Poster 1803P

Phase 1/2 Study of Bavdegalutamide, a PROteolysis TArgeting Chimera (PROTAC) Androgen Receptor Degrader, in Metastatic Castration-Resistant Prostate Cancer: Radiographic Progression-Free Survival in Patients With Androgen Receptor Ligand-Binding Domain Mutations

Daniel P Petrylak[1], Benjamin Garmezy[2], John Shen[3], Arash Rezazadeh Kalebasty[4], Oliver Sartor[5], Robert Dreicer[6], Neeraj Agarwal[7], Maha Hussain[8], Ivor Percent[9], Elisabeth I Heath[10], Richard Gedrich[11], Tinghui Yu[11], Diane Healey[11], Janaki Parameswaran[11], Cora N Sternberg[12], Xin Gao[13]

[1]Smilow Cancer Center, Yale University School of Medicine, New Haven, CT, USA; [2]Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN, USA; [3]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [4]University of California Irvine, Orange, CA, USA; [5]Mayo Clinic, Rochester, MN, USA; [6]University of Virginia Comprehensive Cancer Center, Charlottesville, VA, USA; [7]Huntsman Cancer Institute, University of Utah Comprehensive Cancer Center, Salt Lake City, UT, USA; [8]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [9]Florida Cancer Specialists, Port Charlotte, FL, USA; [10]Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA; [11]Arvinas Operations, Inc., New Haven, CT, USA; [12]Weill Cornell Medicine, New York, NY, USA; [13]Massachusetts General Hospital, Boston, MA, USA

Objectives

- To evaluate the clinical activity of bavdegalutamide (ARV-110), an oral PROTAC androgen receptor (AR) degrader, in patients with metastatic castration-resistant prostate cancer (mCRPC) and tumors harboring:
  - Any *AR* ligand-binding domain (LBD) missense mutation except *AR* L702H alone (*AR* LBD patients)
  - The subgroup of *AR* LBD patients with *AR* T878 and/or H875 mutations without an *AR* L702H mutation (*AR* 878/875 patients)
- To evaluate the safety of bavdegalutamide 420 mg once daily (QD) in patients with mCRPC

Key Findings

- Median radiographic progression-free survival (rPFS) was 8.2 months (95% CI: 3.8–not reached [NR]) in *AR* LBD patients (n=45) and 11.1 months (95% CI: 7.1–NR) in the *AR* 878/875 subgroup (n=26)
- Bavdegalutamide led to a best prostate-specific antigen (PSA) decline of ≥50% in 36.4% of evaluable *AR* LBD patients (n=44) and 53.8% in the *AR* 878/875 subgroup (n=26)
- Objective response rate (ORR) was 10.0% in evaluable *AR* LBD patients (n=20) and 9.1% in the *AR* 878/875 subgroup (n=11); 55.0% and 54.5%, respectively, had stable disease
- There were no grade ≥4 treatment-related adverse events (TRAEs); the most common TRAEs were gastrointestinal symptoms and fatigue

Conclusions

- In this post–novel hormonal agent (NHA) mCRPC population, promising clinical activity for bavdegalutamide, a PROTAC AR degrader, was observed in patients with tumors harboring missense *AR* LBD mutations excluding L702H alone (median rPFS: 8.2 months), including in the subgroup with *AR* 878/875 mutations (median rPFS: 11.1 months)
- Bavdegalutamide 420 mg QD continues to be tolerable with manageable side effects
- These encouraging results in patients with *AR* LBD-mutated mCRPC warrant further investigation

References

1. Boudadi K, et al. *Clin Med Insights Oncol*. 2016;10(suppl 1):1-9. **2.** Lallous N, et al. *Genome Biol*. 2016;17:10. **3.** Jernberg E, et al. *Endocr Connect*. 2017;6(8):R146-R161. **4.** Stewart TF, et al. Presented at ESMO; Sep 9-13, 2022; Paris, France. Poster 1407P. **5.** Neklesa T, et al. Presented at ASCO GU; Feb 8-10, 2018; San Francisco, CA, USA. Poster F6. **6.** Békés M, et al. *Nat Rev Drug Discov*. 2022;21(3):181-200. **7.** Gao X, et al. Presented at ASCO GU; Feb 17-19, 2022; San Francisco, CA, USA. Poster A2.

Disclosure

Dr. Petrylak has served as a consultant for Ada Cap (Advanced Accelerator Applications), Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Gilead Sciences, Incyte, Infinity Pharmaceuticals, Ipsen, Janssen, Merck & Company Inc, Mirati, Monopteros, Pfizer, Pharmacyclics, Regeneron, Roche, Sanofi Aventis, Seattle Genetics, and UroGen. He previously owned stock in Bellicum and Thyme and has received research grants from Ada Cap (Advanced Accelerator Applications), Agensys Inc, Arvinas, Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Bristol Myers Squibb, Clovis Oncology, Daiichi Sankyo Company Limited, Eisai, Eli Lilly, Endocyte, Ferring, Genentech, Gilead Sciences, Innocrin, MedImmune, Medivation, Merck, Mirati, Novartis, Pfizer, Progenics, Replimune, Roche, Sanofi Aventis, and Seattle Genetics.

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. Medical writing and editorial support were provided by Justine Lempart, PhD, and Melissa Austin of Apollo Medical Communications, part of Helios Global Group, and funded by Arvinas Operations, Inc.

Please scan this QR code to **download a copy of the poster**

Copies of this poster obtained through QR and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.

Please scan this QR code with your smartphone app to view a **plain language summary** of the poster

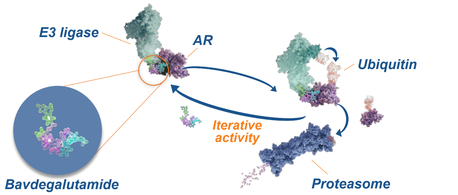
Contact
Daniel P Petrylak;
daniel.petrylak@yale.edu

European Society for Medical Oncology (ESMO) Annual Meeting, Madrid, Spain, October 20–24, 2023

Background

- Patients with mCRPC and mutations in *AR* LBD (amino acids 671–920) have poor prognosis[1-3]
  - In matched real-world cohorts of patients with mCRPC, those with the *AR* LBD mutations T878 and/or H875 had significantly shorter real-world overall survival from first-line treatment initiation than those without these mutations (median: 16.1 months [95% CI: 11.4–26.8] vs 50.7 months [95% CI: 45.4–59.8]; *P*<0.0001)[4]
- Bavdegalutamide (ARV-110) is an oral PROTAC AR degrader that has activity against clinically relevant mutants[5]
- Bavdegalutamide creates a trimer complex with AR and the cereblon E3 ubiquitin ligase to directly trigger ubiquitination and subsequent degradation of AR by the proteasome[6] (**Figure 1**)
- Previously reported data from this phase 1/2 study (NCT03888612) demonstrated clinical activity of bavdegalutamide in pretreated patients with mCRPC, with enhanced activity seen in patients with the *AR* LBD mutations T878 and/or H875[7]

Figure 1: Mechanism of action of bavdegalutamide[a]



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

Please scan this QR code with your smartphone app to view a **video of the mechanism of action of bavdegalutamide**

Methods

- This is a phase 1/2, open-label, dose escalation and cohort expansion study (NCT03888612) of bavdegalutamide in previously treated patients with mCRPC
  - In phase 1, patients with mCRPC received bavdegalutamide 35–700 mg QD or 210–420 mg twice daily
  - In phase 2 (ARDENT), patients with mCRPC were assigned to subgroups based on *AR* mutation status or a clinically defined subgroup (patients who had 1 prior NHA and no prior chemotherapy) and received bavdegalutamide 420 mg QD
- Key eligibility criteria
  - Confirmed mCRPC and disease progression on last line of treatment
    - Phase 1 dose escalation: Disease progression on ≥2 prior lines of systemic therapy, including abiraterone or enzalutamide
    - Phase 2 cohort expansion (ARDENT): 1–2 prior NHAs with ≤1 prior chemotherapy regimen each for castration-sensitive PC and CRPC
- For this exploratory analysis across the phase 1/2 population treated with bavdegalutamide 420 mg QD, efficacy was assessed in patients with any *AR* LBD missense mutation except *AR* L702H alone (*AR* LBD patients) and the subgroup with *AR* 878/875 mutation(s) without an *AR* L702H mutation (*AR* 878/875 patients)
- Safety outcomes were analyzed for all patients across the phase 1 and 2 portions of the study who were treated with bavdegalutamide 420 mg QD

Results

Baseline Characteristics

- As of August 11, 2023, 153 patients across the phase 1/2 study received bavdegalutamide 420 mg QD, including 45 patients with *AR* LBD mutations excluding L702H alone, 26 of whom had *AR* 878/875 without L702H (**Table 1**)

Table 1: Baseline characteristics

Parameter	Total at 420 mg QD (N=153)	*AR* LBD patients (n=45)	*AR* 878/875 patients (n=26)
Age, median (range), y	73 (48–91)	72 (51–83)	71.5 (51–83)
ECOG PS, n (%)[a]			
0	81 (53)	25 (56)	16 (62)
1	71 (46)	20 (44)	10 (38)
Visceral disease, n (%)	49 (32)	14 (31)	7 (27)
Prior lines of treatment, median (range)	4 (1–11)	4 (2–8)	4 (2–7)
Prior treatment, n (%)			
NHA	153 (100)	45 (100)	26 (100)
1 NHA	83 (54)	21 (47)	18 (69)
≥2 NHA	70 (46)	24 (53)	8 (31)
Abiraterone	105 (69)	36 (80)	21 (81)
Enzalutamide or other AR blocker	111 (73)	29 (64)	11 (42)
Taxane chemotherapy	51 (33)	16 (36)	9 (35)

[a]1 patient who received bavdegalutamide 420 mg QD had ECOG PS of 2
AR=androgen receptor; ECOG PS=Eastern Cooperative Oncology Group performance status; LBD=ligand-binding domain; NHA=novel hormonal agent; QD=once daily

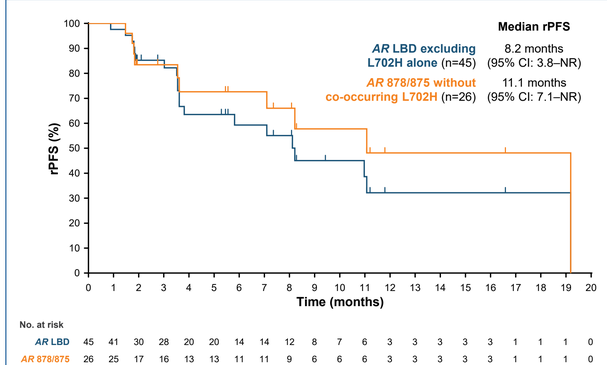
Efficacy

- Median rPFS per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) was 8.2 months (95% CI: 3.8–NR) in *AR* LBD patients (20 events in 45 patients) and 11.1 months (95% CI: 7.1–NR) in the *AR* 878/875 subgroup (10 events in 26 patients; **Figure 2**)
- PSA declines of ≥50% and ≥30%, respectively, after ≥1 month of PSA follow-up were seen in 36.4% and 50.0% of evaluable *AR* LBD patients (n=44) and in 53.8% and 65.4% of patients in the *AR* 878/875 subgroup (n=26; **Figure 3**)
- In response-evaluable patients with measurable disease at baseline, ORR per Response Evaluation Criteria in Solid Tumors v1.1/PCWG3 was 10.0% in *AR* LBD patients (n=20) and 9.1% in the *AR* 878/875 subgroup (n=11); 55.0% and 54.5%, respectively, had stable disease
- 16 (36%) *AR* LBD patients were on treatment for ≥24 weeks (7 [16%] for ≥48 weeks) with 4 ongoing; 11 (42%) *AR* 878/875 patients were on treatment for ≥24 weeks (6 [23%] for ≥48 weeks) with 4 ongoing (**Figure 4**)

Safety

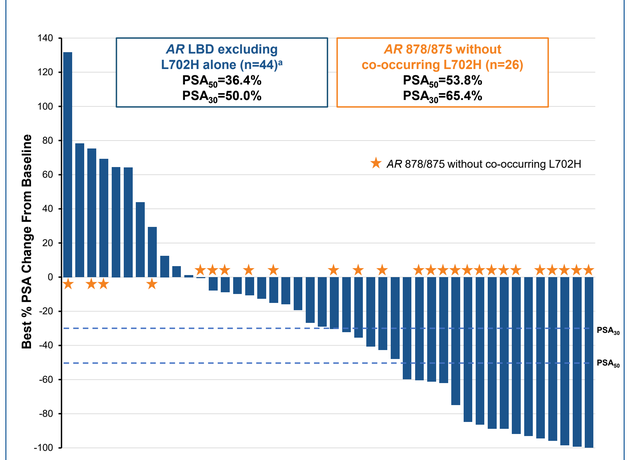
- Across the phase 1/2 study, 147 (96%) of 153 patients treated with bavdegalutamide 420 mg QD had a treatment-emergent adverse event (TEAE); 47 (31%) had a grade 3/4 TEAE
  - 17 (11%) patients had a TEAE leading to dose reduction and 19 (12%) had a TEAE leading to treatment discontinuation
- The most common TRAEs with bavdegalutamide 420 mg QD were nausea, fatigue, and vomiting; no grade ≥4 TRAEs occurred (**Table 2**)

Figure 2: rPFS in *AR* LBD patients and the *AR* 878/875 subgroup



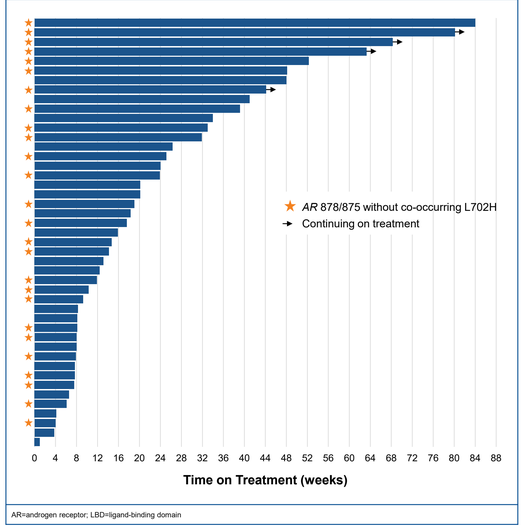
AR=androgen receptor; LBD=ligand-binding domain; NR=not reached; rPFS=radiographic progression-free survival

Figure 3: Best decline in PSA in *AR* LBD patients and the *AR* 878/875 subgroup



[a]Excludes 1 patient who did not have ≥1 PSA assessment ≥1 month after the first dose of bavdegalutamide
AR=androgen receptor; LBD=ligand-binding domain; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%

Figure 4: Duration of treatment in *AR* LBD patients and the *AR* 878/875 subgroup



AR=androgen receptor; LBD=ligand-binding domain

Table 2: TRAEs reported in ≥10% of patients treated with bavdegalutamide 420 mg QD in the phase 1/2 study (N=153)

n (%)	Total	Grade 1	Grade 2	Grade 3
Any TRAE	135 (88)	45 (29)	66 (43)	24 (16)
Nausea	85 (56)	59 (39)	24 (16)	2 (1)
Fatigue	53 (35)	36 (24)	16 (10)	1 (1)
Vomiting	50 (33)	38 (25)	11 (7)	1 (1)
Decreased appetite	39 (25)	21 (14)	18 (12)	0
Diarrhea	37 (24)	27 (18)	7 (5)	3 (2)
Alopecia	28 (18)	24 (16)	4 (3)	NA
Anemia	23 (15)	10 (7)	6 (4)	7 (5)
Decreased weight	19 (12)	10 (7)	9 (6)	0
Increased AST	18 (12)	13 (8)	4 (3)	1 (1)

AST=aspartate aminotransferase; NA=not applicable; QD=once daily; TRAE=treatment-related adverse event