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The HSP90 inhibitor, AT13387, combined with erlotinib improves response in EGFR-driven xenograft models of NSCLC.

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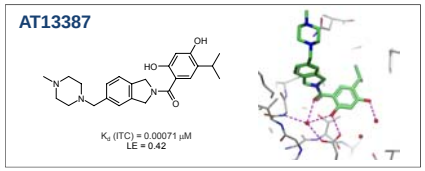
INTRODUCTION

Epidermal Growth Factor Receptor (EGFR) can be activated by point mutations e.g L858R or by deletions in exon19. A subset of non-small cell lung cancer (NSCLC) have activated EGFR and can be successfully treated with EGFR inhibitors such as erlotinib. However, resistance frequently develops to these inhibitors, often due to acquisition of a further T790M mutation in EGFR leading to relapse. Methods to improve response and delay resistance are therefore of value.

Inhibition of the chaperone, HSP90, leads to the depletion of many client proteins, including EGFR, and has the capacity to simultaneously affect many signalling pathways, offering an alternative strategy for targeting EGFR-driven disease.

AT13387 is a potent, second generation HSP90 inhibitor currently being tested in Phase 2 clinical trials. Here we investigated the effects of combining AT13387 and erlotinib in models of EGFR-driven NSCLC.



RESULTS

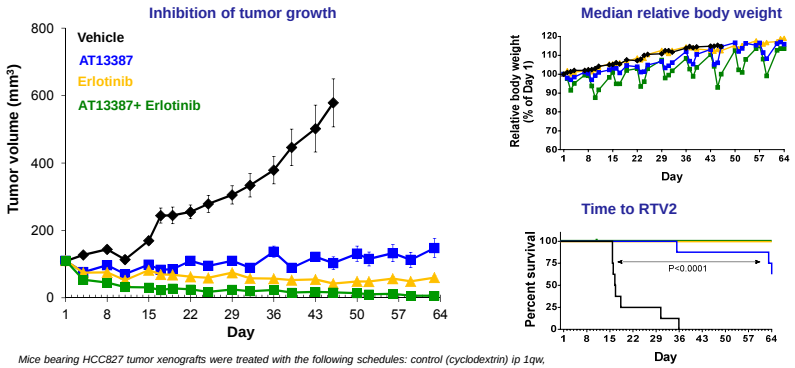
AT13387 was tested in a panel of EGFR-driven NSCLC cell lines and potently inhibited proliferation of both erlotinib-sensitive and -resistant cells

Inhibitory effect of AT13387 on proliferation of EGFR activated NSCLC cell lines

Cell Line	EGFR Genotype	AT13387 IC_{50} (nM)	Erlotinib IC_{50} (nM)
HCC827	Del E746_A750	33	57
NCI-H1975	L858R/T790M	30	>10 000
NCI-H1650	Del E746_A750 /PTEN del	54	>10 000
NCI-H820	Del E746_L751/ T790M/Met↑	49	>10 000

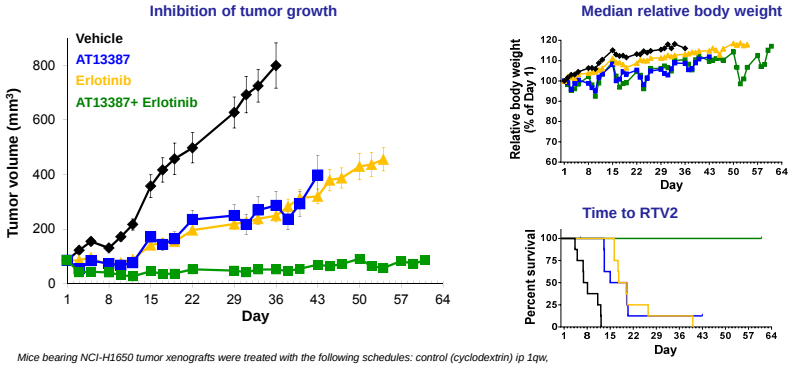
COMBINATION OF AT13387 WITH ERLOTINIB IN EGFR-DRIVEN NSCLC XENOGRAFT MODELS

Effect of combining AT13387 with erlotinib in the HCC827 xenograft model



Mice bearing HCC827 tumor xenografts were treated with the following schedules: control (cyclodextrin) ip 1qw, AT13387 55 mg/kg ip 1qw and erlotinib at 12.5 mg/kg po qd. RTV2: Relative tumor volume of 2.

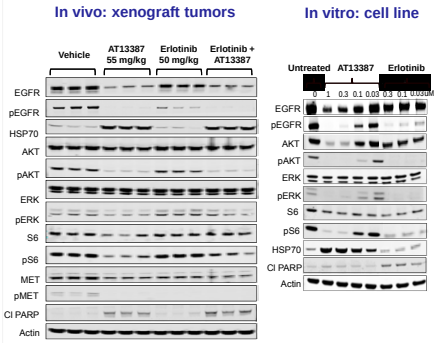
Effect of combining AT13387 with erlotinib in the NCI-H1650 xenograft model



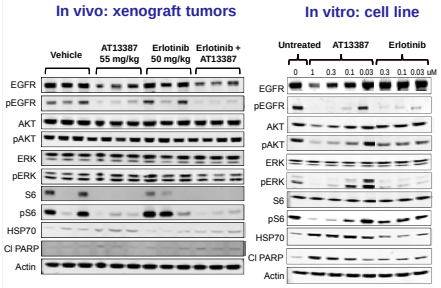
Mice bearing NCI-H1650 tumor xenografts were treated with the following schedules: control (cyclodextrin) ip 1qw, AT13387 55 mg/kg ip 1qw and erlotinib at 12.5 mg/kg po qd.

EFFECTS ON CLIENT PROTEINS AND SIGNALLING

Pharmacodynamic effects of AT13387 and erlotinib treatment in the HCC827 model



Pharmacodynamic effects of AT13387 and erlotinib treatment in the NCI-H1650 model



Mice bearing tumor xenografts were treated with the drug schedules indicated. Cells were treated with indicated doses of AT13387 and/or erlotinib for 24 hours then lysed for protein analysis by western blot with the indicated antibodies.

SUMMARY OF COMBINATION EFFECTS

Effects of combining AT13387 and erlotinib in EGFR-activated xenograft models, HCC827 and NCI-H1650

Cell line	Genetic background	T/C (Median RTV, treated / control)		
		AT13387 55 mg/kg ip 1qw	Erlotinib 12.5 mg/kg po qd	Combination
HCC827 (Day 32)	EGFR Del E746_A750	26%	17% (47% regression)	6% (84% regression)
NCI-H1650 (Day 31)	EGFR Del E746_A750/ PTEN del	35%	36%	6% (50% regression)

AT13387 single-agent treatment inhibited tumor growth in both the HCC827 and NCI-H1650 tumor xenograft models. Treatment with erlotinib caused significant tumor regression in all HCC827 tumors, but was less effective in the NCI-H1650 model. Combination of AT13387 with erlotinib led to an enhancement of tumor growth inhibition over either of the monotherapies in both xenograft models. The combination was well tolerated.

CONCLUSIONS

- AT13387 improved response when combined with erlotinib in EGFR-driven xenograft models, despite the differing initial sensitivities to erlotinib of these models.
- Treatment of cell lines and xenograft tumors with AT13387 led to depletion of EGFR and pEGFR.
- These data suggest that there is therapeutic potential in combining an HSP90 inhibitor, such as AT13387, with erlotinib and support clinical investigation of such a combination.
- AT13387 is currently being tested in a Phase 2 clinical trial in ALK positive NSCLC in combination with crizotinib (NCT01712217).

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 Poster presented at AACR Annual Meeting, San Diego, 2014. (Poster available to download from Astex's website at www.astx.com)