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PROTAC® Protein Degraders in the Clinic

26th JFCR-ISCC

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December 8, 2022

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 receipt of upfront, milestone, and other payments under the Pfizer collaboration, the potential benefits of and the receipt of any related milestones in connection with our arrangements with our collaborative partnerships, statements regarding the potential advantages and therapeutic benefits of bavdegalutamide (ARV-110), ARV-471, ARV-766 and our other discovery programs, the development and regulatory status of our product candidates, such as statements with respect to the potential of our lead product candidates, bavdegalutamide (ARV-110), ARV-471, and ARV-766 and other candidates in our pipeline, and the timing of clinical trials, including the timing to complete enrollment, as well as the presentation and/or publication of 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, our plans with respect to submission of investigational new drug/clinical trial authorization applications, the potential commercialization of any of our product candidates and companion diagnostic partnering, 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: our and Pfizer, Inc.’s (“Pfizer”) performance of our respective obligations with respect to our collaboration with Pfizer; whether we and Pfizer will be able to successfully conduct and complete clinical development for ARV-471; whether we will be able to successfully conduct and complete development for bavdegalutamide (ARV-110) and our other product candidates, including whether we initiate and complete clinical trials for our product candidates and receive results from our clinical trials on our expected timelines, or at all; whether our cash and cash equivalent 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 the Company’s Annual Report on Form 10-K for the year ended December 31, 2021 and subsequent other 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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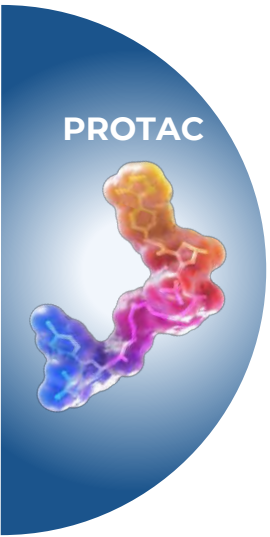
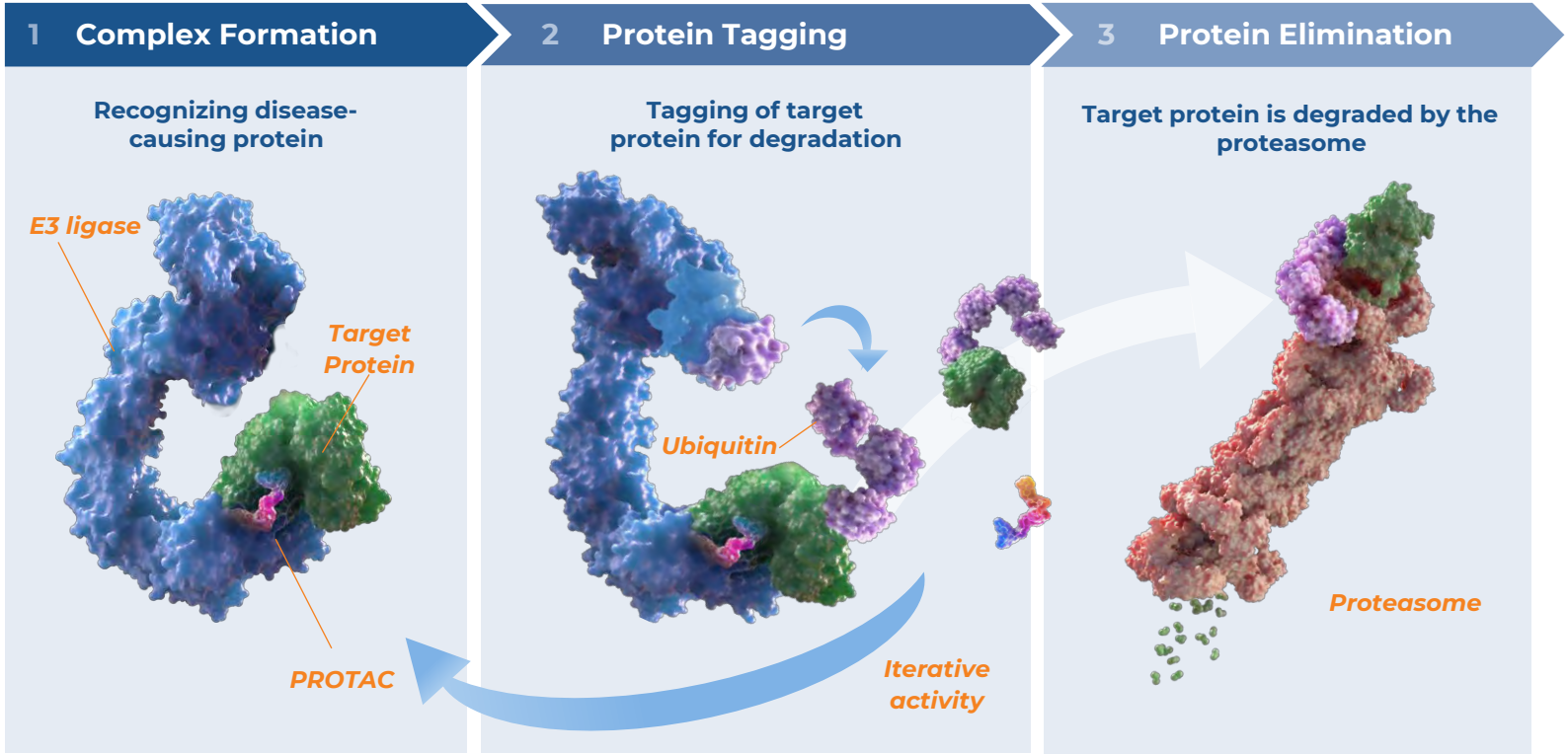
PROTAC® Protein Degraders Harness the Ubiquitin-Proteasome System to Induce the Degradation of Disease-Causing Proteins





PROTAC=PROteolysis TArgeting Chimera

Strong Pipeline With Multiple Compounds Nearing Pivotal Trials

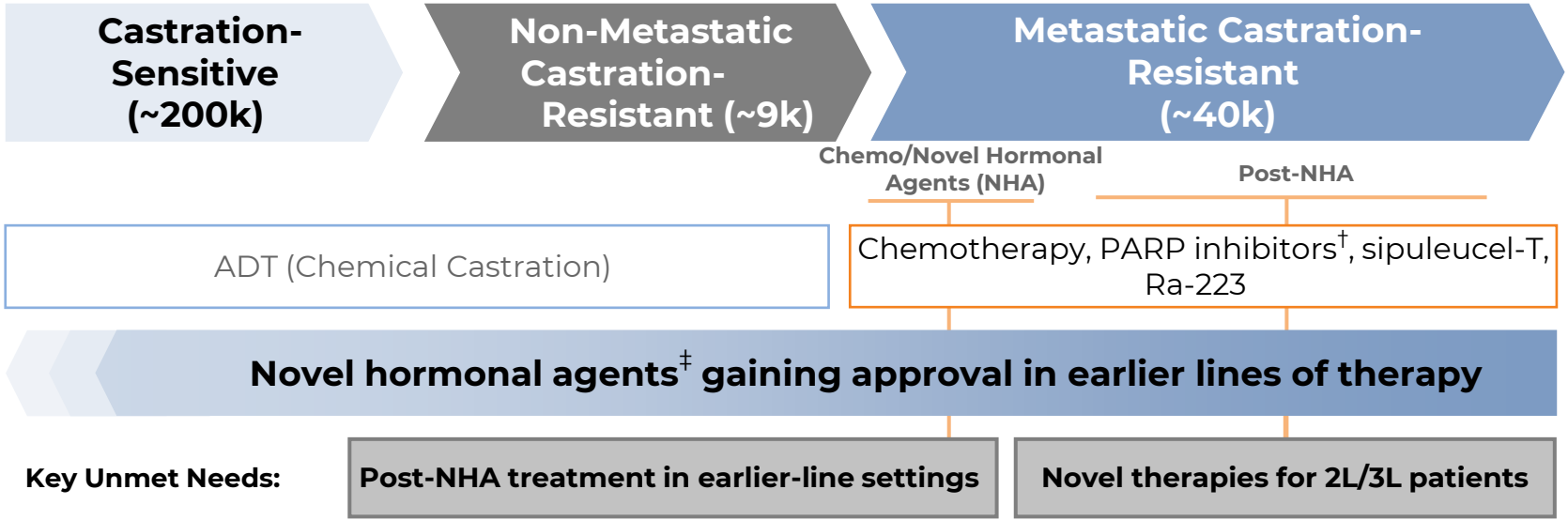
	Program	Indications	Preclinical	Phase 1/1b	Phase 2	Phase 3	Next milestone
Oncology/Immuno-Oncology	**ARV-471** Global co-development and co-commercialization partners with Pfizer	**ER+/HER2- Breast Cancer**	TACTIVE-U: ARV-471 + abemaciclib (Part A) and ARV-471 + ribociclib (Part B)				Add additional targeted therapies (2023)
			TACTIVE-E: ARV-471 + everolimus				Complete enrollment (2023)
			TACTIVE-N: ARV-471 in neoadjuvant setting				Complete enrollment (2023)
			ARV-471 + palbociclib				Phase 1b data (1H 2023)
			VERITAC: ARV-471 monotherapy dose expansion (2L+)				Phase 2 data (4Q 2022)
	Bavdegalutamide (ARV-110)	**Prostate Cancer**	Bavdegalutamide + abiraterone (2L+)				Complete enrollment (2H 2023)
			Bavdegalutamide ARDENT monotherapy dose expansion (2L+)				Publish Phase 2 results
	ARV-766	**Prostate Cancer**	ARV-766 monotherapy dose escalation (2L+)				Phase 1 data (2Q 2023)
			ARV-766 monotherapy dose expansion (2L+)				Complete enrollment
	AR-V7,* BCL6, KRAS-G12D/V,* Myc,* HPK1	**Solid and hematological malignancies**					2 INDs/CTAs through 2023, with 2 programs in IND-/CTA-enabling studies
Neuro	**Tau,* α-Synuclein, mHTT**	**Neurodegenerative Disorders**					

Note: Pipeline is non-exhaustive
Theses agents are currently under investigation. Their safety and effectiveness for these investigational uses have not yet been established.
*Denotes historically undruggable proteins.
2L=second-line; 3L=third-line; CTA=clinical trial authorization; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; IND=investigational new drug

Clinical-Stage Oncology Programs: Bavdegalutamide

Migration of Novel Hormonal Agents to Earlier Settings Has Created Substantial Unmet Need for New Treatments in mCRPC

U.S. Prostate Cancer Treatment Paradigm (# of U.S. patients*)



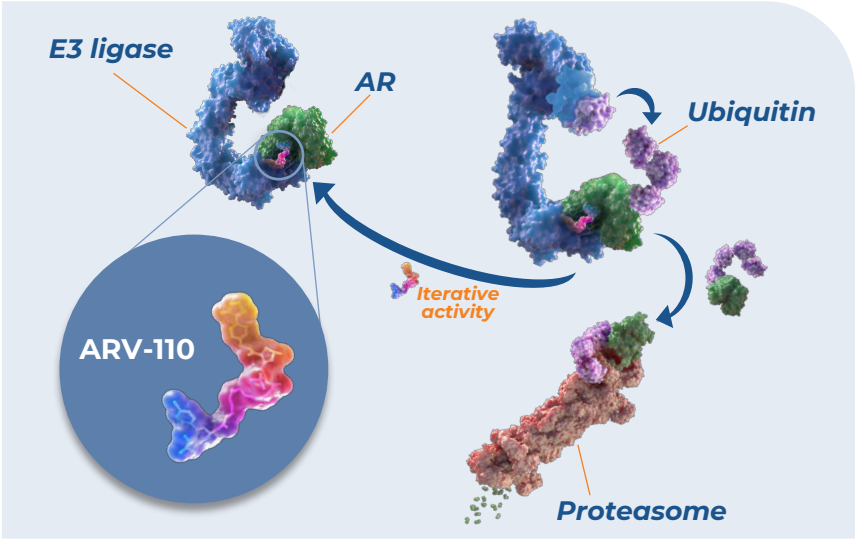
*SEER database. † Approved for patients with BRCA mutation or homologous recombination repair gene-mutated mCRPC that has progressed after AR-directed therapies.

‡Includes enzalutamide, abiraterone, darolutamide, apalutamide.

2L=second-line; 3L=third-line; ADT=androgen deprivation therapy; AR=androgen receptor; BRCA=BReast CAncer gene; mCRPC=metastatic castration resistant prostate cancer; NHA=novel hormonal agent; PARP=poly (ADP-ribose) polymerase

Background

Bavdegalutamide (ARV-110) is a novel, oral PROTAC protein degrader that targets wild-type AR and clinically relevant mutants



In the phase 1 dose escalation study of bavdegalutamide in men with mCRPC who received ≥2 prior therapies (including abiraterone and/or enzalutamide)[1]:

- An exposure-activity relationship was seen in heavily pretreated patients
- Enhanced activity was observed in a biomarker-defined patient subset
  - PSA_{50} rate of 40% in patients with AR T878X/H875Y-positive tumors (n=5)
- 420 mg QD was selected as the RP2D based on safety, PK, and efficacy*

1. Chirnomas D, 28th Prostate Cancer Foundation Annual Scientific Retreat. 2021
*Doses ranged from 35–700 mg QD or 210–420 mg BID
AR=androgen receptor; BID=twice daily; DLT=dose-limiting toxicity; mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetics; PROTAC=PROteolysis TArgeting Chimera; PSA=prostate-specific antigen; PSA_{50}=best PSA declines ≥50%; QD=once daily; RP2D=recommended phase 2 dose; T878X=T878A or T878S

Ongoing Phase 2 Expansion Study (ARDENT) Design (NCT03888612)

Key eligibility criteria

- Confirmed metastatic CRPC
- Disease progression on or since most recent therapy
  - ≥2 rising PSA values (≥2 ng/mL)

BIOMARKER-DEFINED* SUBGROUPS

- 1–2 prior novel hormonal agents
- ≤1 prior chemotherapy regimen each for CSPC and CRPC

T878X/H875Y†	AR T878A/S and/or H875Y
WT/Other	Wild-type AR or AR alterations other than T878A/S, H875Y, L702H, AR-V7
L702H/AR-V7‡	AR L702H or AR-V7 (co-occurring T878X/H875Y included)

CLINICALLY DEFINED, BIOMARKER AGNOSTIC SUBGROUP (≤1 PRIOR LINE FOR CRPC)

Less Pretreated	1 prior novel hormonal agent No prior chemotherapy

Bavdegalutamide administration

- Starting dose of 420 mg QD
- Dose reductions/interruptions permitted for AEs

Primary endpoints

- PSA response rate, RECIST response rate, PFS, and rPFS

Secondary endpoints

- Duration of response
- OS
- AEs and laboratory abnormalities
- PK parameters

Analysis includes complete phase 1 data and interim phase 2 data

- Data cutoff date of December 20, 2021

Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.

*Based on tumor DNA sequencing using circulating tumor DNA or tumor biopsies; †Without AR L702H or AR-V7; ‡AR variants not degraded by ARV-110

AE=adverse event; AR=androgen receptor; CRPC=castration-resistant prostate cancer; CSPC=castration-sensitive prostate cancer; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; PSA=prostate-specific antigen, QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiographic progression-free survival; T878X=T878A or T878S WT=wild-type

Patient Baseline Characteristics

Parameter	Phase 1 (n=71)	Phase 2* (n=124)
Median age (range), y	70 (51–85)	74 (48–91)
ECOG performance status,† n (%)		
0	46 (65)	61 (49)
1	25 (35)	62 (50)
Visceral disease,‡ n (%)	31 (44)	38 (31)
Median no. lines of prior therapy (range)	6 (2–14)	4 (1–11)
Type of prior therapy, n (%)		
Novel hormonal agent	71 (100)	124 (100)
Abiraterone	63 (89)	79 (64)
Enzalutamide§	57 (80)	93 (75)
Abiraterone and enzalutamide§	49 (69)	48 (39)
Chemotherapy	53 (75)	39 (31)

Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.

*Phase 2 enrollment ongoing (December 20, 2021 data cutoff date); †1 patient in phase 2 expansion had ECOG performance status of 2; ‡Soft tissue disease other than lymph node, including liver or lung; §Or other AR blocker (apalutamide or darolutamide)

AR=androgen receptor; ECOG=Eastern Cooperative Oncology Group

TRAEs in ≥10% of Patients Treated With Bavdegalutamide at the RP2D (420 mg QD)

TRAE, n (%)	Total at RP2D (n=138)*			
	Grade 1	Grade 2	Grade 3†	Total
Any TRAE	39 (28)	53 (38)	23 (17)	115 (83)
Nausea	42 (30)	22 (16)	2 (1)	66 (48)
Fatigue	32 (23)	16 (12)	1 (1)	49 (36)
Vomiting	28 (20)	7 (5)	1 (1)	36 (26)
Decreased appetite	19 (14)	15 (11)	1 (1)	35 (25)
Diarrhea	19 (14)	6 (4)	3 (2)	28 (20)
Alopecia	18 (13)	2 (1)	NA	20 (14)
AST increased	12 (9)	4 (3)	1 (1)	17 (12)
Weight decreased	9 (7)	7 (5)	0	16 (12)
Anemia	6 (4)	2 (1)	7 (5)	15 (11)

- There were no grade ≥4 TRAEs at the RP2D
- TRAEs led to bavdegalutamide dose reduction in 11 (8%) patients treated at the RP2D
- TRAEs led to bavdegalutamide discontinuation in 12 (9%) patients treated at the RP2D

Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.

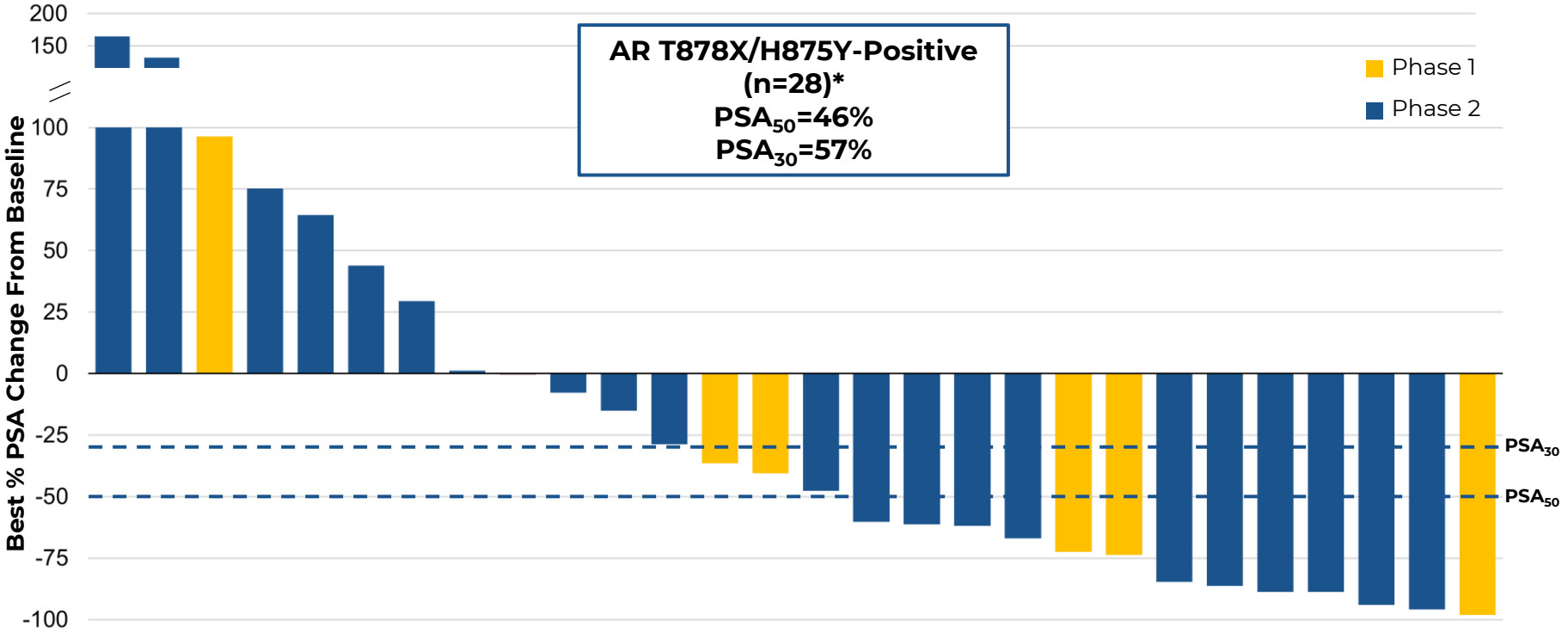
*Includes 14 phase 1 patients (9 treated at 420 mg QD and 5 treated at 210 mg BID) and 124 phase 2 patients

†Additional grade 3 TRAEs were neutrophil count decreased (n=3); lymphocyte count decreased, blood creatinine increased (n=2 each); and platelet count decreased, asthenia, dyspepsia, fall, hyperkalemia, abdominal discomfort, hypertension, blood bilirubin increased, and myocarditis (n=1 each)

AST=aspartate aminotransferase; BID=twice daily; NA=not applicable; QD=once daily; RP2D=recommended phase 2 dose; TRAE=treatment-related adverse event

Data as presented at ASCO GU 2022

46% of Patients With Tumors Harboring AR T878X/H875Y Mutations Had PSA Declines of ≥50%



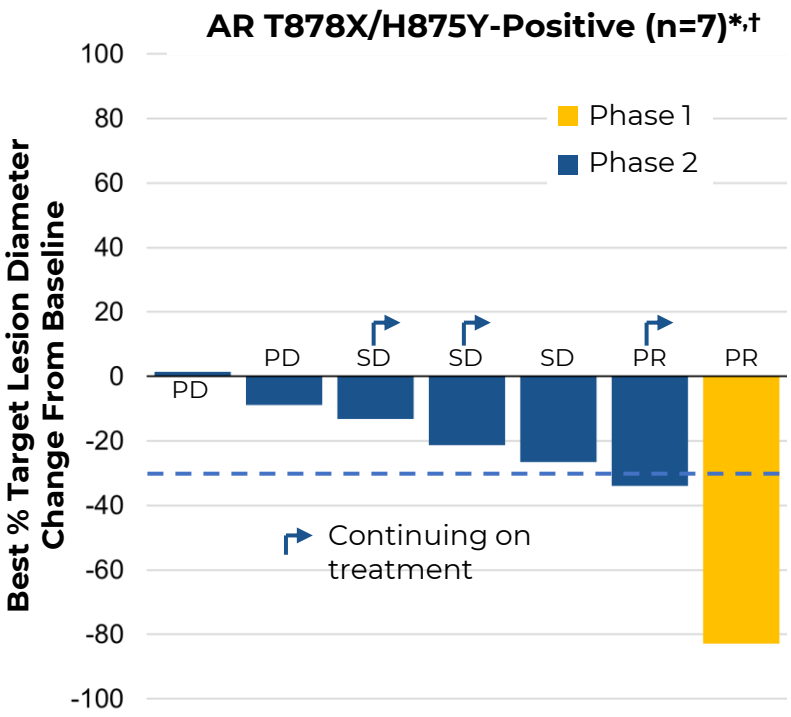
Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.

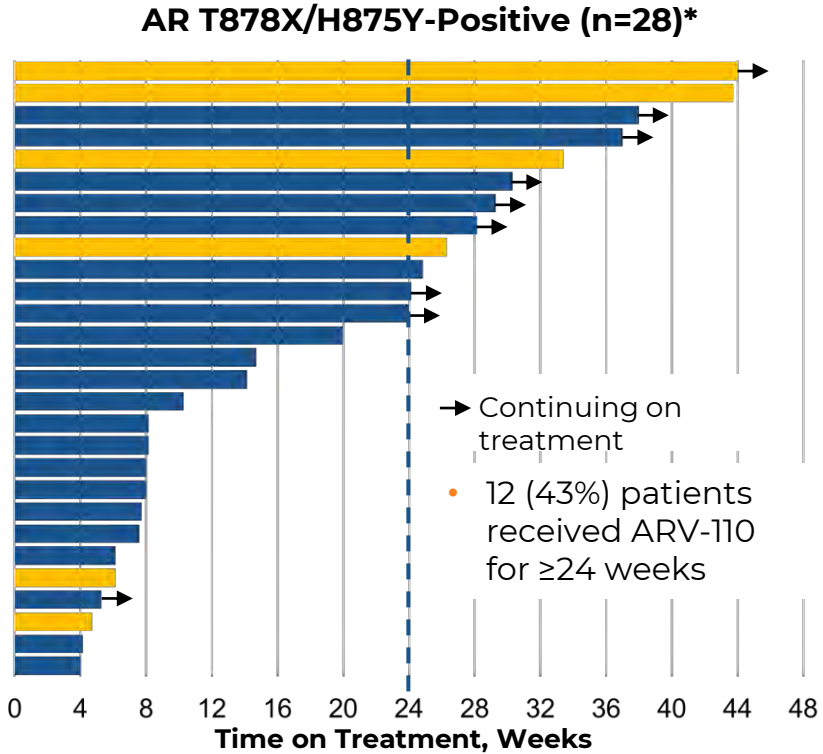
*Includes biomarker-evaluable patients treated at or above the RP2D (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft tumor models (phase 1) and with ≥4 weeks of PSA follow-up

AR=androgen receptor; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%; RP2D=recommended phase 2 dose; T878X=T878A or T878S

Data as presented at ASCO GU 2022

2 of 7 Patients With Tumors Harboring AR T878X/H875Y Mutations Had Confirmed RECIST Partial Responses



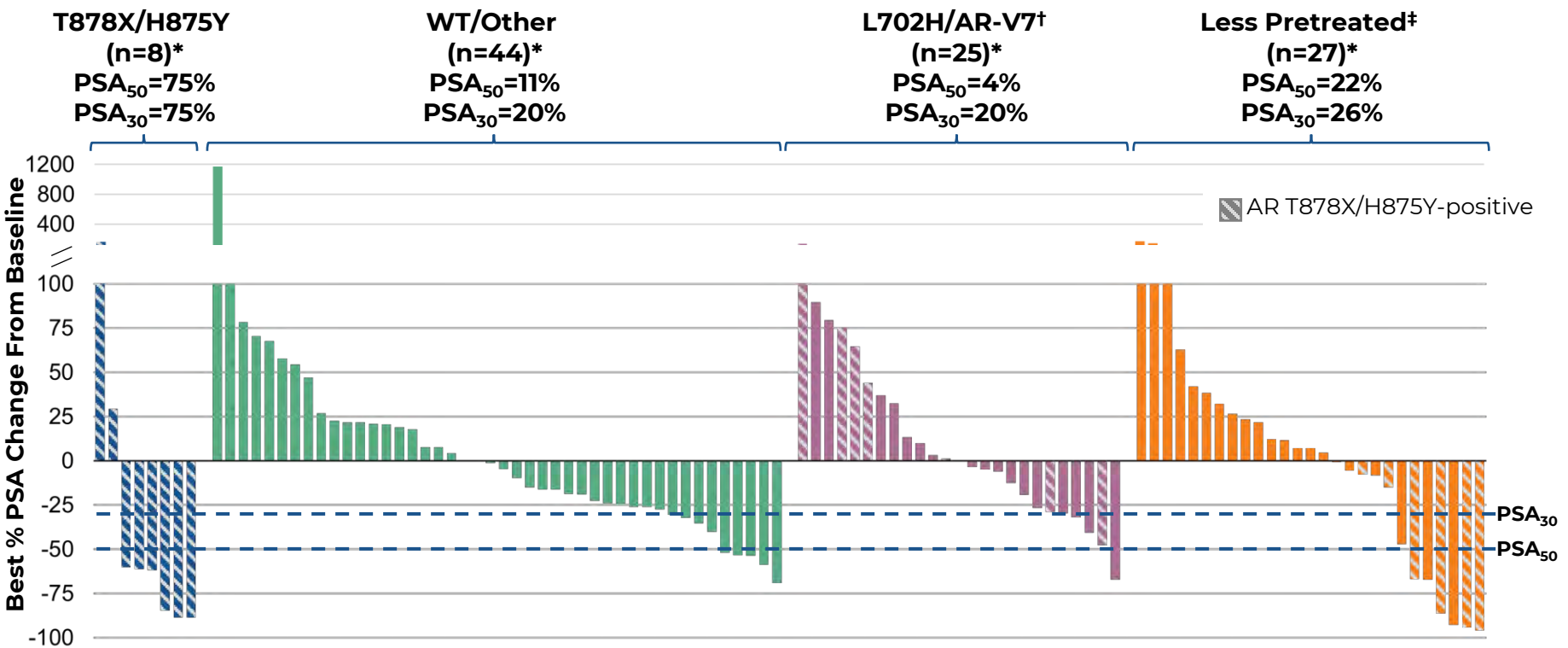


Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.

*Includes biomarker-evaluable patients treated at or above the recommended phase 2 dose (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft tumor models (phase 1); †Includes patients with measurable disease at baseline and ≥1 on-treatment scan; patients with SD as best response and <12 weeks follow-up were excluded

AR=androgen receptor; PD=progressive disease; PR=confirmed partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; T878X=T878A or T878S

PSA Declines of ≥50% Were Seen Across All Subgroups in ARDENT

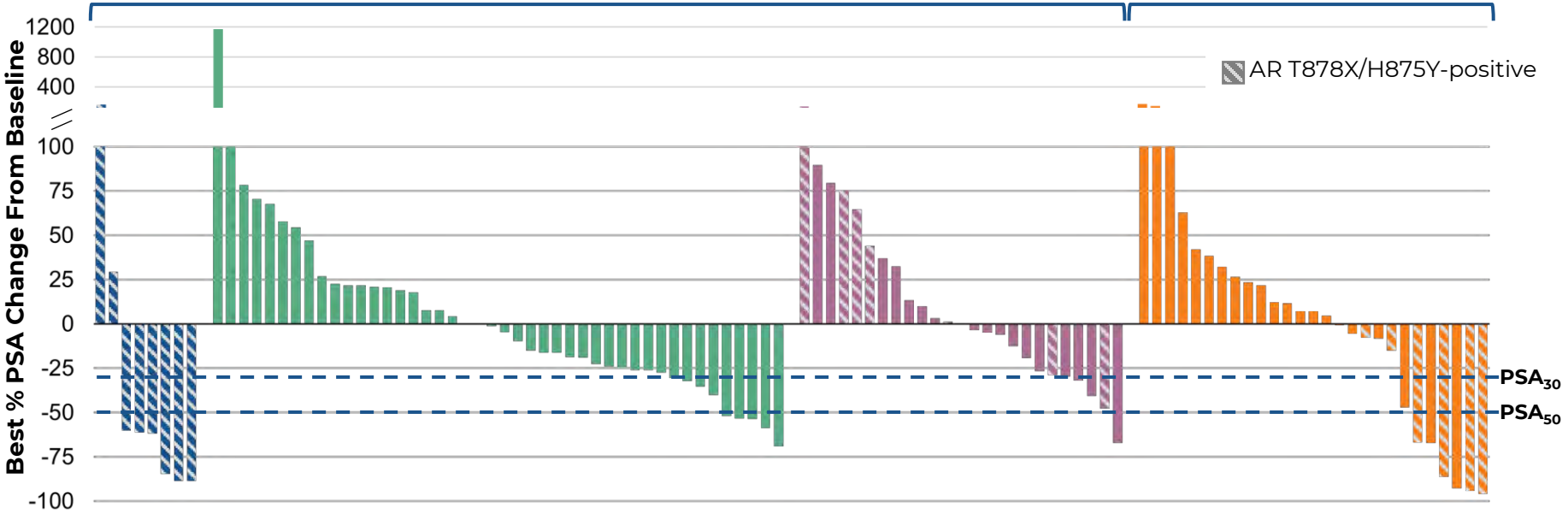


Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.
*Includes biomarker-evaluable patients with ≥4 weeks of PSA follow-up
†Co-occurring T878X/H875Y included; ‡All forms of AR
AR=androgen receptor; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%; T878X=T878A or T878S; WT=wild-type

Non-AR Molecular Profiles Were Similar in the Less Pretreated Subgroup and the More Pretreated, Biomarker-Defined Subgroups

	More Pretreated (Biomarker-Defined) (n=77)*
TP53	57%
BRCA2	8%
PI3K pathway	36%
RB1	9%

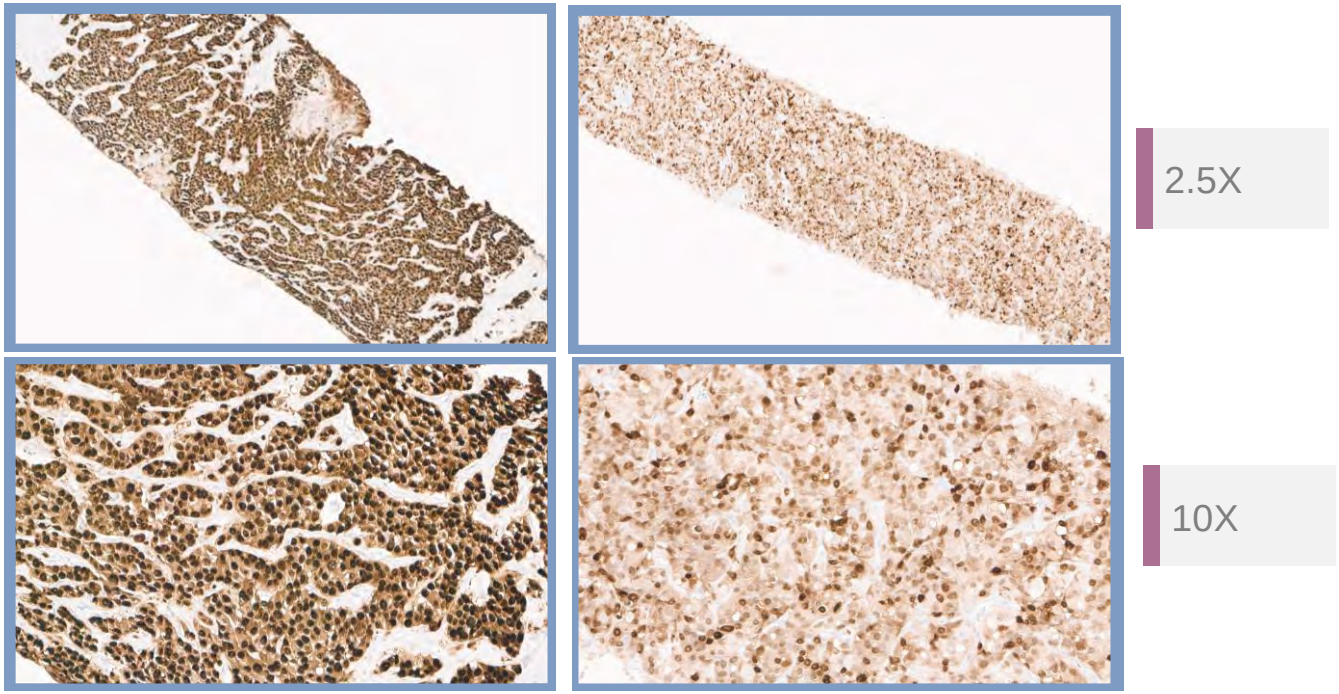
	Less Pretreated† (n=27)*
TP53	48%
BRCA2	15%
PI3K pathway	30%
RB1	11%



Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.
*Includes biomarker-evaluable patients with ≥4 weeks of PSA follow-up; non-AR molecular profile analyses are preliminary and exploratory
†All forms of AR
AR=androgen receptor; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%; T878X=T878A or T878S

AR degradation observed in patient tumor biopsies

Brown:
Androgen receptor

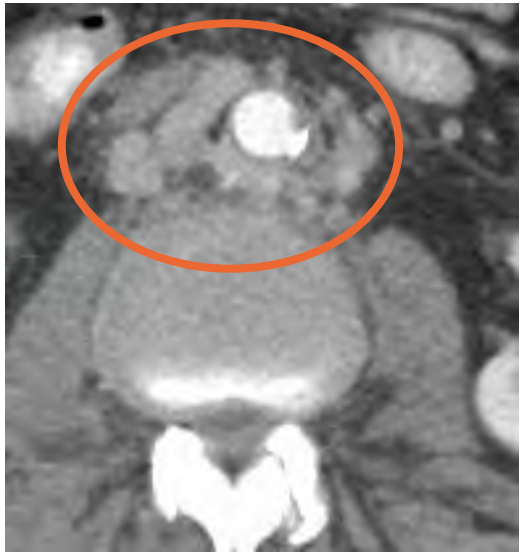


Decreased AR protein levels in an AR wildtype/amplified tumor from a patient following 6 weeks of ARV-110

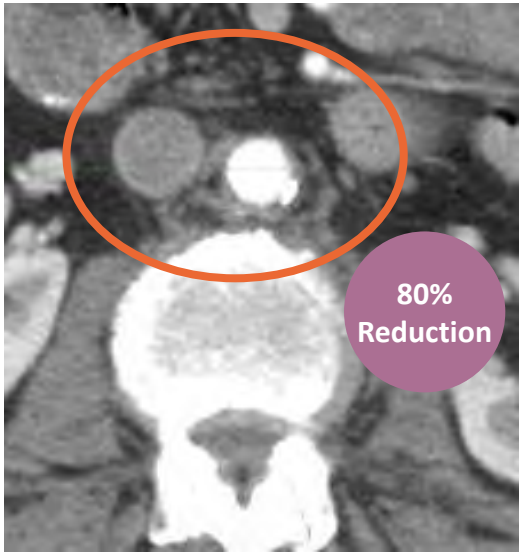
Bavdegalutamide achieved RECIST confirmed response in a patient with extensive prior treatment

Patient Characteristics	
PSA response	**97%** decline
RECIST response	**80%** reduction
Duration of bavdegalutamide	18+ weeks ongoing
Biomarker status	AR H875Y and T878A mutations (associated with resistance to abiraterone or enzalutamide)†
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
†Jernberg E, Endocrine Connections, 2017

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Conclusions

- Bavdegalutamide (ARV-110), a novel AR PROTAC protein degrader, demonstrates clinical activity in patients with mCRPC after 1–2 prior novel hormonal agents, including heavily pretreated patients
  - A 46% PSA_{50} rate and RECIST responses were seen in patients with tumors harboring AR T878X/H875Y mutations, which is likely a particularly AR-dependent, bavdegalutamide-sensitive population
  - PSA declines of ≥50% were also observed in patients without AR T878X/H875Y mutations
- The bavdegalutamide RP2D of 420 mg QD is tolerable with manageable side effects
- Patients in the less pretreated subgroup (based on clinical history) and those in the more pretreated, biomarker-defined subgroups had tumors with similar non-AR molecular profiles
- Bavdegalutamide merits further investigation in patients with mCRPC

Gao, X. et al. Presented at the 2022 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Rapid Abstract Presentation 17.
AR=androgen receptor; mCRPC=metastatic castration-resistant prostate cancer; PROTAC=PROteolysis Targeting Chimera; PSA_{50}=best prostate-specific antigen declines ≥50%; QD=once daily; RP2D=recommended phase 2 dose; T878X=T878A or T878S

Clinical-Stage Oncology Programs: ARV-471

Background

- There is an unmet need for better treatments for ER+ advanced breast cancer; resistance to CDK4/6 inhibitors and endocrine therapy remains a particularly acute challenge, with poor outcomes in patients who have progressed on or after these agents[1,2]
  - The CBR with fulvestrant plus venetoclax vs fulvestrant alone was only 11.8% vs 13.7% in the randomized phase 2 VERONICA study in patients with breast cancer after prior CDK4/6 inhibitor and endocrine therapy[1]
  - ≥66% of patients with metastatic breast cancer treated with CDK4/6 inhibitors develop a genomic alteration representing an ER-independent mechanism of resistance[3]
- Although fulvestrant is a standard therapy for patients with ER+ advanced breast cancer,[4] it has limitations, including its intramuscular route of administration and only 40–50% degradation of ER protein at its optimal dose[5,6]
- ARV-471, a novel, potent, selective, orally bioavailable PROTAC® protein degrader, demonstrated superior ER degradation and antitumor activity compared with fulvestrant in endocrine-sensitive and endocrine-resistant xenograft models[7]
- The objective of this study is to evaluate the safety and clinical activity of ARV-471 in patients with ER+/HER2- locally advanced or metastatic breast cancer who had previously received CDK4/6 inhibitors

Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
1. Lindeman GJ, et al. J Clin Oncol. 2021;39(15_suppl):1004.
2. Juric D, et al. Cancer Res. 2019;79(4 Supplement):GS3-08.
3. Wander SA, et al. Cancer Discov. 2020;10:1174-93.
4. Cardoso F, et al. Ann Oncol. 2020;31:1623-49.
5. Kuter I, et al. Breast Cancer Res Treat. 2012;133:237-46.
6. Robertson, JFR, et al. Breast Cancer Res. 2013;R18.
7. Flanagan JJ, et al. Cancer Res. 2019;79(4 Supplement):P5-04-18.
CBR=clinical benefit rate; CDK=cyclin-dependent kinase; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; PROTAC=PROteolysis TArgeting Chimera

Study Design

- This is a phase 1/2, multicenter, first-in-human, open-label study (NCT04072952) of ARV-471 in patients with ER+/HER2- breast cancer
- In the phase 1 dose escalation portion (3+3 design with backfill), patients had received ≥1 prior CDK4/6 inhibitor, ≥2 prior endocrine therapies, and ≤3 prior lines of chemotherapy; ARV-471 was administered orally with food at a starting dose of 30 mg daily
  - Intrapatient dose escalations were permitted
- The primary objective of the phase 1 dose escalation study was to evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the recommended phase 2 doses
- Other objectives were to assess pharmacokinetics and pharmacodynamics and explore ARV-471's antitumor activity
- CBR (rate of confirmed CR or PR or SD ≥24 weeks) was analyzed in patients enrolled ≥24 weeks prior to the data cutoff

Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
CBR=clinical benefit rate; CDK=cyclin-dependent kinase; CR=complete response; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; MTD=maximum tolerated dose; PR=partial response; SD=stable disease

Patient Baseline Characteristics

- As of September 30, 2021, 60 patients were treated in the phase 1 dose escalation portion of the study with total daily ARV-471 doses ranging from 30 mg to 700 mg
- All patients received prior CDK4/6 inhibitors, 80% received prior fulvestrant, and 78% received prior chemotherapy

Parameter	Total (N=60)	Parameter	Total (N=60)
Median age (range), years	65.5 (38–80)	Median no. lines of prior therapy in any setting (range)†	4 (1–10)
ECOG performance status, n (%)*		Type of prior therapy in any setting, n (%)	
0	29 (48)	CDK4/6 inhibitor	60 (100)
1	30 (50)	Aromatase inhibitors	52 (87)
Sites of metastasis, n (%)		SERD	50 (83)
Bone	33 (55)	Fulvestrant	48 (80)
Liver	23 (38)	Investigational	6 (10)
Lung	13 (22)	Chemotherapy	47 (78)
Other	13 (22)		

Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
*Baseline value missing for 1 patient.
†Median of 3 prior lines in the metastatic setting.
CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; SERD=selective estrogen receptor degrader

ARV-471 was well tolerated at all dose levels; MTD not reached

TRAE in ≥ 10% of patients	30 mg (n=3)		60 mg (n=3)		120 mg (n=7)		180/200 mg (n=11)		360 mg (n=15)		500 mg (n=17)		700 mg (n=4)		Total (N=60)	
	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3
Any TRAE	0	0	3 (50%)	0	6 (86%)	0	6 (55%)	1 (9%)	10 (67%)	1 (7%)	7 (41%)	2 (12%)	2 (50%)	0	34 (57%)	4 (7%)
Nausea	0	0	2 (33%)	0	2 (29%)	0	4 (36%)	0	3 (20%)	0	4 (24%)	1 (6%)	1 (25%)	0	16 (27%)	1 (2%)
Fatigue	0	0	1 (17%)	0	0	0	1 (9%)	0	3 (20%)	0	5 (29%)	0	2 (50%)	0	12 (20%)	0
Vomiting	0	0	0	0	2 (29%)	0	1 (9%)	0	2 (13%)	0	1 (6%)	0	0	0	6 (10%)	0
AST increased	0	0	0	0	1 (14%)	0	2 (18%)	0	0	0	1 (6%)	0	2 (50%)	0	6 (10%)	0

Discontinuation rate <2% (1 out of 60)
Dose reductions <2% (1 out of 60)

Four patients experienced Gr 3 events potentially related to ARV-471 (headache lasting 1-day, single occurrence of asymptomatic increased amylase and lipase, nausea and asymptomatic QTc prolongation, and venous embolism after a minor procedure†)

Data cut-off: 09/30/21

† Advanced breast cancer is highly associated with venous embolisms. Event was included as potentially treatment related, so treatment with ARV-471 was stopped.

MTD, maximum tolerated dose; TRAE, Treatment related adverse event

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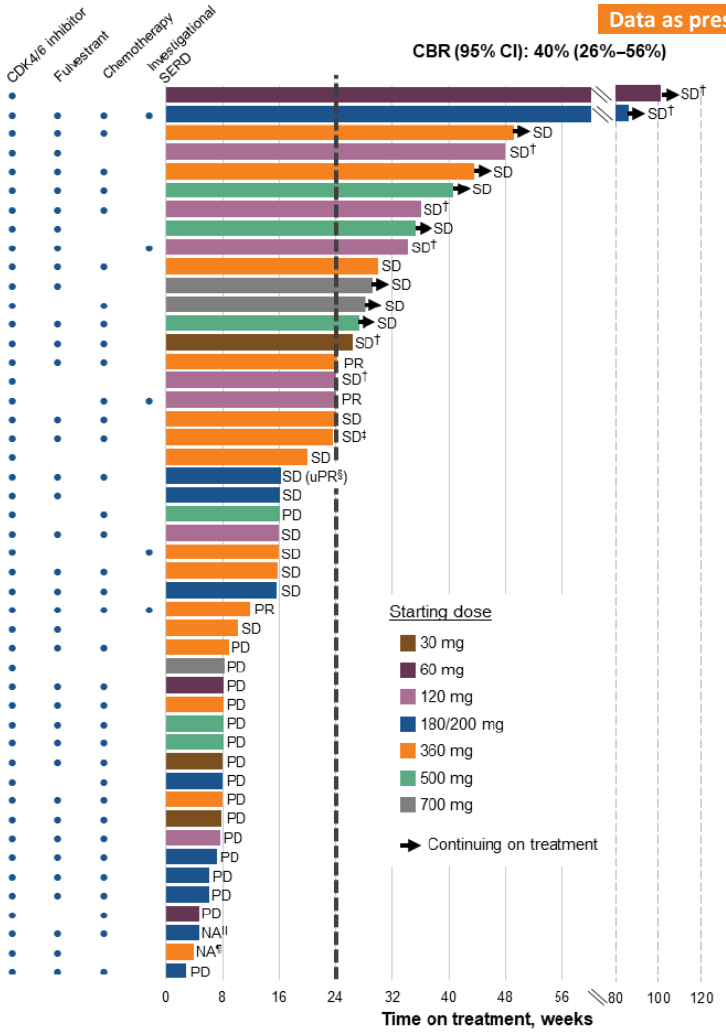
Data as presented at SABCS 2021

CBR

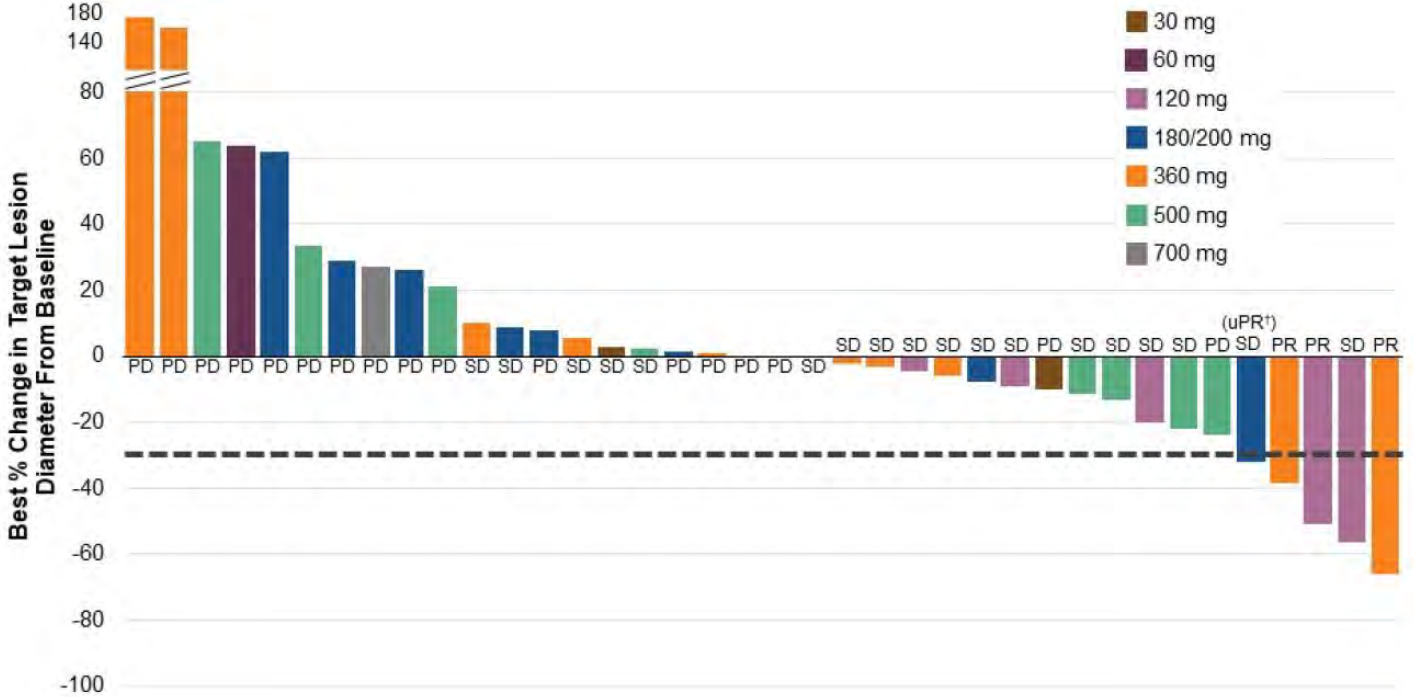
- The CBR (rate of confirmed CR or PR or SD ≥24 weeks)was 40% (95% CI: 26%–56%) in 47 evaluable patients*
- 3 patients had confirmed PRs
- 14 patients were ongoing at the time of data cutoff, including 2 who have been on treatment for >18 months



Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
*Excludes patients unable to complete cycle 1 due to reasons other than PD, toxicity, or death
†Patient had dose escalation from starting dose
‡Week 24 imaging assessment performed at 23.4 weeks (within the window allowed per protocol)
§Patient had disease progression on subsequent scan and discontinued treatment
‖Patient discontinued treatment due to clinical progression before first on-study scan.
¶Patient discontinued treatment due to venous embolism before first on-study scan.
CBR=clinical benefit rate; CDK=cyclin-dependent kinase; NA=not available; PD=progressive disease; PR=confirmed partial response; SD=stable disease; SERD=selective estrogen receptor degrader; uPR=unconfirmed partial response

Tumor Response

- Antitumor activity in response-evaluable patients (n=38)*



Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
*Patients with measurable disease at baseline who had a baseline and ≥1 on-treatment scan. †Patient had disease progression on subsequent scan and discontinued treatment.
PD=progressive disease; PR=confirmed partial response; SD=stable disease; uPR=unconfirmed partial response

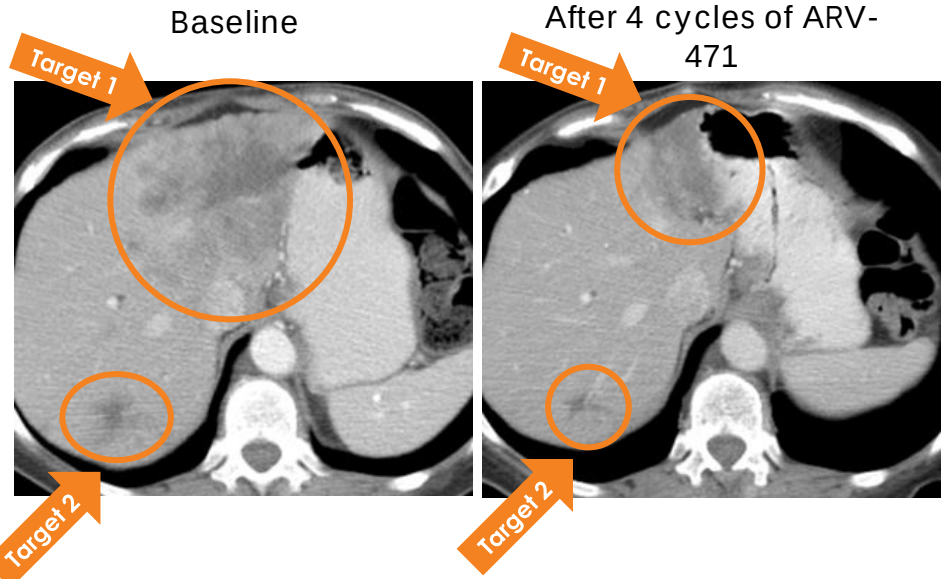
Confirmed Partial Response in Heavily Pretreated Patient With Tumor Harboring *ESR1* Mutation

- Patient with confirmed partial response

Prior therapy
- CDK4/6 inhibitor
  - Palbociclib
- Endocrine therapies
  - 3 aromatase inhibitors
  - Tamoxifen
  - 2 investigational SERDs*
- Other targeted agents
  - Everolimus
- Chemotherapy
  - 1 regimen in neoadjuvant setting
  - 1 regimen in metastatic setting

***ESR1* mutation**
- D538G

ARV-471 treatment
- 120 mg daily for 24 weeks



- **51% reduction in target lesions**
- **Confirmed RECIST partial response**

Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
*Includes 1 selective estrogen receptor-α covalent antagonist
CDK=cyclin-dependent kinase; RECIST=Response Evaluation Criteria in Solid Tumors; SERD=selective estrogen receptor degrader

Pharmacokinetics

- Preliminary pharmacokinetic data showed dose-related increases for AUC_{24} and C_{max} from 30 mg to 500 mg daily doses
- Mean exposure on Day 15 exceeded the nonclinical efficacious range at doses ≥60 mg daily

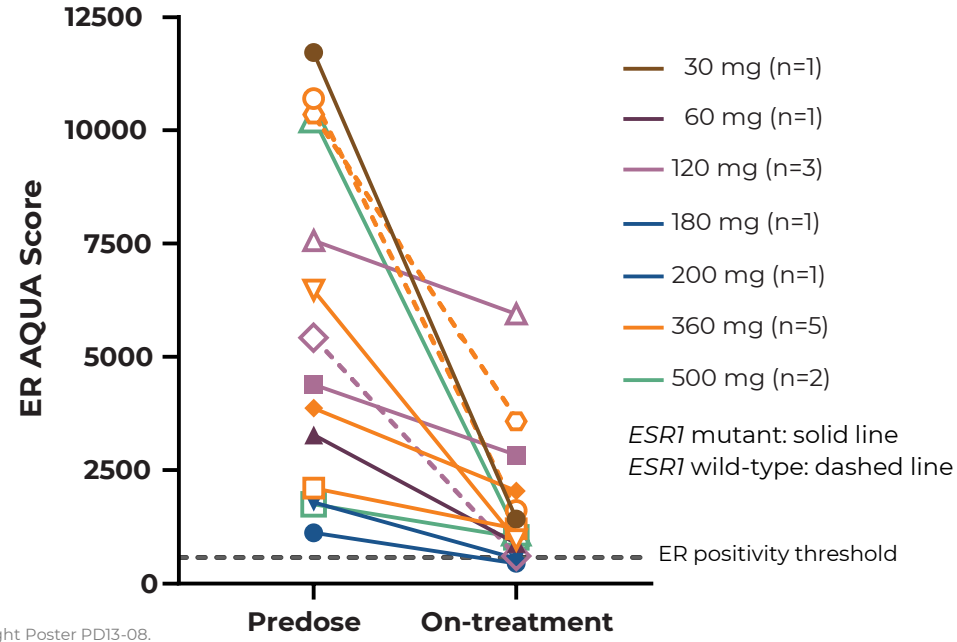
Parameter, mean (% CV)*	30 mg QD (n=3)	60 mg QD (n=3)	120 mg QD (n=7)	180 mg QD (n=6)	200 mg QD (n=4)	360 mg QD (n=15)	500 mg QD (n=3)	250 mg BID (n=7)	700 mg† (n=3)
AUC_{24}, ng·h/mL‡	4138 (23)	7391 (15)	13,854 (13)	20,043 (30)	14,762 (37)	26,794 (26)	33,896 (54)	22,711 (25)	21,220 (58)
C_{max}, ng/ml	22 (24)	405 (8)	800 (6)	1094 (26)	874 (49)	1548 (24)	2563 (76)	2253 (25)	2133 (50)

Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
*Preliminary ARV-471 pharmacokinetic parameters on Day 15 performed using noncompartmental analysis methods; as of September 29, 2021
†400 mg AM/300 mg PM
‡AUC_{12} for 250 mg BID and 700 mg dosing cohorts
AUC_{12}=area under the curve from 0 to 12 hours; AUC_{24}=area under the curve from 0 to 24 hours; BID=twice daily; C_{max}=maximum plasma concentration, CV=coefficient of variation; QD=once daily

ER Degradation

- Robust ER degradation (up to 89%) was observed at all doses up to 500 mg daily, regardless of *ESR1* mutation status
- Median and mean ER degradation across dose levels was 67% and 64%, respectively

- ER degradation* (n=14)



Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
*Data available as of September 3, 2021; median time on treatment at biopsy: 31 days (range: 16–77). ER immunoreactivity analyzed by QIF using the AQUA method, and ER positivity threshold derived by examining AQUA scores and visually inspecting all samples in the dataset to determine a cut-point for ER positivity
AQUA=automated quantitative analysis; ER=estrogen receptor; QIF=quantitative immunofluorescence

Conclusions

- ARV-471 has a manageable safety profile, with mostly low-grade TRAEs
- Pharmacokinetics of ARV-471 were dose-related up to 500 mg daily
- Clinical activity and pharmacodynamic data suggest ARV-471 may have superior ER degradation to fulvestrant[1–3] and has the potential to fill an unmet need for patients with ER+/HER2-breast cancer and prior treatment with CDK4/6 inhibitors
- Data support further development of ARV-471; the phase 2 VERITAC expansion cohort of ARV-471 monotherapy and a phase 1b combination cohort with palbociclib are ongoing, and phase 3 trials are planned

Hamilton, E. et al. Presented at the 2021 San Antonio Breast Cancer Symposium (SABCS). Spotlight Poster PD13-08.
1. Kuter I, et al. Breast Cancer Res Treat. 2012;133:237-46.
2. Robertson, JFR, et al. Breast Cancer Res. 2013;R18.
3. Lindeman GJ, et al. J Clin Oncol. 2021;39(15_suppl):1004.
CDK=cyclin-dependent kinase; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; TRAE=treatment-related adverse event

ARV-471: Moving Forward Rapidly Across the Continuum of Disease

U.S. ER+/HER2- Breast Cancer Treatment Paradigm (~200,000 U.S. patients*)

	Adjuvant (Post-Surgical) Breast Cancer (~160K)	Metastatic Breast Cancer (~50K) First-Line	Metastatic Breast Cancer (~50K) Second/Third-Line	
Supportive Trials to Define Registration Paths	Ongoing **Neoadjuvant** *(Open-label non-comparative vs control)*	Ongoing **Phase 1b (enabling trial):** Combo: ARV-471 + palbociclib	Ongoing **Phase 2:** VERITAC Expansion: ARV-471	Ongoing **Phase 1b** Combo: ARV-471 + CDKi or other targeted therapies†
Pivotal Trials		Expected to initiate in 4Q 2022 **Phase 3 registrational:** Two Phase 3 trials: ARV-471 as monotherapy and combo		

*SEER database; includes U.S. patient population only, †e.g., everolimus or as part of umbrella study with multiple combination agents
CDKi=cyclin-dependent kinase inhibitor; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2

Pfizer

Thank you to the patients & families and the dedicated research staff at our participating sites!