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FTY720 enhances the anti-tumor activity of carboplatin and tamoxifen in a patient-derived xenograft model of ovarian cancer

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ABSTRACT

Ovarian cancer is the fifth leading cause of cancer-related deaths among women in the United States. Although most patients respond to frontline therapy, virtually all patients relapse with chemoresistant disease. This study addresses the hypothesis that carboplatin or tamoxifen + FTY720, a sphingosine analogue, will minimize or circumvent drug-resistance in ovarian cancer cells and tumor models.

In vitro data demonstrate that FTY720 sensitized two drug-resistant (A2780.cp20, HeyA8.MDR) and two high-grade serous ovarian cancer cell lines (COV362, CAOV3) to carboplatin, a standard of care for patients with ovarian cancer, and to the selective estrogen receptor modulator tamoxifen. FTY720 + tamoxifen was synergistic *in vitro,* and combinations of FTY720 + carboplatin or + tamoxifen were more effective than each single agent in a patient-derived xenograft model of ovarian carcinoma. FTY720 + tamoxifen arrested tumor growth. FTY720 + carboplatin induced tumor regressions, with tumor volumes reduced by ~86% compared to initial tumor volumes. Anti-tumor efficacy was concomitant with increases in intracellular proapoptotic lipid ceramide. The data suggest that FTY720 + tamoxifen or carboplatin may be effective in treating ovarian tumors.