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Global Phase 3 Studies Evaluating Vepdegestrant in Estrogen Receptor (ER)+/Human Epidermal Growth Factor Receptor 2 (HER2)- Advanced Breast Cancer: VERITAC-2 and VERITAC-3

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Objectives

- The global, randomized, phase 3 VERITAC-2 (NCT05654623) and VERITAC-3 (NCT05909397) studies with sites in the Asia-Pacific region are evaluating vepdegestrant (ARV-471) in patients with estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer
  - The VERITAC-2 study is comparing the efficacy and safety of vepdegestrant with the selective ER degrader (SERD) fulvestrant in patients with prior combination treatment of cyclin-dependent kinase (CDK)4/6 inhibitor therapy and endocrine therapy
  - The VERITAC-3 study is evaluating the combination of vepdegestrant plus palbociclib as first-line treatment in the advanced setting; a study lead-in is assessing 2 doses of palbociclib (100 mg or 75 mg) with vepdegestrant

Study Status

- Enrollment for the VERITAC-2 study and the VERITAC-3 study lead-in is ongoing
- These global studies have currently open and planned study sites in the following Asia-Pacific countries:
  - VERITAC-2: Australia, China, India, Japan, Republic of Korea, and Taiwan
  - VERITAC-3 study lead-in: Australia, China, and Japan

References

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Disclosure

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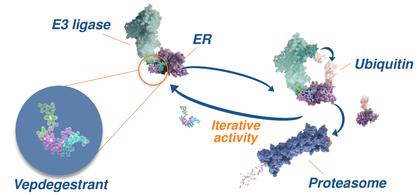
Background

- Vepdegestrant (ARV-471) is a selective, orally administered PROteolysis TArgeting Chimera (PROTAC) ER degrader that directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation (**Figure 1**)[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[2]
- Ongoing phase 1 studies (NCT05463952; NCT05732428) are evaluating vepdegestrant safety and pharmacokinetics (PK) in patients with ER+/HER2- advanced breast cancer in Japan and China, respectively
  - See poster 58P (H Iwata et al) to view the most recent findings of the phase 1 study conducted in Japan
- Vepdegestrant directly induces ER degradation, whereas SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[3]
- In breast cancer xenograft models, vepdegestrant treatment provided substantially greater ER degradation and tumor growth inhibition compared with fulvestrant[1]
- The SERD fulvestrant is administered intramuscularly,[4] and at a dose of 500 mg, ER protein degradation is limited to 40%–50%[5,6]
- In a subset of patients with ER+/HER2- advanced breast cancer who received vepdegestrant 200 mg once daily (n=9) across the phase 1/2 study, up to 95% ER degradation was observed, with a median (range) of 69% (28%–95%)[2]

Vepdegestrant in Combination With Palbociclib

- The CDK4/6 inhibitor palbociclib in combination with an aromatase inhibitor is a standard treatment option for patients with ER+/HER2- breast cancer; palbociclib plus fulvestrant is a standard treatment option after disease progression on endocrine therapy[7]
- In a xenograft model, vepdegestrant plus palbociclib had substantially greater antitumor activity than fulvestrant plus palbociclib[1]
- A phase 1b cohort of the phase 1/2 study is evaluating the safety and clinical activity of vepdegestrant plus palbociclib in patients with ER+/HER2- breast cancer after prior endocrine-based therapy; prior CDK4/6 inhibitor therapy was permitted
  - Preliminary results showed encouraging activity for the combination based on clinical benefit rate (defined as the rate of confirmed complete response, partial response, or stable disease ≥24 weeks analyzed in patients enrolled ≥24 weeks prior to the data cutoff)[8]
  - An increase in palbociclib exposure was observed relative to historical palbociclib PK data[7] and was accompanied by a higher incidence of grade 3/4 neutropenia compared with prior palbociclib and endocrine therapy combination studies,[9,10] which was managed by monitoring and standard palbociclib dose modifications[8]
- Based on these initial findings, further research is warranted regarding the combination of vepdegestrant with palbociclib in patients with advanced breast cancer

Figure 1: Mechanism of action of vepdegestrant[a]



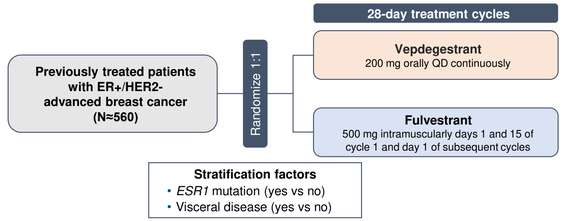
Please scan this QR code to view a **video of the mechanism of action of vepdegestrant**

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

VERITAC-2 Study Design

- In the open-label VERITAC-2 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[a]

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

[a]This is not the complete list of inclusion/exclusion criteria
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

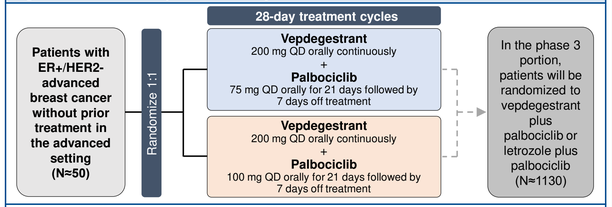
Primary objective	Endpoints
• Evaluate the clinical activity of vepdegestrant compared with fulvestrant	• PFS by blinded independent central review in: – ITT population – *ESR1* mutation population
Secondary objectives	**Endpoints**
• Further evaluate the clinical activity of vepdegestrant compared with fulvestrant	• OS • 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 • EORTC QLQ-C30 • EORTC QLQ-BR23 • 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 investigator assessment per RECIST v1.1
[b]Proportion of patients with confirmed complete response, partial response, or stable disease (or non-CR/non-PD) ≥24 weeks
AE=adverse event; BPI-SF=Brief Pain Inventory-Short Form; CBR=clinical benefit rate; CR=complete response; 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; PD=progressive disease; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; QoL=quality of life; SAE=serious AE

VERITAC-3 Study Design

- VERITAC-3 is an open-label study in patients with ER+/HER2- advanced breast cancer without prior systemic anticancer treatment for advanced disease (**Table 3**) composed of 2 portions
- In the study lead-in portion, approximately 50 patients are randomized to vepdegestrant plus palbociclib at 2 different doses to select the recommended phase 3 dose of palbociclib in combination with vepdegestrant (**Figure 3**)
  - Reduced starting doses of palbociclib (100 mg and 75 mg) were selected to mitigate increased rates of grade 4 neutropenia while maintaining adequate palbociclib exposure when combined with vepdegestrant
- In the planned phase 3 portion of the trial, approximately 1130 patients will be randomized 1:1 to receive vepdegestrant plus palbociclib or letrozole plus palbociclib
  - The primary efficacy endpoint of the phase 3 portion is progression-free survival based on blinded independent central review

Figure 3: VERITAC-3 open-label study lead-in schema



ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; QD=once daily

Table 3: VERITAC-3 key eligibility criteria[a]

Inclusion criteria	Exclusion criteria
• Women or men aged ≥18 years • Confirmed ER+/HER2- locoregional recurrent or metastatic breast cancer • No prior treatment for locoregional recurrent or metastatic disease • ECOG performance status of 0–2 • Measurable disease evaluable per RECIST v1.1 or nonmeasurable bone-only disease	• Disease recurrence while on or within 12 months of completion of adjuvant endocrine therapy • Prior treatment with: – CDK4/6 inhibitors – Fulvestrant – Elacestrant – Other investigational agents, including novel endocrine therapy (SERDs, SERCAs, CERANs)

[a]This is not the complete list of inclusion/exclusion criteria
CDK=cyclin-dependent kinase; CERAN=complete estrogen receptor antagonist; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SERCA=selective estrogen receptor covalent antagonist; SERD=selective estrogen receptor degrader

Table 4: VERITAC-3 lead-in outcome measures

Primary objective	Endpoints
• Identify the RP3D of palbociclib in combination with vepdegestrant	• Within the first 4 cycles of treatment: – Incidence of grade 4 neutropenia – Incidence of dose reductions or discontinuations
Secondary objectives	**Endpoints**
• Evaluate the safety and tolerability of vepdegestrant plus palbociclib	• Incidence of AEs, SAEs, and ECG and laboratory abnormalities
• Evaluate the clinical activity of vepdegestrant plus palbociclib	• ORR,[a] DOR, and CBR[b]
• Evaluate the plasma concentration of vepdegestrant and palbociclib	• Plasma concentration of vepdegestrant and palbociclib

[a]Proportion of patients with confirmed complete response or partial response by investigator assessment per RECIST v1.1
[b]Proportion of patients with confirmed complete response, partial response, or stable disease (or non-CR/non-PD) ≥24 weeks
AE=adverse event; CBR=clinical benefit rate; CR=complete response; DOR=duration of response; ECG=electrocardiogram; ORR=objective response rate; PD=progressive disease; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; RP3D=recommended phase 3 dose; SAE=serious AE