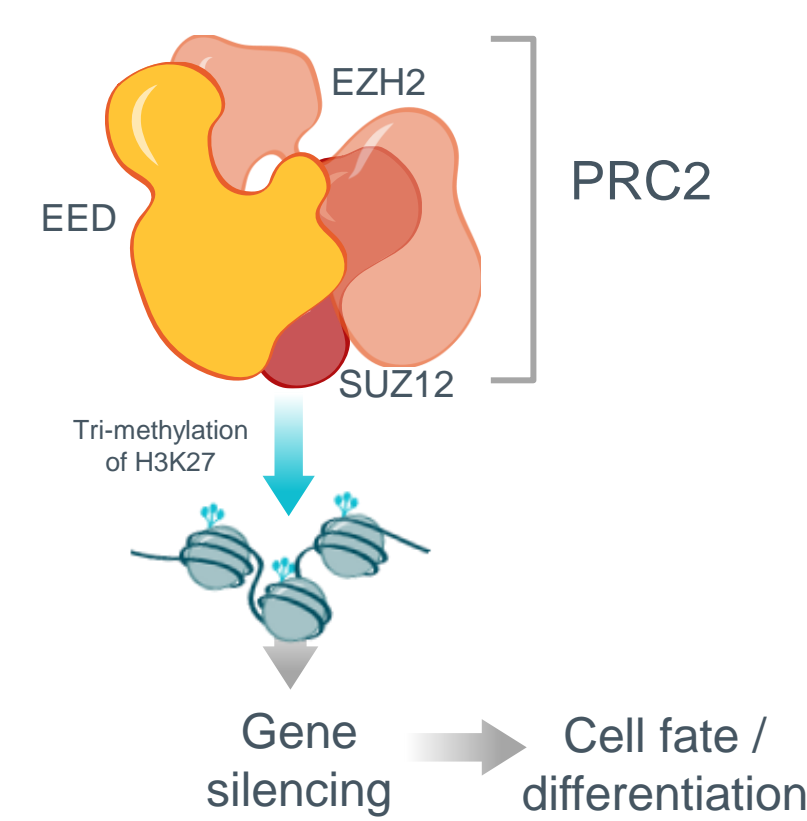


BACKGROUND

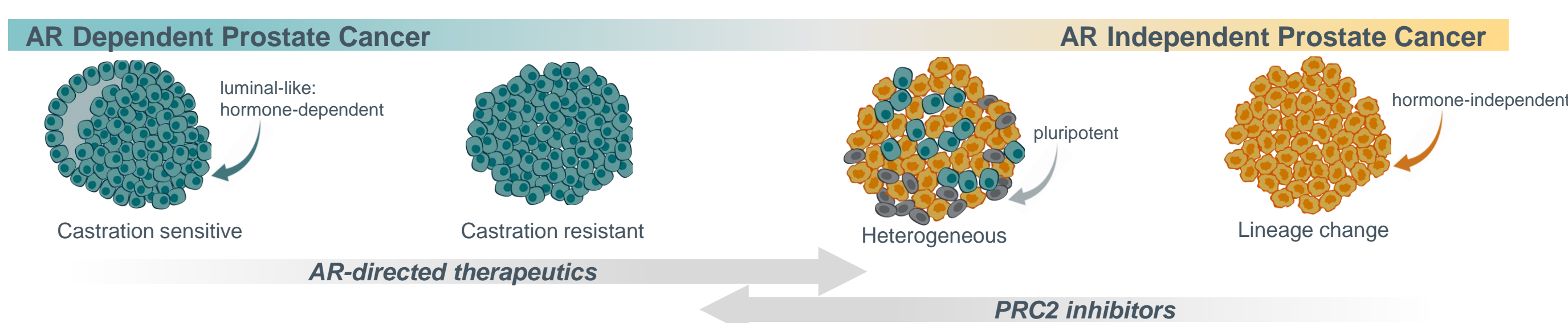
Polycarbonyl repressive complex 2 (PRC2):

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



In prostate cancer:

- Development of tumor cell plasticity contributes to resistance of 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



Targeting PRC2 with ORIC-944:

- First-generation PRC2 inhibitors exhibit poor drug properties and short half-lives, requiring suboptimal dosing regimens, such as twice or three times daily, in the clinic
- Clinical targeting of EZH2 has shown drawbacks in other indications, including the emergence of EZH2 mutations & EZH1 compensation
- ORIC-944 is a second generation, allosteric inhibitor of PRC2 that binds the essential EED subunit to overcome those drawbacks
- ORIC-944 is a highly selective, orally bioavailable inhibitor of PRC2 with nanomolar cell potency, excellent PK and a clean CYP profile in preclinical studies

1. PRC2 Activity Increases as Prostate Cancer Progresses

PRC2 Activity Associates with Prostate Cancer Lineage

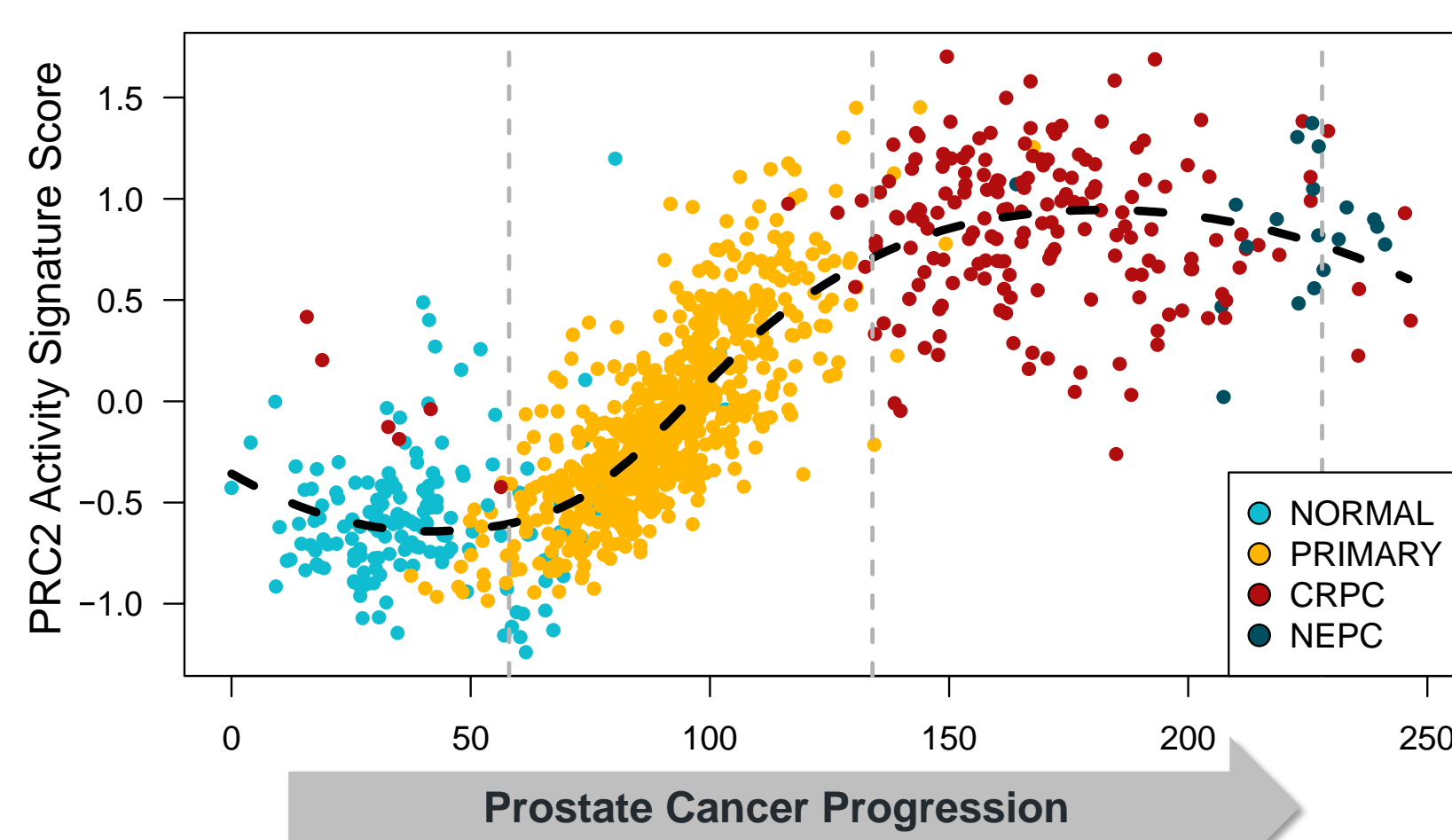
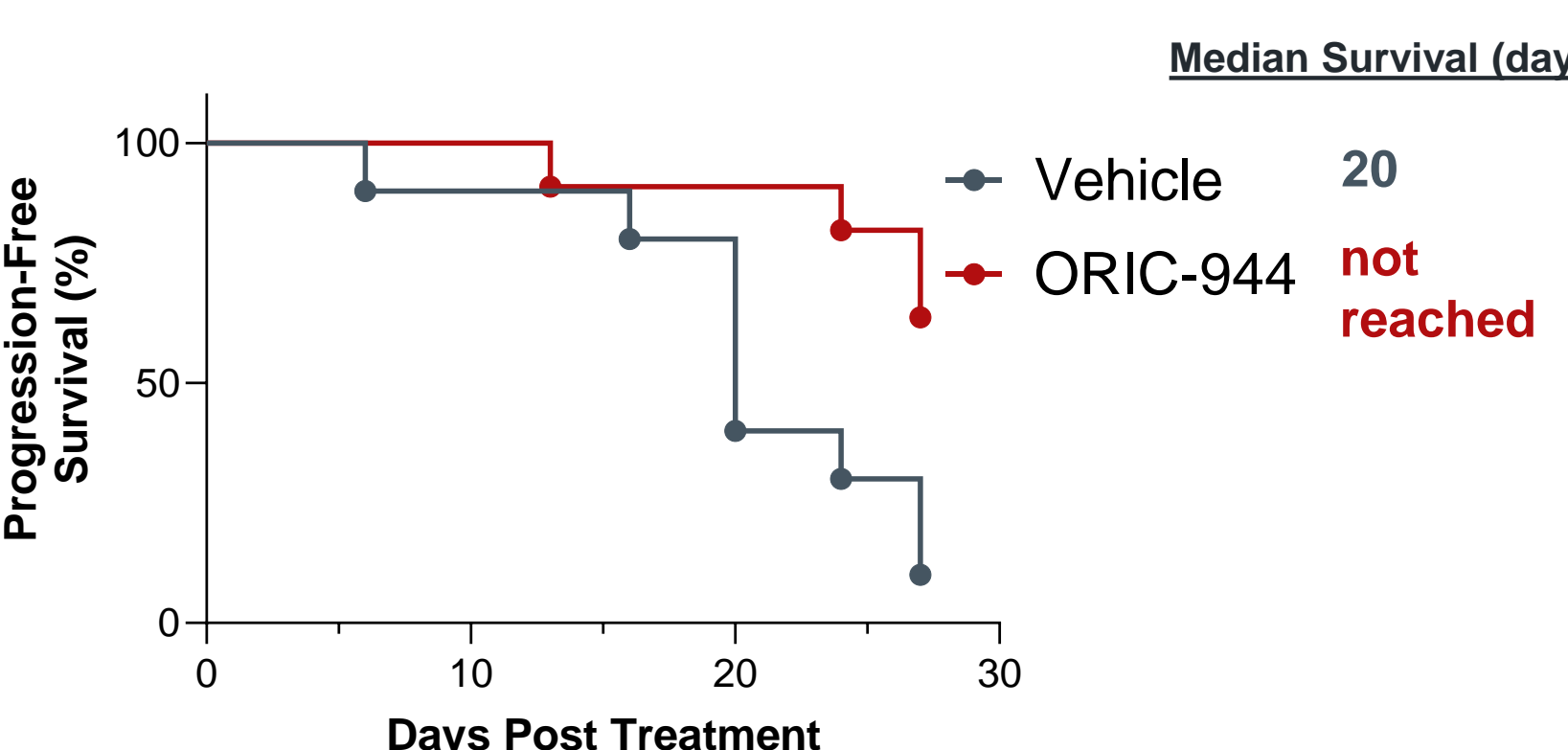


Figure 1. PRC2 activity score as a function of prostate cancer patient progression measured by pseudotime based on n=1,034 normal and prostate tumor RNA-seq samples; Colors indicate patient tumor subtype: normal prostate, blue; primary prostate cancer, gold; castration-resistant prostate cancer (CRPC), red; neuroendocrine prostate cancer (NEPC), grey.

2. AR Inhibition with Castration Engenders Sensitivity to ORIC-944

ORIC-944 Is Efficacious In Vivo in 22Rv1 Xenografts in Hormone-depleted, Castrated Setting



ORIC-944 Is Not Efficacious In Vivo in 22Rv1 Xenografts in High Hormone, Intact Setting

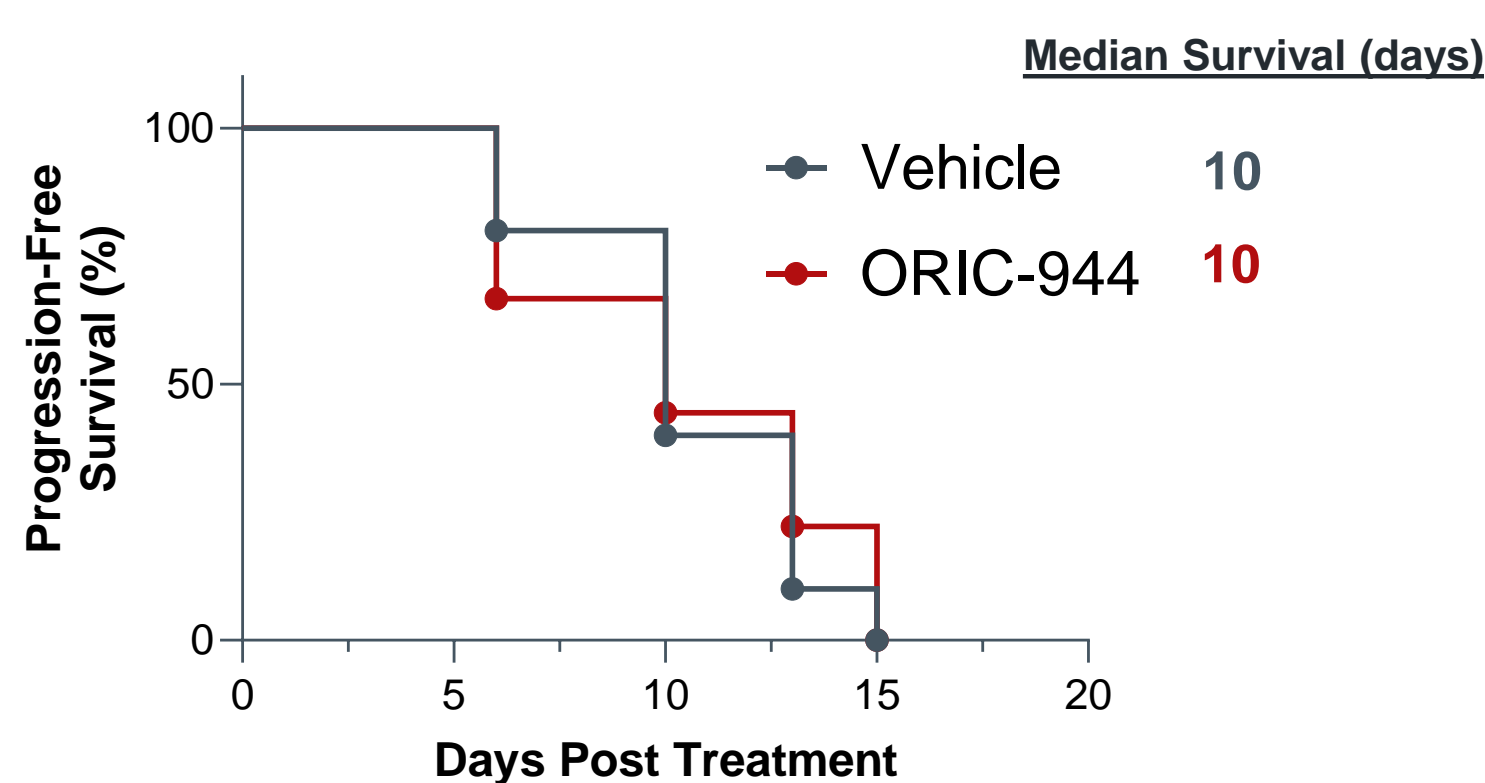
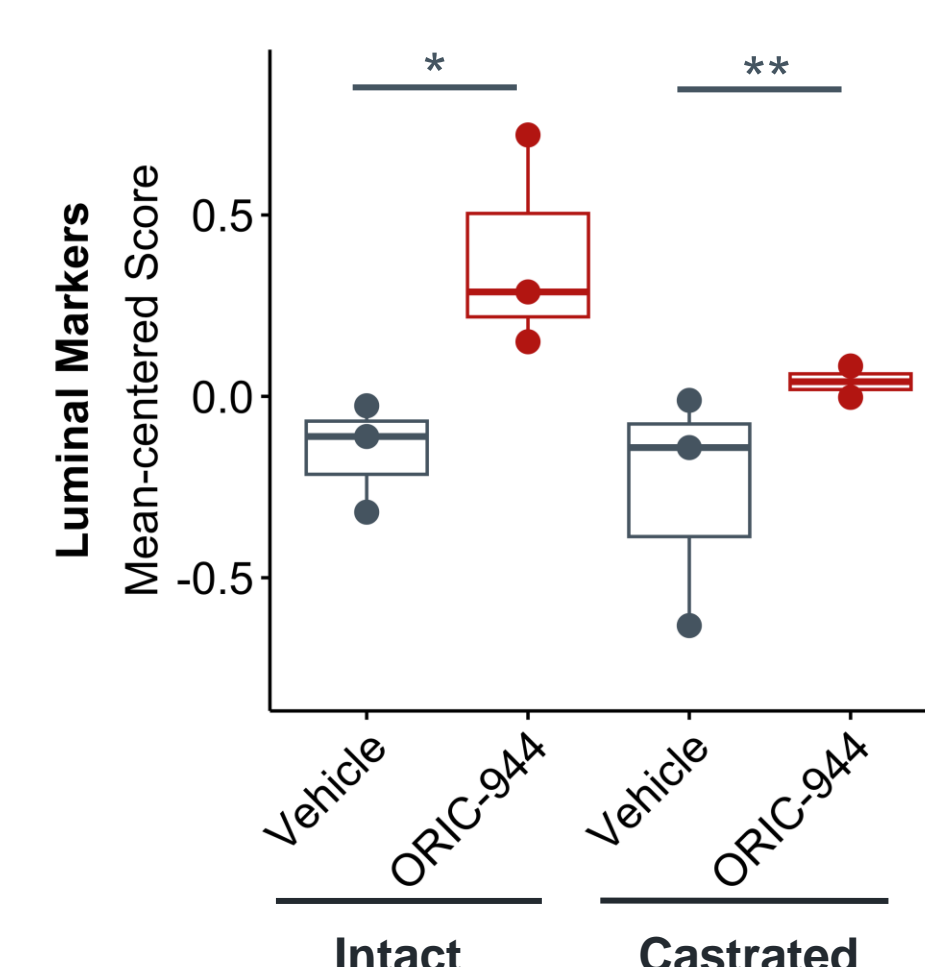


Figure 2. Progression-free survival of 22Rv1 xenograft mice treated with vehicle or ORIC-944 100 mg/kg QD for 28 days in castrated (Left) or for 15 days in intact (Right) setting. Progression defined as tumor volume >500mm³ or death. n=8-10/cohort.

3. ORIC-944 Reinforces a Luminal State and Restricts Lineage Adaptation in Castrated Setting

ORIC-944 Enhances Expression of Luminal Markers in 22Rv1 Intact and Castrated Settings



ORIC-944 Treatment Reduces Accessibility to Lineage Transcription Factors in 22Rv1 Castrated Setting

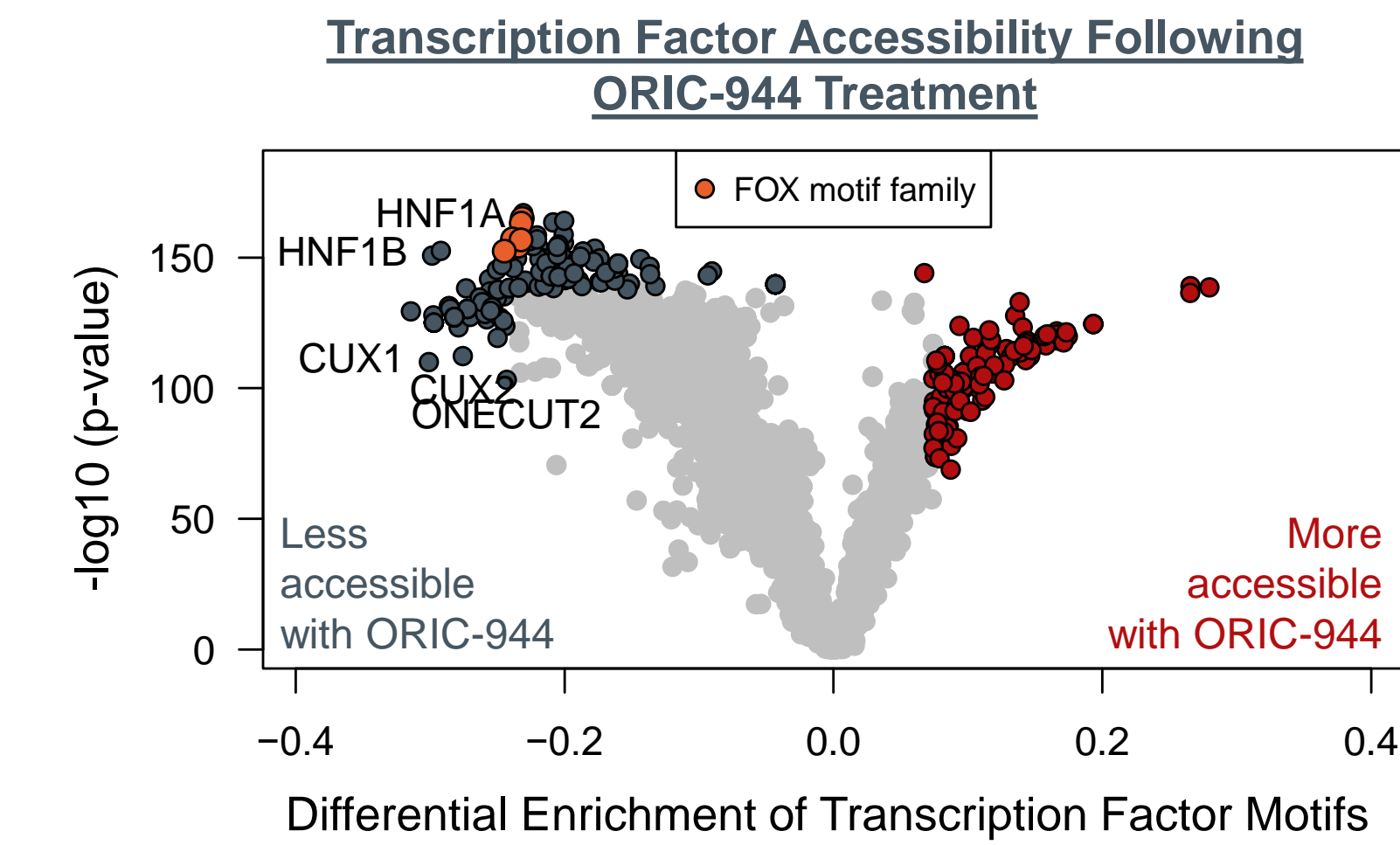
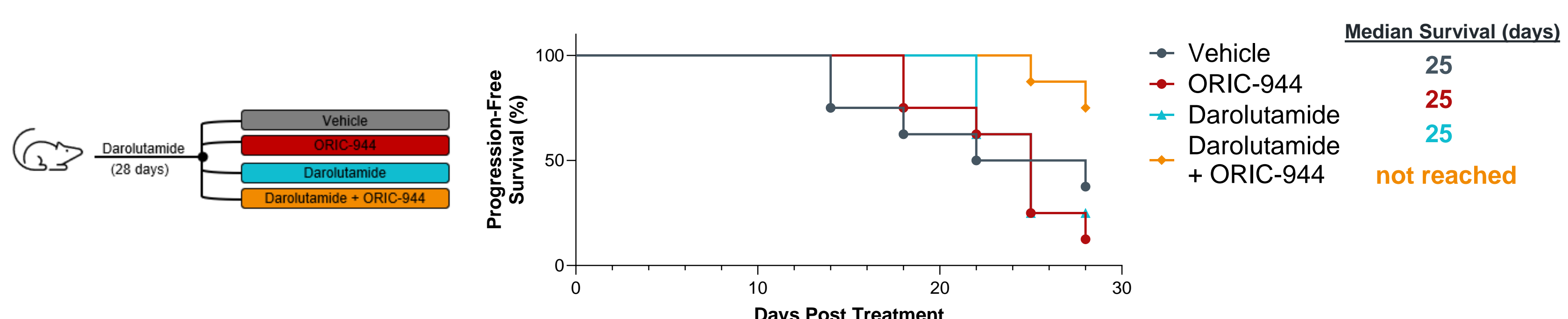


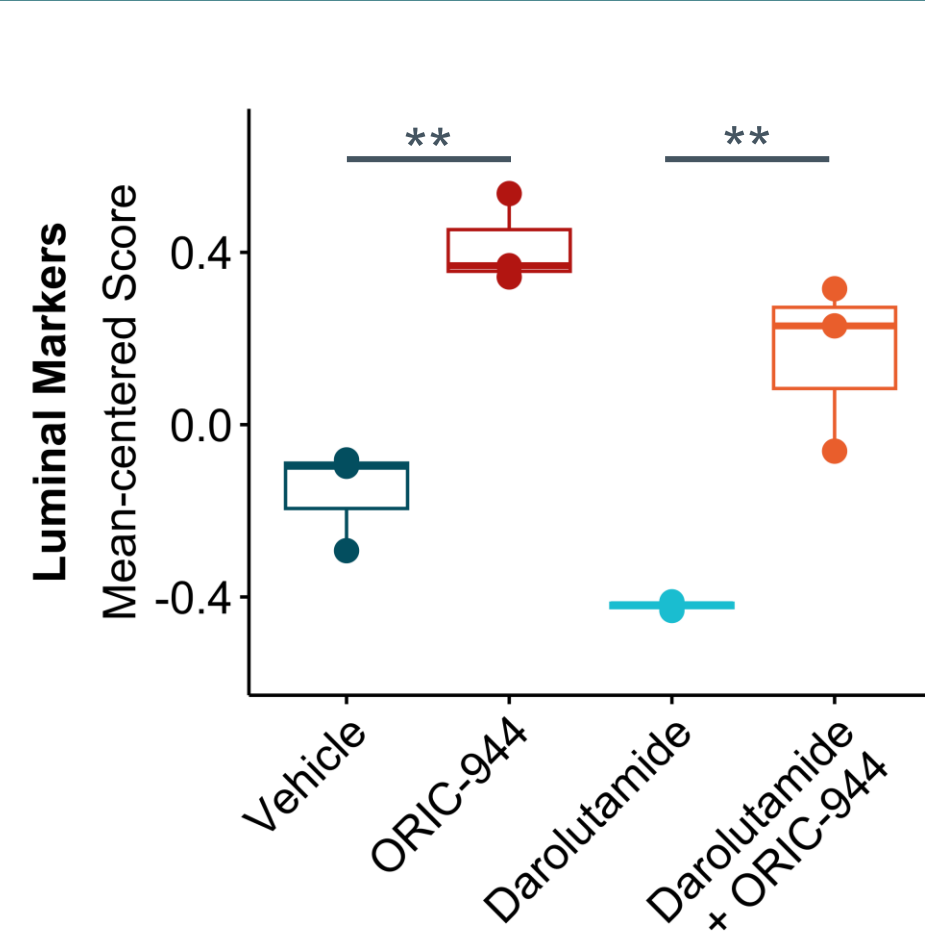
Figure 3. Left. 22Rv1 xenografts were treated with ORIC-944 in the intact and castrated settings in vivo. Luminal marker signature [Liang et al. Prostate Cancer and Prostatic Diseases (2022)]. Weighted Stouffer test on DESeq2 results using the inverse of log₂ Fold Change standard errors as weights; *, p<0.05; **, p<0.01. Right. Differentially accessible transcription factor (TF) motifs called by TOBIAS [Bentsen et al. Nat Comm (2020)] with JASPAR motifs [Rauluseviucite et al. NAR (2024)] on ATAC-seq profiles comparing ORIC-944 treatment vs vehicle in 22Rv1 tumor-bearing castrated mice.

4. ARPI Treatment Resembles Castration and Confers Equivalent ORIC-944 Combination Outcomes in Intact Setting

Progression-Free Survival of Intact 22Rv1 Xenografts



ORIC-944 Increases Luminal Marker Expression in Darolutamide Pre-treated 22Rv1 Xenograft Tumors



ORIC-944 + Darolutamide Reduces Accessibility to Lineage Transcription Factors in 22Rv1 Intact Setting

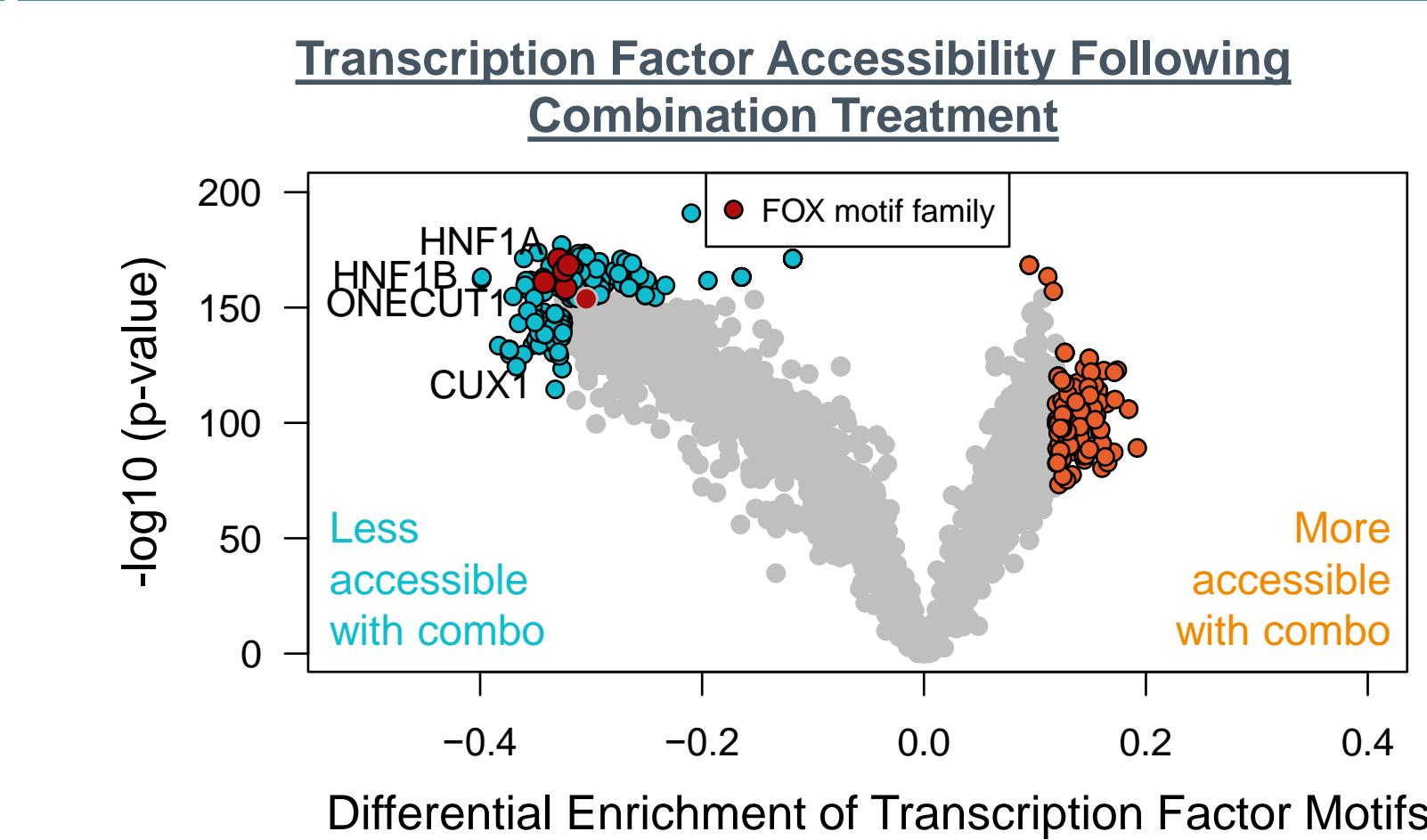
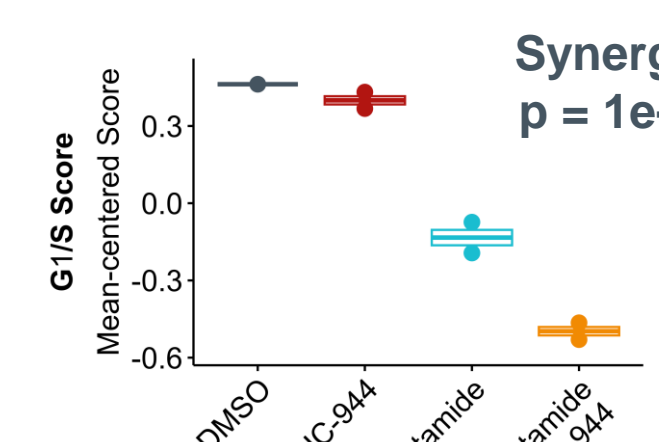


Figure 4. Top. 22Rv1 xenograft mice were pre-treated with darolutamide 50 mg/kg BID for 28 days (14 days before and after implantation). Animals were then randomized by tumor size to treatment groups vehicle, darolutamide 50 mg/kg BID, ORIC-944 100 mg/kg QD or combination for 28 additional days. Progression defined as tumor volume >1000mm³ or death. n=10/cohort. Bottom-Left. Luminal marker expression across the darolutamide pre-treated groups. Same signature and p-value cutoffs as in Figure 3. Bottom-Right. Differentially accessible TF motifs comparing the addition of ORIC-944 to darolutamide vs continuation of single-agent darolutamide in 22Rv1 tumor-bearing intact mice pre-treated with darolutamide.

5. Both ORIC-944 and EZH2 Inhibition Synergize with ARPI in Prostate Cancer Cells In Vitro

In Vitro Antitumor and Transcriptional Synergy of PRC2 Inhibitors and Enzalutamide

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



Equivalent Transcriptional Effects of PRC2 Inhibition Treatment

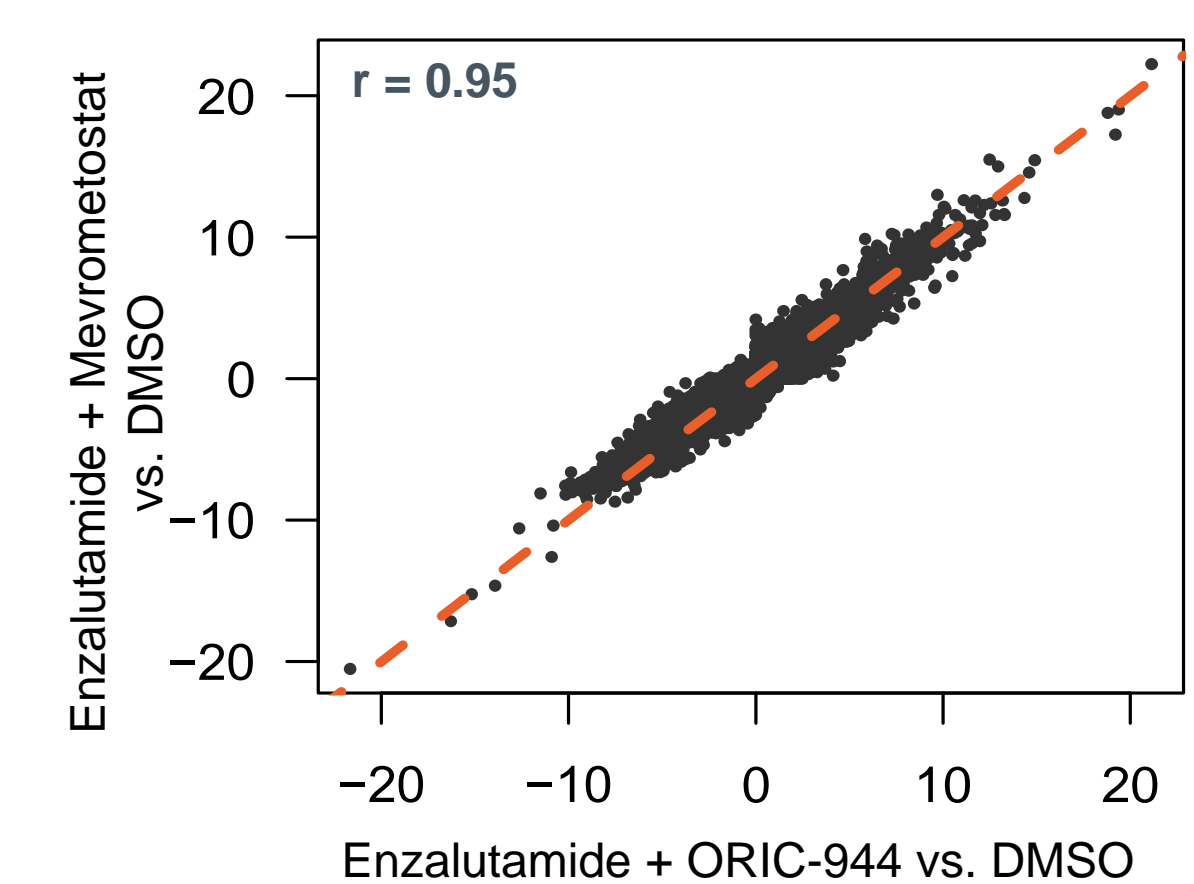
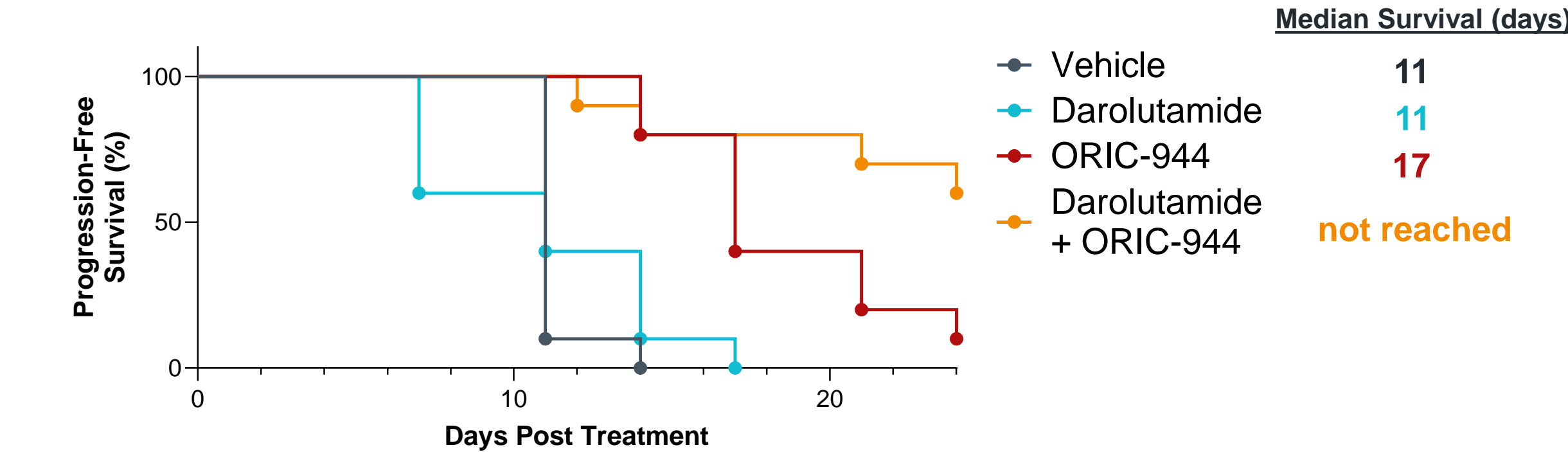


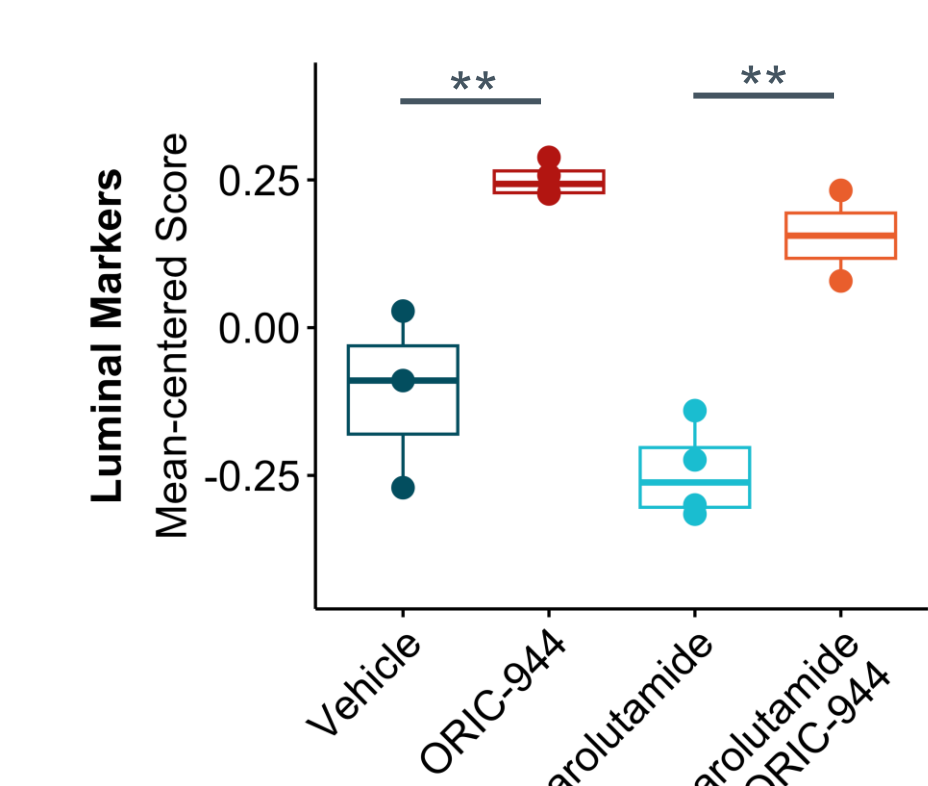
Figure 5. Left. 14-day CellTiter-Glo assay using C4-2 cells grown in FBS. Synergy was scored utilizing three synergy models (Bliss, Loewe, HSA), with >10 synergistic [Ianevski et al. NAR (2022)]. Middle. Representative example of transcriptional synergy observed for enzalutamide + ORIC-944 in LNCaP cells treated in vitro with 1μM of the indicated agents for 7 days, confirming combination cooperativity (G1/S [Tirosh et al. Science (2016)], interaction p-value 1e-5). Right. Correlation analysis of DESeq2-derived test statistics for enzalutamide + ORIC-944 vs. DMSO and enzalutamide + mevrometostat vs. DMSO in LNCaP cells. r = Pearson correlation.

6. ORIC-944 Synergizes with ARPI in Additional CRPC Models via the Same Mechanism

Progression-Free Survival of Intact C4-2 Xenografts



ORIC-944 Increases Luminal Signature Expression in Intact C4-2



ORIC-944 + Darolutamide Reduces Accessibility to Lineage Transcription Factors in Intact C4-2

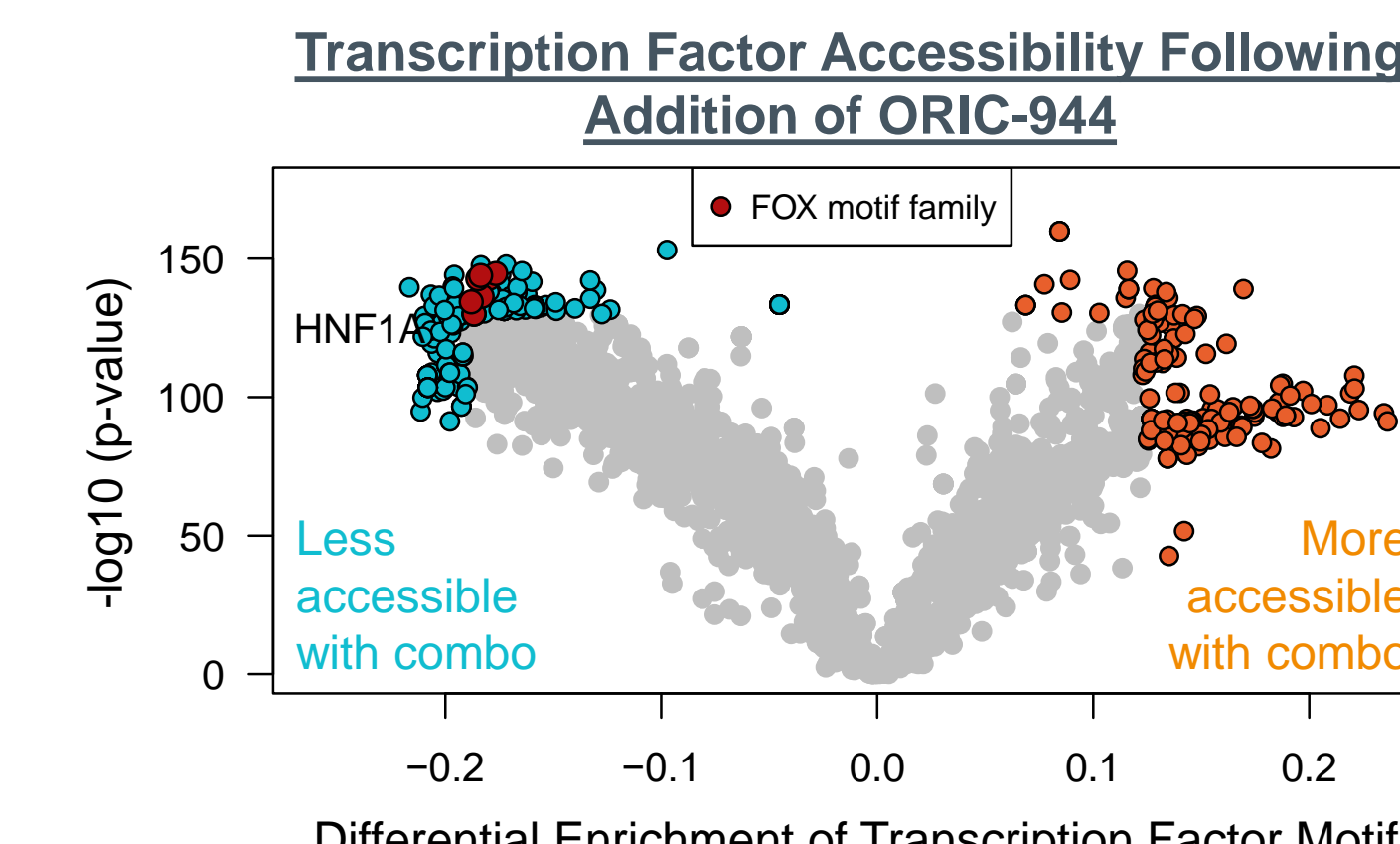
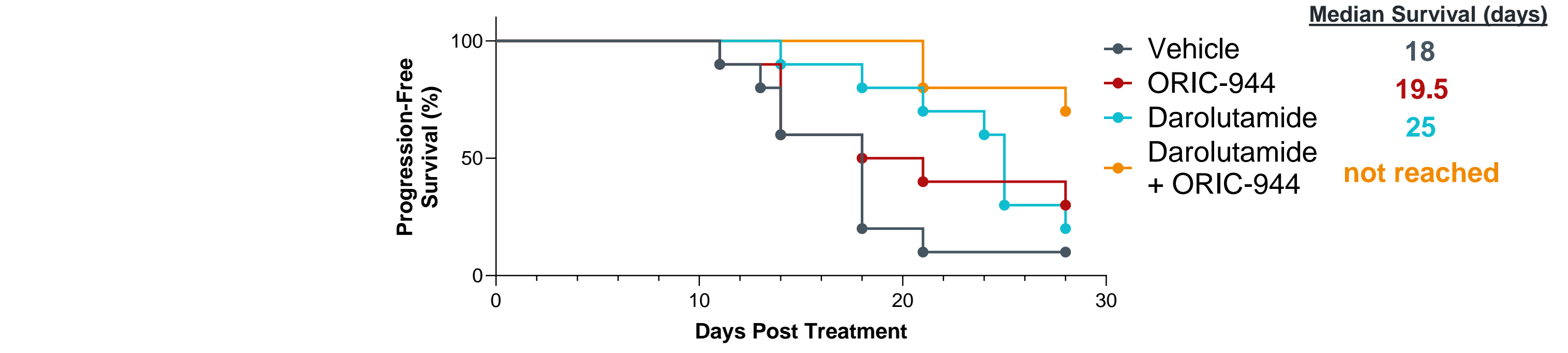


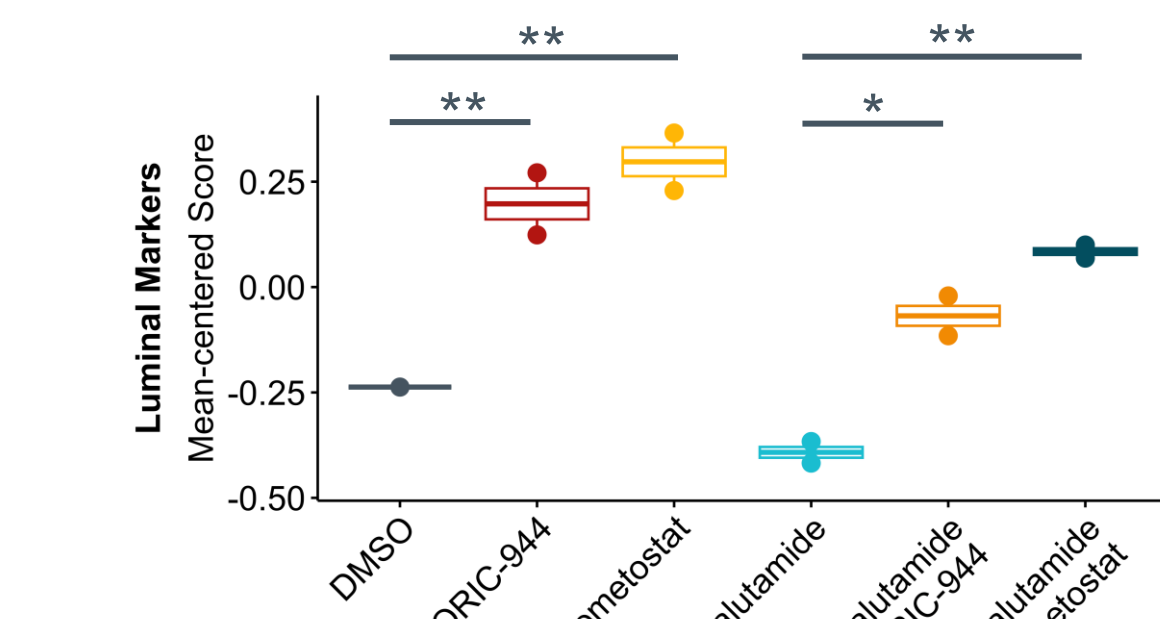
Figure 6. Top. Progression-free survival of intact C4-2 xenograft mice after treatment with vehicle, darolutamide 50 mg/kg BID, ORIC-944 100 mg/kg QD or combination for 24 days. Progression defined as tumor volume >1000mm³ or death. n=10/cohort. Bottom-Left. Luminal marker expression across the C4-2 intact xenografts. Same signature and p-value cutoffs as in Figure 3. Bottom-Right. Differentially accessible TF motifs from the TOBIAS analysis of ATAC-seq data comparing darolutamide + ORIC-944 treatment vs darolutamide in C4-2 tumor-bearing intact mice.

7. ORIC-944 Improves Response to ARPI in Castration Sensitive Prostate Cancer Models

Progression-Free Survival of Castration Sensitive Prostate Cancer (CSPC) Intact LNCaP Xenografts



PRC2i Enhances Luminal Markers in CSPC LNCaP Cells



ARPI Combination Blunts KLK3 Response in CSPC LNCaP Cells

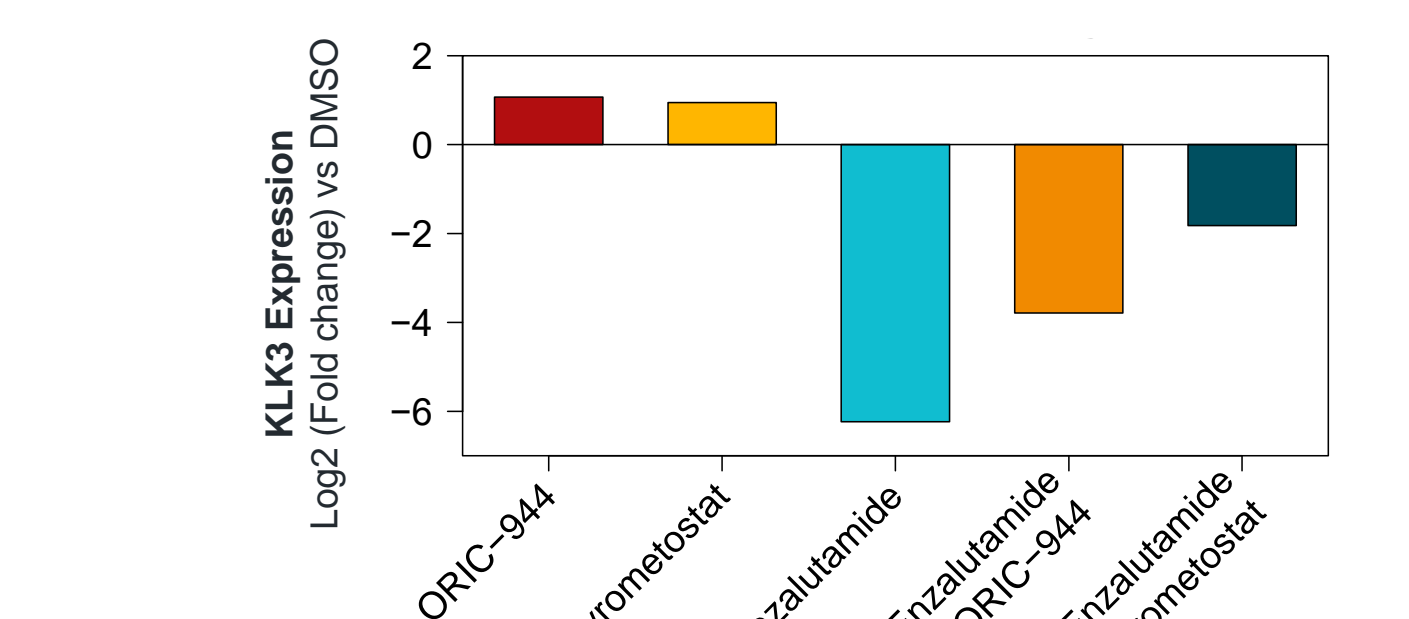


Figure 7. Top. Progression-free survival of intact LNCaP xenograft mice after treatment with vehicle, darolutamide 50 mg/kg BID, ORIC-944 100 mg/kg QD or combination for 28 days. Progression defined as tumor volume >800mm³ or death. n=10/cohort. Bottom-Left. Luminal marker expression in LNCaP cells in vitro treated for 7 days with 1μM of the indicated agents. Same signature and p-value cutoffs as in Figure 3. Bottom-Right. Change in KLK3 expression in LNCaP cells in vitro treated for 7 days with 1μM of the indicated agents relative to DMSO control.

CONCLUSIONS

- ORIC-944 leads to transcriptional and chromatin effects across prostate cancer contexts that mechanistically support the rationale for ARPI combination therapy in CRPC and CSPC
- ORIC-944 induces luminal cell fate and restricts lineage plasticity across prostate cancer models
 - ORIC-944 restores luminal gene expression across multiple prostate cancer models in both intact and castrated settings, as well as CSPC and CRPC contexts
 - ORIC-944 consistently restricts lineage transcription factor accessibility through chromatin remodeling
 - No transcriptional distinction between EED and EZH2 inhibition in prostate cancer models
- ORIC-944 synergizes with ARPI and extends progression-free survival in CRPC and CSPC models in vivo

ORIC-944 in combination with ARPI is currently in a Phase 1b trial (NCT05413421)