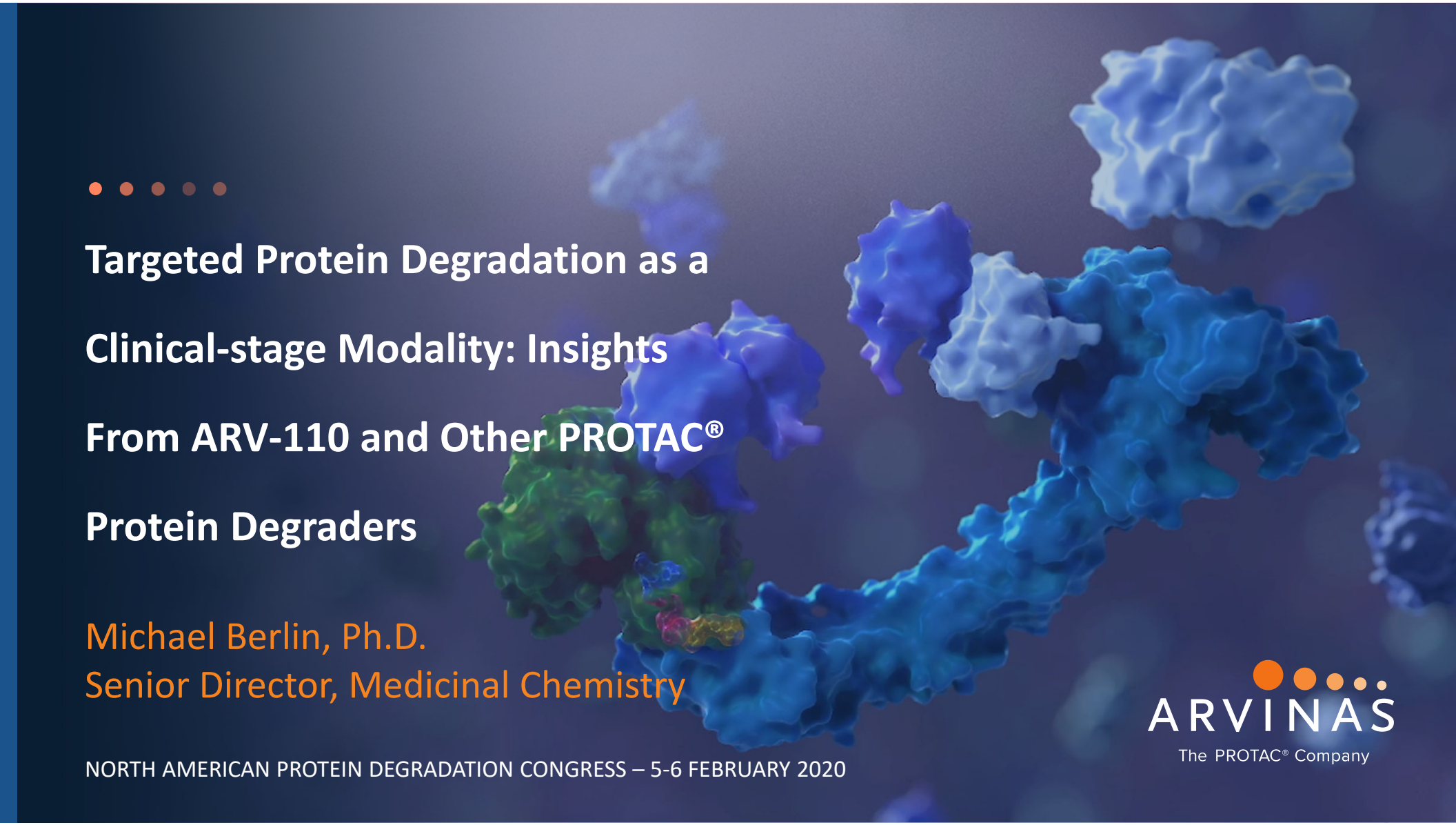
Targeted Protein Degradation as a Clinical-stage Modality: Insights From ARV-110 and Other PROTAC® Protein Degraders



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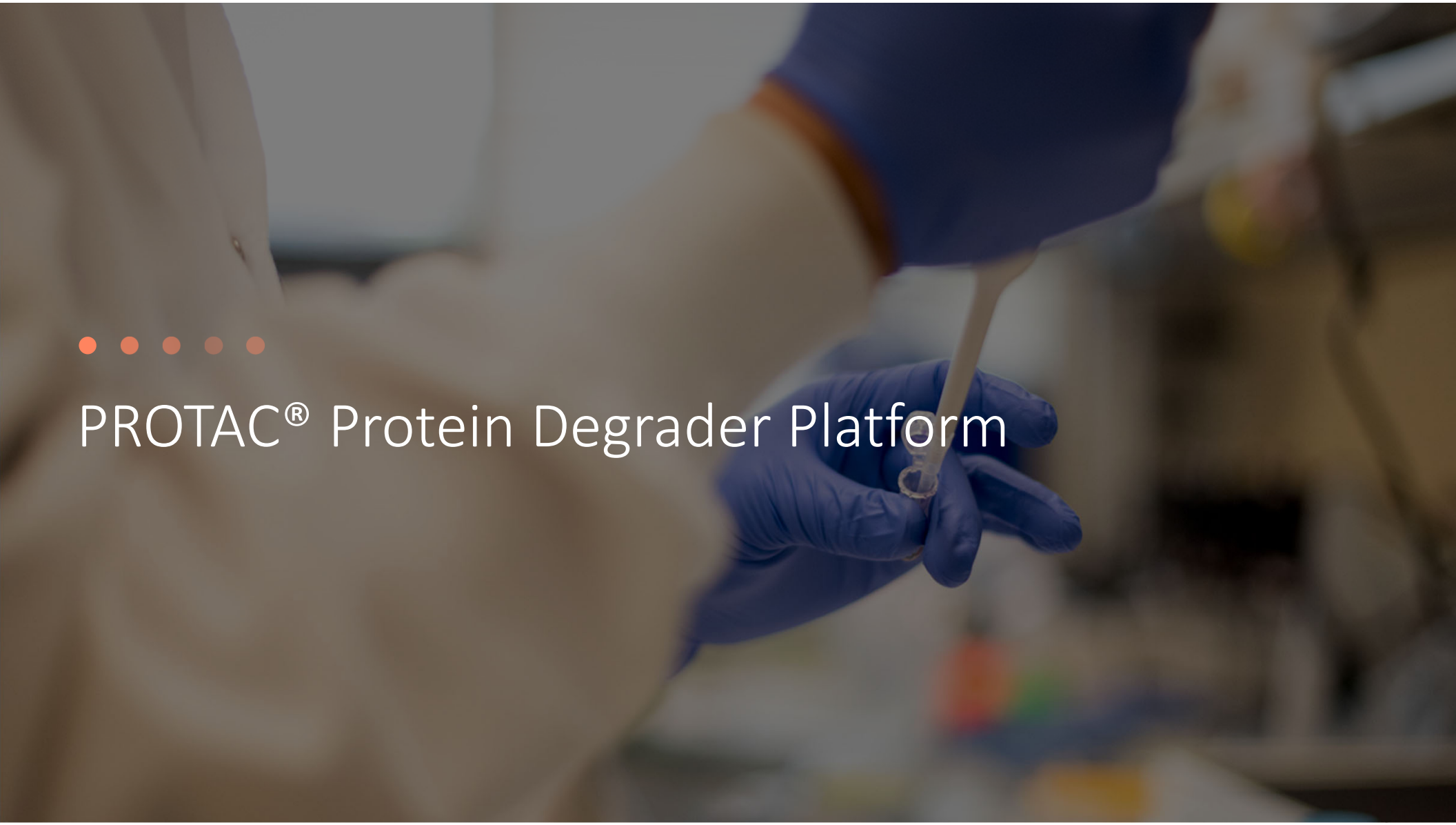
NORTH AMERICAN PROTEIN DEGRADATION CONGRESS – 5-6 FEBRUARY 2020

ARVINAS
The PROTAC® Company

Safe harbor and forward-looking statements

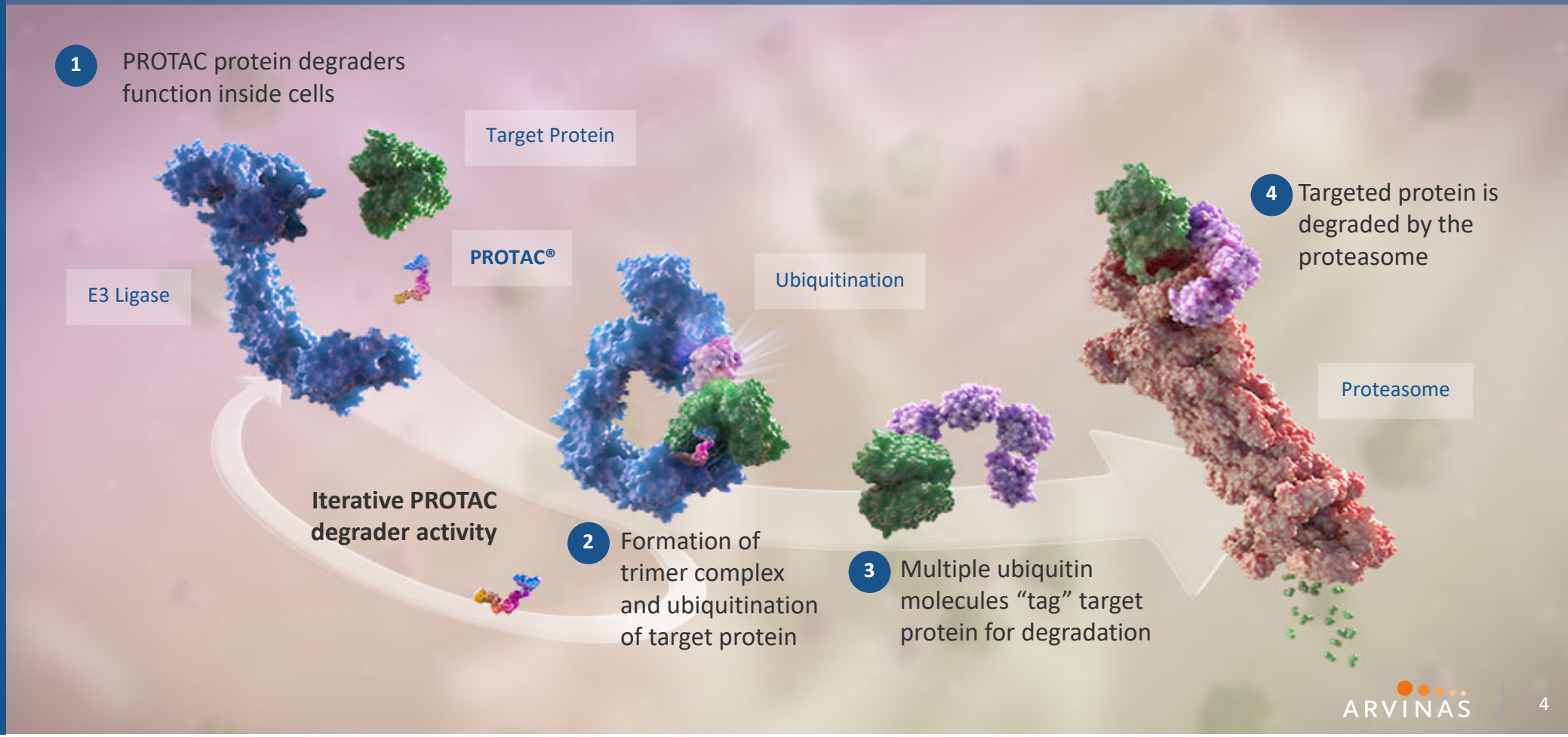
This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the development and regulatory status of our product candidates, such as statements with respect 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, 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 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.



PROTAC® Protein Degrader Platform

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



Leading the way in targeted protein degradation therapeutics

Track Record of Success

- Targets validating the PROTAC® mechanism and platform
- 95% success rate at degrading proteins of interest
- Two clinical-stage programs with initial safety/PK data

Strategic Target Selection

- Recalcitrant targets where PROTAC technology shows differential biology
- Targets requiring exquisite selectivity
- Pipeline balances benefit and risk

Creating Degraders, Including Against "Undruggable" Targets

- Premier ligand discovery technologies
- Database of E3 ligase attributes to guide library expansion
- Predictive dynamic models and structural biology

Turning Degraders into Drugs

- Brain-penetrant and orally bioavailable degraders
- Mechanism and proteomic analytics
- State-of-the-art, disease-specific degradation assays
- Working "Beyond the Rule of 5" since our founding

High potential PROTAC® pipeline, focused on cancer and neurology

1 FTLD-tau, frontotemporal lobar degeneration-tau. 2 PSP, progressive supranuclear palsy. 3 MSA, multiple systems atrophy

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Clinical-stage Oncology Programs

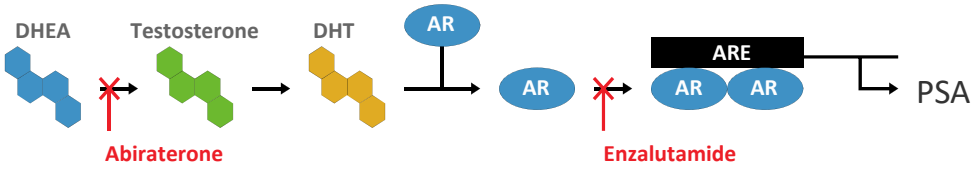
ARV-110 is Arvinas' AR degrader for men with metastatic castration-resistant prostate cancer (mCRPC)

Androgen Receptor (AR) Activity Drives Prostate Cancer

- Prostate cancer is the second leading cause of cancer death in men in the US[1]
- 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**
- **Phase 1 dose escalation data expected 2Q20**

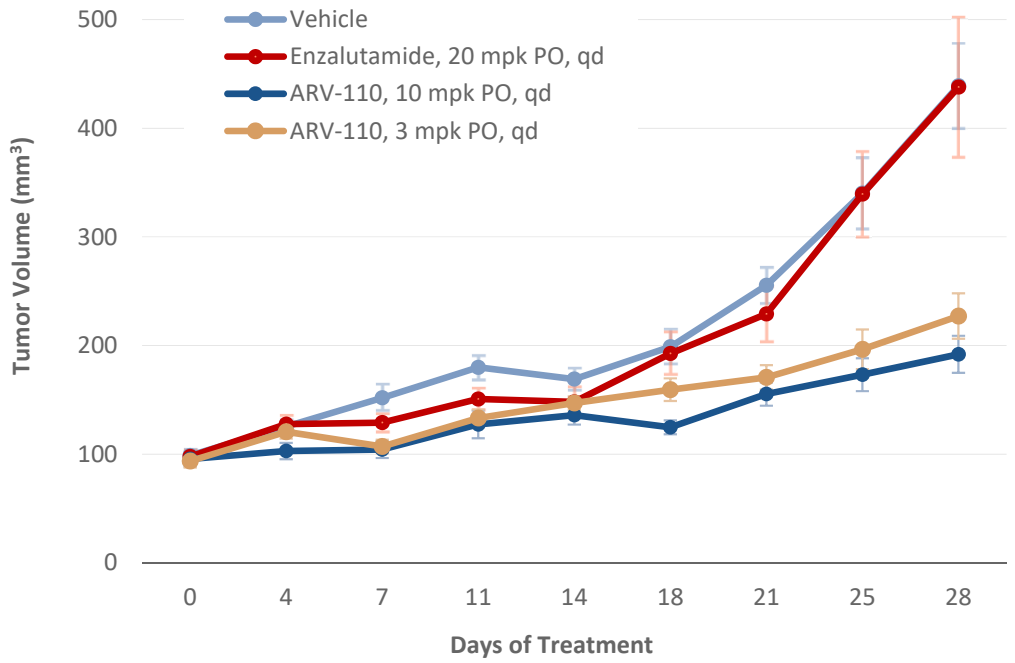


1 According to the American Cancer Society; https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html

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

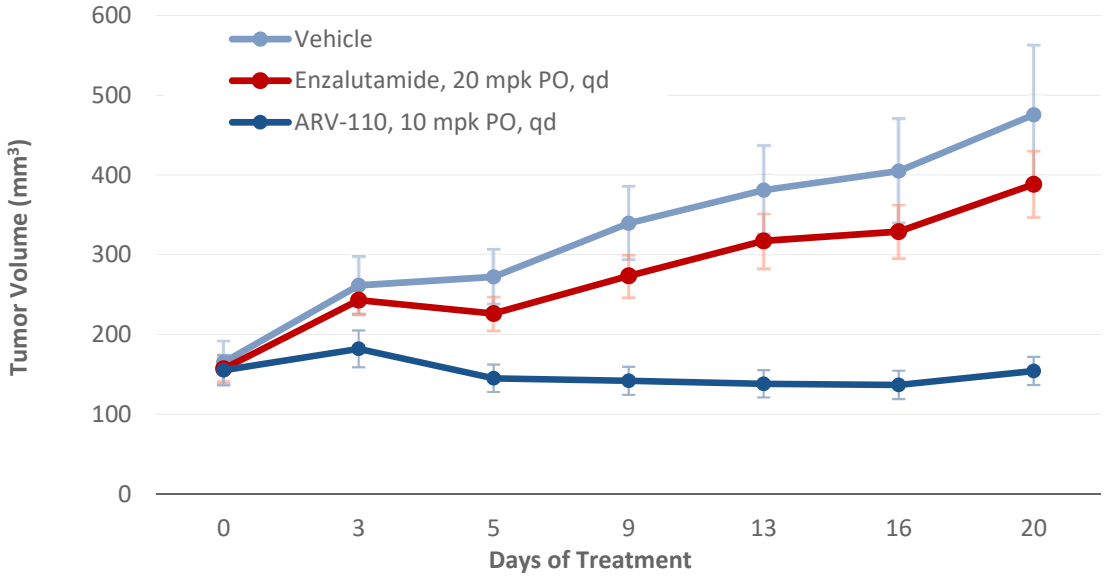
- *In vivo* mouse xenograft model of **acquired enzalutamide resistance** developed at Arvinas
- In this model, VCaP tumors acquired resistance to enzalutamide after being continuously propagated in castrated, enzalutamide treated mice for ~3 years
- Daily and orally delivered ARV-110 significantly inhibited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

Tumor Growth Inhibition in an Enzalutamide-Resistant VCaP Xenograft Model

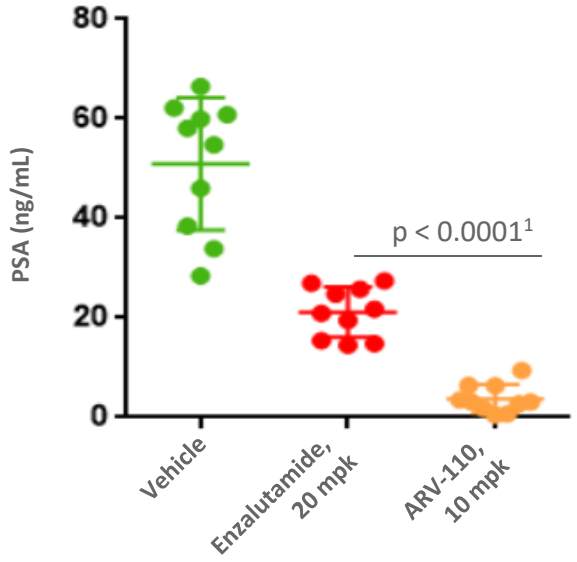


ARV-110 demonstrates efficacy and plasma PSA reduction in an enzalutamide-insensitive patient derived xenograft model

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



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

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

Initial clinical data as of 10/23/19

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 entered the preclinical efficacious range associated with tumor growth inhibition

‡ Day 15 AUCs calculated using imputed 24 hour values

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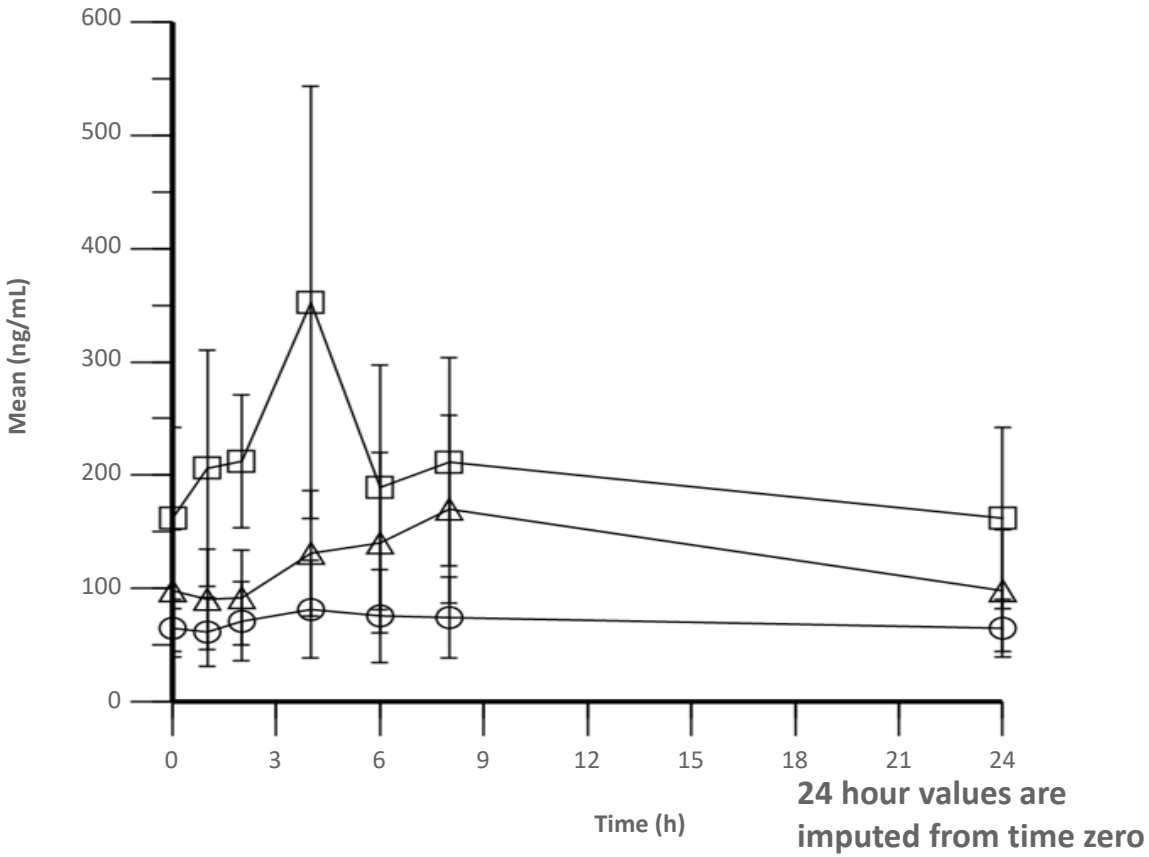
ARV-110 Phase 1 dose escalation: Day 15 pharmacokinetics

Initial clinical data as of 10/23/19



24 hour values are imputed from time zero

T_{max}† = 4 - 8 hours

$t_{1/2}$‡ = Estimated 3 - 7 days

- Cohort 3 (140 mg)
- Cohort 2 (70 mg)
- Cohort 1 (35 mg)

Overall, favorable safety profile observed in the first 3 cohorts

In October, disclosed that the fourth cohort would be 280 mg p.o. q.d.

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

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

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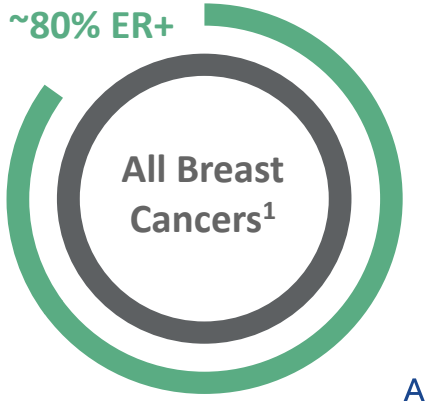
ARV-471 is Arvinas' ER degrader for patients with locally advanced or metastatic breast cancer

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. However, 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**
- **Next data from the Phase 1 dose escalation planned for 2H20**



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

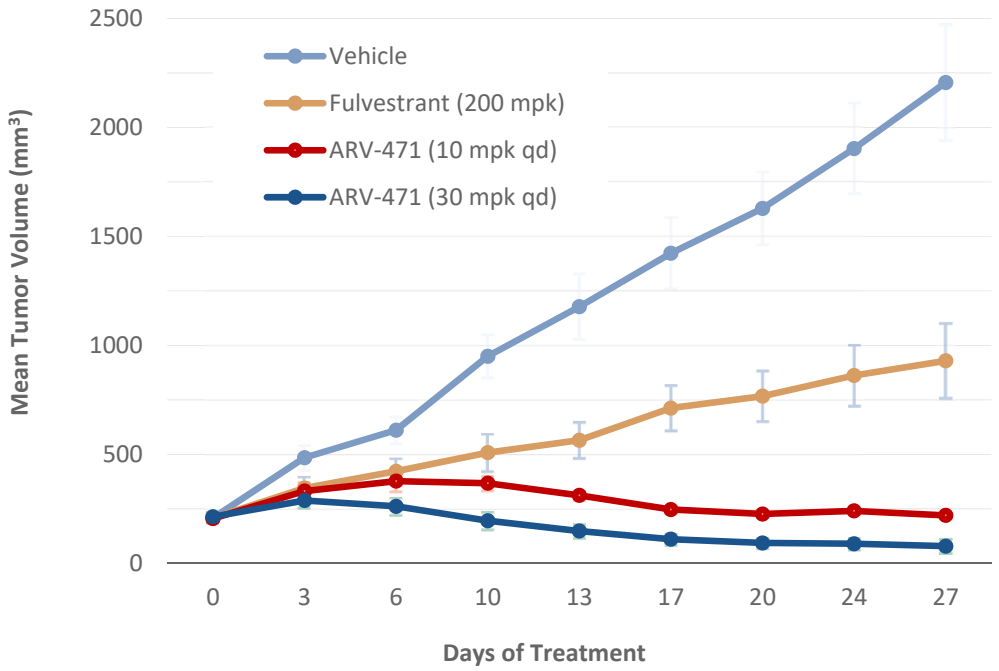
ARVINAS

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

Tumor Growth Inhibition in Patient Derived Xenograft Model with a Y537S ESR1 Mutation



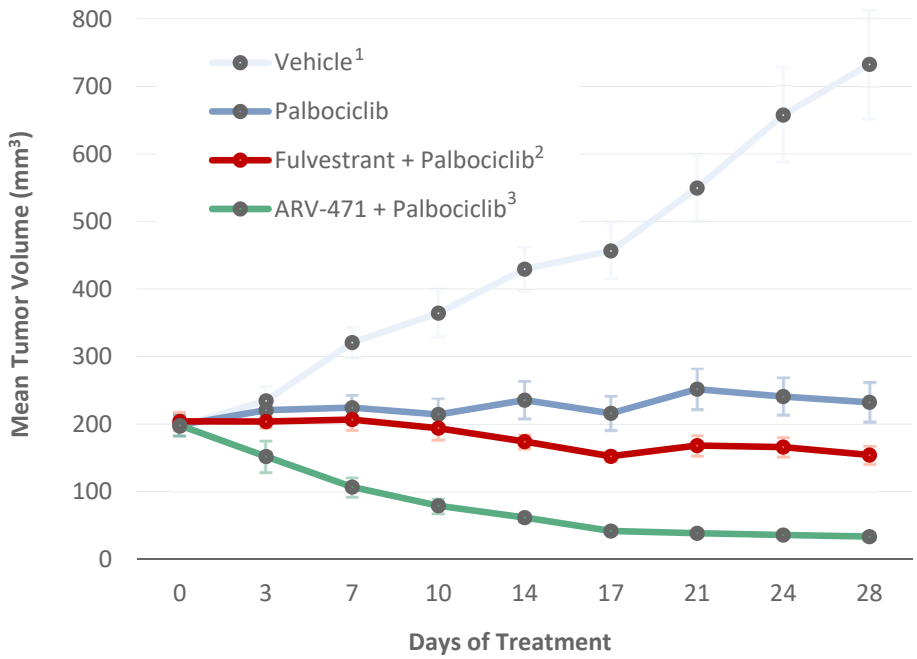
1 Fulvestrant schedule: 2x weekly x2 / q7dx2

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

ARV-471 *In Vivo* Preclinical Development

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

Tumor Growth Inhibition in MCF-7 Xenograft Mouse Model



1 Palbociclib arm: 60 mpk po qd; 94% TGI.
2 Fulvestrant + Palbociclib arm: Fulvestrant 200 mpk sc biwx 2, qwx 3 + palbociclib 60 mpk po qd; 108% TGI
3 ARV-471 + Palbociclib arm: ARV-471 30 mpk po qd + palbociclib 60 mpk po qd; 131% TGI

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

Initial clinical data as of 10/23/19

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

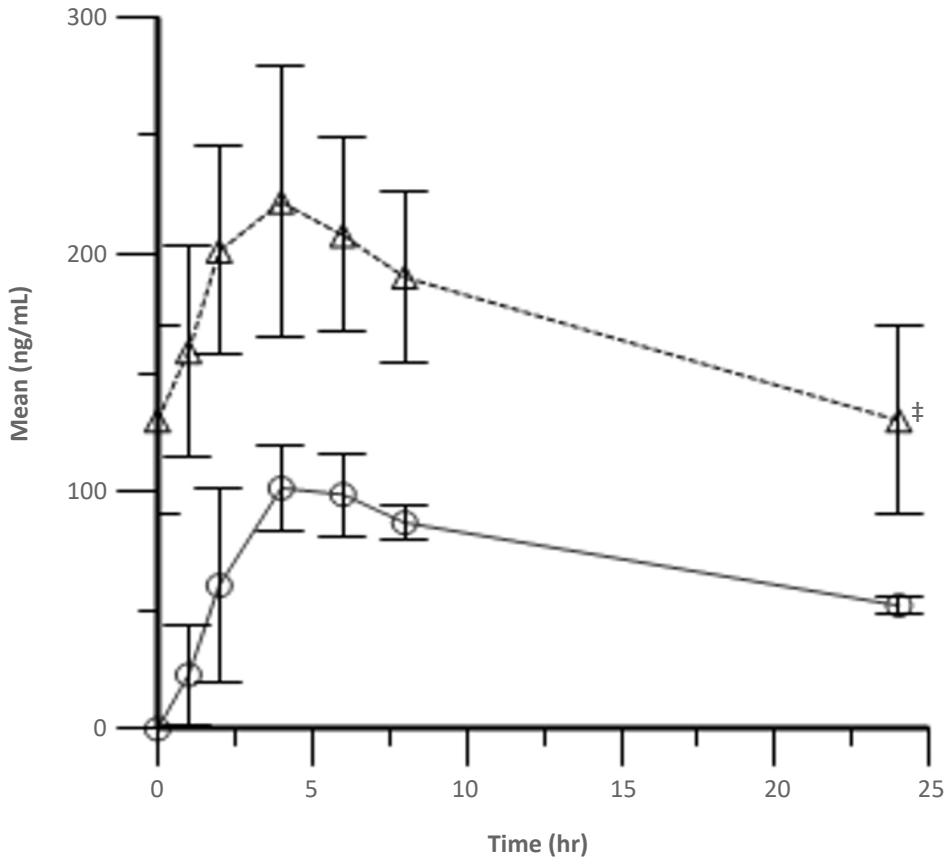
Dose po, qd	Day 1 AUC_{0-24} (ng*h/mL) Mean	Day 1 C_{max} (ng/ml) Mean	Day 15 AUC_{0-24} (ng*h/mL) Mean[1]	Day 15 C_{max} (ng/ml) Mean
30 mg	1690	109	4100	224

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

1 Day 15 AUCs calculated using imputed 24 hour values

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

Initial clinical data as of 10/23/19



‡Day 15 24 hour value is imputed from time zero

T_{max} = 4 hours

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

Day 1

Day 15‡

No treatment-related AEs or DLTs were observed in the first cohort of ARV-471

In October, disclosed that the second cohort would be at 60 mg p.o. q.d.

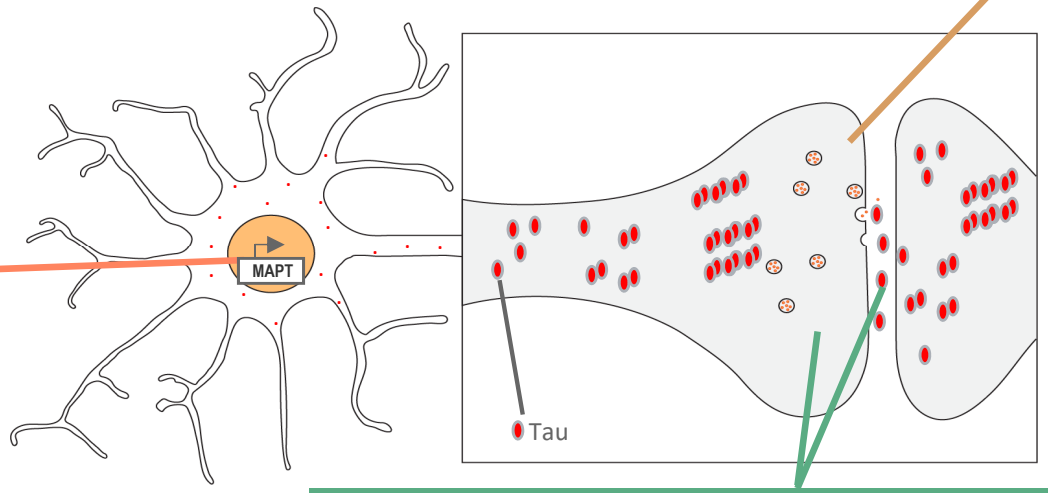
Neurology Research Programs

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

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

ASO

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



Ab

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

PROTAC *Potential*

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

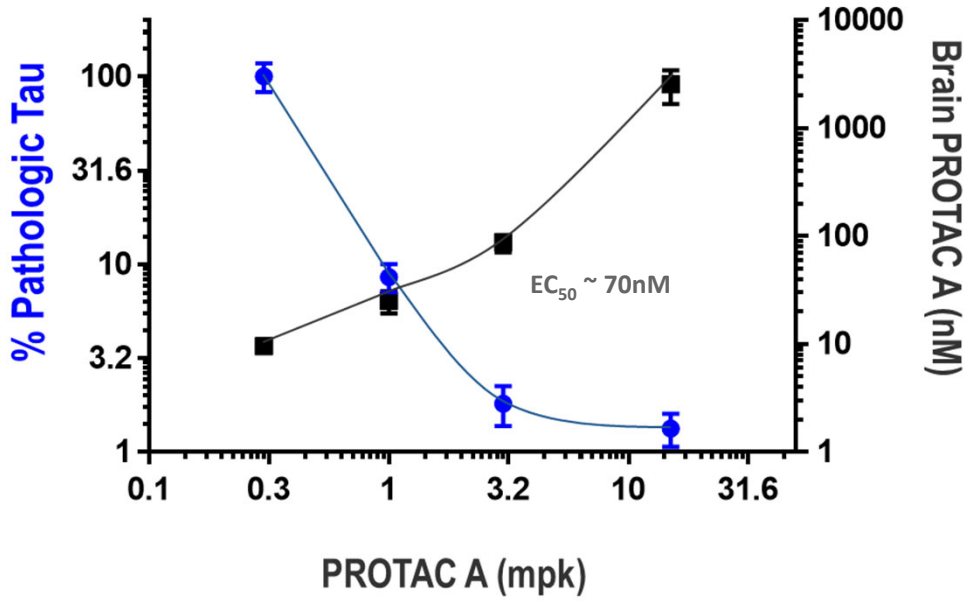
ASO, antisense oligonucleotide; Ab, antibody; CSF, cerebrospinal fluid; BBB, blood-brain barrier

tau PROTAC® Degraders Dose-Dependently Reduce tau (PK/PD) in the Brain of Tauopathy Mice Following Parenteral Administration

Future Efforts

- Aged animal studies are being conducted to assess the ability of the proteasome to degrade pathologic tau
  - may be compromised in neurodegeneration / age
- Building relationships with histopathology and CSF / plasma biomarkers ttau, ptau and NFL in time-course studies

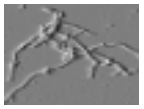
Tg2508[1] Tau Degradation[2] / Exposure Relationship



1 Tg2508 is a murine pathologic tau model (P301L). 2 In hippocampus, 24 h post-parenteral administration.

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

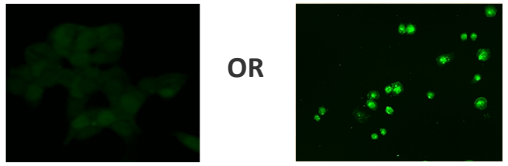
Tau Seeding Reporter Assay



Tau Seed
(Pre-formed fibrils[2] or Cortex Lysates[3])

Modified from Holmes et al., 2014

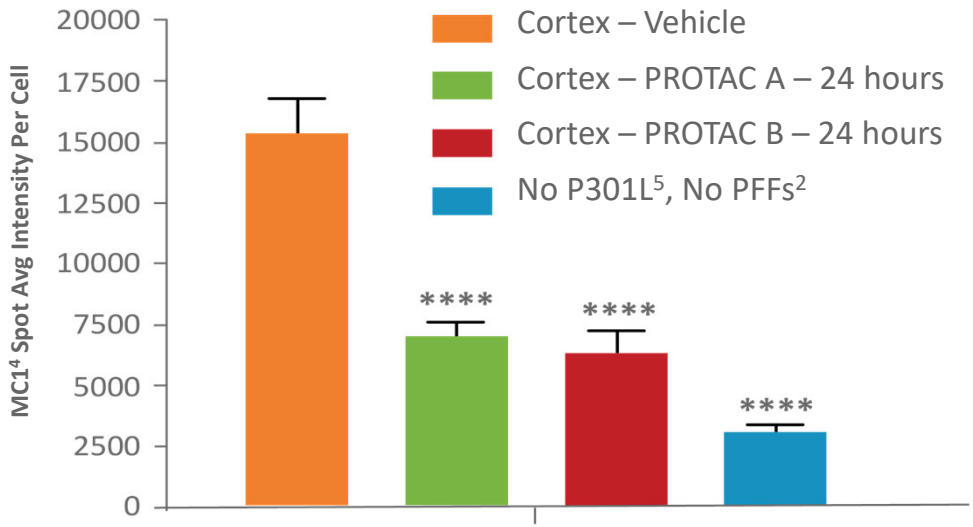
24h



- Tau /- PFF Seeding **+Tau /+ PFF Seeding**

Dox-inducible Tau P301L CHO-K1[1]

PROTAC Treatment Inhibits Tau Seeding *ex-vivo*[4]



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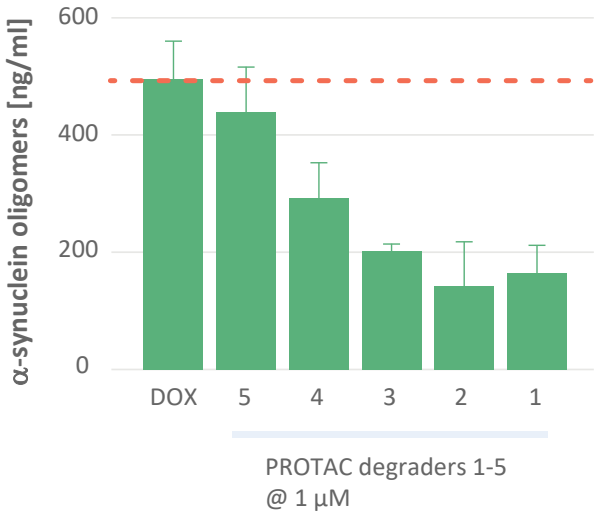
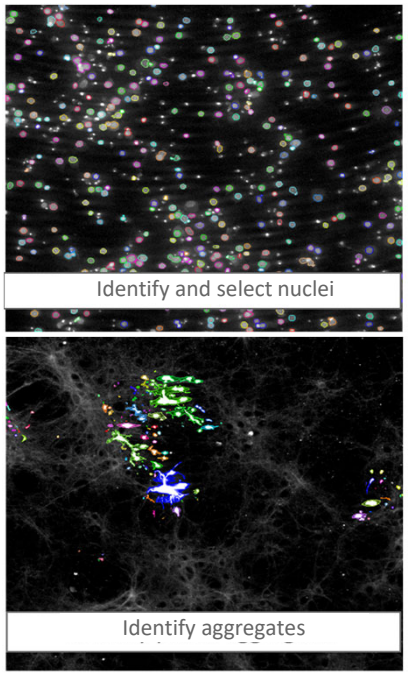
Oligomer-specific PROTAC® molecules degrade human α-synuclein aggregates in primary rat neurons

PROTAC molecules degrade oligomeric α-synuclein species

PROTAC degraders were identified that specifically remove oligomeric α-synuclein

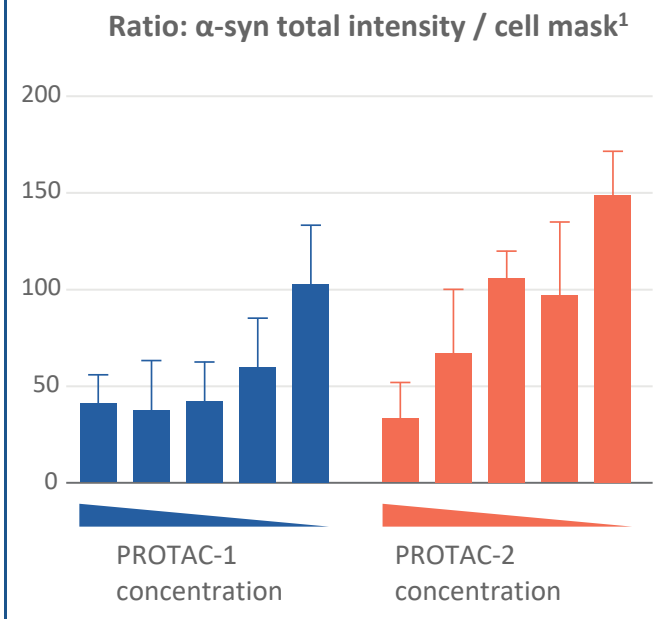


PROTAC-1 and PROTAC-2 degrade α-synuclein aggregates in primary rat neurons expressing human α-synuclein



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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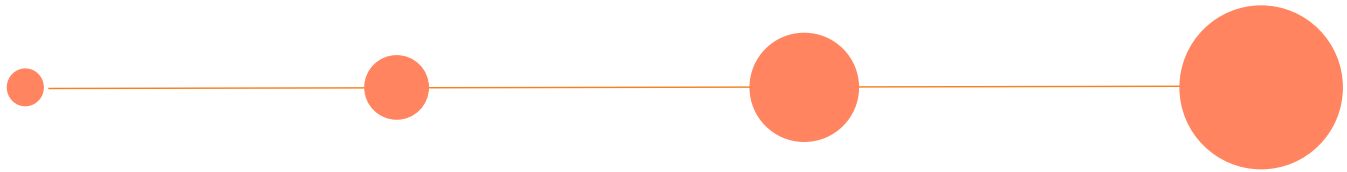
Arvinas' approach in neuroscience reduces risk while proving the concept of protein degradation

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

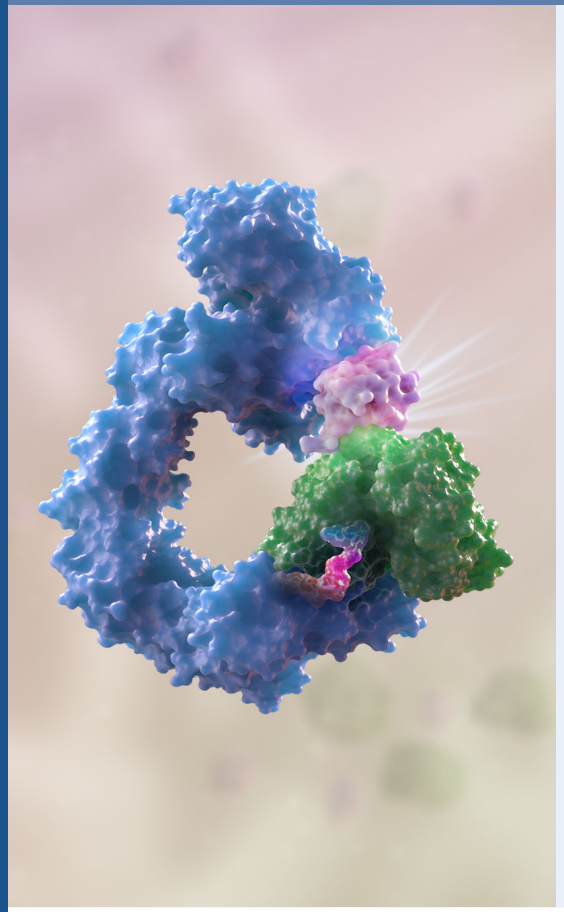
1 Alzheimer's Association; "2018 Alzheimer's Disease Facts and Figures." Alzheimer's and Dementia; V.14; No.3; 2018; p36

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 is making substantial investments in platform expansion and its pipeline, including in undisclosed pipeline targets



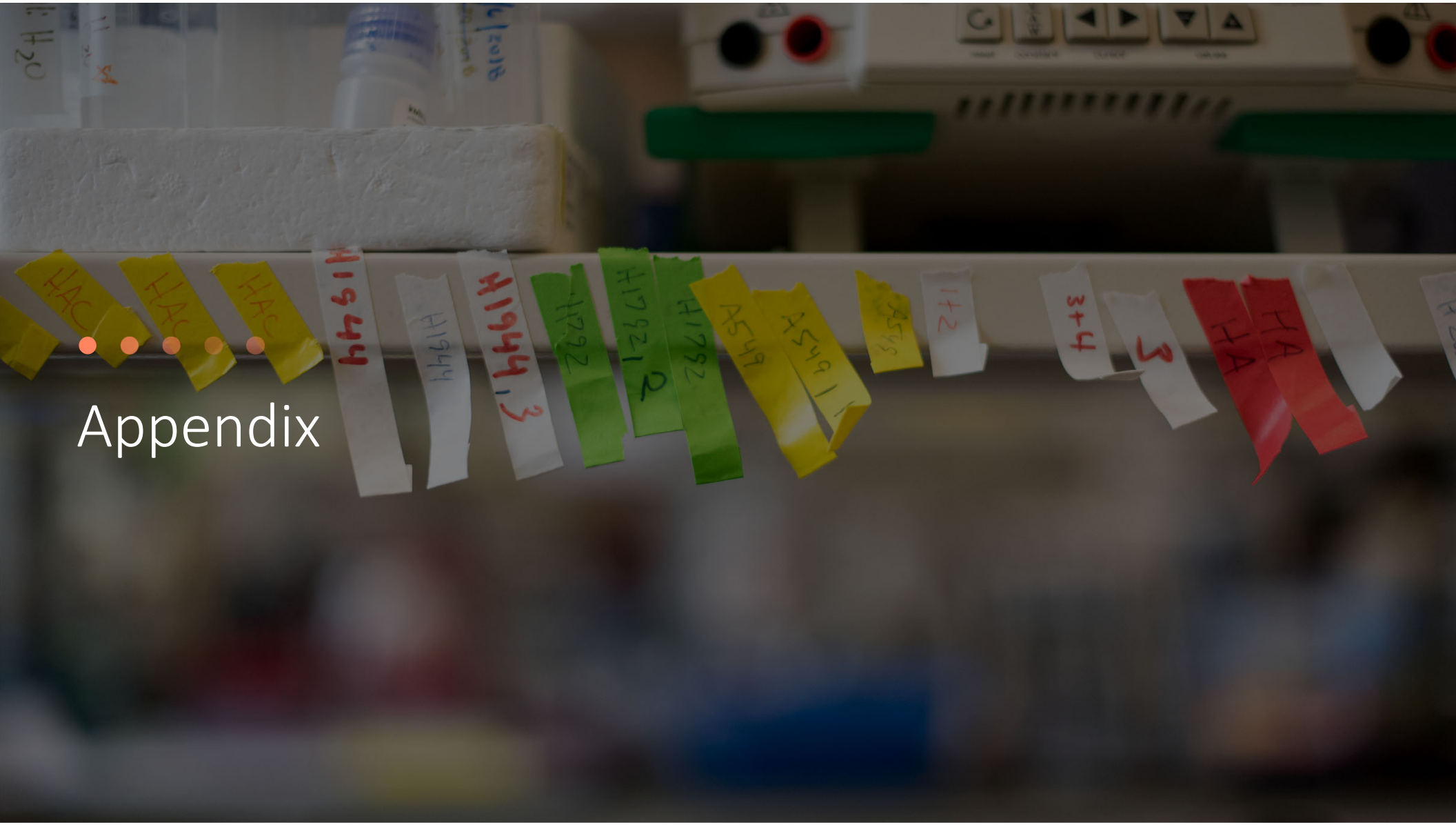
Platform Investment and Expansion

- 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

Thank You!


HAC
HAC
HAC
H1N1 pdm
H1N1
H1N1
H1792
H1792
H1792
A549
A549
A549
1+2
3+4
3
HA
HA

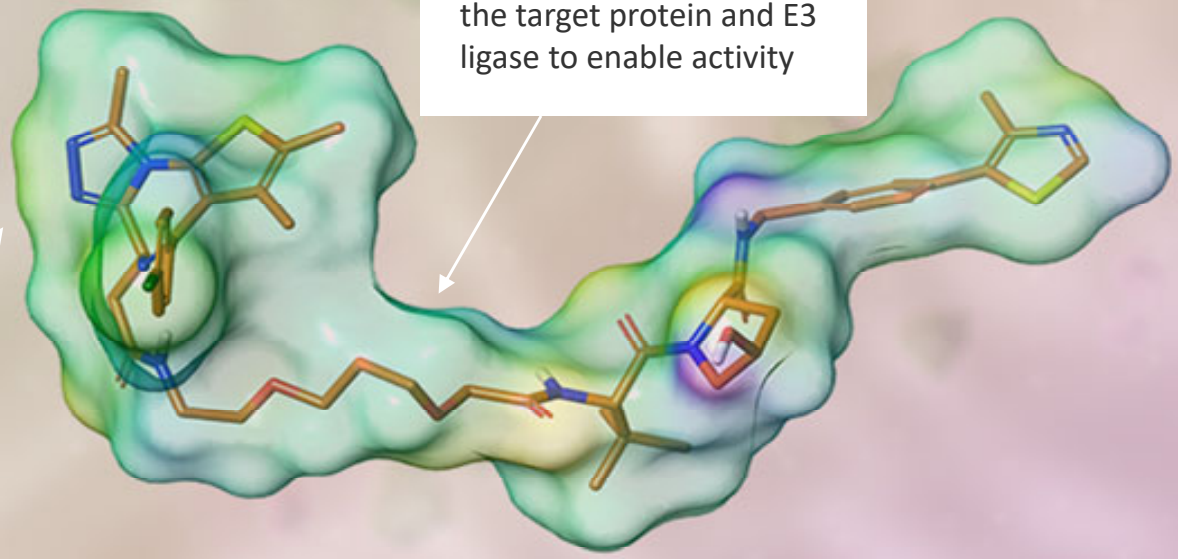
Appendix

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

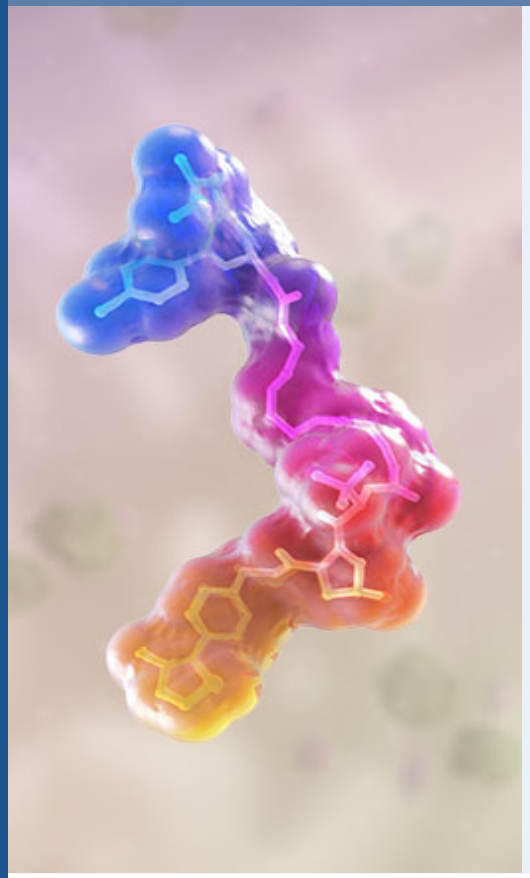
Protein ligand domain ("warhead") targets a specific protein



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

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



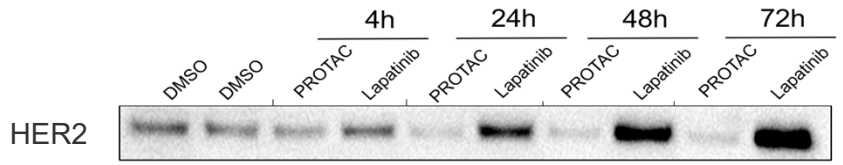
PROTAC protein degraders have distinct advantages over both small molecule inhibitors and gene-based medicines	PROTAC Protein Degraders	Small Molecule Inhibitors	Gene-Based Medicines
Eliminate pathogenic proteins	✓	✗	
Target scaffolding function	✓	✗	
Potential to treat “undruggable” proteins	✓	✗	
Iterative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

Potential advantages of PROTAC® protein degraders over inhibitors

Overcome Target Protein Overexpression

PROTAC degraders can disable this common tumor resistance mechanism

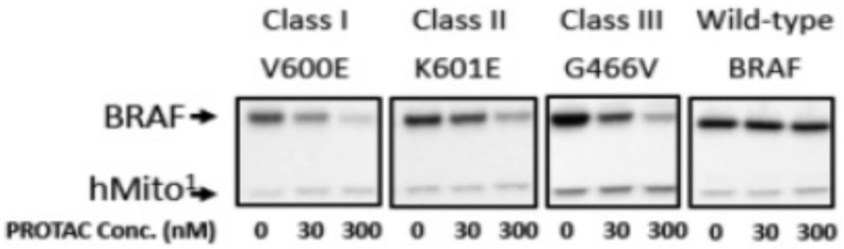
- Lapatinib alone results in HER2-overexpression, but a PROTAC created with lapatinib as the “warhead” degrades natural and overexpressed HER2
- HER2 degraded despite increased RNA levels



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



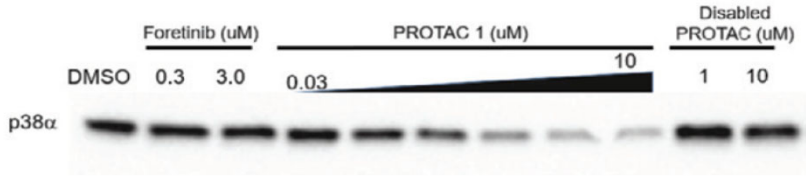
[1] hMito is a protein not targeted to degrade (loading control)

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

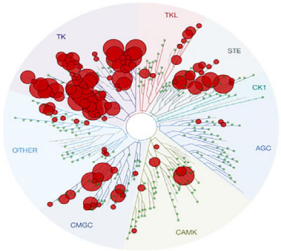


DC_{50} = 210 nM[1]

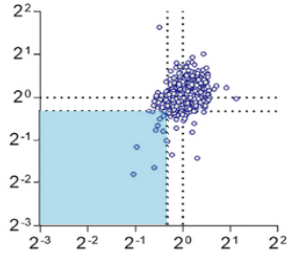
When developed into PROTAC degraders, promiscuous ligands can become selective degraders

- 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



[1] hMito is a protein not targeted to degrade (loading control)

ARV-110 selectively degrades AR

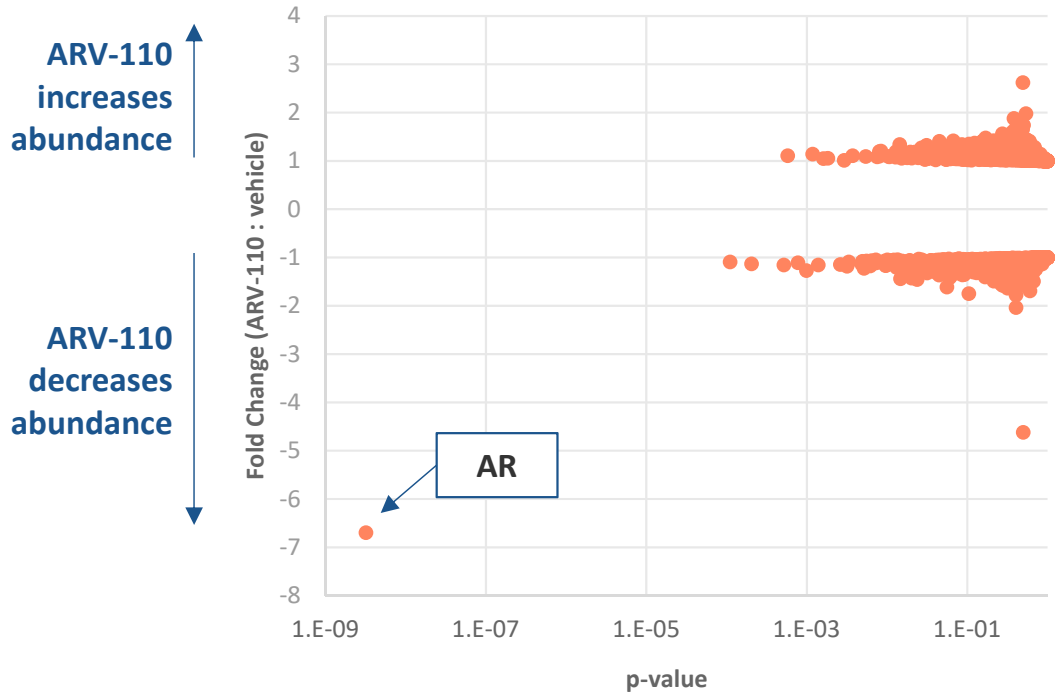
Orally bioavailable androgen receptor-targeted PROTAC protein degrader

- 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: $3x10^{-9}$

Selective Degradation of AR by ARV-110 in VCaP Cells



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

ARV-110: Phase 1 Study

First patient dosed March 2019

DESIGN

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

KEY ENTRY CRITERIA

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

KEY OBJECTIVES

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

BIOMARKERS

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

PSA, Prostate specific antigen. RECIST, Response evaluation criteria in solid tumors

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

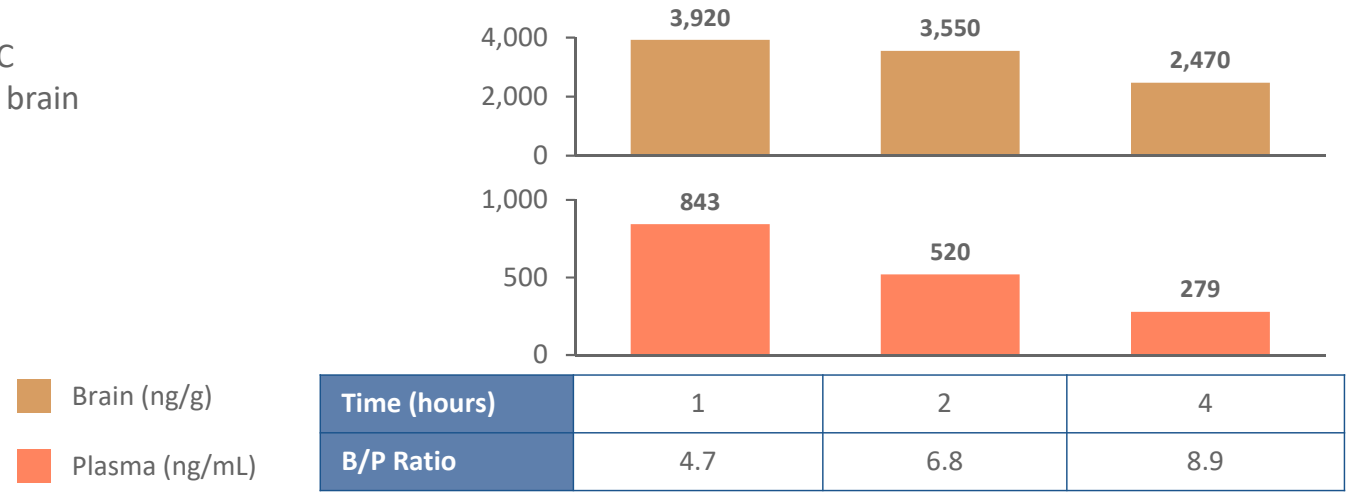
CBR, clinical benefit rate

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



Time (hours)	1	2	4
B/P Ratio	4.7	6.8	8.9

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