Phase I Study Assessing a Two-Consecutive Day (QD x 2) Dosing Schedule of the Hsp90 Inhibitor, AT13387, in Patients with Advanced Solid Tumors

K Do1, G Sperranza1, A Chen1, J Trepel1, M-J Lee1, S Lee1, L Phillips1, J Collins1, M Weil1, R Kinders2, S Khin2, D Allen1, R Parthasarathy2, JH Doroshow1, S Kummer1

1National Cancer Institute, National Institutes of Health, Bethesda, Maryland; 2SAIC-Frederick, Inc. Frederick, MD

BACKGROUND

AT13387 is a synthetic, non-ansamycin, small molecule inhibitor of Hsp90 (Kd 0.71 nM) that binds to the N-terminal ATP-binding site, inhibiting chaperone function and promoting degradation of client proteins. Hsp90 is an important chaperone for client proteins involved in cell survival and proliferation, including Akt, Raf, and Her2/neu. Administration of AT13387 results in down-regulation of key oncoproteins and downstream proteins such as pERK in preclinical models.

STUDY DESIGN

• Accelerated Simon 2B design with 1 patient cohort for the first three dose levels (20, 40, and 80 mg/m²), followed by a 3+3 design starting at DL 2.4
• AT13387 was supplied by the Division of Cancer Treatment and Diagnosis under Collaborative Research and Development Agreement with Araxis Pharmaceuticals.
• Dose Level AT13387 # pts treated
  120 mg/m² 1
  160 mg/m² 1
  200 mg/m² 3
  240 mg/m² 2
  280 mg/m² 2
  320 mg/m² 1
  360 mg/m² 1
• Pharmacokinetics
  • AT13387 administration results in accumulation with repeated dosing.
  • AT13387 inhibition of Hsp90 results in induction of Hsp70 protein levels.

SUMMARY

• 14 patients have been treated up to DLS (160 mg/m²)
• 5/14 patients had SD after 2 cycles
• Induction of Hsp70 was measured in PBMCs at all AT13387 dose levels
• Expression of Hsp9 and Hsp27 mRNA increased by >1.5-fold and 2-fold, respectively, in one patient following treatment with AT13387 at DL3. Expression of pERK and AKT1 changes were significantly decreased
• Serum markers of cellular apoptosis increased in 5/6 patients, though the change was not significant

CONCLUSIONS

• Preliminary data indicate that AT13387 QD x 2, weekly for 3 of 4 weeks, is well tolerated
• PK dose was proportional with no significant plasma accumulation with repeated dosing
• AT13387 inhibition of Hsp90 results in induction of Hsp70 at the transcriptional level in tumor biopsy, and produces a sustained induction of Hsp70 protein in PBMCs
• There is evidence of protein modulation by immunomodify with decreased levels of pERK and pERK in tumor biopsy after treatment with AT13387
• Accrual is ongoing to establish the MTD and obtain tumor biopsies for assessment of drug effect
• Optional ribbon-like trastuzumab scans will be performed to evaluate drug effect on HER2 levels in patients with HER2-expressing tumors

References

Kope E, H Li, Kparos TS et al. Hsp 90 inhibition transiently activates Src kinase and promotes Src-dependent Akt and Erk activation. PNAS 2006; 103: 1130-1135