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TACTIVE-E: phase 1b study of ARV-471, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, in combination with everolimus in ER+/human epidermal growth factor receptor 2 (HER2)-advanced breast cancer

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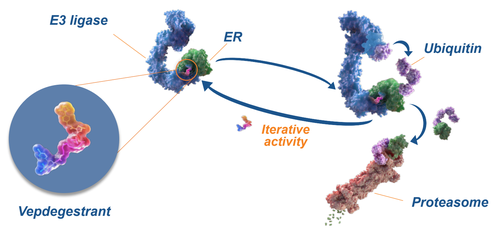
Objective

- The phase 1b TACTIVE-E study (NCT05501769) will evaluate the safety and tolerability, efficacy, and pharmacokinetics of vepdegestrant (ARV-471) in combination with everolimus in patients with previously treated ER+/HER2- advanced or metastatic breast cancer

Background and Rationale

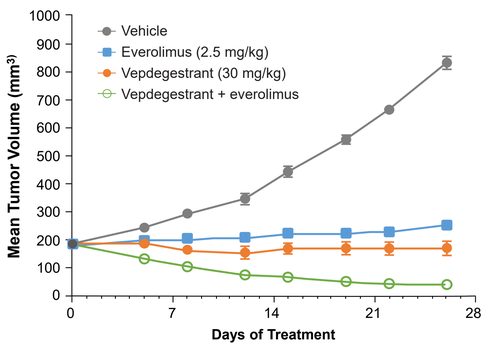
- Vepdegestrant (ARV-471) is an oral PROTAC protein degrader that binds to and degrades both wild-type and mutant ER[1]
- Vepdegestrant directly binds the cereblon E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation (**Figure 1**)
  - In contrast, selective ER degraders (SERDs) indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- In preclinical studies, vepdegestrant demonstrated potent ER degradation, tumor growth inhibition, and tumor regression, including in drug-resistant and mutant ER+ breast cancer models[1]
- In VERITAC, the phase 2 expansion cohort portion of a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy was well tolerated and showed clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer[3]
  - Clinical benefit rate[a] was 37.1% (95% CI: 21.5–55.1) at 200 mg once daily (QD) (n=35)
  - Most adverse events were grade 1/2
- Everolimus, an inhibitor of mammalian target of rapamycin, is approved with exemestane for patients with ER+/HER2- breast cancer after progression on aromatase inhibitors and has shown clinical activity after cyclin-dependent kinase (CDK)4/6 inhibitor treatment[2,4,5]
- In patients with prior CDK4/6 inhibitor therapy, the combination of vepdegestrant and everolimus may offer additional advantages as vepdegestrant can degrade mutant forms of ER,[1] and *ESR1* mutations are enriched in this setting[6]
- Preclinical studies in ER-expressing breast cancer cell lines showed evidence of cell growth inhibition with vepdegestrant plus everolimus, including in cells expressing Y537S or D538G *ESR1* mutations[7]
- Vepdegestrant plus everolimus demonstrated greater tumor growth inhibition in a xenograft breast cancer model than vepdegestrant or everolimus alone (**Figure 2**)[7]

Figure 1: Mechanism of action of vepdegestrant[a]



[a]General PROTAC protein degrader is shown
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera

Figure 2: Vepdegestrant plus everolimus has antitumor activity in an MCF7 breast cancer xenograft model[7]

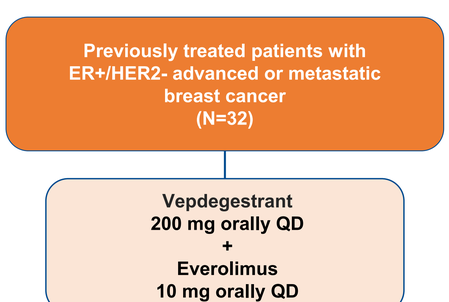


[a]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff

Study Design

- In this open-label, multicenter, phase 1b study, patients receive vepdegestrant 200 mg QD and everolimus 10 mg QD orally in 28-day cycles (**Figure 3**)
- Eligible patients have advanced or metastatic breast cancer and previous treatment with a CDK4/6 inhibitor and endocrine therapy (**Table 1**)
- Outcome measures are shown in **Table 2**
- Enrollment is ongoing

Figure 3: TACTIVE-E trial schema



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

Table 1: TACTIVE-E key eligibility criteria

Inclusion criteria	Exclusion criteria
• Women or men aged ≥18 years • Women must be postmenopausal or on ovarian suppression • Histologically or cytologically confirmed ER+/HER2- advanced (metastatic, recurrent, or unresectable) breast cancer • 1–3 lines of prior anticancer therapy in the advanced/metastatic setting – Progression on or intolerance to a CDK4/6 inhibitor – ≥1 line of endocrine therapy – ≤1 line of chemotherapy • ECOG performance status of 0 or 1	• Untreated brain metastases or brain metastases requiring steroids above physiologic replacement doses • Prior treatment with vepdegestrant or treatment targeting mTOR • Prior treatment with fulvestrant ≤28 days, or with tamoxifen, an aromatase inhibitor, or a CDK4/6 inhibitor ≤14 days of first dose of study drug

CDK=cyclin-dependent kinase; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; mTOR=mammalian target of rapamycin

Table 2: TACTIVE-E outcome measures

Primary objective	Endpoints
• Evaluate the tolerability and safety of vepdegestrant in combination with everolimus	• DLTs to determine the RP2D for vepdegestrant in combination with everolimus • Type, frequency, and severity of AEs and laboratory abnormalities
Secondary objectives	**Endpoints**
• Evaluate the antitumor activity of vepdegestrant in combination with everolimus	• ORR,[a] CBR,[b] and DOR
• Evaluate the PK parameters of vepdegestrant and everolimus	• C_{max} • T_{max} • AUC over 24 hours at steady state

[a]Proportion of patients with confirmed complete response or partial response
[b]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks
AE=adverse event; AUC=area under the concentration-time curve; CBR=clinical benefit rate; C_{max}=maximum plasma concentration; DLT=dose-limiting toxicity; DOR=duration of response; ORR=objective response rate; PK=pharmacokinetic; RP2D=recommended phase 2 dose; T_{max}=time to C_{max}

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Disclosure

Dr Philipovskiy has nothing to disclose.

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Please scan this QR code with your smartphone app to view a **video of the mechanisms of action of vepdegestrant and SERDs**

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