2025 ASCO ANNUAL MEETING

Vepdegestrant, a PROTAC ER Degrader, vs Fulvestrant in ER+/HER2- Advanced Breast Cancer: Results of the Global, Randomized, Phase 3 VERITAC-2 Study

Erika P Hamilton[1], Michelino De Laurentiis[2], Komal Jhaveri[3], Xichun Hu[4], Sylvain Ladoire[5], Anne Patsouris[6], Claudio Zamagni[7], Jiuwei Cui[8], Marina Cazzaniga[9], Timucin Cil[10], Katarzyna Jerzak[11], Christian Fuentes[12], Tetsuhiro Yoshinami[13], Alvaro Rodriguez-Lescure[14], Olga Valota[15], Dongrui R Lu[16], Marcella Martignoni[15], Janaki Parameswaran[17], Xin Zhi[17], Mario Campone[18]

[1]Breast Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN, USA; [2]Istituto Nazionale Tumori IRCCS “Fondazione G. Pascale", Naples, Italy; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Shanghai Cancer Center, Fudan University, Shanghai, China; [5]Centre Georges Francois Leclerc, Dijon, France; [6]Institut de Cancérologie de l'Ouest, Angers, France; [7]IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy; [8]The First Hospital of Jilin University, Changchun, China; [9]Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [10]Health and Science University, Adana City Hospital, Adana, Turkey; [11]Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; [12]Fundación Respirar, Buenos Aires, Argentina; [13]Graduate School of Medicine, Osaka University, Osaka, Japan; [14]Hospital General Universitario de Elche, Elche, Spain; [15]Pfizer, Inc., Milan, Italy; [16]Pfizer, Inc., San Diego, CA, USA; [17]Arvinas Operations, Inc., New Haven, CT, USA; [18]Institut de Cancérologie de l’Ouest Angers-Nantes, Angers, France

Key Takeaways

Vepdegestrant is the first PROTAC to be evaluated in a phase 3 study

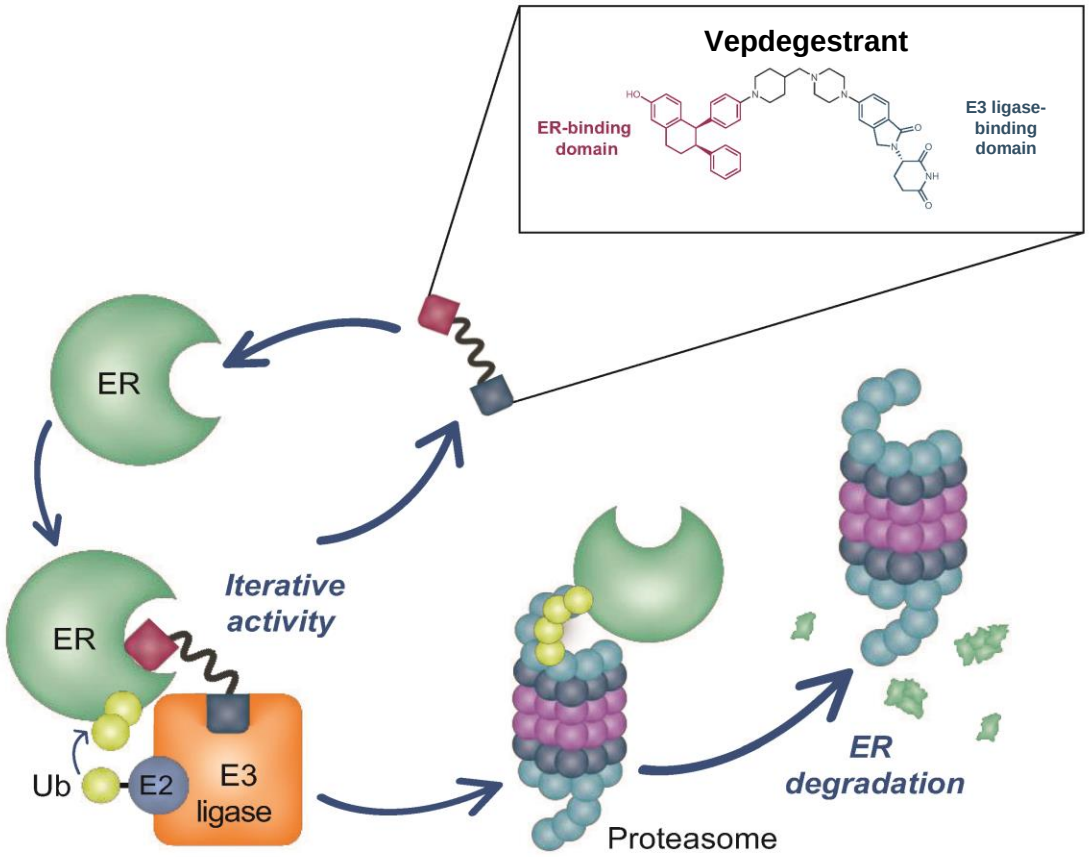
Oral vepdegestrant was well tolerated and demonstrated statistically significant and clinically meaningful improvement in PFS vs fulvestrant in patients with *ESR1*m

Results of the phase 3 VERITAC-2 study support vepdegestrant as a potential treatment option for previously treated *ESR1*m ER+/HER2- advanced breast cancer

*ESR1*m=estrogen receptor 1 gene mutation; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; PFS, progression-free survival; PROTAC=PROteolysis TArgeting Chimera.

Background

- There is no established consensus for treatment of ER+/HER2- advanced breast cancer after progression on first-line ET[1]
- Fulvestrant, a SERD that is administered IM due to poor solubility,[2] has limited PFS benefit following disease progression on a CDK4/6i + ET[3,4]
- Vepdegestrant is a selective, oral PROTAC ER degrader that targets WT and mutant ER[5,6]
- In a first-in-human, phase 1/2 study (NCT04072952), vepdegestrant was well tolerated and demonstrated encouraging clinical activity in heavily pretreated patients with ER+/HER2- advanced breast cancer[7]



Vepdegestrant has a unique MOA that directly harnesses the ubiquitin-proteasome system to degrade ER[8]

CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; IM=intramuscularly; MOA=mechanism of action; PROTAC=PROteolysis TArgeting Chimera; SERD=selective estrogen receptor degrader; Ub=ubiquitin; WT=wild type.

1. Al Sukhun S, et l. *JCO Glob Oncol*. 2024;10:e2300285. 2. Nathan MR, Schmid P. Oncol Ther. 2017;5(1):17-29. 3. Lindeman GJ, et al. Clin Cancer Res. 2022;28(15):3256-67. 4. Bidard FC, et al. J Clin Oncol. 2022;40(28):3246-3256. 5. Békés M, et al. Nat Rev Drug Discov 2022;21(3):181-200. 6. Gough SM, et al. *Clin Cancer Res*. 2024;30(16):3549-3563. 7. Hurvitz SA, et al. SABCS. 2023; PO3-05-08. 8. Hamilton EP, et al. Futur Oncol. 2024;20(32):2447–55.

VERITAC-2: Global Phase 3 Trial of Vepdegestrant

Key Eligibility Criteria

- Age ≥18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 months
  - No prior SERD (eg, fulvestrant, elacestrant)
  - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

Vepdegestrant (n=313)
200 mg orally (once daily)

Fulvestrant (n=311)
500 mg IM
(days 1 and 15 of cycle 1; day 1 of subsequent cycles)

Stratification Factors:
- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

Primary Endpoint:
- PFS by BICR in
  - *ESR1*m population
  - All patients

Secondary Endpoints:
- OS (key secondary)
- CBR and ORR by BICR
- AEs

Data cutoff date: Jan 31, 2025
Clinicaltrials.gov: NCT05654623

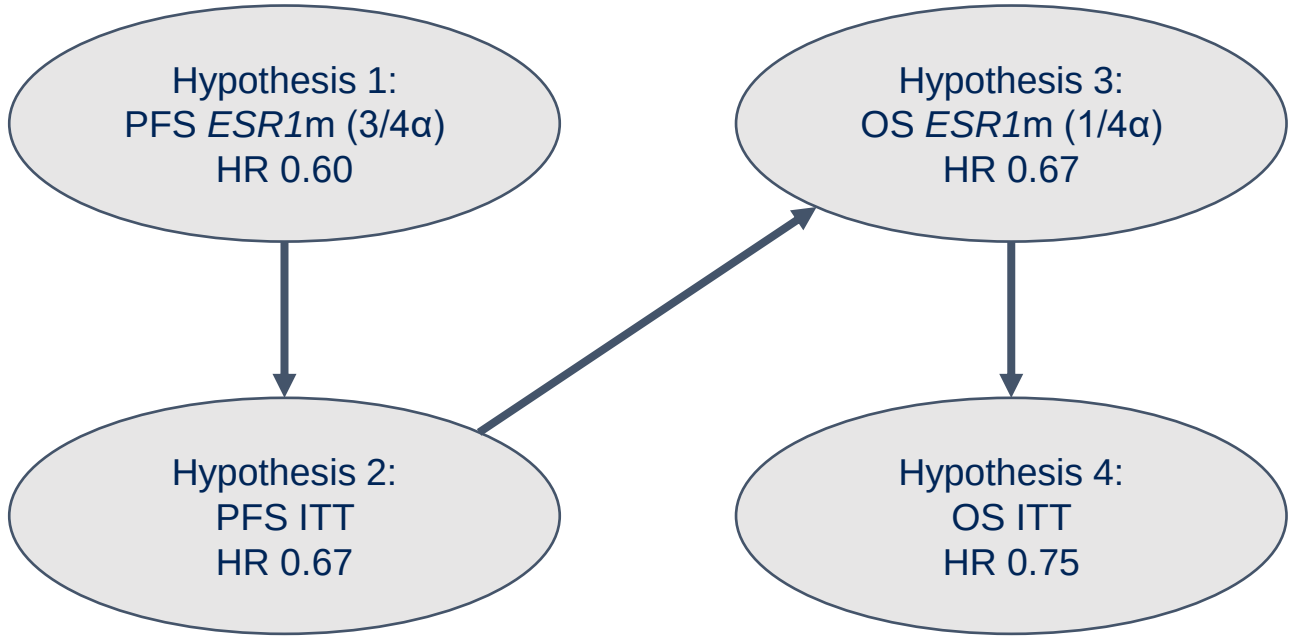
[a]*ESR1*m status was assessed in ctDNA by Foundation Medicine, except in China, where Origmed testing was used.
AE=adverse event; BICR=blinded independent central review; CBR=clinical benefit rate; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; *ESR1*m=estrogen receptor 1 gene mutation; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; IM=intramuscularly; ORR=objective response rate; OS=overall survival; PFS=progression-free survival, SERD=selective estrogen receptor degrader.

VERITAC-2: Statistical Hypothesis Testing Strategy

- Primary endpoint: PFS by BICR
- Key secondary endpoint: OS

- Test in 2 populations:
  - Patients with *ESR1*m
    - HR<0.60 with 88% power
  - All patients (ITT)
    - HR<0.67 with 92.5% power

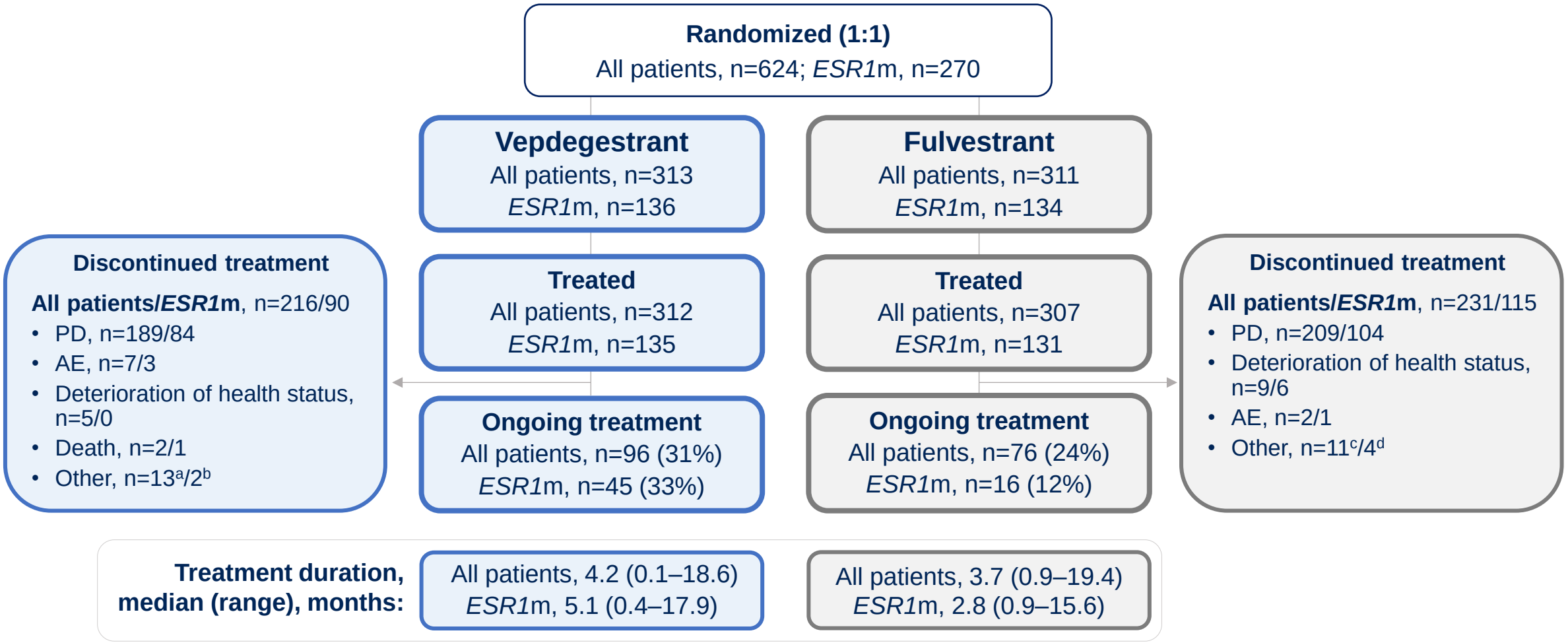
Graphical Multiple Testing Strategy With a Gatekeeping Procedure



Full amount of α is passed from one hypothesis test to the next when the test is positive

BICR=blinded independent central review; *ESR1m*=estrogen receptor 1 gene mutation; HR=hazard ratio; ITT=intention-to-treat; OS=overall survival; PFS=progression-free survival.

VERITAC-2: Patient Disposition



Data cutoff date: January 31, 2025

AE=adverse event; *ESR1m*=estrogen receptor 1 gene mutation; PD=progressive disease.

[a]Other reasons included withdrawal by patient (n=9), physician's decision (n=2), and protocol deviation (n=2). [b]Withdrawal by patient (n=2). [c]Withdrawal by patient (n=7), physician's decision (n=3), and other (n=1). [d]Withdrawal by patient (n=3) and physician's decision (n=1).

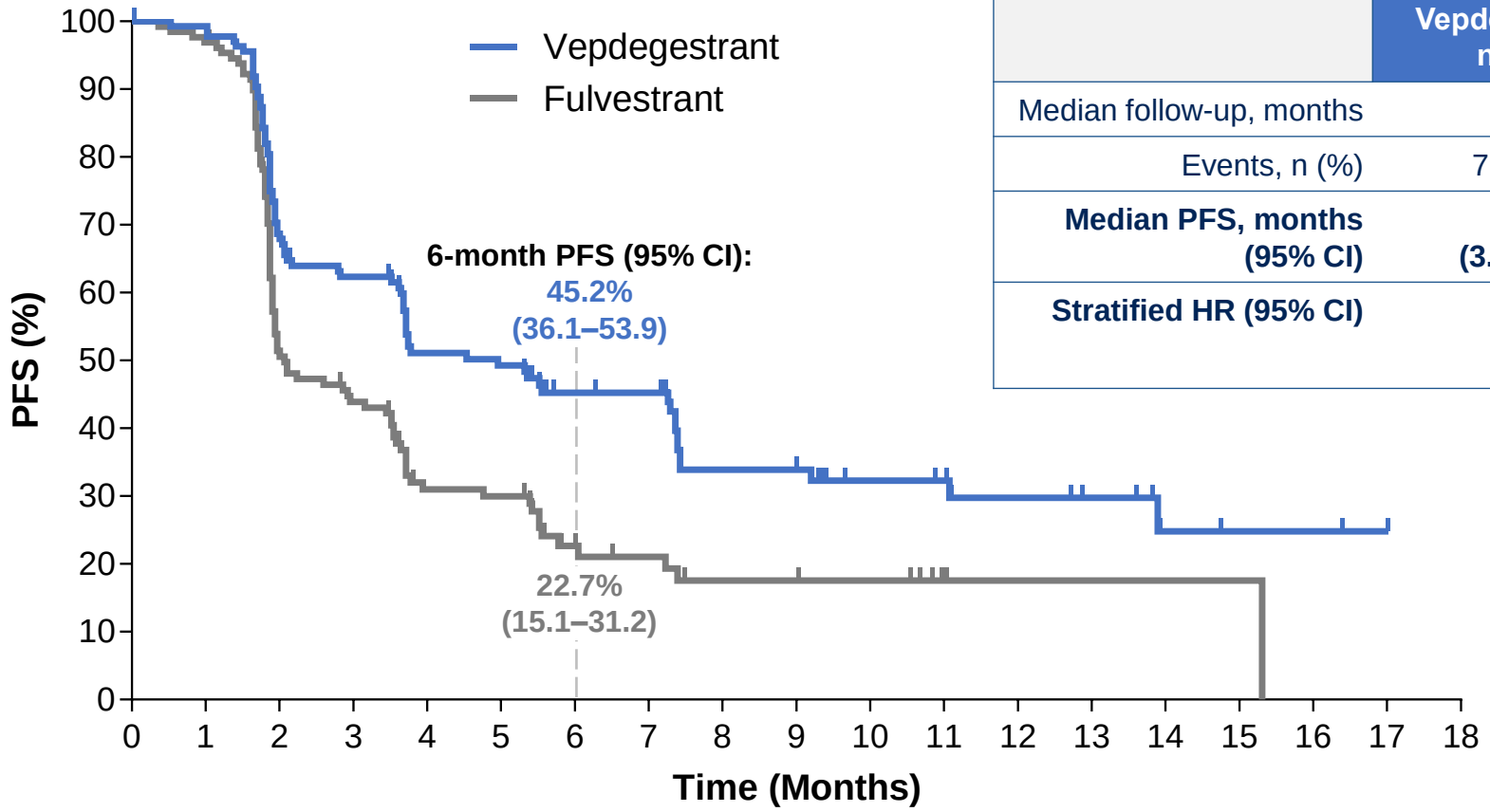
VERITAC-2: Baseline Characteristics

Characteristic	Patients With *ESR1*m		All Patients	
	Vepdegestrant (n=136)	Fulvestrant (n=134)	Vepdegestrant (n=313)	Fulvestrant (n=311)
Median age (range), y	60 (26–87)	60 (34–85)	60 (26–89)	60 (28–85)
Female, %	99	100	99	100
Postmenopausal, %	79	79	78	78
Race, %				
White	43	51	47	46
Black or African American	3	4	2	2
Asian	45	37	39	41
Unknown/NR	9	7	12	9
ECOG PS, %				
0	57	57	61	64
1	43	43	39	36
*ESR1*m, %[a]	100	100	43	43
Sites of disease, %				
Visceral disease	68	68	63	63
Liver metastasis	46	44	40	36
Bone-only disease	18	18	18	20

Characteristic, %	Patients With *ESR1*m		All Patients	
	Vepdegestrant (n=136)	Fulvestrant (n=134)	Vepdegestrant (n=313)	Fulvestrant (n=311)
Measurable disease[b]	71	75	71	71
Prior lines of therapy in advanced/metastatic setting[c]				
1	82	80	82	76
2	18	20	18[d]	23[d]
Prior endocrine therapy	100	100	100	100[e]
Aromatase inhibitor	99	100	99	99
SERM	15	16	16	20
Prior CDK4/6 inhibitor	100	100	100	100
Palbociclib	50	54	46	52
Ribociclib	38	28	36	31
Abemaciclib	16	25	20	21
Other[f]	1	5	4	4

CDK4/6=cyclin-dependent kinase 4/6; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*m=estrogen receptor 1 gene mutation; NR=not reported; SERD= selective estrogen receptor degrader; SERM=selective estrogen receptor modulator.
[a]*ESR1*m status was assessed in pretreatment circulating tumor DNA. [b]Measurable disease assessed by blinded independent central review using Response Evaluation Criteria for Solid Tumors v1.1. [c]Disease progression during or within 12 months from the end of adjuvant therapy was counted as a line of therapy in the advanced/metastatic setting. [d]1 additional patient in the vepdegestrant group and 3 additional patients in the fulvestrant group received 3 prior lines of therapy. [e]1 patient received a prior SERD. [f]Other CDK4/6 inhibitors included birociclib, dalpiciclib, lerociclib.

VERITAC-2 Primary Endpoint: PFS by BICR in Patients With *ESR1*m



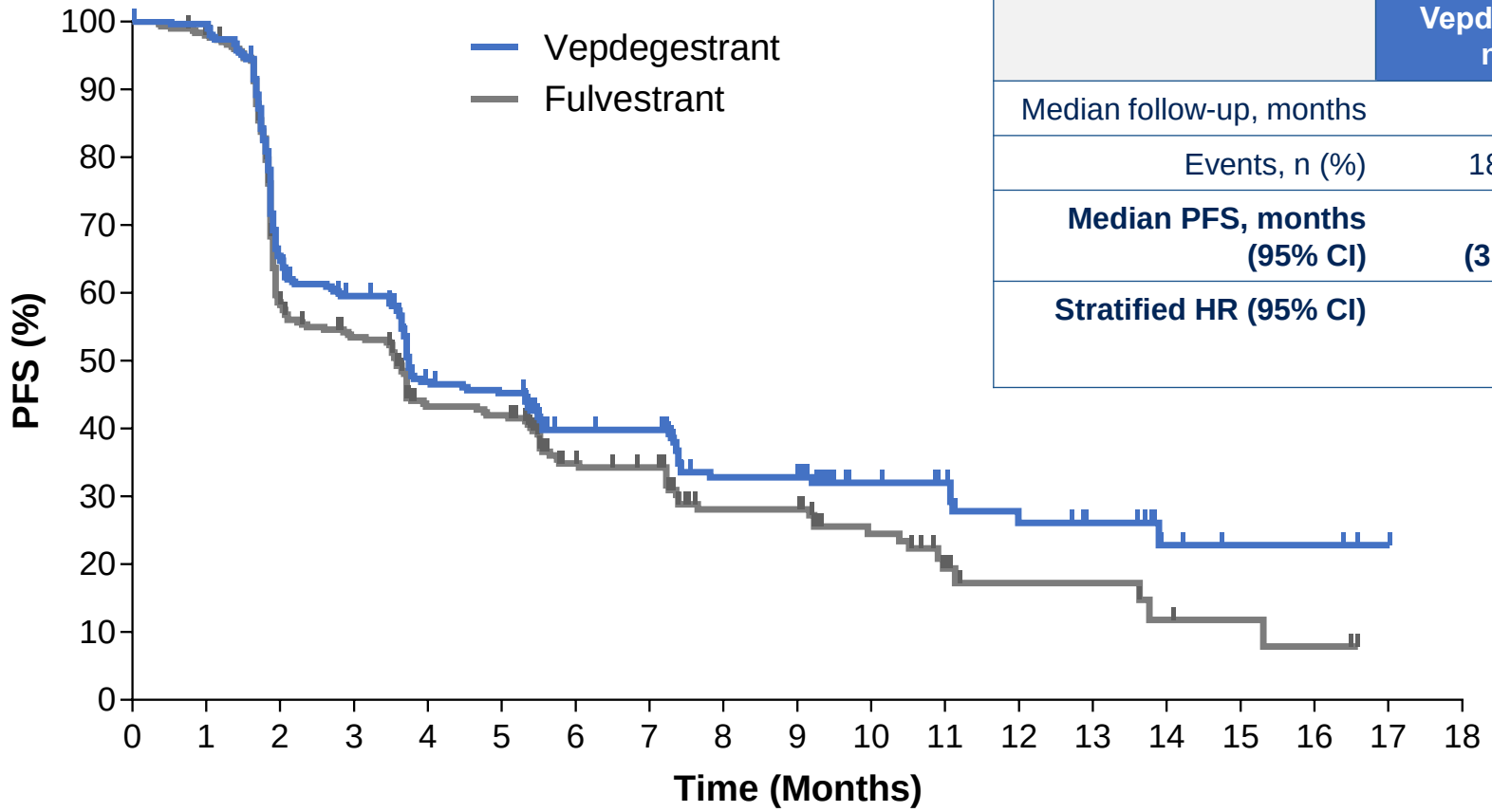
	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P*<0.001	

No. at risk

Vepdegestrant	136	134	87	78	55	53	38	37	22	22	15	14	10	8	4	3	3	2	0
Fulvestrant	134	125	62	52	30	29	15	12	8	8	7	2	1	1	1	1	0	0	0

BICR=blinded independent central review; *ESR1m*=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival.

VERITAC-2 Primary Endpoint: PFS by BICR in All Patients



	Vepdegestrant n=313	Fulvestrant n=311
Median follow-up, months	7.4	7.2
Events, n (%)	186 (59)	198 (64)
Median PFS, months (95% CI)	**3.7 (3.6–5.3)**	**3.6 (2.2–3.8)**
Stratified HR (95% CI)	**0.83 (0.68–1.02)**	
	2-sided *P*=0.07	

No. at risk

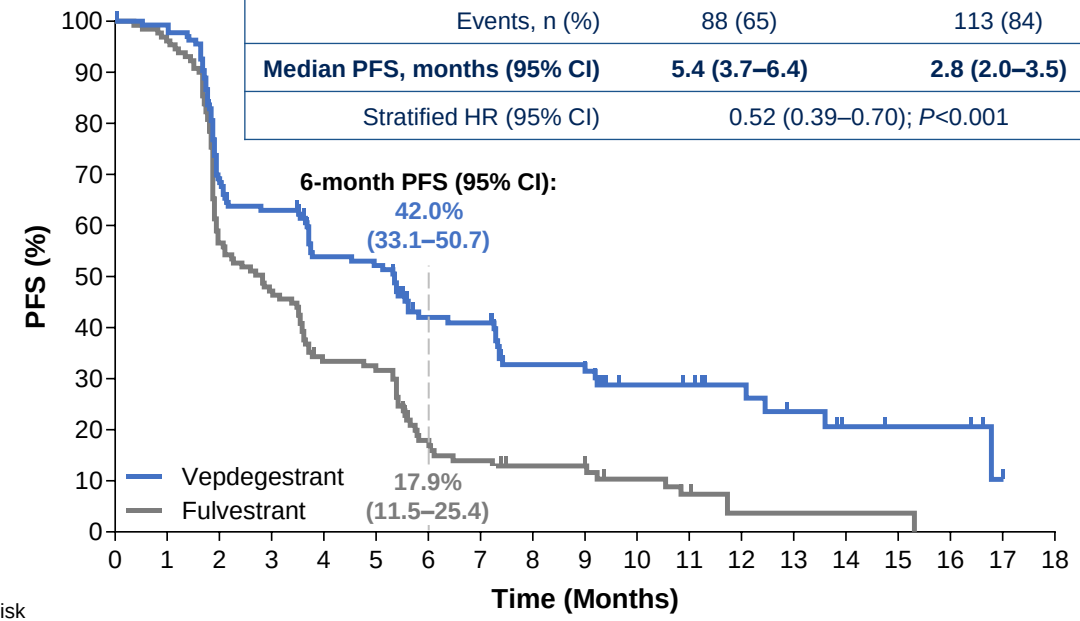
Vepdegestrant	313	306	189	168	113	108	74	72	46	46	28	24	15	12	6	4	4	2	0
Fulvestrant	311	292	162	143	101	98	58	54	36	36	23	12	7	7	4	3	2	0	0

BICR=blinded independent central review; HR=hazard ratio; PFS=progression-free survival.

VERITAC-2: Investigator-Assessed PFS

Patients With *ESR1*m

	Vepdegestrant n=136	Fulvestrant n=134
Events, n (%)	88 (65)	113 (84)
Median PFS, months (95% CI)	**5.4 (3.7–6.4)**	**2.8 (2.0–3.5)**
Stratified HR (95% CI)	0.52 (0.39–0.70); *P*<0.001	

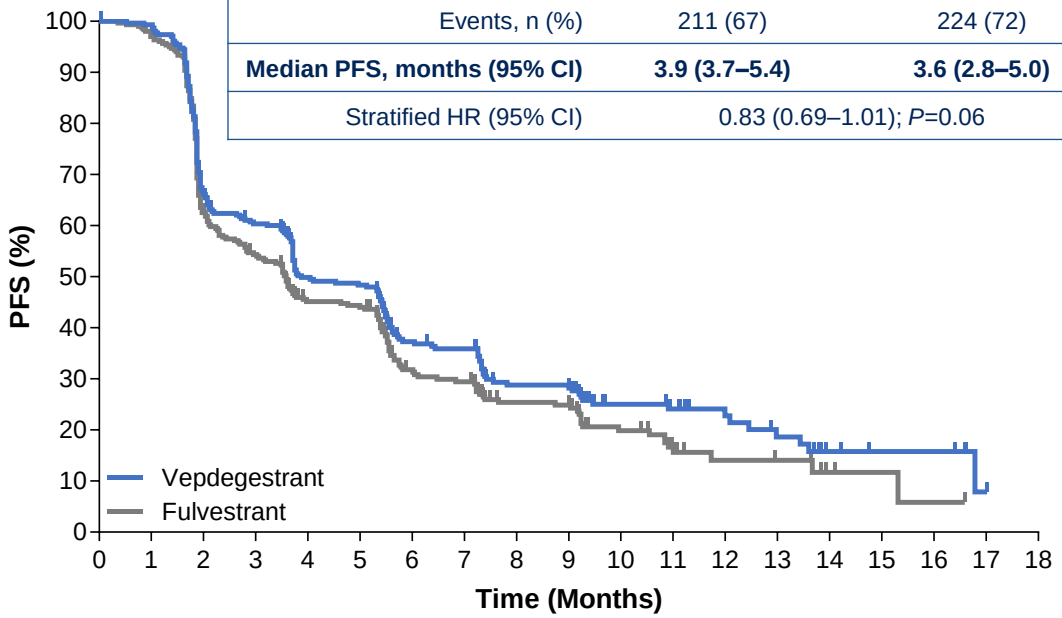


No. at risk

Vepdegestrant	136	134	90	81	64	62	39	38	26	26	16	15	11	8	5	4	4	1	0
Fulvestrant	134	125	72	60	38	36	18	14	11	11	7	4	1	1	1	1	0	0	0

All Patients

	Vepdegestrant n=313	Fulvestrant n=311
Events, n (%)	211 (67)	224 (72)
Median PFS, months (95% CI)	**3.9 (3.7–5.4)**	**3.6 (2.8–5.0)**
Stratified HR (95% CI)	0.83 (0.69–1.01); *P*=0.06	

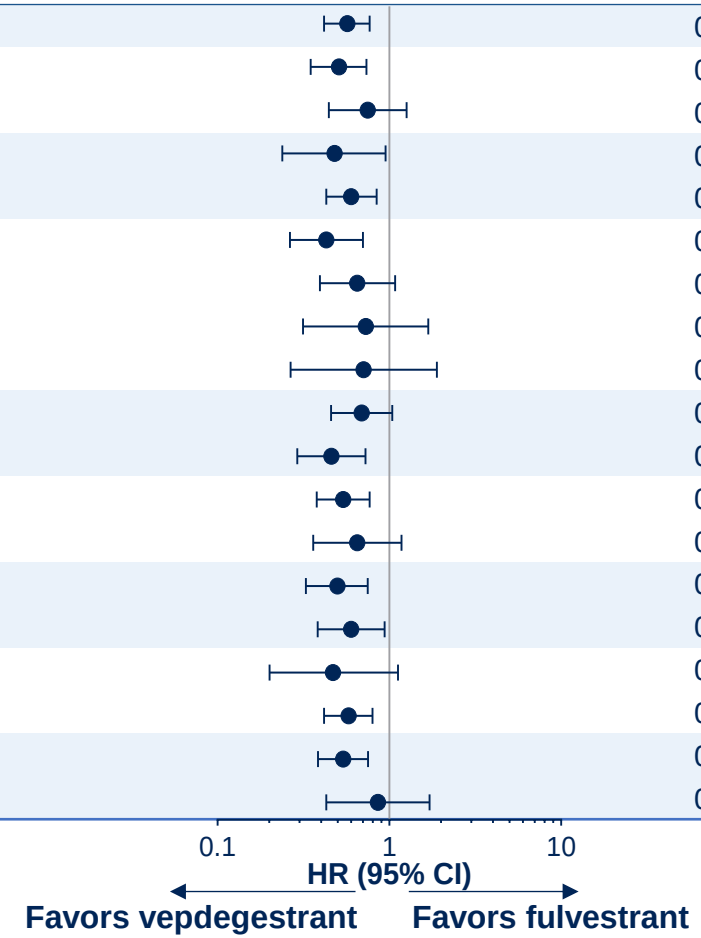


Vepdegestrant	313	304	200	177	133	129	80	76	51	51	29	25	17	13	7	5	5	1	0
Fulvestrant	311	293	184	158	117	114	67	62	46	45	27	16	9	8	3	2	1	0	0

ESR1m=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival.

VERITAC-2 Subgroup Analyses: PFS by BICR in Patients With *ESR1*m

Subgroup		Events/n Vepdegestrant	Events/n Fulvestrant	HR (95% CI)
All patients (stratified)		79/136	95/134	0.57 (0.42–0.77)
Age, years	<65	50/86	66/88	0.51 (0.35–0.74)
	≥65	29/50	29/46	0.75 (0.45–1.26)
Menopausal status	Pre/perimenopausal	14/28	20/28	0.48 (0.24–0.95)
	Postmenopausal	65/108	75/106	0.60 (0.43–0.85)
Geographic region	Asia	32/56	38/50	0.43 (0.26–0.70)
	Europe	25/41	39/56	0.65 (0.40–1.08)
	North America	13/20	10/16	0.73 (0.32–1.69)
	Other	9/19	8/12	0.71 (0.27–1.89)
ECOG PS	0	46/78	49/76	0.69 (0.46–1.04)
	1	33/58	46/58	0.46 (0.29–0.73)
Visceral disease	Yes	59/92	69/91	0.54 (0.38–0.77)
	No	20/44	26/43	0.65 (0.36–1.18)
Liver disease	Yes	45/63	49/59	0.50 (0.33–0.75)
	No	34/73	46/75	0.60 (0.38–0.94)
Bone-only disease	Yes	8/25	15/24	0.47 (0.20–1.23)
	No	71/111	80/110	0.58 (0.42–0.80)
Lines of prior therapy	1	65/112	76/107	0.54 (0.39–0.75)
	2	14/24	19/27	0.86 (0.43–1.72)



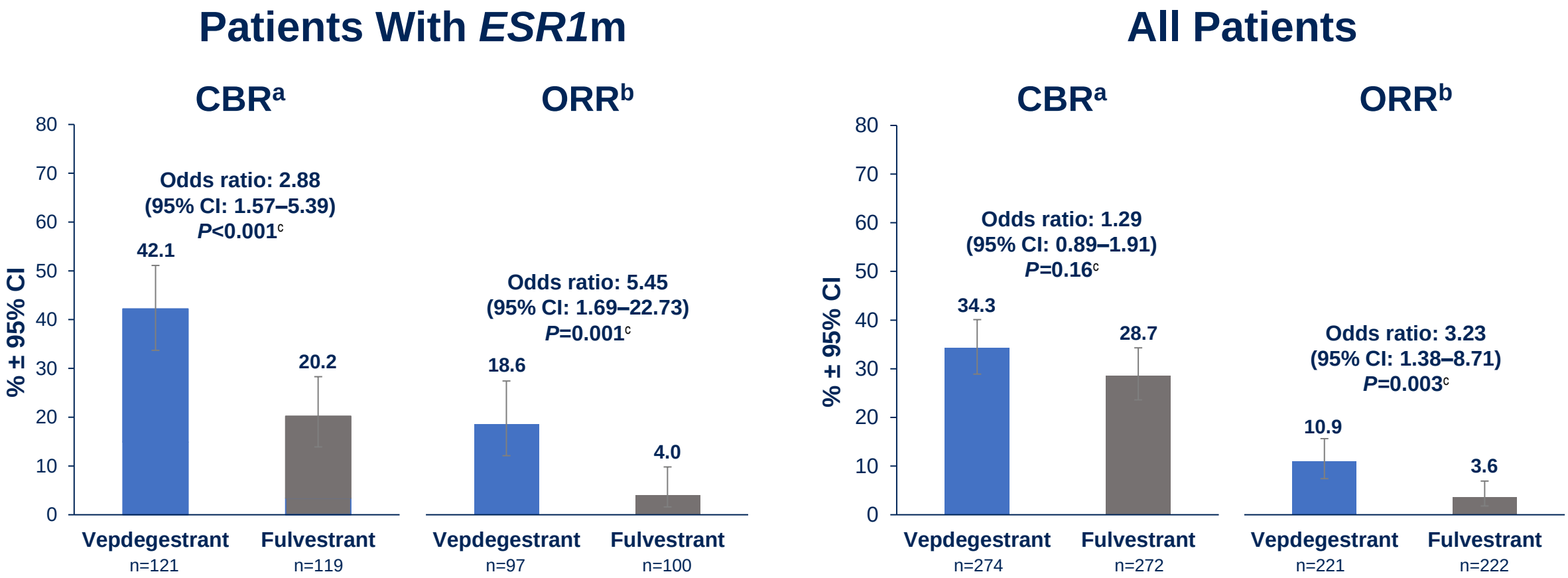
BICR=blinded independent central review; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*m=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival.

Key Secondary Endpoint: OS (Interim)

- OS was immature at data cutoff
- Deaths occurred in 43 patients with *ESR1*m and 80 patients overall, representing 22% and 20% of targeted events, respectively

ESR1m=estrogen receptor 1 gene mutation; OS=overall survival.

Secondary Endpoints: CBR and ORR by BICR



BICR=blinded independent central review; CBR=clinical benefit rate; CR=complete response; *ESR1*m=estrogen receptor gene 1 mutation; ORR=objective response rate; PR=partial response; SD=stable disease.
[a]CBR was defined as the rate of confirmed CR or PR at any time, or SD, non-CR, or non-progressive disease for ≥24 weeks and was estimated in CBR-evaluable patients (those enrolled for ≥24 weeks prior to data cutoff or those with confirmed CR or PR).
[b]ORR was defined as the rate of confirmed CR or PR and was estimated in patients with measurable disease at baseline.
[c]Nominal p-value.

VERITAC-2: Safety and Tolerability (All Treated Patients)

Overview

TEAEs, %	Vepdegestrant (n=312)	Fulvestrant (n=307)
Any grade	87	81
Grade ≥3	23	18
Serious	10	9
Leading to treatment discontinuation	3	1
Leading to dose reduction	2	NA
TRAEs, %		
Any grade	57	40
Grade ≥3	8	3

QT prolongation

- TEAEs: vepdegestrant,10%; fulvestrant, 1%
- A QT interval sub-study (n=88) confirmed a mild increase (11.1 ms) from baseline in mean QTcF, with upper 90% CI (13.7 ms) <20 ms,[f] **indicating no large QT-prolonging effect**

TEAEs in >10% of Patients in Either Group

TEAE, %	Vepdegestrant (n = 312)		Fulvestrant (n = 307)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Fatigue[a]	27	1	16	1
ALT increased[b]	14	1	10	1
AST increased[b]	14	1	10	3
Nausea	13	0	9	1
Anemia[b, c]	12	2	8	3
Neutropenia[d]	12	2[e]	5	1[e]
Back pain	11	1	7	<1
Arthralgia	11	1	11	0
Decreased appetite	11	<1	5	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GI=gastrointestinal; QTcF=corrected QT interval using Fridericia's method; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.
[a]Includes fatigue and asthenia. [b]No between-group differences were observed for ALT/AST increases or anemia based on laboratory values. [c]Includes anemia, hemoglobin decreased, and iron deficiency anemia. [d]Includes neutropenia and neutrophil count decreased. No events led to dose reductions or treatment discontinuation in either treatment group. There were no events of febrile neutropenia in the vepdegestrant group and 1 event of grade 2 febrile neutropenia in the fulvestrant group. [e]1 patient with grade 4 event. [f]Based on a concentration-QTc population modeling analysis.

PRESENTED BY: Erika P Hamilton, MD

Conclusions

- Vepdegestrant is the first PROTAC to be evaluated in a phase 3 study
- Oral vepdegestrant demonstrated statistically significant and clinically meaningful improvement in PFS by BICR vs fulvestrant in patients with *ESR1*m ER+/HER2- advanced breast cancer
- OS analyses remain immature, and follow-up is ongoing
- Vepdegestrant demonstrated a favorable safety profile, evidenced by few AEs (<5%) leading to dose reduction or discontinuation

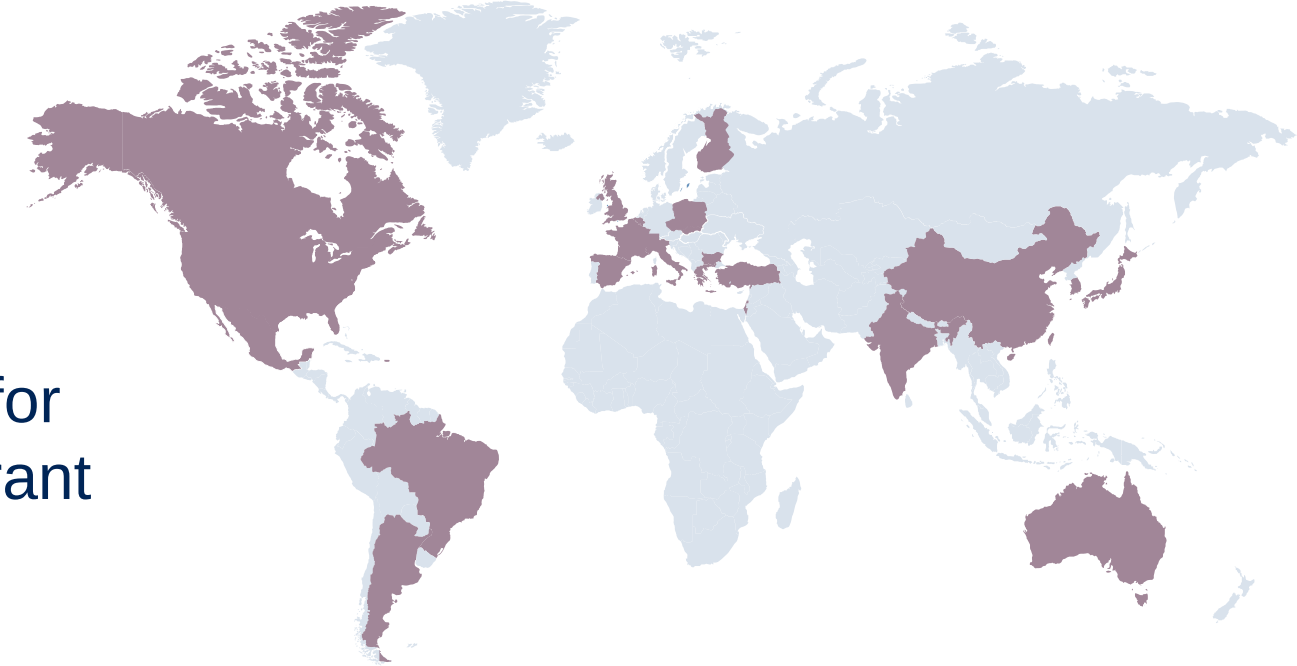
These results support vepdegestrant as a potential treatment option for previously treated *ESR1*m ER+/HER2- advanced breast cancer

AE=adverse event; BICR=blinded independent central review; ER=estrogen receptor; *ESR1*m=estrogen receptor 1 gene mutation; OS=overall survival; PFS=progression-free survival; PROTAC=PROteolysis TArgeting Chimera.

Acknowledgments

- We thank the patients who participated in this study and their caregivers
- We thank all investigators, researchers, and coordinators who contributed to VERITAC-2
- We acknowledge and are grateful for the contributions of the Vepdegestrant Steering Committee

VERITAC-2: Global Phase 3 Trial
Conducted at 213 Sites in 25 Countries



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ORIGINAL ARTICLE

Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in Advanced Breast Cancer

M. Campone,[1] M. De Laurentiis,[2] K. Jhaveri,[3,4] X. Hu,[5] S. Ladoire,[6] A. Patsouris,[7] C. Zamagni,[8] J. Cui,[9] M. Cazzaniga,[10] T. Cil,[11] K.J. Jerzak,[12] C. Fuentes,[13] T. Yoshinami,[14] A. Rodriguez-Lescure,[15] A. Sezer,[16] A. Fontana,[17] V. Guarneri,[18,19] A. Molckovsky,[20] M.-A. Mouret-Reynier,[21] U. Demirci,[22] Y. Zhang,[23] O. Valota,[24] D.R Lu,[25] M. Martignoni,[24] J. Parameswaran,[26] X. Zhi,[26] and E.P. Hamilton,[27] for the VERITAC-2 Study Group*