ASCO Genitourinary Cancers Symposium

Phase 1/2 Study of ARV-110, an Androgen Receptor PROTAC Degrader, in Metastatic Castration-Resistant Prostate Cancer

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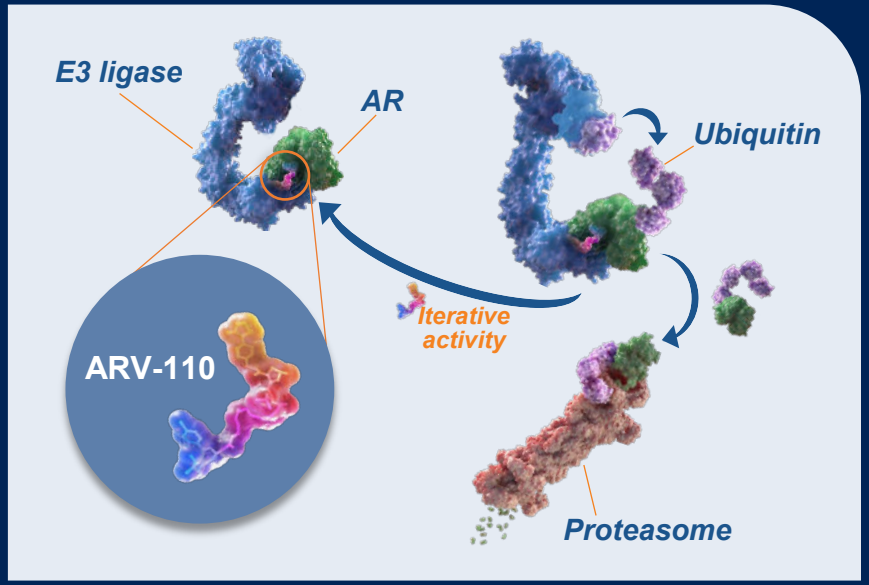
Background

- 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 ARV-110 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

ARV-110 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

*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)

*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

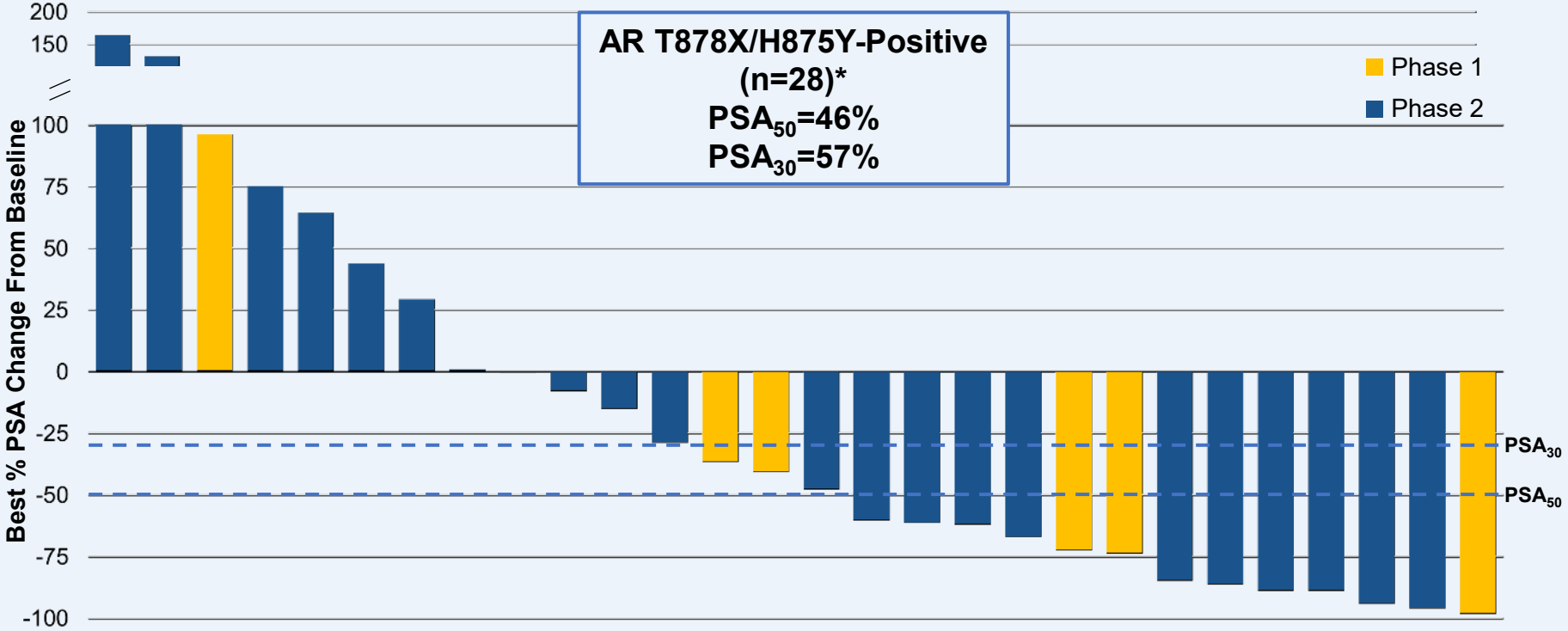
TRAEs in ≥10% of Patients Treated With ARV-110 at the RP2D (420 mg QD)

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 ARV-110 dose reduction in 11 (8%) patients treated at the RP2D
- TRAEs led to ARV-110 discontinuation in 12 (9%) patients treated at the RP2D

*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

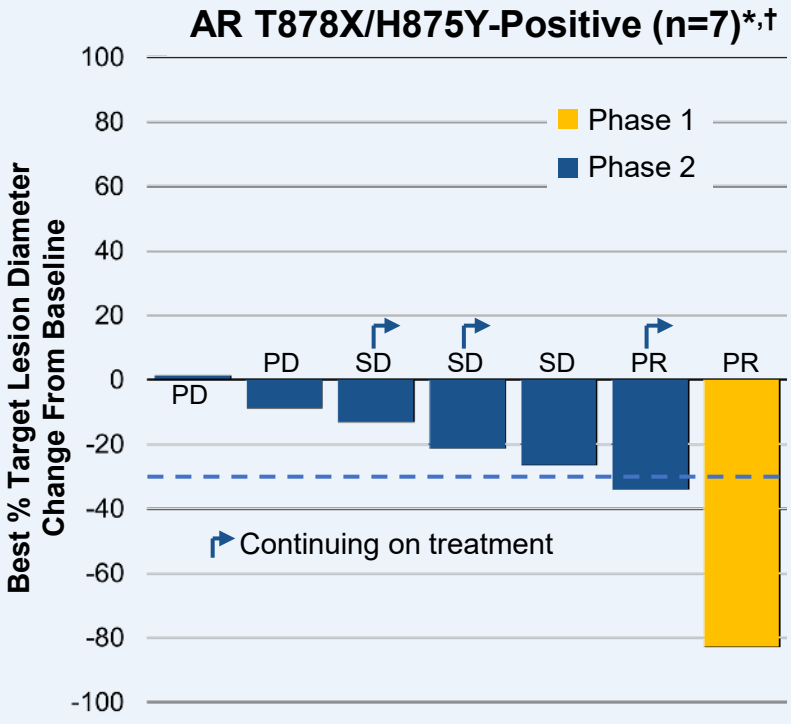
46% of Patients With Tumors Harboring AR T878X/H875Y Mutations Had PSA Declines of ≥50%

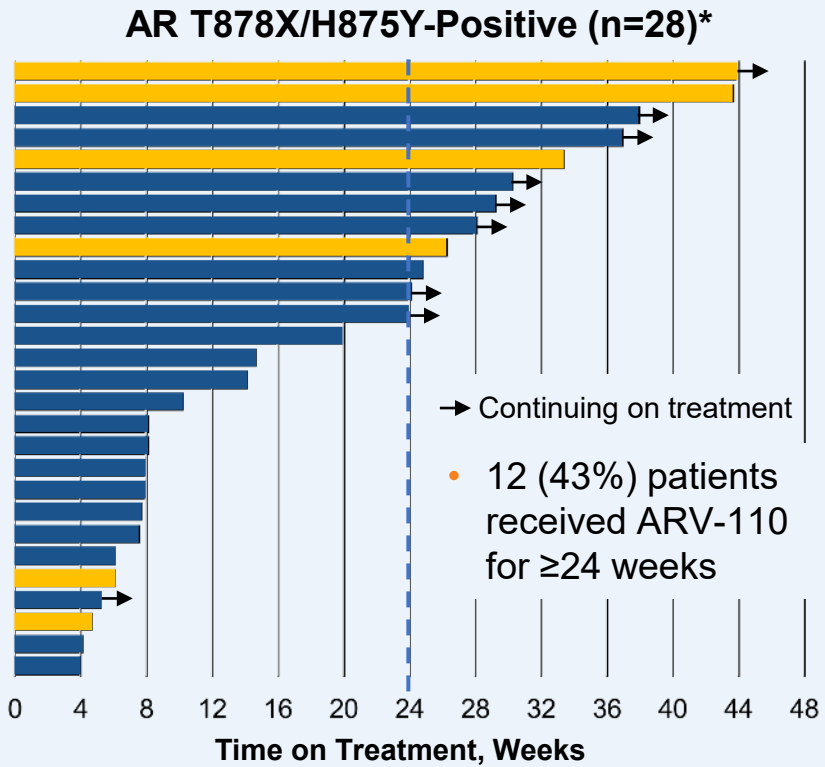


*Includes biomarker-evaluable patients treated at or above the RP2D (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft tumor models (phase 1) and with ≥4 weeks of PSA follow-up

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

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





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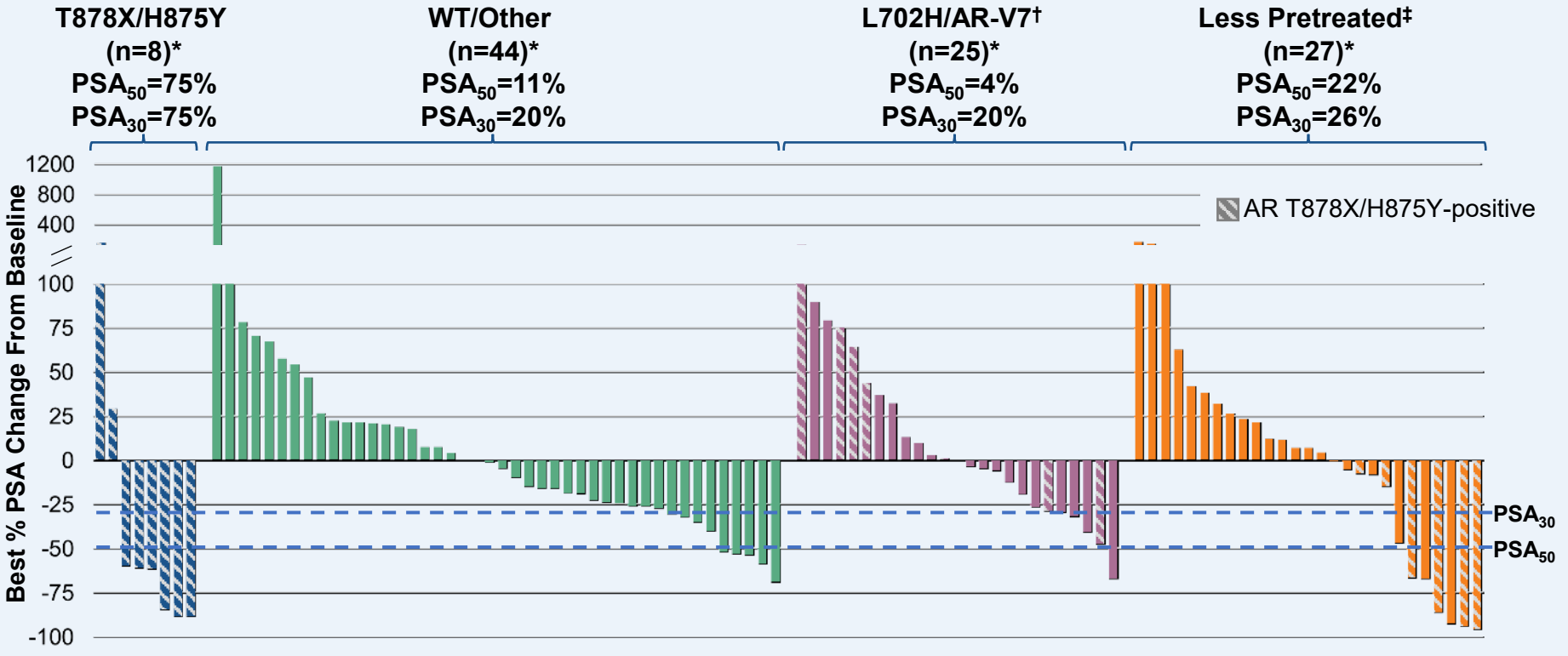
AR=androgen receptor; PD=progressive disease; PR=confirmed partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; T878X=T878A or T878S

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

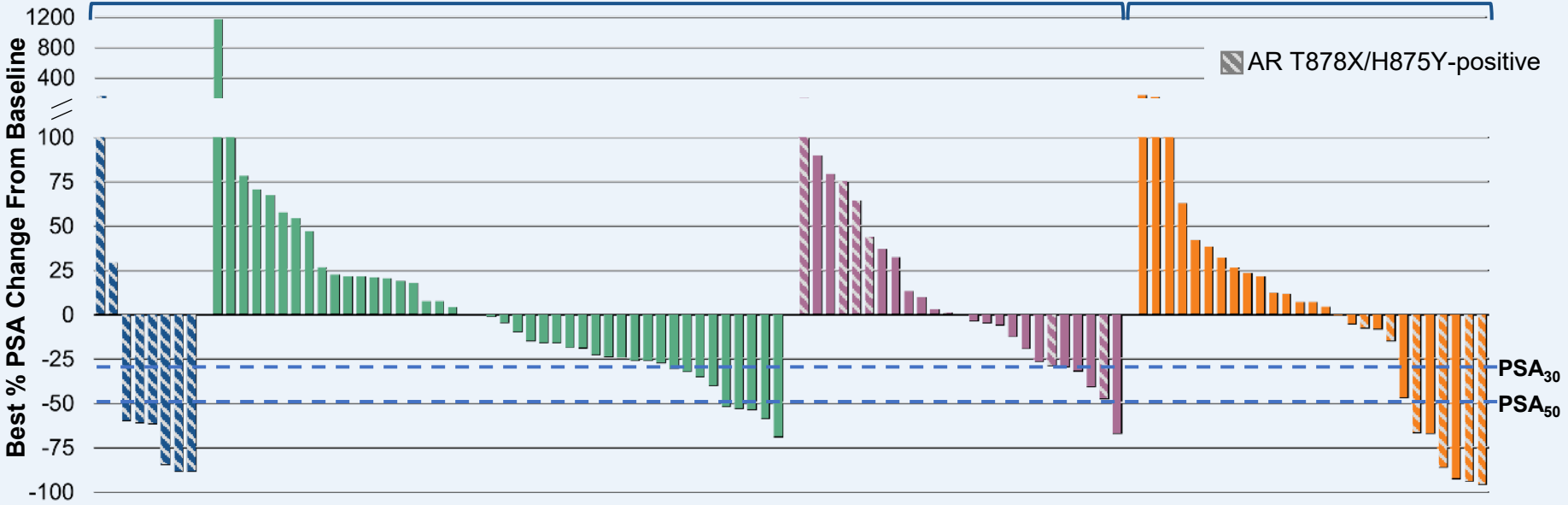


*Includes biomarker-evaluable patients with ≥4 weeks of PSA follow-up
†Co-occurring T878X/H875Y included; ‡All forms of AR
AR=androgen receptor; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%; T878X=T878A or T878S; WT=wild-type

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%



*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

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

Acknowledgments

- We thank the patients who participated in this study and their caregivers, as well as the investigators, researchers, and coordinators who contributed to this study
- This study is sponsored by Arvinas Androgen Receptor, Inc.

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

Phase 1/2 Study of ARV-110, an Androgen Receptor PROTAC Degrader, in Metastatic Castration-Resistant Prostate Cancer

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[1]Massachusetts General Hospital, Boston, MA; [2]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; [3]Oregon Health & Science University, Portland, OR; [4]University of Virginia Cancer Center, Charlottesville, VA; [5]Tulane Cancer Center, New Orleans, LA; [6]Weill Cornell Medicine, New York, NY; [7]Florida Cancer Specialists South, Port Charlotte, FL; [8]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; [9]University of California Irvine Medical Center, Orange, CA; [10]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [11]Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI; [12]Florida Cancer Specialists East, West Palm Beach, FL; [13]Florida Cancer Specialists North, St. Petersburg, FL; [14]Arvinas, Inc., New Haven, CT; [15]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [16]Smilow Cancer Center, Yale School of Medicine, New Haven, CT

Objective

- To evaluate the safety and efficacy of ARV-110 (bavdegalutamide), an oral androgen receptor (AR) PROteolysis TArgeting Chimera (PROTAC) protein degrader, in a phase 1/2 study in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received 1–2 prior novel hormonal agents (NHAs)

Key Findings

- At the recommended phase 2 dose (RP2D) of 420 mg once daily (QD) ARV-110, most treatment-related adverse events (TRAEs) were grade 1 or 2; there were no grade ≥4 TRAEs
- In the population with tumors harboring AR T878X/H875Y mutations:
  - Best prostate-specific antigen (PSA) declines ≥50% (PSA_{50}) and ≥30% (PSA_{30}) were 46% and 57%, respectively, in 28 patients
  - 2 of 7 evaluable patients had confirmed partial responses per Response Evaluation Criteria in Solid Tumors (RECIST)
  - 43% (12/28) of patients received ARV-110 for ≥24 weeks
- PSA declines of ≥50% and ≥30% and tumor shrinkage were also seen in patients without AR T878X/H875Y mutations
- In the phase 2 portion, the prevalence of non-AR molecular alterations was similar in the less pretreated subgroup and the more pretreated, biomarker-defined subgroups

Conclusions

- ARV-110 demonstrates clinical activity in patients with mCRPC after 1–2 prior NHAs, including heavily pretreated patients
  - Patients with AR T878X/H875Y mutations likely represent a particularly AR-dependent, ARV-110–sensitive population
- The ARV-110 RP2D of 420 mg QD was 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
- ARV-110 merits further investigation in patients with mCRPC

Reference

1. Chirnomas D, 28th PCF Annual Scientific Retreat. 2021.

Contact

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Acknowledgments

We thank the patients who participated in this study and their caregivers, and the investigators, researchers, and coordinators who contributed to this study. This study is sponsored by Arvinas Androgen Receptor, Inc.

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Background

- ARV-110 is a novel, oral PROTAC protein degrader that targets wild-type AR and clinically relevant mutants
- A phase 1 dose escalation study evaluated ARV-110 at doses ranging from 35–700 mg QD or 210–420 mg twice daily in men with mCRPC and ≥2 prior therapies (including abiraterone and/or enzalutamide)[1]
  - An exposure-activity relationship was seen in heavily pretreated patients
  - Enhanced activity was seen in a biomarker-defined subset, with a 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, pharmacokinetics, and efficacy

Methods

- The ongoing ARDENT phase 2 expansion study (NCT03888612) is characterizing ARV-110 in patients with confirmed mCRPC and disease progression on or since their most recent therapy (≥2 rising PSA values)
- ARV-110 was administered at a starting dose of 420 mg QD
- Primary endpoints are PSA response rate, RECIST response rate, progression-free survival, and radiographic progression-free survival
- Secondary endpoints are duration of response, overall survival, AEs and laboratory abnormalities, and pharmacokinetic parameters
- This analysis includes complete phase 1 data and interim phase 2 data
  - The data cutoff date was December 20, 2021
- Patients with 1–2 prior NHAs and ≤1 prior chemotherapy regimen each for castration-sensitive prostate cancer and CRPC were enrolled in biomarker-defined subgroups:
  - T878X/H875Y: AR T878A/S and/or H875Y mutations
  - WT/Other: Wild-type AR or AR alterations other than T878A/S, H875Y, L702H, or AR-V7
  - L702H/AR-V7: AR L702H or AR-V7 alterations (co-occurring T878X/H875Y included); AR L702H and AR-V7 are not degraded by ARV-110
- Patients with 1 prior NHA and no prior chemotherapy were enrolled in a clinically defined, biomarker agnostic subgroup (Less Pretreated)

Results

Patients

- 195 patients were enrolled across the phase 1/2 study (**Table 1**)

Table 1: 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)

Parameter	Phase 1 (n=71)	Phase 2 (n=124)
Median no. lines of prior therapy (range)	6 (2–14)	4 (1–11)
Type of prior therapy, n (%)		
NHA	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)

*1 patient in phase 2 expansion had ECOG performance status of 2. †Soft tissue disease other than lymph node. ‡Or other AR blocker (apalutamide/darolutamide). AR=androgen receptor; ECOG=Eastern Cooperative Oncology Group; NHA=novel hormonal agent

Safety

- There were no grade ≥4 TRAEs at the RP2D (**Table 2**)
- TRAEs led to dose reductions in 11 (8%) patients treated at the RP2D and to treatment discontinuations in 12 (9%)

Table 2: Treatment-related adverse events*

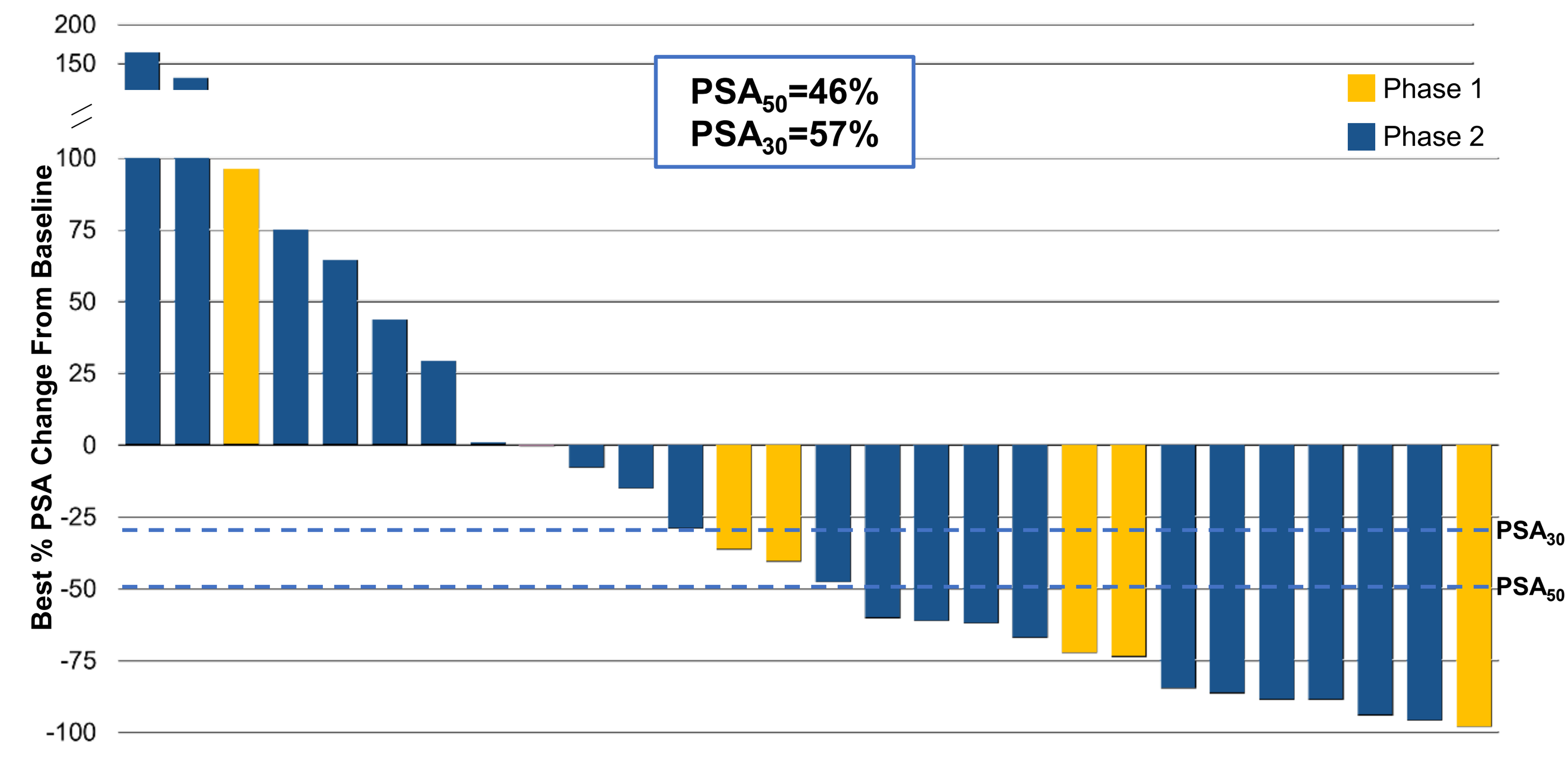
	Total at RP2D (n=138)†			
TRAE, n (%)	Grade 1	Grade 2	Grade 3‡	Total
Any TRAE	39 (28)	53 (38)	23 (17)	115 (83)
Nausea	42 (30)	22 (16)	2 (1)	66 (48)
Fatigue	32 (23)	16 (12)	1 (1)	49 (36)
Vomiting	28 (20)	7 (5)	1 (1)	36 (26)
Decreased appetite	19 (14)	15 (11)	1 (1)	35 (25)
Diarrhea	19 (14)	6 (4)	3 (2)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

*Reported in ≥10% of patients treated at the RP2D. †Includes 14 phase 1 patients (9 treated at 420 mg once daily and 5 treated at 210 mg twice daily) 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; NA=not applicable; RP2D=recommended phase 2 dose; TRAE=treatment-related adverse event

Efficacy

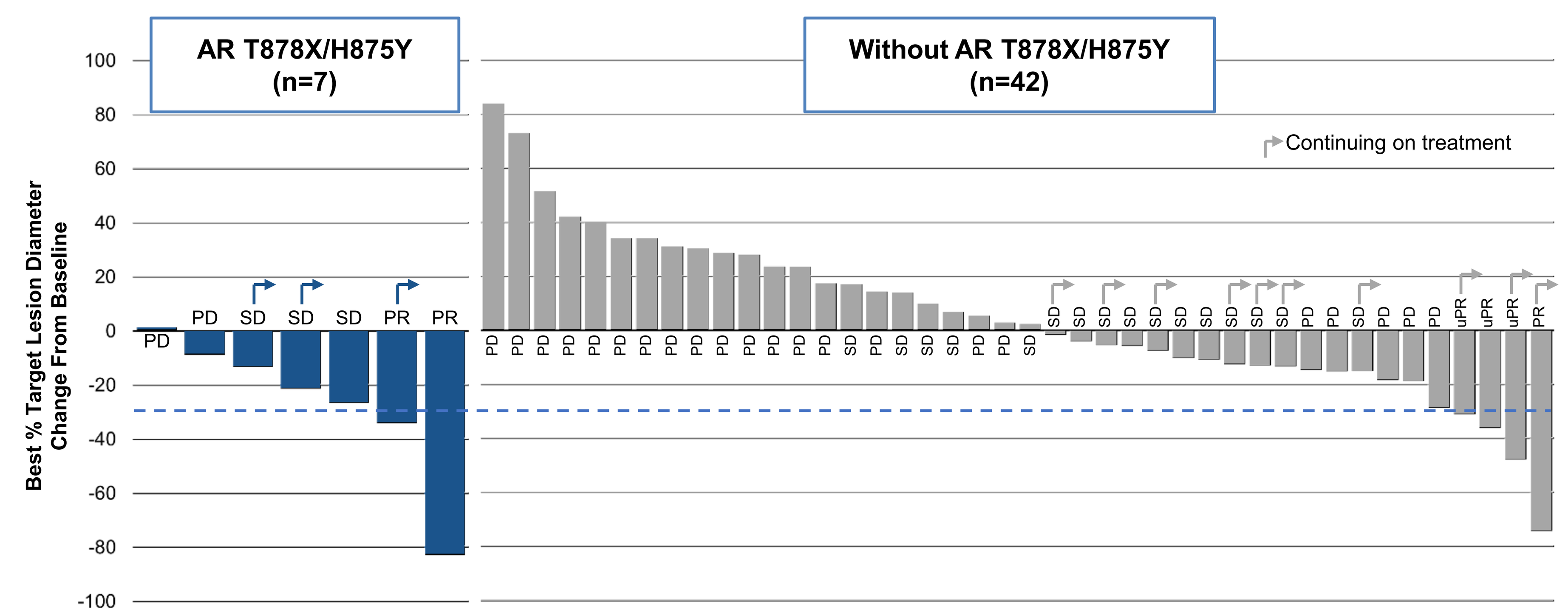
- Best percentage change in PSA from baseline across biomarker-evaluable phase 1/2 patients with ≥4 weeks of PSA follow-up is shown in **Figure 1A**
  - In addition to the T878X/H875Y subgroup, patients in the L702H/AR-V7 and Less Pretreated subgroups as well as in the phase 1 study had AR T878X/H875Y mutations
- The Less Pretreated subgroup in ARDENT had a similar non-AR molecular profile to the more pretreated, biomarker-defined subgroups (T878X/H875Y, WT/Other, and L702H/AR-V7; **Figure 1B**)
- In 28 patients with AR T878X/H875Y-positive tumors, the PSA_{50} rate was 46% and the PSA_{30} rate was 57% (**Figure 2**)
- Across the biomarker- and PSA-evaluable phase 1/2 patient population (n=152), the PSA_{50} rate was 17% and the PSA_{30} rate was 31%
- 2 of 7 patients with tumors harboring AR T878X/H875Y mutations had confirmed RECIST partial responses (**Figure 3**)
- Tumor shrinkage was observed regardless of AR T878X/H875Y mutation status in the phase 1/2 population (**Figure 3**)
- 12 (43%) AR T878X/H875Y-positive patients received ARV-110 for ≥24 weeks; 9 were ongoing as of the data cutoff date (**Figure 4**)

Figure 2: Best percentage change in PSA from baseline in patients with tumors harboring AR T878X/H875Y mutations (n=28)*



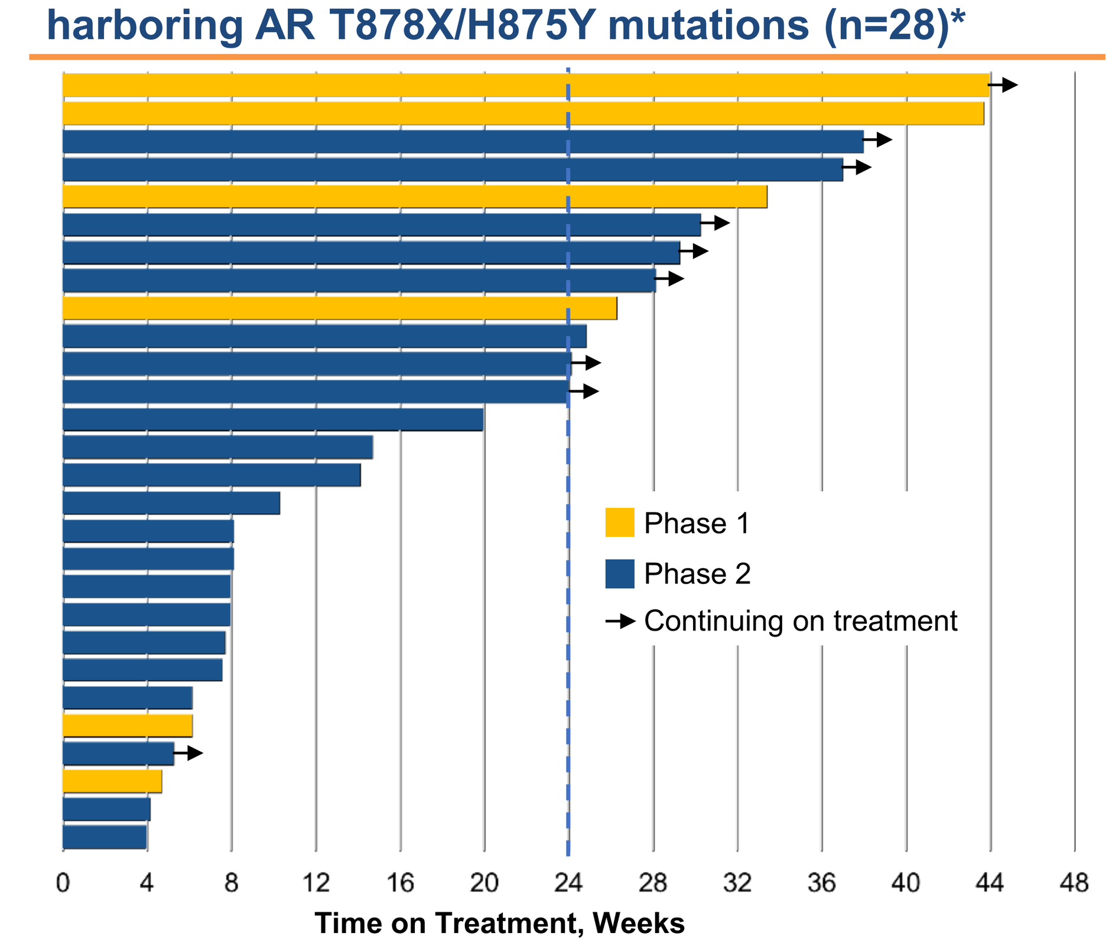
*Includes biomarker-evaluable patients treated at or above the recommended phase 2 dose (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft tumor models (phase 1) and with ≥4 weeks of PSA follow-up.
AR=androgen receptor; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%; T878X=T878A or T878S

Figure 3: Tumor shrinkage in RECIST-evaluable phase 1/2 population*



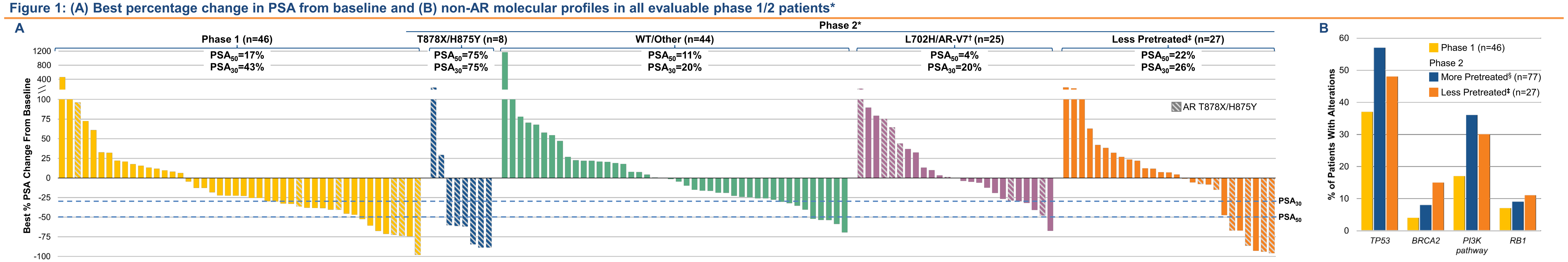
*Includes biomarker-evaluable patients treated at or above the recommended phase 2 dose (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft tumor models (phase 1) and with measurable disease at baseline and ≥1 on-treatment scan; patients with SD as best response and <12 weeks follow-up were excluded.
AR=androgen receptor; PD=progressive disease; PR=confirmed partial response; SD=stable disease; RECIST=Response Evaluation Criteria in Solid Tumors; T878X=T878A or T878S; uPR=unconfirmed partial response

Figure 4: Time on treatment in patients with tumors harboring AR T878X/H875Y mutations (n=28)*



*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).
AR=androgen receptor; PSA=prostate-specific antigen; T878X=T878A or T878S

Figure 1: (A) Best percentage change in PSA from baseline and (B) non-AR molecular profiles in all evaluable phase 1/2 patients*



*Includes biomarker-evaluable patients (those with circulating tumor DNA or tumor samples evaluable by DNA sequencing and, where applicable, blood samples evaluable for AR-V7) 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) and with ≥4 weeks of PSA follow-up; 2 biomarker-evaluable phase 2 patients with limited sequencing data could not be assigned to a subgroup; non-AR molecular profile analyses are preliminary and exploratory. †Co-occurring T878X/H875Y included. ‡All AR forms. §Includes patients in phase 2 biomarker-defined subgroups (T878X/H875Y, WT/Other, and L702H/AR-V7).
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