SF3B1-mutant myelodysplastic syndrome/myeloproliferative neoplasms: a unique molecular and prognostic entity

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Supplementary Table 1: Table comparing clinical, morphological, and molecular characteristics of patients with *SF3B1* mutant CMML, MDS/MPN-RS-T, MDS/MPN-U and MDS. *denotes statistical significance (*P*<0.05).
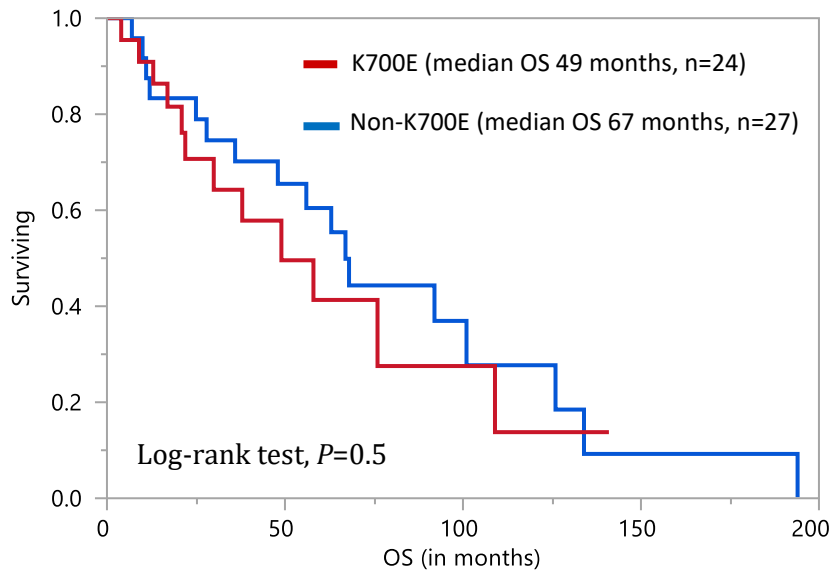
Variable; Median value (range or %)	**All MDS/MPN neoplasm cohort (n=778)**	*SF3B1-mutant CMML (n=18)*	*SF3B1-mutant MDS/MPN-RS-T (n=45)*	*SF3B1-mutant MDS/MPN-U (n=15)*	*SF3B1-mutant MDS (n=75)*	*P value (CMML versus MDS/MPN-RS-T and MDS/MPN-U*	*P value (MDS/MPN versus MDS)*
Age (years)	72 (18-95)	74 (43-86)	74 (49-93)	73 (49-87)	74 (41-94)	0.9	0.98
No. of males;	511 (66)	7 (39)	26 (58)	9 (60)	48 (64)	0.3	0.3
Hb; gm/dl	10.4 (1.4-16.9)	9.6 (6.4-12.6)	9.5 (7.4-13.3)	9.1 (7.3-11.8)	9.5 (7-13.5)	0.6	0.8
WBC count x 10^9 per liter	11.7 (1-469)	7.3 (2.6-96.1)	7.5 (3.9-25.8)	11 (1.8-70.2)	5.2 (1.5-13.1)	0.8	<0.0001*
ANC x 10^9 per liter	5.9 (0-151)	3.1 (0.4-54.7)	4 (1.6-19)	5.6 (0.8-52)	2.9 (0.4-9.4)	0.2	0.001*
AMC x 10^9 per liter	1.9 (0-84)	1.7 (0.2-11.5)	0.6 (0.1-2.8)	0.4 (0.1-4.9)	0.4 (0.06-1)	<0.0001*	<0.0001*
Platelet count x 10^9 per liter	117 (7-1798)	159 (63-359)	546 (454-1243)	550 (121-1040)	268 (62-599)	<0.0001*	<0.0001*
BM ringed sideroblasts (%)	0 (0-90)	45 (0-80)	50 (15-90)	35 (0-80)	40 (5-80)	0.2	0.2
PB blasts (%)	0 (0-19)	0 (0-3)	0 (0-0)	0 (0-2)	0 (0-0)	0.0001*	<0.0001*
BM blasts (%)	2 (0-19)	3 (0-9)	1 (0-2)	3.5 (0-8)	1 (0-4)	<0.0001*	<0.0001*
Abnormal karyotype (excluding sole -Y, %), Evaluable=695	197 (28)	4 (22)	6 (14)	1 (8)	11 (15)	0.5	0.7
Molecular abnormalities (only if overall frequency ≥ 5%)							
ASXL1 (evaluable=528)	235 (45)	3 (21)	9 (23)	5 (33)	10 (13)	0.4	0.4
DNMT3A (evaluable=443)	30 (7)	3 (21)	7 (18)	3 (20)	15 (20)	0.95	0.9
TET2 (evaluable=401)	155 (39)	7 (39)	3 (8)	2 (13)	20 (27)	0.001*	0.002*
IDH2 (evaluable=418)	21 (5)	-	-	-	1 (1)	-	0.7
SRSF2 (Evaluable=444)	179 (40)	4 (22)	-	-	3 (4)	0.001*	0.003*
U2AF1 (Evaluable=442)	27 (6)	-	1 (3)	1 (7)	-	0.5	0.2
ZRSR2 (Evaluable=440)	20 (5)	-	1 (3)	-	2 (3)	0.6	0.6
JAK2 (Evaluable=443)	49 (11)	-	14 (36)	3 (20)	1 (1)	0.005*	<0.0001*
CBL (Evaluable=443)	54 (12)	2 (11)	-	1 (7)	-	0.06	0.1
NRAS (Evaluable=443)	54 (12)	1 (6)	-	2 (13)	-	0.06	0.06

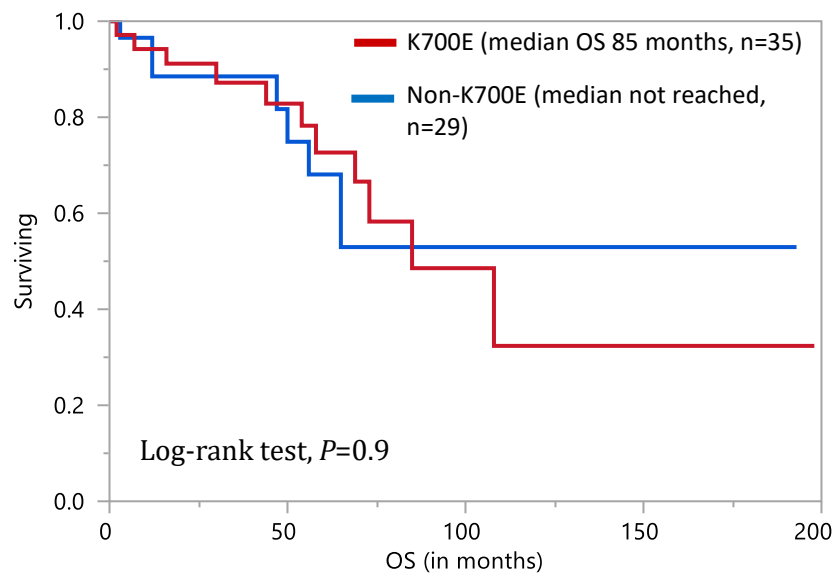|							
Treatment (total evaluable=619)							
Hydrea	302 (54)	7 (47)	18 (42)	8 (67)	1 (2)	0.3	<0.0001*
ESA	249 (45)	10 (67)	26 (60)	9 (75)	52 (84)	0.0001*	<0.0001*
Lenalidomide	27 (5)	-	12 (28)	3 (25)	9 (15)	0.02*	0.3
HMA	156 (29)	4 (29)	4 (9)	7 (58)	10 (16)	0.002*	0.4
Allogeneic HCT	37 (5)	-	-	-	-	-	-
Investigational agent (trial)	48 (9)	1 (7)	1 (2)	-	-	0.7	<0.0001*
Outcomes							
Transformation to AML (%)	123 (16)	2 (11)	1 (3)	1 (7)	2 (3)	0.003*	0.4
Allogeneic HCT (%)	37 (5)	-	-	-	-	-	-
AML-free survival; median months (range)	Median NR	Median NR	Median NR	Median NR	Median NR	0.2	0.1
Overall survival; median months (95% CI)	32 (28-38)	24 (20-67)	67 (38-101)	48 (12-NR)	65 (43-85)	0.3	0.2

Abbreviations: MDS/MPN=Myelodysplastic/myeloproliferative neoplasms; CMML=chronic myelomonocytic leukemia; MDS/MPN-RS-T= Myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis; MDS/MPN-U= Myelodysplastic/myeloproliferative neoplasms, unclassifiable; MDS=myelodysplastic syndromes; WBC = white blood cell; PB=peripheral blood; BM=bone marrow; ANC = absolute neutrophil count; AMC=absolute monocyte count; RS=ring sideroblasts; BM = bone marrow; HCT = hematopoietic stem cell transplant; NR=not reached; CI = confidence interval; AML=acute myeloid leukemia.

Supplementary Figure 1: **Figure showing distribution of _SF3B1_ hotspots across MDS/MPN patients and MDS, and differences in outcomes between the K700E and non-K700E hotspots in MDS/MPN patients.** 1A shows no significant difference in OS between K700E and non-K700E _SF3B1_ mutations in patients with MDS/MPN overlap neoplasms (median, 49 versus 67 months, _P_=0.3) in the Mayo Clinic cohort. 1B shows no significant differences in OS between K700E and non-K700E _SF3B1_ mutations in patients with MDS/MPN overlap neoplasms (median, 85 months versus median not reached, _P_=0.9) in the Moffitt Cancer Center cohort. 1C shows the distribution of _SF3B1_ hotspots across MDS/MPN overlap neoplasm patients. 1D shows distribution of _SF3B1_ hotspots across MDS/MPN overlap neoplasm patients.
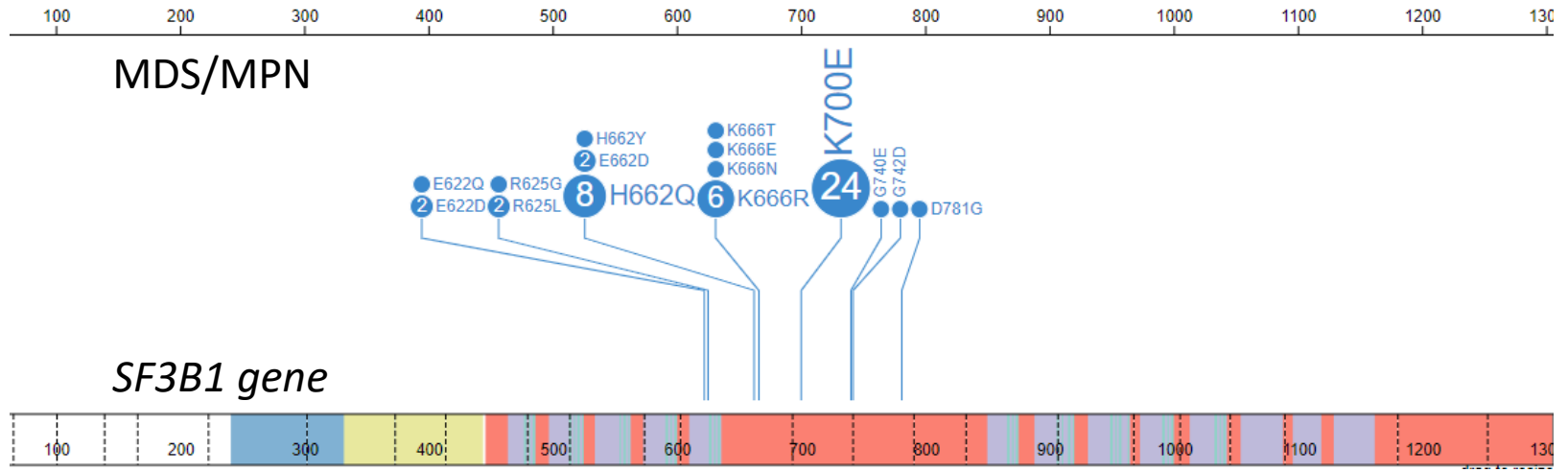
1A:

1B:

Figure shows a Kaplan-Meier survival curve. Y-axis labeled "Surviving" (0.0 to 1.0), X-axis labeled "OS (in months)" (0 to 200).

Legend:
- K700E (median OS 85 months, n=35)
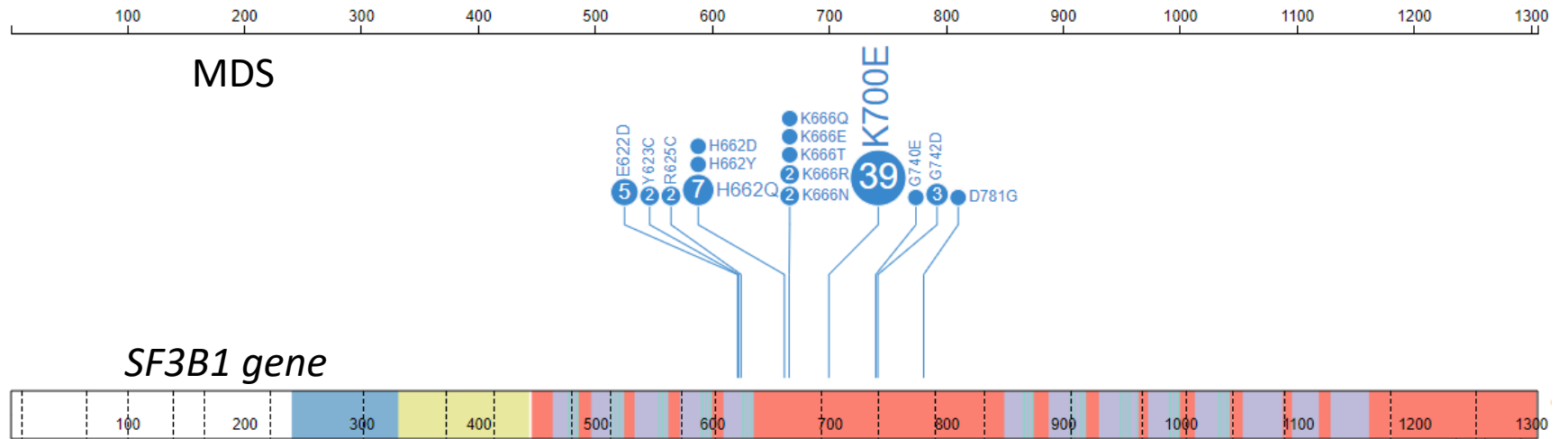- Non-K700E (median not reached, n=29)

Log-rank test, P=0.9

1C: MDS/MPN

1D: MDS

Supplementary table 2: Multivariate analysis of known prognostic features in predicting overall survival among the Mayo Clinic cohort of MDS/MPN and MDS patients. ROC analysis was used to drive cut-offs for hemoglobin and age. The platelet count and BM blast cut-offs were chosen as per established cut-offs from the WHO classification. Cox proportion hazard model was used for the multivariate analysis. *denotes statistical significance ($P<0.05$).

Variable	Multivariate analysis P value (HR, 95% CI)
Age $\geq$ 70 (years)	0.0002 (1.6, 1.3-2.1)*
Hemoglobin < 10 (g/dL)	0.01 (1.4, 1.1-1.7)*
Platelet count $\geq$ 450 (x10^9/µL)	0.9 (1, 0.7-1.4)
BM blast% $\geq$ 5	0.2 (1.2, 0.9-1.6)
CPSS cytogenetic subtypes	
Low	Reference
Intermediate	0.02 (1.5, 1.1-2.1)*
High	<0.0001 (2, 1.4-2.8)*
SF3B1	0.01 (1.5, 1.1-2.1)*
ASXL1	0.04 (1.3, 1-1.63)*

Abbreviations: MDS/MPN=Myelodysplastic/Myeloproliferative neoplasms; ROC=Receiver Operating Characteristic; HR=Hazard Ratio; BM=Bone Marrow; CPSS=CMML-specific prognostic scoring system.