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CLINICAL TRIAL PROTOCOL



# VERITAC-2: a Phase III study of vepdegestrant, a PROTAC ER degrader, versus fulvestrant in ER+/HER2- advanced breast cancer

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## ABSTRACT

Vepdegestrant (ARV-471) is an oral PROTAC ER degrader that binds an E3 ubiquitin ligase and ER to directly trigger ubiquitination of ER and its subsequent proteasomal degradation. In a first-in-human Phase I/II study, vepdegestrant monotherapy was well tolerated with clinical activity in pretreated patients with ER+/HER2- advanced breast cancer. The global, randomized Phase III VERITAC-2 study compares efficacy and safety of vepdegestrant versus fulvestrant in adults with ER+/HER2- advanced breast cancer after treatment with a CDK4/6 inhibitor plus endocrine therapy. Progression-free survival by blinded independent central review (primary end point) will be assessed in the intention-to-treat population and *ESR1* mutation-positive subpopulation. Secondary end points include overall survival, tumor response, safety, pharmacokinetics, patient-reported outcomes, and circulating tumor DNA biomarkers.

**Clinical trial registration:** NCT05654623 (ClinicalTrials.gov)

## PLAIN LANGUAGE SUMMARY

**VERITAC-2 is a clinical trial comparing vepdegestrant, a new drug that degrades estrogen receptors, to an existing treatment called fulvestrant in patients with ER+/HER2- advanced breast cancer:** Estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer grows in response to estrogen, a hormone in the body, and has low levels or no HER2 protein. People living with ER+/HER2- advanced breast cancer that has grown, spread to another part of the body, or cannot be removed by surgery are often treated with cyclin-dependent kinase (CDK) 4/6 inhibitors and endocrine therapies, but their cancer may get worse on these treatments and new treatments are needed. Fulvestrant, an endocrine therapy that attaches to estrogen receptors, lowers estrogen's effect on tumors and can slow or stop cancer growth. Vepdegestrant, a new medicine being tested for ER+ breast cancer, is a PROteolysis TArgeting Chimera (PROTAC) protein degrader that attaches to estrogen receptors and causes them to be tagged for removal by the cell's natural protein disposal system. By removing estrogen receptors, vepdegestrant may cause tumors to stop growing or shrink.

This paper describes the Phase III VERITAC-2 clinical study comparing vepdegestrant versus fulvestrant in people living with ER+/HER2- advanced breast cancer previously treated with a CDK4/6 inhibitor and endocrine therapy.

Patients will be randomly assigned to receive vepdegestrant (a pill taken once daily by mouth) or fulvestrant (a shot given into the muscle). The purpose of the study is to find out how long people live without their cancer getting worse with vepdegestrant or fulvestrant. VERITAC-2 will also look at how long people live during the study, side effects people may experience, and the overall well-being of people throughout the study.

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ARV-471; breast cancer; ER+; fulvestrant; HER2-; PROTAC; targeted protein degradation; vepdegestrant

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## 1. Background

### 1.1. Background & rationale

ER+/HER2- breast cancer is the most common subtype of all breast cancers [1]. ER-mediated signaling is a key driver of ER+ breast cancer pathogenesis. When estrogen binds its receptor, the ER dimerizes and translocates to the nucleus where it forms an active complex to induce expression of genes that promote tumor cell growth and proliferation [1,2]. ER+ breast cancer therapies have focused on disrupting the ER-mediated signaling pathway, including reducing estrogen production, modulating estrogen signaling through the ER, and/or antagonizing/degrading the ER itself [1].

The current preferred first-line therapy for ER+/HER2- advanced/metastatic breast cancer is endocrine therapy (ET) with an aromatase inhibitor in combination with a CDK4/6 inhibitor [1,3]. Unfortunately, despite initial efficacy in most patients, the acquisition of mutations in the estrogen receptor gene *ESR1* and altered gene expression often lead to the development of ET resistance [1], and outcomes remain poor [4–6]. Approximately 40% of patients who received aromatase inhibitors as treatment for metastatic breast cancer have *ESR1* mutations, primarily in the ligand-binding domain of ER [7]; the most common *ESR1* mutations are D538G and Y537S [7]. There is no clear standard of care in the second-line setting, with treatment based upon a number of factors, including agents previously used and consideration of targeted agents based on tumor genomics [8–11]. However, sequential ET is generally recommended in patients with disease progression and presumed endocrine sensitivity [8–11]. Thus, targeting ER remains a cornerstone of disease management, and the development of novel ETs that can overcome resistance is an area of growing interest.

Fulvestrant is a first-in-class selective ER degrader (SERD) initially approved by the U.S. Food and Drug Administration (FDA) in 2002 for patients with ER+/HER2- advanced/metastatic breast cancer [12]. SERDs primarily immobilize ER in the cytoplasm limiting ER-directed gene transcription, and they have also been shown to indirectly lead to ER degradation secondary to conformational changes and/or immobilization of ER [13–15]. Fulvestrant is a standard therapy for patients with ER+/HER2- advanced/metastatic breast cancer; however, it must be administered intramuscularly [16], and at its labeled dose, ER protein degradation is 40–50% [17,18]. Recently, several targeted therapies for patients with advanced/metastatic breast cancer have been approved by the FDA, such as elacestrant for patients with *ESR1*-mutated ER+/HER2- disease [19], capivasertib in combination with fulvestrant for patients with one or more *PIK3CA/AKT1/PTEN* alterations [20], and alpelisib, a PI3K inhibitor approved in combination with fulvestrant for patients with *PIK3CA* mutations who progressed on ET [21]. Alpelisib also demonstrated efficacy among patients who progressed on CDK4/6 inhibitors [22], but those with *ESR1* mutations show resistance to PI3K inhibitors [23]. Overall, there remains an unmet need for therapies with distinct mechanisms of action that can effectively target ER and overcome mechanisms of resistance, particularly in the second-line setting.

### 1.2. Vepdegestrant (ARV-471)

PROteolysis TArgeting Chimera (PROTAC) protein degraders are small molecules that harness the cell's natural protein disposal machinery, the ubiquitin-proteasome system, to induce degradation of a target protein of interest [24,25]. Vepdegestrant is an oral PROTAC ER degrader that induces degradation of wild-type ER and clinically relevant mutants [26]. Vepdegestrant has a half-maximal degradation concentration ($DC_{50}$) of approximately 1 nM in ER+ breast cancer cell lines and induces a similar level of degradation of wild-type and mutant ER [26].

Unlike SERDs, which indirectly lead to ER degradation secondary to conformational changes and/or immobilization, vepdegestrant creates a trimer complex with the E3 ubiquitin ligase and ER to directly induce ubiquitination of ER and its subsequent proteasomal degradation (Figure 1) [25]. Vepdegestrant has iterative activity and can be recycled to bind additional ER target proteins, leading to their degradation.

In preclinical studies of ER+ breast cancer models, vepdegestrant induced ≥90% degradation of wild-type ER and multiple forms of mutant ER in cell lines and inhibited ER-dependent breast cancer cell line proliferation [26]. *In vivo*, vepdegestrant at doses ranging from 3 to 30 mg/kg daily resulted in 85 to 120% tumor growth inhibition (TGI) in an MCF7 orthotopic xenograft model. In this same model, the 30-mg/kg vepdegestrant dose achieved complete TGI (105%) compared with 46% TGI for fulvestrant (200 mg/kg biweekly for 2 weeks and weekly for 2 weeks). In the hormone-independent ER Y537S patient-derived xenograft breast cancer model, vepdegestrant at doses of 10 and 30 mg/kg daily demonstrated tumor regression (99 and 107% TGI, respectively) and reduced ER levels by 79 and 88%, respectively [26]. Fulvestrant demonstrated 62% TGI and reduced ER levels by 63% in the same model in contrast [26].

### 1.3. First-in-human Phase I/II clinical study

Based on the promising preclinical data, a first-in-human Phase I/II study (NCT04072952) of vepdegestrant

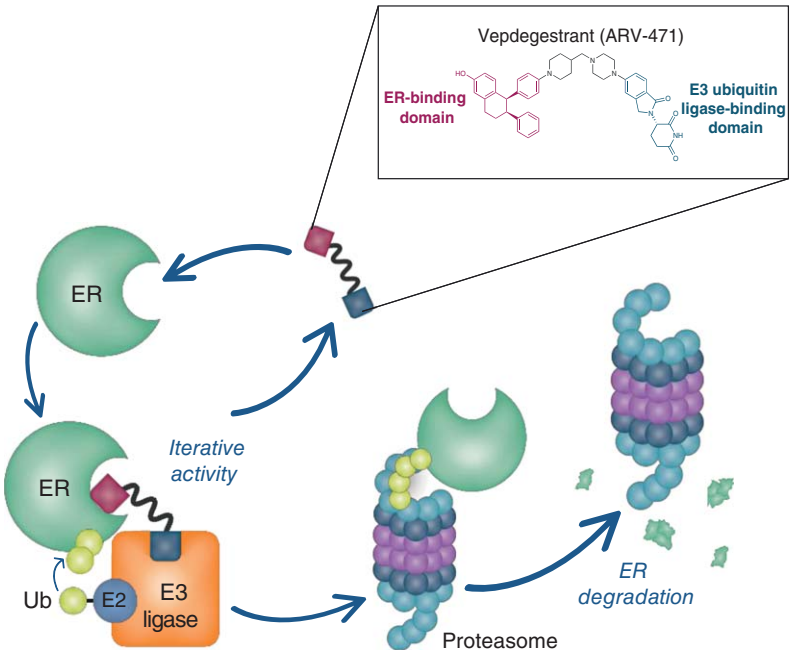


**Figure 1.** Mechanism of action of vepdegestrant.[a]
[a]General PROTAC protein degrader, cereblon E3 ligase, and ER target protein are shown in the schematic. The chemical structure of vepdegestrant is shown in the inset.
PROTAC: PROteolysis TArgeting Chimera.

monotherapy and in combination with the CDK4/6 inhibitor palbociclib was initiated in patients with ER+/HER2- breast cancer; initial results have been presented at several scientific conferences [27–31]. In the Phase I dose escalation portion of this study, vepdegestrant demonstrated antitumor activity and was well tolerated at total daily doses ranging from 30 to 700 mg, with no dose-limiting toxicities [27]. Based on the results of the dose escalation study, vepdegestrant 200 mg once daily (QD) and 500 mg QD were further evaluated in VERITAC, the Phase II expansion cohort of the Phase I/II study. Preliminary results show encouraging clinical activity and a well-tolerated safety profile [28–30]. Vepdegestrant 200 mg QD was selected as the Phase III monotherapy dose based on comparable efficacy and favorable tolerability in heavily pretreated patients with ER+/HER2- advanced breast cancer versus 500 mg QD as well as robust ER degradation in the VERITAC study [28].

## 2. VERITAC-2

### 2.1. Study design

VERITAC-2 (NCT05654623) is an open-label, randomized, global, multicenter, Phase III study comparing the efficacy and safety of vepdegestrant with fulvestrant in adult patients with ER+/HER2- advanced breast cancer after prior combination CDK4/6 inhibitor therapy and ET (Figure 2) [32].

### 2.2. Eligibility criteria

Eligible patients have a confirmed diagnosis of ER+/HER2- locoregional recurrent or metastatic breast cancer not amenable to surgical resection or radiation. Patients must have had one line of prior treatment with a CDK4/6 inhibitor therapy in combination with ET and no more than one additional line of ET wherein the most recent ET was given for ≥6 months before disease progression, and radiological disease progression was during or after the last line of therapy (Table 1).

### 2.3. Objectives & outcome measures

The primary objective is to evaluate the efficacy of vepdegestrant compared with fulvestrant in both the intention-to-treat population and *ESR1* mutation-positive subpopulation, which will be assessed by progression-free survival (PFS) based on blinded independent central review (BICR). Secondary objectives are to further evaluate the efficacy of vepdegestrant compared with fulvestrant, including overall survival (OS) and objective response rate (ORR) by BICR assessment, as well as to evaluate safety and tolerability, the effect of vepdegestrant on QTc, pharmacokinetics (PK) of vepdegestrant and its epimer, ARV-473, patient quality of life, and changes in tumor biomarkers. The primary and secondary end points of the VERITAC-2 study are summarized in Table 2.

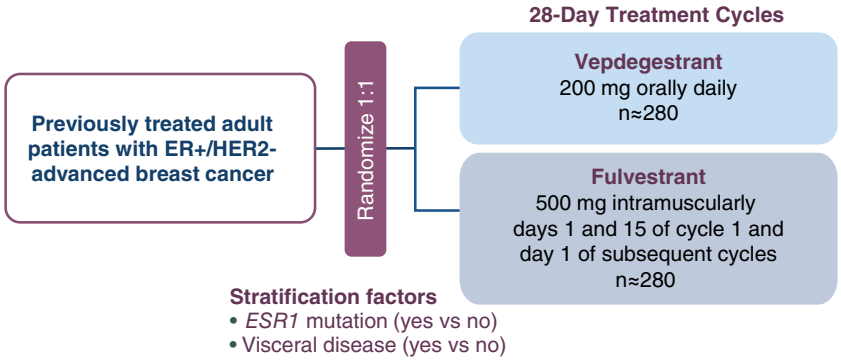


Figure 2. VERITAC-2 study design.

Table 1. VERITAC-2 key eligibility criteria.

| Key inclusion criteria | Key exclusion criteria |
|---|---|
| – Women or men aged ≥18 years<br>○ Women must be post-menopausal or if pre- or peri-menopausal, must agree to initiate or continue use of an LHRH agonist<br>○ Men must agree to initiate or continue use of an LHRH agonist<br>○ WOCBP and men must agree to use contraception<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 ET (only 1 line of CDK4/6 inhibitor in any setting)<br>○ ≤1 ET (in addition to CDK4/6 inhibitor with ET)<br>○ Most recent ET given for ≥6 months prior to disease progression[a]<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>– Inflammatory breast cancer<br>– Advanced, symptomatic visceral spread at risk of life-threatening complications in the short-term<br>– Impaired cardiovascular function or clinically significant cardiovascular disease<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 ET (SERDs, SERCAs, CERANs)<br>○ Chemotherapy for advanced/metastatic disease |

[a]The most recent ET may be the ET component of the CDK4/6 inhibitor line of therapy.
CERAN: Complete estrogen receptor antagonist; ECOG: Eastern Cooperative Oncology Group; ET: Endocrine therapy; RECIST: Response Evaluation Criteria in Solid Tumors; SERCA: Selective estrogen receptor covalent agonist; SERD: Selective estrogen receptor degrader; WOCBP: Women of childbearing potential.

### 2.4. Sample size/recruitment

In total, VERITAC-2 will enroll approximately 560 patients who will be randomized 1:1 to receive vepdegestrant or fulvestrant. Patients will be stratified by the presence or absence of mutation(s) in the *ESR1* gene (determined by blood sample), and the presence or absence of visceral disease, defined as lung, liver, brain, pleural, or peritoneal involvement.

### 2.5. Assignment to interventions

This is an unblinded, open-label study. Specific study intervention for each patient will be assigned using interactive response technology (IRT). Stratified randomization will be centrally allocated using the IRT system. Vepdegestrant will be administered as a 200-mg oral dose QD continuously in each 28-day cycle. Vepdegestrant must be taken with food at approximately the same time every morning. Fulvestrant will be administered as a 500-mg dose intramuscularly on days 1 and 15 of cycle 1, then on day 1 of each cycle starting from day 1 of cycle 2. Patients will continue to receive their assigned treatment until objective disease progression as determined by the investigator, global deterioration of health status requiring discontinuation, unacceptable toxicity, patient refusal of further treatment, pregnancy, significant protocol deviation, or death.

The study began March 3, 2023, and the estimated study completion date is May 15, 2028. Enrollment is ongoing globally; countries with currently enrolling and planned sites as of February 16, 2024, are shown in Figure 3.

### 2.6. Data collection & management

All data pertaining to an individual patient will be logged in a case report form. For all patients, baseline evaluations to assess efficacy will include computerized tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis; patients will also receive a full-body bone scan. Scans will be repeated every 8 weeks for the first 48 weeks from the randomization date and then every 12 weeks thereafter (CT/MRI) and

**Table 2.** VERITAC-2 study end points.

| End points | |
|---|---|
| **Primary** | **PFS in the ITT population and *ESR1* mutation-positive subpopulation**<br>– Time interval from the date of randomization to the date of first documented tumor progression determined by BICR assessment as per RECIST v1.1 or death due to any cause, whichever comes first |
| **Secondary** | **OS**<br>– Time from date of randomization until the date of death due to any cause<br>**ORR**<br>– Proportion of patients with confirmed complete CR or PR by BICR<br>**DOR**<br>– Time from first documented evidence of CR or PR until progressive disease by BICR<br>**CBR**<br>– Proportion of patients with confirmed CR, PR, or SD ≥24 weeks by BICR<br>**Incidence of AEs, SAEs, and ECG and laboratory abnormalities**<br>**QT interval (QTc)**<br>**Plasma concentrations of vepdegestrant and its epimer, ARV-473**<br>**Patient disease-, health-, and treatment-related QOL, assessed by:**<br>– EQ-5D-5L[a]<br>– EORTC QLQ-C30[b]<br>– EORTC QLQ-BR23[c]<br>– BPI-SF[d]<br>**Circulating tumor DNA changes** |

[a]The EQ-5D-5L assesses patients' current state of self-care, usual activities, mobility, pain/discomfort, and anxiety/depression. The visual analog scale score records the respondent's self-rated health status [33].

[b]The EORTC QLQ-C30 contains 1 global QOL score and 5 multi-item functional subscales, including physical, role, emotional, cognitive, and social. Higher scores on QOL/functional domains are indicative of higher levels of functioning. Oncology-related symptoms are assessed using 9 symptom scales, where higher scores are reflective of a greater presence of symptoms [34].

[c]The female and male versions of the EORTC QLQ-BR23 contain 4 functional scales to assess body image, sexual functioning, sexual enjoyment, and future perspective and 4 symptom scales to assess systemic therapy side effects, breast symptoms, arm symptoms, and being upset by hair loss. Higher scores represent greater severity [35].

[d]The BPI-SF assesses pain levels and their effect on daily life [36].

AE: Adverse event; BICR: Blinded independent central review; BPI-SF: Brief Pain Inventory-short form; CBR: Clinical benefit rate; CR: Complete response; DOR: Duration of response; ECG: Electrocardiogram; EORTC QLQ-BR23: European Organization 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: 5-level EQ-5D; ITT: Intention-to-treat; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; QTc: Corrected QT interval; QOL: Quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: Serious AE; SD: Stable disease.

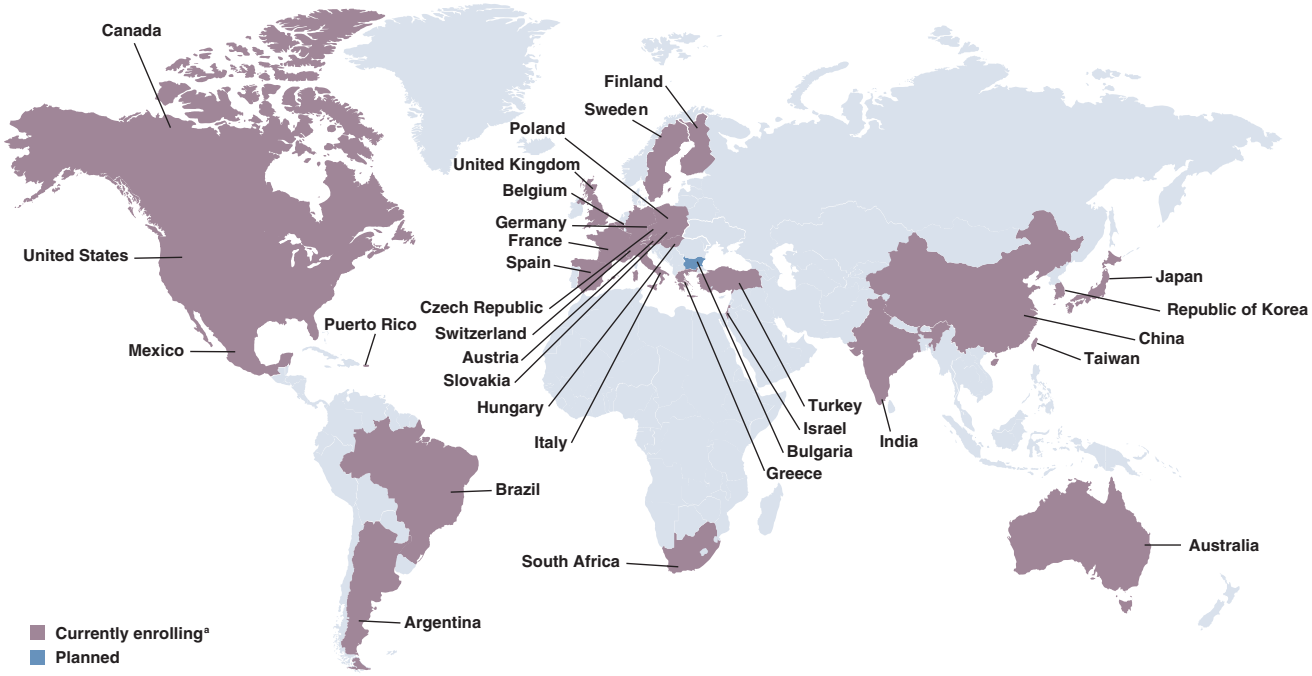


**Figure 3.** Countries with VERITAC-2 study sites.
[a]Countries with active study sites as of June 27, 2024.

24 weeks (bone scan) until radiographically and/or clinically documented disease progression as defined by Response Evaluation Criteria in Solid Tumors v1.1, study treatment discontinuation, discontinuation from overall participation by patient preference, loss to follow-up, or death. All imaging studies will be objectively verified by BICR, and all tumor-based efficacy analyses will be performed using BICR tumor assessments as the primary data source. All adverse events (AEs) and serious AEs (SAEs) will be recorded for each patient through at least 28 calendar days after the last administration of study intervention. AEs/SAEs will be coded using the Medical Dictionary for Regulatory Activities classification system. After treatment discontinuation, all patients will be followed for survival every 3 months until the date of death from any cause. Patient-reported outcome questionnaires will be administered at screening, on day 1 of cycles 1–6 and then on day 1 of subsequent even-numbered cycles, at end of treatment or withdrawal, and at the 28-day posttreatment follow-up.

### 2.7. Planned statistical analyses

All efficacy analyses will be performed using the full analysis set, which includes all enrolled patients who were randomized. All safety analyses will use the safety analysis set, which includes all randomized patients who receive at least one dose of study intervention. Patients will be analyzed according to the treatment they were randomized to receive.

Statistical hypothesis testing of the primary end point (PFS by BICR) and key secondary end point (OS) will be performed in two populations: 1) all randomized patients and 2) patients with *ESR1* mutation. PFS and OS associated with each treatment will be estimated using the Kaplan-Meier method. The median PFS and OS (calculated in months) and associated 95% CIs will be presented by treatment arm. A stratified log-rank test will be used to compare PFS and OS between the two treatment arms.

All safety analyses will be summarized descriptively; summaries of AEs and other safety parameters will be provided as needed/appropriate. The number and percentage of patients who experience any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades.

## 3. Conclusion

Vepdegestrant, a novel, oral PROTAC ER degrader, is a bifunctional small molecule that induces robust ER degradation by harnessing the ubiquitin-proteasome system [26]. In the first-in-human Phase I/II study, vepdegestrant monotherapy was well tolerated and showed evidence of clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer [27–30].

The global, Phase III VERITAC-2 study is the first head-to-head study comparing the efficacy and safety of vepdegestrant with the intramuscular SERD fulvestrant in patients with ER+/HER2- advanced breast cancer after combination CDK4/6 inhibitor therapy and ET.

In addition, vepdegestrant is being investigated as a monotherapy and in combination approaches across multiple treatment settings for ER+ breast cancer, including a Phase III study comparing vepdegestrant in combination with palbociclib versus letrozole in combination with palbociclib (VERITAC-3; NCT05909397), a Phase II noncomparative study evaluating vepdegestrant or anastrozole as neoadjuvant monotherapy (TACTIVE-N; NCT05549505), a Phase Ib study evaluating vepdegestrant in combination with everolimus (TACTIVE-E; NCT05501769), and a Phase Ib/II study evaluating vepdegestrant in combination with the CDK4-selective inhibitor PF-07220060 (TACTIVE-K; NCT06206837). Vepdegestrant is also under evaluation in an umbrella study (TACTIVE-U) in combination with other anticancer treatments (ribociclib, NCT05573555; samuraciclib, NCT06125522; abemaciclib, NCT05548127) in patients with previously treated ER+ advanced/metastatic breast cancer.

Article highlights

**VERITAC-2 study rationale**

- ER-mediated signaling is a key driver of breast cancer pathogenesis in ER+/HER2- breast cancer, which accounts for the majority of all breast cancers.
- Despite the initial efficacy of first-line treatments that use endocrine therapies (ETs), the acquisition of mutations in *ESR1* often leads to the development of ET resistance, leading to disease progression and poor outcomes; there is no clear standard of care in the second-line setting.
- Vepdegestrant is a small-molecule PROteolysis TArgeting Chimera (PROTAC) ER degrader that has a unique mechanism of action that harnesses the ubiquitin-proteasome system to induce direct ubiquitination and subsequent degradation of ER, unlike selective ER degraders, which lead to conformational changes in ER that may indirectly result in ER degradation.
- In preclinical studies, vepdegestrant demonstrated potent ER degradation and robust tumor growth inhibition and regression.
- In a first-in-human Phase I/II dose escalation and cohort expansion clinical study, vepdegestrant was well tolerated and demonstrated antitumor activity; the 200-mg once-daily dose of vepdegestrant was chosen as the recommended Phase III monotherapy dose.

**VERITAC-2 study design**

- VERITAC-2 is an open-label, randomized, global, multicenter, Phase III study comparing the efficacy and safety of vepdegestrant with fulvestrant in adults with ER+/HER2- advanced breast cancer.
- Eligible patients have a confirmed diagnosis of ER+/HER2- locoregional recurrent or metastatic breast cancer not amenable to surgical resection or radiation.
- Patients must also have had one line of prior treatment with CDK4/6 inhibitor therapy in combination with ET and no more than

one additional line of ET wherein the most recent ET was given for ≥6 months before disease progression.
- The primary end point is progression-free survival in both the intention-to-treat population and *ESR1* mutation-positive subpopulation, and key secondary end points include overall survival, objective response rate, duration of response, clinical benefit rate, and safety and tolerability end points.
- This study plans to enroll 560 patients; enrollment is ongoing at the time of publication.

## Acknowledgments

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## Author contributions

All authors contributed to the conception and drafting of the manuscript, participated in critical revisions that contributed to the intellectual content of the manuscript, and provided final approval of the draft to be published.

## Financial disclosure

This study is sponsored by Pfizer, Inc., in collaboration with Arvinas Estrogen Receptor, Inc. Protocol number: C4891001 (A Phase 3, Randomized, Open-Label, Multicenter Trial Of ARV-471 [PF-07850327] vs. Fulvestrant in Participants With Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer Whose Disease Progressed After Prior Endocrine Based Treatment For Advanced Disease [VERITAC-2]).

## Competing interests disclosure

EP Hamilton has served in a consulting/advisory role for Arcus, AstraZeneca, Daiichi Sankyo, Ellipses Pharma, Genentech/Roche, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo Oncology, Mersana, Novartis, Olema Pharmaceuticals, Orum Therapeutics, Pfizer, Inc., Relay Therapeutics, SeaGen, Stemline Therapeutics, Theratechnologies, Tubulis, and Verascity Science; received institutional research support from AbbVie, Accutar Biotechnology, Acerta Pharma, ADC Therapeutics, Akesobio Australia, Amgen, Aravive, Arqule, Artios, Arvinas, Inc., AstraZeneca, Atlas, BeiGene, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, Compugen, Context Therapeutics, Cullinan-Florentine, Curis, CytomX, Daiichi Sankyo, Dana Farber Cancer Hospital, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Ellipses, Elucida Oncology, EMD Serono, FujiFilm, G1 Therapeutics, Genentech/Roche, H3 Biomedicine, Harpoon, Hutchinson MediPharma, Immunogen, Immunomedics, Incyte, Infinity Pharmaceuticals, InventisBio, Jacobio, K-Group Beta, Karyopharm, Kind Pharmaceuticals, Leap Therapeutics, Lilly, Loxo Oncology, Lycera, MabSpace Biosciences, Macrogenics, MedImmune, Mersana, Merus, Millenium, Molecular Templates, Novartis, Nucana, Olema, Oncomed, Onconova Therapeutics, Oncothyreon, ORIC Pharmaceuticals, Orinove, Orum Therapeutics, Pfizer, Inc., PharmaMar, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Plexxicon, Prelude Therapeutics, Profound Bio, Radius Health, Regeneron, Relay Therapeutics, Repertoire Immune Medicine, Rgenix, SeaGen, Sermonix Pharmaceuticals, Shattuck Labs, StemCentRx, Sutro, Syndax, Syros, Taiho, TapImmune, Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem, Zenith Epigenetics, and Zymeworks. C Ma has served in a consulting role for AstraZeneca, Daiichi Sankyo, Genzyme, Gilead Sciences, Lilly, Novartis, Olaris, Pfizer, Inc., Regor, Stemline, Tempus, and TerSera; and has received research funding from Pfizer, Inc. and Puma Biotechnology. M De Laurentiis has received personal fees from AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Eli Lilly, Exact Science, Gilead, Ipsen, Menarini-Stemline, MSD, Novartis, Pfizer, Inc., Pierre Fabre, Roche, Seagen, Takeda, and Veracyte, outside the submitted work. He has stock/ownership interests in Arvinas, Inc. H Iwata has served as invited speaker/advisory board member for AstraZeneca, Chugai, Daiichi Sankyo, Lilly, Pfizer, Sanofi, and Taiho; served as a steering committee member for Amgen, AstraZeneca, Chugai, Daiichi Sankyo, Kyowa Hakko Kirin, MSD, Novartis, Pfizer, Inc., and Sanofi; and served as a local principal investigator for Bayer, Boehringer, Lilly, and Nihon Kayaku. SA Hurvitz has served as an invited speaker for Axis Medical, Cancer Expert Now, Clinical Care Options, ICHE, MJH Associates, Peer Education, PER, PrecisCA, Primo, Projects in Knowledge, Prova Education, Research to Practice, Ultimate Medical Academy, Vaniam, and WebMD; has ownership interest in Ideal Implant and stocks and shares in ROM Tech; she receives royalties from Elsevier, McGraw, Sage, Springer, Wiley, and Wolters Kluwer; is a local principal investigator for Ambrx, Arvinas, Inc., AstraZeneca, Dantari, Dignitana, Eli Lilly, G1 Therapeutics, Genentech/Roche, Gilead, Greenwich Life Sciences, GSK, Immunomedics, Loxo Oncology, Macrogenics, Novartis, OBI Pharma, Orinove, Orum, Pfizer, Inc., Phoenix Molecular Designs, Pieris, Puma Biotechnology, Radius, Sanofi, Seattle Genetics, and Zymeworks; serves as coordinating principal investigator for Celcuity and Daiichi Sankyo; and has received research funding from Ambrx and Samumed. 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## Ethical conduct of research

All protocols/amendments have been approved by an Institutional Review Board at each study site. The study will be conducted in accordance with the ethical principles derived from international guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, and are consistent with International Council of Harmonization/Good Clinical Practice and applicable regulatory requirements. Written consent will be obtained from each study patient. An external data monitoring committee, independent of the study team, will be responsible for ongoing monitoring of the safety of the participants in the trial.

## Previous presentation

Presented at: European Society for Medical Oncology Breast Cancer Annual Conference. Berlin, Germany, 11 May-13 May 2023. Presentation 257TiP [32].

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