

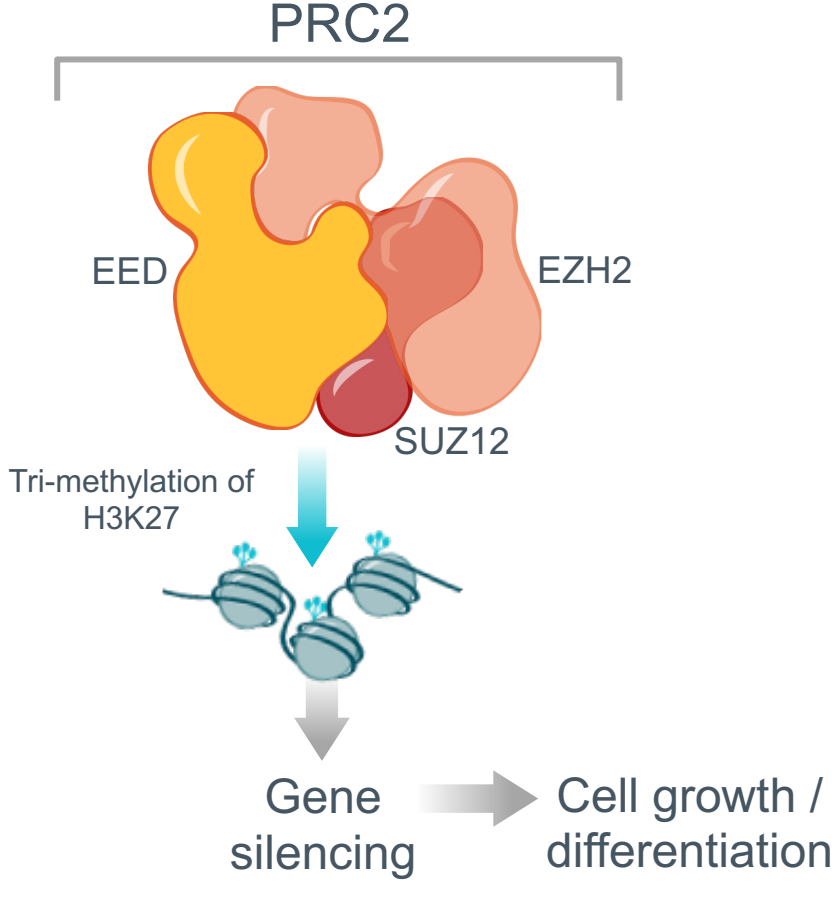
Rinzimetostat, a Next Generation PRC2 Inhibitor, Enhances Luminal Fate and AR Signaling While Restricting Lineage Plasticity in Preclinical Models and Demonstrates Mechanistic Proof-of-Concept in Samples from Patients with mCRPC

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Background of Targeting PRC2

Polycomb Repressive Complex 2 (PRC2):

- Is comprised of three core subunits: EZH2, EED and SUZ12
- Methylates histone H3 lysine 27 (H3K27), leading to transcriptional modulation that can impact cell growth and differentiation
- Has two druggable subunits, EZH2 and EED, with first generation compounds having suboptimal drug properties

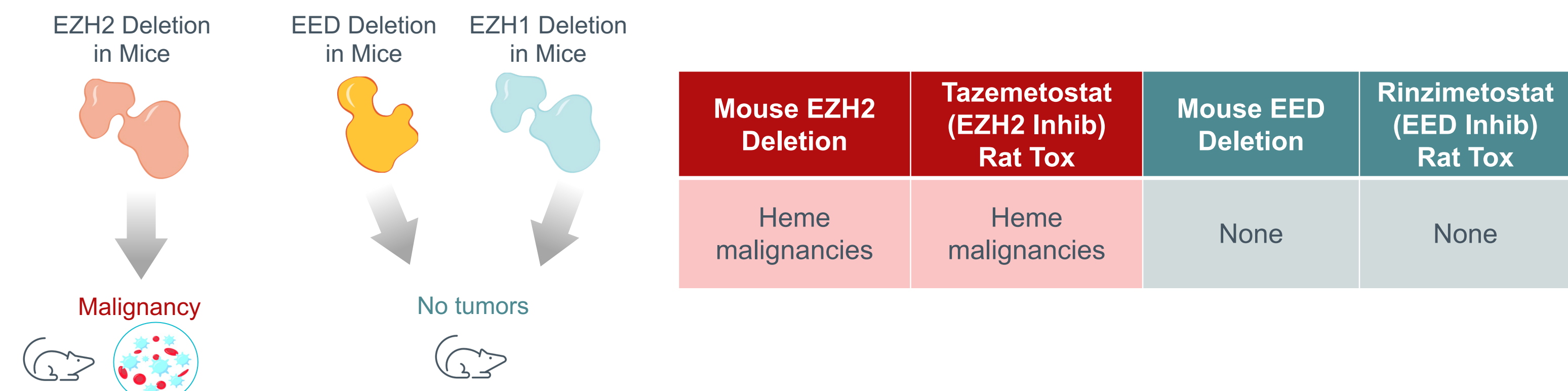


Rinzimetostat Shows Potential Best-in-Class Drug Properties in Head-to-head Preclinical Studies of Clinical Comparators

Clinical Compound	Solubility	Mouse Oral Bioavailability	Mouse Half-Life	CYP Inhibition IC50	CYP Induction	Clinical Half-life, Dosing
Rinzimetostat EED inhibitor	11.7 mg/ml	64%	3-5 hr PO 2.5 hr IV	>10 uM	Clean	~20 hrs QD
Mevrometostat 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
Tulmimetostat EZH1/2 inhibitor	4.9 mg/ml	11%	0.5 hr PO 1.9 hr IV	>10 uM	Moderate 3A4	~6 hrs* QD
Valemetostat EZH1/2 inhibitor	>11 mg/ml	25%	2.8 hr PO 2.5 hr IV	>10 uM	Clean	~11 hrs* QD
Igermetostat EZH2 inhibitor	>11 mg/ml	9%	0.8 hr PO 1.9 hr IV	3 uM 2D6	Moderate 3A4	NA, BID

ORIC data on file. Thermodynamic solubility at pH 2 room temperature. CYPs analyzed are 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 for inhibition, and 1A2, 2B6 and 3A4 for induction assessments.
*Published Data. Clinical half-life estimated for mevrometostat based on published Phase 1 data. Clinical half-life for tulmimetostat estimated for RP2D of 375 mg QD. Valemetostat clinical half-life, Keam *et al.*, Drugs 2022. NA: not available.

Targeting EZH2 Exhibits Higher Risk for Hematologic Tumorigenesis in Rodents than Targeting EED

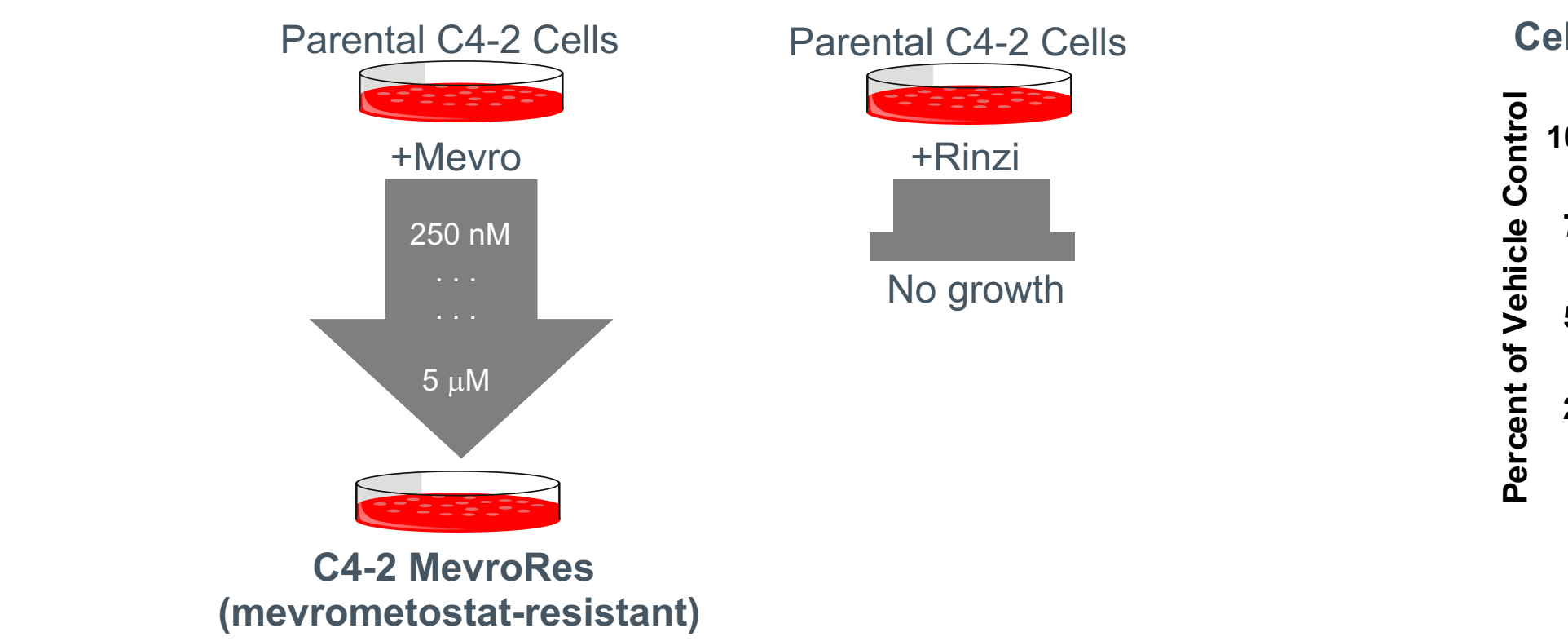


EZH2 genetic deletion in mice induced hematologic malignancies, consistent with tazemetostat results in 13-week rat GLP tox study demonstrating tumorigenesis. EED genetic deletion in mice did not induce hematologic malignancy, consistent with rinzimetostat 13-week rat GLP tox study demonstrating no tumorigenesis.

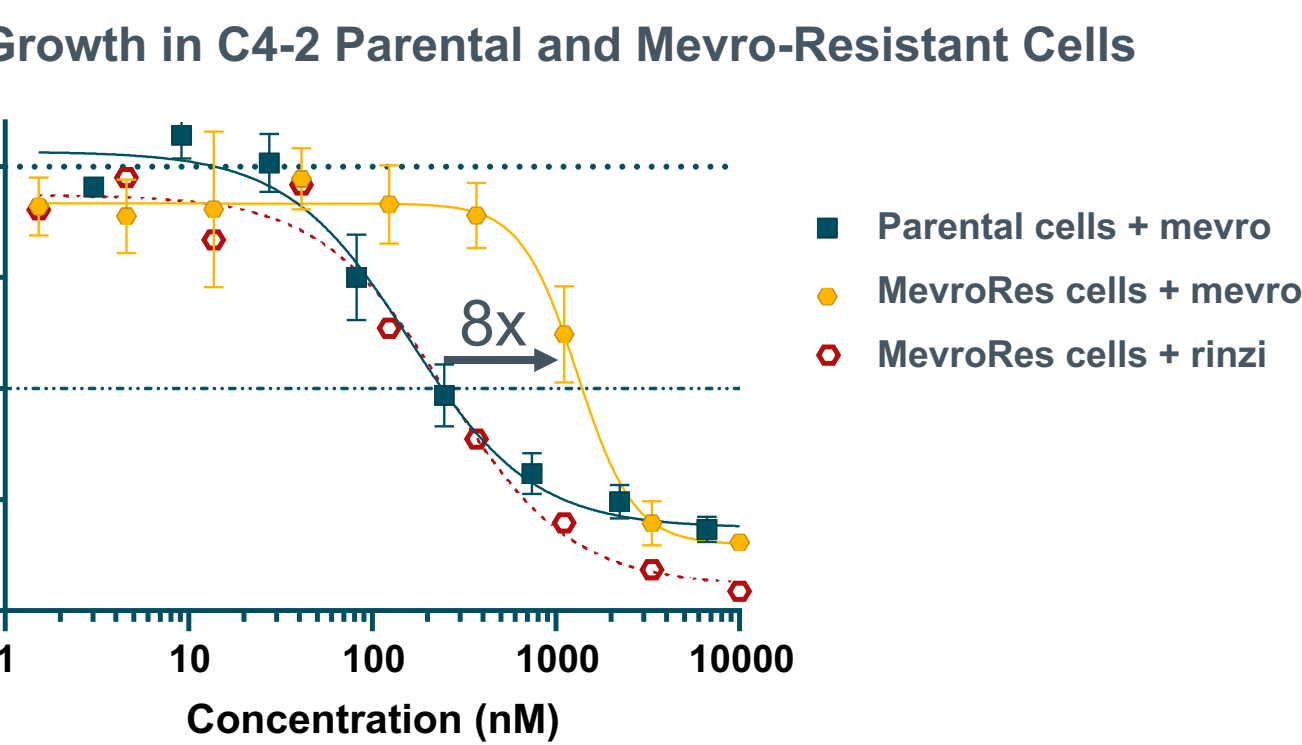
References: Mochizuki-Kashio *et al.*, Blood 2015; Simon *et al.*, Genes and Dev 2012; Huafeng Xie *et al.*, Cell Stem Cell 2014. Tazemetostat GLP tox summary available at <https://dailymed.nlm.nih.gov/dailymed/>

Targeting EED May Avoid Acquired-Resistance Mechanisms Observed for EZH2

Acquired Resistance to Mevrometostat Arose Rapidly, Though Rinzimetostat Outgrowth Has Not Been Observed

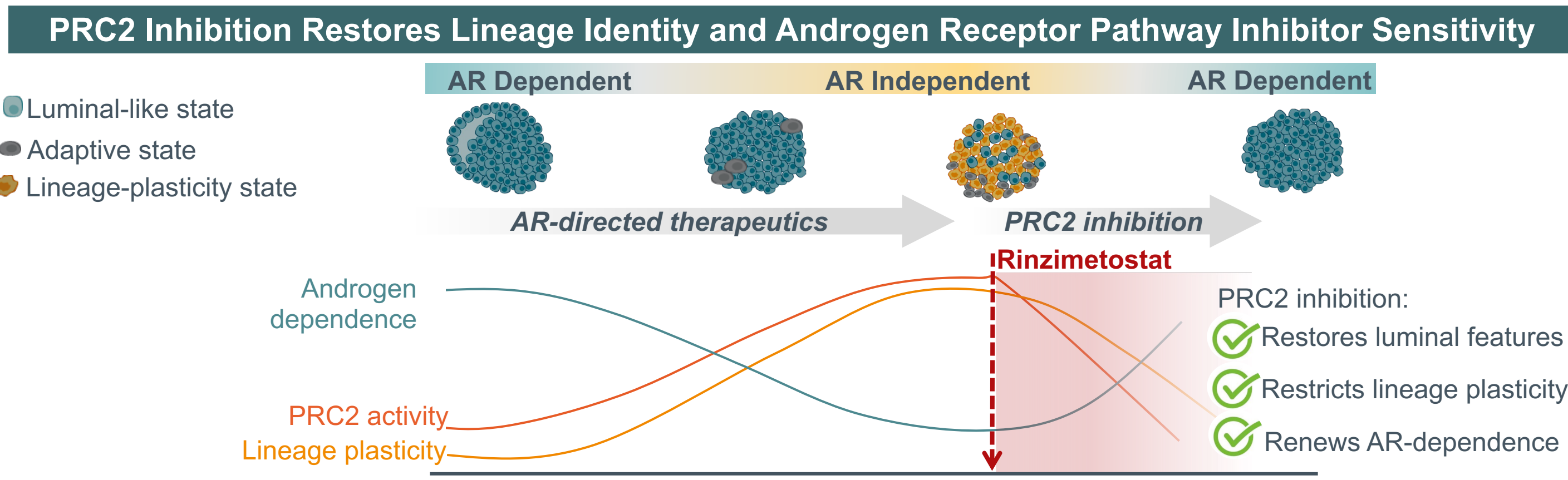


(Left) C4-2 cells were grown in RPMI with 10% FBS, and drug concentration gradually increased over 2 months as cells grew out. Sequencing identified EZH2 Y111H mutation in MevRoRes prostate cells. (Right) Assessment of parental cells vs cells with acquired resistance to mevrometostat in a CellTiterGlo assay at 14 days demonstrated an ~8-fold loss of IC50 cell potency for mevrometostat in cells with acquired resistance. The MevRoRes cells are also resistant to other EZH2 inhibitors (valemetostat, tulmimetostat, tazemetostat, data not shown), while retaining sensitivity to rinzimetostat.

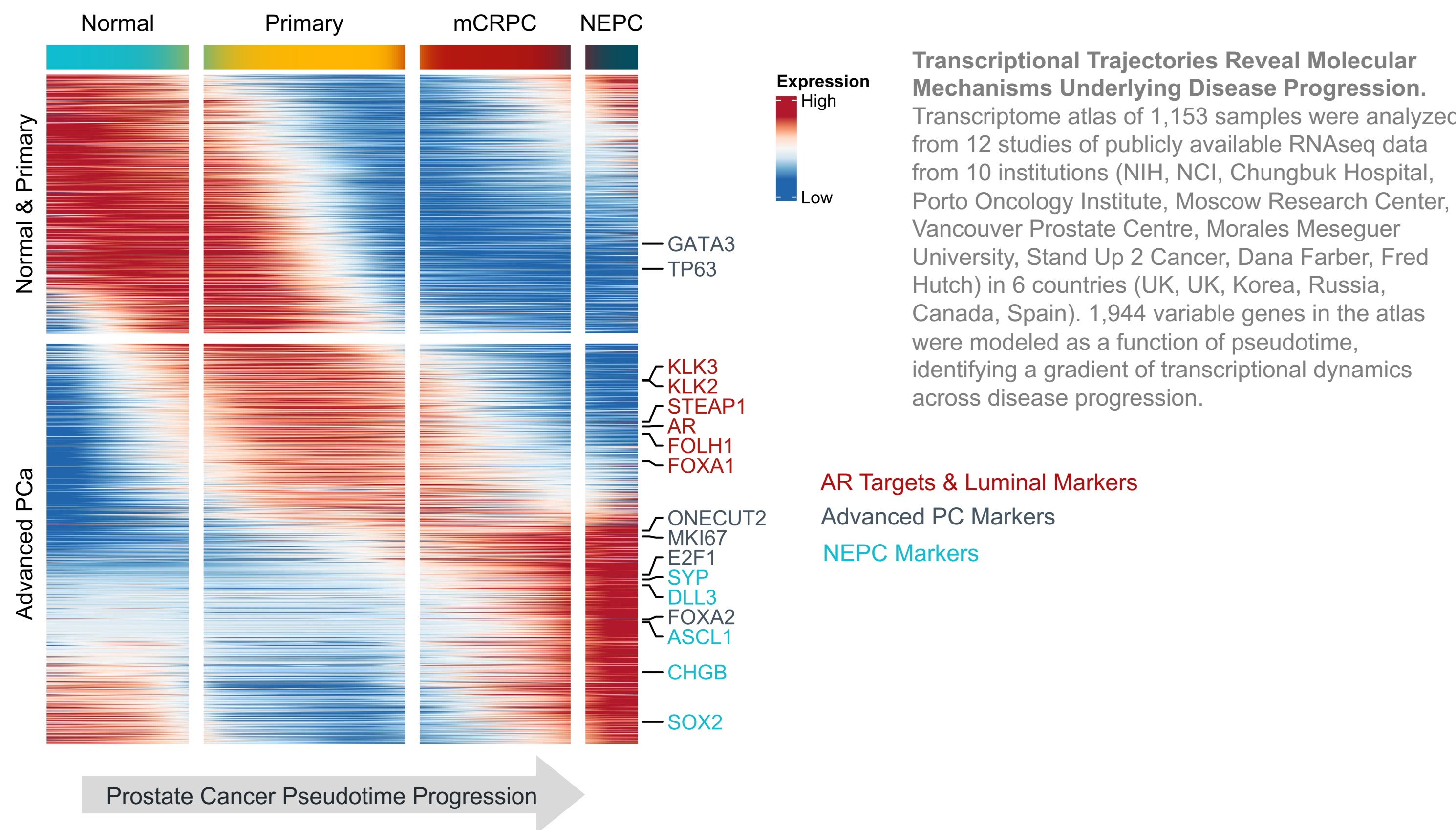


Modeling the Mechanistic Role of PRC2 in Prostate Cancer

- PRC2 activity increases in prostate cancer and associates with lineage plasticity and resistance
- PRC2 inhibitors constrain this process by restricting lineage-escape programs and enforcing a luminal, AR-dependent cell state in preclinical studies

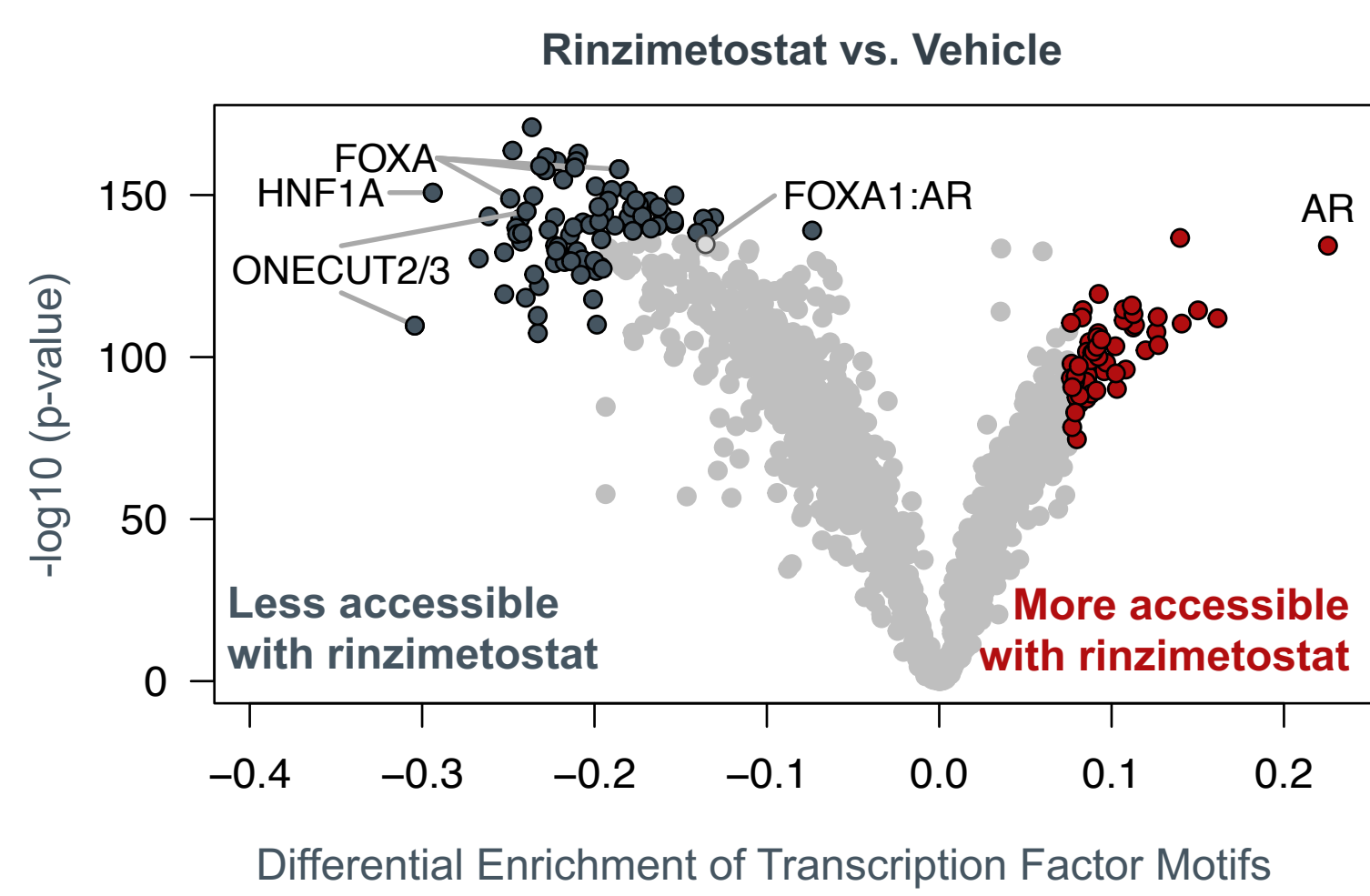


Epigenetically Driven Lineage Plasticity Is a Major Mechanism of Resistance in Prostate Cancer



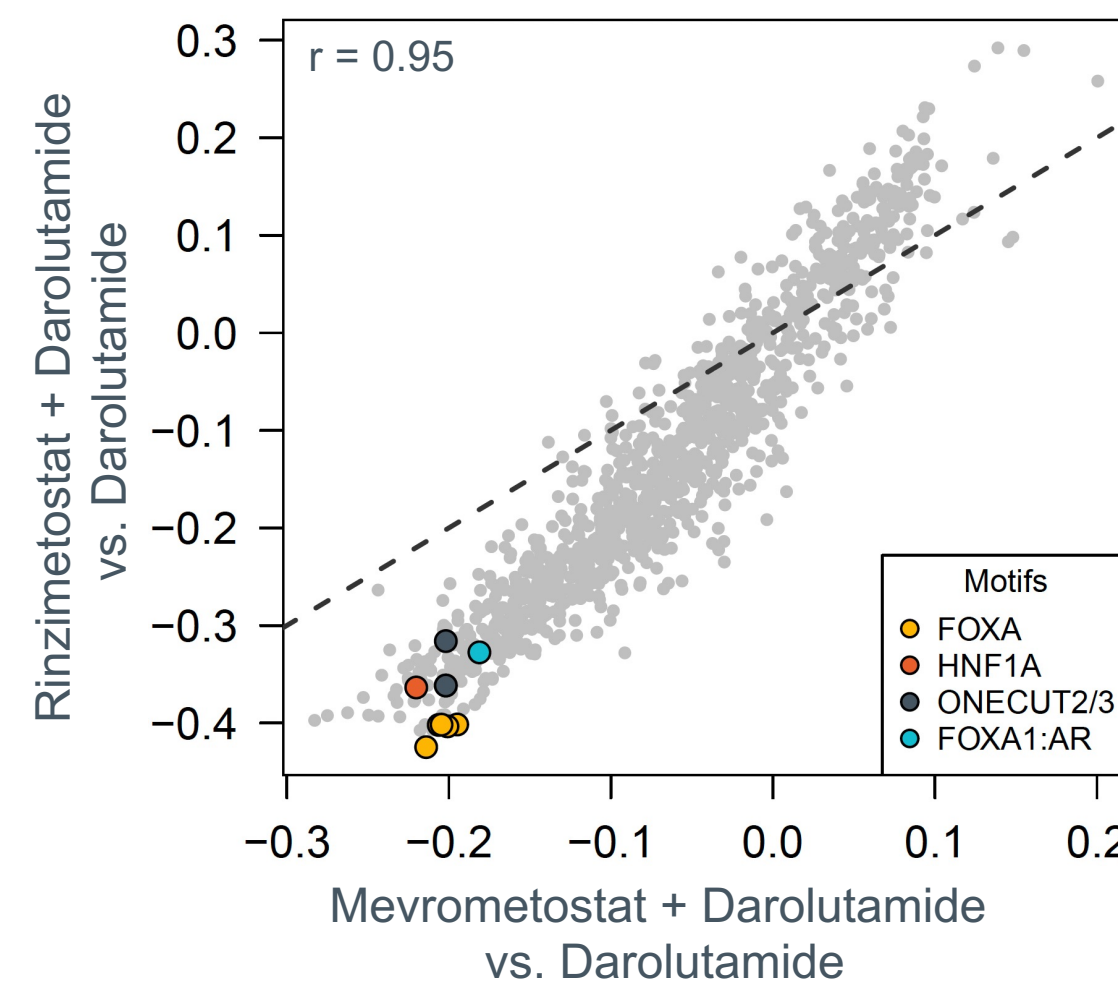
Rinzimetostat Restores Access to AR Motifs and Restricts Accessibility of Lineage Plasticity Genes

ATAC-seq Reveals Differential Accessibility of Transcription Factor Sites



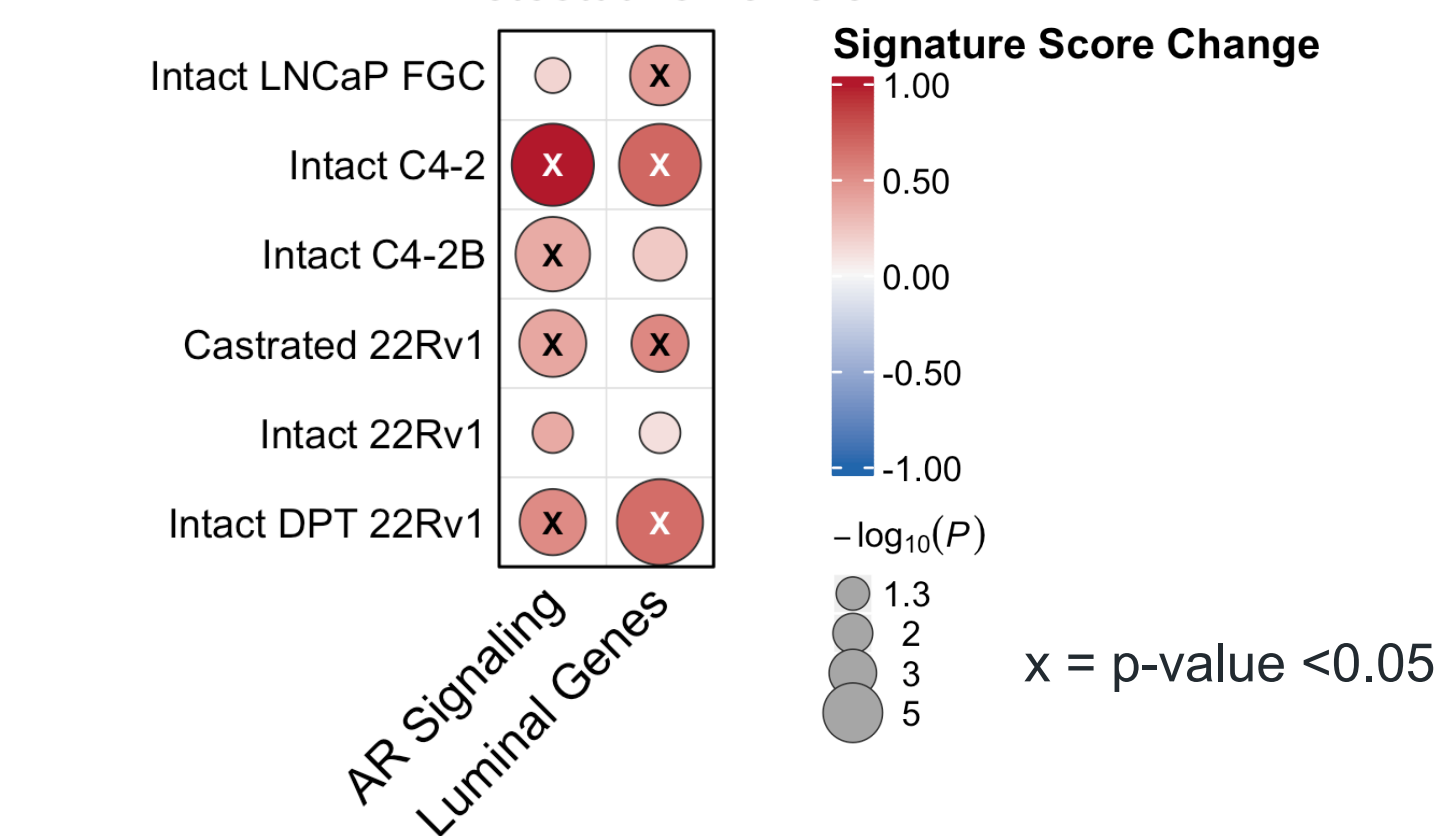
(Left) 22Rv1 tumors from castrated mice collected after 28 days of 100mpk rinzimetostat treatment. ATAC-seq data is down sampled to the sample with the fewest reads and peaks are called using MACS3 with p-value < .01 & fold enrichment greater than 5. Differential enrichment of transcription factor motifs is performed using TOBIAS (Bentsen *et al.* Nat Comm. 2020) with a consolidated set of motifs. (Right) Addition of rinzimetostat vs. mevrometostat to darolutamide (50mpk BID) results in accessibility changes to the same key transcription factor binding sites in LNCaP (CSPC) xenografts after 28 days of treatment. Every point is the TOBIAS-calculated score of motif accessibility change for consolidated motifs. Shown in color are lineage-associated transcription factor motifs with consistently reduced accessibility following treatment with PRC2 inhibitors. r = Pearson correlation.

EED and EZH2 Inhibitors Both Restrain Chromatin Accessibility Sites for Lineage Change



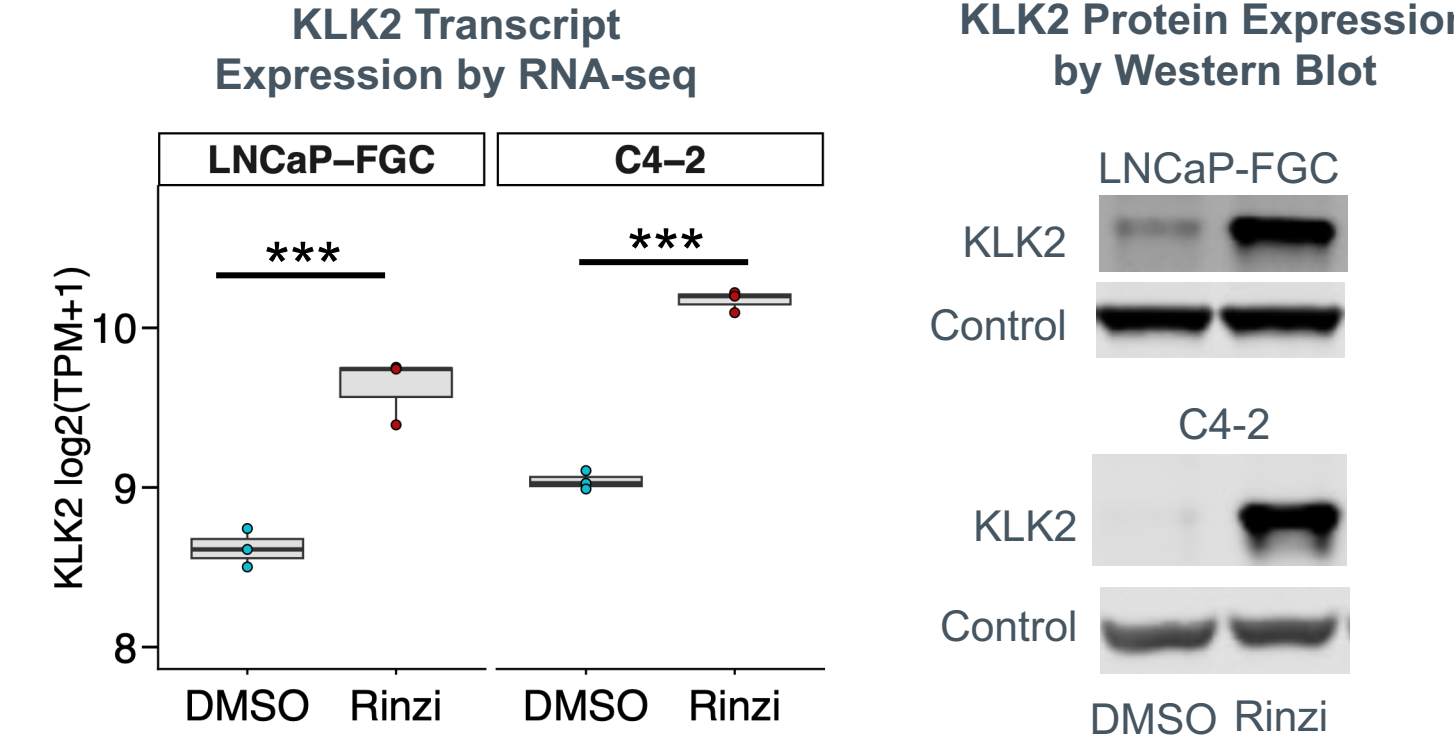
PRC2 Inhibition Induces Luminal Transition and Increases AR Signaling, Leading to ARPI Synergy

Rinzimetostat Consistently Increases AR Signaling and Luminal Gene Signatures In Vivo



(Left) RNA-seq analysis of prostate xenograft tumors from mice treated with 100 mg/kg rinzimetostat or vehicle control for 21–29 days. Gene signature scores in the rinzimetostat group were normalized relative to vehicle controls within each study, revealing consistent increases in AR signaling and luminal lineage signatures across models. x = p<0.05, linear model. (Right) LNCaP cells grown in 10% FBS were treated 14 days with dose-ranging concentrations of AR inhibitor (enzalutamide or darolutamide) and PRC2 inhibitor (rinzimetostat or mevrometostat), alone or in combination, and assayed with CellTiterGlo. Scores of >10 synergistic, 10 to <10 additive, and < -10 antagonistic (Ianevski *et al.*, NAR 2022).

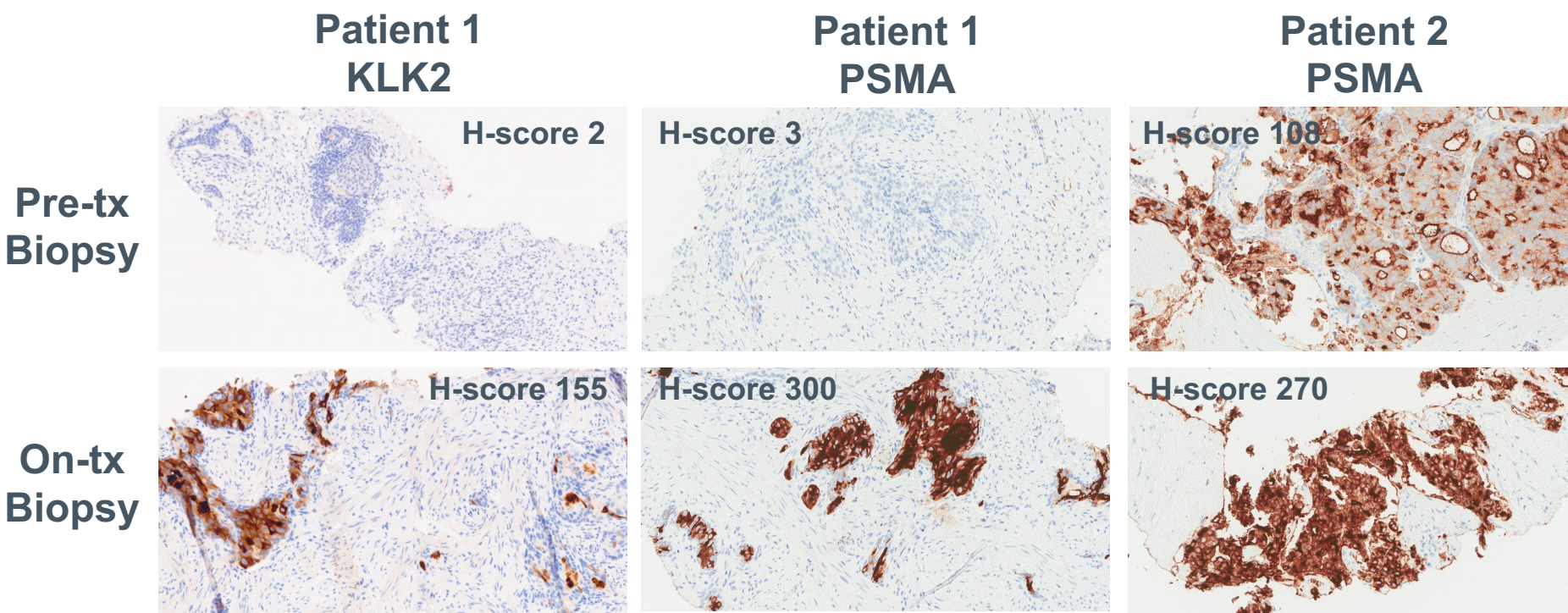
Rinzimetostat Increases Expression of KLK2 in Prostate Cancer Models



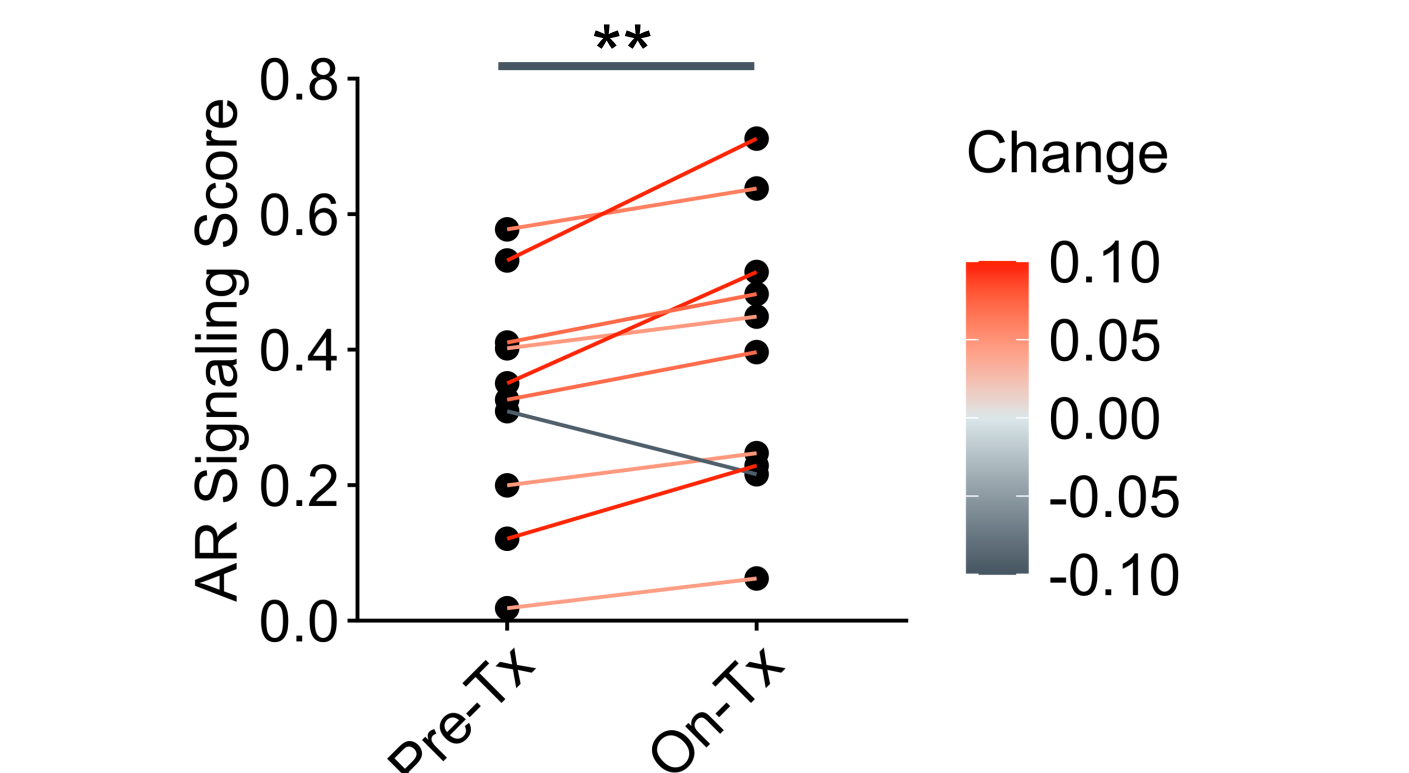
(Left) Increased KLK2 transcript in LNCaP-FGC and C4-2 cells at day 7 and KLK2 protein in LNCaP-FGC and C4-2 cells at day 14 following 1uM rinzimetostat treatment. ***, p<0.001, DESeq2 Wald test. (Right) STEAP1 protein increased in C4-2 xenografts treated with 100mpk QD rinzimetostat for 24 days. Graph displays QuPath quantitation of IHC of whole tumor sections from each treatment group. *, p<0.05, t-test.

Rinzimetostat Increased Luminal and AR associated Markers in Patient Samples from Phase 1 Single-Agent mCRPC Study

PSMA and KLK2 Levels Increased in Patients Treated with Rinzimetostat as a Single-Agent



cfDNA Methylation Indicates Increased AR Signaling in Patients Upon Rinzimetostat Tx



(Left) Tumor biopsies were collected at screening and after 2 cycles of treatment, with biopsy taken from prostate for patient 1 and lymph node for patient 2. The paired pre/on-treatment FFPE tissue samples were stained for prostate-specific membrane antigen (PSMA) and KLK2 by IHC and quantified as H-score by a pathologist. KLK2 staining was not done for patient 2 due to depleted tissue. (Right) Plasma samples were collected at first day of treatment and after 28 days of rinzimetostat dosing. Cell free DNA was sequenced for DNA methylation with the PredicineALERT panel. Shown are DNA methylation scores in patients pre- and on-treatment with rinzimetostat, for methylation regions positively correlated with AR signaling in a training dataset [Zhao *et al.*, Nat Genet. 2020] and validated in CDX samples. **, p<0.01, one-sided paired t-test for on-treatment methylation score change.

Conclusions

- Rinzimetostat is a next-generation PRC2 inhibitor, targeting EED, with optimized drug properties
- Targeting PRC2 via EED may be advantageous over EZH2
 - Resistance to EZH2 inhibitor, mevrometostat, arose rapidly in vitro, but remained sensitive to rinzimetostat
 - Hematologic malignancies were observed in rodents targeting EZH2 genetically in mice or pharmacologically with tazemetostat in rats; no tumors observed for similar EED contexts in rodents
- PRC2 inhibition, targeting either EED or EZH2, modulates prostate tumor lineage and leads to transcriptional and chromatin effects across prostate cancer models that mechanistically support the rationale for ARPI combination therapy
 - Restores luminal features
 - Restricts lineage plasticity
 - Renews AR dependence

Himalayas-1 Phase 3 study of rinzimetostat in combination with darolutamide is ongoing - NCT07723248