Pursuing Treatments for Biomarker-Driven Cancers and Rare Diseases

Jefferies 2019 Healthcare Conference on June 6, 2019
Forward Looking Statements

This presentation and other statements by ArQule contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act including, without limitation, statements with respect to current and proposed clinical trials with the Company’s product candidates derazantinib (ARQ 087), miransertib (ARQ 092), ARQ 751 and ARQ 531, financial operations and results, potential corporate partnerships as well as strategic objectives, business objectives, next steps, pipeline and other goals, clinical targets, projected inflection points, catalysts, market estimates and potentials, opportunities and other strategies. Forward-looking statements are typically identified by words such as “believe,” “expect,” “anticipate,” “intend,” “outlook,” “position,” “goal” and similar expressions, or future or conditional verbs such as “will,” “should,” “would,” and “could.” Forward-looking statements are subject to numerous assumptions, risks and uncertainties. Forward-looking statements speak only as of today, and ArQule assumes no obligation to update them. Actual results may differ materially from forward-looking statements or historical performance due to the factors discussed in this presentation and factors previously disclosed in ArQule’s SEC reports. See discussion of Risk Factors in the Company’s Annual Report on Form 10-K as filed with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this presentation. ArQule’s product candidates are in various stages of development and are not available for sale or use outside of approved clinical trials.

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Experienced Developer of Novel Kinase Inhibitors

Four Novel Oral Compounds in Clinical Development

01. Reversible BTK inhibitor, ARQ 531, that can overcome ibrutinib resistance – wholly owned

02. AKT inhibitor, miransertib, in registrational trial for certain rare overgrowth diseases – wholly owned

03. Next-Gen AKT inhibitor, ARQ 751, for solid tumors – wholly owned

04. FGFR inhibitor, derazantinib, in a registrational trial for intrahepatic cholangiocarcinoma – globally partnered

Biomarker-driven discovery of precision medicines for cancer and rare diseases with potential for accelerated registration paths
<table>
<thead>
<tr>
<th></th>
<th>Class</th>
<th>Indication</th>
<th>Current Stage</th>
<th>Target for Next Stage</th>
<th>Market Potential (est.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARQ 531</td>
<td>Reversible BTK inhibitor</td>
<td>B-cell malignancies</td>
<td>Phase 1a/b</td>
<td>Phase 2 Expansion / Registrational</td>
<td>Large (and growing) blockbuster market potential</td>
</tr>
<tr>
<td>RARE DISEASES</td>
<td>AKT inhibitor</td>
<td>Proteus Syndrome (PROS)</td>
<td>Registral Cohorts: Orphan Designation, Rare Ped. Dis. Des. (PS), Fast Track Des. (PROS)</td>
<td>NDA Filing</td>
<td>Meaningful aggregate prevalence, Rare Pediatric Disease voucher, if approved</td>
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<tr>
<td>ONCOLOGY</td>
<td>AKT inhibitor</td>
<td>Solid tumors / AKT pathway mutations</td>
<td>Phase 1b</td>
<td>Continue or transition to ARQ 751</td>
<td>Blockbuster potential in hormone sensitive tumors</td>
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<tr>
<td>ARQ 751</td>
<td>Next generation AKT inhibitor</td>
<td>Solid tumors / AKT pathway mutations</td>
<td>Phase 1b</td>
<td>Phase 2</td>
<td>Blockbuster potential in hormone sensitive tumors</td>
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<td>DERAZANTINIB</td>
<td>FGFR inhibitor</td>
<td>iCCA (Intrahepatic cholangiocarcinoma)</td>
<td>Registral Cohorts: Orphan Designation</td>
<td>NDA Filing</td>
<td>Partnered – up to $400MM in regulatory and sales milestones plus royalties</td>
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<tr>
<td>Product</td>
<td>MOA</td>
<td>Indication</td>
<td>Rights</td>
<td>IP&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Key 2019 Catalysts</td>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</table>
| **ARQ 531**     | Reversible BTK Inhibitor | B-cell Malignancies               | ArQule 2035 | ▪ Final dose selection  
▪ Commence enrollment of expansion cohorts  
▪ Plan registrational trial in C481S mutated CLL patients (2H19)                                                                                       |              |         |         |             |
| **Miransertib** | AKT Inhibitor           | PROS & Proteus syndrome           | ArQule 2032 | ▪ Commence registrational cohorts in both Proteus syndrome and PROS (1H19)                                                                                                                                       |              |         |         |             |
| **ARQ 751**     | AKT Inhibitor           | Solid tumors / AKT pathway mutations | ArQule 2032 | ▪ Present data from Phase 1b cohorts (2H19)                                                                                                                                                                      |              |         |         |             |
| **Derazantinib**| AKT Inhibitor           | Solid tumors / AKT pathway mutations | ArQule 2032 | ▪ Present data from Phase 1b cohorts (2H19)  
▪ Prioritize for further development (2H19)                                                                                                                                                            |              |         |         |             |
| **ARQ 531**     | AKT Inhibitor           | Solid tumors / AKT pathway mutations | ArQule 2032 | ▪ Present data from Phase 1b cohorts (2H19)  
▪ Prioritize for further development (2H19)                                                                                                                                                            |              |         |         |             |
| **Derazantinib**| FGFR Inhibitor          | Intrahepatic cholangiocarcinoma (iCCA) | basilea ROIVANT 2031 | ▪ Basilea to pursue expanded development strategy  
▪ Sinovant to initiate program in Greater China (1H19)                                                                                           |              |         |         |             |

1. Composition of Matter only, does not include possible extensions  
2. U.S., EU, Japan and ROW  
3. China, Hong Kong, Macau and Taiwan
ARQ 531
Reversible BTK inhibitor in B-cell malignancies
## Targeting BTK in B-cell Malignancies

<table>
<thead>
<tr>
<th>B-CELL MALIGNANCIES</th>
<th>CURRENT THERAPY &amp; UNMET NEED</th>
<th>ARQ 531</th>
<th>MARKET VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Cell malignancies are a diverse group of diseases, including chronic lymphocytic leukemia (CLL), most non-Hodgkin’s lymphomas, other leukemias and myelomas</td>
<td>Ibrutinib and acalabrutinib are irreversible BTK inhibitors that covalently bind the catalytic site</td>
<td>Reversible small molecule next generation BTK inhibitor targeting both WT and C481S-mutant BTK</td>
<td>More than 20,000 patients diagnosed with CLL in the US in 2017(^1)</td>
</tr>
<tr>
<td>BTK is an ubiquitous component of the B-cell receptor (BCR) pathway</td>
<td>Long term treatment with approved BTK inhibitors can lead to mutations, most notably C481S, which leads to resistance</td>
<td>Potent, orally administered, with predictable PK</td>
<td>~85% of CLL patients refractory to ibrutinib develop the C481S mutation(^2)</td>
</tr>
<tr>
<td>BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis and adhesion</td>
<td></td>
<td>Currently in phase 1 trial for B-cell malignancies</td>
<td>Potential to move into earlier lines of therapy and indications beyond CLL</td>
</tr>
</tbody>
</table>


**ARQ 531 Addresses Treatment Resistance via Differentiated Binding Characteristics**

Irreversible BTK inhibitors, such as ibrutinib, covalently bind to cysteine in position 481. A **cysteine to serine mutation** (C481S) prevents this interaction.

ARQ 531 was **specifically designed** to inhibit BTK regardless of the amino acid position in position 481.

1.1 Ångstrom resolution crystal structure of ARQ 531 with BTK.

As a result, both inhibit WT BTK, but **ARQ 531 also** inhibits C481S BTK.

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ARQ 531 Demonstrates **Compelling Activity in CLL in vitro and in vivo**

Dose dependent cytotoxicity to CLL cells *in vitro* at 48h

Superior survival vs ibrutinib in TCL1, a highly predictive murine model of CLL

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Ongoing Phase 1 Dose Escalation in Refractory B-cell Malignancies

**Primary Objectives**: Establish safety and tolerability of ARQ 531 and recommended phase 2 dose (RP2D)

**Secondary Objectives**: Preliminary evidence of anti-tumor activity, PK/PD measures

**Location**: 3+ sites in US with the Ohio State University as the lead

**Design**: 3+3 dose escalation

**Enrollment**: 30-50 B-cell malignancy patients refractory to any B-cell therapy, including but not limited to ibrutinib

**Target Population**:
- Patients with relapsed and refractory (R/R) CLL
  - Must have failed irreversible BTK inhibitor
  - Median lines of therapy: **5.5 (1-12)**
- Other patients with R/R non-Hodgkin’s lymphoma
  - DLCBL, MCL, WM, FL

**ClinicalTrials.gov Identifier**: NCT03162536

**Dose Escalation Paradigm**

- **Cohort 1**: 5 mg QD
- **Cohort 2**: 10 mg QD
- **Cohort 3**: 15 mg QD
- **Cohort 4**: 20 mg QD
- **Cohort 5**: 30 mg QD
- **Cohort 6**: 45 mg QD
- **Cohort 7**: 65 mg QD
- **Cohort 8**: 75 mg QD

**Current**: Cohort cleared for safety and intra-patient dose escalation
Interim Phase 1 Data from ASH 2018 Demonstrates Good Safety Profile and Favorable Drug-Like Properties. . . ¹

Highly Favorable Safety Profile to Date

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All (N=20)</th>
<th>ARQ 531-Related (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>6 (30.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (30.0)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (15.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (15.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (15.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (15.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>Fall</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>3 (15.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>3 (15.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>3 (15.0)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Ear pain</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (10.0)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
</tr>
</tbody>
</table>

Predictable PK Into the Clinically Relevant Ranges

¹Woyach J et al, ASH Annual Meeting 2018
ArQule

As Well as Profound Pharmacodynamic Effects and **Promising Anti-Tumor Activity**¹

**BTK activity/signaling profoundly suppressed at predicted doses/concentrations**

Low dose range cohorts (1-3) showed an average 50% inhibition

Profound pBTK reductions were achieved at ≥ 20 mg dose levels

However, one patient in the 1<sup>st</sup> cohort (5 mg) achieved complete pBTK reduction, was later dose-escalated and achieved a confirmed partial response

CV: Variability of pBTK/BTK ratio determination in the validated whole blood assay was ~±15%

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**BTK activity/signaling correlated with substantial reductions after only 1 scan, despite failing multiple prior therapies**

**Best Responses in Lymphoma** (BTK inhibitor naïve)

Durable partial response was observed in one of three patients with FL

**Best Responses in CLL** (Heavily pretreated: median 6 therapies)

Anti-tumor activity was observed in heavily pretreated CLL patients with BTK-C481S mutations with increasing tumor suppression seen at higher dose levels

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1 Woyach J. et al, ASH Annual Meeting 2018
Phase 1b Open Label, Multicenter, Study of ARQ 531 in Patients with R/R B-cell Malignancies

- **Key Objectives**: To determine safety, tolerability and anti-cancer activity
- **Dose Level**: Recommended dose based on phase 1a
- **Enrollment**: An additional 80-100 patients; multiple cohorts (i.e., CLL patients with C481S-mutant BTK)

**Diagram: Expansion at RP2D**

- **CLL**
  - BTK C481S mutant
  - Richter’s syndrome
- **NHL**
  - DLBCL
  - CNS Lymphoma
  - FL
  - WM
  - MCL
MIRANsertib
AKT inhibitor in Rare Overgrowth Spectrum Disorders
# Targeting AKT in Rare Overgrowth Diseases

<table>
<thead>
<tr>
<th>OVERGROWTH DISEASES</th>
<th>CURRENT THERAPY &amp; UNMET NEED</th>
<th>MIRANSERTIB</th>
<th>MARKET VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group of diseases characterized by excessive aberrant, asymmetric growth of bones, skin and other tissues</td>
<td>No approved systemic treatments for PROS or Proteus syndrome; current Rx relies on expensive and disfiguring surgical amputations</td>
<td>Small molecule pan-AKT inhibitor</td>
<td>Meaningful aggregate prevalence across overgrowth spectrum disorders</td>
</tr>
<tr>
<td>Manifests in early childhood</td>
<td>Proteus syndrome: estimated 200-400 patients in the US and Europe¹</td>
<td>Potent, orally administered with predictable PK</td>
<td>Rare pediatric disease voucher for PS, if approved</td>
</tr>
<tr>
<td>Proteus syndrome caused by mosaic mutation in AKT1 gene</td>
<td>PROS: estimated 3000 – 6000 patients in US and Europe¹</td>
<td>Differentiated mechanism of action relative to other AKT inhibitors</td>
<td>Additional market value outside of US/EU, and in additional indications¹</td>
</tr>
<tr>
<td>PROS family of diseases caused by mosaic mutation in PIK3CA gene</td>
<td></td>
<td>Registrational trial cohorts in PS and PROS ready to commence</td>
<td></td>
</tr>
</tbody>
</table>

¹. See presentation “PS & PROS Primer 2019” at arqule.com
Miransertib Crystal Structure and Mechanism of Action

First generation pan-AKT inhibitor

Potent, orally active, small molecule allosteric inhibitor of AKT

Dual mechanism of action:

01 Binds inactive AKT and prevents membrane localization and activation

02 Binds membrane associated active AKT: direct inhibition

Adapted from www.cbioportal.org
A Mutation in AKT1 Causes Proteus Syndrome

- Somatic mosaic mutation in the AKT1 oncogene causes Proteus syndrome (PS)
- Non-inherited mutation arises randomly during early stages of development before birth
- Single point mutation in AKT1 gene causes tissue overgrowth characteristic of PS
- Mortality of 25% by age 22
- Currently no approved treatments

Identification of underlying mutation allows for development of molecularly targeted treatments

Clinical Manifestations of the Proteus syndrome in a 12-Year-Old Boy.

A Mosaic Activating Mutation in AKT1 Associated with the Proteus Syndrome

Marjorie J. Lindhurst, Julie C. Sapp, Jamie K. Teer… Leslie G. Biesecker
**PROS: A Related Group of Severe Overgrowth Disorders**

- **PIK3CA-related overgrowth spectrum (PROS)** is a group of rare disorders that cause overgrowth of parts of the body due to gain of function mutations in PIK3CA gene.

- Congenital or early onset

- **Disorders include:**
  - CLOVES syndrome
  - Klippel-Trénaunay syndrome (KTS)
  - Megalencephalies (includes MCAP, MPPH, M-CMTc, etc)
  - Facial Infiltrating Lipomatosis (FIL)
  - Fibroadipose hyperplasia (FH)
  - Epidermal Nevi
  - Macrodactyly
  - Macrodystrophica Lipomatosa
  - . . . and many others

- Varying degree of severity, with some tissue specific and others pleiotropic.

- Currently no pharmacotherapy options

- Multiple surgical interventions including debulking, amputation and corrective surgery

- Patients may suffer from severe functional and cosmetic consequences and progress to becoming poor surgical candidates.
**Rapid Path to Approval** in Both PS and PROS

- **Registrational Cohort in PS, N~ 10-12 pts**
- **Registrational Cohort in PROS, N~ 20-24 pts**

**Signal Generation Cohort**

- **Design**: Open Label
- **Primary Endpoint**: Responder analysis, based on objective criteria (e.g. imaging measurements)
- **Enrollment**: 10-12 months
- **Time on drug**: 12 months to primary endpoint
- **Dosing**: 15 mg/m² for first 3 cycles, 25 mg/m² thereafter
- **Signal Generation Cohort**: PS or PROS patients who did not qualify for cohorts 1 or 2
MIRANSELLTIB & ARQ 751

Targeted AKT inhibitors in oncology
Targeting AKT in Oncology

<table>
<thead>
<tr>
<th>CURRENT THERAPY &amp; UNMET NEED</th>
<th>MIRANsertIB</th>
<th>ARQ 751</th>
<th>MARKET VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently no approved AKT inhibitors</td>
<td>Small molecule pan-AKT inhibitor</td>
<td>Orally administered, next generation small molecule AKT inhibitor with predictable PK</td>
<td>3-5% of solid tumors have mutations in the AKT pathway(^1)</td>
</tr>
<tr>
<td>AKT inhibitors in development, either single agent or in combination, show promise in a molecular defined patient population, e.g., breast, prostate and endometrial cancer</td>
<td>Potent, orally administered with predictable PK</td>
<td>Designed to be more potent and selective than miransertib with a wider therapeutic index</td>
<td>PIK3CA mutations present in 32% colon, 27% brain, 25% gastric tumors, 37% endometrial, 31% breast and 2-3% prostate cancers(^2,3,4)</td>
</tr>
<tr>
<td></td>
<td>Differentiated mechanism of action relative to other AKT inhibitors</td>
<td>Binds to the inactive form of AKT preventing membrane localization and activation as well as binding to active form of AKT with direct inhibition</td>
<td>PTEN loss or mutation in up to 59% of stage IV cancers(^5)</td>
</tr>
</tbody>
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## ARQ 751 Trial Design & Next Steps

<table>
<thead>
<tr>
<th>Phase 1a/b trial in solid tumors with AKT, PI3K and PTEN mutations</th>
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</thead>
<tbody>
<tr>
<td><strong>Phase 1a/1b Trial</strong></td>
</tr>
</tbody>
</table>

**Key Objectives:** Establish safety of ARQ 751, PK/PD measures, recommended phase 2 dose and preliminary efficacy  
**Location:** MD Anderson Cancer Center, Houston TX  
**Design:** open-label, single group assignment dose escalation study  
**Enrollment:** 100 patients  
**Target Population:** Patients with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null or other known actionable PTEN mutations  
**ClinicalTrials.gov Identifier:** NCT02761694

**Key Objectives:** Efficacy of ARQ 751  
**Dose Level:** Recommended phase 2 dose  
**Enrollment:** Molecularly defined patient population

**Next Steps**
- Present data from phase 1b cohorts (2H19)  
- Initiate additional trial if supported by phase 1b data (2H19)
ArQule (NASDAQ: ARQL) **Financial Profile**

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
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<td><strong>Common Stock O/S</strong></td>
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<tr>
<td>as of December 31, 2018</td>
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<tr>
<td><strong>Market Cap</strong></td>
<td>$554M</td>
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<tr>
<td>as of March 8, 2019</td>
<td></td>
</tr>
<tr>
<td><strong>2019 Expected Use of Cash</strong></td>
<td>$35-40M</td>
</tr>
<tr>
<td><strong>Projected Cash &amp; Marketable Securities</strong>*</td>
<td>$60-63M</td>
</tr>
<tr>
<td>at December 31, 2019</td>
<td></td>
</tr>
</tbody>
</table>

*Sufficient cash to fund operating expenses into 2021*
THANK YOU