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A phase 1 and pharmacokinetic study of ganetespib (STA-9090), a heat shock protein 90 inhibitor, in combination with docetaxel in subjects with advanced solid tumor malignancies.

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Background: Ganetespib is a potent, next-generation Hsp90 inhibitor that is structurally unrelated to the first-generation ansamycin class of Hsp90 inhibitors and has shown superior activity to these agents in preclinical studies. Ganetespib has been well tolerated and has shown promising single-agent antitumor activity in early trials in multiple cancers. Based on preclinical synergy between ganetespib (G) and docetaxel (D), a phase I pharmacokinetic (PK) and feasibility study was initiated with the combination..

Materials and Methods: Patients (pts) with advanced solid tumor malignancies and ECOG performance status (PS) 0-2 were eligible. Sequential cohorts of pts were treated (3+3 design) with increasing doses of D (day 1) and G (days 1, 8) administered as a 1-hr separate infusion in a 3-week cycle. PK sampling was performed on days 1/8 of cycle 1. The primary endpoint was determination of optimal doses of the two agents for combination therapy..

Results: Thirteen pts were enrolled in the dose escalation phase. Median age-63 (44-72); 2-M, 11-F; ECOG PS 0-1, 1, 12. At dose levels 1 (D-60 mg/m², G-150 mg/m²) and 2 (D-75 mg/m², G-150 mg/m²), none of 6 pts initially treated had a DLT. Two of 4 pts at dose level 3 (D-75 mg/m², G-200 mg/m²) had DLTs (g4 febrile neutropenia and one g4 neutropenia of > 7 days), requiring expansion of dose level 2. As no other DLTS were observed; level 2 was the expansion cohort. Common AEs included neutropenia (n=10), diarrhea, anemia and fatigue (n=4 each), nausea and febrile neutropenia (n=3 each). Common g 3/4 AEs included neutropenia (n=10) and febrile neutropenia (n=3). The median number of cycles received is 4 (1-8), with 6 pts still on study. Among 10 pts evaluable for response, 7 had disease stabilization following cycle 2 (6 weeks), 4 pts to 12 weeks and 1 pt to 18 weeks. PK data from dose level 1 indicates PK similarity

between G administered alone and G administered prior to D. No drug accumulation was observed following once-weekly dosing which is consistent with other studies where G was administered alone. Additional PK data will be presented.

Conclusions: The combination of docetaxel and ganetespib is well tolerated at the recommended doses of 75 mg/m² and 150 mg/m². Promising anti-cancer activity was noted, and a randomized phase II study of the combination has been initiated in advanced NSCLC.