

An open-label phase II study of the Hsp90 inhibitor ganetespib (STA-9090) in patients with advanced non-small cell lung cancer (NSCLC).

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Background: Ganetespib, a potent, non-geldanamycin small molecule Hsp90 inhibitor has shown superior preclinical activity and improved safety profile compared to ansamycins (17-AAG). Ganetespib is broadly active in multiple highly-resistant cancer models. Preclinical data support evaluation of Hsp90 inhibitors in NSCLC driven by a variety of mutant oncogenic proteins.

Methods: Patients (pts) with progressing advanced NSCLC who failed standard of care treatments received 200 mg/m² ganetespib as a 1-hr infusion once weekly for 3 of a 4-wk cycle in a Simon two-stage study design assessing primary endpoint of PFS rate at 16 wks. Patient cohorts were defined by mutation status: A) *mEGFR* B) *mKRAS*, C) *EGFR* and *KRAS* wild type (WT). If $\geq 2/14$ pts in A, B or C were progression-free at 16 wks, enrollment increased to 23 pts for that cohort. Tumor response was assessed every 8 wks. Cohort D was later added to include 35 additional *EGFR* and *KRAS* WT pts with adenocarcinoma histology. Additional mutational analysis of *BRAF*, *PIK3CA*, *ERBB2* and *MET*, as well as FISH analysis for *ALK* translocation, were performed in a subset of patients.

Results: 73 pts (31 M, 42 F; median age 62 yrs, range 28-82; ECOG 0-1; prior therapies range 1-10) received a median of 2 cycles (range 1-12) of ganetespib in cohorts A (14), B (17), and C+D (42). AEs reported in $\geq 20\%$ of pts included diarrhea, fatigue, nausea, anorexia, constipation, and dyspnea and were generally grade 1-2. Cohort expansion criteria were met for cohort C, including a durable partial response (PR) and seven pts with stable disease ≥ 16 wks. Cohort D continues recruitment with preliminary results of two confirmed PRs. Genetic profiling data will be presented.

Conclusions: Ganetespib administered as a single agent is well tolerated in pts with NSCLC at 200 mg/m² once weekly without serious liver or common ocular toxicities seen with other hsp90 inhibitors. Clinical activity has been observed in patients with advanced NSCLC tumors harboring wild-type *EGFR* and *KRAS*.