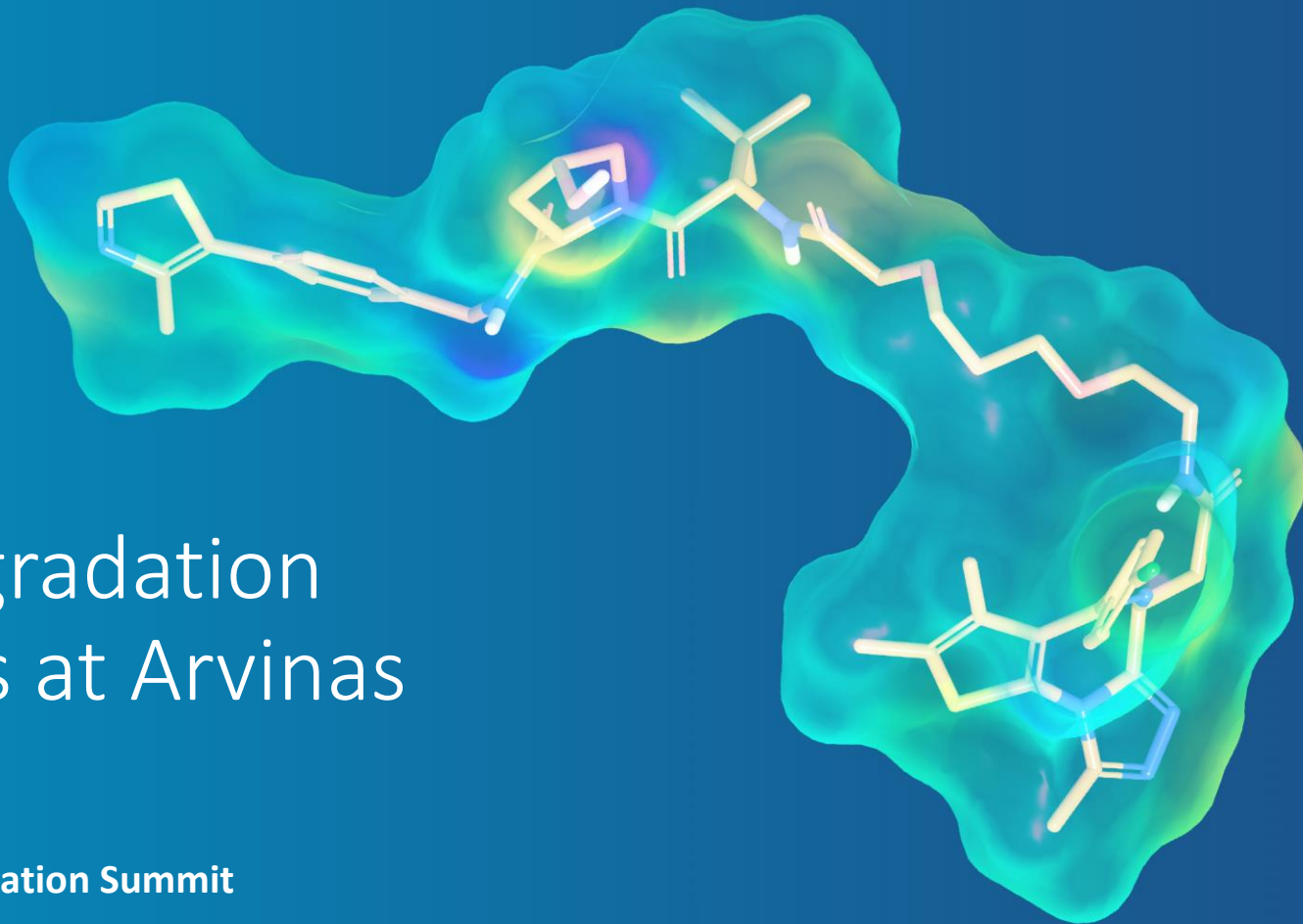




ARVINAS

The PROTAC™ Company
Pioneering Protein Degradation
as a New Therapeutic Modality



Case Study: Protein Degradation Approaches at Arvinas

Targeted Protein Degradation Summit

October 25, 2018

Ian Taylor, PhD

Disclaimer

This presentation contains forward-looking statements that involve substantial risks and uncertainties, including statements regarding our lead product candidates, ARV-110 and ARV-471, and the timing of IND submissions and clinical trials for 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 file INDs for ARV-110 and ARV-471 on our expected timelines, or at all, whether our cash resources will be sufficient to fund the our foreseeable and unforeseeable operating expenses and capital expenditure requirements 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 filings the Company makes with the Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect our current views 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 for, and have a pending registered U.S. trademark application 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.

Arvinas: Company Highlights

History

- Founded July 2013; New Haven, CT
- \$120M IPO, September 2018
- NASDAQ: ARVN

Pipeline

- Wholly owned development pipeline across multiple therapeutic areas
- **ARV-110 (Androgen Receptor)** in patients with metastatic castration-resistant prostate cancer; expected to initiate **Phase 1 in 1Q19**
- **ARV-471 (Estrogen Receptor)** in patients with estrogen receptor-positive (ER+) metastatic breast cancer; expected to initiate **Phase 1 in mid-2019**

Collaborators

- Strategic, discovery-stage partnerships with Pfizer and Genentech
- Exclusive worldwide license to PROTAC degrader technology with Yale University

Outstanding Team

- Strong leadership team with unparalleled protein degrader development experience
- World-class board and advisors, including scientific founder Craig Crews (Yale)



Arvinas Leadership

Leadership Team



John G. Houston, Ph.D.
President & CEO



Sean Cassidy, C.P.A., M.B.A.
CFO



Andy Crew, Ph.D.
SVP Chemistry



Ian Taylor, Ph.D.
SVP Biology



Angela Cacace, Ph.D.
VP Neuro and Platform Biology



John A. Grosso, Ph.D.
VP Chemistry, Mfg. & Controls



Marcia Dougan Moore, M.P.H.
VP Development Operations



Randy Teel, Ph.D.
VP Corporate Development



Steve Weiss
VP Human Resources



Matthew Batters, J.D.
ED Bus. Dev., Trans. & Counsel



Board of Directors

Timothy Shannon, M.D. *Chairman*



John G. Houston, Ph.D.



Ted Kennedy, Jr., J.D.



Jakob Loven, Ph.D.



Brad Margus



Briggs Morrison, M.D.



Kush M. Parmar, M.D., Ph.D.



Liam Ratcliffe, M.D., Ph.D.



Our Strategy



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

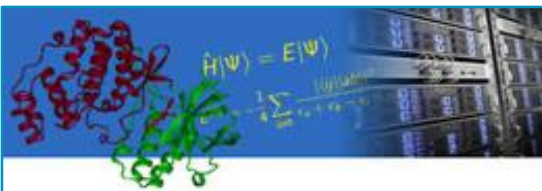


Treat patients with diseases inaccessible to current therapies by degrading “undruggable” targets

- Invest in pipeline and platform and grow our IP to expand our leadership in protein degradation
- Selectively collaborate with strong partners to enhance our capabilities and resources

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

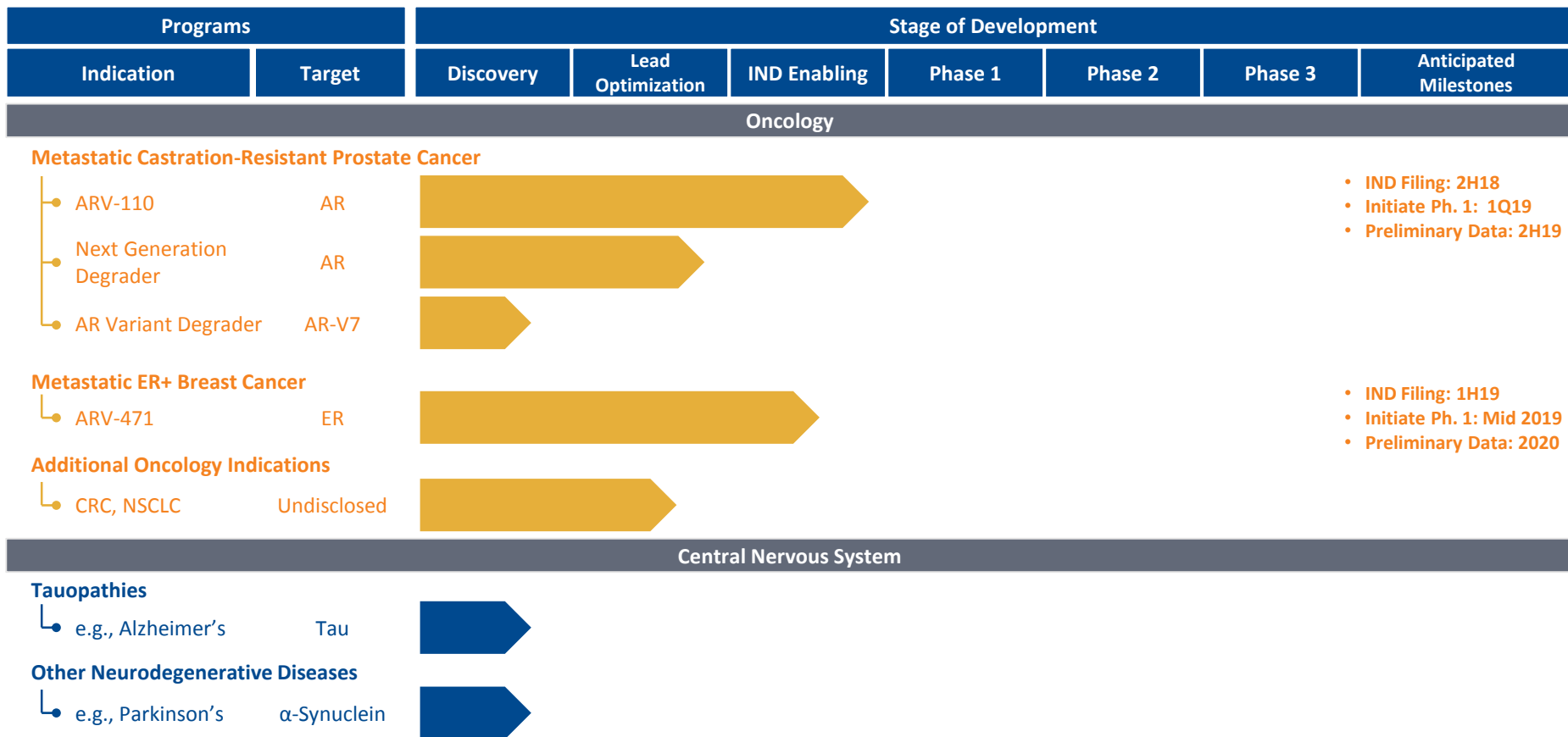
Hit Identification

- >90% Success Rate
- Efficient, Rapid Process
- Linker SAR Generated

Clinical Candidate Optimization

- PROTAC-Specific Design Metrics
- Holistic Optimization Strategy
- Advanced bRo5 Profiles (oral)

Our PROTAC™ Protein Degrader Pipeline

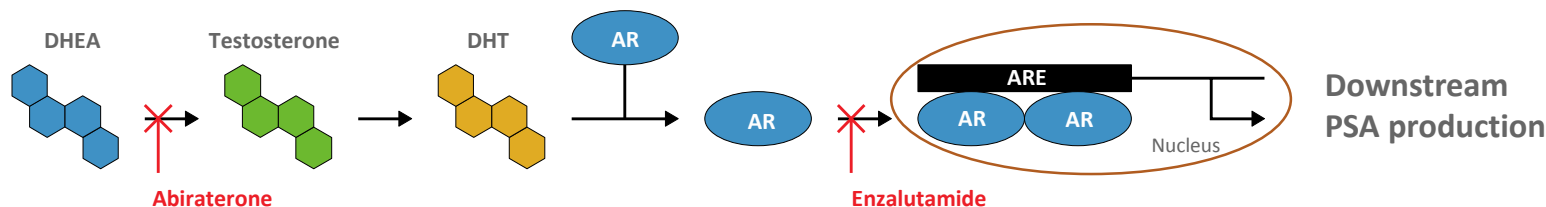


The background of the slide features a molecular structure visualization. It shows a complex organic molecule, possibly a drug candidate, rendered in a stick representation with yellow and purple atoms. This molecule is surrounded by a semi-transparent, yellowish-orange electron density or molecular surface map. The entire scene is set against a solid orange background.

Research and Development Programs

Androgen Receptor and Metastatic Castration Resistant Prostate Cancer (mCRPC)

Prostate cancer is the second leading cause of cancer death in men in the U.S. (~160k diagnosed/yr¹);
35-45k new incidences of mCRPC in the U.S. each year



Androgen Receptor (AR) Activity Drives Prostate Cancer²

- Current agents work by decreasing androgen levels (abiraterone) or blocking androgen binding to AR (enzalutamide)
- 15-25% of patients do not respond to abiraterone or enzalutamide (intrinsic resistance)

Acquired Resistance Mechanisms to Abiraterone and Enzalutamide

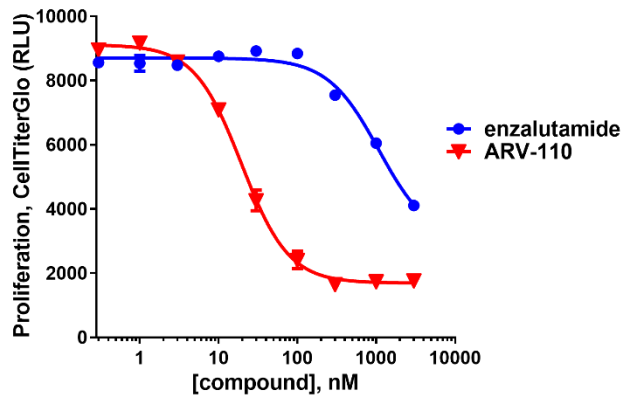
- AR gene amplification (40-60% of patients)
- AR gene enhancer amplification (>70% of patients)
- AR point mutations (~15% of patients)
- Intra-tumoral androgen production

In resistant patients, PSA levels rise, suggesting that AR remains the principal driver of disease

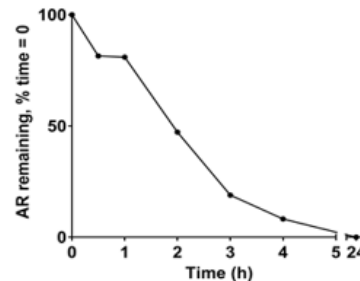
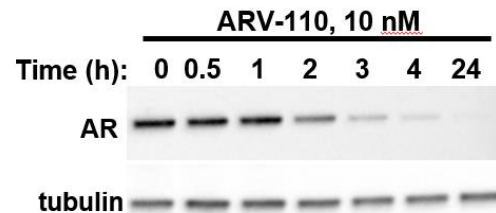
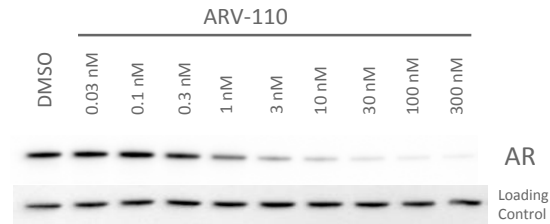
ARV-110 Potently and Rapidly Degrades AR and Inhibits Proliferation Better than Enzalutamide

In vitro studies

- ARV-110 degraded 95% to 98% of AR in multiple cell lines typically used in prostate cancer research, including VCaP cells
 - DC_{50} in VCaP = 1 nM
 - Near-maximal degradation within 4 hours of administration
 - ARV-110 inhibits VCaP proliferation ~60x more potently than enzalutamide



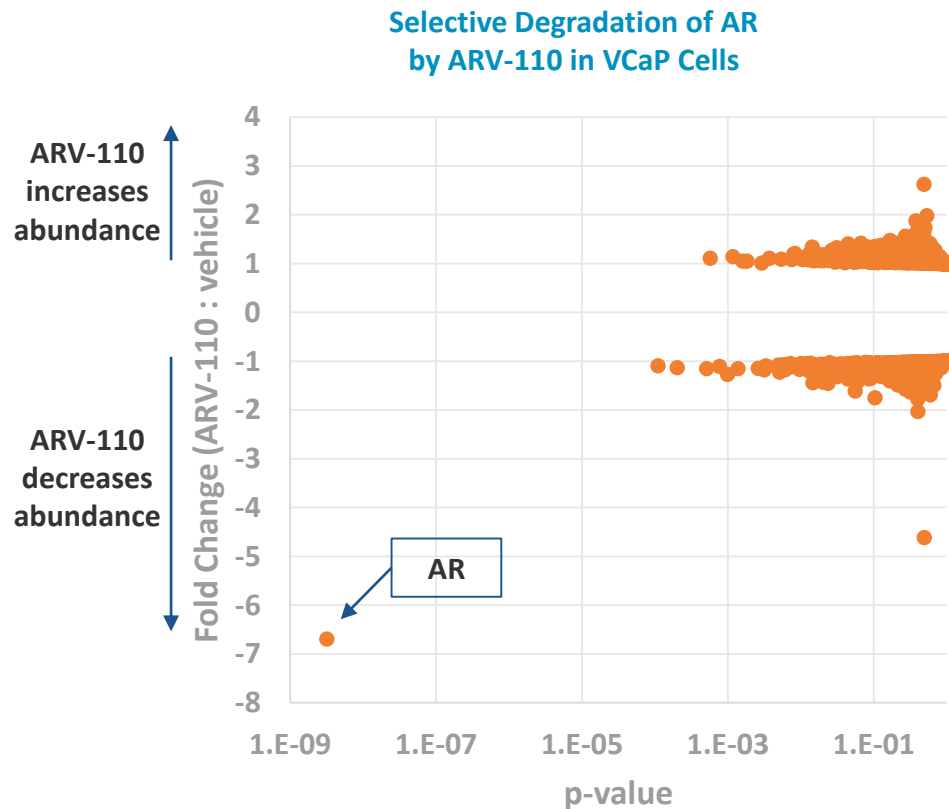
VCaP Cells:



ARV-110: Selectively Degrades AR

Proteomics studies

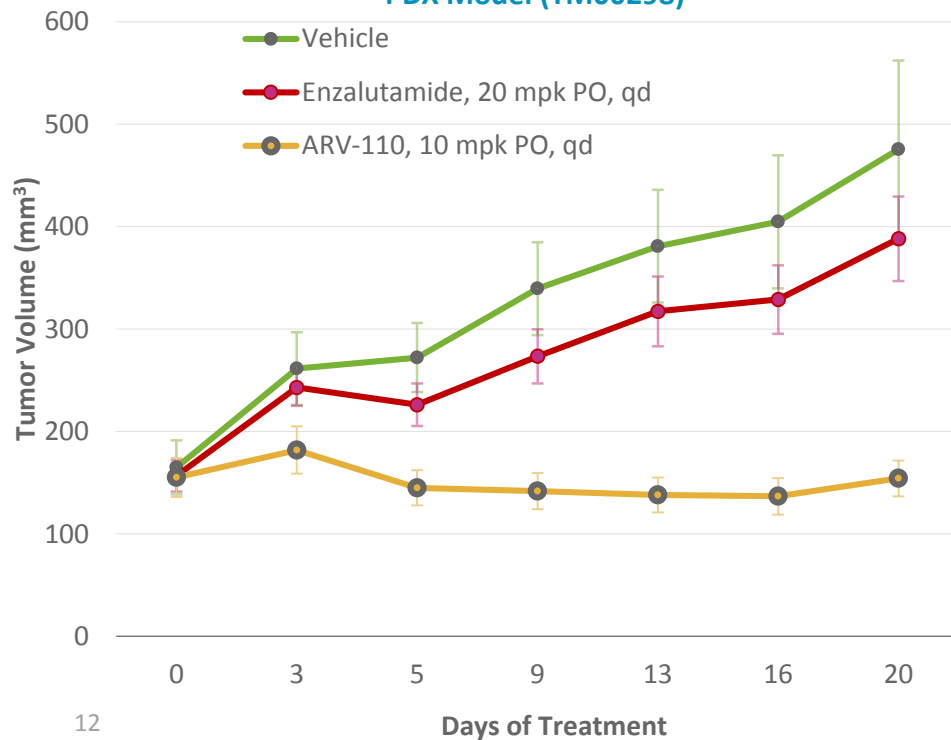
- After 8 hours of treatment of VCaP cells with 10 nM ARV-110 *in vitro*, AR was the only degraded protein among the nearly 4,000 proteins measured
 - 85% $D_{\max}$
 - p-value: 3×10^{-9}
- ARV-110 is highly selective for AR



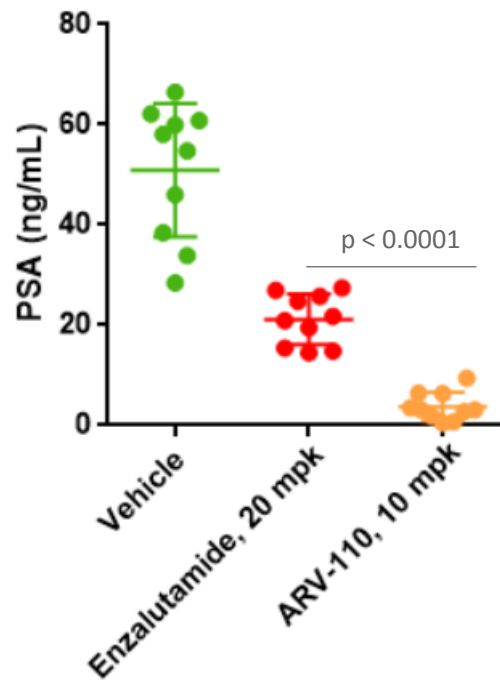
ARV-110 Demonstrates Efficacy and Plasma PSA Reduction in an Enzalutamide-Insensitive Patient Derived Xenograft Model

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

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



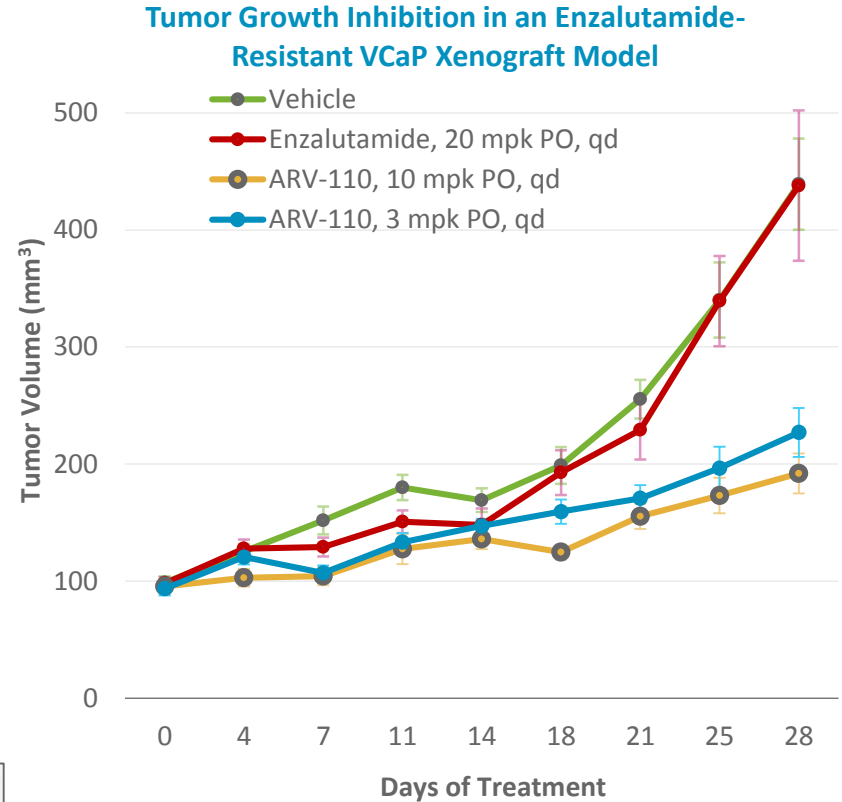
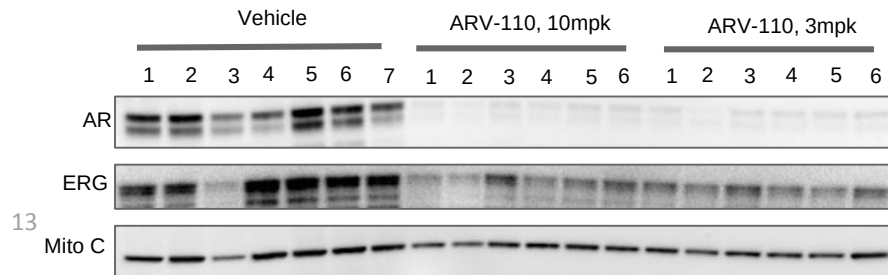
- Plasma PSA levels following ARV-110 treatment significantly decreased vs. mice treated with drug vehicle or enzalutamide



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 approximately 3 years
- Daily and orally delivered ARV-110 significantly inhibited tumor growth (*at right*)
 - 10 mpk ARV-110: 70% tumor growth inhibition

Pharmacodynamics, 16 hrs post last dose:



Our Androgen Receptor-Targeting PROTAC Degradar: ARV-110

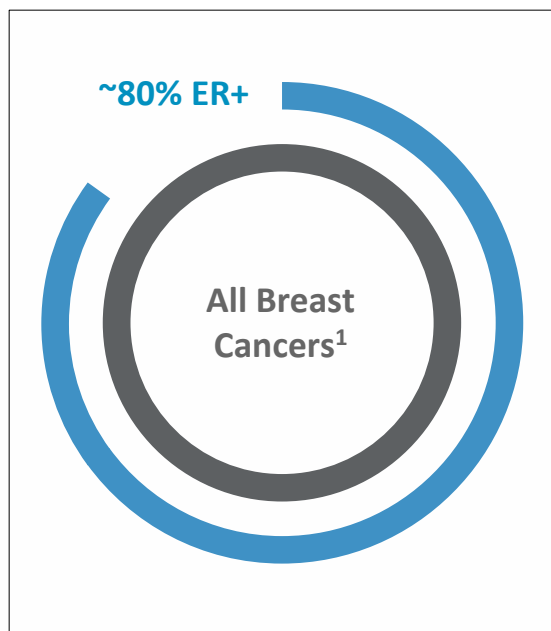


Orally bioavailable androgen receptor-targeted PROTAC protein degrader

- In development for the treatment of men with mCRPC who have progressed on abiraterone and/or enzalutamide
 - Potential to move to earlier lines of therapy
- Overcomes mechanisms of resistance to current standards of care
- Potential to be the first-to-market AR degrader
- Good laboratory practice (GLP) toxicity studies support planned clinical development
- IND expected in 2H18
 - Phase 1 initiation expected in 1Q19
 - Preliminary data expected 2H19
- Program wholly owned by Arvinas

Estrogen Receptor and Breast Cancer

Breast cancer is the second leading cause of cancer death in women



Types of Breast Cancer

- Breast cancer is the second most common cancer in women
- Approximately 266,000 women are expected to be diagnosed with invasive breast cancer in the US in 2018²
- Metastatic breast cancer accounts for ~6% of newly diagnosed cases³

Targeted Approaches to Treat ER+ Breast Cancer

- Fulvestrant has validated the value of ER degradation
- After 6 months of fulvestrant treatment, up to 50% of ER baseline levels remain⁴

A superior ER degrader is needed

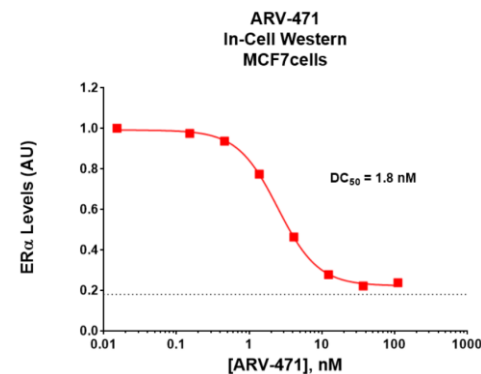
ARV-471 Degrades ER in ER+ Breast Cancer Cell Lines

- ARV-471 induces ER degradation in multiple ER+ cell lines

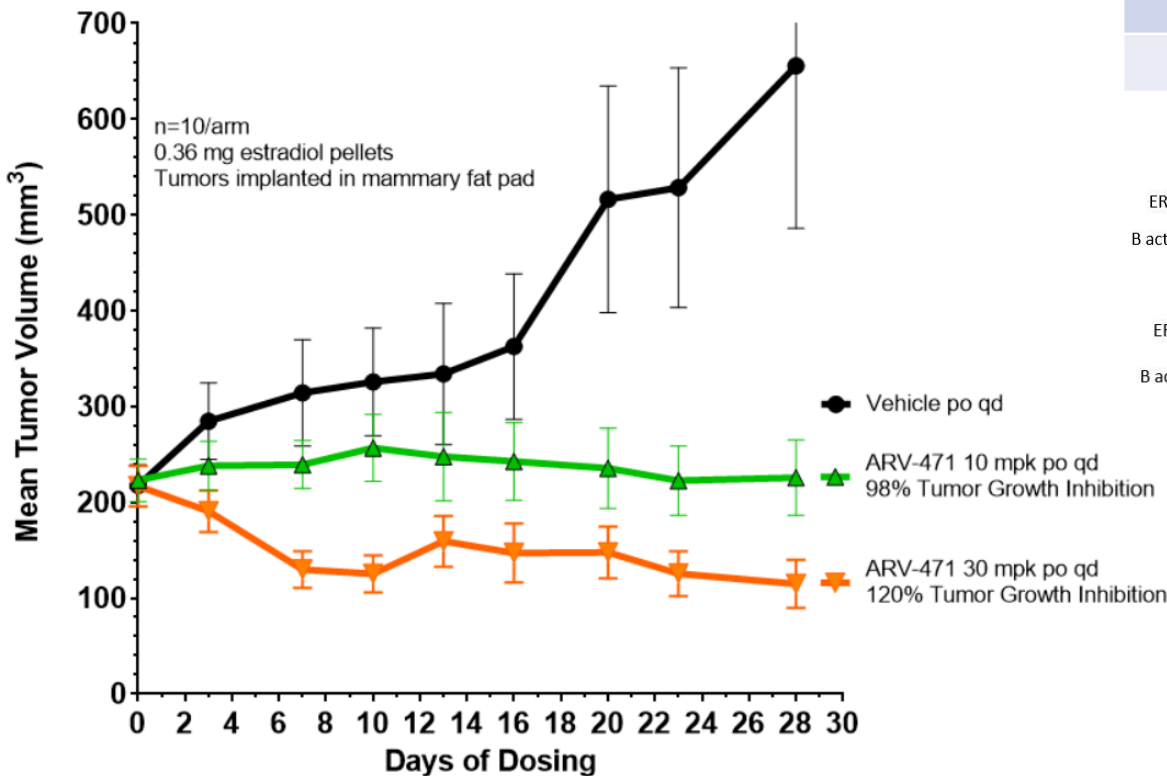
- At right are western blots of MCF-7 cells, 134VI cells, and T47D cells¹, and also ESR1 mutant (D538G, Y537S)-expressing lines

- DC₅₀ = 1.8 nM** in MCF7 cells

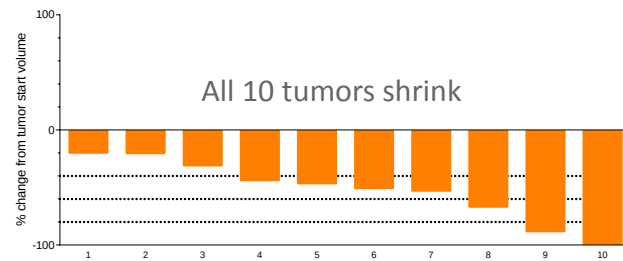
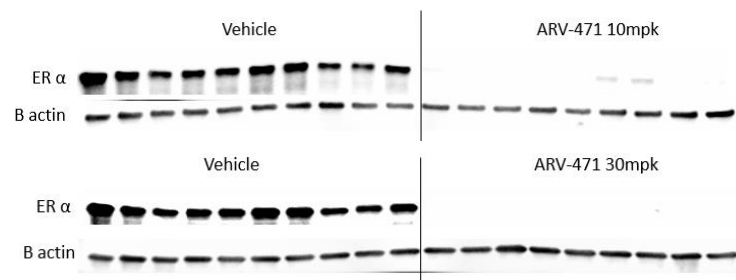
- Proliferation **GI₅₀ = 4 nM**



Orally Dosed ARV-471 Shrinks Tumors and Degrades ER in MCF7 Xenografts



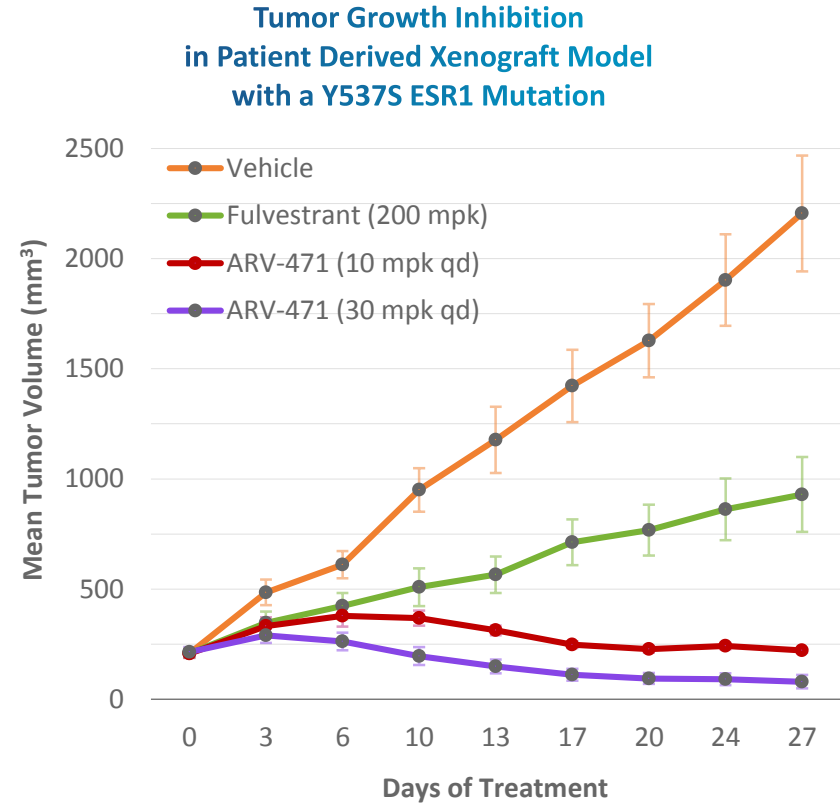
WESTERN BLOT PD (18 hours post last dose)	% ER REDUCTION
10 mpk ARV-471	97
30 mpk ARV-471	94



ARV-471: Superior Tumor Growth Inhibition Versus Fulvestrant in Y537S (ER Gene Mutation) PDX Model

ARV-471 *In Vivo* Preclinical Development

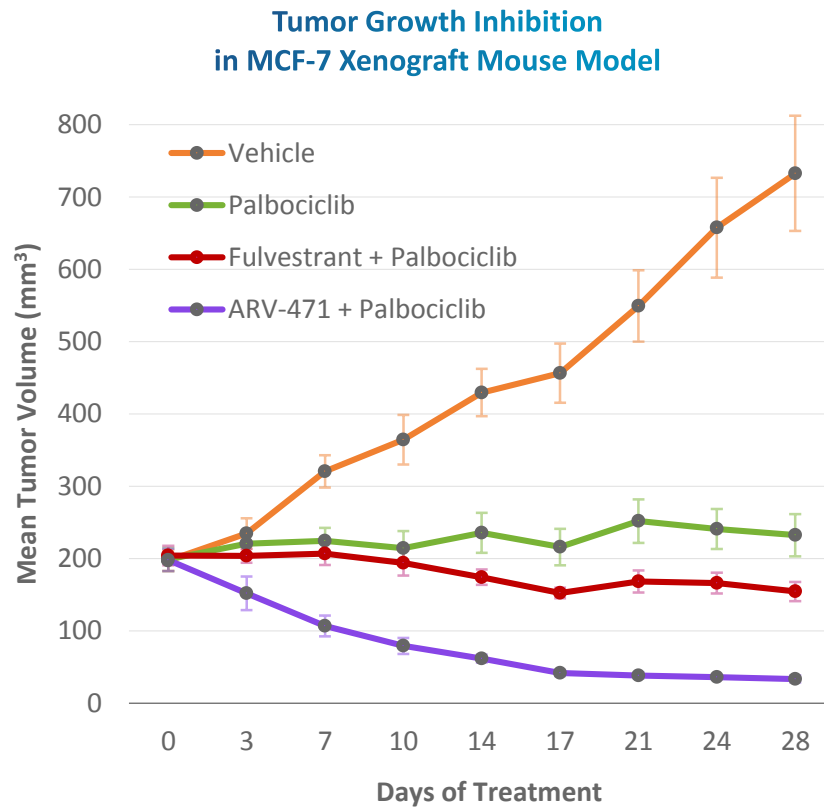
- Oral, daily dose of ARV-110 inhibited tumor growth by 99% at 10 mpk and **106% at 30 mpk** in an ESR1 mutant PDX model (*at right*)
- Superior inhibitor of tumor growth compared to fulvestrant¹
- In corresponding quantitative western blots, ER is reduced by 79% and 88% in the 10 mpk and 30 mpk arms, respectively, vs. 63% for fulvestrant



In Combination with Palbociclib, ARV-471 Exhibits Superior Tumor Shrinkage Versus Fulvestrant

ARV-471 In Vivo Preclinical Development

- **ARV-471 (30 mpk)** achieved significant tumor shrinkage in combination with palbociclib (**131% TGI**)
- Superior tumor shrinkage in combination with palbociclib compared to fulvestrant + palbociclib (108% TGI)



Palbociclib arm: 60 mpk po qd; 94% TGI

Fulvestrant + Palbociclib arm: Fulvestrant 200 mpk sc biwx 2, qwx 3 + palbociclib 60 mpk po qd; 108% TGI

ARV-471 + Palbociclib arm: ARV-471 30 mpk qd + palbociclib 60 mpk po qd; 131% TGI

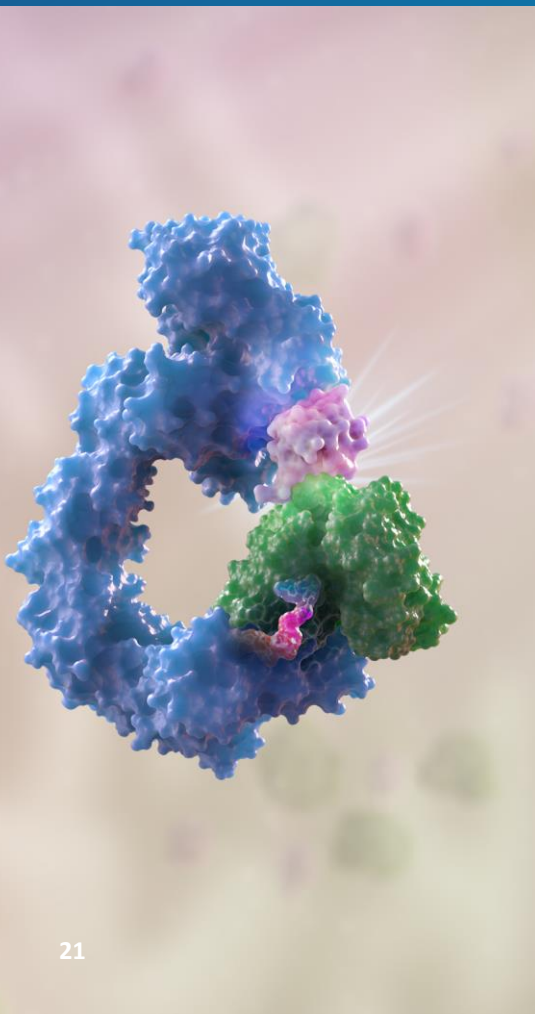
Our Estrogen Receptor-Targeting PROTAC degrader: ARV-471



Orally bioavailable estrogen receptor-targeted PROTAC protein degrader

- In development for the treatment of women with ER+ locally advanced or metastatic breast cancer
- Promising *in vivo* preclinical activity
 - Potent ER degrader
 - Superior tumor growth inhibition vs fulvestrant
- Potential as both a single agent and in combination with CDK4/6 inhibitors
- IND-enabling GLP toxicology studies began in September 2018
- IND expected in 1H19
 - Initiation of Phase 1 expected mid-2019; preliminary data expected in 2020
- Program wholly owned by Arvinas

Advancing the Pipeline; Expanding the Platform



Advance the Portfolio

- Primary focus on Oncology and Neurodegeneration

“Undruggable” Targets

- The 80% of proteins not addressable by small-molecule inhibition may be degradable by our PROTAC degraders’:
 - Ability to degrade proteins via sites other than enzymatic active sites
 - Potential to degrade proteins using weak binders

Platform Expansion

- Identifying and leveraging tissue- and disease-specific E3 ligases
- Enhanced prediction of degradation selectivity

The background of the slide features a molecular docking visualization. It shows a ligand molecule, represented by yellow sticks, bound within a protein's binding pocket. The protein's surface is depicted as a semi-transparent yellow mesh. The entire scene is set against a solid orange background. A horizontal orange band runs across the middle of the slide, containing the text 'Thank You'.

Thank You