

ORIGINAL ARTICLE

Vepdegestrant, a PROTAC Estrogen Receptor Degradar, 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*

ABSTRACT

BACKGROUND

Vepdegestrant is an oral proteolysis-targeting chimera (PROTAC) estrogen receptor (ER) degrader that directly harnesses the ubiquitin–proteasome system.

METHODS

In this phase 3, open-label, randomized trial, we enrolled patients with ER-positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer who had received one previous line of cyclin-dependent kinase 4 and 6 inhibitor therapy plus one line of endocrine therapy (and up to one additional line of endocrine therapy). Patients were randomly assigned in a 1:1 ratio to receive vepdegestrant at a dose of 200 mg orally once every day of each 28-day cycle or fulvestrant at a dose of 500 mg, administered intramuscularly, on day 1 and day 15 of cycle 1 and on day 1 of subsequent cycles, with randomization stratified according to *ESR1*-mutation status and presence or absence of visceral disease. The primary end point was progression-free survival as assessed by blinded independent central review among the patients with *ESR1* mutations and among all the patients who underwent randomization. Progression-free survival was estimated with Kaplan–Meier methods and hazard ratios with a stratified Cox proportional-hazards model.

RESULTS

A total of 624 patients underwent randomization; 313 were assigned to receive vepdegestrant, and 311 to receive fulvestrant. Among the 270 patients with *ESR1* mutations, the median progression-free survival was 5.0 months (95% confidence interval [CI], 3.7 to 7.4) with vepdegestrant and 2.1 months (95% CI, 1.9 to 3.5) with fulvestrant (hazard ratio, 0.58 [95% CI, 0.43 to 0.78]; $P<0.001$). Among all the patients, the median progression-free survival was 3.8 months (95% CI, 3.7 to 5.3) with vepdegestrant and 3.6 months (95% CI, 2.6 to 4.0) with fulvestrant (hazard ratio, 0.83 [95% CI, 0.69 to 1.01]; $P=0.07$). Adverse events of grade 3 or higher occurred in 23.4% of the patients in the vepdegestrant group and in 17.6% of the patients in the fulvestrant group. Adverse events led to treatment discontinuation in 2.9% and 0.7% of the patients, respectively.

CONCLUSIONS

Among patients with ER-positive, HER2-negative advanced breast cancer, vepdegestrant was associated with significantly longer progression-free survival than fulvestrant in the subgroup with *ESR1* mutations but not in the full patient population. (Funded by Pfizer and Arvinas Estrogen Receptor; VERITAC-2 ClinicalTrials.gov number, NCT05654623.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Campone can be contacted at mario.campone@ico.unicancer.fr or at Institut de Cancérologie de l'Ouest Angers-Nantes, Boulevard Professeur Jacques Monod, 44805 Saint-Herblain, France.

*A list of the VERITAC-2 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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CME



ESTROGEN RECEPTOR (ER)-POSITIVE AND human epidermal growth factor receptor 2 (HER2)-negative breast cancer accounts for approximately 70% of breast cancer cases.¹ Standard first-line therapies for ER-positive, HER2-negative advanced breast cancer include endocrine therapy in combination with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors; however, treatment resistance develops and disease progression occurs in most patients.²⁻⁶ Treatment resistance is often driven by genetic mutations, including those in *ESR1*, which occur in approximately 40 to 50% of patients who receive endocrine therapy and a CDK4/6 inhibitor for metastatic disease.^{2,4,7-9}

No consensus on the standard of care for patients who have disease progression while they are receiving endocrine-based therapy has been established. Treatment is determined on the basis of several factors, such as previous therapies, patient preference, and tumor genomics.^{6,10-13} Sequential endocrine-based therapy remains a key approach in patients with disease progression and presumed endocrine sensitivity; however, current therapies have limitations. Fulvestrant, a first-in-class selective ER degrader, has poor solubility and must be administered intramuscularly, which limits the volume and dose.¹⁴ Several targeted therapies are approved for patients who have disease progression while they are receiving endocrine therapy, including elacestrant for *ESR1*-mutated, ER-positive, HER2-negative disease; capivasertib plus fulvestrant for patients with alterations in *PIK3CA*, *AKT1*, *PTEN*, or any combination of these genes; and alpelisib plus fulvestrant for *PIK3CA*-mutated disease.¹⁵⁻¹⁷ However, these agents can be associated with burdensome adverse events such as gastrointestinal symptoms with elacestrant and hyperglycemia, cutaneous reactions, and diarrhea with capivasertib and alpelisib.¹⁵⁻¹⁷

Vepdegestrant (ARV-471) is an oral proteolysis-targeting chimera (PROTAC) ER degrader that directly harnesses the ubiquitin-proteasome system, the primary intracellular protein-disposal mechanism.¹⁸ In contrast to selective ER degraders, which are ER antagonists that lead indirectly to ER degradation,¹⁹⁻²¹ vepdegestrant simultaneously binds ER and an E3 ligase, forming a ternary complex that results in direct polyubiquitination of ER and its degradation by the proteasome.^{18,22} Vepdegestrant was shown to degrade wild-type

and mutant ER in vitro and to lead to more robust ER degradation and tumor growth inhibition than fulvestrant in xenograft models.²² In a first-in-human phase 1-2 study, vepdegestrant monotherapy showed encouraging clinical activity in patients who had received multiple previous lines of treatment for ER-positive, HER2-negative advanced breast cancer.²³

Here, we present the primary analysis of VERITAC-2, a phase 3 clinical trial assessing the efficacy and safety of vepdegestrant as compared with fulvestrant in patients with ER-positive, HER2-negative advanced breast cancer who had previously received endocrine therapy and a CDK4/6 inhibitor.

METHODS

TRIAL DESIGN

VERITAC-2 is a phase 3, multinational, open-label, randomized trial.²⁴ Patients with ER-positive, HER2-negative advanced or metastatic breast cancer were randomly assigned in a 1:1 ratio to receive vepdegestrant at a dose of 200 mg administered orally once every day of each 28-day cycle or fulvestrant at a dose of 500 mg administered intramuscularly on day 1 and day 15 of cycle 1 and on day 1 of subsequent cycles (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.). Randomization was performed centrally with the use of interactive response technology, with stratification according to *ESR1*-mutation status (yes or no) and the presence or absence of any visceral disease (lung, liver, brain, pleural, or peritoneal involvement).

PATIENTS

Patients were eligible to enroll in the trial if they were 18 years of age or older and had a confirmed diagnosis of ER-positive, HER2-negative locoregional recurrent or metastatic breast cancer that was not amenable to surgical resection or radiation and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,²⁵ or nonmeasurable bone-only disease. Patients must have received one previous line of CDK4/6 inhibitor therapy plus endocrine therapy (only one previous CDK4/6 inhibitor was allowed regardless of whether it was given as adjuvant therapy or for advanced or metastatic disease); adjuvant therapy was counted as a line



A Quick Take is available at [NEJM.org](https://www.nejm.org)



of therapy in the context of advanced or metastatic disease if disease progression had occurred during or within 12 months after the receipt of this therapy. Up to one additional line of endocrine therapy was permitted. The most recent endocrine therapy must have been received for at least 6 months before progression occurred. Radiologic disease progression must have occurred during or after the receipt of the last line of therapy. Patients were excluded if they had previously received chemotherapy for advanced disease or if they had previously received fulvestrant or elacestrant; phosphatidylinositol 3-kinase, protein kinase B, or mammalian target of rapamycin inhibitors; or investigational agents, including new endocrine therapies. For complete eligibility criteria, see the protocol, available at NEJM.org.

END POINTS

The primary end point was progression-free survival as assessed by blinded independent central review according to RECIST, version 1.1, among patients with *ESR1* mutations and among all the patients. Secondary end points included overall survival (the key secondary end point), objective response (confirmed complete response or partial response) as assessed by blinded independent central review, and safety.

ASSESSMENTS

Tumors were assessed by computed tomography or magnetic resonance imaging at screening, every 8 weeks for 48 weeks, and every 12 weeks thereafter. Full-body bone scans were performed at screening and every 24 weeks, if clinically indicated. *ESR1*-mutation status was determined by sequencing of circulating tumor DNA from pretreatment blood samples. Adverse events were monitored until 28 days after the completion of treatment or before the initiation of new anticancer therapy, whichever came first. A substudy was conducted in a subgroup of patients in the vepdegestrant group to characterize the effect of vepdegestrant on the corrected QT (QTc) interval according to Fridericia's formula (QTcF). Details of the methods can be found in the Supplementary Appendix.

TRIAL OVERSIGHT

This trial was sponsored by Pfizer in collaboration with Arvinas Estrogen Receptor and was conducted in accordance with principles derived from

international guidelines, including the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation guidelines for Good Clinical Practice, and other applicable laws and regulations. The trial protocol was approved by an institutional review board and ethics committee at each site. All the patients provided written informed consent. Data were collected by trial investigators and analyzed by the sponsors. An external data monitoring committee reviewed aggregate safety data. Professional medical writing assistance was provided by Red Nucleus, a medical communications agency, and funded by the sponsors; all the authors contributed to manuscript development and approved the final version of the manuscript for submission. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

To control the familywise type I error rate at 0.05 (two-sided) at the whole trial level, a graphical multiple testing strategy was used to analyze the primary end point and the key secondary end point. Specifically, 75% of the alpha was allocated for the progression-free survival end point, and 25% for the overall survival end point, to test superiority. Within each end point, a gatekeeping procedure was applied in which the analysis was first conducted in the population of patients with *ESR1* mutations who underwent randomization; if the result was positive, the analysis was to be performed in the intention-to-treat population, which comprised all the patients who underwent randomization. If progression-free survival tests were positive in both populations, the 75% alpha was to be reallocated to the overall survival end point, and overall survival would be tested with the full alpha (0.025). Otherwise, the original allocated 25% alpha would be used for overall survival testing.

We estimated that among approximately 280 patients with *ESR1* mutations, 165 events would provide the trial with 88% power to detect a hazard ratio for disease progression or death of less than 0.60 at a two-sided alpha level of 0.0375. We estimated that among approximately 560 patients in the full patient population, 310 events would provide the trial with 92.5% power to detect a hazard ratio of less than 0.67 at a significance level of

0.0375. The final analysis for the primary end point would be performed when the required number of events occurred in both populations.

In accordance with the statistical analysis plan, the prespecified primary analysis of progression-free survival as assessed by blinded independent central review was performed on the basis of a hypothetical strategy, in which the treatment effect was estimated under the hypothetical assumption that all patients continued to receive their randomly assigned treatment and adhered to the protocol (see the Supplementary Methods section in the Supplementary Appendix). A prespecified supplementary treatment policy analysis of the primary end point that included all progression events without censoring for intercurrent events (e.g., missing assessments or a change of therapy) was performed, the results of which are reported here for the primary end point. Results of the protocol-specified primary analysis according to the hypothetical strategy are reported in the Supplementary Appendix. The median progression-free survival and corresponding 95% confidence intervals were estimated with Kaplan–Meier methods. A stratified log-rank test was used to compare progression-free survival between the groups. The hazard ratios and corresponding 95% confidence intervals were estimated with the use of Cox proportional-hazards models; a weighted Schoenfeld residual test showed no significant violation of the proportional-hazards assumption. Progression-free survival (hazard ratios and 95% confidence intervals) was also evaluated in subgroups defined according to prespecified baseline characteristics. All P values were two-sided.

The statistical analysis plan did not correct for multiplicity for additional secondary end points or subgroups; results are shown as point estimates with 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects. For details regarding statistical methods, see the Supplementary Appendix and the statistical analysis plan included with the protocol.

RESULTS

PATIENTS

Between March 3, 2023, and October 30, 2024, a total of 624 patients underwent randomization at 213 sites in 25 countries; 313 patients were

assigned to receive vepdegestrant, and 311 to receive fulvestrant (Fig. S2). Nearly all the patients (99.5%) were women, the median age was 60.0 years, and 63.1% of the patients had visceral disease at baseline. All the patients had previously received therapy for advanced or metastatic disease; 79.0% of the patients had received one line of therapy and 20.4% of the patients had received two lines (Table 1). The baseline characteristics of the patients were similar in the two treatment groups and were generally representative of patients with ER-positive, HER2-negative advanced breast cancer who had previously received treatment with endocrine therapy and a CDK4/6 inhibitor, except that Black patients were underrepresented (Table S1). Overall, 43.3% of the patients (136 in the vepdegestrant group and 134 in the fulvestrant group) had *ESR1* mutations. Baseline characteristics of the patients with *ESR1* mutations were generally consistent with those of the overall population, although bone and liver metastases were slightly more common among the patients with *ESR1* mutations (Table 1).

TREATMENT

As of the data-cutoff date (January 31, 2025), a total of 96 of 313 patients (30.7%) were still receiving vepdegestrant and 76 of 311 patients (24.4%) were still receiving fulvestrant; the most common reason for treatment discontinuation was disease progression (60.4% in the vepdegestrant group and 67.2% in the fulvestrant group) (Fig. S2). The median treatment duration was 4.2 months (range, 0.1 to 18.6) in the vepdegestrant group and 3.7 months (range, 0.9 to 19.4) in the fulvestrant group. Among the patients with *ESR1* mutations, the percentage of patients who were still receiving treatment was 33.1% in the vepdegestrant group and 11.9% in the fulvestrant group, with a median treatment duration of 5.1 months (range, 0.4 to 17.9) and 2.8 months (range, 0.9 to 15.6), respectively.

EFFICACY

The analysis of the primary end point was conducted with the use of the treatment policy strategy after 185 events (disease progression or death) had occurred among the patients with *ESR1* mutations (82 events in the vepdegestrant group and 103 in the fulvestrant group) and after 410 events had occurred among all the patients (198 events

Characteristic	Patients with <i>ESR1</i> Mutations		All Patients	
	Vepdegestrant (N=136)	Fulvestrant (N=134)	Vepdegestrant (N=313)	Fulvestrant (N=311)
Median age (range) — yr	60.0 (26–87)	60.0 (34–85)	60.0 (26–89)	60.0 (28–85)
Female sex — no. (%)	135 (99.3)	134 (100.0)	311 (99.4)	310 (99.7)
Postmenopausal — no. (%)†	108 (79.4)	106 (79.1)	243 (77.6)	242 (77.8)
Race or ethnic group — no. (%)‡				
White	59 (43.4)	69 (51.5)	148 (47.3)	143 (46.0)
Black or African American	4 (2.9)	5 (3.7)	5 (1.6)	6 (1.9)
Asian	61 (44.9)	50 (37.3)	122 (39.0)	129 (41.5)
American Indian or Alaska Native	0	0	1 (0.3)	4 (1.3)
Unknown or not reported	12 (8.8)	10 (7.5)	37 (11.8)	29 (9.3)
ECOG performance-status score — no. (%)§				
0	78 (57.4)	76 (56.7)	190 (60.7)	198 (63.7)
1	58 (42.6)	58 (43.3)	123 (39.3)	113 (36.3)
<i>ESR1</i> mutation — no. (%)¶	136 (100.0)	134 (100.0)	136 (43.5)	134 (43.1)
Visceral disease — no. (%)	92 (67.6)	91 (67.9)	197 (62.9)	197 (63.3)
Sites of metastasis — no. (%)**				
Bone	115 (84.6)	113 (84.3)	243 (77.6)	224 (72.0)
Liver	63 (46.3)	59 (44.0)	125 (39.9)	113 (36.3)
Lymph node	52 (38.2)	47 (35.1)	122 (39.0)	110 (35.4)
Breast	43 (31.6)	45 (33.6)	107 (34.2)	89 (28.6)
Lung	36 (26.5)	38 (28.4)	86 (27.5)	94 (30.2)
Pleura	16 (11.8)	13 (9.7)	23 (7.3)	27 (8.7)
Chest wall	7 (5.1)	11 (8.2)	19 (6.1)	23 (7.4)
Brain	3 (2.2)	2 (1.5)	4 (1.3)	3 (1.0)
Other††	22 (16.2)	19 (14.2)	54 (17.3)	55 (17.7)
Measurable disease — no. (%)‡‡	97 (71.3)	100 (74.6)	221 (70.6)	222 (71.4)
Bone-only disease — no. (%)§§	25 (18.4)	24 (17.9)	56 (17.9)	61 (19.6)
Locoregional disease recurrence — no. (%)	6 (4.4)	3 (2.2)	12 (3.8)	10 (3.2)
Previous lines of therapy for advanced or metastatic disease — no. (%)¶¶				
1	112 (82.4)	107 (79.9)	256 (81.8)	237 (76.2)
2	24 (17.6)	27 (20.1)	56 (17.9)	71 (22.8)
Previous endocrine therapy for advanced or metastatic disease — no. (%)	136 (100.0)	134 (100.0)	313 (100.0)	311 (100.0)
Aromatase inhibitors	135 (99.3)	134 (100.0)	310 (99.0)	309 (99.4)
SERMs	21 (15.4)	22 (16.4)	49 (15.7)	61 (19.6)
Unspecified	1 (0.7)	0	1 (0.3)	0
Previous CDK4/6 inhibitor setting — no. (%)				
Overall	136 (100.0)	134 (100.0)	313 (100.0)	311 (100.0)
As adjuvant therapy	2 (1.5)	1 (0.7)	7 (2.2)	12 (3.9)
For advanced breast cancer	134 (98.5)	133 (99.3)	306 (97.8)	299 (96.1)

Table 1. (Continued.)

Characteristic	Patients with <i>ESR1</i> Mutations		All Patients	
	Vepdegestrant (N=136)	Fulvestrant (N=134)	Vepdegestrant (N=313)	Fulvestrant (N=311)
Previous CDK4/6 inhibitor — no. (%)				
Palbociclib	68 (50.0)	73 (54.5)	143 (45.7)	163 (52.4)
Ribociclib	52 (38.2)	37 (27.6)	113 (36.1)	95 (30.5)
Abemaciclib	22 (16.2)	33 (24.6)	64 (20.4)	65 (20.9)
Other***	2 (1.5)	7 (5.2)	11 (3.5)	12 (3.9)

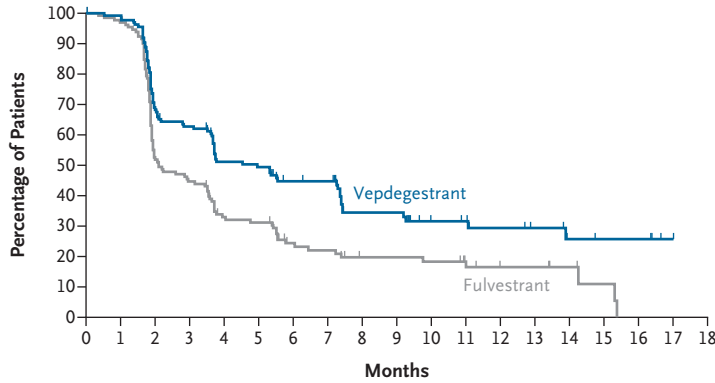
- * Baseline characteristics are reported for all patients who underwent randomization. Randomization was stratified according to *ESR1*-mutation status (yes or no) and the presence or absence of visceral disease. CDK4/6 denotes cyclin-dependent kinase 4 and 6, and SERMs selective estrogen receptor modulators.
- † Three men (two in the vepdegestrant group and one in the fulvestrant group) were assigned a status of “premenopausal or perimenopausal” and were therefore not classified as “postmenopausal.”
- ‡ Race or ethnic group was reported by the patients.
- § The Eastern Cooperative Oncology Group (ECOG) performance-status score ranges from 0 to 5, with higher scores indicating greater disability.
- ¶ *ESR1*-mutation status was assessed by sequencing of circulating tumor DNA from pretreatment blood samples. Samples were analyzed centrally by Foundation Medicine, except for samples from patients in China, which were analyzed by Origimed. For some patients, local laboratory results were used and approved by the sponsor.
- || Visceral disease was defined as the presence of a tumor or lesion in any of the following sites, according to investigator assessment: brain, liver, lung, peritoneum, pleura, or pleural cavity.
- ** Sites of metastasis were determined by the investigator.
- †† The category “Other” includes sites other than the brain that were reported in less than 5% of all the patients.
- ‡‡ Measurable disease was assessed by blinded independent central review with Response Evaluation Criteria for Solid Tumors (RECIST), version 1.1. Eligibility screening for measurable disease was based on investigator assessments. Among all the patients who underwent randomization, 259 patients in the vepdegestrant group and 243 patients in the fulvestrant group had measurable disease at baseline as determined by investigator assessment.
- §§ Bone-only disease was determined by blinded independent central review. Eligibility screening was based on investigator assessment. Among all the patients who underwent randomization, 56 patients in the vepdegestrant group and 74 patients in the fulvestrant group had bone-only disease at baseline as determined by the investigator.
- ¶¶ One additional patient in the vepdegestrant group and three additional patients in the fulvestrant group with protocol deviations received three previous lines of therapy.
- ||| One patient with a protocol deviation received previous treatment with a selective estrogen receptor degrader.
- *** The category “Other” includes birociclib, dalpiciclib, and lerociclib.

in the vepdegestrant group and 212 in the fulvestrant group). Among the patients with *ESR1* mutations, the median follow-up was 7.4 months in the vepdegestrant group and 6.0 months in the fulvestrant group; among all the patients, the median follow-up was 7.4 and 7.2 months, respectively. The median progression-free survival among the patients with *ESR1* mutations was 5.0 months (95% confidence interval [CI], 3.7 to 7.4) in the vepdegestrant group and 2.1 months (95% CI, 1.9 to 3.5) in the fulvestrant group (Fig. 1A). Progression-free survival was significantly longer with vepdegestrant than with fulvestrant among the patients with *ESR1* mutations (hazard ratio for disease progression or death, 0.58 [95% CI, 0.43 to 0.78]; $P < 0.001$). Among all the patients, progression-free survival was not significantly longer with vepdegestrant than with fulvestrant (hazard

ratio, 0.83 [95% CI, 0.69 to 1.01]; $P = 0.07$), with a median progression-free survival of 3.8 months (95% CI, 3.7 to 5.3) with vepdegestrant and 3.6 months (95% CI, 2.6 to 4.0) with fulvestrant (Fig. 1B). These results were consistent with the results of the protocol-specified primary analysis (hypothetical strategy) of progression-free survival (Fig. S3). The results of the prespecified subgroup analyses of progression-free survival among patients with *ESR1* mutations (Fig. 2) and among all the patients (Fig. S4) were similar to the results of the primary analysis. Investigator-assessed progression-free survival (Fig. S5) was consistent with progression-free survival as assessed by blinded independent review.

Data for overall survival were immature; 43 deaths occurred among the patients with *ESR1* mutations and 80 deaths among all the patients,

A Progression-free Survival among Patients with *ESR1* Mutations



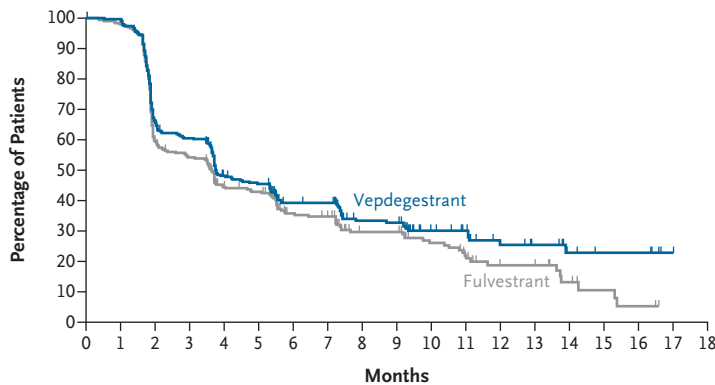
	No. of Events (%)	Median Progression-free Survival <i>mo</i>
Vepdegestrant (N=136)	82 (60.3)	5.0 (3.7–7.4)
Fulvestrant (N=134)	103 (76.9)	2.1 (1.9–3.5)

Hazard ratio for disease progression or death, 0.58 (95% CI, 0.43–0.78)
P<0.001

No. at Risk

Vepdegestrant	136	134	89	80	58	56	41	40	24	24	16	15	11	9	6	5	5	2	0
Fulvestrant	134	128	66	56	37	35	21	19	12	14	13	10	6	6	4	2	0	0	0

B Progression-free Survival among All Patients Who Underwent Randomization



	No. of Events (%)	Median Progression-free Survival <i>mo</i>
Vepdegestrant (N=313)	198 (63.3)	3.8 (3.7–5.3)
Fulvestrant (N=311)	212 (68.2)	3.6 (2.6–4.0)

Hazard ratio for disease progression or death, 0.83 (95% CI, 0.69–1.01)
P=0.07

No. at Risk

Vepdegestrant	313	307	199	180	126	118	84	82	56	55	34	29	17	13	8	6	6	2	0
Fulvestrant	311	297	173	154	115	109	70	66	47	47	33	24	14	14	7	4	2	0	0

Figure 1. Progression-free Survival as Assessed by Blinded Independent Central Review.

Panel A shows the Kaplan–Meier estimates for progression-free survival with vepdegestrant and with fulvestrant among the patients with *ESR1* mutations. The median follow-up was 7.4 months in the vepdegestrant group and 6.0 months in the fulvestrant group. Disease progression occurred in 179 patients (81 patients in the vepdegestrant group and 98 in the fulvestrant group), and death occurred in 6 patients (1 patient in the vepdegestrant group and 5 in the fulvestrant group). Data from 82 patients who were alive and without disease progression at the time of analysis were censored at the time of the patients’ last disease evaluation showing no progression (53 patients in the vepdegestrant group and 29 in the fulvestrant group); data from 3 patients who withdrew consent were also censored (1 in the vepdegestrant group and 2 in the fulvestrant group). Panel B shows the Kaplan–Meier estimates for progression-free survival among all the patients who underwent randomization. The median follow-up was 7.4 months in the vepdegestrant group and 7.2 months in the fulvestrant group. Disease progression occurred in 399 patients (194 patients in the vepdegestrant group and 205 in the fulvestrant group), and death occurred in 11 patients (4 patients in the vepdegestrant group and 7 in the fulvestrant group). Data from 203 patients who were alive and without disease progression at the time of analysis were censored at the time of the patients’ last disease evaluation showing no progression (111 patients in the vepdegestrant group and 92 in the fulvestrant group); data from 11 patients who withdrew consent were also censored (4 patients in the vepdegestrant group and 7 in the fulvestrant group). The analysis was performed on the basis of a treatment policy strategy, in which the treatment difference was estimated regardless of whether an intercurrent event occurred. In this prespecified supplementary analysis, any disease progression or death events captured in the trial were counted as events, regardless of protocol violations, missing assessments, discontinuation of trial treatments, or initiation of new anticancer therapies. The tick marks indicate censored data.

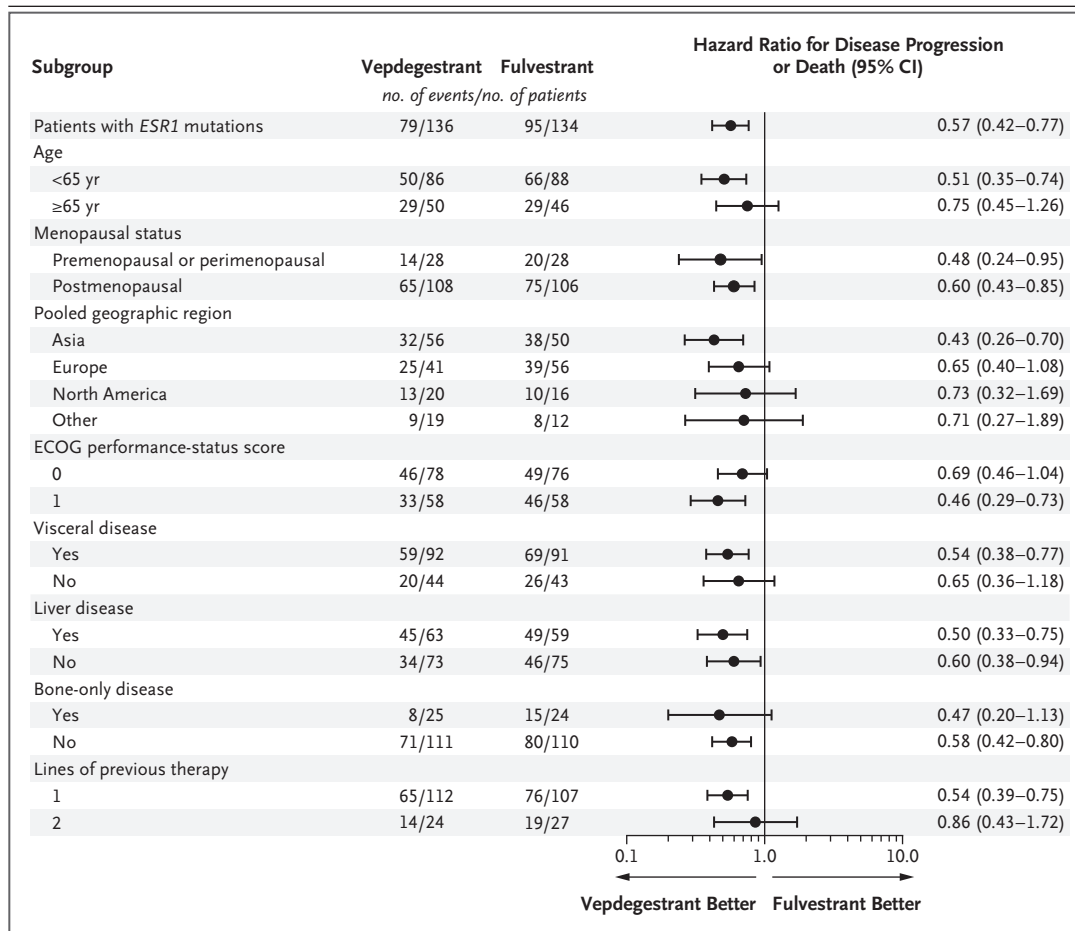


Figure 2. Subgroup Analysis of Progression-free Survival as Assessed by Blinded Independent Central Review among Patients with *ESR1* Mutations.

This analysis of progression-free survival was performed according to the per-protocol hypothetical strategy pre-specified for the primary end point, in which the treatment effect was estimated under the hypothetical assumption that all patients continued to receive their assigned treatment and adhered to the protocol (see the Supplementary Methods section in the Supplementary Appendix). The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects. One man (in the vepdegestrant group) was assigned a status of “premenopausal or perimenopausal.” Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. The presence or absence of liver disease was based on information in the case-report form, and the presence or absence of bone-only disease was determined by blinded independent central review.

which represented 22% and 20% of the targeted number of deaths, respectively. The median overall survival was not reached in either group. Among the patients with *ESR1* mutations, the percentage of patients with an objective response as assessed by blinded independent central review was 18.6% (95% CI, 12.1 to 27.4) in the vepdegestrant group and 4.0% (95% CI, 1.6 to 9.8) in the fulvestrant group (Table S2) and was gen-

erally consistent with the investigator assessment (Table S3).

SAFETY

Among the patients who received at least one dose of treatment, adverse events occurred in 86.9% of the 312 patients receiving vepdegestrant and in 81.4% of the 307 patients receiving fulvestrant. The majority of the patients had grade 1 or 2

adverse events. The most common adverse events (any grade) that were reported in the vepdegestrant group were fatigue (in 26.6% of the patients), an increased aspartate aminotransferase level (14.4%), an increased alanine aminotransferase level (14.4%), and nausea (13.5%), and the most common events that were reported in the fulvestrant group were fatigue (15.6%), arthralgia (10.7%), an increased aspartate aminotransferase level (10.4%), and an increased alanine aminotransferase level (9.8%) (Table 2). Injection-site pain was reported by 8.5% of the patients receiving fulvestrant (not applicable with vepdegestrant). Grade 3 adverse events occurred in 19.2% of the patients in the vepdegestrant group and in 14.0% of the patients in the fulvestrant group; grade 4 adverse events occurred in 1.6% and 2.9%, respectively. The most common grade 3 or 4 adverse events were neutropenia (1.9%) and

hypokalemia (1.9%) in the vepdegestrant group and anemia (3.3%) and an increased aspartate aminotransferase level (2.6%) in the fulvestrant group (Table S4). Adverse events were deemed by the investigator to be related to treatment in 56.7% of the patients receiving vepdegestrant and in 40.4% of those receiving fulvestrant, with grade 3 or 4 treatment-related events occurring in 7.7% and 2.9%, respectively. The most common treatment-related adverse event was fatigue in both the vepdegestrant group (18.6%) and the fulvestrant group (6.8%) (Table S5).

The incidence of serious adverse events was similar in the two groups, occurring in 10.3% of the patients in the vepdegestrant group and in 9.1% of those in the fulvestrant group (Table S6). Ten patients died because of adverse events, including 8 patients in the vepdegestrant group (4 patients from underlying disease progression

Table 2. Most Common Adverse Events.*

Event	Vepdegestrant (N = 312)		Fulvestrant (N = 307)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients (percent)</i>			
Any adverse event	271 (86.9)	73 (23.4)	250 (81.4)	54 (17.6)
Events that occurred in ≥10% of patients in either group†				
Fatigue‡	83 (26.6)	3 (1.0)	48 (15.6)	4 (1.3)
Alanine aminotransferase level increased	45 (14.4)	2 (0.6)	30 (9.8)	2 (0.7)
Aspartate aminotransferase level increased	45 (14.4)	4 (1.3)	32 (10.4)	8 (2.6)
Nausea	42 (13.5)	0	27 (8.8)	2 (0.7)
Anemia§	38 (12.2)	5 (1.6)	24 (7.8)	10 (3.3)
Neutropenia¶	36 (11.5)	6 (1.9)	14 (4.6)	3 (1.0)
Back pain	34 (10.9)	2 (0.6)	20 (6.5)	1 (0.3)
Arthralgia	33 (10.6)	3 (1.0)	33 (10.7)	0
Decreased appetite	33 (10.6)	1 (0.3)	16 (5.2)	0

* Adverse events are shown in the safety analysis population, which included all patients who received at least one dose of vepdegestrant or fulvestrant. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 27.1, and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

† The adverse events are listed if they were reported (in any grade) in at least 10% of the patients in either treatment group and are ordered according to the incidence in the vepdegestrant group.

‡ This category includes fatigue and asthenia.

§ This category includes anemia, decreased hemoglobin level, and iron deficiency anemia.

¶ This category includes neutropenia and decreased neutrophil count. No events led to dose reductions or treatment discontinuation in either treatment group. No febrile neutropenia occurred in the vepdegestrant group, and grade 2 febrile neutropenia occurred once in the fulvestrant group.

and 1 each from malignant neoplasm progression, cerebral ischemia, dyspnea, and age-related causes) and 2 patients in the fulvestrant group (1 from underlying disease progression and hemoptysis and 1 from malignant neoplasm progression); no deaths were considered by the investigator to be related to treatment.

QT prolongation of any grade was reported in 9.9% of the patients in the vepdegestrant group (grade 3, 1.6%) and in 1.3% of those in the fulvestrant group (grade 3, 0.3%); no clinical sequelae (e.g., torsades de pointes or ventricular arrhythmias) were reported in either group. QT prolongation led to vepdegestrant dose reduction in 1 patient but did not lead to treatment discontinuation in either group. In the QTc substudy (involving 88 patients in the vepdegestrant group), categorical analysis indicated that 1 patient (1.1%) had a postbaseline QTcF value greater than 500 msec, and none of the patients had an increase from baseline in QTcF intervals of more than 60 msec. On the basis of a population modeling analysis that evaluated the relationship between vepdegestrant plasma concentrations and QTc, the mean QTcF change from baseline was 11.1 msec (upper limit of the 90% confidence interval, 13.7 msec) with vepdegestrant at a dose of 200 mg once daily. The upper limit of the 90% confidence interval of the model-predicted increase in QTcF was less than 20 msec for all tested scenarios, which indicated no large effect on QTc (i.e., >20 msec)^{26,27} at the recommended vepdegestrant dose of 200 mg once daily.

Adverse events led to dose interruptions in 14.4% of the patients in the vepdegestrant group and in 6.5% of those in the fulvestrant group; dose reductions occurred in 1.9% of the patients in the vepdegestrant group and were not permitted with fulvestrant. Overall, 2.9% of the patients permanently discontinued vepdegestrant and 0.7% discontinued fulvestrant because of adverse events (Table S7).

DISCUSSION

In this phase 3 trial involving patients with ER-positive, HER2-negative advanced breast cancer and disease progression while receiving endocrine therapy plus a CDK4/6 inhibitor, progression-free survival as assessed by blinded independent review was significantly longer with vepdegestrant than with fulvestrant among patients with ESR1

mutations (median, 5.0 months [95% CI, 3.7 to 7.4] vs. 2.1 months [95% CI, 1.9 to 3.5]; hazard ratio, 0.58 [95% CI, 0.43 to 0.78]; $P < 0.001$). No significant improvement in progression-free survival with vepdegestrant was observed in the overall population.

Development of resistance to first-line therapy remains a challenge in the treatment of ER-positive, HER2-negative advanced breast cancer, with resistance often driven by acquired mutations, such as those in ESR1.^{2,4} Therapeutic advances for patients with ER-positive, HER2-negative advanced breast cancer in whom resistance to first-line therapy develops have increasingly focused on biomarker-driven therapeutic strategies.^{15-17,28-30} Elacestrant, an oral selective ER degrader, is currently the only therapy approved specifically for patients with ESR1 mutations.¹⁵ In the EMERALD trial, the median progression-free survival as assessed by blinded independent central review was approximately 2 months longer with elacestrant than with standard care (3.8 months with elacestrant vs. 1.9 months with fulvestrant or an aromatase inhibitor) among patients with ESR1 mutations, and an objective response was observed in 7.1% of the patients receiving elacestrant as compared with 4.7% of those receiving standard care.²⁸ Likewise, imlunestrant, an investigational selective ER degrader, was associated with a median progression-free survival (investigator-assessed) that was nearly 2 months longer than that with standard care (5.5 vs. 3.8 months) in patients with ESR1 mutations in the EMBER-3 trial, with an objective response in 14.3% of the patients receiving imlunestrant and in 7.7% of the patients receiving standard care.⁸ In our trial, the median progression-free survival was nearly 3 months longer with vepdegestrant than with fulvestrant among patients with ESR1 mutations (5.0 vs. 2.1 months), with an objective response in 18.6% of the patients in the vepdegestrant group as compared with 4.0% of those in the fulvestrant group.

We recognize that cross-trial comparisons are complicated by inherent differences among trial designs and patient populations. Of note, all the patients in the VERITAC-2 trial had previously received treatment with a CDK4/6 inhibitor, and patients who had previously received chemotherapy for advanced disease or who had previously received fulvestrant were not permitted to enroll in the trial, whereas in the EMERALD trial, ap-

proximately one fourth of patients with *ESR1* mutations had previously received fulvestrant and one fourth had previously received chemotherapy for advanced disease. In the EMBER-3 trial, approximately one third of patients with *ESR1* mutations had not previously received a CDK4/6 inhibitor.^{8,28} In addition, the patients included in the VERITAC-2 trial must have received their most recent endocrine therapy for at least 6 months before disease progression occurred, an eligibility criterion that was not included in the EMERALD and EMBER-3 trials. However, the performance of fulvestrant in the current trial was in line with that shown in other trials involving patients who had previously received endocrine therapy with a CDK4/6 inhibitor,^{28,29,31-36} which suggests that this inclusion criterion probably did not identify a more endocrine-sensitive population, as may have been expected. In the context of studies in this patient population, our findings appear to support vepdegestrant as a new endocrine therapy with a differentiated mechanism of action and safety profile for patients who currently have limited treatment options in this disease setting.

In vivo data have shown that vepdegestrant induces more robust degradation and superior antitumor activity relative to fulvestrant in an *ESR1* wild-type breast cancer model (data on file, Arvinas).²² However, in the current trial, no difference was observed in progression-free survival with vepdegestrant as compared with fulvestrant in the full patient cohort (median, 3.8 vs. 3.6 months). This finding is consistent with findings in previous trials of endocrine monotherapy involving patients with ER-positive, HER2-negative advanced breast cancer^{8,28,37} and is not unexpected given the complexity of ER signaling pathways. Although the exact mechanisms contributing to this finding are unknown, these results suggest that endocrine sensitivity is preserved in *ESR1*-mutated disease, whereas tumors without *ESR1* mutations may be driven by multiple alternative pathways, which may limit overall benefit from endocrine monotherapy in the second-line setting. In addition, fulvestrant may have limited activity in patients with *ESR1* mutations because of its poor bioavailability, a possibility consistent with in vitro data showing that fulvestrant has a lower binding affinity for mutant ER than for wild-type ER.³⁸

Most patients receiving vepdegestrant had only grade 1 or 2 adverse events, with events leading to

discontinuation and to dose reduction in a small percentage of patients (2.9% and 1.9%, respectively). Fatigue was the most common adverse event in each group and the only adverse event with a between-group difference exceeding 10 percentage points (26.6% with vepdegestrant vs. 15.6% with fulvestrant). A concentration-QTc population modeling analysis from the QTc substudy confirmed a mild increase in mean QTcF (11.1 msec) from baseline, which indicates that vepdegestrant does not have a large QT-prolonging effect at the recommended dose of 200 mg once daily. Given these findings, clinicians should consider recommending avoidance of concomitant use of medications known to prolong QT (and consider monitoring if the use of concomitant QT-prolonging medication is required). Gastrointestinal-related adverse events (e.g., nausea, vomiting, and diarrhea) are commonly reported adverse events with oral selective ER degraders. In the vepdegestrant group in our trial, nausea was reported in 13.5% of the patients (grade 1, 9.3%), vomiting in 6.4% (grade 1, 4.8%), and diarrhea in 6.4% (grade 1, 6.1%); these percentages are lower than those reported in previous trials involving oral selective ER degraders (nausea ranging from 17 to 35%, vomiting ranging from 9 to 19%, and diarrhea ranging from 14 to 21%).^{8,28} Collectively, these findings indicate a favorable safety profile for vepdegestrant.

Trial limitations include the short duration of follow-up, which precluded analyses of overall survival and duration of response. Additional follow-up is needed to further characterize the long-term efficacy and safety of vepdegestrant in this population. Although this multinational trial included a large number of patients with ER-positive, HER2-negative advanced breast cancer, some populations were underrepresented (e.g., Black patients).

Vepdegestrant is a new PROTAC ER degrader that led to significantly longer progression-free survival than fulvestrant in previously treated patients with *ESR1*-mutated, ER-positive, HER2-negative advanced breast cancer. Vepdegestrant had a favorable safety profile with mainly low-grade adverse events and a low incidence of gastrointestinal-related adverse events.

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AUTHOR INFORMATION

Mario Campone, M.D., Ph.D.,¹ Michelino De Laurentiis, M.D., Ph.D.,² Komal Jhaveri, M.D.,^{3,4} Xichun Hu, M.D., Ph.D.,⁵ Sylvain Ladoire, M.D., Ph.D.,⁶ Anne Patsouris, M.D., Ph.D.,⁷ Claudio Zamagni, M.D.,⁸ Jiwei Cui, M.D., Ph.D.,⁹ Marina Cazzaniga, M.D.,¹⁰ Timucin Cil, M.D.,¹¹ Katarzyna J. Jerzak, M.D.,¹² Christian Fuentes, M.D.,¹³ Tetsuhiro Yoshinami, M.D., Ph.D.,¹⁴ Alvaro Rodriguez-Lescure, M.D., Ph.D.,¹⁵ Ahmet Sezer, M.D.,¹⁶ Andrea Fontana, M.D., Ph.D.,¹⁷ Valentina Guarneri, M.D., Ph.D.,^{18,19} Andrea Molckovsky, M.D.,²⁰ Marie-Ange Mouret-Reynier, M.D.,²¹ Umut Demirci, M.D., Ph.D.,²² Yongqiang Zhang, M.D.,²³ Olga Valota, M.S.,²⁴ Dongrui R Lu, M.S.,²⁵ Marcella Martignoni, Ph.D.,²⁴ Janaki Parameswaran, M.D.,²⁶ Xin Zhi, Ph.D.,²⁶ and Erika P. Hamilton, M.D.²⁷

¹Institut de Cancérologie de l'Ouest Angers-Nantes, Saint-Herblain, France; ²Istituto Nazionale Tumori IRCCS "Fondazione

G. Pascale," Naples, Italy; ³Memorial Sloan Kettering Cancer Center, New York; ⁴Weill Cornell Medical College, New York; ⁵Shanghai Cancer Center, Fudan University, Shanghai, China; ⁶Centre Georges Francois Leclerc, Dijon, France; ⁷Institut de Cancérologie de l'Ouest Angers-Nantes, Angers, France; ⁸IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy; ⁹First Hospital of Jilin University, Changchun, China; ¹⁰Phase 1 Research Unit, Fondazione IRCCS San Gerardo, Monza, Italy; ¹¹Health and Science University, Adana City Hospital, Adana, Turkey; ¹²Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto; ¹³Fundación Respirar, Buenos Aires; ¹⁴Graduate School of Medicine, Osaka University, Osaka, Japan; ¹⁵Hospital General Universitario de Elche, Elche, Spain; ¹⁶Baskent University Adana Application and Research Center, Adana, Turkey; ¹⁷Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; ¹⁸Veneto Institute of Oncology, Istituto di Ricovero e Cura a Carattere Scientifico, Padua, Italy; ¹⁹University of Padova, Padua, Italy; ²⁰Grand River Regional Cancer Centre, Kitchener, ON, Canada; ²¹Centre Jean Perrin, Clermont-Ferrand, France; ²²Memorial Ankara Hospital, Ankara, Turkey; ²³Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing; ²⁴Pfizer, Milan; ²⁵Pfizer, San Diego, CA; ²⁶Arvinas Operations, New Haven, CT; ²⁷Breast Cancer Research Program, Sarah Cannon Research Institute, Nashville.

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