2024 ASCO® ANNUAL MEETING

# ARV-766, a PROteolysis TArgeting Chimera (PROTAC) Androgen Receptor Degrader, in Metastatic Castration-Resistant Prostate Cancer: Initial Results of a Phase 1/2 Study

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# Key Takeaways

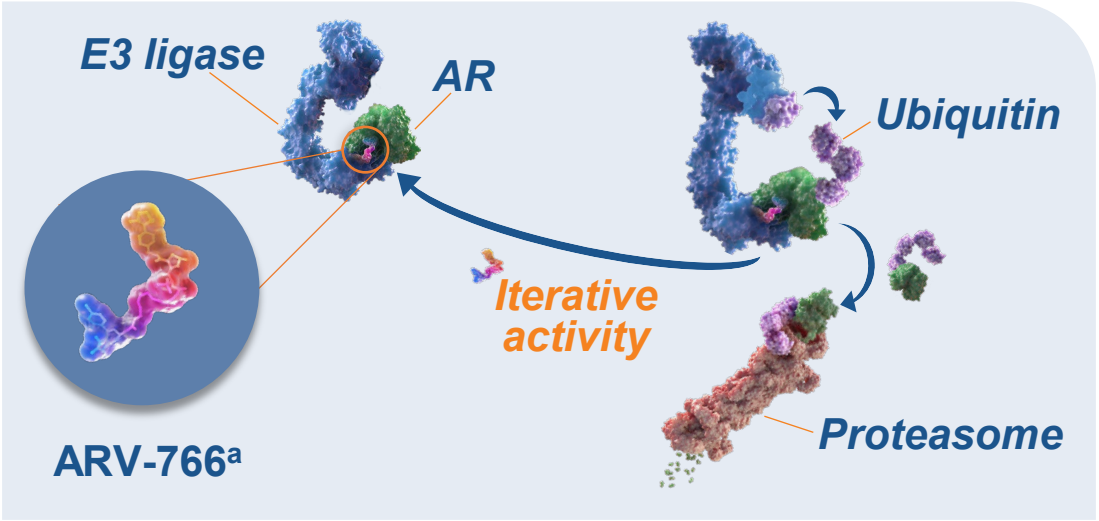
- Mutations in the *AR* LBD (amino acids 671–920) have been associated with poor prognosis in men with mCRPC
- In this phase 1/2 study of the PROTAC AR degrader ARV-766 in previously treated patients with mCRPC:
  - ARV-766 monotherapy was well tolerated
  - ARV-766 showed promising clinical activity in patients with tumors harboring *AR* LBD mutations
- Based on these findings, ARV-766 warrants further development in advanced prostate cancer

AR=androgen receptor; LBD=ligand-binding domain; mCRPC=metastatic castration-resistant prostate cancer; PROTAC=PROteolysis TArgeting Chimera.

# Background

- Patients with mCRPC inevitably develop resistance to available therapies, including ARPIs, and experience disease progression[1]
- ≈20%–25% of men with mCRPC will develop mutations in the *AR* LBD (amino acids 671–920)
  - L702H, H875Y, and T878A are the most common *AR* mutations and are associated with poor prognosis[2–4]

- ARV-766 is a novel, potent, oral PROTAC AR degrader that targets wild-type *AR* and clinically relevant *AR* LBD mutants, including *AR* L702H, H875Y, and T878A




[a]General PROTAC protein degrader is shown.

AR=androgen receptor; ARPI=androgen receptor pathway inhibitor; LBD=ligand-binding domain; mCRPC=metastatic castration-resistant prostate cancer; PROTAC=PROteolysis TArgeting Chimera.

1. Boudadi K and Antonarakis ES. *Clin Med Insights Oncol*. 2016;10(Suppl 1):1-9.
2. Snaterse G, et al. Prostate Cancer Prostatic Dis. 2023;26(2):293-301.
3. Lallous N, et al. Genome Biol. 2016;17:10.
4. Shiota M, et al. Endocr Relat Cancer. 2022;29(10):R143-R155.

# ARV-766 Monotherapy: Study Design[a] (NCT05067140)

## Phase 1 dose escalation (part A)

**Key eligibility criteria**

- Progressive mCRPC
- Ongoing ADT
- ≥2 prior systemic therapies (including ≥1 ARPI)

**Treatment**

- Ascending doses of ARV-766 (20–500 mg orally QD)

**Primary objective**

- Safety and tolerability of ARV-766 to select RP2Ds

## Phase 2 cohort expansion (part B)

**Key eligibility criteria**

- Progressive mCRPC
- Ongoing ADT
- 1–3 prior ARPIs
- ≤2 prior chemotherapy regimens

**Treatment**

- ARV-766 100 mg or 300 mg orally QD (1:1 randomization)

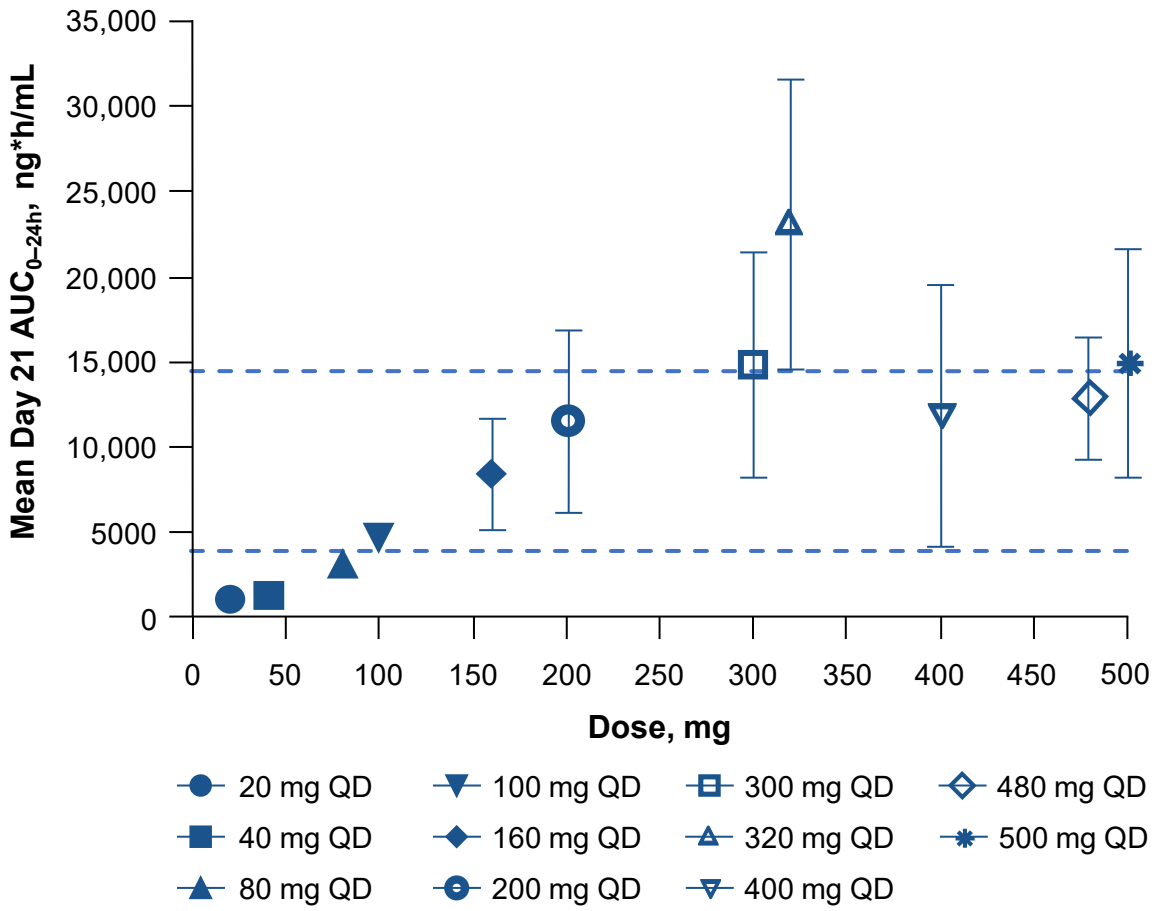
**Primary objective**

- Evaluate the antitumor activity of ARV-766

- Safety was evaluated in all patients treated with ARV-766 across the phase 1/2 study
- For this analysis, antitumor activity[b] was assessed in the subgroup of patients with *AR* LBD mutations
- Data cutoff date for this analysis: April 15, 2024

[a]Parts C and D of this study are assessing ARV-766 in combination with abiraterone.
[b]PSA declines were evaluated in patients with ≥1 month of PSA follow-up; response per PCWG3/RECIST was evaluated in patients with measurable disease at baseline and ≥1 on-treatment scan.
ADT=androgen deprivation therapy; AR=androgen receptor; ARPI=androgen receptor pathway inhibitor; LBD=ligand-binding domain; mCRPC=metastatic castration-resistant prostate cancer; PCWG3=Prostate Cancer Working Group 3; PSA=prostate-specific antigen; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended phase 2 dose.

# ARV-766 Monotherapy: Pharmacokinetics




- Dose-dependent increases in ARV-766 exposure up to 320 mg QD were observed in phase 1 (part A)
  - Exposure accumulation ranged from ≈5- to 8-fold at steady state
- Mean $AUC_{0-24h}$ at steady state for 100 mg QD[a] and 300 mg QD[b] exceeded the minimal preclinical efficacious thresholds
- 100 and 300 mg QD were selected as the RP2Ds for cohort expansion

[a]VCaP tumor xenograft model.
[b]Enzalutamide-resistant model.
AUC=area under the curve from 0 to 24 hours; QD=once daily; RP2D=recommended phase 2 dose; VCaP=Vertebral-Cancer of the Prostate.

# ARV-766 Monotherapy: Patient Baseline Characteristics[a]

| Parameter | Total (N=123) | *AR* LBD Mutations (n=53) |
|---|---|---|
| Median age (range), y | 72 (47–88) | 72 (47–88) |
| ECOG performance status, n (%) | | |
| 0 | 70 (57) | 24 (45) |
| 1 | 53 (43) | 29 (55) |
| Visceral disease, n (%) | 28 (23) | 14 (26) |
| Prior lines of therapy, median (range) | 4 (1–10) | 4 (1–10) |
| Prior ARPI, n (%) | 123 (100) | 53 (100) |
| Abiraterone alone | 36 (29) | 19 (36) |
| Enzalutamide, apalutamide, or darolutamide alone | 31 (25) | 5 (9) |
| ≥2 ARPIs | 56 (46) | 29 (55) |
| Prior taxane, n (%) | 69 (56) | 31 (58) |
| Docetaxel alone | 48 (39) | 20 (38) |
| Cabazitaxel alone | 1 (1) | 1 (2) |
| Docetaxel and cabazitaxel | 20 (16) | 10 (19) |

[a]Includes all patients treated with ARV-766 across the phase 1/2 study

AR=androgen receptor; ARPI=androgen receptor pathway inhibitors; ECOG=Eastern Cooperative Oncology Group; LBD=ligand-binding domain.

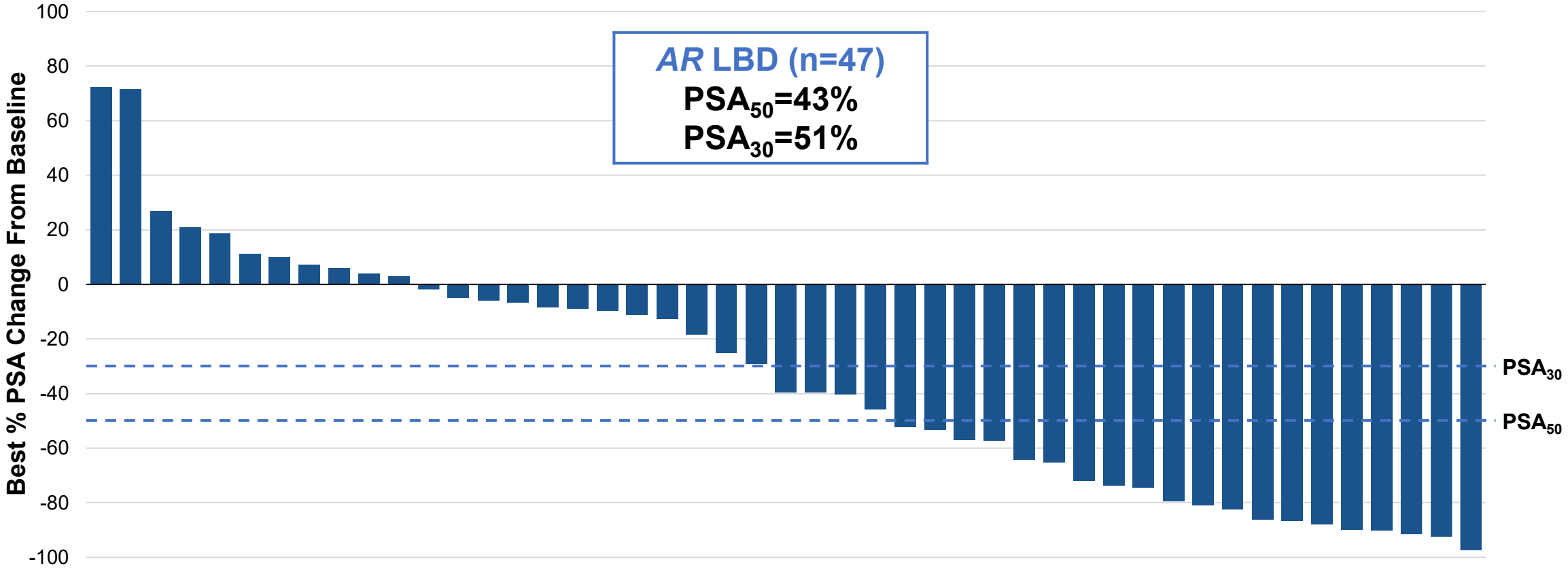
# ARV-766 Monotherapy: Safety

- There were no DLTs, and an MTD was not reached in phase 1 (part A)
- Across all 123 phase 1/2 patients:
  - 118 (96%) had ≥1 any grade TEAE
    - 46 (37%) had a grade 3/4 TEAE
    - 3 (2%) had a grade 5 TEAE[a]
  - 9 (7%) had TEAEs that led to dose reduction of ARV-766
  - 10 (8%) had TEAEs that led to discontinuations of ARV-766

| TRAEs in ≥10% of patients, n (%) | Total (N=123) | | | |
|---|---|---|---|---|
| | Total | Grade 1 | Grade 2 | Grade 3 |
| Fatigue | 41 (33) | 26 (21) | 12 (10) | 3 (2) |
| Nausea | 25 (20) | 16 (13) | 8 (7) | 1 (1) |
| Diarrhea | 19 (15) | 13 (11) | 5 (4) | 1 (1) |
| Increased blood creatinine | 18 (15) | 14 (11) | 4 (3) | 0 |
| Alopecia | 17 (14) | 14 (11) | 3 (2) | NA |
| Decreased appetite | 13 (11) | 4 (3) | 9 (7) | 0 |

[a]Grade 5 TEAEs were death (unknown cause), brain stem stroke, and malignant neoplasm progression (n=1 each).
DLT=dose-limiting toxicity; MTD=maximum tolerated dose; NA=not applicable; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

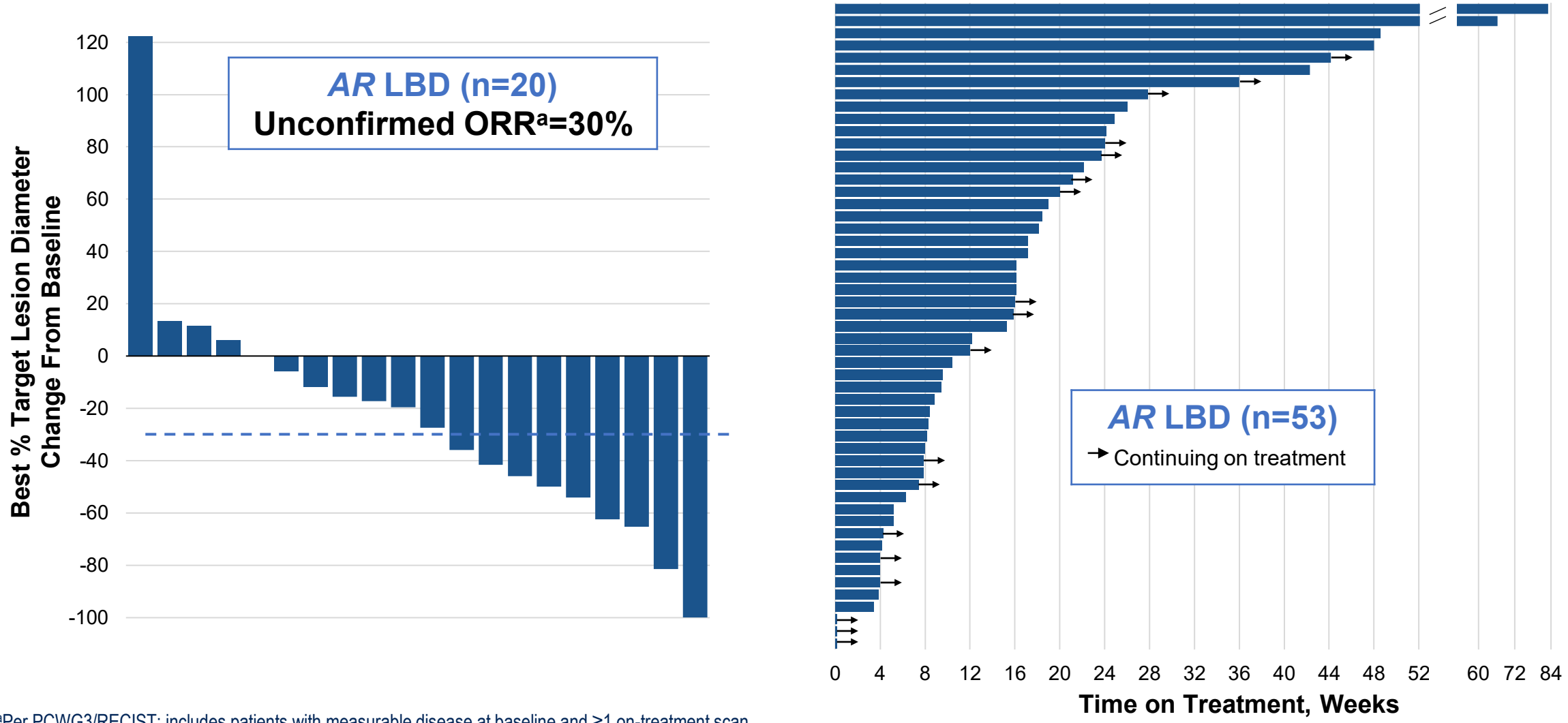
# ARV-766 Monotherapy: Best Declines in PSA in Patients With *AR* LBD Mutations[a]




[a]Includes patients with ≥1 month of PSA follow-up.

AR=androgen receptor; LBD=ligand-binding domain; PSA=prostate-specific antigen; $PSA_{30}$=best PSA declines ≥30%; $PSA_{50}$=best PSA declines ≥50%.

# ARV-766 Monotherapy: Tumor Response and Treatment Duration in Patients With *AR* LBD Mutations




[a]Per PCWG3/RECIST; includes patients with measurable disease at baseline and ≥1 on-treatment scan.

AR=androgen receptor; LBD=ligand-binding domain; ORR=objective response rate; PCWG3=Prostate Cancer Working Group 3; RECIST=Response Evaluation Criteria in Solid Tumors.

# Conclusions

- In this phase 1/2 study of pretreated patients with mCRPC, ARV-766 was well tolerated
- ARV-766 showed promising clinical activity ($PSA_{50}$ of 43%) in patients with tumors harboring *AR* LBD mutations
- ARV-766 warrants further development in advanced prostate cancer

**Acknowledgments**

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AR=androgen receptor; LBD=ligand-binding domain; mCRPC=metastatic castration-resistant prostate cancer; $PSA_{50}$=best prostate-specific antigen declines ≥50%.