

**ORIC-944, a Potent and Selective
Allosteric PRC2 Inhibitor with Best-in-
Class Properties, Demonstrates
Combination Synergy with AR Pathway
Inhibitors in Prostate Cancer Models**

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Minisymposium on Novel Antitumor Agents 5

Disclosure Information

Anneleen Daemen

I have the following financial relationships to disclose:

- Employee of ORIC Pharmaceuticals, Inc.
- Stockholder in ORIC Pharmaceuticals, Inc.

– and –

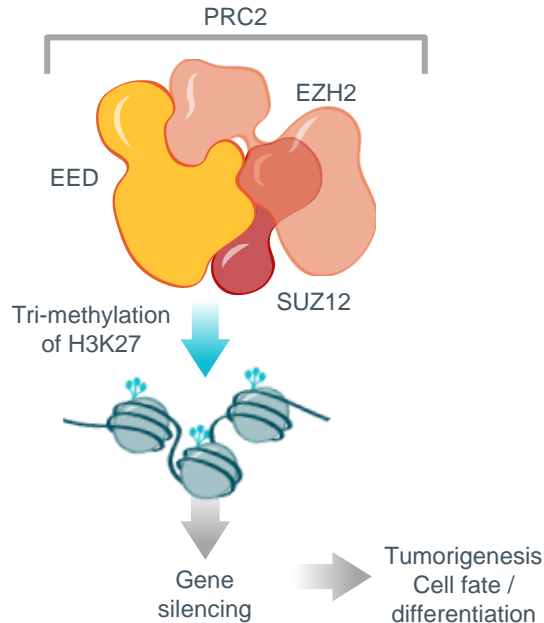
I will discuss the following investigational use in my presentation:

- ORIC-944 in prostate cancer

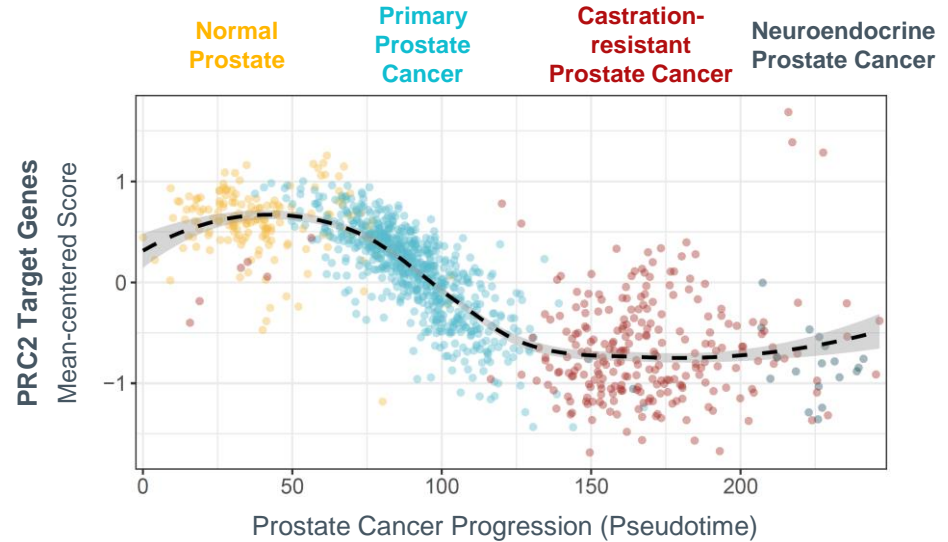
For inquiries or MTA requests please contact lori.friedman@oricpharma.com

PRC2 Plays Pivotal Role in Transcriptional Regulation and Evolves as Prostate Cancer Progresses

PRC2 Function



PRC2 Target Gene Expression Reflects Change in Lineage

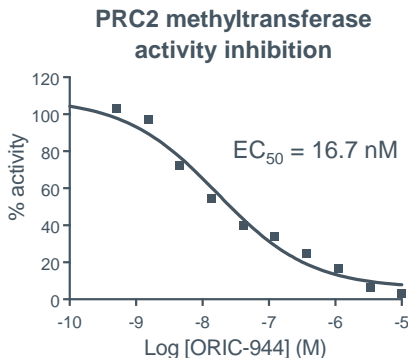
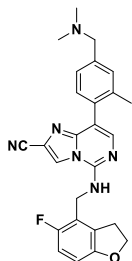


PRC2 is a validated oncogenic target across several cancers with promising therapeutic potential in prostate cancer

ORIC-944 Targets the EED Subunit of PRC2 and Has Favorable Drug Properties

ORIC-944 Was Designed to Have Improved Drug Properties

ORIC-944



ORIC-944 key properties

- ✓ Strong potency
- ✓ Clean CYPs
- ✓ Excellent PK

EED Inhibition May Improve Upon EZH2 Inhibitors

- ORIC-944 allosterically inhibits PRC2 by targeting EED
- Allosteric inhibition of PRC2 through EED may address limitations of EZH2 inhibitors
 - Active against acquired resistant EZH2 mutants⁽¹⁾
 - Inhibit compensatory bypass activity of EZH1⁽²⁾

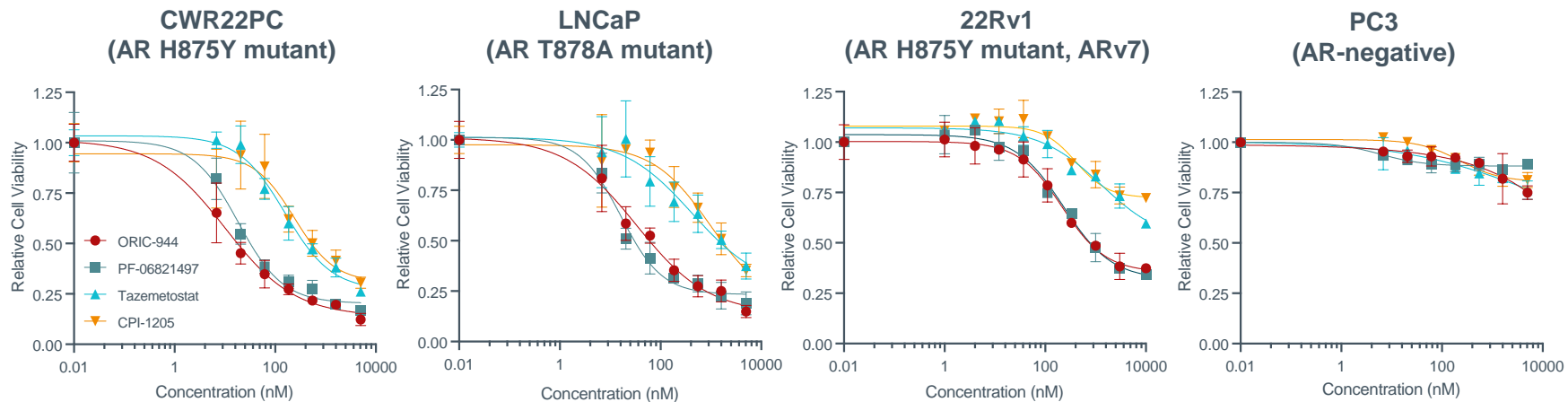
New Drugs on the
Horizon, April 7
(Abstract ND04)



*Allosteric PRC2 inhibition through EED provides many potential benefits over EZH2;
Notably, ORIC-944 has improved drug properties over other PRC2 inhibitors*

ORIC-944 Demonstrates Cell Potency in AR+ Prostate Cancer Lines

In Vitro Potency in Prostate Cancer Cells



EC50 (nM)	CWR22PC	LNCaP	22Rv1	PC3
ORIC-944	10	34	215	>10,000
PF-06821497	18	16	233	>10,000
Tazemetostat	156	425	1,304	>10,000
CPI-1205	241	973	407	>10,000

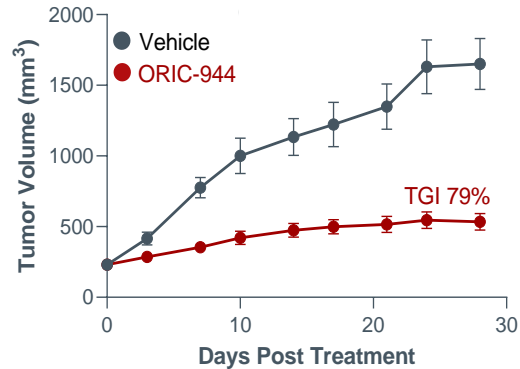
ORIC-944 potency in AR+ prostate cancer cell lines is superior to first generation EZH2 inhibitors tazemetostat and CPI-1205, and comparable to PF-06821497

ORIC-944 May Provide Benefit Across the Spectrum of Prostate Cancer Evolution

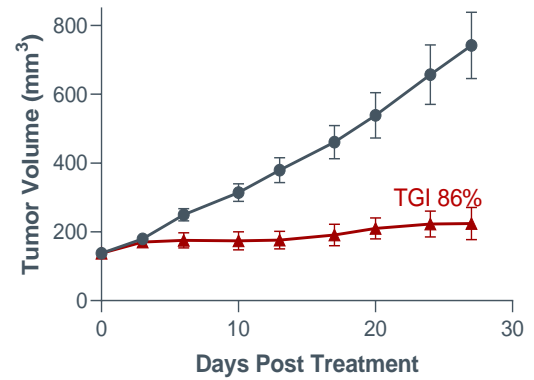
In Vivo Efficacy in Prostate Cancer Models



AR+ Castration-resistant (C4-2)



ARv7+ Castration- and Enza-resistant (22Rv1)



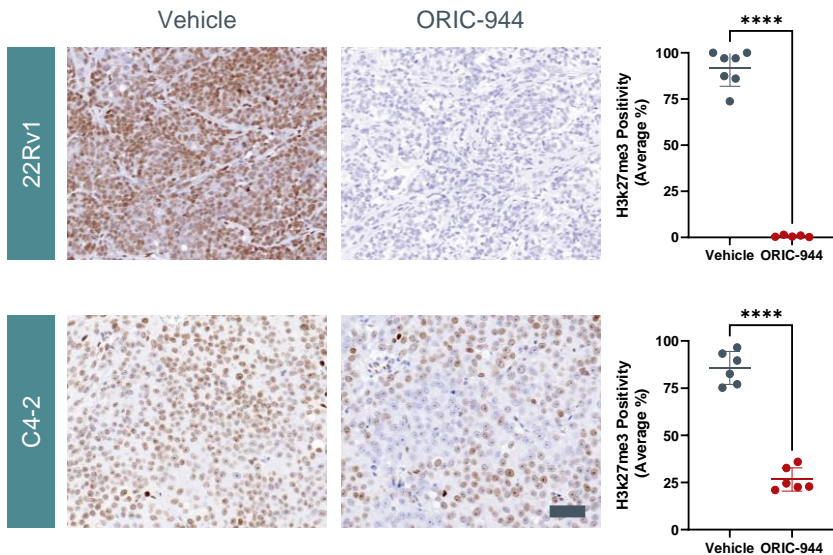
ORIC-944 induces tumor growth inhibition in a spectrum of in vivo prostate cancer models, including AR-positive, AR-mutant, ARv7, castration resistant, and AR inhibitor-resistant

Note: Once daily oral administration of C4-2 and 22Rv1 tumor-bearing castrated mice with vehicle or ORIC-944 200 mpk QD; TGI = $[1 - (TV_f - TV_{i0}) / (TV_f - TV_{c0})] \times 100\%$. Top graphic adopted from Abou et al. Front Oncol (2020).

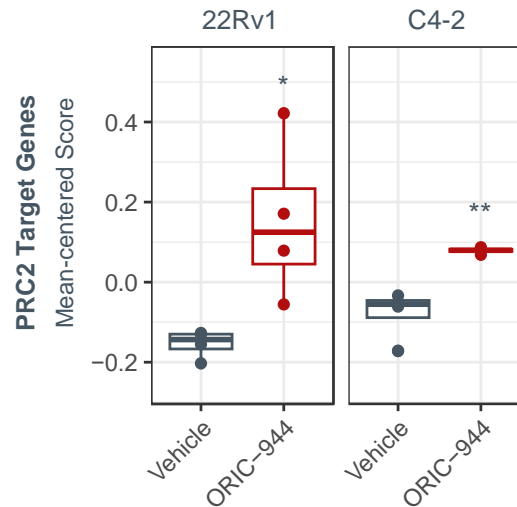
ORIC-944 Treatment Inhibits PRC2 Across Prostate Cancer Models

In Vivo PD Modulation

ORIC-944 Robustly Modulates H3K27me3 in Xenografts



ORIC-944 Upregulates Known PRC2 Target Genes in End-of-study Tumors

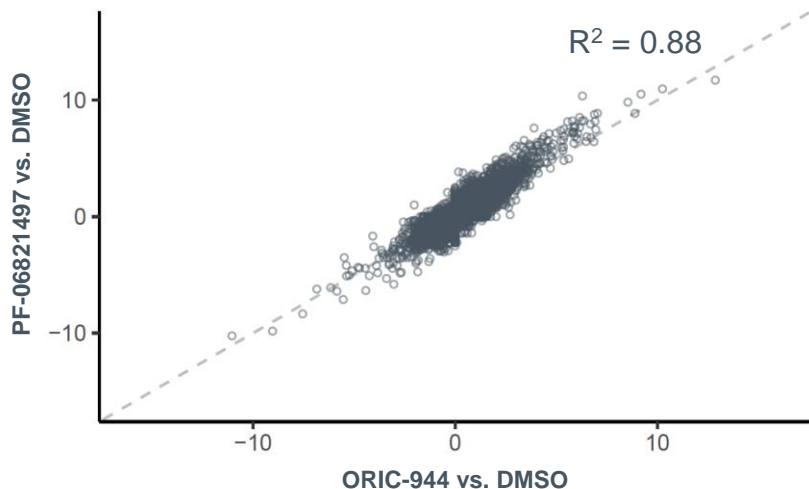


ORIC-944 treatment impacts target genes associated with known PRC2 methylation targets across responsive models

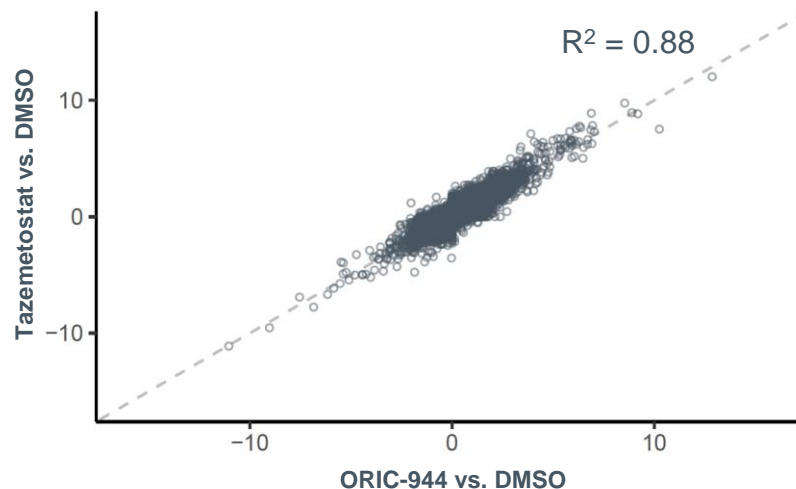
ORIC-944 EED Inhibitor and EZH2 Inhibitors Demonstrate Comparable Impact on Transcription in Prostate Cancer Cells

In Vitro RNA Sequencing

Treatment with EED vs. EZH2 Inhibitor Induce Equivalent Transcriptional Changes in LNCaP Cells



Transcriptional Equivalence of Inhibiting EED and EZH2 Is Confirmed with Second EZH2 Inhibitor



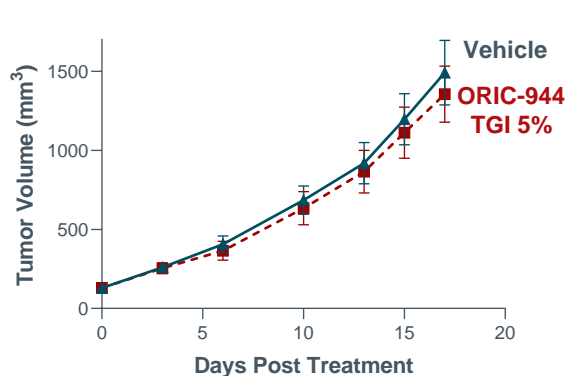
***EED and EZH2 inhibitors have the same transcriptional effects in vitro;
No evidence of a mechanistic distinction between EED and EZH2 inhibition in prostate cancer cells***

Cell State Adaptation to Androgen-depletion Correlates with ORIC-944 Responsiveness as a Single Agent

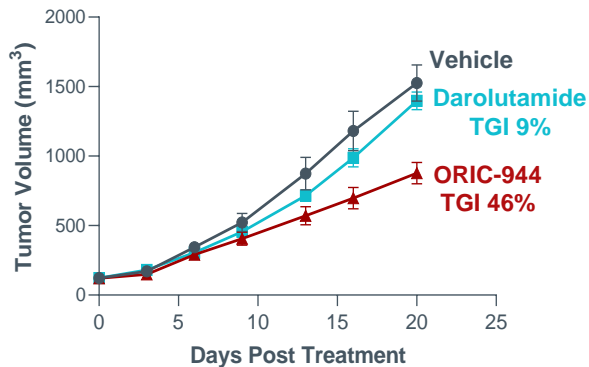
In Vivo Efficacy – Hormone Modulation in 22Rv1 Prostate Cancer Model

Androgen Levels

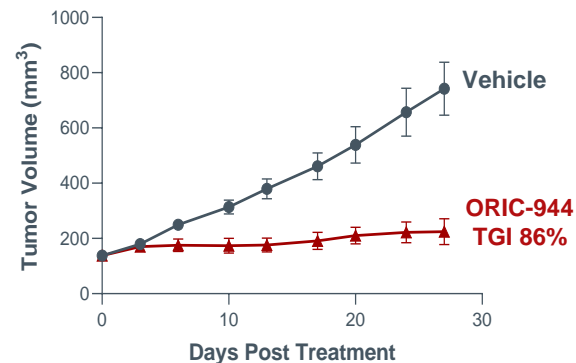
High Hormone, Intact



Low Hormone



Hormone-depleted, Castrated



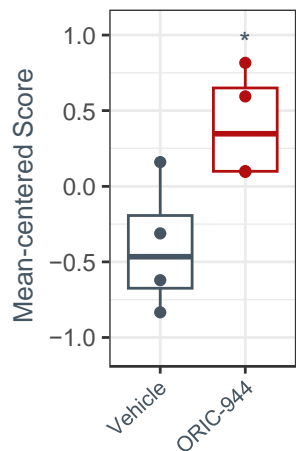
In the 22Rv1 CDX model, suppression of AR signaling engenders sensitivity to PRC2 inhibition

ORIC-944 Increases AR Signaling and Induces Luminal Cell State in 22Rv1 Xenografts

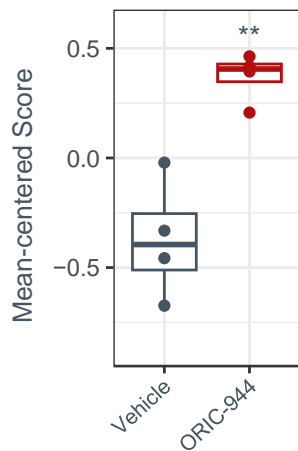
ORIC-944 Increases AR Signaling and Luminal Markers in 22Rv1 Xenografts

Prostate Cells Evade AR-directed Therapies via Cellular Reprogramming, and ORIC-944 Enables Cells to Regain AR Dependency

AR Signaling Genes

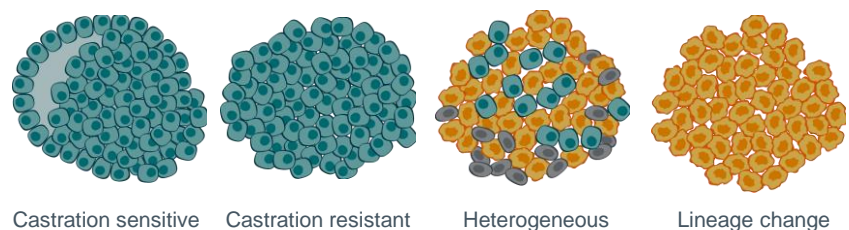


Luminal Markers



AR Dependent Prostate Cancer

AR Independent Prostate Cancer



AR-directed therapeutics

PRC2 inhibitors

- Luminal-like: hormone-dependent
- Pluripotent
- Hormone-independent

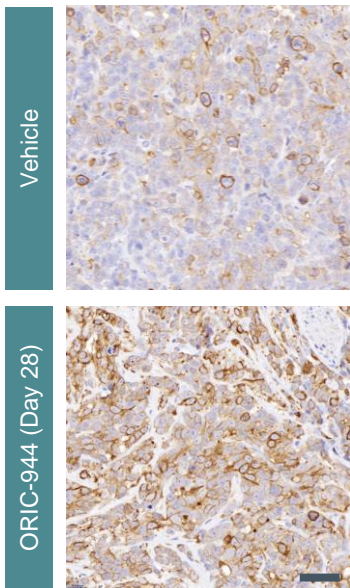
ORIC-944 increases AR signaling and luminal cell state in 22Rv1

Note: Once daily oral administration of 22Rv1 tumor-bearing castrated mice with vehicle or ORIC-944 100 mpk QD x28. AR signaling genes: 33 AR target genes, consistently stimulated by R1881 and suppressed with R1881 + enzalutamide in at least 3 out of 5 AR+ cell lines [ORIC data] and correlated in prostate tumor samples from SU2C [Abida et al. PNAS (2019)]. Luminal markers: Liang et al. Prostate Cancer and Prostatic Diseases (2022). ORIC-944 vs. vehicle, t-test: *, p<0.05; **, p<0.01.

ORIC-944 Induces and Maintains Luminal Cell State in 22Rv1 Xenografts

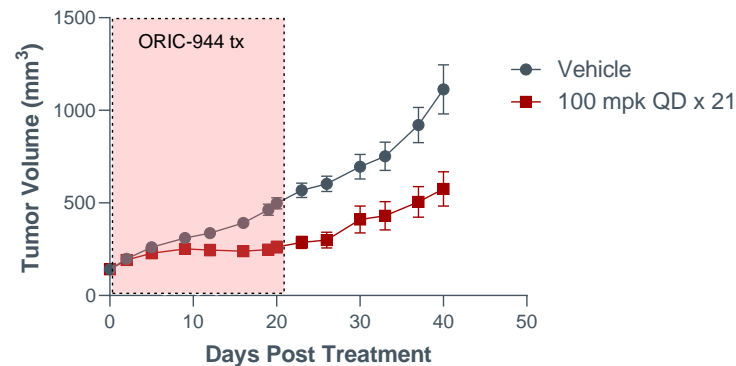
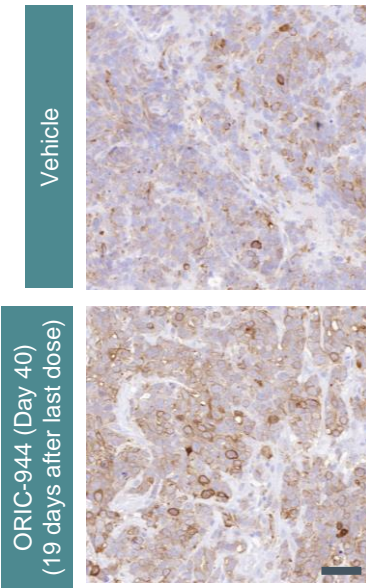
Luminal Cell State Induction Confirmed in 22Rv1 Xenografts at Protein Level

CK8 IHC



Luminal Cell State Marker CK8 Reverses Back After ORIC-944 Withdrawal

CK8 IHC

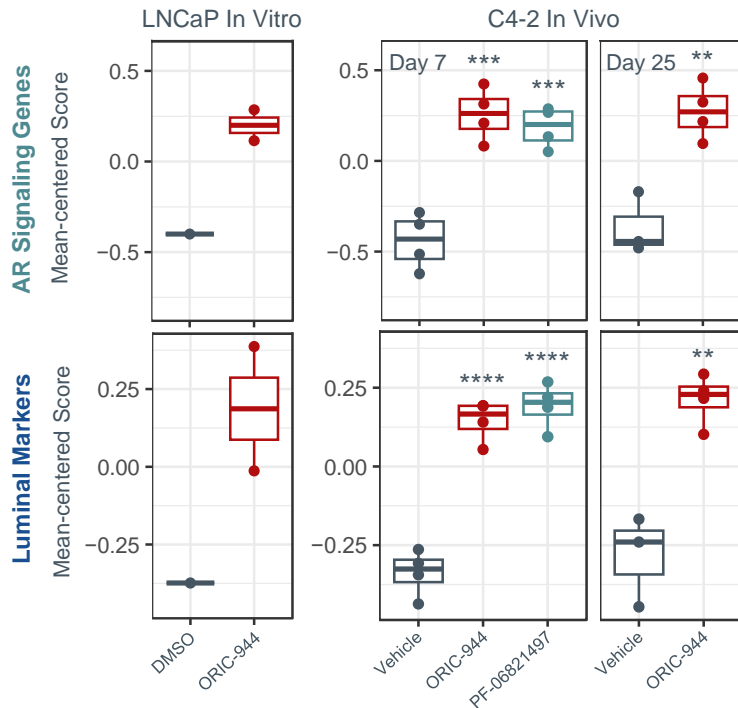


ORIC-944 treatment cessation reverts luminal cell state in 22Rv1

Increased AR Signaling and Induced Luminal State Confirmed Across Multiple CDX and PDX Prostate Cancer Models with PRC2 Inhibitors

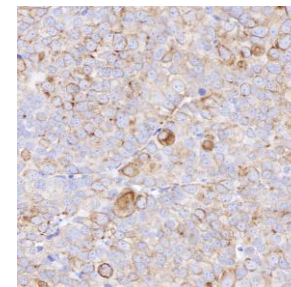
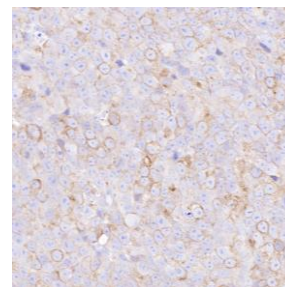
ORIC-944 Enhances AR Signaling and Increases Luminal Markers in LNCaP Cells and C4-2 Xenografts

AR-positive PDX Models Also Demonstrated Increased Luminal Cell State after Treatment with ORIC-944

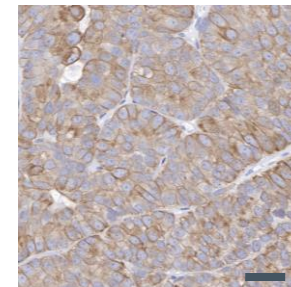
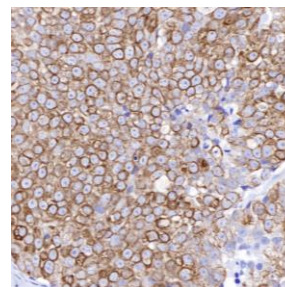


CK8 IHC

Vehicle



ORIC-944

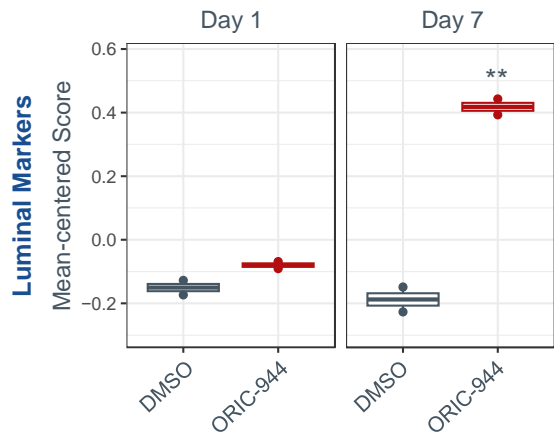


PRC2 inhibitors universally increase AR signaling and luminal cell state markers across prostate cancer models, supporting the hypothesis that this treatment reverts cells to a state which is sensitive to AR inhibition

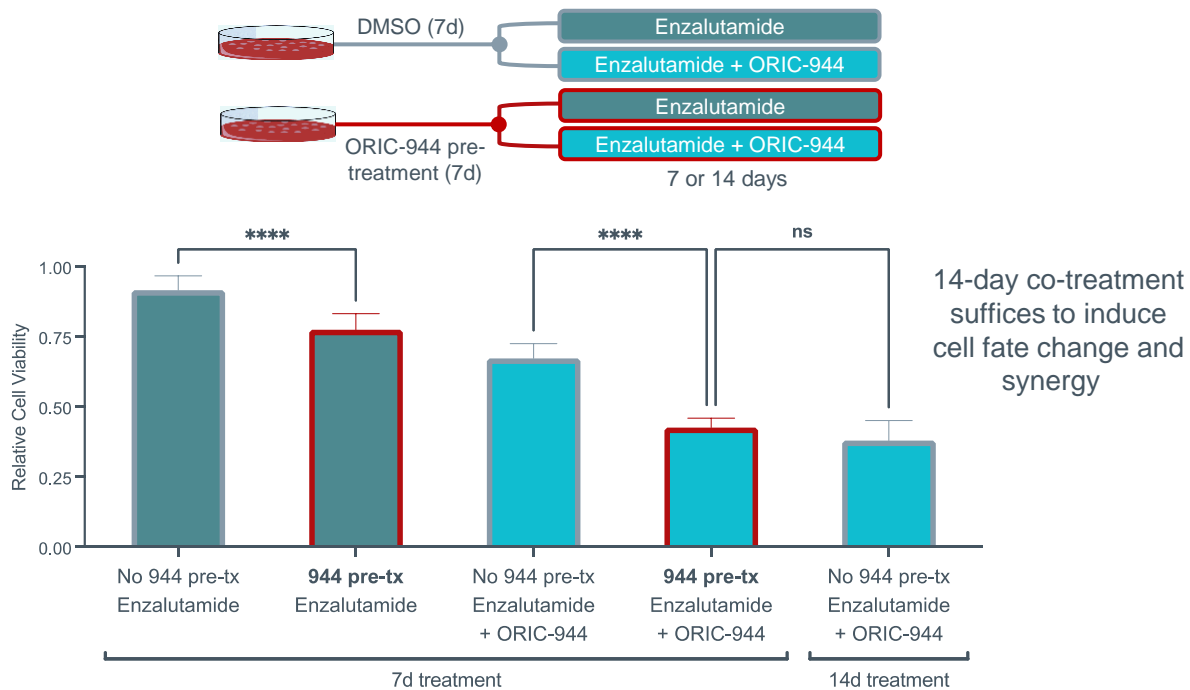
Note: In vitro LNCaP cells in FBS treated with 1 μ M compound for 7 days. Intact C4-2 tumor-bearing mice treated once daily with vehicle, PF-06821497 100 mpk BID, or ORIC-944 100 mpk QD for 7 or 25 days as indicated. Once daily oral administration of prostate cancer patient derived xenograft models in intact mice with vehicle or ORIC-944 100 or 200 mg/kg QD x28. CK8 staining of end-of-study tumors; scale bars 50 μ m. PRC2 inhibitor vs. vehicle, t-test: **, p<0.01; ***, p<0.001; ****, p<0.0001.

ORIC-944 Renders Prostate Cancer Cells More Sensitive to AR Inhibitor

7-day ORIC-944 Treatment Increases Luminal Markers in 22Rv1 Cells



Induced Luminal Cell Fate Tracks with Enhanced Response to Enzalutamide +/- ORIC-944 in 22Rv1 Cells



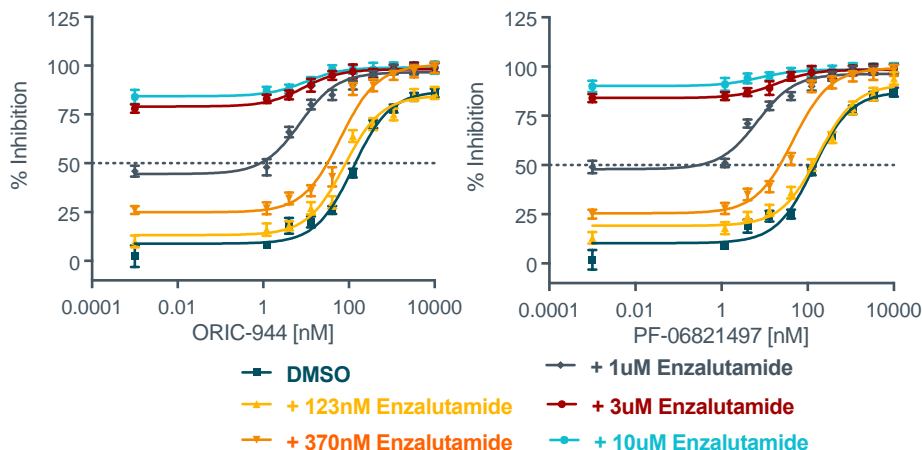
Results are consistent with hypothesis that ORIC-944 enhances AR inhibitor response via induced luminal change

Note: Left – 22Rv1 cells in FBS treated with DMSO or 1uM ORIC-944 for 1 or 7 days. ORIC-944 vs. DMSO, t-test: **, p<0.01. Right – 22Rv1 cells in FBS treated with DMSO, 1uM enzalutamide, 1uM ORIC-944 or the combination for 7 or 14 days, with vs. without pretreatment with 1uM ORIC-944 for 7 days. Shown is the average reduction in viability, with standard deviation, observed in 2 biological replicates with 4 technical replicates each. Significance is based on one-way ANOVA with Tukey's multiple comparisons test for all comparisons, showing only those of interest. ****, p<0.0001; ns, not significant.

ORIC-944 Synergizes with AR Inhibitors in Prostate Cancer Cells

In Vitro PRC2 and AR Inhibitor Combination

ORIC-944 & PF-06821497 Synergistically Combine with Enzalutamide in C4-2 Cells



In Vitro Combination Synergy in C4-2

Drug Combination	Bliss Score	Loewe Score	HSA Score
ORIC-944 + Enzalutamide	10.6	15.8	16.7
PF-06821497 + Enzalutamide	9.9	14.0	15.4

Synergy score interpretation:
 >10: **synergistic**
 10 to -10: *additive*
 <-10: *antagonistic*

ORIC-944 synergy with AR inhibition was confirmed:

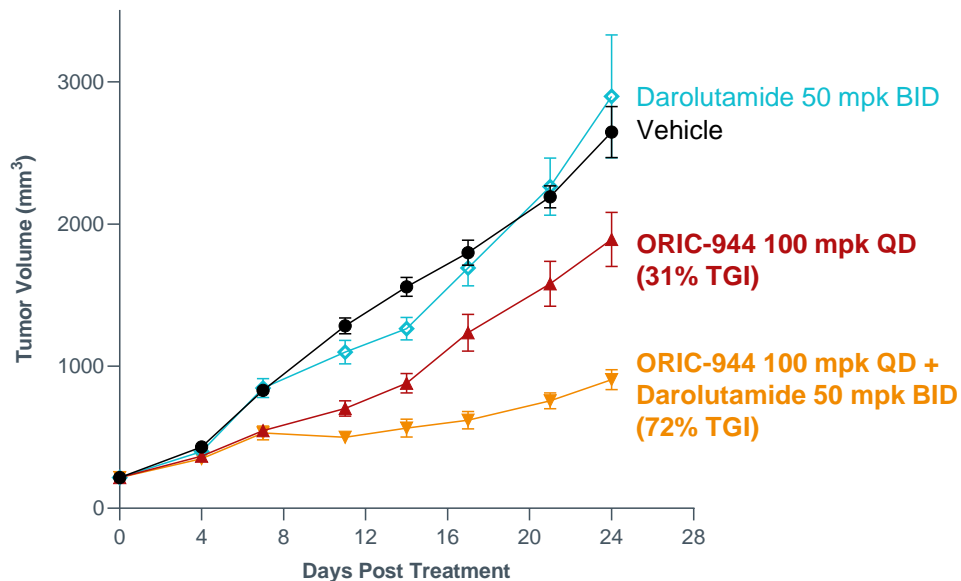
- in additional prostate cancer lines
- with additional AR inhibitor (darolutamide)

ORIC-944 and EZH2 inhibitor synergize with AR inhibitors in prostate cancer models in vitro, at clinical concentrations

ORIC-944 Synergizes with AR Inhibitor in Prostate Cancer Xenograft Model Resistant to AR Inhibition

In Vivo Combination Efficacy in Resistant Prostate Cancer Model

Synergy Observed for Combination of ORIC-944 and Darolutamide in AR+ Model Lacking Response to AR Inhibition



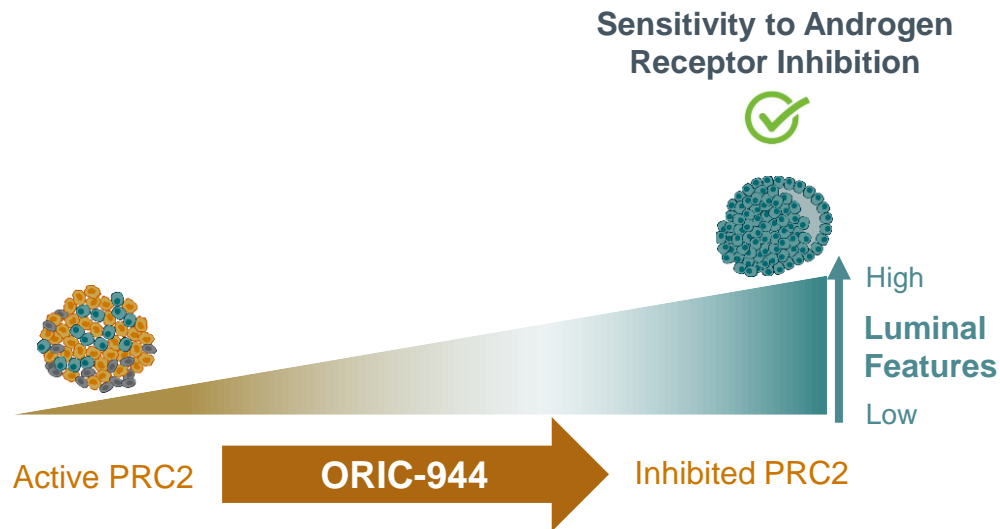
ORIC-944 combination with an AR inhibitor improves therapeutic activity in AR inhibitor refractory setting

Therapeutic Potential of PRC2 Inhibitors in Prostate Cancer May Be Maximized in Combination with AR Inhibitors

Key Takeaways of Mechanistic Hypothesis

- EED inhibitor ORIC-944 induces luminal cell fate across prostate cancer models
- No mechanistic distinction between EED and EZH2 inhibition
- Continuous PRC2 inhibition is needed to maintain luminal cell fate
- Treatment-induced cell fate changes render prostate tumor cells more susceptible to AR inhibition

Model of Mechanistic Hypothesis



Initiating clinical combination study of ORIC-944 with AR inhibitor(s) in patients with prostate cancer

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Mirati Therapeutics

Matthew A. Marx
James G. Christensen

Patients and their
families and caregivers

Presentation access



New Drugs on the Horizon, April 7



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