# ARV-110 Phase 1/2 Dose Escalation: Interim Update

29 May 2020

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The PROTAC® Company

Safe harbor and forward-looking statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the development and regulatory status of our product candidates, such as statements with respect to our lead product candidates, ARV-110 and ARV-471, and the timing of clinical trials and data from those trials for our product candidates, and our discovery programs that may lead to our development of additional product candidates, the potential utility of our technology and therapeutic potential of our product candidates, the potential commercialization of any of our product candidates, 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, 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 our quarterly and annual reports on file with the Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect our current views as of the date of this presentation with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

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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**
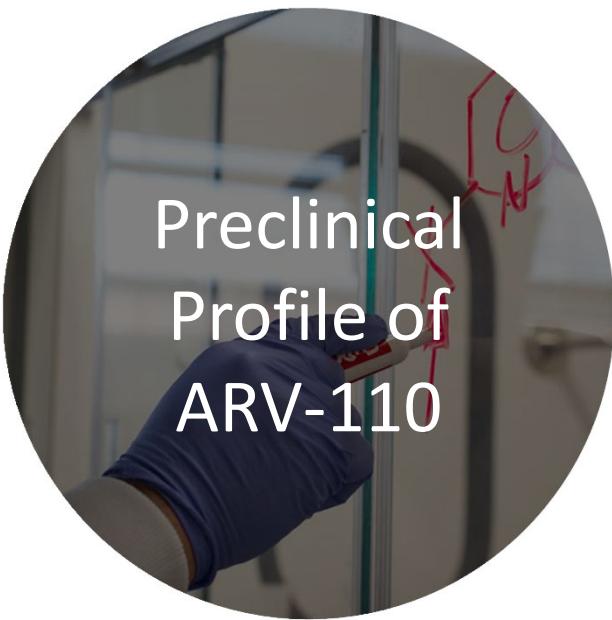
Safety data in humans

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

Preclinical profile translating to patient benefit

Potential for genetically defined development pathway

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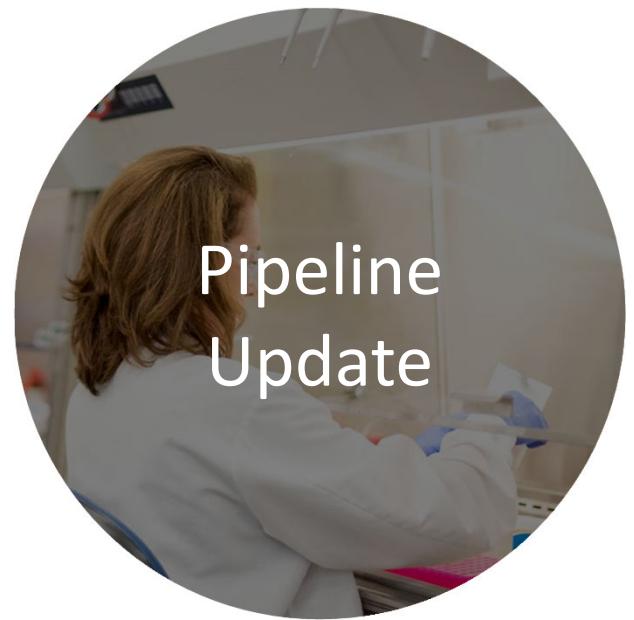
Today's presentation

**Preclinical Profile of ARV-110**
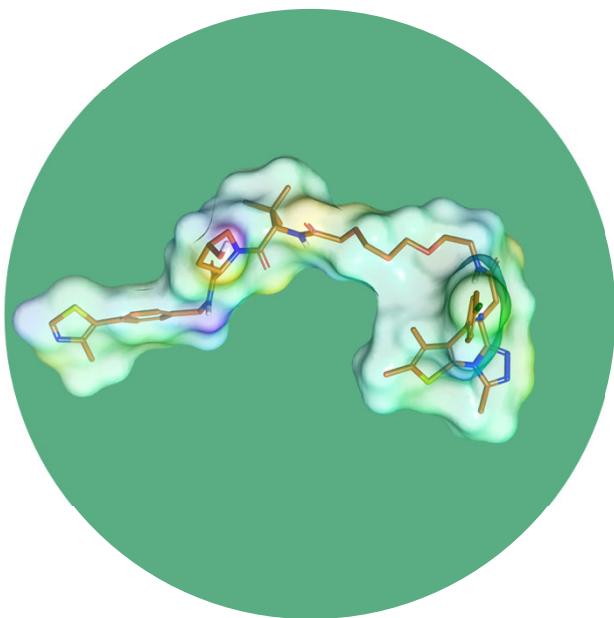
ARV-110 Clinical Data Update

Pipeline Update

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Today is a significant milestone for PROTAC® protein degraders

- First proof of concept for PROTAC® protein degraders

- Benefitting patients where traditional inhibitors have failed

- Validates our confidence in this novel therapeutic modality and our pipeline

Preclinical Profile of ARV-110

New approaches are needed to target the androgen receptor, a critical driver of 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]
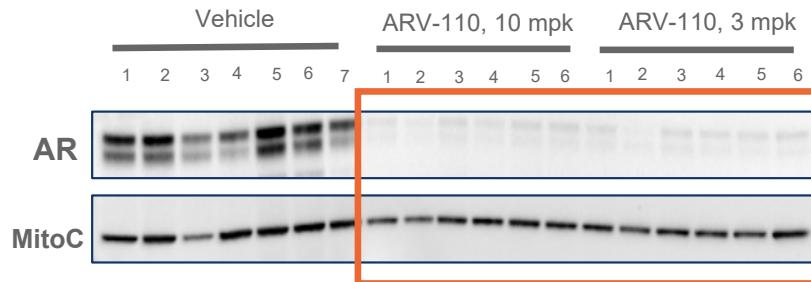
ARV-110 is a PROTAC® protein degrader that targets AR in multiple preclinical models of prostate cancer

ARV-110 targets wildtype and altered androgen receptor (AR) protein

- AR is a critical driver of prostate cancer

- *In vivo* activity in multiple xenograft models with:

  - AR gene amplification

  - AR mutation

  - Enzalutamide resistance and insensitivity

ARV-110 degrades >90% AR protein *in vivo*

Preclinical studies suggest settings where ARV-110 may be more active

- Degrades T878A, H875Y, F877L, and M895V point mutations

- Does <u>not</u> degrade L702H or AR-V7

  - L702H: Point mutation present in 3-10% of mCRPC patients[1]

  - AR-V7: Splice variant lacking the ligand binding domain of AR; ARV-110 may impact signaling via AR-V7 if heterodimerization with full length AR is required

- ARV-110 is <u>not</u> blood-brain barrier penetrant

mCRPC, metastatic castration-resistant prostate cancer
[1]Ledet E, The Oncologist 2019

In October, we showed that ARV-110 was well-tolerated and had reached exposures consistent with preclinical efficacy

Dose level[†]	Key safety findings
35 mg (N = 3)	• No dose limiting toxicities (DLTs) • No treatment related Adverse Events (AEs)
70 mg (N = 4)	• No DLTs • No grade 2/3/4 treatment related AEs
140 mg (N = 3[‡])	
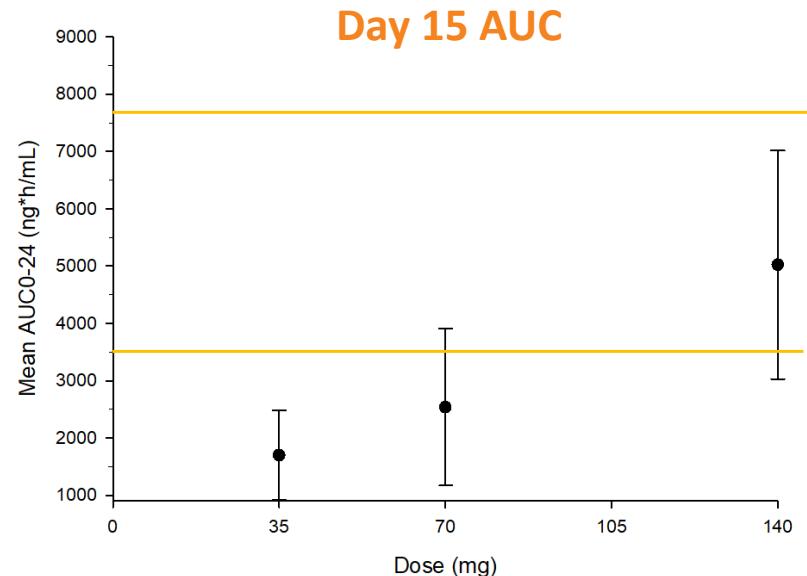
[†]Orally, once daily

[‡]Not including 1 non-evaluable patient (discontinued on day 1; patient's condition had worsened in the interval from screening to the morning of treatment initiation consistent with rapid progression)

[◊]Upper line based on enzalutamide-resistant vertebral cancer of the prostate (VCaP) models.
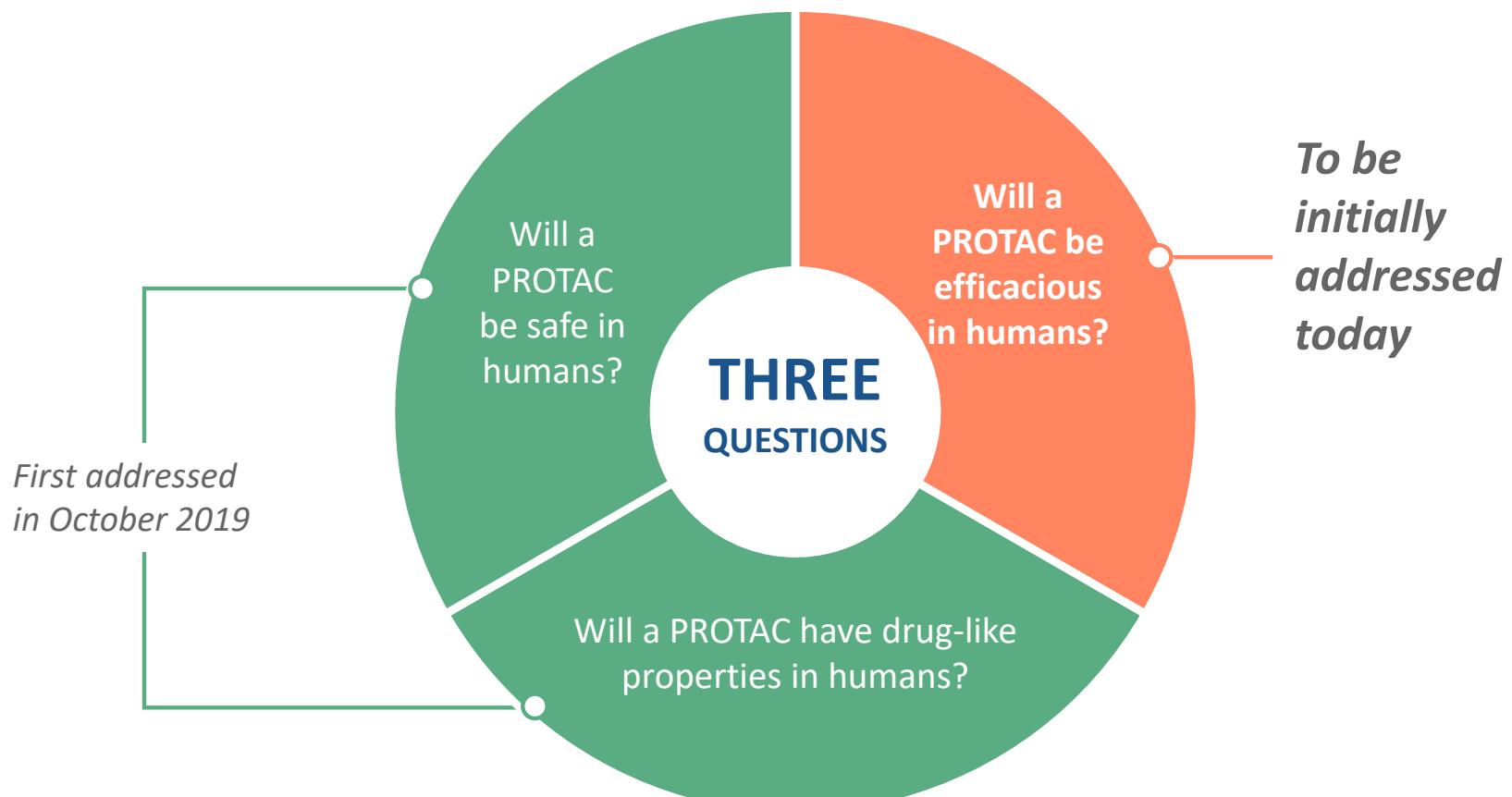
Lower line based on castrated and non-castrated VCaP model

AUC, area under the curve

Day 15 AUC

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

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Today, we will address the third critical question facing PROTAC® protein degraders as a new therapeutic modality

Will a PROTAC be safe in humans?

Will a PROTAC be efficacious in humans?

THREE QUESTIONS

Will a PROTAC have drug-like properties in humans?

To be initially addressed today

First addressed in October 2019

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ARV-110 Clinical Data Update

Our 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)

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Enrolled patients (N=22) have been highly pretreated at baseline

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

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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Evidence supporting potential interaction with rosuvastatin (Crestor®)

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 continues 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 indicate BCRP transporter inhibition by ARV-110[2]
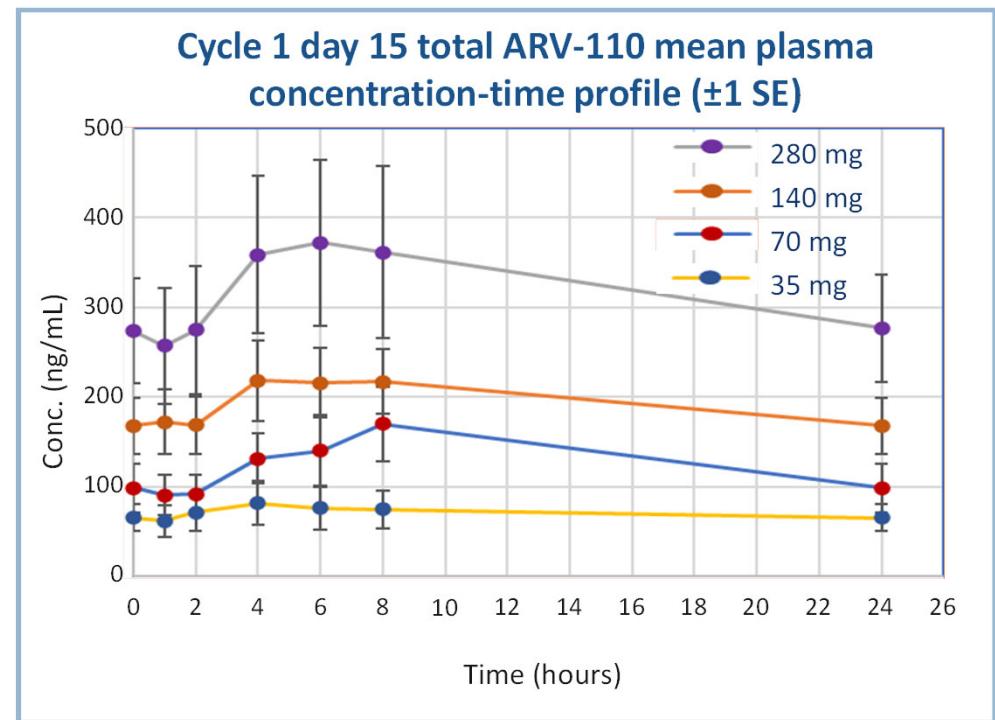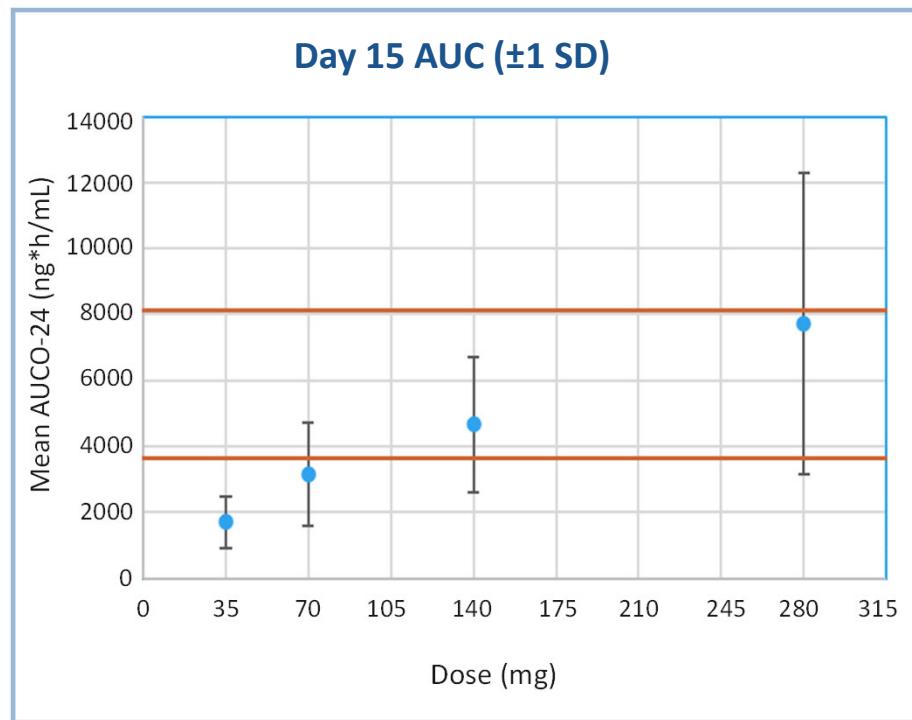
Following introduction of rosuvastatin restriction, no further elevation in LFTs observed

- 6 patients 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's exposures are dose-proportional and continue to demonstrate drug-like pharmacokinetics; half-life supports QD dosing
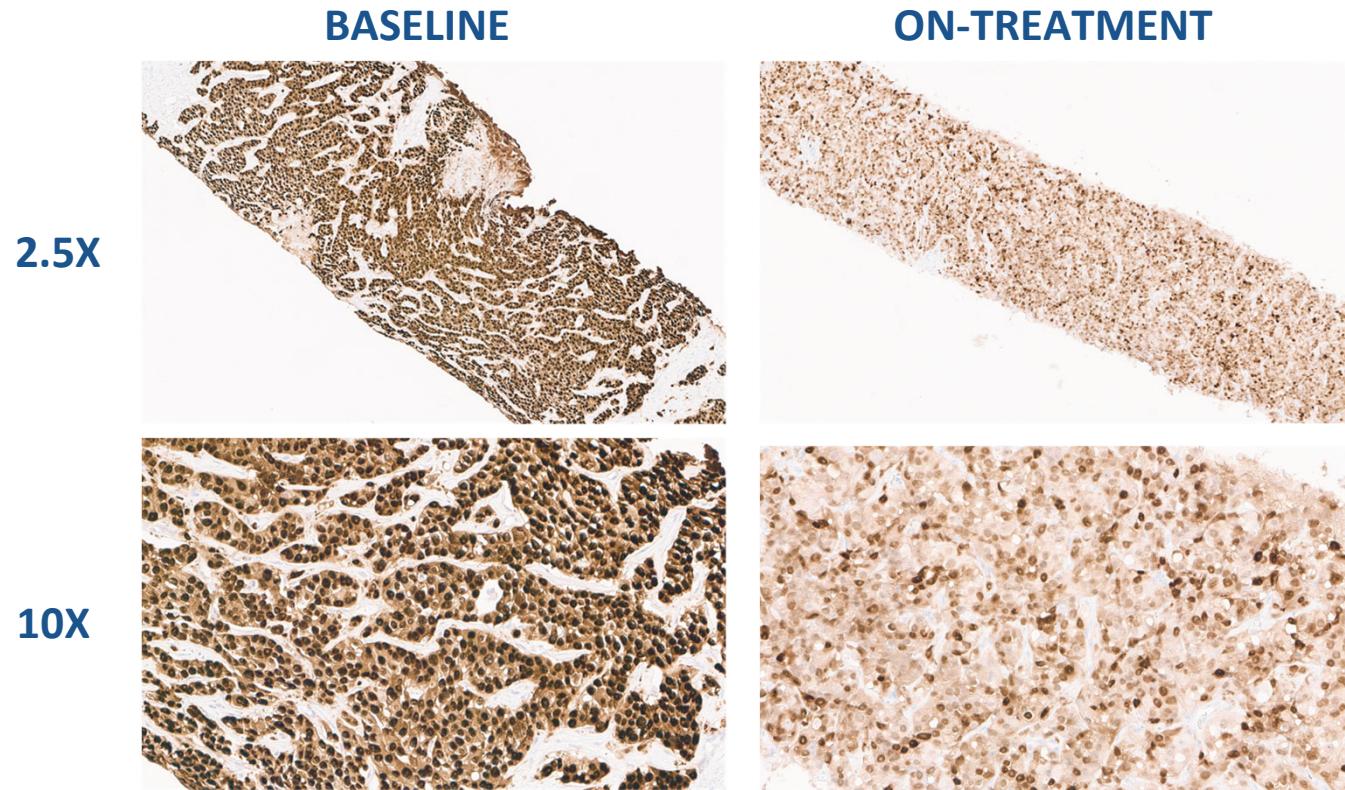
Day 15 AUC (±1 SD)

Cycle 1 day 15 total ARV-110 mean plasma concentration-time profile (±1 SE)

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

$T_{1/2} \approx 110$ hours
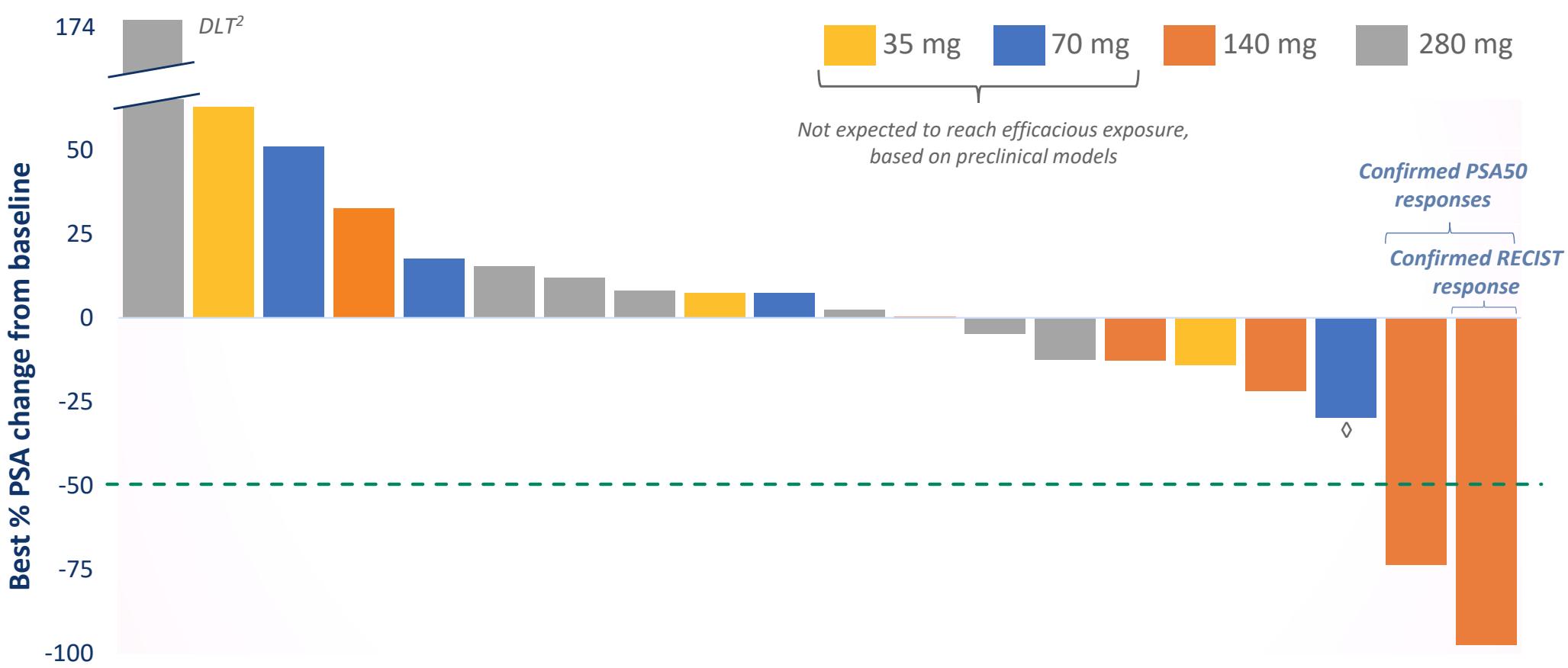
[1]Upper line based on enzalutamide-resistant vertebral cancer of the prostate (VCaP) models. Lower line based on castrated and non-castrated VCaP model

QD, once per day. AUC, area under the curve. Cmax, maximum serum concentration. SD, standard deviation. SE, standard error.

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

BASELINE **ON-TREATMENT**

2.5X

10X
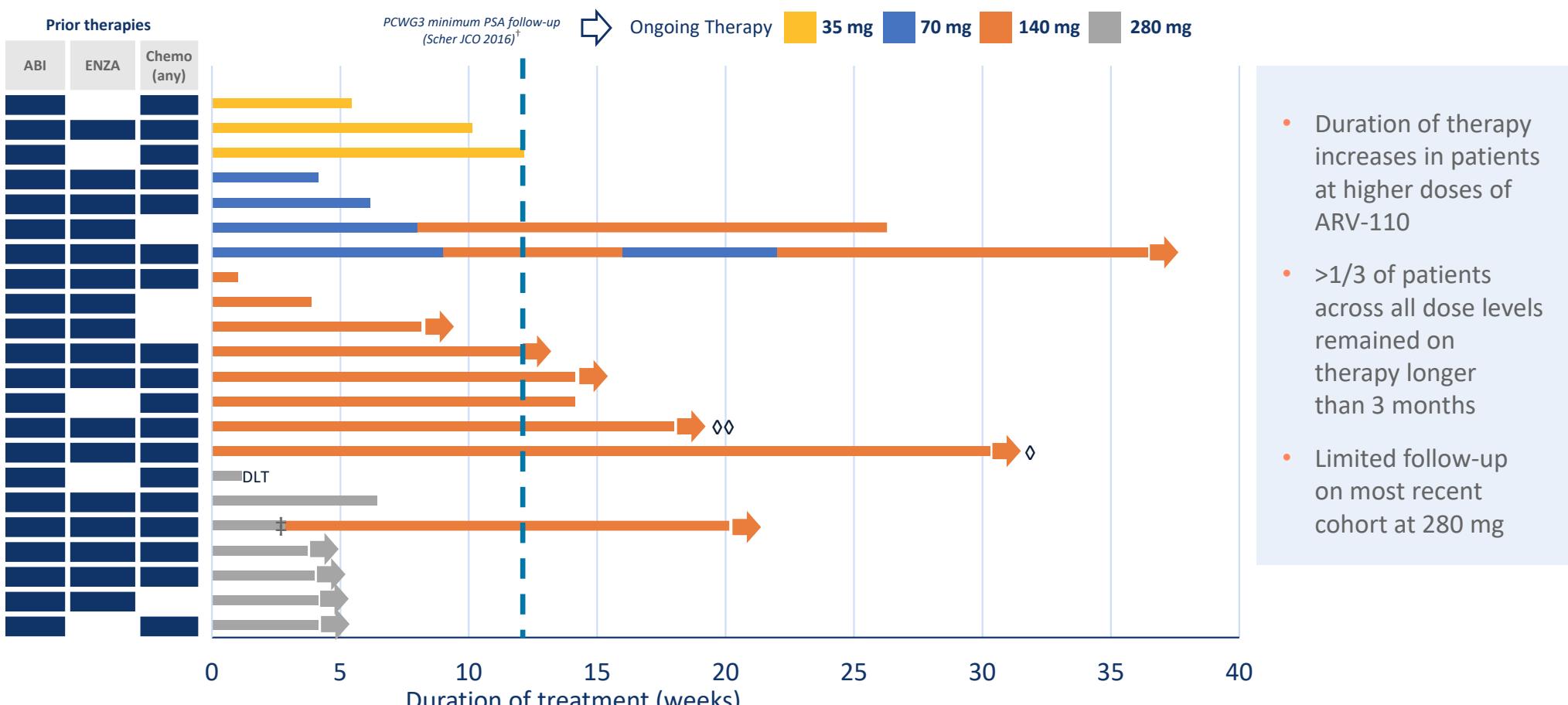
Decreased AR protein levels in an AR wildtype/amplified tumor from a patient following 6 weeks of ARV-110 dosing (280 mg)

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

Legend: 35 mg, 70 mg, 140 mg, 280 mg

Not expected to reach efficacious exposure, based on preclinical models

Confirmed PSA50 responses

Confirmed RECIST response

DLT[2]

Y-axis: Best % PSA change from baseline (174, 50, 25, 0, -25, -50, -75, -100)
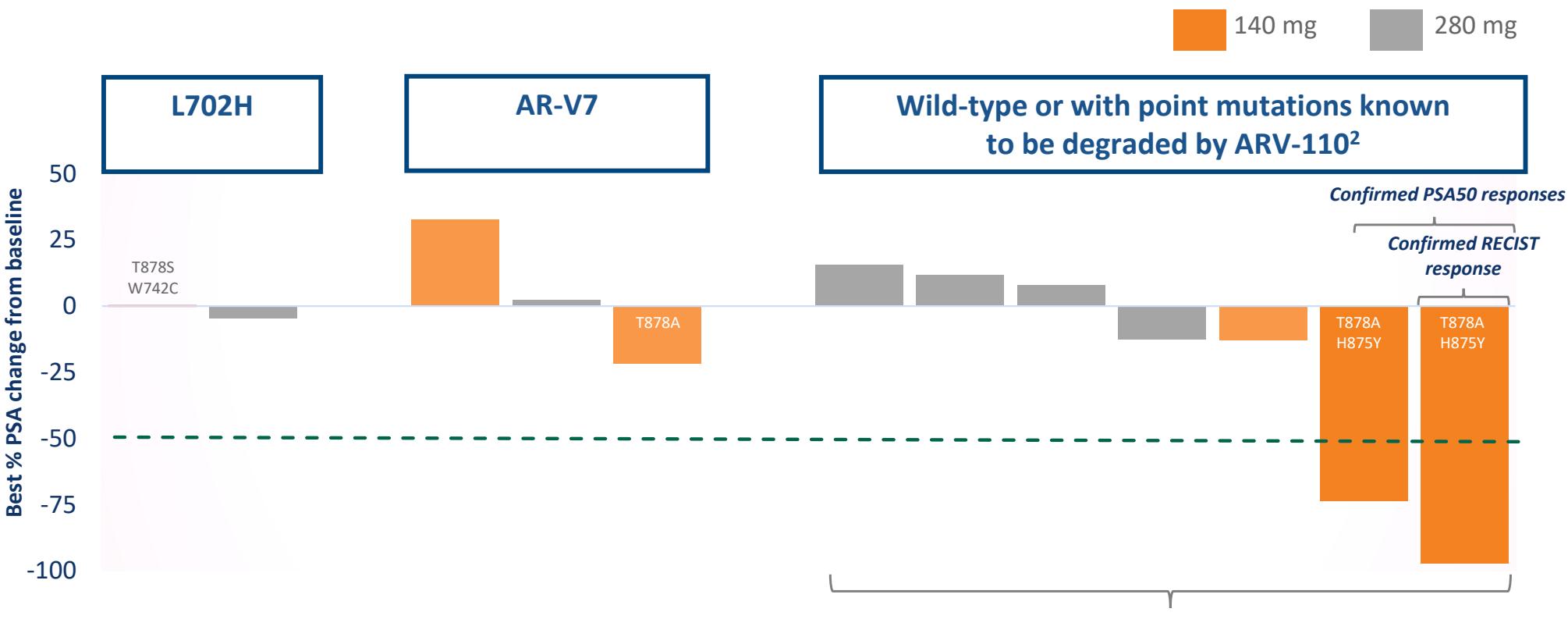
[1]Two of 22 patients were not evaluable: 1 patient had 1 dose and discontinued trial, and 1 patient had PSA less than 1 ng/ml and eligibility by radiographic progression; [2]Treatment discontinued after 2 weeks due to DLT. ◊Patient dose escalated to 140 mg

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Duration of therapy

Prior therapies: ABI, ENZA, Chemo (any)

PCWG3 minimum PSA follow-up (Scher JCO 2016)[†]

Ongoing Therapy — 35 mg — 70 mg — 140 mg — 280 mg

DLT

- 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

Duration of treatment (weeks)

Data as of April 20, 2020
[†]PCWG3, Prostate Cancer Working Group 3; [‡]Dose reduced for non-safety reasons; [◊]PSA50 responder; [◊◊]PSA50/RECIST responder

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AR biomarker status and best % PSA change in patients at ≥140 mg (N=12)[1]

[1]Excluding one patient with DLT associated with rosuvastatin
[2] Based on preclinical studies

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Confirmed PSA responder; non-evaluable by RECIST

Response

- PSA: 74% decline
- No radiographic progression
- Duration of ARV-110: 30 weeks and ongoing

Patient history

- 69 y.o. male
- Extensive bone metastases including the sternum, left first rib, T3, T10 vertebral bodies
- No measurable disease to evaluate
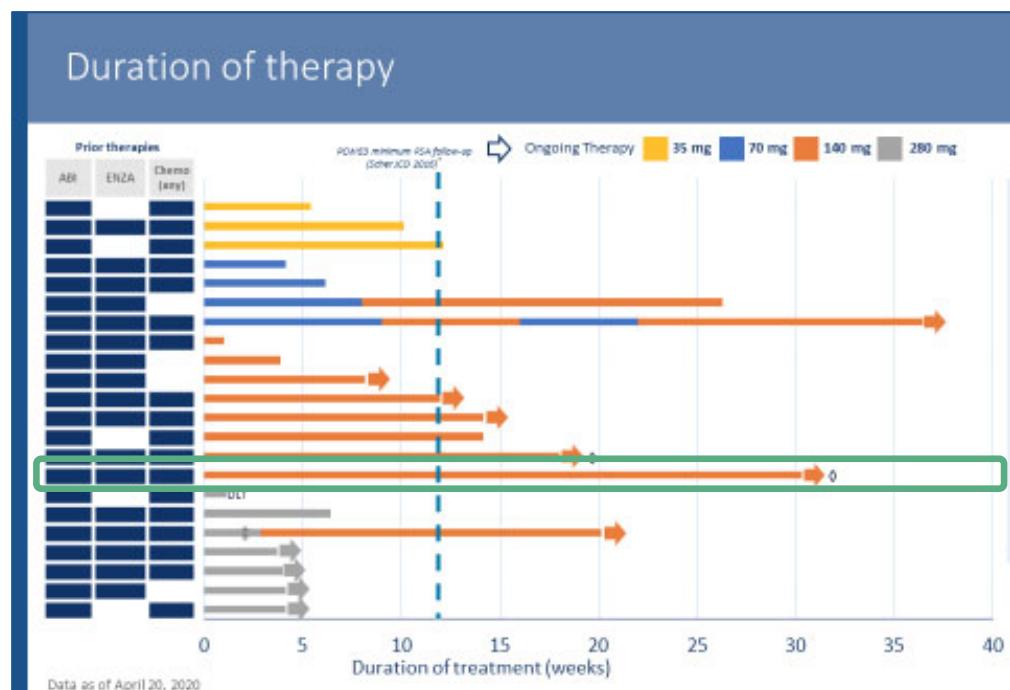
Prior therapy included

- Bicalutamide (HSPC)
- Docetaxel (HSPC)
- Abiraterone
- Radium
- Enzalutamide

Biomarker status

- AR H875Y and T878A mutations (associated with resistance to abiraterone or enzalutamide)[1]

[1]Jernberg E, Endocrine Connections, 2017

Duration of therapy

Data as of April 20, 2020

Confirmed RECIST partial response in a patient with a PCWG3 PSA response

Response

- RECIST: 80% reduction in tumor measurements
- Duration of ARV-110: 18 weeks and ongoing
- PSA: 97% decline

Patient history

- 72 y.o. male
- Extensive disease involving adrenal gland, aortocaval nodes, multiple cone metastases

Prior therapy included

- Bicalutamide
- Enzalutamide
- Provenge
- Abiraterone
- Cabazitaxel

Biomarker status

- AR H875Y and T878A mutations (associated with resistance to abiraterone or enzalutamide)[1]

[1]Jernberg E, Endocrine Connections, 2017

BASELINE CT SCAN

Extensive retroperitoneal adenopathy compressing the inferior vena cava

AFTER 4 CYCLES

Near complete regression of adenopathy

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Exciting path forward

Unequivocal efficacy signal in first-in-human dose escalation study

- Deep, durable, and ongoing responses
- Heavily pretreated population
- Patients resistant to standard of care

Favorable safety profile

- Tolerability consistent with 2nd generation AR therapies
- Manageable drug-drug interaction with breast cancer resistant pump substrates

Clear path ahead

- 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

Pipeline Update

Our high potential PROTAC® pipeline is focused on cancer and neuroscience

	Program		Discovery	Lead Optimization	IND Enabling	Phase 1	Phase 2/3
ONCOLOGY	Prostate Cancer	**ARV-110** Androgen Receptor				●	
		ARV-766 (AR Backup) Androgen Receptor			●		
		AR Variant Degrader AR-V7	●				
	Breast Cancer	**ARV-471** Estrogen Receptor				●	
	Additional I-O and Oncology Programs	**Multiple Indications** Undisclosed Targets		●			
CENTRAL NERVOUS SYSTEM	FTLD-Tau[1], PSP[2], Alzheimer's	**Tau**		●			
	MSA[3], Parkinson's	**α-synuclein**	●				
	Additional Neurology Programs	**Undisclosed Targets**	●				

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ARV-110: Proving the concept of PROTAC® protein degradation

- Preclinical profile translating into clinical benefit

- Signals of efficacy in a heavily pretreated patient population with high unmet need, where traditional inhibitors have failed

- Proves the concept of PROTAC targeted protein degradation, validating our confidence in our pipeline of degraders

- Arvinas is strongly positioned to deliver on milestones in 2020 and beyond

THANK YOU
to our patients, their families, and caregivers!

For More Information

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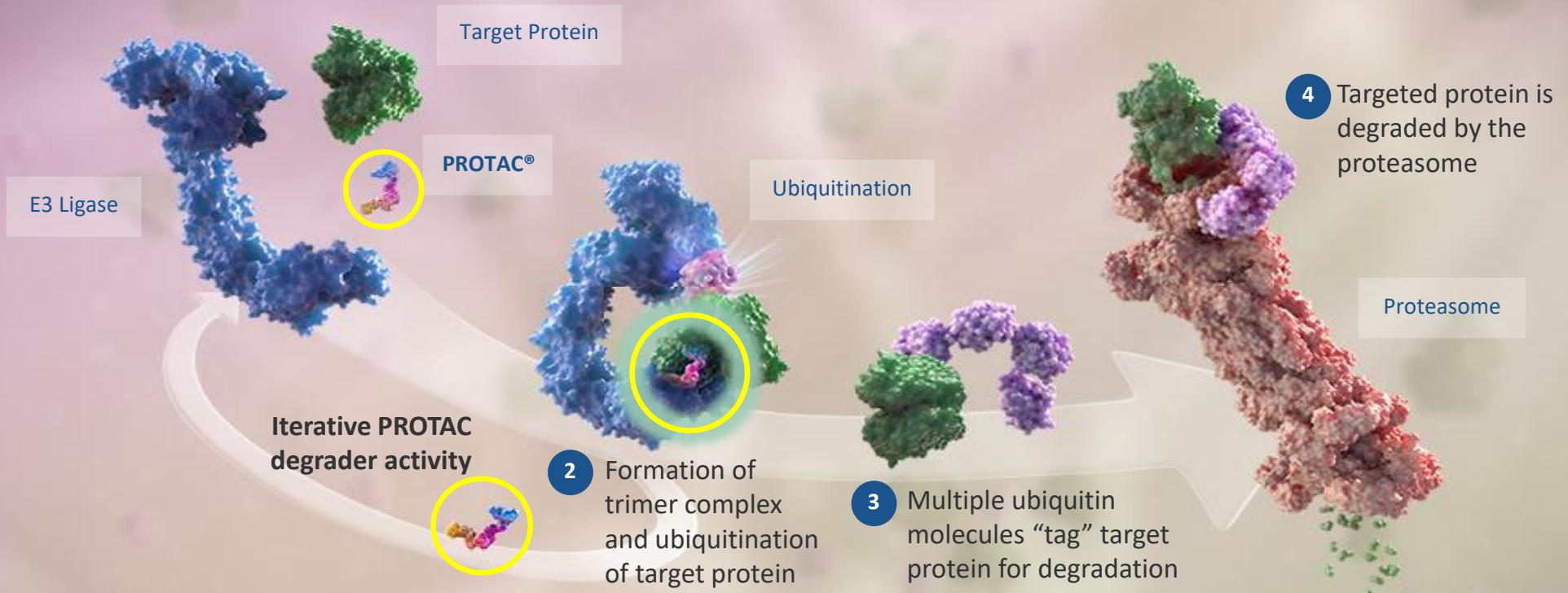
Appendix
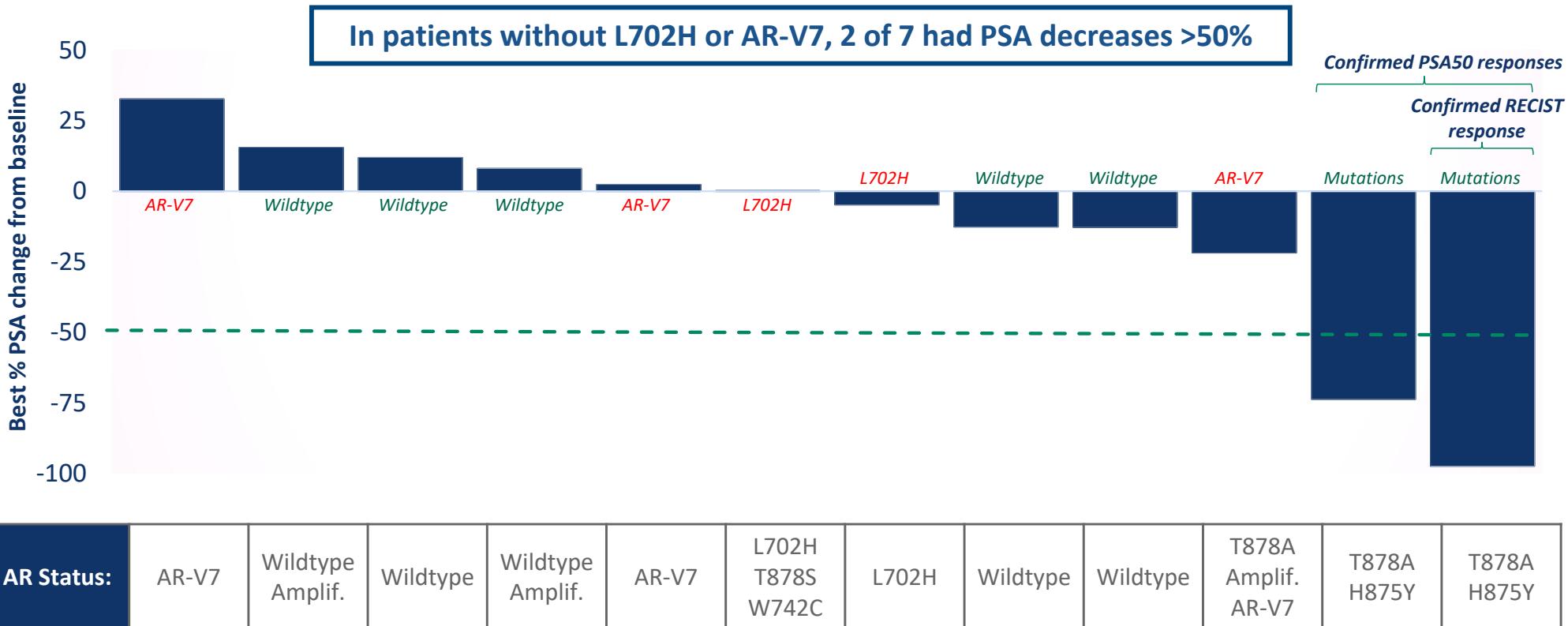
PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins

1 PROTAC protein degraders function inside cells

Target Protein

PROTAC®

E3 Ligase

Ubiquitination

4 Targeted protein is degraded by the proteasome

Proteasome

Iterative PROTAC degrader activity

2 Formation of trimer complex and ubiquitination of target protein

3 Multiple ubiquitin molecules "tag" target protein for degradation

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AR biomarker status and best % PSA change in patients at ≥140 mg (excludes DLT patient; N=12)[1]

In patients without L702H or AR-V7, 2 of 7 had PSA decreases >50%

Confirmed PSA50 responses

Confirmed RECIST response

Best % PSA change from baseline (y-axis: 50, 25, 0, -25, -50, -75, -100)

Bar labels (left to right): AR-V7, Wildtype, Wildtype, Wildtype, AR-V7, L702H, L702H, Wildtype, Wildtype, AR-V7, Mutations, Mutations

AR Status:	AR-V7	Wildtype Amplif.	Wildtype	Wildtype Amplif.	AR-V7	L702H T878S W742C	L702H	Wildtype	Wildtype	T878A Amplif. AR-V7	T878A H875Y	T878A H875Y

[1]One patient discontinued after 2 weeks due to DLT associated with rosuvastatin; AR status based on assays from Epic Sciences, Foundation Medicine (RUO), and OHSU/KDL