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

Biomarker results supporting selection of RP2D from a Phase 1b study of ORIC-101, a glucocorticoid receptor antagonist, in combination with enzalutamide in patients with metastatic prostate cancer progressing on enzalutamide

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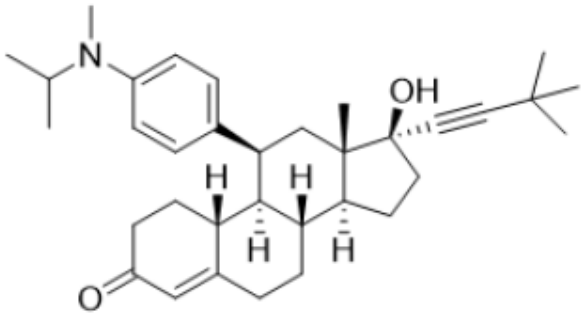
ORIC Pharmaceuticals, South San Francisco, CA

Virtual poster P015

Phase 1b Trial of ORIC-101 in Combination with Enzalutamide in Patients with Metastatic Prostate Cancer Progressing on Enzalutamide (NCT04033328)

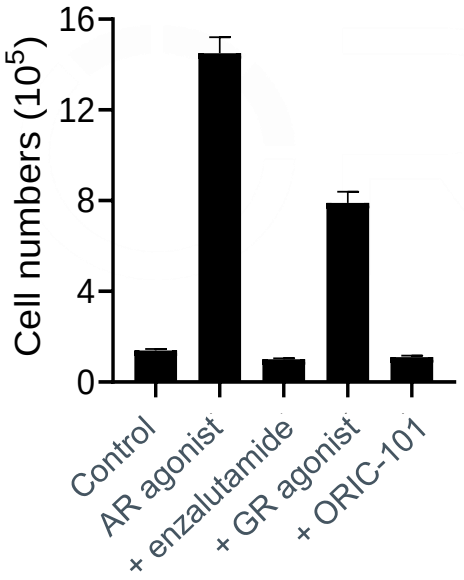
ORIC-101, a potent and selective, orally bioavailable GR antagonist, reverses GR-driven resistance to enzalutamide in preclinical prostate cancer models

ORIC-101



Rew et al, 2018

21-day proliferation experiment in CWR22PC



Zhou et al, Molecular Targets and Cancer Therapeutics Conf 2019

Cohort overview for dose escalation and expansion

Cohort	n	ORIC-101	Enzalutamide
Escalation 1	4	80 mg QD	160 mg
Escalation 2	3	160 mg QD	160 mg
Escalation 3	3	240 mg QD	160 mg
Expansion	15	240 mg QD	160 mg

20August2021 data cutoff date; includes all patients dosed on or before 15Jul2021

- **Primary endpoints:** Recommended Phase 2 Dose (RP2D) and safety
- **Secondary endpoint**: PK

See Abida et al, 2021, virtual poster P040

Exploratory Biomarker Strategy for the Phase 1b Trial of ORIC-101 in Combination with Enzalutamide

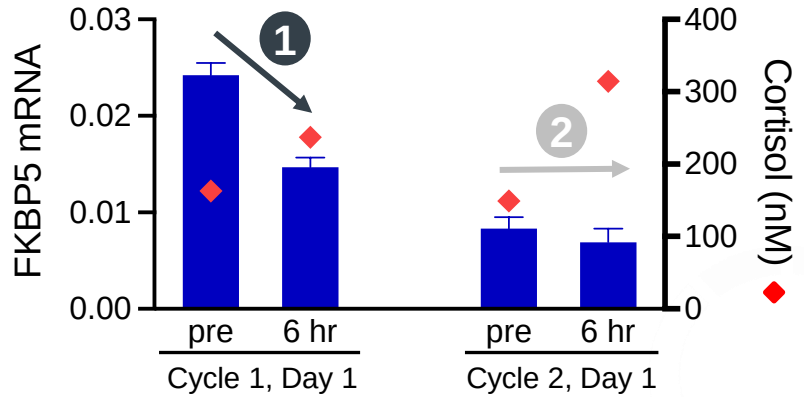
Exploratory biomarkers

Endpoint	Method	Sample	Timepoints	Note
PD biomarkers	RT-qPCR	PBMCs	C1D1, C1D8, C2D1 Pre-, 3 and/or 6 hr post-treatment	FKBP5, GILZ, PER1 (Daemen et al, ASCO 2021, #3110)
GR protein	IHC	Tumor biopsy	Screening, End of C2, EOT	Evaluated in biopsies with >50 tumor cells
AR protein	IHC	Tumor biopsy	Screening, End of C2, EOT	
PTEN loss	IHC	Tumor biopsy	Screening, End of C2, EOT	
AR-V7	IF	Whole blood CTCs	Screening, End of C2, EOT	Epic Sciences
Mutations/CNVs	NGS	Plasma ctDNA	Screening, End of C2, EOT	GuardantOMNI® ctDNA assay PredicineCARE™ ctDNA assay

RT-qPCR: quantitative reverse transcription PCR; PBMC: blood-derived peripheral blood mononuclear cells; IHC: immunohistochemistry; IF: immunofluorescence; CTC: circulating tumor cells (Wise et al, ASCO 2016); NGS: next generation sequencing; ctDNA: circulating tumor DNA; CNV: copy number variant; C1D1: cycle 1, day 1; C2: cycle 2; EOT: end of treatment

PBMC Biomarker Data Indicate On-target PD Modulation

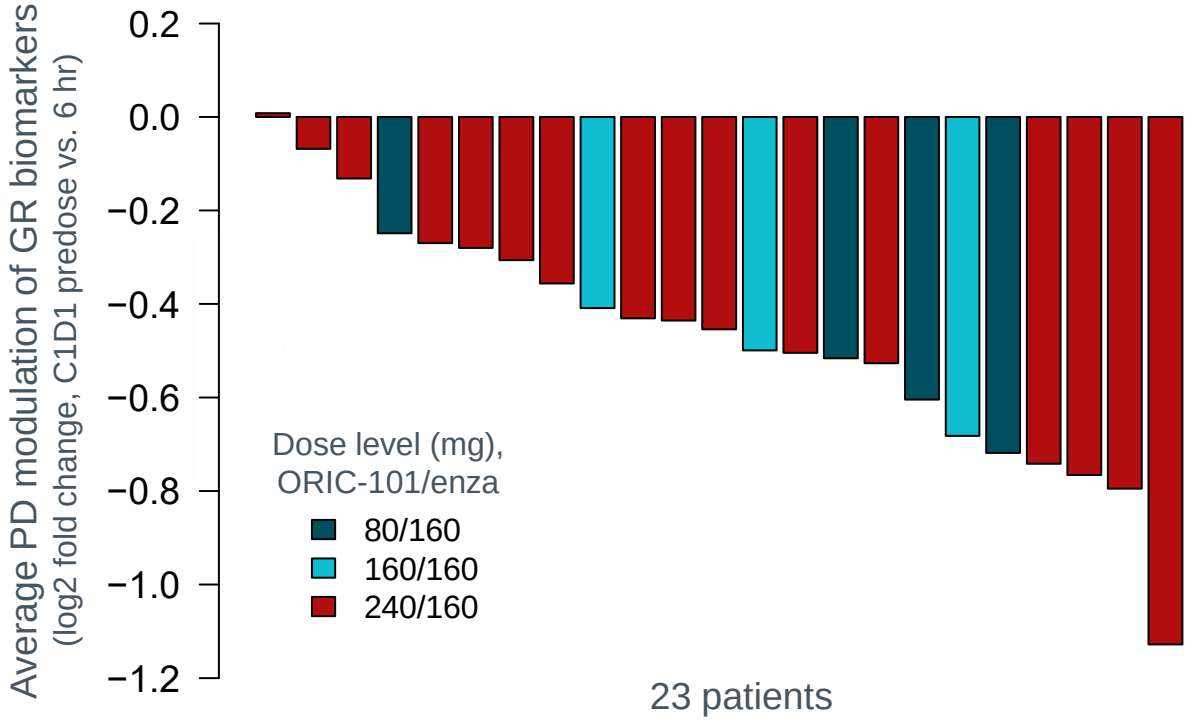
Exemplar patient from dose escalation, dose level 1



mRNA relative to housekeeping gene RPL27, shown as mean + SD for technical triplicates

1. ORIC-101 induces PD modulation on Day 1 (cortisol increase due to feedback)
2. PD suppression is sustained from Cycle 2 onward, independent of cortisol

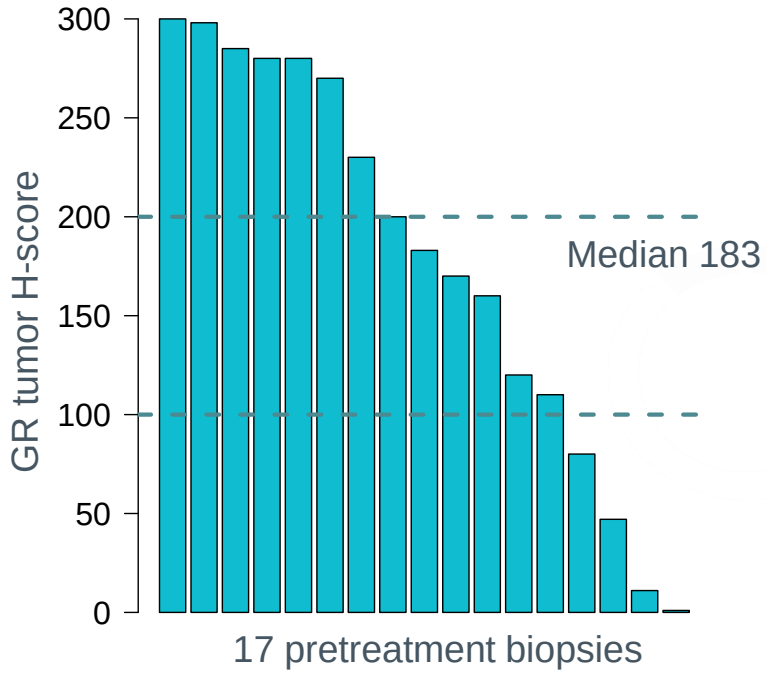
PD modulation on Day 1 after one dose of ORIC-101



- **PD suppression was observed as early as on Day 1 after one dose of ORIC-101, in PBMCs of 22/23 (96%) patients**
- **PD modulation does not show dose dependency, with GR target suppression achieved starting at 80 mg ORIC-101**

GR Protein Detected in Pretreatment Biopsies with ORIC-101-induced Decrease Observable

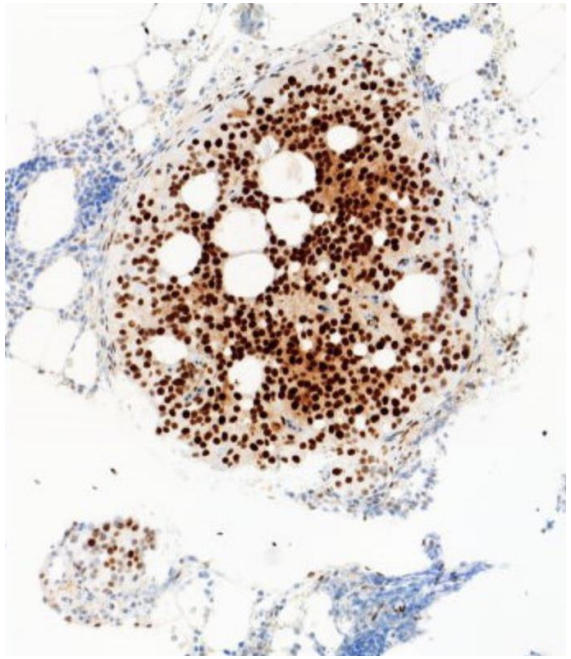
Nuclear GR protein was detected by IHC in 76% of pretreatment biopsies (H-score ⩾100)



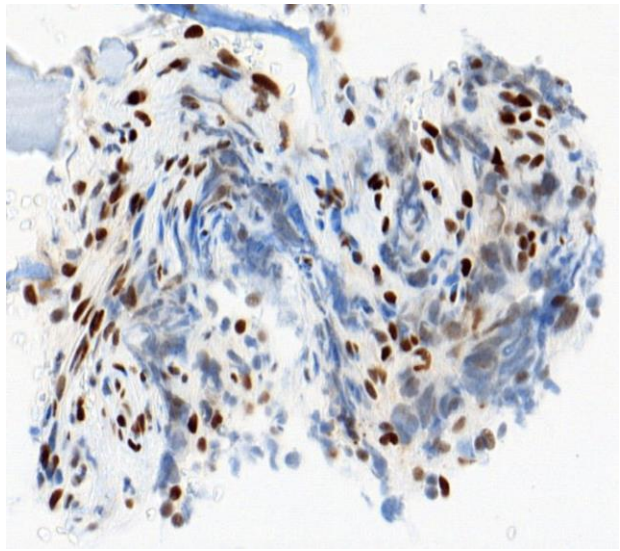
H-score ranges from 0 to 300, defined as (% tumor cells with weak staining) x1 + (% tumor cells with moderate staining) x2 + (% tumor cells with strong staining) x3

On-treatment reduction in GR tumor H-score from 298 to 130

Pretreatment

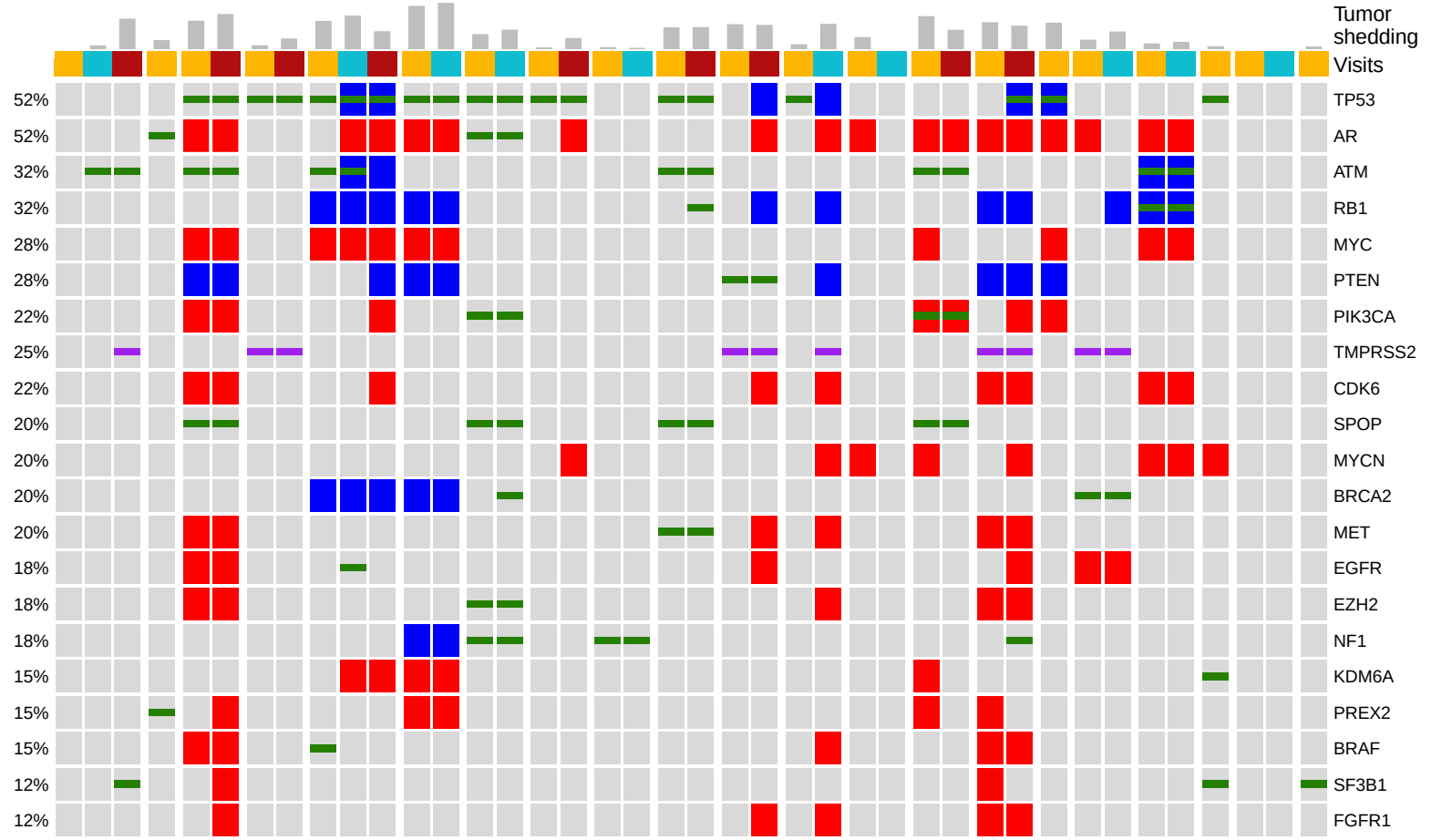


End of Cycle 2



- **On-treatment reduction in GR tumor H-score (>20%) was observed in 5/10 patients with matched tumor biopsies**
- **Data are suggestive of ORIC-101 facilitated, enzalutamide-induced GR+ tumor cell killing**

The Phase 1b Cohort Represents mCRPC Based On Genomic Landscape



Genes altered in at least 4 patients are shown; Visits are grouped by patient; Tumor shedding: log2(max allele frequency + 1); Mutation: nonsense/ missense mutations, in-frame and frameshift insertions/ deletions, splice site mutations; Gain/amp: cfDNA CN ≥2.2 (≥1.2 for X/Y chromosome genes); AR amp (X chr): cfDNA CN ≥2; Deletion (heterozygous and homozygous loss): cfDNA CN ≤1.85

- The amount of tumor shedding in this cohort ranged from 0.25% to 82% (median 9.1%), comparable to a clinical cohort of ~10,000 prostate tumors profiled with Guardant360® (Guardant Health)
- Prevalent genomic alterations at time of enrollment include TP53, RB1, PTEN, BRCA2, SPOP and TMPRSS2-ERG
- Pretreatment AR alterations in ctDNA or CTCs were observed in 38% (8/21) of patients: L702H (n=1), H875Y (n=1), amplification (n=5), ARv7 (n=4)
- Copy number alterations were the primary genomic event occurring on treatment

Association of Baseline Biomarker Data with Clinical Status in ORIC-101 Dose Escalation (n=10)

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
160 mg	Wildtype	No	Yes	Yes
80 mg	H875Y	No	Yes	Yes
80 mg	NE	NE	Yes	Yes
240 mg	Wildtype	No	NE	Yes
160 mg	Wildtype	No	NE	No
240 mg	Wildtype	No	ND	No
240 mg	Wildtype	No	No	No
80 mg	L702H	No	Yes	No
80 mg	Amp	Yes	No	No
160 mg	Amp	Yes	No	No

ND = not done; NE = non evaluable (no tumor cells, no ctDNA, no CTCs); AR amp: cfDNA CN ≥2; AR L702H is activated by cortisol and associated with lack of PSA response to enzalutamide (Torquato et al, 2019; Romanel et al, 2015); Lineage plasticity markers: functional loss of tumor suppressor genes TP53 (LOF mutation), RB1 (homozygous loss or LOH), PTEN (protein and genomic loss) (Ku et al, 2017; Mu et al, 2017; Zou et al, 2017)

- **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**
- **These biomarker data suggest AR-dependent and -independent resistance mechanisms may co-exist through intra- or inter-tumor heterogeneity in some patients**

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

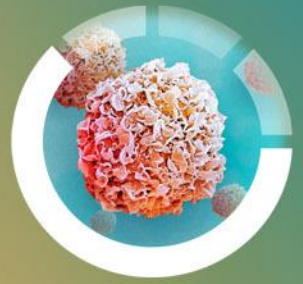
Shown are dose expansion patients with complete biomarker data and who discontinued or completed 3 cycles as of 20August2021

- **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**

ORIC-101 Biomarker Conclusions

- Biomarker data from patients enrolled in the ORIC-101 prostate cancer phase 1b study provide evidence of PD modulation and on-target tumor cell eradication at all dose levels
- Nuclear GR protein was detected in pretreatment biopsies, with median H-score of 183 (out of 300)
- The phase 1b cohort is representative of mCRPC based on genomic profiles and amount of tumor shedding
- Co-occurring tumor characteristics and prognostic factors may be contributing to clinical status
- Tumor genomics 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, with focus on AR resistance variants, markers of lineage plasticity, as well as GR expression

ORIC



OVERCOMING RESISTANCE IN CANCER

Thank you

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