

Poor prognostic implications of myelodysplasia-related gene mutations in both older and younger patients with *de novo* acute myeloid leukemia

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Supplementary Table 1.**Full list of genes studied in targeted NGS sequencing**

Gene Name	Target region (exon)	Gene Name	Target region (exon)
<i>ABL</i>	4-6	<i>KDM6A</i>	full
<i>ASXL1</i>	12	<i>KIT</i>	2, 8-11, 13+17
<i>ATRX</i>	8-10 and 17-31	<i>KRAS</i>	2+3
<i>BCOR</i>	full	<i>MLL</i>	5-8
<i>BCORL1</i>	full	<i>MPL</i>	10
<i>BRAF</i>	15	<i>MYD88</i>	3-5
<i>CALR</i>	9	<i>NOTCH1</i>	26-28, 34
<i>CBL</i>	8+9	<i>NPM1</i>	12
<i>CBLB</i>	9, 10	<i>NRAS</i>	2+3
<i>CBLC</i>	9, 10	<i>PDGFRA</i>	12, 14,18
<i>CDKN2A</i>	full	<i>PHF6</i>	full
<i>CEBPA</i>	full	<i>PTEN</i>	5+7
<i>CSF3R</i>	14-17	<i>PTPN11</i>	3+13
<i>CUX1</i>	full	<i>RAD21</i>	full
<i>DNMT3A</i>	full	<i>RUNX1</i>	full
<i>ETV6</i>	full	<i>SETBP1</i>	4(partial)
<i>EZH2</i>	full	<i>SF3B1</i>	13-16
<i>FBXW7</i>	9+10+11	<i>SMC1A</i>	2, 11, 16+17
<i>FLT3</i>	14+15+20	<i>SMC3</i>	10, 13, 19, 23, 25+28
<i>GATA1</i>	2	<i>SRSF2</i>	1
<i>GATA2</i>	2-6	<i>STAG2</i>	full
<i>GNAS</i>	8+9	<i>TET2</i>	3-11
<i>HRAS</i>	2+3	<i>TP53</i>	2-11
<i>IDH1</i>	4	<i>U2AF1</i>	2+6
<i>IDH2</i>	4	<i>WT1</i>	7+9
<i>IKZF1</i>	full	<i>ZRSR2</i>	full
<i>JAK2</i>	12+14	<i>KDM6A</i>	full
<i>JAK3</i>	13	<i>KIT</i>	2, 8-11, 13+17

Supplementary Table 2.

Comparison of gene mutations between intermediate-risk patients with and without MDS-R mutations

Categories	Variables	Int-risk cohort (n = 317)	Younger population			Older population		
			Without MDS-R mutations (n = 168, 85.7%)	With MDS-R mutations (n = 28, 14.3%)	P value	Without MDS-R mutations (n = 82, 67.8%)	With MDS-R mutations (n = 39, 32.2%)	P value
Activated signaling	<i>FLT3-ITD</i> ^{High $\alpha\beta$}	68 (21.5%)	36 (21.4%)	1 (3.6%)	0.033	24 (29.3%)	7 (17.9%)	0.265
	<i>FLT3-ITD</i> ^{Low $\alpha\beta$}	23 (7.3%)	20 (11.9%)	2 (7.1%)	0.746	1 (1.2%)	0 (0%)	>0.999
	<i>FLT3-TKD</i>	19 (6.0%)	10 (6.0%)	2 (7.1%)	0.683	6 (7.3%)	1 (2.6%)	0.427
	<i>KIT</i>	10 (3.2%)	4 (2.4%)	1 (3.6%)	0.541	5 (6.1%)	0 (0%)	0.174
	<i>NRAS</i>	42 (13.2%)	25 (14.9%)	5 (17.9%)	0.776	9 (11.0%)	3 (7.7%)	0.750
	<i>KRAS</i>	12 (3.8%)	9 (5.4%)	1 (3.6%)	>0.999	1 (1.2%)	1 (2.6%)	0.543
	<i>PTPN11</i>	18 (5.7%)	10 (6.0%)	2 (7.1%)	0.683	4 (4.9%)	2 (5.1%)	>0.999
Tumor suppressor	<i>WT1</i>	31 (9.8%)	21 (12.5%)	2 (7.1%)	0.540	6 (7.3%)	2 (5.1%)	>0.999
	<i>PHF6</i>	11 (3.5%)	4 (2.4%)	3 (10.7%)	0.062	2 (2.4%)	2 (5.1%)	0.593
	<i>NPM1</i>	68 (21.5%)	36 (21.4%)	1 (3.6%)	0.033	24 (29.3%)	7 (17.9%)	0.265
DNA methylation	<i>IDH1</i>	29 (9.1%)	14 (8.3%)	2 (7.1%)	>0.999	8 (9.8%)	5 (12.8%)	0.754
	<i>IDH2</i>	48 (15.1%)	14 (8.3%)	9 (32.1%)	0.001	14 (17.1%)	11 (28.2%)	0.229
	<i>DNMT3A</i>	80 (25.2%)	38 (22.6%)	7 (25.0%)	0.809	27 (32.9%)	8 (20.5%)	0.200
	<i>TET2</i>	41 (12.9%)	12 (7.1%)	0 (0%)	0.222	19 (23.2%)	10 (25.6%)	0.821
Cohesin complex genes	<i>STAG2</i>	18 (5.7%)	0 (0%)	8 (28.6%)	<0.001	0 (0%)	10 (25.6%)	<0.001
	<i>RAD21</i>	5 (1.6%)	2 (1.2%)	0 (0%)	>0.999	1 (1.2%)	2 (5.1%)	0.243
	<i>SMC1A</i>	11 (3.5%)	5 (3.0%)	1 (3.6%)	>0.999	4 (4.9%)	1 (2.6%)	>0.999
	<i>SMC3</i>	2 (0.6%)	1 (0.6%)	0 (0%)	>0.999	1 (1.2%)	0 (0%)	>0.999
Transcription factor	<i>GATA2</i>	19 (6.0%)	10 (6.0%)	3 (10.7%)	0.404	5 (6.1%)	1 (2.6%)	0.663
	<i>ETV6</i>	3 (0.9%)	3 (1.8%)	0 (0%)	>0.999	0 (%)	0 (%)	>0.999

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Chromatin modifiers	<i>BOCR</i>	8 (2.5%)	0 (0%)	4 (14.3%)	<0.001	0 (0%)	4 (10.3%)	0.010
	<i>EZH2</i>	3 (0.9%)	0 (0%)	2 (7.1%)	0.020	0 (0%)	1 (2.6%)	0.322
Spliceosome complex genes	<i>SF3B1</i>	5 (1.6%)	0 (0%)	2 (7.1%)	0.020	0 (0%)	3 (7.7%)	0.032
	<i>SRSF2</i>	19 (6.0%)	0 (0%)	3 (10.7%)	0.023	0 (0%)	16 (41.0%)	<0.001
	<i>U2AF1</i>	18 (5.7%)	0 (0%)	11 (39.3%)	<0.001	0 (0%)	7 (17.9%)	<0.001
	<i>ZRSR2</i>	3 (0.9%)	0 (0%)	1 (3.6%)	0.143	0 (0%)	2 (5.1%)	0.102

^α One young patients with *FLT3*-ITD did not have allelic ratio data. This patient had no MDS-R mutations.

^β Defined as *FLT3* mutated/wild-type allelic ratio ≥ 0.5 .

Supplementary Figure 1. Flow chart of patient selection

Supplementary Figure 2. The relapse-free survival stratified by the status of MDS-R mutations among the total cohort.

Supplementary Figure 3. The relapse-free survival stratified by the status of MDS-R mutations among the elder patients.

Supplementary Figure 4. The relapse-free survival stratified by the status of MDS-R mutations among the younger patients.

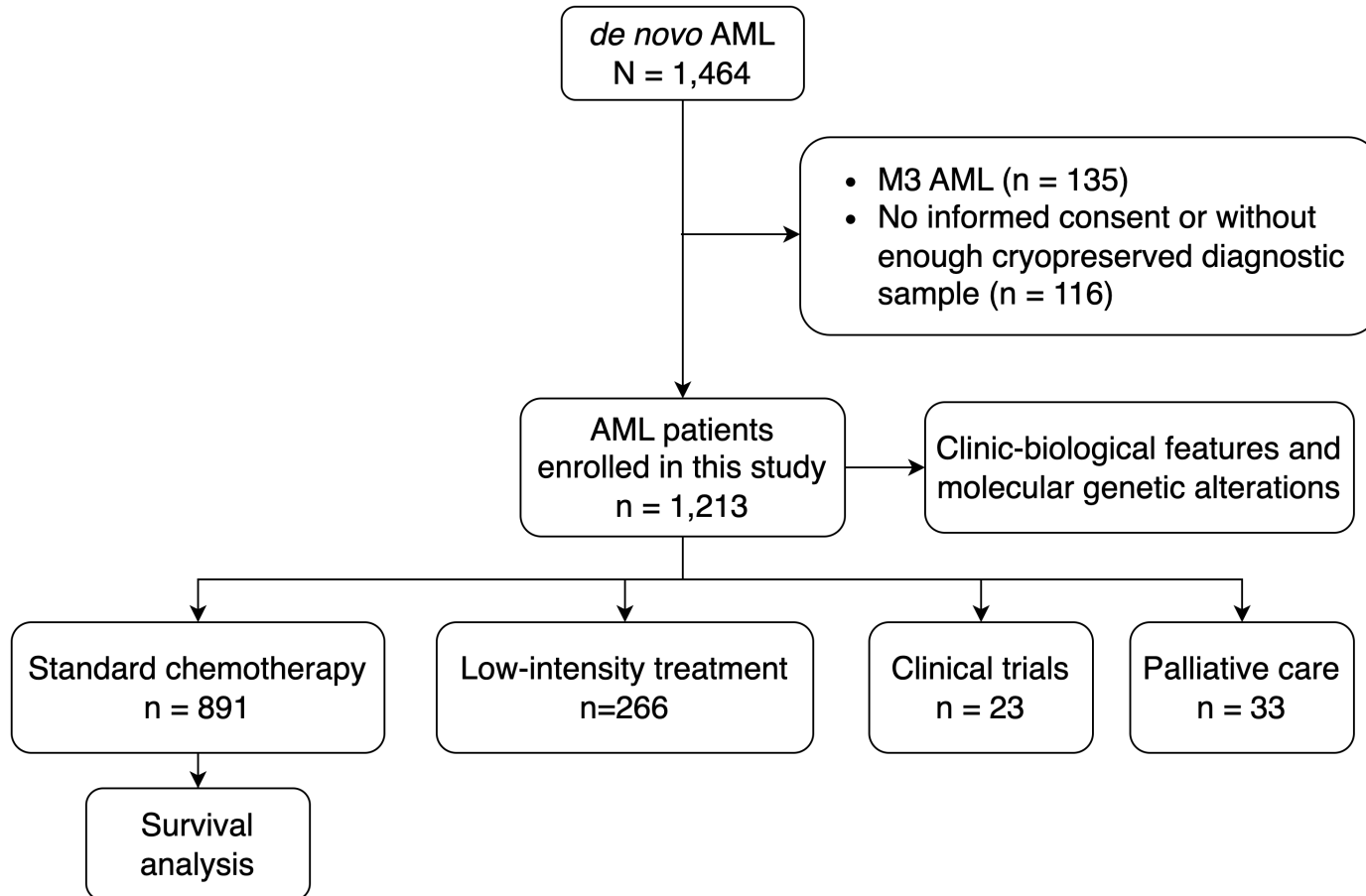
Supplementary Figure 5. The overall survival stratified by the ELN 2017 classification among the total cohort. The intermediate-risk group can be well dichotomized by the status of MDS-R mutations. Red line: patients with favorable-risk genotypes; Yellow line: patients with intermediate-risk genotypes and without MDS-R mutations; Gray line: patients with intermediate-risk genotypes and with MDS-R mutations; Red line: patients with unfavorable-risk genotypes.

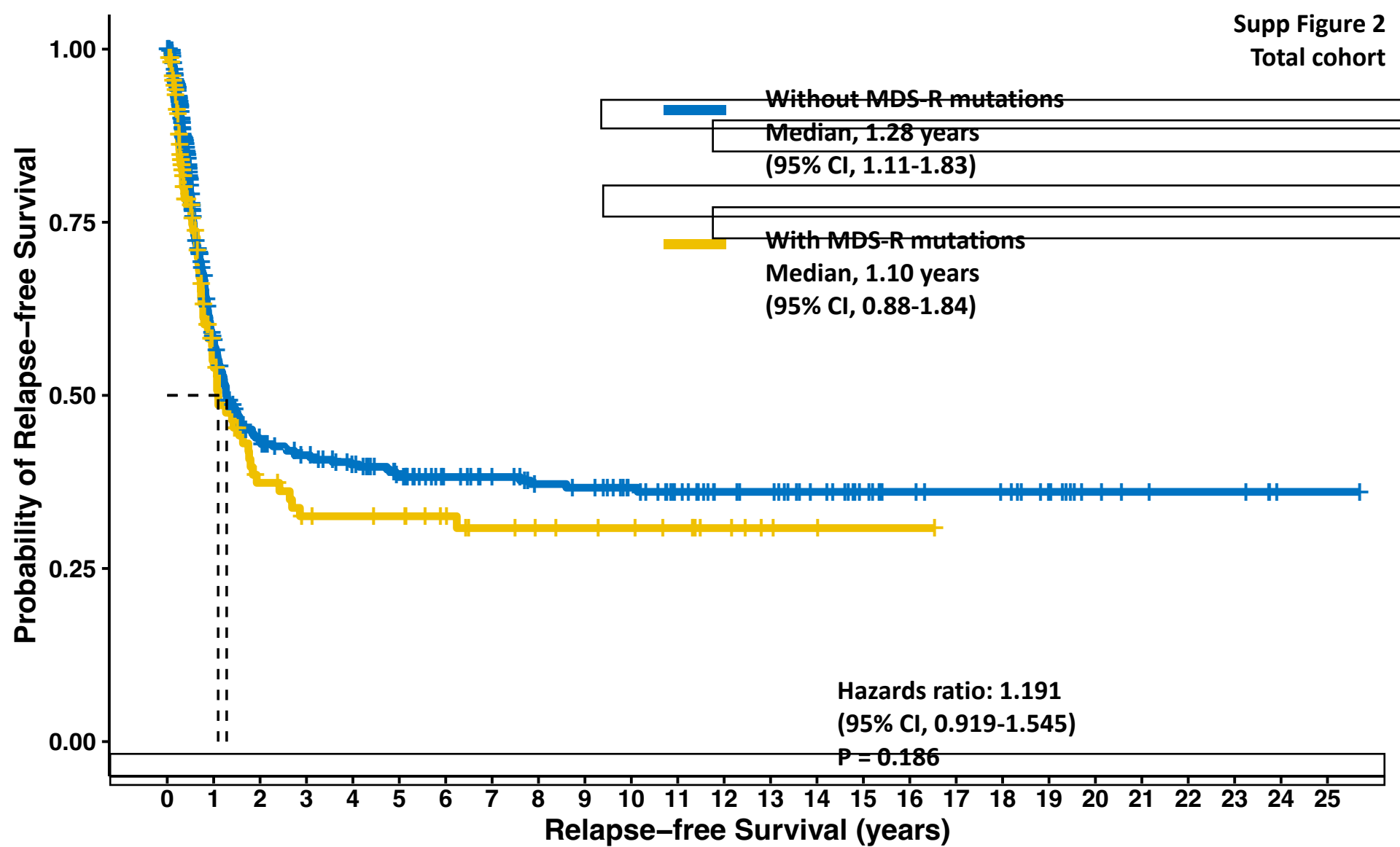
Supplementary Figure 6. The overall survival stratified by the ELN 2017 classification among the elder patients. The intermediate-risk group can be dichotomized by the status of MDS-R mutations. Red line: patients with favorable-risk genotypes; Yellow line: patients with intermediate-risk genotypes and without MDS-R mutations; Gray line: patients with intermediate-risk genotypes and with MDS-R mutations; Red line: patients with unfavorable-risk genotypes.

Supplementary Figure 7. The overall survival stratified by the ELN 2017 classification among the younger patients. Among the patients with intermediate-risk genotypes, those with MDS-R mutations had similar survival to those without MDS-R mutations. Red line: patients with favorable-risk genotypes; Yellow line: patients with intermediate-risk genotypes and without MDS-R mutations; Gray line: patients with

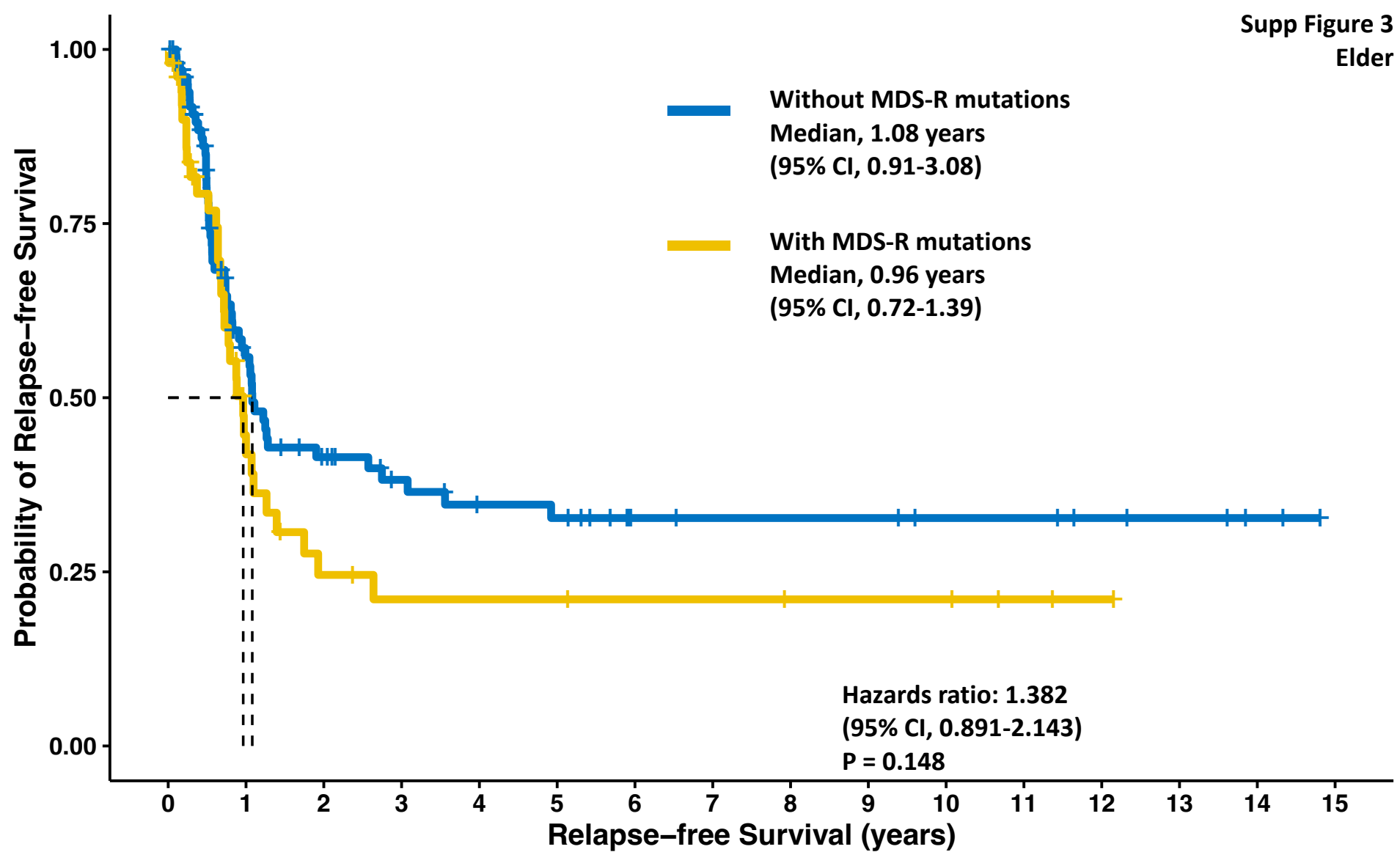
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intermediate-risk genotypes and with MDS-R mutations; Red line: patients with unfavorable-risk genotypes.

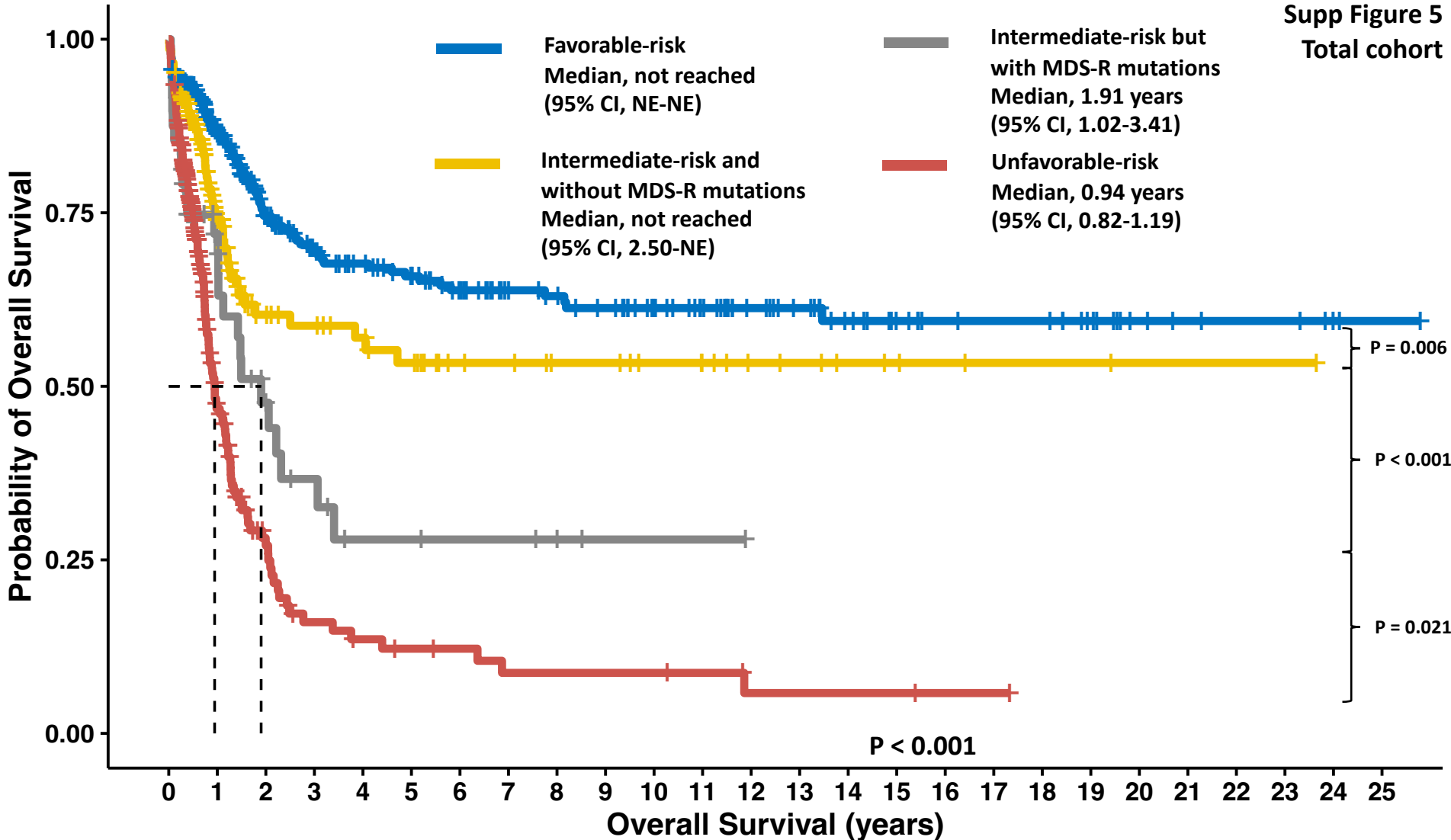




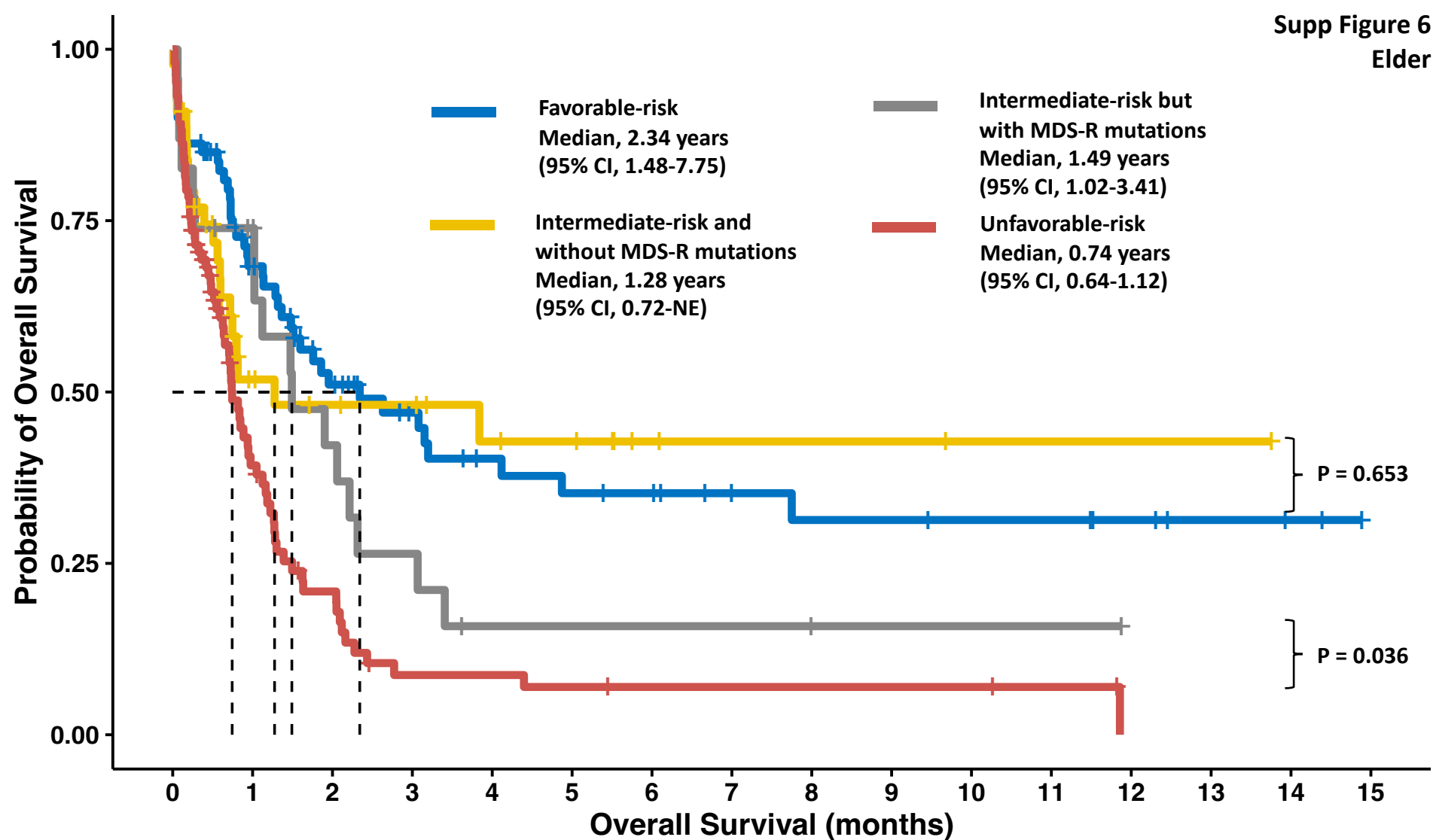
520	200	142	128	116	102	85	78	71	69	61	52	43	41	34	27	22	20	19	14	8	6	5	5	1	1
157	52	32	26	25	24	20	16	14	13	12	10	8	6	3	2	1	1	0	0	0	0	0	0	0	0



104	43	29	22	18	17	10	9	9	7	7	5	4	2	0
51	16	8	6	6	6	5	5	4	4	4	2	1	0	0



34	7	2	2	1	1	5	1	2	7	1	1	4	2	3	0	0	0	0	1	4	5	5	2	1	
206	78	41	37	33	29	20	19	16	16	13	11	8	7	5	4	3	2	2	2	1	1	1	1	0	0
48	25	13	9	5	5	4	4	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	
290	63	25	13	10	8	7	5	5	5	5	4	11	2	2	2	2	1	1	0	0	0	0	0	0	



80	47	30	21	16	14	13	9	8	8	7	7	5	3	2	0
44	15	12	11	8	7	3	2	2	2	1	1	1	1	0	0
23	15	8	5	2	2	2	2	1	1	1	1	0	0	0	0
102	29	14	5	5	4	3	3	3	3	3	2	0	0	0	0

