

# VERITAC-2: a global, randomized phase 3 study of ARV-471, a PROteolysis Targeting Chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

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## 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

## Background and Rationale

- Vepdegestrant (ARV-471) is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants<sup>1</sup>
- Vepdegestrant directly binds the cereblon E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation, whereas SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER<sup>2</sup>
- The SERD fulvestrant must be administered intramuscularly,<sup>3</sup> and at its optimal dose, ER protein degradation is limited to only 40%–50%<sup>4,5</sup>
- In breast cancer xenograft models, vepdegestrant treatment provided substantially greater ER degradation and tumor growth inhibition compared with fulvestrant<sup>1</sup>
- 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<sup>6</sup>
  - Clinical benefit rate (CBR)<sup>a</sup> 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%)
- 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

<sup>a</sup>Rate of confirmed complete response, partial response, or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff

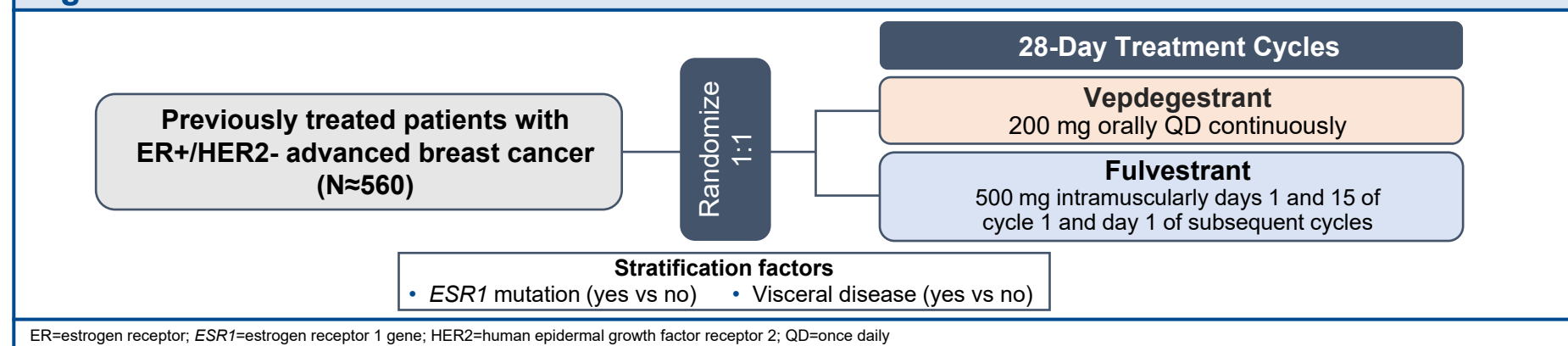
## Study Design

- In this open-label, global, multicenter, phase 3 study (**Figure 1**), patients are randomized 1:1 to receive vepdegestrant or fulvestrant in 28-day cycles
- 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**

## Study Status

- Enrollment is ongoing
- Countries with currently open and planned study sites are shown in **Figure 2**

**Figure 1: VERITAC-2 trial schema**



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

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>Women or men aged ≥18 years</li> <li>Confirmed ER+/HER2- locoregional recurrent or metastatic breast cancer</li> <li>Prior therapies for locoregional recurrent or metastatic disease must fulfill all the following criteria: <ul style="list-style-type: none"> <li>1 line of CDK4/6 inhibitor therapy in combination with endocrine therapy</li> <li>Up to 1 additional endocrine therapy</li> <li>Most recent endocrine treatment given for ≥6 months prior to disease progression</li> <li>Radiological progression during or after the last line of therapy</li> </ul> </li> <li>ECOG performance status of 0 or 1</li> <li>Measurable disease evaluable per RECIST v1.1 or nonmeasurable bone-only disease</li> </ul>	<ul style="list-style-type: none"> <li>Active brain metastases</li> <li>Advanced, symptomatic visceral spread at risk of life-threatening complications in the short term</li> <li>Prior treatment with: <ul style="list-style-type: none"> <li>Vepdegestrant</li> <li>Fulvestrant</li> <li>mTOR, PI3K, or AKT pathway inhibitors</li> <li>PARP inhibitors</li> <li>Other investigational novel endocrine therapy</li> <li>Prior CDK4/6 inhibitor treatment in the neoadjuvant/adjunct setting</li> <li>Chemotherapy for advanced/metastatic disease</li> </ul> </li> </ul>

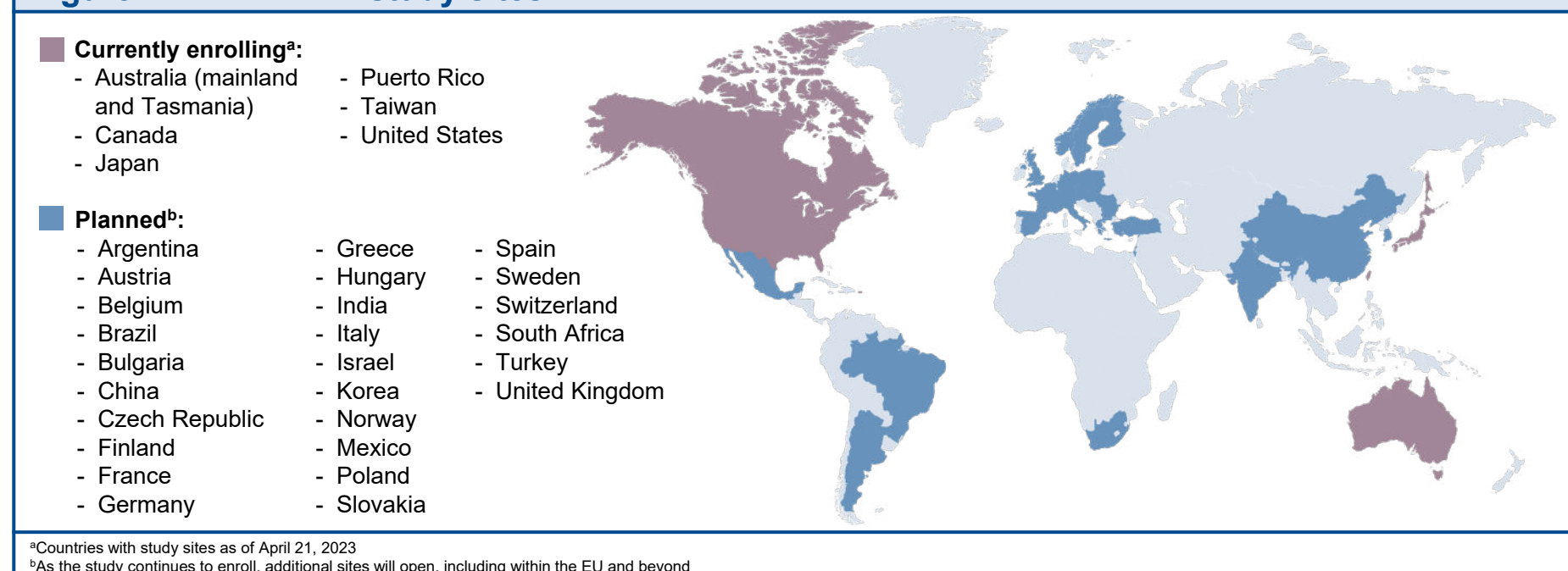
AKT=protein kinase B; CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; mTOR=mammalian target of rapamycin; PARP=poly ADP-ribose polymerase; PI3K=phosphoinositide-3 kinase; RECIST v1.1=Response Evaluation Criteria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

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

Primary objective	Endpoints
<ul style="list-style-type: none"> <li>Evaluate the clinical activity of vepdegestrant compared with fulvestrant</li> </ul>	<ul style="list-style-type: none"> <li>PFS by blinded independent central review in: <ul style="list-style-type: none"> <li>ITT population</li> <li><i>ESR1</i> mutation population</li> </ul> </li> </ul>
Secondary objectives	Endpoints
<ul style="list-style-type: none"> <li>Further evaluate the clinical activity of vepdegestrant compared with fulvestrant</li> <li>Evaluate the safety and tolerability of vepdegestrant compared with fulvestrant</li> <li>Evaluate the effect of vepdegestrant on QTc</li> <li>Evaluate the PK of vepdegestrant</li> <li>Evaluate the effects of vepdegestrant compared with fulvestrant on QoL</li> <li>Evaluate changes in tumor biomarkers with vepdegestrant compared with fulvestrant</li> </ul>	<ul style="list-style-type: none"> <li>OS</li> <li>ORR,<sup>a</sup> DOR, and CBR<sup>b</sup></li> <li>Incidence of AEs, SAEs, and ECG and laboratory abnormalities</li> <li>QT interval</li> <li>Plasma concentration of vepdegestrant</li> <li>EQ-5D-5L</li> <li>EORTC QLQ-C30</li> <li>BPI-SF</li> <li>EORTC QLQ-BR23</li> <li>Circulating tumor DNA changes</li> </ul>

<sup>a</sup>Proportion of patients with confirmed complete response or partial response by blinded independent central review  
<sup>b</sup>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; PK=pharmacokinetics; QoL=quality of life; SAE=serious AE

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



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