**Array-380, a potent, small molecule inhibitor of ErbB2, increases survival in intracranial ErbB2+ xenograft models in mice**

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**Abstract**

Array-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-435), ovarian (SK-OV-3) and N87 (ErbB2+) carcinoma models. In breast cancer patients, brain metastases are a serious unmet medical need. Patients with ErbB2+ breast cancer have a significant increase of incidence of brain metastases following trastuzumab therapy. Here we demonstrate significant single agent activity of Array-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 sinus). In pilot studies, we demonstrated that the blood brain barrier was not disrupted by mechanical injections and that increasing tumor burden correlates negatively with outcome, body weight and survival. In the N87 studies, animals received treatments beginning on Day 2 post-implantation and continuing for up to 21 days. In the BT-474 model, animals were inoculated with BT-474 cells and allowed to grow to a tumor mass of 75 mg before treatment was started (Day 0). Animals in the vehicle- or lapatinib-treated groups did not survive beyond Day 21. Day 21 survival in the Array-380 treated group, 75% of the animals were alive on Day 43. Brain PIKPOD was measured in the N87 model. Array-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 21 days. Animals in the vehicle- or lapatinib-treated groups did not survive beyond Day 21. Day 21 survival in the Array-380 group was 65% while survival rates in the vehicle, lapatinib or nab-lapatinib-treated groups were 25%, 6% and 25%, respectively. Thus Array-380 treatment significantly enhances survival in two ErbB2 driven intracranial xenograft models, with superior activity compared to other ErbB2 agents in these studies. Additionally, Array-380 has demonstrated durable clinical activity in heavily pre-treated patients with ErbB2+ MBC. These preclinical and clinical data suggest that Array-380 may provide benefit to patients with ErbB2+ MBC with brain metastases.

**Introduction**

- Brain is most common site for CNS metastases (15,000 new cases in US/year)
- Increasing incidence as women are living longer due to better treatments for systemic disease
  - 25-40% for HER2- positive metastatic breast cancer
  - 15% for other types of metastatic breast cancer
- Time to progression (i.e., brain failure)
  - HER2+ positive: 1-2 years
- TNBC: 3-5 months
- Current treatment options (with significant side effects)
  - Whole brain radiation therapy (WBRT)
  - Stereotactic radio-surgery (SRS)
  - Surgical resection
- Brain metastases are a leading cause of death in HER 2+ breast cancer patients
- Lapatinib shows limited clinical activity in HER2+ breast cancer brain metastases as single-agent and in combination with capecitabine

**Activity of Array-380** investigated in models of intracranial tumors
- Comparison of efficacy in SC versus intracranial xenografts
- Comparison of efficacy versus lapatinib or nab-lapatinib

**Brain tumor burden associated with decreased survival in NCI-N87 model**

**Summary**

- **Array-380 treatment significantly enhances survival in two ErbB2- driven intracranial xenograft mouse models; with superior activity compared to other lapatinib and neratinib in these studies.**
- **Array-380 forms an active metabolite which maintains sustained brain levels after oral dosing of Array-380 and may contribute to enhanced activity versus other ErbB2 agents.**
- **Additionally, Array-380 has demonstrated durable clinical activity in heavily pre-treated patients with ErbB2+ MBC**

*These preclinical and clinical data suggest that Array-380 may provide benefit to patients with ErbB2+ MBC with brain metastases and warrants further study.*

**References**