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# First in human phase I study - results of a second-generation non-ansamycin Heat Shock Protein 90 (HSP90) inhibitor AT13387 in refractory solid tumors

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## BACKGROUND

- HSP90 is required for functional stabilization of numerous client proteins which function as oncogenes in many tumor settings
- Inhibition of HSP90 results in degradation of those client proteins including mutant forms thus holding the promise of down-regulating multiple aberrant signaling pathways in a wide range of cancers
- The first generation ansamycin-derived HSP90 inhibitors showed initial clinical promise but had suboptimal pharmaceutical properties and encountered off-target pharmacological toxicity
- AT13387 is a second-generation novel potent non-ansamycin HSP90 inhibitor (Kd=0.71 nM) with good tissue distribution, excellent in vivo anti-tumor activity and long tumor half life in preclinical models (65-78 hours)
- This study is the First in Human (FIH) phase 1 study in refractory solid tumors
- Two dosing regimens were explored sequentially:
  - IV twice weekly x3 (days 1, 4, 8, 11, 15, 18) every 4 weeks
  - IV once weekly x3 (days 1, 8, 15) every 4 weeks

## OBJECTIVES

➢ **Primary**
- To identify the Maximum Tolerated Dose (MTD) of AT13387 when administered either twice weekly or once weekly on 3 consecutive weeks of a 4-week cycle

➢ **Secondary**:
- To characterize the safety and tolerability of AT13387 including the identification of Dose Limiting Toxicities (DLTs)
- To define the Pharmacokinetics (PK) of AT13387 in plasma and urine
- To demonstrate the Pharmacodynamic (PD) activity of AT13387 in plasma, circulating PBMC's, and optional tumor biopsies
- An additional objective is to detect preliminary anti-tumor activity of AT13387 in refractory solid tumor patients

## METHODS AND STUDY DESIGN

➢ Standard 3 + 3 design

➢ Main Eligibility Criteria:
- Adult patients with metastatic solid tumors refractory to standard therapy
- ECOG PS ≤ 2
- Adequate bone marrow, hepatorenal, and cardiac functions

➢ Dose Limiting Toxicities (DLTs)
- Neutropenia <0.5 x $10^9$/L for > 5 days or with fever
- Thrombocytopenia <25 x $10^9$/L accompanied by bleeding or thrombocytopenia <10 x $10^9$/L
- Any Grade 3 or 4 non-hematological toxicity which is not a consequence of tumor progression
- More than one individual dose omission of AT13387 during the first cycle of treatment due to the appearance of drug related toxicity

➢ AT13387 was given as an IV infusion over one hour

➢ The MTD of the twice weekly regimen was identified prior to further dose escalation according to a once weekly regimen

## AT13387 DOSE LEVELS AND EXPOSURE

| Dose Level (twice weekly x3 / 4 weeks) | Nb of Patients Treated | Nb of Cycles Received Range (median) |
|---|---|---|
| Cohort 1: 10 mg/m² | 4 | 1 – 3 (2) |
| Cohort 2: 20 mg/m² | 3 | 2 – 6 (2) |
| Cohort 3: 40 mg/m² | 3 | 2– 3 (3) |
| Cohort 4: 80 mg/m² | 5 | 2 – 8 (2) |
| Cohort 5: 120 mg/m² *(MTD)* | 13 | 1 – 4 (2) |
| **Dose Level (once weekly x3 / 4 weeks)** | | |
| Cohort 6: 150 mg/m2 | 4 | 1 – 3 (2) |
| Cohort 7: 180 mg/m2 | 3 | 2 – 3 (3) |
| Cohort 8: 220 mg/m2 | 8 | 1 – 12 (2) |
| Cohort 9: 260 mg/m2 *(MTD)* | 5 | 1 – 12 (2) |
| Cohort 10: 310 mg/m2 | 5 | 2 – 5 (3) |
| TOTAL | 53 | 1 – 12 (2) |

## PATIENT CHARACTERISTICS

| | |
|---|---|
| **Age** | Median 56 years (Range 28 – 76) |
| **Sex** | |
| Male | 27 (51%) |
| Female | 26 (49%) |
| **Performance Status (ECOG )** | |
| 0 | 28 (53%) |
| 1 | 24 (45%) |
| 2 | 1 (2%) |
| **Ethnicity** | |
| White | 42 (79%) |
| Black | 5 (9%) |
| Hispanic | 4 (8%) |
| Asian | 2 (4%) |
| **Diagnosis** | |
| Colorectal Cancer | 13 (25%) |
| Metastatic Melanoma | 9 (17%) |
| Non Small Cell Lung (NSCLC) | 9 (17%) |
| Gastrointestinal Stromal Tumours (GIST) | 7 (13%) |
| Prostate Cancer | 2 (4%) |
| Pancreatic Cancer | 2 (4%) |
| Others | 11 (21%) |
| **Prior Systemic Therapy** | |
| Nb of prior lines of therapy | Median 6 (Range 1 – 14) |

## SAFETY

### Drug-Related AEs ≥ 10% - All Patients (N=53)

| Adverse Event* | Nb of Patients (%) |
|---|---|
| Diarrhea | 32 (60%) |
| Fatigue | 21 (40%) |
| Visual Disturbances (flashes, blurry vision, diplopia, dark/light accommodation difficulties, …) | 19 (36%) |
| Nausea | 14 (26%) |
| Injection site events (pain, inflammation, …) | 13 (25%) |
| Dry Mouth | 12 (23%) |
| Anemia | 11 (21%) |
| Vomiting | 9 (17%) |
| Abdominal Pain | 9 (17%) |
| Systemic infusion reactions (flushing, rash, chills, …) | 8 (15%) |
| Hyponatremia | 7 (13%) |
| Decreased Appetite | 7 (13%) |
| Dizziness | 7 (13%) |
| Headache | 7 (13%) |
| Muscle Spasms | 7 (13%) |
| Insomnia | 6 (11%) |

*All were Gr 1 or 2 except 6 pts Gr 3 (11%), No Gr 4

### Drug-Related Grade 3 AEs (6 patients). No Grade 4 AEs

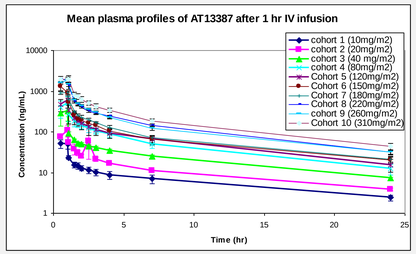
| Dose Level | Nb of Patients treated | Grade 3 AEs |
|---|---|---|
| 80 mg/m² twice weekly | 5 | 1 Hyponatremia |
| 120 mg/m² twice weekly | 13 | 2 Syncope*, 1 Visual Disturbances** |
| 220 mg/m² once weekly | 8 | 1 Increased Dyspnea |
| 310 mg/m² once weekly | 5 | 1 Hyponatremia |

*part of systemic infusion reactions
**fuzzy vision, flashing with ERG changes (cone suppression) all reversible

**MTD and Recommended Phase 2 Dose (RP2D):**
- Twice weekly regimen: 120 mg/m²/dose due to multiple Gr 2 GI AEs, Gr 3 systemic infusion reactions, and 1 Gr 3 visual disturbances (all reversible)
- Once weekly regimen: 260 mg/m² due to multiple Gr 2 GI AEs, and systemic infusion reactions at 310 mg/m² (Maximum Administered Dose or MAD)

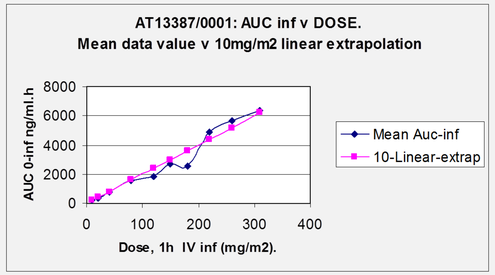
## PHARMACOKINETICS

### PK Profile at Different Dose Levels of AT13387




### AT13387 Dose Linearity

Trend of AUC-Dose proportionality maintained up to 310mg/m²

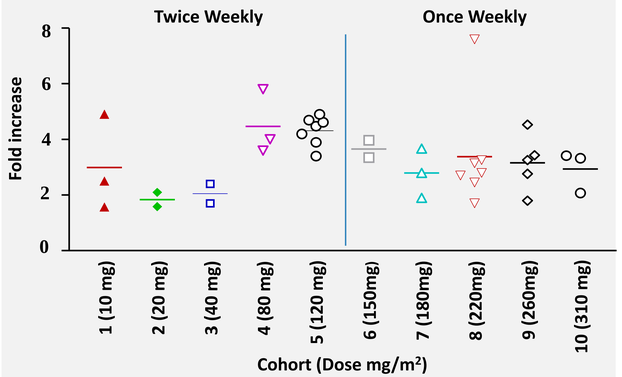



### PK Summary

- The pharmacokinetics of AT13387 following a 1h IV infusion show biphasic distribution with elimination half life of 6.5-9.1 hrs. Exposures (AUC, $C_{max}$) increased dose proportionally from 10 to 310 mg/m².
- AUC 0-t at the 260 mg/m² once weekly(MTD) was 5228 ± 233 ng*hr/mL and $C_{max}$ at 2164 ± 98 ng/mL
- Plasma clearance of AT13387 was independent of dose, showing a mean value of 1.5L/h/kg (sd=0.4L/h/kg) based on data from all dose cohorts
- In patients where a plasma concentration profile was defined on more than one treatment occasion there was low intra-patient variability; exposure to AT13387 did not accumulate in the twice weekly dosing regimen

## PHARMACODYNAMICS

### HSP70 Induction




Maximum fold increase of HSP70 at different dose levels. 2-7 fold increase in HSP70 was observed and exhibited evidence of dose dependence up to Cohort 4

## ANTI-TUMOR ACTIVITY

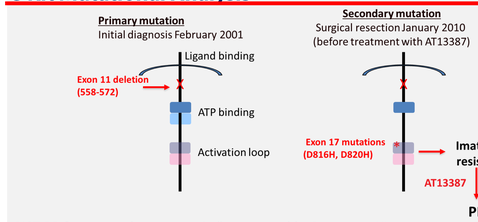
### Objective Response Assessment (N=53)

| Best Response by RECIST Criteria | Nb of Patients (%) |
|---|---|
| Partial Response (PR) | 1 (2%) |
| Stable Disease (SD) | 20 (38%) |
| Progressive Disease (PD) | 18 (34%) |
| Non-Evaluable (NE) | 14 (26%) |
| **TOTAL** | **53 (100%)** |

### Details of Patients with Clinical Benefit: PR, and SD> 5 Months

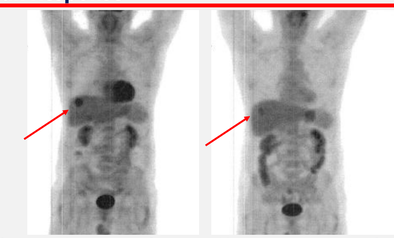
| Patient Number/ Tumor Type | Dose Level | Best Response | Duration of Response |
|---|---|---|---|
| 4010 / GIST | 220 mg/m² once weekly | PR | 8 Months |
| 4006 / GIST | 220 mg/m² once weekly | SD | 7 Months |
| 4011 / GIST | 260 mg/m² once weekly | SD | 11 Months |
| 1007 / Uveal Melanoma | 80 mg/m² twice weekly | SD | 7 Months |
| 1003 / Thyroid Ca | 20 mg/m² twice weekly | SD | 5.2 Months |

### Subject 4010: GIST Partial Response for 8 Months: c-Kit Mutational Analysis




GIST PR for 8 months, 220 mg/m² once weekly. Primary c-Kit mutation in Exon 11 at diagnosis. Secondary mutations in exon 17 associated with imatinib resistance, detected after recurrence (Courtesy of Dr Corless from Oregon Health & Science University)

### Patient 4006: GIST Stable Disease for 7 Months: PET Scan Response



GIST, SD for 7 months, 220mg/m² once weekly ; FDG PET response after 1 cycle

## DISCUSSIONS AND CONCLUSIONS

- AT13387 was well tolerated. MTD and RP2D were:
  - Twice weekly regimen: 120 mg/m²/dose for 3 weeks in 4 weeks cycle
  - Once weekly regimen: 260 mg/m²/dose for 3 weeks in 4 weeks cycle
- DLTs consisted mainly of multiple Gr 2 Adverse Events of GI toxicities (diarrhea, vomiting), systemic infusion reactions, and fatigue. Few patients had Gr 3 toxicities and no Gr 4 AEs were reported
- Visual disturbances were all Gr 1 with only 1 patient reported as Gr 3 due to ERG changes. All were transient and reversible. Visual disturbances are considered on target pharmacological class effects of potent HSP90 inhibition
- PK exposures were dose-dependent and linear
- HSP70 induction of 2-7 fold magnitude was observed representing pharmacodynamic evidence of target engagement
- Objective and durable Partial Response and Stable Disease were observed in 5 patients (including 3 GIST patients)
- Additional patients are being enrolled at the MTD of 260 mg/m² once weekly and a Phase 2 study in relapsed/refractory GIST patients in combination with imatinib is ongoing

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