ARYR-380, a Selective HER2 Inhibitor: From Drug Design to Clinical Evaluation


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We Thank the Patients and Their Families

Introduction

HER2 is a highly closely related cell surface receptor tyrosine kinase that transduces growth signals and is involved in the carcinogenesis of many malignancies. While HER2 is a validated and high-value target, approximately 25% of breast cancers have an amplification of the HER2/neu gene or overexpression of its protein product, HER2. Overexpression of HER2 also occurs in gastric, colorectal, NSCLC, and ovarian cancers. The goal of developing a selective drug that inhibits HER2 without EGFR-related side effects, such as rash and GI issues, is desirable, especially in an approach that minimizes EGFR dose reduction. The high selectivity of GSK2861563 for HER2 has been observed in multiple breast cancer xenograft models (Amini et al. Crit Cancer Res. 2008; 8(3):277-80). Designing a Selective HER2 Inhibitor

We designed a small-molecule HER2 inhibitor that is ATP-competitive, with good HER2 potency in enzyme and cellular assays, had PK liabilities. Compound 1 also had the potential to be metabolized to form the product 2, which, in turn, had poor plasma stability. However, 2 was discovered to have excellent HER2 selectivity. Combining all of the preferred structural elements provides ARRY-380, with improved HER2 selectivity and PK properties.

ARYR-380 is a selective and potent HER2 inhibitor. ARRY-380 is a reversible, ATP-competitive inhibitor with nanomolar selectivity against HER2. ARRY-380 is > 100-fold selective for HER2 vs. EGFR and is equipotent against truncated PHS-HER2. In vivo, ARRY-380 significantly inhibits tumor growth in multiple HER2-dependent xenograft models and showed additive activity in combination with standard-of-care agents.

Proposed Binding Mode of ARRY-380

ARYR-380 inhibits the binding mode of ARRY-380 to HER2 via an interaction with a structural V-D loop and a hydrogen bond with Ser783. Cys775 in EGFR prefers a rotamer that allows interaction with ARRY-380. A dose deconvolution shows decreasing binding potency.

Safety Summary

- All patients treated with ARRY-380 were evaluable for safety at doses of ≥ 25 to 600 mg BID ARRY-380.
- Two reversible Grade 3 DLTs (1 elevated AST and 1 elevated ALT) at BID 600 mg; thus ARRY-380 was declared the MTD. All DLTs consisted of interstitial of doing and upon rechallenge at a lower dose, patients tolerated continued treatment with ARRY-380.
- Other non-DLT Grade 3 events: rash (n = 1), night sweats (n = 1), anemia (n = 1), hypokalemia (n = 2), anorexia (n = 1).
- No Grade 4 treatment-related AEs have been reported.
- No cardiac AEs have been reported.
- Majority of treatment-related AEs have been Grade 1-2.

Phase 1 Clinical Evaluation of ARRY-380

The objectives of this first-in-human Phase 1 dose-escalation and expansion study were to determine the maximum tolerated dose (MTD) and assess the safety, pharmacokinetics (PK), and preliminary efficacy of ARRY-380 in patients with advanced solid tumors that express the HER2 target. All data presented is as of September 1, 2011.

Schedule and Doses of ARRY-380

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<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose Escalation</th>
<th>Dose Evaluation</th>
<th>Dose Escalation</th>
<th>Dose Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRY-380</td>
<td>25 mg to 800 mg BID</td>
<td>25 mg to 800 mg BID</td>
<td>25 mg to 800 mg BID</td>
<td>25 mg to 800 mg BID</td>
</tr>
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Phase 2: Development of ARRY-380

The MTD of ARRY-380 was determined to be 600 mg BID. ARRY-380 has an acceptable safety profile with low incidence and severity of EGFR-related side effects (rash, diarrhea). Preliminary signs of efficacy at doses ≥ 300 mg BID in heavily pre-treated HER2+ MBC pts. Future studies may include combinations with trastuzumab and/or chemotherapy. ARRY-380 has met the original design goal of HER2 selectivity, leading to an acceptable safety profile and preliminary sign of efficacy.

Small-Molecule Inhibitors: Optimization of HER2 Activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>HER2 IC50 (nM)</th>
<th>EGFR IC50 (nM)</th>
<th>HER2 vs. EGFR Selectivity</th>
<th>HER2 Cytotoxicity</th>
<th>HER2 vs. EGFR Cell Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRY-380</td>
<td>5</td>
<td>43</td>
<td>&gt;10000</td>
<td>54</td>
<td>8000</td>
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</table>

Patient Demographics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Median Age (range)</th>
<th>EGFR (male/female)</th>
<th>Race (White/Black/Caucasian)</th>
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</thead>
<tbody>
<tr>
<td>44</td>
<td>58 (31-75)</td>
<td>5/45</td>
<td>6/4/2</td>
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</tbody>
</table>

Efficacy

<table>
<thead>
<tr>
<th>Investigator Assessment</th>
<th>ARRY-380 Dose (BID)</th>
<th>HER2+ MBC Pts (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR + SD 6 months</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>6 months</td>
<td>0</td>
</tr>
<tr>
<td>PO</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Responses in HER2+ MBC Patients with Measurable Disease at Doses ≥ 600 mg BID

- Of the 29 HER2+ MBC patients evaluable for response at doses ≥ 600 mg BID, 20 had measurable disease.
- Of these 20 patients:
  - 2 patients (10%) had a confirmed PR.
  - 1 patient (5%) had an unconfirmed PR.
  - 1 patient (5%) demonstrated SD ≥ 6 months.
  - 4 patients with SD continue on therapy.
- Of patients with follow-up ≥ 6 months (n = 117):
  - 17 patients had either SD ≥ 6 months, PR or CR.

Waterfall Plot of Target Lesions in HER2+ MBC Patients at Doses ≥ 600 mg BID

- Confirmed Response in Multiple Solid Tumors
- CEA decreased from 71.1 ng/mL to 3.5 ng/mL (ULN = 3.0 ng/mL).

Regression of HER2+ Chest Wall Lesions

- Confirmed regression in patient (600 mg BID) previously treated with trastuzumab and lapatinib.

Regression of Visceral Lesions

- ARRY-380 has acceptable safety profile with low incidence and severity of EGFR-related side effects (rash, diarrhea).
- Preliminary signs of efficacy at doses ≥ 300 mg BID in heavily pre-treated HER2+ MBC pts.
- Future studies may include combinations with trastuzumab and/or chemotherapy.
- ARRY-380 has met the original design goal of HER2 selectivity, leading to an acceptable safety profile and preliminary sign of efficacy.