The Complete Estrogen Receptor Antagonist OP-1250 Can Combine with HER2 Inhibition to Inhibit Estrogen Receptor-driven Cellular Proliferation and Shrink Xenograft Tumors in ER+/HER2+ Breast Cancer Models

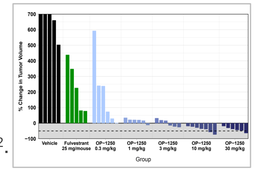
Alison D. Parisian, Leslie Hodges-Gallagher, Richard Sun, Susanna Barratt, Gopinath S. Palanisamy, Julia Lawrence, Pamela Klein, David C. Myles, Cyrus L. Harmon, Peter J. Kushner

Olema Oncology, San Francisco, CA

San Antonio Breast Cancer Symposium
Dec. 7-10, 2021
ABSTRACT # 1618
Poster # P5-08-07

Background

- The human epidermal growth factor receptor 2 (HER2, aka ERBB2) oncogene is overexpressed in approximately 25% of breast cancer tumors and is associated with a high rate of brain metastasis[1].
- Approximately half of HER2+ tumors are also estrogen receptor (ER) positive[1].
- OP-1250 is a complete estrogen receptor antagonist (CERAN), which has been shown to effectively shrink ER+ breast cancer xenografts, including ER mutant models[2].
- While extensively characterized in ER+/HER2- breast cancer models, OP-1250 has not previously been tested in a HER2+ context.



OP-1250 treatment in the HCI-013 PDX model, which contains ESR1 Y537S mutation.

OP-1250 reduces proliferation and degrades the estrogen receptor in combination with HER2 inhibitor tucatinib in ER+/HER2+ cells

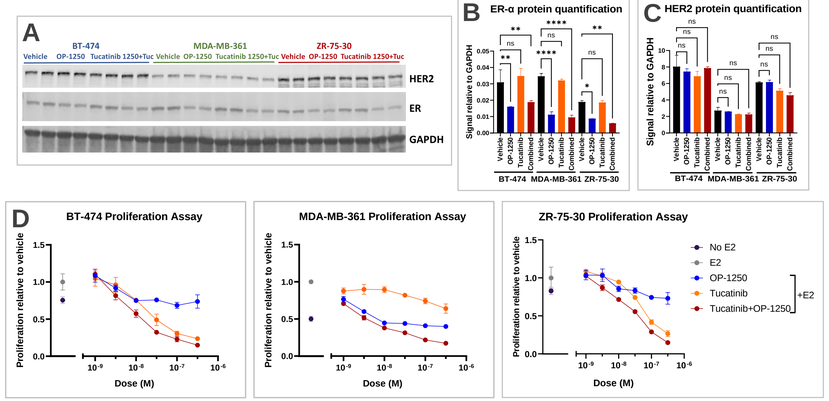


Figure 1. In vitro data of OP-1250 treatment with HER2 inhibitor tucatinib in three ER+/HER2+ cell lines. A-C) Western blot image and quantification of cells treated for 4h with vehicle, 100nM OP-1250, 200 nM tucatinib, or the combination. OP-1250 degrades the estrogen receptor in all cell lines tested. D) Proliferation assays of cells treated for 7 days with OP-1250, tucatinib, or the equimolar combination in stripped serum media supplemented with 500 pM estradiol. All cell lines demonstrate reduction in proliferation with OP-1250 treatment and efficacy of combined compound treatment. * indicates adjusted p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001, **** p-value < 0.0001

OP-1250 reduces proliferation in combination with HER2 inhibitor trastuzumab in ER+/HER2+ cell lines

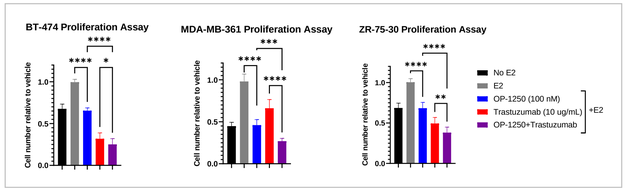


Figure 2. Proliferation assays of ER+/HER2+ cell lines treated for 7 days with 100 nM OP-1250, 10 ug/mL trastuzumab, or the combination in stripped serum media supplemented with 500 pM estradiol. Proliferation is reduced with OP-1250 treatment alone and in combination with trastuzumab. * indicates adjusted p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001, **** p-value < 0.0001

OP-1250 reduces xenograft growth in combination with HER2 inhibitors in cell line and PDX models of ER+/HER2+ breast cancer

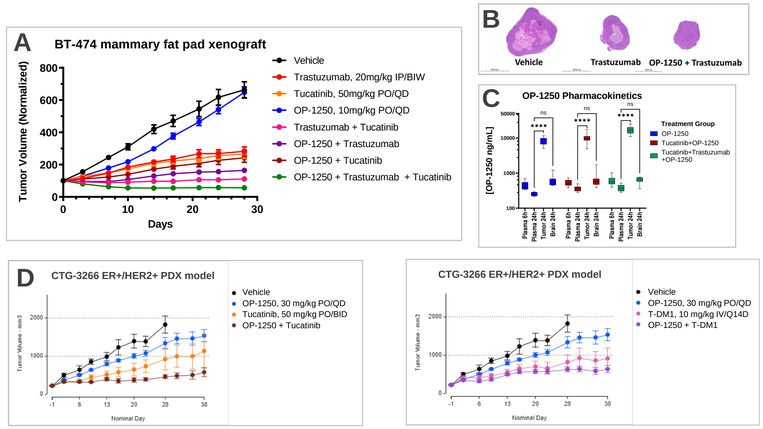


Figure 3. Xenograft studies of ER+/HER2+ cell line or patient-derived xenograft (PDX) treated with OP-1250 and HER2 inhibitors. A-C) BT-474 cell line implanted into the mammary fat pad of NSG mice tumor volume (A) and representative H&E images (B). Tumor shrinkage occurred when OP-1250 was combined with dual HER2 therapy. Pharmacokinetic analysis of OP-1250 levels in plasma, tumor and brain (C) showed enrichment of OP-1250 in BT-474 tumor tissue and brain penetrance. D-E) Tumor growth of CTG-3266 PDX model implanted subcutaneously into nude mice. OP-1250 treatment inhibited growth in this model alone and with HER2 inhibitors tucatinib (D) and ado-trastuzumab emtansine (T-DM1) (E). **** indicates adjusted p-value < 0.0001

OP-1250 in combination with HER2 inhibitors trastuzumab and tucatinib reduces ER+/HER2+ xenograft growth as well or better than chemotherapy capecitabine

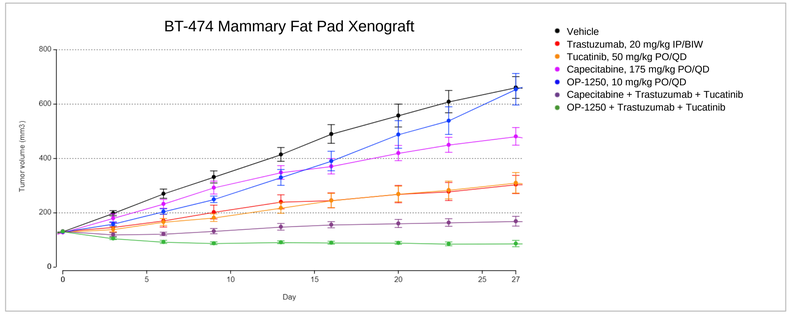


Figure 4. Xenograft model of the ER+/HER2+ BT-474 cell line implanted into the mammary fat pad of NSG mice. The addition of OP-1250 to HER2 inhibitors trastuzumab and tucatinib resulted in greater tumor shrinkage than capecitabine.

Conclusions

- OP-1250 inhibits estrogen receptor-driven proliferation and effectively degrades the estrogen receptor in multiple ER+/HER2+ cell lines.
- The addition of OP-1250 to HER2 inhibitors improved tumor growth inhibition in both ER+/HER2+ cell line-derived xenograft and patient-derived xenograft models.
- OP-1250 exhibits brain penetrance and concentrates in tumors in an ER+/HER2+ xenograft.
- OP-1250 in combination with HER2 inhibitors trastuzumab and tucatinib inhibits ER+/HER2+ xenograft growth at least as well as capecitabine.
- These data provide a strong rationale to study OP-1250 in combination with HER2 targeted agents as a chemotherapy-free treatment for ER+/HER2+ breast cancer.
- A clinical study evaluating the combination of OP-1250 and HER2 targeted agents is planned for 2022.

References

1. Tripathy, D. et al. First-Line Treatment Patterns and Clinical Outcomes in Patients With HER2-Positive and Hormone Receptor-Positive Metastatic Breast Cancer From registHER. The Oncologist 18, 501–510 (2013).

2. Hodges-Gallagher et al., Abstract 4376, Proceedings: AACR Annual Meeting 2020; April 27-28, 2020 and June 22-24, 2020; Philadelphia, PA