The NEW ENGLAND JOURNAL of MEDICINE

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

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Background

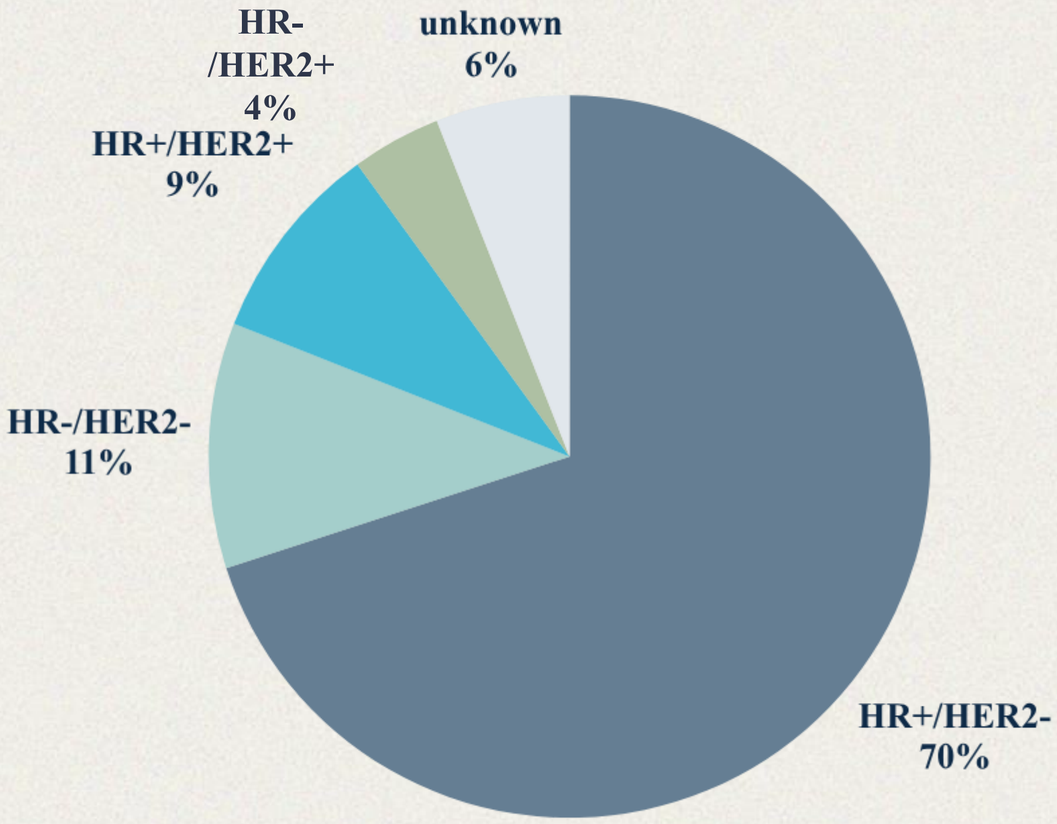
Epidemiology

Global

In 2022, there were an estimated **2.3 million women diagnosed** with breast cancer and **670 000 deaths** globally.

Taiwan

Category



Total 5-Year
Relative Survival

91.7%

Survival

5-Year Relative Survival Percent

NCCN Breast Cancer 2025

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE
RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression	
See BINV-P 1 of 3 for general considerations for therapy selection for HR-positive, HER2-negative disease.	
First-Line Therapy	**Second- and/or Subsequent-Line Therapy**
Preferred Regimens • Aromatase inhibitor + CDK4/6 inhibitor[b] ▸ Aromatase inhibitor + ribociclib (category 1)[c] ▸ Aromatase inhibitor + abemaciclib ▸ Aromatase inhibitor + palbociclib If disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion consider: • Fulvestrant[d] + CDK4/6 inhibitor[b] ▸ Fulvestrant + ribociclib (category 1)[e] ▸ Fulvestrant + abemaciclib (category 1)[e] ▸ Fulvestrant + palbociclib	**Preferred Regimens** • Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g] • For HER2-negative tumors with *PIK3CA* or *AKT1* activating mutations or PTEN alterations, see BINV-Q (6)[h] • Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j] • Targeted therapy, see BINV-Q (6) and BINV-Q (7), and emerging biomarker options, see BINV-Q (8)
Useful in Certain Circumstances • For HER2-negative tumors with *PIK3CA* activating mutations and disease progression on adjuvant endocrine therapy or relapse within 12 months of adjuvant endocrine therapy completion, see BINV-Q (6)	**Useful in Certain Circumstances** • Megestrol acetate • Estradiol • Abemaciclib[l] • Targeted therapy, see BINV-Q (6) and BINV-Q (7), and emerging biomarker options, see BINV-Q (8)
Other Recommended Regimens for first and/or subsequent lines of therapy • For HER2-negative disease and *ESR1* mutated tumors and after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor, see BINV-Q (6) • Fulvestrant) + aromatase inhibitor (anastrozole, letrozole) (category 1)[k] • Fulvestrant • Anastrozole • Letrozole • Tamoxifen • Exemestane	
Footnotes on BINV-P 3 of 3	

Estrogen Receptors (ERs): Overview

Two Major Subtypes: ERα and ERβ

Subtype	**ERα**	**ERβ**
Gene	**ESR1**	ESR2
Dominant Tissue	Mammary Gland, Uterus, Liver, Bone	Brain, Ovary (Gra Prostate (Epitheli Immune System
Primary Function	Proliferation, Growth	Anti-Proliferatior Tumor Suppressi
Mechanism in Cancer	Generally acts as an Oncogene (Tumor-Promoter)	Generally acts as (Inhibits growth)
Therapeutic Implication	**ER(+)** status dictates treatment with **endocrine therapy** (e.g., Tamoxifen).	X

ESR1 mutation

ESR1 mutations are not typically present at the time of initial diagnosis.

In Primary/Treatment-Naïve Tumors	Extremely Rare **(<1%)**	The cancer is still **dependent on the body's natural estrogen**.
Post-Endocrine Therapy Advanced/Metastatic Breast Cancer	**20% - 40%** (Common)	**Therapeutic pressure**. **AIs** create an estrogen-deprived environment, selecting for cancer cells that can **survive without it.**

Initial Treatment
Aromatase inhibitors block estrogen production

Selection Process
Rare cells with ESR1 mutations survive and proliferate

Resistance
- Tumor becomes dominated by ESR1-mutated cells
- Active even without estrogen

AI → complete loss of efficacy
SERM/SERD → reduced sensitivity

ESR1 mutation

Common Mutation Sites

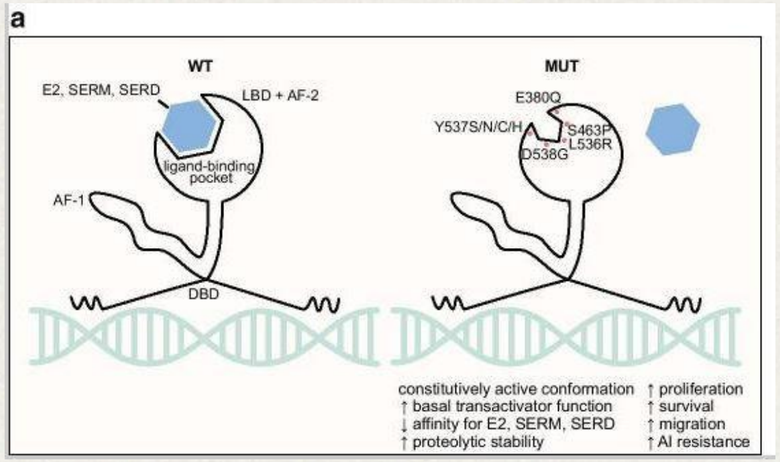
Most common mutations occur in the **ligand-binding domain (LBD)**,
lead to ligand independent ER activity and tumor growth ,partial resistance to tamoxifen and fulvestrant

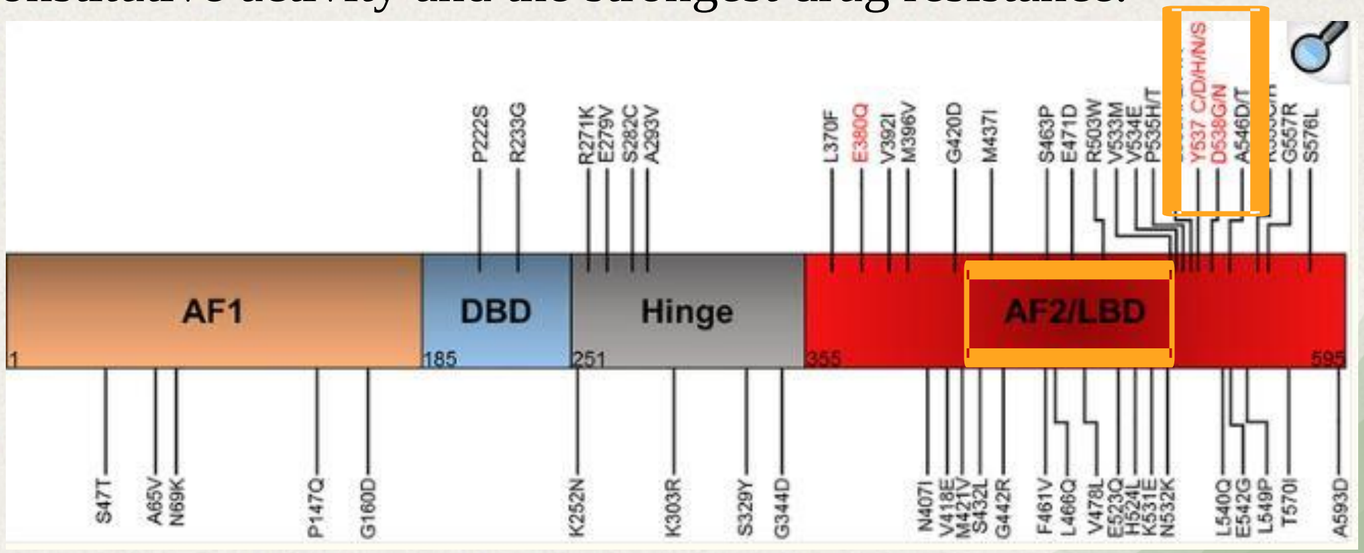
Most Common spots:

- **D538G - Most prevalent (~35% of cases)**
- **Y537S - Second most common (~18%)**
  Partial resistance to tamoxifen and fulvestrant

Most Potent Resistance:

- **Y537S,** often shows the highest level of constitutive activity and the strongest drug resistance.





NCCN Breast Cancer 2025

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection[t]**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
HR-positive, HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Inavolisib + palbociclib + fulvestrant[u]	Category 1	Useful in certain circumstances first-line therapy
HR-positive/ HER2-negative	*PIK3CA* activating mutation	NGS, PCR	Alpelisib + fulvestrant[v]	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative	*PIK3CA or AKT1* activating mutations or *PTEN* alterations	NGS, PCR	Capivasertib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy in select patients[w]
HR-positive/ HER2-negative[x]	*ESR1* mutation[x]	NGS, PCR	Elacestrant	Category 2A	Other recommended regimen subsequent-line therapy

Fulvestrant v.s. Elacestrant

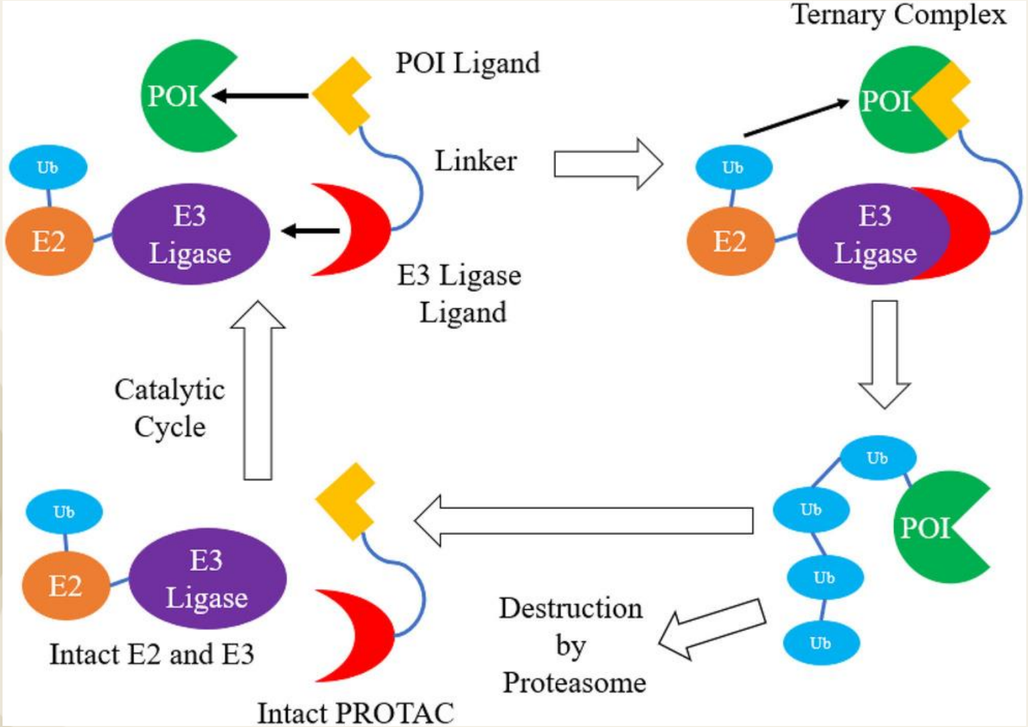
	Fulvestrant	Elacestrant
Mechanism of Action	Intramuscular SERD Does not cross the blood-brain barrier.	Oral SERD Binds to both wild-type (WT) and mutant ER, inducing degradation and antagonism. Crosses the blood-brain barrier.
Pharmacokinetics	Highly potent in vitro but **poor pharmacokinetic properties.** Takes 3-6 months to reach steady-state concentration.	Good oral bioavailability. Achieves stable, steady-state plasma concentration, ensuring consistent target engagement.
Potency WT vs. ESR1 Mutations (IC50)	WT ER: ~0.3 nM (IC50) Y537S/D538G Mutants: 2.0 - 6.3 nM (IC50) (Requires 20-60x higher concentration)	WT ER: ~0.3 nM (IC50) Y537S/D538G Mutants: ~0.4 - 0.8 nM (IC50) (Potency is largely unaffected)
Clinical Status	Approved. A long-standing standard of care, but efficacy is limited in ESR1-mutated disease.	First FDA-approved oral SERD. A new standard of care for ESR1-mutated advanced breast cancer based on the EMERALD trial. (PFS=3.8 months>SOC 1.9months;HR=0.55)
Limitations & Key Side Effects	Inconvenient IM injection Injection site pain Reduced efficacy against ESR1 mutations Side Effects: Hot flashes, fatigue, nausea	Nausea is very common Potential for dyslipidemia (elevated cholesterol/triglycerides) Drug-drug interactions (CYP3A4 substrate)

PROTAC

PROteolysis-TArgeting Chimera

Structure

1. A ligand that binds to the **protein of interest** (POI).
2. A ligand that recruits an **E3 ubiquitin ligase.**
3. A **linker** that connects the two ligands.

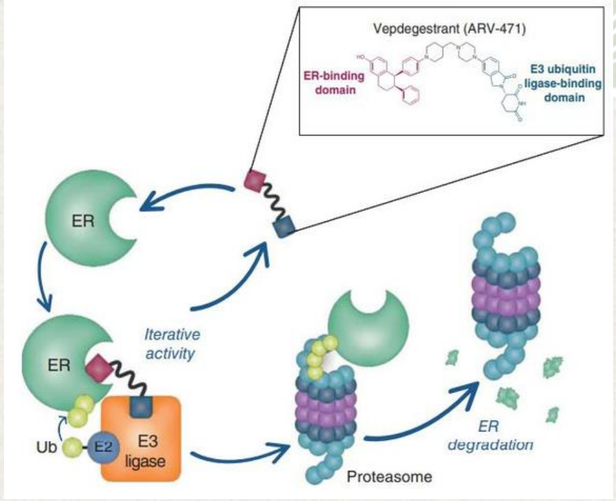


Mode of Action

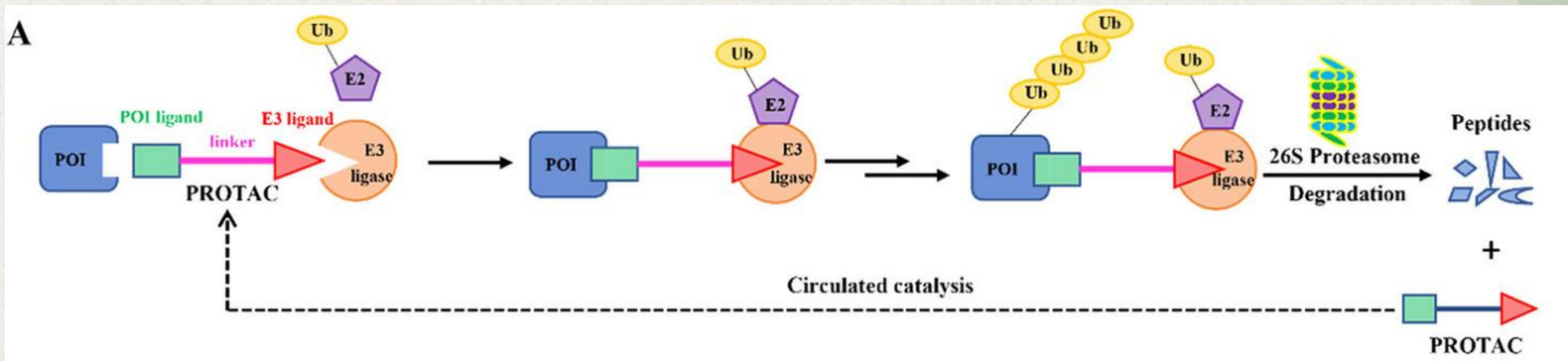
1. PROTAC simultaneously binds the **POI and the E3 ligase**, forming a **ternary complex.**
2. The **E3** ligase transfers **ubiquitin** molecules to the POI, tagging it for **degradation**.
3. The **ubiquitinated POI** is recognized and degraded by the **26S proteasome** into peptides.
4. The PROTAC molecule is released and can engage in another degradation cycle.

Vepdegestrant (ARV-471)

An oral proteolysis-targeting chimera (PROTAC) estrogen receptor (ER) degrader



- Vepdegestrant simultaneously binds **ER** and an CRBN (Cereblon) E3 ligase, forming a ternary complex that results in direct polyubiquitination of ER and its degradation by the proteasome.



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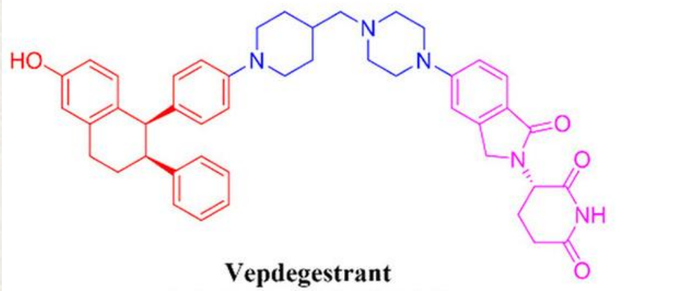


Vepdegestrant
(ARV-471, PF-07850327)

C

Parameters	Vepdegestrant
IC_{50} (nM)[a]	0.99 (recombinant ER)
DC_{50} (nM)[b]	0.94 (MCF7 cells)
D_{max} (%)[c]	95% (MCF7 cells)
GI_{50} (nM)[d]	3.3 (MCF7 cells)/4.5 (T47D cells)
cLogP/LogD/chromLoD[e]	6.8/4.6/5.3
tPSA/ePSA (Å^2)[f]	96/146
HBD/eHBD[g]	2/2
$T_{1/2}$ (h)[h]	6.2 (mouse)/15 (rat)/11 (dog)
F%[i]	59 (mouse)/24 (rat)/5 (dog)

Vepdegestrant

In vitro study: ERα affinity

- IC50:**0.99 nM**
- Ki:**0.28 nM**

Oral Estrogen Receptor PROTAC Vepdegestrant (ARV-471) Is Highly Efficacious as Monotherapy and in Combination with CDK4/6 or PI3K/mTOR Pathway Inhibitors in Preclinical ER$^+$ Breast Cancer Models

Sheryl M. Gough[1], John J. Flanagan[1], Jessica Teh[1], Monica Andreoli[1], Emma Rousseau[1], Melissa Pannone[1], Mark Bookbinder[1], Ryan Willard[1], Kim Davenport[1], Elizabeth Bortolon[1], Gregory Cadelina[1], Debbie Gordon[1], Jennifer Pizzano[1], Jennifer Macaluso[1], Leofal Soto[1], John Corradi[1], Katherine Digianantonio[1], Ieva Drulyte[2], Alicia Morgan[1], Connor Quinn[1], Miklós Békés[1], Caterina Ferraro[1], Xin Chen[1], Gan Wang[1], Hanqing Dong[1], Jing Wang[1], David R. Langley[1], John Houston[1], Richard Gedrich[1], and Ian C. Taylor[1]

Vepdegestrant induced **≥90% degradation** of wild-type ER and **mutant ER(ex:Y537S、D538G、Y537C、E380Q、L536P、V422del...)**, inhibited ER-dependent breast cancer cell line proliferation in vitro, and achieved substantial TGI **(87%–123%)** in MCF7 orthotopic xenograft models, better than those of the ET agent fulvestrant (31%–80% TGI).

less sensitive to modest affinity loss:

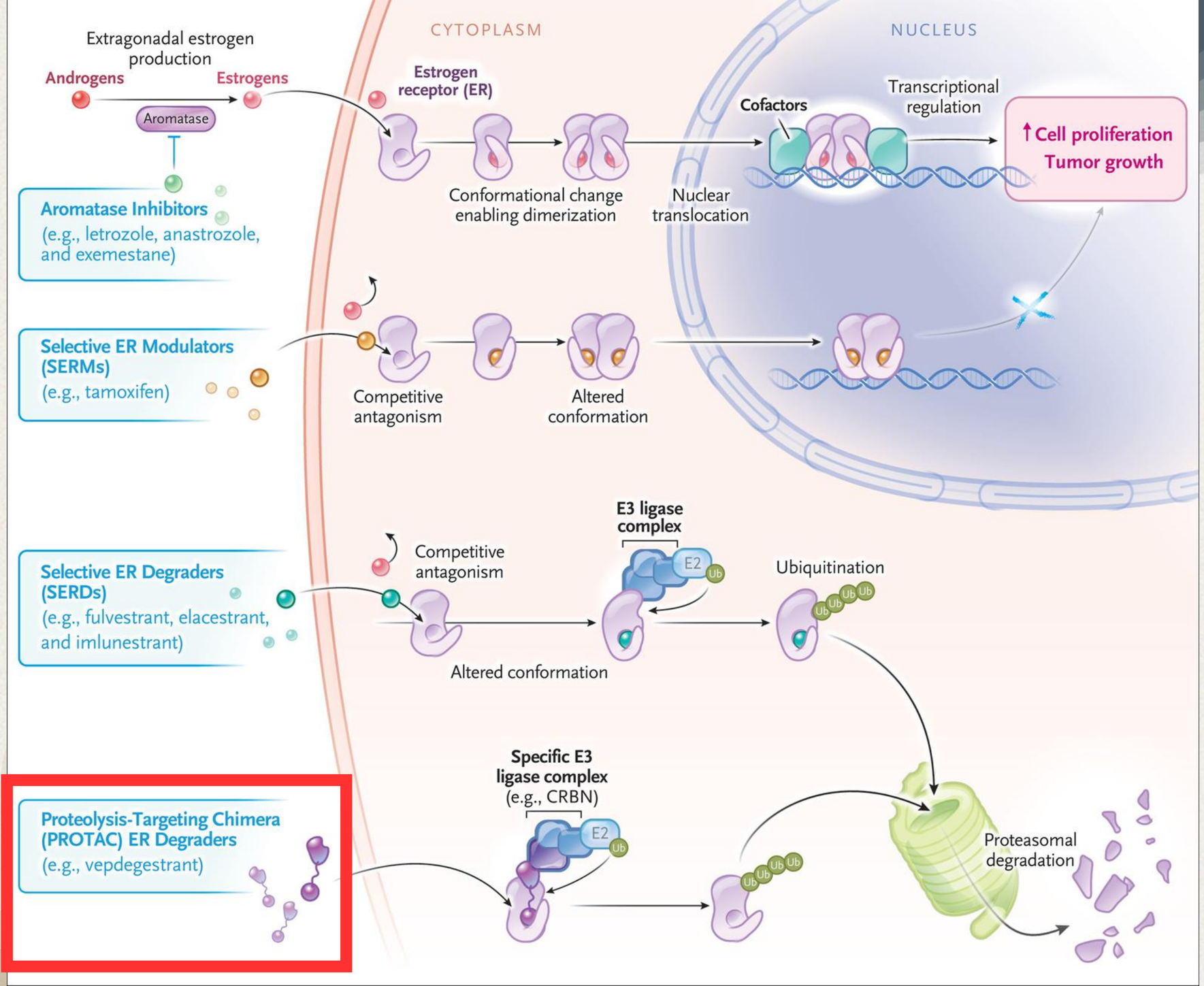
Forms a ternary complex (ER–PROTAC–E3).

New **protein–protein interfaces** create **positive cooperativity**, which can compensate for reduced binary ER–ligand binding caused by mutations.

Net result: still enough complex stability to initiate degradation.

Comparison:SERD v.s. PROTAC

	SERD
Core Mechanism	Occupancy-d
What it does	Orthosteric I Binding dist ubiquitinatio
Role of **Cooperativity**	Not Applica


CYTOPLASM
NUCLEUS
Extragonadal estrogen production
Androgens
Estrogens
Aromatase
Aromatase Inhibitors
(e.g., letrozole, anastrozole, and exemestane)
Estrogen receptor (ER)
Conformational change enabling dimerization
Nuclear translocation
Cofactors
Transcriptional regulation
↑ Cell proliferation
Tumor growth
Selective ER Modulators (SERMs)
(e.g., tamoxifen)
Competitive antagonism
Altered conformation
Selective ER Degraders (SERDs)
(e.g., fulvestrant, elacestrant, and imlunestrant)
Competitive antagonism
E3 ligase complex
E2
Ub
Ubiquitination
Altered conformation
Proteolysis-Targeting Chimera (PROTAC) ER Degraders
(e.g., vepdegestrant)
Specific E3 ligase complex
(e.g., CRBN)
E2
Ub
Proteasomal degradation

02
Methods

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*

Phase III Clinical Trial Design

- Open-label
- Randomized trial
- Multinational

Patient

- 18 years old↑, comfirmed ER(+) HER2(-)
- Not amenable to surgical resection or radiation
- Received **one** previous line of CDK4/6 inhibitor therapy plus endocrine therapy (≥6 months)
- Radiological progression during or after the last line of therapy

Allowed regardless of whether it was given as **adjuvant therapy** or for advanced or metastatic disease (counted as a line of therapy:progression had occurred during or within **12 months**)

Exclusion

- Received chemotherapy
- Received fulvestrant or elacestrant
- Received PI3K , AKT or mTOR inhibitors
- Received investigational agents

Key Stratification Factors
- ESR1-mutation status (yes/no)
- Presence of visceral disease (yes/no)

624 patients
ESR1 mutation, N=270

1:1 ratio

200mg QD PO

Vepdegestrant
All patients, N=313
ESR1 mutation, N=136

Fulvestrant
All patients, N=311
ESR1 mutation, N=134

500mg IM
(day 1 and day 15 of cycle 1 and on day 1 of subsequent cycles)

Key Eligibility Criteria
- Aged ≥18 years
- Histologically or cytologically confirmed ER+/HER2- breast cancer
- Prior therapies for locoregional recurrent or metastatic disease
  - 1 line of CDK4/6 inhibitor therapy in combination with ET
  - ≤1 additional ET
  - Most recent ET given for ≥6 months prior to disease progression
  - Radiological progression during or after the last line of therapy
- Measurable disease evaluable per RECIST v.1.1 or non-measurable bone only disease
- ECOG performance-status score of 0 or 1

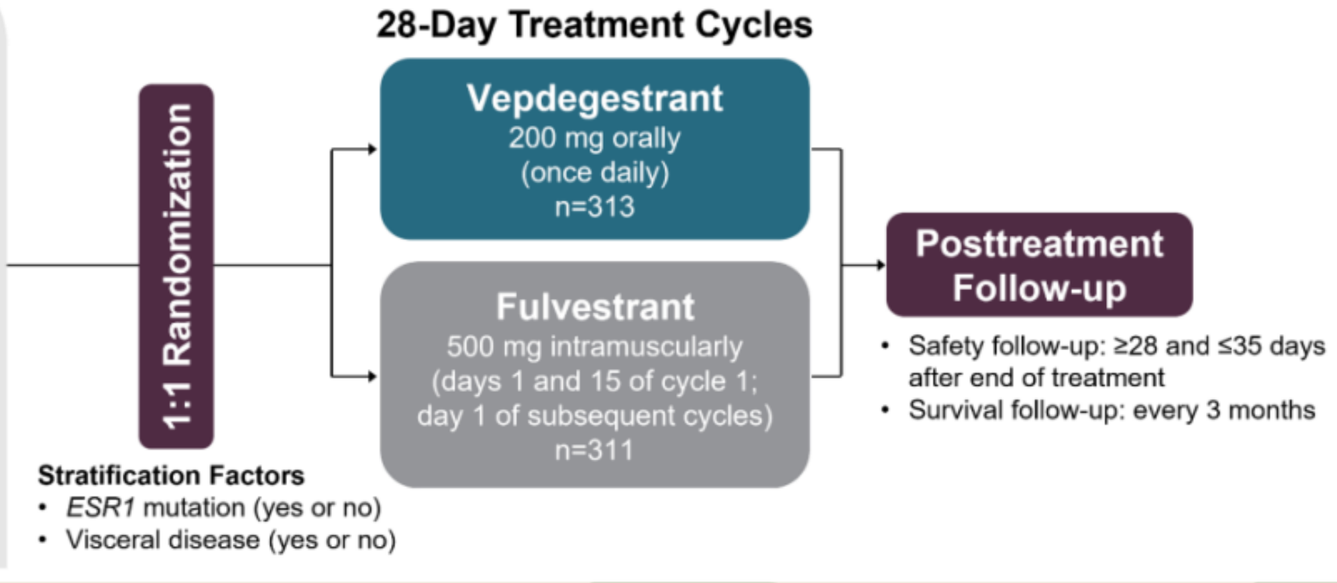


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients with *ESR1* 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)
ESR1 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)

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 *ESR1* 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)

End points

Primary End Points	Secondary End Points
Progression-free survival (PFS)	• Overall survival (the key secondary end point) • Objective response • Safety

Substudy

QT interval

Subgroup of patients in the vepdegestrant group to characterize the effect of vepdegestrant on the corrected **QT (QTc)** interval

Statistical Analysis

Primary & Secondary End Points

- Goal: Maintain **Familywise Type I Error Rate at 0.05** (two-sided) for the entire trial.
- Method: Graphical Multiple Testing Strategy using **α allocation** and a **Gatekeeping Procedure**.

End points	Initial α Allocation	Gatekeeping Sequence (Must pass to proceed)
Primary: PFS (Progression-Free Survival)	75% (α =0.0375)	1. ESR1 Mutant Population →2. ITT (Full) Population
Key Secondary: OS (Overall Survival)	25% (α=0.0125)	Contingent on PFS results.

If PFS is positive in ESR1→ITT (both populations), the 75% PFS α is reallocated to OS.

OS is then tested with the full α (0.025 two-sided).

Otherwise, OS uses its initial 25% α (0.0125 two-sided)

Statistical Analysis

PFS Analysis

Statistical Tools:

1. Kaplan-Meier **Methods** and Stratified Log-rank **Test**.
2. Cox Proportional-Hazards Models (HR and 95% CI)

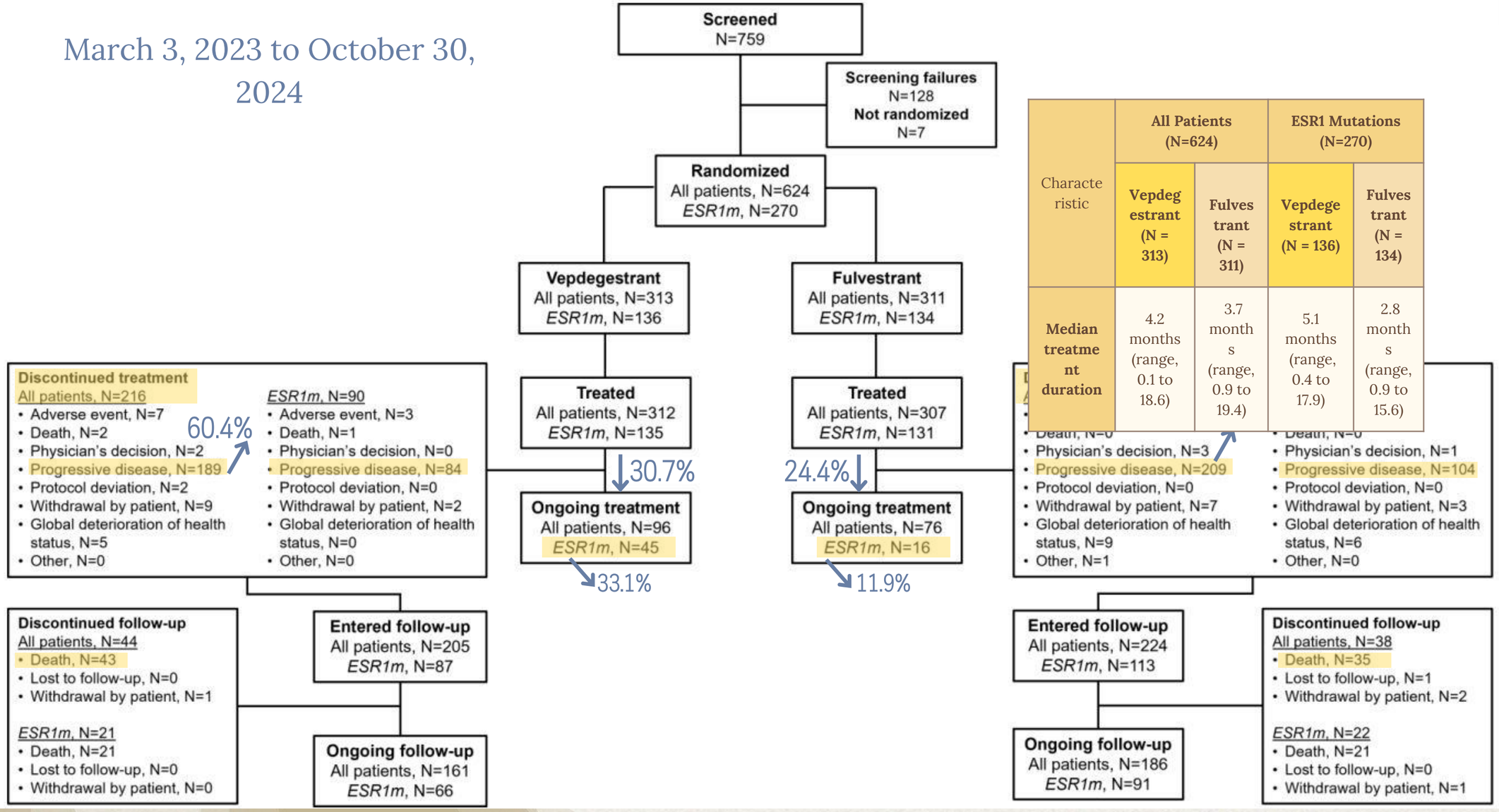
Results presented are from the Pre-specified Supplementary **Treatment Policy Analysis** (includes all progression events without censoring for intercurrent events).

Power/Sample Size :

ESR1 Mutant (~280pts,165 events): 88% power to detect HR<0.60 at α=0.0375.
ITT (~560 pts, 310 events) → 92.5% power to detect HR<0.67

03
Results

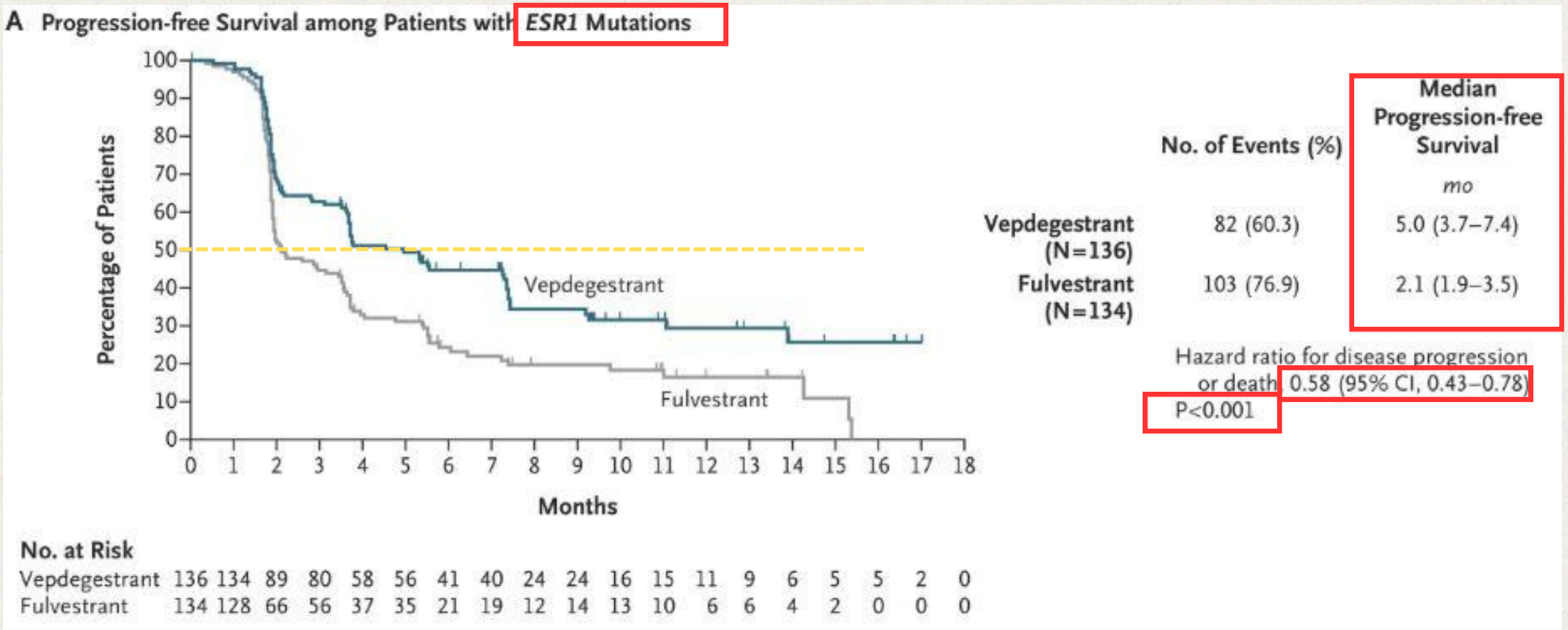
March 3, 2023 to October 30, 2024



Characteristic	All Patients (N=624)		ESR1 Mutations (N=270)	
	Vepdegestrant (N = 313)	Fulvestrant (N = 311)	Vepdegestrant (N = 136)	Fulvestrant (N = 134)
Median treatment duration	4.2 months (range, 0.1 to 18.6)	3.7 months (range, 0.9 to 19.4)	5.1 months (range, 0.4 to 17.9)	2.8 months (range, 0.9 to 15.6)

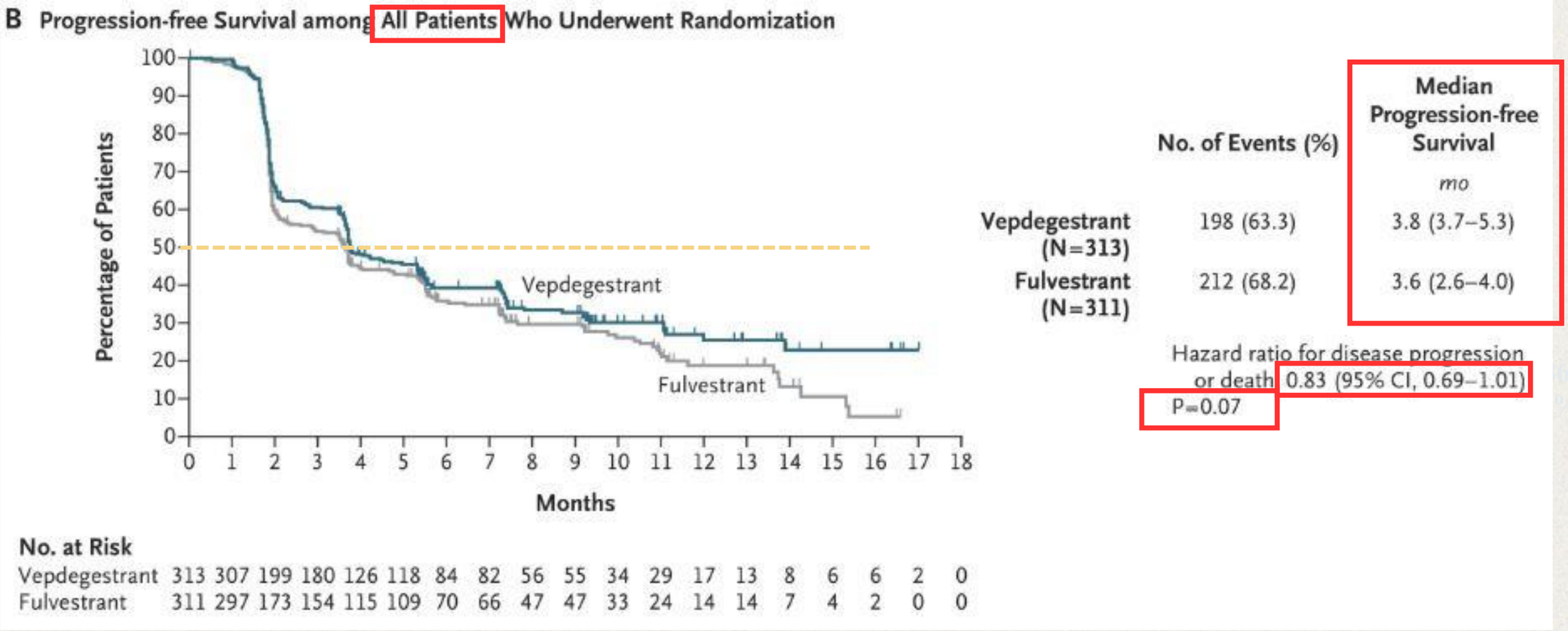
Primary end point

Progression-free survival (PFS)- Kaplan–Meier



Primary end point

Progression-free survival (PFS)- Kaplan–Meier



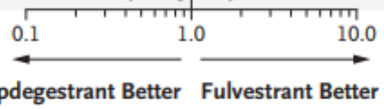
	No. of Events (%)	Median Progression-free Survival
		mo
Vepdegestrant (N=313)	198 (63.3)	3.8 (3.7–5.3)
Fulvestrant (N=311)	212 (68.2)	3.6 (2.6–4.0)

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

Primary end point

PFS-Hazard Ratio

Subgroup	Vepdegestrant	Fulvestrant	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Patients with *ESR1* mutations	79/136	95/134	0.57 (0.42–0.77)
Age			
<65 yr	50/86	66/88	0.51 (0.35–0.74)
≥65 yr	29/50	29/46	0.75 (0.45–1.26)
Menopausal status			
Premenopausal or perimenopausal	14/28	20/28	0.48 (0.24–0.95)
Postmenopausal	65/108	75/106	0.60 (0.43–0.85)
Pooled 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 performance-status score			
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 (0.20–1.13)
No	71/111	80/110	0.58 (0.42–0.80)
Lines of previous therapy			
1	65/112	76/107	0.54 (0.39–0.75)
2	14/24	19/27	0.86 (0.43–1.72)



Secondary end point

Overall survival

43 deaths occurred among the patients with **ESR1 mutations** and **80 deaths** among **all the patients**, which represented 22% and 20% of the targeted number of deaths, respectively.
→The median overall survival was not reached in either group.
→Immature results

Objective response rate

1. Vepdegestrant group：18.6% (95% CI, 12.1 to 27.4)
2. Fulvestrant group：4.0% (95% CI, 1.6 to 9.8)

Safty

no deaths were considered by the investigator to be related to treatment.

Category	Vepdegestrant (n=312)	Fulvestrant (n=307)
Any Adverse Event (AE)	**86.90%**	**81.40%**
Most Common AEs (any grade)	**Fatigue 26.6%** AST increased 14.4% ALT increased 14.4% Nausea 13.5%	**Fatigue 15.6%** Arthralgia 10.7% AST increased 10.4% ALT increased 9.8% Injection-site pain 8.5%
Grade 3 or 4 AEs	23.40%	17.60%
Most Common Grade 3/4 AEs	Neutropenia 1.9% Hypokalemia 1.9%	Anemia 3.3% AST increased 2.6%
Treatment-related AEs	**56.70%**	**40.40%**
Grade 3/4 Treatment-related AEs	7.70%	2.90%
Serious Adverse Events (SAEs)	**10.30%**	**9.10%**
Deaths	8 patients (4 underlying disease progression, 1 malignant neoplasm progression, 1 cerebral ischemia, 1 dyspnea, 1 age-related cause)	2 patients(1 underlying disease progression + hemoptysis, 1 malignant neoplasm progression)
Dose **interruptions** due to AEs	14.40%	6.50%
Dose **reductions** due to AEs	1.90%	Not permitted
Permanent discontinuation due to AEs	2.90%	0.70%

QT prolongation

Incidence

- Vepdegestrant: 9.9% (Grade 3: 1.6%)
- Fulvestrant: 1.3% (Grade 3: 0.3%)

※No clinical sequelae
(e.g., torsades de pointes, ventricular arrhythmias) in either group.
※1 patient in the vepdegestrant arm required dose reduction; no treatment discontinuations occurred.

QTc Substudy

(88 patients, vepdegestrant arm)

- 1 patient (1.1%) had QTcF >500 ms postbaseline.
- No patients had an increase >60 ms from baseline.

Population Modeling Analysis

- At 200 mg once daily: mean QTcF change from baseline = +11.1 ms.
- In all tested scenarios, the upper bound of the 90% CI for predicted QTcF increase was <20 ms

→Indicating **no clinically significant QTc effect at the recommended dose.**

04
Disscusion

End points

ESR1 mutant

Vepdegestrant demonstrated a **statistically significant** and clinically meaningful improvement in **progression-free survival** compared to fulvestrant specifically in patients with **ESR1-mutated, ER+/HER2-** advanced breast cancer.

Overall Population

The **lack of significant benefit in the full patient population** suggests that for tumors without ESR1 mutations, **other resistance mechanisms may be more dominant**, limiting the effectiveness of endocrine monotherapy.

Fulvestrant

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.**

Comparison with Other Therapies

Treatment	Mechanism	Administration	Median PFS in ESR1-mutant	ORR in ESR1-mutant	Key Adverse Events
Vepdegestrant (VERITAC-2)	PROTAC ER degrader	Oral, once daily	5.0 months HR: 0.58	18.60%	**Fatigue (26.6%)**, liver enzyme elevation (~14%), QT prolongation (9.9%)
Elacestrant (EMERALD)	Selective ER degrader	Oral, once daily	3.8 months HR: 0.55	7.10%	**Nausea (35%)**, fatigue (19%), vomiting (19%)
Imlunestrant (EMBER-3)	Selective ER degrader	Oral, once daily	5.5 months HR: 0.72	14.30%	Nausea (17%), fatigue (17%), diarrhea (14%)
SOC (Standard of care)	Selective ER degrader	Intramuscular injection	VERITAC-2 :2.1 months EMERALD :1.9months EMBER-3 :3.8 months	VERITAC-2 :4.0% EMERALD :4.7% EMBER-3 : 7.7%	Fatigue (15.6%), arthralgia (10.7%), injection site pain (8.5%)

Inherent differences：trial designs and patient populations

Limitation

Short Follow-up

The duration of follow-up was short, which meant that key long-term data, such as **overall survival** and **duration of response**, were not yet **mature**.

Underrepresentation

While the trial was multinational, certain populations, such as **Black patients**, were underrepresented, which may limit the generalizability of the findings to all patient groups.

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)

05
Conclusion

Efficacy

- In patients with previously treated, **ESR1-mutated, ER-positive, HER2-negative** advanced breast cancer, the novel PROTAC ER degrader vepdegestrant led to **significantly longer progression-free survival** than the standard therapy fulvestrant.
- Higher **objective response rate** with vepdegestrant in ESR1-mutated disease (18.6% vs. 4.0%)

Vepdegestrant represents a new class of therapy (PROTAC) for ER+ breast cancer.
Supports vepdegestrant as a new endocrine therapy option for ESR1-mutated, ER+/HER2- advanced breast cancer.

Safty

Favorable safety profile

- Most AEs were Grade 1–2; discontinuation (2.9%), dose reduction (1.9%)
- Most common AE: fatigue (26.6% vs. 15.6%)

QTc findings

- No large QT-prolonging effect (>20 ms)
- One patient required dose reduction; no discontinuations

GI adverse events lower than prior oral SERDs

- Nausea：13.5% vs. 17 to 35%
- Vomiting ：6.4% vs. 9 to 19%
- Diarrhea：6.4% vs. 14 to 21%

06
Appraisal

1.Did the study address a clearly formulated research question?

■ Yes ☐ No ☐ Can’t tell

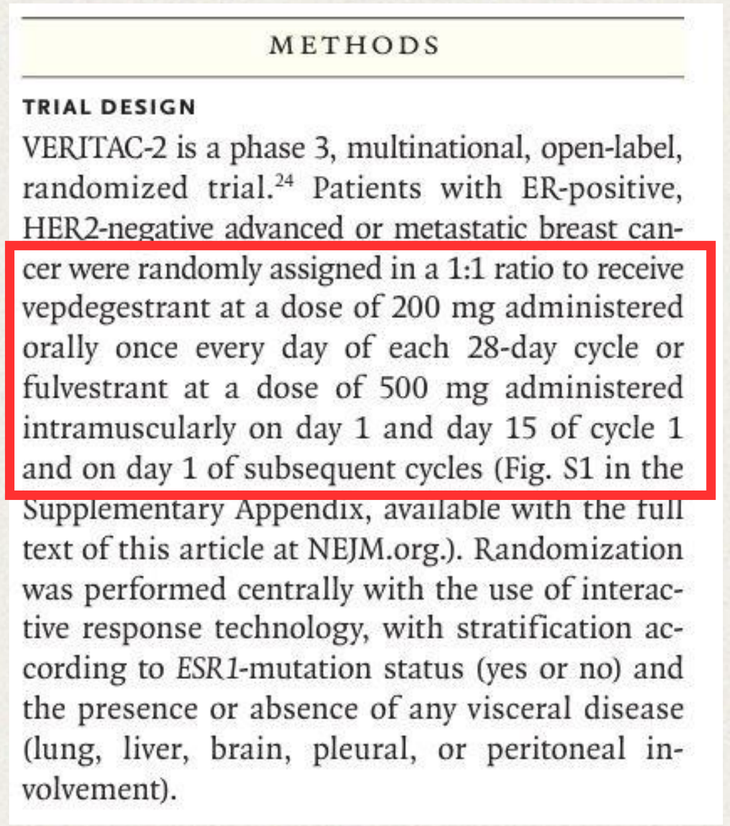
P (Population)	ER(+), HER2(-) advanced breast cancer, previously treated with endocrine therapy + CDK4/6 inhibitor.
I (Intervention)	Vepdegestrant 200 mg orally QD.
C (Comparator)	Fulvestrant 500 mg IM.
O (Outcome)	Primary endpoint = PFS (progression-free survival).

2. Was the assignment of participants to interventions randomised?

■ Yes ☐ No ☐ Can't tell

The methods section explicitly states：

"Patients were randomly assigned in a 1:1 ratio to receive vepdegestrant... or fulvestrant..."



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).

3. Were all participants who entered the study accounted for at its conclusion?

■ Yes ☐ No ☐ Can't tell

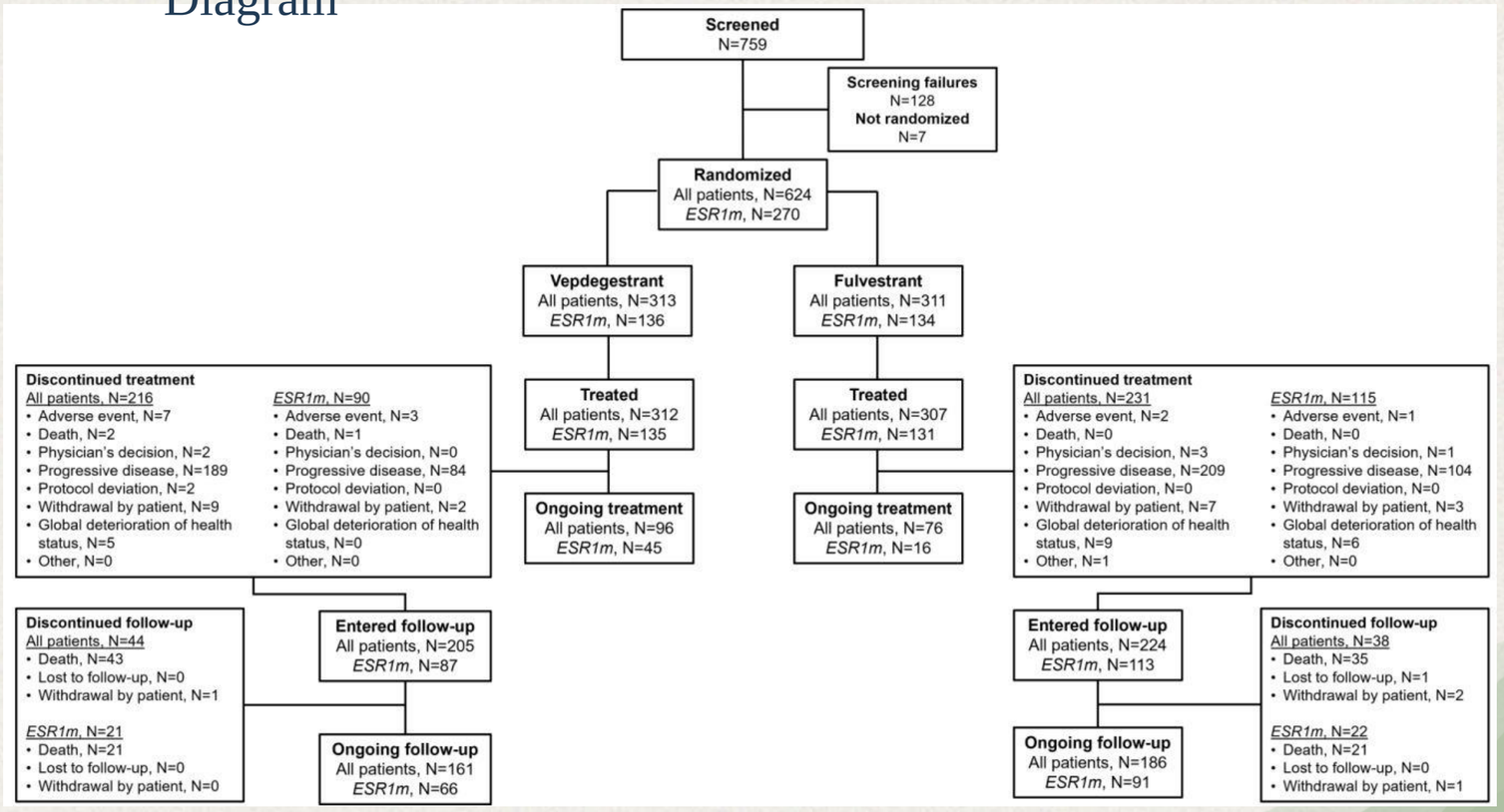
Primary end point:

ITT

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.

CONSORT Diagram



4-1 Were the **participants** 'blind' to intervention they were given?

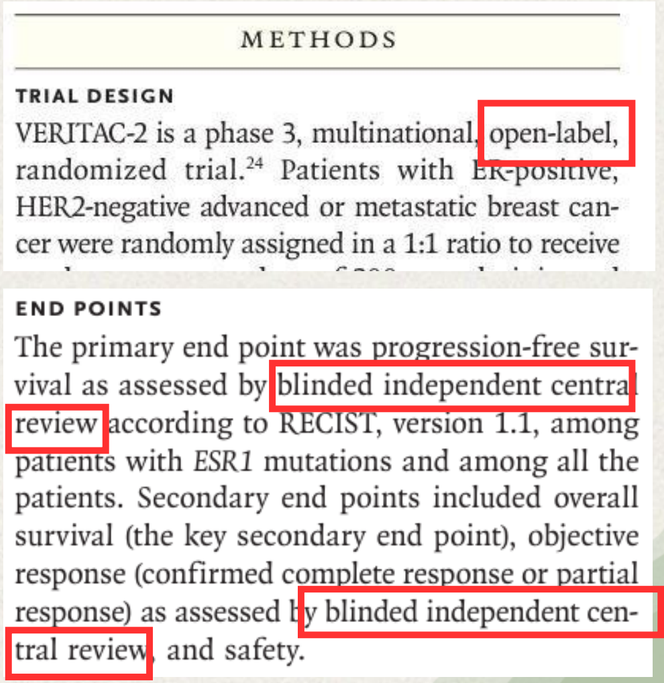
☐ Yes ■ No ☐ Can't tell

4-2 Were the **investigators** 'blind' to intervention they were given?

☐ Yes ■ No ☐ Can't tell

4-3 Were the people **assessing/analysing** outcome/s 'blinded'?

■ Yes ☐ No ☐ Can't tell



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

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.

5. Were the study groups similar at the start of the randomised controlled trial?

- [x] Yes
- [ ] No
- [ ] Can't tell

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients with *ESR1* 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)
ESR1 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)

6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?

■ Yes ☐ No ☐ Can't tell

- **A Clearly Defined Protocol Was Followed for All Participants**

  The trial was conducted according to a single, comprehensive **protocol**, ensuring standardized procedures across both treatment arms.

- **Supportive Care and Concomitant Therapies Were Administered Equally**

  1. The protocol specified that **supportive care** measures were to be given to participants as needed, at the investigator's discretion, regardless of their assigned group.
  2. Rules for allowed and prohibited concomitant therapies were applied to both arms to ensure **consistency of care**

- **Follow-up Intervals Were Identical for Both Groups**

  1. The Schedule of Activities (SoA) outlined the same timeline for **visits, laboratory tests, and efficacy assessments** for both the vepdegestrant and fulvestrant arms.
  2. For example, tumor assessments for all participants were scheduled at the same frequency: "**every 8 weeks for the first 48 weeks from date of randomization and then every 12 weeks thereafter**"

6.9.5. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines.

Participants should receive appropriate supportive care measures throughout duration of the active treatment phase as deemed necessary by the treating investigator including but not limited to the items outlined below:

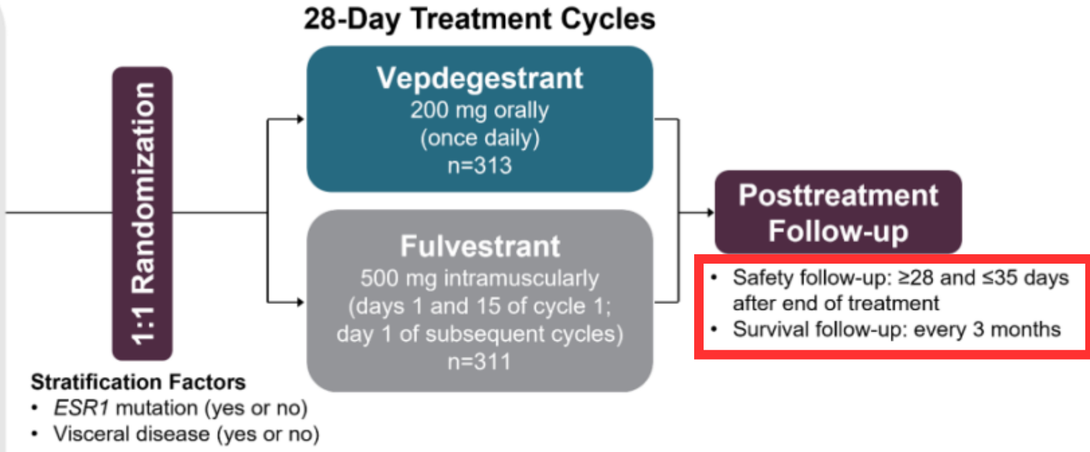
- **Standard therapies** for preexisting medical conditions, medical and/or surgical complications, and palliation. Any medication intended solely for supportive care (e.g., analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion.
- **Bisphosphonates and receptor activator of nuclear factor kappa B ligand** inhibitors for the treatment of osteoporosis or management of existing bone metastases may be continued for participants who have been receiving them at a stable dose for at least 2 weeks prior to randomization. However, the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of participant from the active treatment phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the subject's source documentation.
- **Vaccines** locally approved vaccinations and booster doses are allowed, including Influenza and SARS-CoV-2 as appropriate.

Disease Assessments		
Tumor assessments (other than Bone scan)	X	◄--► Every 8 weeks (±7 days) for the first 12 months from the date of randomization. Then every 12 weeks (± 7 days) thereafter from the date of randomization
Radionuclide Bone Scan, Whole Body	X	◄--► Every 24 weeks (±7 days) from the date of randomization

- **Transfusion**: RBC and PLT transfusion may be used as per Investigator's discretion
- **Anti-infectives** may also be used at the investigator's discretion. Before administration verify any potential drug-drug interaction with the study treatments as per Appendix 10.
- **Anticoagulant's use**:
  Arm A only: Participants who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, warfarin or other warfarin derivatives or other oral anticoagulants (eg, direct Xa inhibitors) may be allowed. When using oral anticoagulants, close monitoring for signs of bleeding is recommended. Consult the product prescribing information for the appropriate coagulation test to be used for monitoring, as required. Refer to Appendix 10 for potential DDI with P-gp sensitive substrates.
  Arm B: refer to the EU SmPC for fulvestrant for anticoagulant's use.

Key Eligibility Criteria

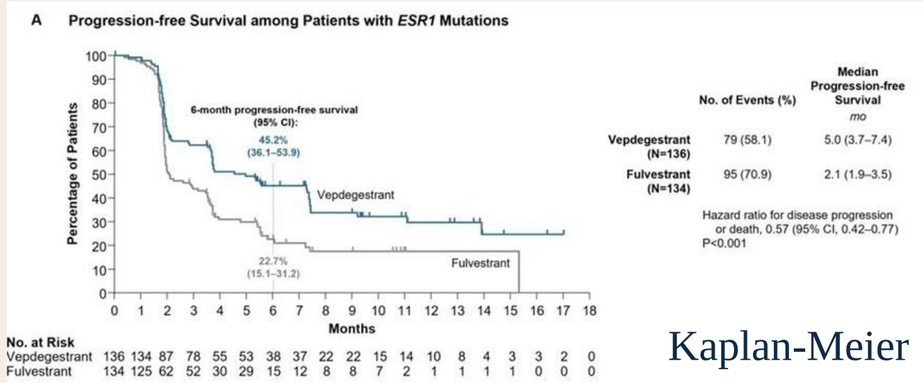
- Aged ≥18 years
- Histologically or cytologically confirmed ER+/HER2- breast cancer
- Prior therapies for locoregional recurrent or metastatic disease
  - 1 line of CDK4/6 inhibitor therapy in combination with ET
  - ≤1 additional ET
  - Most recent ET given for ≥6 months prior to disease progression
  - Radiological progression during or after the last line of therapy
- Measurable disease evaluable per RECIST v.1.1 or non-measurable bone only disease
- ECOG performance-status score of 0 or 1



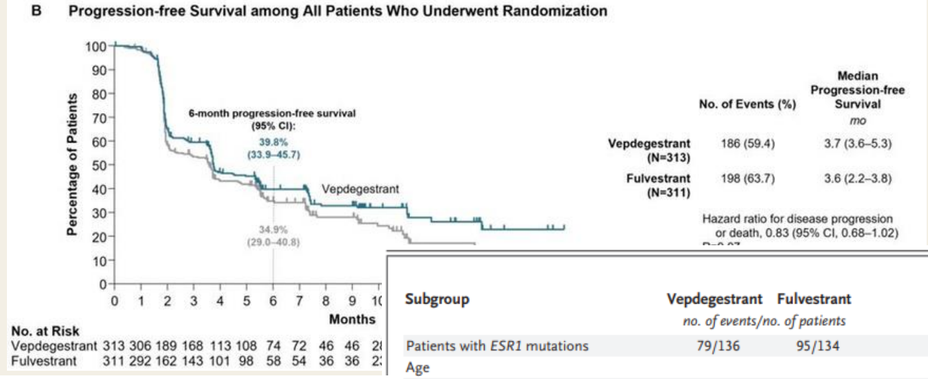
7. Were the effects of intervention reported comprehensively?

- [x] Yes
- [ ] No
- [ ] Can't tell

Primary endpoints



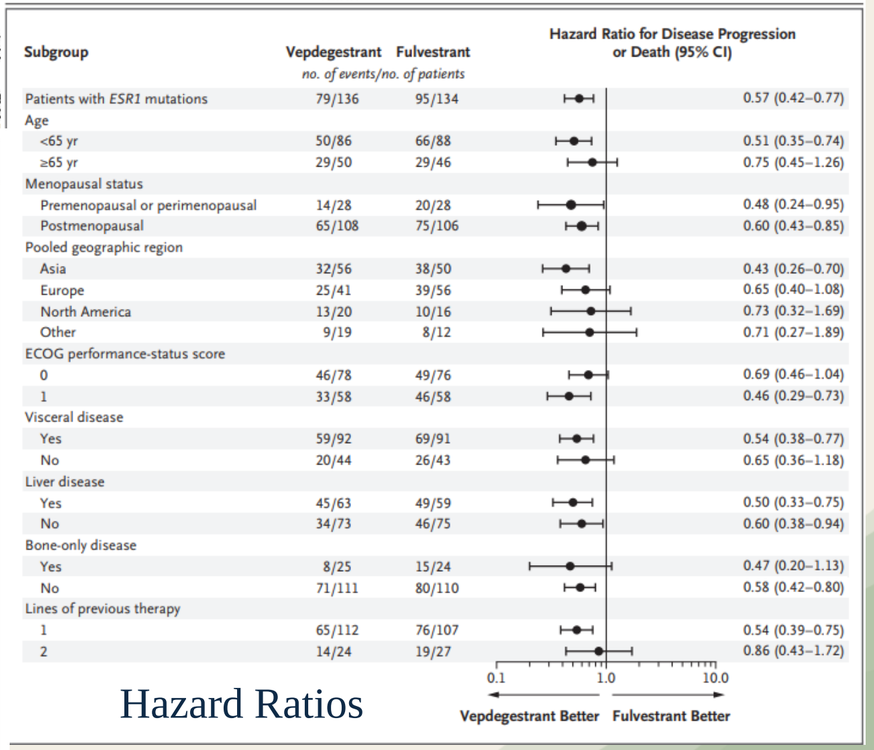
Kaplan-Meier



Safty

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
	number of patients (percent)			
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



Hazard Ratios

8. Was the precision of the estimate of the intervention or treatment effect reported?

■ Yes ☐ No ☐ Can't tell

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.

9. Do the benefits of the experimental intervention outweigh the harms and costs

☐ Yes ☐ No ■ Can't tell

Efficacy

PFS was significantly longer with vepdegestrant than with fulvestrant among patients with ESR1 mutations

Safty

The safety profile was manageable and generally consistent with other endocrine therapies.

- Grade 3 or higher adverse events: vepdegestrant groups were lightly higher than fulvestrant group (23.4% vs. 17.6%)
- Discontinuation due to adverse events remained low in both arms (2.9% vs. 0.7%).

Conclusion

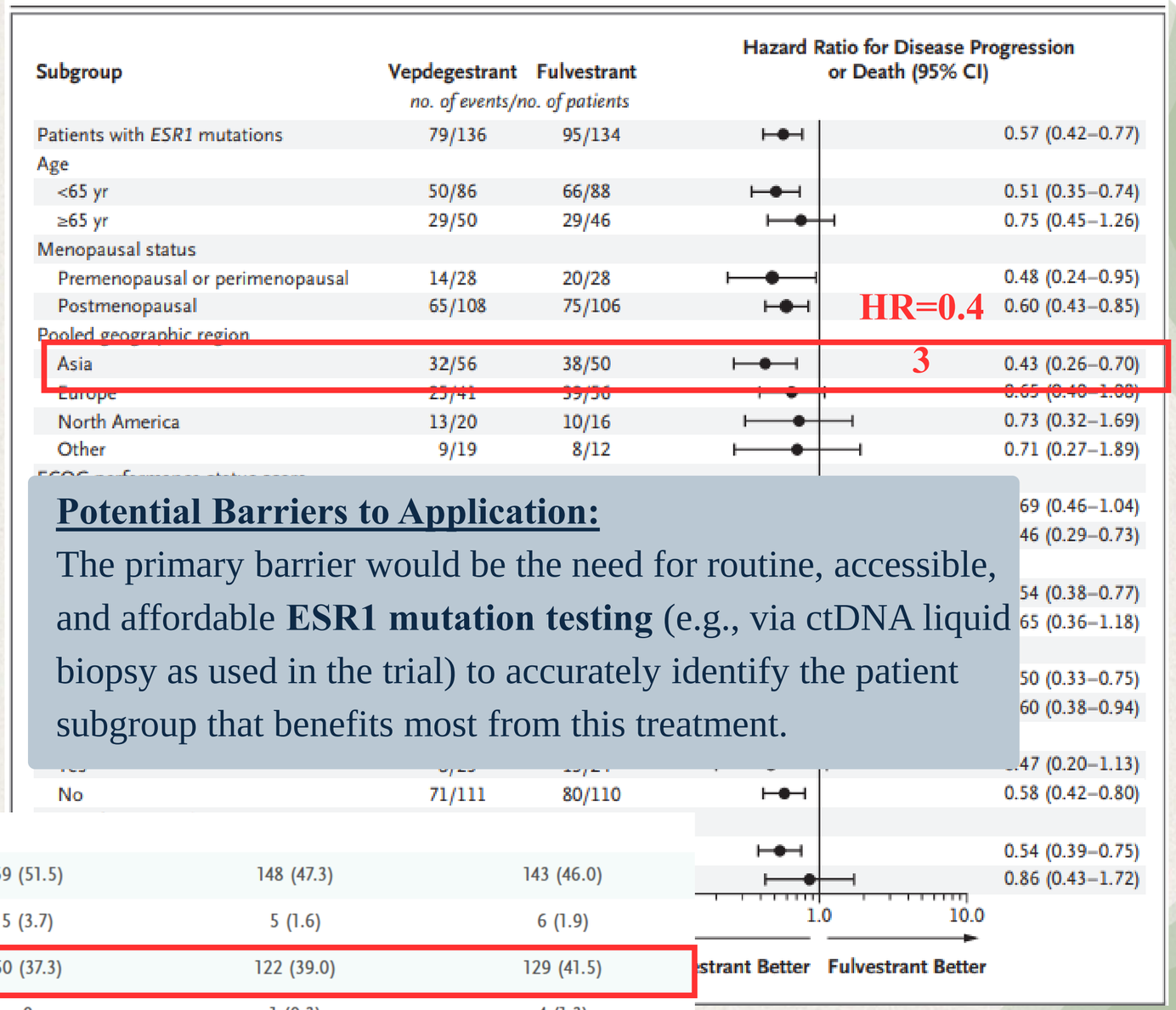
ESR1 mutation: the substantial improvement in disease control appears to justify the manageable increase in side effects.

Cost

Not discussed in the publication.

10. Can the results be applied to your local population/in your context?

- ■ Yes
- ☐ No
- ☐ Can't tell



Potential Barriers to Application:

The primary barrier would be the need for routine, accessible, and affordable **ESR1 mutation testing** (e.g., via ctDNA liquid biopsy as used in the trial) to accurately identify the patient subgroup that benefits most from this treatment.

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)

~40 %

11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

■ Yes ☐ No ☐ Can’t tell

Overall Assessment

The experimental intervention would provide greater value by:

1. Offering a new, demonstrably better **treatment option** for patients with **ESR1 mutations.**
2. Significantly improving patient’s **convenience** and **quality of life** through **oral dosing** versus injection.

Vepdegestrant would represent a valuable new standard of care for this **precisely defined patient population**, offering both improved efficacy and greater convenience.

References

.Campone M, De Laurentiis M, Jhaveri K, Hu X, Ladoire S, Patsouris A, Zamagni C, Cui J, Cazzaniga M, Cil T, Jerzak KJ, Fuentes C, Yoshinami T, Rodriguez-Lescure A, Sezer A, Fontana A, Guarneri V, Molckovsky A, Mouret-Reynier MA, Demirci U, Zhang Y, Valota O, Lu DR, Martignoni M, Parameswaran J, Zhi X, Hamilton EP; VERITAC-2 Study Group. Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in Advanced Breast Cancer. N Engl J Med. 2025 Aug 7;393(6):556-568. doi: 10.1056/NEJMoa2505725. Epub 2025 May 31. PMID: 40454645.

2.Najim O, Seghers S, Sergoynne L, Van Gaver H, Papadimitriou K, Wouters K, Trinh XB, Huizing MT, Tjalma W. The association between type of endocrine therapy and development of estrogen receptor-1 mutation(s) in patients with hormone-sensitive advanced breast cancer: A systematic review and meta-analysis of randomized and non-randomized trials. Biochim Biophys Acta Rev Cancer. 2019 Dec;1872(2):188315. doi: 10.1016/j.bbcan.2019.188315. Epub 2019 Oct 21. PMID: 31647985.

3.Hamilton EP, Ma C, De Laurentiis M, Iwata H, Hurvitz SA, Wander SA, Danso M, Lu DR, Perkins Smith J, Liu Y, Tran L, Anderson S, Campone M. VERITAC-2: a Phase III study of vepdegestrant, a PROTAC ER degrader, versus fulvestrant in ER+/HER2- advanced breast cancer. Future Oncol. 2024;20(32):2447-2455. doi: 10.1080/14796694.2024.2377530. Epub 2024 Jul 29. PMID: 39072356; PMCID: PMC11524203.

4.Harriet Graham,The mechanism of action and clinical value of PROTACs: A graphical review,Cellular Signalling,Volume 99,2022,110446,ISSN 0898-6568

5.McDonnell DP. Degradation of the Estrogen Receptor in Breast Cancer. N Engl J Med. 2025 Aug 7;393(6):604-608. doi: 10.1056/NEJMe2507193. PMID: 40768722.

6. Dustin D, Gu G, Fuqua SAW. ESR1 mutations in breast cancer. Cancer. 2019;125(21):3714-3728.

7.National Comprehensive Cancer Network. (2025). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): [Breast cancer], (Version 4.2025). NCCN

8. Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res. 2021;23(1):85.

9. Jeselsohn R, Buchwalter G, De Angelis C, Brown M, Schiff R. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol. 2015;12(10):573-583.

10.Graham H. The mechanism of action and clinical value of PROTACs: A graphical review. Cell Signal. 2022 Nov;99:110446. doi: 10.1016/j.cellsig.2022.110446. Epub 2022 Aug 19. PMID: 35995302.

11.Hamilton, Erika & Ma, Cynthia & De Laurentiis, Michele & Iwata, Hiroji & Hurvitz, Sara & Wander, Seth & Danso, Michael & Lu, Dongrui & Smith, Julia & Liu, Yuan & Tran, Lana & Anderson, Sibyl & Campone, Mario. (2024). VERITAC-2: a Phase III study of vepdegestrant, a PROTAC ER degrader, versus fulvestrant in ER+/HER2- advanced breast cancer. Future oncology (London, England). 20. 1-9. 10.1080/14796694.2024.2377530.

12.Ma Z, Zhou J. NDA Submission of Vepdegestrant (ARV-471) to U.S. FDA: The Beginning of a New Era of PROTAC Degraders. J Med Chem. 2025 Jul 24;68(14):14129-14136. doi: 10.1021/acs.jmedchem.5c01818. PMID: 40702893.

13.Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. Steroids. 2014 Nov;90:13-29. doi: 10.1016/j.steroids.2014.06.012. Epub 2014 Jun 24. PMID: 24971815; PMCID: PMC4192010.

14.National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program. (n.d.). Cancer stat facts: Female breast cancer subtypes. Retrieved October 9, 2025, from https://seer.cancer.gov/statfacts/html/breast-subtypes.html

Thank You

Take-Home Messages for Clinicians

1. PROTAC Targets the Mutation
   - Vepdegestrant is significantly superior to Fulvestrant, but only for ESR1 mutant patients.
   - ESR1 testing is mandatory after CDK4/6 inhibitor failure.

2. Oral Route Improves QoL
   - Oral dosing (Vepdegestrant) is superior to injection (Fulvestrant).
   - Convenience is the decisive clinical advantage when efficacy is similar.

3. Treatment Enters the Precision Era
   - Treatment decisions must be based on molecular status (ESR1).

Shift from "trial-and-error" to "precision."