Supplementary Table S1. Genes utilized for statistical analyses.

ASXL1	*IDH1*	*NPM1*	*SF3B1*	*ZRSR2*
CBL	*IDH2*	*NRAS*	*SRSF2*	
DNMT3A	*JAK2*	*PHF6*	*TET2*	
ETV6	*KIT*	*RUNX1*	*TP53*	
EZH2	*MPL*	*SETBP1*	*U2AF1*	

Clinical Variable	Median OS (months)	Univariate		Multivariate		
		HR	p-value	HR	95% CI	p-value
Age						
<65 (n = 71)	16.1	0.73	0.14	1.00	0.97-1.02	0.77
>65 (n = 176)	14.1					
Gender						
Male (n = 160)				1.23	0.79-1.91	0.37
Female (n = 87)						
WHO 2016 classification			*0.003	0.99	0.87-1.11	0.80
IPSS-R[#]			*< 0.001			*< 0.001
Very low (n = 15)	NR					
Low (n = 36)	24			1.45	0.39-5.42	0.58
Intermediate (n= 57)	25.8			2.14	0.61-7.52	0.24
High (n = 51)	33.2			2.86	0.83-9.86	0.10
Very High (n = 85)	10.3			6.88	2.05-23.14	0.002
t-MDS						
yes (n = 60)	12.3	1.65	*0.01	1.32	0.81-2.14	0.26
no (n = 187)	17					
ANC						
<1000 (n = 100)	14.2	1.02	0.92			
>1000 (n = 143)	16.1					
Hemoglobin						
<10 (n = 169)	13.7	1.7	*0.01	1.07	0.54-2.11	0.85
>10 (n= 77)	27.9					
Platelets						
<100 (n = 169)	14.1	1.25	0.29			
>100 (n = 77)	18.5					
Number of cytopenias						
0 (n = 16)	35.4					
1 (n = 76)	18.1		*0.03	1.14	0.81-1.61	0.46
2 (n = 100)	12.8					
3 (n = 54)	15					
Bone marrow blast percentage						
<5% (n = 63)	24		0.05	1.08	0.80-1.45	0.61
5-9% (n = 69)	14.4					
≥10% (n = 115)	13.2					
Allo-HCT						
yes (n = 61)	NR	0.35	*<0.001	0.28	0.15-0.52	*<0.001
no (n = 186)	12.4					
Response to HMA						
Response (n = 104)	18.5	0.60	*0.009	0.30	0.20-0.47	*<0.001
No response (n = 143)	12.8					

Supplementary Table S2. Clinical variables predictive of overall survival. Performance of clinical variables as predictors of overall survival, with results of univariate and multivariate analysis displayed. [#]Hazard ratios in multivariate analysis represent comparison of each risk group to the very low risk group. *denotes statistical significance. Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; IPSS-R, revised international prognostic scoring system; NR, not reached; t-MDS, therapy-related MDS; ANC, absolute neutrophil count; Allo-HCT, allogeneic hematopoietic cell transplant; HMA, hypomethylating agent.

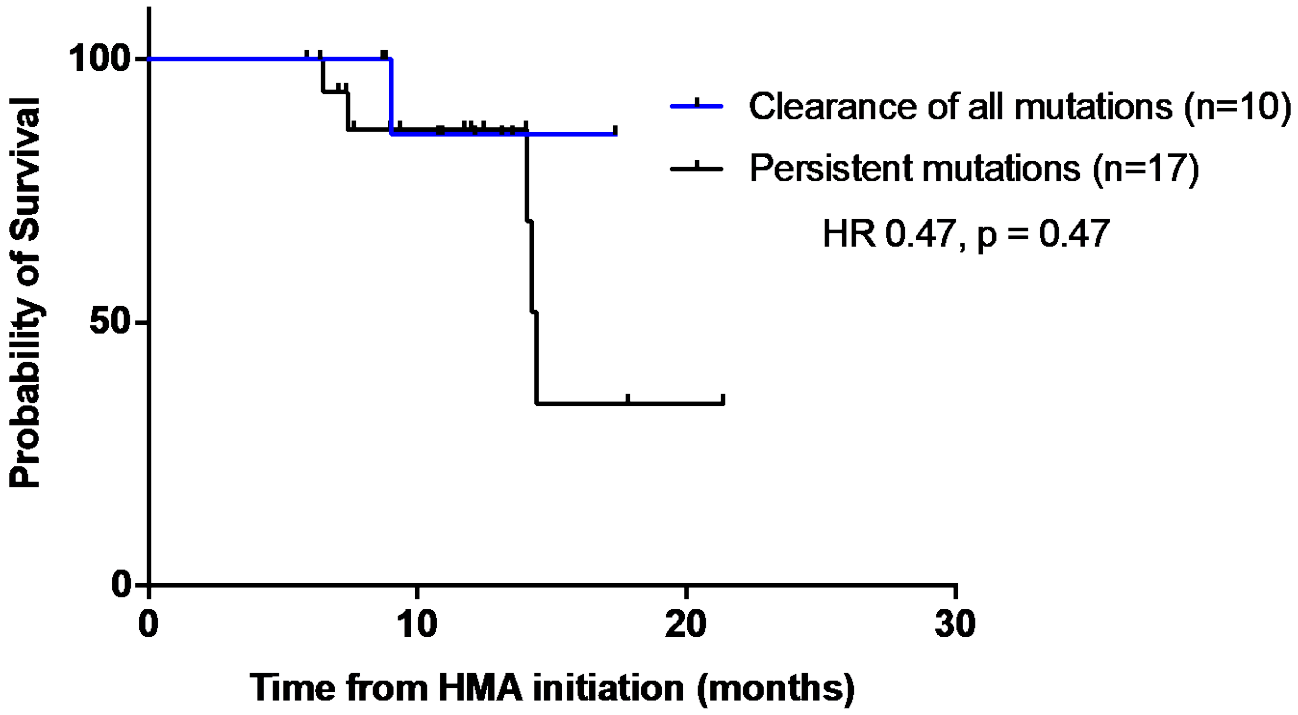
Genotype	CR rate	Univariate	Multivariate		ORR rate	Univariate	Multivariate	
		p-value	OR (95% CI)	p-value		p-value	OR (95% CI)	p-value
Total Cohort (n=165)	12.1%				41.2%			
NGS Result								
No Mutation (n=28)	20.6%	0.21			51.7%	0.22		
≥1 mutation (n=131)	10.8%				39.2%			
TET2								
Mut (n=33)	21.2%	0.07	4.63	*0.02	54.5%	*0.01	1.92	0.12
WT (n=118)	9.3%		(1.31-16.42)		39.0%		(0.84-4.39)	
ASXL1								
Mut (n=44)	4.5%	0.1	0.14	0.09	31.8%	0.16	0.57	0.19
Wt (n=121)	14.9%		(0.02-1.32)		44.6%		(0.24-1.33)	
TET2 Mut/*ASXL1 WT*								
Present (n=21)	33.3%	*0.005	6.51	*0.007	61.9%	0.06	2.3	0.10
Other (n=136)	8.8%		(1.69-25.16)		38.2%		(0.83-6.37)	
DNMT3A								
Mut (n=26)	8.6%	0.31			45.7%	0.85		
WT (n=123)	16.1%				43.0%			
EZH2								
Mut (n=14)	14.3%	0.68			35.7%	0.78		
WT (n=151)	11.9%				41.7%			
DNA Methylation								
Mut (n=63)	11.5%	0.99			50%	0.51		
WT (n=86)	12.2%				41.5%			
Epigenetic Regulation								
Mut (n=100)	13%	>0.99			40%	0.62		
WT (n=57)	12.1%				44.8%			
SF3B1								
Mut (n=11)	9.1%	>0.99			27.3%	0.35		
WT (n=141)	12.8%				44%			
Any Spliceosome								
Mut (n=67)	5.9%	*0.047	0.42	0.19	38.8%	0.51	0.88	0.73
WT (n=84)	16.7%		(0.11-1.55)		45.2%		(0.43-1.80)	
RUNX1								
Mut (n=23)	13%	>0.99			43.5%	0.82		
WT (n=142)	12%				40.8%			
Signaling Pathway								
Mut (n=30)	3.6%	0.20			32.1%	0.29		
WT (n=120)	13.8%				44.7%			

Supplementary Table S3. Molecular predictors of response in the *TP53* wild-type cohort. Summarizes the impact of somatic gene mutations and specific genotypes on overall response rate and complete remission rate. *denotes statistical significance. Abbreviations: CR, complete remission; ORR, overall response rate; OR, odds ratio; CI, confidence interval; NGS, next generation sequencing; Mut, mutant; WT, wild-type.

Genotype	Median OS (months)	Univariate		Multivariate		
		HR	p-value	HR	95% CI	p-value
Total Cohort (n=165)	21.7					
NGS Result						
No Mutation (n=28)	24	0.63	0.18			
≥1 mutation (n=131)	18.6					
Number of Mutations			*0.03	1.16	0.98-1.38	0.08
TET2						
Mut (n=33)	18.6	0.96	0.9			
WT (n=118)	21.7					
ASXL1						
Mut (n=44)	18.6	1.2	0.48			
Wt (n=121)	21.7					
TET2 Mut/*ASXL1* WT						
Present (n=21)	16.1	0.76	0.77			
Other (n=136)	21					
DNMT3A						
Mut (n=26)	12.9	1.6	0.17			
WT (n=123)	19.1					
EZH2						
Mut (n=14)	11.4	4.4	*<0.001	2.30	1.05-5.07	*0.04
WT (n=151)	24					
DNA Methylation Mutation						
Mut (n=63)	17	1.2	0.57			
WT (n=86)	21.7					
Epigenetic Regulation Mutation	17	1.55	0.12			
Mut (n=100)	21.7					
WT (n=57)						
SF3B1						
Mut (n=11)	21	1.06	0.91			
WT (n=141)	19.1					
Any Spliceosome						
Mut (n=67)	21	0.98	0.94			
WT (n=84)	18.1					
RUNX1						
Mut (n=23)	12.4	1.66	0.14			
WT (n=142)	23.8					
Signaling Pathway						
Mut (n=30)	16.1	1.4	0.29			
WT (n=120)	21					

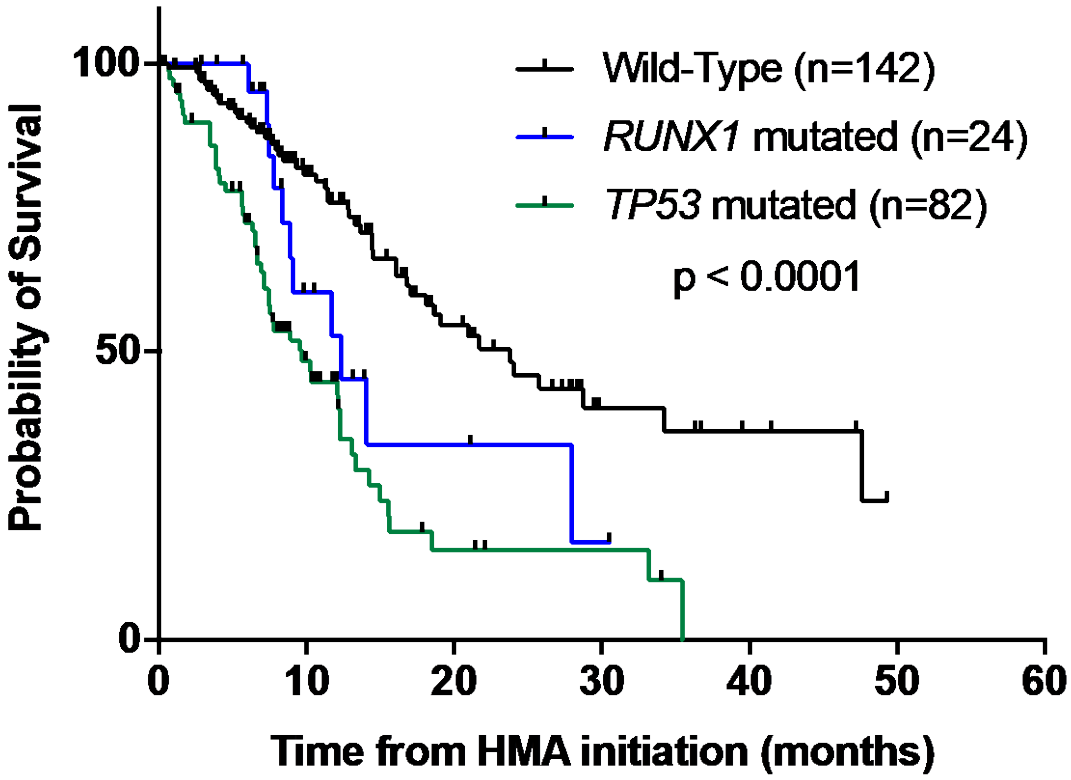
Supplementary Table S4. **Molecular predictors of overall survival in the *TP53* wild-type cohort.** Summarizes the impact of various somatic gene mutations and genotypes on overall survival in the cohort restricted to *TP53* wild-type patients. *denotes statistical significance. Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; NGS, next generation sequencing; Mut, mutant; WT, wild-type.

Supplementary Figure S1. Impact of mutation clearance on overall survival in patients proceeding to allo-HCT



Supplementary Figure S1. Overall survival of all patients who underwent serial molecular analysis prior to proceeding to allo-HCT. Patients who demonstrated complete clearance of all prior detectable mutations with frontline HMA therapy (median OS not reached) are compared to those who had persistent mutations detected (median OS of 14.4 months). Abbreviation: allo-HCT, allogeneic hematopoietic cell transplant.

Supplementary Figure S2. Overall survival by *TP53* and *RUNX1* genotype



Supplementary Figure S2. Overall survival of patients stratified by both *TP53* and *RUNX1* mutation status. Median OS of 23.8 months for wild-type patients, 12.4 months for *RUNX1* mutated patients and 9.7 months for *TP53* mutated patients.