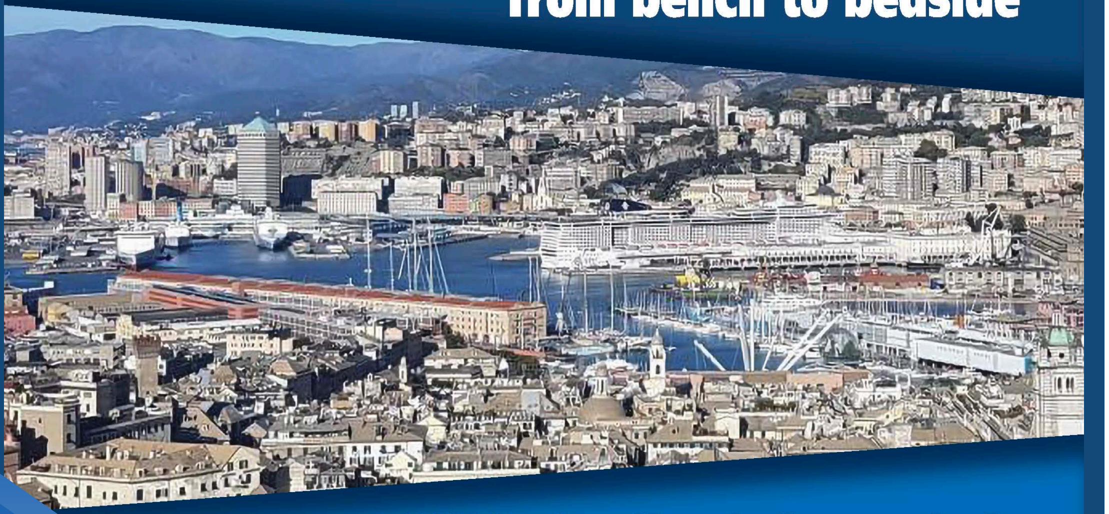
2023 Multiple Myeloma updates: from bench to bedside



NH Marina Hotel, Genoa, Italy
20-21 November 2023

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Current Risk Stratification

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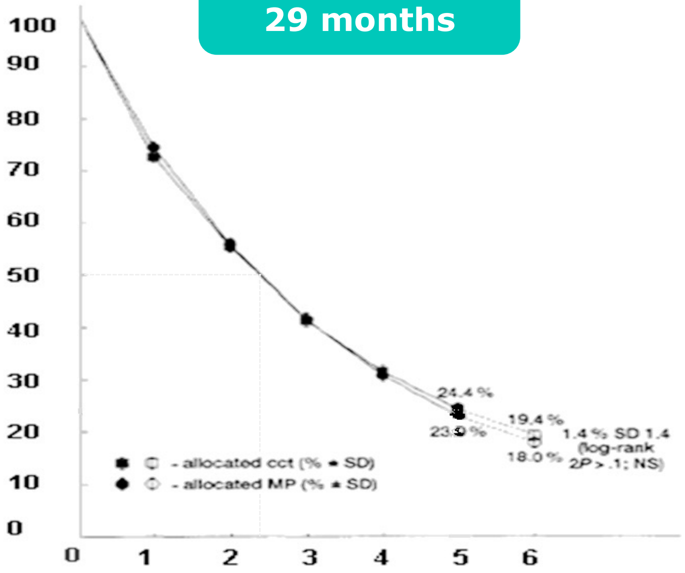
Overall survival in multiple myeloma has improved over the past ~25 years as the treatment landscape has changed[1–4]

Where did we come from?

Melphalan + prednisolone:[1]

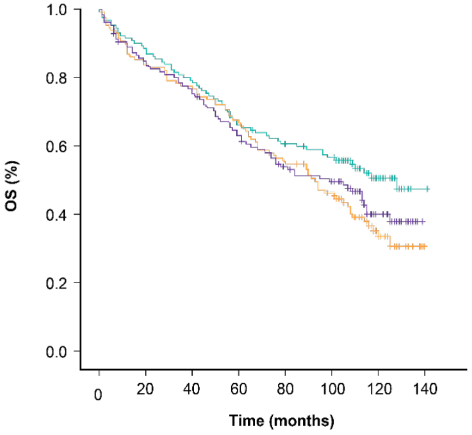
Median OS: 29 months



Where were we yesterday?

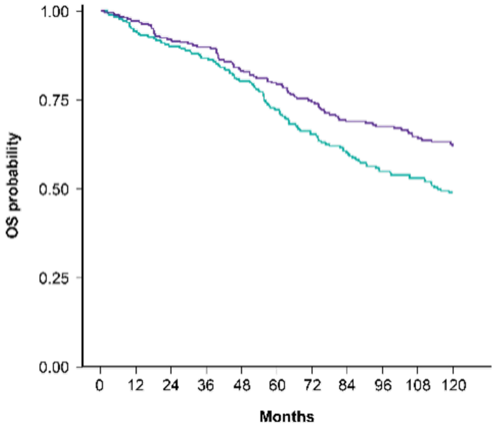
Bortezomib + thalidomide + dexamethasone[2]

10-year OS: 51%



Bortezomib + thalidomide + dexamethasone[3]

10-year OS: 61%



1998

2018

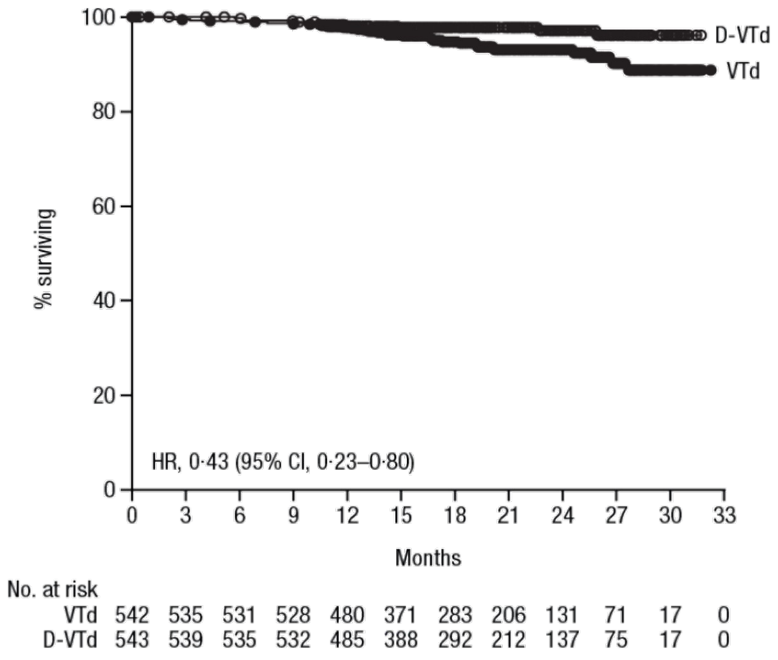
CCT, combination chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; MP, melphalan plus prednisone; SD, standard deviation.

1. Myeloma Trialists' Collaborative Group. *J Clin Oncol* 1998;16:383; 2. Rosinol Dachs L, et al. Presented at ASH 2018. 126; 3. Tacchetti P, et al. Presented at ASH 2018. 125.

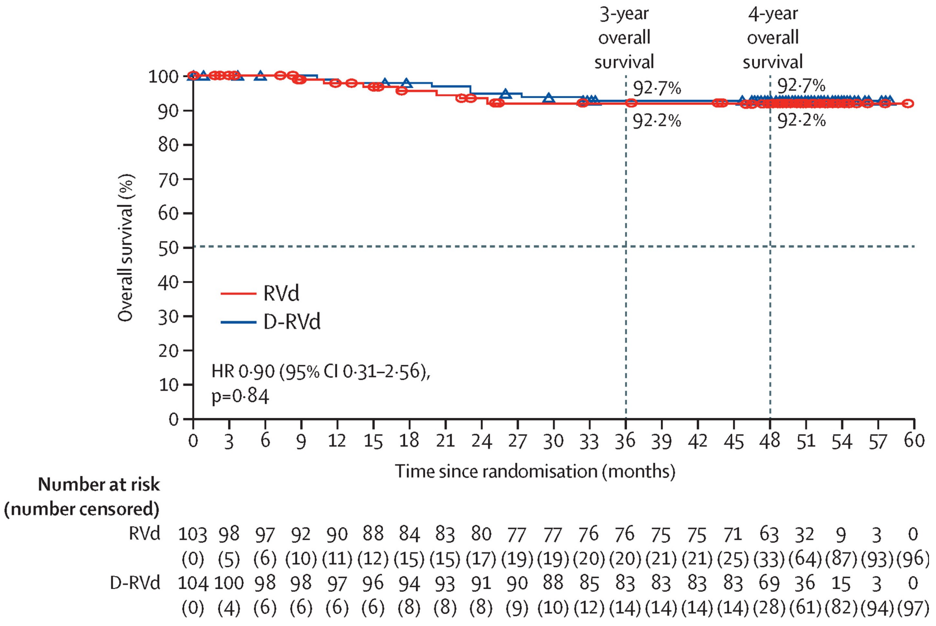
Overall survival in multiple myeloma has improved over the past ~25 years as the treatment landscape has changed[1–4]

Where are we now?

D-VTd[1]



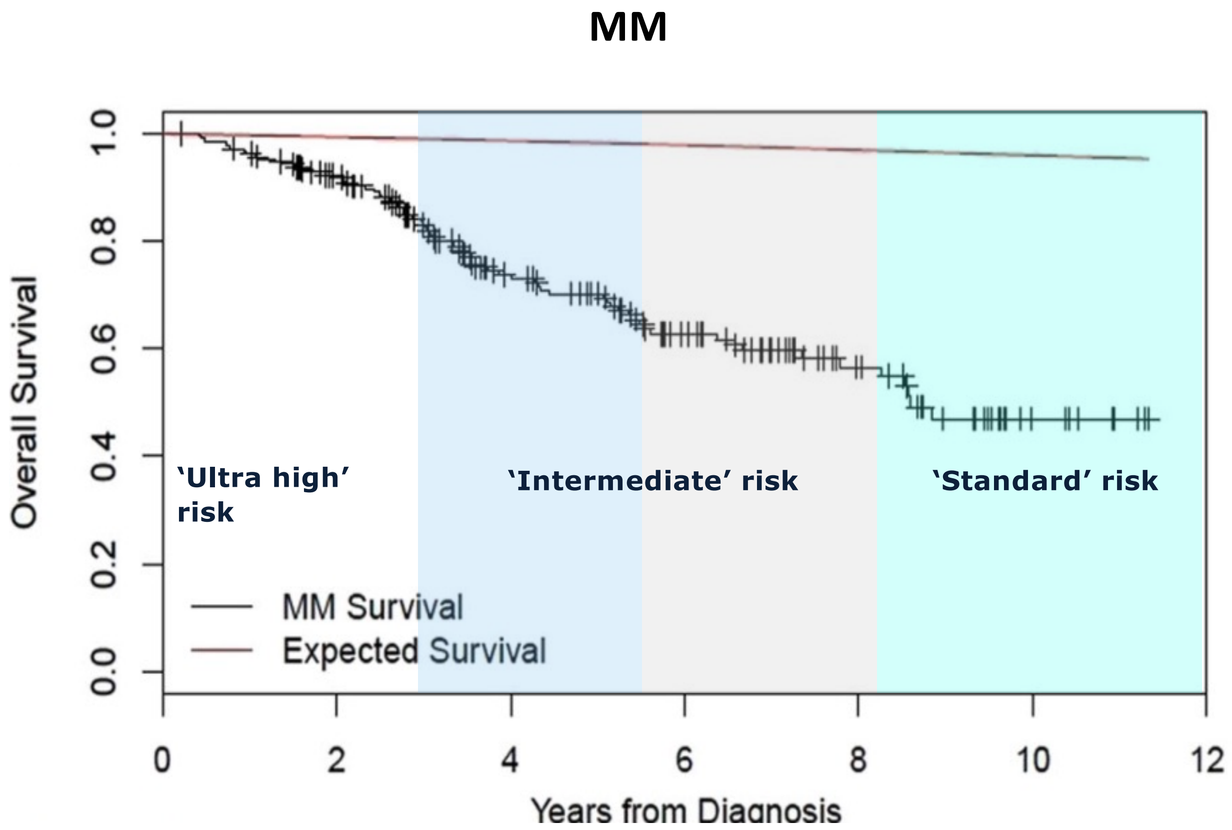
D-VRd[2]



2019-2023

1. Moreau et al. *Lancet* 2019;394:29–38 (including supplement); 2. Voorhees et al, *Lancet haem 2023; Volume 10, ISSUE 10, e825-e837.*

Inferior overall survival in patients with MM compared with a background population

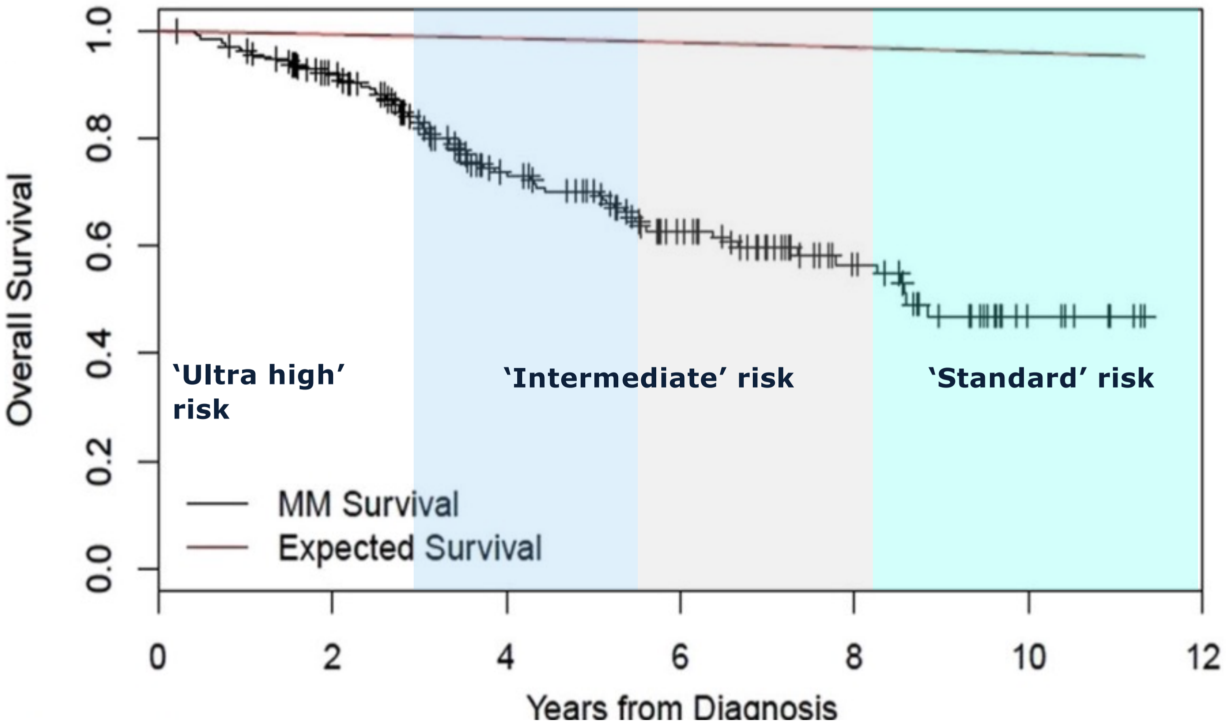


MM

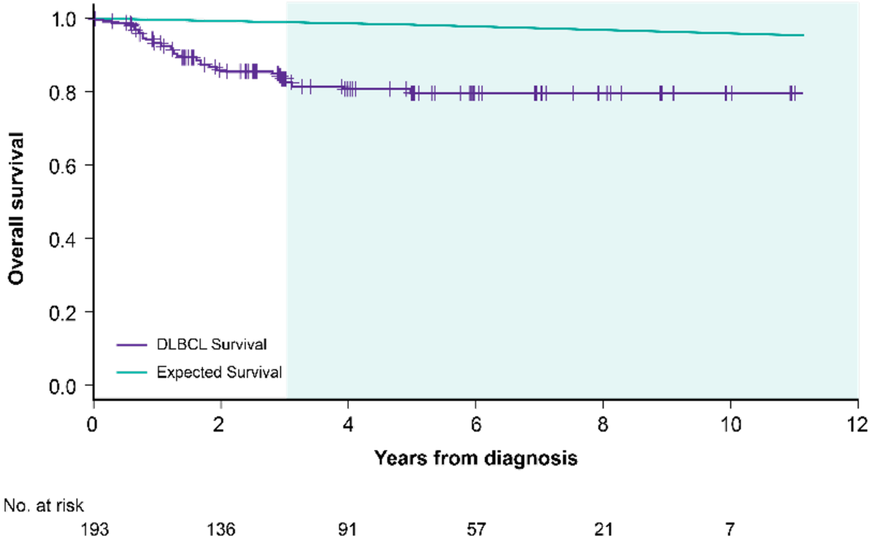
MM, multiple myeloma DLBCL, diffuse large B-cell lymphoma
Ravi P, et al. *Blood Cancer Journal* 2018;8:26.

Risk stratification is key to avoid overtreatment and undertreatment

MM



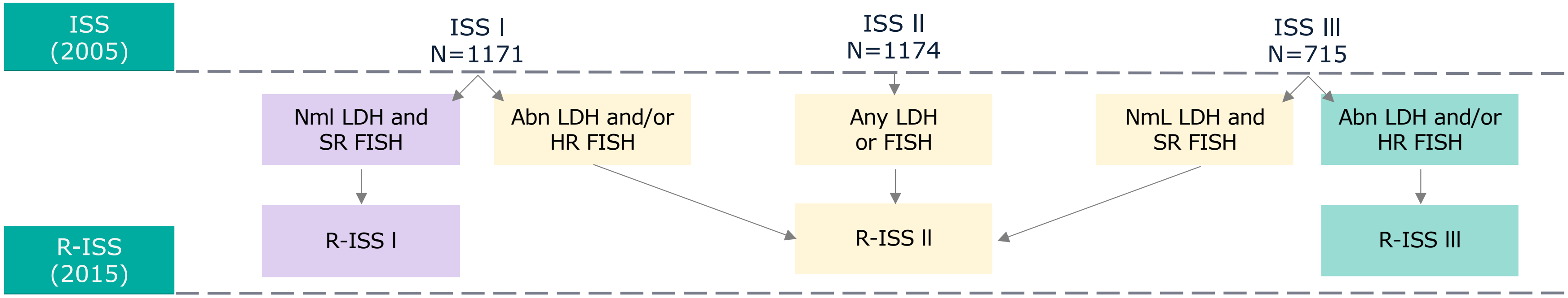
DLBCL



MM, multiple myeloma DLBCL, diffuse large B-cell lymphoma
Ravi P, et al. *Blood Cancer Journal* 2018;8:26.

Standard risk stratification tool from 2015

R-ISS[1]



ISS (2005)

ISS I
N=1171

ISS II
N=1174

ISS III
N=715

Nml LDH and SR FISH

Abn LDH and/or HR FISH

Any LDH or FISH

NmL LDH and SR FISH

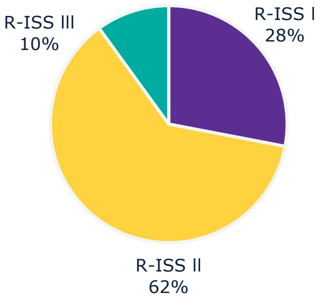
Abn LDH and/or HR FISH

R-ISS (2015)

R-ISS I

R-ISS II

R-ISS III



	R-ISS I (n=871)	R-ISS II (n=1894)	R-ISS III (n=295)
5-year PFS, % (n=3060)	54	36	22
5-year OS, % All (n=3060)	81	60	40
ASCT (n=1998)	83	62	39
No ASCT (n=1062)	75	52	47

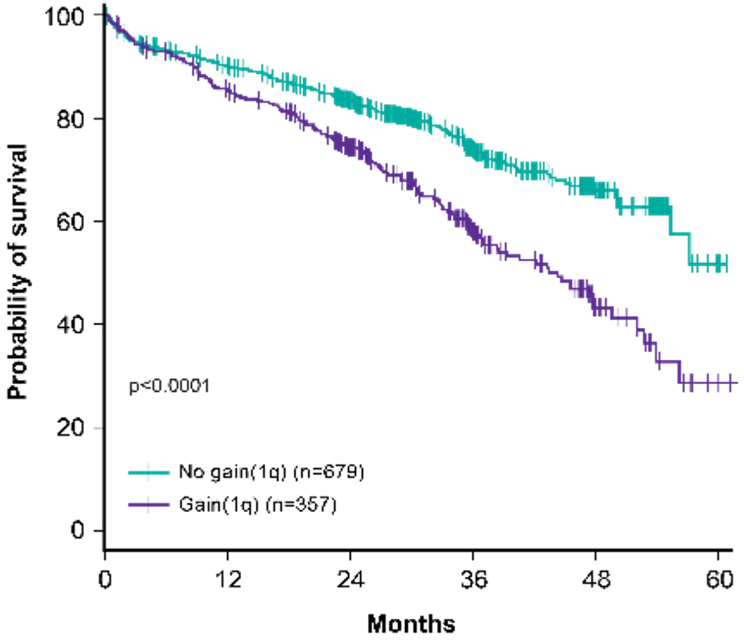
HR-FISH was del(17p) and/or t(4;14)

Data are generated from **3060 patients from 11 international trials** conducted from 2005 to 2012 that were pooled and analysed by the IMWG

ASCT, autologous stem cell transplant; CA, cytogenetic abnormality; HR FISH, high-risk FISH; FISH, fluorescence in situ hybridisation; IMWG, International Myeloma Working Group; LDH, lactate dehydrogenase; OS, overall survival; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; R-ISS, Revised International Staging System.
Dispenzieri A. *Hematology Am Soc Hematol Educ Program* 2016;2016:485–494.

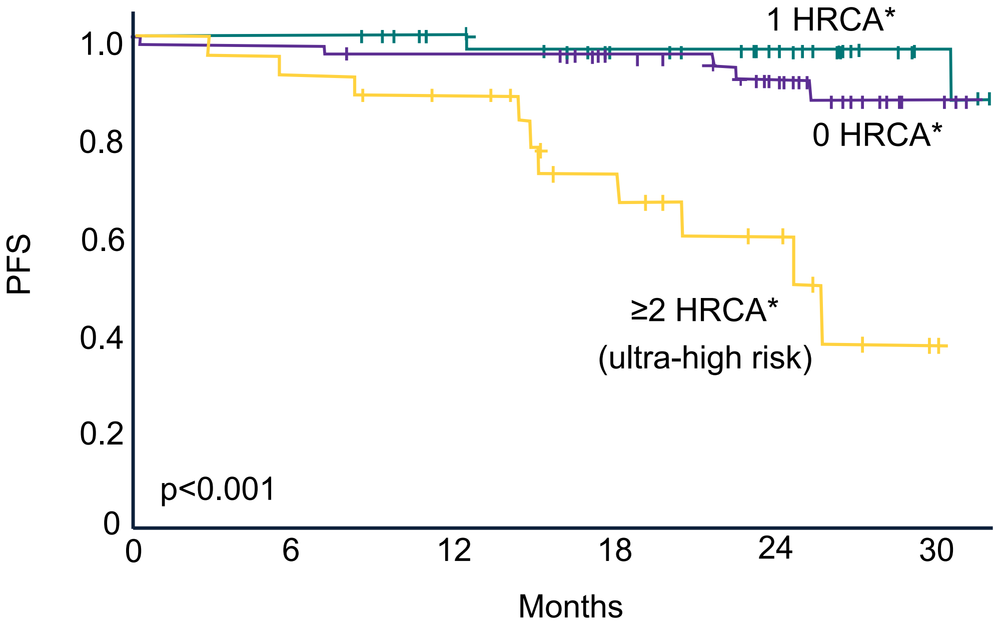
What we understood in the last years?

1q+ is a poor prognostic factor[1]



Patients with ≥2 HRCAs represent an ultra high-risk population[2]

MASTER trial: D-KRd + HDM/ASCT



1. Shah A. *Leukemia* 2018;32:102–110. 2. 2. Costa LJ ASH 2021, abstract 481 (oral presentation).

The number of genetic lesions matters

Methods

17 multi-centre, randomised controlled interventional trials

11421 patients in total study population

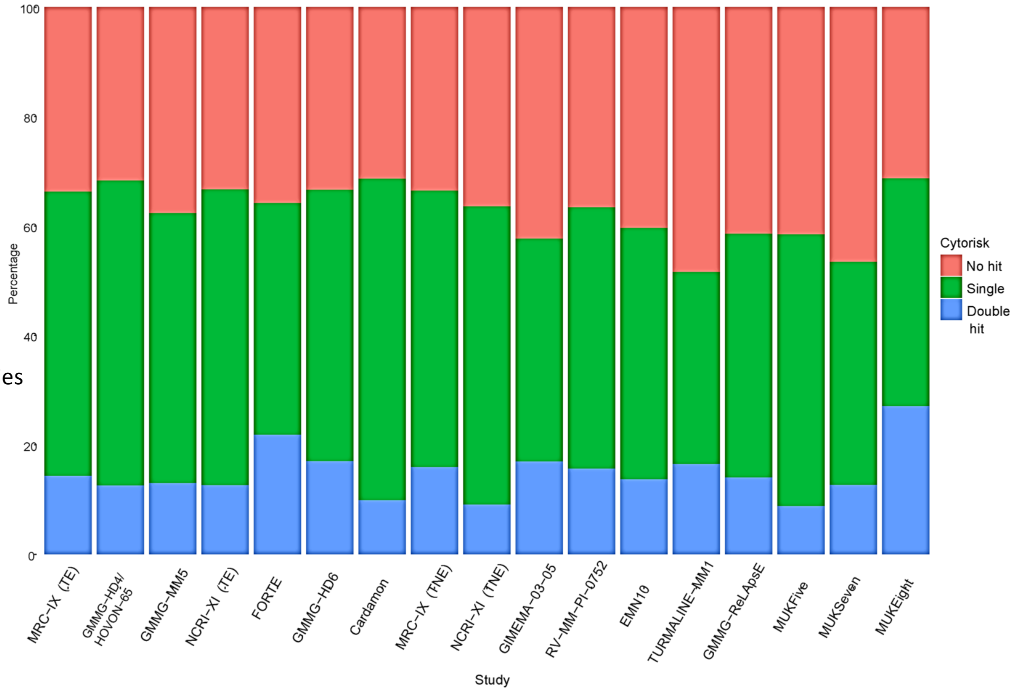
6041 patients with extended genetic profiles

7 NDMM TE trials: 3549 patients
5 NDMM TNE trials: 1511 patients
5 RRMM trials: 1001 patients

NDMM: newly diagnosed multiple myeloma; RRMM: relapsed refractory multiple myeloma

Genetic profile evaluation

Double hit: Two or more high-risk abnormalities [including gain(1q), t(4;14) and del(17p) as a minimum set]



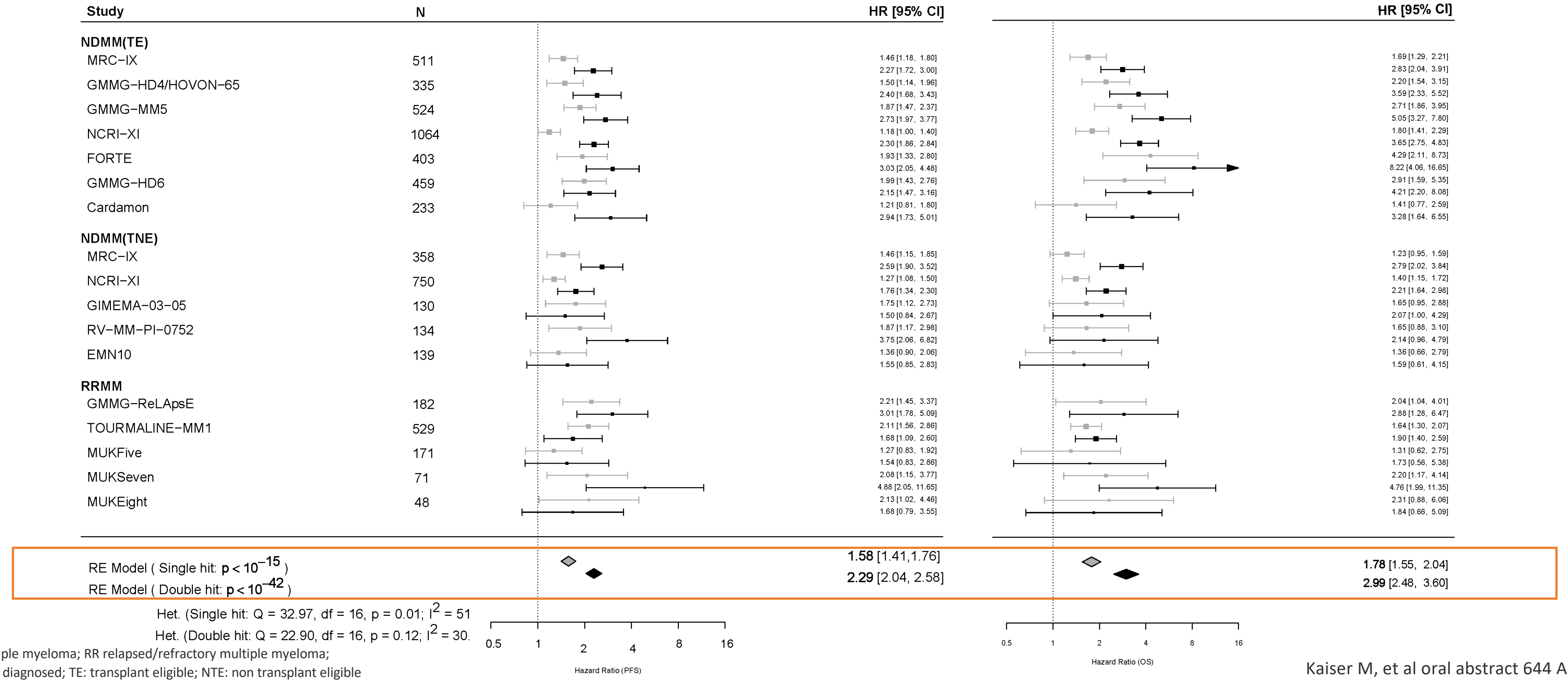
Kaiser M, et al oral abstract 644 ASH 2022

The number of genetic lesions matters

N=6041

Progression free survival

Overall survival



Study	N	PFS HR [95% CI]	OS HR [95% CI]
NDMM(TE)			
MRC−IX	511	1.46 [1.18, 1.80]	1.69 [1.29, 2.21]
		2.27 [1.72, 3.00]	2.83 [2.04, 3.91]
GMMG−HD4/HOVON−65	335	1.50 [1.14, 1.96]	2.20 [1.54, 3.15]
		2.40 [1.68, 3.43]	3.59 [2.33, 5.52]
GMMG−MM5	524	1.87 [1.47, 2.37]	2.71 [1.86, 3.95]
		2.73 [1.97, 3.77]	5.05 [3.27, 7.80]
NCRI−XI	1064	1.18 [1.00, 1.40]	1.80 [1.41, 2.29]
		2.30 [1.86, 2.84]	3.65 [2.75, 4.83]
FORTE	403	1.93 [1.33, 2.80]	4.29 [2.11, 8.73]
		3.03 [2.05, 4.48]	8.22 [4.06, 16.65]
GMMG−HD6	459	1.99 [1.43, 2.76]	2.91 [1.59, 5.35]
		2.15 [1.47, 3.16]	4.21 [2.20, 8.08]
Cardamon	233	1.21 [0.81, 1.80]	1.41 [0.77, 2.59]
		2.94 [1.73, 5.01]	3.28 [1.64, 6.55]
NDMM(TNE)			
MRC−IX	358	1.46 [1.15, 1.85]	1.23 [0.95, 1.59]
		2.59 [1.90, 3.52]	2.79 [2.02, 3.84]
NCRI−XI	750	1.27 [1.08, 1.50]	1.40 [1.15, 1.72]
		1.76 [1.34, 2.30]	2.21 [1.64, 2.98]
GIMEMA−03−05	130	1.75 [1.12, 2.73]	1.65 [0.95, 2.88]
		1.50 [0.84, 2.67]	2.07 [1.00, 4.29]
RV−MM−PI−0752	134	1.87 [1.17, 2.98]	1.65 [0.88, 3.10]
		3.75 [2.06, 6.82]	2.14 [0.96, 4.79]
EMN10	139	1.36 [0.90, 2.06]	1.36 [0.66, 2.79]
		1.55 [0.85, 2.83]	1.59 [0.61, 4.15]
RRMM			
GMMG−ReLApsE	182	2.21 [1.45, 3.37]	2.04 [1.04, 4.01]
		3.01 [1.78, 5.09]	2.88 [1.28, 6.47]
TOURMALINE−MM1	529	2.11 [1.56, 2.86]	1.64 [1.30, 2.07]
		1.68 [1.09, 2.60]	1.90 [1.40, 2.59]
MUKFive	171	1.27 [0.83, 1.92]	1.31 [0.62, 2.75]
		1.54 [0.83, 2.86]	1.73 [0.56, 5.38]
MUKSeven	71	2.08 [1.15, 3.77]	2.20 [1.17, 4.14]
		4.88 [2.05, 11.65]	4.76 [1.99, 11.35]
MUKEight	48	2.13 [1.02, 4.46]	2.31 [0.88, 6.06]
		1.68 [0.79, 3.55]	1.84 [0.66, 5.09]
RE Model (Single hit: $p < 10^{-15}$)		**1.58** [1.41,1.76]	**1.78** [1.55, 2.04]
RE Model (Double hit: $p < 10^{-42}$)		**2.29** [2.04, 2.58]	**2.99** [2.48, 3.60]

Het. (Single hit: Q = 32.97, df = 16, p = 0.01; $I^2 = 51$

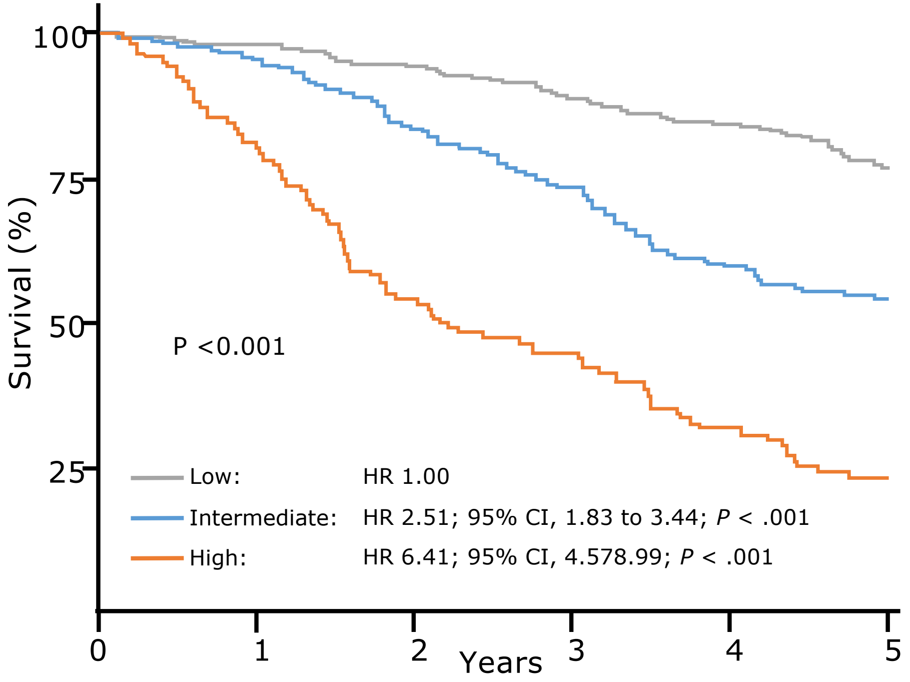
Het. (Double hit: Q = 22.90, df = 16, p = 0.12; $I^2 = 30.$

MM: multiple myeloma; RR relapsed/refractory multiple myeloma;
ND: newly diagnosed; TE: transplant eligible; NTE: non transplant eligible

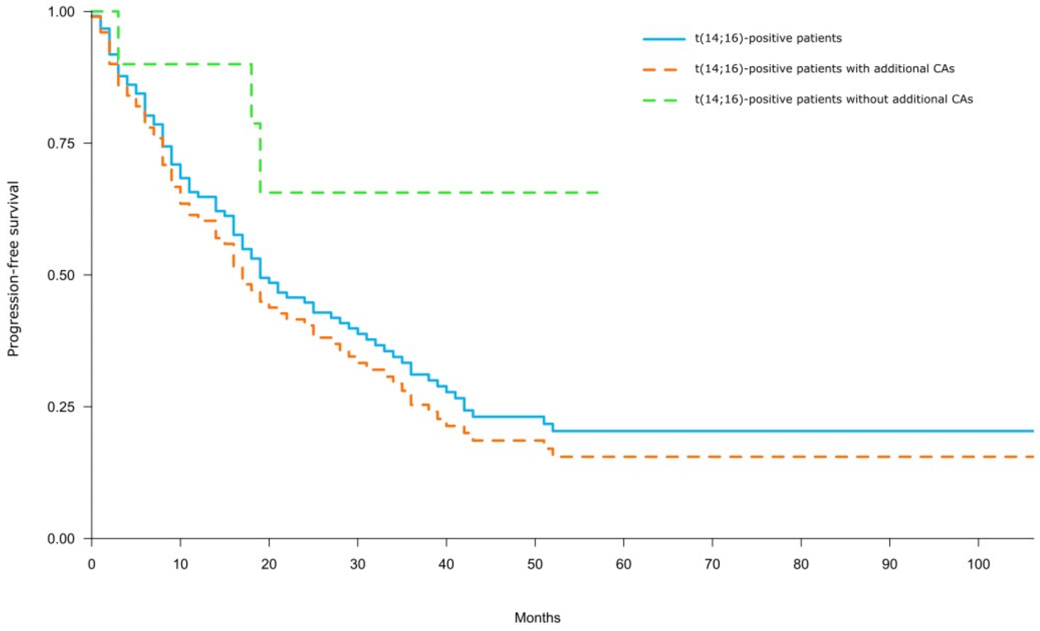
Kaiser M, et al oral abstract 644 ASH 2022

Are all the genetic lesions the same?

Cytogenetic lesions are not all the same[1]



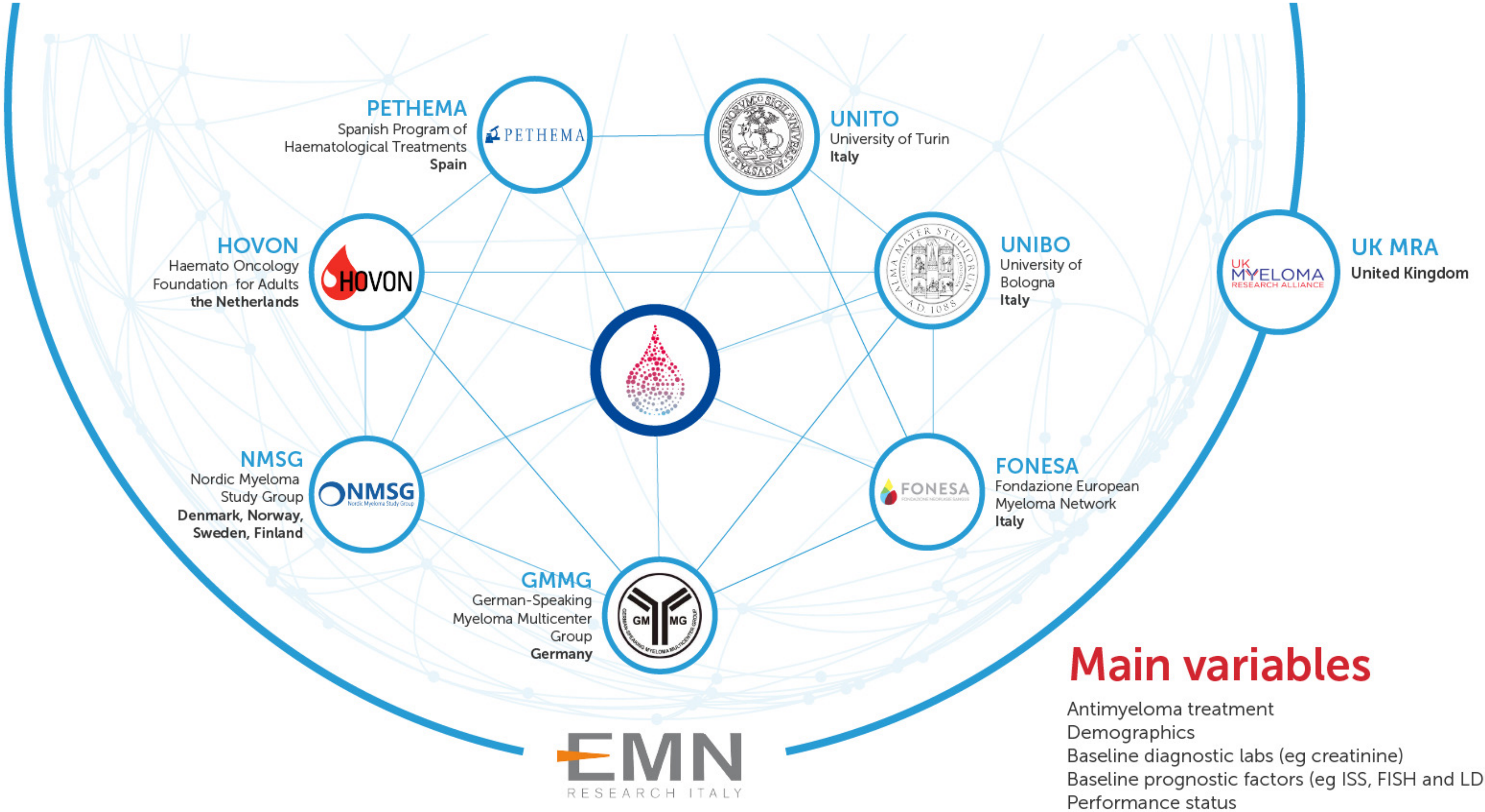
t(14;16) may not be an independent high-risk CA[2]



Cytogenetic PI computed as follows:
0.4 x t(4;14 + 1.2 x del(17p) - 0.3 x trisomy5 + 0.3 x trisomy21 + 0.5 x gain(1q) + 0.8 x del(1p32)
Low-risk: PI ≤0; Intermediate risk: PI > 0 but ≤1; High risk: PI >1

1. Perrott A et al. J Clin Oncol 2019;37:1657–1665.; 2. Mina et al. Blood Cancer Journal (2020)10:40

Redifining risk stratification in NDMM: Harmony project



PETHEMA
Spanish Program of
Haematological Treatments
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University of Turin
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HOVON
Haemato Oncology
Foundation for Adults
the Netherlands

UNIBO
University of
Bologna
Italy

UK MRA
United Kingdom

NMSG
Nordic Myeloma
Study Group
Denmark, Norway,
Sweden, Finland

FONESA
Fondazione European
Myeloma Network
Italy

GMMG
German-Speaking
Myeloma Multicenter
Group
Germany

EMN
RESEARCH ITALY

10843 patients

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)

Patients' characteristics

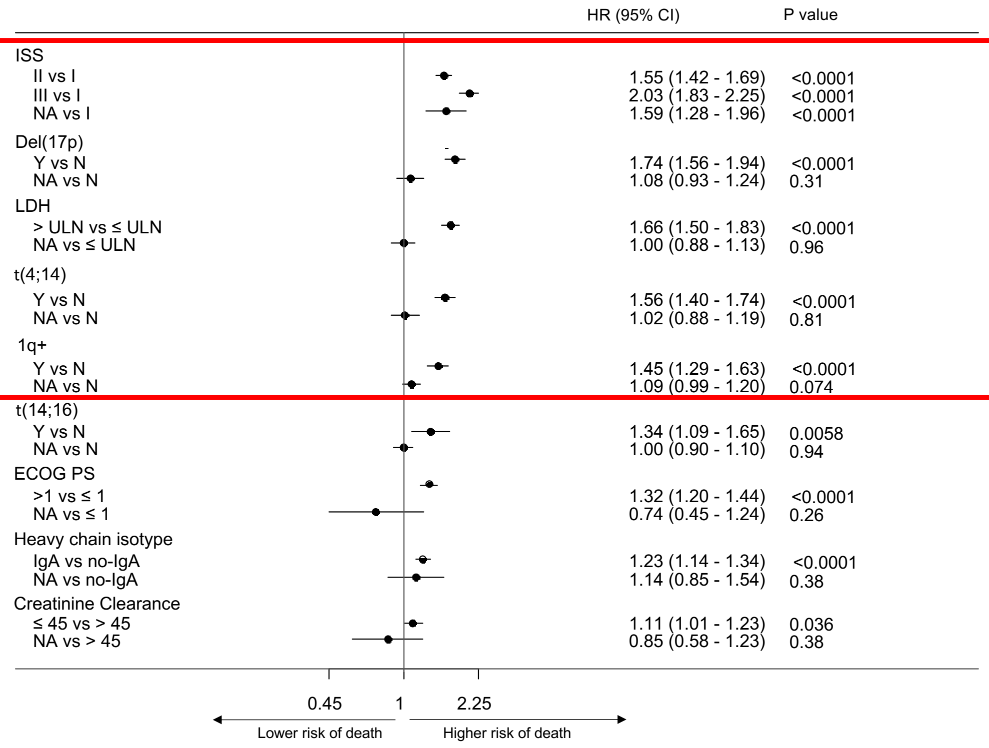
Trial	Patients number	Median Follow-up
EMN01	654	69.1
GIMEMA-MM-03-05	511	71.6
IST-CAR-506	58	56.1
MMY2069	152	53.9
RV-MM-PI-114	102	57.5
RV-MM-PI-209	399	77.2
RV-MM-EMN-441	387	53.9
HOVON 65MM/GMMGHD4	827	98.1
HOVON 87/NSMG18	630	78
GEM05MENO65	389	116
GEM05MAS65	259	82.1
GEM2010MAS65	240	61.6
MM-BO2005	474	125.1
GMMG-MM5	502	63
EMN02 / HOVON 95	1493	78
Myeloma XI (Validation)	**3771**	**59.8**

Population		Training set	Validation set
Total/evaluable N		Total N=7072 (%)	Total N=3771 (%)
Age	Median (IQR)	62- (55-70)	68- (60-74)
	≤ 65	4397 (62)	1575 (42)
	> 65	2675 (38)	2196 (58)
Gender	Female	3216 (45)	1567 (42)
	Male	3856 (55)	2204 (58)
ISS	Stage I	2461 (36)	895 (26)
	Stage II	2724 (40)	1472 (42)
	Stage III	1689 (25)	1118 (32)
	Missing	198	286
LDH	≤ ULN	5557 (86)	2017 (68)
	> ULN	877 (14)	933 (32)
	Missing	638	821
del(17p)	No	4990 (89)	1424 (91)
	Yes	633 (11)	135 (9)
	Missing	1449	2212
t(4;14)	No	4750 (87)	1381 (89)
	Yes	709 (13)	178 (11)
	Missing	1613	2212
1q+	No	1767 (64)	1034 (66)
	Yes	1003 (36)	525 (34)
	Missing	4302	2212
Treatment	IMIDs	2825 (40)	3358 (89)
	IMIDs-PI	3221 (46)	413 (11)
	PI	1026 (15)	-
ASCT eligibility	NTE	2500 (35)	1781 (47)
	TE	4572 (65)	1990 (53)

Abbreviations. HR-CA: High risk chromosomal abnormalities (del(17p) and/or t(4;14)); FISH: fluorescence-in-situ hybridization; CNA: Copy number alteration; ISS: International Staging System; LDH: lactate dehydrogenase; ASCT: autologous stem cell transplantation; PIs: proteasome inhibitors; IMiDs: immunomodulatory drugs

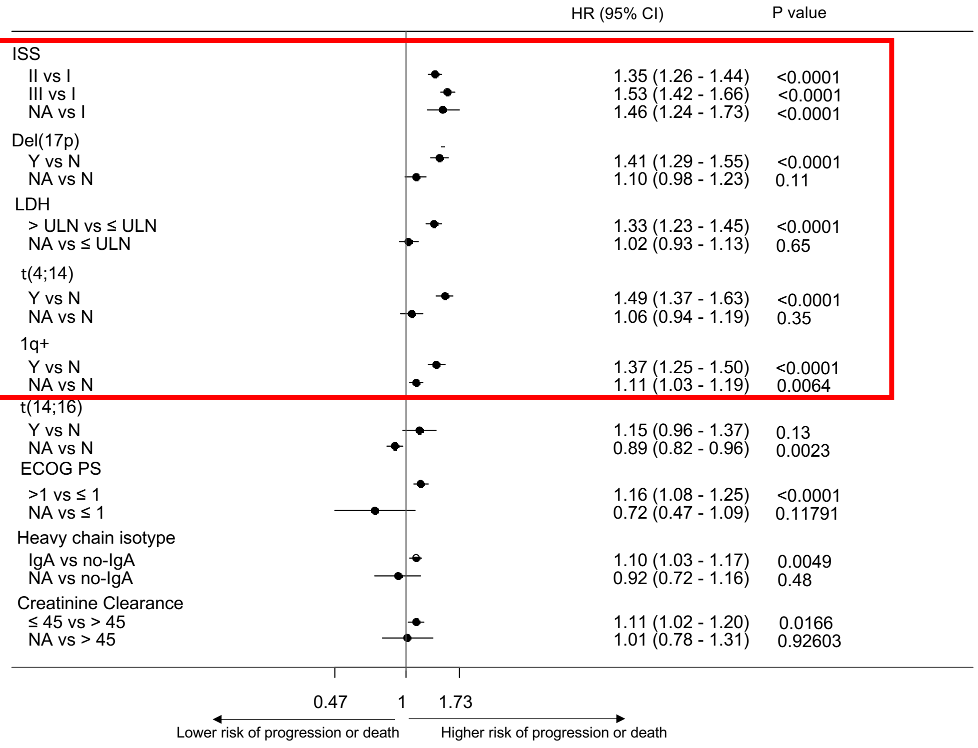
Impact of single risk features (training set)

OS



	HR (95% CI)	P value
ISS		
II vs I	1.55 (1.42 - 1.69)	<0.0001
III vs I	2.03 (1.83 - 2.25)	<0.0001
NA vs I	1.59 (1.28 - 1.96)	<0.0001
Del(17p)		
Y vs N	1.74 (1.56 - 1.94)	<0.0001
NA vs N	1.08 (0.93 - 1.24)	0.31
LDH		
> ULN vs ≤ ULN	1.66 (1.50 - 1.83)	<0.0001
NA vs ≤ ULN	1.00 (0.88 - 1.13)	0.96
t(4;14)		
Y vs N	1.56 (1.40 - 1.74)	<0.0001
NA vs N	1.02 (0.88 - 1.19)	0.81
1q+		
Y vs N	1.45 (1.29 - 1.63)	<0.0001
NA vs N	1.09 (0.99 - 1.20)	0.074
t(14;16)		
Y vs N	1.34 (1.09 - 1.65)	0.0058
NA vs N	1.00 (0.90 - 1.10)	0.94
ECOG PS		
>1 vs ≤ 1	1.32 (1.20 - 1.44)	<0.0001
NA vs ≤ 1	0.74 (0.45 - 1.24)	0.26
Heavy chain isotype		
IgA vs no-IgA	1.23 (1.14 - 1.34)	<0.0001
NA vs no-IgA	1.14 (0.85 - 1.54)	0.38
Creatinine Clearance		
≤ 45 vs > 45	1.11 (1.01 - 1.23)	0.036
NA vs > 45	0.85 (0.58 - 1.23)	0.38

PFS



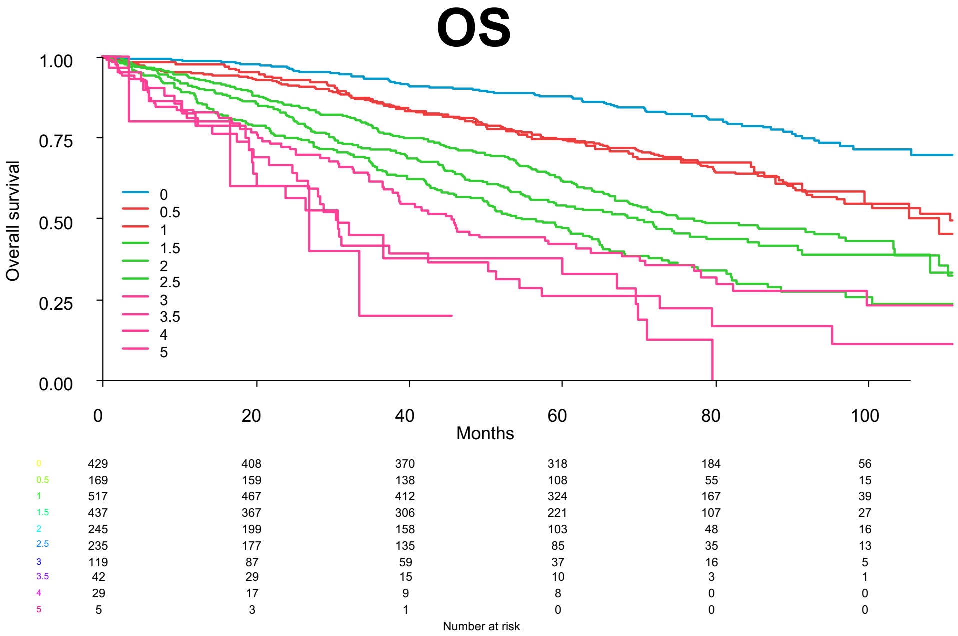
	HR (95% CI)	P value
ISS		
II vs I	1.35 (1.26 - 1.44)	<0.0001
III vs I	1.53 (1.42 - 1.66)	<0.0001
NA vs I	1.46 (1.24 - 1.73)	<0.0001
Del(17p)		
Y vs N	1.41 (1.29 - 1.55)	<0.0001
NA vs N	1.10 (0.98 - 1.23)	0.11
LDH		
> ULN vs ≤ ULN	1.33 (1.23 - 1.45)	<0.0001
NA vs ≤ ULN	1.02 (0.93 - 1.13)	0.65
t(4;14)		
Y vs N	1.49 (1.37 - 1.63)	<0.0001
NA vs N	1.06 (0.94 - 1.19)	0.35
1q+		
Y vs N	1.37 (1.25 - 1.50)	<0.0001
NA vs N	1.11 (1.03 - 1.19)	0.0064
t(14;16)		
Y vs N	1.15 (0.96 - 1.37)	0.13
NA vs N	0.89 (0.82 - 0.96)	0.0023
ECOG PS		
>1 vs ≤ 1	1.16 (1.08 - 1.25)	<0.0001
NA vs ≤ 1	0.72 (0.47 - 1.09)	0.11791
Heavy chain isotype		
IgA vs no-IgA	1.10 (1.03 - 1.17)	0.0049
NA vs no-IgA	0.92 (0.72 - 1.16)	0.48
Creatinine Clearance		
≤ 45 vs > 45	1.11 (1.02 - 1.20)	0.0166
NA vs > 45	1.01 (0.78 - 1.31)	0.92603

Multivariate Cox model adjusted for age, sex, transplant eligibility treatment and missing values. ISS: International Staging System; LDH: lactate dehydrogenase; CNA: Copy number alteration; OS: Overall Survival; PFS: Progression-free Survival.
Poor performance status defined as ECOG>1 or Karnofsky<80.

R2-ISS score definition

Patients with complete data for all risk features (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 CNA	1.47	1.33	0.5
Group	**Number of patients (%)**		**Total additive score**
Low	429 (19.3%)		0
Low-Intermediate	686 (30.8%)		0.5-1
Intermediate-High	917 (41.2%)		1.5-2.5
High	195 (8.8%)		3-5

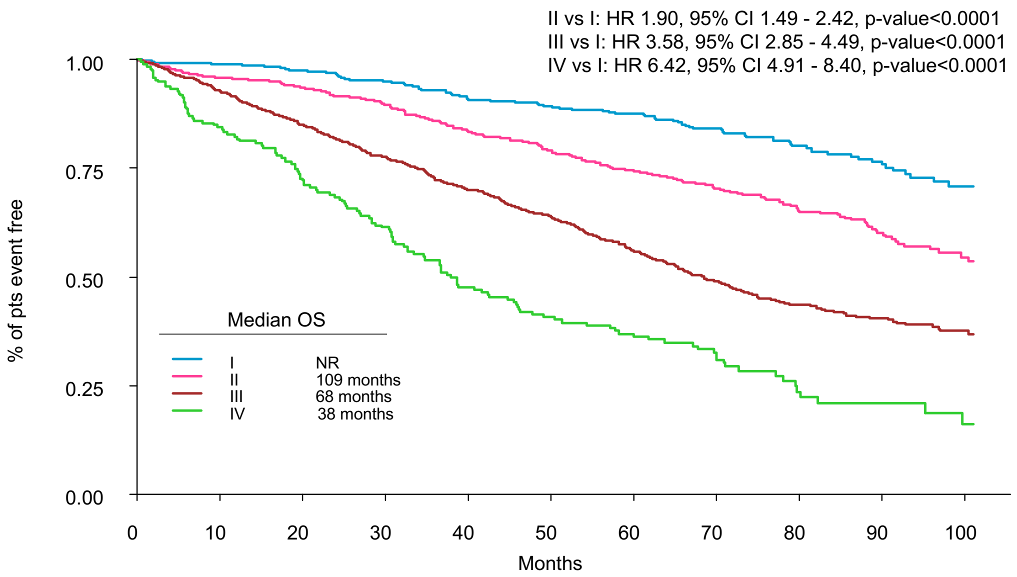


	0	20	40	60	80	100
0	429	408	370	318	184	56
0.5	169	159	138	108	55	15
1	517	467	412	324	167	39
1.5	437	367	306	221	107	27
2	245	199	158	103	48	16
2.5	235	177	135	85	35	13
3	119	87	59	37	16	5
3.5	42	29	15	10	3	1
4	29	17	9	8	0	0
5	5	3	1	0	0	0

Number at risk

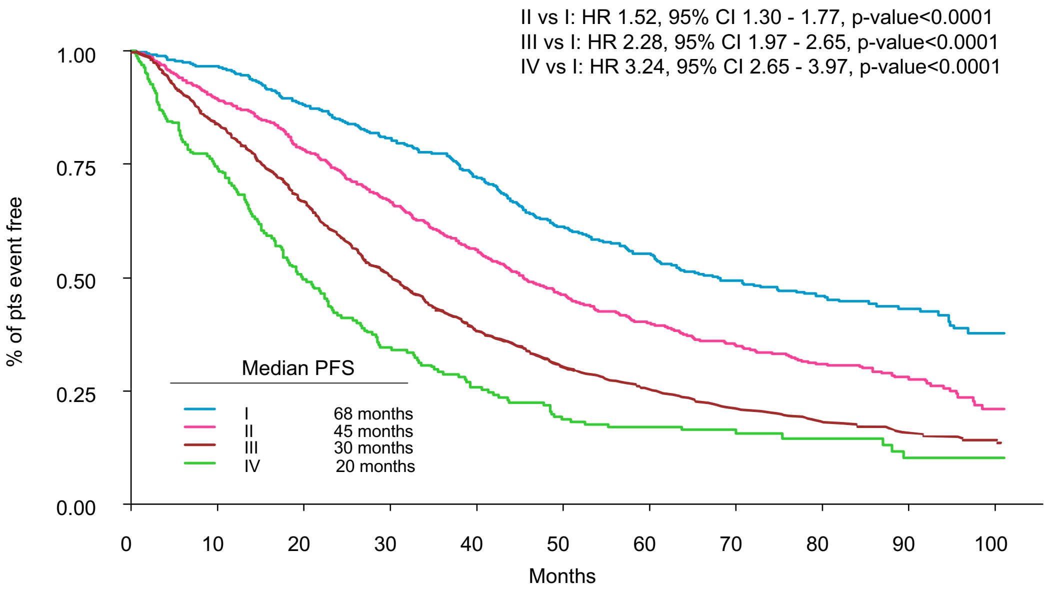
Abbreviations. R2-ISS: Revision 2 of the International Staging System; ISS: International Staging System; LDH: lactate dehydrogenase; CNA: Copy number alteration; OS: Overall Survival; PFS: Progression-free Survival; *calculated on the risk of death, value rounded to the nearest 0.5 with ISS II vs I comparison as reference (score = 1).

R2-ISS: OS and PFS training set


II vs I: HR 1.90, 95% CI 1.49 - 2.42, p-value<0.0001
III vs I: HR 3.58, 95% CI 2.85 - 4.49, p-value<0.0001
IV vs I: HR 6.42, 95% CI 4.91 - 8.40, p-value<0.0001

I	428 (0)	417 (7)	407 (11)	393 (14)	369 (22)	356 (28)	317 (60)	261 (106)	183 (172)	115 (233)	55 (286)
II	686 (0)	646 (12)	626 (17)	597 (19)	550 (26)	514 (33)	432 (86)	346 (151)	222 (253)	129 (333)	54 (399)
III	917 (0)	829 (24)	743 (40)	671 (48)	599 (55)	539 (63)	409 (130)	292 (199)	190 (274)	117 (335)	56 (389)
IV	195 (0)	159 (6)	136 (7)	113 (9)	84 (13)	69 (16)	55 (24)	41 (32)	19 (45)	14 (49)	6 (54)

Number at risk


II vs I: HR 1.52, 95% CI 1.30 - 1.77, p-value<0.0001
III vs I: HR 2.28, 95% CI 1.97 - 2.65, p-value<0.0001
IV vs I: HR 3.24, 95% CI 2.65 - 3.97, p-value<0.0001

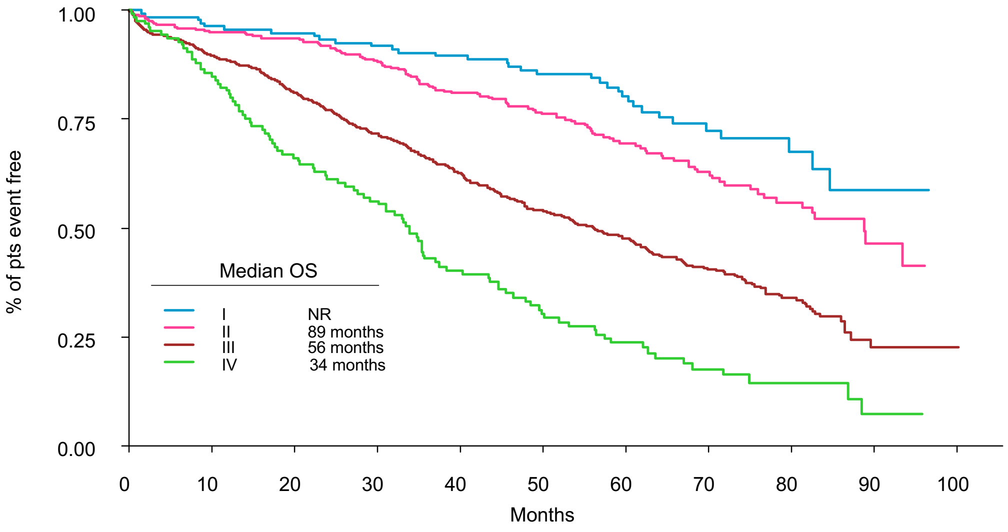
I	428 (0)	407 (7)	368 (10)	336 (12)	294 (18)	246 (22)	202 (42)	156 (69)	113 (101)	70 (138)	31 (170)
II	686 (0)	604 (11)	524 (14)	448 (15)	370 (20)	302 (23)	238 (47)	174 (85)	108 (133)	64 (169)	21 (201)
III	917 (0)	750 (23)	585 (36)	437 (42)	326 (47)	252 (52)	188 (76)	133 (102)	83 (137)	47 (162)	24 (181)
IV	195 (0)	141 (5)	93 (6)	63 (8)	45 (10)	32 (11)	26 (14)	20 (19)	10 (27)	7 (27)	3 (31)

Number at risk

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

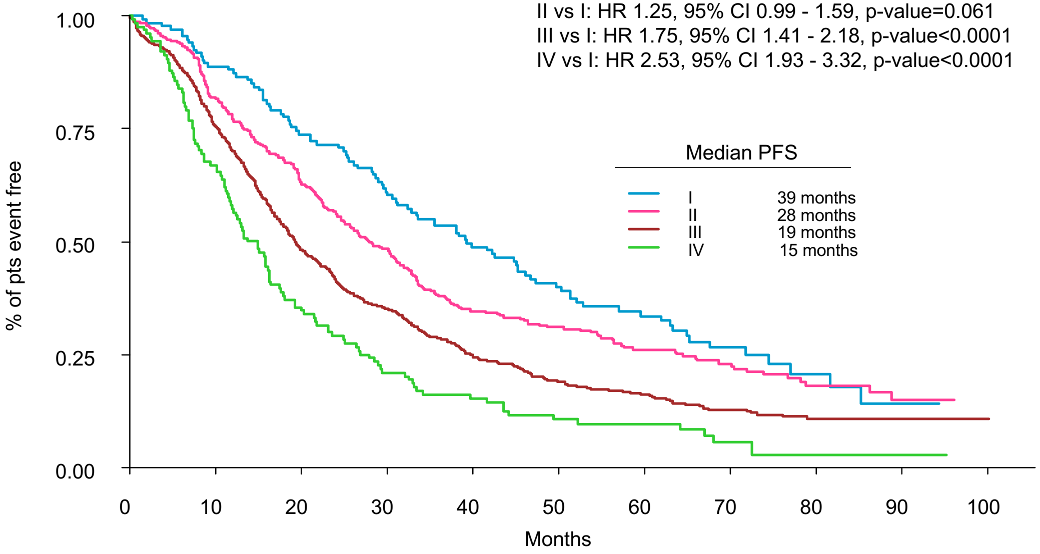
R2-ISS: OS and PFS validation set

II vs I: HR 1.52, 95% CI 1.04 - 2.24, p-value=0.032
III vs I: HR 3.09, 95% CI 2.17 - 4.39, p-value<0.0001
IV vs I: HR 5.71, 95% CI 3.87 - 8.44, p-value<0.0001



I	135 (0)	129 (1)	126 (2)	122 (2)	113 (8)	94 (22)	75 (36)	44 (61)	21 (82)	6 (95)	0 (101)
II	322 (0)	297 (9)	290 (12)	266 (19)	233 (31)	181 (70)	136 (100)	92 (133)	50 (167)	12 (200)	0 (211)
III	627 (0)	540 (23)	485 (28)	424 (32)	351 (53)	271 (86)	205 (121)	139 (160)	70 (214)	12 (258)	1 (269)
IV	130 (0)	106 (6)	80 (8)	68 (8)	47 (10)	32 (14)	22 (17)	13 (21)	8 (24)	2 (28)	0 (30)

Number at risk



II vs I: HR 1.25, 95% CI 0.99 - 1.59, p-value=0.061
III vs I: HR 1.75, 95% CI 1.41 - 2.18, p-value<0.0001
IV vs I: HR 2.53, 95% CI 1.93 - 3.32, p-value<0.0001

I	135 (0)	119 (1)	98 (2)	81 (2)	62 (5)	47 (9)	32 (17)	18 (25)	8 (32)	1 (37)	0 (38)
II	322 (0)	257 (8)	197 (9)	148 (13)	103 (16)	81 (28)	59 (38)	38 (53)	21 (63)	6 (76)	0 (82)
III	627 (1)	454 (25)	289 (26)	209 (27)	143 (31)	100 (44)	71 (58)	40 (76)	17 (94)	6 (105)	1 (110)
IV	130 (0)	83 (6)	44 (6)	26 (6)	18 (7)	11 (9)	9 (10)	3 (13)	1 (14)	1 (14)	0 (15)

Number at risk

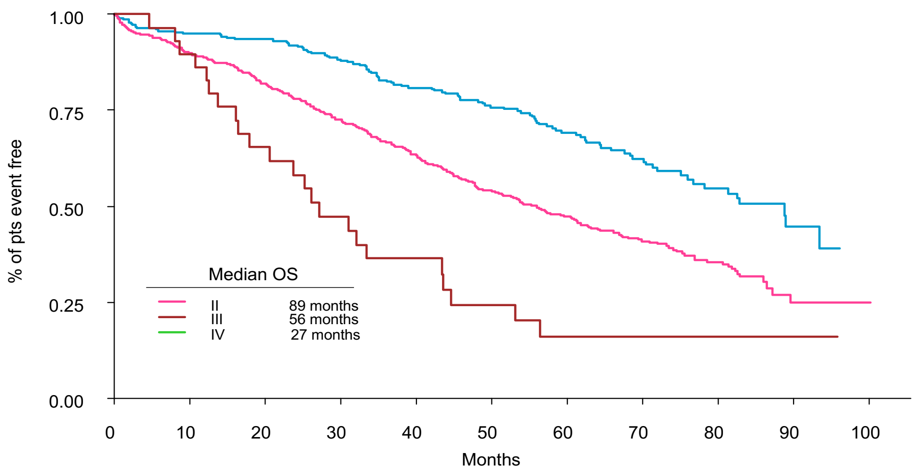
R2-ISS: Revision 2 of the International Staging System; R-ISS: Revised International Staging System;
HR: hazard ratio; OS: Overall Survival; PFS: Progression-free Survival

R2-ISS: redistribution of intermediate risk patients

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

III vs. II: HR 1.93 (95% CI: 1.54–2.42; p<0.0001)
IV vs. II: HR 4.15 (95% CI: 2.63–6.54; p<0.0001)

OS of R-ISS II patients according to R2-ISS (validation set)



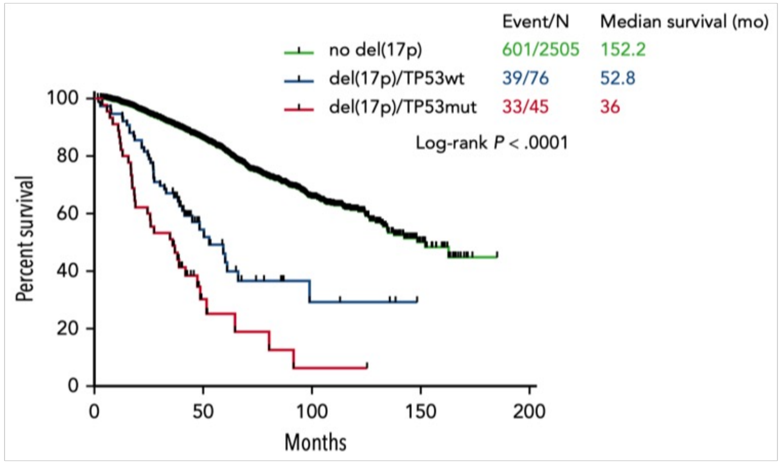
CI, confidence interval; HR, hazard ratio; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; R2-ISS, Revision 2 of the International Staging System.
D'Agostino M, et al. J Clin Oncol 2022;40:3406–3418 (supplementary material).

How can we improve R2-ISS?

Improving the definition of already included risk factors

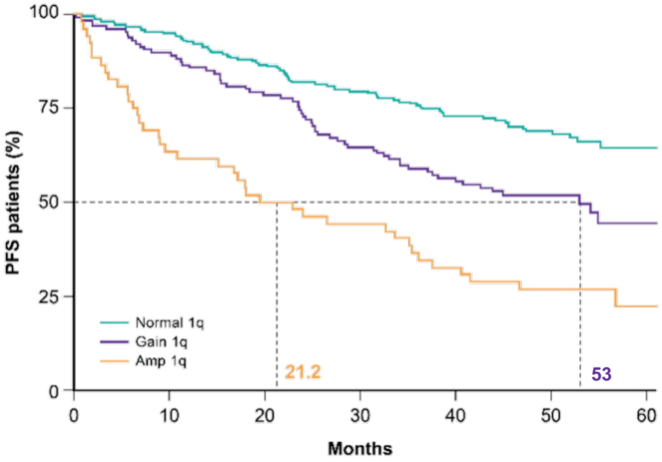
Del(17p)[1]

Del(17p) +/- TP53 mutation



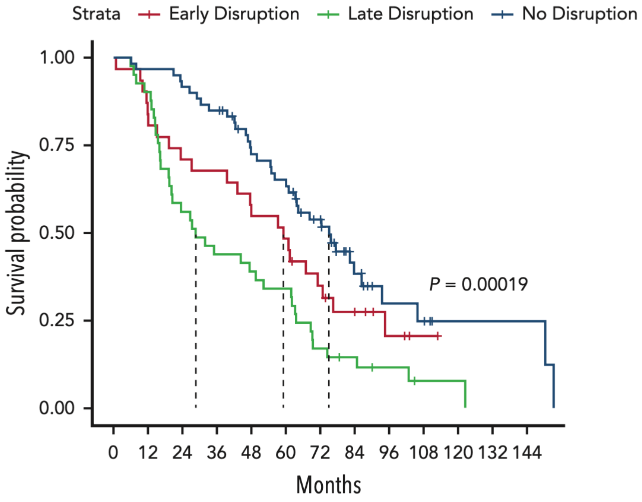
1q[2]

Amp 1q (≥4 copies) vs Gain 1q (3 copies)



t(4;14)[3]

NSD2 disruption site

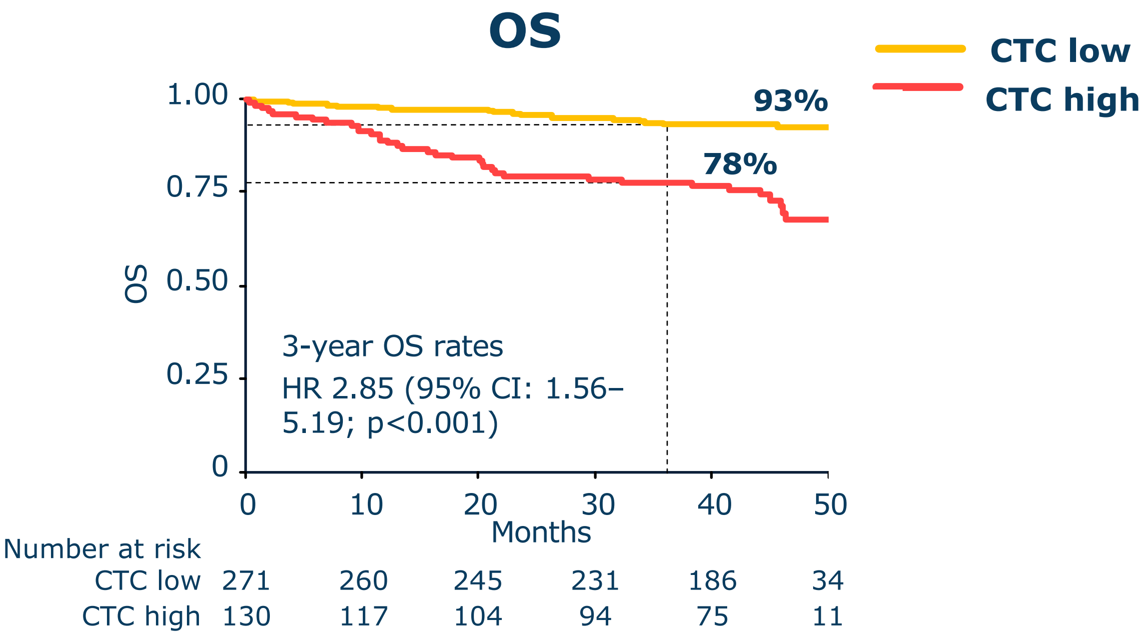


1. Corre J, et al. Blood 2021;137:1192–1195; 2. D'Agostino M, et al. Presented at IMW 2021. Abstract 1062754; 3. Stong N et al Blood. 2023 Mar 30;141(13):1574-1583.

How can we improve R2-ISS?

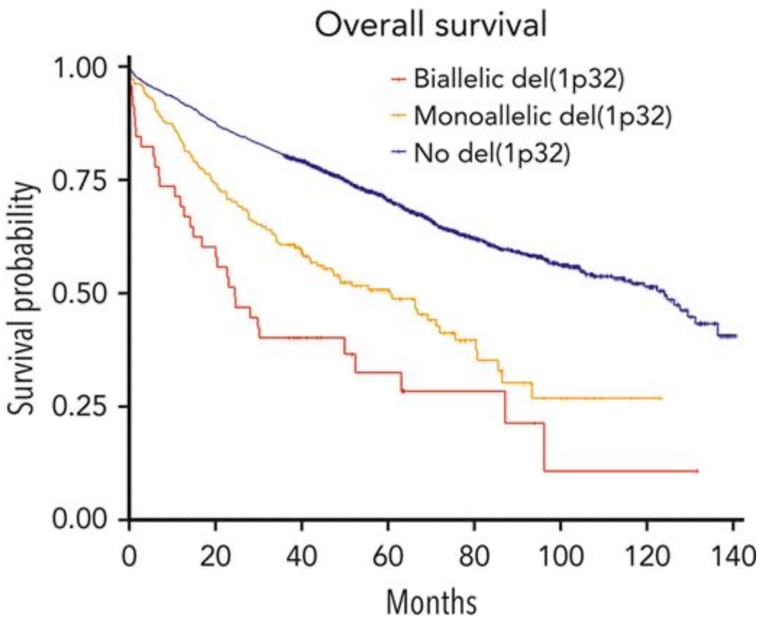
Including other risk factors

CTCs[1]



3-year OS rates
HR 2.85 (95% CI: 1.56–5.19; p<0.001)

1p[2]



1. Bertamini L et al. ASH 2020. Abstract 720. 2. Schavgoulidze A et al. *Blood* (2023) 141 (11): 1308–1315.

How can we improve R2-ISS?

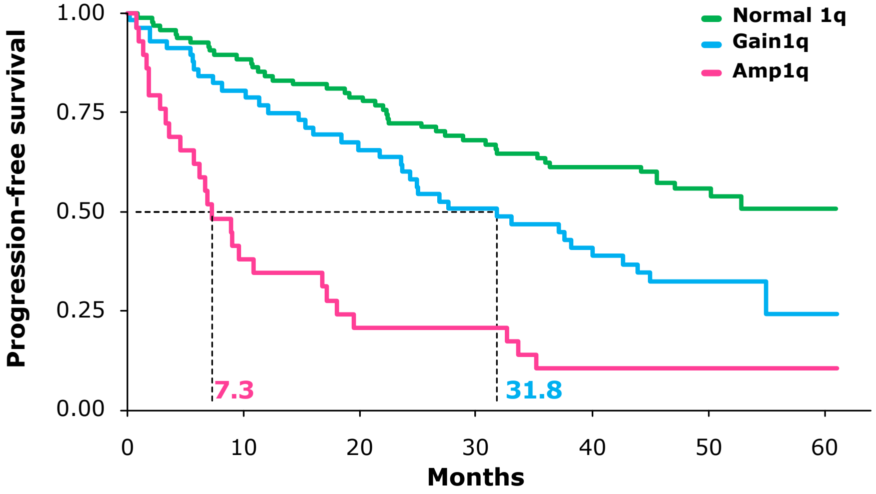
Dynamic risk evaluation

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



	0	10	20	30	40	50	60
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)

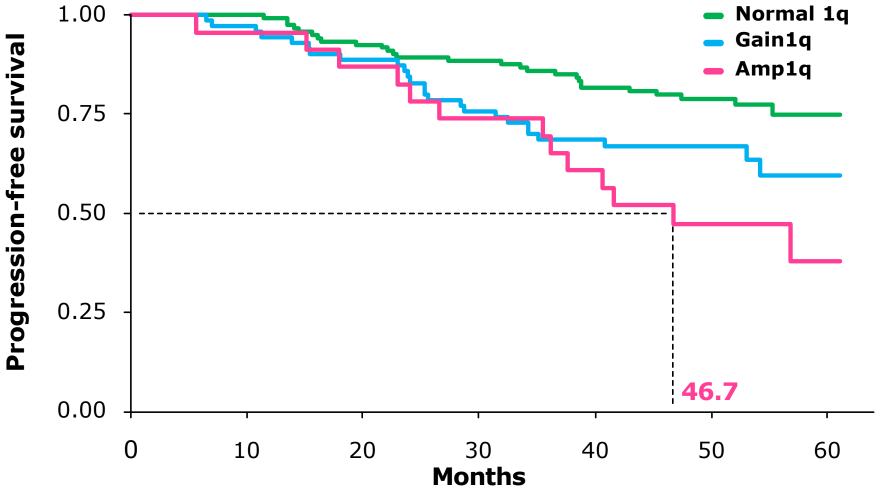
Number at risk (number censored)

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. Gain1q: HR 1.61, 95% CI: 0.82–3.14



	0	10	20	30	40	50	60
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)

Number at risk (number censored)

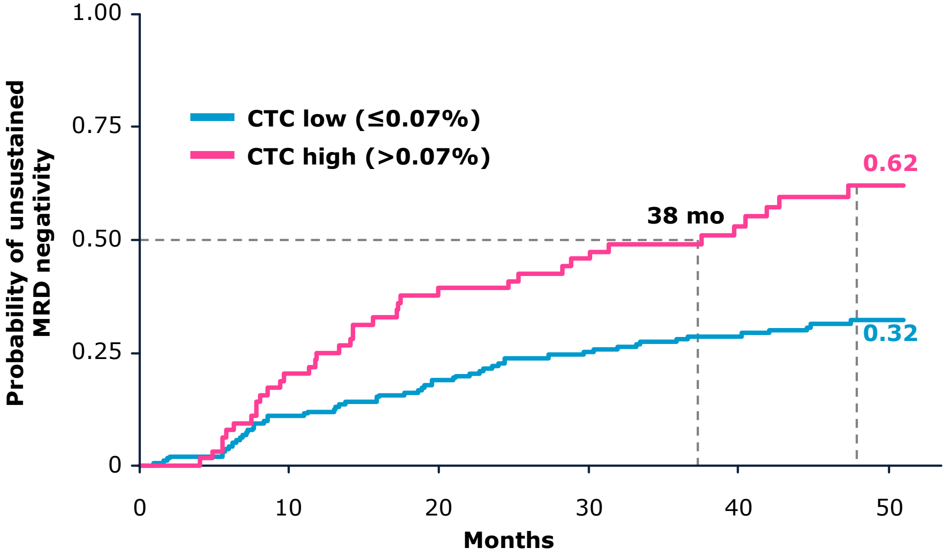
Analysis performed by multiparameter flow cytometry before maintenance in the intention-to-treat population.
CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; neg, negativity; PFS, progression-free survival; pos, positivity.
D'Agostino M, et al. Presented at IMW 2021. Abstract 1062754.

How can we improve R2-ISS?

Dynamic risk evaluation

MRD negativity duration according to CTC

CTC high vs. low: HR 1.86 (95% CI: 1.17–2.96; p=0.0086)

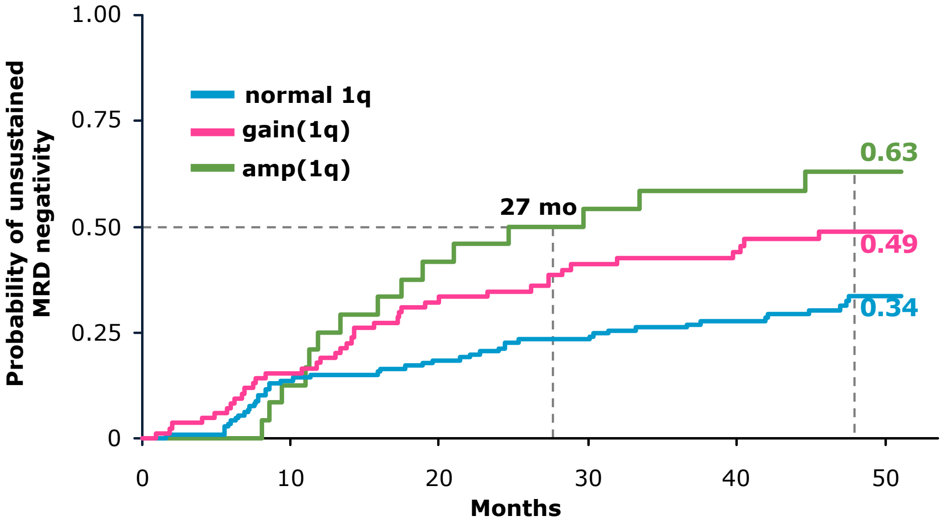


Low	195	167	151	133	116	64
High	64	51	38	33	22	12

Number at risk

MRD negativity duration according to 1q

gain(1q) vs. normal 1q: HR 1.49 (95% CI: 0.95–2.33; p=0.079)
amp(1q) vs. normal 1q: HR 2.12 (95% CI: 1.15–3.93; p=0.017)



Normal	147	125	118	108	88	49
Gain(1q)	86	70	53	44	36	22
Amp(1q)	24	21	14	11	10	5

Number at risk

Cut-off for CTC high vs. low: >0.07% vs. ≤0.07%.[2] gain(1q) defined as ≥10% of nuclei with ≥3 copies of 1q by fluorescence in situ hybridisation and not meeting the definition of amp(1q). amp(1q) defined as ≥20% of nuclei with ≥4 copies of 1q.[3]
CI, confidence interval; CTC, circulating tumour cells; HR, hazard ratio; MRD, minimal residual disease.
1. D'Agostino et al. IMS 2022. Abstract OAB-011; 2. Bertamini L, et al. *J Clin Oncol* 2022;40:3120–3131; 3. D'Agostino M, et al. *Clin Lymphoma Myeloma Leuk* 2021;21:S34.

High-risk definition

Disease related features

- **R-ISS,R2-ISS**
- **Del17p, p53 mutation**
- **Ampl 1q, gain1q**
- **T(4;14), breakpoint location cr4**
- **N of cromosomal abnormalities**
- **Circulating Plasma Cells**
- **Plasma cell Leukemia**
- **Extramedullary disease**
- **Plasmablastic morphology**

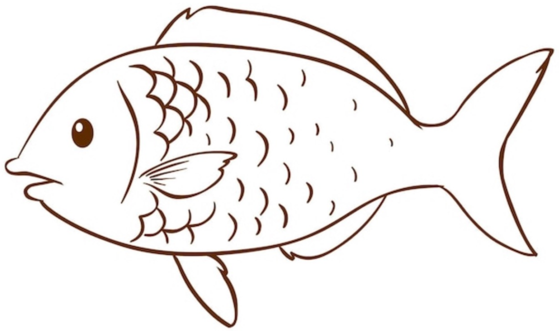
Dinamic risk factors

- **MRD negativity**
- **MRD negativity duration**
- **Early relapse**

New IMS high-risk definition: is it FISH still the standard?

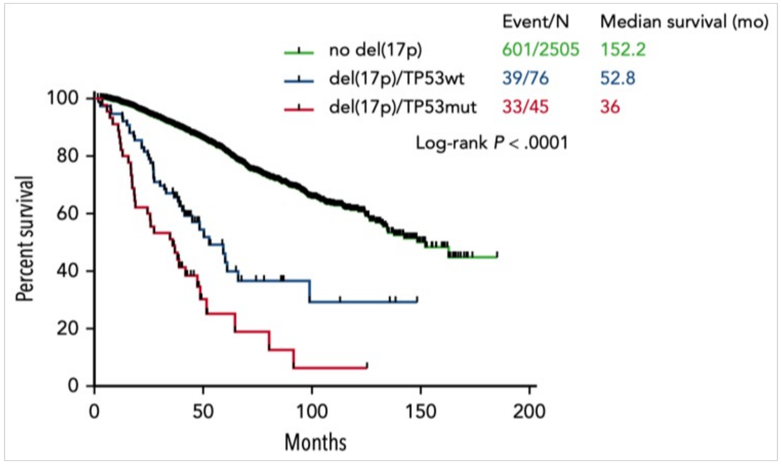
- Del17p (20% cut off) and/or **Tt53 mut**
- t(4;14)/t(4;16)/t(14;20) with 1q gain and/or 1p del;
- 1p32 + 1q gain or **bi-allelic 1p32**

B2MG??????

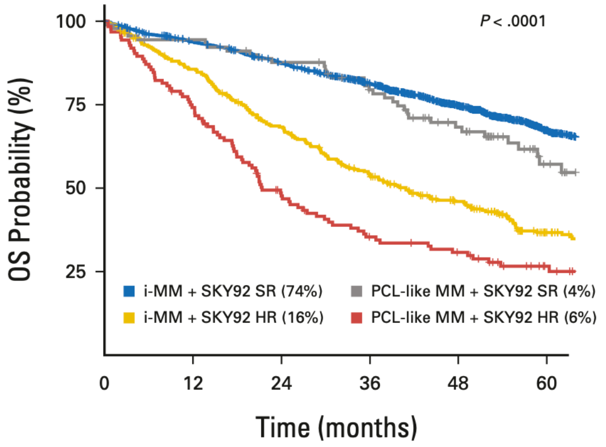


?

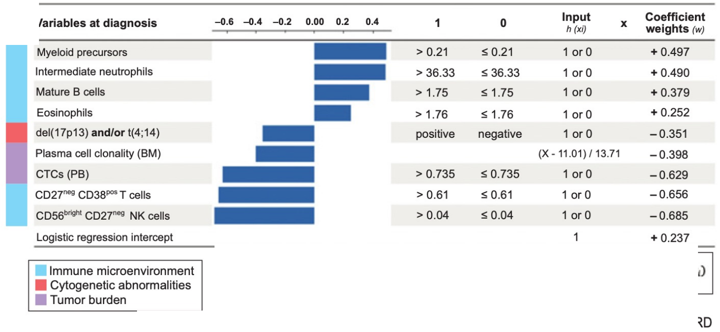
DNA[1]



RNA[2]



Microenvironment and CTCs[3]



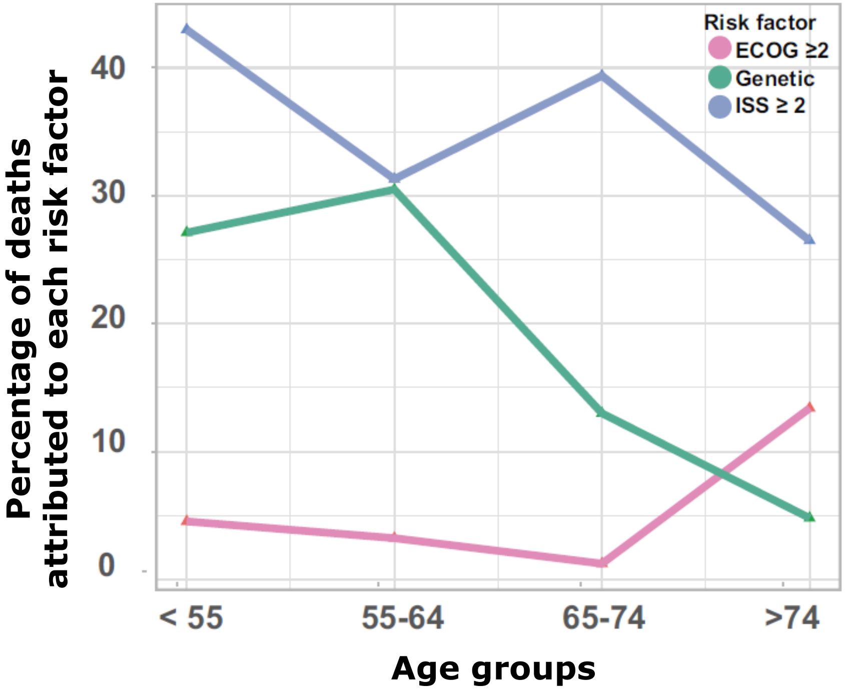
/ariables at diagnosis	1	0	Input $h(x_i)$	x	Coefficient weights (w)
Myeloid precursors	> 0.21	≤ 0.21	1 or 0		+ 0.497
Intermediate neutrophils	> 36.33	≤ 36.33	1 or 0		+ 0.490
Mature B cells	> 1.75	≤ 1.75	1 or 0		+ 0.379
Eosinophils	> 1.76	≤ 1.76	1 or 0		+ 0.252
del(17p13) **and/or** t(4;14)	positive	negative	1 or 0		– 0.351
Plasma cell clonality (BM)			(X - 11.01) / 13.71		– 0.398
CTCs (PB)	> 0.735	≤ 0.735	1 or 0		– 0.629
CD27^{neg} CD38^{pos} T cells	> 0.61	≤ 0.61	1 or 0		– 0.656
CD56^{bright} CD27^{neg} NK cells	> 0.04	≤ 0.04	1 or 0		– 0.685
Logistic regression intercept			1		+ 0.237

1. Corre J, et al. Blood 2021;137:1192–1195; 2. Hofste op Bruinink D et al JCO 2022; 27: 3132-3150.; 3. Guerrero C et al Clin Cancer Res (2022) 28 (12): 2598–2609.

The impact of typical genetic factors on mortality decreases with age

ECOG Performance Status Scale seems to have **more impact on mortality with increasing age**

Attributable risk by age group of ISS≥2, ECOG≥2, and the adverse genetic risk factors (t(4;14), del(17p), del(1p), gain(1q))

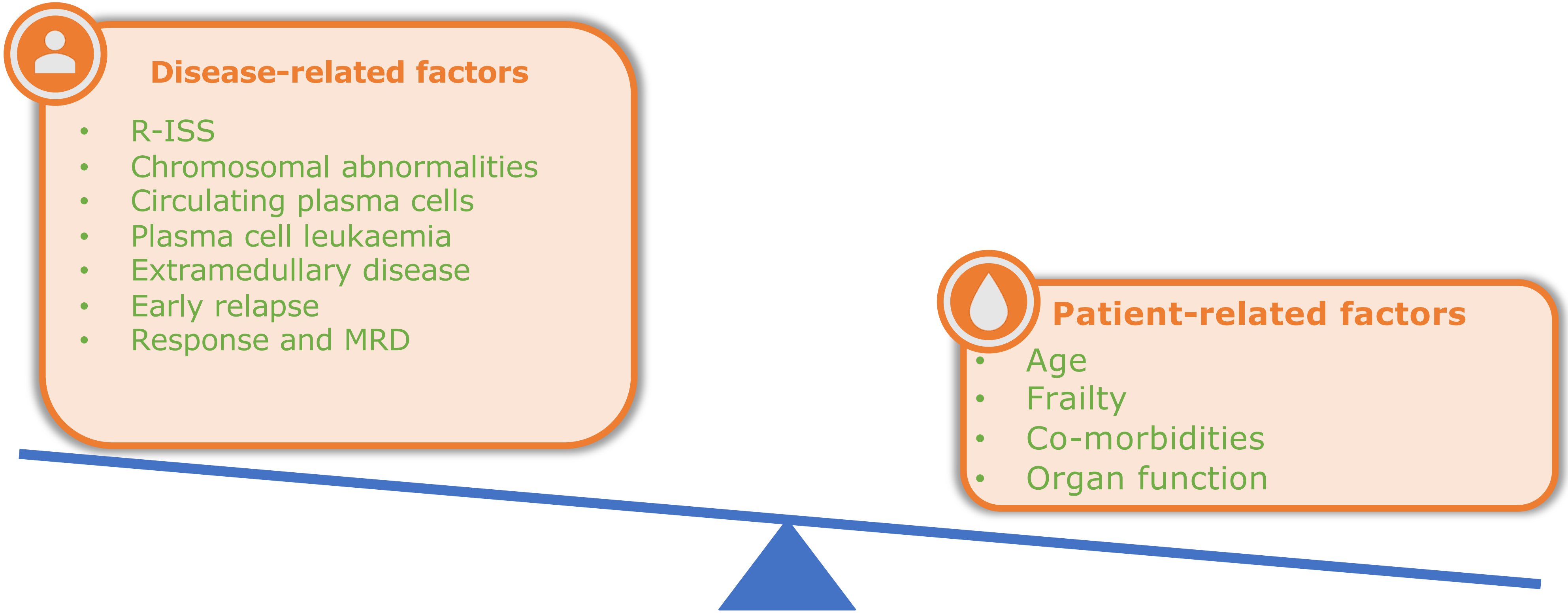


The impact of genetic risk factors **decreases as age increases**

ECOG, Eastern Cooperative Oncology Group.
Boyle EM, et al. *Leukemia* 2022;36:221–224.

All elderly NTE MM are not equal

As patients **age**, the balance for risk tips towards **patient-related factors**



Disease-related factors

- R-ISS
- Chromosomal abnormalities
- Circulating plasma cells
- Plasma cell leukaemia
- Extramedullary disease
- Early relapse
- Response and MRD

Patient-related factors

- Age
- Frailty
- Co-morbidities
- Organ function

MRD, minimal residual disease; NTE, non transplant eligible; R-ISS, Revised International Staging System.

Professional opinion and clinical experience of Dr. Mattia D’Agostino.

Conclusion

- 1q abnormalities should be included in the risk stratification
- The value of multiple high-risk features should be taken into account
- R2-ISS is an additive risk score including 1q and it can be easily updated
- We still have to look at patient-related factors (e.g. frailty) and spatial heterogeneity (EMD, focal lesions)
- A better definition of the current risk factors, new risk factors and a dynamic risk evaluation will improve MM risk stratification
- We need trials uniformly defining high risk disease (IMS definition?) and demonstrating the benefit of risk-adapted treatment (transplant eligibility should not be the only factor impacting first line treatment choice!)

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