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.
- Approximately half of HER2+ tumors are also estrogen receptor-positive.
- OP-1250 is a complete estrogen receptor antagonist (CERAN), which has been shown to effectively shrink ER+ breast cancer xenografts, including ER mutant models.
- While extensively characterized in ER+/HER2- breast cancer models, OP-1250 has not previously been tested in a HER2+ context.

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

- OP-1250 reduces proliferation in combination with HER2 inhibitor trastuzumab in ER+/HER2+ cell lines (Figure 3).
- OP-1250 treatment in the HCl-613 PDX model, which contains ESR1 Y537S mutation.

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

- OP-1250 reduces xenograft growth in combination with HER2 inhibitor trastuzumab and tucatinib in breast cancer models, including ER mutant models (Figure 4).
- The addition of OP-1250 to HER2 inhibitors trastuzumab and tucatinib resulted in greater tumor shrinkage than capcitabine alone.

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 penetration and concentrates in tumors in an ER+/HER2+ xenograft.
- OP-1250 in combination with HER2 inhibitors trastuzumab and tucatinib inhibits ER+ xenograft growth at least as well as capcitabine.

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


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Figure 2. Proliferation assays of ER+/HER2+ cell lines treated for 7 days with 100 nM OP-1250, 10 μg/ml trastuzumab, or the combination in serum-free media supplemented with 500 μM 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.

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 model (A) and representative H&E images (B). Tumor shrinkage occurred when OP-1250 was combined with dual HER2 targeted therapy. Pharmacokinetic analysis indicated 1250 levels in the cell line model. D) Combined OP-1250 and trastuzumab treatment inhibited xenograft growth in this model alone and with HER2 inhibitors tucatinib (D) and ado-trastuzumab emtansine (T-DM1) (E). **** indicates adjusted p-value < 0.0001.

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 capcitabine alone.

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