TPS290

A phase 2 expansion study of ARV-766, a PROTAC androgen receptor degrader, in metastatic castration-resistant prostate cancer

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Objective

- This phase 2 expansion cohort will evaluate the clinical activity and safety of ARV-766 in men with metastatic castration-resistant prostate cancer (mCRPC) who have experienced disease progression on prior novel hormonal agent (NHA) therapy

References

1. Boudadi K, et al. *Clin Med Insights Oncol*. 2016;10(suppl 1):1-9.
2. Békés M, et al. *Nat Rev Drug Discov*. 2022;21(3):181-200.
3. Nalawansha DA, et al. *Cell Chem Biol*. 2020;27(8):998-1014.

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Plain Language Summary
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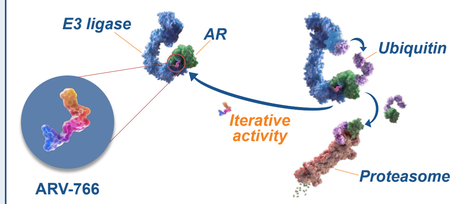
Background and Rationale

- Patients with mCRPC inevitably develop resistance to available therapies and lack curative options[1]
- New therapies that target different pathways, have novel mechanisms of action, and/or address mechanisms of resistance for patients who have progressed on current NHAs (eg, abiraterone, enzalutamide, darolutamide, or apalutamide) are needed to improve outcomes in patients with mCRPC[1]
- The PROteolysis TArgeting Chimera (PROTAC) androgen receptor (AR) degrader ARV-766 is a heterobifunctional small molecule consisting of an AR-binding domain joined by a linker to an E3 ubiquitin ligase–binding domain
- ARV-766 creates a trimer complex with AR and an E3 ubiquitin ligase to directly trigger ubiquitination and subsequent rapid and complete degradation of AR by the proteasome (**Figure 1**)[2]
- ARV-766 can block AR stimulation by androgens through elimination of AR rather than competitive inhibition of the AR binding site (ie, enzalutamide) or inhibiting androgen synthesis (ie, abiraterone)[1,3]
- ARV-766 is a novel, potent, orally administered PROTAC AR degrader
  - ARV-766 degrades not only wild-type AR, but also clinically relevant *AR* ligand–binding domain mutants, including the most prevalent *AR* L702H, H875Y, and T878A mutations (data on file)
- A phase 1 dose escalation portion of a phase 1/2 trial (NCT05067140) was conducted to determine the safety and tolerability of ARV-766 in patients with mCRPC who had progressed on ≥2 prior approved systemic treatments, including ≥1 NHA, and to select the doses evaluated in the phase 2 expansion cohort

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

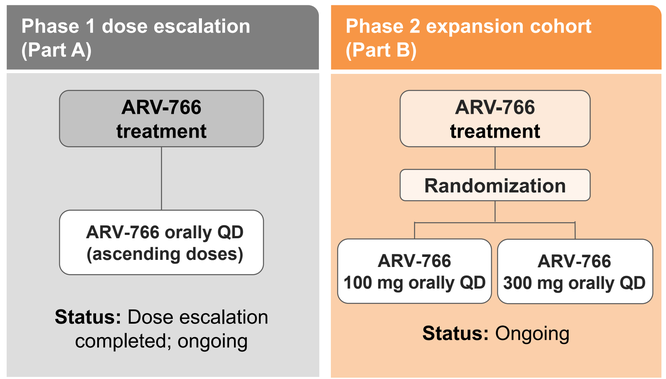


[a]General PROTAC protein degrader is shown
AR=androgen receptor; PROTAC=PROteolysis TArgeting Chimera

Study Design

- In this open-label, multicenter, phase 2 expansion cohort, patients will be randomized to receive oral ARV-766 daily, either 100 mg or 300 mg, in 28-day cycles (**Figure 2**)

Figure 2: Trial schema



QD=once daily

- Eligible patients have mCRPC, prior NHA therapy, and ongoing androgen deprivation therapy (**Table 1**)
- Objectives and endpoints are shown in **Table 2**
- Patients will be enrolled in multiple centers across the United States
- Enrollment is ongoing

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Men aged ≥18 years • Histological, pathological, or cytological confirmed diagnosis of adenocarcinoma of the prostate • Progressive mCRPC • 1–3 prior NHAs (eg, enzalutamide or abiraterone) • ≤2 prior chemotherapy regimens • Ongoing ADT with a gonadotropin-releasing hormone analog or inhibitor, or orchiectomy (surgical or medical castration) • ECOG performance status of 0 or 1	• 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 • Radiation therapy ≤4 weeks from start of treatment or prior irradiation to >25% of the bone marrow • Treatment with investigational drug(s) ≤4 weeks prior to anticipated first dose of study drug • Systemic anticancer therapy ≤2 weeks prior to first dose of study drug (except agents to maintain castrate status) – ≤6 weeks for bicalutamide, mitomycin C, or nitrosoureas – ≤4 weeks for abiraterone

ADT=androgen deprivation therapy; ECOG=Eastern Cooperative Oncology Group; mCRPC=metastatic castration-resistant prostate cancer; NHA=novel hormonal agent

Table 2: Outcome measures[a]

Primary objective	Endpoints
• Evaluate the antitumor activity of ARV-766	• ORR (RECIST) • PSA_{30} rate • PSA_{50} rate
Secondary objective	**Endpoints**
• Evaluate the safety and tolerability of ARV-766	• Frequency and severity of adverse events and laboratory abnormalities

[a]Not all secondary objectives and endpoints are shown
ORR=overall response rate; PSA_{30}=prostate-specific antigen decline of >30%; PSA_{50}=prostate-specific antigen decline of >50%; RECIST=Response Evaluation Criteria in Solid Tumors