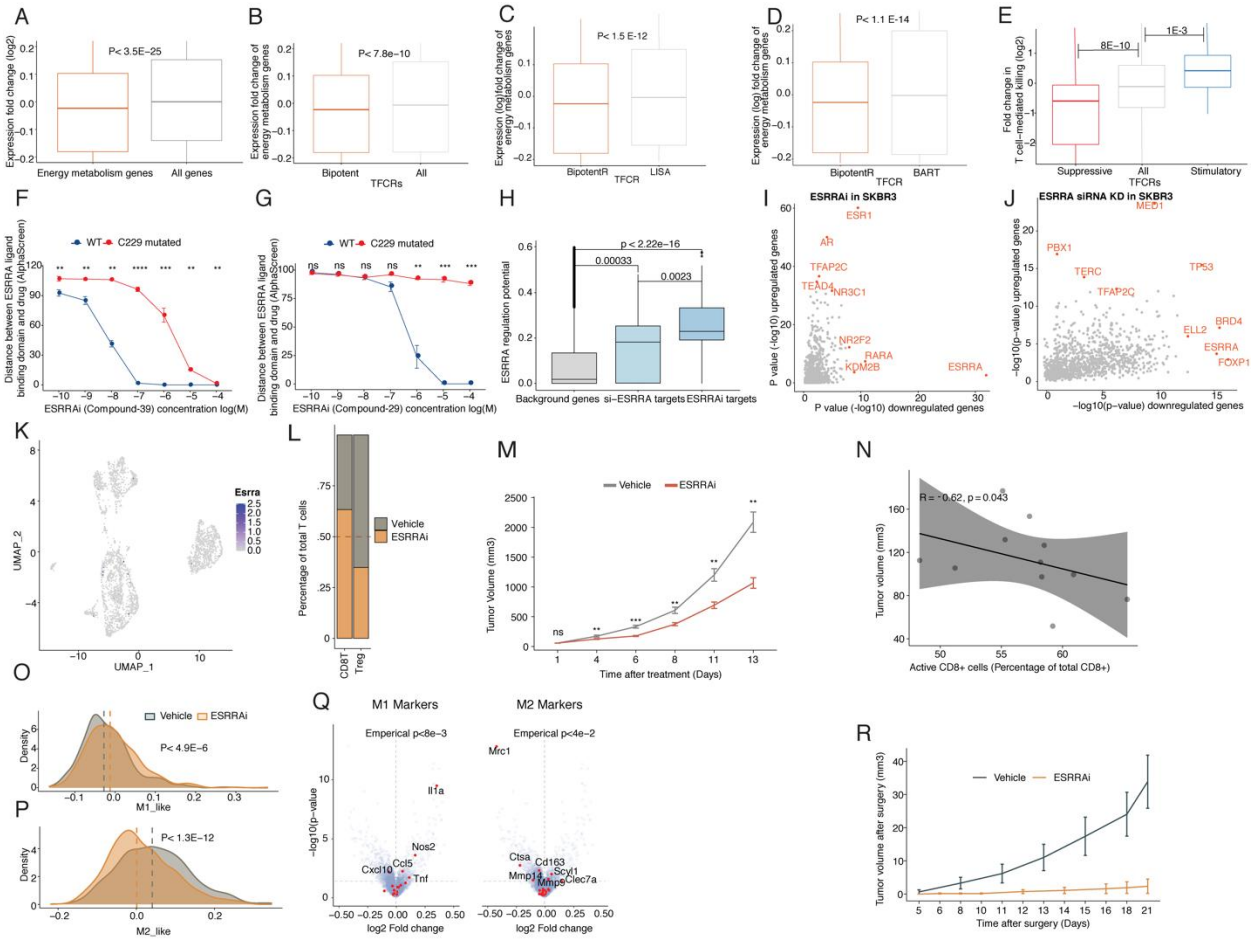


Fig. S2. ESRRA inhibition induces antitumor immunity *in vivo.*

(**A, B**) Validation of BipotentR-identified targets. (**A**) Effect of knockout/knockdown of target identified by BipotentR on expression of genes in energy metabolism pathways. (**B**) Gene expression changes in energy metabolism pathways by knockout of bipotent (immune-metabolic) TFCRs vs. other TFCRs. (**C, D**) Benchmarking BipotentR against other TFCR identification approaches: Effect of knockout/knockdown of target identified by BipotentR on the expression of genes in energy metabolism pathways benchmarked with (**C**) LISA-identified and (**D**) BARTWeb-identified targets. (**E**) Effect of knockout of target identified by BipotentR on T-cell mediated killing of cancer cells. (**F, G**) Effect of concentration on proximity (alphascreen signal) between compounds (39 and 29) and ligand-binding domain of WT or mutated ESRRA. (**H**) The distribution of ESRRA regulatory potentials (sum of ChIP-seq signal weighted by distance from target transcription start sites) for background genes and genes inhibited by siRNA knockdown or drug inhibition of ESRRA. (**I, J**) LISA analysis of up-and down-regulated gene sets by ESRRA inhibition through drug (**I**) or siRNA (**J**). (**K**) ESRRA expression in tumor infiltrating immune cells in 4T1 mouse model.

(**L**) The relative proportion of $CD8^+$ T cells and Tregs in the T-cell populations between ESRRAi and control groups in scRNA-seq data. (**M**) The change in tumor volume over time in ESRRAi and control B16F10 mice (n =10 per group). (**N**) The correlation between tumor volume and fraction of active $CD8^+$ T cells for the ESRRAi treated mice. (**O, P**) Macrophage polarity shifted by ESRRAi shown by M1 (**O**) and M2 (**P**) marker expression density. (Q) Differentially expressed genes of macrophages between ESRRAi and control mice. Labeled genes are M1 and M2 markers. P-value estimated by permutation test (Methods). (**R**) The change of tumor volumes over time (days) in mice after removing tumors by surgery.