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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

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(16_suppl):3009.

Disclosure

Dr. Telli serves as a consultant for AstraZeneca, Blueprint Medicines, Daiichi Sankyo, Genentech, Gilead (DSMC), Glaxo Smith Kline, G1 Therapeutics (DSMC), Guardant, Menarini Stemline, Merck, Natera, Novartis, Pfizer, RefleXion, Replicate, and Sanofi aventis. Dr. Telli reports institutional research funding from Arvinas, AstraZeneca, Bayer, Blueprint Medicines, Genentech/Roche, Glaxo Smith Kline, Hummingbird Biosciences, Merck, OncoSec Medical, and Pfizer.

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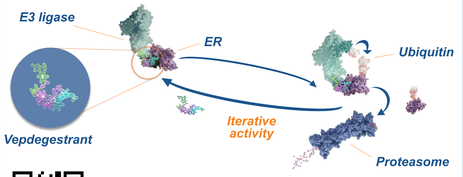
Background

- 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]
  - Please see poster 218P presented by EP Hamilton, et al for the most recent results from this cohort
- 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]

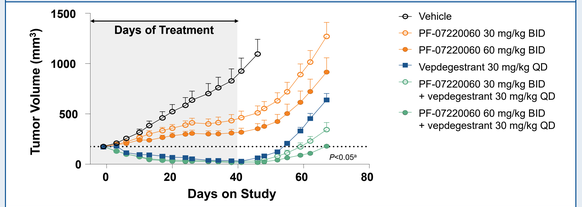
Figure 1: Mechanism of action of vepdegestrant[a]



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

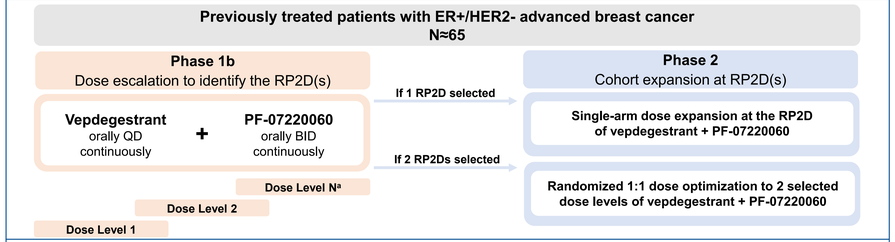


[a]P<0.05, PF-07220060 60 mg/kg BID + vepdegestrant 30 mg/kg QD vs PF-07220060 30 mg/kg BID + vepdegestrant 30 mg/kg QD.
Adapted from Anders L, et al. Presented at: AACR; April 5–10, 2024; San Diego, CA, USA. Poster 595.
BID=twice daily; HER2=human epidermal growth factor receptor 2; HR=hormone receptor;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

Study Design

- This open-label phase 1b/2 study (NCT06206837) 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]Objective response rate 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)