

# XV 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

17, 18 Y 19 DE MAYO DE 2023



# Tratamiento adyuvante en cáncer de mama luminal

## Perspectiva actual

M<sup>a</sup> Isabel Gallegos Sancho  
Oncología Médica  
Hospital General de Segovia

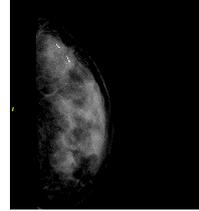


## Conflictos de interés

- Employment: Sacyl, Grupo Recoletas
- Consultancy/honorarium: Roche, Bristol, MSD, Pfizer, Astra-Daichi, Lilly, Palex, Clovis
- Advisory Board: Roche, Pfizer, Novartis, Janseng, Sanofi, Eisai
- Congres Assistance: Roche, Pfizer, Astellas, Gilead, Janseng



Mujer 54 años postmenopáusica,  
No antecedentes familiares de interés



**cT3 cN2 M0**  
CDI G3 RE 7/8 RP 7/8  
Ki 67 20% HER- 1+ Low

ACDDx 4—Px12

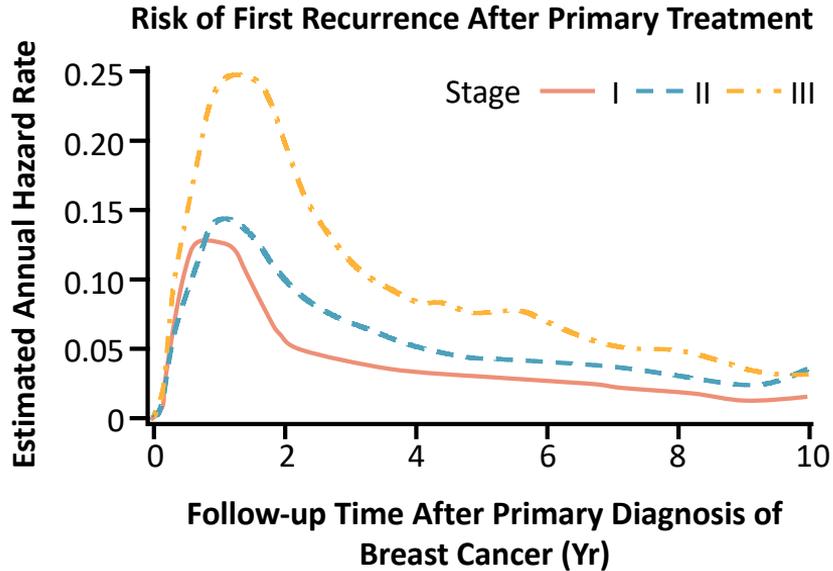
Mastectomía + LA

**cT2(2,5cm) cN2(5/12) M0**  
CDI G2 RE 6/8 RP 5/8  
Ki 67 15% HER- 1+ Low

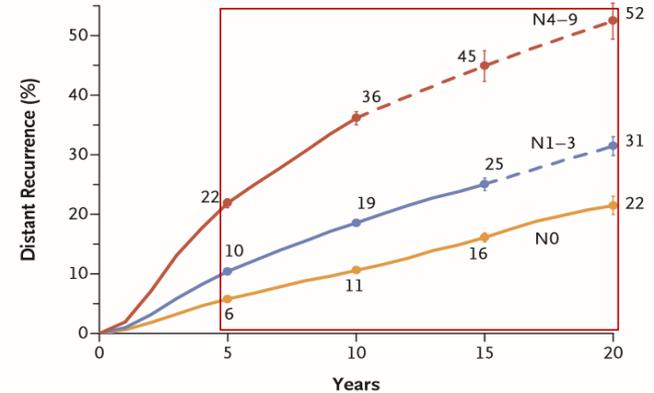
¿Podemos individualizar y  
optimizar el tto adyuvante?



## 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years



### A Risk of Distant Recurrence

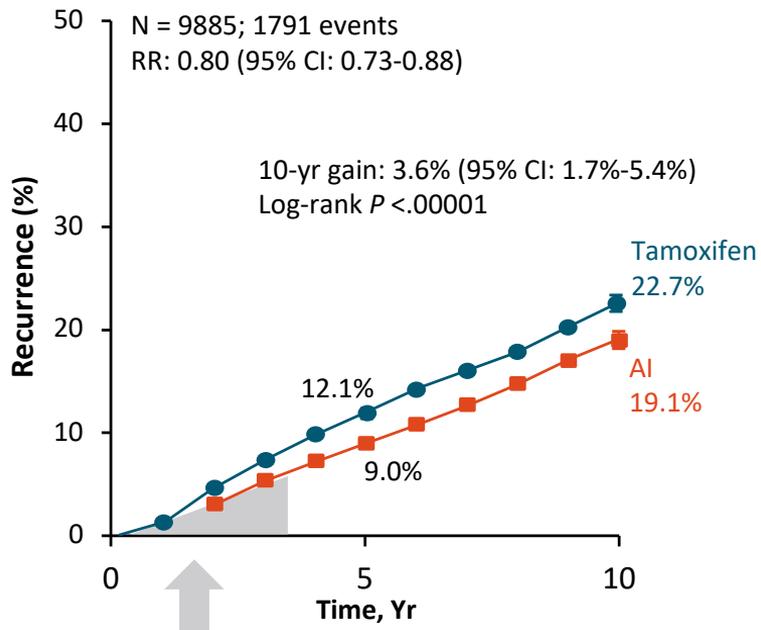


#### No. at Risk

|      |        |        |      |      |     |
|------|--------|--------|------|------|-----|
| N4-9 | 12,333 | 8,116  | 2165 | 259  | 52  |
| N1-3 | 31,936 | 23,576 | 7250 | 949  | 183 |
| N0   | 29,925 | 24,081 | 8571 | 1982 | 414 |

#### No. of Events — annual rate (%)

|      |            |            |           |          |
|------|------------|------------|-----------|----------|
| N4-9 | 2568 (4.8) | 969 (4.0)  | 121 (3.1) | 13 (2.2) |
| N1-3 | 3126 (2.2) | 1421 (1.9) | 241 (1.7) | 39 (1.8) |
| N0   | 1646 (1.2) | 835 (1.1)  | 272 (1.3) | 68 (1.4) |



Primary Endocrine Resistance

## Tratamiento Hormonal

- Tamoxifeno
- Inhibidores Aromatasa
- Supresión ovárica
- Terapia hormonal extendida

- Identificar pacientes HR+ resistencia Primaria y prevenir o retrasar recurrencia con terapia adicional

Cardoso et al. Ann Oncol 2019

Early Breast Cancer Trialist Collaborative Group Lancet 2015



- ❑ Individualizar el riesgo de recurrencia

**Scores, calculadoras de riesgo**

- ❑ Personalización del tto adyuvante

**Plataformas genómicas** para decidir el beneficio de QT y/o duración y tto hormonal

- ❑ Estrategias terapéuticas

**Hormonoterapia:**

Elección del tto y duración del tratamiento



Nuevos agentes

Inhibidores de ciclinas

Inhibidores del parp

SERDs

Otros: papel de los ADCs

# Inhibidores de CDK4/6

## Clinical and Pharmacologic Differences of CDK4/6 Inhibitors in Breast Cancer

Mridula A. George<sup>1\*</sup>, Sadaf Qureshi<sup>2</sup>, Coral Omene<sup>1</sup>, Deborah L. Toppmeyer<sup>1</sup> and Shridhar Ganesan<sup>1</sup>

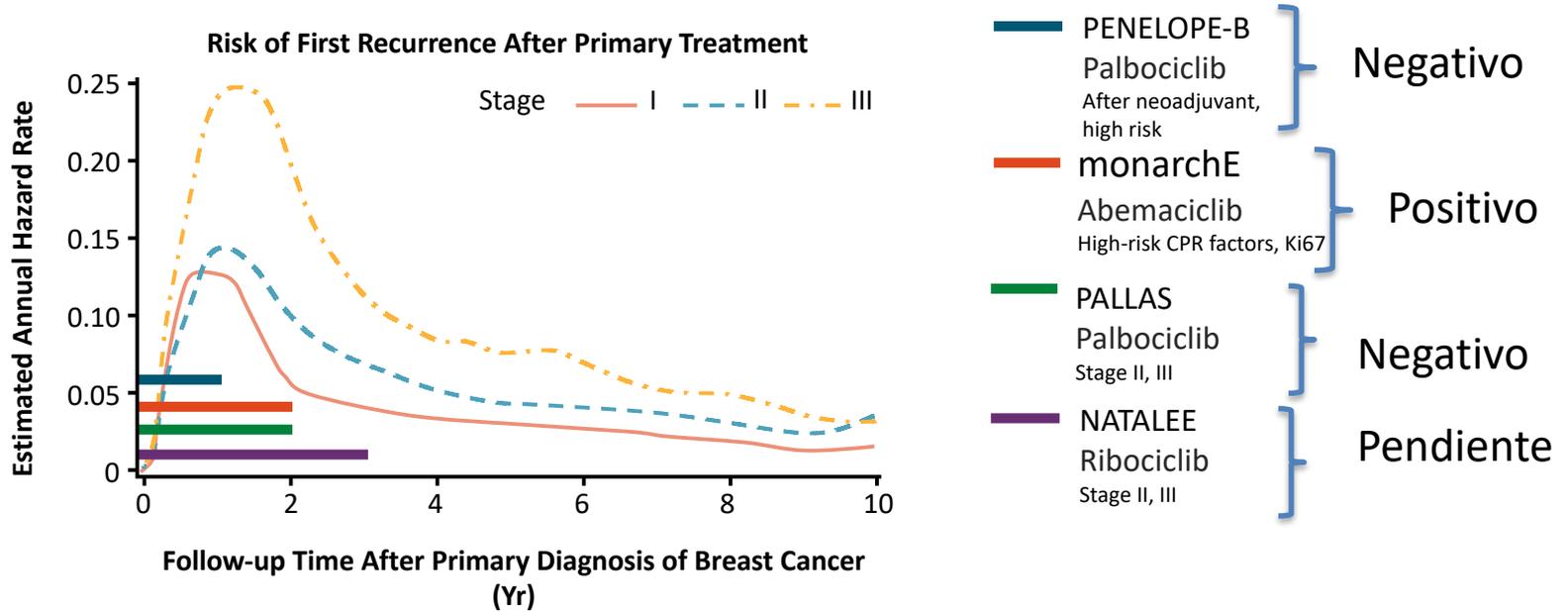
- La progresión del ciclo celular dep de la hiperfosforilación de Rb(INACTIVA) y libera factores de transcripción E2F (ACTIVA EL CICLO CELULAR)
- Esto es facilitado por la activación de CDK4/6 mediante la unión de de Ciclina D
- La expresión de Ciclina D es estimulada por los estrógenos
- Alteraciones genómicas en cáncer pueden activar CDKs
- Inhibición de CDK4/6 lleva a un arresto celular
- Inhibición continua de CDK4/6 puede llevar a un arresto celular, senescencia y apoptosis celular.



✓ Arresto celular

- ✓ La expresión de ciclina D es estimulada por los estrógenos
- ✓ Bloqueando la P de Rb

# ¿Existe algún papel para los inhibidores de CDK4/6 en adyuvancia ?

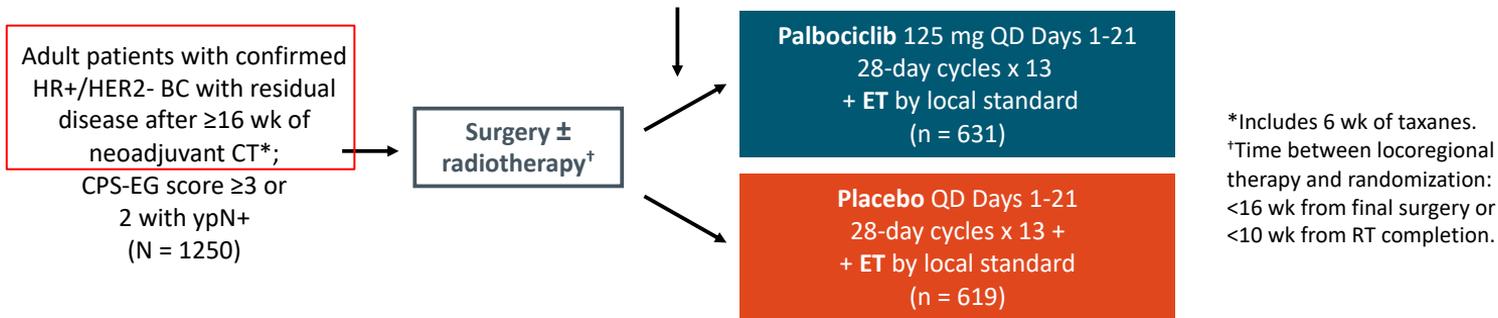




# PENELOPE-B: Palbociclib + ET in HR+/HER2- BC at High Risk of Relapse After Neoadjuvant Chemotherapy

- Randomized, double-blind, placebo-controlled phase III trial

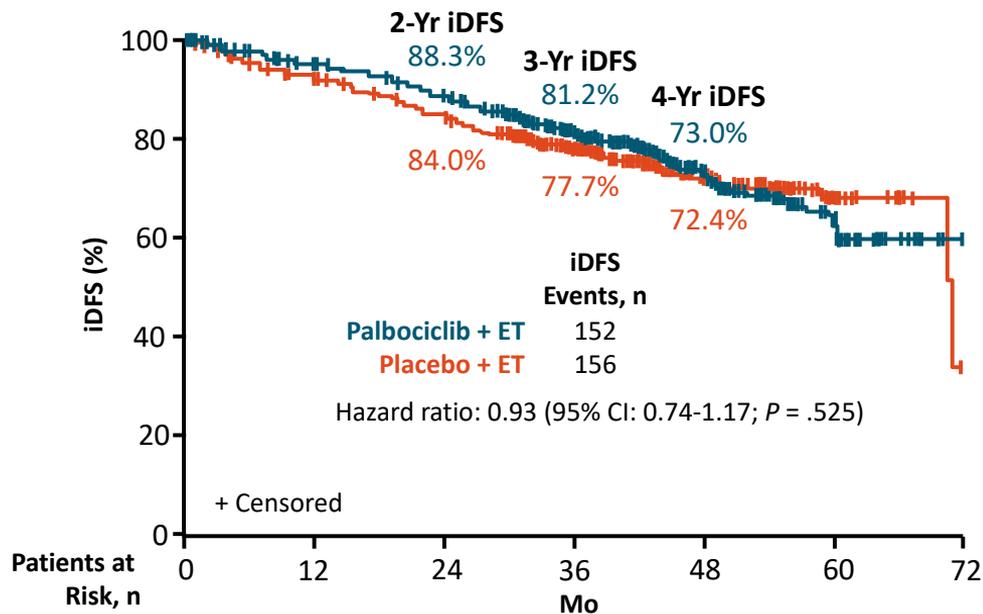
*Stratified by age ( $\leq 50$  vs  $> 50$  yr), nodal status (ypN0-1 vs ypN2-3), Ki-67 ( $> 15\%$  vs  $\leq 15\%$ ), region (Asia vs non-Asia), and CPS-EG score ( $\leq 3$  vs  $2$  and ypN+)*



- Primary endpoint: **iDFS**
- Secondary endpoints include: iDFS excluding second primary invasive non-breast cancers, distant DFS, locoregional RFS, OS, safety, compliance, QoL



## PENELOPE-B: iDFS (Primary Endpoint)

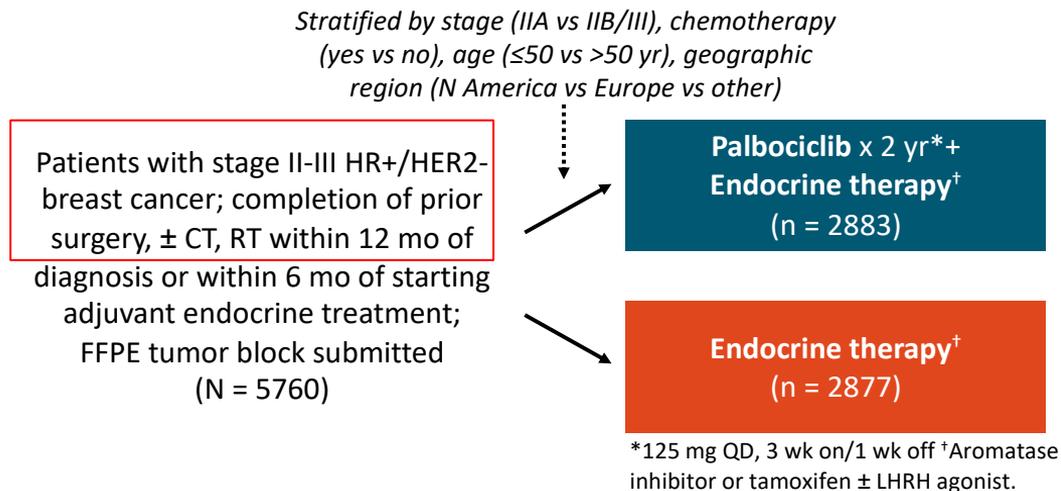


- Median f/u: 42.8 mo
- Types of iDFS events
  - 74% distant recurrences
    - 116 with palbociclib, 111 with placebo
  - 16% invasive locoregional recurrences
    - 21 with palbociclib, 27 with placebo



# PALLAS: Phase III Open-Label Study of Adjuvant Palbociclib + Endocrine Therapy

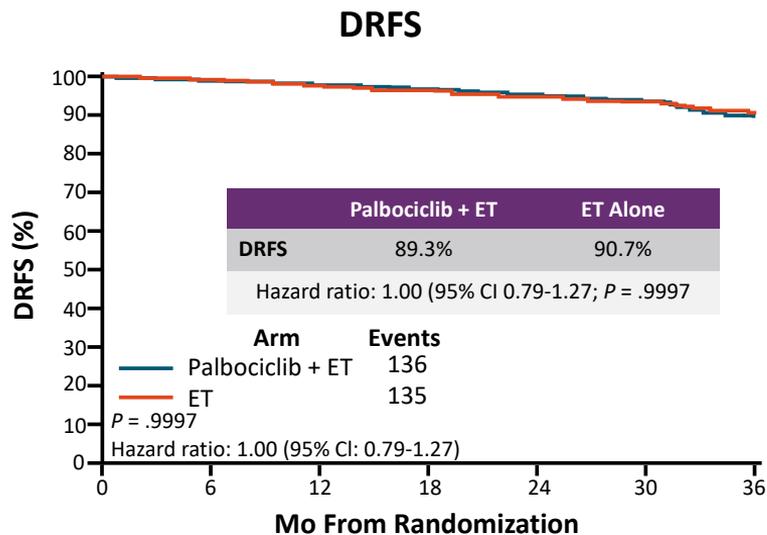
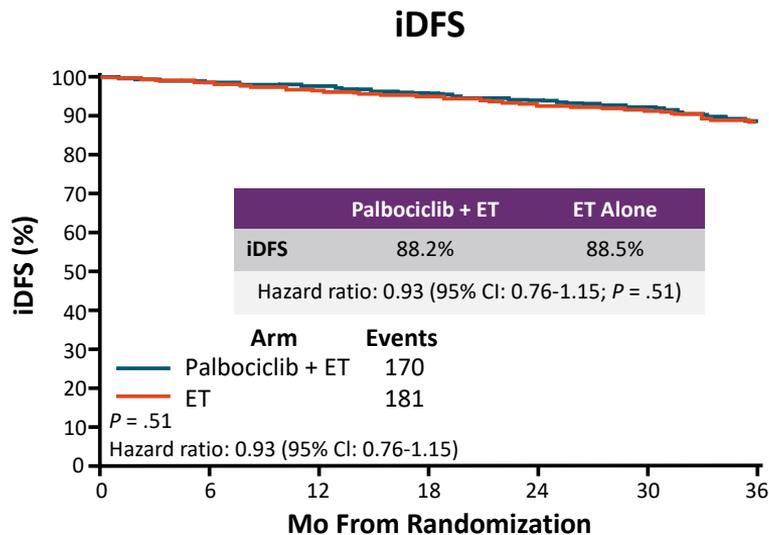
- Multicenter, open-label, randomized phase III trial



- **Primary endpoint:** invasive disease-free survival



## PALLAS: Primary Endpoint iDFS



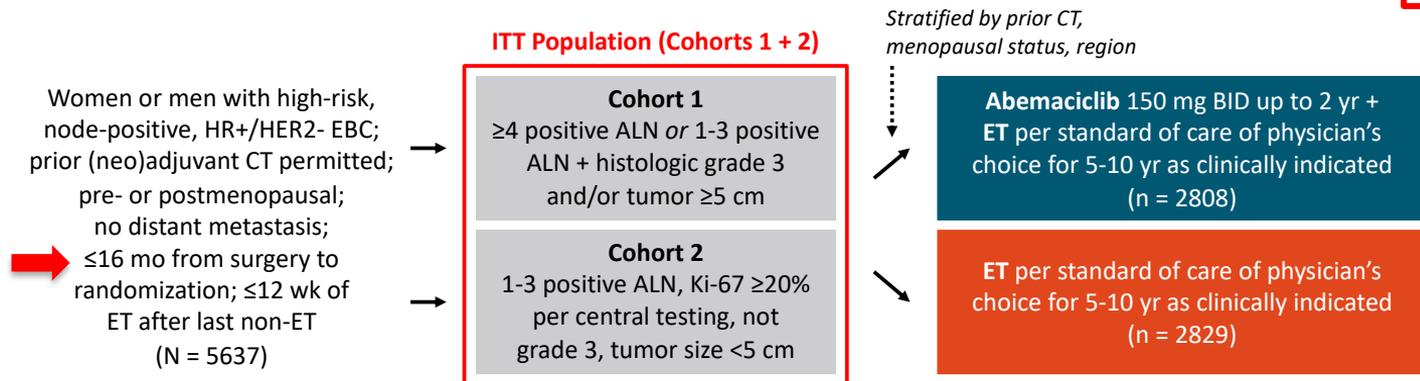
- At a median follow-up of 23.7 mo, no significant difference in either 3-yr iDFS or DRFS was observed



# monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

**2 años de tto  
O1º: IDFS**

- International, randomized, open-label phase III trial



- Primary endpoint:** iDFS
- Key secondary endpoints:** iDFS in Ki-67 high (≥20%) population, distant RFS, OS, safety, PRO, PK

*Johnston et al. JCO 2020  
Johnston et al. Lancet 2023*



# monarchE: Baseline Characteristics

High-risk Disease

| Category <sup>1</sup>                                        |             | Abemaciclib + ET<br>N=2808, n (%) | ET alone<br>N=2829, n (%) |
|--------------------------------------------------------------|-------------|-----------------------------------|---------------------------|
| Number of positive lymph nodes                               | 0           | 7 (0.2)                           | 7 (0.2)                   |
|                                                              | 1-3         | 1119 (39.9)                       | 1143 (40.4)               |
|                                                              | ≥4          | 1680 (59.8)                       | 1679 (59.3)               |
| Histological grade                                           | Grade 1     | 209 (7.4)                         | 215 (7.6)                 |
|                                                              | Grade 2     | 1373 (48.9)                       | 1395 (49.3)               |
|                                                              | Grade 3     | 1090 (38.8)                       | 1066 (37.7)               |
| Primary tumor size by pathology following definitive surgery | <20 mm      | 780 (27.8)                        | 765 (27.0)                |
|                                                              | 20 - 50 mm  | 1369 (48.8)                       | 1419 (50.2)               |
|                                                              | ≥50 mm      | 610 (21.7)                        | 612 (21.6)                |
| Central Ki-67                                                | <20%        | 953 (33.9)                        | 973 (34.4)                |
|                                                              | ≥20%        | 1262 (44.9)                       | 1233 (43.6)               |
|                                                              | Unavailable | 593 (21.1)                        | 623 (22.0)                |
| Progesterone receptor status                                 | Positive    | 2421 (86.2)                       | 2453 (86.7)               |
|                                                              | Negative    | 298 (10.6)                        | 294 (10.4)                |

| Additional high-risk eligibility criteria for patients with 1-3 nodes <sup>2</sup> | Abemaciclib + ET<br>N=2808, n (%) | ET Alone<br>N=2829, n (%) |
|------------------------------------------------------------------------------------|-----------------------------------|---------------------------|
| Tumor size ≥5 cm (pathology) <sup>a</sup>                                          | 249 (8.9)                         | 236 (8.3)                 |
| Tumor size ≥5 cm (imaging) <sup>a, b</sup>                                         | 152 (5.4)                         | 158 (5.6)                 |
| Histologic Grade 3 <sup>a</sup>                                                    | 629 (22.4)                        | 618 (21.8)                |
| Central Ki-67 ≥20% only <sup>c</sup>                                               | 216 (7.7)                         | 237 (8.4)                 |

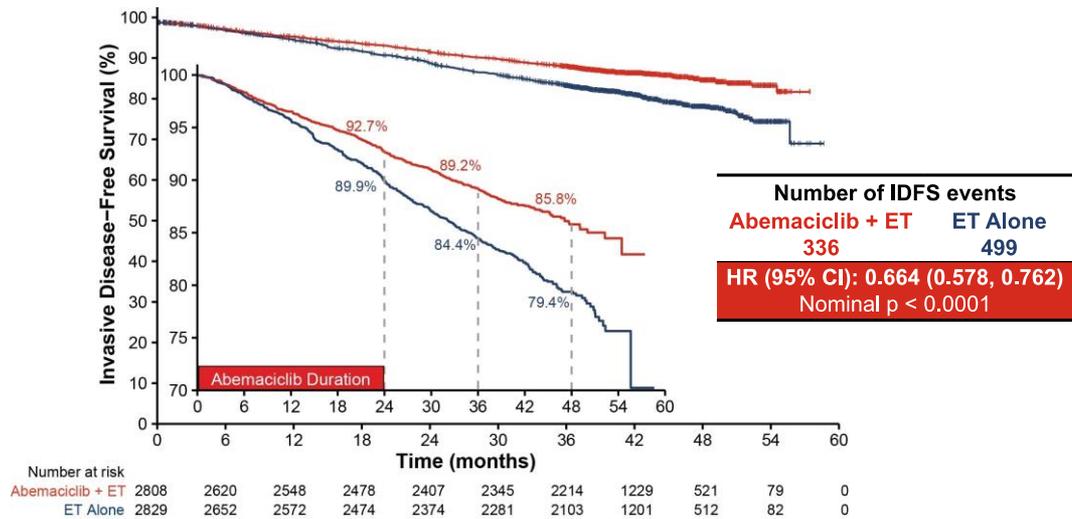


# monarchE: Baseline Characteristics

|                                      |                          | <b>Abemaciclib + ET<br/>N=2808, n (%)</b> | <b>ET Alone<br/>N=2829, n (%)</b> |
|--------------------------------------|--------------------------|-------------------------------------------|-----------------------------------|
| <b>Age</b>                           | <b>Median (range)</b>    | 51 (23-89)                                | 51 (22-86)                        |
| <b>Age categories</b>                | <65 years                | 2371 (84.4)                               | 2416 (85.4)                       |
|                                      | ≥65 years                | 437 (15.6)                                | 413 (14.6)                        |
| <b>Gender</b>                        | Female                   | 2787 (99.3)                               | 2814 (99.5)                       |
|                                      | Male                     | 21 (0.7)                                  | 15 (0.5)                          |
| <b>Region<sup>a</sup></b>            | North America/Europe     | 1470 (52.4)                               | 1479 (52.3)                       |
|                                      | Asia                     | 574 (20.4)                                | 582 (20.6)                        |
|                                      | Other                    | 764 (27.2)                                | 768 (27.1)                        |
| <b>Menopausal status<sup>a</sup></b> | Premenopausal            | 1221 (43.5)                               | 1232 (43.5)                       |
|                                      | Postmenopausal           | 1587 (56.5)                               | 1597 (56.5)                       |
| <b>Prior treatment<sup>a</sup></b>   | Neoadjuvant chemotherapy | 1039 (37.0)                               | 1048 (37.0)                       |
|                                      | Adjuvant chemotherapy    | 1642 (58.5)                               | 1647 (58.2)                       |
|                                      | No chemotherapy          | 127 (4.5)                                 | 134 (4.7)                         |
| <b>Baseline ECOG PS</b>              | 0                        | 2405 (85.7)                               | 2369 (83.8)                       |
|                                      | 1                        | 401 (14.3)                                | 455 (16.1)                        |



## IDFS Benefit in ITT Persists Beyond Completion of Abemaciclib

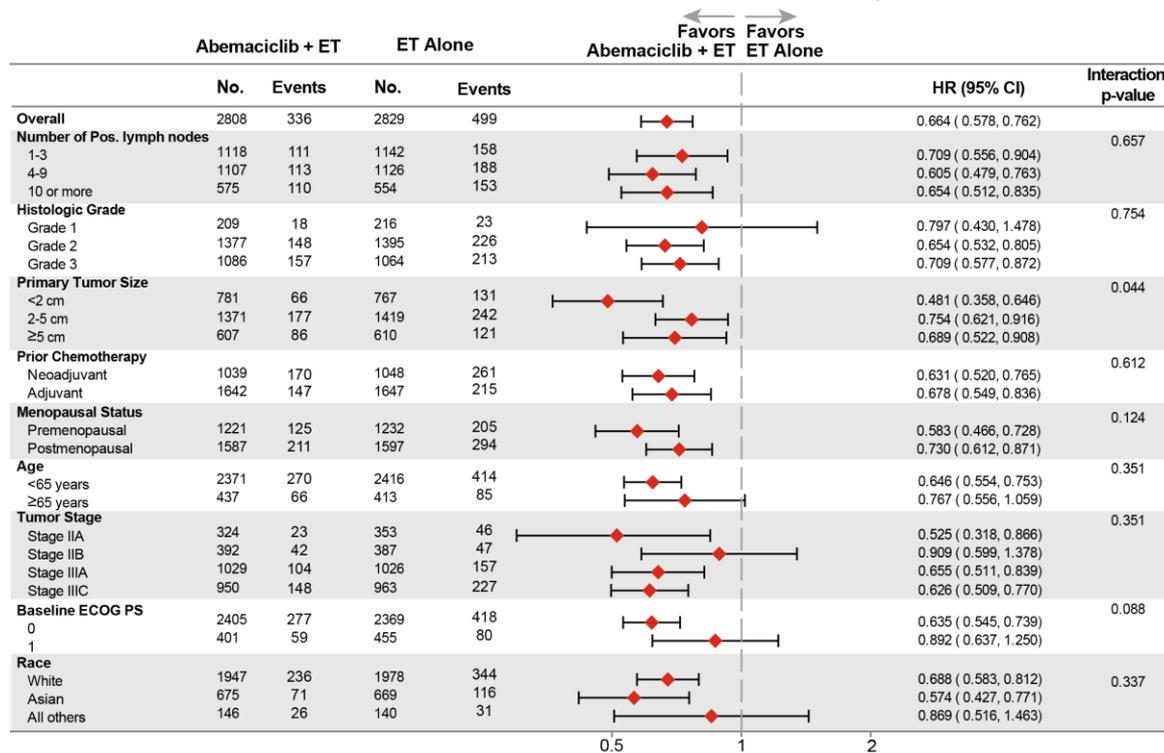


- 6.4%
- HR 0.66

33.6% reduction in the risk of developing an IDFS event with an increase in absolute benefit in IDFS 4-year rates (6.4%) compared to 2-and 3-year IDFS rates (2.8% and 4.8% respectively)

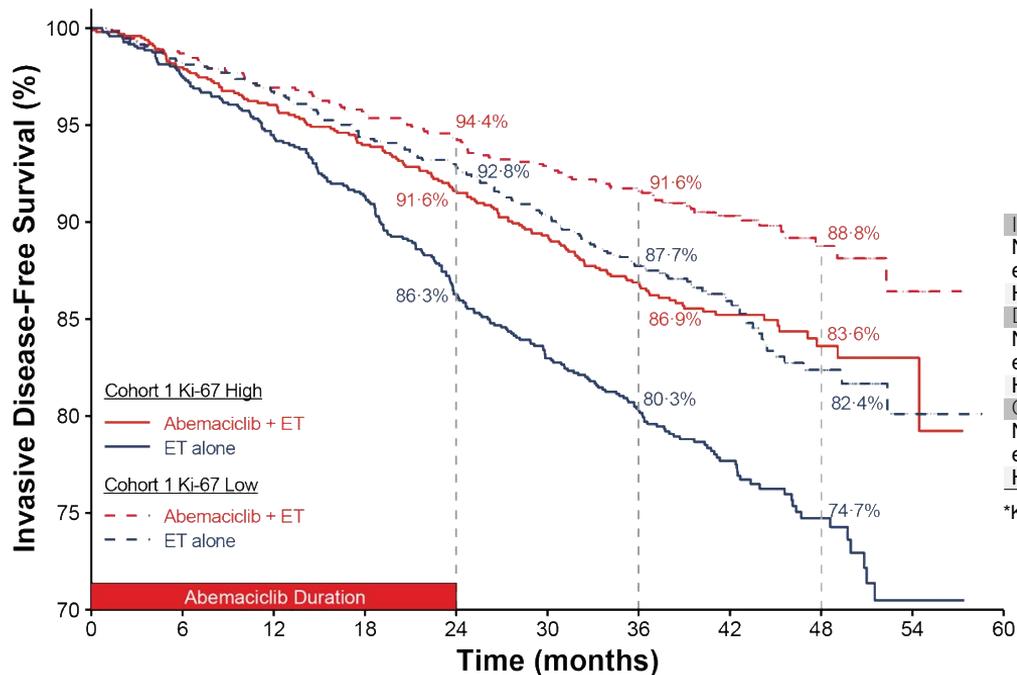
- Follow-up de 4 a , beneficio absoluto en **iDFS 6.4%**, en todos los subgrupos
- Ki factor pronóstico, no predictivo de beneficio a Abemaciclib
- Datos inmaduros de SG, sí diferencias numéricas

# Consistent IDFS Benefit Observed in all Prespecified Subgroups\*





## Ki-67 is Prognostic, but Not Predictive of Abemaciclib Benefit



|                      | Cohort 1*                  |                   |                           |                   |
|----------------------|----------------------------|-------------------|---------------------------|-------------------|
|                      | C1 Ki-67 High              |                   | C1 Ki-67 Low              |                   |
|                      | Abemaciclib + ET<br>N=1017 | ET alone<br>N=986 | Abemaciclib + ET<br>N=946 | ET alone<br>N=968 |
| <b>IDFS</b>          |                            |                   |                           |                   |
| Number of events, n  | 147                        | 224               | 91                        | 141               |
| HR (95% CI)          | 0.618 (0.501, 0.762)       |                   | 0.624 (0.478, 0.814)      |                   |
| <b>DRFS</b>          |                            |                   |                           |                   |
| Number of events, n  | 126                        | 193               | 74                        | 119               |
| HR (95% CI)          | 0.612 (0.488, 0.767)       |                   | 0.613 (0.458, 0.821)      |                   |
| <b>OS (Immature)</b> |                            |                   |                           |                   |
| Number of events, n  | 68                         | 88                | 39                        | 50                |
| HR (95% CI)          | 0.733 (0.533, 1.007)       |                   | 0.772 (0.506, 1.175)      |                   |

\*Ki-67 value was missing in 1203 (23.5%) patients

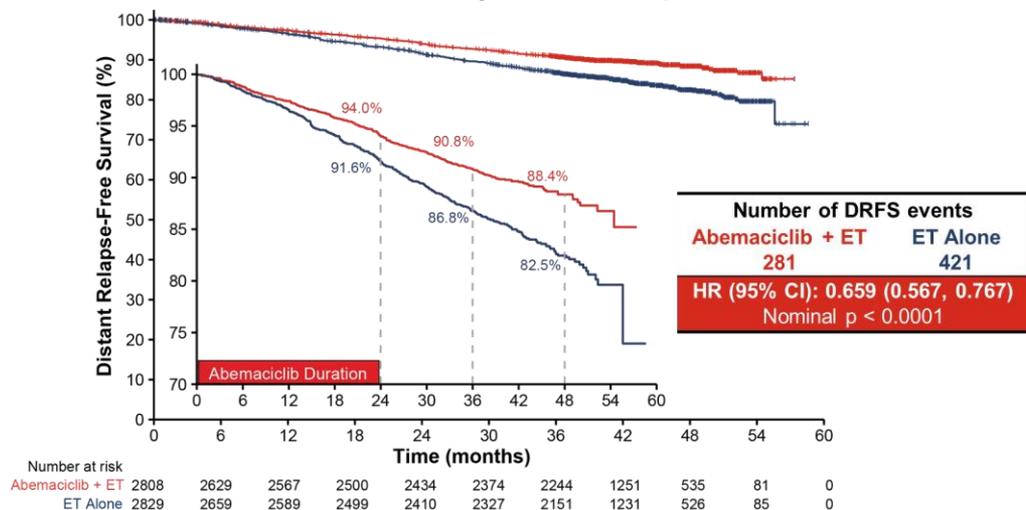
\* 55% Cohorte 1 Ki low

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index



| LOCATION OF RECURRENCE                      | Abemaciclib + ET<br>N=2808 | ET<br>N=2829 |
|---------------------------------------------|----------------------------|--------------|
| Patients with any disease recurrence, n (%) | 215 (7.7)                  | 323 (11.4)   |
| • Distant recurrence                        | 156 (5.6)                  | 245 (8.7)    |
| • Local/regional recurrence                 | 34 (1.2)                   | 54 (1.9)     |
| • Contralateral recurrence                  | 8 (0.3)                    | 12 (0.4)     |
| • Second primary neoplasm*                  | 20 (0.7)                   | 20 (0.7)     |

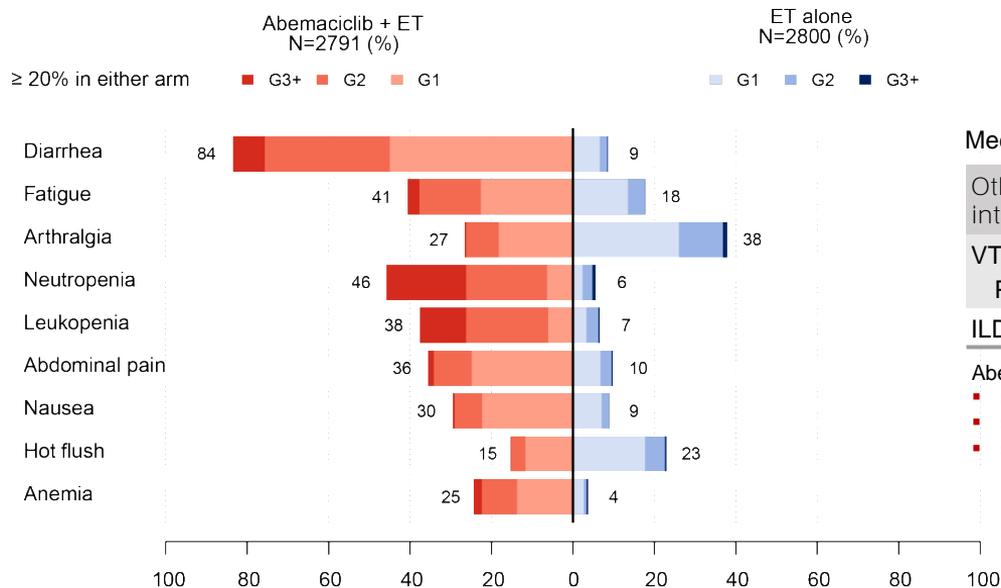
## DRFS Benefit in ITT Persists Beyond Completion of Abemaciclib



34.1% reduction in the risk of developing a DRFS event with an increase in absolute benefit in DRFS 4-year rates (5.9%), compared to 2- and 3-year rates (2.5% and 4.1%, respectively)



# Safety Findings Consistent with Previous Analyses



Median duration of abemaciclib: 23.7 months.

| Other events of interest, any grade | Abemaciclib + ET<br>N = 2791, % | ET Alone<br>N = 2800, % |
|-------------------------------------|---------------------------------|-------------------------|
| VTE                                 | 2.5                             | 0.7                     |
| PE                                  | 1.0                             | 0.1                     |
| ILD                                 | 3.3                             | 1.3                     |

Abemaciclib dose adjustments due to AEs

- dose holds: 61.7%
- dose reductions: 43.6%
- discontinuations 18.5% [8.9% after dose reduction]

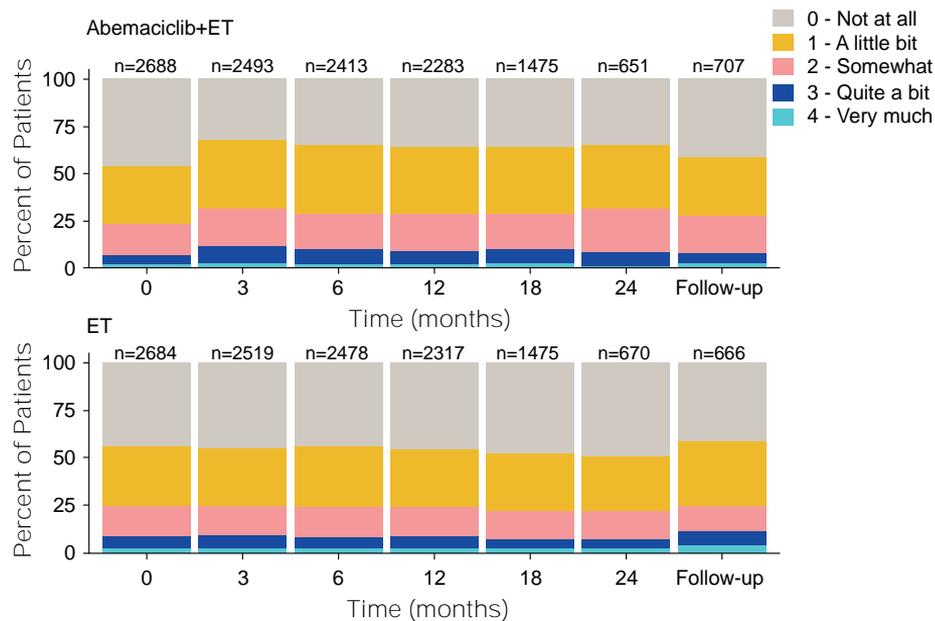
- Grado 3/4: 49% (neutropenia 19% diarrea 8%)
- 42% reducción de dosis
- 18.5% discontinuaciones

*Johnston et al. JCO 2020*  
*Johnston et al. Lancet 2023*



## monarchE: FACT-B GP5 “Bothered by Treatment Side Effect” at PO Analysis

Percent stacked bar plot of PRO on FACT-B GP5



- ◆ Overall patient compliance for PROs was >90%
- ◆ The addition of abemaciclib to ET did not result in a clinically meaningful difference in patients being bothered by treatment-induced side effects
- ◆ The side effects of treatment bothered most patients (in both arms) “a little” or “not at all”
- ◆ Majority of the patients who experienced diarrhea in the abemaciclib arm reported having diarrhea “a little bit” or “somewhat” from 3 months and beyond. In addition, this was more frequently reported in the earlier PRO assessments

*Johnston et al. JCO 2020*  
*Johnston et al. Lancet 2023*

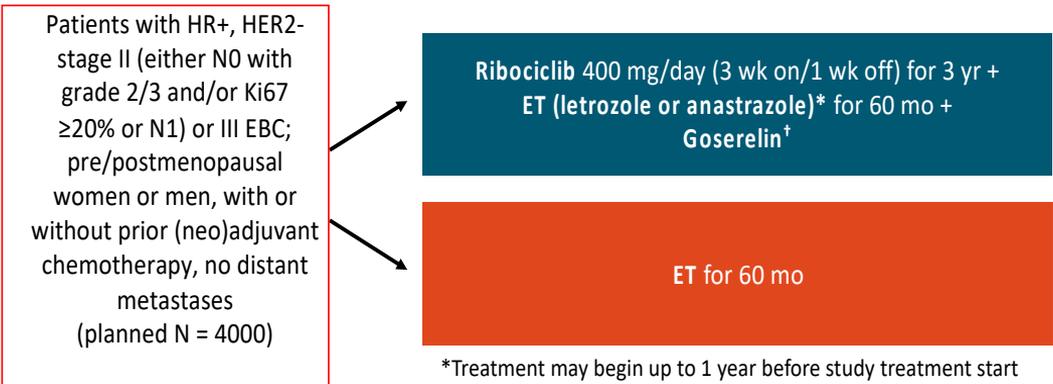
## ¿Porqué diferencias en los estudios de adyuvancia con iCDK4/6?)

|                              | monarchE                                                | PALLAS                                                  | PENELOPE-B              |
|------------------------------|---------------------------------------------------------|---------------------------------------------------------|-------------------------|
| N                            | 5637                                                    | 5600                                                    | 1250                    |
| CDKi                         | Abemaciclib                                             | Palbociclib                                             | Palbociclib             |
| Eligibility                  | ≥N2 or<br>≥N1 and G3 or T3 (1)<br>N1 and Ki-67 ≥20% (2) | Anatomic stage 2 or 3<br>(59% N2 or N1 and G3 or<br>T3) | CPS-EG 3 or 2 with ypN+ |
| CDKi duration, mo            | 24                                                      | 24                                                      | 12                      |
| Follow-up, mo                | 19                                                      | 24                                                      | 43                      |
| 2-yr iDFS (change), %        | 92 vs 89 (3)                                            | NR                                                      | 88 vs 84 (4)            |
| 3-yr iDFS (change), %        | NR                                                      | 88 vs 89 (-1)                                           | 81 vs 78 (3)            |
| 4-yr iDFS (change), %        | NR                                                      | NR                                                      | 73 vs 72 (.6)           |
| DRFS (change), %             | 94 vs 91 (3)                                            | 89 vs 90 (at Yr 3)                                      | No difference           |
| Discontinuation rate, %      | 28                                                      | 42                                                      | 20                      |
| Discontinuation due to AE, % | 17                                                      | 27                                                      | 5                       |
| Completed therapy, %         | 72                                                      | 32                                                      | 80                      |



# NATALEE: Adjuvant Ribociclib + ET in HR+/HER2- EBC

- Multicenter, randomized, open-label phase III trial



\*Treatment may begin up to 1 year before study treatment start date. <sup>†</sup>Premenopausal women and men will also receive goserelin 3.6 mg/28 days.

- **Primary endpoint:** invasive disease-free survival (STEEP criteria)
- **Key secondary endpoints:** recurrence-free survival, distant DFS, overall survival, patient-reported outcomes, and pharmacokinetics; safety and tolerability will also be evaluated

**3 años de tto**  
**O1º: IDFS**

\*ASCO 2023



# Inhibidores del parp



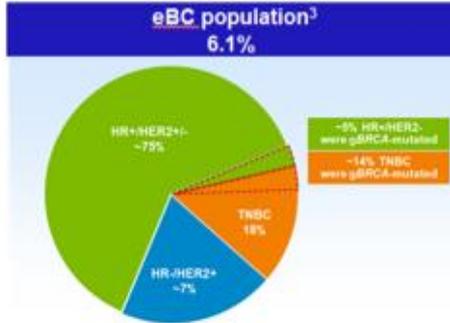
## Prevalence of Germline *BRCA* Mutations Account for a Small Subset of All Breast Cancer Patients

Prevalence of *gBRCA1/BRCA2*:

Total BC Population (all stages)<sup>1</sup>  
 2.7%–6.1%

Total BC Population (metastatic)<sup>2,3</sup>  
 2.7%–4.3%

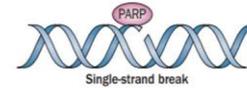
TNBC Population (all stages)<sup>1</sup>  
 9.3%–15.4%



• Up to 16% of all male breast cancers have *BRCA* mutations<sup>4</sup>

## Inhibidores del parp Alteraciones genes de la recombinación homóloga

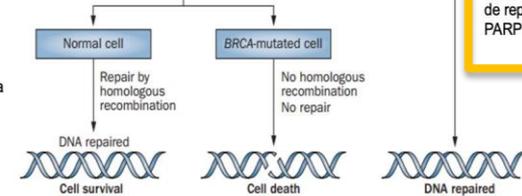
PARP es un mecanismo de reparación de cadena simple



Cuando farmacológicamente se inhibe PARP, no se repara el daño en cadena simple y progresa a daño en cadena doble



Si el mecanismo de reparación está intacto se reparará la doble cadena y la célula sobrevive



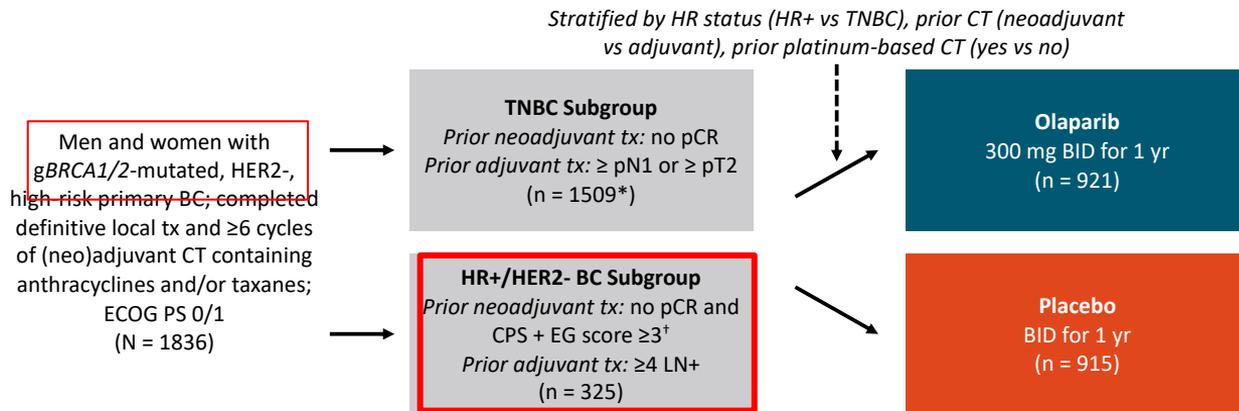
Si hay un defecto en la capacidad de reparación homóloga, la inhibición de PARP resulta letal



# OlympiA: Study Design

**1 año de tto**  
**O1º: iDFS**

- Prespecified interim analysis of international, randomized, double-blind phase III trial (data cutoff: Mar 27, 2020)



Crterios de estratificación:

- HR
- QT neo/ady
- Platino previo

- Primary endpoint:** iDFS
- Secondary endpoints:** distant DFS, OS, safety

\*Excluded n = 2 (both in olaparib arm) due to unconfirmed HER2- status.

<sup>†</sup>Staging system for BC-specific survival after neoadjuvant tx incorporating pretreatment clinical stage, ER status, nuclear grade, pathologic stage (range: 0-6).

*Tutt et al NEJM 2021*



## CPS + EG es un sistema que proporciona una herramienta pronóstica en cancer de mama precoz

- CPS+ EG categorización pronóstica de pacientes con cáncer de mama tras QT NEO versus el estadiaje clínico o patológico solo
- Incorpora: estadiaje clínico, estadiaje patológico, RE y grado nuclear

|                          | Stage <sup>a</sup> /Feature | Points |
|--------------------------|-----------------------------|--------|
| <b>Clinical Stage</b>    | 0                           | 0      |
|                          | IIA                         | 0      |
|                          | IIB                         | 1      |
|                          | IIIA                        | 1      |
|                          | IIIB                        | 2      |
|                          | IIIC                        | 2      |
| <b>Pathologic Stage</b>  | 0                           | 0      |
|                          | I                           | 0      |
|                          | IIA                         | 1      |
|                          | IIB                         | 1      |
|                          | IIIA                        | 1      |
|                          | IIIB                        | 1      |
|                          | IIIC                        | 2      |
| <b>Receptor status</b>   | ER receptor-negative        | 1      |
| <b>Nuclear grade</b>     | Nuclear grade 3             | 1      |
| <b>Total score (0-6)</b> |                             |        |

CPS+ EG > o igual a 3

Mittendorf EA et al. J Clin Oncol. 2011.

## Baseline characteristics

|                                                         | <b>Olaparib<br/>n=921</b> | <b>Placebo<br/>n=915</b> |
|---------------------------------------------------------|---------------------------|--------------------------|
| <b>Age – years, median (interquartile range), years</b> | 42 (36–49)                | 43 (36–50)               |
| <b>Female, n (%)</b>                                    | 919 (99.8)                | 911 (99.6)               |
| <b>BRCA gene affected in germline, n (%)</b>            |                           |                          |
| <i>BRCA1</i>                                            | 657 (71.3)                | 670 (73.2)               |
| <i>BRCA2</i>                                            | 261 (28.3)                | 239 (26.1)               |
| <i>BRCA1 &amp; BRCA2</i>                                | 2 (0.2)                   | 5 (0.5)                  |
| Missing                                                 | 1 (0.1)                   | 1 (0.1)                  |
| <b>Menopausal status (females only), n (%)</b>          |                           |                          |
| Premenopausal                                           | 572/919 (62.2)            | 553/911 (60.7)           |
| Postmenopausal                                          | 347/919 (37.8)            | 358/911 (39.3)           |
| <b>Bilateral invasive breast cancer, n (%)</b>          |                           |                          |
| No                                                      | 881 (95.7)                | 888 (97.0)               |
| Yes                                                     | 40 (4.3)                  | 27 (3.0)                 |



## Baseline characteristics

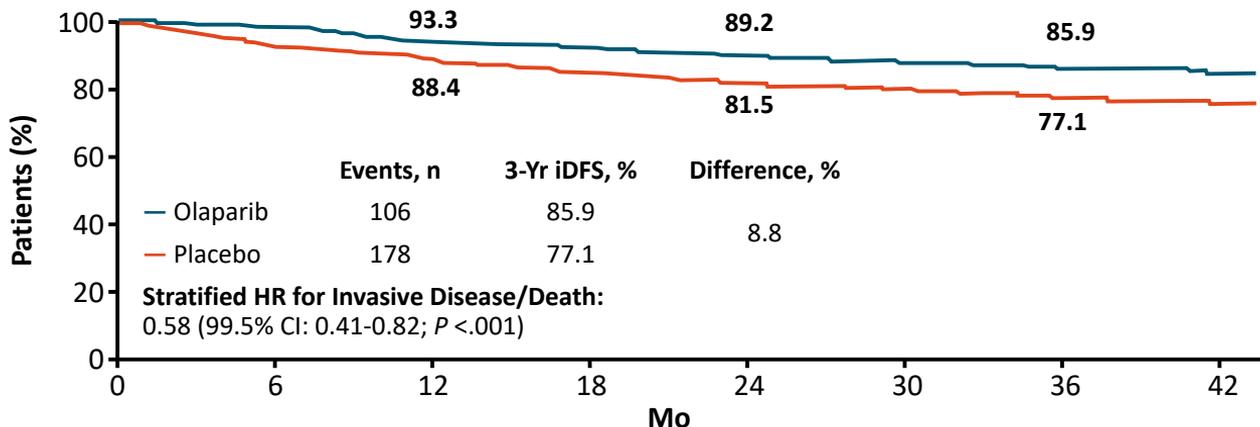
|                                                               | <b>Olaparib<br/>n=921</b> | <b>Placebo<br/>n=915</b> |
|---------------------------------------------------------------|---------------------------|--------------------------|
| <b>Prior (neo)adjuvant chemotherapy, n (%)<sup>a</sup></b>    |                           |                          |
| Adjuvant                                                      | 461 (50.1)                | 455 (49.7)               |
| Neoadjuvant                                                   | 460 (49.9)                | 460 (50.3)               |
| Anthracycline and taxane regimen                              | 871 (94.6)                | 849 (92.8)               |
| Anthracycline regimen (without taxane)                        | 7 (0.8)                   | 13 (1.4)                 |
| Taxane regimen (without anthracycline)                        | 43 (4.7)                  | 52 (5.7)                 |
| <b>(Neo)adjuvant platinum-based chemotherapy, n (%)</b>       |                           |                          |
| No                                                            | 674 (73.2)                | 677 (74.0)               |
| Yes                                                           | 247 (26.8)                | 238 (26.0)               |
| <b>HR status, n (%)<sup>b</sup></b>                           |                           |                          |
| HR-positive / HER2-negative                                   | 168 (18.2)                | 157 (17.2)               |
| TNBC <sup>c</sup>                                             | 751 (81.5)                | 758 (82.8)               |
| <b>Concurrent hormone therapy (HR-positive only), n/N (%)</b> | 146/168 (86.9)            | 142/157 (90.4)           |

**18%**

<sup>a</sup> 7 patients in the Olaparib arm and 15 patients in the placebo arm received less than 5 cycles of (neo)adjuvant chemotherapy. Regimen for 1 patient in the placebo arm was not



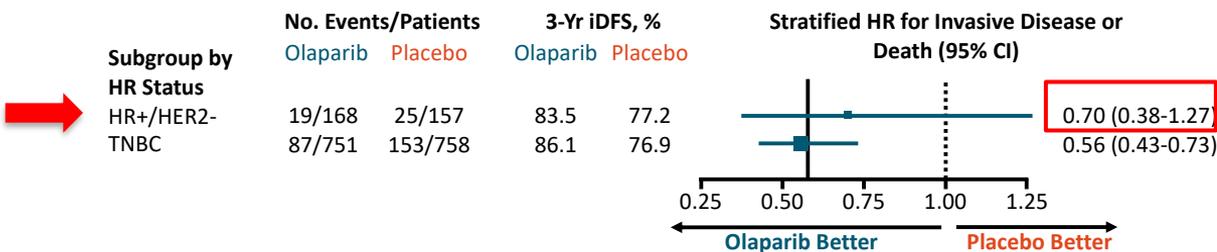
# OlympiA: Invasive Disease-Free Survival (ITT)



- 8.8%
- HR 0.58

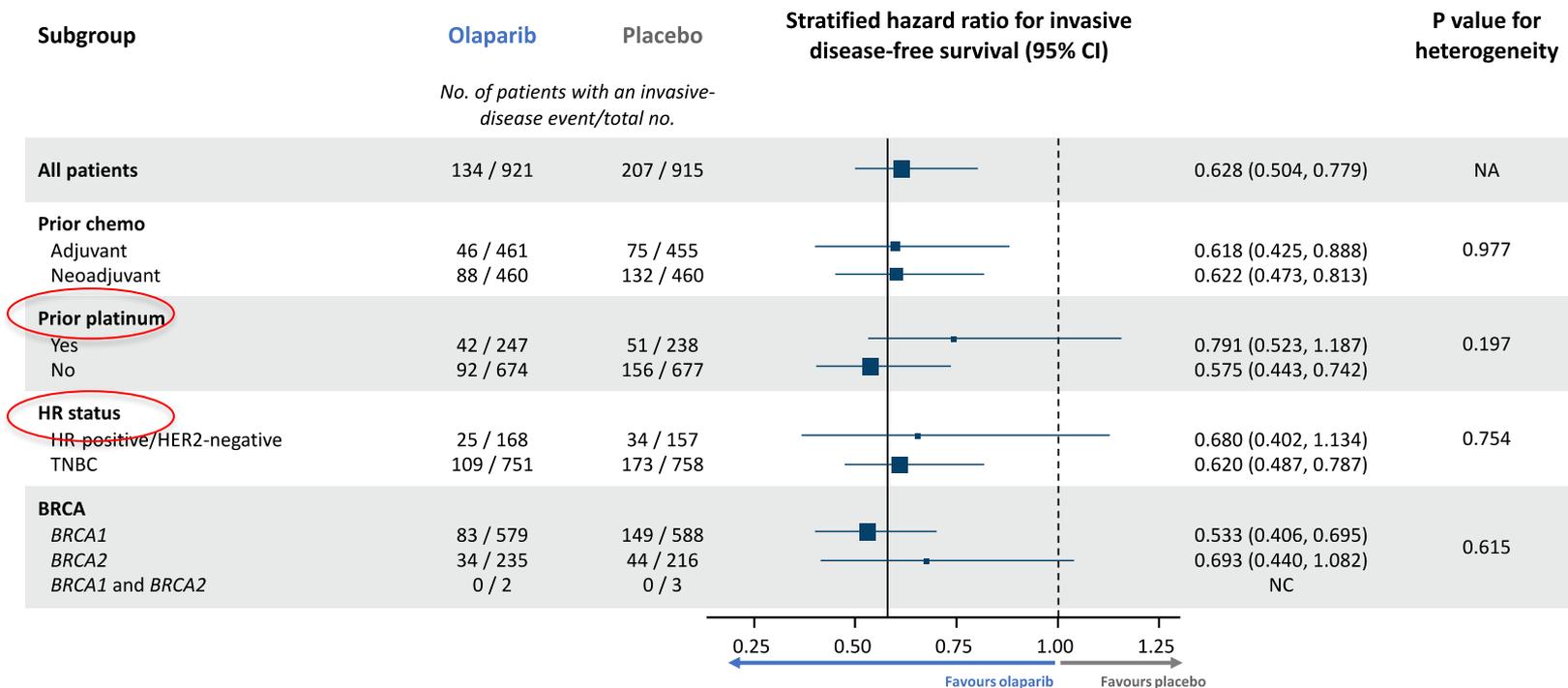
|            | Events, n | 3-Yr iDFS, % | Difference, % |
|------------|-----------|--------------|---------------|
| — Olaparib | 106       | 85.9         | 8.8           |
| — Placebo  | 178       | 77.1         |               |

**Stratified HR for Invasive Disease/Death:**  
 0.58 (99.5% CI: 0.41-0.82;  $P < .001$ )





## A consistent benefit was seen across all IDFS subgroups





## OlympiA: Type of First iDFS Event

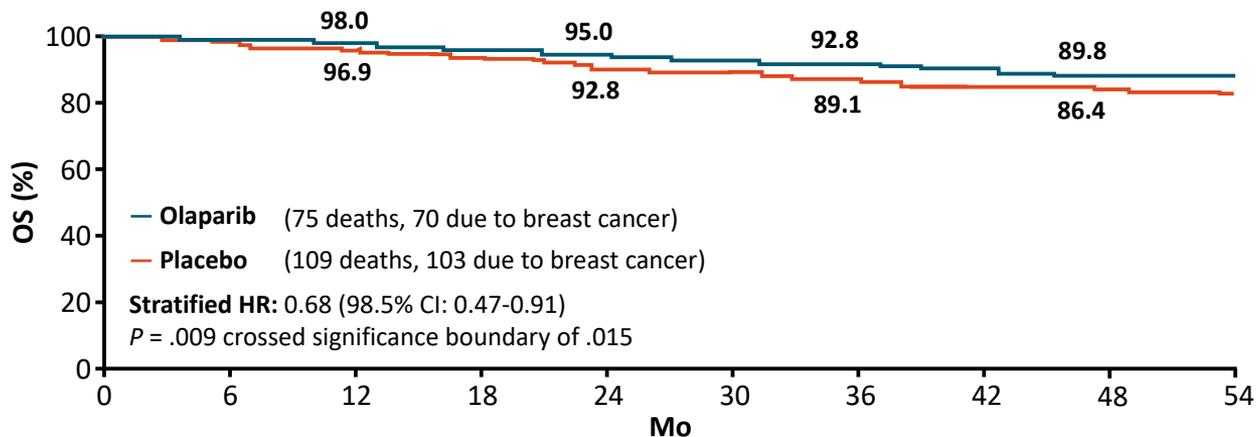
| Type of First iDFS Event, n (%) <sup>1</sup>       | Olaparib (n = 921) | Placebo (n = 915) |
|----------------------------------------------------|--------------------|-------------------|
| Patients with first iDFS event                     | 106 (11.5)         | 178 (19.5)        |
| Distant recurrence                                 | 72 (7.8)           | 120 (13.1)        |
| ▪ Distant CNS recurrence                           | 22 (2.4)           | 36 (3.9)          |
| ▪ Distant excluding CNS recurrence                 | 50 (5.4)           | 84 (9.2)          |
| Regional (ipsilateral) recurrence                  | 6 (0.7)            | 14 (1.5)          |
| Local (ipsilateral) recurrence                     | 7 (0.8)            | 11 (1.2)          |
| Contralateral invasive breast cancer               | 8 (0.9)            | 12 (1.3)          |
| Second primary nonbreast malignancies <sup>2</sup> | 11 (1.2)           | 21 (2.3)          |
| ▪ Ovarian                                          | 1 (0.1)            | 4 (0.4)           |
| ▪ Peritoneal                                       | 0                  | 0                 |
| ▪ Fallopian tube                                   | 1 (0.1)            | 4 (0.4)           |
| ▪ Other                                            | 9 (1.0)            | 13 (1.4)          |
| Deaths without a prior iDFS event*                 | 2 (0.2)            | 0                 |

\*1 due to cardiac arrest, 1 with unknown cause.<sup>2</sup>

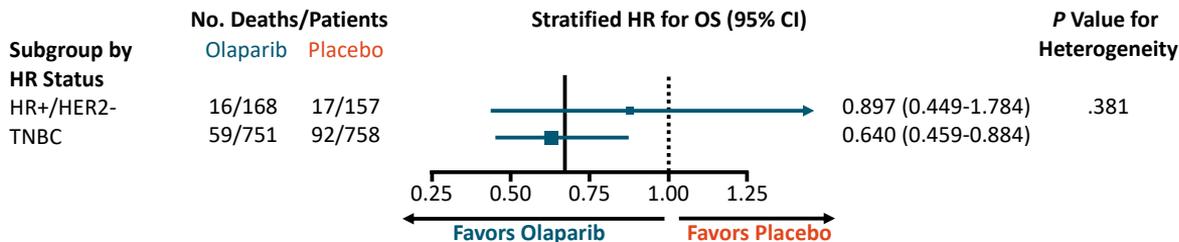




# OlympiA: Overall Survival (IA2; Updated in 2022)



- 3.4%
- HR 0.68



# OlympiA: Safety, Second Interim Analysis

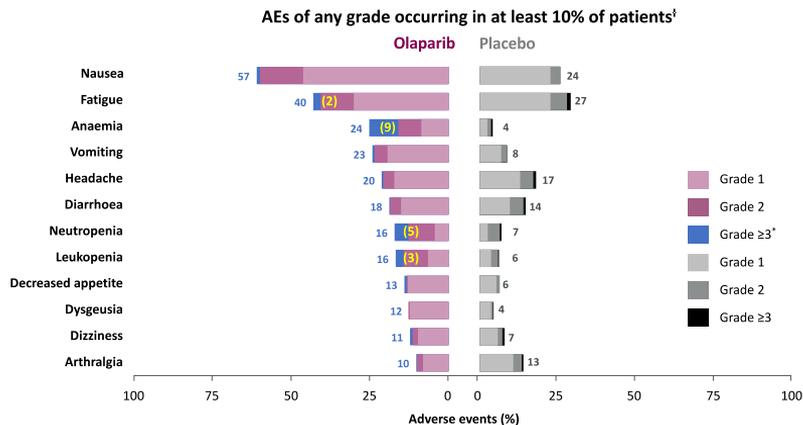
| Safety Outcome, n (%)                   | Olaparib<br>(n = 911) | Placebo<br>(n = 904) |
|-----------------------------------------|-----------------------|----------------------|
| Any AE                                  | 836 (91.8)            | 758 (83.8)           |
| Serious AE                              | 79 (8.7)              | 78 (8.6)             |
| AE of special interest                  | 31 (3.4)              | 51 (5.6)             |
| ▪ MDS/AML                               | 2 (0.2)               | 3 (0.3)              |
| ▪ Pneumonitis                           | 9 (1.0)               | 12 (1.3)             |
| ▪ New primary malignancy                | 21 (2.3)              | 36 (4.0)             |
| Grade ≥3 AE                             | 223 (24.5)            | 102 (11.3)           |
| Grade 4 AE                              | 17 (1.9)              | 4 (0.4)              |
| AE leading to permanent discontinuation | 98 (10.8)             | 42 (4.6)             |

- AEs leading to death: olaparib, n = 1 (cardiac arrest); placebo, n = 2 (AML, ovarian cancer)

\* Anemia grado 3: 9%

Adverse events observed were consistent with other trials of olaparib

- 70% completó el tto
- 18% precisó una reducción de dosis
- 10% interrumpió por AE (anemia, nauseas)

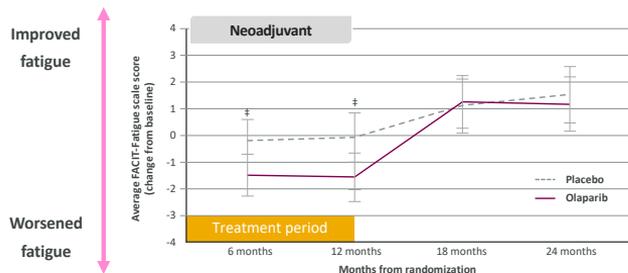


➤ Trasfusiones fueron infrecuentes 5.8%, la mayoría requirieron solo 1\*

# There was no clinically meaningful change in fatigue severity across the duration of the study

Fatigue was the primary PRO endpoint

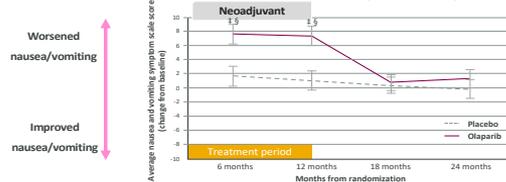
FACT-Fatigue Score\* - Change from baseline



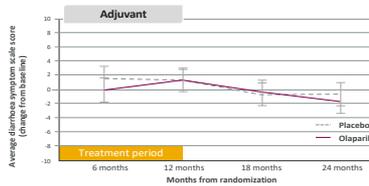
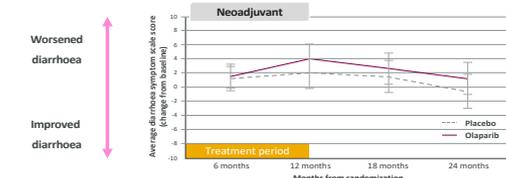
The clinically meaningful difference in nausea and vomiting with olaparib vs. placebo was small and resolved after treatment cessation

There was no clinically meaningful change in diarrhoea QoL score between olaparib and placebo

EORTC QLQ-C30 Nausea and Vomiting Score\* - Change from baseline



EORTC QLQ-C30 diarrhoea Score\* - Change from baseline





# SERDs orales en desarrollo clínico

| Setting            | Elacestrant                                     | Giredestrant                                      | Amcenestrant                                            | Camizestrant                   | Imlunestrant                   |
|--------------------|-------------------------------------------------|---------------------------------------------------|---------------------------------------------------------|--------------------------------|--------------------------------|
| <b>Neoadjuvant</b> | Ph I ELIPSE:<br>NCT04797728<br><i>Completed</i> | Ph II coopERA:<br>NCT04436744<br><i>Completed</i> | Ph II I-SPY EOP:<br>NCT01042379                         | Ph II SERENA-3:<br>NCT04588298 | Ph I EMBER-2:<br>NCT04647487   |
| <b>Adjuvant</b>    |                                                 | Ph III lidERA:<br>NCT04961996                     | Ph III<br>AMEERA-6:<br>NCT05128773<br><i>Terminated</i> |                                | Ph III EMBER-4:<br>NCT05514054 |

- Estudios neo/adyuvante
- Mutacion de ESR1 < 1% en Tumor primario
- Papel de inicio o secuencial, tras la aparición de ESR1

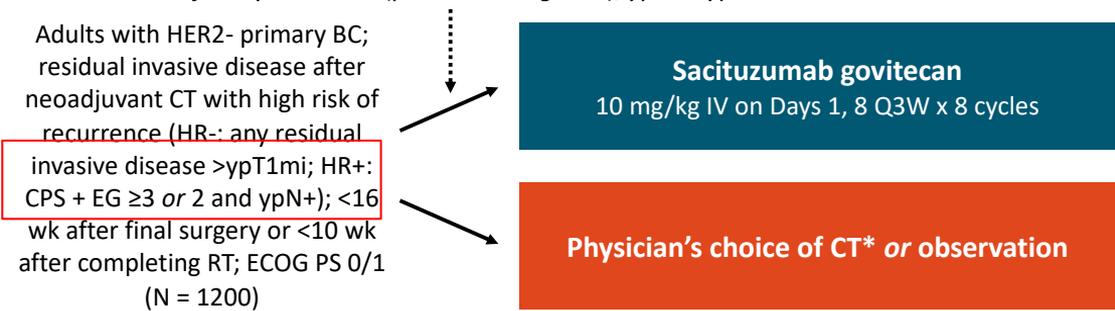
*McDonnell et al. JCO 2021*



## SASCIA: Sacituzumab Govitecan in HER2- EBC at High Relapse Risk After Neoadjuvant CT

- International, open-label, randomized phase III trial

*Stratified by HR status (positive vs negative), ypN vs ypN0*



\*Capecitabine or platinum-based CT x 8 cycles.

- Primary endpoint:** invasive DFS
- Secondary endpoints:** OS, distant DFS, locoregional RFI, invasive DFS and OS in subgroups, safety, compliance, PROs



Con la evidencia actual en una paciente Luminal de alto riesgo

✓ 2 estrategias

**ABEMACICLIB** (+ SLEI) \* estudio población luminal

**OLAPARIB** (+ SLEI y SG) \* estudio que incluyó población luminal

✓ ¿Cuál es nuestro objetivo en adyuvancia?

✓ Seleccionamos por CRITERIO CLINICO/ BIOMARCADOR

✓ Duración del tratamiento/toxicidad/acceso al tto y al biomarcador/coste



## Q and A: A New Standard of Care for Germline BRCA1 and/or BRCA2 Mutation Carriers With Early-Stage Breast Cancer

**Question: For *gBRCA1m* and/or *gBRCA2m* patients with HR-positive, HER2-negative, early-stage, and high-risk breast cancer, should adjuvant olaparib or a cyclin-dependent kinase (CDK) 4/6 inhibitor be used?**

\* Neelam V. Desai, MD<sup>1</sup>; Dana Zakalik, MD<sup>2</sup>; Mark R. Somerfield, PhD<sup>3</sup>; and Nadine M. Tung, MD<sup>1</sup>

On October 12, 2021, the FDA approved abemaciclib along with endocrine therapy for adjuvant treatment of patients with HR-positive, HER2-negative, node-positive, early-stage breast cancer at high risk of recurrence and a Ki-67 score  $\geq 20\%$ .<sup>13</sup> This was based on the monarchE trial,<sup>14</sup> which showed a 3-year iDFS of 88.8% vs 83.4% (hazard ratio, 0.7,  $P < .0001$ ) favoring the addition of two years of adjuvant abemaciclib over standard endocrine therapy alone. However, the PALLAS<sup>15</sup> and PENELOPE-B<sup>16</sup> trials failed to show similar benefit with adjuvant palbociclib, although differences in patient selection, follow-up time, and CDK 4/6 inhibitors make study comparisons challenging. Data on the *gBRCA1m* and/or *gBRCA2m* status of the patients enrolled in the monarchE trial are not

available. The criteria for olaparib use in *gBRCA1m* and/or *gBRCA2m* carriers with HR-positive disease were more restrictive in OlympiA, requiring  $\geq 4$  involved nodes or significant tumor burden after neoadjuvant chemotherapy. Although cross-trial comparison is problematic, the 3-year iDFS benefit and hazard ratios appear similar in the OlympiA and monarchE trials. For *gBRCA1m* and/or *gBRCA2m* carriers who have surgery first and have 1-3 involved nodes, abemaciclib can be considered. For those with  $\geq 4$  involved nodes, either olaparib or abemaciclib is an option with differing toxicity profiles, which may guide treatment selection. There are no data combining a CDK 4/6 inhibitor and a PARP inhibitor, although trials are ongoing (ClinicalTrials.gov identifier: [NCT03685331](https://clinicaltrials.gov/ct2/show/study/NCT03685331)).

In summary, for patients with *gBRCA1m* and/or *gBRCA2m* and high-risk early stage HER2-negative breast cancer who meet the OlympiA trial eligibility, addition of adjuvant olaparib for 1 year is now the new standard of care. Further research is needed to better define optimal ways to integrate various targeted therapies to improve patient outcomes.



## ¿Que sabemos de los iCDK4/6 en población mutada?

- De la población del Monarch-E: Nada
- De estudios de enfermedad M1 luminal:
  - \*Asociación entre gBRCA2 y alteraciones RB1 somáticas:
    - Pacientes con gBRCA2 pero PFS en 1ª línea con iCDK4/6 + HT
    - Pacientes con gBRCA1 y PALB2 peor PFS con iCDK4/6 + HT ( Tempus data base)
    - En RWD pacientes gBRCA resultados más pobres con iCDK4/6 y peor SG

*Safonov et al SABCS 2021*

*Lee et al Cancers 2022*

*Collins et al. Oncol Ther 2021*

# CASO CLINICO LUMINAL alto riesgo

## CONCLUSIONES

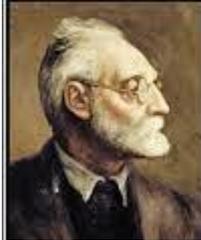
- Pacientes Luminales de riesgo por criterios clínicos, debemos de pensar estrategia “testing BRCA SI criterios OLYMPIA” tenerlas identificadas
- Población seleccionada de alto riesgo, relevancia asociar terapia para disminuir eventos y aumentar SG individualizando la toxicidad.
- 2 Estrategias de TTO en población mutada: \* No tenemos datos de población mutada del estudio MONARCH-E
- 1-3 ganglios con Criterios de Riesgo: ABEMACICLIB
- >4 ganglios: ABEMA o OLAPARIB, diferentes toxicidades, SLEi, SLEi/SG
  - No tenemos datos de la combinación OLAPA+ INHB CDK4/6 estudios en marcha

### gBRCA Wild-Type

Tamoxifeno o IA+/-SO+  
Abemaciclib

### gBRCA Mutated

Tamoxifeno o IA+/-SO+ Olaparib  
\* Considerar empezar HT+Abema tras completar  
Olaparib



La verdadera ciencia enseña, por encima de todo, a dudar y a ser ignorante.

(Miguel de Unamuno)



Gracias !!

[igallegos@saludcastillayleon.es](mailto:igallegos@saludcastillayleon.es)

@isagalls