

Poster Abstract Number: 5984

Overcoming osimertinib resistance in NSCLC with NXP900, a phase 1, highly selective and potent first-in-class total YES1/SRC inhibitor

Neil O. Carragher¹, John C Dawson¹, Enrique Poradosu², Asier Unciti-Broceta¹

¹Edinburgh Cancer Research, CRUK Scotland Centre, Institute of Genetics and Cancer, University of Edinburgh, UK. ²Nuvectis Pharma Inc. 1 Bridge Plaza, 2nd Floor, Fort Lee, NJ, 07024, USA.

Introduction

Mutant-selective epidermal growth factor receptor (EGFR) inhibitors such as osimertinib, demonstrate potent activity in the treatment of EGFR-mutant lung cancer; unfortunately, the development of resistance to such EGFR inhibitors is nearly universal. Recent phosphoproteomic analysis has identified Src family kinases (SFK) activity as an important mechanism of osimertinib resistance (Tozuka et al.). In addition, the SFK member YES1 has been found to sustain EGFR expression in non-small cell lung cancer (NSCLC) cells, including those that harbor the EGFR gatekeeper mutation, T790M and YES1 blockade is synergistic with EGFR inhibition (Cuellar-Vite et al.).

NXP900 (eCF506) is a novel potent and highly selective SRC family kinase (SFK) inhibitor, (IC₅₀ of 0.47 nM against YES1) which possesses a unique/first-in-class binding mode-of-action. NXP900 locks its target into its native “closed” conformation (type 1.5 inhibitor), thereby inhibiting both kinase activity and complex formation with protein partners (Temps et al.). In contrast, multi-kinase inhibitors, including dasatinib and bosutinib, block SRC in the active “open” conformation (type 1 inhibitors) promoting the association of SFK and signaling partners via allosteric facilitation (Higuchi et al.). NXP900 may therefore represent an optimal drug combination partner with osimertinib.

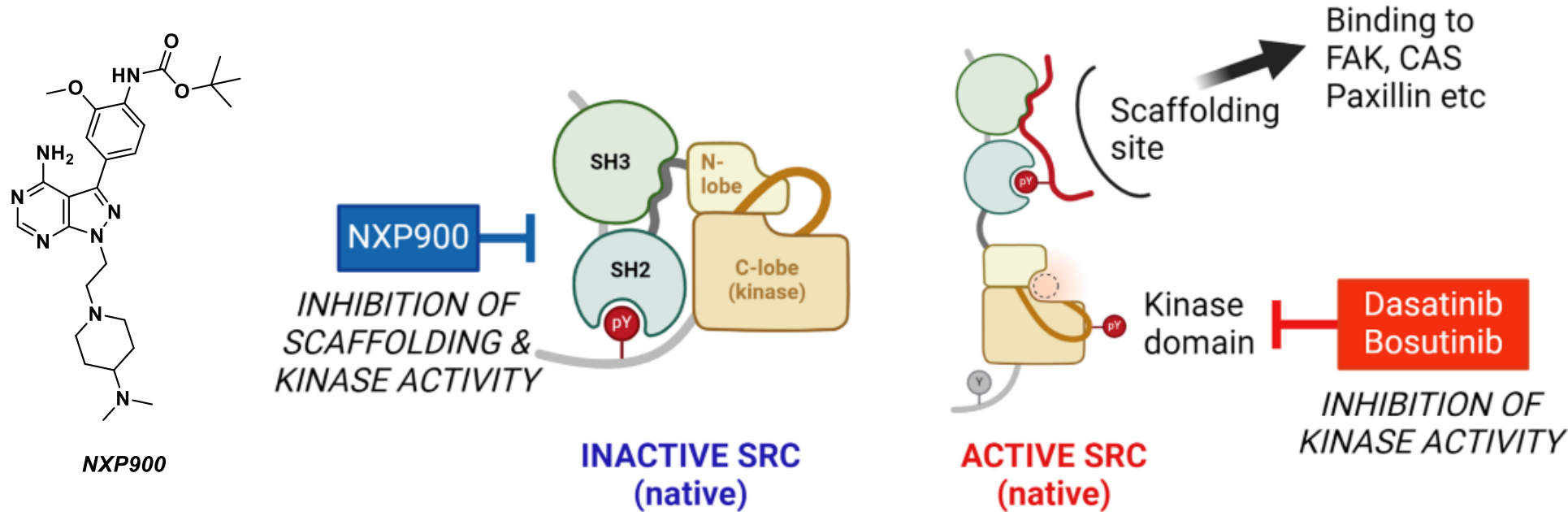


Figure 1. Mechanism of SRC inhibition. NXP900 locks SRC in its native inactive conformation inhibiting both catalytic and scaffolding functions (Created with Biorender).

NXP900 in combination with osimertinib reverses resistance in NSCLC cell lines

Cell Line	NXP900 GI50 (nM)	Osimertinib GI50 (nM)	NXP900 GI50 (nM) + Osimertinib at 160 nM
PC9	605	62	13
PC9-OR1	4,665	1,508	121
PC9-OR3	826	1,377	43

Table 1. Osimertinib resistant NSCLC cell lines (OR1 and OR3) were generated by treatment of PC9 parental cells with increasing concentrations of osimertinib (Codony-Servat et al.). Cell proliferation assay: Cells were diluted in the corresponding ATCC recommended medium and dispensed in a 384-well plate at optimal cell density per line. Cells were treated with the indicated inhibitors for 120 h. ATPlite 1step Assay (Revvity).

NXP900 demonstrates synergy with osimertinib across sensitive and resistant NSCLC lines

- PC9 is a human non-small cell lung cancer (NSCLC) cell line, which has a deletion mutation in exon 19 of the EGFR gene and is dependent on EGFR signaling for survival.
- Proteomic characterization of PC9 derived resistant cells (Codony-Servat et al.) demonstrates similar levels of pEGFR (Tyr 1068) as in parental PC9 line, increased pAKT activation in both, pSRC activation in OR1 and pYAP activation in OR3.
- Synergistic activity was observed across both osimertinib sensitive and resistant NSCLC lines.
- Synergism was enhanced against osimertinib resistant cells.

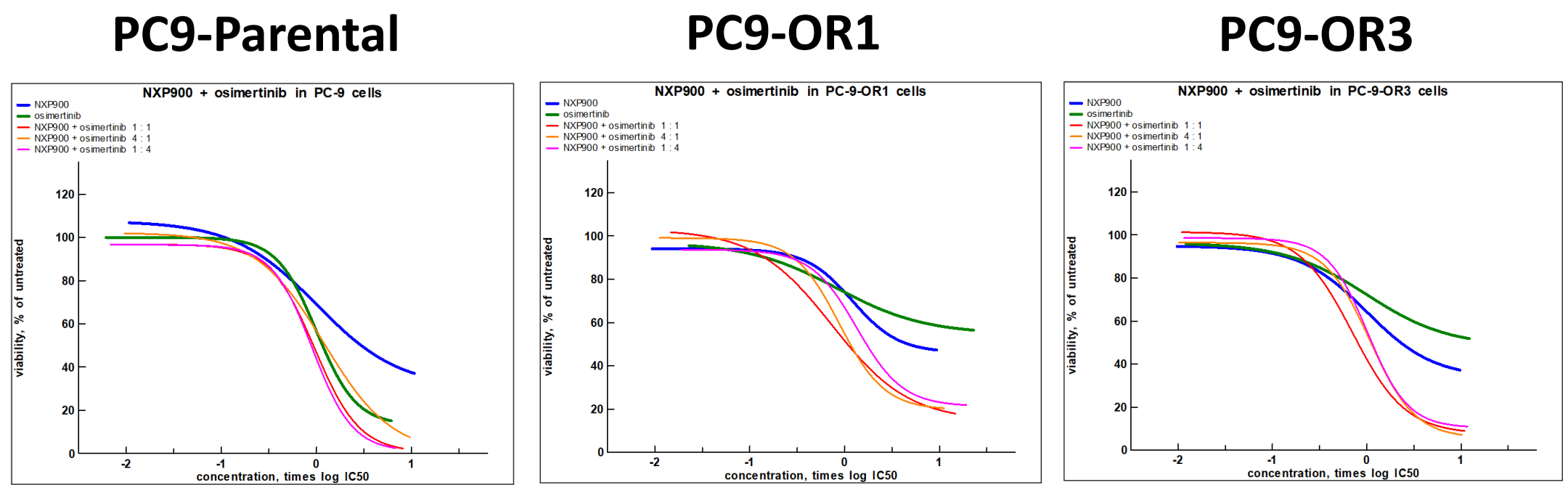


Figure 1. Dose response testing of NXP900 and osimertinib as single agents (blue, green) and fixed IC₅₀ ratio mixtures (orange, pink, red).

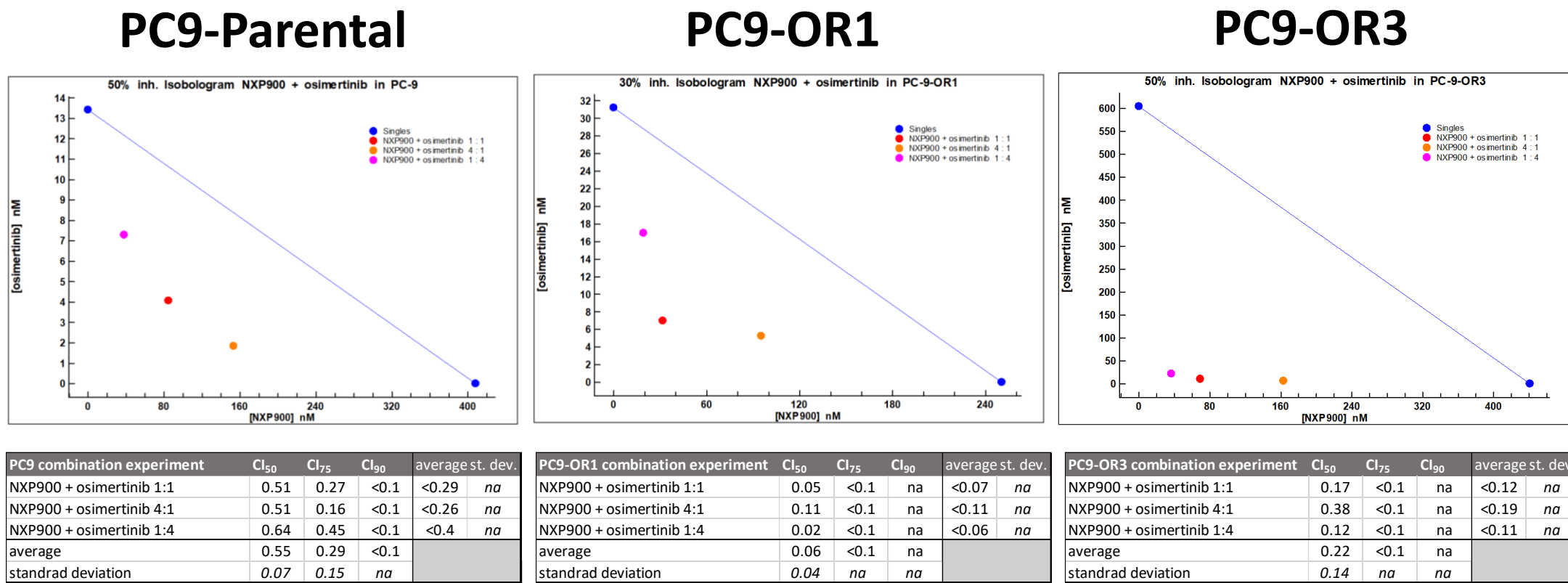


Figure 2. SynergyFinder analysis (Oncolines B.V. Oss, Netherlands): equipotent mixtures of NXP900 and osimertinib at three different fixed ratios (IC₅₀ 1:1; 4:1; 1:4) were tested across parental and resistant (OR1 and OR2) PC9 lines. Drug combination analysis using the combination index (CI) theorem of Chou-Talalay (Chou TC., Cancer Res. 2010,70,440-6) offers quantitative definition for additive effect (CI = 1), synergism (CI < 1), and antagonism (CI > 1) in drug combination. Isobologram analysis indicates potent synergistic combination activity across all cell lines.

In vivo combination study: PC9-OR3 xenograft

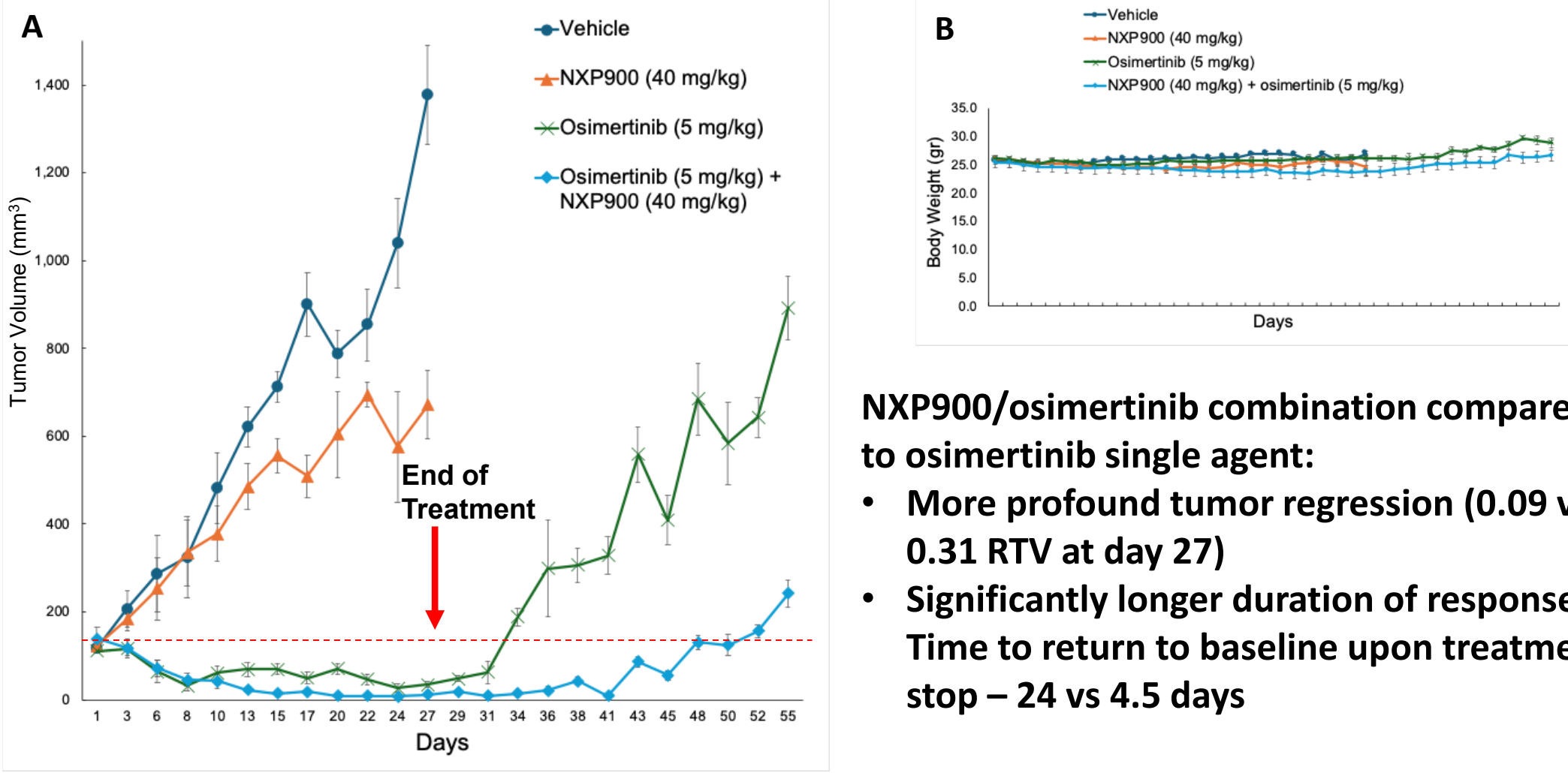


Figure 3. Mice were transplanted with the PC9-OR3 cell line, stratified to the vehicle, single agent and combination groups and treated for 28 days (Mouse Clinic for Cancer & Aging (MCCA) Intervention Unit of the Netherlands Cancer Institute, NKI-AVL). **A.** Tumor growth inhibition, **B.** Body weights. TGI= Tumor growth inhibition, RTV= Relative tumor volume

- NXP900/osimertinib combination compared to osimertinib single agent:**
- More profound tumor regression (0.09 vs 0.31 RTV at day 27)
 - Significantly longer duration of response: Time to return to baseline upon treatment stop – 24 vs 4.5 days

Conclusions

- NXP900 + osimertinib exhibit potent synergistic activity across osimertinib sensitive and resistant NSCLC lines in vitro.
- NXP900/osimertinib combination is well tolerated in mice.
- NXP900/osimertinib combination vs. osimertinib single agent demonstrates profound tumor regression and significantly slower tumor regrowth after completion of the treatment period indicating increased induction of cell death in vivo.

Acknowledgements and Contacts

With thanks to a research grant to the University of Edinburgh provided by Nuvectis Pharma, Inc.

- Neil Carragher, University of Edinburgh: n.carragher@ed.ac.uk
- Asier Unciti-Broceta, University of Edinburgh: asier.ub@ed.ac.uk
- Enrique Poradosu, Nuvectis Pharma Inc.: eporadosu@nuvectis.com

References

- Temps et al., Cancer Res. 2021 Nov (21):5438-5450. doi: 10.1158/0008-5472.CAN-21-0613.
- Higuchi et al., Cell Rep. 2021 Mar 23;34(12):108876. doi: 10.1016/j.celrep.2021.108876.
- Cuellar-Vite et al., Mol Cancer Res. 2025 Jan 23. doi: 10.1158/1541-7786.MCR-24-0309.
- Codony-Servat et al., Transl. Lung Can. Res. 2019, 8(4), 340-351. doi: 10.21037/tlcr.2019.08.22
- Chou T.-C., Cancer Res. 2010 Jan 15;70(2):440-6. doi: 10.1158/0008-5472.CAN-09-1947.