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A Single-Center Study on Frontline Treatment for Multiple Myeloma Patients With 1q Abnormalities

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ABSTRACT

Introduction: Chromosome 1q copy gains (with-1q-gain) is a frequently observed genetic abnormality in multiple myeloma (MM) patients. Recent research has demonstrated that 1q gain is a prognostic factor, linked to poorer clinical outcomes.

Methods: This study was conducted at the Princess Margaret Cancer Centre to examine the clinical outcomes of newly diagnosed MM patients' with-1q-gain or without-1q-gain abnormality. The study included 275 patients, with 161 (58.5%) with-1q-gain abnormality. The median follow-up time for the cohort was 94.3 months (95% CI 30.1–38.6).

Results: The patients' with-1q-gain when compared to without-1q-gain were more likely to have other high-risk cytogenetic abnormalities (34.8% vs. 14.0%, $p < 0.001$) and more advanced disease according to the International Staging System (ISS III, $p < 0.014$). Furthermore, a relatively higher proportion of with-1q-gain patients received tandem autologous stem cell transplant (ASCT) as frontline therapy (36.2% vs. 8.7%, $p \leq 0.001$).

To assess the impact of 1q copy number, patients with 3 copies of 1q (1q-gain3) were compared to those with ≥4 copies (1q-Amp). No significant differences were observed between the two groups.

Conclusion: In conclusion, our study provides insight into the clinical significance of 1q gain abnormality in MM patients at a single center, and highlights its association with adverse prognostic features and treatment outcomes.

1 | Introduction

Multiple myeloma (MM) is a heterogeneous hematological malignancy characterized by the clonal proliferation of plasma cells within the bone marrow. The disease exhibits considerable variability in its clinical presentation, treatment response, and overall prognosis. Cytogenetic abnormalities (CAs) have emerged as important prognostic markers in MM, aiding in risk stratification and treatment decision-making.

Several CAs have unequivocally been established as high-risk factors in myeloma. One such high-risk CA is the translocation t(4:14)(p16;q32), resulting in the dysregulation of two key oncogenes: FGFR3 (fibroblast growth factor receptor 3) and MMSET (multiple myeloma SET domain). The t(4:14) translocation is observed in approximately 15%–20% of MM patients and is associated with poor prognosis, shorter progression-free survival (PFS), and inferior overall survival [1–3].

Another recurrent cytogenetic abnormality is the translocation t(14:16)(q32;q23), which involves the immunoglobulin heavy chain gene (IGH) on chromosome 14 and the gene C-MAF on chromosome 16. This translocation is associated with a more aggressive disease phenotype, resistance to treatment, and reduced survival rates [4]. Deletion of the short arm of chromosome 17 (del17p) is another high-risk genetic abnormality observed in MM. It results in the loss of the TP53 tumor suppressor gene and is associated with poor response to therapy, shorter PFS, and inferior OS [5].

Additional CAs reported in literature that may contribute to disease aggressiveness, treatment resistance, and adverse outcomes in MM patients include translocation t(14:20), del(13q), del(1p), and amplification of chromosome 1q [6–8].

Among the various CAs observed in MM, a gain in the number of copies of chromosome 1q has emerged as one of the most frequently detected abnormalities, affecting up to 40% of patients with newly diagnosed MM [6]. The frequency of 1q gain abnormalities has been observed to increase from the precursor condition, monoclonal gammopathy of undetermined significance (MGUS), to MM. This suggests that 1q alterations may play a crucial role in the transition from MGUS to active myeloma disease [9]. Retrospective studies have shown that patients with 1q gain abnormalities often present more aggressive disease with higher incidence of anemia, thrombocytopenia, hypercalcemia, as well as higher ISS and R-ISS scores [10–12]. In these studies, patients with 1q abnormalities were also associated with poorer progression-free survival (PFS) and overall survival (OS) with the use of standard first-line therapies (bortezomib, immunomodulatory drugs), and autologous stem cell transplant [11]. Similar findings were observed in large, randomized controlled trials such as Myeloma IX, Myeloma XI, and most recently in FORTE in which patients with 1q abnormalities had poorer PFS and OS when compared to patients without 1q gain [10, 13].

At Princess Margaret Cancer Centre, tandem transplants have been the standard of care in combination with the bortezomib-cyclophosphamide-dexamethasone (CyBorD) induction regimen for patients with poor prognosis. This approach is guided by findings from the EMN02/HO95 study and other phase III studies, which showed that tandem ASCT resulted in improved overall survival (OS) compared to single ASCT in patients with advanced Revised International Staging System (R-ISS) disease stage and high-risk cytogenetic features [14].

Despite extensive research, the prognostic significance of 1q gain abnormalities in MM remains a subject of debate. There has been some contradicting evidence, which suggests that 1q gain abnormalities are not an independent marker of poor prognosis when compared to other high-risk CAs [15]. It is evident there is need to further characterize the impact of 1q gain abnormalities in MM. The aim of this study is to enhance our understanding of the genetic landscape and assess the impact of 1q abnormalities on disease presentation, frontline treatment response and patient outcomes in newly diagnosed MM using real-world clinical data from a single Centre in Canada.

2 | Methods

2.1 | Patients Selection

Princess Margaret Cancer Center (PMCC) is a quaternary cancer care center in Toronto, Ontario, Canada that is the major referral center for ASCT in the Greater Toronto Area. The Princess Margaret Cancer Centre MM Database (PMCC-DB) prospectively collects demographic data, disease characteristics, treatments received, responses and other efficacy endpoints for all consented MM patients seen at PMCC. Using PMCC-DB, we reviewed patients diagnosed with MM between January 2017 and March 2021. This study period was selected based on cytogenetic testing and reporting for 1q abnormalities that became a standard of care practice in 2017. All patients who had cytogenetic testing done for 1q abnormalities at diagnosis were eligible for inclusion in the study. Patients were excluded if they had associated amyloid light-chain (AL) amyloidosis or if there was inadequate information to determine disease or treatment response. The study was approved by the University Health Network Research Ethics Board and the analysis was conducted in accordance with the Declaration of Helsinki.

2.2 | Cytogenetic Abnormalities

FISH analysis was performed at time of diagnosis on CD138-enriched Bone Marrow Plasma Cells (BMPCs). Cytogenetic abnormalities were defined as “high-risk” if presence of translocation t(4:14) or t(14:16) or deletion del(17p) as per IMWG guidelines [16]. Standard-risk abnormalities included normal cytogenetics, del(13q), t(11:14) and del(1p). The 1q abnormality in FISH was assessed using the CKS1B gene probe. For copy number analysis patients whose cytogenetics were performed at PMCC only were included. The 1q abnormalities were reported if samples had $\geq 10\%$ BMPCs expressing 3 copies or ≥ 4 copies of 1q.

2.3 | Standard Treatments

As per PMCC institutional policy, patients younger than 75 years and fit were offered ASCT as frontline therapy with a standard CyBor-D induction regimen followed by lenalidomide maintenance. Patients with high-risk disease were offered tandem ASCTs if deemed fit for the procedure. With the availability of 1q abnormality reporting, tandem ASCTs were also offered to limited patients with 1q-gain or with R-ISS stage III disease.

2.4 | Statistical Analysis

Baseline disease and treatment characteristics were summarized by 1q status, and differences in distribution were assessed using χ^2 or Fisher’s exact test and Mann-Whitney U test for categorical and continuous characteristics, respectively. Progression-free survival (PFS) and overall survival (OS) were summarized using the Kaplan-Meier method, and differences by 1q status (and other characteristics) were assessed using the log-rank test. PFS was defined as the time from date of treatment initiation to date of progression on the same regimen. OS was defined as the time from diagnosis date to the date of death. Patients who

did not progress/die were censored at date of last follow up. To identify predictors of survival, a stepwise modeling approach was taken. First, univariate Cox regression models were fit for each predictor of interest. All predictors with p-values less than 0.05 were then incorporated into a single multivariate regression model. All hypothesis tests were two-sided, and p-values <0.05 were considered statistically significant. Statistical analyses were conducted using R version 4.3.0.

3 | Results

3.1 | Baseline Characteristics

A total of 883 patients diagnosed with MM between Jan 2017-Mar 2021 were available in the PMCC database. The study entry criteria of being tested for chromosome 1q abnormality at diagnosis was met in 275 patients (31%). Among them, 161 patients (58.5%) exhibited a gain in 1q while 114 (41.5%) did not show an abnormality (without-1q-gain). Baseline characteristics are detailed in Table 1. At diagnosis, the median age for the entire cohort was 64 years (range 26–96). The median ages of the 1q-gain and without-1q-gain groups were 63 (range 26–86) and 65 years (range 37–96), respectively. In terms of gender distribution, 42.9% and 58.8% of the 1q-gain and without-1q-gain groups were male, respectively. The 1q-gain group was older but did not reach significance ($p = 0.13$) and had a higher proportion of females ($p = 0.02$).

In the 1q-gain and without-1q-gain groups, 34.6% (46/133) and 23.1% (24/104) evaluable patients had ISS stage III disease that was significantly higher for the 1q-gain group ($p = 0.01$), R-ISS was also significantly higher in the same ($p = 0.02$). Among patients with available cytogenetics, high-risk cytogenetics by FISH [t(4;14) or t(14;16) or 17p deletion] was present in 39.7% (56/141) in the 1q-gain group and 16.0% (16/100) of the without-1q-gain group of evaluable patients ($p \leq 0.001$). Each of the IgH rearrangements individually, and del(17p) were also significantly higher in the 1q-gain patients. A second chromosome 1 abnormality, del(1p), was present in 12.4% of the total cohort and was equally represented in the 1q-gain and without-1q-gain groups (Table 1).

The presenting features of anemia, renal failure, elevated Beta-2 microglobulin (B2M), and IgA subtype were notably more prevalent in the 1q-gain group but the differences were not statistically significant. Only the incidence of median LDH levels was significantly higher in the 1q-gain group compared to the without-1q-gain group.

3.2 | Treatment Details

Out of the 275 eligible patients, treatment was initiated in 257 patients. Among the 18 patients who did not start treatment, 2 passed away without treatment and the remaining 16 were asymptomatic and did not require treatment at the time of analysis. Among the newly diagnosed MM patients regardless of 1q abnormality, 217 began treatment with the intention of undergoing ASCT. A total of 194 underwent autologous stem cell transplant (ASCT), with 63 (32.5%) of them also receiving a tandem ASCT. Tandem ASCTs were more prevalent in the 1q-gain group compared to without-1q-gain group, at 36.2% versus 8.7%, respectively ($p = 0.001$).

Post ASCT maintenance therapy was administered in 119 patients (61.3%), using single agent lenalidomide or ixazomib, or a combination of both, as outlined in Table 1. Maintenance was administered after both single and tandem ASCTs in the without-1q-gain group (47.5%) and the 1q-gain group (51.7%).

The primary induction treatment for ASCT was CyBor-D for 99% of patients. Among the non-ASCT group, CyBor-D was administered to 16 (40.0%), RVD to 13 (32.5%), and RD to 11 (27.5%) patients. Daratumumab-containing regimens were the most common both as second line (53.4%) and third line (34.5%) of therapy during this period.

3.3 | Frontline Therapy Response

Frontline treatment responses in the ASCT and non-transplant cohorts are summarized in Table 2. In the ASCT cohort, the overall response rates (ORR = ≥ PR) were above 98% with no significant differences between the 1q-gain and without-1q-gain groups. However, the ORR was higher in the ASCT group when compared with the non-ASCT group.

The frontline ASCT cohort received a Canadian standard, uniform induction regimen of CyBor-D. In 1q-gain patients, the median progression-free survival (PFS) from the initiation of treatment was 59 months (95% CI, 44.1–not estimable) versus median not reached for the without-1q-gain patients at 72 months ($p = 0.01$) (Figure 1A).

The same cohort of patients that initiated treatment when analyzed for OS, the difference between the 1q-gain and without-1q-gain groups did not reach significance with the limited number of patients and follow up ($p = 0.12$) (Figure 1B).

PFS and OS in all patients when stratified by with and without 1q gain and then further stratified by type of frontline therapy, receiving ASCT versus non ASCT, the ASCT group did better in both cohorts (Figure 2A and B).

PFS and OS outcomes in the 1q-gain group further stratified for single or tandem transplant are depicted in Figure 2C and D. In these patients with a 1q abnormality, the single transplant group did equally well as the tandem transplant group for both PFS and OS.

3.4 | High Risk and Standard Risk

We further analyzed the PFS and OS outcomes in 1q-gain and without-1q-gain patients, stratified by high-risk (HR) versus standard-risk (SR) patients, as shown in Figure 3A–D. The HR group included patients with any of the abnormalities t4:14 or t14:16 or del17p. The median PFS of 1q-gain + HR patients was 47.6 months (95% CI 46.5–not estimable), while it was NYR for without-1q-gain + HR patients ($p = 0.13$) (Figure 3A). The OS for the same groups was also not significantly different ($p = 0.23$) (Figure 3B).

TABLE 1 | Baseline disease characteristics of all patients with and without 1q gain abnormality.

Characteristic	ALL (n = 275)	without-1q-gain (n = 114)	1q-gain (n = 161)	p-value
Age at Dx (years)				0.13
Median (Q1,Q3)	64.0 (57.0, 70.0)	63.0 (56.2, 69.0)	65.0 (58.0, 70.0)	
Range (min, max)	(26.0, 96.0)	(26.0, 86.0)	(37.0, 96.0)	
Sex (%)				0.013
Female	139 (50.5)	47 (41.2)	92 (57.1)	
Hb Dx (g/L)				0.10
Median (Q1, Q3)	102.0 (86.5, 121.5)	104.5 (91.5, 123.8)	101 (83, 120)	
Range (min, max)	(47, 152)	123.8) (49, 152)	(47, 152)	
Creatinine Dx (umol/L)				0.14
Median (Q1, Q3)	88.0 (70.0, 139.0)	85.0 (70.0, 113.5)	93.0 (70.0, 152.5)	
Range (min, max)	(20, 2213)	(20, 716)	(45, 2213)	
Missing	14	7	7	
Calcium Dx (nmol/L)				0.86
Median (Q1, Q3)	2.4 (2.3, 2.5)	2.4 (2.3, 2.6)	2.4 (2.3, 2.5)	
Range (min, max)	(1.7, 4.6)	(1.9, 4.4)	(1.7, 4.6)	
Missing	19	9	10	
LDH Dx (U/L)				0.022
Median (Q1,Q3)	199.0 (151.0, 275.0)	181.0 (147.0, 268.5)	214.5 (161.5, 276.8)	
Range (min, max)	(74, 1639)	(74, 1092)	(95, 1639)	
Missing	42	11	31	
B2M Dx (nmol/L)				0.12
Median (Q1, Q3)	305 (212, 538)	277.3 (212.0, 459.8)	335.0 (212.0, 591.6)	
Range (min, max)	(101, 4376)	(101, 2451)	(101.8, 4376.0)	
Missing	43	14	29	
MM HC subtype, n (%)				0.67
lgG	150 (54.5)	66 (57.9)	84 (52.2)	
lgA	62 (22.5)	22 (19.3)	40 (24.8)	
FLC	59 (21.5)	25 (21.9)	34 (21.1)	
lgD	1 (0.4)	0 (0.0)	1 (0.6)	
lgE	1 (0.4)	0 (0.0)	1 (0.6)	
lgM	1 (0.4)	0 (0.0)	1 (0.6)	
Non-secretory	1 (0.4)	1 (0.9)	0 (0.0)	
*__High risk, n (%)__				<0.001
No	169 (61.5)	84 (73.7)	85 (52.8)	
Yes	72 (26.2)	16 (14.0)	56 (34.8)	
Unknown	34 (12.4)	14 (12.3)	20 (12.4)	
t(4:14) Dx, n (%)				0.012
No	221 (80.4)	100 (87.7)	121 (75.2)	
Yes	33 (12.0)	6 (5.3)	27 (16.8)	
Unknown	21 (7.6)	8 (7.0)	13 (8.1)	
t(14:16) Dx, n (%)				0.005
No	198 (72.0)	92 (80.7)	106 (65.8)	

(Continues)

TABLE 1 | (Continued)

Characteristic	ALL ($n = 275$)	without-1q-gain ($n = 114$)	1q-gain (n = 161)	p-value
Yes	18 (6.5)	2 (1.8)	16 (9.9)	
Unknown	59 (21.5)	20 (17.5)	39 (24.2)	
DEL 17P Dx, n (%)				0.011
No	232 (84.4)	102 (89.5)	130 (80.7)	
Yes	33 (12.0)	12 (10.5)	21 (13.0)	
Unknown	10 (3.6)	0 (0.0)	10 (6.2)	
DEL 1P Dx, n (%)				1.00
No	227 (82.5)	98 (85.9)	129 (80.1)	
Yes	34 (12.4)	15 (13.2)	19 (11.8)	
Unknown	14 (5.1)	1 (0.9)	13 (8.1)	
ISS stage Dx, *n* (%)				0.014
I	79 (28.7)	43 (37.7)	36 (22.4)	
II	88 (32.0)	37 (32.5)	51 (31.7)	
III	70 (25.5)	24 (21.1)	46 (28.6)	
Unknown	38 (13.8)	10 (8.8)	28 (17.4)	
R-ISS Dx, *n* (%)				0.016
I	31 (11.3)	18 (15.8)	13 (8.1)	
II	164 (59.6)	73 (64.0)	91 (56.5)	
III	31 (11.3)	7 (6.1)	24 (14.9)	
Unknown	49 (17.8)	16 (14.0)	33 (20.5)	
Frontline therapy, *n* (%)				<0.001
No treatment	18 (7.1)	3 (2.9)	15 (10.1)	
Non-ASCT	40 (15.9)	11 (10.7)	29 (19.5)	
Single ASCT, no maintenance	58 (23.0)	30 (29.1)	28 (18.8)	
Single ASCT, maintenance	73 (29.0)	50 (48.5)	23 (15.4)	
Tandem ASCTs, no maintenance	17 (6.7)	2 (1.9)	15 (10.1)	
Tandem ASCTs, maintenance	46 (18.3)	7 (6.8)	39 (26.2)	
Missing	23	11	12	
Induction regimen, *n* (%)				1.00
CyBor-D/P	214 (98.6)	98 (98.0)	116 (99.1)	
RVD/RD	3 (1.4)	0	3 (0.9)	
Non-ASCT regimen, *n* (%)				0.30
CyBOR-D	16 (40.0)	6 (54.5)	10 (34.5)	
lxaRD/RVD	13 (32.5)	4 (36.4)	9 (31.0)	
RD	11 (27.5)	1 (9.1)	10 (34.5)	
Post-ASCT maintenance regimen, *n* (%)				0.012
DaraRD	1 (0.8)	0 (0.0)	1 (1.6)	
lxaR/lxaRD	21 (17.5)	5 (8.8)	16 (25.4)	
lxazomib/lxaD	13 (10.8)	4 (7.0)	9 (14.3)	
R/RD	85 (70.8)	48 (84.2)	37 (58.7)	

Abbreviations: B2M, Beta 2 microglobulin; Bor & V, Bortezomib; Cy, cyclophosphamide; D, dexamethasone; Dx, diagnosis; Del, deletion; Hb, hemoglobin; HC, heavy chain; Ixa, ixazomib; LDH, lactate dehydrogenase; P, prednisone; R, revlimid.

*High risk was defined as the presence of t(4;14) or t(14;16) or 17p deletion.

TABLE 2 | Frontline ASCT and non-ASCT treatment responses in patients with and without 1q abnormality.

ASCT	All ($n = 217$)	1q-gain ($n = 117$)	Without-1q-gain ($n = 100$)	p-value
Best response				0.35
≥VGPR	169 (82.4)	95 (85.6)	74 (78.7)	
PR	33 (16.1)	14 (12.6)	19 (20.2)	
SD	2 (1.0)	1 (0.9)	1 (1.1)	
PD	1 (0.5)	1 (0.9)	0 (0.0)	
Missing	12	6	6	
ORR (≥ PR)	202 (93.1)	109 (93.2)	93 (93.0)	1.00
Non-ASCT	**All ($n = 40$)**	**+1q ($n = 29$)**	**1q ($n = 11$)**	**p-value**
Best response				0.20
≥VGPR	20 (64.5)	13 (56.5)	7 (87.5)	
PR	6 (19.4)	6 (26.1)	0 (0.0)	
SD	2 (6.5)	1 (4.3)	1 (12.5)	
PD	3 (9.7)	3 (13.0)	0 (0.0)	
Missing	9	6	3	
ORR (≥ PR)	26 (65.0)	19 (65.5)	7 (63.6)	1.00

Abbreviation: ORR, overall response rate; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.

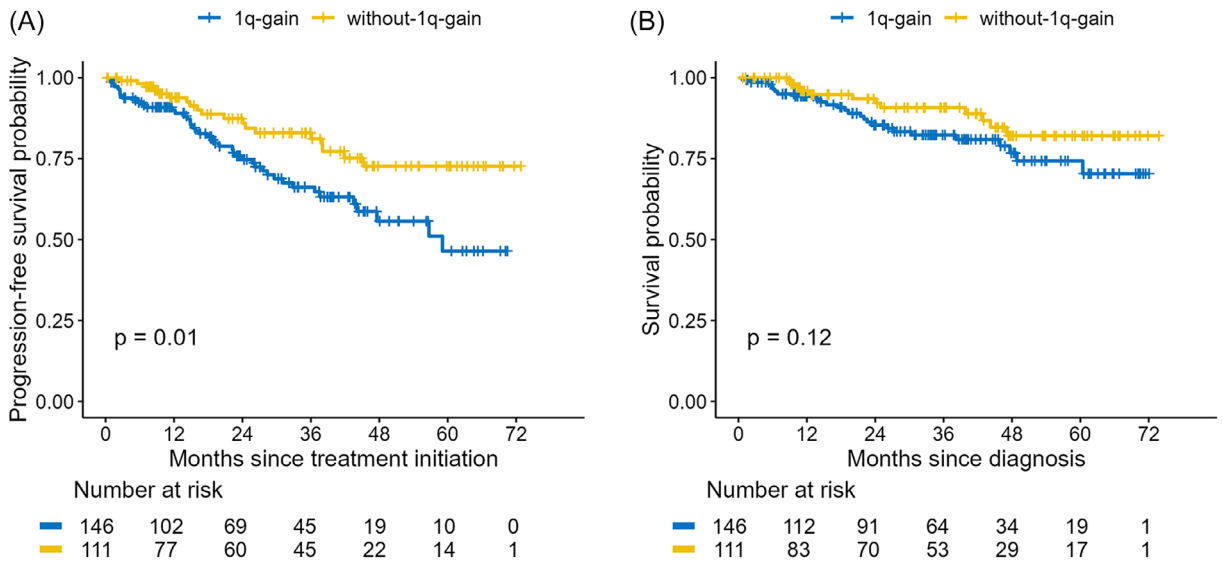

FIGURE 1 | (A) PFS from start of treatment and (B) OS from diagnosis in all patients that initiated frontline therapy ($n = 257$). Patients were stratified by 1q-gain and without-1q-gain abnormality.

In standard-risk patients, defined as negative for t(4:14), t(14:16), or del(17p), progression-free survival (PFS) and overall survival (OS) were analyzed based on the presence or absence of the 1q gain abnormality. PFS was significantly worse in the 1q-gain group compared to the without-1q-gain group ($p = 0.037$) (Figure 3C).

Among the standard-risk patients with 1q-gain receiving treatment, 21 out of 76 (28%) underwent tandem transplants, while 28 (36.8%) received a single ASCT. In both tandem and single ASCT groups, 43% of patients received maintenance therapy post ASCT. In contrast, among standard-risk patients without-1q-gain only 2 out of 81 patients (3%) underwent tandem transplants, while 64 (79%) received a single ASCT, with 61% receiving maintenance therapy post ASCT. The 2 patients in the standard risk with no 1q-gain, del17p, t(4:14) or t(14:16) who received tandem ASCT were high risk by R-ISS criteria.

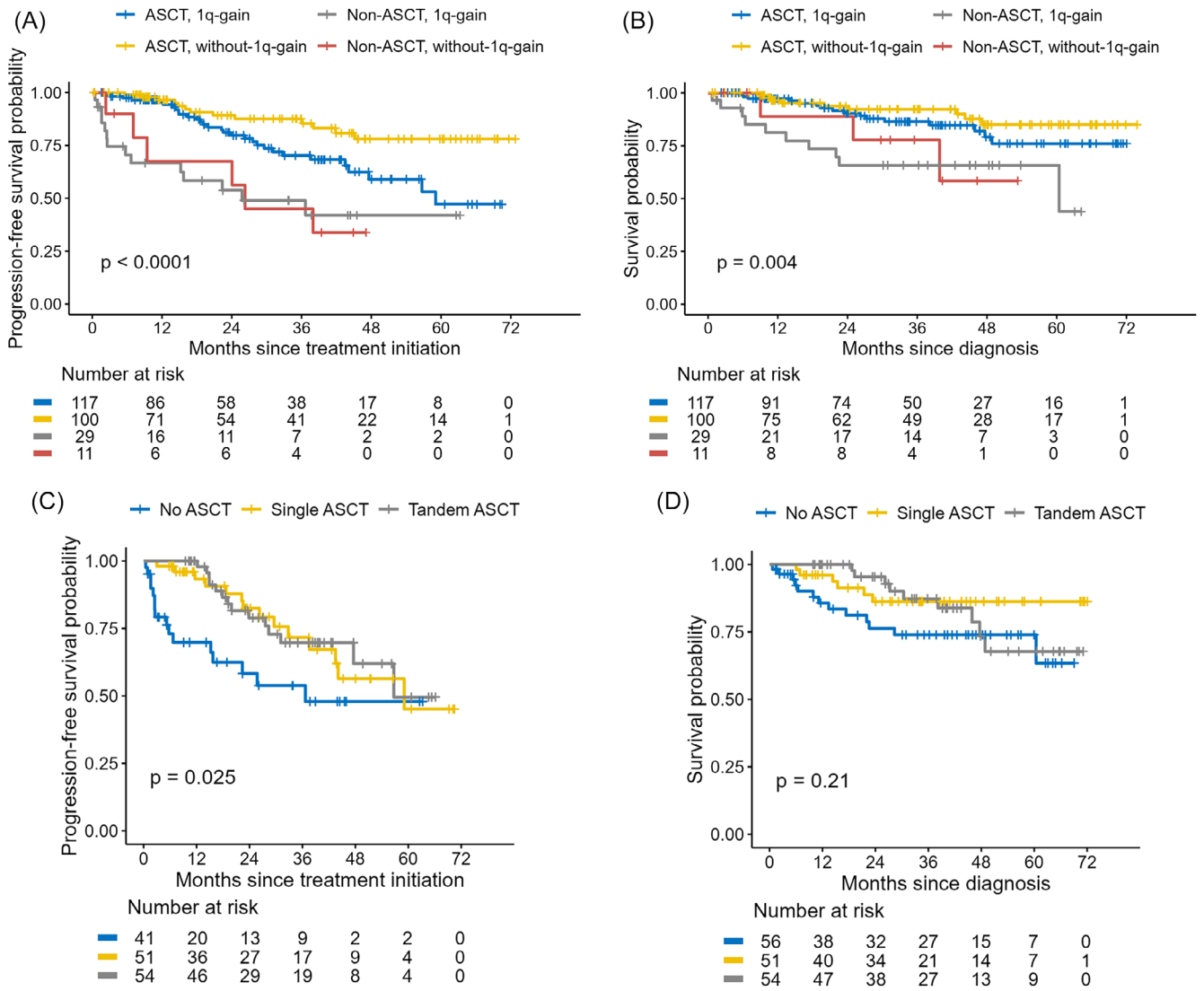

FIGURE 2 | (A) PFS of 1q-gain and without-1q-gain groups stratified by type of frontline therapy. (B) OS of 1q-gain and without-1q-gain groups stratified by type of frontline therapy. (C) PFS in the 1q-gain group stratified by number of ASCT. (D) OS in the 1q-gain group stratified by number of ASCT.

3.5 | Double Hit Cytogenetics

In the 1q-gain group of 161 patients, 13.9% (21/151) had a second HR mutation del17p and 18.2% (27/148) had a t(4:14), both mutations being significantly higher in the 1q-gain group (Table 1). These patients with at least 2 co-abnormalities were characterized as having double hit cytogenetics.

PFS outcomes were compared in the 1q-gain group stratified based on the presence or absence of specific genetic co-abnormalities t(4:14), t(14:16), del17p and del1p. Differences in PFS did not reach significance in any of these groups (Supplemental Data; Figure 1A–D). However, when they were compared for OS, there was significantly shorter survival in 1q-gain patients with a second genetic abnormality del17p ($p = 0.015$), or t(4:14) ($p = 0.047$) respectively versus patients with the absence of the same mutations (Figure 4A and C). The median survival time for t(4:14) is not reached and for del 17p, the median survival time is 48.9 months (95% CI: 23.4–not estimable).

3.6 | Impact of Copy Number, Gain Versus Amplification

The impact of 1q gain abnormality was further explored in the context of copy number gain versus amplification. Bone marrow reports of patients with 1q-gain abnormality were reviewed, identifying 122 cases reporting a percentage of plasma cells for at least 10% of cells with either 3 copies of 1q (1q-gain3) or ≥ 4 copies of 1q (1q-amp).

The two groups were evaluated for baseline disease characteristics comparing age, sex, creatinine, hemoglobin, calcium, LDH, Beta 2 microglobulin, high risk, ISS staging and MM subtypes to reveal only anemia as a significant difference between the 1q-amp and the 1q-gain3 groups. The hemoglobin values of <100 g/L in the 1q-amp group were present in 64.9% versus 43.5% of patients in the 1q-gain3 group, $p = 0.05$. Details are shown in Table S1.

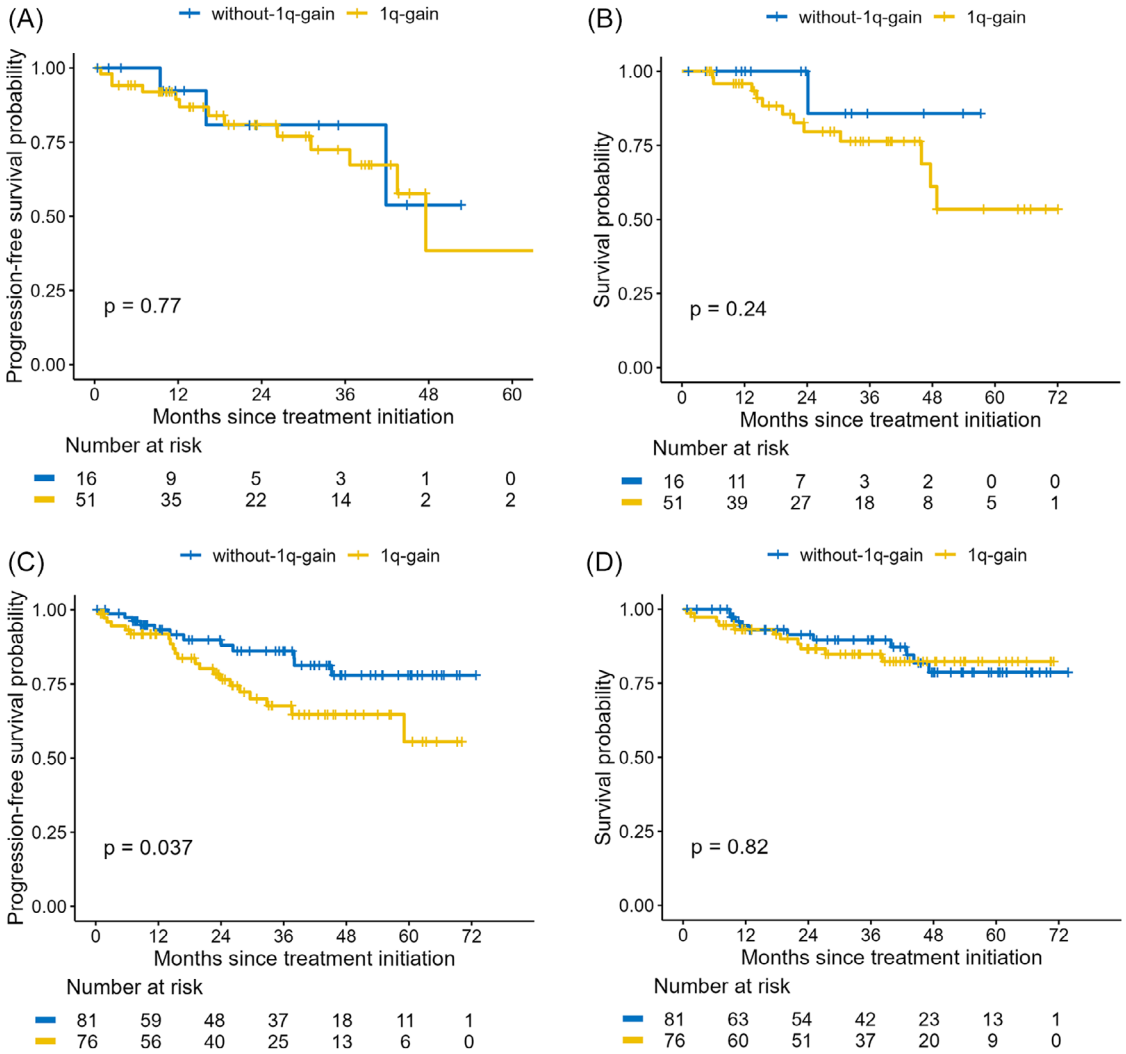

FIGURE 3 | All patients that initiated frontline therapy were stratified by 1q-gain and without-1q-gain abnormality. (A) PFS stratified by high risk in both groups and (B) OS stratified by high risk in both groups; (C) PFS stratified by standard risk in both groups and (D) OS stratified by standard risk in both groups.

The PFS comparisons between 1q-gain3 and 1q-amp stratified by presence or absence of specific cytogenetic abnormalities, t4:14, t14:16 or del17p also showed no significant difference (Figure S1).

3.7 | Univariate and Multivariable Analysis

Univariate and multivariable analyses were performed to determine factors associated with PFS and OS in the full cohort. For the univariate model for both PFS and OS eight predictors were considered, 1q status, age ≥ 70 years, del(17p), t4:14, ISS stage III, male, elevated LDH, and non-ASCT therapy.

The association between PFS and the presence of 1q-gain was significant in both the univariate (HR 2.00, 95% CI 1.17, 3.44, $p = 0.012$) and in the multivariable analysis (and HR 1.74, 95% CI 0.99, 3.06, $p = 0.053$) (Table 3). Other predictors for PFS included t(4:14), stage III and ASCT status.

The 1q-gain status was not significantly associated with OS in both univariate and multivariable analysis. Independent variables significantly associated with OS were not surprisingly del17p, t(4:14), stage III disease and non-ASCT frontline therapy (Table 4).

4 | Discussion

Gain of chromosome 1q is a frequent cytogenetic abnormality and seen as a marker of poor prognosis in MM.

In our retrospective, single center study, 58.5% of newly diagnosed MM patients exhibited a gain in chromosome 1q. This incidence is notably higher than the 35%–40% reported in the literature [11, 12, 15]. This discrepancy may be attributed to Princess Margaret being a referral center for autologous transplant, likely resulting in a higher proportion of patients referred with high-risk disease. Additionally, we do observe a higher percentage (35%) of high-risk disease patients defined by the presence of t(4:14), del(17p) or t(14:16) compared to the 20%–25% reported in literature(11, 12, 14). Gao et al. reported a similar high detection rate of 59.7% 1q gain in their study in the Chinese population. However, their analysis

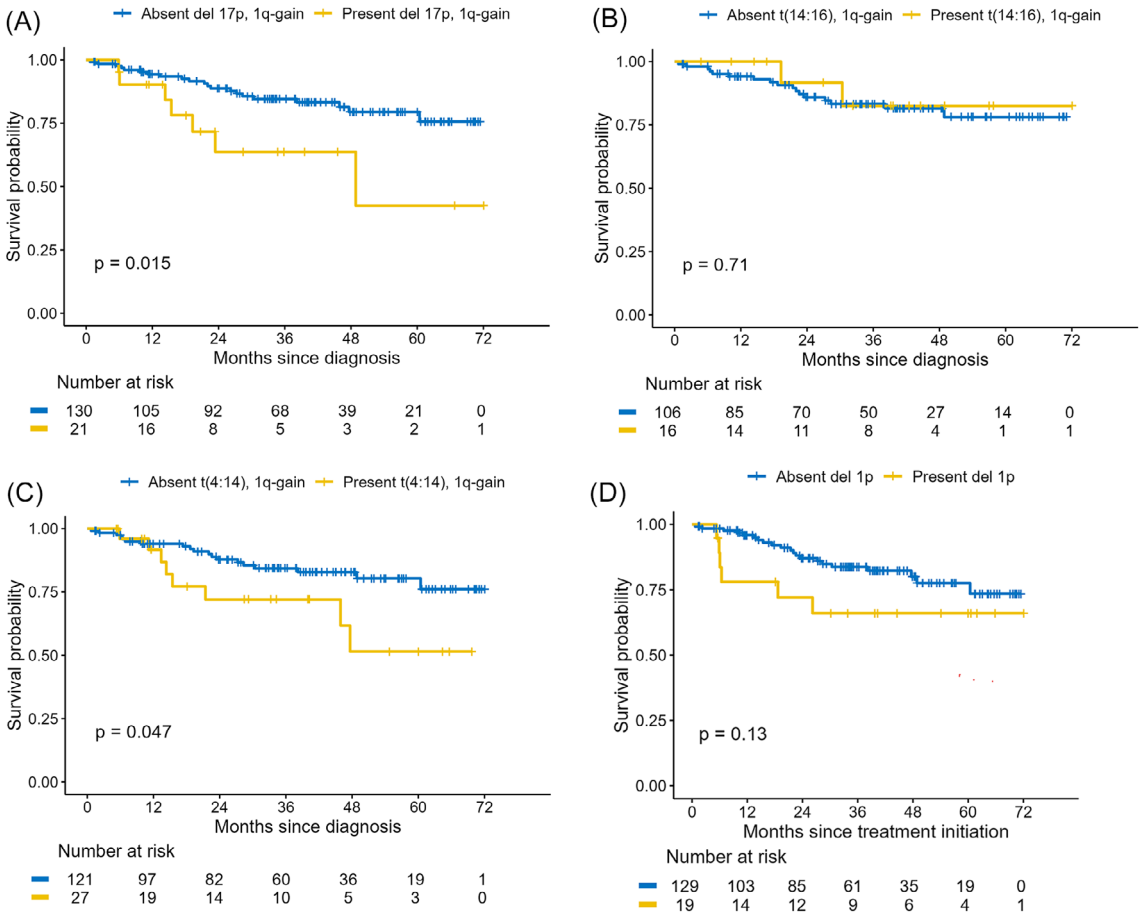

FIGURE 4 | OS outcomes in the 1q-gain group stratified by presence or absence of specific cytogenetic co-abnormalities. (A) Presence and absence of del17p. (B) Presence and absence of translocation t(14:16). (C) Presence and absence of translocation t(4:14). (D) Presence and absence of translocation del 1p.

TABLE 3 | Univariable and multivariable analysis to predict PFS.

Variables	Univariable hazard ratio (95% CI)	*p*-value	Multivariable hazard ratio (95% CI)	*p*-value
1q-gain	2.00 (1.17, 3.44)	**0.012**	1.74 (0.99, 3.06)	**0.053**
Age ≥70	1.76 (1.04, 2.97)	**0.035**	0.54 (0.22, 1.29)	0.16
Del 17P Dx	0.78 (0.31, 1.94)	0.59		
t(4:14) Dx	2.14 (1.12, 4.12)	**0.022**	2.54 (1.27, 5.06)	**0.008**
ISS Stage III	2.25 (1.33, 3.80)	**0.003**	2.27 (1.33, 3.88)	**0.003**
Sex M	0.84 (0.51, 1.38)	0.49		
LDH Dx >250 U/L	1.20 (0.70, 2.08)	0.51		
Non-ASCT	3.41 (2.01, 5.82)	**<0.001**	6.22 (2.53, 15.30)	**<0.001**

The *p*-values in bold are significant, ≤0.05.

used a cut off value of 5% for 1q gain, which is lower than the 10% threshold applied in our study [17]. Other studies have used a threshold as low as 3.5% [18].

In our study, we observed a significantly higher proportion of females in the 1q-gain group (57% vs. 41%). A recent study from MD Anderson Center examining the outcomes of MM patients with 1q gain compared those with 3 copies of 1q to those with >3 copies. Their findings revealed a higher percentage of females in the >3 copies group (61%) compared to the 3 copies group (43%) [19]. We included sex as a variable in our analysis but it was not identified as a predictor for PFS or OS.

TABLE 4 | Univariable and multivariable analysis to predict OS.

Variables	Univariable hazard ratio (95% CI)	*p*-value	Multivariable hazard ratio (95% CI)	*p*-value
1q-gain	1.64 (0.83, 3.23)	0.15		
Age ≥70	1.90 (1.00, 3.60)	**0.050**	1.10 (0.45, 2.68)	
Del 17P Dx	2.18 (0.96, 4.96)	0.062	2.65 (1.11, 6.28)	**0.028**
t(4:14) Dx	2.53 (1.20, 5.33)	**0.014**	2.90 (1.35, 6.23)	**0.007**
ISS Stage III	3.39 (1.72, 6.68)	**<0.001**	3.14 (1.56, 6.31)	**0.001**
Sex M	1.21 (0.65, 2.26)	0.54		
LDH Dx >250 U/L	1.46 (0.58, 3.69)	0.089	2.08 (1.04, 4.15)	**0.038**
Non-ASCT	3.10 (1.58, 6.06)	**<0.001**	4.06 (1.55, 10.63)	**0.004**

The *p*-values in bold are significant, ≤0.05.

In this study we report that the 1q gain abnormality when present at diagnosis is associated with disease aggressiveness and adverse prognostic features including high-risk cytogenetics, stage III disease and increased LDH levels. These findings are not surprising and are consistent with previous reports [20–22]. In a systematic review of 2754 patients enrolled in MM randomized controlled trials published between January 2012 and December 2022, those with 1q gain had worse PFS and OS compared to those without 1q gain [23].

Even though there is lack of a clearly defined pathogenic mechanism, many genes located at the 1q21 region are suspected to contribute to early disease progression and resistance to anti-myeloma treatments. These genes include CKS1B associated with cell cycle regulation [24]; MCL1, an apoptosis regulator contributing to drug resistance [25]; PSMB4, a proteasome subunit essential for protein degradation [26]; ANP32E, involved in cell proliferation and migration [27] and ILF2, involved in gene transcription and RNA processing [28].

When we looked at impact of chromosome 1q abnormality on frontline therapy, primarily ASCT, the overall response rates were comparable between 1q-gain and without-1q-gain patients, however the median PFS in 1q-gain patients was significantly shorter when compared to without-1q-gain patients. This is in agreement with some previous studies that categorized 1q gain as high risk and associated it with disease progression [29].

In our study, patients with 1q gain were more likely to undergo tandem ASCTs. This treatment disparity reflects physician decision to intensify therapy in high-risk patients. Stratifying the 1q- gain group further for single versus tandem ASCTs, our study was unable to establish a beneficial role for tandem ASCTs. It is noteworthy that the 1q-gain group included 40% of high-risk patients, t(4;14), t(14;16), or del(17p). The non-ASCT therapy was clearly inferior which was not surprising as this population was relatively frail and not eligible for transplant.

Similar trend was also observed for overall survival but did not reach significance. Since the 1q-gain group also had other high-risk features the role of 1q gain abnormality contributing to the inferior outcome was analyzed through multivariate discriminant analysis. We found that for PFS, 1q-gain was an independent predictor with a hazard ratio of 1.74 but not for OS. Minguela et al. analyzed 737 real world patients in plasma cell neoplasm and found similar results, confirming that 1q21 gain was an independent prognostic factor for PFS, HR = 1.80 but not for OS, $p = 0.31$ [30].

The 1q-gain group when stratified generally for high risk [t(4:14) or t(14:16) or del17p] versus standard risk did not show any significant differences in PFS or OS. However, with further delineation of 1q-gain stratified specifically for t(4:14) or del17p versus standard risk suggested that these co-abnormalities lead to shorter overall survival in affected patients suggesting a further exacerbation of adverse prognostic implications of 1q gain. This would align with other studies suggesting the synergistic effect of multiple genetic abnormalities on MM prognosis [30–32].

Our analysis found no differences in baseline disease features or PFS between patients with 1q copy number gain and those with amplification of 1q. A detailed analysis of 2596 patients from three trials (GMMG MM5, EudraCT 2010-019173-16, and Myeloma XI) showed that 1q gain negatively affects prognosis, similar to 1q amp, with no clear difference in their impact. This and our data suggests that 1q gain likely has a direct prognostic impact regardless of copy number [33]. Other studies, unlike ours, suggest that patient outcomes in multiple myeloma (MM) are influenced by the specific number of 1q21 copy variations found in the cancer cells [34].

The primary limitation of our study is the high proportion of patients censored prior to progression on frontline therapy. Patients transplanted at PMCC typically return to the care of their local regional hospitals after starting maintenance therapy, only returning to PMCC at the time of relapse. This dynamic underscores the need for longer-term follow-ups to accurately assess OS and determine significant differences.

Additionally, as PMCC is a referral center, many patients receive their initial diagnosis and FISH cytogenetics at external laboratories. While we had access to their pathology reports, uniformity in testing and ensuring a 10% cut off could only be achieved for patients analyzed for copy number.

Our findings suggest that intensified treatment with tandem transplants, in the era of maintenance therapy, may not be an effective regimen for high-risk patients, who continue to have worse outcomes than standard-risk patients. This study also sheds light on the incidence of 1p deletion in relation to 1q gain, contributing to our understanding of chromosome 1 abnormalities.

Further research is needed to clarify the role of chromosome 1 abnormalities in high-risk patients, identify optimal treatments and combinations, and uncover the underlying molecular mechanisms driving these associations.

Author Contributions

A.P., A.S., V.K. and E.M.K. designed the research, collected, analyzed, interpreted data and wrote the paper; K.L. performed statistical analysis. All additional authors collected, interpreted the data and reviewed the paper.

Ethics Statement

The approval for this study was from the University Health Network Research Ethics Board.

Patient Consent Statement

All patients whose data is captured in the Princess Margaret Multiple Myeloma and Plasma Cell Dyscrasia Database have provided informed consent for use of their information for research purposes.

Conflicts of Interest

Kukreti: Honoraria EUSA pharmaceuticals; **Bhella**: Honoraria & consultancy from Kite, Gilead; **Prica**: Honoraria from Astra-Zeneca, Abbvie and Kite Gilead, unrelated to myeloma; **Reece**: Research funding from Otsuka, Celgene, Janssen, Takeda, Merck, BMS, Millennium; Consultancy from Celgene, Jansen, Amgen, Karyopharm, Takeda; Honoraria: Celgene, Janssen, Amgen, Takeda; **Tiedemann**: Honoraria from Sanofi, Janssen, AbbVie; **Trudel**: Honoraria from Sanofi, GSK, Pfizer, BMS, Janssen, Astrazenca, BMS, forus; Research funding from GSK, BMS, Roche, Genentech, Pfizer, Janssen, K36 therapeutics; **Lancman**: Honoraria & consultancy from Janssen, Takeda; Honoraria from Pfizer, Sanofi, Forus.

All remaining authors declare no competing financial interests.

Data Availability Statement

University Health Network Research Ethics Board (UHN REB) does not allow patient level data to be shared. Any aggregate data supporting the findings of this study can be available from the corresponding author upon reasonable request.

Clinical Trial Registration

The authors have confirmed clinical trial registration is not needed for this submission.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.