ORIC-101 is a potent, selective, orally bioavailable GR antagonist. The glucocorticoid receptor (GR) has been studied overexpression across over 20 advanced solid tumors, including pancreatic ductal adenocarcinoma (PDAC), ovarian cancer, and triple negative breast cancer (TNBC). In addition, GR overexpression is associated with worse survival outcomes.

ORIC-101 is a potent, orally bioavailable small molecule GR antagonist with a more favorable cytochrome P450 inhibition profile than prior generation GR antagonists, making it particularly suitable for combination with taxanes.

**Background**

- The glucocorticoid receptor (GR) has been studied for its potential role in mediating resistance to chemotherapy. GR signaling imparts a pro-survival phenotype to the tumor via certain biological processes like epithelial-to-mesenchymal transition (EMT) and anti-apoptosis.
- GR is overexpressed across over 20 advanced solid tumors, including pancreatic ductal adenocarcinoma (PDAC), ovarian cancer, and triple-negative breast cancer (TNBC). In addition, GR overexpression is associated with worse survival outcomes.
- ORIC-101 is a potent, orally bioavailable small molecule GR antagonist with a more favorable cytochrome P450 inhibition profile than prior generation GR antagonists, making it particularly suitable for combination with taxanes.

**Phase 1 Study Design (NCT03928314)**

- **Patient population:**
  - Dose escalation: Locally advanced or metastatic solid tumors.
  - Dose expansion: PDAC, ovarian cancer, TNBC, and tissue-agnostic cohorts, all patients previously treated and progressed on a taxane-containing regimen.
- **Doses Evaluated:** 80 to 240 mg ORIC-101 (capsules) once daily, given either intermittently (5 days on, 2 days off) or as a continuous 21-day dosing regimen, in combination with 75 or 100 mg/m² nab-paclitaxel (nab-pacl) on days 1, 8, and 15 of each 28-day cycle was evaluated following a 3+3 dose escalation scheme.
- **Dose-limiting toxicities (DLTs) were evaluated during Cycle 1 and graded as per NCI CTCAE v6.0.
- **Antitumor activity was assessed by investigator every 8 weeks using RECIST 1.1.**
- **Pharmacokinetics:** ORIC-101 exposure increased with dose from 80 to 240 mg among intermittent and continuous dosing cohorts.
- **Figure depicts one example patient’s PK values at 160 mg, there was no difference in ORIC-101 exposure intermittently (5 days on, 2 days off) or as a continuous 21-day dosing regimen, in combination with 75 or 100 mg/m² nab-paclitaxel (nab-pacl) on days 1, 8, and 15 of each 28-day cycle was evaluated following a 3+3 dose escalation scheme.

**Pharmacokinetics**

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**Preliminary Antitumor Activity Demonstrated in Multiple Patients, Including Those Previously Treated with a Taxane-Containing Regimen**

- **Study Design:**
  - NR IC-101 exposure increased with dose from 80 to 240 mg among intermittent and continuous dosing cohorts.
  - Figure depicts one example patient’s PK values at 160 mg, there was no difference in ORIC-101 exposure intermittently (5 days on, 2 days off) or as a continuous 21-day dosing regimen, in combination with 75 or 100 mg/m² nab-paclitaxel (nab-pacl) on days 1, 8, and 15 of each 28-day cycle was evaluated following a 3+3 dose escalation scheme.
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  - Dose escalation: Locally advanced or metastatic solid tumors.
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**Conclusions**

- **ORIC-101 in combination with nab-paclitaxel was well-tolerated, with no DLTs at the RP2D, and without requirement for prophylactic G-CSF.**
- PK showed no evidence of drug-drug interaction.
- **Antitumor preliminary activity was observed across multiple advanced solid tumors, including in heavily pretreated patients with endometrial, and breast cancers who previously progressed on or after a taxane-containing regimen.**
- Enrollment ongoing in PDAC, ovarian cancer, TNBC, and tissue-agnostic cohorts.