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YES/SRC kinase inhibitor NXP900, currently in clinical development, combines synergistically with fulvestrant against luminal A breast cancer cell lines in vitro and in vivo

Iñigo Lanzagorta Calvillo[1], Boback Kaghazchi[1], Enrique Poradosu[2], Neil O. Carragher[1], and Asier Unciti-Broceta[1]

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

Introduction

The majority of patients with breast cancer present with tumors that are estrogen receptor positive (ER+), thus endocrine therapies have become the main treatment option for this type of cancer. However, endocrine resistance inevitably develops over time, resulting in a clinical challenge to treat this breast cancer subtype. The combination of CDK4/6 inhibitors with endocrine therapy (ET) has emerged as the foremost therapeutic modality for patients afflicted with hormone receptor-positive (HR +)/HER2-negative (HER2-) advanced breast cancer.

The novel YES1/SRC tyrosine kinase inhibitor NXP900, currently in a phase 1 clinical trial, binds SRC in its 'autoinhibited' inactive conformation, thereby inhibiting the phosphorylation and the scaffolding properties of the kinase[1].

Cell-based assays were used to demonstrate the differences between NXP900 and dasatinib, in monotherapy as well as in combination with ET. Lastly, a year-long longitudinal study was undertaken to elucidate the therapeutic potential of NXP900 to treat ER+ cell lines with acquired ET resistance, which can translate into improved treatments for ER+ breast cancer patients.

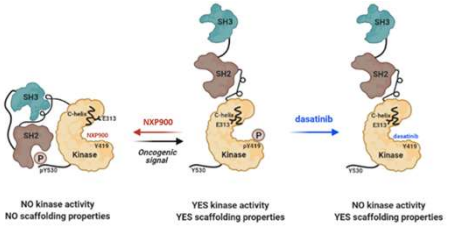


Figure 1. Inhibition of SRC kinase. Comparison between the modes of binding of novel SRC tyrosine inhibitor NXP900 and clinically-approved best-in-class dasatinib.

NXP900 strongly inhibits pSRC-Y419 vs dasatinib

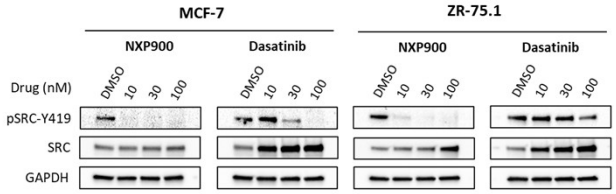
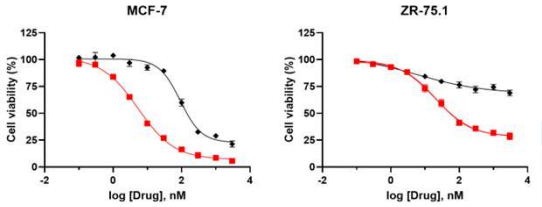


Figure 2. Immunoblotting study. Representative western blots in MCF-7 (n=3) and ZR-75.1 (n=3) after a 24-h treatment showing the differences between each drug in phospho-SRC at the kinase active site and total SRC.

NXP900 is a superior inhibitor of cell proliferation vs dasatinib



Monotherapy IC50s (nM)

	NXP900	Dasatinib
MCF7	6.9	159
ZR-75.1	54	>3,000

Figure 3. Monotherapy in ER+ cells. Representative examples of dose-response curves of MCF-7 (n=3) and ZR-75.1 (n=6) treated with NXP900 (red) and dasatinib (blue) over a period of 5 days, with a concentration range of 0.1 nM to 3 µM. Error bars: ± SEM.

NXP900 demonstrates superior synergy with fulvestrant compared to palbociclib and fulvestrant

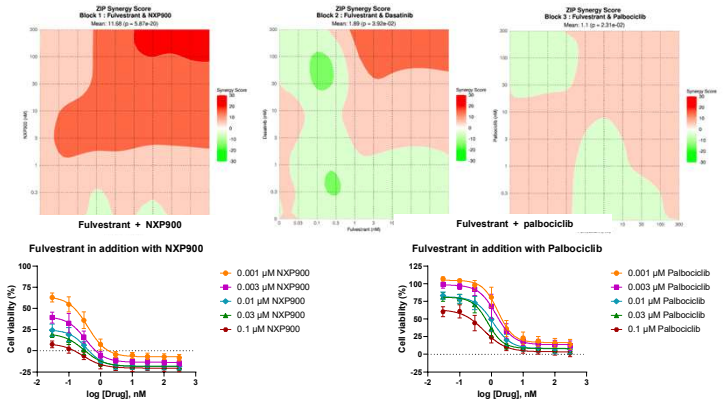


Figure 4. Combination synergy plots. (Top) ZIP synergy analysis and overall scores across the dose-ratio concentration matrix of fulvestrant with (left) NXP900, (middle) dasatinib or (right) palbociclib. MCF-7 (n=3) were treated with a matrix of drug combinations, ranging from 1 nM to 300 nM, for 5 days. Synergy scores were calculated using SynergyFinder+. Data are ZYP synergy of means of independent experiments. Synergy score legend: -10 to 0 (green), 0 to 10 (pink), 10 to 20 (orange), 20 to 30 (red). (Bottom) Right: Dose-response curves of MCF-7 cells treated with fulvestrant in combination with increasing doses (0.1 to 0.001) of (left) NXP900 or (right) palbociclib. Error bars: ± SEM.

MCF7 cells resistant to fulvestrant are highly sensitive to NXP900

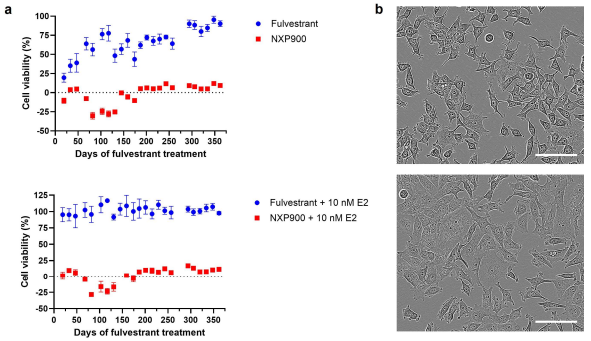


Figure 5. NXP900 maintains drug sensitivity over time in ER+ cells. MCF-7 cells were cultured with 100 nM fulvestrant for 1 year. **a.** Periodically, cells were washed-out for two days in drug free media and treated with 100 nM fulvestrant (blue) and 300 nM NXP900 (red) for 5 d in the absence or presence of 0.01 µM of E2 (Data: ± SEM of independent experiments). **b.** Representative images of MCF7 cells before (top) and after (bottom) acquiring resistance to fulvestrant. Scale bar = 100 µm

Conclusions

- ER+ cell lines are significantly more sensitive to NXP900 compared to the non-selective tyrosine kinase inhibitor dasatinib, indicating the mechanism of inhibition has important biological implications.
- NXP900 is significantly more synergistic with fulvestrant compared to palbociclib, a CDK4/6 inhibitor approved for the treatment of HR+ HER2- advance or metastatic breast cancer. Contrary to palbociclib, NXP900 + fulvestrant combination leads to cell death.
- MCF7 cells with acquired resistance to fulvestrant are highly sensitive to NXP900.
- These data suggests that NXP900 is a promising therapeutic candidate to treat ER+ breast cancer in combination with endocrine therapies.

References

1. Temps et. al. A Conformation Selective Mode of Inhibiting SRC Improves Drug Efficacy and Tolerability. Cancer Res. 2021 Nov 1;81(21):5438-5450. doi: 10.1158/0008-5472.CAN-21-0613.

Acknowledgements and Contact

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

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