TPS5106

Phase 1b study of bavdegalutamide, an androgen receptor PROTAC degrader, combined with abiraterone in patients with metastatic prostate cancer

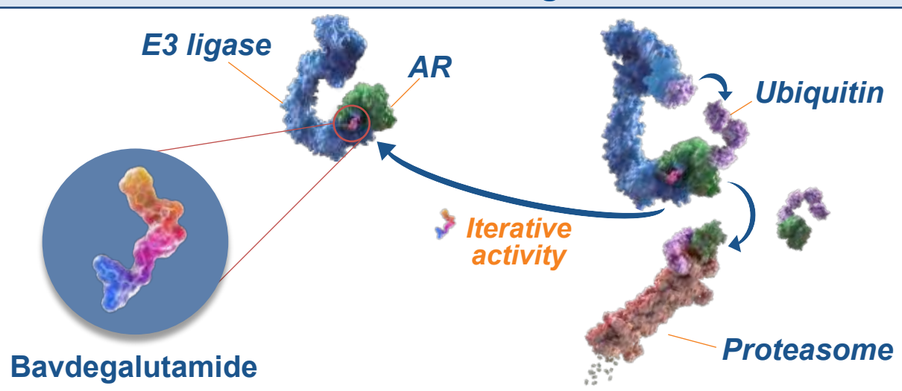
Neal D Shore[1], John Shen[2], Michael E Devitt[3], Haolan Lu[4], Jeanette Alicea[4], Janaki Parameswaran[4], Deborah Chirnomas[4], Xin Gao[5], Meredith McKean[6]

[1]Carolina Urologic Research Center, Myrtle Beach, SC; [2]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; [3]University of Virginia Comprehensive Cancer Center, Charlottesville, VA; [4]Arvinas, Inc., New Haven, CT; [5]Massachusetts General Hospital, Boston, MA; [6]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

Background and Rationale

- Bavdegalutamide (ARV-110), a novel, oral PROteolysis TArgeting Chimera (PROTAC) protein degrader (**Figure 1**), targeted wild-type androgen receptor (AR) and clinically relevant mutants in nonclinical studies and showed tumor growth inhibition in various xenograft models[1]

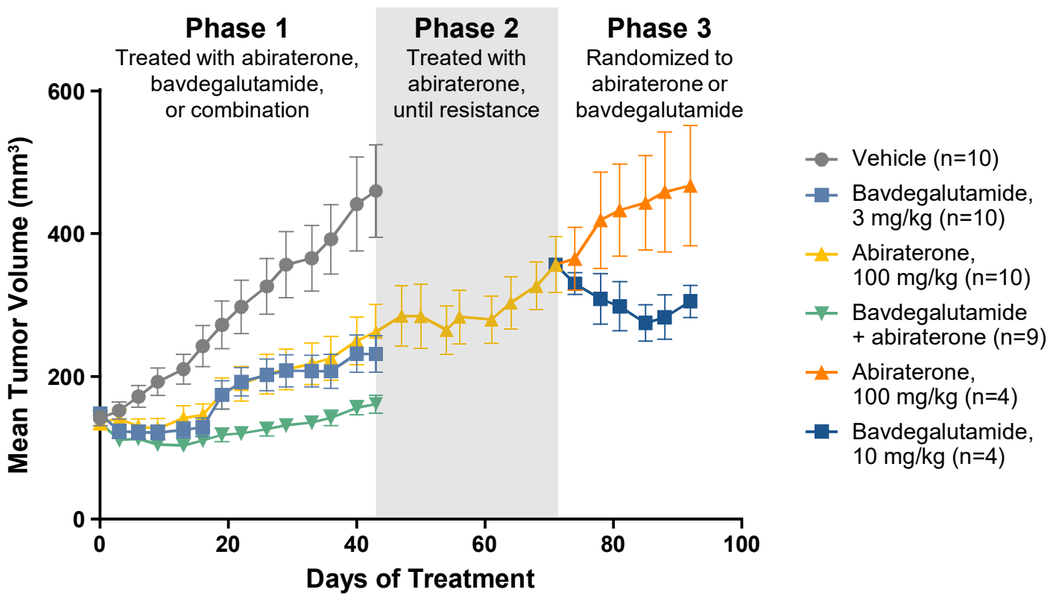
Figure 1: Mechanism of action of bavdegalutamide



AR=androgen receptor

- An ongoing phase 1/2 study (NCT03888612) is evaluating bavdegalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) after 1-2 prior novel hormonal agents (eg, abiraterone and/or enzalutamide), some of whom also had prior chemotherapy[2]
  - Of 28 evaluable patients with tumors harboring AR T878X/H875Y mutations, 46% had best prostate-specific antigen (PSA) declines of ≥50%
  - PSA declines of ≥50% were also observed in patients without AR T878X/H875Y–positive tumors
  - The recommended phase 2 dose (RP2D) of 420 mg once daily was tolerable with manageable side effects
- Abiraterone is approved, in combination with a corticosteroid, for patients with mCRPC or high-risk castration-sensitive prostate cancer (CSPC), but up to a third develop primary resistance to abiraterone and nearly all experience disease progression[3]
- Dual AR pathway inhibition by bavdegalutamide and abiraterone showed potential in a 3-phase nonclinical study in a prostate tumor xenograft model (**Figure 2**)
  - The combination showed greater tumor growth inhibition than either agent alone
  - Bavdegalutamide reduced the volume of abiraterone-resistant tumors
- These data suggest that addition of bavdegalutamide to abiraterone at the initiation of biochemical progression on abiraterone (PSA progression without radiographic progression) may overcome abiraterone resistance and re-establish AR pathway blockade in patients with metastatic prostate cancer

Figure 2: Tumor growth inhibition[a] with bavdegalutamide plus abiraterone and with bavdegalutamide after abiraterone resistance



[a]In castrated mice bearing human vertebral cancer of the prostate (VCaP) tumor xenografts

Objective

- This phase 1b study (NCT05177042) will evaluate the safety, tolerability, and pharmacokinetics of bavdegalutamide in combination with abiraterone in patients with metastatic prostate cancer

Study Design

- In this open-label, multicenter, phase 1b study, patients will receive oral bavdegalutamide, abiraterone, and a corticosteroid daily in 28-day cycles
- Eligible patients have mCRPC or metastatic CSPC and PSA progression on abiraterone without radiographic progression (**Table 1**)
- Primary outcomes are shown in **Table 2**
- Patients will be enrolled in the United States, Canada, France, and the United Kingdom

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Men ≥18 years of age • Histologically, pathologically, or cytologically confirmed adenocarcinoma of the prostate • ECOG performance status of 0 or 1 • Ongoing treatment with stable doses of abiraterone and a concomitant corticosteroid for mCRPC or mCSPC and, prior to signing consent: – PSA progression ≥16 weeks after initiation of abiraterone – ≥2 rising PSA values measured ≥1 week apart – No known radiographic evidence of disease progression while receiving abiraterone • Ongoing androgen deprivation therapy with a gonadotropin-releasing hormone analog or inhibitor or orchiectomy	• Prior treatment with enzalutamide, apalutamide, darolutamide, or experimental AR-directed therapies • Treatment with any chemotherapy, investigational agents, immunotherapy, or hormonal therapy other than gonadotropin-releasing hormone agonists ≤28 days of start of treatment • Radiation therapy ≤4 weeks from start of treatment or prior irradiation to >25% of the bone marrow

AR=androgen receptor; ECOG=Eastern Cooperative Oncology Group; mCRPC=metastatic castration-resistant prostate cancer; mCSPC=metastatic castration-sensitive prostate cancer; PSA=prostate-specific antigen

Table 2: Primary outcome measures

Objective	Endpoints
Evaluate the safety and tolerability of bavdegalutamide plus abiraterone and determine the RP2D and schedule of this combination	• Incidence of first-cycle dose-limiting toxicities • Frequency and severity of AEs and laboratory abnormalities

AE=adverse event; RP2D=recommended phase 2 dose

References

1. Neklesa T, et al. ASCO-GU 2019. Poster #259.
2. Gao X, et al. ASCO-GU 2022. Rapid Oral #17.
3. Buttigliero C, et al. *Cancer Treat Rev.* 2015;41:884-892.

Plain Language Summary

Please scan this Quick Response (QR) code with your smartphone app to view a plain language summary of the poster

Acknowledgments

This study is sponsored by Arvinas Androgen Receptor, Inc. We thank SangHyun Lee, Ryan Willard, Deborah Gordan, and Jennifer Pizzano for their contributions to nonclinical studies. Poster development support was provided by Apollo Medical Communications and funded by Arvinas, Inc.

Contact

Neal D Shore, MD, FACS; nshore@auclinics.com

Presented at the American Society for Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, June 3-7, 2022