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 oncoprotein 'client' proteins and the simultaneous inhibition of many signaling 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 melanomas 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.

RESULTS

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

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

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

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 combination is currently being explored in a Phase 2 clinical trial with an onalespib/crizotinib combination in ALK-positive NSCLC (NCT1712257).
• 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.