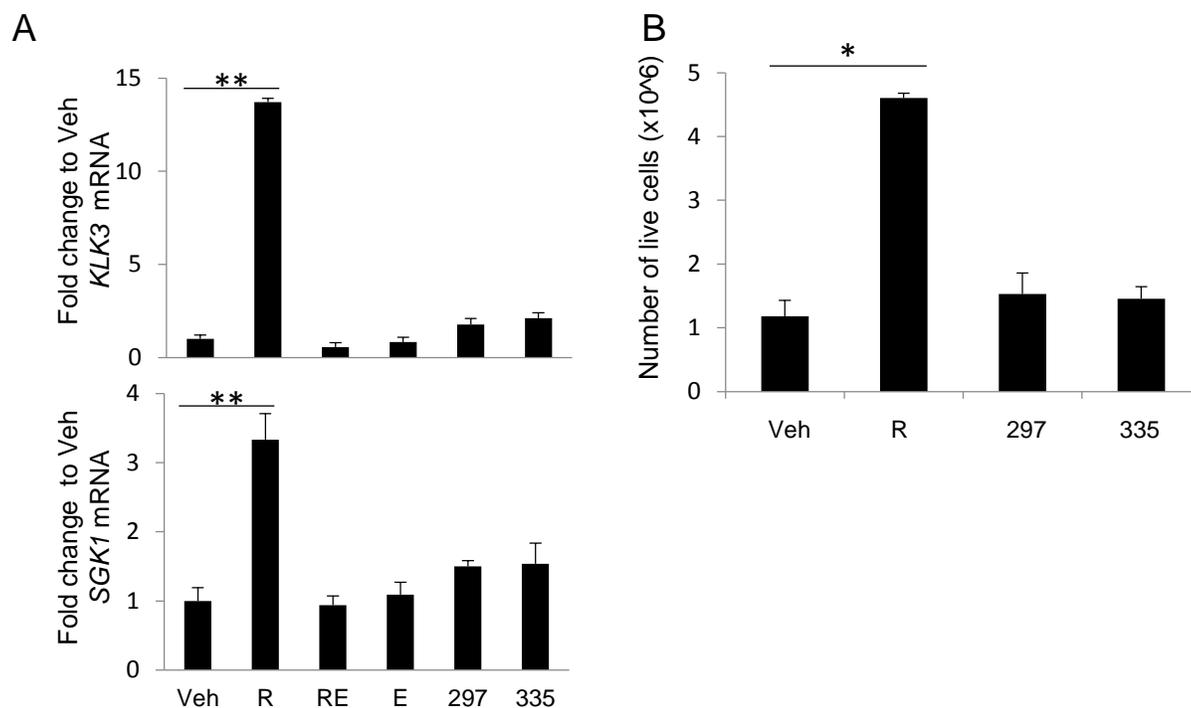
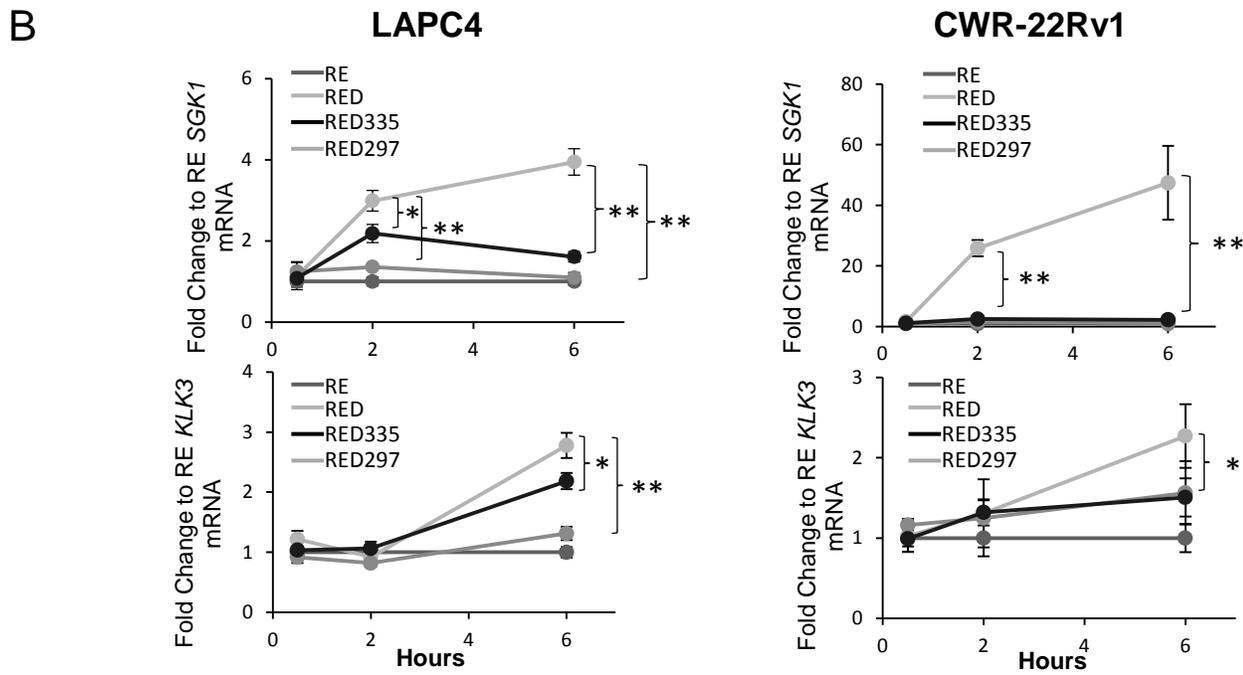
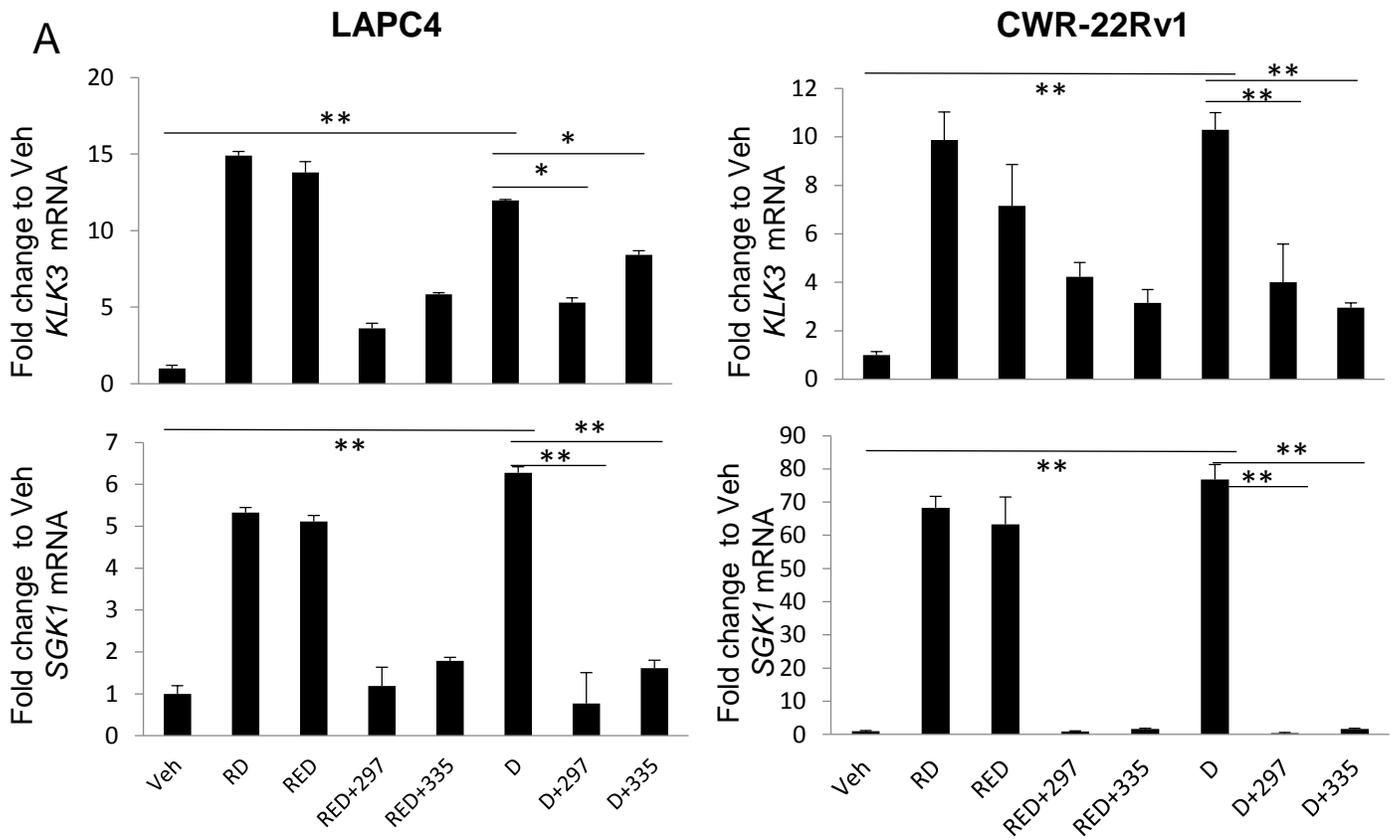


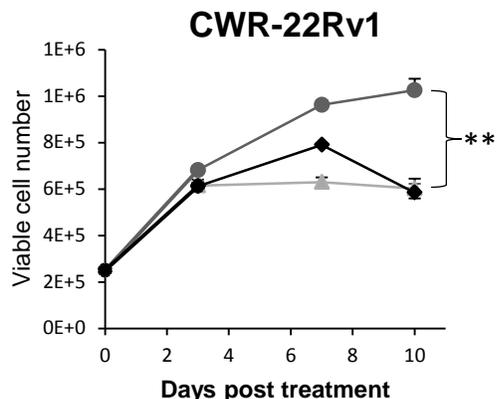
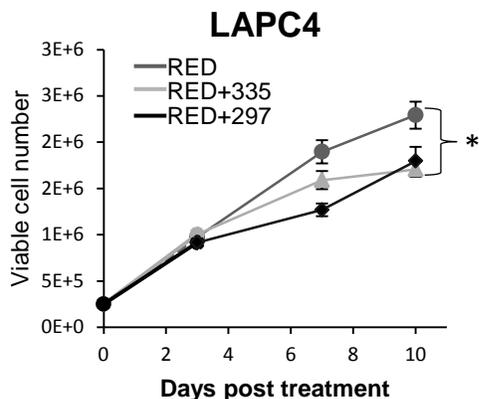
Supplemental Figure 1. Analysis of GR expression. CWR-22Rv1 express higher GR α compared to LAPC4. LAPC4 and CWR-22Rv1 cells were treated with vehicle (Veh), or R1881 (R, 1nM) +/- enzalutamide (E, 10 μ M). DU145 was utilized as a positive control and LNCap as a negative control. **A.** Cell lysates were analyzed by Western blot analysis for GR (antibody detects both α and β) and β -actin. **B.** RNA was isolated and qRT-PCR was performed for *GR α* and *GR β* normalized to *GAPDH* relative to DU145. Errors bars represent SEM.



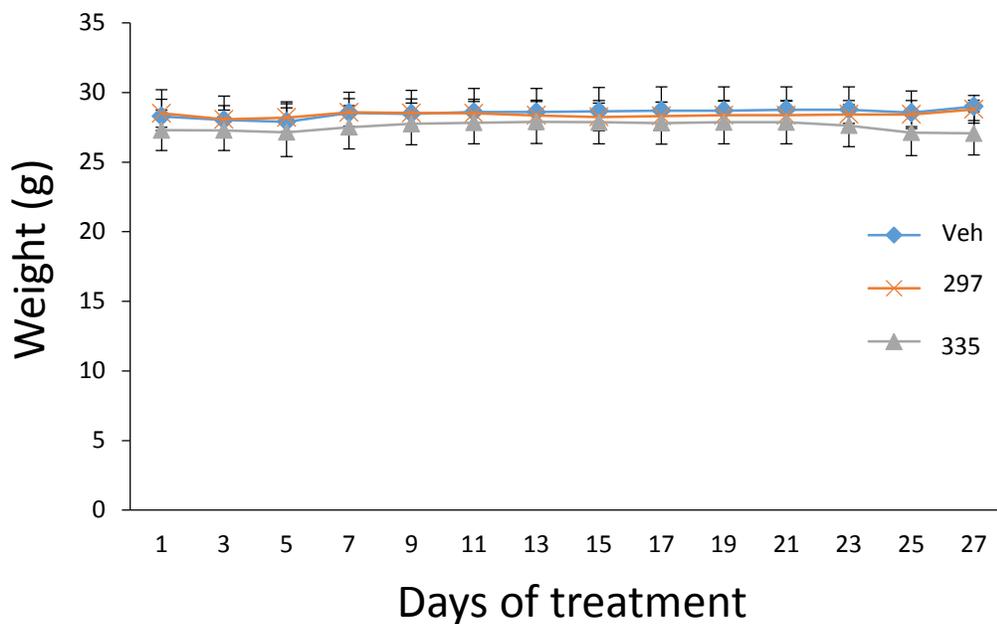
Supplemental figure 2. Single agent treatment of PC cells with CORT108297 or CORT118335 does not impact *KLK3* and *SGK1* mRNA expression or cell viability. **A.** LAPC4 cells were treated with R1881 (R, 1nM), +/- enzalutamide (E, 10 μ M), or CORT108297 (297, 1 μ M), or CORT118335 (335, 1 μ M) for 3 days. RNA was isolated and qRT-PCR was performed. Relative changes in *KLK3* and *SGK1* normalized to *GAPDH* are shown relative to Veh. **B.** LAPC4 cells were plated at 1.25X10⁵ cells per well, then treated with vehicle (Veh), or CORT108297 (297, 1 μ M), or CORT118335 (335, 1 μ M) for 7 days. Error bars indicate SEM. *p<0.05, **p<0.01



Supplemental figure 3. Expression of *KLK3* and *SGK1* is induced by dexamethasone and inhibited by SGRM treatment at various time-points. A. LAPC4 and CWR-22Rv1 cells were treated with R1881 (R, 1nM), +/- enzalutamide (E, 10 μ M), +/- dexamethasone (D, 100nM), +/- CORT108297 (297, 1 μ M), or CORT118335 (335, 1 μ M) for 3 days. **B.** LAPC4 and CWR-22Rv1 cells were treated with vehicle (Veh), R1881 (R, 1nM) and enzalutamide (E, 10 μ M) for three days, then dexamethasone (D, 100nM) and specified SGRM (297 or 335, 1 μ M) were added for 2 or 6 hours and qRT-PCR was performed to quantify *SGK1* and *KLK3* mRNA normalized to *GAPDH*. Data is representative of 3 independent experiments. Error bars represent SEM. Statistical significance was determined by Student's t-test. * p <0.05, ** p <0.01

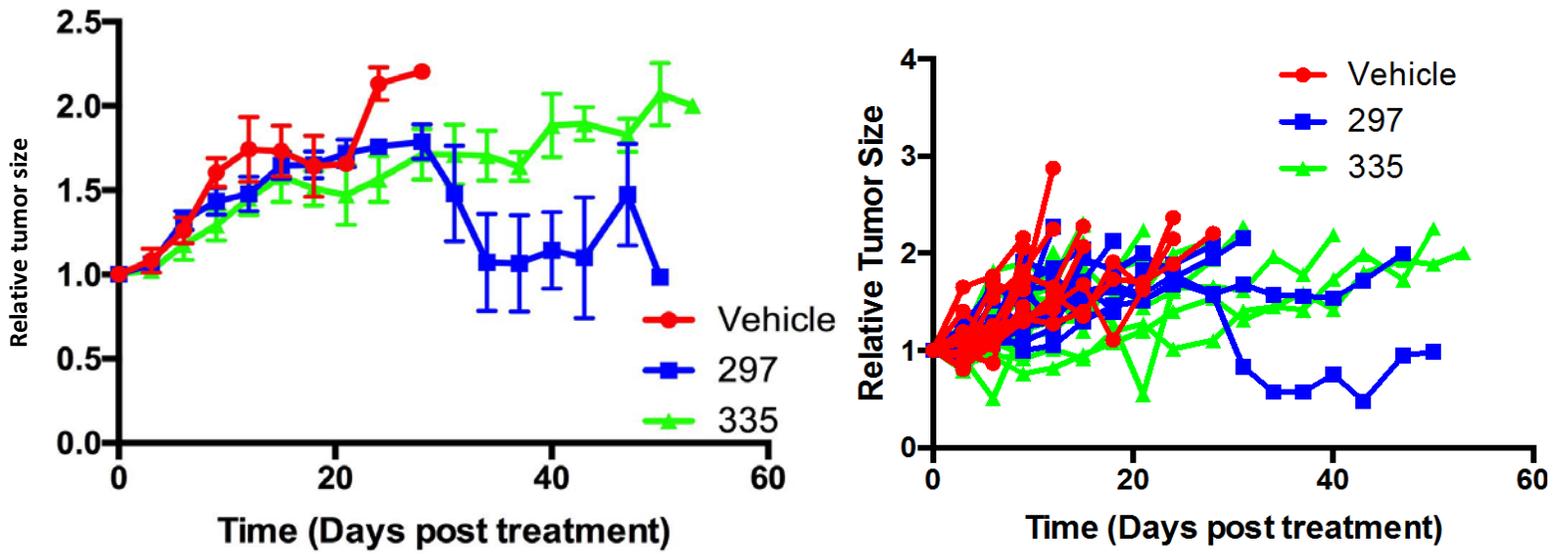


Supplemental figure 4. SGRMs inhibit PC growth following AR blockade. Cells were treated as in Figure 3 then assessed for the total number of viable cells by trypan blue exclusion assay at days 3, 7, and 10. Error bars represent SEM. Statistical significance was determined by Student's t-test, * $p < 0.05$, ** $p < 0.01$.

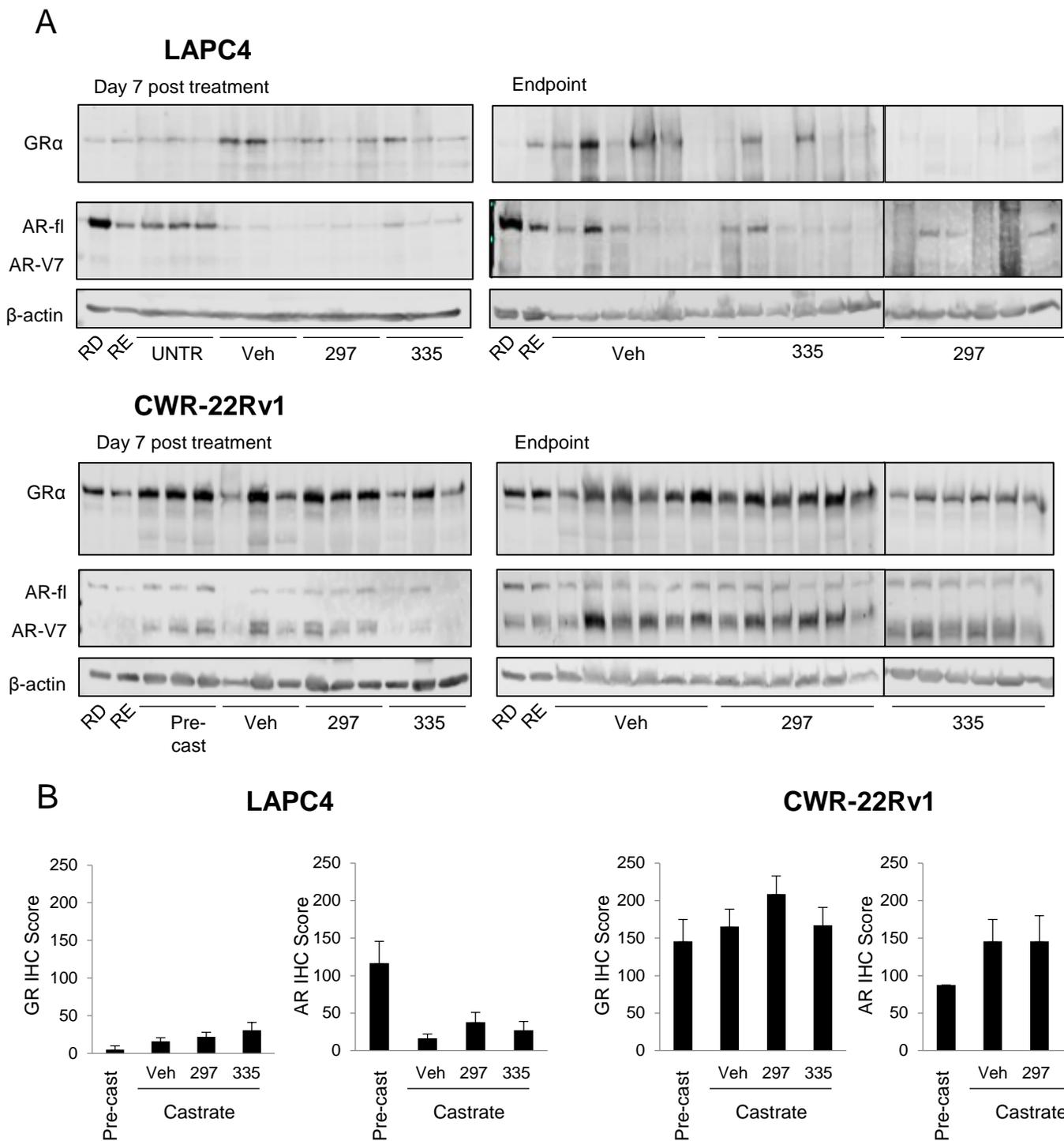


Supplemental figure 5. SGRMs do not impact the weight of mice over 4 weeks of administration. LAPC4 xenografted mice were treated with vehicle (Veh), or 20mg/kg CORT108297 (297), or CORT118335 (335). Error bars represent SEM.

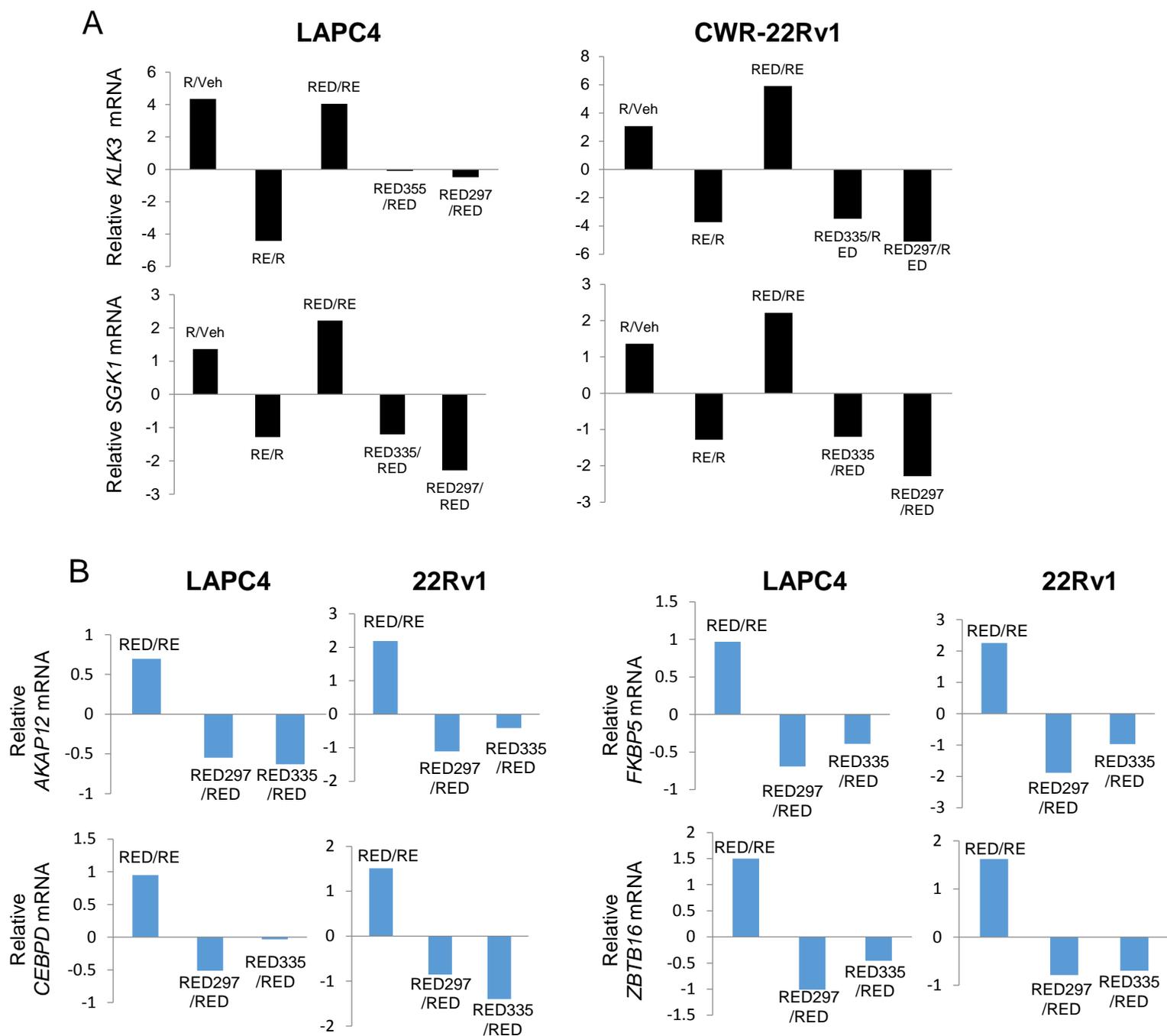
CWR-22Rv1 tumor size over time



Supplemental figure 6. SGRMs inhibit CWR-22Rv1 tumor growth in xenograft mice. Mice were treated as in Figure 4B. Average relative tumor volume of CWR-22Rv1 xenografts (left panel) and individual relative tumor volumes (right panel) are shown.



Supplemental figure 7. GR and AR protein levels are altered in xenografts post castration. LAPC4 and CWR-22Rv1 tumors were dissected from mice prior to castration (Pre-cast), at day 7 following Veh, 297, or 335 treatment, and at the endpoint (tumor doubling from size at castration) and **A**. lysed for Western blot analysis and **B**. formalin-fixed for immunohistochemistry. Cultured LAPC4 and CWR-22Rv1 treated with RD or RE were used as controls. For **A** $n=3-6$ tumors per condition. For **B** serial sections of tumor tissue were labeled with antibodies for GR and AR and slides were analyzed by a pathologist blinded to treatment conditions. Composite scores were determined as described in methods. $n=3$ Pre-cast, $n=8-12$ Veh/297/335. Error bars represent SEM.



Supplemental figure 8. RNA-seq data validates AR and GR dependent gene expression changes and uncovers novel proliferation pathway GR targets. LAPC4 and CWR-22Rv1 cells were treated with R1881 (R, 1nM) and enzalutamide (E, 10 μ M) for 3 days, then dexamethasone (D, 100nM) +/- CORT108297 (297, 1 μ M), or CORT118335 (335, 1 μ M) for 6 hours. RNA was isolated and sequenced. **A** Relative change in FPKM values for *KLK3* and *SGK1* are shown. **B** FPKM values are shown for genes that are involved in IPA proliferation pathways and are upregulated by dexamethasone and downregulated by CORT108297 and CORT118335 in both LAPC4 and CWR-22Rv1 cells.