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):

- 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)
- 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

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

*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)

- 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

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

*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%

AR T878X/H875Y-Positive (n=28)*
PSA$_{50}$=46%
PSA$_{30}$=57%

*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

AR T878X/H875Y-Positive (n=7)*,†

- 12 (43%) patients received ARV-110 for ≥24 weeks

*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 $\geq 50\%$ Were Seen Across All Subgroups in ARDENT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PSA$_{50}$</th>
<th>PSA$_{30}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>T878X/H875Y-positive (n=8)*</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>WT/Other (n=44)*</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>L702H/AR-V7† (n=25)*</td>
<td>4%</td>
<td>20%</td>
</tr>
<tr>
<td>Less Pretreated‡ (n=27)*</td>
<td>22%</td>
<td>26%</td>
</tr>
</tbody>
</table>

*Includes biomarker-evaluable patients with $\geq$4 weeks of PSA follow-up
†Co-occurring T878X/H875Y included; ‡All forms of AR
AR=androgen receptor; PSA=prostate-specific antigen; PSA$_{50}$=best PSA declines $\geq 50\%$; PSA$_{30}$=best PSA declines $\geq 30\%$; 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

<table>
<thead>
<tr>
<th>More Pretreated (Biomarker-Defined) (n=77)*</th>
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<tbody>
<tr>
<td>TP53</td>
</tr>
<tr>
<td>BRCA2</td>
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<tr>
<td>PI3K pathway</td>
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<td>RB1</td>
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*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

Best % PSA Change From Baseline

AR T878X/H875Y-positive

PSA_{30} PSA_{50}
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
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Objective
To evaluate the safety and efficacy of ARV-110 in patients with 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% (PSA50) and ≥30% (PSA30) were seen in 46% and 57%, respectively, in 28 patients; 7 of 28 evaluable patients had partial responses (PRs); 10 (36%) of 27 patients had stable disease (SD) at the RP2D

Results
Patients
195 patients were enrolled across the phase 1/2 study (Table 1) and 110 patients were evaluable at the RP2D

Methods
The ongoing ARDENT phase 2 expansion study (NCT03888612) is evaluating ARV-110 in patients with confirmed mCRPC disease progression or on whose most recent therapy (2 or ≥3 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 (PFS), and radiographic progression-free survival (RPFS)
Secondary endpoints are duration of response, overall survival (OS), and laboratory abnormalities, and pharmacokinetic parameters

Efficacy
Best percentage change in PSA from baseline across biomarker-evaluable phase 1/2 patients with ≥24 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 confirmed subgroups
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 PSA50 was 46% and the PSA30 was 57% (Figure 2)
Across the biomarker- and PSA-defined phase 1/2 population (n=152), the PSA50 was 17% and the PSA30 was 31% (Figure 2)
2 of 7 tumors with ARV-110 harboring T878X/H875Y mutations had confirmed RECIST partial responses (Figures 1A and 2)
Tumor shrinkage was observed regardless of AR T878X/H875Y mutation status in the phase 1/2 population

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

References

Acknowledgments
The authors thank the patients and their caregivers, the investigators, researchers and coordinators who contributed to this study. This study was sponsored by Arvinas Androgen Receptor, Inc.