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

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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.

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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)
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*

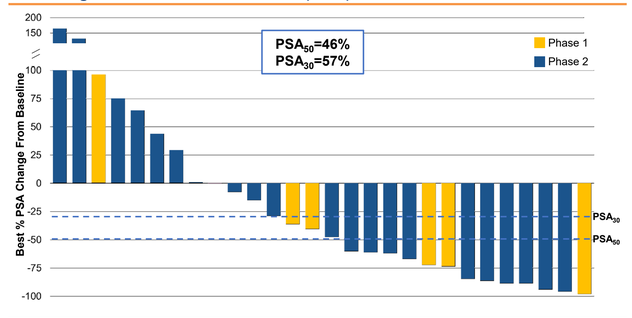
	Total at RP2D (n=138)†			
TRAE, n (%)	Grade 1	Grade 2	Grade 3‡	Total
Any TRAE	39 (28)	53 (38)	23 (17)	115 (83)
Nausea	42 (30)	22 (16)	2 (1)	66 (48)
Fatigue	32 (23)	16 (12)	1 (1)	49 (36)
Vomiting	28 (20)	7 (5)	1 (1)	36 (26)
Decreased appetite	19 (14)	15 (11)	1 (1)	35 (25)
Diarrhea	19 (14)	6 (4)	3 (2)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

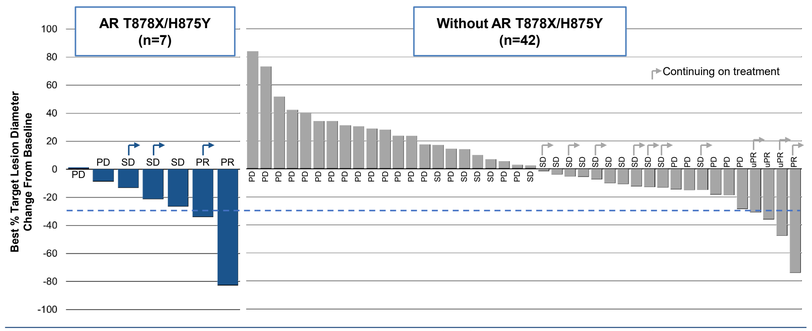
- Best percentage change in PSA from baseline across biomarker-evaluable phase 1/2 patients with ≥4 weeks of PSA follow-up is shown in **Figure 1A**
  - In addition to the T878X/H875Y subgroup, patients in the L702H/AR-V7 and Less Pretreated subgroups as well as in the phase 1 study had AR T878X/H875Y 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)*



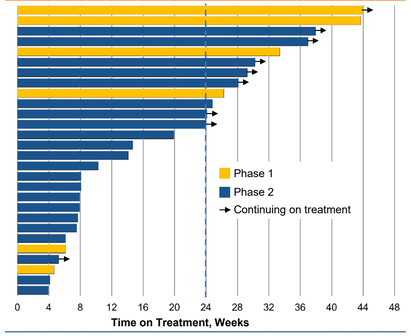
*Includes biomarker-evaluable patients treated at or above the recommended phase 2 dose (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft tumor models (phase 1) and with ≥4 weeks of PSA follow-up.
AR=androgen receptor; PSA=prostate-specific antigen; PSA_{30}=best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

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



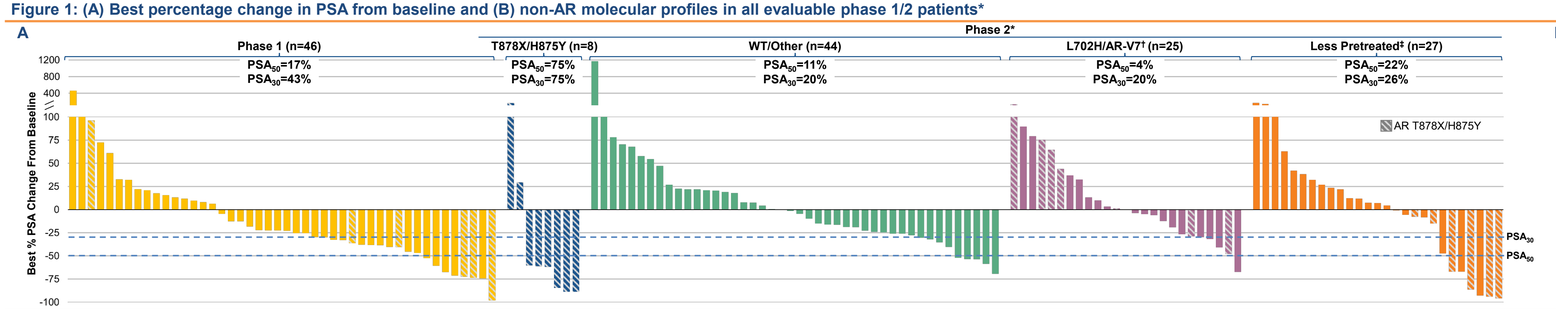
*Includes biomarker-evaluable patients treated at or above the recommended phase 2 dose (phase 1 and 2) or with exposure above the minimum efficacious threshold in nonclinical xenograft tumor models (phase 1) and with measurable disease at baseline and ≥1 on-treatment scan; patients with SD as best response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