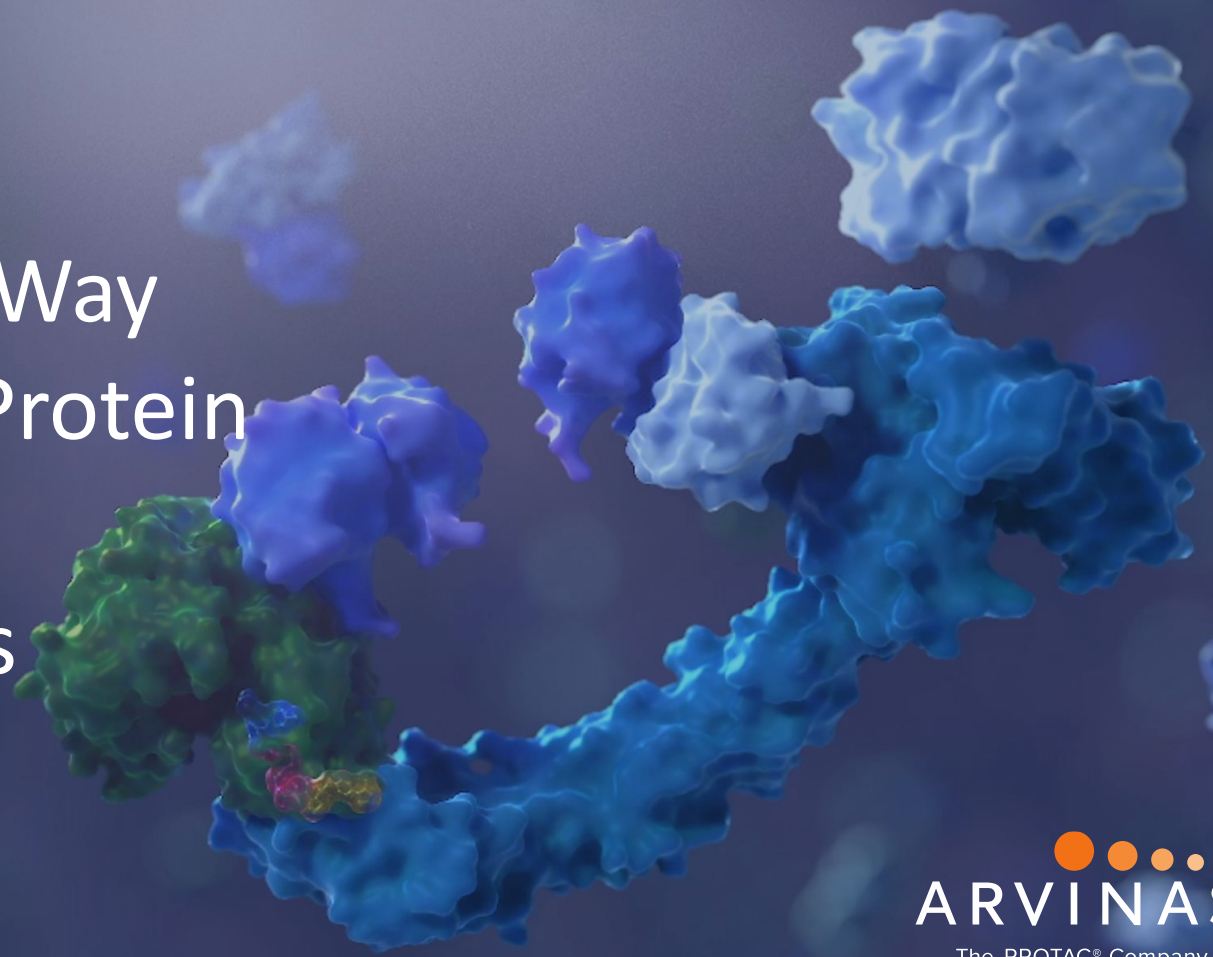
Leading the Way in Targeted Protein Degradation Therapeutics



ARVINAS
The PROTAC® Company

JUNE 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 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 1/2 clinical trials for ARV-110 and ARV-471, complete other clinical trials for our product candidates, and receive results from our clinical trials on our expected timelines, or at all, whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements, each party’s ability to perform its obligations under our collaborations and/or the Bayer joint venture, our expected timeline and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, discussed in the “Risk Factors” section of the Company’s quarterly and annual reports on file with the Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect our current views as of the date of this presentation with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

Clinical-stage leader in protein degradation, a powerful new modality

Novel PROTAC® (proteolysis-targeting chimera) degrader platform

- Elimination of disease-causing proteins, instead of inhibition
- Power of genetic medicines with small-molecule benefits

Strategic, discovery-stage partnerships with Pfizer, Genentech, and Bayer

- Pharmaceutical partnerships across multiple therapeutic areas
- Joint venture (Oerth Bio) with Bayer for agricultural applications
- Up to $2.1B in total potential milestones plus tiered royalties

Platform-enabled pipeline of oncology and neuroscience programs

- ARV-110 for men with metastatic castration-resistant prostate cancer
  - Initial phase 1 data disclosed in 2Q20 showed safety, efficacy signal, and androgen receptor degradation
  - Provides initial proof-of-concept for Arvinas' PROTAC® platform
- ARV-471 for patients with ER-positive / HER2-negative locally advanced or metastatic breast cancer
  - Initial clinical safety/PK data shared in October 2019
- Brain-penetrant PROTAC programs targeting tauopathies, α-synucleinopathies, and other neurological disorders
- All programs fully owned by Arvinas

Leader in targeted protein degradation

- Two clinical-stage, oral degraders
- Brain-penetrant programs to degrade neuroscience targets
- Aggressively investing in the platform to maintain leadership position
- Nearly 150 employees fully dedicated to targeted protein degradation

Strong cash and intellectual property positions

- ~$262.8 M in cash, cash equivalents, and marketable securities as of 3/31/20
- Platform IP complemented by specific product IP

Our recent ARV-110 data validates the potential of our PROTAC® platform, a completely novel therapeutic modality

Efficacy signal in humans

ARV-110 is the **first PROTAC degrader with an efficacy signal in humans,** in a heavily pretreated patient population where **standard of care inhibitors have failed**

Evidence for proof-of-mechanism

The **first evidence for androgen receptor** degradation in patients, showing that **the PROTAC platform is working as intended**

Safety data in humans

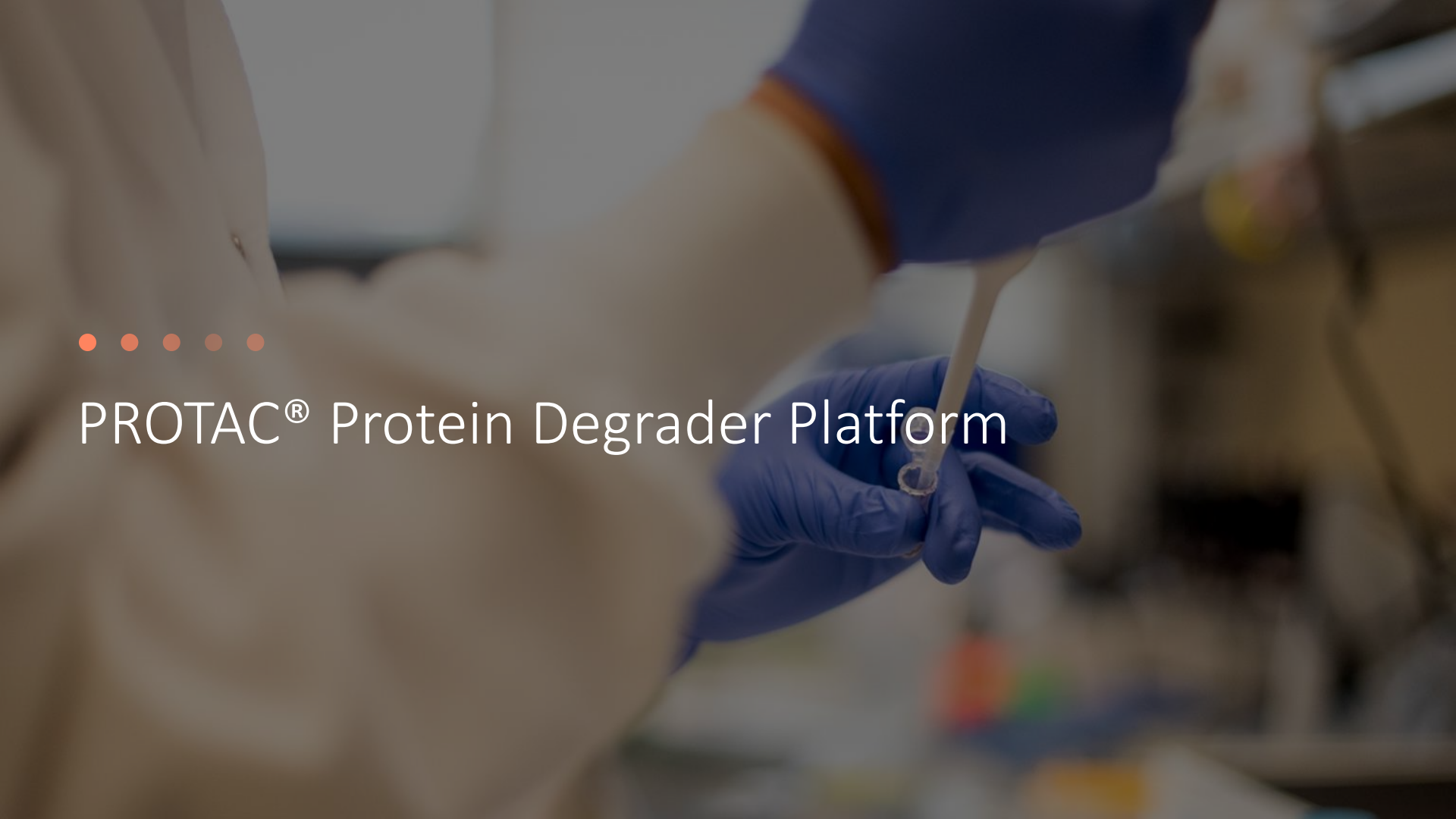
ARV-110 has been generally **well tolerated, and dose escalation continues**

Preclinical profile translating to patient benefit

Potential for genetically defined development pathway

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

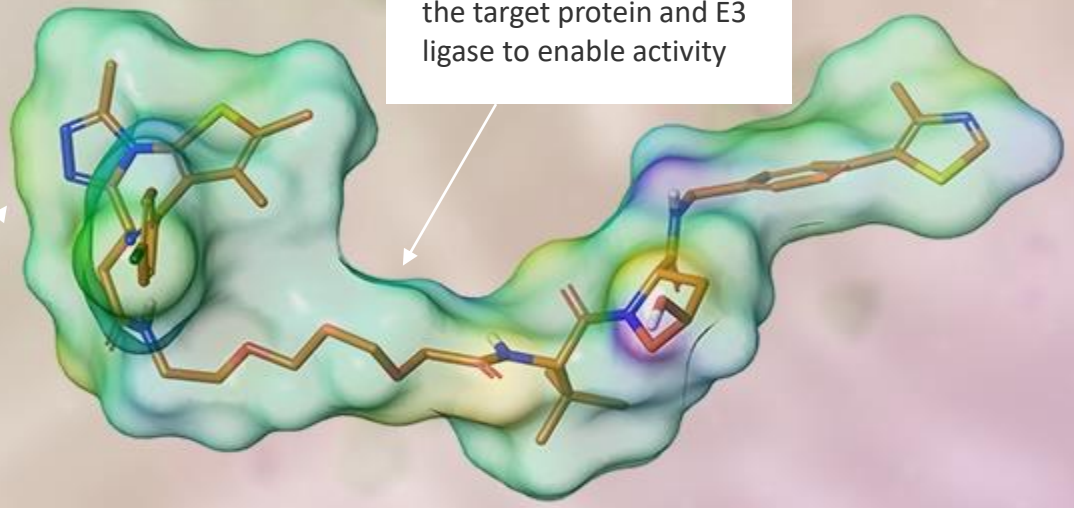


PROTAC® Protein Degrader Platform

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

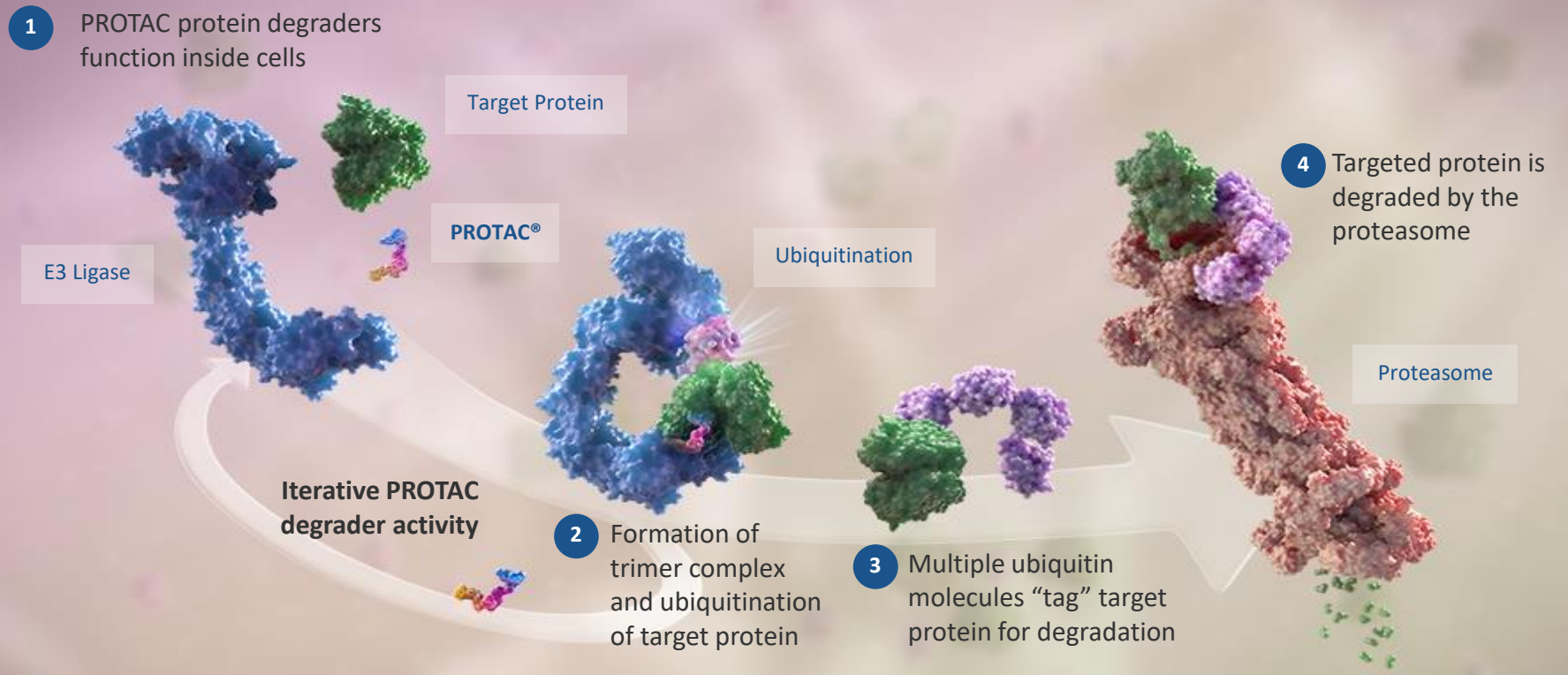


Protein ligand domain (“warhead”) targets a specific protein

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 harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins



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	✓		✗

Clinical-stage Oncology Programs: ARV-110

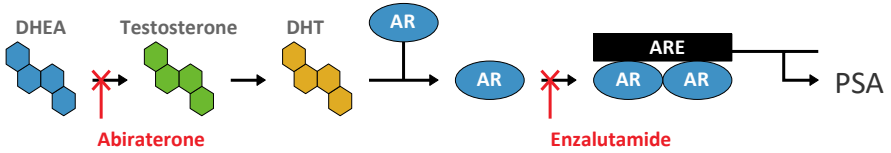
ARV-110 is Arvinas' AR degrader for men with metastatic castration-resistant prostate cancer (mCRPC)

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** (up to 25% of patients)
  - **Intra-tumoral androgen production**
- Despite rapid and dramatic responses to standards of care, all patients progress to the castration resistant state and their tumors continue to be dependent on the AR signaling axis[2]

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
- **Interim phase 1 data disclosed in 2Q20 showed AR degradation and efficacy signal, validating the PROTAC® mechanism and platform**



[1]American Cancer Society; [2]Cancers 2017, 9, 67; doi:10.3390/cancers9060067

Phase 1 study of ARV-110 is a traditional "3+3" dose escalation study in patients that have received ≥2 prior systemic therapies for mCRPC

Design

- "3 + 3" dose escalation; starting dose = 35 mg, orally, once daily with food
- Dose increases dependent on toxicities
  - Range 25% to 100% based on severity of AEs

Inclusion criteria

- Men with mCRPC, regardless of AR status
- 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

Endpoints

Primary:

- Define the maximum tolerated dose and recommended phase 2 dose

Secondary:

- Pharmacokinetics
- Anti-tumor activity (PSA50, RECIST criteria)

Exploratory:

- Biomarkers
  - ctDNA mutational profiling
  - AR levels in optional paired biopsies
  - AR and AR-V7 levels in circulating tumor cells (CTCs)

mCRPC= metastatic castration-resistant prostate cancer. RECIST= Response Evaluation Criteria in Solid Tumors. ctDNA, circulating tumor DNA. PSA, prostate-specific antigen

Enrolled patients in the ARV-110 clinical trial have been highly pretreated at baseline

Data as presented at ASCO 2020 and as of 4/20/20

Patient characteristics	Parameter	N (%)	
Median age (years)		67.5	
ECOG Performance Status	0	15	(68)
	1	7	(32)
Number of prior regimens in mCRPC	≥2	22	(100)
	Mean	5	(NA)
	Median (range, 2-9)	6	(NA)
Prior 2nd generation AR treatment	**Abiraterone acetate (ABI)**	**22**	**(100)**
	Enzalutamide (ENZA)	**17**	**(77)**
	BOTH	**17**	**(77)**
Prior chemotherapy	**Any Chemotherapy**	**17**	**(77)**
	Docetaxel	**13**	**(59)**
	Cabazitaxel	**9**	**(41)**
	Docetaxel and Cabazitaxel	**5**	**(23)**
Other agents	Lutetium	2	(9)
	Radium RA 223	5	(23)
	Sipuleucel-T	5	(23)
	PARP inhibitor	5	(23)

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ARV-110 has been generally well tolerated; potential drug-drug interaction in the two patients taking concomitant rosuvastatin

Data as presented at ASCO 2020 and as of 4/20/20

Related TEAE	35 mg (N=3)		70 mg (N=4)		140 mg (N=8)		280 mg (N=7)		Total (N=22)	
	Gr ≤2	Gr ≥3	Gr ≤2	Gr ≥3	Gr ≤2	Gr ≥3	Gr ≤2	Gr ≥3	N (%)	
Any	-	-	1	1	4	1	5	1	13	(59)
Nausea	-	-	-	-	2	-	4	-	6	(27)
Diarrhea	-	-	1	-	3	-	2	-	6	(27)
Fatigue	-	-	1	-	2	-	2	-	5	(23)
ALT increased	-	-	-	1†	1	-	1	1†	4	(18)
AST increased	-	-	-	1†	2	-	-	1†	4	(18)
Lymphocyte count decreased	-	-	-	-	-	1	3	-	4	(18)
Vomiting	-	-	1	-	1	-	2	-	4	(18)

- Related TEAE in ≥ 10% of patients (N=22)
- 1 of 22 patients had a DLT with ALT/AST Grade 3/4 and renal failure (280 mg)

†Patients on rosuvastatin (N=2)

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Preliminary evidence supports a potential drug-drug interaction with rosuvastatin (Crestor®)

Data as presented at ASCO 2020 and as of 4/20/20

Clinical observations

- 2 of 22 patients received concomitant rosuvastatin
  - First patient with DLT: Grade 3/4 ALT/AST and renal failure
  - Second patient with Grade 3 ALT/AST; re-challenge off rosuvastatin supported contribution of rosuvastatin. Patient was restarted on ARV-110 with no further toxicity

Pharmacologic data supporting rosuvastatin interaction[1]

- Rosuvastatin concentrations increased in both patients with LFT rise compared to baseline
- Subsequent *in vitro* transport pump studies indicated BCRP transporter inhibition by ARV-110[2]

Following introduction of rosuvastatin restriction, no further elevation in LFTs observed

- 6 patients were on other statins, including 3 on atorvastatin (Lipitor®) and no ALT/AST adverse events

FT= liver function tests; DLT= dose-limiting toxicity; BCRP= breast cancer resistance protein; [1]Analyses are exploratory (validated but not GLP compliant)
[2]Following new in vitro BCRP data, restriction has been broadened to include substrates with high risk of clinically significant interactions

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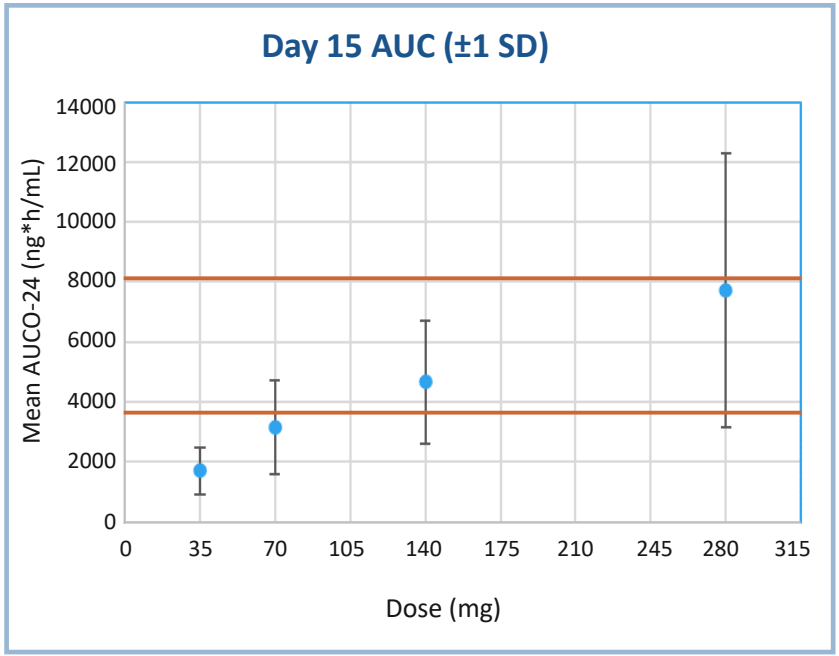
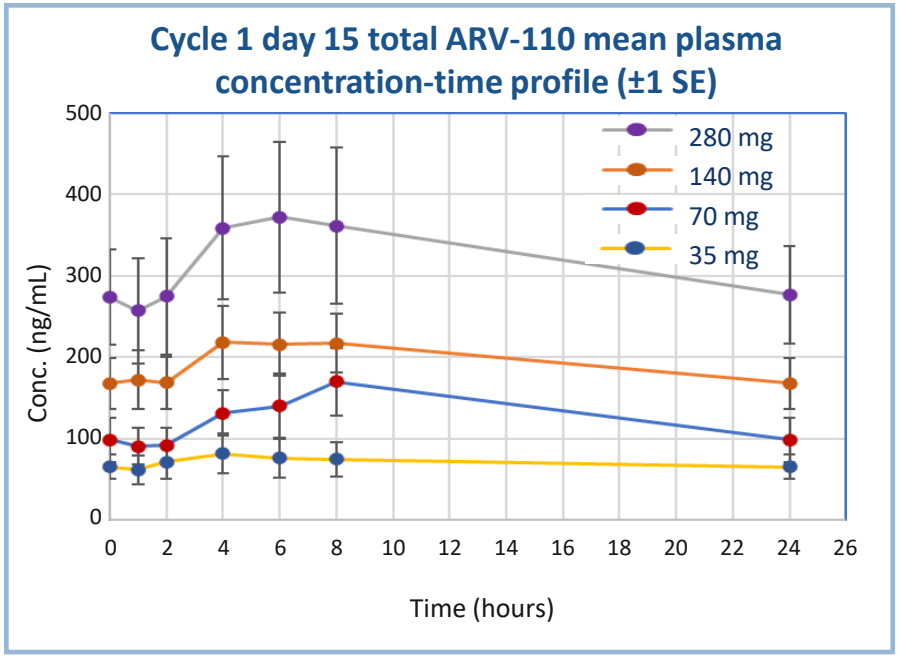
ARV-110 exposures are dose-proportional and demonstrate drug-like pharmacokinetics, with a half life that supports daily dosing

Data as presented at ASCO 2020 and as of 4/20/20





The orange lines represent the minimum efficacious exposures for tumor growth inhibition in various preclinical models[1]

$T_{1/2} \approx 110$ hours

[1]Upper line based on enzalutamide-resistant vertebral cancer of the prostate (VCaP) models. Lower line based on castrated and non-castrated VCaP model
QD, once per day. AUC, area under the curve. Cmax, maximum serum concentration. SD, standard deviation. SE, standard error.

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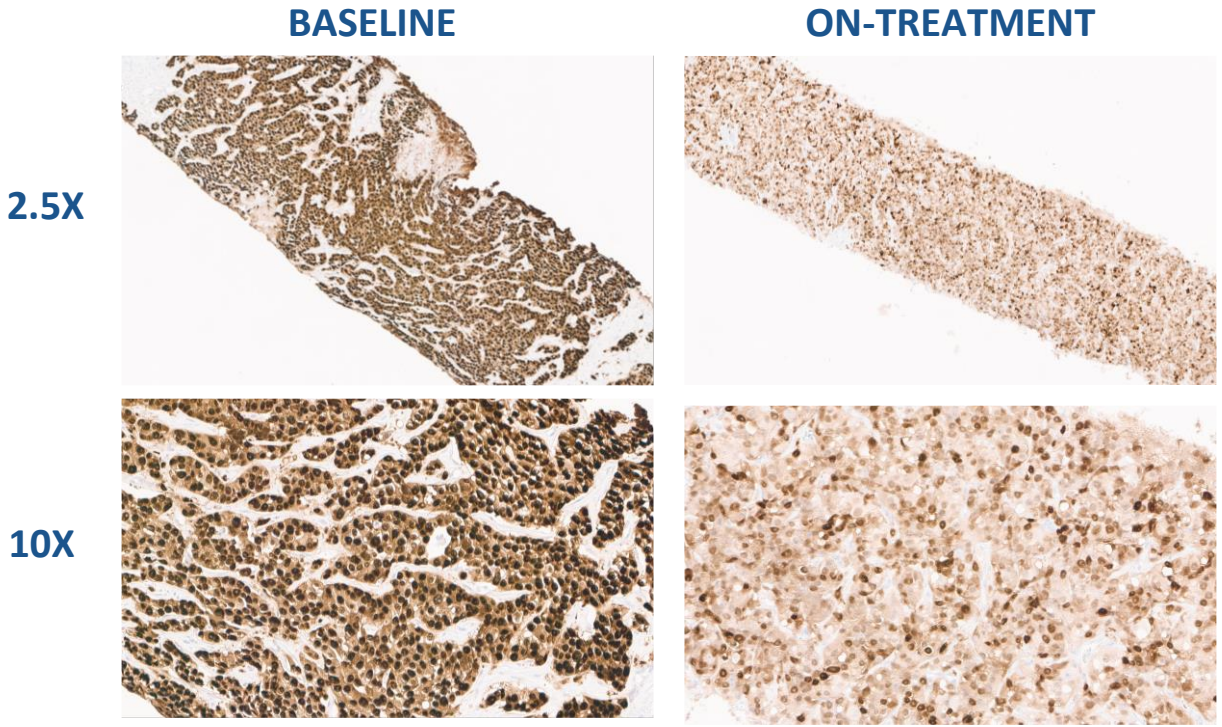
ARV-110 degrades AR in tumor tissue, demonstrating the first proof of mechanism for PROTAC® protein degraders

Data as presented at ASCO 2020 and as of 4/20/20



Decreased AR protein levels in an AR wildtype/amplified tumor from a patient following 6 weeks of ARV-110 dosing (280 mg)

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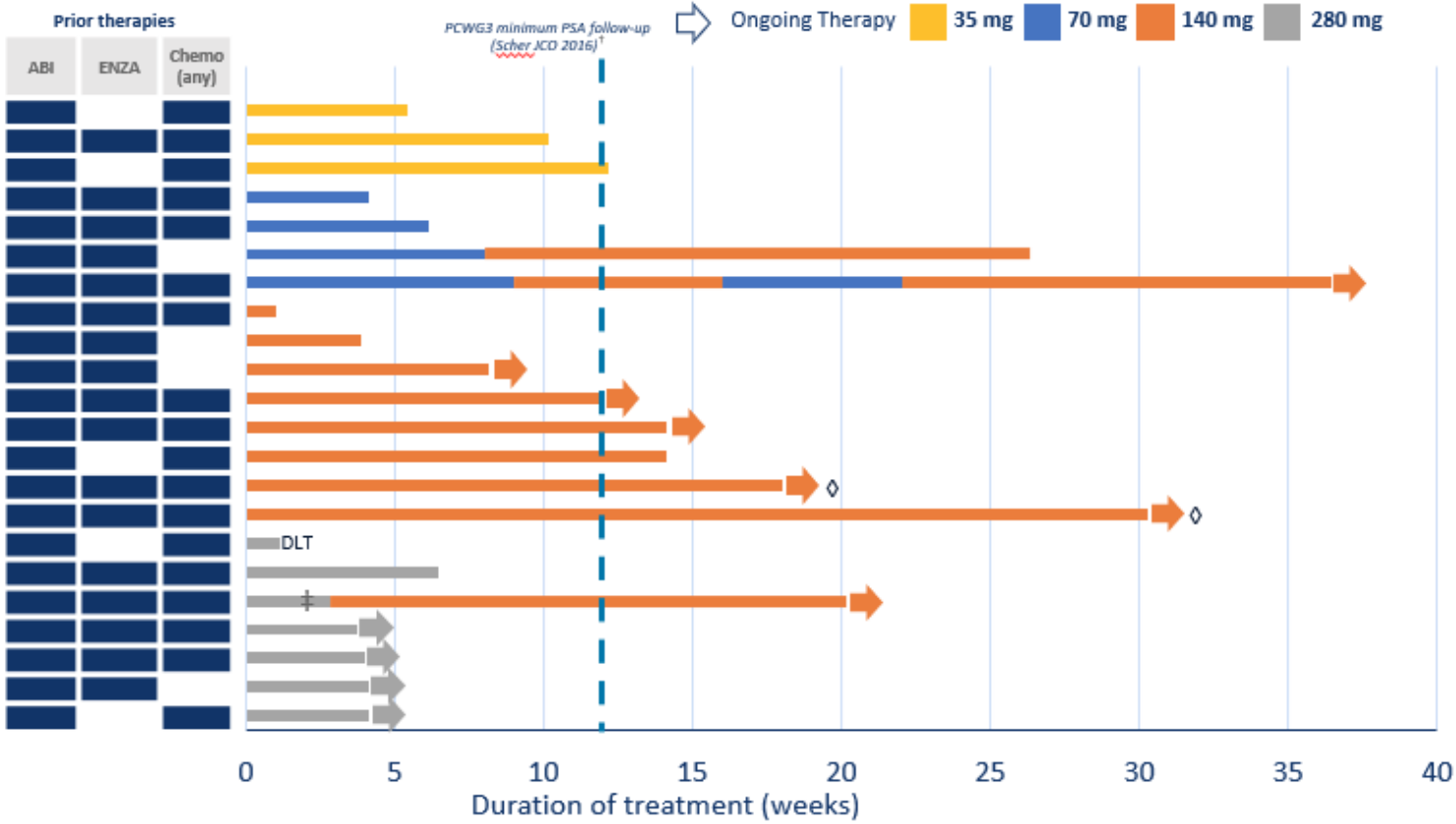
Duration of patient therapy in the ARV-110 dose escalation trial

Data as presented at ASCO 2020 and as of 4/20/20



Duration of therapy increases in patients at higher doses of ARV-110

>1/3 of patients across all dose levels remained on therapy longer than 3 months

Limited follow-up on most recent cohort at 280 mg

Data as of April 20, 2020

†PCWG3, Prostate Cancer Working Group 3; ‡Dose reduced for non-safety reasons; ◊PSA50 responder

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In patients with only ARV-110-degradable forms of AR, 2 of 7 had PSA decreases >50%[1]

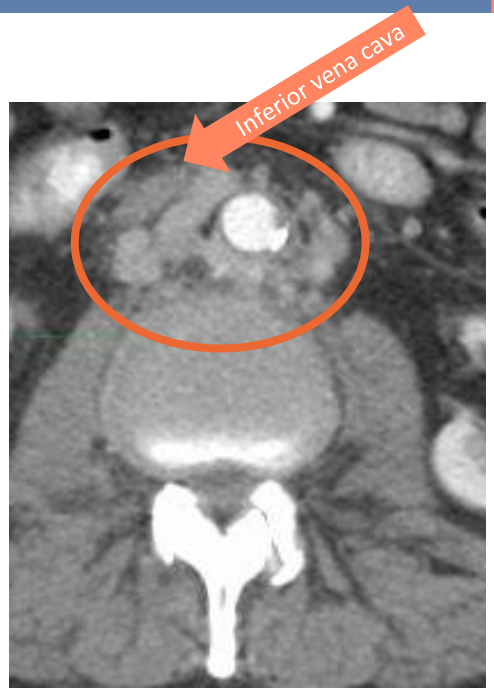
Data as presented at ASCO 2020 and as of 4/20/20

[1]Twelve patients shown exclude one patient with DLT associated with rosuvastatin

Two confirmed PSA50 responders, including one confirmed RECIST partial response

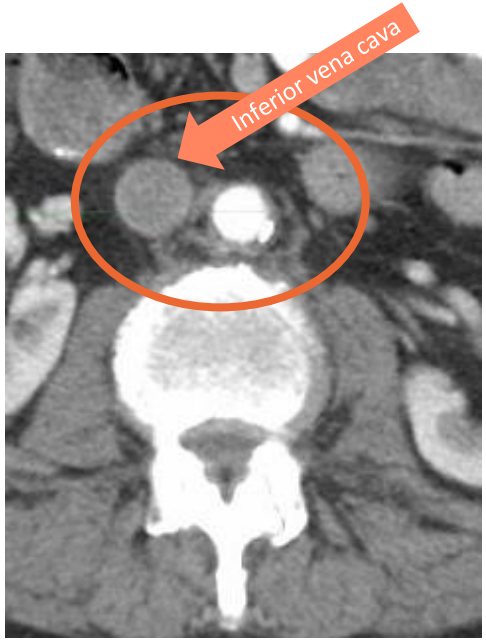
Data as presented at ASCO 2020 and as of 4/20/20

Responding Patient	1	2
PSA response	**74%** decline	**97%** decline
RECIST response	Not measurable	**80%** reduction
Duration of ARV-110	30+ weeks ongoing	18+ weeks ongoing
Biomarker status	AR H875Y and T878A mutations (associated with resistance to abiraterone or enzalutamide)[1]	
Common prior therapies	Enzalutamide, Abiraterone, Bicalutamide	
Other prior therapies	Docetaxel Radium	Provenge Cabazitaxel
History	Extensive bone metastases (sternum, left first rib, T3, T10 vertebral bodies)	Extensive disease involving adrenal gland, aortocaval nodes, multiple cone metastases



BASELINE CT SCAN

Extensive retroperitoneal adenopathy compressing the inferior vena cava



AFTER 4 CYCLES

Near complete regression of adenopathy

[1]Jernberg E, Endocrine Connections, 2017

ARV-110 has an exciting path forward to registrational studies

Data as presented at ASCO 2020 and as of 4/20/20

Unequivocal efficacy signal in First-in-Human dose escalation study

- Deep, durable, and ongoing responses
- Heavily pretreated population
- Patients resistant to SOC

Favorable safety profile

- Tolerability consistent with 2nd generation AR therapies
- Manageable DDI with BCRP substrates

Clear next steps

- 420 mg cohort dosed
- Backfilling patients at 280 mg while dose escalating
- Adding new sites for Phase 2 expansion

AR mutational profile of responders suggests a potential patient selection strategy and accelerated approval path

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Clinical-stage Oncology Programs: ARV-471

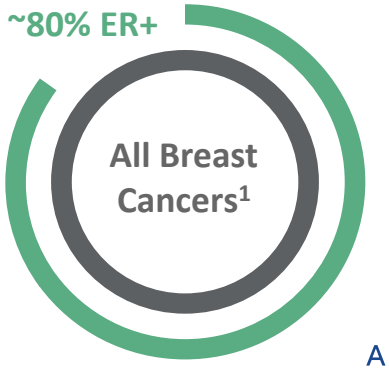
ARV-471 is Arvinas' ER degrader for patients with locally advanced or metastatic breast cancer

Breast cancer is the second most common cancer in women[1]

- **~276,000 women** are expected to be diagnosed with invasive breast cancer in the US in 2020[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
- **Initial clinical data shared October 2019**
- **Updated data from the Phase 1 dose escalation planned for 4Q20**



[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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Phase 1 study of ARV-471 is a traditional “3+3” dose escalation study

Design

- “3 + 3” dose escalation; starting dose at 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)

Inclusion 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

Endpoints

Primary:

- Maximum tolerated dose and recommended phase 2 dose

Secondary:

- Pharmacokinetics
- Anti-tumor activity (RECIST, CBR)

Exploratory:

- 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

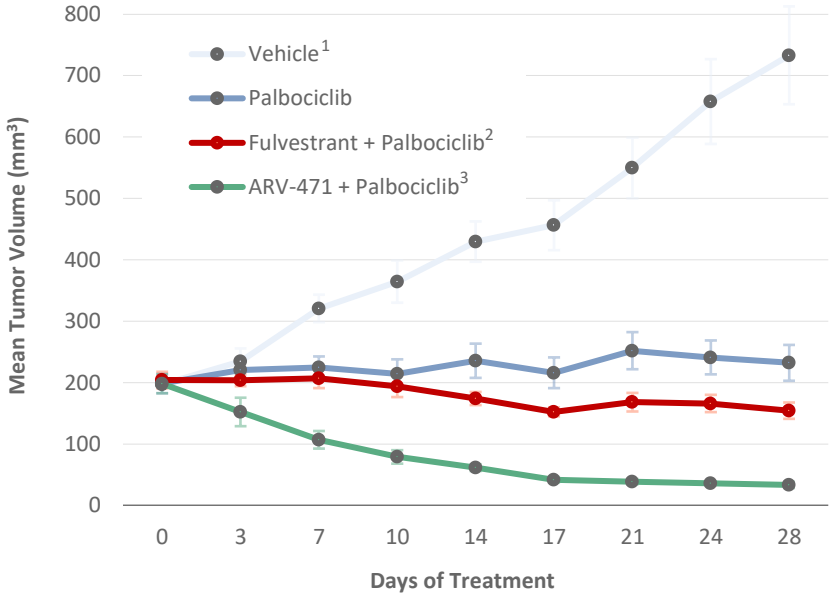
CBR= clinical benefit rate

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

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In the first dose cohort of the 3+3 escalation study of ARV-471, exposure reached the predicted efficacious range

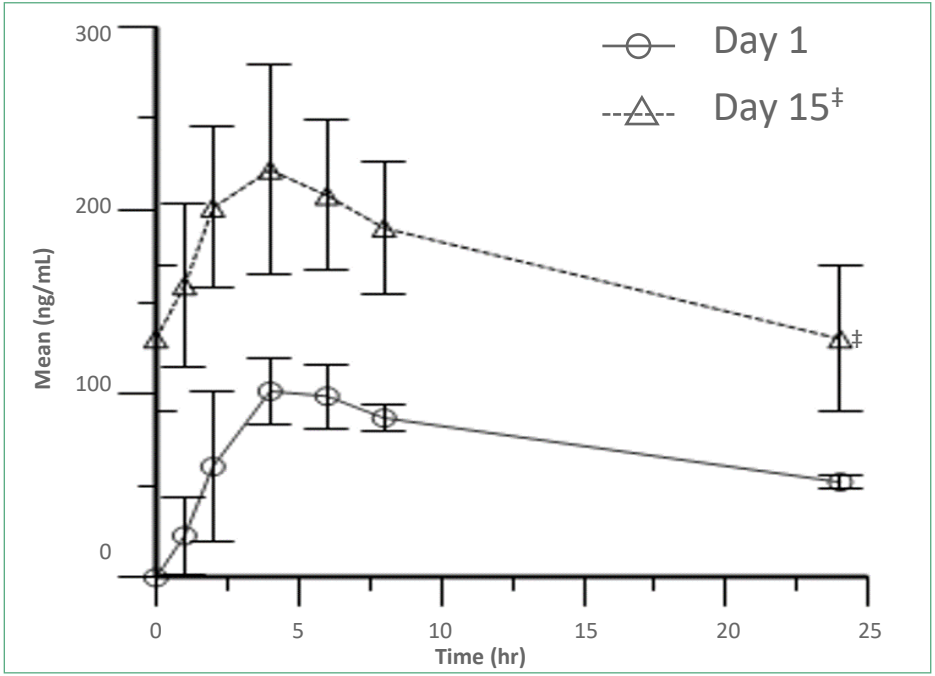
Data as of October 2019

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

30 mg Cohort Phase 1 Data

Day	AUC_{0-24} (ng*h/mL) Mean	C_{max} (ng/ml) Mean
Day 1	1690	109
Day 15	4100†	224



- Exposure at 30 mg entered the preclinical efficacious range associated with tumor growth inhibition
- No treatment-related AEs or DLTs were observed

T_{max} = 4 hrs
$t_{1/2}$ = ~24 hrs

† Day 15 AUCs calculated using imputed 24 hour values; ‡Day 15 24 hour value is imputed from time zero

ARVINAS

Next update on ARV-471 planned for 4Q20

In the first cohort (30 mg), reached exposure levels associated with tumor growth inhibition in preclinical studies

Latest observations†

- Advancing through dose escalation
- Dose-proportional increases in pharmacokinetics
- No dose-limiting toxicities

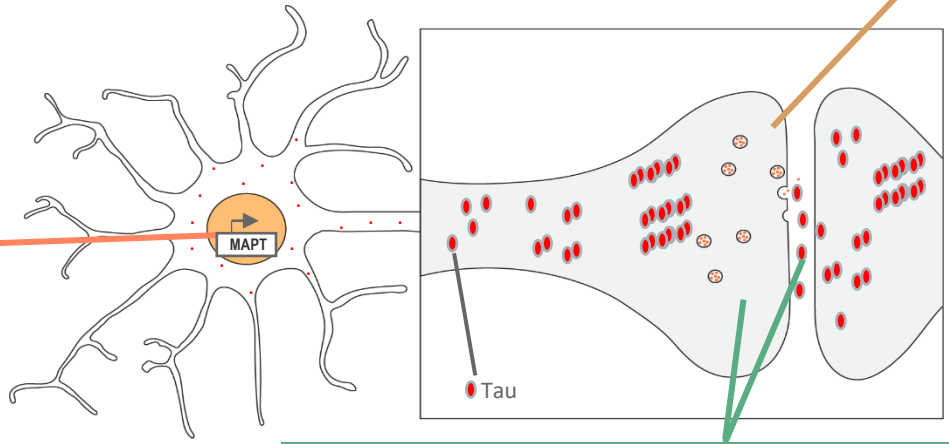
Early evidence of in-tumor ER degradation†

† Statements as of 5/29/20

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

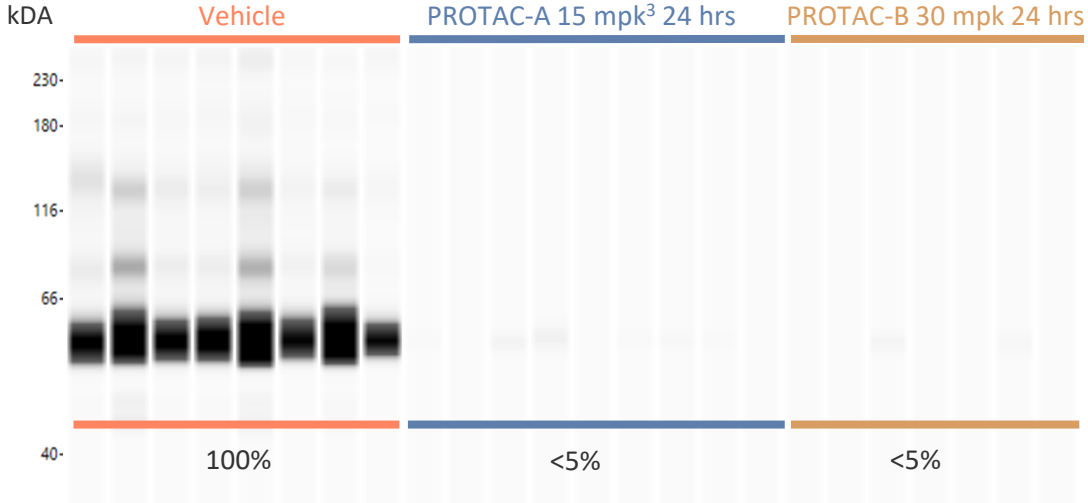
PROTAC *Potential*

- 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

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

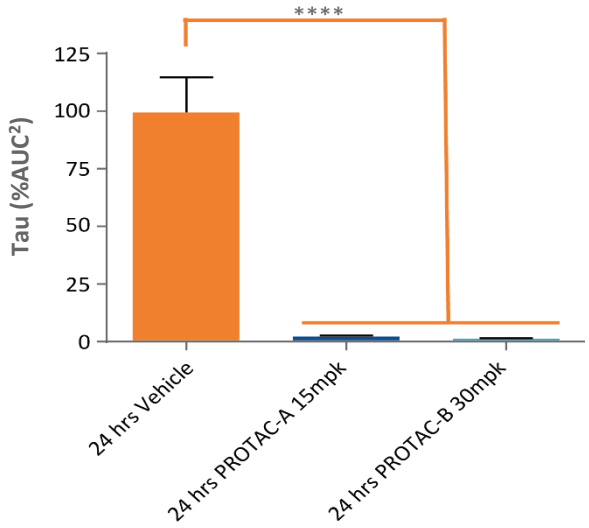
Tau Detection (protein capillary electrophoresis)



24 hours post dose:

- >95% of pathologic tau is degraded
- No significant change in total soluble tau 24 h post dose (data not shown)

Pathologic tau in Tg2508[1] mouse cortex



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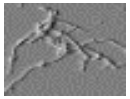
Tau-directed PROTAC® protein degraders inhibit *ex-vivo* tau seeding

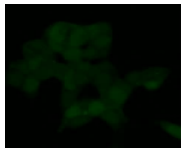
Tau Seeding Reporter Assay



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

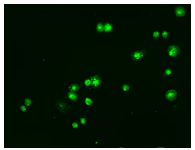
Modified from Holmes et al., 2014

24h



- Tau /- PFF Seeding

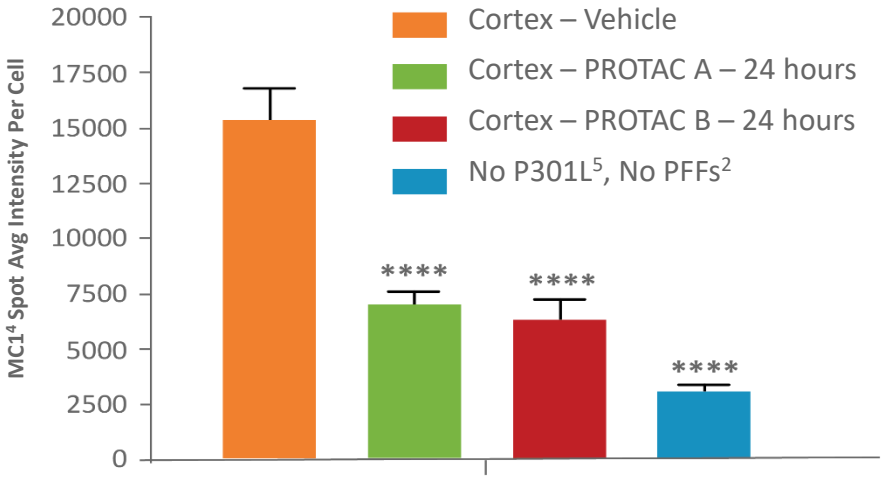
OR



+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.

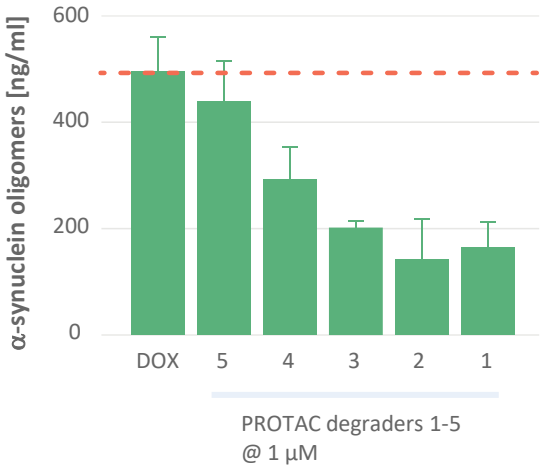
**** Tukey's multiple comparisons test $P < 0.0001$. Comparisons are between the Cortex-Vehicle value and all other values (individually)

ARVINAS

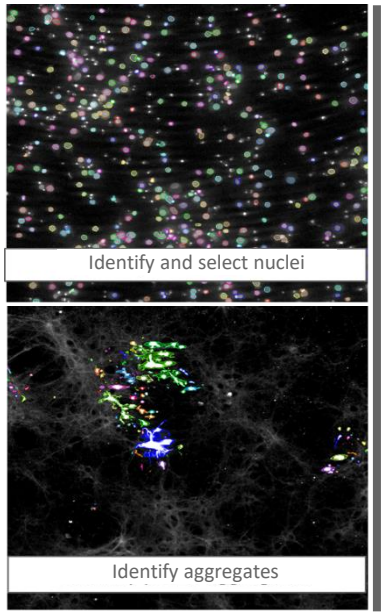
Oligomer-specific PROTAC® molecules degrade human α-synuclein aggregates in primary rat neurons

PROTAC molecules degrade oligomeric α-synuclein species

PROTAC degraders were identified that specifically remove oligomeric α-synuclein

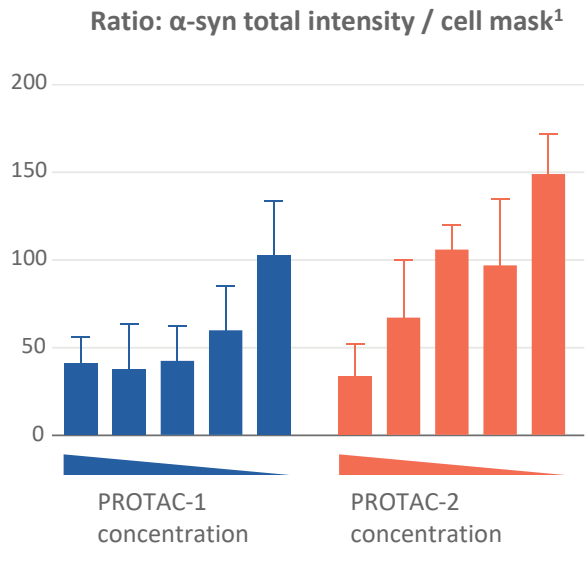


PROTAC-1 and PROTAC-2 degrade α-synuclein aggregates in primary rat neurons expressing human α-synuclein



Neuronal α-synuclein +PFF induction assays[1]

Intensity and area features of α-synuclein aggregates calculated



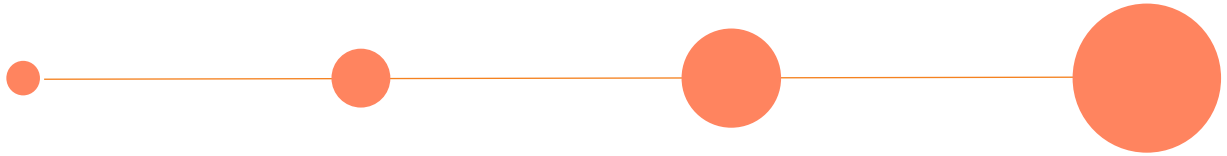
1 Assay is of primary rat neurons expressing A53T human α-synuclein, with pre-formed fibrils (PFF) added or not. In the absence of α-synuclein-specific PROTAC degraders, α-synuclein forms aggregates induced by PFFs (green fluorescence in cellular images). When PROTAC degraders specific for oligomeric α-synuclein are added, the ratio of oligomeric α-synuclein:cell mask (background fluorescence) is decreased (right panel).

ARVINAS

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: "2019 Alzheimer's Disease Facts and Figures" video; https://www.alz.org/alzheimers-dementia/facts-figures

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

Financial snapshot

$263 Million

Cash, cash equivalents, and marketable securities (*as of 3/31/20)*

Guidance

Expect cash, cash equivalents, and marketable securities to fund planned operations into 2022

39.0 Million

Common shares outstanding (*as of 4/24/20)*

Analyst Coverage[1]

BMO, Cantor, Citibank, Evercore, Goldman Sachs, Guggenheim, HC Wainwright, Oppenheimer, Piper Sandler, Roth, Wedbush

1 The foregoing list includes the names of all brokerage firms known by the company as of 6/1/20 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.

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

JUNE 2019

- Pharma target discovery deal, including cardiovascular, gynecologic, and oncologic disease
- Private equity placement
- $60M in upfront, committed funds, and private placement of common stock

erthbio

JUNE 2019

- Agricultural JV; 50:50 ownership
- >$55M in committed funds from Bayer

Potential for nearly $2.1 billion in milestones

Leading the way in targeted protein degradation therapeutics

Strategic Target Selection

- Recalcitrant targets where degradation is required
- Targets requiring exquisite selectivity
- Pipeline balances benefit and risk

Degraders 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

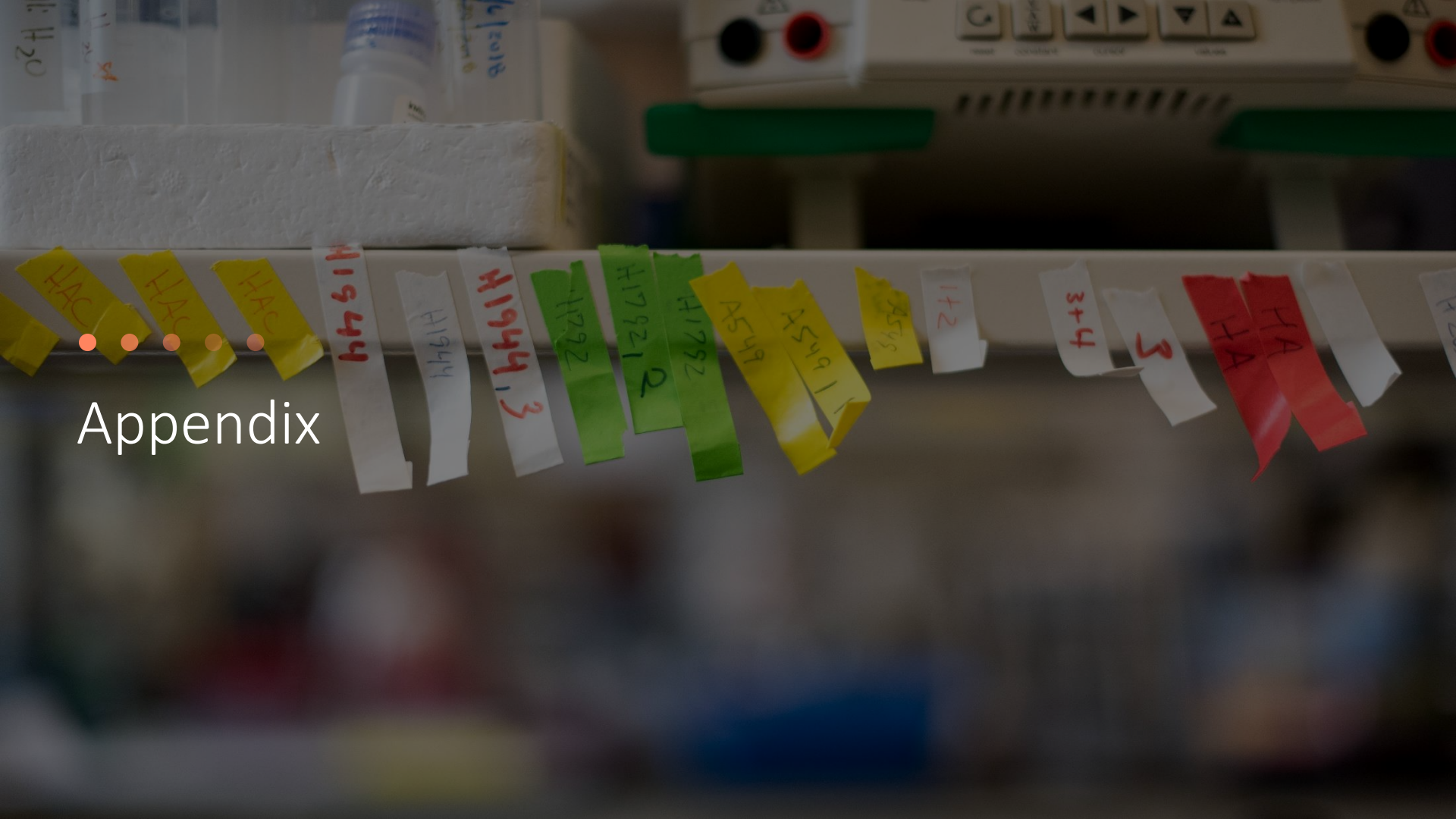
- Brain-penetrant and orally bioavailable degraders
- Mechanism and proteomic analytics
- Disease-specific degradation assays
- Working "Beyond the Rule of 5" since our founding

▶ Initial targets validate the PROTAC® platform

▶ 95% success rate at degrading proteins of interest

▶ Clinical-stage programs with safety, PK, PD, and efficacy data

Thank You!


HAC
HAC
HAC
H1N1
H1N1
H1N1
H3N2
H3N2
H3N2
A549
A549
A549
1+2
3+4
3
HA
HA

Appendix

Arvinas at a glance

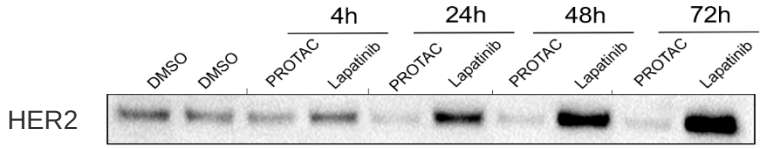
- Clinical-stage biopharmaceutical company focused on developing PROTAC® targeted protein degraders as therapeutics for cancers and other serious diseases
- Founded in 2013; located in New Haven, CT
- ~150 employees and growing, plus >200 FTEs at contract research organizations in Asia
- Driven by four core values: Pioneering, Excellence, Community, and Commitment
- Nasdaq: ARVN (IPO in September 2018)

Potential advantages of PROTAC® protein degraders over inhibitors

Overcome Target Protein Overexpression

PROTAC degraders can disable this common tumor resistance mechanism

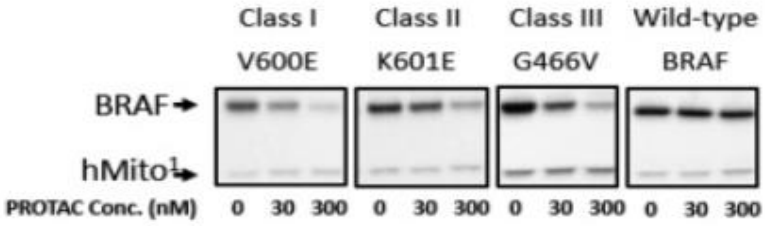
- Lapatinib alone results in HER2-overexpression, but a PROTAC created with lapatinib as the “warhead” degrades natural and overexpressed HER2
- HER2 degraded despite increased RNA levels



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



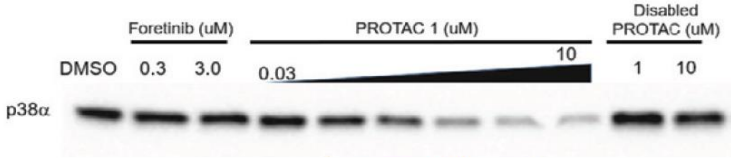
[1] hMito is a protein not targeted to degrade (loading control)

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

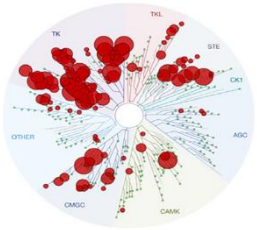


DC_{50} = 210 nM[1]

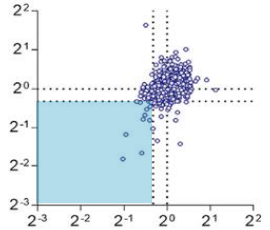
When developed into PROTAC degraders, promiscuous ligands can become selective degraders

- 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

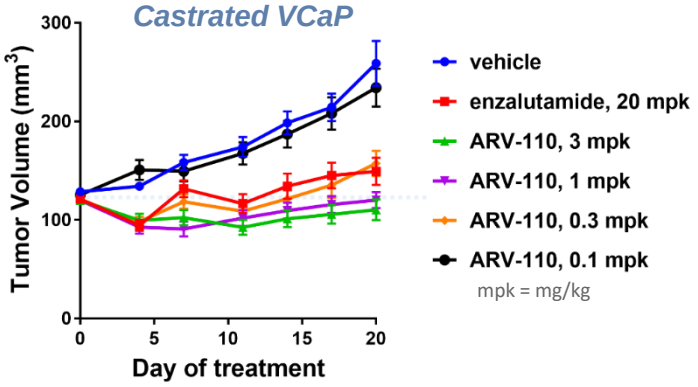


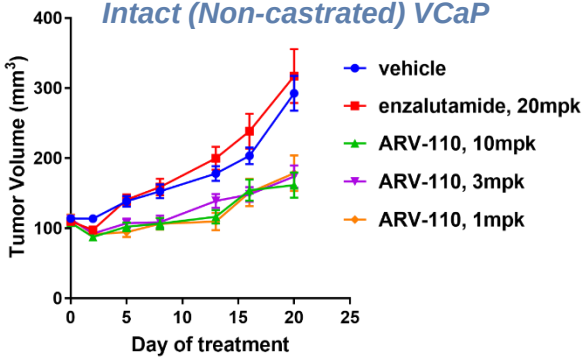
Degrades <10 Proteins

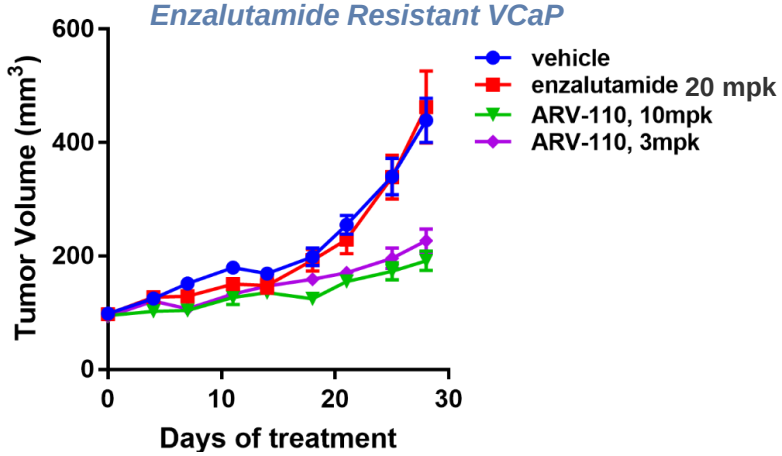


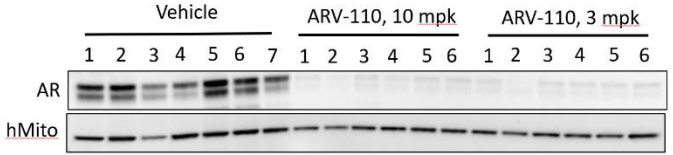
[1] hMito is a protein not targeted to degrade (loading control)

ARV-110 inhibits AR-dependent tumor growth in xenograft models with oral, daily dosing









Dose po, qd	Mean AUC_{0-24} ng*hr/ml[1]	Mean C_{max} ng/ml[2]
1 mpk	3628	224
3 mpk	8106	507

Values represent total drug concentrations

† AUC_{0-24} or Area Under the Curve is a measurement of total exposure from 0-24 hours after last dose
‡ C_{max} is a measurement of peak concentration

ARV-110 selectively degrades AR

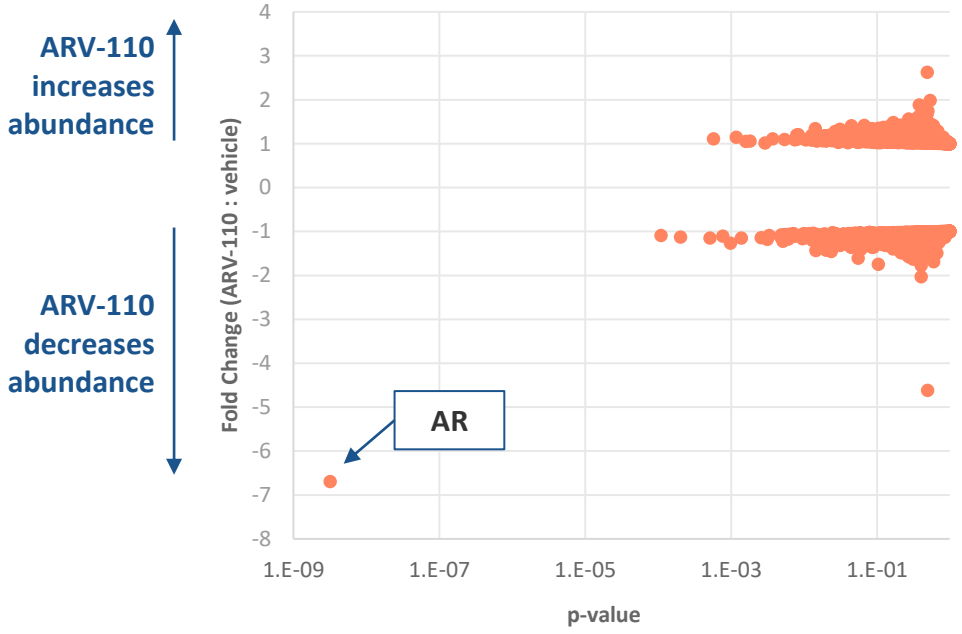
Orally bioavailable androgen receptor-targeted PROTAC protein degrader

- 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: $3x10^{-9}$

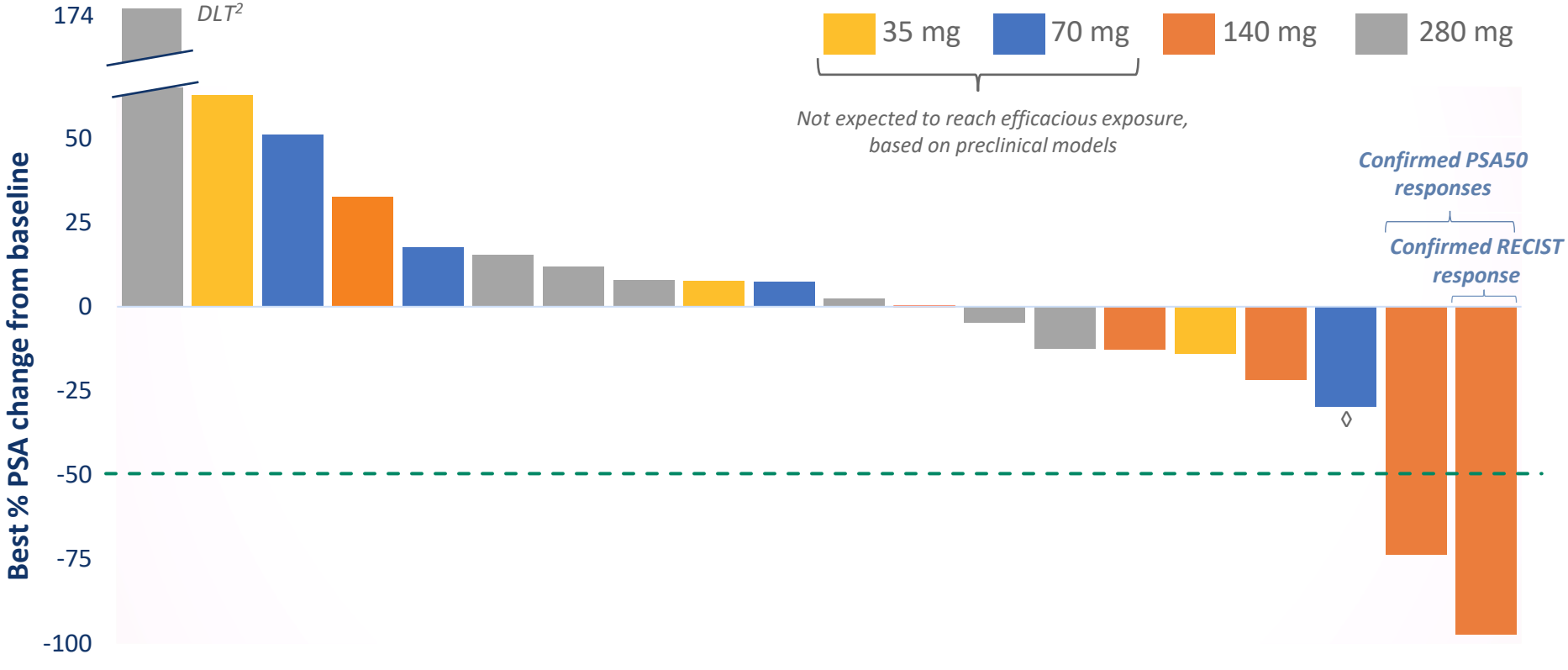
Selective Degradation of AR by ARV-110 in VCaP Cells



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

Best percent change of PSA from baseline in all patients evaluable for safety (N=20)[1]

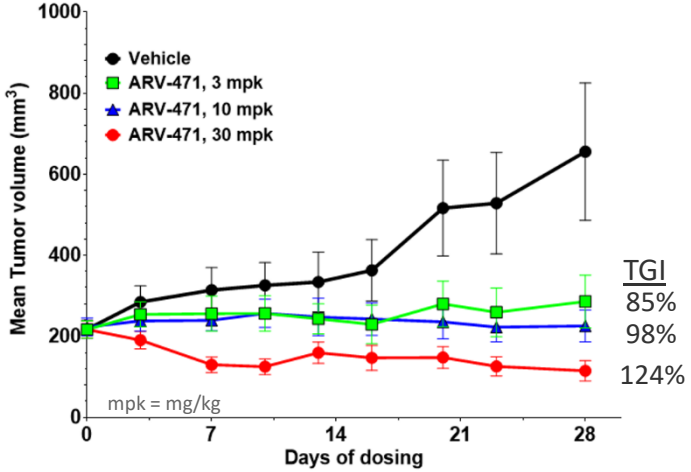
Data as presented at ASCO 2020 and as of 4/20/20



[1]Two of 22 patients were not evaluable: 1 patient had 1 dose and discontinued trial, and 1 patient had PSA less than 1 ng/ml and eligibility by radiographic progression; [2]Treatment discontinued after 2 weeks due to DLT. [◊]Patient dose escalated to 140 mg

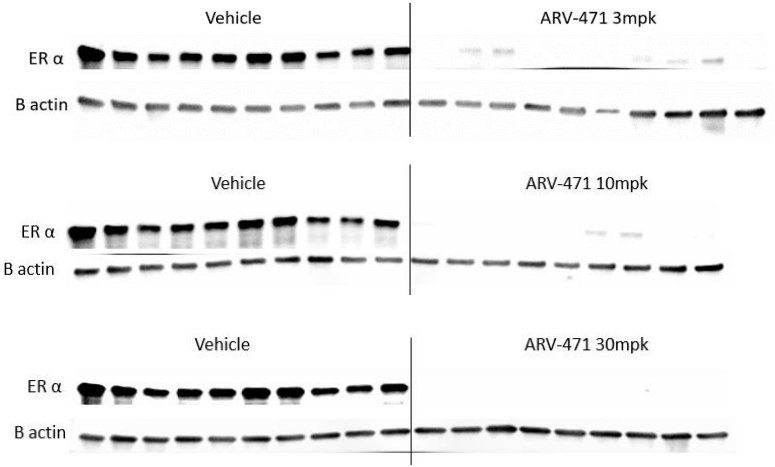
ARVINAS

Orally dosed ARV-471 shrinks tumors and robustly degrades ER in MCF7 xenografts



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

Western Blot PD (18 hours post last dose)	% ER Reduction
3 mpk	95
10 mpk	97
30 mpk	94



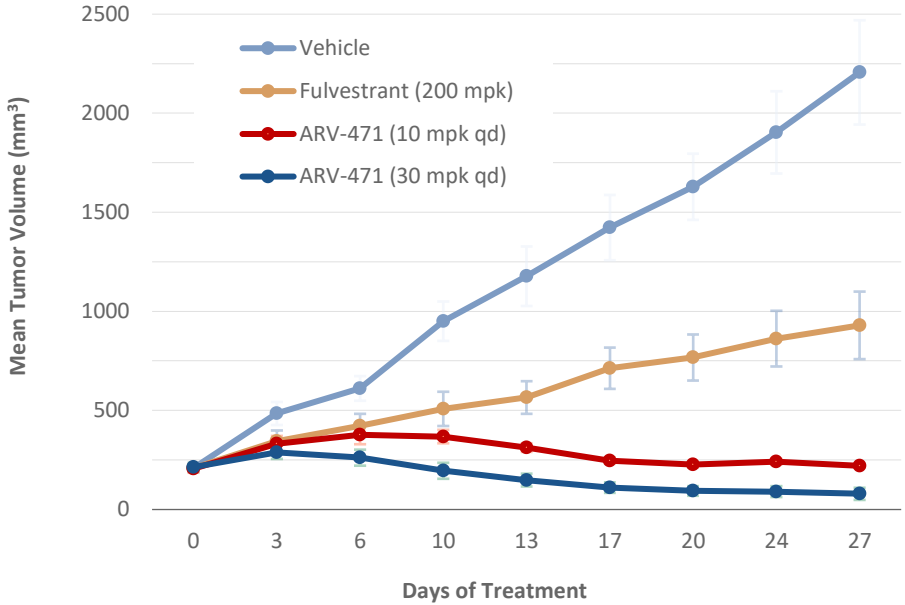
† Single dose
‡ Values represent total drug concentrations

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



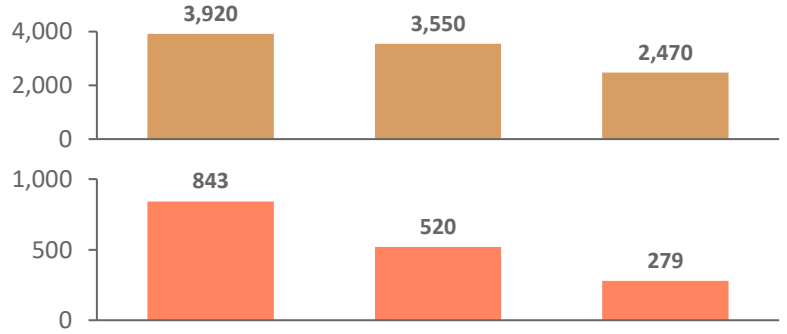
1 Fulvestrant schedule: 2x weekly x2 / q7dx2

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

Seasoned leadership with expertise in advancing novel technologies

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President & CEO

Bristol-Myers Squibb · gsk

Angela Cacace, PhD
VP Neuro and Platform Biology

Fulcrum Therapeutics · Bristol-Myers Squibb

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

Bristol-Myers Squibb · vitae Pharmaceuticals

Ronald Peck, MD
Chief Medical Officer

gsk · TESARO, A GSK company · Bristol-Myers Squibb

Ian Taylor, PhD
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