ABSTRACT

Title	A Phase 1b Clinical Study of NXP900 in Combination with Osimertinib in Patients with Advanced, $EGFR^{Mut+}$ Non-Small Cell Lung Cancer (Study NXP900-103) (Trial in Progress)
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Introduction	SRC family kinases (SFKs) activity has been identified as a driver of non-small cell lung cancer (NSCLC) and as a mediator of acquired resistance to Epidermal Growth Factor Receptor (EGFR) inhibitors[1]. NXP900 is a selective, orally administered type 1.5 SFKs inhibitor that inhibits both the catalytic and scaffolding functions of the target kinase while avoiding paradoxical activation of pro-oncogenic signaling, a phenomenon observed with type 1 inhibitors[2]. Preclinically, the addition of NXP900 to osimertinib resulted in synergistic inhibition of cell proliferation in osimertinib-resistant NSCLC cells and slower tumor regrowth in vivo after 28 days of treatment versus single agent osimertinib[3]. In a completed dose escalation study of single agent NXP900 in patients with advanced solid tumor, 33 patients received NXP900 at doses of 20 to 300 mg/day. The median age was 62 years, 61% were male and the median number of prior lines of anti-cancer treatments was five. The most common treatment emergent adverse events included diarrhea, fatigue, nausea, decreased appetite, dyspnea and vomiting; grade $\geq$ 3 events were rare. Pharmacodynamic analysis showed that NXP900 potently inhibited the autophosphorylation of SRC in peripheral blood mononuclear cells[4]. An expansion study of single agent NXP900 in patients with specific genomic alterations is ongoing. In a clinical drug interaction study[4], 14 healthy male volunteers were administered 200 mg/day of NXP900 daily for up to 9 doses resulting in the CYP3A index substrate concentration increasing by less than 2-fold, indicating that NXP900 it a weak inhibitor of CYP3A (the enzyme primarily responsible for the metabolism of osimertinib). Based on these prior data, a phase 1b study of NXP900 in combination with osimertinib in patients with advanced, EGFR-mutated ($EGFR^{Mut+}$) NSCLC has been initiated (NXP900-103).
Methods	NXP900-103 is a multi-center, open label, Phase 1b dose exploration and expansion study of NXP900 in combination with osimertinib in patients with advanced, $EGFR^{Mut+}$ NSCLC.

	In this study, eligible patients have metastatic or locally advanced $EGFR^{Mut+}$ NSCLC previously treated with osimertinib in the first- or second-line setting, provided they did not have primary refractory disease on osimertinib (defined as no response to prior treatment with osimertinib or progression within the first 6 months of treatment with osimertinib). Up to 3 prior systemic therapies, including in combination with osimertinib, are allowed. Patients with known EGFR mutations that cause resistance to osimertinib (including C797S, L718Q, L792, G796, and G724S), known overexpression of human epidermal growth factor receptor 2 (HER2), progressive brain metastases requiring radiation therapy or steroids, or those with leptomeningeal metastases are ineligible. The study consists of 2 phases: dose exploration and expansion. The dose exploration phase is executed through a series of cohorts where the combination of NXP900 with osimertinib is evaluated for safety and preliminary clinical activity to inform the dose selection for the expansion phase. The patient population, dose, dosing schedule and other operational characteristics for the expansion will be informed by data from the dose exploration phase. The primary objective of the dose exploration is to determine a safe and clinically active combination dose of NXP900 plus osimertinib.
References	1. Sato (2022). SRC Family Kinase Inhibition Targets YES1 and YAP1 as Primary Drivers of Lung Cancer and as Mediators of Acquired Resistance to ALK and Epidermal Growth Factor Receptor Inhibitors. *JCO Precis Oncol. doi:10.1200/PO.22.00088.* 2. Temps (2021). A Conformation Selective Mode of Inhibiting SRC Improves Drug Efficacy and Tolerability. *Cancer Res. doi:10.1158/0008-5472.CAN-21-0613.* 3. Carragher (2025). Overcoming osimertinib resistance in NSCLC with NXP900, a phase 1, highly selective and potent first-in-class total YES1/SRC inhibitor. *American Association for Cancer Research (AACR) Annual Meeting*. 4. Falchook (2025). Clinical safety, pharmacokinetics, pharmacodynamics, and cytochrome P450 interactions for the SRC/YES1 kinase inhibitor NXP900. *AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics*.