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NXP900, a novel, clinical-stage, switch-control YES1/SRC kinase inhibitor, is synergistic with Ras inhibition in Ras sensitive and resistant NSCLC cells

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Introduction

NXP900, a highly-potent, switch-control SRC family kinase (SFK) inhibitor, (IC_{50} of 0.47 nM against YES1), has previously demonstrated high SFK selectivity and the capability to lock the protein at its native "off" conformation (type 1.5 inhibitor), resulting in inhibition of both enzymatic and scaffolding activities[1]. Conversely, multi-kinase inhibitors dasatinib and bosutinib target the "on" conformation (type 1 inhibitors), thus promoting SFK association with signalling partners and, as a consequence, inducing a paradoxical enhancement of SFK activity when the inhibitor dissociates from the ATP site[2].

G12C mutant-selective KRAS inhibitors (KRASi) have been FDA-approved and several mutant-selective, pan-mutant-KRAS, and pan-RAS inhibitors are in development. However, KRASi monotherapy results in limited clinical benefit and face the rapid development of acquired resistance. YAP1 activation and nuclear translocation is associated with drug resistance to KRASi and promotes the survival of drug-tolerant persister cells after therapy. Nuclear localization of YAP1 is regulated by direct phosphorylation by YES1 and SRC kinases[5,6], hence we hypothesized that cells with acquired resistance to sotorasib, an FDA approved G12C KRASi, would be sensitive to the combination of NXP900 and sotorasib.

NXP900 targets multiple mechanisms of acquired resistance to RAS inhibitors: Rationale for combining NXP900 and RAS inhibitors

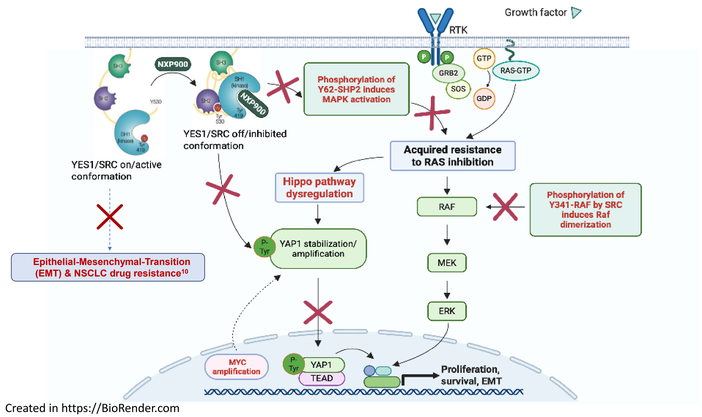

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Figure 1. NXP900 locks SRC in its native inactive conformation inhibiting both catalytic and scaffolding functions thus enabling potent and sustained pharmacodynamic inhibition of the pathway as demonstrated in the FIH dose escalation[7]. Targeting multiple mechanisms of acquired resistance to RAS inhibitors including activation of YAP1, MYC, RAF and SHP2 may enable a more potent clinical effect compared to inhibition of specific pathways (Mechanisms of resistance to Ras inhibition reviewed in 8, 9).

NXP900 potently inhibits SRC auto-phosphorylation in Sotorasib sensitive and resistant NSCLC cels

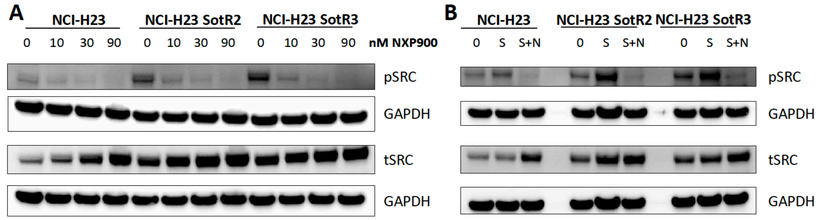
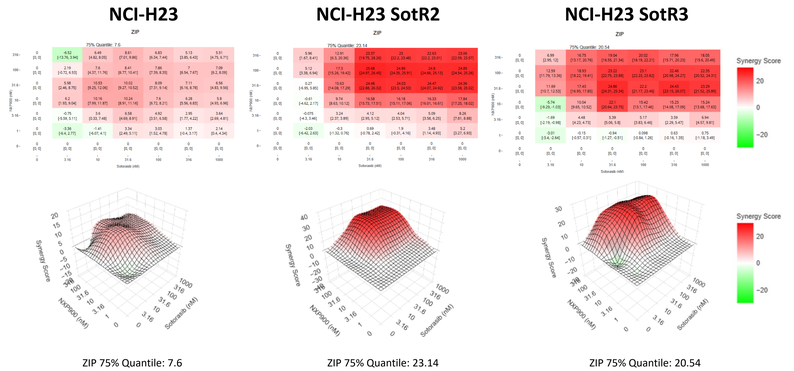


Figure 2. Determination of the effect of NXP900, sotorasib, or NXP900+sotorasib on phosphorylation of SRC. Resistant NSCLC cell lines to sotorasib inhibitors were generated from NCI-H23 NSCLC cells following exposure to increasing concentrations of sotorasib (Pangea Oncology). **A.** Phospho-SRC signal is increased in sotorasib resistant NSCLC cells relative to parental. Phospho-SRC is decreased in parental and resistant NCI-H23 cell lines when treated with NXP900 for 24 hours **B.** Phospho-SRC signal was similar or increased when treating with 30 nM sotorasib for 24 hours compared to vehicle (0 nM) in parental NCI-H23 cells, while phospho-SRC levels were decreased when treating with the combination of 30 nM sotorasib and 30 nM NXP900 in parental and resistant NCI-H23 cell lines.

NXP900 is synergistic with Sotorasib in KRAS driven Sotorasib-resistant NSCLC cells



ZIP 75% Quantile: 7.6 | ZIP 75% Quantile: 23.14 | ZIP 75% Quantile: 20.54

Figure 3. Cell viability assay - Parental and sotarasib resistant (SotR3 and SotR3) NCI-H23 NSCLC cells were diluted in the corresponding ATCC recommended medium and dispensed into a 384-well plate and treated with sotorasib and NXP900 for 120 h and underwent ATPlite viability assay. Full factorial dose-ratio matrix combination studies were performed across parental and resistant cells. Drug combination plots were created using the SynergyFinder+ R package[11]. The Zero Interaction Potency (ZIP) reference model was applied indicating potent additive combination activity across parental and strong synergistic activity in both resistant lines respectively.

NXP900 inhibits nuclear YAP1 localization in NCI-H23 NSCLC cells

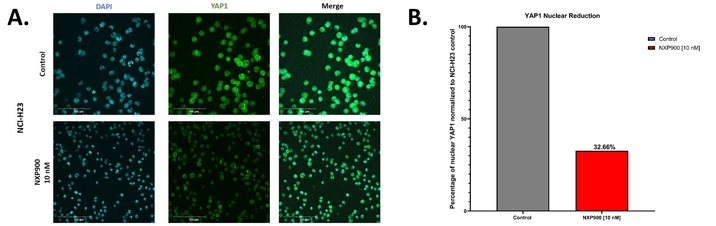


Figure 4. NXP900 treatment inhibits YAP1 nuclear localization in NCI-H23 NSCLC cells. **A.** Immunofluorescent confocal imaging study of YAP1 localization, NXP900 at 10 nM for 48-hours (x40). **B.** Quantification of YAP1 signal intensity in NCI-H23 cells after treatment with NXP900.

Summary and Conclusions

- SRC phosphorylation increased in sotorasib resistant cells and is further induced by treatment with sotorasib.
- NXP900 inhibits SRC phosphorylation, YAP1 nuclear localization and cell proliferation at low nM concentration in sotorasib-sensitive and sotorasib-resistant RAS-mutated NSCLC cells.
- NXP900 is strongly synergistic in sotorasib-resistant RAS-mutated NSCLC cells. Synergy index substantially increases in Ras-resistant cells vs Ras-sensitive cells.
- The data indicates a combination of NXP900 and Ras inhibition may drive clinical benefit to RAS-naïve and RAS-resistant patients, (no DDI expected – a unique attribute due to CYP3A sensitivity of FDA approved Ras inhibitors).
- A single agent Phase 1b study in patients with *FAT1, YES1* and other genomic alterations in solid tumors (NCT05873686) and a combination cohort with Osimertinib in subjects with advanced, EGFR-Mutated Non-Small Cell Lung Cancer (NCT07315113) are actively recruiting.

Acknowledgements and Contacts

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