**Tivozanib Activity in Combination With Capecitabine, 5-fluorouracil (5-FU) or Docetaxel, in Traditional or Engineered Subcutaneous Breast Tumor Models**

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**Abstract**

**Background:** Tumors and fluorouracil (5-FU) are 2 major classes of chemotherapy drugs used to treat advanced breast cancer. Recent clinical data indicate that vascular endothelial growth factor (VEGF) signaling pathway inhibitors exhibit promising activity in combination with the 5-FU/fluorouracil (5-FU) preclinical/clinical drug.

**The antitumor activity of Tivozanib, a potent and selective kinase inhibitor of VEGF receptors 1, 2, and 3, was evaluated alone and in combination with capecitabine in a human epidermal growth factor receptor 2 (Her2)-engineered murine tumor that exhibits tumor resistance. In addition, Tivozanib was evaluated in combination with representative tumors and fluorouracil chemotherapeutic drug in a xenograft model of breast cancer.

**Materials and Methods:** Subcutaneous MDA-MB-453-4T1 engineered murine or MDA-MB-157 human breast tumors were grown in female nude mice. Mice bearing the engineered tumors were treated with oral Tivozanib (5 mg/kg/day) for 9 days, 2 days off schedule, or both drugs in combination. Mice bearing MDA-MB-453-4T1 tumors were treated with oral Tivozanib (20 mg/kg/day) for 14 days on, 7 days off schedule, or both drugs in combination. Mice bearing MDA-MB-157 tumors were treated with oral Tivozanib (20 mg/kg/day) for 14 days on, 2 days off schedule, or both drugs in combination. Tivozanib alone or in combination with capecitabine appeared to reverse induced tumor stasis. Most common adverse events were hypertension and headaches.

**Results:** In the Her2-engineered breast tumor model, treatment with Tivozanib alone or capecitabine alone resulted in continued tumor growth with only modest TG1. However, the combination of Tivozanib plus capecitabine led to complete growth inhibition. In the MDA-MB-453-4T1 xenograft model, Tivozanib monotherapy exhibited robust activity in combination with capecitabine in a breast Her2 tumor that exhibited Tivozanib resistance. In addition, Tivozanib was evaluated in combination with representative tumors and fluorouracil chemotherapeutic drug in a xenograft model of breast cancer.

**Conclusions:** When examined in a Tivozanib-resistant murine breast tumor model, Tivozanib combined with capecitabine appeared to reverse Tivozanib resistance. Tivozanib treatment also potentiated inhibited MDA-MB-157 breast tumor growth and enhanced the antitumor effects of 5-FU and docetaxel.

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