

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

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) ( $\geq 4$  copies) in 2,596 patients with newly diagnosed multiple myeloma (NDMM) from three phase III trials. Gain(1q) and amp(1q) were both associated with shorter progression-free survival (hazard ratio [HR]=1.50, 95% confidence interval [95% CI]: 1.16-1.95,  $P=0.002$  and HR=1.65, 95% CI: 1.25-2.19,  $P=4.8 \times 10^{-4}$ , respectively) and overall survival (HR=1.85, 95% CI: 1.43-2.39,  $P=2.6 \times 10^{-6}$  and HR=2.28, 95% CI: 1.42-3.64,  $P=5.8 \times 10^{-4}$ ) 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 the 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;<sup>1</sup> 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.<sup>2-7</sup> 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, i.e., gain *versus* amp(1q).<sup>6</sup> 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's R-ISS,<sup>8</sup> 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.

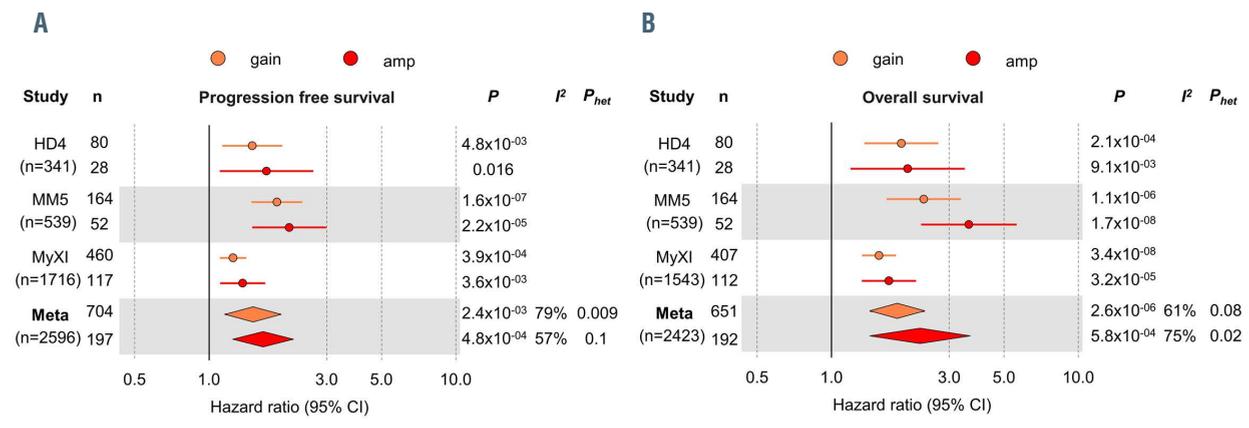
To examine the relationship between gain(1q) and amp(1q) and prognosis and to address shortcomings in earlier studies we investigated 2,596 NDMM trial patients receiving controlled therapy with a proteasome inhibitor or an immunomodulatory drug.

We included patients from three independent phase III trials of NDMM with comparable baseline characteristics

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

Variable	GMMG HD4 and MM5 combined					NCRI Myeloma XI				
	N.	1q21 normal n = 556 <sup>a</sup>	Gain(1q21) n = 244 <sup>a</sup>	Amp(1q21) n = 80 <sup>a</sup>	P-value <sup>b</sup>	N.	1q21 normal n = 1139 <sup>a</sup>	Gain(1q21) n = 460 <sup>a</sup>	Amp(1q21) n = 117 <sup>a</sup>	P-value <sup>b</sup>
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 (x10 <sup>9</sup> /L)	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 ( $\mu$ mol/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 ( $\mu$ mol/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 $\lambda$	879	147 (26%)	98 (40%)	38 (48%)	<0.001	1701	320 (28%)	179 (39%)	50 (43%)	<0.001

<sup>a</sup>Statistics presented as n (%) or median (interquartile range). <sup>b</sup>Statistical tests performed:  $\chi^2$  test of independence; Kruskal-Wallis test; Fisher exact test GMMG: German-speaking Myeloma Multicenter Group; NCRI: National Cancer Research Institute; WHO PS: World Health Organization performance status; ISS: International Staging System; LDH: lactate dehydrogenase; ULN: upper limit of normal; R-ISS: Revised International Staging System.



**Figure 1.** Prognostic impact of gain and amplification of 1q21 in multiple myeloma. Forest plot of a meta-analysis for (A) progression-free survival and (B) overall survival for gain(1q) (orange) and amp(1q) (red), validating the prognostic impact of both lesions in the independent GMMG HD4 and MM5 and the NCR1 Myeloma XI trials. Column "n" shows the number of patients with gain(1q) or amp(1q) per trial. The total number of patients included per trial is shown in brackets in the column "study". Circles show hazard ratio (HR) point estimates and lines indicate the 95% confidence intervals (95% CI). Diamonds depict summary hazard ratios computed under a random-effects model, with 95% confidence intervals given by their width. Unbroken vertical lines represent the null value (HR = 1.0).

for validation purposes (Table 1), comprising the German-speaking Myeloma Multicenter Group (GMMG) HD4 trial (n=341, median follow-up 93 months; EudraCT 2004-000944-26), the GMMG MM5 trial (n=539, 58 months; EudraCT 2010-019173-16) and the UK National Cancer Research Institute (NCR1) Myeloma XI trial (MyXI, n=1,716, 65 months; NCT01554852); the designs and main outcomes of these trials have been previously reported.<sup>9-11</sup> 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, interphase fluorescence *in situ* hybridization analysis was performed as described previously, with a cut-off of 10% for calling 1q abnormalities.<sup>12</sup> For MyXI, multiplexed quantitative reverse transcriptase polymerase chain reaction analysis was used to determine translocation status, and multiplex ligation-dependent probe amplification (MRC Holland) to call copy number aberrations, with a cut-off equivalent to 20% for calling aberrations, as previously described.<sup>2</sup>

The association between categorical and continuous variables was examined using the Fisher exact test and the Wilcoxon rank test, respectively. Progression-free survival was defined as time from enrollment to progression, according to International Myeloma Working Group criteria,<sup>13</sup> or death of any cause. Overall survival was time from enrollment to death of any cause. The Kaplan-Meier method was used for survival analyses. Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals. Meta-analysis was performed using summary statistics under a random effect model. The Cochran Q and I<sup>2</sup> statistics were calculated to test for heterogeneity, with I<sup>2</sup> ≥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 the ISS and R-ISS (Table 1). Associations were stronger for amp(1q) for platelet levels, and stage III of the 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 that amp(1q) was associated with aggressive disease, it had a negative impact on outcome (Figure 1). However, individually per trial and by meta-analysis gain(1q) was independently associated with poor outcome, too, with no discernible difference from amp(1q) and markedly overlapping confidence intervals, despite the significant size of the cohorts and long-term follow-up. For progression-free survival, the meta-analysis hazard ratios and 95% confidence intervals 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 overall survival 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 the highest hazard ratios 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 suggesting that only amp(1q) is a prognostic marker, but in line with reports from other groups.<sup>4-6</sup> Technical variability in calling 1q status and, 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).<sup>12</sup> 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 *versus* 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.<sup>3,14</sup> Of note, a recent study describing significant differences between amp(1q) and gain(1q) only had a median follow-up of less than 2 years, which is short for exploratory survival analyses in NDMM.<sup>6</sup>

To examine the impact of different therapies on 1q copy number aberrations, we performed landmark analy-

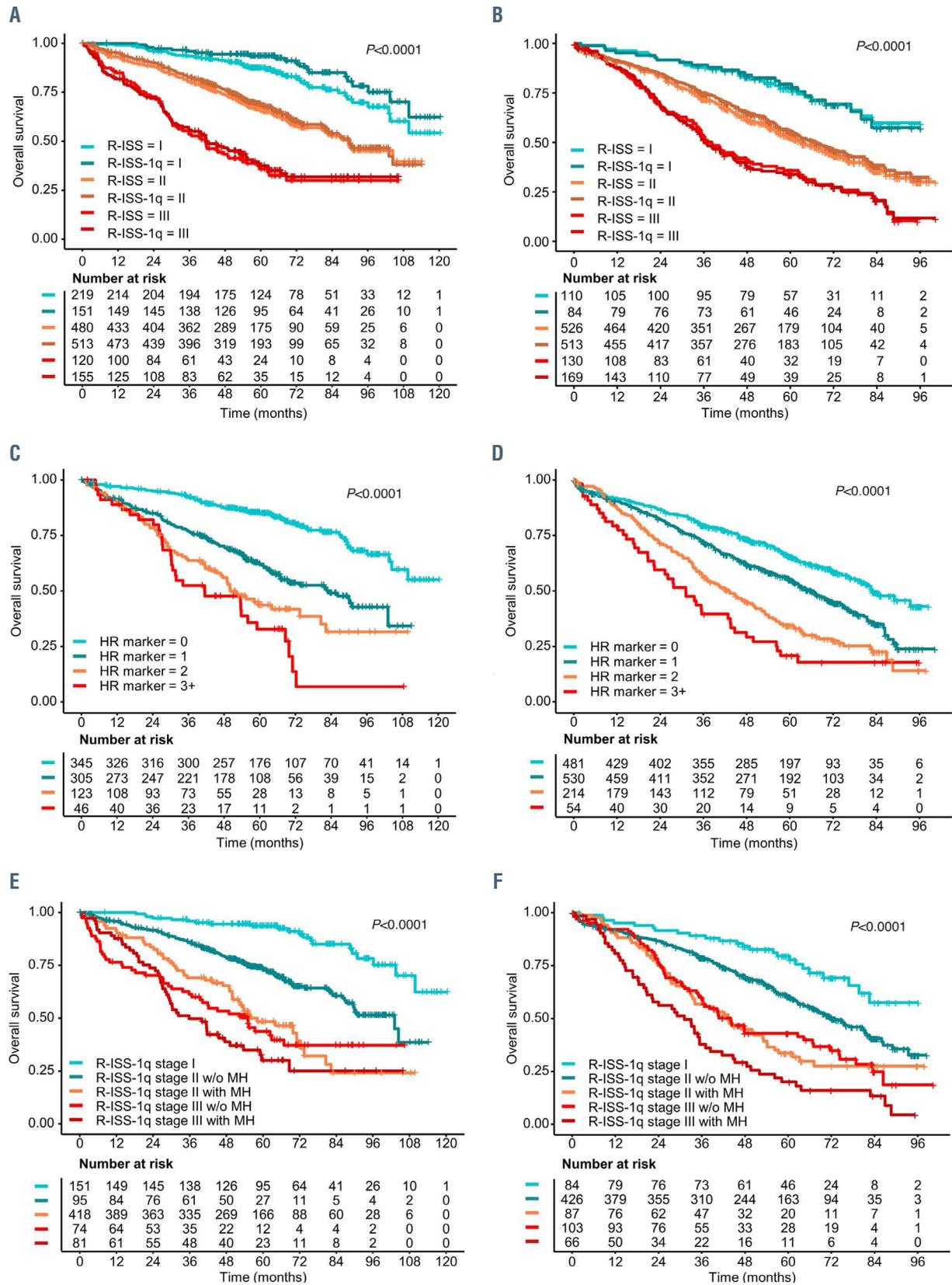


Figure 2. Prognostic impact of gain(1q) in the context of and in combination with other risk markers in multiple myeloma. (A, B) Kaplan-Meier overlay plots demonstrate the impact of including gain(1q) as a risk marker in the Revised International Staging System (R-ISS), termed R-ISS-1q. Plots show overall survival for R-ISS and for R-ISS-1q for the GMMG trials (A) and the Myeloma XI trial (B). (C, D) Kaplan-Meier plots are shown for overall survival of patients in the GMMG trials (C) and Myeloma XI trial (D) 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 lactate dehydrogenase above the upper limit of normal. (E, F) Kaplan-Meier plots for overall survival showing discrimination of high- and ultra-high-risk groups by including information on co-occurrence of risk markers, called multi-hits (MH), for further subgrouping of R-ISS-1q stage II and stage III tumors in GMMG trials (E) and the Myeloma XI trial (F). The corresponding progression-free survival plots are presented in the *Online Supplementary Data*.

ses from the start of maintenance (*Online Supplementary Figure S1*). 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, in which patients received lenalidomide maintenance for 2 years or until progression in the respective treatment arms. Together, gain and amp(1q21) had a similar prognostic impact and neither ongoing bortezomib nor immunomodulatory drug therapy could mitigate it. This is in keeping with reports on the significance of gain(1q) in the context of different induction therapies.<sup>4,5</sup> Since in summary these results did not demonstrate a significant difference in outcome between gain and amp(1q), we subsequently analyzed 1q copy number aberrations 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 progression-free and overall survival (progression-free survival: HR=1.42 [95% CI: 1.11-1.81],  $P=0.005$ ; overall survival HR=1.68 [95% CI: 1.21-2.32],  $P=0.002$ ) (*Online Supplementary Table S1*). 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 that based on the R-ISS. The median progression-free survival 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 overall survival values were not reached (stage I), 89.7/67.2 months (stage II) and 41.9/36.3 months (stage III) (Figure 2, *Online Supplementary Figure S2*).

In the current R-ISS, all patients with ISS II are assigned to stage II, irrespective of the presence or number of risk markers. However, consistently across trials and in line with other data,<sup>15</sup> we found an increasingly adverse outcome, the more risk markers, including gain(1q), t(4;14), t(14;16), del(17p) and lactate dehydrogenase, a patient's tumor showed (*Online Supplementary Figure S2*). 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 two or more markers identified ~18% of stage II patients with significantly poorer outcome than the general stage II group (GMMG: median progression-free survival 26.4 [95% CI: 22.9-34.5] months; MyXI: 19.6 [95% CI: 17.0-29.4] months) (Figure 2, *Online Supplementary Figure S2*). R-ISS-1q stage III patients with multi-hits had very poor outcome (GMMG: median progression-free survival 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,<sup>15</sup> they have not been investigated in the context of R-ISS and are not assessed or reported in the majority of clinical trials to date. Our validation of multi-hits in multiple trial cohorts supports wider reporting, with all markers being accessible through standard fluorescence *in situ* hybridization 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). While the interaction of novel immunotherapies such as bispecific antibodies or chimeric antigen receptor T cells with tumor biology may differ, inclusion of gain(1q) testing should be considered in their clinical development. Our data support integration of gain(1q) and the concept of multi-hits in future consensus risk prediction frameworks for individualizing care and improving tailored management of NDMM patients.

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