Inventing, Developing & Commercializing Targeted Small Molecule Drugs in Cancer

The Design and Early Development of the P38/Tie-2 inhibitor, ARRY-614 in Hematologic Cancers

Kevin Koch PhD
April 6th, 2013
Disclosure Information

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.
- Phenotypic screening identified cytokine synthesis inhibitors
- Four family members: p38α, β, γ, δ: restricted expression
- Activation by phosphorylation induced by chemical, cytokine or metabolic/oxidative stress
- Inflammatory cytokine production
- Amplification of cytokines signals
- Checkpoint kinase: DNA damage
- Apoptosis
- Bone metabolism
p38 Kinase Inhibitor Development History

- p38α inhibitors first developed in inflammatory disease (RA)
  - TNF-α, IL-1β, IL-6, PGE-2 inhibition
- 1st generation Inhibitors
  - Poor human whole blood potency
  - Lack of selectivity
  - Clinical Adverse events
    - Liver enzyme elevations
    - CNS toxicity (higher species pre-clinically)
    - Rash
    - Resistance
- New indications:
  - Hematopoietic function, cancer, COPD, post MI, pain
Two Major Classes of Molecules

**VX-745**
- $p38\alpha IC_{50} = 10 \text{nM}$

**BIRB 796**
- $p38\alpha IC_{50} = 63 \text{nM}$
Co-Crystal of VX-745 in p38α
Co-Crystal of BIRB-796 in p38α

Hydrophobic Pocket

GLU 71

MET 109

PHE 169

Pocket
P38 Inhibitor Design Strategy

- **Challenges**
  - Toxicology
    - Mechanism based, structure related or poor selectivity
- **Whole blood Potency, selectivity and solubility**
- **Solutions**
  - Identify a novel scaffold
  - Compare/contrast toxicology profile of open/closed form of the kinase
  - Eliminate known metabolic and toxic functionality via database mining
  - Minimize BBB penetration by physiochemical parameter control
  - Early exploratory toxicology and TI evaluation
Compounds bind with *optimal* location of their pharmacophore.

Identify consensus binding points by docking of small fragments:
- Monte Carlo Simulation program:
  - Fragments optimized for geometries, charges and non-bonded parameters via high level, validated molecular orbital-based methods.
  - Templates randomly placed within active site 6.5Å.
  - Thousands of trajectories sampled.
  - Cluster and analyze results.
Delve: Optimal Positioning of Lipophilic Aromatic Group
Delve: Best Benzisoxazole Capable of Hinge H-Bond
Overlay of Delve Results

Chemical Connection Requires One Atom
Early Lead - ARRY-190

- p38α IC₅₀ = 60 nM
- HWB IC₅₀ = 1200 nM
- cLogP = 5.3
- MW = 284
- PSA = 36 Å²
- Solubility = 3 µg/mL
- Mouse LPS-induced TNF-α production
  - 44% inhibition at 30 mg/kg, po
BIRB-796 Overlapped with Early Indazole Ketone

ARRAY-797
closed form
p38α selective
Positive Ph2 OA
Phe-Pocket SAR

<table>
<thead>
<tr>
<th>R</th>
<th>p38α IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>28</td>
</tr>
<tr>
<td>CH₂Ph</td>
<td>44</td>
</tr>
<tr>
<td>CH₂C(CH₃)₃</td>
<td>75</td>
</tr>
<tr>
<td>NH₂</td>
<td>28</td>
</tr>
<tr>
<td>N(H)Ph</td>
<td>27</td>
</tr>
<tr>
<td>N(H)CH₂Ph</td>
<td>31</td>
</tr>
<tr>
<td>N(CH₃)₂</td>
<td>120</td>
</tr>
<tr>
<td>N(H)-(\bigtriangleup)</td>
<td>60</td>
</tr>
<tr>
<td>N(H)-(\bigtriangleup)</td>
<td>12</td>
</tr>
<tr>
<td>N(H)-(\bigtriangleup)</td>
<td>3</td>
</tr>
</tbody>
</table>
Crystal Structure of AR-217518

Hydrophobic Pocket

MET 109

PHE 169 Pocket
## ARRY-614 – In Vitro Properties

<table>
<thead>
<tr>
<th>Parameter / Assay</th>
<th>ARRY-614</th>
</tr>
</thead>
<tbody>
<tr>
<td>phospho-p38α IC₅₀</td>
<td>4 nM</td>
</tr>
<tr>
<td>phospho-Tie2 IC₅₀</td>
<td>18 nM</td>
</tr>
<tr>
<td>phospho-HSP27 IC₅₀ (HeLa cell)</td>
<td>2 nM</td>
</tr>
<tr>
<td>LPS-Induced TNFα IC₅₀ (Isolated PBMCs)</td>
<td>4.5 nM</td>
</tr>
<tr>
<td>LPS-Induced TNFα IC₅₀ (Human whole blood)</td>
<td>313 nM</td>
</tr>
<tr>
<td>Panel of 201 kinases @ 1 μM</td>
<td>Tie-2 &lt; Abl &lt; KDR</td>
</tr>
<tr>
<td>hERG Inhibition IC₅₀</td>
<td>~19 μM</td>
</tr>
<tr>
<td>29 Receptors / Ion Channels</td>
<td>No inhibition @ 10 μM</td>
</tr>
<tr>
<td>CYP450 (5 major isoforms)</td>
<td>No inhibition @ 25 μM</td>
</tr>
<tr>
<td>Binding Mode</td>
<td>‘DFG-out’</td>
</tr>
</tbody>
</table>

1 phospho-p38α and phospho-Tie2 IC₅₀s evaluated in a HEK-293 cell line expressing endogenous p38α and exogenously expressed, constitutively active Tie2

2 Indicators of p38 signaling
ARRY-614 Inhibits *in vivo* LPS- and SEA-Induced Cytokines

**Lipopolysaccharide (LPS) - induced cytokines [B-cell driven]**

- **TNFα**
  - Control
  - Vehicle
  - 3 mg/kg
  - 10 mg/kg
  - 30 mg/kg
  - **ED<sub>50</sub>&lt;3 mg/kg**

- **IL-6**
  - Control
  - Vehicle
  - 3 mg/kg
  - 10 mg/kg
  - 30 mg/kg
  - **ED<sub>50</sub>&lt;3 mg/kg**

**Staphylococcus Enterotoxin A (SEA) - induced cytokines [T-cell driven]**

- **TNFα**
  - Control
  - Vehicle
  - 3 mg/kg
  - 10 mg/kg
  - 30 mg/kg
  - **ED<sub>50</sub>&gt;10 mg/kg**

- **IL-6**
  - Control
  - Vehicle
  - 3 mg/kg
  - 10 mg/kg
  - 30 mg/kg
  - **ED<sub>50</sub>&lt;3 mg/kg**

*in vivo Challenge Models* - Male Swiss Webster mice received ARRY-614 30 min prior to challenge by oral gavage and serum sampled 90 min post challenge.
ARRY-614 Development Planning in Cancer

- **Hematological Cancers**
  - Single agent and combination activity of ARRY-614 in MM models

- **Metastatic Bone Disease**
  - Alleviates bone pain and reduces tumor bone destruction in preclinical models

- **Solid Tumors**
  - IL-6 and inflammatory state prognostic for survival in multiple tumor types
  - Checkpoint kinase after DNA damage
ARRAY-614 Inhibits Growth of RPMI 8226 Multiple Myeloma Xenografts

ARRAY-614 shows similar activity to thalidomide in established RPMI 8226 xenografts

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<th>Group</th>
<th>%TGI</th>
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<tr>
<td>25 mg/kg ARRY-614, QD, PO</td>
<td>54%</td>
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<tr>
<td>200 mg/kg Thalidomide, QD, IP</td>
<td>57%</td>
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ARRY-614 is Additive With Chemotherapy In Vivo A2780 Ovarian Carcinoma

Efficacy of ARRY-614 in combination with taxol is greater than taxol alone.

<table>
<thead>
<tr>
<th>Group</th>
<th>%TGI</th>
<th>PR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ARRY-614</td>
<td>14%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Taxol</td>
<td>86%</td>
<td>-</td>
<td>1/8</td>
</tr>
<tr>
<td>ARRY-614/Taxol</td>
<td>95%</td>
<td>4/8</td>
<td>2/8</td>
</tr>
</tbody>
</table>

* p<0.05, taxol vs combo
ARRY-614: Potential in Metastatic Bone Pain

Alleviation of tactile allodynia in Rat Syngeneic MRMT-1 (BC) bone pain model

Withdrawal Threshold (g)

- Vehicle
- Morphine
- 3 mg/kg ARRY-614
- 10 mg/kg ARRY-614
- 30 mg/kg ARRY-614

Baseline
Day 10 (Trt Day 3)
**ARRY-614 Decreases Tumor Bone Destruction**

**S06254 Radiographic results**

![Graph showing radiographic results with different treatment groups.]

- **0** = normal bone
- **1** = minor loss in medullary canal
- **2** = substantial loss of bone in medullary canal with some destruction of cortical bone of proximal tibia
- **3** = substantial loss of bone in medullary canal with major structural damage to cortical bone of proximal tibia

**AR614 does not inhibit growth of this tumor line in vivo when grown subcutaneously**
Cancers of the bone marrow lead to ineffective hematopoiesis & apoptosis of normal progenitor cells

Severe loss of normal blood cells (cytopenias) cause fatigue, bleeding, cardiovascular issues & infections

Risk of progressing to acute myeloid leukemia (AML)

Quality of life & economic burdens up to $100K per year due to frequent transfusions & supportive care

Growing treated population due to increased awareness & therapies

MDS G7 Market Prevalence 2012

All MDS Populations: 156,000

IPSS Low/Int-1
102,000

IPSS Int-2/High
47,000

Del5q
7,000

Non-confidential
Multiple roles for p38 in MDS

Phospho-p38 is upregulated in MDS
- Activated p38 is believed to mediate apoptotic signaling in progenitors

Abnormal Clone → p38

Normal Clone

BMSC → TNFα, IL-6, VEGF, TGFβ


Apoptosis of normal progenitors, decreased blood cell counts
**p38 Inhibitors Have Therapeutic Potential in MDS**

![Diagram showing the effect of p38 inhibition on hematopoiesis]

**Abnormal Clone** → **Normal Progenitor**

- **ARRY-614** inhibits p38, leading to decreased apoptosis and restored normal hematopoiesis.

- **TNFα**, **IL-6**, **VEGF**, and **TGFβ** are inhibited, restoring normal hematopoiesis.

**p38 inhibition may restore normal hematopoiesis by several mechanisms**

- Inhibition of cytokine production
- Inhibition of cytokine signaling
- Blockade of progenitor apoptosis
Evidence for Tie2 / Angiopoietin System in MDS

- Evidence suggest a role for Tie2 signaling pathway in MDS
  - Increased ligand expression in the bone marrow of MDS patients \(^1, 2\)
  - High bone marrow Ang1 expression prognostic indicator of poor outcome \(^2\)
  - The Tie2/Ang signaling axis may represent a pro-survival pathway in AML cells \(^3\)

Quantitative RT-PCR in normal and MDS patient bone marrow\(^1\)

Kaplan-Meier curves of overall survival in newly diagnosed MDS patients stratified by Ang1 expression\(^2\)

# ARRAY-614 Targets Key Unmet Needs in MDS

## MDS Risk Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Low/Int-1</th>
<th>Solo Del(5q)</th>
<th>High/Int-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>~65% of patients</td>
<td>~5% of patients</td>
<td>~30% of patients</td>
<td></td>
</tr>
</tbody>
</table>

## Current Therapies

- **Supportive Care**: EPO, Growth Factors, Transfusions & Iron Chelators
- **HMAs**: Vidaza (azacitidine), Dacogen (decitabine)
- **Revlimid** (lenalidomide)

## ARRAY-614 Opportunities

- ARRAY-614 treating Vidaza, Dacogen or Revlimid failures
- ARRAY-614 in combination with other agents

### No standard of care & poor prognosis for Vidaza / Dacogen failures
- Median Overall Survival for Vidaza failures = 18.5 mos.¹
- Median Overall Survival for MDACC Int-2/High = 7.5 to 11 mos. ¹

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¹Moffitt Cancer Center Study, ASH 2012
ARRY-614-111: Dose-Escalation in Low/Int-1 MDS Patients

Key Objectives
- Primary - Determine safety, tolerability, PK and MTD
- Secondary - Evaluate response per IWG 2006 and PD profile

Inclusion Criteria
- IPSS Low/Int-1 Risk MDS, ECOG status 0-2, low blast count <5%
- No limitation of prior therapies or cytopenias

Exclusion Criteria
- No ongoing treatment for MDS other than transfusions or hematopoietic growth factors

Additional Expansion Criteria
- RBC transfusion dependent (IWG 2006)
ARRAY-614-111 - Dose-Escalation Summary

1200 mg QD
- Maximally administered dose
- MTD not reached
- Expansion at 1200 mg QD

QD Schedule
- 1200 mg QD
  - 1 DLT
  - n=6
- 900 mg
  - No DLT
  - n=3
- 600 mg
  - No DLT
  - n=4
- 400 mg
  - 1 DLT
  - G3 Diarrhea
  - n=7

BID Schedule
- 300 mg BID non-tolerated
- G3 Skin Rash (n=2)
- G3 Asthenia & Jitteriness
- G3 Allergic Reaction to Study Drug
- G3 Muscle Weakness & AST/ALT
- 300 mg
  - 5 DLTs
  - n=7
- 200 mg
  - No DLT
  - n=3
- 400 mg
  - G3 Diarrhea
  - n=7
Hematologic Improvement
Key goal for response in lower risk MDS patients

<table>
<thead>
<tr>
<th>Lineage (blood cell type)</th>
<th>Evaluability Criteria*</th>
<th>Hematologic Improvement Criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell</td>
<td><strong>Erythroid</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hgb ≤ 11 g/dL</td>
<td>Hgb increase by ≥ 1.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Received ≥ 4 RBC transfusions over 8 weeks prior</td>
<td>TR (Reduction of 4 RBC units)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TI (transfusion independence)</td>
</tr>
<tr>
<td>Platelet</td>
<td><strong>Platelet</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets ≤ 100 10^9/L</td>
<td>Absolute increase of ≥ 30 10^9/L for patients starting with &gt; 20 10^9/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase to &gt; 20 10^9/L and by ≥ 100%</td>
</tr>
<tr>
<td>White blood cell (PMNs)</td>
<td><strong>Neutrophil</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANC ≤ 1.0 10^9/L</td>
<td>At least 100% increase and an absolute increase of &gt; 0.5 × 10^9/L</td>
</tr>
</tbody>
</table>

* International Working Group 2006 criteria, 8 weeks duration minimum required for all improvement criteria
**ARRAY-614-111 – Hematologic Improvement**

- **Patient with severe cytopenias**
- **All standards of care have failed**

<table>
<thead>
<tr>
<th>IPSS Risk at Diagnosis/Screening</th>
<th>Int-1 / Int-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline cytopenias</td>
<td>Gr 2 Anemia</td>
</tr>
<tr>
<td></td>
<td>Gr 4 Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Gr 2 Neutropenia</td>
</tr>
<tr>
<td># Prior Therapies Drug - Best response</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Azacitidine - SD (~5 months) →</td>
</tr>
<tr>
<td></td>
<td>Decitabine – SD (~2 months) →</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide – SD (~1 month) →</td>
</tr>
<tr>
<td></td>
<td>Azacitidine –SD (~11 months)</td>
</tr>
</tbody>
</table>

**Red blood cells** - No Transfusions (From Day 1), HI – Hemoglobin (Day 22)

**Platelets** - HI – Platelet (Day 141)

**Neutrophils** – Normalized, but not response-eligible

Continuous ARRY-614 treatment - >29 months
ARRAY-614-111 Response by Initial Dose Cohort

- Despite variability ARRY-614 exposure with the initial formulation evaluated, there is increasing exposure with increasing dose of ARRY-614.
- There is an increase in clinical signal (hematologic improvement) with increasing ARRY-614 dose.

**Preliminary Data as of 21 October 2011**
ARRAY-614-111
Hematologic Improvement Observed

- Refractory patient population - 80% received prior treatment with ≥ 1 HMA
  - All responders had received HMA therapy
- Median duration of treatment 20 weeks
- 38% HI at highest dose (1200 mg daily)
  - 67% of HIs at this dose were bi-lineage responses

International Congress on Targeted Anticancer Therapies 09-Mar-2012

Non-confidential
## ARRAY-614-111
### Common Treatment Related AEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cohort (mg/dose)</th>
<th>Total (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 BID, 300 BID (n=10)</td>
<td>400, 600 QD (n=16)</td>
</tr>
<tr>
<td>CTC Grade:</td>
<td>1/2 3</td>
<td>1/2 3</td>
</tr>
<tr>
<td>Rash*</td>
<td>2 2</td>
<td>3 -</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 -</td>
<td>3 1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>- -</td>
<td>3 -</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 -</td>
<td>2 -</td>
</tr>
<tr>
<td>Fatigue</td>
<td>- 1</td>
<td>- -</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 -</td>
<td>1 -</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>1 -</td>
<td>- -</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>1 1</td>
<td>- 1</td>
</tr>
</tbody>
</table>

*Includes preferred terms of acne, dermatitis acneiform, maculopapular rash, pruritic rash, rash, skin irritation, and skin exfoliation

---

- No Grade 4 or 5 treatment-related events were reported
  - 13/45 (29%) patients had dose reductions due to adverse events
  - 15/45 (33%) patients came off study due to adverse events
ARRAY-614-111
Durable Inhibition of p38α

ARRAY-614 Reduces p-p38 in Patient Bone Marrow

*p<0.05; Data analyzed by ANOVA, Tukey-Kramer post hoc (NS = not significant)
ARRAY-614-111
...Leads to Inhibition of Apoptosis

ARRAY-614 Inhibits Cleaved Caspase-3 (CC3) in MDS Patient Bone Marrow

CC3 Not Elevated in Healthy, Age-Comparable Bone Marrow
ARRAY-614 Summary

- Successful design of a novel p38/Tie-2 inhibitor
- Potent inhibition of p38/Tie2; favorable selectivity and PK
- Mechanistic inhibition of cytokine production
- Activity in a number of preclinical cancer models
- Multi-lineage clinical benefit in MDS patients
- Acceptable safety
- Disease modifying activity in MDS bone marrow

http://clinicaltrials.gov/show/NCT01496495
ARRY-614 Team
with special thanks to our patients and their families

Chemistry
Devan Balachari, Larry Burgess, Tsung Chuang, Chris Clark, David Clarke, John DeMattei, Bob Groneberg, Darren Harvey, Kevin Hunt, Gangyeok Kim, Kevin Koch, Dave Mareska, Matt Medina, Mark Munson, Jim Rizzi, Mareli Rodriguez, Hideo Suzuki

Biology and Computation
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Pharmacology
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Drug Metabolism
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