

SUPPLEMENTARY DATA

Supplemental Table 1: Treatment protocols

Regimen	
INTENSIVE	
Daunorubicin + araC	Daunorubicin* 60 mg/m ² IV day (d) 1-3; AraC 200 mg/m ² (100 mg/m ² for patients ≥ 60 years old). continuous infusion on d 1-7
FLAG-IDA	(fludarabine 30 mg/m ² IV & AraC 2000 mg/m ² IV day 15; idarubicin 10 mg/m ² IV d1-3; granulocyte-colony stimulating agent SC d1-6
NOVE-HIDAC	Mitoxantrone* 10 mg/m ² IV & etoposide 100 mg/m ² d1-5; AraC 1000-1500 mg/m ² every 12 hours for d1-2)
NONINTENSIVE	
Azacitidine	75 mg/m ² SC d1-6
Decitabine	7.5 mg/m ² IV twice daily d1-5
Azacitidine + Venetoclax	75 mg/m ² SC d1-6 or d1-7 and venetoclax 400mg daily d1-28. Dose modifications occurred for drug interactions and cytopenias

araC=cytarabine arabinoside; d=days; IV=intravenous; SC=subcutaneous

*in patients with left ventricular ejection fraction <50%, amascarine was used in lieu of anthracycline

Supplemental Table 2: Univariate analysis for treatment failure in intensively treated patients

Variable (%)	Odds Ratio (95% CI, p value)	P-Value	Global P-value
Age at transformation	1.01 (0.96, 1.06)		0.78
Sex			0.99
Female	Reference		
Male	0.99 (0.35, 2.89)		
Transformation Type			0.93
AP	Reference		
BP	1.08 (0.20, 7.72)		
MPN Diagnosis			0.77
PV/ET	Reference		
MPN-U	2.38 (0.46, 12.5)	0.29	
PMF	1.58 (0.36, 7.41)	0.54	
PPV/PET-MF	1.43 (0.35, 6.33)	0.62	
Number of prior treatments (N=80)			0.54
0-1	Reference		
≥2	1.39 (0.47, 3.96)		
ECOG (N=74)			0.009
0-1	Reference		
≥2	10.4 (1.81, 78.4)		
Spleen Size (N=71)			0.06
Not palpable	Reference		
< 10cm BCM	0.81 (0.15, 3.90)	0.80	
≥10cm BCM	1.06 (0.25, 4.4)	0.94	
Splenectomy	9.50 (1.56, 82.4)	0.02	
Laboratory Parameters†, median (range) [number]			
Hb, g/L (N=77)	0.97 (0.94, 1.00)		0.10
WBC, x 10 ⁹ /L (N=79)	1.00 (0.99, 1.01)		0.91
ANC, x 10 ⁹ /L (N=70)	1.00 (0.98, 1.03)		0.54

Platelets, x 10 ⁹ /L (N=78)	1.00 (0.999, 1.00)		0.66
PB blasts, % (N=78)	1.01 (0.99, 1.03)		0.32
BM blasts, % (N=67)	1.00 (0.98, 1.03)		0.66
LDH, U/L (N=74)	1 (1, 1)		0.08
Albumin, g/L (N=74)	0.94 (0.84, 1.04)		0.23
ELN RISK (N=69)			0.11
Non-adverse	Reference		
Adverse	2.6 (0.83, 9.12)		
Driver Mutations (N=53)			0.31
<i>JAK2/MPL</i>	Reference		
<i>CALR</i>	3.9 (0.62, 24.0)	0.13	
Triple Negative	1.89 (0.40, 8.54)	0.40	
Mutations grouped by pathway (N=53)			
JAK-STAT pathway			0.66
No	Reference		
Yes	0.73 (0.19, 3.19)		
RAS pathway			0.03
No	Reference		
Yes	5.14 (1.16, 23.7)		
RNA Splicing			0.25
No	Reference		
Yes	2.21 (0.55, 8.61)		
Epigenetic Regulation			0.45
No	Reference		
Yes	1.73 (0.44, 8.71)		
Transcription regulation			0.11
No	Reference		

Yes	0.18 (0.009, 1.04)		
Cell Cycle Checkpoint (TP53)			0.004
No	Reference		
Yes	8.17 (2.01, 37.1)		
Number of Mutations (N=98)			0.52
0-1	Reference		
2-3	1.11 (0.18, 9.04)	0.91	
≥	2.31 (0.38, 18.1)	0.36	

Unless otherwise stated N=81

Supplemental Table 3: Univariate analysis for treatment failure in non-intensively treated patients

Variable (%)	Odds Ratio (95% CI, p value)	P-Value	Global P-value
Age at transformation	1.01 (0.95, 1.07)		0.86
Sex			0.60
Female	Reference		
Male	0.72 (0.19, 2.44)		
Transformation Type			0.05
AP	Reference		
BP	3.07 (1.00, 9.92)		
MPN Diagnosis			0.75
PV/ET	Reference		
MPN-U	0.36 (0.01, 4.77)	0.45	
PMF	1.43 (0.29, 7.12)	0.66	
PPV/PET-MF	1.19 (0.28, 4.92)	0.81	
Number of prior treatments (N= 54)			0.11
0-1	Reference		
≥2	2.5 (0.83, 7.97)		
ECOG (N=49)			0.02
0-1	Reference		
≥2	12 (2.04, 230.3)		
Spleen Size (N=52)			0.17
Not palpable	Reference		
< 10cm BCM	2.25 (0.55, 10.4)	0.27	
≥10cm BCM	3.33 (0.77, 18.0)	0.12	
Splenectomy	0.33 (0.02, 3.1)	0.37	
Laboratory Parameters†, median (range) [number]			
Hb, g/L (N=52)	0.97 (0.93, 1.00)		0.04
WBC, x 10 ⁹ /L (N=52)	0.99 (0.97, 1.01)		0.39
ANC, x 10 ⁹ /L (N=50)	0.97 (0.91, 1.01)		0.23

Platelets, x 10 ⁹ /L (N=52)	1.00 (1.00, 1.00)		0.73
PB blasts, % (N=53)	1.06 (1.01, 1.12)		0.04
BM blasts, % (N=43)	1.02 (0.99, 1.05)		0.24
LDH, U/L (N=50)	1 (1, 1)		0.40
Albumin, g/L (N=47)	0.95 (0.82, 1.09)		0.47
ELN RISK (N=49)			0.48
Non-adverse	Reference		
Adverse	1.56 (0.45, 5.34)		
Driver Mutations (N=45)			0.78
<i>JAK2/MPL</i>	Reference		
<i>CALR</i>	0.55 (0.06, 5.01)	0.57	
Triple Negative	1.36 (0.25, 10.53)	0.73	
Mutations grouped by pathway (N=45)			
JAK-STAT pathway			0.45
No	Reference		
Yes	0.42 (0.02, 3.15)		
RAS pathway			0.67
No	Reference		
Yes	1.35 (0.35, 5.87)		
RNA Splicing			0.77
No	Reference		
Yes	0.83 (0.24, 2.84)		
Epigenetic Regulation			0.99
No	Reference		
Yes	1.01 (0.26, 3.76)		
Transcription regulation			0.65
No	Reference		

Yes	1.34 (0.37, 4.91)		
Cell Cycle Checkpoint (TP53)			0.50
No	Reference		
Yes	1.83 (0.36, 13.7)		
Number of Mutations (N=98)			0.76
0-1	Reference		
2-3	1.6 (0.15, 17.3)	0.68	
≥4	2.11 (0.22, 20.05)	0.49	

Unless otherwise stated N=54

Supplemental Table 4: HCT following initial blast reduction strategy

Variable	Regimen					
	Daunorubicin + AraC (N=31)	HD-Ara-C (N=50)	p	HMA N=36	AV N=18	p
HCT Eligible (per study criteria: age <71 with response to initial treatment)						
Yes	21 (68)	38 (76)	0.45	6 (17)	5 (28)	0.48
No	10 (32)	12 (24)		30 (83)	13 (72)	
HCT performed in eligible patients						
Yes	10 (46)	22 (58)	0.59	4 (67)	5 (100)	0.46
No	11 (52)	16 (42)		2 (33)	0	
Why No HCT done	N=11	N=16		N=2	N=0	
No Donor	1 (9)	0	--	0	--	--
Patient Preference	1 (9)	0		1 (50)		
Comorbidity	1 (9)	2 (13)		1 (50)		
Relapse	6 (55)	13 (81)		0		
Death	0	1 (6)		0		
Unknown	2 (18)	0		0		
Time to HCT*, days (range)	152.5 (84-455)	144 (54-358)	0.35	126 (51-233)	101 (73-260)	1.00

*from treatment start

Supplemental Table 5: Univariate analysis for overall mortality

Variable	HR (95%CI)	p-value	Global p-value
Overall Best Response (N=135)			<0.001
Response	Reference		
Non-response	2.77 (1.88, 4.07)		
Treatment intensity			0.93
Non-Intensive	Reference		
Intensive	1.02 (0.69, 1.49)		
Sex			0.74
Female	Reference		
Male	1.07 (0.73, 1.56)		
Age at transformation	1.01 (0.997, 1.03)		0.10
Transformation Type			0.002
AP	Reference		
BP	2.12 (1.33, 3.40)		
MPN Diagnosis			0.96
PV/ET	Reference		
MPNU	1.10 (0.57, 2.13)	0.78	
PMF	1.15 (0.69, 1.93)	0.59	
PPV/PETMF	1.12 (0.69, 1.81)	0.65	
Number of prior treatments (N=137)			0.06
0-1	Reference		
≥2	1.43 (0.99, 2.07)		
ECOG (N=125)			<0.001
0-1	Reference		
≥2	3.53 (2.10, 5.95)		
Spleen Size (N=125)			0.24
Not palpable	Reference		
<10cm	1.07 (0.64, 1.78)	0.80	
≥10cm	1.25 (0.78, 2.00)	0.36	
Splenectomy	2.13 (1.05, 4.31)	0.04	
Hb, g/L (N=132)	0.98 (0.97, 0.99)		<0.001
WBC, x 10⁹/L (N=134)	1.00 (1.00, 1.01)		0.40

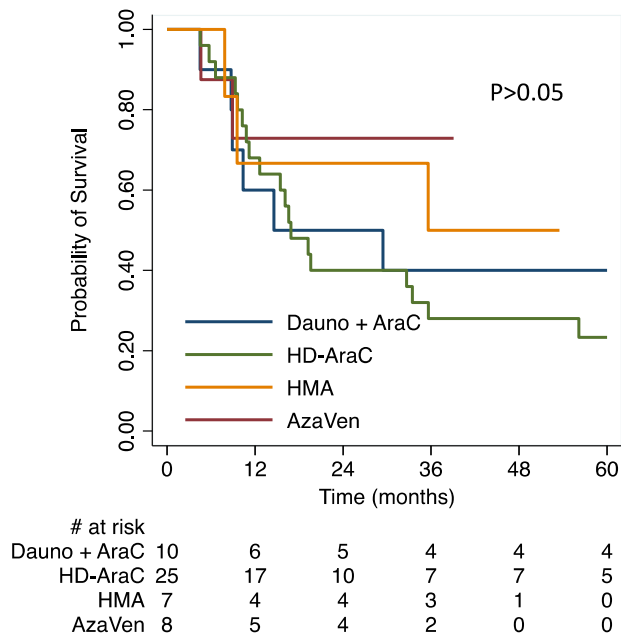
Variable	HR (95%CI)	p-value	Global p-value
ANC , x 10 ⁹ /L (N=123)	1.00 (0.99, 1.01)		0.89
Platelets , x 10 ⁹ /L (N=133)	1.00 (1.00, 1.00)		0.004
PB blasts , % (N=134)	1.01 (1.01, 1.02)		0.002
BM blasts , % (N=113)	1.01 (1.00,1.02)		0.002
LDH , U/L (N=127)	1.00 (1.00,1.00)		0.13
Albumin , g/L (N=124)	0.95 (0.91, 0.99)		0.02
ELN RISK (N=121)			0.004
Non-adverse	Reference		
Adverse	1.86 (1.22, 2.84)		
Driver Mutations (N=101)			0.91
<i>JAK2/MPL</i>	Reference		
<i>CALR</i>	0.86 (0.42, 1.76)	0.68	
Triple Negative	1.01 (0.61, 1.68)	0.96	
Mutations by pathway (N=101)			
JAK-STAT pathway			0.98
No	Reference		
Yes	1.01 (0.60, 1.68)		
Checkpoint (<i>TP53</i>)			0.001
No	Reference		
Yes	2.42 (1.42, 4.12)		
RAS pathway			0.01
No	Reference		
Yes	1.92 (1.15, 3.22)		
RNA Splicing			0.33
No	Reference		
Yes	1.24 (0.80, 1.91)		
Epigenetic Regulation			0.46
No	Reference		
Yes	1.19 (0.75, 1.88)		
Transcription regulation			0.34
No	Reference		
Yes	1.25 (0.79, 1.99)		
Number of Mutations (N=101)			0.040

Variable	HR (95%CI)	p-value	Global p-value
0-1	Reference		
2-3	1.74 (0.88, 3.44)		
≥4	2.27 (1.15, 4.49)		

Unless otherwise specified observations = 138

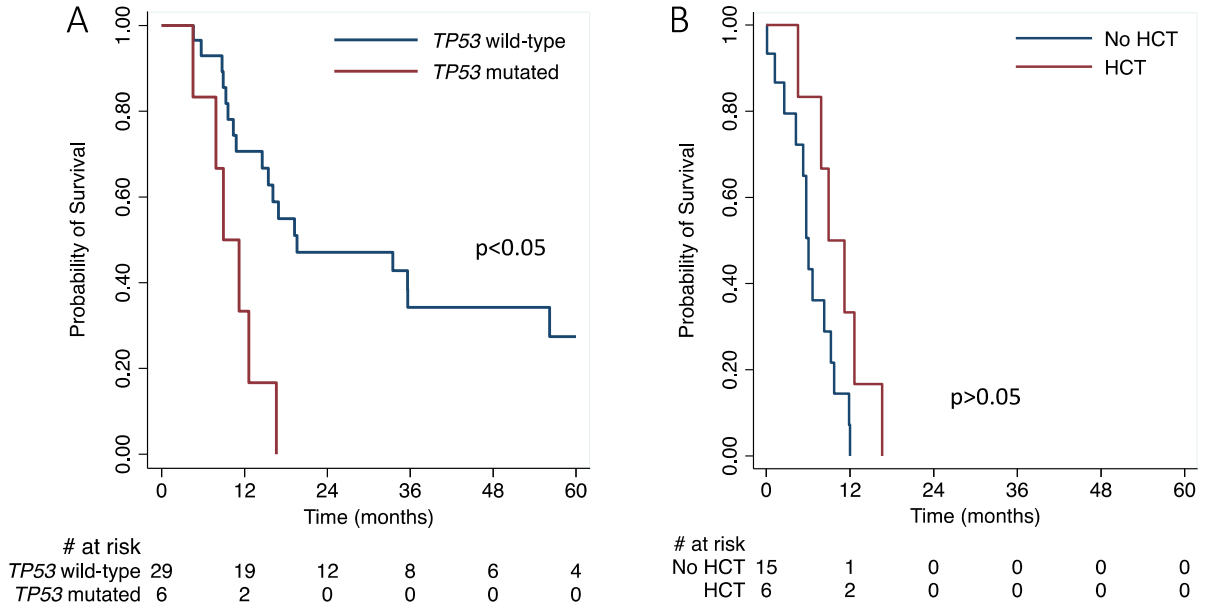
SUPPLEMENTAL FIGURES

Supplemental Figure 1: Kaplan-Meier survival analysis among transplanted patients treated with different blast reduction strategies. Comparison of OS among transplanted patients treated with different pre-transplant blast-reduction strategies.







































Supplemental Figure 2: Kaplan-Meier survival analysis among *TP53* mutated patients.

(A) Survival in all transplanted patients by *TP53* mutation status. (B) Kaplan-Meier survival analysis among *TP53* mutated patients by HCT status. See text for disease status at the time of transplantation.



Supplemental Figure 3: Clearance of AP/BP variants following allogeneic stem cell transplant. Sequential NGS analysis comparing mutations present at MPN-AP/BP diagnosis, following blast reduction therapy and following stem cell transplant is displayed. VAF: Variant allele frequencies (%); NA: sample not available for analysis.

MF #	BP treatment	Response	Gene	Amino acid change	VAF at diagnosis	VAF post-BP treatment	VAF post-transplant	Post-transplant molecular response
MF171	FLAG-IDA	CRi	DNMT3A	p.Arg82His				Clearance
			IKZF1	p.Glu221Serfs*36				
			JAK2	p.Val617Phe				
			NRAS	p.Gly12Asp				
			RUNX1	p.Ser141*				
			RUNX1	p.Asp1981yr				
TP53	p.Arg175His							
MF090	FLAG-IDA	CR	IDH1	p.Arg132His				Clearance
			JAK2	p.Val617Phe				
MF301	Aza-Ven	cMPN	ASXL1	p.Ser1027Ilefs*7				Clearance
			IDH2	p.Arg140Gln				
			MPL	p.Trp515Leu				
			RUNX1	p.Asn139Asp				
			RUNX1	p.Gly641Leufs*74				
			SRSF2	p.Pro95His				
			STAG2	(p.Leu813*				
TET2	p.Ile1873Ihr							
MF224	HMA then FLAG-IDA	cMPN	ASXL1	p.Ser767Profs*5				Clearance
			DNMT3A	p.Ser775Pro				
			JAK2	p.Val617Phe				
MF296	FLAG-IDA	CRi	JAK2	p.Val617Phe		NA		Clearance
			RUNX1	p.Met133_Asn139del		NA		
			TP53	p.?		NA		

