AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

Initial Results from a Phase 1b Study of ORIC-101, a Glucocorticoid Receptor Antagonist, in Combination with Enzalutamide in Patients with Metastatic Prostate Cancer

Wassim Abida[1], Neeraj Agarwal[2], Andrew W. Hahn[3], Neal Shore[4], Paul Sieber[5], Tanya Dorff[6], Mathew Rettig[7], Mathew Smith[8], Paul Monk[9], Rongda Xu[10], Ann Johnson[10], Anneleen Daemen[10], Edna Chow Maneval[10], Pratik S. Multani[10], Rupal Patel[10], Michael J. Morris[1]

[1]MSKCC, New York, NY; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [3]MDACC, Houston, TX; [4]CURC, Myrtle Beach, NC; [5]Keystone Urology Specialists, Lancaster, PA; [6]COH, Duarte, CA; [7] VA Greater Los Angeles, Los Angeles, CA; [8]Massachusetts General Hospital, Boston, MA; [9]Ohio State CCC, Columbus, OH; [10]ORIC, South San Francisco, CA

Poster # P041

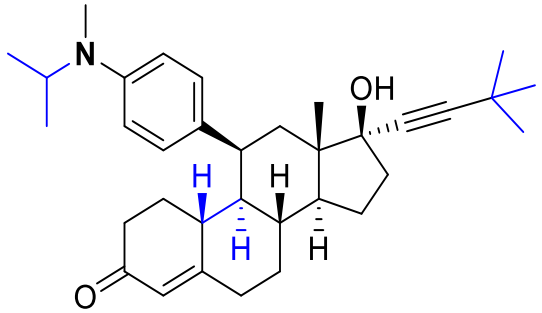
info@oricpharma.com

Background

- Upregulation of the glucocorticoid receptor (GR) is a potential mechanism of resistance to enzalutamide and other androgen receptor (AR) modulators in prostate cancer
- Overexpression of GR has been correlated with poor outcomes in patients with metastatic castration resistant prostate cancer (mCRPC) treated with enzalutamide
- **ORIC-101 is a potent, selective, orally bioavailable small molecule GR antagonist with a favorable cytochrome P450 inhibition profile compared with prior generation GR antagonists**
- ORIC-101 inhibits GR transcriptional activity and blocks prosurvival signals mediated by the activated nuclear hormone receptor

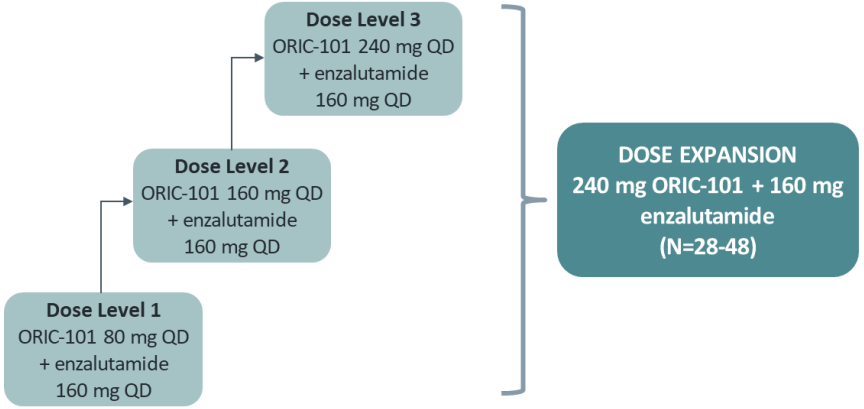
ORIC-101 (Steroidal)
GR antagonism IC_{50} = 7.3 nM
PgR antagonism IC_{50} = 22 nM
CYP3A4 IC_{50} = 1.6 µM
CYP2C8/CYP2C9 IC_{50} > 10 µM

PgR = progesterone receptor



Study Design

- **Objectives:** RP2D, safety, PK/PD, and preliminary antitumor activity of ORIC-101 in combination with enzalutamide in mCRPC patients progressing on enzalutamide
- ORIC-101 was administered orally once daily in combination with enzalutamide 160 mg
- Dose-limiting toxicities (DLTs) were evaluated during Cycle 1 and graded per NCI CTCAE v5.0
- Plasma PK and PD biomarkers were assessed on multiple days and times before and after dosing
  - GR protein expression in 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
  - ***Please see Poster 015 (Daemen et al)***



240 mg ORIC-101 plus 160 mg enzalutamide administered on a continuous once daily dosing regimen was selected as RP2D

Patient Disposition & Demographics

		Non-RP2D (n=7)	RP2D (n=18)	All Patients (N=25)
Patient Disposition, n (%)	Ongoing	0	9 (50)	9 (36)
	Discontinued	7 (100)	9 (50)	16 (64)
	Radiographic Progression	4 (57)	3 (17)	7 (28)
	Clinical Progression	1 (14)	3 (17)	4 (16)
	PSA Progression	1 (14)	2 (11)	3 (12)
	Adverse Event	0	1 (6)	1 (4)
	Other	1 (14)	0	1 (4)
Age (years)	Median (min, max)	70 (60, 82)	71 (53, 82)	70 (53, 82)
ECOG, n (%)	0	7 (100)	11 (61)	18 (72)
	1	0	7 (39)	7 (28)
Total Gleason Score, n (%)	6 - 7	2 (29)	4 (22)	6 (24)
	8 - 10	3 (43)	11 (61)	14 (56)
	Missing/Unknown	2 (29)	3 (17)	5 (20)
Time since start of enzalutamide (months)	Median (min, max)	20.5 (9.4, 69.7)	20.9 (5.5, 80.1)	20.6 (5.5, 80.1)
PSA at study entry (ng/mL)	Median (min, max)	15.6 (1.6, 64.3)	19.3 (2.0, 616.9)	19.0 (1.6, 616.9)
Extent of disease, n (%)	Bone	7 (100)	16 (89)	23 (92)
	Lymph Nodes	4 (57)	6 (33)	10 (40)
	Visceral	2 (29)	1 (6)	3 (12)
Any prior therapy, n (%)	Chemotherapy	0	5 (28)	5 (20)
	Immunotherapy	1 (14)	2 (11)	3 (12)
	Other	0	3 (17)	3 (12)

Note: 20August2021 data cutoff date

Most Common Treatment Related Adverse Events Occurring in More than One Patient

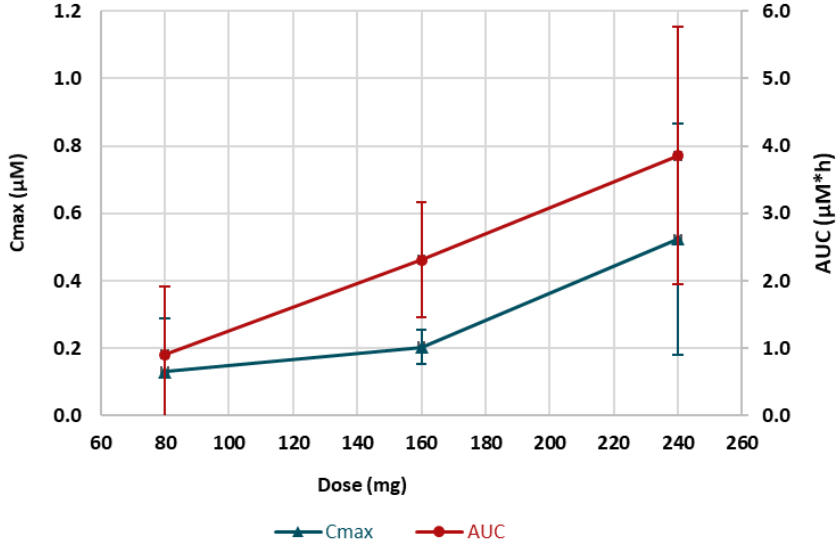
	Non-RP2D (n=7)		RP2D (n=18)		All Patients (N=25)		
Preferred Term, n (%)	**G1-G2**	**G3**	**G1-G2**	**G3**	**G1-G2**	**G3**	**Any**
Fatigue	2 (29)	-	9 (50)	-	11 (44)	-	11 (44)
Nausea	1 (14)	-	7 (39)	1 (6)	8 (32)	1 (4)	9 (36)
Decreased appetite	1 (14)	-	5 (28)	-	6 (24)	-	6 (24)
Constipation	1 (14)	-	3 (17)	-	4 (16)	-	4 (16)
Aspartate aminotransferase increased	2 (29)	-	1 (6)	-	3 (12)	-	3 (12)
Headache	1 (14)	-	2 (11)	-	3 (12)	-	3 (12)
Alanine aminotransferase increased	1 (14)	-	1 (6)	-	2 (8)	-	2 (8)
Blood alkaline phosphatase increased	2 (29)	-	-	-	2 (8)	-	2 (8)
Dysgeusia	-	-	2 (11)	-	2 (8)	-	2 (8)
Dyspepsia	-	-	2 (11)	-	2 (8)	-	2 (8)
Hypokalemia	1 (14)	-	-	1 (6)	1 (4)	1 (4)	2 (8)
Hypophosphatemia	1 (14)	-	1 (6)	-	2 (8)	-	2 (8)
Syncope	-	-	-	2 (11)	-	2 (8)	2 (8)

As of the data cutoff date, no Grade 4 or 5 events have been reported
Majority of the adverse events observed were Grade 1 and 2

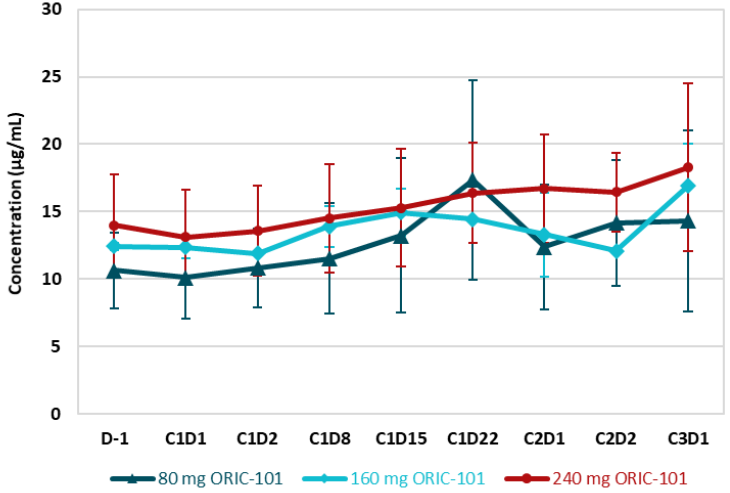
Note: 20August2021 data cutoff date

Pharmacokinetics

ORIC-101 Cmax & AUC

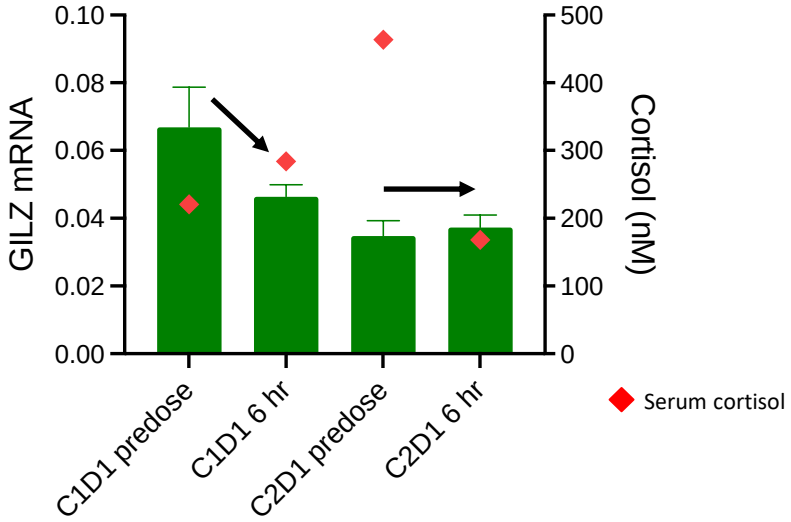


Enzalutamide Predose Concentration



ORIC-101 exposure increased with dose from 80 to 240 mg
Enzalutamide levels did not change significantly with increasing ORIC-101 dose

GR Biomarker Suppression

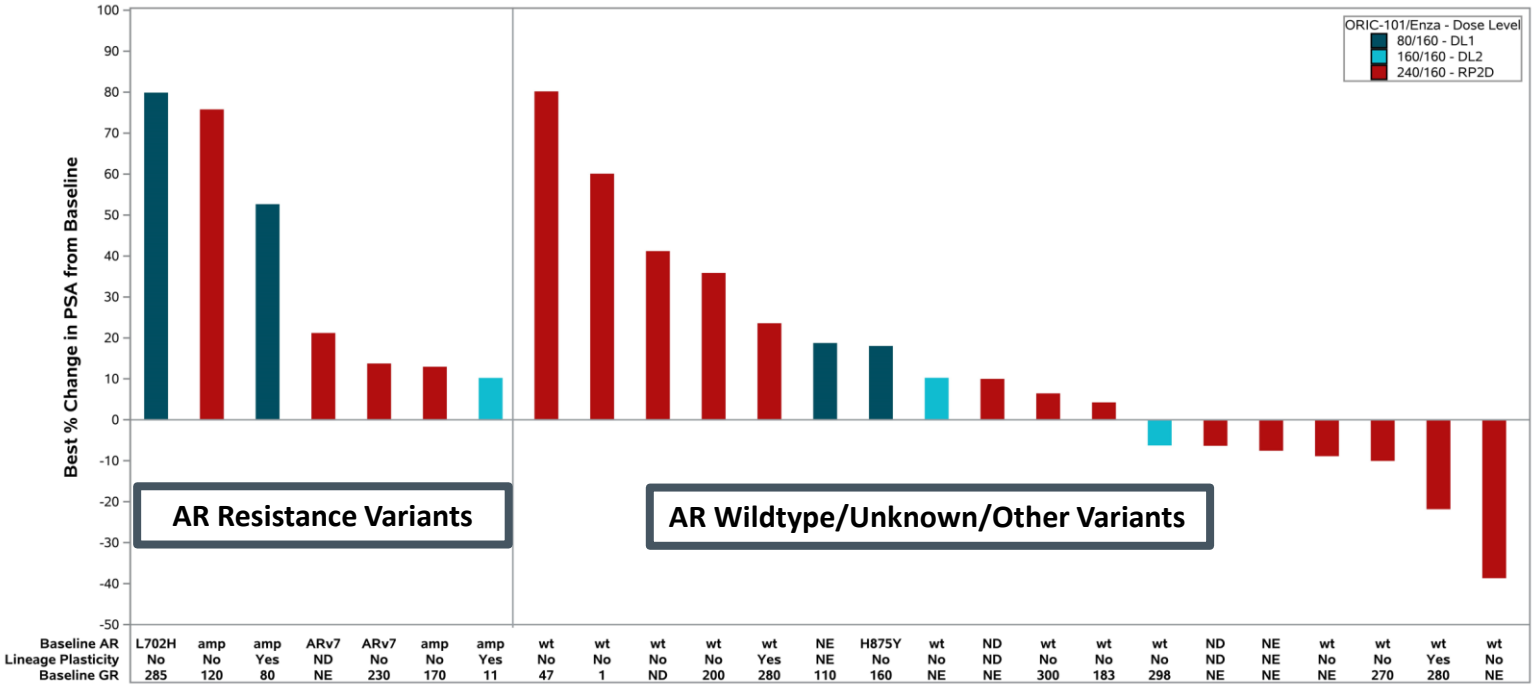


On-target pharmacodynamic modulation was observed as early as after the first dose of ORIC-101

Note: Pharmacodynamic modulation was assessed in blood-derived peripheral blood mononuclear cells (PBMCs)

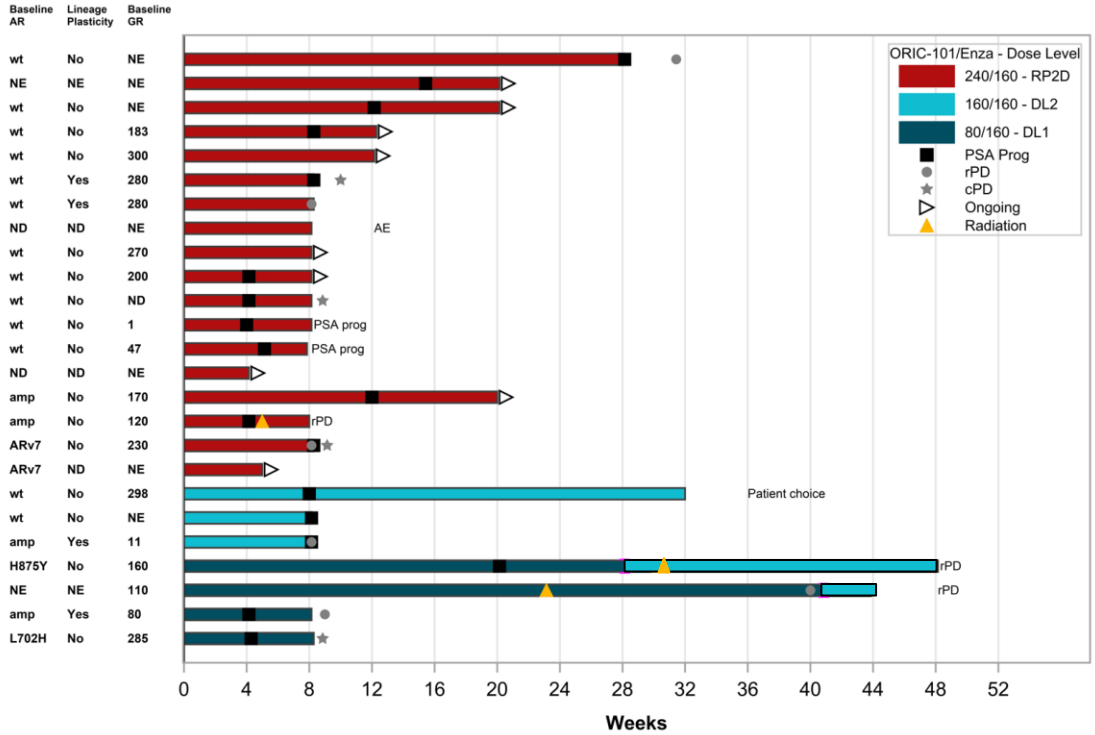
Please see Poster 015 (Daemen et al)

Best Percent Change in PSA from Baseline by AR Status



Note: 20August2021 data cutoff date; includes all patients dosed on or before 15Jul2021; AR resistance variant includes ARv7, L702H, and AR copy number amplification (amp); wt=wild type; NE = non-evaluable; ND=not done; lineage plasticity markers: functional loss of ≥2/3 genes TP53 (LOF mutation), RB1 (homozygous loss or LOH), PTEN (protein and genomic loss); baseline GR H-score = 1×% cells with low (1+) + 2×% cells with intermediate (2+) + 3×% cells with high (3+) staining intensity

Duration of Treatment



Note: 20August2021 data cutoff date; includes all patients dosed on or before 15Jul2021; AR resistance variant includes ARv7, L702H, and AR copy number amplification (amp); wt=wild type; NE = non-evaluable; ND=not done; lineage plasticity markers: functional loss of ≥2/3 genes TP53 (LOF mutation), RB1 (homozygous loss or LOH), PTEN (protein and genomic loss); baseline GR H-score = 1×% cells with low (1+) + 2×% cells with intermediate (2+) + 3×% cells with high (3+) staining intensity

Association of Baseline Biomarker Data with Clinical Status in ORIC-101 Dose Expansion at the RP2D (n=12)

ORIC-101 dose	Pretreatment AR variant (ctDNA, CTC)	Pretreatment alterations in ≥2/3 lineage plasticity markers	Pretreatment GR tumor H-score ≥100 (IHC)	Continued treatment ≥C4
240 mg	Wildtype	No	Yes	Yes
240 mg	Wildtype	No	Yes	Yes
240 mg	Wildtype	No	Yes	Yes
240 mg	Wildtype	No	Yes	Yes
240 mg	Wildtype	NE	NE	Yes
240 mg	NE	NE	NE	Yes
240 mg	Wildtype	No	No	No
240 mg	Wildtype	Yes	Yes	No
240 mg	Wildtype	Yes	Yes	No
240 mg	ARv7 + Amp	No	Yes	No
240 mg	Amp	No	Yes	Yes
240 mg	Amp	No	Yes	No

- ***AR resistance variants (AR L702H, ARv7, amplification), genomic alterations promoting a state of lineage plasticity, and/or low GR protein levels are enriched among patients who discontinued early***
- ***Tumor characterization in association with clinical status provides an opportunity to further identify the appropriate patient population during the ongoing dose expansion portion of the study***

Note: NE = non-evaluable (no tumor cells, no ctDNA, no CTCs); AR amp: cfDNA CN≥2; Lineage plasticity markers: functional loss of tumor suppressor genes TP53 (LOF mutation), RB1 (homozygous loss or LOH), PTEN (protein and genomic loss)

Conclusions

- ORIC-101 in combination with enzalutamide was well tolerated, with no substantial added toxicity
- PK showed no evidence of drug-drug interaction
- The RP2D was selected as 240 mg ORIC-101 plus 160 mg enzalutamide administered on a continuous once daily dosing
- Enrollment in dose expansion is ongoing to evaluate disease control rate as a measure of clinical benefit
  - Disease stabilization will be correlated with AR resistance variants, markers of lineage plasticity, as well as GR expression

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