THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

# Applying new endocrine and targeted therapies to the treatment of HR+ HER2- BC

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# Take home points

- Endocrine therapy + targeted therapies provide new options and better outcomes
- New algorithms- Questions regarding sequence and resistance
- 1st line CDK4/6i are standard in U.S.
- Extraordinary alternatives in 2nd line
  - CRUCIAL to use available biomarkers- WE MUST TEST

    BRCAm- PARPi

    PIK3CA-alpelisib, capivasertib

    AKT, PTEN-capivaserib

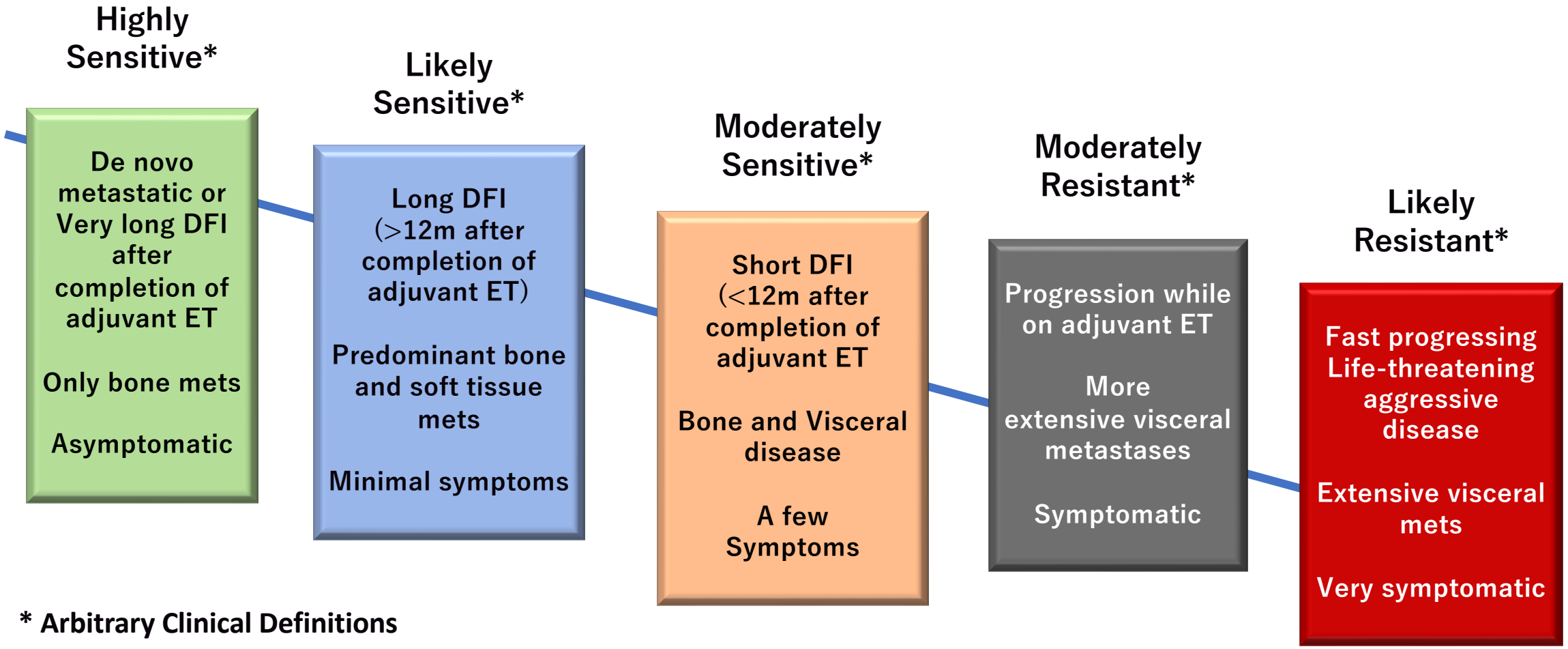
    ESR1-elacestrant

    No mutation- CDKi?, everolimus

    ADCs
- Individualize

# Clinical Spectrum of HR+ Disease

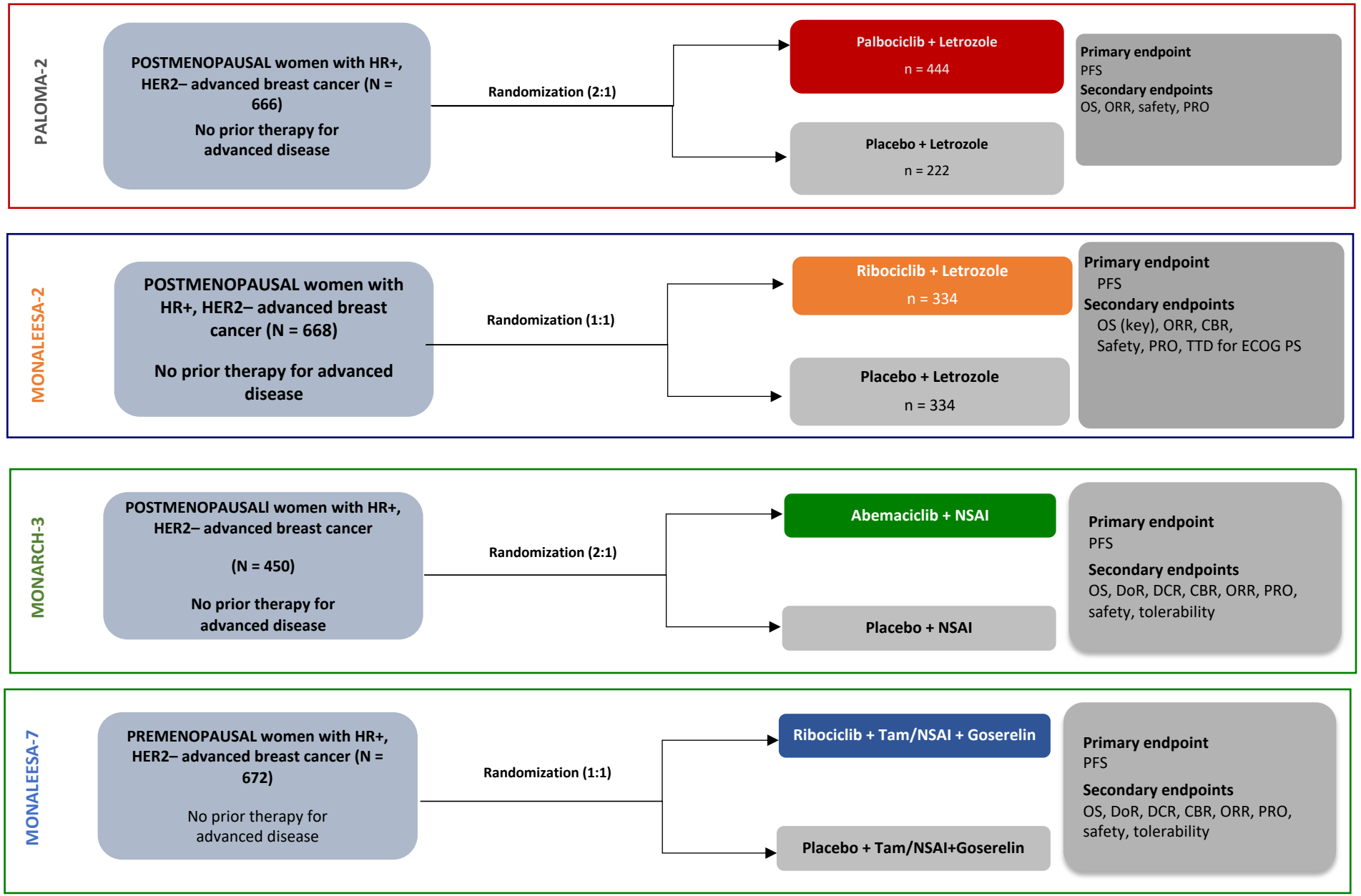
*(considering endocrine sensitivity)*




*** Arbitrary Clinical Definitions**

Courtesy of Carlos Barrios-modified after Llombart-Cusac A, 2022

# CDK inhibitors 1st line



# Randomized phase III trials of CDK4/6 inhibitors in the first line setting

| | PALOMA-2 | MONALEESA-2 | MONALEESA-7 | MONARCH-3 |
|---|---|---|---|---|
| **Regimen** | Letrozole +/- **palbociclib** (2:1) | Letrozole +/- **ribociclib** (1:1) | Goserelin + AI or tamoxifen +/- **ribociclib** (1:1) | AI +/- **abemaciclib** (2:1) |
| **Eligibility** | Postmenopausal, untreated advanced HR+/HER2- BC | Postmenopausal, untreated advanced HR+/HER2- BC | Pre/perimenopausal, untreated advanced HR+/HER2- BC | Postmenopausal, untreated advanced HR+/HER2- BC |
| **Sample size** | 666 | 668 | 672 | 493 |
| **De novo MBC** | 38% | 34% | 41% | 20% |
| **Median PFS (CDK vs. placebo)** | 27.6 vs. 14.5 months (HR 0.56; 0.46-0.69) | 25.3 vs. 16 months (HR 0.57; 0.45-0.60) | 23.8 vs. 13 months (HR 0.55; 0.44-0.69) | 29 vs. 14.8 (HR 0.53; 0.42-0.66) |
| **Median OS (CDK vs. placebo)** | **53.9 vs. 51.2 months** △ **2.7** (HR 0.96; 0.77-1.17)* | **63.9 vs. 51.4 months** △ **12.4** ✓ (HR 0.76, 0.63-0.93) | **58.7 vs. 48 months** △ **10.7** ✓ (HR 0.76; 0.60-0.95) | **66.8 vs. 53.7 months** △ **13.1** (HR 0.84; 0.64-1.01) |
| **Toxicities of interest** | Neutropenia, leukopenia, fatigue | Neutropenia, leukopenia, fatigue, QTc prolongation, transaminitis | Neutropenia, leukopenia, fatigue, nausea, QTc prolongation, transaminitis | Neutropenia, fatigue, diarrhea, nausea, anemia, abdominal pain |

**Abbreviations:** AI: aromatase inhibitor; BC: breast cancer; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; HR+: hormone receptor positive; OS: overall survival; PFS: progression free survival.
*22% of patients had a disease-free interval off less than 12 months, in the other trials, it ranged from 0-7%.

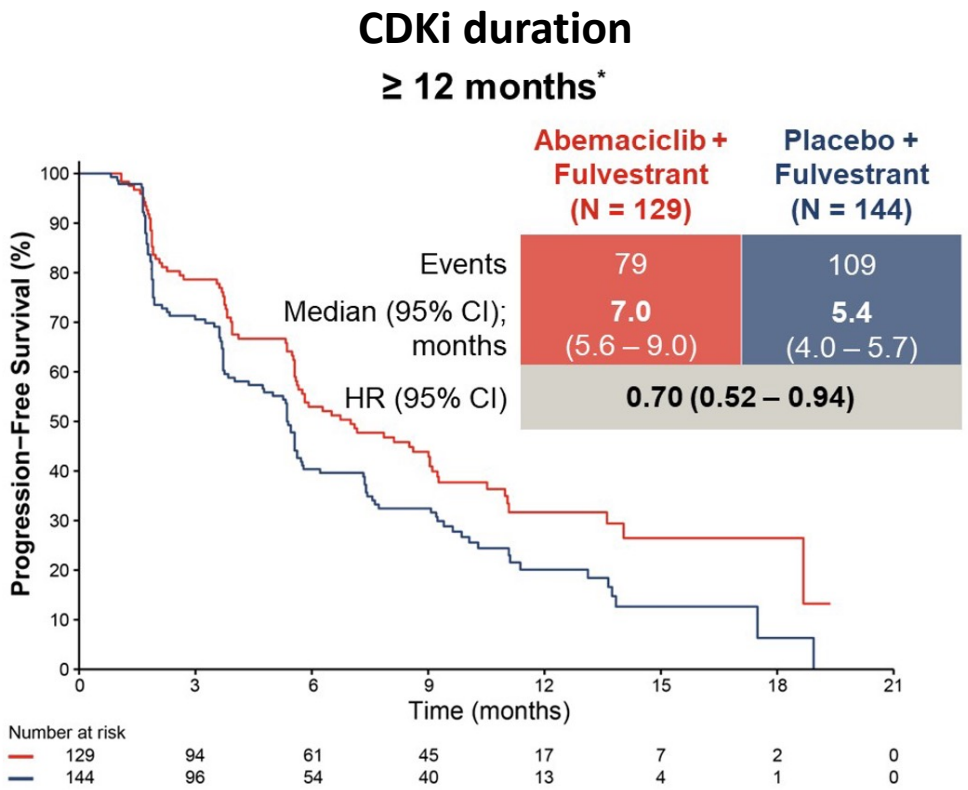
# Switch experience with CDK4/6 inhibitors

| | MAINTAIN | PACE | PALMIRA | PostMONARCH |
|---|---|---|---|---|
| **Phase** | II | II | II | III |
| **Sample size** | 120 (1:1) | 220 (1:1:1) | 198 (2:1) | 368(1:1) |
| **Design**<br><br>**HR+ MBC progression on iCDK 4/6+ET** | Fulvestrant or exemestane +/- ribociclib | Arm A: Fulvestrant<br>Arm B: Fulvestrant + Palbociclib<br>Arm C: Fulvestrant + Palbociclib + Avelumab | Fulvestrant or letrozole +/- palbociclib | Fulvestrant +/- abemaciclib |
| **Initial CDK 4/6 inhibitor** | Palbociclib (84%)<br>Ribociclib (11%) | Palbociclib (90%) | Palbociclib (100%) | Palbociclib (59%)<br>Ribociclib (33%)<br>Abemaciclib 8% |
| **Continuation iCDK 4/6** | Ribociclib | Palbociclib | Palbociclib | Abemaciclib |
| **% iCDK > 12mo** | 67% | 75% | 86% | 71-77% |
| **Continuation ET** | Fulvestrant (83%), exemestane (17%) | Fulvestrant (100%) | Fulvestrant (90%), letrozole (10%) | Fulvestrant (100%) |
| **PFS ET+CDK4/6 inhibitor vs. ET** | **5.3 vs. 2.8 months (HR 0.56)** | 4.6 vs. 4.8 months (HR 1.11) | 4.9 vs. 3.6 months (HR 0.84) | **6.0 vs 5.3 months (HR 0.73)** |

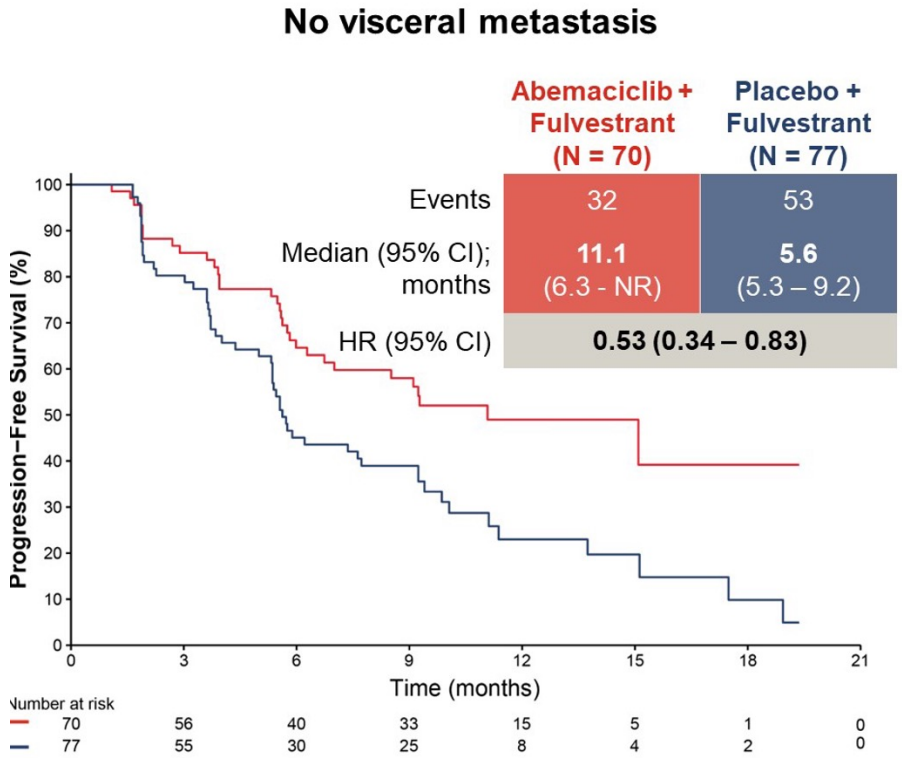
AI: aromatase inhibitor; CDK: cyclin dependent kinase; ER: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; HR+ hormone receptor positive; PFS: progression free survival

Kalinsky K, et al. JCO 2023.
Mayer E, et al. SABCS 2022.
Llombart-Cussac A, et al. ASCO 2023.
Kalinsky K, et al. ASCO 2024

# postMONARCH-subgroup analyses
## (Investigator assessed PFS)




* ≥ 12 months ABC or recurrence after EBC therapy




Kalinsky K, et al. ASCO 2024

# INAVO120 study design

**Key eligibility criteria**

***Enrichment of patients with poor prognosis:***

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and $HbA_{1C}$ <6.0%**

Enrolment period: December 2019-September 2023

**N=325**

**R 1:1**

**Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)****

**Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)****

**Until PD or toxicity**

**SURVIVAL FOLLOW-UP**

**Stratification factors:**

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

## Endpoints

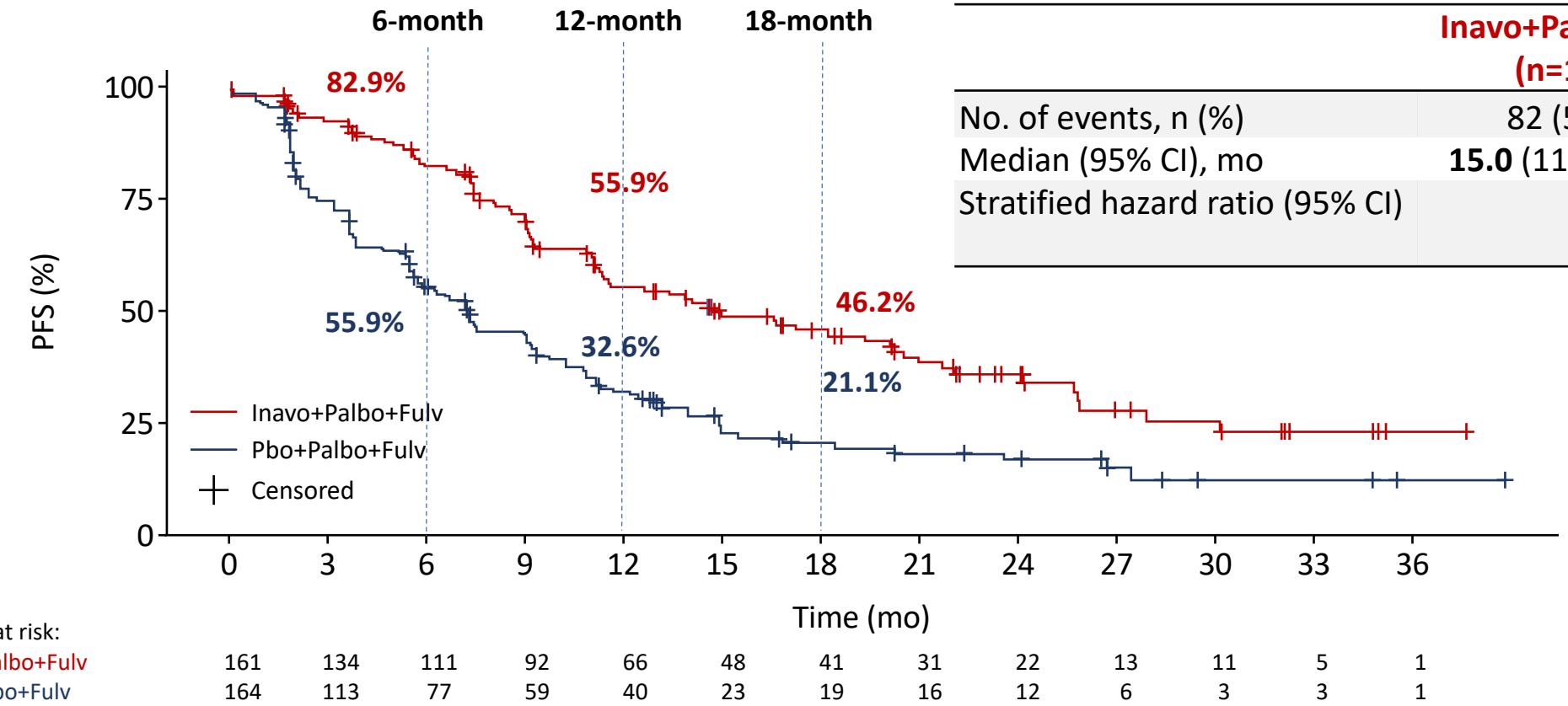
- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid [redacted] In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29:**1634–1657.

Jhaveri K, et al. SABCS 2023

# Primary endpoint: PFS (investigator assessed)

Median follow-up: **21.3 months**




| | Inavo+Palbo+Fulv (n=161) | Pbo+Palbo+Fulv (n=164) |
|---|---|---|
| No. of events, n (%) | 82 (50.9) | 113 (68.9) |
| Median (95% CI), mo | **15.0** (11.3, 20.5) | **7.3** (5.6, 9.3) |
| Stratified hazard ratio (95% CI) | **0.43 (0.32, 0.59)** **p<0.0001** | |

Patients at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inavo+Palbo+Fulv | 161 | 134 | 111 | 92 | 66 | 48 | 41 | 31 | 22 | 13 | 11 | 5 | 1 |
| Pbo+Palbo+Fulv | 164 | 113 | 77 | 59 | 40 | 23 | 19 | 16 | 12 | 6 | 3 | 3 | 1 |

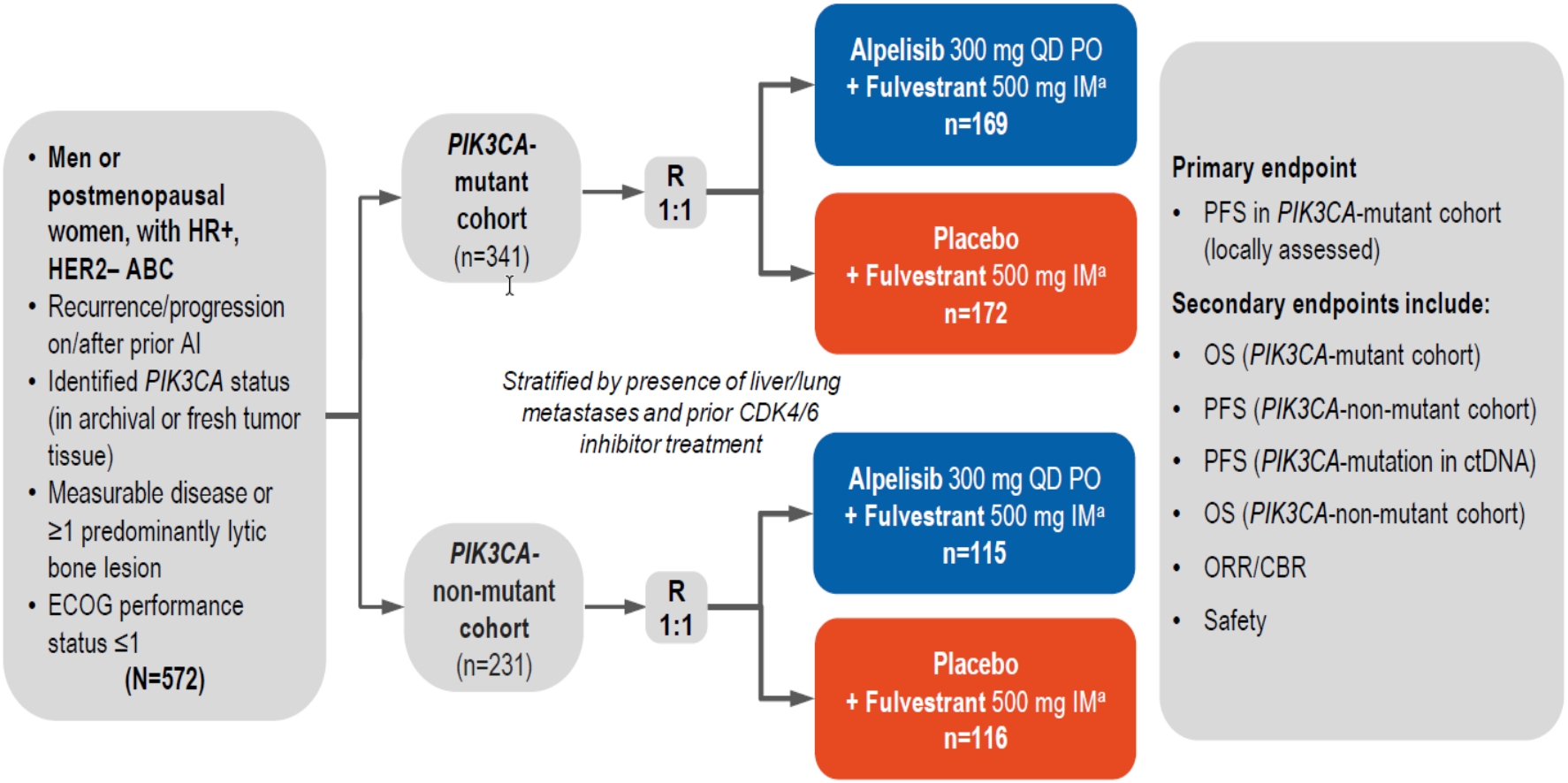
CCOD: 29th September 2023

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Jhaveri K, et al. SABCS 2023

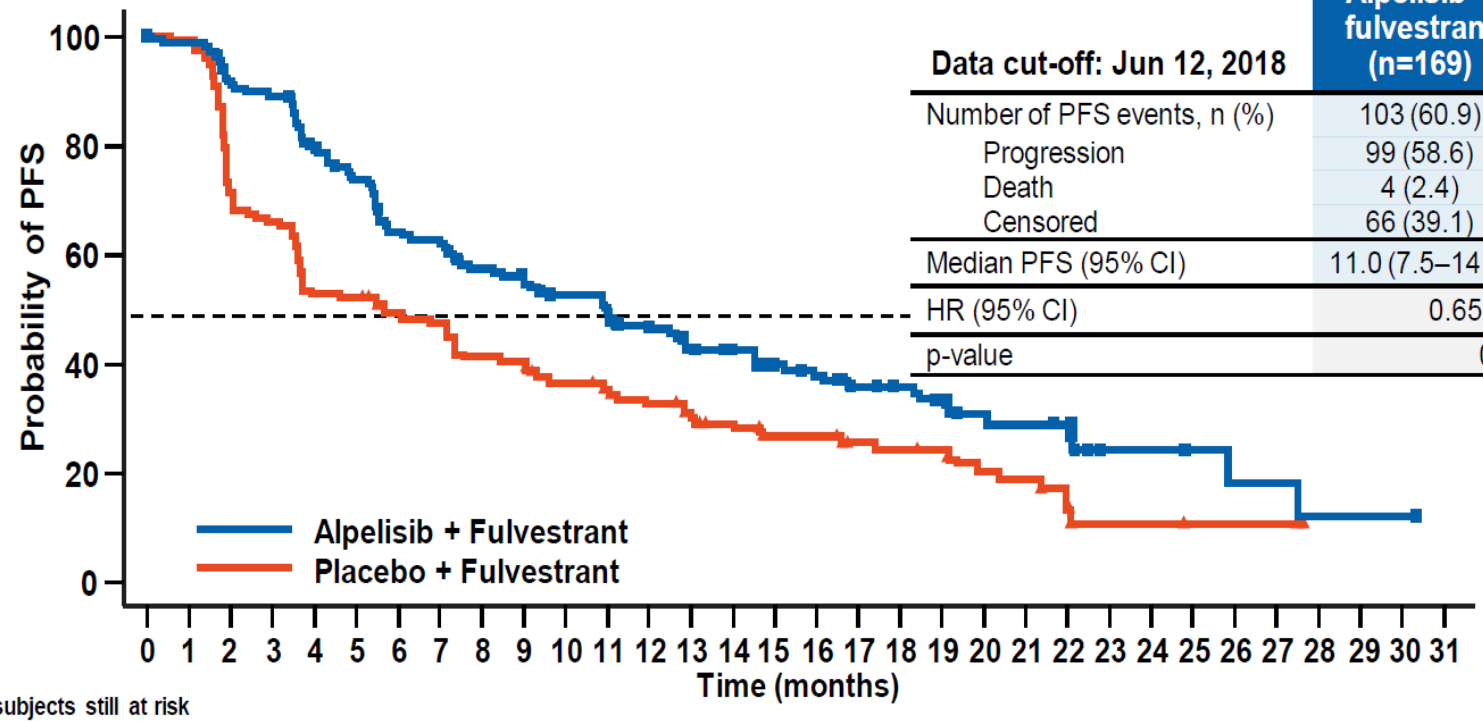
# SOLAR-1 Schema

**Phase III, Randomized, Double-blind, Placebo-controlled Trial Evaluating Alpelisib + Fulvestrant in Men and Postmenopausal Women With HR+, HER2– ABC That Progressed on or After AI**




Andre F. et al. N Engl J Med, 2019

# SOLAR-1: Primary endpoint PFS in the PIK3CA mutant cohort




| Data cut-off: Jun 12, 2018 | Alpelisib + fulvestrant (n=169) | Placebo + fulvestrant (n=172) |
|---|---|---|
| Number of PFS events, n (%) | 103 (60.9) | 129 (75.0) |
| Progression | 99 (58.6) | 120 (69.8) |
| Death | 4 (2.4) | 9 (5.2) |
| Censored | 66 (39.1) | 43 (25.0) |
| Median PFS (95% CI) | 11.0 (7.5–14.5) | 5.7 (3.7–7.4) |
| HR (95% CI) | 0.65 (0.50–0.85) | |
| p-value | 0.00065 | |

Andre F. et al. N Engl J Med, 2019

# Capitello-291

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

### Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

**R1:1 (N=708)**

| | |
|---|---|
| **Capivasertib** | 400 mg twice daily, 4 days on, 3 days off |
| **Fulvestrant** | 500 mg: cycle 1, days 1 & 15; then every 4 weeks |
| **Placebo** | Twice daily, 4 days on, 3 days off |
| **Fulvestrant** | 500 mg: cycle 1, days 1 & 15; then every 4 weeks |

**Stratification factors:**
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

### Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

### Key secondary endpoints

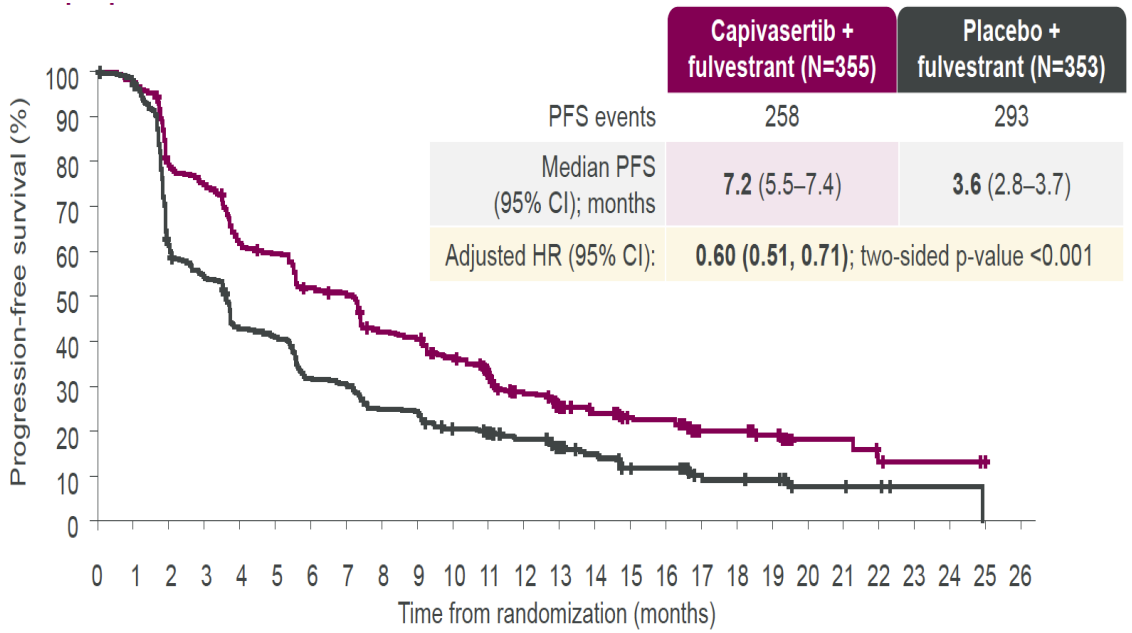
**Overall survival**
- Overall
- AKT pathway-altered tumors

**Objective response rate**
- Overall
- AKT pathway-altered tumors

HER2– was defined as IHC 0 or 1+, or IHC 2+/ISH–. *Region 1: United States, Canada, Western Europe, Australia, and Israel, Region 2: Latin America, Eastern Europe and Russia vs Region 3: Asia.
ABC, advanced (locally advanced [inoperable] or metastatic) breast cancer.
Pre- or peri-menopausal women also received a luteinizing hormone-releasing hormone agonist for the duration of the study treatment

# Dual-primary endpoint

## PFS in overall population



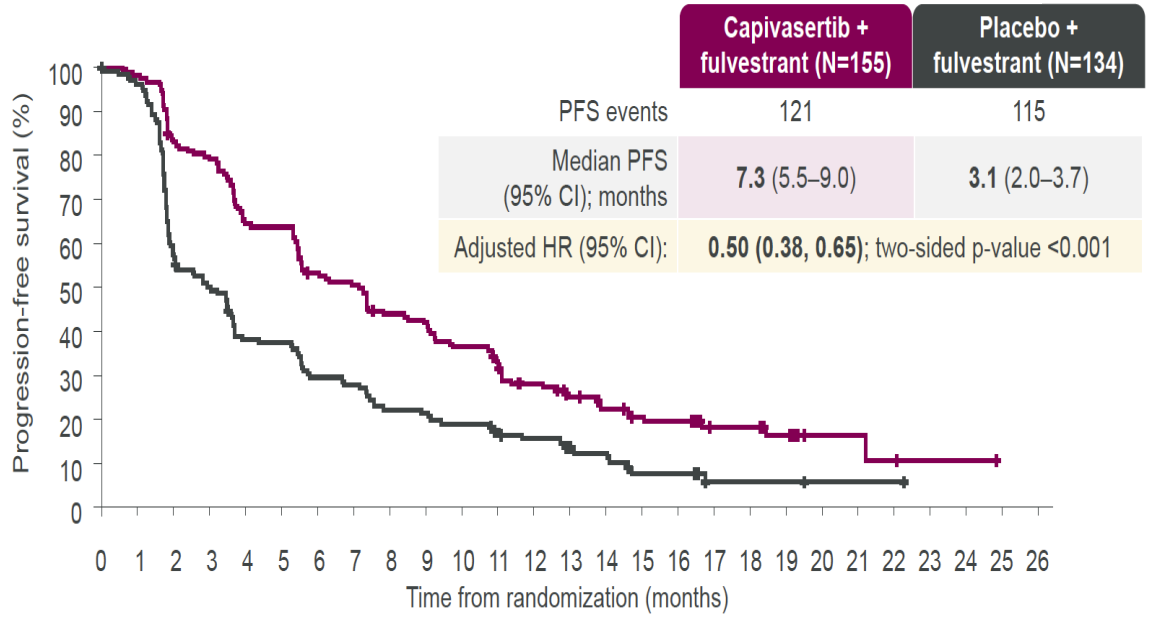

Number of patients at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Capivasertib + fulvestrant | 355 | 330 | 266 | 252 | 207 | 199 | 172 | 166 | 138 | 133 | 115 | 98 | 78 | 64 | 55 | 44 | 43 | 25 | 25 | 21 | 8 | 8 | 5 | 2 | 2 | 1 | 0 |
| Placebo + fulvestrant | 353 | 329 | 207 | 182 | 142 | 136 | 106 | 100 | 83 | 81 | 66 | 59 | 51 | 41 | 33 | 24 | 23 | 12 | 11 | 10 | 4 | 4 | 3 | 1 | 1 | 0 | 0 |

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.



## PFS in altered population




Number of patients at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Capivasertib + fulvestrant | 155 | 150 | 127 | 121 | 99 | 97 | 80 | 76 | 65 | 62 | 54 | 49 | 38 | 31 | 26 | 22 | 21 | 12 | 12 | 9 | 3 | 3 | 2 | 1 | 1 | 0 | 0 |
| Placebo + fulvestrant | 134 | 124 | 77 | 64 | 48 | 47 | 37 | 35 | 28 | 27 | 24 | 20 | 17 | 14 | 11 | 6 | 6 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.



Turner, SABCS 2022

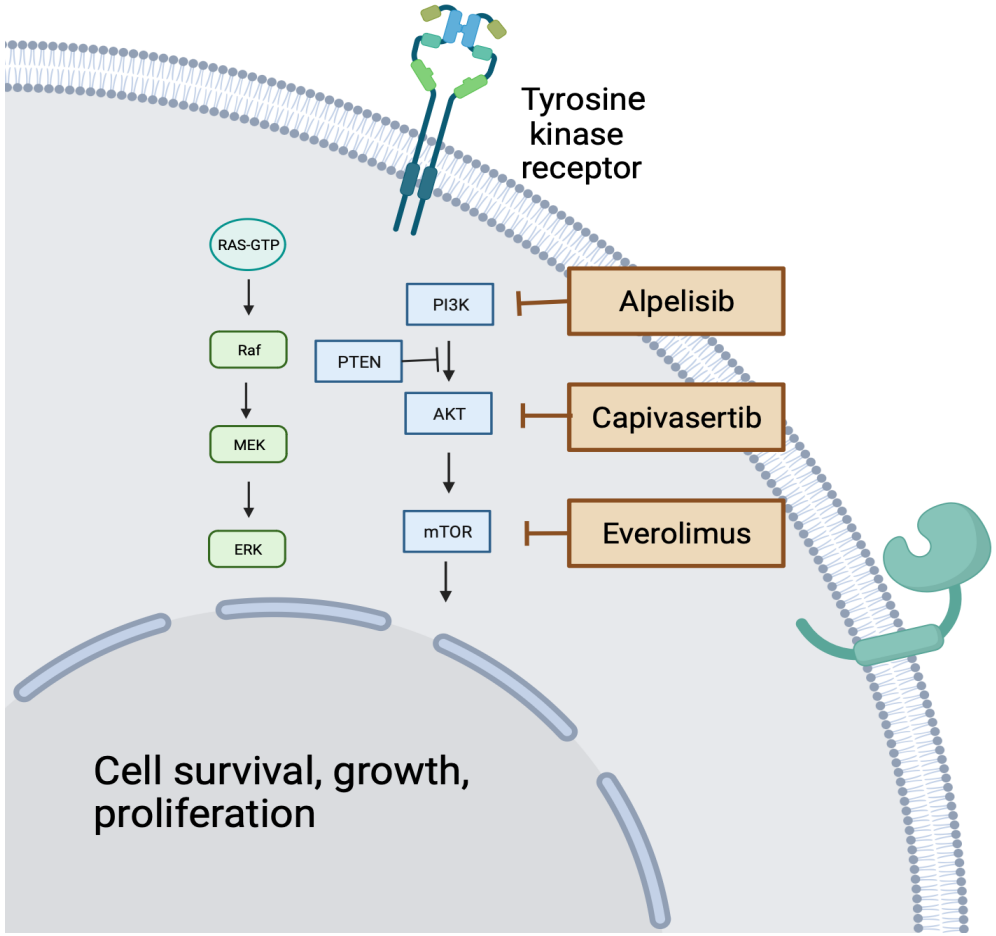
# Current drugs approved for the treatment of MBC that inhibit PIK3CA/AKT/mTOR pathway

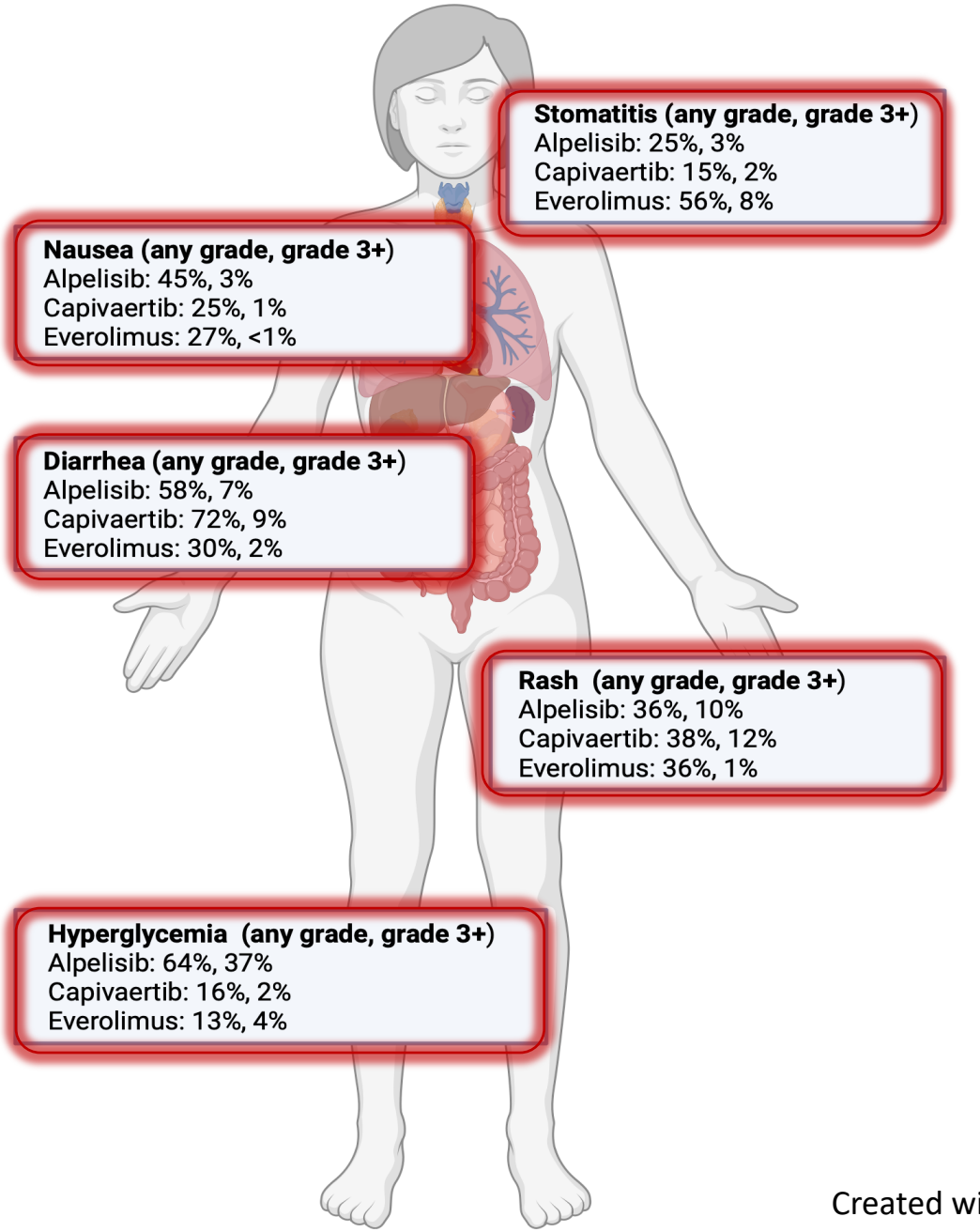
| | Everolimus (BOLERO-2) | Alpelisib (SOLAR-1) | Capivasertib (Capitello-291) |
|---|---|---|---|
| **Mechanism of action** | mTOR inhibitor | PI3Kα-specific inhibitor | AKT inhibitor |
| **Design** | Postmenopausal women (n=724), randomized 2:1 to exemestane + everolimus or placebo | n=572 (341 with PIK3CAm) randomized 1:1 to fulvestrant +alpelisib or placebo | n=708 (289 with AKT pathway alterations, 489 with prior iCDK4/6) randomized 1:1 to fulvestrant + capivasertib or placebo |
| **Median PFS (months)** | **10.6 vs 4.1 mo** | **PIK3CA WT: 7.4 vs. 5.6 mo**<br>**PIK3CAm: 11 vs 5 mo** | **ITT 7.2 vs. 3.6 mo**<br>**altered: 7.3 vs. 3.1** |
| **HR (95%CI)** | 0.36 (0.27-0.47) | 0.65 (0.5-0.85) | Altered 0.50 (0.38-0.65) |
| **US FDA Approval** | 2012 | 2019 for patients with PIK3CA altered MBC HR+ | 2023 for patients with AKT, PTEN, PIK3CA altered HR+ breast cancer |

Baselga J et al, NEJM 2012; Andre F et al NEJM 2029; Turner N et al, NEJM 2023.

Schlam, Chavez-MacGregor, The Breast 2024

# Mechanism of Action and Toxicity Profile

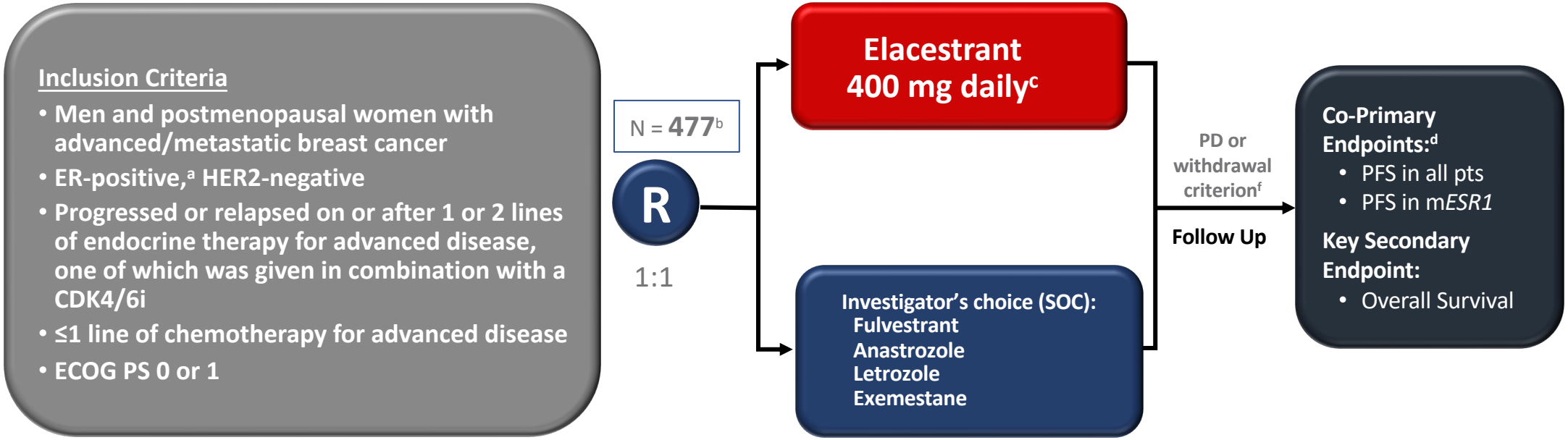



Created with Biorender

Schlam, Chavez-MacGregor, The Breast 2024

# EMERALD Phase 3 Study Design



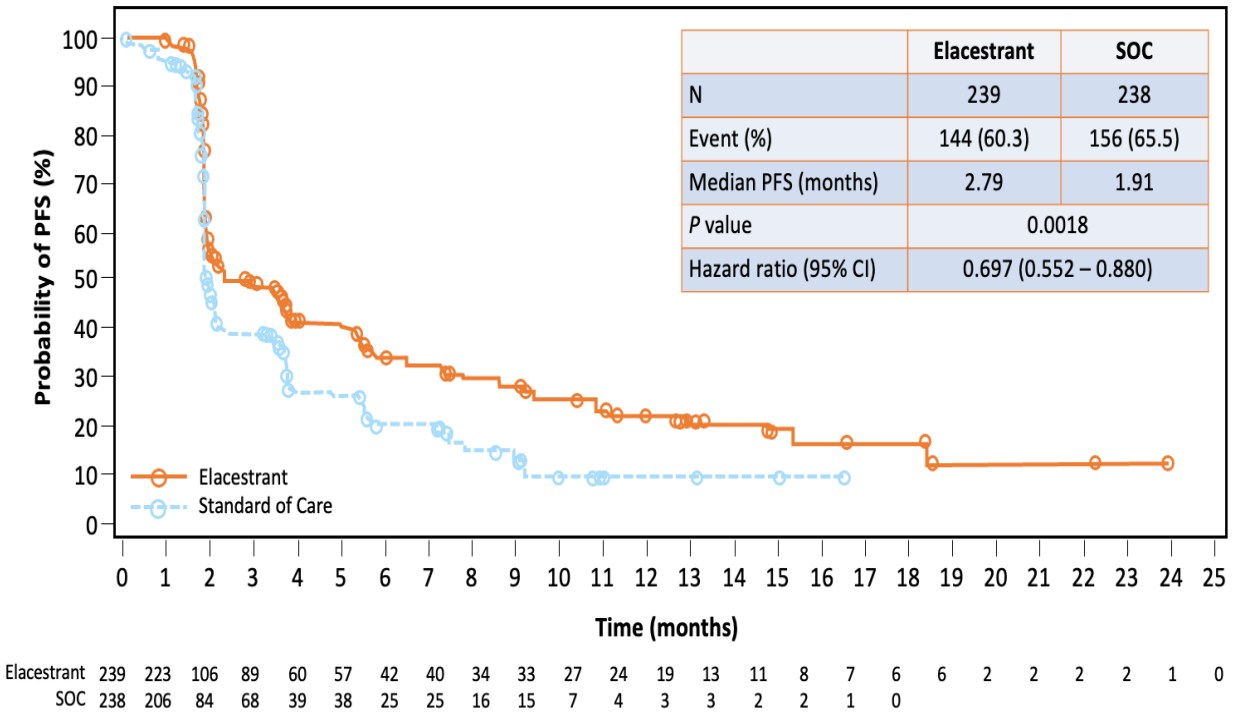

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Blinded Independent Central Review. [e]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay (Guardant health, Redwood City, CA). [f]Restaging CT scans every 8 weeks.

CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS: progression-free survival; Pts, patients; R, randomized. SOC, standard of care.

Bidard, JCO 2022

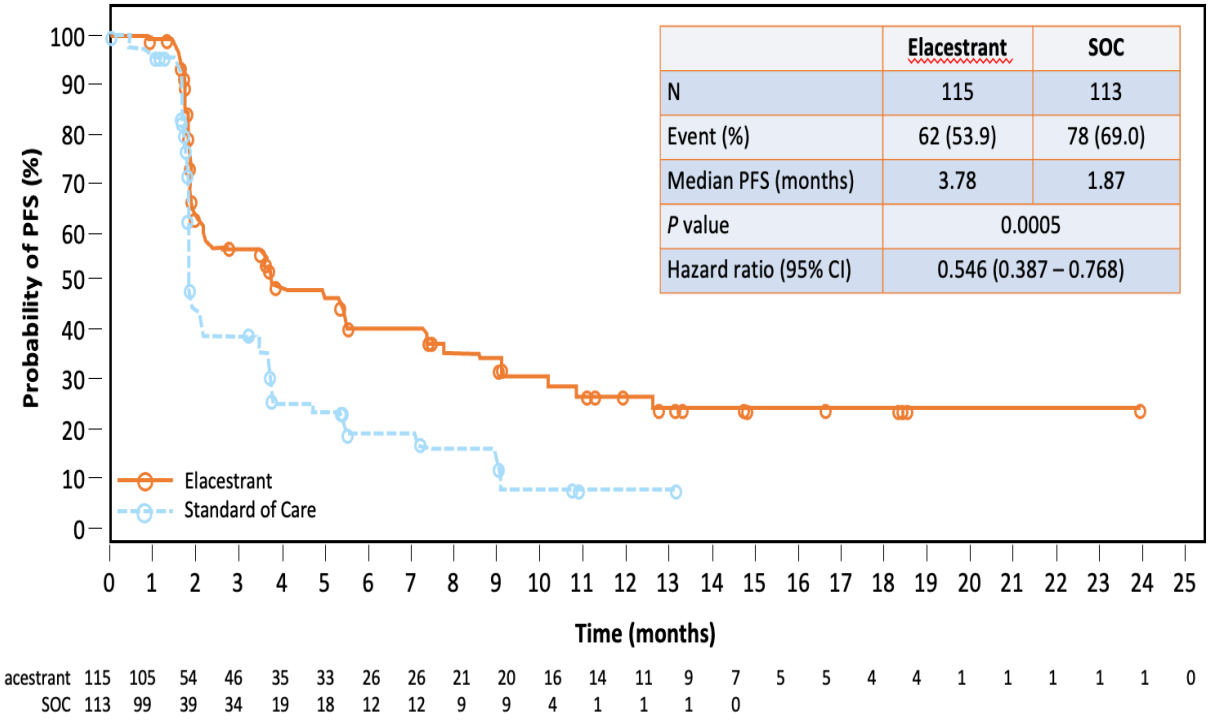
# Primary Endpoint: PFS by IRC

## All Patients (ITT)




| | Elacestrant | SOC |
|---|---|---|
| N | 239 | 238 |
| Event (%) | 144 (60.3) | 156 (65.5) |
| Median PFS (months) | 2.79 | 1.91 |
| *P* value | 0.0018 | |
| Hazard ratio (95% CI) | 0.697 (0.552 – 0.880) | |

## Patients With Tumors Harboring *mESR1*

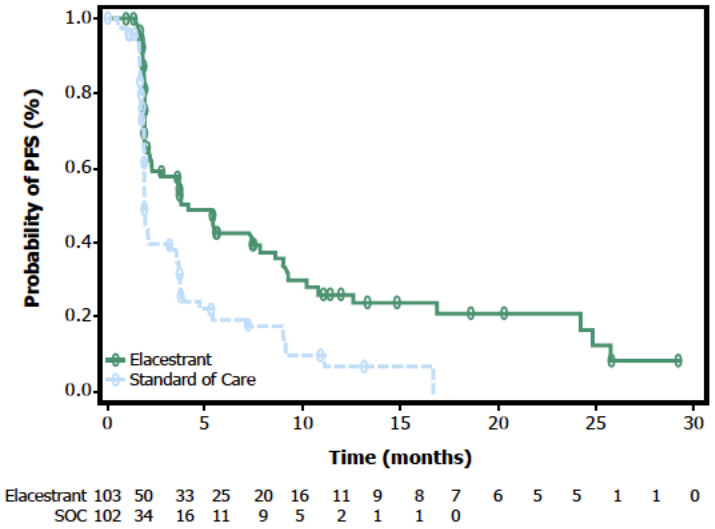



| | Elacestrant | SOC |
|---|---|---|
| N | 115 | 113 |
| Event (%) | 62 (53.9) | 78 (69.0) |
| Median PFS (months) | 3.78 | 1.87 |
| *P* value | 0.0005 | |
| Hazard ratio (95% CI) | 0.546 (0.387 – 0.768) | |

Bidard, JCO 2022

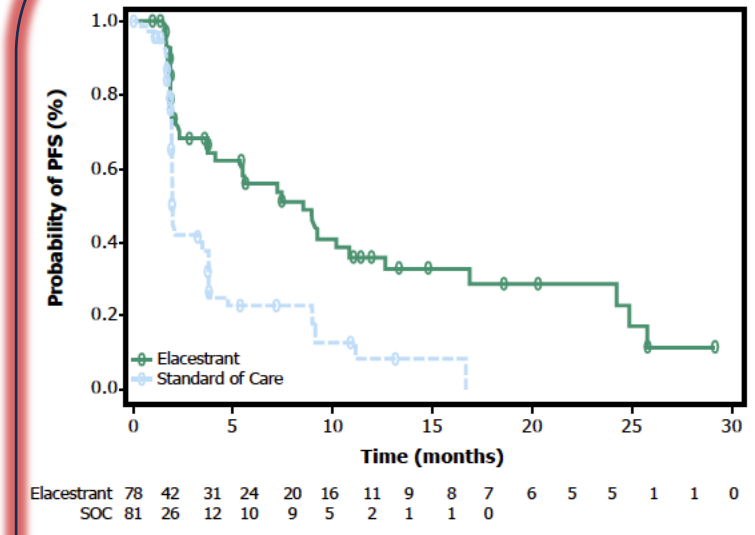
# Patients with *ESR1-mut*: PFS by Duration of CDK4/6i

## At least 6 mo CDK4/6i



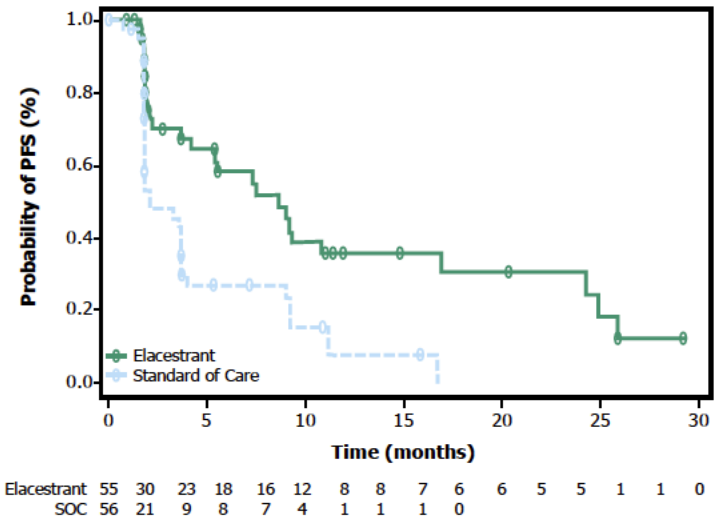

| | Elacestrant | SOC |
|---|---|---|
| Median PFS, months (95% CI) | **4.14** (2.20 - 7.79) | **1.87** (1.87 - 3.29) |
| PFS rate at 12 months (95% CI) | 26.02 (15.12 - 36.92) | 6.45 (0.00 - 13.65) |
| Hazard ratio (95% CI) | **0.517** (0.361 - 0.738) | |

## At least 12 mo CDK4/6i




| | Elacestrant | SOC |
|---|---|---|
| Median PFS, months (95% CI) | **8.61** (4.14 - 10.84) | **1.91** (1.87 - 3.68) |
| PFS rate at 12 months (95% CI) | 35.81 (21.84 - 49.78) | 8.39 (0.00 - 17.66) |
| Hazard ratio (95% CI) | **0.410** (0.262 - 0.634) | |

## At least 18 mo CDK4/6i

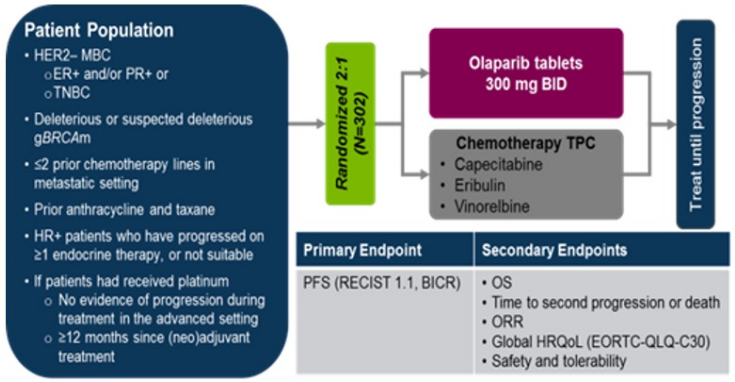



| | Elacestrant | SOC |
|---|---|---|
| Median PFS, months (95% CI) | **8.61** (5.45 - 16.89) | **2.10** (1.87 - 3.75) |
| PFS rate at 12 months (95% CI) | 35.79 (19.54 - 52.05) | 7.73 (0.00 - 20.20) |
| Hazard ratio (95% CI) | **0.466** (0.270 - 0.791) | |

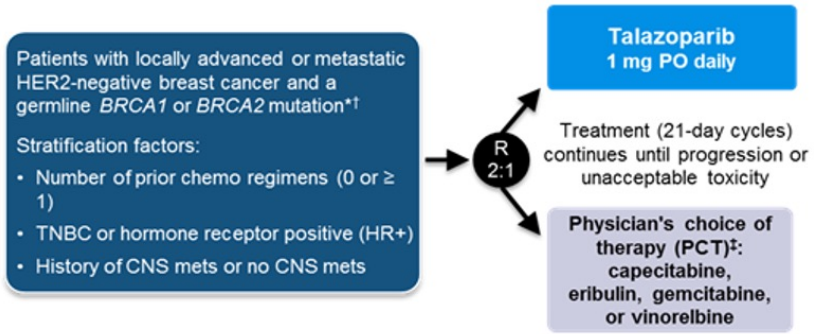
Kaklamani V, SABCS 2022

# Current FDA-approved PARP Inhibitors

## OlympiAD




## EMBRACA




Phase 3, international, open-label study randomized 431 patients in 16 countries and 145 sites

| Drug | ORR PARPi vs. control | mPFS (months) PARPi vs. control | Median DoR (months) PARPi vs. control | mPFS (months) PARPi vs. control | Median DoR (months) PARPi vs. control |
|---|---|---|---|---|---|
| Olaparib | 59.9% vs. 28.8% | 7.0 vs. 4.2 | 6.4 vs. 7.1 | 7.0 vs. 4.2 | 6.4 vs. 7.1 |
| Talazoparib | 62.6% vs. 27.2% | 8.6 vs. 5.6 | 5.4 vs. 3.1 | 8.6 vs. 5.6 | 5.4 vs. 3.1 |


Litton JK et al. *N Engl J Med.* 2018;379(8):753-763.
Robson M et al. *N Engl J Med.* 2017;377(6):523-533.

# DESTINTY-Breast 04 Updated Efficacy and safety

**Patients**[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

**T-DXd**
**5.4 mg/kg Q3W**
**(n = 373)**

HR+ ≈ 480
HR− ≈ 60

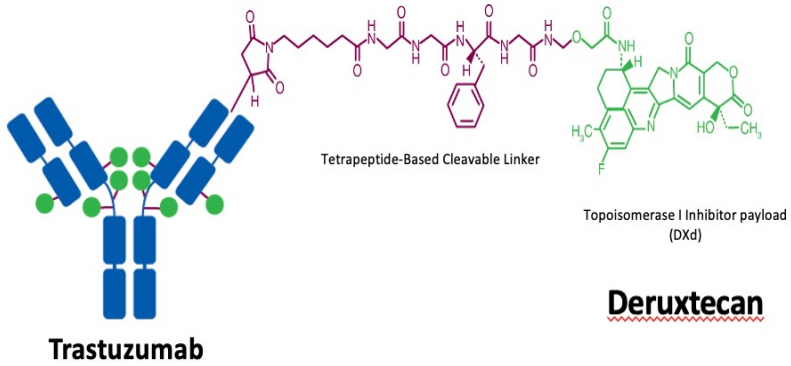
**TPC**
**Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel**[c]
**(n=184)**

**Primary endpoint**
- PFS by BICR (HR+)

**Key secondary endpoints**[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

## Trastuzumab Deruxtecan

- A **humanized anti-HER2 IgG1 mAb** with the same amino acid sequence as trastuzumab
- A **topoisomerase I inhibitor payload**, an exatecan derivative
- A tetrapeptide-based cleavable linker

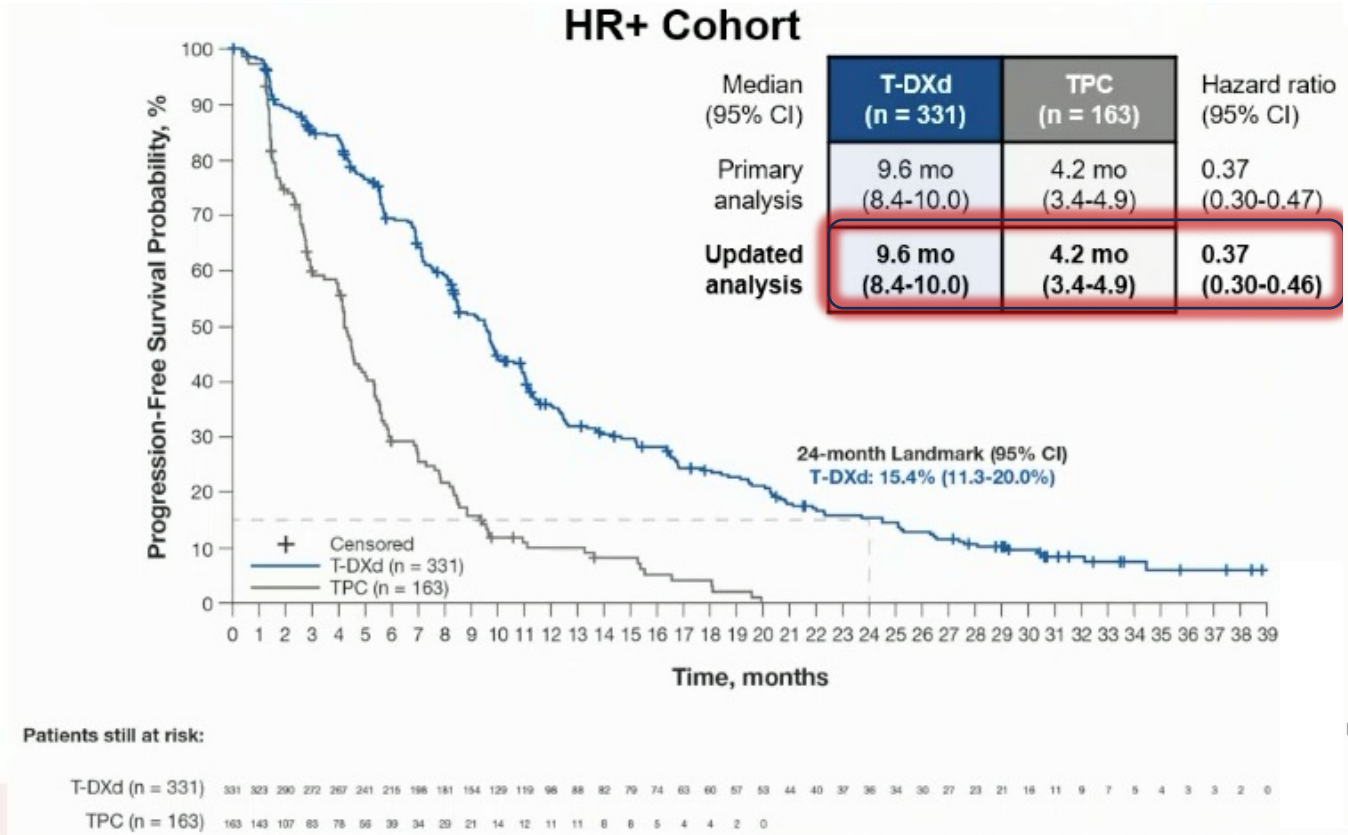


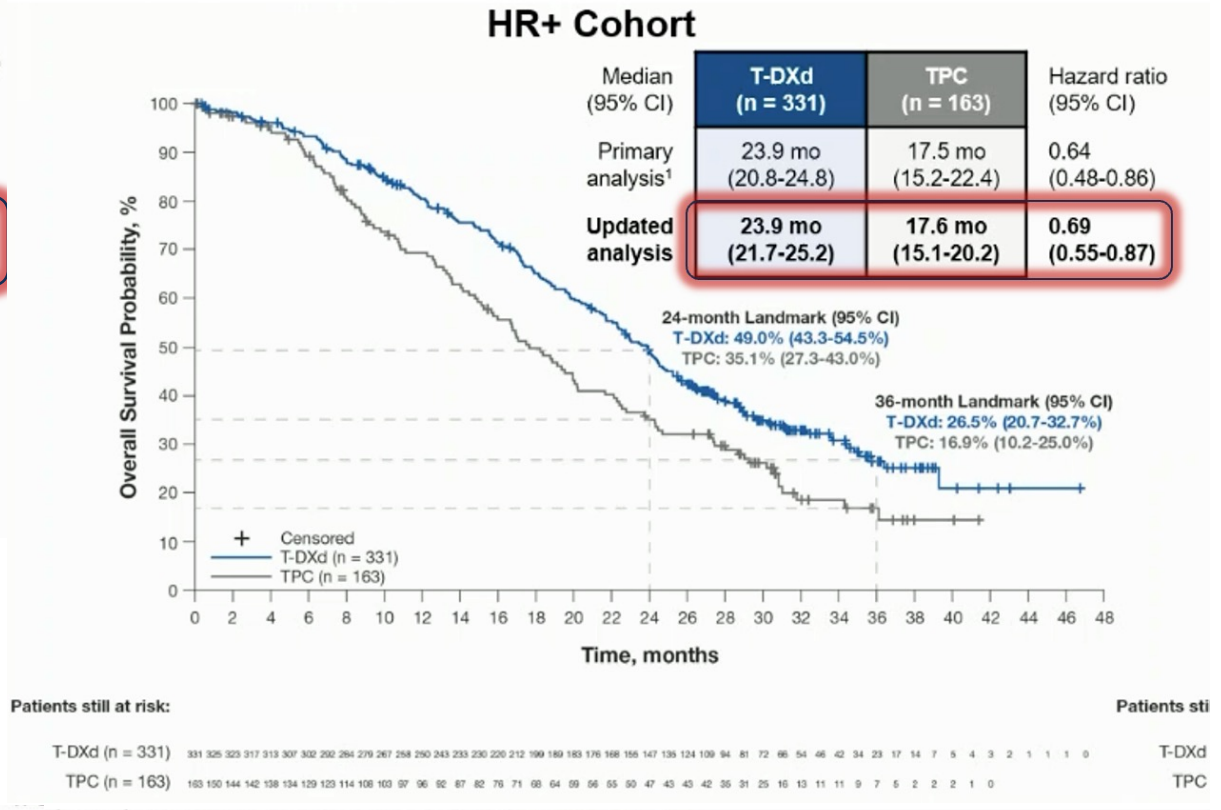

**Stratification factors**
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

Modi S, el at. NEJM 2022

# Updated PFS (median 32 months) by investigator and OS




- Median PFS was consistent with results from the primary analysis,[1] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively, for the T-DXd arm compared with the TPC arm

BICR, blinded independent central review; HR, hormone receptor; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

1. Modi S et al. *N Engl J Med*. 2022;387:9-20.

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# Study design

## DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

### PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

**Prior lines of therapy**

- ≥2 lines of ET ± targeted therapy for mBC
  **OR**
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    **OR**
  - Recurrence ≤24 months of starting adjuvant ET

**Stratification factors**

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

**T-DXd**
**5.4 mg/kg Q3W**
**(n=436)**

**HER2-low = 713**
**HER2-ultralow = 153†**

**TPC**
**(n=430)**

Options: capecitabine, nab-paclitaxel, paclitaxel

### ENDPOINTS

**Primary**

- PFS (BICR) in HER2-low

**Key secondary**

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

**Other secondary**

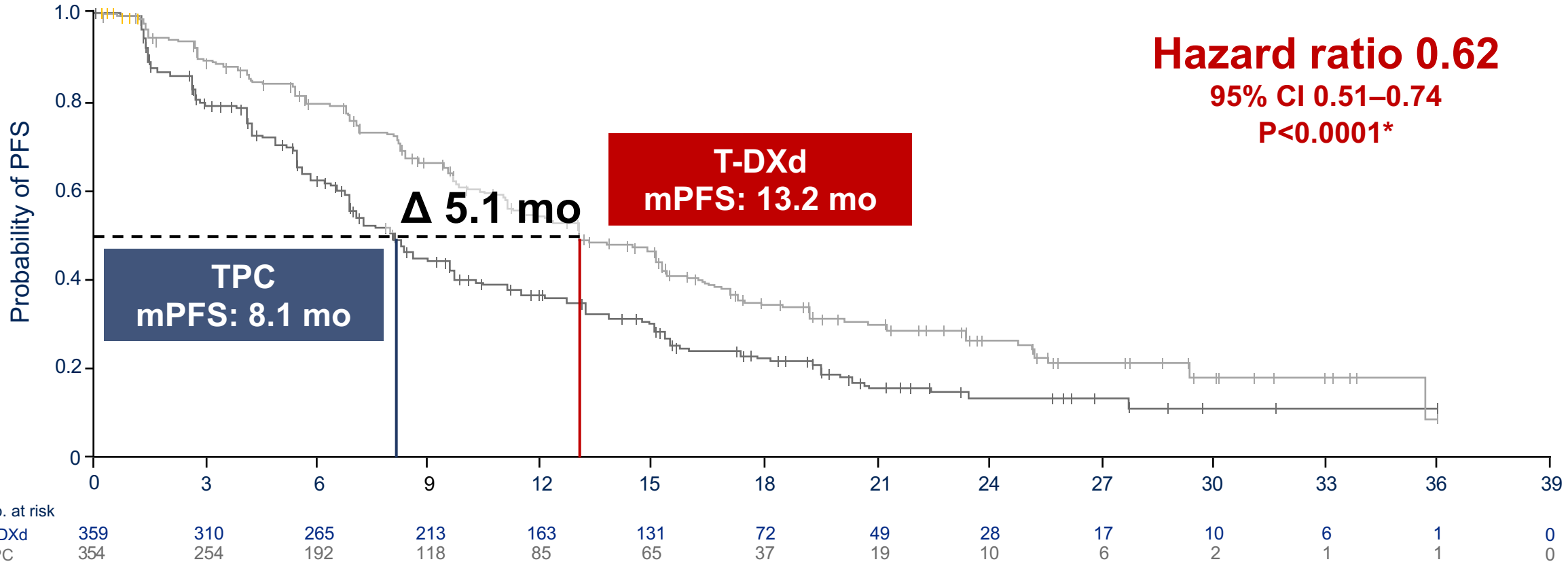
- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*Determined based on the most recent evaluable HER2 IHC sample prior to randomization; HER2-ultralow defined as faint, partial staining of the membrane in ≤10% of the cancer cells (also known as IHC >0<1+); †as determined by IRT (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 by central laboratory testing); ‡to be presented separately

BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

NCT04494425. Updated April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

# PFS (BICR) in HER2-low: primary endpoint



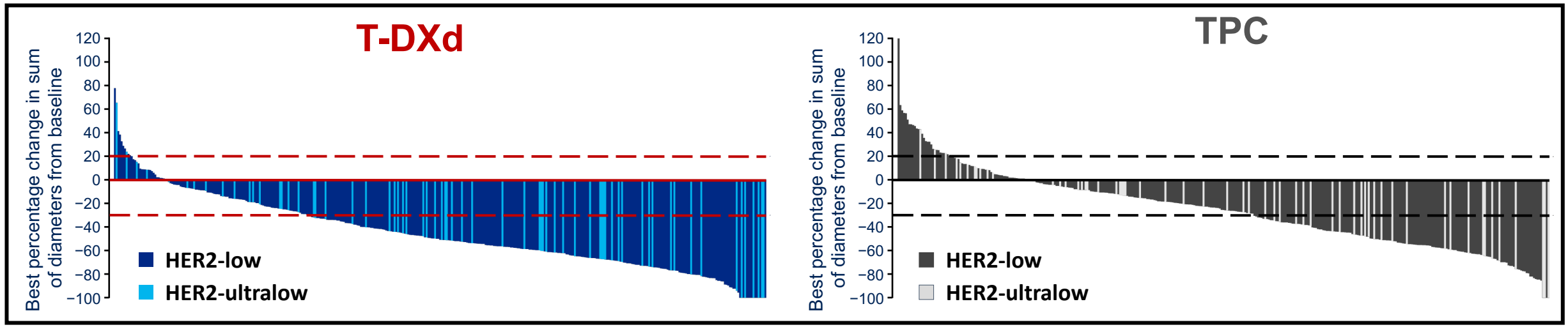

**T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low**

*P-value of <0.05 required for statistical significance

BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano et al, ASCO 2024

# Antitumor activity




| | HER2-low* | | ITT | | HER2-ultralow* | |
|---|---|---|---|---|---|---|
| | T-DXd (n=359) | TPC (n=354) | T-DXd (n=436) | TPC (n=430) | T-DXd (n=76) | TPC (n=76) |
| **Confirmed ORR, n (%)** | **203 (56.5)** | **114 (32.2)** | **250 (57.3)** | **134 (31.2)** | **47 (61.8)** | **20 (26.3)** |
| **Best overall response, n (%)** | | | | | | |
| Complete response | 9 (2.5) | 0 | 13 (3.0) | 0 | 4 (5.3) | 0 |
| Partial response | 194 (54.0) | 114 (32.2) | 237 (54.4) | 134 (31.2) | 43 (56.6) | 20 (26.3) |
| Stable disease | 125 (34.8) | 170 (48.0) | 148 (33.9) | 212 (49.3) | 22 (28.9) | 42 (55.3) |
| **Clinical benefit rate, n (%)†** | 275 (76.6) | 190 (53.7) | 334 (76.6) | 223 (51.9) | 58 (76.3) | 33 (43.4) |
| **Duration of response, median, mo** | 14.1 | 8.6 | 14.3 | 8.6 | 14.3 | 14.1 |

ORR based on RECIST v1.1; response required confirmation after 4 weeks
*HER2-low status determined per IRT data, and HER2-ultralow status determined per central laboratory data; †defined as complete response + partial response + stable disease at Week 24, by blinded independent central review
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITT, intent-to-treat; mo, months; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Curigliano et al, ASCO 2024

# TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

NCT03901339

**Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:**

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

*Treatment was continued until progression or unacceptable toxicity*

**Sacituzumab govitecan**
**10 mg/kg IV**
**days 1 and 8, every 21 days**
**n=272**

**Treatment of physician's choice[b]**
**(capecitabine, vinorelbine, gemcitabine or eribulin)**
**n=271**

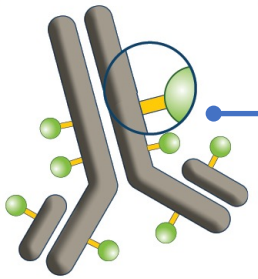
**Endpoints**

**Primary**
- PFS by BICR

**Secondary**
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

**Stratification:**
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

**SN-38 payload (Topo1 inhibitor)** more potent than parent compound, irinotecan



**Humanized anti-Trop-2 Ab**
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

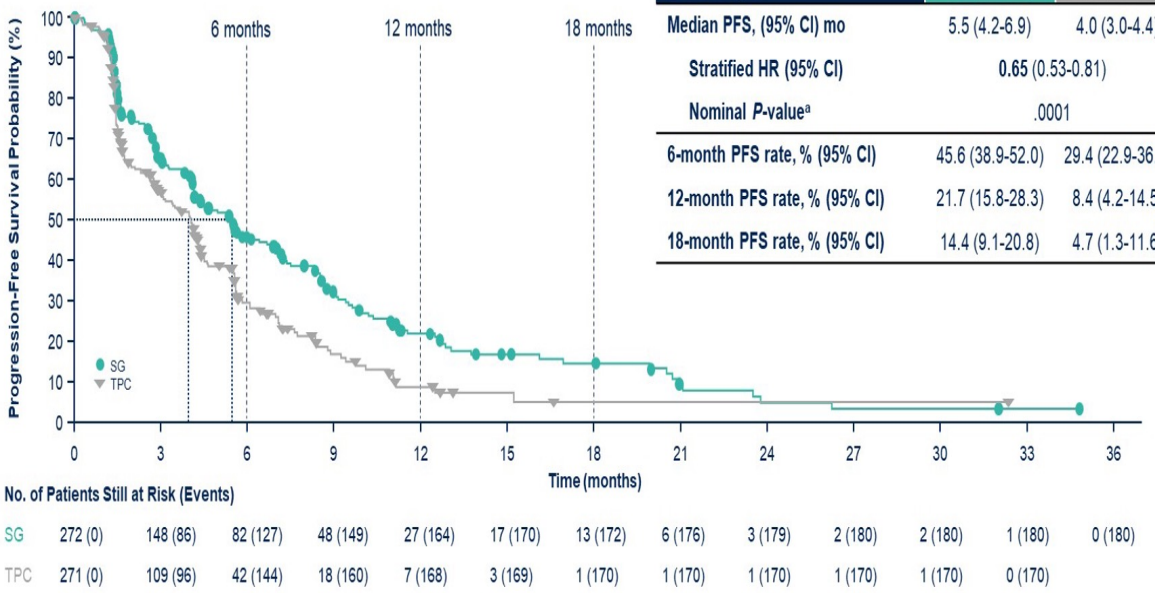
[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; (Neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376.
Rugo H, et al. ESMO 2022. Oral LBA76.

# TROPiCS-02: PFS & OS in the ITT Population

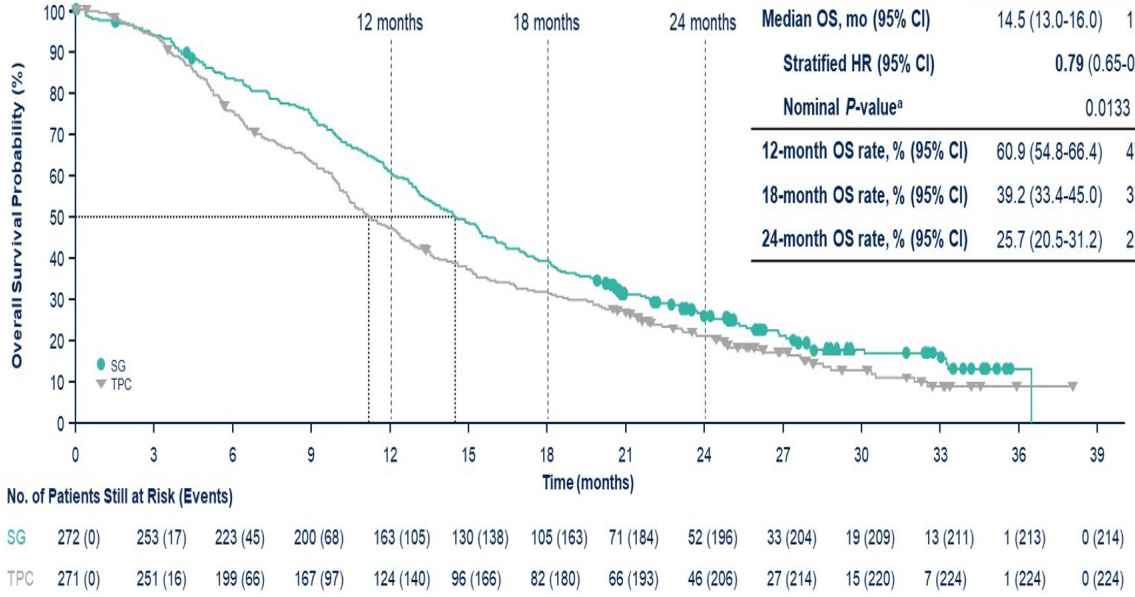
## Extended follow-up

### Progression-Free Survival




| BICR analysis | SG (n = 272) | TPC (n = 271) |
|---|---|---|
| Median PFS, (95% CI) mo | 5.5 (4.2-6.9) | 4.0 (3.0-4.4) |
| Stratified HR (95% CI) | 0.65 (0.53-0.81) | |
| Nominal *P*-value[a] | .0001 | |
| 6-month PFS rate, % (95% CI) | 45.6 (38.9-52.0) | 29.4 (22.9-36.2) |
| 12-month PFS rate, % (95% CI) | 21.7 (15.8-28.3) | 8.4 (4.2-14.5) |
| 18-month PFS rate, % (95% CI) | 14.4 (9.1-20.8) | 4.7 (1.3-11.6) |

### Overall Survival



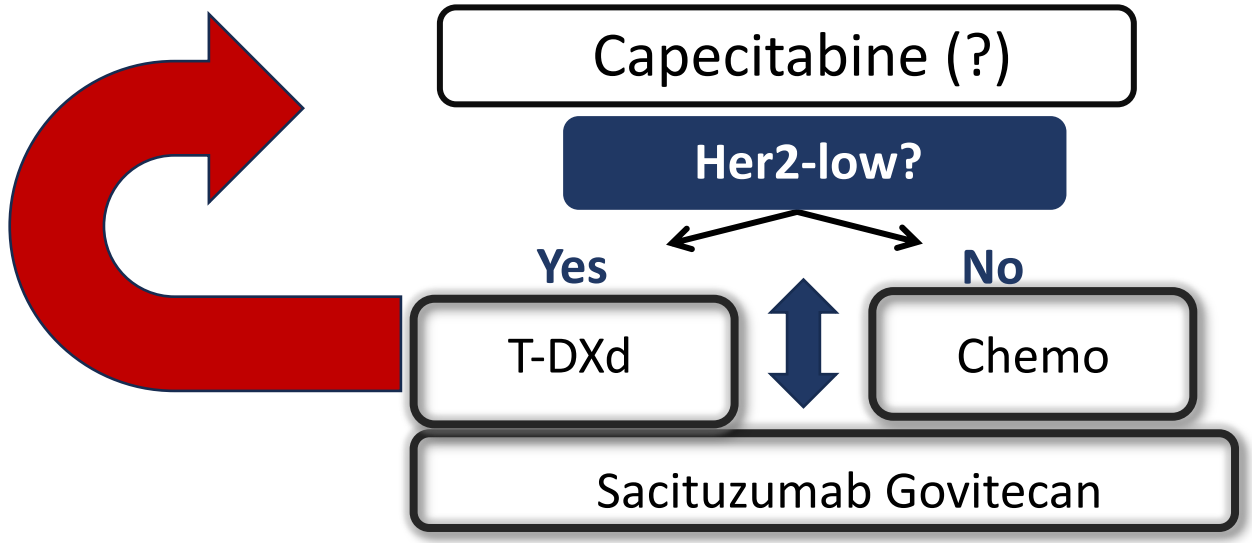

| | SG (n = 272) | TPC (n = 271) |
|---|---|---|
| Median OS, mo (95% CI) | 14.5 (13.0-16.0) | 11.2 (10.2-12.6) |
| Stratified HR (95% CI) | 0.79 (0.65-0.95) | |
| Nominal *P*-value[a] | 0.0133 | |
| 12-month OS rate, % (95% CI) | 60.9 (54.8-66.4) | 47.1 (41.0-53.0) |
| 18-month OS rate, % (95% CI) | 39.2 (33.4-45.0) | 31.7 (26.2-37.4) |
| 24-month OS rate, % (95% CI) | 25.7 (20.5-31.2) | 21.1 (16.3-26.3) |


Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376.
Rugo H, et al. ESMO 2022. Oral LBA76.
Tolaney S, el at. ASCO 2023

# How to integrate in practice?

- 1st line setting **ET+ CDK 4/6i** Inavolisib- for selected patients
- 2nd/ 3rd line-Consider prior ET and response duration (ET sensitivity, CDK4/6i duration)
  - Somatic mutations – ESR1, PIK3CA, AKT, PTEN and Germline *BRCA*
  - CDKi beyond progression possibly in selected patients without targetable mutations

| g*BRCA*m- iPARP | *ESR1*m<br>Elacestrant | PIK3CA<br>Alpelisib + Fulv | PIK3CA, AKT, PTEN<br>Capivasertib + Fulv | No alterations<br>Exe + Everolimus<br>CDKi+Fulv |
|---|---|---|---|---|



# Take home points

- More drugs available translating into more options for our patients
- Endocrine therapy + targeted therapies
  - 1st line CDK4/6i are standard in US
  - Extraordinary alternatives in 2nd line
  - Many questions regarding sequencing, resistance and biomarkers remain unanswered
  - CRUCIAL to use available biomarkers- WE MUST TEST

    BRCAm- PARPi

    PIK3CA-alpelisib, capivasertib

    AKT, PTEN-capivaserib

    ESR1-elacestrant

    No mutation- CDKi?, everolimus

# What we should not forget

- In practice, previous treatment exposure and duration influence our alternatives. Also, previous toxicities, comorbidities, etc.
  - Not all patients with ABC are the same
  - INDIVIDUALIZE
    - Small burden/oligometastatic disease, slow progression
    - High burden/numerous metastases and metastatic sites, rapidly progressing
    - Biological/Genetic/molecular characteristics
    - Characteristics unique to the individual patient
      - Patient preferences
      - Shared-decision

# Thank you

BCRF BREAST CANCER RESEARCH FOUNDATION

SUSAN G. KOMEN FOR THE CURE