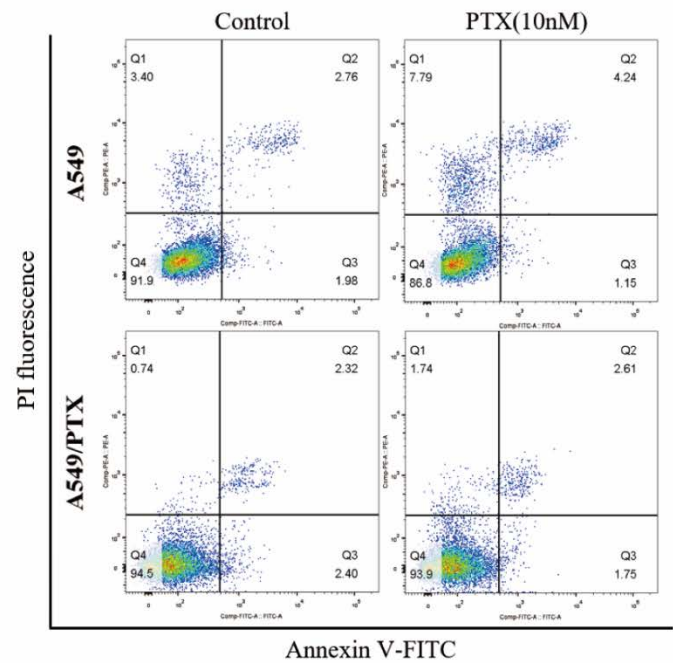
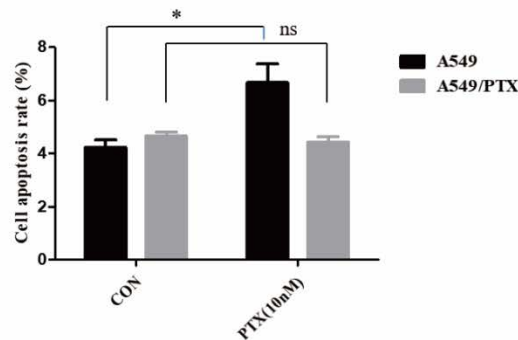


Supplementary Materials:

A.



B.



Cell apoptosis rate(%)	Control	PTX
A549	4.20 ± 0.50	6.68 ± 1.22
A549/PTX	4.67 ± 0.25	4.45 ± 0.33

Figure S1. PTX-resistant cells are resistant to paclitaxel-induced cell death. (A) A549 and A549/PTX-resistant cells were treated with or without paclitaxel (10 nM) for 48h, and apoptotic cells were detected by Annexin V-FITC and PI staining. (B) Cell apoptosis rate was presented according to (A). Values are presented as means±SD from three independent experiments, ns means no significant, \*p<0.05.

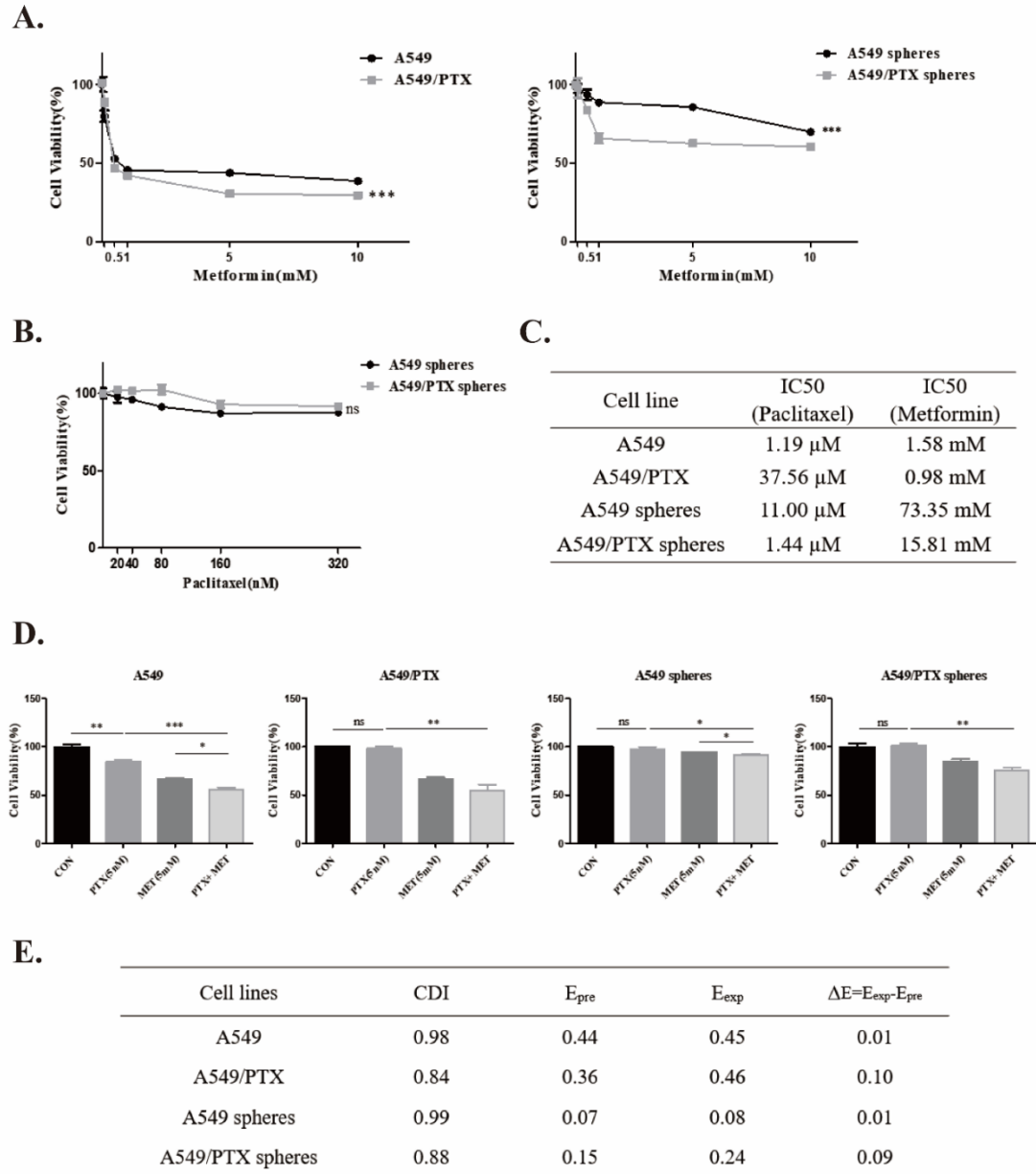


Figure S2. PTX-resistant cells are sensitive to metformin but resistant to paclitaxel in 2D or 3D culture. (**A** and **B**) A549 and A549/PTX cells in 2D or 3D culture were treated with metformin (0.1-10 mM) (**A**) or paclitaxel (20-320 nM) (**B**) for 48 h and viabilities calculated as mean  $\pm$ SD (n=3). (**C**) IC50 values were calculated by the CCK-8 assay. (**D**) A549 and A549/PTX drug-resistant cell lines in 2D or 3D culture were treated with paclitaxel (5 nM), metformin (5 mM) alone or their combination for 48 h and viabilities calculated as mean  $\pm$ SD (n=3). (**E**) Drug interaction was analyzed using the coefficient of drug interaction (CDI) and Bliss independence (BI) models. CDI<1 or  $\Delta E$ >0 indicates a synergistic effect, CDI=1 or  $\Delta E$ =0 indicates an additive effect, CDI>1 or  $\Delta E$ <0 indicates an antagonistic effect. Data are expressed as the mean  $\pm$  SD (n=3), ns means no significant, \*p<0.05, \*\*p<0.01, \*\*\*p<0.001.