Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, plus atirmociclib in ER+/HER2− advanced breast cancer (ABC): TACTIVE-K phase 1b/2 results

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Objective

To assess the efficacy and safety of vepdegestrant plus atirmociclib at the recommended phase 2 doses among patients with previously treated estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) ABC in phases 1b and 2 of the TACTIVE-K study.

Conclusions

- Vepdegestrant plus atirmociclib demonstrated clinical activity in previously treated patients with ER+/HER2− ABC regardless of *ESR1* mutations.
- The safety profile of vepdegestrant plus atirmociclib was consistent with each agent.

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Introduction

- Although endocrine therapy (ET) with or without a cyclin-dependent kinase (CDK) 4/6 inhibitor has shown survival benefits for patients with ER+/HER2− ABC, drug resistance and progression eventually occur in most cases.[1]
  - Mutations in the *ESR1* gene (*ESR1*m) are a key acquired mechanism of resistance to ET and CDK4/6 inhibitors in ER+/HER2− ABC.[2]
- As such, there is an unmet need for therapies that improve clinical outcomes in patients with ER+/HER2− ABC and disease progression on existing ETs and CDK4/6 inhibitor-based therapies, especially for those with *ESR1*m tumors.
- Vepdegestrant (ARV-471) is an orally bioavailable PROTAC ER degrader that directly binds an E3 ubiquitin ligase and ER, triggering proteasomal degradation of ER.[3]
  - Vepdegestrant has been approved by the US FDA for adults with ER+/HER2−, *ESR1*-mutated ABC.[4]
- Atirmociclib (PF-07220060) is a next-generation cell cycle inhibitor that is highly selective for CDK4.[5,6]
- Both vepdegestrant and atirmociclib have shown antitumor activity in patients with ER+/HER2− ABC previously treated with the combination of a CDK4/6 inhibitor and ET.[3,5]
- This phase 1b/2 TACTIVE-K study is evaluating the efficacy and safety of vepdegestrant plus atirmociclib in patients with previously-treated ER+/HER2− ABC.

Methods

- TACTIVE-K was an open-label, multicenter, phase 1b/2 study (NCT06206837).
- The study included a dose escalation/de-escalation phase 1b to select recommended doses, and a randomized phase 2 to further assess efficacy, safety, and pharmacokinetics (PK).
- Key eligibility criteria included:
  - Women or men aged ≥18 years
  - Histologically or cytologically confirmed ER+/HER2− ABC not amenable to surgical resection with curative intent
  - Any lesion (phase 1b) or ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (phase 2)
  - Received ≥1 (phase 1b) or 1–2 (phase 2) prior lines of therapy in the ABC setting.
    - One and only one prior CDK4/6 inhibitor-based regimen in any setting was required in phase 2.
  - Eastern Cooperative Oncology Group performance status of 0 or 1 (phase 1b) or ≤2 (phase 2)
- Patients received vepdegestrant orally once daily continuously and atirmociclib orally twice daily continuously.
- The primary endpoint of phase 2 was objective response rate (ORR); secondary endpoints were antitumor activity (duration of response [DOR], clinical benefit rate [CBR; complete response, partial response, or stable disease for ≥24 wks]), progression-free survival, overall survival, safety, PK parameters of study drugs, and changes in circulating tumor DNA (ctDNA).
- Baseline *ESR1* mutation status (via ctDNA) and its association with efficacy outcomes were also assessed in phase 2.

Results

PATIENTS

- As of February 26, 2026, 70 patients (median age, 60 years) received vepdegestrant 200 mg daily plus atirmociclib 100 mg twice daily (ATI100; phase 1b, n = 9; phase 2, n = 27), or 300 mg twice daily (ATI300; phase 1b, n = 7; phase 2, n = 27) (**Table 1**).
- All patients in the ATI100 group received a prior CDK4/6 inhibitor in any setting (ribociclib, 22.2%; palbociclib, 61.1%, abemaciclib, 19.4%) and 94.1% of patients in the ATI300 group received a prior CDK4/6 inhibitor in any setting (ribociclib, 29.4%; palbociclib, 58.8%; abemaciclib, 20.6%).

Table 1. Demographics and baseline disease characteristics

Characteristic[a]	Vepdegestrant + atirmociclib 100 mg n = 36	Vepdegestrant + atirmociclib 300 mg n = 34
Female sex	35 (97.2)	34 (100)
Median age, years (range)	59.5 (34–80)	60.0 (33–84)
ECOG PS		
0	18 (50.0)	16 (47.1)
1	17 (47.2)	18 (52.9)
2	1 (2.8)	–
Menopausal status		
Pre/perimenopausal	9 (25.0)	4 (11.8)
Postmenopausal	27 (75.0)	30 (88.2)
Visceral disease	26 (72.2)	26 (76.5)
Baseline *ESR1* mutation (phase 2 only)[b,c]		
Yes	13 (48.1)	14 (51.9)
No	13 (48.1)	12 (44.4)
Number of prior regimens, median (range)		
Any setting	3.0 (1–6)	3.0 (1–6)
Advanced/metastatic setting	1.0 (1–3)	1.0 (1–4)
Type of prior therapy in any setting		
CDK4/6 inhibitor	36 (100.0)	32 (94.1)
Ribociclib	8 (22.2)	10 (29.4)
Palbociclib	22 (61.1)	20 (58.8)
Abemaciclib	7 (19.4)	7 (20.6)
Fulvestrant	18 (50.0)	19 (55.9)
Aromatase inhibitor	33 (91.7)	26 (76.5)
Chemotherapy[d]	21 (58.3)	21 (61.8)

[a]Values are reported as n (%), unless otherwise stated. [b]Based on central Guardant Health assessment. [c]Patients with unknown baseline *ESR1* status were excluded. [d]≥1 line of chemotherapy was also permitted in the advanced/metastatic setting and was received by 5 patients in the ATI100 group and 8 patients in the ATI300 group.
CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status.

EFFICACY

- Among patients with measurable disease at baseline, confirmed ORR was 22.6% in the ATI100 group and 33.3% in the ATI300 group (**Table 2**).
- For all treated patients, confirmed ORR was 19.4% (95% CI, 9.8–35.0%) and 32.4% (95% CI, 19.1–49.2%) in the ATI100 and ATI300 groups, respectively.
  - For phase 2 patients with *ESR1*m, confirmed ORR was 23.1% and 42.9% in the ATI100 and ATI300 groups, respectively (**Table 2**).
- The CBR for all treated patients was 47.2% and 61.8% in the ATI100 and ATI300 groups, respectively (**Table 2**).
  - For phase 2 patients with *ESR1*m, CBR was 46.2% and 64.3% in the ATI100 and ATI300 groups, respectively (**Table 2**).
- With median durations of follow-up 12.7 months and 13.8 months, median PFS was 9.1 months and 10.9 months for the ATI100 and ATI300 groups, respectively (**Table 2**).
  - For phase 2 patients with *ESR1*m, PFS was 8.6 months and was not reached in the ATI100 and ATI300 groups, respectively (**Table 2**).
- The median duration of treatment was 6.74 months (range, 1.4–21.3) for the ATI100 group and 10.14 months (range, 0.9–19.0) for the ATI300 group.

Table 2. Clinical antitumor activity

Patients with measurable disease at baseline	Vepdegestrant + atirmociclib 100 mg n = 31	Vepdegestrant + atirmociclib 300 mg n = 33
Confirmed ORR (CR + PR), n (%)	7 (22.6)	11 (33.3)
95% CI	11.4–39.8	19.8–50.4
All treated patients	**Vepdegestrant + atirmociclib 100 mg n = 36**	**Vepdegestrant + atirmociclib 300 mg n = 34**
CBR (CR + PR + SD ≥24 weeks), n (%)	17 (47.2)	21 (61.8)
95% CI	32.0–63.0	45.0–76.1
PFS		
Median (95% CI), months	9.1 (5.4–NE)	10.9 (7.2–NE)
12-month PFS rate, % (95% CI)	46.0 (28.4–61.9)	44.6 (26.8–60.9)
Patients with *ESR1* mutation	**Vepdegestrant + atirmociclib 100 mg n = 13**	**Vepdegestrant + atirmociclib 300 mg n = 14**
Confirmed ORR, n (%)	3 (23.1)	6 (42.9)
95% CI	8.2–50.3	21.4–67.4
CBR, (CR + PR + SD ≥24 weeks), n (%)	6 (46.2)	9 (64.3)
95% CI	23.2–70.9	38.8–83.7
PFS		
Median (95% CI), months	8.6 (3.0–NE)	NR (3.7–NE)
12-month PFS rate, % (95% CI)	34.6 (10.9–60.2)	50.0 (22.9–72.2)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; NE, not estimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

SAFETY

- Two dose-limiting toxicities were reported in phase 1b: a grade 3 platelet count decreased (ATI100) and a grade 3 neutrophil count decreased (ATI300).
- All causality treatment-emergent adverse events (TEAEs) were reported in all patients; 38.9% (ATI100) and 52.9% (ATI300) of patients experienced Grade 3/4 TEAEs; Grade 5 TEAEs occurred in 2 patients in the ATI100 group and 1 patient in the ATI300 group, but none were treatment-related.
- In the ATI100 group, 1 patient (2.8%) discontinued both study treatments and 1 additional patient (2.8%) discontinued atirmociclib due to TEAEs; In the ATI300 group, 3 patients (8.8%) discontinued both study treatments due to TEAEs.
- TEAEs led to dose reduction of atirmociclib in 8 patients (22.2%) in the ATI100 group; TEAEs led to vepdegestrant dose reductions in 2 patients (5.9%) and atirmociclib dose reductions in 4 patients (11.8%) in the ATI300 group.
- Most treatment-related adverse events (TRAEs) were grade 1/2; grade 3 TRAEs were mainly neutropenia (ATI100, 16.7%; ATI300, 35.3%) (**Table 3**) and there were no febrile neutropenia events.
- Overall, the safety data were consistent with the known tolerability profile of each individual agent.

Table 3. Treatment-related[a] AEs reported in ≥20% of patients by maximum grade

AE, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Vepdegestrant + atirmociclib 100 mg n = 36					
Neutropenia[b]	1 (2.8)	9 (25.0)	6 (16.7)	0	16 (44.4)
Fatigue[c]	10 (27.8)	4 (11.1)	0	0	14 (38.9)
Leukopenia[d]	5 (13.9)	5 (13.9)	0	1 (2.8)	11 (30.6)
Electrocardiogram QT prolonged	9 (25.0)	1 (2.8)	0	0	10 (27.8)
Vepdegestrant + atirmociclib 300 mg n = 34					
Neutropenia[b]	2 (5.9)	9 (26.5)	12 (35.3)	0	23 (67.6)
Diarrhea	13 (38.2)	2 (5.9)	1 (2.9)	0	16 (47.1)
Fatigue[c]	9 (26.5)	4 (11.8)	0	0	13 (38.2)
Leukopenia[d]	1 (2.9)	8 (23.5)	3 (8.8)	0	12 (35.3)
Nausea	8 (23.5)	3 (8.8)	0	0	11 (32.4)
Alopecia	9 (26.5)	0	0	0	9 (26.5)
Thrombocytopenia[e]	8 (23.5)	0	0	0	8 (23.5)

[a]Treatment related means related to any study intervention. [b]Includes neutropenia, neutrophil count decreased, and neutrophil percentage decreased. [c]Includes asthenia and fatigue. [d]Includes leukopenia and white blood cell count decreased. [e]Includes thrombocytopenia and platelet count decreased.
AE, adverse event.

PHARMACOKINETICS

- PK parameters including AUC_{tau} and C_{max} for vepdegestrant and atirmociclib (100 mg and 300 mg) at steady state were consistent with previous reports, indicating no clinically impactful drug-drug interactions.

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