

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

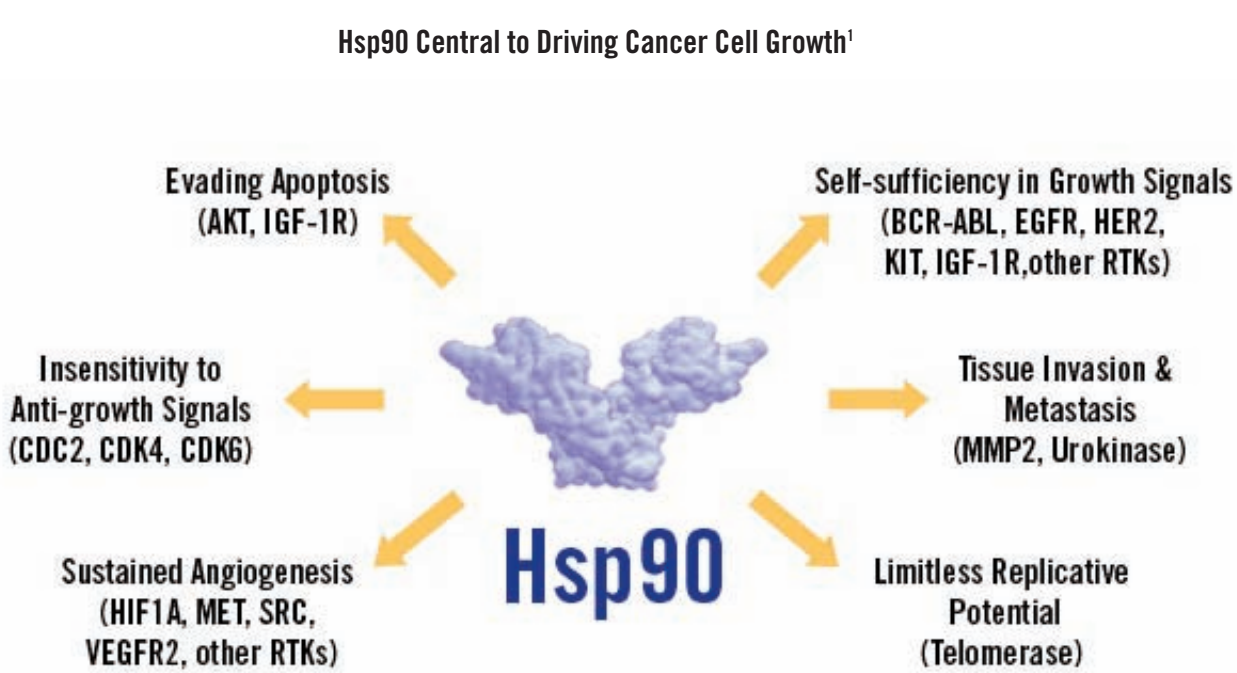
J. W. Goldman¹, R. N. Raju², G. A. Gordon², V. M. Vukovic³, R. Bradley³, L. S. Rosen¹

¹Premiere Oncology, Santa Monica, CA; ²US Oncology, Dayton, OH; ³Synta Pharmaceuticals Corporation, Lexington, MA

BACKGROUND

HSP90 INHIBITION

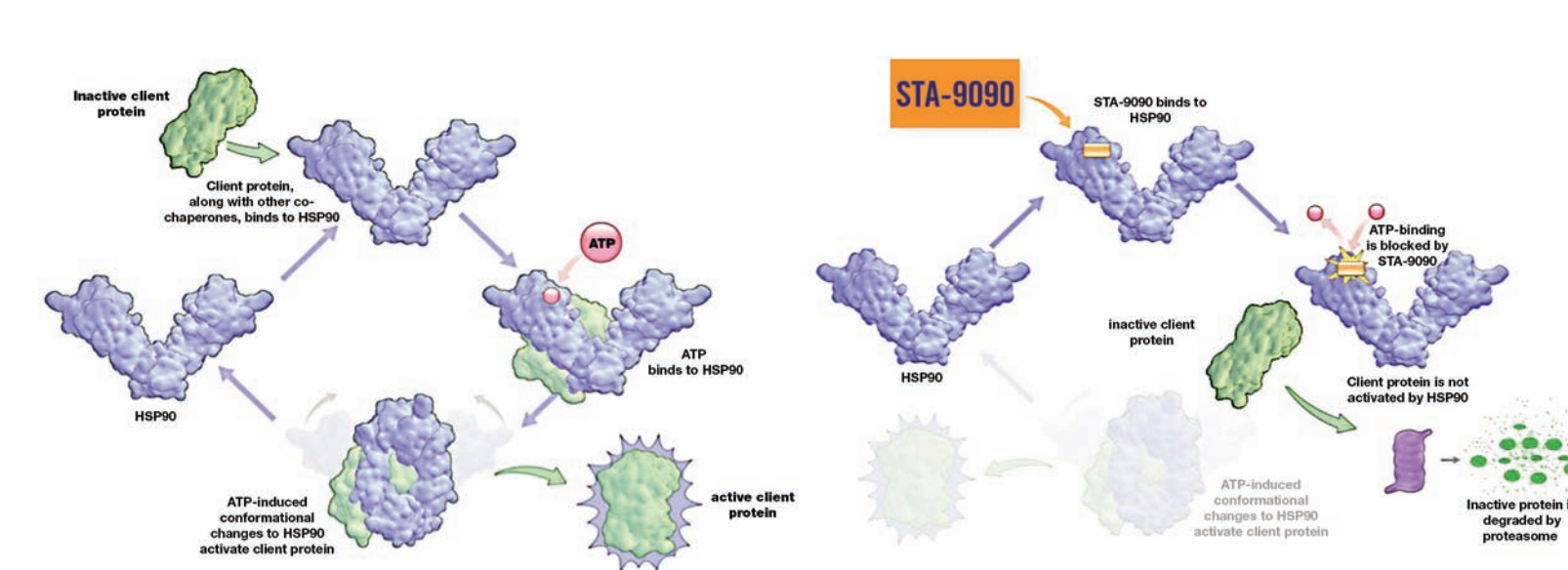
- Hsp90 is a chaperone protein that maintains the proper conformation and function of many proteins that play a critical role in tumor pathophysiology such as EGFR, HER2, c-MET, AKT, BCR-ABL, RAF, CDK4, c-KIT, FLT3, and VEGFR
- Degradation of client proteins by inhibiting Hsp90 allows for simultaneous 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



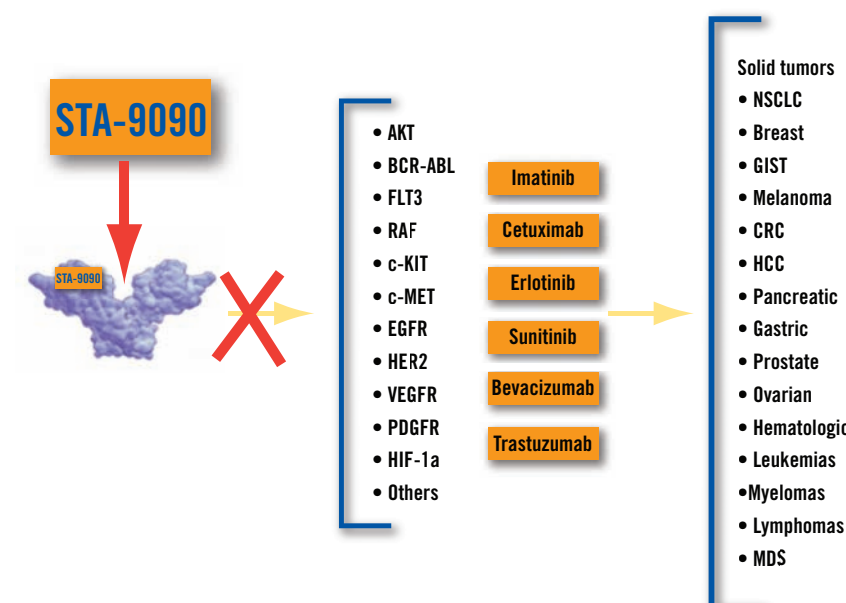
OVERVIEW

- Potent, second-generation small molecule Hsp90 inhibitor^{2,4}
 - 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^{2,4}
- 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 (17-AAG)
- Selectively accumulates in tumors with a tumor half-life of approximately 60 hours
- Penetrates deeply into hypoxic tumors, inhibiting HIF-1 α
- Administered as one hour IV infusion

HSP90 CHAPERONE CYCLE



STA-9090 DEGRADES PROTEINS CRITICAL TO GROWTH OF MULTIPLE CANCERS



METHODS

STUDY DESIGN

- Phase 1, open-label, dose-escalation clinical trial
- Eligible patients had advanced or metastatic solid tumors which were refractory to prior therapies or for which no standard therapy existed
- STA-9090 was administered over a 1-hour infusion, once weekly for 3 weeks, followed by a 1-week dose-free interval (for a 4-week cycle)
- Standard "3 + 3" design; 3 patients enrolled at each dose level, if one patient had a Dose-Limiting Toxicity (DLT) during Cycle 1, three more were enrolled. If ≥ 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 escalated from a starting dose of 7 mg/m² to 14, 23, 35, 49, 65, 86, 114 and 150 mg/m², with continued escalation as appropriate at a 20% increase in dose at each level, with doses administered up to 259 mg/m²
- After the MTD was reached, 6 additional patients were enrolled at the MTD level. Five patients are still on study drug; the data cut-off date was March 15, 2010

RESULTS

PATIENT DEMOGRAPHICS AND BASELINE STATUS

		7-86 mg/m ² (n=22)	114-150 mg/m ² (n=10)	180-216 mg/m ² (n=15)	259 mg/m ² (n=6)
Age	Median	63	58	60	61
Sex	Male	11	3	12	3
	Female	11	7	3	3
Race	White/Caucasian	22	9	12	6
	Other	0	1	3	0
ECOG Status	0	9	3	3	2
	1	11	7	12	4
	2	2	0	0	0
Prior Regimens	<2	1	1	2	1
	≥ 2	21	9	13	5

- Tumor type distribution: NSCLC (10); colon (8); prostate (3); esophageal (3); GIST (2); melanoma [2 (1 ocular)]; SCLC (2); pancreatic (2); ovarian (2); other (19)
- At the time of study enrollment, 51 patients (96%) had Stage 4 cancer, and 2 patients (4%) had unresectable Stage 3 cancer

SUMMARY OF ADVERSE EVENTS

	Number of patients (%)	7-86 mg/m ² (n=22)	114-150 mg/m ² (n=10)	180-216 mg/m ² (n=15)	259 mg/m ² (n=6)
Any AE		22 (100%)	10 (100%)	15 (100%)	6 (100%)
Any Grade 3 AE		14 (64%)	7 (70%)	10 (67%)	5 (83%)
Any Grade 4 AE					1 (16%)
Any SAE		4 (18%)	5 (50%)	3 (20%)	2 (33%)
Any DLT		0	1 (10%)	1 (7%)	3 (50%)
AEs leading to treatment discontinuation*		3 (14%)	0	1 (7%)	0
AEs leading to death*		2 (9%)	1 (10%)	0	0

* Not related to Study Drug

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

	Number of patients (%)	7-86 mg/m ² (n=22)	114-150 mg/m ² (n=10)	180-216 mg/m ² (n=15)	259 mg/m ² (n=6)
Diarrhea		17 (77%)	10 (100%)	14 (93%)	6 (100%)
Fatigue		11 (50%)	3 (30%)	11 (73%)	5 (83%)
Abdominal pain		7 (32%)	5 (50%)	7 (47%)	1 (17%)
Nausea		5 (23%)	3 (30%)	6 (40%)	4 (67%)
Anemia		10 (46%)	2 (20%)	5 (33%)	0
Alkaline phosphatase increased		5 (23%)	2 (20%)	3 (20%)	0
Insomnia		0	5 (50%)	3 (20%)	2 (33%)
AST increased		3 (14%)	2 (20%)	4 (27%)	0
Decreased appetite		2 (9%)	3 (30%)	4 (27%)	0
Dyspnea		3 (14%)	4 (40%)	1 (7%)	1 (17%)
Vomiting		3 (14%)	1 (10%)	3 (20%)	2 (33%)
Constipation		4 (18%)	2 (20%)	2 (13%)	0
Headache		2 (9%)	1 (10%)	4 (27%)	1 (17%)
Peripheral edema		3 (14%)	1 (10%)	4 (27%)	0
Asthenia		2 (9%)	2 (20%)	1 (7%)	2 (33%)
Back pain		4 (18%)	0	1 (7%)	2 (33%)
Hypokalemia		2 (9%)	1 (10%)	3 (20%)	1 (17%)
Hypophosphatemia		3 (14%)	3 (30%)	1 (7%)	0
Urinary tract infection		2 (9%)	2 (20%)	1 (7%)	2 (33%)
ALT increased		2 (9%)	2 (20%)	2 (13%)	0
Dehydration		1 (5%)	0	2 (13%)	3 (50%)
Weight decreased		0	2 (20%)	4 (27%)	0

MOST COMMON ADVERSE EVENTS GRADE ≥ 3 (OCCURRING IN ≥ 2 PATIENTS)

	Number of patients (%)	7-86 mg/m ² (n=22)	114-150 mg/m ² (n=10)	180-216 mg/m ² (n=15)	259 mg/m ² (n=6)
Fatigue		1 (5%)	0	4 (27%)	1 (17%)
Diarrhea		1 (5%)	1 (10%)	1 (7%)	1 (17%)
Hypophosphatemia		0	3 (30%)	1 (7%)	0
Asthenia		1 (5%)	0	0	2 (33%)
Alkaline phosphatase increased		2 (9%)	0	1 (7%)	0
Hyperbilirubinemia		1 (5%)	1 (10%)	1 (7%)	0
Hyponatremia		3 (14%)	0	0	0
Blood amylase increased		1 (5%)	1 (10%)	0	0
Dehydration		1 (5%)	0	0	1 (17%)
Hypokalemia		0	0	2 (13%)	0
Spinal cord compression		1 (5%)	1 (10%)	0	0

DOSE DETERMINATION

- 216 mg/m² was established as the MTD for once-weekly dosing.
 - The highest dose level evaluated was 259 mg/m²
 - DLTs of Grade 3 diarrhea and Grade 3 and 4 asthenia observed at this dose level
 - The once-weekly recommended Phase 2 dose is 200 mg/m²

RESULTS

SAFETY SUMMARY

- Most common adverse events: gastrointestinal events (diarrhea, nausea, vomiting); most events were transient, manageable, and mild or moderate in severity; 8% of patients reported Grade 3 diarrhea; no patients reported severe events of nausea or vomiting
- Serious Adverse Events: 14 patients reported SAEs; dyspnea was reported by 2 patients; all other SAEs were reported in one patient each
- Adverse events leading to discontinuation (none related to study drug): hepatic failure (resulting in death); spinal cord compression; bile duct obstruction; asthenia/malaise/abdominal pain/ascites/fluid retention
- Adverse events resulting in death (none related to study drug): bowel obstruction; respiratory failure

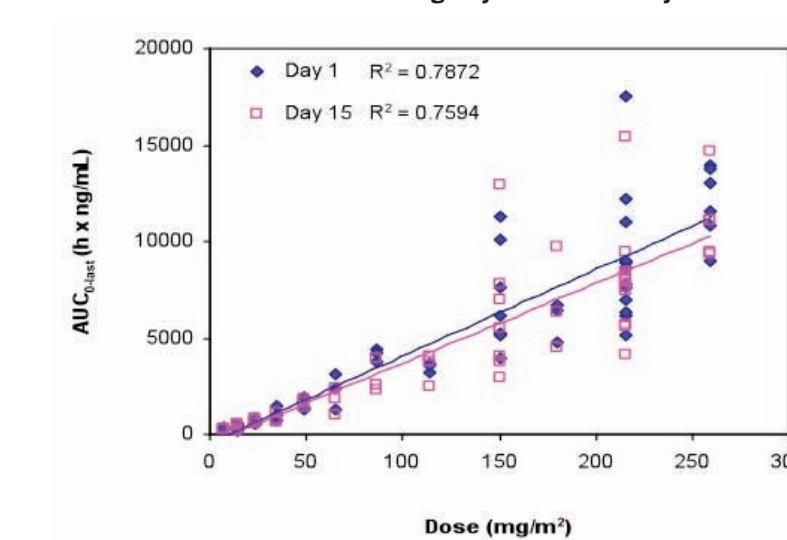
CARDIAC MONITORING

- Decrease in heart rate
 - Asymptomatic, acute, modest and transient decreases in heart rate (5-10 bpm) were seen with consequent expected PR interval prolongation
 - Changes returned to baseline value by the time of ECG evaluation at the next dosing and did not lead to brady-arrhythmia
- QTc interval
 - Small increase of the interval was seen in the higher dose groups (180-216 mg/m²)
 - Finding is modest in scale and not clinically significant
- Cardiac monitoring will continue in ongoing clinical trials

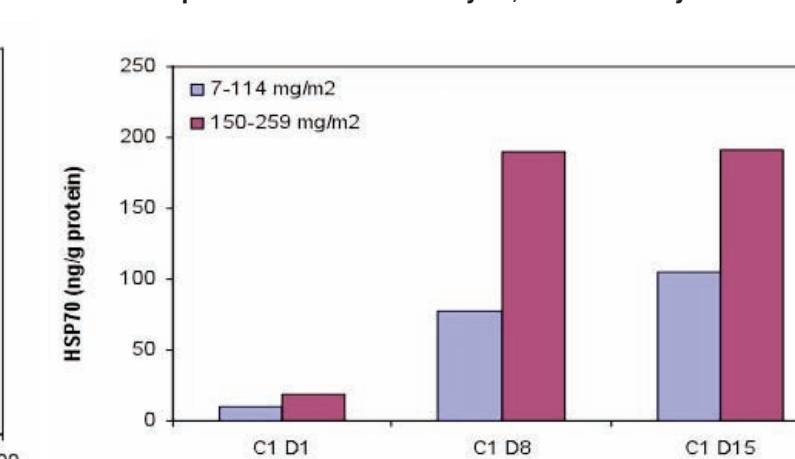
PHARMACOKINETICS AND PHARMACODYNAMICS

- The figure on the left shows a linear relationship between dose and exposure (AUC)
 - 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.
- The figure on the right shows levels of Hsp70 protein in plasma in patients prior to STA-9090 exposure on days 1, 8 and 15 of Cycle 1. Data are pooled into lower dose and higher dose groups due to the small number of patients in each dose cohort. Data shows evidence of dose-dependent biological activity of STA-9090

AUC of STA-9090 on Dosing Days 1 and 15 of Cycle 1



Hsp70 Plasma Levels on Days 1, 8 and 15 of Cycle 1



CLINICAL ACTIVITY PER RECIST CRITERIA

- 42 of 53 enrolled patients were evaluable for response by RECIST criteria as of the March 15 data cut-off date
 - 11 patients discontinued prior to the 8 week response assessment
- 1 patient with colon cancer achieved a confirmed partial response (PR)
- 23 patients achieved stable disease (SD)
 - 16 patients had stable disease for ≥ 16 weeks
 - 4 patients had stable disease < 16 weeks
 - 3 patients have stable disease at Week 8, and remain on study

CASE STUDY #1

- 66-year-old white male with bronchoalveolar non-small cell lung cancer
- Six prior treatment regimens including 8 different drugs
 - Erlotinib, bevacizumab, carboplatin, paclitaxel, pemetrexed, bortezomib and topotecan.
 - Best response: Progressive disease. Treatment duration: 2- 4 months each
 - Rexinoid (investigational). Best response: Stable Disease. Treatment Duration: 3 months
- Enrolled in February 2009, received STA-9090 once-weekly at 150 mg/m²
- 25% reduction in target lesions documented after Cycle 4 (SD)
- Treatment Duration with STA-9090: 13 months
- Adverse events of mild diarrhea and moderate hypophosphatemia

CASE STUDY #2

- 49-year-old white male with Gastrointestinal Stromal Tumor (GIST)
- Five prior treatment regimens with 6 different drugs
 - Imatinib, gemcitabine, docetaxel, sorafenib; Best response: progressive disease. Sunitinib; Best response: stable disease
- Enrolled in July 2009, received STA-9090 once weekly at 216 mg/m²
- After 2 cycles, demonstrated Stable Disease (SD) per RECIST. He continued STA-9090, with an 18% reduction in target lesion size after Cycle 4 (SD).
- Treatment Duration with STA-9090: 8 months before progressive disease.
- Adverse events of mild diarrhea, sleep disturbance and fatigue.

CONCLUSIONS

- STA-9090 was well-tolerated at dose levels of 7- 216 mg/m² administered on a once-weekly schedule
- At the highest dose tested, 259 mg/m², dose-limiting toxicities observed (grade 3 asthenia and diarrhea) were transient and reversible
- The MTD was established at 216 mg/m²
- There was no evidence of severe hepatic or ocular toxicity
- STA-9090 shows linear PK and no accumulation; Day 1 and Day 15 exposures are essentially identical
- Hsp70 plasma levels show evidence of dose-dependent biological activity of STA-9090
- Final study results are expected by end of 2010
- Encouraging signs of clinical activity were observed
- Phase 2 studies in NSCLC, GIST, colon cancer, AML and gastric cancer are ongoing at the 200mg/m² dose

ACKNOWLEDGEMENTS

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