A study of HSP90 inhibitor AT13387 alone and in combination with crizotinib (CZT) in the treatment of non-small cell lung cancer (NSCLC)


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Aim: Hsp90 is a molecular chaperone required for the proper folding and function of the anaplastic lymphoma kinase (ALK) protein. AT13387 (AT), a synthetic Hsp90 inhibitor displays potent antitumor activity and delays the onset of crizotinib (CZT) resistance in ALK-driven lung cancer xenograft models. A 3-Part, Phase 1/2, randomized study was initiated to investigate AT alone or in combination with CZT in patients with NSCLC receiving CZT. Here we present the Phase 1 results.

Methods: The primary objectives were the safety and tolerability of CZT/AT and to select the AT dose for the Phase 2 parts of the study based on assessment of safety and antitumor activity. Secondary endpoints included pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity. Part A utilized a rolling six design to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of the combination. Patients who previously tolerated 8 weeks of CZT at 250 mg BID continued to receive oral CZT at 250 mg BID plus IV AT dosed Days 1, 8, and 15 of a 28 day dosing cycle (dosing cohorts of 150, 180, or 220 mg/m²).

Results: In Part A, 32 patients (median age 59 years, range 29-75 years) were treated in 3 dosing cohorts. All subjects had prior CZT treatment (best prior response being 2 CR, 10 PR, 13 SD, 4 PD, and 3 unknown). AT was escalated up to 220 mg/m² without DLTs. Among the 32 patients, the mean number of AT cycles was 4.2 (range 1-11+). The combination was generally well tolerated with only diarrhea (19%) occurring in more than 5% of subjects as an AT-related AE ≥ Grade 3. PK analysis showed AT exposures were similar to that observed in previous AT phase 1 studies at the same dose levels. CZT exposures were not affected when co-administered with AT. In 24 evaluable pts, 4 RECIST PR were observed and 15/24 subjects had a best response of decrease in tumor size.

Conclusions: Our study represents the first clinical trial of an Hsp90 inhibitor in combination with CZT. CZT/AT doses of 250 mg BID/220 mg/m² were well tolerated with multiple objective responses observed, including in patients progressing on prior CZT, so was selected as the RP2D. Phase 2 studies of CZT/AT in patients prior to or after progression on CZT are ongoing.

Disclosure: N.A. Pennell: Consultant for Genentech; A. Oganesian: Astex employee L. Manlapaz-Espiritu: Astex employee; H. Keer: Astex employee; J. Soria: Advisory Board for Astex & Pfizer; D.R. Camidge: Honoraria from Astex & Pfizer. All other authors have declared no conflicts of interest.