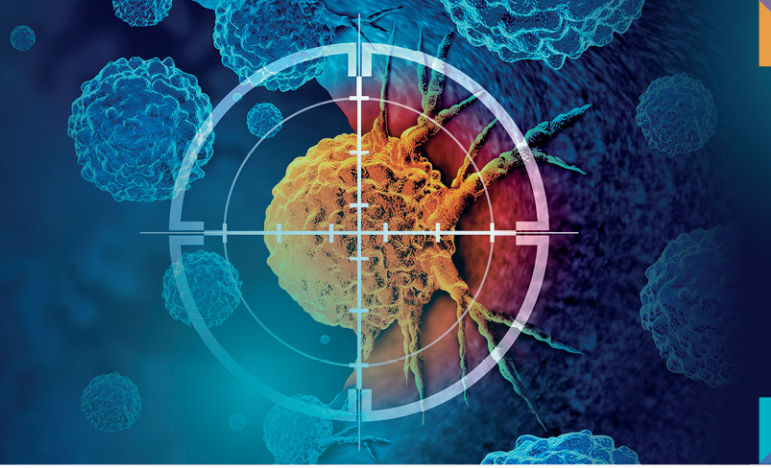
XVIII SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

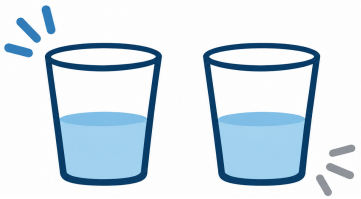
MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER



# Enfermedad luminal: Tratamiento individualizado de la enfermedad avanzada. Identificando resistencias y sensibilidades

Isabel Echavarria Díaz-Guardamino, MD, PhD

Hospital General Universitario Gregorio Marañon



# DISCLOSURES

**Employment:**

Hospital General Universitario Gregorio Marañon

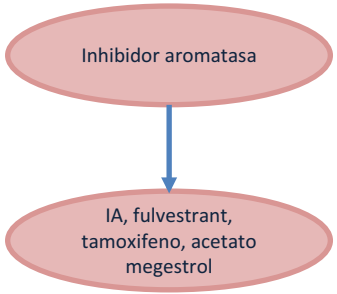
Sociedad Española de Oncología Médica

**Advisory Role:** Lilly, AstraZeneca, Daiichi Sankyo, MSD, Roche

**Speaker fees:** Roche, Pfizer, Lilly, Novartis, AstraZeneca, Daiichi Sankyo, Gilead

# 2012

1st International consensus guidelines for advanced breast cancer (ABC 1)

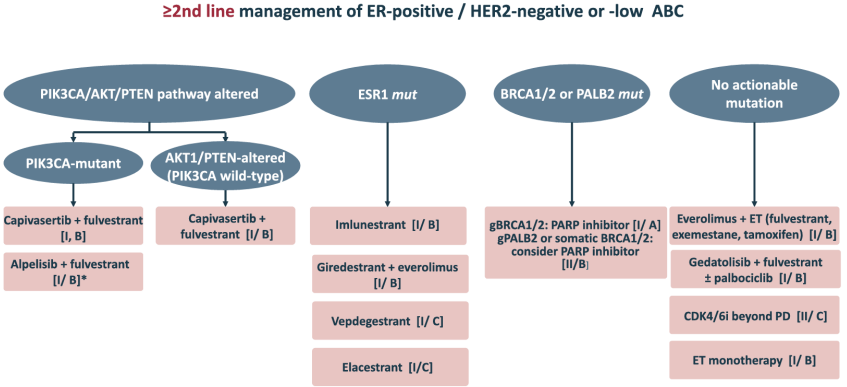



ER +/HER-2 negative ABC.

| Guideline statement | LoE |
|---|---|
| 19) Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, *even in the presence of visceral* disease, unless there is concern or proof of endocrine resistance or there is disease needing a fast response. | 1 A |
| 20) For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine therapy is the first choice. | 1 A |
| 21) The additional endocrine agent should be tamoxifen unless tamoxifen resistance is proven. An AI is also a viable option, but absolutely mandates the use of ovarian suppression/ablation. | 1 B |
| 22) The preferred 1st line ET for postmenopausal patients is an aromatase inhibitor; however, tamoxifen remains a viable option in selected patients. Type and duration of adjuvant ET must be taken into account. | 1 A |
| 23) Optimal post-aromatase inhibitor treatment is uncertain. Available options include, but are not limited to, tamoxifen, another AI (with a different mechanism of action), fulvestrant, and megestrol acetate. | 1 A |
| 24) The addition of everolimus to an AI has shown favourable results in patients with acquired endocrine resistance. However, the majority of the panel believes that additional data/studies are needed before this strategy can be recommended as standard of care. At this time, everolimus is not approved for use in this setting by EU/US regulatory authorities. | Expert opinion |
| 25) Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, though it has not been assessed in randomized trials | 1 C |
| 26) Concomitant CT + ET has not shown a survival benefit and should not be performed outside a clinical trial. | 1 B |

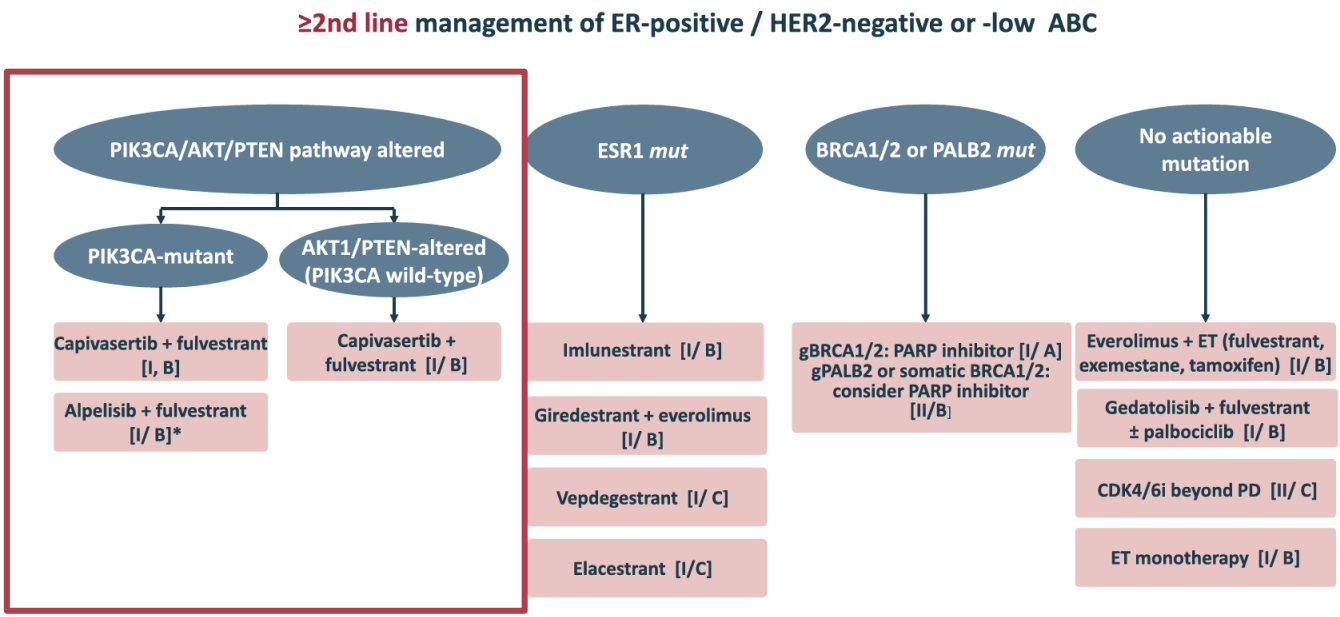
# 2026

8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)



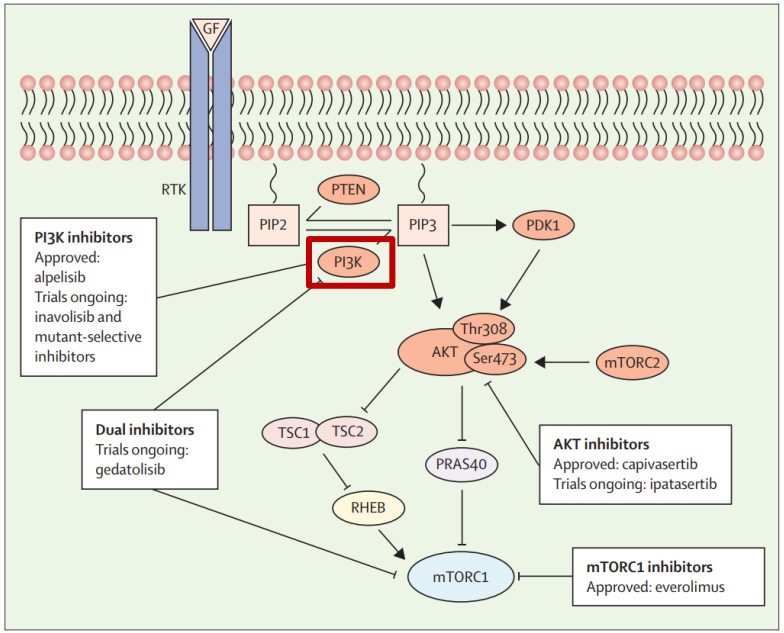

Cardoso F. The Breast 2012. Cardoso F et al. The Breast 2026

8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)




Cardoso F et al. The Breast 2026

# Vía PI3K-AKT-mTOR



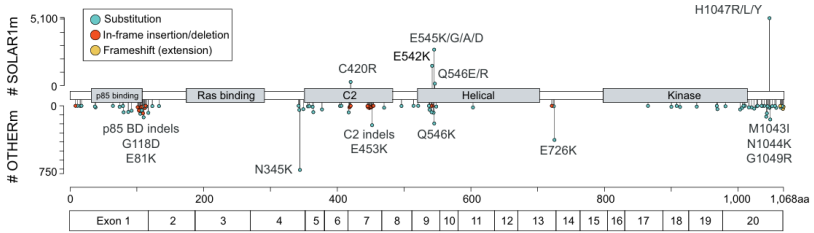

PIK3CA: subunidad catalítica p110α de PI3K.

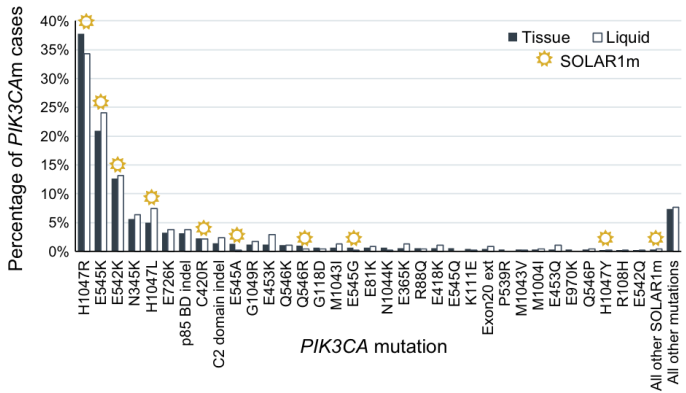
- 35-40% cáncer de mama luminal.
- Mutaciones activadoras de ganancia de función.
- Activación constitutiva → proliferación, supervivencia celular y metabolismo.

Browne, Lancet Oncol 2024. Mosele et al. Ann Oncol 2024

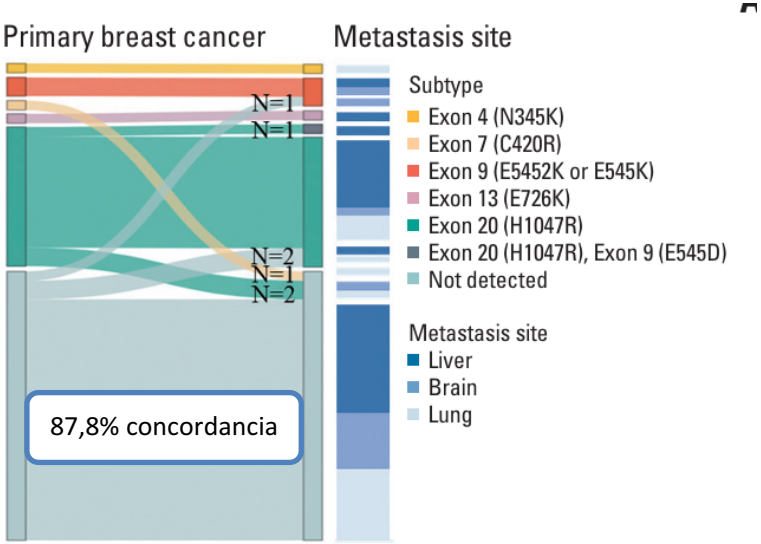
# MUTACIÓN PIK3CA

- Mutaciones recurrentes en exones 9 y 20.
- Determinación por PCR (mutaciones concretas) o mediante NGS




## Analysis of *PIK3CA* Mutation Concordance and Frequency in Primary and Different Distant Metastatic Sites in Breast Cancer



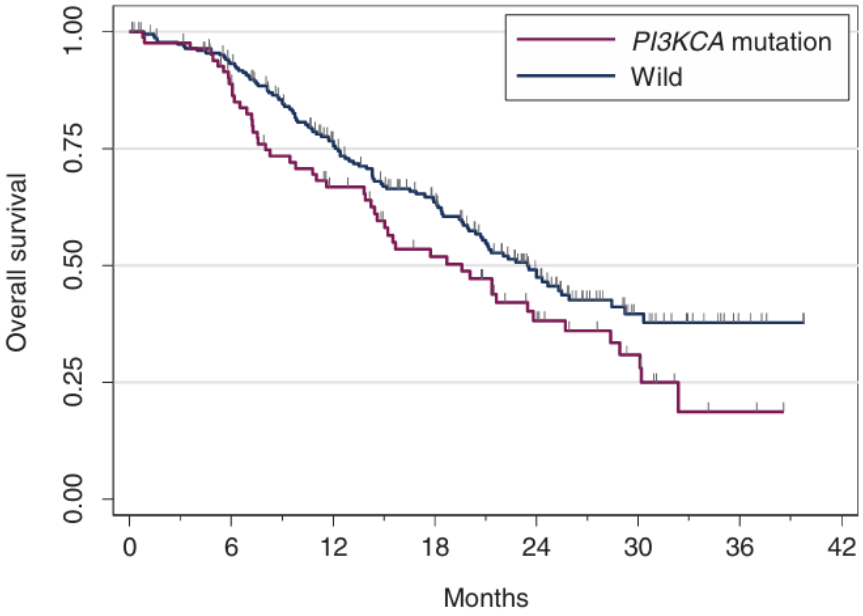

- En general mutaciones troncales.

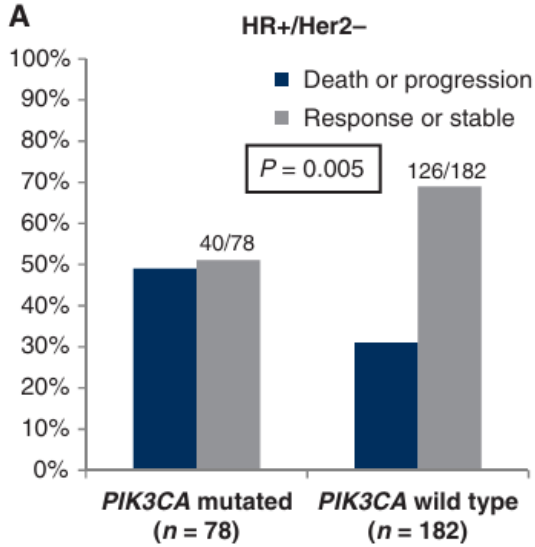
**Un pequeño porcentaje se podrían adquirir durante la evolución (9,8% de discordancias entre tumor primario y metástasis).**

Rugo H et al. Clin Cancer Res 2023. Park et al. Cancer Res Treat 2023

# Vía PI3K-AKT-mTOR: identificando RESISTENCIAS

Mutaciones en *PIK3CA* se asocian con menor sensibilidad a la quimioterapia y peor supervivencia.

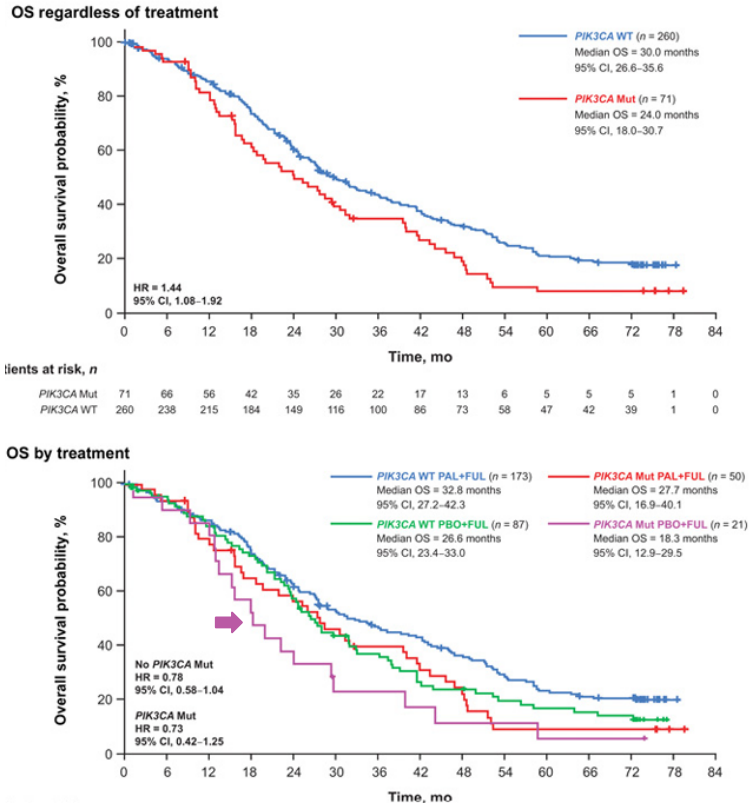



Mosele et al. Ann Oncol 2020

# Mutaciones PIK3CA en la era de los iCDK4/6 en 1ª línea: impacto pronóstico pero no predictivo

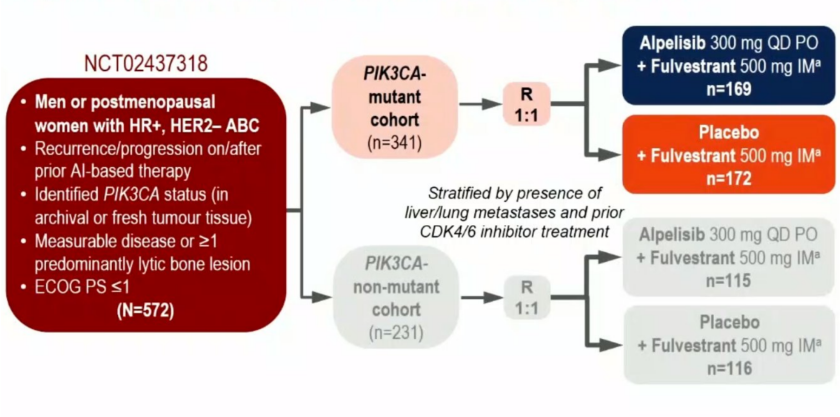
**PALOMA-3**




Cristofanilli M, et al. Clin Cancer Res.

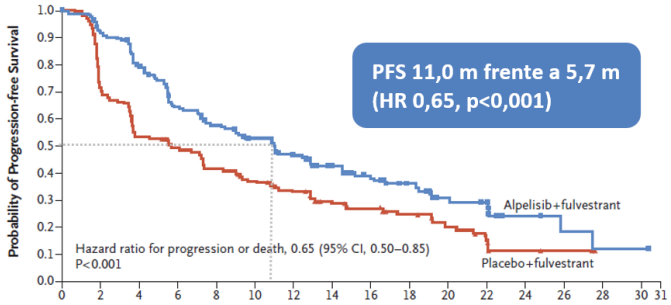
# Mutaciones en PIK3CA

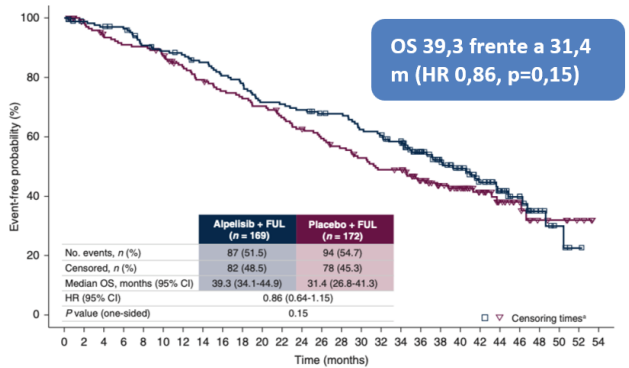
## SOLAR-1 trial: alpelisib for PIK3CAmut HR+ aBC




**≈ 5% con iCDK4/6 previo**

SLP en pacientes con mutación PI3K




André F. NEJM 2019. André F. Ann Oncol 2020

# BYLieve trial

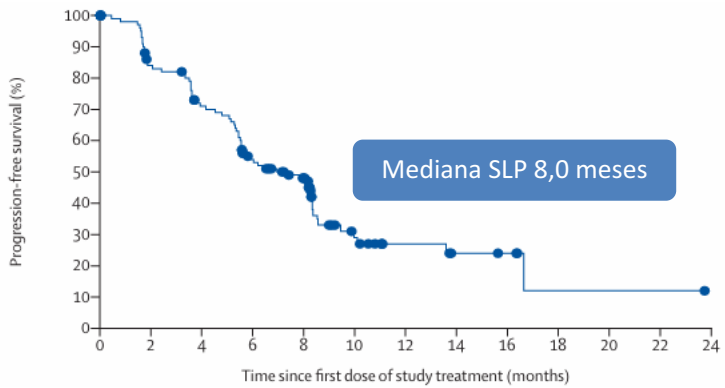
**Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation**

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

**Patients who received CDKi + AI as immediate prior treatment (N=112)[b]**
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]



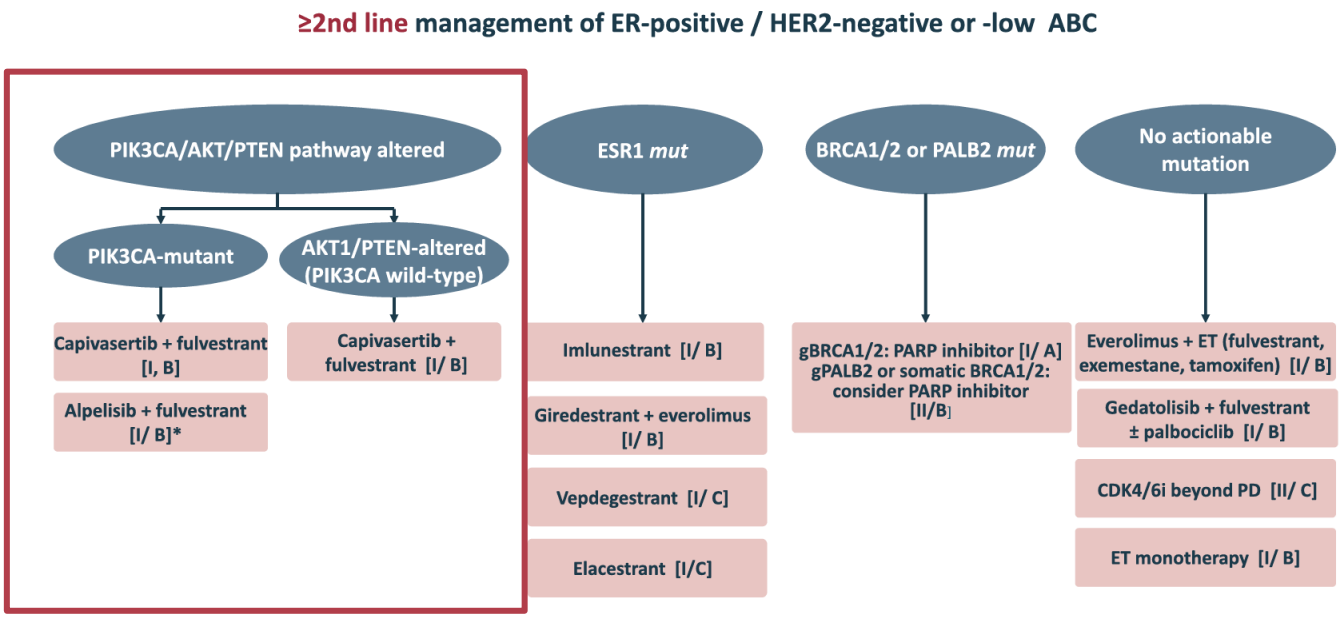

Mediana SLP 8,0 meses

Mediana SG 27,3 meses

ORR 19%

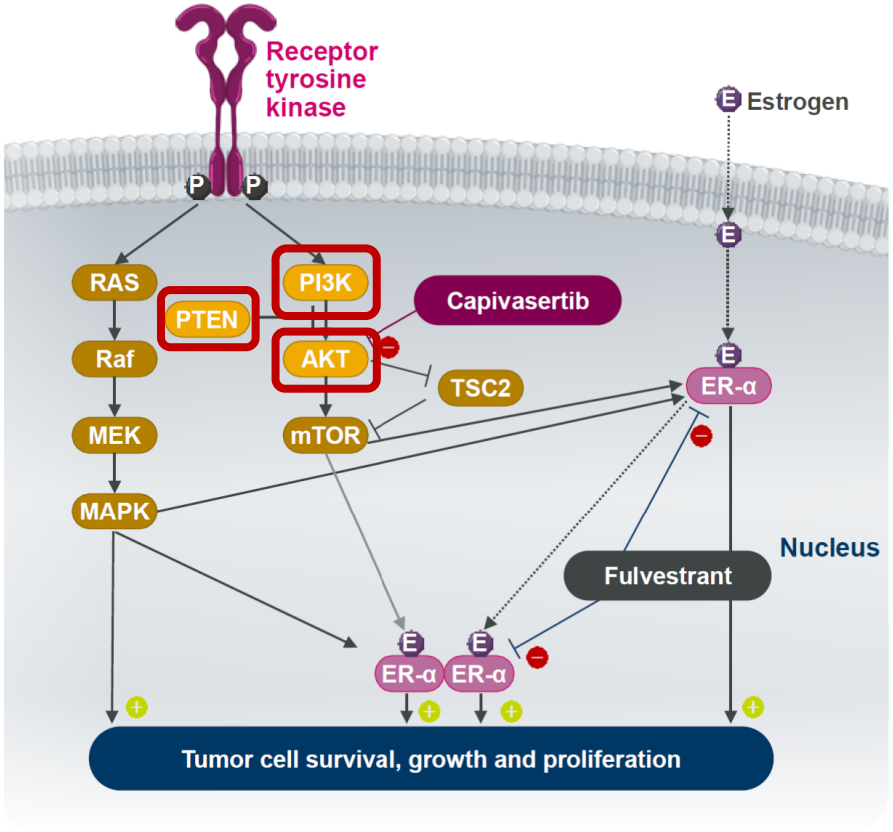
Rugo H et al. Lancet Oncol 2024

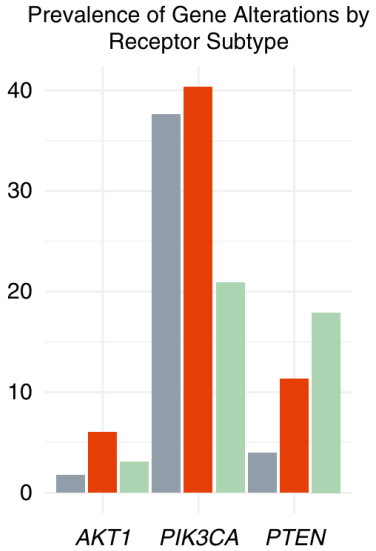
8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)

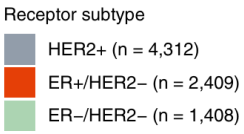



Cardoso F et al. The Breast 2026

# Capivasertib: inhibidor de las 3 isoformas de AKT



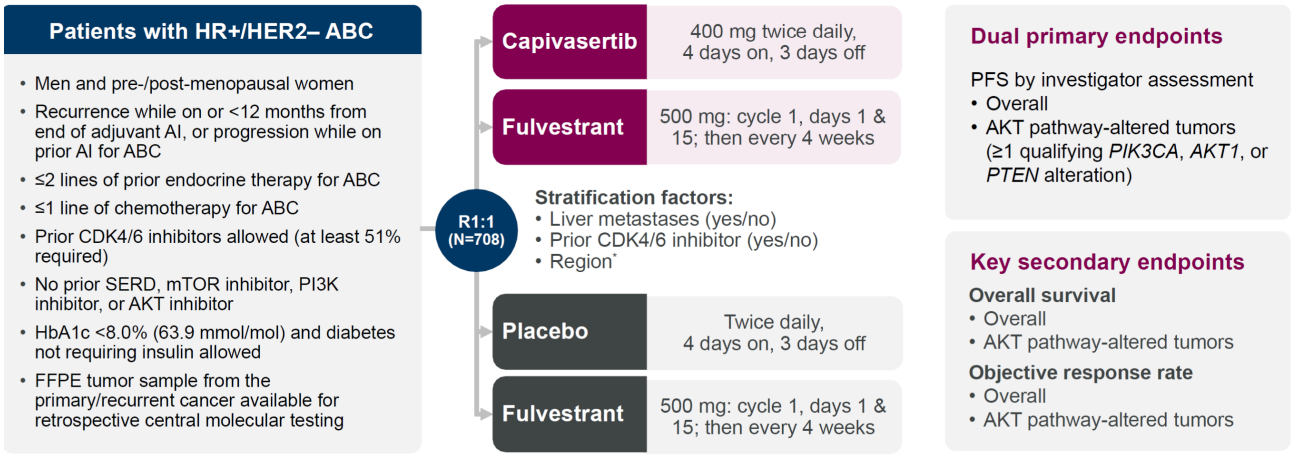

**CM luminal:**

- **PIK3CA: 35-40%**
- **AKT1: 5-7%**
- **PTEN: ≈ 10%**

Millis. JAMA Oncol 2016. Toss. Oncotarget 2018, Tao J. JCO Precision Oncol

# CAPITELLO-291 trial

**Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)**



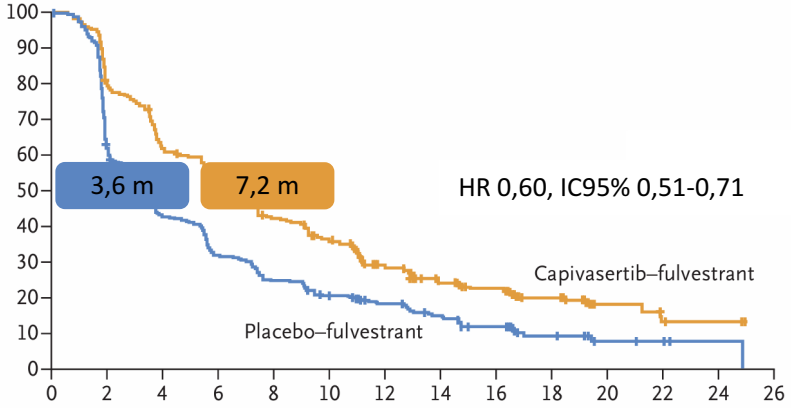

≈ 70% iCDK4/6 previo

≈ 20% quimioterapia previa

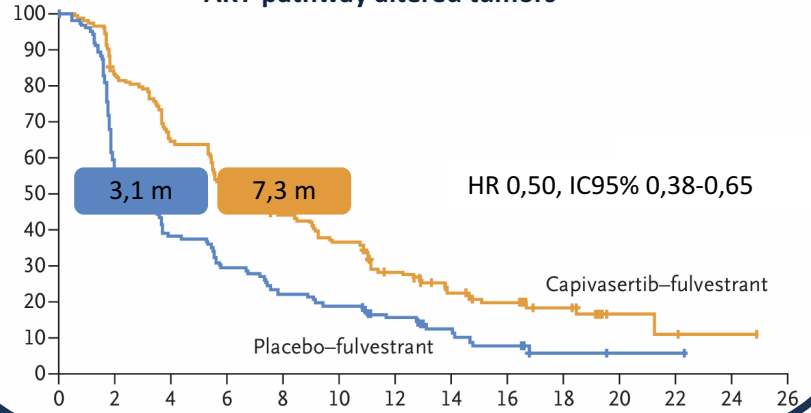
Turner N et al. SABCS 2022. Rugo H. ESMO Breast 2026

# CAPITELLO-291 trial: beneficio en SLP

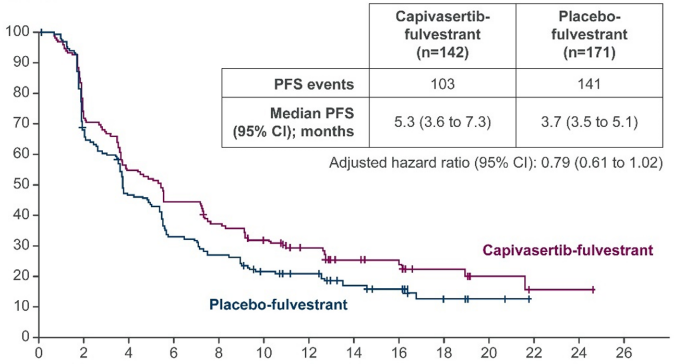
## Overall population



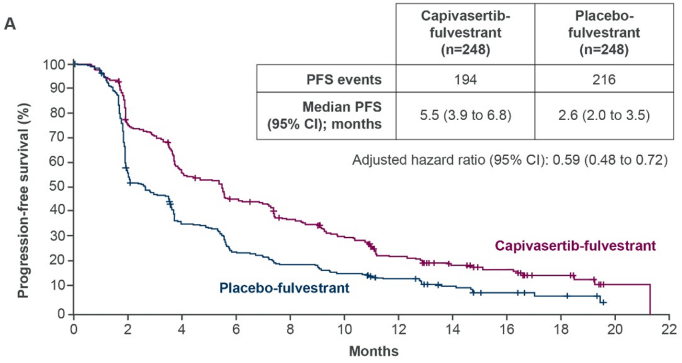

## AKT-pathway altered tumors




## Non-altered tumors



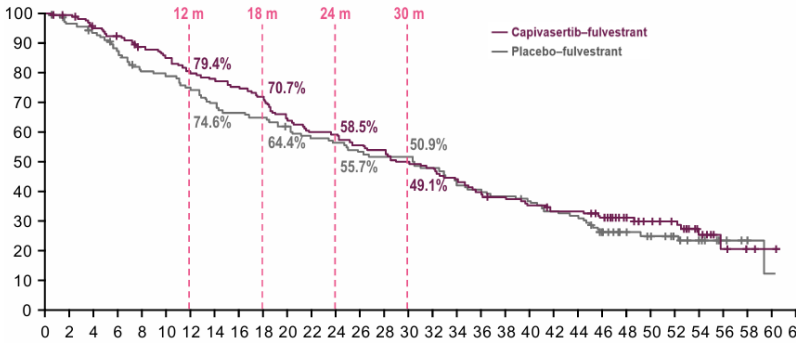

## iCDK4/6 previo




Turner N et al. NEJM 2023

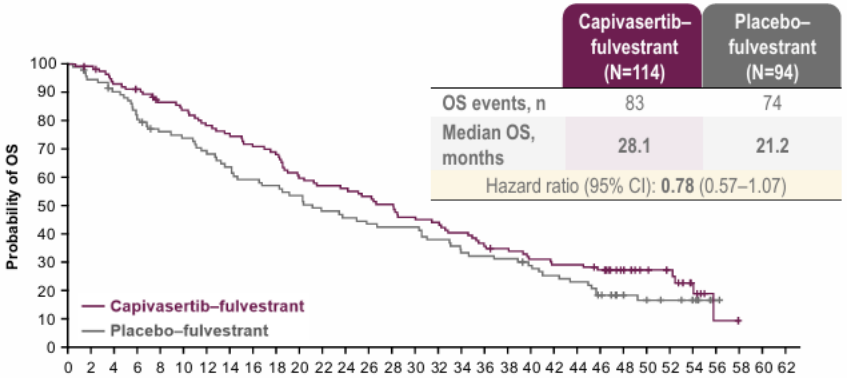
# CAPITELLO-291 trial: no beneficio significativo en SG

**Overall population**




mOS 28,5 vs 30,4 m, HR 0,83, IC95% 0,63-1,10

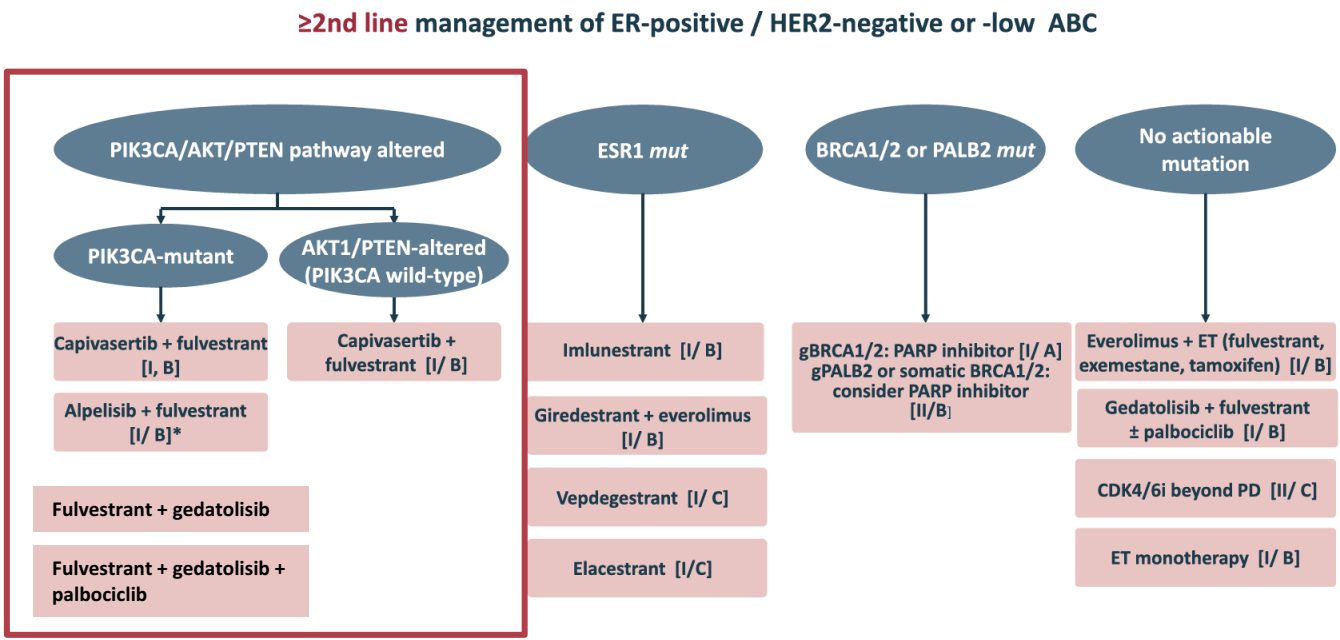
***PIK3CA/AKT1/PTEN*-altered population**




| | Capivasertib–fulvestrant (N=114) | Placebo–fulvestrant (N=94) |
|---|---|---|
| OS events, n | 83 | 74 |
| Median OS, months | 28.1 | 21.2 |
| Hazard ratio (95% CI): **0.78** (0.57–1.07) | | |

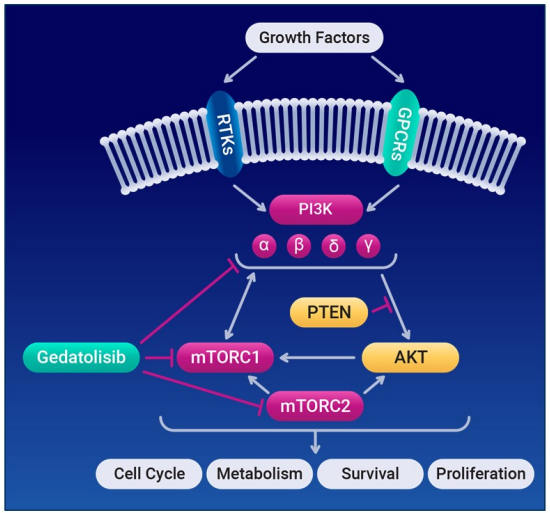
Rugo H et al. ESMO Breast 2026

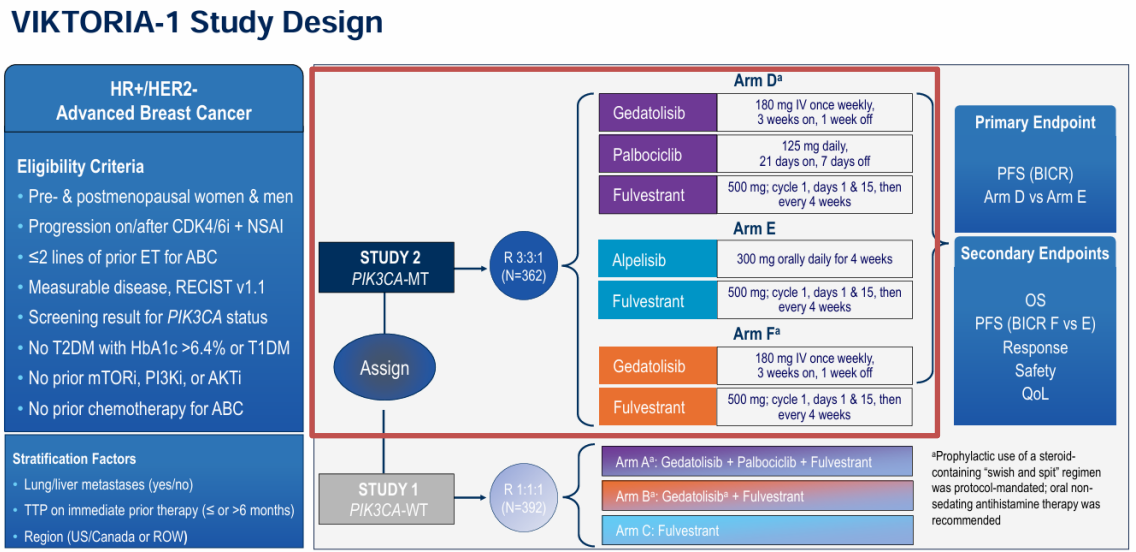
# 8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)




Cardoso F et al. The Breast 2026

# Gedatolisib: inhibidor pan-PI3K y mTORc1/2

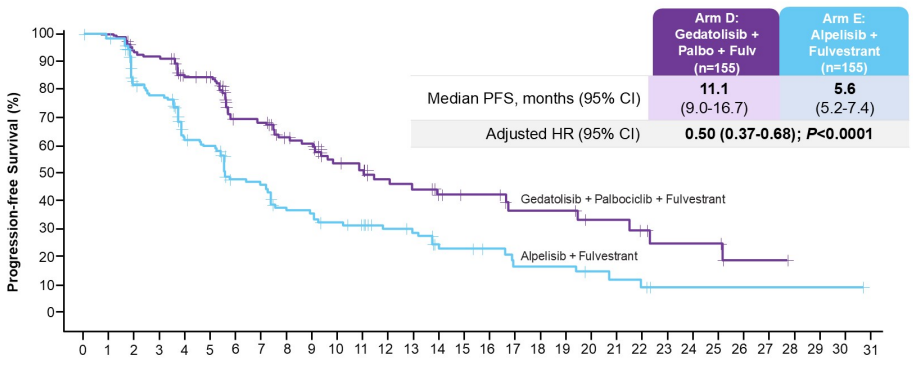


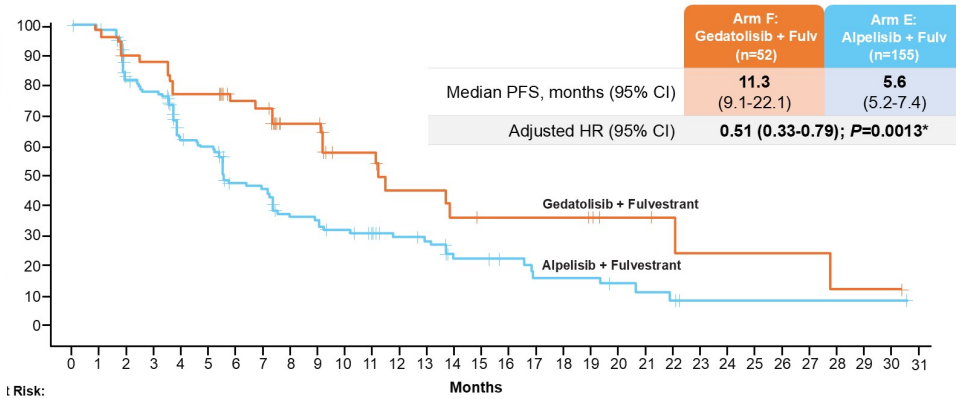

Hurvitz S et al. ASCO 2026. Pistilli B et al. ESMO 2026

# VIKTORIA-1 Study 2: PI3Kmut

## Objetivo 1º: triplete vs FUL-ALPELISIB



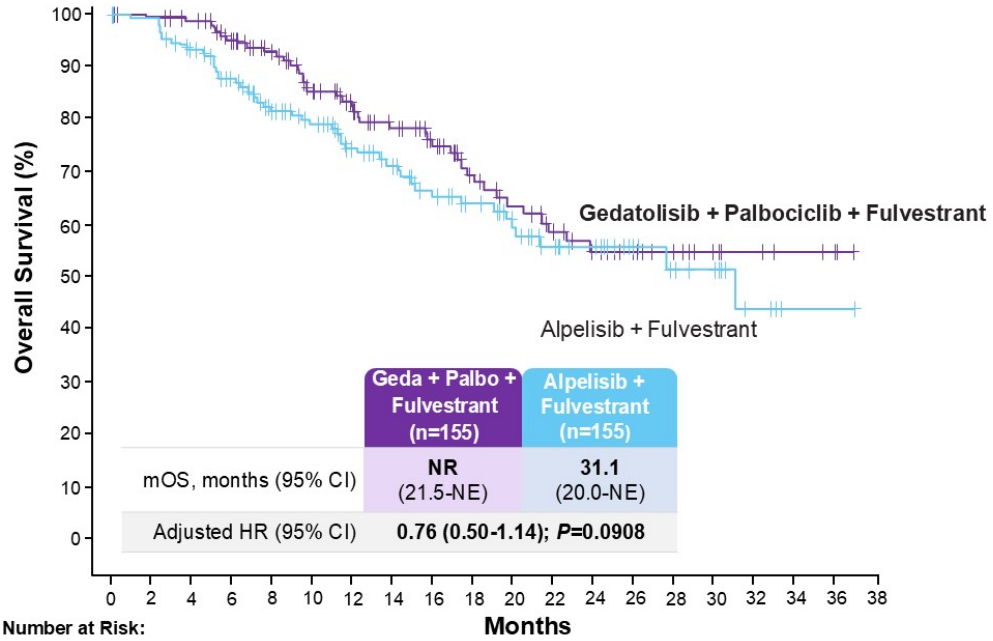

## Objetivo 2º: doblete vs FUL-ALPELISIB

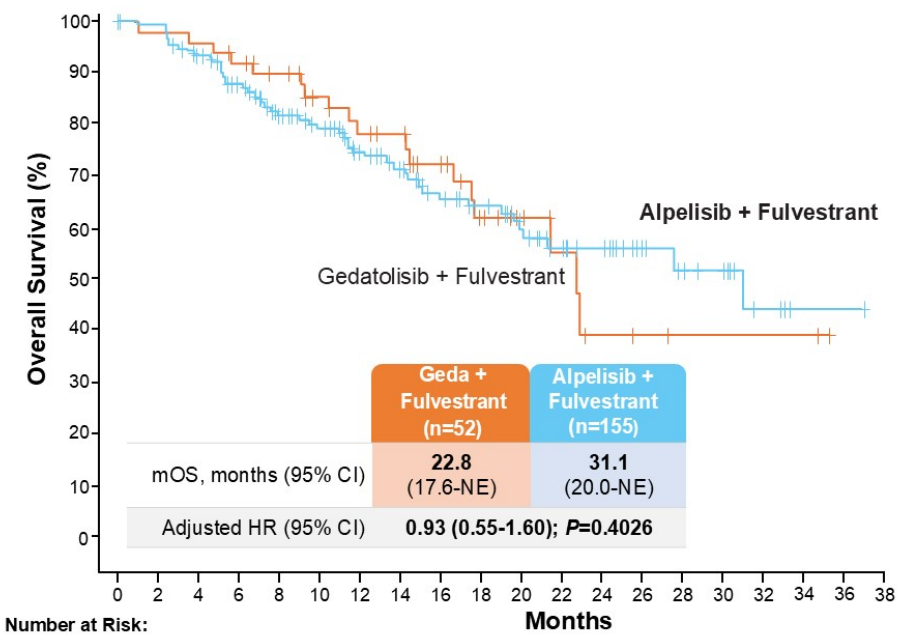



| Endpoint, n (%) | Arm D: Geda + Palbo + Fulv (n=133) | Arm F: Gedatolisib + Fulv (n=42) | Arm E: Alpelisib + Fulv (n=127) |
|---|---|---|---|
| **Objective Response Rate*** | 65 (48.9) | 15 (35.7) | 33 (26.0) |
| **Clinical Benefit Rate†** | 93 (69.9) | 31 (73.8) | 58 (45.7) |
| **Disease Control Rate‡** | 123 (92.5) | 39 (92.9) | 99 (78.0) |
| **Median DOR**, months (95% CI) | 15.7 (9.2-20.6) | 24.2 (7.4-NE) | 7.5 (5.5-15.8) |

Hurvitz S et al. ASCO 2026

# VIKTORIA-1 Study 2 (PI3Kmut): Datos de supervivencia global aún inmaduros




Hurvitz S et al. ASCO 2026

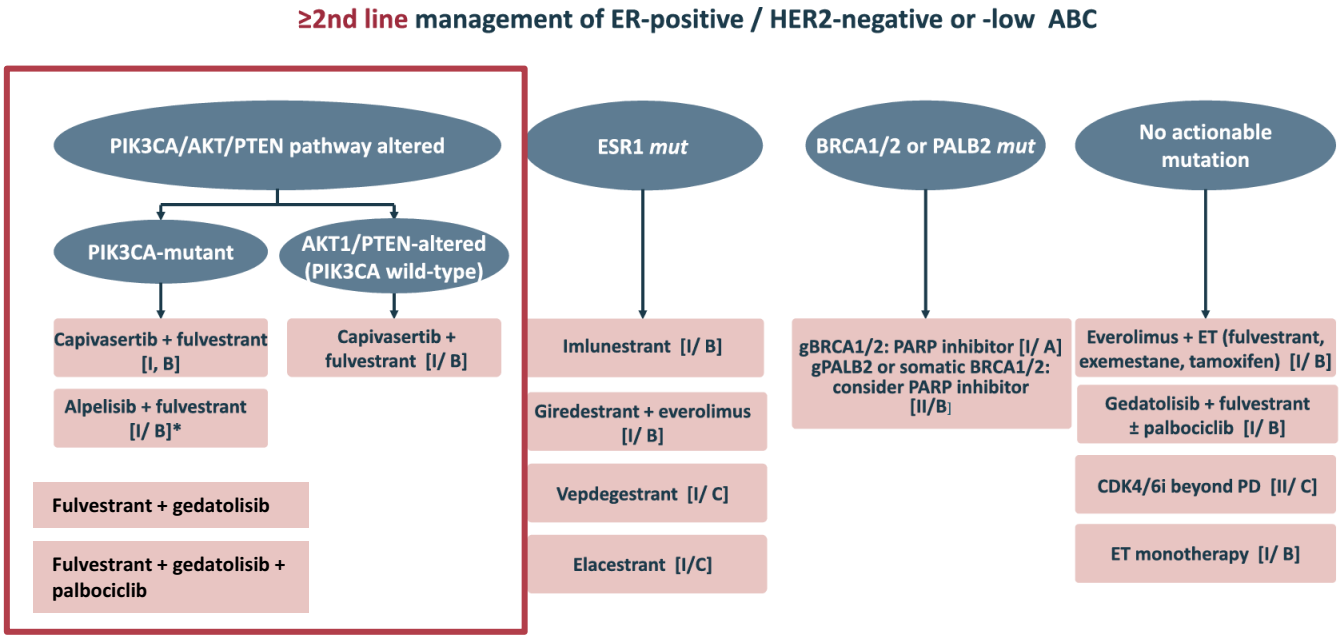
# Safety and Tolerability

## Safety Population in VIKTORIA-1 Study 2

| Exposure | Arm D: Gedatolisib + Palbociclib + Fulvestrant (n=153) | | | Arm F: Gedatolisib + Fulvestrant (n=52) | | | Arm E: Alpelisib + Fulvestrant (n=152) | | |
|---|---|---|---|---|---|---|---|---|---|
| TRAE, n (%)[†] | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| Neutropenia[‡] | 97 (63.4) | 73 (47.7) | 17 (11.1) | 1 (1.9) | 0 | 0 | 2 (1.3) | 0 | 1 (0.7) |
| Stomatitis[‡] | 94 (61.4) | 25 (16.3) | 0 | 32 (61.5) | 3 (5.8) | 0 | 52 (34.2) | 8 (5.3) | 0 |
| Nausea | 70 (45.8) | 5 (3.3) | 0 | 21 (40.4) | 1 (1.9) | 0 | 50 (32.9) | 2 (1.3) | 0 |
| Rash[‡] | 40 (26.1) | 10 (6.5) | 0 | 17 (32.7) | 3 (5.8) | 0 | 56 (36.8) | 23 (15.1) | 0 |
| Vomiting | 39 (25.5) | 0 | 0 | 10 (19.2) | 0 | 0 | 23 (15.1) | 1 (0.7) | 0 |
| Fatigue | 33 (21.6) | 5 (3.3) | 0 | 11 (21.2) | 1 (1.9) | 0 | 32 (21.1) | 4 (2.6) | 0 |
| Diarrhea[§] | 23 (15.0) | 2 (1.3) | 0 | 5 (9.6) | 0 | 0 | 61 (40.1) | 9 (5.9) | 1 (0.7) |
| Hyperglycemia[‡,§] | 23 (15.0) | 4 (2.6) | 0 | 6 (11.5) | 0 | 0 | 88 (57.9) | 21 (13.8) | 1 (0.7) |

Hurvitz S et al. ASCO 2026

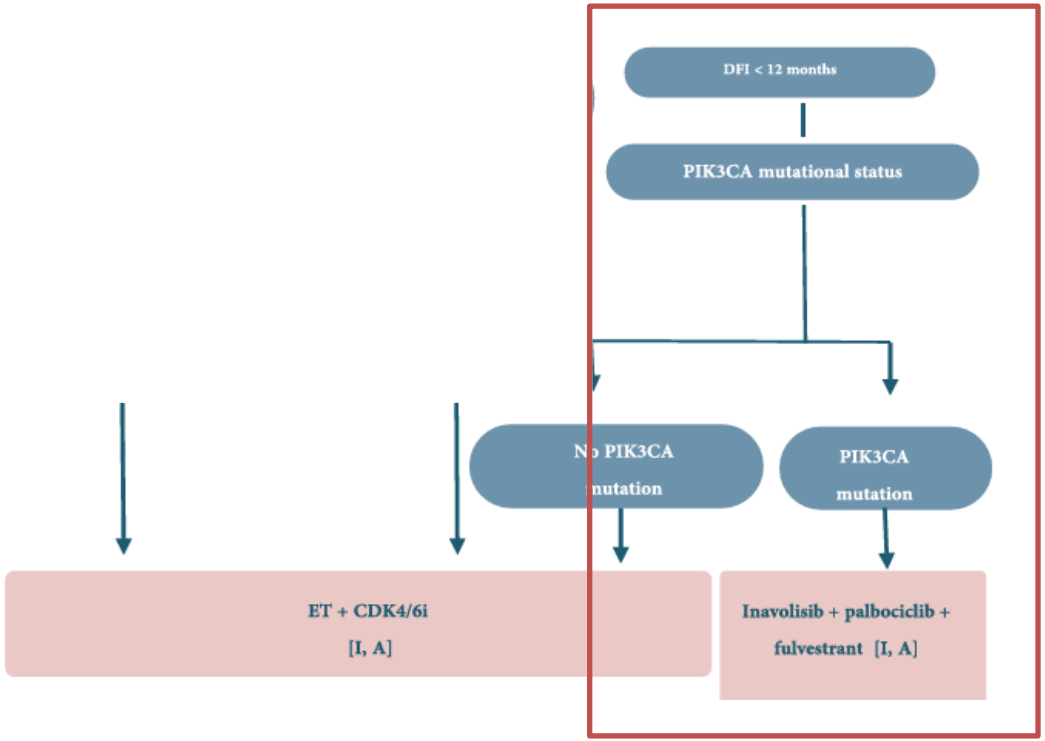
# 8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)




¿? **Triplete vs doblete**
**Pauta de administración**

Cardoso F et al. The Breast 2026

# 1st Line management of ER-positive/HER2-negative or -low ABC

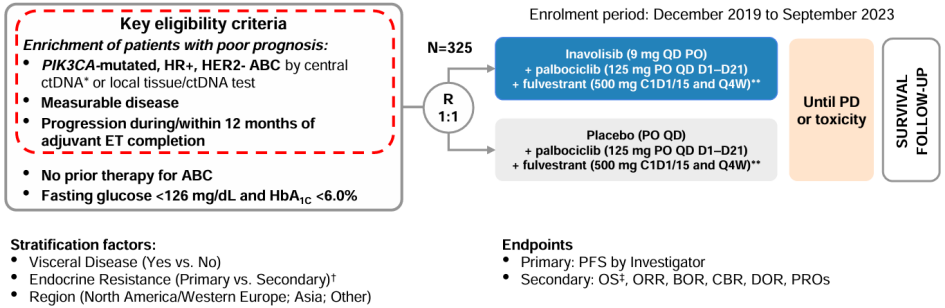





Cardoso F et al. The Breast 2026

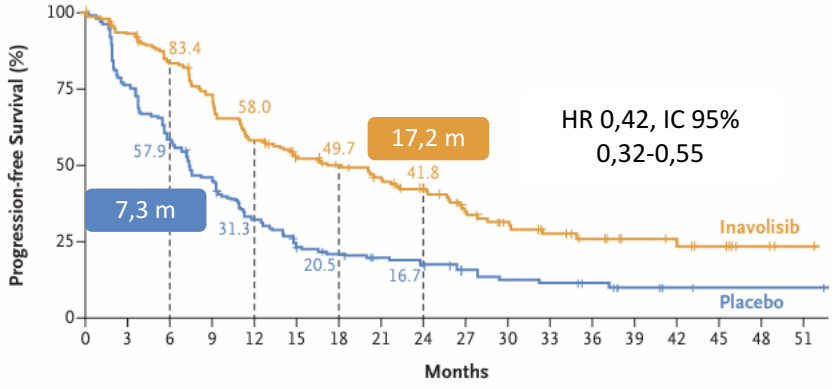
# INAVO-120

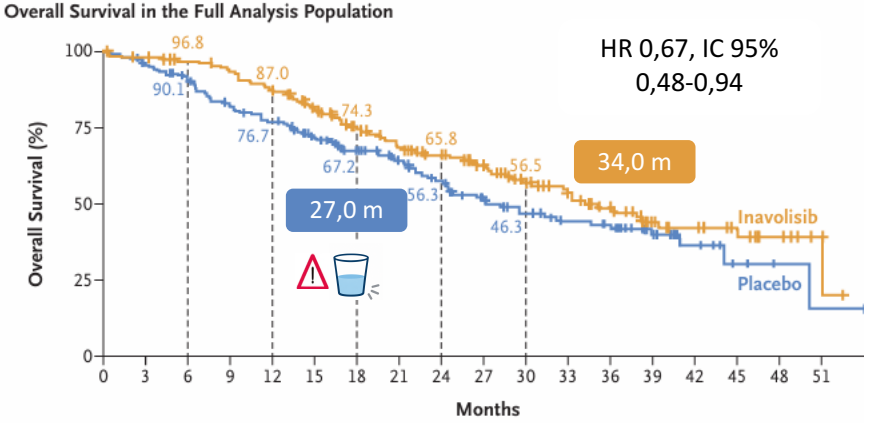
## INAVO120 study design




**Stratification factors:**
- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

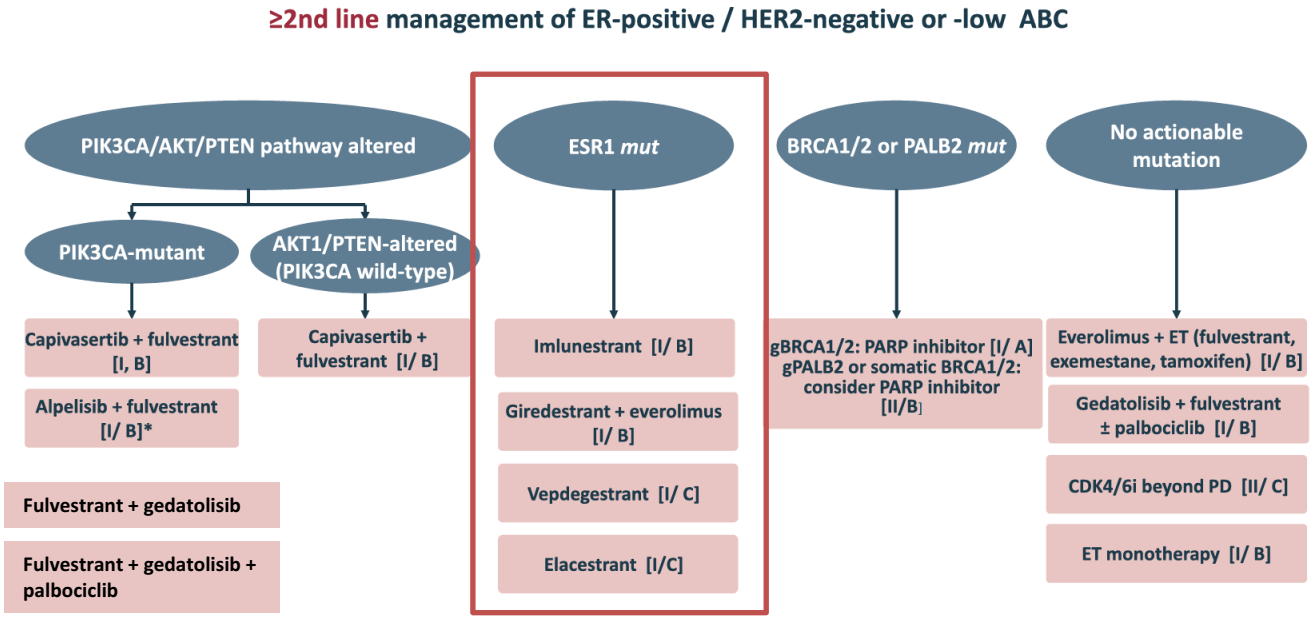
**Endpoints**
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs




Jhaveri K et al. NEJM 2025

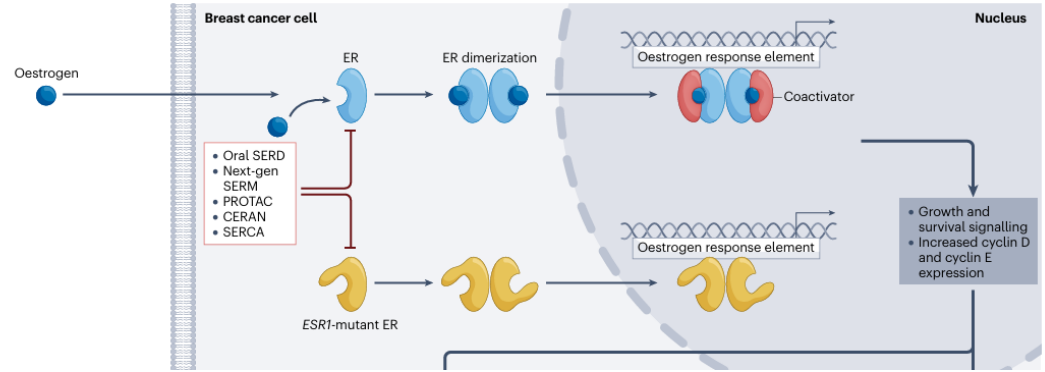
# 8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)

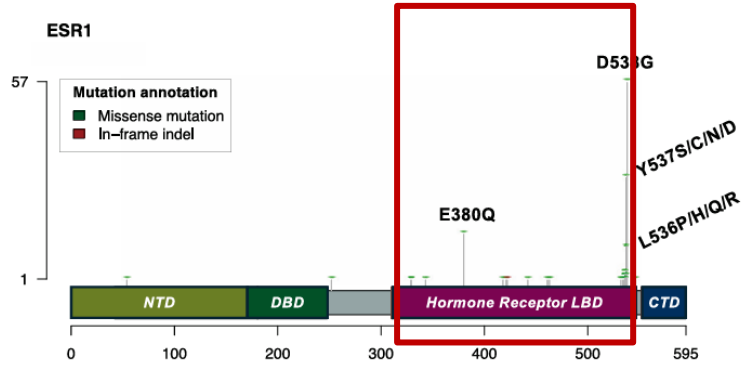


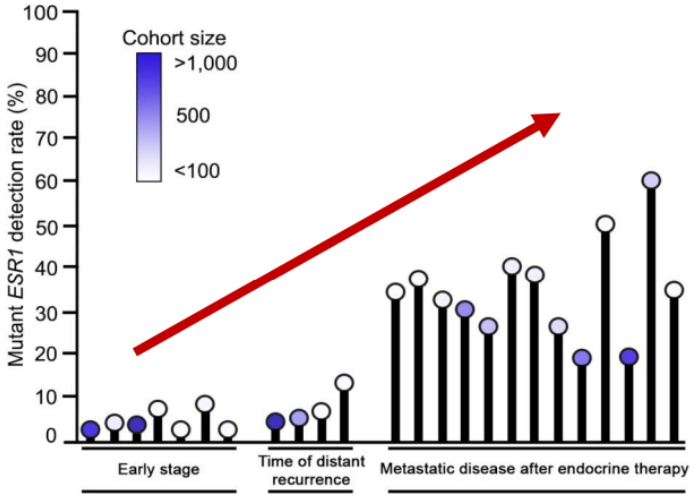

Cardoso F et al. The Breast 2026

# Mutación ESR1

Activación constitutiva del receptor




≈ 5% ≈ 10% ≈ 30-40%

**Enriquecimiento progresivo en mutaciones en ESR1**

Lloyd M et al. Nat Rev Clin Oncol 2024

# FREQUENCY AND PROGNOSTIC SIGNIFICANCE OF *ESR1* MUTATIONS POST-CDK4/6 INHIBITORS IN ER+/HER2– METASTATIC BREAST CANCER: REAL-WORLD DATA FROM THE GEICAM_REGISTEM STUDY

**The incidence of *ESR1* mutations increased with longer duration of 1st line therapy and varied according to the type of treatment received at 1st line.**

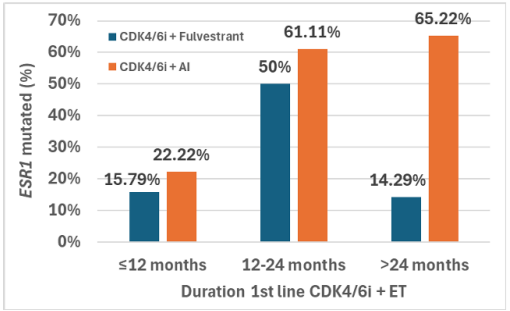
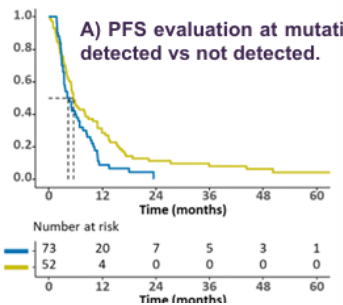
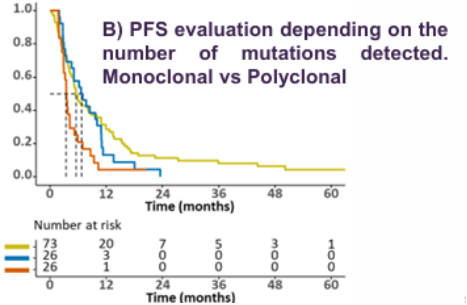



**Figure 1. Distribution of *ESR1* mutations after progression to 1st line. Comparison by ET and 1st line therapy duration.**

**The detection of *ESR1* mutations after CDK4/6i + ET was significantly associated with shorter median progression-free survival (PFS), particularly with polyclonal *ESR1* mutations. *ESR1* mutations were not significantly associated to overall survival (OS) (data not shown).**

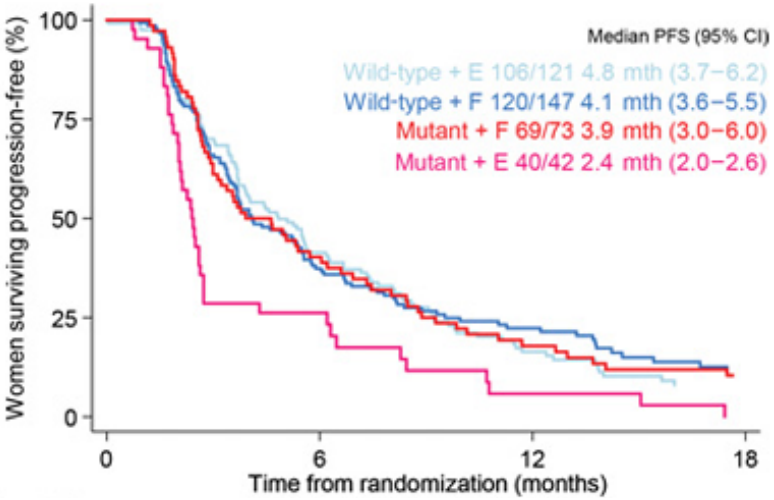
**Figure 3. Prognostic value of *ESR1* mutation after CDK4/6i + ET as 1st line therapy. Evaluation of PFS (months).** aHR: adjusted Hazard Ratio. CI: confidence interval

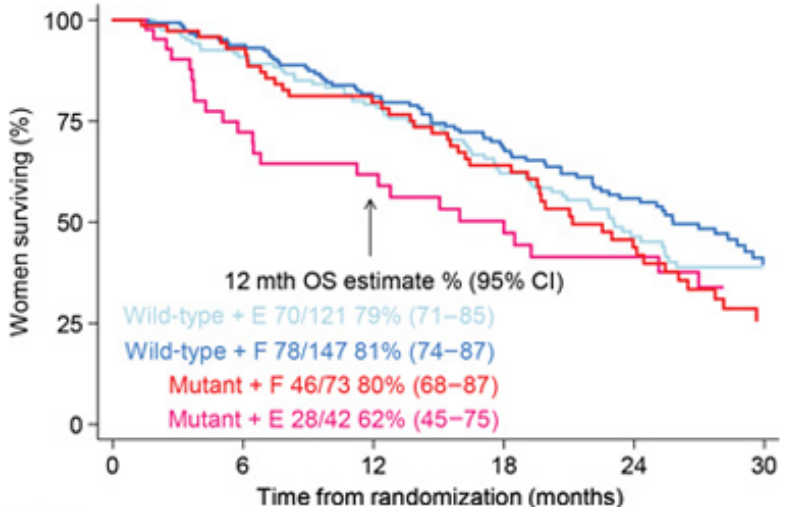



Guerrero Zotano A et al. SABCS 2025

# *ESR1* Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor–Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials A C

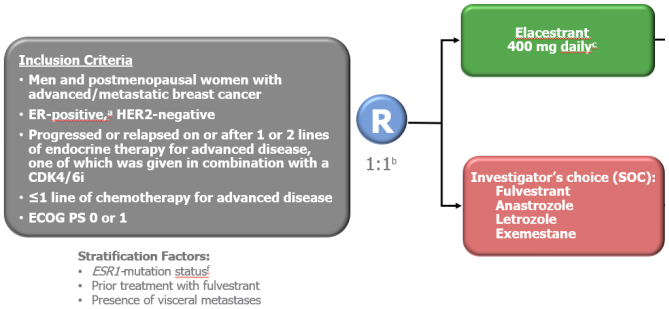


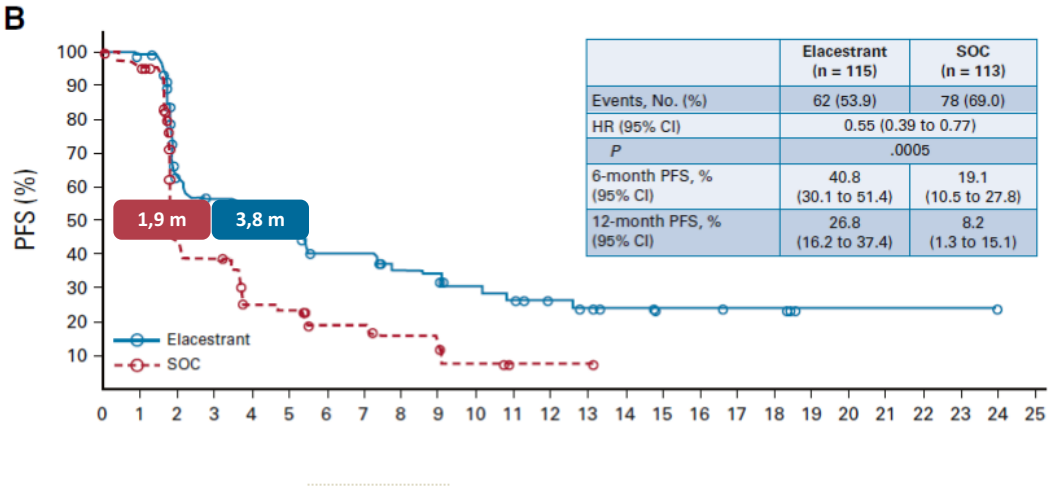

Turner N et al. Clin Cancer Res 2020

# Elacestrant – EMERALD trial

## EMERALD Phase 3 Study Design



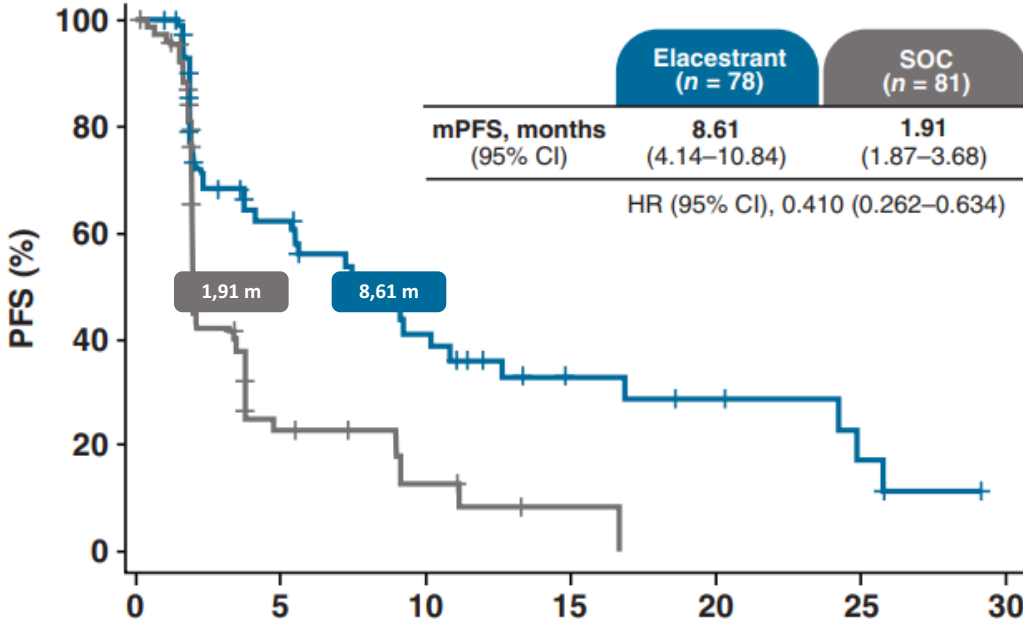

**100% iCDK previo**
**63% 1 línea HT previa**
**20% 1 línea QT previa**




| | 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) |

Bardia A et al. SABCS 2022
Bardia A et al. Clin Cancer Res 2024.

# Beneficio fundamentalmente en pacientes con iCDK previo ≥ 12 m



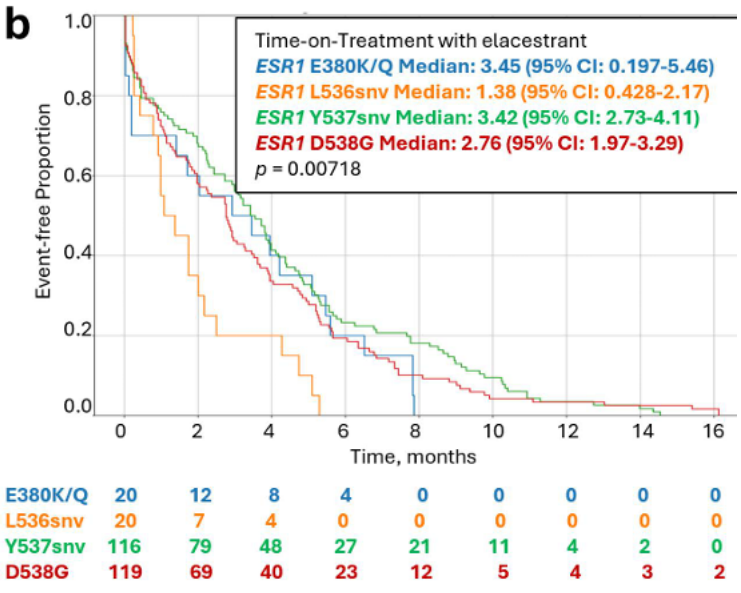

MINISTERIO DE SANIDAD

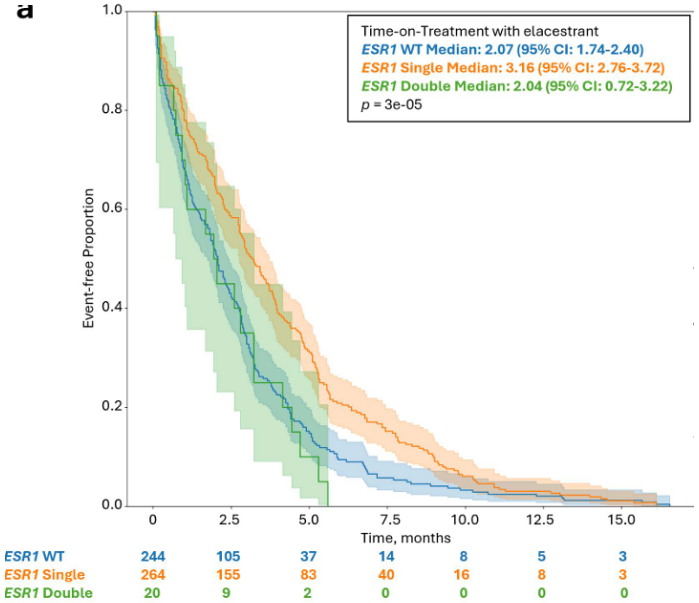
| | | |
|---|---|---|
| ORSERDU en monoterapia está indicado para el tratamiento de hombres y mujeres posmenopáusicas con cáncer de mama localmente avanzado o metastásico, con receptor estrogénico (RE) positivo, HER2 negativo, con una mutación activadora ESR1 que hayan presentado progresión de la enfermedad después de al menos una línea de terapia endocrina incluyendo un inhibidor de CDK 4/6. | Resuelto | Sí, con restricción a la indicación autorizada: Se restringe a pacientes que hayan presentado progresión de la enfermedad después de al menos una línea de terapia endocrina incluyendo un inhibidor de CDK 4/6 y que hayan estado expuestos durante más de 12 meses a inhibidores de CDK 4/6. |

Bardia A et al. SABCS 2022. Bardia A et al. Clin Cancer Res 2024.

# No todas las mutaciones en ESR1 son iguales

**Differential impact of tumor-derived *ESR1* mutations on elacestrant benefit in metastatic breast cancer**




- ↓ beneficio con elacestrant con L536 comparado con Y537 y D538G (HR=2,089).
- ↓ beneficio con elacestrant si mutaciones múltiples en ESR1.

Sledge G et al. Clin Cancer Res 2026

# Imlunestrant – EMBER-3 trial

## ER+, HER2- ABC

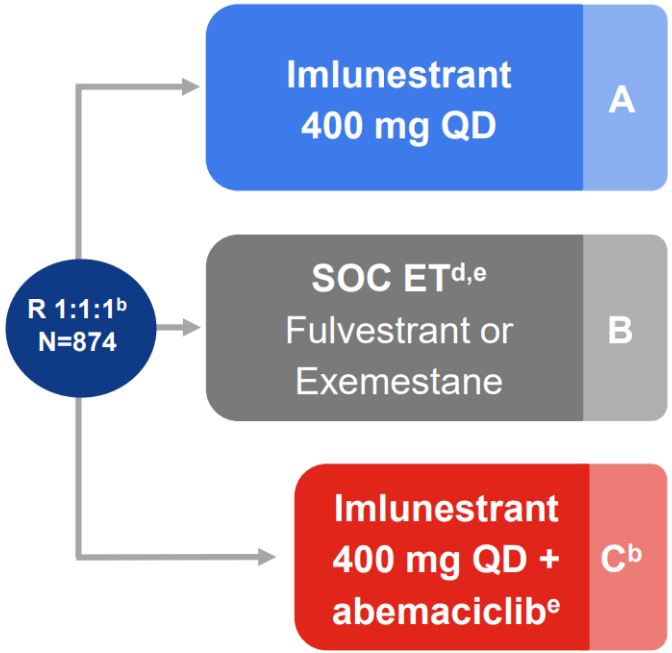
Men and Pre-[a]/Post-menopausal women

**Prior therapy:**

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

**Stratification Factors:**

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]




**Primary Endpoints**

**Investigator-assessed PFS for[f]:**

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all[h] patients

**Key Secondary Endpoints**

- OS, PFS by BICR, and ORR
- Safety

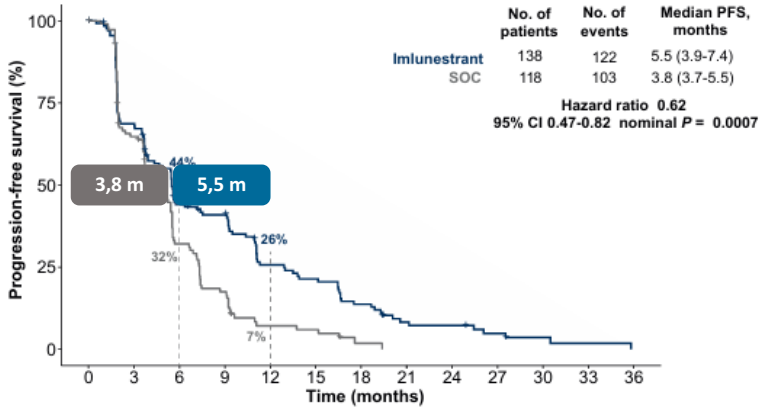
**Exploratory Endpoints**

- PFS and OS for C vs B in all[h] patients

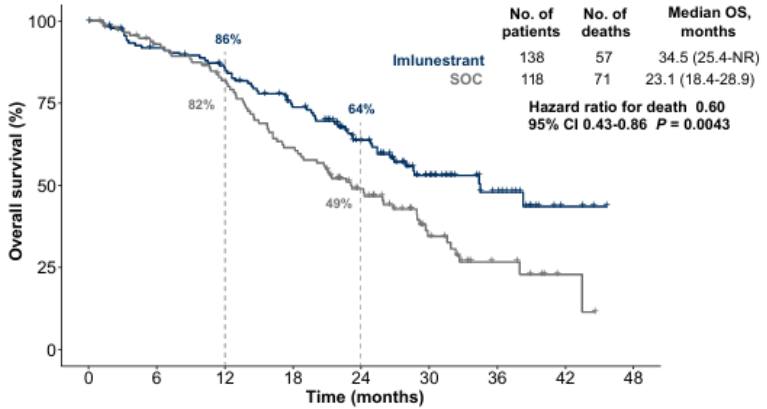
Jhaveri K et al. SABCS 2024

# Imlunestrant se asocia con un beneficio en SLP frente a la TE estándar en pacientes con ESR1mut

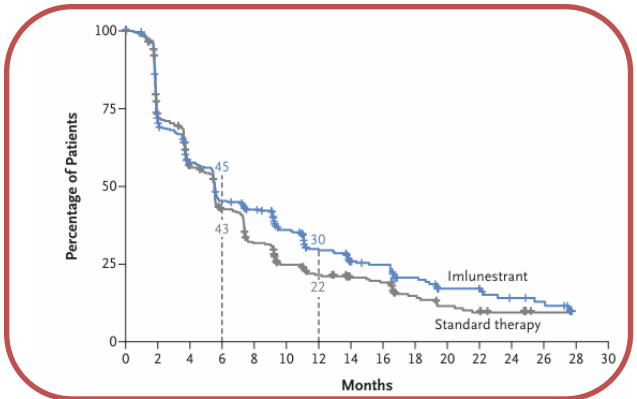
## ESR1mut




↓ 38% del riesgo de progresión o muerte con imlunestrant frente a SOC




Beneficio numérico en SG, no alcanza umbral de significación preestablecido

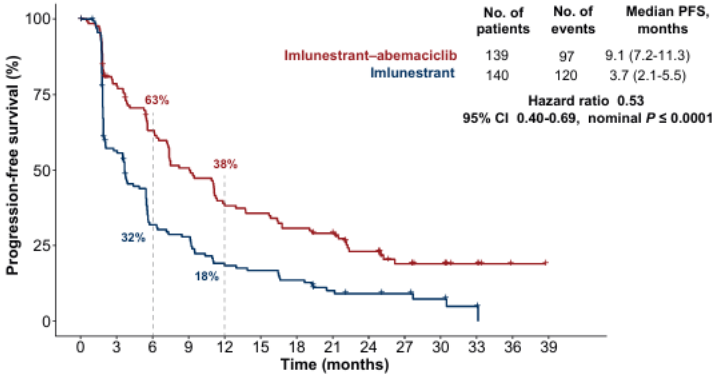



**Sin beneficio en SLP en la población global**
**mSLP 5,6 vs 5,5 m**

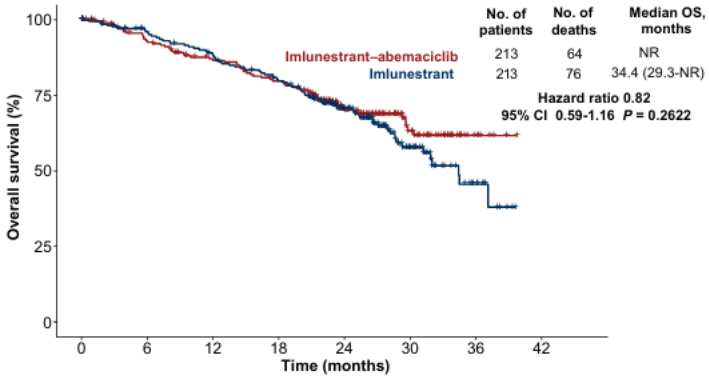
Jhaveri K et al. Ann Oncol 2025. Jhaveri K et al. NEJM 2024

# Imlunestrant y abemaciclib

## SLP en pacientes con iCDK previo

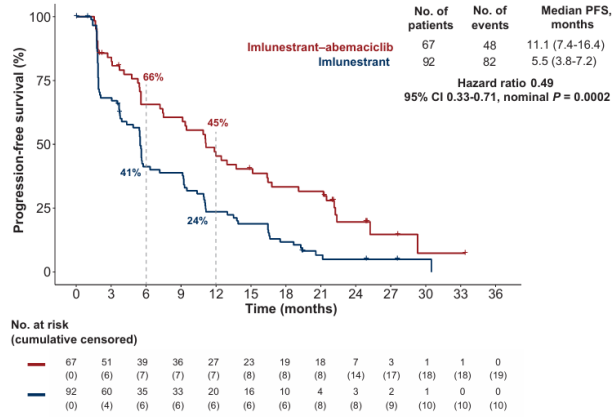



## SG

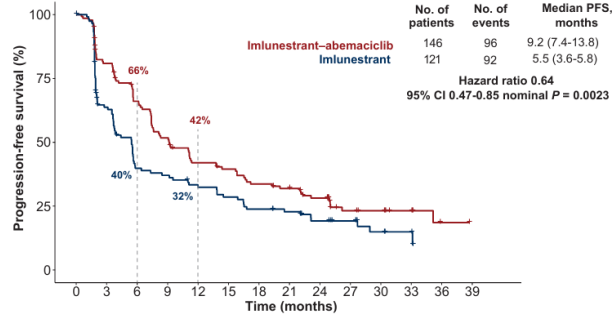



## Beneficio con imlunestrant y abemaciclib independientemente de la mutación en ESR1

ESR1 mut

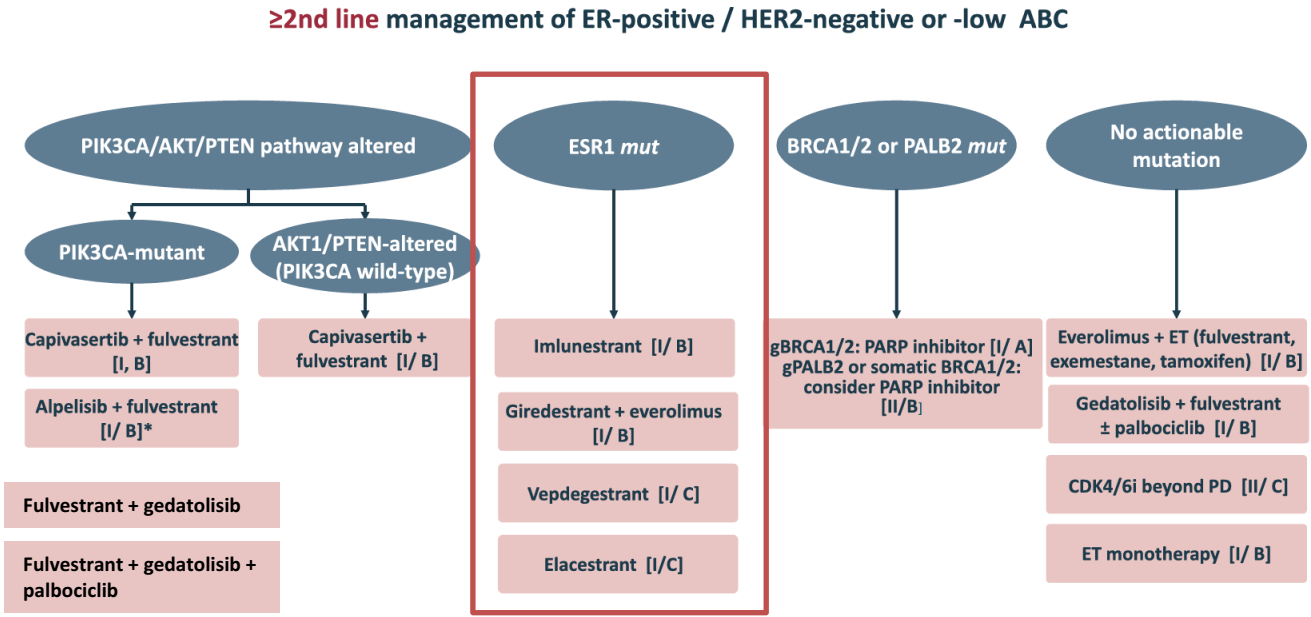



ESR1 wt



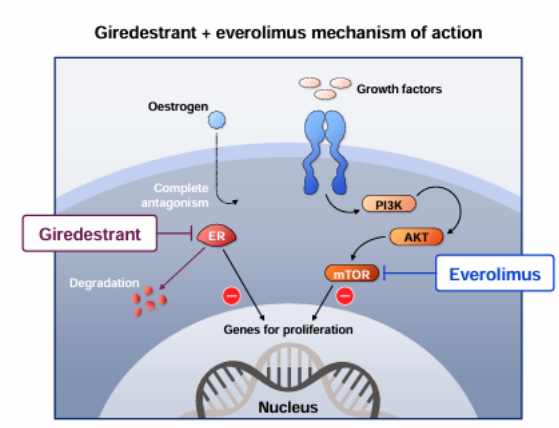

Jhaveri K et al. Ann Oncol 2025

# 8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)




Cardoso F et al. The Breast 2026

# EvERA trial: GIREDESTRANT + EVEROLIMUS




**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)

**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

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

Until PD or unacceptable toxicity

**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)

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

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

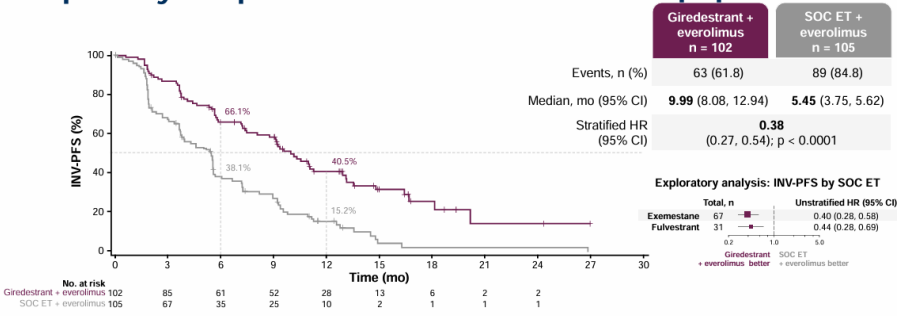
**Key secondary endpoints**

- OS
- INV-assessed ORR, DoR

Mayer E et al. ESMO 2025

# Beneficio con giredestrant y everolimus en la población ESR1mut y población global

## Co-primary endpoint – INV-PFS in the *ESR1*m population

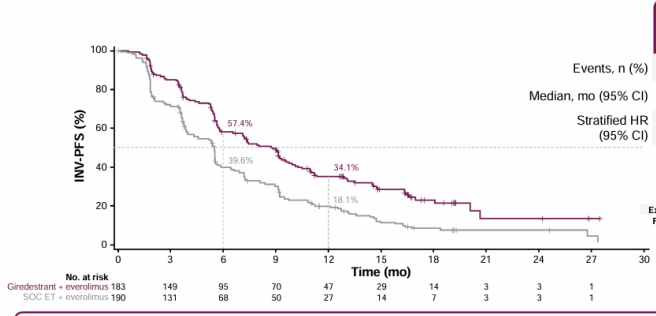



| | Giredestrant + everolimus n = 102 | SOC ET + everolimus n = 105 |
|---|---|---|
| Events, n (%) | 63 (61.8) | 89 (84.8) |
| Median, mo (95% CI) | **9.99** (8.08, 12.94) | **5.45** (3.75, 5.62) |
| Stratified HR (95% CI) | **0.38** (0.27, 0.54); p < 0.0001 | |

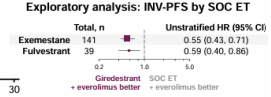



**Combination therapy with giredestrant + everolimus led to a clinically meaningful 62% reduction in the risk of progression or death in patients with *ESR1*m**

## 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**

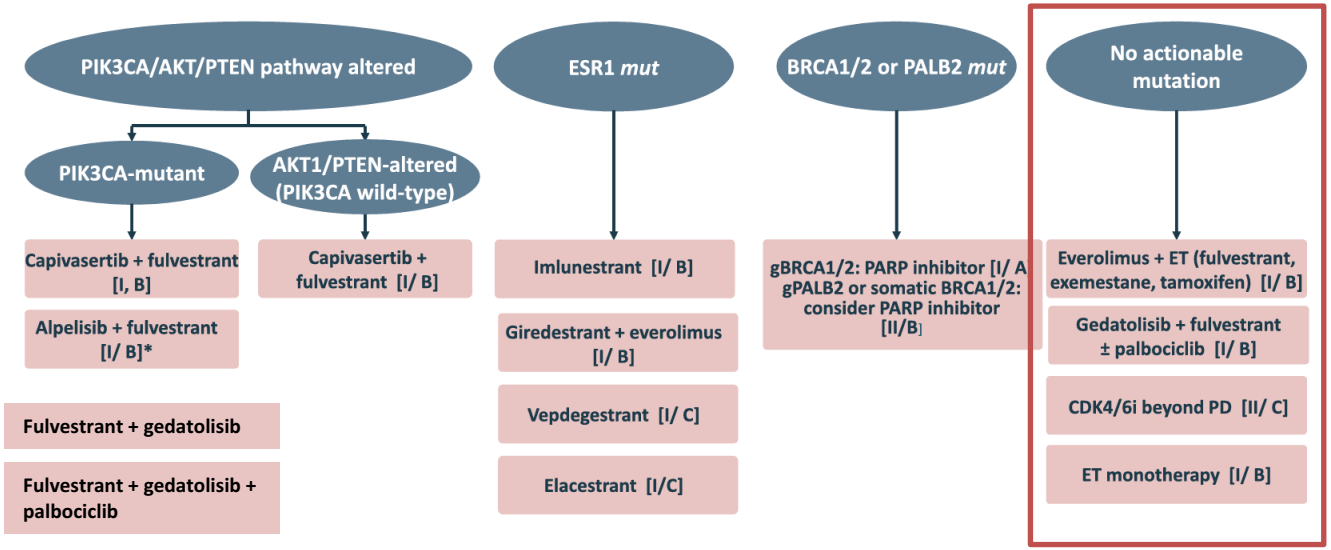
Mayer E et al. ESMO 2025

# Key Observations/Questions
# ESR1m, post CDK4/6i Endocrine Therapies

| Trial | Regimen | ESR1m mPFS (mo) | HR | Comparator |
|---|---|---|---|---|
| evERA | Giredestrant + everolimus | 10.0 vs 5.5 | 0.38 | SOC ET + everolimus |
| EMBER-3 | Imlunestrant + abemaciclib | ~9.4 vs 5.5 (all-comers) | 0.57 | Imlunestrant alone |
| EMBER-3 | Imlunestrant alone | 5.5 vs 3.8 | 0.62 | SOC ET |
| VERITAC-2 | Vepdegestrant | 5.0 vs 2.1 | 0.57 | Fulvestrant |
| EMERALD | Elacestrant | 3.8 vs 1.9 | 0.55 | SOC ET |

- Different populations!
- Focus on control arm
- HR for evERA 0.38 earned against a real combination; other trials with ESR1m tumors largely resistant to control arm

# 8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)

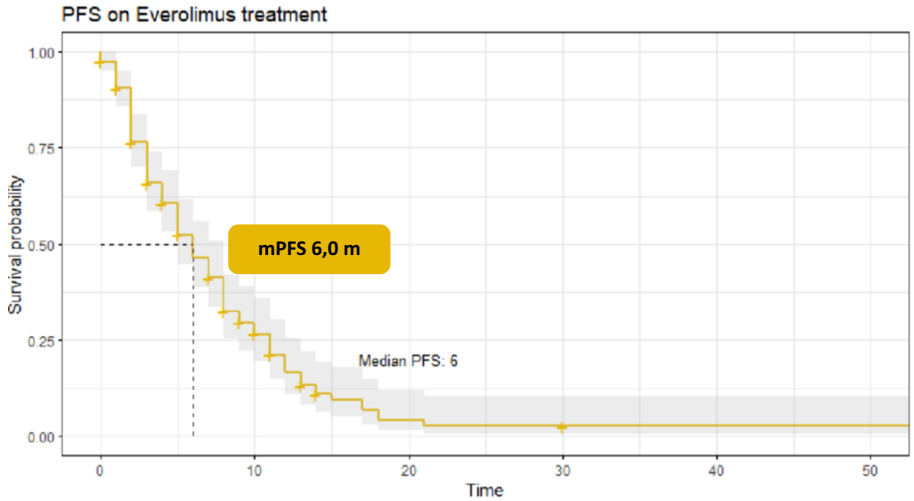



**¿? ¿es necesario tener una mutación accionable para beneficiarse del bloqueo de la vía PI3K?**

Cardoso F et al. The Breast 2026

# Everolimus plus endocrine therapy beyond CDK4/6 inhibitors progression for HR+ /HER2– advanced breast cancer: a real-world evidence cohort

Rodrigo Sánchez-Bayona[1] · Alfonso Lopez de Sa[2] · Yolanda Jerez Gilarranz[3] · Ana Sanchez de Torre[4] · Manuel Alva[1] · Isabel Echavarria[3] · Fernando Moreno[2] · Pablo Tolosa[1] · Blanca Herrero Lopez[3] · Alicia de Luna[2] · Laura Lema[1] · Salvador Gamez Casado[3] · Ainhoa Madariaga[1] · Sara López-Tarruella[3] · Luis Manso[1] · Coralia Bueno-Muiño[4] · Jose A. Garcia-Saenz[2] · Eva Ciruelos[1] · Miguel Martin[3]




- mSLP 6,0 meses.

↑ SLP en subgrupos seleccionados:

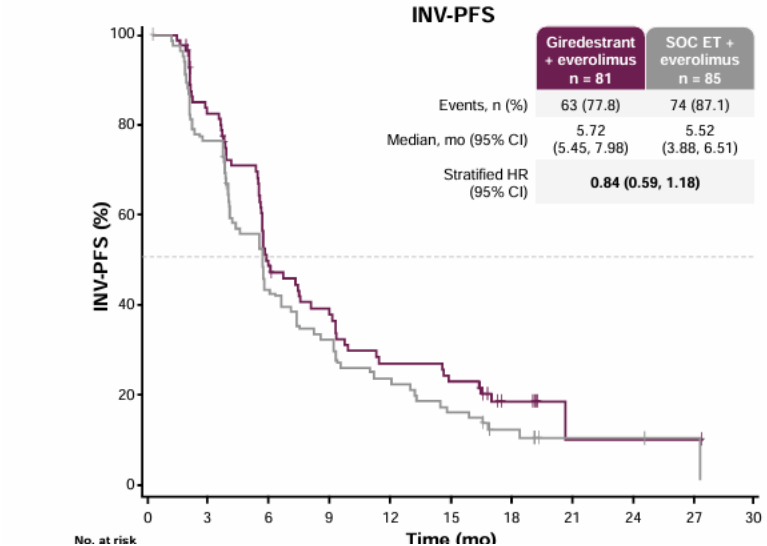
- iCDK ≥ 18 m: 8,7 m
- Sin QT: 7 m
- Sin afectación visceral: 8,0 m

Sánchez-Bayona R et al. Breast Cancer Res Treat 2024

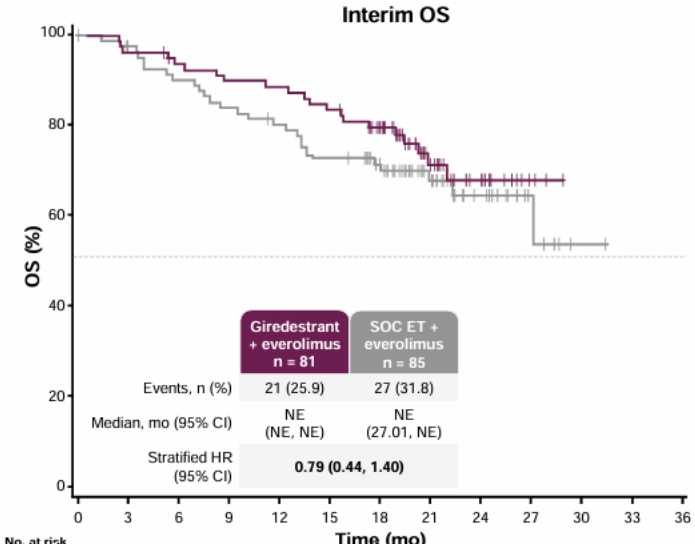
# EvERA trial: GIREDESTRANT + EVEROLIMUS en paciente sin mutación

Breast Cancer

## INV-PFS and interim OS in patients without *ESR1*m detected (exploratory analysis)



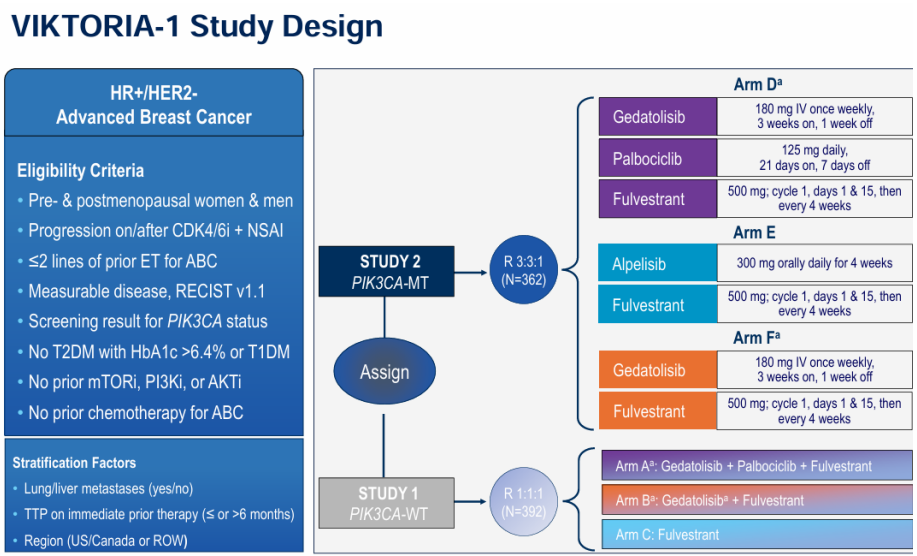

| | Giredestrant + everolimus n = 81 | SOC ET + everolimus n = 85 |
|---|---|---|
| Events, n (%) | 63 (77.8) | 74 (87.1) |
| Median, mo (95% CI) | 5.72 (5.45, 7.98) | 5.52 (3.88, 6.51) |
| Stratified HR (95% CI) | **0.84 (0.59, 1.18)** | |

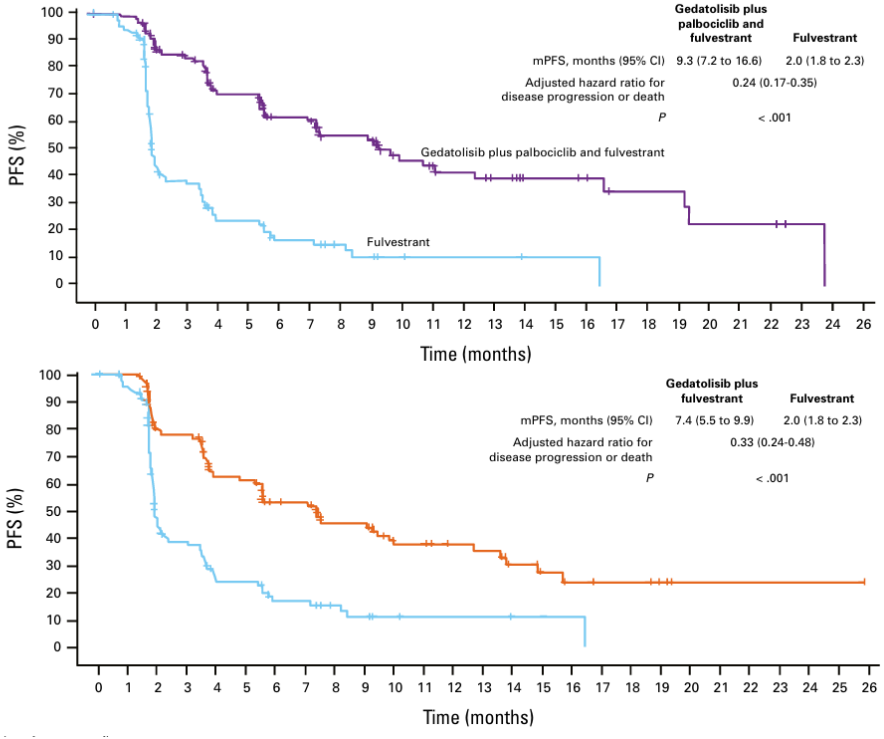



| | Giredestrant + everolimus n = 81 | SOC ET + everolimus n = 85 |
|---|---|---|
| Events, n (%) | 21 (25.9) | 27 (31.8) |
| Median, mo (95% CI) | NE (NE, NE) | NE (27.01, NE) |
| Stratified HR (95% CI) | **0.79 (0.44, 1.40)** | |

Mayer E et al. ESMO 2025

# VIKTORIA-1 Study 1: PI3K WT

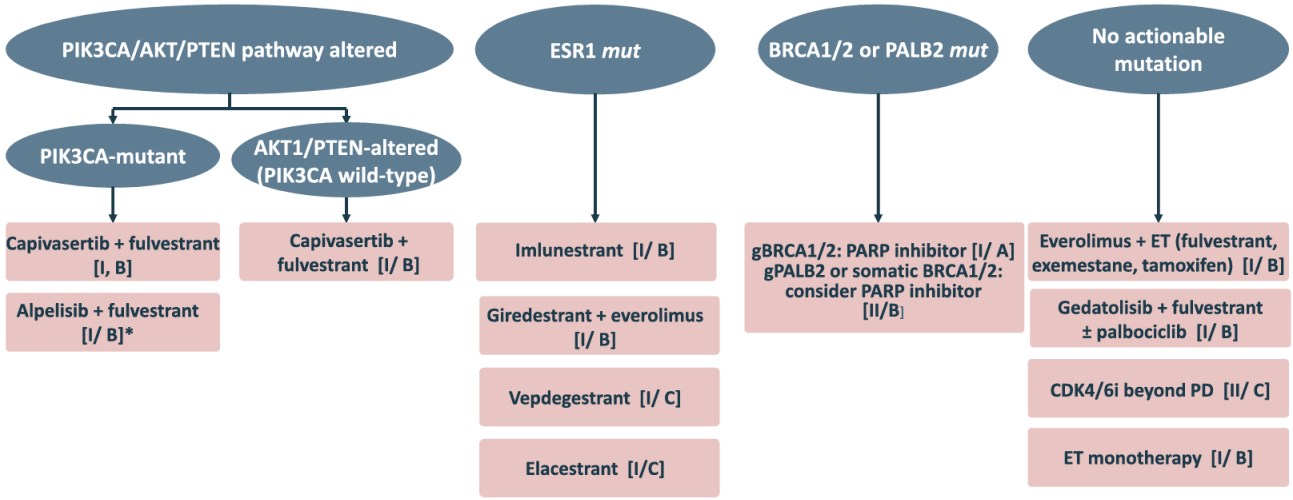



**Rama control subóptima**

Hurvitz S et al. JCO 2026

## ≥2nd line management of ER-positive / HER2-negative or -low ABC

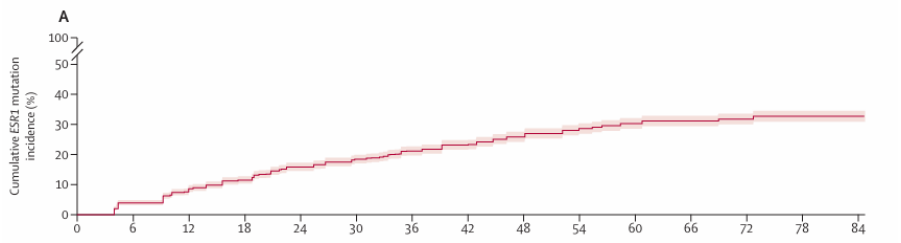



¿? ¿ Cuándo determinar estos biomarcadores?

Recaídas durante o <12 m tras TE adyuvante
Durante 1ª línea con iCDK

Cardoso F et al. The Breast 2026

# Switching to camizestrant at *ESR1* mutation emergence before disease progression during first-line treatment of hormone receptor-positive advanced breast cancer (SERENA-6): extended analysis of a double-blind, placebo-controlled, randomised, phase 3 trial



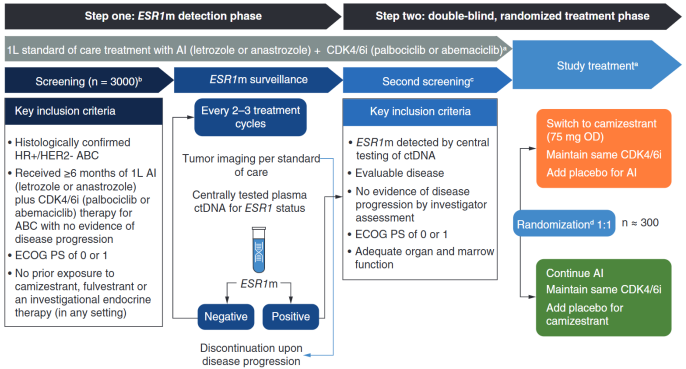
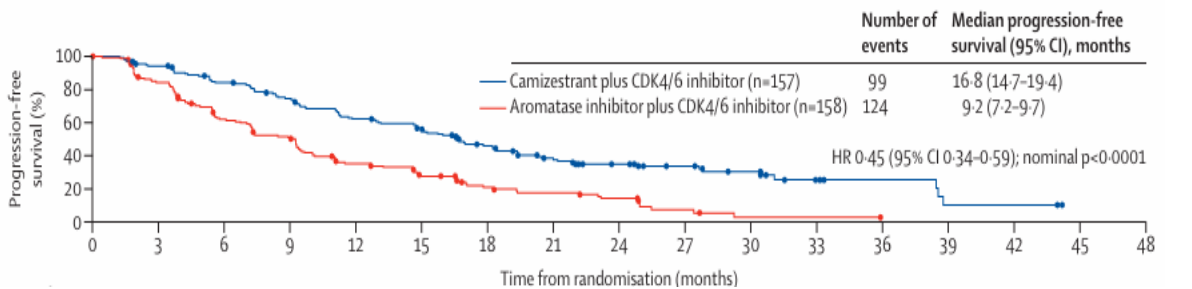
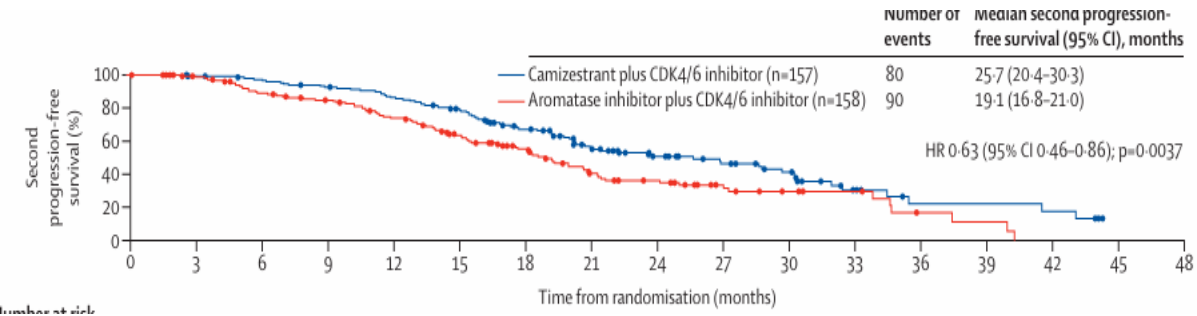



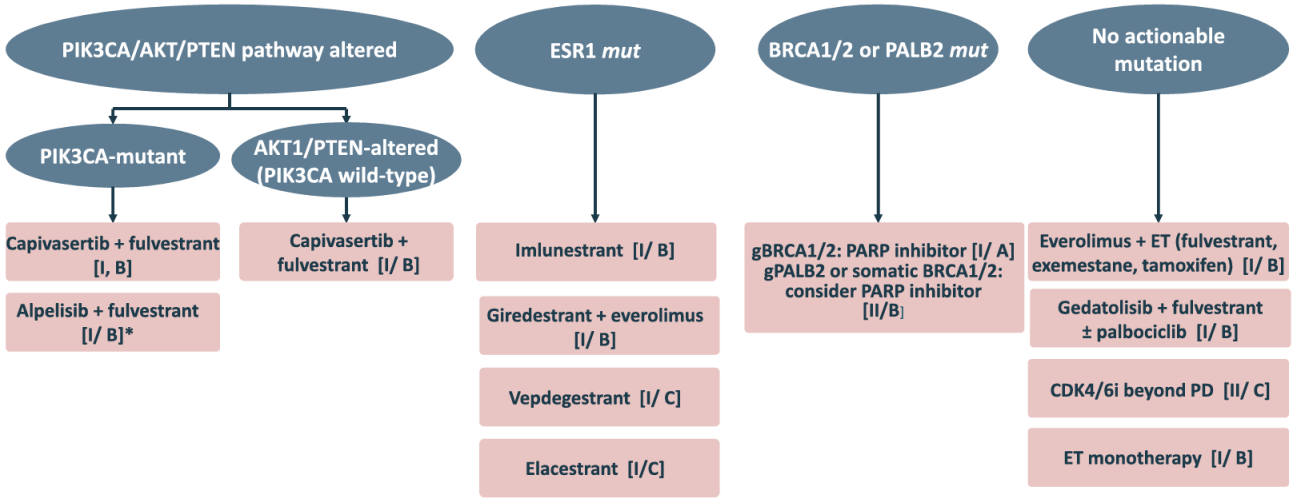

**Figure 2.** SERENA-6 trial schema.




Turner N et al. Lancet Oncol 2026

## ≥2nd line management of ER-positive / HER2-negative or -low ABC



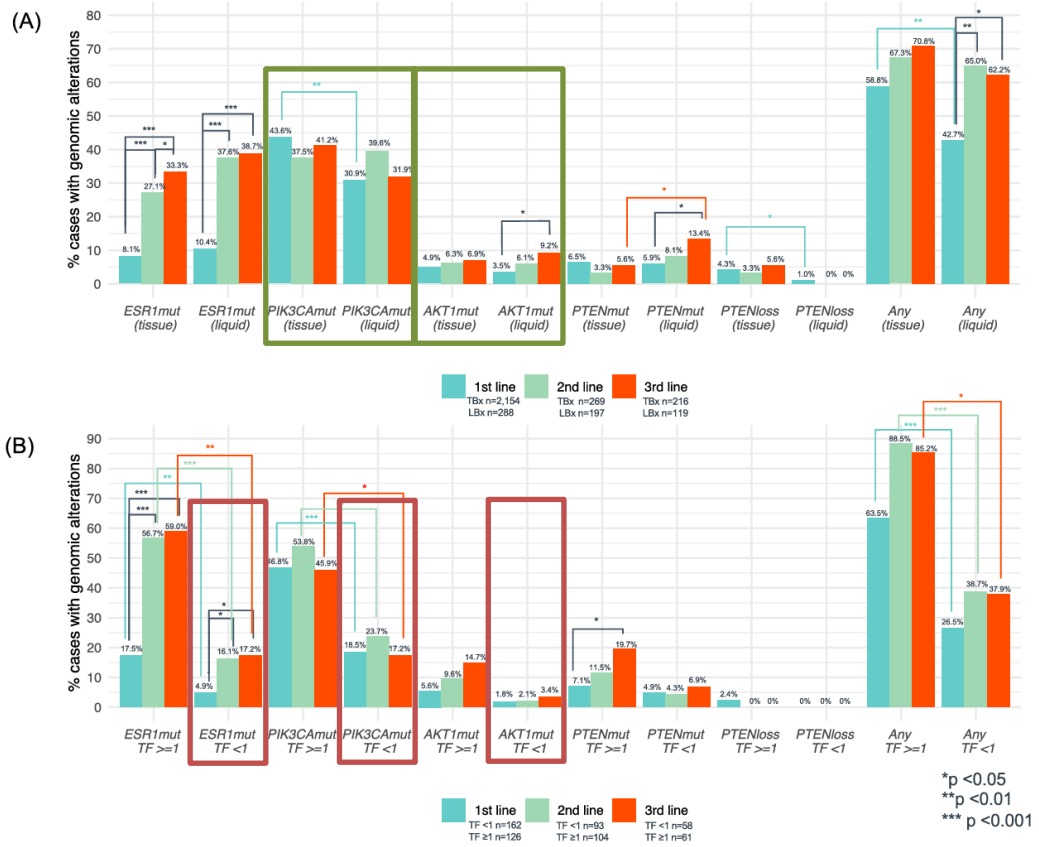

¿? **¿ Cuándo determinar estos biomarcadores?**

Recaídas durante o <12 m tras TE adyuvante
Durante 1ª línea con iCDK

**¿ Dónde determinarlos? Tumor sólido, biopsia líquida**

Cardoso F et al. The Breast 2026

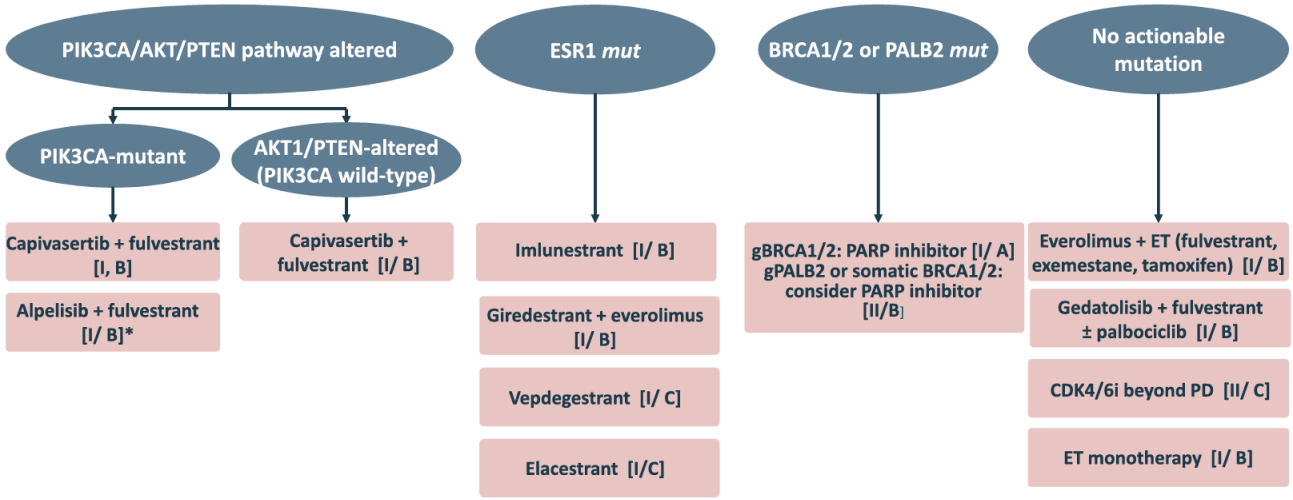
# Comprehensive genomic profiling of *ESR1*, *PIK3CA*, *AKT1*, and *PTEN* in HR(+)HER2(–) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice




**Baja detección si TF < 1%**

Bhave M et al. Breast Cancer Res Treat 2024

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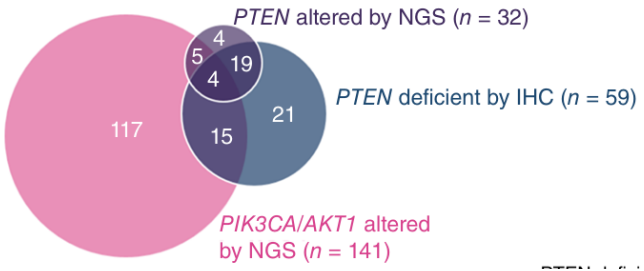
**¿ Técnica? PCR, NGS, IHQ…**

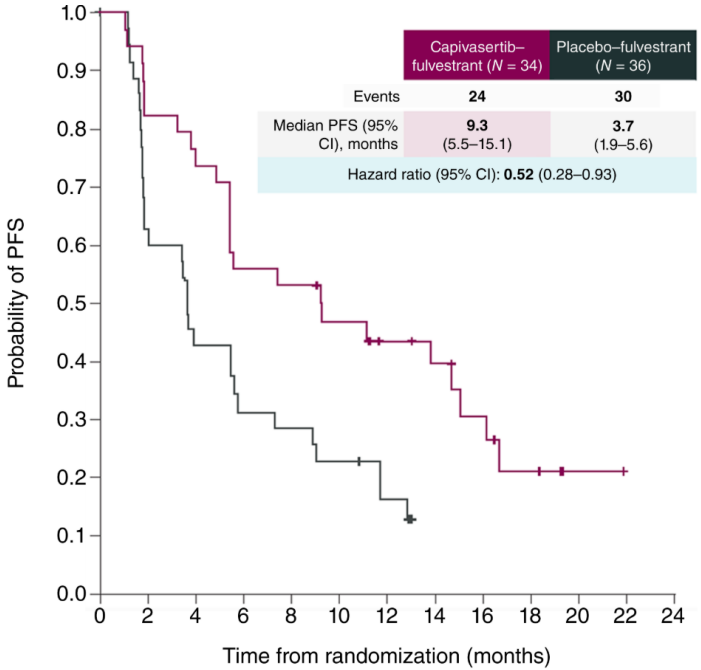
Cardoso F et al. The Breast 2026

# Exploratory Analysis of PTEN Deficiency by Immunohistochemistry from the Phase III CAPItello-291 Trial

**La IHQ de PTEN puede identificar pacientes con deficiencia de PTEN y NGS normal que se benefician del tratamiento con capivasertib**

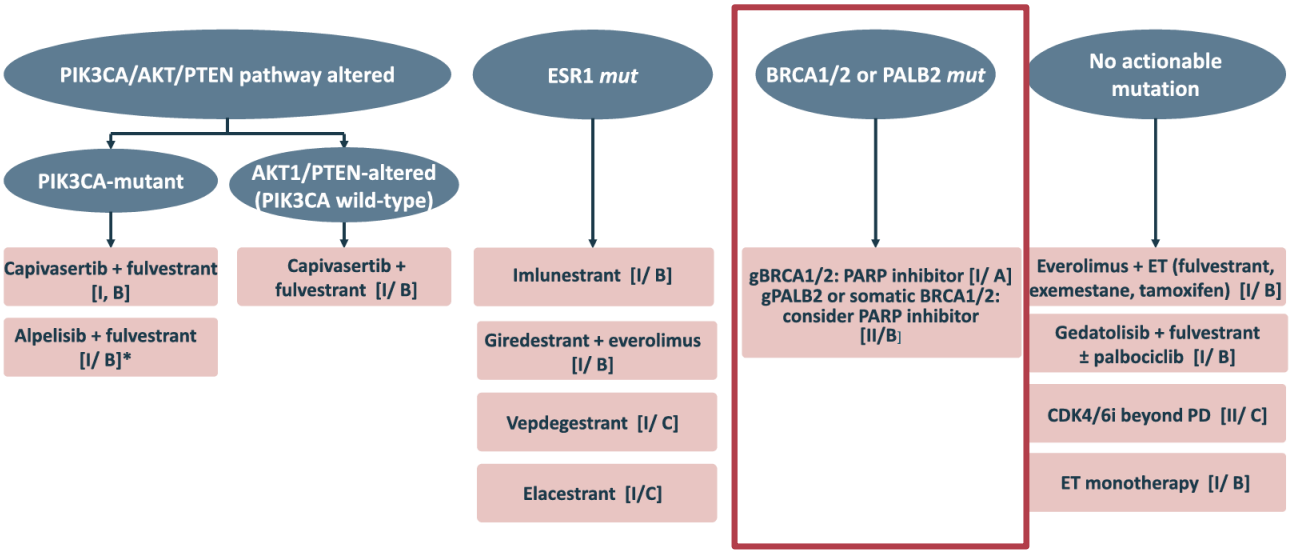
| | *PTEN* status (NGS) | | |
|---|---|---|---|
| | Non-altered | Altered | Subtotal |
| PTEN proficient (IHC) | 278 | 9 | 287 |
| PTEN deficient (IHC) | 36 | 23 | 59 |
| Subtotal | 314 | 32 | 346 |



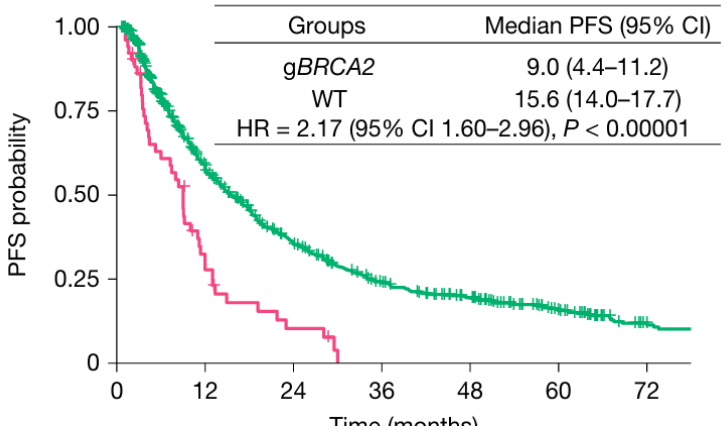

Jhaveri K et al. Clin Cancer Res 2026

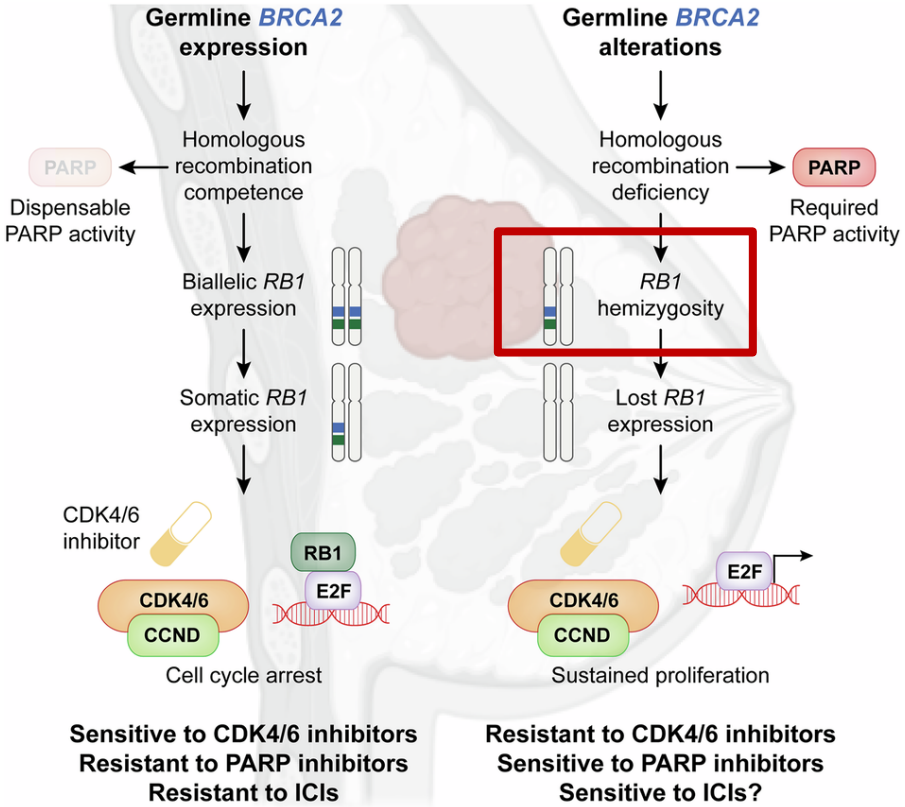
8th International consensus guidelines for the management of advanced breast cancer (ABC8 guidelines)



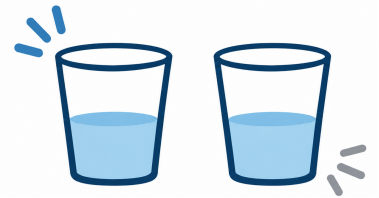

Cardoso F et al. The Breast 2026

# BRCA2 como factor de resistencia a iCDK4/6




Safonov A et al. Nature 2026.Bolini L, NPJ Precision Oncol 2026



## CONCLUSIONES

- La Medicina de Precisión irrumpe en el tratamiento del CM luminal avanzado
    - Identificando resistencias:
        - PI3K y ESR1 se asocian a peor pronóstico y resistencia a tratamientos clásicos.
        - Mutaciones en BRCA2 como marcador de peor SLP con iCDK4/6
    - Identificando sensibilidades:
        - Desarrollo de nuevos tratamientos dirigidos frente a estas alteraciones.
        - Nuevas combinaciones con SLP tras iCDK 6-10 meses
- Nuevas combinaciones con beneficio independiente del estado mutacional .
    - Imlunestrant-abemaciclib
    - Gedatolisib