# Rinzimetostat Blockade of PRC2 Activity, a Key Mechanism of Treatment Resistance, Improves Response of Androgen Receptor Pathway Inhibition Across a Spectrum of Prostate Cancer Models

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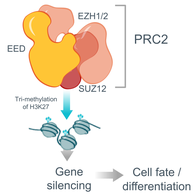
Poster #7132

## BACKGROUND

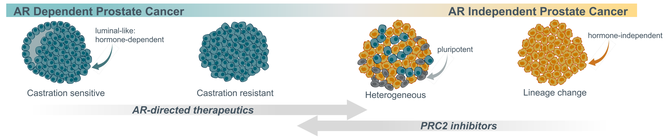
**Polycomb Repressive Complex 2 (PRC2):**

- Comprised of three core subunits EZH2, EED and SUZ12
- Methylates histone H3 at lysine 27 (H3K27), leading to long-term transcriptional modulation with implications for cell growth and differentiation
- Dysregulated in multiple solid tumors, with increased activity associated with poor prognosis in prostate cancer patients




**PRC2 Inhibition in Prostate Cancer:**

- Development of tumor cell plasticity contributes to resistance to androgen receptor (AR) pathway inhibitor (ARPI) therapies; inhibiting PRC2 can reverse this process
- Emerging clinical trial data suggest that combining AR and PRC2 inhibitors may improve outcomes for patients




**Rinzimetostat (ORIC-944) Targets PRC2**:

- Rinzimetostat is a highly selective, orally bioavailable inhibitor of PRC2 via binding the EED subunit and is currently proceeding to late-stage clinical development
- See poster #7120 for rinzimetostat's best-in-class drug properties

## 1. ORIC's Prostate Cancer Transcriptome Atlas

12 studies of publicly-available RNA-seq data

10 institutions: NIH, NCI, Chungbuk Hospital, Porto Oncology Institute, Moscow Research Center, Vancouver Prostate Centre, Morales Meseguer University, Stand-Up 2 Cancer, Dana Farber, Fred Hutch

6 countries: US, UK, Korea, Russia, Canada, Spain

5 patient states: non-tumor normal (n=175), primary CSPC (n=686), mCSPC (n=24), mCRPC (n=223), NEPC (n=45)

**Figure 1.** Publicly accessible datasets consisting of GTEx, GSE80609, TCGA, GSE120741, PRJNA477449, GSE289466, PRJEB21092, GSE268309, phs000915, phs000909, GSE228283 and GSE126078 was assembled. These represent primary, castration-sensitive (CSPC), metastatic castration-resistant (mCRPC), and neuroendocrine prostate cancers (NEPC).

## 2. Tumor Transcriptomes Mirror the Trajectory of Prostate Cancer Disease Progression

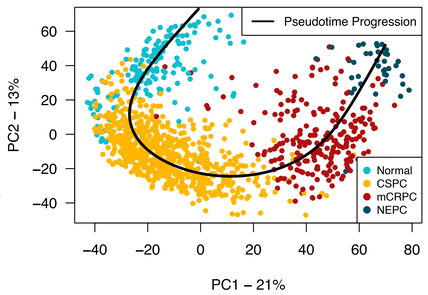



**Figure 2.** Principal component analysis of transcriptomes (n = 1,153) with their 1,626 most variable genes, colored by disease state (in legend). The solid black curve is the pseudotime trajectory inferred by Slingshot [Street et al. BMC Genomics (2018)] fit on the first 2 principal components and on 4 clusters of the data.

## 3. Pseudotime Trajectory Captures Gene Expression Patterns Underlying Therapy Resistance and Lineage Transitions

**Transcriptional Trajectories Reveal Molecular Mechanisms Underlying Disease Progression**

**Disease Stage Associates with Cell State and Therapy Resistance**

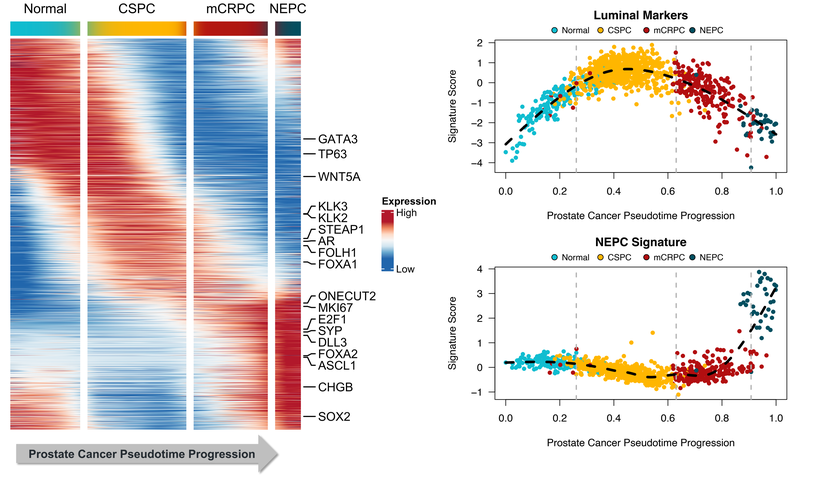



**Figure 3. Left.** 1,944 variable genes in the atlas were modeled as a function of pseudotime, identifying a gradient of transcriptional dynamics across disease progression. **Right.** Expression of luminal markers (top) [Liang et al. Prostate Cancer and Prostatic Diseases (2022)] and the neuroendocrine signature (bottom) [Beltran et al. Nat Med (2016)] across pseudotime. Signatures are calculated as the average of mean-centered log2(CPM+1) expression of each gene. Points are individual tumors and the dashed black line is the smooth function of change across pseudotime modeled by a generalized additive model.

## 4. PRC2 Activity Demonstrates an Early Increase During the Primary Stage of Prostate Cancer and Is High in Metastatic Disease

**PRC2 Activity Increases in Primary Prostate Tumors**

**PRC2 Activity Shows High Levels in mCSPC Tumors**

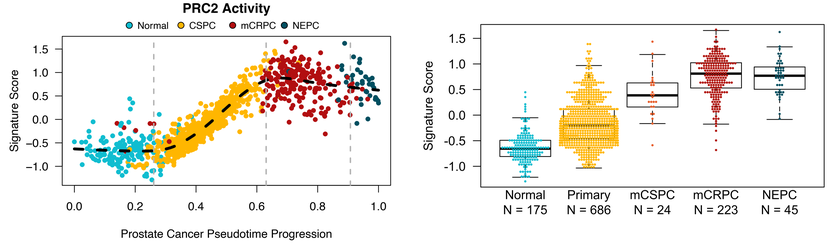
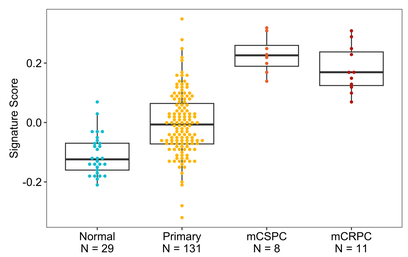



**Figure 4. Top-Left.** PRC2 activity signature calculated as the negative of the averaged mean-centered log2(CPM + 1) expression of PRC2 target genes [Yu et al. Cancer Res (2007)] for each tumor plotted across pseudotime. **Top-Right.** PRC2 activity signature across prostate cancer disease states in ORIC's Prostate Cancer Atlas. **Right.** PRC2 activity signature across prostate cancer disease states from the GSE21032 dataset generated with the Affymetrix Human Exon 1.0 ST microarray [Taylor et al. Cancer Cell (2010)].

**PRC2 Activity Upregulation Is Confirmed in an Independent Study (Taylor et al. 2010)**




## 5. PRC2 Activity Associates with Poor Survival in Localized Primary Prostate Cancer

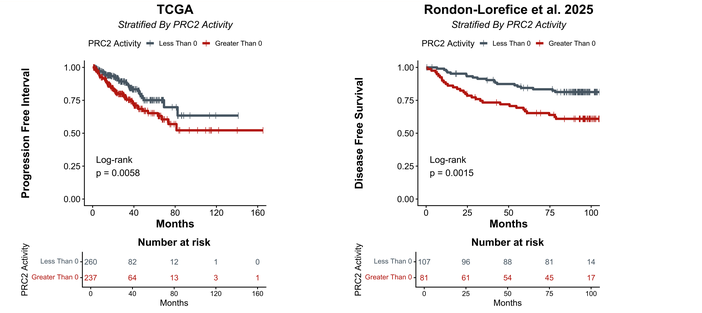
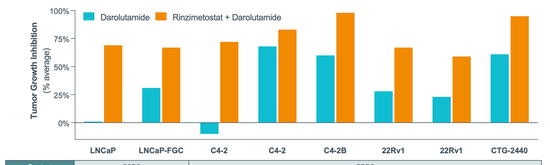



**Figure 5.** Kaplan-Meier survival plots showcase that high PRC2 activity associates with significantly reduced progression free survival in TCGA [The Cancer Genome Atlas Research Network. Cell (2016)] (left) and disease-free survival in the GSE288484 dataset [Rondon-Lorefice et al. Mol Oncol (2025)]. P-value is calculated by the log-rank test.

## 6. Rinzimetostat Improves Efficacy of AR Inhibitor Across CSPC and CRPC Models In Vivo




| Context | CSPC | | CRPC | | | | | |
|---|---|---|---|---|---|---|---|---|
| Setting | Intact | Intact | Intact | Castrated | Intact | Intact | Intact, daro pre-tx | Intact |
| AR Alteration | AR T878A | | | | | AR H875Y, ARv7 | | AR WT |
| Tissue of Origin | ADT-naive patient, lymph node biopsy | LNCaP sub-line, selected for faster growth | LNCaP sub-line, aggressive variant grows in intact or castrated mice | | C4-2 mouse bone metastasis | Castration-resistant CWR22R xenograft | | Post-abiraterone, post-chemo patient, bone biopsy |
| Chemo Sensitivity | Yes | Yes | Yes | | Yes | No | | No |
| PFS (median, days) for vehicle / daro / rinzi / combo | 18 / 18 / 21 / 23 | 18 / 25 / 19.5 / NR | 11 / 11 / 17 / NR | 11 / 12.5 / 27 / NR | 18 / 19.5 / NR / NR | 16 / 16 / 20 / NR | 25 / 25 / 25 / NR | 24 / 44.5 / 27.5 / 55 |

**Figure 6.** Results of in vivo efficacy studies displayed as tumor growth inhibition, calculated as [1-(TVtx, day last – TVtx, day 0)/(TVveh, day last – TVveh, day 0)] × 100%; TV, tumor volume. Progression defined as TV reaching 800 or 1000 $mm^3$, or mortality. Treatments were either single agent darolutamide (blue) at 50 mg/kg BID PO, or darolutamide at 50 mg/kg BID in combination with rinzimetostat at 100 mg/kg QD PO (orange). Prostate cancer model annotations include castration-sensitive vs castration-resistant context, whether grown in intact or castrated mice, AR genotype, the source/biopsy from which each model was derived, chemotherapy sensitivity defined as TGI>40% and progression free survival. WT: wildtype, PFS: progression free survival.

## 7. PRC2 Inhibition Restores Lineage Identity and ARPI Sensitivity

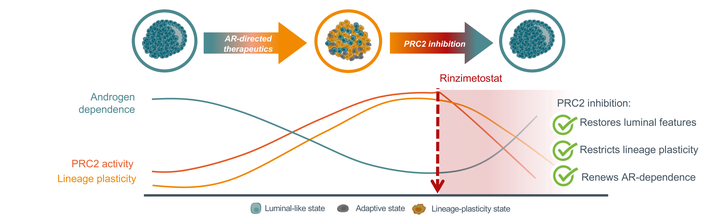



**Figure 7.** Prostate adenocarcinoma is driven by AR. Androgen deprivation and ARPIs are highly effective treatments, but therapeutic resistance eventually develops. PRC2 activity associates with prostate cancer progression and lineage plasticity providing a therapeutic rationale for targeting PRC2. PRC2 inhibition achieves antitumor activity in hormone-depleted contexts and in combination with ARPI.

## CONCLUSIONS

- PRC2 activity associates with disease progression, lineage plasticity, and treatment resistance, highlighting PRC2 as a promising therapeutic target in prostate cancer
- PRC2 activity rises early during the primary stage of prostate cancer and is high in metastatic disease
- Elevated PRC2 activity associates with poor survival in localized primary prostate cancer, suggesting a key role early in the disease
- Rinzimetostat in combination with ARPI darolutamide demonstrated antitumor activity across a breadth of in vivo models representing the prostate cancer continuum
- Taken together, rinzimetostat represents a promising therapy to re-sensitize resistant tumors to ARPIs and block prostate tumor adaptation

***Himalayas-1 Phase 3 study of rinzimetostat in combination with darolutamide initiating in 2026***