PO1-19-12 San Antonio Breast Cancer Symposium (SABCS)® - December 5–9, 2023

# VERITAC-2: A Phase 3 Study of Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor (ER) Degrader, vs Fulvestrant in ER–Positive/Human Epidermal Growth Factor Receptor 2 (HER2)–Negative Advanced Breast Cancer

Mario Campone[1], Cynthia Ma[2], Michelino De Laurentiis[3], Hiroji Iwata[4], Sara A Hurvitz[5], Seth A Wander[6], Michael Danso[7], Dongrui R Lu[8], Julia Perkins Smith[9], Yuan Liu[8], Lana Tran[8], Sibyl Anderson[10], Erika P Hamilton[11]

[1]Institut de Cancérologie de l'Ouest Angers-Nantes, Angers, France; [2]Washington University School of Medicine, St Louis, MO; [3]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale," Naples, Italy; [4]Aichi Cancer Center Hospital, Aichi, Japan; [5]Fred Hutchinson Cancer Center, Seattle, WA; [6]Massachusetts General Hospital Harvard Medical School, Boston, MA; [7]Virginia Oncology Associates, Norfolk, VA; [8]Pfizer Inc., La Jolla, CA; [9]Pfizer Inc., New York, NY; [10]Arvinas Operations, Inc., New Haven, CT; [11]Sarah Cannon Research Institute, Nashville, TN

## Objective

- The phase 3 VERITAC-2 study (NCT05654623) will compare the efficacy and safety of vepdegestrant (ARV-471) with the selective ER degrader (SERD) fulvestrant in patients with ER+/HER2- advanced breast cancer after prior combination cyclin-dependent kinase (CDK)4/6 inhibitor therapy and endocrine therapy

## 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 are participating in this study and their caregivers, as well as the investigators, researchers, and coordinators who are contributing to this study. This study is sponsored in the United States by Arvinas Estrogen Receptor, Inc., and ex-United States by Pfizer 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. Content was initially presented at the European Society for Medical Oncology (ESMO) Breast Cancer Annual Congress, Berlin, Germany, May 11–13, 2023.



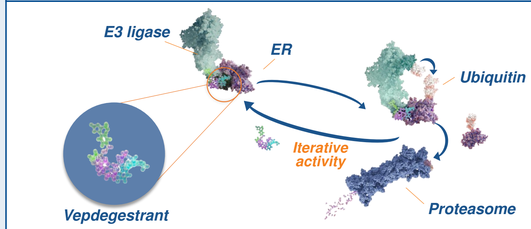
Please scan this QR code to view a **plain language summary** of the poster.



## Background and Rationale

- Vepdegestrant (ARV-471), an oral PROTAC ER degrader, directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER leading to its subsequent proteasomal degradation (**Figure 1**)[1]
- In contrast, SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- The SERD fulvestrant must be administered intramuscularly,[3] and at its optimal dose, ER protein degradation is limited to only 40%–50%[4,5]

**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**

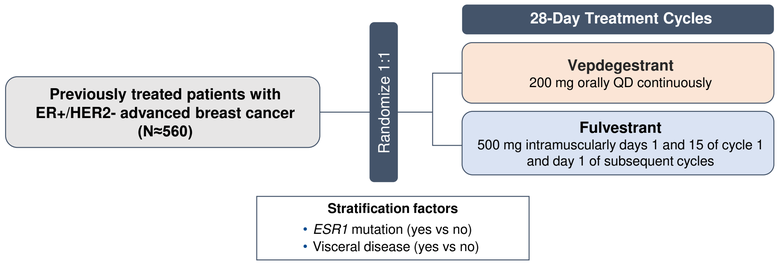
[a]General PROTAC protein degrader, cereblon E3 ligase, and ER target protein are shown
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera; SERD=selective ER degrader

- In breast cancer xenograft models, vepdegestrant treatment provided substantially greater ER degradation and tumor growth inhibition compared with fulvestrant[1]
- In VERITAC, the phase 2 expansion cohort of a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy showed clinical activity and was well tolerated in heavily pretreated patients with ER+/HER2- advanced breast cancer (data cutoff date: June 6, 2022)[6]
  - Clinical benefit rate (CBR; defined as the rate of confirmed complete response, partial response, or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff) was 37.1% (95% CI: 21.5–55.1) and 38.9% (95% CI: 23.1–56.5) in the 200-mg (n=35) and 500-mg (n=36) oral, once-daily (QD) cohorts, respectively
  - Clinical activity was also observed in the mutant *ESR1* subgroup: CBR was 47.4% (95% CI: 24.4–71.1) and 54.5% (95% CI: 32.2–75.6) in the 200-mg (n=19) and 500-mg (n=22) QD cohorts, respectively
  - Most adverse events (AEs) were grade 1/2, with few AEs leading to dose reduction (500 mg, n=3) or discontinuation (200 mg, n=1; 500 mg, n=2)
  - In a subset of patients who received 200 mg QD across the phase 1/2 study (n=9), up to 95% ER degradation was observed, with a median (range) of 69% (28%–95%)
  - Please see poster PO3-05-08 presented by SA Hurvitz, et al, to view the most recent findings of the VERITAC study
- The phase 3 monotherapy dose (200 mg QD) for the current study was chosen based on comparable efficacy and favorable tolerability relative to 500 mg QD, and robust ER degradation

## Study Design

- In this open-label, global, multicenter, phase 3 study, patients are randomized 1:1 to receive vepdegestrant or fulvestrant in 28-day cycles (**Figure 2**)
- Eligible patients have ER+/HER2- advanced breast cancer and prior treatment with a CDK4/6 inhibitor therapy in combination with endocrine therapy (**Table 1**)
- Outcome measures are shown in **Table 2**

**Figure 2: VERITAC-2 trial schema**




ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; QD=once daily

**Table 1: VERITAC-2 key eligibility criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Women or men aged ≥18 years<br>• Confirmed ER+/HER2- locoregional recurrent or metastatic breast cancer<br>• Prior therapies for locoregional recurrent or metastatic disease must fulfill all the following criteria:<br>– 1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy (only 1 line of CDK4/6 inhibitor in any setting)<br>– ≤1 endocrine therapy in addition to CDK4/6 inhibitor with endocrine therapy<br>– Most recent endocrine treatment given for ≥6 months prior to disease progression<br>– Radiological progression during or after the last line of therapy<br>• ECOG performance status of 0 or 1<br>• Measurable disease evaluable per RECIST v1.1 or nonmeasurable bone-only disease | • Active brain metastases<br>• Advanced, symptomatic visceral spread at risk of life-threatening complications in the short term<br>• Prior treatment with:<br>– Vepdegestrant<br>– Fulvestrant<br>– Elacestrant<br>– mTOR, PI3K, or AKT pathway inhibitors<br>– PARP inhibitors<br>– Other investigational agents, including novel endocrine therapy (SERDs, SERCAs, CERANs)<br>– Chemotherapy for advanced/metastatic disease |

AKT=protein kinase B; CDK=cyclin-dependent kinase; CERAN=complete estrogen receptor antagonist; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; mTOR=mammalian target of rapamycin; PARP=poly ADP ribose polymerase; PI3K=phosphoinositide-3 kinase; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SERCA=selective estrogen receptor covalent antagonist; SERD=selective estrogen receptor degrader

**Table 2: VERITAC-2 outcome measures**

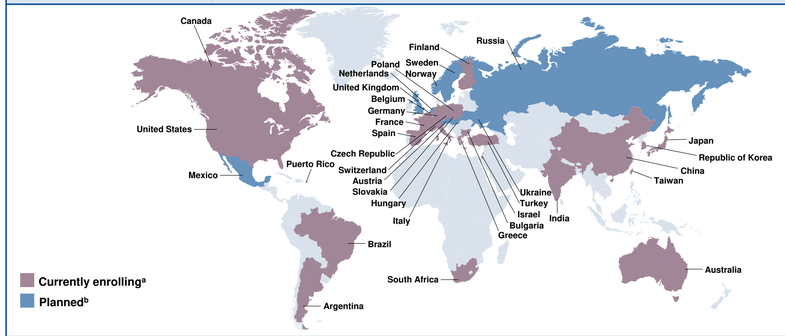
| Primary objective | Endpoints |
|---|---|
| • Evaluate the clinical activity of vepdegestrant compared with fulvestrant | • PFS by blinded independent central review in:<br>– ITT population<br>– *ESR1* mutation population |
| **Secondary objectives** | **Endpoints** |
| • Further evaluate the clinical activity of vepdegestrant compared with fulvestrant | • OS<br>• ORR,[a] DOR, and CBR[b] |
| • Evaluate the safety and tolerability of vepdegestrant compared with fulvestrant | • Incidence of AEs, SAEs, and ECG and laboratory abnormalities |
| • Evaluate the effect of vepdegestrant on QTc | • QT interval |
| • Evaluate the plasma concentration of vepdegestrant | • Plasma concentration of vepdegestrant |
| • Evaluate the effects of vepdegestrant compared with fulvestrant on QoL | • EQ-5D-5L<br>• EORTC QLQ-C30<br>• EORTC QLQ-BR23<br>• BPI-SF |
| • Evaluate changes in tumor biomarkers with vepdegestrant compared with fulvestrant | • Circulating tumor DNA changes |

[a]Proportion of patients with confirmed complete response or partial response by blinded independent central review
[b]Proportion of patients with confirmed complete response, partial response, or stable disease ≥24 weeks
AE=adverse event; BPI-SF=Brief Pain Inventory-Short Form; CBR=clinical benefit rate; DOR=duration of response; ECG=electrocardiogram; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module; EORTC QLQ-C30=EORTC Quality of Life Questionnaire Core; EQ-5D-5L=EuroQol 5 Dimensions-5 Levels; *ESR1*=estrogen receptor 1 gene; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QoL=quality of life; SAE=serious AE

## Study Status

- Enrollment is ongoing
- Countries with currently open and planned study sites are shown in **Figure 3**

**Figure 3: VERITAC-2 study sites**




[a]Countries with active study sites as of October 31, 2023
[b]As the study continues to enroll, additional sites will open, including within the EU and beyond