ARYR-334543 is an orally active, potent small molecule tyrosine kinase inhibitor active against both EGFR and ErbB2. The compound is a reversible, ATP-competitive inhibitor with nanomolar potency in both in vitro and in-cell-based assays showing strong activity against EGFR, ErbB2 and ErbB4.

This compound has very good oral bioavailability in vitro and in vivo (male C57/BL6 mice at 100 mg/kg ARRY-334543 has shown excellent activity in numerous mouse tumor models including growth (27%), breast (BT-474, MDA-MB-435, -453), non-small cell lung (H1650, AS46, 292), colorectal (LVN, HT-29) and gastric (NCI-N87).

Here we demonstrated single agent activity and combinability with trastuzumab, capcitabine or docetaxel in breast, gastric and ovarian carcinoma models. Animals received doses of ARRY-334543 ranging up to 200 mg/kg p.o. and/or trastuzumab at 20 mg/kg, IV. CDDP or GW, and/or capcitabine (200 mg/kg, PO) to mice and/or docetaxel at 10 mg/kg, IV. CDDP dose was fixed at 10 mg/kg. In all tumor models, ARRY-334543 demonstrated significant dose-related tumor growth inhibition (TGI) at 93% and 98% at 200 mg/kg and 100 mg/kg respectively, with dose dependent reductions (60% reduction from baseline) to both dose levels (312 in the 100 mg/kg group and 510 in the 200 mg/kg dose group). Trastuzumab alone provided 53% TGI with a regression (112 animals), ARRY-334543 (100 mg/kg) in combination with trastuzumab showed 93% TGI with regression in 112 animals with BC-1 tumors. CDDP was a single agent produced a 7% TGI with no regressions. In combination with ARRY-334543, there was 19% TGI and regression (112 animals).

In the SK-OV-3 carcinoma model the SK-OV-3 carcinoma tumor line (high in vivo PK/ADME properties and SD = 50% change in tumor size) were implanted in female nude mice (Athymic Ncr:Nu/Nu, i.p). Tumors were measured twice weekly until day 21. All in vivo studies were performed in accordance with IACUC guidelines.

The Study

In Vivo Tumor Growth Studies

BT-474 Human Breast Cancer* Tumors (5-7 mm) were implanted into female nude mice (Athymic Ncr:Nu/Nu, Charles River Laboratories, Inc. (Berkery, MA). The animals were housed in a Unitarian (100% humidity and 12 h light/12 h dark cycle) and fed with autoclaved feed and water. Tumors were measured twice weekly until day 21. All in vivo studies were performed in accordance with IACUC guidelines.

1. Assess activity of ARRY-334543 in preclinical tumor models of breast and other cancers.

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