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AUY922, a novel HSP90 inhibitor: Final results of a first-in-human study in patients with advanced solid malignancies.

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Phase I Studies

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Developmental Therapeutics - Clinical Pharmacology and Immunotherapy

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Abstract Disclosures

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Abstract:

Background: AUY922, a novel isoxazole-based HSP90 inhibitor, causes the degradation of multiple oncogenic cellular proteins and preclinical data suggest broad antitumor activity. **Methods:** Single agent AUY922 was administered as IV infusion over 1h, once weekly, to patients (pts) with advanced solid tumors to determine the maximum tolerated dose (MTD) in a phase I study. Dose escalation was guided by a Bayesian logistic regression model with overdose control. Endpoints included safety, tolerability, preliminary activity, PK, and PD. **Results:** 96 pts received AUY922 at doses of 2-70 mg/m^2 (23 pts at 70 mg/m^2). Pt characteristics: median age 57 yrs, 96% WHO performance status 0 or 1, 41% male, and 82% Caucasian. The most frequently reported adverse events possibly related to AUY922 were diarrhea in 53 pts (55%), nausea in 34 pts (35%), fatigue in 31 pts (32%), night blindness in 19 pts (20%), and vomiting in 18 pts (19%). Visual symptoms (mainly grade 1-2 and mostly reversible) including blurred vision, flashing, and delayed dark/light accommodation were reported starting at 40 mg/m^2, and increased in frequency or severity with dose. Dose limiting toxicities, all grade 3, included atrial flutter (22 mg/m^2), anorexia, fatigue, and diarrhea (40 mg/m^2), asthenia and diarrhea (54 mg/m^2) and diarrhea and darkening of vision (70 mg/m^2). The MTD was 70 mg/m^2. Median duration of exposure was 7.0 weeks (range; 1, 80). Disease stabilization was reported in 16 pts and 9 pts reported partial metabolic response in FDG-PET scans. AUY922 blood concentration followed a bi-exponential decline with a fast a phase ($t_{1/2}$ <10 min) and a slow β phase ($t_{1/2}$ ~60h). Dose-related induction of HSP70, indicating inhibition of HSP90, was seen. A phase II expansion study in pts with advanced breast cancer (HER2+ and ER+) has begun. **Conclusions:** Weekly IV infusion of single agent AUY922 was well tolerated at the MTD of 70 mg/m^2. Disease stabilization was seen in a subset of pts receiving AUY922.

Associated Presentation(s):

1. AUY922, a novel HSP90 inhibitor: Final results of a first-in-human study in patients with advanced solid malignancies.

Meeting: 2010 ASCO Annual Meeting
Presenter: Thomas A. Samuel
Session: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy (Poster Discussion Session)

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