Supplementary Table 1: Clinical and laboratory features and subsequent events of CMML patients' comparison by center (combined Mayo clinic and Moffitt cohort)

Variables [Median or n; range or %]	**Mayo Cohort (n=582)**	**Moffitt Cohort (*n*=277)**	**P-value**
Age in years; median (range)	72 (2-95)	71 (17-95)	0.83
Sex (Male); *n* (%)	388 (66.7%)	195 (69.4%)	0.69
Hemoglobin g/dL; median (range)	10.7 (1.4-16.9)	11 (3.4-15.6)	0.75
WBC x 10^9/L; median (range)	12.8 (1.3-264.8)	13.9 (2.4-288.6)	0.75
ANC x10^9/L; median (range)	6.1 (0.0-151.0)	6.5 (0.1-155.6)	0.58
AMC x 10^9/L; median (range)	2.7 (0.0-84)	2.7 (0.4-35.6)	0.74
Platelets x 10^9/L; median(range)	98 (7.0-1277.0)	104 (2.0-1945.0)	0.49
Presence of IMC; n (%)	340 (58.4%)	154 (55.5%)	1.00
PB blasts %; median (range)	0 (0.0-19.0)	0 (0.0-15.0)	0.98
BM blasts %; median (range)	3 (0.0-19.0)	3 (0.0-19.0)	0.57
FAB CMML subtype **N Evaluable**	582	275	
dCMML; *n* (%) pCMML; *n* (%)	300 (51.5%) 282 (48.5%)	129 (46.9%) 146 (53.1%)	0.63
WHO 2016 CMML subtype **N Evaluable**	560	257	
CMML-0; n (%) CMML-1; n (%) CMML-2; n (%)	327 (58.4%) 135 (24.1%) 98 (17.5%)	163 (63.4%) 56 (21.8%) 38 (14.8%)	0.66
CPSS Cytogenetic risk stratification **N Evaluable**	520	271	
Low; n (%) Intermediate; n (%) High; n (%)	379 (72.9%) 58 (11.2%) 83 (15.9%)	205 (75.6%) 36 (13.3%) 30 (11.1%)	0.59
Next generation sequencing analysis **N Evaluable**	330	277	
1. Epigenetic regulators			
TET2	141 (42.7%)	171 (61.7%)	**0.02**
IDH1	5 (1.5%)	2 (0.7%)	0.76
IDH2	20 (6.1%)	11 (3.9%)	0.56
DNMT3A	21 (6.4%)	20 (7.2%)	0.72
2. Chromatin regulators			
ASXL1	166 (50.3%)	115 (41.5%)	0.20
EZH2	11 (3.3%)	35 (12.6%)	**0.03**
3. Transcription factors			
RUNX1	34 (10.3%)	52 (18.8%)	**0.02**
4. Spliceosome factors			
SRSF2	153 (46.4%)	105 (37.9%)	0.22
U2AF1	23 (6.9%)	19 (6.8%)	0.97
ZRSR2	16 (4.8%)	21 (7.6%)	0.62

5. Cell signaling			
NRAS	49 (14.8%)	46 (16.5%)	0.74
KRAS	19 (5.8%)	N/A	N/A
CBL	49 (14.8%)	42 (15.0%)	0.94
PTPN11	9 (2.7%)	N/A	N/A
JAK2	25 (7.6%)	22 (7.9%)	0.89
CSF3R	4 (1.2%)	N/A	N/A
KIT	11 (3.3%)	14 (5.0%)	0.54
MPL	2 (0.6%)	3 (1.1%)	0.76
CALR	1 (0.3%)	N/A	N/A
6. Tumor suppressor gene			
TP53	9 (2.7%)	8 (2.9%)	1.0
7. Others			
SETBP1	38 (11.5%)	24 (8.6%)	0.63
Mayo Molecular Model N Evaluable	572	277	0.07
Low risk; n (%)	61 (10.7%)	38 (13.6%)	0.07
Intermediate-1 risk; n (%)	179 (31.3%)	106 (38.4%)	
Intermediate-2 risk; n (%)	168 (29.4%)	81 (29.4%)	
High risk; n (%)	164 (28.7%)	52 (18.6%)	
GFM Prognostic Model N Evaluable	572	277	
Low risk; n (%)	271 (47.4%)	114 (41.2%)	0.24
Intermediate risk; n (%)	223 (39.0%)	108(39.1%)	
High risk; n (%)	78 (13.6%)	55 (19.7%)	
IPSS-R Group N Evaluable	512	276	
Very low; n (%)	108 (21.1%)	70 (25.4%)	0.54
Low; n (%)	192 (37.5%)	105 (38.2%)	
Intermediate; n (%)	121 (23.6%)	58 (21.1%)	
High; n (%)	59 (11.5%)	34 (12.1%)	
Very High; n (%)	32 (6.3%)	9 (3.2%)	
Deaths; *n* (%)	353 (60.6%)	126 (45.5%)	-
Leukemic transformation; n (%)	105 (18.0%)	60 (21.6%)	-

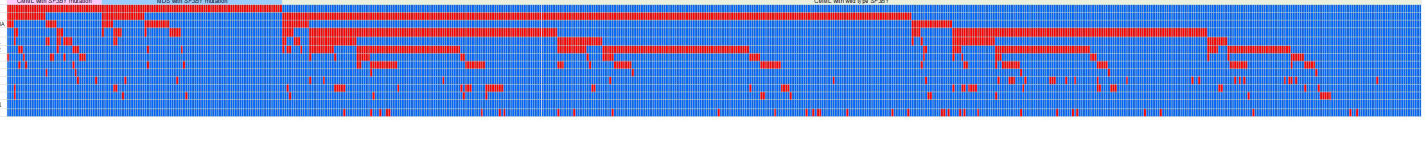
The bold values represent p values that are statistically significant; $p < 0.05$ (Only provided if data is available for all three cohorts).

Key: CMML: chronic myelomonocytic leukemia, AMC: absolute monocyte count; ANC: absolute neutrophil count; IMC: immature circulating cells; WBC: white blood cell count; PB: peripheral blood; BM: bone marrow; WHO: World Health Organization; CPSS-Mol: clinical/molecular CMML-specific prognostic scoring system; dCMML: dysplastic chronic myelomonocytic leukemia; pCMML: proliferative chronic myelomonocytic leukemia; FAB: French-American-British; GFM: Groupe Francophone des Myelodyplasies; IMC: immature myeloid cells; ^{MT}: mutated; ^{WT}: wild type; N/A: not available.; IPSS-R: Revised International Prognostic Scoring System; VAF: Variant Allele Frequency

Supplementary 2: Detailed characteristics, mutational patterns and associated outcomes of patients with *SF3B1* mutated chronic myelomonocytic leukemia with concurrent splicing mutations

Age (Year)	Sex	WHO/FAB CMML subtype	*SF3B1* mutation (nucleotide and amino acid change)	*SF3B1* VAF (%)	Karyotype	Concomitant mutations (VAF%)	Bone Marrow RS (%)	Acute Leukemia Transformation (duration from diagnosis to transformation)	Status at last contact (duration from diagnosis to last contact)
83	M	CMML-0/ Dysplastic	c.2098A>G p.Lys700Glu	23.0	46,XY [20]	***SRSF2;* c.284C>A; p.Pro95His (22%)** *CBL;* c.1384C>T; p.Arg462* (45%)	18	No	Dead (57.3 months)
69	M	CMML-1/ Dysplastic	c.1986C>A p.His662Gln	45.0	46,XY, add(11)(p11.2), der(18)t(1;18)(q32;q21.3) [12]/46,XY [8]	***ZRSR2;* c.396del; p.Glu133Arg (8%)** *KIT*; c.2447A>T; p.Asp816Val (9%) *CBL;* c.1142G>A; p.Cys381Tyr (12%)	70	No	Alive (100.7 months)
43	F	CMML-0/ Proliferative	c.2098A>G p.Lys700Glu	32.0	46,XX [20]	***SRSF2;* c.284C>T; p.Pro95Leu (16%)** *IDH1;* c.394C>A; p.Arg132Ser (46%)	42	No	Dead (6.6 months)
66	M	CMML-0/ Dysplastic	c.1868A>G p.Tyr623Cys	42.0	46,XY [20]	***SRSF2*; c.284C>T; p.Pro95His (45%)** *TET2; c.812C>G; p.Ser271** (33%)	80	No	Dead (60.9 months)
78	M	CMML-0/ Dysplastic	c.2098A>G Lys700Glu c.2293T>A Tyr765Asn	48% 15%	46, XY	*TET2;* c.4082G>A; p.G1361D (46%) and c.4909del; p.L1637Yfs*58 (43%) *ASXL1*; c.1900-1922del; p.E635Rfs*15 (37%)	50	No	Dead (42.3 months)
69	F	CMML-1/ Proliferative	c.2098G>A p.Lys700Glu	45.2	46,XX [19]	***SRSF2;* c.284C>T; p.Pro95His (2.8%)** *TET2;* c.4392G>A; p.Cys1464* (97.3%) *CBL*; c.1142G>A; p.Cys381Tyr (36.6%)	Occasional	No	Alive (16.8 months)
72	M	CMML-1/ Dysplastic	c.2005C>G, p.Gln669Glu	43.1	46,XY [20]	*IDH2*; c.419G>A; p.Arg140Gln (44.2%) ***SRSF2*; c.284C>T; p.Pro95Leu (42.0%)**	>15	Yes (70 months)	Dead (70.3 months)
75	M	CMML-1/ Dysplastic	c.2098A>G p.Lys700glu c.1660A>G; p.Lys554E	N/A	46,XY,del(20)(q11.2q13.1) [18]/ 46,XY [2]	*IDH1*; c.394C>T; p.Arg132Cys *DNMT3A*; c.2111G>C; p.Trp704Ser *RUNX1*; c.971_972insAGTA; p.Ser389Vfs)	>15	No	Alive (35.8 months)
77	M	CMML-2/ Dysplastic	c.2098A>G p.Lys700glu c.1660A>G; p.Lys554E	N/A	46,XY [20]	*TET2*; c. 1285G>A; p.Gly429Arg	>15	Yes (5.1 months)	Alive (20.3 months)

Abbreviations – F: Female, M: Male, WHO/FAB: World Health Organization/French American British Classification, CMML: Chronic Myelomonocytic Leukemia, A: Adenine, G: Guanine, C: Cytosine, T: Thymine, Arg: Arginine, Lys: Lysine, Glu: Glutamic acid, Gly: Glycine, His: Histidine, Gln: Glutamine, Tyr: Tyrosine, Asn: Asparagine, Cys: Cysteine, Asp: Aspartic Acid, Ser: Serine, Trp: Tryptophan, VAF: Variant Allele Frequency, inv: inversion, der: derivative chromosome, RS: Ring Sideroblast


CMML with SF3B1 mutation
MDS with SF3B1 mutation
CMML with wild type SF3B1
SF3B1
TET2
DNMT3A
ASXL1
RUNX1
SRSF2
JAK2
CBL
IDH1
IDH2
EZH2
TP53
SETBP1
U2AF1