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The PROTAC® Company

PROTAC® Targeted Protein Degraders

A New Therapeutic Modality

November 2019

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 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[1]
- 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

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High potential PROTAC® pipeline, focused on cancer and neurology[1]

		Programs [Target]	Discovery	Lead Optimization	IND Enabling	Phase 1	Arvinas Owned
Oncology	Metastatic Castration-resistant Prostrate Cancer	ARV-110 [Androgen Receptor]					✓
		Next Generation Degrader [Androgen Receptor]					✓
		AR Variant Degrader [AR-V7]					✓
	Locally Advanced or Metastatic ER+ / HER2- Breast Cancer	ARV-471 [Estrogen Receptor]					✓
	Additional Oncology Indications	e.g., CRC, NSCLC [Undisclosed]					✓
Neurology	Tauopathies	e.g., PSP[2] [Tau]					✓
	Synucleinopathies	e.g., MSA[3], Parkinson's [α-synuclein]					✓
	Additional Neurology Indications	Various [Undisclosed]					✓

1 Pipeline as of November 8, 2019
2SP, progressive supranuclear palsy
3 MSA, multiple systems atrophy

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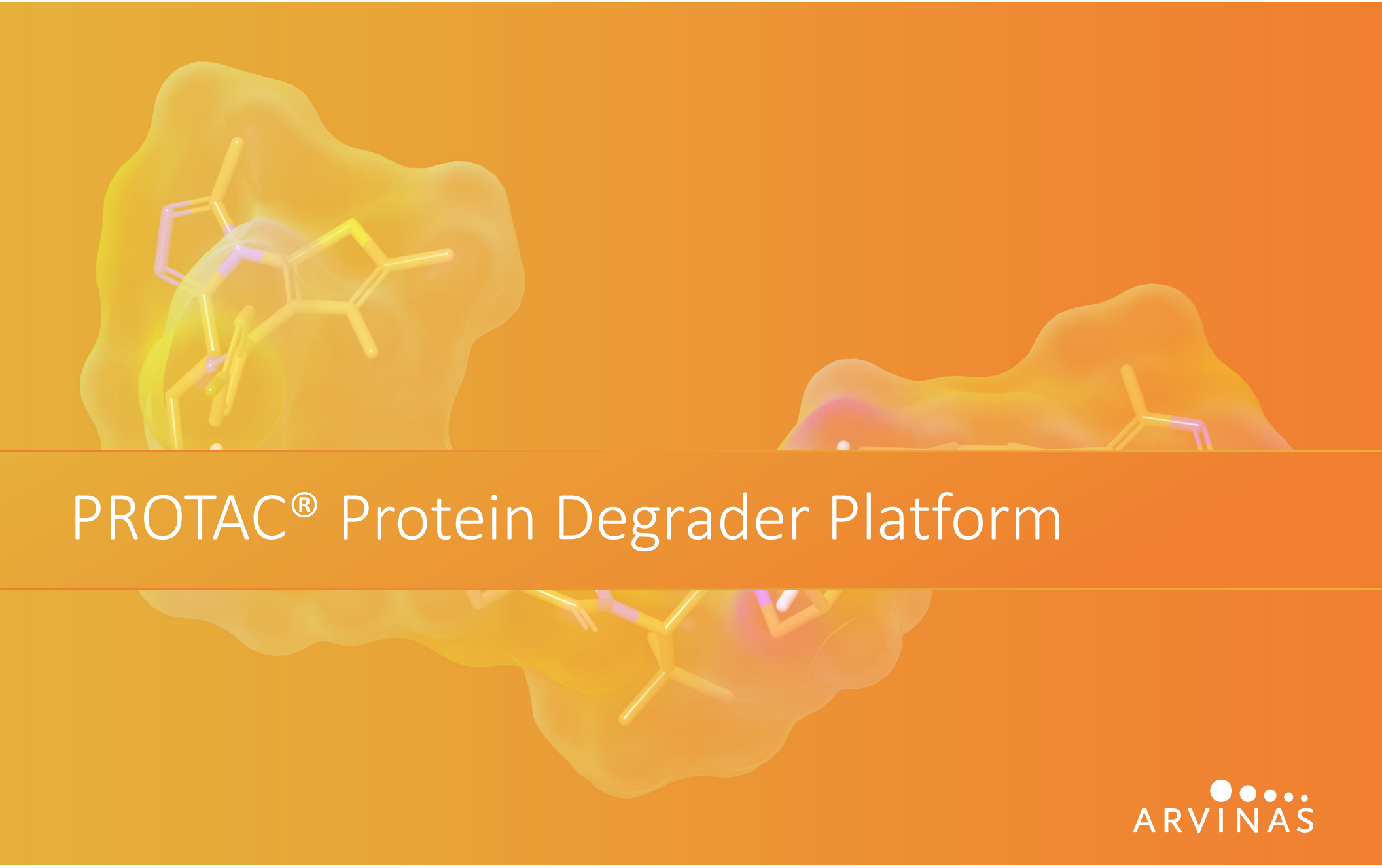

PROTAC® Protein Degrader Platform

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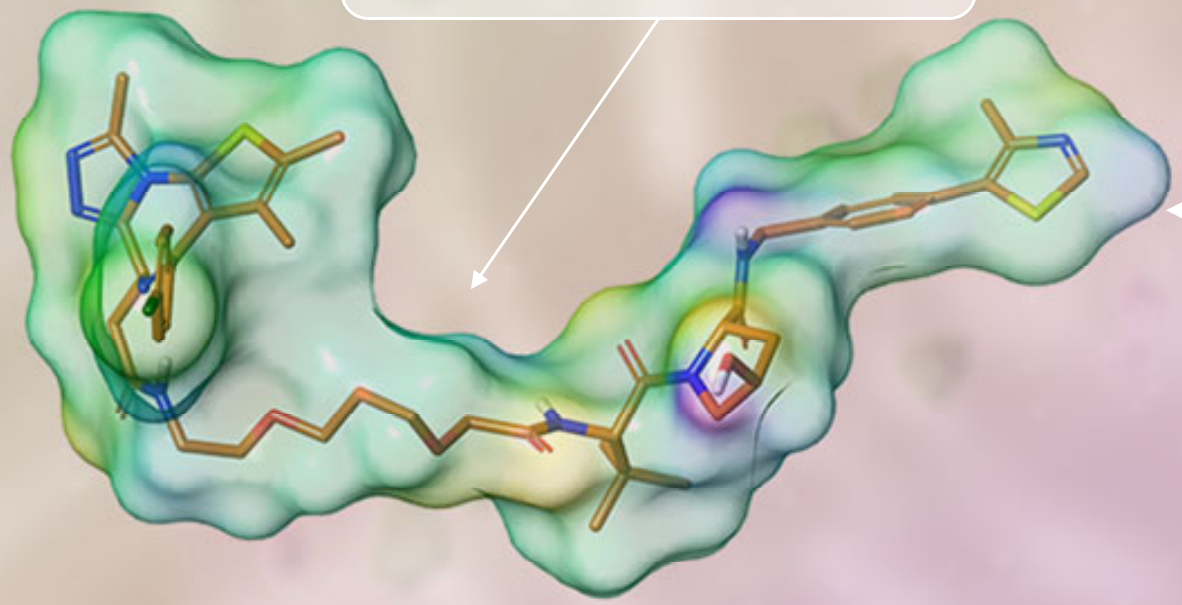
What is a PROTAC® protein degrader?

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

A linker region orients the target protein and E3 ligase to enable activity

Protein ligand domain ("warhead") targets a specific protein



Ligase ligand recruits a specific E3 ubiquitin ligase

All three regions of the PROTAC degrader play a role in the specificity and potency of target degradation

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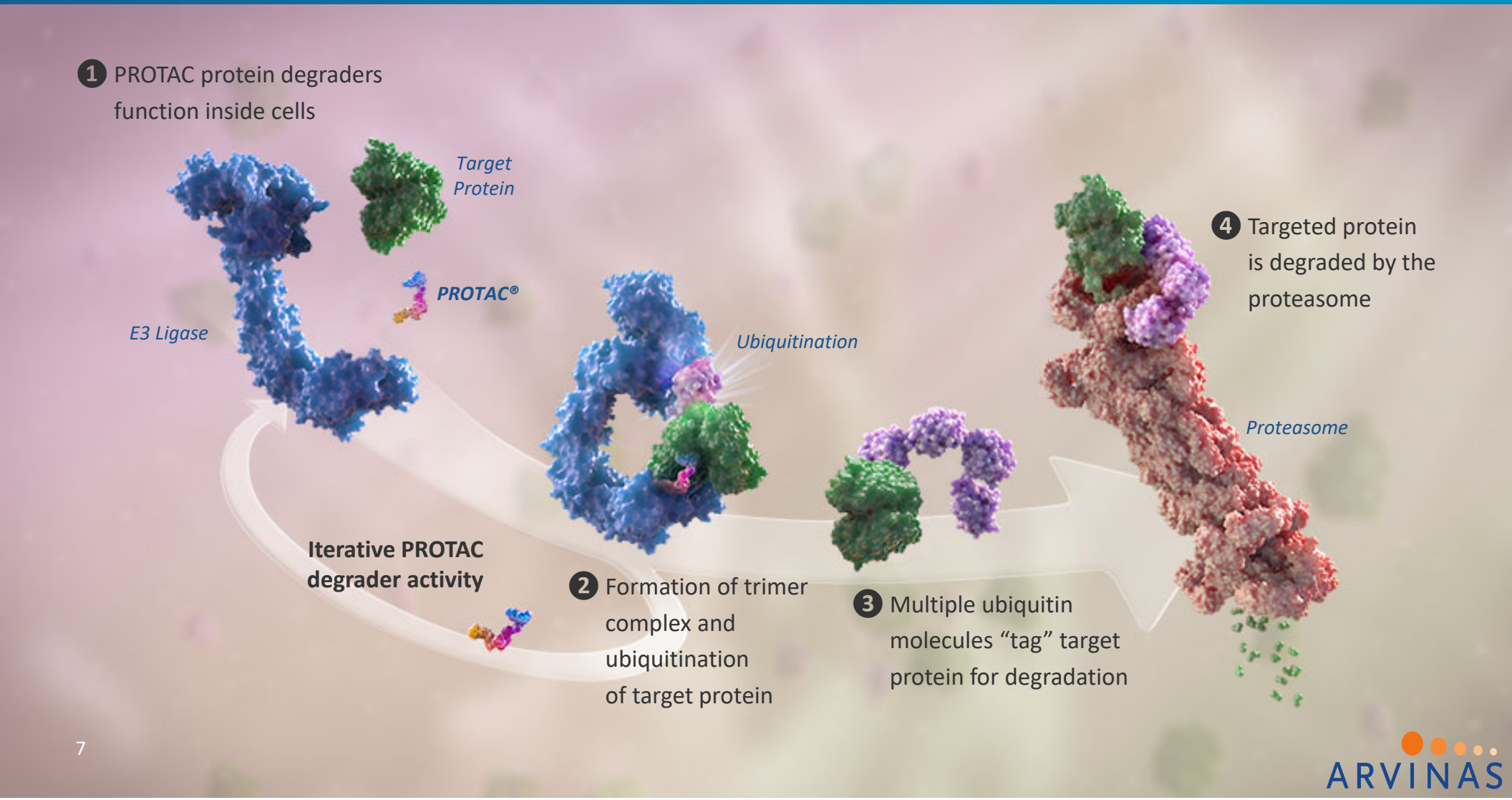
PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins



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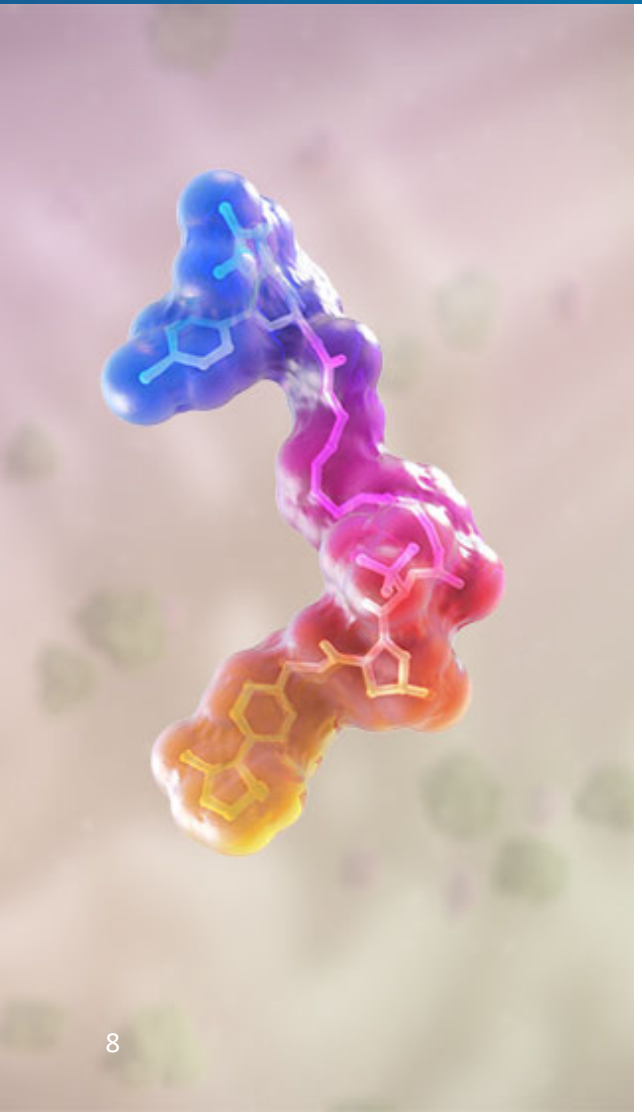
PROTAC® protein degraders combine the advantages of gene-based medicines with the benefits of small molecule therapies



PROTAC protein degraders have distinct advantages over both small molecule inhibitors and gene-based medicines	PROTAC Protein Degraders	Small Molecule Inhibitors	Gene-Based Medicines
Eliminate pathogenic proteins	✓	✗	
Target scaffolding function	✓	✗	
Potential to treat "undruggable" proteins	✓	✗	
Iterative mechanism of action	✓	✗	✗
Broad tissue penetration	✓		✗
Orally bioavailable	✓		✗
Ease of manufacturing	✓		✗

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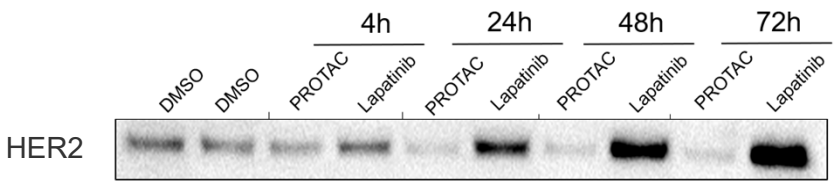
Potential advantages of PROTAC® protein degraders over inhibitors

Overcome Target Protein Overexpression

PROTAC degraders can disable this common tumor resistance mechanism

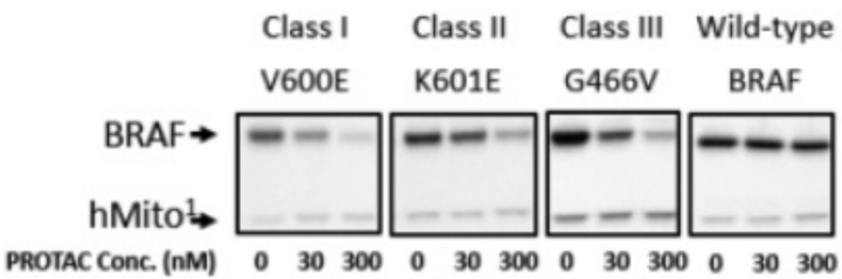
- Lapatinib alone results in HER2-overexpression, but a PROTAC created with lapatinib as the "warhead" degrades natural and overexpressed HER2
- HER2 degraded despite increased RNA levels



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)

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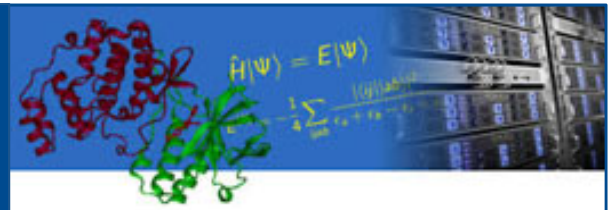
Arvinas' technology and expertise enable effective hit ID and optimized development candidates

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)

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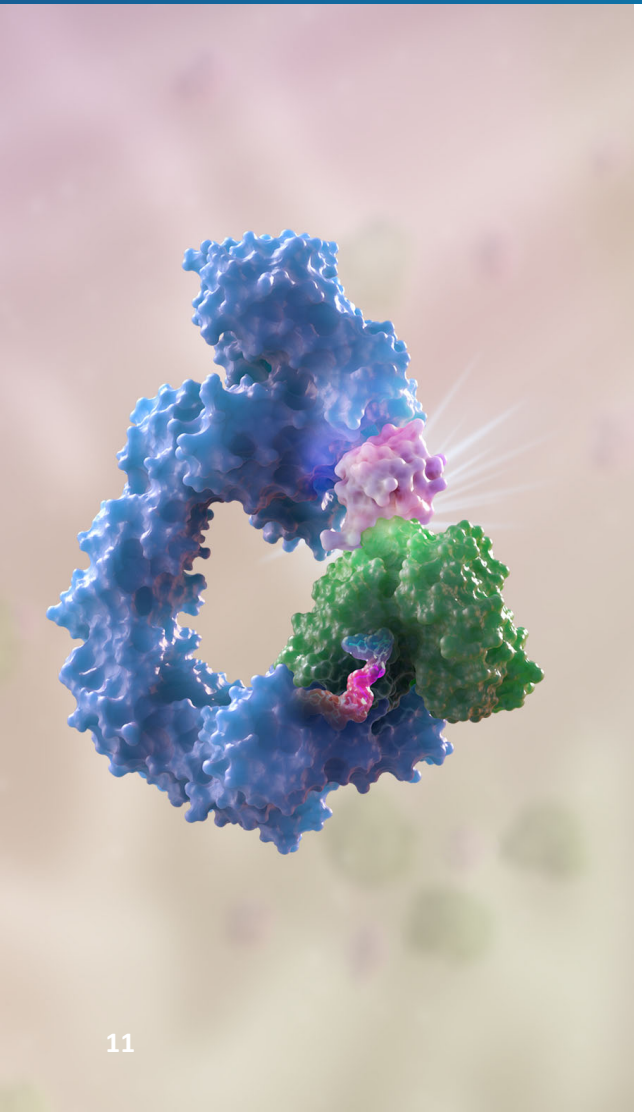
Platform expansion and undisclosed pipeline targets



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

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Clinical-stage Oncology Programs

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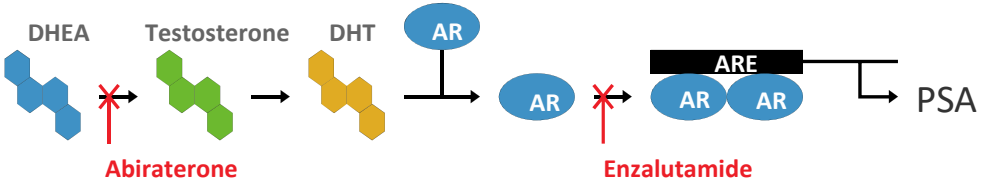
ARV-110 is Arvinas' AR degrader for men with metastatic castration-resistant prostate cancer (mCRPC)[1]

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**



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

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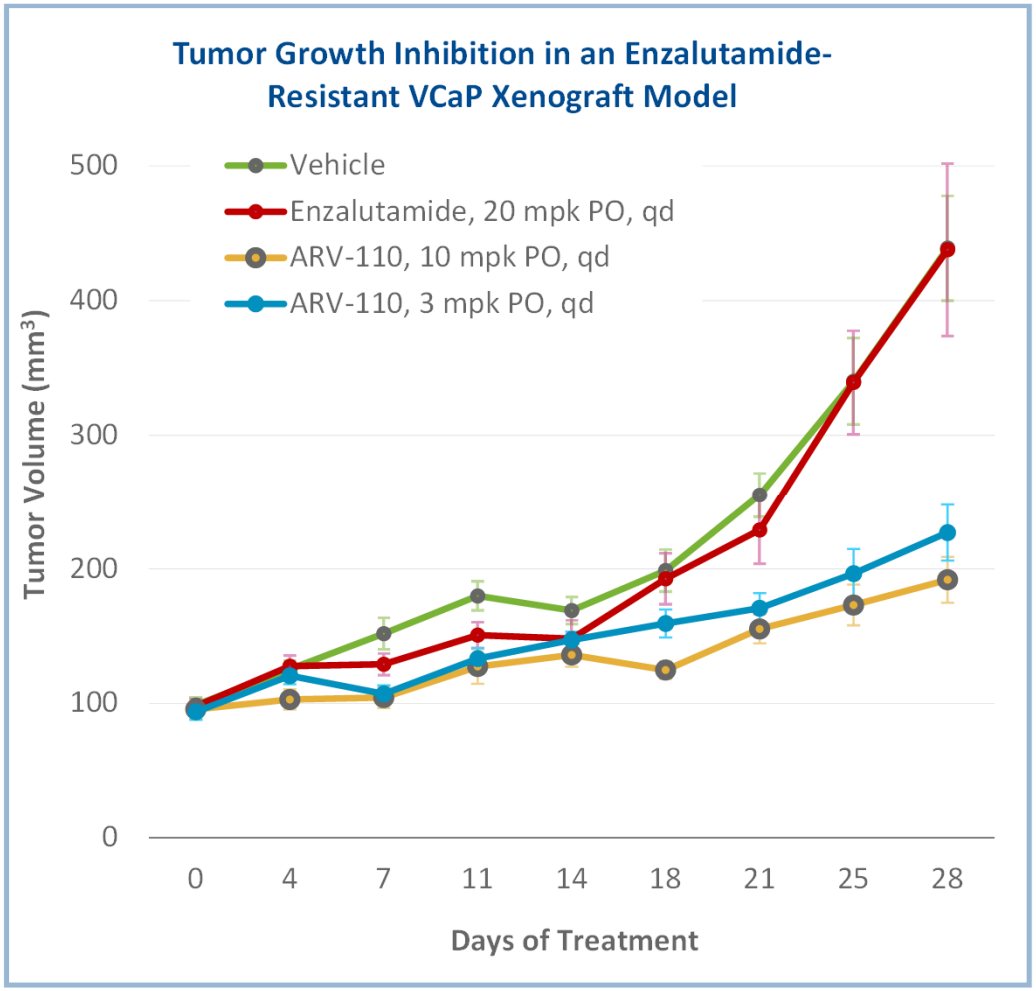
ARV-110 inhibits tumor growth in an *in vivo* model of acquired enzalutamide resistance

- *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



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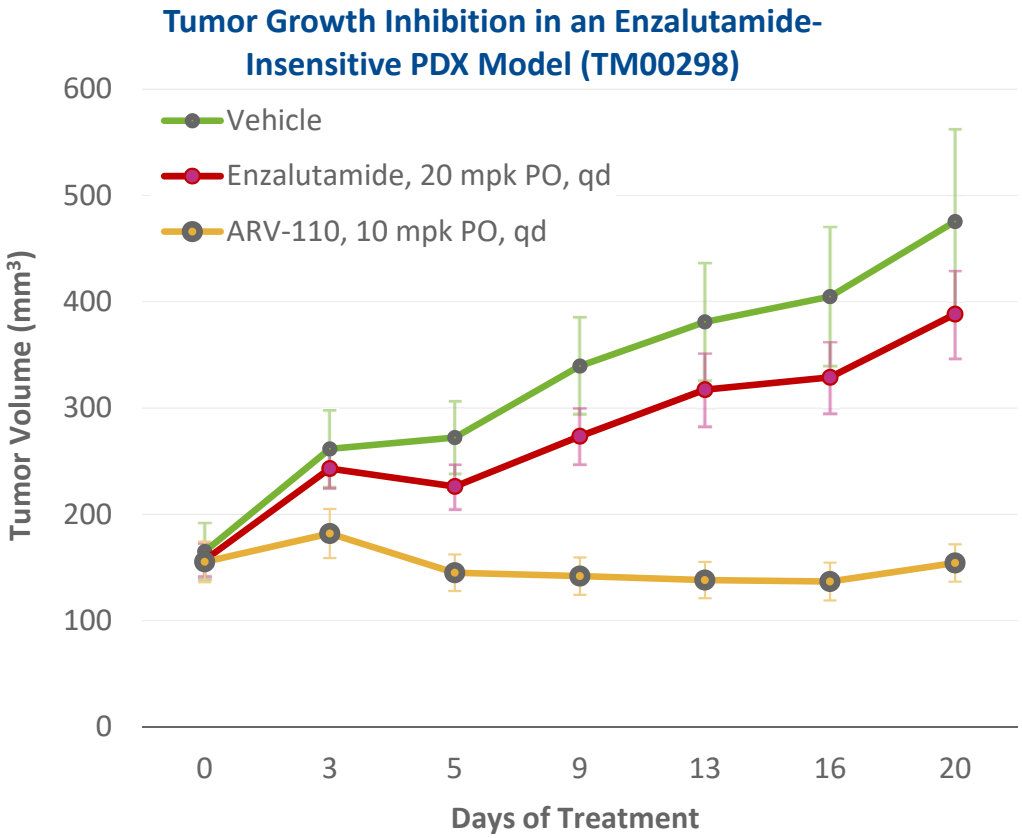
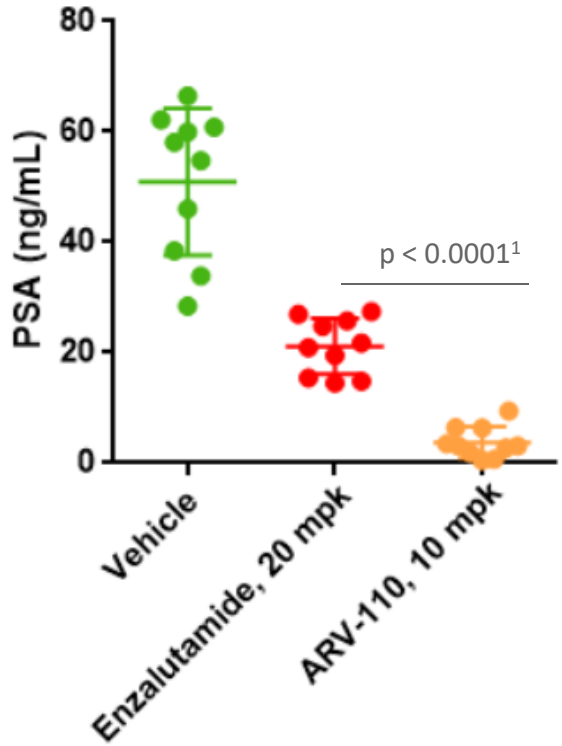
ARV-110 demonstrates efficacy and plasma PSA reduction in an enzalutamide-insensitive patient derived xenograft model

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



- **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

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ARV-110 pharmacokinetics are dose proportional, and exposure has reached the predicted efficacious range

Preclinical Efficacious Exposure Range

Dose (po, qd)	AUC_{0-24} (ng*hr/ml)	C_{max} (ng/ml)
1 mpk	3628	224
3 mpk	8106	507

Phase 1 Data

Dose po, qd	Day 1 AUC_{0-24} (ng*h/mL) Mean	Day 1 C_{max} (ng/ml) Mean	Day 15 AUC_{0-24} (ng*h/mL) Mean‡	Day 15 C_{max} (ng/ml) Mean
35 mg	160.5	11.1	1701	83
70 mg	300	19.6	2538	141
140 mg	865	54	**5023**	**353**

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

‡ Day 15 AUCs calculated using imputed 24 hour values

Initial clinical data as of 10/23/19

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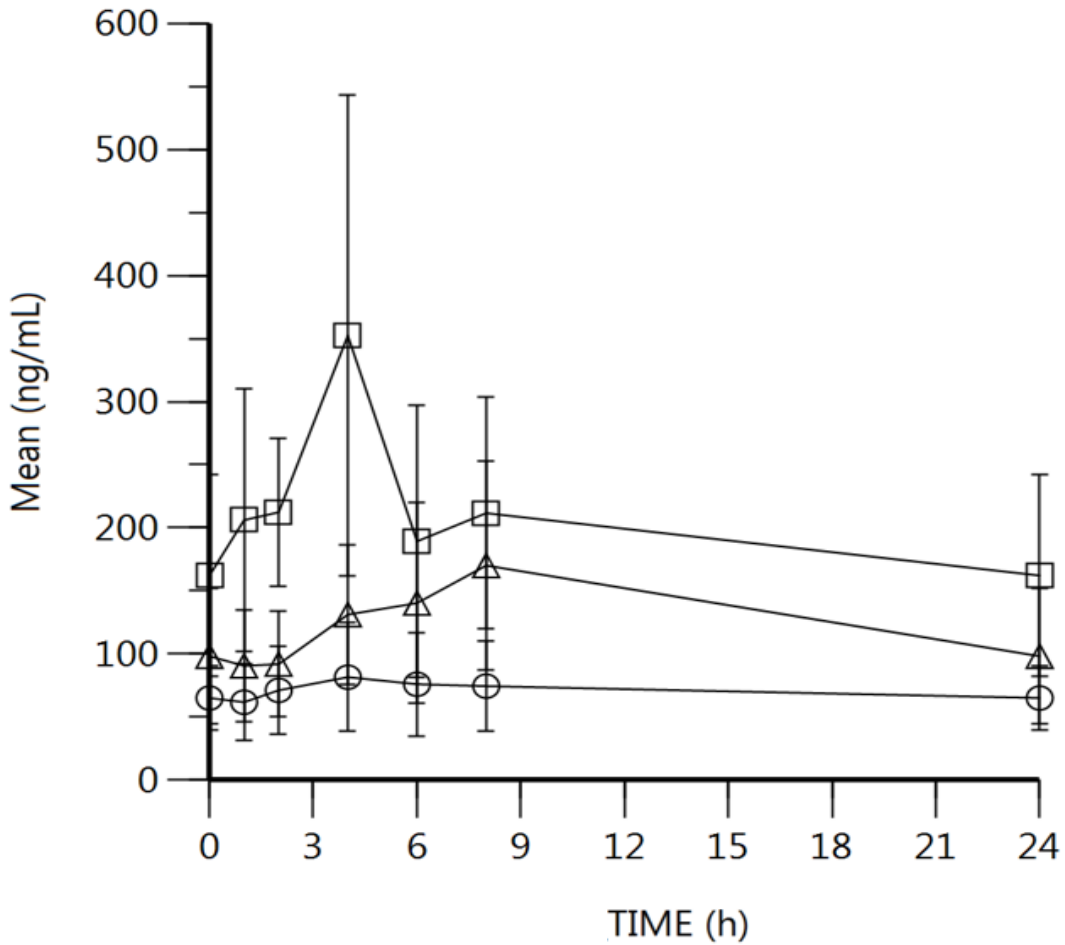
ARV-110 Phase 1 dose escalation: Day 15 pharmacokinetics



T_{max}† = 4 - 8 hours

$t_{1/2}$‡ = Estimated 3 - 7 days

Cohort 3 (140 mg)

Cohort 2 (70 mg)

Cohort 1 (35 mg)

24 hour values are imputed from time zero

† Time of to reach maximum concentration (C_{max})

‡ Effective half-life: rate of accumulation or elimination of a pharmacologic substance

Initial clinical data as of 10/23/19

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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

Dose Level[a]	N	Key Safety Findings
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[b]	3[c]	• No DLTs • No Grade 2/3/4 Treatment Related AEs
280 mg	3	• TBD

[a] Orally, once daily
[b] Data not yet 100% source data verified
[c] 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

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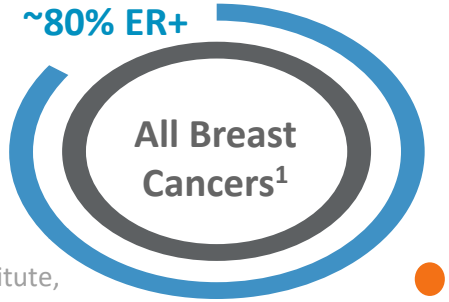
ARV-471 is Arvinas' ER degrader for patients with locally advanced or metastatic breast cancer

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® 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



1. American Cancer Society; 2 Malmgren, J.A., Breast Cancer Res Treat (2018) 167:579–590; 3 National Cancer Institute, Hormone Therapy for Breast Cancer; 4 Gutteridge et. Al., Breast Cancer Res Treat 2004;**88** suppl 1:S177

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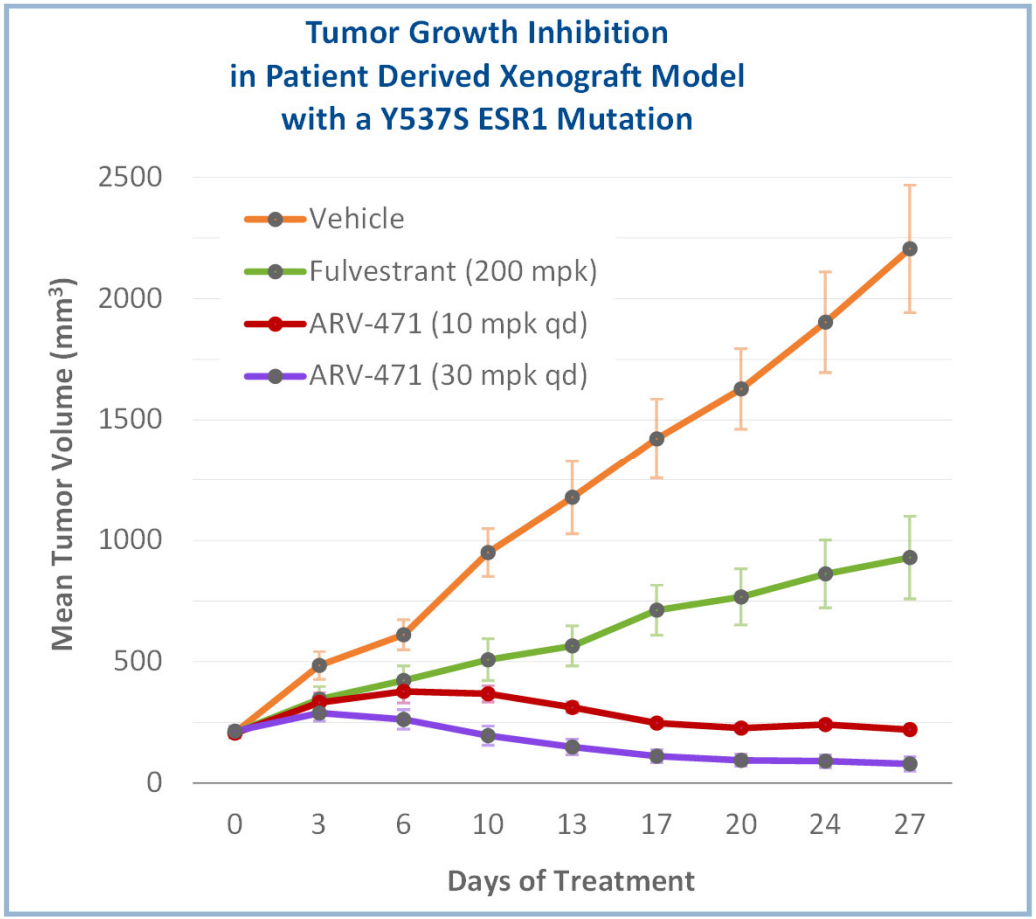
ARV-471: Superior tumor growth inhibition versus fulvestrant in a Y537S (ER gene mutation) PDX model

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

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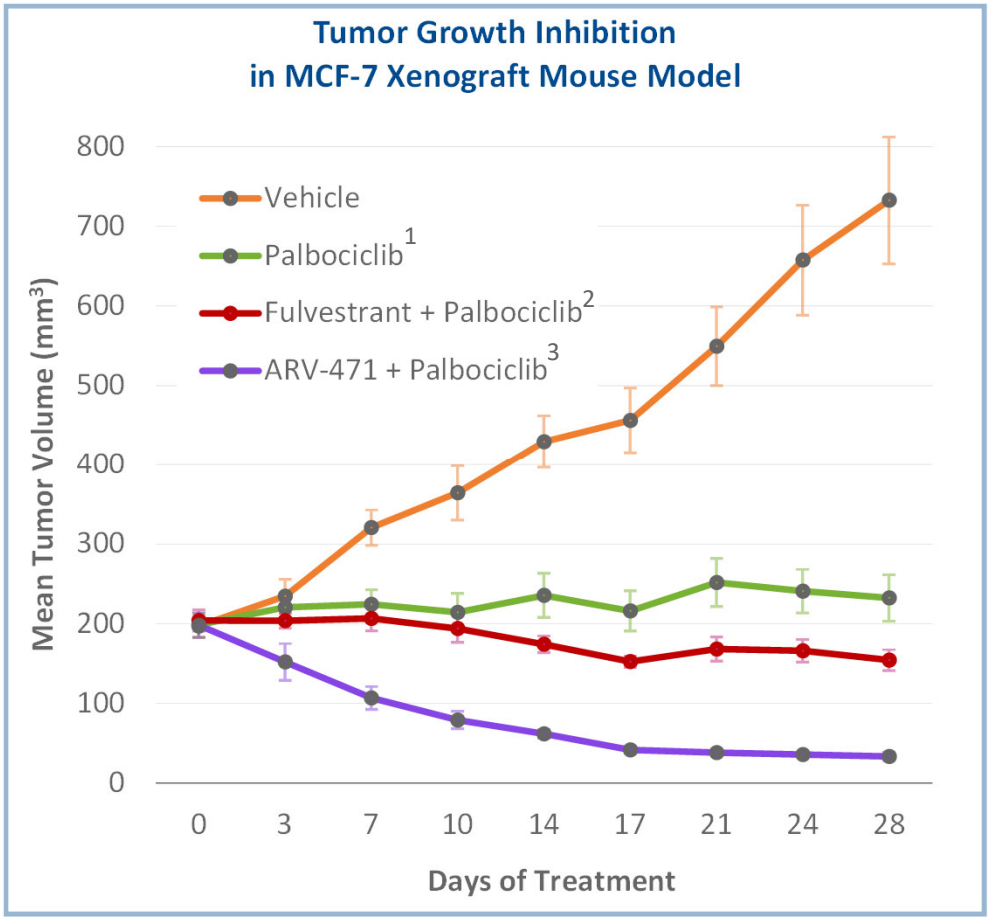
In combination with palbociclib, ARV-471 exhibits superior tumor shrinkage versus fulvestrant

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)



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

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In the first cohort of the ARV-471 Phase 1 dose escalation, exposure reached the predicted efficacious range

Preclinical Efficacious Exposure Range

Dose (po, qd)	Mean AUC_{0-24} (ng*hr/ml)	Mean C_{max} (ng/ml)
3 mpk	658	84
10 mpk	2538	312
30 mpk	5717	962

Phase 1 Data

Dose po, qd	Day 1 AUC_{TAU} (ng*h/mL) Mean	Day 1 C_{max} (ng/ml) Mean	Day 15 AUC_{TAU} (ng*h/mL) Mean[1]	Day 15 C_{max} (ng/ml) Mean
30 mg	1690	109	**4100**	**224**

- 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

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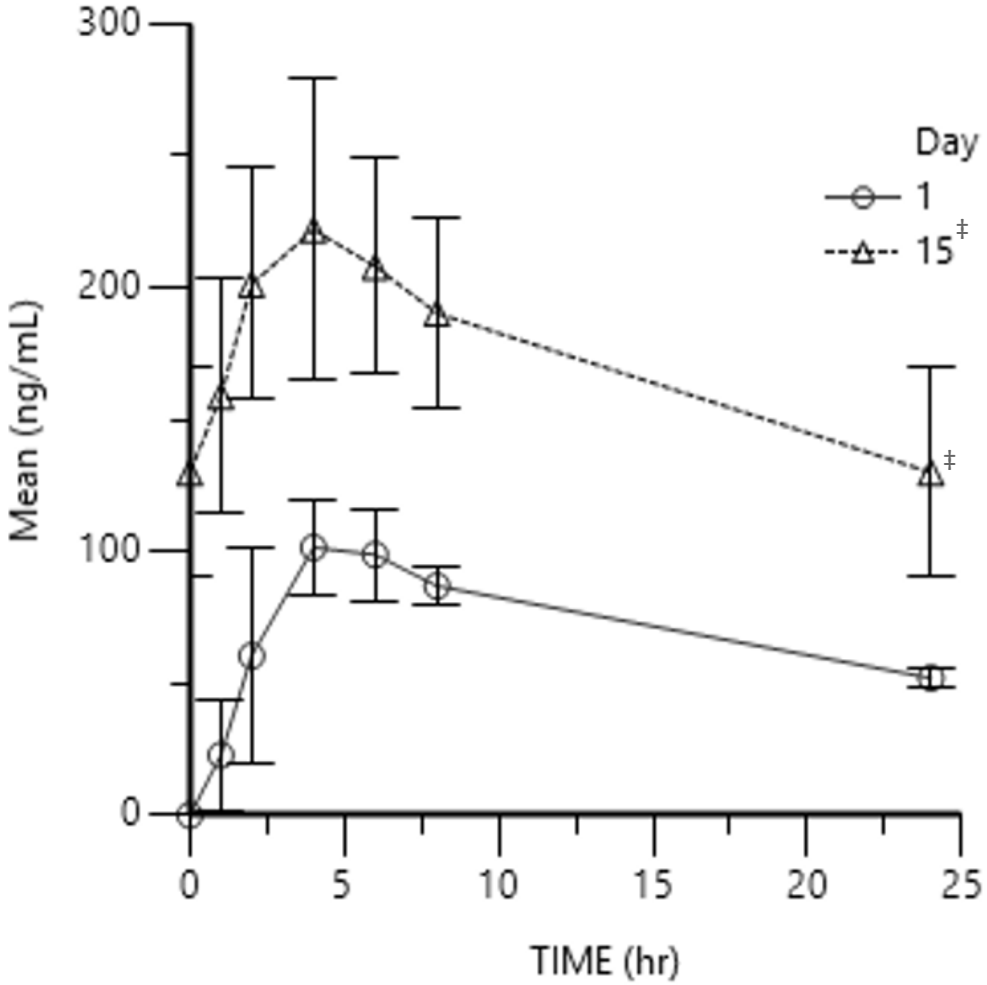
Pharmacokinetics of the first cohort of the ARV-471 Phase 1 dose escalation



T_{max} = 4 hours

$t_{1/2}$ = estimated to be ~24 hours

‡ Day 15 24 hour value is imputed from time zero

Initial clinical data as of 10/23/19

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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

Dose Level+	N	Key Safety Findings
30 mg‡	3	• No DLTs • No Treatment Related AEs
60 mg	3	• TBD

- Trial update planned in 2nd half 2020

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

Initial clinical data as of 10/23/19

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Neurology Research Programs

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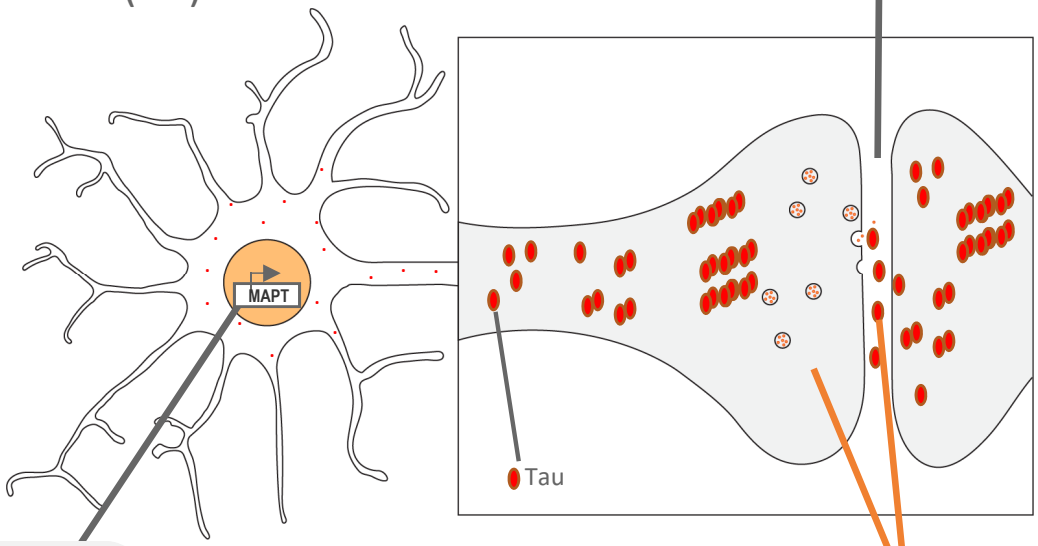
Mutant-specific PROTAC® degraders may reduce intra- and extracellular tau, creating a strong opportunity in neuroscience

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

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



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

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

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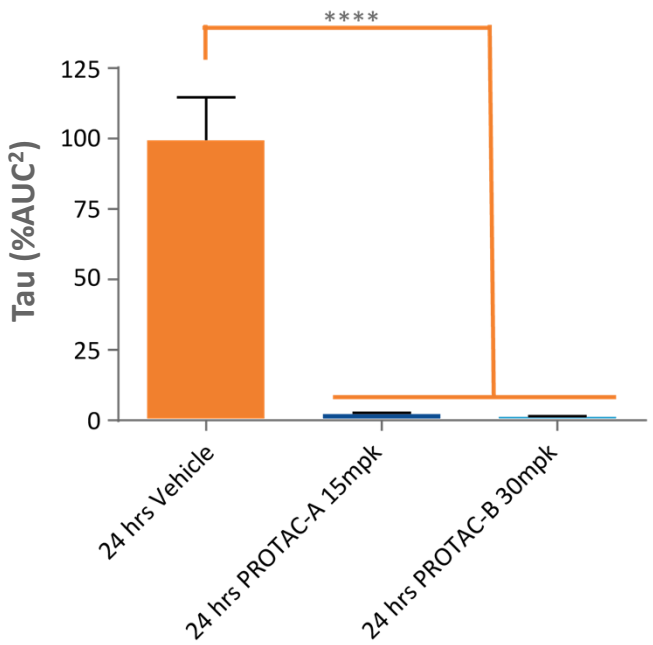
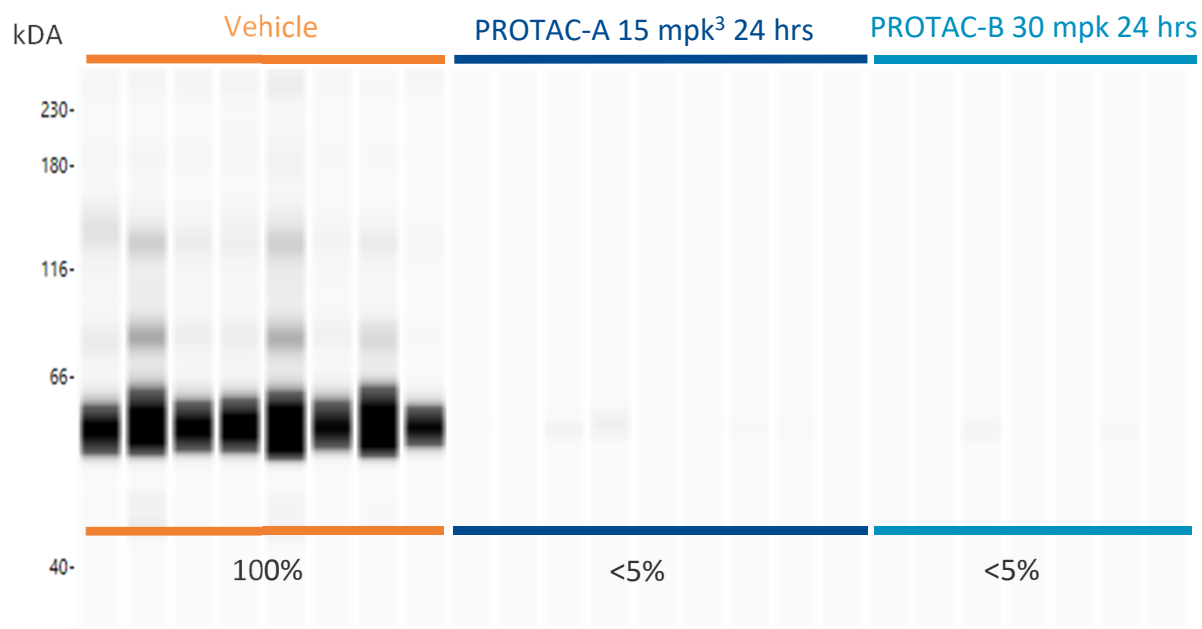
In vivo, tau-directed PROTAC® degraders eliminate >95% of pathologic tau following parenteral administration

Pathologic tau in Tg2508[1] mouse cortex



Tau Detection (protein capillary electrophoresis)



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 mpk, milligrams per kilogram
**** Tukey's multiple comparisons test P < 0.0001

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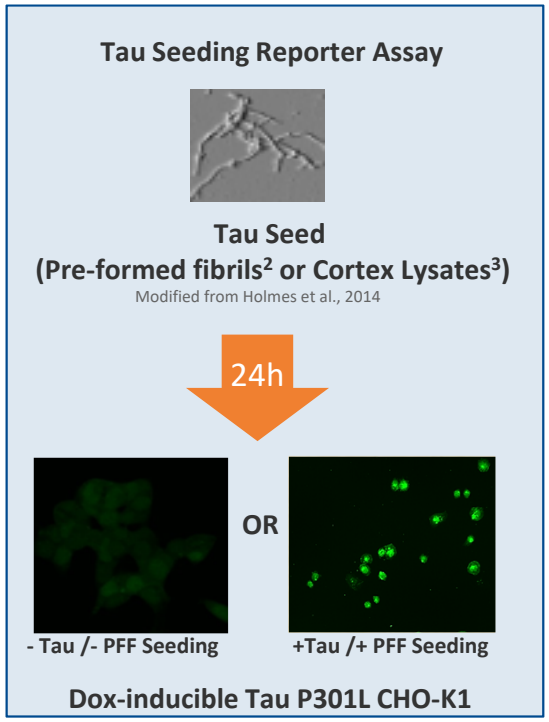
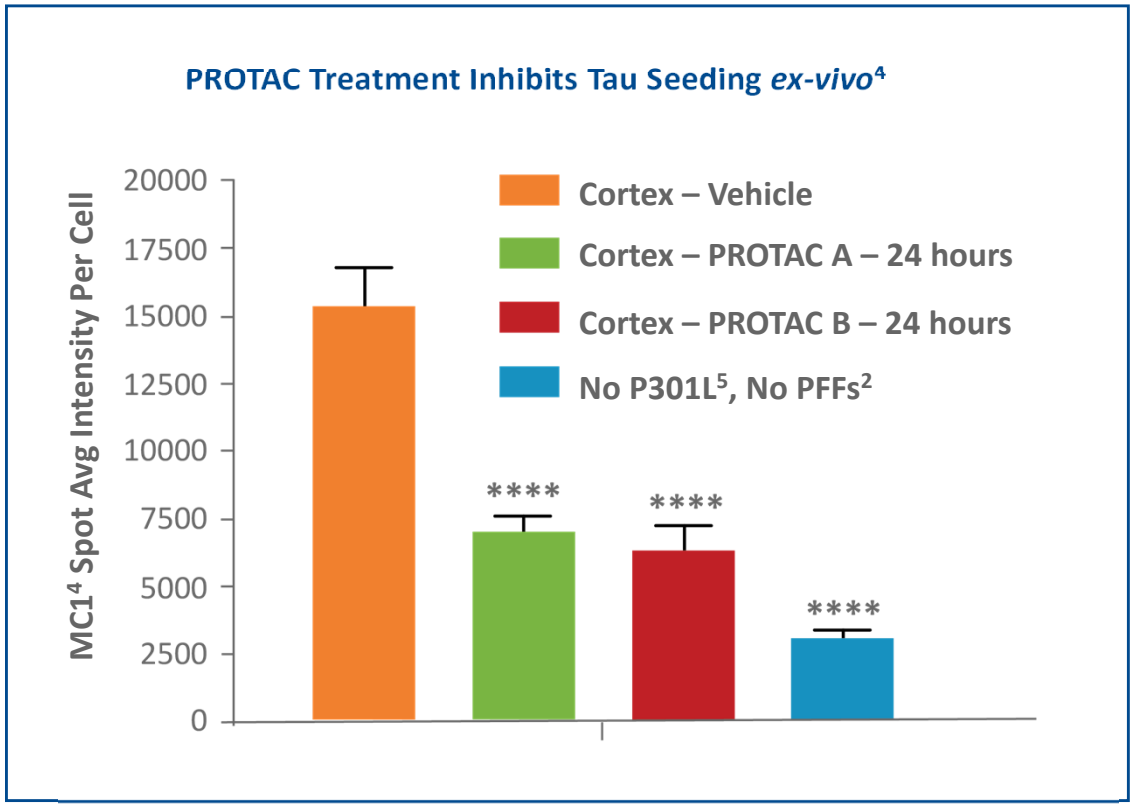
Tau-directed PROTAC® protein degraders inhibit *ex-vivo* tau seeding





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)

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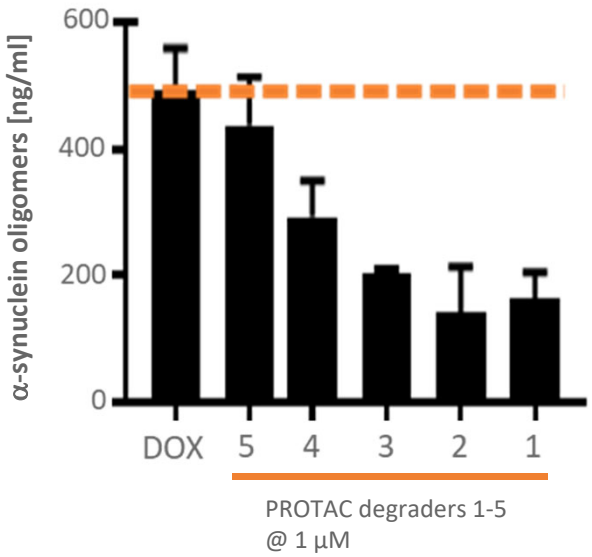
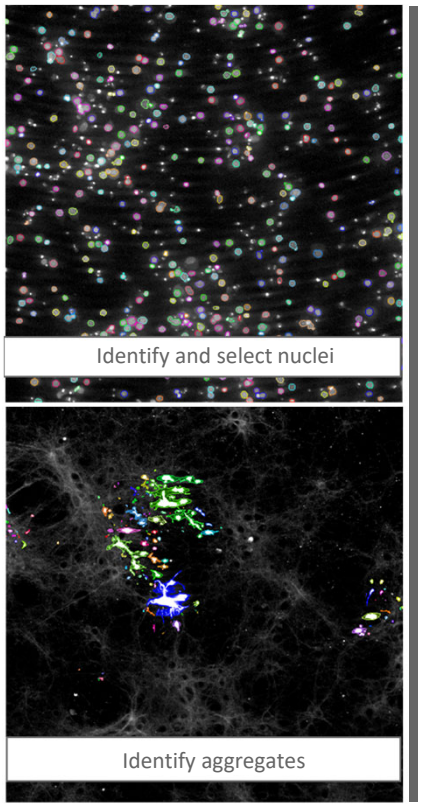
Oligomer-specific PROTAC® molecules human α-synuclein aggregates in primary rat neurons

PROTAC molecules degrade oligomeric α-synuclein species

PROTAC degraders were identified that specifically remove oligomeric α-synuclein

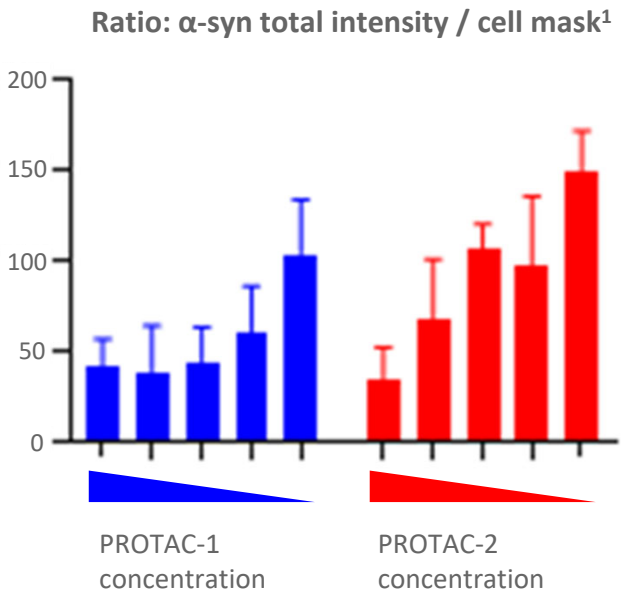


PROTAC-1 and PROTAC-2 degrade α-synuclein aggregates in primary rat neurons expressing human α-synuclein



Neuronal α-synuclein +PFF induction assays[1]

Intensity and area features of α-syuclein aggregates calculated



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).

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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)[1]
α-synuclein	Synuclein mutations, e.g., duplication/ triplication (~4K)[2]	Multiple systems atrophy (~50K)[3]	GBA PD risk allele carriers (~500K)	Parkinson's (~1M)[4]

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
2 Kowal. Movement Disorders 2013, 28: 311-319; Nishioka. Intechopen 2011
3 NINDS; https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Multiple-System-Atrophy
4 Parkinson's Foundation: http://parkinson.org/Understanding-Parkinsons/Causes-and-Statistics/Statistics

ARVINAS

Corporate Overview

ARVINAS

Financial snapshot

$298.2 Million[1]
Pro forma cash, cash equivalents, and marketable securities
as of 9/30/19

Guidance[1]
Expect pro forma cash, cash equivalents, and marketable securities to fund planned operations into 2022

39.0 Million[1]
Pro forma common shares outstanding
as of 9/30/19

Analyst Coverage[2]
BMO, Cantor, Citibank, Evercore, Goldman Sachs, Piper Jaffray, Wedbush

1 Financials, guidance, and shares outstanding include proceeds from the public offering of common shares announced 11/6/19 (includes shoe exercise).
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.

ARVINAS

Strategic partnerships are validating our PROTAC® protein degrader technology

Genentech
A Member of the Roche Group

September 2015

(expanded in November 2017)

- Target discovery deal
- Upfront, development, and commercial milestone aggregate payments in excess of $650M
- Tiered royalties

Pfizer

December 2017

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

BAYER

Oerthbio

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

ARVINAS

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

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Thank you!

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Appendix

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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 approaches (siRNA, gene therapy) lack many of the drug-like properties of traditional small molecules

ARVINAS

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

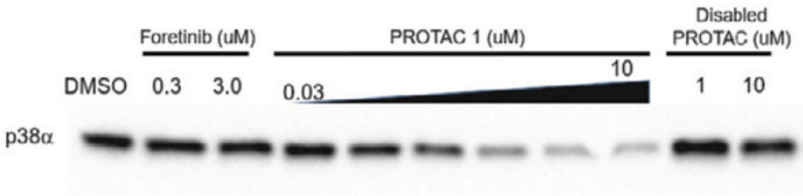
ARVINAS

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 DC_{50} of 210 nM[1]
  - Based on experience, optimization of potency better than 210 nM is likely

A PROTAC degrader based on foretinib has a nanomolar DC_{50} despite a 11 μM binding affinity

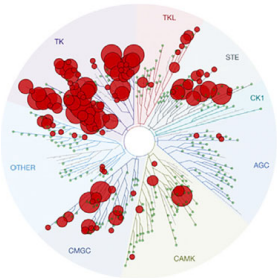


DC_{50} = 210 nM[1]

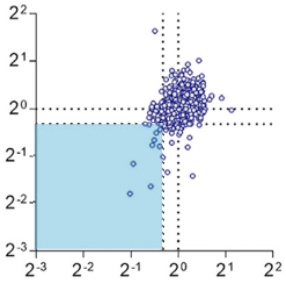
When developed into PROTAC degraders, promiscuous ligands can become selective degraders

- 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*)

Binds 133 Kinases



Degrades <10 Proteins



Source: Bondeson et al., 2018, Cell Chemical Biology
1 DC_{50} = Half-maximal degradation concentration

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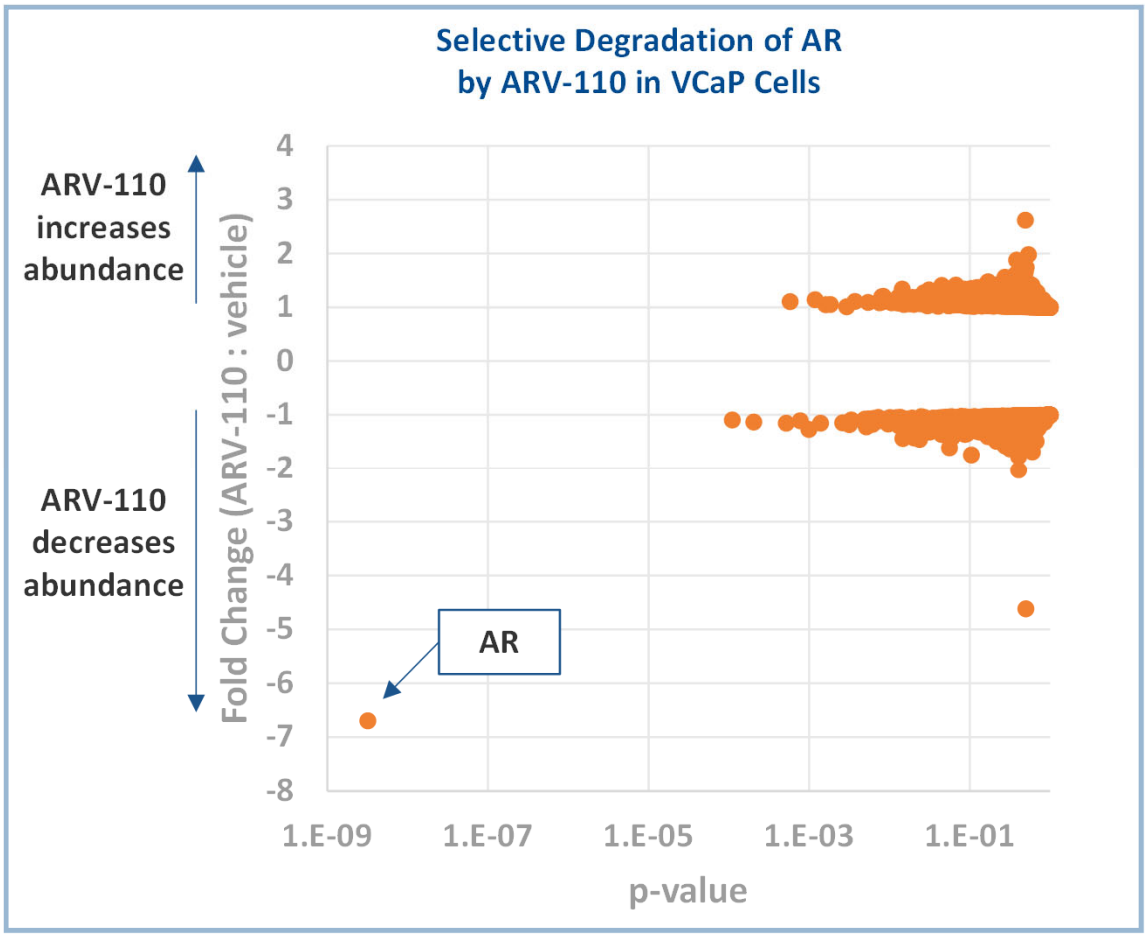
ARV-110 selectively degrades AR

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_{max}[2]
  - p-value: $3x10^{-9}$



1 VCaP, Vertebral Cancer of the Prostate
2 D_{max}, maximal degradation

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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

ARVINAS

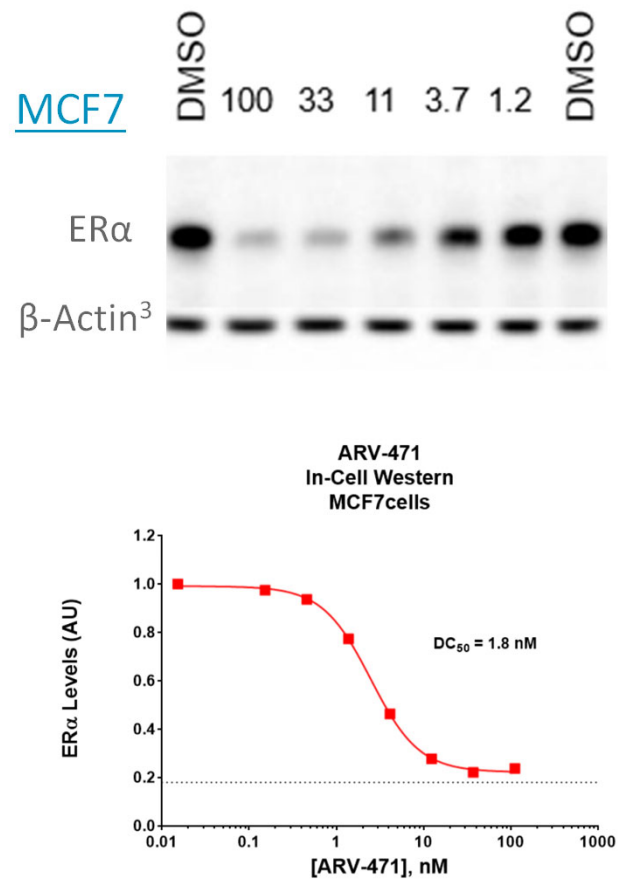
Our estrogen receptor-targeting PROTAC® degrader: ARV-471

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[1]
- **DC_{50} = 1.8 nM** in MCF7 cells[2]



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

ARVINAS

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

PROTAC	Species	Dose (mg/kg)	[Plasma 1h] (ng/ml)	[Brain 1h] (ng/g)	B/P ratio
1	mouse	10	309	227	0.8
2	mouse	10	843	3920	4.7
3	mouse	10	285	1425	5.0

- Over a 4-hour time course, PROTAC degraders are more durable in the brain than in plasma

ARVINAS

Arvinas / Bayer collaboration

Oerthbio

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

BAYER

ARVINAS

Seasoned leadership with expertise in advancing novel technologies

Leadership Team

John G. Houston, PhD
President & CEO

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

Ian Taylor, PhD
Chief Scientific Officer

John A. Grosso, PhD
VP Chemistry, Mfg. & Controls

Marcia Dougan Moore, MPH
VP Development Operations

Kimberly Wehger
VP Information Technology

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.

Leslie Norwalk, Esq.

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

Laurie Smaldone Alsup, M.D.

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