Abstract # 105

AT13387, A Novel, Non-Ansamycin Inhibitor of Heat Shock Protein 90 is Active Against Gastrointestinal Stromal Tumors (GIST)

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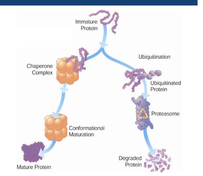
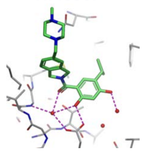
Background

- Heat Shock Protein 90 (HSP90) is an ATP-dependent molecular chaperone that assists in correct folding of a wide variety of oncogenic client proteins. When folded incorrectly, these proteins become subject to ubiquitination and proteasomal degradation.



- HSP90 supports the correct conformation, stabilization, activation, and localization of 'client' oncoproteins, including mutant forms, many of which are involved in tumor progression.
- Therefore, HSP90 holds promise in down-regulating multiple aberrant signaling pathways in a wide range of cancers.[1]
- The first generation ansamycin-derived HSP90 inhibitors showed initial clinical promise but had suboptimal pharmaceutical properties and encountered off-target pharmacological toxicity.[2]
- AT13387 is a fragment derived, 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).

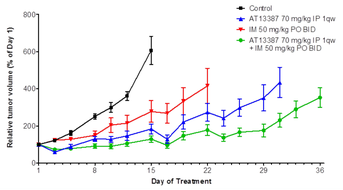
AT13387



- In vivo, AT13387 demonstrated anti-tumor activity in the imatinib-sensitive (GIST-PSW) and imatinib-resistant (GIST430) xenograft models. Induction of HSP70, depletion of phospho-c-KIT and inhibition of c-KIT signaling were observed in both models (Smyth et al. 2012)[3].
- Combination treatment of imatinib and AT13387 in the GIST430 model was well tolerated and significantly enhanced tumor growth inhibition over either monotherapy.

AT13387 Overcomes Imatinib-Resistance in GIST Cell Lines[3]

Cell Line	Kit Mutation		IC_{50} (nM)	
	Primary	Secondary	AT13387	Imatinib
GIST882	Exon 13 K642E	None	82	111
GIST430	Exon 11 Δ560-576	Exon 13 V654A	34	46% I at 300 nM
GIST48	Exon 11 V560D	Exon 17 D820A	55	>1000



GIST-430 (imatinib-resistant) Xenograft Model

Methods

GIST patients were enrolled in two clinical trials

- **Phase 1: Single agent**
  - Key eligibility: advanced unresectable solid tumors including lymphoma refractory to standard therapy
  - Study Design: 3 + 3 dose escalation
    - Objectives: MTD, DLTs, PK, PD, preliminary anti-tumor activity
    - Two dosing regimens of a 28-day cycle:
      - Regimen 1 (twice weekly): 1 4 8 11 15 18
      - Regimen 2 (once weekly): 1 8 15
- **Phase 2: Single agent and in combination with imatinib**
  - Key eligibility: unresectable and/or metastatic malignant GIST relapsed after treatment with up to 3 prior TKIs including imatinib
  - Study Design: Dose Escalation — AT13387 escalating doses QW x3 of a 28-day cycle + imatinib 400 mg daily
    - Objectives: Anti-tumor activity, safety and tolerability, PK, PD

Results

Patient Baseline Characteristics

	Phase 1*	Phase 2‡	All
Number of Patients Enrolled	53	7	---
Number of GIST Patients	7	7	14
Median Age (range)	59 (44 – 70)	64 (39 – 82)	59.5 (39 – 82)
Gender (M:F)	6:1	3:4	9:5
ECOG PS 0 /1	5 / 2	4 / 3	9 / 5
Median prior TKI (range)	3 (1-8)	4 (2-9)	3.5 (1-9)
Median Time of Diagnosis to Study Entry (months)	51	59	55.5

*Phase 1: single agent, escalating doses of AT13387; ‡Phase 2: AT13387 in combination with imatinib

Individual GIST Patient Characteristics

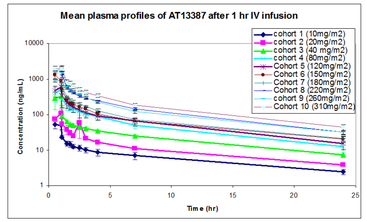
Pt #	Gender	Age	ECOG PS	Time of Diagnosis to AT13387 First Dose (months)	Prior TKI / Best Response	Dose of AT13387 at Study Entry	Best Response / Duration of Best Response
Phase 1 – Single Agent AT13387							
4002	M	44	1	29	Imatinib / SD	120 mg/m² BIW	PD
4003	M	70	1	109	Imatinib / SD	150 mg/m² QW	NE
4005	M	51	0	90	Imatinib / CR Sunitinib / SD	180 mg/m² QW	SD / 43 days
4006	M	59	0	34	Imatinib / PR	220 mg/m² QW	SD / 231 days
4010	M	60	0	120	Imatinib / CR	220 mg/m² QW	PR / 113 days
1023	M	58	0	52	Imatinib / CR Sunitinib/ SD Sorafenib / PD Sunitinib / PD GDC0980 / PD	260 mg/m² QW	PD
4011	F	64	0	4	Imatinib / UKN	260 mg/m² QW	SD / 335 days

Pt #	Gender	Age	ECOG PS	Time of Diagnosis to AT13387 First Dose (months)	Prior TKI / Best Response	Dose of AT13387 + Imatinib at Study Entry	Best Response / Mutation, if known / Duration of Best Response
Phase 2 – AT13387 + Imatinib 400 mg							
106	M	82	1	39	Imatinib / SD Sunitinib / SD	180 mg/m² QW + Imatinib 400 mg QD	PD /c-Kit exon 9 INS AY502-503
105	F	64	1	101	Imatinib / SD Sunitinib / SD Nilotinib / PD	180 mg/m² QW + Imatinib 400 mg QD	NE
104	F	69	0	40	Imatinib / PD Sunitnib / PD Sorafenib / PD	180 mg/m² QW + Imatinib 400 mg QD	PD
101	M	39	0	102	Imatinib / PR	180 mg/m² QW + Imatinib 400 mg QD	PD / c-Kit exon 11 L576P
102	F	74	0	103	Imatinib / CR Sunitinib / CR	180 mg/m² QW + Imatinib 400 mg QD	PR / PDGFRA Exon 18 Deletion 842-845 DIMH / 245 days
103	F	58	1	5	Imatinib / PD Sunitinib / UNKN	180 mg/m² QW + Imatinib 400 mg QD	NE / Wild-type
107	M	41	0	59	Imatinib / PD Sunitinib / PD	180 mg/m² QW + Imatinib 400 mg QD	PD

PD = progressive disease; SD = stable disease; PR = partial response; NE = not evaluable; BIW = twice weekly; QW = once weekly

Phase 1: AT13387 PK Profile

- 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; mean value of 1.5L/h/kg (sd=0.4L/h/kg) based on data from all dose cohorts.
- Low intra-subject variability observed; exposure to AT13387 did not accumulate in the twice weekly dosing regimen.

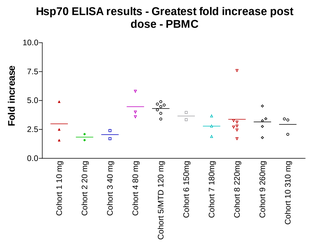
PR and SD > 6 months Pharmacokinetic Parameters

Averages of C_{max}, AUC_{0-t}, T ½ of Day 1 and Day 15

Subject Dose / Cohort (N)	C_{max} (ng/mL) (Cohort Average)	AUC_{0-t} (ng*hr/mL) (Cohort Average)	T ½ (h) (Cohort Average)
4006 220 mg/m² / (N=9)	2755 (2080)	6698 (4803)	11.2 (7.7)
4010 220 mg/m² / (N=9)	1425 (2080)	3444 (4803)	8.1 (7.7)
4011 260 mg/m² / (N=4)	2130 (1965)	5235 (4527)	7.6 (6.5)
102 180 mg/m² / (N=6)	696 (1019)	2240 (3371)	6.8 (6.1)

- The pharmacokinetic profile of GIST patients compared favorably to the overall enrolled patient population.
- Patient 102 exhibited higher clearance 36.2 mL/min/Kg compared to Cohort mean plasma clearance of 25 mL/min/Kg (s.d. 9.0).

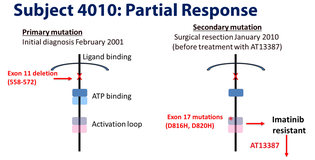
Phase 1: Fold Increase of HSP70 Induction



Across all patients treated, 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.

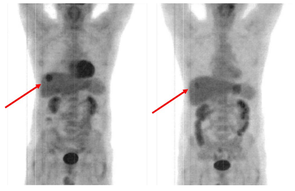
Phase 1: PR and SD > 6 months

Subject 4010: Partial Response



GIST partial response for 4 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).

Subject 4006: Stable Disease

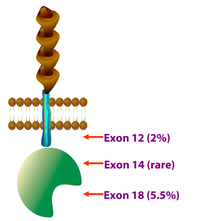


GIST stable disease for > 7 months, 220 mg/m² once weekly. Fluoro-deoxyglucose PET response after Cycle 1.

Phase 2: PR > 6 Months

- Patient 106-102 enrolled into Cohort 1 (180 mg/m² AT13387 + 400 mg imatinib)
- Initial diagnosis November 2002
- Sample analysed from February 2006 from recurrence of GIST
  - After initial diagnosis, patient received imatinib – CR
  - Recurrence Feb 2006. Aug 2006 – Oct 2008 patient received sunitinib – SD
  - Oct 2008 – May 2011 patient received sunitinib – CR
  - Jun 2011 – Patient started AT13387/0002 – PR for 245 days
- No C-KIT mutations
- PDGFR mutations
  - Exon 18 deletion 842-845 (DIMH)

PDGFRα Mutations



Phase 1: Drug-related Adverse Events ≥ 10% by Frequency All Patients (N=53), All were Gr1 or 2 except 6 pts Gr3(11%), No Gr4

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%)

Conclusions

- AT13387 exhibits dose dependent systemic exposure and linear pharmacokinetics. Half-life of AT13387 in GIST patients across Phase 1 and Phase 2, range between 6.8 – 11.2 hours.
- HSP70 induction of 2-7 fold magnitude was observed representing pharmacodynamic evidence of target engagement.
- AT13387 demonstrated clinical activity after failure of multiple TKI treatment with 2 PR of 14 treated patients in Phase1 and Phase 2 thus far.
- Phase 1 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. GIST patients safety profile similar to overall enrolled population.
- AT13387 is a promising agent in GIST, including TKI-resistant c-KIT positive and c-Kit negative GIST.
- Phase 2 study in combination with imatinib is ongoing for imatinib-resistant GIST.

References

1. Koga F et al. Anticancer Research, March 2009;29, 3: 797–807.
2. Jhaveri K et al. Biochimica et Biophysica Acta 2012; 1823; 742–755.
3. Smyth et al 2012, Molecular Cancer Therapeutics; 11: 1799-808

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