In Vivo Activity of ARRY-334543, a Potent, Small Molecule Inhibitor of EGFR/ErbB-2 in combination with trastuzumab or docetaxel

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**Abstract**

ARRY-334543 is an orally active, potent small molecule tyrosine kinase inhibitor targeting both EGFR and ErbB2. The compound is a reversible, ATP-competitive inhibitor with nanomolar potency in both in vitro and cell-based assays showing strong selectivity against EGFR, HER-2 and ErbB-4. This compound has very good in vivo and in vitro PK/ADME properties and has shown excellent activity in primary mouse xenograft models including pancreatic (A431), breast (BT-474, MDA-MB-435), non-small cell lung (H1650, A549, 292), colon (HT-29) and gastric (NIH-3T3) cancer models. Here we demonstrate excellent single agent activity and combinability with trastuzumab or docetaxel in breast, gastric, ovarian and colorectal cancer models. For the BT-474 studies, female SCID beige mice were implanted with tumor fragments. For the SK-OV-3 and NCI-N87 tumor studies, female nude mice were inoculated with s.c. xenografts for the in vivo assays. Tumor size was measured at regular intervals for up to 21 days. In the BT-474 model, ARRY-334543 showed significant inhibition of SK-OV-3 tumor growth at 100 mg/kg works so well that true additivity with trastuzumab could not be demonstrated. ARRY-334543 at 50 mg/kg in combination with trastuzumab showed additive activity with complete regression of all the tumors. Trastuzumab alone provided a 57% TGI with 7/8 significant regressions. Trastuzumab alone provided a 57% TGI with 7/8 significant regressions. Additionally, we report excellent single agent activity including improved time to progression (TTP) in several Phase II clinical trials in patients with advanced cancers.

**Goals**

1. Demonstrate activity of ARRY-334543 in preclinical tumor models of breast and ovarian cancer
   - overexpressing ErbB2
   - overexpressing EGFR and ErbB2

2. Demonstrate activity of ARRY-334543 with trastuzumab or docetaxel in preclinical models
   - tolerability
   - enhanced pharmacodynamic activity

**Methods**

Mice were subcutaneously inoculated with 10^6 tumor cells (5 x 10^6) into the right flank. Tumor cells (5 x 10^6) were implanted in female CB.17 SCID mice (Harlan, Inc.). BT-474 Human Breast Carcinoma* TRITC labeled, NIH-3T3, SK-OV-3, NIH-3T3 (292), SK-OV-3, A431, A549, H1650, 292, HT-29, and NIH-3T3, (NIH-3T3) and nude mice, respectively. Tumor size was measured at regular intervals for up to 21 days.

**Results**

**Tumor Growth Inhibition (TGI)** (Figure 3)

**NCI-N87**

**EGFR/ErbB2-Expressing Human Gastric Carcinoma**

**SK-OV-3**

**3.** ARRY-334543 at 50 mg/kg in combination with trastuzumab showed additive activity with 1 CR and 6 PRs.

**4.** ARRY-334543 at 50 mg/kg in combination with docetaxel showed additive activity with 1 CR and 6 PRs.

**5.** ARRY-334543 at 50 mg/kg in combination with trastuzumab showed additive activity with complete regression of all the tumors.

**Safety of ARRY-334543**

**TGI studies**

ARY-334543 was well tolerated at doses up to 200 mg/kg for up to 21 days in numerous in vivo studies alone and in combination with other anticancer agents. There were no significant changes in body weight or clinical pathology.

**GLP Safety Studies**

A comprehensive battery of GLP safety studies on ARR-334543 has been completed. ARR-334543 is well tolerated in rats and cynomolgus monkeys across a dose range.

**Summary**

ARRY-334543 is a potent ErbB receptor family inhibitor and has demonstrated excellent inhibition of EGFR and ErbB2 phosphorylation in a number of in vivo tumor models and superior inhibition of tumor growth in numerous xenograft models.

ARRY-334543 has shown superior preclinical tumor inhibitory activity to that of lapatinib in several tumor models including NCI-N87, A431 and NCI-H1975 (AACR 2008, Abstract #44B).

In the studies presented in this poster, ARR-334543 shows:

- significant tumor growth as well as tumor regression in the ErbB-overexpressing SK-OV-3 ovarian carcinoma model and in the dual EGFR/ErbB2 overexpressing SK-OV-3 ovarian and NCI-N87 gastric carcinoma models.

Enhanced anti-tumor activity with increased CRs and PRs in combination with trastuzumab or docetaxel at low doses of ARRY-334543.

- very good tolerability in combination with trastuzumab or docetaxel

ARRY-334543 is currently in Phase 2 studies in several tumor types in combination with SCLC therapies.