A Phase 1/2 Study of the Potent Hsp90 Inhibitor STA-9090 Administered Once Weekly in Subjects with Hematologic Malignancies

Jeffrey E. Lancet, MD[1], B. Douglas Smith, MD[2], Robert Bradley[3], Rami S. Komrokji, MD[4], Florentina Teofilovici, MD[3] and David A. Rizzieri, MD[5]

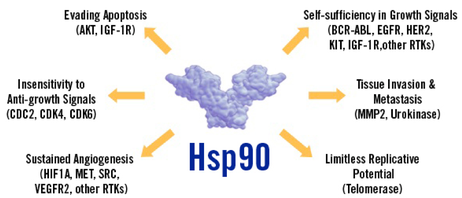
[1]Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL, [2]at Johns Hopkins, Kimmel Cancer Center, Baltimore, MD, [3]Medical, Synta Pharmaceuticals Corp., Lexington, MA, [4]Moffitt Cancer Center, Tampa, FL, [5]Division of Cellular Therapy, Duke University Medical Center, Durham, NC

BACKGROUND

Hsp90 Background

- Hsp90 is a chaperone protein that controls the folding and processing of proteins that drive tumor development and progression
- Hsp90 clients include many proteins that play a critical role in tumor pathophysiology such as EGFR, HER2, c-MET, AKT, BCR-ABL, RAF, CDK4, c-KIT, FLT3, and VEGFR
- Degradation of client proteins allows for simultaneous targeting of multiple oncogenic signaling pathways
- Kinase client proteins are generally dependent on Hsp90 regardless of mutatational status - wild type, TKI-sensitive, TKI-resistant – which creates potential for use in multiple settings

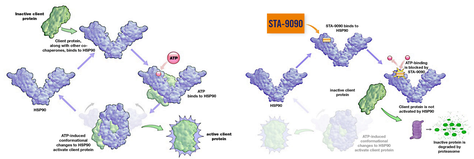
Hsp90 Central to Driving Cancer Cell Growth



STA-9090 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

Hsp90 Chaperoning Cycle



METHODS

Study Design

- Phase 1/2, open-label, dose-escalation clinical trial
- Eligible subjects had acute myeloid leukemia (AML), advanced myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), and myeloproliferative neoplasms (MPN) that had relapsed or were refractory to standard therapy
- STA-9090 was administered over a 1 hour infusion, once weekly for four weeks (a 4-week cycle)
- Pharmacokinetic (PK) samples were collected immediately prior to and at the end of the infusion on days 1, 8, 15 and 22 in cycle 1. In addition, a 2 hour post infusion start sample was collected on cycle 1 day 1
- Plasma samples were collected for HSP70 protein analysis prior to dosing on days 1, 8 and 15
- Bone marrow aspirates and blood samples were collected for biomarker and client protein analysis
- The study was designed to enroll three dose cohorts of six subjects each (120 mg/m^2, 150 mg/m^2, and 200 mg/m^2)
- Before dose escalation there must be at least six evaluable subjects
- Evaluable subjects must have received 4 doses of STA-9090 during cycle 1 and have a subsequent follow up visit or experience a dose limiting toxicity (DLT).
- Subjects who discontinue from the study for reasons other than DLT before completing cycle 1 could be replaced
- Because of discontinuations for reasons other than DLTs, the first two cohorts each enrolled nine subjects
- Enrollment is currently continuing in the 200 mg/m^2 cohort. At the time of the data cut-off (September 10, 2010), 3 subjects were in the treatment phase of the study

RESULTS

Demographic and Baseline Status

	120 mg/m^2 (n=9)	150 mg/m^2 (n=9)	200 mg/m^2 (n=10)	Total (n=28)
Age				
Median	49	66	58	63
Sex				
Male	7 (78%)	5 (56%)	6 (60%)	18 (64%)
Female	2 (22%)	4 (44%)	4 (40%)	10 (36%)
Race				
White/ Caucasian	8 (89%)	9 (100%)	8 (80%)	25 (89%)
Black/African American	0	0	1 (10%)	1 (4 %)
Other	1 (11%)	0	1 (10%)	2 (7%)
Ethnicity				
Hispanic or Latino	1 (11%)	0	0	1 (4%)
Not Hispanic or Latino	8 (89%)	9 (100%)	9 (90%)	26 (92%)
Unknown	0	0	1 (10%)	1 (4 %)
ECOG Status				
0	3 (33%)	0	3 (30%)	6 (21%)
1	5 (56%)	5 (56%)	3 (30%)	13 (46%)
2	1 (11%)	4 (44%)	1 (10%)	6 (21%)
unknown	0	0	3 (30%)	3 (11%)
Primary Cancer Type				
AML	5 (56%)	8 (89%)	8 (80%)	21 (75%)
ALL	1 (11%)	0	1 (10%)	2 (7%)
AML/ALL	1 (11%)	1 (11%)	0	2 (7%)
CML	2 (22%)	0	0	2 (7%)
MDS	0	0	1 (10%)	1 (4%)

- Patients had received a median of 3 (range, 1-7) prior treatment regimens
- Of the 28 subjects, 10 (36%) had stopped their most recent therapy due to treatment failure, lack of response or disease progression. Two (7%) had stopped their most recent therapy due to intolerance or toxicity. Eleven (39%) stopped when the prior treatment was complete, and 1 (4%) stopped because they developed a resistance mutation against the therapy

Summary of Adverse Events

Number of subjects (%)	120 mg/m^2 (n=9)	150 mg/m^2 (n=9)	200 mg/m^2 (n=9)	Total (n=27)
Any AE	9 (100)	9 (100)	9 (100)	27 (100)
Any related AE	8 (89)	9 (100)	8 (89)	25 (93)
Any ≥ Grade 3 AE	6 (67)	9 (100)	3 (33)	18 (67)
Any SAE	5 (56)	6 (67)	2 (22)	13 (48)
Any DLT	1 (11)	0	0	1 (4)
AEs leading to treatment discontinuation	2 (22)	2 (22)	0	4 (15)
AEs with an outcome of death	1 (11)	0	0	1 (4)

* AEs are not available yet for one subject who is still on-treatment

Most Common Adverse Events (≥15% of all subjects)

Number of Subjects (%)	120 mg/m^2 (n=9)	150 mg/m^2 (n=9)	200 mg/m^2 (n=9)	Total (n=27)
Diarrhea	8 (89)	8 (89)	6 (67)	22 (82)
Fatigue	4 (44)	6 (67)	4 (44)	14 (52)
Decreased Appetite	3 (33)	5 (56)	2 (22)	10 (37)
Nausea	2 (22)	5 (56)	3 (33)	10 (37)
Dehydration	1 (11)	4 (44)	3 (33)	8 (30)
Headache	4 (44)	1 (11)	3 (33)	8 (30)
Insomnia	1 (11)	4 (44)	2 (22)	7 (26)
Dyspnea	3 (33)	1 (11)	2 (22)	6 (22)
Febrile Neutropenia	2 (22)	3 (33)	1 (11)	6 (22)
Vomiting	1 (11)	3 (33)	2 (22)	6 (22)
Upper Abdominal Pain	2 (22)	3 (33)	0	5 (19)
Constipation	1 (11)	3(33)	1 (11)	5 (19)
Dizziness	2 (22)	2 (22)	1 (11)	5 (19)
Hyponatremia	0	4(44)	1 (11)	5 (19)
Peripheral edema	4 (44)	0	1 (11)	5 (19)
Pneumonia	3 (33)	2 (22)	0	5 (19)
Pyrexia	2 (22)	3 (33)	0	5 (19)

Most Common Grade ≥3 Adverse Events (occurred in ≥2 subjects)

Number of subjects (n%)	120 mg/m^2 (n=9)	150 mg/m^2 (n=9)	200 mg/m^2 (n=9)	Total (n=27)
Febrile Neutropenia	2 (22)	2 (22)	1 (11)	5 (19)
Anemia	2 (22)	2 (22)	0	4 (15)
Fatigue	2 (22)	1 (11)	0	3 (11)
Hypokalemia	1 (11)	2 (22)	0	3 (11)
Thrombocytopenia	2 (22)	1 (11)	0	3 (11)
Back pain	1 (11)	1 (11)	0	2 (7)
Hyponatremia	0	2 (22)	0	2 (7)
Nausea	0	1 (11)	1 (11)	2 (7)
Neutropenia	1 (11)	0	1 (11)	2 (7)
Pneumonia	2 (22)	0	0	2 (7)
Vomiting	0	1 (11)	1 (11)	2 (7)

- Gastrointestinal adverse events were most common, with 89% of subjects reporting events in this body system. Diarrhea was the most common event; the majority of diarrhea events were mild/moderate in severity. Sixty-seven percent of subjects had general adverse events, including fatigue (52%)
- There was no apparent dose-response relationship for any adverse events
- Thirteen subjects reported Serious Adverse Events (SAEs); 9 subjects had more than 1 SAE. Febrile neutropenia was reported in 6 subjects, pneumonia in 3 subjects, and back pain and transfusion reactions in 2 subjects each. All other SAEs were reported in one subject each
- One subject had an SAE of diarrhea, nausea, and vomiting, all considered at least possibly related to study drug. This subject was in the 200 mg/m^2 dose group
- Adverse events led to discontinuation of study drug in 4 subjects
  - Events that led to discontinuation included progression of AML (resulting in death), blast crisis, leukocytosis, and abnormal liver function tests (elevation of ALT, AST, bilirubin and alkaline phosphatase).
- One dose limiting toxicity of hyperbilirubinemia was reported, in a subject in the at 120 mg/m^2 dose group

Responses to Study Drug

- The median number of dosing cycles of STA-9090 initiated was 2 (std dev 1.6, range 1-8)
- The mean duration of treatment was 44 days (SD 48.4, range 1-220)
- Fourteen subjects initiated at least 2 dosing cycles
  - One subject with AML initiated 6 cycles, and one subject with CML initiated 8 cycles
- Seventeen subjects had a best response of persistent disease. Six subjects had progressive disease (PD). Five subjects did not have response assessments (ND)

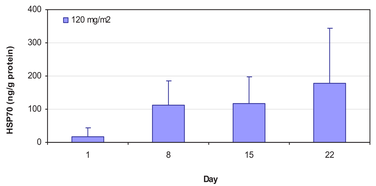
Responses to Study Drug

	Total Treated	Persistent Disease	PD	ND
AML	21	11	5	5
CML	2	2	0	0
MDS	1	1	0	0
ALL/AML	4	3	1	0
Total N (%)	28	17 (61)	6 (21)	5 (18)

Hsp70 Pharmacodynamics

- Mean HSP70 protein concentrations increased following the first STA-9090 administration and continued to rise following later doses
- HSP70 protein concentrations remained elevated between doses, providing evidence of prolonged pharmacologic activity in this once-weekly dosing protocol

HSP70 Protein versus Day

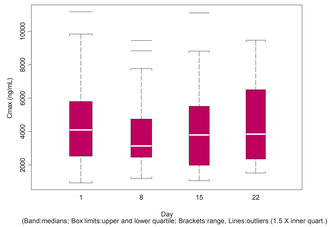


CLIENT PROTIEN DATA: PENDING

Pharmacokinetics

- Mean STA-9090 exposures (C_{max}) did not differ across dosing days (Fig 1)
- STA-9090 concentration declined rapidly following infusion termination with concentrations averaging 18% (median 13%) of C_{max} 1 hour after infusion termination.

STA-9090 Cmax values by Day (Normalized to 200 mg/m2)



(Band:medians; Box limits:upper and lower quartile; Brackets:range, Lines:outliers (1.5 X inner quart.)

p-value = 0.9492, for comparison of log-transformed Cmax across Days

CONCLUSIONS

- In patients with advanced hematologic malignancies, STA-9090 has been well tolerated up to dose levels of 200 mg/m^2
- Although no formal responses were reported in this refractory patient population, 3 patients had hematological control for 3 (AML), 6 (AML) and 8 (CML) cycles of treatment
- The recommended Phase 2 dose has not yet been determined.

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