ARRAY-380: A Selective, Oral HER2 Inhibitor for the Treatment of Solid Tumors

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President and Chief Scientific Officer
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Kevin Koch

I have the following financial relationships to disclose:

I am stockholder in and employee of Array BioPharma Inc

- and -

I will discuss Phase 1 investigational use in my presentation.
ErbB Receptor Tyrosine Kinases

- The ErbB family consists of four closely related receptors
  - ErbB1 (EGFR)
  - ErbB2 (HER2)
  - ErbB3
  - ErbB4

- Ligand binding induces dimerization and kinase activation
- Auto-phosphorylation recruits proteins and activates signaling pathways

Figure Adapted from SABiosciences
Product Profile – Oral, Selective HER2 Inhibitor

- HER2 inhibition is a validated, high value target
  - Breast Cancer > Gastric, CRC, NSCLC, Ovarian
- Oral activity
  - Early lines and adjuvant settings
- Minimize off target activities
  - Eliminate EGFR - GI, Rash issues
  - Enhance the ability to combine with SOC agents
- Trastuzumab resistance
  - p95 truncated HER2 receptor
- CNS penetration
  - HER2+ brain metastasis
- Leverage Array’s Pan ErbB inhibitor program
Binding Pocket Differences: EGFR vs HER2

- Residues of EGFR or ErbB2 within Van der Waals contact of Inhibitors,
- Cys775 vs. Serine783 is the only residue difference

![Diagram showing binding pocket differences between EGFR and HER2](image)

Most kinases, the Cys775 / Ser783 residue is a branched hydrophobe
Optimization for HER2 Activity

**HER2 IC₅₀ = 7 nM**
**EGFR IC₅₀ = 50 nM**
**HER2 (Cell) EC₅₀ = 35 nM**

**Potential Metabolite**

**HER2 IC₅₀ = 12 nM**
**EGFR IC₅₀ = 54 nM**
**HER2 (Cell) EC₅₀ = 14 nM**

**PK issues**

**Permeability issues**

**ARRAY-380**
**Improved selectivity, potency and PK**
Proposed Binding Model of ARRY-380

EGFR + ARRY-380

- Unsatisfied H-bond acceptor

Cys775

- Enhanced interaction with Ser 783

HER2 + ARRY-380

- Compensating H-bond

Ser783

- Diminished interaction with structural water in EGFR
ARRY-380: A Potent, Selective HER2 Inhibitor

- ARRAY-380 is ATP-competitive, reversible and selective for HER2
  - Estimated $K_i$ for ErbB receptors
    - HER2: 1.8 nM
    - EGFR: 72 nM
    - ErbB4: 276 nM
- No activity against ~100 other kinases at 1 μM
- Minimal activity against other kinases at 10 μM

<table>
<thead>
<tr>
<th>Kinase</th>
<th>% Inhibition 10 μM ARRY-380</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKCμu</td>
<td>55</td>
</tr>
<tr>
<td>CK1_y</td>
<td>59</td>
</tr>
<tr>
<td>EphA1</td>
<td>66</td>
</tr>
<tr>
<td>EphA2</td>
<td>58</td>
</tr>
<tr>
<td>Flt4</td>
<td>62</td>
</tr>
<tr>
<td>KIT</td>
<td>52</td>
</tr>
<tr>
<td>Lck</td>
<td>69</td>
</tr>
<tr>
<td>Mer</td>
<td>61</td>
</tr>
</tbody>
</table>
ARRY-380: Potent & Selective HER2 Inhibitor

- Reversible, selective inhibitor of HER2 target
- Potent Activity in 50% Human Serum
- Inhibitor of Trastuzumab-resistant p95 truncated HER2
  - ~30% of Stage III/IV patients

<table>
<thead>
<tr>
<th>Compound</th>
<th>HER2 IC$_{50}$ (nM)</th>
<th>EGFR IC$_{50}$ (nM)</th>
<th>p95 HER2 IC$_{50}$ (nM)</th>
<th>HER2 IC$_{50}$ (nM) 50% Human Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRAY-380</td>
<td>8</td>
<td>4000</td>
<td>7</td>
<td>67</td>
</tr>
<tr>
<td>Irreversible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>competitor</td>
<td>7</td>
<td>8</td>
<td>NT</td>
<td>39</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>49</td>
<td>31</td>
<td>NT</td>
<td>810</td>
</tr>
</tbody>
</table>
## ARRY-380 Inhibits Growth of HER2-Overexpressing Xenograft Model

<table>
<thead>
<tr>
<th>Model</th>
<th>Cancer</th>
<th>ARRY-380 Dose</th>
<th>Best Response</th>
<th>vs. competitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT-474</td>
<td>Breast</td>
<td>100 mg/kg, QD</td>
<td>88% TGI</td>
<td>Superior vs. trastuzumab (57% TGI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regr. 4/6 animals</td>
<td></td>
</tr>
<tr>
<td>N87</td>
<td>Gastric</td>
<td>100 mg/kg, QD</td>
<td>84% TGI</td>
<td>Superior vs. lapatinib (61% TGI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regr. 4/8 animals</td>
<td></td>
</tr>
<tr>
<td>N87</td>
<td>Gastric</td>
<td>150 mg/kg, QD</td>
<td>96% TGI</td>
<td>Superior vs. trastuzumab (67% TGI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CR 2/7 animals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regr. 7/7 animals</td>
<td></td>
</tr>
<tr>
<td>SKOV-3</td>
<td>Ovarian</td>
<td>100 mg/kg, BID</td>
<td>97% TGI</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CR 1/8 animals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regr. 8/8 animals</td>
<td></td>
</tr>
<tr>
<td>3T3-rErbB2</td>
<td>Mouse fibroblast; engineered</td>
<td>100 mg/kg, BID</td>
<td>91% TGI</td>
<td>Superior vs. lapatinib (59% TGI)</td>
</tr>
</tbody>
</table>

Trastuzumab 20 mg/kg Q3D, lapatinib 100 mg/kg BID (maximum efficacious dose for both molecules)
TGI: Tumor Growth Inhibition
CR: Complete Response, no measurable tumor
Regr: Regression, > 50% decrease in tumor size

All ARRY-380 doses shown were well tolerated
ARRY-380: Active in SKOV-3 Ovarian Carcinoma

Animals dosed day 1-22

ARRAY-380 dosed at 100 mg/kg BID resulted in 100% regressions, one cure and prolonged tumor growth suppression
ARRY-380: Combinations *In Vivo*

<table>
<thead>
<tr>
<th>Model</th>
<th>Cancer</th>
<th>ARRY-380 Dose</th>
<th>Combination</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BT-474</strong></td>
<td>Breast</td>
<td>100 mg/kg, QD</td>
<td>trastuzumab 20 mg/kg, IP, QW</td>
<td>Super-Additive</td>
</tr>
<tr>
<td>(SCID mice)</td>
<td></td>
<td></td>
<td></td>
<td>Increased regressions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased CR</td>
</tr>
<tr>
<td><strong>BT-474</strong></td>
<td>Breast</td>
<td>50 mg/kg, QD</td>
<td>docetaxel 10 mg/kg, IP, QW</td>
<td>Additive</td>
</tr>
<tr>
<td>(SCID mice)</td>
<td></td>
<td></td>
<td></td>
<td>Increased regressions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased CR</td>
</tr>
<tr>
<td><strong>SKOV-3</strong></td>
<td>Ovarian</td>
<td>50 mg/kg, QD</td>
<td>bevacizumab 10 mg/kg, IP, Q4Dx3</td>
<td>Additive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased regressions</td>
</tr>
</tbody>
</table>

CR: Complete Response, no measurable tumor
Regression, ≥ 50% decrease in tumor size
ARRY-380: Preclinical Combination Activity

- Superior single agent activity
- Synergistic with Trastuzumab

<table>
<thead>
<tr>
<th></th>
<th>%PRs</th>
<th>%CRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

**BT-474 HER2+ Breast Carcinoma Model**

Graph showing tumor volume over time for different treatments.
ARRY-380: HER2 Inhibitors and Brain Metastases

- HER2⁺ Breast cancer brain metastases: serious un-met need
  - Limited brain penetration for protein therapeutics
  - May become the primary site for progression

- Lapatinib shows limited clinical activity in HER2+ Br Ca brain metastases
  - Single-agent
  - Capecitabine combination

- Investigated activity of ARRY-380 in a model of brain metastases
  - Comparison of efficacy in s.c. versus brain tumors
  - Comparison of ARRY-380 efficacy versus lapatinib
ARY-380 Increases Survival – Intracranial Tumor

- S.C. and Intracranial NCI-N87 gastric carcinoma tumor model
- Both drugs at MTD in Intracranial experiment

NCI-N87: **Subcutaneous** tumor implantation

NCI-N87: **Intracranial** tumor implantation

**ARY-380 & lapatinib active**

**ARRY-380 active; lapatinib inactive**
ARRAY-380: Clinical Program in US and Canada

- **ARRAY-380-101 – Phase 1 Dose-escalation (Complete)**
  - Access safety, tolerability & PK in patients with advanced cancer
  - 27/33 Patients were HER2+ cancer
  - Measurable & non-measurable (e.g. skin metastases) disease

- **ARRAY-380 – Phase 1 Expansion (ongoing)**
  - Confirm safety and explore efficacy and PD markers
  - ~ 20 patients with HER2+ metastatic breast cancer
  - Mandatory paired biopsies (pre-dose and Cycle 1 Day 15)
  - Measurable & non-measurable (e.g. skin metastases) disease

- **ARRAY-380-102 Healthy subject relative-bioavailability study**
ARRY-380: Pharmacokinetics

- Plasma samples: pre- and post-dose on Days 1, 3 and 15
  - Day 1 fasted, Day 3 fed, Day 3+ without regard to food
  - No apparent food effect

- Pharmacokinetics are linear and independent of dose

- Plasma AUC and $C_{\text{max}}$ values nearly dose-proportional

- ARRY-380 $t_{1/2}$ and accumulation similar across dose levels

- The overall median $t_{1/2}$ for ARRY-380 was 5.27 hours
  - Supports BID dosing

- Plasma concentrations exceed HER2 IC$_{90}$ at multiple doses
ARRY-380: Steady - State Clinical PK

 ARRAY-380-101 GeoMean ARRY-380 Cp/t plots – Day 15

GeoMean exposure at doses of 300 mg BID and greater exceed the HER2 IC$_{90}$ for the majority of the dosing interval.

Cellular ICs determined in the presence of 50% human serum
## ARRY-380: Phase 1 Patient Characteristics

### Patient Baseline Characteristics (n=33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>58 (31-77)</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>5:28</td>
</tr>
<tr>
<td>Performance Status (ECOG)</td>
<td>10:20:3</td>
</tr>
<tr>
<td>Median # of Previous Systemic Treatments (range)</td>
<td>5 (1-15)</td>
</tr>
</tbody>
</table>

### Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>HER2 Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
</tr>
<tr>
<td>Breast</td>
<td>26*</td>
</tr>
<tr>
<td>Prior trastuzumab, n (%)</td>
<td>-</td>
</tr>
<tr>
<td>Prior lapatinib, n (%)</td>
<td>-</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1</td>
</tr>
<tr>
<td>Salivary Gland</td>
<td>1</td>
</tr>
</tbody>
</table>

* Results for one patient were HER2- for the primary tumor, HER2+ for metastases.
Patients with Measurable Disease

ARRY-380 shrinks tumors in 51% of HER2+ patients

All tumor types are MBC unless noted. salivary gland (SG); colorectal (CRC)

* Unconfirmed PR: Patient had 53% regression at the end of Cycle 2, PD at Cycle 3

** Confirmed PR: Complete regression of all target lesions, reduced CEA from 71.7 to 3.5

Preliminary data 01 Sept 2010
Confirmed Partial Response – 100% Tumor Shrinkage

- Patient had a confirmed partial response associated with significant reductions in CEA and CA27.29
- 6 prior regimens including trastuzumab (best response of SD) & lapatinib (best response of PD)

Pre- and Post-Dose CT Scans

Baseline

Cycle 2
Confirmed Partial Response

Reductions in CEA and 27.29

- CA27.29 (ng/mL)
- CEA (U/mL)

Normal Range
- CEA: 0.0-3.0 U/mL
- CA27.59: 0.0-38.0 ng/mL

CEA at Cycle 3 (3.5 U/mL) and Cycle 4 (3.5 U/mL) above upper limit of normal (3.0 U/mL)
Regression of Visceral Lesions

- HER2+ breast cancer patient (200 mg BID)
- Prior trastuzumab
- 42% reduction* in a liver metastasis (cycle 4)

*Not classified as a PR due to the appearance of a new lesion in this timeframe
Regression of HER2+ Chest Wall Lesions

- Biopsy-confirmed HER2+ chest wall lesions regressed in a breast cancer patient (650 mg BID)
- Previously treated with trastuzumub & lapatinib
HER2+ Colorectal Cancer Patient (300 mg BID)

- 49 year old male
  - HER2 status confirmed ICH 3+ and FISH amplified
- 8 prior lines of therapy
  - 5-FU, capecitabine, gimatecan, cediranib, leucovorin, oxaliplatin, irinotecan, bevacizumab
- Response
  - 17.3% reduction in target lesions (liver, lung and lymph nodes)
  - CEA (NR: 0.0-4.0 ug/L) dropped from 64 to 7.7 (Cycle 2)
  - CA 19-9 (NR: 0.0-37.0 KU/L) dropped from 100 to 16 (Cycle 2)
  - Progressive disease at the end Cycle 6
**ARRY-380: Highly Competitive Safety Profile**

**ARRY-380: Transient, low % G2, G3 AEs at MTD**

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Events¹ for Doses ≥ 300 mg BID</th>
<th>300 N=3</th>
<th>500 N=4</th>
<th>600/650 N=10</th>
<th>800 N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose / N</strong></td>
<td>300</td>
<td>500</td>
<td>600/650</td>
<td>800</td>
</tr>
<tr>
<td><strong>CTCAE</strong> Grade AE:</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Inc. ALT/AST</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rash³</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

¹occurring in > 10% of patients, at any time during treatment; Preliminary data Oct 2010
²dose-limiting toxicity
³includes events of dermatitis acneiform, rash, maculopapular rash, pruritic rash, and skin exfoliation
Activity in HER2+ Patients Evaluable for Response

PR: Partial Response
uPR: Unconfirmed Partial Response

* Reduced to 650 mg BID during cycle 1 due to DLT
** Reduced to 600 mg BID during cycle 1 due to DLT
***All tumor types are HER2+ MBC unless noted
ARRY-380 - Summary

- Potent, oral and selective HER2 inhibitor
- Preclinical efficacy: mono-therapy and in combination
  - p95 truncated receptors
  - HER2+ brain tumors
  - Synergistic with Trastuzumab
- Favorable clinical PK
  - Clinical exposures predict >90% inhibition of HER2
- Low frequency and severity of adverse events
- Durable clinical activity in heavily pretreated HER2+ patients
  - Trastuzumab and Lapatinib resistant patients
Clinical Investigators – Phase 1 Dose escalation
MD Anderson Cancer Center (Dr. Stacy Moulder)
Cancer Centre of Southeast Ontario (Dr. Tara Baetz)
BCCA-Vancouver (Dr. Stephen Chia)

Clinical Investigators – Phase 1 Expansion Study
MD Anderson Cancer Center (Dr. Stacy Moulder)
University of Colorado (Dr. Virginia Borges)
BCCA-Vancouver (Dr. Stephen Chia)

The Array BioPharma Team