Heterobifunctional Degrader Molecules that lead to the clearance of Pathologic Proteins in Neurodegeneration

Angela Cacace, Ph.D.
VP Neuroscience & Platform Biology
Arvinas
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 the 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 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, initiate and 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 ubiquitin-proteasome system to induce the degradation of disease-causing proteins.
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></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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>NSCLC, CRC, Pancreatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>Solid Malignancies</td>
<td></td>
<td></td>
<td></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></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>
ARV-471 and ARV-110: Proof-of-concept and opportunities to benefit patients in large areas of unmet need

**ARV-471**
Estrogen receptor-degrading PROTAC®

*Breast Cancer*

- Potential best profile of any ER-targeting therapy:
  - Tolerability
  - **ER degradation**
  - Clinical benefit

- Initiated Phase 2 VERITAC trial; while Phase 1 dose escalation continues

- Potential future endocrine therapy of choice in both adjuvant and metastatic settings

- >200k patients† per year with high unmet need

**ARV-110**
Androgen receptor-degrading PROTAC®

*Prostate Cancer*

- **AR degradation** and clear signals of efficacy observed in late-line mCRPC

- Extensive molecular profiling of tumors to understand drivers of resistance

- Initiated Phase 2 ARDENT trial; two potential paths to registration: 3L molecularly defined, and broader 1L/2L

- >250k patients† per year with high unmet need

† US incidence data from SEER database

AR, androgen receptor; ER, estrogen receptor

Data as presented 12/14/2020
**ARV-471: ER Degradation & Confirmed RECIST Partial Response (cPR) in late-stage patients with extensive prior therapy**

**Baseline**

**After treatment 60 mg ARV-471**

**Baseline CT Scan**

**After 4 Cycles**

**Estrogen receptor**  **Nuclei**  **Cytokeratin**

**ER degradation tumor biopsies**

Data as presented 12/14/2020

51% reduction in target lesions (RECIST partial response)
Integrated PROTAC® drug discovery for Neurology

**Genetic Disease:**
Protein is the cause of the disease

**Translational Medicine:**
Biomarkers support efficient path to assessing efficacy in humans

**PK/PD Models:**
Protein target engagement in vivo

**Discovery Engine:**
- Ligand ID-DEL, HTS, HT-chem/SAR
- E3KnowlegeBASE, structure, AI

**Neurodegeneration**
- Precision Medicine
- Genetic/Proteinopathy
- Target root cause
- PROTAC differentiator
- Biomarker PoC

**PK/PD Models:**
DMSO
11.1 33.3 100 300 nM PROTAC
A66130
A66129

**Discovery Engine:**
- Biophysics, Ternary, Mechanistic
- Degradation, Proteomics

**Translational Medicine:**
Biomarkers support efficient path to assessing efficacy in humans

**Discovery Engine:**
- Ligand ID-DEL, HTS, HT-chem/SAR
- E3KnowlegeBASE, structure, AI

**Neurodegeneration**
- Precision Medicine
- Genetic/Proteinopathy
- Target root cause
- PROTAC differentiator
- Biomarker PoC
PROTAC® heterobifunctional degrader molecules create a strong opportunity in neuroscience compared to other modalities.

PROTAC® degrader small molecules may overcome the limitations of other platforms.

**PROTAC Potential**
- Reduce intra- and extracellular pathologic protein
- Discriminate between wild type and pathologic protein
- Oral administration with BBB biodistribution

**PROTAC Tenets -- Differentiation from small molecule inhibitors**
- Dominant Driver Mutations
- Undruggable
- Protein Aggregates
- Scaffolding Function
- Mutant / Isoform Selectivity
- Gene Amplification / Protein Overexpression

**ASO**
- Requires intrathecal dosing
- Does not discriminate wt from pathologic protein

**Ab**
- Blocks only extracellular pathologic protein
- IV dosing results in only 0.5% in CSF
PROTAC® small molecules can degrade tau P301L insoluble aggregates

In vitro insoluble tau PROTAC degradation

In vivo insoluble tau PROTAC degradation

Reduced Seed Potential

Ex vivo brain extracts

Tg2508 24h post single PROTAC IV dose

PK-PD

Insoluble PHF1 Tau (%Veh)

Brain exposure (nM)

Dose (mg/kg)

Tg2508 brain extracts 24h post single IV dose

MC1 Signal

** * on mechanism

* Cortex – Vehicle
  * Cortex – PROTAC A – 24 hours
  * Cortex – PROTAC B – 24 hours
  * P301L, No PFF seeds

** ****
Neuromuscular Diseases: PROTAC®s degrade toxic aggregating protein within muscle cells

**Fit with Neuroscience Strategy**

**Other CNS Diseases**
- Genetic Neuromuscular
  - Core Strategy
    - Neurodegeneration
      - Precision Medicine
      - Genetic/Proteinopathy
      - Target root cause
      - PROTAC differentiator
      - Biomarker PoC

**Neuromuscular degeneration**
Mouse Model (3xQD PO)

**hiPSC-patient derived myotubes**
Potent Degradation of aggregate

*Functional studies are ongoing in mouse model*
PROTAC® targets mutant and spares WT to tackle genetically defined disease target in CNS

Fit with Tenets of PROTACs

- Dominant Driver Mutations
- Protein Aggregation
- Scaffolding Function
- Gene Amplification / Protein Overexpression
- Mutant / Isoform Selectivity
- Undruggable

PROTAC selectively degrades mutant and spares WT protein

WT DC$_{50}$ >5µM
Mutant protein DC$_{50}$ = 23nM
PROTAC®-B is on mechanism and degrades endogenous target in iPSC-derived microglia
PROTAC®-B dose-dependently and durably degrades target in brain 24h following single oral administration.

**PROTAC-A and B Dose-Response PK/PD**

In Cortex 24h post dose

**PROTAC-B PK/PD**

In Cortex following time-course

- **Degradation (% CTL)**
  - PROTAC-A: 5.2 nM DC50
  - PROTAC-B: 70 nM DC50

- **Exposure PROTAC-B log M**
  - Iloq
  - Time (days)
Building and accelerating exciting high potential neurology bifunctional degrader small molecule pipeline

Opportunity: No Approved Disease Modifying Therapies in Neurodegenerative Diseases

<table>
<thead>
<tr>
<th>Neurology</th>
<th>Pre-Exploratory</th>
<th>Exploratory</th>
<th>Lead Optimization</th>
<th>Clinical Candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tauopathies</td>
<td>e.g., FTLD-tau, PSP&lt;sup&gt;1&lt;/sup&gt;, Alzheimer’s Disease [Tau]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synucleinopathies</td>
<td>e.g., MSA&lt;sup&gt;2&lt;/sup&gt;, Parkinson’s [a-synuclein]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington’s</td>
<td>Huntington’s Disease (mHTT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed Indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Progressive Supranuclear Palsy
2. Multiple Systems Atrophy
3. [a-synuclein]
4. [mHTT]
Thank you to the fantastic team at Arvinas!!!