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The HSP90 inhibitor, onalespib (AT13387), delays the emergence of resistance to erlotinib in an EGFR-driven xenograft model

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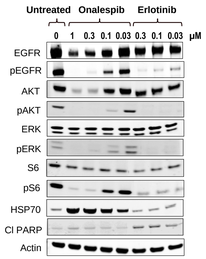
INTRODUCTION

Kinase inhibitors have been used successfully in the clinic, but relapse is common due to the emergence of resistance. Inhibition of HSP90 leads to the depletion of oncogenic 'client' proteins and the simultaneous inhibition of many signalling pathways. As such, the use of HSP90 inhibitors to overcome resistance has been widely investigated.

Onalespib (AT13387) is a potent, second generation HSP90 inhibitor, which has been studied in many preclinical models of kinase inhibitor resistance. Recent findings indicate that an upfront combination of onalespib and either vemurafenib or crizotinib, in models of mutant BRAF melanoma or ALK-translocated non-small cell lung cancer (NSCLC), can delay the emergence of resistance to these therapies (Smyth et al 2014, Wallis et al 2014). Here we have extended this work to a combination of onalespib and erlotinib in an EGFR-driven NSCLC model.

Effect of onalespib on an EGFR$^+$ cell line (HCC827)



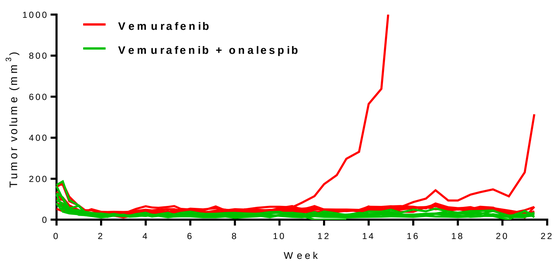
Onalespib treatment depletes client proteins (EGFR, AKT) and inhibits signalling pathways (AKT, ERK) in an EGFR-dependent cell line in vitro.

Combining onalespib upfront with vemurafenib or crizotinib delays the emergence of resistance in mutant BRAF melanoma and ALK-translocated NSCLC xenograft models

mBRAF Melanoma

(Smyth et al 2014)

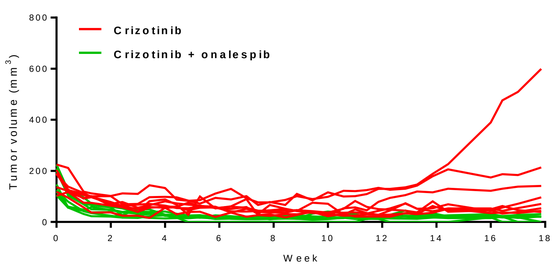
Mice bearing SK-MEL-28 (mutant BRAF) tumor xenografts were continuously treated with vemurafenib 50 mg/kg po bid and onalespib 70 mg/kg ip 1qw



ALK+ NSCLC

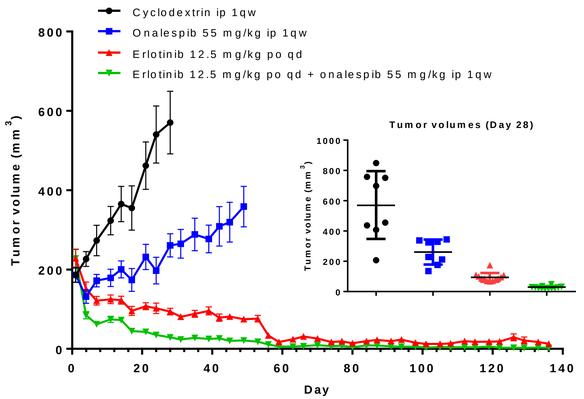
(Wallis et al 2014)

Mice bearing H2228 (EML4-ALK) tumor xenografts were continuously treated with crizotinib 50 mg/kg po qd and onalespib 55 mg/kg ip 1qw



RESULTS

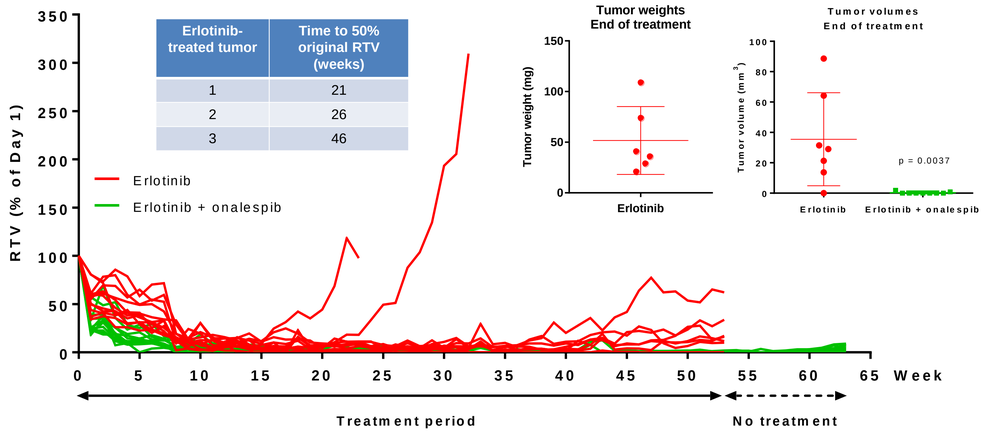
Effect of combining onalespib with erlotinib on the emergence of resistance in a EGFR-dependent NSCLC (HCC827) xenograft model

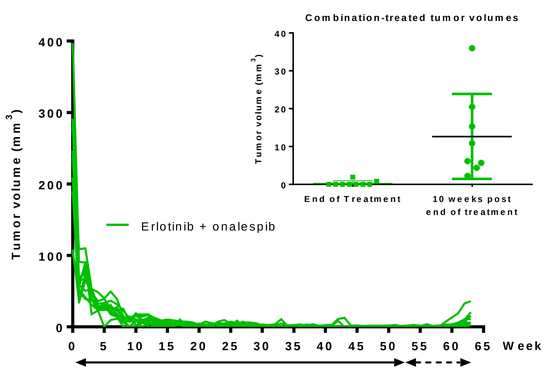


Mice bearing HCC827 tumor xenografts were continuously treated with the following schedules: control (cyclodextrin) ip 1qw, onalespib 55 mg/kg ip 1qw and erlotinib at 12.5 mg/kg po qd. Dosing of the erlotinib monotherapy and erlotinib/onalespib combination groups was continued for up to 53 weeks.

Treatment	Times to CR (Days)	
	Median	Range
Erlotinib	79	56 - 171
Erlotinib + onalespib	56	31 - 59

- All tumors in the monotherapy and combination groups regressed rapidly initially and achieved complete response (CR), but combination treatments achieved CR earlier than the monotherapy.
- Tumor relapse whilst on treatment was only observed in monotherapy treated tumors; 3 tumors reached 50% of their original size over the time of the study and a further 5 were detectable at the end of the study.
- No combination-treated tumors relapsed during treatment. These tumors remained undetectable for 6 weeks after the end of treatment, after which signs of regrowth could be seen.
- Relapsed tumors were excised and cultured ex-vivo for further analysis.





Dosing of the erlotinib/onalespib combination group was continued for up to 53 weeks. AT13387 treatment finished on day 336, erlotinib treatment on day 370. Tumors were then monitored for a further 10 weeks.

CONCLUSIONS

- An upfront combination of onalespib with erlotinib delayed the emergence of resistance in an EGFR-dependent NSCLC xenograft model.
- Delaying the emergence of resistance with upfront combinations of onalespib and kinase inhibitors has now been demonstrated in 3 different preclinical models of kinase inhibitor resistance (vemurafenib and crizotinib in models of mutant BRAF melanoma and ALK-dependent NSCLC, respectively).
- The concept of delaying the emergence of resistance with an upfront combinations is currently being explored in a Phase 2 clinical trial with an onalespib/crizotinib combination in ALK-positive NSCLC (NCT01712217).
- These data suggest that using an HSP90 inhibitor combination upfront in the clinic to delay resistance could be investigated in further indications with targeted therapies.
- Although the use of HSP90 inhibitors alone may be effective in some clinical situations, their use in upfront combinations with kinase inhibitors has the potential for much wider benefit.

References

Smyth et al 2014 MCT: 13; 2793-804

Wallis et al 2014 TAT Oral Presentation

Poster presented at AACR Annual Meeting, Philadelphia, 2015. (Poster available to download from Astex's website at www.astx.com)