

SUPPLEMENTAL MATERIALS

Supplementary Figure 1. Waterfall plots displaying gene mutations, karyotype abnormalities and information about treatment with JAK inhibitors of the overt PMF (A), pre-PMF (B) and post-PV/ET MF (C) cohorts. *Abbreviations:* ET: essential thrombocythemia; HMR: high molecular risk; JAKi: JAK inhibitors.; HMR: high molecular risk; MF: myelofibrosis; PMF: primary myelofibrosis; Pre-PMF: pre-fibrotic primary myelofibrosis; PV: polycythemia vera.

Supplementary Figure 2. A. Lollipop plot and table showing type and location along the protein sequence of the 25 *NRAS*^{MT} identified in the MF cohort (top) and separately in overt PMF, pre-PMF and post-*PV/ET MF (bottom). **B.** Lollipop plot and table showing type and location along the protein sequence of the 13 *KRAS*^{MT} identified in the MF cohort (top) and separately in overt PMF, pre-PMF and post-*PV/ET MF (bottom). **C.** Lollipop plot and table showing type and location along the protein sequence of the 26 *CBL*^{MT} identified in the MF cohort (top) and separately in overt PMF, pre-PMF and post-*PV/ET MF (bottom). The number of recurrently detected alterations is indicated by the text within each disc, as well as by disc size. Colors indicate the type of mutation: blue, missense; purple, splice site; orange, nonsense; red, frameshift; gray, in-frame insertion/deletion. All mutations were merged to construct the mutation profile using the web-based tool ProteinPaint (<https://pecan.stjude.cloud/proteinpaint/>). *Abbreviations:* ET: essential thrombocythemia; MF: myelofibrosis; PMF: primary myelofibrosis; Pre-PMF: pre-fibrotic primary myelofibrosis; PV: polycythemia vera; Sec-MF: secondary myelofibrosis; VAF: variant allele frequency

Supplementary Figure 3. A. Box plot showing the distribution of variant allele frequency of phenotypic driver mutations (*JAK*, *CALR*, *MPL*) and *RAS/CBL*^{MT}. **B.** Box plot showing the distribution of variant allele frequency *NRAS*, *KRAS* and *CBL* mutations separately. *Abbreviations:* ^{MT}: mutated.

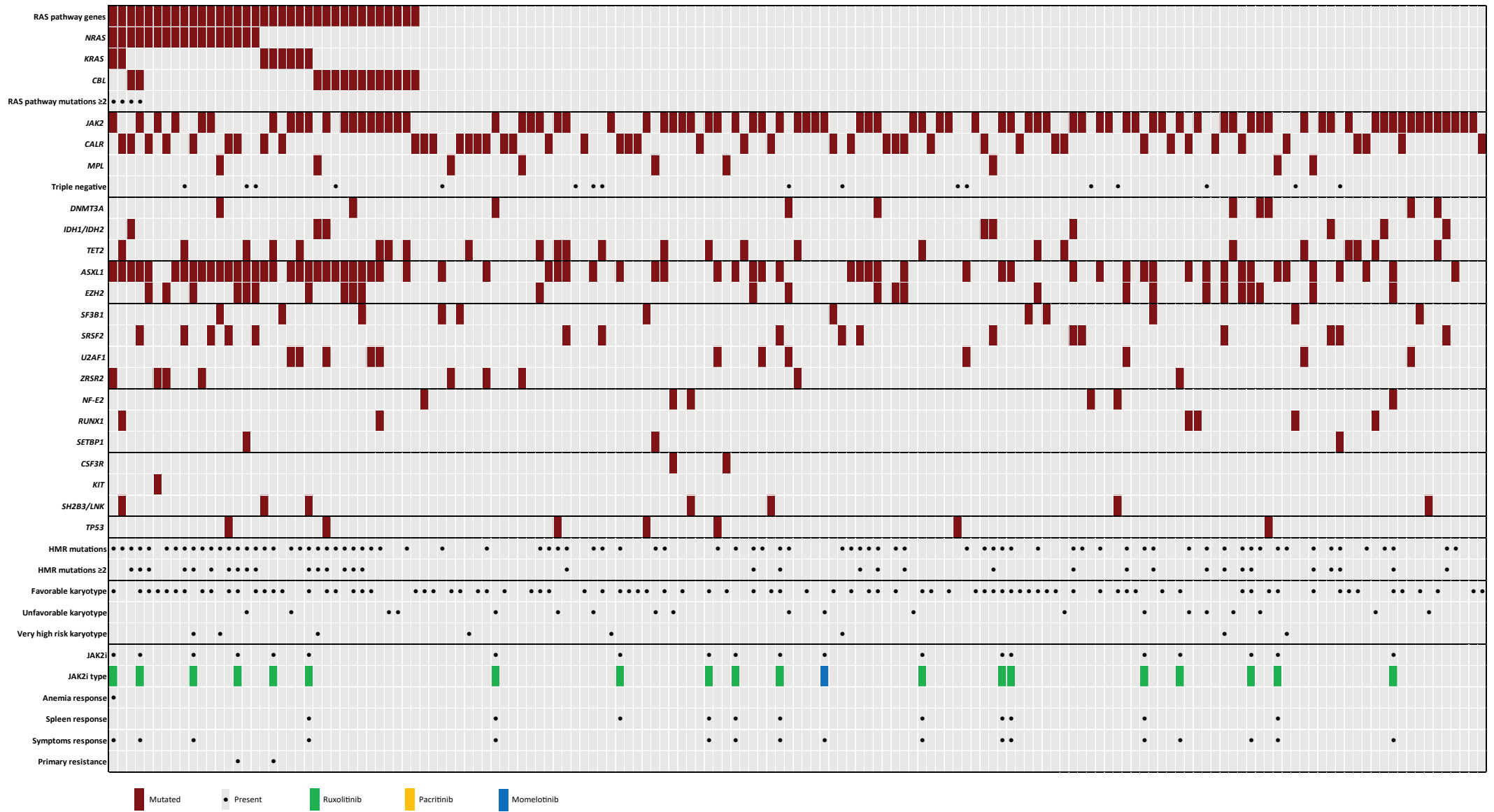
Supplementary Figure 4. Kaplan-Meier estimates of overall survival in patients with over PMF (A), pre-PMF (B) and post-PV/ET MF (C) by the presence or absence of *RAS/CBL*^{MT}. *Abbreviations:* CI: confidence interval; ET: essential thrombocythemia; MF: myelofibrosis; ^{MT}: mutated; OS: overall survival; PMF: primary myelofibrosis; pre-PMF: pre-fibrotic primary myelofibrosis; PV: polycythemia vera; ^{WT}: wild type.

Supplementary Figure 5. Five year-cumulative incidence of leukemic transformation survival in patients with over PMF (A), pre-PMF (B) and post-PV/ET MF (C) by the presence or absence of *RAS/CBL*^{MT}. *Abbreviations:* CI: confidence interval; CuI: cumulative incidence; ET: essential thrombocythemia; MF: myelofibrosis; ^{MT}: mutated; PMF: primary myelofibrosis; pre-PMF: pre-fibrotic primary myelofibrosis; PV: polycythemia vera; ^{WT}: wild type.

Supplementary Figure 6. A-B. Cross tables illustrating risk re-distribution of patients according to *RAS/CBL*-enhanced MIPSS70 (**A**) *RAS/CBL*-enhanced MIPSS70-plus (**B**) compared to their original MIPSS70 and MIPSS70-plus categorization, respectively. Coloured bars represent the MIPSS/MIPSS70-plus risk stratification (x-axis) in the context of the stratification based on the new scoring systems (represented by the rows). **C-D.** Three-year ROC curves and AUC values representing the relative prognostic power of standard and *RAS/CBL*-enhanced MIPSS70 (**C**) and MIPSS70-plus (**D**). *Abbreviations:* AIC: Akaike information criterion; AOU: area under curve; LFS: leukemia-free survival; MIPSS70: mutation-enhanced international prognostic score system; OS; overall survival; ROC: receiver operator characteristic.

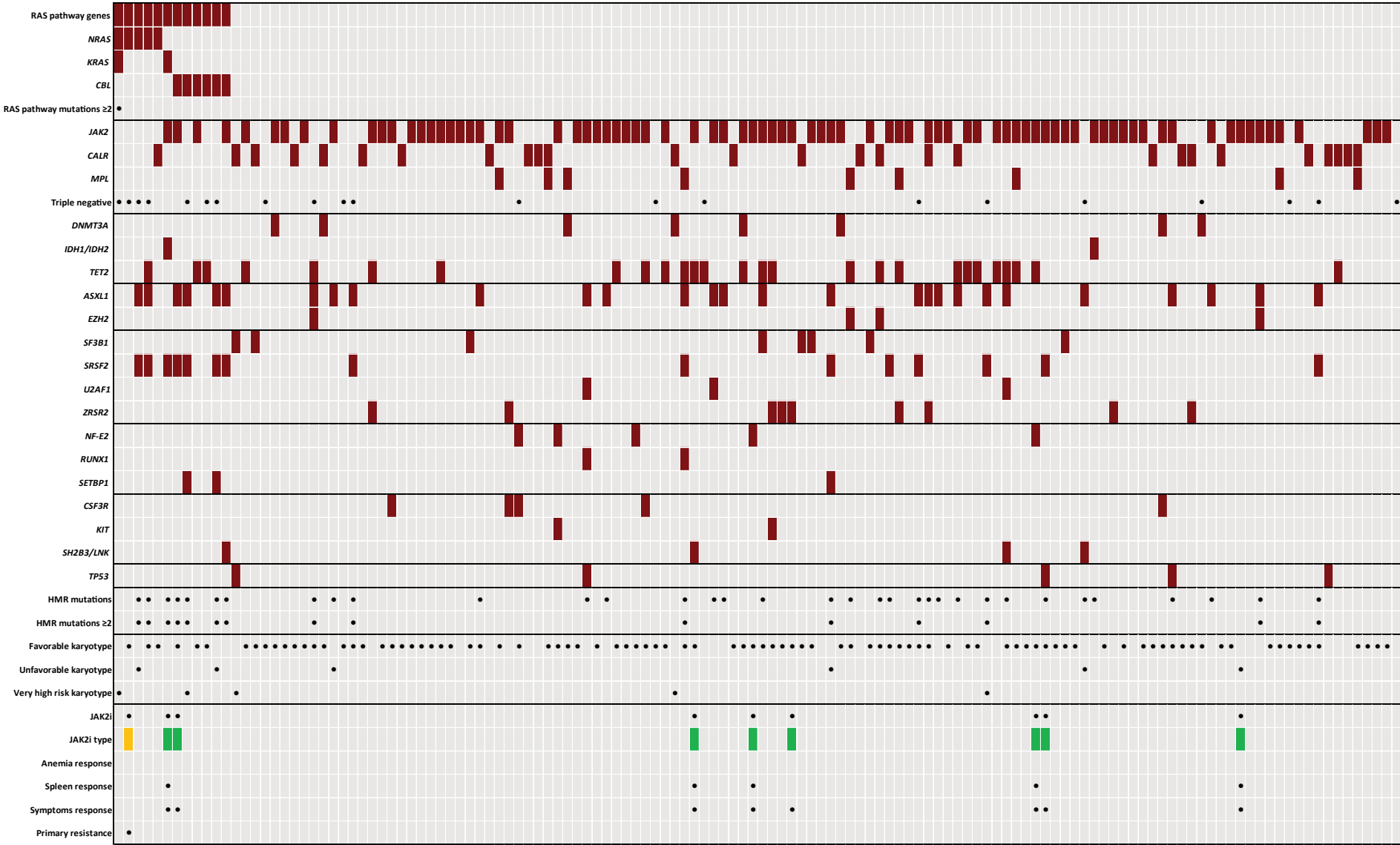
Supplementary Figure 1A

Overt PMF

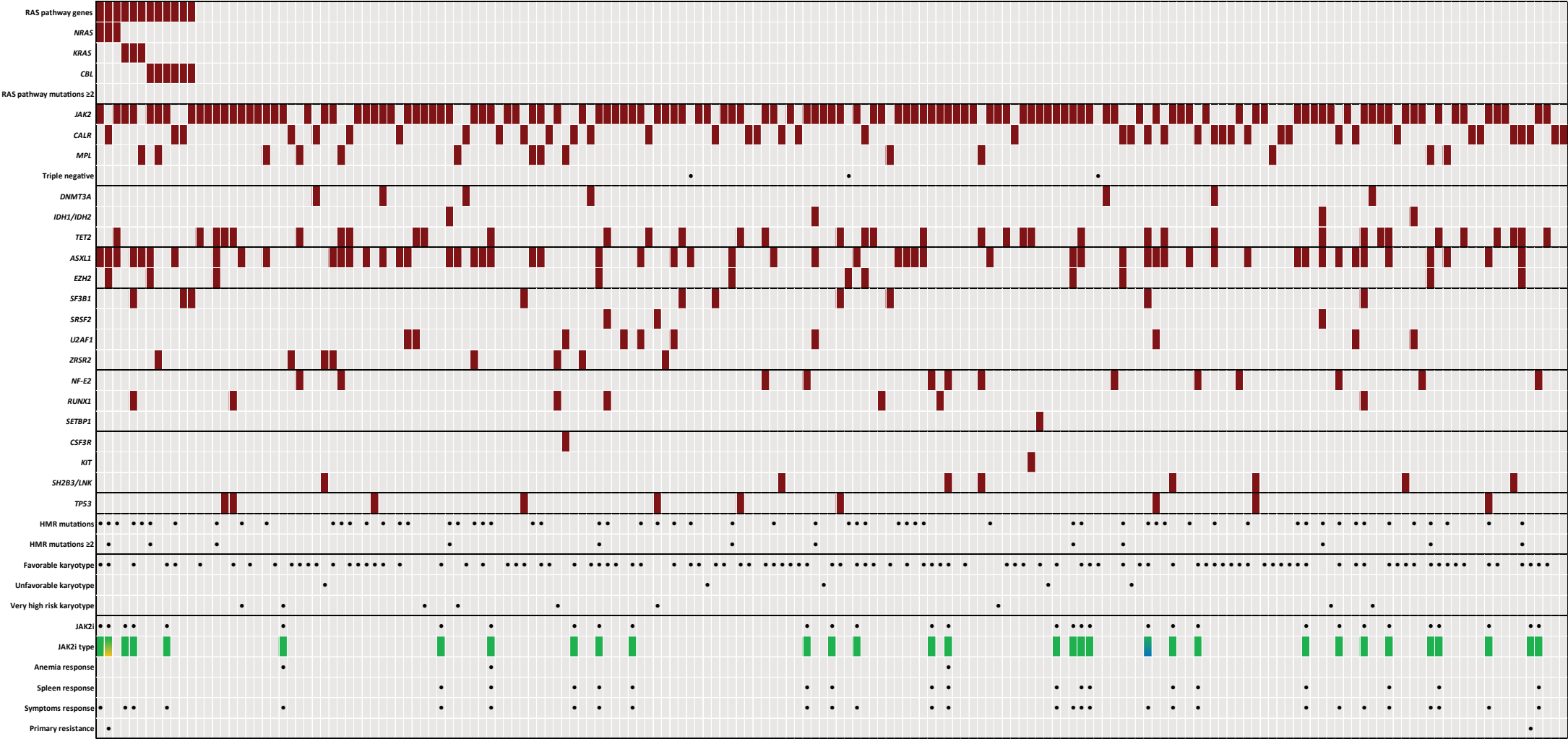


Supplementary Figure 1B

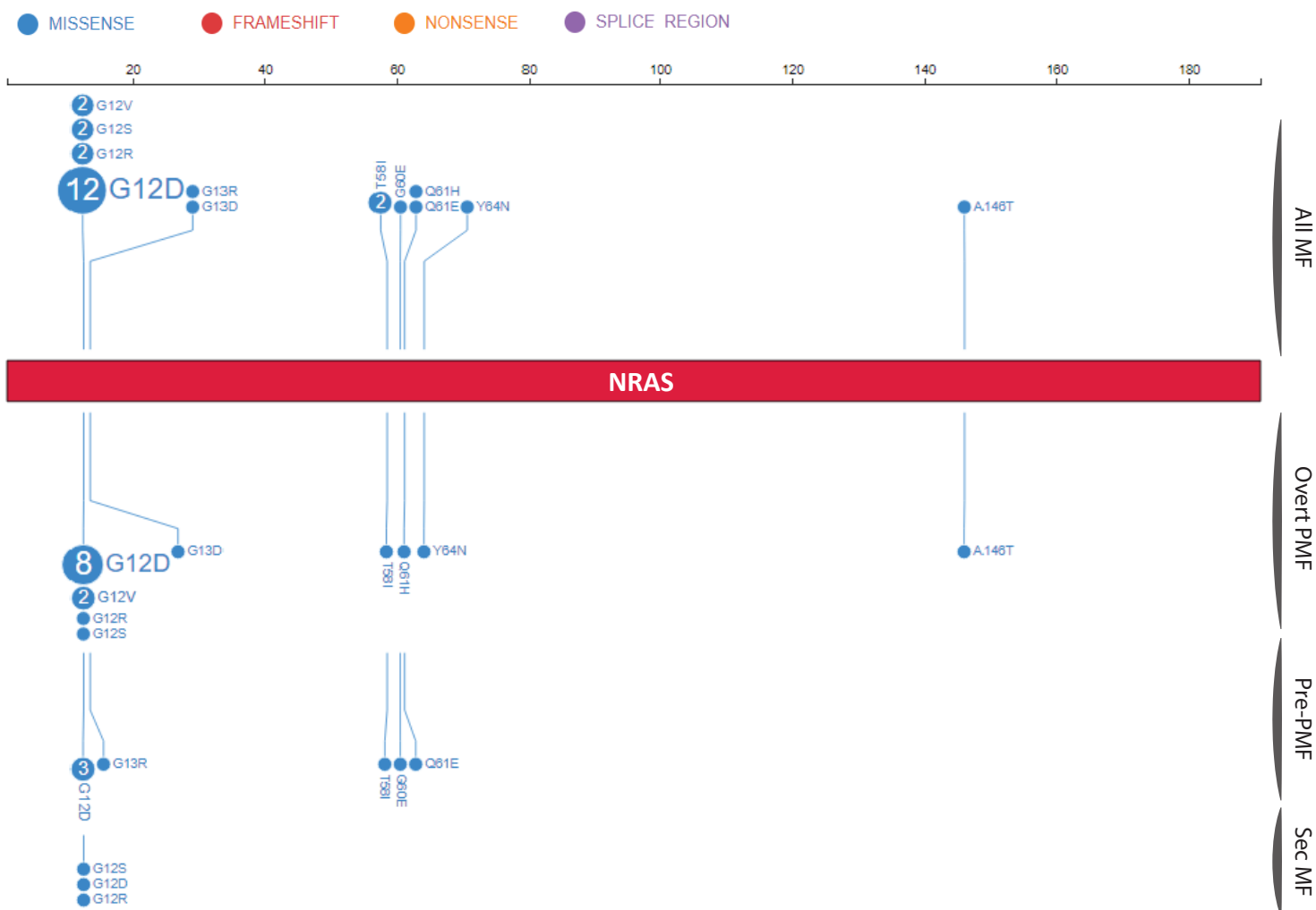
Pre-PMF



Post-PV/ET MF

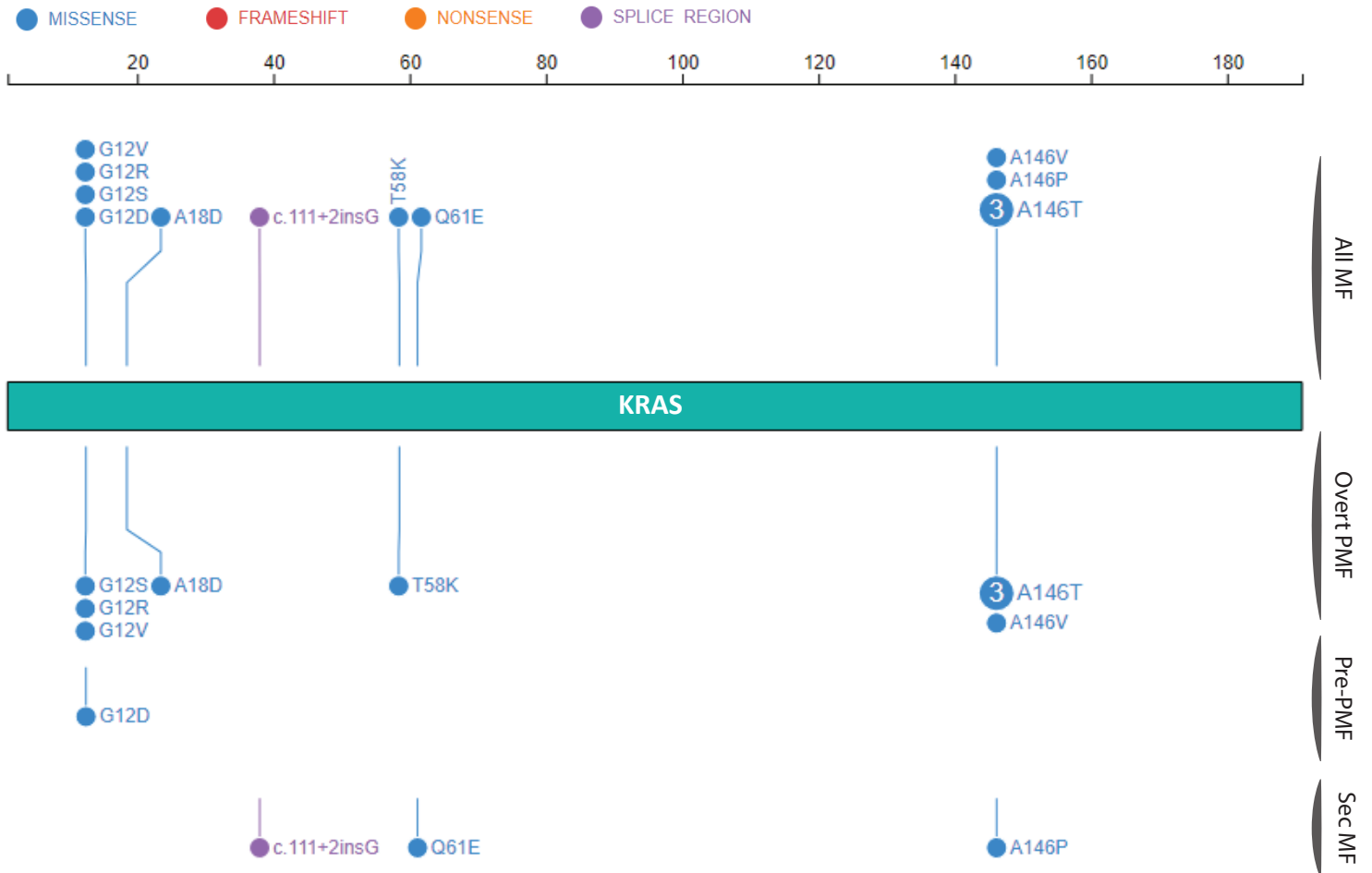


Supplementary Figure 2A



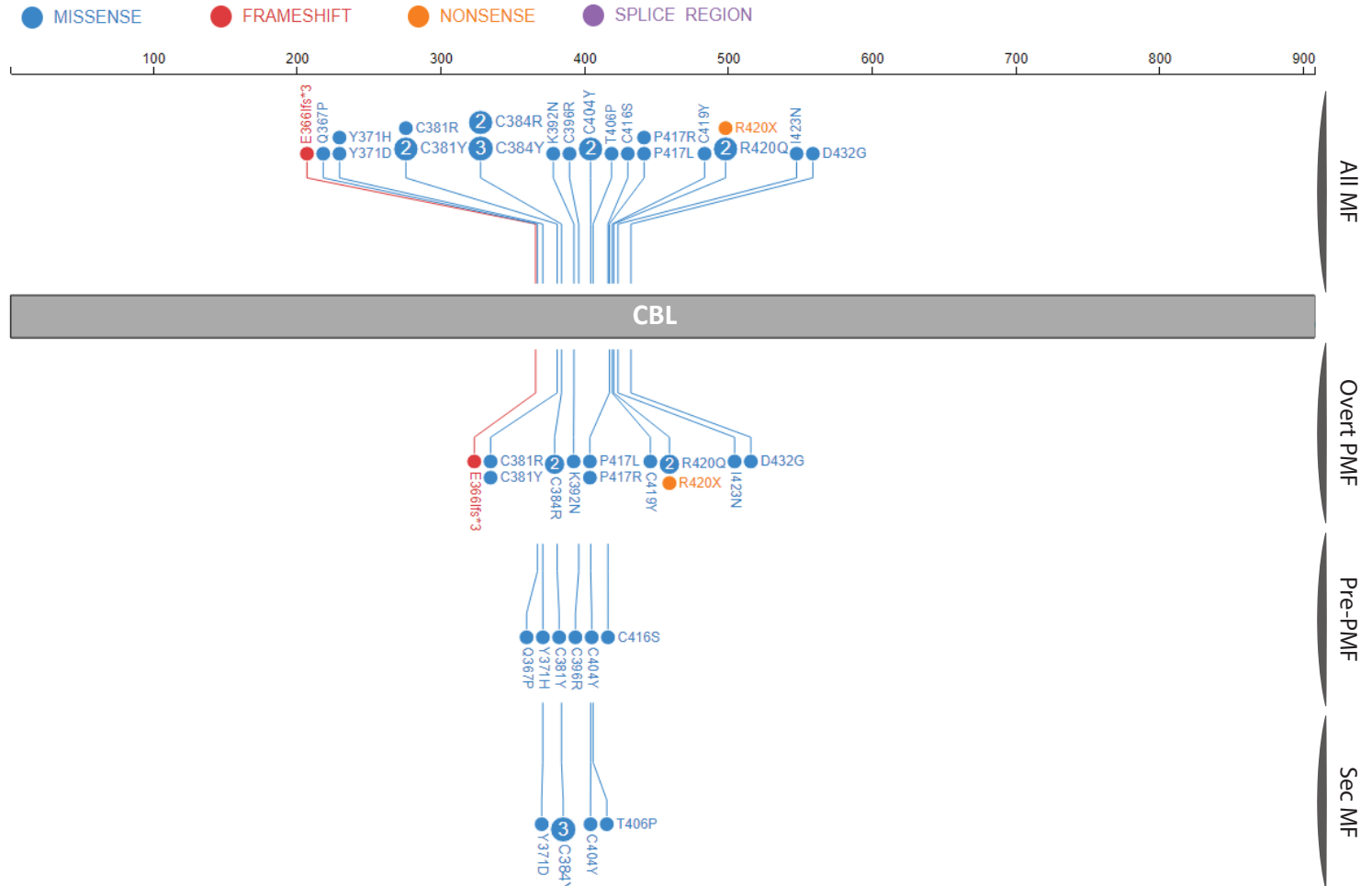
NRAS									
Patient code	MF subtype	Transcript	Genome location	Nucleotide change	Exon	Amino acid change	NRAS VAF	Mutation type	
27	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	43	Missense	
53	Overt PMF	NM_002524.5	chr1:115256528-115256528	c.183A>C	3	p.Q61H	16	Missense	
65	Overt PMF	NM_002524.5	chr1:115256521-115256521	c.190T>A	3	p.Y64N	39	Missense	
72	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	47	Missense	
86	Overt PMF	NM_002524.5	chr1:115258744-115258744	c.38G>A	2	p.G13D	39	Missense	
90	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	12	Missense	
105	Pre-PMF	NM_002524.5	chr1:115256538-115256538	c.173C>T	3	p.T58I	10	Missense	
105	Pre-PMF	NM_002524.5	chr1:115256530-115256530	c.181C>G	3	p.Q61E	9	Missense	
107	Overt PMF	NM_002524.5	chr1:115258748-115258748	c.34G>A	2	p.G12S	9	Missense	
174	Overt PMF	NM_002524.5	chr1:115258748-115258748	c.34G>C	2	p.G12R	20	Missense	
179	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	3	Missense	
207	Pre-PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	42	Missense	
257	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	11	Missense	
258	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	51	Missense	
286	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>T	2	p.G12V		Missense	
292	Pre-PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	27	Missense	
293	Overt PMF	NM_002524.5	chr1:115256538-115256538	c.173C>T	3	p.T58I	4	Missense	
298	Pre-PMF	NM_002524.5	chr1:115256532-115256532	c.179G>A	3	p.G60E	11	Missense	
298	Pre-PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	38	Missense	
332	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	49	Missense	
343	Overt PMF	NM_002524.5	chr1:115252204-115252204	c.436G>A	4	p.A146T	16	Missense	
395	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	47	Missense	
431	Overt PMF	NM_002524.5	chr1:115258747-115258747	c.35G>T	2	p.G12V	48	Missense	
440	Pre-PMF	NM_002524.5	chr1:115258745-115258745	c.37G>C	2	p.G13R	44	Missense	
1035	Post-PV/ET MF	NM_002524.5	chr1:115258748-115258748	c.34G>A	2	p.G12S	49	Missense	
1123	Post-PV/ET MF	NM_002524.5	chr1:115258747-115258747	c.35G>A	2	p.G12D	17	Missense	
1163	Post-PV/ET MF	NM_002524.5	chr1:115258748-115258748	c.34G>C	2	p.G12R	9	Missense	

Supplementary Figure 2B



KRAS								
Patient code	MF subtype	Transcript	Genome location	Nucleotide change	Exon/Intron	Amino acid change	KRAS VAF	Mutation type
90	Overt PMF	NM_033360.4	chr12:25378562-25378562	c.436G>A	4	p.A146T	39	Missense
140	Overt PMF	NM_033360.4	chr12:25378562-25378562	c.436G>A	4	p.A146T	4	Missense
173	Overt PMF	NM_033360.4	chr12:25380285-25380285	c.173C>A	3	p.T58K	13	Missense
225	Overt PMF	NM_033360.4	chr12:25398285-25398285	c.34G>A	2	p.G12S	48	Missense
255	Overt PMF	NM_033360.4	chr12:25398285-25398285	c.34G>C	2	p.G12R	33	Missense
257	Overt PMF	NM_033360.4	chr12:25378562-25378562	c.436G>A	4	p.A146T	9	Missense
292	Pre-PMF	NM_033360.4	chr12:25398284-25398284	c.35G>A	2	p.G12D	7	Missense
314	Overt PMF	NM_033360.4	chr12:25398284-25398284	c.35G>T	2	p.G12V	25	Missense
346	Overt PMF	NM_033360.4	chr12:25378561-25378561	c.437C>T	4	p.A146V	44	Missense
358	Overt PMF	NM_033360.4	chr12:25398266-25398266	c.53C>A	2	p.A18D	52	Missense
1081	Post-PV/ET MF	NM_033360.4	chr12:25378562-25378562	c.436G>C	4	p.A146P	23	Missense
1178	Post-PV/ET MF	NM_033360.4	chr12:25398205-25398205	c.111+2_111+3insG	3	-		Splice site
1217	Post-PV/ET MF	NM_033360.4	chr12:25380277-25380277	c.181C>G	3	p.Q61E	2	Missense

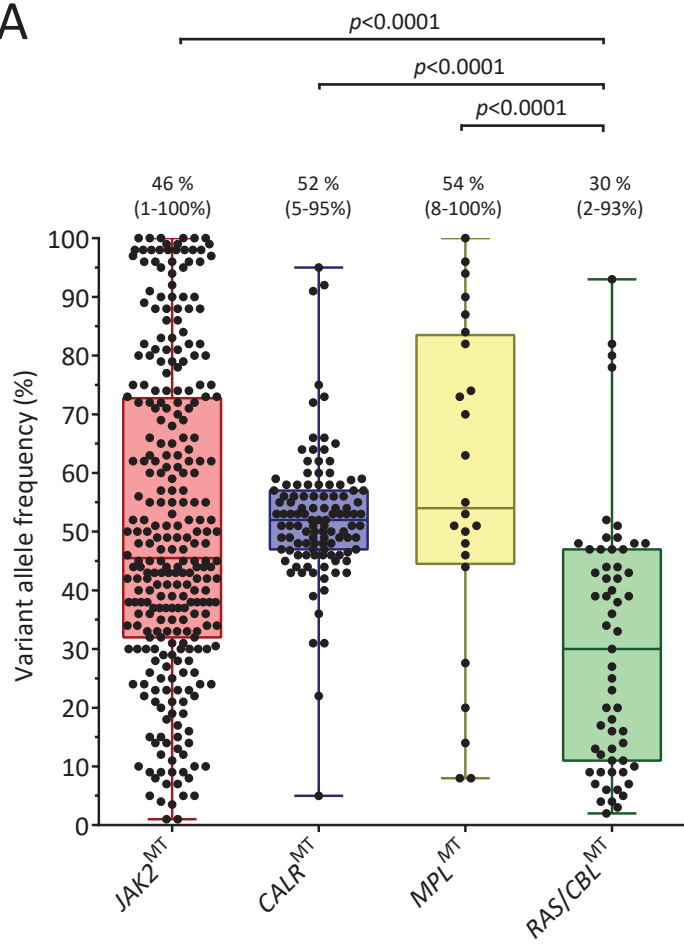
Supplementary Figure 2C



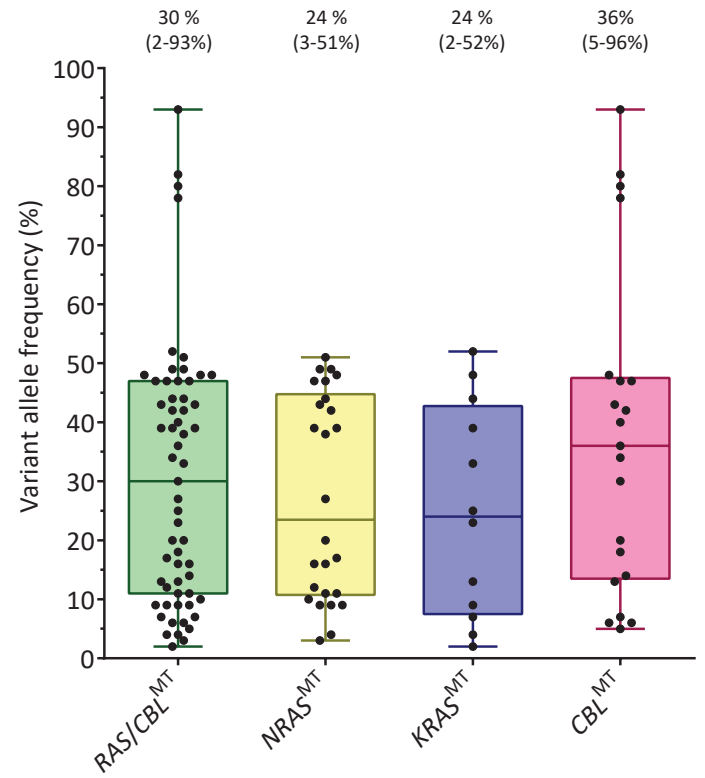
CBL								
Patient code	MF subtype	Transcript	Genome location	Nucleotide change	Exon/Intron	Amino acid change	CBL VAF	Mutation type
15	Pre-PMF	NM_005188.3	chr11:119148922-119148922	c.1142G>A	8	p.C381Y	18	Missense
48	Pre-PMF	NM_005188.3	chr11:119148880-119148880	c.1100A>C	8	p.Q367P	30	Missense
58	Pre-PMF	NM_005188.3	chr11:119148966-119148966	c.1186T>C	8	p.C396R	80	Missense
88	Overt PMF	NM_005188.3	chr11:119149242-119149242	c.1250C>T	9	p.P417L		Missense
119	Overt PMF	NM_005188.3	chr11:119148922-119148922	c.1142G>A	8	p.C381Y	13	Missense
130	Pre-PMF	NM_005188.3	chr11:119149239-119149239	c.1247G>C	9	p.C416S	6	Missense
144	Overt PMF	NM_005188.3	chr11:119149251-119149251	c.1259G>A	9	p.R420Q		Missense
179	Overt PMF	NM_005188.3	chr11:119149242-119149242	c.1250C>G	9	p.P417R	7	Missense
197	Pre-PMF	NM_005188.3	chr11:119148891-119148891	c.1111T>C	8	p.Y371H	47	Missense
293	Overt PMF	NM_005188.3	chr11:119149251-119149251	c.1259G>A	9	p.R420Q	34	Missense
294	Overt PMF	NM_005188.3	chr11:119149260-119149260	c.1268T>A	9	p.I423N	40	Missense
302	Pre-PMF	NM_005188.3	chr11:119148991-119148991	c.1211G>A	8	p.C404Y	48	Missense
304	Overt PMF	NM_005188.3	chr11:119148921-119148921	c.1141T>C	8	p.C381R	93	Missense
322	Overt PMF	NM_005188.3	chr11:119148930-119148930	c.1150T>C	8	p.C384R	82	Missense
380	Overt PMF	NM_005188.3	chr11:119148956-119148956	c.1176G>T	8	p.K392N	6	Missense
391	Overt PMF	NM_005188.3	chr11:119149250-119149250	c.1258C>T	9	p.R420*	78	Nonsense
396	Overt PMF	NM_005188.3	chr11:119149287-119149287	c.1295A>G	9	p.D432G	14	Missense
399	Overt PMF	NM_005188.3	chr11:119148554-119148555	c.1095_1095+1insATCCCAT	8	p.E366Ifs*3		Frameshift
416	Overt PMF	NM_005188.3	chr11:119149248-119149248	c.1256G>A	9	p.C419Y		Missense
429	Overt PMF	NM_005188.3	chr11:119148930-119148930	c.1150T>C	8	p.C384R	5	Missense
1024	Post-PV/ET MF	NM_005188.3	chr11:119148991-119148991	c.1211G>A	8	p.C404Y	42	Missense
1080	Post-PV/ET MF	NM_005188.3	chr11:119148931-119148931	c.1151G>A	8	p.C384Y	43	Missense
1145	Post-PV/ET MF	NM_005188.3	chr11:119148931-119148931	c.1151G>A	8	p.C384Y		Missense
1196	Post-PV/ET MF	NM_005188.3	chr11:119148891-119148891	c.1111T>G	8	p.Y371D	36	Missense
1248	Post-PV/ET MF	NM_005188.3	chr11:119148931-119148931	c.1151G>A	8	p.C384Y	20	Missense
1253	Post-PV/ET MF	NM_005188.3	chr11:119148996-119148996	c.1216A>C	8	p.T406P	47	Missense

Supplementary Figure 3

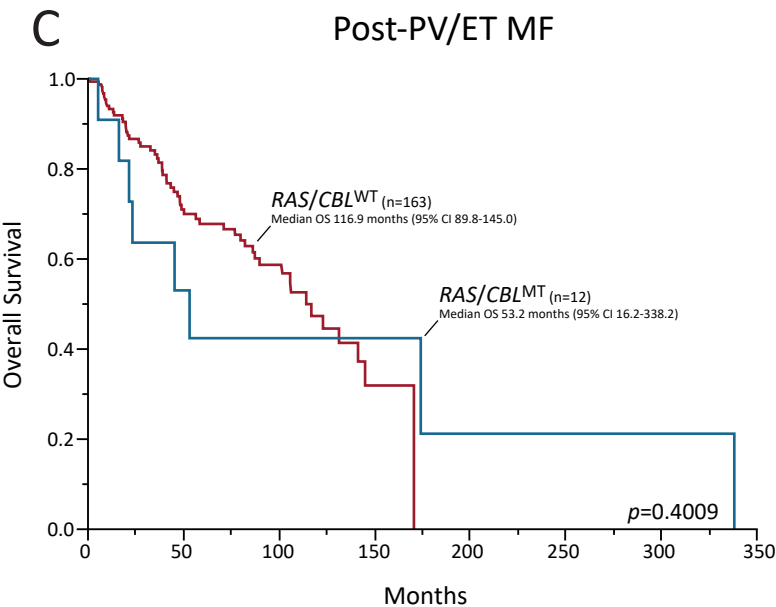
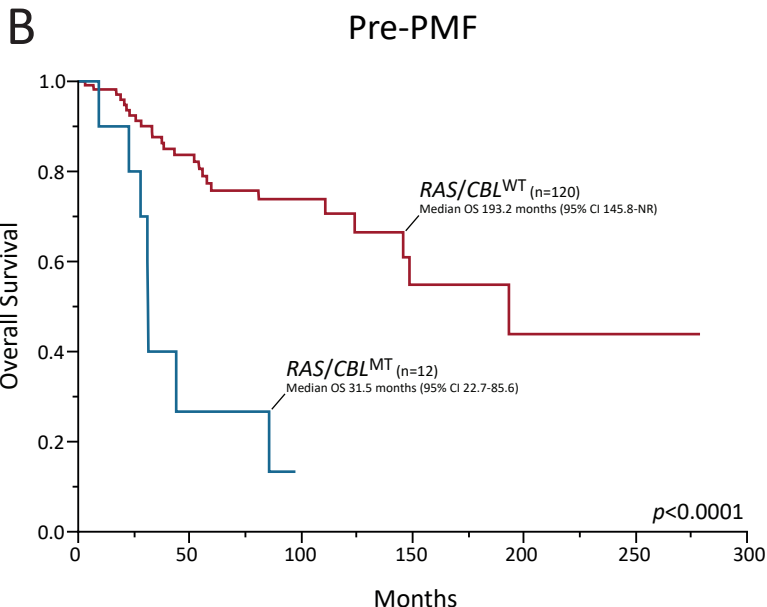
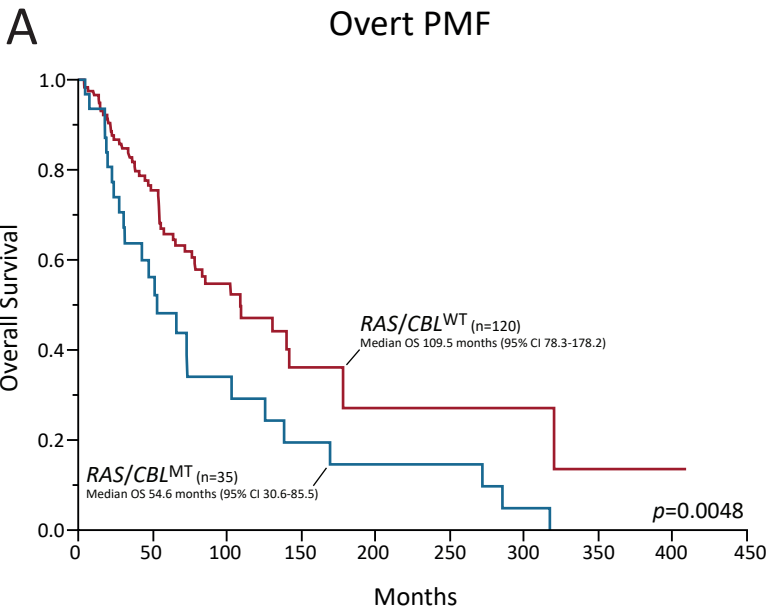
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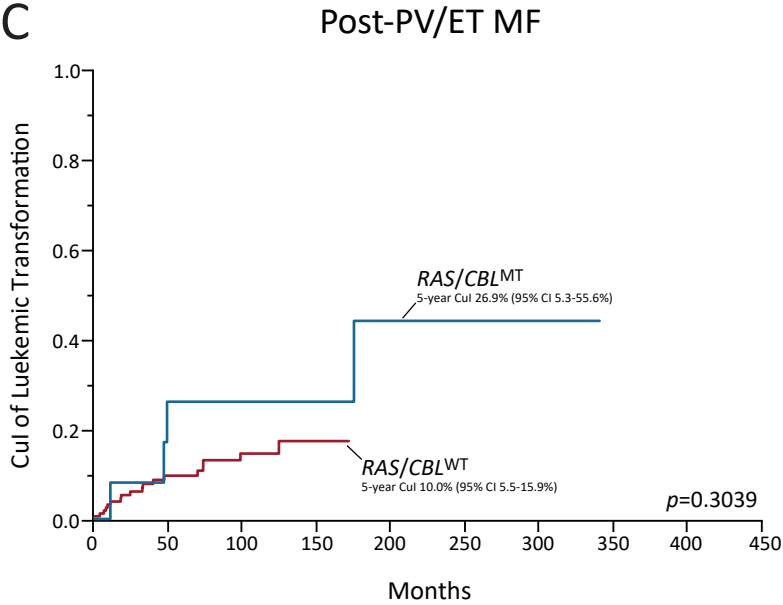
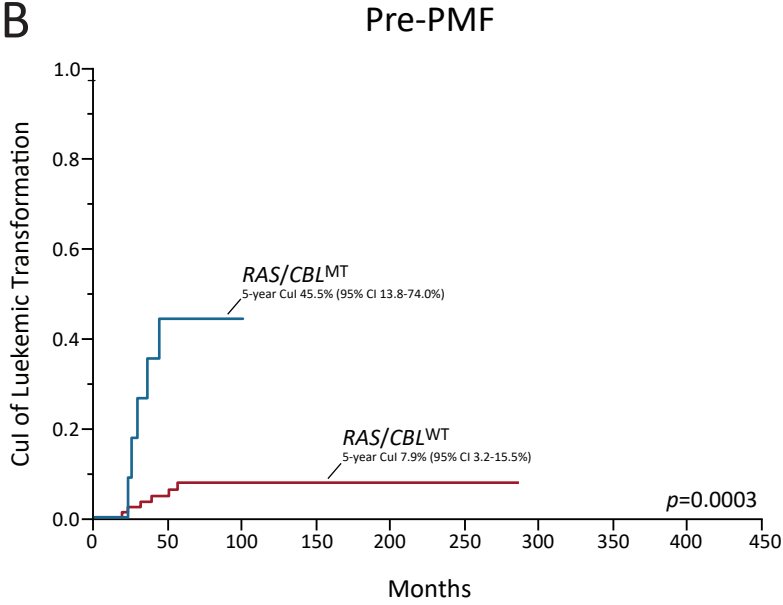
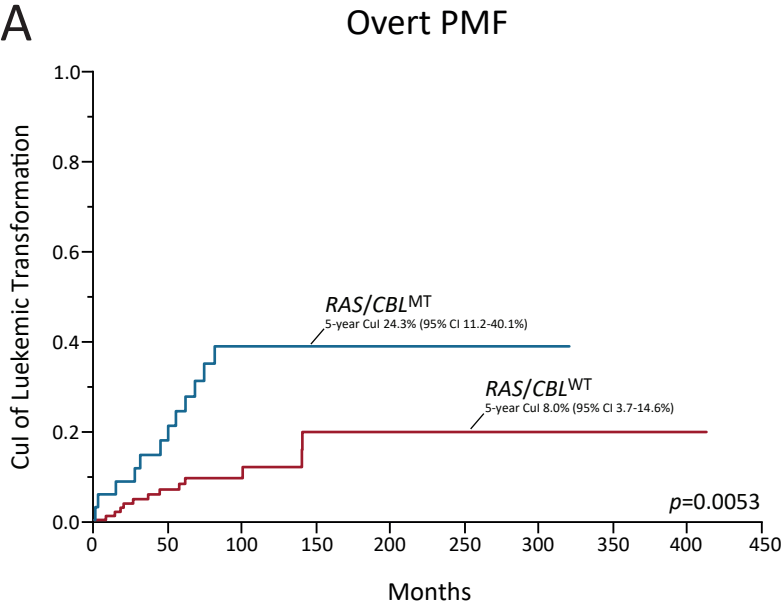
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Supplementary Figure 4

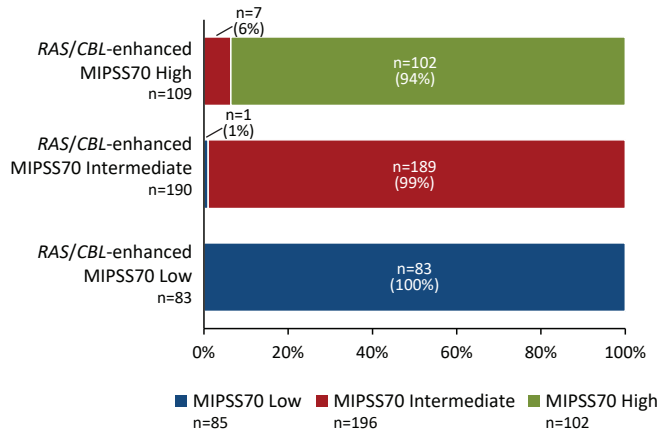


Supplementary Figure 5

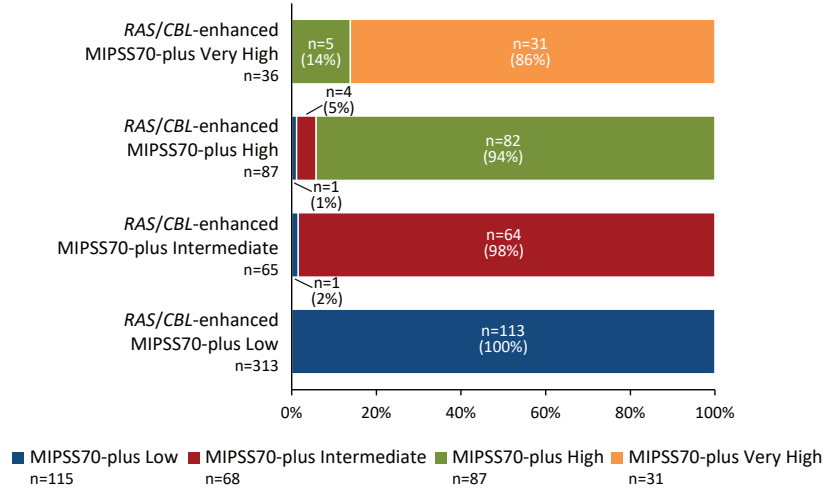


Supplementary Figure 6

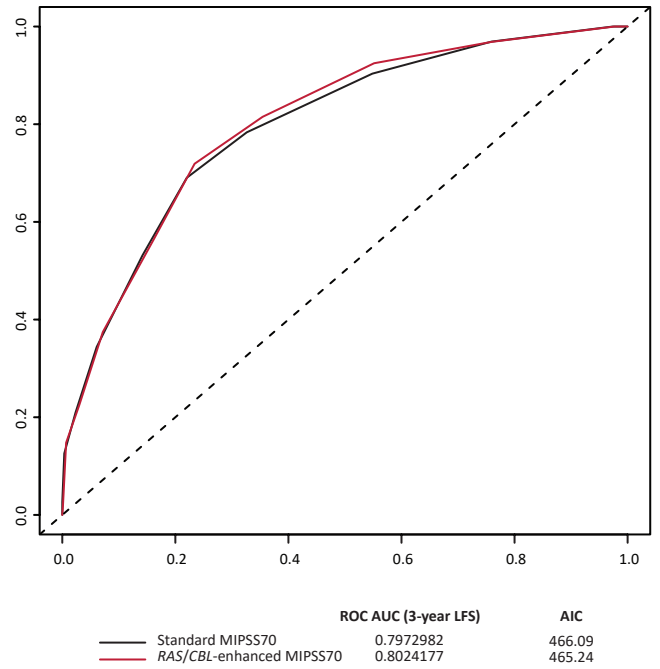
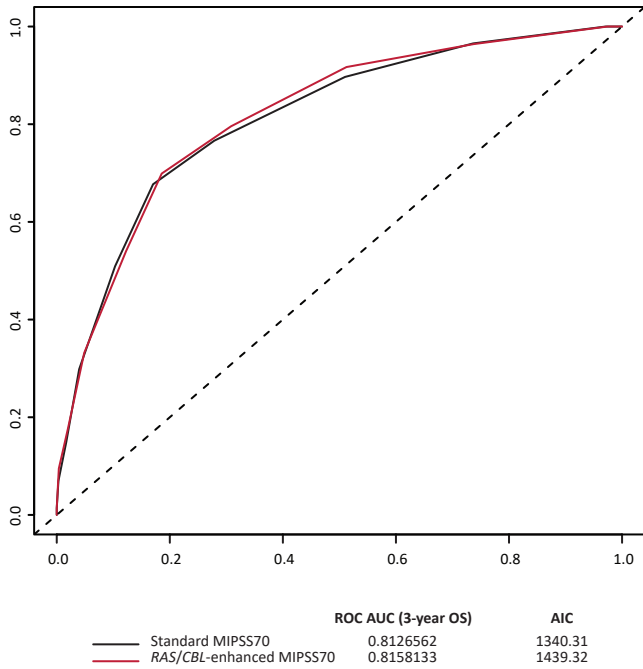
A MIPSS70 vs *RAS/CBL*-enhanced MIPSS70 Risk distribution



B MIPSS70-plus vs *RAS/CBL*-enhanced MIPSS70-plus Risk distribution



C MIPSS70 vs *RAS/CBL*-enhanced MIPSS70 3-year ROC AUC for OS and LFS



D MIPSS70-plus vs *RAS/CBL*-enhanced MIPSS70-plus 3-year ROC AUC for OS and LFS

