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

Patrice Lee1, Deborah Anderson1, Karyn Bouhana1, Jennifer Garsus1, Cheryl Napier1, Anna Avrutskaya1, Angela White2, Tracy Pheneiger1 and Jim Winkler1

Array BioPharma Inc, Boulder Colorado1, Piedmont Research Center, LLC, Morrisville, NC2

**Abstract**

ARRY-380 is a novel orally active, potent small molecule tyrosine kinase inhibitor targeting ErbB2. The compound is a recombinant, ATP-competitive inhibitor with nanomolar potency against ErbB2 in both vitro and in intact assays. This compound has very good in vivo and in vitro PK properties and has shown excellent activity in numerous mouse tumor models including breast (BT-474, MDA-MB-435), 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 mice were implanted with tumor fragments. For the SK-OV-3 tumor models, female nude mice were inoculated with cells subcutaneously in the flank. Animals received: doses of ARRY-380 ranging up to 200 mg/kg, PO; and trastuzumab at 20 mg/kg, IP, QWx3, and/or docetaxel at 15 mg/kg, QW, and/or bevacizumab at 10 mg/kg, QW. 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 and 80% at 100 mg/kg) with numerous partial regressions (>50% reduction from baseline size) at the highest dose level (9 of 12 animals). Complete response was observed at the higher dose. Trastuzumab showed limited TGI with no regressions. ARRY-380 (300 mg/kg) in combination with trastuzumab showed a 98% TGI with complete regressions in 12/13 animals and two partial regressions. At doses of 100 mg/kg of ARRY-380 in combination with trastuzumab, 10/12 animals had complete regressions. Docetaxel as a single agent produced a 59% TGI with no regressions. In combination with ARRY-380 (100 mg/kg), there was an 81% TGI and five partial regressions. In the SK-OV-3 model, ARRY-380 demonstrated significant dose-related tumor growth inhibition (TGI; 30% at 50 mg/kg, 80% and 100 mg/kg) with partial regressions (<50% reduction from baseline size) at the highest dose level in 15/15 animals. Bevacizumab alone provided a 15% TGI with no regressions. ARRY-380 (200 mg/kg), BEV in combination with bevacizumab showed 80% TGI with partial regressions in 7/10 animals and one durable response. From this work we have demonstrated superb single agent activity for ARRY-380 in the BT-474 human breast carcinoma xenograft model and the SK-OV-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.

**Methods**

**In Vivo Activity of ARRY-380**

In Vivo Activity of ARRY-380

**Results**

**Tumor Response**

**SKOV-3 Human Ovarian Carcinoma Xenograft: Expressing ErbB2/EGFR**

**Combination Therapy (SCID Mice)**

**Competition Therapy with Bevacizumab**

**Safety of ARRY-380**

**Summary**

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

**Characteristics of ARRY-380**

**In Vivo Activity of ARRY-380**

**Combination Therapy (SCID Mice)**

**Competition Therapy with Bevacizumab**

**Safety of ARRY-380**

**Summary**

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

**Characteristics of ARRY-380**

**In Vivo Activity of ARRY-380**

**Combination Therapy (SCID Mice)**

**Competition Therapy with Bevacizumab**

**Safety of ARRY-380**

**Summary**

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

**Characteristics of ARRY-380**

**In Vivo Activity of ARRY-380**

**Combination Therapy (SCID Mice)**

**Competition Therapy with Bevacizumab**

**Safety of ARRY-380**

**Summary**

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

**Characteristics of ARRY-380**

**In Vivo Activity of ARRY-380**

**Combination Therapy (SCID Mice)**

**Competition Therapy with Bevacizumab**

**Safety of ARRY-380**

**Summary**

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

**Characteristics of ARRY-380**

**In Vivo Activity of ARRY-380**

**Combination Therapy (SCID Mice)**

**Competition Therapy with Bevacizumab**

**Safety of ARRY-380**

**Summary**