***Lipotecan induces more radiation-induced DNA damages than sorafenib***

To analyze the different impacts on DNA damage between Lipotecan and sorafenib, γ-H2AX foci per cell was counted in Huh7 and PLC5 cells treated with radiation (10 Gy) alone, combined radiation and Lipotecan, and combined radiation and sorafenib. Sorafenib did not increase the number of γ-H2AX foci/cell compared with radiation alone at 8 h in both Huh7 and PLC5 cells (16.2 ± 0.6 vs. 14.3 ± 0.8 and 10.6 ± 0.3 vs. 12.0 ± 0.9, respectively, *p*= 0.07) (Supplementary Fig. 5A). The results show that Lipotecan (Supplementary Fig. 5B) but not sorafenib enhanced radiation-induced DNA damage in HCC cells.

**Supplementary Fig. 5. Superior radiosensitizing effect of topoisomerase 1 inhibitor (TOP1i, Lipotecan) to sorafenib on hepatocellular carcinoma (HCC) cells.** (A) Sorafenib enhanced the radiosensitization of HCC cell lines, Huh7 better than PLC5 in clonogenic survival assays. Cells were seeded in six-well plates and treated with different doses of radiation (2.5–10 Gy) following 1-h pretreatment with various doses of sorafenib, or DMSO vehicle. Cells were then cultured for an additional 7 days. The surviving fraction was determined as described in Materials and Methods. All experiments were performed independently in triplicate. Quantitative results of clonogenic assays after combination treatment with sorafenib and irradiation (RT). Data are means ± SD. At each dose level, the colony count was expressed as a fraction of the number in the corresponding control group. (B) The average number of γ-H2AX foci after RT-induced DNA damage with/without sorafenib in Huh7 and PLC5 cells. Lines, mean (n = 3); Bars, S.D, \**p* < 0.05. Cell lines were exposed to ionizing irradiation of 10 Gy either alone or combined with sorafenib. The concentrations of sorafenib were 0.5 μM for Huh7 cells, and 3 μM for PLC5 cells, respectively. The cells were then incubated for 4 h before harvest. Data are from a representative experiment of at least triplicate.

