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

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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.

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 Biogene).

Xenograft tumors were generated by subcutaneous implantation on the right lower flank of the thigh at a cell density of 2x10⁶ cells/mouse, at 0.1 ml Matrigel dilution/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.

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Results

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.

Characterization of Xenografted Cell Lines

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Mutation in SWI/SNF Genes a</th>
<th>Other Notable Mutations and Genomic Alterations b</th>
<th>Other Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>RL95-2</td>
<td>ARID1A, ARID1B, G817N, truncating mutation c</td>
<td>SMARCA4, SMARCC1, SMARCA2</td>
<td>MII high</td>
</tr>
<tr>
<td>KLE</td>
<td>ARID1B (N935S, truncating mutation) c</td>
<td>BRCA2, FXN, CNN high</td>
<td>MSS</td>
</tr>
<tr>
<td>SNG-M</td>
<td>ARID1A, SMARC4</td>
<td>P103CA, KRAS</td>
<td>MII high</td>
</tr>
</tbody>
</table>

Inhibition of Cell Proliferation and Tumor Growth Inhibition

ARID1A Protein Expression

<table>
<thead>
<tr>
<th>ARID1A</th>
<th>J-Actin</th>
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ARID1A Protein Expression

Cells of ARID1A-mutated ovarian carcinoma (NCT05226507)

• Inhibition of cell proliferation and tumor growth inhibition in various diseases, including cancer [2,3].

• The integrated stress response (ISR) plays a crucial role in the regulation of various cellular processes, including cell proliferation and apoptosis.

• NXP800 is a clinical stage, antineoplastic, oral, small molecule GCN2 kinase activator.

• NXP800 demonstrated robust antitumor activity in preclinical models, including in ARID1a-mutated ovarian carcinoma.

• NXP800 is currently being investigated in a Phase 1b clinical trial in patients with platinum resistant ARID1a-mutated ovarian carcinoma.

• Loss of ARID1A protein expression was confirmed by western blots using lysate of DMS 53 cells as a positive control.

• ARID1A is the most frequently mutated SWI/SNF subunit across cancer types with an estimated prevalence of 35% in endometrial carcinomas.

• Induction of ARID1B is highly prevalent in undifferentiated and desmoplastic endometrial cancers (approx. 38%) and is associated with an aggressive phenotype.

• 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.

References

1) Pasqua et al., “HSF1 Pathway Inhibitor Clinical Candidate (CCT361814/NXP800)” in NXP800 was discovered at The Institute of Cancer Research, Sutton, London (approx. 36%) and is associated with an aggressive phenotype.


5) Stewart et al., “NXP800 versus cisplatin in ARID1a-mutated Ovarian Clear Cell Carcinomas: A Randomized Controlled Trial”, AACR, 2022.


Acknowledgements

• NXP800 is licensed to Nuvectis Pharma, Inc.

• Open for enrollment, conducted in collaboration with GOG (GOG-3087) and ENGOT (ENGOT-GYN5/NCR/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

- Histologic ovarian clear cell and endometrioid carcinomas

• ARID1A is the most frequently mutated SWI/SNF subunit across cancer types with an estimated prevalence of 35% in endometrial carcinomas [7].

• Induction of ARID1B is highly prevalent in undifferentiated and desmoplastic endometrial cancers (approx. 38%) and is associated with an aggressive phenotype [8].

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