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VERITAC-3: A Randomized Phase 3 Study, With a Lead-in, of First-Line Vepdegestrant + Palbociclib vs Letrozole + Palbociclib in Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer

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Objective

- The global, phase 3 VERITAC-3 study (NCT05909397) is evaluating the combination of vepdegestrant plus palbociclib as first-line treatment in patients with estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer; a study lead-in is assessing 2 doses of palbociclib (100 mg or 75 mg) with vepdegestrant

References

1. Flanagan JJ, et al. Presented at SABCS; Dec 4-8, 2018; San Antonio, TX. Poster P5-04-18.
2. Hurvitz SA, et al. Presented at SABCS; Dec 6-10, 2022; San Antonio, TX. Oral presentation GS3-03.
3. Ibrance. Prescribing information. Pfizer Inc; 2023.
4. Arvinas data on file.
5. Finn RS, et al. *N Engl J Med.* 2016;375(20):1925-1936.
6. Turner NC, et al. *N Engl J Med.* 2018;379(20):1926-1936.

Acknowledgments

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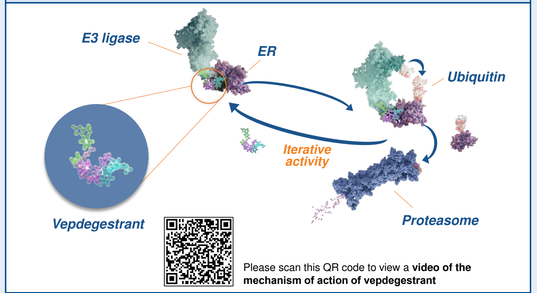
Background and Rationale

- Vepdegestrant (ARV-471), an oral PROteolysis TArgeting Chimera (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 the phase 2 portion (VERITAC) of a first-in-human, phase 1/2 study (NCT04072952), vepdegestrant 200 mg once daily was well tolerated and had clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer, and was selected as the recommended phase 3 dose (RP3D) for vepdegestrant monotherapy[2]
  - Please see poster PO3-05-08 presented by SA Hurvitz, et al to view the most recent findings of the VERITAC study
- The cyclin-dependent kinase (CDK)4/6 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[3]

Figure 1: Mechanism of action of vepdegestrant[a]

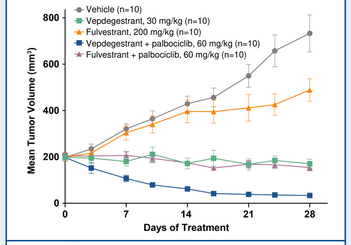


Please scan this QR code to view a **video of the mechanism of action of vepdegestrant**

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

- In a xenograft model, vepdegestrant plus palbociclib had substantially greater antitumor activity than fulvestrant plus palbociclib (**Figure 2**)[1]
- A phase 1b cohort of NCT04072952 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)[4]
  - An increase in palbociclib exposure was observed relative to historical palbociclib pharmacokinetic data[3] and was accompanied by a higher incidence of grade 3/4 neutropenia compared with prior palbociclib and endocrine therapy combination studies,[5,6] which was well managed by monitoring and standard palbociclib dose modifications[4]
    - Please see poster PS15-03 presented by EP Hamilton, et al, to view the most recent findings of the phase 1b cohort
    - Please see poster PO5-14-11 presented by B Jermain, et al, to view findings of the pharmacokinetic/pharmacodynamic model to guide dose optimization of palbociclib in combination with vepdegestrant
- Based on these initial findings, further research is warranted regarding the combination of vepdegestrant with palbociclib in patients with advanced breast cancer

Figure 2: Tumor growth inhibition[a] with vepdegestrant plus palbociclib[1]



[a]Orthotopic MCF7/estradiol xenograft model

Study Design

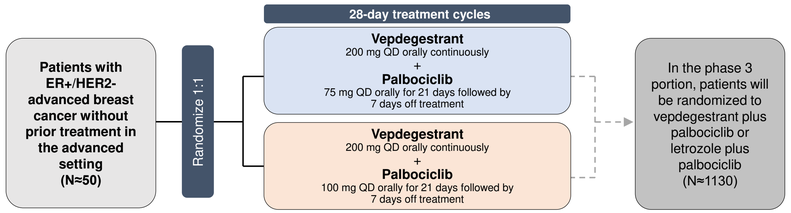
- VERITAC-3 is an open-label study in patients with ER+/HER2- advanced breast cancer without prior systemic anticancer treatment for advanced disease (**Table 1**) composed of 2 portions:
  - In the study lead-in portion, approximately 50 patients are randomized to vepdegestrant plus palbociclib at 2 different doses to select the RP3D of palbociclib in combination with vepdegestrant (**Figure 3**)
    - Outcome measures of the study lead-in are shown in **Table 2**
  - In the planned phase 3 portion of the trial, approximately 1130 patients will be randomized 1:1 to 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

Table 1: VERITAC-3 key eligibility criteria

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)

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

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



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

Table 2: VERITAC-3 lead-in outcome measures

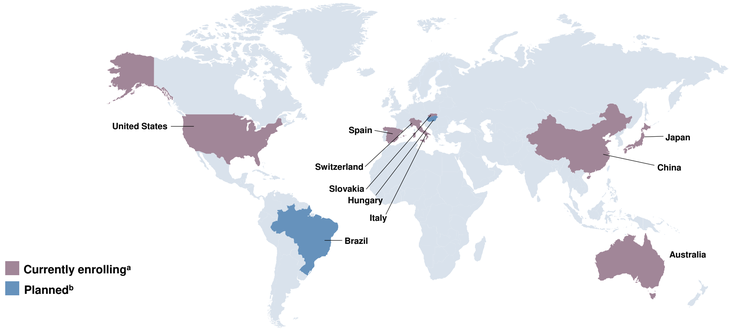
Primary objective	Endpoints
• Identify the RP3D of palbociclib in combination with vepdegestrant	• Within the first 4 cycles of treatment: – Incidence of grade 4 neutropenia – Incidence of dose reductions or discontinuations
Secondary objectives	**Endpoints**
• Evaluate the safety and tolerability of 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 concentrations of vepdegestrant and palbociclib	• Plasma concentrations 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

Study Status

- Enrollment of the study lead-in is ongoing
- Countries with currently open and planned study sites of the study lead-in are shown in **Figure 4**

Figure 4: VERITAC-3 lead-in study sites



[a]Countries with study sites as of November 2, 2023
[b]As the study continues to enroll, additional sites will open, including within the EU and beyond