In vivo studies demonstrate differences in target inhibition and anticancer efficacy between NXP900 and dasatinib in ovarian clear cell carcinoma model

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Introduction

We have developed and characterized the first small molecule—NXP900 (eCF506)—that locks SRC in its native inactive conformation, thereby inhibiting both enzymatic and scaffolding functions. NXP900 displays high selectivity across the kinome. Pharmacodynamic analysis

NXP900 displays high selectivity across the kinome

To compare the kinase-wide activity profile of NXP900 (0.5 μM) and dasatinib (1 μM), an enzymatic inhibition screen was performed against 326 wildtype and mutant kinases and NXP900 activity was compared to previous data on dasatinib. NXP900 and dasatinib exhibit overlapping but distinct kinase inhibition profiles; NXP900 shows greater selectivity across the kinome compared to dasatinib.

Pharmacodynamic assay

Pharmacodynamic (PD) assays for NXP900 and dasatinib were performed in vitro using recombinant kinases.

In Vivo efficacy study

In Vivo Efficacy study was performed in CD1 nude female mice (n=25, 5 mice per group); Xenograft tumors were generated by dissolving in vehicle (Figure 6). Pharmacodynamic (PD) assays for NXP900 and dasatinib were performed in cell culture and in vivo.

Discussion

Current type I SRC inhibitors in late-stage clinical development or approved (e.g. bosutinib, saracatinib and dasatinib) bind to the catalytic domain of SFK members in their active conformation. While this binding mode inhibits the catalytic activity of SFKs, they are still free to interact with binding partners, such as Focal Adhesion Kinase (FAK) and Yes-associated protein (YAP) and signal through their scaffolding function. Higuchi et al reported that type I SRC inhibitors such as dasatinib enhance SRC–FAK complex formation contributing to paradoxical activation of the SRC-FAK signalling complex. In this study we show in a TOV-21G ovarian clear cell carcinoma model with high YAP expression, NXP900, in contrast to dasatinib treatment, results in sustained inhibition of SRC activity in vivo with no evidence of paradoxical activation. NXP900 further inhibited in vivo tumour growth and nuclear localization of YAP in TOV-21G cells in a dose dependent manner.

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References


