

Abstract # 3051

## **A phase 1 dose-escalation study of the Hsp90 inhibitor ganetespib (STA-9090) administered twice weekly in patients with solid tumors: Updated report.**

D. C. Cho, E. I. Heath, J. M. Cleary, E. L. Kwak, L. Gandhi, D. P. Lawrence, C. Zack, F. Teofilovici, R. Bradley, M. D. Karol, G. Shapiro, P. LoRusso

Beth Israel Deaconess Medical Center, Boston, MA; Karmanos Cancer Institute/ Wayne State University, Detroit, MI; Dana Farber Cancer Institute, Boston, MA; Division of Hematology and Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Karmanos Cancer Institute, Detroit, MI; Synta Pharmaceuticals Corporation, Lexington, MA

**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. It has been well tolerated and shown promising antitumor activity in early trials in multiple cancers. Preclinical data indicate that different client proteins show disparate expression kinetics upon Hsp90 inhibition. Therefore, twice-weekly dosing may be needed in some tumor types.

**Methods:** Patients (pts) with solid tumors who have exhausted standard treatment options received ganetespib as a 1 hr infusion twice weekly for 3 weeks (wks) of a 28 day cycle until disease progression. Serial PK and pharmacodynamic samples were obtained during cycle 1. Safety assessments included frequency and grade of AEs, laboratory parameters and ECG changes.

**Results:** Data are presented for 49 pts (22 M, 27 F; median age 55 yrs, range 32-81; ECOG status range 0-2) treated at doses from 2-144 mg/m<sup>2</sup>. Pts received a median of 2 (range 1-12) cycles of ganetespib. AEs reported in  $\geq 20\%$  of pts treated at doses from 2-120 mg/m<sup>2</sup> are fatigue, diarrhea, nausea, anemia, abdominal pain, constipation, anorexia, vomiting, and headache; the majority of events were mild to moderate in severity with absence of severe liver, ocular, cardiac and renal toxicity. Two DLTs (elevated transaminases) have been reported in the 10 and 144 mg/m<sup>2</sup> cohorts; expansion of the latter cohort is ongoing. Ganetespib shows linear PK, rapid distribution, a mean terminal half-life of 10-14 hours, a volume of distribution greater than total body water and no accumulation in plasma. HSP70 plasma protein levels will be presented. A confirmed durable PR by RECIST has been seen in a pt with metastatic melanoma. Additionally, 2 NSCLC pts who received 6 months of treatment had durable SD, with tumor shrinkage.

**Conclusions:** Ganetespib has been well tolerated at dose levels up to 120 mg/m<sup>2</sup> administered twice weekly. Preliminary safety profile, activity signals and differences in client protein kinetics warrant continued evaluation of ganetespib using a twice-weekly dosing regimen. Dose escalation continues.