Poster 390P

Vepdegestrant, a PROteolysis TArgeting Chimera (PROTAC) Estrogen Receptor Degrader, in Estrogen Receptor+/Human Epidermal Growth Factor Receptor 2- Advanced Breast Cancer: Update of Dose Escalation Results From a Phase 1/2 Trial

Erika P Hamilton[1], Hyo S Han[2], Anne F Schott[3], Antoinette R Tan[4], Rita Nanda[5], Dejan Juric[6], Natasha Hunter[7], Pamela Munster[8], Bruno Fang[9], George Zahrah[10], Jennifer Ranciato[11], Richard Gedrich[11], Eric Zhi[11], Yuanyuan Zhang[11], Weiwei Tan[12], Cecile Mather[11], Julia Perkins Smith[13], Sibyl Anderson[11], Sara A Hurvitz[14]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Rogel Cancer Center, University of Michigan Medical School, Ann Arbor, MI, USA; [4]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [5]University of Chicago, Chicago, IL, USA; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Fred Hutchinson Cancer Center, Seattle Cancer Care Alliance, Seattle, WA, USA; [8]University of California San Francisco, San Francisco, CA, USA; [9]Astera Cancer Care, East Brunswick, NJ, USA; [10]Norwalk Hospital, Norwalk, CT, USA; [11]Arvinas Operations, Inc., New Haven, CT, USA; [12]Pfizer Inc., San Diego, CA, USA; [13]Pfizer Inc., New York, NY, USA; [14]Fred Hutchinson Cancer Center, Seattle, WA, USA

Objective

- To evaluate the safety, clinical activity, and pharmacokinetics (PK) of vepdegestrant (ARV-471), an oral PROTAC estrogen receptor (ER) degrader, in previously treated patients with ER+/human epidermal growth factor receptor 2 (HER2)- locally advanced or metastatic breast cancer

Key Findings

- With 13.8 months median follow-up, vepdegestrant at total daily doses ranging from 30 mg to 700 mg was well tolerated, with no dose-limiting toxicities (DLTs) reported in the phase 1, dose escalation portion of the study
- Most treatment-related adverse events (TRAEs) were grade 1/2
- Vepdegestrant showed antitumor activity with a clinical benefit rate (CBR) of 36.1% (95% CI: 25.9–47.4) and a confirmed objective response rate (ORR) of 11.5% (95% CI: 4.7–22.2)
- Dose-dependent increases in area under the plasma concentration-time curve for 0-24 hours (AUC_{24}) and maximum plasma concentration (C_{max}) were seen at doses up to 500 mg total daily dose
- Substantial on-treatment reductions in mutant *ESR1* circulating tumor DNA (ctDNA) levels were observed after 1 cycle and sustained over multiple cycles

Conclusions

- With longer follow-up of the dose escalation portion of this study, vepdegestrant continued to be well tolerated across all doses and showed clinical activity in heavily pretreated patients (4 median prior regimens, 100% prior cyclin-dependent kinase [CDK]4/6 inhibitors, 100% prior aromatase inhibitors, and 82% prior fulvestrant) with ER+/HER2- advanced breast cancer
- Dose-dependent increases were seen for vepdegestrant exposure up to 500 mg total daily dose
- Data support further development of vepdegestrant; 2 ongoing phase 3 studies are evaluating vepdegestrant in patients with ER+/HER2- advanced breast cancer
  - VERITAC-2 (NCT05654623) is evaluating vepdegestrant 200 mg once daily (QD) vs fulvestrant as second/third-line treatment
  - VERITAC-3 (NCT05909397) is evaluating the combination of vepdegestrant plus palbociclib as first-line treatment

References

1. Flanagan JJ, et al. Presented at SABCS; Dec 4-8, 2018; San Antonio, TX, USA. Poster P5-04-18.
2. Hanker AB, et al. *Cancer Cell*. 2020;37(4):496-513.
3. Kuter I, et al. *Breast Cancer Res Treat*. 2012;133(1):237-246.
4. Robertson JFR, et al. *Breast Cancer Res*. 2013;15(2):R18.
5. Hamilton E, et al. Presented at SABCS; Dec 7-10, 2021; San Antonio, TX, USA. Poster PD13-08.
6. Hurvitz SA, et al. Presented at SABCS; Dec 6-10, 2022; San Antonio, TX, USA. Oral presentation GS3-03.

Disclosure

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.

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. Medical writing and editorial support were provided by Justine Lempart, PhD, and Melissa Austin of Apollo Medical Communications, part of Helios Global Group, and funded by Arvinas Operations, Inc.

Please scan this QR code to **download a copy of the poster**

Please scan this QR code with your smartphone app to view a **plain language summary** of the poster

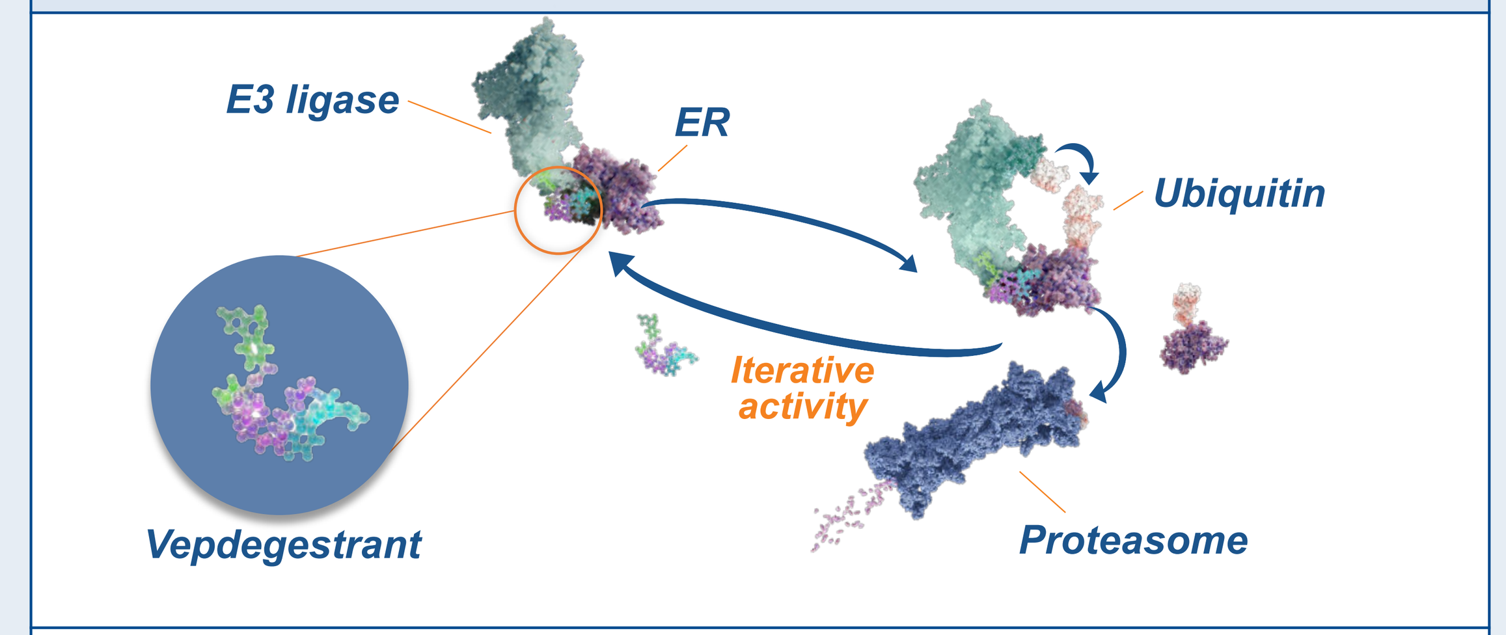
Contact
Erika P Hamilton;
erika.hamilton@sarahcannon.com

European Society for Medical Oncology (ESMO) Annual Meeting, Madrid, Spain, October 20–24, 2023

Background

- Vepdegestrant (ARV-471) is an oral PROTAC ER degrader that directly binds an E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation (**Figure 1**)[1]
- Selective ER degraders (SERDs), such as fulvestrant, indirectly recruit the ubiquitin-proteasome system secondary to conformational changes and/or immobilization of ER; fulvestrant induces 40%–50% ER protein degradation at its optimal dose[2-4]
- Vepdegestrant treatment yielded substantially greater ER degradation and tumor growth inhibition than fulvestrant in breast cancer xenograft models[1]
- In previously reported analyses of this phase 1/2 study (NCT04072952), vepdegestrant was well tolerated and had clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer
  - The phase 1, dose escalation portion (30–700 mg total daily dose) identified vepdegestrant 200 mg QD and 500 mg QD as the recommended phase 2 doses (RP2Ds),[5] and the phase 2 VERITAC cohort expansion portion established 200 mg QD as the recommended phase 3 dose (RP3D)[6]
  - In evaluable patients treated at the RP3D across the phase 1/2 study, mean ER degradation was 71%[6]
- Herein, we present updated data from the phase 1, dose escalation portion of this study after an additional 20 months of follow-up from the first report[5]

Figure 1: Mechanism of action of vepdegestrant[a]



[a]General PROTAC protein degrader, cereblon E3 ligase, and ER target protein are shown
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera

Please scan this QR code with your smartphone app to view a **video showing how the mechanisms of action of vepdegestrant and SERDs differ**

Methods

- In the phase 1, dose escalation portion (3+3 design with backfill) of this phase 1/2, multicenter, open-label study in patients with ER+/HER2- breast cancer, vepdegestrant was given orally with food at a starting dose of 30 mg daily
- Key eligibility criteria
  - ER+/HER2- advanced breast cancer
  - ≥1 prior CDK4/6 inhibitor
  - ≥2 prior endocrine therapies
  - ≤3 prior lines of chemotherapy
- The primary objective of the phase 1, dose escalation portion of the study was to evaluate the safety and tolerability of vepdegestrant to identify the RP2Ds; these results have been previously reported[5]
- This analysis reports secondary and exploratory objectives
  - Secondary objectives included PK and antitumor activity (CBR is defined as the rate of confirmed complete response, partial response, or stable disease ≥24 weeks analyzed in patients enrolled ≥24 weeks prior to the data cutoff)
  - Change from baseline in *ESR1* mutation-positive ctDNA was an exploratory outcome

Results

Baseline Characteristics

- As of June 6, 2023, 83 patients received vepdegestrant at total daily doses ranging from 30 mg to 700 mg
- All patients received prior CDK4/6 inhibitors and aromatase inhibitors, 83.1% received prior chemotherapy, and 81.9% received prior fulvestrant (**Table 1**)

Table 1: Baseline characteristics

Characteristic	Total (N=83)	Characteristic	Total (N=83)
Sex, n (%)		Baseline *ESR1* status, n (%)[b]	
Female	82 (98.8)	Mutant	43 (51.8)
Age, median (range), y	64.0 (36–80)	Wild type	37 (44.6)
ECOG PS, n (%)[a]		Prior treatment, median (range)	
0	42 (50.6)	Any setting	4.0 (1–12)
1	40 (48.2)	Metastatic setting	3.0 (0–8)
Visceral disease, n (%)	54 (65.1)	Type of prior therapy, n (%)	
Sites of metastasis, n (%)		CDK4/6 inhibitor	83 (100)
Bone	50 (60.2)	Aromatase inhibitor	83 (100)
Liver	43 (51.8)	Fulvestrant	68 (81.9)
Lung	16 (19.3)	Chemotherapy	
Other	15 (18.1)	Any setting	69 (83.1)
		Metastatic	50 (60.2)

[a]Baseline ECOG PS was unknown in 1 patient. [b]Baseline *ESR1* status was unknown or missing in 3 patients
CDK=cyclin-dependent kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*=estrogen receptor 1

Safety

- No DLTs occurred
- Overall, 80 (96.4%) patients experienced treatment-emergent adverse events; most were grade 1/2 (**Table 2**)
- There were no TRAEs of grade ≥4; the most common TRAEs were fatigue (26.5%) and nausea (24.1%; **Table 3**)

Table 2: Treatment-emergent adverse event summary

	Vepdegestrant total daily dose									
Characteristic	30 mg (n=3)	60 mg (n=3)	100 mg (n=13)	120 mg (n=7)	180 mg (n=7)	200 mg (n=8)	360 mg (n=15)	500 mg (n=22)	700 mg (n=4)	Total (N=83)[a]
TEAEs, n (%)										
Any grade	3 (100)	3 (100)	12 (92.3)	7 (100)	7 (100)	8 (100)	15 (100)	21 (95.5)	3 (75.0)	80 (96.4)
Grade 3/4	1 (33.3)	1 (33.3)	2 (15.4)	0	1 (14.3)	1 (12.5)	2 (13.3)	6 (27.3)	1 (25.0)	16 (19.3)
Grade 5	0	0	0	0	0	0	0	1 (4.5)[b]	0	1 (1.2)[b]
Leading to vepdegestrant discontinuation	0	0	1 (7.7)	0	1 (14.3)	0	1 (6.7)	1 (4.5)	0	5 (6.0)
Leading to dose reduction	0	0	0	0	0	0	0	2 (9.1)[c]	2 (50.0)[d]	4 (4.8)

[a]1 patient had missing dose group information and was only included in the total N; numbers in the Total column may not match the individual dose columns. [b]Cardiac arrest considered unrelated to vepdegestrant. [c]Nausea (grade 3) and fatigue (grade 3). [d]QT prolongation (grade 3) and carpal tunnel syndrome (grade 2)
TEAE=treatment-emergent adverse event

Table 3: Treatment-related adverse events reported in ≥10% of patients overall

	Vepdegestrant total daily dose																			
	30 mg (n=3)		60 mg (n=3)		100 mg (n=13)		120 mg (n=7)		180 mg (n=7)		200 mg (n=8)		360 mg (n=15)		500 mg (n=22)		700 mg (n=4)		Total (N=83)[a]	
TRAE, n (%)	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3
Any TRAEs	0	0	3 (100)	0	12 (92.3)	0	6 (85.7)	0	4 (57.1)	0	5 (62.5)	1 (12.5)	11 (73.3)	1 (6.7)	12 (54.5)	3 (13.6)	1 (25.0)	1 (25.0)	54 (65.1)	6 (7.2)
Fatigue	0	0	1 (33.3)	0	3 (23.1)	0	1 (14.3)	0	1 (14.3)	0	2 (25.0)	0	4 (26.7)	0	8 (36.4)	0	2 (50.0)	0	22 (26.5)	0
Nausea	0	0	2 (66.7)	0	2 (15.4)	0	2 (28.6)	0	2 (28.6)	0	2 (25.0)	0	3 (20.0)	0	6 (27.3)	1 (4.5)	1 (25.0)	0	20 (24.1)	1 (1.2)
Arthralgia	0	0	1 (33.3)	0	4 (30.8)	0	3 (42.9)	0	1 (14.3)	0	1 (12.5)	0	0	0	2 (9.1)	0	0	0	12 (14.5)	0
Constipation	0	0	0	0	2 (15.4)	0	1 (14.3)	0	0	0	2 (25.0)	0	3 (20.0)	0	3 (13.6)	0	0	0	11 (13.3)	0
Hot flush	0	0	0	0	3 (23.1)	0	0	0	0	0	2 (25.0)	0	1 (6.7)	0	5 (22.7)	0	0	0	11 (13.3)	0
Headache	0	0	0	0	3 (23.1)	0	1 (14.3)	0	0	0	0	1 (12.5)	2 (13.3)	0	2 (9.1)	0	0	0	8 (9.6)	1 (1.2)

[a]1 patient had missing dose group information and was only included in the total N
Gr=grade; TRAE=treatment-related adverse event

Efficacy

- CBR across all vepdegestrant dose groups (N=83) was 36.1% (95% CI: 25.9–47.4); CBR across patients with *ESR1* mutations (n=43) was 48.8% (95% CI: 33.3–64.5)
- Of 61 patients with baseline measurable disease, 7 had a confirmed partial response, resulting in a confirmed ORR of 11.5% (95% CI: 4.7–22.2; **Figure 2**)
- At data cutoff, 29 patients had treatment for ≥24 weeks (8 for ≥48 weeks) with 5 patients ongoing

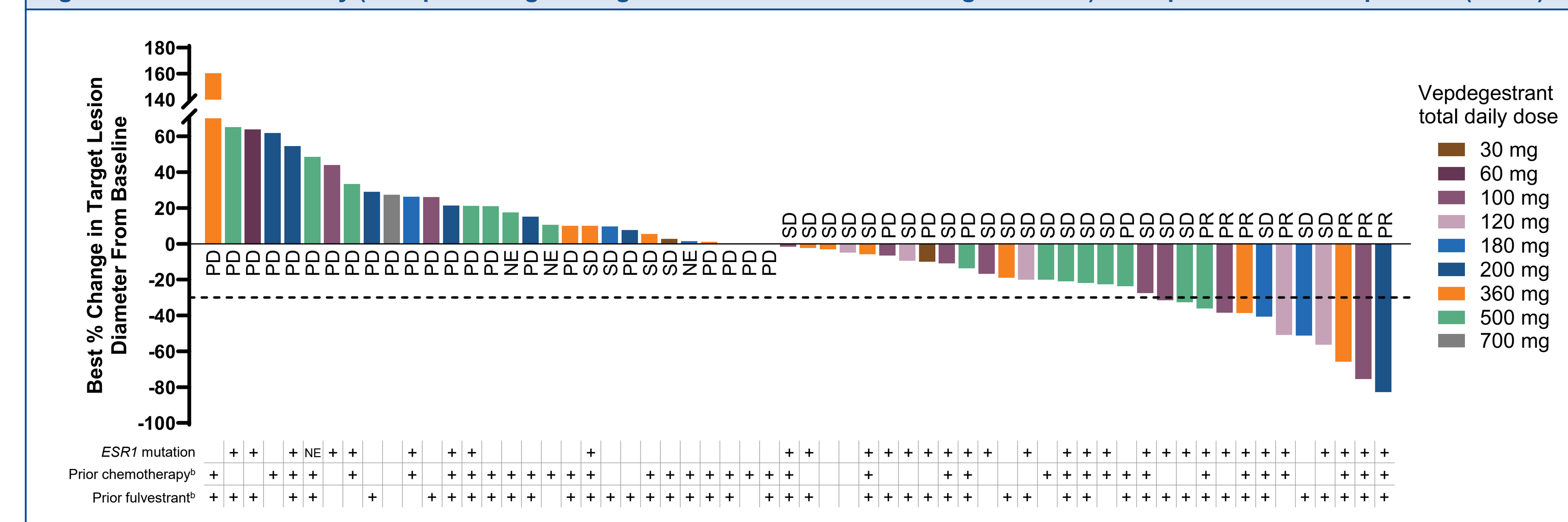
Pharmacokinetics

- PK on day 15 showed dose-dependent increases for AUC_{24} and C_{max} from 30 mg to 500 mg total daily dose (**Table 4**)

ctDNA

- After treatment with vepdegestrant 30–700 mg total daily dose for 1 cycle, substantial on-treatment reductions in mutant *ESR1* ctDNA levels were observed after 1 cycle and sustained over multiple cycles (**Figure 3**)

Figure 2: Antitumor activity (best percentage change from baseline in sum of target lesions) in response-evaluable patients (n=60[a])



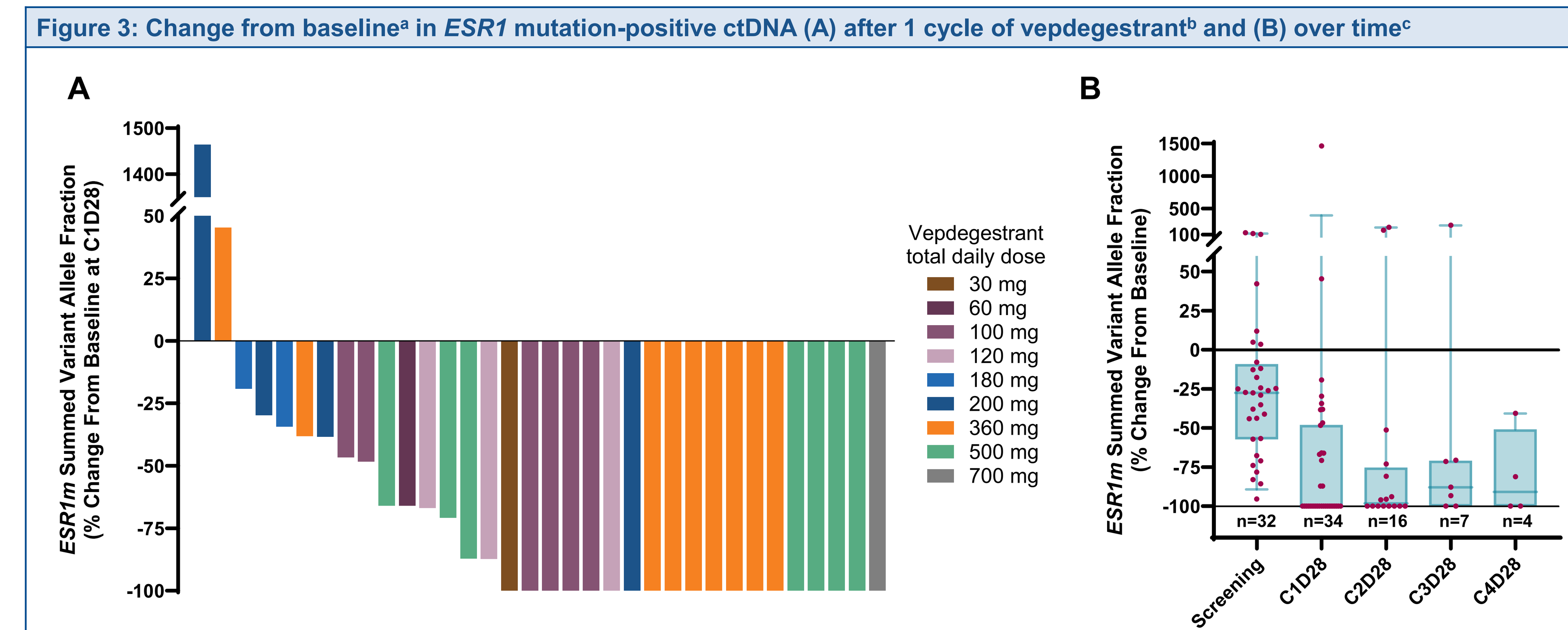
[a]1 patient had baseline measurable disease but was missing postbaseline values. [b]In the metastatic setting
ESR1=estrogen receptor 1 gene; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

Table 4: Vepdegestrant PK parameters on day 15

	Vepdegestrant dose										
								500 mg daily		700 mg daily	
Geometric mean (%CV)	30 mg QD (n=3)	60 mg QD (n=3)	100 mg QD (n=7)	120 mg QD (n=7)	180 mg QD (n=6)	200 mg QD (n=8)	360 mg QD (n=15)	500 mg QD (n=11)	250 mg BID (n=8)	700 mg QD (n=1)	400 mg AM, 300 mg PM (n=2)
AUC_{tau} (ng*h/mL)	4051 (26)	7324 (15)	8898 (39)	13,714 (13)	19,225 (32)	15,459 (34)	25,931 (27)	34,585 (35)	20,559 (34)	26,572[a]	35,360, 14,815[a]
C_{max} (ng/mL)	219 (27)	405 (8)	522 (46)	799 (6)	1062 (27)	866 (40)	1502 (27)	1883 (31)	2058 (34)	1530[a]	3360, 1510[a]

[a]Expressed as individual values when N<3
AUC_{tau}=area under the plasma concentration-time curve during a dosing interval, where tau=24 hours for QD dosing and 12 hours for BID dosing; BID=twice daily; C_{max}=maximum plasma concentration; CV=coefficient of variation; PK=pharmacokinetic; QD=once daily

Figure 3: Change from baseline[a] in *ESR1* mutation-positive ctDNA (A) after 1 cycle of vepdegestrant[b] and (B) over time[c]



[a]Baseline samples were obtained on C1D1 prior to dosing. [b]34 of the 37 patients with *ESR1* mutation-positive ctDNA evaluable samples at baseline had evaluable samples at C1D28. [c]Aggregate data for all patients with *ESR1* mutation-positive ctDNA samples across all doses in the phase 1 dose escalation portion of the study; error bars are the 95% CI, the bottom and top of the box are the 25th and 75th percentiles, and the line is the median
C=cycle; ctDNA=circulating tumor DNA; D=day; *ESR1m*=estrogen receptor 1 gene mutant