PS15-03 San Antonio Breast Cancer Symposium (SABCS)® - December 5–9, 2023

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

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Objective

- To evaluate the safety, clinical activity, and pharmacokinetics (PK) 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 study were heavily pretreated (4 median prior regimens across disease settings, 87% with prior CDK4/6 inhibitors, 80% with prior fulvestrant, and 76% with chemotherapy [46% in metastatic setting])
- There were no dose-limiting toxicities (DLTs) or grade 5 treatment-emergent adverse events (TEAEs) with vepdegestrant plus palbociclib; grade 4 treatment-related neutropenia occurred in 41% of patients with no febrile neutropenia
- 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; objective response rate (ORR) was 41.9% (95% CI: 24.5–60.9) in 31 response-evaluable patients
  - CBR was 72.4% (95% CI: 52.8–87.3) in patients with mutant *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 in 13 responders was 10.2 months (95% CI: 9.5–not reached [NR])
- Median progression-free survival (PFS) was 11.1 months (95% CI: 8.2–NR), with 22 (48%) events in all 46 patients
- PK showed dose-dependent exposure for vepdegestrant, consistent with data for vepdegestrant administered as monotherapy; palbociclib exposure was similar across vepdegestrant dose levels and 46%–58% higher compared with historical palbociclib PK data
- After 1 cycle of treatment, mean change in *ESR1* mutant circulating tumor DNA (ctDNA) was −96.8% (SD: 6.3%) in 22 evaluable patients

Conclusions

- The combination of vepdegestrant plus palbociclib demonstrated robust clinical activity in patients with ER+/HER2- advanced breast cancer who had received extensive prior treatment
- The safety profile of vepdegestrant plus palbociclib was generally consistent with the known safety profiles of the 2 agents except for an increased occurrence of neutropenia, which was managed with laboratory monitoring and standard 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 the safety and efficacy profile, vepdegestrant 200 mg once daily (QD) was chosen as the dose for combination with palbociclib

References

1. Flanagan JJ, et al. Presented at SABCS; Dec 4–8, 2018; San Antonio, TX. Poster P5-04-18. 2. Hanker AB, et al. *Cancer Cell*. 2020;37(4):496-513. 3. Hamilton EP, et al. Presented at SABCS; Dec 7–10, 2021; San Antonio, TX. Poster PD13-08. 4. Hurvitz SA, et al. Presented at SABCS; Dec 6–10, 2022; San Antonio. TX. Oral presentation GS3-03. 5. Ibrance. Prescribing information. Pfizer Inc.; 2015.

Acknowledgments

We thank the patients who participated in this study and their caregivers, as well as the investigators, researchers, and coordinators who contributed to this study. This study is sponsored by Arvinas Estrogen Receptor, Inc. Poster development support was provided by Apollo Medical Communications, part of Helios Global Group, and funded by Arvinas Operations, Inc.

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Background

- Vepdegestrant (ARV-471), an oral PROTAC ER degrader, directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation[1]
- In contrast, selective ER degraders (SERDs) indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER[2]
- 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[1]
- In a phase 1/2 study (NCT04072952), vepdegestrant monotherapy had a favorable safety profile and encouraging clinical activity, and showed robust ER degradation and substantial decreases in *ESR1* mutant allele fraction in previously treated patients with advanced breast cancer; vepdegestrant 200 mg QD was selected as the recommended phase 3 monotherapy dose[3,4]
- The phase 1b cohort of this study is evaluating vepdegestrant in combination with palbociclib

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:
  - 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, duration of response, and PK parameters
- Enrollment in these 4 dose levels is complete; we report data as of June 6, 2023

Results

Baseline Characteristics

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

Table 1: Baseline characteristics

Characteristic	Total (N=46)
Sex, n (%)	
Female	45 (98)
Median age, y (range)	62 (29–78)
ECOG PS, n (%)[a]	
0	32 (70)
1	14 (30)
Visceral disease, n (%)	33 (72)
Sites of metastasis, n (%)	
Bone	34 (74)
Liver	22 (48)
Lung	14 (30)
Other	7 (15)

Characteristic	Total (N=46)
Baseline *ESR1* status, n (%)[a]	
Mutant	29 (63)
Wild type[b]	15 (33)
Prior regimens, median (range)	
Any setting	4 (1–11)
Metastatic setting	3 (0–7)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	40 (87)
Palbociclib	36 (78)
Aromatase inhibitor	44 (96)
Fulvestrant	37 (80)
Chemotherapy	
Any setting	35 (76)
Metastatic setting	21 (46)

[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**)
- Treatment-related adverse events to either vepdegestrant or palbociclib are shown in **Table 3**
- 70% of patients had reported neutropenia that led to 1 palbociclib dose reduction (62% and 75%, respectively, in the vepdegestrant 200 mg QD and 500 mg QD cohorts)
- 39% of patients had reported neutropenia that led to 2 palbociclib dose reductions (38% and 30%, respectively, in the vepdegestrant 200 mg QD and 500 mg QD cohorts)
- 1 patient in the vepdegestrant 200 mg QD cohort and 2 in the 500 mg QD cohort had neutropenia that led to the discontinuation of palbociclib only; all 3 patients continued with vepdegestrant alone
- 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	42 (91)	19 (90)	18 (90)
Grade 5	0	0	0
Vepdegestrant dose reduction	5 (11)	2 (10)	3 (15)
Vepdegestrant discontinuation	4 (9)	3 (14)	1 (5)
Palbociclib dose reduction	34 (74)	15 (71)	15 (75)
Palbociclib discontinuation	8 (17)	5 (24)	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 total population

n (%)	Total (N=46)[a]			200 mg QD cohort (n=21)			500 mg QD cohort (n=20)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Neutropenia	46 (100)	22 (48)	19 (41)	21 (100)	10 (48)	8 (38)	20 (100)	9 (45)	9 (45)
Fatigue	28 (61)	2 (4)	0	13 (62)	1 (5)	0	12 (60)	1 (5)	0
Decreased platelet count	23 (50)	4 (9)	1 (2)	11 (52)	1 (5)	0	10 (50)	2 (10)	1 (5)
Anemia	16 (35)	3 (7)	0	7 (33)	0	0	7 (35)	2 (10)	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[b]	10 (22)	1 (2)	0	4 (19)	0	0	6 (30)	1 (5)	0
Diarrhea	8 (17)	0	0	2 (10)	0	0	4 (20)	0	0
Nausea	8 (17)	0	0	2 (10)	0	0	5 (25)	0	0
Hot flush	7 (15)	0	0	2 (10)	0	0	3 (15)	0	0
Alopecia	6 (13)	NA	NA	2 (10)	NA	NA	3 (15)	NA	NA
Arthralgia	6 (13)	0	0	3 (14)	0	0	3 (15)	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]9 patients had grade 1 QT prolonged, and 1 patient had grade 3 QT prolonged (with a left bundle branch block) and continued study treatment; patients with baseline grade 1 QT prolongation were eligible for the study
NA=not applicable; QD=once daily; TRAE=treatment-related adverse event; WBC=white blood cell

Efficacy

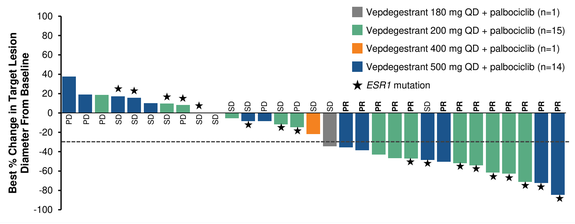
- CBR and ORR are shown in **Table 4**
- 13 of 31 (41.9%) response-evaluable patients had confirmed PR (**Figure 1**)
- Median duration of response in 13 responders was 10.2 months (95% CI: 9.5–NR)
- Median PFS, based on 22 (48%) events in all patients, was 11.1 months (95% CI: 8.2–NR; **Figure 2**)
- 29 (63%) patients received vepdegestrant for ≥24 weeks (15 [33%] for ≥48 weeks), with 18 ongoing as of the data cutoff date (**Figure 3**)
  - 14 (67%) patients received vepdegestrant 200 mg QD for ≥24 weeks (4 [19%] for ≥48 weeks), with 11 ongoing as of the data cutoff date
  - 10 (50%) patients received vepdegestrant 500 mg QD for ≥24 weeks (6 [30%] for ≥48 weeks), with 4 ongoing as of the data cutoff date

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 (26.6–78.7)	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)

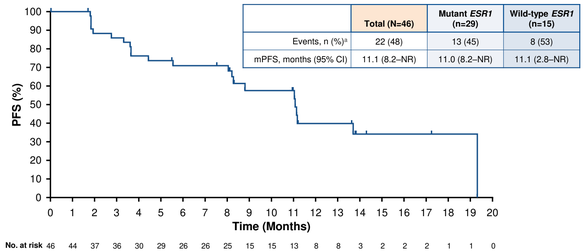
[a]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks
[b]Includes 2 patients who received vepdegestrant 180 mg QD and 3 who received vepdegestrant 400 mg QD
[c]Baseline *ESR1* status was missing for 2 patients who received vepdegestrant 500 mg QD
[d]In patients with measurable 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

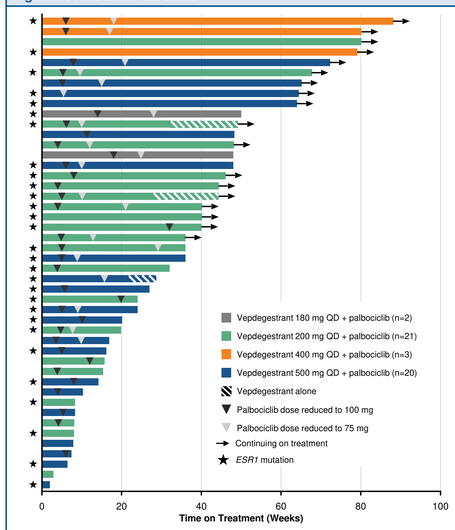
Figure 2: Preliminary PFS analysis



	Total (N=46)	Mutant *ESR1* (n=29)	Wild-type *ESR1* (n=15)
Events, n (%)[a]	22 (48)	13 (45)	8 (53)
mPFS, months (95% CI)	11.1 (8.2–NR)	11.0 (8.2–NR)	11.1 (2.8–NR)

[a]2 (100%) events occurred in patients who received vepdegestrant 180 mg QD, 8 (38%) who received vepdegestrant 200 mg QD, 0 who received vepdegestrant 400 mg QD, and 12 (60%) patients who received vepdegestrant 500 mg QD; includes 2 patients with missing baseline *ESR1* status
ESR1=estrogen receptor 1 gene; mPFS=median progression-free survival; NR=not reached; PFS=progression-free survival; QD=once daily

Figure 3: Treatment duration



ESR1=estrogen receptor 1 gene; QD=once daily

PK and ctDNA

- PK showed dose-dependent exposure for vepdegestrant, consistent with data for vepdegestrant administered as monotherapy, indicating that co-administration of palbociclib does not impact the PK of vepdegestrant
- Cross-trial comparison showed that palbociclib steady-state exposure was 46%–58% higher than the historical palbociclib PK data (data on file)
  - A similar increase in palbociclib exposure was observed with vepdegestrant 200 mg QD and 500 mg QD
- In 22 evaluable patients across dose cohorts, mean change in *ESR1* mutant ctDNA after 1 cycle of treatment was −96.8% (SD: 6.3%), with 15 (68%) patients showing complete clearance of the *ESR1* mutant allele(s) at this time point (**Figure 4**)

Figure 4: Change in *ESR1* mutation-positive ctDNA after 1 cycle of treatment

C1D1 samples were obtained prior to dosing
C=cycle; ctDNA=circulating tumor DNA; D=day; *ESR1*m=estrogen receptor 1 gene mutation-positive

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Dr. Hamilton has served as a consultant or in an advisory role for Arcus, AstraZeneca, Daiichi Sankyo, Ellipses Pharma, Genentech/Roche, Greenwich LifeSciences, iTeos, Janssen, Lilly, Loxo, Mersana, Novartis, Olema Pharmaceuticals, Orum Therapeutics, Pfizer, Relay Therapeutics, Seagen, Stemline Therapeutics, Theratechnologies, Tubulis, and Verascity Science. She has received research grants from AbbVie, Accutar Biotechnology, Acerta Pharma, ADC Therapeutics, Akesobio Australia, Amgen, Aravive, ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, BeiGene, Black Diamond, Bliss Biopharmaceutical, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, Compugen, Context Therapeutics, Cullinan-Florentine, Curis, CytomX, Daiichi Sankyo, Dana-Farber Cancer Institute, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Ellipses Pharma, Elucida Oncology, EMD Serono, Fujifilm, G1 Therapeutics, Genentech/Roche, H3 Biomedicine, Harpoon, Hutchison MediPharma, ImmunoGen, Immunomedics, Incyte, Infinity Pharmaceuticals, InventisBio, Jacobio, K-Group Beta, Karyopharm, Kind Pharmaceuticals, Leap Therapeutics, Lilly, Loxo Oncology, Lycera, MabSpace Biosciences, MacroGenics, MedImmune, Mersana, Merus, Millennium, Molecular Templates, Novartis, NuCana, Olema, OncoMed, Onconova Therapeutics, Oncothyreon, ORIC Pharmaceuticals, Orinove, Orum Therapeutics, Pfizer, PharmaMar, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Plexxikon, Prelude Therapeutics, ProfoundBio, Radius Health, Regeneron, Relay Therapeutics, Repertoire Immune Medicine, Rgenix, Seagen, Sermonix Pharmaceuticals, Shattuck Labs, Stemcentrx, Sutro, Syndax, Syros, Taiho, TapImmune, Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem Oncology, Zenith Epigenetics, and Zymeworks.

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Vepdegestrant + Palbociclib: Study Design and Patients

Key eligibility criteria for the phase 1b combination cohort[a]:

- ER+/HER2- advanced breast cancer
- Measurable or nonmeasurable disease per RECIST v1.1
- ≥1 prior endocrine therapy and ≤2 chemotherapy regimens for advanced disease[b]

Treatment:

Vepedegestrant orally QD continuously
- 180 mg (n=2)
- 200 mg (n=21)
- 400 mg (n=3)
- 500 mg (n=20)

+

Palbociclib orally 125 mg QD for 21 days followed by 7 days off treatment in 28-day cycles

AEs managed with standard dose modifications

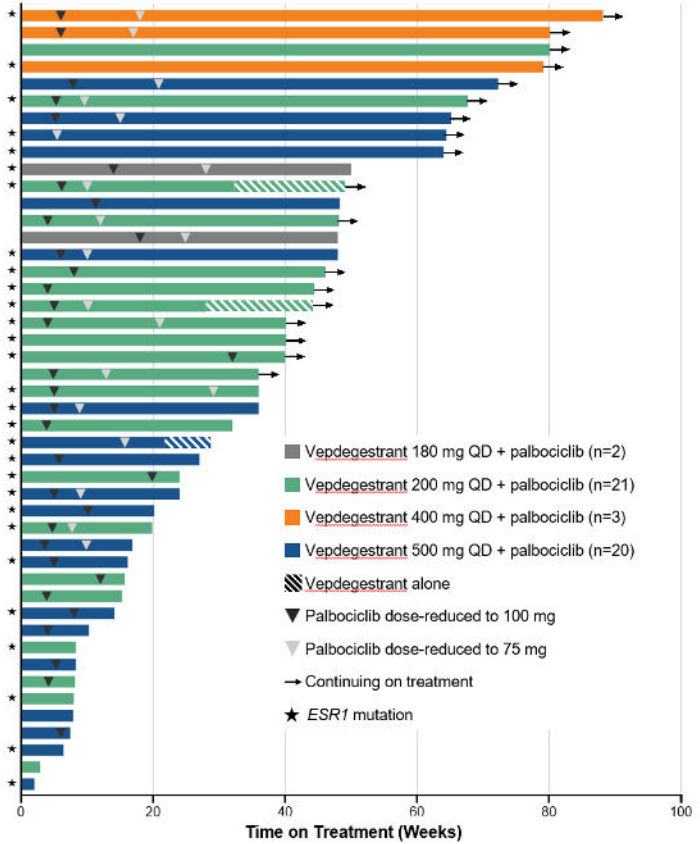
Characteristic	Total (N=46)
Female, n (%)	45 (98)
Median age, y (range)	62 (29–78)
Baseline *ESR1* status, n (%)[c]	
Mutant	29 (63)
Wild type[d]	15 (33)
Prior regimens, median (range)	
Any setting	4 (1–11)
Metastatic setting	3 (0–7)
Type of prior therapy (any setting), n (%)	
CDK4/6 inhibitor	40 (87)
Palbociclib	36 (78)
Aromatase inhibitor	44 (96)
Fulvestrant	37 (80)
Chemotherapy	
Any setting	35 (76)
Metastatic setting	21 (46)

[a]Patients with baseline grade 1 QT prolongation were eligible. [b]Prior CDK4/6 inhibitor treatment permitted. [c]Baseline *ESR1* status was missing for 2 patients. [d]*ESR1* mutation not detected.
AE=adverse event; CDK=cyclin-dependent kinase; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors

Vepdegestrant + Palbociclib: Safety & Treatment Duration

TRAEs,[a] n (%)	Total (N=46) Any grade	Grade 3	Grade 4
Neutropenia	46 (100)	22 (48)	19 (41)
Fatigue	28 (61)	2 (4)	0
Decreased platelet count	23 (50)	4 (9)	1 (2)
Anemia	16 (35)	3 (7)	0
Decreased WBC count	12 (26)	5 (11)	2 (4)
Constipation	11 (24)	0	0
QT prolonged[b]	10 (22)	1 (2)	0
Diarrhea	8 (17)	0	0
Nausea	8 (17)	0	0
Hot flush	7 (15)	0	0
Alopecia	6 (13)	NA	NA
Arthralgia	6 (13)	0	0
Decreased appetite	5 (11)	1 (2)	0
Vomiting	5 (11)	0	

- There were no DLTs or grade 5 TEAEs; no patients had febrile neutropenia



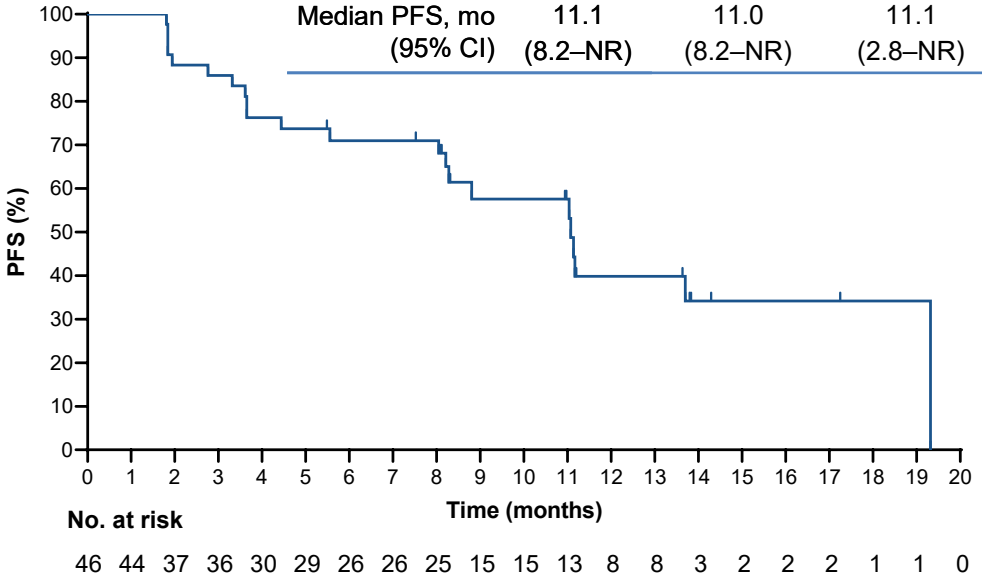
[a]In ≥10% of total population. [b]9 patients had grade 1 QT prolonged, and 1 patient had grade 3 QT prolonged (with a left bundle branch block) and continued study treatment.
DLT=dose-limiting toxicity; *ESR1*=estrogen receptor 1 gene; NA=not applicable; QD=once daily; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event; WBC=white blood cell

Vepdegestrant + Palbociclib: Efficacy

CBR[a]	Total[b] (N=46)	Mutant *ESR1* (n=29)	Wild-type *ESR1* (n=15)
% (95% CI)	63.0 (47.5–76.8)	72.4 (52.8–87.3)	53.3 (26.6–78.7)
ORR[c]	**(n=31)**	**(n=17)**	**(n=12)**
% (95% CI)	41.9 (24.5–60.9)	47.1 (23.0–72.2)	41.7 (15.2–72.3)

- Median DOR in 13 responders was 10.2 months (95% CI: 9.5–NR)

	Total[b] (N=46)	Mutant *ESR1* (n=29)	Wild-type *ESR1* (n=15)
Events, n (%)[d]	22 (48)	13 (45)	8 (53)
Median PFS, mo (95% CI)	11.1 (8.2–NR)	11.0 (8.2–NR)	11.1 (2.8–NR)



[a]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks
[b]Includes 2 patients with missing *ESR1* status
[c]In patients with measurable disease at baseline; includes 2 patients with missing baseline *ESR1* status
[d]2 (100%) events occurred in patients who received vepdegestrant 180 mg QD, 8 (38%) who received vepdegestrant 200 mg QD, 0 who received vepdegestrant 400 mg QD, and 12 (60%) patients who received vepdegestrant 500 mg QD
CBR=clinical benefit rate; DOR=duration of response; *ESR1*=estrogen receptor 1 gene; NR=not reached; ORR=objective response rate: PFS=progression-free survival; QD=once daily

Vepdegestrant + Palbociclib: Conclusions

- The combination of vepdegestrant plus palbociclib demonstrated robust clinical activity (CBR of 63.0%, ORR of 41.9%, and median PFS of 11.1 months) in patients with ER+/HER2- advanced breast cancer who had received extensive prior treatment (4 median prior regimens across disease settings, 87% with prior CDK4/6 inhibitors, 80% with prior fulvestrant, and 76% with chemotherapy [46% in metastatic setting])
- The safety profile of vepdegestrant plus palbociclib was generally consistent with the known safety profiles of the 2 agents except for an increased occurrence of neutropenia, which was managed with laboratory monitoring and standard dose modifications of palbociclib, resulting in no febrile neutropenia and few palbociclib discontinuations
- Based on the safety and efficacy profile, vepdegestrant 200 mg QD was chosen as the dose for combination with palbociclib

Acknowledgments

- We thank the patients who participated in this study and their caregivers, as well as the investigators, researchers, and coordinators who contributed to this study
- This study is sponsored by Arvinas Estrogen Receptor, Inc

Plain Language Summary

Please scan this QR code to view a plain language summary

CBR=clinical benefit rate; CDK=cyclin-dependent kinase; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; ORR=objective response rate; PFS=progression-free survival; QD=once daily