PD10-03

Subgroup Analyses of VERITAC-2: A Phase 3 Trial of Vepdegestrant, a PROTAC ER Degrader, vs Fulvestrant in ER+/HER2- Advanced Breast Cancer

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 J Jerzak[11], Christian Fuentes[12], Tetsuhiro Yoshinami[13], Alvaro Rodriguez-Lescure[14], Olga Valota[15], Dongrui R Lu[16], Marcella Martignoni[15], Samuel Dychter[16], Michael Lachowicz[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-Saint-Herblain, 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, S.r.l., 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

Objective

- To report subgroup analyses of progression-free survival (PFS) assessed by blinded independent central review (BICR) from the phase 3 VERITAC-2 trial comparing vepdegestrant vs fulvestrant in previously treated patients with estrogen receptor (ER) 1 gene-mutated (*ESR1m*), ER+/human epidermal growth factor receptor 2 (HER2)- advanced breast cancer

Key Findings

- Among 270 patients with *ESR1*m tumors randomized to vepdegestrant (n=136) or fulvestrant (n=134), 21% were pre/perimenopausal, 80% and 61% had received prior cyclin dependent kinase 4/6 inhibitor (CDK4/6i) therapy for ≥12 and ≥18 months, respectively, 45% had liver metastases, and 42% had a *PIK3CA*, *AKT1*, or *PTEN* alteration at baseline
- PFS by BICR was prolonged with vepdegestrant vs fulvestrant across all evaluated subgroups, including:
  - Pre/perimenopausal (hazard ratio [HR; 95% CI] 0.48 [0.24–0.95]) and postmenopausal patients (0.60 [0.43–0.85])
  - Patients treated with prior CDK4/6 inhibitor therapy for <12 months (0.94 [0.48–1.84]), ≥12 months (0.51 [0.37–0.73]), and ≥18 months (0.45 [0.30–0.69])
  - Patients with (0.50 [0.33–0.75]) and without liver metastases (0.60 [0.38–0.94])
  - Patients with (0.70 [0.44–1.12]) and without *PIK3CA*/*AKT1*/*PTEN* alterations (0.54 [0.36–0.80])

Conclusions

- Vepdegestrant was associated with PFS benefit compared with fulvestrant across clinically relevant subgroups of previously treated patients with *ESR1m*, ER+/HER2- advanced breast cancer
- These findings were consistent with the primary analysis of VERITAC-2, which demonstrated statistically significant (HR [95% CI] 0.57 [0.42–0.77]; *P*<0.001) and clinically meaningful improvement in PFS by BICR with vepdegestrant vs fulvestrant in patients with *ESR1m* ER+/HER2- advanced breast cancer[1]
- These analyses provide further information in key prognostic patient subgroups that may inform clinical treatment decisions for patients with *ESR1*m breast cancer

References

1. Campone M, et al. N Engl J Med. 2025;393(6):556-68.
2. Hamilton EP, et al. Target Oncol. 2025;1-14.
3. Gough SM, et al. Clin Cancer Res. 2024;30(16):3549-63.

View a copy of this poster

View a plain language summary of this poster

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 was sponsored by Pfizer, Inc, in collaboration with Arvinas Estrogen Receptor, Inc. Medical writing support was provided by Lela Creutz, PhD, of Arvinas Operations, Inc.

Contact: Erika Hamilton: erika.hamilton@scri.com

San Antonio Breast Cancer Symposium (SABCS)
San Antonio, TX, USA; December 9-12, 2025

Background

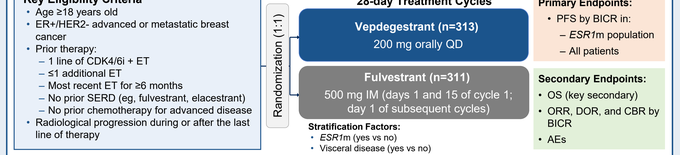
- Vepdegestrant is an oral PROteolysis TArgeting Chimera (PROTAC) ER degrader that directly harnesses the ubiquitin-proteasome system, the primary intracellular protein-disposal machinery[2]
- In contrast to selective ER degraders (eg, fulvestrant, elacestrant, imlunestrant), which are ER antagonists that indirectly lead to ER degradation, vepdegestrant simultaneously binds ER and an E3 ligase, resulting in ubiquitination of the ER protein and its degradation by the proteasome[2,3]
- The phase 3 VERITAC-2 trial is comparing vepdegestrant vs fulvestrant in patients with ER+/HER2- advanced breast cancer previously treated with endocrine therapy plus a CDK4/6i[1]
  - The primary endpoint of VERITAC-2 was met among patients with *ESR1m* tumors, showing statistically significant and clinically meaningful prolongation of PFS by BICR with vepdegestrant vs fulvestrant (median: 5.0 vs 2.1 months; HR [95%CI] 0.57 [0.42–0.77]; *P*<0.001)
  - Vepdegestrant was well tolerated, with low rates of gastrointestinal adverse events (AEs), grade ≥3 AEs, discontinuations, and dose reductions due to AEs
- Here, we report the results of subgroup analyses of PFS among patients with *ESR1*m disease in VERITAC-2

Methods

Study Design

- VERITAC-2 is a global, open-label, randomized phase 3 trial (**Figure 1**)
- The primary endpoint, PFS by BICR, was assessed across clinically relevant subgroups without adjustments for multiplicity
- These analyses were not statistically powered to detect group differences and interpretation is limited by the small sample size within some subgroups
- All subgroups reported here were prespecified analyses, except for prior CDK4/6i therapy duration threshold of 18 months
- The data cutoff date for these analyses was Jan 31, 2025

Figure 1: VERITAC-2 (NCT05654623) study design



AE=adverse event; BICR=blinded independent central review; CBR=clinical benefit rate; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; DOR=duration of response; ER=estrogen receptor; ET=endocrine therapy; *ESR1m*=*ESR1m*=estrogen receptor 1 gene-mutated; HER2=human epidermal growth factor receptor 2; IM=intramuscularly; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QD=once daily, SERD=selective ER degrader.

Results

Patients

- Among 270 patients with *ESR1*m tumors randomized to vepdegestrant (n=136) or fulvestrant (n=134), 21% were premenopausal or perimenopausal, 80% and 61% had received CDK4/6i for ≥12 and ≥18 months, respectively, 45% had liver metastases, and 42% had *PIK3CA/AKT1/PTEN* alterations at baseline (**Table 1**)

Table 1: Baseline characteristics of patients with *ESR1*m tumors

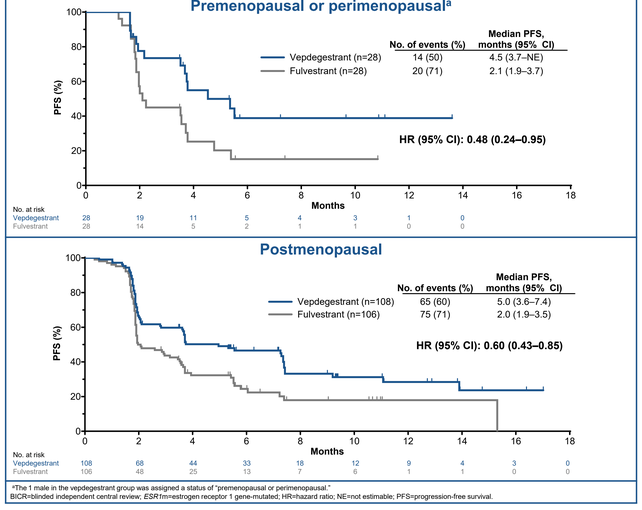
		Vepdegestrant (n=136)	Fulvestrant (n=134)
Median age (range), years		60 (26–87)	60 (34–85)
Female, n (%)		135 (99)[a]	134 (100)
Menopausal status, n (%)	Premenopausal or perimenopausal	28 (21)[a]	28 (21)
	Postmenopausal	108 (79)	106 (79)
Duration of prior CDK4/6i therapy, n (%)	<12 months	31 (23)	22 (16)
	≥12 months	105 (77)	112 (84)
	≥18 months	77 (57)	87 (65)
Liver metastases, n (%)	Yes	63 (46)	59 (44)
	No	73 (54)	75 (56)
PIK3CA, *AKT1*, or *PTEN* alteration, n (%)	Yes	58 (43)	55 (41)
	No	78 (57)	79 (59)

[a]The 1 male in the vepdegestrant group was assigned a status of "premenopausal or perimenopausal."
CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; *ESR1m*=estrogen receptor 1 gene-mutated.

Subgroup analyses of BICR-assessed PFS

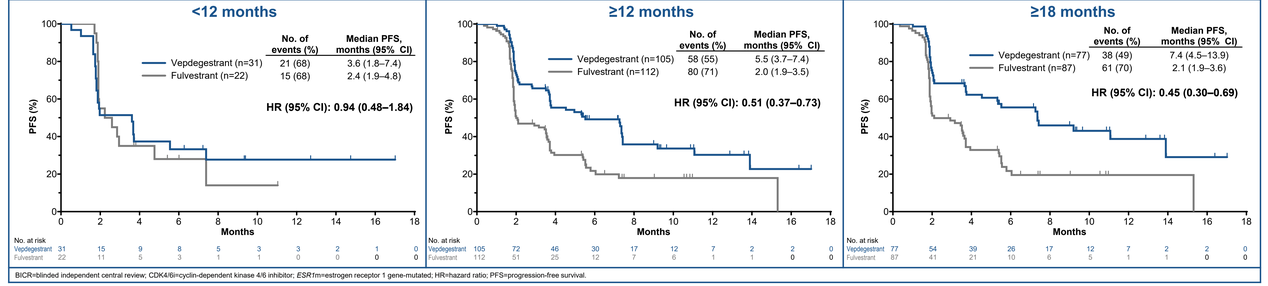
- PFS by BICR was prolonged with vepdegestrant vs fulvestrant across all evaluated subgroups, including pre/perimenopausal and postmenopausal patients (**Figure 2**), patients treated with a CDK4/6i for <12, ≥12, and ≥18 months (**Figure 3**), patients with and without liver metastases (**Figure 4**), and patients with and without *PIK3CA/AKT1/PTEN* mutations (**Figure 5**)

Figure 2: BICR-assessed PFS by menopausal status in patients with *ESR1*m tumors



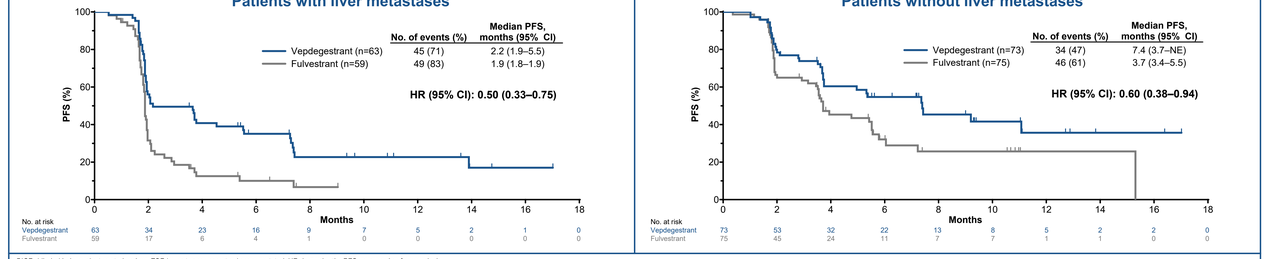
[a]The 1 male in the vepdegestrant group was assigned a status of "premenopausal or perimenopausal."
BICR=blinded independent central review; *ESR1m*=estrogen receptor 1 gene-mutated; HR=hazard ratio; NE=not estimable; PFS=progression-free survival.

Figure 3: BICR-assessed PFS by duration of prior CDK4/6i therapy among patients with *ESR1*m tumors



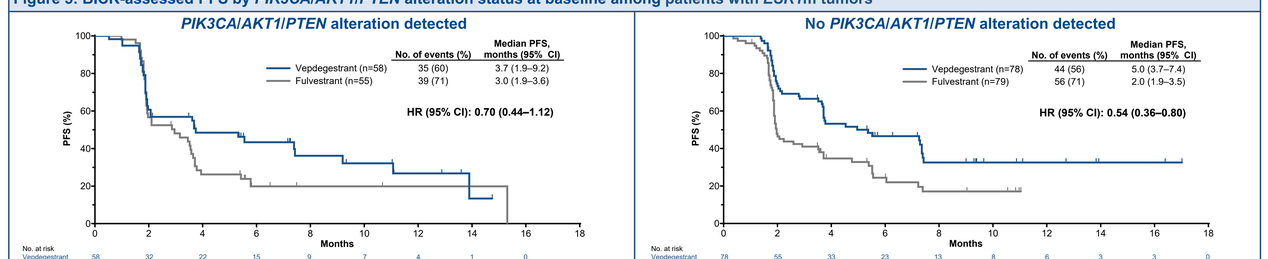
BICR=blinded independent central review; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; *ESR1m*=estrogen receptor 1 gene-mutated; HR=hazard ratio; PFS=progression-free survival.

Figure 4: BICR-assessed PFS by presence or absence of liver metastases at baseline among patients with *ESR1*m tumors



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

Figure 5: BICR-assessed PFS by *PIK3CA/AKT1/PTEN* alteration status at baseline among patients with *ESR1*m tumors



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