BACKGROUND

- Pacritinib is a novel orally active daily dual JAK2/FLT3 inhibitor.
- The major signaling pathway for erythropoietin and MPL is through receptor activation of JAK2 and subsequent phosphorylation of STAT3 proteins. Inhibition of JAK2 therefore is expected to be associated with anemia and thrombocytopenia through inhibition of normal EPO and MPL signaling and both have been observed with current JAK inhibitors.
- In preclinical models of myeloproliferative diseases in a JAK2(V617F) dependent SET-T2 myeloproliferative model, treatment with pacritinib was not associated with cytopenia at optimal effective dosing of 100mg/kg (human equivalent dose 840mg) given orally, once daily. JAK2-JAB1 and 5 pathway inhibition.

AIMS

- This present integrated analysis was performed to quantify clinical toxicities of pacritinib, with a focus on hematologic effects.

METHODS

- We reviewed the safety database which included 4 clinical studies: a phase 1 study in advanced myelofibrosis, a phase 1 and a phase 2 study in advanced lymphoid malignancies, and a phase 1 study in myeloblastosis.

RESULTS

- In phase 1 and 2 clinical trials, a total of 191 patients (pts) were treated with pacritinib: 129 with advanced myelofibrosis including 122 myelofibrosis pts (primary 72/122 (59%) and 7 AML pts, and 62 with advanced lymphoid malignancies, including 38 NHL pts & 24 Hodgkin lymphoma pts.
- The median age was 65 years and the median time from initial diagnosis was 3.8 years. 44% of pts with myeloid disorders had baseline platelet counts <100,000/µL.
- Pacritinib was dosed from 100 to 600 mg daily during phase 1 and at 400 mg equivalent dose 840mg) given orally, twice daily, despite JAK2-STAT3 and 5 associated with cytopenias at optimal effective dosing of 150mg/kg (human equivalent dose)

Hematological Safety (See figures)

- There was no clinically significant decline in mean hemoglobin or platelet count from baseline values.
- Of the 30 patients with myeloid disorders with baseline platelet counts <50,000/µL, the median decline in platelet count observed at the end of study was 3,000/µL.
- In the 11 patients with myeloid malignancies with baseline platelet counts <50,000/µL, no dose reductions were required for worsening thrombocytopenia.

AEs Related Dose Interruption/ Reduction or Discontinuation in All Pacritinib Studies

- Most common adverse events (AEs) that led to study drug discontinuation included:
- Neutropenia (11.8%) and anemia (11.5%).
- Twenty-two deaths (6.7%) reported as treatment emergent AEs with a fatal event occurring in 4,5%. AEs that led to study drug discontinuation included:
- Neutropenia (11.8%) and anemia (11.5%).

Adverse Events (AEs)

- The most common AEs were gastrointestinal (9%) and hematologic (8%) with early administration of standard anti-diarrheal agents.

Time to First Gastrointestinal Event (Safety Populations in Lymphoid Studies) SB1518-001 and SB1518-005