PROTAC® Targeted Protein Degraders
A New Therapeutic Modality

November 2019
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 and ARV-471, and the timing of clinical trials and data from those trials 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 and our collaborative partnerships, the potential benefits of the Bayer joint venture in the agricultural field, 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 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.

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Arvinas: Clinical-stage leader in protein degradation, a powerful new modality

Novel PROTAC® (proteolysis-targeting chimera) degrader platform
- Benefits of small molecule inhibitors and gene-based medicines
- Built with foundational technology and foremost experts from Yale University

Full worldwide development and commercialization rights for lead programs
- ARV-110 - Metastatic castration-resistant prostate cancer; Phase 1 initiated 1Q19; received “Fast Track” designation from FDA in May 2019. Initial clinical safety/PK data shared Oct. 2019
- ARV-471 - Estrogen receptor-positive / HER2-negative locally advanced or metastatic breast cancer; Phase 1 initiated 3Q19. Initial clinical safety/PK data shared Oct. 2019
- Brain-penetrant PROTAC programs targeting tauopathies and α-synucleinopathies

Strategic, discovery-stage partnerships with Pfizer, Genentech, and Bayer
- Up to $2.1B in potential milestones plus tiered royalties
- Partnerships across broad set of therapeutic areas and a JV for agricultural applications

Strong cash and IP positions
- First targeted protein degradation company to IPO (NASDAQ: ARVN; September 2018)
- ~$298M in pro forma cash, cash equivalents, and marketable securities as of 9/30/19
- Broad platform IP, complemented by specific product IP

Team built for success
- Strong leadership team with unparalleled protein degrader development experience
- World-class Board and scientific advisors, including Craig Crews (PROTAC inventor)

1 Pro forma to include proceeds from a public offering of common shares announced on 11/6/19
# High potential PROTAC® pipeline, focused on cancer and neurology

<table>
<thead>
<tr>
<th>Programs [Target]</th>
<th>Discovery</th>
<th>Lead Optimization</th>
<th>IND Enabling</th>
<th>Phase 1</th>
<th>Arvinas Owned</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic Castration-resistant Prostate Cancer</strong></td>
<td>ARV-110 [Androgen Receptor]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Next Generation Degrader [Androgen Receptor]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>AR Variant Degrader [AR-V7]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Locally Advanced or Metastatic ER+ / HER2- Breast Cancer</strong></td>
<td>ARV-471 [Estrogen Receptor]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Additional Oncology Indications</strong></td>
<td>e.g., CRC, NSCLC [Undisclosed]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tauopathies</strong></td>
<td>e.g., PSP² [Tau]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Synucleinopathies</strong></td>
<td>e.g., MSA³, Parkinson's [α-synuclein]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Additional Neurology Indications</strong></td>
<td>Various [Undisclosed]</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

1 Pipeline as of November 8, 2019
2 PSP, progressive supranuclear palsy
3 MSA, multiple systems atrophy
PROTAC® Protein Degrader Platform
What is a PROTAC® protein degrader?

A proteolysis-targeting chimera (PROTAC) degrader is a chimeric, modular small molecule engineered to induce the degradation of disease-causing proteins by the ubiquitin-proteasome system.

All three regions of the PROTAC degrader play a role in the specificity and potency of target degradation.
PROTAC® protein degraders harness the ubiquitin-proteasome system 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.

Iterative PROTAC degrader activity.
PROTAC® protein degraders combine the advantages of gene-based medicines with the benefits of small molecule therapies

PROTAC protein degraders have distinct advantages over both small molecule inhibitors and gene-based medicines:

<table>
<thead>
<tr>
<th>Advantage</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>
Potential advantages of PROTAC® protein degraders over inhibitors

Overcome Target Protein Overexpression

**PROTAC degraders can disable this common tumor resistance mechanism**

- Lapatinib alone results in HER2-overexpression, but a PROTAC created with lapatinib as the “warhead” degrades natural and overexpressed HER2
- HER2 degraded despite increased RNA levels

Selectively Eliminate Mutated Proteins

**PROTAC degraders can differentiate between mutant and wild type proteins**

- The three mutants of BRAF shown (V600E, K601E, G466V) differ from the wild type by a single point mutation, but are degraded by a BRAF-targeted PROTAC that spares the wild type

1 hMito is a protein not targeted to degrade (loading control)
Arvinas’ technology and expertise enable effective hit ID and optimized development candidates.

**Capabilities**

**Computational Chemistry**
- Molecular Dynamics Simulations
- Site Directed Mutagenesis
- GPU-enabled

**Structural Information**
- X-Ray, SAR
- Ligand Optimization

**Medicinal Chemistry**
- Fit-for-Purpose PROTAC™ Matrix
- Rapid Synthesis
- Diversity

**Discovery Process**

**Target Selection**
- Differential Biology/Profile
- Chemical Equity
- Biophysics

**Predictive Hit Identification**
- >90% Success Rate
- Efficient, Rapid Process
- Linker SAR Generated

**Clinical Candidate Optimization**
- PROTAC-Specific Design Metrics
- Holistic Optimization Strategy
- Advanced bRo5 Profiles (oral)
Platform investment and expansion

Platform Investment and Expansion

- Enhanced prediction of degradation selectivity
  - Rapid narrowing of “zone of ubiquitination”
  - Improve speed to mutant vs. wild type specificity
- DEL screening and other approaches to incorporating tissue and disease-specific E3 ligases
- Expansion into new disease areas, e.g., immuno-oncology, either independently or with partners

Undisclosed “Undruggable” and Difficult-to-Drug Targets

- Many (up to ~80%) proteins have not been traditionally addressable by small-molecule inhibition
  - Since PROTAC degraders do not require tight target binding, the “undruggable” space may be available
- PROTAC degraders also advantageous for “difficult to drug” targets where existing therapies leave substantial unmet need
Clinical-stage Oncology Programs
ARV-110 is Arvinas’ AR degrader for men with metastatic castration-resistant prostate cancer (mCRPC)\(^1\)

**Androgen Receptor (AR) Activity Drives Prostate Cancer**

- Current agents work by decreasing androgen levels (abiraterone) or blocking androgen binding to AR (enzalutamide)
- 15-25% of patients never respond to abiraterone or enzalutamide (intrinsic resistance)
- Acquired resistance mechanisms to abiraterone and enzalutamide include:
  - AR gene amplification (40-60% of patients)
  - AR gene enhancer amplification (>70% of patients)
  - AR point mutations (~15% of patients)
  - Intra-tumoral androgen production

**PROTAC® Degrader ARV-110**

- First-in-class AR degrader being tested in men with metastatic castration-resistant prostate cancer who have progressed on standards of care (enzalutamide, abiraterone)
- In preclinical models, overcomes known resistance mechanisms to enzalutamide and abiraterone
- Highly selective degradation of AR; not brain penetrant
- Received FDA “Fast Track” designation in May 2019
- Initial safety/pharmacokinetic data shared Oct. 2019
- Completed Phase 1 dose escalation data expected 1H20

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1. According to the American Cancer Society, prostate cancer is the second leading cause of cancer death in men in the U.S. (~174k diagnosed/yr1); 35-45k new incidences of mCRPC in the U.S. each year
ARV-110 inhibits tumor growth in an *in vivo* model of acquired enzalutamide resistance

- *In vivo* mouse xenograft model of **acquired enzalutamide resistance** developed at Arvinas
- In this model, VCaP tumors acquired resistance to enzalutamide after being continuously propagated in castrated, enzalutamide treated mice for ~3 years
- Daily and orally delivered ARV-110 significantly inhibited tumor growth (*at right*)
  - 10 mpk ARV-110: 70% tumor growth inhibition
ARV-110 demonstrates efficacy and plasma PSA reduction in an enzalutamide-insensitive patient derived xenograft model

- Orally delivered ARV-110 significantly inhibited tumor growth in these *intrinsically enza-insensitive* tumors (TGI: 100%)

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tumor Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>100 ± 10</td>
</tr>
<tr>
<td>Enzalutamide, 20 mpk PO, qd</td>
<td>200 ± 20</td>
</tr>
<tr>
<td>ARV-110, 10 mpk PO, qd</td>
<td>300 ± 30</td>
</tr>
</tbody>
</table>

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

1 p value refers to ARV-110 vs. enzalutamide
ARV-110 pharmacokinetics are dose proportional, and exposure has reached the predicted efficacious range

### Preclinical Efficacious Exposure Range

<table>
<thead>
<tr>
<th>Dose (po, qd)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (ng*hr/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mpk</td>
<td>3628</td>
<td>224</td>
</tr>
<tr>
<td>3 mpk</td>
<td>8106</td>
<td>507</td>
</tr>
</tbody>
</table>

### Phase 1 Data

<table>
<thead>
<tr>
<th>Dose po, qd</th>
<th>Day 1 AUC&lt;sub&gt;0-24&lt;/sub&gt; (ng*h/mL) Mean</th>
<th>Day 1 C&lt;sub&gt;max&lt;/sub&gt; (ng/ml) Mean</th>
<th>Day 15 AUC&lt;sub&gt;0-24&lt;/sub&gt; (ng*h/mL) Mean&lt;sup&gt;‡&lt;/sup&gt;</th>
<th>Day 15 C&lt;sub&gt;max&lt;/sub&gt; (ng/ml) Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 mg</td>
<td>160.5</td>
<td>11.1</td>
<td>1701</td>
<td>83</td>
</tr>
<tr>
<td>70 mg</td>
<td>300</td>
<td>19.6</td>
<td>2538</td>
<td>141</td>
</tr>
<tr>
<td>140 mg</td>
<td>865</td>
<td>54</td>
<td><strong>5023</strong></td>
<td><strong>353</strong></td>
</tr>
</tbody>
</table>

- Accumulation occurs between Day 1 and Day 15
- Exposure at 140 mg has entered the preclinical efficacious range associated with tumor growth inhibition

<sup>‡</sup> Day 15 AUCs calculated using imputed 24 hour values

Initial clinical data as of 10/23/19
ARV-110 Phase 1 dose escalation: Day 15 pharmacokinetics

\[ T_{\text{max}^+} = 4 - 8 \text{ hours} \]
\[ t_{1/2}^{\pm} = \text{Estimated 3 - 7 days} \]

\[ T_{\text{max}^+} \] = Time of to reach maximum concentration \( (C_{\text{max}}) \)
\[ t_{1/2}^{\pm} \] = Effective half-life: rate of accumulation or elimination of a pharmacologic substance

Initial clinical data as of 10/23/19
In the first 3 cohorts of the ARV-110 Phase 1 dose escalation, we observed an overall favorable safety profile.

- Three cohorts through 28 day dose limiting toxicity evaluation period; fourth cohort enrolling

<table>
<thead>
<tr>
<th>Dose Level&lt;sup&gt;a&lt;/sup&gt;</th>
<th>N</th>
<th>Key Safety Findings</th>
</tr>
</thead>
</table>
| 35 mg                  | 3 | • No Dose Limiting Toxicities (DLTs)  
                           • No Treatment Related Adverse Events (AEs) |
| 70 mg                  | 4 | • No DLTs  
                           • No Grade 2/3/4 Treatment Related AEs |
| 140 mg<sup>b</sup>     | 3<sup>c</sup> | • No DLTs  
                           • No Grade 2/3/4 Treatment Related AEs |
| 280 mg                 | 3 | • TBD |

<sup>a</sup> Orally, once daily

<sup>b</sup> Data not yet 100% source data verified

<sup>c</sup> Not including 1 non-evaluable patient (discontinued on day 1; patient’s condition had worsened in the interval from screening to the morning of treatment initiation consistent with rapid progression of his cancer)

Initial clinical data as of 10/23/19
Breast cancer is the second most common cancer in women\(^1\)

- \(~268,000\) women are expected to be diagnosed with invasive breast cancer in the US in 2019\(^1\)
- Metastatic breast cancer accounts for \(~6\%) of newly diagnosed cases\(^2\)
- \(80\%\) of breast cancers are estrogen receptor (ER) positive\(^3\)
- Fulvestrant has demonstrated the value of ER degradation in breast cancer
- After 6 months of fulvestrant treatment, up to 50% of ER baseline levels remain\(^4\)

**PROTAC\(^\circledR\) Degrader ARV-471**

- ARV-471 is in development for the treatment of patients with ER+ locally advanced or metastatic breast cancer
- Ph 1 trial initiated in 3Q2019, and initial clinical data shared October 2019
- After Phase 1 dose escalation, a Phase 1b trial in combination with CDK4/6 inhibitor is planned

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\(~80\%\) ER+
ARV-471: Superior tumor growth inhibition versus fulvestrant in a Y537S (ER gene mutation) PDX model

**ARV-471 In Vivo Preclinical Development**

- Oral, daily dose of ARV-471 inhibited tumor growth by 99% at 10 mpk and 106% at 30 mpk in an ESR1 mutant PDX model (at right)
- Superior inhibitor of tumor growth compared to fulvestrant\(^1\)
- In corresponding quantitative western blots, ER is reduced by 79% and 88% in the 10 mpk and 30 mpk arms, respectively, vs. 63% for fulvestrant

1 Fulvestrant schedule: 2x weekly x2 / q7dx2
In combination with palbociclib, ARV-471 exhibits superior tumor shrinkage versus fulvestrant.

**ARV-471 In Vivo Preclinical Development**

- Achieved significant tumor shrinkage in combination with palbociclib (131% TGI) in an MCF-7 xenograft mouse model.
  - In all 10 mice in experiment, tumors reduced by >80%.
- Superior tumor shrinkage (in combination with palbociclib) compared to fulvestrant (108% TGI).

**Tumor Growth Inhibition in MCF-7 Xenograft Mouse Model**

1. Palbociclib arm: 60 mpk po qd; 94% TGI.
2. Fulvestrant + Palbociclib arm: Fulvestrant 200 mpk sc biwx 2, qwx 3 + palbociclib 60 mpk po qd; 108% TGI.
3. ARV-471 + Palbociclib arm: ARV-471 30 mpk po qd + palbociclib 60 mpk po qd; 131% TGI.
In the first cohort of the ARV-471 Phase 1 dose escalation, exposure reached the predicted efficacious range.

**Preclinical Efficacious Exposure Range**

<table>
<thead>
<tr>
<th>Dose (po, qd)</th>
<th>Mean AUC(_{0-24}) (ng*hr/ml)</th>
<th>Mean C(_{\text{max}}) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mpk</td>
<td>658</td>
<td>84</td>
</tr>
<tr>
<td>10 mpk</td>
<td>2538</td>
<td>312</td>
</tr>
<tr>
<td>30 mpk</td>
<td>5717</td>
<td>962</td>
</tr>
</tbody>
</table>

**Phase 1 Data**

<table>
<thead>
<tr>
<th>Dose po, qd</th>
<th>Day 1 AUC(_{\text{TAU}}) (ng*h/mL) Mean</th>
<th>Day 1 C(_{\text{max}}) (ng/ml) Mean</th>
<th>Day 15 AUC(_{\text{TAU}}) (ng*h/mL) Mean(^1)</th>
<th>Day 15 C(_{\text{max}}) (ng/ml) Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>1690</td>
<td>109</td>
<td>4100</td>
<td>224</td>
</tr>
</tbody>
</table>

- Accumulation occurs between Day 1 and Day 15
- Exposure at 30 mg has entered the preclinical efficacious range associated with tumor growth inhibition

1 Day 15 AUCs calculated using imputed 24 hour values

Initial clinical data as of 10/23/19
Pharmacokinetics of the first cohort of the ARV-471 Phase 1 dose escalation

\[ T_{\text{max}} = 4 \text{ hours} \]

\[ t_{1/2} = \text{estimated to be } \sim 24 \text{ hours} \]

‡ Day 15 24 hour value is imputed from time zero

Initial clinical data as of 10/23/19
No treatment-related AEs or DLTs were observed in the first cohort of ARV-471

• First cohort through 28 day dose limiting toxicity evaluation period; second cohort enrolling

<table>
<thead>
<tr>
<th>Dose Level†</th>
<th>N</th>
<th>Key Safety Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg‡</td>
<td>3</td>
<td>• No DLTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No Treatment Related AEs</td>
</tr>
<tr>
<td>60 mg</td>
<td>3</td>
<td>• TBD</td>
</tr>
</tbody>
</table>

• Trial update planned in 2nd half 2020

† Orally, once daily
‡ Data not yet 100% source verified

Initial clinical data as of 10/23/19
Neurology Research Programs
Mutant-specific PROTAC® degraders may reduce intra- and extracellular tau, creating a strong opportunity in neuroscience

- PROTAC degraders may overcome the limitations of other platforms, including antisense oligonucleotides (ASO) and monoclonal antibodies (Ab)

**ASO**
- Degrades mRNA, impacting intra- and extracellular tau
- Does not discriminate between wild type and pathologic tau
- Requires intrathecal dosing

**Ab**
- Blocks only extracellular pathologic tau
- IV dosing results in only 0.5% in CSF

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

ASO, antisense oligonucleotide; Ab, antibody; CSF, cerebrospinal fluid; BBB, blood-brain barrier
In vivo, tau-directed PROTAC® degraders eliminate >95% of pathologic tau following parenteral administration.

Pathologic tau in Tg2508¹ mouse cortex

24 hours post dose:
- >95% of pathologic tau is degraded
- No significant change in total soluble tau 24 h post dose (data not shown)

¹ Tg2508 is a murine pathologic tau model (P301L). ² AUC, area under the curve; ³ 3 mpk, milligrams per kilogram

**** Tukey's multiple comparisons test P < 0.0001
Tau-directed PROTAC® protein degraders inhibit ex-vivo tau seeding

1 Tau P301L CHO-K1 is a cell line expressing a doxycycline-inducible tau mutation linked to FTDP-17 (frontotemporal dementia and parkinsonism linked to chromosome 17). 2 Pre-formed fibrils (PFFs) are used to “seed” tau aggregation. 3 Cortex lysates are from Tg2508 mice. 4 MC1 is an antibody that detects a pathologic conformation of tau. 5 “No P301L,” no doxycycline induction.

**** Tukey's multiple comparisons test P < 0.0001. Comparisons are between the Cortex-Vehicle value and all other values (individually)
Oligomer-specific PROTAC® molecules human α-synuclein aggregates in primary rat neurons

**PROTAC molecules degrade oligomeric α-synuclein species**

*PROTAC degraders were identified that specifically remove oligomeric α-synuclein*

![Graph showing PROTAC molecules concentration and α-synuclein levels](image)

- PROTAC degraders 1-5 @ 1 µM

**PROTAC-1 and PROTAC-2 degrade α-synuclein aggregates in primary rat neurons expressing human α-synuclein**

*Neuronal α-synuclein +PFF induction assays*

*Intensity and area features of α-synuclein aggregates calculated*

![Graph showing ratio of α-syn total intensity to cell mask](image)

**Ratio: α-syn total intensity / cell mask**

1 Assay is of primary rat neurons expressing A53T human α-synuclein, with pre-formed fibrils (PFF) added or not. In the absence of α-synuclein-specific PROTAC degraders, α-synuclein forms aggregates induced by PFFs (green fluorescence in cellular images). When PROTAC degraders specific for oligomeric α-synuclein are added, the ratio of oligomeric α-synuclein:cell mask (background fluorescence) is decreased (right panel).
Arvinas’ approach in neuroscience

Approach: Prove the concept with PROTAC® degraders in defined populations while pursuing larger, multifactorial indications

Conceptual

- Tau
  - FTDP (~3K)
  - Progressive supranuclear palsy (~20K)
  - ApoE4 AD risk allele carriers (600-900K)
  - Alzheimer’s (~6M)

- α-synuclein
  - Synuclein mutations, e.g., duplication/triplication (~4K)
  - Multiple systems atrophy (~50K)
  - GBA PD risk allele carriers (~500K)
  - Parkinson’s (~1M)

FTDP, frontotemporal dementia and parkinsonism; GBA, glucocerebrosidase gene; AD, Alzheimer’s disease; PD, Parkinson’s disease
1 Alzheimer’s Association; “2018 Alzheimer’s Disease Facts and Figures.” Alzheimer’s and Dementia; V.14; No.3; 2018; p36
3 NINDS; https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Multiple-System-Atrophy
Corporate Overview
$298.2 Million\textsuperscript{1}
Pro forma cash, cash equivalents, and marketable securities
\textit{as of 9/30/19}

39.0 Million\textsuperscript{1}
Pro forma common shares outstanding
\textit{as of 9/30/19}

Guidance\textsuperscript{1}
Expect pro forma cash, cash equivalents, and marketable securities to fund planned operations into 2022

Analyst Coverage\textsuperscript{2}
BMO, Cantor, Citibank, Evercore, Goldman Sachs, Piper Jaffray, Wedbush

\textsuperscript{1} Financials, guidance, and shares outstanding include proceeds from the public offering of common shares announced 11/6/19 (includes shoe exercise).
\textsuperscript{2} The foregoing list includes the names of all brokerage firms known by the company as of 11/8/19 to have analysts covering the company. This list may not be complete and is subject to change as firms add or delete coverage. Please note that any opinions, estimates or forecasts regarding the company made by these analysts are theirs alone and may not represent the opinions, estimates or forecasts of the company.
Strategic partnerships are validating our PROTAC® protein degrader technology

September 2015
(expanded in November 2017)
• Target discovery deal
• Upfront, development, and commercial milestone aggregate payments in excess of $650M
• Tiered royalties

December 2017
• Target discovery deal
• Upfront, development, and commercial milestone aggregate payments up to $830M
• Tiered royalties

June 2019
• Pharma target discovery deal, including CV, gynecologic, and oncologic disease
• Oerth Bio (agriculture JV; 50:50 share)
• Private equity placement
• ~$115M in total upfront and committed funds

Potential for nearly $2.1 billion in milestones
The PROTAC® Company: Leading in protein degradation therapeutics

- Believed to have the first targeted protein degraders in the clinic
- Leading platform and product IP, driven by nearly two decades of PROTAC protein degradation research
- First to publish data on orally available PROTAC protein degraders
- Leadership team with experience getting drugs to market
- Strong financial position to advance the platform and product candidates
Thank you!
Appendix
The need for a new approach

Our understanding of the proteins responsible for causing certain diseases has greatly outpaced innovation.

Up to 80% of the human proteome is still considered “undruggable” and not addressable via small molecule inhibitors.

Current treatment options for many diseases are suboptimal and/or suffer from rapid onset of resistance.

Nucleic acid-based approaches (siRNA, gene therapy) lack many of the drug-like properties of traditional small molecules.
Our strategic approach to proving and delivering a novel technology platform

- Clinically validate the PROTAC® protein degrader concept with well-defined targets
- Prioritize additional targets where degradation has the potential to be superior to existing modalities
- Treat patients with diseases inaccessible to current therapies by degrading “undruggable” targets

- Invest in our pipeline and our platform and grow our IP to expand our leadership in protein degradation
- Selectively collaborate with strong partners to expand the impact of PROTAC protein degraders into new areas
Weak or promiscuous ligands can be converted into potent and selective PROTAC® degraders

When developed into PROTAC degraders, weak binders can become potent degraders

- Foretinib is a relatively weak binder to p38α
- PROTAC 1 is a foretinib-based PROTAC degrader with a p38α binding affinity of 11 μM
- Despite its 11 μM binding affinity, PROTAC 1 has a DC₅₀ of 210 nM¹
  - Based on experience, optimization of potency better than 210 nM is likely

When developed into PROTAC degraders, promiscuous ligands can become selective degraders

- Foretinib binds to 133 protein kinases (left panel)
- In cells treated with a foretinib-based PROTAC degrader, only a small subset of cellular proteins are degraded (blue-shaded quadrant of the right panel)

A PROTAC degrader based on foretinib has a nanomolar DC₅₀ despite a 11 μM binding affinity

DC₅₀ = 210 nM¹

Source: Bondeson et al., 2018, Cell Chemical Biology
1 DC₅₀ = Half-maximal degradation concentration
ARV-110 selectively degrades AR

**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 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: 3x10$^{-9}$

1 VCaP, Vertebral Cancer of the Prostate
2 $D_{\text{max}}$, maximal degradation
ARV-110: Phase 1 Study
First patient dosed March 2019

Design:
- “3 + 3” dose escalation; starting dose = 35 mg, orally, once daily (po, qd) with food
- Dose increases dependent on toxicities: range 25% (if 1 DLT in 6 pts) to 100% (≤Grade 1 Adverse Events)

Key Entry Criteria:
- Men with mCRPC
- At least two prior systemic therapies, at least one of which was abiraterone or enzalutamide
- Disease progression on most recent therapy
  - Rising PSA or 2+ new lesions upon bone scan

Key Objectives:
- Maximum Tolerated Dose/ Recommended Phase 2 Dose/ Safety
- Pharmacokinetics
- Anti-Tumor Activity (PSA, RECIST)
- Biomarkers

Biomarkers:
- AR degradation in circulating tumor cells (CTCs) and pre- vs post-treatment biopsies (when available)
- AR (and other) gene mutations, amplifications in circulating tumor DNA (ctDNA)
- AR-V7 in CTCs

PSA, Prostate specific antigen. RECIST, Response evaluation criteria in solid tumors
Our estrogen receptor-targeting PROTAC® degrader: ARV-471

Orally bioavailable estrogen receptor-targeted PROTAC protein degrader

- ARV-471 is in development for the treatment of patients with ER+ locally advanced or metastatic breast cancer
- Potential as both a single agent and in combination with CDK4/6 inhibitors

ARV-471 Degrades ER in ER+ Breast Cancer Cell Lines

- ARV-471 induces ER degradation in multiple ER+ breast cancer cell lines, including MCF-7 cells and ESR1-mutant lines
- $DC_{50} = 1.8 \text{ nM}$ in MCF7 cells

1 Also tested: MB-134-VI, T47D, D538G, Y537S, ZR-75-1, BT474, CAMA-1
2 $DC_{50} =$ Half-maximal degradation concentration
3 Beta-actin is a protein ARV-471 and fulvestrant are not targeted to degrade, and is included as a loading control
ARV-471: Phase 1 Study
First patient dosed August 2019

**Design:**
- “3 + 3” dose escalation; starting dose = 30 mg orally, once daily (po, qd) with food
- Dose increases dependent on toxicities: range 25% (if 1 DLT in 6 pts) to 100% (≤Grade 1 Adverse Events)

**Key Entry Criteria:**
- ER+/HER2- advanced breast cancer
- At least two prior endocrine therapies in any setting, and a CDK4/6 inhibitor
- Up to three prior cytotoxic chemotherapy regimens

**Key Objectives:**
- Maximum Tolerated Dose/ Recommended Phase 2 Dose/Safety
- Pharmacokinetics
- Anti-tumor activity (RECIST, CBR)
- Biomarkers

**Biomarkers:**
- ER gene (ESR1) mutational status in ctDNA and/or tumor tissue
- ER, Progesterone Receptor and Ki-67 levels in pre- and post-treatment tumor biopsies in patients with accessible tumor tissue

CBR, clinical benefit rate
Our PROTAC® degraders can be engineered to cross the blood-brain barrier (BBB)

- Micromolar rodent brain exposure achieved after peripheral (IV) administration
- Brain-to-plasma ratio >0.5 achievable with PROTAC degraders

<table>
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<th>PROTAC</th>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>[Plasma 1h] (ng/ml)</th>
<th>[Brain 1h] (ng/g)</th>
<th>B/P ratio</th>
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</table>

- Over a 4-hour time course, PROTAC degraders are more durable in the brain than in plasma
In June 2019, Bayer and Arvinas announced a $110+ million partnership to develop human PROTAC® therapies and launch Oerth Bio, a separate joint venture to develop PROTAC® degraders for agricultural applications.

**Pharmaceutical collaboration and direct equity investment**
- Focus on gynecology, oncology, and cardiovascular disease targets
- Upfront and committed funding exceeds $60 million (including equity investment)
- Over $685 million in potential milestone payments, plus commercial royalties

**Oerth Bio, an agriculture-focused joint venture**
- Oerth Bio to develop agricultural products using PROTAC® degrader technology
- Potential for weed, pest, and disease control applications
- Over $55 million in committed funding by Bayer to Oerth Bio
- Bayer and Arvinas share ownership and governance of Oerth Bio equally

Combined with Genentech and Pfizer, potential for nearly $2.1 billion in milestones
Seasoned leadership with expertise in advancing novel technologies

**Leadership Team**

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- Ronald Peck, MD  
  Chief Medical Officer
- Angela Cacace, PhD  
  VP Neuro and Platform Biology
- Matthew Batters, JD  
  VP Bus. Development & Counsel
- Randy Teel, PhD  
  VP Corporate Development
- Steve Weiss  
  VP Human Resources
- Sean Cassidy, CPA, MBA  
  Chief Financial Officer
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  Chief Scientific Officer
- John A. Grosso, PhD  
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- Laurie Smaldone Alsup, M.D.
For more information

www.arvinas.com

Press/Media
pr@arvinas.com

Investors
ir@arvinas.com

Business Development
bd@arvinas.com

Careers
careers@arvinas.com