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TACTIVE-U: Phase 1b/2 Umbrella Study of Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor (ER) Degrader, Combined With Other Anticancer Treatments in ER-Positive Advanced or Metastatic Breast Cancer

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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)
  - Sub-study C is evaluating the combination of vepdegestrant plus samuraciclib (NCT06125522)

References

1. Flanagan JJ, et al. Presented at SABCS; Dec 4-8, 2018; San Antonio, TX. Poster P5-04-18.
2. Hanker AB, et al. *Cancer Cell*. 2020;37(4):496-513.
3. Hurvitz SA, et al. Presented at SABCS; Dec 6-10, 2022; San Antonio, TX. Oral presentation GS3-03.
4. Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649.
5. Spring LM, et al. *Curr Oncol Rep*. 2019;21(3):25.
6. Wander SA, et al. *Cancer Discov*. 2020;10(8):1174-1193.
7. Verzenio. Prescribing information. Lilly USA; 2021.
8. Kisqali. Prescribing information. Novartis; 2023.
9. Teh J, et al. Presented at AACR; Apr 14-19, 2023; Orlando, FL. Poster 3075.
10. CDK7 Inhibitor. Carrick Therapeutics. Accessed Oct 10, 2023. https://www.carricktherapeutics.com/pipeline/cdk7-inhibitor.
11. Coombes RC, et al. *Nat Commun*. 2023;14(1):4444.

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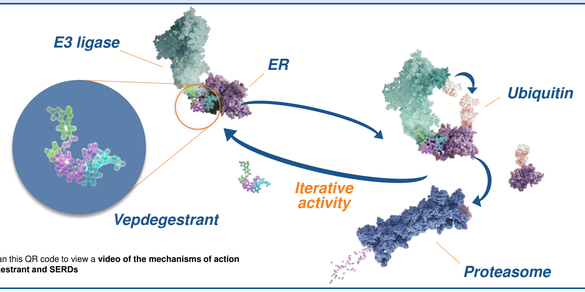
Background

- Vepdegestrant (ARV-471), an oral PROTAC ER degrader, directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER leading to its subsequent proteasomal degradation (**Figure 1**)[1]
- In contrast, selective ER degraders indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]

Figure 1: Mechanism of action of vepdegestrant[a]

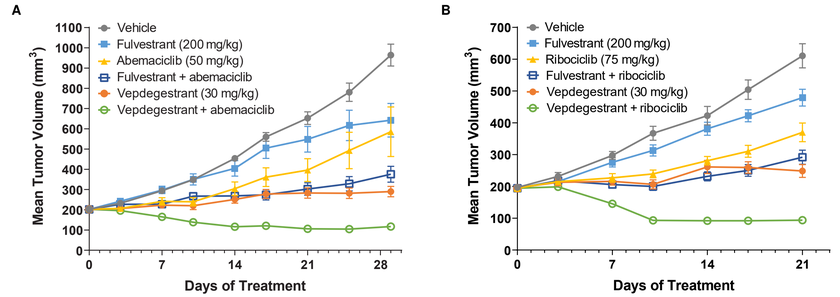


Please scan this QR code to view a **video of the mechanisms of action of vepdegestrant and SERDs**

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

- In the phase 2 VERITAC study (NCT04072952), vepdegestrant had clinical activity and was well tolerated in heavily pretreated patients (4 median prior regimens; 100% with prior cyclin-dependent kinase (CDK)4/6 inhibitors, 74% with prior fulvestrant, and 74% with prior chemotherapy across all lines) with ER+/human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer (data cutoff date: June 6, 2022)[3]
  - 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) was 37.1% (95% CI: 21.5–55.1) at 200 mg once daily
  - Most treatment-related adverse events were grade 1/2
  - Please see SABCS poster PO3-05-08 presented by SA Hurvitz, et al, to view updated results from VERITAC
- CDK4/6 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 in combination with an aromatase inhibitor or fulvestrant for ER+/HER2- advanced or metastatic breast cancer[7,8]
  - Abemaciclib is also approved as a monotherapy and in combination with other agents in additional breast cancer settings[7]
- In preclinical studies, vepdegestrant combined with abemaciclib or ribociclib showed evidence of synergistic interactions in ER+ breast cancer cell lines and greater tumor growth inhibition in a xenograft breast cancer model compared with fulvestrant in combination with these agents (**Figure 2**)[9]
- Samuraciclib is a selective, oral, CDK7 inhibitor that is in clinical development for solid tumors[10]
  - In an initial study in combination with fulvestrant, samuraciclib showed evidence of activity in patients with ER+/HER2- advanced breast cancer and previous CDK4/6 inhibitor treatment[11]

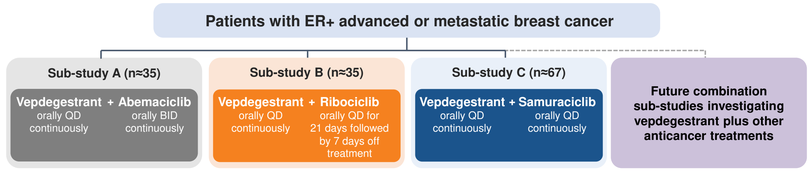
Figure 2: Inhibition of breast cancer cell growth with vepdegestrant plus (A) abemaciclib or (B) ribociclib vs fulvestrant[9]



Study Design

- Sub-studies A, B, and C are evaluating vepdegestrant plus abemaciclib, ribociclib, and samuraciclib, respectively (**Figure 3**)
  - A dose escalation/de-escalation approach is being used to determine the recommended phase 2 dose of vepdegestrant in combination with abemaciclib, ribociclib, or samuraciclib
- Eligible patients have previously treated confirmed ER+/HER2- advanced or metastatic breast cancer (**Table 1**)
- Key outcome measures are shown in **Table 2**
- Drug-drug interaction (DDI) is being assessed in all 3 sub-studies through a monotherapy lead-in in the phase 1b portion of sub-study A and dedicated DDI assessment cohorts in sub-study B (with ≈6–12 participants per dose cohort) and sub-study C (with ≈3–6 participants per dose cohort; **Table 3**)

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 • Up to 2 lines of prior therapy for advanced or metastatic disease; 1 line of any CDK4/6 inhibitor–based regimen is required (independent of the setting, eg, adjuvant or advanced/metastatic 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

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 outcome measures

	Phase 1b	Phase 2
Primary objectives	**Primary endpoints**	
• Evaluate the tolerability and clinical activity of vepdegestrant plus abemaciclib, ribociclib, or samuraciclib	• DLTs	• Objective response[a]
Secondary objectives	**Secondary endpoints**	
• Evaluate the clinical activity of vepdegestrant plus abemaciclib, ribociclib, or samuraciclib – additional measures	• Objective response[a] • CBR[b] • DOR • PFS	• CBR[b] • DOR • PFS • OS
• Evaluate the safety and tolerability of vepdegestrant plus abemaciclib, ribociclib, or samuraciclib	• Type, frequency, and severity of AEs • Laboratory abnormalities	• Type, frequency, and severity of AEs • Laboratory abnormalities
• Evaluate the pharmacokinetics of vepdegestrant plus abemaciclib, ribociclib, or samuraciclib	• Plasma concentrations of study drugs	• Plasma concentrations of study drugs
• Evaluate changes in tumor biomarkers with vepdegestrant plus abemaciclib, ribociclib, or samuraciclib		• Circulating tumor DNA changes • *TP53* mutation status (sub-study C)

[a]Confirmed complete response or partial response
[b]Proportion of patients with confirmed complete response, partial response, or stable disease ≥24 weeks
AE=adverse event; CBR=clinical benefit rate; DLT=dose-limiting toxicity; DOR=duration of response; OS=overall survival; PFS=progression-free survival; *TP53*=tumor protein p53

Table 3: TACTIVE-U DDI assessment outcome measures

Objectives	Endpoints
• Evaluate the effect of vepdegestrant on the pharmacokinetics of abemaciclib and active metabolites M2, M18, and M20 (sub-study A), ribociclib (sub-study B), or samuraciclib (sub-study C)	• AUC_{tau} and C_{max} of abemaciclib, M2, M18, and M20, with and without vepdegestrant (sub-study A) • AUC_{tau} and C_{max} of ribociclib with and without vepdegestrant (sub-study B) • AUC_{0-72} and C_{max} of samuraciclib with and without vepdegestrant (sub-study C)
• Evaluate the effect of ribociclib (sub-study B) and samuraciclib (sub-study C) on the pharmacokinetics of vepdegestrant	• AUC_{tau} and C_{max} of vepdegestrant with and without ribociclib (sub-study B) • AUC_{tau} and C_{max} of vepdegestrant with and without samuraciclib (sub-study C)

AUC_{0-72}=area under the concentration-time curve from time 0 to 72 hours post dose administration; AUC_{tau}=area under the concentration-time curve over dosing interval; C_{max}=maximum concentration; DDI=drug-drug interaction

Study Status

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