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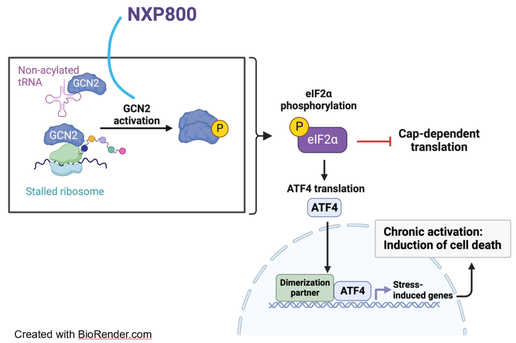
NXP800, a novel, small-molecule GCN2 kinase activator, demonstrates potent single-agent activity in ARID1A and ARID1B-deficient endometrial cancer xenograft models

Ramez N. Eskander[1], Bradley J. Monk[2], Brian M. Slomovitz[3], Enrique Poradosu[4], Allison Woods[4], Shay Shemesh[4], Paul A. Clarke[5], Robert Te Poele[5], Marissa V. Powers[5], Paul Workman[5], Shannon N. Westin[6]

[1]Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Diego Rebecca and John Moores Cancer Center, La Jolla, CA, [2]HonorHealth Research Institute, University of Arizona College of Medicine, Creighton University School of Medicine Phoenix, [3]Division of Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach, FL 33140, [4]Nuvectis Pharma, Inc., 1 Bridge Plaza N., Fort Lee, NJ 07024, [5]Centre for Cancer Drug Discovery, Division of Cancer Therapeutics, The Institute of Cancer Research, London, UK, [6]Dept. of Gynecologic Oncology and Reproductive Medicine, UT MD Anderson Cancer Center, Houston TX

NXP800: Introduction and MoA

- NXP800 is a clinical stage, antineoplastic, oral, small molecule GCN2 kinase activator. In a panel of human carcinoma cell lines NXP800 induced the expression of genes associated with activation of the integrated stress response (ISR) and demonstrated robust antiproliferative activity [1].
- The ISR is an intracellular signal transduction network that regulates the response to various stresses; when dysregulated, it is implicated in the pathogenesis of various diseases, including cancer [2,3] .
- NXP800 demonstrated robust antitumor activity in preclinical models, including in ARID1a-mutated ovarian carcinoma [4] and cholangiocarcinoma [5].
- NXP800 is currently being investigated in a Phase 1b clinical trial in patients with platinum resistant ARID1a-mutated ovarian carcinoma (NCT05226507) in collaboration with the GOG Foundation and the European Network of Gynecological Oncological Trial Groups (ENGOT). FDA granted Fast Track Designation to the NXP800 development program in this indication.
- Here we describe an *in vivo* study of NXP800 in ARID1A and ARID1B-deficient endometrial cancer xenografts, supporting the clinical development of NXP800 in endometrial cancer.



NXP800 causes activation of GCN2 kinase, resulting in:

Chronic activation of the integrated stress response (ISR)

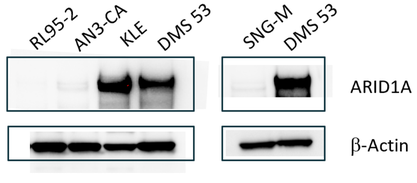
Inhibition of cap-dependent translation

Inhibition of Cell proliferation and Tumor Growth Inhibition

Materials and Methods

- Animal strain - CD1 Nude mice (nu/nu, Charles River). Human endometrial cancer cell lines: RL95-2 (ATCC), KLE (ATCC), SNG-M (Creative Bioarray).
- Xenograft tumors were generated by subcutaneous implantation on the right lower flank of the thigh at a cell density of $2x10^6$ cells/mouse, at 0.1 ml Matrigel dilution volume/injection.
- Experiment groups and dose/regimen: Vehicle, NXP800 (35 mg/kg, oral gavage); QD on days 0-4, 7-11, 14-18, 21-25, 28-30.
- Loss of ARID1A protein expression was confirmed by western blots using lysate of DMS 53 cells as a positive control.

ARID1A Protein Expression



Characterization of Xenografted Cell Lines

Cell Line	Mutation in SWI/SNF Genes [a]	Other Notable Mutations and Genomic Alterations [a]	Other Characteristics
RL95-2	ARID1A, ARID1B (G817fs, truncating mutation)[b] SMARCA4, SMARCAL1, SMARCC1, SMARCD2	PTEN, PIK3R1, BRCA2	MSI high
KLE	ARID1B (N935fs, truncating mutation) [b]	BRCA2, FBXW7, CNV high	MSS
SNG-M	ARID1A, SMARCA4	PI3KCA, KRAS	MSI high

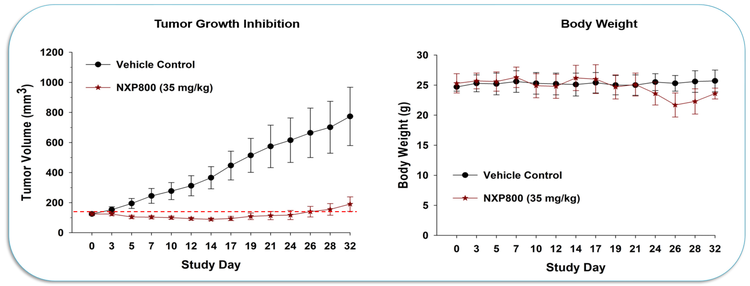
Predicted Sensitivity to Chemotherapy [c] [6]

Cell Line	Cisplatin	Doxorubicin	Paclitaxel
RL95-2	Resistant	Sensitive	Sensitive
KLE	Moderately sensitive	Moderately sensitive	Slightly sensitive
SNG-M	Resistant	Resistant	Resistant

a. COSMIC Cell Line Gene Mutation Profiles.
b. ARID1A and ARID1B genes encode the alternate, but obligatory, DNA-targeting subunit of the switch/sucrose non-fermentable (SWI/SNF) complex.
c. Drug-susceptibility signatures developed from the NCI60 dataset for the conventional chemotherapeutic agents were applied to the microarray data of endometrial cancers to predict the probability of sensitivity of each cell line.

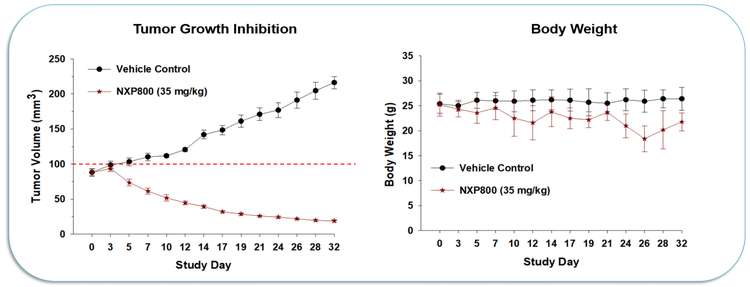
Results

RL95-2



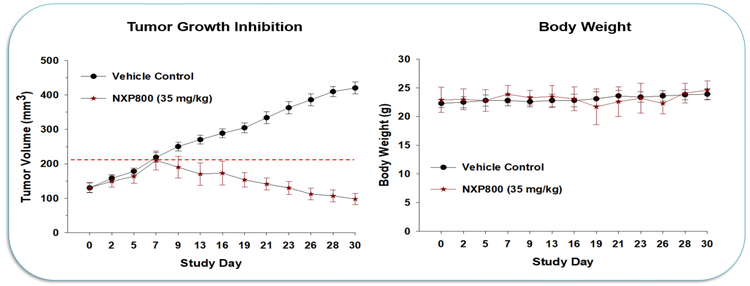
	Relative Tumor Volume (RTV28)	Tumor Growth Inhibition (TGI)
Vehicle	6.2	--
NXP800 (35 mg/kg)	2.0	67%

KLE



	Relative Tumor Volume (RTV28)	Tumor Growth Inhibition (TGI)
Vehicle	2.5	--
NXP800 (35 mg/kg)	0.2	91%

SNG-M



	Relative Tumor Volume (RTV28)	Tumor Growth Inhibition (TGI)
Vehicle	3.2	--
NXP800 (35 mg/kg)	0.61	81%

Highlights and Conclusions

- ARID1A is the most frequently mutated SWI/SNF subunit across cancer types with an estimated prevalence of 35% in endometrial carcinomas [7].
- Inactivation of ARID1B is highly prevalent in undifferentiated and dedifferentiated endometrial cancers (approx. 36%) and is associated with an aggressive phenotype [8].
- NXP800 demonstrated robust antitumor activity in ARID1A and ARID1B mutated xenografts of endometrial carcinoma, at a well-tolerated dose, including in models of poorly differentiated tumors, supporting the clinical development of NXP800 in endometrial cancer.

Phase 1b - NXP800 in Platinum Resistant, ARID1a-mutated Ovarian Carcinoma

- Open for enrollment, conducted in collaboration with GOG (GOG-3087) and ENGOT (ENGOT-GYN5/NCRI/NXP800-101) (NCT05226507)
- Key Inclusion / Exclusion criteria
  - ARID1a mutation as determined by DNA based Next Generation Sequencing
  - Disease progression within 6 months from completion of platinum-based therapy
  - Histology: ovarian clear cell and endometrioid carcinomas

References, Contacts and Acknowledgements

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Contacts

Shay Shemesh, Nuvectis Pharma: sshemesh@nuvectis.com
Enrique Poradosu, Nuvectis Pharma: eporadosu@nuvectis.com

Acknowledgments

- NXP800 was discovered at The Institute of Cancer Research, Sutton, London (Pasqua et al.," HSF1 Pathway Inhibitor Clinical Candidate (CCT361814/NXP800) Developed from a Phenotypic Screen as a Potential Treatment for Refractory Ovarian Cancer and Other Malignancies", *J Med Chem, 2023.)*.
- NXP800 is licensed to Nuvectis Pharma, Inc.