Are somatic mutations predictive of response to erythropoiesis stimulating agents in lower risk myelodysplastic syndromes?

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For the GFM, FISM AND D-MDS

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Supplemental data:

Table legends

Sup Table 1. Baseline patient characteristics.

Sup Table 2. Response rate by gene mutations. OR: odds ratio. . *List of genes analyzed: ASXL1, ATRX, BCOR, BCORL1, BRAF, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KDM6A, KIT, KRAS, NRAS, PHF6, PTPN11, RAD21, RHOA, RIT1, RUNX1, SETBP1, SF3B1, SRSF2, STAG1, STAG2, STAT3, TET2, TP53, U2AF1, WT1, ZRSR2*.

Sup table 1. Baseline patient characteristics.

	n	%
Gender		
female	35	0.44
Age		
>75Y	33	0.42
WHO classification		
RA	17	0.22
RARS	19	0.24
RCMD	21	0.25
RAEB1	18	0.23
DEL5Q	2	0.03
MDS-U	2	0.03
Cytogenetics (IPSS)		
FAVORABLE	19	0.24
INTERMEDIATE	27	0.34
NORMAL	31	0.39
NA	2	0.03
IPSS		
LOW	35	0.45
INT-1	42	0.53
NA	2	0.02
IPSS-R		
VERY LOW	5	0.06
LOW	46	0.58
INT	26	0.33
NA	2	0.02
Marrow dysplastic features		
Dyserythropoiesis	67	0.85

Dysgranulopoiesis	49	0.62
Dysmegakaryopoiesis	53	0.67
Multilineage dysplasia	54	0.68
Serum EPO (U/l) median (range)	59 (9-402)	
<100	55	0.7
Serum ferritin (ng/ml) median (range)	407 (11-1876)	
<400	37	0.47
RBC Transfusion dependency		
yes	21	0.26
no	59	0.74

Sup Table 2. Response rate by gene mutations.

gene mutation	number of mutations	number of mutated patients (% of response)	number of wild type patients (% response)	OR	p Fisher's test
SF3B1	32	32 (56)	47 (68)	0.54[0.21-1.39]	0.24
TET2	29	24 (62)	55 (66)	0.88 [0.33-2.38]	0.80
ASXL1	22	22 (61)	57 (66)	0.79 [0.31-2.02]	0.63
DNMT3A	17	16 (50)	63 (65)	0.46 [0.15-1.42]	0.24
RUNX1	10	10 (60)	69 (65)	0.8 [0.21-3.11]	0.73
STAG2	9	9 (56)	70 (65)	0.65 [0.16-2.65]	0.71
U2AF1	8	8 (75)	71 (63)	1.73 [0.32-9.22]	0.70
SRSF2	7	7 (57)	72 (65)	0.71 [0.14-3.42]	0.69
CBL	5	4 (75)	75 (64)		
IDH1	2	2 (0)	77 (68)		
IDH2	3	3 (0)	76 (68)		
IDH1/IDH2	5	4 (0)	75 (68)		
EZH2	4	3 (66)	76 (65)		
RAS (N and K)	4	4 (50)	75 (66)		
ZRSR2	2	2 (100)	77 (63)		
JAK2	1	1 (100)	78 (64)		
PTPN11	1	1 (0)	78 (65)		
BCOR	1	1 (0)	78 (65)		
PHF6	1	1 (0)	78 (65)		
KDM6	1	1 (0)	78 (65)		
TP53	1	1 (100)	78 (64)		
DNA methylation (TET2, IDH1/2, DNMT3A)		42 (59)	37 (70)	0.62 [0.24-1.58]	0.32

Chromatin modifiers (ASXL1, EZH2, KDM6)	24 (54)	55 (69)	0.62 [0.20-1.42]	0.21
Splicing factors (SF3B1, SRSF2, U2AF1, ZRSR2)	51 (65)	28 (64)	1.0 [0.39-2.67]	0.97
Transcription factors (RUNX1, TP53, BCOR, PHF6)	13 (54)	66 (67)	0.58 [0.17-1.95]	0.38
Signaling pathways (NRAS, CBL, JAK2, PTPN11)	10 (60)	69 (65)	0.8 [0.20-3.11]	0.75

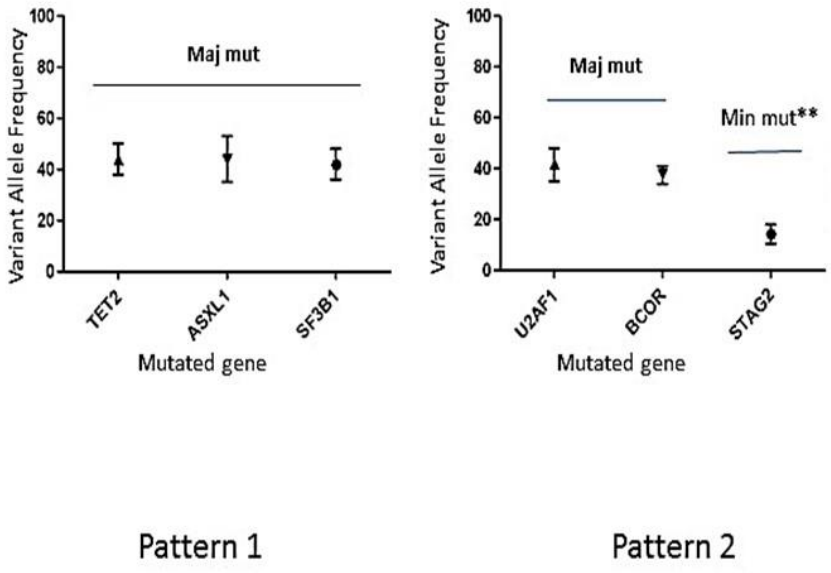
Figures legends

Sup Figure 1. Patterns of clonal evolution. Patients were classified in 2 patterns.

The comparison of the VAF of each mutated gene in each individual reveals 2 types of clonal patterns. For every VAF mutation, depth was considered to calculate 95% confidence intervals calculated using a Wilson test based on binomial distribution. In patients harboring at least 2 mutations, the clonal heterogeneity was evaluated by χ^2 test to determine if the VAF were significantly different or not. In the former situation, the mutations with significantly higher VAF were considered as major (major mut), and the other ones as minor (minor mut). In patients with only one mutation, this mutation was considered as major by the absence of other mutations among the genes tested. 45 patients had only one major clone containing 1 to 5 major mutations (pattern 1), 34 had a major subclone and one or two minor subclones (pattern 2).

Sup Figure 2A, 2B, 2C. Impact on OS of **2A)** the number of mutations (>2 (blue line) or <=2(red line)), **2B)** the number of mutations (from 0 to 6), **2C)** IPSS-R.

Sup Fig 1.



Sup Fig 1.

Sup Figure 2A, 2B, 2C. Impact on OS of **2A)** the number of mutations (>2 (blue line) or <=2(red line)), **2B)** the number of mutations (from 0 to 6), **2C)** IPSS-R.

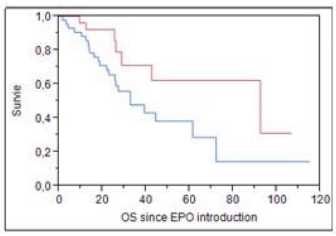


Fig S1A. P=0.04

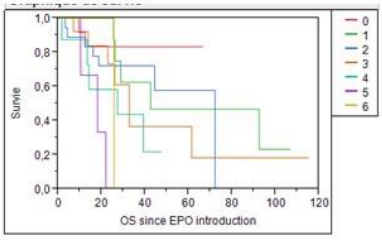


Fig S1B. P=0.01

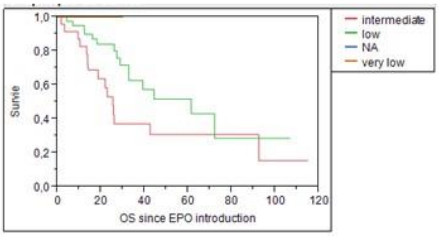


Fig S1C. P=0.09