Initial Results from a Phase 1b Study of ORIC-101, a Glucocorticoid Receptor Antagonist, in Combination with Nab-Paclitaxel in Patients with Advanced Solid Tumors

Abstract 2553

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2021 ASCO ANNUAL MEETING

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, selective, 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.

ORIC-101 (Steroidal)
GR antagonism IC_{50} = 7.3 nM
PgR antagonism IC_{50} = 22 nM
CYP3A4 IC_{50} = 1.6 μM
CYP2C8/CYP2C9 IC_{50} > 10 μM

PgR = progesterone receptor

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-pac) on days 1, 8, and 15 of each 28-day cycle was evaluated following a 3+3 dose escalation scheme.

Dose Level	n	ORIC-101	ORIC-101 regimen	Nab-pac
1	3	240 mg QD	Intermittent	100 mg/m²
1A	3	80 mg QD	Intermittent	75 mg/m²
2A	3	160 mg QD	Intermittent	75 mg/m²
3A	3	240 mg QD	Intermittent	75 mg/m²
2B (RP2D)	9	160 mg QD	Continuous	75 mg/m²
Expansion (RP2D)	10	160 mg QD	Continuous	75 mg/m²

- Dose-limiting toxicities (DLTs) were evaluated during Cycle 1 and graded as per NCI CTCAE v5.0.
- Antitumor activity was assessed by investigator every 8 weeks using RECIST 1.1.
- Plasma PK was assessed on day 1 and after repeat dosing.
- GR protein expression in archival or fresh tumor tissue was determined via IHC, and PD modulation in blood-derived peripheral blood mononuclear cells (PBMCs) was assessed by RT-qPCR for GR target genes – ***Abstract #3110 (Daemen et al).***

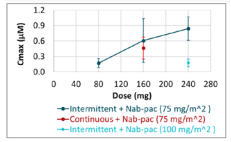
Patient Disposition, Baseline Characteristics, Safety Profile (enrollment cutoff 31 March 2021)

n (%), median (range)	Non-RP2D (n=12)	RP2D (n=19)	TOTAL (N=31)
Ongoing	0	7 (37)	7 (23)
Discontinued	12 (100)	12 (63)	24 (77)
Disease Progression	6 (50)	10 (53)	16 (52)
Adverse Event	5 (42)	1 (5)	6 (19)
Other	1 (8)	1 (5)	2 (6)
Age, years	54 (44, 80)	61 (24, 74)	60 (24, 80)
Sex			
Male	7 (58)	5 (26)	12 (39)
Female	5 (42)	14 (74)	19 (61)
ECOG			
0	4 (33)	5 (26)	9 (29)
1	8 (67)	14 (74)	22 (71)
Tumor Type			
PDAC	4 (33)	7 (37)	11 (35)
Ovarian	0	4 (21)	4 (13)
TNBC	0	2 (11)	2 (6)
Other Solid Tumor	8 (67)	6 (32)	14 (45)
Number of Prior Therapies	2 (1, 6)	4 (2, 12)	4 (1, 12)
Prior Taxane	2 (17)	19 (100)	21 (68)

- At Dose Level 1 (240 mg ORIC-101 + 100 mg/m² nab-pac), 2 patients experienced DLTs of Gr 3 fatigue and Gr 4 neutropenia and thrombocytopenia, respectively. No further DLTs were observed in subsequent cohorts.
- **RP2D: 160 mg ORIC-101 QD continuously for 21 days with nab-pac on days 1, 8, and 15 of each 28-day cycle, without requirement for prophylactic granulocyte colony-stimulating factor (G-CSF).**

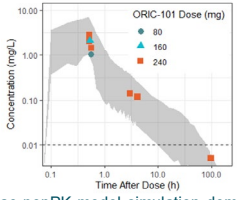
Treatment-Related Adverse Events >10% or Grade ≥3, n (%)	Non-RP2D (n=12)		RP2D (n=19)		TOTAL (N=31)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea	5 (42)	1 (8)	7 (37)	-	12 (39)	1 (3)
Fatigue	5 (42)	1 (8)	4 (21)	-	9 (29)	1 (3)
Anemia	4 (33)	3 (25)	4 (21)	-	8 (26)	3 (10)
Diarrhea	7 (58)	-	1 (5)	-	8 (26)	-
Leukopenia	5 (42)	3 (25)	3 (16)	-	8 (26)	3 (10)
Neutropenia	4 (33)	2 (17)	3 (16)	2 (11)	7 (23)	4 (13)
Aspartate aminotransferase increased	5 (42)	1 (8)	1 (5)	-	6 (19)	1 (3)
Vomiting	3 (25)	-	3 (16)	-	6 (19)	-
Alopecia	3 (25)	-	2 (11)	-	5 (16)	-
Alanine aminotransferase increased	4 (33)	1 (8)	-	-	4 (13)	1 (3)
Hypotension	2 (17)	1 (8)	-	-	2 (6)	1 (3)
Thrombocytopenia	2 (17)	1 (8)	-	-	2 (6)	1 (3)
Hepatic failure (Grade 5)	1 (8)	1 (8)	-	-	1 (3)	1 (3)
Hyperbilirubinemia	1 (8)	1 (8)	-	-	1 (3)	1 (3)
Laryngeal inflammation	1 (8)	1 (8)	-	-	1 (3)	1 (3)
Liver injury	1 (8)	1 (8)	-	-	1 (3)	1 (3)
Rash maculo-papular	-	-	1 (5)	1 (5)	1 (3)	1 (3)
Syncope	1 (8)	1 (8)	-	-	1 (3)	1 (3)

Pharmacokinetics



ORIC-101 exposure increased with dose from 80 to 240 mg among intermittent dosing cohorts.

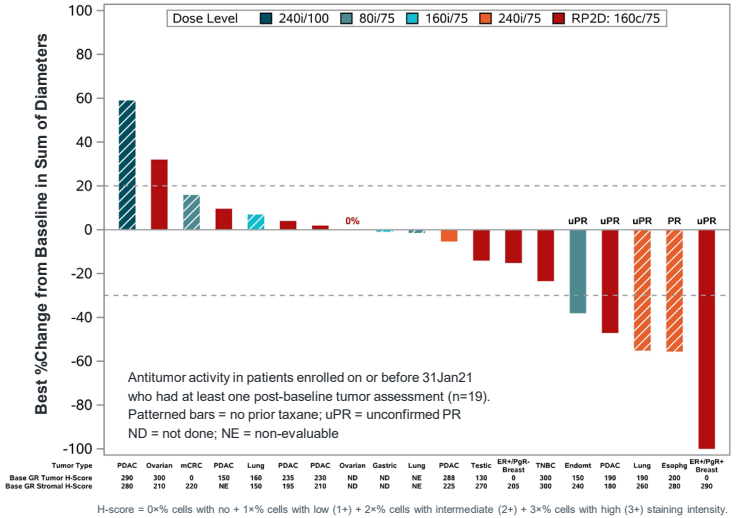
At 160 mg, there was no difference in ORIC-101 Cmax between intermittent and continuous dosing.



A nab-pac popPK model simulation demonstrated no change in observed concentrations with varying doses of ORIC-101, indicating no drug-drug interaction.

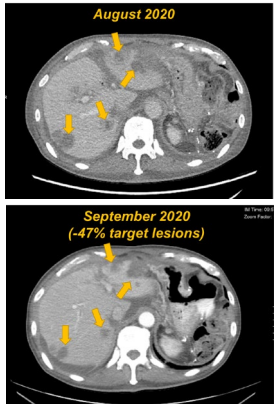
- Figure depicts one example patient's PK values at multiple dose levels of ORIC-101 vs predicted nab-pac (gray shaded region).

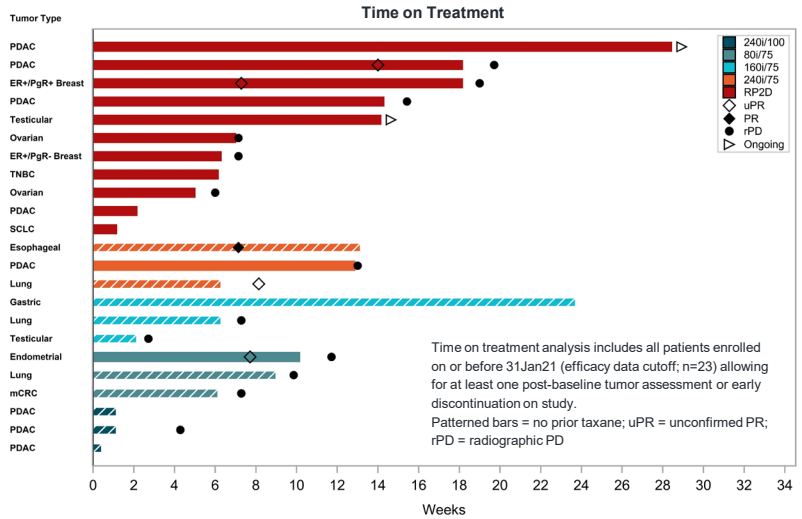
Preliminary Antitumor Activity Demonstrated in Multiple Patients, Including Those Previously Treated with a Taxane-Containing Regimen



H-score = 0×% cells with no + 1×% cells with low (1+) + 2×% cells with intermediate (2+) + 3×% cells with high (3+) staining intensity.

- 66M with metastatic PDAC
- Treated at the RP2D
- Prior therapies: FOLFIRINOX, gemcitabine with nab-pac
- PFS of 19.7 weeks





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.**
- **Preliminary antitumor activity was observed across multiple advanced solid tumors, including in heavily pretreated patients with PDAC, endometrial, and breast cancers who previously progressed on or after a taxane-containing regimen.**
- **Enrollment is ongoing in PDAC, ovarian cancer, TNBC, and tissue-agnostic cohorts.**

Thank you to the patients and their families for participating in this trial