The Promise of PROTAC® Protein Degraders: What’s Next for Arvinas’ Pipeline & Platform

John G. Houston, PhD
President and Chief Executive Officer, Arvinas, Inc.

14 October 2020
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, and the potential commercialization of any of our product candidates. 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, 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 our 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.
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"

Scientific Publications for PROTAC® Degradation

Arvinas Founded

Number of Publications


0 20 40 60 80 100 120 140 160 180

Arvinas

0 2 3 5 6 2 2 5 2 8 2 4 5 7 10 12 21 54 159

材料及び方法

合成系のラジカル付与方式: 第1のプロテアーゼ (1,400,000 g) は先に示したように、NADH/NAD+ とアデニラーゼの存在により、酸化還元系のラジカル生成を誘起する。さらに、Arvinas の創設は2012年でした。
Protein degradation field has driven interest and investment, culminating in substantial patient and business impact.

The expanding modalities of protein degradation:

- Heterobifunctional Small Molecules
- Molecular Glues
- Lysosome Targeting Chimeras
- Autophagy Targeting Chimeras
- Autophagosome Tethering Compounds

20+ focused companies

$3B+ investment since 2013

4+ IPOs since 2018

Multiple candidates in clinical studies

Efficacy proof-of-concept in human patients

Source: Company websites, S-1 filings, and industry research reports
Arvinas is 160+ 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**

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

**Bioscience in Connecticut**

- 39,000 employees across 2,500 companies¹
- Strong academic base for R&D partnerships

¹BioCT 2019 Report
Arvinas has led the targeted protein degradation field since its inception...

**Built Arvinas’ Foundation as a Pioneer in Protein Degradation**
- Pioneered targeted protein degradation with our PROTAC® platform, making pivotal breakthroughs
- Capitalized Arvinas to drive growth and investment in our platform and capabilities
- Built a deep, broad pipeline of PROTAC® protein degraders
- Forged foundational partnerships

**2019-2020**
- Proved the Concept of Our PROTAC® Discovery Engine
  - Moved two programs into the clinic, each addressing an area of substantial unmet need for patients
  - Initial evidence for efficacy, safety, and proof of degradation mechanism of PROTAC® degraders in human trials
  - Expanded our wholly-owned PROTAC® pipeline to 20+ programs
  - Embraced the challenge of improving agriculture with our JV, OerthBio

**2013-2018**
- Built Arvinas’ Foundation as a Pioneer in Protein Degradation
...and made significant breakthroughs along the way!
Arvinas’ breakthroughs are driven by our integrated PROTAC® Discovery Engine

**PROTAC® Discovery Engine**

1. **Ligase Selection and 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
   - Arvinas Next Generation Linker Evolution (ANGLE)
   - Predictive computational modeling
   - 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
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.
Strategic partnerships expand the impact of our PROTAC® Discovery Engine

These partnerships expand PROTAC® degraders beyond oncology and beyond human therapeutics, while maintaining full ownership of our pipeline.
Our fully-owned two clinical-stage PROTAC® protein degraders have the potential to address significant unmet need in advanced disease:

**ARV-110**  
(AR PROTAC®)

- Targets the androgen receptor (AR), a highly validated driver of prostate cancer
- Early clinical proof-of-concept (safety, AR degradation, efficacy) demonstrated May 2020
- Fully-owned; US peak sales potential of $2-3B

**ARV-471**  
(ER PROTAC®)

- Targets the estrogen receptor (ER), a highly validated driver of ER+/HER2- breast cancer
- Early clinical safety and pharmacokinetic data presented October 2019
- Fully-owned; US peak sales potential of $4-5B
We are developing ARV-110 to be a potentially first- and best-in-class AR-targeted therapy for prostate cancer

Clear initial efficacy signal in dose escalation, in the most advanced patient population tested with an AR-directed therapy

Safety profile acceptable for potential use in frontline settings

Exploring a fast-to-market, biomarker-driven strategy for accelerated approval in 2L+ mCRPC

Potential to address unmet patient need in 1L mCRPC and mCSPC (~45k patients)

Next ARV-110 update anticipated Q4 2020

Note: Data presented at ASCO 2020 and as of 4/20/20. RECIST, response evaluation criteria in solid tumors; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer
ARV-471 is a potential first- and best-in-class ER degrader for ER+ locally advanced or metastatic breast cancer

**Strong clinical profile**:  
- Early evidence of ER degradation in the Phase 1 dose escalation  
- No DLTs; dose escalation continues  
- Dose-proportional pharmacokinetics

**Superior ER degradation and tumor inhibition in preclinical studies**

**Fast-to-market strategy with potential indication in 2L+ ER+/HER2- mBC**

**Potential expansion to 1L ER+ breast cancer (~50k patients) in combination with CDK4/6i**

*Next ARV-471 update anticipated Q4 2020*

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1As of 5/29/2020. DLT, dose-limiting toxicity
ARV-110 and ARV-471 have provided clinical proof-of-concept for PROTAC® degraders

- Degradation of AR and ER demonstrates proof-of-mechanism in human patients
- Safety initially observed in two different programs in two different patient populations
- ARV-110 overcame prior resistance to AR therapy, showing the translation of ARV-110’s preclinical profile into patient benefit
- Reinforces our confidence in Arvinas’ extensive and promising preclinical pipeline
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.
Our previously disclosed pipeline includes innovative therapies for oncology 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 2/3</th>
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<tbody>
<tr>
<td>ARV-110</td>
<td>mCRPC</td>
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<td>ARV-766</td>
<td>AR Next Gen</td>
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<td>ARV-V7</td>
<td>mCRPC</td>
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<td>ARV-471</td>
<td>ER+/HER2- Breast Cancer</td>
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<td>Additional I-O and Oncology Programs</td>
<td>Multiple Indications</td>
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<td>Tau</td>
<td>FTLD-Tau, PSP, Alzheimer’s</td>
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<td>Alpha Synuclein</td>
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Note: Pipeline is non-exhaustive. mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; FTLD-tau, frontotemporal lobar degeneration-tau; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy
Today: Introducing five targets for which PROTAC® protein degraders have high potential to differentiate from other drug modalities

<table>
<thead>
<tr>
<th>Target</th>
<th>Differential Biology Based on the Tenets of PROTAC® Degraders</th>
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<tr>
<td>BCL6</td>
<td>Target scaffolding function of BCL6</td>
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<tr>
<td>KRAS</td>
<td>Target “undruggable” KRAS mutants (e.g., G12V, G12D)</td>
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<tr>
<td>Myc</td>
<td>Directly degrade “undruggable” Myc vs. other indirect approaches</td>
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<tr>
<td>HPK1</td>
<td>Address potential scaffolding function</td>
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<tr>
<td>mHTT</td>
<td>Selectively degrade mutant huntingtin (mHTT) protein</td>
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</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

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
We are taking a comprehensive approach to degrading KRAS

**KRAS**

- KRAS is the most frequently mutated gene in human cancer and is a classic “undruggable” target due to its lack of deep “pockets”
- We are creating pan-KRAS mutant, in addition to mutant-specific (e.g., G12D and G12V), degraders
- As a proof of concept, we have successfully developed *in vivo* active KRAS G12C-specific PROTAC® degraders

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

*Leveraging learnings from KRAS G12C development to accelerate other KRAS degraders’ development with anticipated IND in 2023*
Arvinas’ current pipeline encompasses a range of validated and undruggable targets in oncology, I-O, and neuroscience.

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<td>AR indications</td>
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<td>BCL6</td>
<td>B-cell Malignancies</td>
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<td>IND 2022</td>
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<td>KRAS</td>
<td>NSCLC, CRC, Pancreatic</td>
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<td>IND 2023</td>
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<td>Undisclosed</td>
<td>Solid Malignancies</td>
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<td>Undisclosed</td>
<td>Neurodegeneration</td>
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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.
Over the next two years, we anticipate a rapid pace of milestones

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<tr>
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<th>2020 Q4</th>
<th>2021</th>
<th>2022</th>
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<tbody>
<tr>
<td><strong>ARV-110</strong></td>
<td>• Program update</td>
<td>• Completed Phase 1 data</td>
<td>• Full Phase 2 data</td>
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<tr>
<td><strong>(mCRPC)</strong></td>
<td>• Initiation of Phase 2</td>
<td>• Phase 2 interim data</td>
<td>• Combination study data</td>
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<td></td>
<td></td>
<td>• Initiation of combination study</td>
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<tr>
<td><strong>ARV-471</strong></td>
<td>• Interim Phase 1 data</td>
<td>• Completed Phase 1 data</td>
<td>• Interim Phase 2 data</td>
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<tr>
<td><strong>(ER+/HER2-breast cancer)</strong></td>
<td>• Initiation of combination study with CDK4/6i</td>
<td>• Initiation of Phase 2</td>
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<tr>
<td><strong>ARV-766</strong></td>
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<td>• Initiate Phase 1</td>
<td>• Phase 1 data</td>
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<tr>
<td><strong>(AR PROTAC®)</strong></td>
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<td></td>
<td>• Initiate Phase 2</td>
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Note: mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-
Arvinas’ 2024 Vision: Ascending to new heights in bringing the benefits of PROTAC® degraders to patients

Integrated biotech poised for launch
- First PROTAC® degraders proven to benefit patients in registrational studies
- Sustainably nominating ≥1 clinical candidate per year
- Our 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
Thank You!