# New Agents and New Applications of Targeted Therapy for HR+ HER2- Metastatic Breast Cancer

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Celebrating Women Chair in Breast Cancer Research

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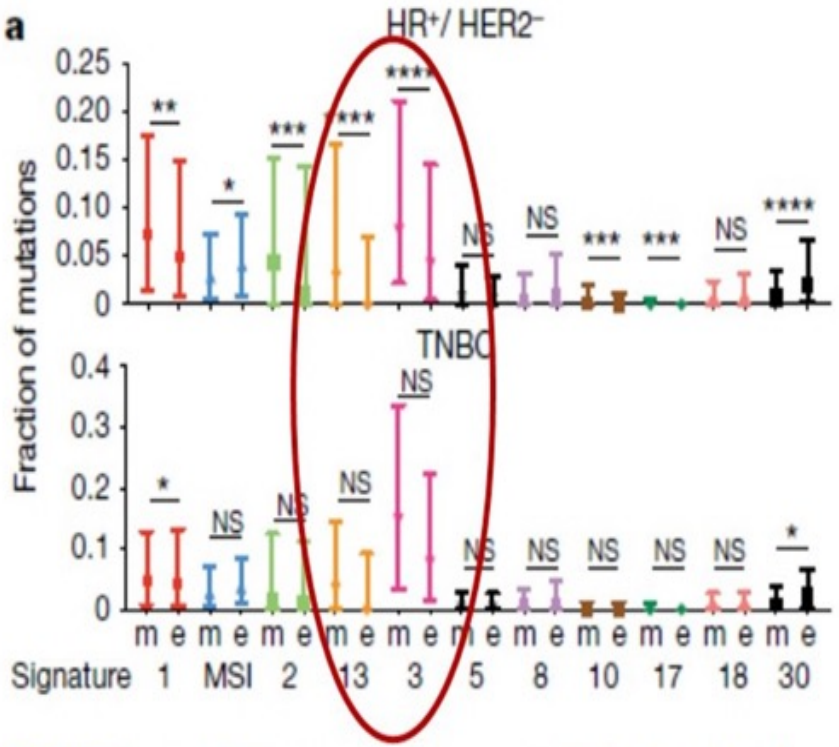
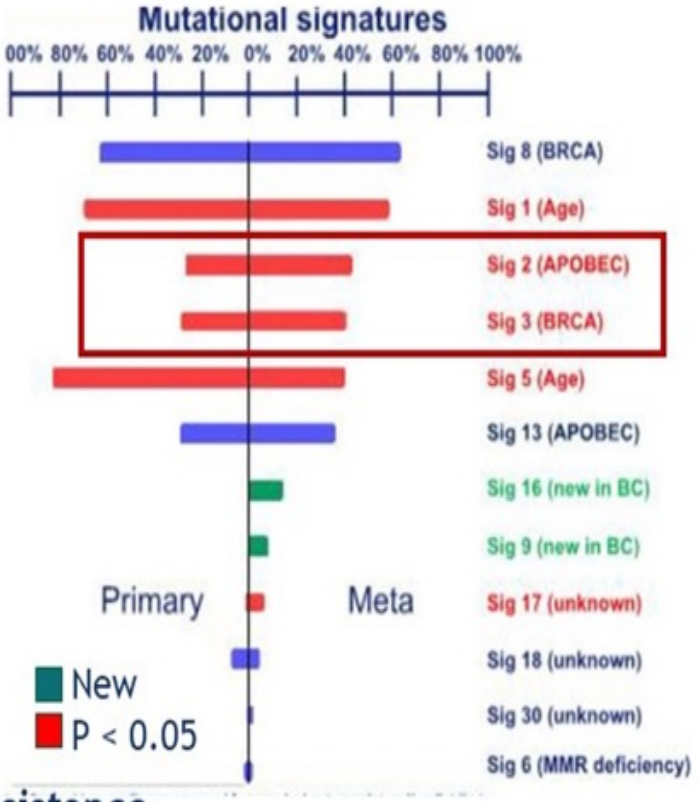
# Comparison of Mutational Signatures in MBC compared to EBC

## French Cohort




## CPCT-02 Cohort




**APOEBEC mutations may be associated with therapy resistance**

Law et al. Sci Adv 2016; Bertucci et al. Nature 2019; Angus et al. SABCS 2018

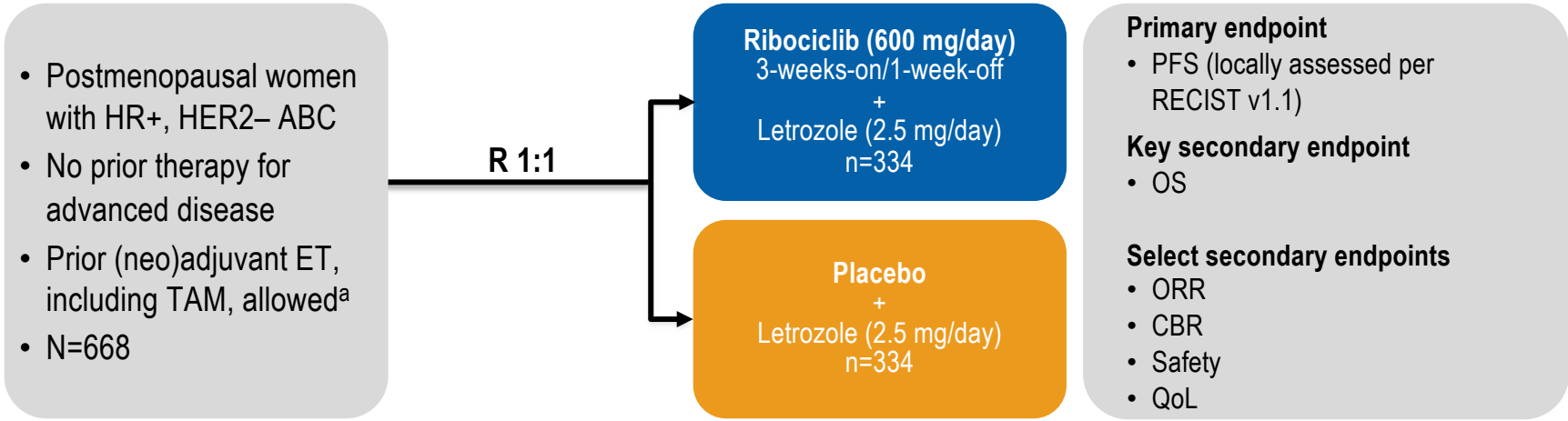
# Overview of first-line CDK 4/6 inhibitor trials

| Trial | PFS Δ | HR/P value | OS Δ | HR/P value |
|---|---|---|---|---|
| PALOMA 1 | 10 mos. | 0.49/.004 | 3 mos. | 0.9/.28 |
| PALOMA 2 | 10 mos. | 0.58/SS | 2.7 mos. | 0.96/.34 |
| FLIPPER* | 10 mos. | 0.52/.002 | NR | NA |
| MONALEESA 2 | 9 mos. | 0.57/SS | 12.5 mos. | 0.76/.004 |
| MONARCH 3 | 28/15 mos. | 0.54/.000021 | NR | NA |
| MONALEESA 3 | 15 mos. | 0.55/SS | NR/52 mos. | 0.64/SS |
| MONALEESA 7 | 10 mos. | 0.55/SS | NR/41 mos. | 0.71/.01 |

* FLIPPER evaluated addition of Palbociclib to fulvestrant

Slamon et al Annals of Oncology 2021, Hortobagyi et al ESMO 2021, Im et al NEJM 2019, Johnston et al NPJ Breast Cancer 2019, Finn et al BCRT 2020, Albanell et al ESMO 2020

# MONALEESA-2 study design




Stratified by the presence/absence of liver and/or lung metastases



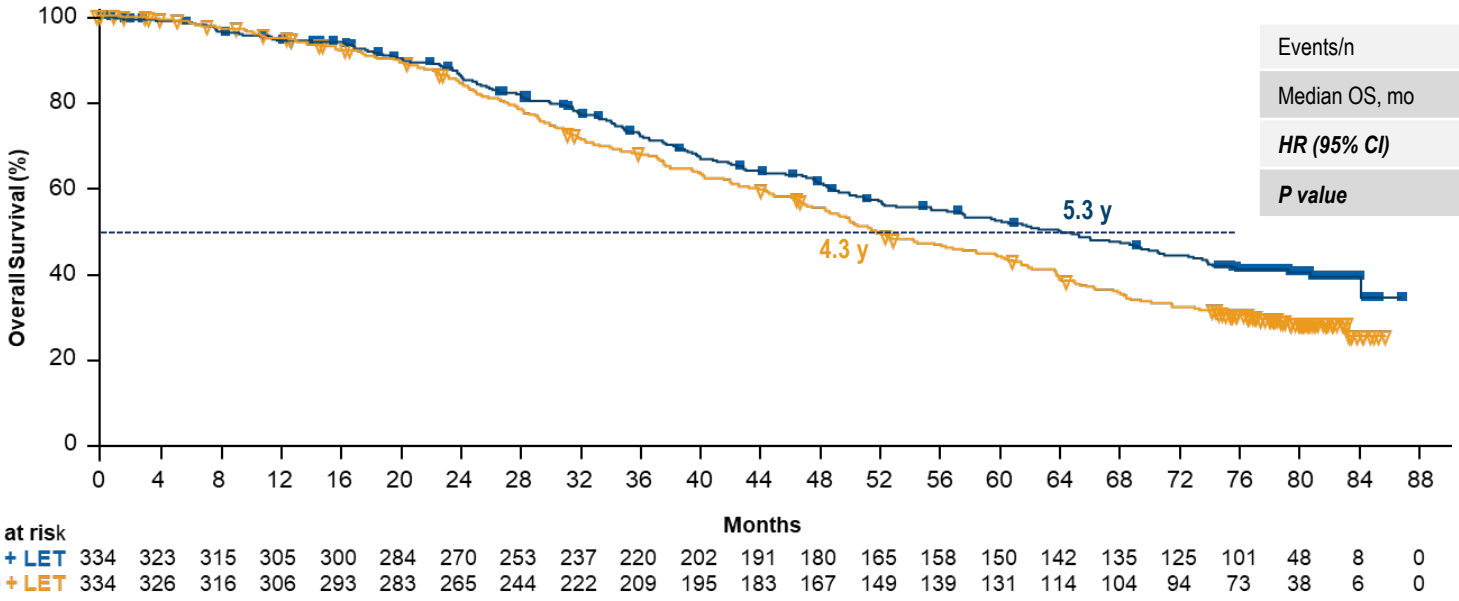
ABC, advanced breast cancer; CBR, clinical benefit rate; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TAM, tamoxifen.

[a]Treatment-free interval > 12 months from completion of treatment until randomization required for prior NSAI use.

Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748.

# RIB achieved statistically significant OS benefit in ML-2

## Improvement in mOS was 12.5 months with RIB + LET



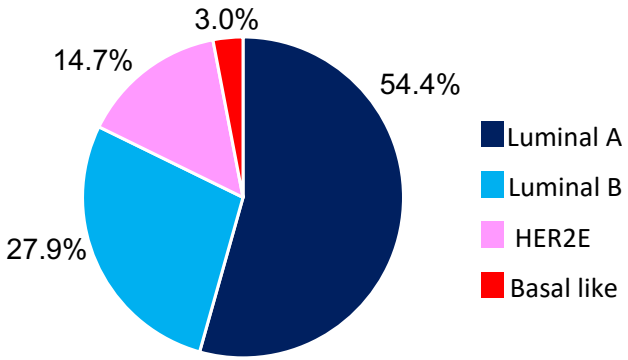

| | RIB + LET | PBO + LET |
|---|---|---|
| Events/n | 181/334 | 219/334 |
| Median OS, mo | 63.9 | 51.4 |
| ***HR (95% CI)*** | ***0.76 (0.63 – 0.93)*** | |
| ***P value*** | ***0.004*** | |

*The P value of 0.004 crossed the prespecified boundary to claim superior efficacy*

HR, hazard ratio; ML-2, MONALEESA-2; LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

Gabriel N. Hortobagyi et al. NEJM 2022

# Correlative Analysis of Overall Survival by Intrinsic Subtype Across the MONALEESA-2, -3, and -7 Studies of Ribociclib + Endocrine Therapy in Patients with HR+/HER2– ABC




**Samples in this analysis (N = 997)[a]:**

RIB + ET (n = 585) and PBO + ET (n = 412)

- MONALEESA-2: 318 samples
- MONALEESA-3: 414 samples
- MONALEESA-7: 265 samples

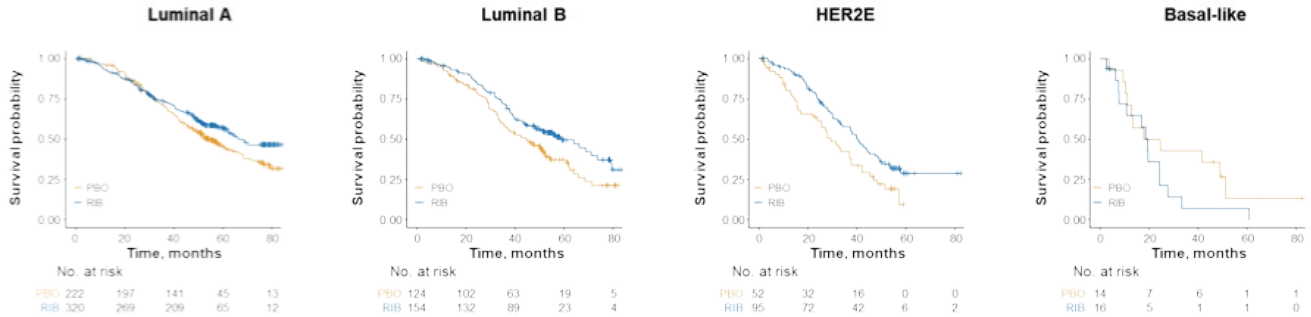
71% were from primary tumors in the pooled dataset

- MONALEESA-2: 73% primary
- MONALEESA-3: 74% primary
- MONALEESA-7: 68% primary

Intrinsic subtype was prognostic for OS in multivariable models

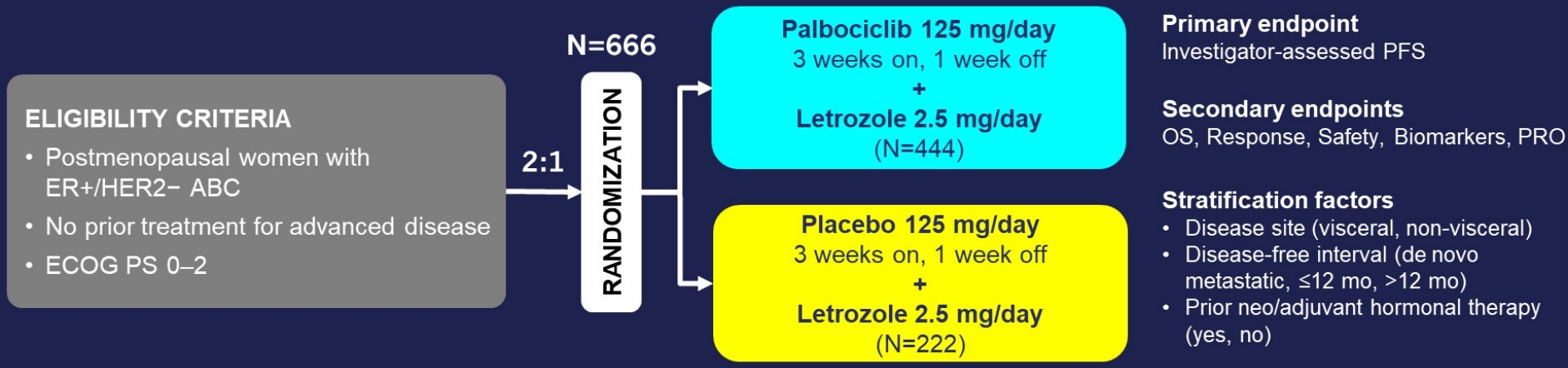
| | RIB + ET | | | PBO + ET | | |
|---|---|---|---|---|---|---|
| | Adjusted Hazard Ratio[a] | 95% CI | *P* Value | Adjusted Hazard Ratio[a] | 95% CI | *P* Value |
| **Luminal A** | 1.00 | - | - | 1.00 | - | - |
| **Luminal B** | 1.16 | 0.86-1.57 | 0.32 | 1.47 | 1.08-2.00 | 0.013 |
| **HER2E** | 1.83 | 1.33-2.52 | 0.00023 | 2.87 | 1.93-4.26 | < .0001 |
| **Basal-like** | 7.06 | 3.73-13.40 | < .0001 | 2.35 | 1.20-4.58 | 0.012 |

Univariable analysis: OS benefit with RIB + ET in Luminal A, Luminal B, and HER2E subtypes; Basal-like subtype did not demonstrate OS benefit with RIB + ET (small sample size; n = 30 total; 3% in each arm)




Carey et al, SABCS 2021

# PALOMA-2 Study Design




**Primary endpoint**
Investigator-assessed PFS

**Secondary endpoints**
OS, Response, Safety, Biomarkers, PRO

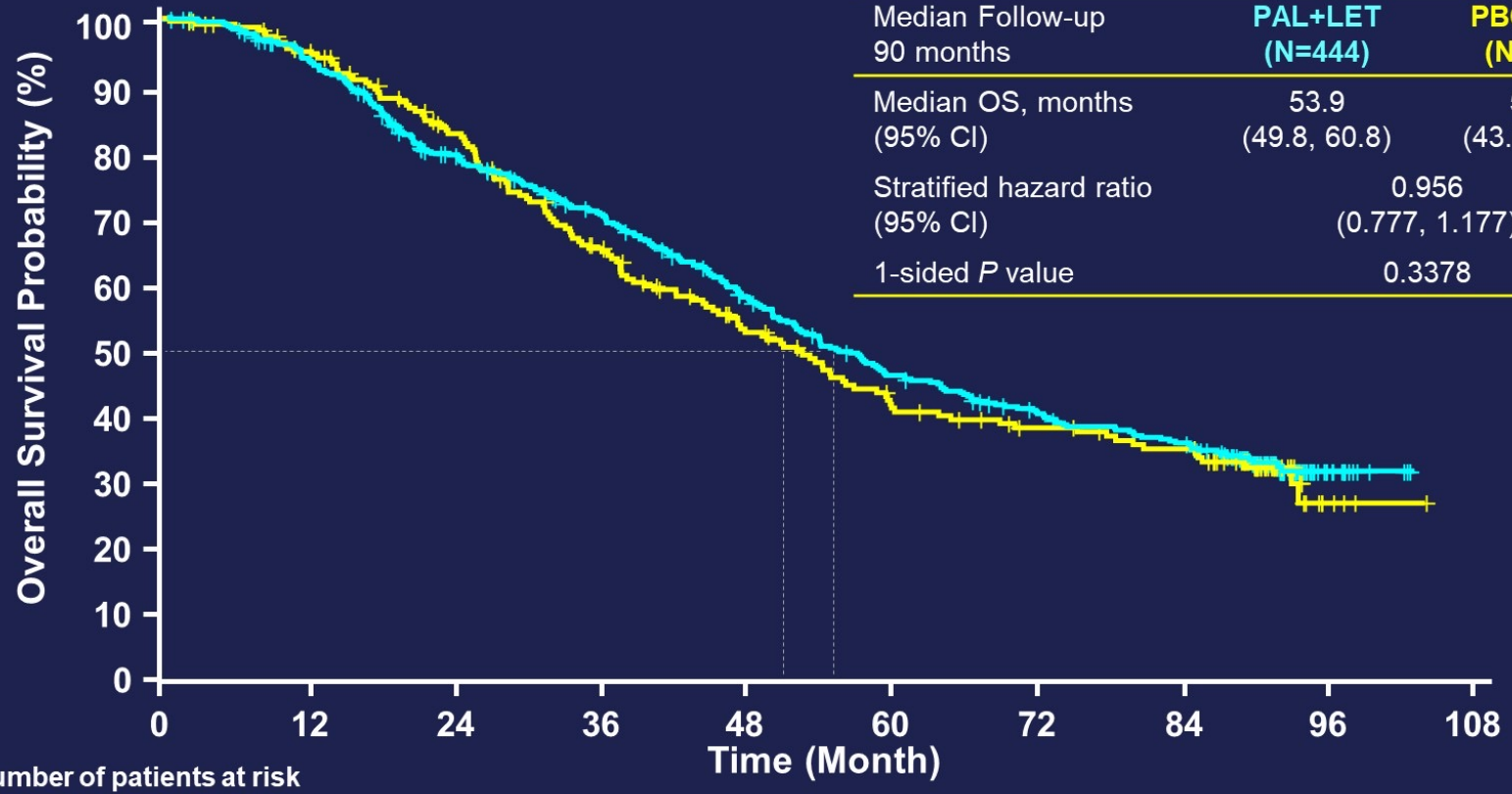
**Stratification factors**
- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic, ≤12 mo, >12 mo)
- Prior neo/adjuvant hormonal therapy (yes, no)

**Statistical Assumptions for PFS as Primary Endpoint:**
- Sample size determined to detect ~44% improvement in median PFS from 9 months for the control arm to 13 months for the palbociclib arm
- Assuming a true hazard ratio of 0.69 in favor of the palbociclib arm (90% power with 1-sided $\alpha$=0.025)

**Statistical Assumptions for OS as Secondary Endpoint:**
- Assumption for the control arm median OS of 34 to 46 months (~35% improvement)
- 390 events required to detect a hazard ratio of 0.74 or less (80% power with 1-sided $\alpha$=0.025)

ABC=advanced breast cancer; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome.

# Overall Survival – ITT




| Median Follow-up 90 months | PAL+LET (N=444) | PBO+LET (N=222) |
|---|---|---|
| Median OS, months (95% CI) | 53.9 (49.8, 60.8) | 51.2 (43.7, 58.9) |
| Stratified hazard ratio (95% CI) | 0.956 (0.777, 1.177) | |
| 1-sided *P* value | 0.3378 | |

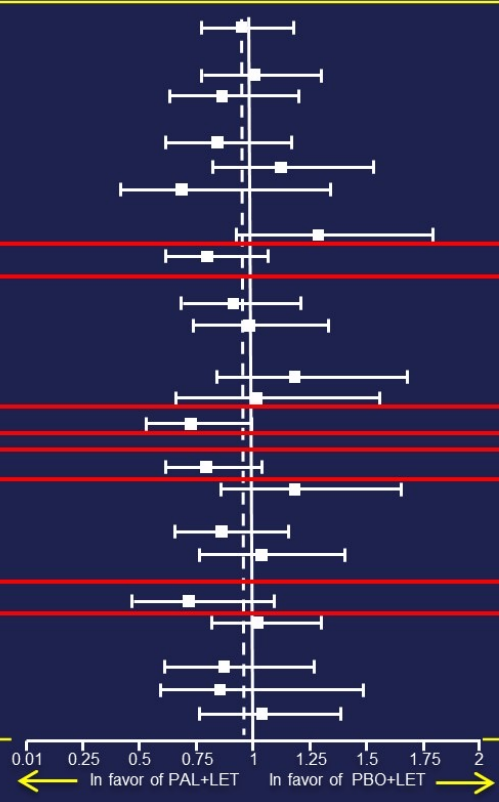
Number of patients at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PAL+LET | 444 | 400 | 325 | 280 | 222 | 174 | 145 | 128 | 13 | 0 |
| PBO+LET | 222 | 203 | 168 | 126 | 95 | 72 | 60 | 53 | 4 | 0 |

ITT=intent-to-treat; LET=letrozole; OS=overall survival; PAL=palbociclib; PBO=placebo.

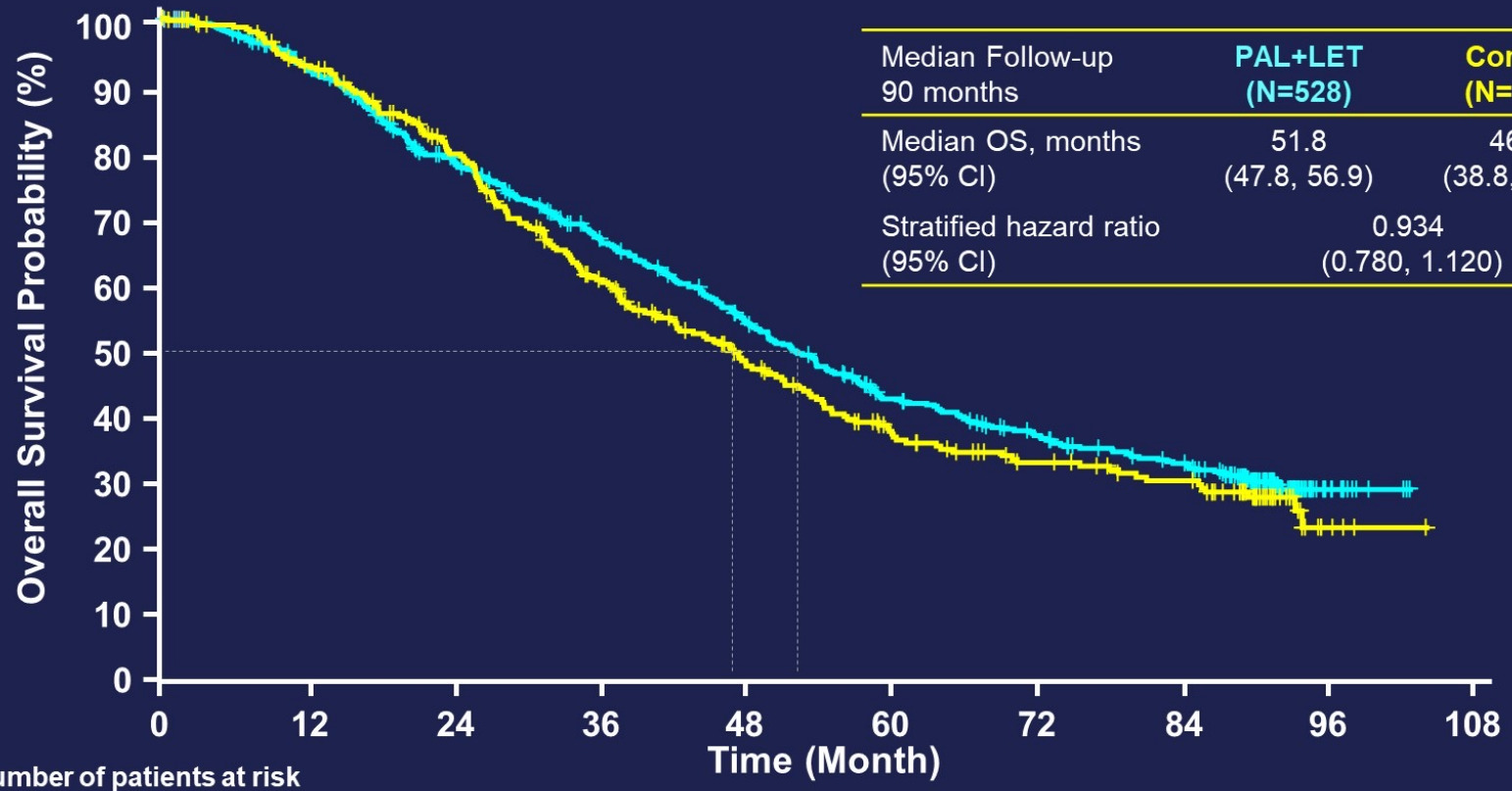
# Overall Survival in Subgroups – ITT Population

| Subgroup | | Median OS (95% CI) | | Missing Survival Data (%) | |
|---|---|---|---|---|---|
| | | PAL+LET | PBO+LET | PAL+LET | PBO+LET |
| **All randomized patients** | | 53.9 (49.8, 60.8) | 51.2 (43.7, 58.9) | 13 | 21 |
| Age | <65 y | 53.3 (47.0, 60.8) | 54.4 (44.8, 60.2) | 11 | 21 |
| | ≥65 y | 58.6 (49.8, 66.7) | 47.4 (36.2, 60.4) | 17 | 21 |
| Region | North America | 53.8 (47.3, 61.3) | 49.4 (37.0, 57.0) | 16 | 23 |
| | Europe | 52.3 (46.0, 63.8) | 53.8 (42.3, 78.7) | 11 | 17 |
| | Asia/Pacific | 73.4 (47.3, NE) | 55.1 (32.2, NE) | 14 | 29 |
| ECOG performance status | 0 | 58.2 (52.1, 66.0) | 85.9 (53.8, NE) | 11 | 28 |
| | 1/2 | 47.3 (41.3, 60.8) | 38.8 (32.2, 49.8) | 16 | 16 |
| Disease site | Visceral | 48.1 (42.3, 53.8) | 44.8 (32.2, 53.8) | 13 | 23 |
| | Non-visceral | 60.8 (53.8, 72.3) | 59.7 (47.4, 85.3) | 14 | 20 |
| Disease-free interval | De novo metastatic | 54.6 (47.0, 69.1) | 60.4 (49.8, 93.8) | 10 | 24 |
| | ≤12 months | 45.7 (36.1, 51.1) | 37.7 (27.1, 56.4) | 12 | 29 |
| | >12 months | 66.3 (52.1, 79.7) | 47.4 (37.7, 57.0) | 17 | 15 |
| Prior endocrine therapy | Yes | 53.3 (48.0, 62.9) | 44.6 (34.3, 52.8) | 16 | 18 |
| | No | 55.1 (47.3, 71.4) | 60.4 (49.8, 93.8) | 10 | 25 |
| Prior chemotherapy | Yes | 51.6 (45.6, 58.6) | 44.6 (36.2, 54.4) | 13 | 18 |
| | No | 58.4 (50.5, 71.7) | 58.9 (47.7, 81.0) | 14 | 24 |
| Bone-only disease | Yes | 63.5 (53.9, 79.7) | 52.3 (42.3, 59.7) | 16 | 15 |
| | No | 51.6 (46.9, 57.6) | 49.8 (38.8, 60.4) | 13 | 23 |
| Number of disease sites | 1 | 59.1 (53.8, 73.9) | 54.4 (45.4, 70.3) | 15 | 18 |
| | 2 | 60.8 (47.9, 87.2) | 54.5 (33.5, NE) | 15 | 37 |
| | ≥3 | 48.1 (41.3, 53.8) | 45.8 (32.4, 57.0) | 12 | 15 |




ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; LET=letrozole; NE=not estimable; PAL=palbociclib; PBO=placebo.

# PALOMA-1 and PALOMA-2 Combined OS Analysis



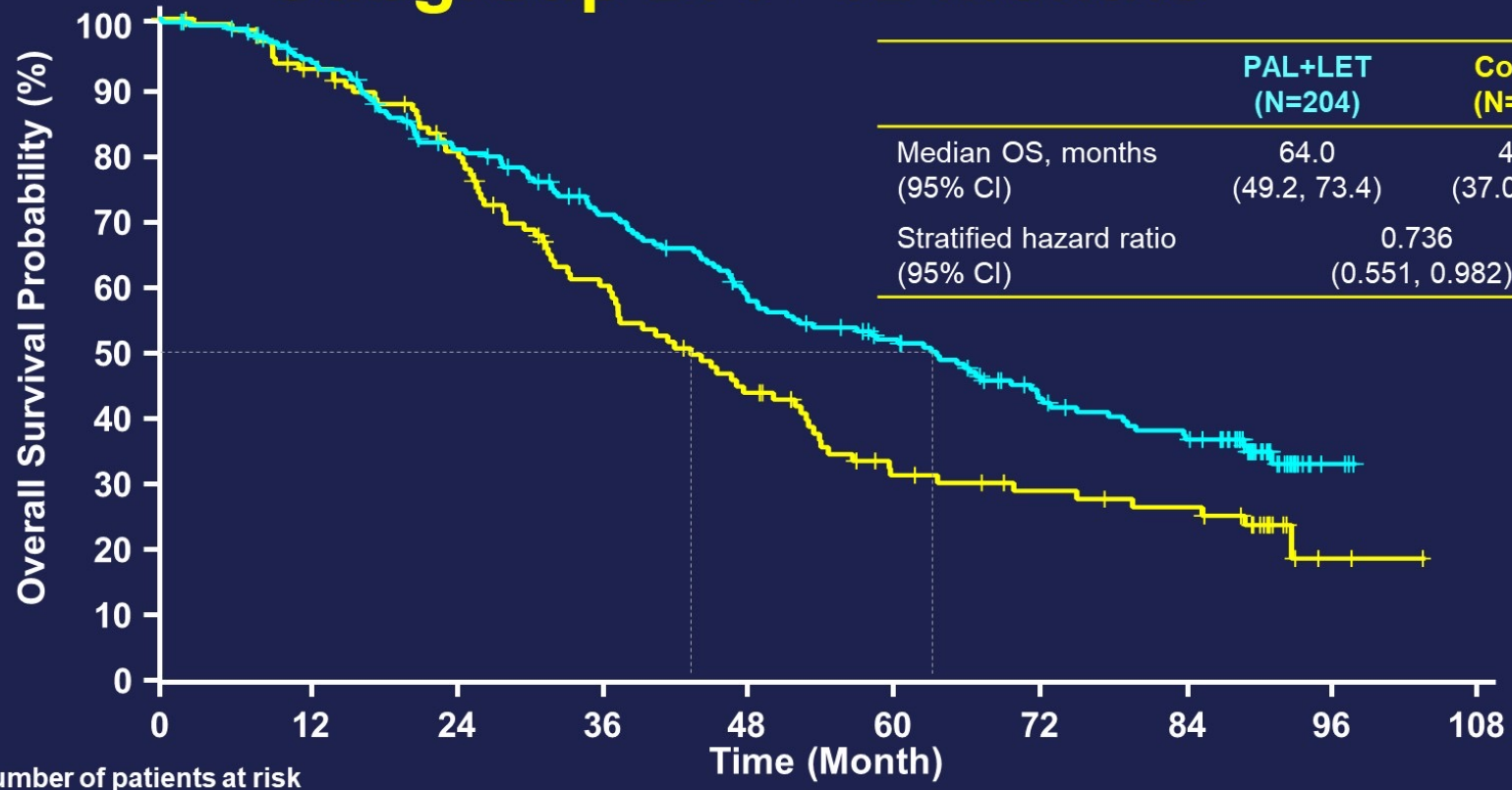

| Median Follow-up 90 months | PAL+LET (N=528) | Control (N=303) |
|---|---|---|
| Median OS, months (95% CI) | 51.8 (47.8, 56.9) | 46.8 (38.8, 52.3) |
| Stratified hazard ratio (95% CI) | 0.934 (0.780, 1.120) | |

Number of patients at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PAL+LET | 528 | 473 | 388 | 318 | 250 | 187 | 153 | 128 | 13 | 0 |
| Control | 303 | 270 | 220 | 159 | 116 | 82 | 63 | 53 | 4 | 0 |

LET=letrozole; OS=overall survival; PAL=palbociclib.

# PALOMA-1 and PALOMA-2 Combined OS Analysis: Subgroup DFI >12 months




| | PAL+LET (N=204) | Control (N=123) |
|---|---|---|
| Median OS, months (95% CI) | 64.0 (49.2, 73.4) | 44.6 (37.0, 53.2) |
| Stratified hazard ratio (95% CI) | 0.736 (0.551, 0.982) | |

Number of patients at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PAL+LET | 204 | 185 | 154 | 130 | 106 | 88 | 68 | 57 | 3 | 0 |
| Control | 123 | 109 | 91 | 66 | 48 | 32 | 25 | 22 | 2 | 0 |

DFI=disease-free interval; LET=letrozole; OS=overall survival; PAL=palbociclib.

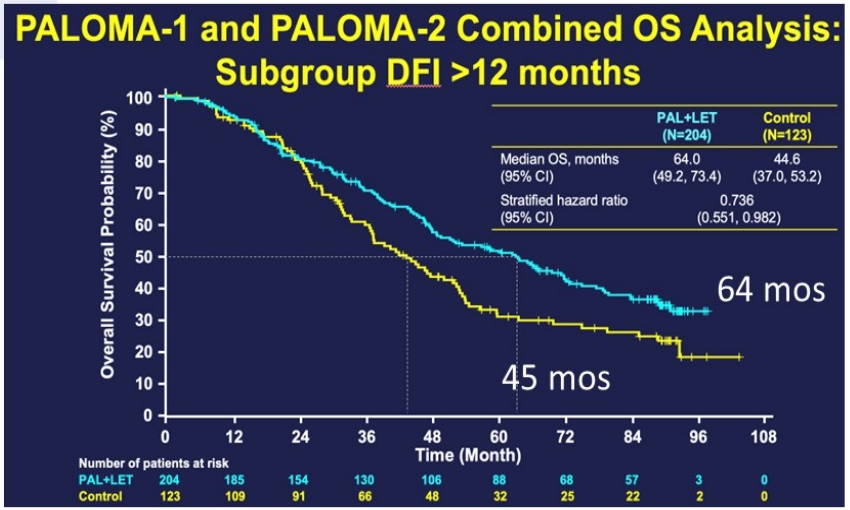
# Why are there OS differences between the studies?

| Randomized P3 Trials | PALOMA-2 Palbociclib | MONALEESA-2 Ribociclib | MONALEESA-7 Ribociclib | MONALEESA-3 Ribociclib 1L Cohort |
|---|---|---|---|---|
| De novo mBC | 38% | 34% | 41% | 20% |
| Disease-free interval | | | | |
| DFI ≤ 12 mos | 22% | 1% | 7% | 0% |
| DFI > 12 mos | 40% | NR | 53% | 80% |
| DFI > 24 mos | NR | 60% | NR | NR |

- **DFI ≤ 12 mos in Paloma 1 ~ 35%**
- **Combined OS analysis with PALOMA-1 planned**
- **Analysis by DFI subgroup unplanned**

**No substantial differences in prior therapy, visceral disease, use of subsequent CDK46i in placebo arm, other variables**

Limitations:
- Post hoc analyses
- Definition of "missing survival data"




Finn et al NEJM 2016; Hortobagyi et al. NEJM 2016; Tripathy et al Lancet Oncol 2018; Slamon et al. NEJM 2020

2022 ASCO® ANNUAL MEETING

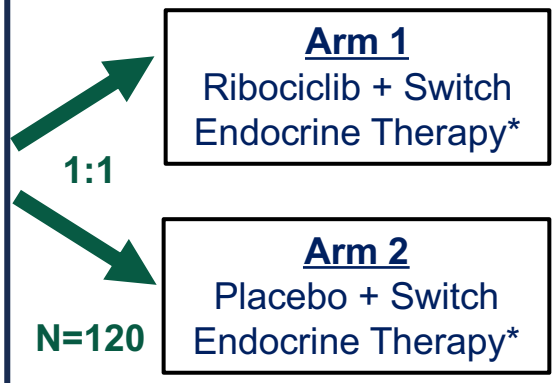
# A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER2 negative breast cancer: MAINTAIN Trial

Kevin Kalinsky, Melissa K Accordino, Cody Chiuzan, Prabhjot Mundi, Meghna S Trivedi, Yelena Novik, Amy Tiersten, Amelia Zelnak, George Raptis, Lea Baer, Sun Y Oh, Erica Stringer-Reasor, Sonya Reid, Eleni Andreopoulou, William Gradishar, Kari B Wisinski, Anne O'Dea, Ruth O'Regan, Katherine D Crew, Dawn L Hershman

# Schema

**Key Entry Criteria**

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed




**Primary Endpoint**

- Progression free survival
  - Locally assessed per RECIST 1.1

**Secondary Endpoints**

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

Kevin Kalinsky, MD, MS

# Patient Characteristics and Prior Treatment

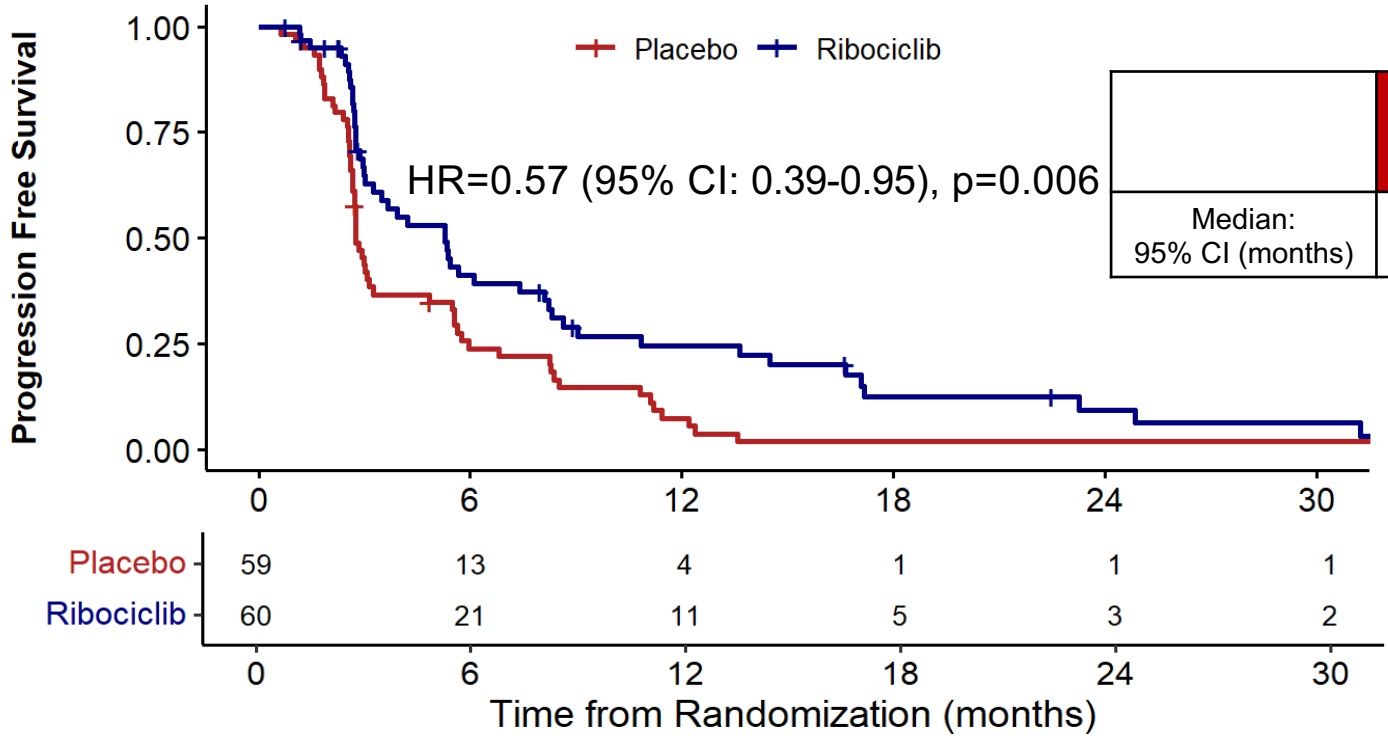
| | Placebo (n=59) | Ribociclib (n=60) |
|---|---|---|
| **Female - no. (%)** | 58 (99%) | 60 (100%) |
| **Median age – years (IQR)** | 59 (52-65) | 55 (48-67) |
| **Race or ethnic group – no. (%)** | | |
| White | 42 (71%) | 46 (77%) |
| Black | 8 (14%) | 5 (8%) |
| Asian | 2 (3%) | 5 (8%) |
| Other or not specified | 7 (12%) | 4 (7%) |
| **ECOG PS – no. (%)** | | |
| 0 | 38 (64%) | 40 (67%) |
| 1 | 21 (36%) | 20 (33%) |
| **De Novo Metastasis at Dx - no. (%)*** ** | 32 (54%) | 21 (35%) |
| **Visceral Metastasis – no. (%)** | 35 (59%) | 36 (60%) |
| **Bone-Only Disease – no. (%)** | 9 (15%) | 13 (22%) |
| **> 2 prior ET for MBC – no. (%)** | 11 (19%) | 11 (18%) |
| **Chemotherapy for MBC – no. (%)** | 7 (12%) | 4 (7%) |

| | Placebo (n=59) | Ribociclib (n=60) |
|---|---|---|
| **Prior CDK 4/6 inhibitor – no. (%)** | | |
| Palbociclib* | 51 (86%) | 52 (87%) |
| Ribociclib** | 8 (14%) | 6 (10%) |
| Abemaciclib | 0 (0%) | 2 (3%) |
| **Median duration of prior CDK 4/6 inhibitor – months (IQR)** | 17 (11-23.5) | 15.5 (12-21) |
| **Prior CDK 4/6 inhibitor duration– no. (%)****** | | |
| ≤ 12 months | 21 (36%) | 18 (30%) |
| > 12 months | 38 (64%) | 42 (70%) |
| **Prior CDK 4/6 inhibitor in metastatic setting - no. (%)** | 59 (100%) | 60 (100%) |
| **Intervening treatment after progression on prior CDK 4/6 inhibitor - no. (%)** | 6 (10%) | 1 (2%) |

* Includes 1 pt who did not tolerate prior abemaciclib and 2 pts with insurance issues with ribociclib; ** Includes 1 pt who did not tolerate prior palbociclib; ***p=0.035; **** 10 pts (17%) in placebo arm and 7 pts (12%) pts in ribociclib arm on prior CDK4/6 inhibitor ≤ 6 months; IQR = interquartile range

Kevin Kalinsky, MD, MS

# Primary Endpoint: Progression Free Survival (PFS)




| | Placebo + ET (n=59) | Ribociclib + ET (n=60) |
|---|---|---|
| Median: 95% CI (months) | **2.76** (2.66-3.25) | **5.29** (3.02-8.12) |

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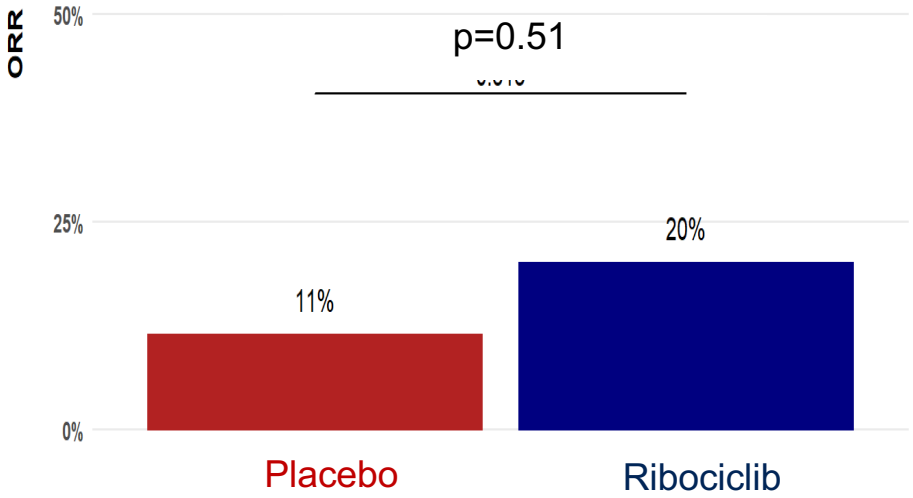
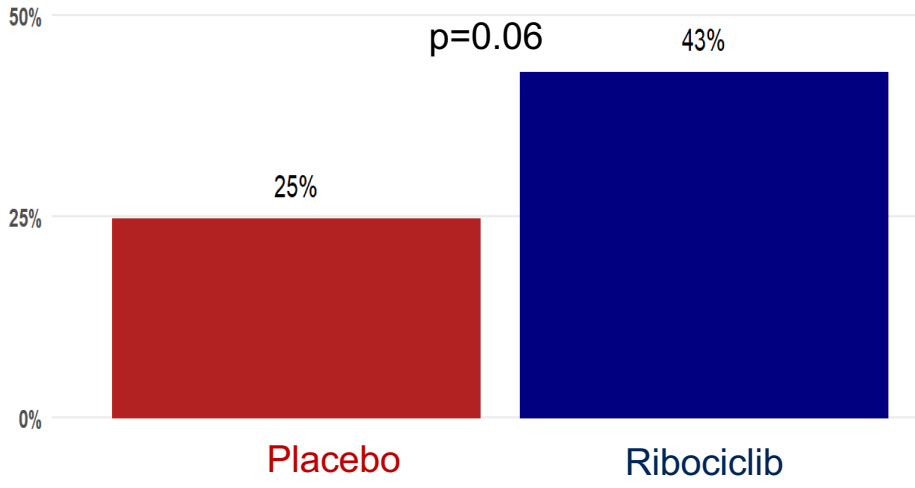
# Overall Response and Clinical Benefit Rate

## Overall Response Rate (n=70)




| | Placebo + ET (n=35) | Ribociclib + ET (n=35) |
|---|---|---|
| CR | 0 (0%) | 2 (6%) |
| PR | 4 (11%) | 5 (14%) |
| Median DOR (IQR) (mos) | 14.8 (6.7-21.3) | 18.8 (11.4-50.2) |

## Clinical Benefit Rate (n=105)



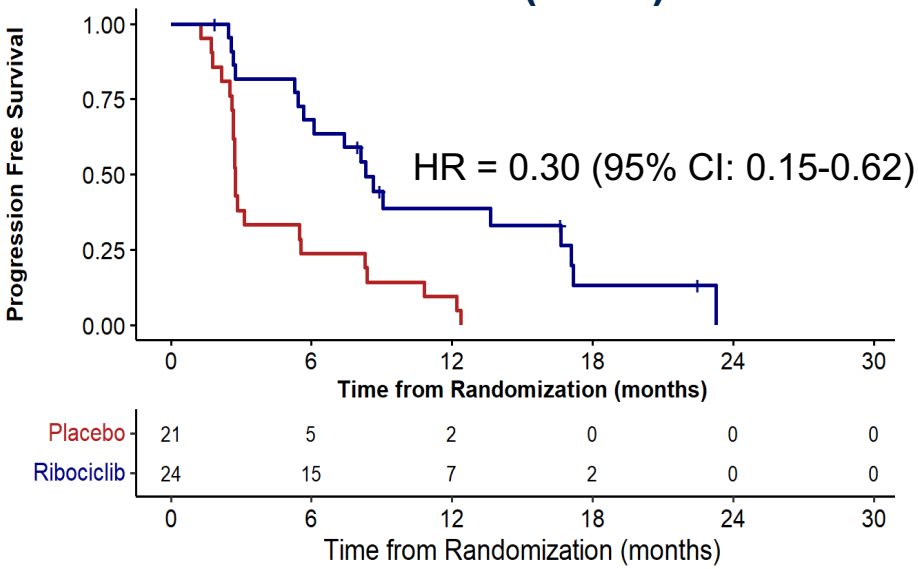

| | Placebo + ET (n=57) | Ribociclib + ET (n=49) |
|---|---|---|
| CR, PR, or SD ≥ 24 weeks | 14 (25%) | 21 (43%) |

IQR = Interquartile Range, CR = Complete response, PR = Partial Response, DOR = Duration of Response, SD = Stable Disease

Kevin Kalinsky, MD, MS

# Exploratory Analysis
# PFS: Fulvestrant and *ESR1* Mutation Status

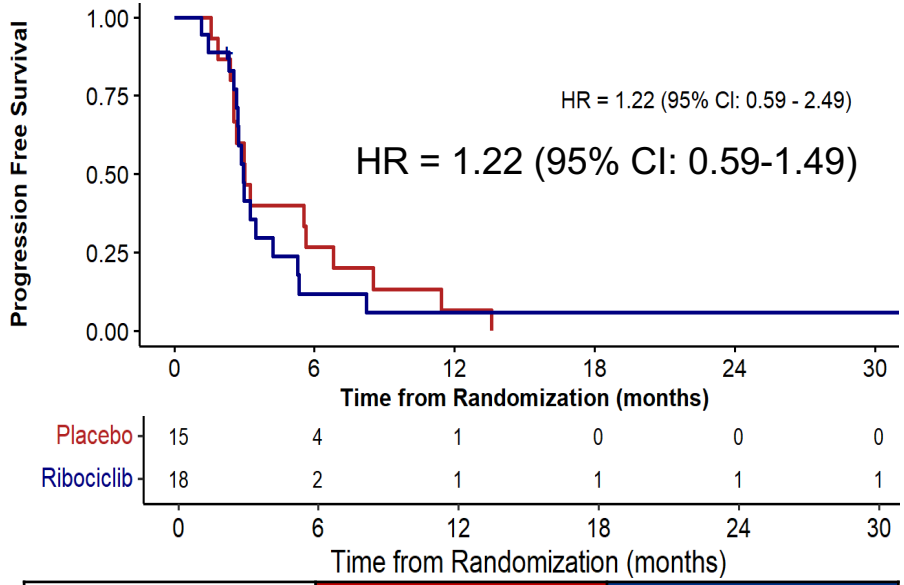
## *ESR1* WT (n=45)




| | Placebo (n=21) | Ribociclib (n=24) |
|---|---|---|
| Median (95% CI) (mos) | **2.76** (2.66-5.49) | **8.32** (5.65-16.63) |

0/24 pts (0%) had *CCND1* and/or *FGFR1* amplification on ribociclib arm

## *ESR1* Mutant (n=33)




| | Placebo (n=15) | Ribociclib (n=18) |
|---|---|---|
| Median (95% CI) (mos) | **3.02** (2.53-5.62) | **2.96** (2.66-4.21) |

9/18 (50%) pts with *CCND1* and/or *FGFR1* amplification on ribociclib arm

Kevin Kalinsky, MD, MS

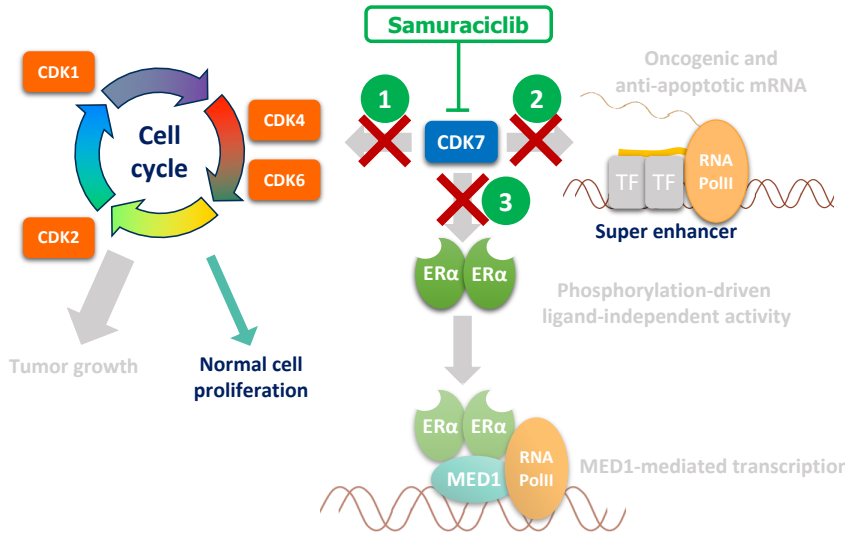
# Study of samuraciclib (CT7001), a first-in-class, oral, selective inhibitor of CDK7, in combination with fulvestrant in pts with advanced HR+, HER2-negative BC

San Antonio Breast Cancer Symposium®, December 7–10, 2021

## The CDK7 inhibitor samuraciclib (CT7001)

- Once-daily, oral, small molecule, ATP-competitive, selective inhibitor of CDK7
- Synergistic with hormonal therapy in HR+ breast cancer xenograft models
- Blocks CDK7-mediated oncogenic effects

1. The cell cycle through phosphorylation of other CDKs
2. Transcription of oncogenic and anti-apoptotic genes
3. Signaling by and activation of hormone receptors (ER and AR)




Patel H, et al. Mol Cancer Ther 2018;17:1156–66

Coombs et al, SABCS 2021

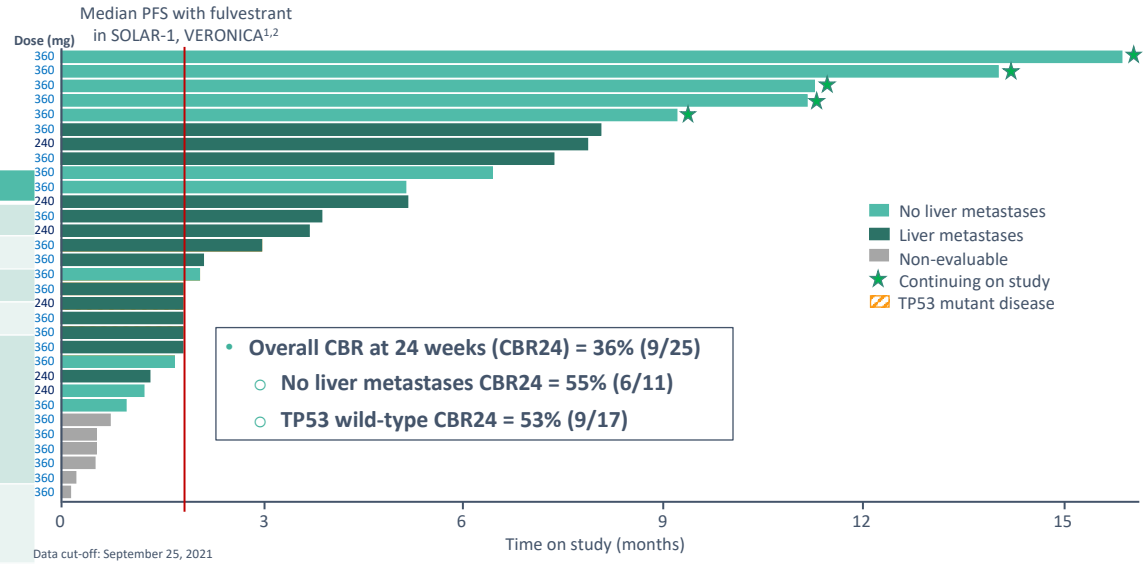
## Module 2A

- Female, aged ≥18 years
- Histologically confirmed, metastatic or locally advanced, ER+ and/or PGR+, HER2- breast cancer
- Measurable disease
- Prior CDK4/6 inhibitor therapy
- No prior fulvestrant
- ≤1 line of chemotherapy or ≤2 lines of endocrine therapy for advanced breast cancer

**Samuraciclib 240 mg QD + fulvestrant 500 mg q4w (n=6)**

**Samuraciclib 360 mg QD + fulvestrant 500 mg q4w (n=25)**

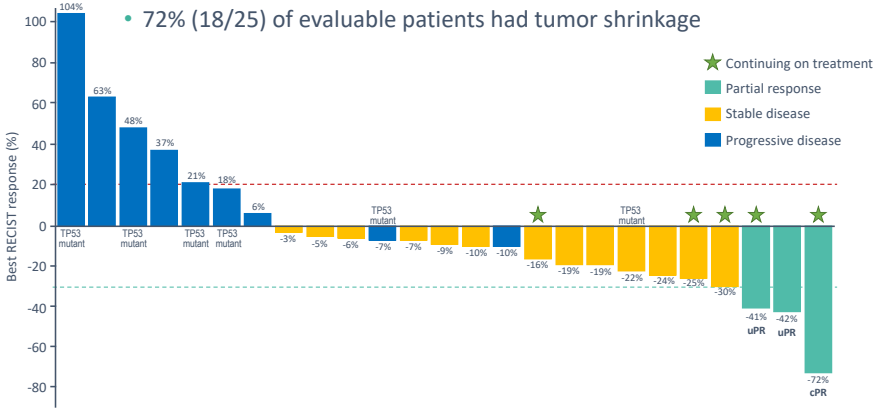
| Characteristic | N = 31 |
|---|---|
| Median age, years (range) | 60 (41–81) |
| Female, n (%) | 31 (100) |
| RECIST v1.1 measurable disease, n (%) | 31 (100) |
| ER+/PGR+, n (%) | 31 (100) |
| Location of lesions, n (%)* | |
| Visceral disease | 25 (81) |
| Bone | 18 (58) |
| Liver | 14 (45) |
| Lymph node | 11 (36) |
| Other | 6 (19) |
| Lines of prior endocrine therapy for metastatic disease, n (%) | |
| ≥1 | 31 (100) |
| ≥2 | 4 (13) |
| Prior CDK4/6 inhibitor-containing therapy, n (%) | 31 (100) |
| Prior chemotherapy, n (%) | |
| Metastatic setting | 7 (23) |
| Adjuvant setting | 10 (32) |
| Neoadjuvant setting | 3 (10) |



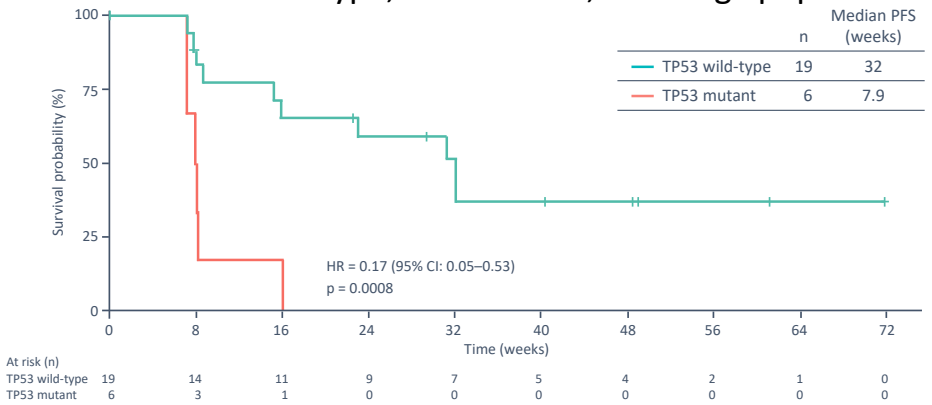

Data cut-off: September 25, 2021

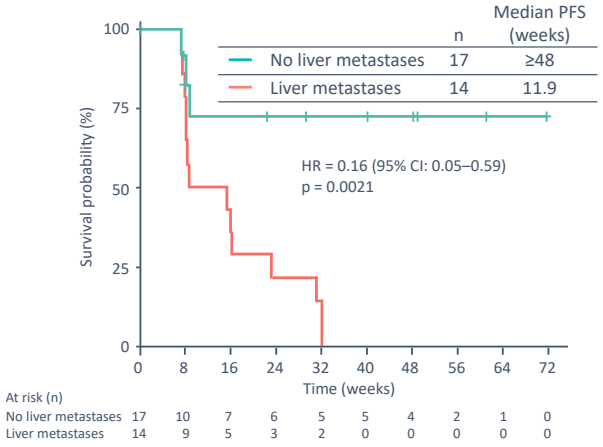
1. Lindeman GJ, et al. J Clin Oncol 2021;39(Suppl.):Abstract 1004; 2. Juric D, et al. Presented at SABCS 2018:Abstract GS3-08

# Clinical Efficacy and Toxicity




Preclinical data indicate that CDK7i activates the p53 pathway in TP53 wild-type, HR+ BC cells, inducing apoptosis




| Adverse event | All grades, n (%) | Grade ≥3, n (%) |
|---|---|---|
| Diarrhea | 28 (90) | 6 (19) |
| Nausea | 25 (81) | 3 (10) |
| Vomiting | 23 (74) | 1 (3) |
| Fatigue | 11 (36) | 1 (3) |
| Decreased appetite | 9 (29) | 0 |
| Abdominal pain | 7 (23) | 0 |
| AST increased | 4 (13) | 0 |
| Dysgeusia | 4 (13) | 0 |
| Headache | 4 (13) | 0 |
| Upper abdominal pain | 4 (13) | 0 |

- 11 had dose reductions
  - 2 discontinued
- 6 discontinued due to AE
- Ondansetron now standard pre-medication

## Next steps

Samuraciclib has been granted fast-track status by the US FDA

Combinations with oral SERDs planned

# FAKTION: trial design

**Eligibility**[a]
- Post-menopausal women
- ER+/HER2– metastatic or unresectable locally advanced breast cancer
- Progression on AI for advanced breast cancer **or** relapse on adjuvant AI
- Maximum 1 line of chemotherapy for metastatic breast cancer (mBC)
- Maximum 3 lines of endocrine therapy for mBC
- Measurable or non-measurable disease
- Type II diabetes allowed if controlled

**Exclusion**
- Prior fulvestrant or PI3K/AKT/mTOR inhibitor therapy

N = R

**N = 69**
**Fulvestrant** 500 mg every 4 weeks + loading dose
**Capivasertib** 400 mg twice daily 4 days on/3 days off from cycle 1 day 15

**N = 71**
**Fulvestrant** 500 mg every 4 weeks + loading dose
**Placebo** twice daily 4 days on/3 days off from cycle 1 day 15

**1:1 allocation balanced on**
- Pathway activation status (*PIK3CA* mutation/low PTEN expression)
- Measurable/no-measurable disease
- Primary/secondary AI resistance

**Primary endpoint**
Investigator-assessed PFS in the intent-to-treat (ITT) population

**Secondary endpoints**
- Safety and toxicity
- Objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS) in the ITT population
- PFS/ORR/CBR in participants with PI3K/AKT/PTEN pathway altered and pathway non-altered tumours

**Statistical considerations**
- Prespecified statistical analysis plan for the updated OS, PFS and biomarker subgroup analyses
- Cox regression adjusted for measurable disease status and level of resistance to AI treatment used to determine hazard ratios (HRs) with 95% confidence intervals (CIs)
- Significance set at the 2-sided 0.05 level

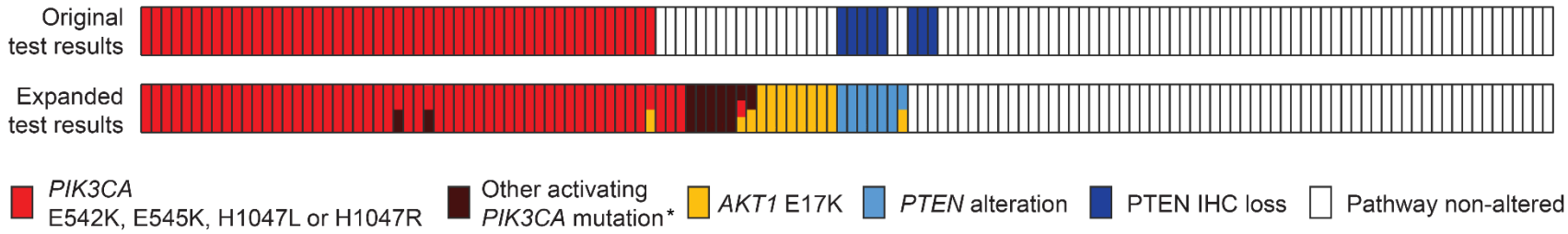
[a]Participants were recruited from 2015–2018 and had no exposure to CDK4/6 inhibitors, which are now first-line standard of care in combination with endocrine therapy.

AI, aromatase inhibitor; CBR, clinical benefit rate; CI, confidence interval; ER, oestrogen receptor; HER2−, human epidermal growth factor receptor 2-negative; HR, hazard ratio; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

RH Jones FRCP PhD

# FAKTION: expanded testing[a] identified pathway alterations in 20 (25%) tumours originally classified as non-altered

- Eight carried *AKT1* E17K (*AKT1* was not tested in the original panel)
- Five had a *PIK3CA* activating mutation not tested in the original panel
- Three had a *PIK3CA* mutation that was tested but not detected by the original panel due to limited sensitivity
- One carried a *PTEN* inactivating alteration
- Three had more than one type of *AKT1*, *PTEN* or *PIK3CA* alteration

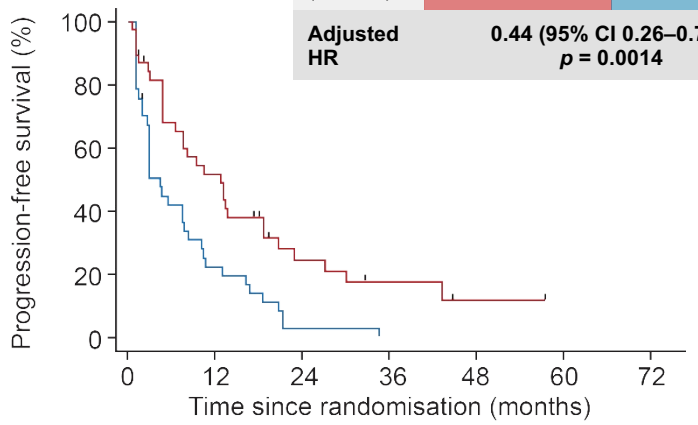



[a]Testing of tissue and/or plama samples.
*R88Q, N345K, C420R, E542K, E545X, Q546X, M1043I, M1043V, H1047X, G1049R (where X represents any change in amino acid residue). IHC, immunohistochemistry.

# FAKTION: PFS in the expanded pathway altered and pathway non-altered subgroups

## Pathway altered

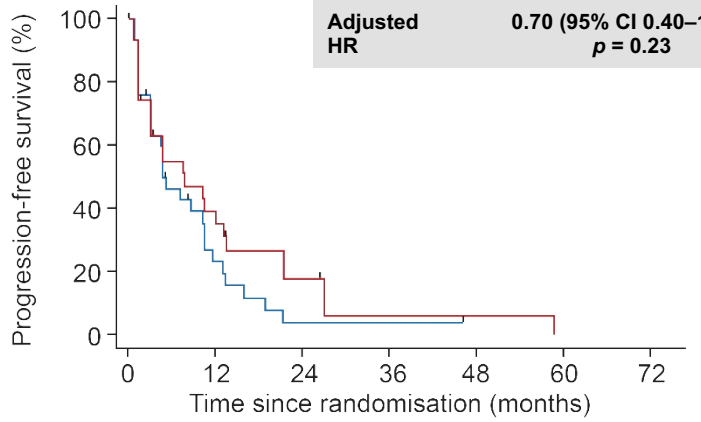
| | Fulvestrant + capivasertib (n = 39) | Fulvestrant + placebo (n = 37) |
|---|---|---|
| Median PFS (95% CI) | 12.8 months (6.6–18.8) | 4.6 months (2.8–7.9) |
| **Adjusted HR** | **0.44 (95% CI 0.26–0.72); *p* = 0.0014** | |




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fulvestrant plus placebo | 37 | 8 | 1 | 0 | 0 | 0 | 0 |
| Fulvestrant plus capivasertib | 39 | 19 | 7 | 3 | 1 | 0 | 0 |

## Pathway non-altered

| | Fulvestrant + capivasertib (n = 30) | Fulvestrant + placebo (n = 34) |
|---|---|---|
| Median PFS (95% CI) | 7.7 months (3.1–13.2) | 4.9 months (3.2–10.5) |
| **Adjusted HR** | **0.70 (95% CI 0.40–1.25); *p* = 0.23** | |




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fulvestrant plus placebo | 34 | 6 | 1 | 1 | 0 | 0 | 0 |
| Fulvestrant plus capivasertib | 30 | 10 | 4 | 1 | 1 | 0 | 0 |

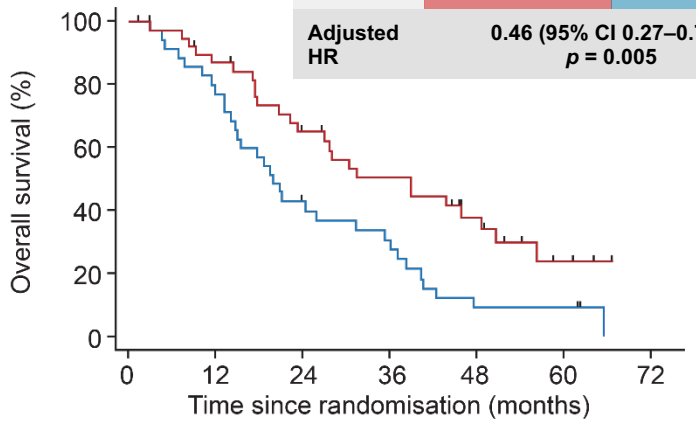
Tick marks on plots show censoring events. CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

DCO Nov 2021

# FAKTION: OS in the expanded pathway altered and pathway non-altered subgroups

## Pathway altered

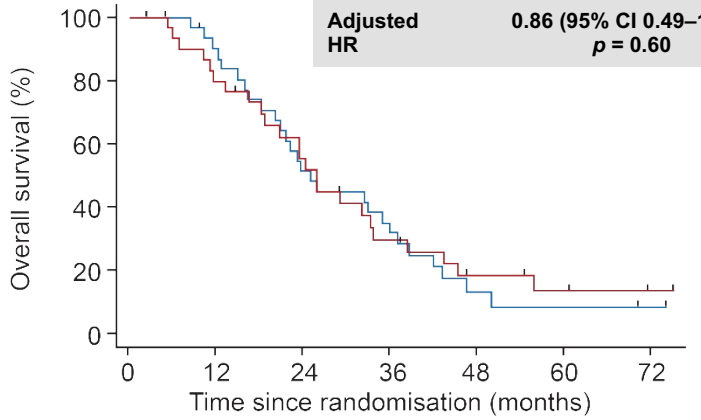
| | Fulvestrant + capivasertib (n = 39) | Fulvestrant + placebo (n = 37) |
|---|---|---|
| Median OS (95% CI) | 38.9 months (23.3–50.7) | 20.0 months (14.8–31.4) |
| **Adjusted HR** | **0.46 (95% CI 0.27–0.79); *p* = 0.005** | |




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fulvestrant plus placebo | 37 | 27 | 14 | 10 | 3 | 3 | 0 |
| Fulvestrant plus capivasertib | 39 | 33 | 23 | 17 | 10 | 3 | 0 |

## Pathway non-altered

| | Fulvestrant + capivasertib (n = 30) | Fulvestrant + placebo (n = 34) |
|---|---|---|
| Median OS (95% CI) | 26.0 months (18.4–33.8) | 25.2 months (20.3–36.2) |
| **Adjusted HR** | **0.86 (95% CI 0.49–1.52); *p* = 0.60** | |



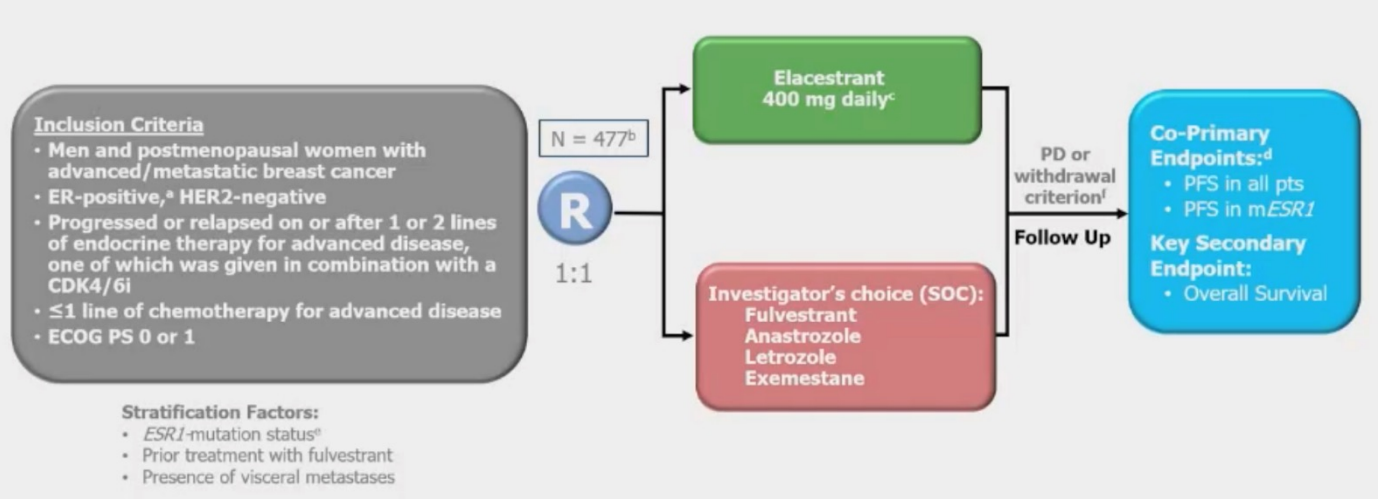

| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fulvestrant plus placebo | 34 | 28 | 16 | 11 | 3 | 2 | 1 |
| Fulvestrant plus capivasertib | 30 | 24 | 16 | 8 | 5 | 3 | 1 |

Tick marks on plots show censoring events. CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

DCO Nov 2021

# EMERALD: Elacestrant vs TPC in ER+/HER2- MBC

- Elacestrant (RAD1901) is an oral SERD
- Previously demonstrated single-agent activity in patients following CDK4/6i and fulvestrant
- Confirmed activity in tumors with ESR1 mutations



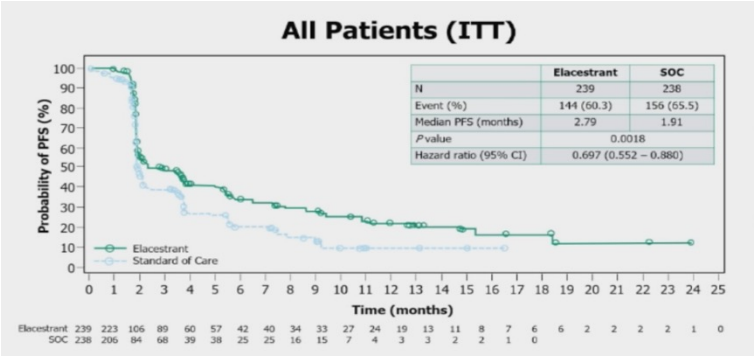

**Key Patient and Disease Characteristics:**

- Median age 63y
- Visceral mets 68–73%
- Bone only disease 12–16%
- 1 prior line of ET 54–64%
- 1 prior line of CT 20–28%

Bardia et al, SABCS 2021.

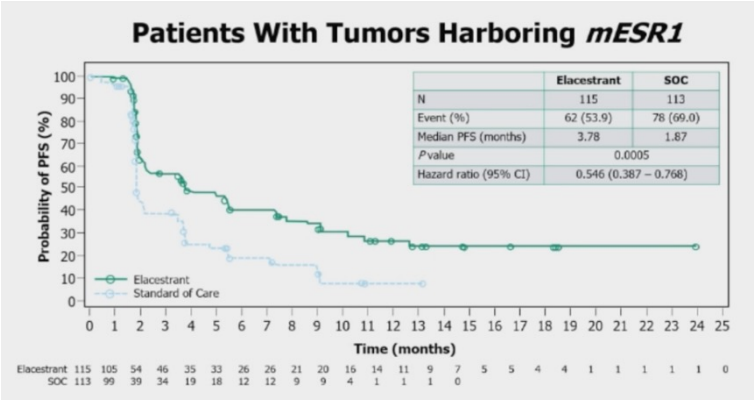
# EMERALD: Efficacy

## Progression-free Survival




**30% improvement in mPFS with elacestrant**

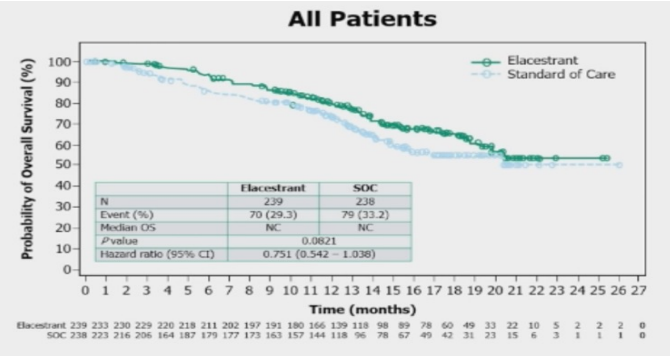
Elacestrant vs fulvestrant
mPFS 2.8mo vs 1.9mo
HR 0.684 (95% CI, 0.521–0.897)
p=0.0049

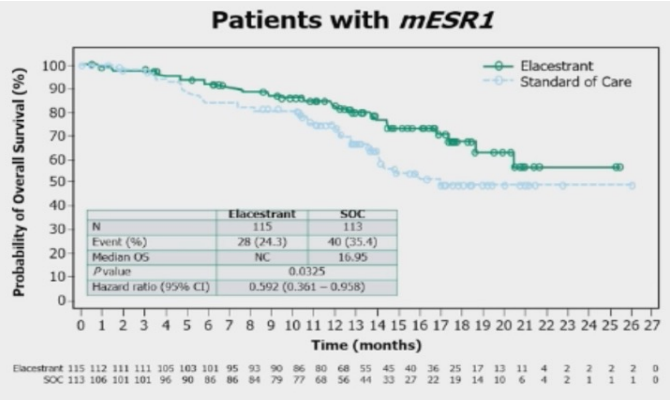



**45% improvement in mPFS with elacestrant**

Elacestrant vs fulvestrant
mPFS 3.78mo vs 1.87mo
HR 0.504 (95% CI, 0.341–0.741)
p=0.0005

## Overall Survival




Bardia et al, SABCS 2021.

# EMERALD: Toxicity

| | Elacestrant N = 237, n (%) | | SOC | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total N = 229, n (%) | | Fulvestrant N = 161, n (%) | | AI N = 68, n (%) | |
| **Preferred Term** | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Nausea | 83 (35.0) | 6 (2.5) | 43 (18.8) | 2 (0.9) | 26 (16.1) | - | 17 (25.0) | 2 (2.9) |
| Fatigue | 45 (19.0) | 2 (0.8) | 43 (18.8) | 2 (0.9) | 35 (21.7) | 1 (0.6) | 8 (11.8) | 1 (1.5) |
| Vomiting | 45 (19.0) | 2 (0.8) | 19 (8.3) | - | 12 (7.5) | - | 7 (10.3) | - |
| Decreased appetite | 35 (14.8) | 2 (0.8) | 21 (9.2) | 1 (0.4) | 12 (7.5) | - | 9 (13.2) | 1 (1.5) |
| Arthralgia | 34 (14.3) | 2 (0.8) | 37 (16.2) | - | 28 (17.4) | - | 9 (13.2) | - |
| Diarrhea | 33 (13.9) | - | 23 (10.0) | 2 (0.9) | 14 (8.7) | 1 (0.6) | 9 (13.2) | 1 (1.5) |
| Back pain | 33 (13.9) | 6 (2.5) | 22 (9.6) | 1 (0.4) | 16 (9.9) | 1 (0.6) | 6 (8.8) | - |
| Aspartate aminotransferase increased | 31 (13.1) | 4 (1.7) | 28 (12.2) | 2 (0.9) | 20 (12.4) | 2 (1.2) | 8 (11.8) | - |
| Headache | 29 (12.2) | 4 (1.7) | 26 (11.4) | - | 18 (11.2) | - | 8 (11.8) | - |
| Constipation | 29 (12.2) | - | 15 (6.6) | - | 10 (6.2) | - | 5 (7.4) | - |
| Hot flush | 27 (11.4) | - | 19 (8.3) | - | 15 (9.3) | - | 4 (5.9) | - |
| Dyspepsia | 24 (10.1) | - | 6 (2.6) | - | 4 (2.5) | - | 2 (2.9) | - |
| Alanine aminotransferase increased | 22 (9.3) | 5 (2.1) | 23 (10.0) | 1 (0.4) | 17 (10.6) | - | 6 (8.8) | 1 (1.5) |

Treatment-related AEs leading to discontinuation were infrequent (E 3.4% vs. TPC 0.9%)

# Conclusions: HR+ HER2- Metastatic Breast Cancer

**How to improve efficacy of standard options?** CDK 4/6 inhibitors

- 1L OS improvement with ribociclib
- 1L palbociclib no OS improvement (22% pts ET-resistant)
- Ribociclib plus fulvestrant superior to fulvestrant post-progression on mainly palbociclib + AI – phase II trial

**How to overcome resistance?** mTOR or PIK3CA inhibition or SERD

- Everolimus approved for use post-progression on NSAI with everolimus
- Alpelisib + fulvestrant active post-progression on CDK 4/6 inhibitor with *PIK3CA* mutation
- Elacestrant more effective than fulvestrant/AI post CDK 4/6 inhibitor, especially with *ESR1* mutation – multiple oral SERDs in development
- Capivasertib, samuraciclib, enobasarm (AR agonist) hold promise

**New Therapies for Endocrine Therapy-Resistant HR+ HER2-MBC**

- Trastuzumab deruxtecan for HER2 low
- Sacituzumab