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ARRY-380, a Potent, Small Molecule Inhibitor of ErbB2, Increases Survival in Intracranial ErbB2+ Xenograft Models in Mice

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Abstract

ARRY-380 is an orally active, potent small molecule targeting ErbB2 inhibitor currently in clinical development in patients with ErbB2+ metastatic breast cancer (MBC). This compound has shown excellent activity in numerous SC mouse tumor models including breast (BT-474, MDA-MB-453), ovarian (SK-OV-3) and gastric (N87) carcinoma models. In breast cancer patients, brain metastases are a serious unmet medical need. Patients with ErbB2+ breast cancer have a significantly increased incidence of brain metastases following trastuzumab therapy. Here we demonstrate significant single agent activity of ARRY-380 in two ErbB2+ intracranial mouse xenograft models. For these studies, female nude mice received intracranial implantations of tumor cells (either NCI-N87 or BT-474) by direct injection into the brain parenchyma (via the sagittal suture). In pilot studies, we demonstrated that the blood brain barrier was not disrupted by mechanical injections and that increasing tumor burden correlates negatively with neurologic outcome, body weight and survival. In the N87 studies, animals received treatments beginning on Day 2 post-implantation and continuing for up to 6 weeks. Dose groups (n=12/group) were vehicle, ARRY-380 at MTD (75 mg/kg, PO, BID) or lapatinib at MTD (50 mg/kg, PO, BID). All animals in the vehicle- or lapatinib–treated groups did not survive beyond Day 22. In the ARRY-380-treated-group, 75% of the animals were alive on Day 43. Brain PK/PD was also evaluated in the N87 model. ARRY-380 and its active metabolite caused a significant reduction in brain pErbB2 (80%). In the BT-474 model, animals received treatments beginning on Day 2 post-implantation and continuing for up to 8 weeks. Dose groups (n=13/group) were vehicle, ARRY-380 at MTD (75 mg/kg, PO, BID), lapatinib at MTD (50 mg/kg, PO, BID) or neratinib at MTD (40 mg/kg, PO, QD). On Day 56, survival in the ARRY-380 group was 69% while survival rates in the vehicle, lapatinib or neratinib–treated groups were 23%, 8% and 23%, respectively. Thus ARRY-380 treatment significantly enhances survival in two ErbB2 driven intracranial tumor xenograft models, with superior activity compared to other ErbB2 agents in these studies. Additionally, ARRY-380 has demonstrated durable clinical activity in heavily pre-treated patients with ErbB2+ MBC. These preclinical and clinical data suggest that

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ARRY-380 may provide benefit to patients with ErbB2+ MBC with brain metastases.

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