Lasoxifene alone or in combination with palbociclib is an effective treatment for therapy-resistant ER-positive metastatic breast cancer

Introduction
Patients with estrogen receptor positive (ER+) Metastatic Breast Cancer (MBC) are typically treated with fulvestrant, a selective estrogen receptor degrader, or a combination of fulvestrant and palbociclib (CDK4/6 Inhibitor). Approximately 25-40% of patients with ER+ MBC have mutations in the ligand-binding domain of ERα. One of the most common mutations is Y357S, which confers ERα constitutive activity and renders tumors resistant to endocrine therapies. Lasoxifene, a selective estrogen receptor modulator (SERM), was developed for the treatment of vaginal atrophy and osteoporosis. A previous study performed in a mutant ERα+ MCF-7 xenografts model mouse, showed that losaxifene was more effective than fulvestrant at inhibiting tumor growth and metastasis to the liver and lung. In the current dose/response study, we compared the efficacy of lasoxifene + palbociclib combinations to fulvestrant + palbociclib combinations. Engineered and luciferase-GFP tagged MCF-7 Y357S cells were injected into the mammary ducts of NSG mice (MND model) and tumor progression was monitored by live imaging of primary tumors, as well as ex vivo imaging and biochemical analysis of metastatic sites at study endpoint. All dose combinations of lasoxifene + palbociclib were more effective than fulvestrant + palbociclib at inhibiting primary tumor growth as well as bone, lung, liver and brain metastasis. These data show that lasoxifene has potential as an effective therapy for endocrine resistant, mutant ERα+ metastatic breast cancer.

Lasoxifene + palbociclib is more effective than fulvestrant + palbociclib and significantly more effective than fulvestrant alone at inhibiting metastasis to the lung

Lasoxifene + palbociclib is more effective than fulvestrant + palbociclib and significantly more effective than fulvestrant alone at inhibiting metastasis to the liver

Lasoxifene + palbociclib is more effective than fulvestrant + palbociclib and significantly more effective than fulvestrant alone at inhibiting metastasis to bone and brain

Results
Lasoxifene + palbociclib is significantly more effective than palbociclib alone or a combination of fulvestrant and palbociclib at reducing primary tumors growth and final tumor weight

CONCLUSIONS
Lasoxifene alone or in combination with palbociclib is an effective inhibitor of tumor growth for the MCF7 Y357S ER+ MBC xenograft model.
Lasoxifene + palbociclib is significantly more effective than fulvestrant + palbociclib at inhibiting tumor growth and metastasis to the liver, lung, bone and long bones. Excellent correlation between ex vivo imaging and IHC or HE assessments of metastatic burden.
Importantly, lasoxifene + palbociclib produces a synergistic inhibition of tumor growth and metastasis. In addition, lasoxifene appears to drive synergism in combination with palbociclib, whereas palbociclib appears to drive synergism in combination with fulvestrant.
Lasoxifene shows promise as an effective therapy for women with ER+ metastatic breast cancers that express constitutively active ERα mutations, such as D538G and Y357S. A phase 2 clinical trial is currently under way to evaluate Lasoxifene versus Fulvestrant in Advanced or Metastatic ER+/HER2+ Breast Cancer with an ERα Mutation.