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Poster

In Vivo Activity of ARRY-380, a Potent, Small Molecule Inhibitor of ErbB2 in Combination with Trastuzumab, Docetaxel or Bevacizumab

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Abstract

ARRY-380 is an orally active, potent small molecule tyrosine kinase inhibitor targeting ErbB2. The compound is a reversible, ATP-competitive inhibitor with nanomolar potency against ErbB2 in both in vitro and in cellbased assays. This compound has very good in vivo and in vitro PK/ADME properties and has shown excellent activity in numerous mouse tumor models including breast (BT-474, MDA-MB-453), ovarian (SKOV-3) and gastric (N87) carcinoma models. Here we demonstrate excellent single agent activity and combinability with trastuzumab, docetaxel or bevacizumab in breast and ovarian carcinoma models. For the BT-474 studies, female SCID beige mice were implanted with tumor fragments. For the SKOV-3 tumor studies, female nude mice were inoculated with cells subcutaneously in the flank. Animals received: doses of ARRY-380 ranging up to 200 mg/kg/d, PO; and/or trastuzumab at 20 mg/kg, IP, Q3D or QW;and/or docetaxel at 10 mg/kg, IV, Q3D; and/or bevacizumab at 10 mg/kg, IP, Q4D x3. Tumor size was measured at regular intervals and animals were monitored out to 90 days to determine tumor-free survival In the BT-474 model, ARRY-380 demonstrated significant dose-related tumor growth inhibition (TGI; 50% at 50 mg/kg/d and 96% at 100 mg/kg/d) with numerous partial regressions (>50% reduction from baseline size) at the higher dose level (9 of 12 animals). One complete response was observed at the higher dose. Trastuzumab alone provided a 45% TGI with no regressions. ARRY-380 (50 mg/kg/d) in combination with trastuzumab showed a 98% TGI with complete regressions in 9/12 animals and two partial regressions. At dose of 100 mg/kg/d of ARRY-380 in combination with trastuzumab, there was 100% TGI and all animals had complete regressions. Docetaxel as a single agent produced a 55% TGI with no regressions. In combination with ARRY-380 (50 mg/kg/d), there was an 81% TGI and five partial regressions. In the SKOV-3 model, ARRY-380 demonstrated significant doserelated tumor growth inhibition (TGI; 39% at 50 mg/kg, BID and 96% at 100 mg/kg, BID) with partial regressions (>50% reduction from baseline size) at the higher dose level in all animals. Bevacizumab alone provided a 55% TGI with no regressions. ARRY-380 (50 mg/kg, BID) in combination with bevacizumab showed 80% TGI with partial

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responses in 7/8 animals and one stable disease. From this work we have demonstrated superb single agent activity for ARRY-380 in the BT-474 human breast carcinoma xenograft model and the SKOV-3 human ovarian carcinoma model. In addition, ARRY-380 has shown additive activity and tolerability with trastuzumab, docetaxel and bevacizumab. ARRY-380 has entered Phase I clinical trials in patients with advanced cancers.

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