# ORAL SERD

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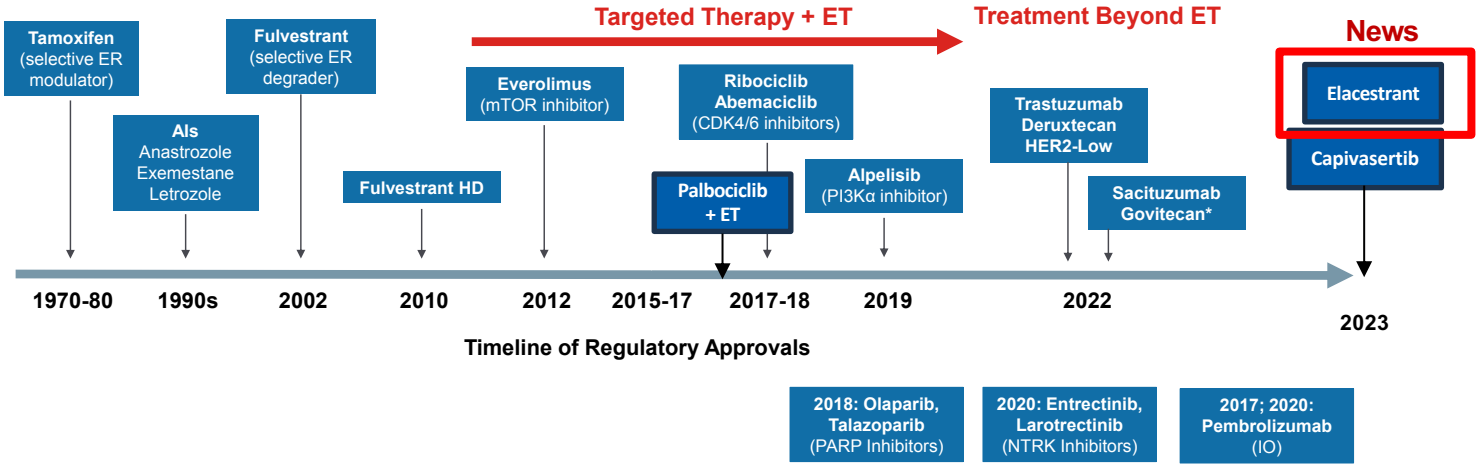
# DECLARATION OF INTERESTS

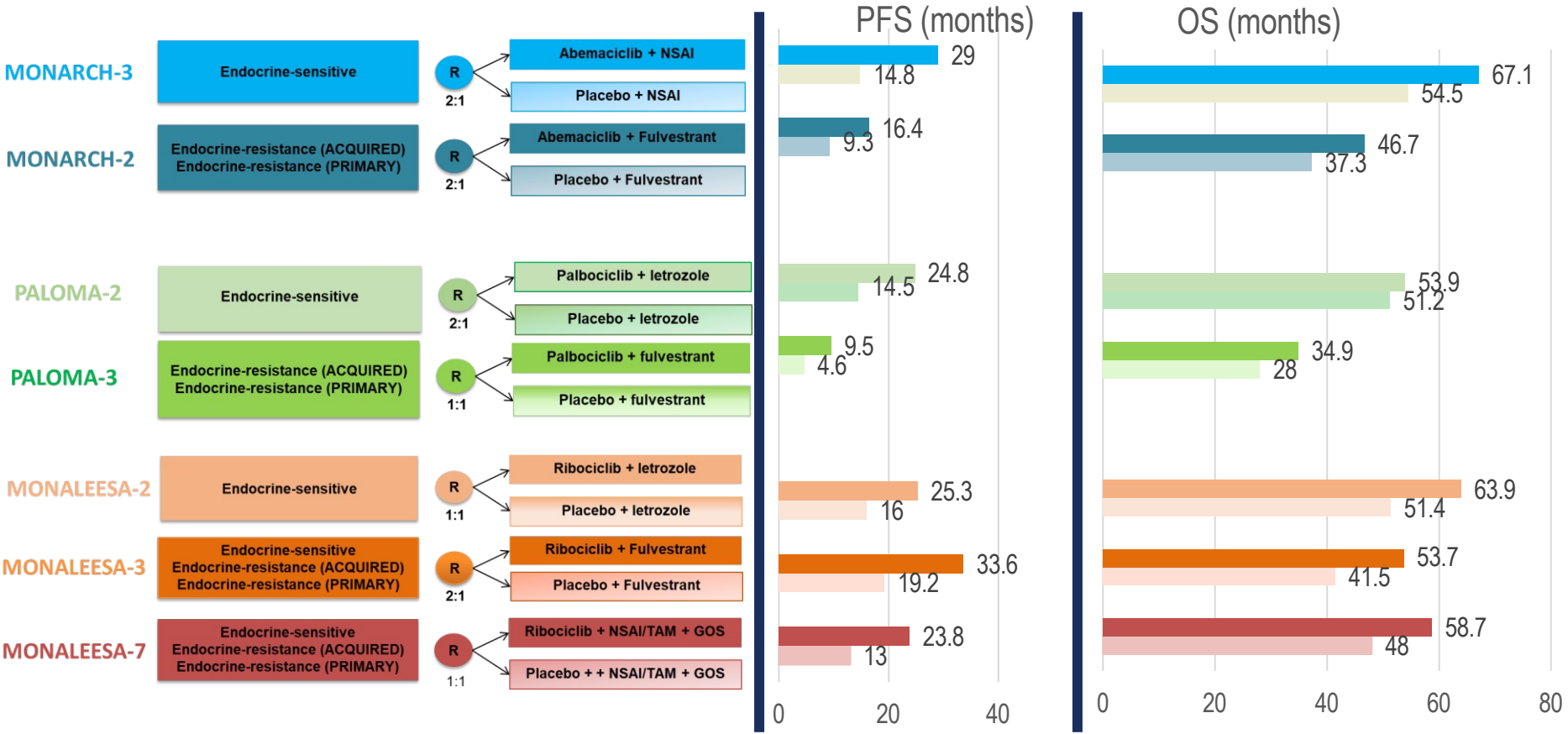
Honoraria for advisory board and consultancy: Roche, Novartis, Lilly, Seagen, Daiichi Sankyo, Astra Zeneca, Merck, Exact Sciences

# EVOLVING TREATMENT LANDSCAPE OF ER+ MBC



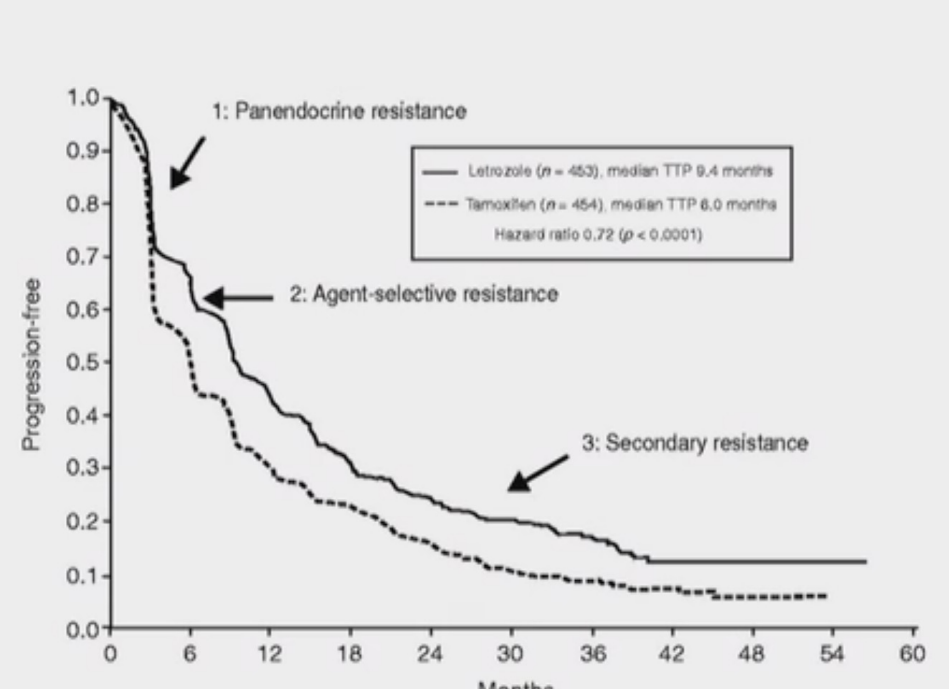

' NCCN endorsed. Anastrozole PI. Exemestane PI. Letrozole PI. Fulvestrant PI. Everolimus PI. Palbociclib PI. Ribociclib PI. Abemaciclib PI. Alpelisib PI. Brufsky. Cancer Treat Rev. 2017;59:22. Lim E. Oncology ¦Williston Park). 2012;26:688. Croxtall. Drugs. 2011;71:363. Cohen. Oncologist. 2001;6:4. Adapted from http://www.nccn.org/professionals/physician_gls/pdf/breast.pdfJM. NCCN Guidelines Breast Version 4.2022.

# THE TRASFORMATIVE EFFECT OF CDK4/6 INHIBITORS




Finn RS, Lancet Oncol. 2015; Finn RS, N Engl J Med. 2016; G.N. Hortobagyi, NEJM 2016; Goetz, MP JCO 2017; Slamon, JCO 2018; Tripathy D, Lancet Oncol. 2018, Goetz MPI, ESMO 2022

# BUT THE CDK4/6 ET-RESISTANCE STILL OCCURS




**PRIMARY ENDOCRINE RESISTANCE**

- Relapse while on the first 2 years of adjuvant ET
- PD within the first 6 months of first-line ET for ABC, while on ET

**SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE**

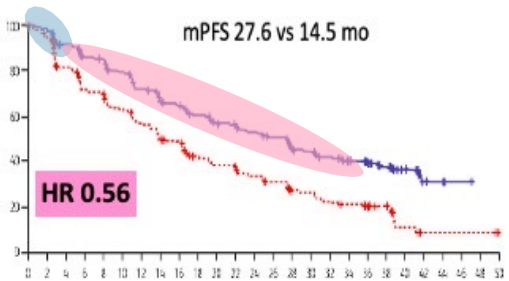
- Relapse while on adjuvant ET but after the first 2 years
- Relapse within 12 months of completing adjuvant ET
- PD ≥6 months after initiating ET for ABC, while on ET

Cardoso, Ann Oncol 2020

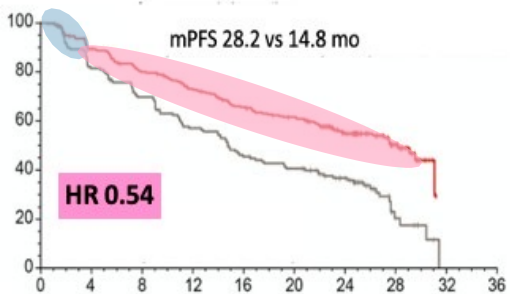
Mouridsen, J Clin Oncol 2001; Ellis, The Oncologist 2004

# THE CDK4/6 ET-RESISTANCE IS THE RULE

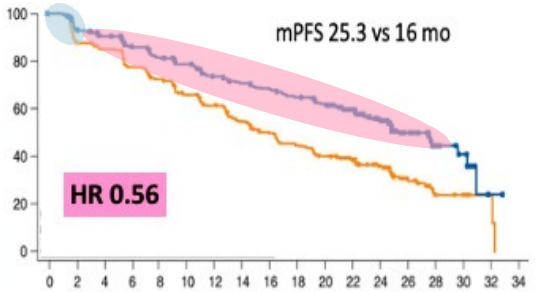
**PALOMA-2** (n=666) [1,2]



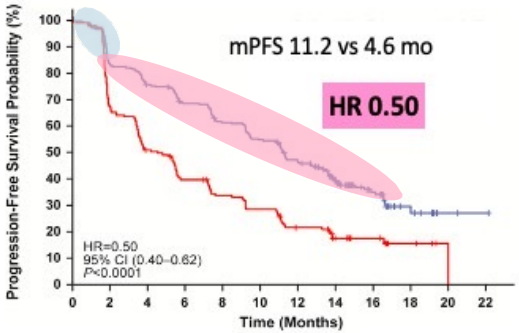

**MONARCH-3** (n=493) [3,4]



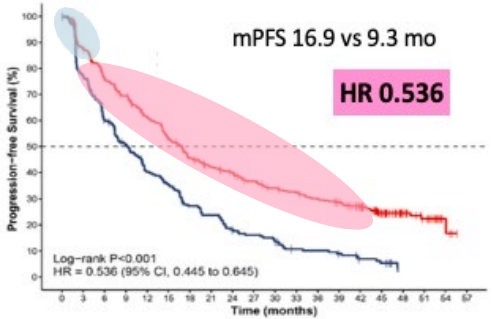

**MONALEESA-2** (n=668) [5,6]



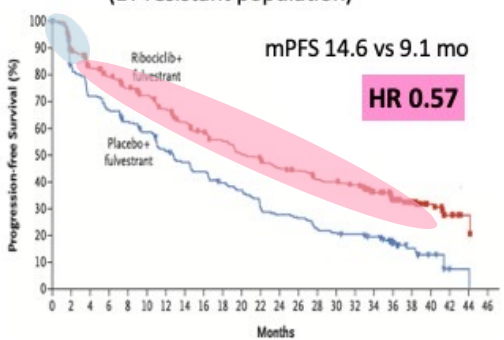

**PALOMA-3** (n=521) [7]




**MONARCH-2** (n=669) [8]

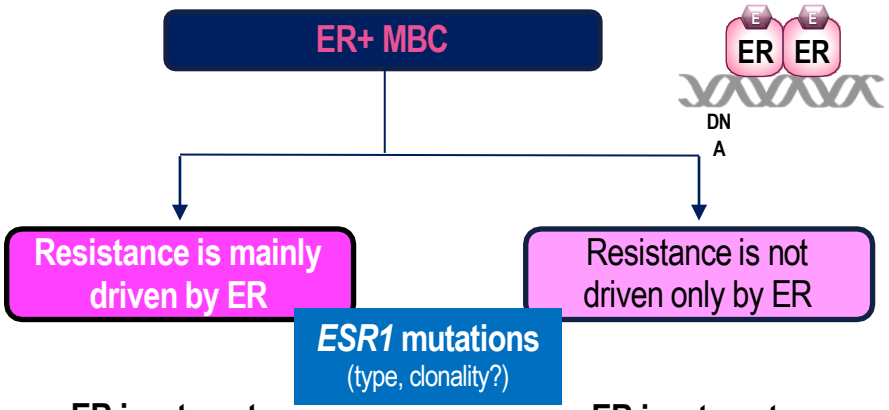



**MONALEESA-3** (n=346) [9]
(ET-resistant population)



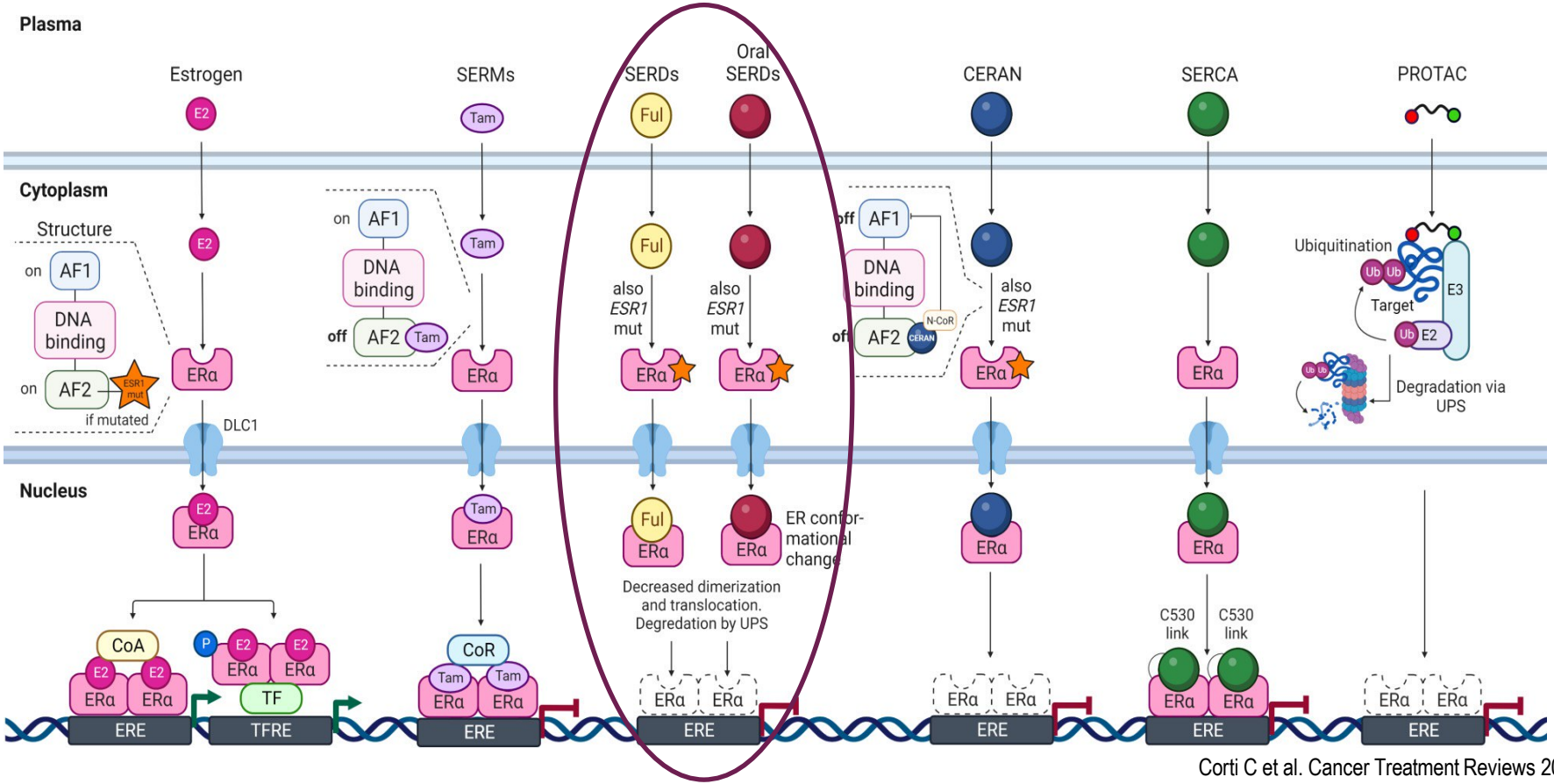

1 Finn, NEJM 2016.
2 Rugo, Breast Cancer Res Treat, 2019.
3 Goetz, JCO 2017.
4 Johnston, NPJ Breast Cancer 2019.
5 Hortobagyi, N EJM 2016.
6 Hortobagyi, Ann Oncol 2018.
7 Turner, NEJM 2020.
8 Sledge, JAMA Oncol 2020.
9 Slamon, NEJM 2020.

# HOW TO DEAL WITH ENDOCRINE RESISTANCE




Courtesy of Carmine De Angelis

# ORAL SERDs




Corti C et al. Cancer Treatment Reviews 2023

# ORAL SERDs IN THE CLINIC

| | EMERALD | SERENA-2 | EMBER-3 | AMEERA-3 | acelERA |
|---|---|---|---|---|---|
| **Treatment** | **Elacestrant** | **Camizestrant** | **Imlunestrant +/-** abemaciclib | **Amcenestrant** | **Giredestrant** |
| **Control Arm** | fulvestrant / AIs | fulvestrant | fulvestrant / exemestane | fulvestrant / AIs / tamoxifen | fulvestrant / AIs |
| **Phase (n)** | Phase 3 (478) | Phase 2 (240) | Phase 3 (800) | Phase 2 (367) | Phase 2 (303) |
| **Patients** | Men or postmenopausal women | Postmenopausal women | Men or postmenopausal women | Men or women (any menopausal status) | Men or women (any menopausal status) |
| **Prior CDK4/6i** | **Required (100%)** | Permitted | Permitted | Permitted (79.7%) | Permitted (42%) |
| **Allowed Prior Fulvestrant** | **YES** | NO | NO | YES | YES |
| **Allowed Prior Chemotherapy in mBC** | **YES** | YES | NO | YES | YES |
| **Data readout** | **Positive (Registrational)** | Positive (Non-Registrational) | Ongoing | Negative | Negative |

AI, aromatase inhibitor.

Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium (SABCS) 2022; December 6-10, 2022; San Antonio, TX. Presentation GS3-01.

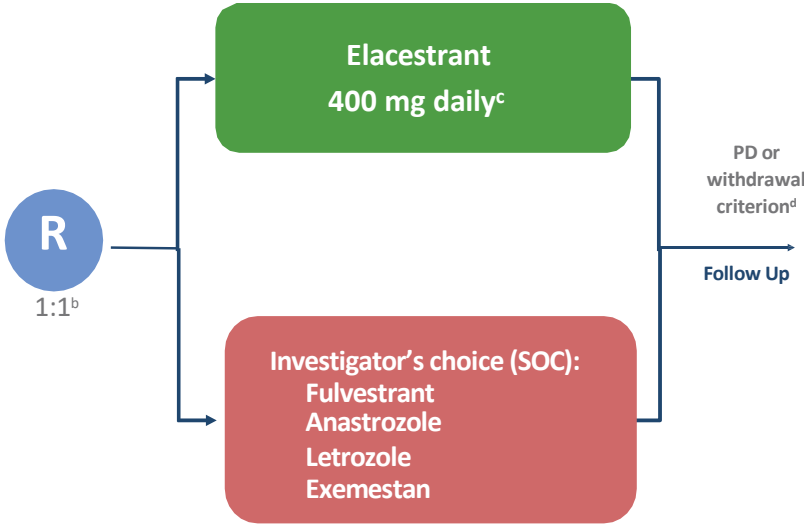
# EMERALD: STUDY DESIGN

**Inclusion Criteria**

- Men and postmenopausal women with advanced/metastatic breast cancer
- ER-positive,[a] HER2-negative
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy for advanced disease, one of which was given in combination with a CDK4/6i
- ≤1 line of chemotherapy for advanced disease
- ECOG PS 0 or 1

**Stratification Factors:**

- *ESR1*-mutation status[f]
- Prior treatment with fulvestrant
- Presence of visceral metastases




**Two Primary Endpoints:[e]**

- PFS in all pts
- PFS in *ESR1*-mut

ESR1 mut 48%, Lung/liver mets 68%, CT in ABC 20%, Prior fulvestrant 30%

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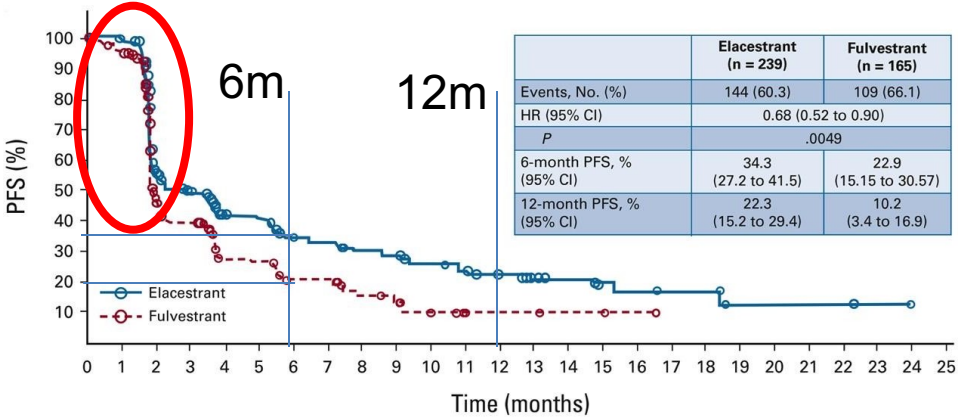
# EMERALD PRIMARY ENDPOINT: PFS

## All Patients

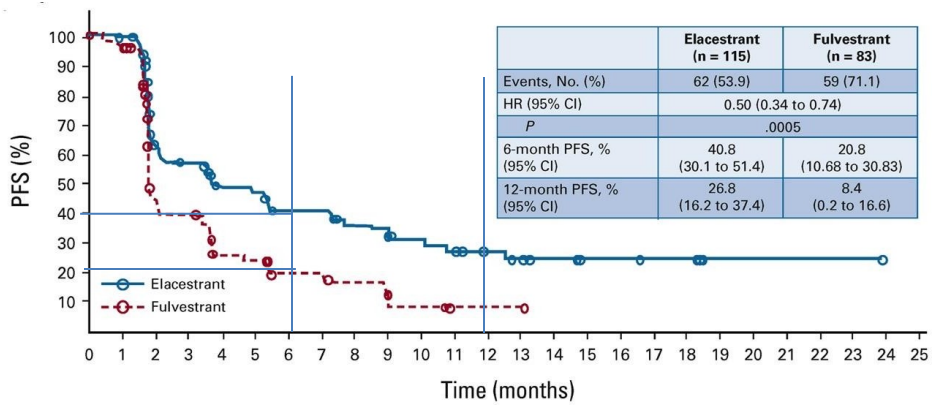



| | Elacestrant (n = 239) | Fulvestrant (n = 165) |
|---|---|---|
| Events, No. (%) | 144 (60.3) | 109 (66.1) |
| HR (95% CI) | 0.68 (0.52 to 0.90) | |
| *P* | .0049 | |
| 6-month PFS, % (95% CI) | 34.3 (27.2 to 41.5) | 22.9 (15.15 to 30.57) |
| 12-month PFS, % (95% CI) | 22.3 (15.2 to 29.4) | 10.2 (3.4 to 16.9) |

No. at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Elacestrant | 239 | 106 | 60 | 42 | 34 | 27 | 19 | 11 | 7 | 6 | 2 | 2 | 0 |
| Fulvestrant | 165 | 62 | 33 | 21 | 14 | 5 | 2 | 1 | 0 | | | | |

## Patients with ESR1mut




| | Elacestrant (n = 115) | Fulvestrant (n = 83) |
|---|---|---|
| Events, No. (%) | 62 (53.9) | 59 (71.1) |
| HR (95% CI) | 0.50 (0.34 to 0.74) | |
| *P* | .0005 | |
| 6-month PFS, % (95% CI) | 40.8 (30.1 to 51.4) | 20.8 (10.68 to 30.83) |
| 12-month PFS, % (95% CI) | 26.8 (16.2 to 37.4) | 8.4 (0.2 to 16.6) |

No. at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Elacestrant | 115 | 54 | 35 | 26 | 21 | 16 | 11 | 7 | 5 | 4 | 1 | 1 | 0 |
| Fulvestrant | 83 | 29 | 16 | 10 | 8 | 3 | 1 | 0 | | | | | |

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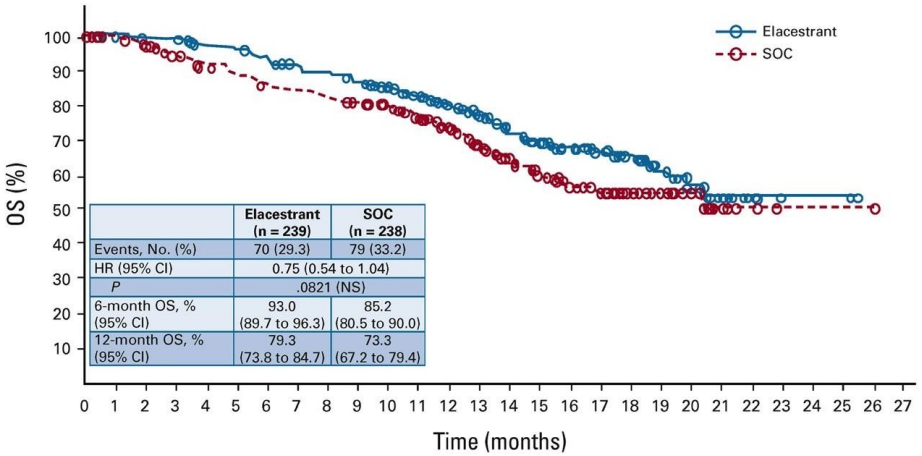
# EMERALD: OS (INTERIM ANALYSIS)

## All Patients

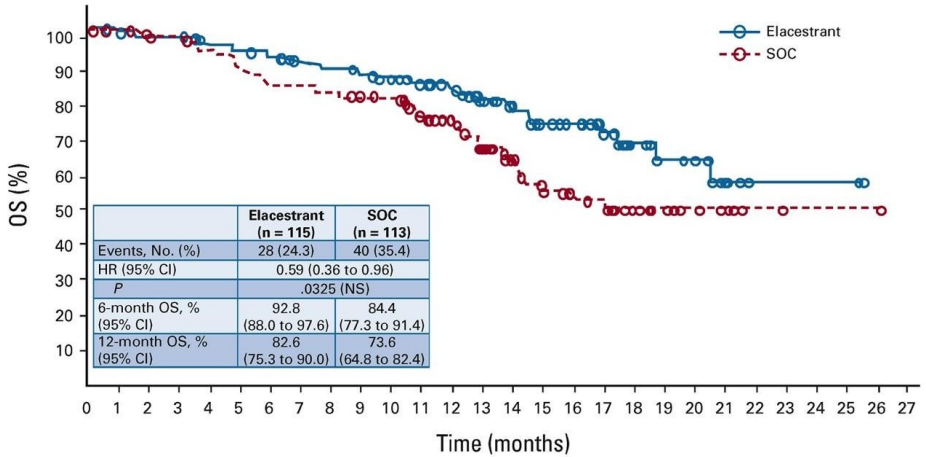



| | Elacestrant (n = 239) | SOC (n = 238) |
|---|---|---|
| Events, No. (%) | 70 (29.3) | 79 (33.2) |
| HR (95% CI) | 0.75 (0.54 to 1.04) | |
| *P* | .0821 (NS) | |
| 6-month OS, % (95% CI) | 93.0 (89.7 to 96.3) | 85.2 (80.5 to 90.0) |
| 12-month OS, % (95% CI) | 79.3 (73.8 to 84.7) | 73.3 (67.2 to 79.4) |

No. at risk:

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Elacestrant | 239 | 233 | 230 | 229 | 220 | 218 | 211 | 202 | 197 | 191 | 180 | 166 | 139 | 118 | 98 | 89 | 78 | 60 | 49 | 33 | 22 | 10 | 5 | 2 | 2 | 2 | 0 |
| SOC | 238 | 223 | 216 | 206 | 164 | 187 | 179 | 177 | 173 | 163 | 157 | 144 | 118 | 96 | 78 | 67 | 49 | 42 | 31 | 23 | 15 | 6 | 3 | 1 | 1 | 1 | 0 |

## Patients with ESR1mut




| | Elacestrant (n = 115) | SOC (n = 113) |
|---|---|---|
| Events, No. (%) | 28 (24.3) | 40 (35.4) |
| HR (95% CI) | 0.59 (0.36 to 0.96) | |
| *P* | .0325 (NS) | |
| 6-month OS, % (95% CI) | 92.8 (88.0 to 97.6) | 84.4 (77.3 to 91.4) |
| 12-month OS, % (95% CI) | 82.6 (75.3 to 90.0) | 73.6 (64.8 to 82.4) |

No. at risk:

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Elacestrant | 115 | 112 | 111 | 111 | 105 | 103 | 101 | 95 | 93 | 90 | 86 | 80 | 68 | 55 | 45 | 40 | 36 | 25 | 17 | 13 | 11 | 4 | 2 | 2 | 2 | 2 | 0 |
| SOC | 113 | 106 | 101 | 101 | 96 | 90 | 86 | 86 | 84 | 79 | 77 | 68 | 56 | 44 | 33 | 27 | 22 | 19 | 14 | 10 | 6 | 4 | 2 | 1 | 1 | 1 | 0 |

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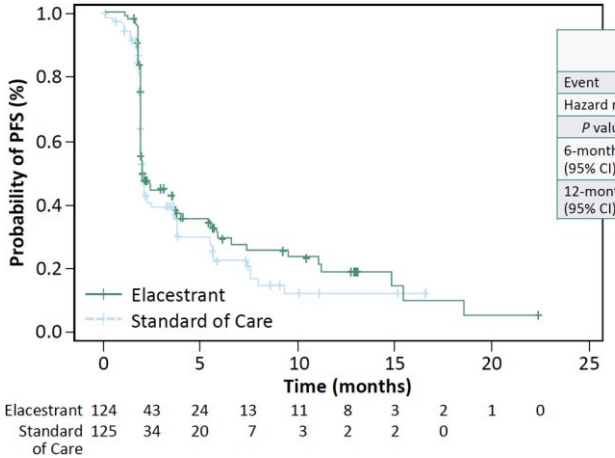
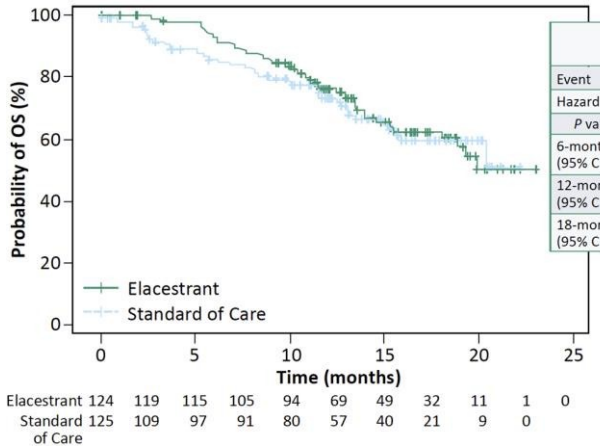
# EMERALD: RESULTS IN ESR1 WT

PFS




| | Elacestrant (N=124) | SOC (N=125) |
|---|---|---|
| Event | 82 | 78 |
| Hazard ratio (95% CI) | 0.863 (0.628 – 1.186) | |
| *P* value | 0.308 | |
| 6-month PFS, % (95% CI) | 28.58 (18.98 – 38.18) | 21.85 (12.71 – 30.99) |
| 12-month PFS, % (95% CI) | 18.16 (8.60 – 27.73) | 11.22 (2.82 – 19.62) |

OS




| | Elacestrant (N=124) | SOC (N=125) |
|---|---|---|
| Event | 42 | 39 |
| Hazard ratio (95% CI) | 0.915 (0.589 – 1.424) | |
| *P* value | 0.691 | |
| 6-month OS, % (95% CI) | 93.2 (97.5 – 100.0) | 86.2 (79.9 – 92.5) |
| 12-month OS, % (95% CI) | 76.4 (68.5 – 84.2) | 73.3 (64.9 – 81.7) |
| 18-month OS, % (95% CI) | 62.7 (52.9 – 72.5) | 59.5 (48.8 – 70.3) |

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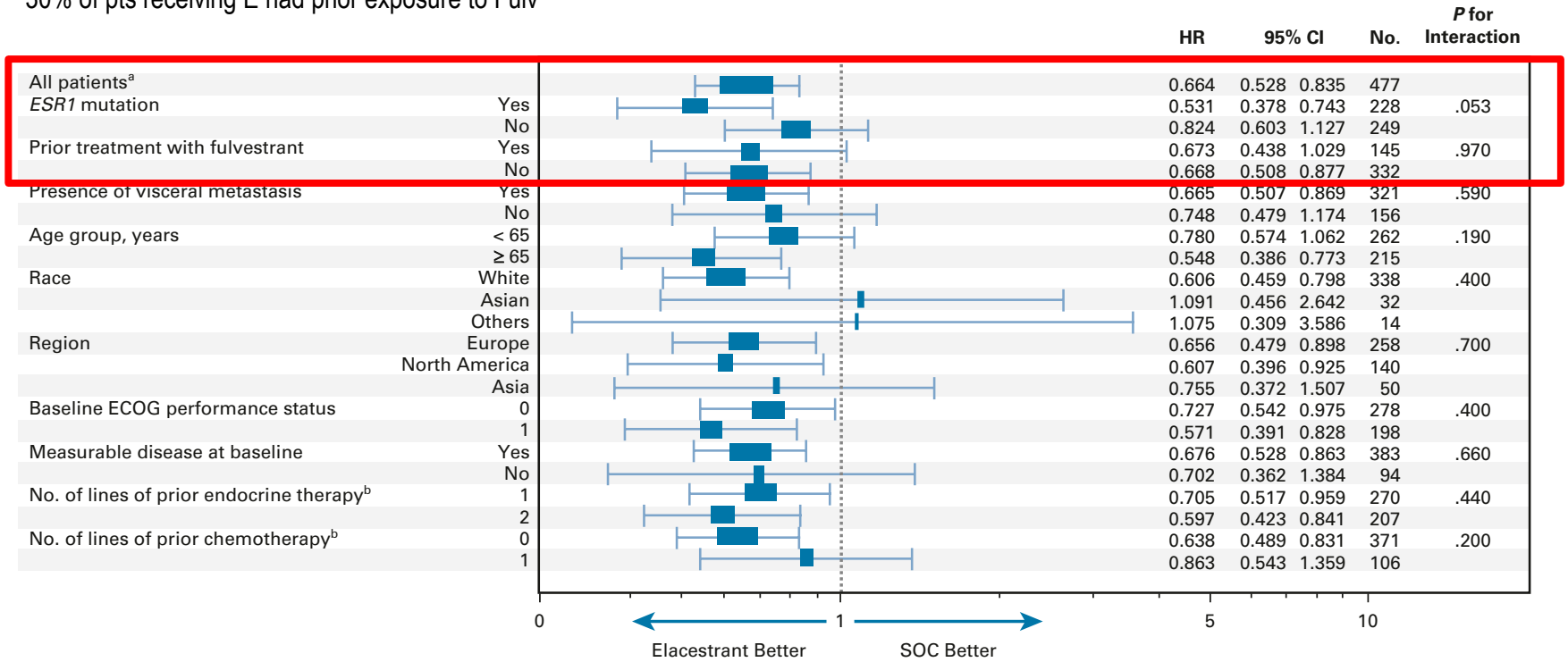
# SUBGROUP ANALYSIS OF PFS

30% of pts receiving E had prior exposure to Fulv

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# PFS ANALYSIS BY DURATION OF CDK4/6i

| Duration on CDK4/6i in the Metastatic Setting | < 6 Months | | 6- 12 Months | | 12 - 18 Months | | ≥ 18 Months | |
|---|---|---|---|---|---|---|---|---|
| All Patients | Elacestrant (n=29) | SOC Hormonal Therapy (n=29) | Elacestrant (n=52) | SOC Hormonal Therapy (n=46) | Elacestrant (n=52) | SOC Hormonal Therapy (n=40) | Elacestrant (n=98) | SOC Hormonal Therapy (n=119) |
| Median PFS, months (95% CI) | 3.55 (1.87 - 9.43) | 1.87 (1.74 - 2.20) | 1.91 (1.84 - 1.94) | 1.87 (1.81 - 2.14) | 3.52 (1.87 - 7.29) | 1.84 (1.84 - 1.87) | 5.45 (2.33 - 8.61) | 3.29 (1.87 - 3.71) |
| PFS rate at 6 months, % (95% CI) | 34.54 (9.75 - 59.33) | 19.52 (4.21 -34.83) | 14.91 (3.12 - 26.70) | 12.79 (0.46 - 25.11) | 35.40 (19.80 - 51.00) | 12.83 (0.09 - 25.56) | 44.72 (33.24 - 56.20) | 25.12 (15.13 -35.10) |
| PFS rate at 12 months, % (95% CI) | 23.03 (0.00 - 47.78) | 11.71 (0.00-24.15) | 7.46 (0.00 - 19.35) | NA | 24.78 (8.07 - 41.49) | 4.28 (0.00 - 12.33) | 26.70 (15.61 - 37.80) | 8.23 (0.00 - 17.07) |
| PFS rate at 18 months, % (95% CI) | 11.51 (0.00 - 31.71) | 11.7 (0.00 -24.15) | 7.46 (0.00 - 19.35) | NA | 18.59 (2.22 - 34.95) | NA | 21.03 (9.82 - 32.23) | 4.11 (0.00 - 11.33) |
| Hazard ratio (95% CI) | 0.709 (0.347 - 1.405) | | 1.070 (0.638 - 1.814) | | 0.367 (0.204 - 0.654) | | 0.703 (0.482 - 1.019) | |
| ESR1-mut | Elacestrant (n=9) | SOC Hormonal Therapy (n=8) | Elacestrant (n=25) | SOC Hormonal Therapy (n=21) | Elacestrant (n=23) | SOC Hormonal Therapy (n=25) | Elacestrant (n=55) | SOC Hormonal Therapy (n=56) |
| Median PFS, months (95% CI) | 1.87 (1.64 - . ) | 1.87 (1.68 - 5.55) | 1.91 (1.87 - 2.79) | 1.84 (1.68 - 3.45) | 5.49 (1.94 - . ) | 1.84 (1.84 - 1.94) | 8.61 (5.45 - 16.89) | 2.10 (1.87 - 3.75) |
| PFS rate at 6 months, % (95% CI) | NA | 14.29 (0.00 -40.21) | 5.46 (0.00 - 15.78) | 7.22 (0.00 - 20.35) | 49.32 (25.11 - 73.53) | 13.65 (0.00 - 30.31) | 58.57 (43.02 - 74.12) | 27.06 (13.05 - 41.07) |
| PFS rate at 12 months, % (95% CI) | NA | 0 | 0 | 0 | 36.99 (9.28 - 64.70) | 6.82 (0.00 - 19.43) | 35.79 (19.54 - 52.05) | 7.73 (0.00 - 20.20) |
| PFS rate at 18 months, % (95% CI) | NA | 0 | 0 | 0 | 24.66 (0.00 - 51.69) | NA | 30.68 (13.94 - 47.42) | 0 |
| Hazard ratio (95% CI) | 1.565 (0.424 - 5.769) | | 1.122 (0.547 - 2.347) | | 0.302 (0.126 - 0.677) | | 0.466 (0.270 - 0.791) | |

Bardia A, et al., SABCS 2022

# SAFETY PROFILE

| AEs[c] Occurring in ≥ 10% of Patients in Any Arm | Elacestrant | | Total | | Fulvestrant | | AI | |
|---|---|---|---|---|---|---|---|---|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Nausea | 83 (35.0)[d] | 6 (2.5) | 43 (18.8) | 2 (0.9) | 26 (16.1) | 0 | 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)[e] | 2 (0.8) | 19 (8.3) | 0 | 12 (7.5) | 0 | 7 (10.3) | 0 |
| Decreased appetite | 35 (14.8) | 2 (0.8) | 21 (9.2) | 1 (0.4) | 12 (7.5) | 0 | 9 (13.2) | 1 (1.5) |
| Arthralgia | 34 (14.3) | 2 (0.8) | 37 (16.2) | 0 | 28 (17.4) | 0 | 9 (13.2) | 0 |
| Diarrhea | 33 (13.9) | 0 | 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) | 0 |
| AST increased | 31 (13.1) | 4 (1.7) | 28 (12.2) | 2 (0.9) | 20 (12.4) | 2 (1.2) | 8 (11.8) | 0 |
| Headache | 29 (12.2) | 4 (1.7) | 26 (11.4) | 0 | 18 (11.2) | 0 | 8 (11.8) | 0 |
| Constipation | 29 (12.2) | 0 | 15 (6.6) | 0 | 10 (6.2) | 0 | 5 (7.4) | 0 |
| Hot flush | 27 (11.4) | 0 | 19 (8.3) | 0 | 15 (9.3) | 0 | 4 (5.9) | 0 |
| Dyspepsia | 24 (10.1) | 0 | 6 (2.6) | 0 | 4 (2.5) | 0 | 2 (2.9) | 0 |
| ALT increased | 22 (9.3) | 5 (2.1) | 23 (10.0) | 1 (0.4) | 17 (10.6) | 0 | 6 (8.8) | 1 (1.5) |

| Event | Elacestrant (n = 237) | SOC | | |
|---|---|---|---|---|
| | | Total (n = 229) | Fulvestrant (n = 161) | AI (n = 68) |
| Any AE | 218 (92.0) | 197 (86.0) | 144 (89.4) | 53 (77.9) |
| Grade 3 and 4[a] | 64 (27.0) | 47 (20.5) | 33 (20.5) | 14 (20.6) |
| Grade 5[b] | 4 (1.7) | 6 (2.6) | 5 (3.1) | 1 (1.5) |
| Leading to dose reduction | 7 (3.0) | 0 | 0 | Not applicable |
| Leading to study drug discontinuation | 15 (6.3) | 10 (4.4) | 6 (3.7) | 4 (5.9) |

Bidard et al, JCO 2022

# EMERALD CONCLUSION

EMERALD demonstrated that elacestrant as a single agent reduces the risk of progression or death, as compared with current SOC single-agent endocrine therapies.

Therefore, when single-agent endocrine therapy is appropriate at a later line, elacestrant is a more effective option than fulvestrant or an AI

Competitive treatments in case of PI3K and/or AKT alteration with double ET/TT

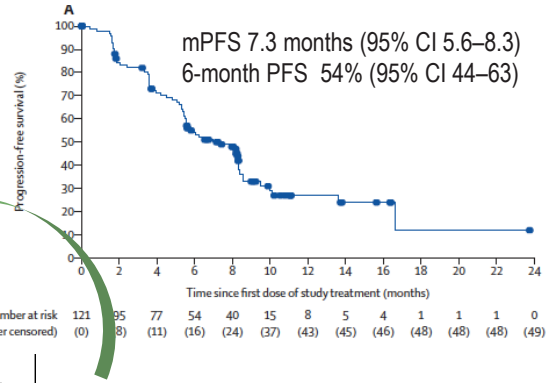
# ALPELISIB + ET

## BYlieve Ph2 Trial

Alpelisib following progression on or after previous therapy, including CDK4/6 inhibitors

**Fulvestrant + Alpelisib**
**N=127**
**121 patients centrally confirmed *PIK3CA* mutation**

Local or central testing of tumour tissue or plasma




mPFS 7.3 months (95% CI 5.6–8.3)
6-month PFS 54% (95% CI 44–63)

**Supplementary Table 5. Comparison of matching methods**

| | N | | Alpelisib + Fulvestrant m-PFS, mo (95% CI) | Standard Treatment (Flatiron Health/FMI CGDB) m-rwPFS, mo (95% CI) | *P* Value |
|---|---|---|---|---|---|
| | BYLieve Cohort A | Real-world Cohort | | | |
| Unadjusted results | 120[a] | 95 | 7·3 (5·6-8·3) | 3·6 (3·1-6·1) | 0·005 |
| Weighting by odds[b] | 120[a] | 116 | 7·3 (5·3-9·2)[c] | 3·7 (2·2-5·3)[c] | 0·004 |
| 1:1 greedy nearest neighbour matching | 76 | 76 | 8·0 (5·6-8·6) | 3·5 (3·0-5·4) | 0·004[d] |
| 1:1 exact matching | 61 | 61 | 6·5 (5·3-8·3) | 3·4 (2·9-3·9) | 0·008[d] |

Flatiron Health/FMI CGDB, US Flatiron Health-Foundation Medicine Clinico-genomic Database; m-PFS, median progression-free survival; m-rwPFS, median-real-world progression-free survival.

Post-hoc exploratory matched progression-free survival analyses with standard treatments in a real-world cohort (N=95)

Rugo H, et al. Lancet Oncol 2021

# CAPIVASERTIB + ET

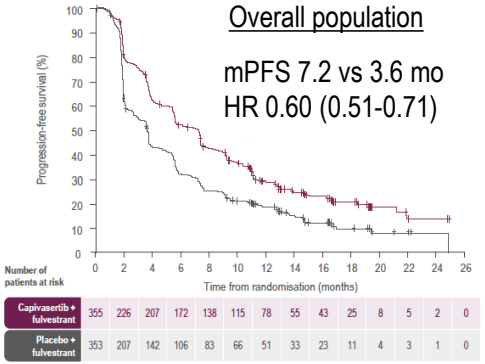
CAPITELLO-291: Phase 3 trial

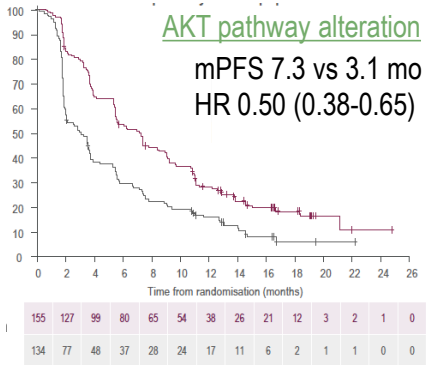
HR+/HER2- AI resistant* ABC
Prior MBC chemo lines ≤1
N=708

Control
Fulv+Placebo
N= 353

Experimental
Fulv + Capivasertib
N= 355

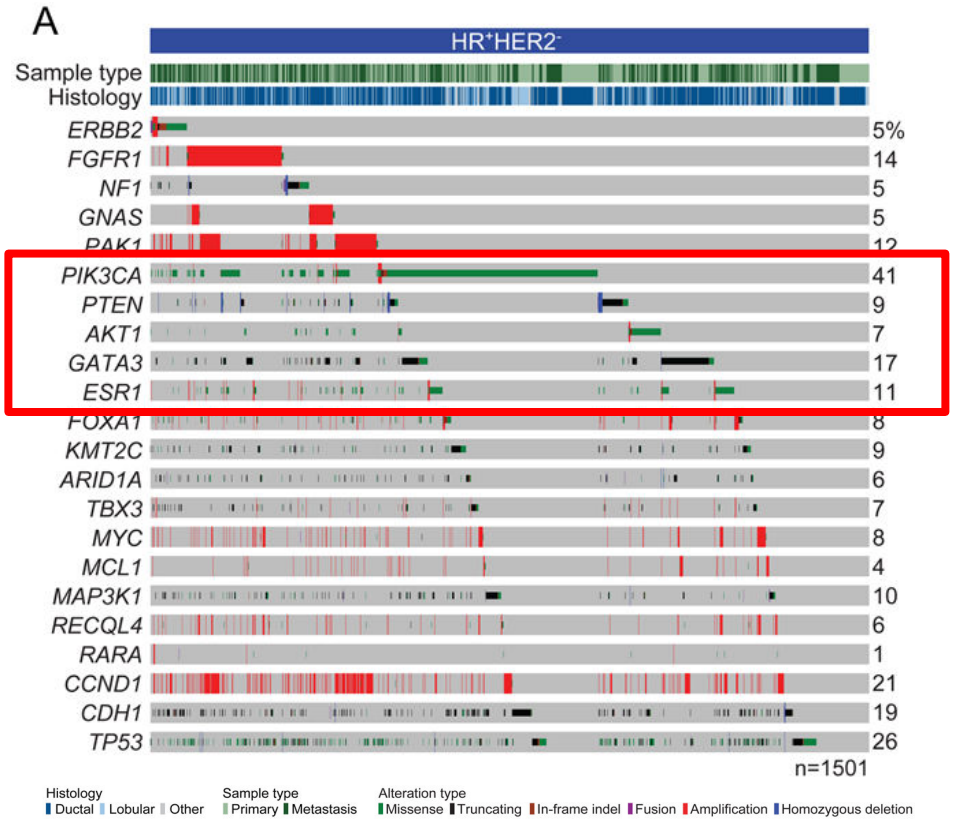
Patients with a pathway alteration don't do better with capivasertib than the WT population.




Presented by Nicolas Turner ESMO Breast 2023
Turner N, et al NEJM 2023

# The Genomic Landscape of ER+ BC




Genomic sequencing of 1,501 HR+ BC, with detailed clinical information and treatment outcomes.

In 692 BC previously exposed to HT, an increased number of alterations in genes involved in the MAPK pathway and in the ER transcriptional machinery has been observed

Razavi Cancer Cell 2018

# ELACESTRANT APPROVAL

## FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer

FDA approval

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Orserdu

*elacestrant*

Medicine | Human

Share | RSS

Authorised
This medicine is authorised for use in the European Union

EMA approval

*SISF/UPC/AR/AA* *Rep.143/2023*

AIFA
AGENZIA ITALIANA DEL FARMACO

**UFFICIO PROCEDURE CENTRALIZZATE**

**CLASSIFICAZIONE DI MEDICINALI PER USO UMANO AI SENSI DELL'ART. 12 COMMA 5 DEL DECRETO-LEGGE 13 SETTEMBRE 2012 N. 158 CONVERTITO NELLA LEGGE 8 NOVEMBRE 2012 N. 189**

**DETERMINA**

1. Le confezioni del seguente medicinale per uso umano di nuova autorizzazione, corredate di numero di AIC e classificazione ai fini della fornitura:

- ORSERDU

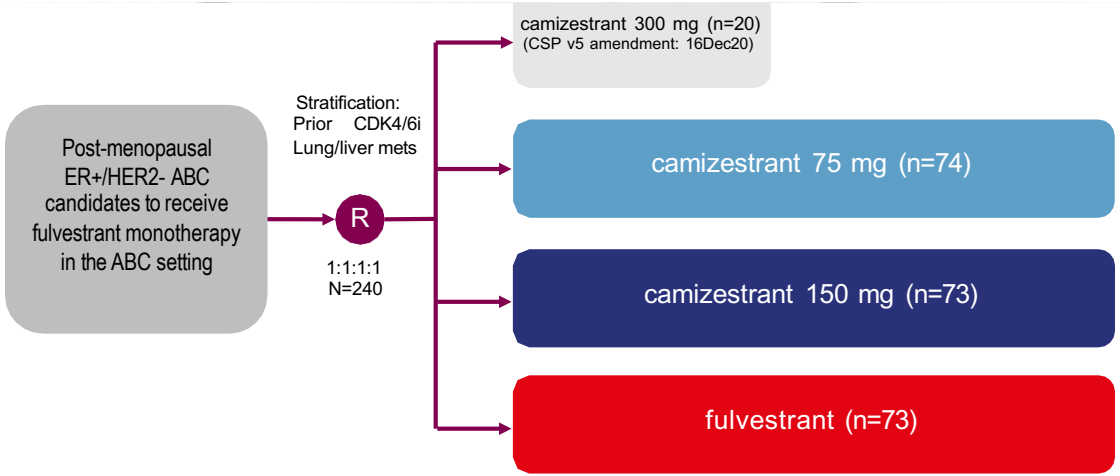
descritte in dettaglio nell'Allegato, che fa parte integrante del presente provvedimento, sono collocate in apposita sezione della classe di cui all'art. 12, comma 5 della legge 8 novembre 2012 n. 189, denominata Classe C (nn), dedicata ai farmaci non ancora valutati ai fini della rimborsabilità.

AIFA approval

# SERENA-2: TRIAL DESIGN

**Key inclusion/exclusion criteria:**

- Recurrence or progression on at least 1L of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line CT in ABC setting
- Measurable and non-measurable disease

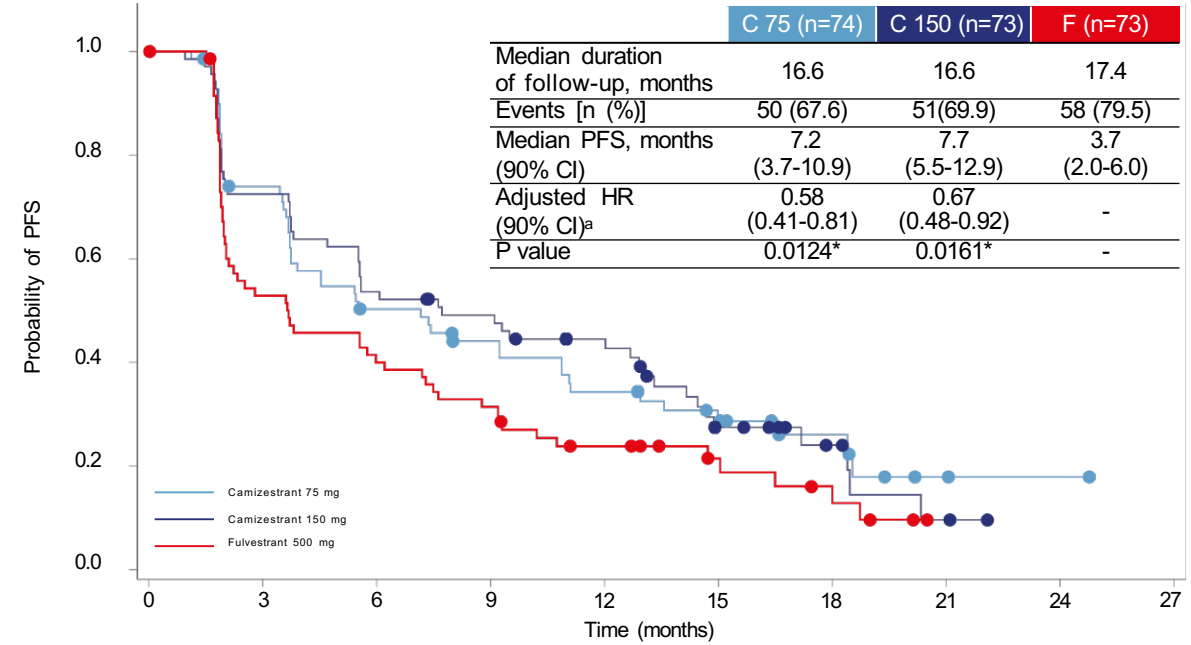



**ESR1 mut 37%**
**Prior CDK4/6i 50%**
**Lung/liver mets 58%**
**CT in ABC 20%**

- **Primary endpoint**: PFS (investigator assessment*)
- **Secondary endpoints**: CBR24, ORR, OS, safety
- Translational endpoints: serial ctDNA analysis including ESR1m, serial CTCs analysis

Olivera M, et al. SABCS 2022

# PFS BY INVESTIGATOR ASSESSMENT




| | C 75 (n=74) | C 150 (n=73) | F (n=73) |
|---|---|---|---|
| Median duration of follow-up, months | 16.6 | 16.6 | 17.4 |
| Events [n (%)] | 50 (67.6) | 51(69.9) | 58 (79.5) |
| Median PFS, months (90% CI) | 7.2 (3.7-10.9) | 7.7 (5.5-12.9) | 3.7 (2.0-6.0) |
| Adjusted HR (90% CI)[a] | 0.58 (0.41-0.81) | 0.67 (0.48-0.92) | - |
| P value | 0.0124* | 0.0161* | - |

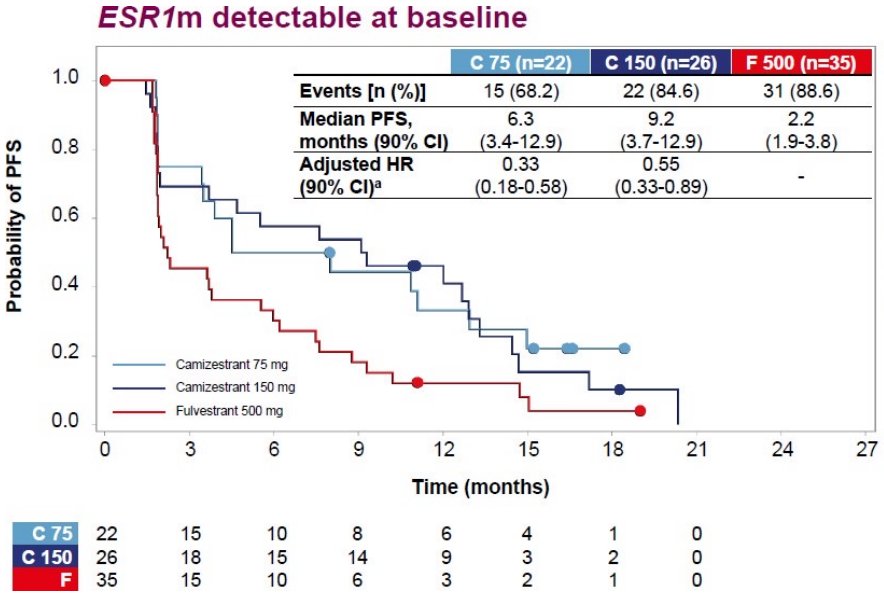
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| C 75 | 74 | 50 | 33 | 27 | 21 | 14 | 7 | 2 | 1 | 0 |
| C 150 | 73 | 50 | 37 | 32 | 25 | 12 | 6 | 2 | 0 | |
| F | 73 | 37 | 28 | 22 | 14 | 8 | 5 | 0 | | |

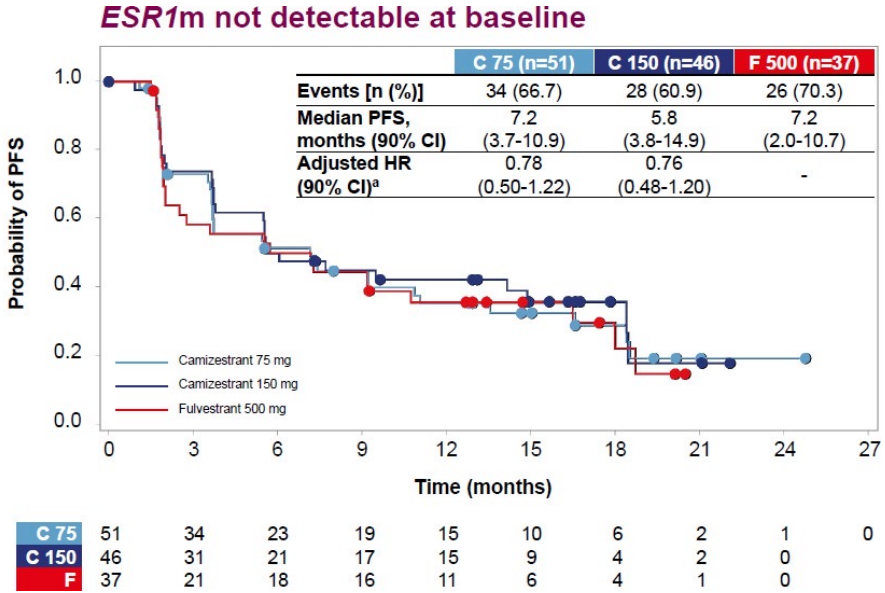
*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

CDK4/6i: CDK4/6 inhibitor; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival

Olivera M, et al. SABCS 2022

# PFS BY DETECTABLE ESR1M

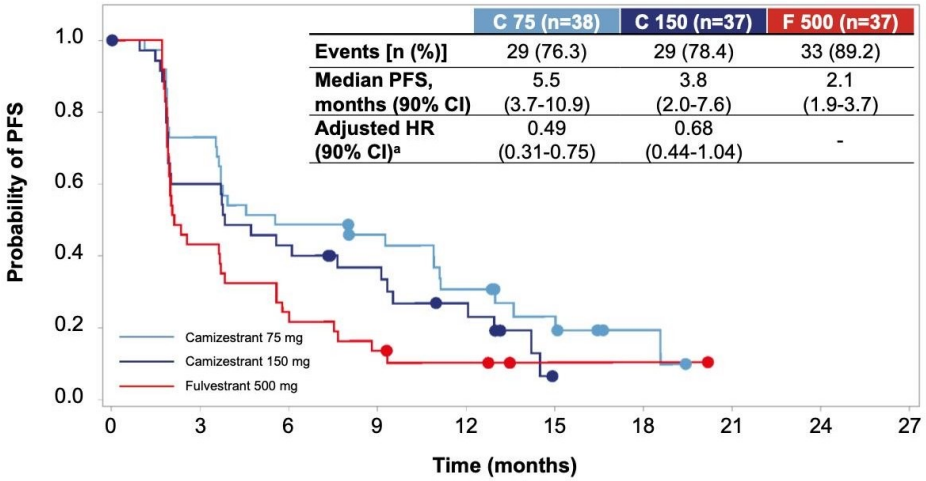



Olivera M, et al. SABCS 2022

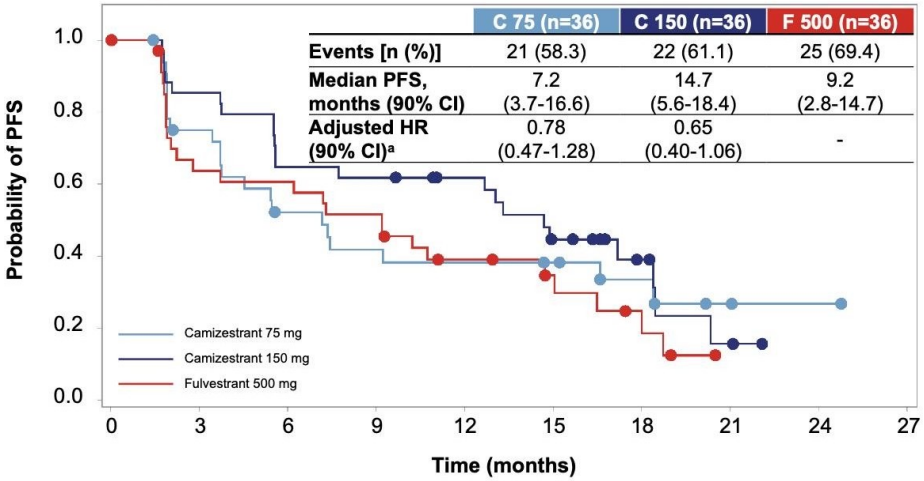
# PFS BY PRIOR CDK4/6i

## Prior CDK4/6i




| | C 75 (n=38) | C 150 (n=37) | F 500 (n=37) |
|---|---|---|---|
| Events [n (%)] | 29 (76.3) | 29 (78.4) | 33 (89.2) |
| Median PFS, months (90% CI) | 5.5 (3.7-10.9) | 3.8 (2.0-7.6) | 2.1 (1.9-3.7) |
| Adjusted HR (90% CI)[a] | 0.49 (0.31-0.75) | 0.68 (0.44-1.04) | - |

## No prior CDK4/6i




| | C 75 (n=36) | C 150 (n=36) | F 500 (n=36) |
|---|---|---|---|
| Events [n (%)] | 21 (58.3) | 22 (61.1) | 25 (69.4) |
| Median PFS, months (90% CI) | 7.2 (3.7-16.6) | 14.7 (5.6-18.4) | 9.2 (2.8-14.7) |
| Adjusted HR (90% CI)[a] | 0.78 (0.47-1.28) | 0.65 (0.40-1.06) | - |

Olivera M, et al. SABCS 2022

# ONGOING PHASE III TRIALS IN MBC

| Trial ID | Drug | Patient cohort(s) | Sample size | Primary Endpoint | Setting |
|---|---|---|---|---|---|
| **NCT04964934 (SERENA-6)** | camizestrant | E: camizestrant + palbociclib or abemaciclib;<br>C: anastrozole or letrozole + palbociclib or abemaciclib | 300 | mPFS | ER+/HER2-, ESR1 mutated |
| **NCT04711252 (SERENA-4)** | camizestrant | E: camizestrant + palbociclib<br>C: anastrazole + palbociclib | 1342 | mPFS | ER+/HER2- mBC, ≥ 1L (AI or TAM pre-treated) |
| **NCT04975308 (EMBER-3)** | imlunestrant | E: imlunestrant<br>E: imlunestrant + abemaciclib<br>C: exemestane or fulvestrant | 860 | mPFS | ER+/HER2- mBC, ≥ 1L |
| **NCT05306340 (evERA)** | giredestrant | E: giredestrant + everolimus<br>C: exemestane + everolimus | 320 | mPFS | ER+/HER2- mBC, ≥ 1L (after CDK4-6i) |
| **NCT04546009 (persevERA)** | giredestrant | E: giredestrant + letrozole-matching placebo + palbociclib<br>C: letrozole + giredestrant-matching placebo + palbociclib | 978 | mPFS | ER+/HER2- mBC, without therapeutic options |
| **NCT04478266 (AMEERA-5)** | amcenestrant | E: amcenestrant + letrozole-matching placebo<br>C: letrozole + amcenestrant matching placebo | 1066 | mPFS | ER+/HER2- mBC, ≥ 1L (SERD naïve) |



Adapted from Corti C et al. Cancer Treatment Reviews 2023

# HOW TO IMPLEMENT ORAL SERDs IN THE CLINIC

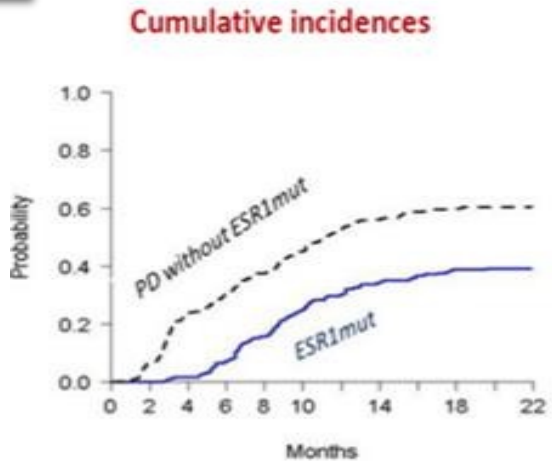
# ESR1-MUT AS MECHANISM OF ACQUIRED RESISTANCE

<1-6%

At initial diagnosis of mBC

30–55%

On/after 1L AI in metastatic setting




| | During the first 6 months of AI+Palbo (n) | After the first 6 months of AI+Palbo (n) |
|---|---|---|
| ESR1wt | 81.3% (74) | 47.0% (71) |
| ESR1mut | 18.7% (17) | 53.0% (80) |

*ESR1mut* is rare in early PD

But is a major mechanism of resistance after 6 months

Berger et al. *BMJ Open.* 2022;12:e055821. Bidard F-C et al. Poster presented at: SABCS; December 7–10, 2021; Virtual. Poster OT2-11-05.

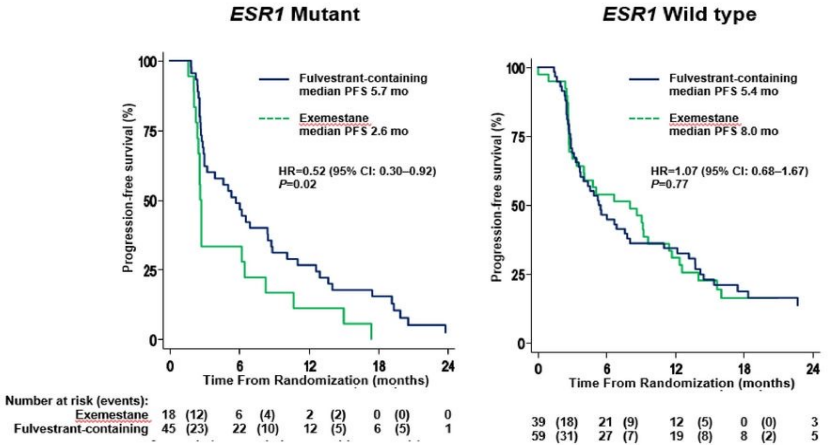
# PREVALENCE OF ESR1-mut (ctDNA) in ER+ mBC

| Trial | Study treatment | Patient population | *ESR1* mutation frequency |
|---|---|---|---|
| **MONALEESA-2**[1] | Letrozole +/- Ribociclib | 1st line ER+ MBC | **4.0%** |
| **BOLERO-2**[2] | Exemestane +/- Everolimus | ER+ MBC after PD on ET | **28.8%** |
| **FERGI**[3] | Fulvestrant +/- Pictilisib | ER+ MBC after PD on ET | **40.0%** |
| **PALOMA-3**[4] | Fulvestrant +/- Palbociclib | ER+ MBC after PD on ET | **25.3%** |
| **SOFeA**[4] | Fulvestrant +/- Anastrozole | ER+ MBC after PD on ET | **39.1%** |

1. Hortobagyi GN et al 2018 2.Chandarlapaty S et al 2016 3.Spoerkle JM et al 2016 4. Fribbens C et al 2016 5. Razavi et al Cancer Cell 2018

# THE ROLE OF ESR1-mut

ESR1 Mutation Analysis by Digital PCR in the Randomized Phase III SoFEA Study

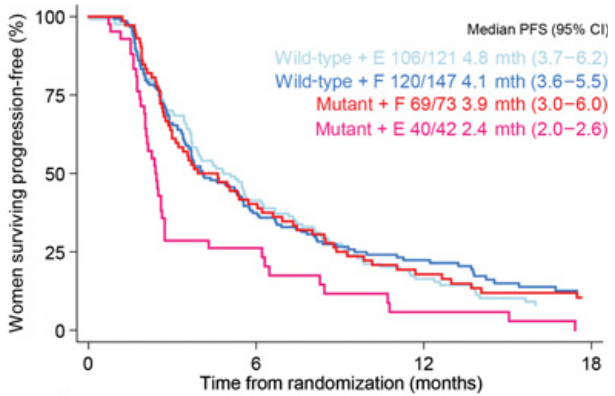



Johnston et al. *Lancet Oncol*, 2013; 989-98. O'Leary et al. AACR, 2016. Fribbens et al. *J Clin Oncol*, 2016 (in press).

16

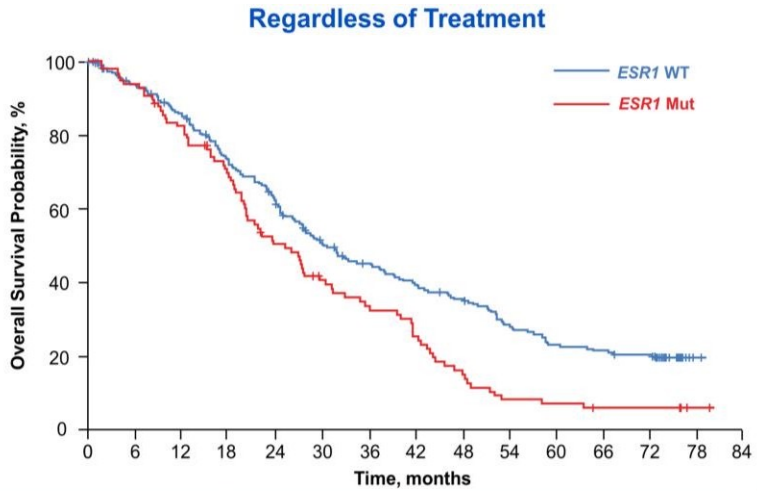
**_ESR1_ Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor–Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials** A C

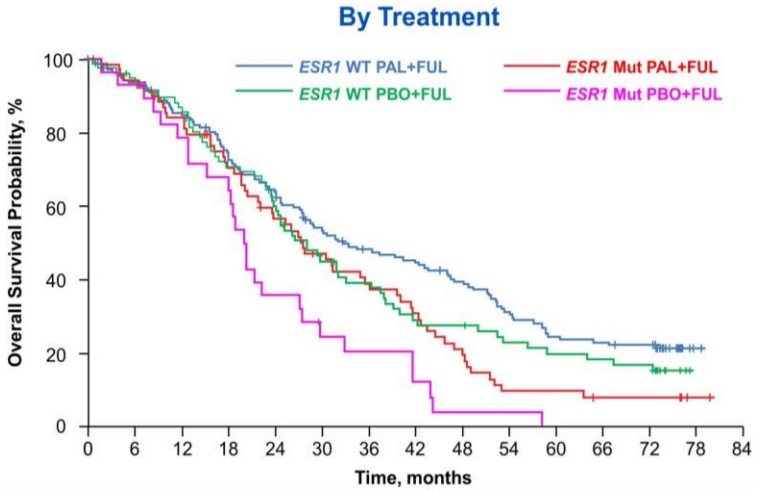
Nicholas C. Turner[1,2], Claire Swift[2], Lucy Kilburn[3], Charlotte Fribbens[1,2], Matthew Beaney[1], Isaac Garcia-Murillas[1], Aman U. Budzar[4], John F.R. Robertson[5], William Gradishar[6], Martine Piccart[7], Gaia Schiavon[8], Judith M. Bliss[3], Mitch Dowsett[1,2], Stephen R.D. Johnston[2], and Stephen K. Chia[9]




Detection of ESR1-mut in baseline ctDNA is associated with inferior PFS and OS in pts with exemestane vs. fulvestrant.

# ESR1 MUTATIONS ASSOCIATED WITH POOR PROGNOSIS




| | No *ESR1* Mutation | *ESR1* Mutation |
|---|---|---|
| Patients, n (%) | 234 (70.7) | 97 (29.3) |
| Median OS (95% CI), mo | 30.7 (26.6–37.5) | 25.4 (20.2–30.6) |
| Hazard ratio (95% CI) | 1.58 (1.22–2.06) | |

| | Palbociclib + Fulvestrant | Placebo + Fulvestrant | Palbociclib + Fulvestrant | Placebo + Fulvestrant |
|---|---|---|---|---|
| | No *ESR1* Mutation | | *ESR1* Mutation | |
| Patients, n (%) | 154 (69.1) | 80 (74.1) | 69 (30.9) | 28 (25.9) |
| Median OS (95% CI), mo | 32.8 (27.4–46.1) | 28.0 (23.6–36.3) | 27.7 (20.4–36.1) | 20.2 (15.3–27.1) |
| Hazard ratio (95% CI) | 0.81 (0.59–1.11) | | 0.59 (0.37–0.94) | |

Cristofanilli M et al., ASCO 2021

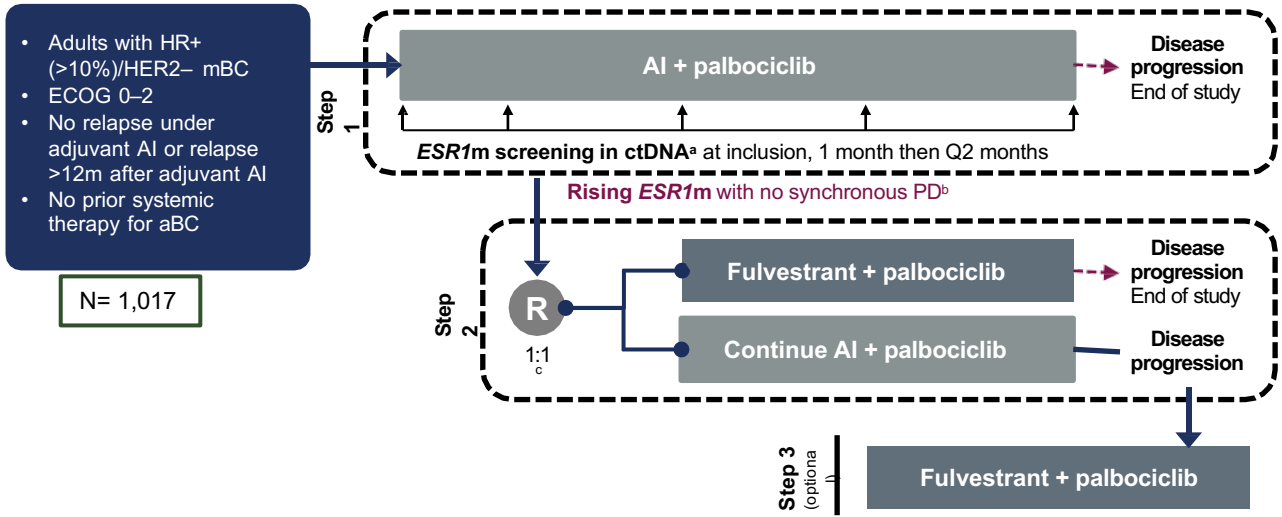
# TACKLING MOLECULAR OR CLINICAL PROGRESSION?

@ clinical progression?

@ acquirement of endocrine resistance (i.e. ESR1)?

# PADA-1: STUDY DESIGN

PAlbociclib and ctDNA for ESR1m detection (PADA-1) is a randomised, open-label, phase III trial that aimed to evaluate the safety and efficacy of a switch from AI to fulvestrant combined with palbociclib upon detection of rising ESR1m in ctDNA in patients with HR+/HER2– mBC




**Co-primary endpoints**

- Safety: grade ≥3 haematological AEs
- PFS from randomisation (Step 2)[d]

**Secondary endpoints**

- PFS from cross-over (Step 3)[d]
- Time to strategy failure (Step 2&3)
- Chemotherapy-free survival (Step 2&3)
- PFS from inclusion[d]
- AEs and SAEs (grade ≥3 extra-haematological)
- QoL score[e]
- OS
- ctDNA detection at different time points

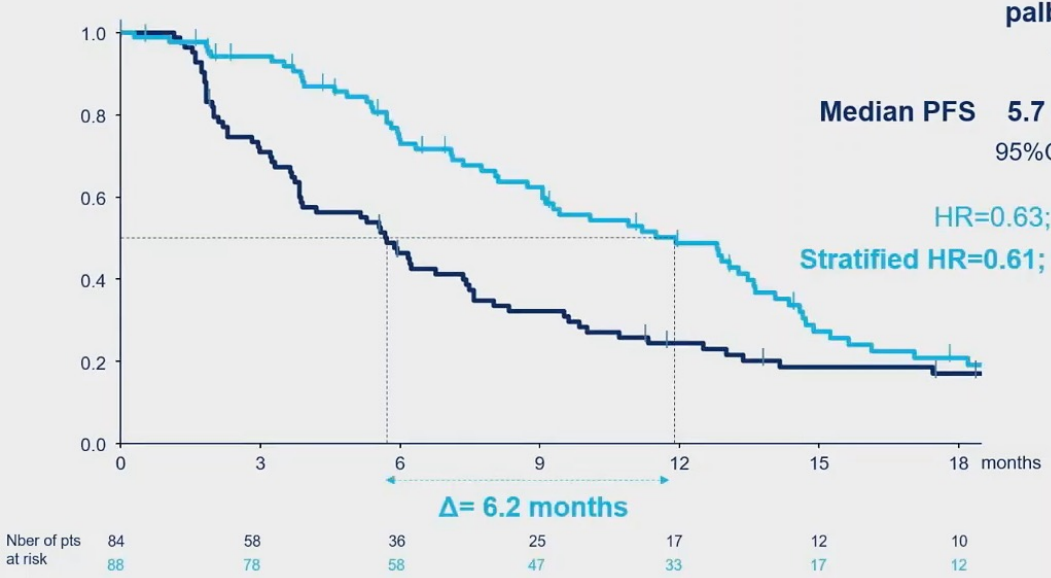


Bidard F-C et al. Presented at ASCO Annual Meeting; May 29–31, 2020; Virtual. J Clin Oncol;38(suppl 15): Abstract 1010.

# PADA-1: RESULTS

## PADA-1: Primary analysis: Progression-Free Survival after randomization

- Median FU in step #2: 26 months (range: 0-36m); N=136 PFS events



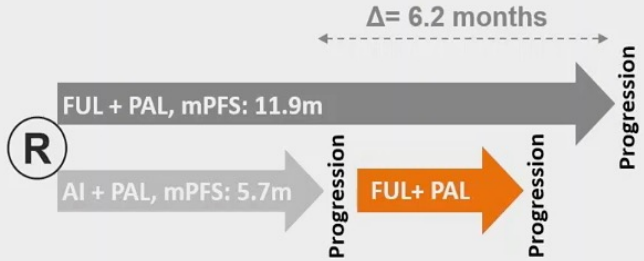

| | palbociclib + AI | palbociclib + FUL |
|---|---|---|
| Median PFS | 5.7 months | 11.9 months |
| | 95%CI [3.9;7.5] | 95%CI [9.1;13.6] |

HR=0.63; 95%CI[0.45-0.88], p=0.007

**Stratified HR=0.61; 95%CI[0.43;0.86], p=0.005**

# PADA-1: RESULTS

## PADA-1: Progression-Free Survival in the optional cross-over cohort

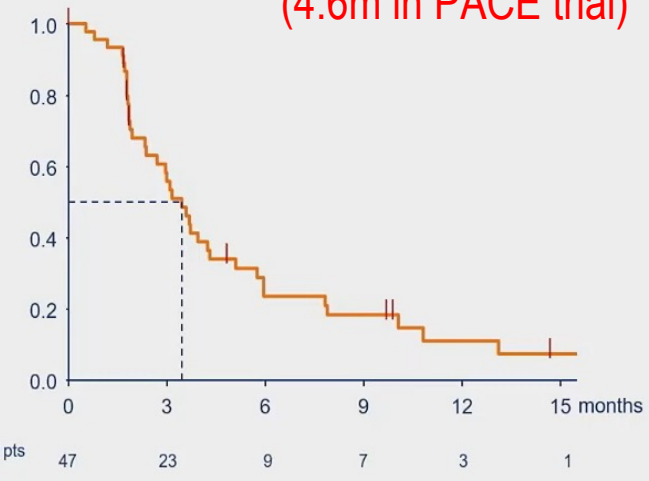



As of July 31st, 2021:

- N= 69 pts had a PD in the AI+PAL arm
- **N= 47 pts participated in the optional 2nd line cross-over cohort**

**Median 2nd line PFS with FUL+PAL**
3.5 months 95%CI=[2.7;5.1]

(4.6m in PACE trial)



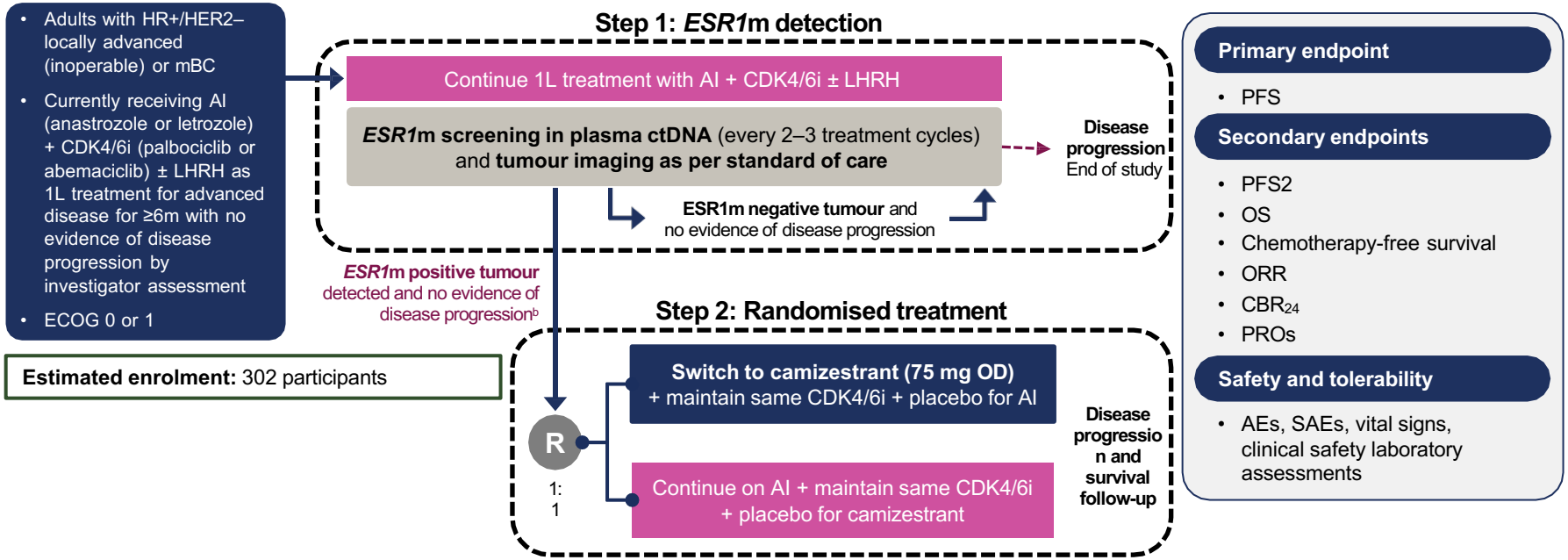

The relevant Δ is PFS 1 – PFS2
i.e. Δ= 11.9– 9.2 m= 2.7m

Is this Δ clinically meaningful ?

**Caveat SERENA 6 *vs* SERENA 4**

# SERENA-6: STUDY DESIGN

Ongoing randomised, double-blind study to evaluate the safety and efficacy of camizestrant in combination with CDK4/6i (palbociclib or abemaciclib) vs AI + CDK4/6i in pts with HR+/HER2– mBC upon detection of ESR1m without disease progression on 1L therapy

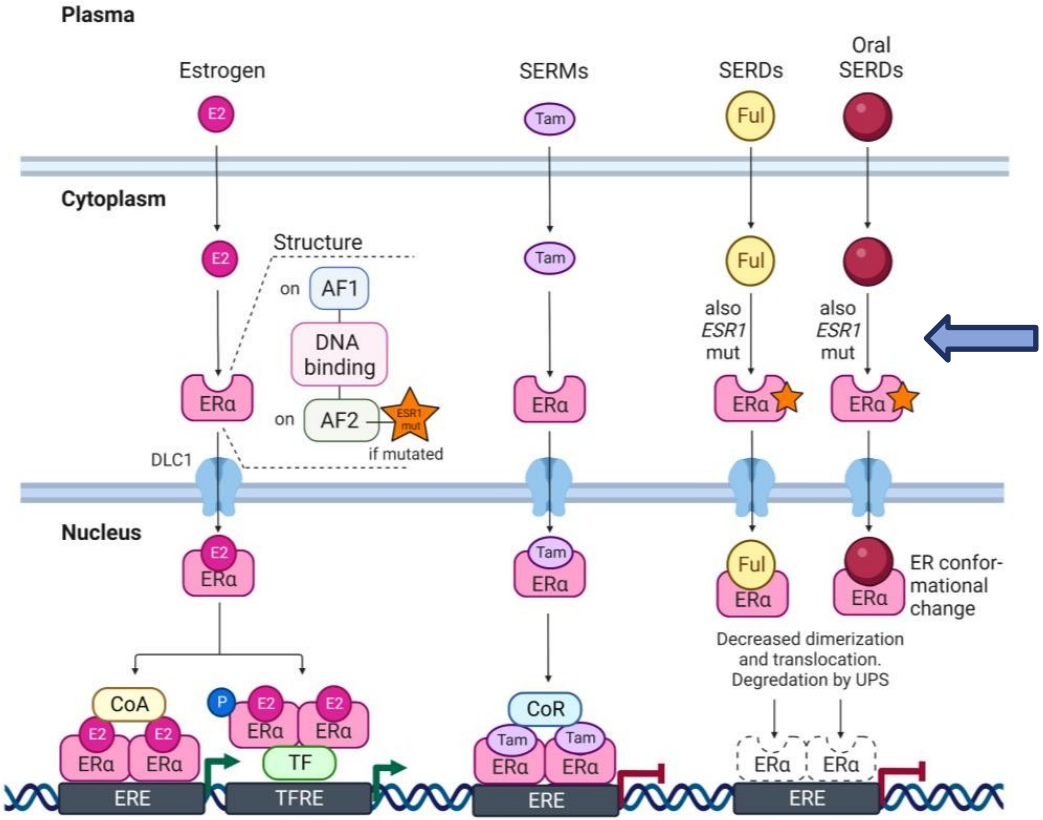





ClinicalTrials.gov Identifier: NCT04964934; Bidard F-C et al. Poster presented at: SABCS; December 7–10, 2021; Virtual. Poster OT2-11-05.

# BRIDGING THE PRESENT (mBC) AND THE FUTURE (eBC)

# BRIDGING THE PRESENT (mBC) AND THE FUTURE (eBC)




## RATIONALE FOR ORAL SERDs USE IN THE EBC

Oral SERDs: more potent inhibitors of ER (both ESR1-mut and ESR1-wt), compared to AI and Tam, thus expecting efficacy to be translated also in the adjuvant setting

# UNASWERED QUESTIONS: EARLY BC (Neoadj)

SABCS SAN ANTONIO BREAST CANCER SYMPOSIUM®

DECEMBER 5-9, 2023 | @SABCSSanAntonio

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center

AACR American Association for Cancer Research

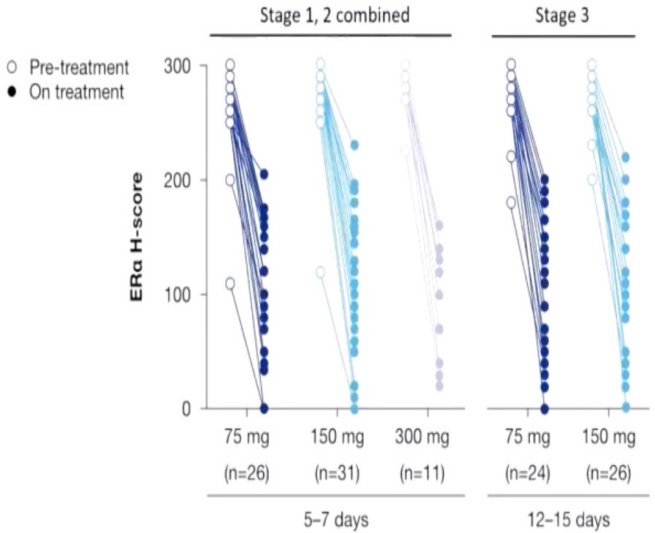
## SERENA-3: A randomized pre-surgical window of opportunity study assessing dose and duration of camizestrant treatment in post-menopausal women with ER-positive, HER2-negative primary breast cancer

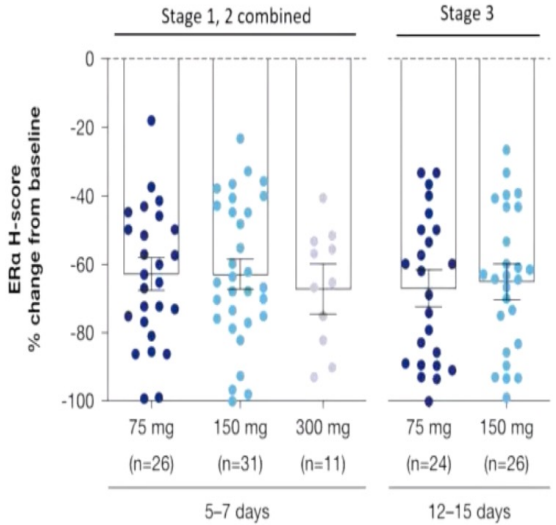
*John FR Robertson MD[1], Teimuraz Gogitidze MD[2], Zaza Katashvili MD[3], Juan Enrique Bargalló Rocha MD[4], Ekaterine Arkania MD[5], Iain Moppett MD[6], Kwok-Leung Cheung MD[7], Gia Nemsadze MD[8], Maxine Ajimi PhD[9], Itziar Irurzun Arana PhD[9], Justin PO Lindemann MBChB, MBA[9], Teresa Klinowska PhD[10], Alastair Mathewson PhD[9], Christopher J Morrow PhD[9], Myria Nikolaou PhD[9], Giorgi Dzagnidze MD, PhD[11].*

# BACKGROUND

- Camizestrant is a next-generation oral SERD and pure ER antagonist[1,2]
- SERENA-1 (NCT03616587) demonstrated the safety, tolerability and preliminary clinical efficacy of a range of doses of camizestrant (25 to 450 mg) as monotherapy, with dose-dependent exposure[3,4]
- SERENA-2 (NCT04214288) demonstrated the safety and superior efficacy of 75 and 150 mg camizestrant compared with fulvestrant[5]
- SERENA-3 (NCT04588298) explored the biological effects of 75, 150 and 300 mg camizestrant in post-menopausal women with ER+, HER2- primary breast cancer

# % CHANGE FROM BASELINE (ER+)

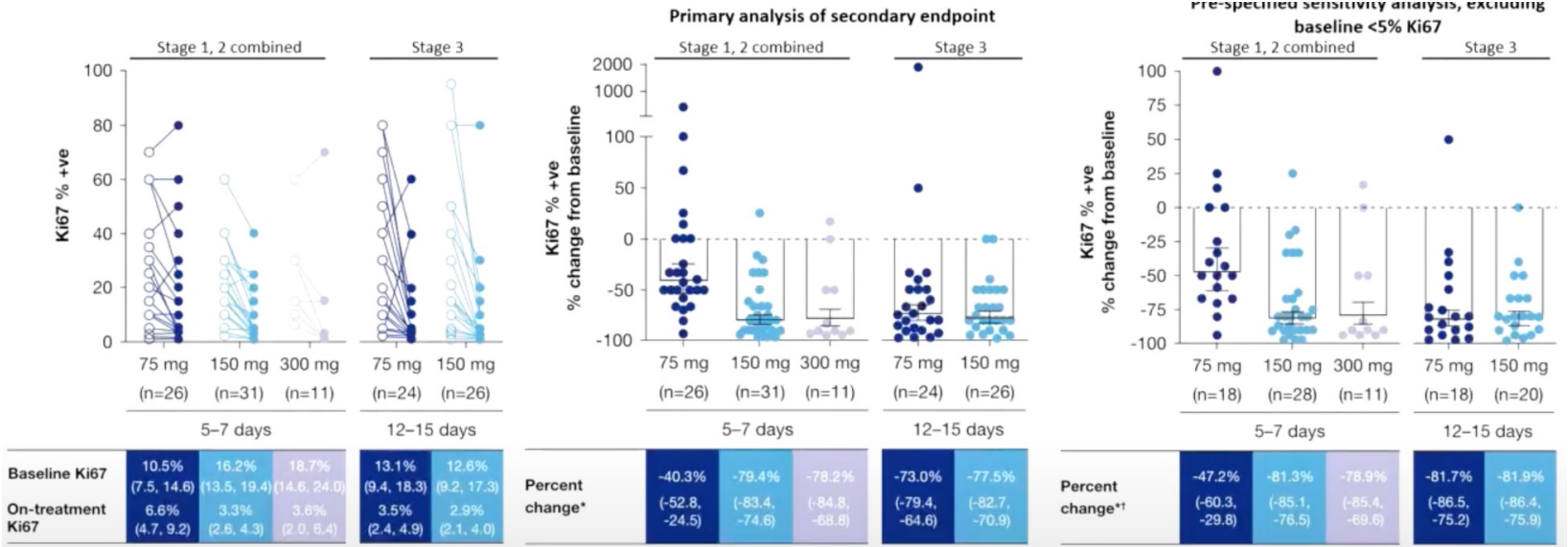



| | | | | | |
|---|---|---|---|---|---|
| Baseline ER | 270.0 (259.8, 280.2) | 277.9 (270.2, 285.6) | 282.3 (273.1, 291.5) | 282.1 (274.5, 289.7) | 285.0 (278.8, 291.2) |
| On-treatment ER | 100.2 (86.1, 114.3) | 108.2 (93.9, 122.6) | 95.5 (75.3, 115.6) | 94.8 (77.2, 112.4) | 101.3 (85.5, 117.1) |
| Percentage change* | -62.7 (-67.5, -57.9) | -62.8 (-67.1, -58.4) | -67.1 (-74.5, -59.7) | -66.9 (-72.3, -61.5) | -65.0 (-70.3, -59.8) |

- ER levels at baseline, and degree of degradation on treatment, are similar across 75, 150 and 300 mg doses.

# % CHANGE FROM KI67 BASELINE (ER+)




- After 5–7d exposure, camizestrant 75 mg reduced Ki67 score to a lesser degree than 150 and 300 mg
- After 12–15d exposure, camizestrant 75 and 150 mg reduced Ki67 score to a similar substantial degree (~82%)
- PK steady state does not necessarily translate to PD steady state

# ONGOING PHASE 3 TRIALS IN EBC

| Trial ID | Drug | Phase | Patient cohort(s) | Sample size | Primary Endpoint | Setting |
|---|---|---|---|---|---|---|
| **NCT05512364 (TREAT ctDNA)** | Elacestrant | 3 | E: elacestrant monotherapy<br>C: standard ET (the same pts were receiving at the time of ctDNA detection) | 220 | DMFS | High-risk (either stage IIB-III or ≥ypT1c and/or ypN+) |
| **NCT04436744 (lidERA)** | Giredestrant | 3 | E: giredestrant<br>C: ET of physician's choice | 221 | iDFS | stage I-III |
| **(** ✕ **§** | Amcenestrant | 3 | E: amcenestrant<br>C: tamoxifen | 3738 (2 patients enrolled, prematurely discontinued) | iBCFS | pts who have discontinued adjuvant AI due to treatment-related toxicity |
| **NCT05774951 (CAMBRIA1)** | Camizestrant | 3 | E: camizestrant<br>C: continue standard ET of investigator's choice | 4300 | iBCFS | High-risk eBC after at least 2 years (no more than 5 years) of ET |

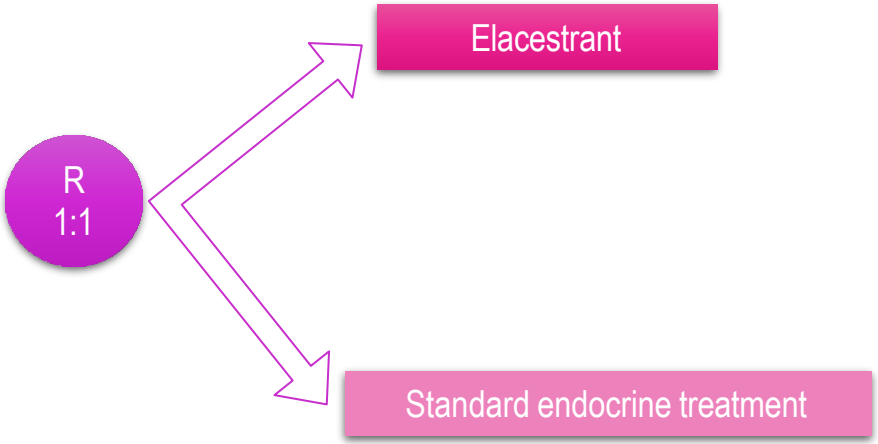
Adapted from Corti C et al. Cancer Treatment Reviews 2023

# TREAT ctDNA (EORTC-2129-BCG)

## Elacestrant vs standard ET in pts with ER+/HER2- BC and ctDNA relapse

**Key Eligibility Criteria**

- Elevated risk of recurrence after definitive treatment for ER+ (≥ 10%), HER2- eBC, defined as either:
  - Stage IIB/III disease and completion of adjuvant chemotherapy, OR
  - Completion of at least 4 cycles of NACT and RD at surgery of ≥ ypT1c or ypN+
- ctDNA+ by RaDaR assay
- Patients must have received at least 2 years and up to 7 years of ET
- Previous adjuvant CDK4/6i or PARPi allowed (completed ≥12 months before registration)
- No prior treatment with SERDs or investigational ER antagonist




| | |
|---|---|
| Primary Objective: | Distant metastasis free survival (DMFS) |
| Secondary Objectives: | 1.ctDNA elimination rate at month 1 defined as the proportion of randomised patients who had a negative ctDNA test result at month 1 |

ClinicalTrials.gov Identifier: NCT05512354

# CAMBRIA-1

## Camizestrant as extended treatment following 2–5 years of standard ET

**Inclusion Criteria**
- ER-positive (>10%), HER2-negative eBC
- Intermediate or high risk of recurrence (based on clinical / genomic features)
- Completed definitive surgery
- Completed 2–5 years of adjuvant ET ± abemaciclib and currently receiving ET (within past 3 months)
- Planning 5 further years of adjuvant ET
- Free of invasive disease
- ECOG PS ≤1

**Exclusion Criteria**
- Disease recurrence on adjuvant ET

R 1:1

**Arm A**
ET (AI or tamoxifen ± OFS)

**5 years of treatment**

**Arm B**
Camizestrant (150 mg, once daily) ± OFS

Pre-menopausal women and men will receive OFS mandatory in camizestrant arm, per local guideline in control arm

**Primary Endpoint**
- Invasive BC-free survival

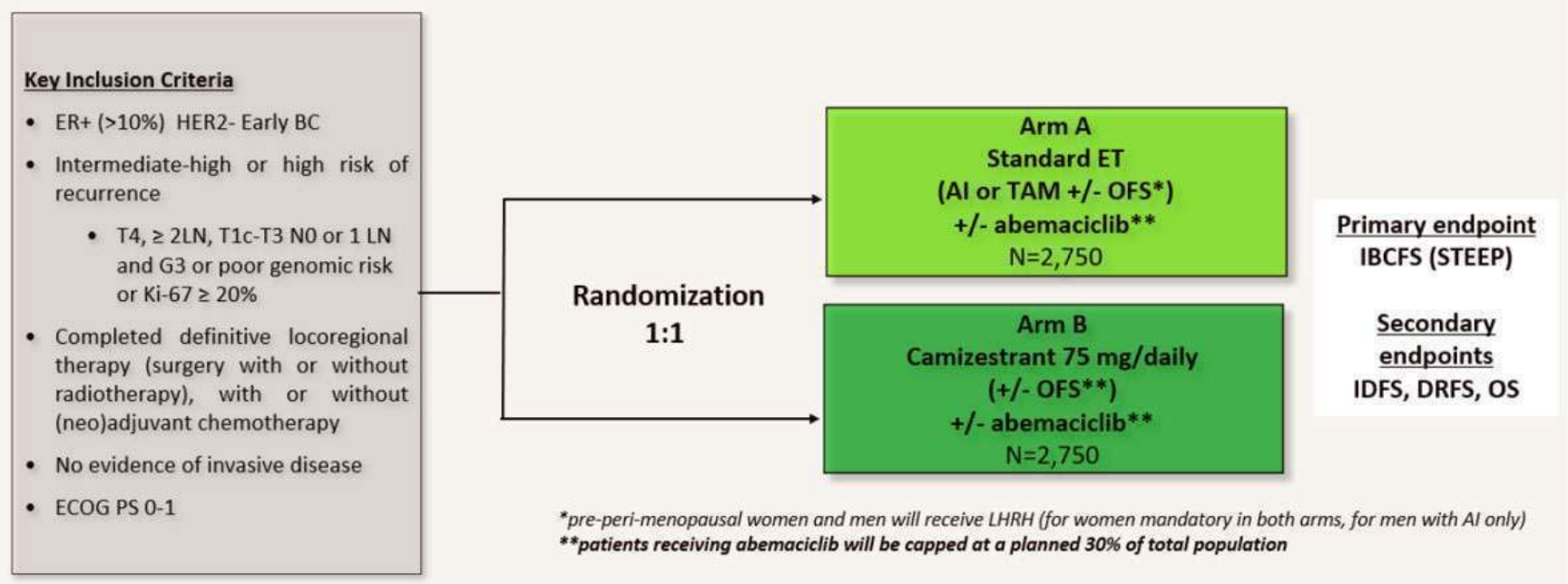
**Secondary Endpoints**
- Invasive disease-free survival
- Distant relapse-free survival
- Overall survival

**Other endpoints**
- Safety (including TEAEs and SAEs)
- Patient-reported tolerability and QoL
- Pharmacokinetics

ClinicalTrials.gov Identifier: NCT05774951

# CAMBRIA-2

Camizestrant as upfront treatment in ER+/HEr2- high risk eBC



# lidERA


## A study of giredestrant as single-agent adjuvant therapy

Patients with ER-positive, HER2-negative eBC
- Medium- or high-risk disease
- Postmenopausal or pre-/peri-menopausal women, and men*
- Prior surgery with curative intent
- Completed (neo)adjuvant chemotherapy (if administered) and/or surgery <12 months prior to enrolment; ≤4 weeks of prior endocrine therapy

N = 4100

R 1:1

- Giredestrant 30 mg QD
- Physician's choice of adjuvant endocrine monotherapy†

Long-term follow-up (5 years)

Patients are categorised as medium- or high-risk based on anatomical (tumour size, nodal status) and biological features (grade, Ki67, gene signatures [OncotypeDx or MammaPrint] if available)

* For men and pre-/peri-menopausal women, LHRH agonist will be administered according to local prescribing information.
† Physician's choice of adjuvant endocrine monotherapy refers to either tamoxifen, anastrozole, letrozole or exemestane to be dosed according to prescribing information.

### Primary endpoint

- Invasive disease-free survival (IDFS), excluding second primary non-breast cancers; time from randomisation to the occurrence of IDFS events.

### Secondary endpoints

- Overall survival
- IDFS (per STEEP‡) including second primary non-breast cancer
- Disease free survival
- Distant recurrence-free interval
- Locoregional recurrence-free interval
- Safety
- Pharmacokinetics
- Patient-reported outcomes

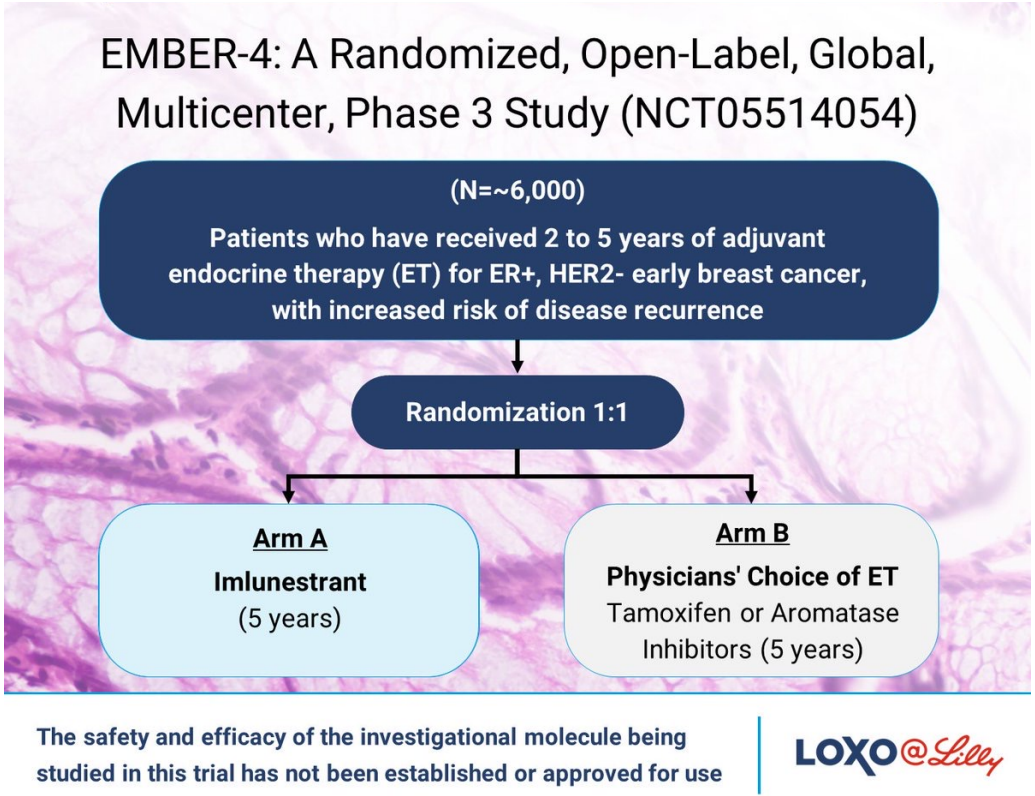
‡ STEEP System as defined by Hudis CA, *et al. J Clin Oncol* 2007; **25**:2127–2132



ClinicalTrials.gov Identifier: NCT04436744

# EMBER-4

A study of Imlunestrant as single-agent adjuvant therapy




ClinicalTrials.gov NCT05514054

# UNASWERED QUESTIONS: EARLY BC

1. Superior to approved ET in all comers?

   - Ki67 reduction and CCCA @week 2: Giredestrant > Anastrozole (-80% vs -67%) in coopERA trial (Hurvitz et al ESMO 2021)
   - Better adherence ? Advantage with Oral SERDs dose reduction possible unlike AI/TAM (MTD not reached in ph1 and lowest dose also potent)

2. SERD alone or SERD + Abem in High Risk pts ?

3. Optimal timing ? Upfront strategy (SERD vs AI/Tam) vs switch strategy (after 2y) vs Extended ET

4. Await resuts from on-going RCT

# CONCLUSIONS

What we know so far:

- Greatest benefit in ESR1mut and prior long-responders to CDK4/6i
- Not an option in early progressors

Open questions:

- New 1L ET backbone? After 1L, in combo or as monotherapy?
- Tackling molecular or clinical progression? Clinical utility?
- Implementation in the early setting
- Use in combo (SERD+AI) ?