Figure S1. Combined sequencing analysis of ATAC-seq and RNA-seq.

A, Correlation coefficient heatmap generated by hierarchical clustering of all ATAC-seq samples. **B,** Principal component analysis of ATAC-seq samples. Each point represents one ATAC-seq replicate of C4-2 or C4-2R. **C,** Venn diagram of consensus peaks identified by ATAC-seq between C4-2 and C4-2R. **D,** Average density plot (top) and chromatic accessibility heatmap (bottom) around the 1.5 kb upstream and downstream of each DAP. The shades of pink (C4-2) and purple (C4-2R) indicate signal intensity. **E,** Heatmap of normalized read density for DAPs. **F,** Pie chart of DAPs among different functional elements of the genome. **G,** Venn diagram of DEGs in RNA-seq and DAPs in ATAC-seq. A total of 114 genes are found to have the same trend in both cases.

Figure S2. AhR-GSTM2 regulatory network accounts for resistance to ENZ.

A, Chemical structure of GSTM2 inhibitor NBD. **B,** IC_{50} of NBD on different GST isoforms. The data are obtained from published literature (Giorgio et al. JBC 2005). **C,** IB to detect different GST isoforms in C4-2, C4-2R and 22Rv1. **D, E,** Viability assays in C4-2R and 22Rv1 treated with the indicated concentrations of NBD. Data are scaled into percentage and normalized to the untreated group (NBD = 0), then shown as mean ± SD (n = 8). **F,** Reporter assay to detect the transcriptional activity of AhR in C4-2 and C4-2R. The data are normalized to C4-2 and shown as mean ± SD (n = 4). The experiment is repeated twice, and one is shown. **G,** Viability assay in C4-2R treated with the indicated concentrations of CH. Data are scaled into percentage and normalized to the untreated group (CH = 0), then shown as mean ± SD (n = 8). **H, I,** Viability assays in 22Rv1 treated with the indicated concentrations of CH for 3 days (H) and 6 days (I). Data are scaled into percentage and normalized to the untreated group, then shown as mean ± SD (n = 8). *****, $p < 0.05$.

Figure S3. Elevated GSTM2 confers resistance to SG-ARIs through inhibition of the p38 MAPK pathway.

A, Antioxidant genes by GSEA of C4-2 and C4-2R. The systematic name of the gene set used is M5938. **B,** IB of three common ROS scavengers upon treated with 20μM ENZ for 48 hours. **C,** Viability assay in C4-2 treated with DMSO or 5mM NAC for 3 days. Results are normalized to Ctrl and scaled into percentage, then shown as mean ± SD (n = 8). **D,** GSEA of p38 MAPK pathways using ATAC-seq DAPs identified in C4-2R. **E,** Viability assays in LNCaP and C4-2 treated with DMSO or the indicated concentrations of SB for 3 days. Results are normalized to Ctrl and scaled into percentage, then shown as mean ± SD (n = 8). **F,** IB of three common antioxidant proteins in C4-2 upon treated with 20μM ENZ, APA or DARO for 48 hours. ns, not significant ($p > 0.1$).

Figure S4. In vivo and clinical confirmation of GSTM2 and the OS salvage system leading to resistance to SG-ARIs.

A, B, Body weight of nude mice over the treatment period (A), as well as the final body weight upon harvest (B). ns, not significant ($p > 0.1$). **C,** IB to detect the expression of GSTM2 in different treatment group of 22Rv1 xenograft tumors. Three random mice from each group are shown, except for E+N and D+N groups, in which all three mice are shown. The full-length AR (AR-FL) and AR variant 7 (AR-V7) are shown to confirm the authenticity of 22Rv1, which is known to express these two AR isoforms. **D, E,** Spearman correlations of CYP1B1 and GSTM2 in prostate adenocarcinoma samples (C, n = 495) and paired normal prostate tissues (D, n = 52) from TCGA-PRAD database. **F-I,** Spearman correlations of AhR and GSTM2, CYP1B1 and GSTM2 in prostate adenocarcinoma samples (E and G, n = 156) and normal prostate tissues (F and H, n = 29) from MSKCC database (Barry et al., Cancer Cell 2010, PMID: 20579941). **J, K,** Spearman correlations of AhR and GSTM2 in castration-resistant prostate cancer (CRPC) samples that are exposed (I, n = 128) or naïve (J, n = 121) to second-generation ARIs from SU2C/PCF Dream Team database. **L,** Kaplan-Meier curve of remaining probability of time on treatment of all patients (n=75) that are medicated with SG-ARIs in Fig. 8G. **M,** Kaplan-Meier curve of survival probability of patients that are medicated with ENZ (n = 22) in Fig. 8G. **N-P,** Pathways by GSEA of 7 NRs and 18 Rs treated with ENZ from PNAS 2020 (Alumkal et al., PMID: 32424106). All gene sets are from MSigDB-GSEA, and individual systematic name is: M17243 (M), M20 (N) and M39615 (O).