**Introduction:** Neoadjuvant endocrine therapy is often utilized to downstage Estrogen Receptor positive (ER+) breast cancer prior to surgery. However, this approach is sometimes met with endocrine resistance mechanisms within the tumor. This trial examines the safety and efficacy of tamoxifen in combination with an mTORC1/2 inhibitor, TAK-228, in the neoadjuvant treatment of ER+ breast cancer.

**Methods:** In this single arm, open label trial, pre- and post-menopausal women were enrolled to receive neoadjuvant tamoxifen (20 mg daily) with TAK-228 (30 mg weekly) for 16 weeks prior to surgery. Patient had tissue sampling at baseline, week 6, and week 16. The primary endpoint was change in Ki-67 from baseline to 6 weeks. The toxicity, change in tumor size, pathologic complete response rate, PEPI score, and baseline Oncotype Dx score were also assessed.

**Results:** Twenty-eight women were enrolled on the trial, and 25 completed the entire study course. The combination of tamoxifen and TAK-228 resulted in a significant reduction in Ki-67 from 18.3% to 15.2% (p = 0.0023). The drug was also found to be safe and tolerable. While nausea and hyperglycemia were common side effects, these were manageable. The tumor size also significantly decreased with the treatment, with a median decrease of 0.75 centimeters (p < 0.0001). There were no pathologic complete responses.

**Conclusion:** Tamoxifen and TAK-228 is an effective neoadjuvant treatment for ER+ breast cancer, with significant reduction in both Ki-67 and tumor size.

**Keywords:** TAK-228; Breast Cancer; Hormone Receptor Positive; mTOR Inhibitor; Neoadjuvant Therapy