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## **A Phase I Study of the Potent Hsp90 Inhibitor STA-9090 Administered Twice Weekly In Subjects with Hematologic Malignancies.**

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**Background:** STA-9090 is a potent, second-generation, small-molecule Hsp90 inhibitor, with a chemical structure unrelated to the first-generation, ansamycin family of Hsp90 inhibitors (e.g., 17-AAG or IPI-504). STA-9090 induces the loss of Hsp90 client proteins that are important in hematologic cancers, including BCR-ABL, c-KIT, FLT3, WT1, and JAK2. In preclinical studies, STA-9090 has shown potency up to 100 times greater than the first-generation Hsp90 inhibitors as well as activity against a wider range of kinases. In in vitro and in vivo models, STA-9090 has shown potent activity against a broad range of leukemias, lymphomas, and multiple myeloma.

**Methods:** The primary objective of this Phase I multicenter study (NCT00858572) was to determine the maximum tolerated dose (MTD) of STA-9090 given twice weekly in patients with acute myeloid leukemia (AML), advanced myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), and myeloproliferative neoplasms (MPN). An adaptive statistical design methodology was used to determine dose escalation. Safety, pharmacokinetics (PK), pharmacodynamic (PD), and clinical activity were evaluated. Dosing for 4 consecutive weeks constituted one dosing cycle. Serial pharmacokinetic (PK) samples were collected pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, and 24 hours post-dose on study days 1 and 22, and pre-dose and 1 hour post at all other visits in cycle 1. Plasma samples were collected for HSP70 protein analysis. Safety assessments included the number and grade of adverse events (AEs), changes from baseline in laboratory parameters, and evaluation of electrocardiogram changes.

**Results:** 22 patients (14 males, 8 females; median age 62 years, range 33-80; Eastern Cooperative Oncology Group [ECOG] status range [0-2]) received STA-9090 twice weekly. Patients with the following disease types were treated: AML (n=7), CML (n=8), MDS (n=3), and MPN (n=4). The median time from initial diagnosis to first treatment was 19 months; patients had received a median of 2 (range, 1-9) prior treatments and 27% were refractory to their most recent therapy. Dosing with STA-9090 was at 14 mg/m<sup>2</sup> (4 patients), 22 mg/m<sup>2</sup> (4 patients), 30 mg/m<sup>2</sup> (3 patients), 70mg/m<sup>2</sup> (3 patients), and 110 mg/m<sup>2</sup> (8 patients). Patients received a median of 2 (range, 1-8) cycles of STA-9090. AEs reported in ≥25% of patients were diarrhea, nausea, fatigue, abdominal pain, anemia, increased alanine aminotransferase, arthralgia, increased aspartate aminotransferase, dyspnea, hypokalaemia, thrombocytopenia, and vomiting. The majority of AEs were mild to moderate in severity. There have been 3 patients with dose limiting toxicities: one at 14 mg/m<sup>2</sup> (grade 3 hyponatremia and hyperbilirubinemia) and two at 110 mg/m<sup>2</sup> (grade 3 prolonged QTc and transaminitis). At the time of abstract submission, the MTD has not been defined. STA-9090 exhibited linear PK with exposures (AUC and Cmax) increasing in proportion to dose. One hour following infusion termination, plasma concentrations declined by approximately 10 fold, and by 100 fold within approximately 8 to 10 hours. STA-9090 showed no drug accumulation with twice weekly dosing. STA-9090 was well distributed, exhibiting an apparent volume of distribution greater than total body water. HSP70 protein levels increased following STA-9090 administration and remained elevated prior to subsequent doses indicating a durable biological impact of the drug. Clinical responses include 1 patient with CML (dosed at 14 mg/m<sup>2</sup>) and 1 patient with AML (dosed at 110 mg/m<sup>2</sup>) who had best responses of hematological improvement lasting 2 and 3 months, respectively. In addition, 4 patients with myelofibrosis (1 patient dosed at 14 mg/m<sup>2</sup> and 3 dosed at 70 mg/m<sup>2</sup>) had stable disease as best response; 1 of these responses lasted for 7 months and the patient went on to receive an allogenic stem cell transplant. Further response evaluation is ongoing.

**Conclusions:** In patients with hematologic malignancies, STA-9090 is well tolerated up to dose levels of 110 mg/m<sup>2</sup> given twice weekly. Induction of HSP70 protein levels provides evidence of in vivo biological activity. A favorable PK profile, preliminary signs of pharmacodynamic activity, and early clinical activity signals warrant continued evaluation of single-agent STA-9090 using a twice weekly dosing regimen.