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Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, Plus Palbociclib in Estrogen Receptor+/Human Epidermal Growth Factor Receptor 2- Advanced Breast Cancer: Updated Phase 1b Cohort Results

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Objective

- To evaluate the safety and clinical activity of different dose levels of the PROTAC estrogen receptor (ER) degrader vepdegestrant (ARV-471) in combination with the cyclin-dependent kinase (CDK)4/6 inhibitor palbociclib in previously treated patients with ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

Key Findings

- The 46 patients enrolled in the phase 1b study were heavily pretreated (median 4 prior therapies in any setting: 87% with CDK4/6 inhibitors, 80% with fulvestrant, and 78% with chemotherapy [48% in metastatic setting])
  - As of December 2023, 16 (35%) patients received vepdegestrant for >12 months and 11 (24%) for ≥6 to ≤12 months; 12 (26%) patients were ongoing
- There were no dose-limiting toxicities (DLTs) or grade 5 treatment-emergent adverse events (TEAEs) for vepdegestrant plus palbociclib; grade 4 treatment-related neutropenia occurred in 44% of all patients, with no febrile neutropenia
- The clinical benefit rate (CBR) was 63.0% (95% CI: 47.5–76.8) in 46 patients treated across different dose levels of vepdegestrant plus palbociclib; the objective response rate (ORR) in 31 response-evaluable patients was 41.9% (95% CI: 24.5–60.9)
  - The CBR was 72.4% (95% CI: 52.8–87.3) in patients with mutations in the estrogen receptor 1 gene (*ESR1*; n=29) and 53.3% (95% CI: 26.6–78.7) in those with wild-type *ESR1* (n=15); ORR was 47.1% (95% CI: 23.0–72.2) in response-evaluable patients with mutant *ESR1* (n=17) and 41.7% (95% CI: 15.2–72.3) in those with wild-type *ESR1* (n=12)
  - Median duration of response (DOR) in 13 responders was 14.6 months (95% CI: 9.5–not reached [NR])
- Median progression-free survival (mPFS) was 11.2 months (95% CI: 8.2–16.5) with 27 events in all 46 patients
  - mPFS was 13.9 months (95% CI: 8.1–NR) with 12 events in the 200-mg once daily (QD) cohort (n=21)
- Robust early on-treatment decreases in mutant *ESR1* circulating tumor DNA (ctDNA) were sustained through later cycles in evaluable patients in the 200-mg QD cohort (n=13)
- After 1 cycle of treatment, median change in tumor fraction was −98.9% in patients with quantifiable tumor fraction at the beginning of cycle 1 (n=28); changes in tumor fraction were not clearly associated with *ESR1* mutant status or CBR

Conclusions

- With 6 months of additional follow-up from the first data report of this phase 1b cohort, the combination of vepdegestrant plus palbociclib continued to show robust clinical activity in patients with ER+/HER2- advanced breast cancer who had received extensive prior treatment, regardless of *ESR1* mutation status
- The safety profile of vepdegestrant plus palbociclib remained consistent with the known safety profiles of the 2 agents, except for increased grade 4 neutropenia, which was managed with laboratory monitoring and dose modifications, resulting in no febrile neutropenia and few palbociclib discontinuations
- The combination of vepdegestrant with lower starting doses of palbociclib (100 mg or 75 mg) is being evaluated in the VERITAC-3 study lead-in (NCT05909397)
- Based on safety and efficacy, vepdegestrant 200 mg QD was chosen as the dose for combination with palbociclib

References

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Disclosure

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Background

- Vepdegestrant (ARV-471), an oral PROTAC ER degrader, creates a trimer complex with an E3 ubiquitin ligase and ER to directly induce ubiquitination of ER and its subsequent proteasomal degradation[1]
- In contrast, selective ER degraders (SERDs) indirectly lead to ER degradation, secondary to conformational changes and/or immobilization of ER[1]
- In breast cancer xenograft models, vepdegestrant plus the CDK4/6 inhibitor palbociclib showed substantially greater tumor growth inhibition than the SERD fulvestrant plus palbociclib, supporting investigation in patients with breast cancer[2]
- In a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy had a favorable safety profile and encouraging clinical activity in previously treated patients with advanced breast cancer; vepdegestrant 200 mg QD was selected as the recommended phase 3 monotherapy dose[3]
- A phase 1b cohort of the first-in-human study is evaluating the combination of vepdegestrant plus palbociclib in patients with ER+/HER2- breast cancer after prior endocrine-based therapy; prior CDK4/6 inhibitor therapy was permitted[4]
  - Preliminary results showed robust clinical activity for the combination (data cutoff: 6 Jun 2023)[4]
- Here, we present updated safety and efficacy data from the phase 1b cohort after 6 additional months of follow-up (data cutoff: 18 December 2023)

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

Methods

- Key eligibility criteria for the phase 1b combination cohort were as follows:
  - Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer
  - Measurable or nonmeasurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
  - ≥1 prior endocrine therapy and ≤2 chemotherapy regimens for advanced disease; prior CDK4/6 inhibitor treatment was permitted
- Vepdegestrant was given orally QD continuously at doses of 180 mg, 200 mg, 400 mg, or 500 mg
- Palbociclib was administered according to the recommended starting dose (125 mg orally QD for 21 days followed by 7 days off treatment in 28-day cycles)[5]
  - Adverse events (AEs) were managed with standard palbociclib dose reductions
- The primary endpoints were DLTs in the first cycle and safety (AEs and laboratory abnormalities)
- Secondary endpoints included CBR (rate of confirmed complete response, partial response [PR], or stable disease ≥24 weeks), ORR per RECIST v1.1, PFS, and DOR
- Enrollment in these 4 dose levels is complete

Results

Baseline Characteristics

- 46 patients were enrolled between February 23, 2021, and September 21, 2022, and received vepdegestrant doses of 180 mg QD (n=2), 200 mg QD (n=21), 400 mg QD (n=3), or 500 mg QD (n=20) in combination with palbociclib (**Table 1**)

Table 1: Baseline characteristics

Characteristic	Total (N=46)	Characteristic	Total (N=46)
Sex, n (%)		Baseline *ESR1* status, n (%)[a]	
Female	45 (98)	Mutant	29 (63)
		Wild type[b]	15 (33)
Median age, y (range)	62 (29–78)	Prior regimens, median (range)	
ECOG PS, n (%)		Any setting	4 (1–11)
0	32 (70)	Metastatic setting	3 (0–7)
1	14 (30)		
Visceral disease, n (%)	33 (72)	Type of prior therapy, n (%)	
		CDK4/6 inhibitor	40 (87)
Sites of metastasis, n (%)		Palbociclib	36 (78)
Bone	34 (74)	Aromatase inhibitor	45 (98)
Liver	22 (48)	Fulvestrant	37 (80)
Lung	14 (30)	Chemotherapy	
Other	7 (15)	Any setting	36 (78)
		Metastatic setting	22 (48)

[a]Baseline *ESR1* status was missing for 2 patients.[b]*ESR1* mutation not detected.
CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1 gene.

Safety

- There were no DLTs or grade 5 TEAEs (**Table 2**)
- 7 (15%) patients reported TEAEs that led to discontinuation of vepdegestrant, including 1 patient in the 200-mg QD cohort due to grade 1 weight decrease related to vepdegestrant; 10 (22%) patients reported TEAEs that led to palbociclib discontinuation
- 4 patients discontinued palbociclib and continued vepdegestrant alone: 3 patients discontinued palbociclib due to neutropenia (1 in the 200-mg QD cohort and 2 in the 500-mg QD cohort), and 1 patient discontinued palbociclib due to a cerebrovascular accident (200-mg QD cohort)
- Treatment-related adverse events (TRAEs) to either vepdegestrant or palbociclib are shown in **Table 3**; grade 3/4 TRAEs attributed to either agent in ≥10% of total population were neutropenia (91%) and decreased white blood cell count (15%)
- No patients had febrile neutropenia

Table 2: TEAE summary

n (%)	Total (N=46)[a]	200-mg QD cohort (n=21)	500-mg QD cohort (n=20)
Any grade	46 (100)	21 (100)	20 (100)
Grade 3/4	43 (93)	19 (90)	19 (95)
Grade 5	0	0	0
Vepdegestrant dose reduction	5 (11)	2 (10)	3 (15)
Vepdegestrant discontinuation	7 (15)	5 (24)	2 (10)
Palbociclib dose reduction	36 (78)	16 (76)	16 (80)
Palbociclib discontinuation	10 (22)	7 (33)	3 (15)

[a]Includes 2 patients who received vepdegestrant 180 mg QD and 3 patients who received vepdegestrant 400 mg QD.
QD=once daily; TEAE=treatment-emergent adverse event.

Table 3: TRAEs attributed to either vepdegestrant or palbociclib in ≥10% of the total population

	Total (N=46)[a]			200-mg QD cohort (n=21)			500-mg QD cohort (n=20)		
n (%)	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Neutropenia[b]	46 (100)	22 (48)	20 (44)	21 (100)	10 (48)	8 (38)	20 (100)	9 (45)	10 (50)
Fatigue	29 (63)	3 (7)	0	13 (62)	1 (5)	0	13 (65)	2 (10)	0
Decreased platelet count	23 (50)	3 (7)	1 (2)	11 (52)	1 (5)	0	10 (50)	1 (5)	1 (5)
Anemia	16 (35)	2 (4)	0	7 (33)	0	0	7 (35)	1 (5)	0
Decreased WBC count	12 (26)	5 (11)	2 (4)	5 (24)	2 (10)	1 (5)	5 (25)	1 (5)	1 (5)
Constipation	11 (24)	0	0	5 (24)	0	0	6 (30)	0	0
QT prolonged[c]	11 (24)	2 (4)	0	4 (19)	0	0	6 (30)	1 (5)	0
Nausea	11 (24)	0	0	2 (10)	0	0	7 (35)	0	0
Diarrhea	8 (17)	0	0	2 (10)	0	0	4 (20)	0	0
Hot flush	8 (17)	0	0	2 (10)	0	0	4 (20)	0	0
Alopecia	6 (13)	N/A	N/A	2 (10)	N/A	N/A	3 (15)	N/A	N/A
Arthralgia	6 (13)	0	0	3 (14)	0	0	3 (15)	0	0
Increased AST	5 (11)	0	0	3 (14)	0	0	1 (5)	0	0
Decreased appetite	5 (11)	1 (2)	0	1 (5)	1 (5)	0	3 (15)	0	0
Vomiting	5 (11)	0	0	3 (14)	0	0	2 (10)	0	0

[a]Includes 2 patients who received vepdegestrant 180 mg QD and 3 patients who received vepdegestrant 400 mg QD. [b]Neutropenia led to 1 palbociclib dose reduction in 74% of patients (67% in the 200-mg QD cohort and 80% in the 500-mg QD cohort) and an additional palbociclib dose reduction in 37% of patients (33% in the 200-mg QD cohort and 35% in the 500-mg QD cohort). [c]8 patients had maximum grade 1 QT prolonged, and 2 patients had maximum grade 3 QT prolonged (1 with a left bundle branch block) and continued study treatment; patients with baseline grade 1 QT prolongation were eligible for the study.
AST=aspartate aminotransferase; N/A=not applicable; QD=once daily; TRAE=treatment-related adverse event; WBC=white blood cell.

Efficacy

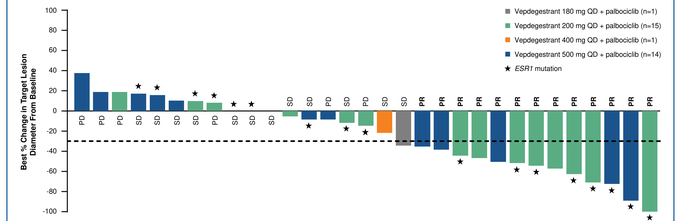
- CBR and ORR are shown in **Table 4**
- 13 of 31 (41.9%) response-evaluable patients had confirmed PR (**Figure 1**)
- Median DOR in 13 responders was 14.6 months (95% CI: 9.5–NR)
- Median PFS, based on 27 (59%) events in all patients, was 11.2 months (95% CI: 8.2–16.5; **Figure 2**)
- As of the cutoff date, 16 (35%) patients received vepdegestrant for >12 months (11 [24%] for ≥6 to ≤12 months), with 12 patients ongoing (**Figure 3**)
  - In the 200-mg QD cohort, 9 (43%) patients received vepdegestrant for >12 months (4 [19%] for ≥6 to ≤12 months), with 7 patients ongoing
  - In the 500-mg QD cohort, 4 (20%) patients received vepdegestrant for >12 months (5 [25%] for ≥6 to ≤12 months), with 3 patients ongoing

Table 4: CBR[a] and ORR

CBR	Total (N=46)[b]	200-mg QD cohort (n=21)	500-mg QD cohort (n=20)
% (95% CI)	63.0 (47.5–76.8)	66.7 (43.0–85.4)	50.0 (27.2–72.8)
Mutant *ESR1*	(n=29)	(n=14)	(n=12)[c]
% (95% CI)	72.4 (52.8–87.3)	78.6 (49.2–95.3)	58.3 (27.7–84.8)
Wild-type *ESR1*	(n=15)	(n=7)	(n=6)[c]
% (95% CI)	53.3 (26.6–78.7)	42.9 (9.9–81.6)	50.0 (11.8–88.2)
ORR[d]	**(n=31)[e]**	**(n=15)**	**(n=14)**
% (95% CI)	41.9 (24.5–60.9)	53.3 (25.6-78.7)	35.7 (12.8–64.9)
Mutant *ESR1*	(n=17)	(n=10)	(n=7)[c]
% (95% CI)	47.1 (23.0–72.2)	60.0 (26.2–87.8)	28.6 (3.7–71.0)
Wild-type *ESR1*	(n=12)	(n=5)	(n=5)[c]
% (95% CI)	41.7 (15.2–72.3)	40.0 (5.3–85.3)	60.0 (14.7–94.7)

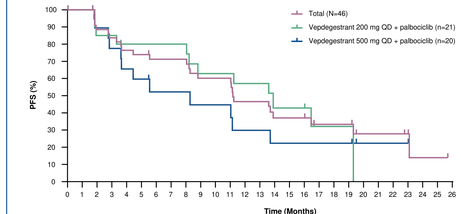
[a]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks. [b]Includes 2 patients who received vepdegestrant 180 mg QD and 3 who received vepdegestrant 400 mg QD. [c]Baseline *ESR1* status was missing for 2 patients who received vepdegestrant 500 mg QD. [d]In patients with measurable disease at baseline. [e]Includes 1 patient who received vepdegestrant 180 mg QD and 1 who received vepdegestrant 400 mg QD.
CBR=clinical benefit rate; *ESR1*=estrogen receptor 1 gene; ORR=objective response rate; QD=once daily.

Figure 1: Antitumor activity (best percentage change from baseline in sum of target lesions) in response-evaluable patients (n=31)



ESR1=estrogen receptor 1 gene; PD=progressive disease; PR=confirmed partial response; QD=once daily; SD=stable disease.

Figure 2: PFS analysis



	Overall		
	Total (N=46)	200-mg QD cohort (n=21)	500-mg QD cohort (n=20)
Events, n (%)	27 (59)[a]	12 (57)	12 (60)
mPFS, months (95% CI)	11.2 (8.2–16.5)	13.9 (8.1–NR)	8.3 (3.6–13.7)
	Mutant *ESR1*		
	Total (n=29)	200-mg QD cohort (n=14)	500-mg QD cohort (n=12)[b]
Events, n (%)	16 (55)	7 (50)	7 (58)
mPFS, months (95% CI)	13.7 (8.2–NR)	13.9 (8.1–NR)	8.3 (2.8–13.7)
	Wild-type *ESR1*		
	Total (n=15)	200-mg QD cohort (n=7)	500-mg QD cohort (n=6)[b]
Events, n (%)	10 (67)	5 (71)	4 (67)
mPFS, months (95% CI)	11.1 (2.8–19.3)	11.2 (1.8–NR)	7.4 (1.8–NR)

[a]2 (100%) events occurred in patients who received vepdegestrant 180 mg QD and 1 (33%) event occurred in a patient who received vepdegestrant 400 mg QD. [b]Baseline *ESR1* status was missing for 2 patients who received vepdegestrant 500 mg QD.
ESR1=estrogen receptor 1 gene; mPFS=median PFS; NR=not reached; PFS=progression-free survival; QD=once daily.

Figure 3: Treatment duration

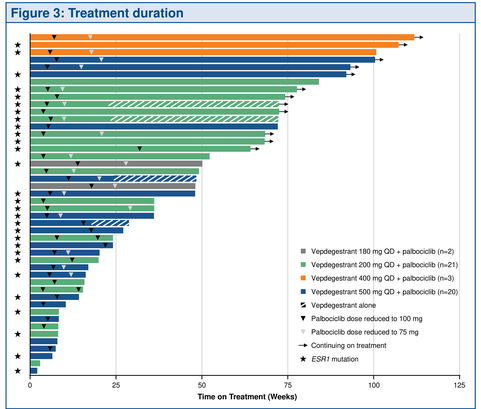
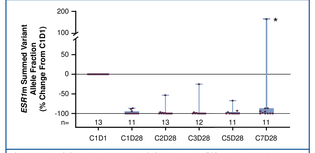


Figure shows palbociclib dose reductions due to adverse events.
ESR1=estrogen receptor 1 gene; QD=once daily.

ctDNA and Tumor Fraction

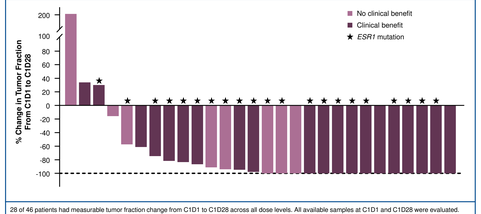
- Changes in *ESR1* mutant ctDNA were evaluated longitudinally through cycle 7 of treatment for patients in the 200-mg QD cohort; robust early on-treatment decreases were sustained through later cycles (**Figure 4**)
- Exploratory ctDNA analyses found marked reduction in tumor fraction after 1 treatment cycle across all dose groups, regardless of *ESR1* mutant status or CBR (median change, −98.9%; **Figure 5**)

Figure 4: Change in *ESR1* mutation–positive ctDNA in the vepdegestrant 200-mg QD cohort



*Outlier patient at C7D28: patient progressed at C9D28, shortly after *ESR1*m variant allele fraction increase.
All samples available from the indicated time points in *ESR1*m patients from the 200-mg QD cohort were analyzed and are presented. Error bars are the 95% CI.
C=cycle; ctDNA=circulating tumor DNA; D=day; *ESR1*m=estrogen receptor 1 gene mutation-positive; QD=once daily.

Figure 5: Changes in tumor fraction (ctDNA as a fraction of total cfDNA) after 1 cycle of treatment



28 of 46 patients had measurable tumor fraction change from C1D1 to C1D28 across all dose levels. All available samples at C1D1 and C1D28 were evaluated. Missing data are due to unquantifiable tumor fraction measurement at either of these time points, missing samples, or tumor fraction=0 at C1D1.
C=cycle; cfDNA=cell-free DNA; ctDNA=circulating tumor DNA; D=day; *ESR1*=estrogen receptor 1 gene.