Validation and molecular integration of the RR6 model to predict survival after 6 months of therapy with ruxolitinib

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Supplemental Table 1. Results of univariate and multivariate Cox proportional hazards model of OS for RR6 model and genetic variables

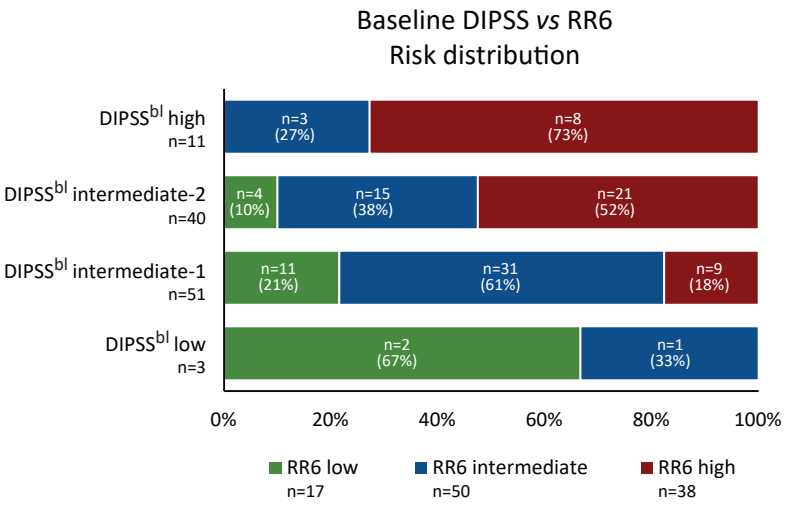
	Univariate		Multivariate	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
RR6 model				
Low risk	Reference		Reference	
Intermediate risk	1.7 (0.7-4.3=	.2	1.4 (0.5-3.5)	.5
High risk	4.9 (2.0-12.2)	**.0005**	4.4 (1.7-11.1)	**.0020**
MPN drivers				
JAK2 mutated; n (%)	0.8 (0.4-1.4)	.4		
JAK2^{V617F} AB; median (range); evaluable=81	-	.1		
CALR mutated; n (%)	1.3 (0.6-2.6)	.5		
MPL mutated; n (%)	0.3 (0-2.4)	.3		
Myeloid neoplasm-associated genes				
ASXL1 mutated; n (%); evaluable=103	1.7 (1-2.9)	**.0447**		
CBL mutated; n (%); evaluable=100	2.9 (0.7-12.1)	.1		
CSF3R mutated; n (%); evaluable=86	-	-		
CUX1 mutated; n (%); evaluable=79	-	-		
DNMT3A mutated; n (%); evaluable=99	0.9 (0.1-6.2)	.9		
EZH2 mutated; n (%); evaluable=103	1.5 (0.6-3.4)	.4		
IDH1/2 mutated; n (%); evaluable=103	2.2 (0.5-9.3)	.3		
KIT mutated; n (%); evaluable=98	-	-		
KRAS mutated; n (%); evaluable=97	1.5 (0.6-3.7)	.4		
NF-E2 mutated; n (%); evaluable=90	0.8 (0.3-2)	.6		
NRAS mutated; n (%); evaluable=97	1.8 (0.9-3.9)	.1		
PTPN1 mutated; n (%); evaluable=86	0.9 (0.2-3.6)	.8		
RUNX1 mutated; n (%); evaluable=98	2 (0.8-5.1)	.1		
SETBP1 mutated; n (%); evaluable=86	5 (0.7-38)	.1		
SF3B1 mutated; n (%); evaluable=99	0.4 (0.1-1.6)	0.2		
SH2B3/LNK mutated; n (%); evaluable=99	2 (0.9-4.3)	.1		
SRSF2 mutated; n (%); evaluable=103	2.9 (1.2-7.4)	**.0237**		
TET2 mutated; n (%); evaluable=100	1.1 (0.6-2)	.7		
TP53 mutated; n (%); evaluable=98	-	-		
U2AF1 mutated; n (%); evaluable=99	1.7 (0.2-12.5)	.6		
ZRSR2 mutated; n (%); evaluable=86	1.8 (1.8-3.8)	.8		
HMR mutations[†]; n (%); evaluable=103	2.2 (1.3-3.7)	**.0048**	2.5 (1.4-4.6)	**.0023**
≥2 HMR mutations; n (%); evaluable=103	1.7 (0.8-3.7)	.2		
≥1 RASp mutation[‡]; n (%); evaluable=99	3.4 (1.4-8.2)	**.0064**	6.1 (2.2-17)	**.0005**
Cytogenetics				
Conventional two-tiered cytogenetic; evaluable=92				
Favorable karyotype; n (%)	Reference		Reference	
Unfavorable karyotype; n (%)	2.1 (1.1-4.2)	**.0263**	3.2 (1.5-6.7)	**.0019**
Revised three-tiered cytogenetic; evaluable=92				
Favorable karyotype; n (%)	Reference			
Unfavorable karyotype; n (%)	1.5 (0.8-2.8)	.2		
Very high risk karyotype; n (%)	2.5 (0.7-8.2)	.1		

Notes: [†]HMR mutations include pathogenic variants in any of the following genes: *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SRSF2* or *U2AF1*; ≥2 HMR mutations indicates the presence of 2 or more mutations (2 or more mutations in the same gene are counted as 1). [‡]RAS pathway mutations include pathogenic variants in any of the following genes: *NRAS*, *KRAS*, and *CBL*.

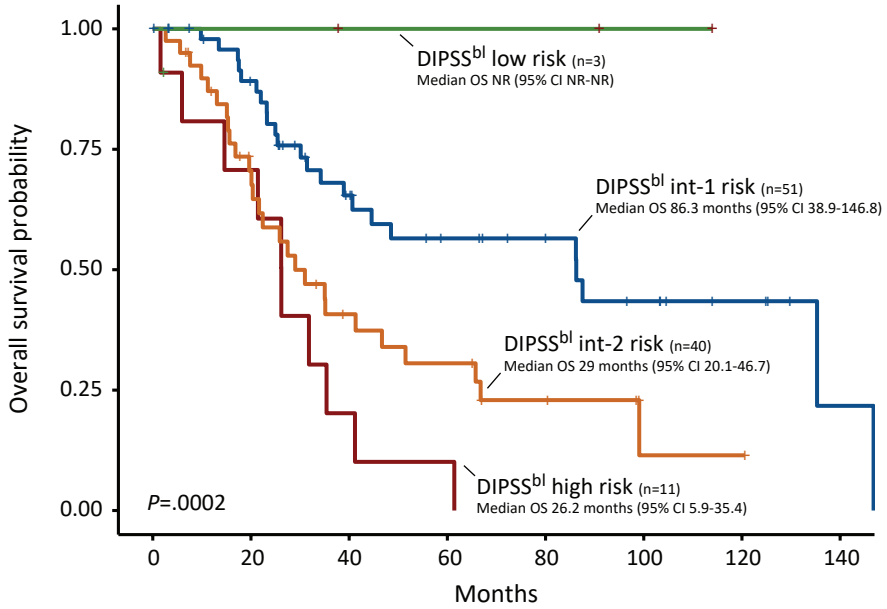
Abbreviations: AB: allele burden; HMR: high molecular risk mutation; MPN: myeloproliferative neoplasm; RASp: RAS pathway; RR6: Response to Ruxolitinib After 6 Months.

Supplemental Figure 1

A



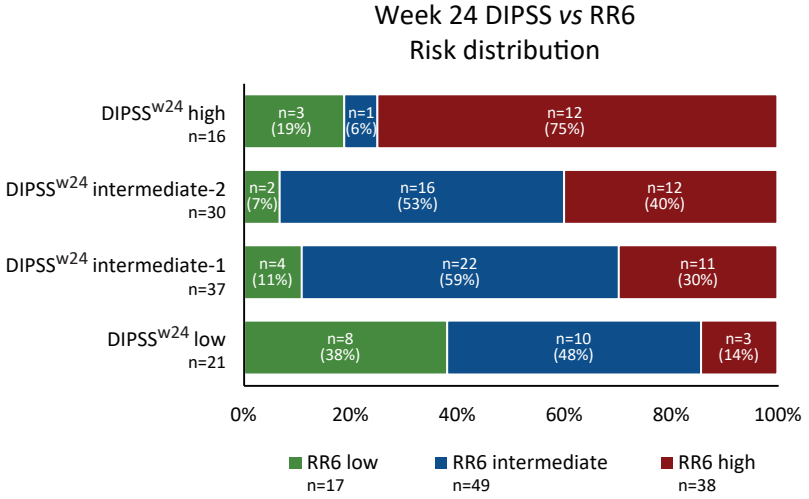
B



Number at risk

DIPSS^bl low risk	3	3	2	2	2	1	0	0
DIPSS^bl intermediate-1 risk	51	40	24	17	14	9	5	1
DIPSS^bl intermediate-2 risk	40	24	12	9	5	1	1	0
DIPSS^bl high risk	11	7	2	1	0	0	0	0

C



Supplemental Figure 1. Patient distribution and overall survival according to the RR6 and DIPSS models. **A**. Cross table illustrating risk distribution of patients across the RR6 model and $DIPSS^{bl}$. **B.** Kaplan-Meier estimates of overall survival in ruxolitinib-treated patients according to $DIPSS^{bl}$. **C.** Cross table illustrating risk distribution of patients across the RR6 model and $DIPSS^{w24}$. *Abbreviations*: CI: confidence interval; $DIPSS^{bl}$: Dynamic International Prognostic Scoring System at baseline; $DIPSS^{w24}$: Dynamic International Prognostic Scoring System at week 24; NR: not reached; OS: overall survival; RR6: Response to Ruxolitinib After 6 Month.

Supplemental Figure 2

Comparison of the prognostic performance of RR6 model and its integration with high molecular risk signatures in transplant-age patients (<70 years)									
		Events at 12 months		Events at 24 months		Events at 36 months		Events at 48 months	
	C-index	Brier score	AUC	Brier score	AUC	Brier score	AUC	Brier score	AUC
RR6	67.3	0.021	77.1	0.052	79.2	0.084	70.8	0.106	78.7
HMR^{mt†}	60.6	0.022	59.2	0.056	64.8	0.090	64.2	0115	66.6
RASp^{mt‡}	50.4	0.022	45.7	0.058	48.3	0.097	51.3	0.127	51.6
RR6+HMR^{mt}	70.8	0.021	80.0	0.052	85.2	**0.082***	75.1	**0.102***	**82.2***
RR6+RASp^{mt}	67.0	0.021	78.1	0.052	78.8	0.084	69.6	0.106	77.7
RR6+HMR^{mt}+RASp^{mt}	**71.0***	0.021	**80.6***	0.052	**85.6***	**0.082***	**75.2***	**0.102***	81.9

Supplemental Figure 2. Comparison of the prognostic performance of RR6 model and its integration with high molecular risk signatures in a cohort of 116 transplant-age patients (≤70 years). *Notes:* Asterisk and bold indicate the best values. †HMR mutations include pathogenic variants in any of the following genes: *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SRSF2* or *U2AF1*. ‡RAS pathway mutations include pathogenic variants in any of the following genes: *NRAS*, *KRAS* or *CBL*. *Abbreviations:* AUC: area under the curve; HMR^{mt}: high molecular risk mutation; $RASp^{mt}$: RAS pathway mutation; RR6: Response to Ruxolitinib After 6 Month.