TPS1121

TACTIVE-U: phase 1b/2 umbrella study of ARV-471, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, combined with other anticancer treatments in ER+ advanced or metastatic breast cancer

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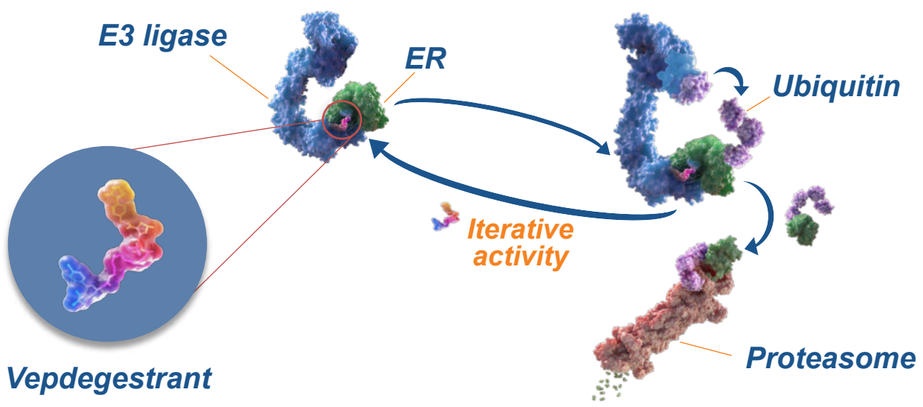
Background and Rationale

- Vepdegestrant (ARV-471) is a selective, orally administered PROTAC ER degrader[1]
- Vepdegestrant directly binds the cereblon E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation (**Figure 1**)

Figure 1: Mechanism of action of vepdegestrant[a]

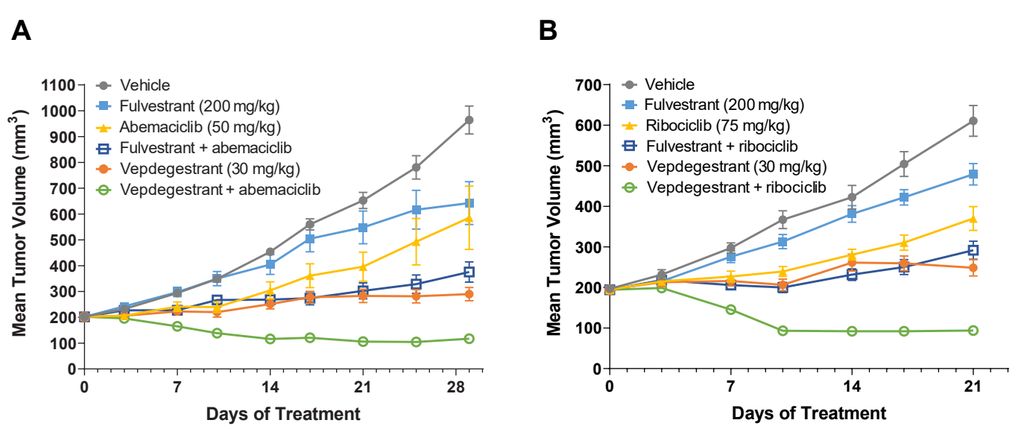


[a]General PROTAC protein degrader is shown
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera

- In contrast, selective ER degraders (SERDs) indirectly lead to ER degradation as a result of conformational changes and/or immobilization of ER[2]
- Vepdegestrant was well tolerated and showed evidence of clinical activity in the phase 2 VERITAC study (NCT04072952) in heavily pretreated patients with ER+/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer[3]
  - Clinical benefit rate[a] was 37.1% (95% CI: 21.5–55.1) at 200 mg once daily (QD) and 38.9% (95% CI: 23.1–56.5) at 500 mg QD
  - Most treatment-related adverse events were grade 1/2
- Cyclin-dependent kinase (CDK)4/6 inhibitors in combination with endocrine therapy have shown survival benefit in ER+ metastatic breast cancer, but resistance and disease progression eventually occur in almost all patients[4-6]
- The CDK4/6 inhibitors abemaciclib and ribociclib are approved as first- and second-line treatment for ER+/HER2- advanced or metastatic breast cancer in combination with endocrine therapy[7,8]
  - Abemaciclib is also approved as a monotherapy and in combination with other agents in additional breast cancer settings[7]
- Vepdegestrant combined with abemaciclib or ribociclib showed evidence of synergistic interactions in ER+ breast cancer cells and greater tumor growth inhibition in a xenograft breast cancer model compared with fulvestrant in combination with these agents[9] (**Figure 2**)

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

Figure 2: Inhibition of breast cancer cell growth with vepdegestrant plus abemaciclib (A) or ribociclib (B) vs fulvestrant in preclinical models[9]



Please scan this QR code with your smartphone app to view a **plain language summary** of the poster

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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Objective

- The open-label, multicenter, phase 1b/2 TACTIVE-U umbrella study is investigating the safety and clinical activity of vepdegestrant (ARV-471) in combination with other anticancer treatments in patients with previously treated ER+ advanced or metastatic breast cancer
  - Sub-Study A is evaluating the combination of vepdegestrant plus abemaciclib (NCT05548127)
  - Sub-Study B is evaluating the combination of vepdegestrant plus ribociclib (NCT05573555)

Study Design

- Sub-Studies A and B are evaluating vepdegestrant plus abemaciclib or ribociclib, respectively (**Figure 3**)
  - A dose escalation/de-escalation approach will be used to determine the recommended phase 2 dose of vepdegestrant in combination with abemaciclib or ribociclib
- Eligible patients have previously treated confirmed ER+/HER2- advanced or metastatic breast cancer (**Table 1**)
- Key outcome measures are shown in **Table 2**

Figure 3: TACTIVE-U trial schema

BID=twice daily; ER=estrogen receptor; QD=once daily

Table 1: TACTIVE-U key eligibility criteria

Inclusion criteria	Exclusion criteria
• Women or men aged ≥18 years • Histologically or cytologically confirmed ER+/HER2- advanced or metastatic breast cancer not amenable to surgical resection with curative intent • ≤2 lines of prior therapy for advanced or metastatic disease – 1 line of any CDK4/6 inhibitor–based regimen in any setting • ECOG performance status of 0 or 1 • ≥1 measurable lesion as defined by RECIST v1.1	• Newly diagnosed brain metastases or symptomatic CNS metastases or carcinomatous meningitis/leptomeningeal disease • Inflammatory breast cancer • Visceral crisis at risk of life-threatening complications in the short term • Known history of drug-induced pneumonitis or other significant symptomatic deterioration of lung functions

CDK=cyclin-dependent kinase; CNS=central nervous system; 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

Table 2: TACTIVE-U key outcome measures

	Phase 1b	Phase 2
Primary objective	**Primary endpoint**	
• Evaluate the tolerability and clinical activity of vepdegestrant plus abemaciclib or ribociclib	• DLTs	• Objective response[a]
Secondary objectives	**Secondary endpoints**	
• Evaluate the clinical activity of vepdegestrant plus abemaciclib or ribociclib – additional measures	• Objective response[a] • CBR[b] • DOR • PFS	• CBR[b] • DOR • PFS • OS
• Evaluate the safety and tolerability of vepdegestrant plus abemaciclib or ribociclib	• Type, frequency, and severity of AEs • Laboratory abnormalities	• Type, frequency, and severity of AEs • Laboratory abnormalities
• Evaluate the pharmacokinetics of vepdegestrant plus abemaciclib or ribociclib	• Plasma concentrations of study drugs • AUC_{tau} and C_{max} of study drugs (Sub-Study B only)	• Plasma concentrations of study drugs
• Evaluate changes in tumor biomarkers with vepdegestrant plus abemaciclib or ribociclib		• Circulating tumor DNA changes

[a]Objective response refers to confirmed complete response or partial response
[b]CBR refers to proportion of patients with confirmed complete response, partial response, or stable disease ≥24 weeks
AE=adverse event; AUC_{tau}=area under the concentration-time curve over dosing interval; CBR=clinical benefit rate; C_{max}=maximum concentration; DLT=dose-limiting toxicity; DOR=duration of response; OS=overall survival; PFS=progression-free survival

Study Status

- Enrollment is currently ongoing
- Future combination sub-studies investigating vepdegestrant plus other anticancer treatments will be included in TACTIVE-U

References

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