Am J Cancer Res 2025;15(2):501-516
www.ajcr.us /ISSN:2156-6976/ajcr0160493

Original Article

Dissecting the high-risk property of 1q gain/amplification in patients with newly diagnosed multiple myeloma

Xinyue Liang[1,2*], Weiling Xu[3*], Fan Zhou[4], Wenyang Huang[5], Xingcheng Yi[2], Yingjie Zhang[1], Yurong Yan[1], Nan Zhang[1], Jingxuan Wang[1], Xiaoxiao Sun[1], Rui Hu[1], Yufeng Zhu[1], Xintian Ma[1], Yue Sun[2], Maozhou Lan[2], Mengtuan Long[2], Shaji K Kumar[6], Yun Dai[2], Fengyan Jin[1]

[1]Department of Hematology, The First Hospital of Jilin University, Changchun, Jilin, China; [2]Laboratory of Cancer Precision Medicine, The First Hospital of Jilin University, Changchun, Jilin, China; [3]Department of Radiology, The First Hospital of Jilin University, Changchun, Jilin, China; [4]Department of Hematology and Oncology, Shanghai Jing'an District Zhabei Central Hospital, Shanghai, China; [5]State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Tianjin, China; [6]Division of Hematology, Mayo Clinic College of Medicine, Rochester, MN, USA. [*]Equal contributors.

Received September 12, 2024; Accepted January 27, 2025; Epub February 15, 2025; Published February 28, 2025

Abstract: 1q gain/amplification (1q+) is the most common cytogenetic abnormality (CA), with a frequency of 30-50% in patients with newly diagnosed multiple myeloma (NDMM). Although accumulating evidence supports 1q+ as a "high-risk" CA (HRCA), several issues remain to be addressed to understand its true prognostic property. We retrospectively analyzed a cohort of 934 patients with NDMM from three centers in China, who had baseline data available for 1q+ [including 1q21 gain (3 copies) and amplification (> 3 copies)] detected by fluorescence in situ hybridization in isolated CD138$^+$ cells, and who received first-line treatment with novel agents including proteasome inhibitors, immunomodulatory drugs, or both. Minimal residue disease (MRD) was assessed using next-generation flow cytometry. In this cohort, 1q+ patients accounted for 53% of all patients. 1q+ patients were characterized by larger tumor burden, more advanced diseases, adverse complications, and frequent concurrence of other CAs (particularly HRCAs) at diagnosis. Concurrence of HRCAs [del(17p), t(4;14), and t(14;16); known as double-hit MM], but not standard-risk CA, markedly worsened the outcome of 1q+ patients, compared to those with 1q+ only (progression-free survival/PFS: hazard ratio/HR 1.63, 95% confidence interval/CI 1.21-2.20, $P = 0.0013$; overall survival/OS: HR 1.96, 95% CI 1.40-2.74, $P < 0.0001$). 1q+ modulated the risk levels defined by the Revised International Staging System (R-ISS). Although the overall response rate was not significantly different between patients with or without 1q+, fewer 1q+ patients achieved complete response or better and minimal residue disease negativity (MRD$^-$). MRD$^-$ attainment substantially prolonged PFS (HR 4.03, 95% CI 2.59-6.29, $P < 0.0001$) and OS (HR 3.72, 95% CI 2.24-6.19, $P < 0.0001$) of 1q+ patients. While 1q+ patients had relatively shorter MRD$^-$ duration, sustained MRD$^-$ significantly improved the PFS and OS of 1q+ patients. Together, 1q+ is an HRCA and a major component of double-hit MM, while the risk-adapted and MRD-tailored therapy may best help manage this high-risk population.

Keywords: 1q gain, cytogenetic abnormality, double hit, minimal residue disease, multiple myeloma

Introduction

Multiple myeloma (MM) is a common hematologic malignancy characterized by diverse clinical features, therapeutic responses, and outcomes, largely driven by its high biological heterogeneity [1]. The introduction of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and more recently CD38 monoclonal antibodies (mAbs) and chimeric antigen receptor T-cell immunotherapy (CAR-T) has significantly improved the therapeutic response and survival of MM patients [2]. However, a number of patients still experience poor prognosis (e.g., early relapse and mortality) with a predicted overall survival (OS) less than 3 years, known as high-risk MM (HRMM) [3].

Recurrent cytogenetic abnormalities (CAs) are considered the most robust prognostic predictor for the outcome of patients with newly diagnosed MM (NDMM) [1], with del(17p), t(4;14),

https://doi.org/10.62347/FXVH4425

t(14;16), and t(14;20) defined as high-risk CAs (HRCAs) by the International Myeloma Working Group (IMWG) [4]. 1q gain/amplification (1q+) is the most common CA, accounting for 20-50% of NDMM patients [5, 6]. Most evidence indicates 1q+ as an independent prognostic risk factor [7]. However, this could not be verified in some studies [8]. Several studies reveal that only 1q amplification (copy number ≥ 4), but not 1q gain (3 copies), displays an inferior impact on prognosis [9]. Nonetheless, owing to accumulating evidence supporting its high-risk property, 1q+ has been included in multiple risk stratification systems developed recently, including the Second Revision of the International Staging System (R2-ISS) and the Mayo Additive Staging System (MASS) [10, 11]. Because 1q+ often co-exists with other HRCAs [12], a debate arises about whether 1q+ represents a true driver of poor prognosis or just a byproduct of high-risk biology [13]. Importantly, as 1q+ confers intrinsic resistance to frontline agents (e.g., bortezomib) [6, 14], an effective therapy for 1q+ patients is lacking [15]. Moreover, 1q+ patients display significantly shorter survival than those without 1q+ in the majority of the randomized trials evaluating various novel agents and therapies [16]. 1q+ remains an adverse CA even in the patients who received autologous stem cell transplant (ASCT) and post-transplant maintenance [17]. It remains uncertain whether the newer therapies (e.g., CD38 mAbs, CAR-T, XPO-1 inhibitors, etc.) would benefit this subset of high-risk patients [18, 19]. Of note, recent findings suggest that attainment of undetectable minimal residual disease (MRD^-) may abrogate the adverse impact of certain HRCAs [13, 20]. Alternatively, risk-adapted maintenance after induction with bortezomib, lenalidomide, and dexamethasone (VRd) has been proposed to manage patients carrying HRCAs [21]. However, the prognostic effect of 1q+ is highly heterogeneous and probably dynamic (e.g., due to changes in the MRD status) [22]. Therefore, it is important to better understand the high-risk property of 1q+, to personalize risk-adapted therapy for heterogeneous 1q+ patients. To this end, we conducted this retrospective study to dissect the prognostic impact of 1q+ (1q gain or amplification) using a large cohort involving three participating centers and an independent cohort from the Analysis of the Clinical Outcomes in Multiple Myeloma to Personal Assessment (CoMMpass) trial (NCT01454297, available via http://research.themmrf.org).

Materials and methods

Patient selection

This was a multi-center retrospective study that analyzed patient data from three centers. For patients to be eligible for this study, the following criteria must be met: who were newly diagnosed with MM, treated with PI, IMiD, or both for first-line treatment, and had baseline 1q+ [including 1q21 gain (3 copies) and amplification (> 3 copies) data available. The exclusion criteria included a) Baseline 1q+ information not available; b) Treatment information not available; or c) First-line treatment without novel agents (PIs and/or IMIDs). To validate the effect of upfront treatment on the outcome of 1q+ patients, we also obtained the data for patients eligible for this study from the CoMMpass cohort. The study was approved by the Institutional Review Board (IRB) of the First Hospital of Jilin University (Approval # 2022-069) and conducted in accordance with the Declaration of Helsinki. Written informed consent for participation in this study was obtained from all patients.

Fluorescence in situ hybridization (FISH)

FISH was routinely performed to assess CAs in bone marrow (BM) CD138-positive cells as reported previously [23]. The probes for 1q+, deletion 17p [del(17p)], deletion 1p [del(1p)], and deletion 13q [del(13q)] were obtained from Kanglu Biotechnology Co., Ltd. (Wuhan, China). The probes for t(4;14), t(14;16), and t(11;14) were purchased from Abbott Laboratories S.A. (Shanghai, China). Cutoff values for defining the presence of CAs were adopted from the routine diagnostic criteria in our real-life practice [23]. Del(17p), t(4;14), and t(14;16) were defined as HRCAs according to the Revised International Staging System (R-ISS) [24].

Next-generation flow cytometry (NGF)

NGF was performed to monitor the MRD status in BM samples, using a modified 2-tube 8-color assay (tube 1: cKappa-FITC/cLambda-PE/CD138-Percp-cy5.5/CD27-PE-CY7/CD22-APC/CD19-APC-H7/CD38-BV421/CD45-Viogreen;

tube 2: CD56-FITC/CD200-PE/CD28-Percp-cy5.5/CD117-PE-CY7/CD19-APC/CD20-APC-H7/CD38-BV421/CD45-Viogreen) as reported earlier [25]. The absence of PCs or their percentage below the limit of detection (LOD) was considered MRD negative [26]. Duration of MRD negativity was defined as the time from the first achievement of MRD negativity to becoming MRD-positive, progressive disease (PD), or last follow-up. Sustained MRD negativity was defined as MRD negativity lasting for a minimum of a year, according to the IMWG consensus criteria [27]. Loss of MRD negativity was defined as conversion from MRD negativity to becoming MRD-positive and/or PD within a year.

Clinical outcomes

Time to relapse (TTR) was defined as the time from the start of initial therapy until disease relapse. Progression-free survival (PFS) was defined as the duration from the start of initial therapy until disease progression, relapse, or death due to any cause. Patients who did not progress or relapse were censored on the last date when they were seen alive and event-free. OS was defined as the time from the start of initial therapy to death from any cause or the last follow-up date. Therapeutic responses were evaluated according to the IMWG's criteria [27, 28].

Statistical analysis

The data for baseline characteristics are expressed as the number and percentage of patients. The Chi-square test or Fisher exact probability test was used to compare baseline clinical characteristics. PFS, OS, and duration of MRD negativity were expressed as median time (months). Probabilities for PFS and OS were estimated using the Kaplan-Meier method, with differences tested for statistical significance using the (two-sided) log-rank test. Univariate and multivariate analyses was performed to evaluate the impact of variables using the Cox regression model. Hazard ratios (HRs) with 95% confidence interval (CI) were estimated by the Cox proportional hazards model. The Wilcoxon rank sum test was used to analyze a continuous variable. All statistical analyses were conducted using SPSS software (version 22.0) and R packages survival and survminer in R/Bioconductor (version 3.6.1). $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and frontline treatment

A total of 1,610 patients from November 27, 2009 to November 20, 2019 were screened (**Figure 1A**), of whom 934 patients were eligible for this study. The demographics, baseline clinical characteristics, and treatment of all eligible patients, including 496 with 1q+ and 438 without 1q+, were summarized in **Table 1**. There were no significant differences in age (median 60 years, range 32-84 years vs. 61 years, range 27-87 years) and sex (male: 56.7% versus 60.7%) between patients with and without 1q+. More 1q+ patients had IgA (27.8% versus 20.3%, $P = 0.008$) or IgD isotype (9.5% versus 3.2%, $P < 0.001$; **Figure 1B**), anemia (74.8% versus 62.6%, $P < 0.001$; **Figure 1C**), International Staging System (ISS) III (56.9% versus 49.5%, $P = 0.025$; **Figure 1D**), R-ISS III (33.6% versus 24.3%, $P = 0.004$; **Figure 1E**), greater tumor burden (bone marrow plasma cells/BMPCs ≥ 30%: 71.3% versus 60.2%, $P = 0.008$; beta-2-microglobulin/β2-MG ≥ 5.5 mg/L: 63.6% versus 50.6%, $P = 0.003$; lactate dehydrogenase/LDH ≥ upper limit of normal/ULN: 33.1% versus 22.1%, $P < 0.001$; **Figure 1F**), and thrombocytopenia (19.4% versus 13.7%, $P = 0.019$; **Figure 1F**), compared to those without 1q+. More 1q+ patients also carried another HRCA such as t(4;14) (17.7% versus 11.9%, $P = 0.031$) and t(14;16) (3.9% versus 0.6%, $P = 0.004$), or adverse CA like del(13q) (55.8% versus 37.0%, $P < 0.001$) than those without 1q+ (**Figure 1G**).

Of 934 patients, 28.3% received PI plus IMiD-based triplet therapy for induction, including bortezomib + lenalidomide + dexamethasone (VRd), bortezomib + thalidomide + dexamethasone (VTD), bortezomib + pomalidomide + dexamethasone (VPD), and others (12.5%); 48.7% received PI-based doublet therapy (mainly Vd); and 23.0% received IMiD-based doublet therapy (mostly Rd). Only a few patients (< 5%) received daratumumab.

Effect of concurrent HRCAs on PFS and OS of 1q+ patients

Of 496 1q+ patients, 150 carried only 1q+, who had significantly worse outcomes than those carrying standard-risk CA [SRCA e.g., del(13q), t(11;14), and del(1p)], with median PFS of 21.9

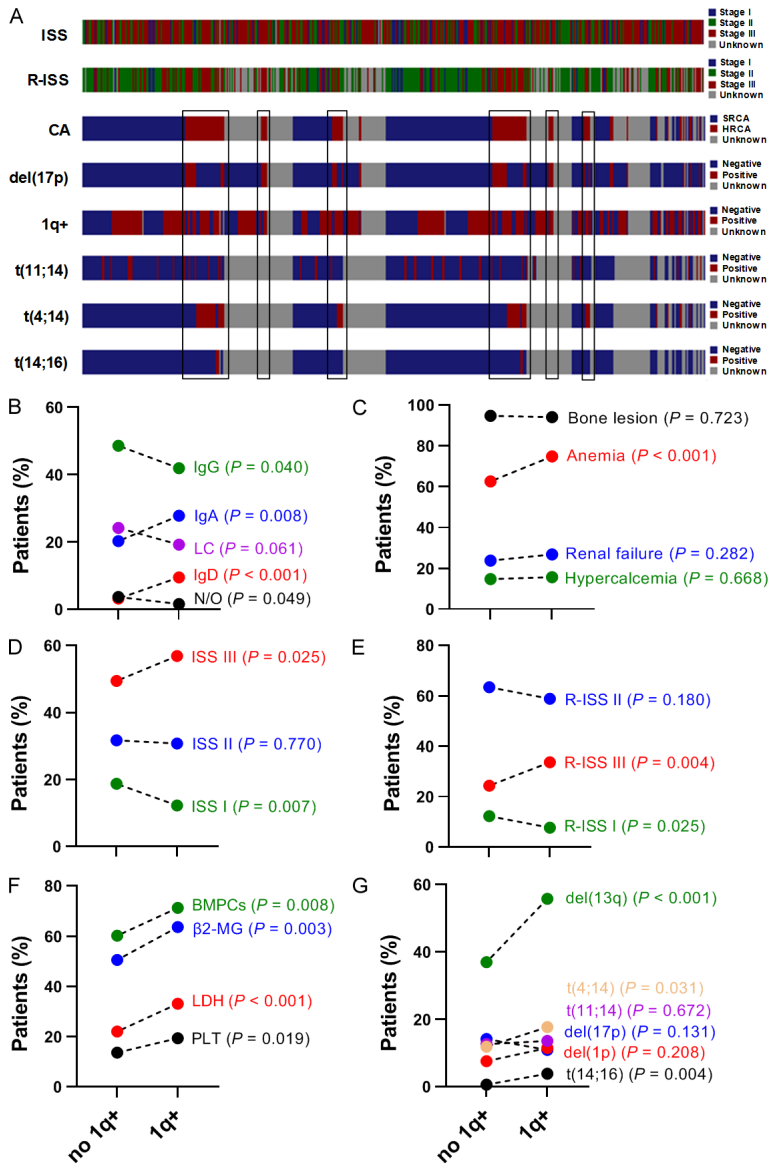


Figure 1. Baseline clinical characteristics. (A) Distribution of patients (n = 1,160) according to staging (ISS and R-ISS) and different CAs. (B-G) Comparison of baseline characteristics between patients with (n = 496) and without 1q+ (n = 438), including M protein isotypes (B), complications (C), ISS stages (D), R-ISS stages (E), laboratory abnormalities (F), and CAs (G). ISS, International Staging System; R-ISS, revised International Staging System; CA, cytogenetic abnormality; N/O, non/oligosecretory; BMPCs, bone marrow plasma cells; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase; PLT, platelet.

vs. 30.9 months (HR 1.39, 95% CI 1.09-1.77, *P* = 0.0081) and OS of 45.6 vs. 58.6 months (HR 1.50, 95% CI 1.12-2.01, *P* = 0.0067). However, there was no significant difference between patients carrying only 1q+ and those carrying HRCAs [del(17p), t(4;14), and/or t(14;16)], with median PFS of 21.9 vs. 18.2 months (HR 1.06, 95% CI 0.92-1.23, *P* = 0.4222) and OS of 45.6 vs. 42.0 months (HR 1.02, 95% CI 0.85-1.21, *P* = 0.8528). Following univariate analyses on all baseline characteristics, multivariate analysis revealed 1q+ as an independent factor for OS (HR 1.40, 95% CI 1.10-1.79, *P* = 0.0007; Table S1). Considering the cut-off of 20% for 1q+ as recommended by the European Myeloma Network (EMN) [29], we compared the outcome of 1q+ patients with 5-20% and > 20% in our cohort. There were no significant differences in both PFS (HR 1.16, 95% CI 0.80-1.69, *P* = 0.4317; Figure S1A) and OS (HR 1.13, 95% CI 0.74-1.74, *P* = 0.5635; Figure S1B) between them, consistent with the observations reported earlier [30].

Concurrence of HRCAs [defined as del(17p), t(4;14), or t(14;16)], known as double-hit MM [9], was common in patients carrying HRCAs (see **Figure 1A**, indicated by square). 18.3% and 49.0% of analyzable 1q+ patients (n = 459) also carried HRCA and SRCA, respectively. Comparing with patients carrying only 1q+, the concurrence of 1q+ and HRCAs led to a significantly shorter PFS (HR 1.63, 95% CI 1.21-2.20, *P* = 0.0013; **Figure 2A**) and OS (HR 1.96, 95% CI 1.40-2.74, *P* < 0.0001; **Figure 2B**), while there were no significant differences in most baseline characteristics between the two groups (except more males and R-ISS III in 1q+ patients with concurrent HRCAs than those with 1q+ only). However, this phenomenon was not observed in the case of SRCAs, regarding either PFS (HR = 1.19, 95% CI 0.94-1.51, *P* = 0.1537; **Figure 2C**) or OS (HR = 1.23, 95% CI 0.93-1.63, *P* = 0.1496; **Figure 2D**).

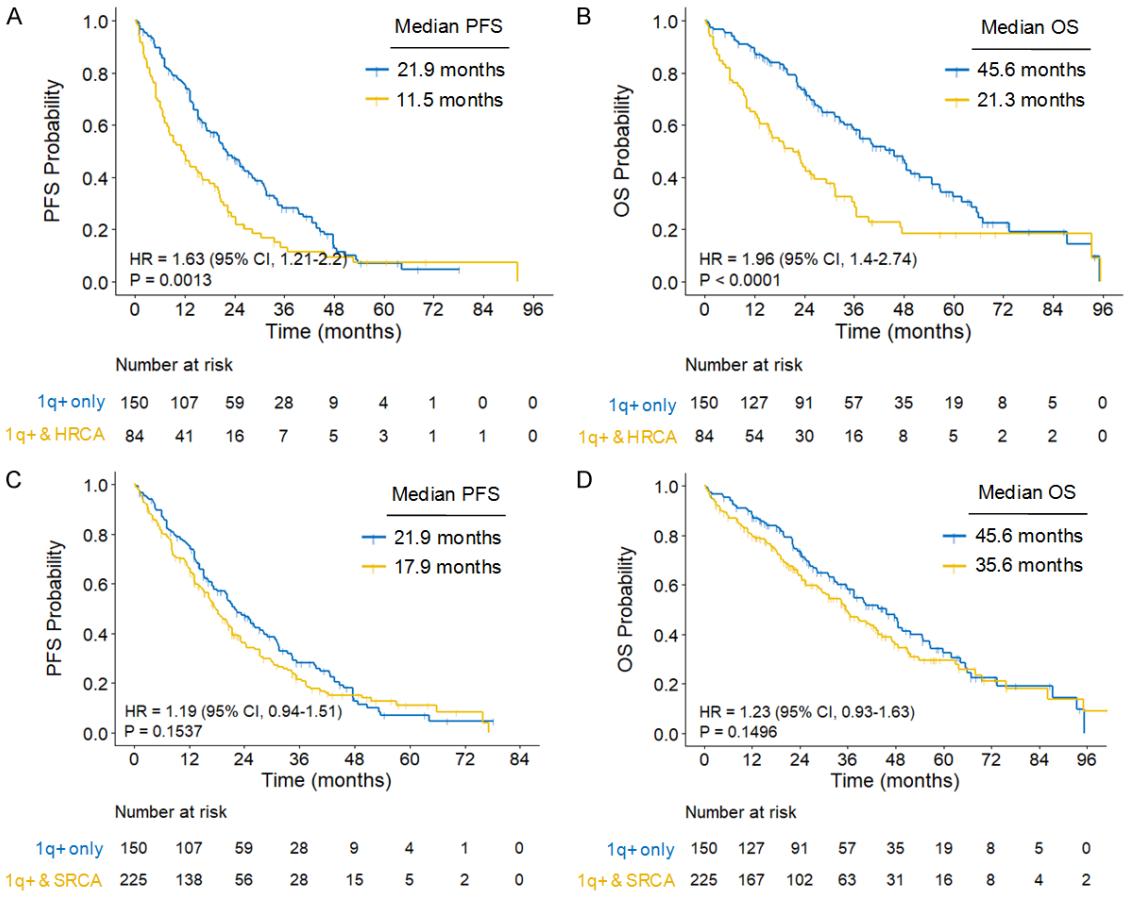
Table 1. Clinical characteristics and treatment (N = 934)

	N (%)
Age, yrs	
Median (range)	61 (27-87)
≥ 65	311 (33.3)
< 65	623 (66.7)
Sex	
Male	547 (58.6)
Female	387 (41.4)
M protein	
IgG	421 (45.1)
IgA	227 (24.3)
IgD	61 (6.5)
Light chain	201 (21.5)
Non/oligosecretory	24 (2.6)
ISS	
I	143 (15.3)
II	292 (31.3)
III	499 (53.4)
R-ISS	(n = 826)
I	81 (9.8)
II	503 (60.9)
III	242 (29.3)
BMPCs, %	(n = 514)
≥ 30	339 (66.0)
< 30	175 (34.0)
β2-MG, mg/L	(n = 519)
≥ 5.5	298 (57.4)
< 5.5	221 (42.6)
LDH, U/L	(n = 881)
≥ 220	247 (28.0)
< 220	634 (72.0)
CsCa, mmol/L	(n = 931)
> 2.75	142 (15.3)
≤ 2.75	789 (84.7)
Cr, μmol/L	
> 177	237 (25.4)
≤ 177	697 (74.6)
Hb, g/L	(n = 888)
< 100	614 (69.1)
≥ 100	274 (30.9)
EM disease	(n = 933)
Yes	172 (18.4)
No	761 (81.6)
PLT, 10^9/L	(n = 932)
< 100	156 (16.7)
≥ 100	776 (83.3)
FISH	
1q+	496/934 (51.3)
del(17p)	116/934 (12.4)
del(13q)	439/934 (47.0)
del(1p)	35/364 (9.6)
t(11;14)	97/739 (13.1)
t(4;14)	108/721 (15.0)
t(14;16)	17/721 (2.6)
Induction	
PI-based	455 (48.7)
IMiD-based	215 (23.0)
PI plus IMiD-based	264 (28.3)
ASCT	
Yes	98 (10.5)
No	836 (89.5)

N, number; yrs, years; M protein, monoclonal protein type; ISS, International Staging System; R-ISS, revised International Staging System; BMPCs, bone marrow plasma cells; β2-MG, β2-microglobulin; LDH, lactate dehydrogenase; CsCa, serum corrected calcium; Cr, serum creatinine; Hb, hemoglobin; EM, extramedullary; PLT, platelet; ALB, albumin; FISH, fluorescence in situ hybridization; PI, proteasome inhibitor; IMiD, immunomodulatory drug; ASCT, autologous stem-cell transplantation.

We further analyzed the effect of individual concurrent CA on the outcome of 1q+ patients by comparing them with those only carrying 1q+. Concurrence of t(14;16) led to the worst outcome of 1q+ patients, with median PFS of 5.0 months (HR 3.28, 95% CI 1.82-5.90, $P < 0.0001$; **Figure 2E**) and OS of 22.9 months (HR 3.29, 95% CI 1.70-6.35, $P = 0.0004$; **Figure 2F**). A similar phenomenon, although to a lesser extent, was observed in the case of del(17p), with a median PFS of 13.0 months (HR 1.50, 95% CI 1.06-2.12, $P = 0.0221$) and OS of 23.3 months (HR 1.50, 95% CI 1.19-2.61, $P = 0.0046$). Concurrence of t(4;14) also moderately shortened median PFS (18.2 months; HR = 1.22, 95% CI 0.87-1.70, $P = 0.2572$) and OS (43.6 months; HR = 1.22, 95% CI 0.82-1.82, $P = 0.3321$) of 1q+ patients.

In addition, while del(1p) itself was not significantly associated with OS in univariate analyses (HR 1.407, 95% CI 0.89-2.22, $P = 0.144$), concurrence of del(1p) markedly worsen the outcome of 1q+ patients, with median PFS and OS of 8.3 months (HR 1.55, 95% CI 0.94-2.55, $P = 0.0886$; **Figure 2E**) and 15.3 months (HR 2.26, 95% CI 1.32-3.88, $P = 0.0031$; **Figure**



E

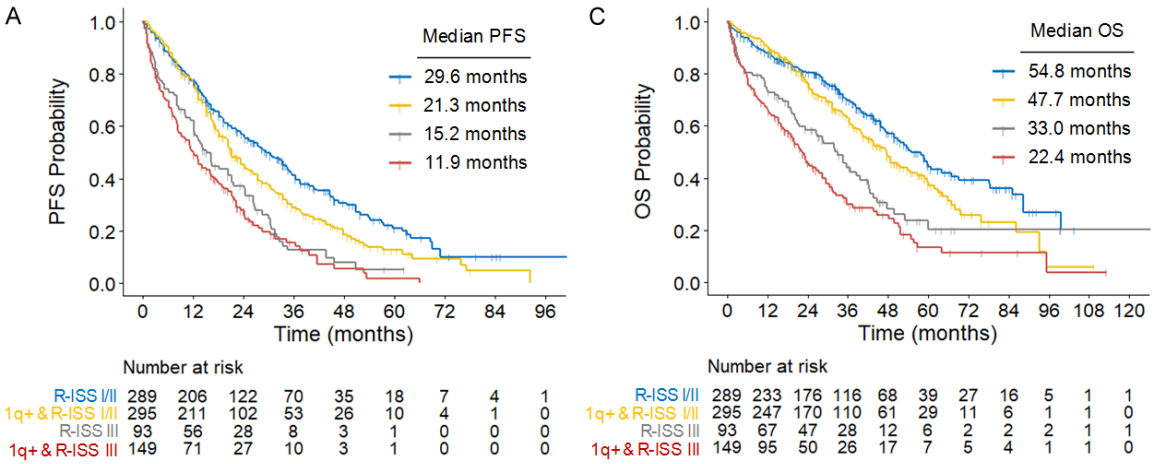
	PFS		
	Median	HR (95% CI)	*P*
1q only	21.9	Reference	
1q + del(17p)	13.0	1.50 (1.06-2.12)	0.0221
1q + del(13q)	16.4	1.37 (1.09-1.72)	0.0075
1q + del(13q) only	17.9	1.24 (0.97-1.58)	0.0846
1q + del(1p)	8.3	1.55 (0.94-2.55)	0.0886
1q + t(4;14)	18.2	1.22 (0.87-1.70)	0.2572
1q + t(14;16)	5.0	3.28 (1.82-5.90)	<0.0001
1q + t(11;14)	21.3	0.91 (0.62-1.33)	0.6332

F

	OS		
	Median	HR (95% CI)	*P*
1q only	45.6	Reference	
1q + del(17p)	23.3	1.50 (1.19-2.61)	0.0046
1q + del(13q)	31.4	1.39 (1.06-1.81)	0.0171
1q + del(13q) only	36.8	1.19 (0.89-1.58)	0.2421
1q + del(1p)	15.3	2.26 (1.32-3.88)	0.0031
1q + t(4;14)	43.6	1.22 (0.82-1.82)	0.3321
1q + t(14;16)	22.9	3.29 (1.70-6.35)	0.0004
1q + t(11;14)	44.7	1.11 (0.71-1.75)	0.6410

Figure 2. Impact of concurrent cytogenetic abnormalities on the outcomes of 1q+ patients. (A, B) Kaplan-Meier estimates of progression-free survival/PFS (A) and overall survival/OS (B) for 1q+ patients with or without concurrent high-risk cytogenetic abnormality [HRCA, including del(17p), t(4;14), and t(14;16)]. (C, D) Kaplan-Meier estimates of PFS (C) and OS (D) for 1q+ patients with or without concurrent standard-risk cytogenetic abnormality [SRCA, including del(13q), del(1p), and t(11;14)]. (E, F) Univariate analysis of PFS (E) and OS (F) for various concurrent cytogenetic abnormalities in 1q+ patients.

2F), comparing with those carrying only 1q+. Interestingly, concurrence of del(13q) also shortened median PFS (16.4 months; HR 1.37, 95% CI 1.09-1.72, *P* = 0.0075) and OS (31.4 months; HR 1.39, 95% CI 1.06-1.81, *P* = 0.0171). Due to its high incidence (e.g., 47% in our cohort), the inferior effect of del(13q) on 1q+ patients may stem from other concurrent HRCAs [31]. To address this issue, we analyzed the impact of concurrent del(13q) alone. Concurrence of only del(13q) did not significantly affect PFS (median, 17.9 months; HR =



B

	PFS	
	HR (95% CI)	*P*
I/II vs III	1.43 (1.25-1.64)	<0.0001
I/II vs I/II + 1q	1.31 (1.07-1.61)	0.0079
III vs III + 1q	1.19 (0.89-1.59)	0.2364
III vs I/II + 1q	1.57 (1.21-2.04)	0.0008
I/II + 1q vs III + 1q	1.37 (1.22-1.54)	<0.0001

D

	OS	
	HR (95% CI)	*P*
I/II vs III	1.44 (1.23-1.69)	<0.0001
I/II vs I/II + 1q	1.30 (1.01-1.67)	0.0427
III vs III + 1q	1.37 (1.00-1.89)	0.0521
III vs I/II + 1q	1.64 (1.21-2.23)	0.0015
I/II + 1q vs III + 1q	1.50 (1.32-1.71)	<0.0001

Figure 3. Effects of 1q+ on the risk stratification by the R-ISS. Kaplan-Meier estimates of PFS (A, B) and OS (C, D) according to the R-ISS staging with and without addition of 1q+.

1.24, 95% CI 0.97-1.58, *P* = 0.0846) and OS (median, 36.8 months; HR = 1.19, 95% CI 0.89-1.58, *P* = 0.2421) of 1q+ patients.

Effect of 1q+ on the risk stratification by the R-ISS

Compared with their counterparts without 1q+, R-ISS I or II patients with 1q+ had significantly shorter median PFS (21.3 vs. 29.6 months; HR 1.31, 95% CI 1.07-1.61, *P* = 0.0079; **Figure 3A** and **3B**) and OS (47.7 vs. 54.8 months; HR 1.30, 95% CI 1.01-1.67, *P* = 0.0427; **Figure 3C** and **3D**). A similar phenomenon was also observed in the case of R-ISS III patients, although the differences were not significant, regarding PFS (11.9 vs. 15.2 months; HR 1.19, 95% CI 0.89-1.59, *P* = 0.2364) and OS (22.4 vs. 33.0 months; HR 1.37, 95% CI 1.00-1.89, *P* = 0.0521). However, the R-ISS maintained its ability to discriminate PFS (HR 1.37, 95% CI 1.22-1.54, *P* < 0.0001) and OS (HR 1.50, 95% CI 1.32-1.71, *P* < 0.0001) in 1q+ patients.

Effect of different therapies on therapeutic responses and outcomes of 1q+ patients

All patients received doublet or triplet therapy containing PI, IMiD, or both for induction in the real-world setting (**Table 1**). Consistent with an earlier report [12], no significant differences were observed in objective response rate (ORR, ≥ partial response/PR; Figure S2A) or the best response rate (≥ very good partial response/VGPR; Figure S2B) between patients with and without 1q+ who received PI, IMiD, or both, and ASCT. Of note, fewer 1q+ patients achieved ≥ complete response (CR) after induction with PI-based therapy (*P* = 0.028; **Figure 4A**) or stringent complete response (sCR) after ASCT (*P* = 0.001; **Figure 4B**), compared with those without 1q+. However, no significant differences were observed in patients who received IMiD or PI plus IMiD therapies. There were no differences in OS between 1q+ patients who received doublet and triplet therapy (HR 1.27, 95% CI 0.98-1.65, *P* = 0.0727; **Figures 4C** and S2C, S2D). 1q+ patients who received ASCT had significantly longer OS than those without ASCT (HR 2.46, 95% CI 1.57-3.85, *P* < 0.0001; **Figure 4D**). In the CoMMpass cohort, 1q+ patients who received triplet had longer OS than those who received doublet (HR 1.99, 95% CI 1.16-3.39, *P* = 0.0118; **Figure 4E**); the results for patients with versus without ASCT (HR 2.45, 95% CI 1.46-4.12, *P* = 0.0007; **Figure 4F**) were analogous to those observed in our cohort. Surprisingly, the OS of 1q+ patients was

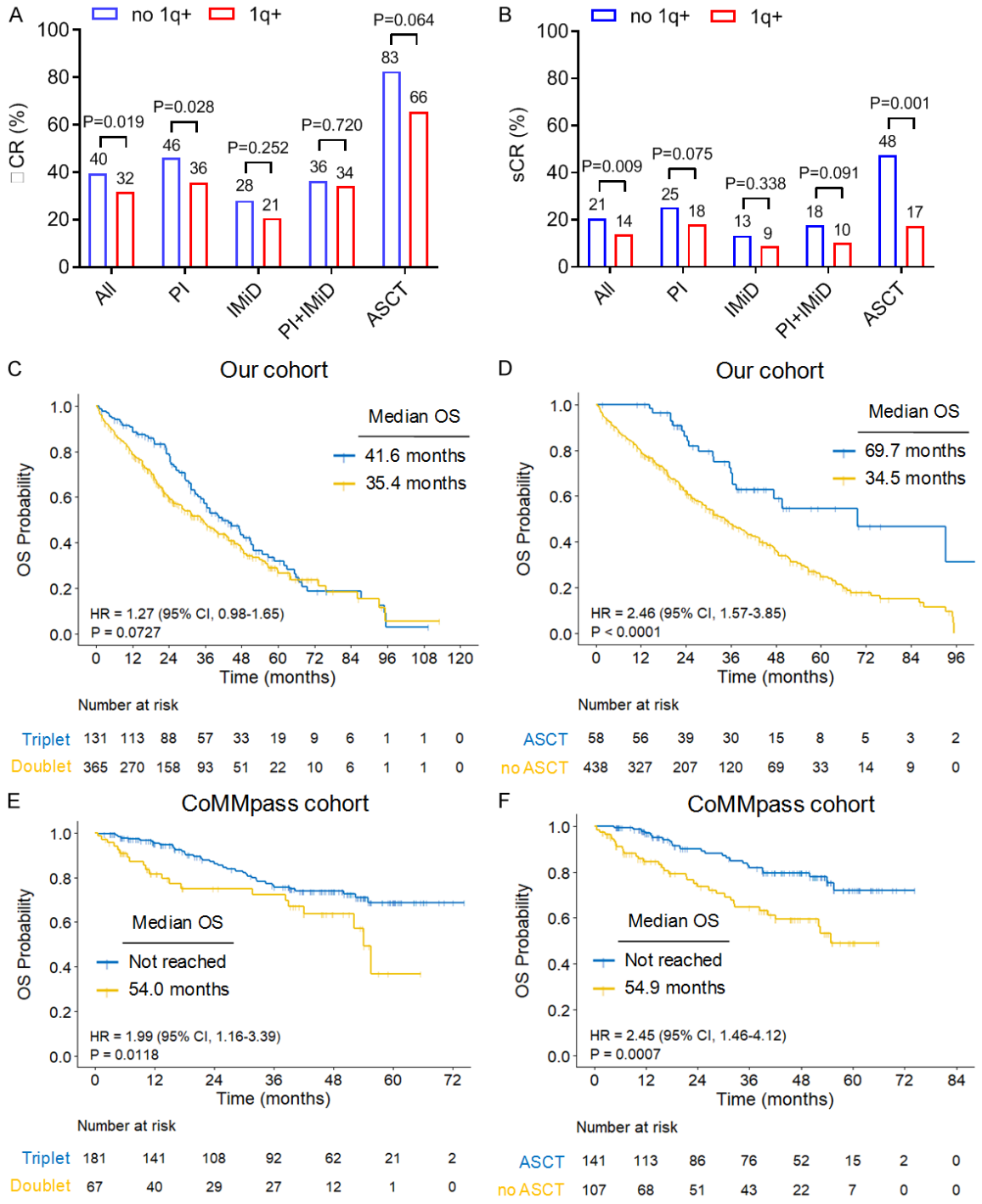


Figure 4. Effects of frontline treatment on therapeutic responses and survival of 1q+ patients. (A, B) Percentage of patients with or without 1q+ who achieved ≥ complete response/CR (A) or stringent complete response/sCR (B). (C, D) Kaplan-Meier estimates of OS for 1q+ patients who received proteasome inhibitor (PI)- or immunomodulatory drug (IMiD)-based (doublet) versus PI plus IMiD-based (triplet) induction (C), or autologous stem-cell transplantation (ASCT) versus no ASCT (D) in our cohort. (E, F) Kaplan-Meier estimates of OS for 1q+ patients who received doublet versus triplet induction (E), or ASCT versus no ASCT (F) in the CoMMpass cohort.

almost identical to those without 1q+ after carfizomib-based induction with or without following ASCT in the CoMMpass cohort (Figure S2E and S2F). Unfortunately, only a few patients

received carfizomib-based therapy in our cohort, which did not allow us to further verify this observation.

Impact of the MRD status on the outcome of 1q+ patients

In 201 patients with available MRD data (the median LOD of 3.86×10^{-5}), fewer 1q+ patients achieved MRD$^-$ than those without 1q+ (42% versus 53%), particularly in the subgroup of patients who received PI-based therapy (40% versus 55%) or ASCT (72% versus 96%), although the differences were not statistically significant (**Figure 5A**). The first MRD test was conducted when patients achieved an objective response (CR, VGPR, or PR), while the time points for subsequent tests varied during consolidation, maintenance, and follow up, with the median test number of 3 times (range 1-11 times) per patient. The median time to MRD$^-$ was not different between patients with and without 1q+ (HR 1.15, 95% CI 0.81-1.64, P = 0.4387; Figure S3A). The median duration of MRD$^-$ was shorter, although not significantly, in 1q+ patients than those without 1q+ (29.1 months versus not reached; HR 0.65, 95% CI 0.33-1.28, P = 0.2149; **Figure 5B**). However, when treated as a continuous variable, the duration of MRD$^-$ was significantly different between patients with and without 1q+ (P = 0.031). Comparing with their counterparts who failed to achieve MRD$^-$, 1q+ patients who achieved MRD$^-$ sharply prolonged PFS (HR 4.03, 95% CI 2.59-6.29, P < 0.0001; **Figure 5C**) and OS (HR 3.72, 95% CI 2.24-6.19, P < 0.0001; **Figure 5D**). In patients who achieved MRD$^-$, there were however no significant differences between patients with and without 1q+ in PFS (HR 1.46, 95% CI 0.88-2.43, P = 0.1404; **Figure 5E**) and OS (HR 1.28, 95% CI 0.71-2.32, P = 0.4146; **Figure 5F**). Moreover, while 1q+ patients who lost the MRD$^-$ status within 12 months had a longer median time to relapse (TTR) than those who had persistent MRD$^+$ (26.4 versus 11.6 months), the MRD$^-$ duration > 12 months substantially prolonged TTR (not reached; Figure S3B). Consistently, sustained MRD$^-$ (> 12 months) diminished the differences in PFS (Figure S3C) and OS (Figure S3D) between patients with and without 1q+ (median not reached for all cases).

Discussion

In our previous study, we have demonstrated that patients carrying 1q+ are considerably heterogeneous with diverse outcomes and thus require risk stratification for more precise treatment [23]. Here, we further conducted this study to explore the basis for such heterogeneity in this population, involving baseline characteristics, frontline therapies, and therapeutic responses (particularly MRD). As the most common CA, 1q+ was seen in about half of NDMM patients in our cohort, relatively more frequent than 30-40% reported in Western countries [5]. Consistent with previous studies [12, 32], 1q+ patients were more frequently characterized by advanced diseases (e.g., ISS III and R-ISS III), large tumor burden (e.g., BMPCs, β2-MG, and LDH), adverse complications (e.g., anemia and thrombocytopenia), and frequent concurrence of other CAs (including HRCAs). However, it could not be excluded that these unfavorable baseline characteristics might be attributed to the late presentation of participants at diagnosis in our cohort. It is also worth noting that approximately 10% of 1q+ patients had IgD isotype, significantly more frequent than those without 1q+ (3%). This is a rare but aggressive isotype of MM [33], which is however relatively more common in the population of Chinese patients with MM [34].

1q+ has long been recognized as an unfavorable marker and used for risk stratification in MM [35-37]. Although the association between 1q+ and poor outcomes has been well documented [32], the true impact of 1q+ on the prognosis remains a debate [13]. For example, poor outcomes of 1q+ patients have been considered a byproduct of high-risk tumor biology due to its high frequency of concurrence with other HRCAs [8]. To exclude such a potential influence from concurrent HRCAs, we analyzed the outcome of patients carrying 1q+ only. Notably, these patients had significantly worse outcomes (both PFS and OS) than patients who carry SRCAs, but similar to those carrying HRCAs such as del(17p), t(4;14), and/or t(14;16), suggesting 1q+ itself as an independent “HRCA”. Co-existence of two or more HRCAs, known as a type of double-hit MM [9], confers more aggressive disease and worse outcomes than a single HRCA [38-40]. We found that about 70% of 1q+ patients carried

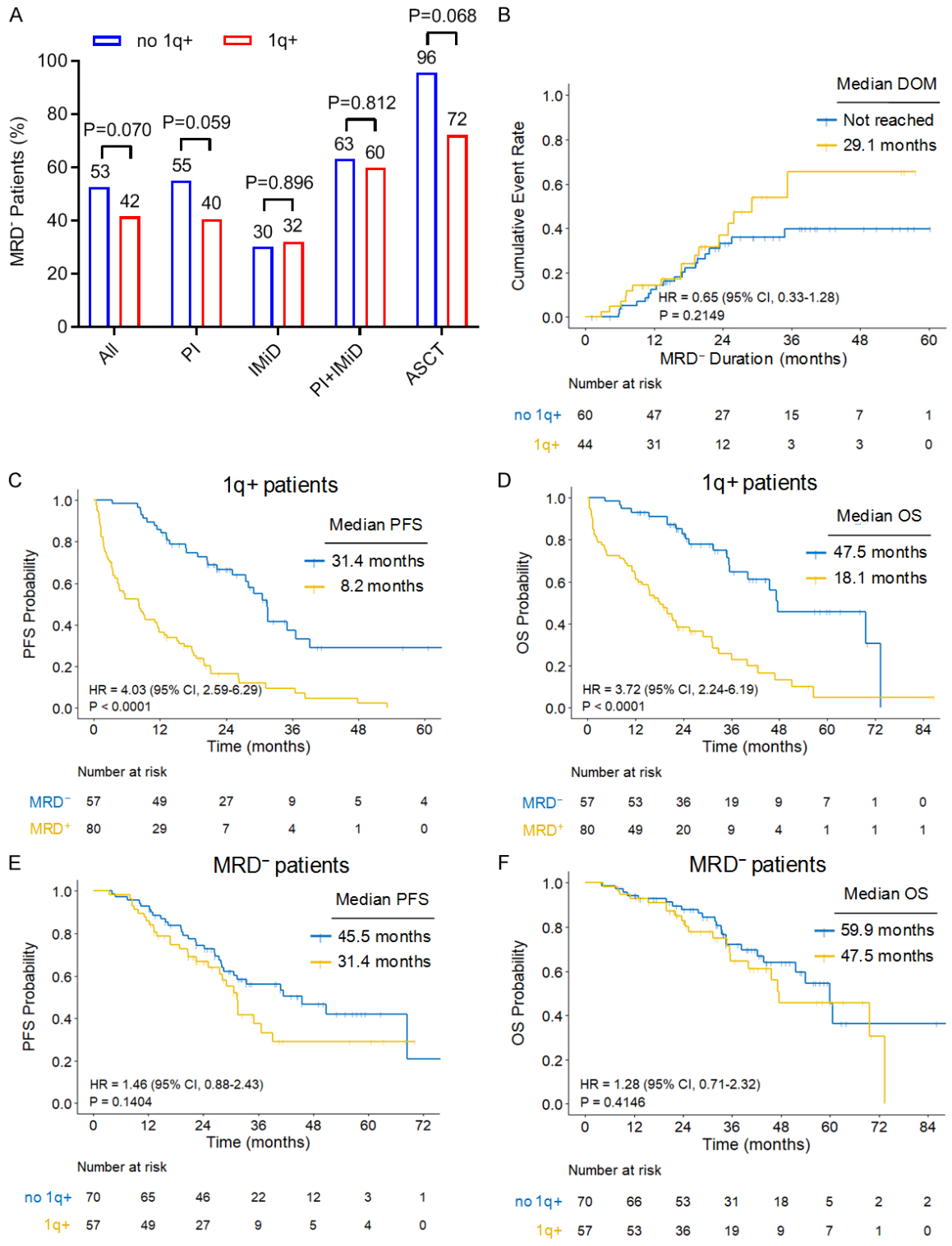


Figure 5. Effects of the minimal residue disease (MRD) status on the outcomes of 1q+ patients. (A) Percentage of patients with or without 1q+ who achieved MRD negativity (MRD⁻). (B) Kaplan-Meier estimates of the MRD⁻ duration for patients with or without 1q+. (C, D) Kaplan-Meier estimates of PFS (C) and OS (D) for 1q+ patients who achieved MRD⁻ or remained persistent MRD (MRD⁺). (E, F) Kaplan-Meier estimates of PFS (E) and OS (F) for patients with or without 1q+ who achieved MRD⁻.

two or more other CAs, particularly HRCAs (accounting for ~25% of 1q+ patients). Concurrence of HRCAs, but not SRCAs, significantly shortened PFS and OS of 1q+ patients than those carrying only 1q+, while no significant differences between one and two or more concurrent HRCAs [7, 12]. Moreover, our analysis of each concurrent HRCA showed that concurrence of t(14;16) or del(17p), rather than t(4;14), markedly shortened PFS and OS of 1q+ patients. Interestingly, concomitant del(17p) and t(4;14) are associated with inferior survival of 1q+ patients who receive ASCT [17]. These observations provide more evidence supporting the definition of double-hit MM by the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) 3.0 [41], but also raise a notion that it may be necessary to pinpoint which concurrent HRCA(s) are exactly involved in double-hit MM. In addition, the concurrence of certain SRCAs [(e.g., del(1p) and probably del(13q) as well] might also worsen the outcomes of 1q+ patients [42, 43]. In this context, biallelic and to a lesser degree monoallelic deletion of 1p32 have been identified as a strong prognostic factor in patients with NDMM, while the concurrence of other HRCAs (including 1q+) further shortens the OS of patients with del(1p32) [44]. Therefore, our observations that the impact of different concurrent CAs varies may provide a potential explanation for the high heterogeneity in the prognosis of 1q+ patients.

The bulk of evidence suggests that frontline treatment with PIs and IMiDs, or both, and ASCT could improve poor outcomes of 1q+ patients but not fully overcome the adverse prognostic property of 1q+ [16, 17, 45]. For example, the Forte study has shown that the triplet therapy combining carfilzomib, lenalidomide, and dexamethasone (KRD), followed by ASCT, abrogates the dismal outcome of patients with 1q gain (3 copies), rather than amplification (> 3 copies) [46]. The efficacy of the CD38 mAb daratumumab has been demonstrated in HRMM patients, in which the data for 1q+ patients are however limited [18, 47]. Emerging evidence has demonstrated that achievement of MRD negativity (MRD^-) may improve or even overcome the poor outcome of patients carrying HRCAs [22, 48, 49]. Of note, baseline high risk due to HRCAs may be transformed to standard risk via achieving MRD negativity, or vice versa due to persistent MRD [22, 50]. However, the effect of the MRD status on the outcomes of 1q+ patients remains largely uncertain. We observed that although 1q+ patients had a relatively lower probability of achieving MRD negativity and a shorter duration of MRD negativity than those without 1q+, the attainment of MRD negativity strikingly prolonged PFS and OS of 1q+ patients. Once MRD negativity sustained for a year or longer, the outcomes of 1q+ patients were virtually identical to those without 1q+, with almost no patients experiencing disease progression or death during 6-year follow-up. Thus, our observations suggest that durable MRD negativity might conquer the adverse effect of 1q+, highlighting the importance of achieving and maintaining deep remission (particularly MRD^-) for this high-risk population of 1q+ patients. They also suggest that MRD-tailored treatment may be particularly helpful in improving the outcomes of these patients. However, because the time point for the MRD test was not fixed (except the first time), a possibility that the interval of the MRD tests may affect time to MRD^- or duration of MRD^- could not excluded.

The main limitations of this study include its retrospective nature and overall relatively poor outcomes of patients in our cohort, probably in association with a large proportion of patients who carried HRCAs and had advanced diseases (e.g., ISS III and R-ISS III) at diagnosis. Other limitations of this study cohort included that the information for certain baseline characteristics [e.g., for BMPCs, karyotypes, and FISH for del(1p)] was not available at one participating center, that immunoglobulin heavy chain (IGH) rearrangements were not further classified to t(4;14), t(11;14), and t(14;16) in a considerable part of patients, and that only a small number of patients received ASCT and maintenance, which limited the analyses for their impact on the outcome of patients. Since the data cutoff date of this study was November 20, 2019, only a few patients received newer agents (e.g., anti-CD38 mAbs such as daratumumab that was approved for transplant-ineligible and -eligible patients with NDMM on May 7, 2018 and September 26, 2019, respectively). For the same reason, the sensitivity of MRD tests was relatively low due to the unavailability of highly sensitive approaches currently used in the clinic. Thus, caution needs to be taken to explain our observations in the current practice.

Conclusions

This study verified 1q+ itself as an independent risk factor, irrespective of all other baseline characteristics (e.g., age, disease stage, tumor burden, complications, and concurrent HRCAs) and treatments in a cohort with a high proportion of 1q+ patients, all of whom received doublet or triplet therapy. 1q+ patients displayed a considerable heterogeneity in baseline characteristics, therapeutic responses, and outcomes, which can be at least partially attributed to the concurrence of different CAs, particularly HRCAs such as t(14;16) and del(17p). The poor outcome of 1q+ patients could be ameliorated by durable MRD negativity. Therefore, our observations could help develop the risk-adapted and MRD-tailored therapy to overcome the adverse prognostic property of 1q+ and thus warrant further validation in a prospective setting.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant # 81471165, 81670190, 81670189, 81870160, 81971108, 82270207, and 82370202) and Jilin Provincial Scientific and Technological Development Program (Grant # 20190201042JC, 20190201163JC, 20210509010RQ, and YDZJ202301ZYTS021).

All patients had given written informed consent to the use of clinical data.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yun Dai, Laboratory of Cancer Precision Medicine, The First Hospital of Jilin University, 519 Dongminzhu Street, Changchun 130061, Jilin, China. Tel: +86-13578948346; ORCID: 0000-0003-2285-0818; E-mail: daiyun@jlu.edu.cn; Dr. Fengyan Jin, Department of Hematology, Cancer Center, The First Hospital of Jilin University, 71 Xinmin Street, Changchun 130012, Jilin, China. Tel: +86-13844989638; ORCID: 0000-0003-2288-556X; E-mail: fengyanjin@jlu.edu.cn

References

[1] Kumar SK and Rajkumar SV. The multiple myelomas - current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol 2018; 15: 409-421.

[2] van de Donk NWCJ, Pawlyn C and Yong KL. Multiple myeloma. Lancet 2021; 397: 410-427.

[3] Zamagni E, Barbato S and Cavo M. How I treat high-risk multiple myeloma. Blood 2022; 139: 2889-2903.

[4] Atrash S, Flahavan EM, Xu T, Ma E, Karve S, Hong WJ, Jirau-Lucca G, Nixon M and Ailawadhi S. Treatment patterns and outcomes according to cytogenetic risk stratification in patients with multiple myeloma: a real-world analysis. Blood Cancer J 2022; 12: 46.

[5] Croft J, Ellis S, Sherborne AL, Sharp K, Price A, Jenner MW, Drayson MT, Owen RG, Chown S, Lindsay J, Karunanithi K, Hunter H, Gregory WM, Davies FE, Morgan GJ, Cook G, Atanesyan L, Savola S, Cairns DA, Jackson G, Houlston RS and Kaiser MF. Copy number evolution and its relationship with patient outcome-an analysis of 178 matched presentation-relapse tumor pairs from the Myeloma XI trial. Leukemia 2021; 35: 2043-2053.

[6] Jin F, Gao G, Dong Y, Li C, Huang W, Zhang L, Zhu Q, Yuan R, Xu L, Xu Y, Xu Q, Kumar SK and Dai Y. A multi-center epidemiological and prognostic analysis of cytogenetic abnormalities in a cohort of 1015 Chinese patients with newly-diagnosed multiple myeloma. Blood 2019; 134; 3094.

[7] Giri S, Huntington SF, Wang R, Zeidan AM, Podoltsev N, Gore SD, Ma X, Gross CP, Davidoff AJ and Neparidze N. Chromosome 1 abnormalities and survival of patients with multiple myeloma in the era of novel agents. Blood Adv 2020; 4: 2245-2253.

[8] Schmidt TM, Fonseca R and Usmani SZ. Chromosome 1q21 abnormalities in multiple myeloma. Blood Cancer J 2021; 11: 83.

[9] Walker BA, Mavrommatis K, Wardell CP, Ashby TC, Bauer M, Davies F, Rosenthal A, Wang H, Qu P, Hoering A, Samur M, Towfic F, Ortiz M, Flynt E, Yu Z, Yang Z, Rozelle D, Obenauer J, Trotter M, Auclair D, Keats J, Bolli N, Fulciniti M, Szalat R, Moreau P, Durie B, Stewart AK, Goldschmidt H, Raab MS, Einsele H, Sonneveld P, San Miguel J, Lonial S, Jackson GH, Anderson KC, Avet-Loiseau H, Munshi N, Thakurta A and Morgan G. A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia 2019; 33: 159-170.

[10] D'Agostino M, Cairns DA, Lahuerta JJ, Wester R, Bertsch U, Waage A, Zamagni E, Mateos MV, Dall'Olio D, van de Donk NWCJ, Jackson G, Rocchi S, Salwender H, Bladé Creixenti J, van der Holt B, Castellani G, Bonello F, Capra A, Mai EK, Dürig J, Gay F, Zweegman S, Cavo M,

Kaiser MF, Goldschmidt H, Hernández Rivas JM, Larocca A, Cook G, San-Miguel JF, Boccadoro M and Sonneveld P. Second revision of the International Staging System (R2-ISS) for overall survival in multiple myeloma: a European Myeloma Network (EMN) report within the HARMONY project. J Clin Oncol 2022; 40: 3406-3418.

[11] Abdallah NH, Binder M, Rajkumar SV, Greipp PT, Kapoor P, Dispenzieri A, Gertz MA, Baughn LB, Lacy MQ, Hayman SR, Buadi FK, Dingli D, Go RS, Hwa YL, Fonder AL, Hobbs MA, Lin Y, Leung N, Kourelis T, Warsame R, Siddiqui MA, Kyle RA, Bergsagel PL, Fonseca R, Ketterling RP and Kumar SK. A simple additive staging system for newly diagnosed multiple myeloma. Blood Cancer J 2022; 12: 21.

[12] Abdallah N, Greipp P, Kapoor P, Gertz MA, Dispenzieri A, Baughn LB, Lacy MQ, Hayman SR, Buadi FK, Dingli D, Go RS, Hwa YL, Fonder A, Hobbs M, Lin Y, Leung N, Kourelis T, Warsame R, Siddiqui M, Lust J, Kyle RA, Bergsagel L, Ketterling R, Rajkumar SV and Kumar SK. Clinical characteristics and treatment outcomes of newly diagnosed multiple myeloma with chromosome 1q abnormalities. Blood Adv 2020; 4: 3509-3519.

[13] Corre J, Munshi NC and Avet-Loiseau H. Risk factors in multiple myeloma: is it time for a revision? Blood 2021; 137: 16-19.

[14] Shaughnessy JD Jr, Qu P, Usmani S, Heuck CJ, Zhang Q, Zhou Y, Tian E, Hanamura I, van Rhee F, Anaissie E, Epstein J, Nair B, Stephens O, Williams R, Waheed S, Alsayed Y, Crowley J and Barlogie B. Pharmacogenomics of bortezomib test-dosing identifies hyperexpression of proteasome genes, especially PSMD4, as novel high-risk feature in myeloma treated with total therapy 3. Blood 2011; 118: 3512-3524.

[15] Schmidt TM, Barwick BG, Joseph N, Heffner LT, Hofmeister CC, Bernal L, Dhodapkar MV, Gupta VA, Jaye DL, Wu J, Goyal S, Chen Z, Boise LH, Lonial S, Nooka AK and Kaufman JL. Gain of chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. Blood Cancer J 2019; 9: 94.

[16] Neupane K, Fortuna GG, Dahal R, Schmidt T, Fonseca R, Chakraborty R, Koehn KA, Mohan M, Mian H, Costa LJ, Sborov D and Mohyuddin GR. Alterations in chromosome 1q in multiple myeloma randomized clinical trials: a systematic review. Blood Cancer J 2024; 14: 20.

[17] Pasvolsky O, Ghanem S, Milton DR, Rauf M, Tanner MR, Bashir Q, Srour S, Saini N, Lin P, Ramdial J, Nieto Y, Tang G, Aljawai Y, Khan HN, Kebriaei P, Lee HC, Patel KK, Thomas SK, Weber DM, Orlowski RZ, Shpall EJ, Champlin RE and Qazilbash MH. Outcomes of patients with multiple myeloma and 1q gain/amplification receiving autologous hematopoietic stem cell transplant: the MD Anderson cancer center experience. Blood Cancer J 2024; 14: 4.

[18] Premkumar V, Pan S, Lentzsch S and Bhutani D. Use of daratumumab in high risk multiple myeloma: a meta-analysis. EJHaem 2020; 1: 267-271.

[19] Harrison SJ, Perrot A, Alegre A, Simpson D, Wang MC, Spencer A, Delimpasi S, Hulin C, Sunami K, Facon T, Vlummens P, Yong K, Campana F, Inchauspé M, Macé S, Risse ML, van de Velde H and Richardson P. Subgroup analysis of ICARIA-MM study in relapsed/refractory multiple myeloma patients with high-risk cytogenetics. Br J Haematol 2021; 194: 120-131.

[20] Costa LJ and Usmani SZ. Defining and managing high-risk multiple myeloma: current concepts. J Natl Compr Canc Netw 2020; 18: 1730-1737.

[21] Joseph NS, Kaufman JL, Dhodapkar MV, Hofmeister CC, Almaula DK, Heffner LT, Gupta VA, Boise LH, Lonial S and Nooka AK. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. J Clin Oncol 2020; 38: 1928-1937.

[22] Paiva B, Puig N, Cedena MT, Rosiñol L, Cordón L, Vidriales MB, Burgos L, Flores-Montero J, Sanoja-Flores L, Lopez-Anglada L, Maldonado R, de la Cruz J, Gutierrez NC, Calasanz MJ, Martin-Ramos ML, Garcia-Sanz R, Martinez-Lopez J, Oriol A, Blanchard MJ, Rios R, Martin J, Martinez-Martinez R, Sureda A, Hernandez MT, de la Rubia J, Krsnik I, Moraleda JM, Palomera L, Bargay J, Van Dongen JJM, Orfao A, Mateos MV, Blade J, San-Miguel JF and Lahuerta JJ; GEM (Grupo Español de Mieloma)/PETHEMA (Programa Para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Group. Measurable residual disease by next-generation flow cytometry in multiple myeloma. J Clin Oncol 2020; 38: 784-792.

[23] Yang P, Chen H, Liang X, Xu W, Yu S, Huang W, Yi X, Guo Q, Tian M, Yue T, Li M, Zhang Y, Zhang M, Yan Y, Hu Z, Kumar SK, Zhou F, Dai Y and Jin F. Proposed risk-scoring model for estimating the prognostic impact of 1q gain in patients with newly diagnosed multiple myeloma. Am J Hematol 2023; 98: 251-263.

[24] Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BG, Anderson KC, Sonneveld P, San

Miguel J, Cavo M, Rajkumar SV and Moreau P. Revised international staging system for multiple myeloma: a report from international myeloma working group. J Clin Oncol 2015; 33: 2863-2869.

[25] Yang P, Xu W, Liang X, Yu S, Yi X, Liu M, Tian M, Yue T, Zhang Y, Yan Y, Hu Z, Guo Q, Zhang N, Wang J, Sun X, Hu R, Kumar SK, Dai Y and Jin F. Dynamic monitoring of minimal residual disease in newly-diagnosed multiple myeloma. Am J Hematol 2023; 98: E61-E64.

[26] Costa LJ, Derman BA, Bal S, Sidana S, Chhabra S, Silbermann R, Ye JC, Cook G, Cornell RF, Holstein SA, Shi Q, Omel J, Callander NS, Chng WJ, Hungria V, Maiolino A, Stadtmauer E, Giralt S, Pasquini M, Jakubowiak AJ, Morgan GJ, Krishnan A, Jackson GH, Mohty M, Mateos MV, Dimopoulos MA, Facon T, Spencer A, Miguel JS, Hari P, Usmani SZ, Manier S, McCarthy P, Kumar S, Gay F and Paiva B. International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. Leukemia 2021; 35: 18-30.

[27] Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, Miguel JS and Avet-Loiseau H. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016; 17: e328-e346.

[28] Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, Blade J, Richardson P, Orlowski R, Siegel D, Jagannath S, Facon T, Avet-Loiseau H, Lonial S, Palumbo A, Zonder J, Ludwig H, Vesole D, Sezer O, Munshi NC and San Miguel J; International Myeloma Workshop Consensus Panel 1. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117: 4691-4695.

[29] Ross FM, Avet-Loiseau H, Ameye G, Gutiérrez NC, Liebisch P, O'Connor S, Dalva K, Fabris S, Testi AM, Jarosova M, Hodkinson C, Collin A, Kerndrup G, Kuglik P, Ladon D, Bernasconi P, Maes B, Zemanova Z, Michalova K, Michau L, Neben K, Hermansen NE, Rack K, Rocci A, Protheroe R, Chiecchio L, Poirel HA, Sonneveld P, Nyegaard M and Johnsen HE; European Myeloma Network. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica 2012; 97: 1272-1277.

[30] Gao L, Liu Y, Li Y, Feng L, Wang Z, Wen L, Wang F, Huang X, Lu J and Lai Y. The importance of FISH signal cut-off value and copy number variation for 1q21 in newly diagnosed multiple myeloma: is it underestimated? Clin Lymphoma Myeloma Leuk 2022; 22: 535-544.

[31] Corre J, Montes L, Martin E, Perrot A, Caillot D, Leleu X, Belhadj K, Facon T, Hulin C, Mohty M, Fontan J, Macro M, Brechignac S, Jaccard A, Stoppa AM, Orsini-Piocelle F, Adiko D, Voillat L, Keddar F, Barry M, Demarquette H, Certain MN, Plantier I, Roussel M, Hébraud B, Filleron T, Attal M and Avet-Loiseau H. Early relapse after autologous transplant for myeloma is associated with poor survival regardless of cytogenetic risk. Haematologica 2020; 105: e480-e483.

[32] Weinhold N, Salwender HJ, Cairns DA, Raab MS, Waldron G, Blau IW, Bertsch U, Hielscher T, Morgan GJ, Jauch A, Davies FE, Hänel M, Cook G, Scheid C, Houlston R, Goldschmidt H, Jackson G and Kaiser MF. Chromosome 1q21 abnormalities refine outcome prediction in patients with multiple myeloma - a meta-analysis of 2,596 trial patients. Haematologica 2021; 106: 2754-2758.

[33] Zagouri F, Kastritis E, Symeonidis AS, Giannakoulas N, Katodritou E, Delimpasi S, Repousis P, Terpos E and Dimopoulos MA; Greek Myeloma Study Group. Immunoglobulin D myeloma: clinical features and outcome in the era of novel agents. Eur J Haematol 2014; 92: 308-312.

[34] Liu J, Hu X, Jia Y, Lu J, Lee JH, Kim K, Chen W, Liu A, Liu Y, Chen Q, Zhang C, Suh C, Kim MK, Zhou F, Chng WJ, Kumar SK, Durie B, Hou J, Fu W and Du J. Clinical features and survival outcomes in IgD myeloma: a study by Asia Myeloma Network (AMN). Leukemia 2021; 35: 1797-1802.

[35] Audil HY, Cook JM, Greipp PT, Kapoor P, Baughn LB, Dispenzieri A, Gertz MA, Buadi FK, Lacy MQ, Dingli D, Fonder AL, Hayman SR, Hobbs MA, Muchtar E, Siddiqui M, Gonsalves WI, Hwa YL, Leung N, Lin Y, Kourelis TV, Warsame R, Kyle RA, Ketterling RP, Rajkumar SV and Kumar SK. Prognostic significance of acquired 1q22 gain in multiple myeloma. Am J Hematol 2022; 97: 52-59.

[36] Fonseca R, Van Wier SA, Chng WJ, Ketterling R, Lacy MQ, Dispenzieri A, Bergsagel PL, Rajkumar SV, Greipp PR, Litzow MR, Price-Troska T, Henderson KJ, Ahmann GJ and Gertz MA. Prognostic value of chromosome 1q21 gain by fluorescent in situ hybridization and increase CKS1B expression in myeloma. Leukemia 2006; 20: 2034-2040.

[37] Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, Munshi N, Palumbo A, Miguel JS, Sonneveld P, Cavo M, Usmani S, Durie BG and Avet-Loiseau H; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. Leukemia 2014; 28: 269-277.

[38] Boyd KD, Ross FM, Chiecchio L, Dagrada GP, Konn ZJ, Tapper WJ, Walker BA, Wardell CP, Gregory WM, Szubert AJ, Bell SE, Child JA, Jackson GH, Davies FE and Morgan GJ; NCRI Haematology Oncology Studies Group. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. Leukemia 2012; 26: 349-355.

[39] Minguela A, Vasco-Mogorrón MA, Campillo JA, Cabañas V, Remigia MJ, Berenguer M, García-Garay MC, Blanquer M, Cava C, Galian JA, Gimeno L, Soto-Ramírez MF, Martínez-Hernández MD, de la Rubia J, Teruel AI, Muro M and Periago A. Predictive value of 1q21 gain in multiple myeloma is strongly dependent on concurrent cytogenetic abnormalities and first-line treatment. Am J Cancer Res 2021; 11: 4438-4454.

[40] Hanamura I. Gain/amplification of chromosome arm 1q21 in multiple myeloma. Cancers (Basel) 2021; 13: 256.

[41] Garifullin A, Voloshin S, Shuvaev V, Martynkevich I, Kleina E, Chechetkin A, Bessmeltcev S, Kuzyaeva A, Schmidt A, Kuvshinov A and Pavlova I. Significance of modified risk stratification mSmart 3.0 and autologous stem cell transplantation for patients with newly diagnosed multiple myeloma. Blood 2019; 134: 5593.

[42] Binder M, Rajkumar SV, Ketterling RP, Greipp PT, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Hayman SR, Hwa YL, Zeldenrust SR, Lust JA, Russell SJ, Leung N, Kapoor P, Go RS, Gonsalves WI, Kyle RA and Kumar SK. Prognostic implications of abnormalities of chromosome 13 and the presence of multiple cytogenetic high-risk abnormalities in newly diagnosed multiple myeloma. Blood Cancer J 2017; 7: e600.

[43] Varma A, Sui D, Milton DR, Tang G, Saini N, Hasan O, Mukherjee A, Joseph JJ, Bashir Q, Rondon G, Srour S, Popat UR, Hosing CM, Nieto Y, Kebriaei P, Alousi AM, Ahmed S, Mehta R, Khouri IF, Ahmed H, Iyer S, Weber DM, Thomas SK, Manasanch E, Lee HC, Patel K, Ciurea SO, Shpall EJ, Orlowski RZ, Champlin RE and Qazilbash MH. Outcome of multiple myeloma with chromosome 1q gain and 1p deletion after autologous hematopoietic stem cell transplantation: propensity score matched analysis. Biol Blood Marrow Transplant 2020; 26: 665-671.

[44] Schavgoulidze A, Talbot A, Perrot A, Cazaubiel T, Leleu X, Manier S, Buisson L, Mahéo S, Do Souto Ferreira L, Pavageau L, Hulin C, Marolleau JP, Voillat L, Belhadj K, Divoux M, Slama B, Brechignac S, Macro M, Stoppa AM, Sanhes L, Orsini-Piocelle F, Fontan J, Chretien ML, Demarquette H, Mohty M, Avet-Loiseau H and Corre J. Biallelic deletion of 1p32 defines ultra-high-risk myeloma, but monoallelic del(1p32) remains a strong prognostic factor. Blood 2023; 141: 1308-1315.

[45] Perrot A, Lauwers-Cances V, Tournay E, Hulin C, Chretien ML, Royer B, Dib M, Decaux O, Jaccard A, Belhadj K, Brechignac S, Fontan J, Voillat L, Demarquette H, Collet P, Rodon P, Sohn C, Lifermann F, Orsini-Piocelle F, Richez V, Mohty M, Macro M, Minvielle S, Moreau P, Leleu X, Facon T, Attal M, Avet-Loiseau H and Corre J. Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. J Clin Oncol 2019; 37: 1657-1665.

[46] D'Agostino M, Ruggeri M, Aquino S, Giuliani N, Arigoni M, Gentile M, Olivero M, Vincelli ID, Capra A, Mussatto C, Ledda A, Tacchetti P, Musolino C, Cellini C, Patriarca F, Ballanti S, Calogero R, Musto P, Boccadoro M and Gay F. Impact of gain and amplification of 1q in newly diagnosed multiple myeloma patients receiving carfilzomib-based treatment in the forte trial. Blood 2020; 136: 38-40.

[47] Giri S, Grimshaw A, Bal S, Godby K, Kharel P, Djulbegovic B, Dimopoulos MA, Facon T, Usmani SZ, Mateos MV and Costa LJ. Evaluation of daratumumab for the treatment of multiple myeloma in patients with high-risk cytogenetic factors: a systematic review and meta-analysis. JAMA Oncol 2020; 6: 1759-1765.

[48] Costa LJ, Chhabra S, Medvedova E, Dholaria BR, Schmidt TM, Godby KN, Silbermann R, Dhakal B, Bal S, Giri S, D'Souza A, Hall A, Hardwick P, Omel J, Cornell RF, Hari P and Callander NS. Daratumumab, carfilzomib, lenalidomide, and dexamethasone with minimal residual disease response-adapted therapy in newly diagnosed multiple myeloma. J Clin Oncol 2022; 40: 2901-2912.

[49] Goicoechea I, Puig N, Cedena MT, Burgos L, Cordón L, Vidriales MB, Flores-Montero J, Gutierrez NC, Calasanz MJ, Ramos MM, Lara-Astiaso D, Vilas-Zornoza A, Alignani D, Rodriguez I, Sarvide S, Alameda D, Garcés JJ, Rodriguez S, Fresquet V, Celay J, Garcia-Sanz R, Martinez-Lopez J, Oriol A, Rios R, Martin-Sanchez J, Martinez-Martinez R, Sarra J, Hernandez MT, de la Rubia J, Krsnik I, Moraleda JM, Palomera L, Bargay J, Martinez-Climent JA,

Orfao A, Rosiñol L, Mateos MV, Lahuerta JJ, Blade J, San Miguel J and Paiva B. Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma. Blood 2021; 137: 49-60.

[50] Avet-Loiseau H, Lauwers-Cances V, Corre J, Moreau P, Attal M and Munshi N. Minimal residual disease in multiple myeloma: final analysis of the IFM2009 trial. Blood 2017; 130: 435.

Table S1. Univariate and multivariate analyses of OS in the entire cohort (N = 934)

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, ≥ 65 vs. < 65 yrs	1.26 (1.05-1.52)	0.02	1.43 (1.12-1.83)	< 0.01
Male vs. female	1.08 (0.90-1.29)	0.42	-	-
ISS III vs. I/II	1.82 (1.51-2.19)	< 0.01	1.52 (1.14-2.03)	< 0.01
LDH, ≥ vs. < 220 U/L	2.00 (1.65-2.43)	< 0.01	1.67 (1.29-2.16)	< 0.01
CsCa, < vs. ≥ 2.75 mmol/L	1.87 (1.50-2.34)	< 0.01	1.63 (1.19-2.23)	< 0.01
Cr, ≤ vs. > 177 μmol/L	1.70 (1.40-2.07)	< 0.01	1.23 (0.92-1.63)	0.16
Hb, < vs. ≥ 100 g/L	1.47 (1.19-1.81)	< 0.01	0.93 (0.69-1.24)	0.60
PLT, < vs. ≥ 100×10^9/L	2.55 (2.03-3.19)	< 0.01	1.81 (1.30-2.51)	< 0.01
1q+, pos. vs. neg.	1.39 (1.16-1.67)	< 0.01	1.40 (1.10-1.79)	< 0.01
del(17p), pos. vs. neg.	1.51 (1.18-1.93)	< 0.01	1.21 (0.88-1.68)	0.24
del(13q), pos. vs. neg.	1.34 (1.12-1.61)	< 0.01	1.19 (0.93-1.52)	0.17
t(11;14), pos. vs. neg.	1.22 (0.90-1.65)	0.19	-	-
t(4;14), pos. vs. neg.	1.22 (0.92-1.63)	0.17	-	-
t(14;16), pos. vs. neg.	2.58 (1.41-4.73)	< 0.01	1.97 (1.06-3.67)	0.03

OS, overall survival; N, number; HR, hazard ratio; CI, confidence interval; *P*, *p* value; yrs, years; ISS, International Staging System; LDH, lactate dehydrogenase; CsCa, serum corrected calcium; Cr, serum creatinine; Hb, hemoglobin; PLT, platelet; pos, positive; neg, negative.

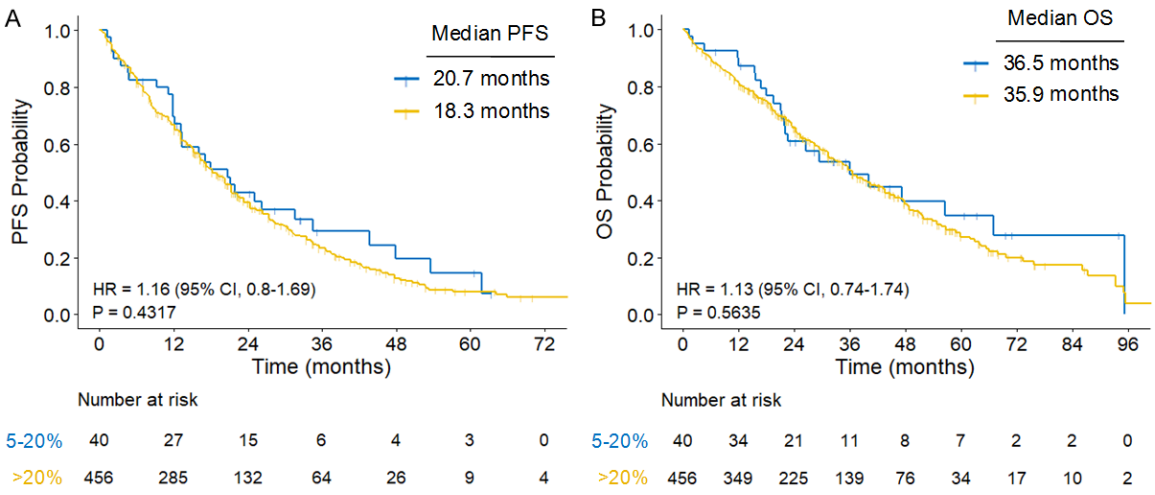


Figure S1. Survival of 1q+ patients according to different cutoff values. (A, B) Kaplan-Meier estimates of progression-free survival/PFS (A) and overall survival/OS (B) for 1q+ patients defined by the cutoff of 5-20% vs. > 20%.

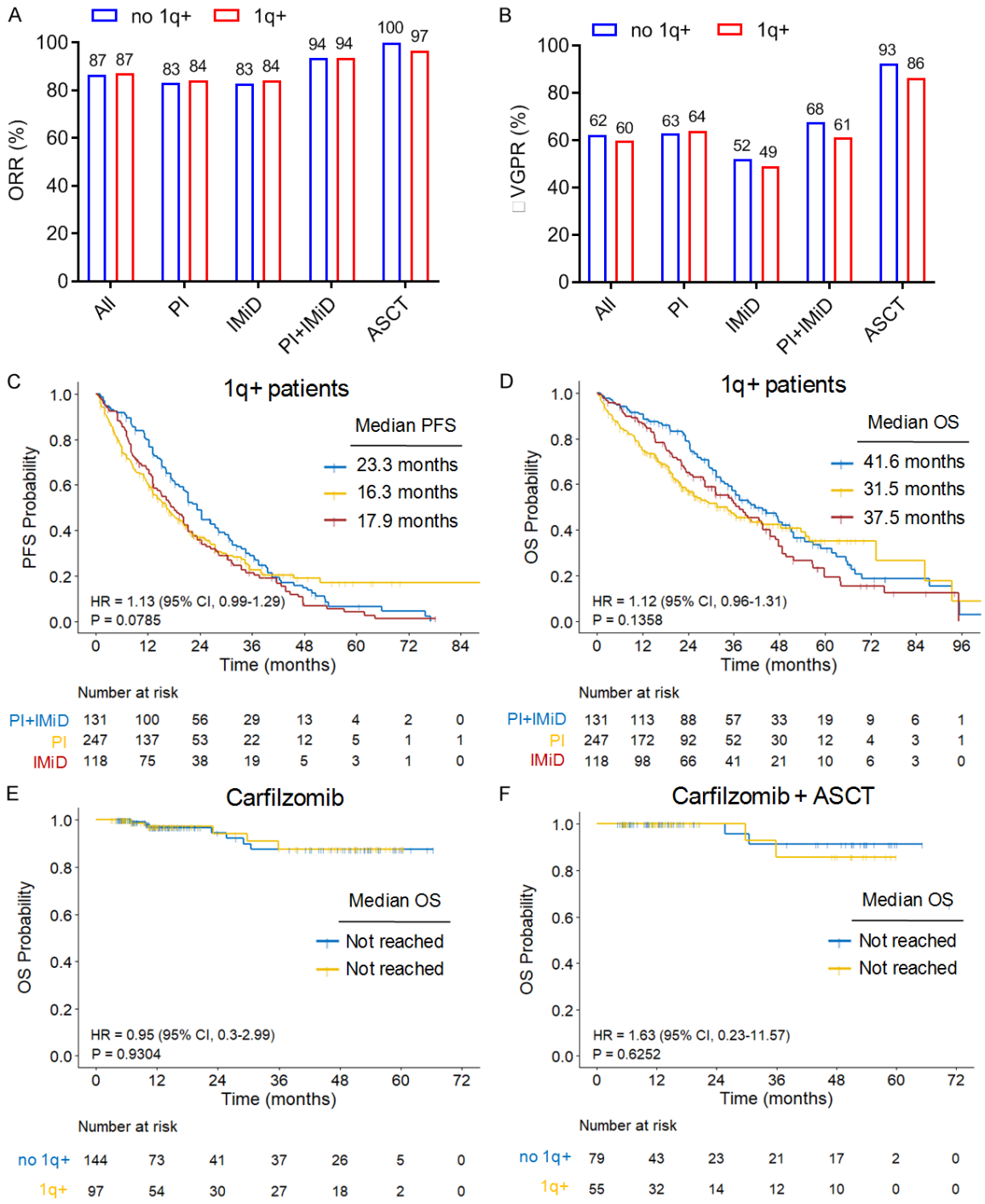


Figure S2. Effects of different therapies on response and survival of 1q+ patients. (A, B) Percentage of patients with or without 1q+ who achieved ≥ partial response/PR (objective response rate/ORR) (A) or ≥ very good partial response/VGPR (B). (C, D) Kaplan-Meier estimates of PFS (C) and OS (D) for 1q+ patients who received proteasome inhibitor/PI, immunomodulatory drug/IMiD, or both. (E, F) Kaplan-Meier estimates of OS for patients with or without 1q+ who received carfilzomib-based induction (E) and following ASCT (F) in the CoMMpass cohort.

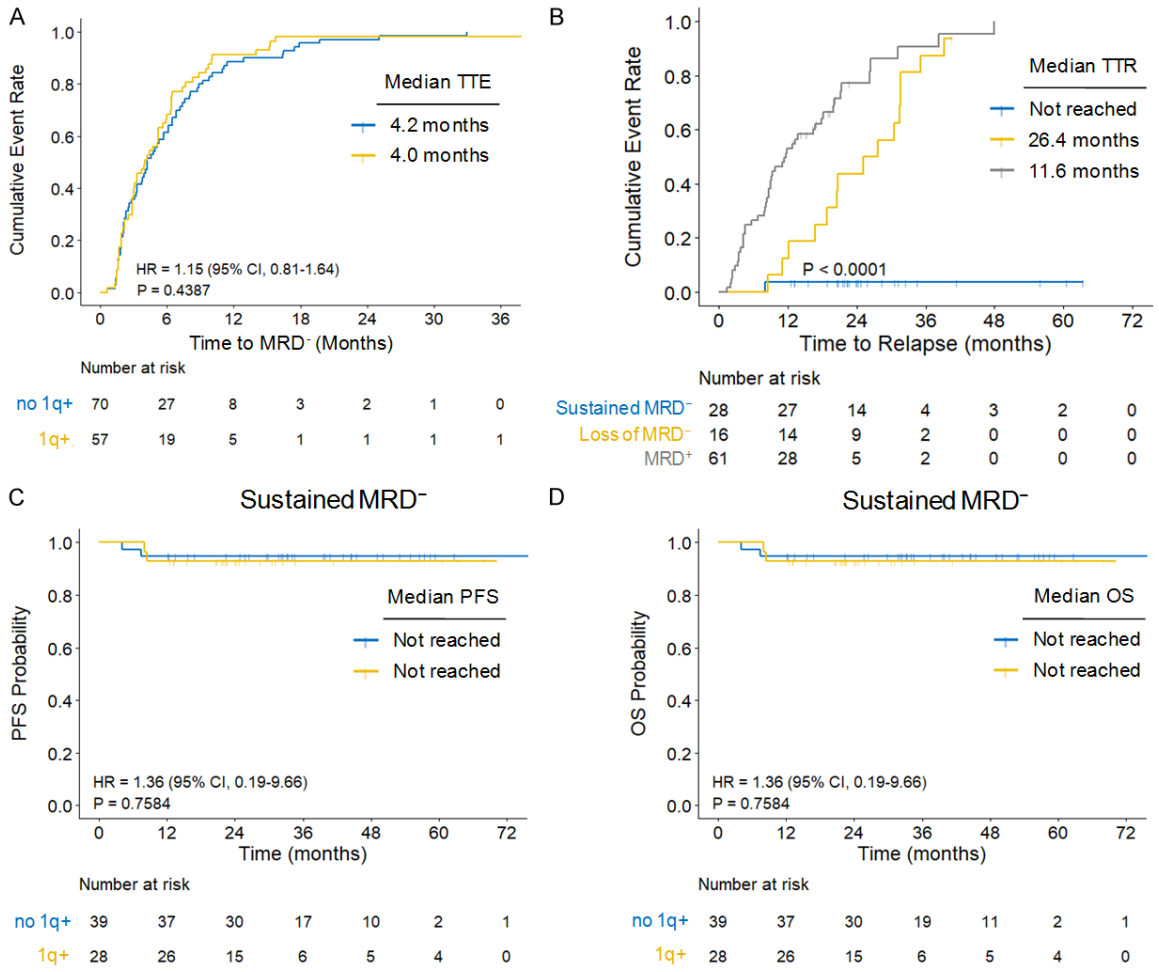


Figure S3. Impact of the minimal residue disease (MRD) status on the outcome of 1q+ patients. (A) Kaplan-Meier estimates of time to event (TTE; i.e., MRD⁻). (B) Kaplan-Meier estimates of time to relapse (TTR) in patients with sustained MRD⁻, loss of MRD⁻, and persistent MRD (MRD⁺). (C, D) Kaplan-Meier estimates of PFS (C) and OS (D) in patients with or without 1q+ who achieved sustained MRD⁻.