III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

# PAPEL ACTUAL DE LOS SERD EN CÁNCER DE MAMA LUMINAL METASTÁSICO

Josefina Cruz Jurado
Unidad de mama. Oncología médica. HUC Tenerife

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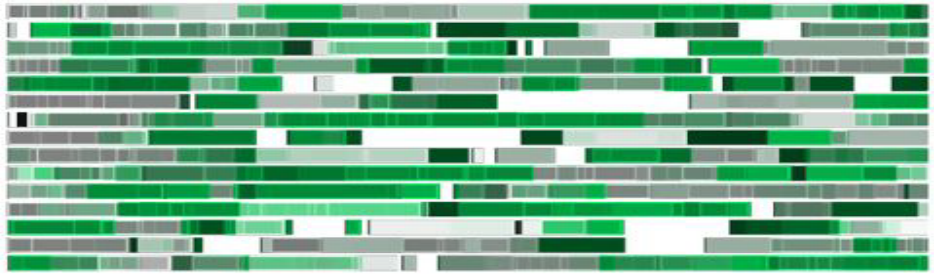

## DISCLOSURES

Entity: Glaxo, AstraZeneca, Roche, Novartis, Pharmamar, Eisai, Lilly, Pierre Fabre, Daichii Sankyo, Seagen, Gilead, Deciphera and Pfizer (speaker honoraria).

Consultant/advisory role: Entity: AstraZeneca, Roche,Gilead, Novartis, Pharmamar, Eisai, Lilly,Pfizer, Seagen and Daichii Sankyo , Deciphera

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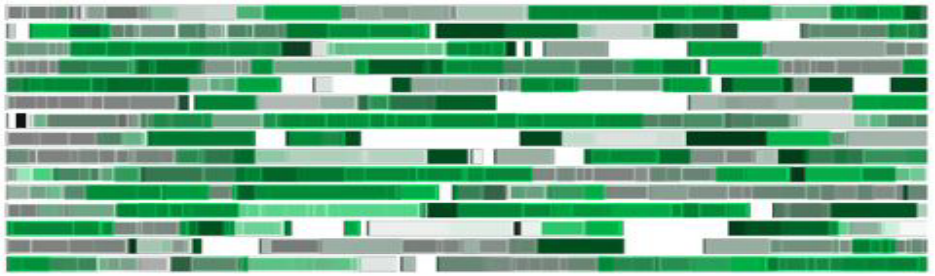

## GUÍAS ESMO ENFERMEDAD LUMINAL AVANZADA

Al diagnóstico precisamos

| | |
|---|---|
| • In HR-positive, HER2-negative MBC: | |
| ○ HER2-ultralow status by IHC | II, A |
| ○ ***PIK3CA*** [ESCAT score: I-A], ***AKT1/PTEN*** [ESCAT I/II] and ***ESR1*** [ESCAT score: I-A] (after AI treatment) mutational status | I, A |

| | |
|---|---|
| • In HER2-negative MBC: | |
| ○ HER2-low status by IHC/ISH | I, A |
| ○ Germline ***BRCA1/2*** [ESCAT score: I-A] | I, A |
| ○ Germline ***PALB2*** [ESCAT II-B] mutational status | III, C |

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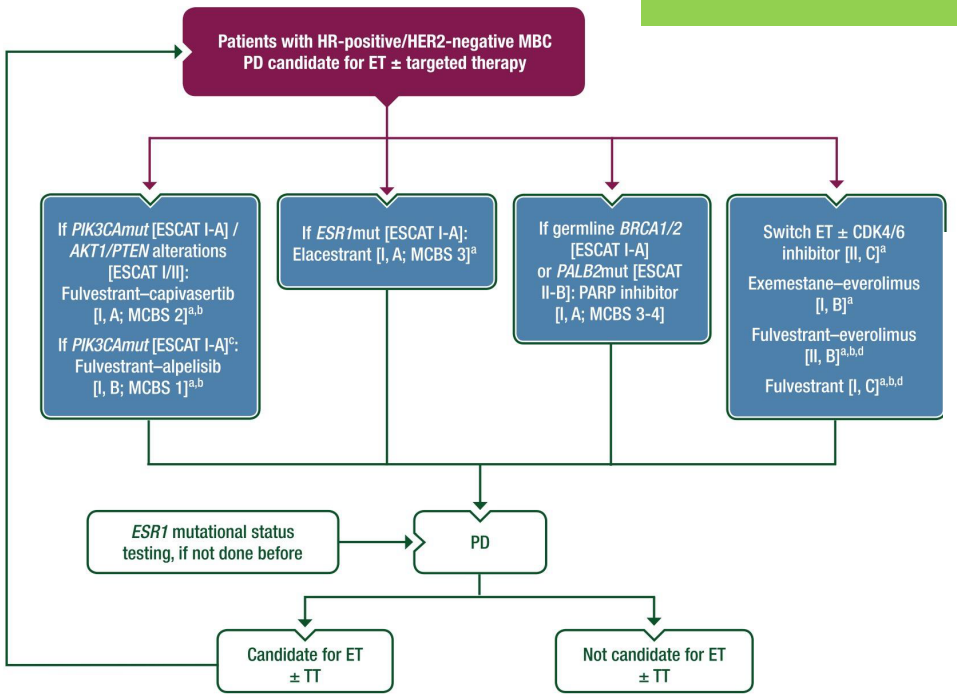
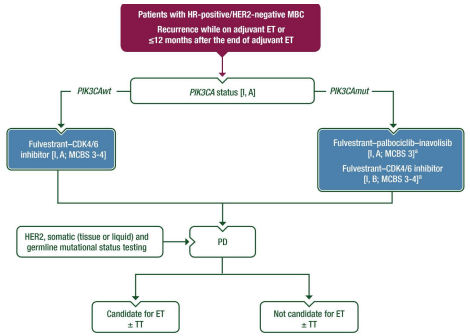
## TRAS FALLO A 1º LÍNEA CON CDK4/6

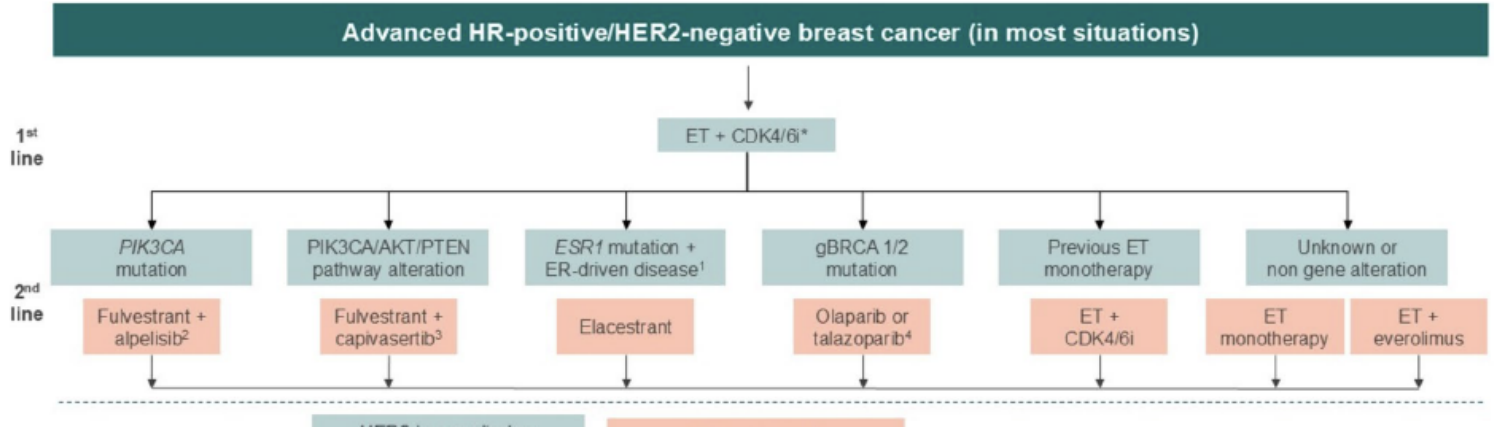
**GUIAS ESMO**




**GUIAS GEICAM SOLTI**

Clinical and Translational Oncology (2026) 28:126–147



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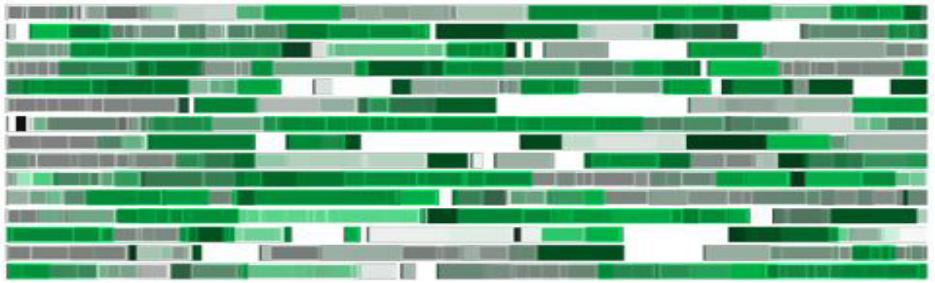
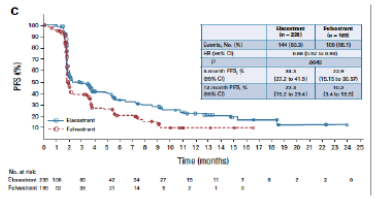


# NECESIDAD CLÍNICA NO CUBIERTA

- **Resistencia endocrina tras CDK4/6i**
- **Limitaciones de IA y fulvestrant**
- **Mutaciones ESR1 como mecanismo central**

## Fulvestrant tras CDKI…

Fulvestrant monotherapy has been evaluated as a control arm in two prospective trials post-CDK4/6i use. In the Phase III EMERALD study, all patients had progressed on 1–2 lines of endocrine therapy, including one in combination with a CDK4/6i. The fulvestrant monotherapy control arm had a median PFS of 1.9 months (95% CI 1.87–2.1).
Patients had a 6-month PFS rate of 22.9% and a 12-month PFS rate of 10.2%]. .




In VERONICA, a phase II study of VEN + F vs F in ER-positive, HER2-negative LA/MBC.
Fulvestrant monotherapy was also associated with a clinical benefit rate of13.7% and a PFS of 1.94 months (95% CI 1.84–3.55), suggesting a limited utility of this option post-front-line endocrine therapy

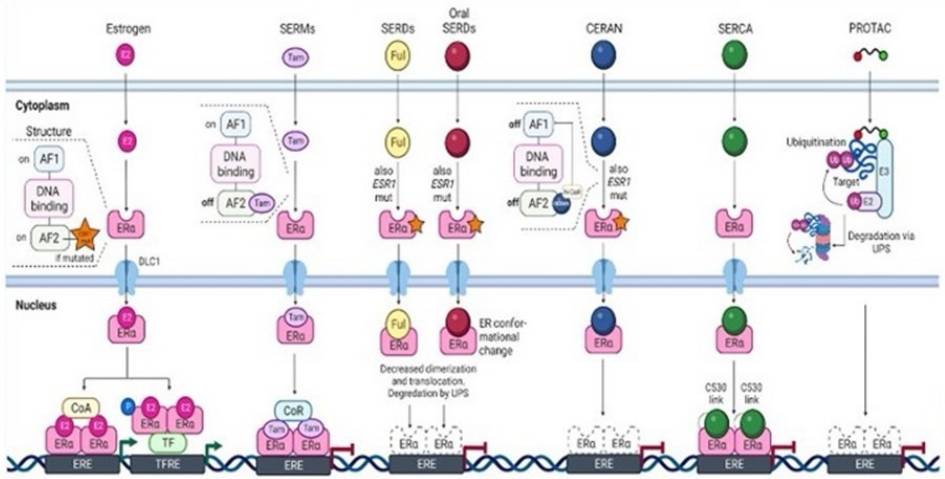
**Table 3.** List of genomic alterations level I/II according to ESCAT in advanced breast cancer

| Gene | Alteration | Estimated prevalence | ESCAT score | Drug class matched | References |
|---|---|---|---|---|---|
| *ERBB2* | Amplifications | 15%-20% | IA | Anti-HER2 monoclonal antibodies<br>HER2 TKIs<br>Anti-HER2 ADCs | Baselga et al., *N Engl J Med* 2012[55]<br>Krop et al., *Lancet Oncol* 2014[56]<br>Lin et al., *J Clin Oncol* 2020[57]<br>Saura et al., *J Clin Oncol* 2020[58]<br>Rugo et al., *JAMA Oncol* 2021[59] |
| | Hotspot mutations | 4% | IIB | Pan-HER TKIs<br>Anti-HER2 ADCs | Hyman et al., *Nature* 2018[51]<br>Smyth et al., *Cancer Discov* 2020[60]<br>Li et al., *Ann Oncol* 2023[61] |
| *PIK3CA* | Hotspot mutations | 30%-40% | IA (ER-positive HER2-negative ABC) | α-specific PI3K inhibitors* | André et al., *N Engl J Med* 2019[62]<br>Rugo et al., *Lancet Oncol* 2021[63] |
| *ESR1* | Mutations | 30%-40% | IA (ER-positive HER2-negative ABC | SERDs | Bidard et al., *J Clin Oncol* 2022[64]<br>Bardia et al., *Cancer Res* 2023[65] |
| *BRCA1/2* | Germline pathogenic/likely pathogenic variants | 4% | IA | PARP inhibitors | Litton et al., *N Engl J Med* 2018[66]<br>Robson et al., *Eur J Cancer* 2023[67] |
| | Somatic mutations | 3% | IIB | PARP inhibitors | Tung et al., *J Clin Oncol* 2020[68] |
| *PTEN* | Mutations/deletions | 7% | I/II | AKT inhibitors | Schmid et al., *J Clin Oncol* 2020[69]<br>Turner et al., *N Engl J Med* 2023[70] |
| *AKT1* | Mutations (p. E17K) | 5% | I/II | AKT inhibitors | Kalinsky et al., *JAMA Oncol* 2021[71]<br>Turner et al., *N Engl J Med* 2023[70] |
| *PALB2* | Germline pathogenic/likely pathogenic variants | 1% | IIB | PARP inhibitors | Tung et al., *J Clin Oncol* 2020[68]<br>Gruber et al., *Nat Cancer* 2022[72] |

DOI: 10.1200/JCO.22.00338 *Journal of Clinical Oncology* 40, no. 28 (October 01, 2022) 3246-3256.
DOI: 10.1200/JCO.2021.39.15_suppl.1004 *Journal of Clinical Oncology* 39, no. 15_suppl (May 20, 2021) 1004-1004.

# Novel ER-Targeting Agents

| **SERD** Selective Estrogen Receptor Degrader | **PROTAC** Proteolysis Targeting Chimera | **CERAN** Complete Estrogen Receptor Antagonist | **Novel SERMs** Selective Estrogen Receptor Modulators |
|---|---|---|---|
| Elacestrant*, Imlunestrant*, Giredestrant, Camizestrant | Vepdegestrant | Palazestrant | Lasofoxifene |

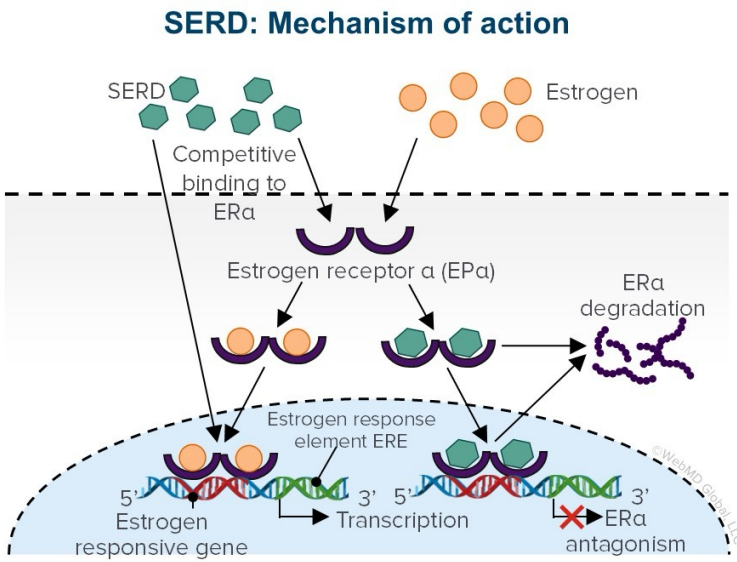


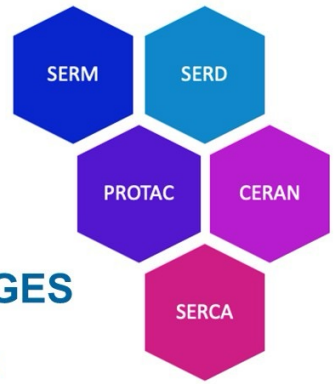

*FDA Approved

**Novel ER-DRIVEN agents** differing in potency as **degraders vs. antagonistic activity,** which are in **different stages of development** and **different disease contexts**


Adapted from Chiara Corti Cancer Treatment Reviews, 2023, 102569

# Oral SERDs: MOA May Address Endocrine Resistance in MBC

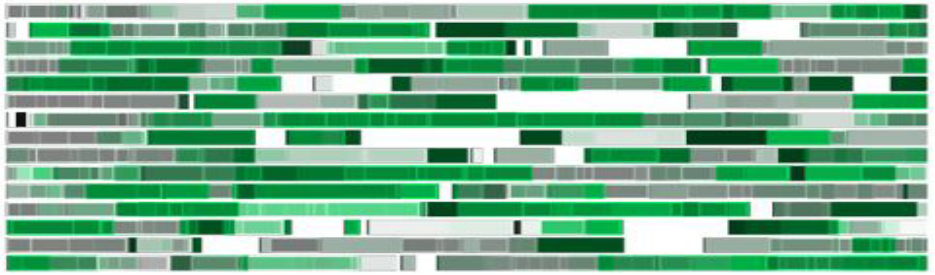



## KEY ADVANTAGES

- Oral formulation
- Higher potency
- Activity in ESR1 mutant MBC
- Activity in post-ET and CDK4/6i treated patients

Hernando et al. Int J Mol Sci 2021; slide adapted from Erika Hamilton



## Novel Oral Endocrine Therapies

| AGENT | DISEASE SETTING | SELECT ONGOING TRIALS |
|---|---|---|
| **ORAL SERDs** | | |
| Elacestrant | Advanced/Metastatic | EMERALD, ELEVATE |
| | Adjuvant | ELEGANT |
| Giredestrant | Advanced/Metastatic | preservERA, acelERA, evERA |
| | Neoadjuvant | coopERA |
| | Adjuvant | lidERA |
| Camizestrant | Advanced/Metastatic | SERENA-1,-2,-4, -6 |
| | Neoadjuvant | SERENA-3 |
| | Adjuvant | CAMBRIA-1, CAMBRIA-2 |
| Imlunestrant | Advanced/Metastatic | EMBER |
| | Neoadjuvant | EMBER-2 |
| | Adjuvant | EMBER-4 |
| **OTHER NOVEL AGENTS** | | |
| Vepdegestrant | Advanced/Metastatic | VERITAC-2, VERITAC-3 |
| Palazestrant | Advanced/Metastatic | OPERA-1, OPERA-2 |
| Lazofoxefine | Advanced/Metastatic | ELAINE-1, ELAINE-2, ELAINE-3 |

# Oral SERDs as monotherapy for pretreated HR+/HER2- MBC: EMERALD Phase 3 Study

## KEY ELIGIBILITY CRITERIA

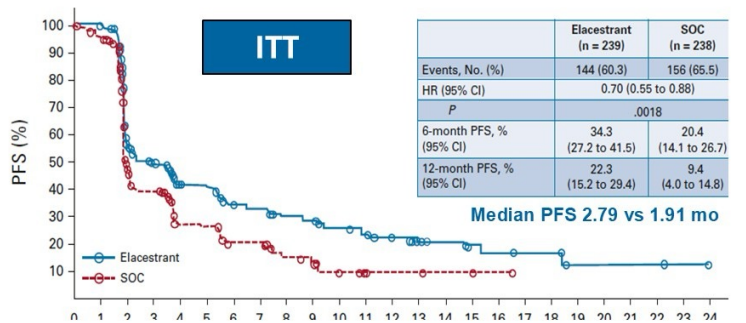
- ER+/HER2– MBC
- 1-2 prior lines of ET, **one of which in combination with CDK4/6i**
- **≤1 line of chemotherapy** for MBC

RANDOMIZED 1:1

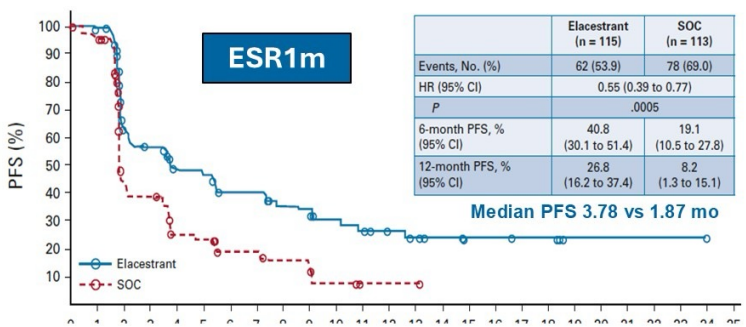
- **Elacestrant** 400 mg[a]
- **Investigator's choice (SOC)**: Fulvestrant, Anastrozole, Letrozole, Exemestane

PD or withdrawal criterion[b]

**Primary endpoints[c]:** PFS in all, PFS in *ESR1*mut
**Secondary endpoints:** OS, safety




| | Elacestrant (n = 239) | SOC (n = 238) |
|---|---|---|
| Events, No. (%) | 144 (60.3) | 156 (65.5) |
| HR (95% CI) | 0.70 (0.55 to 0.88) | |
| *P* | .0018 | |
| 6-month PFS, % (95% CI) | 34.3 (27.2 to 41.5) | 20.4 (14.1 to 26.7) |
| 12-month PFS, % (95% CI) | 22.3 (15.2 to 29.4) | 9.4 (4.0 to 14.8) |



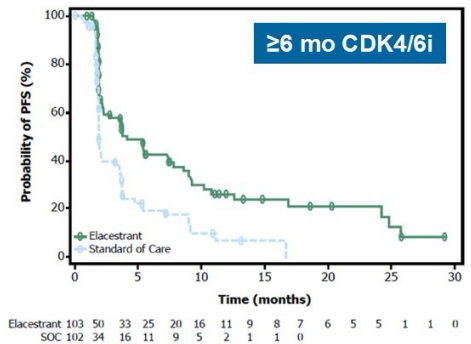

| | Elacestrant (n = 115) | SOC (n = 113) |
|---|---|---|
| Events, No. (%) | 62 (53.9) | 78 (69.0) |
| HR (95% CI) | 0.55 (0.39 to 0.77) | |
| *P* | .0005 | |
| 6-month PFS, % (95% CI) | 40.8 (30.1 to 51.4) | 19.1 (10.5 to 27.8) |
| 12-month PFS, % (95% CI) | 26.8 (16.2 to 37.4) | 8.2 (1.3 to 15.1) |

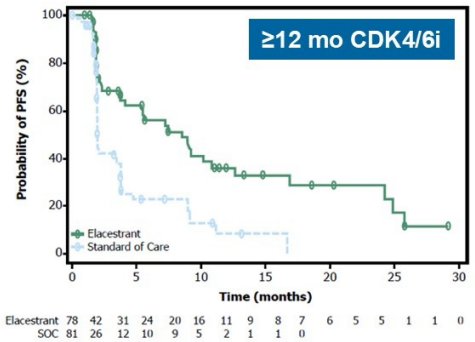
Dana-Farber Cancer Institute | San Antonio Breast Cancer Symposium

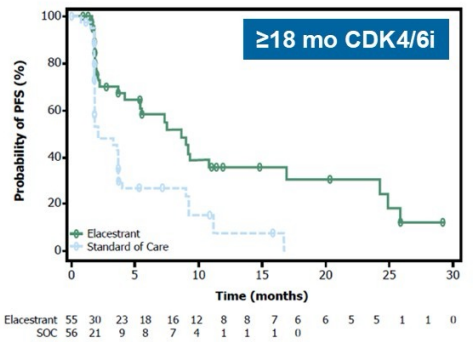
Bardia A. Cancer Res. 2022;82(4_Supplement):GS2-02-GS2-02;

# EMERALD: PFS in *ESR1*mut by Duration of Prior CDK4/6i

## PFS by Duration of CDK4/6i in Patients With ESR1mut Tumors




| PFS by Duration of CDK4/6i | ≥6 Months | | ≥12 Months | | ≥18 Months | |
|---|---|---|---|---|---|---|
| | Elacestrant (n=103) | SOC (n=102) | Elacestrant (n=78) | SOC (n=81) | Elacestrant (n=55) | SOC (n=56) |
| mPFS, mo (95% CI) | 4.14 (2.20-7.79) | 1.87 (1.87-3.29) | 8.61 (4.14-10.84) | 1.91 (1.87-3.68) | 8.61 (5.45-16.89) | 2.10 (1.87-3.75) |
| 12-mo PFS rate, % (95% CI) | 26.02 (15.12-36.92) | 6.45 (0.00-13.65) | 35.81 (21.84-49.78) | 8.39 (0.00-17.66) | 35.79 (19.54-52.05) | 7.73 (0.00-20.20) |
| HR (95% CI) | **0.517** (0.361-0.738) | | **0.410** (0.262-0.634) | | **0.466** (0.270-0.791) | |

Dana-Farber Cancer Institute

SAN ANTONIO BREAST CANCER SYMPOSIUM

Bardia A, et al. SABCS 2022. Abstract GS3-01.

# Oral SERDs as monotherapy for pretreated HR+/HER2- MBC: EMBER-3 Phase 3 Study

## KEY ELIGIBILITY CRITERIA

- ER+/HER2– MBC
- 1-2 prior lines of ET **+/- CDK4/6i**
- **≤1 line of chemotherapy** for MBC

RANDOMIZED 1:1:1 N=874

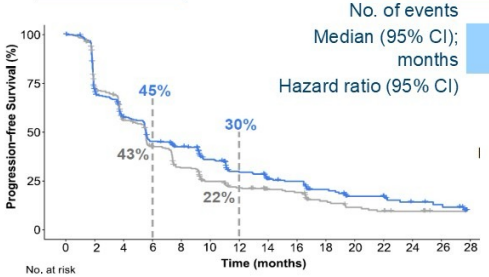
- **Imlunestrant** 400 mg QD
- **SOC ET**
- **Imlunestrant 400 mg QD + abemaciclib**

**Primary endpoints[c]:** PFS imlu vs SOC ITT, Imlu vs SOC ESR1, imlu + abema vs imlu ITT,

**Secondary endpoints:** OS, safety

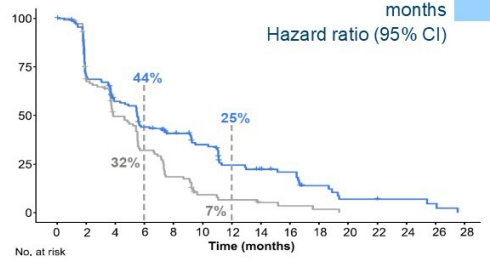
## ITT

| | Imlunestrant n=331 | SoC ET n=330 |
|---|---|---|
| No. of events | 237 | 253 |
| Median (95% CI); months | **5.6** (5.3–7.3) | **5.5** (4.6–5.6) |
| Hazard ratio (95% CI) | **0.87 (0.72–1.04)** *p*-value 0.12 | |



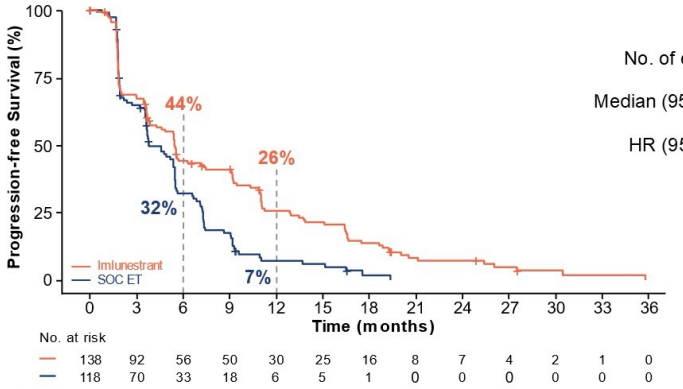

## ESR1m

| | Imlunestrant n=138 | SoC ET n=118 |
|---|---|---|
| No. of events | 109 | 102 |
| Median (95% CI); months | **5.5** (3.9-7.4) | **3.8** (3.7-5.5) |
| Hazard ratio (95% CI) | **0.62 (0.46–0.82)** *p*-value <0.001 | |




DCO: 24 June 2024. [a]Median follow-up for patients with *ESR1*m was 16.7 months (imlunestrant group) and 13.8 months (SoC ET group); [b]Median follow-up for all patients was 16.6 months (imlunestrant group) and 16.8 months (SoC ET group); [c]At full alpha after recycling. CI=confidence interval; DCO=data cutoff; *ESR1*m=estrogen receptor 1 mutation; ET=endocrine therapy; PFS=progression-free survival; SoC=standard of care. Jhaveri KL, et al. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2410858. Online ahead of print.

## Primary Endpoint: PFS of Imlunestrant vs SOC ET in Patients With *ESR1*m




| | Imlunestrant n=138 | SOC ET n=118 |
|---|---|---|
| No. of events | 122 | 103 |
| Median (95% CI) | **5.5** (3.9-7.4) | **3.8** (3.7-5.5) |
| HR (95% CI) | **0.62 (0.47-0.82)** | |
| | Nominal *p*-value[a] = 0.0007 | |

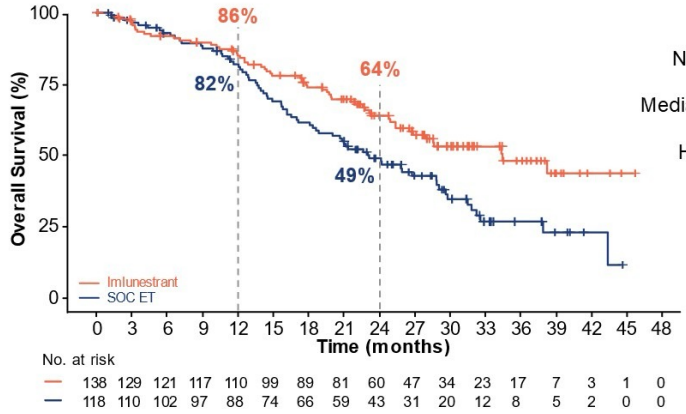
**PFS benefit of imlunestrant was sustained in patients with *ESR1*m**

[a]Reached formal statistical significance at primary PFS analysis. Note: Median follow-up was 27.6 months across both arms.
*CI, confidence interval; ESR1m, estrogen receptor 1 gene mutation; HR, hazard ratio; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.*





## Secondary Endpoint: Interim OS of Imlunestrant vs SOC ET at 50% Maturity in Patients With *ESR1*m




| | Imlunestrant n=138 | SOC ET n=118 |
|---|---|---|
| No. of deaths | 57 | 71 |
| Median (95% CI) | **34.5** (25.4-NR) | **23.1** (18.4-28.9) |
| HR (95% CI) | **0.60 (0.43-0.86)** | |
| | *p*-value = 0.0043* | |

**p*-value did not achieve prespecified threshold for significance (*p*=0.0000004 at IA2)

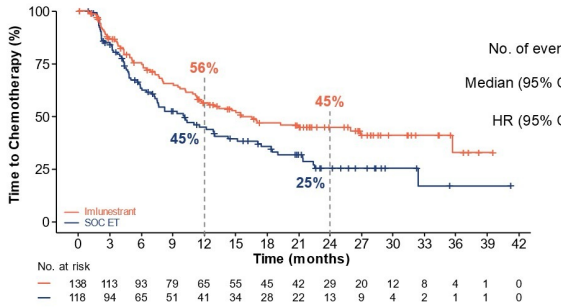
**Imlunestrant led to an ~11 month numerical improvement in median OS in patients with *ESR1*m**

Note: The median follow-up was 29.5 months across both arms.
*CI, confidence interval; ESR1m, estrogen receptor 1 gene mutation; HR, hazard ratio; IA2, Interim Analysis 2; NR, not reached; OS, overall survival; SOC ET, standard of care endocrine therapy.*





## Exploratory Endpoint: TTC of Imlunestrant vs SOC ET in Patients With *ESR1*m




| | Imlunestrant n=138 | SOC ET n=118 |
|---|---|---|
| No. of events | 70 | 74 |
| Median (95% CI) | **15.6** (11.4-35.8) | **10.2** (7.3-13.0) |
| HR (95% CI) | **0.66 (0.48-0.92)** | |

# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

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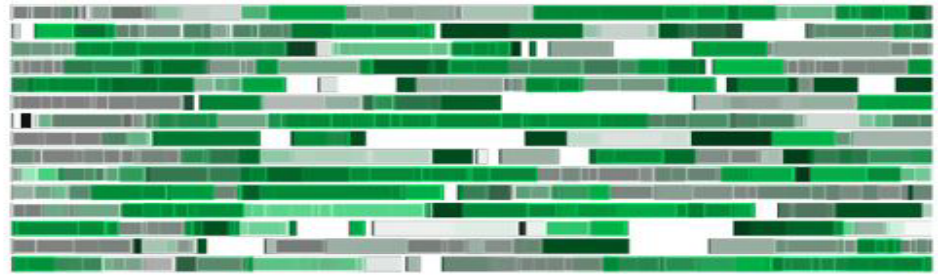


# evERA Study Design

## A global, randomised, open-label, Phase III trial

### Key Eligibility Criteria*

- ER+, HER2– aBC (1–3L of therapy)
- ≤ 2 prior lines of ET in the aBC setting
- PD or relapse during/post-CDK4/6i + ET
- No prior chemotherapy in the aBC setting
- Measurable disease per RECIST v1.1 or evaluable bone metastases

* Trial was enriched to 55% of patients with *ESR1*m at baseline (centrally tested via circulating tumour DNA)

### Stratification Factors

- Prior treatment with fulvestrant (yes vs no)
- *ESR1*m (yes vs no/indeterminate)
- Site of disease (visceral [lung and/or liver involvement] vs non-visceral)

**Enrolment period: August 2022 to October 2024**

N = 373*

R 1:1

- **Giredestrant (30 mg) + everolimus (10 mg)†**
- **SOC ET‡ + everolimus (10 mg)† ‡Exemestane/fulvestrant/tamoxifen**

**Until PD or unacceptable toxicity**

† Dexamethasone mouthwash prophylaxis and treatment was strongly recommended per SWISH trial protocol[1]

### Co-primary endpoints (RECIST v1.1)

- INV-PFS in patients whose tumours had *ESR1*m
- INV-PFS in the ITT population

### Key secondary endpoints

- OS
- INV-assessed ORR, DoR

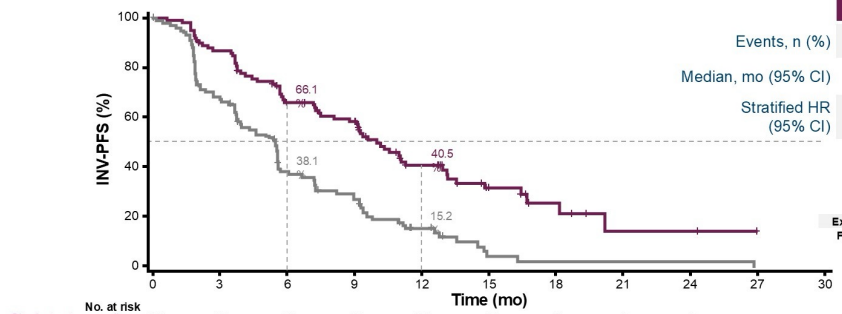
ClinicalTrials.gov number, NCT05306340. Adapted from Mayer EL, *et al.* SABCS 2022 (poster OT2-01-07) with permission.

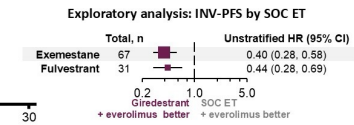
1–3L, first to third line; aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DoR, duration of response; ER+, oestrogen receptor-positive; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; HER2–, HER2-negative; INV, investigator-assessed; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC ET, standard of care endocrine therapy. 1. Rugo HS, *et al. Lancet Oncology* 2017; **18**:654–662.



# Co-primary Endpoint – INV-PFS in the ESR1m Population

| | Giredestrant + everolimus n = 102 | SOC ET + everolimus n = 105 |
|---|---|---|
| Events, n (%) | 63 (61.8) | 89 (84.8) |
| Median, mo (95% CI) | **9.99** (8.08, 12.94) | **5.45** (3.75, 5.62) |
| Stratified HR (95% CI) | **0.38** (0.27, 0.54); p < 0.0001 | |




**Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1*m**

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 11.14 mo (giredestrant + everolimus) and 5.68 mo (SOC ET + everolimus); stratified HR, 0.49; 95% CI: 0.34, 0.71. CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; INV, investigator-assessed; mo, months; PFS, progression-free survival; SOC ET, standard of care endocrine therapy.

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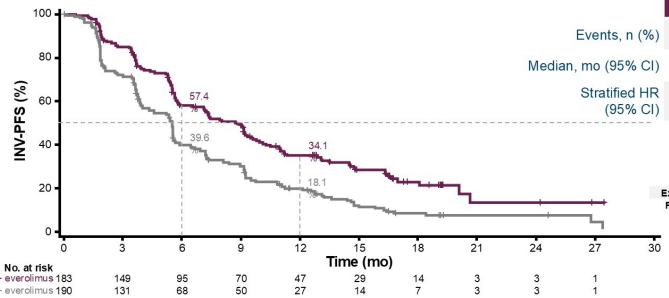
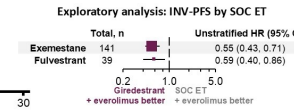
# Co-primary Endpoint – INV-PFS in the ITT Population

| | Giredestrant + everolimus n = 183 | SOC ET + everolimus n = 190 |
|---|---|---|
| Events, n (%) | 126 (68.9) | 163 (85.8) |
| Median, mo (95% CI) | 8.77 (6.60, 9.59) | 5.49 (4.01, 5.59) |
| Stratified HR (95% CI) | **0.56** (0.44, 0.71); p < 0.0001 | |




**Combination therapy with giredestrant + everolimus led to a clinically meaningful 44% reduction in the risk of progression or death in patients in the ITT population**

Data cutoff: 16 July 2025. PFS by blinded independent radiologist was similar to INV-PFS: Median PFS was 10.32 mo (giredestrant + everolimus) and 7.26 mo (SOC ET + everolimus); stratified HR, 0.66; 95% CI: 0.50, 0.87.

## What About Co-mutations?

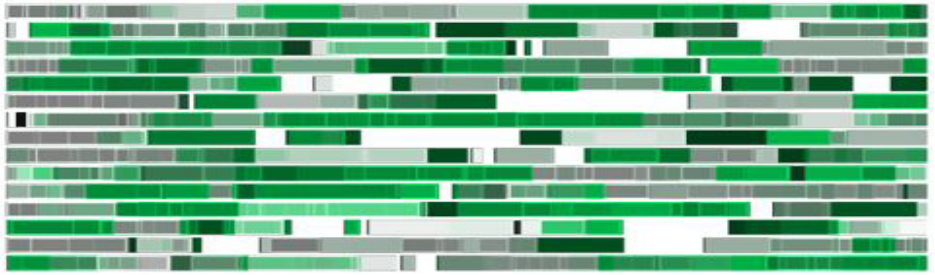
- Both ESR1 and PIK3CA mutations are prevalent in pretreated ER+ HER2- MBC
- Can co-occur in about 15% of cases
- What is best treatment strategy?

## EMERALD Subgroup Analysis: PFS by Subgroup in ESR1m Patients With ≥12 Mo of CDK4/6i

| Subgroup | Patients, n (%) | Median PFS, Mo (95% CI) | | HR (95% CI) |
|---|---|---|---|---|
| | | Elacestrant | SoC | |
| All *ESR1*m | 159 (100) | 8.6 | 1.9 | 0.41 (0.26-0.63) |
| *ESR1*m with liver and/or lung mets | 113 (71) | 7.3 | 1.9 | 0.35 (0.21-0.59) |
| *ESR1*m and *PIK3CA*m | 62 (39) | 5.5 | 1.9 | 0.42 (0.18-0.94) |
| *ESR1*m and *TP53*m | 61 (38) | 8.6 | 1.9 | 0.30 (0.13-0.64) |
| *ESR1*m and HER2 low | 77 (48) | 9.0 | 1.9 | 0.30 (0.14-0.60) |

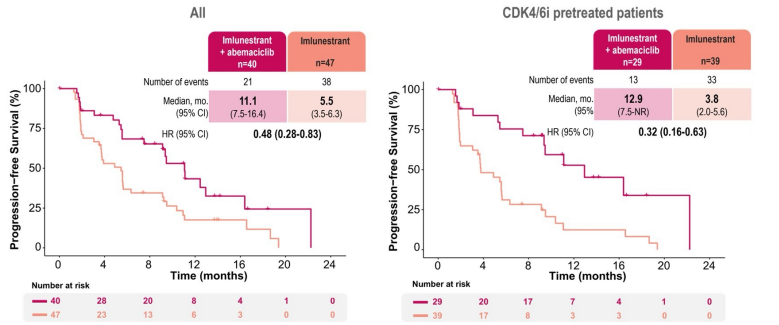
Bardia. Clin Cancer Res. 2024;30:4299.





## EMBER-3: PFS by ESR1 and PI3K-pathway Co-mutation Status in all Patients and CDK4/6i Pretreated Patients

In patients with both *ESR1*m and PI3K-pathway mutations

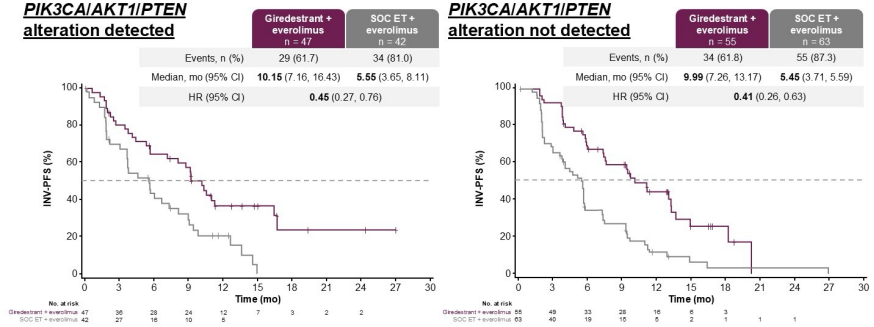



Dana-Farber Cancer Institute | San Antonio Breast Cancer Symposium



## INV-PFS by *PIK3CA*/*AKT1*/*PTEN* alteration status (*ESR1*m population)

San Antonio Breast Cancer Symposium | UT Health San Antonio | AACR




Data cutoff: July 16, 2025. HR estimates are unstratified. *AKT1*, AKT serine/threonine kinase 1; CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; mo, months; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; SOC ET, standard-of-care endocrine therapy.

# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

## A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026

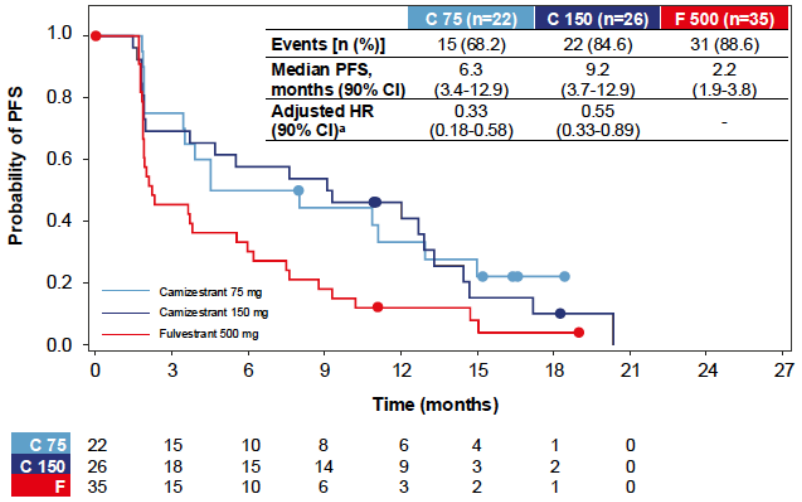
# SERD EARLIER...

**Camizestrant, a next-generation oral SERD, versus fulvestrant in post-menopausal women with oestrogen receptor-positive, HER2-negative advanced breast cancer (SERENA-2): a multi-dose, open-label, randomised, phase 2 trial**

*Mafalda Oliveira, Denys Pominchuk, Zbigniew Nowecki, Erika Hamilton, Yaroslav Kulyaba, Timur Andabekov, Yevhen Hatko, Tamar Melkadze, Gia Nemsadze, Patrick Neven, Vladimir Vladimirov, Claudio Zamagni, Hannelore Denys, Frédéric Forget, Zsolt Horvath, Alfiya Nesterova, Maxine Ajimi, Bistra Kirova, Teresa Klinowska, Justin P O Lindemann, Delphine Lissa, Alastair Mathewson, Christopher J Morrow, Zuzana Traugottova, Ruaan van Zyl, Ekaterine Arkania*

## PFS in patients by detectable *ESR1*m

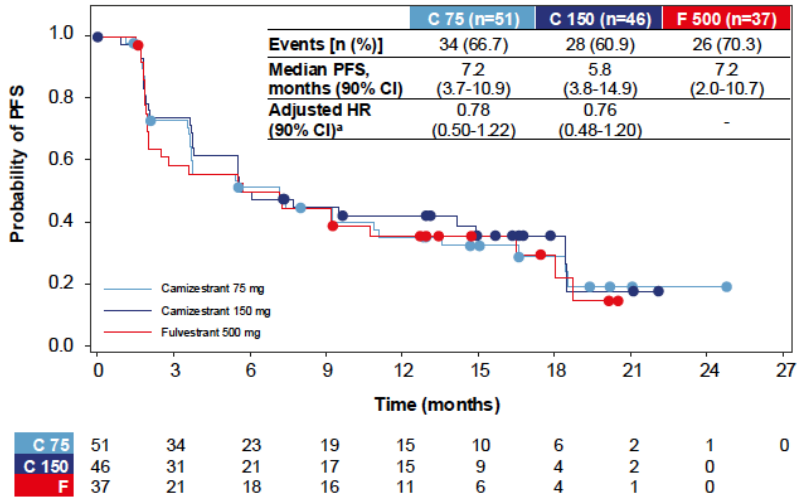
### *ESR1*m detectable at baseline




| | C 75 (n=22) | C 150 (n=26) | F 500 (n=35) |
|---|---|---|---|
| Events [n (%)] | 15 (68.2) | 22 (84.6) | 31 (88.6) |
| Median PFS, months (90% CI) | 6.3 (3.4-12.9) | 9.2 (3.7-12.9) | 2.2 (1.9-3.8) |
| Adjusted HR (90% CI)[a] | 0.33 (0.18-0.58) | 0.55 (0.33-0.89) | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| C 75 | 22 | 15 | 10 | 8 | 6 | 4 | 1 | 0 |
| C 150 | 26 | 18 | 15 | 14 | 9 | 3 | 2 | 0 |
| F | 35 | 15 | 10 | 6 | 3 | 2 | 1 | 0 |

### *ESR1*m not detectable at baseline




| | C 75 (n=51) | C 150 (n=46) | F 500 (n=37) |
|---|---|---|---|
| Events [n (%)] | 34 (66.7) | 28 (60.9) | 26 (70.3) |
| Median PFS, months (90% CI) | 7.2 (3.7-10.9) | 5.8 (3.8-14.9) | 7.2 (2.0-10.7) |
| Adjusted HR (90% CI)[a] | 0.78 (0.50-1.22) | 0.76 (0.48-1.20) | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| C 75 | 51 | 34 | 23 | 19 | 15 | 10 | 6 | 2 | 1 | 0 |
| C 150 | 46 | 31 | 21 | 17 | 15 | 9 | 4 | 2 | 0 | |
| F | 37 | 21 | 18 | 16 | 11 | 6 | 4 | 1 | 0 | |

- In the sub-population of patients with detectable *ESR1*m at baseline, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

[a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

CI: confidence interval; CDK4/6i: CDK4/6 inhibitor; ESR1m: mutation in estrogen receptor 1 gene; HR: hazard ratio; PFS: progression-free survival

# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

## A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026

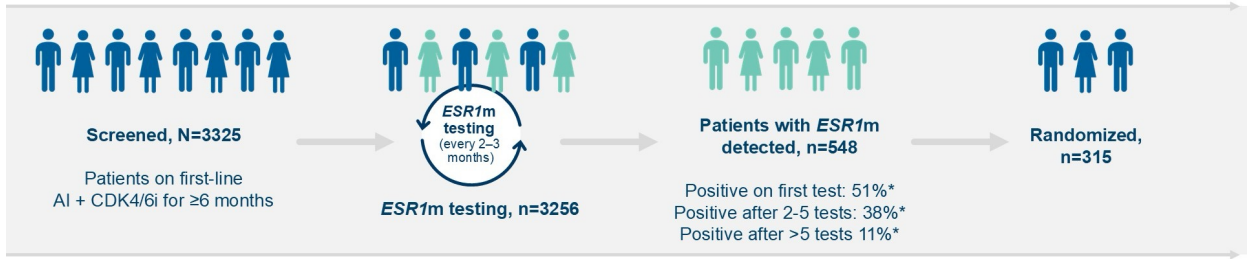
# SERD EARLIER...

## What About Moving SERDs Earlier Into Treatment?

- **SERDs may have greatest benefit for ESR1 mutated cancers**
- **What if they are used at time of development of ESR1 mutation?**



## SERENA-6: *ESR1*m Surveillance During 1L AI+CDK4/6i




**Patients tested for *ESR1*m in ctDNA with Guardant360 CDx every 2–3 months at time of routine staging scans**

**Patients ongoing in surveillance when screening closed, n=1949**

**Discontinued (n=233) due to:**

Screen failure (n=200)
- Concurrent disease progression (n=53)
- Patient not meeting other eligibility criteria (n=48)
- Reason not provided (n=99)

Withdrew consent, lost to follow-up or unknown (n=33)

**A crude estimate of the proportion of patients with emergent *ESR1*m during the study period is 42%, calculated from the 548 patients with a positive test/ (the number of patients tested for *ESR1*m [n=3256] minus the number of patients that were still ongoing in surveillance when screening closed [n=1949]).**

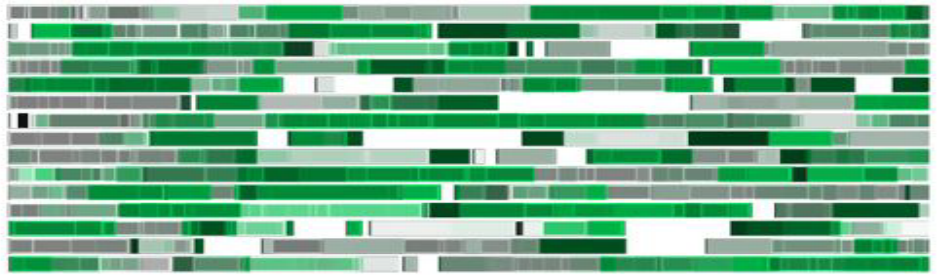
Number of tests to obtain a positive *ESR1*m test result based on n=521 patients who met all the eligibility criteria for the *ESR1*m surveillance step. Patients were screened for inclusion into the study from 264 sites in 23 countries. Of the 3325 patients screened for inclusion, ctDNA from patient blood samples were tested for *ESR1*m using Guardant360CDx (Guardant Health, Redwood City, CA, US).

Turner et al, ASCO 2025

# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

## A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

## SEVILLA, 12 Y 13 DE FEBRERO DE 2026



## SERENA-6: Step 2 Study Design

Phase III, randomized, double-blind, placebo-controlled study (NCT04964934)

- Female/male patients with ER+/HER2– ABC*
- All patients that have received AI + CDK4/6i (palbociclib, ribociclib, or abemaciclib) as initial endocrine-based therapy for ABC for at least 6 months
- *ESR1*m detected in ctDNA with no evidence of disease progression

R 1:1
N=315

Camizestrant (75 mg qd) + continuing CDK4/6i + placebo for AI

Continuing AI (anastrozole/ letrozole) + CDK4/6i + placebo for camizestrant

**STRATIFICATION FACTORS**
- Visceral vs non-visceral
- *ESR1*m detection at first test vs at a subsequent test
- Time from initiation of AI + CDK4/6i to randomization: <18 vs ≥18 months
- Palbociclib vs ribociclib vs abemaciclib

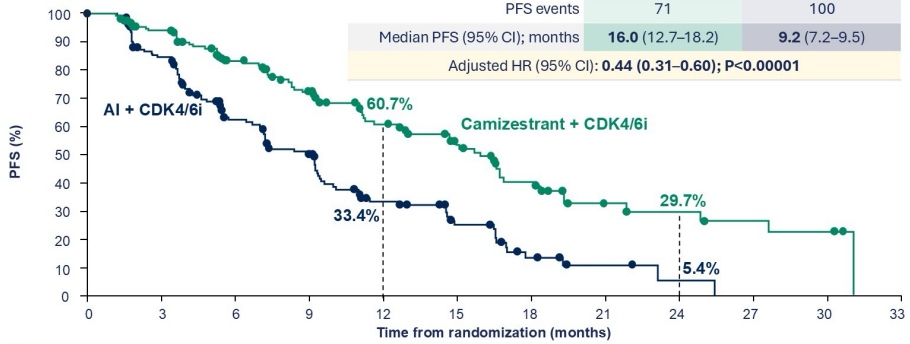
Treatment continued until disease progression, unacceptable toxicity, patient withdrawal or death

**PRIMARY ENDPOINT**
PFS by investigator assessment (RECIST v1.1)

**SECONDARY ENDPOINTS**
- PFS2**
- OS**
- Safety
- Patient-reported outcomes

## SERENA-6: Primary Endpoint: Investigator-assessed PFS

| | Camizestrant + CDK4/6i (N=157) | AI + CDK4/6i (N=158) |
|---|---|---|
| PFS events | 71 | 100 |
| Median PFS (95% CI); months | **16.0** (12.7–18.2) | **9.2** (7.2–9.5) |
| Adjusted HR (95% CI): **0.44 (0.31–0.60); P<0.00001** | | |




**Number of patients at risk**

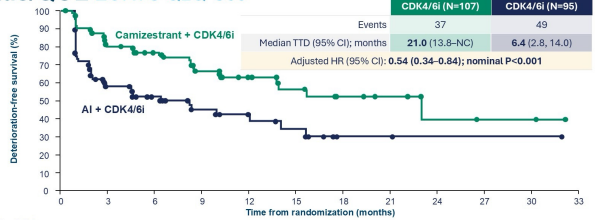
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Camizestrant + CDK4/6i | 157 | 138 | 105 | 82 | 55 | 41 | 26 | 11 | 9 | 7 | 6 | 0 |
| AI + CDK4/6i | 158 | 124 | 73 | 55 | 29 | 17 | 7 | 3 | 1 | 0 | 0 | 0 |

P-value crossed the threshold for significance (P=0.0001). PFS was defined per RECIST v1.1. HR was estimated using the Cox proportional hazard model adjusted for stratification factors.
CI, confidence interval; HR, hazard ratio.

Turner et al, ASCO 2025
Erica L. Mayer MD, MPH | 2025 23

## SERENA-6: Time to Deterioration in Global Health Status/QOL EORTC QLQ-C30

| | Camizestrant + CDK4/6i (N=107) | AI + CDK4/6i (N=95) |
|---|---|---|
| Events | 37 | 49 |
| Median TTD (95% CI); months | **21.0** (13.8–NC) | **6.4** (2.8, 14.0) |
| Adjusted HR (95% CI): **0.54 (0.34–0.84); nominal P<0.001** | | |




**Number of patients at risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Camizestrant + CDK4/6i | 107 | 72 | 59 | 40 | 24 | 16 | 9 | 6 | 3 | 2 | 2 | 0 |
| AI + CDK4/6i | 95 | 42 | 26 | 16 | 11 | 8 | 2 | 2 | 1 | 1 | 1 | 0 |

**Camizestrant + CDK4/6i also delayed the time to deterioration in pain compared with AI + CDK4/6i**

Assessments were conducted at baseline, weeks 4, 8 and 12 and then every 6 weeks until PFS2. Analysis conducted in patients with a baseline score and at least one post-baseline assessment. TTD in global health status/quality of life, an exploratory endpoint, was defined as the time from randomization to first deterioration that was confirmed at a subsequent timepoint measured using the European Organization for Research and Treatment of Cancer 30-item quality-of-life questionnaire (**EORTC QLQ-30**). Deterioration was defined as a decrease from baseline ≥10.6. HR was estimated using the Cox proportional hazard model stratified by time of *ESR1*m detection (one test vs more than one test), and time from initiation of AI + CDK4/6i to randomization (<18 months vs. ≥18 months). NC, not calculable; TTD, time to deterioration.

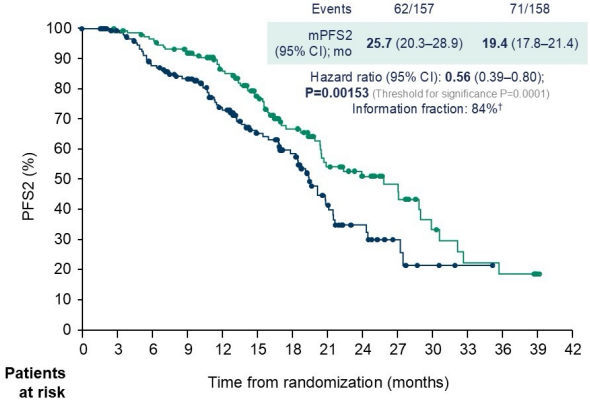
Turner et al, ASCO 2025
Erica L. Mayer MD, MPH | 2025 25

## Switching to camizestrant + CDK4/6i prolongs time to second progression and time to second subsequent therapy

SAN ANTONIO BREAST CANCER SYMPOSIUM®

### Updated PFS2*

| | CAMI + CDK4/6i | AI + CDK4/6i |
|---|---|---|
| Events | 62/157 | 71/158 |
| mPFS2 (95% CI); mo | **25.7** (20.3–28.9) | **19.4** (17.8–21.4) |
| Hazard ratio (95% CI): **0.56** (0.39–0.80); **P=0.00153** (Threshold for significance P=0.0001) Information fraction: 84%† | | |




**Patients at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CAMI + CDK4/6i | 157 | 149 | 143 | 134 | 113 | 86 | 56 | 38 | 28 | 17 | 10 | 6 | 5 | 0 |
| AI + CDK4/6i | 158 | 149 | 127 | 114 | 85 | 62 | 49 | 25 | 14 | 7 | 3 | 1 | 0 | 0 |

(m)PFS2, (median) PFS2; TSST, time to second subsequent therapy.
*Second pre-specified data cut **DCO2: June 30, 2025.** †Information fraction: the number of PFS2 events at this interim analysis divided by the number of PFS2 events expected at final analysis, multiplied by 100.
There were 60/157 TSST events in the camizestrant + CDK4/6i arm and 77/158 in the AI + CDK4/6i arm. The PFS2 and TSST hazard ratio and 95% CI are estimated using a stratified Cox proportional hazards model stratified by *ESR1*m detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6i to randomization.

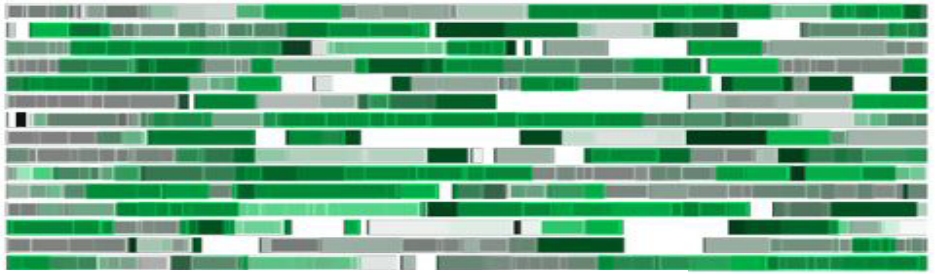
Switching to camizestrant + CDK4/6i treatment led to a clinically meaningful prolongation in PFS2 compared with continuing AI + CDK4/6i, demonstrating that the PFS gain is maintained in the subsequent line of therapy

- The **time to second subsequent therapy** (defined as the time from randomization to receiving a second subsequent therapy, or death) also favored the camizestrant + CDK4/6i arm compared with the AI + CDK4/6i arm; **hazard ratio (95% CI): 0.57 (0.40–0.81)**
- The magnitude of benefit in time to second subsequent therapy was **consistent with PFS2**

# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

## A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026



## What About Toxicity of Oral SERDs?

- SERDs are well tolerated as monotherapy
- No synergistic toxicity with a targeted agent, but combinations may introduce toxicity from partner

## Safety of Oral SERD Monotherapy in the Second-Line Setting[a]

**Common any grade adverse events (≥15% incidence), %**

| Elacestrant in EMERALD | |
|---|---|
| Dose | 400 mg (n = 237) |
| Nausea | 35 |
| Fatigue | 19 |
| Vomiting | 19 |

| Imlunestrant in EMBER-3 | |
|---|---|
| Dose | 400 mg (n = 327) |
| Fatigue | 22.6 |
| Diarrhea | 21.4 |
| Nausea | 17.1 |

| Camizestrant in SERENA-2 | | |
|---|---|---|
| Dose | 75 mg (n = 74) | 150 mg (n = 73) |
| Bradycardia | 0 | 17 |
| Photopsia | 12 | 25 |
| Asthenia | 8 | 15 |
| Fatigue | 6 | 20 |

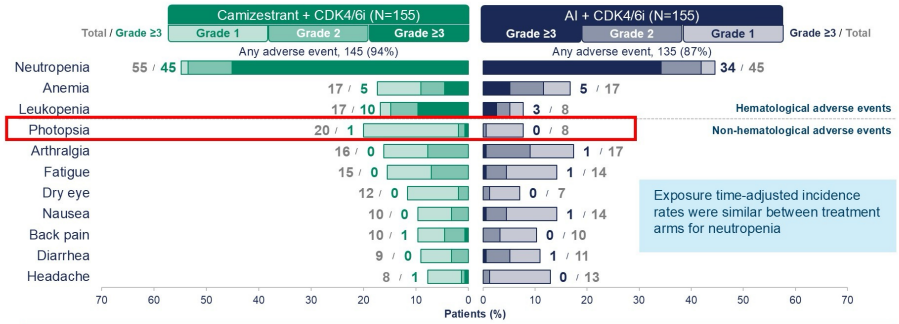
**Grade ≥3 adverse events (≥2% incidence), %**

| Elacestrant in EMERALD | |
|---|---|
| Dose | 400 mg (n = 237) |
| Nausea | 2.5 |
| Back pain | 2.5 |
| ALT increased | 2.1 |

| Imlunestrant in EMBER-3 | |
|---|---|
| Dose | 400 mg (n = 327) |
| Neutropenia | 2.1 |
| Anemia | 2.1 |

| Camizestrant in SERENA-2 | | |
|---|---|---|
| Dose | 75 mg (n = 74) | 150 mg (n = 73) |
| Fatigue | 0 | 3 |
| Hypertension | 1 | 3 |

## SERENA-6: Adverse Events (≥10% of patients)




Exposure time-adjusted incidence rates were similar between treatment arms for neutropenia

**Photopsia (brief flashes of light in the peripheral vision) did not impact daily activities:** If experienced, visual effects had no/minimal impact on daily activities, were typically ≤1 minute, ≤3 days/week, and reversible. There were no structural changes in the eye and no changes in visual acuity.

Neutropenia is reported as a group term that includes neutropenia and decreased neutrophil count; anemia is reported as a group term that includes anemia and hemoglobin decreased; leukopenia is reported as a group term that includes leukopenia and white blood cell count decrease. Bradycardia and sinus bradycardia were reported in the camizestrant + CDK4/6i arm only, in 8 patients (5.2%) and 4 patients (2.6%), respectively. No (sinus) bradycardia AEs were grade ≥3, and none of these events required treatment discontinuation. Impact of visual effects was measured using the Visual Symptom Assessment Questionnaire.

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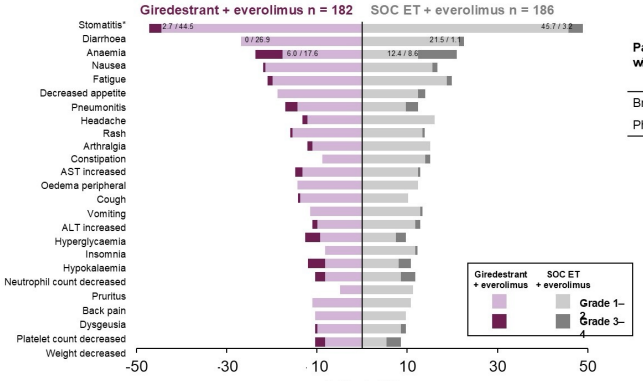
## evERA: AE Overview

**Common TEAEs (≥ 10% of patients in either arm)**




**Selected AEs**

| Patients with AE, n | Giredestrant + everolimus n = 182 | | SOC ET + everolimus n = 186 | |
|---|---|---|---|---|
| | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 |
| Bradycardia† | 7 (3.8) | 0 | 1 (0.5) | 0 |
| Photopsia | 0 | 0 | 0 | 0 |

- Data cutoff: 16 July 2025. * Dexamethasone mouthwash prophylaxis and tr… recommended per SWISH trial protocol (Rugo HS, *et al. Lancet Oncology* 2017; 18:654–662).
- † Assessed as a medical concept using grouped terms; all events were Grade 1, non-serious and no treatment interruptions/interventions were needed. All events had resolved by data cutoff.
- AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC ET, standard of care endocrine therapy; TEAE, treatment-emergent adverse event.

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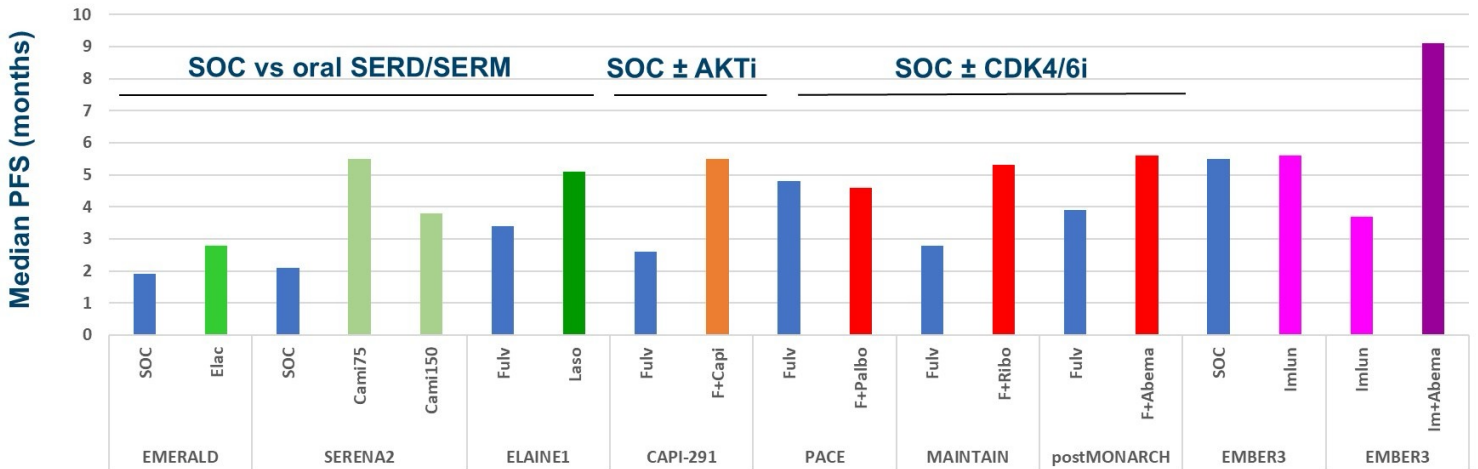
EL Mayer et al. ESMO 2025

## Median Progression Free Survival in Recent Randomized Trials of Endocrine Therapy:

Outcomes among patients with prior CDK4/6 inhibitor treatment*




*there are a lot of problems with cross study comparisons, especially in unplanned subset analyses: extent/types of prior therapy, variable tumor genomics/biomarker profile, SOC options, sample size, exposure vs resistance, investigator vs BICR, etc.

** Denotes subset of larger study cohort

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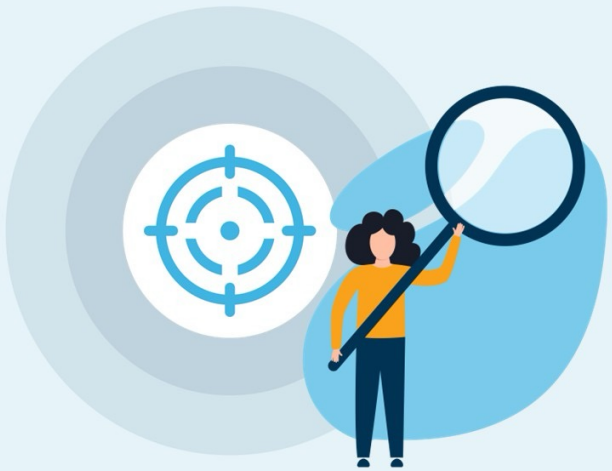
Slide adapted from Hal Burstein MD PhD

## What About Other Promising Novel Endocrine Therapies?

- **PROTAC:** Vepdegestrant
- **CERAN:** Palazestrant
- **SERM:** Lazofoxefine



# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

## A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026

## VERITAC-2: Global Phase 3 Trial of Vepdegestrant

**KEY ELIGIBILITY CRITERIA**

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

Randomization (1:1)

**28-DAY TREATMENT CYCLES**

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

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

**STRATIFICATION FACTORS:**
- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

**PRIMARY ENDPOINTS:**
- PFS by BICR in
  - *ESR1*m population
  - All patients

**SECONDARY ENDPOINTS:**
- OS (key secondary)
- CBR and ORR by BICR
- AEs

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

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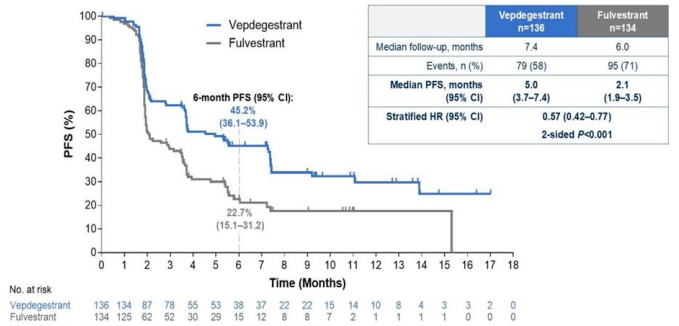
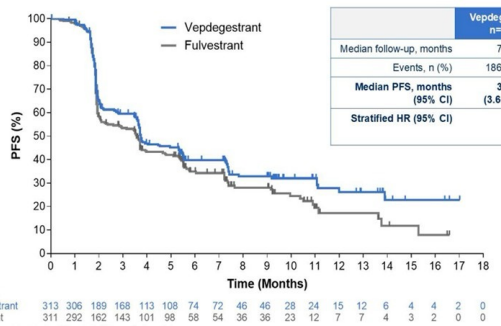
## VERITAC-2 Primary Endpoint: PFS by BICR

### ESR1 mutant population




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

### ITT population




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

BICR=blinded independent central review; HR=hazard ratio; PFS=progression-free survival.
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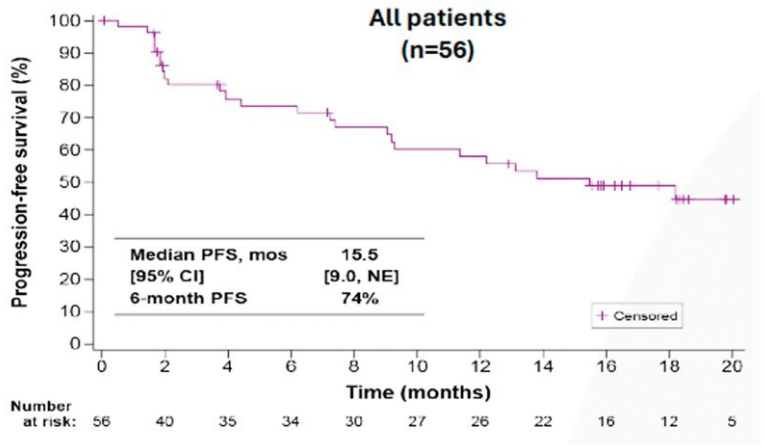
# Palazestrant: Phase 2/3 Development

**Phase 2 monotherapy/ribociclib combination:**

- Monotherapy: ORR 27%, PFS about 5 months in both ESR1m and ITT populations
- Combination with ribociclib:

| Subgroup | N | mPFS (mo) |
|---|---|---|
| ITT | 56 | 15.5 |
| Post-CDK | 40 | 12.2 |
| ESR1nmd post-CDK | 24 | 9.2 |
| ESR1mut post-CDK | 14 | 13.8 |




**OPERA-1**

- Phase 3 2L monotherapy dose optimization study of palazestrant monotherapy vs SOC ET monotherapy for ER+, HER2- MBC, post ET and CDK4/6i

**OPERA-2**

- Phase 3 1L study of palazestrant with ribociclib vs letrozole with ribociclib for 1L ER+, HER2– MBC

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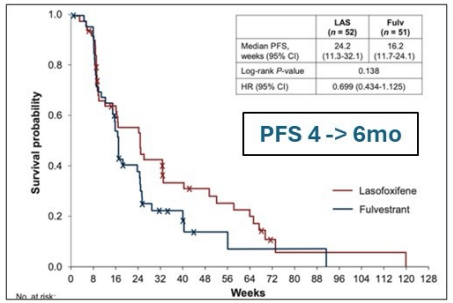
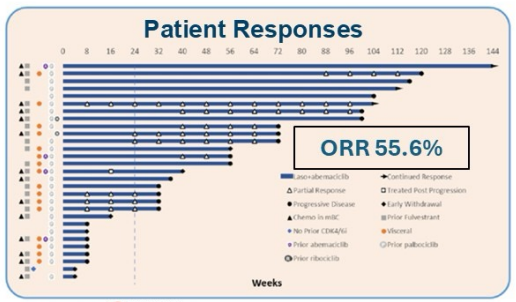
Lin N et al. ESMO 2025; Hamilton et al, Breast Cancer Res 2025

# Lasofoxifene: Phase 2/3 Development

**ELAINE 1: Phase 2 Trial of Lasofoxifene vs Fulvestrant for ER+/HER2- MBC with an ESR1 mutation**




**ELAINE 2: Phase 2 Trial of Lasofoxifene + Abemaciclib in ER+/HER2- MBC with an ESR1 Mutation**




**ELAINE 3 (NCT05696626): Open-label, phase 3, multicenter, randomized-controlled study in 18 countries**

**Participants**
- Women and men
- ER+/HER2-, locally advanced or metastatic breast cancer
- Progressed on AI plus palbociclib or ribociclib
- ≥1 *ESR1* mutation
- ***Enrollment goal:*** 400 patients (200 per group)

**Lasofoxifene** (oral; 5 mg/day) **plus** **abemaciclib** (oral; 150 mg BID)

**Randomized 1:1**

**Fulvestrant** (IM; 500 mg on days 1, 15, and 29, then monthly) **plus** **abemaciclib** (oral; 150 mg BID)

Taken until disease progression, death, unacceptable toxicity, or study withdrawal

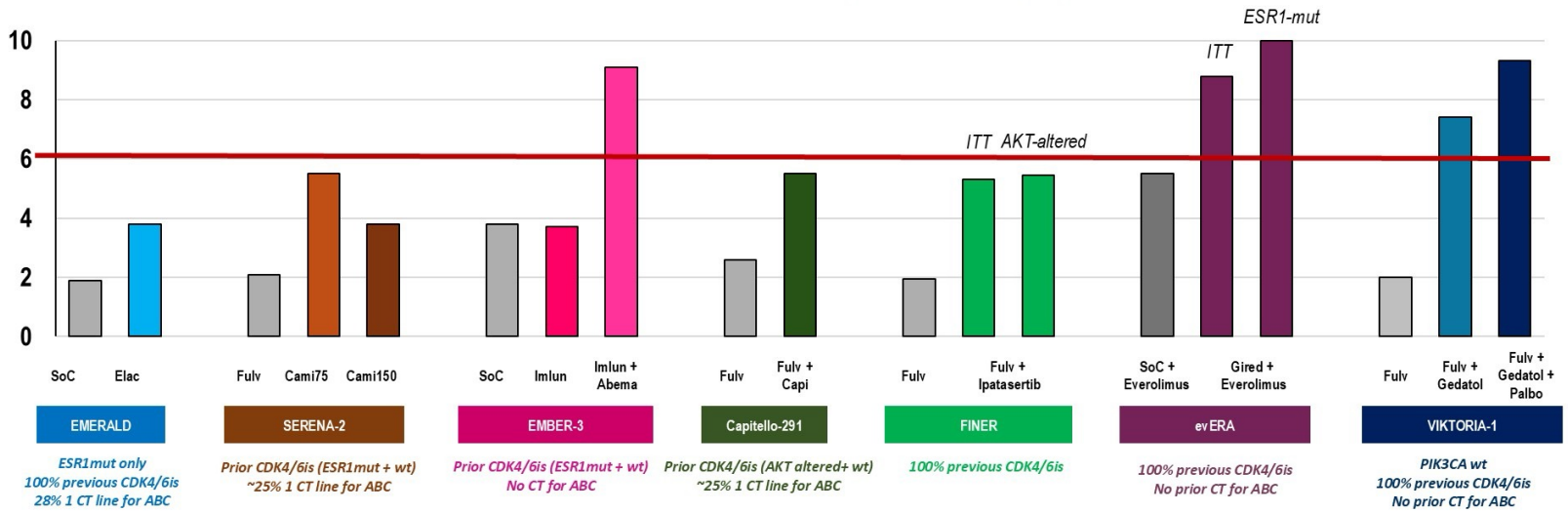
**Endpoints**
- **Primary**
  - Progression-free survival
- **Secondary**
  - Objective response rate
  - Overall survival
  - Clinical benefit rate
- **Other**
  - *ESR1* MAF changes
  - Time to chemo-therapy
  - Quality of life
  - Safety

**Statistical Analysis**
- Target sample size is 400 based on progression-free survival
- Outcomes between treatments will be compared using a stratified, Cox proportional hazards model and stratified logrank test

Goetz et al, Ann Oncol 2023; Damodaran S et al. Ann Oncol. 2023
Goetz MP et al. ASCO 2024. Abstract TPS1127.

# Pushing Beyond the 6-month PFS Ceiling after CDK4/6 Inhibitors

## Novel endocrine agents combined with targeted therapies represents the future of ET-based treatment in CDK4/6i-pretreated population

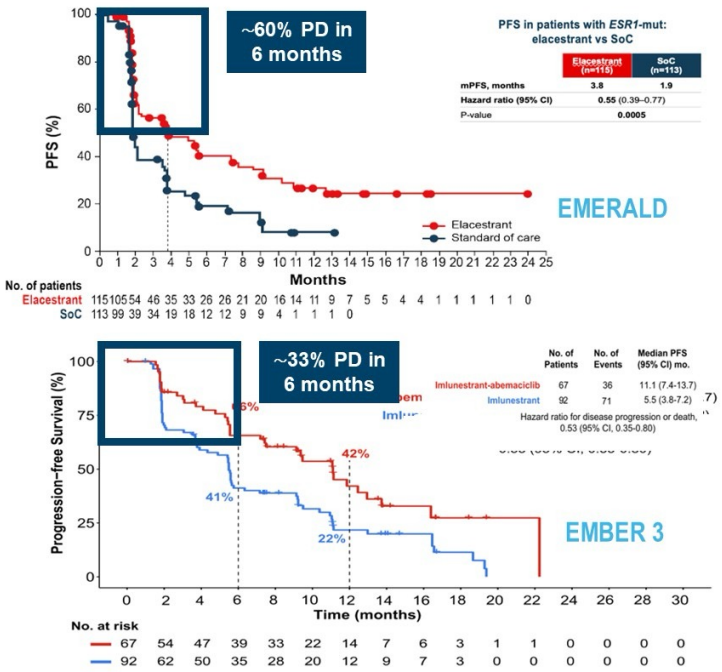


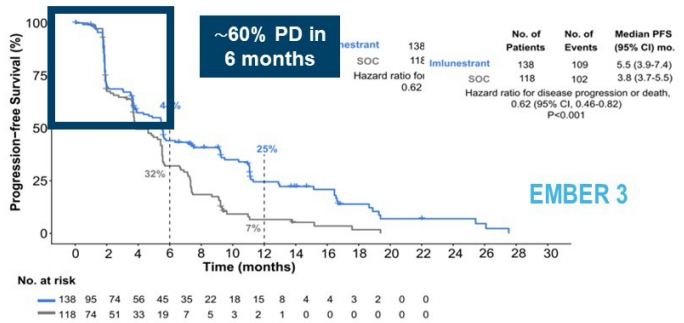

Bardia A et al SBACS 2021; Bidard FC et al JCO 2022; Oliveira M et al Lancet Oncol 2024; Jhaveri et al SABCS 2024 & NEJM 2024; Turner NC et al NEJM 2023; Chia S et al ASCO 2025; Mayer E et al ESMO 2025; Hurvitz S et al ESMO 2025

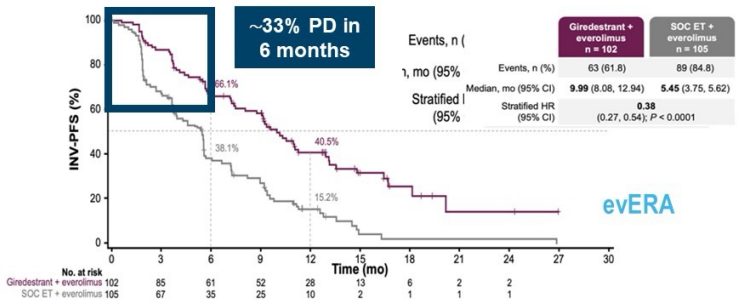
Adapted from Alessandra Gennari MD PhD

# SERD Combination is Superior to Monotherapy

## Early progression in ESR1 mut: single agent SERD vs SERD + targeted therapy

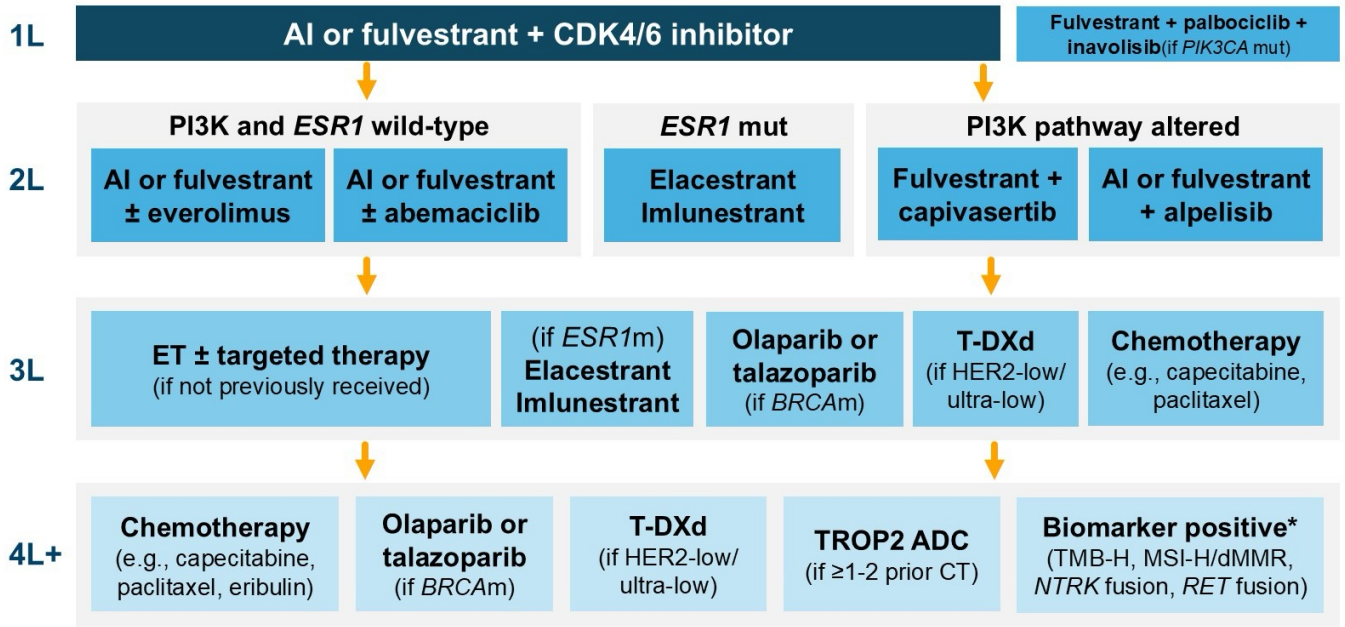



Mayer EL et al, ESMO 2025. Bidard FC et al. J Clin Oncol. 2022. Jhaveri KL et al. N Engl J Med. 2025.

# Treatment Algorithm for HR+/HER2- MBC




**Elacestrant aprobado por FDA y EMA. No precio en España**

**Imlunestrant aprobado por FDA**

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Slide adapted from Ana Garrido-Castro.

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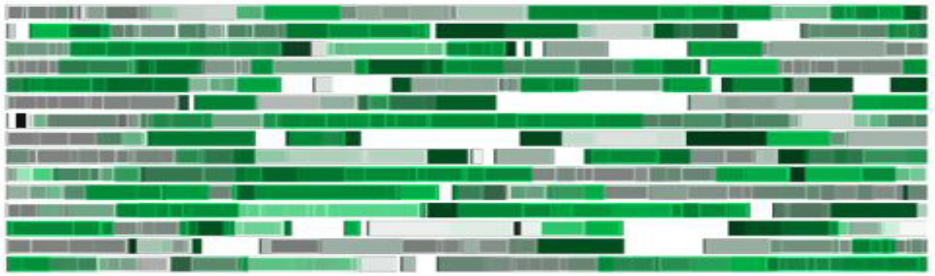

## CONCLUSIONES

- Los nuevos moduladores del receptor de estrógeno parecen afianzar su papel en la segunda línea tras el uso de inhibidores de ciclinas,sobretodo en ESR-1 mutados, siendo una formulación oral, con toxicidad aceptable y el único problema: la toxicidad económica que puede suponer su uso.

- Parece que, en combinación, como nos contarán en la próxima charla, pueden tener mayor eficacia y ser el futuro en la segunda línea.

- El uso temprano con la monitorización de ctDNA mejora la supervivencia libre de progresión, y la calidad de vida? Pero aumentará la SG?

- En enfermedad precoz ya tenemos datos positivos de Giredestrant! Y varios estudios en marcha con diferentes SERD +/- combinados con inhibidores de ciclinas, que pueden ayudar a aumentar la tasa de curación en CM luminal


Gracias!