**SUPPLEMENTARY FIGURE LEGENDS**

**FIGURE S1.** p53 protein expression and the 2D synergy landscape between APR-246 and radiation in p53WT, p53Mut, and p53Null HCT116 cells. (A) The basic levels of p53 protein were examined in p53WT, p53Mut, and p53Null cells by Western blotting. GAPDH was used as interval control. Data represents the mean ± SD of protein band intensities taken from three independent experiments. These were normalized to the intensity of GAPDH;(B)**.** The semi-log dose curves for the three HCT116 cell lines to calculate IC50 of APR-246 without radiation. (C). The semi-log dose-response curves of radiation for the indicated HCT116 cell lines with different p53 status under different concentrations of APR-246 treatment; (D). The semi-log dose-response curves of APR-246 for the indicated HCT116 cell lines with different p53 statuses under different radiation doses; (F-H). 2D synergy landscape, and ZIP synergy score of APR-246 and radiation in p53WT (F), p53Mut (G) and p53Null (H) cells. Red area refers to synergy and green area refers to antagonism.

**FIGURE S2.** The synergistic effect of APR-246 with radiation in normal colonic epithelial (CCD841 CoN) and fibroblast (CCD18 Co) cell lines. (A) The semi-log dose-response curves of radiation for the indicated cell- lines post different concentration of APR-246 treatment. (B) The semi-log dose-response curves of APR-246 for the indicated cells under different radiation doses. (C) Half maximal inhibitory concentration (IC50) of APR-246 treatment under different radiation doses in the indicated cell lines based on cell viability, Bars represent mean viability (n=3). (D) A representative synergy 3D image of co-treatment APR-246 and radiation in CCD841 CoN cells. (E) A representative synergy 3D image of co-treatment APR-246 and radiation in CCD18 Co cells. (F) Mean synergy score of the co-treatment of APR-246 and radiation in the indicated cell lines. Bars represent mean viability (n=3).

**FIGURE S3.** Impact of APR-246 or/and radiation on cell cycle perturbation in p53WT, p53Mut, and p53Null HCT116 cells. (A-F), Representative cytogram and histograms of p53WT (A, B), p53Mut (C, D), and p53Null (E, F) cells showing cell cycle profiles following treatment with control, APR-246 alone, radiation alone, and in combination. Percentage of cell population in each phase of the cell cycle is shown. Graph represents the mean ± SD of three independent experiments.

**FIGURE S4.** Impact of APR-246 or/and radiation on ROS production and apoptosis in p53WT, p53Mut, and p53Null HCT116 cells.(A),ROS positive cells were detected with flow cytometry. The representative histograms of ROS positive cells in p53WT, p53Mut and in p53Null cells after different treatments and ROS staining. (B), Representative histograms of apoptosis from Annexin V/PI analysis detected by flow cytometry are shown.

**FIGURE S5.** The potential synergistic effect of APR-246 with radiation in primary cell cultures.(A). The semi-log dose-response curves of radiation for the indicated primary cancer cell cultures under different concentrations of APR-246 treatment; (B). Half maximal inhibitory concentration (IC50) of APR- 246 treatment under different radiation doses in the indicated primary cancer cell cultures based on cell viability. Bars represent mean IC50 (n=3); (C). The semi-log dose-response curves of APR-246 for the indicated primary cancer cell cultures under different radiation doses; (D). Half maximal inhibitory concentration (IC50) of radiation under different concentrations of APR-246 treatment in the indicated primary cancer cell cultures based on cell viability. Bars represent mean IC50 (n=3); (E). Representative images of cell phase distribution and quantified histograms in primary cell cultures. Data are mean ± S.D. of three independent experiments. \*p < 0.05, \*\*p < 0.01, n.s. not *statistically* significant. F, The representative scatter plot of apoptosis in primary cell cultures; (F). Representative flow cytometry images of cell apoptosis in indicated primary cell cultures.

**FIGURE S6.** The differential genes regulated by TP53 in HCT116 cell lines with different p53 status post radiation treatment**.** DEGs in transcriptional regulation by TP53 pathway through comparing radiation treatment with control in p53WT, p53Mut and p53Null cells. Upregulated genes were in red and downregulated DEGs in blue.

**FIGURE S7.** The DEGs and enriched Reactome Pathways in HCT116 cell lines with different p53 status post APR-246 treatment alone.(A). Volcano plot of DEGs between APR-246 and control in indicated HCT116 cell lines. Fold change (x axis) is plotted against statistical significance (y axis) for each gene. Genes upregulated with a log (fold change) ≥1 and p < 0.05 are depicted in red, and those downregulated with a log (fold change) ≥1 and p < 0.05 in green. Grey represents genes that did not differ significantly between APR-246 treatment and control. The top 10 most significant gene were labelled; (B). The top 20 enriched Reactome Pathways found in the analysis of DEGs between APR-246 treatment and control in HCT116 p53Mut cells; (D). The top 20 enriched Reactome Pathways found in the analysis of DEGs between APR-246 treatment and control in HCT116 p53Null cells.

**FIGURE S8.** The deregulated genes in selected pathways between combination versus radiation alone in p53WT, p53Mut, and p53Null HCT116 cells.(A-C). the actinomorphic diagram showing the enriched genes of selected pathways in p53WT (A), p53Mut (B), andp53Null (C) cells.

**FIGURE S9.** The PPI of enriched genes in cell cycle and mRNA splicing pathways in HCT116 cell lines. (A-C). PPI analysis of core enriched genes in cell cycle pathway of p53WT (A), p53Mut (B), and p53Null (C) cells. (D-F). PPI analysis of enriched genes in mRNA splicing pathway of p53WT (D), p53Mut (E), and p53Null (F) cells.

**FIGURE S10.** The PPI of enriched genes in apoptosis and Transcriptional Regulation by *TP53* *et al* pathways comparing combination versus radiation alone in HCT116 cell lines. (A, B). PPI analysis of enriched genes in apoptosis pathway of p53WT (A) and p53Mut (B) cells, respectively; (C, D). PPI analysis of enriched genes in transcriptional regulation by TP53 pathway of p53WT (C) and p53Mut (D) cells, respectively; **(**E-G).PPI of genes enriched in DNA replication (E), base excision repair (F), and autophagy (G) in p53Null cells when comparing combination treatment to radiation alone.