Arvinas PROTAC® Discovery Engine: How Arvinas’ Platform Targets Disease-Causing Proteins in Oncology and Beyond
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.
Arvinas is 180+ colleagues strong and growing, benefitting from the experience and resources of the Connecticut biotech sector.

**Mission**

We invent PROTAC® protein degraders designed to destroy disease-causing proteins and improve the lives of patients suffering from cancer, neurological disorders, and other serious diseases.

**Core Values**

Pioneering, Excellence, Community, & Commitment

**People**

- 180+ highly experienced drug development professionals in New Haven, Connecticut
- 200+ FTEs at contract research organizations

**Bioscience in Connecticut**

- 39,000 employees across 2,500 companies
- Strong academic base for R&D partnerships

---

1. BioCT 2019 Report
We are well on our way to our 2024 vision

**Integrated biotech poised for launch**

- Goal to have first PROTAC® degraders proven to benefit patients in registrational studies
- Sustainably nominating ≥1 clinical candidate per year
- PROTAC Discovery Engine delivering candidates with tissue- and disease-specific degradation
- Completing build-out of the resources and capabilities to bring PROTAC therapeutics to market
Our target selection strategy is designed to build the optimal portfolio of PROTAC® protein degraders

Guiding principles for our portfolio strategy

• Focus on targets where degradation of the disease-causing protein will result in differential biology and patient outcomes versus other modalities

• Build on our established expertise and capabilities in oncology, immuno-oncology, and neuroscience

• Create a diversified, risk-balanced portfolio of validated and undruggable targets
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>IND 2021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV-766</td>
<td>Other AR indications</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>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.
Arvinas’ PROTAC® Discovery Engine
Arvinas’ breakthroughs are driven by our integrated PROTAC® Discovery Engine

**PROTAC Discovery Engine**

1. **Target/Ligase Selection & Ligand Identification**
   - E3 KnowledgeBASE of novel E3 ligases
   - Novel warheads for undruggable targets and new ligands for E3 ligases
   - Advanced screening capabilities, including proprietary DNA-encoded libraries tailored for PROTAC development

2. **Rapid PROTAC Design**
   - Optimizing the Zone of Ubiquitination
   - Predictive computational modeling
   - Arvinas Next Generation Linker Evolution (ANGLE)
   - State-of-the-art proteomics capabilities

3. **Turning Degraders Into Drugs**
   - “Arvinas Rules” for drug-like properties, including blood-brain barrier penetration and oral bioavailability in humans
   - Deep knowledge of in vivo PK/PD and efficacy relationships

Arvinas’ platform is built from nearly 20 years of experience, know-how, and IP
600+ E3 ligases in the human genome (RING, HECT, RBR, CRL adapters)

- multi-prong bioinformatic analysis of tissue expression
- clues about sub-cellular localization?

Initial focus on CNS & tumor-enriched E3s

- is the activity confirmed?
- substrates known?

Next level analysis

- KO phenotype?
- structurally enabled?
- cancer cell line dependency?

High Value
E3 Ligases
Identified
Arvinas PROTAC Discovery Engine: From Ligase to PROTAC

**Degrader Mechanisms Group**

- **Protein Sciences & Structural Biology**
  - Protein design
  - Crystallography-grade protein & assay reagents
  - X-ray crystallography
  - CryoEM

- **Biophysics & Biochemical Assays**
  - SPR, TR-FRET, aLISA, MST, etc
  - Ternary complex assays
  - Screen design & validation
  - Screen follow-up & hit-to-lead

- **Mechanistic Cell Biology & PROTAC SAR**
  - High throughput, plate-based degradation assays
  - Understanding of degradation mechanisms
  - Cell-based assay development & PROTAC profiling

**Platform Chemistry**

- **DEL synthesis, selections & hit confirmation**
  - DEL assay development & screening
  - DEL hit selection (AI-enabled)
  - DEL hit resynthesis & medicinal chemistry for hit-to-lead
  - CADD and modeling
DNA Encoded Library Design, Synthesis & Selection
Proprietary Ligand Identification / Optimization: e.g. New E3s, Undrugged Proteins of Interest

**Chemoinformatics**
- Optimize for PROTACs
- Maximize diversity
- Eliminate undesirable functional groups

**DEL Chemistry**
- Focus on 2- and 3-cycle libraries
- Commercial and proprietary reagents

**DEL Selections**
- Multiple condition selection
- NGS decoding and AI enabled analysis
- Off-DNA synthesis
- Chemistry/SBDD optimization
- PROTAC-ability evaluation
Putting it all together: New E3 ligase to PROTAC degrader

Ligase selection

Deep understanding of ligase mechanism

E3 Ligand ID & optimization

Conversion to PROTAC degrader

Human E3 ligase tissue enrichment profiles

Idealized tissue-enrichment profile 1

Idealized tissue-enrichment profile 2

E3 class I

E3 class II

NanoLuc-substrate loading control

WB: substrate (endogenous)

WB: loading control

Ligase:substrate displacement assay (aLISA competition)

% probe displacement

competitor [µM]

Ligase:substrate (normalized HiBiT signal)

% substrate remaining

HiBiT-substrate degradation

potency evolution

NanoLuc-substrate

NanoLuc-substrate loading control

Deep understanding of ligase mechanism

E3 Ligand ID & optimization

Conversion to PROTAC degrader

Ligase selection

NanoLuc-substrate

NanoLuc-substrate loading control

WB: substrate (endogenous)

WB: loading control

Ligase:substrate displacement assay (aLISA competition)

% probe displacement

competitor [µM]

Ligase:substrate (normalized HiBiT signal)

% substrate remaining

HiBiT-substrate degradation

potency evolution

NanoLuc-substrate

NanoLuc-substrate loading control

Deep understanding of ligase mechanism

E3 Ligand ID & optimization

Conversion to PROTAC degrader

Ligase selection

NanoLuc-substrate

NanoLuc-substrate loading control

WB: substrate (endogenous)

WB: loading control

Ligase:substrate displacement assay (aLISA competition)

% probe displacement

competitor [µM]

Ligase:substrate (normalized HiBiT signal)

% substrate remaining

HiBiT-substrate degradation

potency evolution
Our deep understanding of the Zone of Ubiquitination informs the structure-based design of PROTAC® degraders.

We design PROTAC degraders to optimize the position of lysine residues within the Zone of Ubiquitination.
**Arvinas proprietary predictive modeling: ligand & trimer modeling / PROTAC design method**

**POI**

**E3 Ligase**

**Step 1:** Sampling ligand / linker conformations in E3 ligase and POI using MD simulations (~1 million frames)

**Step 2:** Superimpose linker domains to generate trimer models, sample protein-protein interactions and identify high probability states

**Step 3:** Calculation of protein-protein interaction binding free energies $\Delta G$ using Arvinas proprietary Dissociation Free Energy (DFE)

**Step 4:** Model low energy trimer(s) into full E3-E2-Ub complex to identify zone of ubiquitination and high probability ubiquitination sites

**Zone of Ubiquitination**

Ubiquitination probability for each Lysine in POI
PROTAC PK/PD Modeling: Predicting in vivo target degradation from in vitro degradation experiments and PK data

- **In vitro degradation after a single 3 mg/kg PO dose**
  - Dots: Experimental Data
  - Lines: Model Predictions

- **In vivo degradation after a single 0.03-10 mg/kg PO doses**
  - Plasma PK after single 0.03-10 mg/kg PO doses
  - Time (hours)
  - Plasma concentration (nM)

- **Tumor POI (%)**
  - 0 to 100
  - Time (hours)

- **Dots: Experimental Data**
  - Lines: Model Predictions

- **Clearance**
  - PO dose
  - Plasma

- **Cell Permeability**
  - Tumor distribution

- **K_{syn} K_{deg}
  - POI
  - Ternary complex

- **E3**
  - K_{D,E3}
  - Proteasome

- **Recycle**
  - Degraded POI

- **Degraded POI**
  - X

- **Degradation after 5 hours**
  - POI (% baseline)
  - (nM)
Arvina Clinical Stage Programs
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*

- Phase 1 ongoing in a highly refractory patient population
- Potential best profile of any ER-targeting therapy:
  - Tolerability
  - ER degradation
  - Clinical benefit

**ARV-110**

Androgen receptor-degrading PROTAC®

*Prostate Cancer*

- Extensive molecular profiling of tumors to understand drivers of resistance
- AR degradation and clear signals of efficacy observed in late-line mCRPC
- Initiated Phase 2 ARDENT trial; two potential paths to registration: 3L molecularly defined, and broader 1L/2L

† US incidence data from SEER database

AR, androgen receptor; ER, estrogen receptor

>200k patients† per year with high unmet need

>250k patients† per year with high unmet need
Platform Validation: PROTACs can have drug-like properties

ARV-471’s PK is dose proportional; exposures far exceed preclinical efficacy thresholds

The orange line represents the efficacious exposure for tumor regression in preclinical models†

Effective half-life ($T_{1/2}$) $\approx 28$ hours

† AUC24=5717 ng*h/mL for preclinical effective exposure in preclinical model (mice@30mpk).

AUC, area under the curve; SE, standard error

Data as presented 12/14/2020
Platform Validation: PROTACs can have excellent safety profiles

**ARV-471 is well tolerated at all dose levels; no Grade 3 adverse events**

<table>
<thead>
<tr>
<th>TRAE in ≥ 10% of Patients</th>
<th>30 mg (N=3)</th>
<th>60 mg (N=3)</th>
<th>120 mg (N=7)</th>
<th>180 mg (N=5)</th>
<th>360 mg (N=3)</th>
<th>Total (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1</td>
<td>Gr 2</td>
<td>Gr 1</td>
<td>Gr 2</td>
<td>Gr 1</td>
<td>Gr 2</td>
</tr>
<tr>
<td>Any</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Adverse events were primarily Grade 1; No dose limiting toxicities

Data cut-off: November 11, 2020
TRAE, Treatment related adverse event

Data as presented 12/14/2020
Platform Validation: PROTAC mechanism of action in humans

*ER degradation by ARV-471 observed in patient tumor biopsies*

**Method**: ER immunoreactivity analyzed by quantitative immunofluorescence (QIF) using the automated quantitative analysis (AQUA) method

**Red**: Estrogen receptor

**Blue**: Nuclei

**Green**: Tumor (cytokeratin)

**Baseline**

**After treatment with 60 mg ARV-471**
The Ultimate Platform Validation: PROTACs can Benefit Patients
Confirmed RECIST Partial Response (cPR) in late-stage patients with extensive prior therapy

Baseline CT Scan

ARV-471 (120 mg PO QD)

Target 1

Target 2

ARV-110 (140 mg PO QD)

Extensive retroperitoneal adenopathy compressing the inferior vena cava

Near complete regression of adenopathy

After 4 Cycles

Baseline CT Scan

51% Reduction

80% Reduction
Recently Disclosed Preclinical Programs
For recently introduced targets, PROTAC® protein degraders are likely to differentiate from other drug modalities.

<table>
<thead>
<tr>
<th>Target</th>
<th>Differential Biology Based on the Tenets of PROTAC® Degraders</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCL6</td>
<td>Target scaffolding function of BCL6</td>
</tr>
<tr>
<td>KRAS</td>
<td>Target “undruggable” KRAS mutants (e.g., G12V, G12D)</td>
</tr>
<tr>
<td>Myc</td>
<td>Directly degrade “undruggable” Myc vs. other indirect approaches</td>
</tr>
<tr>
<td>HPK1</td>
<td>Address potential scaffolding function</td>
</tr>
<tr>
<td>mHTT</td>
<td>Selectively degrade mutant huntingtin (mHTT) protein</td>
</tr>
</tbody>
</table>
Most B cell lymphomas are dependent on constitutive or deregulated expression of BCL6, a transcriptional repressor of:

- Cell cycle checkpoints
- Terminal differentiation
- Apoptosis
- DNA damage response

PROTAC® degradation would address the scaffolding function of BCL6.

Arvinas’ BCL6 program is aiming for an oral, best-in-class targeted therapy for B-cell malignancies.

After oral dosing, PROTAC® X achieved >95% degradation of BCL6 in vivo.

Optimizing in vivo tumor growth inhibition activity and selecting a candidate to take forward with anticipated IND in 2022.
KRAS: In vivo Characterization of Arvinas’ PROTAC® degraders

As a proof of concept, we have successfully developed KRAS G12C-specific PROTAC® degraders.

**Six hours after a single dose, PROTAC® Y degraded >80% of KRAS G12C in vivo**

Robust (>80%) KRAS degradation can be achieved in vivo and translates into excellent tumor growth inhibition.

**Leveraging learnings from KRAS G12C development to accelerate other mutant KRAS degraders**
Congratulations to all as we approach the 20th anniversary of first PROTAC® publication. We have come a long way!

Source: PubMed; Keyword words used: "Proteolysis-targeting chimera" OR "PROTAC®" OR "PROTAC® protein degraders" OR "protein degraders" OR "Targeted Protein Degradation" OR "Protein Degradation"
Thank You!