A NOVEL ERK1/2 INHIBITOR HAS POTENT ACTIVITY IN KRAS-MUTANT NON-SMALL CELL LUNG CANCER MODELS

INTRODUCTION

Kras mutations occur in 25-30% of non-small cell lung cancer (NSCLC) patients. Although, NSCLC patients harboring EGFR or ALK mutations can benefit from personalized therapies, there are currently no approved targeted therapies for KRAS-mutant NSCLC tumors. The constitutive activation of the MAPK pathway in these tumors provided the rationale for targeting MEK1/2 (MEK). However, when tested clinically, MEK inhibitors had limited activity.

As ERK1/2 (ERK) is the primary downstream effector of the MAPK pathway, it is hypothesized that ERK inhibitors may prove to be less susceptible to intrinsic bypasses than MEK inhibitors and therefore have the potential to overcome the limitations of MEK inhibitors in KRAS-mutant NSCLC.

Using fragment-based drug discovery we have developed a novel, potent and selective ERK inhibitor, which inhibits in vitro ERK catalytic activity with a low nm IC50 value and has strong anti-proliferative effects in KRAS-mutant NSCLC cell lines.

In addition to inhibiting ERK catalytic activity, the compound also inhibits the phosphorylation of ERK by MEK and confers a decrease in cellular pERK levels in KRAS-mutant NSCLC cell lines (in vitro and in vivo pharmacodynamics (PD) studies).

Once daily oral dosing of the lead compound (50 mg/kg) conferred significant anti-tumor activity in a range of KRAS-mutant NSCLC in vivo models.

This work demonstrates the in vitro and in vivo activity of a novel, highly potent, selective ERK inhibitor in models of KRAS-mutant NSCLC and supports the further optimisation of this series of compounds for clinical development.

1. A novel potent and selective ERK inhibitor

• The lead compound inhibits ERK catalytic activity with an IC50 of 3 nM (as determined in an ERK TRF Kinase assay).

• It binds to the active site of ERK2 (where the adenosine of ATP binds) and then expands in an elongated shape, exploiting a pocket which is created by an unusual movement of the P-Loop Tyr36 residue.

2. Inhibition of ERK catalytic activity and the proliferation of KRAS-mutant NSCLC cells

• The lead compound potently inhibited ERK catalytic activity in NCI-H358 and Calu-6 (KRAS-mutant NSCLC) cell lines, with an IC50 value of 11 nM and 15 nM, respectively.

• The lead compound potently inhibited the proliferation of a panel of KRAS-mutant NSCLC cell lines. 55% of the KRAS-mutant NSCLC cell lines exhibited antiproliferative IC50 values ranging from 1 nM to 500 nM.

3. Modulation of pERK levels and MAPK signalling in KRAS-mutant NSCLC cell lines

• We have previously shown that the lead compound prevents the phosphorylation of ERK by MEK, but does not inhibit MEK activity.

• Here we confirm that the lead compound confers a decrease in the phosphorylation of ERK itself in both NCI-H358 and Calu-6 cell lines.

4. Anti-tumour activity in KRAS-mutant NSCLC tumor xenografts

• Once daily oral administration of 50 mg/kg lead compound conferred significant anti-tumor activity (p < 0.0001) in the HCC44 KRAS-mutant NSCLC xenograft model and significant tumour regression (p = 0.0001) in the Calu-6 KRAS-mutant NSCLC xenograft model.

• These data support the further optimisation of this compound series for future clinical development.

SUMMARY AND CONCLUSIONS

The direct targeting of ERK is an attractive therapeutic approach for the treatment of KRAS-mutant NSCLC.

Using fragment-based drug discovery we have developed a novel, potent and selective ERK inhibitor, which in addition to inhibiting ERK catalytic activity also inhibits the phosphorylation of ERK by MEK.

The compound potently inhibits ERK signalling and the proliferation of KRAS-mutant NSCLC cell lines.

In vivo, the compound confers significant anti-tumor activity in several KRAS-mutant NSCLC xenograft models.

These data support the further optimisation of this compound series for future clinical development.

References:
1. Jove et al. (2010) JAMA. 317(18),1844-1853

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