Effects of G1T48, a novel orally bioavailable selective estrogen receptor degrader (SERD), and the CDK4/6 inhibitor, G1T38, on tumor growth in an animal model of tamoxifen resistant breast cancer

Abstract

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Background: The combination of targeting the CDK4/6 and ER signaling pathways with palbociclib and fulvestrant is a proven therapeutic strategy for the treatment of ER positive breast cancer. However, the antiproliferative properties of fulvestrant require monthly intramuscular injections to patients, which limit the pharmacokinetic and pharmacodynamic activity of the compound. Therefore, an orally available compound that more rapidly reaches steady state may lead to a better clinical response in patients. Here we report the preclinical characterization of G1T48, a novel, orally bioavailable, non-steroidal small molecule inhibitor of ERs, which is a potent, selective degrader that regulates ERs in vitro in vivo in ER-positive models of breast cancer.

Methods: Breast cancer cells expressing clinically relevant ER mutations (ER-Y537S, ER-D538G) were treated with G1T48, and mechanistically distinct SERMs/SERDs and cellular proliferation was assessed by measuring DNA content (Hoechst dye). Overexpression of luciferase bearing variants of ER-Y537S and ER-D538G in viable and non-viable breast cancer models was evaluated in vivo in ER-positive models of breast cancer.

Results: G1T48 inhibited the growth of long term estrogen deprived (LTED) MCF7 breast cancer cells.

Conclusions: G1T48 enhances ER-dependent MCF7 cell proliferation in response to estrogen or growth factors.

Summary

G1T48 is an orally bioavailable potent and efficacious antagonist with SERD activity. G1T48 regulates ER target gene transcription in a manner similar to fulvestrant, a pure antiestrogen with demonstrated efficacy in aromatase/astrocytoma refractory breast cancer. G1T48 inhibits the growth of long term estrogen deprived (LTED) MCF7 breast cancer cells.

G1T48 inhibits the growth of estrogen-dependent MCF7 xenograft tumors. Overexpression of estrogen-responsive murine breast tumors were randomized to treatment with vehicle or G1T38 (50 mg/kg), G1T48 (30 or 100 mg/kg), alone or together, p.o. daily, 2-way ANOVA comparison of average tumor volumes throughout treatment, followed by Bonferroni multiple comparison test, indicated increased response to the combination of G1T48 (30 mg/kg) and G1T38.

G1T38 is currently being evaluated in combination with Fulvestrant in a Phase 1b/2a trial in ER+, HER2- breast cancer patients (NCT02983071).

G1T48 and G1T38 both inhibit the growth of tamoxifen resistant (TamR) xenograft tumors.

G1T48 and G1T38 inhibit the growth of tamoxifen resistant (TamR) xenograft tumors. TAMR xenograft tumors were randomized to treatment with vehicle or G1T38 (50 mg/kg), G1T48 (30 or 100 mg/kg), alone or together, p.o. daily, 2-way ANOVA comparison of average tumor volumes throughout treatment, followed by Bonferroni multiple comparison test, indicated increased response to the combination of G1T48 (30 mg/kg) and G1T38.