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RESEARCH ARTICLE

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Cytogenomic array detects a subset of myelodysplastic syndrome with increased risk that is invisible to conventional karyotype

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Abstract

Conventional karyotyping is essential standard practice in the initial evaluation of myelodysplastic syndrome (MDS) and is the most impactful single component of the Revised International Prognostic Scoring System (IPSS-R). While single nucleotide polymorphism array (SNP-A) has demonstrated the ability to detect chromosomal defects with greater sensitivity than conventional karyotype, widespread adoption is limited by the unknown additional prognostic impact of SNP-A analysis. Here, we investigate the significance of additional SNP-A abnormalities in the setting of MDS and demonstrate differences in survival of patients with additional abnormalities, even those initially characterized as relatively lower risk either by cytogenetic score or IPSS-R. Our findings identify specific abnormalities, particularly *KMT2A* partial tandem duplication, that are invisible to conventional karyotype and potentially contribute to the poor prognosis of MDS patients. Furthermore, these results demonstrate the added value of SNP-A analysis in identifying patients who may benefit from more aggressive therapy, particularly those who would otherwise be classified into lower risk categories.

KEYWORDS

cytogenomic array, MDS, myelodysplastic syndrome, SNP array, SNP-A

1 | INTRODUCTION

Prognostic classification of myelodysplastic syndrome (MDS) relies heavily on cytogenetic abnormalities and is currently utilized to guide therapeutic decision making, including identifying appropriate candidates for bone marrow transplantation. Indeed, cytogenetic risk is the most heavily weighted component of the Revised International Prognostic Scoring System (IPSS-R), which categorizes patients into multiple risk groups of ascending associated poor prognosis.[1] While conventional karyotype is the gold standard for detection of genomic abnormalities in both diagnostic and prognostic settings, single nucleotide polymorphism arrays (SNP-As) have emerged as potential means of further categorizing prognostic risk beyond traditional karyotyping in many hematologic malignancies due to the assay's greater sensitivity in detecting unbalanced chromosomal defects and copy-neutral loss of heterozygosity (CN-LOH).[2-6] However, widespread adoption and incorporation into prognostic algorithms has not yet occurred despite evidence of the clinical significance of SNP-A in combination with already established karyotypic features.[5-8] We therefore sought to refine our understanding of the significance of additional SNP-A abnormalities and their impact on prognosis and ultimately risk of death. In particular, given the high frequency of MDS cases showing a normal karyotype,[9,10] we were especially interested in the potential impact of SNP-A in this group of patients.

Sarah M. Choi and Steven B. Van Norman contributed equally to this study.

2 | MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the University of Michigan. We retrospectively reviewed 108 consecutive patients who underwent karyotyping and Thermo Fisher Cytoscan™ array (SNP-A) analysis[11] for diagnosis/classification of a suspected myeloid neoplasm and identified 77 patients with a diagnosis of de novo MDS, excluding therapy-related cases. Among these, we identified cases for which additional abnormalities were detected by SNP-A analysis that were not identified using conventional karyotype. We reviewed each patient's electronic medical record including laboratory values at diagnosis (hemoglobin, absolute neutrophil count [ANC], platelet count, and bone marrow blast percentage). We then compared overall survival (OS) based on the presence or absence of additional cytogenomic abnormalities detected by SNP-A on groups that were stratified by cytogenetic risk and IPSS-R score (Figure 1). OS was calculated from date of diagnosis to date of death, censoring for patients alive at the completion of the study. Patients with both low-risk karyotype (very good-intermediate cytogenetic risk group) and consistent SNP-A results were compared to patients with similar low-risk karyotype but with additional SNP-A abnormalities. These groups were also stratified by the IPSS-R, and survival was compared in patients with and without additional SNP-A abnormalities. Unpaired *t*, Mann-Whitney, Chi-Square, and Fisher's tests were used as applicable to compare differences in characteristics between groups with and without additional abnormalities. Log-rank (Mantle-Cox) test was used to compare OS between the groups.

3 | RESULTS AND DISCUSSION

Of the 77 patients for whom both karyotype and SNP-A were performed (Table 1), 36 cases had additional abnormalities detected by SNP-A (47% of all cases; Table 2; Figure 2). Follow-up time ranged from 1.5 to 85 months (Table 1). Deletions were the most common finding (29 instances), followed by CN-LOH (19 instances). The most prevalent single abnormality detected was *KMT2A*(*MLL*) partial tandem duplication (*KMT2A*-PTD) (five cases). Additional abnormalities included cryptic deletions involving *TET2* (3), *RUNX1* (2), and *CUX1* (1). SNP-A detected a monosomy 7 in two cases whose conventional cytogenetics showed a normal karyotype after examining adequate number of metaphase cells.

Cases with and without additional SNP-A abnormalities showed similar overall distribution of morphologic categorization and no statistically significant differences in hemoglobin, ANC, platelet count, bone marrow blast percentage, or IPSS-R (Table 1; Figure S1).

Among matched cases with very good-intermediate cytogenetic risk, those that had additional abnormalities detected on SNP-A showed worse OS (median 35.4 months) than those that did not have additional abnormalities (median survival not reached; Figure 3A; $P = 0.010$). Similar observations were seen when cases were stratified into matching IPSS-R categories, where very low-intermediate risk cases with additional SNP-A abnormalities showed worse OS (median 35.4 months) similar to cases of high-very high risk (median 31.3 months) compared to very low-intermediate risk cases without additional SNP-A abnormalities (median 62.6 months; Figure 3B; $P = 0.020$).

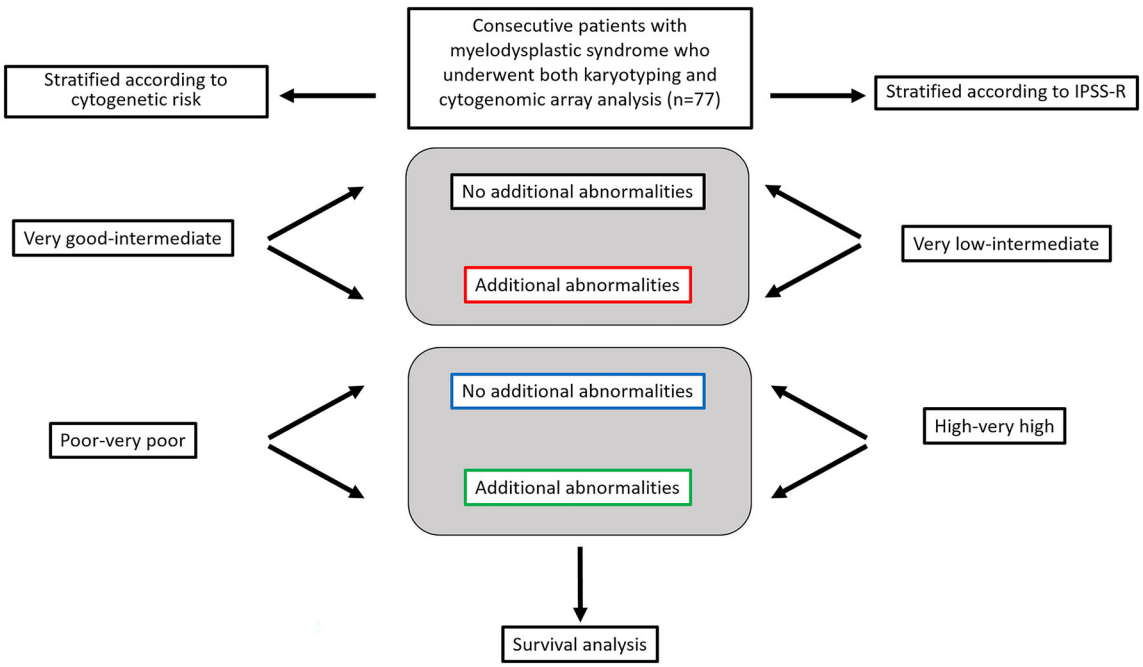

FIGURE 1 Study design. MDS cases for which both karyotyping and cytogenomic array (SNP-A) was performed were stratified by (a) cytogenetic risk and (b) Revised International Prognostic Scoring System (IPSS-R). They were then further stratified based on the presence or absence of additional SNP-A abnormalities. Survival analysis was performed. MDS, myelodysplastic syndrome; SNP-A, single nucleotide polymorphism array [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical characteristics of study group

		Cytogenetic risk group					
		Very good-intermediate			Poor-very poor		
	Total	No additional SNP-A abnormalities	Additional SNP-A abnormalities	*P*	No additional SNP-A abnormalities	Additional SNP-A abnormalities	*P*
Number of patients	77	33	26		8	10	
Age		66 (59-74)	71 (64-78)	*0.18*	64.4 (60.6-75.5)	71.2 (62.9-80.0)	*0.36*
Sex	77			*0.59*			*0.64*
Male	50	20	18		6	6	
Female	27	13	8		2	4	
Initial diagnosis	77			*0.29*			*0.46*
MDS-SLD	8	3	4		1	0	
MDS-MLD	35	17	10		4	4	
MDS-EB1	12	6	2		2	2	
MDS-EB2	22	7	10		1	4	
IPSS-R		3 (2.5-4.9)	2.75 (1.5-4.25)	*0.16*	6 (4.25-7.6)	7.25 (6-8.5)	*0.14*
ANC, k/μL		1.6 (0.8-3.4)	1.7 (1.0-2.5)	*0.79*	0.9 (0.3-2.3)	0.8 (0.5-1.4)	*0.85*
Hgb, g/dL		9.8 (8.1-11.5)	9.6 (8.0-10.9)	*0.73*	9.0 (7.6-9.9)	9.1 (8.0-9.5)	*0.56*
Plt, k/μL		75.5 (53-191)	118 (66-180)	*0.6*	65 (30-110)	43 (18-59)	*0.37*
BM blast percent, %		2.3 (0.9-6.1)	2.0 (1.0-4.3)	*0.95*	1.8 (0.3-6.7)	3.4 (1.3-9.8)	*0.24*
Therapy				*0.8*			*NA*
Supportive		15	12		2	4	
Hypomethylating agent		18	12		5	7	
Transplant		9	5		3	0	
Other		5	6		0	0	
Median follow up time, months		32.6	26.5		21.7	7.2	
		IPSS-R					
		Very low-intermediate risk			High-very high		
		No additional SNP-A abnormalities	Additional SNP-A abnormalities	*P*	No additional SNP-A abnormalities	Additional SNP-A abnormalities	*P*
Number of patients	77	26	20		18	13	
Age		67.9 (59.7-75.0)	74.0 (62.8-79.8)	*0.22*	62.5 (59.5-71.4)	69.1 (65.4-76.3)	*0.14*
Sex	77			*0.35*			*>0.99*
Male	50	15	15		12	8	
Female	27	11	5		6	5	
Initial diagnosis	77			*0.16*			*0.69*
MDS-SLD	8	5	3		0	0	
MDS-MLD	35	16	11		4	4	
MDS-EB1	12	4	1		5	2	
MDS-EB2	22	1	5		9	7	
IPSS-R		2.75 (2-3.5)	2 (1.5-3)	*0.3*	6 (5.5-6.5)	6.25 (5.6-7.9)	*0.3*
ANC, k/μL		1.6 (0.8-3.3)	2 (1.1-2.6)	*0.37*	1.2 (0.4-3.1)	0.9 (0.5-1.9)	*0.83*
Hgb, g/dL		10.1 (8.6-12.3)	10.1 (8.1-11.3)	*0.66*	8.3 (7.5-9.8)	9.0 (7.6-9.4)	*0.86*
Plt, k/μL		87.5 (69.5-164)	118 (69.8-189)	*0.62*	44 (28-81)	45 (24-122)	*0.98*
BM blast percent, %		1.6 (0.6-2.5)	1.9 (0.8-2.1)	*0.77*	8 (1.5-10)	7.4 (2.1-12)	*0.58*
Therapy				*0.99*			*0.19*

(Continues)

TABLE 1 (Continued)

	IPSS-R					
	Very low-intermediate risk			High-very high		
	No additional SNP-A abnormalities	Additional SNP-A abnormalities	*P*	No additional SNP-A abnormalities	Additional SNP-A abnormalities	*P*
Supportive	14	10		3	6	
Hypomethylating agent	13	9		10	10	
Transplant	5	3		7	2	
Other	4	3		1	3	
Median follow up time, months	46.2	26.5		24.2	10.3	

Note: Median value (25th-75th percentile) displayed; "Other" therapy (therapies not listed above).
Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; Hgb, hemoglobin; IPSS-R, Revised International Prognostic Scoring System; NA, unable to perform; Plt, platelet count; SNP-A, single nucleotide polymorphism array.

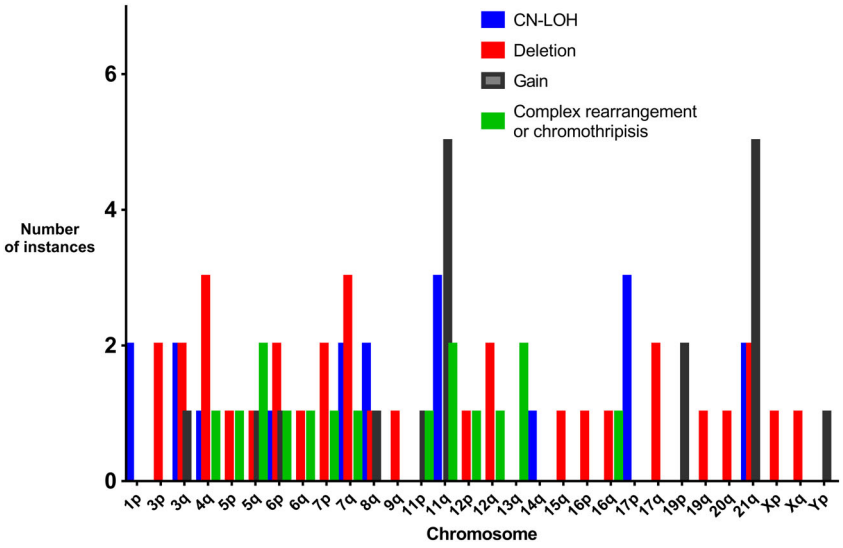

FIGURE 2 Frequency of additional SNP-A abnormalities. The number of instances of each type of additional abnormality, which were not detected by conventional karyotype, is depicted for each chromosome. CN-LOH, copy-neutral loss of heterozygosity; SNP-A, single nucleotide polymorphism array [Color figure can be viewed at wileyonlinelibrary.com]

On the contrary, in cases with either poor-very poor cytogenetic risk or high-very high IPSS-R score, the presence of additional SNP-A abnormalities did not show a statistically significant impact on OS though a trend toward poorer survival was observed (Figures 3A, $P = 0.054$ and Figures 3B, $P = 0.052$). This finding suggests that the prognostic impact of SNP-A abnormalities may be primarily concentrated in cases that would otherwise be classified as lower risk either by cytogenetic score or IPPS-R.

We questioned whether or not incorporating additional SNP-A findings would impact the calculated IPSS-R. Taking into consideration cases with anomalies that were greater than 5 Mb excluding CN-LOH and small focal deletions and gains, only two cases changed IPSS-R (one from very low to intermediate; one from very low to low). In terms of our analysis, therefore, there was no impact on survival.

Based on our previous observation of a small cohort of low-risk MDS cases of *KMT2A*-PTD which showed poor OS,[12] we questioned whether this single abnormality could be responsible for the survival differences of the cases with additional SNP-A abnormalities. When *KMT2A*-PTD cases were excluded from the analysis, the effects of additional SNP-A abnormalities when stratifying patients according to cytogenetic risk and IPSS-R were somewhat abrogated. A trend toward poorer survival was still noticeable, but no longer statistically significant (Figure 4A; $P = 0.069$ and Figure 4B; $P = 0.063$). Consequently, *KMT2A*-PTD may be at least partly responsible for the worse survival seen in patients with additional SNP-A abnormalities and otherwise very good-intermediate cytogenetic risk or very low-intermediate IPSS-R, though other abnormalities may also contribute to a lesser extent. Genomic locations of *KMT2A*-PTD in five cases are shown in Figure 5.

To summarize, our findings suggest that the presence of additional SNP-A abnormalities, detected in almost half of MDS cases, has further impact on prognosis and OS than that afforded by conventional karyotype analysis. Cases identified as very good-intermediate cytogenetic risk that have additional SNP-A abnormalities demonstrate OS approaching that of patients with poor-very poor cytogenetic risk. Similarly, cases identified as very low-intermediate risk by IPSS-R demonstrate OS more similar to patients with high-very high risk by IPSS-R. Although a significant component of these differences may be

TABLE 2 Additional abnormalities detected by cytogenomic array

				SNP-A results			SNP-A and karyotype comparison		
Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
1	46,XY[20]	Good	Good	arr[hg19] 4q11q35.2(52 686 799-190 921 709)x2 hmz	90	138.2		4q CN-LOH	
2	47,XXX?c[20]	Good	Good	arr[hg19] 21q11.2q22.3 (14 386 012-48 084 820)x2 hmz	30 to 90	33.7		21q CN-LOH	
				arr[hg19] Xp22.33q28(168 546-155 233 731)x3	100	155.1	Yes		
3	46,XY[16]	Good	Intermediate	arr[hg19] 15q14q22.2(35 437 654-61 211 671)x1-2	15	25.8		15q deletion	
4	46,XY[20]	Good	Poor	arr[hg19] 6q23.2q23.3 (134 365 000-136 607 455)x1	100	2.2		6q deletion	
				arr[hg19] 7p22.3q36.3(43 360-159 119 707)x1-2	7	159.1		–7	
				arr[hg19] 11q13.1q25(65 577 515-134 942 626)x2 hmz	100	69.4		11q CN-LOH	
5	46,XX[20]	Good	Good	arr[hg19] 7q35q36.3(144 958 661-159 119 220)x2 hmz	90	14.2		7q CN-LOH	
				arr[hg19] 11q23.3(118 338 293-118 354 345)x2-3	45	16 kb		11q gain (KMT2A-PTD)	
6	46,XY[20]	Good	Good	arr[hg19] 11q12.2q25(60 804 709-134 942 626)x2 hmz	90	74.1		11q CN-LOH	
				arr[hg19] 11q23.3(118 338 293-118 349 247)x2-3	>50	11 kb		homozygous KMT2A-PTD	
7	46,XX[20]	Good	Good	arr[hg19] 11q23.3(118 123516-118 470 527)x2-4	80	347 kb		11q gain (KMT2A-PTD)	
				arr[hg19] 11q24.3(128 408 210-128 699 707)x2-3	80	291 kb		11q24.3 gain	
8	46,XY[20]	Good	Good	arr[hg19] 1p36.33p34.1(882 802-45 000 436)x2 hmz	90	44.1		1p CN-LOH	
9	46,XY[20]	Good	Good	arr[hg19] 3q11.1q29(93 735 022-197 851 260)x2 hmz	35	104.1		3q CN-LOH	
				arr[hg19] 4q24(106 130 009-106 190 922)x1-2	50	61 kb		4q deletion including TET2	
10	46,XX[20]	Good	Good	arr[hg19] 7q21.3q36.3 (97 735 123-159 119 220)x2 hmz	50	61.4		7q CN-LOH	

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
				arr[hg19] 21q11.2q22.3 (15 867 134-48 084 820)x2 hmz	50	32.2		21q CN-LOH	
11	46,XX[20]	Good	Good	arr[hg19] 8q11.23q24.3 (53 704 149-146 292 734)x2 hmz	15	92.6		8q CN-LOH	
12	46,XY[20]	Good	Good	arr[hg19] 4q22.1q35.2 (92 145 040-190 921 709) x2 hmz	10	98.8		4q CN-LOH	
13	46,XY[20]	Good	Poor	arr[hg19] 7p22.3q36.3(43 360–159 119 707)x1-2	12	159.1		–7	
14	46,XY[20]	Good	Good	arr[hg19] 3q21.3q29(126 531 213-197 851 260)x2 hmz	85	71.3		3q CN-LOH	
				arr[hg19] 7q22.1(99 829 321-102 058 793)x1-2	80	2.2		7q deletion including CUX1	
				arr[hg19] 21q22.12(36 294 421-37 432 271)x1-2	85	1.1		21q deletion including RUNX1	
15	46,XX [20]	Good	Good	arr[hg19] 11q23.3(118 338 521-118 355 688)x2-3	30	17 kb		11q gain (KMT2A-PTD)	
16	46,XY[20]	Good	Good	arr[hg19] 4q24(105 995 910-106 227 999)x1-2	90	0.2		4q deletion including TET2	
17	46,XY[20]	Good	Good	arr[hg19] 21q22.12(36 002 849-37 408 933)x1-2	80	1.4		21q deletion including RUNX1	
18	46,XY[20]	Good	Good	arr[hg19] 9q34.3(139 101 277-139 734 766)x1	80	0.6		9q deletion (constitutional?)	
				arr[hg19] 11q23.3(118 335 185-118 359 052)x3	80	24 kb		11q gain (KMT2A-PTD)	
19	46,XY[20], NUP98 rearrangement (80% by FISH)	Good	Good	arr[hg19] 5q35.3(176 650 787-176 768 901)x2-3	80	0.1		5q gain	
				arr[hg19] 11p15.4(3 764 205-3 832 210)x2-3	80	68 kb		11p gain associated with NUP98-NSD1 translocation	

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
20	46,XY,del(5)(q15q33)[4]/46,XY[1]	Good	Good	arr[hg19] 1p36.33p31.3(903 425-65 250 982)x2 hmz	60	64.3		1p CN-LOH	
				arr[hg19] 5q15q33.2(93 274 523-154 360 732)x1-2	40	64.1	Yes		
21	46,XY,del(5)(q15q31)[19]/46,XY[1]	Good	Good	arr[hg19] 3p13p11.1(70 310 611-88 552 092)x1-2	60	18.2		3p deletion	
				arr[hg19] 5q15q31.1(95 982 582-131 916 380)x1-2	70	35.9	Yes		
22	46,XX,del(5)(q13q33)[12]/46,XX[8]	Good	Good	arr[hg19] 5q14.2q34(81 856 536-160 672 001)x1-2	50	78.8	Yes		
				arr[hg19] 12p13.31p13.1 (10 000 550-13 258 017)x1-2	30	3.3		12p deletion including ETV6	
24	46,XY,del(13)(q12q14)[7]/46,XY[18]	Intermediate	Intermediate	arr[hg19] 4q24(105 942 532-106 564 759)x1-2	95	0.6		4q deletion including TET2	
				arr[hg19] 13q13.1q14.3 (33 109 828-53 700 736)x1-2	25	20.6	Yes		
				arr[hg19] Xq28 or Yq12 (154941868-155 233 731 or 59 044 874-59 336 737)x1-2	95	0.3		Xq28 or Yq12 deletion (not specific)	
26	47,XY,+8[18]/46,XY[2]	Intermediate	Intermediate	arr[hg19] 8p23.3q24.3(158 048-146 295 771)x2-3	30	146.1	Yes		
				arr[hg19] 11q13.2q25(67 015 468-134 942 626)x2 hmz	50	69.9		11q CN-LOH	
27	47,XX,+8[14]/46,XX[6]	Intermediate	Intermediate	arr[hg19] 3q26.2(168 582 060-170 230 667)x2-3	90	1.6		3q gain	
				arr[hg19] 8p23.3q11.1(158 048-47 126 524)x2-3	65	47			
				arr[hg19] 8q11.1q11.21 (47 127 862-51 456 633)x1-2	90	4.3		8q deletion (+8 actually had small deletion near centromere)	
				arr[hg19] 8q11.21q24.3 (51 456 754-146 295 771)x2-3	65	94.8			
29	44,XX,add(4)(q23),−5,+6,der(6;12)t (6;12)(p21;p11.2)del(6)(p12p21),der	Very poor	Very poor	arr[hg19] 4q25(109 354 361-111 191 990)x1	100	1.8		4q25 deletion	

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
	(6)t(6;13)(p21;q14)del(6)(p12p21),der(11)dup(11)(q13q13)del(11)(q23q23),−13,add(14)(p11.2),del(18)(q21q23)[cp13]/45,sl,+mar[7]			arr[hg19] 4q32.3q35.2 (167 790 246-190 957 473)x1	100	23.2	Yes		add(14p) not observed
				arr[hg19] 5p15.33p15.2(113 576-13 611 558)x1	100	13.5		Monosomy 5 as 5p deletion, 5q deletion and marker	
				arr[hg19] 5q11.2q35.1 (53 519 660-171 907 198)x1	100	118.4			
				arr[hg19] 6p24.1p22.1 (11 797 999-27 746 178)x1	100	15.9		6p22p24 deletion	
				arr[hg19] 6p22.1p21.1 (30 105 444-44 326 337)x3	100	14.2	Yes		
				arr[hg19] 6p21.1p12.1 (44 326 504-56 764 165)x1	100	12.4	Yes		
				arr[hg19] 6p12.1q27(56 768 218-170 919 482)x3	100	114.2	Yes		
				arr[hg19] 11p11.12q25 (51 126 723-134 938 470)cx	100	83.8		11 Abnormalities complex	
				arr[hg19] 12p13.2p11.21 (11 658 944-31 485 751)x1	100	19.8	Yes		
				arr[hg19] 13q11q34(19 436 286-115 107 733)cx	100	95.7		13q chromothripisis	
				arr[hg19] 17q22(54 260 365-55 515 281)x1	100	1.3		17q deletion	
				arr[hg19] 18q21.2q23(52 763 256-78 014 123)x1	100	25.3	Yes		
30	43,XY,der(3)t(3;16)(p12;q13),der(5)t(3;5)(p12;q13),−12,der(13)t(12;13)(q12;q34),der(17)t(17;20)(p13;p11.2),−20,idic(22)(p11.2)[cp18]/46,XY[2]	Very poor	Very poor	arr[hg19] 3p21.2p12.2 (50 699 382-83 166 160)x1-2	65	32.5	Yes		
				arr[hg19] 3p11.2q22.3 (87 417 120-136 702 414)x1-2	10	49.3		3p11.2q22.3 deletion	16q and 13q abnormalities balanced
				arr[hg19] 5q13.2q35.3 (72 110 523-180 719 789)x1-2	65	108.6	Yes		
				arr[hg19] 8q24.13q24.21 (126 229 398-130 825 360)x2-3	65	4.6		8q gain	

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
				arr[hg19] 12p13.33q12(173 786-46 058 033)x1-2	65	45.9	Yes		
				arr[hg19] 12q13.11q13.12 (48 829 668-49 813 922)x1-2	65	1		12q13 deletion	
				arr[hg19] 12q21.1q21.2 (75 107 892-76 608 109)x1-2	65	1.5		12q21 deletion	
				arr[hg19] 14q11.2q32.33 (20 511 672-107 285 437)x2 hmz	90	86.8		14q CN-LOH	
				arr[hg19] 16p11.2(28 689 085-32 922 512)x1-2	65	4.2		16p deletion	
				arr[hg19] 17p13.3p13.1(9474-8 172 907)x1-2	65	8.2	Yes		
				arr[hg19] 19q13.32q13.33 (47 126 613-49 500 959)x1-2	65	2.4		19q deletion	
				arr[hg19] 20p12.1(15 681 353-17 022 497)x1-2	65	1.4		Chromosome 20 abnormalities complex	
				arr[hg19] 20p11.21q11.21 (22 735 537-29 871 042)x1-2	65	7.1			
				arr[hg19] 20q11.21(29 874 663-31 364 166)x3	100	1.5			
				arr[hg19] 20q11.21q13.33 (31 382 491-62 897 159)x1-2	65	31.5			
				arr[hg19] 22q11.1q13.33 (16 888 899-51 197 838)x2-3	55	34.3	Yes		
31	47,XY,t(1;3)(p13;q21),del(4)(q21q25), del(11)(q14q24),+19,del(20)(q11.2q13.3) [4]	Very poor	Very poor	arr[hg19] 4q21.23q25(84 749 459-109 483 856)x1-2	60	24.7	Yes		t(1;3) not observed
				arr[hg19] 11q14.2q24.1 (86 711 530-123 487 591)x1-2	60	36.8	Yes		
				arr[hg19] 17q11.2(29 262 000-30 466 769)x1-2	60	1.2		17q deletion involving NF1	
					20	58.7	Yes		

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
				arr[hg19] 19p13.3q13.43(260 911-58 956 888)x2-3					
				arr[hg19] 20q11.21q13.31 (31 062 502-56 290 652)x1-2	50	25.2	Yes		
				arr[hg19] 21q22.12(36 202 439-36 282 500)x2-3	100	80 kb		21q gain (partial duplication of RUNX1)	
				arr[hg19] Xp22.2(15 644 219-16 702 011)x1-2	50	1.1		Xp deletion involving ZRSR1	
32	44-46,XY,der(2)ins(2;6)(q23;p24p12)add(2)(q23),der(3)t(3;12)(p24;p13),add(4)(q12),der(5;22)(p10;q10),−6,der(12)t(3;12)t(?6;12)(q12;q24),der(19)dup(19)(q13.1q13.4)add(19)(q13.4),+mar[cp17]/43-44,sl,add(X)(p11.2),−der(2)ins(2;6)add(2),+add(2)(q32),−der(3)t(3;12),+3,+6,−7,−der(12)t(3;12)t(6;12),+add(12)(p13),add(19)(p13),add(?21)(p11.2),+del(?22)(q11.2q13),−mar[cp3]	Very poor	Very poor	arr[hg19] 3p26.3p12.3(61 891-74 491 151)cx	80	74.4	Yes		
				arr[hg19] 4q12q32.2(57 131 170-163 425 170)cth	80	106.3		add(4q) chromothripisis	Chromosomes 2 and 12 abnormalities to be balanced
				arr[hg19] 5q11.2q12.1 (54 136 001-60 742 205)x1-2	90	6.6	Yes		
				arr[hg19] 5q12.1q35.3 (61 997 673-177 260 317)x1-2	90	115.3	Yes		
				arr[hg19] 6p25.3p24.2(156 974-10 880 159)x1-2	80	10.7		6p deletion	
				arr[hg19] 16q22.3q23.2 (73 602 589-80 595 329)x1-2	80	7		16q deletion	
				arr[hg19] 17p13.3p11.2(18 900-16 402 114)x2 hmz	90	16.4		17p CN-LOH	
				arr[hg19] 19q13.11q13.43 (34 783 132-58 956 888)x2-3	80	24.2	Yes		
				arr[hg19] 20q11.23q13.32 (34 882 014-58 360 984)x1-2	20	23.5		20q deletion	
				arr[hg19] 21q22.13q22.3 (39 246 697-43 050 829)x2-3	30	3.8		21q gain	
				arr[hg19] 22q11.1q13.1 (16 888 899-38 450 184)x2-3	80	21.6	Yes		
				arr[hg19] 22q13.1q13.33 (39 235 339-51 197 838)x2-3	80	12	Yes		

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
33	44,XY,t(1;12)(q21;q24.1),−3,add(3)(p11),der(5)t(3;5)(p13;q23),−6,−7,+11,der(11)t(3;11)(q21;q13)[15]/46,XY[5]	Very poor	Very poor	arr[hg19] 1q21.3q22(153 368 019-155 017 913)x1-2	30	1.7	Yes		Chromosome 11 abnormalities to be balanced
				arr[hg19] 3p26.1q29(4 103 600-197 851 936)cx	30	193.8	Yes		
				arr[hg19] 5q23.2q35.3 (124 723 524-180 719 789)x1-2	30	56	Yes		
				arr[hg19] 6p25.3p22.3(156 974-24 311 197)x1-2	30	24.2	Yes		
				arr[hg19] 6p22.2p22.1 (26 553 570-28 222 528)x1-2	30	1.7	Yes		
				arr[hg19] 6p21.1p12.3 (43 395 395-47 462 571)x2-3	30	4.1		Loss of 6 and 7 complex	+11
				arr[hg19] 6p12.3q27(47 467 934-170 919 482)x1-2	30	123.5			
				arr[hg19] 7p21.3p21.1(8 299 324-16 722 353)x1-2	30	8.4			
				arr[hg19] 7p13p12.1(44 817 005-50 784 997)x1-2	30	6			
				arr[hg19] 7q11.21(63 083 343-66 898 842)x1-2	30	3.8			
				arr[hg19] 7q35q36.3(144 075 389-159 119 707)x1-2	30	15			
				arr[hg19] 17p13.3p11.2(18 900-17 027 255)x2 hmz	40	17		17p CN-LOH	
57	46,X,del(Y)(q11.23)[8]/46,XY[12]	Good	Good	arr[hg19] Yp11.31q11.221 (2 650 140-19 576 531)x1-2	40	16.9		Yp gain [del(Y) to be idic(Yq)]	
				arr[hg19] Yq11.221q11.23 (19 585 828-28 799 937)x0-1	40	8.7			
69	45-46,XY,dic(3;5)(5pter->5q11.2::3p12->3q29::3p22->3pter),del(7)(q21q36),+0-1mar[cp18]/46,XY[2]	Very poor	Very poor	arr[hg19] 3p22.2p12.1 (37 299 213-83 644 799)x1-2	70	46.4	Yes	5q deletion complex	
				arr[hg19] 5q11.1q12.3 (49 430 268-64 262 486)x1-2	20 to 55	14.8	Yes		

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
				arr[hg19] 5q12.3q13.3 (66 243 349-76 743 838)x1-2	25 to 70	10.5	Yes		
				arr[hg19] 5q14.3q35.3 (85 913 148-180 719 789)x1-2	70	94.8	Yes		
				arr[hg19] 7q21.13q36.3 (88 745 758-159 119 707)x1-2	70	70.4	Yes		
70	46~49,XX,−2,del(5)(q15q33),−6,del(6)(p23p24),−7,−13,−15,+16,del(16)(q12q24),+17,add(17)(p11.2),add(17)(p12),−18,−19,−21,+1~2r,+3~5mar[cp10]/46,XX[10]	Very poor	Very poor	arr[hg19] 2q33.1q37.3 (201 635 517-242 783 384)x1-2	15	41.2	Yes		
				arr[hg19] 5q13.3q35.3 (73 921 819-180 719 789)x1-2	15	106.8	Yes		
				arr[hg19] 6p22.3p22.1 (18 309 604-28 848 258)x4-6	amp	10.5		6p amplification	
				arr[hg19] 13q11q34(19 436 286-115 107 733)x1-2	15	95.7	Yes		Loss of 7, 15, abnormalities on chromosome 16 and 17 not seen by array
				arr[hg19] 19p13.2(10 856 592-12 040 283)x4-7	amp	1.2		19p amplification	
				arr[hg19] 19p13.2p13.12 (13 477 560-15 274 712)x2-5	amp	1.8		19p amplification	
				arr[hg19] 21q21.1(19 629 216-20 241 815)x4-7	amp	0.6		21q amplification	
				arr[hg19] 21q22.12q22.3 (35 848 786-48 097 372)x2-3	40	12.2		21q gain	
73	45,XX,der(4)t(4;?13)(q35;q14),−13,−16,der(17)t(?16;17)(p11.2;p11.2),+der(?)t(?;1)(?;p31) [18]/44-45,XX,−8,dic(8;10)(q26;q2?2)ins(10;1)(q26;p31p36),-16,der(17)t(?16;17)[cp2]	Very poor	Very poor	arr[hg19] 1p36.33p32.1(849 466-59 863 870)x2-3	80	59	Yes		The subclone −8 and dic(8;10) not observed
				arr[hg19] 1p31.1(71 990 325-73 466 675)x2-3	85	1.5	Yes		
				arr[hg19] 4q35.2(190 712 389-190 957 473)x1-2	85	0.3	Yes		
				arr[hg19] 8q23.1q24.3 (108 384 827-146 292 734)x2 hmz	85	37.9		8q CN-LOH	

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
				arr[hg19] 13q21.31q21.33 (65 565 962-69 826 807)x1-2	85	4.3		Loss of 13 complex	
				arr[hg19] 13q33.1(103 508 960-103 531 681)x1-2	85	23 kb			
				arr[hg19] 13q33.1(103 592 015-104 256 190)x1-2	85	0.7			
				arr[hg19] 13q33.2q33.3 (105 264 673-109 888 382)x1-2	85	4.6			
				arr[hg19] 16q11.2q24.3 (46 503 572-90 155 062)x1	100	43.7	Yes		
				arr[hg19] 17p13.3p11.2(525-17 988 254)x1	95	18	Yes		
74	45,XY,del(5)(q22q33),der(17;20)(q10;p10) [3]/46,sl,del(7)(q11.2q36),+8 [5]/44,sl,−7[6]/85-94,slx2,add(11)(q12)x2,+1-2mar,4-11dmin[cp4]/46,XY[2]	Very poor	Very poor	arr[hg19] 5q21.3q33.3 (106 203 054-157 533 436)x1-2	30	51.3	Yes		
				arr[hg19] 7p22.3q36.3(43 360–159 119 707)x1-2	15	159.1	Yes		
				arr[hg19] 8p23.3q24.3(158 048-146 295 771)x2-3	10	146	Yes		
				arr[hg19] 11q13.4(70 735 084-74 545 922)x1-2	10	3.8			
				arr[hg19] 11q13.4q14.1 (74 950 287-80 597 434)x2-3	10	5.7		add(11q) complex	Near tetraploid clone not observed
				arr[hg19] 11q14.1q14.3 (80 885 537-92 686 784)x1-2	10	11.8			
				arr[hg19] 11q22.1q22.3 (97 942 172-103 313 943)x1-2	10	5.4			
				arr[hg19] 11q22.3q23.3 (104 772 138-117 129 522)x1-2	10	12.4			
				arr[hg19] 11q23.3(117 940 196-118 570 397)x2-3	80	0.6			
				arr[hg19] 11q23.3q24.2 (118 719 566-126 066 194)x1-2	10	7.4			
					amp	8.7			

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
				arr[hg19] 11q24.2q25 (126 201 307-134 938 470)x3-5					
				arr[hg19] 17p13.3p11.2(525-21 722 139)x1-2	30	21.7	Yes		
				arr[hg19] 20q11.22q13.33 (32 359 017-62 915 555)x1-2	30	32.6	Yes		
				arr[hg19] 21q21.3q22.3 (30 253 288-48 097 372)x2-3	10	17.8		21q gain	
76	46-48,XX,del(1)(p22p36.1),del(2)(p24),del(3)(p21),−5,der(6)t(1;6)(p13;q25),der(7)add(7)(p21)del(7)(q32q36),+8,+8,+8,del(11)(q22q23),−12,+13,del(13)(q12q14)x2,add(16)(q11.2),add(17)(p13),add(19)(p13),−21, +0-2mar[cp20]	Very poor	Very poor	arr[hg19] 1p21.1p13.3 (103 620 493-108 243 851)x1-2	70	4.6	Yes		
				arr[hg19] 3q26.33(180 626 349-180 728 459)x1-2	70	0.1		3q deletion	
				arr[hg19] 5p15.33p14.1(113 576-24 705 254)x1-2	80	24.6		Loss of 5 complex	
				arr[hg19] 5p14.1p13.2 (26 602 764-36 629 258)x1-2	80	10			
				arr[hg19] 5q14.3(86 075 402-91 536 195)x1-2	80	5.5			
				arr[hg19] 5q21.1q32(99 149 791-149 316 740)x1-2	80	50.2			
				arr[hg19] 5q33.1q34(151 060 202-163 263 177)x1-2	80	12.2			
				arr[hg19] 6q11.1q13(62 118 669-73 010 280)x1-2	80	10.9	Yes		
				arr[hg19] 6q24.2q25.1 (144 387 634-152 252 413)x1-2	80	7.9	Yes		
				arr[hg19] 7p21.3p21.1 (11 371 004-17 035 173)x1-2	80	5.7	Yes		
				arr[hg19] 7p14.1(37 771 693-40 371 298)x1-2	80	2.6	Yes		
				arr[hg19] 7q33q36.3(134 801 961-159 119 707)x1-2	80	24.3	Yes		
					Pentasomy	146.1	Yes		

(Continues)

TABLE 2 (Continued)

Patient	Karyotype	Cytogenetic risk	Cytogenetic risk after array (anomalies >5 Mb but excluding CN-LOH and small focal deletions, duplications)	SNP-A results			SNP-A and karyotype comparison		
				Array results	%	Size (Mb)	SNP-A concordant with karyotype	Additional abnormality	Additional karyotypic abnormality not in SNP-A
				arr[hg19] 8p23.3q24.3(158 048-146 295 771)x3-4					
				arr[hg19] 12p12.3q22(15 277 112-95 085 949)cx	80	79.8		Loss of 12 complex	
				arr[hg19] 13q11q13.1(19 436 286-32 565 539)x2-3	70	13.1	Yes		
				arr[hg19] 13q13.1q21.31 (32 576 910-64 735 038)x1-2	70	32.2	Yes		
				arr[hg19] 13q21.31q34 (64 738 525-115 107 733)x2-3	70	50.4	Yes		
				arr[hg19] 16q12.1(48 341 743-50 857 833)x1-2	80	0.4		add(16q) complex	
				arr[hg19] 16q12.1q24.3 (51 570 940-90 155 062)x1-2	80	2.5			
				arr[hg19] 16q11.2q12.1 (46 580 413-47 022 778)x1-2	80	38.6			
				arr[hg19] 17p13.3p11.2(18 900-20 697 797)x2 hmz	80	20.7		17p CN-LOH	Loss of 21 not observed

Abbreviations: amp, amplification; CN-LOH, copy-neutral loss of heterozygosity; KMT2A-PTD, KMT2A partial tandem duplication; PTD, partial tandem duplication; SNP-A, single nucleotide polymorphism array.

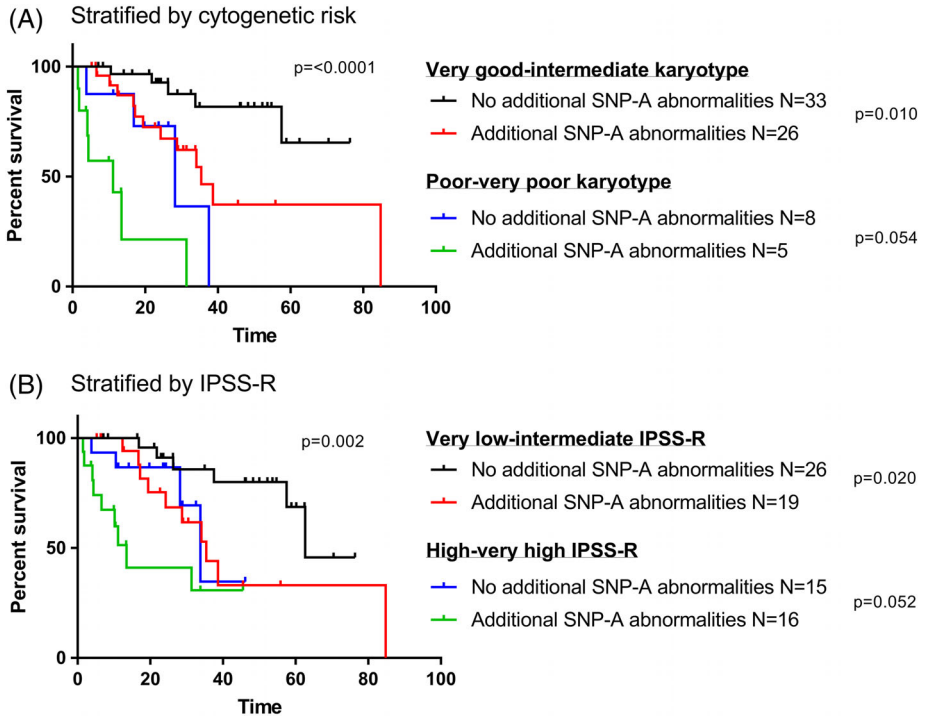

FIGURE 3 The presence of additional SNP-A abnormalities negatively impacts survival in patients with very good-intermediate cytogenetic risk and very low-intermediate IPSS-R. Survival analysis of patients stratified by cytogenetic risk (A; $P < 0.0001$) and by IPSS-R (B; $P = 0.002$) was performed comparing cases with and without additional SNP-A abnormalities. A, Cases with very good-intermediate cytogenetic risk with additional SNP-A abnormalities showed worse overall survival than those that did not have additional abnormalities ($P = 0.010$; black and red groups). SNP-A abnormalities had no statistically significant survival impact in cases with poor-very poor cytogenetic risk ($P = 0.054$; green and blue groups). B, Very low-intermediate IPSS-R cases with additional SNP-A abnormalities showed worse overall survival compared to those without additional abnormalities ($P = 0.020$; black and red groups). SNP-A abnormalities had no statistically significant survival impact in cases with high-very high IPSS-R score ($P = 0.052$; green and blue groups). IPSS-R, Revised International Prognostic Scoring System; SNP-A, single nucleotide polymorphism array [Color figure can be viewed at wileyonlinelibrary.com]

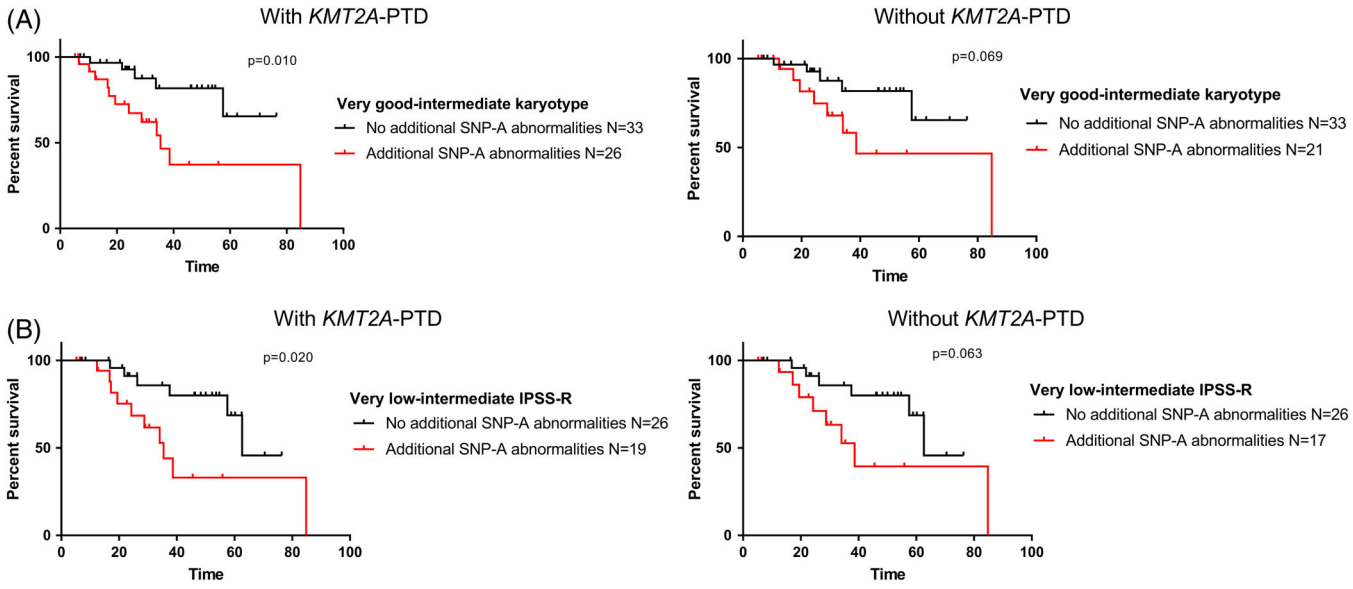

FIGURE 4 *KMT2A*-PTD significantly impacts survival of patients with additional SNP-A abnormalities. A, Patients with very good-intermediate karyotype showed worse survival in the presence of additional SNP-A abnormalities ($P = 0.010$), an effect which was abrogated but not completely eliminated when cases of *KMT2A*-PTD were excluded ($P = 0.069$). B, Similar survival effects were seen in cases with very low-intermediate IPSS-R with ($P = 0.020$) and without ($P = 0.063$) *KMT2A*-PTD. IPSS-R, Revised International Prognostic Scoring System; *KMT2A*-PTD, *KMT2A* partial tandem duplication; SNP-A, single nucleotide polymorphism array [Color figure can be viewed at wileyonlinelibrary.com]

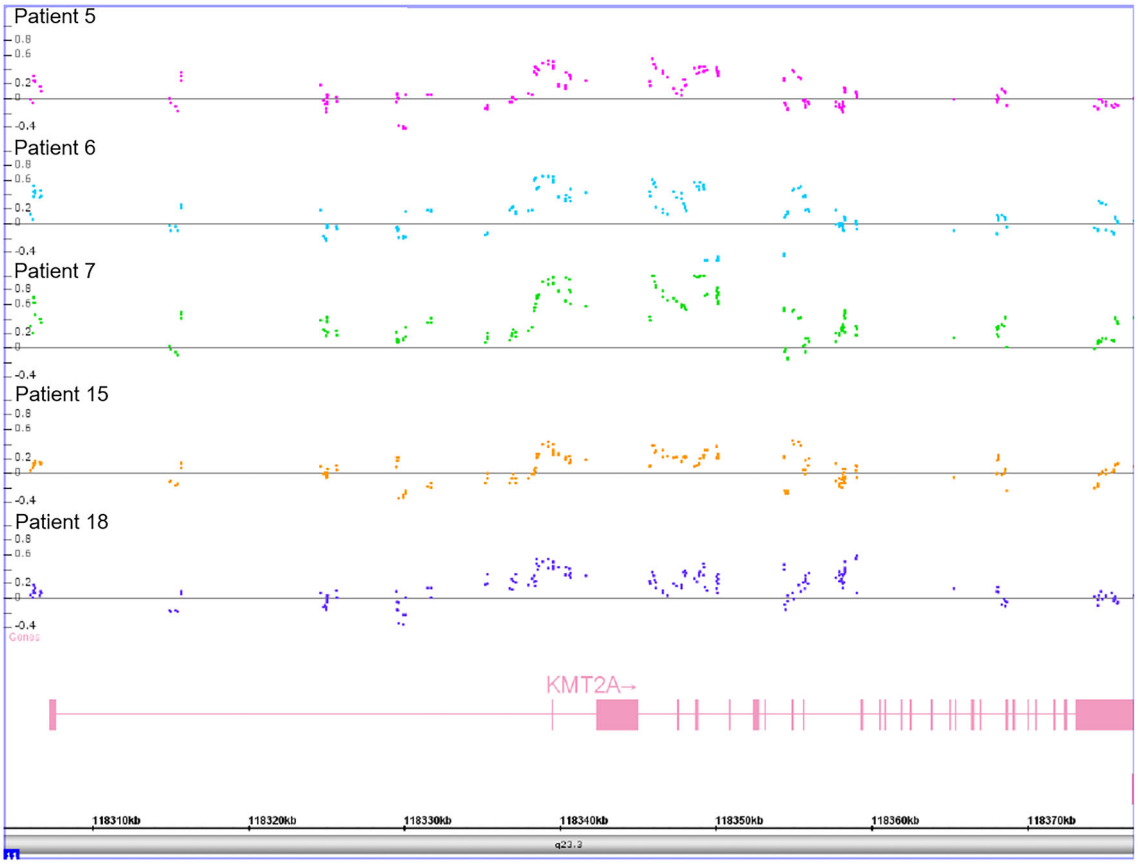

FIGURE 5 Genomic locations and graphic display of array results for *KMT2A*-PTD. Patient 7 had gain of 11q23.3 at the other homologue of chromosome 11. *KMT2A*-PTD, *KMT2A* partial tandem duplication [Color figure can be viewed at wileyonlinelibrary.com]

accounted for by the presence of *KMT2A*-PTD, the data imply that other additional abnormalities also impact the prognosis of MDS.

Although the types of abnormalities we noted in our study were largely similar to those reported in previous studies analyzing SNP-A in MDS patients,[4-7] the frequency of additional SNP-A abnormalities in our study of 47% was higher than previous reports, which showed a range of 18% to 39% of cases with additional SNP-A abnormalities. The increased frequency we observed could potentially be due to higher resolution of our array platform and as well as our analysis. Coincident with this observation, *KMT2A*-PTD was only rarely reported in these prior studies, whereas in our study this abnormality was the most common additional SNP-A abnormality observed.

The data also demonstrate that the effect of additional SNP-A abnormalities is particularly profound in cases that have very good-intermediate karyotypic features or cases of otherwise low-intermediate risk by IPSS-R. Thus, the SNP-A may be more effectively utilized in these particular cases and, perhaps not surprisingly, is more limited in usefulness in cases that already have definitive poor risk features. Moreover, because a large proportion of cases in the very low-intermediate risk/very good-intermediate cytogenetic groups are patients with a normal karyotype, SNP-A is a potentially useful tool in further delineating risk subgroups within this substantial fraction of MDS cases. Interestingly, the survival of patients in our study was longer than those of prior studies that performed survival analysis,[5,7] which showed a median survival of 43 to 50 months in patients with favorable or normal karyotype without SNP-A abnormalities and 16 to 20 months in patients with additional SNP-A abnormalities. The relatively increased OS seen in our cohort compared to prior studies may potentially be attributed to either differences in patient population, clinical practice, or a consequence of relatively smaller cohort size.

The contribution of individual specific abnormalities to prognosis also remains an area of future investigation. Our data suggest *KMT2A*-PTD may be partially responsible for the poorer survival seen in MDS patients, who otherwise might be classified as having lower risk disease, though a definitive determination is limited by the small number of *KMT2A*-PTD. Additionally, two cases also identified CN-LOH as additional anomalies on chromosome arms 7q and 11q, respectively, which contain the genes *EZH2* on 7q and *CBL* on 11q, both recurrently mutated in MDS with suggested adverse prognostic impact.[13-16] Consequently, the relative contribution of *KMT2A*-PTD to prognosis requires further confirmation in larger sample study. Because patients with additional SNP-A abnormalities have poorer OS and relatively increased risk, the presence of these abnormalities may potentially identify these patients as candidates for more urgent therapeutic intervention including transplantation.

While conventional karyotype continues as expected standard practice in MDS diagnosis, the appropriate utilization of other related ancillary testing to provide a comprehensive genetic assessment is an important as-yet unresolved issue. For example, fluorescence in situ hybridization (FISH) analysis can also detect additional abnormalities outside of karyotype,[17,18] however the National Comprehensive Cancer Network (NCCN) practice guidelines currently only recommend FISH in cases where standard cytogenetics cannot be obtained.[19] The American Society for Clinical Pathology also supports a similar recommendation.[20] The European Society for Medical Oncology (ESMO) practice guidelines slightly differ in this respect as they acknowledge a potential benefit of FISH in cytogenetically normal cases and thus recommend FISH in the setting of normal karyotype.[21] A similar algorithm could potentially be applied with respect to SNP-A by focusing its utilization in cases that would otherwise be designated of lower risk. Recent studies have attempted to compare the relative detection rates of abnormalities across different modalities and have confirmed overall relatively higher resolution in SNP-A[22] and next generation sequencing platforms which complement standard cytogenetics and FISH analysis.[23] Outside of larger genomic alterations, the impact of point mutations, which have also been implicated in survival of MDS patients with further prognostic relevance,[15,24] remains another area for subsequent investigation. As clinical standard of care does not yet include testing for point mutations, we were unable to ascertain their significance in the context of additional SNP-A abnormalities, but this is an area in which further analysis is warranted.

In conclusion, these findings demonstrate the potential prognostic and therapeutic impact of the cytogenomic array, with particular utility in MDS cases that would otherwise be classified as very low-intermediate risk.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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