

Abstract # 10011

## **An open label phase 2 study of the Hsp90 inhibitor ganetespib (STA-9090) in patients (pts) with metastatic and/or unresectable GIST.**

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**Background:** Ganetespib, a potent, synthetic small-molecule inhibitor of Hsp90, has shown an improved safety profile relative to 1<sup>st</sup>-generation agents as well as promising signals of antitumor activity in early clinical studies, including one pt with PDGFRA<sup>D842V</sup> mutant GIST. Preclinical studies have shown that human GIST cells with primary or secondary TKI-resistance mutations are highly sensitive to ganetespib, justifying this phase 2 trial in GIST.

**Methods:** Pts with advanced GIST following failure of prior therapy (tx) received ganetespib (200 mg/m<sup>2</sup>) as a 1 hour IV infusion qw for 3 wks of a 28 day cycle. GIST status was assessed q8 wks per RECIST, until progression. In this Simon's 2 stage study design, if  $\geq 4/23$  pts in Stage 1 had clinical benefit (CR+PR+SD  $\geq 16$  wks) enrolment would continue with Stage 2. Hsp90 client protein levels were analyzed in biopsies pre-tx and 24-48 h post-ganetespib in a subset of pts.

**Results:** 26 pts (15 M, 11 F; median age 53 yrs, range 33-67; ECOG status 0-1; median 5 prior tx regimens, range 3-12, wild-type PDGFRA) received a median of 2 cycles of ganetespib (range 1-8). AEs reported in  $>20\%$  of pts were generally NCI CTC grade 1-2 and included diarrhea, fatigue, nausea, vomiting, increased alkaline phosphatase, headache, insomnia, and abdominal pain. 12/23 evaluable pts had SD (4 SD  $\geq 16$  wks, 8 SD  $\geq 8$  wks), meeting formal criteria to enroll Stage 2. However, analysis of client proteins in paired tumor biopsies from 4 pts did not show prolonged inhibition of activated KIT or its downstream pathways. These data suggest the once-weekly tx schedule is likely not optimal for inhibition of KIT. At this time, accrual has been limited to pts with PDGFRA mutations to allow further preclinical development of alternative schedules and combinations.

**Conclusions:** Ganetespib given by once-weekly dosing was well tolerated in pts with heavily pre-treated advanced GIST, with no evidence of severe liver, ocular, cardiac or renal toxicity. Disease stabilization was seen in a subset of pts. Advanced preclinical modeling is ongoing to optimize the impact of ganetespib on mutant KIT in GIST.