Phase 1 Dose-Escalation/Expansion Study of the p38/Tie2 Inhibitor ARRY-614 in Patients with IPSS Low/Int-1 Risk Myelodysplastic Syndromes

ASH 2011, Abstract 118


1H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
2Winship Cancer Institute of Emory University, Atlanta, GA
3University of Texas M.D. Anderson Cancer Center, Houston, TX
4Array BioPharma Inc., Boulder, CO
Disclosures

- No conflict of interest to disclose
Background: Lower Risk MDS

• The majority of patients with myelodysplastic syndromes (MDS) present with lower risk disease
  • International Prognostic Scoring System (IPSS) score ≤ 1.0

• Treatment goal is hematologic improvement (HI) to alleviate symptomatic cytopenias and improve quality of life
  • Limited treatment options for anemia
  • Management of neutropenia and thrombocytopenia is a major unmet need

• No treatment options for patients for whom hypomethylating agents (HMAs) have failed
Dual Inhibition of p38 and Tie2 by ARRY-614

Block Myelosuppression in Bone Marrow

**p38 MAPK in MDS**
- Over-activated, leading to inappropriate production of myelosuppressive cytokines (Navas et al. Blood. 2006. 108: 4170.)

**Tie2 in MDS – Emerging Target**
- Dysregulated, may be a survival factor for the AML blast (Keith et al. BJH. 2007. 137: 206.)
- Increased signaling associated with poor prognosis (Cheng et al. BJC. 2011. 105: 975.)

- Stress/Inflammatory Stimuli (Cytokines, Hypoxia, FasL)
  - TNF-α, IL-6, Chemokines
  - Decreased RBC, WBC, platelets
- Apoptosis
- Pleiotropic effects on Progenitors and AML blasts

- Ang-1
- Ang-2
ARRY-614 Phase 1 Study Design
Phase 1, open-label, dose-escalation study in MDS patients

**Dose Escalation Phase**
(N = 35)

- **QD, mg/dose**
  - 400*
  - 600
  - 900
  - 1200

- **BID, mg/dose**
  - 200
  - 300

*Both fasted and fed cohorts evaluated

**Expansion Phase**
(QD)
(N = 10)

**MTD**

**Study Objectives**

- **Primary**
  - Determine safety, tolerability and MTD
  - Characterize PK
- **Secondary**
  - Evaluate response per IWG 2006
  - Explore PD profile

- Standard 3+3 design
- 2 dosing schedules (fasted)
- A cycle is continuous oral dosing for 28 days
Key Eligibility Criteria

• Inclusion/Exclusion Criteria
  • IPSS Low/Int-1 Risk MDS at screening
  • No limit on number of prior therapies or cytopenias
  • ECOG PS 0-2
  • No concurrent MDS treatments allowed except supportive therapies (transfusions or growth factors)

• Additional Criteria During Expansion Phase
  • RBC transfusion dependent (IWG 2006)
  • Hematopoietic growth factors not allowed in Cycle 1
Baseline Characteristics (1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years (range)</td>
<td>72 (47 – 84)</td>
</tr>
<tr>
<td>Median years since diagnosis (range)</td>
<td>3.3 (0.2 – 16.3)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>39 / 6</td>
</tr>
<tr>
<td>IPSS Risk at screening</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>34 (76)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (24)</td>
</tr>
<tr>
<td>1</td>
<td>28 (62)</td>
</tr>
<tr>
<td>2</td>
<td>6 (13)</td>
</tr>
</tbody>
</table>

For all analyses, data up to 01 Aug 2011
## Baseline Characteristics (2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 45 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Blasts</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>40 (89)</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>4  (9)</td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>26 (58)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>19 (42)</td>
</tr>
<tr>
<td><strong>Transfusions</strong></td>
<td></td>
</tr>
<tr>
<td>Any RBC</td>
<td>36 (80)</td>
</tr>
<tr>
<td>Transfusion Dependent IWG 2006²</td>
<td>28 (62)</td>
</tr>
<tr>
<td>Platelets</td>
<td>7  (16)</td>
</tr>
</tbody>
</table>

¹ One patient did not have results
² ≥ 4 RBC units within 8 weeks of first dose
## Baseline Characteristics (3)

<table>
<thead>
<tr>
<th>Lineage</th>
<th>N = 45</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td><strong>Erythroid (Hgb; g/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 11</td>
<td>41</td>
<td>(91)</td>
<td></td>
</tr>
<tr>
<td>Neutrophils ($\times 10^9$/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>9</td>
<td>(20)</td>
<td></td>
</tr>
<tr>
<td>≤ 0.5</td>
<td>7</td>
<td>(16)</td>
<td></td>
</tr>
<tr>
<td><strong>Platelets ($\times 10^9$/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 – 100</td>
<td>10</td>
<td>(22)</td>
<td></td>
</tr>
<tr>
<td>20 – 50</td>
<td>9</td>
<td>(20)</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>6</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of Cytopenias</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 1</td>
<td>20</td>
<td>(45)</td>
<td></td>
</tr>
<tr>
<td>2 – 3</td>
<td>25</td>
<td>(55)</td>
<td></td>
</tr>
</tbody>
</table>
Prior Therapies

- Median number of prior therapies (range): 3 (0 – 9)
- 80% received treatment with ≥ 1 HMA

AZA=azacitidine, ESA=erythropoiesis stimulating agents, DEC=decitabine, LEN=lenalidomide, GCSF=granulocyte colony stimulating factor, HDACi=histone deacetylase inhibitor
Treatment Summary

• Enrollment complete, 7 patients ongoing
• Median duration of treatment (range): 20 weeks (1 – 80)

For all analyses, data up to 01 Aug 2011
Dose-Limiting Toxicities

**Total Daily Dose (mg/dose)**

- **QD Schedule**
  - 1200 mg QD (maximally administered dose (12 x 100 mg capsules))
  - MTD not reached
  - 1 DLT
  - G3 Skin Rash
- 900 mg QD
  - No DLT
- 600 mg QD
  - No DLT
- 400 mg QD
  - 1 DLT
  - G3 Diarrhea

- **BID Schedule**
  - 1200 mg BID
  - Not tolerated
  - 5 DLTs
  - G3 Skin Rash (n=2)
  - G3 Asthenia & Jitteriness
  - G3 Allergic Reaction to Study Drug
  - G3 Muscle Weakness & Elevated AST/ALT
- 300 mg BID
  - Not tolerated
  - G3 Skin Rash (n=2)
- 300 mg BID
  - 5 DLTs
  - G3 Skin Rash (n=2)
  - G3 Asthenia & Jitteriness
  - G3 Allergic Reaction to Study Drug
  - G3 Muscle Weakness & Elevated AST/ALT
- 200 mg BID
  - No DLT

**DLT Criteria (First Cycle):**

- Grade 3/4 nausea, vomiting, or diarrhea despite maximum supportive care
- Any other Gr 3/4 non-hematologic AE
- Neutrophils: Gr 4 (if Gr 0/1 at baseline [BL]) OR < 0.1 x 10^9/L and decrease of > 75% from BL (if Gr ≥ 2 at BL) for > 7 days
- Platelets: Gr 4 (if Gr 0/1 at BL) OR < 10 x 10^9/L for > 7 days and decrease of > 75% from BL (if Gr ≥ 2 at BL)
- Interruption of dosing or delay of starting C2 beyond Day 56

**QD Schedule**

- 1200 mg QD
  - 1 DLT
  - G3 Skin Rash
- 900 mg QD
  - No DLT
- 600 mg QD
  - No DLT
- 400 mg QD
  - 1 DLT
  - G3 Diarrhea

**BID Schedule**

- 1200 mg BID
  - Not tolerated
  - 5 DLTs
  - G3 Skin Rash (n=2)
  - G3 Asthenia & Jitteriness
  - G3 Allergic Reaction to Study Drug
  - G3 Muscle Weakness & Elevated AST/ALT
- 300 mg BID
  - Not tolerated
  - G3 Skin Rash (n=2)
- 300 mg BID
  - 5 DLTs
  - G3 Skin Rash (n=2)
  - G3 Asthenia & Jitteriness
  - G3 Allergic Reaction to Study Drug
  - G3 Muscle Weakness & Elevated AST/ALT
- 200 mg BID
  - No DLT
# Treatment-Related AEs (≥ 5%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cohort (mg/dose)</th>
<th>CTC Grade</th>
<th>200 – 300 BID (n=10)</th>
<th>400 – 600(^1) QD (n=16)</th>
<th>900 QD (n=3)</th>
<th>1200 QD (n=16)</th>
<th>Total (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash(^2)</td>
<td></td>
<td>1/2</td>
<td>3</td>
<td>1/2</td>
<td>3</td>
<td>1/2</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Dry skin</td>
<td></td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>ALT increased</td>
<td></td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

1 Includes 5 patients who were treated in the 400 mg QD fed cohort
2 Includes preferred terms of acne, dermatitis acniform, maculopapular rash, pruritic rash, rash, skin irritation, and skin exfoliation

- 8/45 (18%) patients had dose reductions due to treatment-related AEs
- 8/45 (18%) patients came off study due to treatment-related AEs
ARRY-614 Pharmacokinetics

1200 mg QD provides 24 hour target coverage >IC$_{50}$

Exposure increases with increasing dose

![Graph showing ARRY-614 Concentration vs Time and AUC$_{tau}$ vs ARRY-614 Dose]
Reduced Apoptosis in Bone Marrow

- phospho-p38 observed at baseline and decreased following treatment
- Increased apoptosis at baseline which decreases by >75% over 4 months

Presence of cleaved caspase 3 (CC3) is indicative of apoptosis

*Cycle 4 statistically different from screening (ANOVA, Dunn’s multiple comparison test post hoc); n = 6 – 9
Disease-Associated EPO Decreased

- Plasma EPO decreases in patients regardless of reaching HI

† Lowest statistically different from baseline (Wilcoxon Signed Rank test)
‡ Change in responder statistically different from non-responder (Mann Whitney U test)
HI Responses

- Overall, durable HI observed in 13 of 44 evaluable patients (30%)
  - 5 bi-lineage responses

<table>
<thead>
<tr>
<th>N patients</th>
<th>HI-E n = 41</th>
<th>HI-P n = 25</th>
<th>HI-N n = 16</th>
<th>Total HI N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (%)</td>
<td>8 (20)</td>
<td>5 (20)</td>
<td>5 (31)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Median duration, weeks (range)</td>
<td>32 (9-80)</td>
<td>16 (8-67)</td>
<td>21 (14-26)</td>
<td></td>
</tr>
</tbody>
</table>

5 of 7 platelet transfusion-dependent patients became transfusion independent (TI) for a median duration of 20 weeks (range 15 – 31)
3 of 28 RBC transfusion-dependent patients became TI for a median duration of 21 weeks (range 11 – 72)

- Responder (n = 13) baseline characteristics
  - All ≥ 1 prior HMA
  - 12 IPSS Int-1
  - 11 2-3 cytopenias
  - 6 abnormal cytogenetics¹

¹Includes one each: Pseudodiploid Clone, T(1;8)(Q21;Q22), Del (7), Pseudo Hyperdiploid Clone del (20q), del 5q, and Trisomy 8
Trend for Increased HI by Dose

IWG 2006 HI by Total Daily Dose

- 38% HI at highest dose (1200 mg daily)
- 67% bi-lineage responses


Activity Across MDACC Risk Groups

  - Refines the prognostic values of IPSS
  - Dynamic model for evaluating patients throughout the course of their disease

- Baseline characteristics used to retrospectively calculate MDACC score
  - 19 lower risk patients per IPSS would have been at higher risk per MDACC score at study entry; 6/19 achieved HI

- HI and time on study was similar between MDACC higher and lower risk
ARRY-614 MDS Summary

- QD dosing schedule well tolerated at doses up to 1200 mg
  - MTD not reached
  - Optimized formulation in clinical trials
- Decreases in phospho-p38 and apoptosis consistent with on target effect
- Multi-lineage HI observed in patients for whom HMAs had failed
  - 30% HI overall
  - 38% HI at 1200 mg QD; 67% multi-lineage
- Encouraging results in this heavily pre-treated population warrants additional investigation
Acknowledgments

Patients and their families

- Moffitt Cancer Center
  - Alan List
  - Jeffrey Lancet
  - Heather Orr
  - Debra VanDonkelaar
- Emory
  - H. Jean Khoury
  - Andrena Lawrence
  - Mersiha Torlak
- MDACC
  - Guillermo Garcia-Manero
  - Hagop Kantarjian
  - Maria Cielo Foudray
  - Elias Jabbour
  - Jin Jin
  - Little Pullock
- Array BioPharma Inc.

All staff and personnel who helped on the study

Slides can be downloaded from: www.arraybiopharma.com