OP-1250, a Complete Estrogen Receptor Antagonist (CERAN) that penetrates the brain and prevents lethality from intracranial xenograft tumors expressing mutant ESR1

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BACKGROUND: CERANs completely antagonize the estrogen receptor (ER)

OP-1250 shrinks mutant ESR1 tumors in the brain and prevents lethality in an intracranial model of metastasis

10 mg/kg OP-1250 prolongs survival in ER+ brain metastasis model

Key Findings and Clinical Implications

- OP-1250 is a potent CERAN (Complete ER antagonist) of both wild type and mutant ERs.
- OP-1250 shrinks breast tumors expressing mutant ERα in a PDX model of endocrine resistance.
- OP-1250 penetrates the rodent brain, with 1.5 times more OP-1250 in brain than plasma.
- OP-1250 prevents lethality from brain metastasis

The observed preclinical safety profile and efficacy data clearly support the clinical development of OP-1250. A phase 1 dose escalation and expansion study of OP-1250 in previously treated patients with ER+ metastatic breast cancer will be initiated in 2020 and will include an exploratory cohort of CNS patients.

OP-1250 was administered orally (PO) at 10 mg/kg with a 50 mg/kg loading dose administrated the first week.

OP-1250 is a novel orally bioavailable CERAN with preclinical features including:

- Completely inactivates wild type and mutant ERα by inhibiting both AF1 and AF2
- Completely blocks estrogen-driven proliferation in all ER+ breast cancer cell lines tested
- Robustly degrades ERα in all cell lines tested
- Exhibits a PK profile optimal for daily oral dosing and exhibits low toxicity

Shrinks tumors in multiple tamoxifen-resistant xenograft and endocrine-resistant mutant ESR1 PDX models

Here we investigate the ability of OP-1250 to penetrate the brain and shrink tumors in an ER+ brain metastasis xenograft model.

OP-1250 shrinks breast tumors expressing mutant ESR1Y537S at 3-10 mg/kg

[Graph and data table showing tumor growth inhibition and survival benefits of OP-1250 treatment compared to controls]

[Graph showing plasma and brain levels of OP-1250 and metabolites, with OP-1250 reaching higher brain levels than plasma]

[Graph showing Kaplan-Meier survival curves for OP-1250 treated and control groups, with prolonged survival in treated group]

ST941/PDX cells (ESR1 Y537S) resisted to serially grown tumors.

Activating mutations confer estrogen-independent activation. These mutations often occur with endocrine therapy resistance.

These mutations are present in the tumors of patients with ER+ breast cancer.

Complete ER Antagonists (CERANs), such as fulvestrant (Faslodex), are potential antagonists to block this activation.

OP-1250 is a potent CERAN (Complete ER antagonist) of both wild type and mutant ERs.

OP-1250 shrinks breast tumors expressing mutant ERα in a PDX model of endocrine resistance.

OP-1250 penetrates the rodent brain, with 1.5 times more OP-1250 in brain than plasma.

OP-1250 shrinks tumors in an intracranial xenograft model of brain metastasis.

OP-1250 prevents lethality from brain metastasis.

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