OP-1250 is a Complete Estrogen Receptor Antagonist (CERAN) and Selective Estrogen Receptor Degrader (SERD) that robustly shrinks wild-type and mutant ER+ breast tumors in preclinical xenograft models

OP-1250 is a small molecule drug candidate with many promising features for the treatment of ER+ breast cancer:
- Completely inactivates wild type and constitutively active variants of ER by inhibiting both AF1 and AF2
- Degradates ERs and completely blocks estrogen-driven proliferation in all ER+ breast cancer cell lines tested
- Shrinks tumors in multiple endocrine resistant xenografts and mutant ER537S PDX models
- Well tolerated in animal studies
- Exhibits a PK profile optimal for daily oral dosing
- OP-1250 is currently in a phase I/II trial for recurrent, locally advanced or metastatic ER+/HER2- breast cancer
- We recently reported that OP-1250 penetrates the neocortex, with up to 1.5 times more OP-1250 measured in the brain than in plasma

Rationale for investigating OP-1250 to treat ER+ breast cancer brain metastases:
- Although clear clinical evidence is lacking for treating patients with endocrine therapy several anecdotal reports indicate tamoxifen is efficacious in some patients
- Tamoxifen and its metabolites have been detected in human brain tissue at levels up to 46-fold higher than those measured in serum
- In a recent previous study 10 mg/kg OP-1250, robustly shrunk tumors expressing mutant ERs in an intracranial breast cancer model
- Here we compare the activity of OP-1250 versus tamoxifen, fulvestrant and olaparib to shrink tumors in an intracranial xenograft tumor model

Intracranial patient derived xenograft (PDx) tumor model with breast cancer cells expressing mutant ESR1-Y537S receptors

10 mg/kg OP-1250 is superior to tamoxifen, fulvestrant and olaparib in shrinking mutant ESR1-Y537S tumors in an intracranial model of ER+ breast cancer brain metastasis

Key findings and clinical significance
- Here we report that OP-1250 shrinks tumors in a preclinical intracranial xenograft metastatic tumor model expressing mutant estrogen receptor ESR1-Y537S. All tumors responded to OP-1250 treatment in 8/9 tumors treated with OP-1250 alone and 1/9 tumors treated with OP-1250 + Ribociclib were undetectable after 100 days.
- OP-1250 treatment was superior in shrinking ER+ tumors in this model compared to other endocrine therapies tested, including olaparib, fulvestrant and tamoxifen
- OP-1250 treatment does not interfere with the growth of juvenile mice in this model
- OP-1250 prevented death in all animals at day 120 in this brain tumor model
- These data suggest that OP-1250 may be an active treatment for breast cancer patients with recurrent, locally advanced or metastatic ER+/HER2- tumors whose disease has progressed on prior endocrine therapy.

References:
1) Hodges-Gallagher, et al., poster SABCS 2019
2) Hodges-Gallagher, et al., poster SABCS 2020
3) Hodges-Gallagher, et al., poster AACR 2020
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Olema Oncology, San Francisco, CA
Minerva Imaging, Copenhagen, Denmark