Nuvectis Pharma, Inc.

Innovative Precision Medicine for Serious Conditions of Unmet Medical Need in Oncology

January 2025

NuvectisPharma, Inc.

(NASDAQ: NVCT)

Forward Looking Statements

Nuvectis Pharma, Inc.

Certain statements in this presentation constitute “forward-looking statements“within the meaning of the federal securities laws, which statements are subject to substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this press release are forward-looking statements. Forward-looking statements contained in this press release may be identified by the use of words such as “anticipate,” “believe,” “contemplate,” “could,” “estimate,” “expect,” “intend,” “seek,” “may,” “might,” “plan,” “potential,” “predict,” "project," “target,” “aim,” “should,” “will,” “would,” or the negative of these words or other similar expressions, although not all forward-looking statements contain these words. Forward-looking statements are based on Nuvectis Pharma, Inc.'s current expectations, including safety and efficacy data generated to date for NXP800 and NXP900, estimates, and projections about future events and trends that we believe may affect our business, financial condition, results of operations, prospects, business strategy, and financial needs. The outcome of the events described in these forward-looking statements are subject to inherent uncertainties, risks, assumptions, market and other conditions, and other factors that are difficult to predict and include statements and data regarding the preclinical studies for NXP800 and NXP900, and the Phase 1a data for NXP800 and the NXP900 Phase 1a study to date, as well as the clinical expectations for the ongoing NXP800 Phase 1b study in platinum-resistant, ARID1a-mutated ovarian carcinoma, including the potential ability of a higher dose intensity going forward in the NXP800 Phase 1b study to generate satisfactory safety and efficacy results, statements regarding NXP800's potential ability to become a therapeutic option for the treatment of platinum-resistant, ARID1a-mutated ovarian carcinoma, cholangiocarcinoma, and potentially other cancer indications, and the timing for completion of the clinical trials, including the ongoing NXP800 investigator-initiated study in cholangiocarcinoma and statements regarding NXP900's therapeutic potential. Further, certain forward-looking statements are based on assumptions as to future events that may not prove to be accurate. These and other risks and uncertainties are subject to market and other conditions and described more fully in the section titled “Risk Factors” in our 3Q 2024 Form 10-Q and our other public filings with the Securities and Exchange Commission (“SEC”). However, these risks are not exhaustive and new risks and uncertainties emerge from time to time, and it is not possible for us to predict all risks and uncertainties that could have an impact on the forward-looking statements contained in this press release or other filings with the SEC. Any forward-looking statements contained in this press release speak only as of the date of this press release. We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances on which any such statement is based, except as may be required by law, and we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

Nuvectis Pharma – Key Highlights

Our Approach to Precision Medicine

- Select and acquire novel, rationally-designed drug candidates
- Focus on drug development for serious conditions of unmet need in oncology

NXP800

- Ongoing clinical trials
  - ARID1a-mutated, platinum resistant ovarian carcinoma (Fast Track Designation, Orphan Drug Designation)
  - Cholangiocarcinoma (Orphan Drug Designation)

NXP900

- Phase 1a dose escalation ongoing
- Potential indications: YES1/SRC-driven solid tumors, cancers of squamous cell origin, ALK positive / EGFR-mutated NSCLC (combination)

Management Team with Strong Track Record

- 3 approved drugs in 4 indications in the US and EU and multiple strategic deals
- Cash runway into H1 2026

Management Team

Track record of success

Ron Bentsur
Chairman & Chief Executive Officer

Enrique Poradosu, PhD
Chief Scientific & Business Officer

Shay Shemesh
Chief Development & Operations Officer

Auryxia® (ferric citrate) tablets

Jelmyto® (mitomycin)

ELZONRIS® (tagraxofusp-erzs) Injection

KERYX BIOPHARMACEUTICALS, INC

UroGen® Pharma

Stemline®

Nuvectis Precision Medicine Pipeline

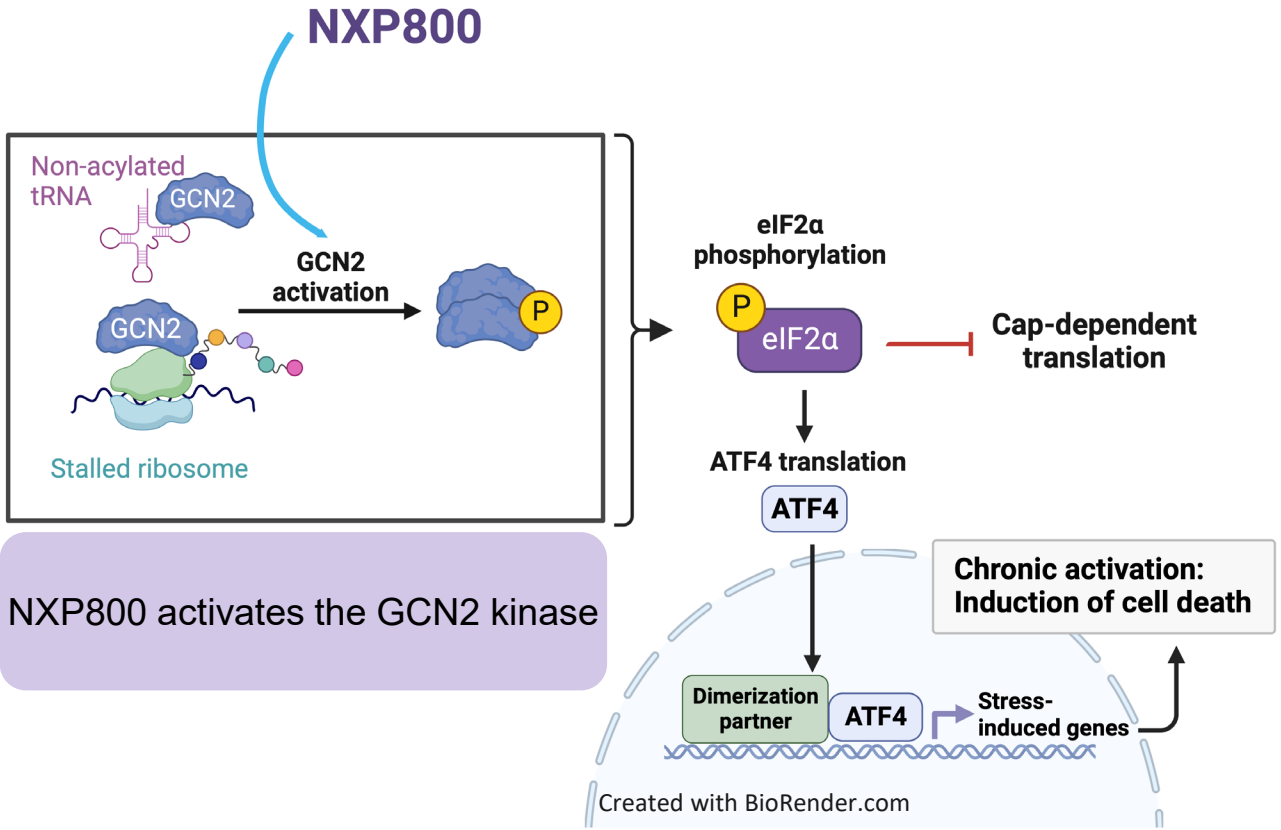
DRUG CANDIDATE	INDICATION	DISCOVERY / LEAD OPTIMIZATION	IND ENABLING	PHASE 1A	PHASE 1B	COLLABORATIONS
NXP800 [a] (GCN2 activator)	**ARID1a mutated ovarian cancer** • Ovarian clear cell carcinoma • Ovarian endometrioid carcinoma	*Fast Track Designation, Orphan Drug Designation*				GOG FOUNDATION; ENGOT European Network of Gynaecological Oncological Trial groups
	Cholangiocarcinoma (IST)	*Orphan Drug Designation*				MAYO CLINIC HEALTH SYSTEM
NXP900 [b] (SRC/YES1 inhibitor)	• **YES1 / SRC-driven solid tumors** • **Cancers of squamous cell origin** • **ALK positive / EGFR-mutated NSCLC (combination)**	*All-comer dose escalation ongoing*				

a. Exclusive worldwide rights acquired from the Institute of Cancer Research, UK.
b. Exclusive worldwide rights acquired from the University of Edinburg.

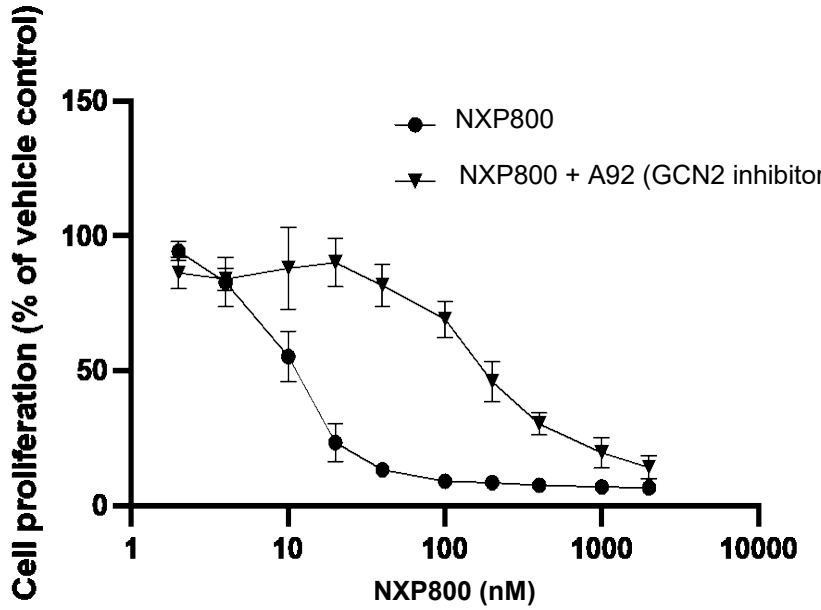
About NXP800

NXP800 Mechanism of Action

NXP800 is a GCN2 kinase activator



NXP800 activates the GCN2 kinase



- Inhibition of cap-dependent translation and chronic activation of the integrated stress response (ISR) ➔ Cancer cell death
- ARID1a-mutated tumors display an increased dependence on translation

Target validation

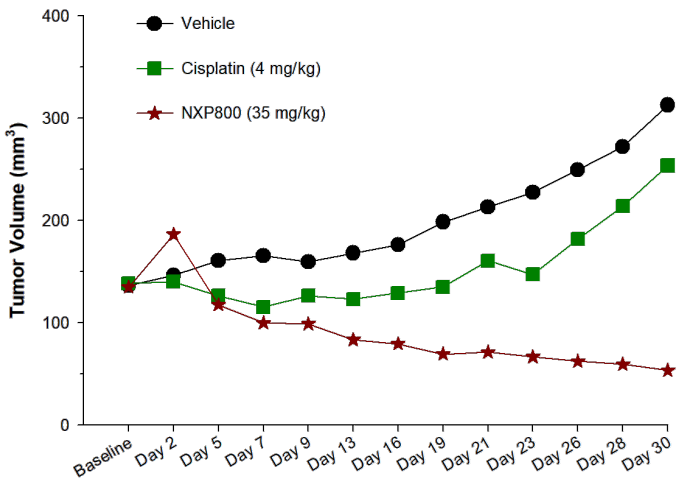
The GCN2 inhibitor A92 antagonizes the antiproliferative effect of NXP800 in ARID1a- mutated SKOV3 cells (approx. 50-fold change in GI_{50})

Powers et al., AACR 2023

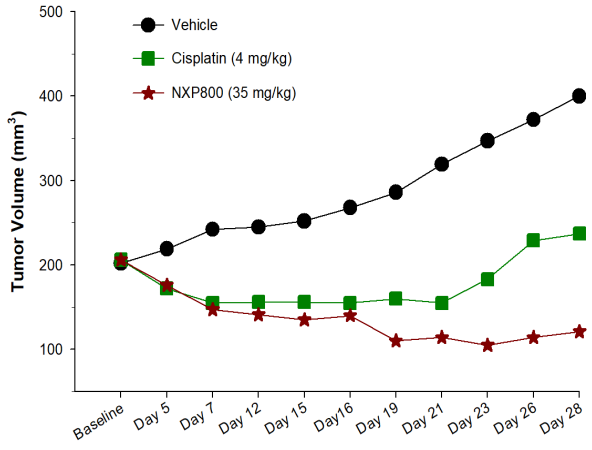
Substantial Antitumor Activity in ARID1a-Mutated Ovarian Carcinoma Xenografts (NXP800 vs. Cisplatin)

Preclinical proof of concept leading to selection of initial target indication

SKOV-3 (Cisplatin Resistant)



TOV-21G (Cisplatin Sensitive)



Disease	Est. Total Incidence (US) [a]	Est. # of Patients w/ ARID1a Deficiency
Ovarian Clear Cell Carcinoma	2,200	1,320
Ovarian Endometrioid Carcinoma	2,200	660

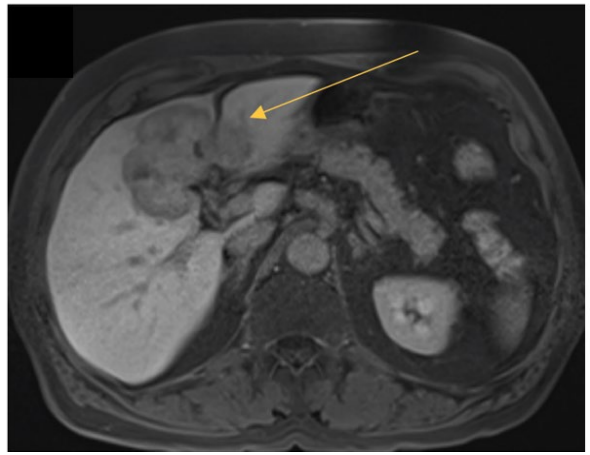
a. Based on data from the American Cancer Society, 2022

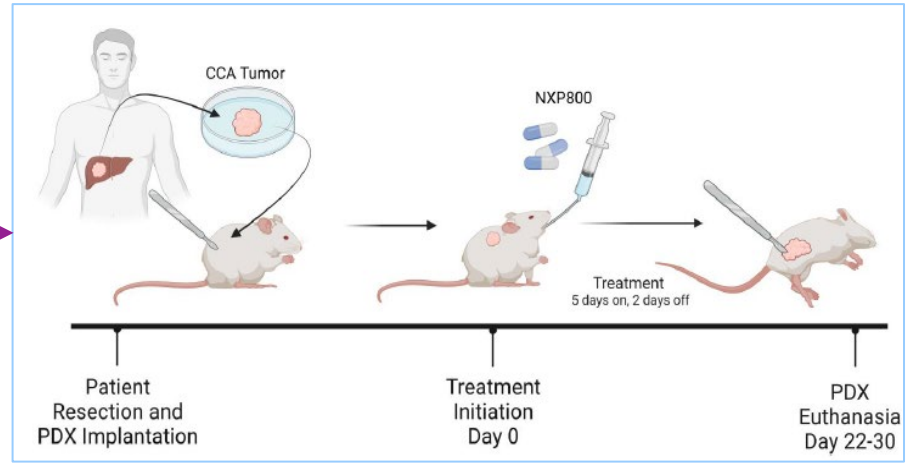
Substantial Antitumor Activity in Cholangiocarcinoma

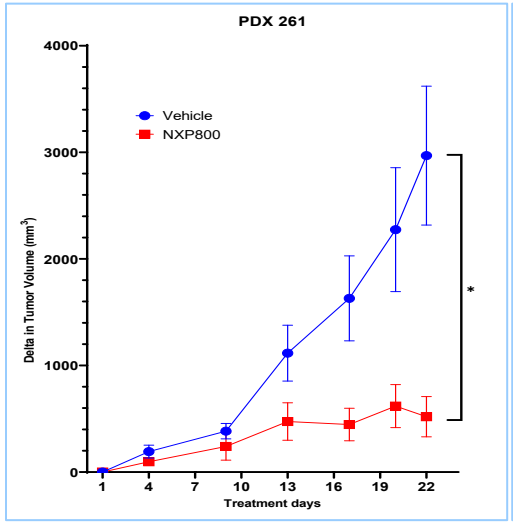
Additional potential development opportunities

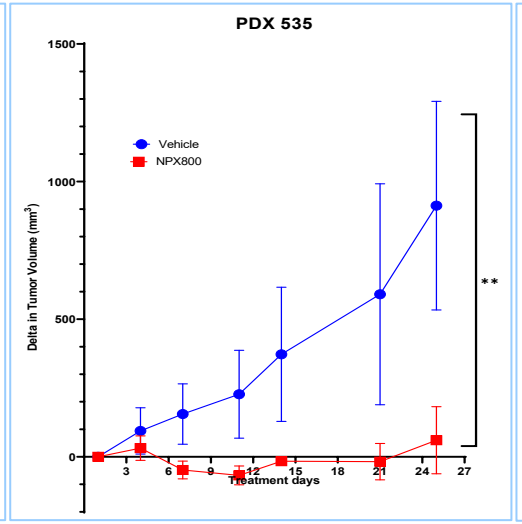
- Cholangiocarcinoma (CCA) is a lethal malignancy with poor prognosis arising from the biliary tree
- Approx. 10,000 new cases/year in the US [a]

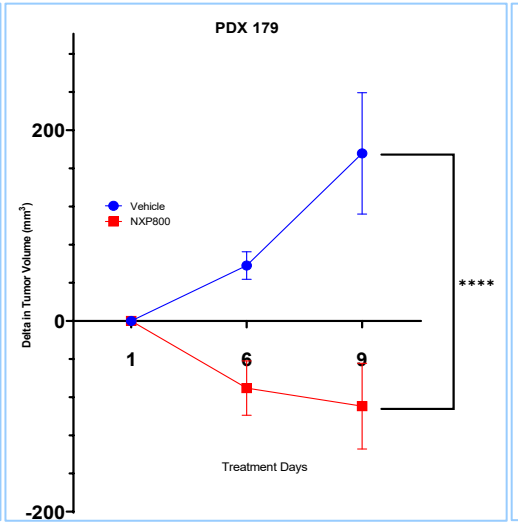
a. The cholangiocarcinoma foundation, cholangiocarcinoma.org/key-statistics

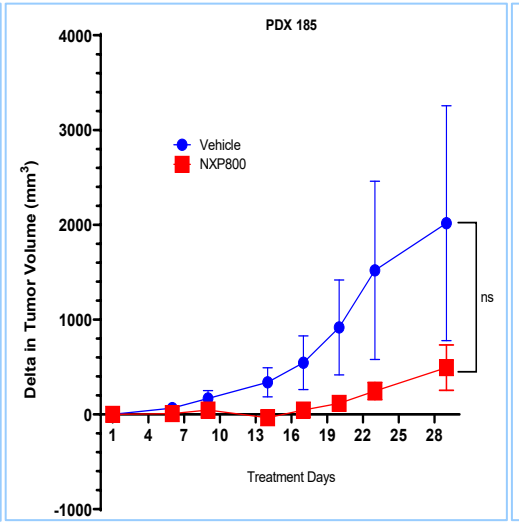


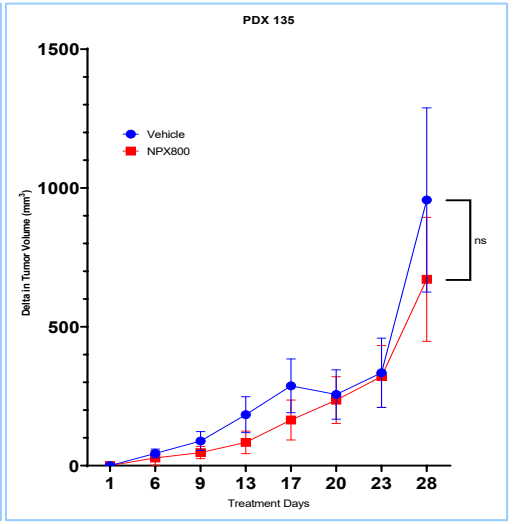












Tumor volume following NXP800 treatment in NOD SCID flank **(A)** *ARID1A* frameshift mutation **(B)** *FGFR1* and *2* overexpression **(C)** *HSF1* amplification **(D)** *PBRM1* variation **(E)** *BRAF* mutation (Carlsson et al., AACR 2024)

NXP800 Potential Opportunity in Multiple Cancers

ARID1a is an important mutation that can be used as a patient selection strategy [a]

Indication	Estimated Incidence (US)	ARID1a mutation prevalence	Estimated Number of Patients with ARID1a protein loss (US)
Ovarian Cancer (Clear Cell and Endometrioid)	4,350	52.9%	2,300
Endometrial Carcinoma	66,200	35.6%	23,600 [b]
Cholangiocarcinoma	8,000	17.5%	1,400
Urothelial	75,350	34.0%	25,600
Hepatocellular	34,000	26.7%	9,070
Gastric	26,550	24.9%	6,600

a. The ARID1a mutation detection assay is a standard part of commercially and clinically available NGS panels.
b. Estimate based on a weighted average of the ARID1a mutation prevalence within the major endometrial histology subtypes.

Recent Data Update from Ongoing Phase 1b

- Three dosing regimens have been evaluated to date in twelve patients
  - QD regimen: 75 mg/day and 50 mg/day, each regimen administered to two patients
  - Intermittent regiment: eight patients were treated with 50 mg/day on a five days on / two days off schedule
- Prior therapies
  - All patients failed at least two prior lines of systemic chemotherapy, including at least one prior platinum-based chemotherapy regimen, and most had also failed treatment with bevacizumab
- Efficacy: antitumor activity was observed with best responses including one patient with an unconfirmed partial response and six patients with stable disease, including tumor shrinkage
- Safety
  - In the four patients treated on a QD regimen - three experienced Grade 4 thrombocytopenia
  - In the eight patients treated with NXP800 using the intermittent dosing schedule the highest grade of thrombocytopenia observed was Grade 2 (one patient)
  - Other than thrombocytopenia, the most common treatment emergent adverse events included nausea, fatigue, vomiting, diarrhea and constipation, the majority of which were Grade 1-2

About NXP900

NXP900 Key Highlights

Precision Medicine Approach

- Discovered at the University of Edinburgh, Scotland
- A potent, novel, small molecule inhibitor of YES1/SRC signaling
- YES1-Hippo pathway alteration associated with sensitivity to NXP900 in squamous cell models

Differentiated Features

- Highly selective
- Unique mechanism of action - Complete shut-down of the SRC pathway by scaffold and catalytic domain inactivation

Strong Preclinical Proof of Concept

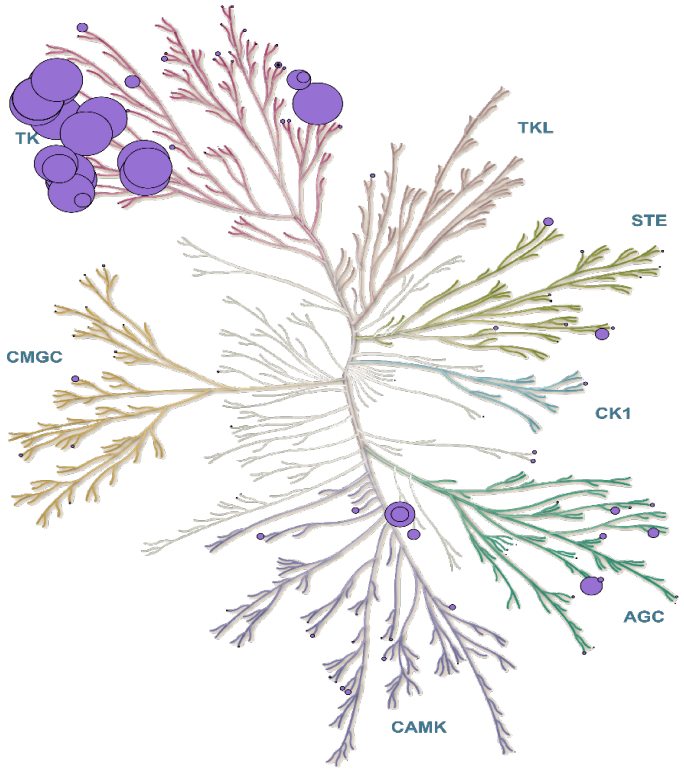
- POC in multiple xenograft models – significant single-agent activity in squamous cell cancer models
- Ability to re-sensitize resistant NSCLC cells to Osimertinib, preclinical synergistic effect with ALK inhibitors

Phase 1 Program

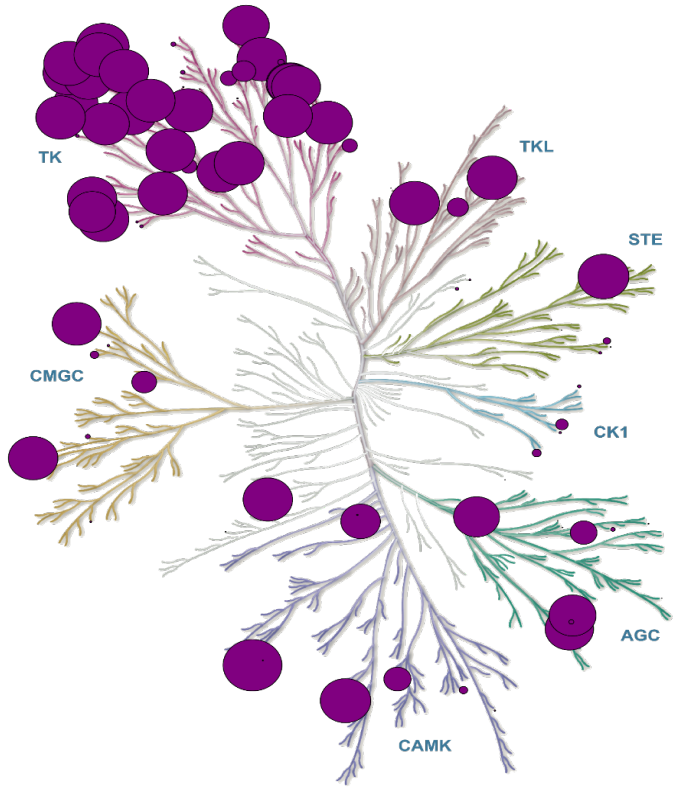
- Phase 1a dose escalation clinical trial ongoing

NXP900 Kinome Profiling Demonstrates High Selectivity

NXP900



Dasatinib

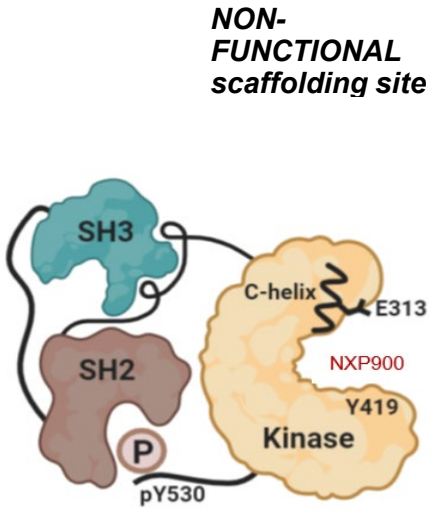


Note: Dasatinib data from Remsing Rix et al., Leukemia 23, 477–485 (2009), NXP900 data from AACR 2022.

NXP900 Completely Shuts Down Signaling of Non-receptor Tyrosine Kinases of the SRC Family

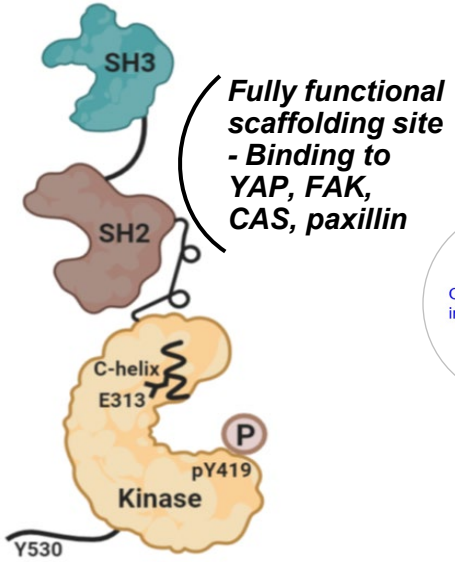
Differentiated vs. other multi-kinase inhibitors that only achieve a partial SRC pathway shut down

NXP900: Complete shutdown of the SRC pathway



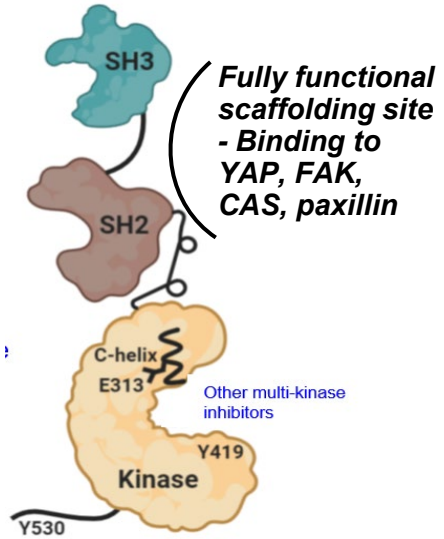
Closed, inactive conformation locked by NXP900

No inhibitor: Fully active SRC



Open, active conformation no inhibitor

Other multi-kinase inhibitors: Partial shutdown of the SRC pathway



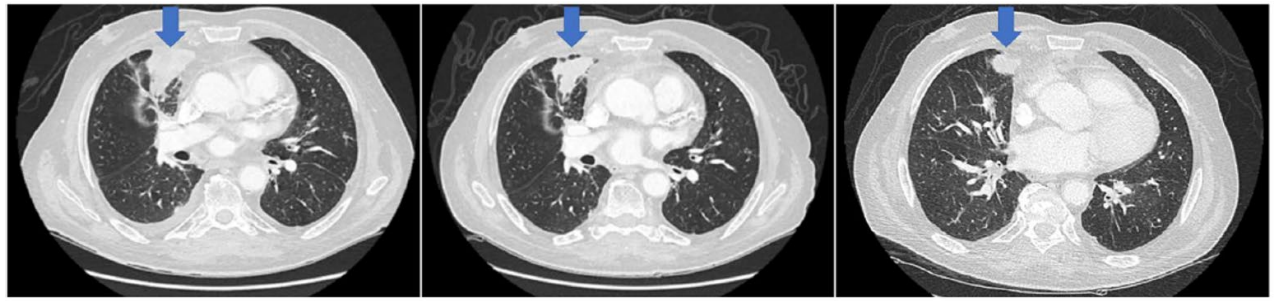
Open, active conformation stabilized by other multi-kinase inhibitors

Single Agent Strategy 1: YES1 Gene Amplification

A patient with YES1-amplified lung adenocarcinoma with no established primary driver alteration responded to SFK inhibition [a]

Case Study

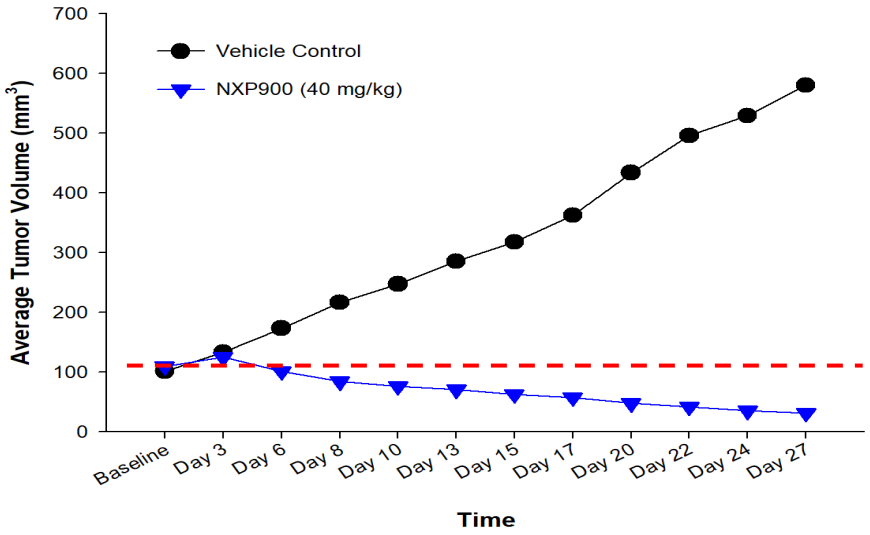
- 81 y/o man diagnosed with de novo stage 4 lung adenocarcinoma (LUAD) in 2016.
- Prior therapies
  - First-line - carboplatin plus pemetrexed plus bevacizumab for 5 months
  - Second line - nivolumab for 10 months
- MSK-IMPACT testing revealed YES1 amplification without any established primary driver alteration
  - Treatment with dasatinib was initiated
  - **Confirmed partial response by RECIST 1.1, with a 69% reduction in size of his target lesion**



Baseline 5.1cm | 6 weeks 4.2cm | 10 weeks 1.6cm

Hypothesis confirmation achieved *in vivo* with NXP900 in a YES1 amplified model – **Profound tumor regression**

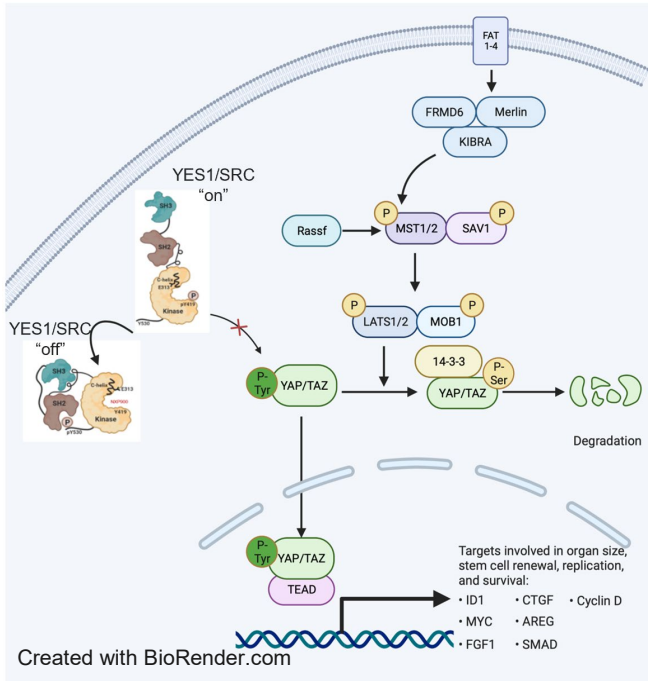
YES1 amplified cells (KYSE70)



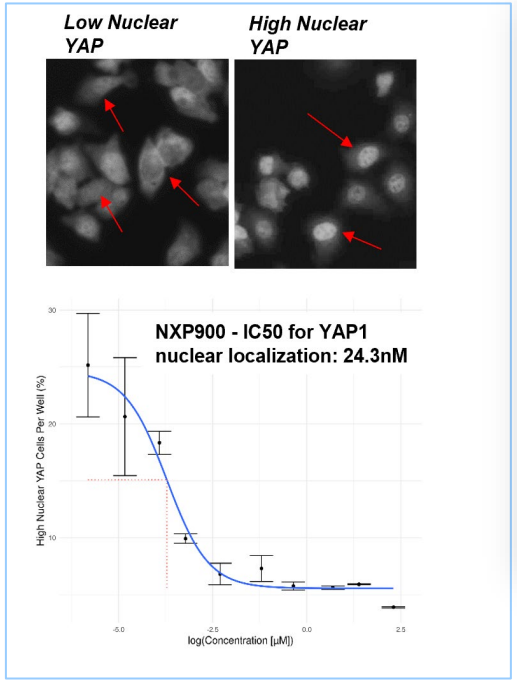
a. *Sato et al., JCO Precis Oncol, 2022*

Single Agent Strategy 2:
Targeting YES1 in Cancers of Squamous Cell Origin

Mechanistic Rationale

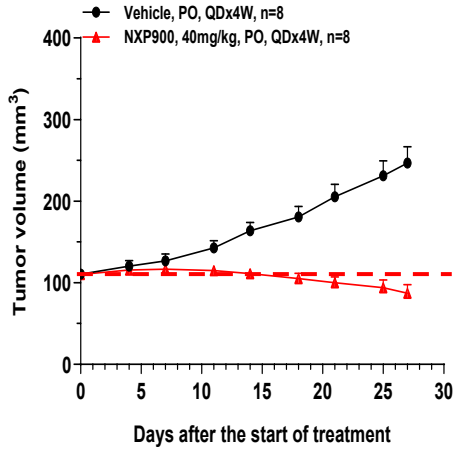


Biomarker Activity

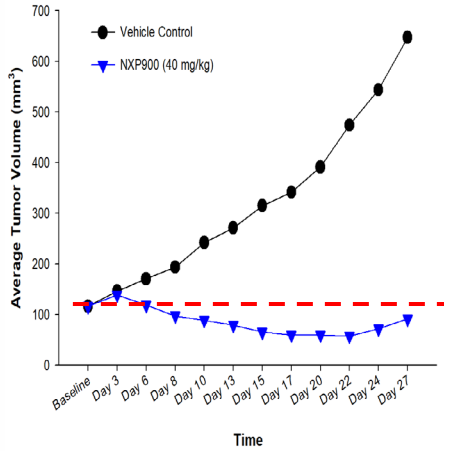


Preclinical POC *In Vivo*

KYSE-140 - Esophageal Cancer

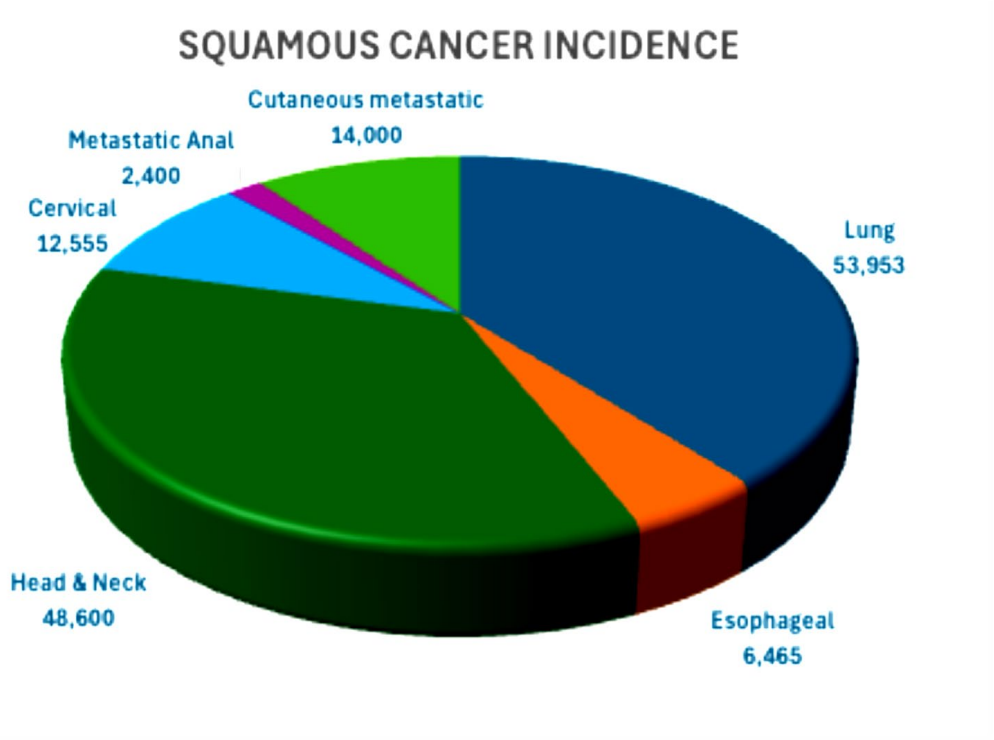


CAL27 - Head and Neck Cancer (tongue)



- Hippo pathway alterations (FAT1-4, YAP1, TAZ) are highly prevalent in cancers of squamous cell origin
- Hippo activation depends on YES1 activity via tyrosine phosphorylation and nuclear localization of YAP1
- Significant unmet medical need opportunities within the squamous cancer universe ➔ **Regulatory opportunity**

NXP900 Single Agent: Market Opportunity

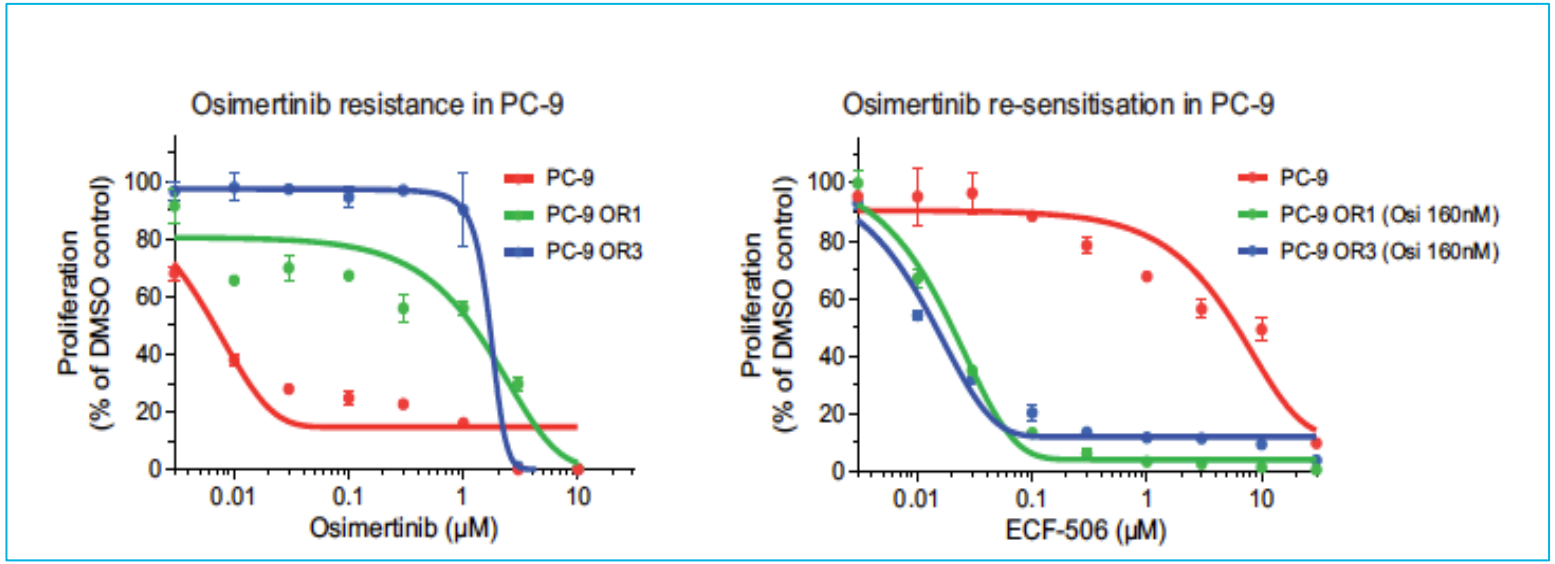


Combination Strategy

YES1 and SRC have been validated in development of resistance to EGFR and ALK inhibitors in NSCLC

- ALK and EGFR targeted agents have demonstrated potent and durable activity in NSCLC.
- However, emergence of resistance to ALK and EGFR targeting drugs is inevitable.
- SRC, YES1 and YAP1 activation have been extensively validated preclinically and in clinical samples.

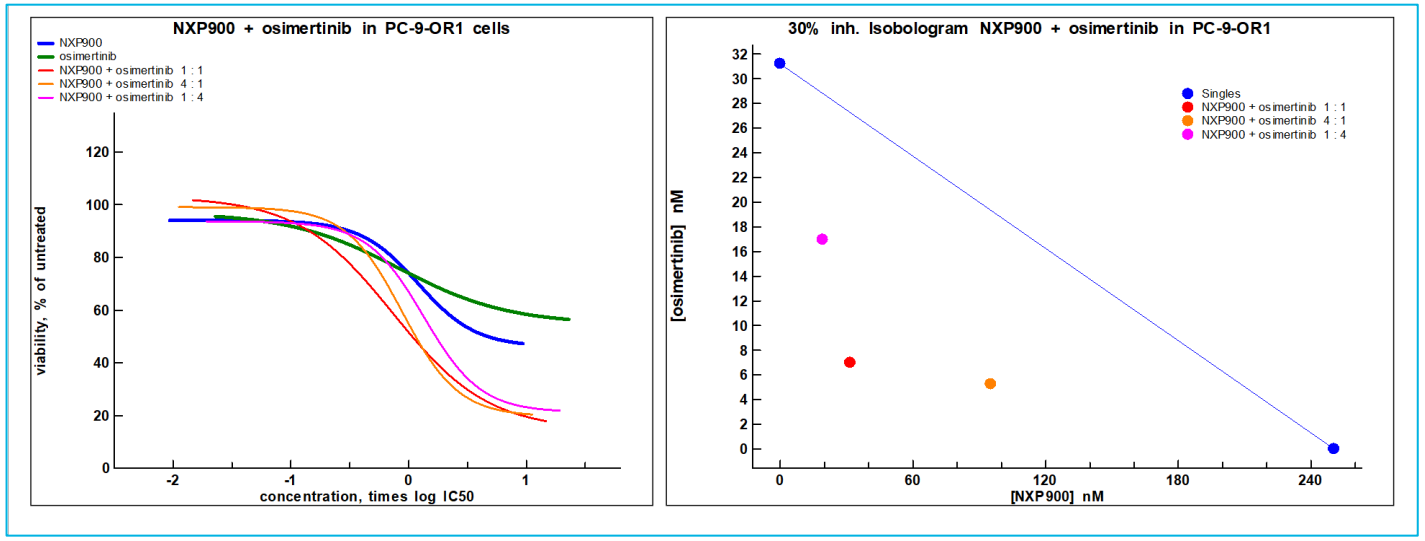
NXP900 in combination with osimertinib overcomes resistance in vitro
(Nature Com., AstraZeneca R&D, April 2022



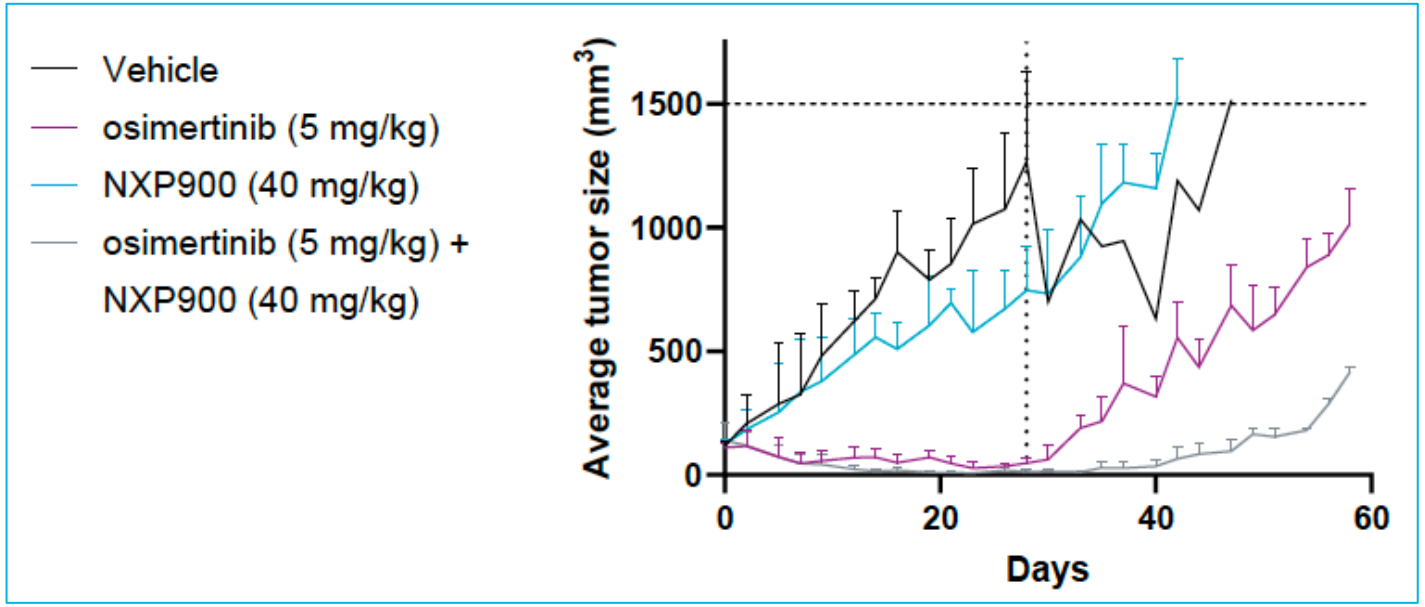
NSCLC = Non-small cell lung cancer, eCF506 = NXP900

NXP900/osimertinib Synergy *in vitro* and *in vivo* in Osimertinib-resistant NSCLC Cells

NXP900 restores sensitivity *in vitro* to osimertinib in resistant cells at low nanomolar concentrations



Combination achieves potent tumor regression in vivo and longer duration of the response after end of treatment compared to single agent osimertinib



Resistance to ALK Inhibitors in NSCLC

Acquired resistance to ALK inhibitors increases single agent sensitivity to NXP900 *in vitro*

NXP900 inhibits proliferation of crizotinib resistant cells

Cell line	Alectinib	Lorlatinib	NXP900
NCI-H3122	364	1.9	14,347
NCI-H3122_CriR1	777	3.1	73
NCI-H3122_CriR3	2,101	47	56

NXP900 inhibits proliferation of alectinib resistant cells

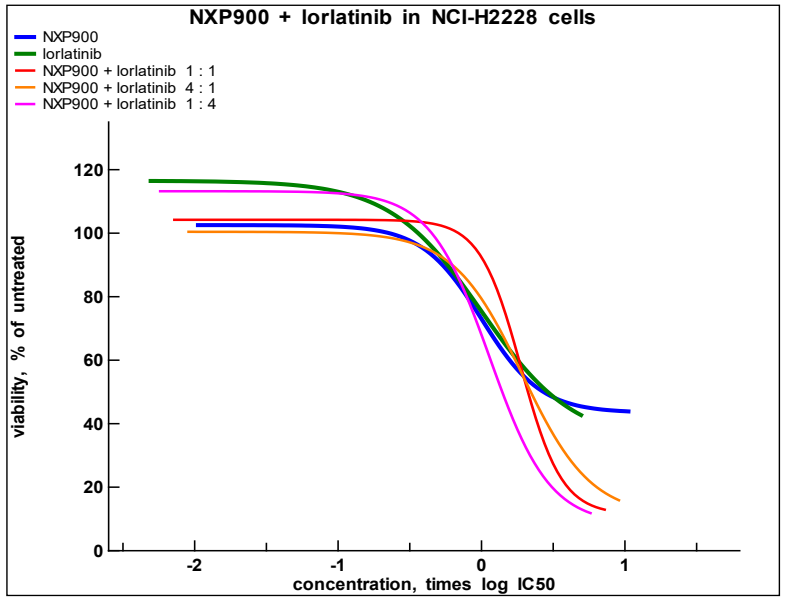
Cell line	Alectinib	Lorlatinib	NXP900
NCI-H2228	76	1.3	82
NCI-H2228_AleR1	6,460	801	26
NCI-H2228_AleR2	6,614	172	19
NCI-H2228_AleR3	2,962	421	30
NCI-H2228_AleR5	2,158	323	22
NCI-H2228_AleR14	>31,600	8,583	44
NCI-H2228_AleR20	>31,600	5,141	30

Data presented at the 2024 ENA conference

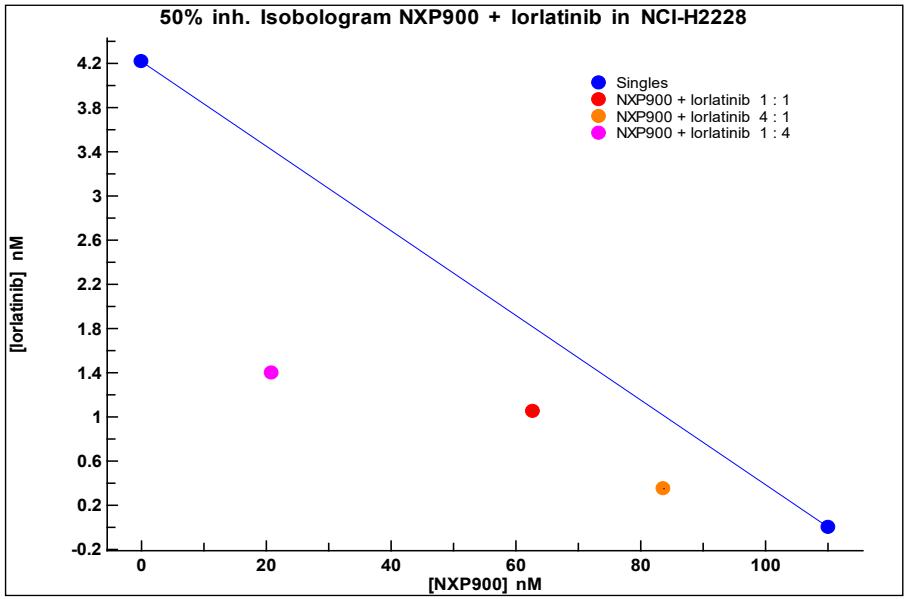
- NXP900 demonstrated potent single agent activity in ALK fusion driven cell lines with acquired resistance to ALK inhibitors expressing different variants of ALK
- No secondary mutations in the ALK fusion gene were observed using whole exome sequencing ➔ acquired resistance to ALK inhibitors in these cell lines is driven by a bypass mechanism
- Acquired resistance to crizotinib and alectinib resulted in cross resistance to lorlatinib in most resistant clones
- Acquired resistance to ALK inhibitors increased cells sensitivity to NXP900 compared to its potency in ALK inhibitor-sensitive cell lines ➔ resistant cells dependency on the SRC/YES1 pathway is increased.

NXP900/lorlatinib Synergy *in vitro* in ALK-driven NSCLC Cells

Overlays

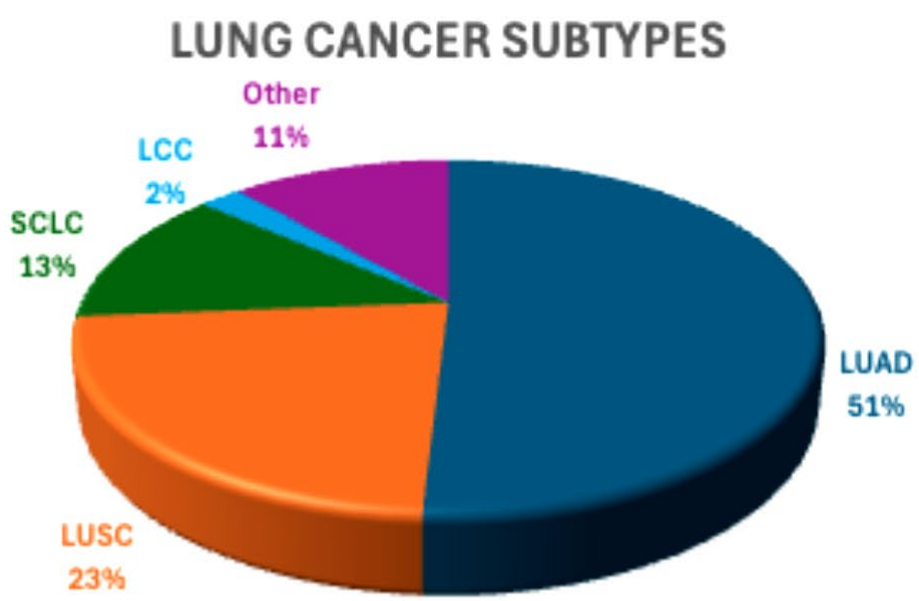


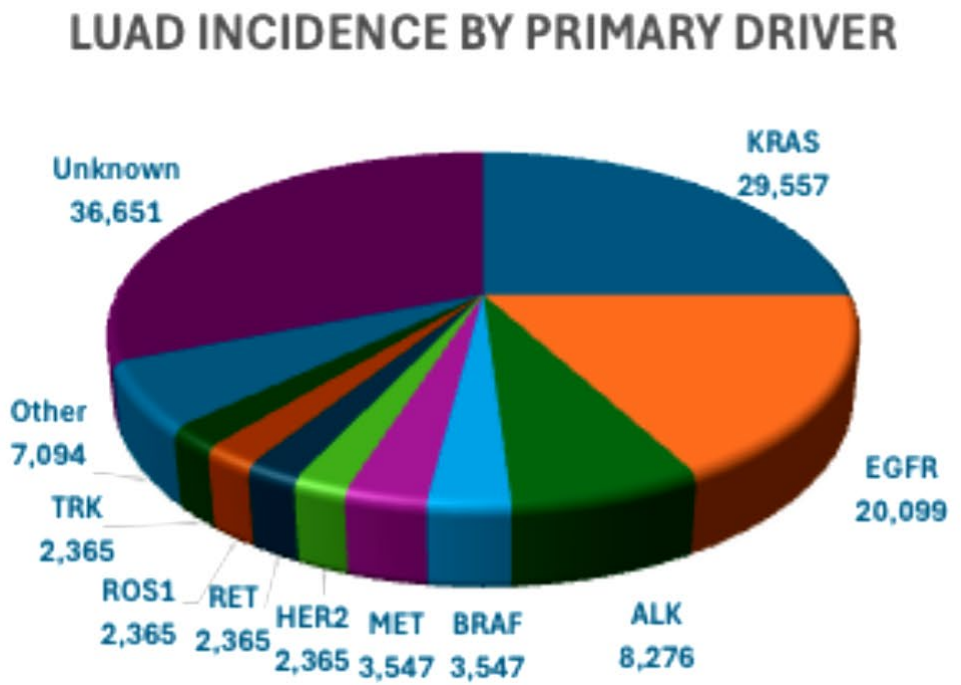
Isobologram



- NXP900 synergy with lorlatinib was demonstrated at low nanomolar concentrations
- The combination of NXP900 and lorlatinib results in significant reduction of cells viability compared with treatment with single agent lorlatinib or NXP900.
- Similar results achieved in combination with alectinib (not shown).

NXP900 Combination in NSCLC: Market Opportunity





Adapted from: Targeted therapy for rare lung cancers: Status, challenges, and prospects (Mol Therapy, 2023)

- Despite the demonstrated clinical activity of ALK and EGFR targeting agents in NSCLC, development of resistance to treatment is inevitable
- Preclinical POC achieved for NXP900 in combination with ALK and EGFR inhibitors (lorlatinib, alectinib and osimertinib respectively)

NXP900: Phase 1a Ongoing

Patients with advanced solid tumors

Clinicaltrials.gov NCT05873686

Phase 1a Dose Escalation

Starting dose of 20 mg, QD

Primary Objective:

Select doses/schedules for Phase 1b

Key Endpoints:

Assess Pharmacokinetics, pharmacodynamics, lab abnormalities, dose limiting toxicities

Financial and NVCT Stock Highlights

Financials

Ticker	NVCT
Cash	$17.2M as of 09/30/2024

Insider Ownership

Founders and >5% holders	Approx. 60%

Research Coverage

H.C. WAINWRIGHT & CO.	Joe Pantginis
LADENBURG THALMANN ESTABLISHED 1876	Aydin Huseynov
ROTH · MKM	Jonathan Aschoff

Nuvectis Investment Highlights

Precision medicine pipeline for serious conditions of unmet medical need in oncology

2025 Milestones

- Follow up data and completion of the Phase 1b study of NXP800 in platinum resistant, ARID1a-mutated ovarian cancer; completion of the Phase 1a dose escalation study and commencement of the Phase 1b program for NXP900
- Presentations at medical and scientific conferences

NXP800

- ARID1a mutated, platinum resistant ovarian cancer - Phase 1b ongoing
- Cholangiocarcinoma – IST/Mayo Clinic commenced

NXP900

- Highly selective compound, differentiated from other YES1/SRC-kinase inhibitors
- Phase 1a ongoing

Management Team with Strong Track Record

- 3 approved drugs in 4 indications in the US, EU approvals and multiple strategic deals
- Generated significant shareholder value

Nuvectis Pharma, Inc.

Innovative Precision Medicine for Serious Conditions of Unmet Medical Need in Oncology

January 2025

NuvectisPharma, Inc.

(NASDAQ: NVCT)