

First in human phase 1 trial of the SRC family kinase inhibitor NXP900 in patients with advanced solid tumors

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Introduction

- ❖ SRC family kinases (SFKs) are key components of signaling pathways implicated in carcinogenesis and have been shown to be highly activated in tumor tissue. The role of SFKs in cell proliferation, survival, migration, invasion, metastasis, and drug resistance has been extensively described¹⁻³.
- ❖ NXP900 is a novel, selective SFK inhibitor, including low nanomolar potency against YES1 (0.47nM) and SRC (2.4nM), and only minimal inhibitory activity against kinases outside the SFK.
- ❖ NXP900 has a unique binding mode of action (MOA), whereby it locks its target into its native “closed” conformation (type 1.5 inhibitor), resulting in inhibition of both the kinase and the scaffolding functions of the target kinase. This MOA differentiates NXP900 from other multi-kinase inhibitors, that, among other kinases, also inhibit the kinase activity of SFK targets. These multi-kinase inhibitors lock their targets in the active “open” conformation (type 1 inhibitors), and in the case of SFK targets, while this results in inhibition of the kinase activity, it also promotes the association of SFK with pro-cancer signaling partners.

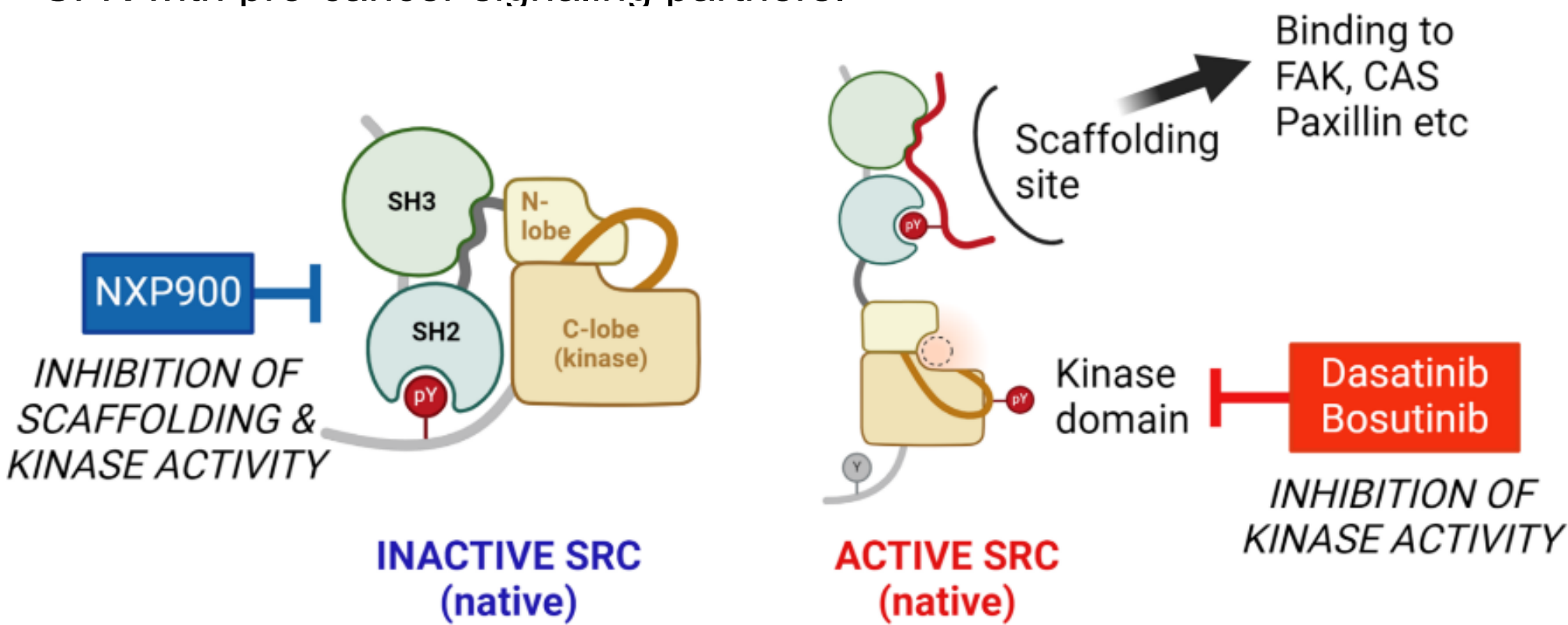


Figure 1. Mechanism of SRC inhibition. NXP900 locks SRC in its native inactive conformation resulting in inhibition of both the kinase and scaffolding functions (Created with Biorender).

Methods

- ❖ The Phase 1a portion of Study NXP900-101 (NCT05873686), is a first-in-human, dose escalation clinical trial of NXP900 in patients with advanced solid tumors. NXP900 capsules are administered orally once daily.
- ❖ The primary objective of the study is to identify a dosing regimen with an acceptable safety profile and clinically relevant pharmacokinetics and pharmacodynamics (PK/PD) for additional clinical investigations.
- ❖ The key safety endpoints are estimations of the incidence and intensity of adverse events and identification of the highest tolerable dose. To characterize the PK/PD profile of NXP900, serial blood samples were collected after single and multiple doses of NXP900.

Baseline Characteristics

Parameter	N = 29
Age (years)	
Median (Range)	62 (36 - 89)
Sex (n,%)	
Female	11 (38)
Male	18 (62)
ECOG PS (n,%)	
0	5 (17)
1	24 (83)
Prior Lines of Anticancer Treatment ^a	
Median (Range)	5 (1 – 20)
a. Including surgery	

Pharmacokinetics and Pharmacodynamics

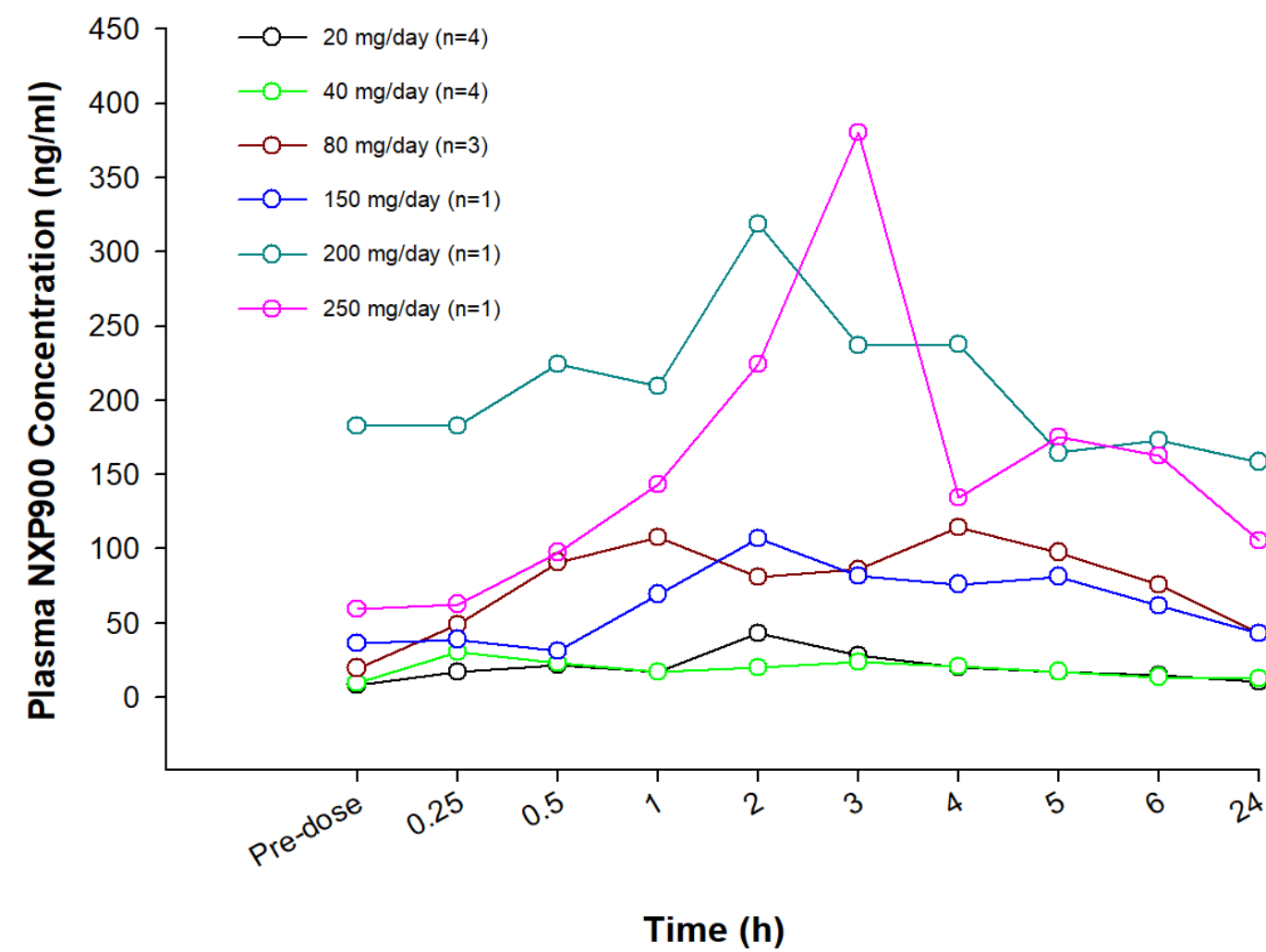


Figure 2. NXP900 concentration in plasma at steady state (cycle 2, day 1): Preliminary PK demonstrated increased systemic exposure with increased doses, rapid absorption with median peak plasma concentration of 3 hours (range: 0.5 – 6), and median terminal half-life of approximately 11 hours (range: 8 - 21) after a single oral dose. Multiple dosing resulted in moderate drug accumulation.

NXP900 potentially inhibited the autophosphorylation of SRC (pSRC) across a range of clinically relevant doses in peripheral blood mononuclear cells.

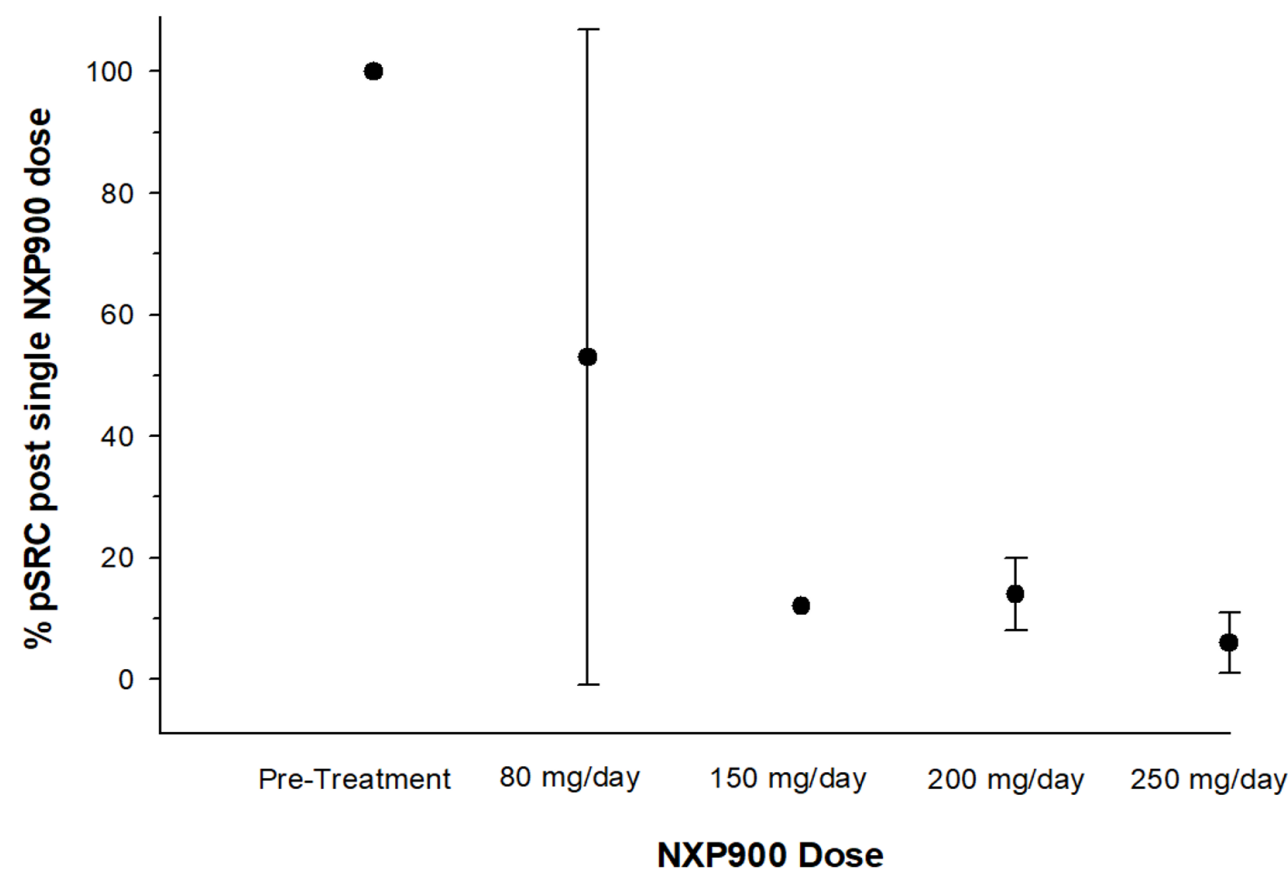


Figure 3. Characterization of pSRC in PBMCs from patients treated with NXP900: Best response 2-24 hours after a single dose of NXP900 (Oncolines B.V. Oss, Netherlands; phospho-Y419 SRC was determined using the AlphaLISA kit/Revvity).

Treatment Emergent Adverse Events

Adverse Event ^a , n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Fatigue	3 (10)	7 (24)	2 (7)	0 (0)	0 (0)	12 (41)
Diarrhea	6 (21)	4 (14)	1 (3)	0 (0)	0 (0)	11 (38)
Nausea	6 (21)	4 (14)	0 (0)	0 (0)	0 (0)	10 (34)
Abdominal pain	1 (3)	3 (10)	2 (7)	0 (0)	0 (0)	6 (21)
Dyspnea	2 (7)	2 (7)	2 (7)	0 (0)	0 (0)	6 (21)
Vomiting	5 (17)	1 (3)	0 (0)	0 (0)	0 (0)	6 (21)
Back pain	0 (0)	3 (10)	2 (7)	0 (0)	0 (0)	5 (17)
Decreased appetite	1 (3)	4 (14)	0 (0)	0 (0)	0 (0)	5 (17)
Hypokalemia	1 (3)	4 (14)	0 (0)	0 (0)	0 (0)	5 (17)
Pneumonia ^b	0 (0)	1 (3)	3 (10)	0 (0)	1 (3)	5 (17)
ALT increase	3 (10)	0 (0)	1 (3)	0 (0)	0 (0)	4 (14)
AST increase	2 (7)	0 (0)	2 (7)	0 (0)	0 (0)	4 (14)
Constipation	3 (10)	1 (3)	0 (0)	0 (0)	0 (0)	4 (14)
Headache	3 (10)	1 (3)	0 (0)	0 (0)	0 (0)	4 (14)
Hypoxia ^b	0 (0)	1 (3)	3 (10)	0 (0)	0 (0)	4 (14)

a. Reported in >10%, includes all subjects that took at least 1 dose of NXP900 across all doses (20-250 mg/day).

b. None of the pneumonia and hypoxia events were considered related to NXP900.

Highlights and Conclusions

- ❖ NXP900 has an acceptable safety profile in patients with advanced solid tumors. The DLT dose level has not been identified in doses up to 250 mg/day.
- ❖ Exposure levels leading to potent pharmacodynamic response achieved; target inhibition observed across a range of tolerated doses.
- ❖ The Phase 1b portion of the study is planned in patients with advanced cancers with YES1 gene amplifications and hippo pathway related genomic alterations including in FAT1 and NF2 genes.

References

- Garmendia 2022. YES1: A Novel Therapeutic Target and Biomarker in Cancer. *Mol. Cancer Ther.*
- Hamanaka 2019 . YES1 Is a Targetable Oncogene in Cancers Harboring YES1 Gene Amplification. *Cancer Res.*
- Raji 2023. Role of c-Src in Carcinogenesis and Drug Resistance. *Cancers (Basel).*

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