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ARV-766, a PROTAC Androgen Receptor Degrader, Combined With Abiraterone in Novel Hormonal Agent–Naïve Metastatic Prostate Cancer: Phase 1 Cohort (Part C) of a Phase 1/2 Study

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Key Points

- ARV-766, a PROteolysis TArgeting Chimera (PROTAC) androgen receptor (AR) degrader, was well tolerated as monotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received prior novel hormonal agent (NHA) therapy (eg, abiraterone or enzalutamide) in parts A and B of a phase 1/2 study
  - Analyses of antitumor activity are ongoing
- Part C of the study will assess the safety, tolerability, and drug-drug interaction of the combination of ARV-766 and abiraterone in patients with NHA-naïve metastatic prostate cancer; part D will then assess the antitumor activity of this combination

References

1. Snyder LB, et al. Presented at AACR 2023. ND03.
2. Boudadi K, et al. Clin Med Insights Oncol. 2016;10(suppl 1):1-9.

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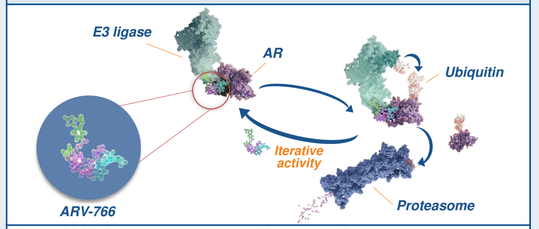
Background

- ARV-766 is a PROTAC AR degrader that creates a trimer complex with AR and an E3 ubiquitin ligase to directly trigger ubiquitination and subsequent degradation of AR by the proteasome (**Figure 1**)
- ARV-766 showed degradation activity against wild-type AR as well as clinically relevant mutants in preclinical experiments and robust tumor growth inhibition in mouse models of prostate cancer[1]
- In the first-in-human study of ARV-766 (NCT05067140), parts A (dose escalation) and B (cohort expansion) are assessing ARV-766 monotherapy in men with mCRPC
- Abiraterone is an NHA that is used to treat patients with mCRPC or metastatic castration-sensitive prostate cancer (mCSPC)
- Abiraterone acts upstream of AR by depleting androgen biosynthesis, and patients may become resistant to abiraterone through AR upregulation, AR mutations or splice variants, and/or alternative oncogenic signaling pathways[2]
- Due to its ability to degrade wild-type and mutant AR and act on the AR pathway downstream of abiraterone, ARV-766 might enhance abiraterone efficacy when the 2 drugs are combined
- Part C of this study will assess the addition of ARV-766 to abiraterone for the treatment of men with NHA-naïve metastatic prostate cancer

Figure 1: Mechanism of action of ARV-766[a]



[a]General PROTAC protein degrader, cereblon E3 ligase, and AR target protein are shown
AR=androgen receptor; PROTAC=PROteolysis TArgeting Chimera

Safety of ARV-766 Monotherapy (Parts A and B)

- Parts A and B of the study are evaluating ARV-766 monotherapy in patients with mCRPC and prior NHA treatment (**Figure 2**)
  - Part A (dose escalation) assessed the safety and tolerability of ARV-766 to select recommended phase 2 doses (RP2Ds)
  - Part B (cohort expansion) is evaluating the antitumor activity of the RP2Ds
- As of August 23, 2023, 84 patients with mCRPC were treated with ARV-766 monotherapy in parts A and B
- Treatment-related adverse events (TRAEs) reported in ≥10% of patients who received ARV-766 monotherapy are shown in **Table 1**
  - There were no grade ≥4 TRAEs with ARV-766 monotherapy
- 3 patients had TRAEs leading to ARV-766 discontinuation

Table 1: TRAEs with ARV-766 monotherapy reported in ≥10% of patients (N=84)

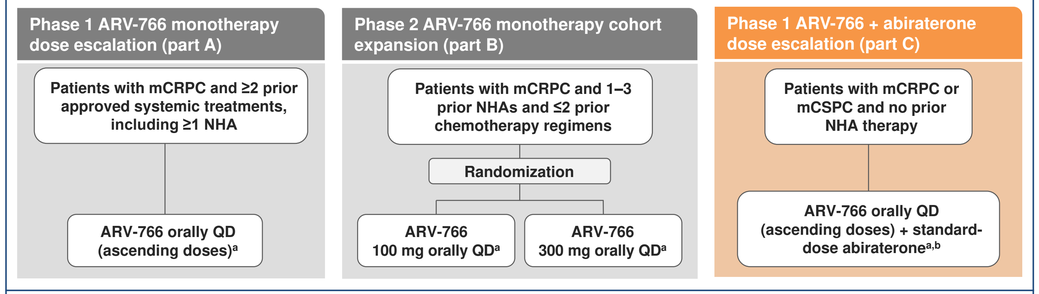
n (%)	Any grade	Grade 3[a]
Fatigue	24 (29)	2 (2)
Nausea	12 (14)	0
Diarrhea	9 (11)	1 (1)
Vomiting	9 (11)	0
Decreased appetite	9 (11)	0
Alopecia	8 (10)	NA

[a]There were no grade ≥4 TRAEs
NA=not applicable; TRAE=treatment-related adverse event

ARV-766 + Abiraterone Study Design (Part C)

- In part C, patients will receive ARV-766 in combination with abiraterone (**Figure 2**)
- Patients eligible for part C have confirmed metastatic prostate cancer (**Table 2**)
  - Patients have mCRPC or mCSPC and no prior treatment with an NHA
- Dose escalation will follow a 3+3 cohort design based on safety and pharmacokinetic parameters
- The primary objective and endpoints are shown in **Table 3**

Figure 2: Study schema



[a]Patients will also receive androgen deprivation therapy
[b]Patients will receive a concomitant corticosteroid with abiraterone
mCRPC=metastatic castration-resistant prostate cancer; mCSPC=metastatic castration-sensitive prostate cancer; NHA=novel hormonal agent; QD=once daily

Table 2: Key eligibility criteria for part C

Inclusion criteria	Exclusion criteria
• Men aged ≥18 years • Histologically, pathologically, or cytologically confirmed diagnosis of adenocarcinoma of the prostate • ECOG performance status of 0 or 1	• Prior treatment with an NHA (abiraterone, enzalutamide, darolutamide, or apalutamide) • Symptomatic brain metastases requiring steroids above physiologic replacement doses • Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease, or previous gastric resection or lap band surgery

ECOG=Eastern Cooperative Oncology Group; NHA=novel hormonal agent

Table 3: Outcome measures for part C

Primary objective	Primary endpoints
• Evaluate the safety and tolerability of ARV-766 in combination with abiraterone	• DLTs during the first cycle • Type, frequency, severity, and relationship to study drug of adverse events • Type, frequency, and severity of laboratory abnormalities

DLT=dose-limiting toxicity