

Discovery of ORIC-944, a Novel Inhibitor of PRC2 with Best-in-Class Properties for the Treatment of Prostate Cancer

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Disclosures

Lori Friedman

I have the following relevant financial relationships to disclose:

- Employee and Stockholder of: ORIC Pharmaceuticals, Inc.
- Consultant for: Twist Bioscience, ProfoundBio
- Board member: NextRNA Therapeutics

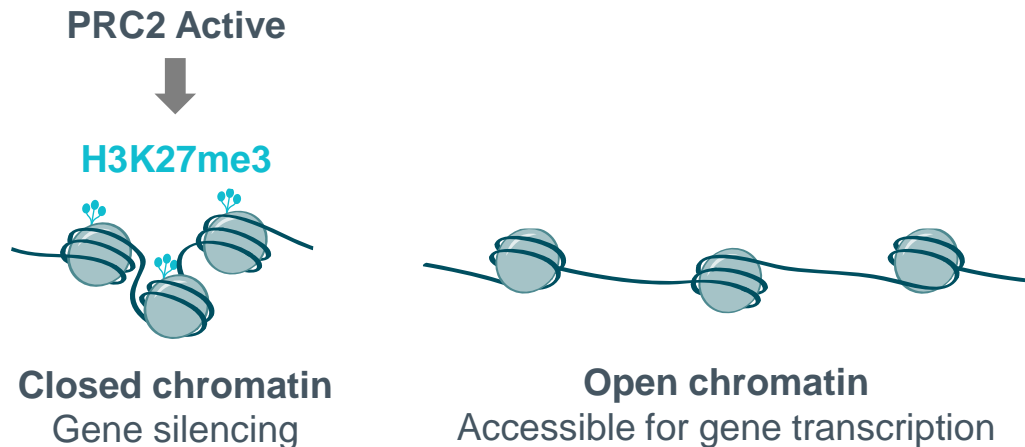
I will discuss the following investigational use in my presentation:

- ORIC-944 in the treatment of prostate cancer

PRC2 Plays Pivotal Role in Transcriptional Regulation and Cancer

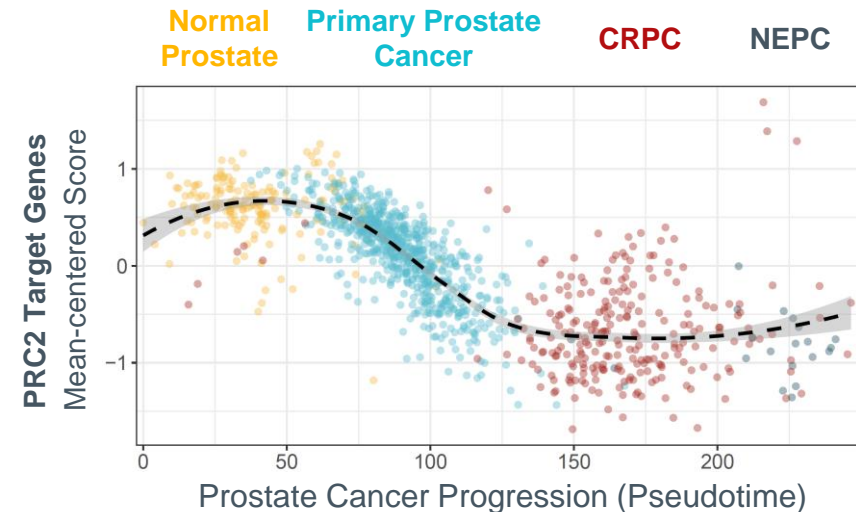
PRC2 Functions in Transcriptional Regulation and Gene Silencing

- PRC2 is a chromatin modifying enzyme complex that:
 - catalyzes the methylation of histone H3 at lysine 27
 - maintains gene transcriptional repression
 - plays an essential role in the maintenance of cellular identity ⁽¹⁾



PRC2 Target Gene Expression Changes as Prostate Cancer Evolves

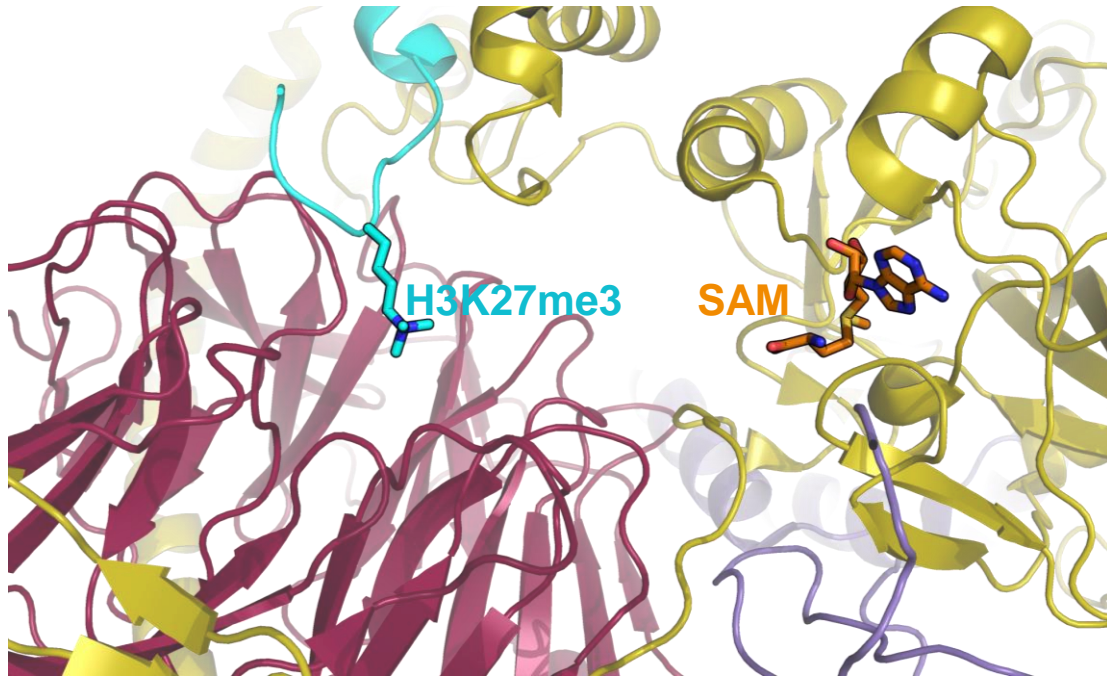
- Prostate cancers have dysregulation of PRC2 ⁽²⁾ ⁽³⁾
 - PRC2 is implicated in prostate tumor evolution and cell fate
 - PRC2 is a potential therapeutic dependency



PRC2 has promising therapeutic potential in prostate cancer

PRC2 Is a Validated Target with Two Druggable Subunits

PRC2 Structures Are Utilized in Drug Discovery



PRC2 subunits:

EED

EZH2

SUZ12

Binding sites:

H3K27me3

SAM

PRC2 Druggable Subunits

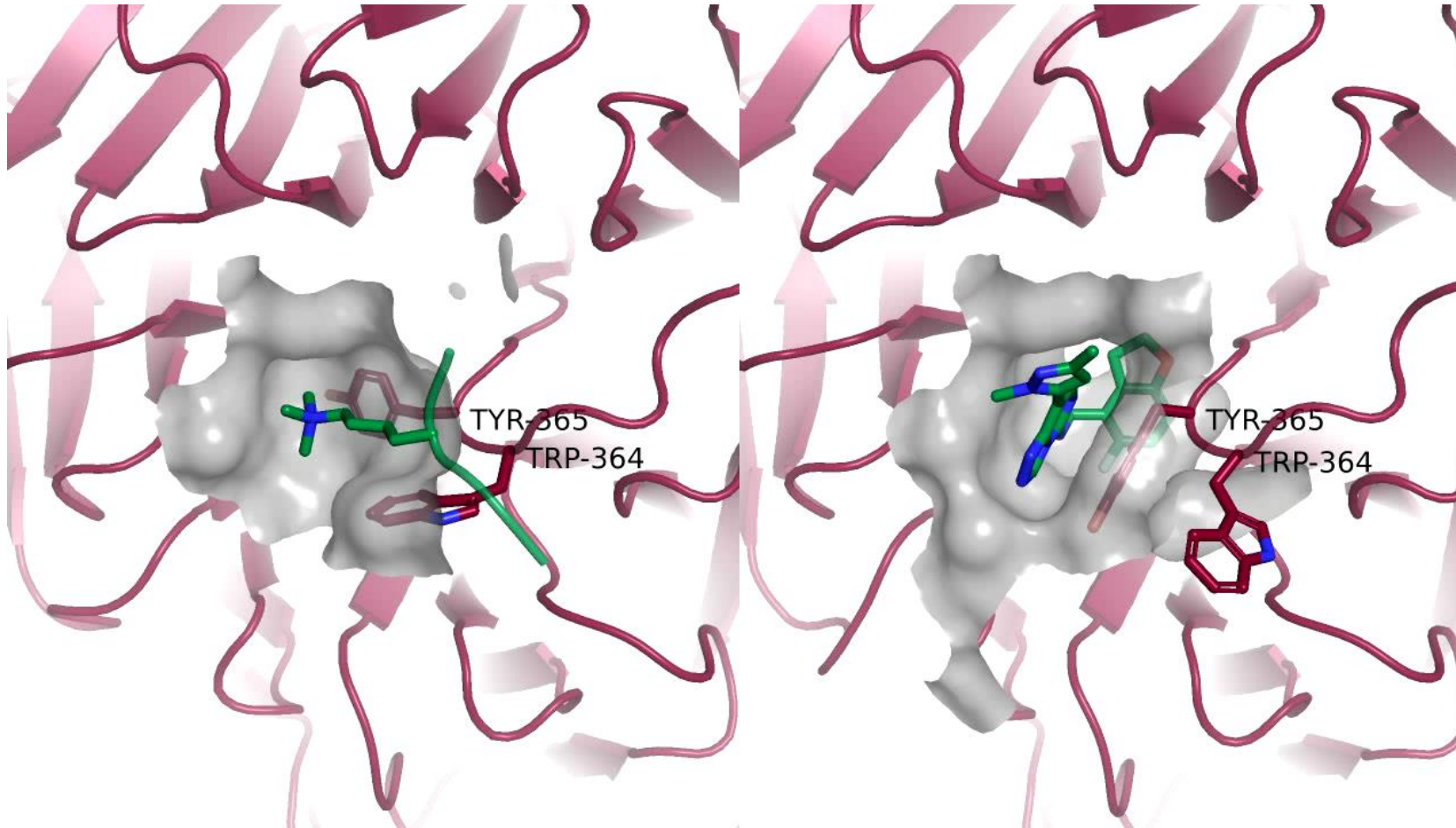
- EZH2 is responsible for histone H3K27 tri-methylation
 - Target of first-generation inhibitors, approvals in epithelioid sarcoma, lymphomas
 - First generation inhibitors have poor drug properties
- EED is responsible for histone binding at H3K27me3
 - Target of ORIC-944

We aimed to allosterically target EED to achieve improved drug properties and meet a best-in-class profile

Allosteric Approach to Targeting EED Subunit Leveraged the Cryptic Pocket

Histone H3K27me3 Binding Pocket in the EED Protein

EED Deep Cryptic Pocket Revealed with Triazolopyrimidine Binding

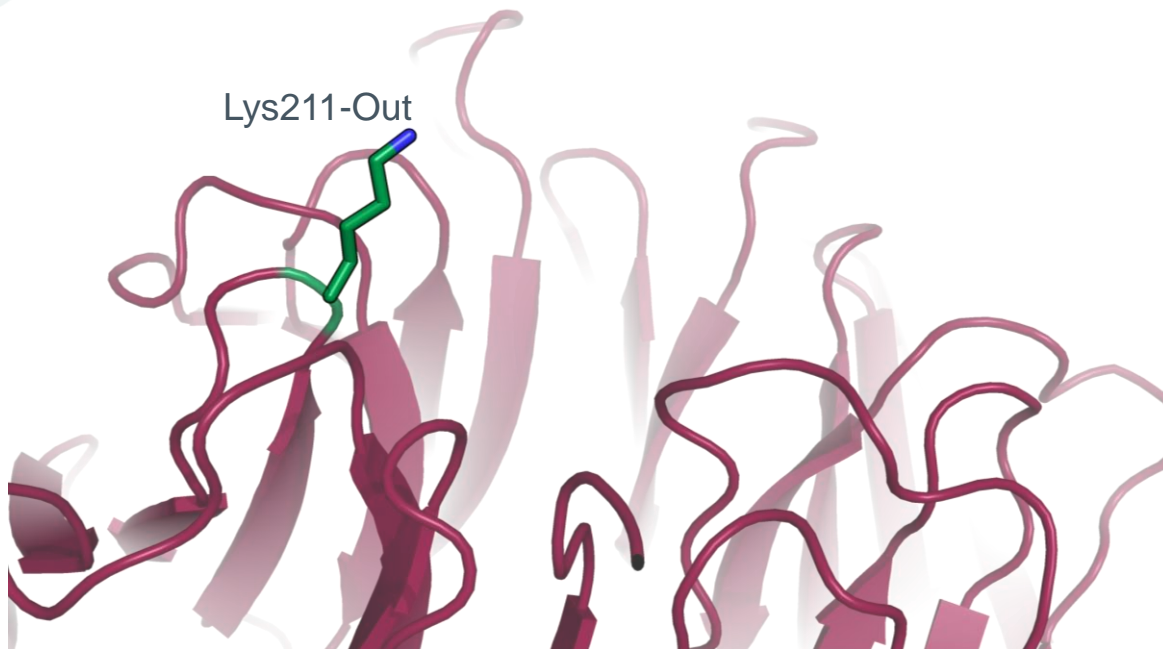


- Initial starting point was a triazolopyrimidine-based literature* compound
- Crystal structure of EED showed inhibitor binding in the H3K27me3 pocket via the 'aromatic cage'
- Upon inhibitor binding, Tyr365 and Trp364 move to form a deep cryptic pocket

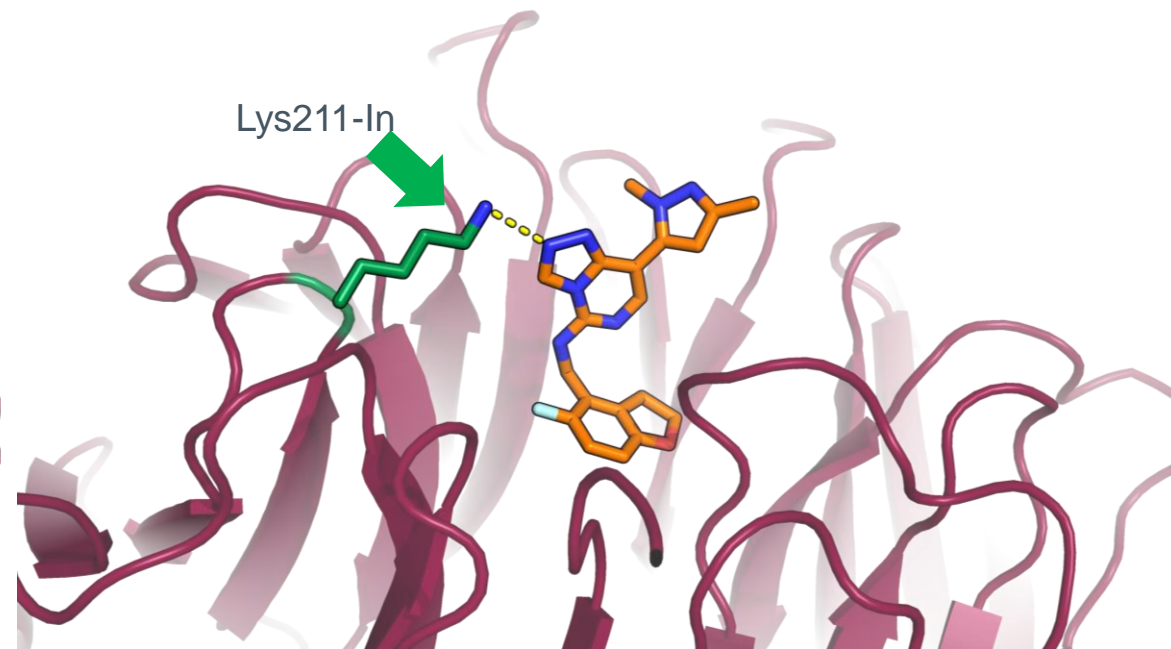
Compounds demonstrated binding to EED in the histone H3K27me3 binding pocket

Distinct Lys211 Rotamers in EED Apo Versus Inhibitor-Bound Structures

EED Apo Structure



EED Co-crystallization with Triazolopyrimidine

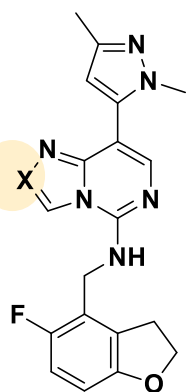
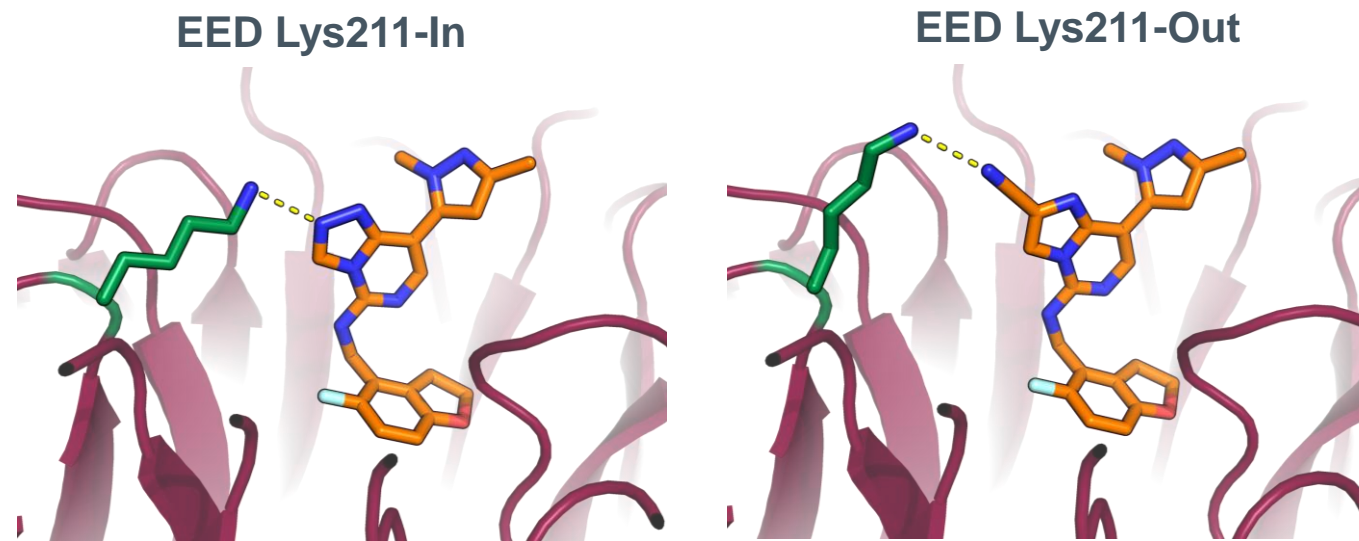


- Evaluation of apo structures revealed the majority were Lys211-Out
- Early inhibitors of EED adopted a Lys211-In conformation with 3.2 Angstrom shift
- Hypothesized that the Lys211-In conformation may be energetically unfavorable
- Initiated structure-based drug design by progressing from an early 2-substituted imidazo-pyrimidine that targets the cryptic pocket with Lys211-Out

Strategy of leveraging Lys211-Out as the favored rotamer, using structure-based-drug-design for differentiation of SAR and physicochemical properties

Substitution at the 2-Position of Imidazo-Pyrimidine Core Resulted in a Lys211-Out Rotamer

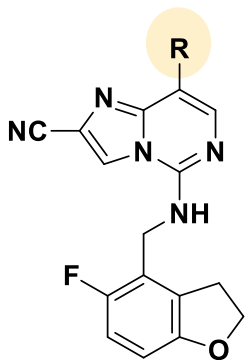
- Progressed from an early 2-substituted imidazopyrimidine* that targets the cryptic pocket
- Addition of a nitrile to the imidazo-pyrimidine core resulted in good potency with Lys211-Out interaction
- Additional changes to the imidazo-pyrimidine core (e.g., 6,6 bicyclics) decreased potency or increased intrinsic clearance



X	Biochemical PRC2 Activity IC ₅₀ (nM)	Cell-based H3K27me3 IC ₅₀ (nM)	Solubility (mg/mL)	HLM Cl _{int} (mL/min/kg)
N	6	10	-	-
C-CO ₂ H	8	>10,000	940	9
C-CONH ₂	11	21	<0.4	69
C-CH ₂ OH	71	-	1.39	10
C-CN	7	37	0.9	101

SAR evaluation to improve solubility and metabolic stability, maintain strong potency

Evaluated Aromatic Head Groups to Achieve Increased Solubility



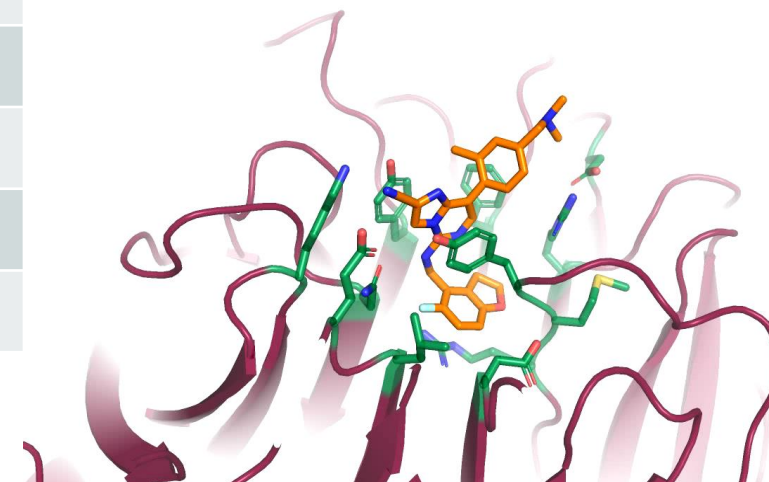
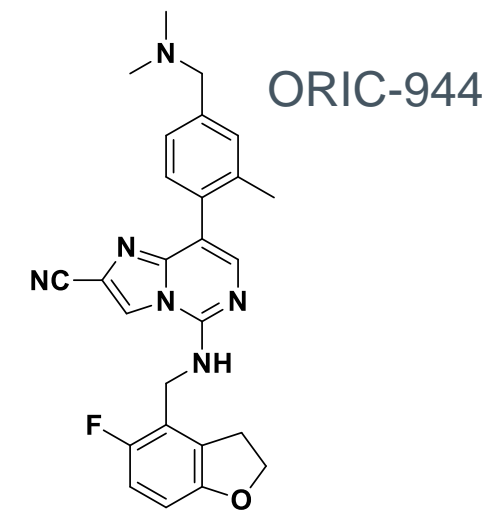
- SAR of the 1,3-dimethylpyrazole was the most productive towards potency, solubility and HLM Cl_{int}
 - Various heterocycles only modestly improved solubility
 - Adding amines to phenyl group significantly increased solubility, with good stability and potency
- Additional SAR exploration revealed the dihydrobenzofuran moiety is optimal to fill the cryptic pocket

R	Biochemical PRC2 IC ₅₀ (nM)	Cell-based H3K27me3 IC ₅₀ (nM)	Solubility (mg/mL)	HLM Cl_{int} (mL/min/kg)
	6	13	0.9	101
	190	385	-	186
	29	189	1.4	77
	2.4	107	2.6	107
	2.5	29	19	41

Investigation into head group was productive in improving solubility while retaining good potency and clearance

ORIC-944 Displays Best-in-Class Potential in Preclinical Drug Properties

Assessment	ORIC-944 Characterization
EED binding EC ₅₀ / Biochemical PRC2 EC ₅₀	106 pM / 16.7 nM
Cell based H3K27me3 IC ₅₀	26.6 nM
Thermodynamic Solubility	11.7 mg/ml
Permeability MDCK P _{app (A-B)} (10 ⁻⁶ , cm/s) / Efflux ratio	8.3 / 1.3
Liver Microsome Clearance (M/R/D/C/H) (mL/min/kg)	56 / 33 / 27 / 37 / 9.0
Hepatocyte Clearance (M/R/D/C/H) (mL/min/kg)	74 / 38 / 24 / 35 / 15
In Vivo Clearance (M/R/D/C) (mL/min/kg)	30 / 60 / 21 / 34
Oral Bioavailability In Vivo F% (M/R/D/C)	64 / 60 / 33 / 17
CYP inhibition (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4)	>10 uM
CYP induction (fold at 3uM) (1A2 / 2B6 / 3A4)	0.8 / 1.3 / 0.7

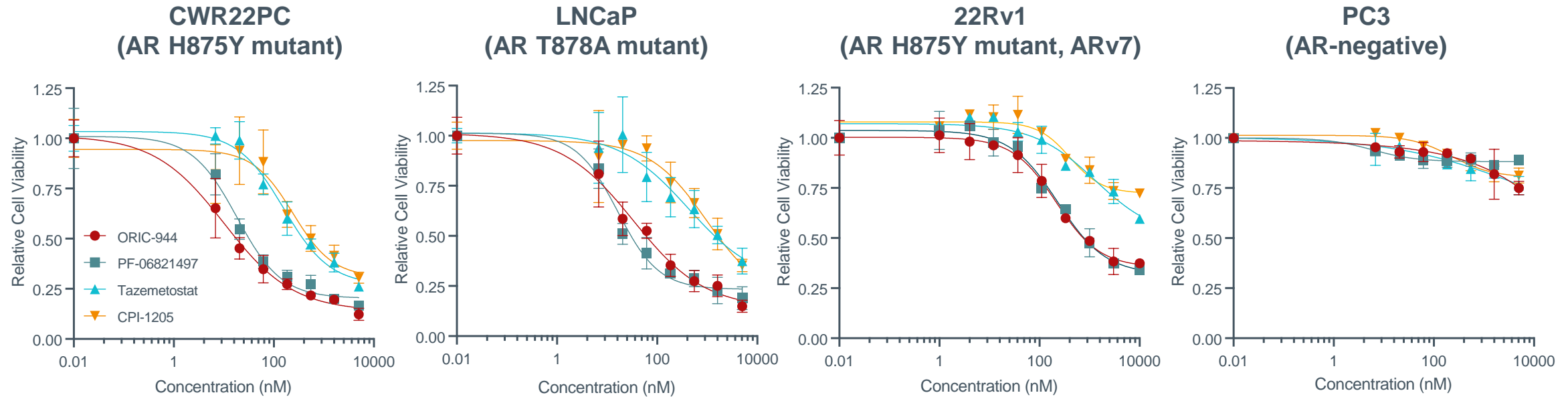


ORIC-944 has picomolar biochemical potency, nanomolar cell potency, and a clean CYP profile

Note: Binding assay measures inhibition of recombinant EED to bind biotinylated H3K27me3 peptide. Biochemical IC₅₀ based on PRC2 complex hotspot methyltransferase assay and monitors transfer of tritiated methyl groups from SAM to core histone proteins; Cell based H3K27me3 assay performed in Pfeiffer cells in ELISA format. Thermodynamic solubility at pH 2 room temperature

ORIC-944 Cell Potency in AR-positive Prostate Cancer Cell Lines

Cell Growth Assay Comparing ORIC-944 EED Inhibitor to EZH2 Inhibitors



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 prostate cancer cell lines is superior to first generation EZH2 inhibitors tazemetostat and CPI-1205, and comparable to PF-06821497

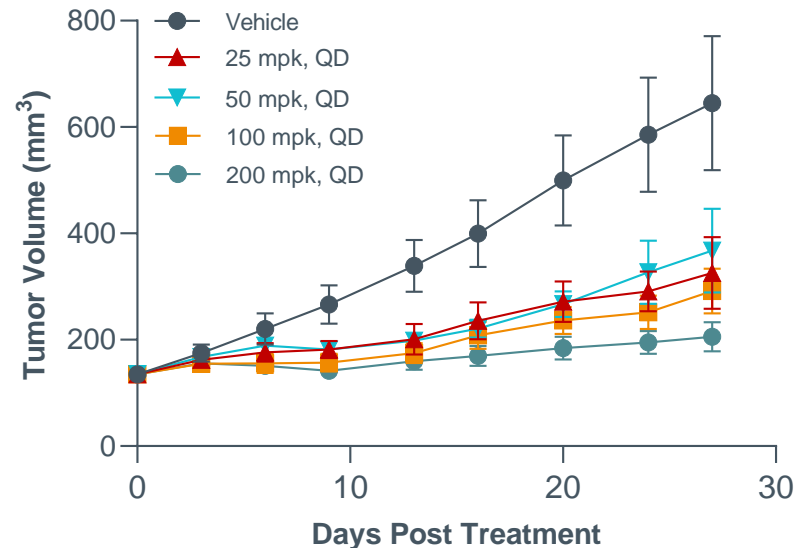
ORIC-944 Single-Agent In Vivo Efficacy Corresponds with Tumor PD

In Vivo Efficacy and PD in Prostate Cancer Model Resistant to AR Inhibitors

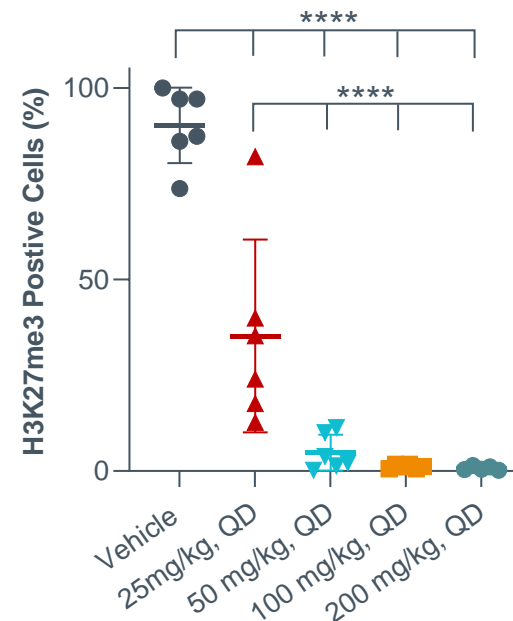
ORIC-944 Inhibited Tumor Growth and Decreased H3K27me3 with No Significant Body Weight Loss

ORIC-944 Results in Upregulated Expression of PRC2 Target Genes

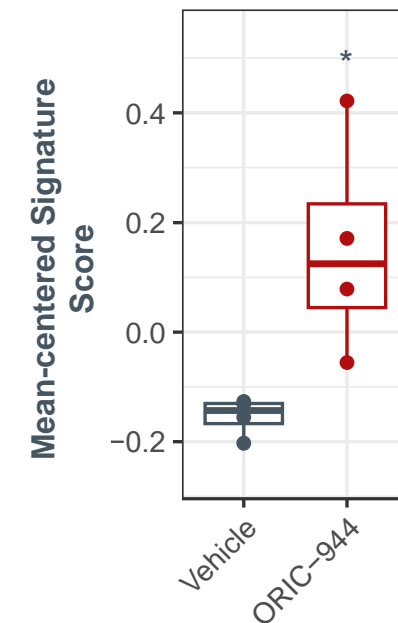
ORIC-944 Efficacy in 22Rv1 Xenograft (AR H875Y mutant, ARv7)



H3K27me3 in End-of-Study 22Rv1 Tumors



Expression of Known PRC2 Target Genes in End-of-Study Tumors



ORIC-944 inhibits tumor growth and decreases H3K27me3 in prostate cancer xenografts, resulting in increased expression of known PRC2 methylation target genes

ORIC-944 Drug Properties versus Comparators Illustrates Best-in-Class Potential

Head-to-head Preclinical Studies of Clinical Comparators

Clinical Compound	Solubility	Mouse Oral Bioavailability	Half-life in Mice	CYP Inhibition IC50	CYP Induction	Clinical Half-life, Dosing
ORIC-944 EED inhibitor	11.7 mg/ml	64%	3-5 hr PO 2.5 hr IV	>10 uM	Clean	~20 hrs QD
PF-06821497 EZH2 inhibitor	0.5 mg/ml	7.6%	1.2 hr PO 2.4 hr IV	>10 uM	Clean	<4 hrs* BID
Tazemetostat EZH2 inhibitor	6.9 mg/ml	34%	0.8 hr PO 2.3 hr IV	1-4 uM + time-dependent inhibition	Strong 3A4	~3 hrs* BID
CPI-0209 EZH2 inhibitor	4.9 mg/ml	11%	0.5 hr PO 1.9 hr IV	>10 uM	Moderate 3A4	~6 hrs* QD

ORIC-944 improves solubility, oral bioavailability, half-life, and CYP issues observed in comparator compounds

Source: ORIC data on file. Thermodynamic solubility at pH 2 room temperature

Note: *Published Data. Clinical half-life estimated for PF-06821497 based on published Phase 1 data. Clinical half-life for CPI-0209 estimated for RP2D of 375 mg QD.

Initial Clinical Data Demonstrates ORIC-944 Potential Best-in-Class PK Profile

Preliminary Phase 1b Pharmacokinetic Data

Clinical PK Reveals ~20 hour Half-life and Increasing Exposures with Dose Escalation

Clinical Cohort	Estimated t _{1/2} (hours)*
Dose level 1 (100mg QD)	~17
Dose level 2 (200mg QD)	~19
Dose level 3 (400mg QD)	~18
Dose level 4 (600mg QD)	~26
Dose level 5 (900mg QD)	~20

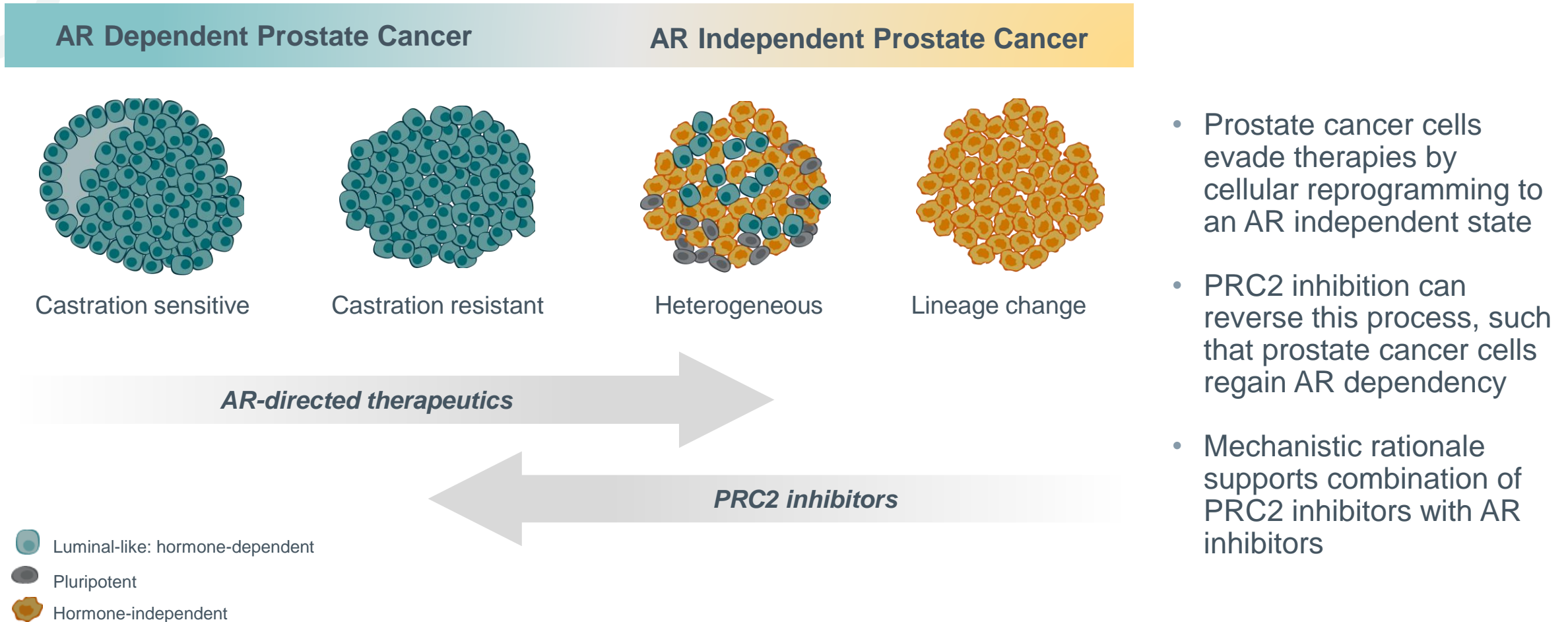
Excellent PK Profile Observed for ORIC-944 in Patients with Prostate Cancer

- Increased exposure with dose level
 - No sign of CYP autoinduction that is observed with first-generation PRC2 inhibitors
- Clinical half-life of approximately 20 hours
 - Supports QD dosing
 - Superior to other PRC2 inhibitors
- Low peak-to-trough may facilitate better efficacy and safety

Dose exploration continues with favorable plasma half-life of approximately 20 hours and PK consistent with best-in-class drug properties

*The t_{1/2} values at Cycle 2 Day 1 were roughly estimated with a terminal phase spanning less than 2 half-lives. Mean half-life is shown for each cohort of patients.

PRC2 Epigenetic Dysregulation Plays a Key Mechanistic Role During the Progressive Reprogramming of Prostate Cancers Treated with AR Inhibitors



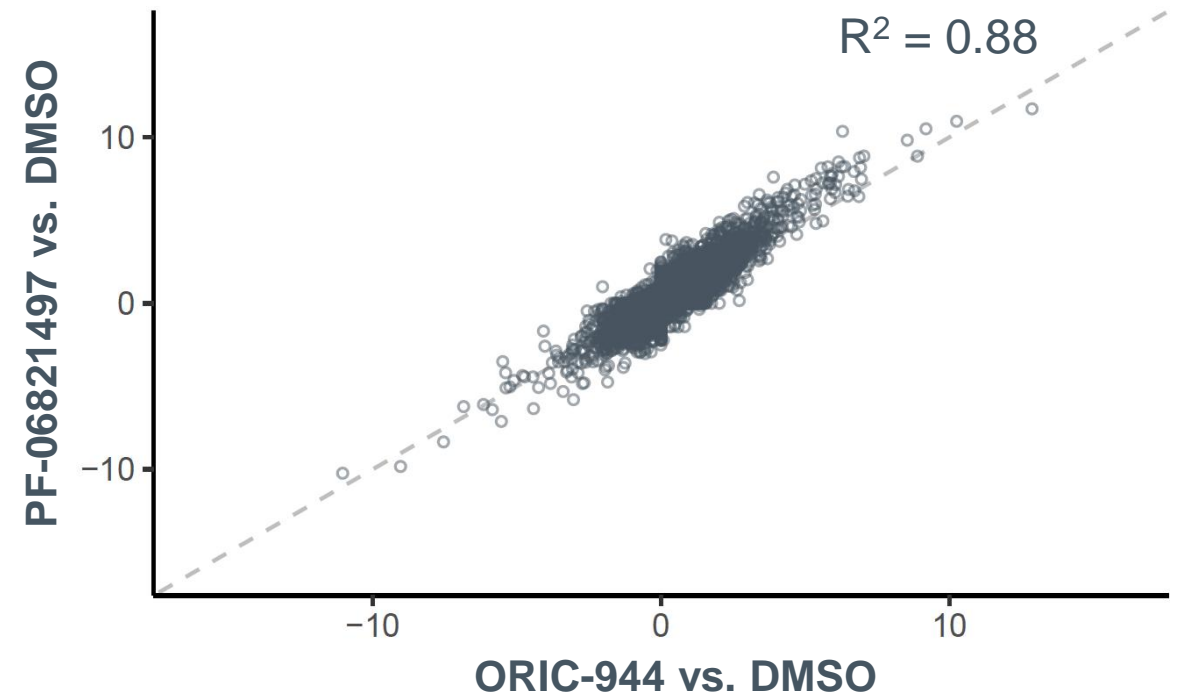
Therapeutic potential of PRC2 inhibitors in prostate cancer is maximized in combination with AR inhibitors

RNA-Seq Analysis in Prostate Cells Demonstrates Comparable Impact on Transcription for ORIC-944 EED Inhibitor and PF-06821497 EZH2 Inhibitor

Identifying Impact of ORIC-944 or PF-06821497 Treatment on Gene Expression

- LNCaP prostate cells treated for 7 days with either EED inhibitor or EZH2 inhibitor vs DMSO
- Transcriptional effects determined by RNA sequencing
- Each dot represents a gene's differential expression (t-statistics) by treatment
- Expression changes by treatment are highly correlated with $R^2 = 0.88$

Equivalent Transcriptional Changes Observed with EED Inhibitor and EZH2 Inhibitor Treatment

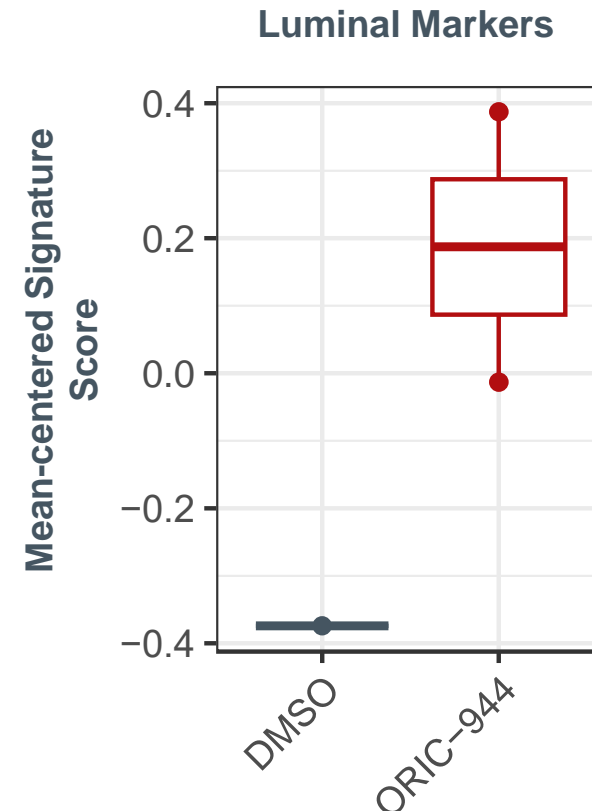
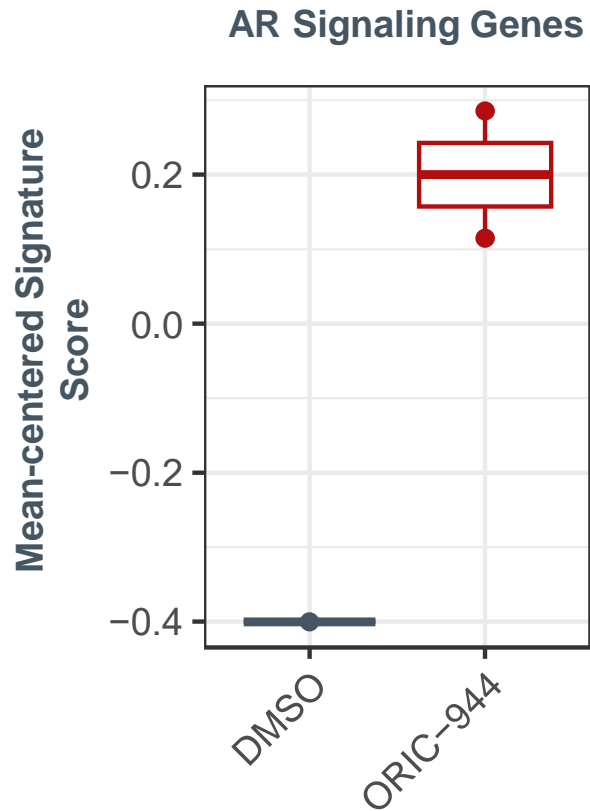


EED and EZH2 inhibitors have the same transcriptional effects in prostate cancer cell lines

ORIC-944 Increases AR Signaling and Induces Luminal State in Prostate Cancer Cells

ORIC-944 Enhanced AR Signaling in LNCaP Prostate Cancer Cells

Increased Expression of Luminal Markers Indicate Re-differentiation of LNCaP Prostate Cancer Cells



More info in
Minisymposium
April 9th, 2.50pm
Ballroom 6 DE
(Abstract #6586)

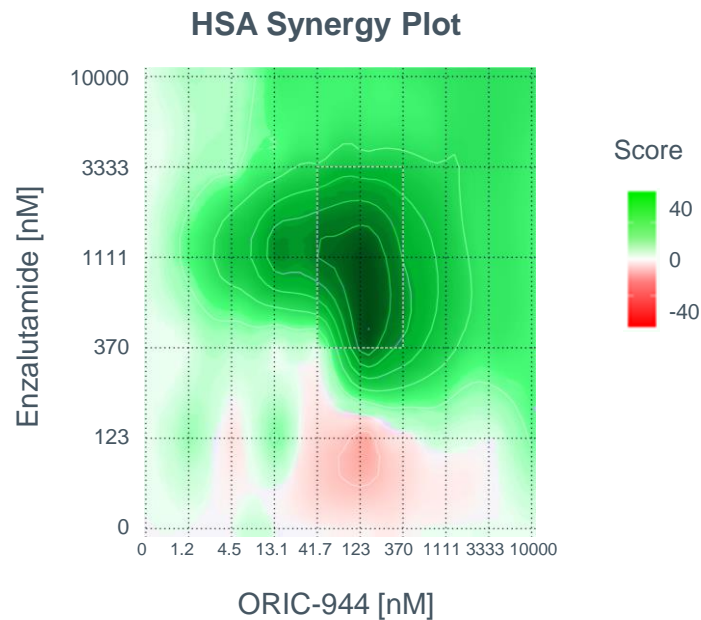
Increased AR signaling and luminal cell state markers support the hypothesis that treatment with PRC2 inhibitors restores a cell state which has enhanced sensitivity to AR inhibitors

Note: In vitro LNCaP cells in FBS treated with 1uM compound for 7 days. Boxplots show average median-centered expression of luminal markers [Liang et al. Prostate Cancer and Prostatic Diseases (2022)] and 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)]).

ORIC-944 Synergizes with AR Inhibitors in Prostate Cancer Cells

Combination Potential of PRC2 Inhibition and AR Inhibition

In Vitro Combination of ORIC-944 with AR Inhibitor at Clinically Relevant Concentrations



- 14 day CellTiter-Glo assay
- C4-2 prostate cancer cell line
- Synergy scoring via multiple models*

In Vitro Synergy in Prostate Cancer Cells Treated with ORIC-944 and AR inhibitor

Treatments	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)

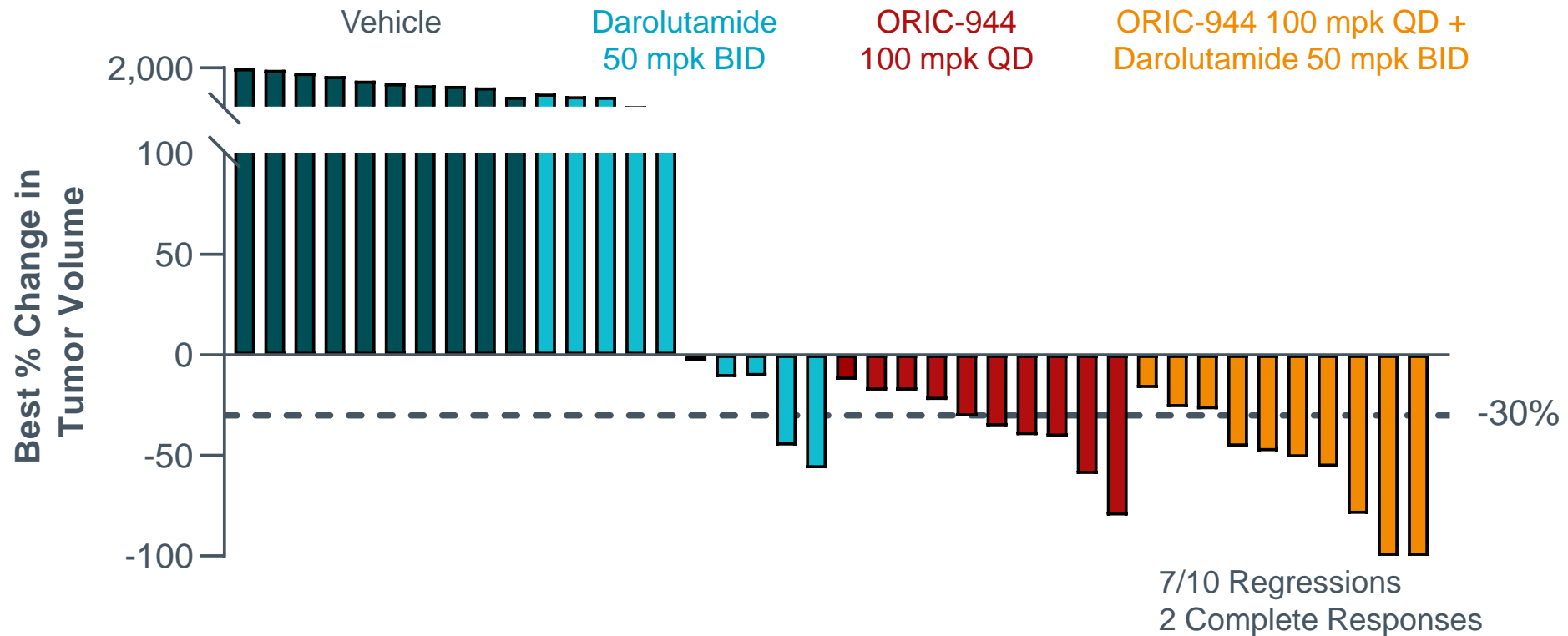
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ORIC-944 synergizes with AR inhibitors in prostate cancer cells, at concentrations relevant to clinic

ORIC-944 Leads to In Vivo Regressions in Combination with AR Inhibitor in Prostate Cancer Xenograft Tumors

In Vivo Combination Efficacy in Prostate Cancer Model

ORIC-944 + AR Inhibitor Combination Increases Depth of Regression and Induces Complete Responses in 26 Days

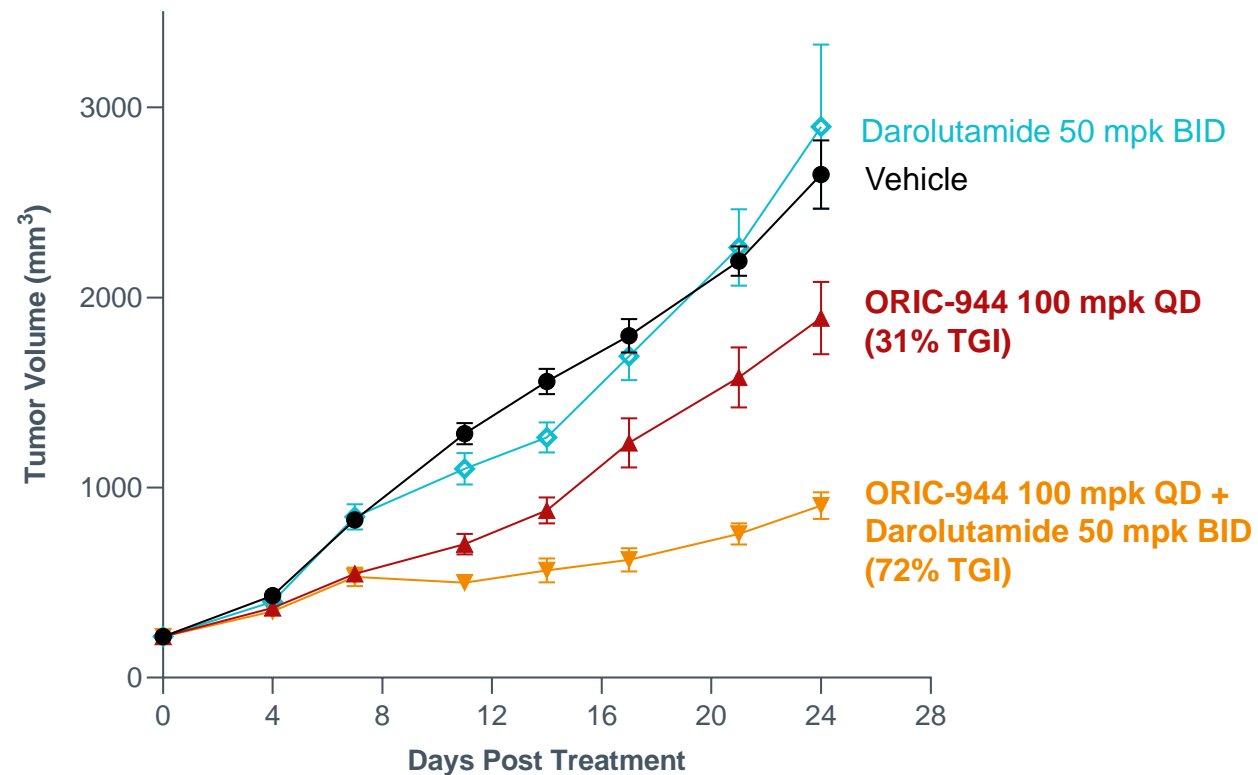


Combination of ORIC-944 with darolutamide leads to increased regressions including complete responses; Exposures in combination comparable to single agent doses, indicating no drug-drug-interaction; no drug-related tolerability issues

In Vivo Synergy of ORIC-944 with AR Inhibitor in Prostate Cancer Xenograft Model

In Vivo Combination Efficacy in Resistant Prostate Cancer Model

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

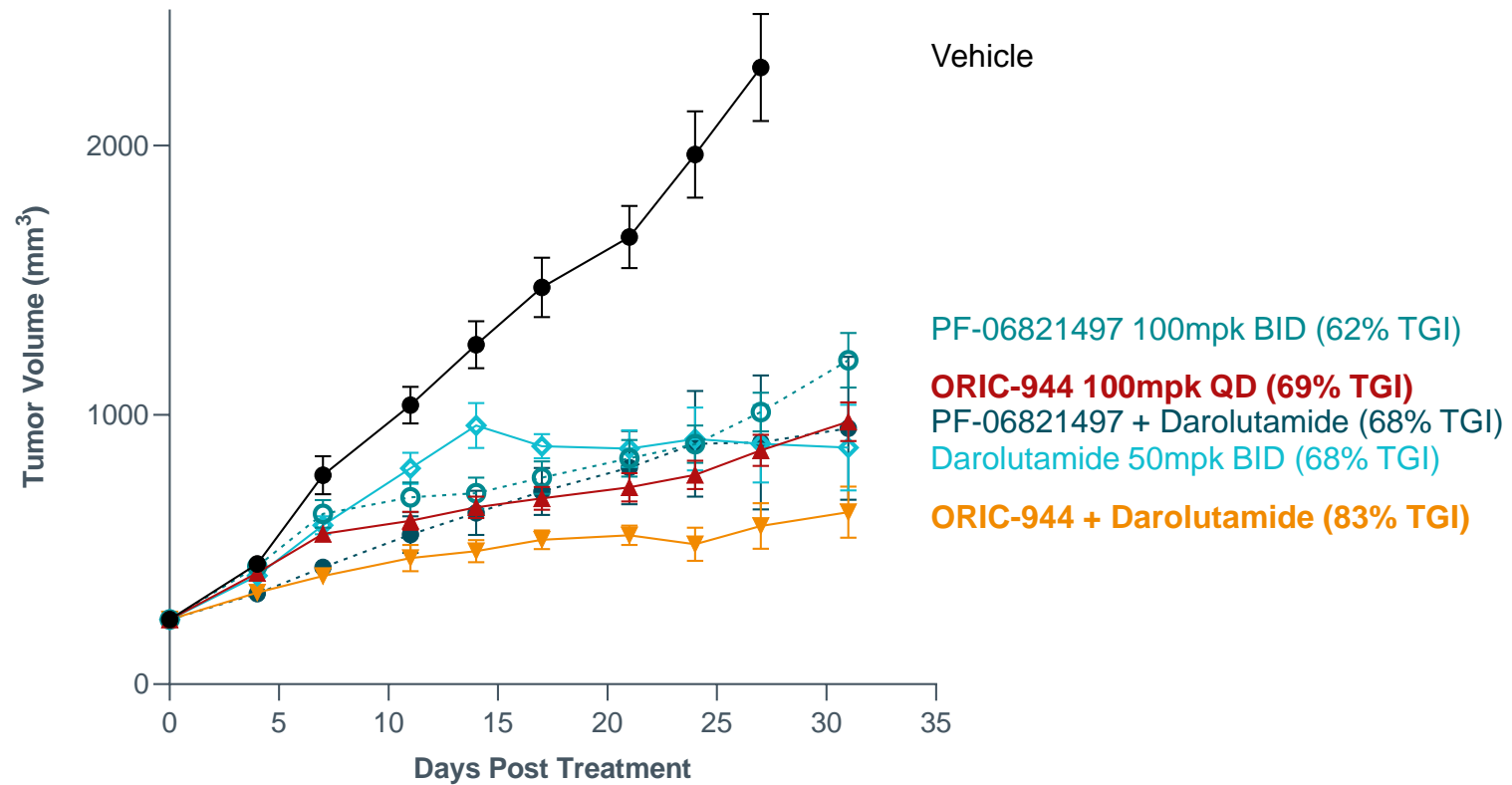


ORIC-944 combination with AR inhibitor improves therapeutic activity in AR inhibitor refractory setting

ORIC-944 Combination with AR Inhibitor Provides Better Anti-tumor Activity than Either Agent Alone

In Vivo Combination Efficacy in Prostate Cancer Model Responsive to AR Inhibition

ORIC-944 and Darolutamide Combination May Provide Better Activity than PF-06821497 Combination

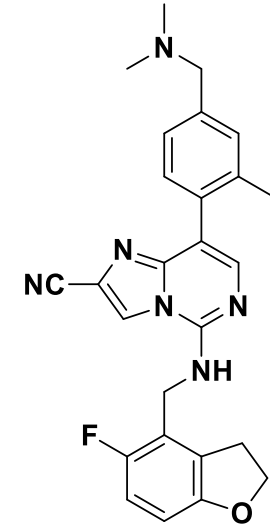


ORIC-944 addition to AR inhibitor improves therapeutic activity

ORIC-944 Summary

ORIC-944 Preclinical Characterization

- Discovery program aimed to create PRC2 inhibitor with best-in-class properties
 - ✓ Allosteric targeting of a cryptic pocket in EED
 - ✓ Leveraged Lys211-out
 - ✓ SAR focus on solubility and metabolic stability
- ORIC-944 key properties:
 - ✓ Strong potency
 - ✓ Clean CYPs
 - ✓ Excellent PK
 - ✓ MOA induces luminal cell state and increases AR signaling in prostate cancer models
 - ✓ Synergistic with AR inhibitors in prostate cancer models



ORIC-944

Initial Clinical Dose Escalation Results for ORIC-944

- ✓ Half-life ~20 hours supports QD dosing
- ✓ Maximal decrease ($\geq 75\%$) in H3K27me3 in monocytes from peripheral blood
- ✓ Well tolerated to date, with only grade 1 and 2 treatment related adverse events at dose levels less than 900 mg QD

ORIC-944 demonstrated potential best-in-class drug properties with favorable safety and strong PK profile supporting QD dosing; Initiating clinical combination study with AR inhibitor(s)

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**Presentation
access**



Patients and their families and caregivers

Mechanistic insights will be provided in Minisymposium session on April 9th at 2.50pm in ballroom 6 DE, Abstract #6586

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