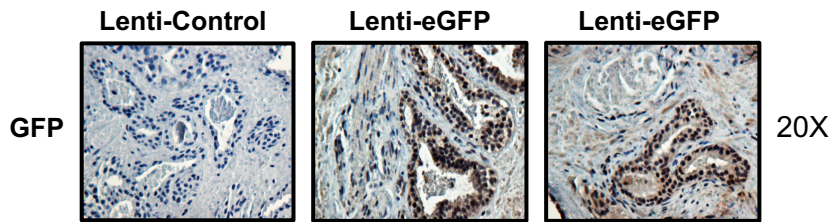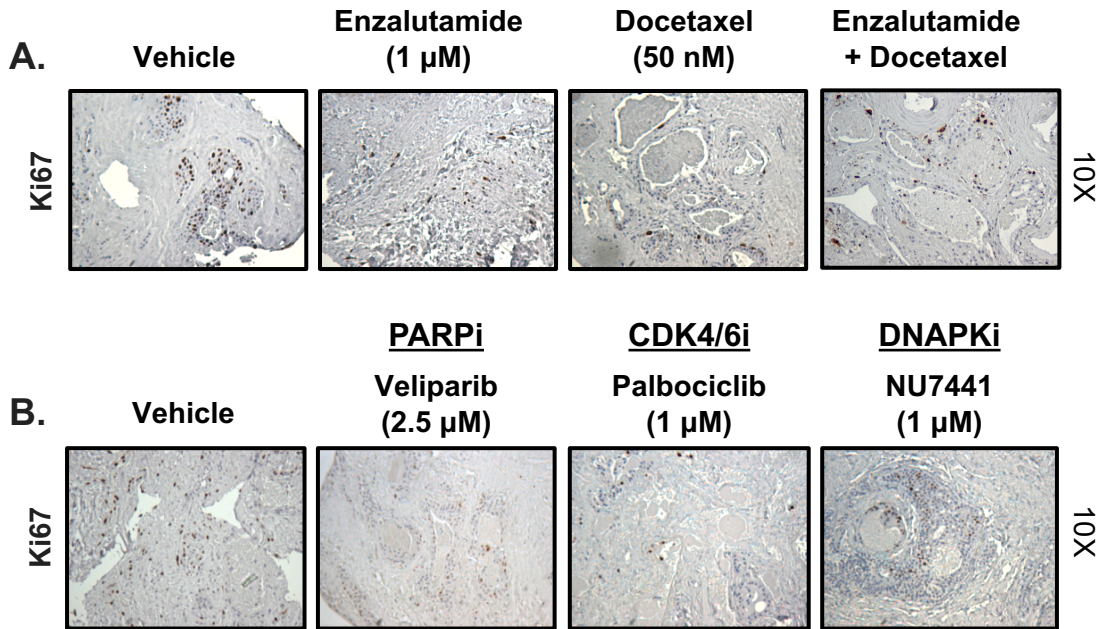**Supplemental Figure 1**

Supplementary Figure 1. **PCa PDE model sustains endogenous AR signaling.**
A-B. AR and PSA immunostaining of three additional PDE tumor tissue with matched non-neoplastic tissue after 6 days of *ex vivo* culture shown at 40X magnification. **C.** To validate histology, immunohistochemical staining was performed as a cocktail of antibodies to Acetyl Co-A racemase and the basal cell markers p63 & HMW keratin. Alkaline phosphatase (Red) was used to detect racemase expression. DAB (Brown) was used to detect basal cells. Images shown at 40X, n=3. **D.** IHC images of PDE tissues with no antibody staining as a negative control. Images shown at 10X, n=3.

Lenti-Control   Lenti-eGFP   Lenti-eGFP

GFP

20X

Supplemental Figure 2. **PDE model is amenable to transfection.** Expression of GFP was achieved through lentirviral transduction of PDE with an GFP-expressing lentivirus for 6 days to show efficiency of infection. Representative images show GFP IHC for tissue transfected with control plasmid (Lenti-Control) and GFP (Lenti-eGFP) after 6 days in *ex vivo* culture. Images are shown at 20X.

A. Vehicle | Enzalutamide (1 µM) | Docetaxel (50 nM) | Enzalutamide + Docetaxel — Ki67 — 10X

B. Vehicle | PARPi Veliparib (2.5 µM) | CDK4/6i Palbociclib (1 µM) | DNAPKi NU7441 (1 µM) — Ki67 — 10X

Supplemental Figure 3. **Various treatments reduce growth in PDE model. A.** For Ki67 images shown in Figure 4A, this figure shows the corresponding 10X magnification images for vehicle, AR antagonist (Enzalutamide), Taxane (Docetaxel), and AR antagonist (Enzalutamide) + Taxane (Docetaxel) treated tumors. **B.** Similarly for Ki67 images shown in Figure 4B, this figure shows the corresponding 10X magnification images for vehicle, PARP Inhibitor (Veliparib), CDK 4/6 Inhibitor (PD), and DNAPK Inhibitor (NU7441).

Supplemental Table 1. Pathological Characteristics of Tumors Used in this Study

PDE	Age at Prostatectomy (years)	PSA (ng/mL)	Gleason Grade	Pathological Stage	Race	Samples Acquired
1	68	8.4	3+4=7	cT1c	Caucasian	E, I
2	69	5.3	3+4=7	cT2b	Caucasian	E, I
3	66	7.4	4+4=8	T1c	Caucasian	E, I
4	57	4.0	3+4=7	n/a	Caucasian	I, R
5	70	10.3	4+4=8	cT1c	Hispanic	I, R
6	55	n/a	3+4=7	n/a	not recorded	I, R
7	60	5.7	4+3=7	cT1c	Caucasian	I, R
8	57	7.4	4+5=9	cT1c	not recorded	I
9	74	10.3	4+4=8	n/a	Caucasian	I, R
10	59	n/a	4+4=8	n/a	not recorded	I
11	86	5.2	4+3=7	cT1c	Caucasian	I, R, T
12	51	14.9	3+4=7	n/a	Caucasian	I, R, T
13	66	5.3	3+4=7	n/a	not recorded	I, R, T
14	61	4.8	4+4=8	n/a	African American	I
15	60	5.7	4+3=7	cT1c	Caucasian	I
16	68	46.2	4+3=7	n/a	African American	I
17	63	7.6	3+4=7	cT1c	not recorded	I
18	65	4.9	4+3=7	T1c	Caucasian	I
19	71	4.0	3+4=7	T1c	not recorded	I
20	68	3.7	3+4=7	T1c	African American	I
21	68	7.1	4+4=8	T1c	not recorded	I, T
22	72	37.5	4+5=9	n/a	Caucasian	I
23	54	4.6	4+5=9	T1c	not recorded	I
24	70	5.4	3+4=7	n/a	African American	I, T
25	53	4.3	3+4=7	T3a	not recorded	E
26	59	4	4+5=9	T3a	not recorded	E
27	71	6.5	4+3=7	T3a	not recorded	E
28	60	11.6	3+4=7	T3a	not recorded	E
29	53	8.3	3+4=7	T3a	not recorded	E
30	71	8.9	3+4=7	T3a	not recorded	E
31	60	9	3+4=7	T3a	not recorded	E
32	67	9.2	3+4=7	T3a	not recorded	E
33	75	10	4+3=7	T3a	not recorded	E
34	70	5.4	4+3=7	T3a	not recorded	E
35	71	3.6	4+5=9	T3b	not recorded	E
36	66	5.2	3+4=7	T2c	not recorded	E
37	55	9.7	3+4=7	T2c	not recorded	E

Abbreviations: E – ELISA, I – IHC, R – RNA, and T – TME analyses