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Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, Plus Abemaciclib in Estrogen Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced or Metastatic Breast Cancer: TACTIVE-U Preliminary Phase 1b Results

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Objective

- To evaluate the safety, clinical activity, and pharmacokinetics (PK) of the PROTAC estrogen receptor (ER) degrader vepdegestrant (ARV-471) in combination with the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor abemaciclib in previously treated patients with ER-positive (ER+)/human epidermal growth factor 2–negative (HER2-) advanced breast cancer

Key Findings

- Of 16 patients enrolled in the phase 1b portion of the study, 100% received prior CDK4/6 inhibitors, 88% prior aromatase inhibitors, 31% prior fulvestrant, and 69% prior chemotherapy (31% in the metastatic setting)
- There were no dose-limiting toxicities (DLTs) or grade ≥4 treatment-emergent adverse events (TEAEs) with vepdegestrant plus abemaciclib; grade 3 treatment-related neutropenia occurred in 5 patients and was manageable with dose modifications
- Clinical benefit rate (CBR) among all patients was 62.5% (95% CI: 38.6–81.5), and objective response rate (ORR) among patients with measurable disease at baseline was 26.7% (95% CI: 10.9–52.0); CBR was the same in patients with and without mutations in the estrogen receptor 1 gene (*ESR1;* CBR: 62.5%; 95% CI: 30.6–86.3), and ORR in those with measurable disease at baseline was 37.5% (95% CI: 13.7–69.4) and 14.3% (95% CI: 2.6–51.3), respectively
- Area under the concentration-time curve from time 0 to time tau (AUC_{tau}) and maximum observed concentration (C_{max}) of abemaciclib increased slightly, 13% and 16%, respectively, when dosed with vepdegestrant compared with abemaciclib alone

Conclusions

- The safety profile of vepdegestrant in combination with abemaciclib in patients with ER+/HER2- advanced breast cancer was manageable and generally consistent with the known profiles of each agent
- Encouraging preliminary signs of clinical benefit were observed with the combination of vepdegestrant and abemaciclib in previously treated patients; CBR was the same in patients with wild-type and mutant *ESR1*
- Preliminary PK data showed a minor effect of vepdegestrant on the exposure of abemaciclib and its active metabolites and indicated no significant drug interaction
  - This finding is consistent with a small effect of vepdegestrant on abemaciclib exposure identified using model-based prediction (see SABCS 2024 poster P4-08-13 presented by W Tan et al for results from a study evaluating cytochrome P450 3A4–mediated drug interaction risks for vepdegestrant)
- The phase 2 portion of the study is ongoing and is further evaluating the combination at the full standard doses of vepdegestrant 200 mg once daily and abemaciclib 150 mg twice daily; the phase 2 portion is fully enrolled with 21 patients as of September 24, 2024
- Additional ongoing sub-studies for TACTIVE-U are evaluating vepdegestrant plus ribociclib (sub-study B; NCT05573555) and samuraciclib (sub-study C; NCT06125522); the ongoing phase 1b/2 TACTIVE-K study is evaluating vepdegestrant in combination with the CDK4 inhibitor atirmociclib (PF-07220060; NCT06206837)

References

1. Békés M, et al. Nat Rev Drug Discov. 2022;21(3):181-200.
2. Hamilton EP, et al. Presented at ESMO; October 20–24, 2023; Madrid, Spain. Poster 390P.
3. Hurvitz SA, et al. Presented at SABCS; December 5–9, 2023; San Antonio, Texas, USA. Poster PO3-05-08.
4. Gough SM, et al. Clin Cancer Res. 2024;30(16):3549-63.
5. Isaacs C, et al. Presented at SABCS; December 5–9, 2023; San Antonio, Texas, USA. Poster PO2-20-04.
6. Posada M, et al. J Clin Pharmacol. 2020;60(7):915-30.

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Background

Please scan this QR code to view **a video of the mechanism of action of vepdegestrant**

- Vepdegestrant (ARV-471) is an investigational, orally administered PROTAC ER degrader that directly binds an E3 ubiquitin ligase and ER, triggering proteasomal degradation of ER[1]
- In a first-in-human phase 1/2 study, vepdegestrant monotherapy was well tolerated and showed evidence of clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer[2,3]
- In a breast cancer xenograft model, vepdegestrant in combination with the CDK4/6 inhibitor abemaciclib showed greater tumor growth inhibition compared with fulvestrant plus abemaciclib, supporting investigation in patients with breast cancer[4]
- The open-label, phase 1b/2 TACTIVE-U umbrella study is evaluating the safety, efficacy, and PK of vepdegestrant in combination with other anticancer treatments in patients with previously treated ER+ advanced or metastatic breast cancer[5]
- Here, we report preliminary phase 1b results from the ongoing phase 1b/2 TACTIVE-U sub-study A (NCT05548127) investigating vepdegestrant in combination with abemaciclib (data cutoff: August 30, 2024)

Methods

- Key eligibility criteria were as follows:
  - Histologically or cytologically confirmed ER+/HER2- advanced or metastatic breast cancer not amenable to surgical resection with curative intent
  - ≥1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
  - 1 or 2 prior therapies for advanced/metastatic disease; 1 line of prior CDK4/6 inhibitor–based regimen in any setting was required, and patients who needed a dose reduction due to an adverse event (AE) with previous CDK4/6 inhibitor therapy were excluded
  - Eastern Cooperative Oncology Group performance status ≤1
- Following a 7-day PK lead-in with abemaciclib administered alone in a subset of patients, all patients received vepdegestrant 200 mg orally once daily and abemaciclib 150 mg orally twice daily (both continuously)
- The primary endpoint of the phase 1b portion of the study was DLTs in the first cycle; secondary endpoints included safety, PK (plasma concentrations of abemaciclib and active metabolites, N-desethylabemaciclib [M2], hydroxy-N-desethylabemaciclib [M18], and hydroxyabemaciclib [M20]), and antitumor activity (CBR and ORR)

Results

Baseline Characteristics

- As of August 30, 2024, 16 patients received vepdegestrant in combination with abemaciclib in the phase 1b portion of the study (**Table 1**)

Table 1: Demographics and baseline characteristics

Characteristic	Total (N=16)
Sex, n (%)	
Female	16 (100)
Median age, years (range)	56 (38–79)
ECOG PS, n (%)	
0	9 (56)
1	7 (44)
Visceral disease, n (%)	12 (75)
Sites of metastases, n (%)	
Bone	12 (75)
Liver	9 (56)
Lymph node	5 (31)
Lung	4 (25)
Breast	2 (13)
Pleura	2 (13)
Adrenal gland	1 (6)
Chest wall	1 (6)
Other	1 (6)
Baseline *ESR1* status, n (%)	
Mutant	8 (50)
Wild-type[a]	8 (50)
Prior regimens, median (range)	
Any setting	2 (1–5)
Metastatic setting	1 (1–2)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	16 (100)
Ribociclib	8 (50)
Palbociclib	7 (44)
Abemaciclib	1 (6)
Fulvestrant	5 (31)
Aromatase inhibitor	14 (88)
Chemotherapy	
Any setting	11 (69)
Metastatic setting	5 (31)

[a]Wild-type *ESR1* indicates a valid ctDNA sequencing result was generated but no *ESR1* mutation was detected.
CDK4/6=cyclin-dependent kinase 4/6; ctDNA=circulating tumor DNA; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene.

Safety

- There were no DLTs or grade 4/5 TEAEs (**Table 2**)
  - TEAEs led to dose reductions of vepdegestrant in 2 (13%) patients and of abemaciclib in 7 (44%) patients
- 1 patient permanently discontinued both study treatments due to a TEAE of grade 1 pleural effusion; this was not considered related to either study treatment
- Treatment-related AEs reported in ≥10% of patients were mostly grade 1/2 (**Table 3**)
  - Neutropenia (any grade: 38%; grade 3: 31%) was manageable with dose modifications

Table 2: TEAE summary

n (%)	Total (N=16)
Any grade	16 (100)
Grade 3	7 (44)
Vepdegestrant dose reduction due to TEAEs	2 (13)[a]
Abemaciclib dose reduction due to TEAEs	7 (44)[b]

[a]2 TEAEs in 2 patients: grade 3 neutropenia (n=1) and grade 2 fatigue (n=1). [b]8 TEAEs in 7 patients: grade 2 fatigue (n=3), grade 2 anemia (n=1), grade 2 muscular weakness (n=1), grade 2 diarrhea (n=1), grade 3 neutropenia (n=1), and grade 3 neutrophil count decreased (n=1).
TEAE=treatment-emergent adverse event.

Table 3: TRAEs attributed to either vepdegestrant or abemaciclib in ≥10% of patients

n (%)	Total (N=16)	
	Any grade	Grade 3
Diarrhea	13 (81)	0
Nausea	7 (44)	0
Fatigue	7 (44)	2 (13)
Neutropenia[a]	6 (38)	5 (31)
Decreased appetite	4 (25)	0
Abdominal pain	3 (19)	0
Vomiting	3 (19)	0
Anemia	2 (13)	1 (6)
Abdominal distension	2 (13)	0
Headache	2 (13)	0
Alopecia	2 (13)	0
Rash	2 (13)	0
Hot flush	2 (13)	0

[a]Includes neutropenia, neutrophil count decreased, and neutrophil percentage decreased.
TRAE=treatment-related adverse event.

Efficacy

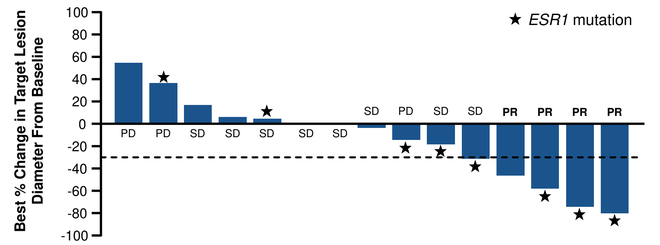
- CBR and ORR are shown in **Table 4**
- 4 patients had confirmed partial response and 6 had stable disease for ≥24 weeks per RECIST v1.1 (**Figure 1**)
- Median treatment duration was ~6.6 months (**Figure 2**)
  - 12 patients received vepdegestrant and abemaciclib for ≥4 cycles and 11 for ≥5 cycles; 5 were ongoing at the time of data cutoff

Table 4: CBR and ORR

	Total (N=16)	Mutant *ESR1* (n=8)	Wild-type *ESR1*[a] (n=8)
CBR[b], % (95% CI)	62.5 (38.6–81.5)	62.5 (30.6–86.3)	62.5 (30.6–86.3)
	Total (n=15)	**Mutant *ESR1* (n=8)**	**Wild-type *ESR1*[a] (n=7)**
ORR[c], % (95% CI)	26.7 (10.9–52.0)	37.5 (13.7–69.4)	14.3 (2.6–51.3)

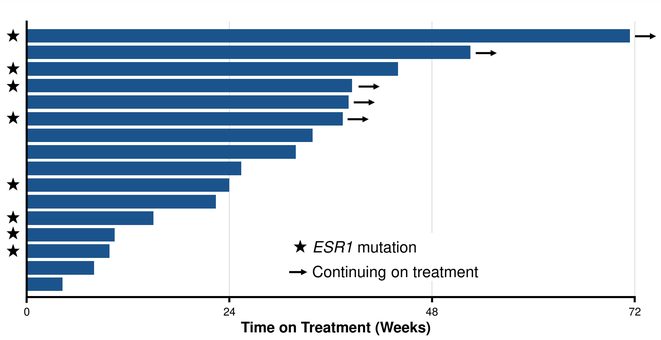
[a]Wild-type *ESR1* indicates a valid ctDNA sequencing result was generated but no *ESR1* mutation was detected. [b]Rate of confirmed complete response, partial response, or stable disease for ≥24 weeks. [c]In patients with measurable disease at baseline.
CBR=clinical benefit rate; ctDNA=circulating tumor DNA; *ESR1*=estrogen receptor 1 gene; ORR=objective response rate.

Figure 1: Antitumor activity (best percentage change from baseline in sum of target lesions) in response-evaluable patients (n=15)



Includes patients with measurable disease at baseline.
ESR1=estrogen receptor 1 gene; PD=progressive disease; PR=partial response; SD=stable disease.

Figure 2: Treatment duration (N=16)



ESR1=estrogen receptor 1 gene.

Pharmacokinetics

- The exposure of abemaciclib and total active species (AUC_{tau} and C_{max}) increased slightly when dosed with vepdegestrant compared with abemaciclib alone (**Table 5**)

Table 5: Plasma PK parameters

Analyte	Test/reference ratio (90% CI)[a]	
	AUC_{tau} (ng*h/mL)	C_{max} (ng/mL)
Abemaciclib	113.2 (93.4–137.3)	115.6 (95.3–140.1)
Metabolite M2	124.5 (114.1–135.9)	127.1 (116.8–138.3)
Metabolite M18	107.1 (90.1–127.5)	110.6 (89.8–136.1)
Metabolite M20	107.0 (94.1–121.6)	94.5 (86.0–103.8)
Total active species[b]	115.3 (104.0–127.9)[c]	115.6 (104.2–128.1)[c]

[a]Test/reference ratios were calculated as vepdegestrant plus abemaciclib (test) vs abemaciclib alone (reference) and are based on adjusted geometric means, and n=7 for all. Ratios and 90% CIs are expressed as percentages. [b]Abemaciclib and its active metabolites (M2, M18, and M20). [c]Potency-adjusted unbound AUC_{tau} (nmol*h/L) and C_{max} (nmol/L) ratios of active species were calculated as previously described by Posada et al.[6]
AUC_{tau}=area under the concentration-time curve from time 0 to time tau; C_{max}=maximum observed concentration; M2=N-desethylabemaciclib; M18=hydroxy-N-desethylabemaciclib; M20=hydroxyabemaciclib; PK=pharmacokinetic.