# Rounds with the Investigators: Compelling Teaching Cases Focused on the Role of Endocrine-Based Therapy in the Management of Breast Cancer

*Part 2 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®*

**Wednesday, December 11, 2024**

**7:15 PM – 9:15 PM CT (8:15 PM – 10:15 PM ET)**

## Faculty

**Matthew P Goetz, MD**
**Sara A Hurvitz, MD, FACP**
**Komal Jhaveri, MD, FACP**
**Virginia Kaklamani, MD, DSc**
**Seth Wander, MD, PhD**

## Moderator

**Neil Love, MD**

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**Moderator**
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# Dr Goetz — Disclosures
# Faculty

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# Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Metastatic Breast Cancer

*Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®*

**Thursday, December 12, 2024**

**7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)**

## Faculty

**Erika Hamilton, MD**
**Kevin Kalinsky, MD, MS**
**Ian E Krop, MD, PhD**
**Joyce O'Shaughnessy, MD**
**Sara M Tolaney, MD, MPH**

## Moderator

**Neil Love, MD**

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Save The Date

# Fourth Annual
# National General Medical Oncology Summit

***A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute***

**Friday to Sunday, February 28 to March 2, 2025**

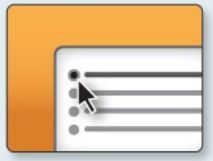
Fontainebleau Hotel, Miami Beach, Florida

**Moderated by Neil Love, MD**

# Clinicians in the Meeting Room

**Networked iPads are available.**

**Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.**



**Answer Survey Questions: Complete the pre- and postmeeting surveys.**

**Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.**

***For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.***

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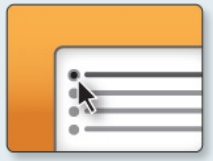
# Clinicians Attending via Zoom

**Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.**



**Answer Survey Questions: Complete the pre- and postmeeting surveys.**

**Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.**

**Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.**

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# About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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# Rounds with the Investigators: Compelling Teaching Cases Focused on the Role of Endocrine-Based Therapy in the Management of Breast Cancer

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**Komal Jhaveri, MD, FACP**
**Virginia Kaklamani, MD, DSc**
**Seth Wander, MD, PhD**

## Moderator

**Neil Love, MD**

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# Agenda

**Module 1:** Role of CDK4/6 Inhibitors in Hormone Receptor (HR)-Positive Localized Breast Cancer – Dr Hurvitz

**Module 2:** Incorporation of CDK4/6 Inhibitors into the Management of HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) – Dr Wander

**Module 3:** Evolving Role of PI3K Inhibitors for HR-Positive mBC Harboring PIK3CA Mutations – Dr Goetz

**Module 4:** Clinical Utility of AKT Inhibitors for Patients with Progressive HR-Positive mBC – Dr Jhaveri

**Module 5:** Oral Selective Estrogen Receptor Degraders (SERDs) for HR-Positive mBC – Dr Kaklamani

## 2018 and 2024 Surveys of Clinical Investigator (CI) Use of Postoperative Systemic Therapy After Prior Neoadjuvant Treatment of HER2-Positive Breast Cancer (HER2+ BC)

**Abstract: P3-11-20**

**Thursday, December 12, 2024**
**12:00 PM – 2:00 PM**

## Second-Line, Post-CDKi Treatment of Metastatic ER+ HER2-Negative Breast Cancer (ER+ mBC): The Impact of a 30-Minute CME Video on Treatment Choices of Community-Based General Medical Oncologists (GMOs)

**Abstract: P4-08-12**

**Thursday, December 12, 2024**
**5:30 PM – 7:00 PM**

## Key Factors Affecting Clinical Investigators' Use of Oral SERDs in Current Management of ER-Positive, HER2-Negative, ESR1-Mutated (ER+/HER2-/ESR1+) Metastatic Breast Cancer That Has Relapsed After Treatment with a CDK4/6 Inhibitor/Endocrine Therapy

**Abstract: P4-12-15**

**Thursday, December 12, 2024**
**5:30 PM – 7:00 PM**

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio Mays Cancer Center | AACR American Association for Cancer Research®

DECEMBER 10–13, 2024

HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

# Imlunestrant, an Oral Selective Estrogen Receptor Degrader (SERD), as Monotherapy and Combined with Abemaciclib, for Patients with ER+, HER2- Advanced Breast Cancer (ABC), Pretreated with Endocrine Therapy (ET): Results of the Phase 3 EMBER-3 trial

**Komal L. Jhaveri,**[1] Patrick Neven,[2] Monica Lis Casalnuovo,[3] Sung-Bae Kim,[4] Eriko Tokunaga,[5] Philippe Aftimos,[6] Cristina Saura,[7] Joyce O'Shaughnessy,[8] Nadia Harbeck,[9] Lisa A. Carey,[10] Giuseppe Curigliano,[11] Antonio Llombart-Cussac,[12] Elgene Lim,[13] María de la Luz García Tinoco,[14] Joohyuk Sohn,[15] André Mattar,[16] Qingyuan Zhang,[17] Chiun-Sheng Huang,[18] Chih-Chiang Hung,[19] Jorge Luis Martinez Rodriguez,[20] Manuel Ruiz Borrego,[21] Rikiya Nakamura,[22] Kamnesh R. Pradhan,[23] Christoph Cramer von Laue,[23] Emily Barrett,[23] Shanshan Cao,[23] Xuejing Aimee Wang,[23] Lillian M. Smyth,[23] François-Clément Bidard[24]

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Imlunestrant with or without Abemaciclib in Advanced Breast Cancer

K.L. Jhaveri, P. Neven, M.L. Casalnuovo, S.-B. Kim, E. Tokunaga, P. Aftimos, C. Saura, J. O'Shaughnessy, N. Harbeck, L.A. Carey, G. Curigliano, A. Llombart-Cussac, E. Lim, M...L. García Tinoco, J. Sohn, A. Mattar, Q. Zhang, C.-S. Huang, C.-C. Hung, J.L. Martinez Rodriguez, M. Ruíz Borrego, R. Nakamura, K.R. Pradhan, C. Cramer von Laue, E. Barrett, S. Cao, X.A. Wang, L.M. Smyth, and F.-C. Bidard, for the EMBER-3 Study Group*

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# Agenda

**Module 1: Role of CDK4/6 Inhibitors in Hormone Receptor (HR)-Positive Localized Breast Cancer – Dr Hurvitz**

**Module 2:** Incorporation of CDK4/6 Inhibitors into the Management of HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) – Dr Wander

**Module 3:** Evolving Role of PI3K Inhibitors for HR-Positive mBC Harboring PIK3CA Mutations – Dr Goetz

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**Module 5:** Oral Selective Estrogen Receptor Degraders (SERDs) for HR-Positive mBC – Dr Kaklamani

# Role of CDK4/6 inhibitors in hormone receptor-positive (HR+) localized breast cancer

**Sara A. Hurvitz, MD, FACP**

*Professor of Medicine*
*Smith Family Endowed Chair in Women's Health*
*Head, Division of Hematology/Oncology,*
*University of Washington School of Medicine*
*Senior Vice President, Clinical Research Division,*
*Fred Hutchinson Cancer Center*

Fred Hutch Cancer Center

UNIVERSITY of WASHINGTON

# Identifying Patients at High Risk for Recurrence

## FDA[1], EMA[2], NCCN[3]

- ≥ 4 positive ALN

*or*

- 1 to 3 positive ALN and ≥ 1 of the following:
  - Tumor grade 3 or
  - Tumor size ≥ 5 cm

## ASCO®[4], ESMO[5]

- ≥ 4 positive ALN

*or*

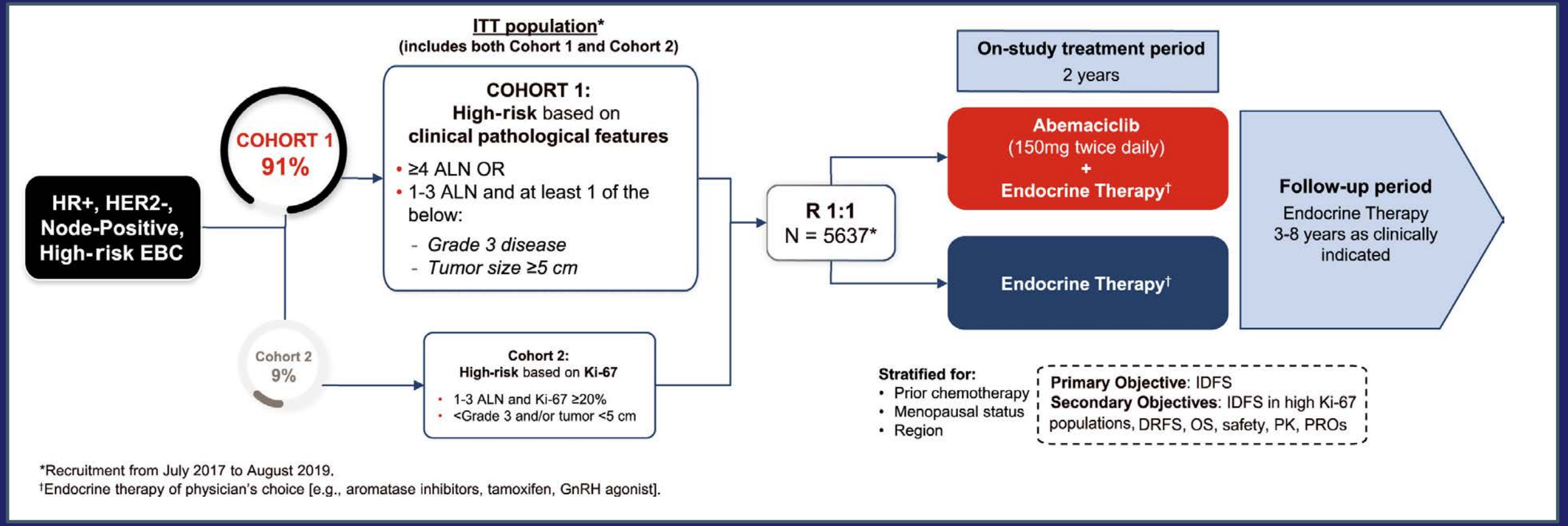
- 1 to 3 positive ALN and ≥ 1 of the following:
  - Tumor grade 3
  - Tumor size ≥ 5 cm
  - Ki-67 ≥ 20%

## Other Factors That Guide Decision Making

- Age
- Genetic testing
- Molecular profiling
- ER, PR status

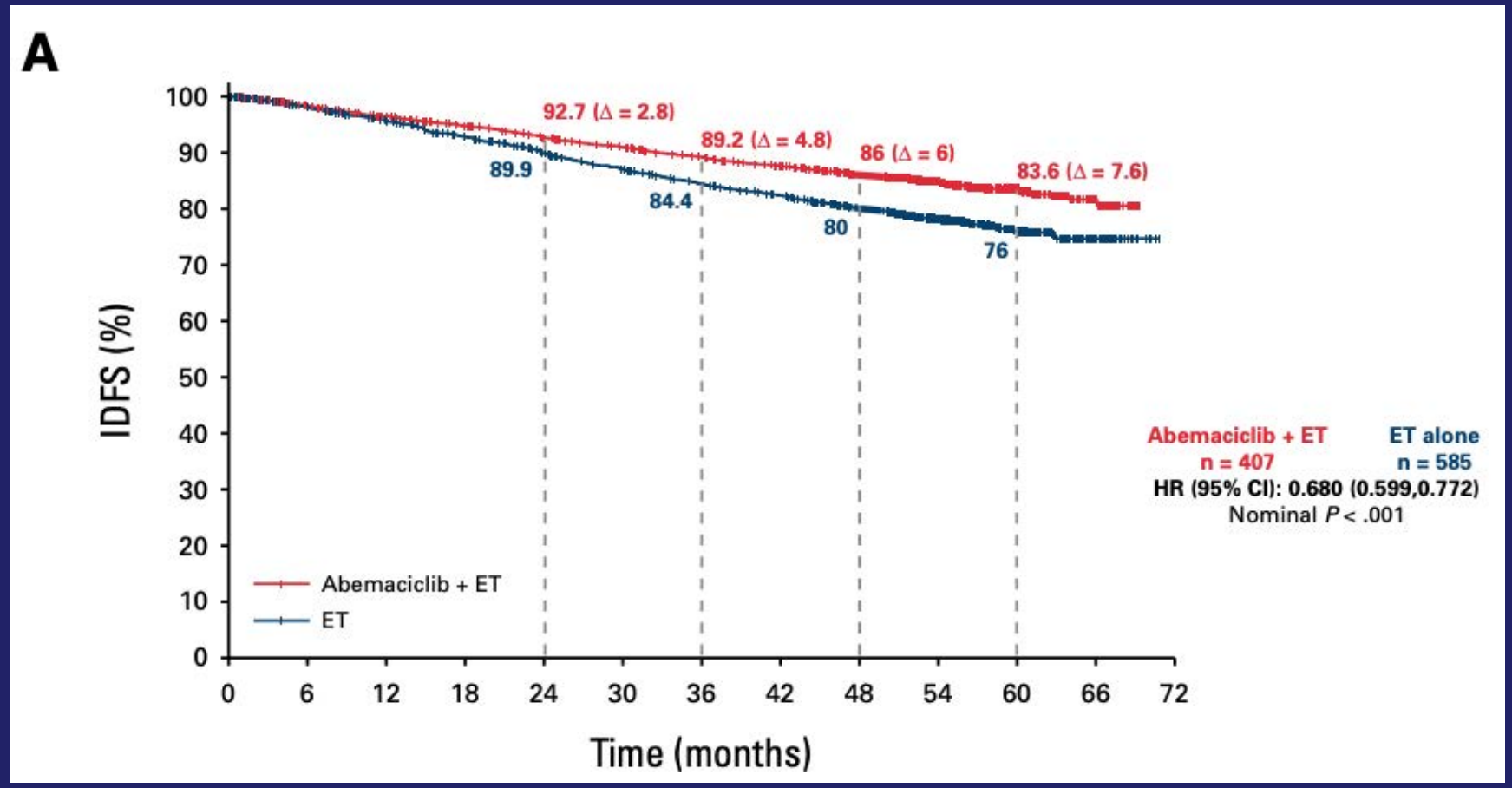
- ALN, axillary lymph node; ASCO®, American Society of Clinical Oncology; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.
- 1. Abemaciclib [PI]. Approved 2017. Revised January 2024; 2. Abemaciclib [PI]. EMA. Approved October 29, 2018. Updated July 12, 2023; 3. NCCN. Breast cancer (v4=5.2023). 2023. Accessed January 11, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; 4. Giordano SH, et al. J Clin Oncol. 2022;40:307-309; 5. Paluch-Shimon S, et al. Ann Oncol. 2022;33:1097-1118.

# monarchE Study Design (NCT03155997): 5-year efficacy results




Median follow-up time is 4.5 years (54 months)
All patients are off abemaciclib
More than 80% of patients have been followed for at least 2 years since completing abemaciclib

# monarchE: IDFS 54-month median follow up




<u>iDFS absolute improvement</u>

2-year: 2.8%

3-year: 4.8%

5-year: 7.6%

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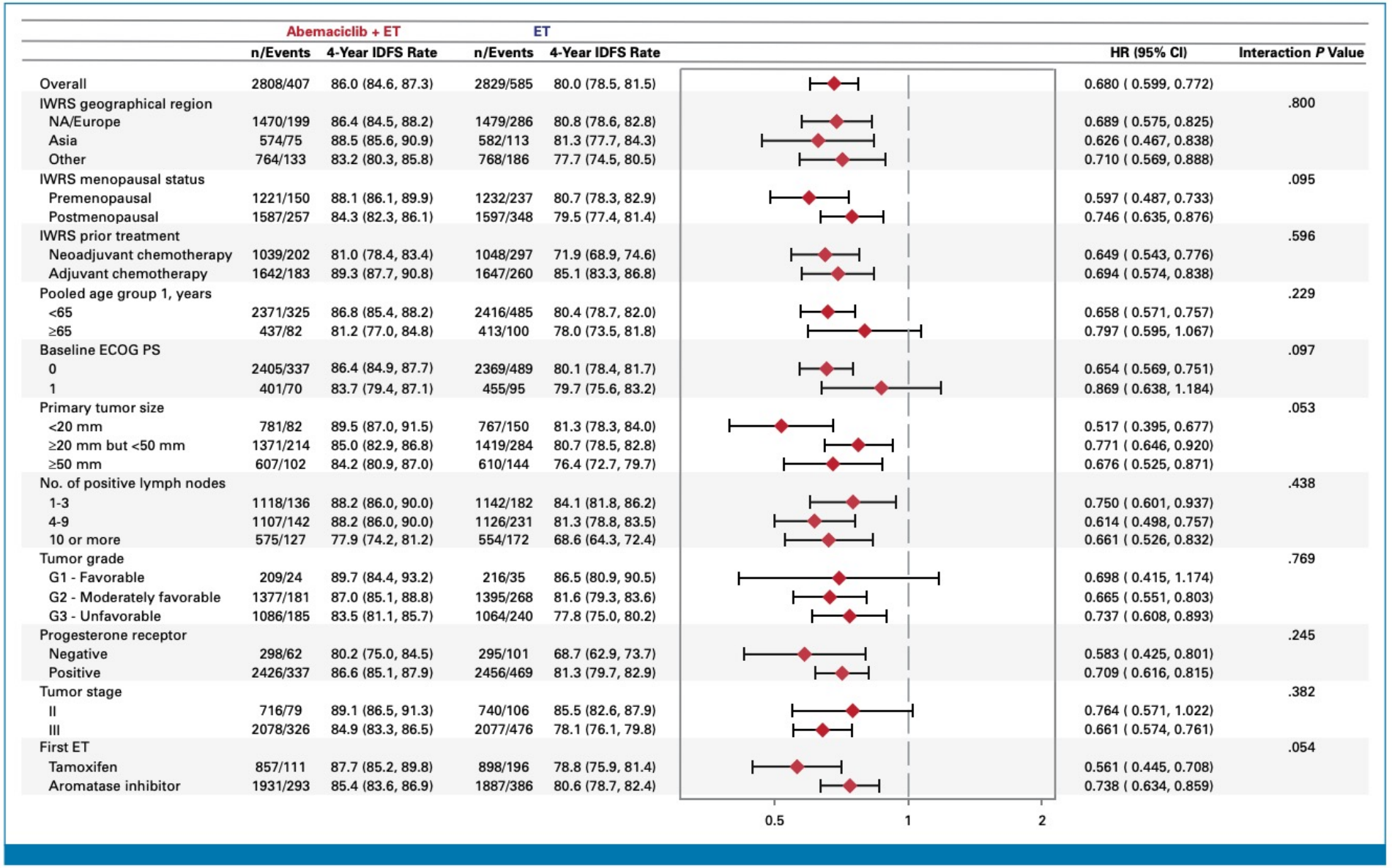
# monarchE IDFS Subgroup Analysis

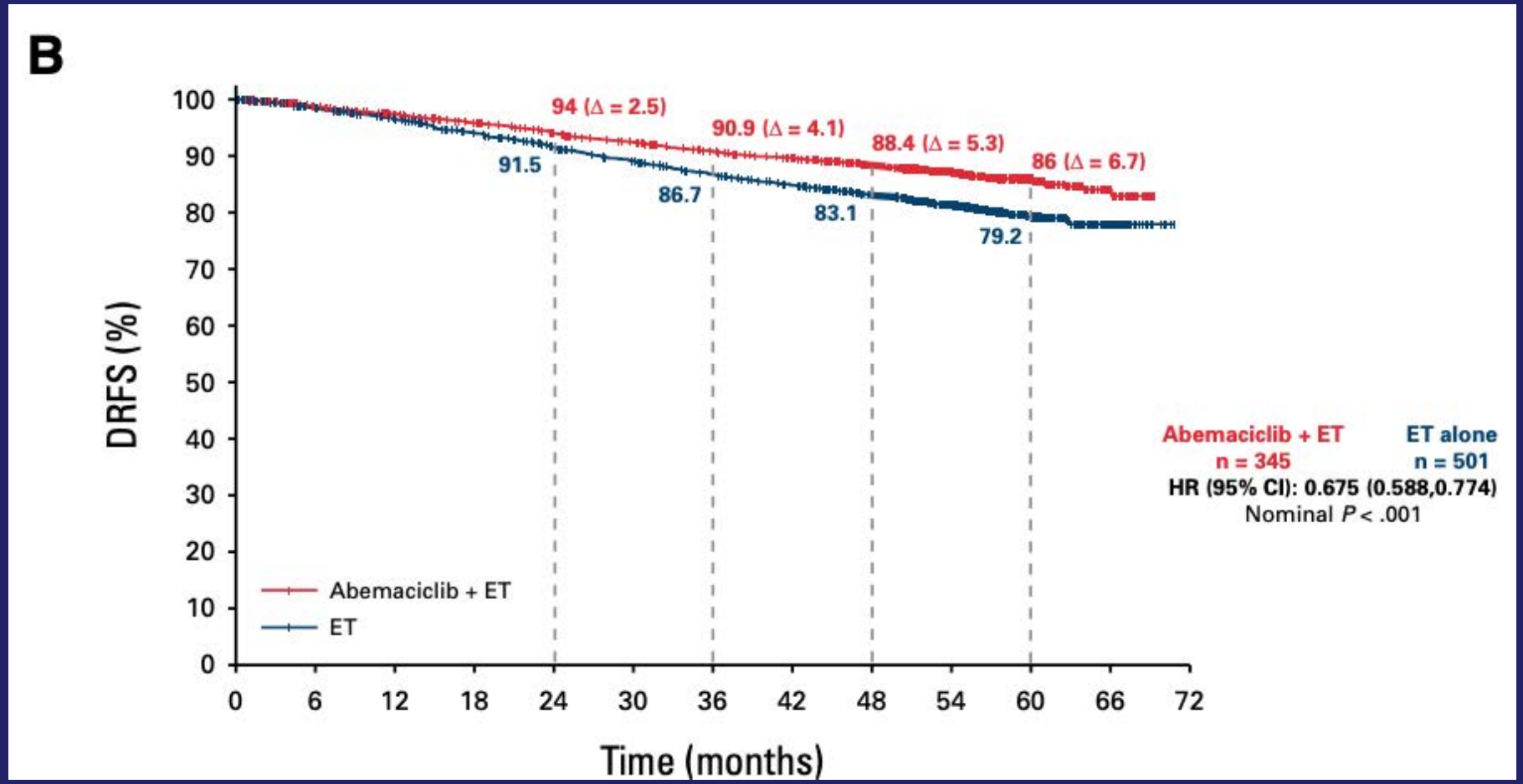


| | Abemaciclib + ET | | ET | | | |
|---|---|---|---|---|---|---|
| | n/Events | 4-Year IDFS Rate | n/Events | 4-Year IDFS Rate | HR (95% CI) | Interaction *P* Value |
| Overall | 2808/407 | 86.0 (84.6, 87.3) | 2829/585 | 80.0 (78.5, 81.5) | 0.680 ( 0.599, 0.772) | |
| IWRS geographical region | | | | | | .800 |
| NA/Europe | 1470/199 | 86.4 (84.5, 88.2) | 1479/286 | 80.8 (78.6, 82.8) | 0.689 ( 0.575, 0.825) | |
| Asia | 574/75 | 88.5 (85.6, 90.9) | 582/113 | 81.3 (77.7, 84.3) | 0.626 ( 0.467, 0.838) | |
| Other | 764/133 | 83.2 (80.3, 85.8) | 768/186 | 77.7 (74.5, 80.5) | 0.710 ( 0.569, 0.888) | |
| IWRS menopausal status | | | | | | .095 |
| Premenopausal | 1221/150 | 88.1 (86.1, 89.9) | 1232/237 | 80.7 (78.3, 82.9) | 0.597 ( 0.487, 0.733) | |
| Postmenopausal | 1587/257 | 84.3 (82.3, 86.1) | 1597/348 | 79.5 (77.4, 81.4) | 0.746 ( 0.635, 0.876) | |
| IWRS prior treatment | | | | | | .596 |
| Neoadjuvant chemotherapy | 1039/202 | 81.0 (78.4, 83.4) | 1048/297 | 71.9 (68.9, 74.6) | 0.649 ( 0.543, 0.776) | |
| Adjuvant chemotherapy | 1642/183 | 89.3 (87.7, 90.8) | 1647/260 | 85.1 (83.3, 86.8) | 0.694 ( 0.574, 0.838) | |
| Pooled age group 1, years | | | | | | .229 |
| <65 | 2371/325 | 86.8 (85.4, 88.2) | 2416/485 | 80.4 (78.7, 82.0) | 0.658 ( 0.571, 0.757) | |
| ≥65 | 437/82 | 81.2 (77.0, 84.8) | 413/100 | 78.0 (73.5, 81.8) | 0.797 ( 0.595, 1.067) | |
| Baseline ECOG PS | | | | | | .097 |
| 0 | 2405/337 | 86.4 (84.9, 87.7) | 2369/489 | 80.1 (78.4, 81.7) | 0.654 ( 0.569, 0.751) | |
| 1 | 401/70 | 83.7 (79.4, 87.1) | 455/95 | 79.7 (75.6, 83.2) | 0.869 ( 0.638, 1.184) | |
| Primary tumor size | | | | | | .053 |
| <20 mm | 781/82 | 89.5 (87.0, 91.5) | 767/150 | 81.3 (78.3, 84.0) | 0.517 ( 0.395, 0.677) | |
| ≥20 mm but <50 mm | 1371/214 | 85.0 (82.9, 86.8) | 1419/284 | 80.7 (78.5, 82.8) | 0.771 ( 0.646, 0.920) | |
| ≥50 mm | 607/102 | 84.2 (80.9, 87.0) | 610/144 | 76.4 (72.7, 79.7) | 0.676 ( 0.525, 0.871) | |
| No. of positive lymph nodes | | | | | | .438 |
| 1-3 | 1118/136 | 88.2 (86.0, 90.0) | 1142/182 | 84.1 (81.8, 86.2) | 0.750 ( 0.601, 0.937) | |
| 4-9 | 1107/142 | 88.2 (86.0, 90.0) | 1126/231 | 81.3 (78.8, 83.5) | 0.614 ( 0.498, 0.757) | |
| 10 or more | 575/127 | 77.9 (74.2, 81.2) | 554/172 | 68.6 (64.3, 72.4) | 0.661 ( 0.526, 0.832) | |
| Tumor grade | | | | | | .769 |
| G1 - Favorable | 209/24 | 89.7 (84.4, 93.2) | 216/35 | 86.5 (80.9, 90.5) | 0.698 ( 0.415, 1.174) | |
| G2 - Moderately favorable | 1377/181 | 87.0 (85.1, 88.8) | 1395/268 | 81.6 (79.3, 83.6) | 0.665 ( 0.551, 0.803) | |
| G3 - Unfavorable | 1086/185 | 83.5 (81.1, 85.7) | 1064/240 | 77.8 (75.0, 80.2) | 0.737 ( 0.608, 0.893) | |
| Progesterone receptor | | | | | | .245 |
| Negative | 298/62 | 80.2 (75.0, 84.5) | 295/101 | 68.7 (62.9, 73.7) | 0.583 ( 0.425, 0.801) | |
| Positive | 2426/337 | 86.6 (85.1, 87.9) | 2456/469 | 81.3 (79.7, 82.9) | 0.709 ( 0.616, 0.815) | |
| Tumor stage | | | | | | .382 |
| II | 716/79 | 89.1 (86.5, 91.3) | 740/106 | 85.5 (82.6, 87.9) | 0.764 ( 0.571, 1.022) | |
| III | 2078/326 | 84.9 (83.3, 86.5) | 2077/476 | 78.1 (76.1, 79.8) | 0.661 ( 0.574, 0.761) | |
| First ET | | | | | | .054 |
| Tamoxifen | 857/111 | 87.7 (85.2, 89.8) | 898/196 | 78.8 (75.9, 81.4) | 0.561 ( 0.445, 0.708) | |
| Aromatase inhibitor | 1931/293 | 85.4 (83.6, 86.9) | 1887/386 | 80.6 (78.7, 82.4) | 0.738 ( 0.634, 0.859) | |



Rastogi P, et al. J Clin Oncol 2024;42:987-993

# monarchE: DRFS 54-month median follow up




DRFS absolute improvement

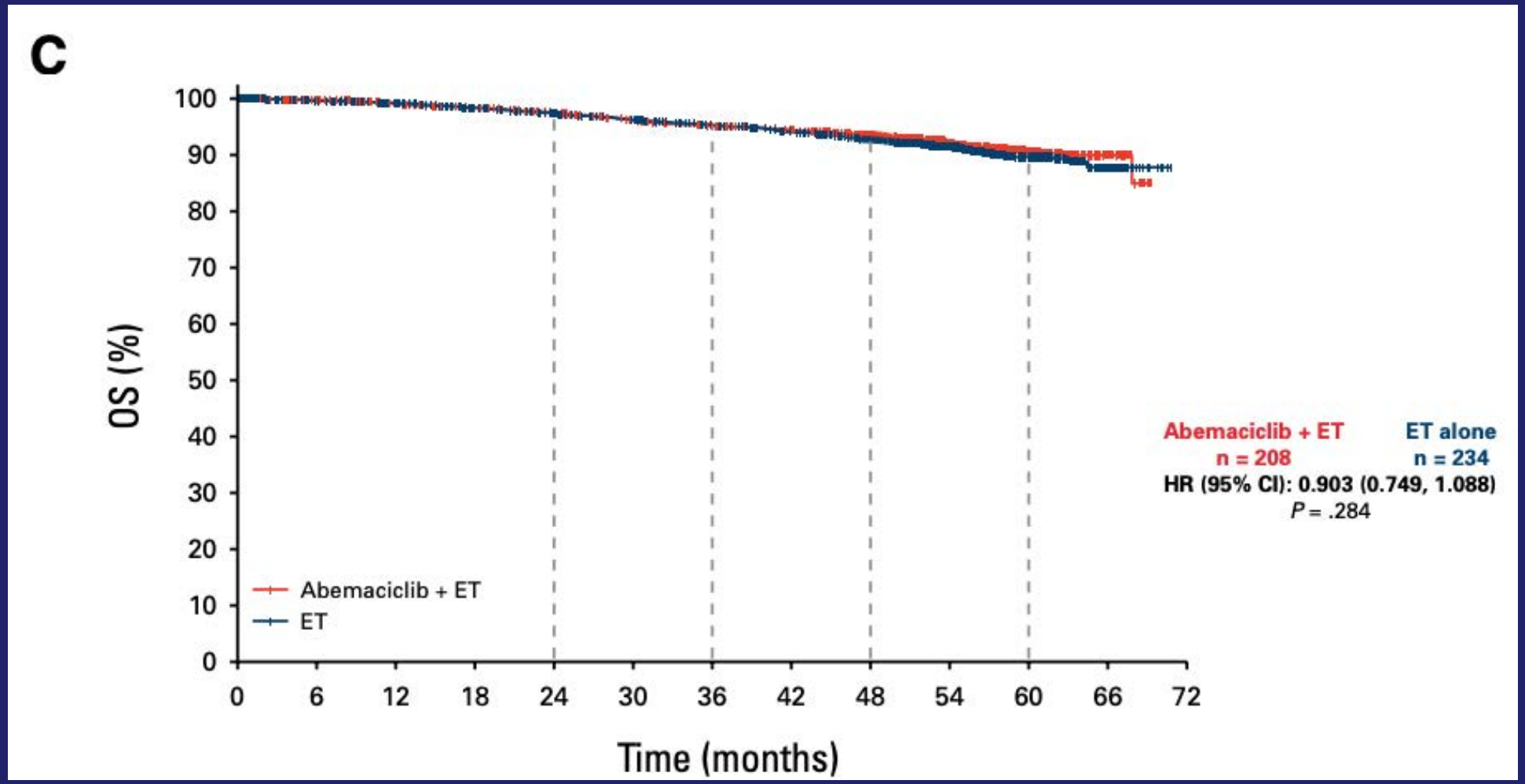
2-year: 2.5%

3-year: 4.1%

5-year: 6.7%

Rastogi P, et al. J Clin Oncol 2024;42:987-993

# monarchE: Overall Survival 54-month median follow up




Rastogi P, et al. J Clin Oncol 2024;42:987-993

# monarchE Safety Findings

| AEs in Either Arm (≥20%), n (%) | Abemaciclib + ET (n=2791) | | ET Only (n=2800) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Diarrhea | 2333 (83.6)[a] | 218 (7.8) | 244 (8.7) | 6 (0.2) |
| Fatigue[b] | 1140 (40.8) | 80 (2.9) | 505 (18.0) | 4 (0.1) |
| Abdominal pain[b] | 996 (35.7) | 39 (1.4) | 278 (9.9) | 9 (0.3) |
| Nausea[b] | 825 (29.6) | 14 (0.5) | 253 (9.0) | 2 (<0.1) |
| Leukopenia | 1052 (37.7) | 318 (11.4) | 186 (6.6) | 11 (0.4) |
| Neutropenia | 1281 (45.9) | 548 (19.6) | 158 (5.6) | 24 (0.9) |
| Arthralgia[b] | 740 (26.5) | 9 (0.3) | 1060 (37.9) | 29 (1.0) |
| Anemia | 684 (24.5) | 58 (2.1) | 108 (3.9) | 12 (0.4) |
| Hot flush[b] | 431 (15.4) | 4 (0.1) | 644 (23.0) | 10 (0.4) |

ILD: 3% all grade, 0.4% grade 3/4, 0.1% grade 5
VTE: 2.5% (4.3% with tamoxifen, 1.8% with AI)

[a] One Grade 5 event occurred. [b] Maximum CTCAE Grade of 3.

1. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90. 2. Rastogi P, et al. SABCS 2020. Abstract GS-101. 3. Harbeck N, et al. *Ann Oncol*. 2021;32(12):1571-1581. 4. Rugo H et al Annals of Oncology 2022;33:616.

# Abemaciclib: FDA Prescribing Information and Guideline Recommendations

## USPI: Abemaciclib Indication in EBC[1]

Abemaciclib in combination with ET (tamoxifen or an AI) is indicated for the adjuvant treatment of adult patients with HR+, HER2-, node-positive, EBC at high risk of recurrence

## NCCN® Recommendations[2]

For the treatment of HR+, HER2-, node-positive, high-risk EBC, the NCCN® recommends consideration of 2 years of abemaciclib in combination with ET as a Category 1, Preferred treatment option[a]

## ASCO Recommendations[3,4]

For the treatment of patients with HR+, HER2-, node-positive, high-risk EBC meeting the criteria of the ITT monarchE population, ASCO recommends abemaciclib for 2 years plus ET for ≥5 years[b]

[a] Based on NCCN Breast Cancer Guidelines Version 5.2024. High risk is defined as ≥4 positive ALNs, or 1-3 positive ALNs with either grade 3 disease or tumor size ≥5 cm. Category 1 is based upon high-level evidence, where there is uniform NCCN® consensus that the intervention is appropriate.

[b] Based on the ASCO 2024 Rapid Recommendation Update, high risk of recurrence is defined as having ≥4 positive ALNs or 1-3 positive ALNs with at least one of the following: grade 3 disease, tumor size ≥5 cm, or Ki-67 ≥20%. The panel recommends considering the benefits, risks, costs, and preferences for each individual patient when deciding whether to recommend therapy. Among patients meeting criteria for both monarchE and NATALEE, the panel also notes that, of the 2 CDK4/6i, abemaciclib has longer follow-up, a deepening benefit over time, a shorter duration of therapy, and FDA approval in the adjuvant setting. In this case, the panel favors using abemaciclib, reserving use of ribociclib in patients who have a contraindication to (eg, pre-existing high-grade diarrhea) or intolerance of abemaciclib. The panel characterized the strength of the ribociclib recommendation as conditional, pending future efficacy data and regulatory updates.

1. Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024. 2. NCCN Guidelines®. Breast Cancer. Version 5.2024. 3. Freedman RA, et al. *J Clin Oncol.* 2024;42(18):2233-2235. 4. Caswell-Jin JL, et al. *JCO Oncol Pract*. 2024. doi.org/10.1200/OP-24-00663 (Ahead of print).

# NATALEE study design

- Adult patients with HR+/HER2– EBC
- Prior ET allowed up to 12 mo
- **Anatomic stage IIA[a]**
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%;
      - Oncotype DX® Breast Recurrence Score ≥ 26; OR
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomic stage IIB[a] & III**
  - Stage IIB: N0 or N1
  - Stage III: N0, N1, N2, or N3

**N=5101[b]**

**R 1:1[c]**

**Ribociclib**
400 mg/day
3 weeks on/1 week off
for 3y

**NSAI**
Letrozole or anastrozole[d] for ≥5y
**+ goserelin** in premenopausal women and men

**NSAI**
Letrozole or anastrozole[d] for ≥5y
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**Primary Endpoint**
- iDFS using STEEP criteria

**Secondary Endpoints**
- Recurrence-free survival
- Distant disease-free survival
- OS
- PROs
- Safety and tolerability
- PK

**Exploratory Endpoints**
- Loco-regional recurrence-free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

**Randomization stratification**
**Anatomic stage:** II vs III
**Menopausal status:** Premenopausal women & men vs postmenopausal women
**Receipt of prior (neo)adjuvant chemotherapy:** yes/no
**Geographic location:** North America/Western Europe/Oceania vs Rest of world

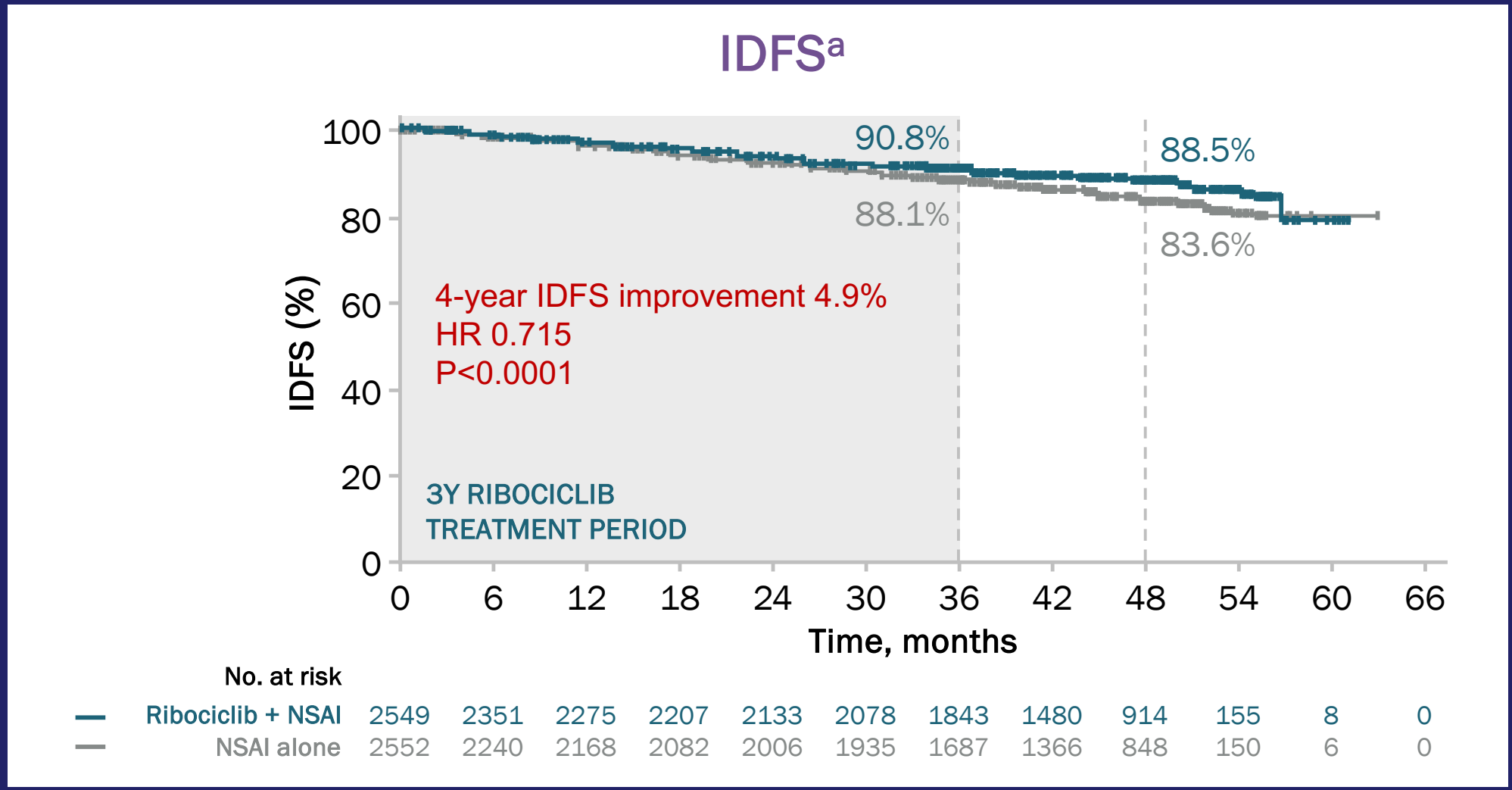
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HR+/HER2 −, hormone receptor-positive/ human epidermal growth factor receptor 2-negative; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. A trial to evaluate efficacy and safety of ribociclib with endocrine therapy as adjuvant treatment in patients with HR+/HER2- early breast cancer (NATALEE). Accessed September, 2022. https://clinicaltrials.gov/ct2/show/NCT03701334. 2. Slamon DJ, et al. J Clin Oncol. 2019;37(suppl 15). Abstract TPS597.

# Baseline characteristics

| Parameter | RIB + NSAI n = 2549 | NSAI alone n = 2552 | All patients N = 5101 |
|---|---|---|---|
| **Age, median (min-max), years** | 52 (24-90) | 52 (24-89) | 52 (24-90) |
| **Menopausal status, n (%)** | | | |
| Premenopausal women and men[a] | 1126 (44) | 1132 (44) | 2258 (44) |
| Postmenopausal women | 1423 (56) | 1420 (56) | 2843 (56) |
| **Anatomic stage[b,c], n (%)** | | | |
| Stage IIA | 479 (19) | 521 (20) | 1000 (20) |
| Stage IIB | 532 (21) | 513 (20) | 1045 (20) |
| Stage III | 1528 (60) | 1512 (59) | 3040 (60) |
| **Nodal status at diagnosis, n (%)** | | | |
| NX | 272 (11) | 264 (10) | 536 (11) |
| N0 | 694 (27) | 737 (29) | 1431 (28) |
| N1 | 1050 (41) | 1049 (41) | 2099 (41) |
| N2/N3 | 483 (19) | 467 (18) | 950 (19) |
| **Prior ET, n (%)[d]** | | | |
| Yes | 1824 (72) | 1801 (71) | 3625 (71) |
| **Prior (neo)adjuvant CT, n (%)** | | | |
| Yes | 2249 (88) | 2245 (88) | 4494 (88) |
| **ECOG PS, n (%)** | | | |
| 0 | 2106 (83) | 2132 (84) | 4238 (83) |
| 1 | 440 (17) | 418 (16) | 858 (17) |

[a] In the RIB+NSAI arm there were 11 men (0.4%) and in the NSAI alone arm there were 9 men (0.4%). [b] A total of 14 patients with Stage I disease were included: 9 pts (0.4%) in the RIB + ET arm and 5 pts (0.2%) in the ET alone arm. [c] Stage is derived using TNM from surgery for patients having not received (neo)adjuvant treatment, or as worst stage derived using TNM at diagnosis and TNM from surgery for patients having received (neo)adjuvant treatment. [d] Prior OFS was received by 670 pts (26.3%) in the RIB + NSAI arm and 620 pts (24.3%) in the NSAI alone arm.
CT, chemotherapy; ET, endocrine therapy; N0, no nodal involvement; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, 10 or more axillary lymph nodes or collarbone lymph nodes; NSAI, nonsteroidal aromatase inhibitor; NX, regional nodes were not assessed.

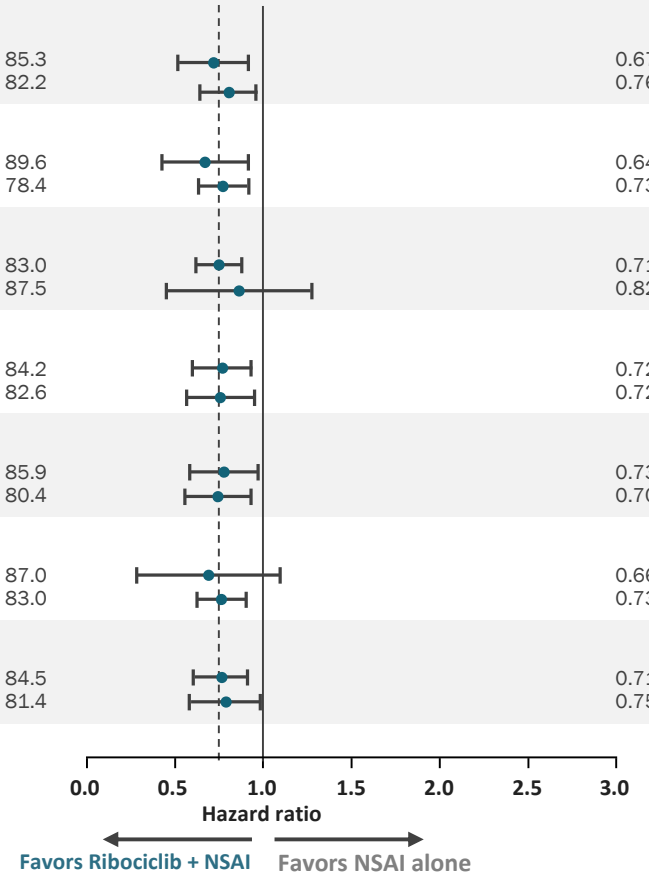
# NATALEE: IDFS at 44.2 mos




Fasching P, et al ESMO 2024 LBA13

# NATALEE: IDFS Across Subgroups

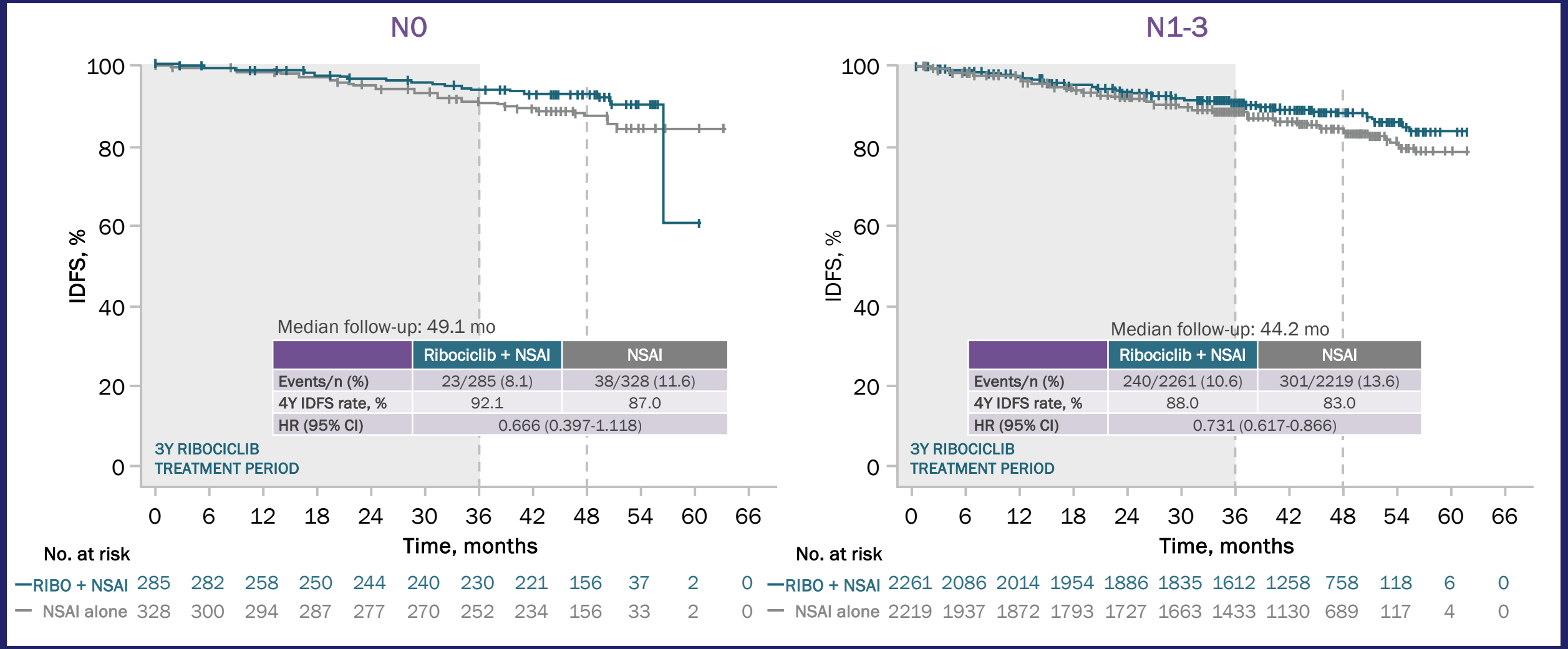
| Subgroup | Ribociclib + NSAI Events/n | Ribociclib + NSAI 4Y IDFS rate, % | NSAI alone Events/n | NSAI alone 4Y IDFS rate, % | Hazard ratio | 95% CI |
|---|---|---|---|---|---|---|
| **Menopausal Status** | | | | | | |
| Men and premenopausal women | 99/1125 | 90.7 | 137/1132 | 85.3 | 0.677 | 0.523-0.877 |
| Postmenopausal women | 164/1424 | 86.8 | 203/1420 | 82.2 | 0.760 | 0.619-0.933 |
| **AJCC Stage** | | | | | | |
| Stage II | 62/1012 | 93.9 | 96/1034 | 89.6 | 0.644 | 0.468-0.887 |
| Stage III | 200/1527 | 84.3 | 244/1512 | 78.4 | 0.737 | 0.611-0.888 |
| **Prior Chemotherapy** | | | | | | |
| Yes | 238/2249 | 88.2 | 309/2245 | 83.0 | 0.715 | 0.604-0.846 |
| No | 25/300 | 90.7 | 31/307 | 87.5 | 0.827 | 0.488-1.401 |
| **Region** | | | | | | |
| North America/Western Europe/Oceania | 151/1563 | 88.9 | 195/1565 | 84.2 | 0.726 | 0.587-0.898 |
| Rest of world | 112/986 | 88.0 | 145/987 | 82.6 | 0.722 | 0.564-0.925 |
| **Ki-67 Status[a]** | | | | | | |
| Ki-67 ≤20% | 106/1199 | 89.9 | 142/1236 | 85.9 | 0.737 | 0.573-0.948 |
| Ki-67 >20% | 113/920 | 86.3 | 149/937 | 80.4 | 0.709 | 0.555-0.905 |
| **Nodal Status[b,c]** | | | | | | |
| N0 | 23/285 | 92.1 | 38/328 | 87.0 | 0.666 | 0.397-1.118 |
| N1-N3 | 240/2261 | 88.0 | 301/2219 | 83.0 | 0.731 | 0.617-0.866 |
| **Prior ET** | | | | | | |
| Yes | 176/1830 | 89.2 | 227/1807 | 84.5 | 0.718 | 0.589-0.874 |
| No | 87/719 | 86.7 | 113/745 | 81.4 | 0.752 | 0.568-0.994 |




The IDFS benefit with ribociclib + NSAI across subgroups was consistent with that observed in the ITT population

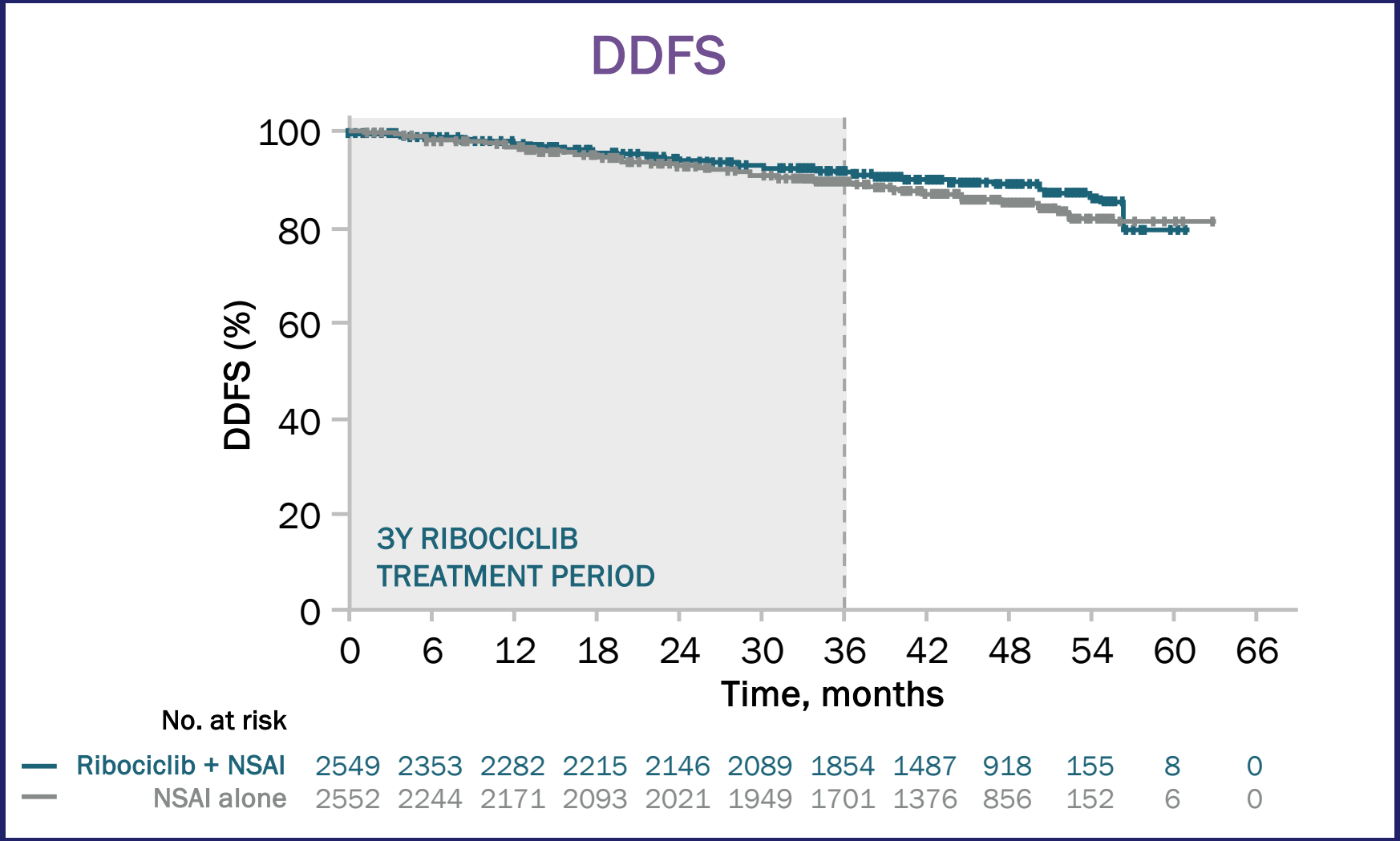
Fasching P, et al ESMO 2024 LBA13

# NATALEE: IDFS based on nodal status




Fasching P, et al ESMO 2024 LBA13

# NATALEE: DDFS at 44.2 mos

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# NATALEE: Treatment Emergent AEs

| AEs of Special Interest and Clinical Relevance in Either Arm, % | Ribociclib + NSAI (n=2526) | | NSAI (n=2441) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Neutropenia[a] | 62.8 | 44.4 | 4.5 | 0.9 |
| Febrile neutropenia | 0.3 | 0.3 | 0 | 0 |
| Arthralgia | 38.8 | 1.0 | 44.4 | 1.3 |
| Liver-related AEs[b] | 26.7 | 8.6 | 11.4 | 1.7 |
| Nausea | 23.5 | 0.2 | 7.9 | <0.1 |
| Headache | 22.9 | 0.4 | 17.2 | 0.2 |
| Fatigue | 22.8 | 0.8 | 13.5 | 0.2 |
| Diarrhea | 14.6 | 0.6 | 5.5 | 0.1 |
| Prolonged QT interval[c] | 5.4 | 1.0 | 1.6 | 0.7 |
| Prolonged ECG QT | 4.4 | 0.2 | 0.8 | <0.1 |
| ILD pneumonitis[d] | 1.6 | 0.0 | 0.9 | 0.1 |
| VTE[e] | 1.1 | 0.6 | 0.5 | 0.3 |

**Neutropenia, arthralgia, liver-related AEs, nausea, and headache were the most common AEs of special interest and clinical relevance in patients administered ribociclib along with ET**

[a] Including neutropenia and neutrophil count decreased. [b] Including all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] Grouped term. [d] Including all preferred terms identified by standardized MedDRA queries for ILD. [e] Includes all preferred terms identified by standardized MedDRA queries for VTE.
Fasching PA, et al. ESMO 2024. Abstract LBA13.

# FDA approves ribociclib with an aromatase inhibitor and ribociclib and letrozole co-pack for early high-risk breast cancer



On September 17, 2024, the Food and Drug Administration approved ribociclib (Kisqali, Novartis Pharmaceuticals Corporation) with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence. Additionally, FDA also approved the ribociclib and letrozole co-pack (Kisqali Femara Co-Pack, Novartis Pharmaceuticals Corporation) for the same indication.

# Ribociclib: FDA Prescribing Information & Guideline Recommendations

## USPI: Ribociclib Indication in EBC[1]

Ribociclib is indicated in combination with an AI for the adjuvant treatment of people with HR+, HER2- stage II and III early breast cancer at high risk of recurrence, including those with node-negative disease

## NCCN® Recommendations[2]

For the treatment of HR+, HER2-, node-positive or node-negative, high-risk EBC, the NCCN® recommends consideration of 3 years of ribociclib in combination with AI as a Category 1, Preferred treatment option[a]

## ASCO Recommendations[3,4]

For the treatment of patients with HR+, HER2-, high-risk EBC of anatomic stage II or III meeting the criteria of the NATALEE population, ASCO recommends ribociclib for 3 years plus ET[b]

[a] Based on NCCN Breast Cancer Guidelines Version 5.2024. High risk is defined as any lymph node involvement or if no nodal involvement either tumor size ≥5 cm, or if tumor size 2-5 cm, either grade 2 (and high genomic risk or Ki-67 ≥20%), or grade 3. Category 1 is based upon high-level evidence, where there is uniform NCCN® consensus that the intervention is appropriate. [b] Based on the ASCO 2024 Rapid Recommendation Update, the panel notes that for most patients with node-negative disease, the risks of ribociclib may outweigh the benefits, except for some patients with the highest risk node-negative disease. The panel recommends considering the benefits, risks, costs, and preferences for each individual patient when deciding whether to recommend therapy. Among patients meeting criteria for both monarchE and NATALEE, the panel also notes that, of the 2 CDK4/6i, abemaciclib has longer follow-up, a deepening benefit over time, a shorter duration of therapy, and FDA approval in the adjuvant setting. In this case, the panel favors using abemaciclib, reserving use of ribociclib in patients who have a contraindication to (eg, pre-existing high-grade diarrhea) or intolerance of abemaciclib. The panel characterized the strength of the ribociclib recommendation as conditional, pending future efficacy data and regulatory updates.

1. Ribociclib [US PI]. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation, 2024. 2. NCCN Guidelines®. Breast Cancer. Version 5.2024. 3. Freedman RA, et al. *J Clin Oncol.* 2024;42(18):2233-2235. 4. Caswell-Jin JL, et al. *JCO Oncol Pract.* 2024. doi.org/10.1200/OP-24-00663 (Ahead of print).

# Effect of Dose Adjustments

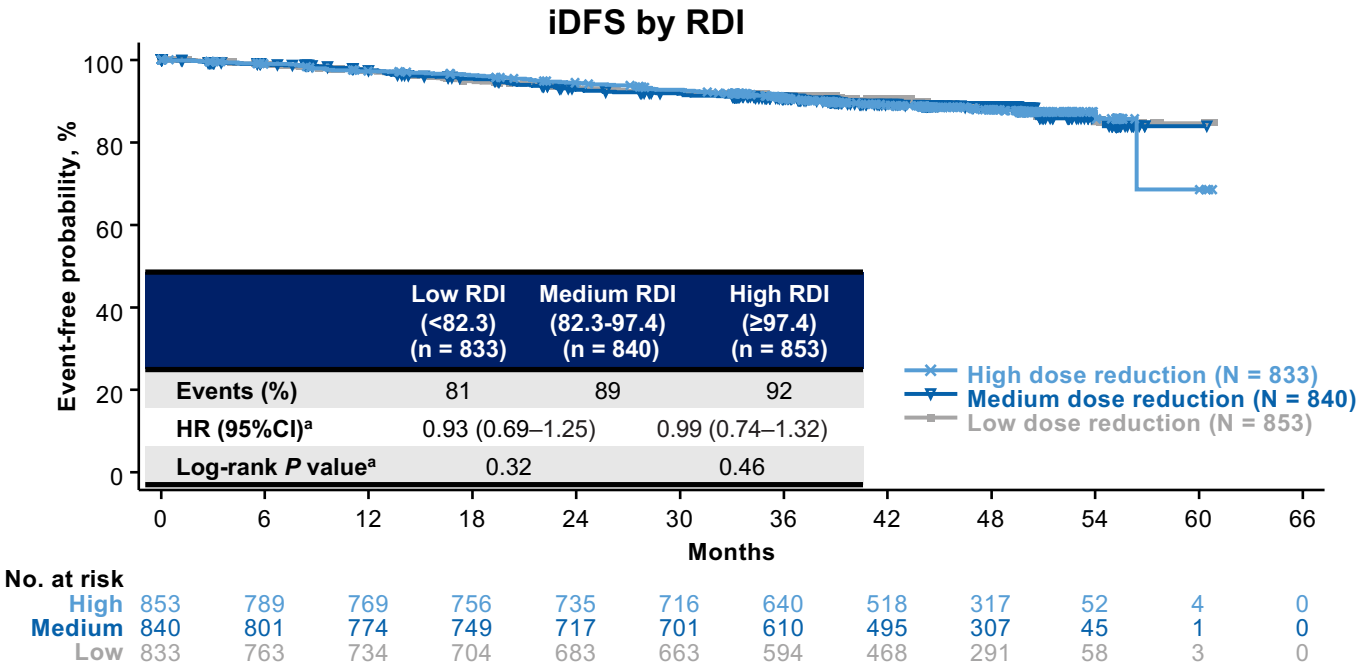
# NATALEE 4-Year Landmark: Dose Reductions In Ribo Arm

- Among the 2526 patients treated in the ribociclib + NSAI arm, 687 (27.2%) had a ribociclib dose reduction, and 1839 (72.8%) did not
  - Baseline characteristics were balanced between patients with and without dose reduction
- Among 687 patients with a RIB dose reduction, the median time to RIB dose reduction was 3.3 months, and the most common reason for a dose reduction was an AE (84.7% [582/687])
- Among those who discontinued ribociclib due to an AE (n = 509), 358 (70.3%) had no prior dose reduction
- The median duration of ribociclib exposure was similar among patients with and without a dose reduction (median, 35.7 months in both groups)

| AEs requiring dose reduction in ≥0.5% of patients, n (%) | Ribociclib + NSAI n = 2526 | |
|---|---|---|
| | All grade | Grade ≥3 |
| **Neutropenia**[a] | 355 (14.1) | 308 (12.2) |
| **ALT increased** | 48 (1.9) | 22 (0.9) |
| **Leukopenia**[b] | 44 (1.7) | 15 (0.6) |
| **Fatigue** | 27 (1.1) | 4 (0.2) |
| **AST increased** | 17 (0.7) | 3 (0.1) |

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] Combined preferred terms "neutropenia" (all grades, 212 [8.4%]; grade ≥3, 181 [7.2%]) + "neutrophil count decreased" (all grades, 143 [5.7%]; grade ≥3, 127 [5.0%]). [b] Combined preferred terms "leukopenia" (all grades, 18 [0.7%]; grade ≥3, 8 [0.3%]) + "white blood cell count decreased" (all grades, 26 [1.0%]; grade ≥3, 7 [0.3%]).
**Reference:** Hamilton E et al. Poster presented at: SABCS 2024; December 10-13, 2024; San Antonio, TX. Poster P1-11-16.

# NATALEE 4-Year Landmark: iDFS by RDI of Ribo



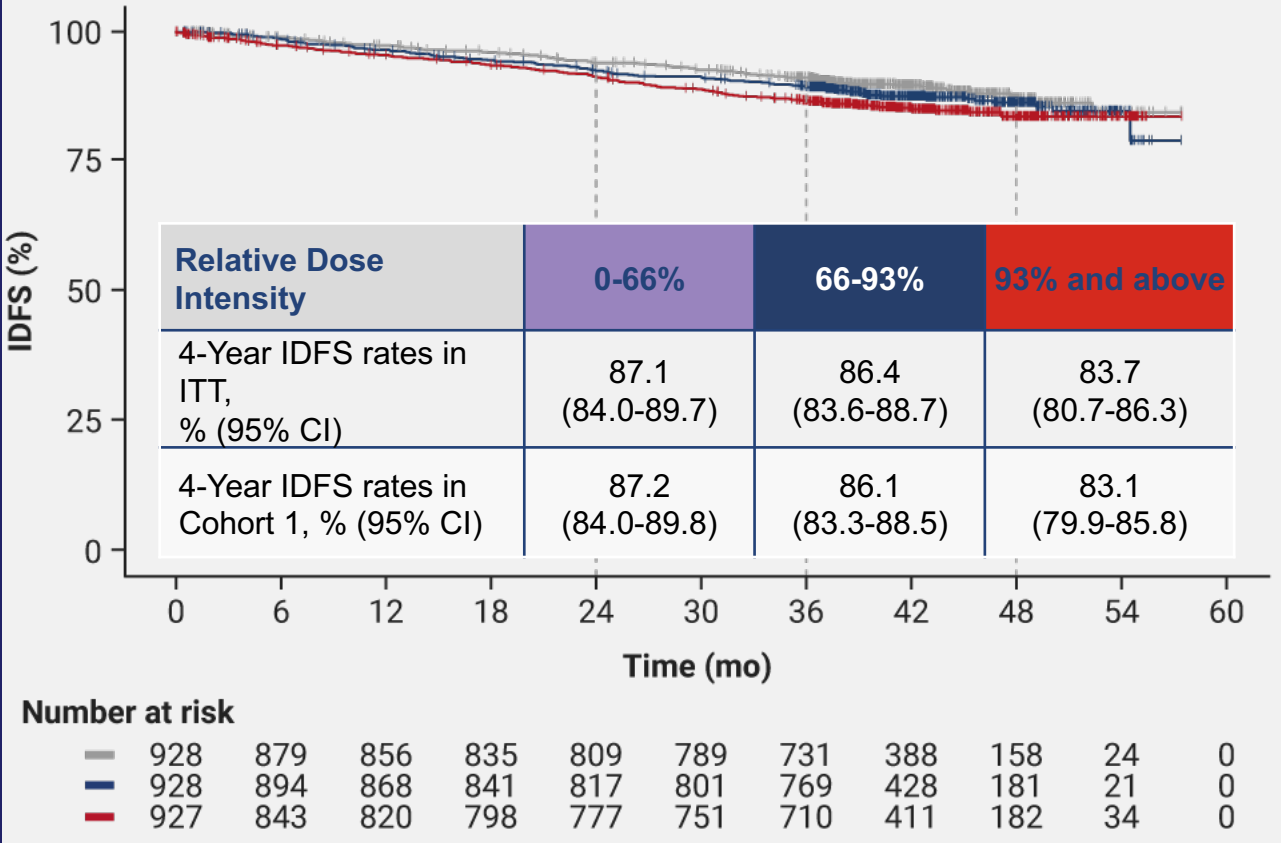

- iDFS was similar in all patients who received RIB (n = 2526) irrespective of the RDI of RIB; low, medium, and high RDI had similar iDFS (low vs high HR, 0.931; medium vs high HR, 0.985)
- When adjusted RDI was used to account for patients who discontinued RIB earlier than 36 months, iDFS remained similar in all patients regardless of adjusted RDI (low vs high HR, 0.83; medium vs high HR, 1.12)
- LM analyses demonstrated that patients with RIB dose reduction had similar post-LM time iDFS compared to those who did not

**LM Analysis of iDFS Rates by Dose Reductions**

| LM Time, months[a] | Pts on treatment longer than LM time,n (%) | Dose reduction prior to LM time | Subgroup, n (%) | 3-Year post-LM time, iDFS rate (95% CI)[b] | Post-LM time, hazard ratio (95% CI)[c] |
|---|---|---|---|---|---|
| 3 | 2204 (87.3) | Yes | 252 (11.4) | 93.1 (89.0-95.7) | **0.84 (0.54-1.30)** |
| | | No | 1952 (88.6) | 90.4 (89.0-91.7) | |
| 6 | 2041 (80.8) | Yes | 360 (17.6) | 91.9 (88.4-94.4) | **0.80 (0.54-1.19)** |
| | | No | 1681 (82.4) | 90.6 (89.0-92.0) | |
| 12 | 1906 (75.5) | Yes | 405 (21.2) | 92.2 (88.9-94.5) | **0.81 (0.54-1.21)** |
| | | No | 1501 (78.8) | 91.0 (89.2-92.4) | |

# monarchE: Efficacy and Treatment Duration by Relative Dose Intensity

## IDFS According to Relative Dose Intensity[a]




| Relative Dose Intensity | 0-66% | 66-93% | 93% and above |
|---|---|---|---|
| 4-Year IDFS rates in ITT, % (95% CI) | 87.1 (84.0-89.7) | 86.4 (83.6-88.7) | 83.7 (80.7-86.3) |
| 4-Year IDFS rates in Cohort 1, % (95% CI) | 87.2 (84.0-89.8) | 86.1 (83.3-88.5) | 83.1 (79.9-85.8) |

| | No Dose Reduction n=1570 | One Dose Reduction n=832 | Two dose Reductions n=389 |
|---|---|---|---|
| **Treatment duration, months** Median (Q1-Q3) | 23.7 (14.9–23.8) | 23.7 (20.6–23.8) | 23.7 (13.2–23.8) |
| >3 months, % | 86 | 95 | 94 |
| >6 months, % | 81 | 90 | 86 |
| >12 months, % | 76 | 81 | 76 |
| >18 months, % | 73 | 77 | 70 |
| **Cumulative Dose, mg** Median (Q1-Q3) | 192,450 (112,900–210,900) | 137,475 (*98,825–151,950*) | 77,200 (50,100–96,500) |
| **Relative Dose Intensity[a], %** Median (Q1-Q3) | 94.6 (83.4-99.0) | 66.5 (59.5-74.4) | 40.2 (34.5-50.7) |

[a] Relative dose intensity was defined as the average daily dose of abemaciclib received by each patient over the treatment duration, relative to the full dose (150 mg twice per day). Dose reductions of up to two 50-mg dose levels (100 or 50 mg) were permitted during the on-study treatment period.

Goetz MP, et al. *NPJ Breast Cancer.* 2024;10(1):34.

# Summary: Two Approved Adjuvant CDK4/6is

| | NATALEE (ribociclib) | monarchE (abemaciclib) |
|---|---|---|
| N | 5101 | 5637 |
| Length of CDK4/6i | 3 years | 2 years |
| Prior chemotherapy | 88% | 95% |
| Grade 3 | 27% | 38% |
| Node negative | 28% | 0.2% |
| N1 | 41% | 40% |
| ≥N2 | 19% | 60% |
| Median follow up | 44.2 mos | 54 mos |
| 3-year iDFS | 90.4% vs. 87.1%<br>Δ3.3%, HR 0.748, P=0.0014 | 89.2% vs 84.4%<br>Δ4.8% |
| 4-year iDFS | 88.5% vs. 83.6%<br>Δ4.9%, HR 0.715, P<0.0001 | |
| 5-year IDFS | Not reached | 83.6 vs. 76.0%<br>Δ7.6%, HR 0.680, p<0.001 |

# NATALEE and monarchE
# Patient Population Comparison for Adjuvant CDK 4/6 Inhibitors

| AJCC Anatomical Staging[1] | TN (M0) | NATALEE[2] | monarchE[3] |
|---|---|---|---|
| **Stage IA** | T1N0 | | |
| **Stage IB** | T0N1mi | | |
| | T1N1mi | | G3 or Ki67 ≥ 20% |
| **Stage IIA** | T0N1 | | |
| | T1N1 | | G3 or Ki67 ≥ 20% |
| | T2N0 | G3, or G2 with Ki-67 ≥ 20% or high genomic risk | |
| **Stage IIB** | T2N1 | | G3 or Ki67 ≥ 20% |
| | T3N0 | | |
| **Stage IIIA** | T0N2 | | |
| | T1N2 | | |
| | T2N2 | | |
| | T3N1 | | |
| | T3N2 | | |
| **Stage IIIB** | T4N0 | | |
| | T4N1 | | |
| | T4N2 | | |
| **Stage IIIC** | Any TN3 | | |

1. Giuliano AE, et al. Breast cancer. In: Amin MB, et al, eds. AJCC Cancer Staging Manual. 8th ed. Springer; 2017:587-636; 2. Slamon DJ, et al. J Clin Oncol. 2019;37(suppl 15):Abstract TPS597; 3. ClinicalTrials.gov. Accessed January 11, 2024. https://clinicaltrials.gov/ct2/show/NCT03155997.

# Conclusions

- High risk ER+ breast cancer available adjuvant options:
  - Node positive
    - Abemaciclib
    - Ribociclib
  - Node negative, Stage II
    - Ribociclib

# Faculty Case Presentations

# Case Presentation – Dr Wander

55yo postmenopausal woman (G2P2)
PMH: HTN, HLD, Hypothyroidism
Meds: Levothyroxine, Lisinopril

Initial Presentation:
Diagnostic imaging with 2.5cm RUQ breast lesion, normal-appearing axilla
Biopsy with grade 2 ER+ (90%, strong), PR+ (20%, weak), HER2 IHC 1+

Therapeutic Approach:
Upfront breast excision and SLNB; pathology with 2.7cm, grade 2, margins negative, 2/3 SLN positive (all micrometastatic)
Onco*type* DX 35
Adjuvant chemotherapy with **docetaxel and cyclophosphamide** x4 (well tolerated)
Completed adjuvant XRT to breast and axilla
Planning for extended adjuvant AI therapy with **letrozole** x7y + **ribociclib** x3y

# Case Presentation – Dr Goetz

A 44-year-old pre-menopausal woman presents with a clinical T3, grade 3, cN+, ER+/HER2-, ductal carcinoma involving the right breast. Ki-67 was 45%. The patient underwent germline mutation testing that *demonstrated* a *BRCA2* pathogenic variant (PV). Mammogram and MRI confirmed the right breast tumor with at least one involved axillary lymph node, but no evidence for any abnormalities in the left breast. A PET scan was negative for distant metastatic disease.

The patient received neoadjuvant chemotherapy (AC-T) and following completion of chemotherapy, elected for lumpectomy and ALND. Pathology at the time of surgery demonstrated a 4 cm tumor (80% cellularity) with four involved lymph nodes, including two with extracapsular extension. RCB score was III.

In addition to adjuvant radiation, what systemic therapy would you recommend:

a. Letrozole alone for 5 years
b. Letrozole for 5 years plus 2 years of abemaciclib
c. Letrozole for 5 years plus olaparib for 1 year, followed by ribociclib for 3 years
d. Letrozole for 5 years, olaparib for 1 year followed by abemaciclib for 2 years

# Case Presentation – Dr Goetz (Continued)

Answer: This patient has a locally advanced breast cancer with several high-risk features including T size, nodal involvement, high nuclear grade, and extensive residual disease following standard neoadjuvant chemotherapy. The presence of a pathogenic *BRCA2* mutation and extensive residual disease makes her eligible to receive adjuvant olaparib, which when administered for 1 year following surgery concurrently with hormonal therapy, reduces the risk for invasive disease or death (HR 0.58; 99.5% CI, 0.41 to 0.82; P<0.001; see Tutt et al. NEJM 2021). The presence of high-risk features (four or more positive axillary lymph nodes, or between one and three positive axillary lymph nodes and either grade 3 disease or tumor size of 5 cm or larger) makes her eligible for adjuvant abemaciclib, which when administered for two years concurrent with hormonal therapy reduces the risk of invasive disease or death (HR 0·664 (95% CI 0·578-0·762, p<0·0001). Answer 1 and 2 are incorrect, as these approaches would deny the patient treatments proven to reduce the risk of recurrence and death. While answer 3 is possible, requiring the patient to take an additional 1 year (3 vs 2) of adjuvant CDK 4/6 without an obvious benefit for the 2$^{nd}$ year would be suboptimal and potentially more costly. Answer 4 is the best answer

# Agenda

**Module 1:** Role of CDK4/6 Inhibitors in Hormone Receptor (HR)-Positive Localized Breast Cancer – Dr Hurvitz

**Module 2: Incorporation of CDK4/6 Inhibitors into the Management of HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) – Dr Wander**

**Module 3:** Evolving Role of PI3K Inhibitors for HR-Positive mBC Harboring PIK3CA Mutations – Dr Goetz

**Module 4:** Clinical Utility of AKT Inhibitors for Patients with Progressive HR-Positive mBC – Dr Jhaveri

**Module 5:** Oral Selective Estrogen Receptor Degraders (SERDs) for HR-Positive mBC – Dr Kaklamani

RTP RESEARCH TO PRACTICE

Mass General Brigham
Mass General Cancer Center

# Incorporation of CDK4/6 Inhibitors into the Management of HR-Positive, HER2-Negative Metastatic Breast Cancer

December 11th, 2024

Endocrine Based Therapy in Breast Cancer: SABCS 2024

Research To Practice

San Antonio, TX

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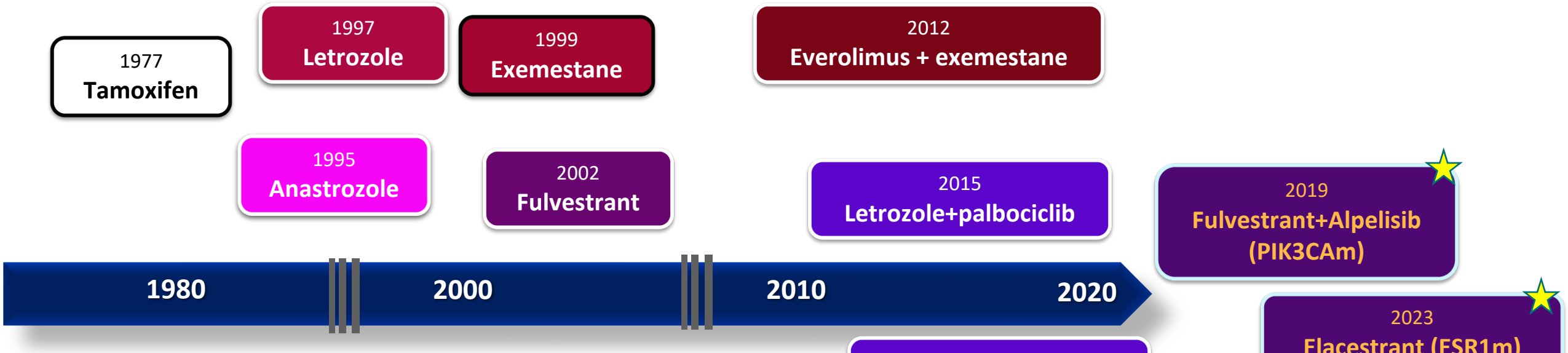
# Evolving Insights into CDK4/6i Therapy

- Today's Therapeutic Landscape and Resistance Mechanisms
- Key adverse events for CDK4/6i-based therapies
- Updated overall survival data for 1st line AI + CDK4/6i therapies
  - PALOMA-2, MONALEESA-2, and MONARCH 3
- New insights into CDK4/6i deployment: SONIA and RIGHT Choice
- CDK after CDK therapy in the postMONARCH trial
- Optimizing CDK4/6i selection: patient and disease-related factors
- Shifting therapeutic approaches and future directions

# Metastatic Breast Cancer: The Road to Personalized Therapy




**Hormonal Therapies:**

- **Selective ER Modulators - Tamoxifen**
- **Aromatase Inhibitors – Letrozole, Anastrozole, Exemestane**
- **Selective ER Degraders – Fulvestrant >> Elacestrant**

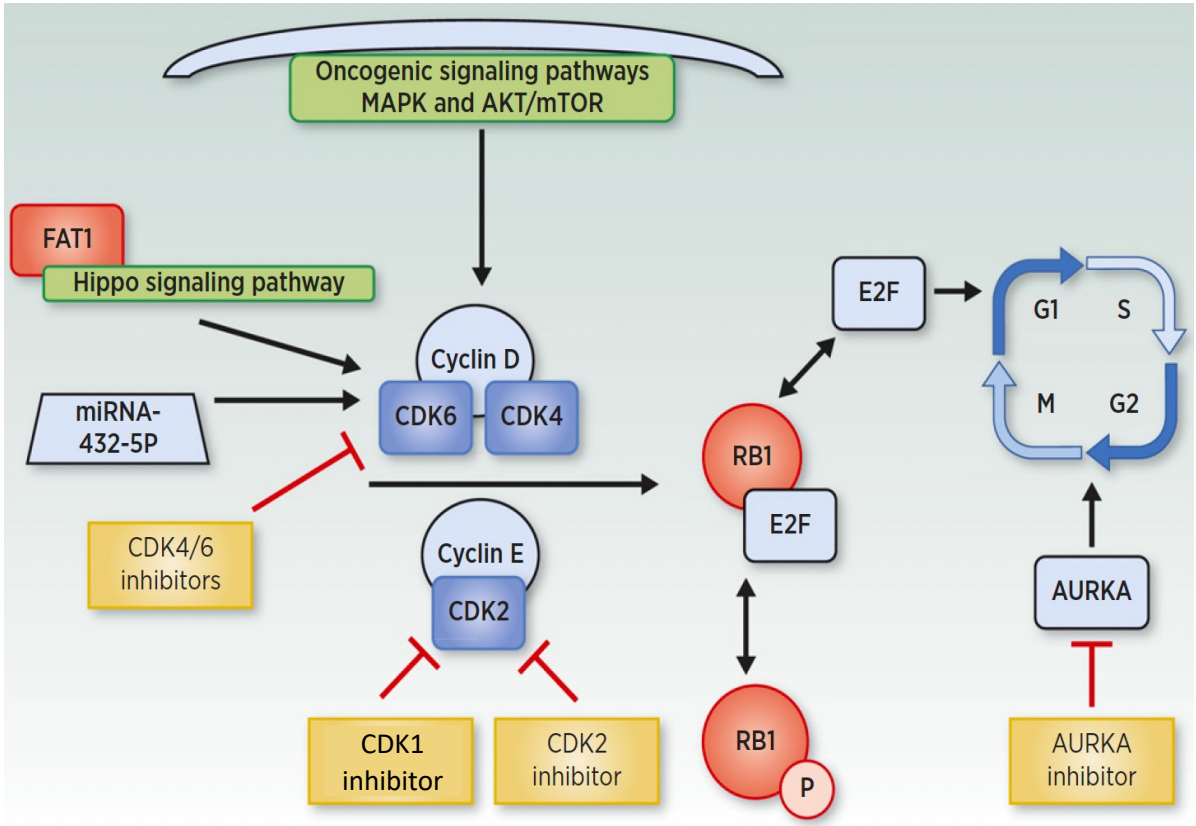
**Targeted Therapies:**

- **CDK4/6 inhibitors – Palbociclib, Ribociclib, Abemaciclib**
- **PI3K, mTOR, AKT inhibitors – Everolimus, Alpelisib, Capivasertib, Inavolisib**

# Resistance Drivers Define New Therapeutic Targets

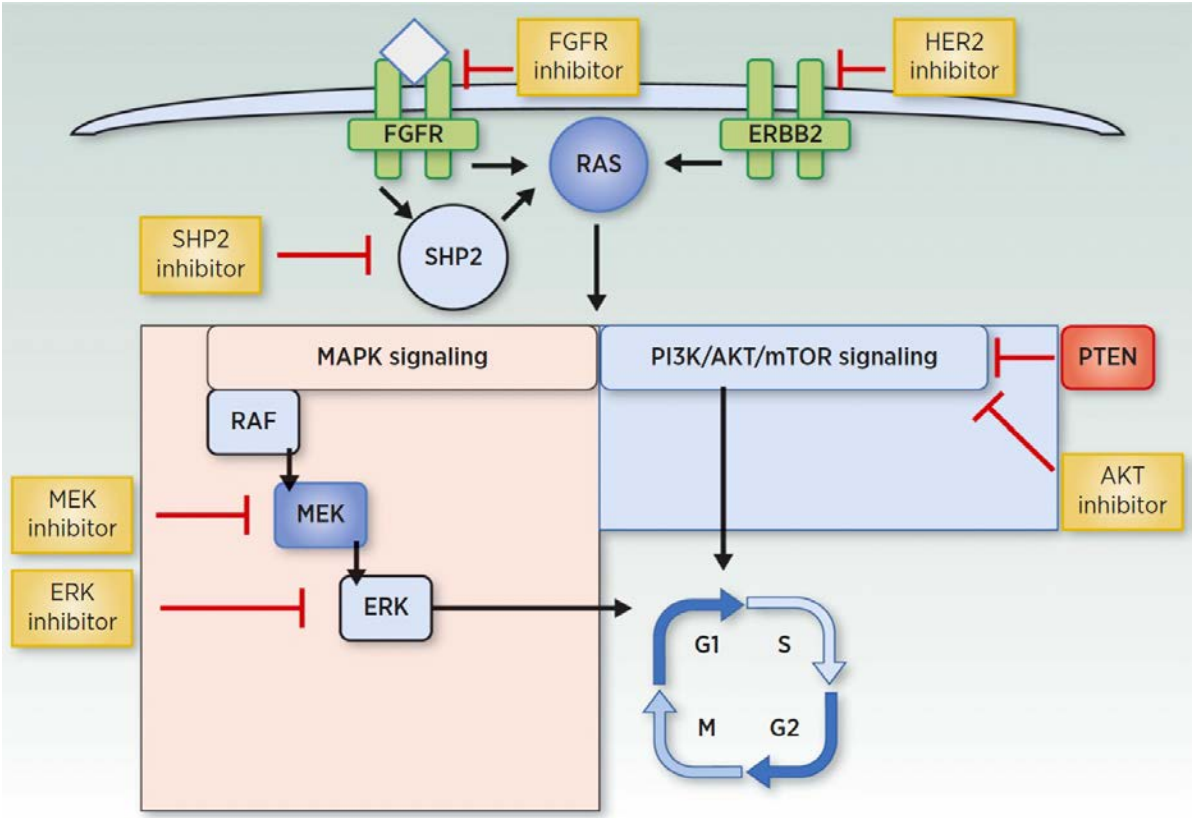
## Cell cycle regulators

CCNE/CDK2
RB1/AURKA
FAT1/CDK6




## Oncogenic growth signaling mediators

Receptor tyrosine kinases
RAS / MAPK pathway
PI3K/AKT/mTOR pathway




Lloyd MR et al CCR 2022

# CDK4/6i Drug Dosing and Toxicity

| | Palbociclib | Ribociclib | Abemaciclib | Notes |
|---|---|---|---|---|
| Schedule (starting dose) | 1 pill daily Days 1-21 of 28-day cycle | 3 pills daily Days 1-21 of 28-day cycle | 1 pill twice daily Continuous | |
| Neutropenia | ++ | ++ | + | *Febrile Neutropenia <2% Overall |
| Diarrhea | | + | ++ | |
| Cr Elevation | | | + | *No impact on GFR |
| LFT elevation | | + | + | |
| Qt Prolongation | | + | | *Initiate with Qt<450 |
| Pneumonitis | + | + | + | *1-2% risk treat with steroids and stop drug |

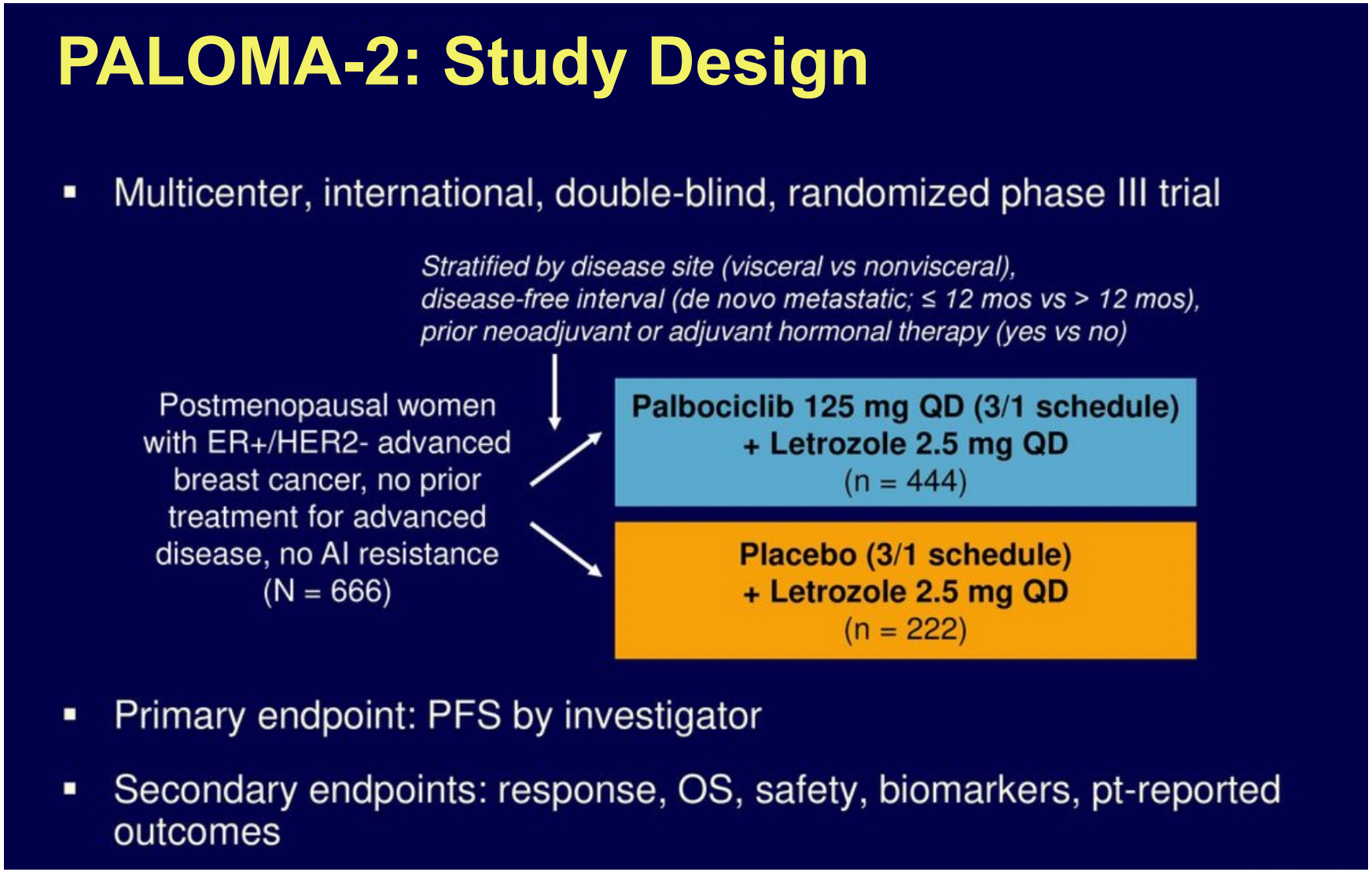
Ettl J. *Breast Care* 2019:14: 86-92

# CDK4/6i First-Line Studies

| Trial | PFS Δ | HR/P value | OS Δ | HR/P value |
|---|---|---|---|---|
| PALOMA-1[1] | 10 mos. | 0.49/.004 | 3 mos. | 0.9/.28 |
| PALOMA-2[2] | 10 mos. | 0.48/.001 | 2.7 mos. | 0.956/.34 |
| MONALEESA-2[3] | 9 mos. | 0.57/<.00001 | 12.5 mos. | 0.76/.004 |
| MONARCH-3[4] | 28/15 mos. | 0.54/.000021 | 13.1 mos. | 0.804/.0664 |
| MONALEESA-3[5] | 15 mos. | 0.55/<.001 | NR/52 mos. | 0.64/NA |
| MONALEESA-7[6] | 10 mos. | 0.55/<.0001 | NR/41 mos. | 0.71/.01 |

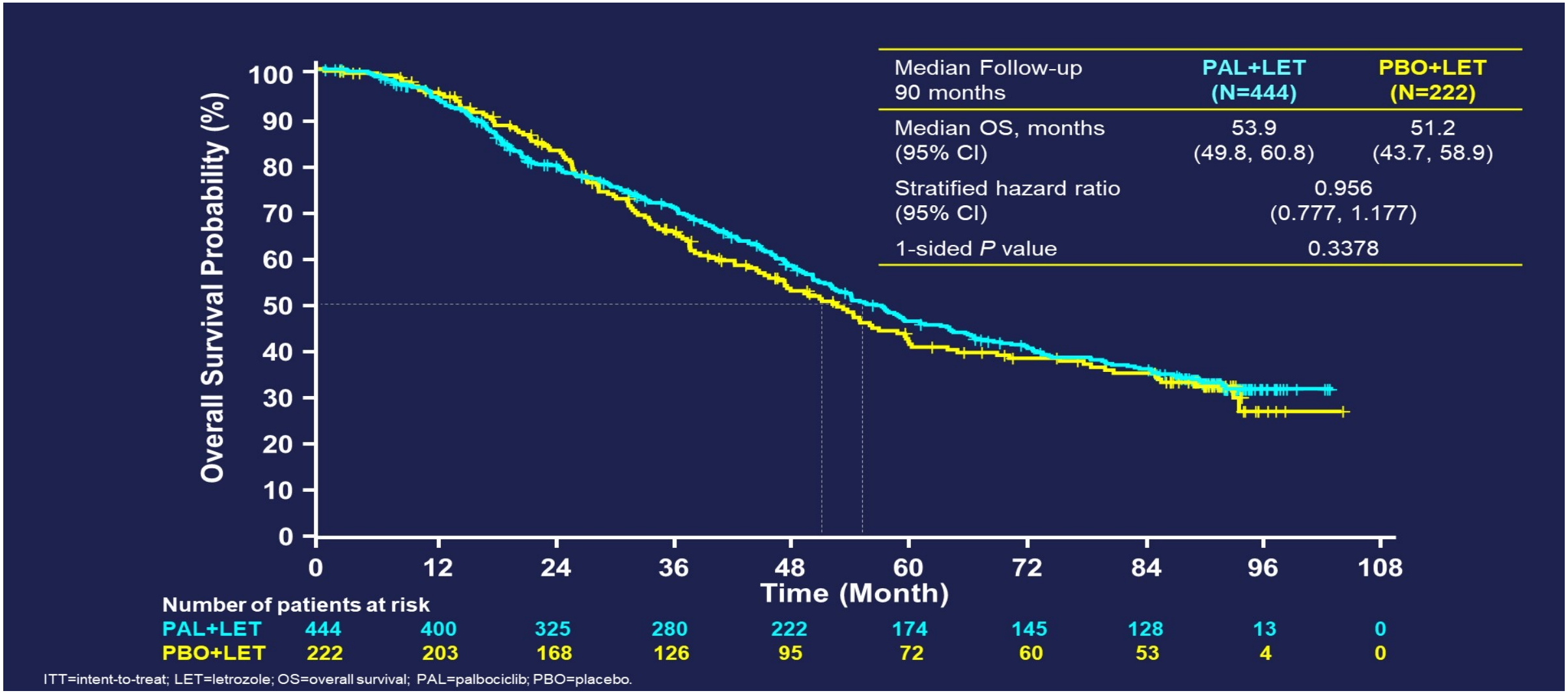
1. Finn RS, et al. *BCRT.* 2020;184(1):23-35. 2. Slamon DJ, et al. J Clin Oncol 2024;42(9):994-1000. 3. Hortobagyi G, et al. ESMO 2021. Abstract LBA17_PR. 4. Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5. 5. Slamon D, et al. *Ann Oncol.* 2021;32(8):1015-1024. 6. Im SA, et al. *N Engl J Med.* 2019;381:3017-316.

# PALOMA-2: First-line Palbociclib




Finn R, et al. ASCO 2022. Abstract LBA1003.

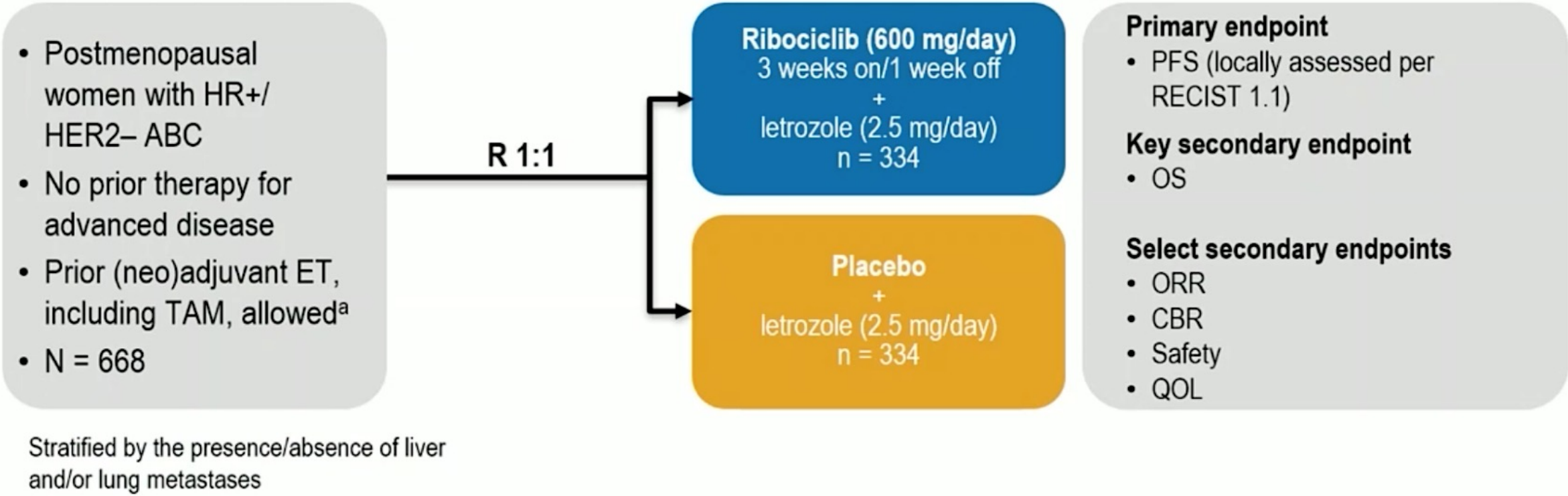
# PALOMA-2: Overall Survival (Palbociclib)




| 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 | |

Finn R, et al. ASCO 2022. Abstract LBA1003; Slamon DJ et al. *J Clin Oncol* 2024;42(9):994-1000.

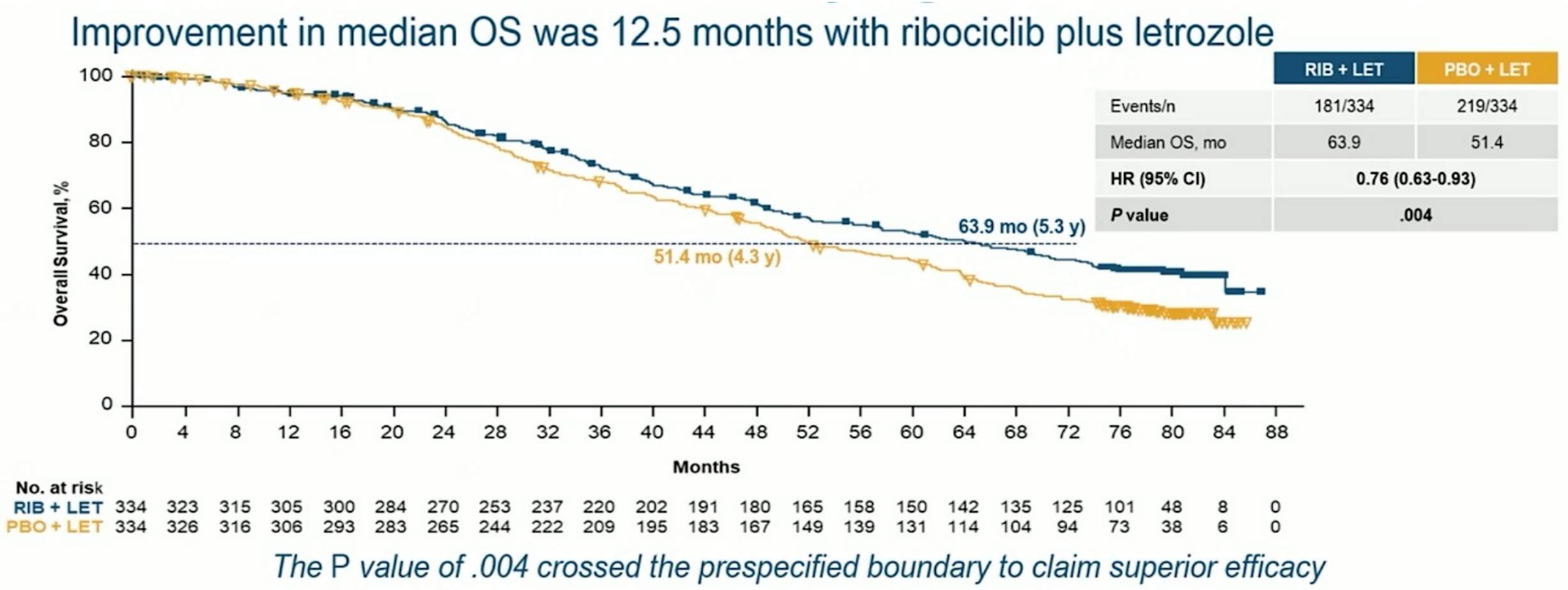
# MONALEESA-2: First-line Ribociclib




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

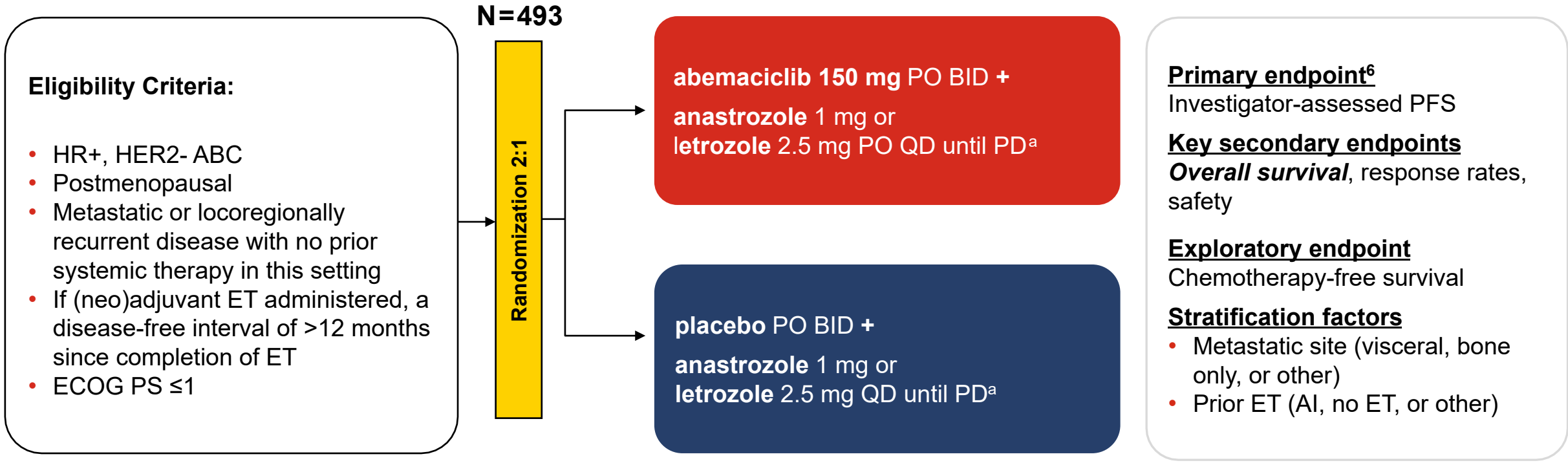
Hortobagyi G, et al. ESMO 2021. Abstract LBA17_PR.

# MONALEESA-2 Overall Survival (Ribociclib)



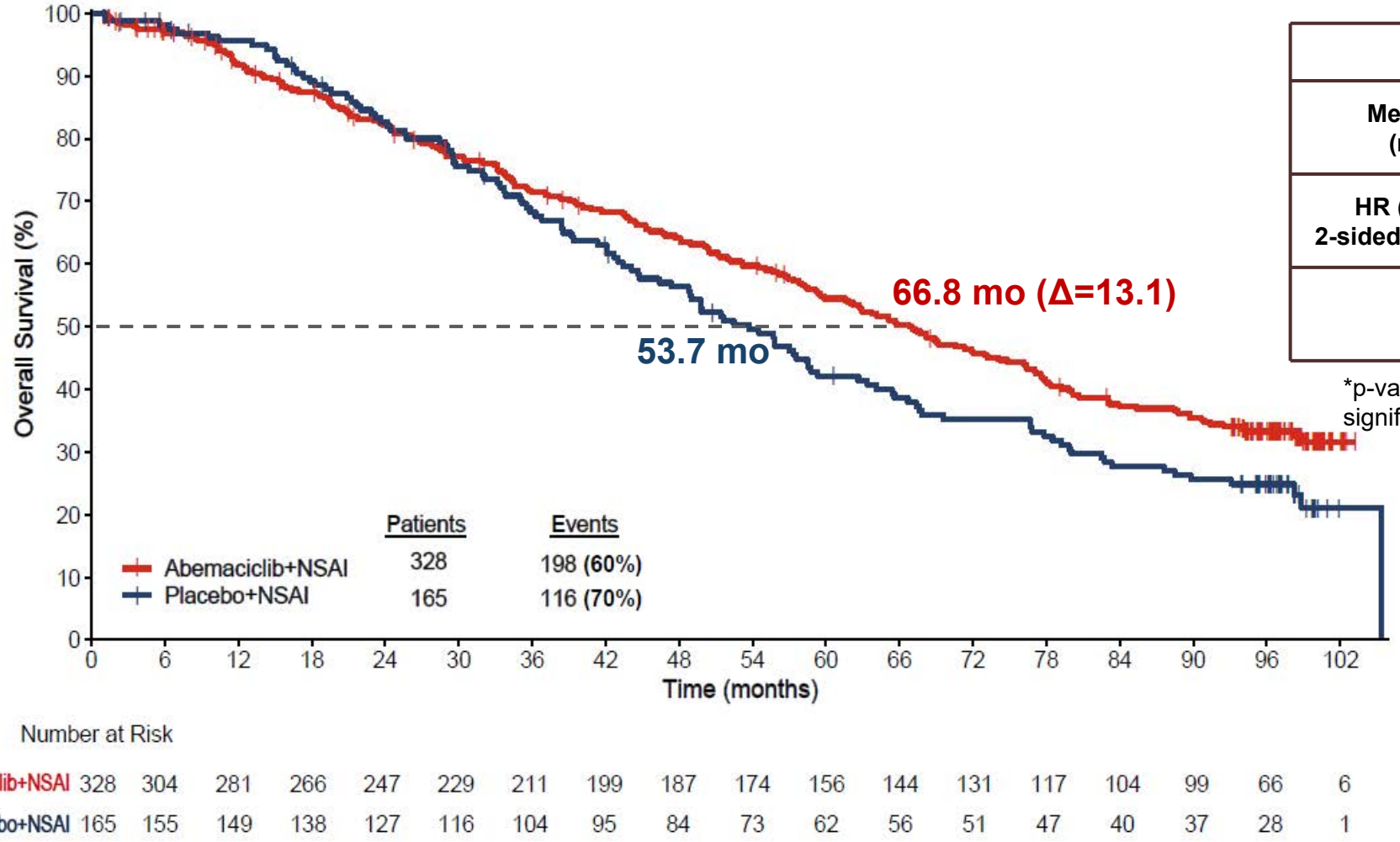

Hortobagyi G et al. ESMO 2021. Abstract LBA17_PR; Hortobagyi GN et al. *N Engl J Med* 2022;386:942-50.

# MONARCH 3 Study Design




Goetz M et al. SABCS 2023, GS01-12.

# OS in the ITT Population




Number at Risk

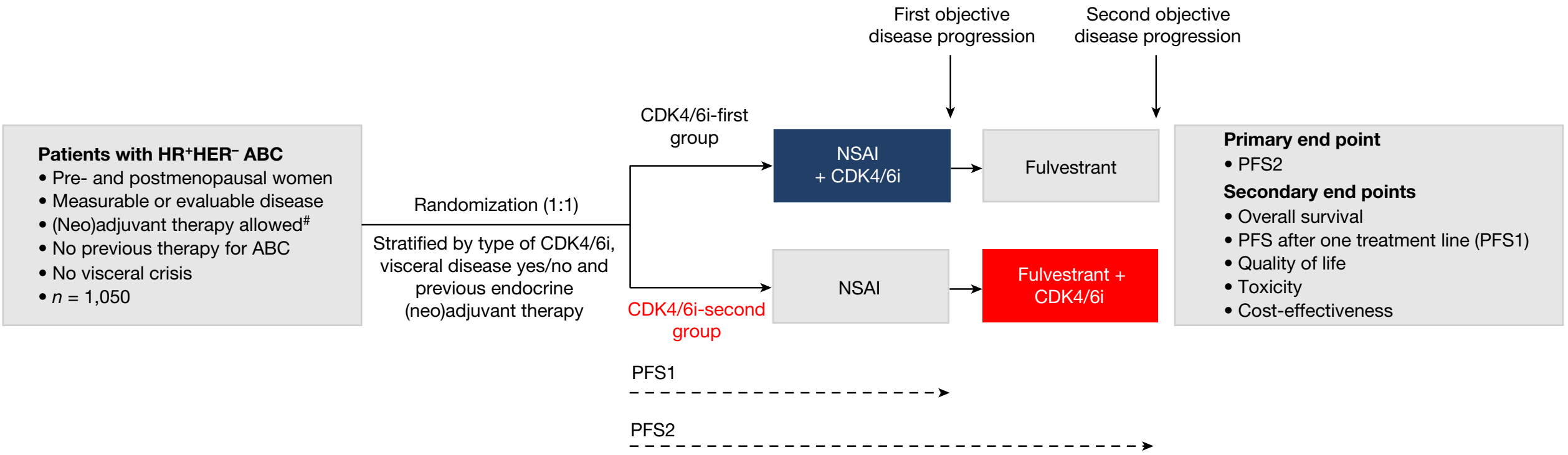
| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abemaciclib+NSAI | 328 | 304 | 281 | 266 | 247 | 229 | 211 | 199 | 187 | 174 | 156 | 144 | 131 | 117 | 104 | 99 | 66 | 6 |
| Placebo+NSAI | 165 | 155 | 149 | 138 | 127 | 116 | 104 | 95 | 84 | 73 | 62 | 56 | 51 | 47 | 40 | 37 | 28 | 1 |

| | abemaciclib + NSAI | placebo + NSAI |
|---|---|---|
| **Median OS (months)** | 66.8 | 53.7 |
| **HR (95% CI) 2-sided *P* value** | 0.804 (0.637-1.015) p=0.0664* | |
| Final OS Analysis Data cut: 29 Sep 2023 | | |

*p-value did not reach threshold (0.034) for statistical significance at this final analysis

Goetz M et al. SABCS 2023, GS01-12.

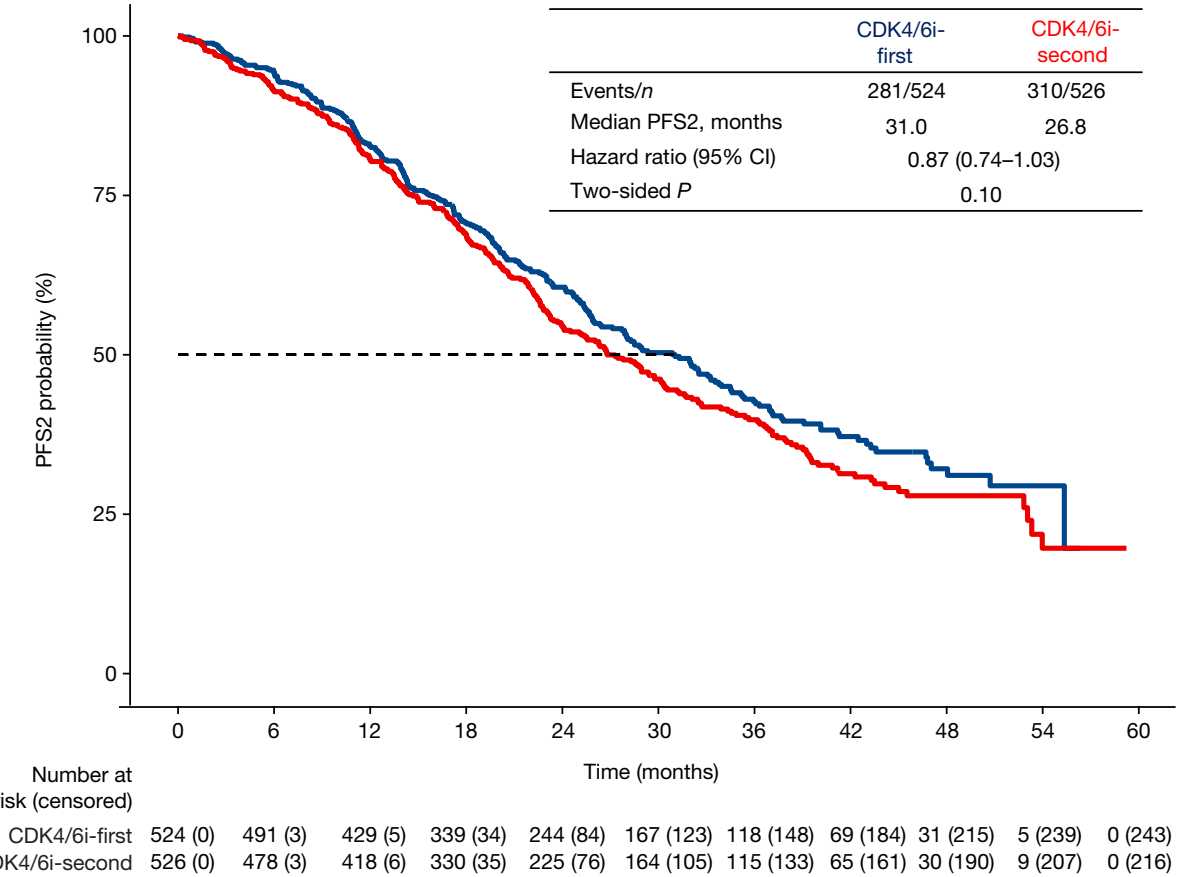
# SONIA: Phase III CDK4/6i 1st vs 2nd Line Setting




35% de novo metastatic
64% treatment-free interval >24m (for prior antiE2 exposure)
91% palbociclib; 8% ribociclib

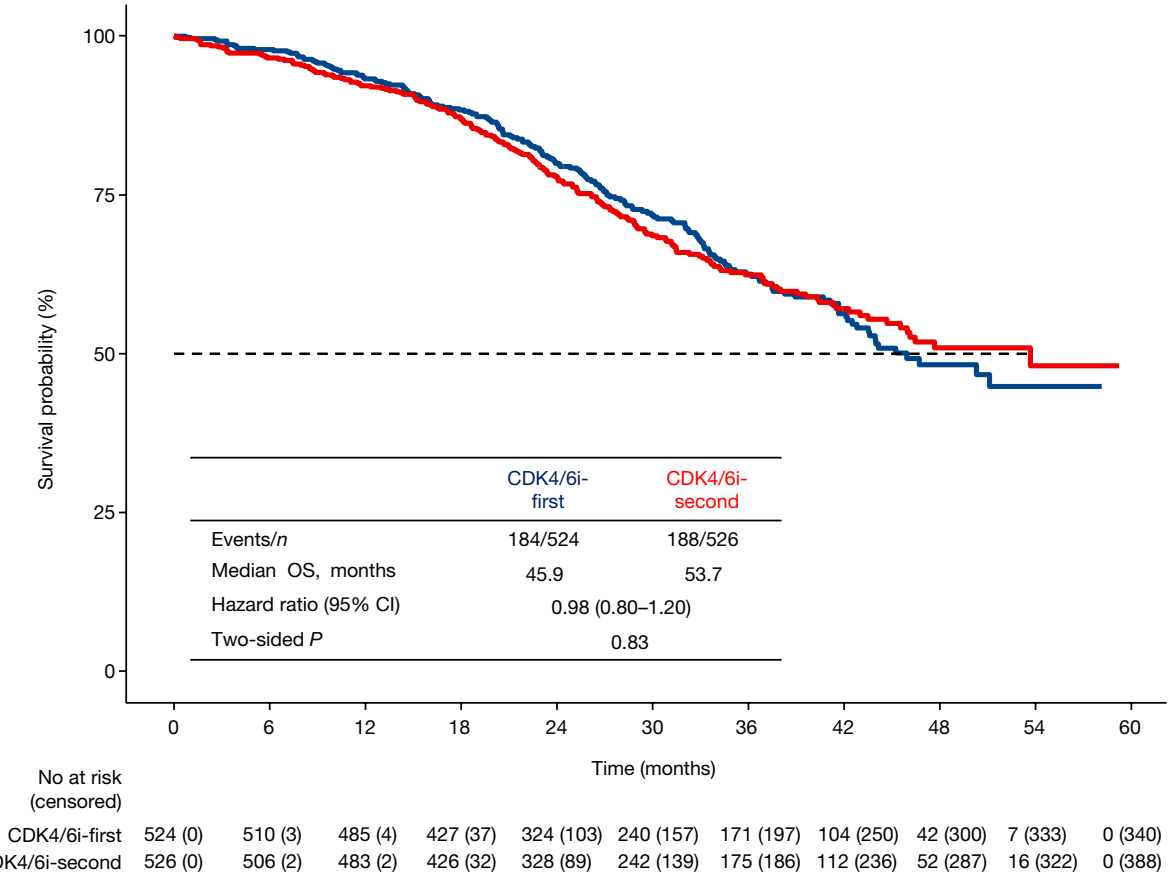
Sonke GS et al. Nature 2024

# SONIA: Clinical Outcomes




| | CDK4/6i-first | CDK4/6i-second |
|---|---|---|
| Events/*n* | 281/524 | 310/526 |
| Median PFS2, months | 31.0 | 26.8 |
| Hazard ratio (95% CI) | 0.87 (0.74–1.03) | |
| Two-sided *P* | 0.10 | |

| Number at risk (censored) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CDK4/6i-first | 524 (0) | 491 (3) | 429 (5) | 339 (34) | 244 (84) | 167 (123) | 118 (148) | 69 (184) | 31 (215) | 5 (239) | 0 (243) |
| CDK4/6i-second | 526 (0) | 478 (3) | 418 (6) | 330 (35) | 225 (76) | 164 (105) | 115 (133) | 65 (161) | 30 (190) | 9 (207) | 0 (216) |



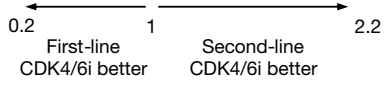

| | CDK4/6i-first | CDK4/6i-second |
|---|---|---|
| Events/*n* | 184/524 | 188/526 |
| Median OS, months | 45.9 | 53.7 |
| Hazard ratio (95% CI) | 0.98 (0.80–1.20) | |
| Two-sided *P* | 0.83 | |

| No at risk (censored) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CDK4/6i-first | 524 (0) | 510 (3) | 485 (4) | 427 (37) | 324 (103) | 240 (157) | 171 (197) | 104 (250) | 42 (300) | 7 (333) | 0 (340) |
| CDK4/6i-second | 526 (0) | 506 (2) | 483 (2) | 426 (32) | 328 (89) | 242 (139) | 175 (186) | 112 (236) | 52 (287) | 16 (322) | 0 (388) |

Sonke GS et al. Nature 2024

# SONIA: Clinical Outcomes

| Subgroup | CDK4/6i-first | CDK4/6i-second | Hazard ratio (99% CI) | | *P* for interaction |
|---|---|---|---|---|---|
| | Number of events/total number | | | | |
| **All randomly assigned patients#** | 281/524 | 310/526 | 0.87 | (0.74–1.03) | |
| **Prespecified** | | | | | |
| **Previous (neo)adjuvant endocrine therapy** | | | | | 0.34 |
| No | 126/266 | 151/272 | 0.81 | (0.59–1.10) | |
| Yes | 155/258 | 159/254 | 0.95 | (0.71–1.28) | |
| **Previous (neo)adjuvant chemotherapy** | | | | | 0.12 |
| No | 153/312 | 183/316 | 0.78 | (0.59–1.04) | |
| Yes | 128/212 | 127/210 | 1.01 | (0.73–1.40) | |
| **De novo metastatic disease** | | | | | 0.62 |
| No | 186/342 | 202/344 | 0.89 | (0.69–1.16) | |
| Yes | 95/182 | 108/182 | 0.79 | (0.54–1.15) | |
| **Visceral disease** | | | | | 0.42 |
| No | 118/233 | 136/234 | 0.80 | (0.58–1.10) | |
| Yes | 163/291 | 174/292 | 0.93 | (0.70–1.23) | |
| **Bone-only disease** | | | | | 0.33 |
| No | 237/433 | 258/435 | 0.90 | (0.71–1.14) | |
| Yes | 44/91 | 52/91 | 0.64 | (0.37–1.11) | |
| **Type of CDK4/6i** | | | | | 0.55 |
| Palbociclib | 257/472 | 267/447 | 0.86 | (0.68–1.07) | |
| Ribociclib | 24/51 | 39/72 | 1.05 | (0.52–2.12) | |
| **Post hoc** | | | | | |
| **Histological subtype** | | | | | 0.07 |
| Lobular | 61/95 | 53/86 | 0.79 | (0.61–1.01) | |
| NST | 202/394 | 241/407 | 1.15 | (0.70–1.89) | |
| **Menopausal status** | | | | | 0.02 |
| Pre- or perimenopausal | 35/69 | 50/76 | 0.55 | (0.29–1.02) | |
| Postmenopausal | 246/455 | 260/450 | 0.95 | (0.75–1.19) | |
| **Treatment-free interval (for AI)** | | | | | 0.61 |
| ≤24 months | 20/26 | 14/20 | 1.67 | (0.53–5.23) | |
| >24 months | 67/127 | 66/129 | 1.08 | (0.69–1.70) | |
| No previous AI | 194/371 | 230/377 | 0.79 | (0.61–1.02) | |
| ***PIK3CA* mutation status†** | | | | | 0.08 |
| Absent | 28/42 | 37/68 | 1.11 | (0.57–2.19) | |
| Present | 15/33 | 29/48 | 0.57 | (0.23–1.44) | |




Sonke GS et al. Nature 2024

# RIGHT Choice: RIB + ET vs Combination CT in Patients With Aggressive HR+/HER2– aBC

- Pre-/perimenopausal women
- HR+/ HER2- aBC (>10% ER+)
- No prior systemic therapy for aBC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic nonvisceral disease
- ECOG PS ≤2[b]
- Total bilirubin ≤1.5 ULN
- N=222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

**R 1:1**

**Ribociclib**
(600 mg, 3 weeks on/1 week off)
**+**
**Letrozole or anastrozole + goserelin**

**Investigators' choice of combination CT[e]**

**Docetaxel + capecitabine**
**Paclitaxel + gemcitabine**
**Capecitabine + vinorelbine**

**Tumor imaging evaluation**
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

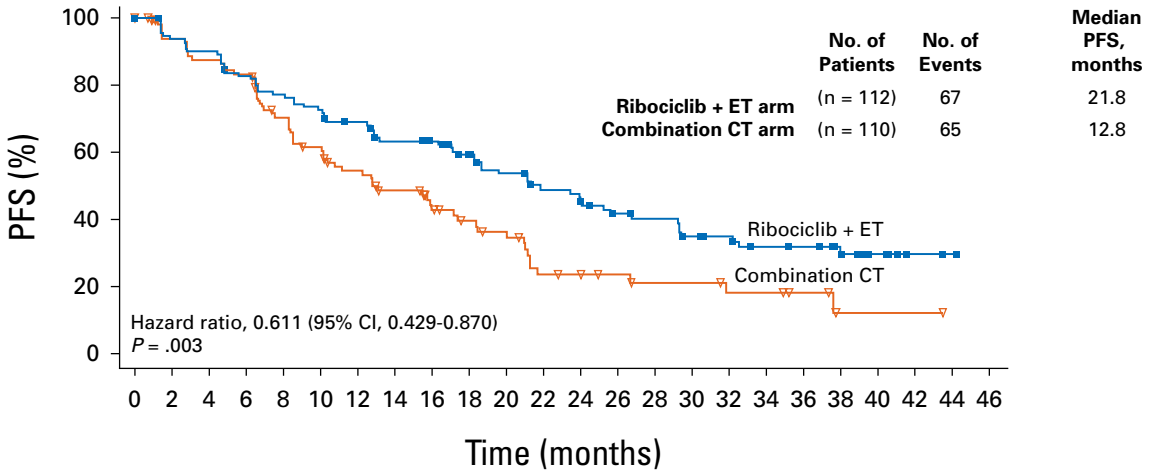
**Primary endpoint**
- PFS (locally assessed per RECIST 1.1)

**Secondary endpoints**
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QoL

**Exploratory endpoints**
- Biomarker analyses
- Healthcare resource utilization

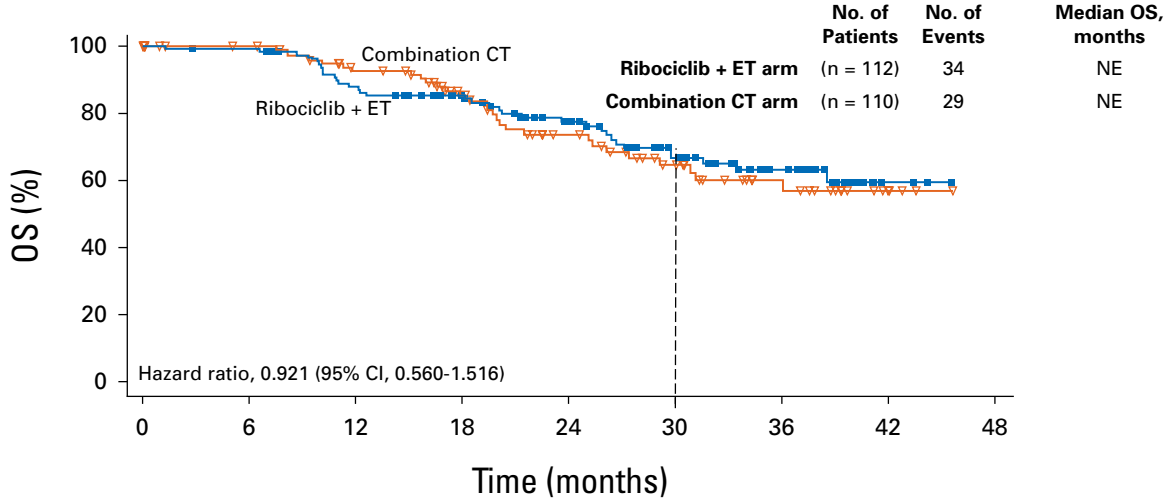
Lu YS et al SABCS 2022. GS1-10.

# RIGHT Choice: Clinical Outcomes




**No. at risk**

| | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET arm | 112 | 103 | 99 | 90 | 84 | 79 | 73 | 65 | 63 | 55 | 48 | 41 | 39 | 32 | 30 | 25 | 23 | 19 | 17 | 13 | 6 | 2 | 1 | 0 |
| Combination CT arm | 110 | 90 | 84 | 79 | 63 | 54 | 46 | 38 | 29 | 24 | 21 | 13 | 12 | 10 | 8 | 8 | 6 | 6 | 4 | 1 | 1 | 1 | 0 | 0 |



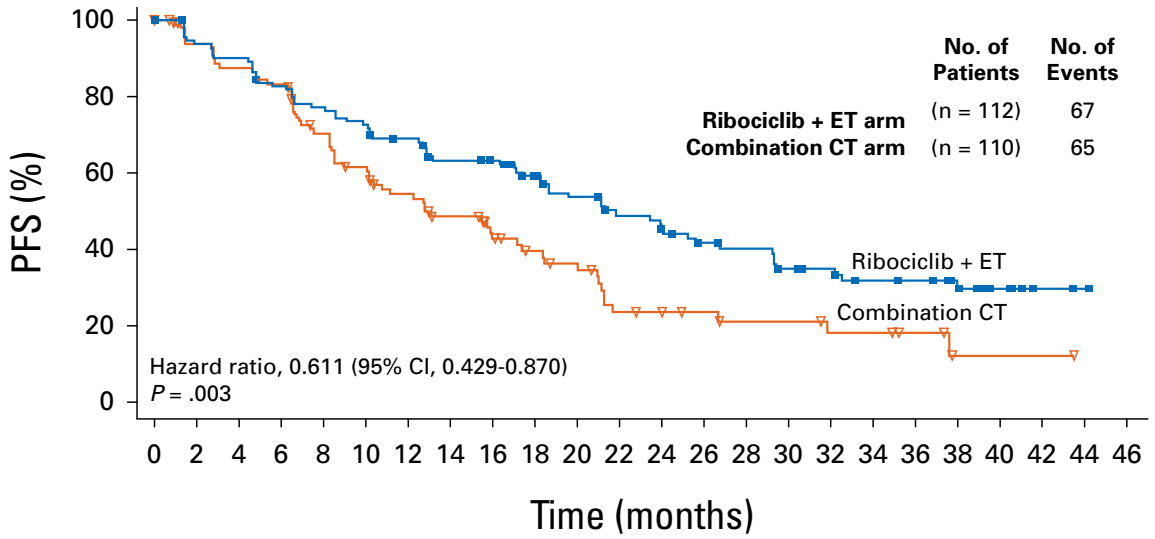

**No. at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET arm | 112 | 110 | 94 | 80 | 63 | 45 | 25 | 3 | 0 |
| Combination CT arm | 110 | 97 | 83 | 65 | 44 | 31 | 19 | 5 | 0 |

| Outcome Measures | Ribociclib + ET (n = 112)[a] | Combination CT (n = 110)[a] |
|---|---|---|
| Best overall response | | |
| Complete response | 7 (6.3) | 3 (2.7) |
| Partial response | 67 (59.8) | 65 (59.1) |
| Stable disease | 27 (24.1) | 20 (18.2) |
| Progressive disease | 9 (8.0) | 6 (5.5) |
| Unknown | 2 (1.8) | 16 (14.5) |
| ORR,[b] No. (%)<br>95% CI | 74 (66.1)<br>56.5 to 74.7 | 68 (61.8)<br>52.1 to 70.9 |
| CBR,[c] No. (%)<br>95% CI | 91 (81.3)<br>72.8 to 88.0 | 82 (74.5)<br>65.4 to 82.4 |

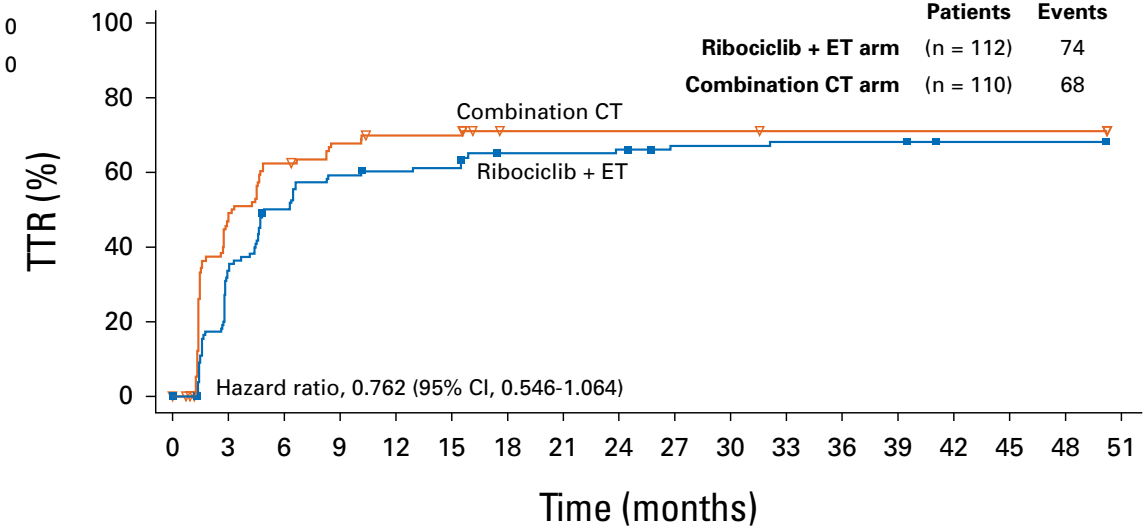
Lu YS et al JCO 2024

# RIGHT Choice: Clinical Outcomes




| | No. of Patients | No. of Events | Median PFS, months |
|---|---|---|---|
| **Ribociclib + ET arm** | (n = 112) | 67 | 21.8 |
| **Combination CT arm** | (n = 110) | 65 | 12.8 |

| **No. at risk** | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET arm | 112 | 103 | 99 | 90 | 84 | 79 | 73 | 65 | 63 | 55 | 48 | 41 | 39 | 32 | 30 | 25 | 23 | 19 | 17 | 13 | 6 | 2 | 1 | 0 |
| Combination CT arm | 110 | 90 | 84 | 79 | 63 | 54 | 46 | 38 | 29 | 24 | 21 | 13 | 12 | 10 | 8 | 8 | 6 | 6 | 4 | 1 | 1 | 1 | 0 | 0 |



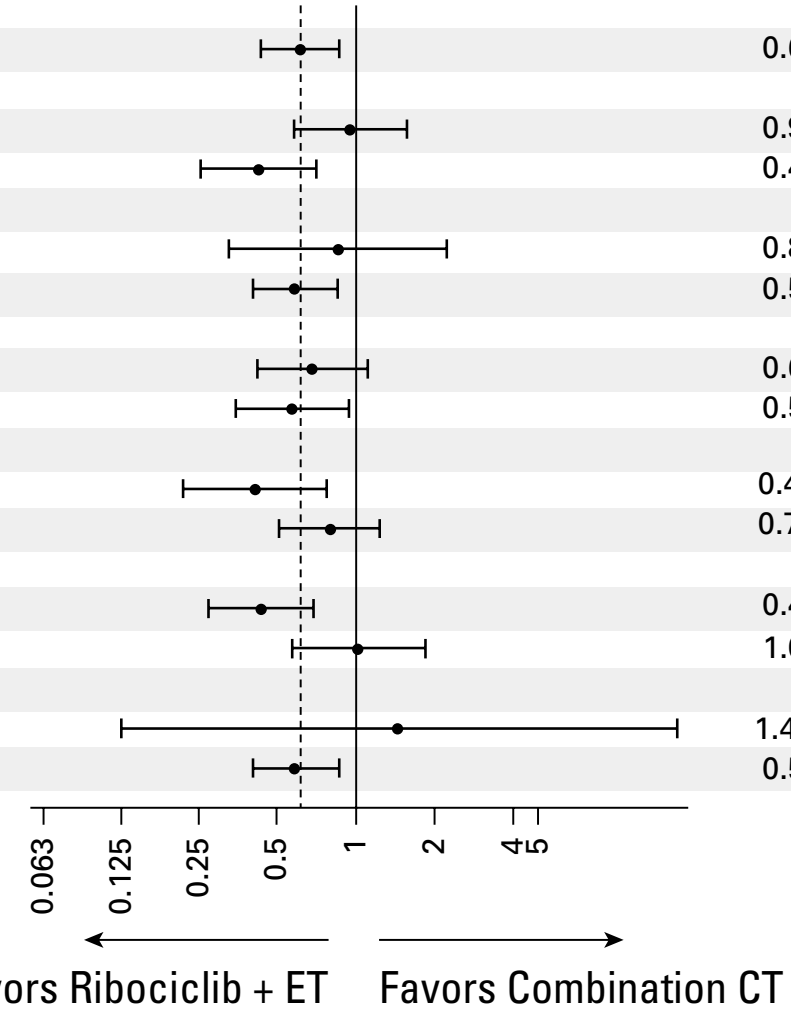

| | No. of Patients | No. of Events | Median TTR, months |
|---|---|---|---|
| **Ribociclib + ET arm** | (n = 112) | 74 | 4.9 |
| **Combination CT arm** | (n = 110) | 68 | 3.2 |

| **No. at risk** | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET arm | 112 | 72 | 54 | 44 | 42 | 41 | 35 | 35 | 34 | 31 | 31 | 30 | 30 | 30 | 27 | 27 | 27 | 0 |
| Combination CT arm | 110 | 50 | 36 | 30 | 27 | 27 | 22 | 22 | 22 | 22 | 22 | 21 | 21 | 21 | 21 | 21 | 21 | 0 |

Lu YS et al JCO 2024

# RIGHT Choice: Clinical Outcomes

| Subgroup | Ribociclib + ET Arm n/N | Combination CT Arm n/N | Hazard Ratio (95% CI) |
|---|---|---|---|
| All patients | 67/112 | 65/110 | 0.611 (0.429, 0.870) |
| Visceral crisis status (yes *v* no) | | | |
| Yes | 37/57 | 27/49 | 0.953 (0.574, 1.582) |
| No | 30/55 | 38/61 | 0.423 (0.254, 0.704) |
| Disease-free interval, years | | | |
| <2 | 11/14 | 8/9 | 0.851 (0.325, 2.231) |
| ≥2 | 56/98 | 57/101 | 0.581 (0.398, 0.847) |
| Presence of liver metastasis (yes *v* no) | | | |
| Yes | 35/54 | 32/53 | 0.681 (0.420, 1.106) |
| No | 32/58 | 33/57 | 0.565 (0.343, 0.933) |
| Age, years | | | |
| <40 | 19/32 | 28/38 | 0.410 (0.217, 0.776) |
| ≥40 | 48/80 | 37/72 | 0.789 (0.505, 1.232) |
| De novo (yes *v* no) | | | |
| Yes | 36/70 | 45/73 | 0.432 (0.270, 0.689) |
| No | 31/42 | 20/37 | 1.016 (0.562, 1.836) |
| Estrogen receptor status | | | |
| <50 | 4/8 | 3/4 | 1.457 (0.124, 17.079) |
| ≥50 | 57/95 | 56/96 | 0.585 (0.398, 0.860) |




Lu YS et al JCO 2024

# postMONARCH Trial: Abemaciclib After Prior CDK4/6i Progression

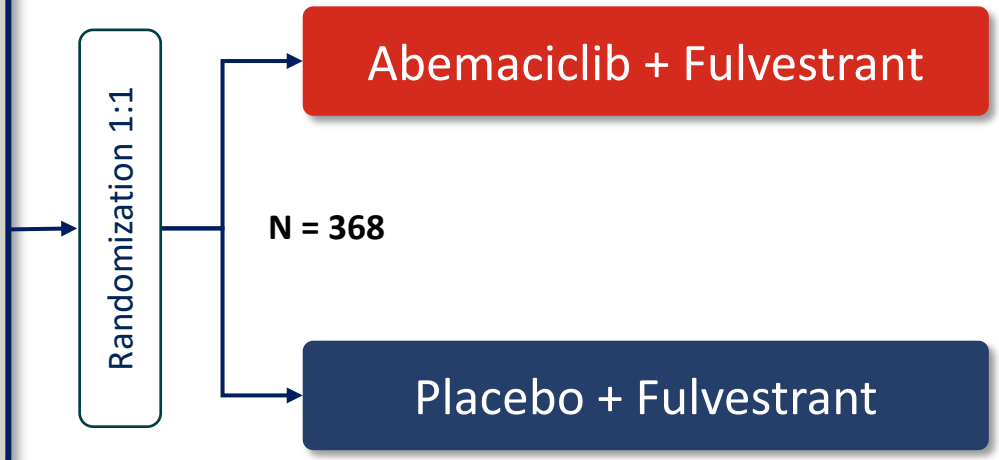
**Eligibility**

HR+, HER2- ABC

Men & Pre/post menopausal women

Prior Therapy:

- **ABC**: Disease progression on CDK4/6i + AI as initial therapy
- **Adjuvant**: Disease recurrence on/after CDK4/6i + ET
- No other therapy for ABC




**Primary Endpoint:**
Investigator-Assessed PFS

**Secondary Endpoints:**
OS, PFS by BICR, ORR, CBR, DCR, DoR, Safety, PK & PRO

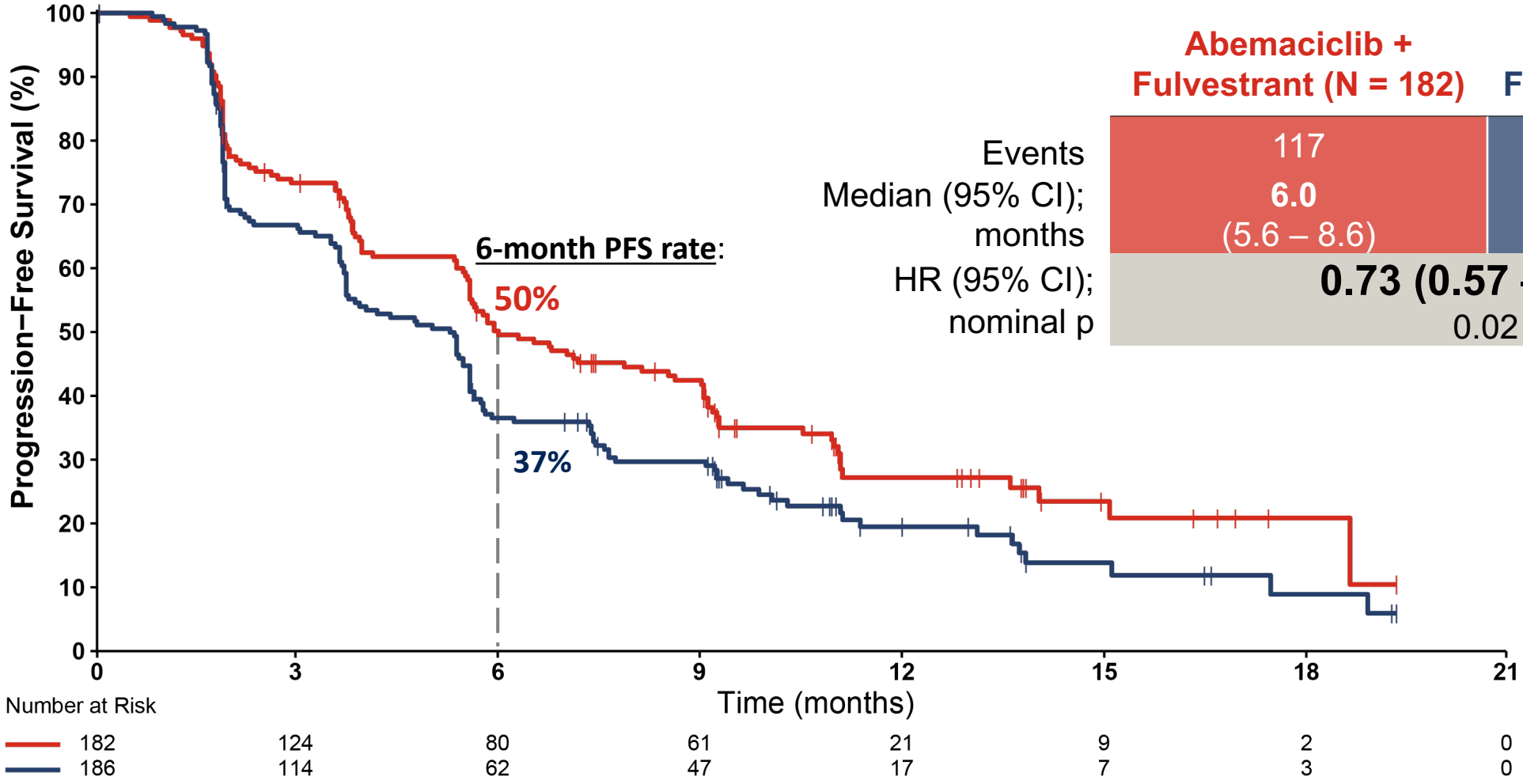
**Stratification Factors:**

- Duration of prior CDK4/6i
- Visceral metastases
- Geographic region

- Enrolled March 2022 to June 2023 across 96 centers in 16 countries
- Scans every 8 weeks for the first 12 months, then every 12 weeks
- Primary outcome targeted 251 events; interim analysis planned at ~70% of events
- Assuming a hazard ratio (HR) of 0.70, ~80% power to detect abemaciclib superiority, with a cumulative 2-sided type I error of 0.05
- Biomarker ctDNA analyzed by GuardantINFINITY™ assay

Kalinsky K et al ASCO 2024

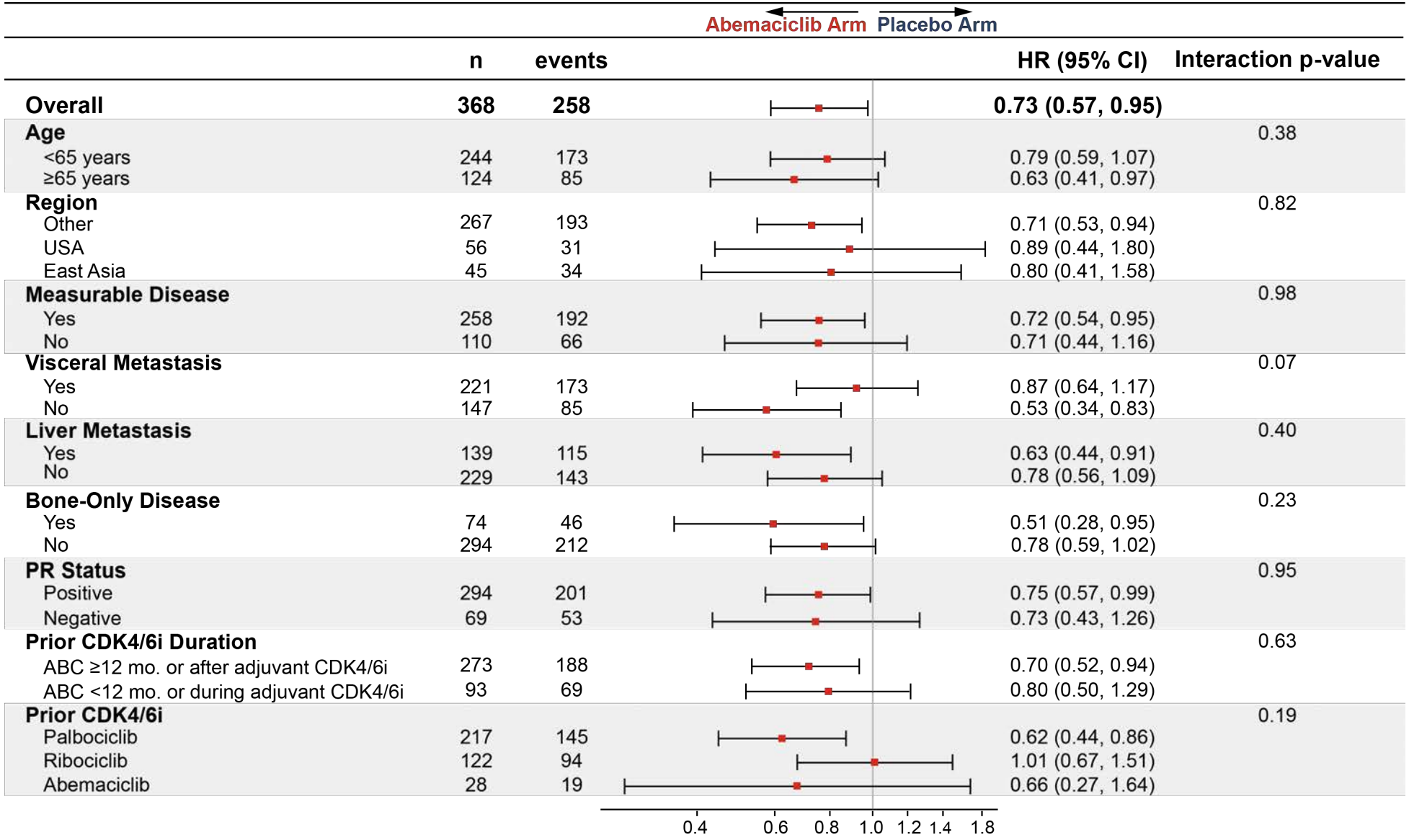
# Primary Analysis: Abemaciclib Improved Investigator-Assessed PFS




| | Abemaciclib + Fulvestrant (N = 182) | Placebo + Fulvestrant (N = 186) |
|---|---|---|
| Events | 117 | 141 |
| Median (95% CI); months | **6.0** (5.6 – 8.6) | **5.3** (3.7 – 5.6) |
| HR (95% CI); nominal p | **0.73 (0.57 – 0.95)** 0.02 | |

Kalinsky K et al ASCO 2024

# Investigator-Assessed PFS by Subgroup: Consistent Abemaciclib Effect Across Subgroups

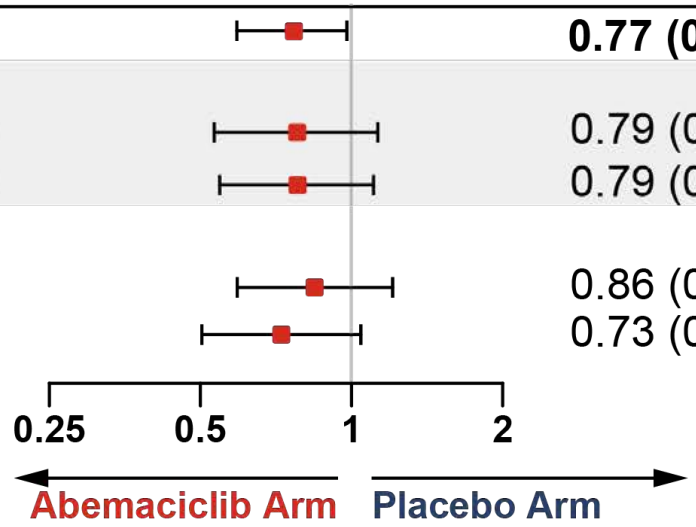



Kalinsky K et al ASCO 2024

# Exploratory: Consistent Effect Across Biomarker Subgroups

| | | Abemaciclib + Fulvestrant N=182 | Placebo + Fulvestrant N=186 |
|---|---|---|---|
| **ctDNA Evaluable Population** | | 161 (88%) | 159 (85%) |
| **Biomarker Status** | *ESR1* mutation | 40% | 51% |
| | *PIK3CA* or *PTEN* or *AKT1* alteration | 46% | 52% |

| Subgroup | n | events | HR (95% CI) | Interaction p-value |
|---|---|---|---|---|
| **ctDNA Evaluable Population** | **320** | **230** | **0.77 (0.59 to 1.00)** | |
| ***ESR1*** | | | | 0.98 |
| Detected | 145 | 110 | 0.79 (0.54 to 1.15) | |
| Not detected | 175 | 120 | 0.79 (0.55 to 1.13) | |
| ***PIK3CA* or *AKT1* or *PTEN*** | | | | 0.55 |
| Detected | 156 | 118 | 0.86 (0.60 to 1.23) | |
| Not detected | 164 | 112 | 0.73 (0.51 to 1.06) | |




Biomarker ctDNA by GuardantINFINITY assay

Kalinsky K et al ASCO 2024

# Optimizing CDK4/6i Selection: Patient and Drug Factors

Patient/Disease-Related Factors:

- Functional status/co-morbidities (eg. GI-related issues, baseline cytopenias, prior DVT…)
- Line of therapy (1st line with AI, 2nd line with Fulvestrant)
- Pattern of disease and organ function (eg. bone-only, visceral compromise, brain involvement…)

Drug-Related Factors:

- Dosing preference (3w on/1w off vs continuous/twice daily)
- Concurrent medications (eg. baseline QTc…)

Emerging Questions:

- How do molecular/genomic factors impact selection (eg. ESR1 alterations in the 1st line, PIK3CAm and INAVO120 triplet)?
- Best approach to patients who have received adjuvant CDK4/6i (ribociclib OR abemaciclib)

# Metastatic Breast Cancer: Case Summary and Approach

45 yo > de novo metastatic HR+/HER2- breast cancer with bone involvement

1st Line::
AI/OS + CDK4/6i
(Ribociclib)

Fulvestrant + Palbo
+ Inavolisib
(PIK3CAm,
ET refractory)

NGS
Biopsy/ctDNA @
baseline
ctDNA @
progression

2nd Line::
Fulvestrant +/- Abemaciclib

Fulvestrant + Alpelisib
(PIK3CAm)

Fulvestrant + Capivasertib
(PIK3CAm, AKTm, PTENm)

Elacestrant
(ESR1m)

Olaparib
(BRCAm)

NGS
ctDNA at
progression

3rd Line (and beyond)::
Antiestrogen + Everolimus

Trastuzumab Deruxtecan (ADC, HER2-low)

Chemotherapy (many choices)

Sacituzumab Govitecan (ADC)

**Ongoing clinical trials exploring:
New antiestrogens
New CDK4/2 inhibitors
New targeted agents (PI3K, RAS pathway)
New ADCs

# Faculty Case Presentations

# Case Presentation – Dr Hurvitz

- 46 yo woman presents with a locally advanced left breast invasive ductal carcinoma ER+ PR- HER2 1+ by IHC detected after she noticed nipple inversion. Staging scans revealed 1 cm biopsy-proven metastasis in left upper lung and lytic lesions in the sternum, T4, T6 and L4.
- She has a bilateral oophorectomy and receives letrozole plus ribociclib.
- Lung lesion disappears after 4 months being on therapy and bone lesions improve. She remains on 1$^{st}$ line therapy for 28 months when she develops progression in the liver.

# Case Presentation – Dr Kaklamani

- 54 yo postmenopausal patient diagnosed with *de novo* metastatic disease. Liver biopsy shows ER+ PR+ HER2 1+ breast ca. Patient is started on palbociclib and letrozole and has tumor response for 2.5 years at which time her liver metastases are showing progression.

# Agenda

**Module 1:** Role of CDK4/6 Inhibitors in Hormone Receptor (HR)-Positive Localized Breast Cancer – Dr Hurvitz

**Module 2:** Incorporation of CDK4/6 Inhibitors into the Management of HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) – Dr Wander

**Module 3: Evolving Role of PI3K Inhibitors for HR-Positive mBC Harboring PIK3CA Mutations – Dr Goetz**

**Module 4:** Clinical Utility of AKT Inhibitors for Patients with Progressive HR-Positive mBC – Dr Jhaveri

**Module 5:** Oral Selective Estrogen Receptor Degraders (SERDs) for HR-Positive mBC – Dr Kaklamani

RTP RESEARCH TO PRACTICE

# Evolving Role of PI3K Inhibitors for HR-Positive mBC Harboring PIK3CA Mutations

**Matthew Goetz, M.D.**
**Erivan K. Haub Family Professor of Cancer Research**
**Honoring Richard F. Emslander, M.D.**
**Professor of Oncology and Pharmacology**
**Department of Oncology**
**Mayo Clinic in Rochester, MN**

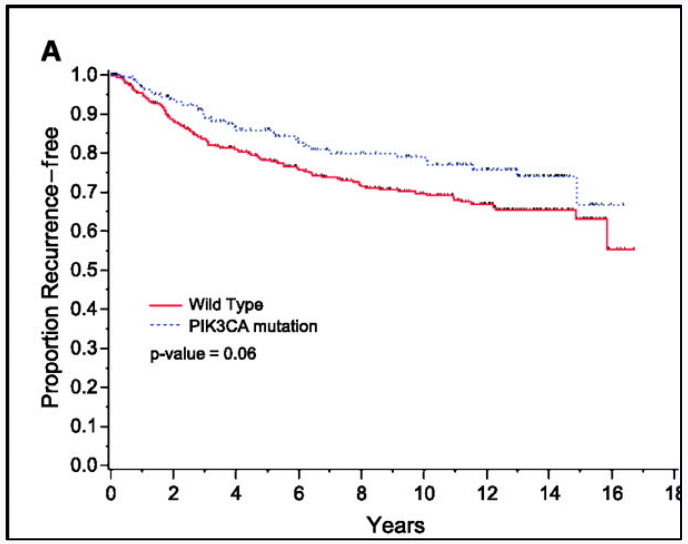
# Outline

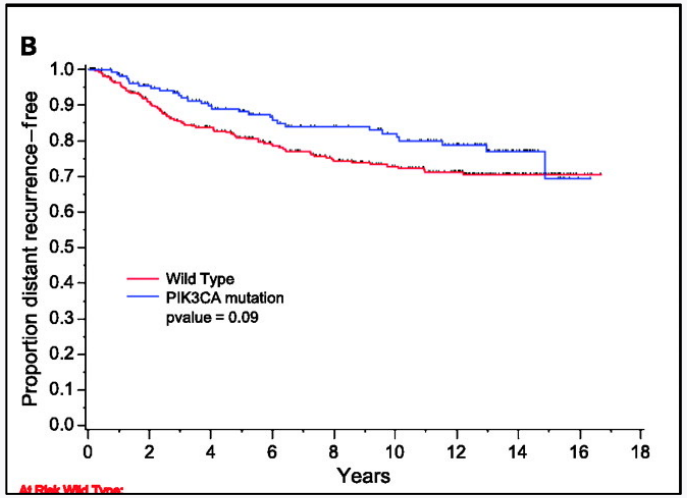
- Prevalence and prognostic significance of PIK3CA mutations in HR-positive mBC; optimal timing and methodology for identification
- Mechanistic similarities and differences between inavolisib and alpelisib; implications for efficacy and tolerability
- Key findings from the Phase III INAVO120 study evaluating inavolisib in combination with palbociclib and fulvestrant as first-line therapy for patients with endocrine-resistant, HR-positive, HER2-negative mBC with PIK3CA mutations
- Long-term data with alpelisib-based treatment for patients with progressive HR-positive mBC with PIK3CA mutations
- Spectrum, frequency and severity of toxicities documented with inavolisib- and alpelisib-containing therapy

# Background

- The phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway plays a key role in cell growth, protein translation, autophagy, metabolism, and cell survival
- Activating mutations of the p110α catalytic subunit of PI3K (*PI3KCA)*, phosphatase and tensin homolog (PTEN) loss, and AKT mutations have been identified in up to 40% of breast cancer patients.
- Prognostic effects of PIK3CA mutations are controversial, and relate to endocrine sensitivity.

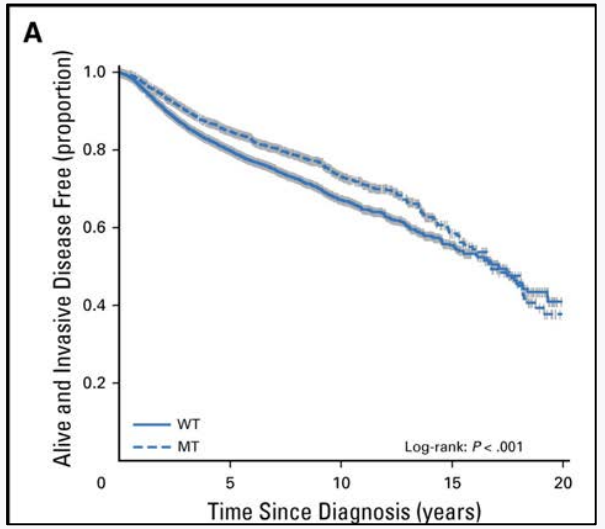
## PIK3CA Mutation Associates with Improved Outcome in Early-Stage Breast Cancer

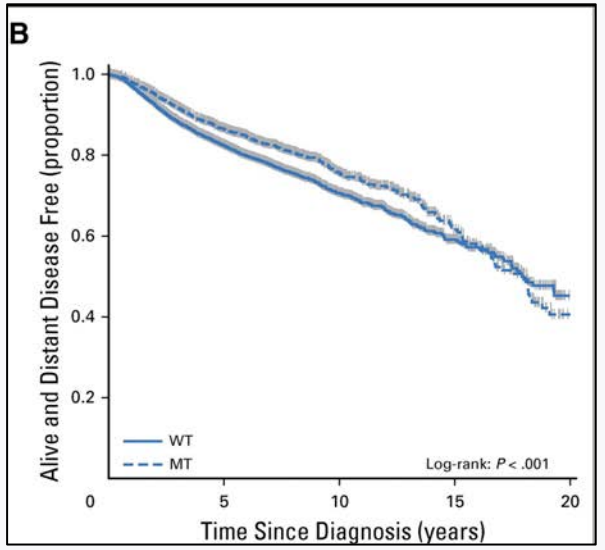



Kalinsky et al. Clin Canc Res 2009

## Tumor PIK3CA Genotype and Prognosis in Early-Stage Breast Cancer: A Pooled Analysis of Individual Patient Data

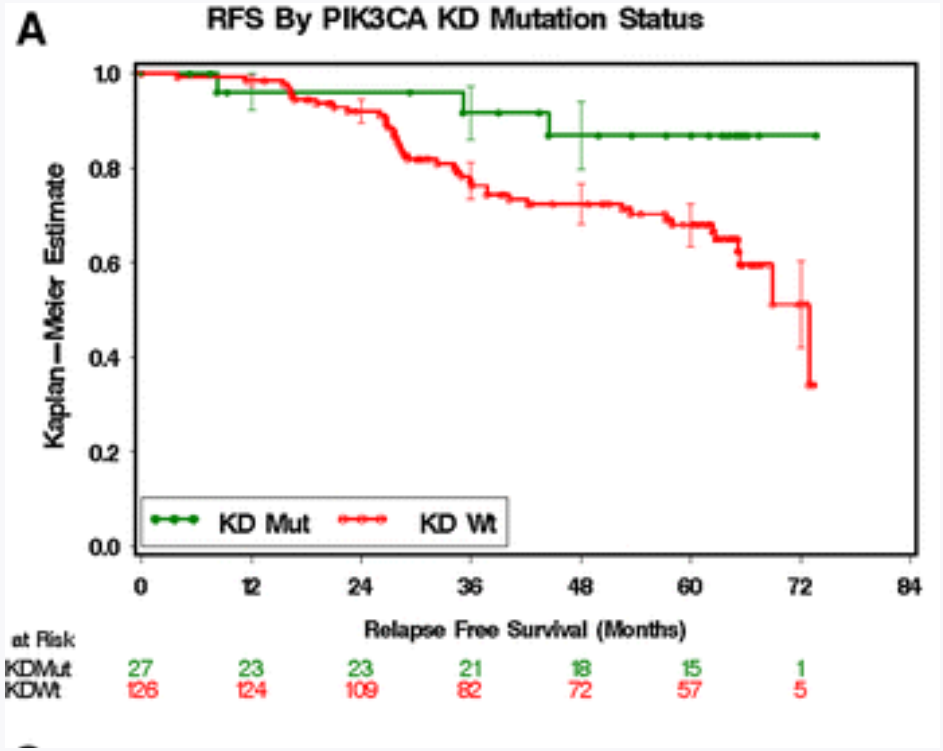



Zardavas et al. J Clin Oncol 2018

# PIK3CA mutations and response to neoadjuvant endocrine therapy for estrogen receptor positive breast cancer

| Ki-67 [geometric mean (95% CI)] | PIK3CA mutation status | | |
|---|---|---|---|
| | HD mutation | HD wt | *mut* vs. wt, *P*-value[†] |
| P024 | | | |
| Letrozole | | | |
| Pre | 2.69 (0.8–9.0) | 3.74 (2.38–5.89) | 0.9085 |
| Surgery | 0.23 (0.1–0.53) | 0.48 (0.29–0.8) | |
| *P*-value—pre vs. post within genotype[a] | 0.0313 | 0.0001 | |
| Tamoxifen | | | |
| Pre | 4.72 (2.9–7.66) | 6.29 (4.48–8.83) | 0.2251 |
| Surgery | 2.65 (1.24–5.65) | 1.43 (0.92–2.25) | |
| *P*-value—pre vs. post within genotype[a] | 0.0840 | 0.0001 | |
| RAD 2222 letrozole alone arm | | | |
| Pre | 38.52 (26.85–55.26) | 19.44 (13.78–27.44) | 0.2680 |
| Surgery | 3.72 (0.5–27.51) | 0.88 (0.42–1.85) | |
| *P*-value—pre vs. post within genotype[a] | 0.002 | 0.0001 | |
| POL & Z1031 | | | |
| Pre | 18.18 (10.23–32.31) | 15.76 (12.46–19.93) | 0.1153 |
| Surgery | 0.63 (0.11–3.42) | 2.66 (1.76–4.03) | |
| *P*-value—pre vs. post within genotype[a] | 0.0012 | 0.0001 | |




Ellis et al. Breast Cancer Res Treat. 2010 Jan;119(2):379–390.

# PIK3CA Mutations in the 1st and 2nd line Metastatic Setting in the letrozole and fulvestrant only arms of MONARCH 2/3: What is the difference?

- [1]MONARCH 3 letrozole/placebo:
  - mPFS: **25.5 months (mt)** vs 14.6 months (wt)
- [2]MONARCH 2: fulvestrant/placebo:
  - mPFS: **5.7 months (mt)** vs 12.3 months (wt)

1) Goetz et al. Clin Cancer Res 2024
2) Tolaney et al. Clin Cancer Res 2022

# What drives PIK3CA mutations from a good to poor prognostic factor……..?
# Long term estrogen deprivation

JCI The Journal of Clinical Investigation

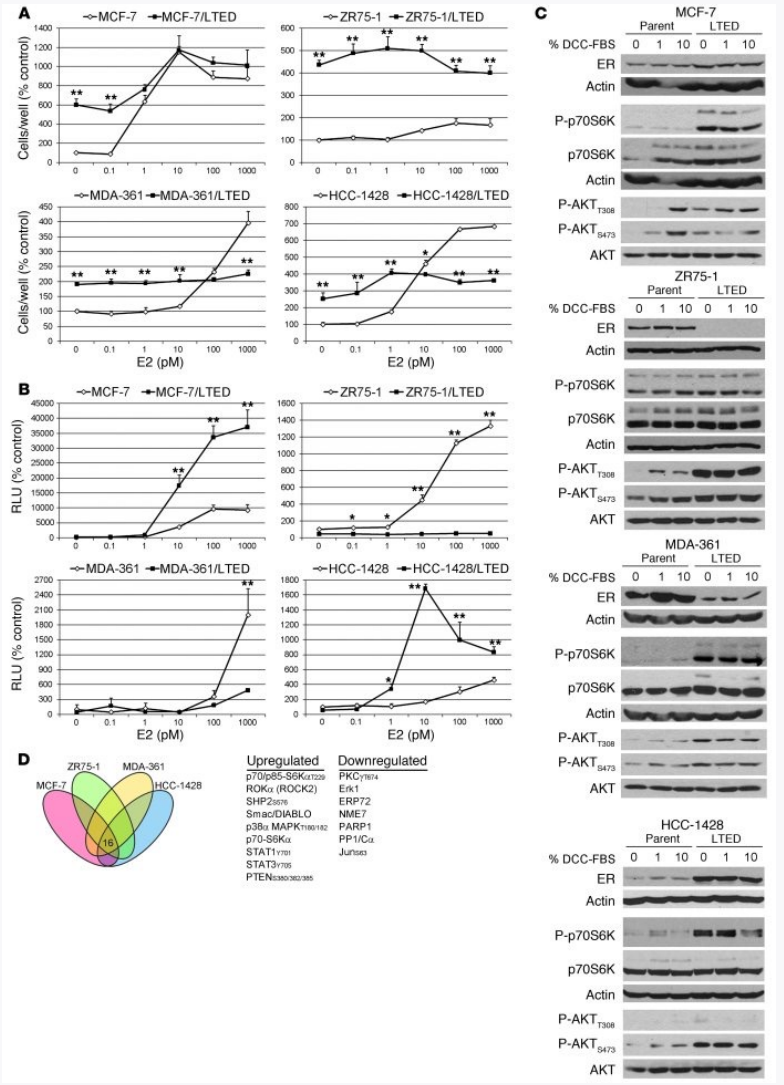
## Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor–positive human breast cancer

Todd W. Miller, … , Yu Shyr, Carlos L. Arteaga

*J Clin Invest.* 2010;120(7):2406-2413. https://doi.org/10.1172/JCI41680.

Research Article Oncology

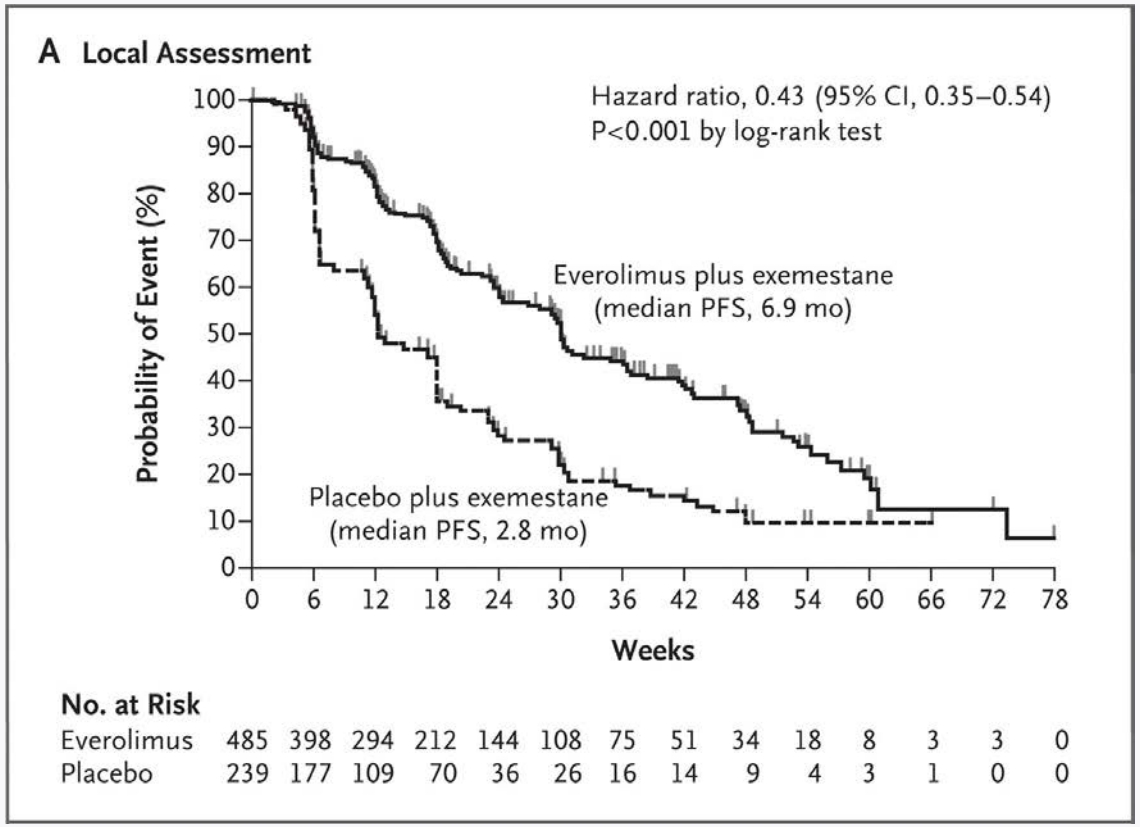
Many breast cancers exhibit a degree of dependence on estrogen for tumor growth. Although several therapies have been developed to treat individuals with estrogen-dependent breast cancers, some tumors show de novo or acquired resistance, rendering them particularly elusive to current therapeutic strategies. Understanding the mechanisms by which these cancers develop resistance would enable the development of new and effective therapeutics. In order to determine mechanisms of escape from hormone dependence in estrogen receptor–positive (ER-positive) breast cancer, we established 4 human breast cancer cell lines after long-term estrogen deprivation (LTED). LTED cells showed variable changes in ER levels and sensitivity to 17β-estradiol. Proteomic profiling of LTED cells revealed increased phosphorylation of the mammalian target of rapamycin (mTOR) substrates p70S6 kinase and p85S6 kinase as well as the PI3K substrate AKT. Inhibition of PI3K and mTOR induced LTED cell apoptosis and prevented the emergence of hormone-independent cells. Using reverse-phase protein microarrays, we identified a breast tumor protein signature of PI3K pathway activation that predicted poor outcome after adjuvant endocrine therapy in patients. Our data suggest that upon adaptation to hormone deprivation, breast cancer cells rely heavily on PI3K signaling. Our findings also imply that acquired resistance to endocrine therapy in breast cancer may be abrogated by combination therapies targeting both ER and PI3K pathways.




Miller et al. J Clin Invest. 2010;120(7):2406-2413

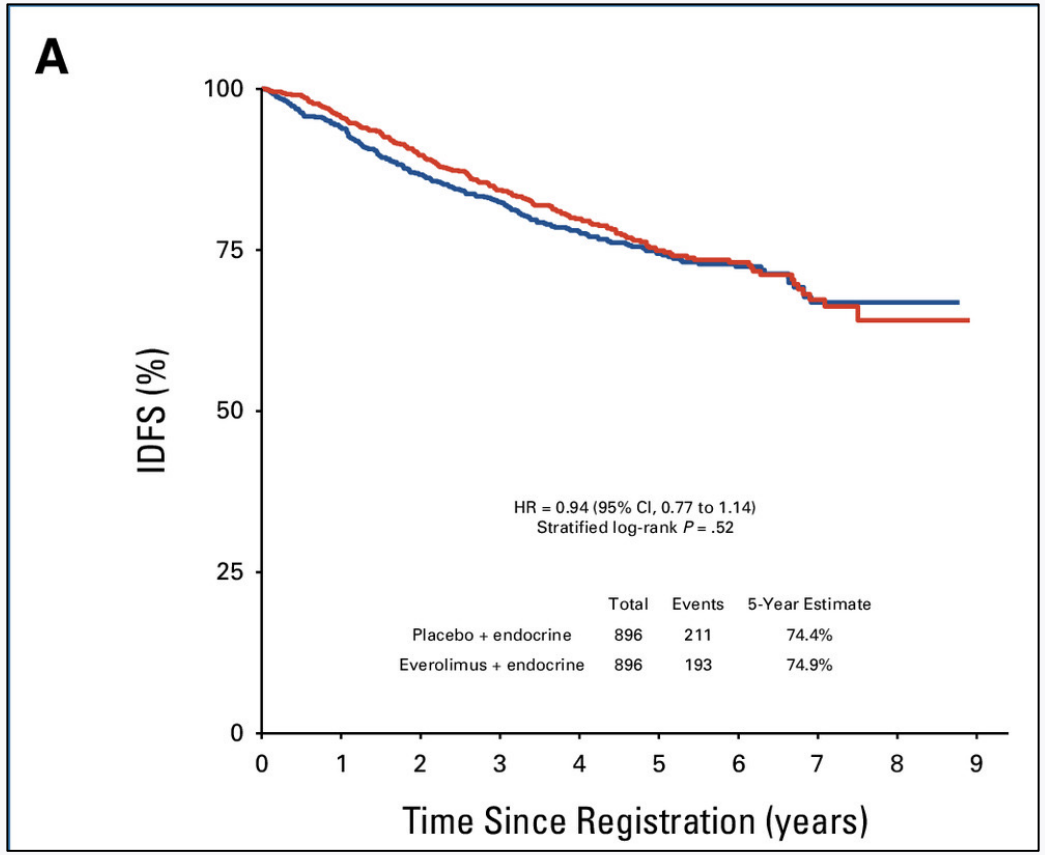
# Everolimus: Endocrine Resistant vs Endocrine Sensitive Setting

Everolimus in Postmenopausal Hormone Receptor-Positive Advanced Breast Cancer




Baselga et al. NEJM 2012

Phase III Trial of Endocrine Therapy ± 1 Year of Everolimus in HR+, Early-Stage Breast Cancer

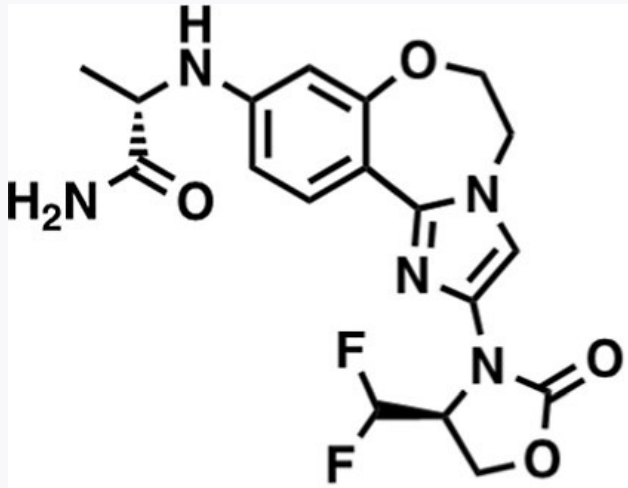



Chavez-MacGregor et al. J Clin Oncol 2024

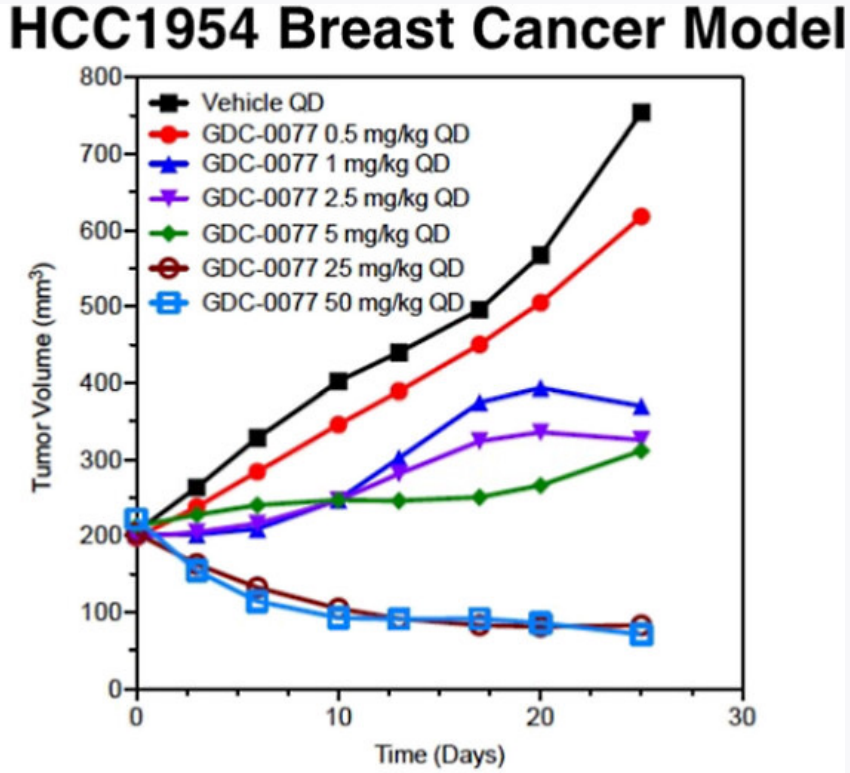
# Outline

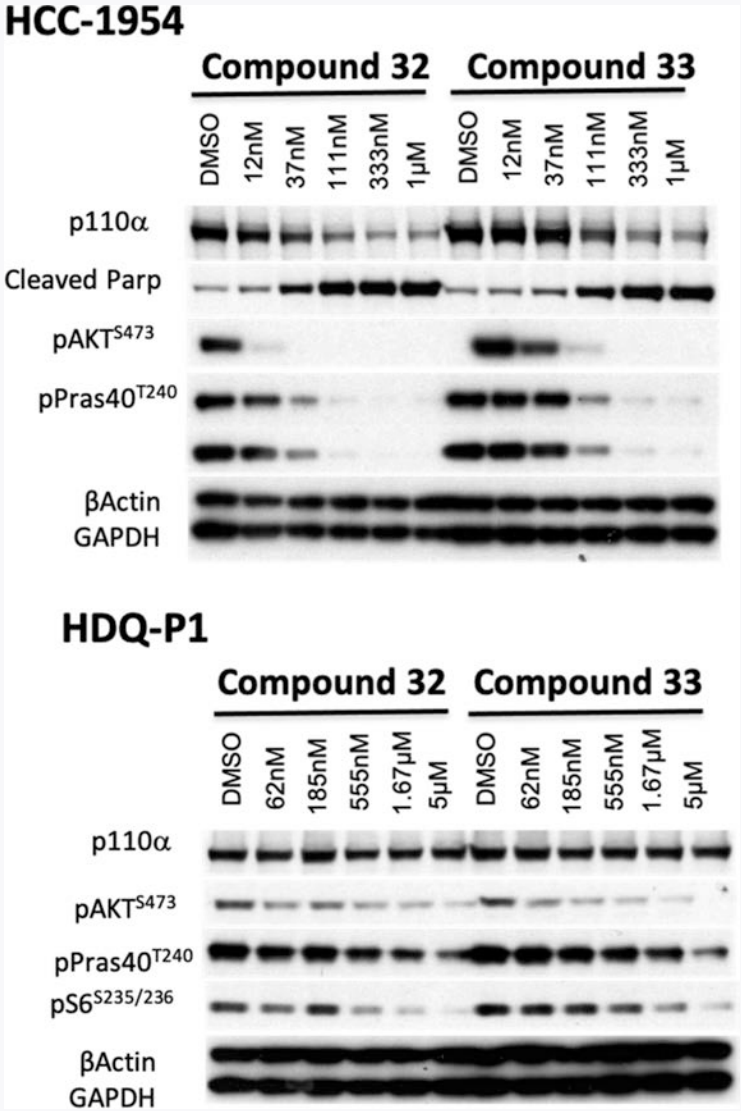
- Prevalence and prognostic significance of PIK3CA mutations in HR-positive mBC; optimal timing and methodology for identification
- Mechanistic similarities and differences between inavolisib and alpelisib; implications for efficacy and tolerability
- Key findings from the Phase III INAVO120 study evaluating inavolisib in combination with palbociclib and fulvestrant as first-line therapy for patients with endocrine-resistant, HR-positive, HER2-negative mBC with PIK3CA mutations
- Long-term data with alpelisib-based treatment for patients with progressive HR-positive mBC with PIK3CA mutations
- Spectrum, frequency and severity of toxicities documented with inavolisib- and alpelisib-containing therapy

# Inavolisib: ATP-competitive inhibitor of PI3Kα with selective degradation of the mutant p110α protein, with 300-fold selectivity over the other Class I PI3K isoforms.



**GDC-0077**
PI3Kα Ki 0.034 nM
PI3Kδ Ki 12.2 nM
mutant-p110α degrader




Hanan EJ et al. J Med Chem. 2022 Dec 22;65(24):16589-16621.

# Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2-negative locally advanced or metastatic breast cancer: Phase III INAVO120 primary analysis

Jhaveri et al. SABCS 2023

# INAVO120 study design

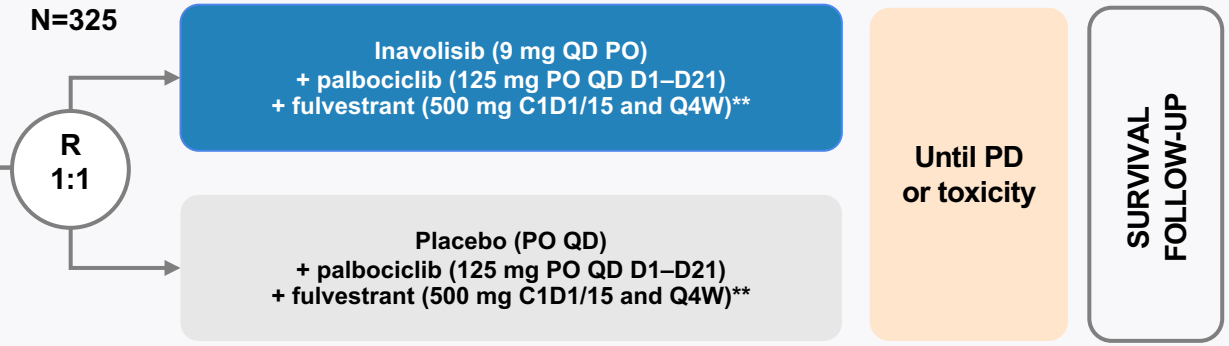
Enrolment period: December 2019 to September 2023

**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%**




**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 (Foundation Medicine). 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.

# Demographics and baseline disease characteristics

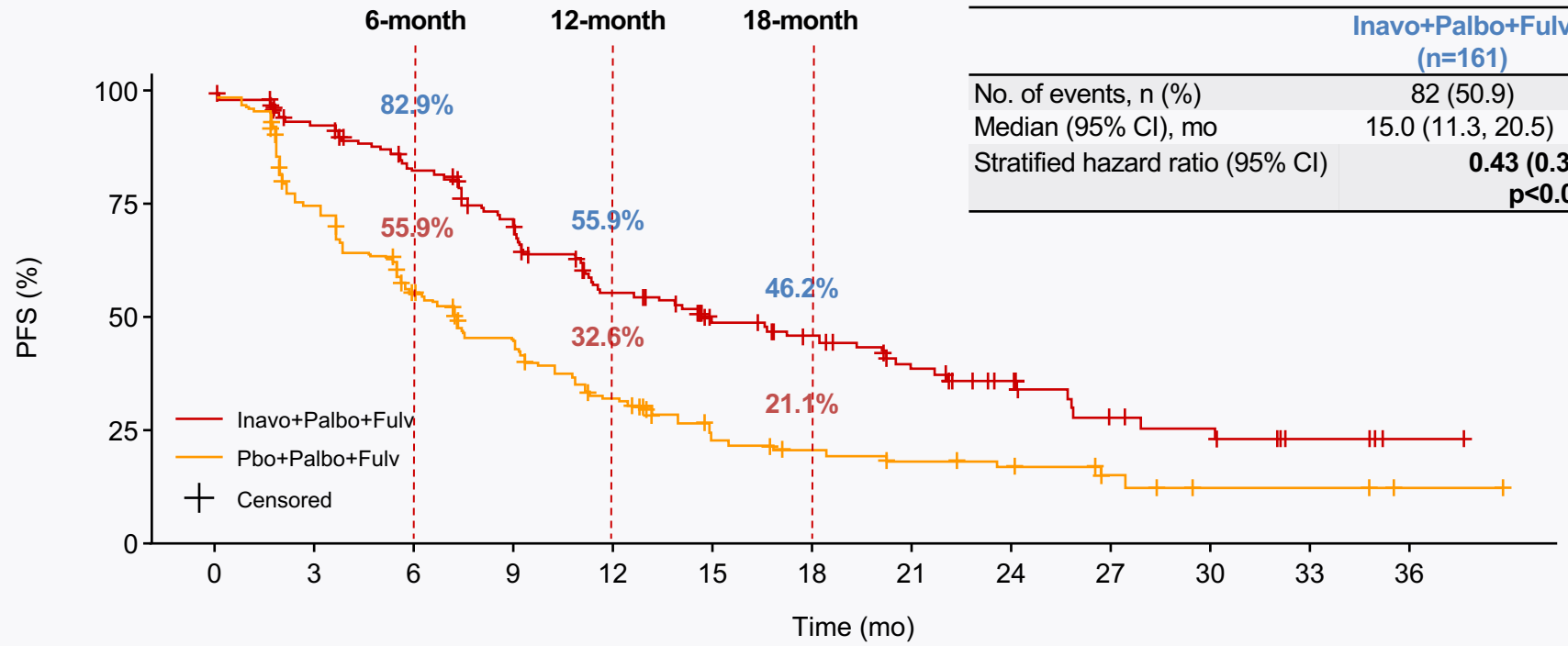
| | Inavo+Palbo+Fulv (n=161) | Pbo+Palbo+Fulv (n=164) |
|---|---|---|
| **Age (year)** | | |
| Median | 53.0 | 54.5 |
| Min–Max | 27–77 | 29–79 |
| **Sex, n (%)** | | |
| Female | 156 (96.9) | 163 (99.4) |
| **Race, n (%)** | | |
| Asian | 61 (37.9) | 63 (38.4) |
| Black or African American | 1 (0.6) | 1 (0.6) |
| White | 94 (58.4) | 97 (59.1) |
| **ECOG PS, n (%)** | | |
| 0 | 100 (62.1) | 106 (64.6) |
| 1 | 60 (37.3) | 58 (35.4) |
| **Menopausal status at randomization, n (%)** | | |
| Premenopausal | 65 (40.4) | 59 (36.0) |
| Postmenopausal | 91 (56.5) | 104 (63.4) |

| | Inavo+Palbo+Fulv (n=161) | Pbo+Palbo+Fulv (n=164) |
|---|---|---|
| **Number of organ sites, n (%)** | | |
| 1 | 21 (13.0) | 32 (19.5) |
| 2 | 59 (36.6) | 46 (28.0) |
| ≥3 | 81 (50.3) | 86 (52.4) |
| **Visceral disease, n (%)*** | 132 (82.0) | 128 (78.0) |
| Liver | 77 (47.8) | 91 (55.5) |
| Lung | 66 (41.0) | 66 (40.2) |
| Bone only† | 5 (3.1) | 6 (3.7) |
| **ER‡ and PgR status, n (%)** | | |
| ER+/PgR+ | 113 (70.2) | 113 (68.9) |
| ER+/PgR- | 45 (28.0) | 45 (27.4) |
| **Endocrine resistance , n (%)**** | | |
| Primary | 53 (32.9) | 58 (35.4) |
| Secondary | 108 (67.1) | 105 (64.0) |

301 (92.6%) pts were enrolled per ctDNA testing (284 [94.4%] central, 17 [5.6%] local) and 24 (7.4%) were enrolled per local tissue testing

* "Visceral" (yes/no) refers to lung, liver, brain, pleural, and peritoneal involvement; † Patients with evaluable bone-only disease were not eligible; patients with disease limited to the bone but with lytic or mixed lytic/blastic lesions, and at least one measurable soft-tissue component per RECIST 1.1, may be eligible. ‡ Defined as 10% per ASCO-CAP guidelines. ** Endocrine resistance was defined per 4th ESO–[ESMO] International Consensus Guidelines for Advanced Breast Cancer. Primary resistance: Relapse while on the first 2 years of adjuvant endocrine therapy. Secondary resistance: Relapse while on adjuvant endocrine therapy after at least 2 years or relapse within 12 months of completing adjuvant endocrine therapy. ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor, Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

# Primary endpoint: PFS (investigator-assessed)




| | 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:

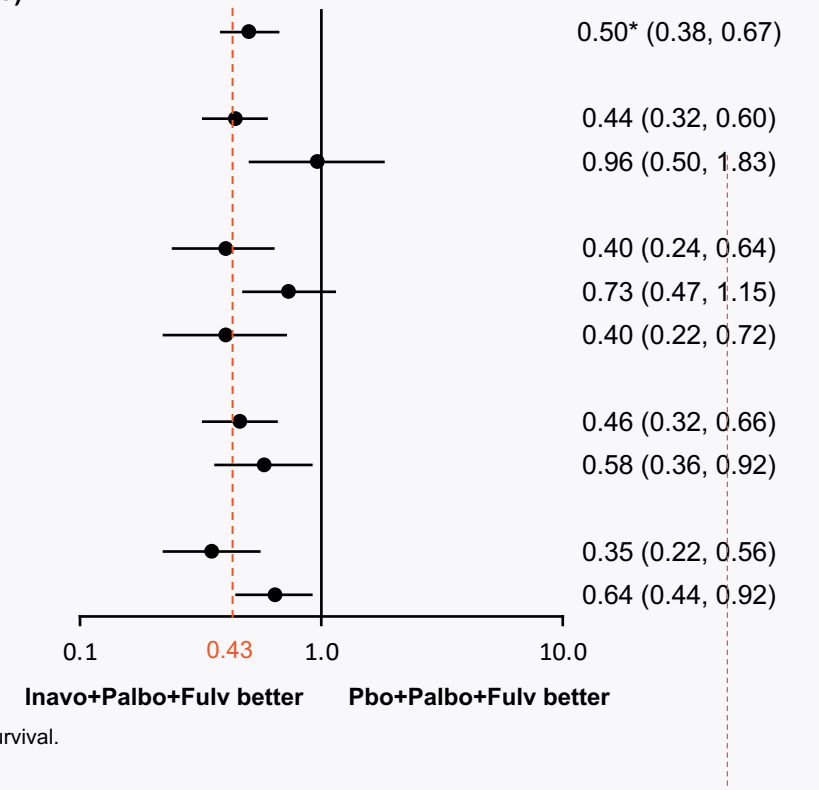
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inavo+Palbo+Fulv | 161 | 134 | 111 | 92 | 66 | 48 | 41 | 31 | 22 | 13 | 11 | 5 | 1 |
| Pbo+Palbo+Fulv | 164 | 113 | 77 | 59 | 40 | 23 | 19 | 16 | 12 | 6 | 3 | 3 | 1 |

Median follow-up:
**21.3 months**

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

# PFS (investigator-assessed) in key subgroups 1/2

| | Inavo+Palbo+Fulv | | Pbo+Palbo+Fulv | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| | n | Median (mo) | n | Median (mo) | |
| **All patients** | 161 | 15.0 | 164 | 7.3 | 0.50* (0.38, 0.67) |
| **Age, years** | | | | | |
| <65 | 136 | 16.6 | 130 | 7.2 | 0.44 (0.32, 0.60) |
| ≥65 | 25 | 9.3 | 34 | 10.7 | 0.96 (0.50, 1.83) |
| **Region** | | | | | |
| Asia | 56 | 14.6 | 58 | 5.8 | 0.40 (0.24, 0.64) |
| North America/Western Europe | 63 | 13.8 | 64 | 9.3 | 0.73 (0.47, 1.15) |
| Other | 42 | 21.0 | 42 | 5.6 | 0.40 (0.22, 0.72) |
| **ECOG PS at baseline** | | | | | |
| 0 | 100 | 16.6 | 106 | 7.4 | 0.46 (0.32, 0.66) |
| 1 | 60 | 11.4 | 58 | 5.6 | 0.58 (0.36, 0.92) |
| **Menopausal status at randomization** | | | | | |
| Premenopausal | 65 | 20.1 | 59 | 6.5 | 0.35 (0.22, 0.56) |
| Post-menopausal | 91 | 13.4 | 104 | 7.5 | 0.64 (0.44, 0.92) |

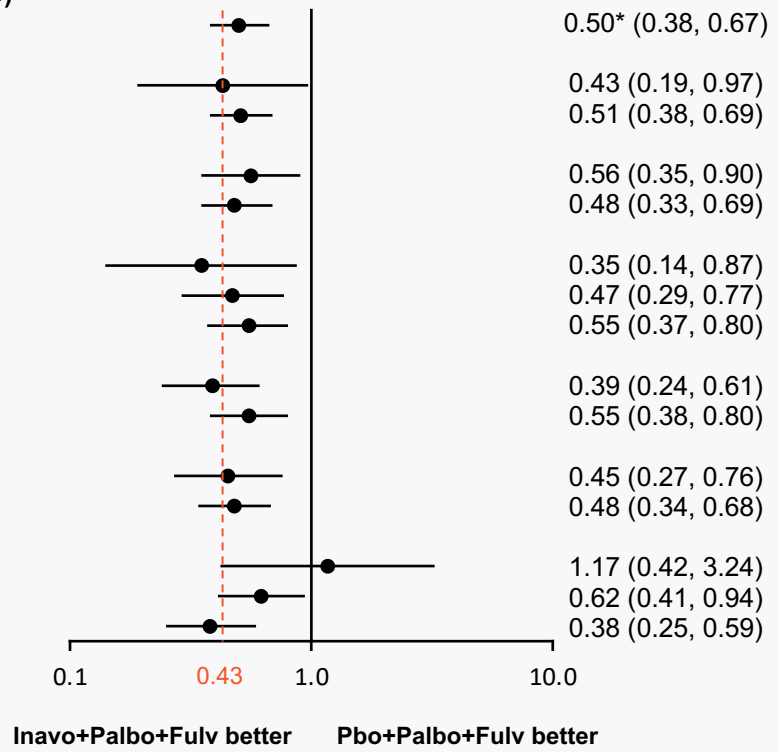



* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Fulv, fulvestrant; Inavo, inavolisib; mo, months, Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

# PFS (investigator-assessed) in key subgroups 2/2

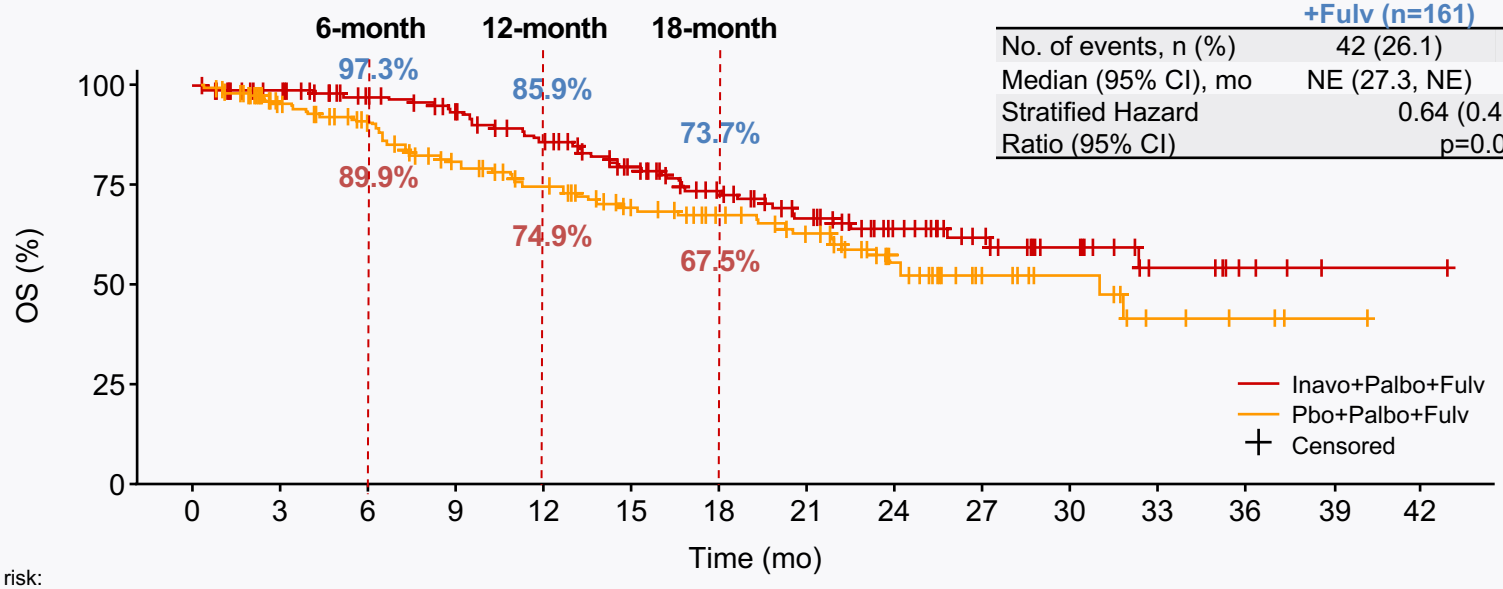
| | Inavo+Palbo+Fulv | | Pbo+Palbo+Fulv | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| | n | Median (mo) | n | Median (mo) | |
| **All patients** | 161 | 15.0 | 164 | 7.3 | 0.50* (0.38, 0.67) |
| **Visceral disease** | | | | | |
| No | 29 | 25.8 | 36 | 7.4 | 0.43 (0.19, 0.97) |
| Yes | 132 | 13.8 | 128 | 7.2 | 0.51 (0.38, 0.69) |
| **Liver metastasis at enrollment** | | | | | |
| No | 84 | 24.2 | 73 | 11.3 | 0.56 (0.35, 0.90) |
| Yes | 77 | 11.0 | 91 | 5.6 | 0.48 (0.33, 0.69) |
| **Number of metastatic organs at enrollment** | | | | | |
| 1 | 21 | 20.2 | 32 | 7.4 | 0.35 (0.14, 0.87) |
| 2 | 59 | 18.2 | 46 | 7.4 | 0.47 (0.29, 0.77) |
| ≥3 | 81 | 14.1 | 86 | 7.3 | 0.55 (0.37, 0.80) |
| **Endocrine resistance** | | | | | |
| Primary | 53 | 11.4 | 58 | 3.7 | 0.39 (0.24, 0.61) |
| Secondary | 108 | 18.2 | 105 | 9.7 | 0.55 (0.38, 0.80) |
| **HR status** | | | | | |
| ER+/PgR- | 45 | 11.1 | 45 | 5.6 | 0.45 (0.27, 0.76) |
| ER+/PgR+ | 113 | 18.2 | 113 | 7.4 | 0.48 (0.34, 0.68) |
| **Prior (neo)adjuvant endocrine therapy** | | | | | |
| Aromatase inhibitor and tamoxifen | 18 | 11.0 | 19 | 12.9 | 1.17 (0.42, 3.24) |
| Aromatase inhibitor only | 60 | 10.9 | 71 | 5.8 | 0.62 (0.41, 0.94) |
| Tamoxifen only | 82 | 21.0 | 73 | 7.4 | 0.38 (0.25, 0.59) |




* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

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

# Key secondary endpoint: Overall survival (interim analysis)




| | Inavo+Palbo +Fulv (n=161) | Pbo+Palbo +Fulv (n=164) |
|---|---|---|
| No. of events, n (%) | 42 (26.1) | 55 (33.5) |
| Median (95% CI), mo | NE (27.3, NE) | 31.1 (22.3, NE) |
| Stratified Hazard Ratio (95% CI) | 0.64 (0.43, 0.97) p=0.0338 | |

Patients at risk:

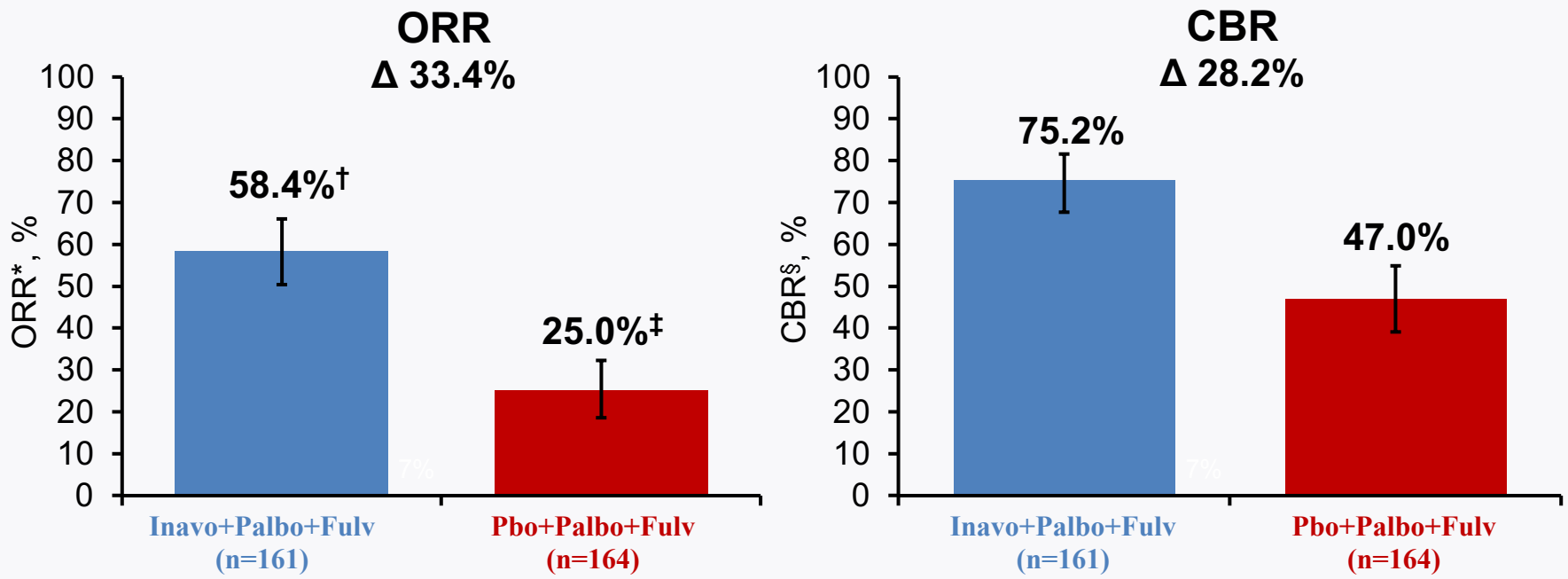
| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inavo+Palbo+Fulv | 161 | 143 | 127 | 114 | 101 | 85 | 69 | 56 | 38 | 26 | 17 | 8 | 4 | 1 | 1 |
| Pbo+Palbo+Fulv | 164 | 139 | 120 | 98 | 87 | 72 | 61 | 52 | 33 | 19 | 11 | 5 | 3 | 1 | 0 |

Median follow-up: **21.3 months**

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

# Secondary endpoints: ORR and CBR (investigator-assessed)




* Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Abstract 1003

2024 ASCO ANNUAL MEETING

# First-line inavolisib/placebo + palbociclib + fulvestrant (Inavo/Pbo+Palbo+Fulv) in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced/metastatic breast cancer who relapsed during/within 12 months (mo) of adjuvant endocrine therapy completion: INAVO120 Phase III randomized trial additional analyses.

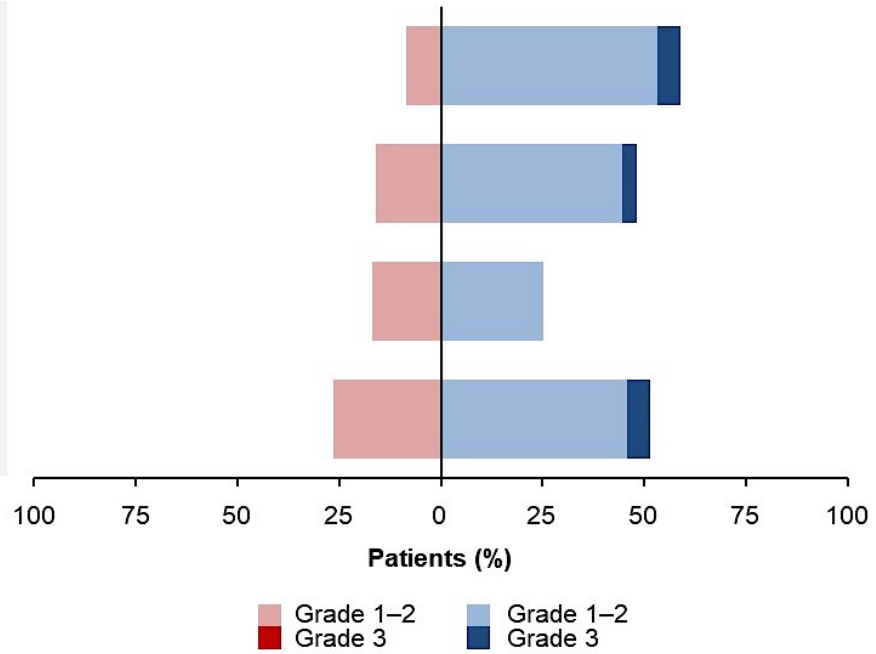
Dejan Juric, Kevin Kalinsky, Nicholas Turner, Komal L Jhaveri, Peter Schmid, Sherene Loi, Cristina Saura, Seock-Ah Im, Patrapim Sunpaweravong, Huiping Li, Antonino Musolino, Qingyuan Zhang, Zbigniew Nowecki, Roland Leung, Eirini Thanopoulou, Noopur Shankar, Guiyuan Lei, Jacob Devine, Thomas J Stout, Sibylle Loibl

**Presenting author: Dejan Juric, MD**

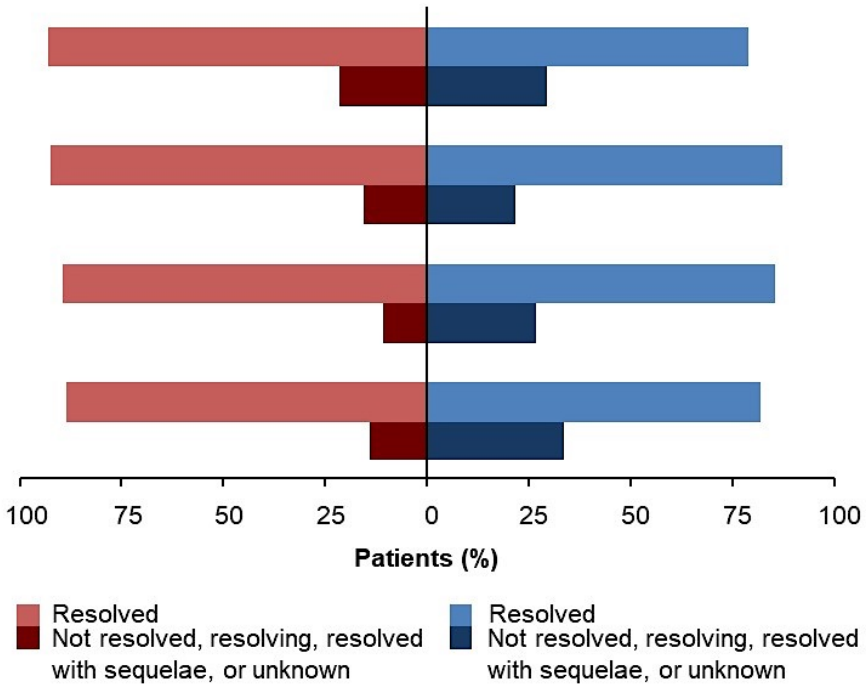
Mass General Cancer Center, Department of Medicine, Harvard Medical School, Boston, MA

# Safety

## Key selected AEs




## Resolution of key selected AEs*†




*** Majority of key selected AEs had resolved ('resolution' was per investigator decision) by the CCOD; some patients were enrolled close to the CCOD and AE follow-up is ongoing for these patients.**

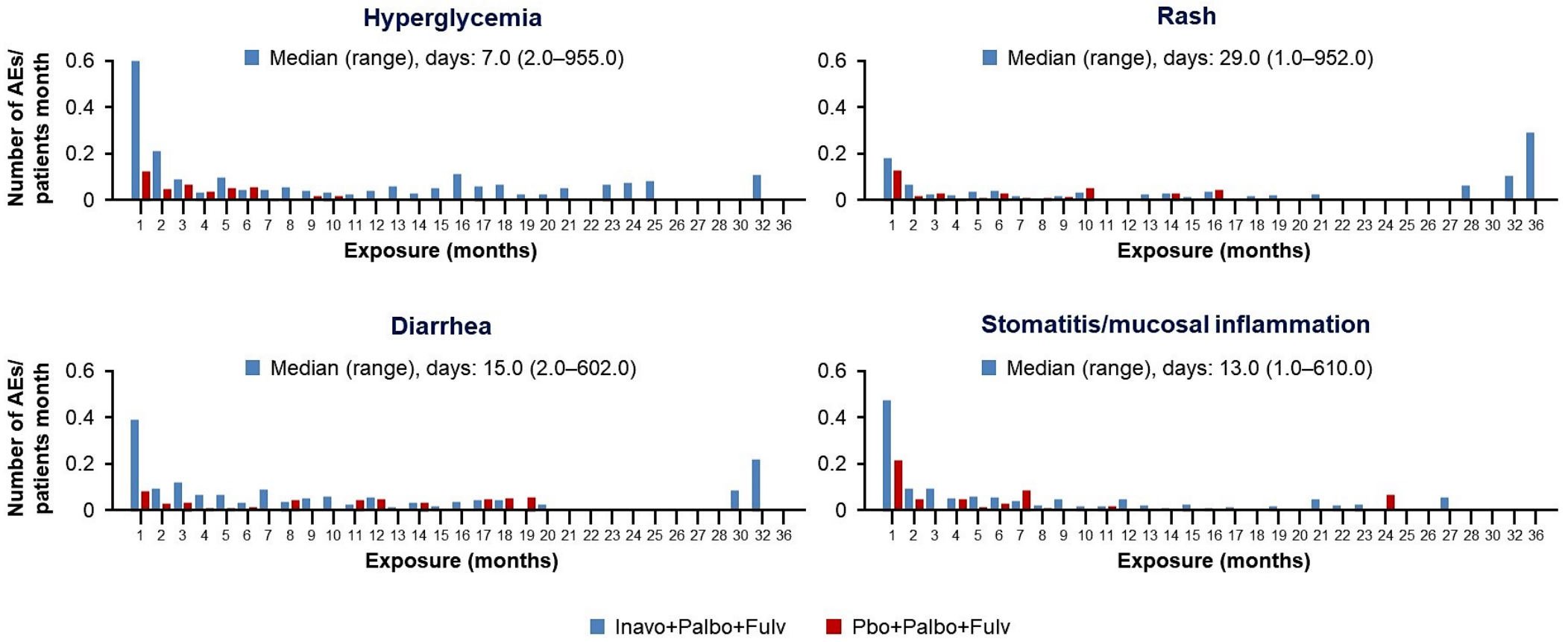
† Denominators are patients with at least one AE (hyperglycemia, Inavo+Palbo+Fulv: n = 95, Pbo+Palbo+Fulv: n = 14; diarrhea, Inavo+Palbo+Fulv: n = 78, Pbo+Palbo+Fulv: n = 26; rash, Inavo+Palbo+Fulv: n = 41, Pbo+Palbo+Fulv: n = 28; and stomatitis/mucosal inflammation, Inavo+Palbo+Fulv: n = 83, Pbo+Palbo+Fulv: n = 43).

AE, adverse event; CCOD, clinical cutoff date; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.



Juric D et al. ASCO 2024; Abstract 1003

# Time to onset of key selected AEs*




* Median time to onset of first occurrence of the AE, i.e. if an AE was resolved and recurred in the same patient it is not included a second time in this dataset.
AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.



Juric D et al. ASCO 2024; Abstract 1003

# Inavolisib treatment interruption, reduction, and discontinuation due to key selected AEs

Discontinuation rate of inavolisib due to any AE was 6.2%[1]

| Patients, n (%) | Hyperglycemia | Diarrhea | Rash | Stomatitis/ mucosal inflammation |
|---|---|---|---|---|
| **Inavolisib interruption due to AE** | 44 (27.2) | 11 (6.8) | 2 (1.2) | 16 (9.9) |
| **Inavolisib reduction due to AE** | 4 (2.5) | 2 (1.2) | 1 (0.6) | 6 (3.7) |
| **Inavolisib discontinuation due to AE** | 1 (0.6)* | 0 | 0 | 1 (0.6) |

Data are for the Inavo+Palbo+Fulv arm (n = 162).
* One patient discontinued due to an AE of Type 2 diabetes in the Inavo+Palbo+Fulv arm, which was not captured under hyperglycemia.
AE, adverse event; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib.
1. Jhaveri KL, *et al*. SABCS 2023 (Abstract GS03-13).



Juric D et al. ASCO 2024; Abstract 1003

# Outline

- Prevalence and prognostic significance of PIK3CA mutations in HR-positive mBC; optimal timing and methodology for identification
- Mechanistic similarities and differences between inavolisib and alpelisib; implications for efficacy and tolerability
- Key findings from the Phase III INAVO120 study evaluating inavolisib in combination with palbociclib and fulvestrant as first-line therapy for patients with endocrine-resistant, HR-positive, HER2-negative mBC with PIK3CA mutations
- Spectrum, frequency and severity of toxicities documented with inavolisib- and alpelisib-containing therapy
- Long-term data with alpelisib-based treatment for patients with progressive HR-positive mBC with PIK3CA mutations

# Inavolisib: Adverse events with any grade AEs ≥ 20% incidence in either treatment group

| Adverse Events | Inavo+Palbo+Fulv (N=162) | | Pbo+Palbo+Fulv (N=162) | |
|---|---|---|---|---|
| | All Grades | Grade 3–4 | All Grades | Grade 3–4 |
| **Neutropenia** | **144 (88.9%)** | **130 (80.2%)** | **147 (90.7%)** | **127 (78.4%)** |
| Thrombocytopenia | 78 (48.1%) | 23 (14.2%) | 73 (45.1%) | 7 (4.3%) |
| **Stomatitis/Mucosal inflammation** | **83 (51.2%)** | **9 (5.6%)** | **43 (26.5%)** | **0** |
| Anemia | 60 (37.0%) | 10 (6.2%) | 59 (36.4%) | 3 (1.9%) |
| **Hyperglycemia** | **95 (58.6%)** | **9 (5.6%)** | **14 (8.6%)** | **0** |
| **Diarrhea** | **78 (48.1%)** | **6 (3.7%)** | **26 (16.0%)** | **0** |
| **Nausea** | **45 (27.8%)** | **1 (0.6%)** | **27 (16.7%)** | **0** |
| **Rash** | **41 (25.3%)** | **0** | **28 (17.3%)** | **0** |
| Decreased Appetite | 38 (23.5%) | <2% | 14 (8.6%) | <2% |
| Fatigue | 38 (23.5%) | <2% | 21 (13.0%) | <2% |
| COVID-19 | 37 (22.8%) | <2% | 17 (10.5%) | <2% |
| Headache | 34 (21.0%) | <2% | 22 (13.6%) | <2% |
| Leukopenia | 28 (17.3%) | 11 (6.8%) | 40 (24.7%) | 17 (10.5%) |
| Ocular Toxicities | 36 (22.2%) | 0 | 21 (13.0%) | 0 |

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

# Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

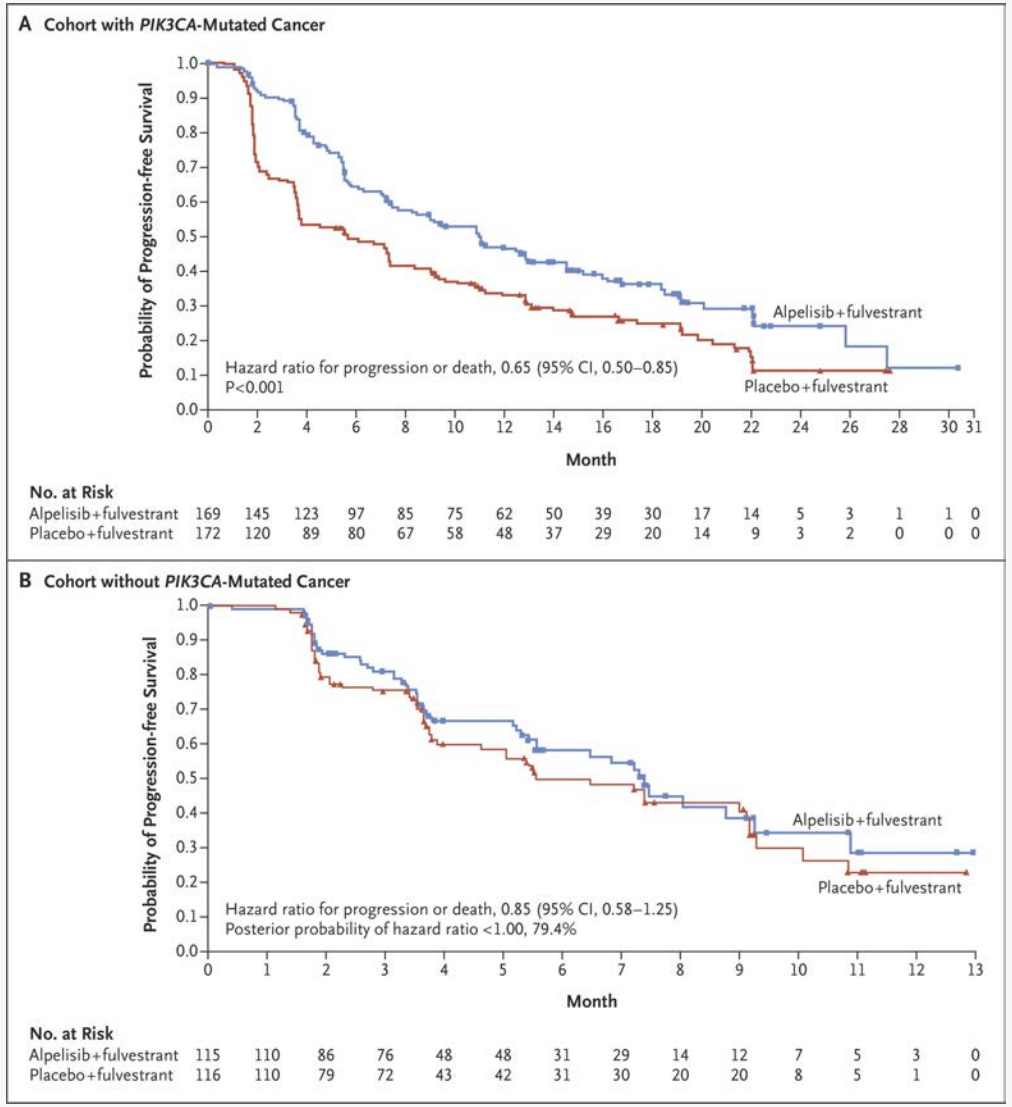


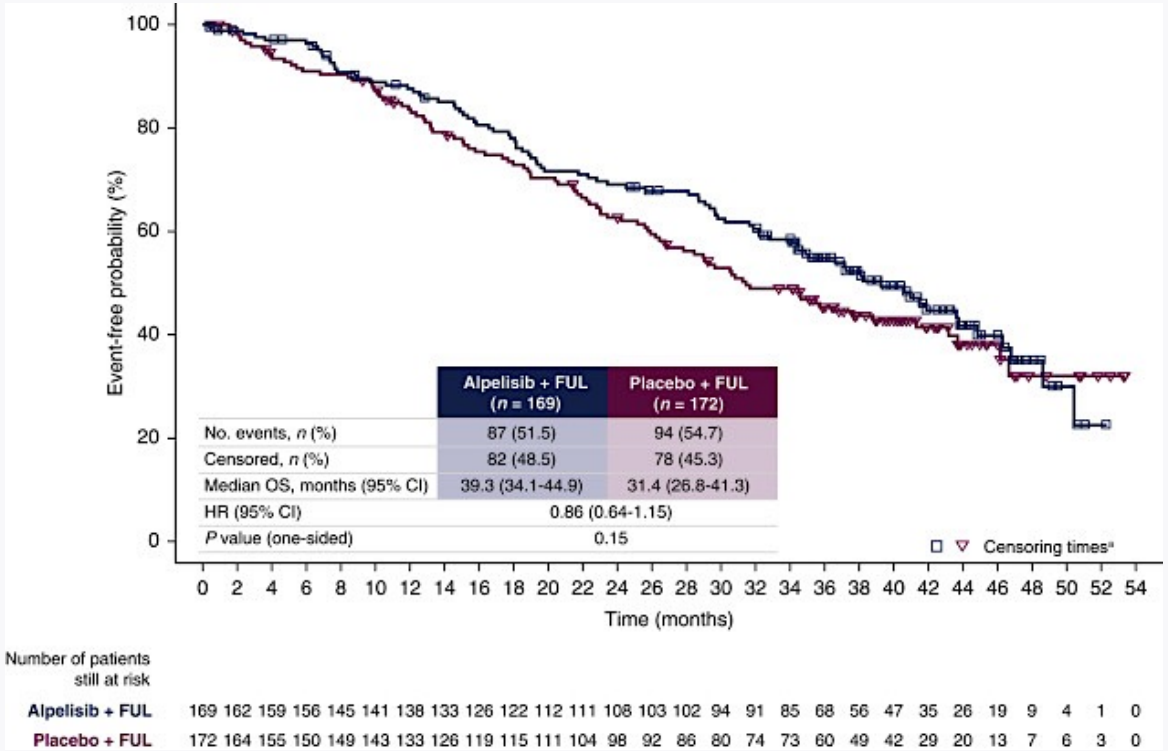

**Table 3.** Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.*

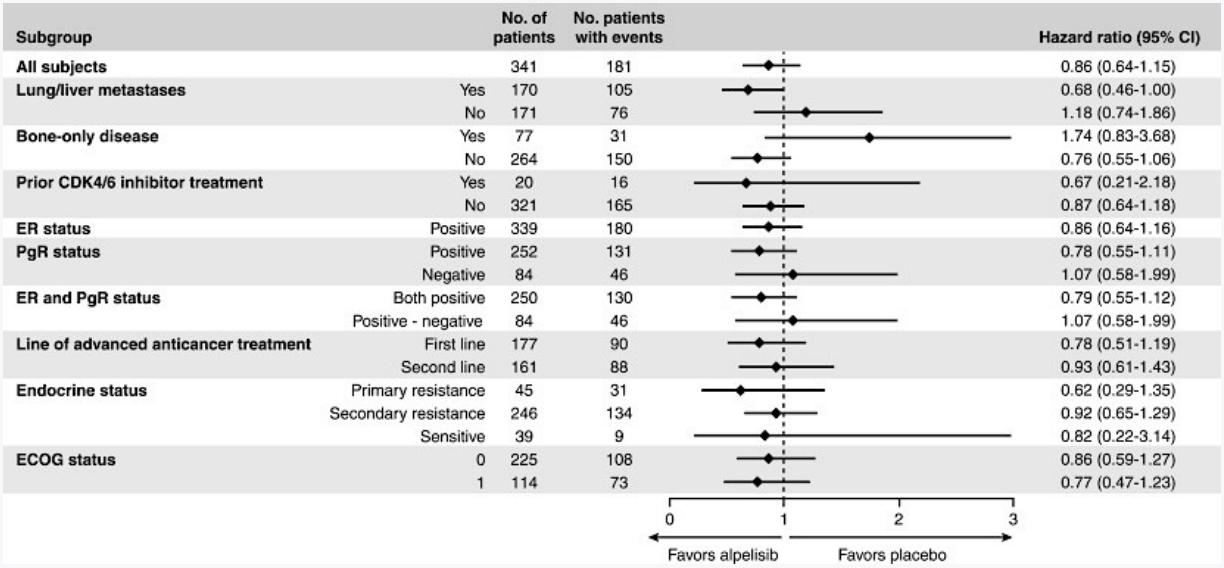
| Adverse Event | Alpelisib–Fulvestrant Group (N=284) | | | Placebo–Fulvestrant Group (N=287) | | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| | number of patients (percent) | | | | | |
| Any adverse event | 282 (99.3) | 183 (64.4) | 33 (11.6) | 264 (92.0) | 87 (30.3) | 15 (5.2) |
| Hyperglycemia† | 181 (63.7) | 93 (32.7) | 11 (3.9) | 28 (9.8) | 1 (0.3) | 1 (0.3) |
| Diarrhea‡ | 164 (57.7) | 19 (6.7) | 0 | 45 (15.7) | 1 (0.3) | 0 |
| Nausea‡ | 127 (44.7) | 7 (2.5) | 0 | 64 (22.3) | 1 (0.3) | 0 |
| Decreased appetite | 101 (35.6) | 2 (0.7) | 0 | 30 (10.5) | 1 (0.3) | 0 |
| Rash§ | 101 (35.6) | 28 (9.9) | 0 | 17 (5.9) | 1 (0.3) | 0 |
| Vomiting‡ | 77 (27.1) | 2 (0.7) | 0 | 28 (9.8) | 1 (0.3) | 0 |
| Weight loss | 76 (26.8) | 11 (3.9) | 0 | 6 (2.1) | 0 | 0 |
| Stomatitis | 70 (24.6) | 7 (2.5) | 0 | 18 (6.3) | 0 | 0 |
| Fatigue | 69 (24.3) | 10 (3.5) | 0 | 49 (17.1) | 3 (1.0) | 0 |
| Asthenia | 58 (20.4) | 5 (1.8) | 0 | 37 (12.9) | 0 | 0 |
| Alopecia | 56 (19.7) | 0 | 0 | 7 (2.4) | 0 | 0 |
| Mucosal inflammation | 52 (18.3) | 6 (2.1) | 0 | 3 (1.0) | 0 | 0 |
| Pruritus | 51 (18.0) | 2 (0.7) | 0 | 16 (5.6) | 0 | 0 |
| Headache | 50 (17.6) | 2 (0.7) | 0 | 38 (13.2) | 0 | 0 |
| Dysgeusia | 47 (16.5) | 0 | 0 | 10 (3.5) | 0 | 0 |
| Arthralgia | 32 (11.3) | 1 (0.4) | 0 | 47 (16.4) | 3 (1.0) | 0 |

Permanent discontinuation of alpelisib or placebo due to adverse events occurred in 71 patients (25.0%) receiving alpelisib–fulvestrant and in 12 (4.2%) receiving placebo–fulvestrant. The most frequent adverse events leading to the discontinuation of alpelisib were hyperglycemia (in 18 patients [6.3%]) and rash (in 9 [3.2%]);

Andre et al. NEJM 2019

# Alpelisib plus fulvestrant for *PIK3CA*-mutated, HR+, HER2- advanced breast cancer: final OS results from SOLAR-1




Andre et al. Annals of Oncology 2021

# PI3K/AKT/mTOR Targeting Drugs

| | Patient mutation status | Line of treatment | Combined therapy | Primary endpoint | Phase of development | Trial name | Trial registration number |
|---|---|---|---|---|---|---|---|
| **PI3K inhibitors** | | | | | | | |
| Inavolisib (trial 1) | *PIK3CA* | First line, advanced* | Inavolisib plus palbociclib plus fulvestrant *vs* placebo plus palbociclib, plus fulvestrant | Progression-free survival | 3 | INAVO120 | NCT04191499 |
| Inavolisib (trial 2) | *PIK3CA* | After progression on CDK4/6 inhibitor in advanced setting† | Inavolisib plus fulvestrant *vs* alpelisib plus fulvestrant | Progression-free survival | 3 | INAVO121 | NCT05646862 |
| Alpelisib | *PIK3CA* DNA non-suppression C2D1 | First line, advanced* | Alpelisib plus fulvestrant *vs* palbociclib plus fulvestrant | Progression-free survival | 2 | SAFIR 03 | NCT05625087 |
| TOS-358 | *PIK3CA* | Not specified | Monotherapy | Dose-limiting toxicities, adverse events | 1 | TOS-358-001 | NCT05683418 |
| LOXO-783‡ | *PIK3CA* (3140A>G [His1047Arg]) | Arm dependent§ | Multiple treatment groups¶ | Dose-limiting toxicities | 1 | PIKASSO-01 | NCT05307705 |
| STX-478‡ | PIK3CA (His1047Xxx)‖ | Not specified | STX-478 as monotherapy or in combination with fulvestrant | Dose-limiting toxicities | 1/2 | SCORPION | NCT05768139 |
| RLY-2608‡ | *PIK3CA* | After endocrine therapy and CDK4/6 inhibitor, maximum one line of chemotherapy in advanced setting | Multiple treatment groups** | Dose-limiting toxicities, adverse events | 1/2 | ReDiscover | NCT05216432 |
| **Pan-AKT inhibitor** | | | | | | | |
| Ipatasertib | ctDNA non-suppression C1D15 | After endocrine therapy,†† maximum one line of chemotherapy in advanced setting | Ipatasertib plus palbociclib plus fulvestrant *vs* palbociclib plus fulvestrant | Progression-free survival | 2 | FAIM | NCT04920708 |
| Capivasertib | Mutation not required | After endocrine therapy‡‡ | Capivasertib plus fulvestrant plus CDK4/6inhibitor (palbociclib or ribociclib) *vs* fulvestrant plus CDK4/6 inhibitor (palbociclib or ribociclib) | Dose-limiting toxicities, adverse events, progression-free survival | 1b/3 | CAPItello-292 | NCT04862663 |
| **mTOR inhibitor** | | | | | | | |
| RMC-5552§§ | Mutation not required | Not specified | Monotherapy | Dose-limiting toxicities, adverse events | 1 | RMC-5552-001 | NCT04774952 |
| **Dual inhibitor** | | | | | | | |
| Gedatolisib¶¶ | Mutation not required | After CDK4/6 inhibitors plus aromatase inhibitor in advanced setting | Multiple treatment arms‖‖ | Progression-free survival | 3 | VIKTORIA-1 | NCT05501886 |

# Faculty Case Presentations

# Case Presentation – Dr Hurvitz

- 58 yo woman was diagnosed at age 45 with left breast stage II pT2pN0 ER+PR+ HER2 2+, FISH- breast cancer. Onco*type* DX RS 22. Genetic testing negative. She has surgery, radiation, tamoxifen/ovarian suppression x 5 years.
- 8 years later (age 52) develops metastatic disease to bones only. Has bilateral oophorectomy and receives palbociclib/anastrozole. Disease control x 4 years.
- Progression in bones and lungs (age 56). Biopsy of lung with sequencing: *PIK3CA* mut. Starts keto diet and then alpelisib plus fulvestrant with antihistamine daily.
- Excellent disease control for 2 years
- Progression of disease in liver and lungs.  Biopsy: ER+ PR- HER2 1+. NGS: *ESR1* mut, *PIK3CA* mut, *HER2* mut. Next treatment?

# Case Presentation – Dr Jhaveri

- 63-year-old postmenopausal female with stage III invasive ductal breast cancer, s/p mastectomy on the right that revealed a 3.8 cm grade 3 tumor with 4/13 LN, ER+ PR+ HER2 IHC 1+ s/p adjuvant ACT and radiation on letrozole X 3 years, presented with back pain
- Staging showed liver and bone metastases
- Liver biopsy confirmed MBC ER+ PR+ HER2 IHC 0
- Tissue NGS: *PIK31047R* mutation, no other alterations
- Genetics: negative

# Case Presentation – Dr Jhaveri (Continued)

## How will you treat this patient?

1. Fulvestrant plus CDK4/6 inhibitor
2. Exemestane plus Everolimus
3. Fulvestrant plus Alpelisib
4. Fulvestrant plus Capivasertib
5. Capecitabine
6. Inavolisib + Fulvestrant + Palbociclib
7. ADCs, if available

**Answer:** Inavolisib + Fulvestrant + Palbociclib - started on trial, had PR and remains on trial for almost 5 years

Reports fatigue, had intermittent grade 1 diarrhea, required dose reduction of Palbociclib due to neutropenia

# Agenda

**Module 1:** Role of CDK4/6 Inhibitors in Hormone Receptor (HR)-Positive Localized Breast Cancer – Dr Hurvitz

**Module 2:** Incorporation of CDK4/6 Inhibitors into the Management of HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) – Dr Wander

**Module 3:** Evolving Role of PI3K Inhibitors for HR-Positive mBC Harboring PIK3CA Mutations – Dr Goetz

**Module 4: Clinical Utility of AKT Inhibitors for Patients with Progressive HR-Positive mBC – Dr Jhaveri**

**Module 5:** Oral Selective Estrogen Receptor Degraders (SERDs) for HR-Positive mBC – Dr Kaklamani

RTP RESEARCH TO PRACTICE

# Clinical Utility of AKT Inhibitors for Patients with Progressive HR-Positive mBC

**Komal Jhaveri, MD, FACP**
Patricia and James Cayne Chair for Junior Faculty
Associate Attending, Breast Medicine and Early Drug Development Service
Section Head, Endocrine Therapy Research Program
Clinical Director, Early Drug Development Service
Memorial Sloan Kettering Cancer Center

Associate Professor
Weill Cornell Medical College
New York, New York

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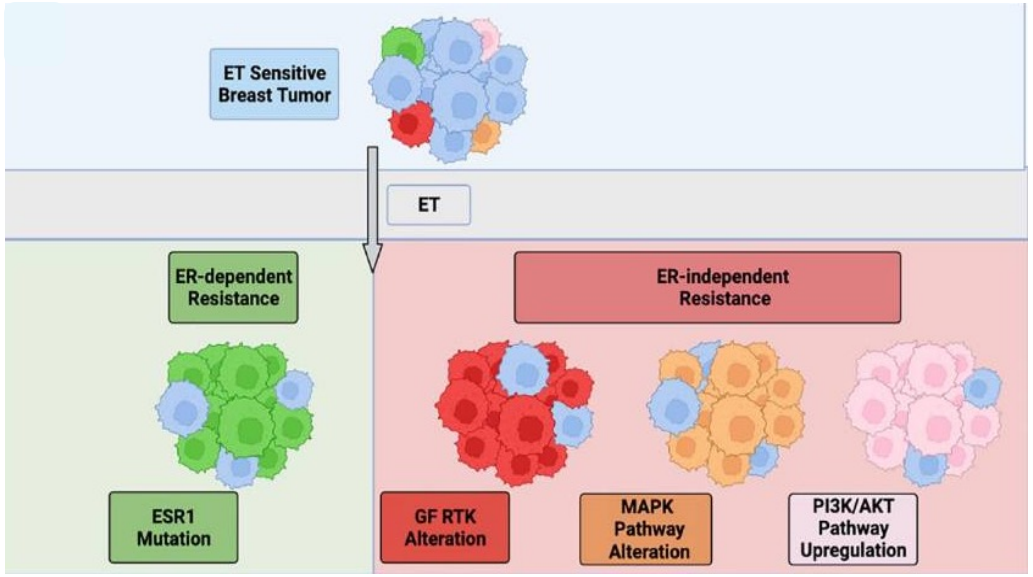
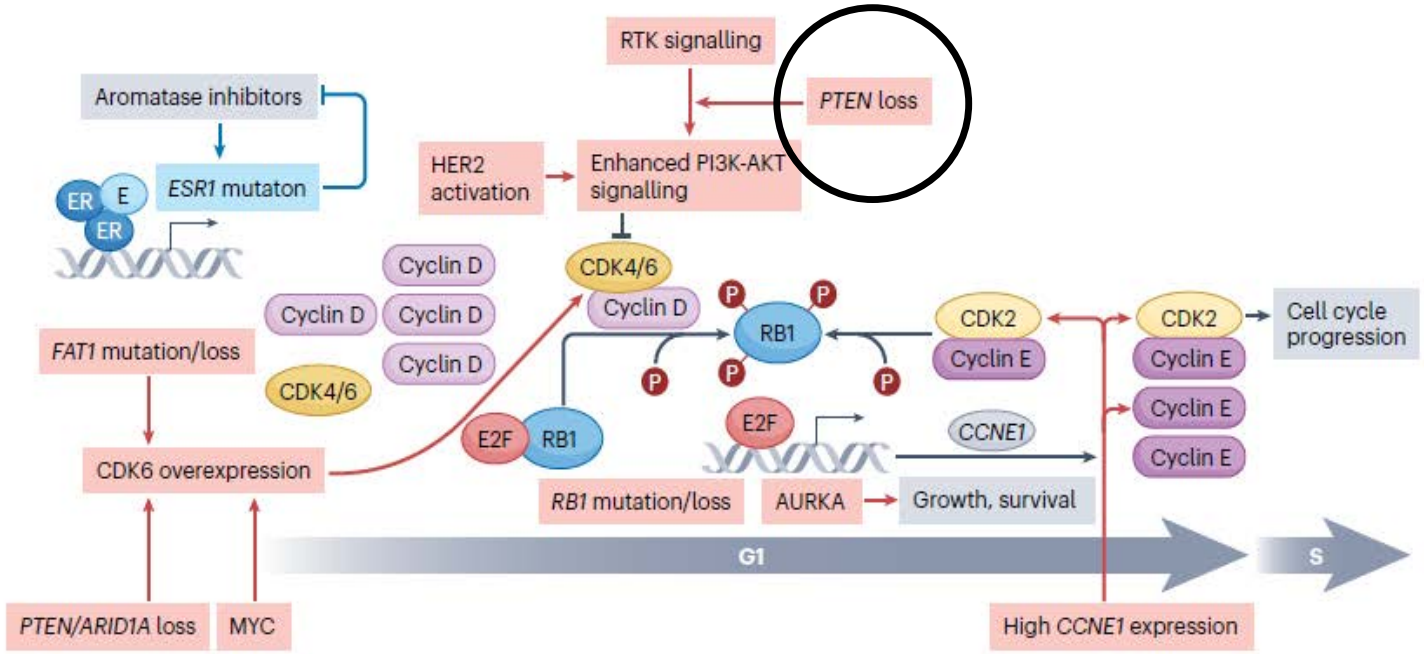
# Mechanism of Resistance to ET+ CDK4/6 Inhibitors: Unmet Need



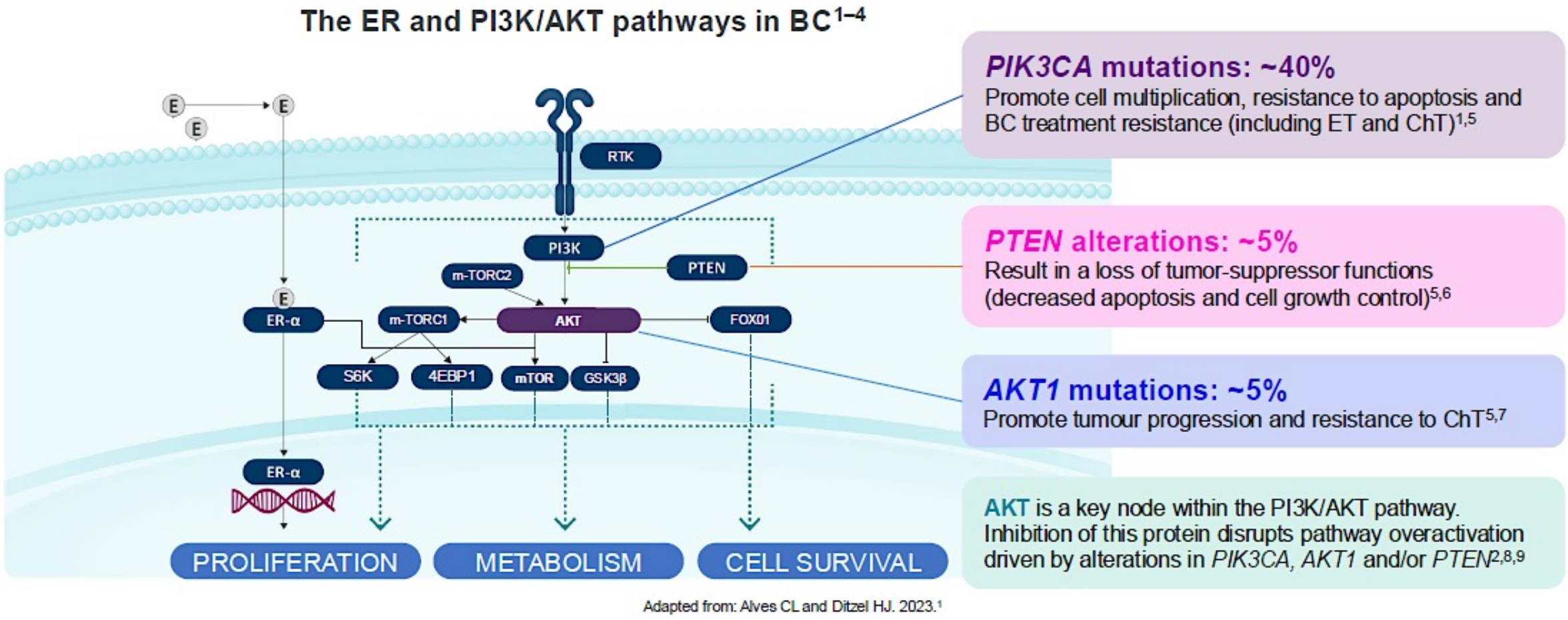

ER dependent and independent mechanism of resistance




Mechanisms of resistance to CDK4/6 inhibitors

Lloyd MR, et al. Ther Adv Med Oncol 2022, Vol. 14: 1–25; Morrison, Loibl, Turner Nat Review Clinical Oncology 2024

# Genes within the PI3K/AKT pathway are frequently altered in BC resulting in pathway overactivation, leading to tumor growth and treatment resistance[1,2]




Adapted from: Alves CL and Ditzel HJ. 2023.[1]

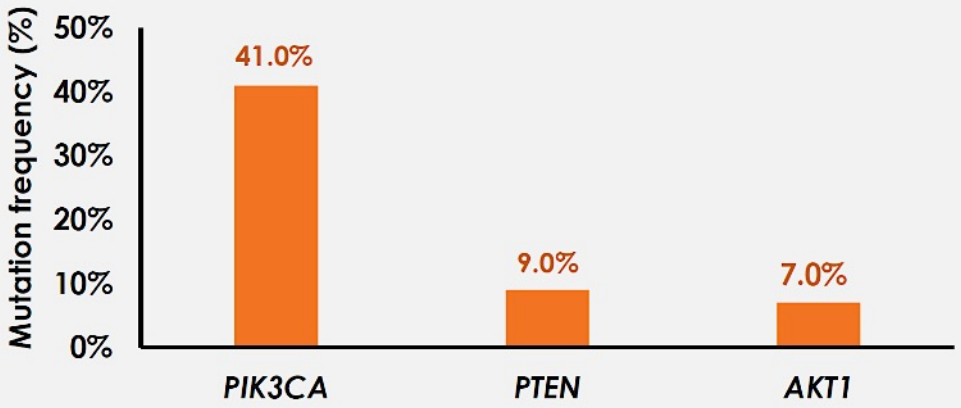

1. Alves CL and Ditzel HJ. *Int J Mol Sci.* 2023;24:4522; 2. Miller TW, et al. *Breast Cancer Res.* 2011;13:224; 3. du Rusquec P, et al. *Ther Adv Med Oncol*. 2020;12:1–12; 4. Ebrahimnezhad M, et al. *Biomed Pharmacother* 2023:169:115900; 5. Rascio F, et al. *Cancers (Basel).* 2021;13:3949; 6. Mery B, et al. Int J Mol Sci. 2021;22:13512; 7. Hua H, et al. J Hematol Oncol. 2021;14:128; 8. Miricescu D, et al. Int J Mol Sci. 2020;22:173;
9. Davies BR, et al. Mol Cancer Ther. 2012;11:873–887.

# Prevalence of PIK3CA, AKT and PTEN Alterations in HR+ MBC

| Frequency of AKT Pathway Alterations in HR+/HER2- mBC | |
|---|---|
| **Alteration** | **Frequency** |
| *PIK3CA* mutation | 28–46%[1-5] |
| *AKT1* mutation | 1–11%[1-5] |
| *PTEN* mutation | 1–14%[1-4] |

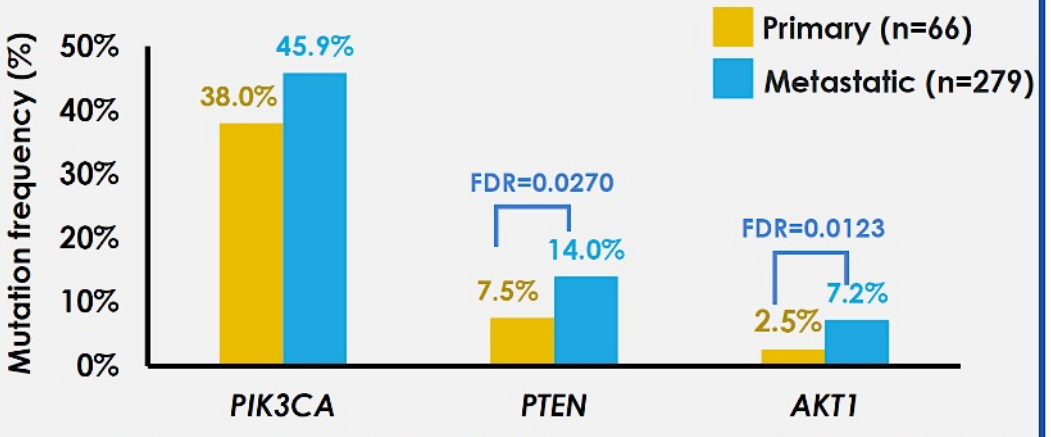
- Further research is required to understand to what extent exposure to CDK4/6i-ET treatment increases the frequency of AKT-pathway mutations, as *PTEN*, *AKT1* and *PIK3CA* alterations have been observed pre- and post-exposure.[1,2,6,7,8,9]
- Testing of metastatic tissue is preferred to inform mBC treatment decisions.[10]

**Mutation frequency in prospectively sequenced HR+/HER2- BC samples (n=1,501) at a single US centre** [11]




- 762 metastatic tumours (Stage I–IV at diagnosis) with prior ET from the prospective cohort vs. 739 primary tumours from TCGA
- Mutation frequencies were similar between primary and metastatic tissue*

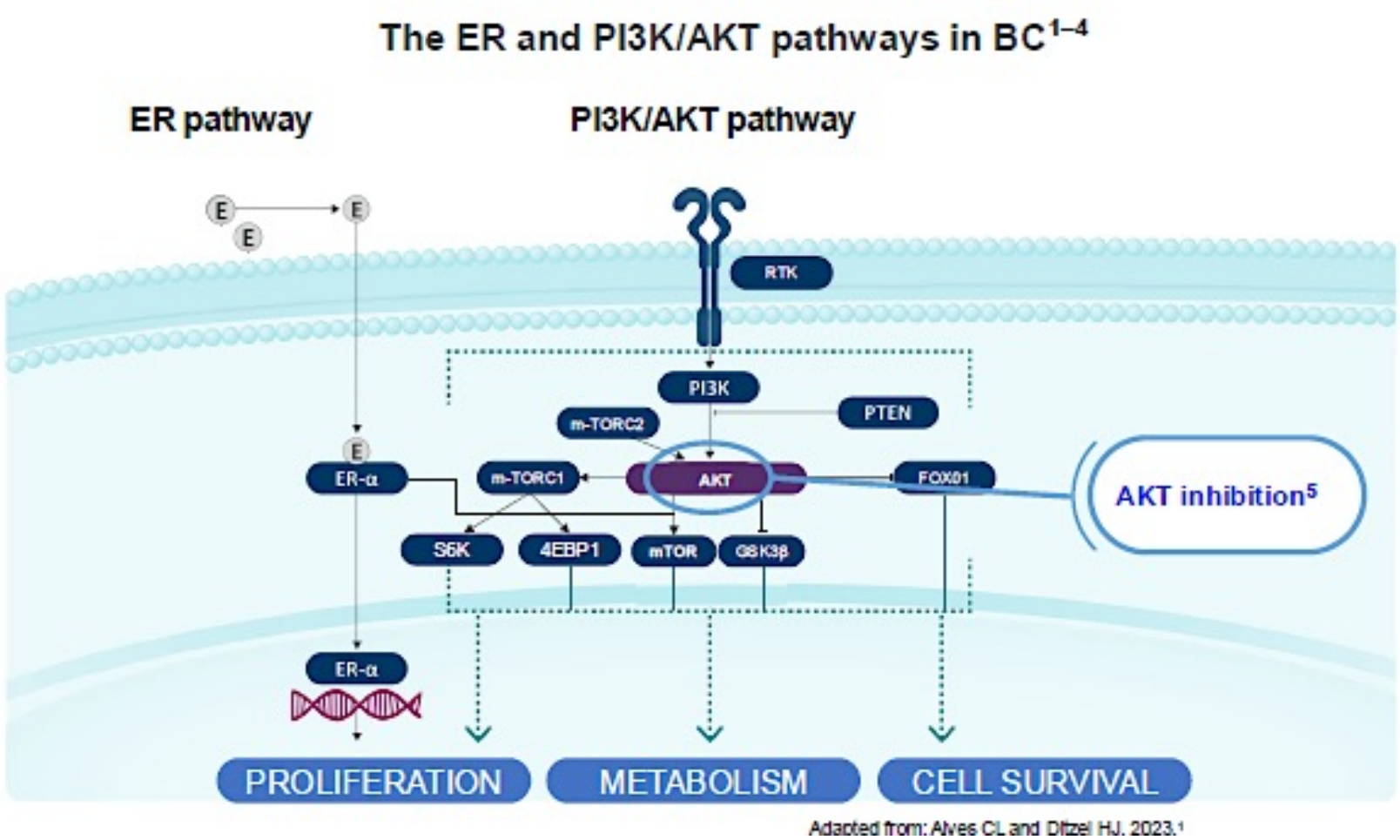
**Mutation frequency in prospectively collected HR+/HER2- BC samples from 49 centres in The Netherlands** [12,13]




- 279 metastatic tumours from prospective collection vs. 66 primary tumours from TCGA and BASIS
- *PTEN* and *AKT1* were more frequently mutated in metastatic vs. primary BC (FDR<0.05)


1. Angus L et al. *Nat Genet*. 2019;51(10):1450-1458; 2. Mosele F et al. *Ann Oncol*. 2020;31(3):377-386; 3. Chung JH et al. *Ann Oncol*. 2017;28(11):2866-2873; 4. Pezo RC et al. *Breast Cancer Res Treat*. 2018;168(1):159-168; 5. Paul MR et al. *J Clin Invest.* 2020;130(8):4252-4265.; 6. Wander SA et al. *Cancer Discov.* 2020;10(8):1174-1193; 8-6. 7. Miller TW et al. *J Clin Invest.* 2010;120(7):2406-2413; 8. Razavi P et al. Cancer Cell. 2018;34(3):427-438.e6.; 11-8. 9. NCCN Guidelines®. Breast Cancer. Version 1.2024. Published online January 25, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; 10. Burstein HJ et al. J Clin Oncol. 2023;41(18):3423-3425. 11. Rosin J et al. *Breast Cancer Res Treat*. 2023;201(2):161-169; 12.. Bertucci F et al. *Nature*. 2019;572(7767):E7; 13. O'Leary B et al. *Cancer Discov*. 2018;8(11):1390-1403;

# Capivasertib is a potent AKT inhibitor




Potent inhibition of AKT broadens actionable biomarkers beyond *PIK3CA* alterations to include *AKT1* and *PTEN* alterations[6–8]

1. Alves CL and Ditzel HJ. Int J Mol Sci. 2023;24:4522; 2. Miller TW, et al. Breast Cancer Res. 2011;13:224; 3. du Rusquec P, et al. Ther Adv Med Oncol. 2020;12:1–12; 4. Ebrahimnezhad M, et al. Biomed Pharmacother 2023:169:115900; 5. ASCO Post. Available at: https://ascopost.com/issues/april-25-2023/emerging-success-with-novel-targeted-therapies-in-endocrine-resistant-metastatic-breast-cancer/ (Accessed September 2024); 6. Turner N, et al. N Engl J Med. 2023;388:2058–2070; 7. Smyth LM, et al. Clin Cancer Res. 2020;26:3947–3957; 8. AstraZeneca. Capivasertib Prescribing Information. November 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218197s000lbl.pdf. (Accessed September 2024).

# Capivasertib in Advanced ER-Positive Breast Cancer
## *Phase 2 FAKTION Trial*

- Capivasertib is a potent and selective inhibitor of all 3 isoforms of AKT
- In Phase II FAKTION trial, addition of capivasertib to fulvestrant doubled median **PFS (10.3 vs 4.8 mo, HR 0.58)**

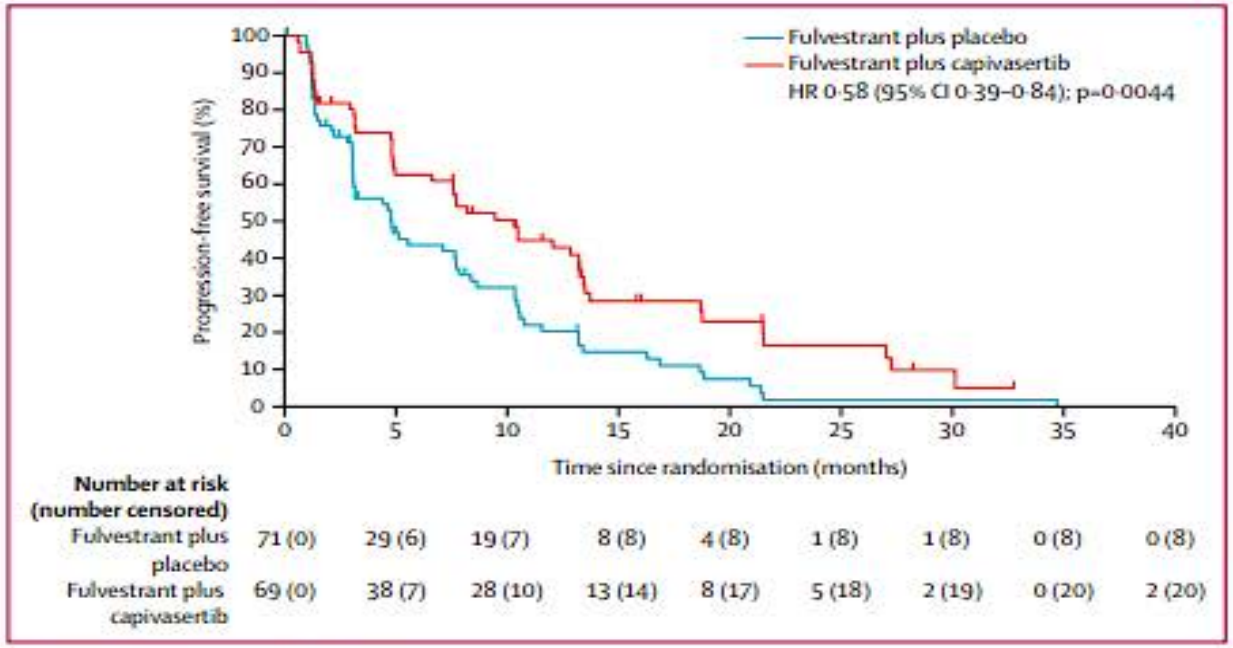
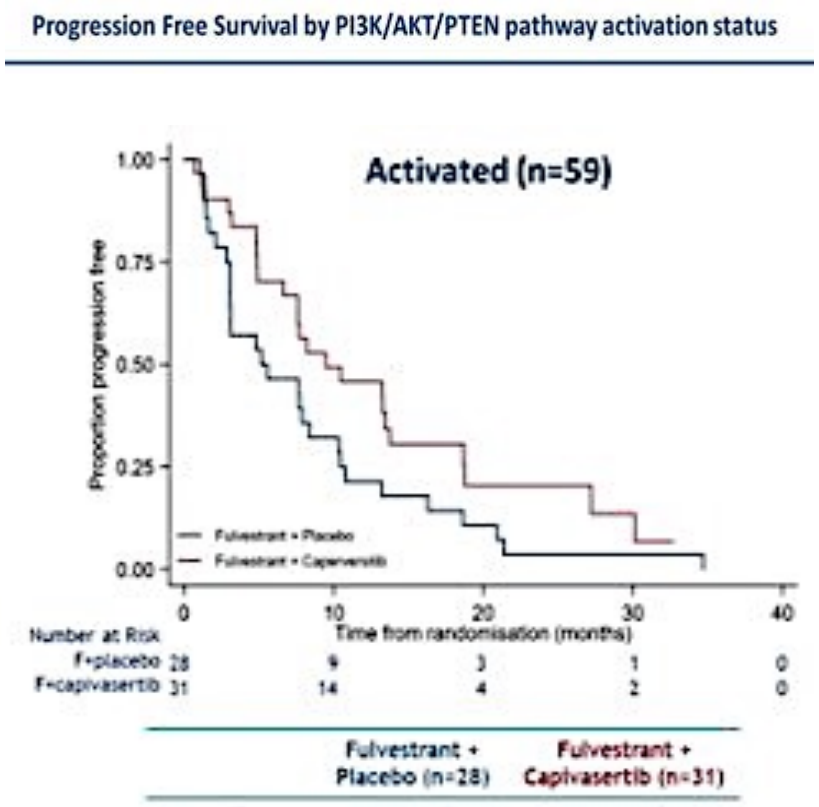



***Figure 2:*** **Progression-free survival**
HR=hazard ratio.

Notable toxicities affecting > 10% of study population: Diarrhea (Gr 3/4 14%), rash (Gr 3/4 20%), hyperglycemia (Gr 3/4 4%).




- Benefit appeared independent of activated pathway, albeit only tested for limited *PIK3CA* mutations by ddPCR and PTEN protein loss by IHC
- AKT1 not examined

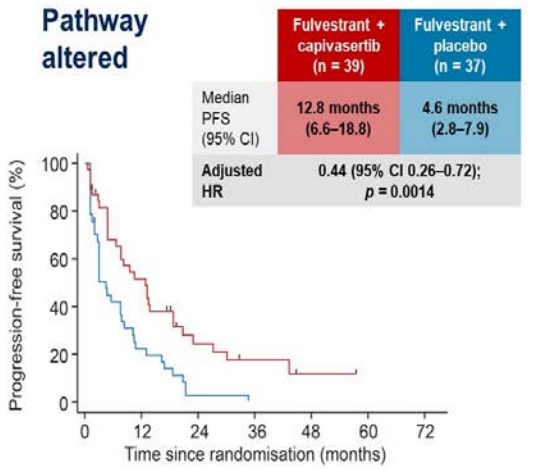
Jones RH et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2020;21(3):345-357.

# Capivasertib in Advanced ER-Positive Breast Cancer
## *Phase 2 FAKTION Trial*

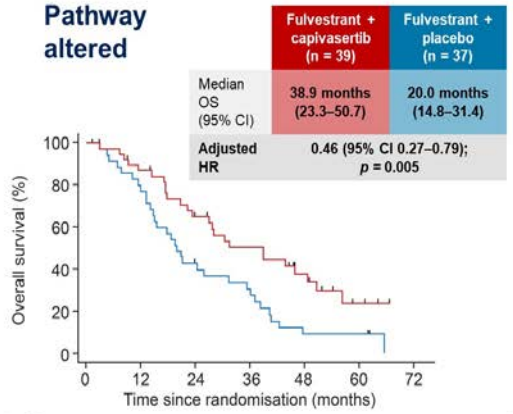


- Updated efficacy data after median 60 months follow-up
- Expanded NGS testing used to identify *AKT1* E17K mutation, additional activating *PIK3CA* mutations, and *PTEN* alterations predicted to result in loss of function
- PI3K/AKT/PTEN alterations found in 54% of participants in ITT population (vs 42% using original ddPCR / IHC methods)
- PFS and OS data indicated that capivasertib mainly benefited the pathway alerted subgroup
  - Median PFS 12.8 mo vs 4.6 mo (HR 0.44; *P* = .0014)
  - Median OS 39.8 mo vs 20.0 mo (HR 0.46; *P* = .005)

**FAKTION: PFS in the expanded pathway altered**



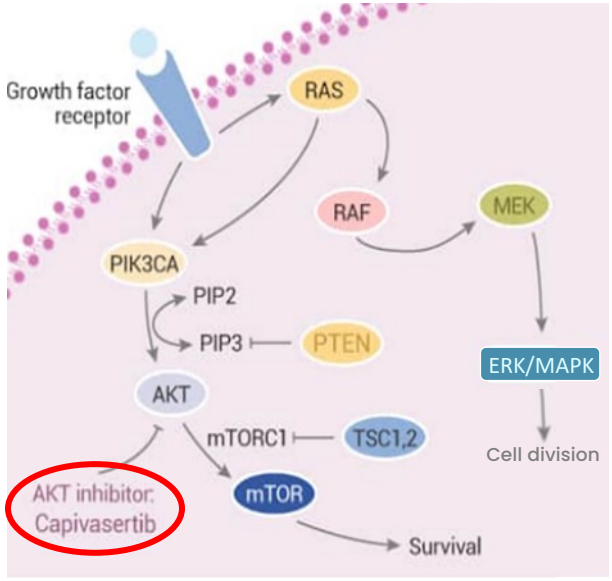

**FAKTION: OS in the expanded pathway altered**




NGS, next-generation sequencing.

Howell SJ et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol. 2022;23(7):851-864

# CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Study Design[1,2]




**Eligibility**

- HR+/HER2–* aBC
- Men and pre/peri/postmenopausal women
- Recurrence 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 tumour sample from the primary/recurrent cancer available for retrospective central molecular testing

Stratification Factors
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region

**Randomization 1:1 N=708**

Treatment until PD, unacceptable toxicity, or withdrawal of consent

- **Capivasertib + Fulvestrant‡**
- **Placebo + Fulvestrant**

**Co-primary Endpoints**

- **Progression-free survival in:**
  - Overall population
  - AKT pathway-altered tumours (≥ 1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

**Secondary Endpoints**

- **Overall survival in:**
  - Overall population
  - AKT pathway-altered tumors
- **Objective response rate in:**
  - Overall population
  - AKT pathway-altered tumours

1. Turner NC et al. Abstract GS3-04: GS3-04 Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial. SABCS 2022. Abstract GS3-04. Available at: https://aacrjournals.org/cancerres/article/83/5_Supplement/GS3-04/717531/Abstract-GS3-04-GS3-04-Capivasertib-and. Accessed November 2024. 2. Turner NC et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2023;388(22):2058-2070.

# CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: Baseline Demographics

| Patient Characteristics, n (%) | | Overall Population | | AKT Pathway Altered | |
|---|---|---|---|---|---|
| | | C+F (n=355) | P+F (n=353) | C+F (n=155) | P+F (n=134) |
| Median age (range), years | | 59 (26-84) | 58 (26-90) | 58 (36-84) | 60 (34-90) |
| Metastatic sites | Bone only | 51 (14.4) | 52 (14.7) | 25 (16.1) | 16 (11.9) |
| | Liver[d] | 156 (43.9) | 150 (42.5) | 70 (45.2) | 53 (39.6) |
| | Visceral | 237 (66.8) | 241 (68.3) | 103 (66.5) | 98 (73.1) |
| HR status[e] | ER+/PR+ | 255 (71.8) | 246 (69.7) | 116 (74.8) | 101 (75.4) |
| | ER+/PR– | 94 (26.5) | 103 (29.2) | 35 (22.6) | 31 (23.1) |
| | Unknown | 5 (1.4) | 4 (1.1) | 4 (2.6) | 2 (1.5) |
| Endocrine resistance | Primary | 127 (35.8) | 135 (38.2) | 60 (38.7) | 55 (41.0) |
| | Secondary | 228 (64.2) | 218 (61.8) | 95 (61.3) | 79 (59.0) |
| Prior endocrine therapy for ABC | 0 | 40 (11.3) | 54 (15.3) | 14 (9.0) | 20 (14.9) |
| | 1 | 286 (80.6) | 252 (71.4) | 130 (83.9) | 96 (71.6) |
| | 2 | 29 (8.2) | 47 (13.3) | 11 (7.1) | 18 (13.4) |
| **Prior CDK4/6i for ABC** | | **245 (69.0)** | **244 (69.1)** | **113 (72.9)** | **91 (67.9)** |
| Prior CT | (Neo)adjuvant | 180 (50.7) | 170 (48.2) | 79 (51.0) | 67 (50.0) |
| | ABC | 65 (18.3) | 64 (18.1) | 30 (19.4) | 23 (17.2) |
| AKT pathway alteration | | 155 (43.7) | 134 (38.0) | - | - |

Turner NC, et al. *N Engl J Med.* 2023;388(22_suppl):S1-S20.

# Baseline and Tumor Characteristics: AKT Pathway Alterations

| Alteration | | Capivasertib + Fulvestrant (n=355) | Placebo + Fulvestrant (n=353) |
|---|---|---|---|
| **Any AKT pathway alteration, %** | | **43.7** | **38.0** |
| ***PIK3CA*** | Any | **32.7** | **29.2** |
| | *PIK3CA* only | **31.0** | **26.1** |
| | *PIK3CA* and *AKT1* | **0.6** | **0.6** |
| | *PIK3CA* and *PTEN* | **1.1** | **2.5** |
| ***AKT1* only** | | **5.1** | **4.2** |
| ***PTEN* only** | | **5.9** | **4.5** |
| **Non-altered AKT pathway, %** | | **56.3** | **62.0** |
| **AKT pathway alteration not detected** | | **40.0** | **48.4** |
| **Unknown** | | **16.3** | **13.6** |
| | No sample available | 2.8 | 1.1 |
| | Pre-analytical failure | 11.0 | 9.6 |
| | Post-analytical failure | 2.5 | 2.8 |

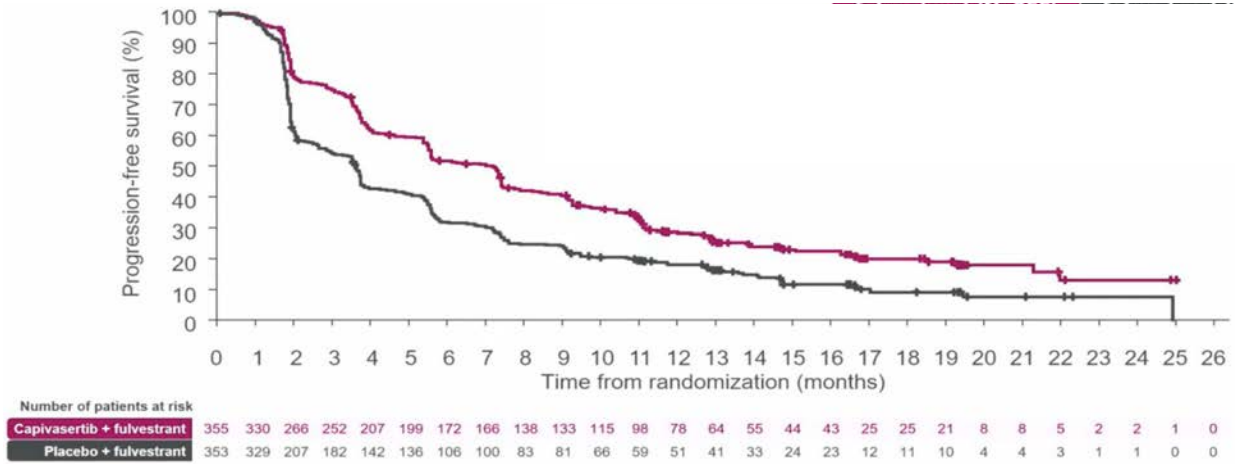
*AKT1,* serine/threonine kinase 1 gene; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; *PTEN,* phosphatase and tensin homolog gene.

Turner NC, et al. *N Engl J Med.* 2023;388(22_suppl):S1-S20.

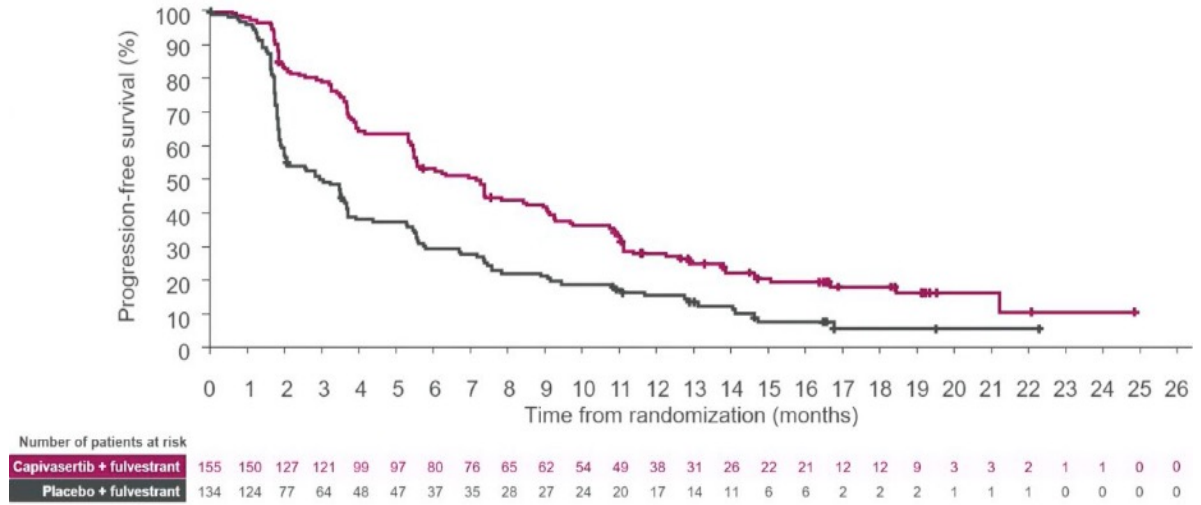
# CAPItello-291 Phase 3 Trial of Capivasertib + Fulvestrant in AI-Resistant HR+/HER2– MBC: PFS [1, 2]

**~70% prior CDK 4/6 inhibitors**
**~20% prior chemo**

### PFS by Investigator in Overall Population




### PFS by Investigator in the AKT Pathway-Altered Population




| Overall Population | C+F (n=355) | P+F (n=353) |
|---|---|---|
| PFS events | 258 | 293 |
| Median PFS, mo (95% CI) | 7.2 (5.5-7.4) | 3.6 (2.8-3.7) |
| Adjusted HR (95% CI) | 0.60 (0.51-0.71) | |
| Two-sided *P* value | <0.001 | |

| AKT Pathway-Altered Population | C+F (n=155) | P+F (n=134) |
|---|---|---|
| PFS events | 121 | 115 |
| Median PFS, mo (95% CI) | 7.3 (5.5-9.0) | 3.1 (2.0-3.7) |
| Adjusted HR (95% CI) | 0.50 (0.38-0.65) | |
| Two-sided *P* value | <0.001 | |

1. Turner NC et al. Abstract GS3-04: GS3-04 Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial. SABCS 2022. Abstract GS3-04. Available at: https://aacrjournals.org/cancerres/article/83/5_Supplement/GS3-04/717531/Abstract-GS3-04-GS3-04-Capivasertib-and. Accessed November 2024. 2. Turner NC et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med. 2023;388(22):2058-2070.

# CAPItello-291: PFS by Subgroup

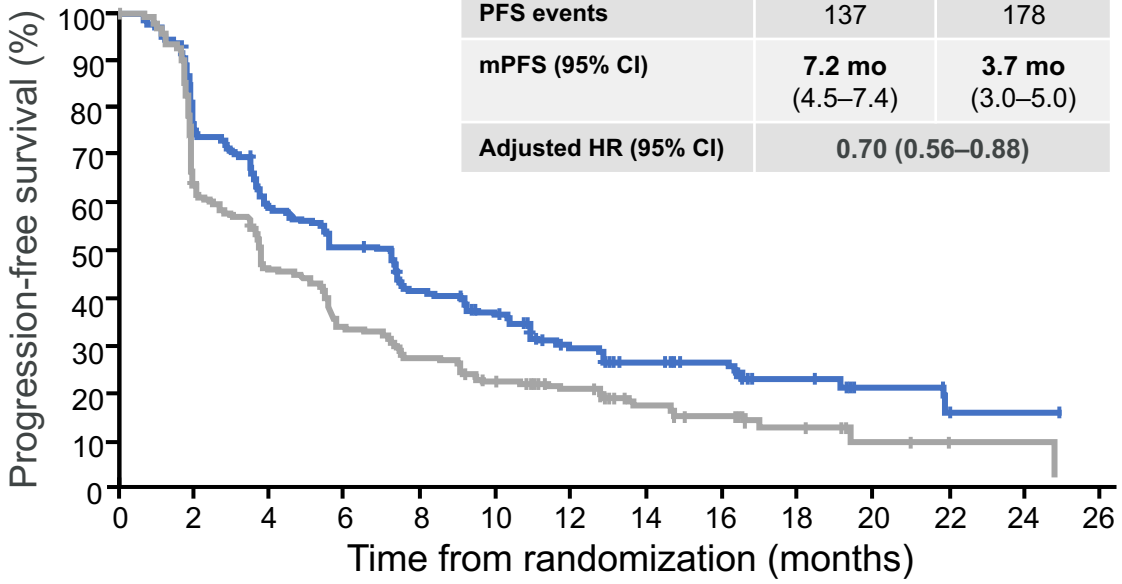
| Subgroup | Median PFS (95% CI); months | | |
|---|---|---|---|
| | Capi + fulvestrant | Placebo + fulvestrant | HR (95% CI) |
| **Prior CDK4/6 Exposure** | | | |
| yes | **5.5 months** (3.9-6.8) | **2.6 months** (2.0-2.5) | 0.59 months (0.48-0.72) |
| no | **10.9 months** (7.4-13.0) | **7.2 months** (4.8-7.9) | 0.64 months (0.45-0.90) |
| **Liver Metastases** | | | |
| yes | **3.8 months** (3.5-5.5) | **1.9 months** (1.8-1.9) | 0.61 months (0.48-0.78) |
| no | **9.2 months** (7.4-11.1) | **5.5 months** (3.9-5.8) | 0.6 months (0.48-0.76) |
| **Chemotherapy-naive** | | | |
| yes | **3.8 months** (3.0-7.3) | **2.1 months** (1.9-3.6) | 0.55 months (0.36-0.62) |
| no | **7.3 months** (5.6-8.2) | **3.7 months** (3.4-5.1) | 0.62 months (0.51-0.75) |

Oliveira M et al. ESMO Breast 2023. Abstract 187O.

# CAPItello-291: Progression-free Survival in Patients without AKT Pathway-altered Tumors

## Including Patients with Unknown NGS Results

| | CAPI + F (n=200) | PBO + F (n=219) |
|---|---|---|
| PFS events | 137 | 178 |
| mPFS (95% CI) | **7.2 mo** (4.5–7.4) | **3.7 mo** (3.0–5.0) |
| Adjusted HR (95% CI) | 0.70 (0.56–0.88) | |

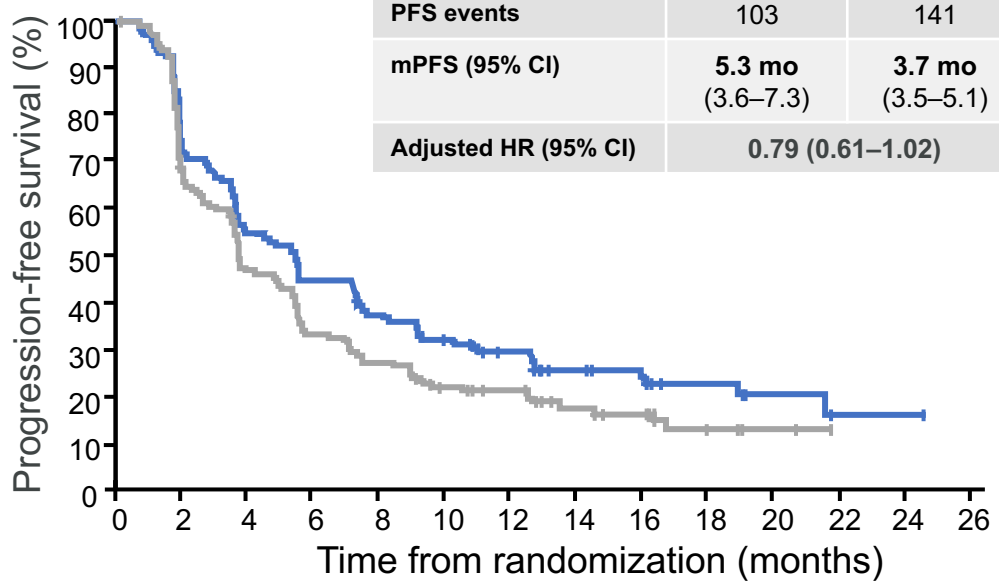



No. at risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CAPI + F | 200 | 139 | 108 | 92 | 73 | 61 | 40 | 29 | 22 | 13 | 5 | 3 | 1 | 0 |
| PBO + F | 219 | 130 | 94 | 69 | 55 | 42 | 34 | 22 | 17 | 9 | 3 | 2 | 1 | 0 |

## Excluding Patients with Unknown NGS Results

| | CAPI + F (n=142) | PBO + F (n=171) |
|---|---|---|
| PFS events | 103 | 141 |
| mPFS (95% CI) | **5.3 mo** (3.6–7.3) | **3.7 mo** (3.5–5.1) |
| Adjusted HR (95% CI) | 0.79 (0.61–1.02) | |




No. at risk

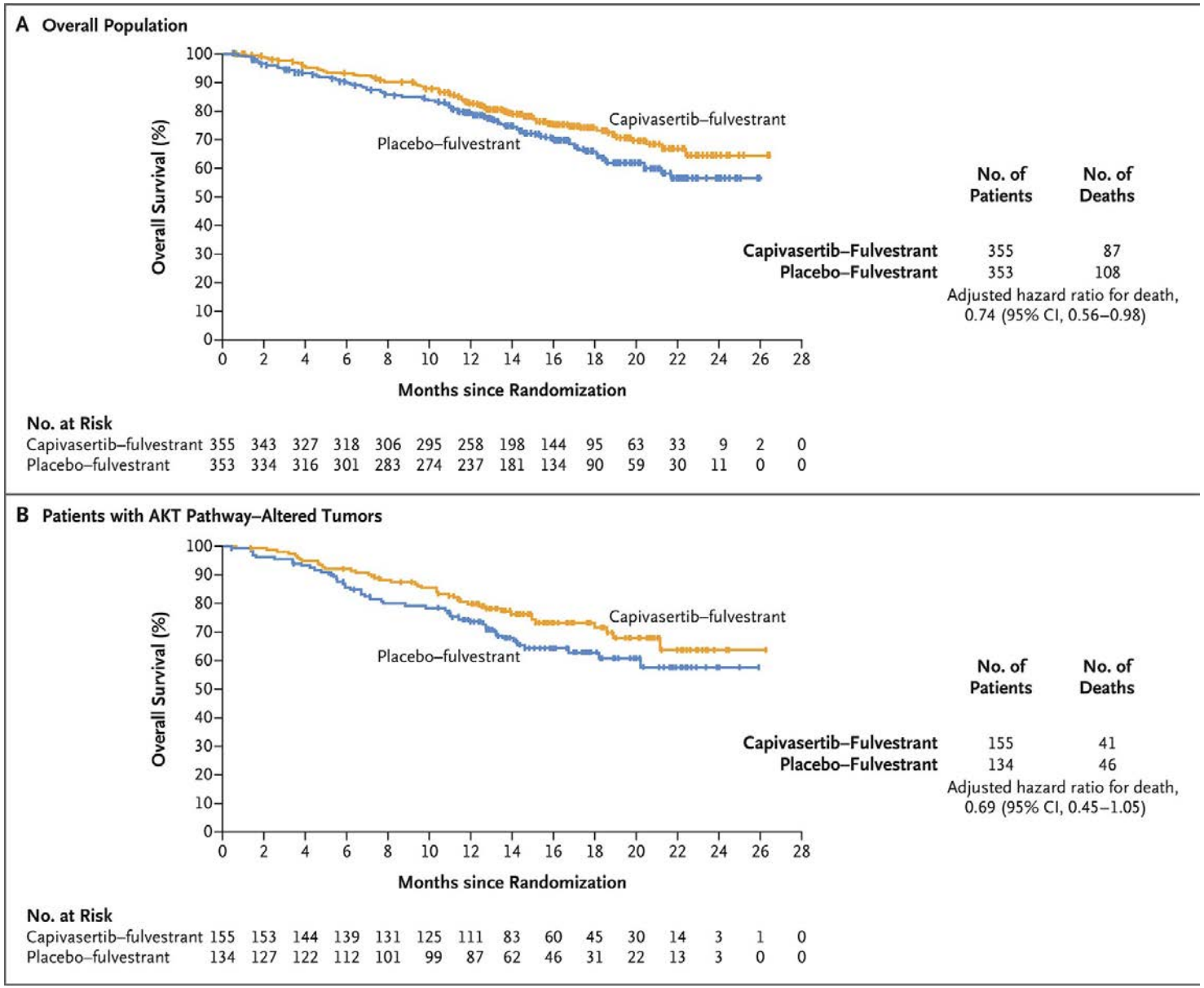
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CAPI + F | 142 | 95 | 72 | 58 | 47 | 38 | 28 | 18 | 15 | 9 | 4 | 3 | 1 | 0 |
| PBO + F | 171 | 109 | 75 | 52 | 42 | 30 | 26 | 17 | 14 | 6 | 2 | 1 | 0 | 0 |

Tick marks indicate censored data. 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.
CAPI, capivasertib; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; F, fulvestrant; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Turner NC, et al. *N Engl J Med.* 2023;388:2058-2070. DOI: 10.1056/NEJMoa2214131.

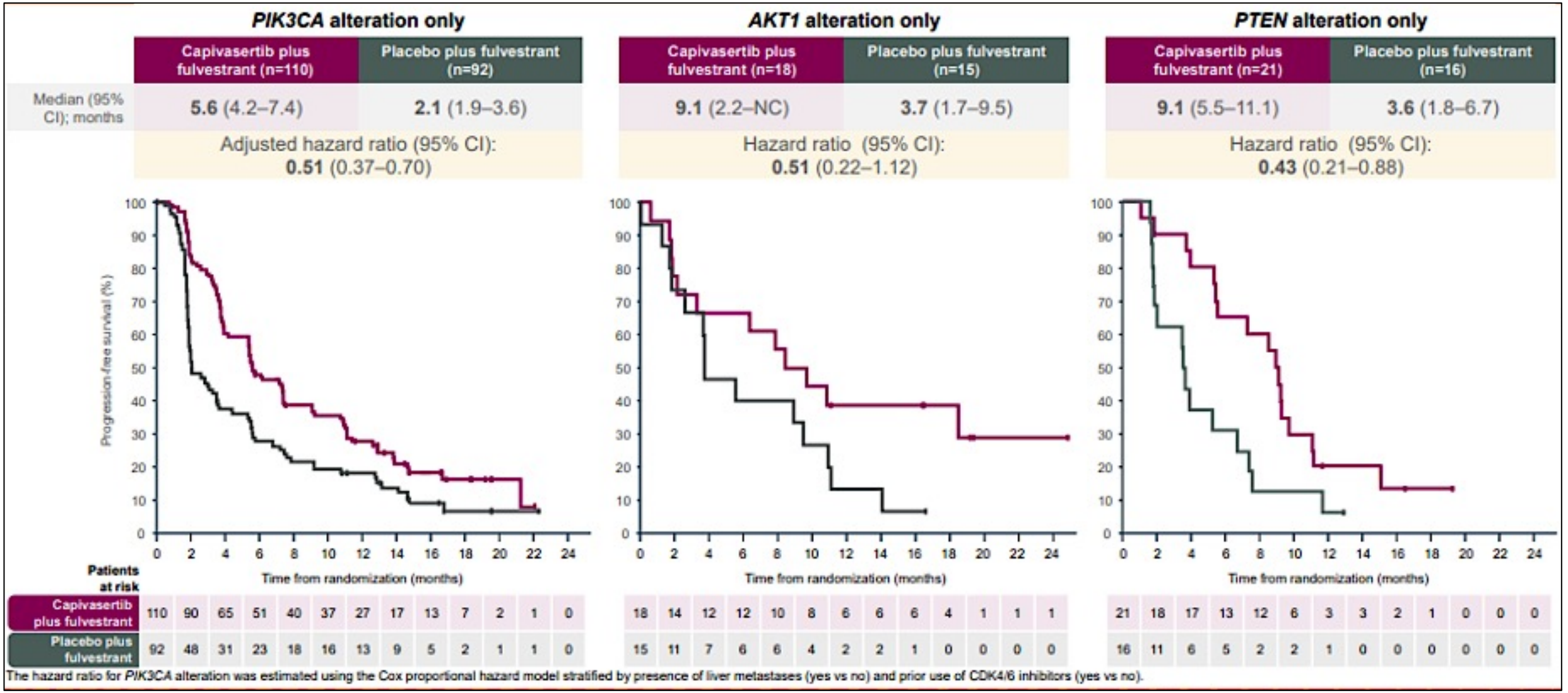
# CAPItello-291: OS in Overall Population and AKT-Pathway Altered

- Consistent benefit with capivasertib + fulvestrant was observed across clinically relevant subgroups in both the overall population and AKT pathway-altered population
- OS at 18 months:
  - Overall population: 73.9% capi vs. 65% placebo
  - AKT-pathway altered: 73.2% capi vs. 62.9% placebo




Turner NC, et al. N Engl J Med. 2023;388(22):2058-2070.

# Observed PFS benefit was consistent across gene alterations (Global Population)




Howell S et al SABCS 2023

# CAPItello-291: PFS2 and TFSC

| | PIK3CA/AKT1/PTEN-altered Population | |
|---|---|---|
| | Capivasertib + F (n=155) | Placebo + F (n=134) |
| **Second Progression Free Survival** | | |
| **Median, months** | 15.5 | 10.8 |
| HR (95% CI) | 0.52 (0.38–0.71) | |
| **Time To First Subsequent Chemotherapy** | | |
| **Median, months** | 11.0 | 6.0 |
| HR (95% CI) | 0.56 (0.42–0.74) | |

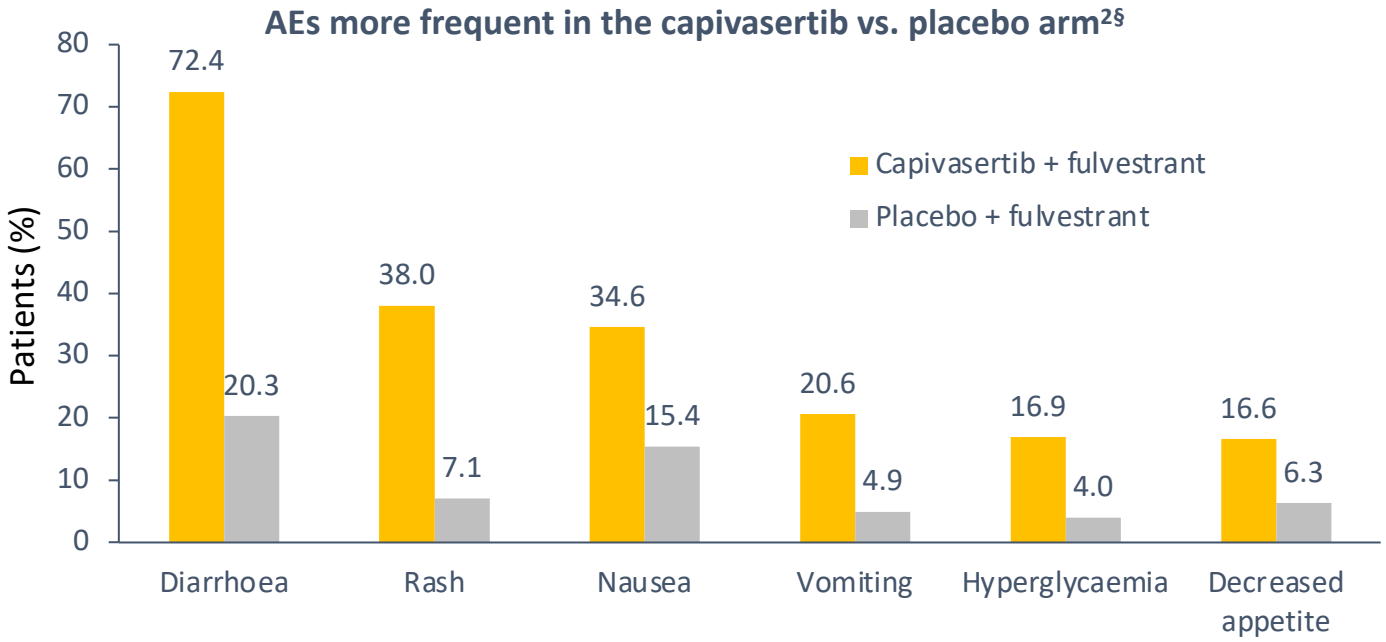
**The benefit of capivasertib + F was retained through PFS2. In addition, capivasertib + F also resulted in a clinically meaningful delay in the initiation of chemotherapy compared to F alone.**

Rugo HS. ESMO Breast 2024. Abstract #183MO. Capivasertib and fulvestrant (F) for patients (pts) with aromatase inhibitor (AI)-resistant HR+/HER2- advanced breast cancer (ABC): Second progression-free survival (PFS2) and time to first subsequent chemotherapy (TFSC) in the CAPItello-291 trial. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-breast-cancer-2024/capivasertib-and-fulvestrant-f-for-patients-pts-with-aromatase-inhibitor-ai-resistant-hr-her2-advanced-breast-cancer-abc-second-progress. Accessed November 2024.

# Capivasertib + fulvestrant was well tolerated[1,2]

**CAPItello-291 (Phase III; N = 708)**

| Patients with ≥1 AE, n (%) | Capivasertib + fulvestrant (n = 355) | Placebo + fulvestrant (n = 350) |
|---|---|---|
| Any AE[1] | 343 (96.6) | 288 (82.3) |
| Grade 3–4 AE[1] | 148 (41.7) | 54 (15.4) |
| Hyperglycaemia* | 8 (2.3) | 1 (0.3) |
| Diarrhoea* | 33 (9.3) | 1 (0.3) |
| Stomatitis* | 7 (2.0) | 0 |
| Rash† | 43 (12.1) | 1 (0.3) |
| Grade 5 AE[1‡] | 4 (1.1) | 1 (0.3) |
| SAE[1] | 57 (16.1) | 28 (8.0) |
| **AE leading to tx discontinuation[2]** | 46 (13.0) | 8 (2.3) |
| Capivasertib/placebo | 33 (9.3) | 2 (0.6) |
| Capivasertib/placebo and fulvestrant | 13 (3.7) | 6 (1.7) |




* Reported as a single term; † The group term of rash includes the preferred terms of rash, rash macular, maculopapular rash, rash popular and rash pruritic; ‡ Grade 5 events included acute myocardial infarction, cerebral haemorrhage, pneumonia aspiration and sepsis (all n = 1) in the capivasertib + fulvestrant arm and COVID-19 (n = 1) in the placebo + fulvestrant arm. No grade 5 events were classified as related to capivasertib/placebo by the local investigator. The safety analysis population included all patients who received at least one dose of the study drug; § Diarrhoea, rash, and hyperglycaemia were reported as grouped terms.
AE, adverse event; SAE, serious adverse event; tx, treatment.

Turner NC, *et al. N Engl J Med* 2023; **388:**2058–2070; 2. Rugo HS, *et al*. ESMO Open 2024; **9:**103697.

# Rash and Diarrhea Management

## Diarrhea

*Initiate medical therapy at grade 1*

| Grade 2 | Recurrent grade 2 or 3 | Grade 4 |
|---|---|---|
| Resume same dose | Reduce by 1 dose level | Discontinue treatment |

**Onset:** 8 days
**Dose reduction:** 8%
**Discontinuation:** 2%

## Rash

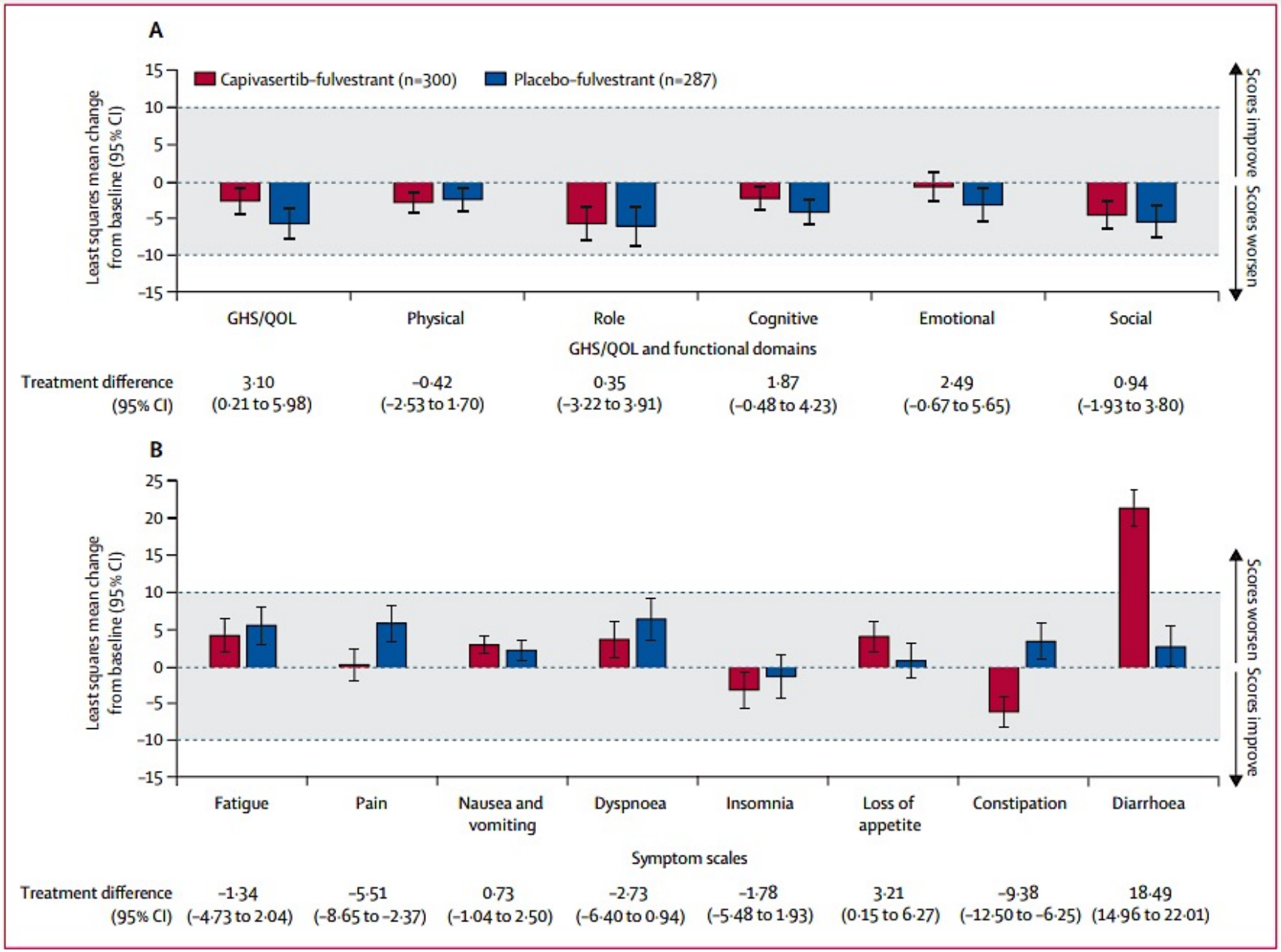
*Hold starting at grade 2 until ≤grade 1*

| Grade 2 or 3 and resolves ≤28 days | Recurrent grade 2 or 3 and resolves >28 days | Recurrent grade 3 or 4 |
|---|---|---|
| Resume same dose | Reduce by 1 dose level | Discontinue treatment |

**Onset:** 12 (10-15) days
**Discontinuation:** 4.5%

Capivasertib Prescribing Information; Rugo et al, ASCO 2023; ESMO Open 2024

# CAPItello-291: PRO




Oliveira et al Lancet Oncology 2024

# NCCN Guidelines



National Comprehensive Cancer Network®

## NCCN Guidelines Version 2.2024
## Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

**TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE**

**Biomarkers Associated with FDA-Approved Therapies**

| Breast Cancer Subtype | Biomarker | Detection | FDA-Approved Agents | NCCN Category of Evidence | NCCN Category of Preference |
|---|---|---|---|---|---|
| HR-positive/ HER2-negative[w] | *PIK3CA* activating mutation | NGS, PCR (Blood or tumor tissue if blood negative) | Alpelisib + fulvestrant[x] | Category 1 | Preferred second- or subsequent-line therapy |
| HR-positive/ HER2-negative[y] | *PIK3CA* or *AKT1* activating mutations or *PTEN* alterations | NGS, (Blood or tumor tissue if blood negative) | Capivasertib + fulvestrant[y] | Category 1 | Preferred second- or subsequent-line therapy in select patients[y] |
| HR-positive/ HER2-negative[z] | *ESR1* mutation | NGS, PCR (Tumor tissue or blood) | Elacestrant[z] | Category 2A | Other recommended regimen |
| Any | Germline *BRCA1* or *BRCA2* mutation | Germline sequencing | Olaparib<br>Talazoparib | Category 1 | Preferred |
| Any | *NTRK* fusion | FISH, NGS, PCR (Tumor tissue or blood) | Larotrectinib[aa]<br>Entrectinib[aa] | Category 2A | Useful in certain circumstances |
| Any | MSI-H/dMMR | IHC, NGS, PCR, (Tumor tissue) | Pembrolizumab[bb,cc]<br>Dostarlimab-gxly[dd] | Category 2A | |
| Any | TMB-H (≥10 mut/Mb) | NGS (Tumor tissue or blood) | Pembrolizumab[bb,cc] | Category 2A | |
| Any | *RET*-fusion | NGS (Tumor tissue or blood) | Selpercatinib[ee] | Category 2A | |

## Treatment Algorithm for HR+/HER2- MBC

# Phase 3 CAPItello-292 (NCT04862663) Study Design

- Adults ≥18 years of age with metastatic or locally ABC
- Histologically confirmed HR-positive/HER2-negative
- Disease relapse while on, or within 12 months of the end of (neo)adjuvant endocrine therapy[a]
- No prior endocrine therapy for ABC
- No prior CDK4/6 inhibitor for ABC
- No more than one line of chemotherapy for ABC
- No prior or concurrent treatment with systemic AKT, PI3K, and/or mTOR inhibitors

**R1:1 (N≈628)**

| | |
|---|---|
| Capivasertib | Orally twice daily (4 days on, 3 days off) |
| CDK4/6 inhibitor[b] | Orally once daily (for 21 days of each 28-day cycle) |
| Fulvestrant | 500 mg IM (every 28 days; loading dose on cycle 1, day 15) |
| CDK4/6 inhibitor[b] | Orally once daily (for 21 days of each 28-day cycle) |
| Fulvestrant | 500 mg IM (every 28 days; loading dose on cycle 1, day 15) |

**Primary**
- PFS by BICR

**Secondary**
- OS
- PFS in patients with *PIK3CA*, *AKT1*, and/or *PTEN* alterations in their tumors
- PFS2, ORR, DoR, CBR at 24 weeks
- HRQoL

**Safety and tolerability**

The inclusion of ribociclib as an investigator's choice of CDK4/6 inhibitor in Phase 3 will be initiated after the combination RP3D has been established in Phase 1b.

Clinical Study Protocol version 5.0

[a]Prior treatment with a (neo)adjuvant endocrine therapy (ET; single agent or in combination) and radiologic evidence of breast cancer recurrence or progression while on, or within 12 months of the end of, (neo)adjuvant ET (tamoxifen, AI, or oral SERD); [b]Investigator's choice of CDK4/6 inhibitor: palbociclib or ribociclib.

HER2-negative is defined as IHC 0, or 1+ or IHC2+/ISH−; ABC, advanced breast cancer; BICR, blinded independent central review; HRQoL, health-related quality of life; RP3D, recommended Phase 3 dose

Rugo et al, SABCS 2023 TIP: PO2

# Faculty Case Presentations

# Case Presentation – Dr Wander

63yo woman, G1P1
PMH: HTN, prior CVA without residual deficits (no DM, A1c WNL)
Meds: Losartan, ASA 81mg

Initial Diagnosis:
De novo metastatic disease with bone pain; PET CT with two liver lesions (<2cm, normal LFTs); liver biopsy with ER+ (80%, strong), PR+ (80%, strong), HER2 IHC 2+ FISH CN 2.3 ratio 1.1 Group 5 negative
*Baseline ctDNA: PIK3CA E545K (15%), TMB low, MSS*

1st line metastatic therapy: **Letrozole** + **Ribociclib** x 36 months, followed by liver and bone progression
*Updated ctDNA: PIK3CA E545K (20%), ESR1 D538G (5%), RB1 splice site alteration, TMB low, MSS*

2nd line metastatic therapy: **Capivasertib** + **Fulvestrant**

# Case Presentation – Dr Kaklamani

- Male 65 yo with initial diagnosis of L BC ER+ PR+ HER2 – breast ca. 2.5 cm tumor and 2+LN. Declines chemotherapy and is given tamoxifen x 5 years.
- 3 years after initiating tamoxifen he is found to have bone and liver metastases and a biopsy shows ER+ PR+ HER2- breast ca. NGS testing shows AKT1 mutation.
- Initiates therapy with ribociclib, LHRH agonist and letrozole and has progression free interval of 22 mo.
- At disease progression he is given capivasertib and fulvestrant and LHRH agonist is continued.

# Agenda

**Module 1:** Role of CDK4/6 Inhibitors in Hormone Receptor (HR)-Positive Localized Breast Cancer – Dr Hurvitz

**Module 2:** Incorporation of CDK4/6 Inhibitors into the Management of HR-Positive, HER2-Negative Metastatic Breast Cancer (mBC) – Dr Wander

**Module 3:** Evolving Role of PI3K Inhibitors for HR-Positive mBC Harboring PIK3CA Mutations – Dr Goetz

**Module 4:** Clinical Utility of AKT Inhibitors for Patients with Progressive HR-Positive mBC – Dr Jhaveri

**Module 5: Oral Selective Estrogen Receptor Degraders (SERDs) for HR-Positive mBC – Dr Kaklamani**

RTP RESEARCH TO PRACTICE

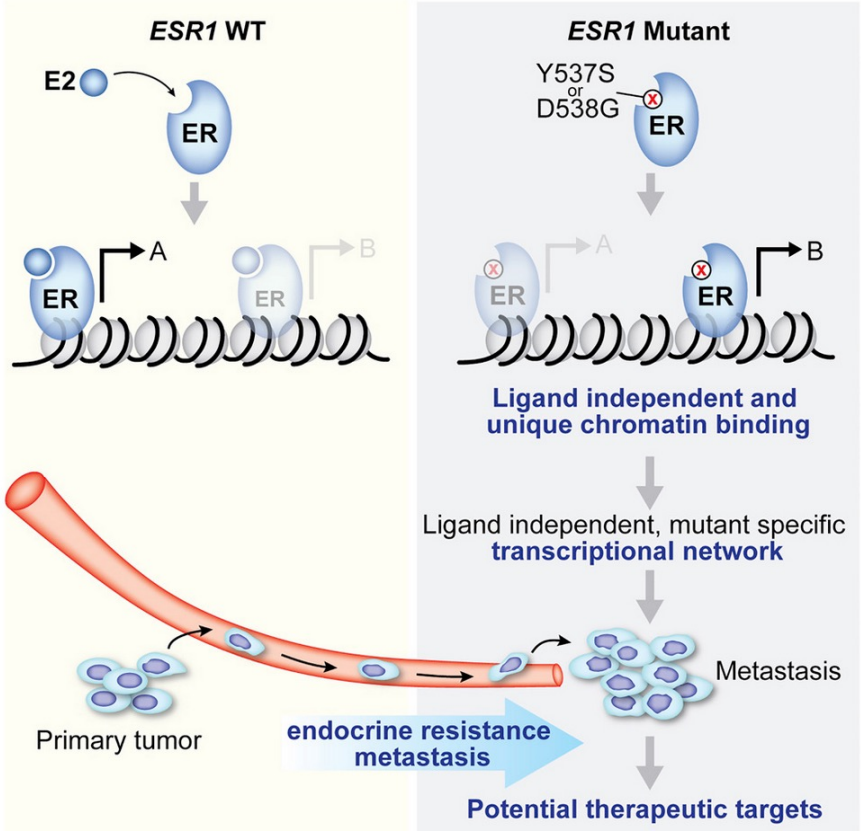
# Oral Selective Estrogen Receptor Degraders (SERDs) for HR-Positive mBC

Virginia Kaklamani, MD DSc
Professor of Medicine
Leader, Breast Oncology Program

# *ESR1*$_{mut}$: function & landscape

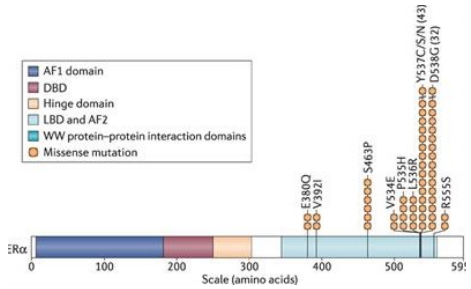
*ESR1*$_{mut}$ allow **ligand-independent ERα (re)activation**

Pro-metastatic transcriptional program




Jeselsohn *et al* ., Cancer Cell 2018

**Hotspot activating mutations**




| *ESR1* mutation | Frequency | Preclinical sensitivity to fulvestrant |
|---|---|---|
| E380Q | 19% | Yes |
| L536/H/P/R | 7% | Yes |
| Y537S | 11% | No |
| Y537C | 6% | Yes |
| Y537N | 5% | Yes |
| D538G | 32% | Yes |

Toy *et al.*, Cancer Discov 2017

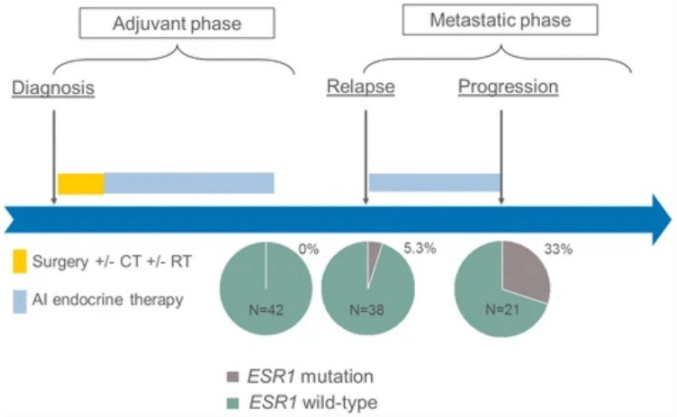
**Detected after resistance to AI given at stage IV**

ER-negative BC: 0%

Non metastatic ER+ BC: <1%

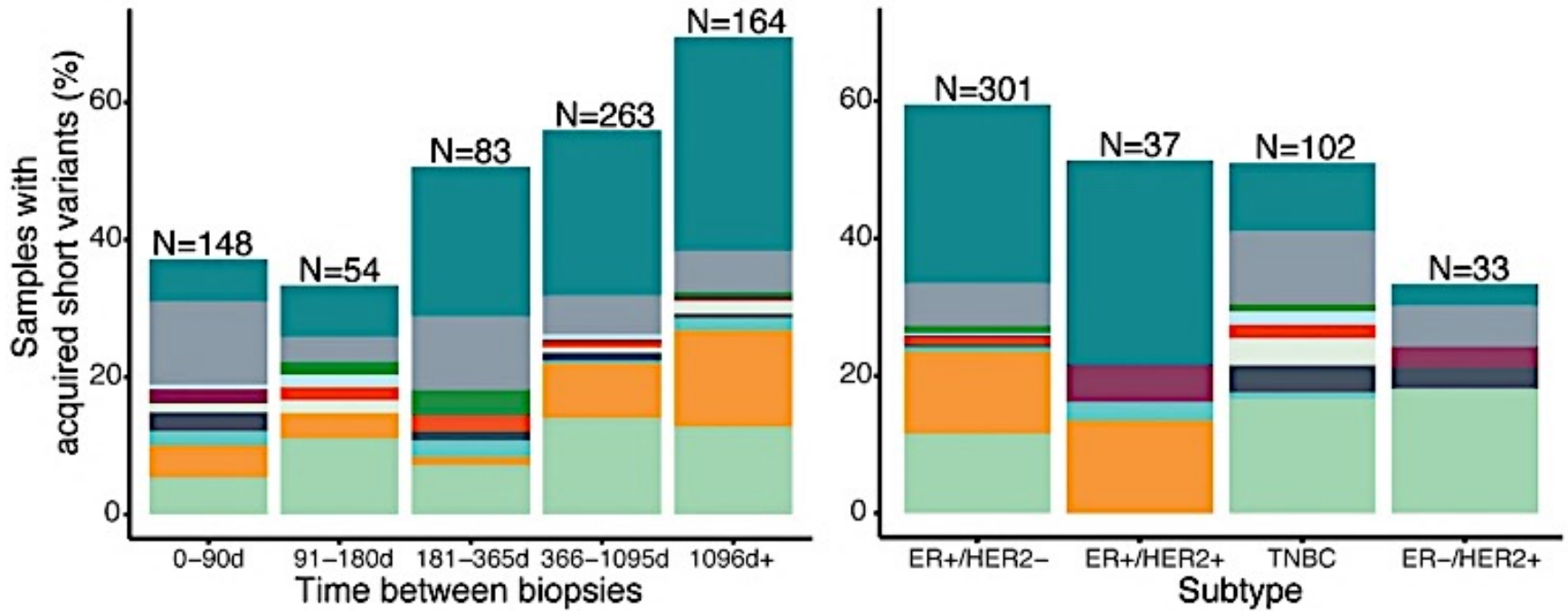
Metastatic ER+ BC (at relapse): ~5%

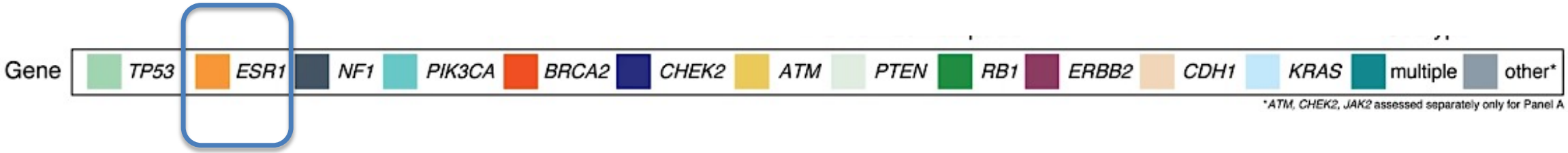
Metastatic ER+ BC (after resistance to aromatase inhibitors): ~40%




Allouchery *et al.*, BCR 2018

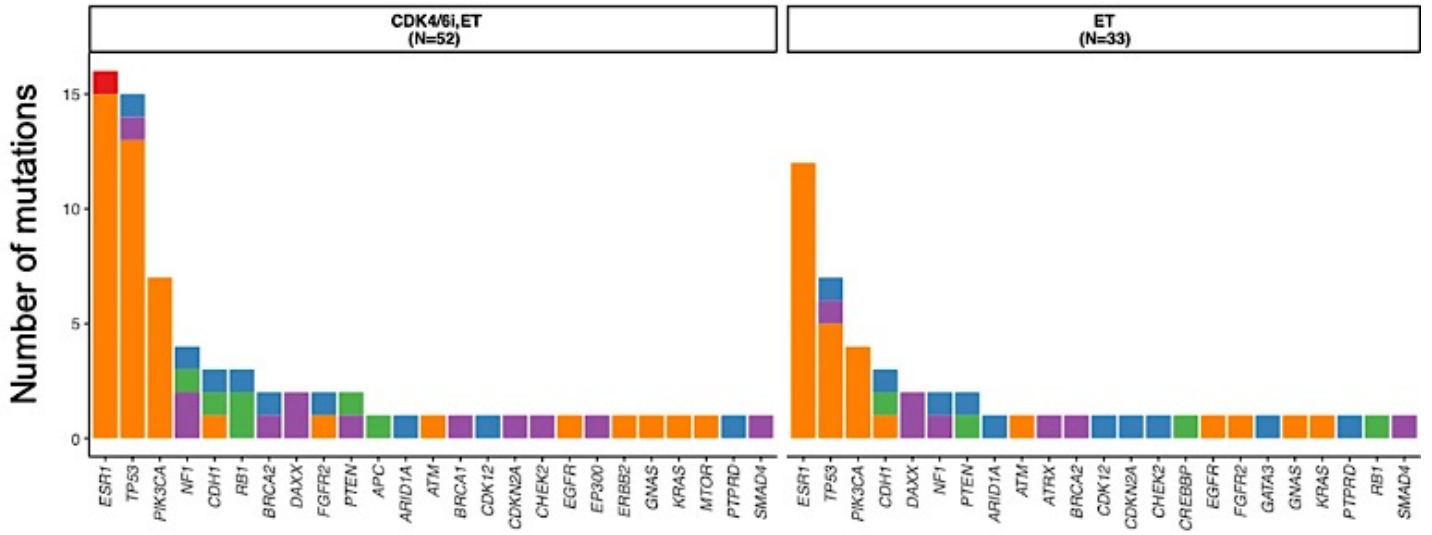
# *ESR1m* increase over time

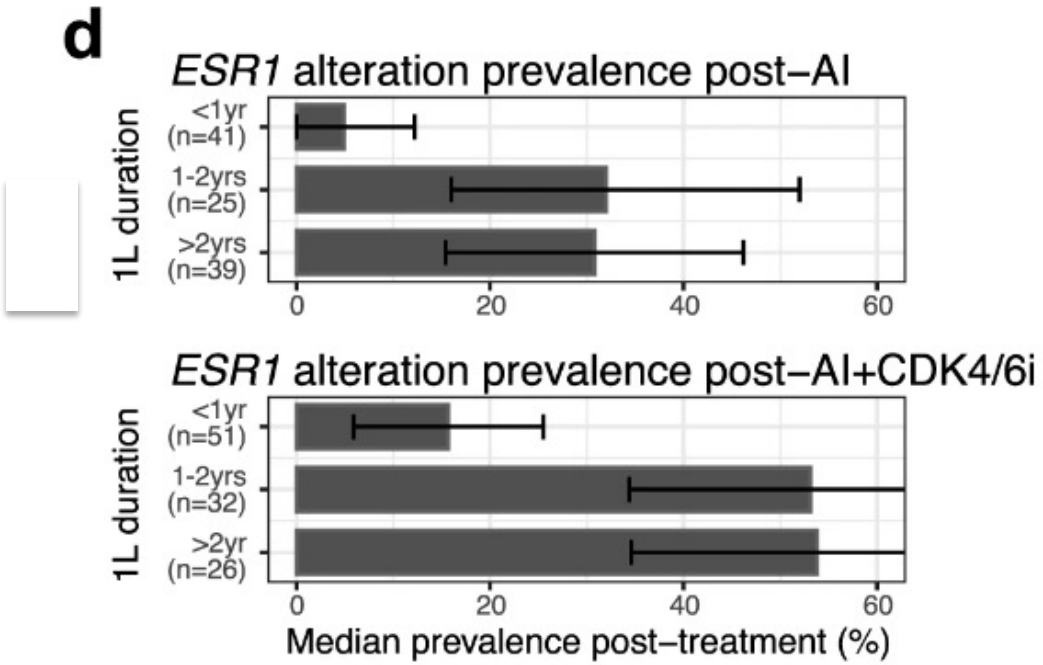



Sivakumar Nat Comm 2022

# *ESR1m* more prevalent after CDK4/6i

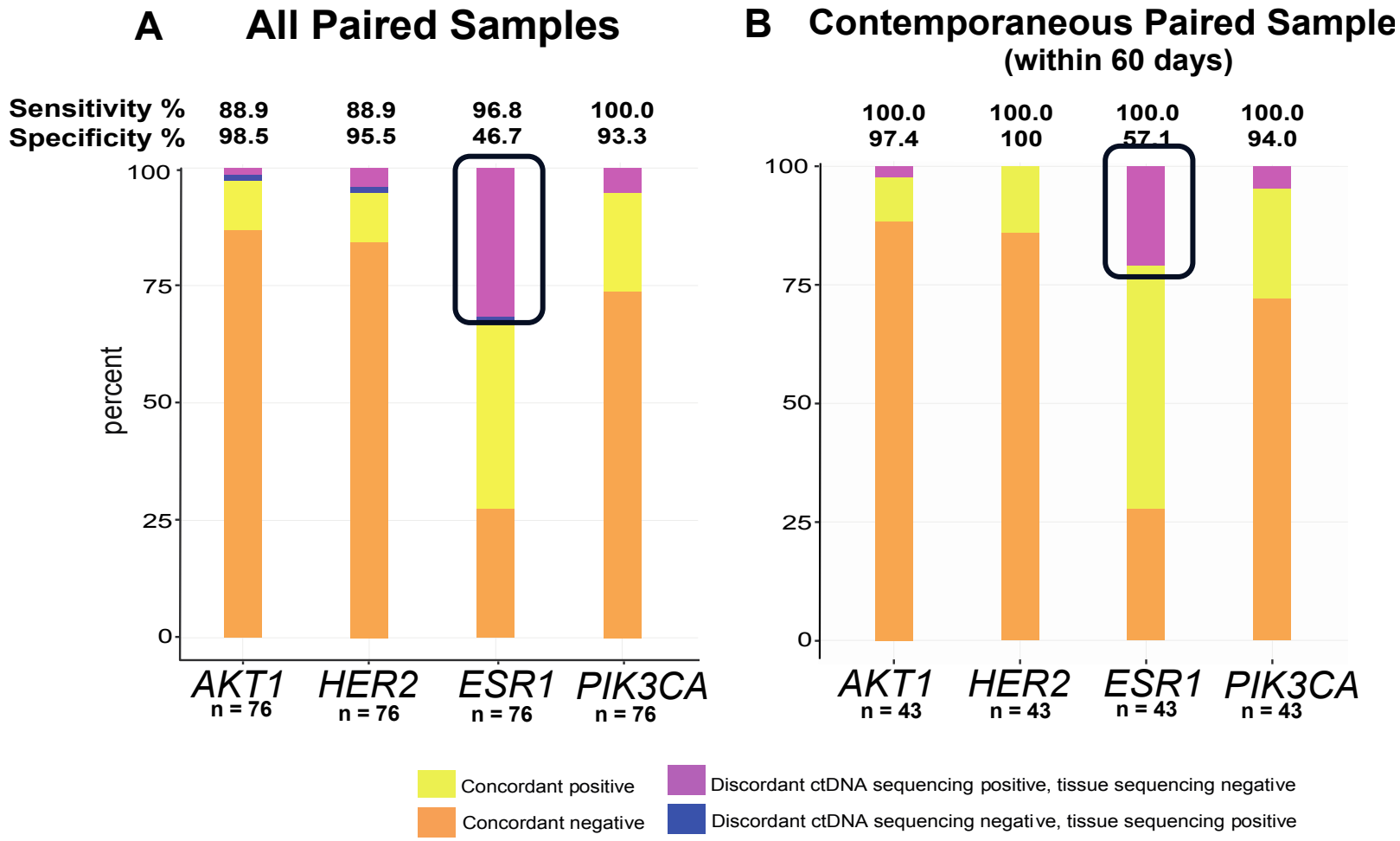



Sivakumar et al *Nat Comm* 2022
Chaudhary et al *npj Breast Cancer* 2024

# *ESR1* mutation testing – liquid biopsy testing preferred

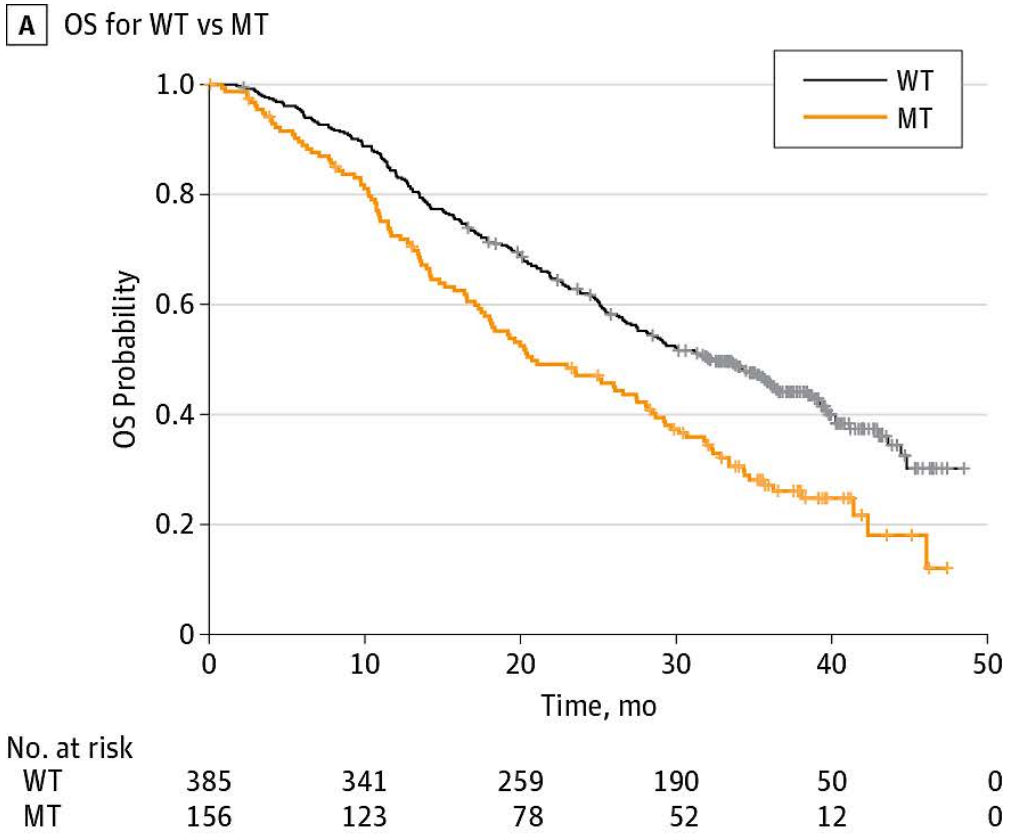
Tissue – liquid concordance in plasmaMATCH study

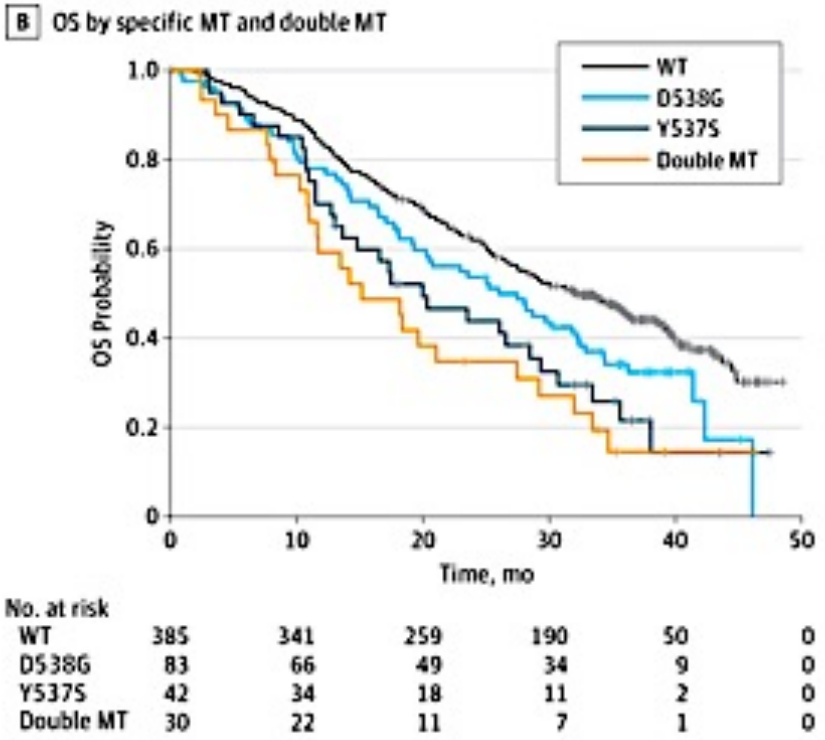



Turner et al Lancet Oncology 2021

Burstein et al JCO 2023

# BOLERO-2: Worse outcomes in *ESR1mt*

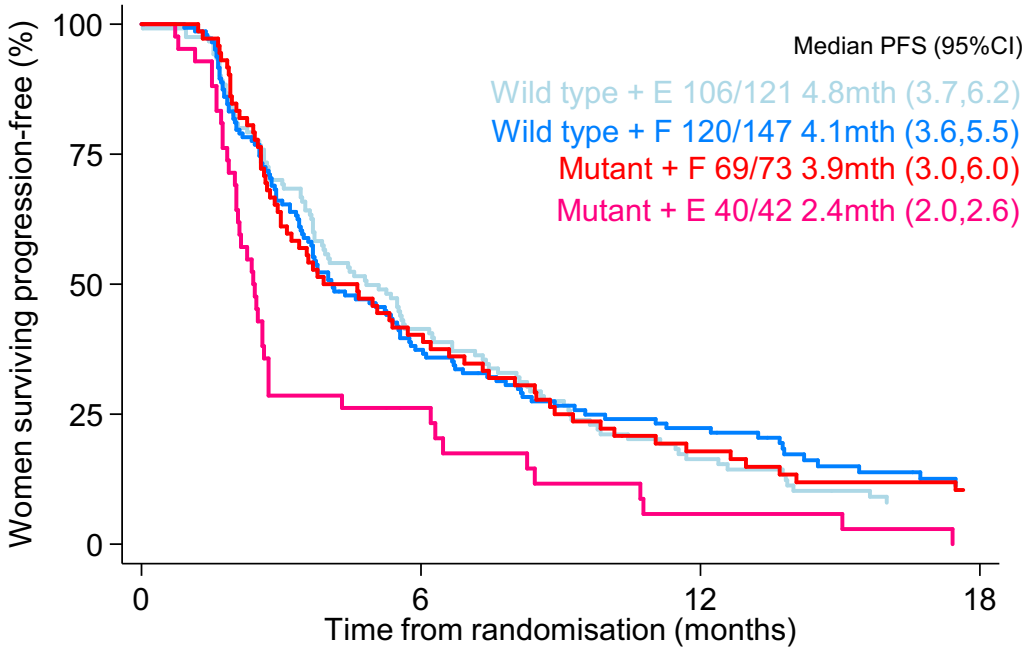



JAMA Oncol. 2016;2(10):1310-1315. doi:10.1001/jamaoncol.2016.1279

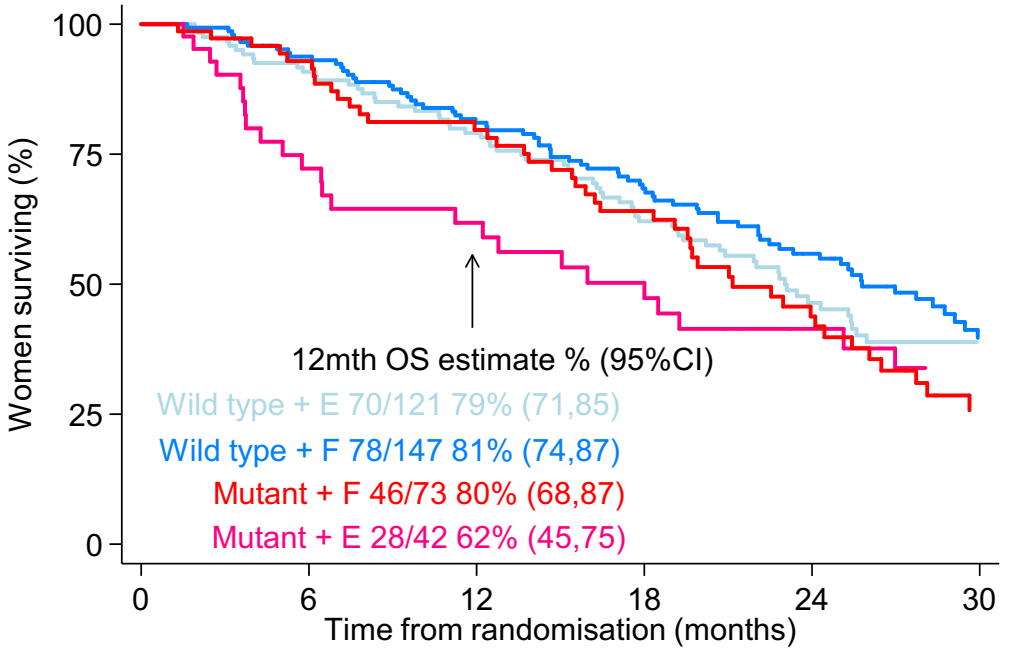
# *ESR1* Mutations: SoFEA and EFFECT Combined Analysis

## *ESR1*-mutant breast cancer has poor outcome if treated with further AI




N at risk (events)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Wild type + E | 121 | (70) | 49 | (28) | 17 | (8) | 7 |
| Wild type + F | 147 | (87) | 50 | (19) | 25 | (10) | 8 |
| Mutant + E | 42 | (31) | 9 | (7) | 2 | (2) | 0 |
| Mutant + F | 73 | (43) | 29 | (16) | 12 | (5) | 6 |



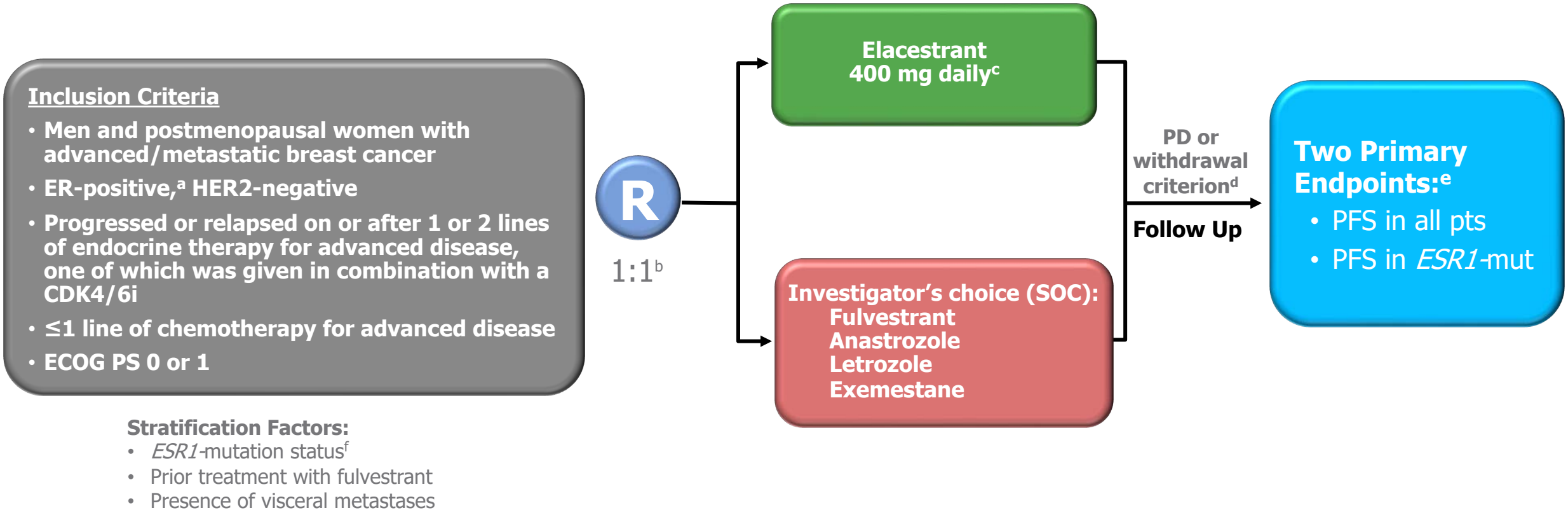

N at risk (events)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wild type + E | 121 | (11) | 109 | (14) | 93 | (19) | 68 | (15) | 37 | (6) | 21 |
| Wild type + F | 147 | (9) | 134 | (18) | 113 | (17) | 89 | (15) | 59 | (13) | 26 |
| Mutant + E | 42 | (11) | 28 | (4) | 22 | (4) | 17 | (3) | 11 | (2) | 6 |
| Mutant + F | 73 | (5) | 64 | (9) | 52 | (10) | 38 | (11) | 23 | (8) | 9 |

*ESR1* mutations detected in 30% (151/383) baseline samples

Turner NC et al. *Clin Cancer Res.* 2022;26(19):5172-5177.

# EMERALD Phase 3 Study Design



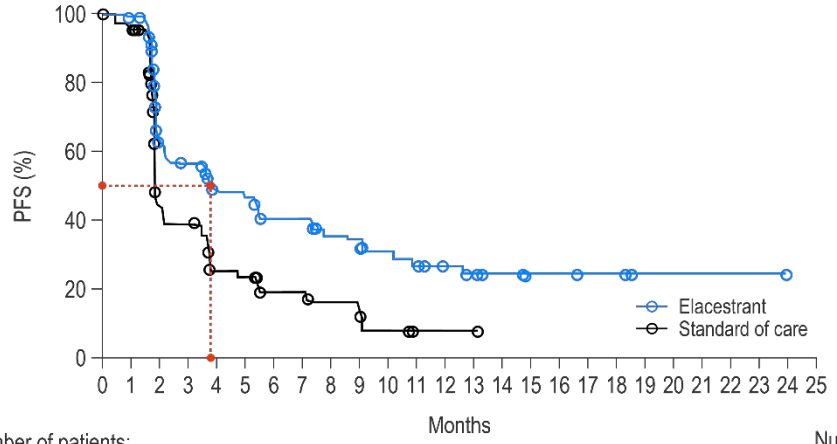

[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis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

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

# EMERALD: Elacestrant provides a 45% reduction in risk of progression or death vs SoC in patients with *ESR1* mutations

## PFS in patients with *ESR1*-mut: elacestrant vs SoC

| | Elacestrant (n=115) | SoC (n=113) |
|---|---|---|
| mPFS, months | **3.8** | **1.9** |
| HR (95% CI) | **0.55** (0.39–0.77) | |
| p-value | **0.0005** | |

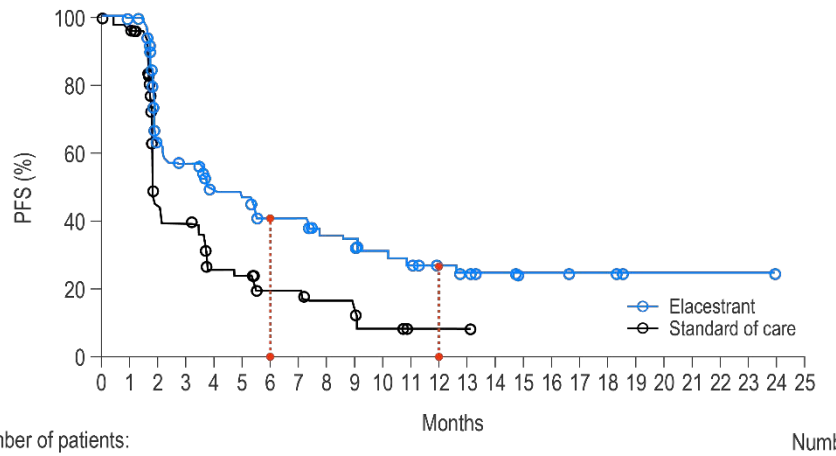



Number of patients:

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Elacestrant** | 115 | 105 | 54 | 46 | 35 | 33 | 26 | 26 | 21 | 20 | 16 | 14 | 11 | 9 | 7 | 5 | 5 | 4 | 4 | 1 | 1 | 1 | 1 | 1 | 0 |
| **SoC** | 113 | 99 | 39 | 34 | 19 | 18 | 12 | 12 | 9 | 9 | 4 | 1 | 1 | 1 | 0 | | | | | | | | | | |

## PFS in patients with *ESR1*-mut: elacestrant vs SoC

| | Elacestrant (n=115) | SoC (n=113) |
|---|---|---|
| PFS rate at 6 mo, % (95% CI) | **40.8** (30.1–51.4) | **19.1** (10.5–27.8) |
| PFS rate at 12 mo, % (95% CI) | **26.8** (16.2–37.4) | **8.2** (1.3–15.1) |
| HR (95% CI) | **0.55** (0.39-0.77) | |
| p-value | **0.0005** | |

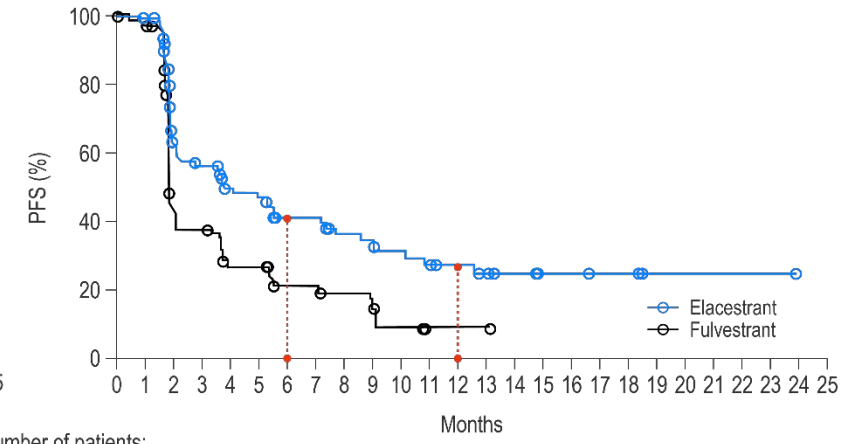



Number of patients:

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Elacestrant** | 115 | 105 | 54 | 46 | 35 | 33 | 26 | 26 | 21 | 20 | 16 | 14 | 11 | 9 | 7 | 5 | 5 | 4 | 4 | 1 | 1 | 1 | 1 | 1 | 0 |
| **SoC** | 113 | 99 | 39 | 34 | 19 | 18 | 12 | 12 | 9 | 9 | 4 | 1 | 1 | 1 | 0 | | | | | | | | | | |

## PFS in patients with *ESR1*-mut: elacestrant vs fulvestrant*

| | Elacestrant (n=115) | Fulvestrant (n=83) |
|---|---|---|
| PFS rate at 6 mo, % (95% CI) | **40.8** (30.1–51.4) | **20.8** (10.7–30.8) |
| PFS rate at 12 mo, % (95% CI) | **26.8** (16.2–37.4) | **8.4** (0.2–16.6) |
| HR (95% CI) | **0.50** (0.34–0.74) | |



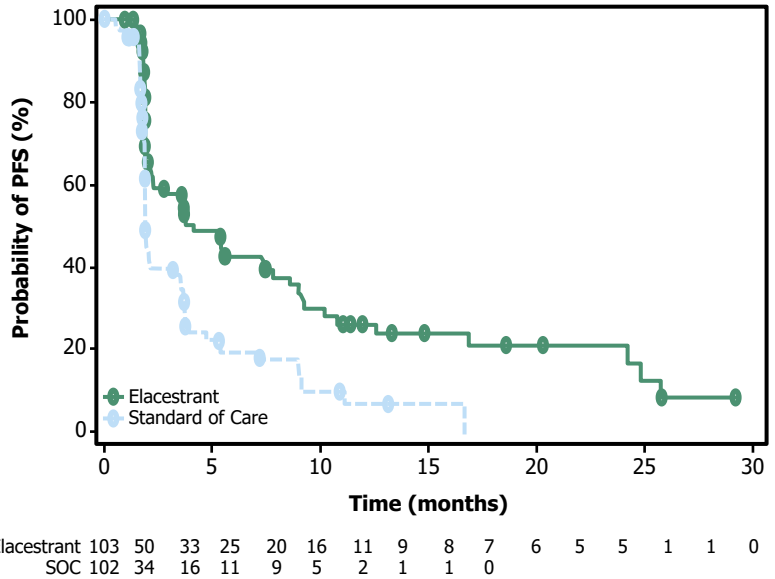

Number of patients:

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

*Exploratory analysis; patients without *ESR1*-mut: n=250, 52% of the ITT population.
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; PFS, progression-free survival; SoC, standard of care.
Bidard FC et al. *J Clin Oncol* 2022;40:3246–3256.

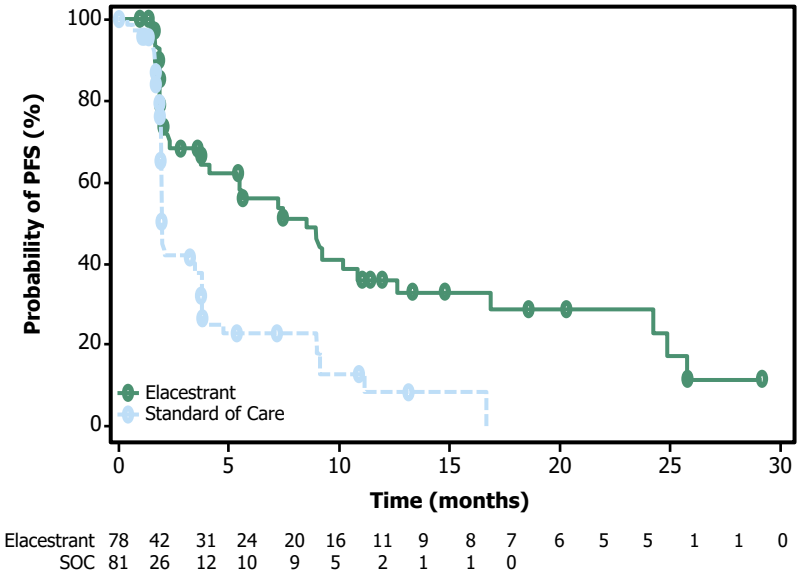
# Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

## At least 6 mo CDK4/6i



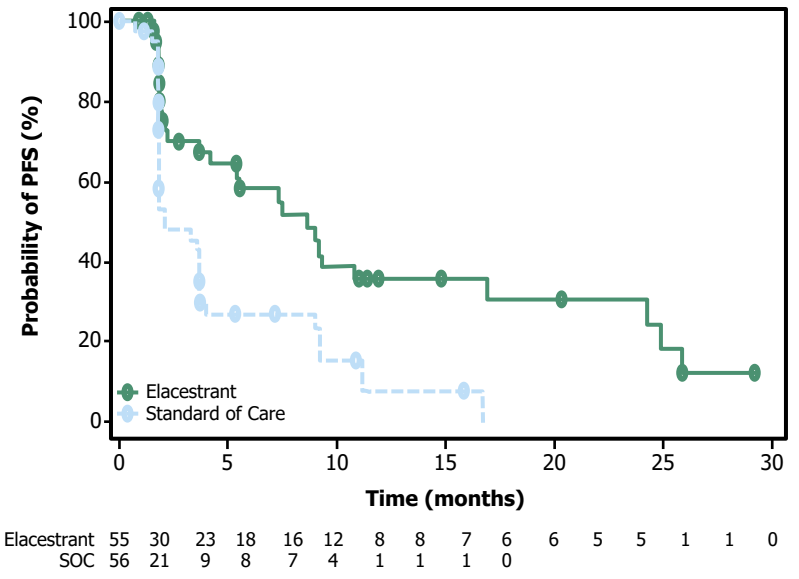

| | Elacestrant | SOC Hormonal Therapy |
|---|---|---|
| Median PFS, months (95% CI) | **4.14** (2.20 - 7.79) | **1.87** (1.87 - 3.29) |
| PFS rate at 12 months, % (95% CI) | 26.02 (15.12 - 36.92) | 6.45 (0.00 - 13.65) |
| Hazard ratio (95% CI) | **0.517** (0.361 - 0.738) | |

## At least 12 mo CDK4/6i




| | Elacestrant | SOC Hormonal Therapy |
|---|---|---|
| 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) | |

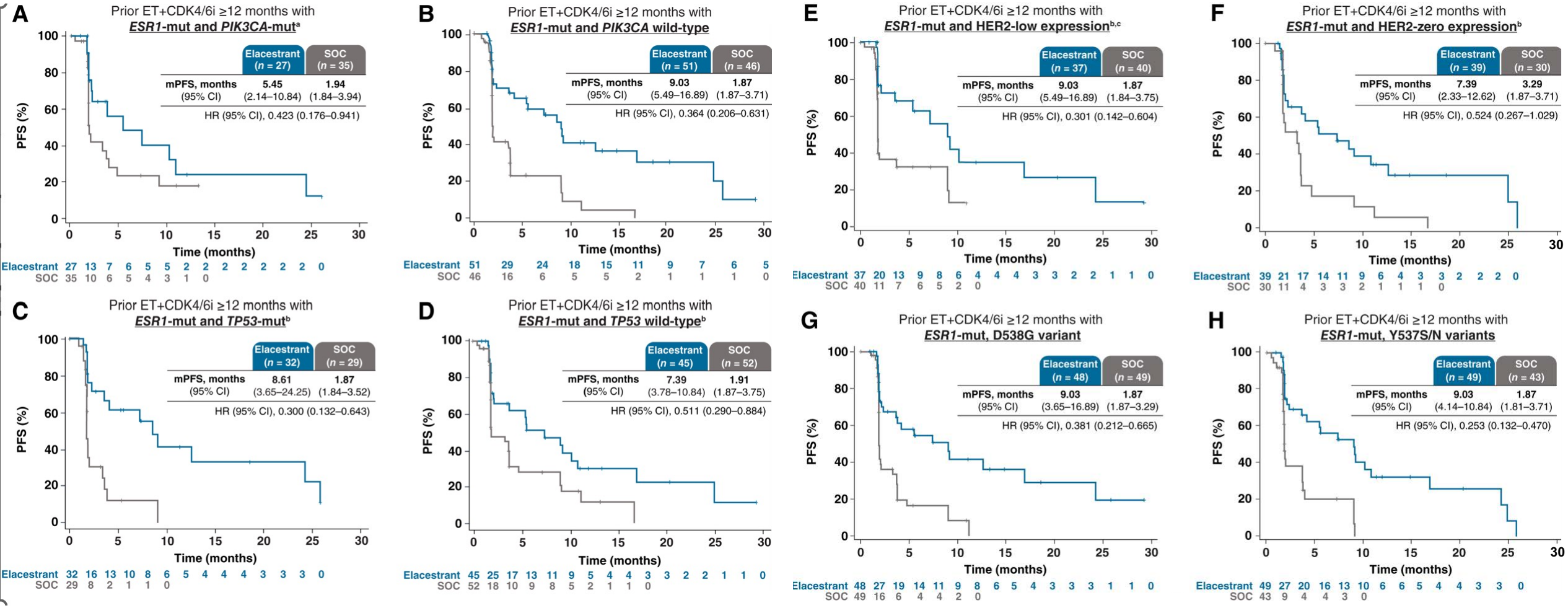
## At least 18 mo CDK4/6i




| | Elacestrant | SOC Hormonal Therapy |
|---|---|---|
| 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) | |

Bardia et al CCR 2024

# Elacestrant in ER+, HER2− Metastatic Breast Cancer with ESR1-Mutated Tumors: Subgroup Analyses from the Phase III EMERALD Trial by Prior Duration of Endocrine Therapy plus CDK4/6 Inhibitor and in Clinical Subgroups



# Phase I clinical trial of imlunestrant

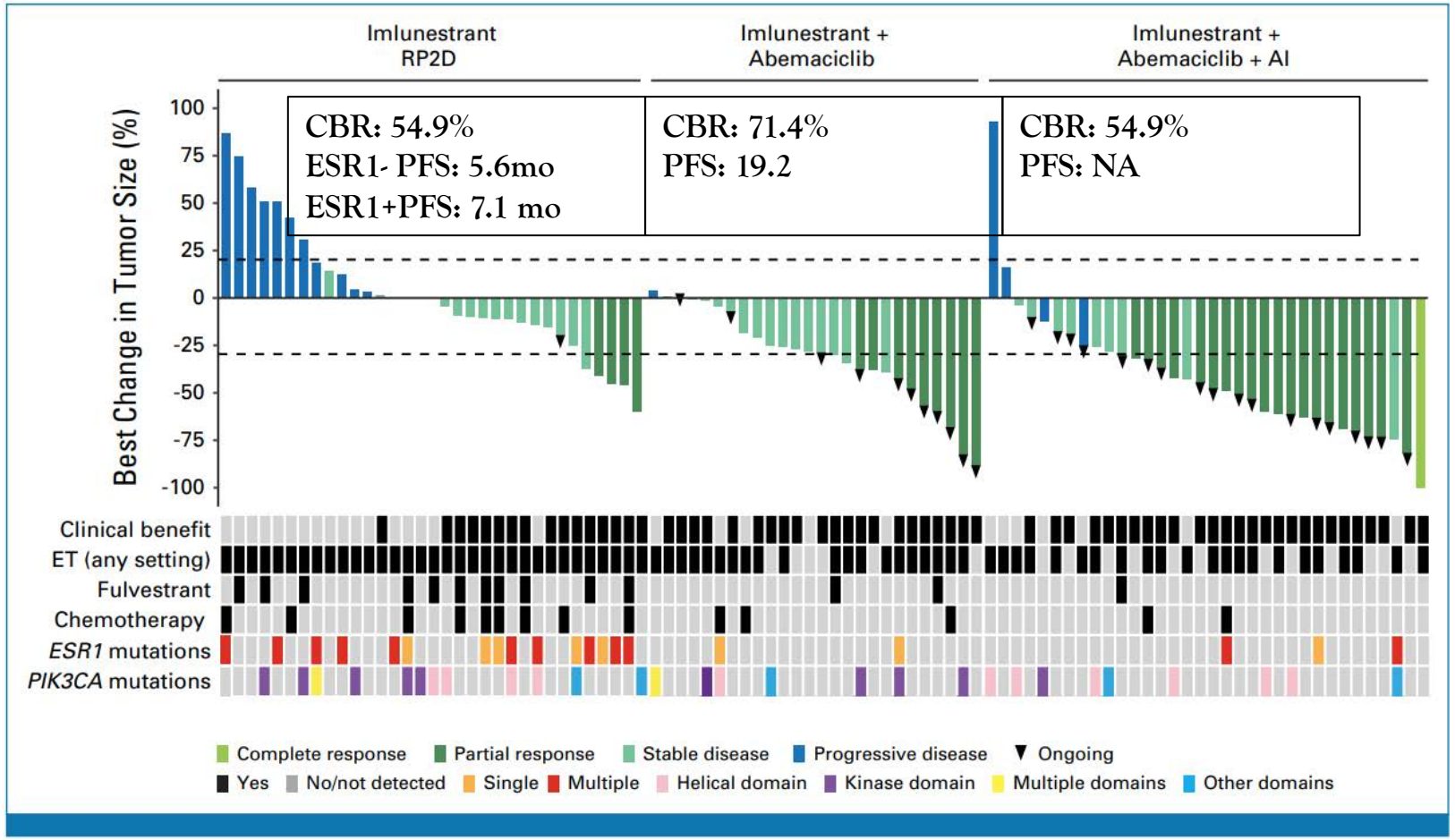



**FIG 3.** Tumor response in patients with ER+/HER2− ABC who received imlunestrant monotherapy at the RP2D or in combination with abemaciclib with or without AI. Waterfall plot for best percentage change in tumor size in patients with measurable disease who received imlunestrant monotherapy at the RP2D (n = 34), imlunestrant + abemaciclib (n = 28), and imlunestrant + abemaciclib + AI (n = 34). Each bar represents one patient. ABC, advanced breast cancer; AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; RP2D, recommended phase II dose.

Jhaveri et al JCO 2024

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# EMBER-3 Study Design

## ER+, HER2- ABC

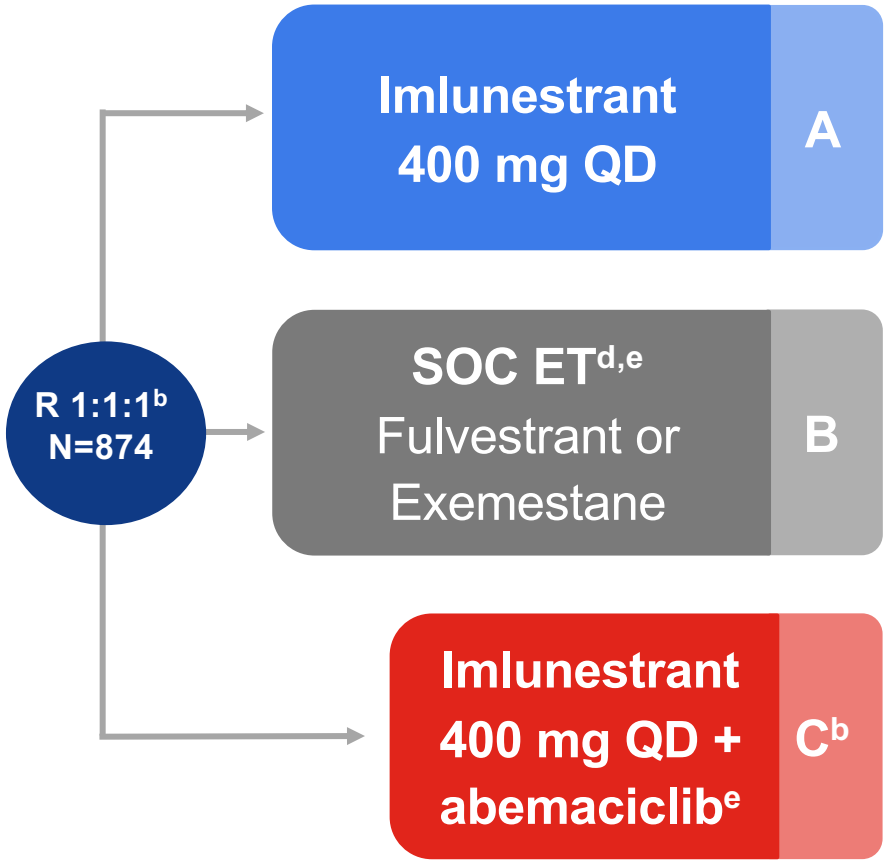
Men and Pre-[a]/Post-menopausal women

**Prior therapy:**

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

**Stratification Factors:**

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




## Primary Endpoints

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

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

## Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

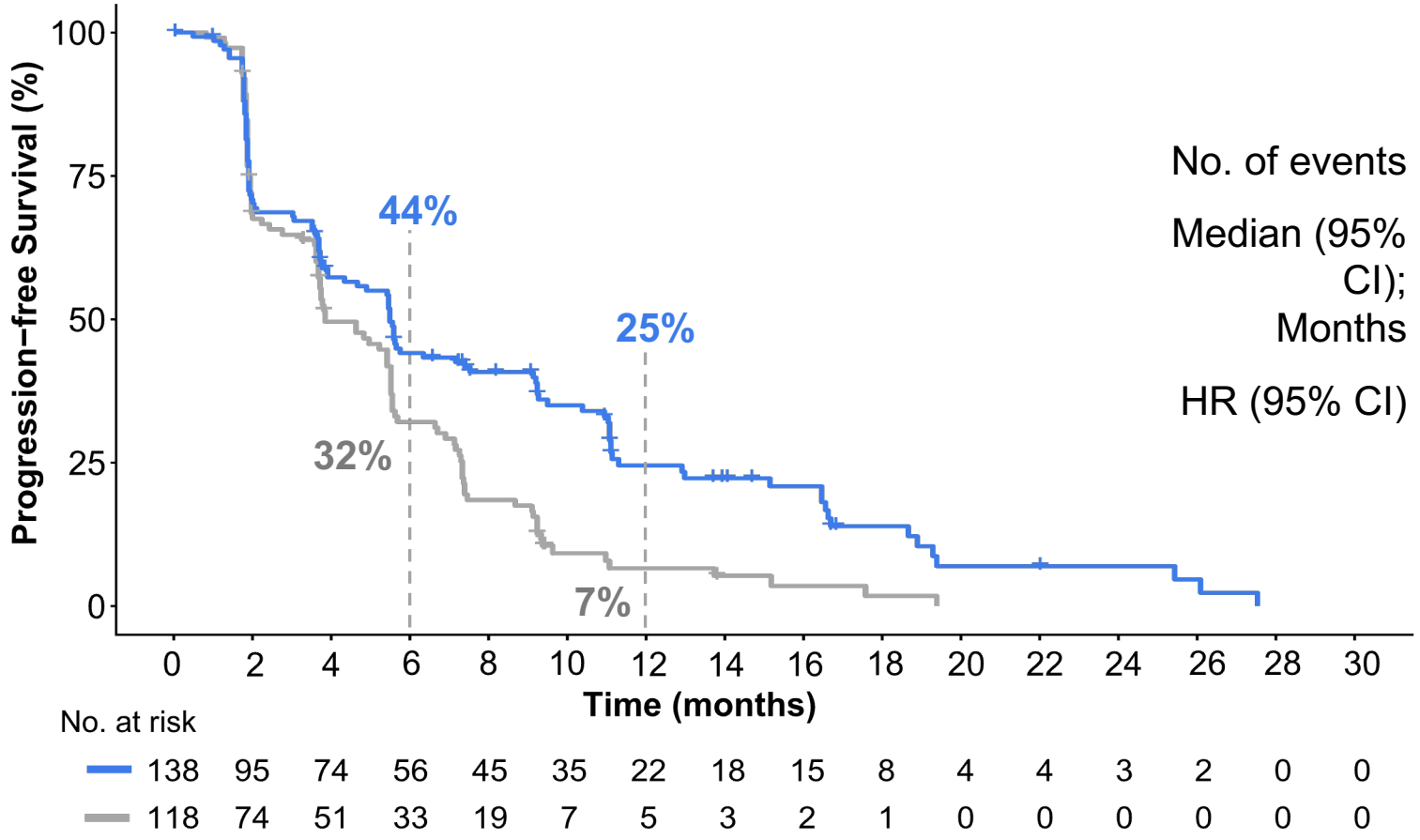
## Exploratory Endpoints

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

ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i, CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 243 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.

Jhaveri K et al. SABCS 2024;Abstract GS0-01.

# Primary Endpoint: Imlunestrant vs SOC ET Investigator-assessed PFS in Patients with *ESR1*m

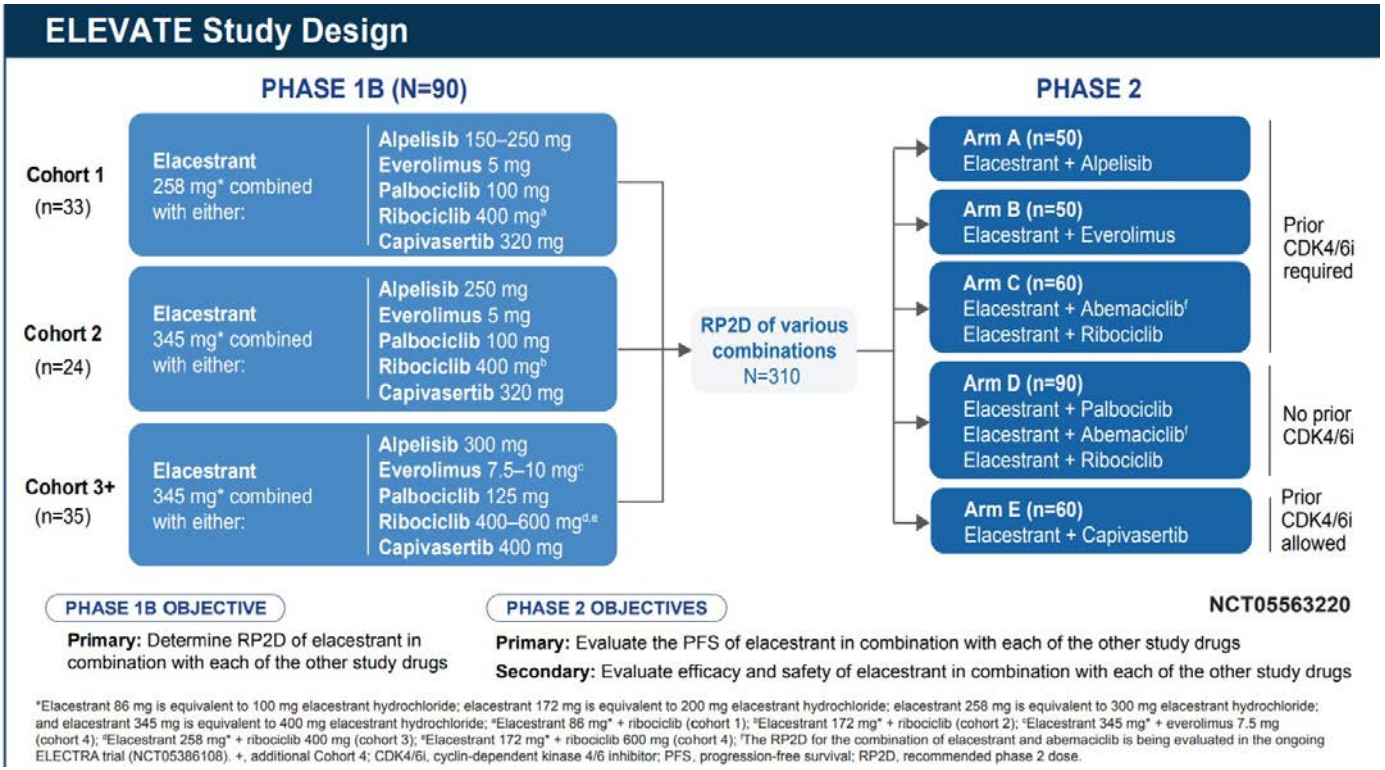



| | Imlunestrant n=138 | SOC ET n=118 |
|---|---|---|
| No. of events | 109 | 102 |
| Median (95% CI); Months | **5.5** (3.9-7.4) | **3.8** (3.7-5.5) |
| HR (95% CI) | **0.62 (0.46-0.82)[a]** *p*-value<0.001 | |

**Imlunestrant led to a 38% reduction in the risk of progression or death in patients with *ESR1*m**

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; RMST, restricted mean survival time; SOC ET, standard of care endocrine therapy. [a] Due to evidence of non-proportional hazards, a sensitivity analysis of PFS using RMST was conducted. Estimated RMST at 19.4 months was 7.9 months (95% CI 6.8-9.1) in the imlunestrant arm vs 5.4 months (95% CI 4.6-6.2) in the SOC ET arm [difference 2.6 months (1.2.-3.9)].

Jhaveri K et al. SABCS 2024;Abstract GS1-01.




| | ORR | CBR | mPFS |
|---|---|---|---|
| Elacestrant+ Everolimus | 22% | 72% | |
| Elacestrant +_ abemaciclib | 26% | 70% | 8.7mo |

# SERENA-1

| | ORR | CBR | mPFS |
|---|---|---|---|
| Camizestrant + Ribociclib | 16.7% | 55% | 8.1mo |

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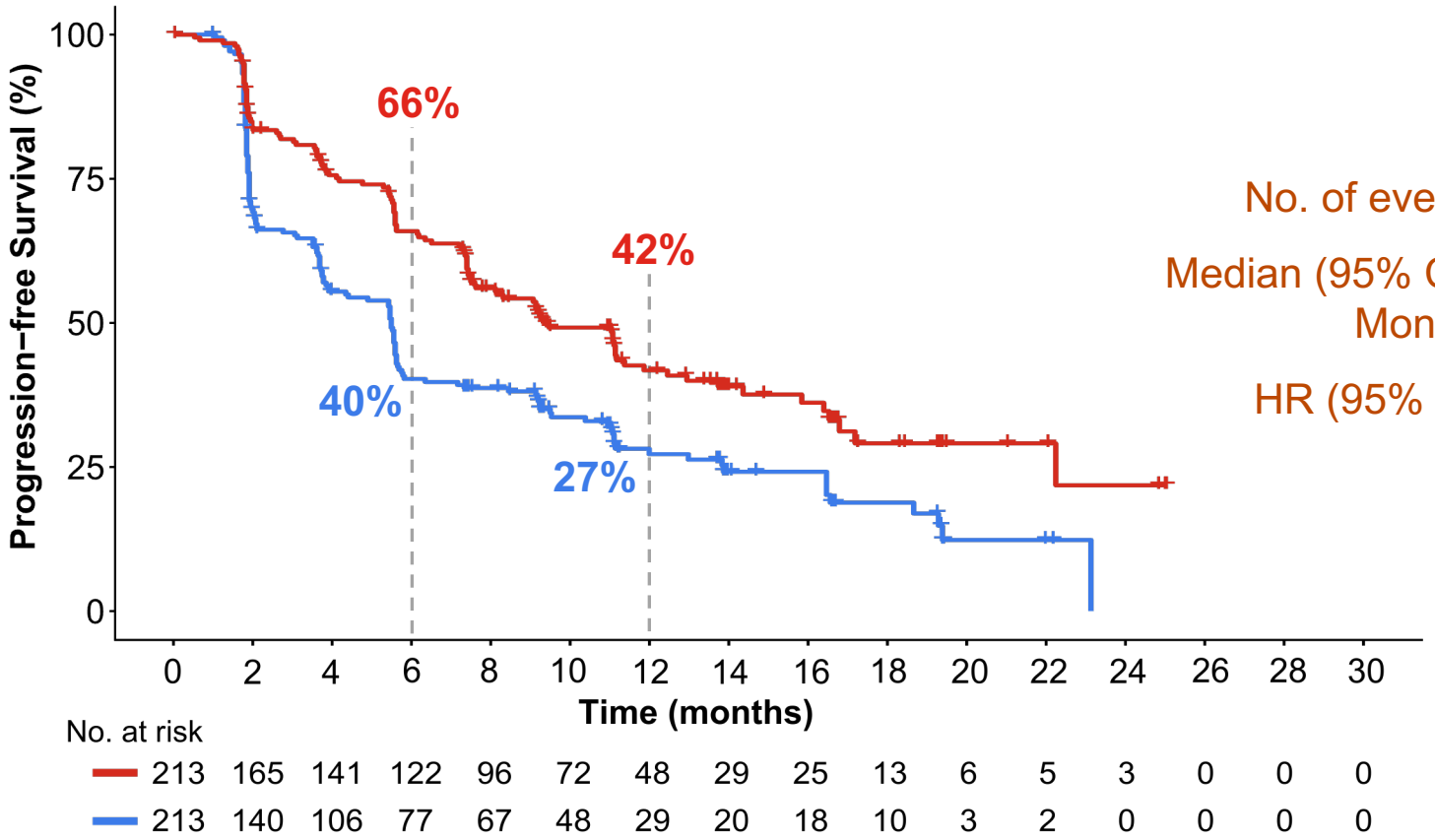
Rugo et al SABCS 2024; Ruiz-Borrego et al SABCS 2024

# EMBER-3: Primary Endpoint: Imlunestrant + Abemaciclib vs Imlunestrant Investigator-assessed PFS in All Patients




| | Imlunestrant + abemaciclib n=213 | Imlunestrant n=213[a] |
|---|---|---|
| No. of events | 114 | 149 |
| Median (95% CI); Months | **9.4** (7.5-11.9) | **5.5** (3.8-5.6) |
| HR (95% CI) | **0.57 (0.44-0.73)** *p*-value <0.001 | |

**Imlunestrant + abemaciclib led to a 43% reduction in the risk of progression or death over imlunestrant alone in all patients**

CI, confidence interval; HR, hazard ratio. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm.

Jhaveri K et al. SABCS 2024;Abstract GS1-01.

# AMEERA-3: Ph 2 trial of amcenestrant vs ET in ER+/HER2- MBC

**Eligibility Criteria**
- Pre/peri-[a] and postmenopausal women or men[a]
- ER+[b]/HER2– aBC
- ≤ 2 prior lines of ET for aBC
- Progression on or after ET in the adjuvant or advanced setting
- ≤ 1 chemotherapy or targeted agent for aBC
- ECOG PS 0 or 1

N = 290[c]

R
1:1

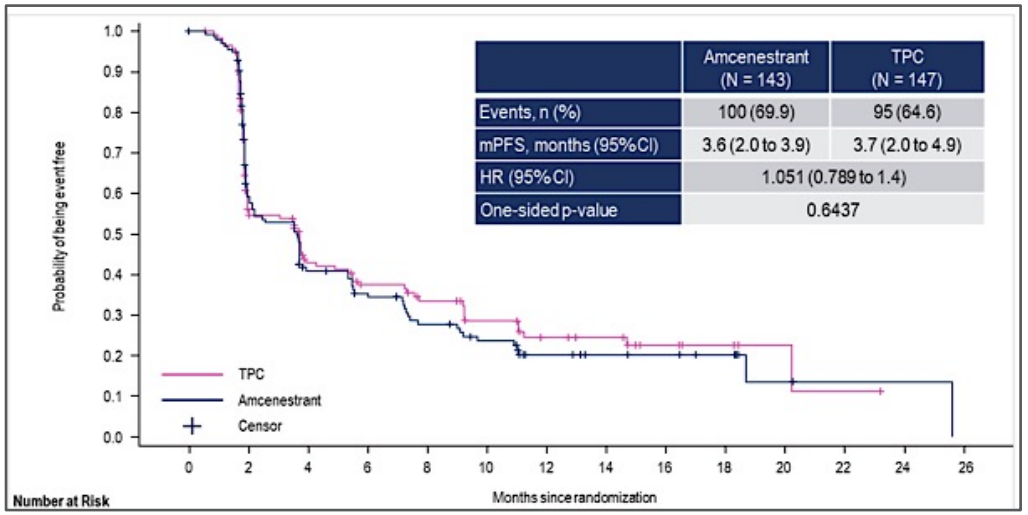
**Amcenestrant 400 mg PO QD**
4 x 100mg capsules
(N = 143)

*28-day cycles*

**Endocrine TPC[d]**
(N =147)
- Fulvestrant
- Aromatase inhibitor
  (anastrozole, letrozole or exemestane)
- Tamoxifen

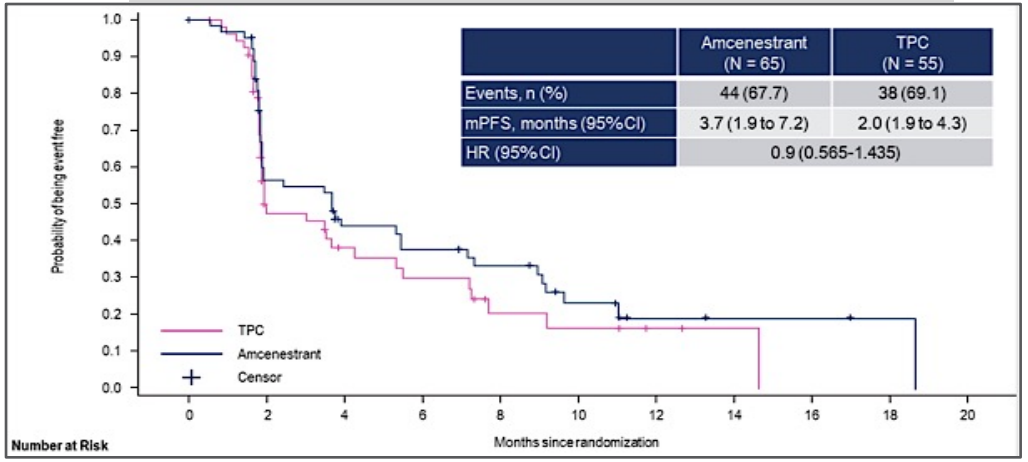
**Stratification factors**
- Presence of visceral metastases: Yes or No
- Prior treatment with CDK4/6i where available (i.e., approved in the region and reimbursed): Yes or No (≤ 20% may be naïve to CDK4/6i)
- ECOG Performance Status: 0 or 1

## Primary EP: PFS in ITT population




| | Amcenestrant (N = 143) | TPC (N = 147) |
|---|---|---|
| Events, n (%) | 100 (69.9) | 95 (64.6) |
| mPFS, months (95%CI) | 3.6 (2.0 to 3.9) | 3.7 (2.0 to 4.9) |
| HR (95%CI) | 1.051 (0.789 to 1.4) | |
| One-sided p-value | 0.6437 | |

## Secondary EP: PFS in pts with BL ESR1 mutations




| | Amcenestrant (N = 65) | TPC (N = 55) |
|---|---|---|
| Events, n (%) | 44 (67.7) | 38 (69.1) |
| mPFS, months (95%CI) | 3.7 (1.9 to 7.2) | 2.0 (1.9 to 4.3) |
| HR (95%CI) | 0.9 (0.565-1.435) | |

## Pt population:

Prior CDK 4/6i -79%; prior FULV -10%; prior chemo -11%.
ESR1 mutations: 40%

Although there was numerical improvement in PFS in both ITT and ESR1 mutant populations, it was not statistically significant

Amcenestrant is no longer in clinical development

SARAH CANNON Research Institute

Tolaney S et al. ESMO 2022; Tolaney JCO 2023

# acelERA Breast Cancer Ph 2 trial of giredestrant vs ET in ER+/HER2- MBC

Giredestrant is a highly potent, non-steroidal, oral selective SERD

- ER+/HER2– LA/mBC
- Post- or pre-/peri-menopausal women, and men*
- 1 or 2 prior lines of systemic therapy for LA/mBC:
  - 1 must be ET (≥ 6 months)
  - ≤ 1 targeted agent
  - ≤ 1 chemotherapy allowed

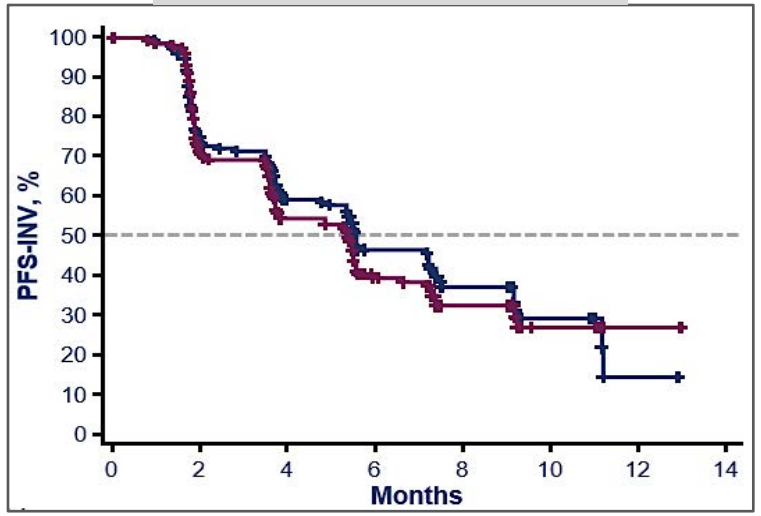
**N = 303**

R 1:1

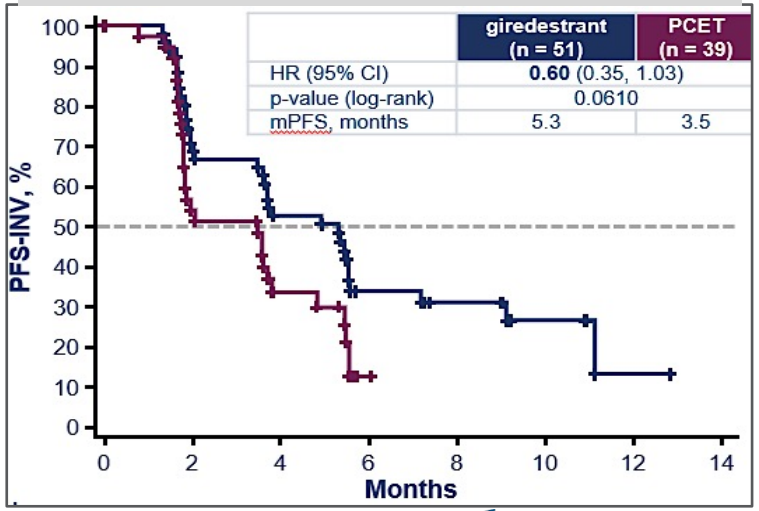
**giredestrant**
30 mg PO QD

**Physician's choice of mono ET**
(fulvestrant or AI)

**Primary EP: PFS in ITT population**




**Secondary EP: PFS in ESR1 mutant subgroup**




## Pt population:

Prior CDK 4/6i -42%; prior FULV -19%; prior chemo -32%.
ESR1 mutations: 40%

There was no improvement in PFS in the ITT populations and a modest improvement in the ESR1 mutant subset.

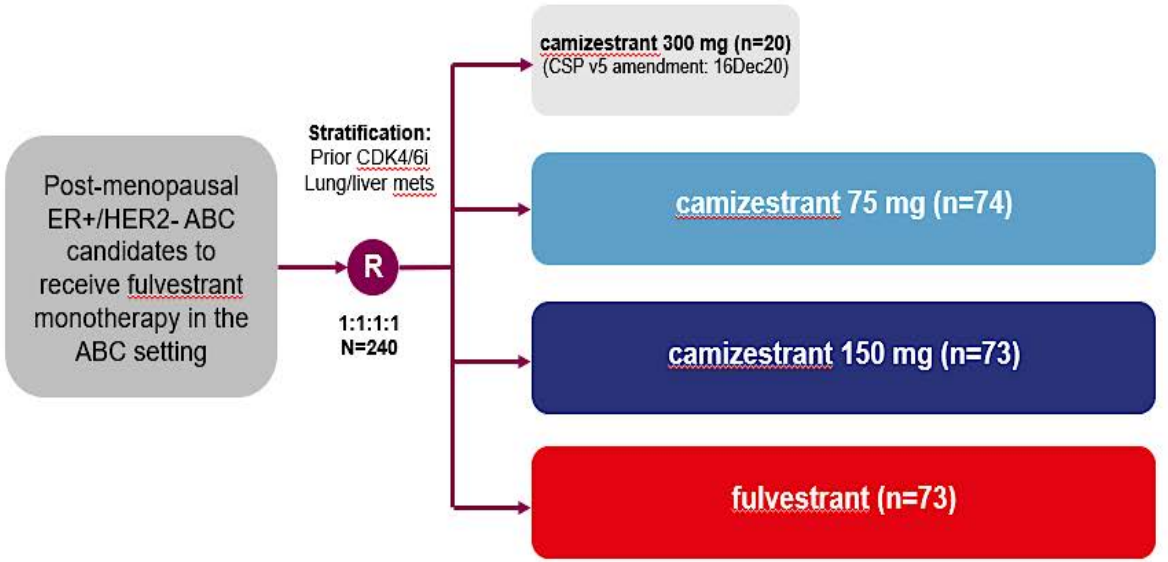
SARAH CANNON Research Institute

Martin M et al. ESMO 2022; Martin JCO 2024

# SERENA-2: Study design and patient population

**Key inclusion/exclusion criteria:**

- Recurrence or progression on at least one line 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




- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

**Patient population**

| | C 75 (n=74) | C 150 (n=73) | F (n=73) |
|---|---|---|---|
| Lung/liver mets | 58.1% | 58.9% | 58.9% |
| ESR1m detectable | 29.7% | 35.6% | 47.9% |
| Adjuvant AI | 40.5% | 35.6% | 31.5% |
| AI for MBC | 55.4% | 67.1% | 67.1% |
| Prior CDK 4/6i | 51.4% | 50.7% | 50.7% |

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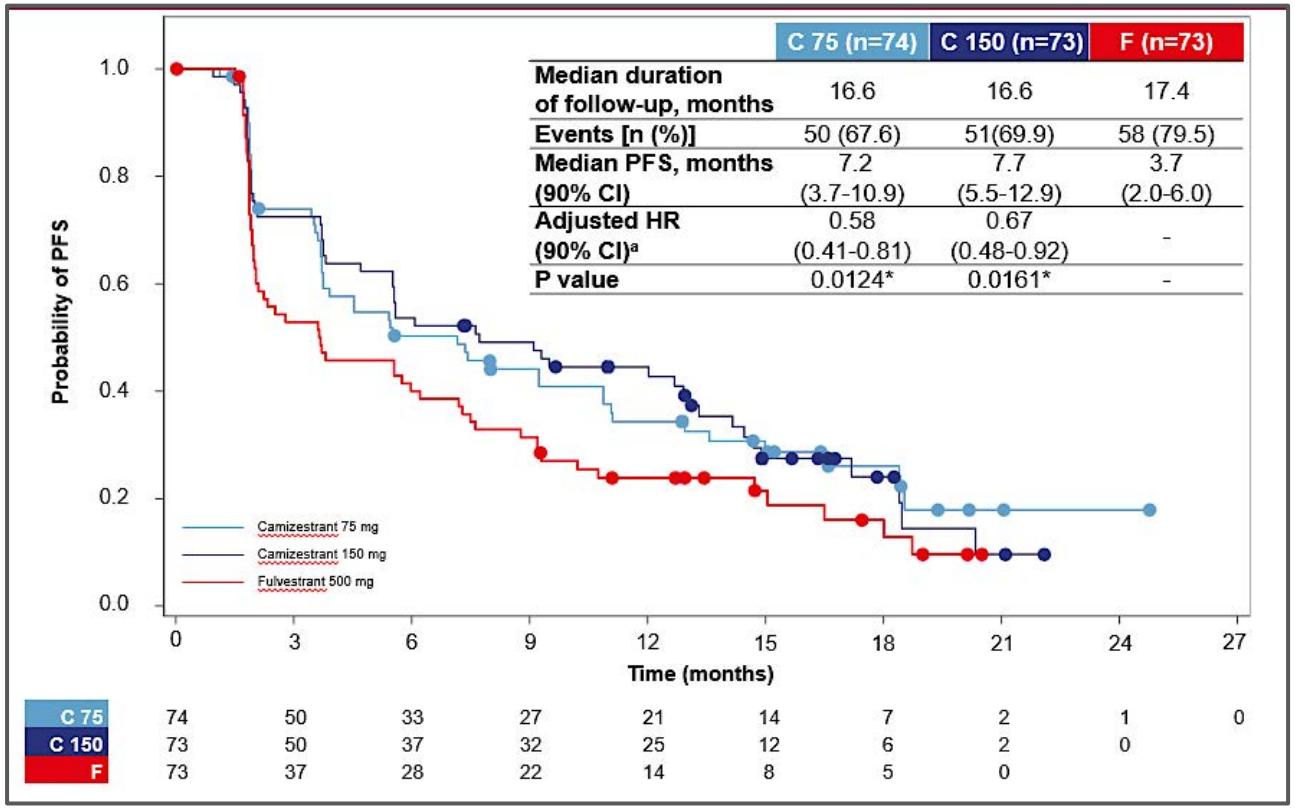
Oliveira M et al. SABCS 2022, GS3-02

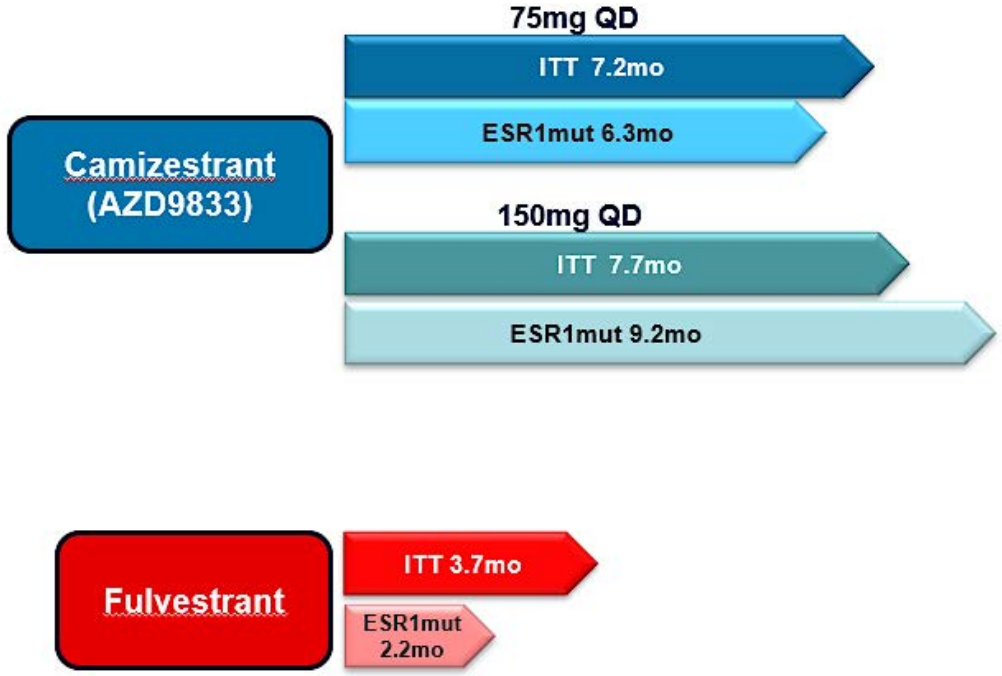
# SERENA-2: Progression-free survival

## PFS in overall patient population




| | 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* | - |

## PFS in pts based on detectable ESR1mut




**Camizestrant improved PFS over fulvestrant in all patients including those with detectable ESR1 mutations**

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Oliveira M et al. SABCS 2022, GS3-02; Oliveira M et al. Lancet Oncol 2024

# Safety of Oral SERDs

| SERD | Elacestrant | Imlunestrant | Camizestrant | Giredestrant |
|---|---|---|---|---|
| Adverse Events | Nausea (35%), fatigue (19%), vomiting (19%), decreased appetite, arthralgias | Nausea (17%), diarrhea (21%), fatigue (23%), arthralgia, urinary tract infection, constipation, headache | Visual disturbances (24%), bradycardia (26%), nausea, fatigue (18%), dizziness, vomiting, and asthenia | Fatigue (14%), arthralgia, back pain, nausea (10%), diarrhea (9%), cough, constipation |

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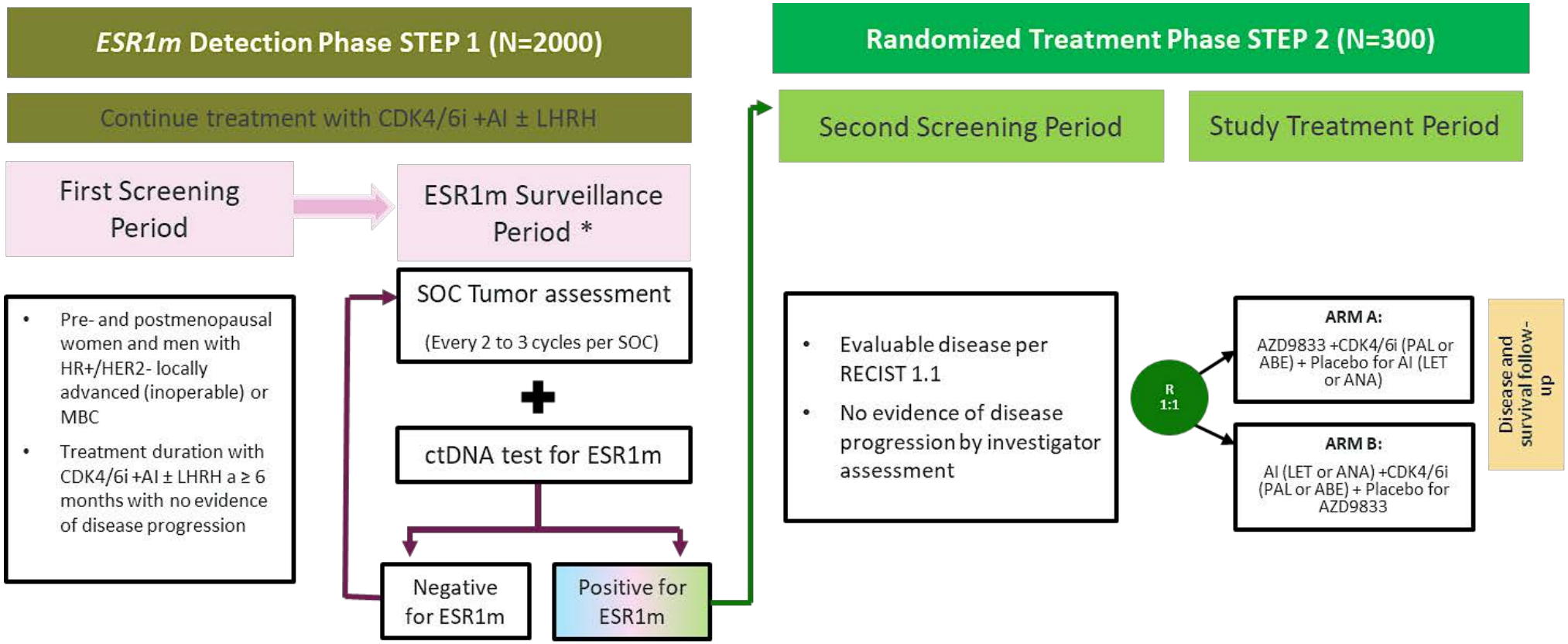
Bardia et al JCO 2021; Jhaveri et al SABCS 2024; Oliveira et al SABCS 2022; Martin JCO 2024

# SERENA-6: Early switch strategy to oral SERD in ESR1-mutant ER+/HER2- MBC

## NCT04964934

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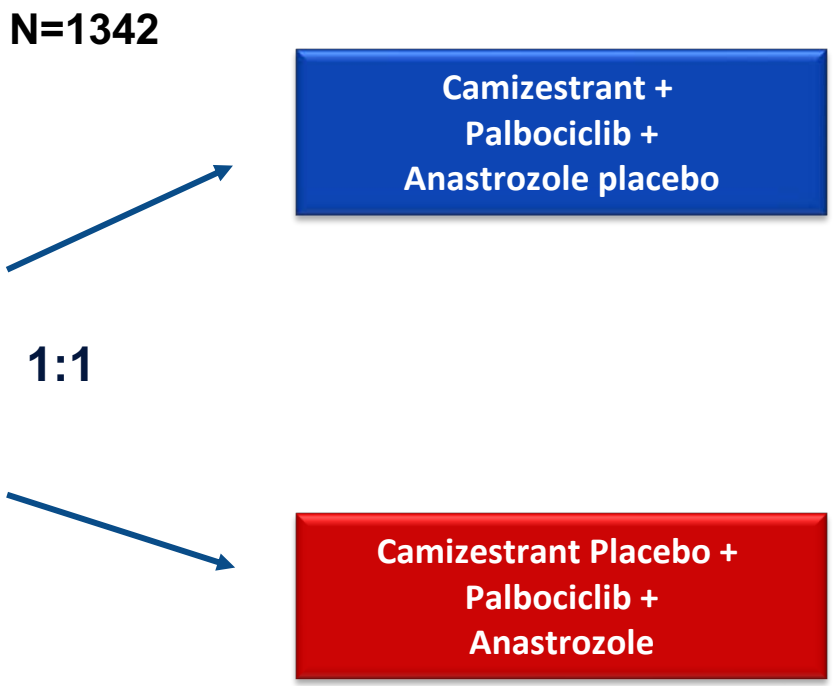
# SERENA-4: Camizestrant + palbociclib as 1L therapy for HR+/HER2- MBC

NCT04711252

- Pre/post menopausal women & male pts with ER+/HER2- MBC
- No prior systemic therapy for metastatic disease
- Recurrence from early-stage disease:

- At least 24 months of an AI with a TFI > 12 months **OR**
- At least 24 months of tamoxifen

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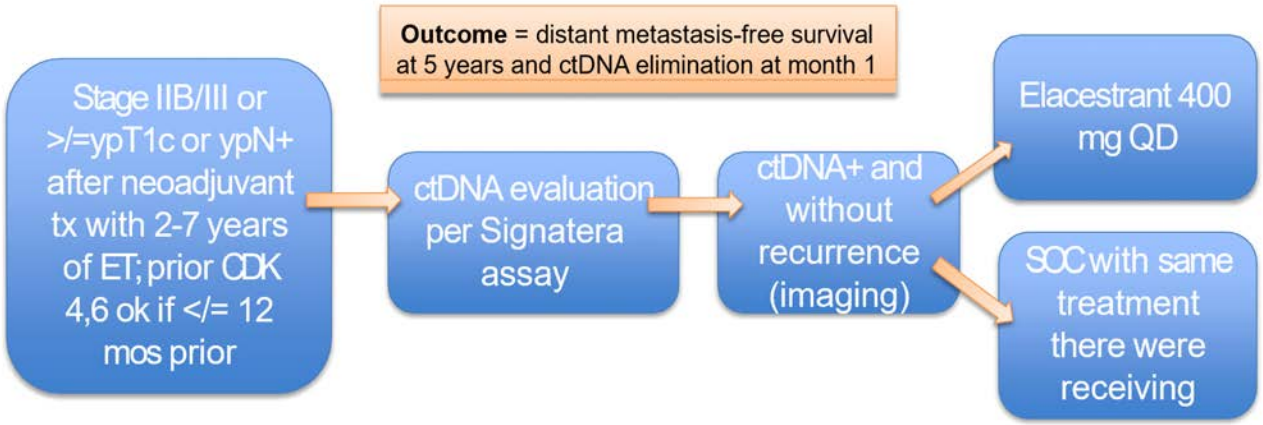
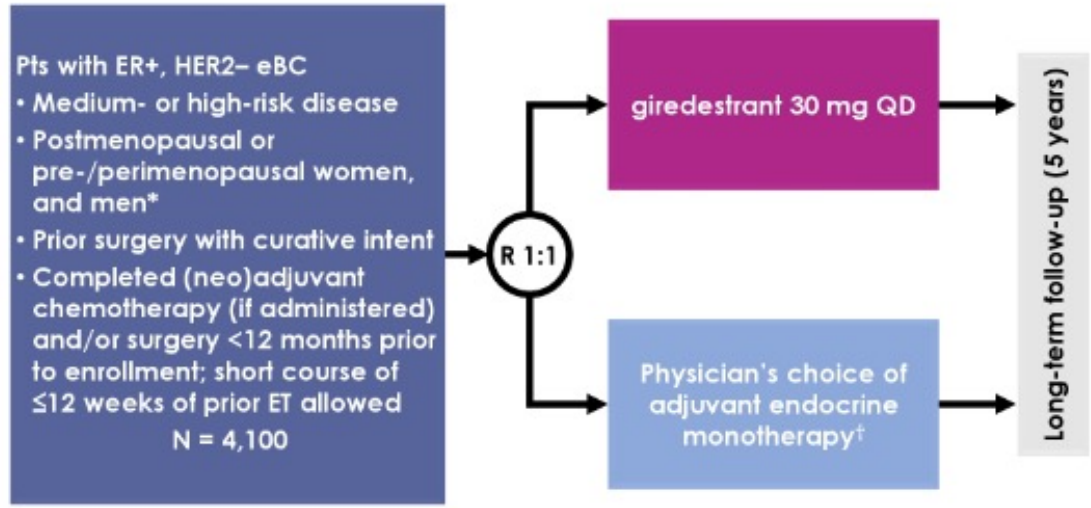
# TREAT ctDNA



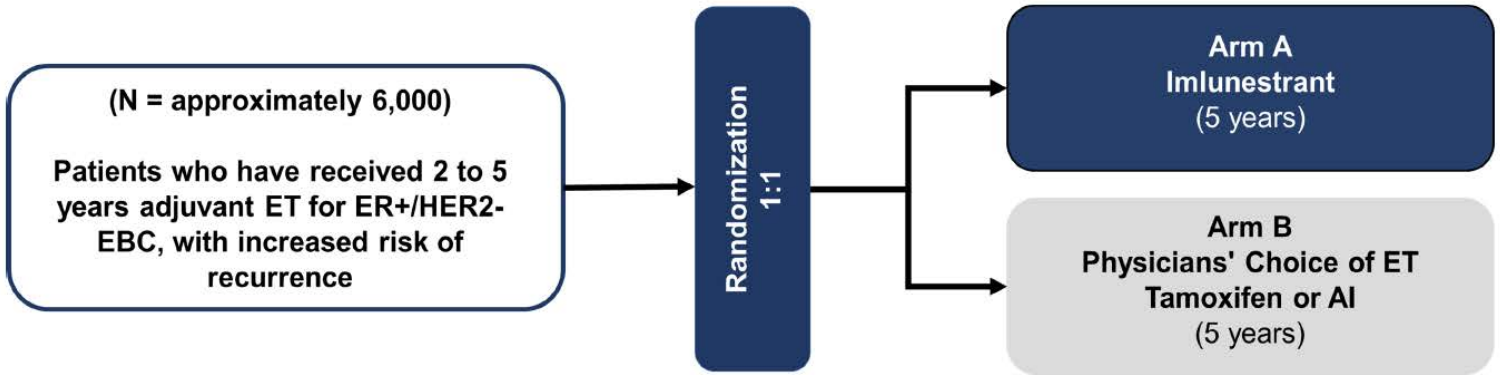

*opening soon (study chairs Ignatidiadis and Saloustros)

Adapted from https://clinicaltrials.gov/study/NCT05512364

# lidERA Breast Cancer trial




**EMBER-4 is a randomized, open-label, global, multicenter, phase 3 study (NCT05514054)**




**Stratification Factors:**

- Time from initial adjuvant ET
- Prior adjuvant CDK4/6 inhibitor treatment
- Nodal status
- Menopausal status at diagnosis
- Geographic region

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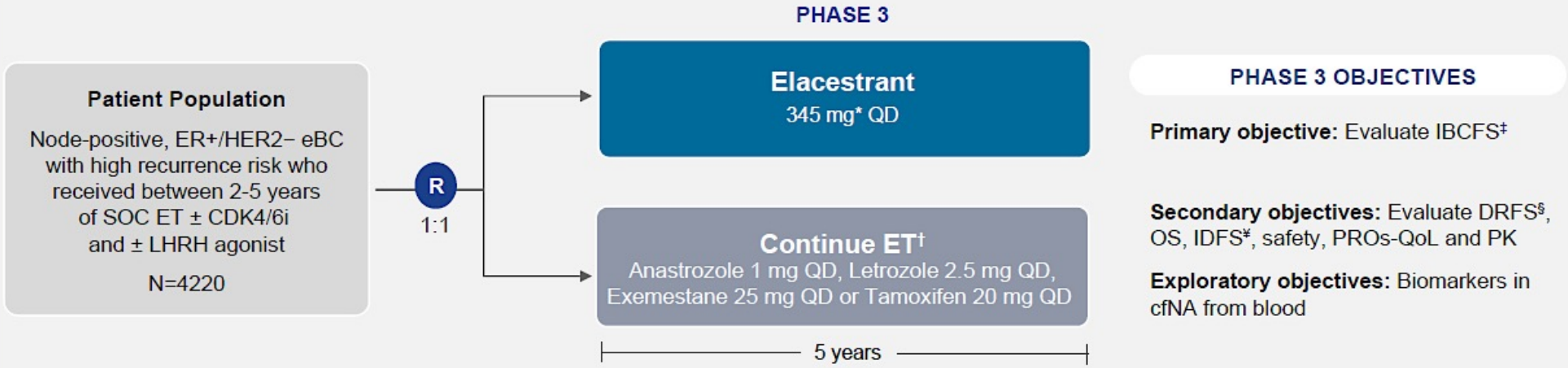
# ELEGANT Study Design

## A randomized phase 3 study of elacestrant vs standard ET in patients with ER+/HER2− eBC with a high risk of recurrence




### PHASE 3 OBJECTIVES

**Primary objective:** Evaluate IBCFS‡

**Secondary objectives:** Evaluate DRFS§, OS, IDFS¥, safety, PROs-QoL and PK

**Exploratory objectives:** Biomarkers in cfNA from blood

### STRATIFICATION FACTORS

- Menopausal status (pre/perimenopausal vs post-menopausal)
- Prior CDK4/6i treatment in the adjuvant setting (yes or no)
- Time since curative surgery (≤48 mo vs >48 mo)

*Elacestrant 345 mg is equivalent to 400 mg elacestrant dihydrochloride. †Change in endocrine therapy after randomization in the control arm from an AI to another AI or to tamoxifen is allowed as per investigator's judgment. Assessed by the time from date of randomization to the date of first occurrence of: ‡Ipsilateral invasive breast tumor recurrence, local/regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death attributable to any cause; §Distant recurrence, or death attributable to any cause; ¥Local/regional recurrence, contralateral recurrence, secondary primary non-breast invasive cancer, distant recurrence, or death attributable to any cause.

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; cfNA, cell-free nucleic acid; DRFS, distant relapse-free survival; eBC, early breast cancer; ER, endocrine receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IBCFS, invasive breast cancer-free survival; IDFS, invasive disease-free survival; LHRH, luteinizing hormone-releasing hormone; OS, overall survival; PK, pharmacokinetics; PROs, patient-reported outcomes; QD, once daily; QoL, quality of life; SOC, standard of care.

# Faculty Case Presentations

# Case Presentation – Dr Jhaveri

- 64 years old postmenopausal woman with ECOG 1 diagnosed with de novo MBC (T2N2M1) to the bones
- Bone Biopsy: ER 95% PR 40% HER2 IHC 1+
- Tissue NGS *PI3E545K* mutation, genetics negative, no other actionable alteration
- After 13 months on 1L Letrozole + Ribociclib, had POD in lungs and liver. She is asymptomatic with normal liver function tests
- Post progression liquid biopsy : confirmed *PI3E545K and ESR1D538G* mutations

# Case Presentation – Dr Jhaveri (continued)

- What would be your next treatment of choice?
  1. SERD
  2. Fulvestrant + Abemaciclib
  3. Fulvestrant + Everolimus
  4. Capecitabine
  5. Capivasertib + Fulvestrant
  6. Trastuzumab Deruxtecan

  Started on EMBER-3: Was randomized to the Imlunestrant + Abemaciclib arm, remained on trial X 11 months with progression in lungs

  Had grade 2 diarrhea, abemaciclib was dose reduced to 100mg BID

# Dr Goetz – Patient Case 2

Presented at the age of 40 with an abnormal screening mammogram. Right skin sparing mastectomy demonstrated 7.5 cm of DCIS with 4 mm focus of grade 2 invasive ductal carcinoma. 1/2 sentinel lymph nodes were positive for metastatic disease. Tumor cells were ER 100%, PR 90%, HER2 0. Patient declined adjuvant chemotherapy and endocrine therapy.

Presented with distant recurrence 2 years later with multiple skeletal metastases, right axillary lymphadenopathy, multiple mediastinal and hilar lymph nodes. Bone biopsy demonstrated ER 95%, PR 1%, HER2 negative. ctDNA demonstrated CCNE1 amplification. She was treated with ribociclib, lupron, and letrozole for 18 months until she presented with progression/new disease in the iliac bones bilaterally. However, the previously noted areas of axillary involvement and other areas of bony involvement remain stable to improving. At that point, the ribociclib and lupron were maintained but the patient was switched from letrozole to fulvestrant . She remained progression free for 6 months until PET-demonstrated progression of disease with multiple liver lesions. Liver biopsy confirmed metastatic breast cancer, ER strongly positive/HER2 negative. Guardant testing performed, demonstrated ESR1 mutation (Y537S).

Patient was treated with single agent abraxane locally for 5 months until progression, with new liver lesions. Patient started on elecestrant at that point. Interval CT scan at 2 and 4 months demonstrated interval decrease in size and number of previously seen liver lesions. Progression of disease at 6 months (new liver and bone lesions)

# Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Metastatic Breast Cancer

*Part 3 of a 3-Part CME Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®*

**Thursday, December 12, 2024**

**7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)**

## Faculty

**Erika Hamilton, MD**
**Kevin Kalinsky, MD, MS**
**Ian E Krop, MD, PhD**
**Joyce O'Shaughnessy, MD**
**Sara M Tolaney, MD, MPH**

## Moderator

**Neil Love, MD**

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