Differential Activity of ARRY-543, a Potent, Small Molecule Inhibitor of EGFR/ErbB2 Compared to Lapatinib in In Vivo Xenograft Models


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**Abstract (modified from published version)**

ARRY-543 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 in cell-based assays. This compound has very good in vivo and in vivo PK/ADME properties and has shown excellent activity in numerous in vivo tumor models. In a series of experiments, we show that ARRY-543 has superior activity to lapatinib in several subcutaneous and orthotopic xenograft models varied for EGFR and ErbB2 expression. ARRY-543 at dose levels as low as 10 mg/kg demonstrated significant tumor growth inhibition (TGI) in the N87 gastric carcinoma xenograft model. In the N87 TGI study, animals received oral doses of vehicle, ARRY-543 or lapatinib (100 mg/kg, 25, 50 and 100 mg/kg, BID, PO, respectively. Lapatinib administration at 50 and 100 mg/kg was associated with significant tumor regressions, whereas lapatinib produced 1 regression. The ARRY-543 dose–response curve was determined to be 1:2 in early Phase 1 studies.

**Summary**

ARRY-543, a potent EGFR/ErbB2 inhibitor, demonstrates excellent inhibition of EGFR and ErbB2-2 phosphorylation in a number of in vivo tumor models.

ARRY-543 inhibits tumor growth in several human xenograft models in the mice. These include:
- n NCi-N87 - Gastric carcinoma
- a a431 - Epidermoid carcinoma
- h1650 - NSCL carcinoma

**Methods**

**Physicochemical/Pharmacokinetic (PK/PK)** Study

In vivo drug concentrations were determined by protein precipitation and LC/MS/MS analysis of plasma samples. A total of 12 animals per group were treated with vehicle, ARRY-543 at dose levels of 25, 50 and 100 mg/kg, BID, PO, respectively. Lapatinib administration at 50 and 100 mg/kg was associated with significant tumor regressions, whereas lapatinib produced 1 regression. The ARRY-543 dose–response curve was determined to be 1:2 in early Phase 1 studies.

**Pharmacokinetics**

In vivo drug concentrations were determined by protein precipitation and LC/MS/MS analysis of plasma samples. A total of 12 animals per group were treated with vehicle, ARRY-543 at dose levels of 25, 50 and 100 mg/kg, BID, PO, respectively. Lapatinib administration at 50 and 100 mg/kg was associated with significant tumor regressions, whereas lapatinib produced 1 regression. The ARRY-543 dose–response curve was determined to be 1:2 in early Phase 1 studies.

**Results**

**Tumor Growth Inhibition**

ARRY-543 showed dose-related inhibition of NCI-N87 tumor growth at all doses. Lapatinib showed significant inhibition of tumor growth but the magnitude of inhibition at the 1 hr timpoint was less than that seen with ARRY-543. ARRY-543 demonstrated excellent dose-proportional tumor growth inhibition (TGI) and lapatinib showed significant inhibition of tumor growth at all timepoints. Lapatinib showed good inhibition of ErbB2 phosphorylation at all timepoints but the magnitude of inhibition at the 1 hr timpoint was less than that seen with ARRY-543.

**Safety of ARRY-543**

TGI studies showed that ARRY-543 was well tolerated at doses up to 200 mg/kg for up to 21 days in murine in vivo studies. There were no significant changes in body weight or clinical pathology.

**GLP Safety Studies**

A comprehensive battery of GLP safety studies on ARRY-543 has been completed. ARRY-543 was well tolerated in rats and mice and confirmed multiple toxicologic studies.

**Phase 1 Clinical Studies**

ARRY-543 was well tolerated up to 400 mg BID. ARRY-543 demonstrated excellent dose-dependent pharmacokinetics with no evidence of drug-drug interactions, high efficacy across a broad range of dose levels, excellent inhibition of EGFR and ErbB2-2 phosphorylation in a number of in vivo tumor models.

**Summary**

ARRY-543, a potent EGFR/ErbB2 inhibitor, demonstrates excellent inhibition of EGFR and ErbB2-2 phosphorylation in a number of in vivo tumor models.

ARRY-543 inhibits tumor growth in several human xenograft models in the mice. These include:
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**Activity in these models was superior to that seen with lapatinib.**

In the NCi-N87 dual ErbB2/EGFR driven gastric carcinoma model, ARRY-543 treatment at 100 mg/kg BID resulted in 5 regressions, whereas lapatinib produced 1 regression. PD studies in this tumor type demonstrate excellent and sustained inhibition of EGFR and ErbB2 with ARRY-543. ARRY-543 activity against EGFR is greater than that observed with lapatinib over a 24 hr period.

ARRY-543 is in clinical development with Phase 2 studies commencing in mid-2008.

**Conclusion**

ARRY-543 is a potent small molecule inhibitor of EGFR/ErbB2 that shows differential activity in vivo compared to lapatinib in a variety of xenograft models.