

# A phase I dose-escalation study of the Hsp90 inhibitor STA-9090 administered twice weekly in patients with solid tumors

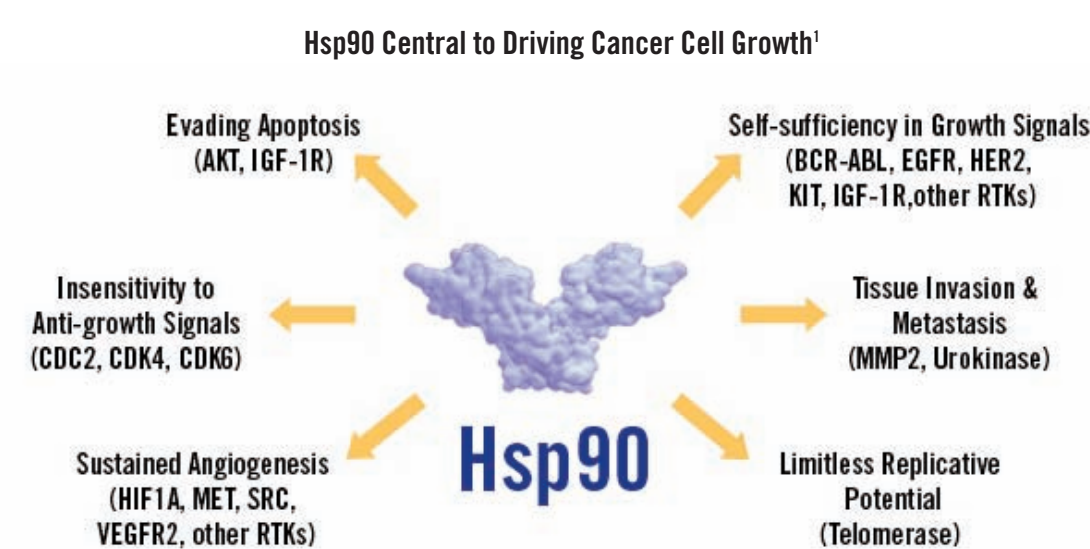
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## BACKGROUND

### HSP90 INHIBITION

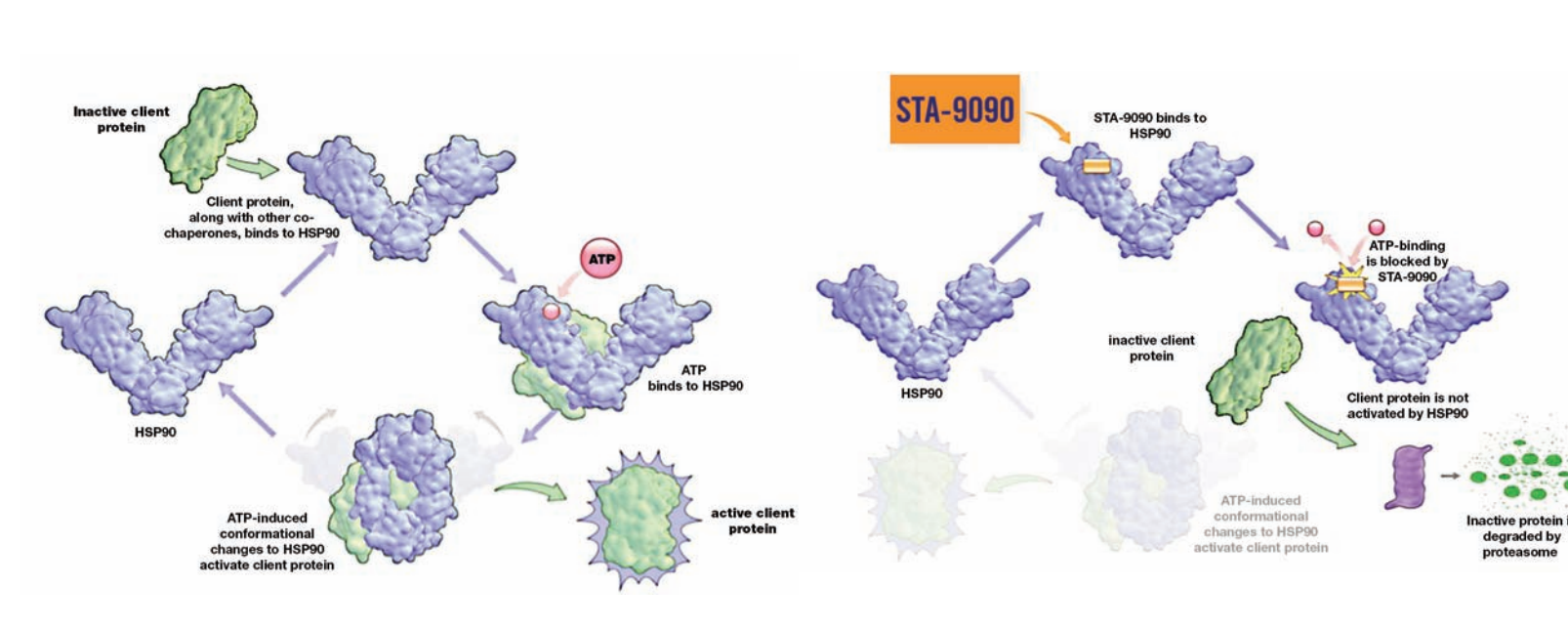
- Hsp90 is a chaperone protein that maintains the proper conformation and function of many proteins that play a critical role in tumor pathophysiology such as EGFR, HER2, c-MET, AKT, BCR-ABL, RAF, CDK4, c-KIT, FLT3, and VEGFR
- Degradation of client proteins by inhibiting Hsp90 allows for simultaneous targeting of multiple oncogenic signaling pathways
- Kinase client proteins are generally dependent on Hsp90 regardless of mutational status - wild type, TKI-sensitive, TKI-resistant – which creates potential for use in multiple settings



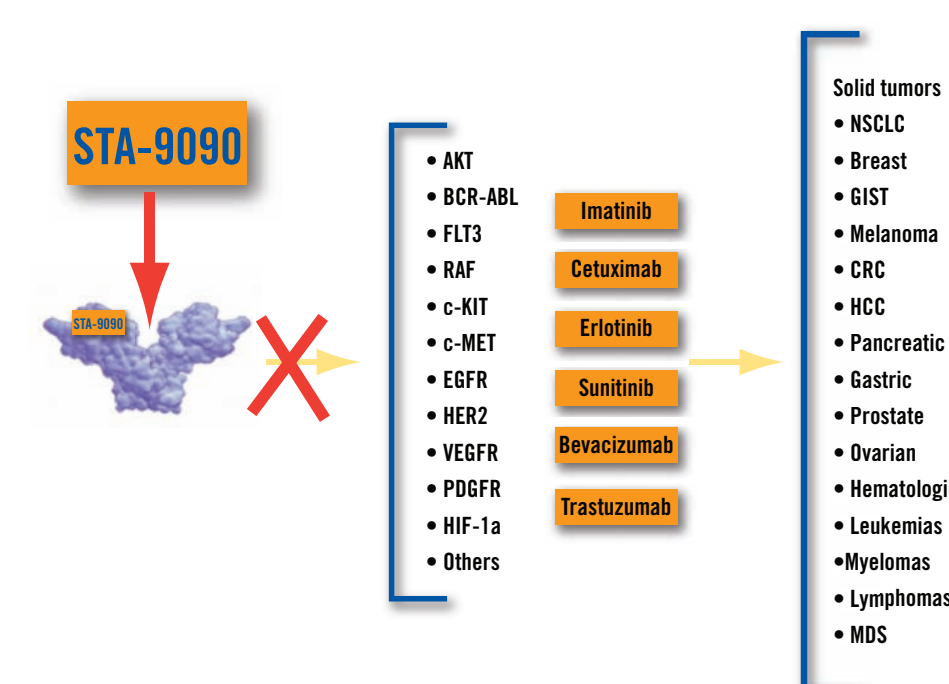
### STA-9090 OVERVIEW

- Potent, second-generation small molecule Hsp90 inhibitor<sup>2,4</sup>
  - Structurally unrelated to first-generation Hsp90 inhibitors (such as 17AAG and IPI-504)
  - Up to 100 times more potent than first-generation Hsp90 inhibitors
- Shows strong activity in broad range of solid tumor and hematologic cancer models including lung, prostate, colon, breast, gastric, pancreatic, melanoma, AML, CML<sup>2,4</sup>
- Activity seen in models resistant to kinase inhibitors including imatinib, erlotinib, sunitinib, and dasatinib as well as in models resistant to first-generation Hsp90 inhibitors (17AAG)
- Selectively accumulates in tumors with a tumor half-life of approximately 60 hours
- Penetrates deeply into hypoxic tumors, inhibiting HIF-1 $\alpha$
- Administered as one hour IV infusion

### HSP90 CHAPERONE CYCLE



## STA-9090 DEGRADES PROTEINS CRITICAL TO GROWTH OF MULTIPLE CANCERS



## METHODS

### STUDY DESIGN

- Phase I, open-label, dose-escalation clinical trial
- Eligible patients had advanced or metastatic solid tumors for which no standard therapy exists
- STA-9090 was administered over a 1 hour infusion, twice weekly for three weeks, followed by a 1-week dose-free interval (for a 4-week cycle)
- Standard "3 + 3" design; three patients enrolled at each dose level, if one patient had a Dose-Limiting Toxicity (DLT) during Cycle 1, three more were enrolled. If  $\geq 2$  of the 6 patients had a DLT during Cycle 1, the prior dose level was declared the Maximum Tolerated Dose (MTD)
- The dosing levels were planned to escalate from a starting dose of 2 mg/m<sup>2</sup> to 4, 7, 10, 14, 19, 25, 33, 40 and 48 mg/m<sup>2</sup>. However, data from other ongoing dose escalation studies demonstrated good tolerability at higher dose levels (see Poster # 2529), so the protocol was amended to allow faster escalation to 25, 50 and 100 mg/m<sup>2</sup>
- At this time, enrollment is continuing at 100 mg/m<sup>2</sup>. Data was not yet available for the patients in this cohort at the data cut-off date (March 15, 2010)

## RESULTS

### DEMOGRAPHICS AND BASELINE STATUS

|   |                 | 2-10 mg/m <sup>2</sup><br>(n=17) | 14-25 mg/m <sup>2</sup><br>(n=12) | 50 mg/m <sup>2</sup><br>(n=7) |
|---|-----------------|----------------------------------|-----------------------------------|-------------------------------|
| Age                                     | Median          | 55                               | 57                                | 56                            |
| Sex                                     | Male            | 8                                | 5                                 | 3                             |
|   | Female          | 9                                | 7                                 | 4                             |
| Race                                    | White/Caucasian | 15                               | 11                                | 6                             |
|   | Other           | 2                                | 1                                 | 1                             |
| ECOG Status                             | 0               | 6                                | 4                                 | 2                             |
|   | 1               | 7                                | 6                                 | 4                             |
|   | 2               | 4                                | 2                                 | 1                             |
| Best response to prior systemic therapy | CR              | 0                                | 0                                 | 1                             |
|   | PR              | 1                                | 0                                 | 1                             |
|   | SD              | 3                                | 5                                 | 1                             |
|   | PD              | 6                                | 2                                 | 1                             |
|   | Unknown/NA      | 6                                | 5                                 | 3                             |

Tumor type distribution: Melanoma (9); colon (7); NSCLC (4); pancreatic (2); other (14)

All patients had Stage 4 metastatic cancer at the time of study enrollment

### SUMMARY OF ADVERSE EVENTS

| Number of patients (%)                   | 2-10 mg/m <sup>2</sup><br>(n=17) | 14-25 mg/m <sup>2</sup><br>(n=12) | 50 mg/m <sup>2</sup><br>(n=7) |
|--|----------------------------------|-----------------------------------|-------------------------------|
| Any AE                                   | 17 (100%)                        | 12 (100%)                         | 6 (85%)                       |
| Any Grade 3 AE                           | 9 (53%)                          | 9 (75%)                           | 5 (71%)                       |
| Any SAE                                  | 7 (41%)                          | 4 (33%)                           | 2 (29%)                       |
| Any DLT                                  | 1 (5.9%)                         | 0                                 | 0                             |
| AEs leading to treatment discontinuation | 4 (24%)                          | 2 (17%)                           | 2 (29%)                       |
| AEs leading to death                     | 2 (12%)                          | 2 (17%)                           | 0                             |

### MOST COMMON OVERALL ADVERSE EVENTS ( $\geq 10\%$ OF ALL PATIENTS)

| Number of patients (%)         | 2-10 mg/m <sup>2</sup><br>(n=17) | 14-25 mg/m <sup>2</sup><br>(n=12) | 50 mg/m <sup>2</sup><br>(n=7) |
|--------------------------------|----------------------------------|-----------------------------------|-------------------------------|
| Fatigue                        | 8 (47%)                          | 7 (58%)                           | 2 (33%)                       |
| Nausea                         | 5 (29%)                          | 6 (50%)                           | 2 (33%)                       |
| Anemia                         | 3 (18%)                          | 5 (42%)                           | 4 (67%)                       |
| Diarrhea                       | 1 (6%)                           | 6 (50%)                           | 4 (67%)                       |
| Decreased appetite             | 3 (18%)                          | 4 (33%)                           | 1 (17%)                       |
| Vomiting                       | 4 (24%)                          | 2 (17%)                           | 2 (33%)                       |
| Abdominal pain                 | 3 (18%)                          | 3 (25%)                           | 1 (17%)                       |
| Headache                       | 5 (29%)                          | 1 (8%)                            | 1 (17%)                       |
| AST increased                  | 1 (6%)                           | 3 (25%)                           | 2 (33%)                       |
| Alkaline phosphatase increased | 0                                | 4 (33%)                           | 1 (17%)                       |
| Cough                          | 4 (24%)                          | 1 (8%)                            | 0                             |
| Hypomagnesemia                 | 1 (6%)                           | 2 (17%)                           | 2 (33%)                       |
| Weight decreased               | 2 (12%)                          | 3 (25%)                           | 0                             |
| Abdominal pain upper           | 2 (12%)                          | 2 (17%)                           | 0                             |
| ALT increased                  | 2 (12%)                          | 1 (8%)                            | 1 (17%)                       |
| Back pain                      | 2 (12%)                          | 2 (17%)                           | 0                             |
| Constipation                   | 1 (6%)                           | 3 (25%)                           | 0                             |
| Dizziness                      | 1 (6%)                           | 2 (17%)                           | 1 (17%)                       |
| Dyspnea                        | 4 (24%)                          | 0                                 | 0                             |
| Gait disturbance               | 2 (12%)                          | 2 (17%)                           | 0                             |
| Hypokalemia                    | 1 (6%)                           | 2 (17%)                           | 1 (17%)                       |
| Musculoskeletal pain           | 1 (6%)                           | 3 (25%)                           | 0                             |
| Peripheral edema               | 3 (18%)                          | 1 (8%)                            | 0                             |

## RESULTS

### MOST COMMON GRADE $\geq 3$ ADVERSE EVENTS (OCCURRING IN $\geq 2$ PATIENTS)

| Number of subjects (%) | 2-10 mg/m <sup>2</sup><br>(n=17) | 14-25 mg/m <sup>2</sup><br>(n=12) | 50 mg/m <sup>2</sup><br>(n=7) |
|------------------------|----------------------------------|-----------------------------------|-------------------------------|
| Diarrhea               | 0                                | 1 (8%)                            | 2 (33%)                       |
| Abdominal pain         | 1 (6%)                           | 1 (8%)                            | 0                             |
| AST increased          | 0                                | 0                                 | 2 (33%)                       |
| Disease progression    | 1 (6%)                           | 1 (8%)                            | 0                             |
| Dyspnea                | 2 (12%)                          | 0                                 | 0                             |
| Hyponatremia           | 0                                | 2 (17%)                           | 0                             |
| INR Increased          | 1 (6%)                           | 1 (8%)                            | 0                             |
| Pulmonary embolism     | 1 (6%)                           | 1 (8%)                            | 0                             |

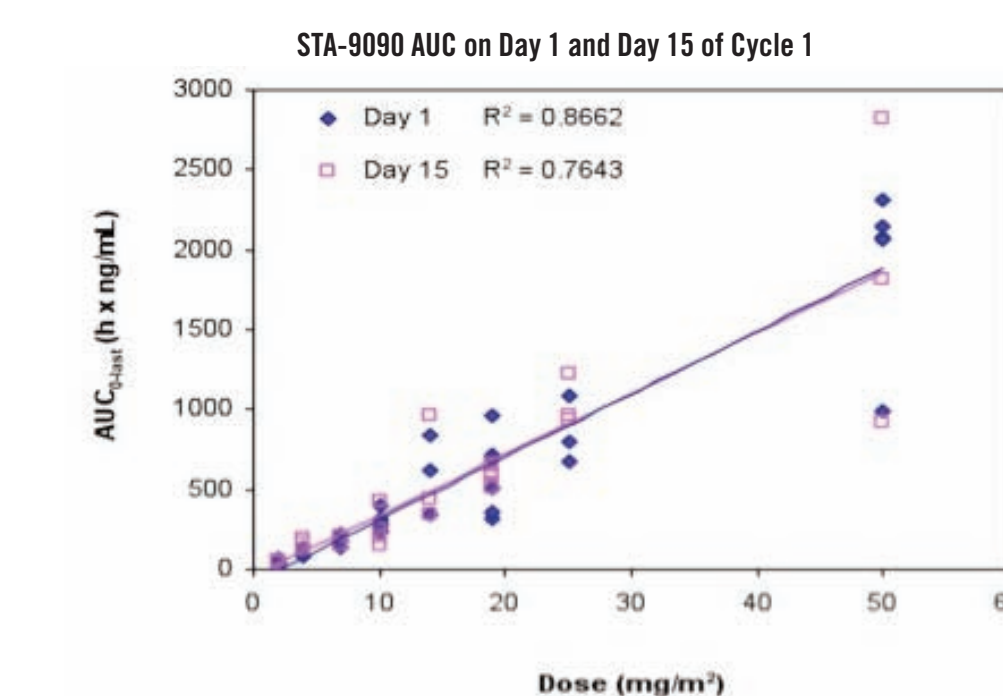
- Most common adverse events:
  - Gastrointestinal events (diarrhea, nausea, vomiting)
  - Most events were transient, and mild or moderate in severity
  - 9% of patients reported severe diarrhea, and one patient each reported severe nausea or vomiting (3%)
- Serious Adverse Events:
  - Reported by 13 patients
  - Events reported in more than one patient were disease progression, dyspnea, and pulmonary embolism, each in two patients
  - All other SAEs were reported in one patient each
- Adverse events leading to discontinuation of study drug:
  - Occurred in 8 patients
  - Pneumonia, pruritus, nausea, pyrexia, ALT increase, and AST increase (in a patient with hepatocellular carcinoma) were reported in 1 patient each
  - The event of ALT increase was considered a DLT (in a patient at 10 mg/m<sup>2</sup> dose)
  - Events that led to discontinuation and resulted in death were dyspnea (with disease progression in a patient with NSCLC), and dyspnea/hypoxia/rales (in a patient with neuroendocrine tumor)
- Adverse events resulting in death:
  - Disease progression (2 patients), saddle pulmonary embolus (1 patient), and dyspnea (1 patient)

### CLINICAL ACTIVITY PER RECIST CRITERIA

- 26 of 36 enrolled patients were evaluable for response as of the March 15, 2010 date cut-off date
  - 2 patients had not yet reached the Week 8 response assessment, and 8 patients discontinued prior to the Week 8 response assessment
- 1 patient with melanoma achieved a confirmed partial response (PR)
- 10 patients achieved stable disease (SD)
- The Maximum Tolerated Dose (MTD) has not yet been reached; dose escalation continues

### PHARMACOKINETICS

- Figure below shows a linear relationship between dose and exposure (AUC)
- Overlapping regression lines indicate essentially identical exposures on Day 1 and Day 15
- No drug accumulation is seen upon multiple dosing
- Concentrations rise rapidly during infusions
- Biphasic pharmacokinetics are observed: plasma concentration declines by approximately 10 fold within 1 hour, and approximately 100 fold within 10 hours of infusion termination



## CONCLUSIONS

- STA-9090 appears to be well-tolerated at the dose levels administered in this regimen of twice-weekly dosing to date (from 2-50 mg/m<sup>2</sup>)
- Enrollment in the study continues, with the objective of identifying the MTD and recommended Phase 2 dose for a twice-weekly schedule
- STA-9090 shows linear PK and no accumulation; Day 1 and Day 15 exposures are essentially identical
- Encouraging early signs of clinical activity have been observed although the MTD has not been reached yet
- Safety and tolerability are also being assessed in a once-weekly dosing regimen, data presented in Poster #2529
- The once-weekly schedule has been selected for ongoing Phase 2 studies in NSCLC, GIST, colon cancer, AML and gastric cancer

## ACKNOWLEDGEMENTS

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