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Chromosome 1q21 abnormalities refine outcome prediction in patients with multiple myeloma – a meta-analysis of 2,596 trial patients

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AUTHORSHIP CONTRIBUTIONS

NW and MFK designed the study and analyzed the data. NW, RSH and MFK wrote the manuscript. NW, MFK, HJS, DAC, MSR, GW, IWB, UB, TH, GJM, AJ, FED, MH, GC, CS, HG and GJ collected and curated data, revised and approved the manuscript.

CONFLICTS OF INTEREST

HJS reports Honoraria from: AbbVie, Takeda; Travel support from: Amgen, Bristol-Myers Squibb, Janssen, Sanofi, Celgene. DAC reports research funding from Celgene Corporation, Amgen, and Merck Sharp and Dohme. MSR reports honoraria: Celgene, BMS, Novartis, Janssen, Takeda; consulting or advisory role: Celgene, BMS, Novartis, Janssen, Takeda; research funding: Celgene, Novartis, AMGEN; travel, accomodations, expenses: Janssen, BMS, Takeda. IWB reports research funding: Celgene, BMS, Janssen. MHä reports honoraria: Novartis, Amgen, Roche, Takeda; consulting or advisory role: Celgene. GJM has received research funding from Janssen; consultancy fees and honoraria from Bristol-Myers

Squibb, Roche, Amgen, GSK, Karyopharm and Takeda; and consultancy fees, honoraria, and research funding from Celgene Corporation. FED has received consultancy fees and honoraria from Amgen, AbbVie, Takeda, Janssen, Celgene and Roche. GC has received consultancy fees, honoraria, research funding, and speakers' bureau fees from Takeda, Celgene Corporation, Janssen, and Amgen; consultancy fees and honoraria from Bristol-Myers Squibb and Roche; and consultancy fees, honoraria, and speakers' bureau fees from Sanofi. CS reports honoraria: BMS, Janssen, Celgene, Novartis, Amgen, Takeda; consulting or advisory role: BMS, Janssen, Celgene, Novartis, Amgen, Takeda; speakers bureau: Takeda; research funding: Takeda, Novartis; travel, accomodations, expenses: BMS, Janssen, Celgene, Novartis, Amgen, Takeda. HG reports honoraria: Amgen, BMS, Celgene, Chugai, Janssen, Novartis, Takeda; consulting or advisory role: Amgen, BMS, Celgene, Chugai, Janssen, Novartis, Takeda; speakers bureau: Amgen, BMS, Celgene, Janssen, Novartis, Takeda; research funding: Amgen, BMS, Celgene, Chugai, Janssen, Novartis, Takeda; travel, accomodations, expenses: BMS, Celgene, Janssen, Novartis, Takeda. GHJ has received consultancy fees, honoraria and speakers' bureau fees from Roche, Amgen, Janssen, and Merck Sharp and Dohme; and consultancy fees, honoraria, travel support, research funding, and speakers' bureau fees from Celgene Corporation and Takeda. MFK has received consultancy fees and travel support from Janssen, Bristol-Myers Squibb and Takeda; consultancy fees from AbbVie, Seattle Genetics, GSK; consultancy fees and honoraria from Amgen; and consultancy fees, and research funding from Karyopharm, Janssen and Celgene Corporation. All other authors report no COI.

LETTER TO THE EDITOR

The prognostic value of additional copies of chromosome 1q remains debated. To address this uncertainty, we performed a validation and meta-analysis of gain(1q) (3 copies) and amp(1q) (≥4copies) in 2,596 NDMM patients from three phase 3 trials. Gain(1q) and amp(1q) were both associated with shorter progression free (PFS) (hazard ratio (HR) 1.50, 95% confidence interval (CI) 1.16-1.95, P=0.002 and HR 1.65, 95% CI 1.25-2.19, $P=4.8x10^{-4}$, respectively) and overall survival (OS) (HR 1.85, 95% CI 1.43-2.39, $P=2.6x10^{-6}$ and HR 2.28, 95% CI 1.42-3.64, $P=5.8x10^{-4}$) by meta-analysis as well as in each trial individually; there was no statistically significant difference in outcome between the two copy number states. Gain(1q)/amp(1q) was independently prognostic in context of the Revised International Staging System (R-ISS) and refined risk prediction, by enabling identification of ultra high-risk tumors across trials.

Additional copies of 1q21 are one of the commonest genetic abnormalities in multiple myeloma (MM),[1] however their value as a prognostic marker remains controversial. While several studies showed that 1q21 gain is an independent poor prognostic factor, other studies have failed to support a relationship.[2–7] Previous studies have often been small or conducted outside of clinical trials, thus having limited power to demonstrate a relationship, especially as assays can be complicated by heterogeneity in terms of copy number (gain vs. amp(1q)).[6] In contrast to t(4;14) or del(17p), 1q21 status is not included among the high-risk markers listed by the International Myeloma Working Group (IMWG) Revised International Staging System (R-ISS),[8] and as a result it has invariably not been reported in most clinical trials over the past decade. Its prognostic relevance in the context of modern therapies is hence poorly defined.

To examine the relationship between gain(1q) and amp(1q) and prognosis and to address shortcomings in earlier studies we have studied 2,596 newly diagnosed (ND) MM trial patients receiving controlled therapy with proteasome inhibitor or immunomodulatory (IMiD) drugs.

We included patients from three independent phase 3 trials of NDMM with comparable baseline characteristics for validation purposes (**Table 1**), comprising the GMMG HD4 (n=341, median follow-up 93 months; EudraCT 2004-000944-26), GMMG MM5 (n=539, 58 months; EudraCT 2010-019173-16) and the UK NCRI Myeloma XI (MyXI, n=1,716, 65 months; NCT01554852) trials, designs and main outcomes of which have been previously reported.[9–11] All patients provided written informed consent. GMMG trials were approved by ethics committees of the University of Heidelberg and all participating sites, and MyXI was

approved by the UK South Central ethics committee (reference 09/H0604/79), research ethics committees at participating centers and the UK Medicines and Healthcare Products Regulatory Agency.

For GMMG, iFISH analysis was performed as described previously, with a cut-off of 10% for calling 1q abnormalities.[12] For MyXI, multiplexed qRT-PCR was used to determine translocation status, and multiplex ligation-dependent probe amplification (MLPA; MRC Holland) to call copy number aberrations (CNAs), with a cut-off equivalent to 20% for calling aberrations, as previously described.[2]

The association between categorical and continuous variables was examined using Fisher's exact test and the Wilcoxon rank test, respectively. Progression-free survival (PFS) was defined as time from enrolment to progression, according to International Myeloma Working Group criteria,[13] or death of any cause. Overall survival (OS) was time from enrolment to death of any cause. The Kaplan-Meier method was used for survival analyses. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Meta-analysis was performed using summary statistics under a random effect model. Cochran's Q and I^2 statistics were calculated to test for heterogeneity, with $I^2 \geq 75\%$ being considered substantial heterogeneity. All analyses were performed using R version 3.6.3.

The frequencies of 1q21 abnormalities were consistent between GMMG (HD4 and MM5 combined) and MyXI trial patients, with gain(1q) being seen in 28% and 27%, and amp(1q) detectable in 9% and 7% of patients, respectively. Laboratory parameters indicative of aggressive disease were associated with both gain and amp(1q), including reduced hemoglobin and platelet levels, elevated plasma creatinine and stage III of ISS and R-ISS (**Table 1**). Associations were stronger for amp(1q) for platelet levels, and stage III of ISS and R-ISS. Translocations t(4;14) and t(14;16) were enriched in gain and amp(1q), the association between amp(1q) and t(4;14) being stronger.

Not surprisingly, given amp(1q) was associated with aggressive disease, it negatively impacted outcome (**Fig. 1**). However, individually per trial and by meta-analysis gain(1q) was independently associated with poor outcome, too, with no discernible difference to amp(1q) and markedly overlapping confidence intervals, despite the significant size of the cohorts and long-term follow-up. For PFS, the meta-analysis HRs and 95% CIs were 1.50 (1.16-1.95), P=0.002 for gain(1q), and 1.65 (1.25-2.19), P<0.001 for amp(1q). The respective values for OS were 1.85 (1.43-2.39), P<0.001 and 2.28 (1.42-3.64), P<0.001, respectively. We observed moderate to substantial heterogeneity, since the effect sizes differed between

trials, with GMMG-MM5 showing highest HRs for both gain and amp(1q), yet consistent similarity in outcomes between the 1q copy number states, validating our finding in three independent datasets.

Our findings on gain(1q) are in contrast to recently published data that suggested only amp(1q) as a prognostic marker, but in line with reports by other groups.[4–6] Technical variability in calling 1q status, but in particular differences in follow-up time may account for some of these discrepancies: for HD4, a previously published analysis with shorter follow-up suggested inferior outcome for amp(1q) over gain(1q).[12] However, with extended follow-up shown here these differences levelled out as relapses in the gain(1q) group accumulated over time. Similar effects were observed for shorter vs. extended observation time in MyXI. This is in line with the ongoing evolution of 1q aberrations, which have been shown to be of clinical significance.[3,14] Of note, the recent study describing significant differences between amp(1q) and gain(1q) only had median follow-up of less than 2 years, which is short for exploratory survival analyses in NDMM.[6]

To examine the impact of different therapies on 1q CNAs, we performed landmark analyses from start of maintenance (**Supplemental Fig. 1)**. There was no significant difference between gain and amp(1q) for arm A (thalidomide) or arm B (bortezomib) of HD4, both being associated with adverse outcome. The same held true for MM5 and MyXI, where patients in respective treatment arms received lenalidomide maintenance for 2 years or until progression, respectively. Together, gain and amp(1q21) had a similar prognostic impact and neither ongoing bortezomib nor IMID therapy could mitigate it. This is in keeping with reports on gain(1q) significance in context of different induction therapies.[4,5] Since in summary these results did not demonstrate a significant difference in outcome between gain and amp(1q) , we subsequently jointly analyzed 1q CNAs under the overarching label ‘gain(1q)’.

To examine if gain(1q) is independent of the R-ISS, we performed multivariate Cox-regression analyses, including R-ISS risk markers individually. By meta-analysis, gain(1q) was associated with both PFS and OS (PFS: HR 1.42 (95% CI: 1.11-1.81), *P*=0.005; OS HR 1.68 (95% CI: 1.21-2.32), *P*=0.002, **Supplemental table 1**). The same held true for all R-ISS markers. Having established its independent impact, we investigated the additional value gain(1q) could bring to the R-ISS. Considering gain(1q) as an equivalent risk marker in the R-ISS, termed R-ISS-1q, 68/219 GMMG and 29/125 MyXI patients were upstaged from stage I to stage II and 35/480 GMMG and 46/600 MyXI patients from stage II to stage III, with nearly identical outcome discrimination between groups compared to the R-ISS. Median PFS for R-ISS-1q was 55.4 (GMMG) and 45.3 (MyXI) months for stage I, 35.7 and 28.5

months for stage II, and 21.5 and 18.4 months for stage III. The respective OS values were not reached (stage I), 89.7/67.2 months (stage II) and 41.9/36.3 months (stage III) (**Fig. 2**, **Supplemental Fig. 2)**.

In the current R-ISS, all patients with ISS II are assigned to stage II, irrespective of presence or number of risk markers. However, consistently across trials and in line with other data15, we found an increasingly adverse outcome, the more risk markers, including gain(1q), t(4;14), t(14;16), del(17p) and LDH, a patient's tumor showed (**Supplemental Fig. 2**). Specifically, patients with two or more co-occurring tumor risk markers (also called hits) had significantly worse outcome than those with a single marker in isolation. Combining this information with the R-ISS-1q, co-occurrence of ≥2 markers identified ~18% of stage II patients with significantly poorer outcome than the general stage II group (GMMG: median PFS 26.4 (95% CI: 22.9-34.5) months; MyIX: 19.6 (95% CI: 17.0-29.4) months, **Fig. 2 & Supplemental Fig. 2**). R-ISS-1q stage III patients with multi-hits had very poor outcome (GMMG: median PFS 18.5 (95% CI: 14.9-25.9) months; MyXI: 15.9 (95% CI: 11.8-20.0) months). Although multi-hit tumors have been recognized as a predictor of ultra high-risk disease,[15] they have not been investigated in context of R-ISS and are not assessed or reported in the majority of clinical trials to date. Our validation of multi-hit in multiple trial cohorts supports wider reporting, with all markers being accessible through standard FISH diagnostics.

In conclusion, gain(1q) is associated with inferior survival in NDMM, irrespective of current standard therapies, and should be considered as an independent risk factor. Whether additional risk factors may also refine risk prediction will be the subject of future studies and their useful integration subject to international consensus, taking accessibility to testing into account, which is well established for gain(1q). Whilst interaction of novel immunotherapies such as bispecific antibodies or CAR-T cells with tumor biology may differ, inclusion of gain(1q) testing should be considered in their clinical development. Our data supports integration of gain(1q) and the concept of multi-hits in future consensus risk prediction frameworks for individualizing care and improving tailored management for NDMM patients.

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TABLES

Table 1. Clinical and laboratory characteristics in relation to 1q status in GMMG and Myeloma XI.

	GMMG HD4 and MM5 combined					NCRI Myeloma XI				
Variable	n	1q21 normal n = 556[1]	Gain(1q21) n = 244[1]	Amp(1q21) n= 80[1]	p-value[2]	N	1q21 normal n = 1139[1]	Gain(1q21) n = 460[1]	Amp(1q21) n = 117[1]	p-value[2]
Male gender	512	320 (58%)	144 (59%)	48 (60%)		1034	691 (61%)	274 (60%)	69 (59%)	
Age	880	58 (52, 63)	58 (52, 64)	58 (53, 64)	0.4	1716	67 (59, 72)	67 (60, 74)	66 (62, 72)	0.1
WHO PS	873				0.09	1644				0.5
0		237 (43%)	106 (44%)	31 (39%)			406 (37%)	146 (33%)	42 (38%)	
1		269 (49%)	105 (44%)	39 (49%)			471 (43%)	192 (44%)	40 (36%)	
2		41 (7.4%)	21 (8.7%)	7 (8.8%)			165 (15%)	67 (15%)	20 (18%)	
3+		5 (0.9%)	9 (3.7%)	3 (3.8%)			56 (5.1%)	31 (7.1%)	8 (7.3%)	
Hemoglobin (g/l)	865	110 (95, 123)	99 (88, 114)	97 (88, 113)	**<0.001**	1716	108 (95, 120)	105 (93, 117)	98 (89, 109)	**<0.001**
Platelets (/nl)	880	254 (203, 312)	224 (170, 282)	186 (144, 262)	**<0.001**	1716	241 (194, 300)	222 (172, 275)	198 (138, 250)	**<0.001**
Creatinine (µmol/l)	867	92 (76, 121)	98 (80, 129)	105 (83, 141)	**0.03**	1716	86 (71, 109)	90 (72, 115)	93 (79, 118)	**0.018**
Calcium (mmol/l)	878	2.32 (2.20, 2.48)	2.36 (2.20, 2.50)	2.39 (2.25, 2.51)	0.12	1715	2.41 (2.31, 2.52)	2.41 (2.33, 2.57)	2.45 (2.38, 2.63)	**<0.001**
ISS	857				**0.006**	1032				**0.006**
I		229 (42%)	79 (33%)	23 (30%)			183 (27%)	59 (21%)	10 (14%)	
II		186 (34%)	86 (36%)	22 (30%)			298 (44%)	127 (46%)	26 (37%)	
III		127 (23%)	75 (31%)	30 (41%)			204 (30%)	90 (33%)	35 (49%)	
LDH > ULN	860	100 (18%)	66 (28%)	19 (24%)	**0.014**	1427	289 (30%)	117 (31%)	32 (33%)	0.8
t(4;14)	876	37 (6.7%)	38 (16%)	29 (37%)	**<0.001**	1716	90 (7.9%)	74 (16%)	37 (32%)	**<0.001**
t(14;16)	860	7 (1.3%)	10 (4.3%)	4 (5.1%)	**0.009**	1716	25 (2.2%)	21 (4.6%)	4 (3.4%)	**0.031**
del(17p)	879	65 (12%)	27 (11%)	8 (10%)	0.9	1716	101 (8.9%)	35 (7.6%)	12 (10%)	0.6
R-ISS	819				**<0.001**	868				**0.004**
I		151 (29%)	53 (23%)	15 (21%)			96 (16%)	25 (11%)	4 (6.9%)	
II		312 (60%)	132 (58%)	36 (50%)			401 (69%)	163 (71%)	36 (62%)	
III		56 (11%)	43 (19%)	21 (29%)			85 (15%)	40 (18%)	18 (31%)	
Light chain	879				**<0.001**	1701				**<0.001**
lambda		147 (26%)	98 (40%)	38 (48%)			320 (28%)	179 (39%)	50 (43%)	

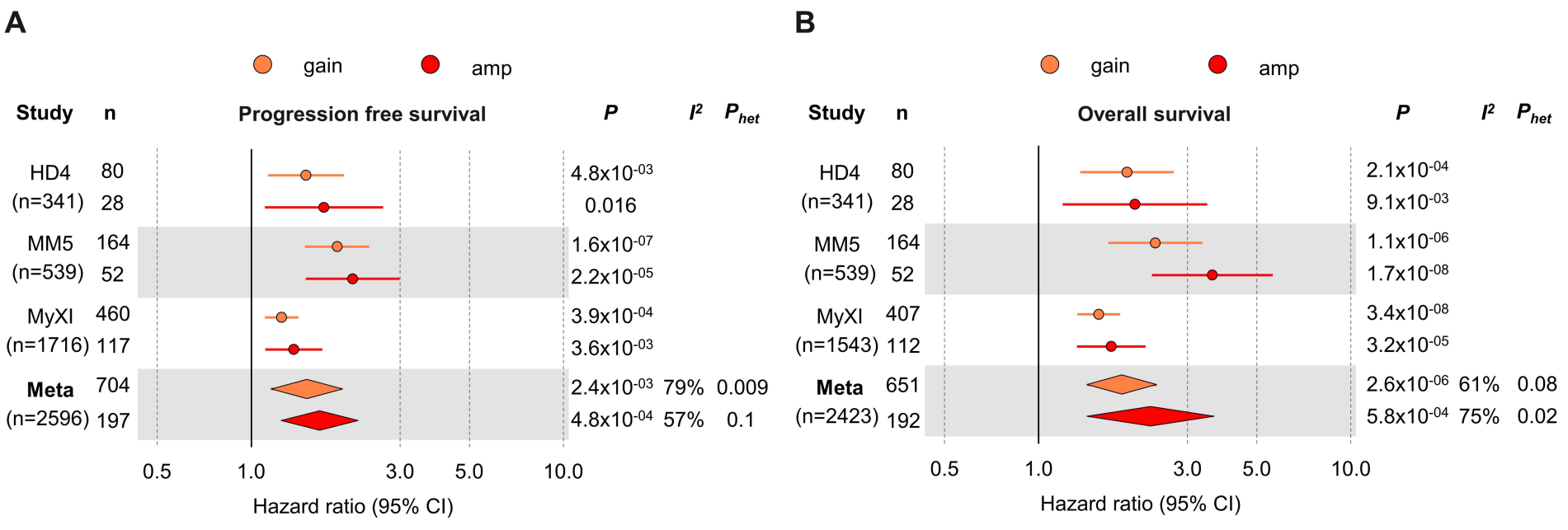
[1]Statistics presented: n (%); Median (IQR)

[2]Statistical tests performed: chi-square test of independence; Kruskal-Wallis test; Fisher's exact test

FIGURE LEGENDS

FIGURE 1. Prognostic impact of gain and amplification of 1q21 in multiple myeloma. Forest plot of a meta-analysis for **(A)** PFS and **(B)** OS for gain(1q) (orange) and amp(1q) (red), validating the prognostic impact of both lesions in the independent GMMG HD4 and MM5 and the NCRI Myeloma XI trials. Column "n" shows the number of patients with gain(1q) or amp(1q) per trial, respectively. The total number of patients included per trial is shown in brackets in column "study". Circles show HR point estimates and lines 95% CIs. Diamonds depict summary HRs computed under a random-effects model, with 95% CIs given by their width. Unbroken vertical lines represent the null value (HR = 1.0).

FIGURE 2. Prognostic impact of gain(1q) in context of and in combination with other risk markers in multiple myeloma. A-B: Kaplan-Meier overlay plots demonstrate the impact of including gain(1q) as a risk marker in R-ISS, termed R-ISS-1q. Plots show OS for R-ISS and for R-ISS-1q for **A)** GMMG and **B)** Myeloma XI. **C-D:** Kaplan-Meier plots are shown for OS for GMMG (**C**) and Myeloma XI (**D**) patients according to the number of risk markers present in these patients, including gain(1q) and R-ISS markers del(17p), t(4;14), t(14;16) or LDH above upper limit of normal, respectively. **E-F:** Kaplan-Meier plots for OS showing discrimination of high- and ultra-high-risk groups by including information on co-occurrence of risk markers, called multi-hit, for further sub-grouping of R-ISS-1q stage II and stage III tumors in **E)** GMMG and **F)** Myeloma XI. The corresponding OS plots are presented in Supplemental Data.


A
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HD4
(n=341)
80
28
4.8x10-03
0.016
MM5
(n=539)
164
52
1.6x10-07
2.2x10-05
MyXI
(n=1716)
460
117
3.9x10-04
3.6x10-03
Meta
(n=2596)
704
197
2.4x10-03
4.8x10-04
79%
57%
0.009
0.1
0.5
1.0
3.0
5.0
10.0
Hazard ratio (95% CI)
B
gain
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Study
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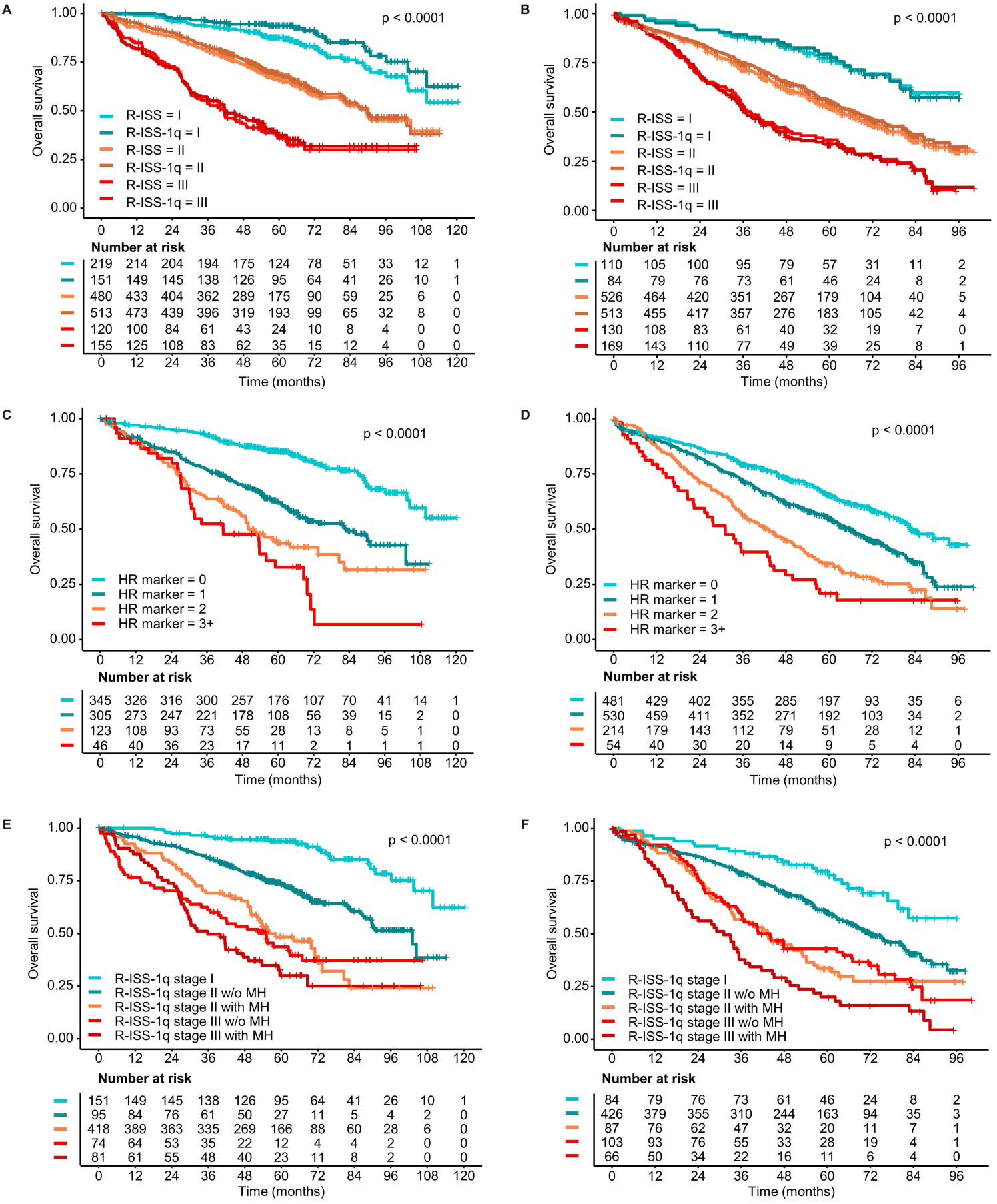
Overall survival
P
I²
P het
HD4
(n=341)
80
28
2.1x10-04
9.1x10-03
MM5
(n=539)
164
52
1.1x10-06
1.7x10-08
MyXI
(n=1543)
407
112
3.4x10-08
3.2x10-05
Meta
(n=2423)
651
192
2.6x10-06
5.8x10-04
61%
75%
0.08
0.02
0.5
1.0
3.0
5.0
10.0
Hazard ratio (95% CI)

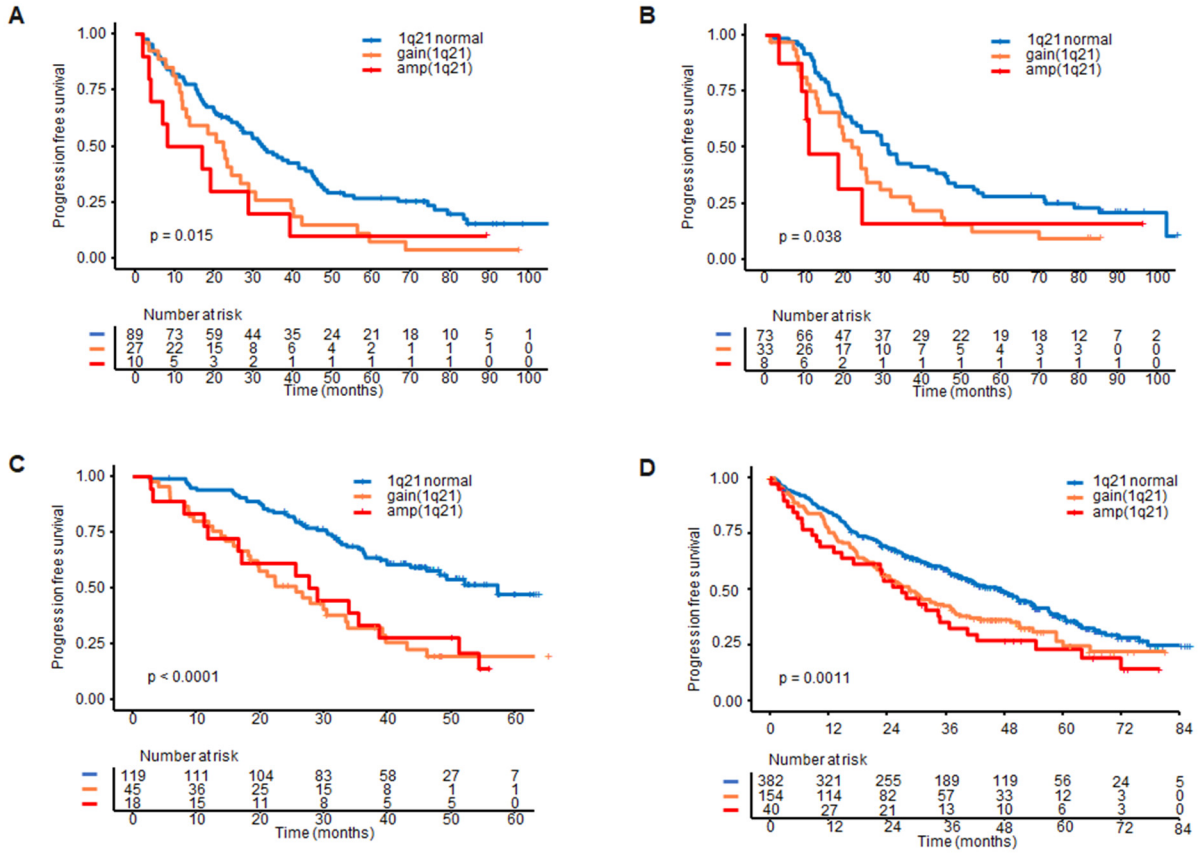

A
p < 0.0001
Overall survival
1.00
0.75
0.50
0.25
0.00
R-ISS = I
R-ISS-1q = I
R-ISS = II
R-ISS-1q = II
R-ISS = III
R-ISS-1q = III
0 12 24 36 48 60 72 84 96 108 120
Number at risk
219 214 204 194 175 124 78 51 33 12 1
151 149 145 138 126 95 64 41 26 10 1
480 433 404 362 289 175 90 59 25 6 0
513 473 439 396 319 193 99 65 32 8 0
120 100 84 61 43 24 10 8 4 0 0
155 125 108 83 62 35 15 12 4 0 0
0 12 24 36 48 60 72 84 96 108 120
Time (months)
B
p < 0.0001
Overall survival
1.00
0.75
0.50
0.25
0.00
R-ISS = I
R-ISS-1q = I
R-ISS = II
R-ISS-1q = II
R-ISS = III
R-ISS-1q = III
0 12 24 36 48 60 72 84 96
Number at risk
110 105 100 95 79 57 31 11 2
84 79 76 73 61 46 24 8 2
526 464 420 351 267 179 104 40 5
513 455 417 357 276 183 105 42 4
130 108 83 61 40 32 19 7 0
169 143 110 77 49 39 25 8 1
0 12 24 36 48 60 72 84 96
Time (months)
C
p < 0.0001
Overall survival
1.00
0.75
0.50
0.25
0.00
HR marker = 0
HR marker = 1
HR marker = 2
HR marker = 3+
0 12 24 36 48 60 72 84 96 108 120
Number at risk
345 326 316 300 257 176 107 70 41 14 1
305 273 247 221 178 108 56 39 15 2 0
123 108 93 73 55 28 13 8 5 1 0
46 40 36 23 17 11 2 1 1 1 0
0 12 24 36 48 60 72 84 96 108 120
Time (months)
D
p < 0.0001
Overall survival
1.00
0.75
0.50
0.25
0.00
HR marker = 0
HR marker = 1
HR marker = 2
HR marker = 3+
0 12 24 36 48 60 72 84 96
Number at risk
481 429 402 355 285 197 93 35 6
530 459 411 352 271 192 103 34 2
214 179 143 112 79 51 28 12 1
54 40 30 20 14 9 5 4 0
0 12 24 36 48 60 72 84 96
Time (months)
E
p < 0.0001
Overall survival
1.00
0.75
0.50
0.25
0.00
R-ISS-1q stage I
R-ISS-1q stage II w/o MH
R-ISS-1q stage II with MH
R-ISS-1q stage III w/o MH
R-ISS-1q stage III with MH
0 12 24 36 48 60 72 84 96 108 120
Number at risk
151 149 145 138 126 95 64 41 26 10 1
95 84 76 61 50 27 11 5 4 2 0
418 389 363 335 269 166 88 60 28 6 0
74 64 53 35 22 12 4 4 2 0 0
81 61 55 48 40 23 11 8 2 0 0
0 12 24 36 48 60 72 84 96 108 120
Time (months)
F
p < 0.0001
Overall survival
1.00
0.75
0.50
0.25
0.00
R-ISS-1q stage I
R-ISS-1q stage II w/o MH
R-ISS-1q stage II with MH
R-ISS-1q stage III w/o MH
R-ISS-1q stage III with MH
0 12 24 36 48 60 72 84 96
Number at risk
84 79 76 73 61 46 24 8 2
426 379 355 310 244 163 94 35 3
87 76 62 47 32 20 11 7 1
103 93 76 55 33 28 19 4 1
66 50 34 22 16 11 6 4 0
0 12 24 36 48 60 72 84 96
Time (months)

SUPPLEMENTAL TABLES

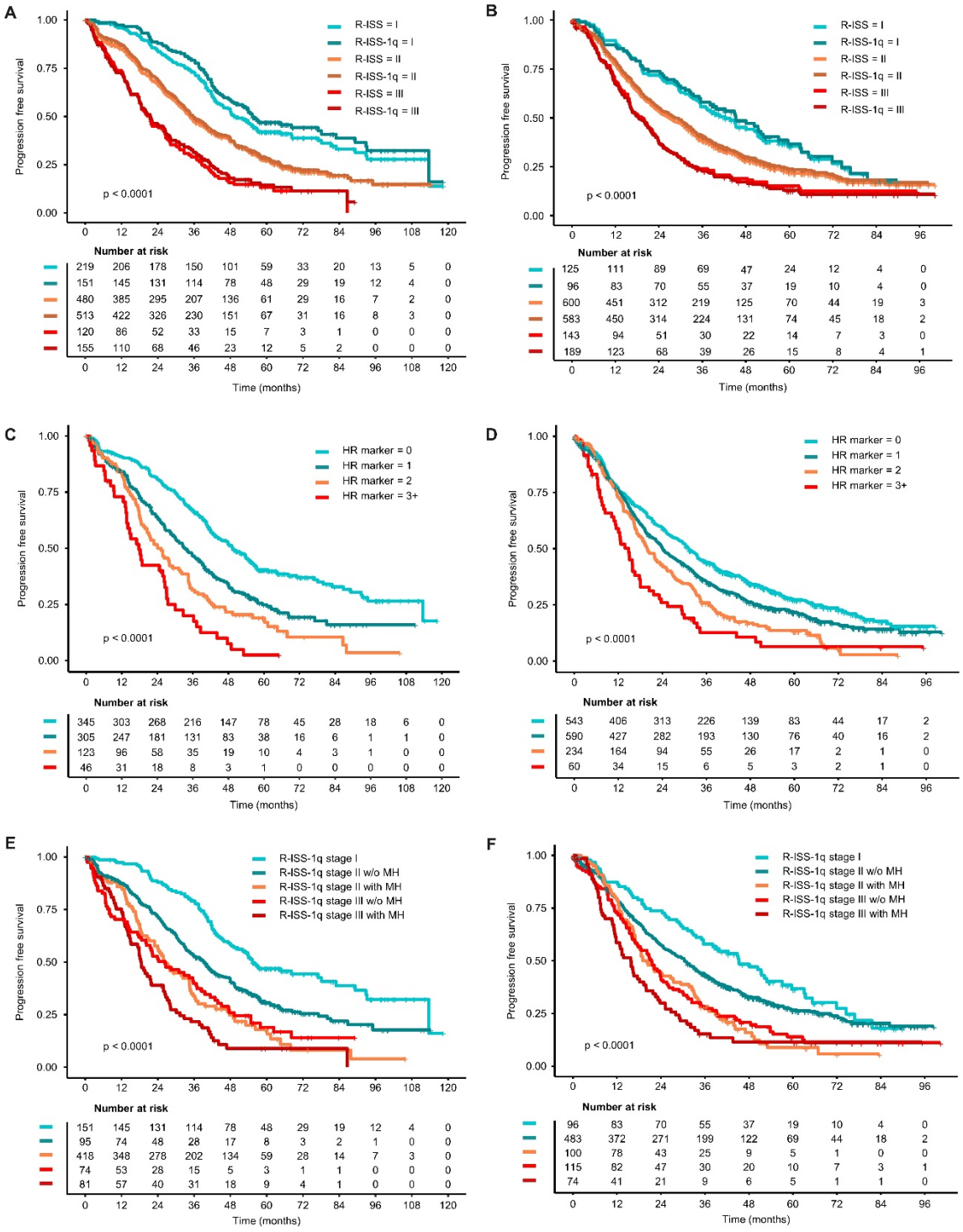
Supplemental Table 1. Multivariate Cox-regression analysis including gain(1q) and individual R-ISS risk variables.

		PFS					OS				
Variable	**Study**	**Coef**	**SE**	***P***	**I^2**	**P_{het}**	**Coef**	**SE**	***P***	**I^2**	**P_{het}**
gain(1q)	HD4	0.34	0.15	0.02			0.50	0.18	0.006		
	MM5	0.56	0.12	<0.001			0.83	0.17	<0.001		
	MyXI	0.18	0.08	0.04			0.29	0.11	0.008		
	Meta	0.35	0.12	**0.005**	72	0.03	0.52	0.17	**0.002**	72	0.03
ISS II	HD4	0.30	0.16	0.06			0.56	0.21	0.008		
	MM5	0.42	0.14	0.002			0.70	0.22	0.002		
	MyXI	0.17	0.10	0.10			0.35	0.15	0.02		
	Meta	0.27	0.08	**<0.001**	11	0.32	0.48	0.11	**<0.001**	0	0.40
ISS III	HD4	0.52	0.17	0.003			0.79	0.23	<0.001		
	MM5	0.53	0.14	<0.001			1.07	0.22	<0.001		
	MyXI	0.44	0.11	<0.001			0.81	0.15	<0.001		
	Meta	0.48	0.08	**<0.001**	0	0.87	0.87	0.11	**<0.001**	0	0.56
t(4;14)	HD4	0.48	0.19	0.01			0.40	0.22	0.07		
	MM5	0.23	0.18	0.21			0.34	0.22	0.13		
	MyXI	0.54	0.13	<0.001			0.41	0.16	0.01		
	Meta	0.44	0.09	**<0.001**	4	0.35	0.39	0.11	**<0.001**	0	0.97
t(14;16)	HD4	0.04	0.43	0.93			-0.02	0.52	0.97		
	MM5	0.70	0.29	0.02			0.82	0.36	0.02		
	MyXI	0.33	0.23	0.16			0.46	0.26	0.08		
	Meta	0.40	0.17	**0.02**	0	0.40	0.50	0.20	**0.01**	0	0.40
del(17p)	HD4	0.70	0.22	0.001			0.94	0.24	<0.001		
	MM5	0.39	0.17	0.02			0.65	0.21	0.002		
	MyXI	0.55	0.12	<0.001			0.86	0.15	<0.001		
	Meta	0.53	0.09	**<0.001**	0	0.50	0.82	0.11	**<0.001**	0	0.61
LDH > normal	HD4	0.20	0.17	0.24			0.36	0.20	0.07		
	MM5	0.29	0.13	0.03			0.09	0.19	0.63		
	MyXI	0.10	0.09	0.26			0.30	0.11	0.006		
	Meta	0.16	0.07	**0.01**	0	0.47	0.27	0.09	**0.002**	0	0.56

SUPPLEMENTAL FIGURES



Supplemental Fig. 1. Prognostic impact of gain and amplification of 1q21 in multiple myeloma. Kaplan-Meier plots for PFS landmarked from start of maintenance therapy for **A)** the thalidomide treatment arm of HD4, **B)** the bortezomib treatment arm of HD4, **C)** MM5 arms A1 and A2, which received lenalidomide for 2 years, and **D)** the lenalidomide maintenance arm of NCRI Myeloma XI, from maintenance randomization.



Supplemental Fig. 2. Prognostic impact of gain(1q) and the number of high risk markers in context of the R-ISS. A-B: Kaplan-Meier overlay plots demonstrate the impact of including gain(1q) as a risk marker in R-ISS, termed R-ISS-1q. Plots show PFS for R-ISS and for R-ISS-1q for **A)** GMMG and **B)** Myeloma XI. **C-D:** Kaplan-Meier plots are shown for PFS for GMMG (**C**) and Myeloma XI (**D**) patients according to the number of risk markers present in these patients, including gain(1q) and R-ISS markers del(17p), t(4;14), t(14;16) or LDH above upper limit of normal, respectively. **E-F:** Kaplan-Meier plots for PFS showing discrimination of high- and ultra-high-risk groups by including information on co-occurrence of risk markers, called multi-hit, for further sub-grouping of R-ISS-1q stage II and stage III tumors in **E)** GMMG and **F)** Myeloma XI.