First in Human Study with ARQ 092, a Novel Pan AKT-Inhibitor: Results from the Advanced Solid Tumors Cohorts

Mansoor Saleh (1), Kyri Papadopoulos (2), Alireza Arabnia (1), Amita Patnaik (2), Robin M. Stein (1), Federica Cattaneo (3), Giovanni Abbadessa (3), Jonathan Greenberg (4), Steven Warren (4), and Anthony Tolcher (2)

(1) Georgia Cancer Specialist Affiliated with Northside Hospital Cancer Institute, Atlanta, GE, USA
(2) South Texas Accelerated Research Therapeutics (START) Center for Cancer Care, San Antonio, TX, USA
(3) ArQule, Inc., Woburn, MA, USA
(4) Daiichi Sankyo, Edison, NJ, USA
Speaker Bureau for Novartis, Roche/Genentech, Bristol Myers Squibb
AKT SIGNALING PATHWAY IS A THERAPEUTIC TARGET IN ONCOLOGY

AKT Signal Transduction Is a Critical Node Serving a Variety of Cellular Functions Including Survival, Proliferation and Protein Synthesis

- AKT signal pathway is aberrantly dysregulated in a wide range of tumor types
- Extensive molecular evidence validates the pathway as target in cancer

Vivanco I et al., Nat Rev Cancer, 2:489-501, 2002

Meric-Bernstam and Gonzalez-Angulo, J Clin Oncol 2009
ARQ 092 IS A NOVEL, ATP-INDEPENDENT, SELECTIVE PAN-AKT INHIBITOR

Co-crystal X-Ray Structure, Biochemical and Anti-Proliferative Properties of ARQ 092

ARQ092 inhibits AKT in an ATP-independent manner and binds to the Pleckstrin Homology Domain, preventing ATP from being allocated

<table>
<thead>
<tr>
<th>Biochemical Assay IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
<th>In Vitro IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1</td>
<td>AKT2</td>
</tr>
<tr>
<td>ARQ 092&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.9</td>
</tr>
<tr>
<td>MK-2206&lt;sup&gt;2&lt;/sup&gt;</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>1</sup>Chan T. et al., AACR 2011, Abstract Number A230
<sup>2</sup>Yan L. et al., AACR 2009: Abstract Number: DDT01-1

*PTEN deficiency  ** PI3KCA mutation
Strong Antitumor Activity in the AN3-CA (PTEN-Deficient) Xenograft Model

IN VIVO ACTIVITY OF ARQ 092

Tumor Weight (mg)

Days Post Implantation

Vehicle
ARQ 092 50 mg/kg Q1Dx10
ARQ 092 100 mg/kg Q1Dx10
ARQ 092 150 mg/kg Q1Dx8
ARQ 092 200 mg/kg Q2Dx5

Vehicle
-15%
-55%
-60%
-74%

S473pAKT
Thr246pPRAS40

Tumor sample ICH before and after single dose of ARQ 092 at 200 mg/kg

Chan T. et al., AACR 2011, Abstract A230
ARQ 092-101: FIRST IN HUMAN PHASE I STUDY
Endpoints and Eligibility

**KEY INCLUSION CRITERIA**

- Histologically/cytologically documented advanced/metastatic solid tumors in subjects who failed standard therapy
- ECOG PS ≤ 2
- RECIST measurable disease

**PRIMARY ENDPOINTS**

- Safety and tolerability in subjects with advanced solid tumors

**SECONDARY ENDPOINTS**

- Pharmacokinetic profile
- Pharmacodynamic activity (in blood and eventually in tumor)
- MTD and RP2D
- Preliminary evidence of activity

**EXPLORATORY ENDPOINTS**

- Association between markers of the AKT signaling pathway, toxicity and clinical activity
- Changes in different pathways and potential combinations of interest

**KEY EXCLUSION CRITERIA**

- History of Type 1 or 2 diabetes mellitus requiring regular medication (other than metformin)
- Hypercholesterolemia or hypertriglyceridemia \( \geq \) G2
- HbA1C >8%
- LVEF < 50% by echocardiogram/MUGA scan
- No previous treatment with AKT inhibitors
- No cancer therapy within 4 weeks (2 weeks for orally administered drugs)
- No major surgery or Rx tx within 4 weeks
ARQ 092-101: STUDY DESIGN

• Open label
• Cohorts 1-5: dose doubled
• From cohort 6: modified Fibonacci scheme (increase by 30% until RP2D)
• 3+3* subjects per cohort (*if DLT)
• Intra-subject dose escalation not allowed
• Enrollment: November 2011 through February 15th 2013, US

DOSE ESCALATION

Oral, once-daily ARQ 092, 28-day cycle

COHORT
1 2 3 4 5 6 7

DOSE
10 mg QOD
10 mg QD
20 mg QD
40 mg QD
80 mg QD
60 mg QD intermittent schedule

MTD IF ≤ 1 DLT OUT OF 6 TREATED SUBJECTS

DLT if occurrence within the first cycle of:

• Standard DLT criteria
• ≥ G3 hyperglycemia
  - fasting blood glucose > 250 mg/dL or non-fasting > 500 mg/dL requiring insulin (uncontrolled with metformin)

PK SAMPLING
Cycle 1: DLT window
1, 2
8
15, 16
22
29
Cycle 2
36
43
50
58

PD SCHEDULE
TUMOR ASSESSMENT
### ARQ 092-101: BASELINE SUBJECTS CHARACTERISTICS

**Enrollment:** November 2011 - Ongoing, GCS (Atlanta) and START (San Antonio), 31 Subjects Screened, 28 Enrolled as of February 15th 2013

<table>
<thead>
<tr>
<th></th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=28</strong></td>
<td></td>
</tr>
<tr>
<td>Median Age, yrs</td>
<td>62.0 (46-79)</td>
</tr>
<tr>
<td>Male/Female, n (%)</td>
<td>9/16 (36/64)</td>
</tr>
<tr>
<td>ECOG PS 0/1/2, n</td>
<td>10/13/2 (40/52/8)</td>
</tr>
<tr>
<td>Median number of prior antineoplastic regimens (range)</td>
<td>4 (1-10)</td>
</tr>
<tr>
<td>Patients with ≥ 3 prior regimens, n (%)</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Primary tumor type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Uterine, n (%)</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Colon, n (%)</td>
<td>5 (17.8)</td>
</tr>
<tr>
<td>NSCLC, n (%)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Prostate, n (%)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Bladder, n (%)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Other*, n (%)</td>
<td>11 (39.2)</td>
</tr>
</tbody>
</table>

*Includes meningioma, breast, sarcoma, melanoma, esophagus, ovary, head and neck, bronchial carcinoid, endocrine pancreas, neuroendocrine
## ARQ 092-101: TREATMENT-EMERGENT ADVERSE EVENTS

Dose-Specific Related and Unrelated AEs as of February 15th 2013

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Grades</th>
<th>DOSE, mg/day</th>
<th>Total (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (%)</td>
<td>10 QOD (n=4)</td>
<td>10 (n=3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maculo-Papular Rash</td>
<td>3-4 (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ARQ 092-101: DRUG-RELATED HYPERGLYCEMIA PRECEDES RASH

No Subject Discontinued Treatment Due to Rash

<table>
<thead>
<tr>
<th>Subject</th>
<th>Med History</th>
<th>Daily Dose</th>
<th>Dose</th>
<th>Drugdosing</th>
<th>Drugholding</th>
</tr>
</thead>
<tbody>
<tr>
<td>#17</td>
<td>Diabetes Type II</td>
<td>80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#18</td>
<td></td>
<td>80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#19</td>
<td>G1 Intermittent Hyperglycemia</td>
<td>80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#21</td>
<td></td>
<td>80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#23</td>
<td>Diabetes Type II</td>
<td>60 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graph showing the progression of hyperglycemia and rash over time for each subject.
<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Subjects Enrolled</th>
<th>DLT</th>
<th>Recovery in 14 Days</th>
<th>Dose Reduction Tolerated</th>
<th>Reason for Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg QD</td>
<td>7</td>
<td>#15 G4 Congestive Heart Failure (day 15)</td>
<td>NO</td>
<td>NA</td>
<td>DLT (off study wk 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>#19 G3 Maculo-Papular Rash (day 23)</td>
<td>YES</td>
<td>40 mg QD (day 28)</td>
<td>PD (off study wk 24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>#21 G3 Hyperglycemia Requiring Insulin (day 21)</td>
<td>YES</td>
<td>NA</td>
<td>Investigator Decision (off study wk 5)</td>
</tr>
<tr>
<td>60 mg QD</td>
<td>7</td>
<td>#24 G3 Increased AST (day 21)</td>
<td>YES</td>
<td>40 mg QD (day 35)</td>
<td>Clinical Progression (off study wk 8)</td>
</tr>
</tbody>
</table>

- MTD* for daily schedule was not formally declared

*highest dose not causing DLT in >1 out of 6 patients during the first treatment cycle
ARQ 092-101: PHARMACOKINETIC PROFILE

- ARQ 092 has a manageable PK profile
- Slow absorption, median $T_{\text{max}}$ range from 4-8 hrs for most subjects
- Low clearance, mean half-life range from 19-53 hrs
- Accumulation ratio ($\text{AUC C1Day15/ AUC C1Day1}$) range from 3-9
- ARQ 092 exposure increased in an approximately dose-proportional fashion
### ARQ 092-101: PHARMACODYNAMIC MARKERS

#### P-AKT in Platelet Rich Plasma (PRP) Assay and Plasma Glucose Change

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tumor type</th>
<th>PRP pAKT Baseline</th>
<th>PRP pAKT Day 15</th>
<th>Decrease in PRP pAKT%</th>
</tr>
</thead>
<tbody>
<tr>
<td>#17</td>
<td>Colon</td>
<td>23.8</td>
<td>11.6</td>
<td>-51.1</td>
</tr>
<tr>
<td>#18</td>
<td>Uterine*</td>
<td>40.9</td>
<td>2.8</td>
<td>-93.3</td>
</tr>
<tr>
<td>#19</td>
<td>Neuroendocrine**</td>
<td>24.3</td>
<td>2.1</td>
<td>-91.6</td>
</tr>
<tr>
<td>#20</td>
<td>Colon</td>
<td>25.1</td>
<td>6.4</td>
<td>-74.7</td>
</tr>
<tr>
<td>#21</td>
<td>Uterine*</td>
<td>24.5</td>
<td>4.9</td>
<td>-85.9</td>
</tr>
<tr>
<td>#22</td>
<td>Uterine</td>
<td>24</td>
<td>8.6</td>
<td>-64.3</td>
</tr>
<tr>
<td>#23</td>
<td>Uterine</td>
<td>10.2</td>
<td>3.3</td>
<td>-67.8</td>
</tr>
<tr>
<td>#24</td>
<td>Colon</td>
<td>12.1</td>
<td>5.6</td>
<td>-54.1</td>
</tr>
<tr>
<td>#26</td>
<td>Prostate</td>
<td>10.7</td>
<td>4.5</td>
<td>-57.9</td>
</tr>
</tbody>
</table>

*On study > 6 months  **On study for 6 months  °PTEN deletion

**Median Plasma Glucose Concentration (mg/dl)**

- **Baseline**
- **Week 3 (Day 21)**

**Dosages:**
- 80 mg
- 60 mg

**Dosage Regimens:**
- 10mg QOD
- 10mg QD
- 20mg QD
- 40mg QD
- 60mg QD
- 80mg QD
ARQ 092 PRELIMINARY ACTIVITY PROFILE
Effect on Tumor Size in Evaluable Subjects

- Best % change from baseline
- Neuroendocrine
- Melanoma
- Ovarian
- Sarcoma
- Bladder
- Meningioma
- Esophagus
- NSCLC
- Colon
- Endometrial

- Progression Disease
- Stable Disease

n=20
Ongoing
AKT1 mutation

#5    #4    #12   #20   #23  #11   #7   #22   #13    #2    #16   #6     #8    #19    #9    #10   #24   #3   #17   #18
ARQ 092-101: DURATION OF EXPOSURE (as of February 15th 2013)

- 28 subjects enrolled. 7 subjects on study ≥ 4 months; of them:
  - 4 subjects with long-term disease stabilization (≥ 6 months)
  - 1 subject on study for 13 months and ongoing
- 5 subjects ongoing (median 2 months)
ARQ 092-101: FIRST IN HUMAN STUDY IN ADVANCED SOLID TUMORS

- ARQ 092 has a safety profile consistent with that predicted by preclinical models
- Early hyperglycemia preceding rash might be a crucial differentiating feature of ARQ 092
- Drug exposure increases in a dose-dependent fashion
- Dose-dependent AKT pathway inhibition is obtained in peripheral blood
- MTD on a continuous daily schedule has not been formally declared
- Preliminary signals of single agent activity in patients with advanced solid tumors have been documented:
  - 4 heavily pretreated subjects experienced long-term (≥ 6 months) stable disease
- PK and clinical data support intermittent dosing schedules, currently planned in advanced solid tumors and recurrent lymphoma
- Clinically valuable combinations with targeted agents in preclinical settings are warranted
ACKNOWLEDGEMENTS

Our heartfelt gratitude to the patients and their families

Georgia Cancer Specialists Affiliated with Northside Hospital Cancer Institute, Atlanta, GE, USA
Alireza Arabnia, Mansoor Saleh, Robin M. Stein

South Texas Accelerated Research Therapeutics (START) Center for Cancer Care, San Antonio, TX, USA
Elaine Golden, Kyri Papadopoulos, Amita Patnaik, Anthony Tolcher

ArQule, Inc., Woburn, MA, USA
Giovanni Abbadaessa, Federica Cattaneo, Yinpu Chen, Beverly Fellows, Dora Ferrari, Maria Lamar, Ron Savage, Manish Tandon, Brian Schwartz, Yunxia Wang

Daiichi Sankyo, Edison, NJ, USA
Jonathan Greenberg, Jarema Kochan, Prasanna Kumar, Lori Varty, Steven Warren

Ce3, Guilford, CT, USA
Susan Albert, Samira Ali