PO3-05-08 San Antonio Breast Cancer Symposium (SABCS)® - December 5–9, 2023

Updated Results From VERITAC Evaluating Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor (ER) Degrader, in ER–Positive/Human Epidermal Growth Factor Receptor 2 (HER2)–Negative Advanced Breast Cancer

Sara A Hurvitz[1], Anne F Schott[2], Cynthia Ma[3], Rita Nanda[4], George Zahrah[5], Natasha Hunter[1], Antoinette R Tan[6], Melinda L Telli[7], Jesus Anampa Mesias[8], Rinath Jeselsohn[9], Pamela Munster[10], Eric Zhi[11], Elizabeth Duperret[11], Cecile Mather[11], Erika P Hamilton[12], Hyo S Han[13]

[1]Fred Hutchinson Cancer Center, Seattle, WA; [2]University of Michigan Medical School, Ann Arbor, MI; [3]Washington University School of Medicine, St. Louis, MO; [4]University of Chicago Medicine, Chicago, IL; [5]Nuvance Health, Norwalk, CT; [6]Levine Cancer Institute, Atrium Health, Charlotte, NC; [7]Stanford University School of Medicine, Stanford, CA; [8]Albert Einstein College of Medicine, Bronx, NY; [9]Dana-Farber Cancer Institute, Boston, MA; [10]University of California San Francisco, San Francisco, CA; [11]Arvinas Operations, Inc., New Haven, CT; [12]Sarah Cannon Research Institute, Nashville, TN; [13]Moffitt Cancer Center, Tampa, FL

Objective

- To further evaluate the clinical activity and safety of 200-mg once-daily (QD) vepdegestrant (ARV-471), an oral PROTAC ER degrader, in patients with ER+/HER2- advanced breast cancer after ≥1 prior endocrine regimen and ≥1 prior cyclin-dependent kinase (CDK)4/6 inhibitor

Key Findings

- In the phase 2 VERITAC study, among heavily pretreated patients (4 median prior regimens, 100% with prior CDK4/6 inhibitors, 74% with prior fulvestrant, and 74% with prior chemotherapy across all lines) with ER+/HER2- advanced breast cancer who received vepdegestrant 200 mg QD:
  - Clinical benefit rate (CBR) was 37.1% (95% CI: 21.5–55.1) in all evaluable patients (n=35) and 47.4% (95% CI: 24.4–71.1) in evaluable patients with *ESR1* mutations (n=19)
  - Median progression-free survival (PFS) was 3.5 months (95% CI: 1.8–8.2) in all patients and 5.7 months (95% CI: 1.8–8.5) in patients with *ESR1* mutations
  - After 1 treatment cycle, reduction in mutant *ESR1* circulating tumor DNA (ctDNA) levels was observed in all evaluable patients, with sustained reduction across multiple cycles
  - Treatment-emergent adverse events (TEAEs) did not lead to any dose reductions, but 2 (5.7%) patients discontinued vepdegestrant due to a TEAE; treatment-related adverse events (TRAEs) were mostly grade 1/2

Conclusions

- With 12 months of additional follow-up from the first data report of the phase 2 VERITAC study, durable clinical activity with vepdegestrant 200 mg QD was seen in heavily pretreated patients with ER+/HER2- advanced breast cancer, and was associated with sustained reduction in mutant *ESR1* ctDNA levels
- Vepdegestrant 200 mg QD continued to show a favorable safety profile
- The ongoing global, randomized, phase 3 VERITAC-2 study (NCT05654623) is evaluating vepdegestrant 200 mg QD vs intramuscular fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination CDK4/6 inhibitor therapy and endocrine therapy
  - Please see poster PO1-19-12 presented by M Campone, et al, to view the study design of VERITAC-2

References

1. Flanagan JJ, et al. Presented at SABCS; Dec 4-8, 2018; San Antonio, TX. Poster P5-04-18.
2. Hanker AB, et al. *Cancer Cell.* 2020;37(4):496-513.
3. Nathan MR, et al. *Oncol Ther.* 2017;5(1):17-29.
4. Kuter I, et al. *Breast Cancer Res Treat.* 2012;133(1):237-246.
5. Robertson JFR, et al. *Breast Cancer Res.* 2013;15(2):R18.
6. Hurvitz SA, et al. Presented at SABCS; Dec 6-10, 2022; San Antonio, TX. Oral presentation GS3-03.

Acknowledgments

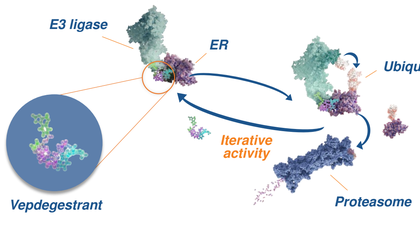
We thank the patients who participated in this study and their caregivers, as well as the investigators, researchers, and coordinators who contributed to this study. This study is sponsored by Arvinas Estrogen Receptor, Inc. Medical writing and editorial support were provided by Sarah Marshall, PhD, Nathan Yardley, 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 view a **plain language summary** of the poster.

Background

- Vepdegestrant (ARV-471), an oral PROTAC ER degrader, directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation (**Figure 1**)[1]
- In contrast, selective ER degraders (SERDs) indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- Limitations of the SERD fulvestrant include its intramuscular route of administration[3] and only 40%–50% ER protein degradation at the 500-mg dose[4,5]
- Vepdegestrant treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]
- The phase 2 expansion (VERITAC) of a phase 1/2 study (NCT04072952) tested 2 vepdegestrant doses (200 mg QD and 500 mg QD) in heavily pretreated patients with ER+/HER2- advanced breast cancer[6]
  - Vepdegestrant 200 mg QD was selected as the phase 3 monotherapy dose based on comparable efficacy and favorable tolerability vs 500 mg QD as well as robust ER degradation (data cutoff: June 6, 2022)[6]
  - In evaluable patients treated at the 200-mg QD dose across the phase 1/2 study, median (range) ER degradation was 69% (28%–95%)[6]
- Here, we present updated data for the vepdegestrant 200-mg QD cohort after 12 additional months of follow-up

Figure 1: Mechanism of action of vepdegestrant[a]



Please scan this QR code to view a **video of the mechanisms of action of vepdegestrant and SERDs**

[a]General PROTAC protein degrader, cereblon E3 ligase, and ER target protein are shown
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera; SERD=selective ER degrader

Methods

- **Key eligibility criteria for VERITAC:**
  - Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer
  - Measurable or nonmeasurable disease per Response Evaluation Criteria in Solid Tumors version 1.1
  - ≥1 prior endocrine regimen (≥1 regimen for ≥6 months in the locally advanced or metastatic setting)
  - ≥1 prior CDK4/6 inhibitor
  - ≤1 prior chemotherapy regimen in the locally advanced or metastatic setting
- **Endpoints:**
  - Primary endpoint was CBR (rate of confirmed complete response, partial response [PR], or stable disease ≥24 weeks) analyzed in patients enrolled for ≥24 weeks prior to the data cutoff
  - Secondary endpoints were objective response rate (ORR), duration of response, PFS, overall survival, safety, and pharmacokinetic parameters
  - Exploratory endpoints included *ESR1* mutation status and ctDNA levels
- The data cutoff date for this analysis was June 6, 2023

Results

Baseline Characteristics

- 35 patients received vepdegestrant 200 mg QD (**Table 1**)

Table 1: Baseline characteristics

Characteristic	Total (N=35)	Characteristic	Total (N=35)
Sex, n (%)		Baseline mutation status, n (%)	
Female	34 (97.1)	*ESR1*	
Median age (range), y	63 (42–79)	Mutant	19 (54.3)
ECOG PS, n (%)		Wild type	16 (45.7)
0	21 (60.0)	Prior regimens, median (range)	
1	14 (40.0)	Any setting	4 (1–9)
Visceral disease, n (%)	25 (71.4)	Metastatic setting	3 (0–7)
Sites of metastasis, n (%)		Type of prior therapy, n (%)	
Bone	26 (74.3)	CDK4/6 inhibitor	35 (100)
Liver	21 (60.0)	Aromatase inhibitor	31 (88.6)
Lung	11 (31.4)	Fulvestrant	26 (74.3)
Other	2 (5.7)	Chemotherapy	
		Any setting	26 (74.3)
		Metastatic setting	16 (45.7)

CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene

Efficacy

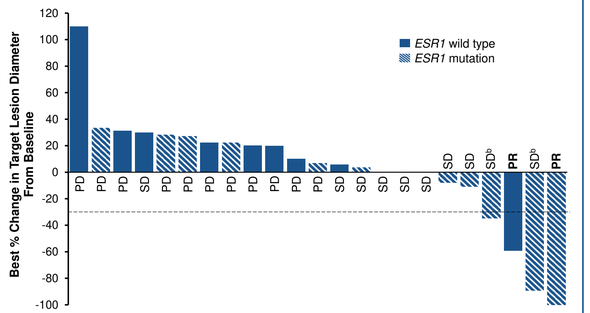
- CBR was 37.1% in the overall population and 47.4% in patients with mutant *ESR1* (**Table 2**)
- ORR in all evaluable patients (n=33) was 8.3% (95% CI: 1.0–27.0); 2 patients had a confirmed PR (**Figure 2**)
- Median PFS was 3.5 months (95% CI: 1.8–8.2) in all evaluable patients and 5.7 months (95% CI: 1.8–8.5) in patients with *ESR1* mutations
- 14 (40%) patients had received vepdegestrant for ≥24 weeks and 4 (11%) for ≥48 weeks; 1 patient was ongoing at the time of data cutoff (**Figure 3**)

Table 2: Clinical benefit rate[a]

	All patients 200 mg QD (N=35)	Mutant *ESR1* 200 mg QD (n=19)
CBR, % (95% CI)	37.1 (21.5–55.1)	47.4 (24.4–71.1)

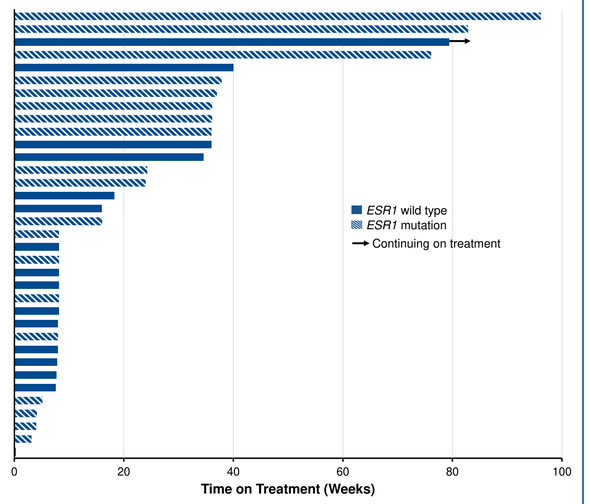
[a]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks
CBR=clinical benefit rate; *ESR1*=estrogen receptor 1 gene; QD=once daily

Figure 2: Tumor response[a]



[a]Includes patients with measurable disease (n=23); 1 patient with measurable disease at baseline and PD as best objective response was excluded due to lack of complete set of target lesion measurements on study
[b]Patient had an unconfirmed partial response
ESR1=estrogen receptor 1 gene; PD=progressive disease; PR=confirmed partial response; SD=stable disease

Figure 3: Treatment duration



ESR1=estrogen receptor 1 gene

Safety

- TEAEs of any grade were reported in 91.4% of patients; 34.3% of patients experienced a grade 3/4 TEAE
  - 1 patient had a grade 5 serious TEAE of acute respiratory failure (unrelated to vepdegestrant treatment) in the setting of disease progression
- 2 (5.7%) patients discontinued vepdegestrant due to a TEAE
  - 1 patient discontinued due to grade 3 QT prolongation; QT prolongation was present at baseline, and the patient received a concomitant QT-prolonging drug during vepdegestrant treatment and had hypokalemia
  - 1 patient discontinued due to grade 3 anemia
- No patient required a dose reduction from vepdegestrant 200 mg QD due to a TEAE
- TRAEs were mostly grade 1/2 (**Table 3**)

Table 3: Treatment-related adverse events reported in ≥10% of patients

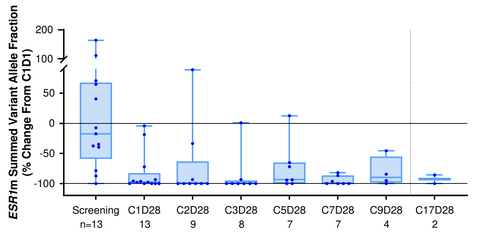
	200 mg QD (N=35)		
n (%)	Grade 1	Grade 2	Grade 3/4[a]
Any TRAE	12 (34.3)	15 (42.9)	2 (5.7)
Fatigue	8 (22.9)	7 (20.0)	0
Hot flush	7 (20.0)	0	0
Arthralgia	4 (11.4)	0	0
Nausea	3 (8.6)	3 (8.6)	0
ALP increased	3 (8.6)	1 (2.9)	0
AST increased	3 (8.6)	1 (2.9)	0

[a]Grade 3/4 TRAEs were grade 3 QT prolonged (n=1; same TEAE that led to discontinuation), grade 3 thrombocytopenia, and grade 4 hyperbilirubinemia (n=1)
ALP=alkaline phosphatase; AST=aspartate aminotransferase; QD=once daily; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event

ctDNA

- Among evaluable patients, substantial on-treatment decreases in mutant *ESR1* ctDNA levels were observed after 1 cycle of treatment with vepdegestrant 200 mg QD, which were sustained for multiple cycles (**Figure 4**)

Figure 4: Change from C1D1[a] in *ESR1* mutation-positive ctDNA over time[b]



Error bars are the 95% CI, the bottom and top of the box are the 25th and 75th percentiles, and the line is the median
[a]C1D1 samples were obtained prior to dosing. [b]16/35 patients had *ESR1* mutations at C1D1; 14 patients had an *ESR1* mutation at C1D1 and had a posttreatment sample available for analysis; only 2 patients with *ESR1* mutations remained on study through C17 and had sustained decreases in *ESR1* mutation-positive ctDNA levels
C=cycle; ctDNA=circulating tumor DNA; D=day; *ESR1*m=estrogen receptor 1 gene mutation-positive