The HSP90 Inhibitor, AT13387, Displays Single Agent Activity in Erlotinib-Sensitive and -Resistant Models of EGFR-Activated NSCLC

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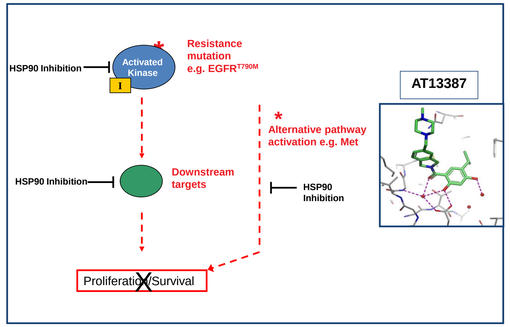
INTRODUCTION

Epidermal growth factor receptor (EGFR) is activated in subsets of non-small cell lung cancer (NSCLC) by point mutations such as L858R and deletions in exon19. EGFR-tyrosine kinase inhibitors such as gefitinib and erlotinib have been successfully used to treat tumors with these mutations, but responses tend to be limited by the development of resistance, often through further mutations in EGFR such as T790M.

Both EGFR and its mutated forms are clients of HSP90 and are dependent on this molecular chaperone for their stability. In addition, proteins in many signalling pathways also rely on HSP90 activity and are depleted when HSP90 is inhibited. HSP90 inhibition is therefore a promising potential therapy for EGFR-driven NSCLC, which should be effective on both EGFR inhibitor-sensitive and -resistant disease.

AT13387 is a fragment-derived, potent HSP90 inhibitor (Kd 0.71nM) currently being tested in a number of Phase 2 trials including one in NSCLC.

Rationale for overcoming kinase inhibitor resistance via HSP90 inhibition



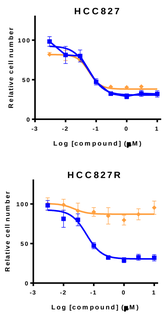
Here we describe the activity of AT13387 in preclinical models of NSCLC driven by EGFR, including models resistant to erlotinib.

INHIBITORY EFFECT OF AT13387 ON CELL PROLIFERATION

AT13387 was tested in a panel of EGFR-driven NSCLC cell lines and potently inhibited proliferation of both erlotinib-sensitive and -resistant cells including a cell line with acquired erlotinib resistance (HCC827R).

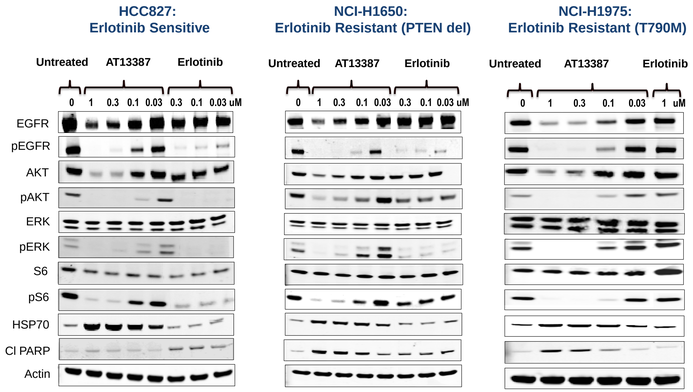
Cell Line	EGFR Genotype	Erlotinib Sensitivity	AT13387 IC_{50} (nM)	Erlotinib IC_{50} (nM)
HCC827	Del E746_A750	sensitive	33	57
NCI-H1975	L858R/T790M	resistant	30	>10 000
NCI-H1650	Del E746_A750 PTEN del	Intermediate/ resistant	54	>10 000
NCI-H820	Del E746_L751/ T790M/Met↑	resistant	49	>10 000
HCC827R	N/D (generated in-house)	resistant	24	> 10 000

HCC827R cell line was generated by culturing HCC827 cells in the presence of increasing concentrations of erlotinib until resistance was acquired.



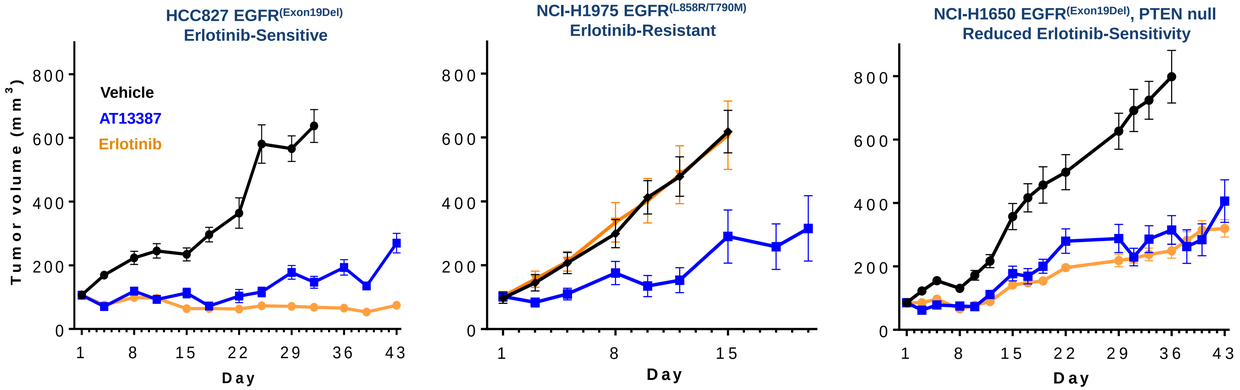
IN VITRO SIGNALLING: DEPLETION OF CLIENT PROTEINS

AT13387 treatment of EGFR-activated cell lines depleted EGFR and its phospho-form, irrespective of mutation status (L858R, T790M, Exon19 deletion). Decreases in the levels of phospho-ERK and phospho-S6 indicated that EGFR signalling was being inhibited.



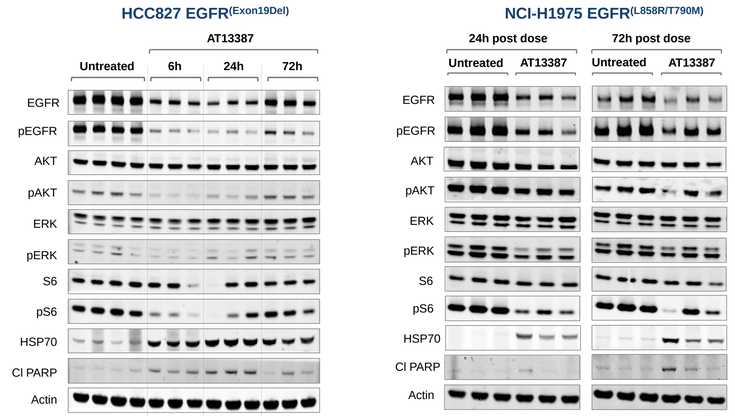
Cells were treated with indicated doses of AT13387 for 24 hours .

AT13387 IS EFFECTIVE IN ERLOTINIB-SENSITIVE AND -RESISTANT EGFR-ACTIVATED XENOGRAFT MODELS



AT13387 inhibited the growth of EGFR-activated tumor xenografts, irrespective of their sensitivity to erlotinib.

Mice were treated with the following schedules: vehicle (cyclodextrin) ip 1qw, AT13387 70 mg/kg ip 1qw and erlotinib at 12.5 mg/kg po qd (HCC827 & NCI-H1650) or 75 mg/kg po qd (NCI-H1975).



Levels of EGFR and phospho-EGFR were depleted for up to 72 hours in xenograft tumors treated with a single dose of 70 mg/kg AT13387, whilst a reduction in phospho-ERK and phospho-S6 again demonstrated an inhibition of signalling.

SUMMARY AND CONCLUSIONS

- AT13387 is effective in a number of EGFR-activated NSCLC preclinical models, including those resistant to erlotinib.
- Treatment of cell lines and xenograft tumors with AT13387 leads to depletion of EGFR and pEGFR, irrespective of mutation status, and inhibits the ERK and AT downstream signalling pathways.
- These data suggest that AT13387 treatment may also be a potential approach for combating EGFR inhibitor resistance in the clinic.
- AT13387 is currently being tested in a number or Phase 2 trials including one in NSCLC.

REFERENCES

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