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Clinical characteristics and treatment outcomes of newly diagnosed multiple myeloma with chromosome 1q abnormalities

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Key Points

- +1q is associated with high tumor burden and advanced disease stage in newly diagnosed MM.
- +1q is associated with decreased OS independent of other HR cytogenetic abnormalities, disease stage, and age.

A gain in chromosome 1q (+1q) is among the most common cytogenetic abnormalities in multiple myeloma (MM). It is unclear whether +1q is independently associated with decreased overall survival (OS). The objective of this study was to evaluate the impact of +1q on clinical characteristics, treatment response, and survival outcomes. We included 1376 Mayo Clinic patients diagnosed with MM from 2005 to 2018 who underwent fluorescence in situ hybridization testing at diagnosis with a panel including the +1q probe. A gain in 1q was found in 391 patients (28%) and was associated with anemia, hypercalcemia, high tumor burden, International Staging System (ISS) stage 3, high-risk (HR) translocations, and chromosome 13 abnormalities. There was no difference in overall response or deeper responses to proteasome inhibitor (PI)–, immunomodulatory drug (iMiD)–, or PI plus IMiD–based induction. Time to next treatment was shorter in patients with +1q compared with those without +1q (19.9 vs 27.7 months; $P < .001$). On univariate analysis, +1q was associated with increased risk of death (risk ratio [RR], 1.9; $P < .001$), and decreased OS was seen in all treatment groups. +1q was independently associated with decreased OS on multivariate analysis when other HR cytogenetic abnormalities, ISS stage 3, and age ≥70 years were included (RR, 1.5; $P < .001$). Gain of >1 copy of 1q was not associated with worse OS compared with gain of 1 copy (4.9 vs 4.3 years; $P = .21$). +1q was associated with high tumor burden, advanced disease stage, and HR translocations. It is independently associated with decreased OS, even in the setting of novel therapy and transplant.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and contributes to ~2% of deaths resulting from cancer.[1,2] It is characterized by clinical and genetic heterogeneities, reflected in markedly variable patient outcomes and therefore demanding identification of prognostic factors for risk stratification.[3] Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) are among the most powerful adverse prognostic markers in newly diagnosed MM; t(4;14), t(14;16), and del(17p) have been incorporated into the definition of high-risk (HR) disease.[4,5] The routine use of FISH has uncovered additional cytogenetic abnormalities associated with clinical features and with potential prognostic significance in newly diagnosed patients.[6] A gain in the long arm of chromosome 1 (+1q) is among the most common cytogenetic abnormalities in MM. This abnormality

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can lead to dysregulation of several genes, including *CKS1B*,[7] MCL-1,[8] and ADAR1,[9] and is associated with disease progression along the spectrum from monoclonal gammopathy of undetermined significance and smoldering MM to relapsed MM.[10] Although several studies have suggested that +1q is associated with inferior outcomes,[11-13] other studies have not confirmed that it is an independent adverse prognostic factor.[14,15] The objective of this study was to evaluate the impact of +1q on clinical characteristics, treatment outcomes, and overall survival (OS) in a large cohort of newly diagnosed MM patients treated with novel agents, with or without autologous stem cell transplantation.

Methods

Patients and study design

This was a retrospective study including all patients seen in Mayo Clinic in Rochester, Minnesota, from 2006 to 2018 within 90 days from diagnosis; patients were identified using a prospectively maintained database, and additional laboratory and clinical data for these patients were obtained by review of electronic medical records. The cohort included 1376 patients diagnosed with MM between December 2005 and February 2018 who had cytogenetic analysis by FISH performed within 1 year before diagnosis or after diagnosis but <6 months from the start of first-line treatment and for whom the FISH panel included the probe for +1q. The study was approved by the Mayo Clinic Institutional Review Board. All patients had authorized the use of their electronic medical record data for research. FISH analysis was performed on bone marrow samples as previously described[16] using unsorted plasma cells. The following enumeration probes were used in the panel: 1q/1p (1q22/TP73; in house, custom developed), 3 centromere (D3Z1), 7 centromere (D7Z1), 9 centromere (D9Z1), 15 centromere (D15Z4), 13q14 (RB1), 13q34 (LAMP1), 17p13.1 (TP53), and 17 centromere (D17Z1). Dual-color, dual-fusion probes targeting t(11;14) CCND1/immunoglobulin H (IgH), and breakapart probes targeting IgH and 8q24.1 (MYC), were also used. If an IgH rearrangement other than t(11;14) was found by the IgH breakapart probe, reflex testing was performed using dual-color, dual-fusion probes to identify the translocation partner: t(4;14)(p16.3;q32) FGFR3/IgH, t(14;16)(q32;q23) IgH/MAF, t(14;20)(q32;q12) IgH/MAFB, and t(6;14)(p21;q32) CCND3/IgH. The 1q22 probe was introduced for clinical use as part of the myeloma FISH panel in Mayo Clinic starting in August 2014. For samples obtained before this date, testing for +1q was performed as an add-on test by scoring a total of 200 cells from samples not subjected to plasma cell enrichment; after this date, 1q testing was performed as part of the myeloma FISH panel by scoring a total of 50 cells from samples enriched with plasma cells using the cytoplasmic immunoglobulin stain. The threshold for +1q was 3.5%.

Statistical analysis

First, we compared baseline clinical characteristics of patients with +1q and those without +1q using Fisher's exact and Wilcoxon rank sum tests for categorical and continuous variables, respectively. Staging was performed in accordance with the International Staging System (ISS) for MM.[17] Then, we compared treatment outcomes between the 2 groups, including overall response rate (ORR), rate of very good partial response (VGPR) or better, and time to next treatment (TTNT), according to type of first-line induction chemotherapy: proteasome inhibitor (PI)–, immunomodulatory drug (IMiD)–, and PI plus IMiD–based treatment. ORR, defined as a partial response or better, and rate of VGPR or better were compared between the groups using Fisher's exact test. Treatment responses were defined in accordance with the International Myeloma Working Group consensus criteria.[18] TTNT was defined as time of start of first-line treatment to time of start of second-line treatment. The impact of +1q on OS was evaluated using univariate and multivariate Cox proportional hazards models. An HR IgH translocation was defined by the presence of any of the following: t(4;14), t(14;16), or t(14;20)[4,19]; all other IgH translocations were considered standard-risk (SR) translocations. OS was defined as the time from diagnosis until death resulting from any cause or last follow-up. OS and TTNT curves were generated using the Kaplan-Meier method and compared using the log-rank test. For all tests, $P < .05$ was considered statistically significant. All statistical analyses were performed using JMP software (SAS Institute, Cary, NC).

Results

Clinical characteristics

Among all patients, +1q (defined by ≥3 total copies of 1q) was found in 391 (28%). Median age was higher for patients with +1q compared with those without +1q (66 vs 64 years). Patients with +1q were more likely to have anemia, thrombocytopenia, hypercalcemia, elevated lactate dehydrogenase, elevated β_2-microglobulin, and/or a higher proportion of bone marrow plasma cells. A higher proportion of patients with +1q had ISS stage 3 (45% vs 35%), IgA isotype for M protein, and/or λ light chain isotype; a lower proportion of patients with +1q had light chain MM. In addition, +1q was associated with an HR IgH translocation (25% vs 11%), monosomy 13 (48% vs 36%), and del(13q) (14% vs 7%). In contrast, patients with +1q were less likely to have t(11;14). There was no difference in the cooccurrence of trisomies between the 2 groups (Table 1). Among patients with +1q, we compared clinical characteristics based on primary cytogenetic abnormalities: HR IgH translocation (without trisomy), SR IgH translocation (without trisomy), or trisomy (without IgH translocation); the groups included 71, 52, and 145 patients, respectively. Among patients with +1q, those with an HR translocation were more likely to have thrombocytopenia (52% vs 21% vs 22%, respectively; $P = .001$), higher serum M spike (median, 3.5 vs 1.1 vs 2.7 g/dL, respectively; $P = .01$), and urinary M spike (0.3 vs 0.1 vs 0 g per 24 hours, respectively; $P = .03$), but they were less likely to have lytic lesions (51% vs 67% vs 73%, respectively; $P = .02$). Otherwise, there were no differences in clinical characteristics between the 3 groups (supplemental Table 1).

Treatment outcomes with first-line therapy

Treatment data were available for 1320 of 1376 patients, including 1215 with treatment response data. More than 95% of patients received first-line induction chemotherapy with novel agents. The drugs used in first-line treatment are shown in supplemental Figure 1; 581 patients underwent postinduction transplantation, including tandem transplantation in 7 patients (1 of these patients had +1q). There was no difference in ORR to induction chemotherapy between patients with +1q and those without +1q with PI- (82% vs 79%; $P = .59$), IMiD- (77% vs 84%; $P = .17$), or PI plus IMiD–based induction (96% vs 93%; $P = .34$). Similarly, there was no difference in rate of VGPR or better

Table 1. Baseline characteristics

	All (N = 1376)	No +1q (n = 985)	+1q (n = 391)	P
Age, y				
Median	64	64	66	.009
IQR	57-71	57-70	59-72	
≥70 (vs <70)	381 (28)	253 (26)	128 (33)	.009
Male sex	834 (61)	611 (62)	223 (57)	.10
ECOG PS				
≥2 (vs 0-1)	95 (19)	64 (18)	31 (22)	.38
Hb, g/dL				
Median	10.9	11.1	10.4	<.001
IQR	9.4-12.4	9.6-12.7	8.9-11.9	
<10 (vs ≥10)	406 (33)	258 (29)	148 (42)	<.001
Platelets, × 10^9/L				
Median	210	214	193	<.001
IQR	162-259	168-264	142-244	
<150 (vs ≥150)	171 (20)	108 (17)	63 (27)	.001
Serum creatinine, mg/dL				.047
Median	1.0	1.0	1.1	
IQR	0.9-1.5	0.8-1.3	0.9-1.7	
LDH, units/L				
Median	165	162	174	.02
IQR	138-201	137-194	138-219	
>222 (vs ≤222)	147 (16)	90 (14)	57 (23)	<.001
B2M, μg/mL				
Median	4.1	3.9	4.8	<.001
IQR	2.8-7.4	2.7-6.9	3.3-8.8	
>5.5 (vs ≤5.5)	383 (36)	254 (33)	129 (43)	.002
Albumin, g/dL				
Median	3.6	3.6	3.5	.007
IQR	3.2-3.8	3.3-3.8	3.2-3.7	
≤3.5 (vs >3.5)	507 (49)	353 (47)	156 (54)	.05
Calcium, mg/dL				
Median	9.5	9.5	9.5	.88
IQR	9.1-10.1	9.1-10.1	9.0-10.2	
≥11 (vs <11)	110 (9)	68 (8)	42 (13)	.01
Lytic lesions	763 (69)	554 (70)	209 (67)	.47
BMPCs, %				
Median	50	50	60	<.001
IQR	30-70	25-70	40-80	
≥50 (vs <50)	712 (55)	474 (51)	238 (66)	<.001
Serum M spike, g/dL				.05
Median	2.5	2.4	2.8	
IQR	0.6-3.9	0.6-3.8	0.8-4.2	
Urine M spike, g/24 h				.002
Median	0.04	0.03	0.13	
IQR	0-0.5	0-0.4	0-0.8	
Immunoglobulin isotype				
IgA	263 (25)	160 (21)	103 (35)	<.001
IgG	626 (60)	463 (61)	163 (55)	.06
LC MM	141 (13)	117 (16)	24 (8)	.001
Involved LC Λ	385 (36)	247 (33)	138 (45)	<.001
ISS stage				
1	245 (24)	197 (27)	48 (17)	
2	383 (38)	275 (38)	108 (38)	
3	384 (38)	255 (35)	129 (45)	<.001
3 (vs 1/2)	384 (38)	255 (35)	129 (45)	.003
PCLI, %				
Median	0.8	0.8	1.0	.01
IQR	0.3-1.5	0.2-1.4	0.4-2.2	
≥2 (vs <2)	82 (19)	54 (16)	28 (28)	.009
SR FISH abnormality				
Trisomy	790 (59)	558 (58)	232 (60)	.46
t(11;14)	273 (20)	221 (23)	52 (13)	<.001
Del(13q)	128 (9)	72 (7)	56 (14)	<.001
Monosomy 13	530 (39)	344 (36)	186 (48)	<.001
HR FISH abnormality				
t(4;14)	129 (10)	69 (7)	60 (16)	<.001
t(14;16)	57 (4)	29 (3)	28 (7)	<.001
t(14;20)	15 (1)	5 (1)	10 (3)	.002
Del(17p)/monosomy 17	174 (13)	130 (14)	44 (11)	.32
First-line induction chemotherapy				
PI based	472 (36)	337 (36)	135 (36)	
IMiD based	465 (35)	366 (39)	99 (27)	
PI + IMiD based	374 (28)	239 (25)	135 (36)	
Other	9 (1)	6 (1)	3 (1)	
First-line transplantation	581 (44)	426 (45)	155 (42)	

Comparison of clinical characteristics, prevalence of cytogenetic abnormalities, and first-line treatments in patients with +1q and without +1q. Median (IQR) is presented for continuous variables and n (%) for categorical variables.

B2M, β_2-microglobulin; BMPC, bone marrow plasma cell; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; LC, light chain; LDH, lactate dehydrogenase; PCLI, plasma cell labeling index.

between patients with and without +1q with PI- (42% vs 44%; $P = .66$), IMiD- (31% vs 29%; $P = .70$), or PI plus IMiD–based induction chemotherapy (63% vs 55%; $P = .18$). Among patients who underwent postinduction transplantation, similar ORRs (99% vs >99%) and rates of VGPR or better to first-line treatment (82% vs 80%; $P = .64$) were seen among patients with and without +1q (Figure 1; supplemental Table 2).

For the overall cohort, TTNT after initiation of first-line therapy was shorter for patients with +1q compared with patients without +1q; median TTNTs were 19.9 (95% confidence interval [CI], 17.2-22.9 months) and 27.7 months (95% CI, 25.3-30.3 months) in the 2 groups, respectively ($P < .001$). Among patients who received PI-based first-line treatment, median TTNT was shorter for those with +1q (15.0 months; 95% CI, 8.1-17.7 months) compared with those without +1q (22.4 months; 95% CI, 18.9-25.9 months; $P = .004$).

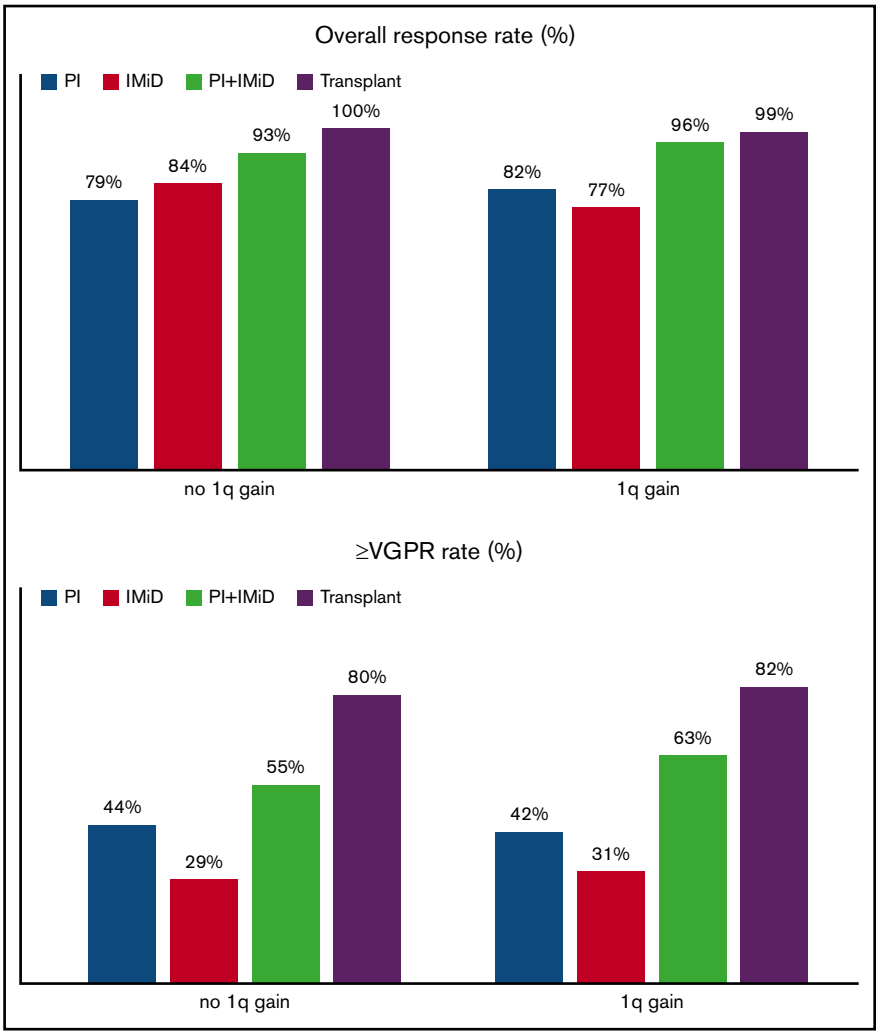

Figure 1. Response to first-line treatment. ORR and rate of VGPR or better to PI-, IMiD-, or PI plus IMiD–based first-line induction chemotherapy and transplantation in patients with and without +1q.

Similarly, TTNT was shorter for those with +1q (20.5 months; 95% CI, 15.3-26.6 months) compared with those without +1q (31.2 months; 95% CI, 27.6-35.1 months; $P < .001$) among patients who received IMiD-based treatment. Among those who received a PI plus IMiD–based regimen, there was no significant difference in TTNT between those with +1q (27.6 months; 95% CI, 22.2-36.8 months) and those without +1q (33.0 months; 95% CI, 27.0-40.6 months; $P = .17$; Figure 2). TTNT was shorter in patients with +1q compared with patients without +1q among those who underwent stem cell transplantation after first-line induction chemotherapy (median TTNT, 29.8 vs 37.1 months; $P = .01$) and among those who received first-line treatment with chemotherapy only (median TTNT, 8.5 vs 13.9 months; $P < .001$; Figure 3A-B).

Among patients who underwent stem cell transplantation, there was a trend toward shorter TTNT for patients with +1q compared with those without +1q when the first-line treatment was PI (26.9 vs 35.2 months; $P = .35$), IMiD (28.7 vs 38.7 months; $P = .06$), or PI plus IMiD based (32.0 vs 38.5 months; $P = .13$), but this was not statistically significant. Among patients who did not undergo transplantation, there was a trend toward shorter TTNT with +1q for those receiving PI- (4.7 vs 6.0 months; $P = .13$) or PI plus IMiD–based induction (15.0 vs 19.8 months; $P = .49$) and a statistically significant reduction for those receiving IMiD-based induction (14.4 vs 20.8 months; $P = .009$).

We then compared TTNT between patients with +1q and an HR IgH translocation (without trisomy), +1q and an SR IgH translocation (without trisomy), and +1q and trisomy (without IgH translocation) and patients without +1q. TTNTs were 19.6 months (95% CI, 13.0-26.7 months), 16.9 months (95% CI, 9.1-27.6 months), 24.4 months (95% CI, 17.7-28.7 months), and 27.7 months (95% CI. 25.3-30.3 months) in the 4 groups, respectively ($P = .008$; supplemental Figure 2A).

There was no significant difference in TTNT between patients who had +1q in the absence of an HR IgH translocation (median TTNT, 20.0 months; 95% CI, 17.2-24.4 months), patients who had an HR IgH translocation in the absence of +1q (median TTNT, 22.0 months; 95% CI, 16.7-26.4 months), and patients with both +1q and an HR IgH translocation (median TTNT, 18.4 months; 95% CI, 11.0-25.4 months); TTNT was significantly longer in patients with neither +1q nor an HR IgH translocation (median TTNT, 29.3 months; 95% CI, 26.8-31.3 months; $P < .001$). These results are shown in supplemental Figure 3A.

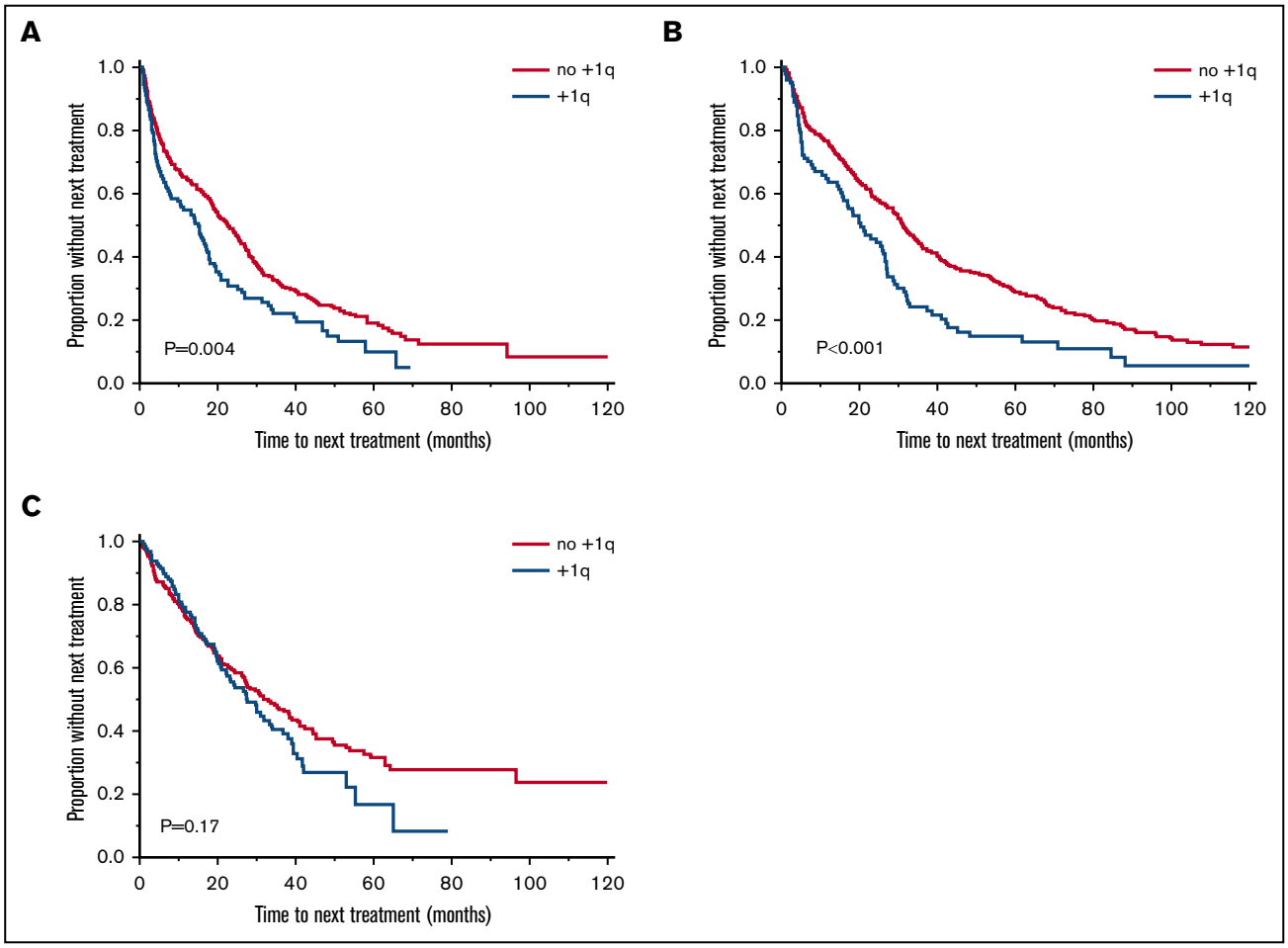

Figure 2. TTNT after first-line treatment. TTNT (months) in patients with (blue curve) and without +1q (red curve) among those who received PI- (A), IMiD- (B), and PI plus IMiD–based first line treatment (C).

OS outcomes

Median estimated follow-up in the entire cohort was 4.0 years (interquartile range [IQR], 2.2-6.1 years); median OS was 7.4 years (95% CI, 6.5-8.5 years). Median OS was significantly shorter for patients with +1q (5.3 years; 95% CI, 4.5-6.0 years) compared with those without +1q (8.8 years; 95% CI, 7.7-9.3 years; $P < .001$). Among patients who received first-line treatment with a PI-based regimen, OS was shorter in patients with +1q (5.0 years; 95% CI, 3.4-6.1 years) compared with those without +1q (8.1 years; 95% CI, 6.6-10.3 years; $P < .001$). Similarly, OS was also shorter in patients with +1q (5.3 years; 95% CI, 3.3-6.3 years) compared with those without +1q (8.8 years; 95% CI, 7.2-9.4 years) among those who received IMiD-based treatment ($P < .001$). Among those who received PI plus IMiD–based treatment, OS was also shorter in patients with +1q (6.2 years; 95% CI, 4.7 years to not reached [NR]) compared with patients without +1q (NR; 95% CI, 6.7 years to NR; $P = .005$; Figure 4). In addition, OS was shorter for patients with +1q compared with those without +1q among patients who underwent transplantation after first-line induction chemotherapy (7.5 vs 11.1 years; $P < .001$) and among those who received first-line treatment with chemotherapy only (3.7 vs 6.5 years; $P < .001$; Figure 3C-D). Among all patients who underwent transplantation, including first-line transplantation or transplantation later in the disease course (842 patients), OS from transplantation was shorter in patients with +1q (5.5 years; 95% CI, 4.5-7.1 years) compared with those without +1q (8.9 years; 95% CI, 8.2-10.8 years; $P < .001$).

Among those who underwent transplantation after first-line chemotherapy, OS was shorter for patients with +1q compared with those without +1q with IMiD- (8.5 vs 11.4 years; $P = .01$) and PI plus IMiD–based treatment (6.2 years vs NR; $P = .04$). There was no difference in OS in patients with +1q and those without +1q with PI-based treatment (median OS, NR vs 9.8 years, respectively; $P = .25$). Among patients who did not undergo transplantation, OS was significantly shorter with +1q in patients who received PI- (3.4 vs 6.0 years; $P < .001$), IMiD- (3.3 vs 6.5 years; $P < .001$), or PI plus IMiD–based treatment (6.8 vs 7.7 years; $P = .03$).

OS was 3.7 years (95% CI, 2.4-9.1 years) in patients with +1q and an HR translocation, 5.0 years (95% CI, 3.3-6.8 years) in patients with +1q and an SR translocation, 5.6 years (95% CI, 4.9-6.3 years) in patients with +1q and trisomy, and 8.8 years (95% CI, 7.7-9.3 years) in patients without +1q ($P < .001$; supplemental Figure 1B).

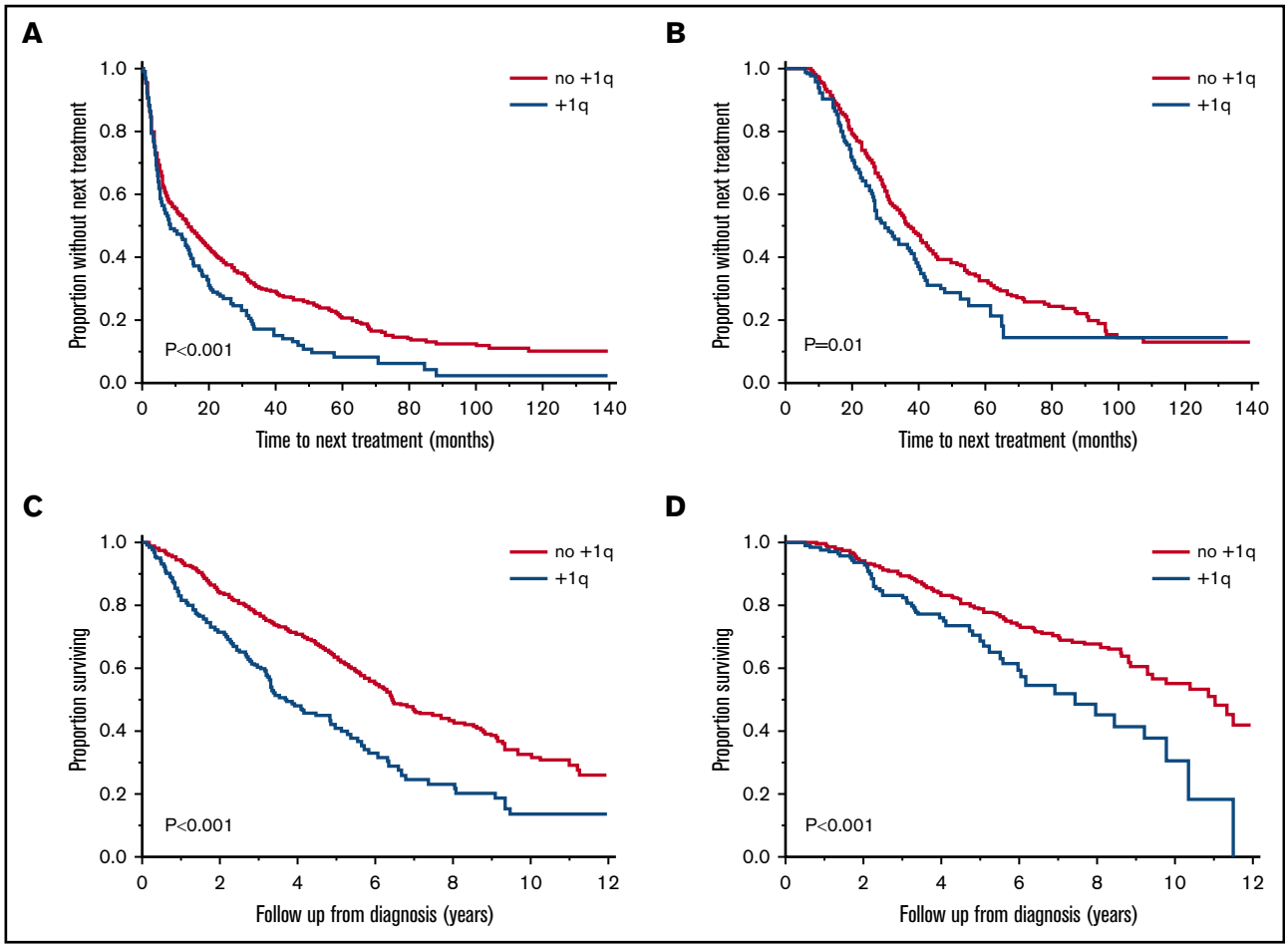

Figure 3. TTNT and OS by transplantation status. TTNT (months) in patients with (blue curve) and without +1q (red curve) among those who received chemotherapy alone (A) and those who underwent postinduction transplantation (B). OS in patients with (blue curve) and without +1q (red curve) among those who received chemotherapy alone (C) and those who underwent postinduction transplantation (D).

There was no significant difference in OS between patients who had +1q in the absence of an HR IgH translocation (median OS, 5.5 years; 95% CI, 4.9-6.2 years), patients who had an HR IgH translocation in the absence of +1q (median OS, 4.5 years; 95% CI, 3.4-6.3 years), and patients with both +1q and an HR IgH translocation (median OS, 3.7 years; 95% CI, 2.9-6.1 years); OS was significantly longer in patients with neither +1q nor an HR IgH translocation (median OS, 9.2 years; 95% CI, 8.6-10.1 years; $P <$ .001). These results are shown in supplemental Figure 3B.

OS was compared between patients with +1q and without +1q based on age (≥70 or <70 years) and ISS stage (3 or 1/2). OS was shorter in patients with +1q compared with those without +1q in patients age <70 years (6.0 vs 9.4 years; $P <$ .001) and in patients age ≥70 years (3.7 vs 5.9 years; $P <$ .001). Similarly, OS was shorter in patients with +1q compared with those without +1q in patients with ISS stage 1/2 (6.1 vs 8.8 years; $P <$ .001) and in patients with stage 3 MM (3.3 vs 5.3 years; $P =$ .001). Among patients with an HR IgH translocation (n = 201), there was no significant difference in OS between patients with +1q (3.7 years; 95% CI, 2.9-6.1 years) and those without +1q (4.5 years; 95% CI, 3.4-6.3 years; $P =$ .48; Figure 5A). Among patients with an SR IgH translocation (n = 456), patients with +1q had significantly shorter survival (5.4 years; 95% CI, 3.3-6.8 years) compared with those without +1q (8.8 years; 95% CI, 7.0-11.1 years; $P <$ .001; Figure 5B). Similarly, among patients with trisomy (without IgH translocation; n = 546), OS was shorter in patients with +1q (5.6 years; 95% CI, 4.9-6.3 years) compared with those without +1q (9.7 years; 95% CI, 8.6-11.3 years; $P <$ .001; Figure 5C).

On univariate analysis, risk of death was increased for patients with +1q (risk ratio [RR], 1.9; 95% CI, 1.6-2.3; $P <$ .001). On multivariate analysis including +1q and other cytogenetic abnormalities associated with increased risk of death on univariate analysis [ie, HR IgH translocation, del(17p), and monosomy 13], +1q was associated with increased risk of death (RR, 1.7; 95% CI, 1.5-2.1; $P <$ .001). However, monosomy 13 was not associated with OS when other cytogenetic abnormalities were included. On multivariate analysis including +1q, HR IgH translocation, del(17p), ISS stage 3, and age ≥70 years, +1q was independently associated with decreased OS (RR, 1.5; 95% CI, 1.2-1.8; $P <$ .001; Table 2).

When we compared OS between patients who had +1q without other HR cytogenetic abnormalities [HR IgH translocation and

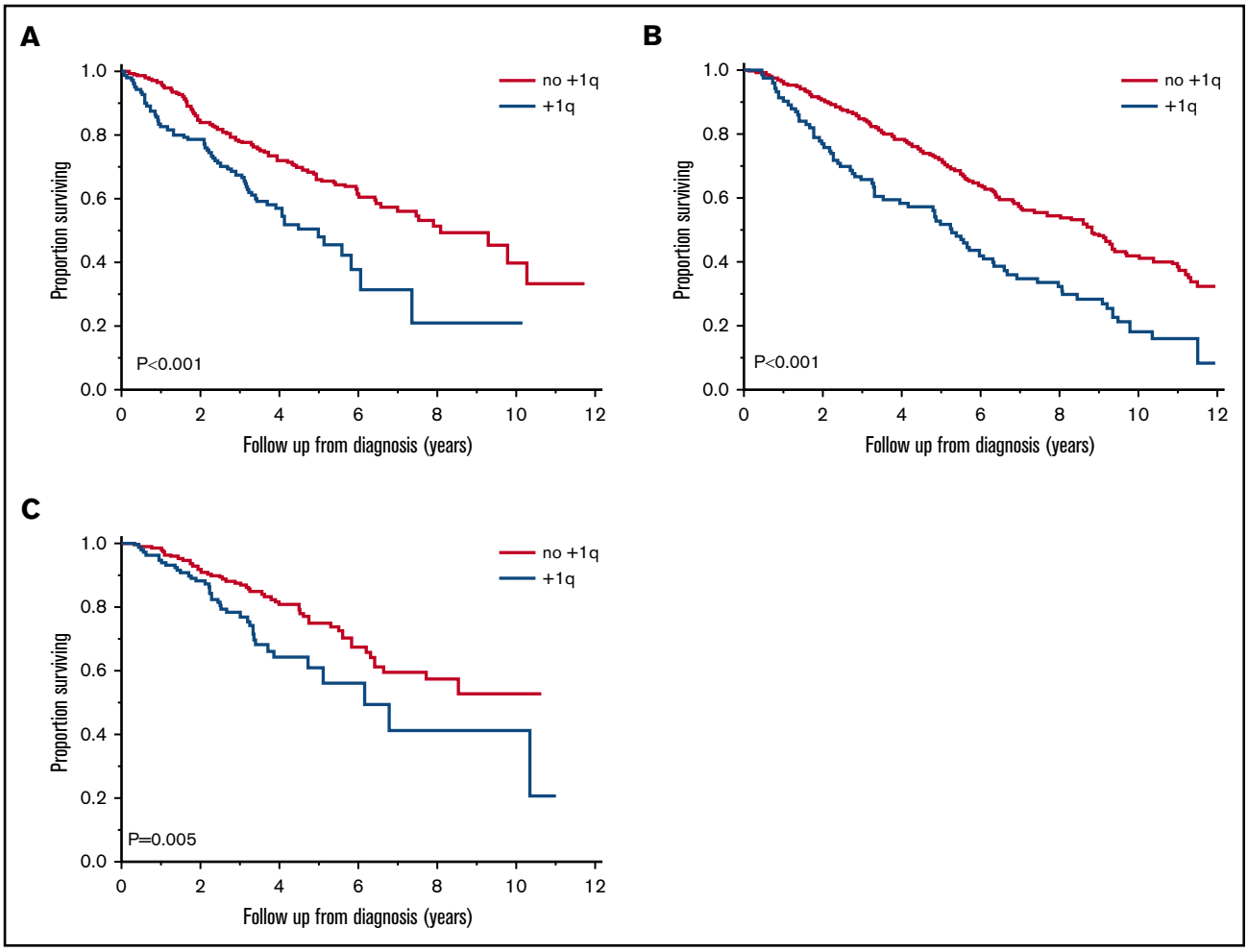

Figure 4. OS by first-line treatment. OS (years) among patients with (blue curve) and without (red curve) +1q among those who received PI- (A), IMiD- (B), and PI plus IMiD–based (C) first-line treatment.

del(17p)] and patients with 1 HR cytogenetic abnormality [either HR IgH translocation or del(17p)], there was no significant difference between the 2 groups; median OS rates were 5.6 and 5.1 years in the 2 groups, respectively ($P = .22$). Median OS (9.4 years) was significantly longer in patients who did not have +1q, an HR IgH translocation, or del(17p) ($P < .001$; Figure 5D).

Impact of copy number and clone size

We performed a subgroup analysis including 155 patients with +1q, where information on the percentage of cells with ≥3 copies of 1q was available. For these patients, samples not enriched for plasma cells were used, and a total of 200 cells were scored. Of these, 50 had a gain of >3 copies of 1q (1q amplification), and 105 had a gain of 3 copies. A higher proportion of patients with 1q amplification had elevated lactate dehydrogenase compared with patients with 1q gain (32% vs 16%; $P = .04$). Otherwise, there were no significant differences in clinical characteristics between the 2 groups (data not shown). TTNT was 19.6 months (95% CI, 15.3-24.4 months) in patients with 1 copy gain and 14.4 months (95% CI, 4.6-21.0 months) in patients with 1q amplification ($P = .10$; Figure 6A). There was no difference in OS between the 2 groups; median OS times were 4.9 years (95% CI, 3.3-5.8 years) and 4.3 years (95% CI, 2.4-5.6 years) in the 2 groups, respectively ($P = .21$; Figure 6B). Median cell percentage with +1q was 14.5% (IQR, 8.5% to 30.5%); 61 patients had a gain in ≥20% of cells, and 13 patients had a gain in ≥50% of cells. There was a trend toward decreased OS in patients with a gain in ≥20% of cells compared with patients with a gain in <20% of cells (median OS, 3.5 vs 5.1 years), but this was not statistically significant ($P = .10$). There was also no significant difference in OS between patients with +1q in ≥50% of cells compared with patients with +1q in <50% of cells (median OS, 3.3 vs 4.8 years; $P = .42$). Among patients with +1q, 50 had a gain of >1 copy (1q amplification). Median percentage of cells with 1q amplification in these patients was 8% (IQR, 5% to 25%); 13 patients had 1q amplification in ≥20% of cells, and only 2 patients had >50% of cells with 1q amplification. Median OS times were 4.5 and 4.1 years in patients with ≥20% and <20% of cells with 1q amplification, respectively ($P = .66$).

Discussion

In this study, we found that +1q is common at diagnosis of MM, seen in ~28% of patients, and that it is associated with anemia,

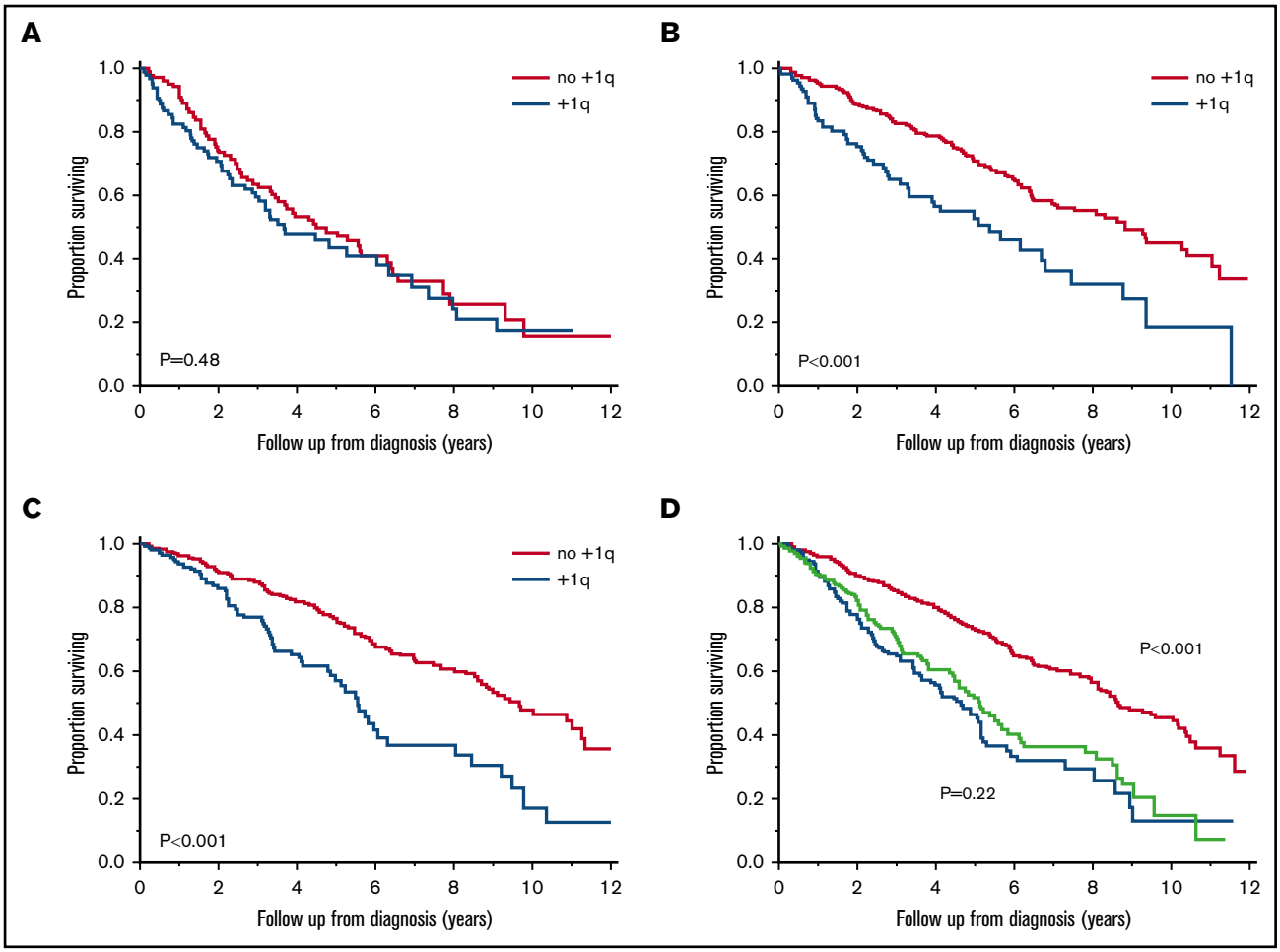

Figure 5. Impact of +1q on OS. Comparison of OS (years) in patients with (blue curve) and without +1q (red curve) among those with an HR IgH translocation (A), an SR IgH translocation (B), or trisomy (without IgH translocation) (C). (D) Comparison of OS (years) in patients with +1q without other HR abnormalities (green curve), patients with 1 HR abnormality but without +1q (blue curve), and patients with no +1q or other HR abnormalities (red curve).

thrombocytopenia, hypercalcemia, markers of high tumor burden, advanced disease stage, IgA MM, and HR IgH translocation; these findings are consistent with results from previous studies.[10,14,20,21] However, there have been inconsistent results on the prognostic value of +1q; in some studies, +1q was found to be independently associated with inferior outcomes, whereas in others, the inferior outcomes were attributed to its cooccurrence with other HR cytogenetic abnormalities and/or its association with advanced disease.[11-14] In a metaanalysis by Shah et al[11] including 1905 newly diagnosed MM patients from the National Cancer Research Institute Myeloma XI and Medical Research Council Myeloma IX trials, +1q was independently associated with poor OS (hazard ratio, 1.68; $P < .001$) on multivariate analysis including HR translocation [t(4;14), t(14;16), or t(14;20)] and advanced ISS stage. In contrast, in the study by Fonseca et al[14] including 159 patients treated with high-dose therapy and transplantation, +1q

Table 2. Multivariate analysis for survival

	Univariate		Multivariate (FISH abnormalities only)		Multivariate (all)	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
+1q	1.9 (1.6-2.3)	<.001	1.7 (1.5-2.1)	<.001	1.5 (1.2-1.8)	<.001
HR IgH translocation	2.0 (1.7-2.5)	<.001	1.5 (1.2-1.9)	<.001	1.9 (1.5-2.4)	<.001
Del(17p)	2.0 (1.6-2.5)	<.001	1.9 (1.5-2.3)	<.001	1.6 (1.2-2.0)	<.001
Monosomy 13	1.4 (1.2-1.7)	<.001	1.2 (1.0-1.4)	.09	—	—
ISS stage (3 vs 1/2)	1.9 (1.6-2.3)	<.001	—	—	1.8 (1.4-2.1)	<.001
Age ≥70 y	2.1 (1.8-2.5)	<.001	—	—	2.3 (1.9-2.8)	<.001

OS univariate and multivariate analyses including +1q, HR IgH translocation, del(17p), monosomy 13, advanced ISS stage, and old age.

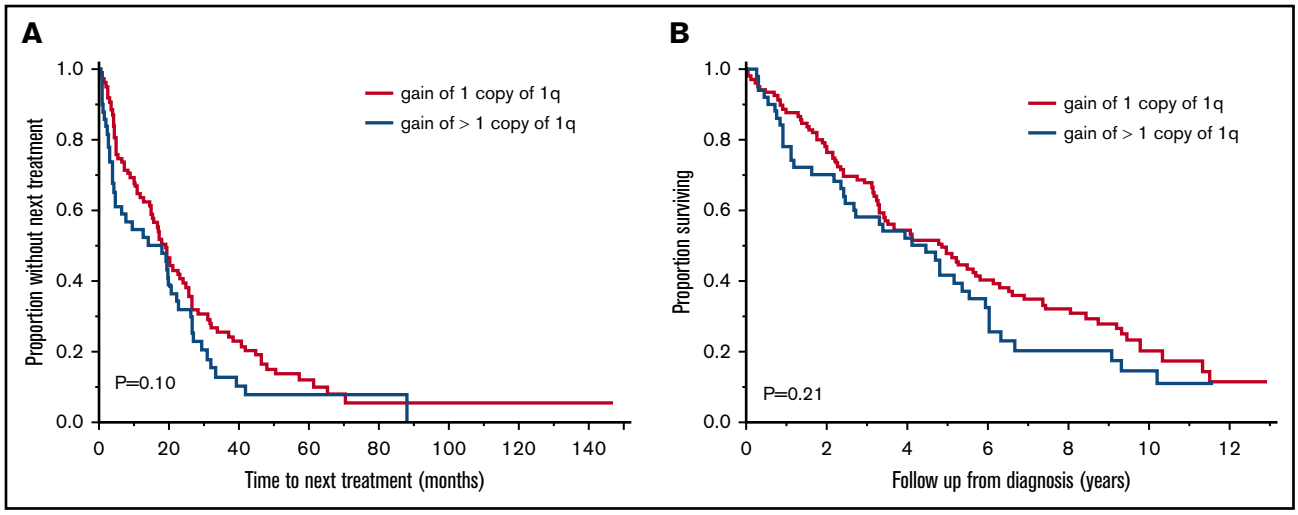

Figure 6. Impact of 1q copy number on TTNT and OS. Comparison of TTNT (months) (A) and OS (years) (B) in patients with gain of 1 copy of 1q (red curve) and patients with gain of >1 copy of 1q (amplification; blue curve).

was not an independent prognostic marker for OS on multivariate analysis when other HR cytogenetic abnormalities and markers of proliferative disease were included [(t4;14) and plasma cell labeling index]. In our study, we found that +1q was associated with decreased OS on multivariate analysis when other HR cytogenetic abnormalities [HR translocation and del(17p)] were included. The prognostic value of +1q was also retained on multivariate analysis when advanced ISS stage and older age were included. We did not observe a significant difference in OS among patients with an HR translocation. However, among patients with an SR translocation and patients with trisomy, presence of +1q was associated with significantly shorter survival. We also observed similar OS in patients with +1q and patients with an HR abnormality other than 1q [either HR IgH translocation or del(17p)], which also highlights the individual prognostic value of +1q. Thus, +1q may have a role in further risk stratification in newly diagnosed patients.

We did not observe any difference in response rate, including ORR and deeper response, to PI-, IMiD-, or PI plus IMiD–based therapy between patients with +1q and those without +1q. However, TTNT was shorter in patients with +1q who received induction chemotherapy only and in those with +1q who underwent postinduction transplantation. This is also consistent with results from previous studies, where decreased progression-free survival is seen in patients with +1q, despite similar responses to various novel treatment-based induction regimens and to transplantation.[12,22] Furthermore, OS was decreased in patients with +1q compared with patients without +1q regardless of first-line induction chemotherapy (PI, IMiD, or PI plus IMiD), and inferior outcomes were not overcome by transplantation. Interestingly, when the analysis was limited to patients who underwent postinduction transplantation, we observed similar OS between patients with and without +1q with PI-based induction and inferior OS in patients with +1q with IMiD- or PI plus IMiD–based induction. These findings may suggest benefit from PI-based induction followed by stem cell transplantation in patients with +1q, but they are insufficient to favor PI-based induction over IMiD-based induction at this time. Nonetheless, the data available so far highlight the need for more effective therapeutic options, including identification of targetable molecular abnormalities in patients with +1q.[23]

The additional prognostic impact of 1q amplification has also been previously evaluated; in the metaanalysis by Shah et al,[11] there was no significant difference in OS between patients with +1q and those with amplification (hazard risk, 1.36; $P = .09$). Similar results were seen in several other studies.[22,24] In a recent study by Schmidt et al,[20] gain of >1 copy of 1q was associated with significantly decreased progression-free survival compared with a single copy gain of 1q, but the impact on OS was not assessed. In our study, there was no difference in OS between patients with 1q amplification and those with gain of 1 copy of 1q. We observed a statistically insignificant trend toward decreased OS in patients with +1q in ≥20% of cells compared with patients with +1q in <20% of cells. These results are similar to the findings of An et al,[24] who reported that an increase in copy number or clone size did not confer worse prognosis. It is important to highlight that in our study, among evaluable patients, only 13 had ≥50% of plasma cells with +1q and only 2 had 1q amplification in ≥50% of plasma cells. At this time, there are insufficient data to ascertain whether additional copies of 1q or an increase in clone size is associated with progressively worse outcomes.

This study is limited by its retrospective design and heterogeneity of treatment regimens. The lack of significant survival differences in this study between patients with +1q and those without +1q in the HR IgH translocation group may be due to the relatively short follow-up; this should be evaluated in future studies.

In conclusion, gain of 1q is associated with end-organ damage and higher tumor burden. Although patients with +1q are more likely to have concurrent HR cytogenetic abnormalities, +1q is associated with decreased OS independent of other HR abnormalities and ISS stage. Inferior outcomes are not mitigated by currently available treatment options, including transplantation. Therefore, patients with +1q should be considered to have HR disease at diagnosis, and future efforts should be geared toward identification of more effective therapies for patients harboring this abnormality.

Authorship

Contribution: N.A. and S.K.K. collected and analyzed the data, wrote the first draft, and approved the final version of the manuscript; P.K., M.A.G., A.D., M.Q.L., S.R.H., F.K.B., D.D., R.S.G., Y.L.H., A.F., M.H., Y.L., N.L., T.K., R.W., M.S., J.L., R.A.K., and S.V.R. managed patients, revised the manuscript critically, and approved the final version of the manuscript; and P.G., L.B.B., L.B., and R.K. revised the manuscript critically and approved the final version of the manuscript.

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