Activating checkpoints to selectively kill cancer cells

Broad Spectrum, Targeted Approaches To Cancer Treatment:
Activated Checkpoint Therapy℠ Platform
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Activating checkpoints to selectively kill cancer cells

ArQule’s Oncology R&D Portfolio
<table>
<thead>
<tr>
<th>Compound</th>
<th>Discovery Research</th>
<th>GLP tox. Testing</th>
<th>Phase 1 clinical</th>
<th>Phase 2 clinical</th>
</tr>
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<tbody>
<tr>
<td>ARQ 501</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>1st generation E2F activator</td>
<td></td>
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<tr>
<td>ARQ 171</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>2nd generation E2F activator</td>
<td></td>
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<tr>
<td>ARQ 197</td>
<td></td>
<td></td>
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<td>X</td>
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<tr>
<td>C-met inhibitor</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ARQ 450RP</td>
<td>X</td>
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<tr>
<td>Mitotic checkpoint activator</td>
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<tr>
<td>ARQ 350RP</td>
<td>X</td>
<td></td>
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<tr>
<td>B-Raf kinase inhibitor</td>
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</tr>
</tbody>
</table>
Additional discovery research stage programs

- ARQ 250RP: HSP90 program
- ARQ 700RP: HDAC program
- ARQ 300RP: Eg5 program
- ARQ 800RP: Chk2 program
- ARQ 150RP: Checkpoint modulators
- ARQ 850RP: p53 program
- ARQ 580RP: ARQ 501 conjugates
Two Clinical Stage Oncology Programs

- E2F1 Checkpoint activator: Phase 2
- c-MET inhibitor: Phase 1
Two Clinical Stage Oncology Programs

- E2F1 Checkpoint activator: Phase 2
- c-MET inhibitor: Phase 1
ARQ 501: Roche Partnership

- Announced April 2, 2004
- Deal terms up to $276 million for E2F program
- >$15 million received to date; revenue booked at $6.6 million per annum 2004-2009
- Roche was granted option to in-license E2F compounds on completion of defined studies, in return for further payment
- Royalties, milestones and co-promotion rights to ArQule
“We screen more than 1,600 companies a year, draw up 100 business cases, send 30 to a committee, and carry out due diligence on 15-20, leading to 5-10 deals.”

Peter Hug, Head of Roche Pharma Partnering. Financial Times, May 27th, 2005
Activated Checkpoints: A Unique Mechanism Of Action To Selectively Identify And Eradicate Cancerous Cells
Activated Checkpoint Therapy℠ - Differential Effects

ARQ 501 + target → Checkpoint Activation (E2F1) → Forces apoptotic cell death in presence of irreparable DNA damage → Institutes DNA repair in presence of minor DNA damage → Allows normal cell division in absence of DNA damage
Dual Induction of Apoptosis and Senescence in Cancer Cells by Chk2 Activation: Checkpoint Activation as a Strategy against Cancer

Chang-Rung Chen, Wenxian Wang, Harry A. Rogoff, Xiaotong Li, William Mang, and Chiang J. Li

July 15th, 2005
ARQ 501 - First Generation
E2F1 Checkpoint Activator
ARQ 501 Phase 1 Overview - Primary Endpoint

To assess tolerability and to identify a recommended dosing regimen for Phase 2 initiation

- Achieved for monotherapy
- Anticipated imminently for combination therapy
Clinical Development – Phase 1 Current Status*

- **Protocol ARQ 501-101**
  - Phase I monotherapy in advanced solid tumors
  - Investigated three infusion regimens
  - Dosed up to 660mg/m$^2$

- **Protocol ARQ 501-212**
  - Phase I gemcitabine combination study
  - Dosed up to 450mg/m$^2$

- **Protocol ARQ 501-111**
  - Phase I docetaxel combination study
  - Dosed up to 390mg/m$^2$

* As of end Dec, 2005
Monotherapy results

- 64 patients
  - 30 received 10 - 450mg/m² over 1 hour
  - 34 received 450 - 660mg/m² over 3 hours

- Recommended Phase 2 monotherapy doses
  - 390mg/m² over 1 hour
  - 450mg/m² over 3 hours
Plasma levels of drug at or above predicted therapeutic concentration
Reversible hemolytic anemia appears to be dose related adverse event
38 patients evaluable for activity

- 2 partial response
- 3 minor response
- 13 stable disease
<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor Type</th>
<th>Dose (mg/m²)</th>
<th>Infusion Duration (hr)</th>
<th>Weeks on Study</th>
<th>Best Response</th>
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<tbody>
<tr>
<td>1001</td>
<td>Uterine leiomyosarcoma</td>
<td>10 → 20</td>
<td>1</td>
<td>130+</td>
<td>PR</td>
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<tr>
<td>1008</td>
<td>Rectal adenocarcinoma</td>
<td>200 → 280</td>
<td>1</td>
<td>32</td>
<td>SD</td>
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<td>2016</td>
<td>Metastatic SCC of the parotid gland</td>
<td>550 → 390</td>
<td>3-1</td>
<td>14</td>
<td>MR 21% reduction</td>
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<td>2025</td>
<td>Adrenal cortical carcinoma</td>
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<td>1</td>
<td>62</td>
<td>PR</td>
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<td>Pancreatic ductal adenocarcinoma</td>
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<td>3</td>
<td>11</td>
<td>SD</td>
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<tr>
<td>1038</td>
<td>SCC tongue</td>
<td>450</td>
<td>3</td>
<td>18</td>
<td>MR 21% reduction</td>
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<tr>
<td>2039</td>
<td>Pancreatic adenocarcinoma</td>
<td>450</td>
<td>3</td>
<td>26</td>
<td>MR 17% reduction</td>
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<td>1041</td>
<td>Leiomyosarcoma</td>
<td>450</td>
<td>3</td>
<td>18</td>
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Subject 2025 – CT Scans of Two Target Lesions

Pre-treatment

Week 32
"Significance of responses reported in single agent Phase 1 studies of investigational anticancer agents"

<table>
<thead>
<tr>
<th>Drug</th>
<th>No.enrolled/No.evaluables</th>
<th>CR</th>
<th>PR</th>
<th>MR/SD</th>
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<tbody>
<tr>
<td>Iressa®</td>
<td>64/NR</td>
<td>0</td>
<td>4</td>
<td>8</td>
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<tr>
<td>Velcade® (solid)</td>
<td>43/NR</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Velcade® (hem)</td>
<td>27/NR</td>
<td>1</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Avastin®</td>
<td>25/23</td>
<td>0</td>
<td>0</td>
<td>12</td>
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<td>Erbitux®</td>
<td>30/28</td>
<td>0</td>
<td>0</td>
<td>18</td>
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<tr>
<td>Tarceva®</td>
<td>40/39</td>
<td>1</td>
<td>0</td>
<td>7</td>
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## Phase 2 Program

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Treatment</th>
<th>Recruitment target</th>
<th>Endpoint</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Leiomyosarcoma</td>
<td>ARQ 501</td>
<td>Approximately 30 patients</td>
<td>Objective response rate</td>
<td>First center open for recruitment</td>
</tr>
<tr>
<td>Head and Neck Cancer</td>
<td>ARQ 501</td>
<td>tba*</td>
<td>tba</td>
<td>To be initiated mid-year 2006</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>ARQ 501 + gemcitabine</td>
<td>Approximately 66 patients</td>
<td>Progression free survival</td>
<td>Centers being initiated</td>
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<tr>
<td>Ovarian Cancer</td>
<td>ARQ 501 + paclitaxel</td>
<td>tba</td>
<td>tba</td>
<td>To be initiated second half 2006</td>
</tr>
</tbody>
</table>

* tba = to be announced
Two Clinical Stage Oncology Programs

- E2F1 Checkpoint activator: Phase2
- c-MET inhibitor: Phase1
Two Clinical Stage Oncology Programs

- E2F1 Checkpoint activator: Phase 2
- c-MET inhibitor: Phase 1
ARQ 197 -
c-MET inhibitor
Receptor Tyrosine Kinase inhibitor - selectively against c-MET target
Highly effective in killing a variety of human cancer cells in culture
Demonstrated potent anti-tumor activity against human cancers in mouse models
Demonstrated potent activity against cancer metastasis and invasiveness
c-MET Role In Oncogenesis

- Mediates the signals for a variety of physiological processes including migration, invasion, cell proliferation, apoptosis and angiogenesis
- A wide variety of human cancers exhibit constitutively dysregulated c-Met activity
- These alterations have been strongly implicated in tumor progression, metastasis and poor clinical prognosis
- The inappropriate expression of c-Met in most cancers and its role in controlling multiple signal transduction pathways involved in tumor growth and metastasis render this enzyme a highly compelling therapeutic target for human cancer

See Corso et al: “Cancer therapy: can the challenge be MET?”
Trends in Molecular Medicine Vol 11 No 8 June 2005
ARQ 197 Efficacy Against Xenografted Human Breast Carcinoma (MDA-MB 231)

Control

ARQ 197 200mg/kg po qM-F

T/C = 21%

P = 0.009 < 0.05

Days Post Inoculation

Mean tumor volume, mm3

Last po.
**ARQ 197 Phase 1 Trial Design**

- **Standard dose escalation protocol in adult patients with locally advanced or metastatic cancer**
  - Initial dose 10mg oral twice daily for two weeks out of three
  - Dosing increases to 20mg bd followed by 1.4 fold increases with 3 patients per cohort up to MTD
  - Approximately 45-50 patients anticipated

- **Clinical trial centers initiated**
  - Dr. Rosen - Santa Monica
  - Dr. Bukowski – Cleveland Clinic
Financials & Milestones
## ArQule Financials

<table>
<thead>
<tr>
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<th>12/31/05</th>
<th>2006 guidance</th>
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<tbody>
<tr>
<td>Revenues</td>
<td>$52.9M</td>
<td>$6.5M - $7M</td>
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<tr>
<td>Net Loss</td>
<td>$7.5M</td>
<td>$33M - $39M</td>
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<tr>
<td>Loss per share</td>
<td>$0.22</td>
<td>$0.93 - $1.10</td>
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<tr>
<td>Cash/Equivalents</td>
<td>$140.6M</td>
<td>$82M - $88M</td>
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</table>

Sufficient cash to take ARQ 501 through Ph 2 trials
2006 Milestones

- Initiate multi-trial, Phase 2 clinical program with ARQ 501
- Initiate Phase 1 clinical trial with ARQ 197
- Initiate Phase 1 clinical trial with another compound
- Present Phase 1 results with ARQ 501