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 Speranza¹, 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 Kummar¹



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BACKGROUND

AT13387 is a synthetic, non-ansamycin, small molecule inhibitor of Hsp90 (Kd 0.71 nM) that binds to the Nterminal 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 downregulation of key oncoproteins and downstream proteins such as pERK in preclinical models.

OBJECTIVES

- Define the safety and tolerability, and establish the maximum tolerated dose (MTD), of AT13387 administered IV QD x 2, weekly for 3 of 4 weeks; q 28d cycle
- Determine the pharmacokinetics (PK) and assess the pharmacodynamic (PD) effects of AT13387 in PBMCs and tumor biopsies

STUDY DESIGN

 Accelerated Simon 2B design with 1-patient cohorts for the first three dose levels (20, 40, and 80 mg/m²), followed by a 3+3 design starting at DL 4.

•AT13387 was supplied by the Division of Cancer Treatment and Diagnosis under Collaborative Research and Development Agreement with Astex Pharmaceuticals



- Optional pre- and post-treatment tumor biopsies performed at baseline and after the last dose of AT13387 in cycle 1 (on D16 or D17).
- Blood samples for PBMCs collected at baseline, prior to first AT13387 administration and immediately pre-dose on cycle 1, D2, D15, and D16. Blood samples for PK analyses obtained at baseline and after the start of infusion
- at 0.5, 1, 1.5, 2, 3, 4, 7, 10, 22 and 24 hours on D1 and D15 of cycle 1.
- Blood sampling for soluble PD markers performed at baseline, prior to first AT13387 administration and pre-dose on cycle 1, D16.

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*Number of patients experiencing adverse events felt to be related to study treatment by grade, listed as worst grade for each pt, grade 2 or higher; only grade 1 events were seen for dose levels 1-3

- **†**1 DLT (1 pt with liver metastases) at DL5, Gr 3 AST/ALT
- **‡**Visual disturbance (3 pts): 2 patients (Gr 1), 1 patient (Gr 2); symptoms were reversible, no objective findings on opthalmologic exam









Pharmacokinetics



• <10% urinary drug excretion detectable for 24 h after drug administration (not shown)

- AT13387 dose levels

- for 3 of 4 weeks, is well tolerated
- PBMCs

1530-1536.

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SUMMARY

• 14 patients have been treated up to DL5 (160 mg/m²) • 5/14 patients had SD after 2 cycles

• Induction of Hsp70 was measured in PBMCs at all

• Expression of Hsp70 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 by ELISA, though the change was not significant

CONCLUSIONS

Preliminary data indicate that AT13387 QD x 2, weekly

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

There is evidence of protein modulation by immunoassay with decreased levels of pAkt 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 indium-labeled trastuzumab scans will be performed to evaluate drug effect on HER2 levels in patients with HER2-expressing tumors

References

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