISS
Integration of FISH cytogenetics and clinical staging

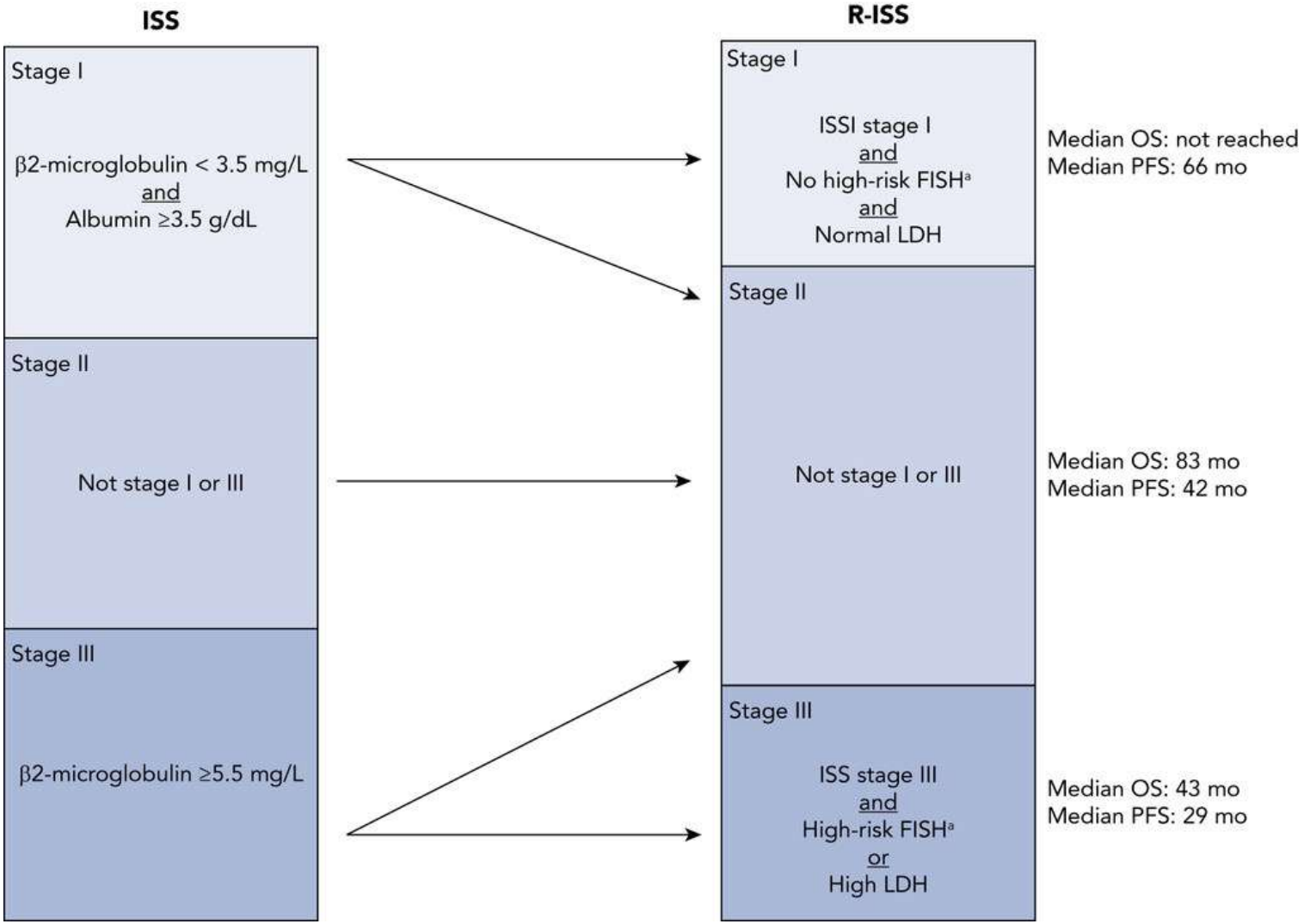


R-ISS I: ISS I and standard risk cytogenetic abnormality (CA) by FISH and normal LDH (28%)

R- ISSII: no ISS I or III (62%)

R-ISS III: ISS III and either high-risk CA [del 17, t(4;14) e t (14;16)] by FISH or abnormal LDH (10%)

Antonio Palumbo et al. JCO 2015



ISS and R-ISS for multiple myeloma.Abbreviations: FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R-ISS, Revised International Staging System.aHigh-risk FISH abnormalities: t(4;14), t(14;16), and/or del(17p).

Costa et al, JNCCN 2020

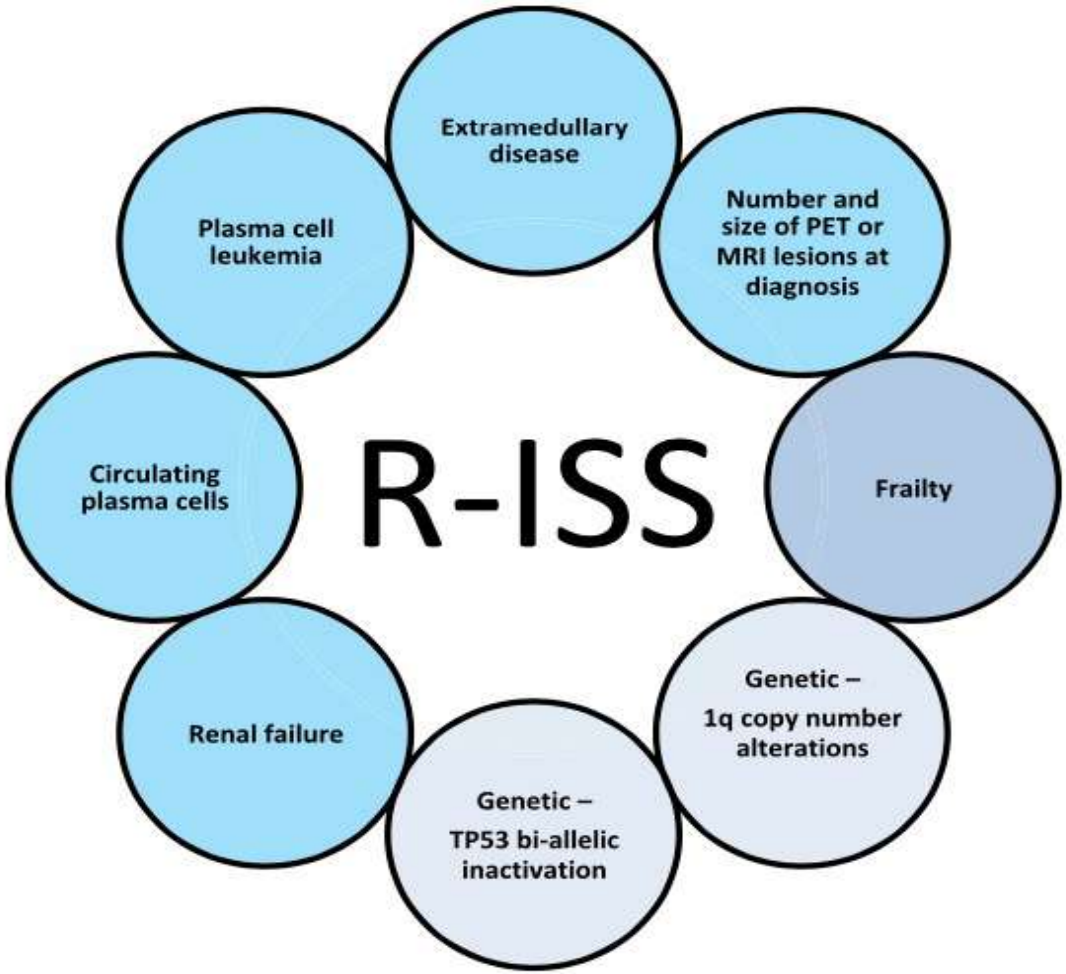


FIGURE 1. Proposed Modifications to Revised International Scoring System to Incorporate Additional High-Risk Features

Caro et al, ASCO Educational Book 2021

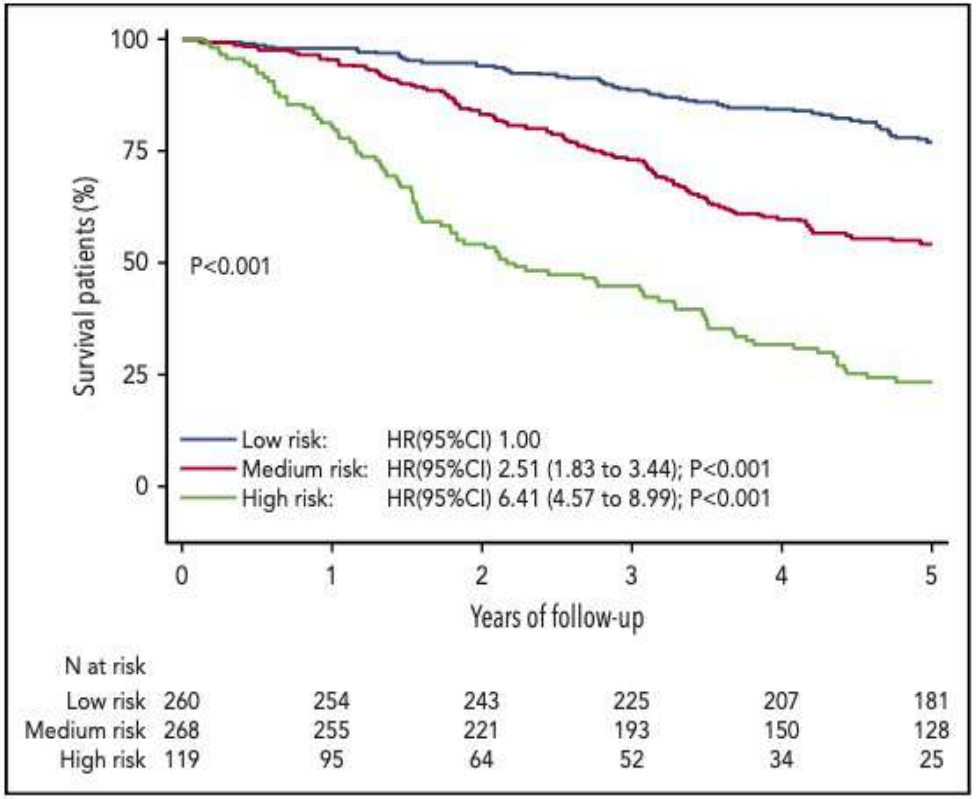
PROGNOSTIC FACTORS IN MM : IS IT TIME FOR A REVISION?

abnormality	frequency	molecular target(s)	controversies
t(4;14)	12-15%	FGFR3 and NSD2	-Unfavourable prognosis overcome by bortezomib -Prognosis worsen by concomitant del (1p32)
t(14;16)	3%	cMAF	Independent value?
gain(1q21)	30% (at least 1 copy)	CKS1B ?	> 3 copies have independent prognostic value
del (1p32)	8%	CDKN2C and FAF1	strong negative prognostic value
del (17p)	8%	TP53 deleted or mutated or both	At least 50% marrow plasma cells

Corre' J et al, Blood 2021

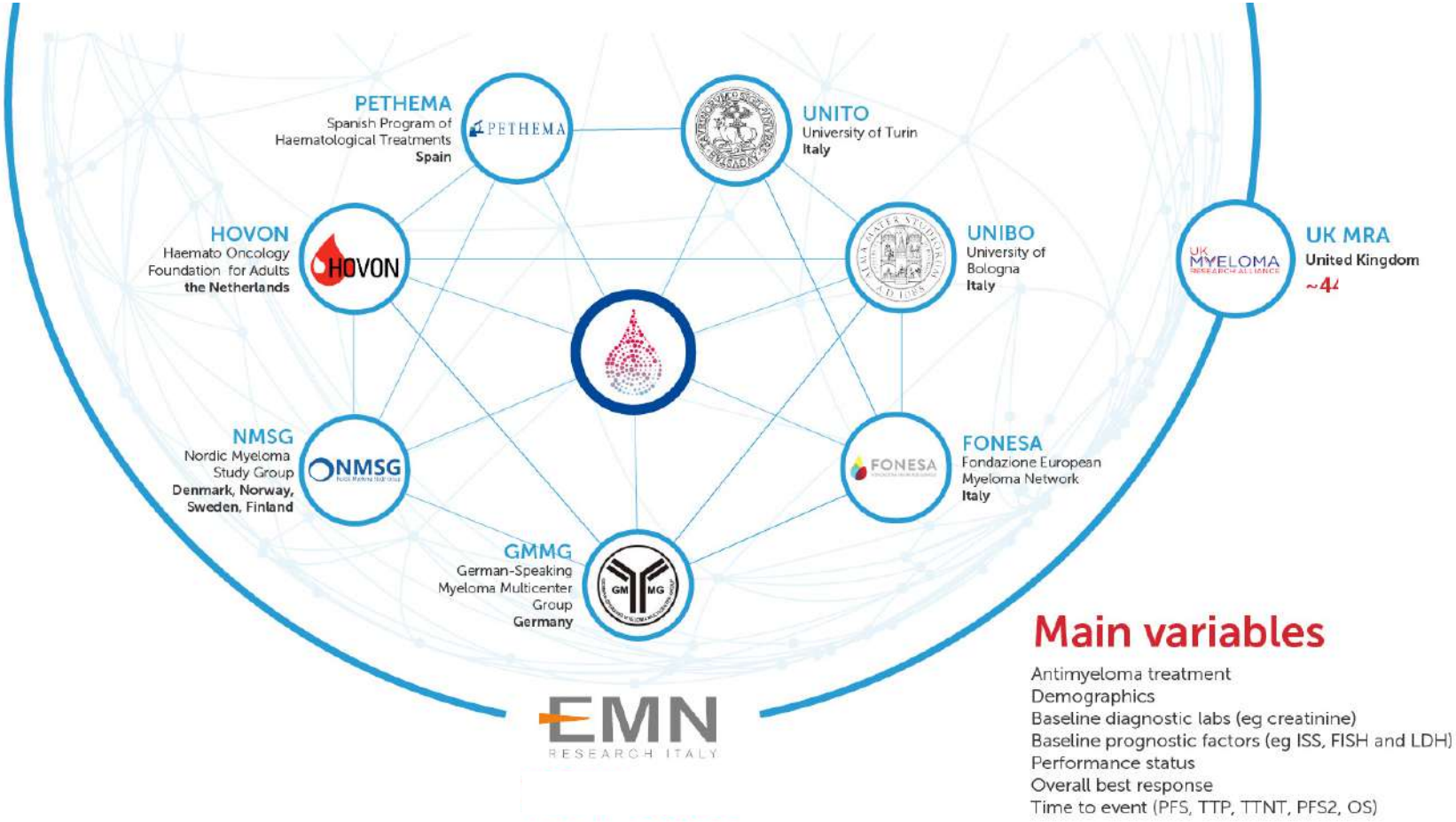
Table 1. Weighted cytogenetic prognosis factors in MM

Cytogenetic factor	Coefficient
Trisomy 5	−0.3
Trisomy 21	0.3
t(4;14)	0.4
Gain 1q	0.5
del(1p32)	0.8
del(17p)	1.2
Risk (scote = sum of coefficients)	
Low	≤0
Intermediate	>0 and ≤1
High	>1



Corre' J et al, Blood 2021

Harmony project



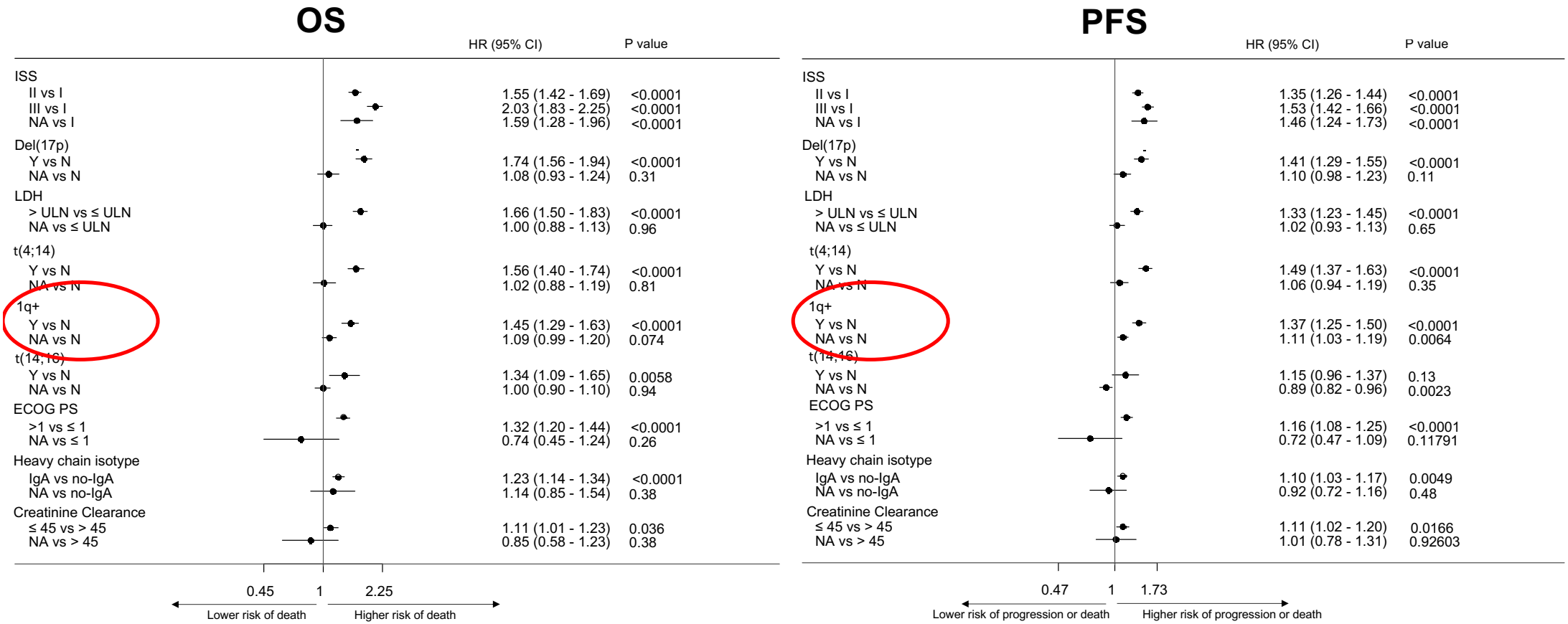
Main variables

Antimyeloma treatment
Demographics
Baseline diagnostic labs (eg creatinine)
Baseline prognostic factors (eg ISS, FISH and LDH)
Performance status
Overall best response
Time to event (PFS, TTP, TTNT, PFS2, OS)

10843 patients from 16 clinical trials from 2005 to 2016

D'Agostino M. SIE 2021, ASH 2021

Impact of single-risk features (training set)



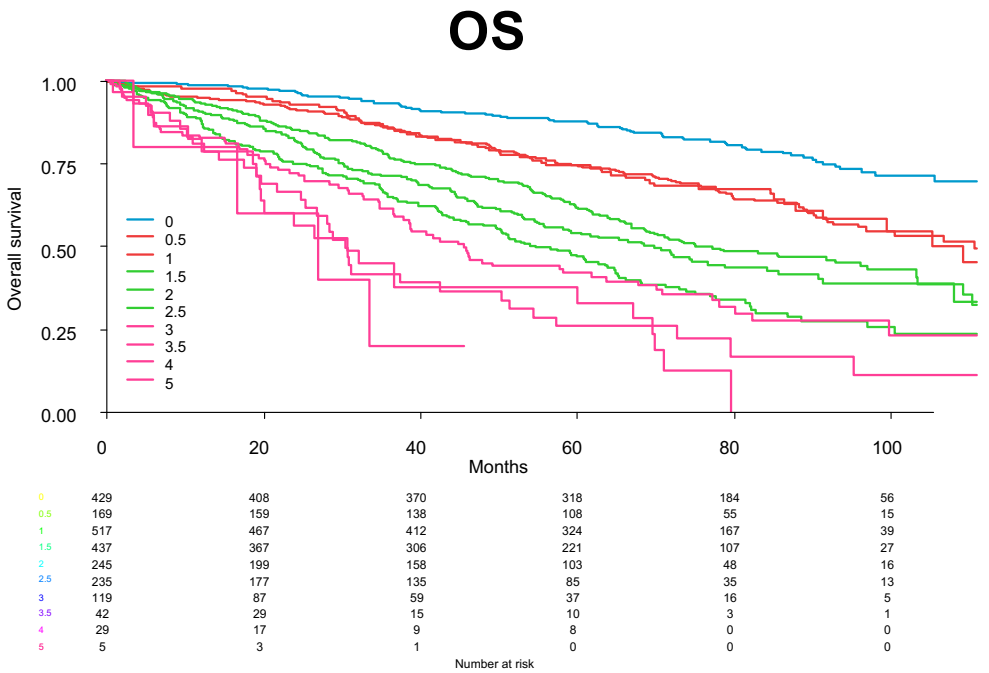
Multivariate Cox model adjusted for age, sex, transplant eligibility treatment and missing values.
Poor performance status defined as Eastern Cooperative Oncology Group (ECOG) performance status >1 or Karnofsky performance status <80.

Abbreviations. HR: hazard ratio; ISS: International Staging System stage; LDH: lactate dehydrogenase; CNA: copy number alteration; OS: overall survival; PFS: progression-free survival

R2-ISS score definition

Patients with complete data for all risk features in the training set (n=2227)

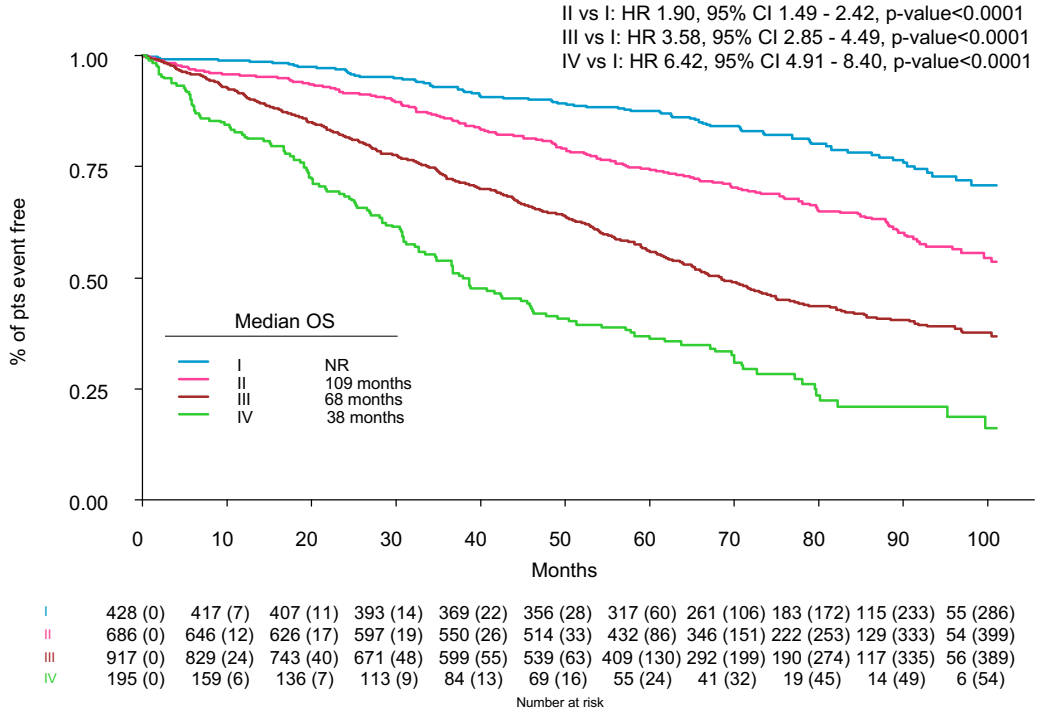
Risk feature	OS hazard ratio	PFS hazard ratio	Score value*
ISS II	1.75	1.44	1
ISS III	2.54	1.76	1.5
Deletion 17p	1.82	1.43	1
High LDH	1.60	1.37	1
Translocation 4;14	1.53	1.40	1
1q+	1.47	1.33	0.5
Group	**Number of patients (%)**		**Total additive score**
Low (I)	429 (19.3%)		0
Low-Intermediate (II)	686 (30.8%)		0.5-1
Intermediate-High (III)	917 (41.2%)		1.5-2.5
High (IV)	195 (8.8%)		3-5

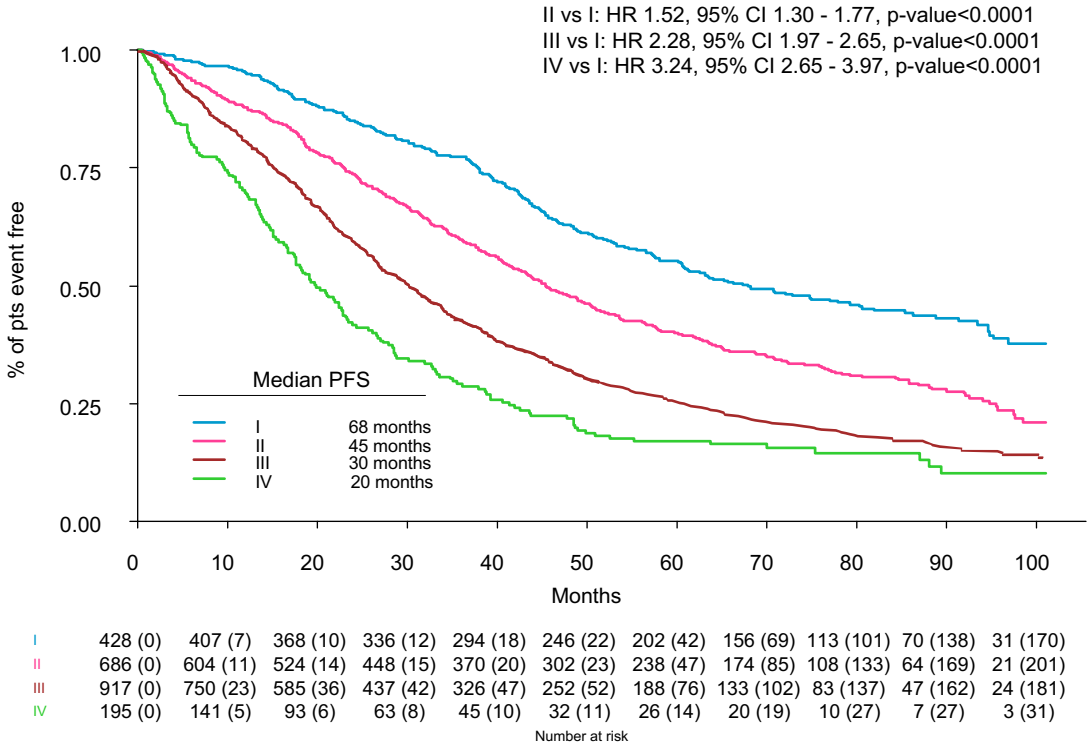


*calculated on the risk of death, value rounded to the nearest 0.5 with ISS II vs I comparison as reference (score = 1).

Abbreviations. R2-ISS: Revision 2 of the International Staging System; ISS: International Staging System stage; LDH: lactate dehydrogenase; OS: overall survival; PFS: progression-free survival.

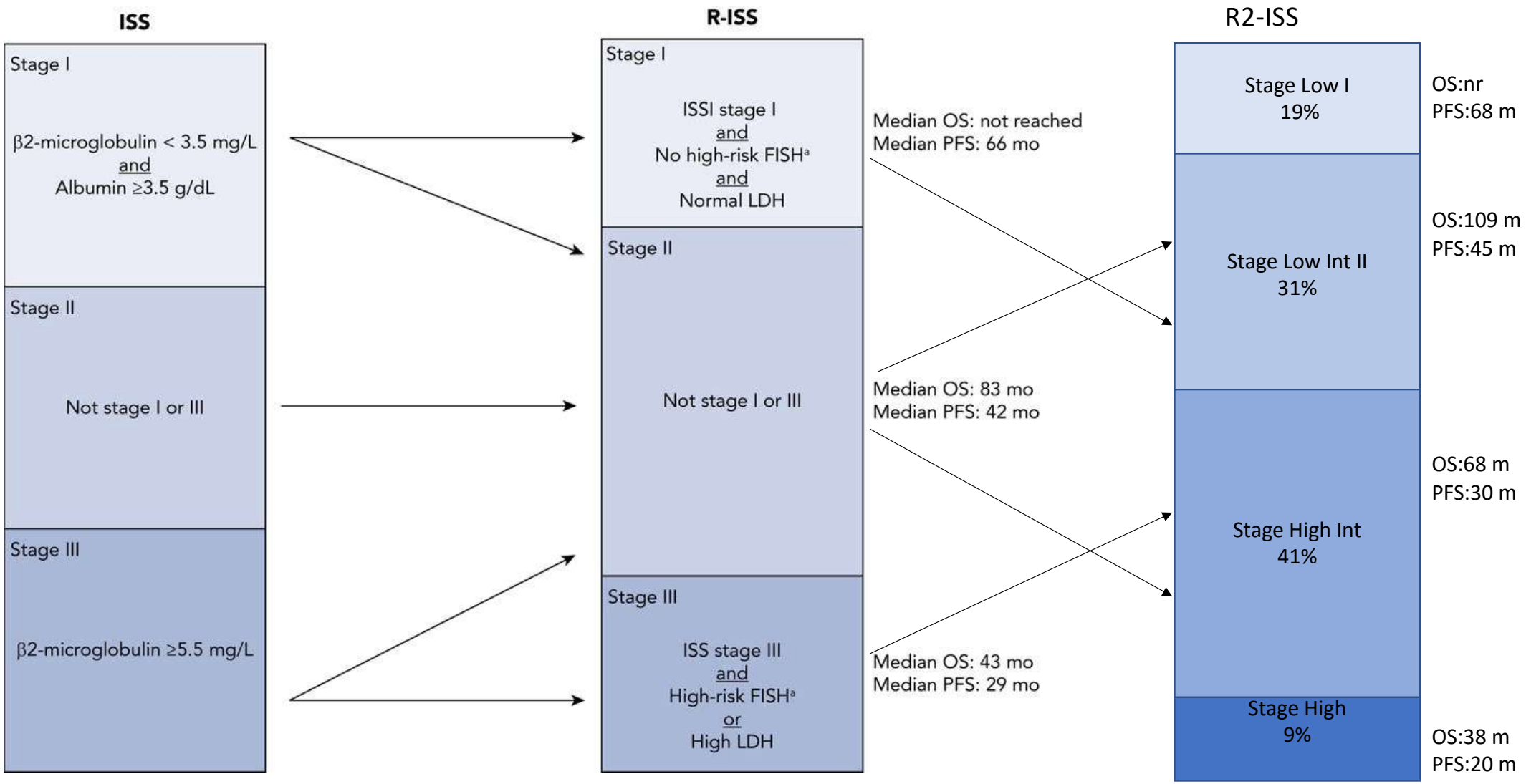
R2-ISS: OS and PFS training set





Prognostic score	R2-ISS low I (N=428)	R2-ISS low-int II (N=686)	R2-ISS int-high III (N=917)	R2-ISS high IV (N=195)
R-ISS I	428	169	0	0
R-ISS II	0	517	811	44
R-ISS III	0	0	106	151

Abbreviations. R2-ISS: Revision 2 of the International Staging System; R-ISS: Revised International Staging System; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval.

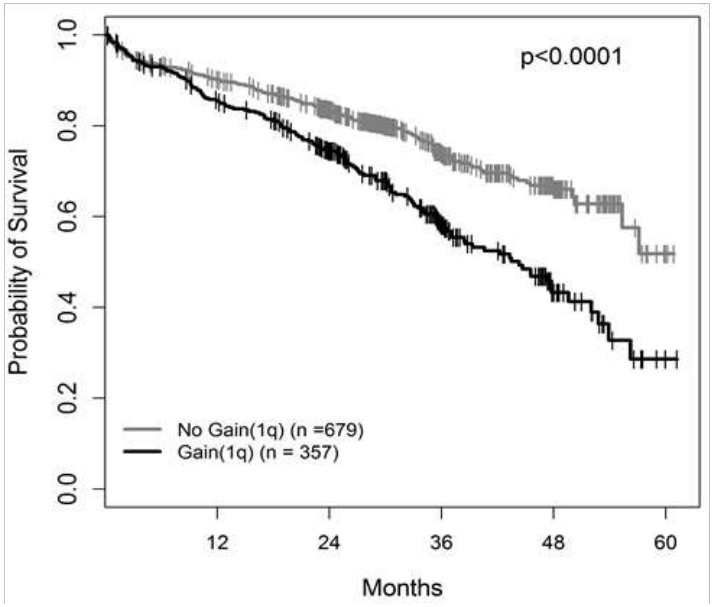


ISS and R-ISS for multiple myeloma.Abbreviations: FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; R-ISS, Revised International Staging System.aHigh-risk FISH abnormalities: t(4;14), t(14;16), and/or del(17p).

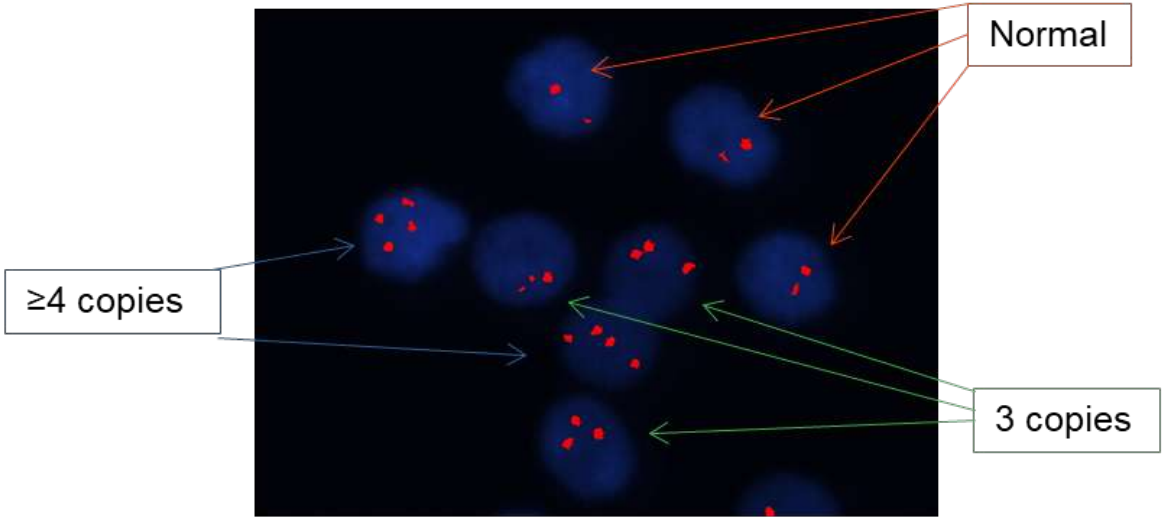
Patriarca F, personal comunication

Gain1q (3 copies of 1q) vs Amp1q (amplification, ≥4 copies of 1q) in carfilzomib-treated NDMM patients (Forte study)

1q CNA is a poor prognostic factor in NDMM[1]



1q copy number may predict patients' outcome[2-3]



METHODS: Gain1q defined as ≥ 10% of nuclei with 3 copies of 1q and Amp1q defined as ≥ 20% of nuclei with ≥4 copies of 1q By FISH on purified CD38+ marrow PC in 474 pts at baseline

CNA: Copy Number Alteration; NDMM: Newly Diagnosed Multiple Myeloma.

1. Shah et al Leukemia 32, 102–110 (2018); 2. Walker et al. Leukemia 33, 159–170(2019); 3. Schmidt et al Blood Cancer Journal 9, 94 (2019).

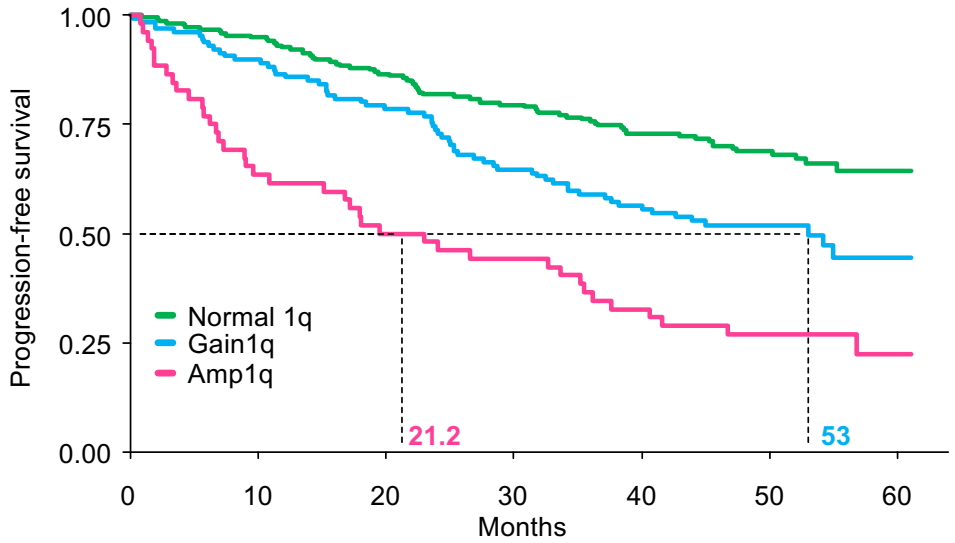
D'Agostino M, IMW 2021

Survival analysis

Group	3-y PFS	Median PFS (months)	3-y OS	Median OS (months)
Normal 1q	76%	Not reached	93%	Not reached
Gain1q	59%	53	87%	Not reached
Amp1q	37%	21.2	55%	53.5

PFS

Gain1q vs. Normal 1q: HR 1.65, 95% CI 1.16 - 2.34, p=0.0052
Amp1q vs. Normal 1q: HR 3.13, 95% CI 2.08 - 4.69, p<0.0001
Amp1q vs. Gain1q: HR 1.90, 95% CI 1.27 - 2.84, p=0.0020

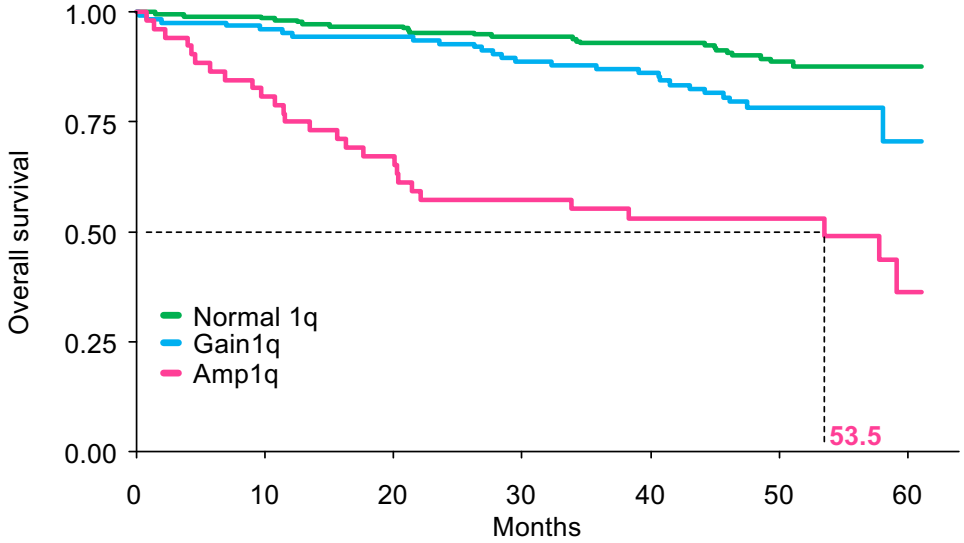


Normal 1q	219 (0)	205 (3)	185 (5)	168 (7)	149 (12)	89 (65)	10 (140)
Gain1q	129 (0)	112 (4)	97 (5)	79 (6)	66 (9)	37 (33)	2 (65)
Amp1q	52 (0)	33 (0)	26 (0)	23 (0)	17 (0)	10 (5)	3 (10)

Number at risk (number censored)

OS

Gain1q vs. Normal 1q: HR 1.71, 95% CI 0.97 - 3.01, p=0.066
Amp1q vs. Normal 1q: HR 4.99, 95% CI 2.8 - 8.87, p<0.0001
Amp1q vs. Gain1q: HR 2.92, 95% CI 1.69 - 5.04, p=0.0001



Normal 1q	219 (0)	213 (3)	206 (6)	198 (9)	186 (18)	112 (85)	12 (184)
Gain 1q	129 (0)	120 (4)	115 (7)	107 (8)	99 (13)	52 (52)	4 (99)
Amp 1q	52 (0)	42 (0)	34 (1)	29 (1)	24 (4)	18 (11)	4 (21)

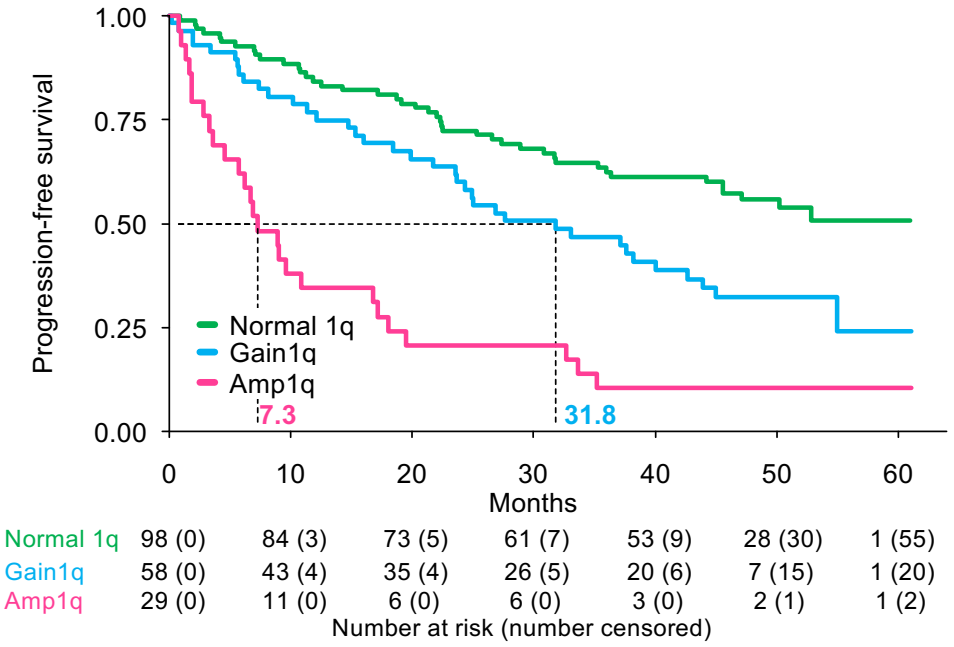
Number at risk (number censored)

Abbreviations. PFS: progression-free survival; OS: overall survival; y: year; HR, hazard ratio.

PFS by MRD

MRD pos (10^{-5})*

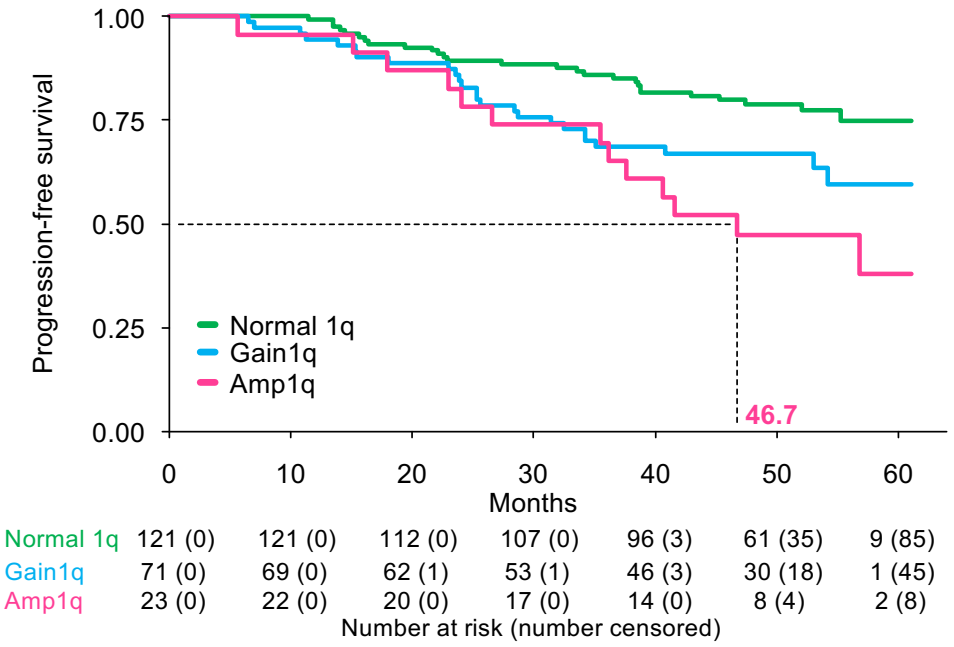
Gain1q vs. Normal 1q: HR 1.83, 95% CI 1.18 - 2.86
Amp1q vs. Normal 1q: HR 4.74, 95% CI 2.88 - 7.80
Amp1q vs. Gain1q: HR 2.58, 95% CI 1.56 - 4.29



Number at risk (number censored)							
Normal 1q	98 (0)	84 (3)	73 (5)	61 (7)	53 (9)	28 (30)	1 (55)
Gain1q	58 (0)	43 (4)	35 (4)	26 (5)	20 (6)	7 (15)	1 (20)
Amp1q	29 (0)	11 (0)	6 (0)	6 (0)	3 (0)	2 (1)	1 (2)

MRD neg (10^{-5})*

Gain1q vs. Normal 1q: HR 1.81, 95% CI 1.05 - 3.13
Amp1q vs. Normal 1q: HR 2.92, 95% CI 1.5 - 5.65
Amp1q vs. Gain 1q: HR 1.61, 95% CI 0.82 - 3.14



Number at risk (number censored)							
Normal 1q	121 (0)	121 (0)	112 (0)	107 (0)	96 (3)	61 (35)	9 (85)
Gain1q	71 (0)	69 (0)	62 (1)	53 (1)	46 (3)	30 (18)	1 (45)
Amp1q	23 (0)	22 (0)	20 (0)	17 (0)	14 (0)	8 (4)	2 (8)

Analysis performed by multiparameter flow cytometry (MFC) before maintenance in the intention-to-treat population.

PFS: progression-free survival; HR, hazard ratio; MRD: minimal residual disease, POS, positivity; NEG, negativity.

GENE EXPRESSION PROFILES

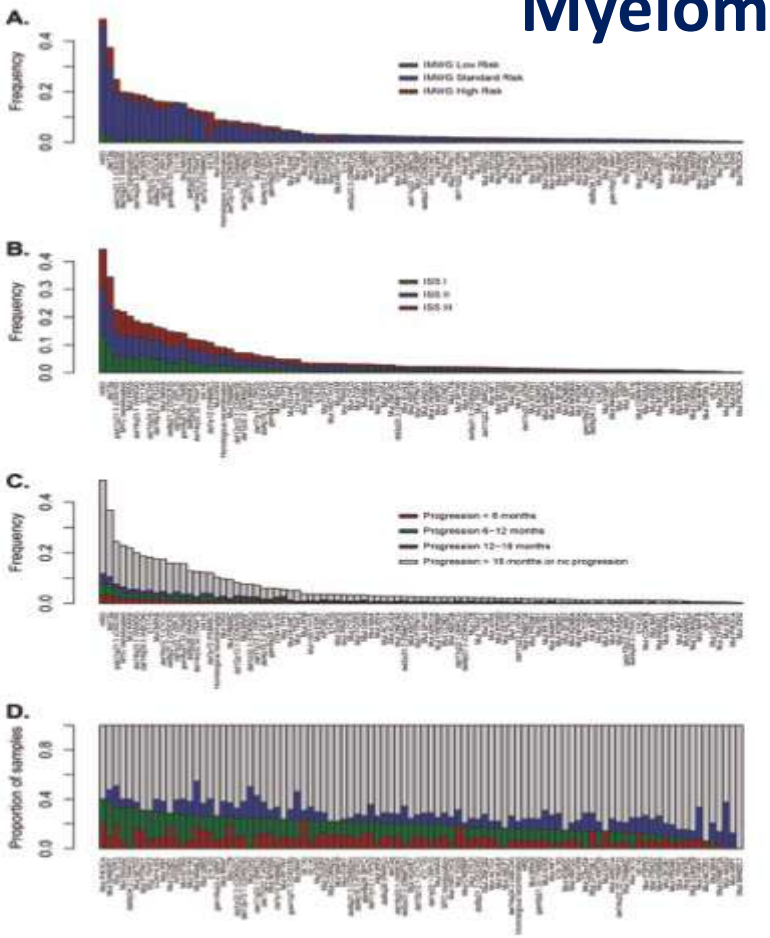
Table 2
Summary of main reported prognosis signatures allowing identification of high risk multiple myeloma patients

No single gene is common across the 8 signatures.

Signature	Number of genes	Number of common genes with 70-gene signature	Number of common genes with 92-gene signature	Clinical significance
UAMS (21)	70 genes	70 genes	2 genes (BIRC5, LTBP1)	Identifies low and high risk patients at diagnosis and relapse. The high risk patients overexpress genes mapping at 1q21, 1q22, 1q43–q44 and 8q21–8q24 regions.
HOVON-65/GMMG-HD4 (EMC92) (20)	92 genes	2 genes (BIRC5, LTBP1)	92 genes	An independant prognosis marker identifying high risk patients at diagnosis and relapse.
Intergroupe Francophone du Myelome (9)	15 genes	None	1 gene (FAM49A)	Identifies high risk patients featured by overexpression of genes involved in cell cycle.
Chromosome instability signature (CINGECS) (15)	214 genes	**7 genes**	**15 genes**	Signature is based on copy-number alterations identified by aCGH.. It alows separating MM patients in 4 groups : low, 2 intermediates and high risk group.
Centrosome index signature (CNTI) (16)	4 genes	None	None	An independant prognosis factor that identifies high risk patients featured by higher sensitivity to aurora kinase inhibitor.
Cell death signature (18)	6 genes	None	None	Based on the presence of genomic deletions involving cell death genes, it identifies low and high risk patients.
7-gene prognostic signature HMCL 6-gene signature for non *t*(4;14) patients (17)	7 genes 6 genes	None None	None None	Based on MM cell lines, identify low, intermediate and high risk MM patients and can discriminate low and high risk patients within molecular sub-groups, especially in non *t*(4 ;14).
Proliferation signature (19)	50 genes	3 genes (BIRC5, ASPM, CKS1B)	6 genes (ESPL1, MCM6, NCAPG, SPAG5, ZWINT, BIRC5)	Identifies 3 groups of MM associated with high, intermediate and low risk. It correlates with chromosomal aberrations (amp(1q) and del(13p)) and molecular subgroups.
Number of overlapping genes	None			

Szalat et al, Clin Cancer Research 2016

Myeloma genoma project

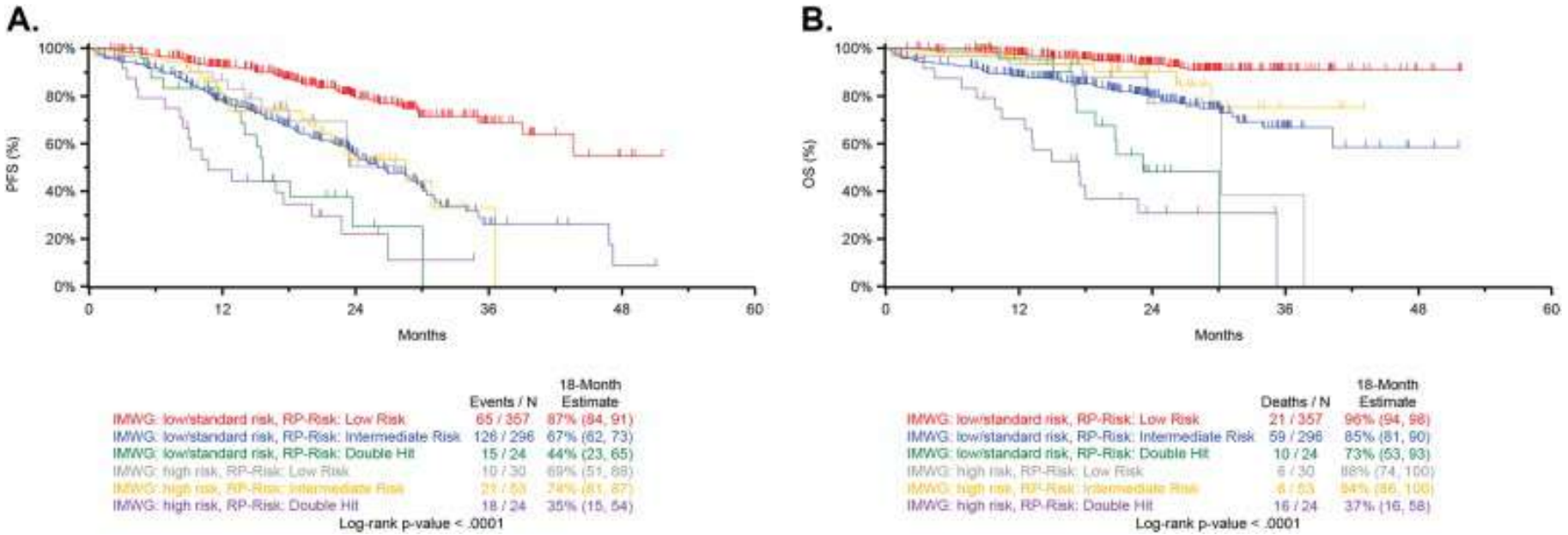


NGS data of 1273 NDMM pts across Europe and USA

The distribution of driver mutations, translocations, and copy number alterations by risk groups

Walker BA et al, Leukemia 2019

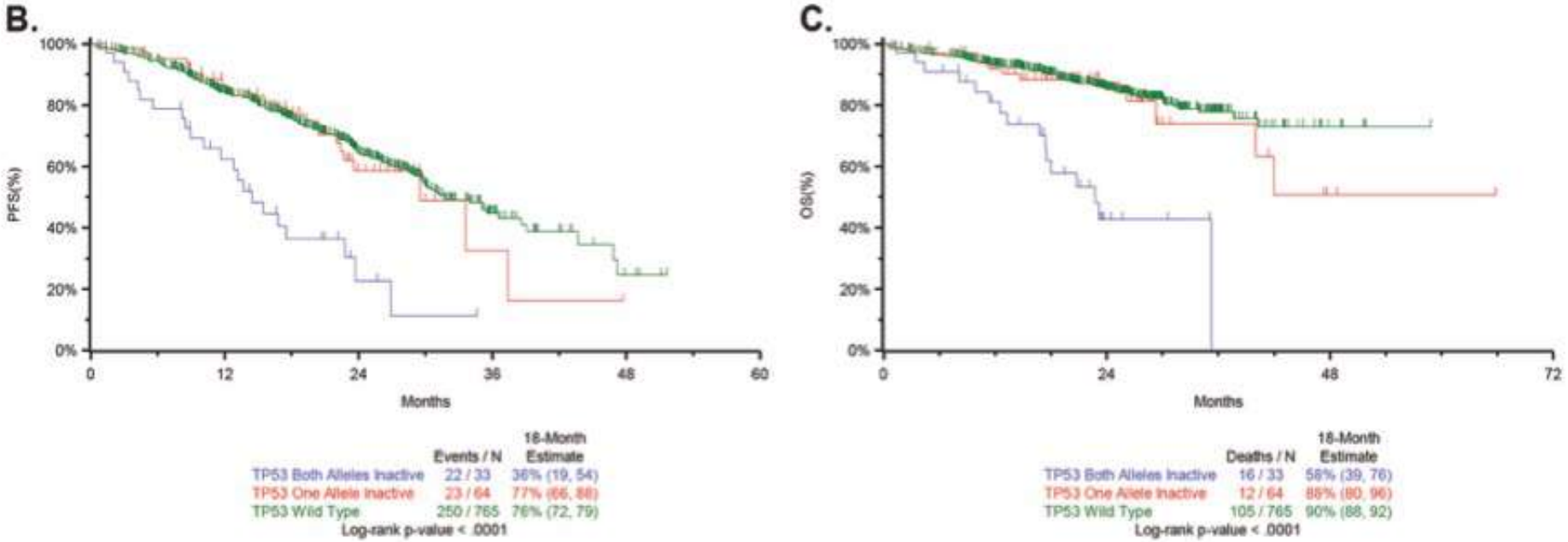
DOUBLE HIT MULTIPLE MYELOMA



A high-risk subgroup was defined by recursive partitioning using either a) bi-allelic TP53 inactivation or b) amplification (≥4 copies) of CKS1B (1q21) on the background of International Staging System III, comprising 6.1% of the population (median PFS = 15.4 months; OS = 20.7 months)

Walker BA et al, Leukemia 2019

BI-ALLELIC INACTIVATION OF TP53

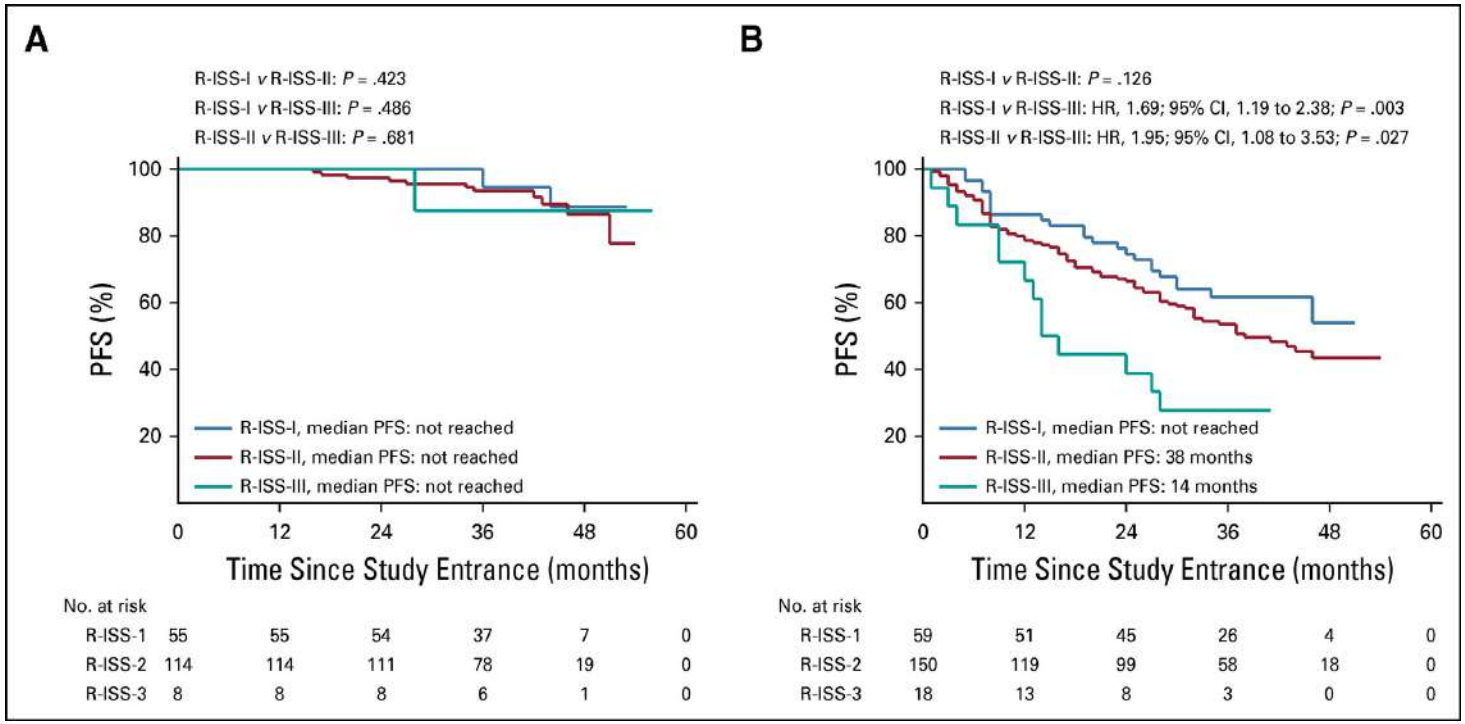


TP53 deletion was seen in 9.0% and mutations in 5.5% of patients.

Any event at TP53 was found in 14.5% and bi-allelic events in 3.7% of patients.

Walker BA et al, Leukemia 2019

RISK AT DIAGNOSIS AND DINAMIC RISK (MRD by NGF)



UNDETECTABLE MRD

205/458 pts (45%)

14/205 (7%) relapsed

PERSISTENT MRD

Paiva B et al, JCO 2020

CONCLUSIONS

The definition of risk in MM continues to evolve.

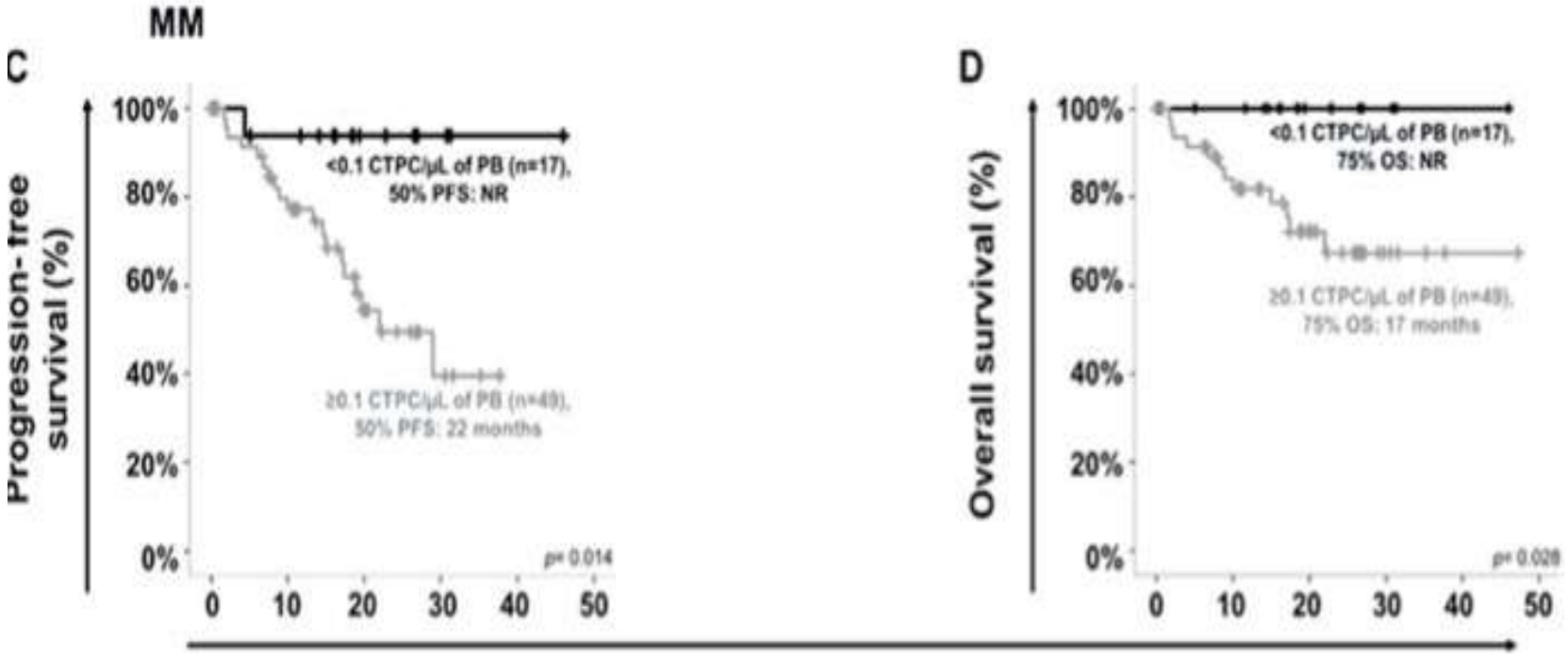
High–risk cytogenetics and clinical features standardized in R-ISS should be integrated by:

-amplification (≥4 copies) of 1q21 (R2-ISS)

-genomic data (biallelic inactivation of TP53 and ≥4 copies of CKS1B)

-dynamic evaluation of MRD

TUMORAL CIRCULATING PLASMA CELLS by NEXT GENERATION FLOW



Sonaja-Flores et al, Blood Cancer J 2018