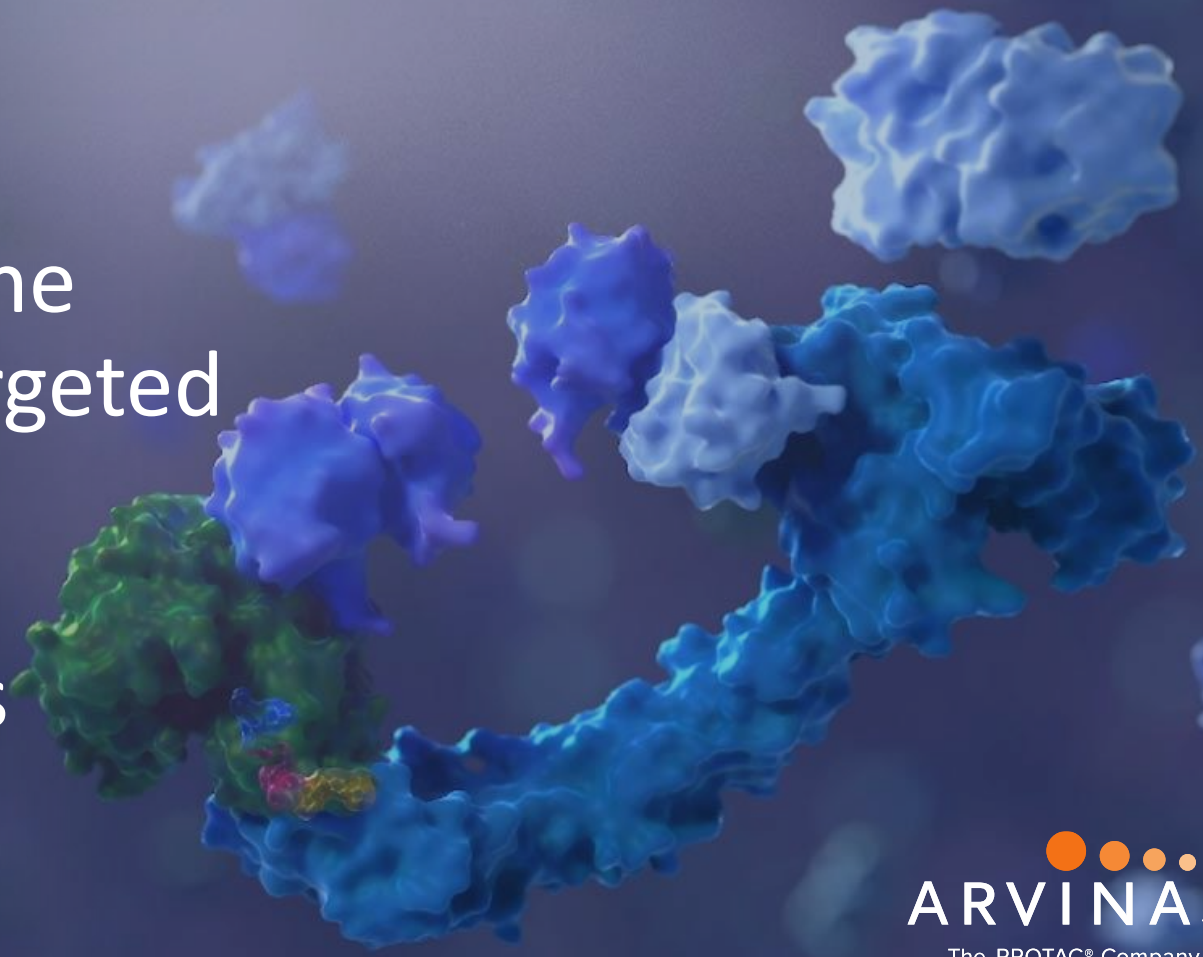
Pioneering the Future of Targeted Protein Degradation Therapeutics



March 2021

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, ARV-471 and ARV-766 and other candidates in our pipeline, and the timing of clinical trials and data from those trials and plans for registration for our product candidates, and our discovery programs that may lead to our development of additional product candidates, the potential utility of our technology and therapeutic potential of our product candidates, the potential commercialization of any of our product candidates, the potential benefits of 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.

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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

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

Two clinical programs with human proof-of-concept

- **ARV-471** has the potential to a best-in-class estrogen receptor (ER)-targeting therapy
  - Demonstrated profound ER degradation, tumor responses, and an outstanding safety profile in patients with breast cancer
  - VERITAC Phase 2 dose expansion trial ongoing
- **ARV-110** has demonstrated signals of safety and efficacy in men with late-line metastatic castrate-resistant prostate cancer
  - ARDENT Phase 2 dose expansion trial ongoing

Robust pipeline of 20+ oncology, I-O, and neuroscience programs

- Pipeline targets include "undruggable" proteins (e.g., KRAS, Myc) and more validated targets
- Neuroscience targets for brain-penetrant PROTAC® degraders include tau, α-synuclein, and mHTT
- ARV-766, a next-generation androgen receptor (AR) degrader, expected to begin human trials in 1H21
- Expected 2022 IND filings include BCL6, tau, and an undisclosed oncology target
- Five IND filings expected in 2021-2023
- All programs fully owned by Arvinas

Clinically validated targeted protein degradation platform

- Our PROTAC® Discovery Engine has generated industry-leading breakthroughs (e.g., brain penetrance)
- Elimination of disease-causing proteins, not just inhibition
- Power of genetic medicines with small-molecule benefits
- Proprietary knowledge, including our E3 KnowledgeBase, Zone of Ubiquitination, and Arvinas Rules
- Strong discovery partnerships with Genentech, Pfizer, and Bayer

mHTT, mutant huntingtin; IND, investigational new drug

Arvinas' pipeline encompasses a range of validated and undruggable targets in oncology, I-O, and neuroscience

	ARVN Program	Indication	Exploratory	Research	IND Enabling	Phase 1	Phase 2	Phase 3
Oncology / Immuno-oncology	ARV-110	mCRPC						
	ARV-766	mCRPC			IND 2021			
	AR-V7	mCRPC						
	ARV-471	ER+/HER2- Breast Cancer						
	BCL6	B-cell Malignancies		IND 2022				
	KRAS	NSCLC, CRC, Pancreatic		IND 2023				
	Undisclosed	Solid Malignancies		IND 2022				
	Myc	Solid Malignancies						
	HPK1	Solid Malignancies						
Neuroscience	Tau	FTLD-TAU, PSP, AD		IND 2022				
	Alpha Synuclein	MSA, Parkinson's						
	mHTT	Huntington's						
	Undisclosed	Neurodegeneration						

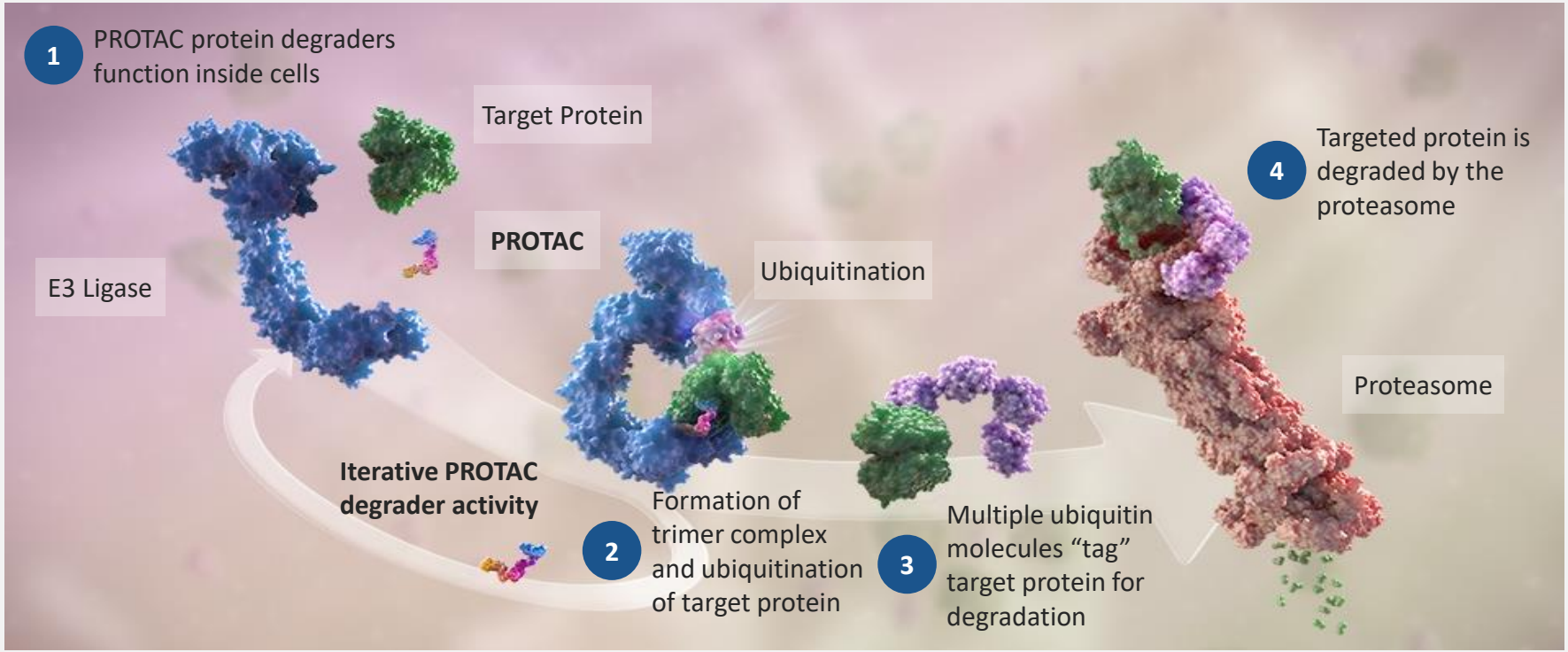
Note: Pipeline is non-exhaustive and IND dates are anticipated.
mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; NSCLC, non-small-cell lung carcinoma; CRC, colorectal cancer; FTLD-tau, frontotemporal lobar degeneration-tau; PSP, progressive supranuclear palsy; MSA, multiple systems atrophy

Rapid pace of anticipated milestones in 2021-2022

	2021	2022
ARV-471 (ER PROTAC®)	• Share completed Phase 1 data • Share interim CDK4/6i combination study data • Initiate Window of Opportunity study • Initiate additional combination study(s)	• Share interim VERITAC Phase 2 data • Share completed CDK4/6i combination data • Share interim data from other combinations
ARV-110 (AR PROTAC®)	• Share completed Phase 1 data • Share ARDENT Phase 2 interim data • Initiate combination study(s)	• Share full ARDENT Phase 2 data • Share interim combination data
ARV-766 (AR PROTAC®)	• Initiate Phase 1	• Share Phase 1 data • Initiate Phase 2
INDs	• ARV-766	• BCL6 • Tau • Undisclosed (oncology)

Arvinas’ PROTAC® Discovery Engine

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

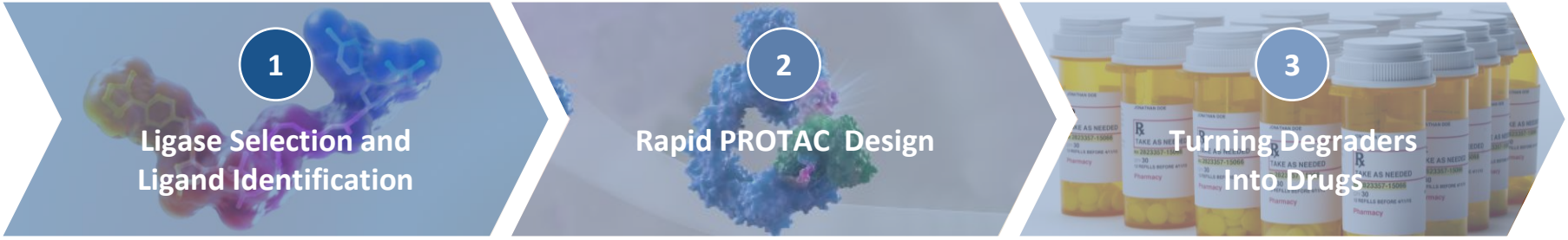


PROTAC® protein degraders combine the advantages of gene-based medicines with the benefits of small molecule therapies

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	✓		✗

Arvinas' breakthroughs are driven by our integrated PROTAC® Discovery Engine

PROTAC Discovery Engine



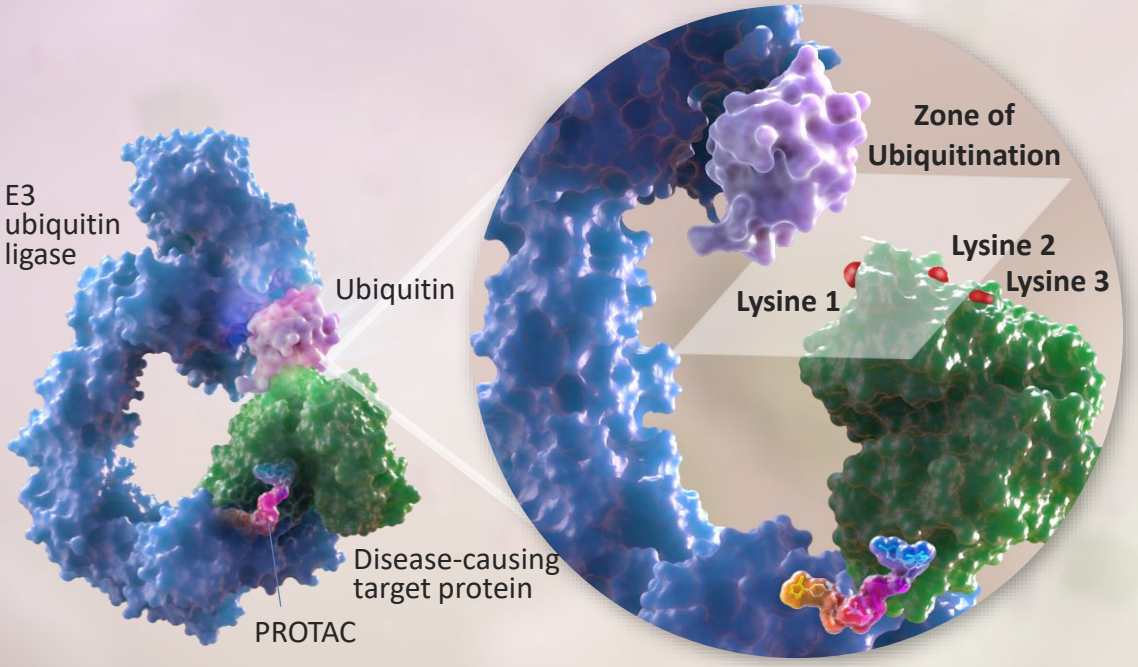
- E3 KnowledgeBASE of novel E3 ligases
- Novel warheads for undruggable targets and new ligands for E3 ligases
- Advanced screening capabilities, including proprietary DNA-encoded libraries tailored for PROTAC development

- Optimizing the Zone of Ubiquitination
- Arvinas Next Generation Linker Evolution (ANGLE)
- Predictive computational modeling
- State-of-the-art proteomics capabilities

- "Arvinas Rules" for drug-like properties, including blood-brain barrier penetration and oral bioavailability in humans
- Deep knowledge of in vivo PK/PD and efficacy relationships

Arvinas' platform is built from nearly 20 years of experience, know-how, and IP

Our deep understanding of the Zone of Ubiquitination informs the structure-based design of PROTAC® degraders



Lysine 1	High probability: Lysine 1
Lysine 2	Medium probability: Lysine 2
Lysine 3	Low probability: Lysine 3

We design PROTAC degraders to optimize the position of lysine residues within the Zone of Ubiquitination

Strategic partnerships expand the impact of our PROTAC® Discovery Engine

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Genentech
A Member of the Roche Group

September 2015
(expanded in November 2017)
Target discovery deal

Pfizer

December 2017
Target discovery deal

BAYER

Orthbio

June 2019
Target discovery deal and agriculture-focused joint-venture to fight crop disease and other challenges facing the global food supply

These partnerships expand the impact of PROTAC degraders beyond oncology and beyond human therapeutics, while maintaining full ownership of our pipeline

Clinical-stage Oncology Programs: ARV-471

Now in its VERITAC Phase 2 dose expansion, ARV-471 is emerging as a leading therapy in a large area of unmet need

Data as presented 12/14/2020

ARV-471

Estrogen receptor-degrading PROTAC®

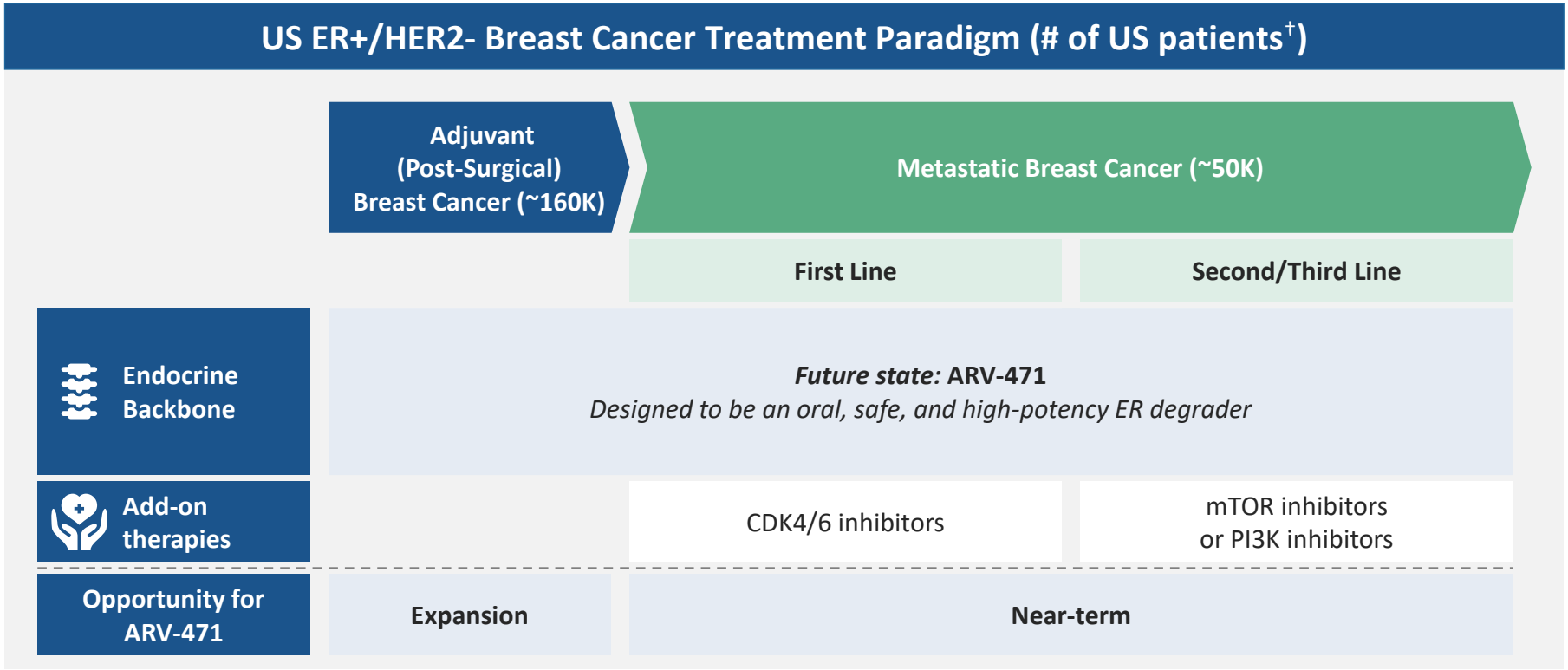
Breast Cancer

- Potential future endocrine therapy of choice in both adjuvant and metastatic settings
- Potential best profile of any ER-targeting therapy
- High unmet need: >200k patients per year in the US alone†, and potential opportunity >$15b
- Highest clinical benefit rate (42%) of any ER-targeting therapy in a Phase 1 does escalation, in the most advanced patient population††
- 200 mg selected for the VERITAC Phase 2 dose expansion, while Phase 1 dose escalation continues
- Leading tolerability profile observed versus clinical-stage SERDs
- Traditional small-molecule manufacturing requirements
- Most potent degradation of any ER-targeting therapy†††

SERD, selective estrogen receptor degrader

† US incidence data from SEER database; †† See comparison on slide 25; ††† See comparison on slide 21

We are developing ARV-471 to be the endocrine backbone of choice for ER+/HER2- breast cancer treatment



† US incidence from SEER Database
CDK: cyclin-dependent kinases, Pi3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin

Our ARV-471 first-in-human study is a traditional “3+3” dose escalation

Design

- “3 + 3” dose escalation
- ARV-471 administered orally, once daily with food
- Starting dose: 30 mg

Endpoints

Primary:

- Maximum tolerated dose and recommended Phase 2 dose

Key Secondary:

- Safety and tolerability
- Pharmacokinetics
- Pharmacodynamics: Quantify ER in paired biopsies (baseline and on-treatment)
- Efficacy: RECIST, Clinical Benefit Rate (CBR) defined as confirmed PRs and CRs + ≥ 24-week SD

All Phase 1 patients are post-CDK4/6 inhibitor treatment; high rate of ER-independent resistance

Phase 1 Inclusion Criteria

- ER+/HER2- advanced breast cancer
- **Disease progression on CDK4/6 inhibitor**
- ≥ 2 prior endocrine therapies in any setting
- Up to 3 prior chemotherapy regimens in advanced breast cancer

Believed to be the only trial of an ER-targeting therapy requiring prior CDK4/6 treatment

- After CDK4/6 inhibitor treatment, **~66%** of breast cancers have ER-independent mechanisms of resistance†
- Outcomes are poor following CDK4/6 inhibitor therapy, e.g., for fulvestrant:
  - Median PFS = 1.8 months††
  - CBR estimated ≤20%††

† Wander 2020; †† Juric SABCS 2018 Subset Analysis of SOLAR1.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor. PFS, progression-free survival; TTF, time to treatment failure; CBR, clinical benefit rate

ARV-471 Phase 1 patients received extensive prior therapy (N = 21)

Data as presented 12/14/2020

Patient Characteristics	Parameter	N (%)	
Median age (years)		64	
ECOG performance status	0 1	10 11	(48) (52)
Prior visceral disease (liver, lung)		10	(48)
Median prior lines of therapy total (range 1-9)		5	(NA)
Median number of prior endocrine regimens		3	(NA)
Type of prior therapies in advanced settings			
CDK 4/6 inhibitor		**21**	**(100)**
Fulvestrant		**15**	**(71)**
Chemotherapy		**8**	**(38)**
Investigational SERD		**5**	**(24)**
Other therapies		**14**	**(67)**

ECOG, Eastern Cooperative Oncology Group; CDK4/6, cyclin-dependent kinases; SERD, selective estrogen receptor degrader

ARV-471 is well tolerated at all dose levels; no Grade 3 adverse events

Data as presented 12/14/2020

TRAE in ≥ 10% of Patients	30 mg (N=3)		60 mg (N=3)		120 mg (N=7)		180 mg (N=5)		360 mg (N=3)		Total (N=21)	
	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	Gr 1	Gr 2	N (%)	
Any	-	-	2	-	4	-	2	1	2	-	11	(52)
Nausea	-	-	2	-	1	-	-	1	1	-	5	(24)
Arthralgia	-	-	1	-	2	-	1	-	-	-	4	(19)
Fatigue	-	-	1	-	-	-	1	-	2	-	4	(19)
Decreased appetite	-	-	-	-	1	-	-	-	2	-	3	(14)

Adverse events were primarily Grade 1; No dose limiting toxicities

Data cut-off: November 11, 2020
TRAE, Treatment related adverse event

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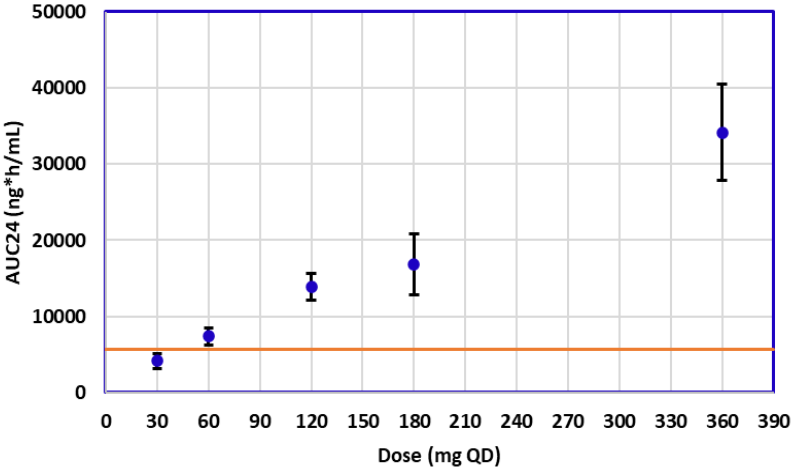
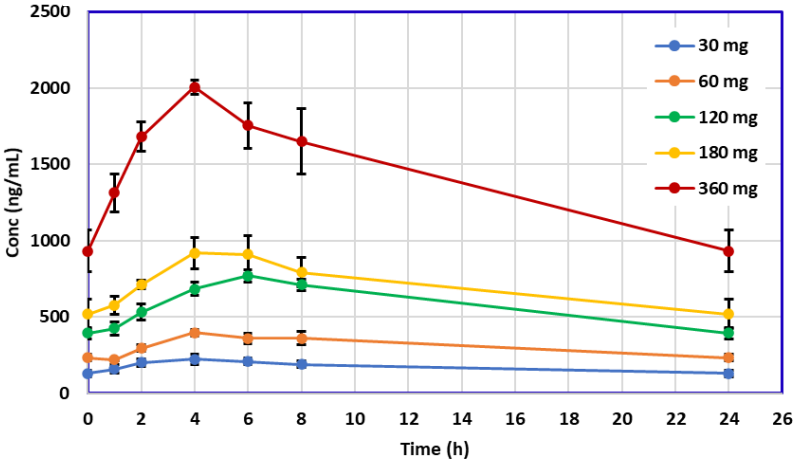
ARV-471's PK is dose proportional; exposures far exceed preclinical efficacy thresholds

Data as presented 12/14/2020





The orange line represents the efficacious exposure for tumor regression in preclinical models †

Effective half-life ($T_{1/2}$) ≈ 28 hours

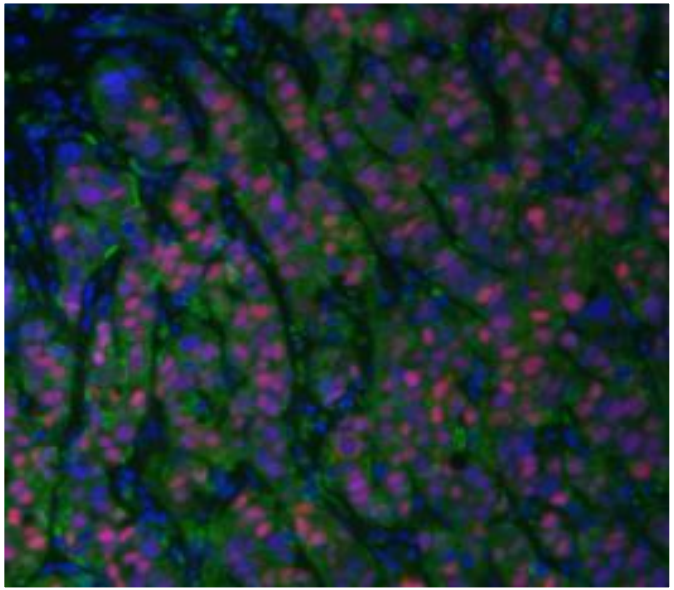
† AUC24=5717 ng*h/mL for preclinical effective exposure in preclinical model (mice@30mpk).
AUC, area under the curve; SE, standard error

ER degradation observed in patient tumor biopsies

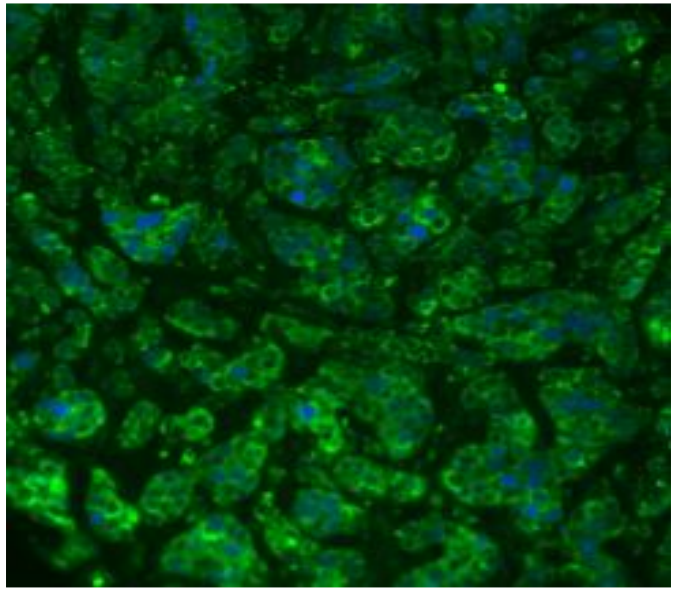
Red: Estrogen receptor

Blue: Nuclei

Green: Tumor (cytokeratin)



Baseline

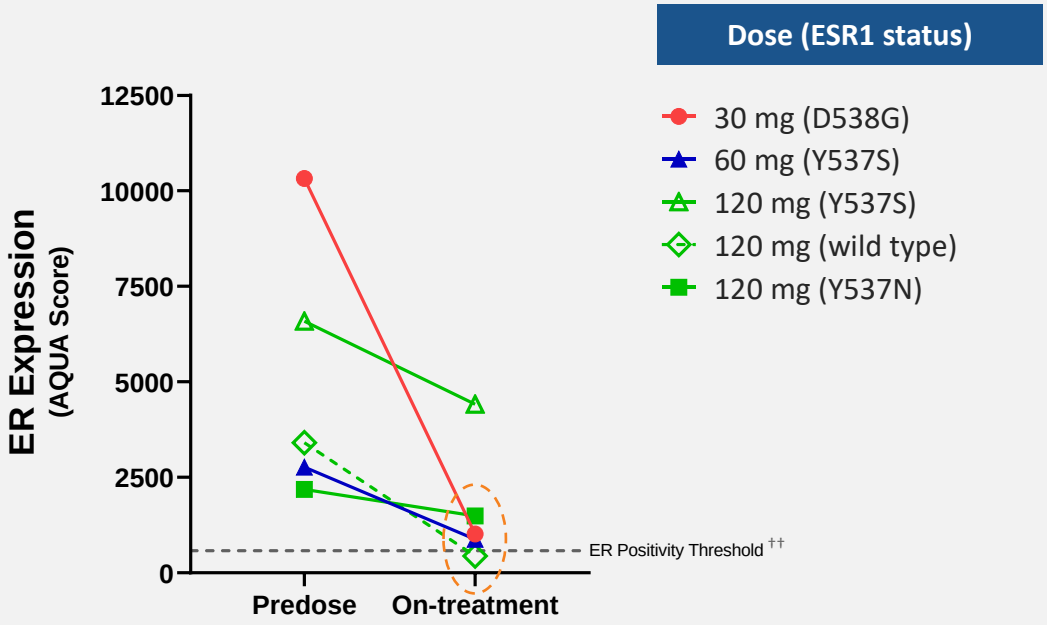


After treatment with 60 mg ARV-471

Method: ER immunoreactivity analyzed by quantitative immunofluorescence (QIF) using the automated quantitative analysis (AQUA) method

ARV-471 degraded ER up to 90% through the 120 mg dose level

ER Expression in Paired Tumor Biopsies†



- Degradation up to 90%; average of 62%
- Degradation **superior to fulvestrant** *(previously reported: 40-50%)†††*
- Degradation of **wild type ER and ESR1** mutant proteins

† ER immunoreactivity analyzed by quantitative immunofluorescence (QIF) using the automated quantitative analysis (AQUA) method. †† Derived by examining AQUA scores and visually inspecting all samples in the dataset to determine a cut-point for ER positivity. ††† Fulvestrant degradation reported as 40-50% in Robertson et al., Breast Cancer Research (2013) and Kuter et al., Breast Cancer Res Treat (2012). ESR1, Estrogen Receptor 1

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Confirmed RECIST Partial Response (cPR) in a patient with extensive prior therapy and an ESR1 mutation at 120 mg

Data as presented 12/14/2020

Extensive prior therapy

CDK4/6 inhibitor: Palbociclib

Endocrine therapies: 6 Agents
- Aromatase inhibitors x 3
- Tamoxifen
- Investigational SERDs X 2†

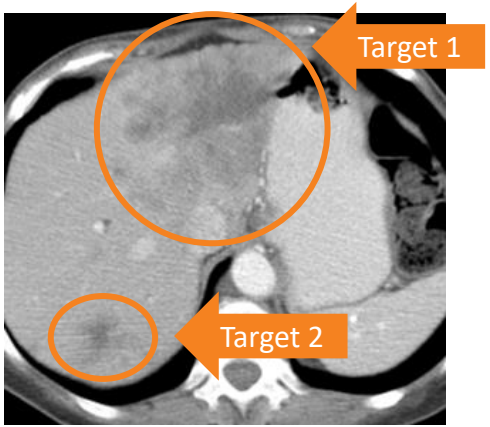
Other targeted agents: Everolimus

Chemotherapy: 2 Regimens
- 1 neoadjuvant + 1 metastatic

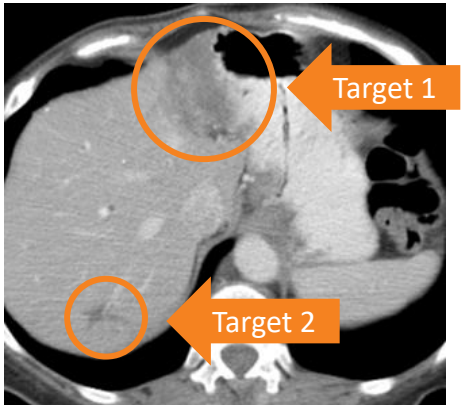
ESR1 mutations

D538G

Baseline CT Scan



After 4 Cycles

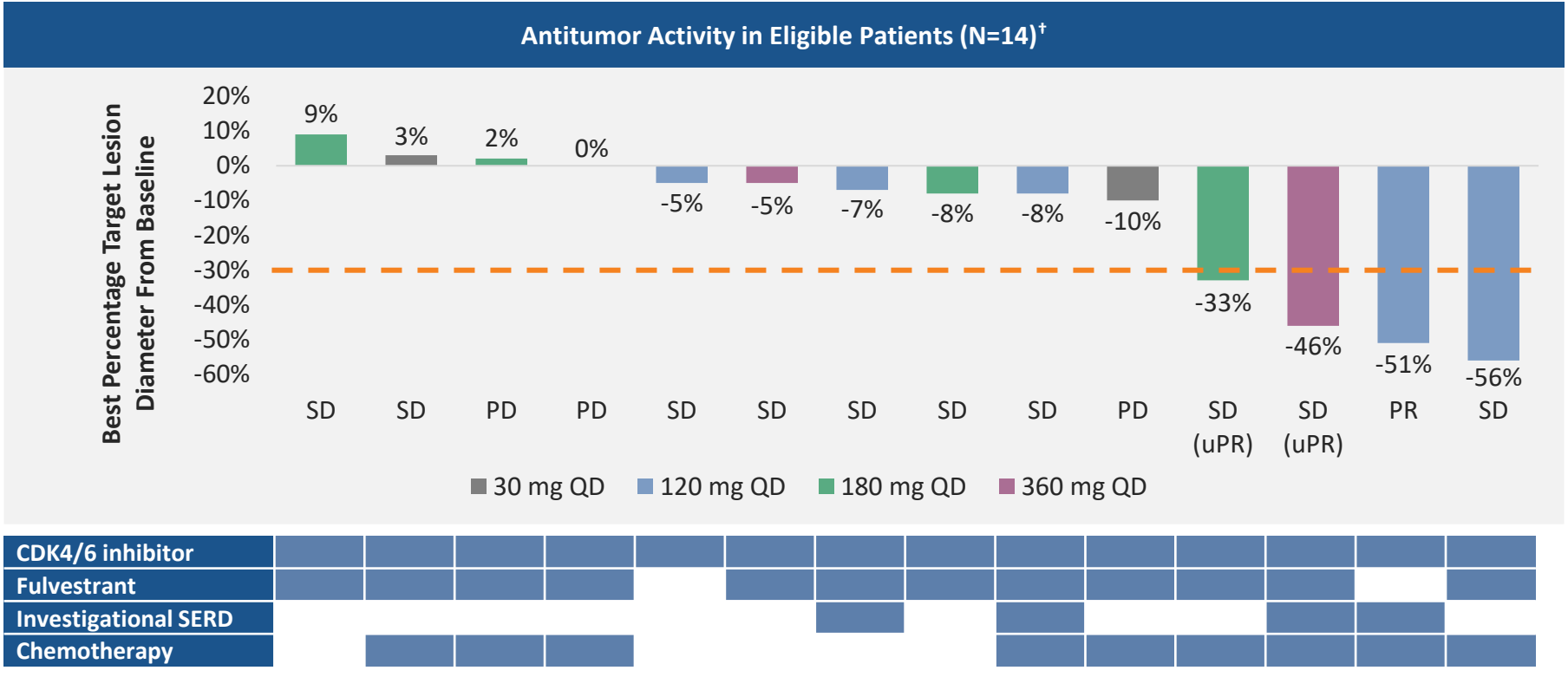


51% reduction in target lesions (RECIST partial response)

† Includes one selective ERα covalent antagonist.
CDK: cyclin-dependent kinases

ARV-471 demonstrates promising anti-tumor activity in late line patients

Data as presented 12/14/2020



† 7 patients out of 21 are excluded from graph due to no measurable disease at baseline (n=4), discontinuation of treatment without post-treatment target lesion measurements (n=2), and discontinuation after 2 doses due to non-compliance (n=1).

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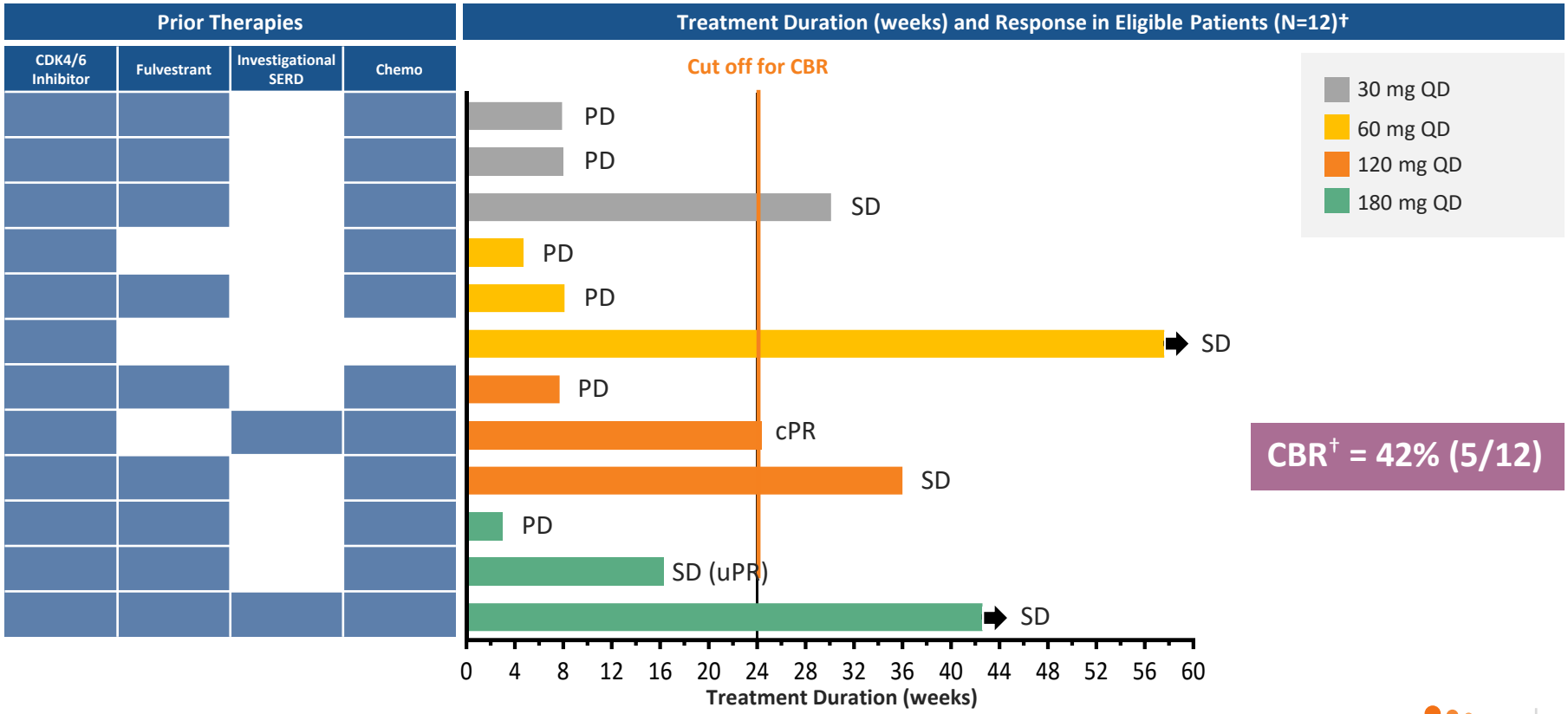
ARV-471 achieves a high clinical benefit rate (42%) in this heavily pretreated population through the 180 mg dose level

Data as presented 12/14/2020



CBR† = 42% (5/12)

† Excludes 8 patients enrolled < 24 weeks prior to the data cut-off of November 28, 2020 and 1 patient who received 2 doses of ARV-471 and discontinued due to non-compliance, †† CBR defined as SD persisting ≥ 24 weeks, or a best response of confirmed CR or PR.

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Comparison of ARV-471 profile with Phase 1 data for clinical-stage SERDs

Data as presented 12/14/2020

Phase 1 Data Comparison									
Drug Candidate	CDK4/6i Pretreated Patients *(0 – 100%)*	Clinical Benefit Rate	Mean ER Degradation in Patient Tumors	Select TRAEs (> 5% of Patients)					
				Gastrointestinal (GI) AEs			Other AEs		
				Diarrhea	Nausea	Vomiting	Bradycardia	Visual disturbance	
ARV-471	100%	42%	62% *Interim*		●	●			
H3B-6545	87%	34%	*Not reported*	●	●	●	●		
ZN-C5	87%	40%	*Not reported*	●	●	●			
Rintodestrant	70%	30%	28%	●	●	●			
SAR439859	63%	34%	*Not reported*	●	●	●			
AZD9833†	62%	35%	<50%††		●	●	●	●	
GDC9545	59%	41%	<50%††	●	●		●		

ARV-471 has the potential to be a best-in-class ER-directed therapy

Source: H3B-6545 SABCS 2020 Poster, ZN-C5 SABCS 2020 Poster, Rintodestrant SABCS 2020, SAR439859 SABCS 2020 Poster, AZD9833 SABCS 2020 and ASCO 2020 Posters, GDC-9545 SABCS 2019 Poster. This comparison utilizes data from different Phase 1 trials and presents a non-head-to-head summary comparison.
† Reported AEs are from ASCO 2020 Poster; ††Visual estimation based on ER degradation data provided by each company.

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We initiated our VERITAC Phase 2 expansion trial of ARV-471 with a once daily, oral dose of 200 mg

Trial Design

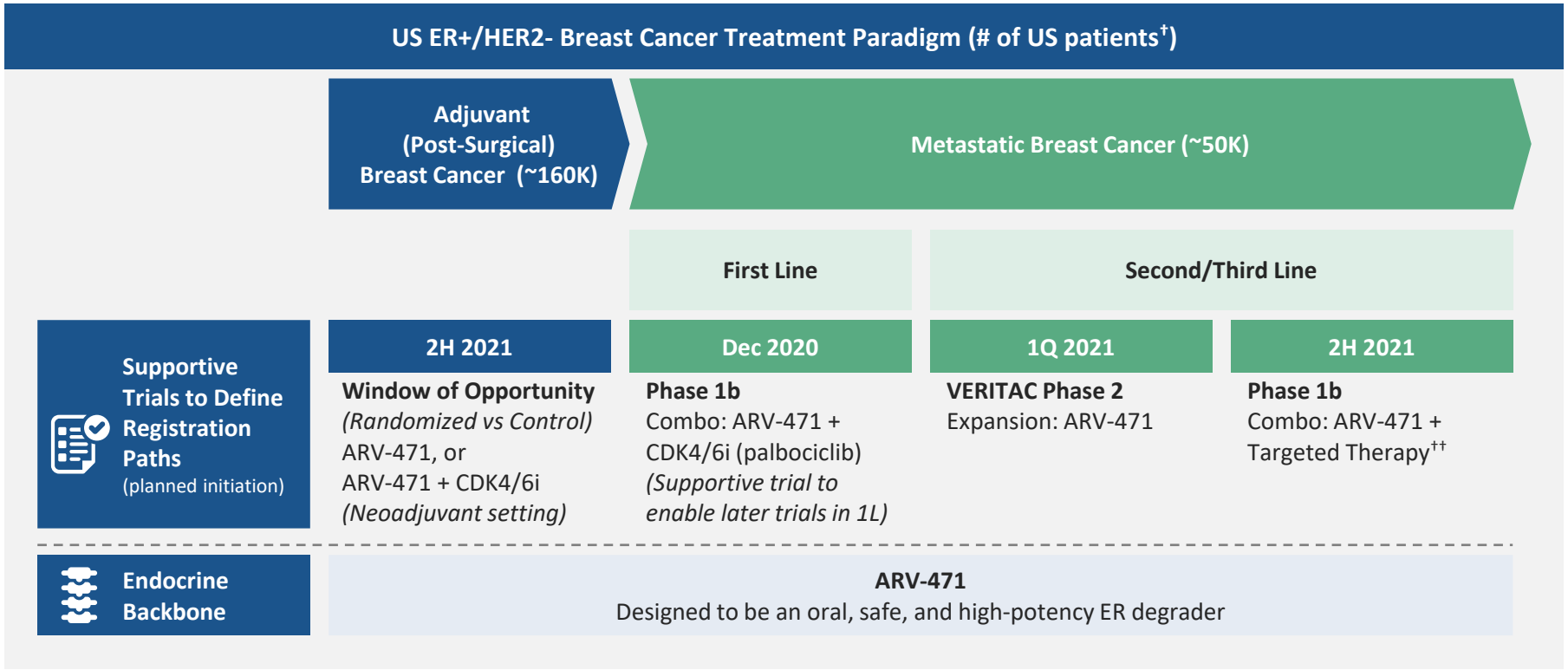
- Single arm Phase 2 monotherapy expansion trial (N=50)
- Dose: 200 mg per day (oral)
- Key inclusion criteria:
  - Prior CDK4/6 inhibitor therapy
  - ≤ 1 prior chemotherapy regimen for advanced disease
  - ≥ 6 months duration with ≥ 1 prior endocrine therapy

Endpoints

- Primary: Clinical benefit rate at 24 weeks
- Secondary:
  - RECIST response rate, duration of response, and PFS
  - Safety
  - PK
  - Biomarkers (paired biopsies for ER degradation in selected patients)

We plan to select a second dose based on data from the ongoing Phase 1 dose escalation

We aim to characterize the activity of ARV-471 across ER+/HER2- breast cancer treatment lines



† SEER database; includes US patient population only, †† E.g., everolimus or alpelisib
CDK, cyclin-dependent kinase

ARV-471: Evidence for best-in-class potential in a large area of unmet need

Data as presented 12/14/2020

Strong Evidence for Best-in-Class Profile

- **Superior degradation to fulvestrant and SERDs**†
- **Strong efficacy signal** in a predominantly ER-independent population
- **Well tolerated**

Clear Development Path

- Potential for **2L/3L approval as monotherapy** or in combination
- Planned **combinations with CDK4/6 inhibitors in adjuvant or early metastatic cancers**

Large Unmet Need and Opportunity

- In the US alone, ER+/HER2- breast cancer represents an **addressable patient population of >200K**†† **per year** and a market opportunity of **>$15B**

† Fulvestrant degradation reported in Robertson et al., Breast Cancer Research (2013) and Kuter et al., Breast Cancer Res Treat (2012). †† US incidence from SEER Database.

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Clinical-stage Oncology Programs: ARV-110

ARV-110 has the potential to address unmet need across multiple stages of prostate cancer

Data as presented 12/14/2020

ARV-110

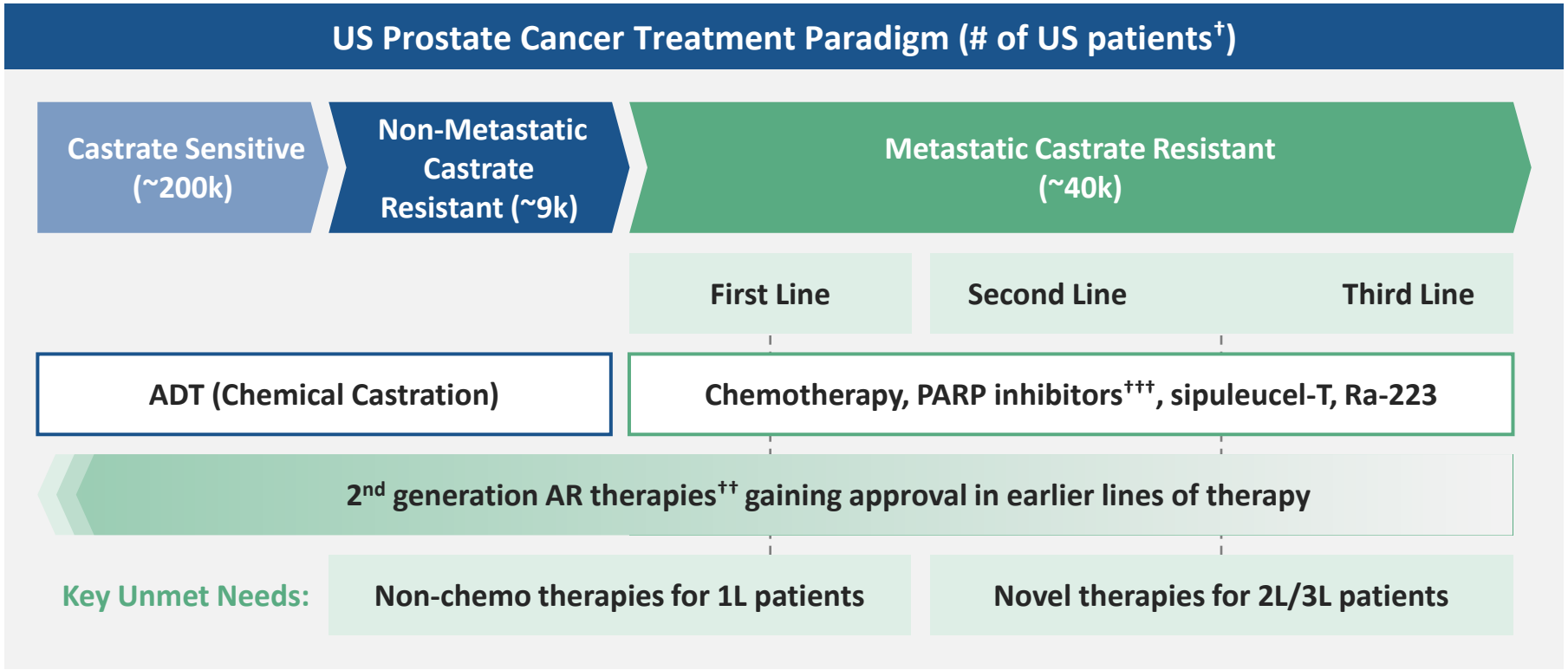
Androgen receptor-degrading PROTAC®

Prostate Cancer

- Two potential paths to registration: 3L molecularly defined, and broader 1L/2L
- Potential best-in-class profile
- High unmet need: >250k patients per year in the US alone†, and potential opportunity >$8b
- In Phase 1, 40% PSA50 in a molecularly-defined, highly refractory mCRPC population
- AR degradation and late-line activity suggest strong potential across multiple stages of prostate cancer
- Well tolerated, and oral route of administration
- Traditional small-molecule manufacturing requirements
- ARDENT Phase 2 dose expansion begun at 420 mg; Phase 1 dose escalation trial continues

mCRPC, metastatic castrate resistance prostate cancer; CSPC, metastatic castrate sensitive prostate cancer
† US incidence data from SEER database

Migration of second-generation AR therapies to earlier settings has created substantial unmet need for new treatments in mCRPC



† SEER database,†† Includes enzalutamide, abiraterone, darolutamide, apalutamide, ††† Approved for BRCA mutant/DNA Deficient Repair (DDR) patients progressed on 2nd gen AR-directed therapies. ADT, androgen deprivation therapy; mCRPC, metastatic castrate resistant prostate cancer

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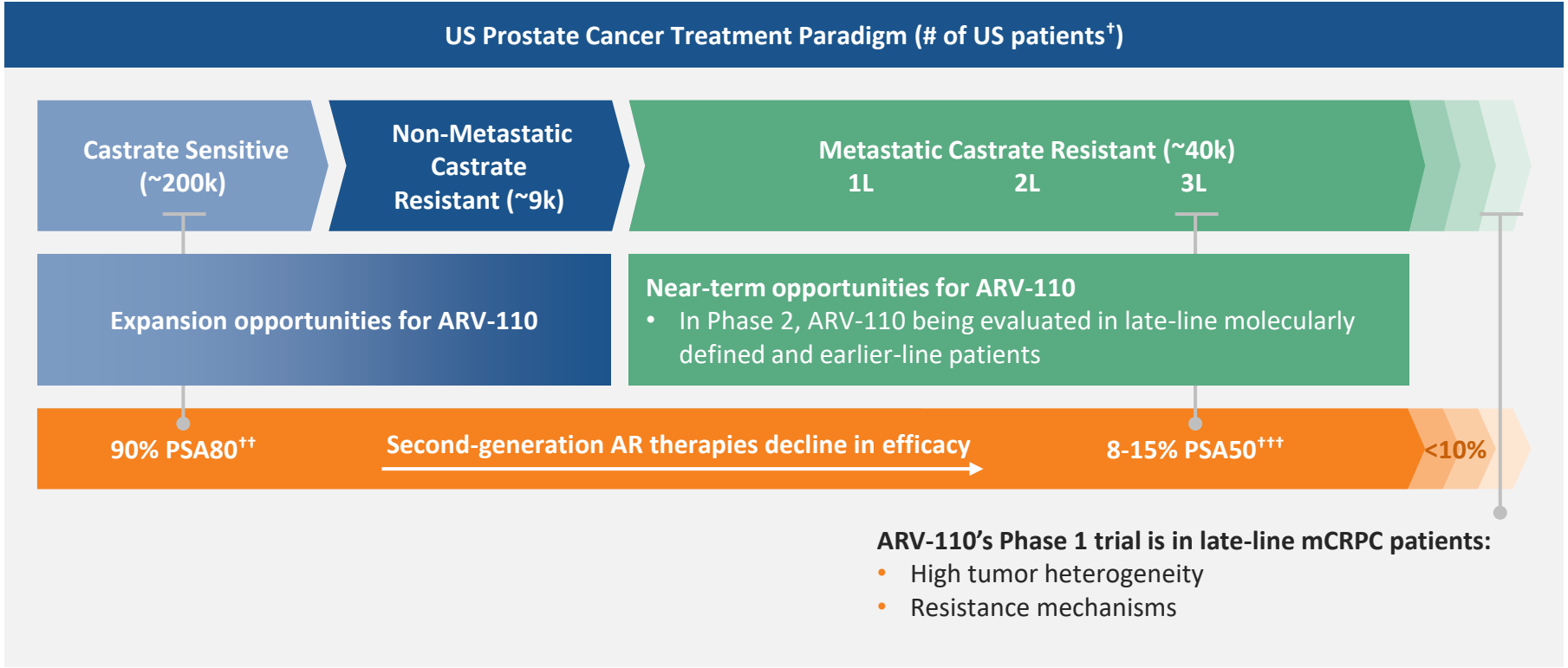
Our strategy is to develop ARV-110 across treatment settings of prostate cancer



† SEER database; †† Tombal, Lancet Oncology 2014; ††† de Wit R, N Engl J Med. 2019; Hussain, ESMO 2019.

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)

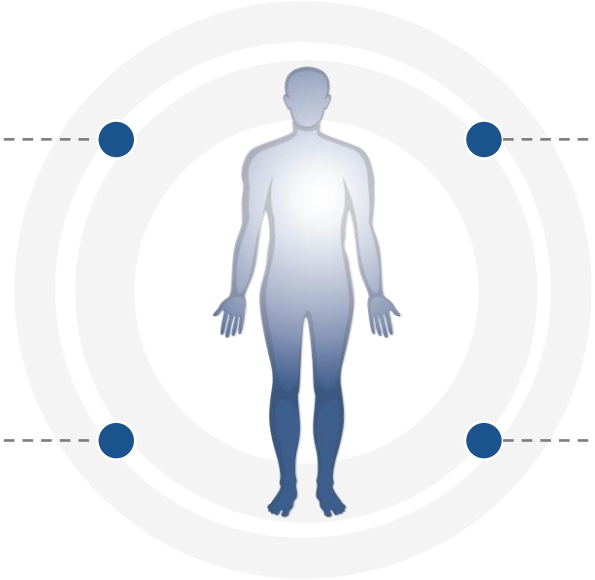
mCRPC= metastatic castration-resistant prostate cancer. RECIST= Response Evaluation Criteria in Solid Tumors. ctDNA, circulating tumor DNA. PSA, prostate-specific antigen

ARV-110 is showing early clinical benefit in highly refractory patients

Data as presented 12/14/2020

Median prior therapies **5**

Patients treated with both abiraterone and enzalutamide **82%**



76% Patients treated with prior chemotherapy

84% Patients with non-AR mutations

Existing AR-directed therapies **expected to be ineffective**

High tumor heterogeneity suggests **low dependence on AR**

ARDENT Phase 2 has initiated with a once daily, oral dose of 420 mg

Design informed by Phase 1 learnings

Promising antitumor activity in heavily pre-treated patients with limited treatment options

PSA reduction is associated with **plasma exposure**

AR molecular profiling identifies **a molecularly defined**, late line population that may **have greatest response to ARV-110**

Activity in wild-type AR patients supports **broader use**

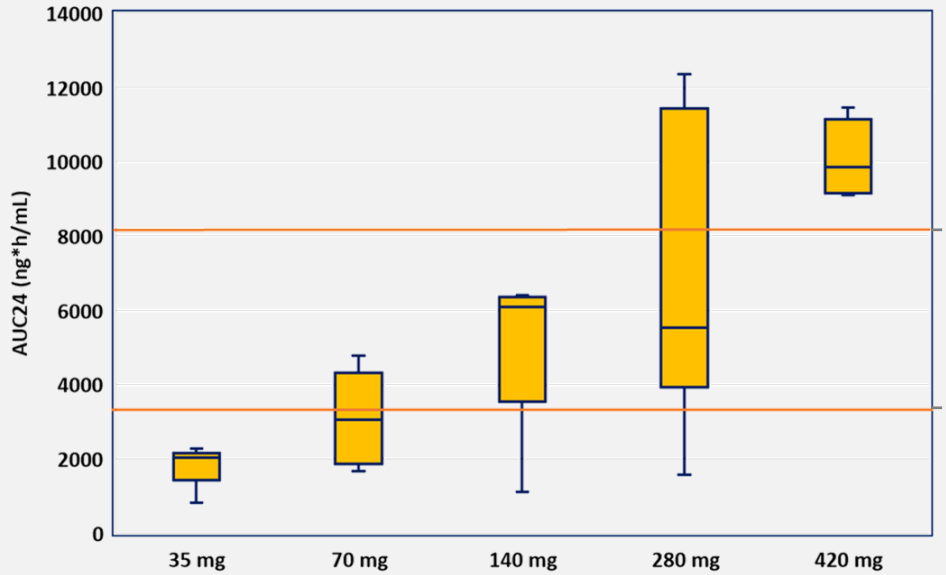
ARV-110 is well tolerated, allowing continued dose escalation up to current dose of 700 mg daily†, and potentially **supporting use in earlier lines of therapy**

† Safety cut-off date: October 2, 2020

At 420 mg, exposures exceed the predicted efficacious threshold observed in a preclinical enzalutamide-resistant model

Data as presented 12/14/2020

ARV-110 AUC_{24} Across Total Daily Doses (C1D15/21)†††



Predicted efficacious threshold based on an **enzalutamide-resistant prostate cancer** model ††

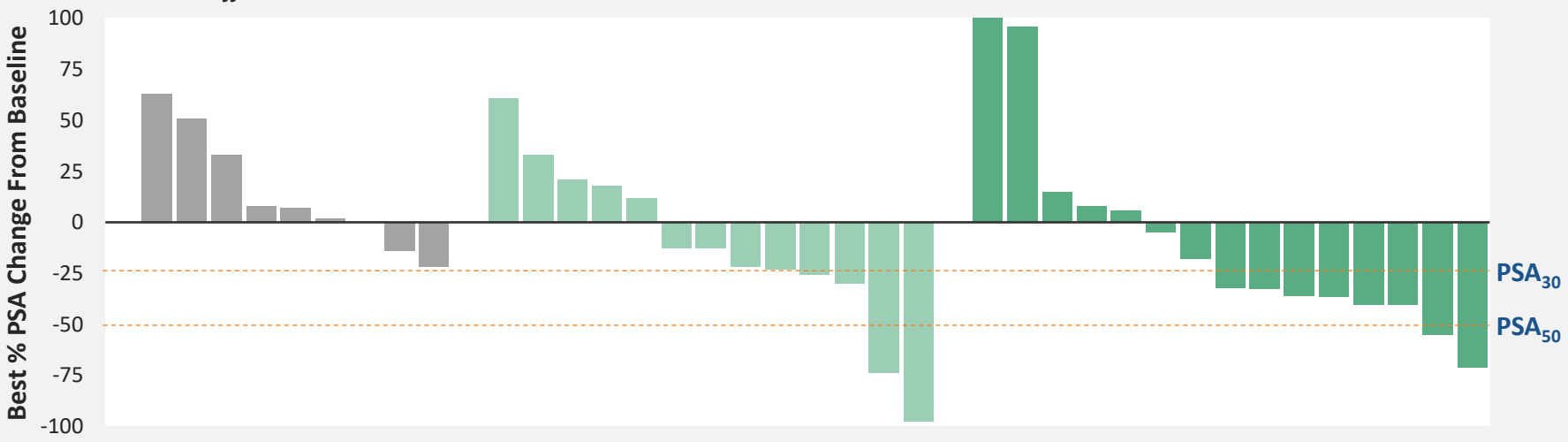
Predicted **minimum** efficacious threshold based on a standard prostate cancer model†

† The minimum preclinical efficacious threshold represents the AUC associated with tumor growth inhibition in standard VCAP models, †† This efficacious threshold represents the AUC associated with tumor growth inhibition in a preclinical enzalutamide-resistant VCaP model, ††† Includes both qd and bid dosing for the 420 mg total daily dose

ARVINAS

Increased ARV-110 clinical activity at higher exposures

Best PSA Change By Preclinical Efficacious Threshold (N=37)†



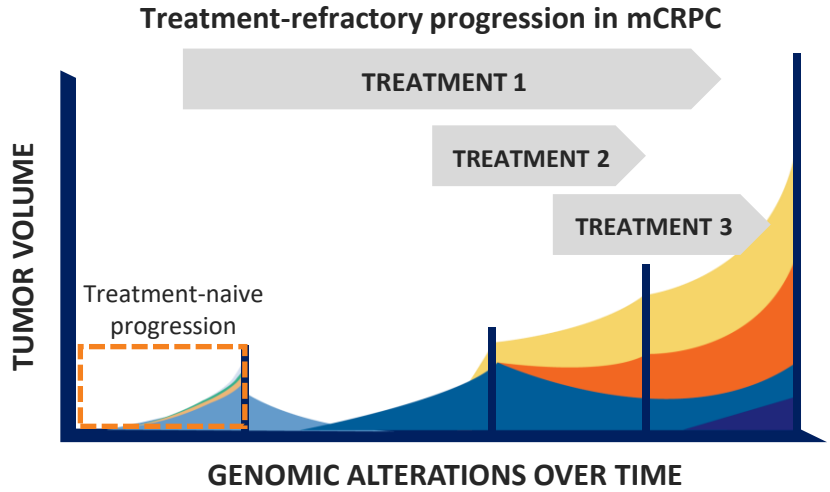
Exposure-activity relationship informs and supports Phase 2 dose selection

† Data as of 30-Nov-2020, †† Exposures in this range did not show anti-tumor activity, ††† Preclinical exposures in this range were sufficient to overcome enzalutamide resistance in preclinical models.

ARVINAS

We have identified ARV-110-sensitive populations despite significant tumor heterogeneity in our patient population

Genomic alterations are known to increase over time and with multiple treatments in mCRPC



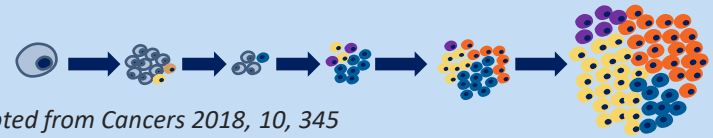


Figure adapted from Cancers 2018, 10, 345

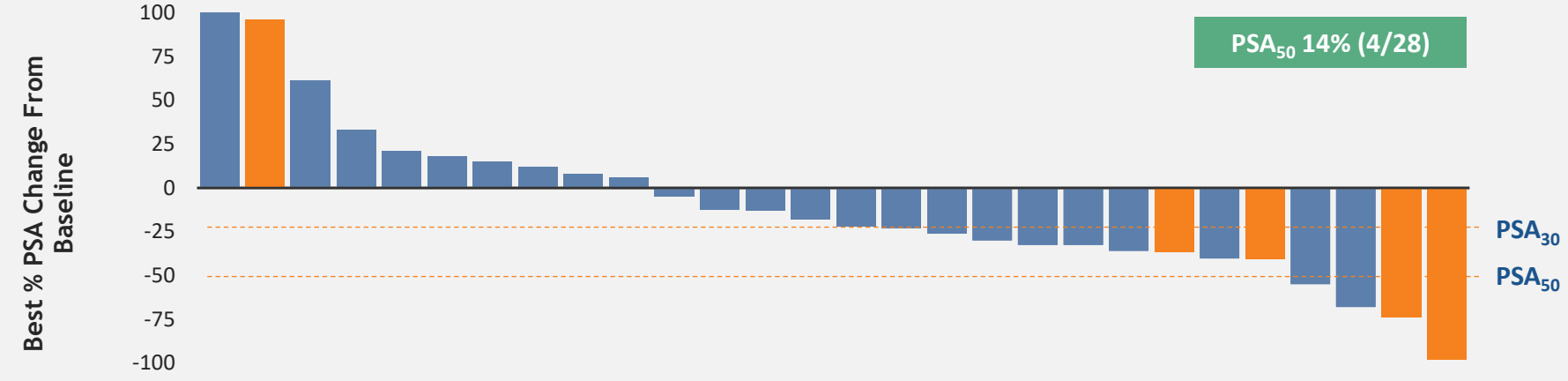
- **Genetic context, an important determinant of response, is the basis for our Phase 2 patient selection strategy**
- The tumors of patients in our Phase 1 dose escalation are highly heterogeneous
  - 84% have non-AR mutations††
  - Potential for high AR-independence
  - <10% PSA response expected
- In our studies, we are testing for mutations using 70- and now 324-gene panels†

† Genetic profiling for most Phase 1 patients was done using the FoundationOne®Liquid test (70-gene panel), additional Phase 1 and Phase 2 patients: FoundationOne®Liquid CDx (324-gene panel). †† Data as of 12/14/2020

ARVINAS

In our late stage, genetically heterogeneous population, we have identified potential molecularly defined subgroups of patients sensitive to ARV-110

Best PSA Change In All Patients Above Minimum Exposure Threshold (N= 28) †††



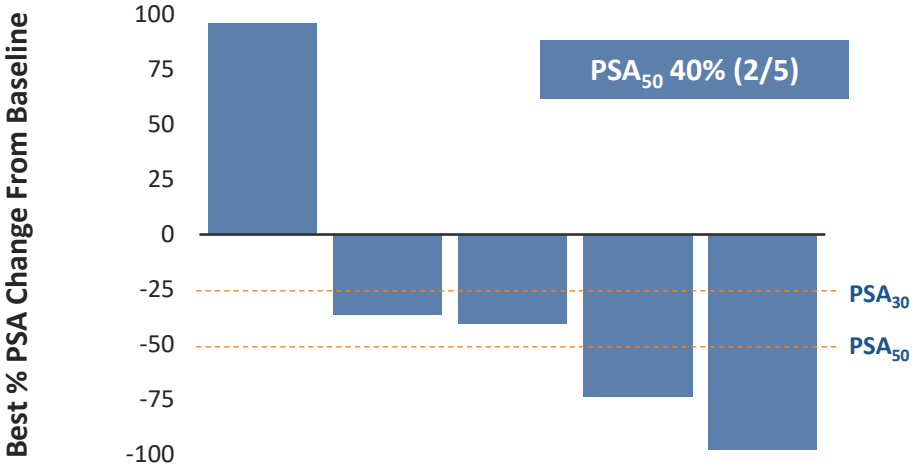
AR Status	Amp	T878A, H875Y, L702H	Amp	WT	WT	Amp	Amp	WT	Amp	W742C	L702H	WT	WT	WT	WT	WT	WT	WT	Amp	WT	WT	T878A, T878S, L702H	WT	T878A, F877L, V716M, L702H	WT	WT	T878A, H875Y	T878A, H875Y
AR-V7††			+	+	+										+				+		+	+						
Other Genes Altered (n)	1	2	1	2	2	0	2†	1	2	4	3†	0	2	0	1	1†	0	2	1†	1	3	5†	0	6†	2	0	3	1

20/28 (71%) of patients have either T878/H875 or wild-type AR

Each column represents one patient. † Includes genes with multiple alterations, †† Epic Sciences, Genetic profiling: FoundationOne®Liquid (70-gene panel), ††† Data as of 30-Nov-2020.

Four of five (80%) patients with T878/H875 mutations had PSA reductions, representing a potential accelerated approval population

Best PSA Change In Patients with AR T878/H875 mutations (N=5)††



AR Status	T878A, H875Y, L702H	T878A, T878S, L702H	T878A, F877L, L702H, V716M	T878A, H875Y	T878A, H875Y
AR-V7†††		+			
Other Genes Altered (n)	2	5†	6†	3	1
Treatment Duration (months)	1.4→	1.8	6.2→	7.7	10.1

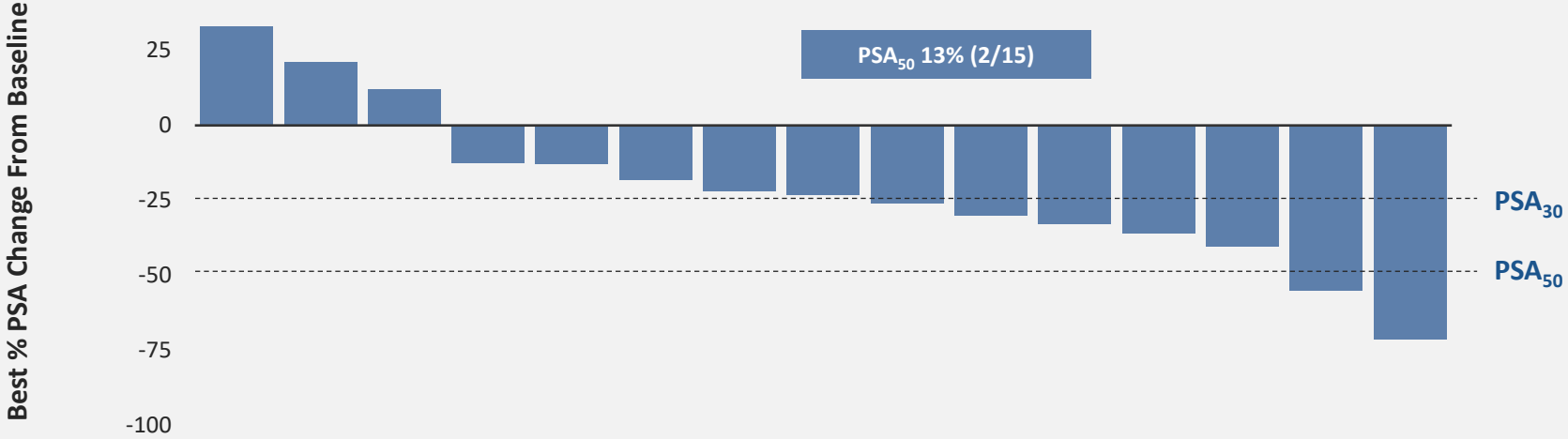
- Multiple AR mutations could be a "signature" for continued AR dependence
- PSA levels declined even in the presence of significant tumor heterogeneity, AR-V7, and L702H
- T878/H875 patients are a molecularly defined population for enrichment in our ongoing Phase 2 dose expansion, and represent a potential path to accelerated approval

Each column represents one patient. † Includes genes with multiple alterations, †† Includes all patients dosed above the minimum efficacious threshold and with T878/H875 AR (may include other forms of AR), ††† Epic Sciences, Genetic profiling: FoundationOne®Liquid (70-gene panel), →Patient remained on treatment as of November 30, 2020

ARV-110 is also active in refractory mCRPC patients with tumors expressing wild-type AR

Data as presented 12/14/2020

Best PSA Change In Patients with Wild-Type AR (N=15)††



AR Status	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT
AR-V7†††	+	+					+					+			
Other Genes Altered (n)†	2	2	1	0	2	0	1	1†	0	2	1	3	0	2	0

Wild-type AR-containing tumors represent a broader population sensitive to ARV-110

Each column represents one patient. † Includes genes with multiple alterations, †† Includes all patients dosed above the minimum efficacious threshold and with wild type AR, ††† Epic Sciences, Genetic profiling: FoundationOne®Liquid (70-gene panel).

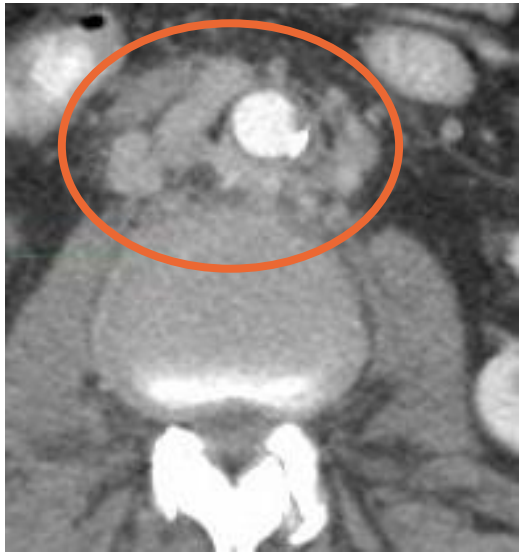
ARVINAS

RECIST confirmed response in a patient with extensive prior treatment

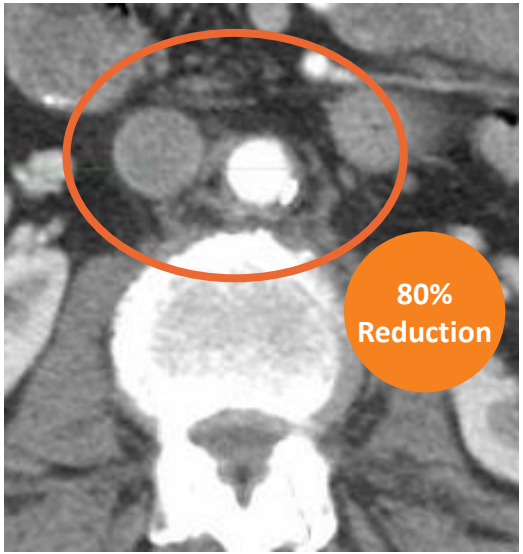
Data as presented at ASCO 2020 and as of 4/20/20

Patient Characteristics	
PSA response	**97%** decline
RECIST response	**80%** reduction
Duration of ARV-110	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	Provenge Cabazitaxel
History	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



RECIST: Response evaluation criteria in solid tumors
[1]Jernberg E, Endocrine Connections, 2017

Strong profile for ARDENT Phase 2 expansion trial at 420 mg, oral, once daily

Parameter	Phase 1 Results
Safety data†	✓ (Well tolerated; no TRAEs Gr >2)
Dose response and exposure threshold††	✓
Efficacy data††	✓
Strong signal in molecularly defined patient populations	✓
High potential for patient benefit in earlier-line, more AR-dependent patients	✓

Opportunity to select a second dose in 2021

† Safety cut-off date: October 2, 2020
†† For patients with molecular profiling, PK and PSA data as of 30-Nov-2020.

ARVINAS

ARDENT will evaluate efficacy in both late-line, molecularly defined patients, and in a broader, early-line mCRPC population

Features of the ARDENT Phase 2 Design

- Enriches T878/H875 for exploration as a potential population for accelerated approval, and retains optionality for others
- Enrolls earlier, more AR-dependent populations
- Provides a subgroup for all screened patients

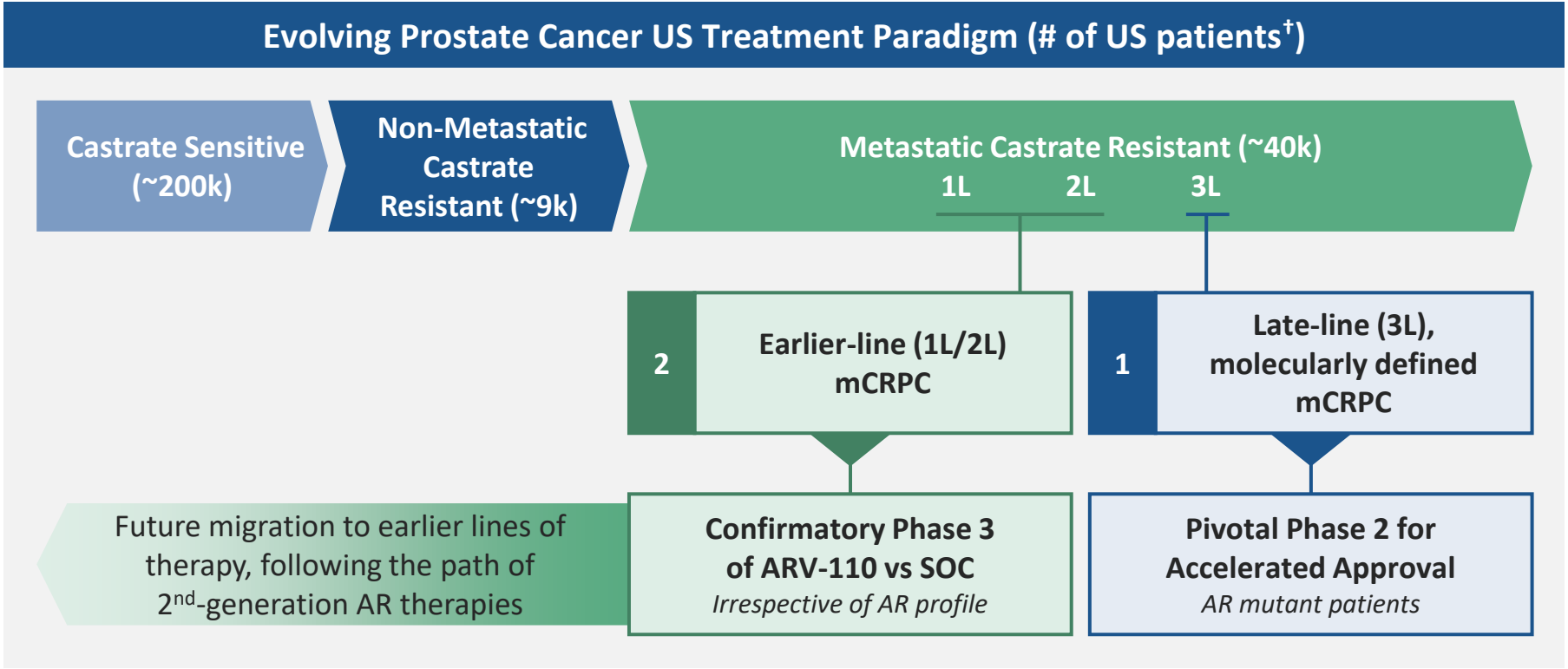
Patient Subgroup†	Tumor Characteristics
T878/H875	T878 and/or H875 AR mutated
Other AR degradable by ARV-110	AR wild type, amplified, and resistance-driving point mutations
AR not degradable by ARV-110	Tumors with L702H and AR-V7
Less-pretreated patients	Chemo-naïve, and progressed on abiraterone OR enzalutamide (*not both*)
Total N = ~100	

Potential registrational paths

1. **Late-line (3L), molecularly defined mCRPC**
   Potential for accelerated approval
2. **Earlier-line (1L/2L) mCRPC**
   Via confirmatory study

† Tumors are heterogeneous, so patients may fall into multiple subgroups for post-hoc analysis.

ARV-110's planned registrational path aligns with unmet need in mCRPC, and offers potential label expansion into earlier settings



† SEER database
SOC, standard of care; mCRPC, metastatic castrate resistant prostate cancer

ARV-110: Potential to address unmet need across multiple stage of prostate cancer

Data as presented 12/14/2020

Potential for Best-in-Class Profile

- Driving **tumor responses and PSA reductions** in a molecularly defined, late-line mCRPC population
- **Late-line activity** suggests **strong potential in CSPC**
- **Well tolerated**

Clear Development Path

- **Two potential registrational paths**
  - **Accelerated approval** in molecularly defined mCRPC
  - **Broader 1L/2L** mCRPC

Large Unmet Need and Opportunity

- High unmet need across all stages of prostate cancer
- Including CSPC, addressable patient population of >250K† per year in the US alone translates into a >$8B market opportunity

† US incidence from SEER Database
CSPC, castrate sensitive prostate cancer

ARVINAS

Preclinical Programs

PROTAC® protein degraders are designed to differentiate from other drug modalities

Target	Differential Biology Based on the Tenets of PROTAC® Degraders
BCL6 - *Transcription factor implicated in B cell lymphomas*	**Target scaffolding function of BCL6**
KRAS - *Oncogenic cell growth regulator*	**Target "undruggable" KRAS mutants (e.g., G12V, G12D)**
Myc - *Oncogenic transcription factor driving tumor cell proliferation*	**Directly degrade "undruggable" Myc vs. other indirect approaches**
HPK1 - *Suppressor of T cell activation; immuno-oncology target*	**Address potential scaffolding function**
mHTT - *Key target for Huntington's disease*	**Selectively degrade mutant huntingtin (mHTT) protein**

Detail follows

Arvinas' BCL6 program is aiming for an oral, best-in-class targeted therapy for B-cell malignancies

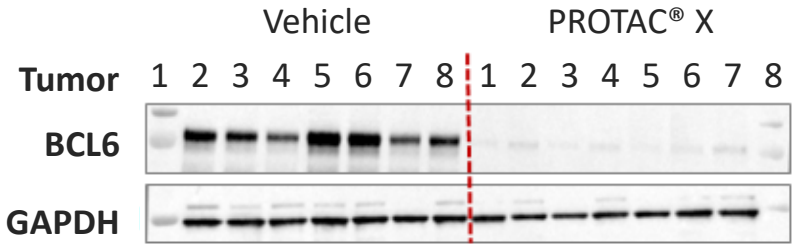
BCL6

Most B cell lymphomas are dependent on constitutive or deregulated expression of BCL6, a transcriptional repressor of:

- Cell cycle checkpoints
- Terminal differentiation
- Apoptosis
- DNA damage response

PROTAC® degradation would address the scaffolding function of BCL6

After oral dosing, PROTAC® X achieved >95% degradation of BCL6 in vivo



Farage DLBCL xenograft model

Optimizing in vivo tumor growth inhibition activity and selecting a candidate to take forward with anticipated IND in 2022

We are taking a comprehensive approach to degrading KRAS

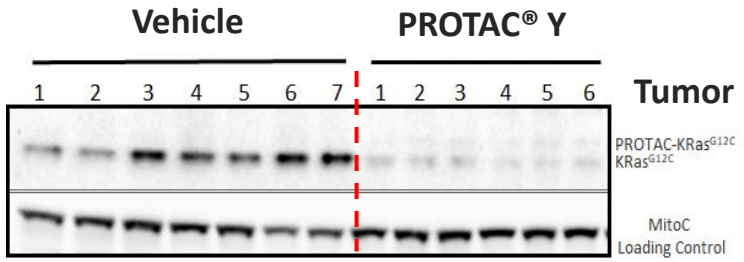
KRAS

KRAS is the most frequently mutated gene in human cancer and is a classic "undruggable" target due to its lack of deep "pockets"

We are creating pan-KRAS mutant, in addition to mutant-specific (e.g., G12D and G12V), degraders

As a proof of concept, we have successfully developed *in vivo* active KRAS G12C-specific PROTAC® degraders

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



MiaPaCa-2 xenograft model

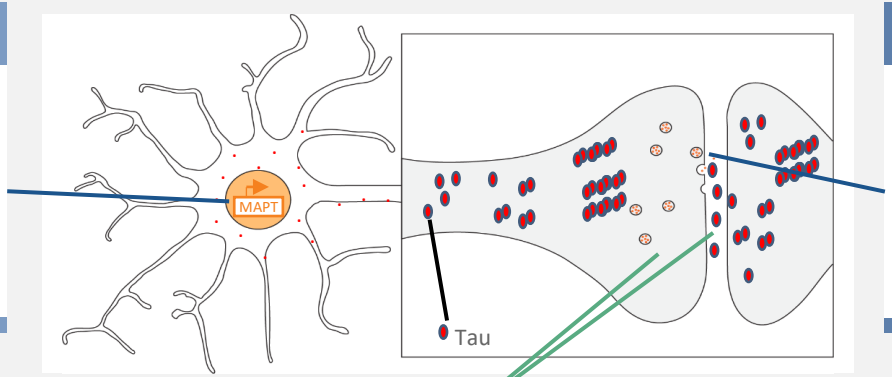
Leveraging learnings from KRAS G12C development to accelerate other KRAS degraders' development with anticipated IND in 2023

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 (ASOs) and monoclonal antibodies

ASOs

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



Antibodies

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

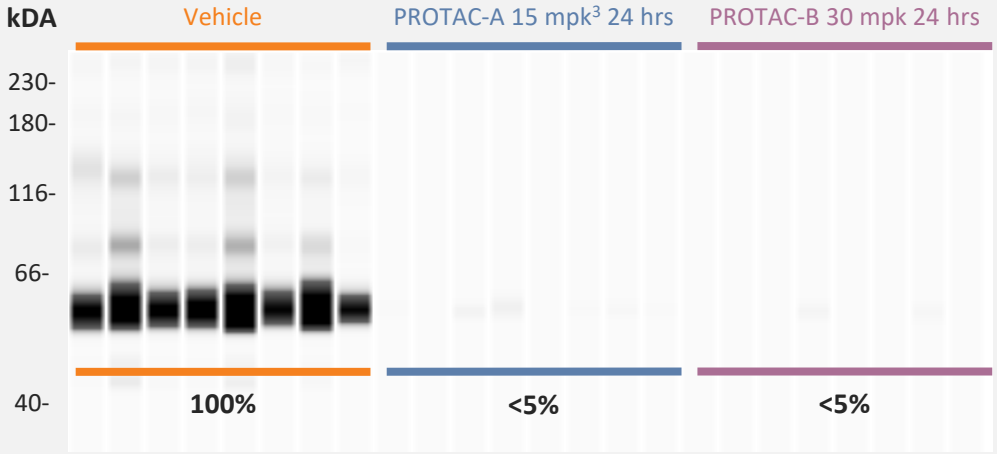
PROTAC *Potential*

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

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

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

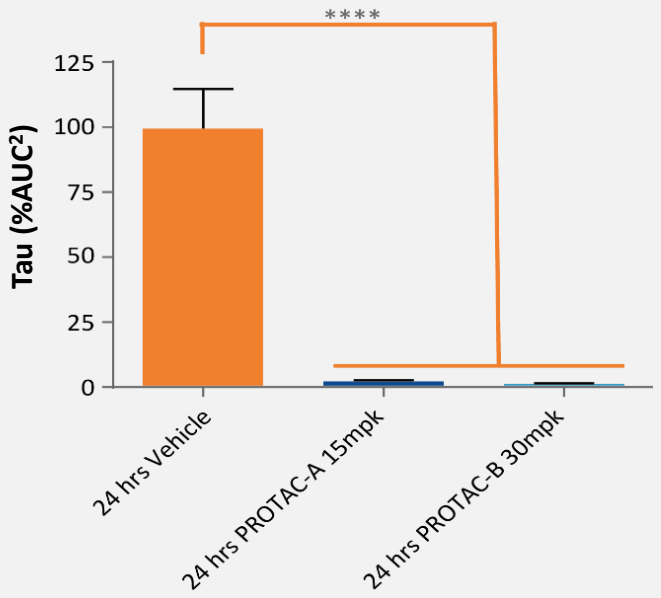
Tau Detection (protein capillary electrophoresis)



24 hours post dose:

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

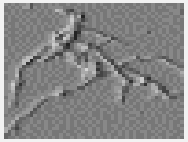
Pathologic tau in Tg2508[1] mouse cortex



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

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

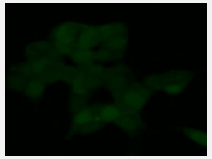
Tau Seeding Reporter Assay



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

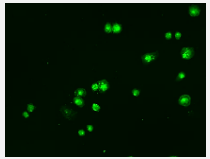
Modified from Holmes et al., 2014

24h



- Tau /- PFF Seeding

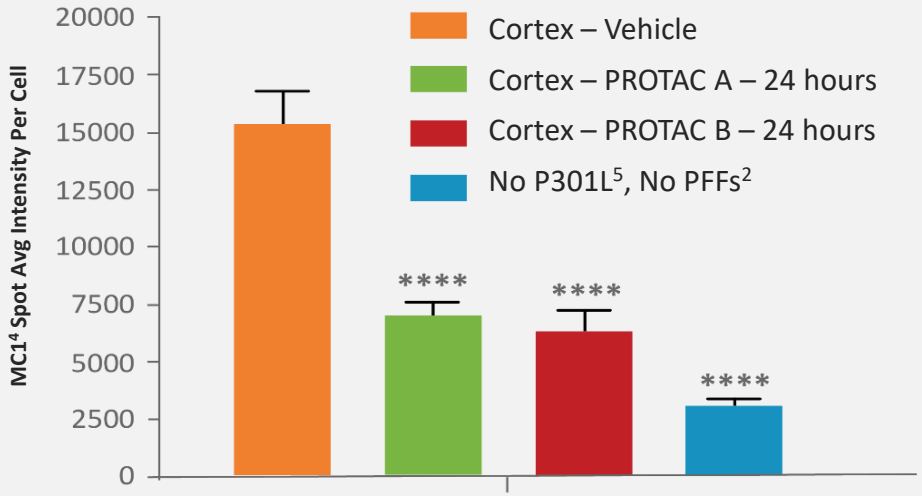
OR



+Tau /+ PFF Seeding

Dox-inducible Tau P301L CHO-K1[1]

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



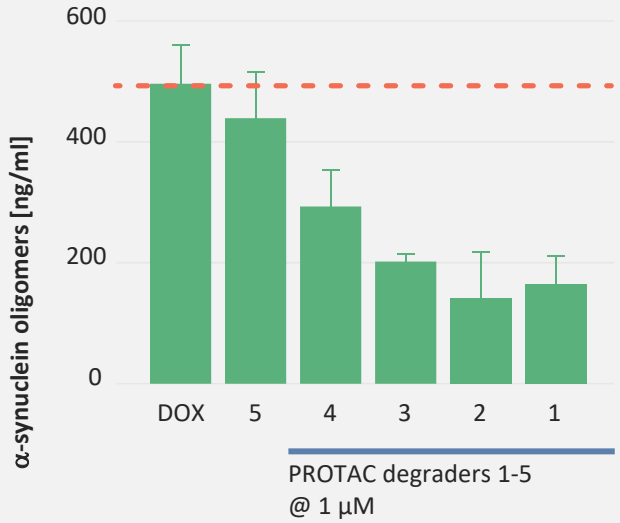
1 Tau P301L CHO-K1 is a cell line expressing a doxycycline-inducible tau mutation linked to FTDP-17 (frontotemporal dementia and parkinsonism linked to chromosome 17). 2 Pre-formed fibrils (PFFs) are used to "seed" tau aggregation. 3 Cortex lysates are from Tg2508 mice. 4 MC1 is an antibody that detects 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

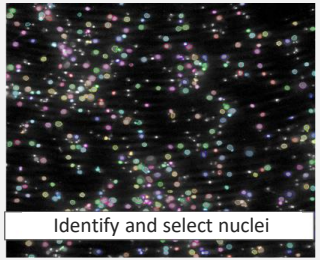
Oligomer-specific PROTAC® molecules degrade human α-synuclein aggregates in primary rat neurons

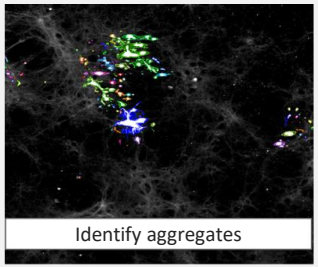
PROTAC molecules degrade oligomeric α-synuclein species

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

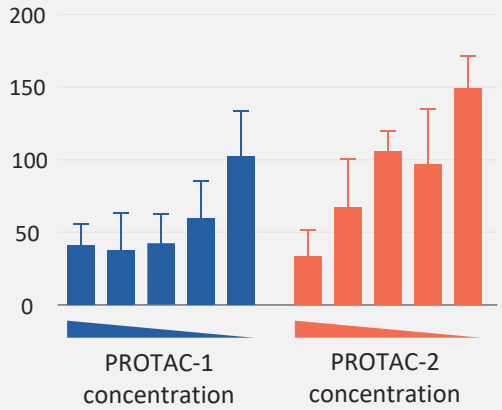




Neuronal α-synuclein +PFF induction assays[1]

Intensity and area features of α-synuclein aggregates calculated

Ratio: α-syn total intensity / cell mask[1]



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).

Corporate Overview

Arvinas is 190+ colleagues strong and growing, benefitting from the experience and resources of the Connecticut biotech sector

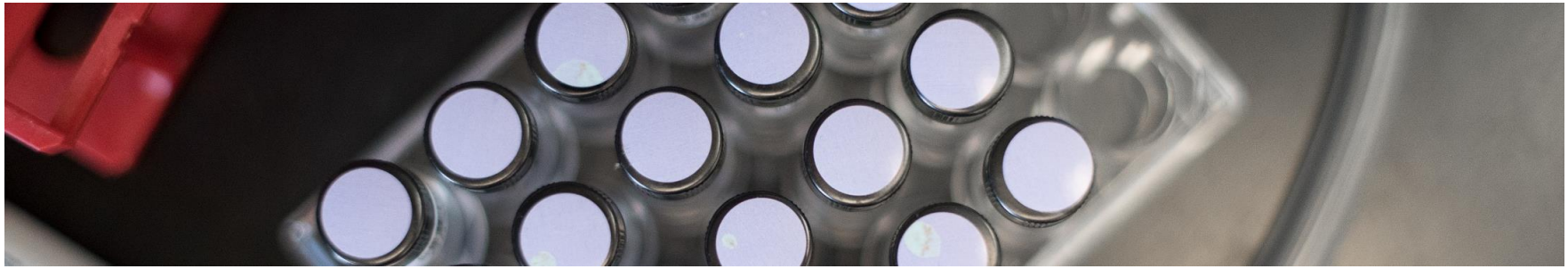
Mission

We invent PROTAC® protein degraders designed to destroy disease-causing proteins and improve the lives of patients suffering from cancer, neurological disorders, and other serious diseases

Core Values	• Pioneering, Excellence, Community, & Commitment
People	• 190+ highly experienced drug development professionals in New Haven, Connecticut • 200+ FTEs at contract research organizations
Bioscience in Connecticut	• 39,000 employees across 2,500 companies[1] • Strong academic base for R&D partnerships

[1]BioCT 2019 Report (link)

Financial snapshot



~$689 Million
Cash, cash equivalents, and marketable securities
(as of 12/31/20)

Guidance[1]
Expect cash, cash equivalents, and marketable securities to fund planned operations into 2024

48.9 Million[1]
Common shares outstanding

Analyst Coverage[2]
BMO, Cantor, Citibank, Evercore, Goldman Sachs, Guggenheim, HC Wainwright, Oppenheimer, Piper Sandler, Roth, Wedbush

1 Share count as disclosed in Form 10k filed with the SEC on 3/3/21; 2 The foregoing list includes the names of all brokerage firms known by the company as of 3/3/21 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.

We are well on our way to our 2024 vision

ARVINAS
2024 Vision

Integrated biotech poised for launch

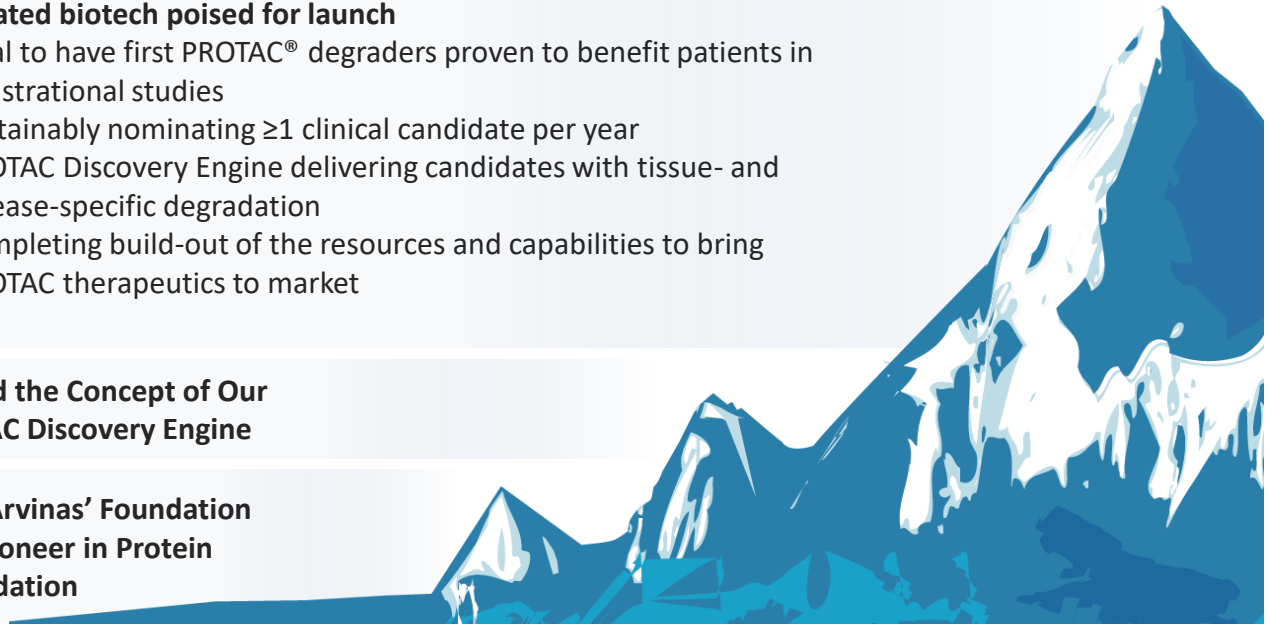
- Goal to have first PROTAC® degraders proven to benefit patients in registrational studies
- Sustainably nominating ≥1 clinical candidate per year
- PROTAC Discovery Engine delivering candidates with tissue- and disease-specific degradation
- Completing build-out of the resources and capabilities to bring PROTAC therapeutics to market

2019-2020

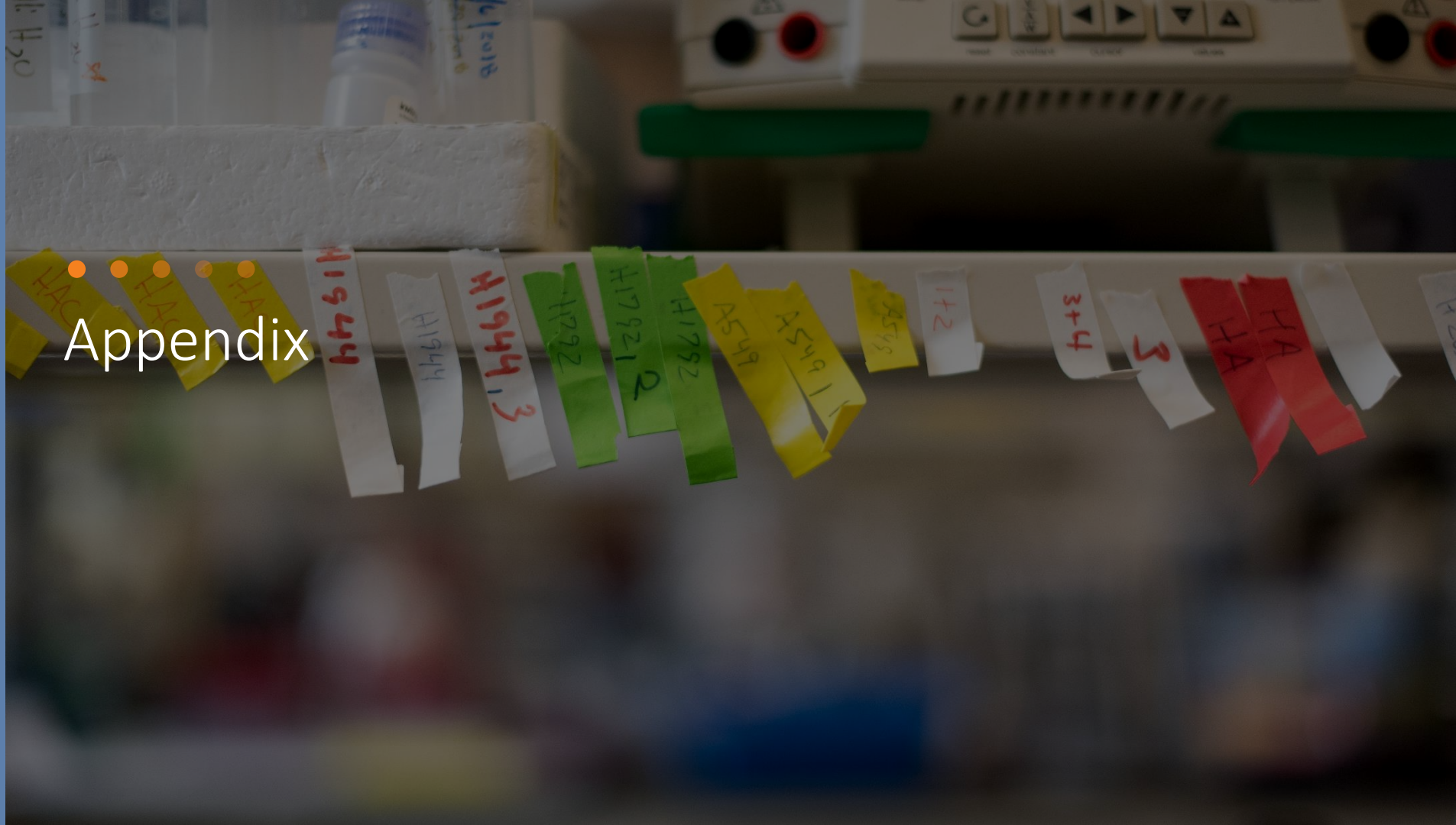
Proved the Concept of Our PROTAC Discovery Engine

2013-2018

Built Arvinas' Foundation as a Pioneer in Protein Degradation



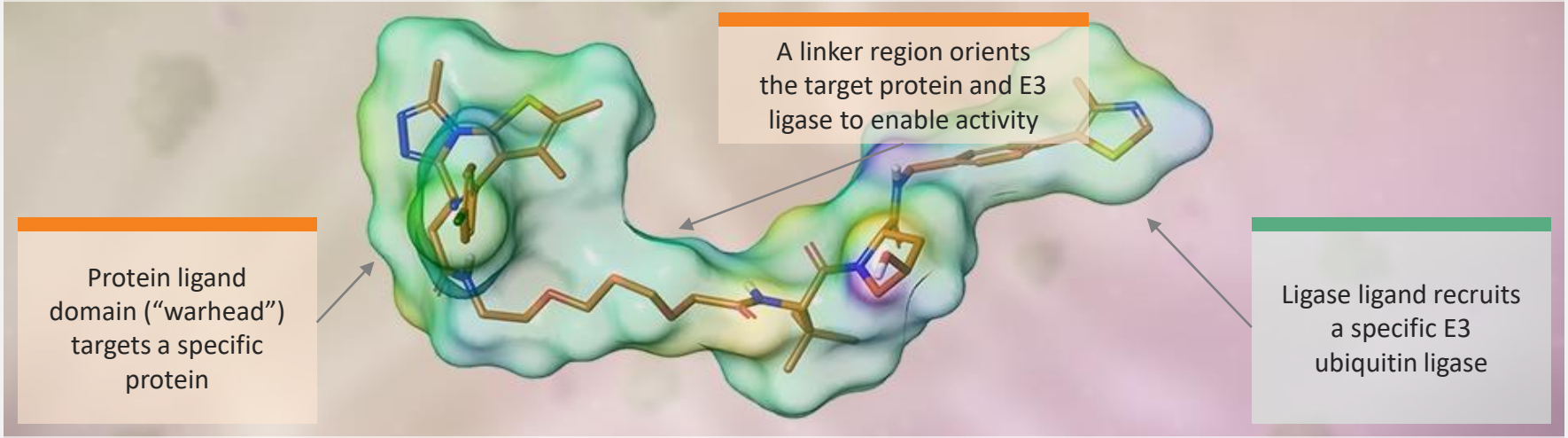
Thank You!



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

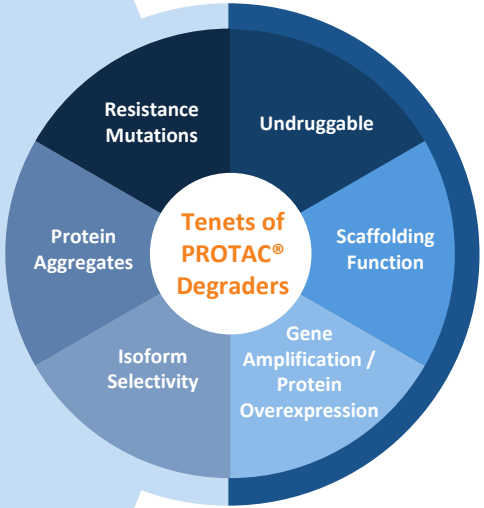


All three regions of the PROTAC degrader play a role in the specificity and potency of target degradation

Our target selection strategy is designed to build the optimal portfolio of PROTAC® protein degraders

Guiding principles for our portfolio strategy

- Focus on targets where degradation of the disease-causing protein will result in differential biology and patient outcomes versus other modalities
- Build on our established expertise and capabilities in oncology, immuno-oncology, and neuroscience
- Create a diversified, risk-balanced portfolio of validated and undruggable targets



Regression in chest wall lesions in a patient with extensive prior therapy and multiple ESR1 mutations at 180 mg

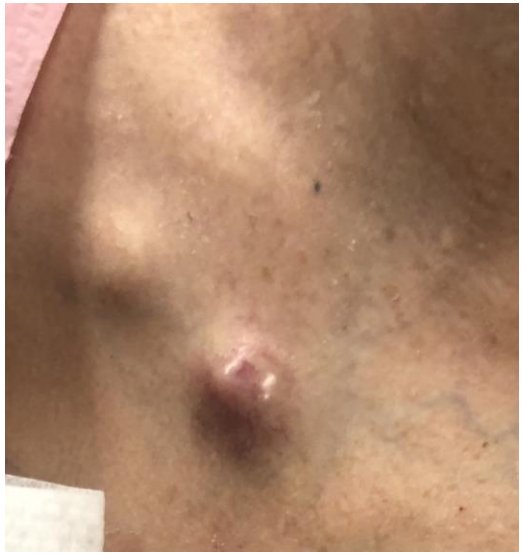
Extensive Prior therapy

- CDK4/6 inhibitor:
  - Palbociclib, Abemaciclib
- Endocrine therapies: 3 Agents
  - Aromatase inhibitors x 2
  - Fulvestrant
- Other targeted agents: Everolimus
- Chemotherapy: 4 Regimens
  - 1 neoadjuvant + 3 metastatic

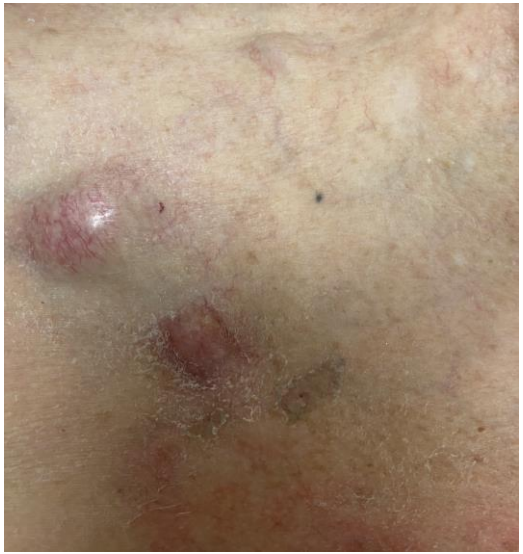
ESR1 mutations

- D538G, E380Q, V422del, L536P

Baseline (Associated Bleeding)



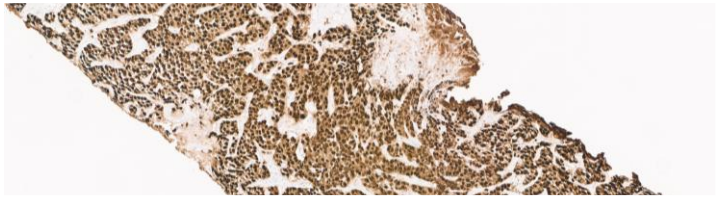
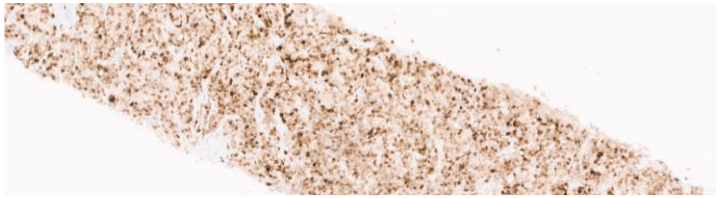
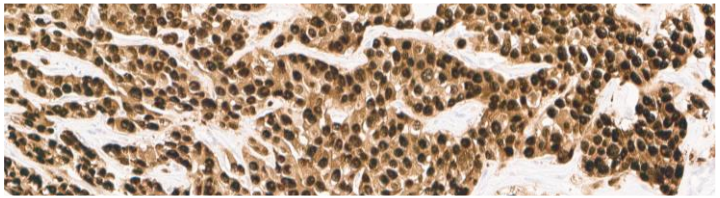
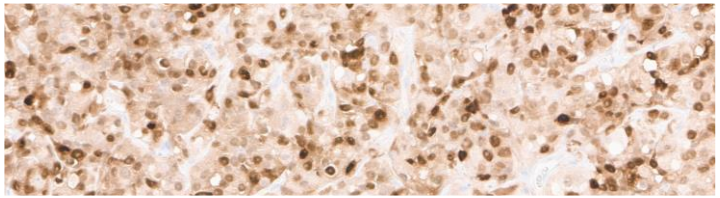
After 4 Cycles (No Bleeding)



CDK, cyclin-dependent kinases

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

	BASELINE	ON-TREATMENT
2.5X		
10X		

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

ARVINAS

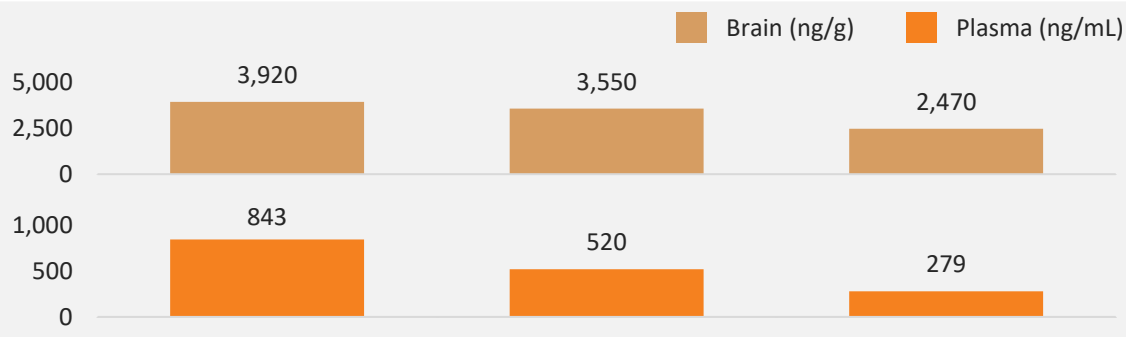
PROTAC® degraders can be engineered to cross the blood-brain barrier (BBB)

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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