Selective Inhibitors of the ErbB-Family of Receptor Tyrosine Kinase

Eli Wallace, Ph.D.
Director of Medicinal Chemistry
April 2, 2011
Disclosure Information

2011 AACR Annual Meeting
Eli Wallace

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.
Rationale for pan-ErbB Inhibition in Cancer

- ErbB receptors undergo various alterations in human tumors
  - EGFR
    - Gene amplification/overexpression and mutations found in many cancers (lung, gastric, HNSCC, biliary, pancreatic)
  - ErbB2
    - Gene amplification/overexpression found in multiple cancers (breast, gastric, endometrial, salivary gland, ovarian)
  - ErbB3
    - Frequently coexpressed with ErbB2
  - Aberrant ErbB signaling is generally associated with aggressive disease and poor clinical outcome
ErbB Receptor Tyrosine Kinases

- The ErbB family consists of four closely related receptors

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

Figure Adapted from SABiosciences
ErbB Receptor Tyrosine Kinases

- Growth Factor Signaling is Complex

- Many tumor types co-express multiple ErbB receptors and ligands
- Redundant homo- and heterodimers can mediate signaling

Figure Adapted from SABiosciences
Target pan-ErbB Inhibitor

- Aberrant ErbB signaling is generally associated with aggressive disease and poor clinical outcome

- Growth factor signaling is complex with many tumor types co-expressing multiple receptors and ligands

- Tumors that activate redundant ErbB dimers are refractory to selective ErbB inhibitors

**Hypothesis** - pan-ErbB inhibitor will have broader activity than selective ErbB inhibitors in tumors that signal through multiple ErbB family members

- Potential Indications – Gastric, Head & Neck, Biliary
Project Goals

- Potent, Selective, Reversible, Oral pan-ErbB Inhibitor
- Drug-like Inhibitor
  - Clinical Development Unobstructed by Pharmacokinetics
- Activity in Dual Expressing Tumors
- Simultaneously Explore ErbB2 Selective Inhibitor
  - “ARRY-380: A selective, oral HER2 inhibitor for the treatment of solid tumors” Dr. Kevin Koch - New Drugs on the Horizon 1– Sunday April 3
Pan ErbB Inhibitor – Initial Approach

- Investigate Successful Drug Moieties
  - Quinazoline - Balance of potency, selectivity, pharmacokinetics

- Crystal Structure of EGFR kinase domain and erlotinib

Stamos et al JBC 2002, 277 (48), 46265
Pan ErbB Inhibitor – Initial Approach

- Investigate Successful Drug Moieties
  - Quinazoline - Balance of potency, selectivity, pharmacokinetics

Erlotinib
EGFR inhibitor
Pan ErbB Inhibitor – Initial Approach

- Investigate Successful Drug Moieties
  - Quinazoline - Balance of potency, selectivity, pharmacokinetics
  - Cyano-Guanidines – Balance of polarity and permeability
**Cyano Guanidines - Potent Dual Inhibitors**

![](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>EGFR Cell</th>
<th>ErbB2 Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="R1" /></td>
<td>153</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="R2" /></td>
<td>33</td>
<td>111</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="R3" /></td>
<td>184</td>
<td>127</td>
</tr>
</tbody>
</table>

*IC_{50} in nanomolar*

...Poor in vitro ADME properties and no oral exposure in mice

Joe Lyssikatos, Qian Zhao, George Topalov
Serendipity

- **General Route**

  ![Chemical Diagram]

  - Unexpected Product - Oxazolidine

  ![Chemical Diagram]

  EGFR cell IC$_{50}$ 42 nM
  ErbB2 cell IC$_{50}$ 99 nM

Qian Zhao, George Topalov, Ha Young Kim
Oxazolidine Lead

Potent, Orally Bioavailable Lead – Opportunity for Optimization

 EGFR Cell  42
 ErbB2 Cell  99
 Mouse Pharmacokinetics  AUC 2.0 μg.hr/ml @ 10 mg/kg
 Kinase selectivity (17 kinases)  No inhibition at 10 μM
 Properties  MW 478 / Clog P > 6.5

IC50 in nanomolar

Qian Zhao, George Topalov, Ha Young Kim
### Head Group SAR

- Potency Obtainable with More Polar Analogs

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compound</th>
<th>HG</th>
<th>EGFR Cell</th>
<th>ErbB2 Cell</th>
<th>Clog P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image" alt="Structure" /></td>
<td>42</td>
<td>99</td>
<td>&gt;6.5</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure" /></td>
<td>11</td>
<td>17</td>
<td>5.8</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure" /></td>
<td>80</td>
<td>112</td>
<td>4.7</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure" /></td>
<td>183</td>
<td>65</td>
<td>5.1</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure" /></td>
<td>214</td>
<td>84</td>
<td>5.0</td>
</tr>
</tbody>
</table>
## Head Group SAR

### Selectivity

![Head Group SAR Diagram]

<table>
<thead>
<tr>
<th>Compound</th>
<th>HG</th>
<th>R</th>
<th>EGFR Cell</th>
<th>ErbB2 Cell</th>
<th>Selectivity EGFR / ErbB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>![Compound Image]</td>
<td>12</td>
<td>2117</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>![Compound Image]</td>
<td>44</td>
<td>25</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>![Compound Image]</td>
<td>249</td>
<td>20</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>![Compound Image]</td>
<td>Enzyme 460</td>
<td>218</td>
<td>&gt; 50</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>![Compound Image]</td>
<td>OMe</td>
<td>218</td>
<td>2017</td>
<td>0.1</td>
</tr>
</tbody>
</table>

IC\textsubscript{50} in nanomolar

George Topalov, Andy Ren, Alex Buckmelter, Jeremy Hans, Gene Tarlton, Josh Tullis, Greg Miknis
### Oxazolidine versus Dihydro-oxazole

- **Dihydro-oxazole – Improved Pharmacokinetics**

---

**SAR -**
- potency / selectivity
- ADME
- safety / efficacy

---

#### Compound

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>EGFR Cell(^1)</th>
<th>ErbB2 Cell(^1)</th>
<th>Rat Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 mg/kg PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CL(^2)</td>
</tr>
<tr>
<td>8</td>
<td>oxazolidine</td>
<td>214</td>
<td>84</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31% ER</td>
</tr>
<tr>
<td>14</td>
<td>dihydro-oxazole</td>
<td>93</td>
<td>67</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2% ER</td>
</tr>
</tbody>
</table>

1. IC\(_{50}\) in nanomolar
2. ml/min/kg
3. μg.hr/ml
ARRY-543: A Potent, Selective ErbB Inhibitor

- Balanced inhibition of ErbB kinases
- Selective for the ErbB family members
  - No inhibition of > 150 other kinases
- Potent in cell based assays
  - Activity on clinically important mutants
- Reversible inhibitor – opportunity for good safety profile

<table>
<thead>
<tr>
<th></th>
<th>EGFR</th>
<th>ErbB2</th>
<th>ErbB4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzyme IC$_{50}$</strong></td>
<td>7 nM</td>
<td>0.5 nM</td>
<td>4 nM</td>
</tr>
<tr>
<td><strong>Cellular IC$_{50}$</strong> (phospho-receptor)</td>
<td>43 nM</td>
<td>36 nM</td>
<td>130 nM</td>
</tr>
<tr>
<td><strong>Mutant Cell IC$_{50}$</strong> (Exon 19 Del)</td>
<td>100 nM</td>
<td>47 nM (p95 Del)</td>
<td>---</td>
</tr>
</tbody>
</table>
ARRY-543 Displays Favorable PK in Preclinical Species

- Good oral exposure – 50 to 100% F in rat and monkey
- Low-to-moderate CL
  - Human Predicted Liver Extraction Ratio – 33 to 48%
- $V_{ss}$ indicative of tissue penetration
- Good Permeability – no efflux in Caco-2
- Exposure not limited by solubility

...combined with potency led to efficacy in dual and ErbB2 driven models of cancer
Absence of Growth Factors – ErbB2 Expression and Signaling

Growth Inhibition (IC$_{50}$ (nM) / fold shift)

<table>
<thead>
<tr>
<th></th>
<th>No Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC$_{50}$(nM)</td>
</tr>
<tr>
<td>ARRAY-543</td>
<td>87</td>
</tr>
<tr>
<td>Selective ErbB2</td>
<td>6</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>1500</td>
</tr>
</tbody>
</table>
N87 Human Gastric Carcinoma – ErbB2 or Dual Driven

Presence of Growth Factors – Dual Expression and Signaling

Growth Inhibition (IC$_{50}$ (nM) / fold shift)

<table>
<thead>
<tr>
<th></th>
<th>No Stimulation</th>
<th>Epiregulin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC$_{50}$(nM)</td>
<td>IC$_{50}$(nM)</td>
</tr>
<tr>
<td>ARRAY-543</td>
<td>87</td>
<td>312</td>
</tr>
<tr>
<td>Selective ErbB2</td>
<td>6</td>
<td>132</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>1500</td>
<td>892</td>
</tr>
</tbody>
</table>

- Similar results with EGF, heregulin β1, betacellulin, amphiregulin, HB-EGF, TGF$\alpha$
- In the presence of EGF, an increase in EGFR homodimers and EGFR:ErbB2 heterodimers was observed (Monogram Bioscience)

Ryan Blackwell, Jenn Garrus
Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft

### Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>% TGI</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Erlotinib 100 mg/kg / QD</td>
<td>53</td>
<td>0/8</td>
</tr>
<tr>
<td>ARRY-380 50 mg/kg / QD</td>
<td>49</td>
<td>1/8</td>
</tr>
<tr>
<td>Erlotinib 50 mg/kg / QD + ARRAY-380 50 mg/kg / QD*</td>
<td>82</td>
<td>8/8</td>
</tr>
</tbody>
</table>

TGI – tumor growth inhibition
PR - Partial response, ≥ 50% regression of an individual tumor
*Dose of Erlotinib was dropped from 100 to 50 mg/kg on day 8 due to tolerability

Karyn Bouhana, Shannon Winski, Patrice Lee
Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>% TGI</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Erlotinib 100 mg/kg / QD</td>
<td>53</td>
<td>0/8</td>
</tr>
<tr>
<td>ARRAY-380 50 mg/kg / QD</td>
<td>49</td>
<td>1/8</td>
</tr>
<tr>
<td>Erlotinib 50 mg/kg / QD + ARRAY-380 50 mg/kg / QD *</td>
<td>82</td>
<td>8/8</td>
</tr>
<tr>
<td>ARRAY-543 100 mg/kg / BID</td>
<td>90</td>
<td>7/8</td>
</tr>
</tbody>
</table>

TGI – tumor growth inhibition
PR - Partial response, ≥ 50% regression of an individual tumor
*Dose of Erlotinb was dropped from 100 to 50 mg/kg on day 8 due to tolerability
Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>% TGI</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Erlotinib 100 mg/kg / QD</td>
<td>53</td>
<td>0/8</td>
</tr>
<tr>
<td>ARRAY-380 50 mg/kg / QD</td>
<td>49</td>
<td>1/8</td>
</tr>
<tr>
<td>Erlotinib 50 mg/kg / QD + ARRAY-380 50 mg/kg / QD*</td>
<td>82</td>
<td>8/8</td>
</tr>
<tr>
<td>ARRAY-543 25 mg/kg / BID</td>
<td>43</td>
<td>0/8</td>
</tr>
<tr>
<td>ARRAY-543 50 mg/kg / BID</td>
<td>58</td>
<td>1/8</td>
</tr>
<tr>
<td>ARRAY-543 100 mg/kg / BID</td>
<td>90</td>
<td>7/8</td>
</tr>
</tbody>
</table>

TGI – tumor growth inhibition
PR - Partial response, ≥ 50% regression of an individual tumor
*Dose of Erlotinib was dropped from 100 to 50 mg/kg on day 8 due to tolerability

Karyn Bouhana, Shannon Winski, Patrice Lee
Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft
- Efficacy correlates with inhibition of both receptors

EGFR / ErbB2 PD – 100 mg/kg ARRY-543

EGFR / ErbB2 dimers detected
BT474 Human Breast Carcinoma: ARRY-543 +/- trastuzumab

- Significant inhibition of tumor growth at 50 and 100 mg/kg
  - At 100 mg/kg complete response observed in 8 of 10 animals
- Trastuzumab also had significant TGI (53%) as a single agent

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>% TGI</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRY-543 50 mg/kg</td>
<td>69</td>
<td>0/11</td>
</tr>
<tr>
<td>ARRY-543 100 mg/kg</td>
<td>98</td>
<td>8/10</td>
</tr>
<tr>
<td>trastuzumab 20 mg/kg</td>
<td>53</td>
<td>0/10</td>
</tr>
</tbody>
</table>

TGI – tumor growth inhibition
CR: Complete response, 100% regression of an individual tumor
Efficacy correlates with inhibition of ErbB2 and Akt

PD Assay – 100 mg/kg ARRY-543

Tracy Pheneeger, Shannon Winski, Patrice Lee and Piedmont Research Center
BT474 Human Breast Carcinoma: ARRY-543 +/- trastuzumab

- ARRY-543 + trastuzumab - additive activity with complete response in all mice

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>% TGI</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRY-543 50 mg/kg</td>
<td>69</td>
<td>0/11</td>
</tr>
<tr>
<td>ARRY-543 100 mg/kg</td>
<td>98</td>
<td>8/10</td>
</tr>
<tr>
<td>trastuzumab 20 mg/kg</td>
<td>53</td>
<td>0/10</td>
</tr>
<tr>
<td>ARRY-543 (50 mg/kg) + t-mab</td>
<td>99</td>
<td>11/11</td>
</tr>
</tbody>
</table>

TGI - tumor growth inhibition
CR: Complete response, 100% regression of an individual tumor
Summary – Nonclinical Studies

- ARRYY-543 is a potent, well-tolerated, reversible, orally bioavailable ErbB family inhibitor

- In efficacy studies, ARRYY-543 demonstrated dose-dependent inhibition of tumor growth, with regressions
  - ARRYY-543 inhibits growth in multiple tumor types
    - EGFR-expressing (wild-type and mutant – exon 19 deletion)
    - ErbB2-expressing xenograft tumors
    - Dual-responsive tumors

- In combination studies with capecitabine, docetaxel, trastuzumab and cetuximab
  - ARRYY-543 was well-tolerated with combination drugs
  - ARRYY-543 had additive or super-additive activity with combination drugs
  - Increased regressions in combination
ARRY-543 Clinical Results

- Five Phase Ia and Ib Studies Completed with 543 Monotherapy and in Combination with Cytotoxic Therapies
  - > 200 patients treated

- Single Agent Safety
  - MTD 500 mg BID
    - DLTs were Grade 3 anorexia and Grade 3 increased AST/ALT
    - Events of rash were mild-to-moderate in severity
    - No treatment-related cardiac events have been reported

- Cytotoxic Combination Safety
  - MTDs determined in capecitabine, docetaxel, and gemcitabine Phase 1b studies

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>ARRY-543 MTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>docetaxel + GCSF</td>
<td>500 mg BID</td>
</tr>
<tr>
<td>capecitabine</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>gemcitabine</td>
<td>300 mg BID</td>
</tr>
</tbody>
</table>

1The single agent MTD of 500 mg BID precluded additional dose escalation so a non-tolerated dose was not achieved with the docetaxel combination

- No Change in Pharmacokinetics of Either Agent in Any of the Combinations
ARRY-543 – Exposure Increases with Dose

- At steady state during BID dosing, ARRY-543 exposure tends to increase with increasing dose
- Clinical Development Unobstructed by Pharmacokinetics

- $t_{1/2} \sim 7\ h$
- $T_{\text{max}} \sim 3\ h$
- Peak-to-Trough Ratio $\sim 2$

All values are geometric means

Kevin Litwiler
Mean ARRY-543 exposure at 400 mg BID in patients is predicted to inhibit both ErbB2 and EGFR > 90%
**ARRY-543 – Preliminary Clinical Activity**

- **Biliary Cancer Patient (ARRY-543 Monotherapy, 400 mg BID)**
  - 3\(^{rd}\)-line, progressed after:
    - 1\(^{st}\)-line gemcitabine (Best response = PR)
    - 2\(^{nd}\) line cisplatin/5-FU (Best response = PD)
    - EGFR (3+) Status supports activity against EGFR

![Graph showing CA 19-9 levels](image)

- **Minor Response**
  - 25% ↓ in target lesions
Metastatic Breast Cancer (ARRY-543 Monotherapy, 400 mg BID)
- Significant activity in MBC associated with HER2 expression
- The patients with the highest percent regression of target lesions were positive for both EGFR & HER2
ARRY-543/ Varlitinib

- Potent, reversible, oral and selective ErbB family inhibitor

- Favorable clinical PK
  - Clinical exposures predict >90% inhibition of EGFR and ErbB2

- Demonstrated acceptable / competitive safety profile when dosed as monotherapy or in combination with chemotherapeutic agents

- Demonstrates evidence of clinical activity in both ErbB2+ and EGFR+ cancers

- Opportunity to differentiate as first-in-class in “dual-responsive” tumor types
ARY-543 Contributors
Special thanks to our patients and their families

Clinical Investigators
- Dr. Meyer – Vanderbilt University
- Dr. Gelmon – BCCA – Vancouver
- Dr. Cohen – Fox Chase Cancer Center
- Dr. Ellard – BCCA-Kelowna
- Dr. Bendell – Sarah Cannon Research Institute
- Dr. Jonker – Ottawa Cancer Centre
- Dr. Hotte – Juravinski Cancer Centre
- Dr. Weekes – University of Colorado
- Dr. Infante – Sarah Cannon Research Institute
- Dr. Wolpin – Dana-Farber Cancer Institute
- Dr. Camidge – University of Colorado
- Dr. Molina – Mayo Clinic
- Dr. Dent – Ottawa Cancer Centre
- Dr. Borges – University of Colorado
- Dr. Dy – Roswell Park
- Dr. Kwak – Mass General Hospital
- Dr. Gordon – Premiere Oncology - Arizona
- Dr. Rosen – Premier Oncology – Santa Monica

Everyone at Array BioPharma