genitourinary tumours, prostate

A PHASE 1/2 STUDY OF AT13387, A HEAT SHOCK PROTEIN 90 (HSP90) INHIBITOR IN COMBINATION WITH ABRITERONE ACETATE (AA) AND PREDNISONE (P) IN PATIENTS (PTS) WITH CASTRATION-RESISTANT PROSTATE CANCER (mCRPC) NO LONGER RESPONDING TO AA

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Aim: Hsp90 is a molecular chaperone required for the proper folding and function of multiple client proteins including the androgen receptor (AR). AT13387 (AT), a synthetic Hsp90 inhibitor displays activity against multiple prostate cancer models. A 2-part, Phase 1/2, randomized study was initiated to investigate the combination of AT + AA/P in mCRPC pts progressing on AA.

Methods: The primary objectives were the safety and tolerability of AT/AA/P and to select the treatment regimen for the Ph2, based on assessment of safety and antitumor activity. Secondary endpoints included pharmacokinetics (PK), pharmacodynamics (PD), and progression-free survival (PFS). Part 1 used a rolling six design to determine the maximum tolerated dose (MTD) of the AT/AA/P combination. All pts continued to receive oral AA/P (1000 mg Qd/5 mg BID) at progression, being randomized to receive 1 of 2 AT dosing regimens: AT at the starting dose of 220 mg/m² IV once weekly for 3 weeks (R1), or 120 mg/m² on Days 1 & 2 weekly for 3 weeks (R2) in a 4-week cycle. PD studies evaluated AR expression in tissue and circulating tumor cells (CTC) pre and post AT treatment.

Results: Overall 48 patients were treated (R1: AT at 220-260 mg/m²; R2: AT at 120-160 mg/m²). The most frequent AT- treatment related ≥ Grade 3 toxicities were diarrhea (21%) and fatigue (13%). Diarrhea was dose-limiting for both regimens (AT at 260 mg/m² and 160 mg/m² for R1 and R2, respectively). PK analysis showed that AT exposures were similar to what was observed in previous studies while AA exposures appeared to be ~30% lower when co-administered with AT. PD analyses indicated limited target knockdown. Multiple subjects showed transient decreases in PSA but no PCWG2 PSA responses or objective RECIST tumor responses were observed and the study did not proceed to Ph2.

Conclusions: Our study represents the first clinical trial of an Hsp90 inhibitor in combination with AA/P. MTDs were reached for once-weekly (220 mg/m²) and twice-weekly (120 mg/m²) regimens; however AT + AA/P did not demonstrate adequate antitumor activity at these doses for the study to proceed to Part 2.

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