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POSTER ABSTRACTS

631.CHRONIC MYELOID LEUKEMIA: BIOLOGY AND PATHOPHYSIOLOGY, EXCLUDING THERAPY

A Dual-Specific Inhibitor of Rock/Aurk, RR-1752, for Primary Myelofibrosis

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Myelofibrosis (MF) is a clonal myeloproliferative neoplasm (MPN) characterized by driver mutations in JAK2, CALR, and MPL resulting in constitutive activation of JAK-STAT signaling. Abnormalities in megakaryocyte (MK) numbers and morphology are a common feature of MF where abnormal MKs are associated with bone marrow fibrosis and pro-inflammatory cytokine release. Therapies that target constitutive JAK-STAT signaling and atypical megakaryocytes could provide clinical benefit for patients with MF. ROCK and Aurora kinase (AURK) are overexpressed in MPN and linked to dysregulated MKs of patients with MPN. We therefore tested the activity of RR-1752, a dual-specific inhibitor of ROCK and AURK, in preclinical models of MF. RR-1752 acted as an inhibitor of pSTAT3 in IL-2 stimulated human PBMC 1h post stimulation and significantly inhibited phosphorylated myosin light chain 2 (pMLC2) in two human MPN cell lines, HEL-92.1.7 and UKE-1, confirming an on-target action. RR-1752 inhibited colony formation by HEL-92.1.7 and UKE-1, (IC_{50} = 25.2 nM and 54.6 nM respectively). RR-1752 also induced cell cycle arrest in HEL-92.1.7 and UKE-1 specifically at the G2/M checkpoint. RR-1752 was also tested in a hematopoietic colony formation assays of MF patient derived $CD34^+$ cells. RR-1752 led to concentration specific inhibition of MF patient derived $CD34^+$ cell colony formation between 100-190 nM demonstrating relevant activity against patient-derived MF samples (51% inhibition at 190 nM as compared to vehicle control). These data were in line with flow cytometrically determined cell viability data of MF $CD34^+$ cells cultured in the presence of varying concentrations of RR-1752 in liquid culture. The in vivo activity of RR-1752, was examined using the human HEL- 92.1.7 cell line, homozygous for both $JAK2^{V617F}$ and $p53^{M133K}$ in a mouse xenograft model. The effects of RR-1752 alone and in combination with ruxolitinib were compared to single agent ruxolitinib. The administration of RR-1752, 25 mg/kg PO daily resulted in a significant ($p<0.01$) improvement in median survival (31 days) compared to ruxolitinib alone, 45 mg/kg PO daily (21 days). RR-1752 5.0 mg/kg PO QD plus ruxolitinib 45 mg/kg PO QD also resulted in a significant improvement in survival ($p<0.05$) compared to single agent ruxolitinib but was inferior to single agent RR-1752 at 25mg/kg. The demonstrated activity in MF patient derived $CD34^+$ cells combined with the significant improvement in survival compared to the approved drug ruxolitinib in an aggressive, JAK2/p53 mutant MF xenograft model provides a compelling case for its evaluation as a therapeutic modality in MF patients. Dose optimization of RR-1752 alone and in combination with ruxolitinib in the HEL-92.1.7 IV dissemination model as well as testing in the hMPL-W515L-evoked myelofibrosis model is ongoing. Conventional treatments for MF have largely focused on symptom management but RR-1752 treatment could result not only in beneficial symptom improvement but also important disease modifying potential by inhibiting JAK-STAT signaling, cell cycle progression and targeting dysregulated MKs.

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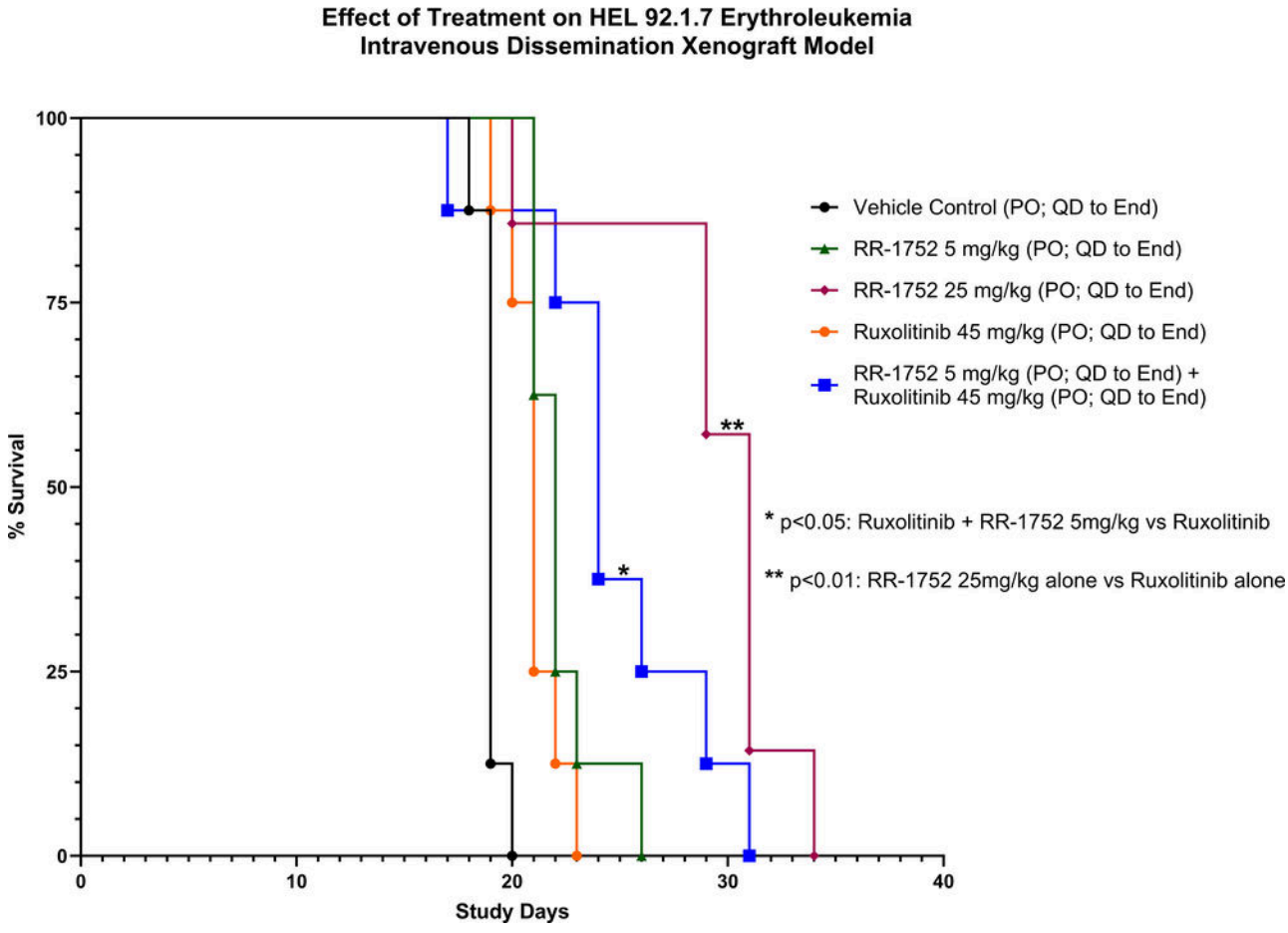

Figure 1

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