HSP90 Inhibition by AT13387 can Overcome and Delay the Appearance of Resistance to Tyrosine Kinase Inhibitors in Lung Cancer Models

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Targeted Anticancer Therapies
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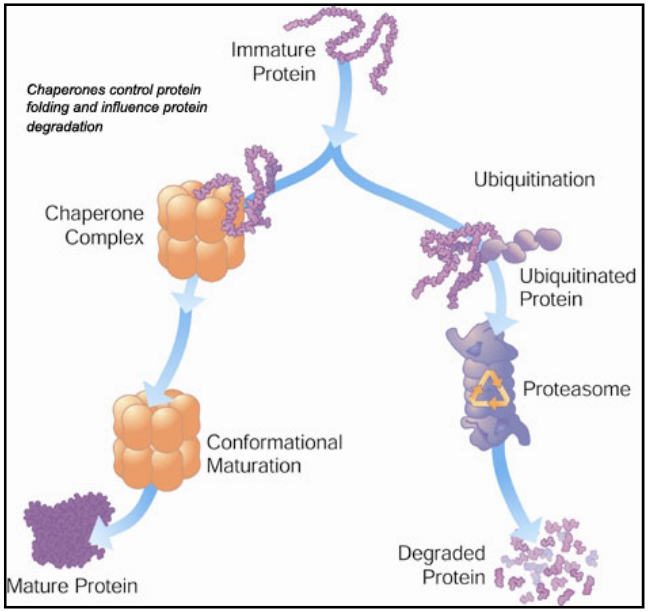
Disclosures

All authors are employees of Astex Pharmaceuticals

HSP90 and Resistance

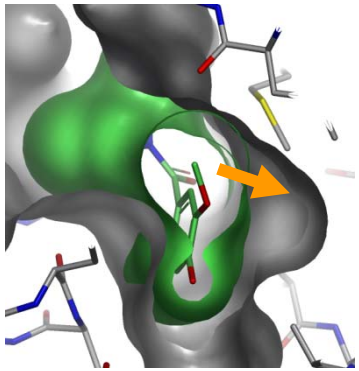
- **HSP90**
  - Chaperone to many oncogenic client proteins including in NSCLC (e.g. ALK and EGFR)
  - Inhibition of HSP90 simultaneously disrupts multiple signalling pathways
- **Resistance to Targeted Therapies**
  - Tyrosine kinase inhibitors are used successfully to treat subsets of NSCLC (e.g. crizotinib, erlotinib)
  - BUT responses are limited due to development of resistance mediated by multiple mechanisms
- **HSP90 and Resistance**
  - **HSP90 inhibition may be used to combat resistance to TKIs regardless of mechanism**
    - Overcoming acquired resistance
    - Delaying the emergence of resistance

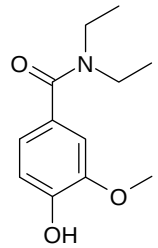


Centioni V, 2005

Discovery of AT13387: A Potent HSP90 Inhibitor

Fragment

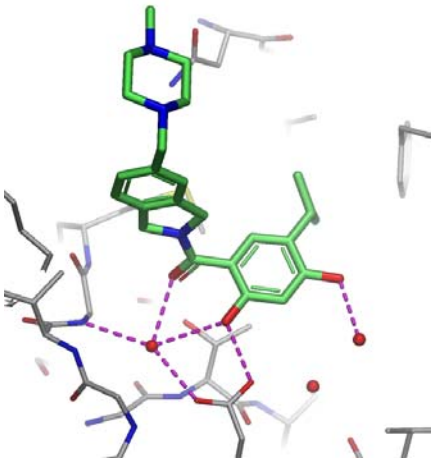


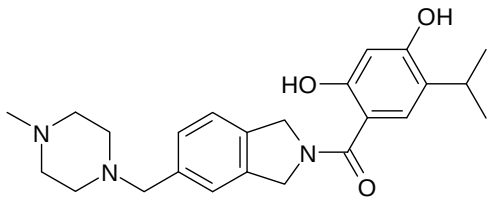


K_d (ITC) = 790 μM
LE = 0.26

- Potency increase
- Modification of physical properties to improve efficacy
- Rational SAR to modify hERG activity

Candidate (AT13387)





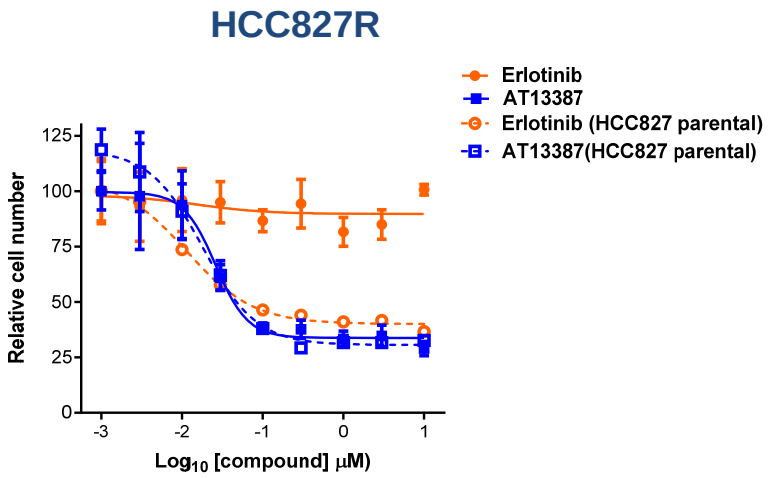
K_d (ITC) = 0.00071 μM
LE = 0.42

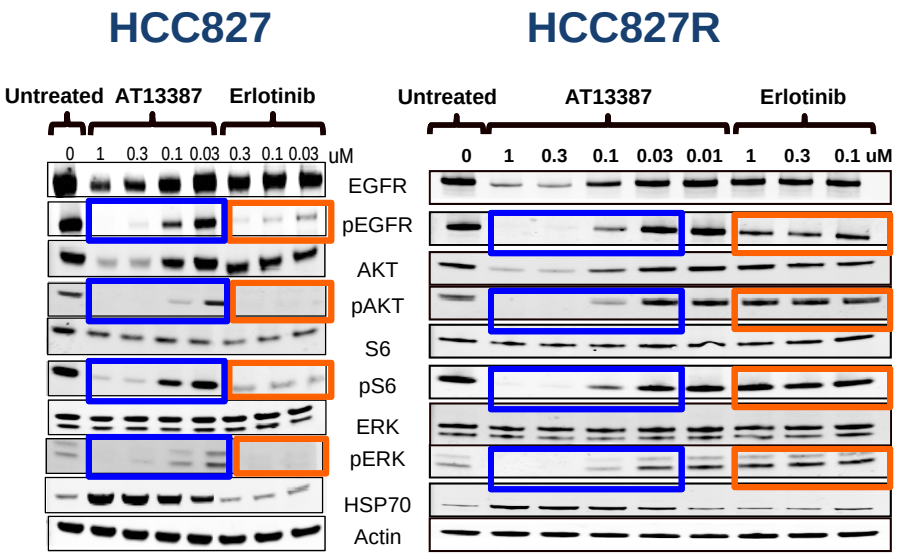
Murray et al J Med Chem 2010
Woodhead et al J Med Chem 2010

Currently in Phase II Clinical Trials

AT13387 Overcomes Resistance to Tyrosine Kinase Inhibitors

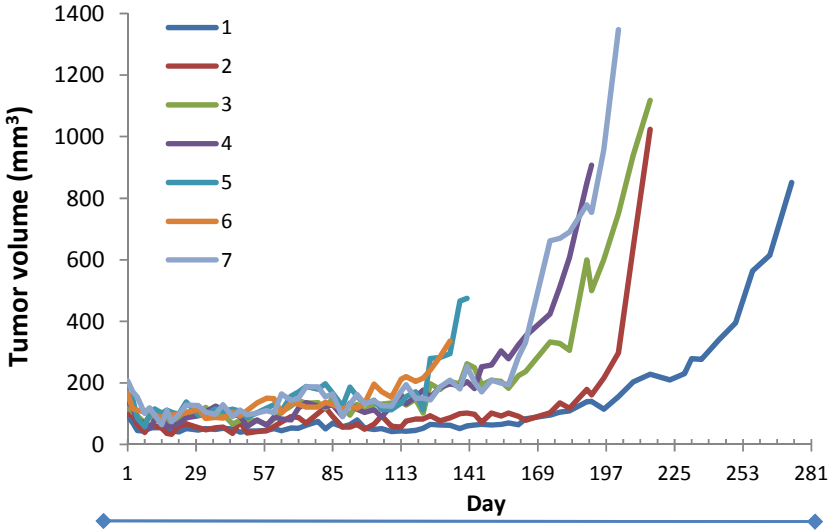
Cell Line	Inhibition of proliferation Erlotinib IC_{50} (nM)	Inhibition of proliferation AT13387 IC_{50} (nM)
HCC827	57	33
NCI-H1650	>10000	54
NCI-H1975	>10000	30
NCI-H820	>10000	49
HCC827R	**>10000**	**24**



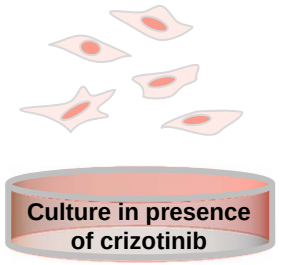


AT13387 Overcomes Acquired Resistance to Crizotinib in ALK+ NSCLC Models

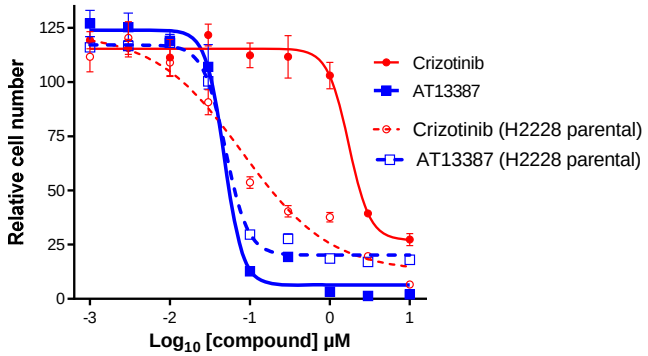
H2228 tumor xenografts treated with crizotinib



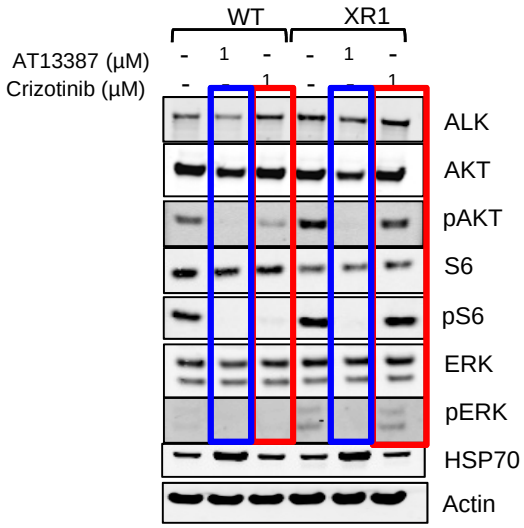
Individual tumors
Ex vivo culture



H2228XR1

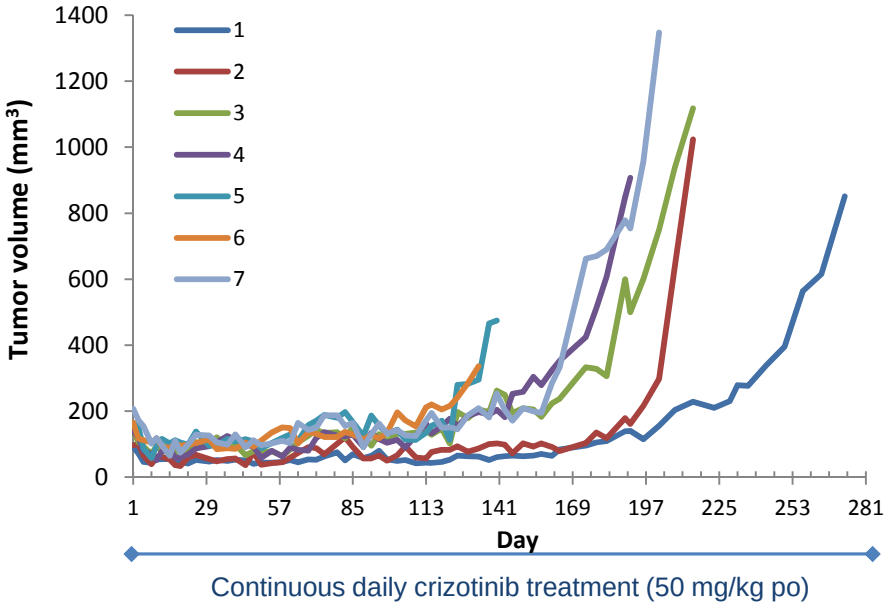


H2228



AT13387 Inhibits Tumor Growth of an ALK+ Xenograft with Acquired Crizotinib Resistance

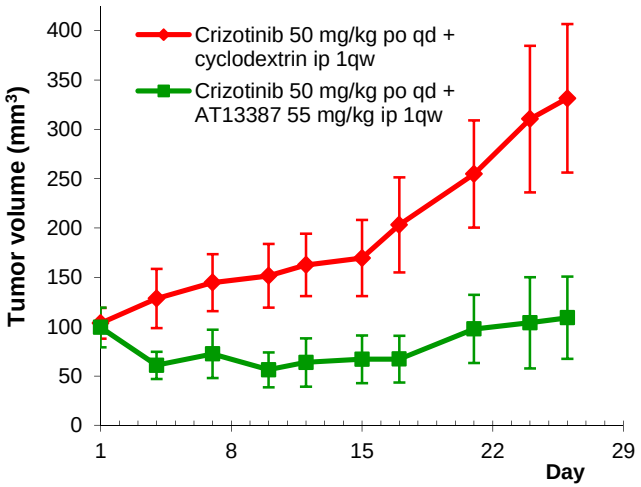
H2228 tumor xenografts treated with crizotinib



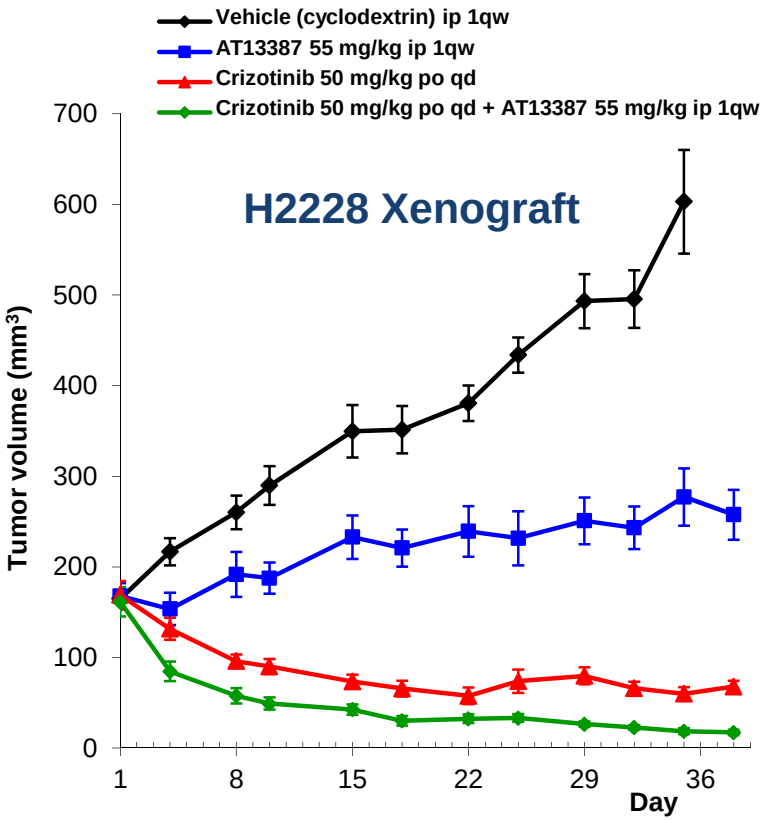
Continuous daily crizotinib treatment (50 mg/kg po)

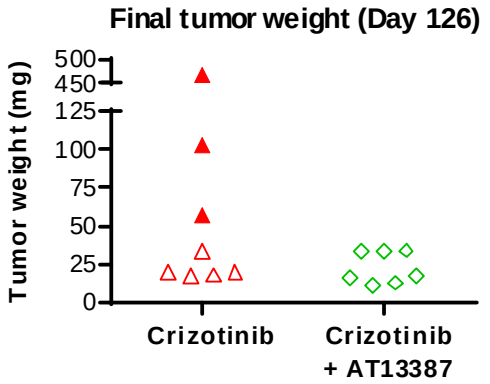
Tumor #6 transplanted

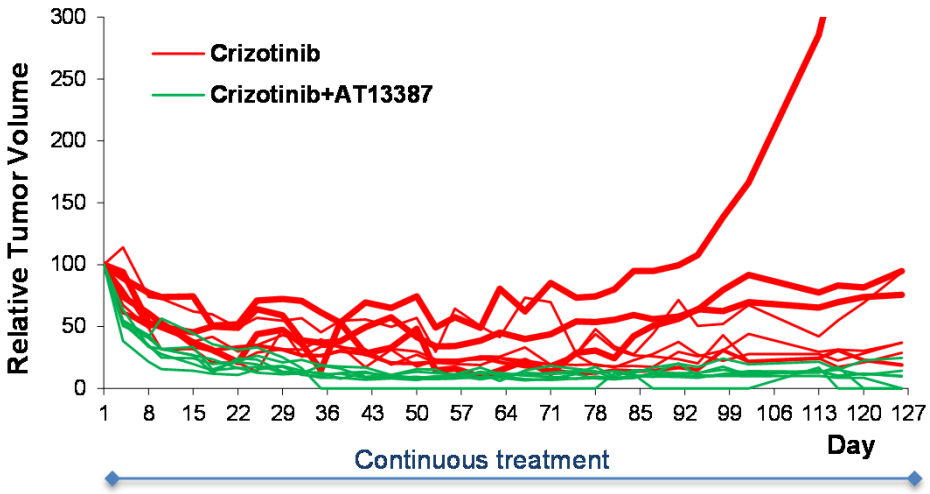
H2228R treated with AT13387



AT13387 Delays the Emergence of Crizotinib Resistance in an ALK-Dependent Xenograft



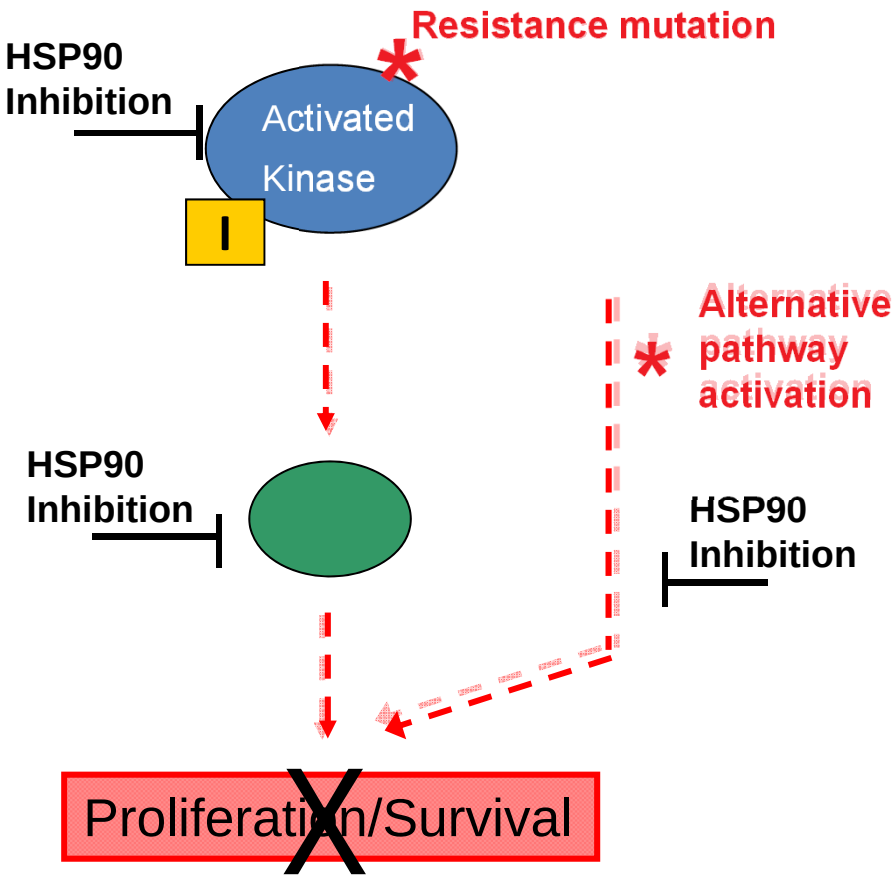




- Combination of AT13387 and crizotinib shows improved inhibition of tumor growth over monotherapies
- Combining crizotinib upfront with AT13387 delays the emergence of resistance in vivo

Conclusions

- Inhibition of HSP90 by AT13387 overcomes acquired resistance to erlotinib and crizotinib in NSCLC models.
- **An upfront combination of the HSP90 inhibitor, AT13387, with crizotinib can extend the duration of response and delay the emergence of resistance in an ALK-dependent model**
- Data support clinical testing of front-line combination of AT13387 with TKIs in NSCLC
- A randomized Phase II trial of AT13387 in ALK-positive NSCLC as single agent or in combination with crizotinib is ongoing (NCT01712217)



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