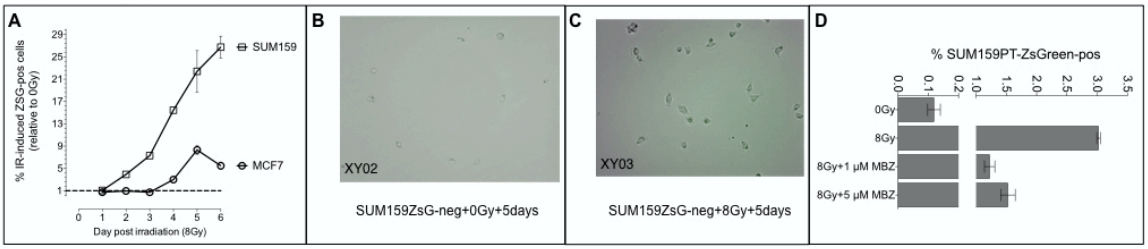
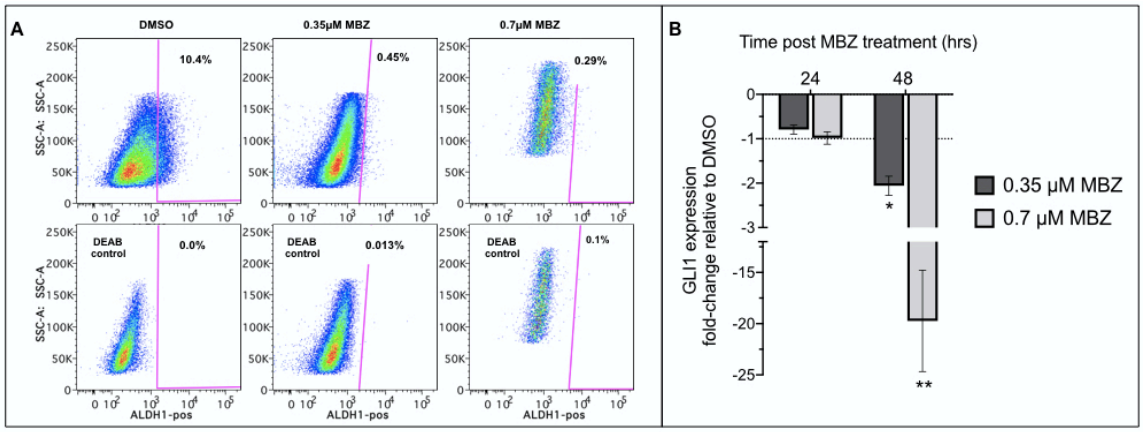
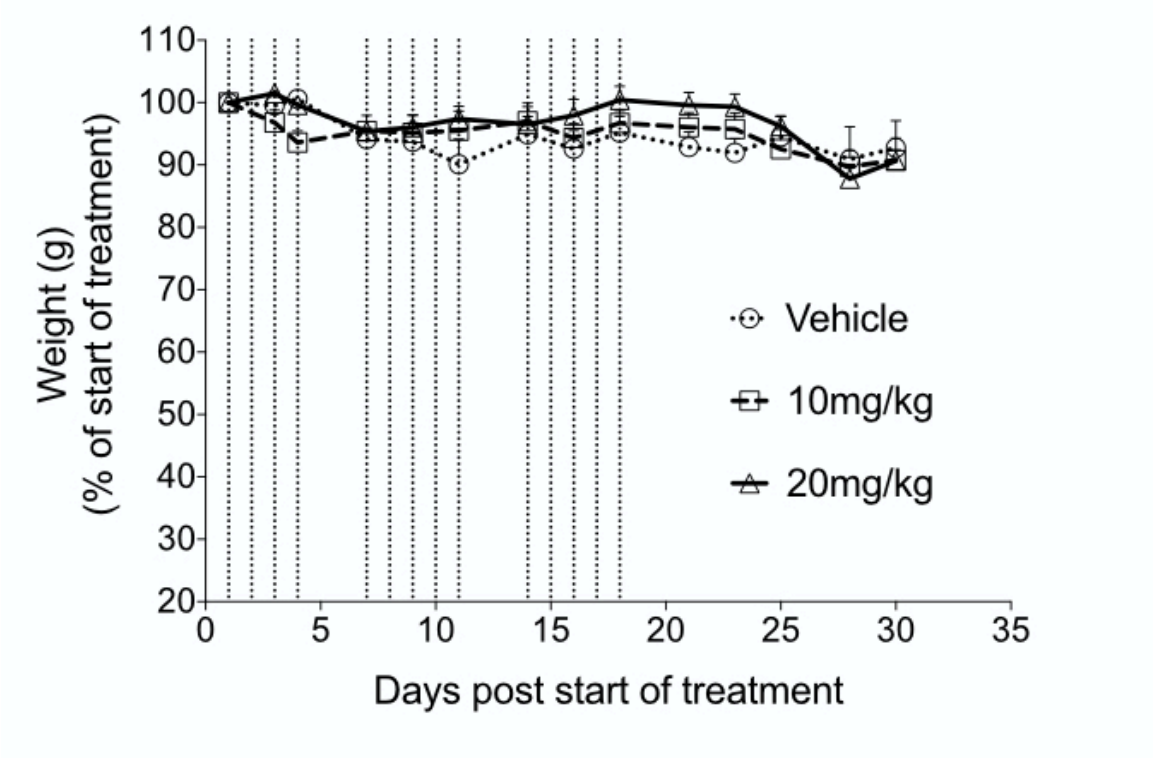


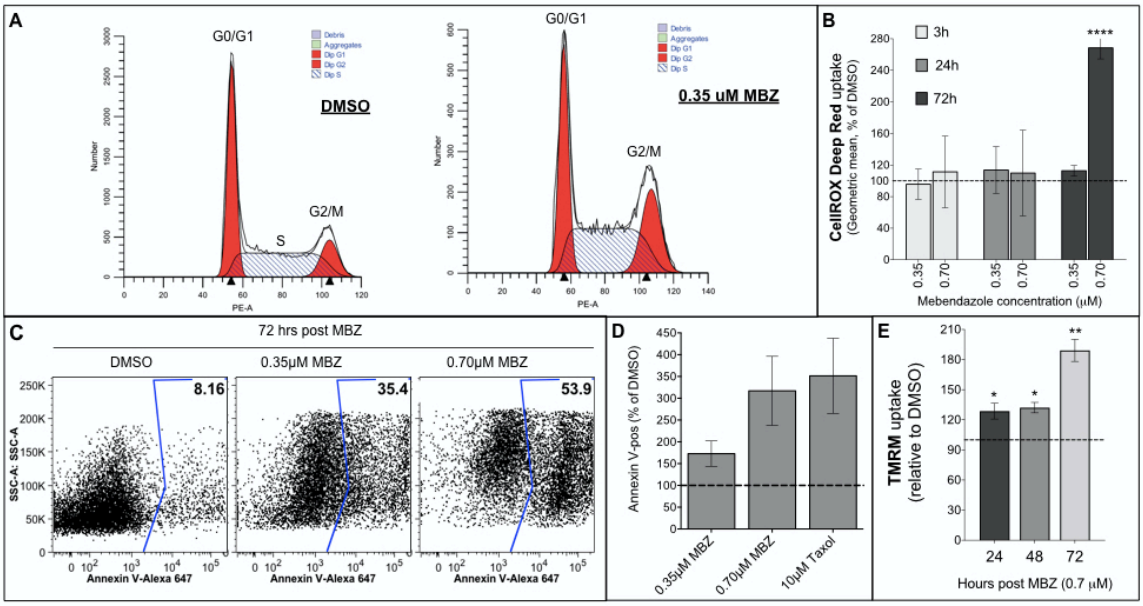
Supplementary Figure 1. Mebendazole inhibits radiation-induced reprogramming of breast cancer cells (**A**) ZSG-pos BCICs from SUM159PT-ZsGreen-cODC line were depleted via high-speed FACS and plated on 6-well plates, treated with a single dose of MBZ and irradiated 1 hr later. After 5 days, cells were removed and the % of IR-induced ZSG-pos BCICs was analyzed via flow cytometry. In (**B**) and (**C**) sorted ZsGreen-neg SUM159PT cells were plated in chamber slides, allowed to attach overnight and placed on a fluorescent microscope stage equipped with a heated and humidified chamber. Images of the cells were taken every 30 minutes for 5 days and compiled in a time-lapse movie. (**D**) SUM159-ZsG-neg sorted cells were plated on 6-well plates, allowed to attach overnight, and the next day treated with the indicated concentrations of MBZ 1 hour prior to IR exposure. 5 days later the % of IR-induced ZsG-pos cells was analyzed via flow cytometry.



Supplementary Figure 2. Mebendazole inhibits the expression of Gli1. (**A**) SUM159PT monolayer cultures were treated with a single dose of MBZ at the indicated concentrations and 5 days later the % of BCICs was determined based on ALDH1 activity (ALDH1-pos) using the ALDEFLUOR assay and determining the ALDH1-pos-associated fluorescence via flow cytometry. Pre-treatment with DEAB (which inhibits the activity of ALDH1) is used as a negative control for setting the analysis gates (bottom panels). (**B**) SUM159PT cells were treated with the indicated concentrations of MBZ. At the indicated time points mRNA was isolated, reverse transcribed into cDNA and the relative change in gene expression for Gli1 was determined via real-time quantitative PCR.



Supplementary Figure 3. Mebendazole is safe to administer for extended periods of time. Treatment with mebendazole i.p. for three weeks on a 5-days on, 2-days off schedule showed no systemic toxicity.



Supplementary Figure 4. Mebendazole induces apoptosis. (**A**) Representative flow cytometry plots of PI staining for cell cycle analysis at 24 hours post DMSO or MBZ treatment. (**B**) SUM159PT cells were treated with MBZ at the indicated concentrations and stained with CellROX Deep Red at the indicated time points for analyzing the formation of reactive oxygen species. Unpaired, two-tailed *t*-test: ****$P < 0.00001$. (**C**) Representative flow cytometry plots of Annexin-V staining for apoptosis at 72 hrs post MBZ treatment. (**D**) Treatment of SUM159PT cells with a single dose of 0.7μM MBZ results in a similar percentage of Annexin-V-pos cells as treating with 10μM Taxol. (**E**) Treatment with 0.7μM MBZ hyperpolarizes the mitochondrial membrane potential in treated cells. Mitochondrial membrane potential was measured by the uptake of Tetramethylrhodamine, Methyl Ester (TMRM) via flow cytometry. Student's t-test: *$P < 0.01$, **$P < 0.001$.