Poster: TPS1131

TACTIVE-K: Phase 1b/2 Study of Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, in Combination With PF-07220060, a Cyclin-Dependent Kinase 4 Inhibitor, in Estrogen Receptor+/Human Epidermal Growth Factor Receptor 2- Advanced Breast Cancer

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Objective

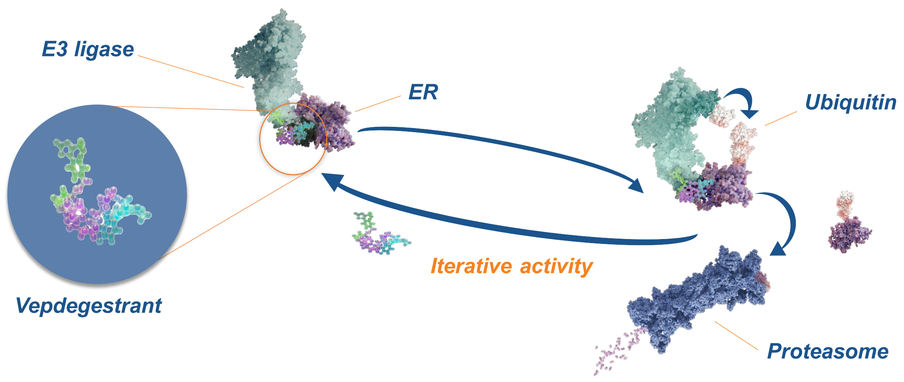
- The phase 1b/2, open-label, multicenter TACTIVE-K study (NCT06206837) will evaluate the safety and preliminary efficacy of vepdegestrant (ARV-471) combined with the cyclin-dependent kinase (CDK)4-selective inhibitor PF-07220060 in patients with estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

Background

- Vepdegestrant (ARV-471), an oral PROTAC ER degrader, has a unique mechanism of action that harnesses the ubiquitin-proteasome system to induce degradation of the ER[1] (**Figure 1**)
  - Vepdegestrant is a bifunctional molecule consisting of an ER-binding domain joined by a linker to an E3 ubiquitin ligase-binding domain[1]
  - The trimer complex formed by vepdegestrant, ER, and the E3 ubiquitin ligase directly induces ubiquitination of ER and its subsequent degradation by the proteasome[1]
- Initial results from a phase 1b cohort of a phase 1/2 study (NCT04072952) showed that vepdegestrant, in combination with the CDK4/6 inhibitor palbociclib, had robust clinical activity (clinical benefit rate [CBR], 63.0%) in heavily pretreated patients with ER+/HER2- advanced breast cancer[2]
- PF-07220060 is an investigational CDK4-selective inhibitor, which unlike CDK4/6 inhibitors, spares CDK6 blockade and demonstrates less neutropenia in preclinical in vivo models[3]
- In a first-in-human phase 1/2a study (NCT04557449), PF-07220060 combined with letrozole or fulvestrant showed encouraging efficacy (CBR, 52.4%) and tolerability (grade 3 neutropenia, 15.4%; no grade 4 neutropenia) in patients with advanced hormone receptor-positive/HER2- metastatic breast cancer who had received ≥2 lines of treatment, including endocrine therapy and CDK4/6 inhibitors[4]
- In preclinical tumor models, the combination of vepdegestrant with PF-07220060 effectively suppressed tumor growth to a greater extent than either agent alone (**Figure 2**)[3]

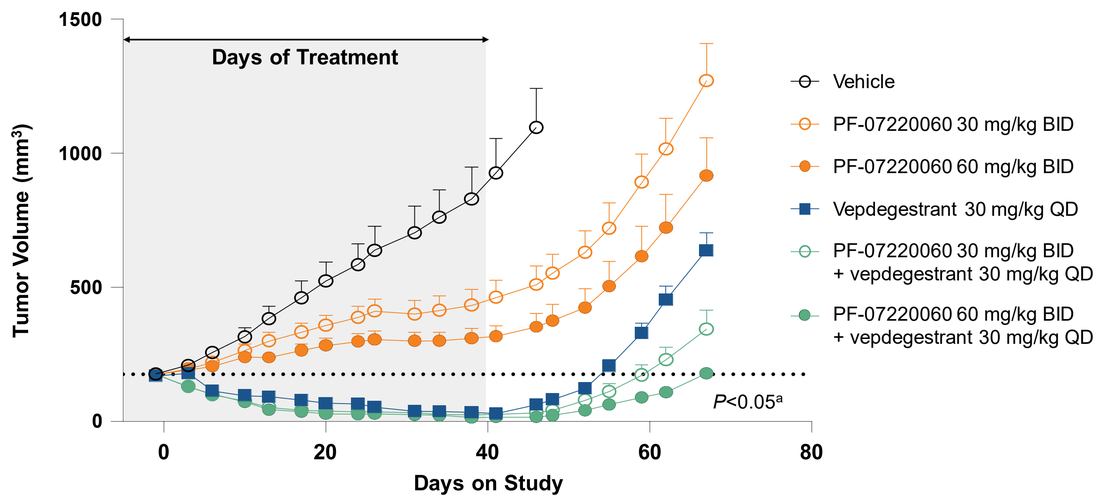
Figure 1: Mechanism of action of vepdegestrant[a]

Please scan this QR code with your smartphone app to view **a video of the mechanism of action of vepdegestrant.**



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

Figure 2: Tumor growth inhibition with vepdegestrant plus PF-07220060 in an HR+/HER2- MCF7 cell line–derived xenograft model

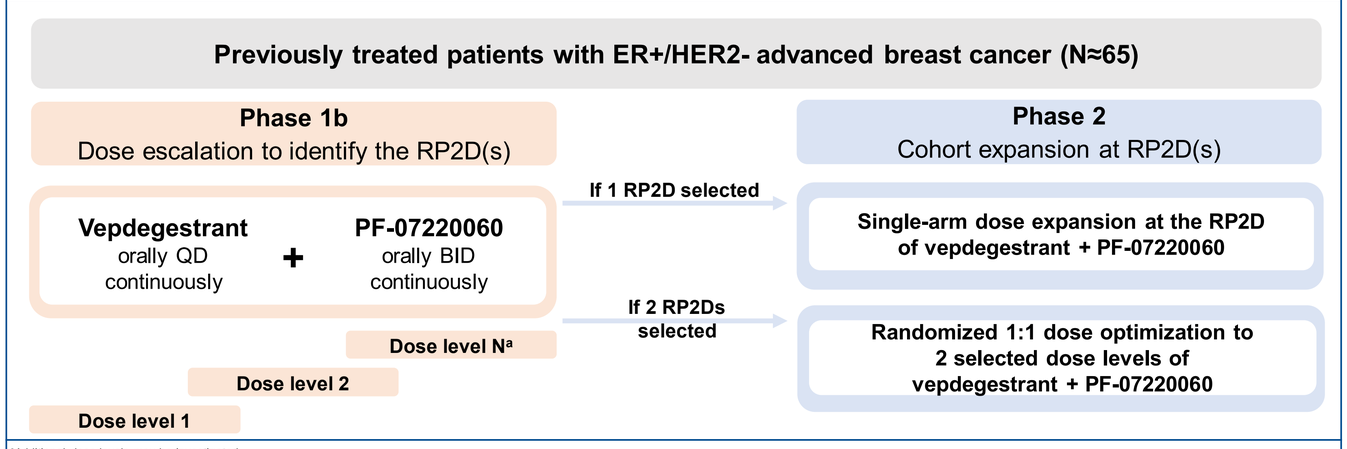


[a]*P*<0.05, PF-07220060 60 mg/kg BID + vepdegestrant 30 mg/kg QD vs PF-07220060 30 mg/kg BID + vepdegestrant 30 mg/kg QD.
Adapted from Anders L, et al. Presented at: AACR; April 5–10, 2024; San Diego, CA, USA. Poster 595.
BID=twice daily; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; QD=once daily.

Study Design

- This open-label phase 1b/2 study will use an escalation/de-escalation approach to determine the recommended phase 2 dose (RP2D) of vepdegestrant in combination with PF-07220060 (**Figure 3**)
  - Up to 2 RP2Ds may be determined in phase 1b, allowing for 1:1 randomization to 2 selected doses in phase 2
- Eligible patients have confirmed ER+/HER2- breast cancer, previously treated and not amenable to surgical resection with curative intent at the time of enrollment (**Table 1**)
- Key outcome measures are shown in **Table 2**

Figure 3: TACTIVE-K trial schema



[a]Additional dose levels may be investigated.
BID=twice daily; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; RP2D=recommended phase 2 dose; QD=once daily.

Table 1: TACTIVE-K key eligibility criteria

Inclusion criteria	Exclusion criteria
• Women or men aged ≥18 years • Histologically or cytologically confirmed ER+/HER2- breast cancer not amenable to surgical resection with curative intent • Phase 1b – ≥1 line of SOC therapy for advanced or metastatic breast cancer – Measurable or nonmeasurable disease – ECOG performance status of 0 or 1 • Phase 2 – 1–2 lines of prior ET for advanced or metastatic breast cancer (most recent ET-based treatment for >6 months); 1 line of prior CDK4/6 inhibitor–based regimen in any setting required – ≥1 measurable lesion as defined by RECIST v1.1 – ECOG performance status ≤2	• Visceral crisis at risk of life-threatening complications in the short term • Newly diagnosed brain metastases or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease • Inflammatory breast cancer

CDK=cyclin-dependent kinase; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SOC=standard of care.

Table 2: TACTIVE-K key outcome measures

	Phase 1b	Phase 2
Primary objectives	**Primary endpoints**	
• Evaluate the tolerability and antitumor activity of vepdegestrant in combination with PF-07220060	• Dose-limiting toxicities	• ORR[a] per RECIST v1.1 as determined by investigator assessment
Key secondary objectives	**Key secondary endpoints**	
• Evaluate the antitumor activity of vepdegestrant in combination with PF-07220060	• ORR[a] per RECIST v1.1 as determined by investigator assessment • DOR by investigator assessment • CBR[b] by investigator assessment • PFS by investigator assessment	• DOR by investigator assessment • CBR[b] by investigator assessment • PFS by investigator assessment
• Evaluate the safety and tolerability of vepdegestrant in combination with PF-07220060	• Incidence of AEs, treatment-related AEs, SAEs, and treatment-related SAEs • Laboratory abnormalities • ECG parameters	• Incidence of AEs, treatment-related AEs, SAEs, and treatment-related SAEs • Laboratory abnormalities • ECG parameters
• Evaluate the pharmacokinetics of vepdegestrant in combination with PF-07220060	• Plasma concentrations of study drugs • Pharmacokinetic parameters of study drugs at steady-state (C_{max}, T_{max}, AUC_{last})	• Plasma concentrations of study drugs
• Evaluate changes in tumor biomarkers with vepdegestrant in combination with PF-07220060		• Circulating tumor DNA changes

[a]ORR 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_{last}=area under the plasma concentration time-curve from zero to the last measured concentration; CBR=clinical benefit rate; C_{max}=maximum observed serum drug concentration; DOR=duration of response; ECG=electrocardiogram; ORR=objective response rate; PFS=progression-free survival; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SAE=serious AE; T_{max}=time taken to reach C_{max}.

Study Status

- Enrollment is currently ongoing
- To view currently recruiting sites, please visit clinicaltrials.gov (NCT06206837)

References

1. Flanagan JJ, et al. Presented at: SABCS; Dec 4–8, 2018; San Antonio, TX, USA. Poster P5-04-18.
2. Hamilton EP, et al. Presented at: SABCS; Dec 5–9, 2023; San Antonio, TX, USA. Poster PS15-03.
3. Anders L, et al. Presented at: AACR; April 5–10, 2024; San Diego, CA, USA. Poster 595.
4. Yap TA, et al. J Clin Oncol. 2023;41(suppl 16):3009.

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