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

Tomoko Smyth, Jon Lewis, Keisha Hearn, Aurélie Courtin, Neil Thompson, John Lyons, Nicola Wallis

*Astex Pharmaceuticals, 436 Cambridge Science Park, Milton Road, Cambridge, UK

INTRODUCTION

Epidermal Growth Factor Receptor (EGFR) can be activated by point mutations e.g. L858R or by deletions in exons 19. 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

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>EGFR Genotype</th>
<th>AT13387 IC50 (nM)</th>
<th>Erlotinib IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC827</td>
<td>Del E746_A750</td>
<td>33</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>NCI-H1975</td>
<td>L858R/T790M</td>
<td>30</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>NCI-H1965</td>
<td>Del E746_A750</td>
<td>54</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>NCI-H820</td>
<td>Del E746_L858R/PTEN del</td>
<td>49</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- AT13387 improved response when combined with erlotinib in EGFR-driven xenograft models, despite the differing 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).