Clinical safety, pharmacokinetics, pharmacodynamics, and cytochrome P450 interactions for the SRC/YES1 kinase inhibitor NXP900

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Introduction

Kinases of the SRC family of kinases (SFK) are highly activated in various tumor tissues, promoting cell adhesion, invasion, proliferation, survival and angiogenesis. NXP900 is a selective SFK inhibitor that locks its target in its native "closed" conformation (type 1.5 inhibitor), resulting in inhibition of both the catalytic and scaffolding functions of the kinase while avoiding paradoxical activation of pro-oncogenic signaling, a phenomenon observed with type 1 inhibitors. In xenograft studies, tumors harboring specific genetic alterations, including YES proto-oncogene 1 (YES1) amplification and mutations along the Hippo Pathway, were sensitive to treatment with NXP900 as monotherapy. In combination, the addition NXP900 to lorlatinib and osimertinib resulted in synergistic inhibition of cell proliferation in lorlatinib and osimertinib-resistant non-small cell lung cancer cell lines.

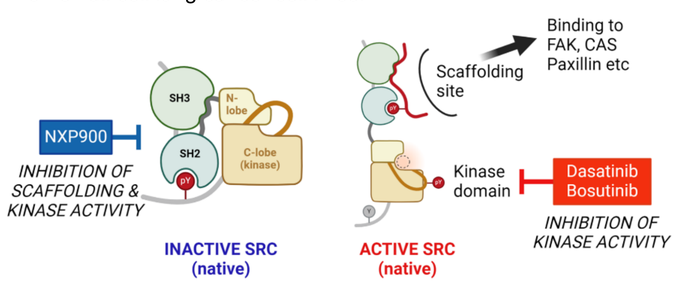


Figure 1. Mechanism of SRC inhibition. NXP900 locks SRC in its native inactive conformation resulting in inhibition of both the kinase and scaffolding functions (Created with Biorender).

Methods

Two clinical studies, NXP900-101 (a dose escalation study in patients with advanced solid tumors) and NXP900-104 (a drug-drug interaction study in healthy volunteers) have been completed. The primary objective of Study NXP900-101 was to identify a dosing regimen with an acceptable safety profile and clinically relevant pharmacokinetics and pharmacodynamics (PK/PD). The primary objective of Study NXP900-104 was to characterize the interaction of NXP900 with the Cytochrome P450 (CYP) enzymes 1A2, 2B6 and 3A.

Baseline Characteristics

Parameter	NXP900-101 (N=33)
Age (years)	
Median (Range)	62 (36 - 89)
Sex (n,%)	
Female	13 (39)
Male	20 (61)
ECOG PS (n,%)	
0	8 (24)
1	25 (76)
Prior Lines of Anticancer Treatment	
Median (Range)	5 (1 - 11)

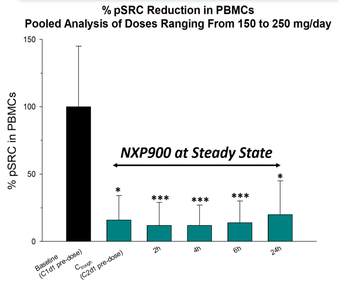
Common Treatment Emergent Adverse Events

Adverse Event	NXP900-101 (N= 33)					
N (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Diarrhea	7 (21)	7 (21)	1 (3)	0 (0)	0 (0)	15 (45)
Fatigue	4 (12)	9 (27)	2 (6)	0 (0)	0 (0)	15 (45)
Nausea	7 (21)	5 (15)	0 (0)	0 (0)	0 (0)	12 (36)
Decreased appetite	2 (6)	8 (24)	0 (0)	0 (0)	0 (0)	10 (30)
Dyspnea	3 (9)	2 (6)	3 (9)	0 (0)	0 (0)	8 (24)
Vomiting	6 (18)	1 (3)	0 (0)	0 (0)	0 (0)	7 (21)
Back pain	1 (3)	3 (9)	2 (6)	0 (0)	0 (0)	6 (18)
Hypokalemia	2 (6)	4 (12)	0 (0)	0 (0)	0 (0)	6 (18)
Abdominal pain	1 (3)	3 (9)	1 (3)	0 (0)	0 (0)	5 (15)
Cough	4 (12)	1 (3)	0 (0)	0 (0)	0 (0)	5 (15)
Hypoxia	0 (0)	1 (3)	4 (12)	0 (0)	0 (0)	5 (15)
Pneumonia [a]	0 (0)	1 (3)	3 (9)	0 (0)	1 (3)	5 (15)

Includes all AEs with incidence ≥15% in all subjects that took at least 1 dose of NXP900 across all dose levels (20 - 300 mg/day).

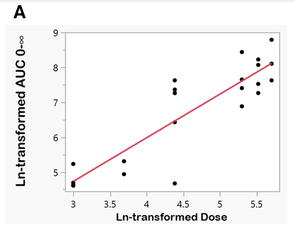
a. None of the reported cases of pneumonia were considered related to NXP900.

Pharmacodynamics

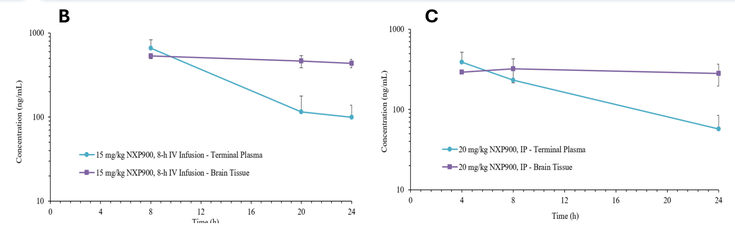


- Treatment with NXP900 resulted in substantial reduction of pSRC in peripheral blood mononuclear cells (PBMCs) (pooled analysis of available data across the dose range at each timepoint; One Way ANOVA was used for statistical comparisons).
- PD response was rapid, initially observed after a single dose and maintained at steady state.
- phospho-Y419 SRC was determined using an AlphaLISA kit (Revvity); Assay performed by Oncolines B.V. Oss, Netherlands.

Clinical PK



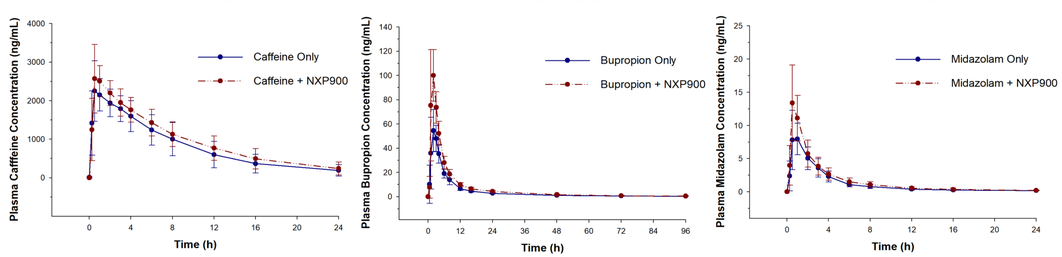
Brain Penetration (Nonclinical)



A. NXP900 exhibits a linear dose-exposure relationship in plasma samples from patients with advanced cancers (R^2=0.78, p<0.001).
B,C. NXP900 penetrates the brain in biologically and clinically relevant concentrations following 8h IV and single IP administrations in rats.

Clinical Drug Interaction Study in Healthy Volunteers

NXP900 is not an inducer of key CYP450 enzymes



A cocktail of the CYP450 substrates caffeine (1A2 substrate), bupropion (2B6 substrate) and midazolam (3A substrate) was administered to healthy volunteers +/- NXP900 to evaluate the CYP induction potential of NXP900.

Summary

- NXP900 is a highly selective, brain-penetrating, type 1.5 YES1/SRC kinase inhibitor that inhibits both the catalytic and scaffolding functions of its target while avoiding paradoxical activation of pro-oncogenic signaling.
- In patients with advanced cancers, the safety of NXP900 administered once daily at doses ranging from 20 to 300 mg/day was acceptable, with diarrhea, fatigue and nausea being the most common adverse events, mostly reported as Grade 1-2. NXP900 exhibited linear dose-exposure relationship in plasma and elicited a robust pharmacodynamic response at doses ≥150 mg/day.
- In a clinical drug interaction study in healthy volunteers NXP900 did not induce the activity of key CYP450 enzymes, a key consideration for the combination strategy.
- A phase 1b study of NXP900 as monotherapy in patients with advanced solid tumors with YES1, FAT1, NF2 and other genomic alterations is ongoing (NCT05873686).

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