Discovery of ARV-110, a first in class androgen receptor degrading PROTAC® for the treatment of men with metastatic castration resistant prostate cancer

Lawrence B. Snyder, PhD
Executive Director Medicinal Chemistry
Arvinas Inc, New Haven, CT
Lawrence Snyder

I have the following financial relationships to disclose:
Stockholder in: Arvinas Inc
Employee of: Arvinas Inc
Safe Harbor and Forward Looking Statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the development and regulatory status of our product candidates, such as statements with respect to our lead product candidates, ARV-110, ARV-471 and ARV-766 and other candidates in our pipeline, and the timing of clinical trials and data from those trials and plans for registration for our product candidates, and our discovery programs that may lead to our development of additional product candidates, the potential utility of our technology and therapeutic potential of our product candidates, the potential commercialization of any of our product candidates, the potential benefits of our arrangements with Yale University, our collaborative partnerships, and the Bayer joint venture, and the sufficiency of our cash resources. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make as a result of various risks and uncertainties, including but not limited to: whether we will be able to successfully conduct Phase 1/2 clinical trials for ARV-110 and ARV-471, complete other clinical trials for our product candidates, and receive results from our clinical trials on our expected timelines, or at all, whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements, each party’s ability to perform its obligations under our collaborations and/or the Bayer joint venture, our expected timeline and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, discussed in the “Risk Factors” section of the Company’s quarterly and annual reports on file with the Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect our current views as of the date of this presentation with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

The Arvinas name and logo are our trademarks. We also own the service mark and the registered U.S. trademark for PROTAC®. The trademarks, trade names and service marks appearing in this presentation are the property of their respective owners. We have omitted the ® and ™ designations, as applicable, for the trademarks named in this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

PROTAC® protein degraders harness the UPS to induce the degradation of disease-causing proteins.

1. PROTAC protein degraders function inside cells.
2. Formation of trimer complex and ubiquitination of target protein.
3. Multiple ubiquitin molecules “tag” target protein for degradation.
4. Targeted protein is degraded by the proteasome.

PROTAC® protein degraders combine the advantages of gene-based medicines and small molecule inhibitors

<table>
<thead>
<tr>
<th>PROTAC protein degraders have distinct advantages over both small molecule inhibitors and gene-based medicines</th>
<th>PROTAC™ Protein Degraders</th>
<th>Small Molecule Inhibitors</th>
<th>Gene-Based Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminate pathogenic proteins</td>
<td>✓</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Target scaffolding function</td>
<td>✓</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Potential to treat “undruggable” proteins</td>
<td>✓</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Iterative mechanism of action</td>
<td>✓</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Broad tissue penetration</td>
<td>✓</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Orally bioavailable</td>
<td>✓</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Ease of manufacturing</td>
<td>✓</td>
<td>✗</td>
<td></td>
</tr>
</tbody>
</table>
Arvinas’ pipeline encompasses a range of validated and undruggable targets in oncology, I-O, and neuroscience.

<table>
<thead>
<tr>
<th>ARVN Program</th>
<th>Indication</th>
<th>Exploratory</th>
<th>Research</th>
<th>IND Enabling</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV-110</td>
<td>mCRPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV-766</td>
<td>mCRPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IND 2021</td>
</tr>
<tr>
<td>AR-V7</td>
<td>mCRPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV-471</td>
<td>ER+/HER2- Breast Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCL6</td>
<td>B-cell Malignancies</td>
<td></td>
<td></td>
<td>IND 2022</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>NSCLC, CRC, Pancreatic</td>
<td></td>
<td></td>
<td>IND 2023</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>Solid Malignancies</td>
<td></td>
<td></td>
<td>IND 2022</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myc</td>
<td>Solid Malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPK1</td>
<td>Solid Malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau</td>
<td>FTLD-TAU, PSP, AD</td>
<td></td>
<td></td>
<td>IND 2022</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Synuclein</td>
<td>MSA, Parkinson’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mHTT</td>
<td>Huntington’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>Neurodegeneration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Pipeline is non-exhaustive and IND dates are anticipated.
mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; NSCLC, non-small-cell lung carcinoma; CRC, colorectal cancer; FTLD-tau, frontotemporal lobar degeneration-tau; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy

Orally bioavailable androgen receptor-targeted PROTAC protein degrader

- ARV-110 is in development for the treatment of men with mCRPC who have progressed on abiraterone and/or enzalutamide
- Appears to overcome mechanisms of resistance to current standards of care
- \( DC_{50} = 1 \text{ nM} \) in VCaP cells\(^1\)

**ARV-110 Selectively Degrades AR**

- After 8 hours of treatment of VCaP cells with 10 nM ARV-110 in vitro, AR was the only degraded protein among the nearly 4,000 proteins measured
  - 85\% \( D_{\text{max}} \)\(^2\)
  - \( p\)-value: \( 3 \times 10^{-9} \)

---

1 VCaP, Vertebral Cancer of the Prostate
2 \( D_{\text{max}} \), maximal degradation
Orally delivered ARV-110 significantly inhibited tumor growth in these enza-insensitive tumors (TGI: 100%)

- Plasma PSA levels following ARV-110 treatment significantly decreased vs. mice treated with vehicle or enzalutamide

Tumor Growth Inhibition in an Enzalutamide-Insensitive PDX Model (TM00298)

- Vehicle
- Enzalutamide, 20 mpk PO, qd
- ARV-110, 10 mpk PO, qd

1 p value refers to ARV-110 vs. enzalutamide
ARV-110 is showing early clinical benefit in highly refractory patients

- Median prior therapies: 5
- 76% of patients treated with prior chemotherapy
- 82% of patients treated with both abiraterone and enzalutamide
- 84% of patients with non-AR mutations
- Existing AR-directed therapies expected to be ineffective
- High tumor heterogeneity suggests low dependence on AR
At 420 mg, exposures exceed the predicted efficacious threshold observed in a preclinical enzalutamide-resistant model.

---

The minimum preclinical efficacious threshold represents the AUC associated with tumor growth inhibition in standard VCAP models, †† This efficacious threshold represents the AUC associated with tumor growth inhibition in a preclinical enzalutamide-resistant VCap model, ††† Includes both qd and bid dosing for the 420 mg total daily dose.
Results include one confirmed RECIST partial response

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA response</td>
<td>97% decline</td>
</tr>
<tr>
<td>RECIST response</td>
<td>80% reduction</td>
</tr>
<tr>
<td>Duration of ARV-110</td>
<td>18+ weeks ongoing</td>
</tr>
<tr>
<td>Biomarker status</td>
<td>AR H875Y and T878A mutations (associated with resistance to abiraterone or enzalutamide)¹</td>
</tr>
<tr>
<td>Common prior therapies</td>
<td>Enzalutamide, Abiraterone, Bicalutamide</td>
</tr>
<tr>
<td>Other prior therapies</td>
<td>Provenge, Cabazitaxel</td>
</tr>
<tr>
<td>History</td>
<td>Extensive disease involving adrenal gland, aortocaval nodes, multiple cone metastases</td>
</tr>
</tbody>
</table>

**Baseline CT Scan**
- Extensive retroperitoneal adenopathy compressing the inferior vena cava

**After 4 Cycles**
- Near complete regression of adenopathy

---

¹Jernberg E, Endocrine Connections, 2017

RECIST: Response evaluation criteria in solid tumors
Evolution of AR Degrading PROTACs Leading to ARV-110

**Early Discovery Efforts**
- Multiple E3 recruiting ligands
- Multiple AR binders

**1. Potent degradation and encouraging %F**
- High CI

**2. Possible candidate**
- In vivo potency suboptimal
- Crystallized to high melting solid

**3. Good in vitro degradation potency**
- Possible autoinduction signal
- AR ligand by itself agonist
- In vivo potency superseded by 4

**4. Possible candidate**
- Dose escalation exposure suboptimal

**ARV-110**
Drug Discovery and Development is a Team Sport