Genetic landscape and clinical outcomes of patients with *BCOR* mutated myeloid neoplasms

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Supplemental Methods

NGS analysis

DNA was extracted from fresh bone marrow aspirates and sequencing was performed using a targeted next-generation sequencing (NGS) panel. The Mayo Clinic myeloid NGS panel includes 42 genes commonly mutated in MNs: *ANKRD26, ASXL1, BCOR, CALR, CBL, CEBPA, CSF3R, DDX41, DNMT3A, ELANE, ETNK1, ETV6, EZH2, FLT3, GATA1, GATA2, IDH1, IDH2, JAK2, KDM6A, KIT, KRAS, MPL, NPM1, NRAS, PHF6, PTPN11, RAD21, RUNX1, SETBP1, SH2B3, SF3B1, SRP72, SMC3, SRSF2, STAG2, TERT, TET2, TP53, U2AF1, WT1*, and *ZRSR2*. The library preparation, sequencing and data analysis were performed as described.[1] Briefly, libraries were prepared using the Agilent SureSelect-XT Target Enrichment Kit (SureSelectXT, Agilent, Santa Clara, CA). and sequencing was performed on MiSeq or HiSeq platforms (Illumina, San Diego, CA) at the Mayo Clinic Clinical Genome Sequencing Laboratory. Pathogenic and likely pathogenic variants calling was performed as described.[2] Only variants at sites with a total read depth > 100, supported by more than five alternate variant reads and a variant allele frequency (VAF) ≥ 5%, were retained for further analysis.

References:

1. Mehta N, He R, Viswanatha DS. Internal Standardization of the Interpretation and Reporting of Sequence Variants in Hematologic Neoplasms. *Mol Diagn Ther*. 2021;25(4):517–526.
2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*. 2015;17(5):405–424.

Supplemental Tables

Table S1. Gene mutations identified in patients with wt*BCOR* AML and MDS.

	AML (N=155)	MDS (N=105)	*P*
ASXL1	25 (16.1%)	29 (27.6%)	0.04
CALR	1 (0.6%)	0 (0%)	1
CBL	3 (1.9%)	5 (4.8%)	0.35
CEBPA	8 (5.2%)	1 (1.0%)	0.14
CSF3R	2 (1.3%)	0 (0%)	0.66
DNMT3A	33 (21.3%)	8 (7.6%)	0.005
ETV6	0 (0%)	2 (1.9%)	0.32
EZH2	5 (3.2%)	5 (4.8%)	0.76
FLT3	25 (16.1%)	0 (0%)	< 0.001
GATA2	5 (3.2%)	2 (1.9%)	0.80
IDH1	6 (3.9%)	1 (1.0%)	0.3
IDH2	27 (17.4%)	2 (1.9%)	< 0.001
JAK2	8 (5.2%)	3 (2.9%)	0.55
KIT	5 (3.2%)	0 (0%)	0.16
KRAS	6 (3.9%)	0 (0%)	0.10
MPL	1 (0.6%)	1 (1.0%)	1
NOTCH1	1 (0.6%)	0 (0%)	1
NPM1	20 (12.9%)	1 (1.0%)	0.001
NRAS	14 (9.0%)	0 (0%)	0.004
PHF6	4 (2.6%)	4 (3.8%)	0.84
PTPN11	5 (3.2%)	3 (2.9%)	1
RUNX1	21 (13.5%)	13 (12.4%)	0.93
SETBP1	4 (2.6%)	4 (3.8%)	0.84
SF3B1	6 (3.9%)	20 (19.0%)	< 0.001
SRSF2	24 (15.5%)	18 (17.1%)	0.85
TET2	29 (18.7%)	21 (20.0%)	0.92
TP53	27 (17.4%)	15 (14.3%)	0.62
U2AF1	13 (8.4%)	14 (13.3%)	0.28
WT1	19 (12.3%)	0 (0%)	< 0.001
ZRSR2	1 (0.6%)	9 (8.6%)	0.003

Table S2. Diseases associated with BCOR mutations.

Disease	Number of patients (N=138)
MDS	63 (45.6%)
AML	36 (26.1%)
Others	
CCUS	9 (6.5%)
MPN	7 (5.1%)
Aplastic anemia	7 (5.1%)
CMML	6 (4.3%)
MDS/MPN overlap (not CMML)	5 (3.6%)
Follicular lymphoma	2 (1.4%)
CLL	1 (0.7%)
PNH	1 (0.7%)
T-cell ALL	1 (0.7%)

Table S3. Correlation of m*BCOR* AML and MDS with other genes.

	m*BCOR* AML		m*BCOR* MDS	
Gene	**Odds ratio**	***P* value**	**Odds ratio**	***P* value**
ASXL1	1.06	0.94	1.05	0.89
CBL	1.56	1		
CEBPA	0.59	0.86	4.74	0.3
DNMT3A	2.09	0.06	3.72	0.003
EZH2	2.76	0.36	0.68	0.92
FLT3	1.27	0.63		
GATA2			3.35	0.28
IDH1	3.11	0.18	3.18	0.65
IDH2	1.83	0.16	0.34	0.56
JAK2	0.59	0.86	1.14	1
KIT	0.95	1		
KRAS	1.53	1		
NRAS	1.65	0.57		
PHF6	1.18	1	1.71	0.71
PTPN11	1.83	0.86	0.6	1
RUNX1	5.63	< 0.001	5.56	< 0.001
SETBP1			0.45	0.72
SF3B1	1.53	1	0.46	0.098
SRSF2	0.52	0.27	1.38	0.42
TET2	0.29	0.28	1.04	0.92
TP53	0.64	0.61	0.21	0.02
U2AF1	2.2	0.24	3.95	0.0002
WT1	0.68	0.71		
ZRSR2			0.19	0.13

Table S4. *U2AF1* mutation variants in m*BCOR* patients stratified by disease.

	***U2AF1* mutation variant**		
Disease	**Q157R (N=3)**	**S34F (N=34)**	**S34Y (N=3)**
AML	0 (0%)	6 (17.6%)	0 (0%)
MDS	3 (100%)	20 (58.8%)	3 (100%)
MPN	0 (0%)	2 (5.9%)	0 (0%)
CCUS	0 (0%)	4 (11.8%)	0 (0%)
Other	0 (0%)	2 (5.9%)	0 (0%)

Abbreviations: AML: acute myeloid leukemia, CCUS: clonal cytopenia of undetermined significance, MDS: myelodysplastic syndrome, MPN: myeloproliferative neoplasms.

Table S5. Univariate analysis for 3-year survival after *BCOR* mutation detection.

Variable	HR	Lower 0.95	Upper 0.95	*P*
Gender	0.97	0.55	1.73	0.93
AML (vs. MDS)	0.72	0.43	1.21	0.21
Abnormal karyotype at NGS	1.33	0.79	2.21	0.28
Complex karyotype	3.17	1.69	5.96	**<0.001**
ASXL1 (n=24)	1.47	0.84	2.59	**0.18**
FLT3	1.48	0.67	3.25	0.33
IDH1	1.18	0.43	3.26	0.75
JAK2	1.70	0.53	5.45	0.37
PHF6	0.89	0.28	2.83	0.84
RUNX1	0.84	0.51	1.40	0.51
SF3B1	0.57	0.21	1.58	0.28
SRSF2	1.21	0.61	2.39	0.58
TET2	1.11	0.56	2.20	0.76
U2AF1	0.94	0.54	1.62	0.82
ZRSR2	0.85	0.12	6.16	0.87
VAF ≥ 40%	1.54	0.82	2.91	**0.18**
Splice site mutation	0.38	0.12	1.22	**0.105**
Nonsense mutation	1.16	0.68	1.98	0.58
Hemoglobin ≥ 10 g/dl	0.72	0.41	1.25	0.24
Platelets ≥ 100000/mcl	1.01	0.60	1.70	0.97
Age at NGS ≥ 70 years	2.04	1.20	3.47	**0.01**
Monosomy 7	1.81	0.56	5.85	0.32
Monosomal karyotype	1.54	0.55	4.26	0.41
Prior chemotherapy	1.20	0.59	2.44	0.61
Multimutated BCOR	1.94	0.60	6.29	0.27
CEBPA	1.94	0.60	6.21	0.27
DNMT3A	0.70	0.39	1.27	0.24
EZH2 (n=5)	2.76	0.98	7.73	**0.05**
GATA2	0.91	0.28	2.91	0.87
IDH2	0.82	0.35	1.91	0.65
KRAS (n=5)	3.03	0.93	9.86	**0.07**
NRAS	0.77	0.33	1.79	0.54
PTPN11	1.12	0.27	4.61	0.87
SETBP1	2.69	0.37	19.77	0.33
STAG2	0.60	0.26	1.41	0.24
TP53 (n=7)	1.79	0.78	4.17	**0.18**
WT1 (n=3)	2.53	0.79	8.14	0.12
Frameshift mutation	1.23	0.73	2.07	0.43
Bone marrow blasts ≥ 10%	1.26	0.74	2.13	0.4
alloSCT (time dependent)	0.25	0.11	0.57	**0.001**

Abbreviations: alloSCT: allogeneic stem cell transplant, AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, NGS: next generation sequencing, VAF: variant allele frequency.

Table S6. Univariate competing risk analysis for relapse at 3-years after alloSCT.

Variable	HR	Lower 0.95	Upper 0.95	*P*
Gender	1.22	0.247	5.99	0.81
MDS (vs. AML)	3.36	0.365	30.9	0.28
Abnormal karyotype	1.95	0.42	9.03	0.39
Monosomy 7	3.85	1.63	9.11	**0.002**
Complex karyotype	1.83	0.372	8.96	0.46
Monosomal karyotype	1.83	0.372	8.96	0.46
ASXL1 (n=5)	3.29	0.648	16.7	**0.15**
DNMT3A	1.79	0.345	9.34	0.49
FLT3	NA			
GATA2 (n=2)*	9	1.7	47.7	**0.0098**
IDH1	1.5	0.207	10.9	0.69
IDH2	NA			
JAK2	NA			
KDM6A	NA			
KIT	NA			
KRAS	NA			
MPL	NA			
NF1	NA			
NPM1	NA			
NRAS	NA			
PHF6	NA			
PTPN11	NA			
RUNX1 (n=12)	3.8	0.765	18.9	**0.1**
SETBP1	NA			
SF3B1 (n=2)*	8.26	2.45	27.9	**0.0007**
SRSF2	NA			
STAG2	0.875	0.0909	8.42	0.91
TET2	1.88	0.181	19.5	0.6
TP53	NA			
U2AF1	NA			
WT1	NA			
ZRSR2 (n=1)*	5.52	2.1	14.5	**0.0005**
Bone marrow blast ≥ 10% at NGS	1.43	0.282	7.2	0.67
Age ≥ 70 years at NGS	NA			
High risk co-mutations	2.57	0.326	20.3	0.37
High HCT-CI score	2.06	0.426	9.94	0.37
CR at alloSCT	0.727	0.156	3.38	0.68
Melphalan	0.225	0.0267	1.9	**0.17**
Busulphan§	3.11	0.588	16.4	**0.18**
TBI	1.31	0.136	12.6	0.81
Cyclophosphamide	1.48	0.321	6.82	0.62
RIC	0.362	0.0809	1.62	**0.18**
Matched related donor	0.427	0.0495	3.68	0.44
Major/bidirectional ABO mismatch	NA			
CMV D-/R+	0.599	0.0676	5.3	0.64
PTCy	0.971	0.139	6.8	0.98

* Not included in multivariate analysis due to small number of cases.

§ Not included in multivariate analysis due to collinearity with melphalan.

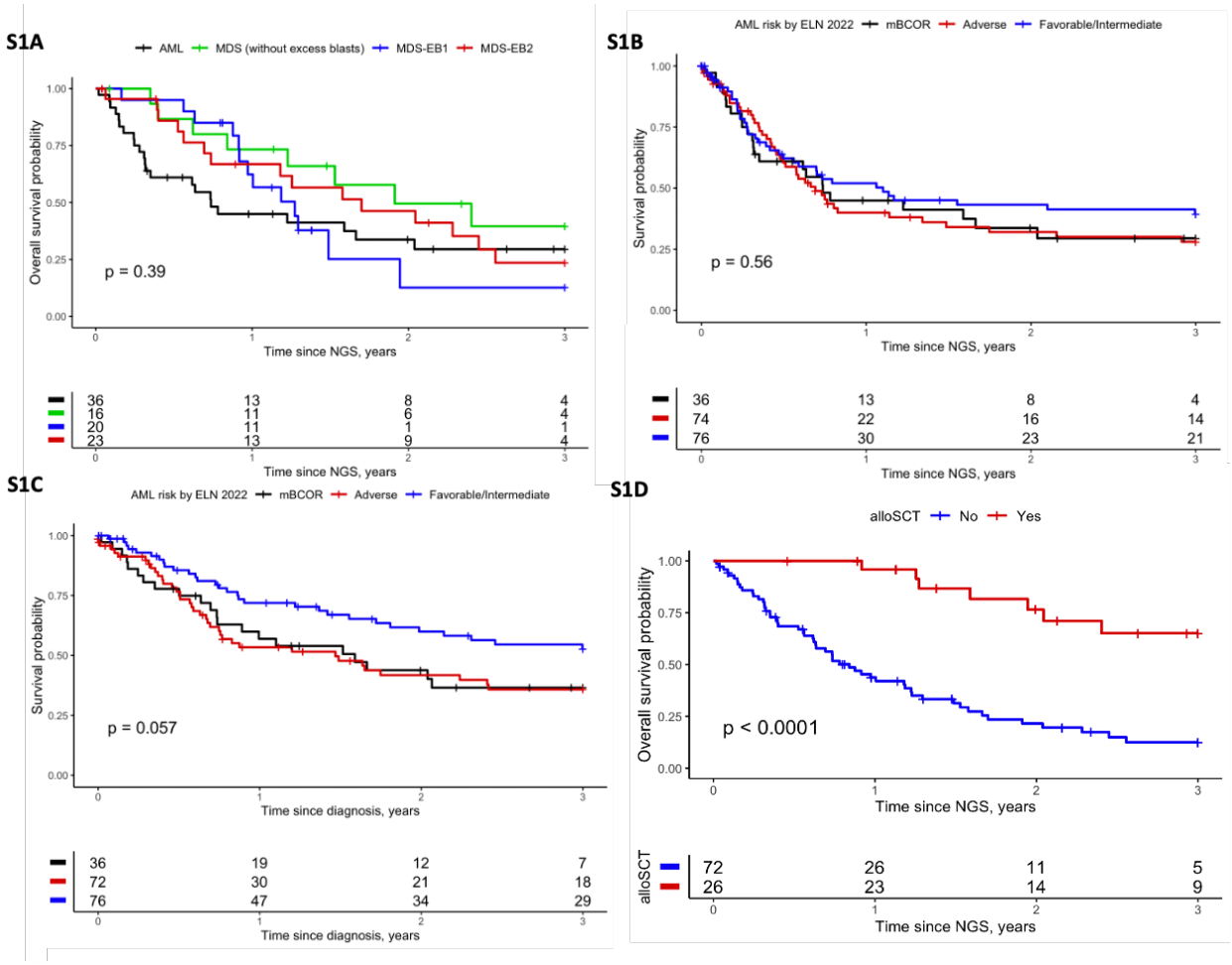
Table S7. Univariate analysis for 3-year post-alloSCT survival.

Variable	HR	upper CI	lower CI	P
Male gender	0.6538	0.1543	2.771	0.564
MDS (*vs.* AML)	4.955	0.6026	40.75	**0.137**
Abnormal karyotype	2.31	0.5731	9.31	0.239
Complex karyotype	4.99	0.9075	27.43	**0.0646**
ASXL1	0.9455	0.116	7.709	0.958
BCOR	NA			
>1 *BCOR* mutation	NA			
CALR	NA			
CBL	NA			
CEBPA	NA			
CSF3R	NA			
DDX41	NA			
DNMT3A	NA			
ETV6	NA			
EZH2	NA			
FLT3	NA			
GATA2 (n=2)*	21.98	1.374	351.6	**0.0289**
IDH1	1.356	0.166	11.08	0.776
IDH2	NA			
JAK2 (n=1)*	10.64	0.9642	117.5	**0.0536**
KDM6A	NA			
KIT	NA			
KRAS	NA			
MPL	NA			
NF1	NA			
NPM1	NA			
NRAS	NA			
PHF6	NA			
PTPN11	NA			
RUNX1	0.4589	0.09235	2.28	0.341
SETBP1	NA			
SF3B1	1.584	0.1941	12.92	0.668
SMC3	NA			
SRSF2	NA			
STAG2	0.682	0.08373	5.556	0.721
TET2	NA			
TP53	1.308	0.1603	10.68	0.802
U2AF1	0.979	0.1967	4.873	0.979
WT1	NA			
ZRSR2	2.86	0.342	23.91	0.332
Splice-site	NA			
Frameshift	NA			
Nonsense	NA			
Age ≥ 70 years at diagnosis	1.972	0.2292	16.97	0.536

Hemoglobin ≥ 10 g/dL	0.7768	0.1844	3.273	0.731
Platelets ≥ 100 x 10^9 cells/L	1.093	0.2606	4.582	0.903
Age ≥ 70 years at NGS	0.9644	0.1177	7.903	0.973
High risk co-mutations (by ELN 2017)	0.6535	0.1557	2.743	0.561
HCT-Ci score ≥ 3	1.756	0.4184	7.368	0.442
MRD status before alloSCT	NA			
CR at alloSCT	0.5487	0.1354	2.223	0.401
Melphalan	1.105	0.2751	4.435	0.888
Busulphan	1.436	0.3568	5.776	0.611
TBI	NA			
Cyclophosphamide	0.4391	0.05376	3.586	0.44
RIC	3.241	0.3979	26.4	0.272
Major or bidirectional ABO mismatch	NA			
CMV D-/R+	3.415	0.3493	33.38	0.291
PT-Cy*	3.824	0.8528	17.14	**0.0798**

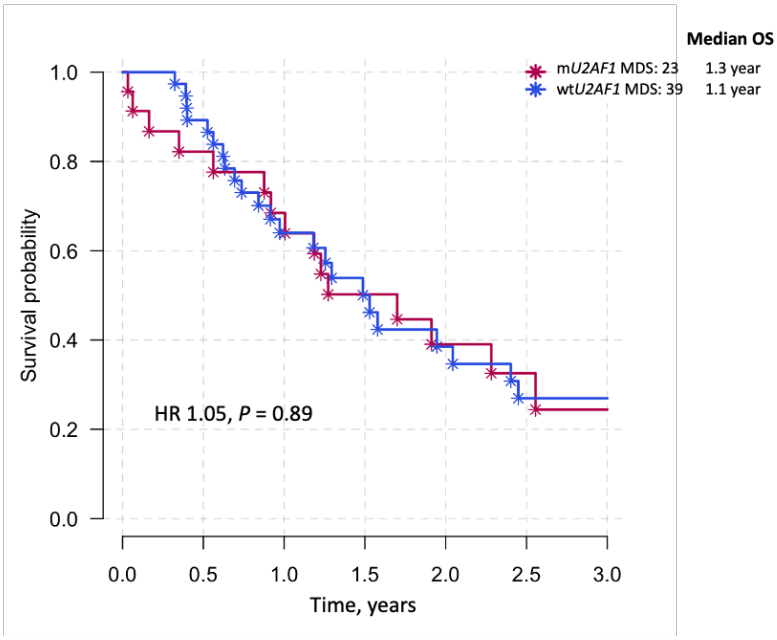
* Not included in multivariate analysis due to small number of cases.

Supplemental Figures

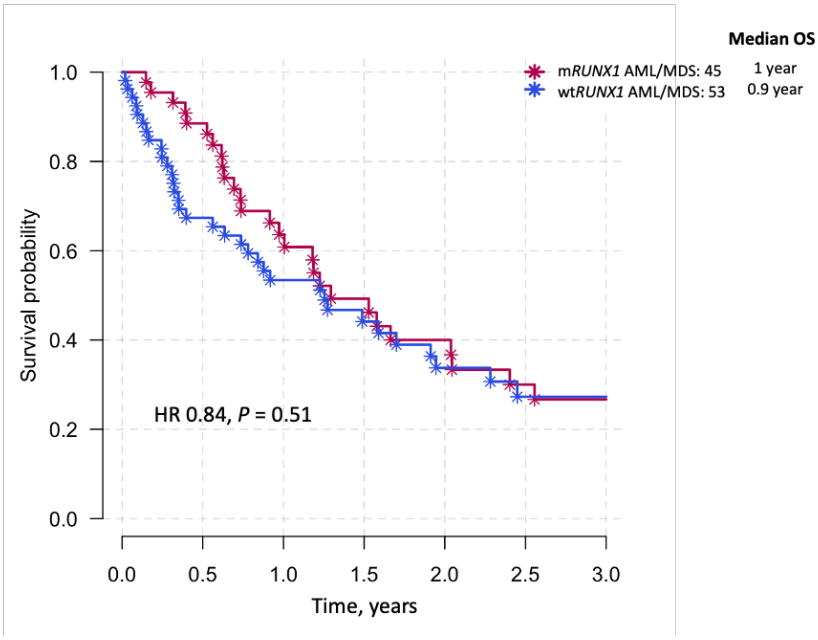


Supplemental Figure 1. Survival analysis of patients with BCOR mutations. A. Survival among patients with mBCOR AML/MDS stratified by AML and MDS subtype. **B.** Survival from NGS among patients with AML stratified by presence/absence of BCOR mutation and ELN 2022 risk stratification. **C.** Survival from diagnosis among patients with AML stratified by presence/absence of BCOR mutation and ELN 2022 risk stratification. **D.** Survival among patients with mBCOR AML/MDS stratified by alloSCT.

S2A

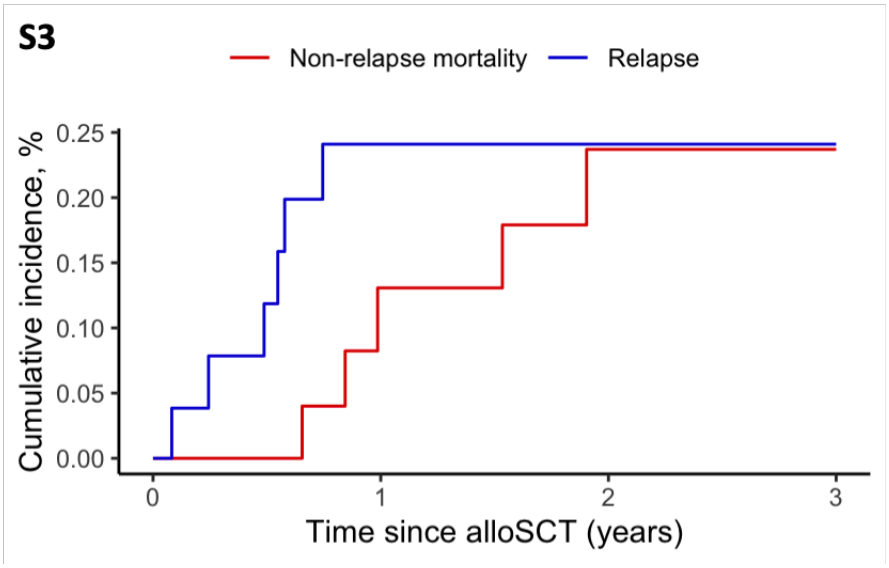


S2B

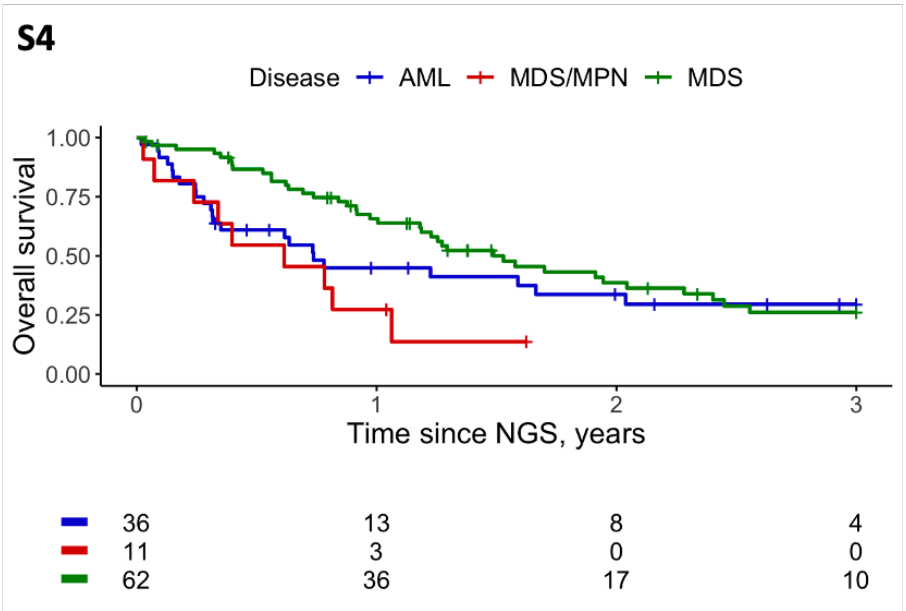


Supplemental Figure 2. Survival among patients with mBCOR stratified by co-mutations.

A. *U2AF1* mutation in m*BCOR* MDS, **B.** *RUNX1* mutation in m*BCOR* AML/MDS.



Supplemental Figure 3. Competing risk analysis for non-relapse mortality and relapse after alloSCT.



Supplemental Figure 4. Survival among patients with m*BCOR* MDS/MPN overlap syndrome compared to m*BCOR* AML and MDS.