Supplementary Data

"AMG 925, a FLT3/CDK4 dual inhibitor for treating AML"

Table S1. Selectivity profile of AMG 925 (K_d for kinases with POC < 20 at 1 μM in KenomScan)

Kinase	K_d (nM)	Kinase	K_d (nM)	Kinase	K_d (nM)	Kinase	K_d (nM)
TTK/Mps-1	0.17	CSNK2A1	7.5	CSF1R	52	JNK1	150
CDK4-cyclinD1	0.19	FLT3(R834Q)	13	STK16	52	KIT	150
CDK4-cyclinD3	0.74	CLK4	15	TYK2	58	DYRK2	160
GAK	0.96	PLK4	21	MEK4	71	ICK	160
FLT3(D835Y)	1.1	CLK1	23	KIT(D816V)	72	IRAK3	160
FLT3(D835H)	1.2	MEK3	25	MKNK2	73	RSK3	160
CSNK2A2	2	ERK8	32	PIP5K2C	73	PDGFRB	180
FLT3	2.3	PFTK1	32	KIT(V559D)	80	RSK1	190
FLT3(K663Q)	3.8	JNK3	34	KIT(L576P)	81	AMPK-alpha2	200
FLT3(ITD)	3.9	PCTK1	35	TRKB	83	RIOK2	220
FLT3(N841I)	4	JNK2	44	TRKA	97	CDKL5	270
DYRK1A	4.1	MEK5	46	MST4	120	GSK3B	540
DYRK1B	5.9	CDK2	48	RSK2	120	BIKE	660
CLK2	6.1	TRKC	49	JAK1	150		

POC: percent of control = test compound signal - positive control signal / (negative control signal-positive control signal) × 100. K_d values were determined at DiscoveRx with a proprietary competitive binding assay (S1).

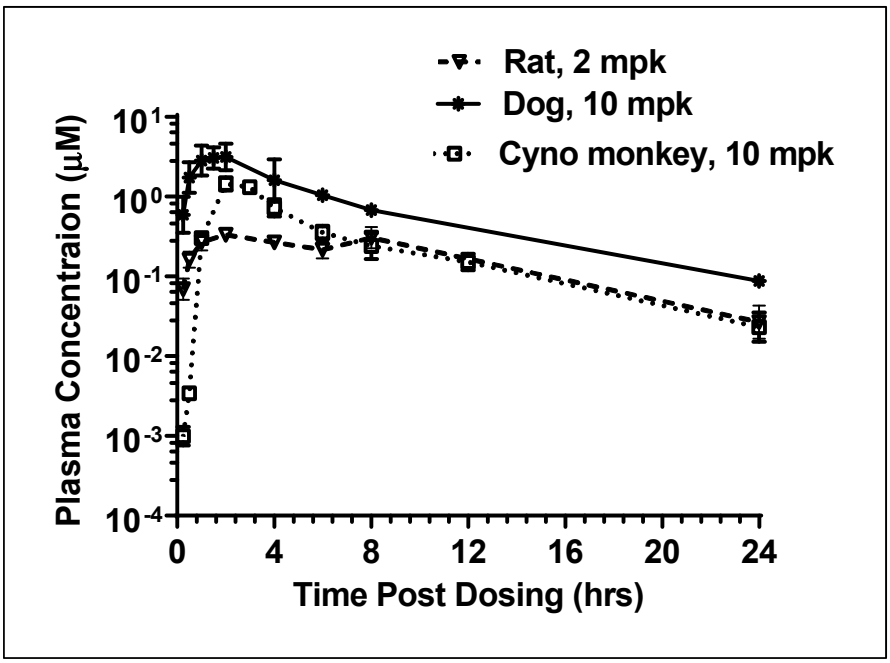

Figure S1. Plasma concentration-time profiles of AMG 925 in rat, dog, and cynomolgus monkey following oral administration. Vehicle was water/acetate/Tween (pH4, v/v/v = 96/3/1) for rat and 20% captisol for dog and monkey. n = 3, mpk = mg/kg, data presented as mean ± SD.

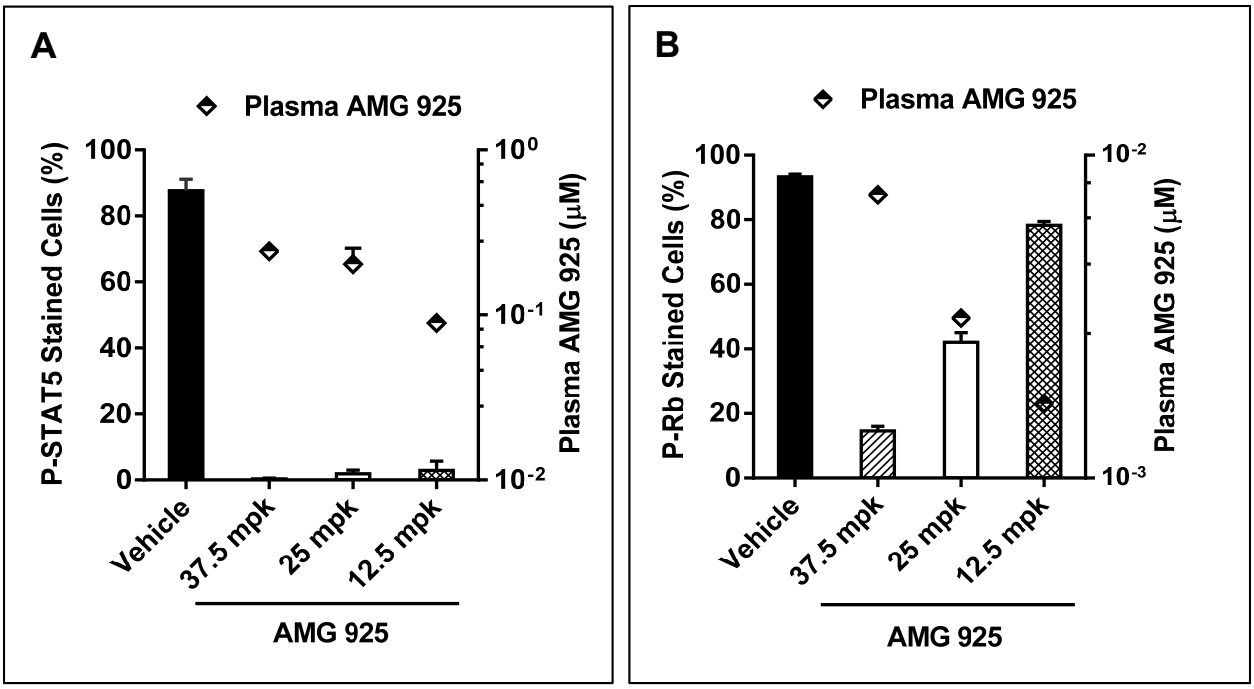

Figure S2. Inhibition of STAT5 and Rb phosphorylation by AMG 925 in MOLM13-Luc tumor cells in bone marrow. To assess the effect of AMG 925 on phosphorylation of STAT5 (P-STAT5) and Rb (P-Rb) in the tumor cells in bone marrow, mice were injected with MOLM13-Luc cells and allowed 14 days to engraft. Mice were then randomized into groups of 3 and treated twice with AMG 925, 6 hours apart. At 8 and 24 hrs after the first dose administration, mice were sacrificed and femurs harvested and processed for IHC detection of P-STAT5 and P-Rb, respectively. Plasma samples were collected for concentration of AMG 925 at the same time. Concentrations of unbound AMG 925 were indicated. All groups were statistically different from vehicle ($p < 0.001$) as analyzed by paired T-test. n = 3, mpk = mg/kg, data presented as mean ± SEM.

Supplementary References

1. www.kinomescan.com.