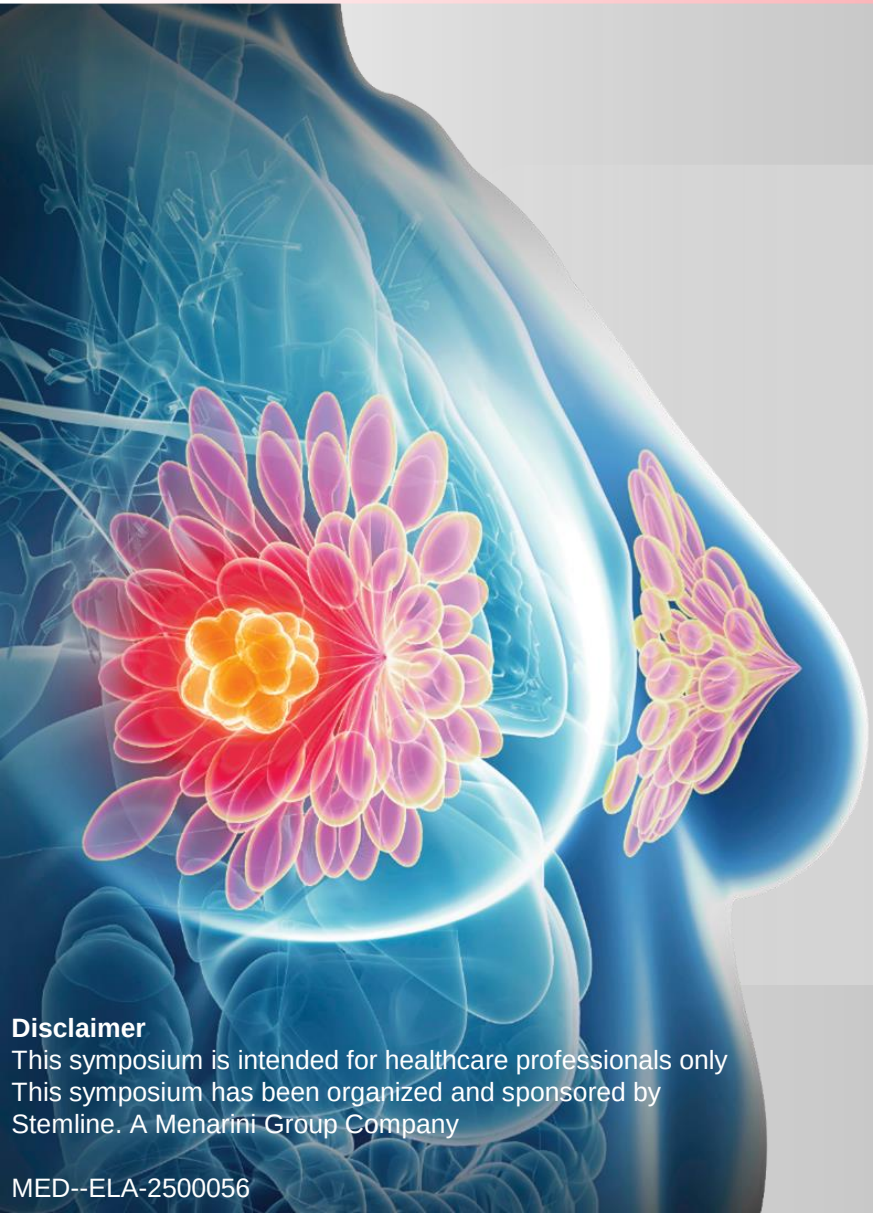

# Treatment Strategies and Sequencing After ET + CDK4/6i for Patients With ER+/HER2- Metastatic Breast Cancer

**Disclaimer**
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MED--ELA-2500056

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Professor and chair of the Department of Obstetrics and Gynecology at the University of Ulm, Germany, where he undertakes research and is principal investigator in a number of clinical studies and was previously chair in Heinrich-Heine-University, Düsseldorf. He is specialized in gynecological oncology, with a focus on breast cancer. His research received numerous international awards, including those of ASCO, AACR and SABCS.

**Sherko Kümmel, MD, PhD** – *Interdisciplinary Breast Unit Clinics of Essen-Mitte*

Clinical Director and Chairman of the Interdisciplinary Breast Unit Clinics of Essen-Mitte in Germany, where he is also Lead of the Breast Cancer Research Program. He is also Executive Board Member of AGO and a Scientific Director of the WSG, an academic study group for breast cancer.

**Michail Ignatiadis, MD, PhD** – *Institut Jules Bordet, Hôpital Universitaire de Bruxelles*

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# Acknowledgement and disclosures

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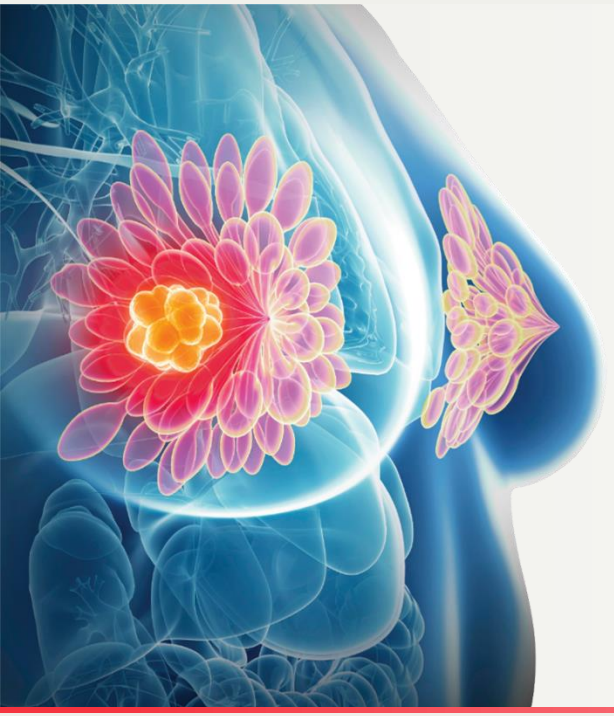
# Treatment strategies and sequencing after ET + CDK4/6i for patients with ER+/HER2- metastatic breast cancer

| Time | Title | Presenter |
|---|---|---|
| 18:15 – 18:20 | Opening and introduction | Wolfgang Janni |
| 18:20 – 18:50 | Treatment landscape for ER+/HER2- metastatic breast cancer | Sherko Kümmel |
| 18:50 – 19:00 | Emerging biomarkers in metastatic breast cancer | Michail Ignatiadis |
| 19:00 – 19:15 | Discussion and Q&A | Wolfgang Janni |



CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2.



# Treatment Landscape for ER+/HER2- Metastatic Breast Cancer

Sherko Kümmel

Interdisciplinary Breast Unit Clinics of Essen-Mitte

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

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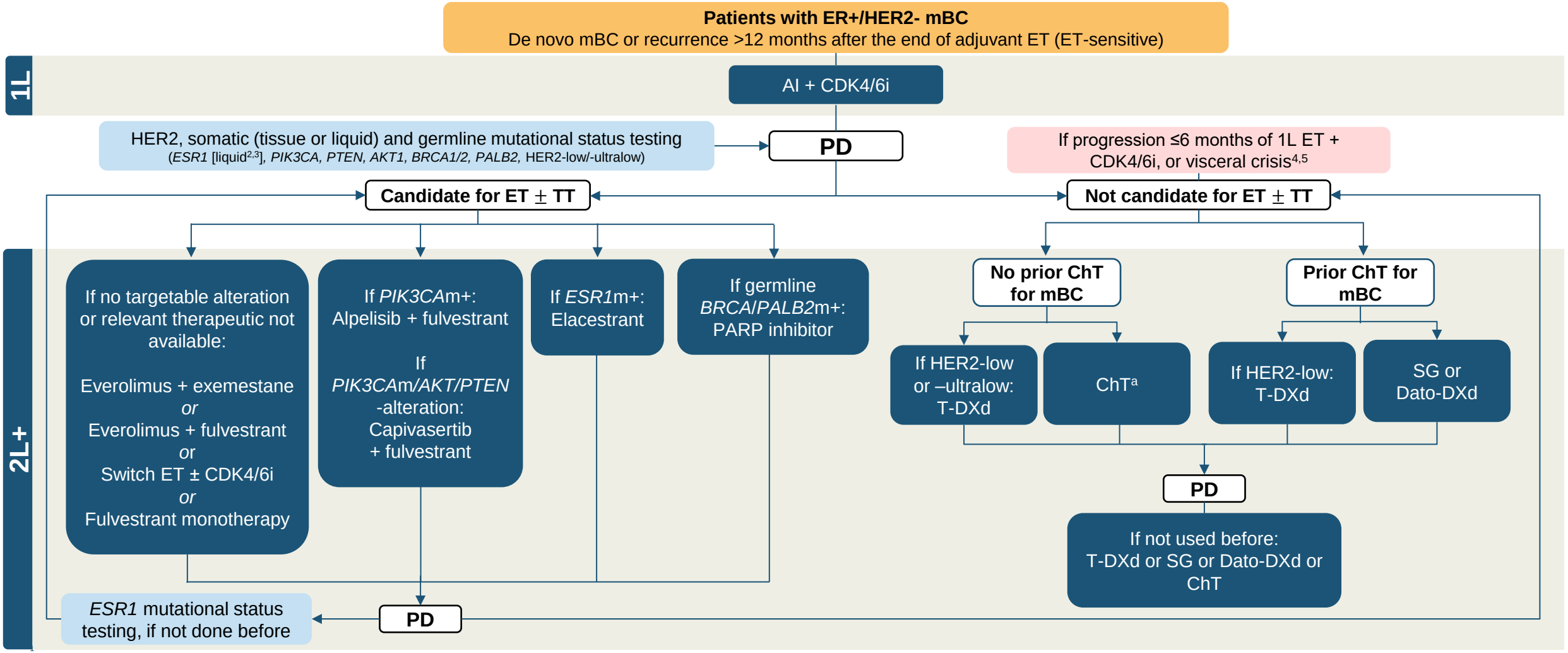
# AI + CDK4/6i is the SOC in 1L mBC. At progression, patients should be tested for genomic alterations to define the optimal treatment[1]




[a]Taxane–bevacizumab or capecitabine–bevacizumab. 1/2L , first/second line; AI, aromatase inhibitor; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; mBC, metastatic breast cancer; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; SG, sacituzumab govitecan; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed April 2025); 2. Burstein HJ, et al. J Clin Oncol. 2023;41(18):3423-3425; 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2025. © *National Comprehensive Cancer Network*, Inc. 2024. All rights reserved. Accessed March 18, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 4. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110-2122; 5. Cardoso F, et al. *Breast*. 2024:76:103756.

# Resistance to ET in ER+/HER2− mBC can be classified by clinical and molecular variables[1-5]

**Clinical definition**

| Primary endocrine resistance | Secondary endocrine resistance |
|---|---|
| PD within first 6 months of 1L ET-based therapy, while on ET (regardless of CDK4/6i use)[1] | PD after ≥6 months of 1L ET[1]<br>*or*<br>PD after any duration of 2L+ ET-based therapy[1] |

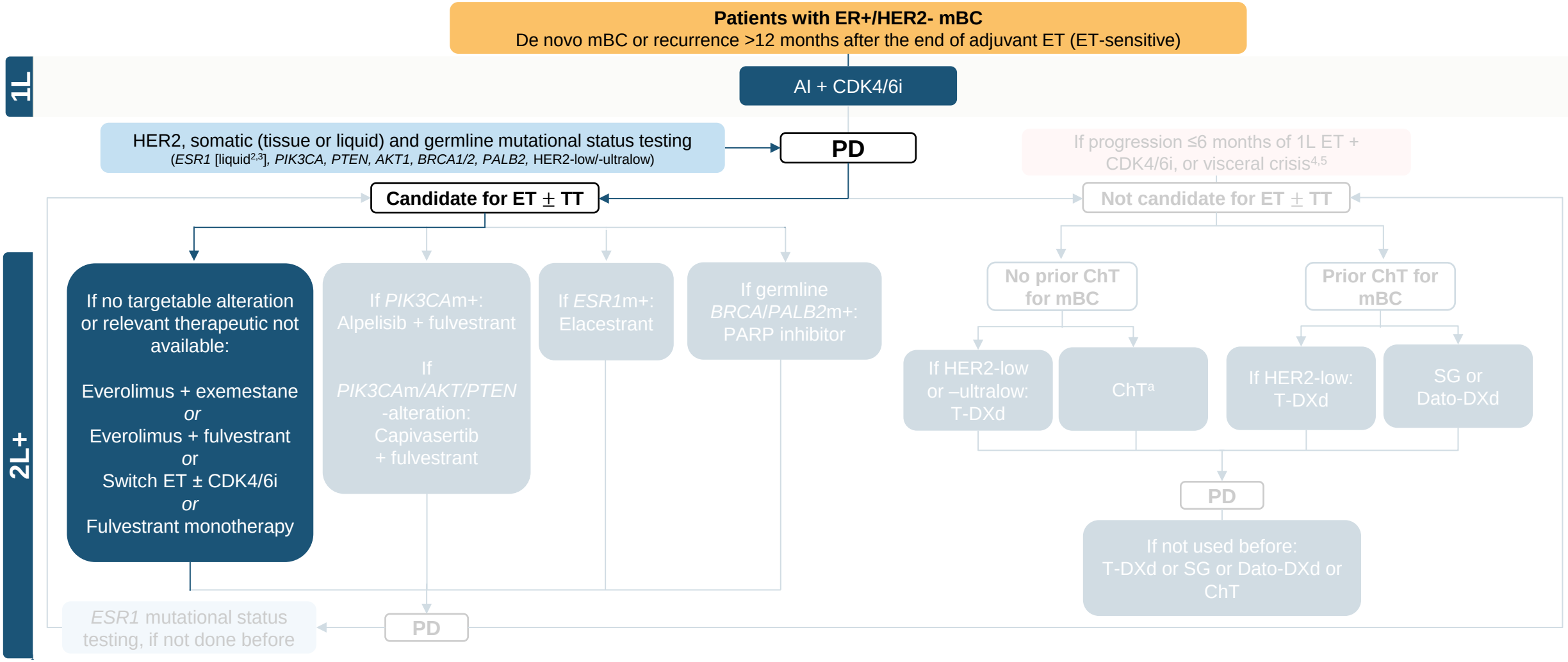
**Molecular definition**

| Intrinsic | Acquired |
|---|---|
| Alterations of the **PI3K/AKT/mTOR, *BRCA1/2* mutations**, *RB1* loss, *TP53* activation, etc.[2-4] | Mechanisms of resistance, such as ***ESR1* mutations**, occurring after prior endocrine therapy in mBC[3,5] |

1/2L, first/second line; AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1,* estrogen receptor 1 gene; ET, endocrine therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PD, progressive disease; PI3K, phosphoinositide 3-kinase.

1. Cardoso F, et al. Breast. 2024;76:103756; 2. Rani A, et al. *Front Endocrinol (Lausanne).* 2019;10:245; 3. Xu P, et al. *Acta Pharmacol Sin.* 2021;42:171-178; 4. Karlsson E, et al. SABCS. 2023.PO5-13-02; 5. Brett JO, et al. *Breast Cancer Res*. 2021;23:85.

# Second-line treatment choice is defined by the eligibility to receive endocrine therapy and driven by biomarker status[1,2]




[a]Taxane–bevacizumab or capecitabine–bevacizumab. 1/2L , first/second line; AI, aromatase inhibitor; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; mBC, metastatic breast cancer; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; SG, sacituzumab govitecan; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

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# mTOR inhibitor plus ET has been associated with shorter mPFS in patients with prior CDK4/6i and *ESR1* mutation tumors

| | BOLERO-2[1–3] | RWD Rozenblit et al.[4] | RWD Vasseur et al.[5] | TRINITI-1[6] |
|---|---|---|---|---|
| **Phase (n)** | Ph3 (724) | N/A (246) | N/A (57) | Ph1/2 (95) |
| **Experimental arm** | Everolimus + exemestane | Everolimus + ET | Everolimus + fulvestrant | Everolimus + exemestane + ribociclib |
| **Control arm** | Placebo + exemestane | N/A | N/A | N/A |
| **Previous CDK4/6i**<br>Yes<br>*No* | <br>-<br>100% | <br>22%<br>78% | <br>100%<br>- | <br>100%<br>- |
| ***ESR1*-mut, %** | 30% | N/A | N/A | 34% |
| **mPFS all patients**<br>mPFS, months<br>HR (95% CI) | <br>**7.8 vs 3.2**<br>0.45 (0.38-0.54) | **mTTNT**<br>*Prior CDK4/6i:* **4.3**<br>*No prior CDK4/6i:* **6.2** | <br>**6.8** | <br>**5.7** |
| **mPFS *ESR1*-mut**<br>mPFS, months<br>HR (95% CI) | <br>**5.4 vs 2.8**<br>0.52 (0.36-0.75) | <br>**N/A** | <br>**N/A** | <br>**3.5[a]** |

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***

[a] N = 89 patients had a baseline ctDNA biomarker assessment.

2L, second line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1*, estrogen receptor 1 gene; ctDNA, circulating tumor DNA; ET, endocrine therapy; HR, hazard ratio; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin; mTTNT, median time to next therapy; mut, mutation; N/A not available; RWD, real world data.

1. Yardley DA, et al. *Adv Ther*. 2013;30:870–884; 2. Cook M, et al. *Oncologist*. 2021;26:101–106; 3. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2:1310-1315; 4. Rozenblit M, et al. *Breast Cancer Res.* 2021;23:14; 5. Vasseur, et al. *Oncogene. 2024;*43:1214–1222 ( including Suppl); 6. Bardia A, et al. *Clin Cancer Res*. 2021;27:4177-4185.

# CDK4/6 inhibitor re-challenge

MAINTAIN and postMONARCH are the only positive trials in 100% prior CDK4/6i exposed patients, showing both ribociclib and abemaciclib deliver benefit mainly after palbociclib. Benefit has not been demonstrated in patients with *ESR1*-mut tumors[1,4]

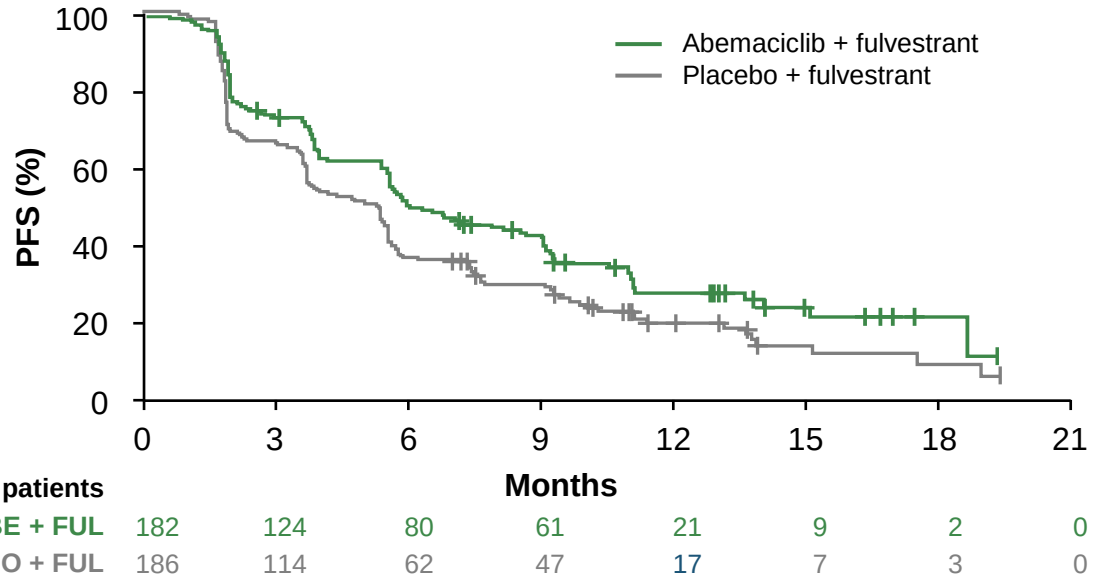
| | MAINTAIN[1] | PACE[2] | PALMIRA[3] | postMONARCH[4] |
|---|---|---|---|---|
| **Outcomes** | **POSITIVE all comers**<br>**NEGATIVE *ESR1*-mut** | **NEGATIVE** | **NEGATIVE** | **POSITIVE all comers** |
| **Phase (n)** | Ph2 (119) | Ph2 (220) | Ph2 (198) | Ph3 (368) |
| **Experimental arm** | Ribociclib +<br>fulvestrant or exemestane | Palbocilcib +<br>fulvestrant[a] | Palbociclib +<br>fulvestrant or letrozole | Abemaciclib +<br>fulvestrant |
| **Prior CDK4/6i** | Palboclicib 87%<br>Ribociclib 10%<br>Abemaciclib 3% | Palboclicib 91%<br>Ribociclib 5%<br>Abemaciclib 4% | Palboclicib 100% | Palboclicib 59%<br>Ribociclib 33%<br>Abemaciclib 8% |
| **Control arm** | Fulvestrant or exemestane | Fulvestrant | Fulvestrant or letrozole | Fulvestrant |
| ***ESR1*-mut,%** | 30% | 50% | N/A | 40% |
| **mPFS all patients**<br>mPFS, months<br>HR (95% CI) | **5.3 vs 2.8**<br>0.57 (95% CI 0.39-0.85) | **4.6 vs 4.8**<br>1.11 (90% CI 0.79-1.55) | **4.9 vs 3.6**<br>0.84 (95% CI 0.66-1.07) | **6.0 vs 5.3**<br>0.73 (95% CI 0.57-0.95) |
| **mPFS *ESR1*-mut**<br>mPFS, months<br>HR (95% CI) | **3.0 vs 3.0**<br>1.22 (95% CI 0.59-2.49) | **5.2 vs 3.3**<br>0.68 (90% CI 0.42-1.09) | **Not reported** | **Not reported**<br>0.79 (95% CI 0.54-1.15) |

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***

[a]Palbociclib + fulvestrant + avelumab arm not considered for this table.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HR, hazard ratio; mPFS, median progression-free survival; Ph, phase; N/A not available.
mut, mutation; NS, not significant; PBO, placebo; PFS, progression-free survival; N/A not available.
1. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004–4013; 2. Mayer EL, et al. J Clin Oncol. 2024;42:2050-2060; 3. Llombart-Cussac A, et al. *J Clin Oncol*. 2023;41:S1001–S1001 (oral presentation); 4. Kalinsky K, et al. *J Clin Oncol*. 2024;42: Abstract LBA1001.

# postMONARCH: 0.7 months absolute benefit difference, mainly after prior palbociclib[1]

## postMONARCH[a]




| | ABE + FUL (N=182) | PBO + FUL (N=186) |
|---|---|---|
| **mPFS, mo** [95% CI] | **6.0** [5.6–8.6] | **5.3** [3.7–5.6] |
| **HR** [95% CI] | **0.73** [0.57–0.95] | |
| Nominal p-value | 0.02 | |

## postMONARCH: Subgroup analysis

| Subgroup | N (%) | Events | HR (95% CI) | Interaction p-value |
|---|---|---|---|---|
| **Visceral metastasis** | | | | *0.07* |
| Yes | 221 (60) | 173 | 0.87 (0.64-1.17) | |
| No | 147 (40) | 85 | 0.53 (0.34-0.83) | |
| **Liver metastasis** | | | | *0.40* |
| Yes | 139 (38) | 115 | 0.63 (0.44-0.91) | |
| No | 229 (62) | 143 | 0.78 (0.56-1.09) | |
| **Prior CDK4/6i** | | | | *0.19* |
| Palbociclib | 217 (59) | 145 | 0.62 (0.44-0.86) | |
| Ribociclib | 122 (33) | 94 | 1.01 (0.67-1.51) | |
| Abemaciclib | 28 (8) | 19 | 0.66 (0.27-1.64) | |
| ***ESR1*-mut[b]** | | | | *0.98* |
| Detected | 145 (45) | 110 | 0.79 (0.54-1.15) | |
| Not detected | 175 (55) | 120 | 0.79 (0.55-1.13) | |

[a]Investigator-assessed PFS; [b]Biomarker ctDNA by GuardantINFINITY assay, evaluated population n=320.
ABE, abemaciclib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ctDNA, circulating tumor DNA; *ESR1,* estrogen receptor 1 gene; FUL, fulvestrant; HR, hazard ratio; PBO, placebo; mPFS, median progression-free survival; mut, mutation.

1. Kalinsky K, et al. *J Clin Oncol*. 2024;42: Abstract LBA1001.

# EMBER-3: Study design and baseline demographics[1]

## Study design

**ER+, HER2- ABC**

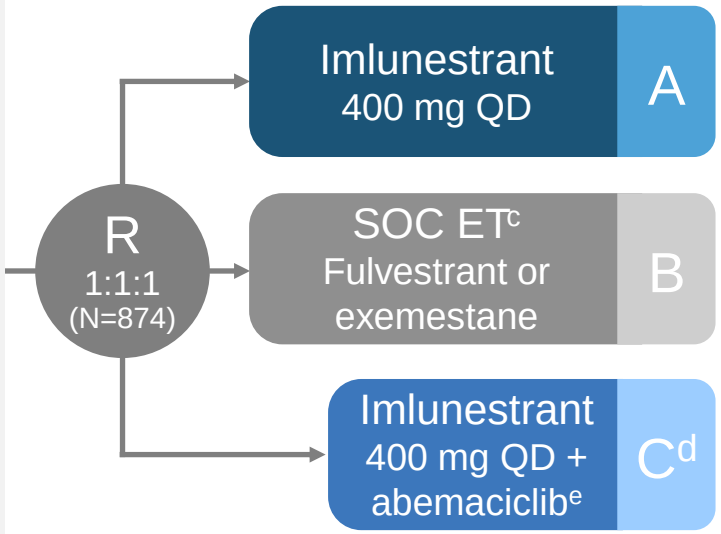
Men and pre-[a]/post-menopausal women

**Prior therapy:**

- **(Neo)adjuvant:** Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **aBC:** Progression on 1L AI ± CDK4/6i
- No other therapy for aBC

**Stratification factors:**

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




**Primary endpoints**

**Investigator-assessed PFS for:**

- A vs B in patients with *ESR1*-mut
- A vs B in all patients
- C vs A in all patients

**Key secondary endpoints:**

- OS, PFS by BICR, and ORR
- Safety

## Baseline demographics

| Characteristic | | Imlunestrant n=331 | SOC ET n=330 | Imlunestrant + abemaciclib n=213 |
|---|---|---|---|---|
| **Median age, years (range)** | | 61 (28-87) | 62 (27-89) | 62 (36-87) |
| **Post-menopausal, %** | | 84 | 86 | 86 |
| **Region, %** | East Asia | 25 | 26 | 31 |
| | North America/ Western Europe | 38 | 39 | 45 |
| | Other | 37 | 36 | 24 |
| **PR-positive, %** | | 78 | 79 | 74 |
| ***ESR1*-mut, %[e]** | | 42 | 36 | 32 |
| **PI3K pathway mutations, %** | | 39 | 39 | 41 |
| **Prior chemotherapy, %** | Yes | 0 | 0 | 0 |
| | No | 100 | 100 | 100 |
| **Prior fulvestrant, %** | Yes | 0 | 0 | 0 |
| | No | 100 | 100 | 100 |
| **Most recent ET,%** | | | | |
| As (neo)adjuvant therapy | | 32 | 34 | 30 |
| For aBC | | 63 | 63 | 68 |
| **Prior CDK4/6i,%** | Overall | 59 | 57 | 65 |
| As adjuvant therapy | | 4 | 4 | 3 |
| For aBC | | 55 | 53 | 62 |

Table adapted from Jhaveri KL et al, 2025

[a]A GRH agonist was required in men and premenopausal women; [b]East Asia vs United States/European Union vs others; [c]Investigator's choice, labeled dose; [d]Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [e]*ESR1*-mut status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China, "Analysis conducted in all concurrently randomized patients.

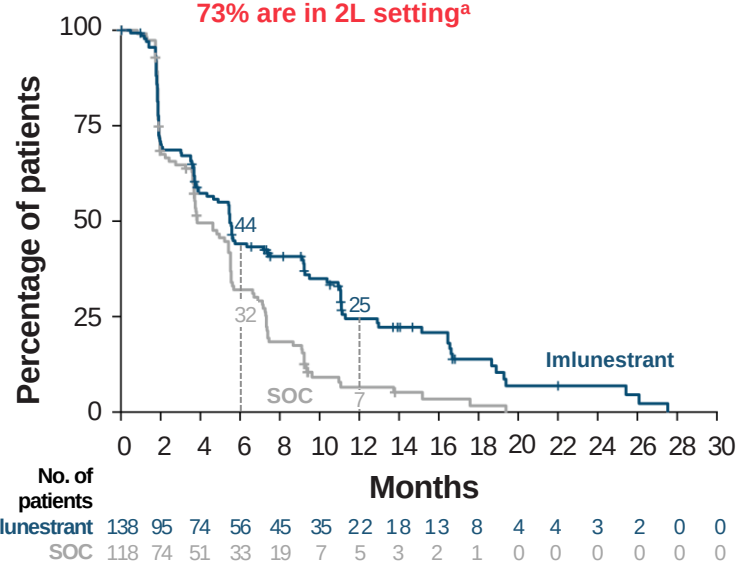
1L, first line; aBC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA, ER, estrogen receptor, *ESR1,* estrogen receptor 1 gene; ET endocrine therapy; mut, mutation; GRH, gonadotropin-releasing hormone; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; QD, once daily; SOC ET, standard of care endocrine therapy.

1.Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189-1202.

# Imlunestrant monotherapy provided PFS benefit over standard therapy among patients with *ESR1* mutations. Imlunestrant did not show benefit in the all-patient population[1]

## mPFS in patients with *ESR1*-mut

67% HAD prior CDK4/6i therapy[a]
21% are in 1L setting[a]
73% are in 2L setting[a]

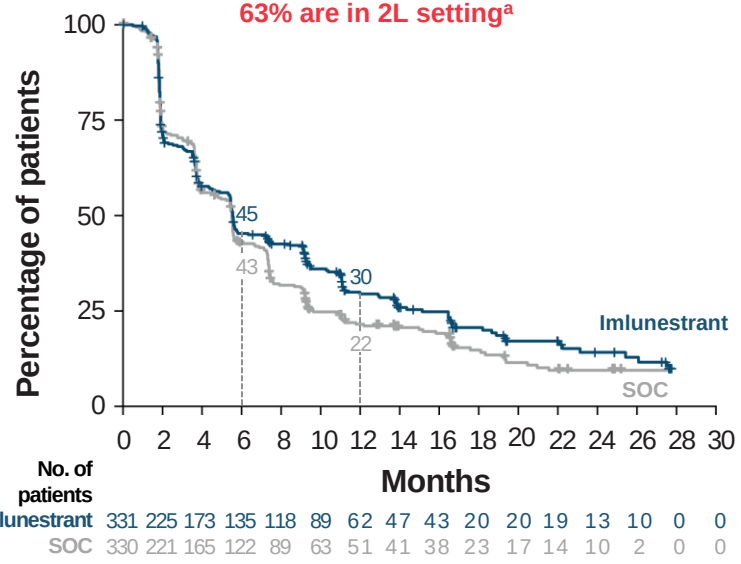



| No. of patients | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imlunestrant | 138 | 95 | 74 | 56 | 45 | 35 | 22 | 18 | 13 | 8 | 4 | 4 | 3 | 2 | 0 | 0 |
| SOC | 118 | 74 | 51 | 33 | 19 | 7 | 5 | 3 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| | IMLU (n=138) | SOC (n=118) |
|---|---|---|
| mPFS, mo | 5.5 | 3.8 |
| HR [95% CI] | 0.62 [0.46–0.82] | |
| p-value | < 0.001 | |

## mPFS in all patients

59% HAD prior CDK4/6i therapy[a]
32% are in 1L setting[a]
63% are in 2L setting[a]



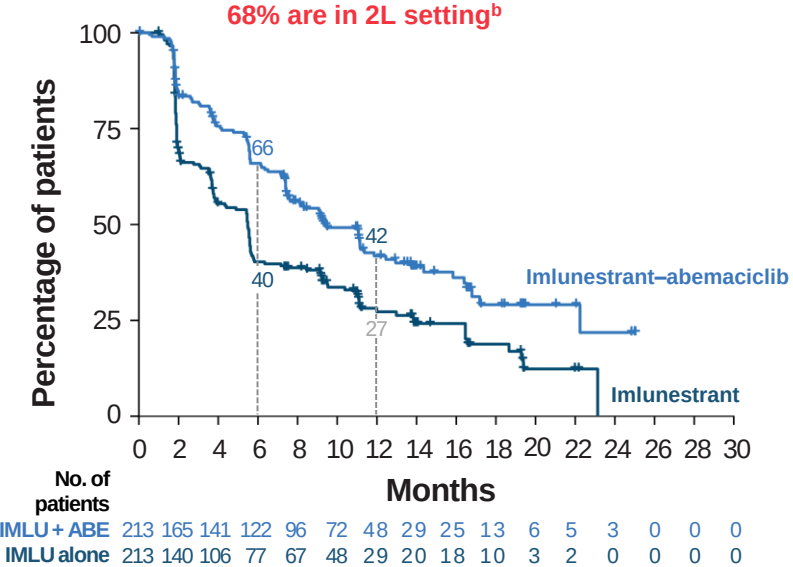

| No. of patients | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Imlunestrant | 331 | 225 | 173 | 135 | 118 | 89 | 62 | 47 | 43 | 20 | 20 | 19 | 13 | 10 | 0 | 0 |
| SOC | 330 | 221 | 165 | 122 | 89 | 63 | 51 | 41 | 38 | 23 | 17 | 14 | 10 | 2 | 0 | 0 |

| | IMLU (n=331) | SOC (n=330) |
|---|---|---|
| mPFS, mo | 5.6 | 5.5 |
| HR [95% CI] | 0.87 [0.72–1.04] | |
| p-value | 0.12 | |

# Imlunestrant + abemaciclib combination provided PFS benefit vs imlunestrant alone in all comers[1]

## mPFS in all patients

65% HAD prior CDK4/6i therapy[b]
30% are in 1L setting[b]
68% are in 2L setting[b]




| No. of patients | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IMLU + ABE | 213 | 165 | 141 | 122 | 96 | 72 | 48 | 29 | 25 | 13 | 6 | 5 | 3 | 0 | 0 | 0 |
| IMLU alone | 213 | 140 | 106 | 77 | 67 | 48 | 29 | 20 | 18 | 10 | 3 | 2 | 0 | 0 | 0 | 0 |

| | IMLU + ABE (n=213) | IMLU alone (n=213) |
|---|---|---|
| mPFS, mo | 9.4 | 5.5 |
| HR [95% CI] | 0.57 [0.44–0.73] | |
| p-value | < 0.001 | |

[a]Baseline characteristic for patients in the imlunestrant arm only: [b]Baseline characteristic for patients in the imlunestrant-abemaciclib arm only.
1/2L, first/second line; ABE, abemaciclib; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1*, estrogen receptor 1 gene; HR, hazard ratio; IMLU, imlunestrant; (m)PFS, (median) progression-free survival; SOC, standard of care.

1.Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189-1202.

# EMBER-3: The safety profiles of imlunestrant and imlunestrant–abemaciclib were consistent with previous findings[1]

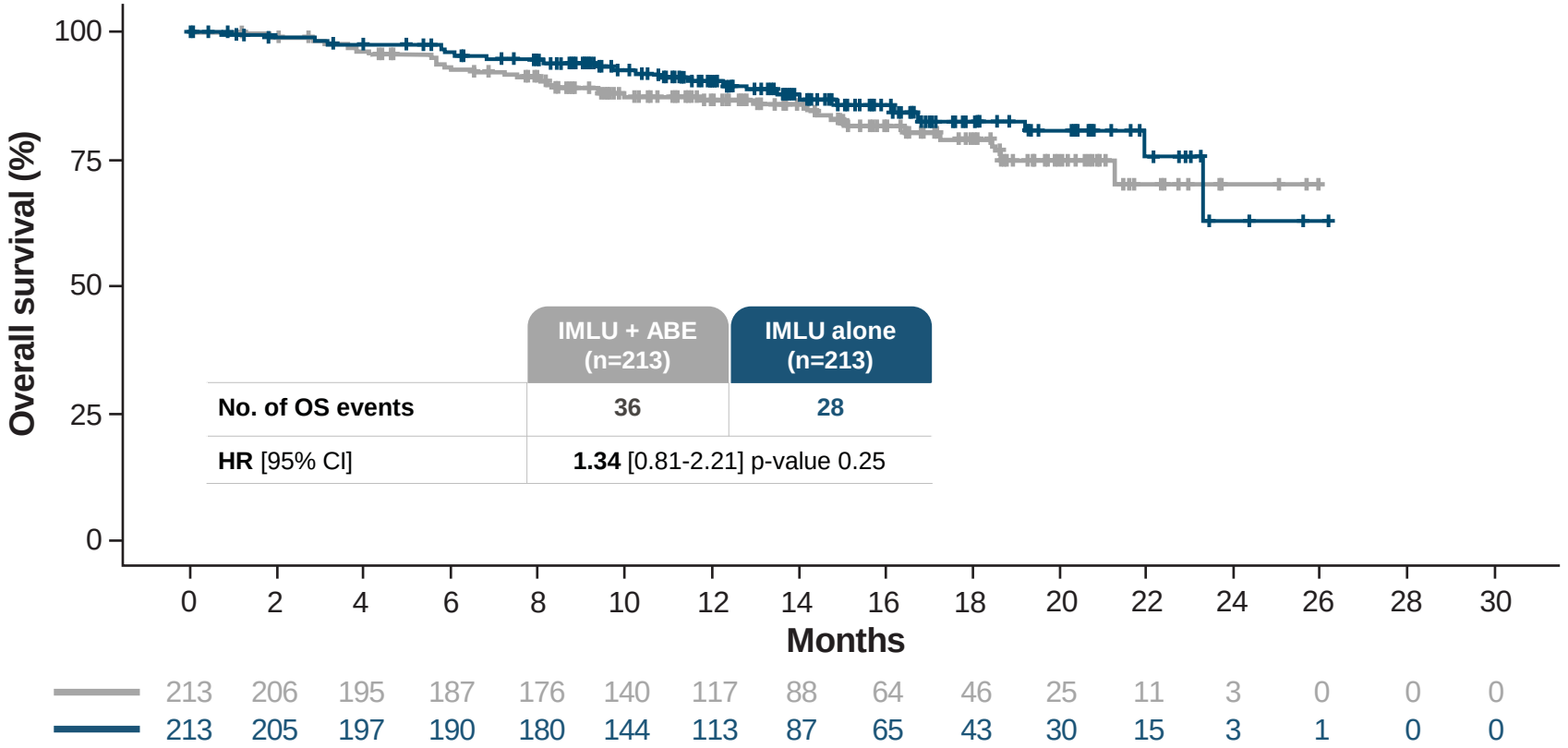
| | Imlunestrant (n=327) | | SOC ET (n=324) | |
|---|---|---|---|---|
| **Adverse events in ≥10% of patients, %** | **All grades** | **Grade ≥3** | **All grades** | **Grade ≥3** |
| Fatigue | 23 | <1 | 13 | 1 |
| Diarrhea | 21 | <1 | 12 | 0 |
| Nausea | 17 | <1 | 13 | 0 |
| Arthralgia | 14 | 1 | 14 | <1 |
| AST increased | 13 | 1 | 13 | 1 |
| Back pain | 11 | 1 | 7 | <1 |
| ALT increased | 10 | <1 | 10 | 1 |
| Anemia | 10 | 2 | 13 | 3 |
| **Adverse events in ≥20% of patients, %** | **Imlunestrant + abemaciclib (n=208)** | | **SOC ET (n=324)** | |
| Diarrhea | 86 | 8 | 12 | 0 |
| Nausea | 49 | 2 | 13 | 0 |
| Neutropenia | 48 | 20 | 13 | 3 |
| Anemia | 44 | 8 | 13 | 1 |
| Fatigue | 39 | 5 | 13 | 1 |
| Vomiting | 31 | 1 | 5 | <1 |
| Leukopenia | 26 | 4 | 5 | 0 |
| Hypercreatinemia | 22 | 1 | 7 | 0 |
| Abdominal pain | 20 | 2 | 5 | <1 |
| Decreased appetite | 20 | 1 | 4 | <1 |

ALT, Alanine aminotransferase AST, aspartate aminotransferase; SOC ET, standard of care endocrine therapy.

1.Jhaveri KL, et al. *N Engl J Med.* 2025;392:1189-1202.

# Survival with imlunestrant ± abemaciclib[1]

- Overall survival analyses are early
- Only 15% of events for planned analysis




ABE, abemaciclib; CI, confidence interval; HR, hazard ratio; IMLU, imlunestrant; OS, overall survival.
1. Burstein HJ. Discussant of EMBER-3 trial. SABCS 2024; Abstract GS1-01.

# Oral SERD/SERM in combination with abemaciclib after prior CDK4/6 inhibitor treatment[1]

| Study | SERD/SERM + abemaciclib | Sample size | mPFS in combination with abemaciclib | Reference |
|---|---|---|---|---|
| EMBER-3 | Imlunestrant + abemaciclib | 139<br>36[a] | 9.1 mo<br>11.1 mo | Jhaveri et al. *NEJM* 2024 |
| ELECTRA/ ELEVATE | Elacestrant + abemaciclib | 24<br>11[a] | 8.7 mo<br>8.7 mo | Rugo et al. SABCS 2023 |
| ELAINE 2 | Lasofoxifene + abemaciclib | 29[a] | 12.3 mo | Damodaran et al. *Ann Oncol* 2023 |

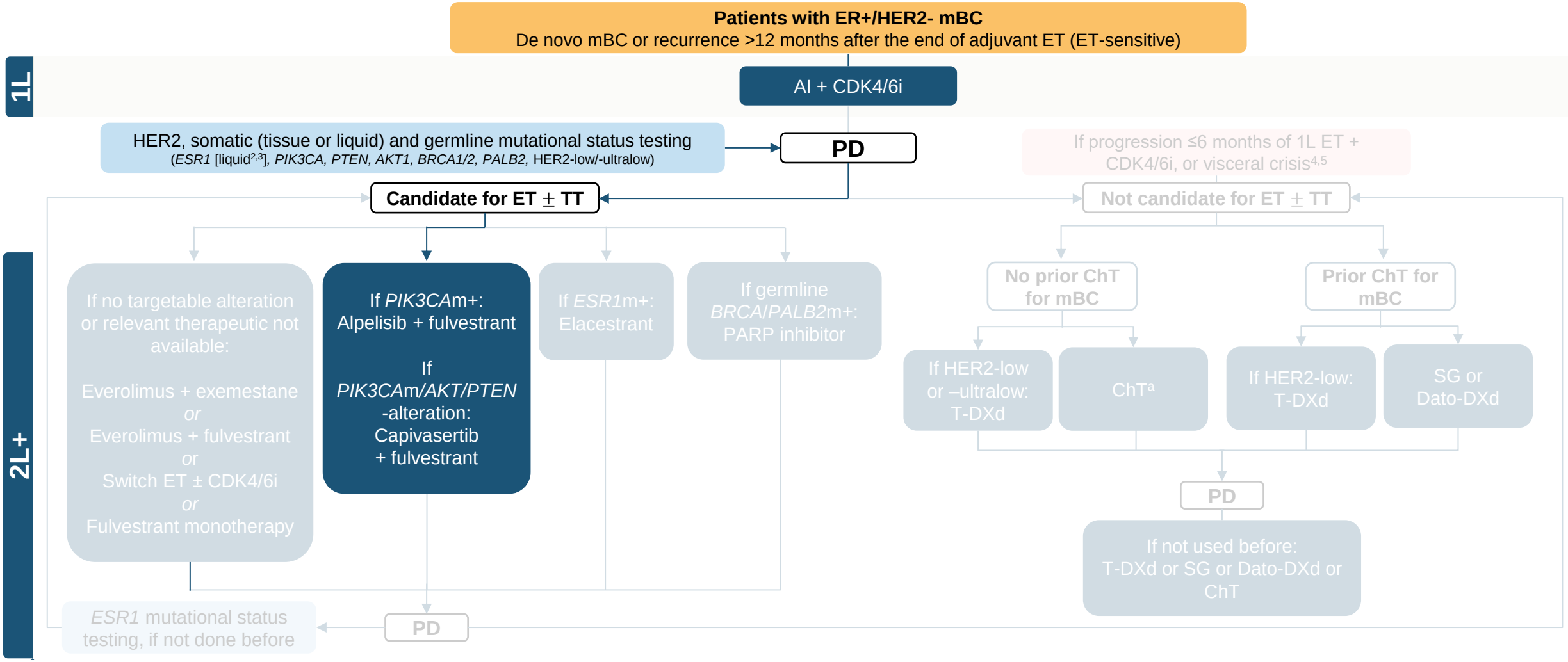
[a]*ESR1*-mut

SAN ANTONIO BREAST CANCER SYMPOSIUM®

CDK4/6i, cyclin dependent kinase 4/6 inhibitor; *ESR1*, estrogen receptor 1 gene; mo, months; mPFS, median progression free survival; mut, mutation; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator

1. Burstein HJ. Discussant of EMBER-3 trial. SABCS 2024; Abstract GS1-01.

# Second-line treatment choice is defined by the eligibility to receive endocrine therapy and driven by biomarker status[1,2]



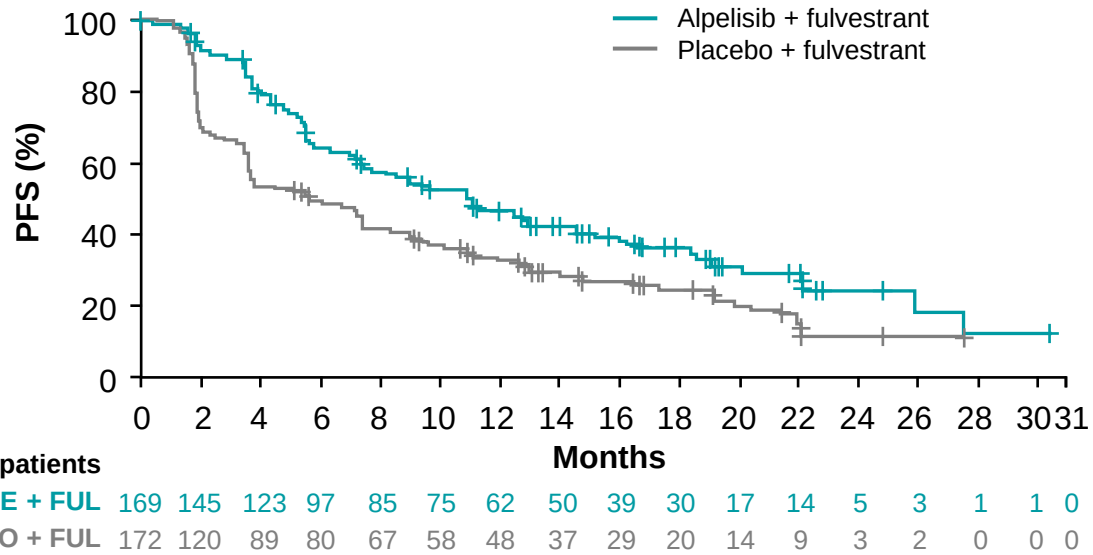

[a]Taxane–bevacizumab or capecitabine–bevacizumab. 1/2L , first/second line; AI, aromatase inhibitor; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; mBC, metastatic breast cancer; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; SG, sacituzumab govitecan; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed April 2025); 2. Burstein HJ, et al. J Clin Oncol. 2023;41(18):3423-3425; 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2025. © *National Comprehensive Cancer Network*, Inc. 2024. All rights reserved. Accessed March 18, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 4. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110-2122; 5. Cardoso F, et al. *Breast*. 2024:76:103756.

# Alpelisib + fulvestrant in patients with ER+/HER2− and *PIK3CA*-mut mBC

## SOLAR-1: *PIK3CA*-mut[1]

**Patients HAD NOT received prior CDK4/6i therapy[a]**



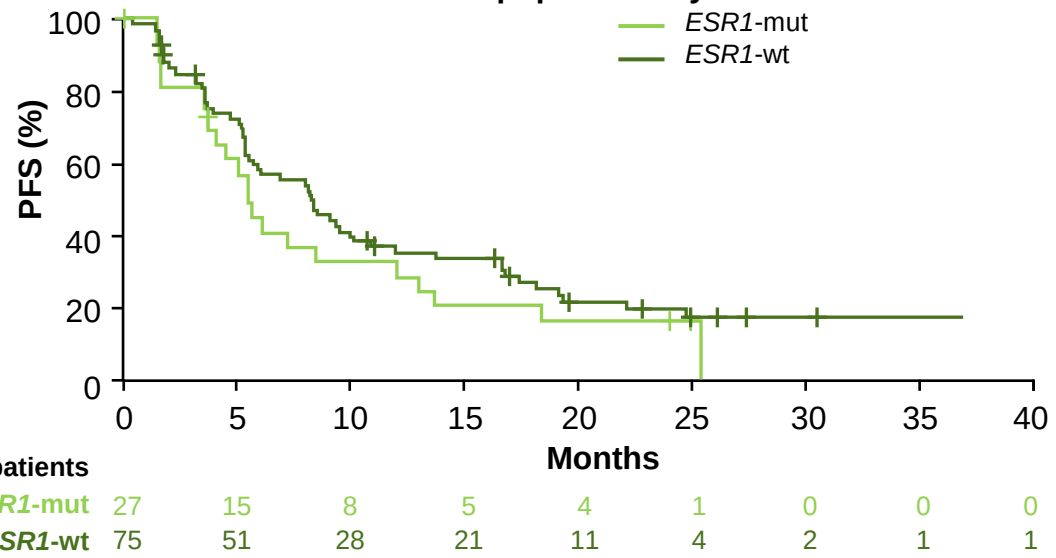

| No. of patients | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ALPE + FUL | 169 | 145 | 123 | 97 | 85 | 75 | 62 | 50 | 39 | 30 | 17 | 14 | 5 | 3 | 1 | 1 | 0 |
| PBO + FUL | 172 | 120 | 89 | 80 | 67 | 58 | 48 | 37 | 29 | 20 | 14 | 9 | 3 | 2 | 0 | 0 | 0 |

| | ALPE + FUL (n=169) | PBO + FUL (n=172) |
|---|---|---|
| **mPFS, mo** [95% CI] | **11** [7.5–14.5] | **5.7** [3.7–7.4] |
| **HR** [95% CI] | **0.65** [0.50–0.85] | |
| **Log-rank p-value** | <0.001 | |

## BYLieve[2,3]

**Patients HAD received prior CDK4/6i therapy**

**Cohort A: PFS in total population by *ESR1*-mut status[2,3]**




| No. of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *ESR1*-mut | 27 | 15 | 8 | 5 | 4 | 1 | 0 | 0 | 0 |
| *ESR1*-wt | 75 | 51 | 28 | 21 | 11 | 4 | 2 | 1 | 1 |

| | Total[2] (n=127) | *ESR1*-mut[3] (n=27) | *ESR1*-wt[3] (n=75) |
|---|---|---|---|
| **mPFS, mo** [95% CI] | **8.0** [5.6–8.6] | **5.6** [3.8–12.0] | **8.3** [5.5–10.1] |

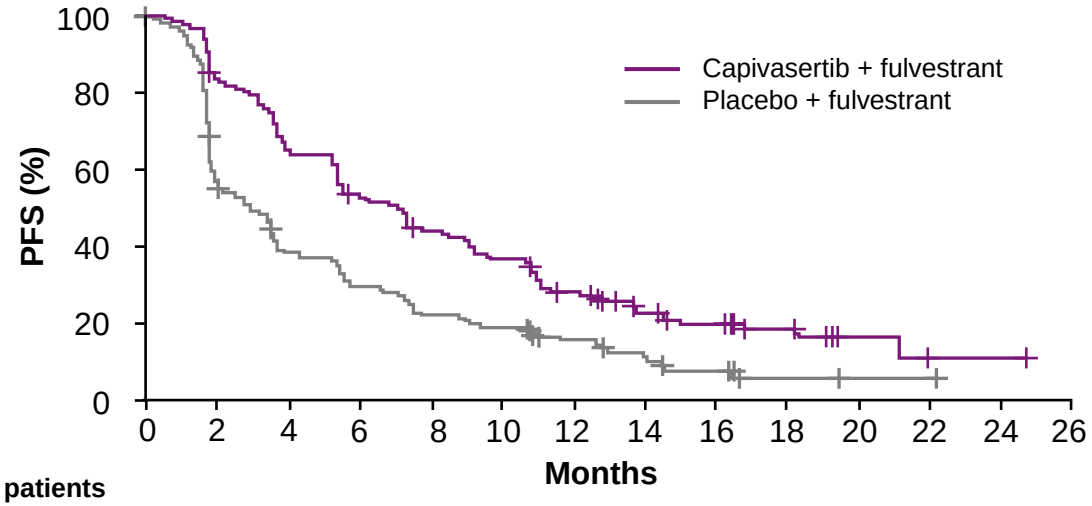
[a]5.9% of patients had received prior CDK4/6 inhibitor therapy for mBC.

ALPE, alpelisib; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; (m)PFS, (median) progression-free survival; mBC, metastatic breast cancer; mut, mutation; PBO, placebo; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; wt, wild type.

1. André F, et al. *N Engl J Med*. 2019;380:1929–1940; 2. Chia S, et al. ASCO 2023. Abstract P1078; 3. Turner S, et al. SABCS 2021. PD15-01.

# CAPItello-291: Reduced mPFS benefit for capivasertib + fulvestrant with prior CDK4/6 inhibitor exposure as well as with prior chemo

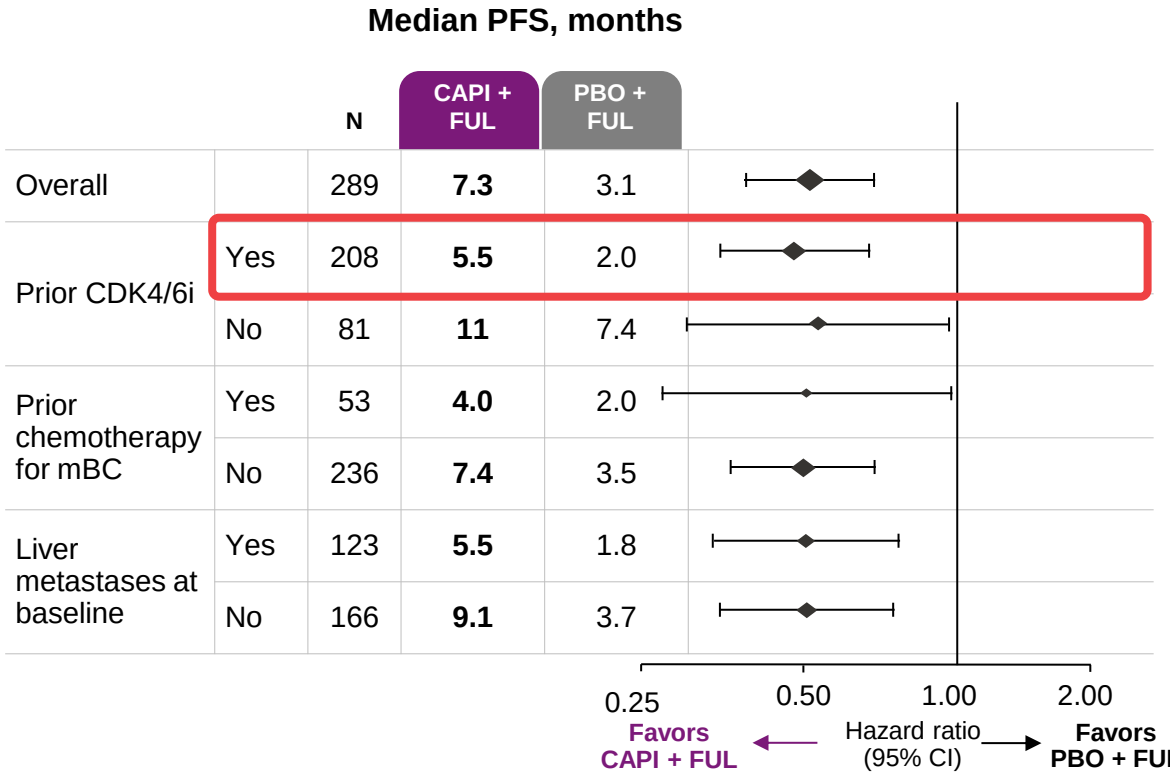
## CAPitello-291: AKT pathway–altered tumors[1]




| No. of patients | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CAPI + FUL | 155 | 127 | 99 | 80 | 65 | 54 | 38 | 26 | 21 | 12 | 3 | 2 | 1 | 0 |
| PBO + FUL | 134 | 77 | 48 | 37 | 28 | 24 | 17 | 11 | 6 | 2 | 1 | 1 | 0 | 0 |

| | CAPI + FUL (n=155) | PBO + FUL (n=134) |
|---|---|---|
| **mPFS, mo[1]** | **7.3** | **3.1** |
| [95% CI] | [5.5–9.0] | [2.0–3.7] |
| **Adjusted HR** | **0.50** | |
| [95% CI] | [0.38–0.65] | |
| **p-value** | <0.001 | |

## CAPitello-291: Impact of prior CDK4/6i therapy[2]




**Data on *ESR1* mutations are not available**

AKT, protein kinase B; CAPI, capivasertib; CDK4/6, cyclin-dependent kinase 4/6 inhiibitor; CI, confidence interval; FUL, fulvestrant; *ESR1*, estrogen receptor 1 gene; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression free survival; mut, mutation; PBO, placebo.

1. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070; 2. Oliveira M., et al. *Ann Oncol*. 2023;8:101223–101223. Poster 187O.

# Safety of ET combination regimens for second-line+, ER+/HER2− mBC

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***

| | mTOR inhibitors + ET | | *PIK3CA* inhibitors + ET | | AKT-pathway[a] inhibitors + ET | |
|---|---|---|---|---|---|---|
| | Everolimus[1] | | Alpelisib[2] | | Capivasertib[3] | |
| | All grades | Grade 3/4 | All grades | Grade 3/4 | All grades | Grade 3/4 |
| **Adverse event incidence for combinations, %** | | | | | | |
| Neutropenia | – | – | – | – | – | – |
| Leukopenia | – | – | – | – | – | – |
| Anemia | 16 | 6 | – | – | 10 | 2 |
| **Stomatitis** | **56** | **8** | **25** | **3** | **15** | **2** |
| **Rash** | **36** | **1** | **36** | **10** | **38** | **12** |
| **Diarrhea** | **30** | **2** | **58** | **7** | **72** | **9** |
| **Hyperglycemia** | **13** | **4** | **64** | **33** | **16** | **2** |
| Fatigue | 33 | 4 | 24 | 4 | 21 | 1 |
| Nausea | 29 | 0 | 45 | 3 | 35 | 1 |
| **Discontinuation rate, %** | **19** | | **25** | | **13** | |

**PI3K/AKT/mTOR pathway inhibitors** are associated with Grade 3/4 diarrhea, rash, hyperglycemia and stomatitis

[a]*PIK3CA/AKT1/PTEN*.

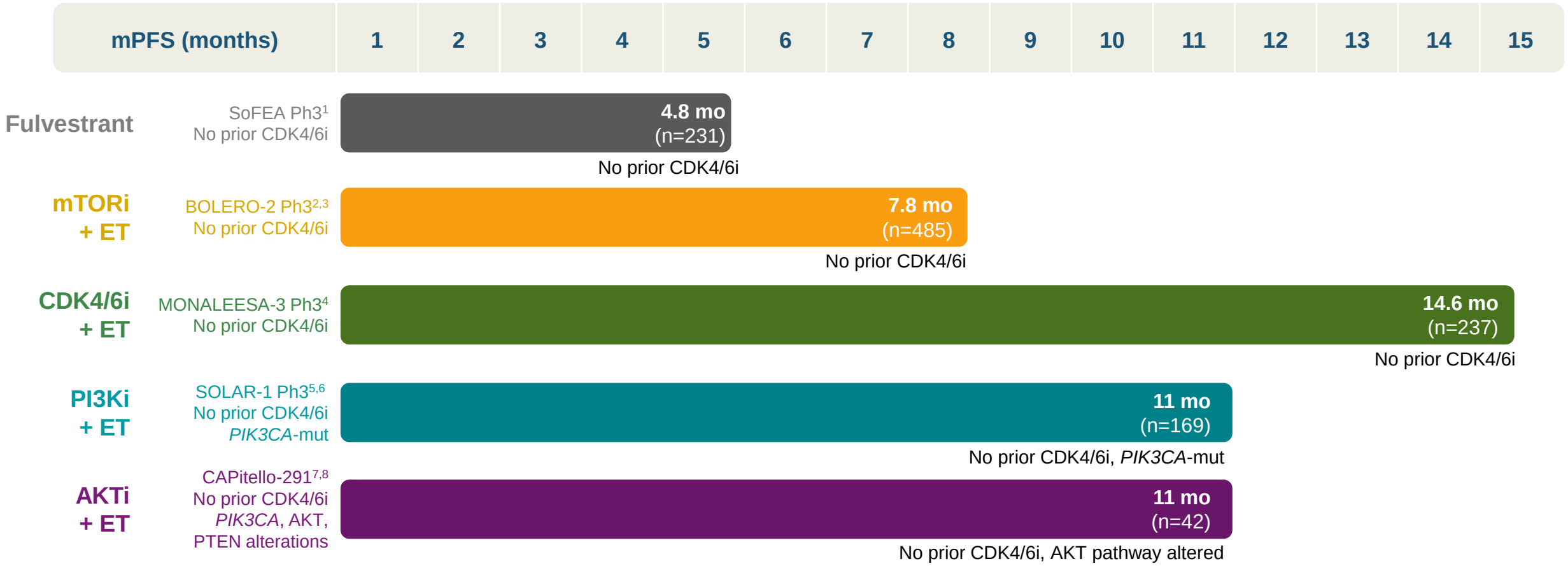
AKT, protein kinase B; ET, endocrine therapy; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; ; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog.

1. Baselga J, et al.*N Engl J Med*. 2012;366:520-529; 2. Andre F, et al. *N Engl J Med*. 2019;380:1929–1940; 3. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070.

# Summary - Efficacy of 2L+ ET regimens for ER+/HER2- mBC with no prior CDK4/6 inhibitor therapy

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***

**No prior CDK4/6i**



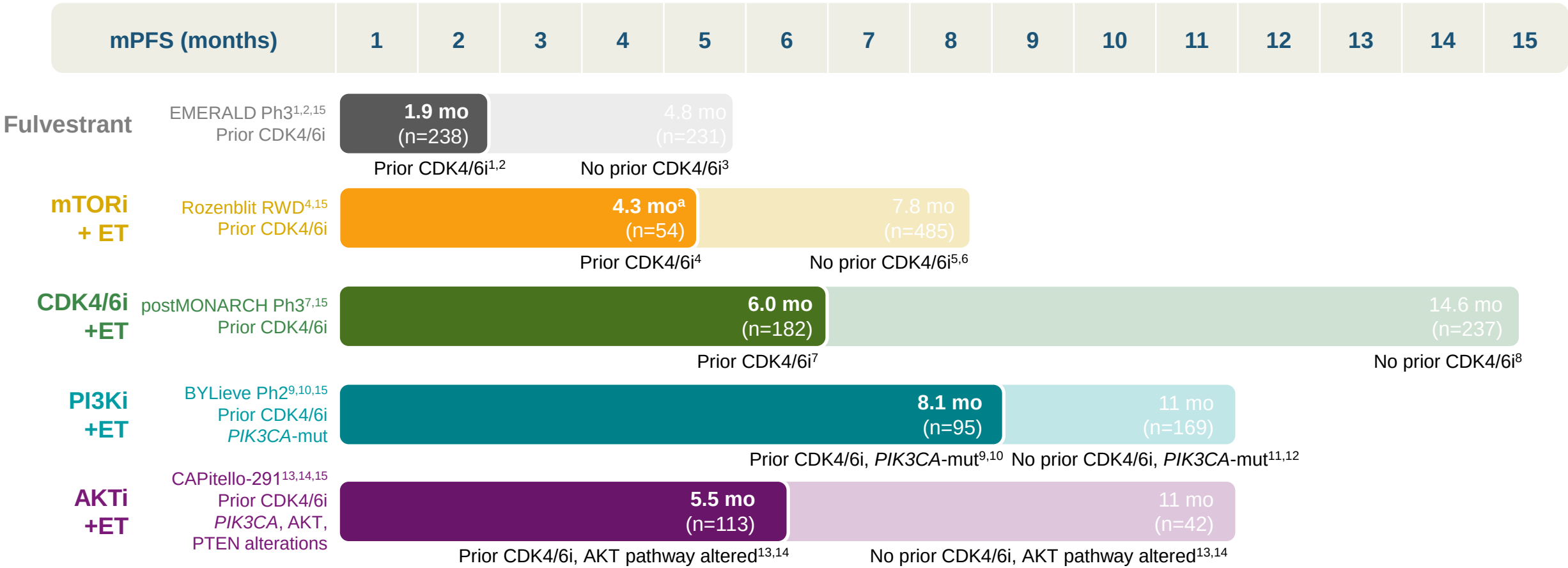

mPFS of studies represent n of intervention group.

2L, second line, AKT(i), protein kinase B (inhibitor); ET, endocrine therapy; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; mPFS, median progression-free survival; mut, mutation; mTORi, mammalian target of rapamycin inhibitor; PI3Ki, phosphoinositide 3-kinase inhibitor; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog.

1. Johnston SR, et al. *Lancet Oncol*. 2013;14:989-998; 2. Afinitor (everolimus) SmPC 2022; 3. Baselga J, et al. *N Engl J Med*. 2012;366:520–529; 4. Slamon DJ, et al. *N Engl J Med*. 2020; 382:514–524; 5. Piqray (alpelisib) SmPC 2023; 6. Andre F, et al. *N Engl J Med*. 2019; 380:1929-1940; 7. Oliveira M., et al. *Ann Oncol*. 2023;8:101223–101223. Poster 187O; 8. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070.

# Summary - PFS duration is consistently lower in patients with prior CDK4/6 inhibitor therapy

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***




mPFS of studies represent n of intervention group.

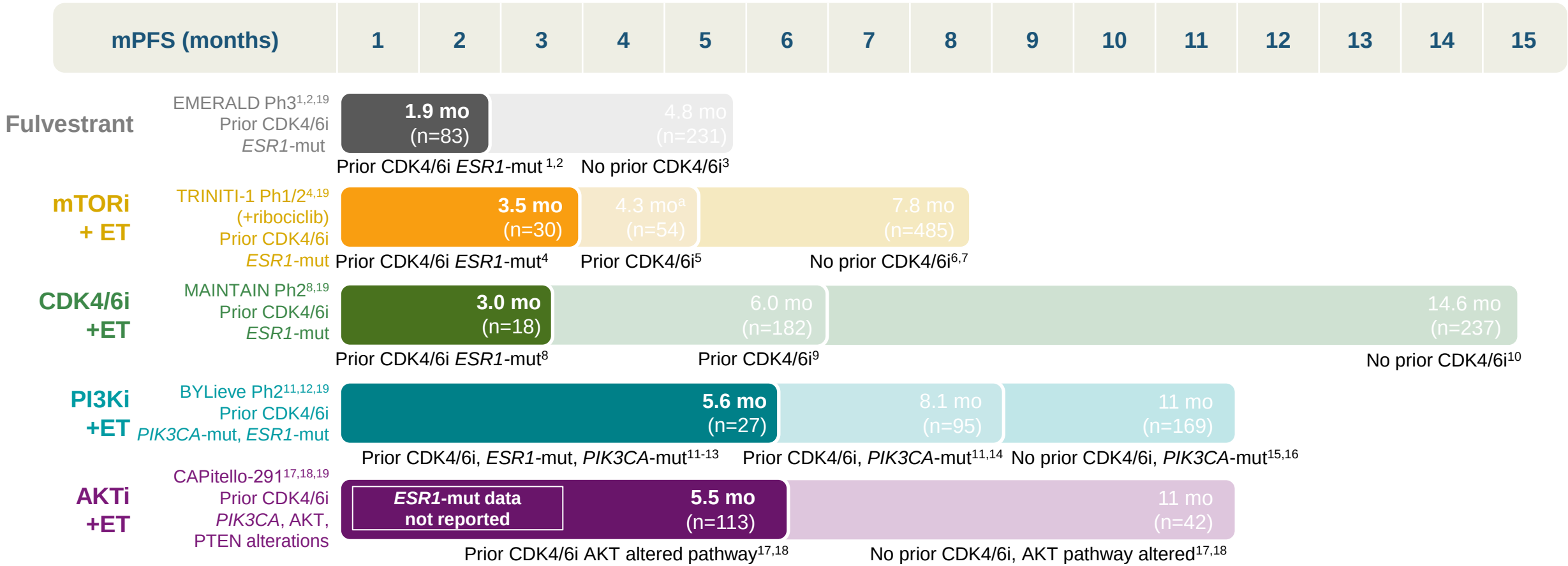
[a]Time to next treatment. AKT(i), protein kinase B (inhibitor); CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; FUL, fulvestrant; mTORi, mammalian target of rapamycin inhibitor; mut, mutated; (m)PFS, (median) progression-free survival; PI3Ki, phosphoinositide 3-kinase inhibitor; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog.

1. Orserdu (elacestrant) SmPC 2023; 2. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256; 3. Johnston SR, et al. *Lancet Oncol*. 2013;14:989-998; 4. Rozenblit M, et al. *Breast Cancer Res*. 2021;23:14; 5. Afinitor (everolimus) SmPC 2022; 6. Baselga J, et al. *N Engl J Med*. 2012;366:520-529; 7. Kalinsky K, et al. ASCO 2024. Abstract LBA1001; 8. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524; 9. Rugo HS, et al. *Lancet Oncol*. 2021;22:489-498; 10. Chia S, et al. *J Clin Oncol.* 2023;41(suppl 16). Abstract 1078; 11. Piqray (alpelisib) SmPC 2023; 12. Andre F, et al. *N Engl J Med*. 2019;380:1929-1940; 13. Oliveira M, et al. Ann Oncol. 2023;8:101223-101223. Poster 187O; 14. Turner NC et al. *N Engl J Med*. 2023;388:2058-2070; 15. Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309.

# Summary - PFS duration is consistently lower in patients with prior CDK4/6 inhibitor therapy and *ESR1*-mut

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***

**Prior ET + CDK4/6i AND *ESR1*-mut**

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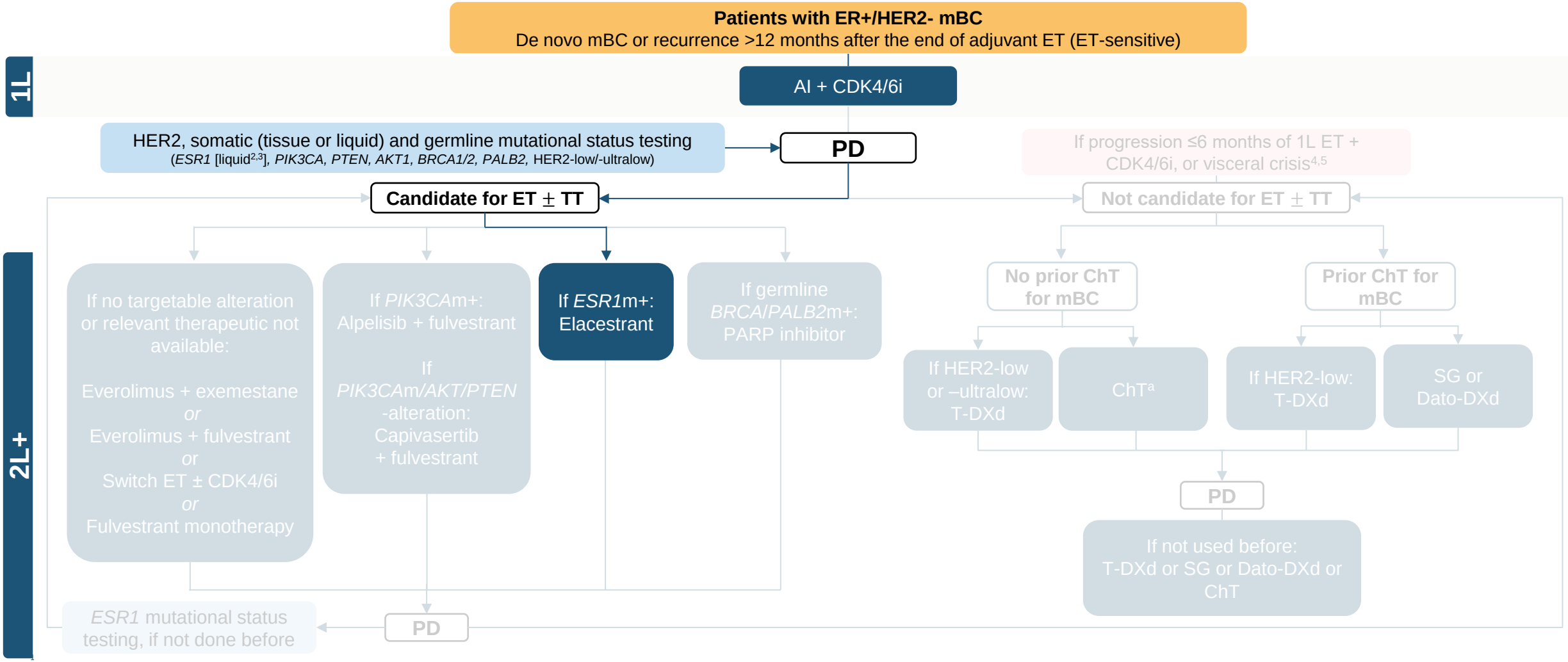
1. Orserdu (elacestrant) SmPC 2023; 2. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256; 3. Johnston SR, et al. *Lancet Oncol*. 2013;14:989-998; 4. Bardia A, et al. *Clin Cancer Res*. 2021;27:4177-4185; 5. Rozenblit M, et al. *Breast Cancer Res*. 2021;23:14; 6. Afinitor (everolimus) SmPC 2022; 7. Baselga J, et al. *N Engl J Med*. 2012;366:520-529; 8. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004-4013; 9. Kalinsky K, et al. ASCO 2024. Abstract LBA1001; 10. Slamon DJ, et al. *N Engl J Med*. 2020; 382:514-524; 11. Rugo HS, et al. *Lancet Oncol*. 2021;22:489-498; 12.Turner N, et al. SABCS 2021. Abstract PD15-01; 13. Fillbrunn M, et al. *BMC Cancer*. 2022;22:1002. 14. Chia S, et al. *J Clin Oncol*. 2023;41(suppl 16). Abstract 1078; 15. Piqray (alpelisib) SmPC 2023; 16. Andre F, et al. *N Engl J Med*. 2019; 380:1929-1940; 17. Oliveira M, et al. *Ann Oncol*. 2023;8:101223-101223. Poster 187O; 18. Turner NC, et al. *N Engl J Med*. 2023;388:2058-2070. 19. Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309.

# Second-line treatment choice is defined by the eligibility to receive endocrine therapy and driven by biomarker status[1,2]




[a]Taxane–bevacizumab or capecitabine–bevacizumab. 1/2L , first/second line; AI, aromatase inhibitor; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; mBC, metastatic breast cancer; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; SG, sacituzumab govitecan; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

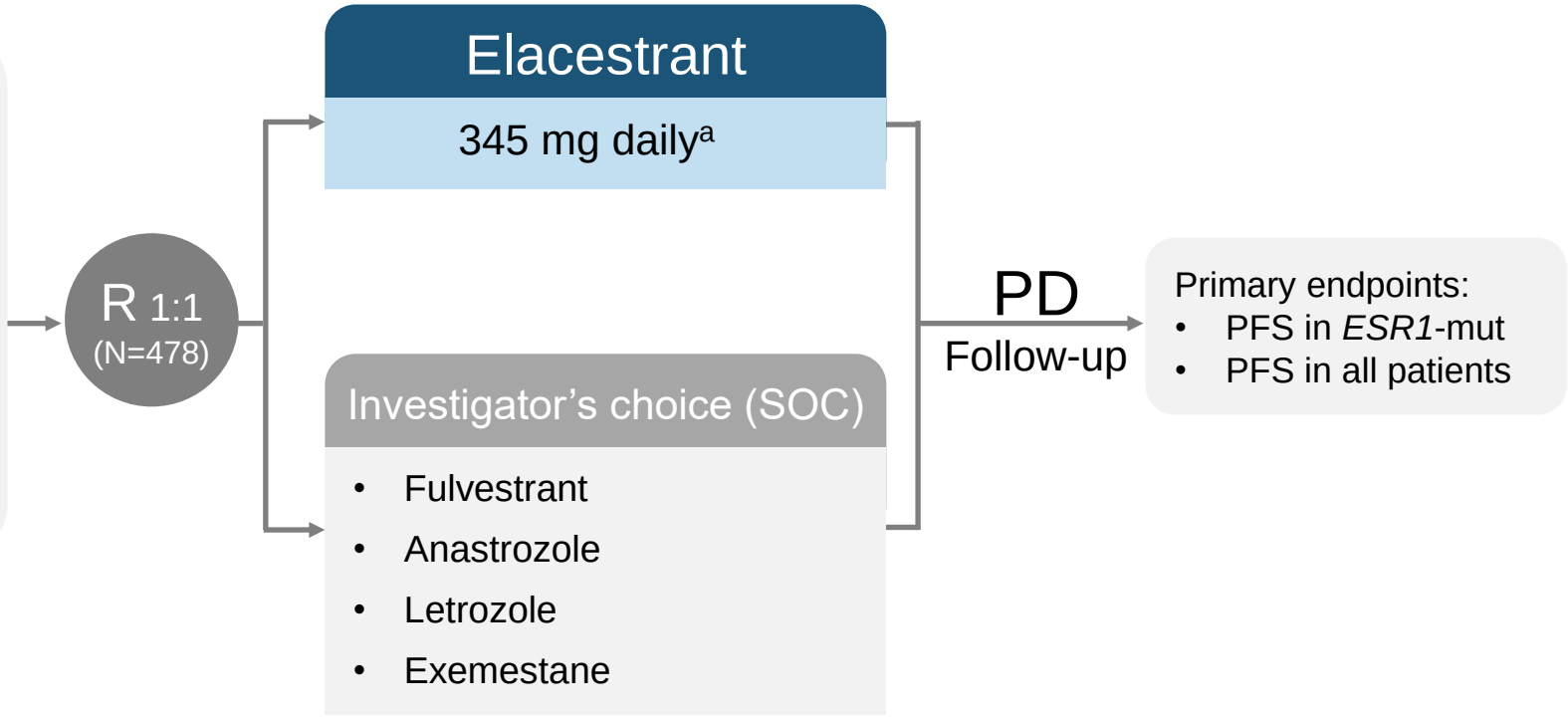
Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed April 2025); 2. Burstein HJ, et al. J Clin Oncol. 2023;41(18):3423-3425; 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2025. © *National Comprehensive Cancer Network*, Inc. 2024. All rights reserved. Accessed March 18, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 4. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110-2122; 5. Cardoso F, et al. *Breast*. 2024:76:103756.

# EMERALD: Phase 3 trial of elacestrant vs SOC endocrine therapy[1]

**100% of patients HAD received prior CDK4/6i therapy**

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

Stratification factors
- *ESR1*-mut status
- Presence of visceral metastases
- Prior treatment with fulvestrant




[a]345 mg of elacestrant is equivalent to 400 mg of elacestrant dihydrochloride.
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; *ESR1,* estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mut, mutation; PD, progressive disease; PFS, progression-free survival; R, randomization; SOC, standard of care.

1.Bidard FC, et al. *J Clin Oncol.* 2022;40:3246–3256.

# EMERALD trial baseline characteristics[1]

| | Elacestrant (N=115) | | SOC | |
|---|---|---|---|---|
| | All (N=239) | *ESR1*-mut (N=115) | All (N=239) | *ESR1*-mut (N=113) |
| Median age, years (range) | 63 (24-89) | 64 (28-89) | 63 (32-83) | 63 (32-83) |
| Female, n (%) | 233 (97.5) | 115 (100) | 238 (99.6) | 113 (100) |
| ECOG PS, n (%) | | | | |
| 0 | 143 (59.8) | 67 (58.3) | 135 (56.5) | 62 (54.9) |
| 1 | 96 (40.2) | 48 (41.7) | 103 (43.1) | 51 (45.1) |
| Visceral metastasis[a], n (%) | 163 (68.2) | 81 (70.4) | 170 (71.1) | 84 (74.3) |
| Prior CDK4/6i, n (%) | 239 (100) | 115 (100) | 239 (100) | 113 (100) |
| No. of prior lines of ET in the advanced or metastatic setting, n (%) | | | | |
| 1 | 129 (54.0) | 73 (63.5) | 142 (59.4) | 69 (61.1) |
| 2 | 110 (46.0) | 42 (36.5) | 97 (40.6) | 44 (38.9) |
| Prior therapies for advanced or metastatic disease, n (%) | | | | |
| Fulvestrant | 70 (29.3) | 27 (23.5) | 75 (31.4) | 28 (24,8) |
| Aromatase inhibitor | 193 (80.8) | 101 (87.8) | 194 (81.2) | 96 (85.0) |
| Tamoxifen | 19 (7.9) | 9 (7.8) | 15 (6.3) | 9 (8.0) |
| No. of prior lines of chemotherapy in the advanced or metastatic setting, n (%) | | | | |
| 0 | 191 (79.9) | 89 (77.4) | 180 (75.3) | 81 (71.7) |
| 1 | 26 (20.1) | 26 (22.6) | 59 (24.7) | 32 (28.3) |

[a]Includes lung, liver, brain, pleural, and peritoneal involvement.

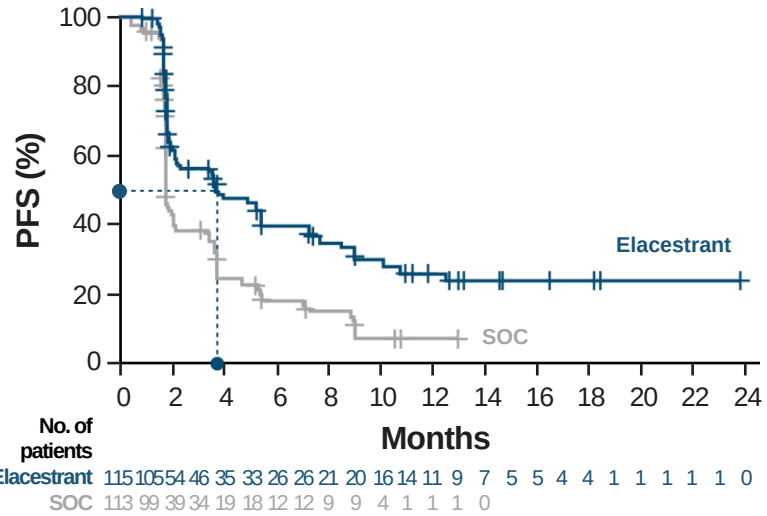
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; mut, mutation; SOC, standard of care.

1. Adapted from Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256.

# EMERALD: Elacestrant provides improved PFS results vs SOC in patients with *ESR1* mutations

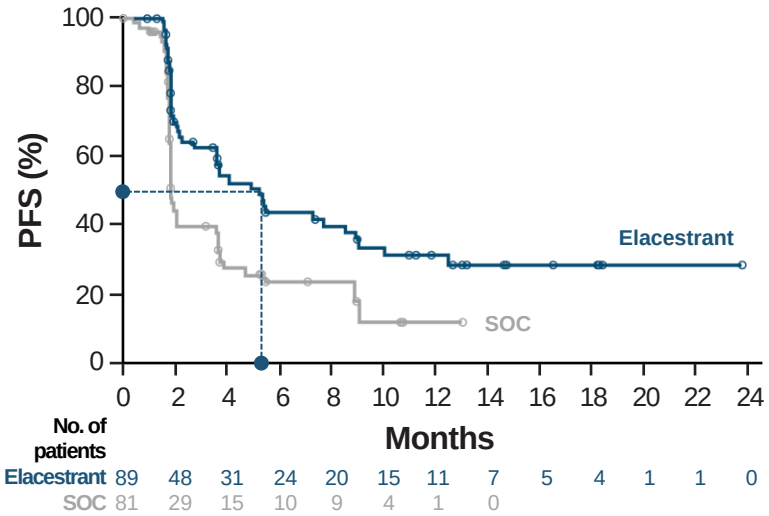
## 45% reduction in risk of progression or death[1]

PIVOTAL STUDY



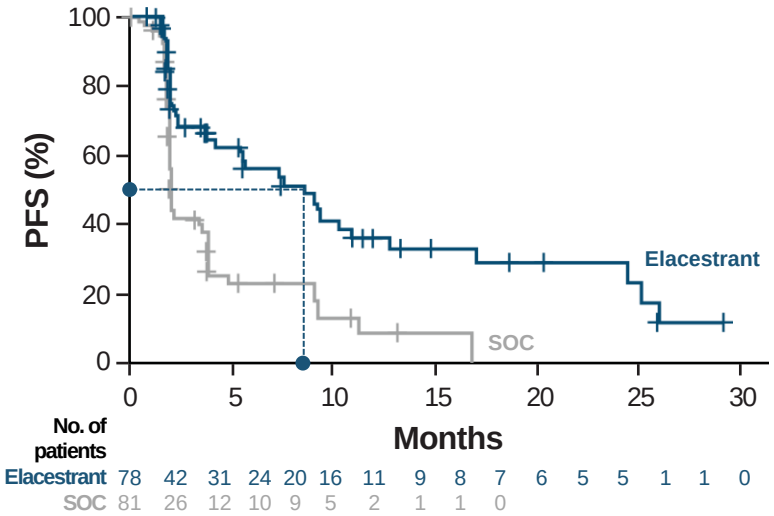

| | Elacestrant (n=115) | SOC (n=113) |
|---|---|---|
| **mPFS, mo** | **3.8** | **1.9** |
| **HR** [95% CI] | **0.55** [0.39–0.77] | |
| **p-value** | 0.0005 | |

## Clinically meaningful PFS improvement in patients who did not receive prior chemotherapy[2]




| | Elacestrant (n=89) | SOC (n=81) |
|---|---|---|
| **mPFS, mo** [range] | **5.3** [3.7–9.0] | **1.9** [1.9–3.7] |
| **HR** [95% CI] | **0.54** [0.36–0.80] | |
| **p-value** | 0.00235 | |

## Post-hoc analysis: ≥12 months duration of prior ET + CDK4/6i therapy is positively associated with mPFS[3,4]




| | Elacestrant (n=78) | SOC (n=81) |
|---|---|---|
| **mPFS, mo** [95% CI] | **8.6** [4.1–10.8] | **1.9** [1.9–3.7] |
| **12-mo PFS, %** [95% CI] | **35.8** [21.8–49.8] | **8.39** [0.0–17.7] |
| **HR** [95% CI] | **0.41** [0.26–0.63] | |

[a]Calculated with covariates; [b]Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.

CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; *ESR1*, estrogen receptor 1 gene; (m)PFS, (median) progression-free survival; mut, mutation; SOC, standard of care.

1. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256; 2. Kaklamani V, et al. *J Clin Oncol.* 2022;40(16 suppl). Abstract 1100; 3. Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309; 4. Bardia A, et al. SABCS 2022. Abstract GS3–01.

# In tumors with retained endocrine-sensitivity (longer exposure to prior ET + CDK4/6i), *ESR1* mutations are a main driver of disease[1,2]

| ***Patients with ≥12 months of prior ET + CDK4/6i*** | **% (n)** | **Elacestrant** mPFS, months | **SOC** mPFS, months | **HR** [95% CI] |
|---|---|---|---|---|
| **All *ESR1*-mut patients** | **100** (159) | **8.6** | **1.9** | **0.41** [0.26–0.63] |
| *PIK3CA*-mut[a] | **39** (62) | **5.5** | **1.9** | **0.42** [0.18–0.94] |
| Bone metastases[b] | **86** (136) | **9.1** | **1.9** | **0.38** [0.23–0.62] |
| Liver and/or lung metastases[c] | **71** (113) | **7.3** | **1.9** | **0.35** [0.21–0.59] |
| *TP53*-mut | **38** (61) | **8.6** | **1.9** | **0.30** [0.13–0.64] |
| HER2-low expression[d] | **48** (77) | **9.0** | **1.9** | **0.30** [0.14–0.60] |
| High *ESR1* VAF | **50** (79) | **9.1** | **1.9** | **0.36** [0.19–0.69] |
| Low *ESR1* VAF | **50** (79) | **8.6** | **1.9** | **0.51** [0.26–0.99] |

**This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.**

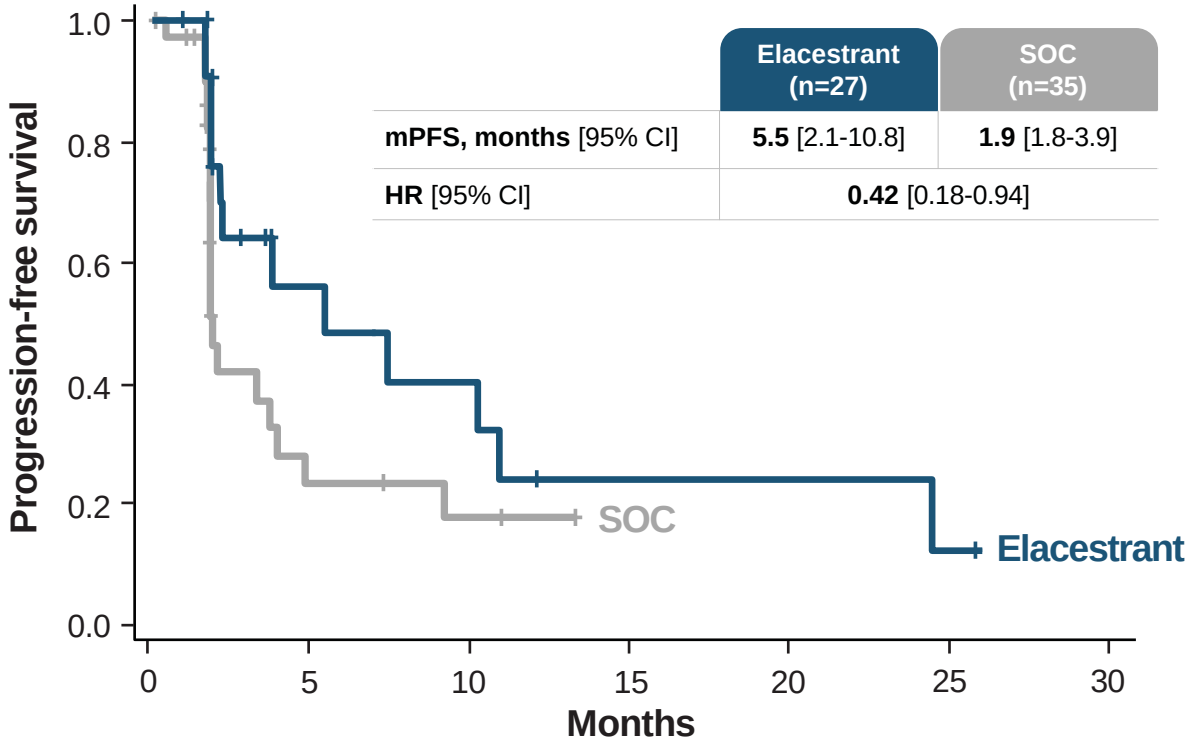
[a]Includes E545K, H1047R, E542K, and others; [b]85% of patients had bone and other sites of metastases (30% of these patients had no liver or lung involvement); [c]55% of patients had liver and other sites of metastases (10% of these patients had no lung or bone involvement); 25% of patients had lung and other sites of metastases (2% of these patients had no liver or bone involvement); [d]Locally assessed HER2 immunohistochemistry 1+, and 2+ with no in situ hybridization amplification; Data not available for all patients.

CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CI, confidence interval; *ESR1,* estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; (m)PFS, (median) progression-free survival; mut, mutation; VAF, variant allele frequency.

1.Bardia A, et al. *Clin Cancer Res.* 2024;30:4299-4309; 2. Bardia A, et al. SABCS 2024. P1-01-25.

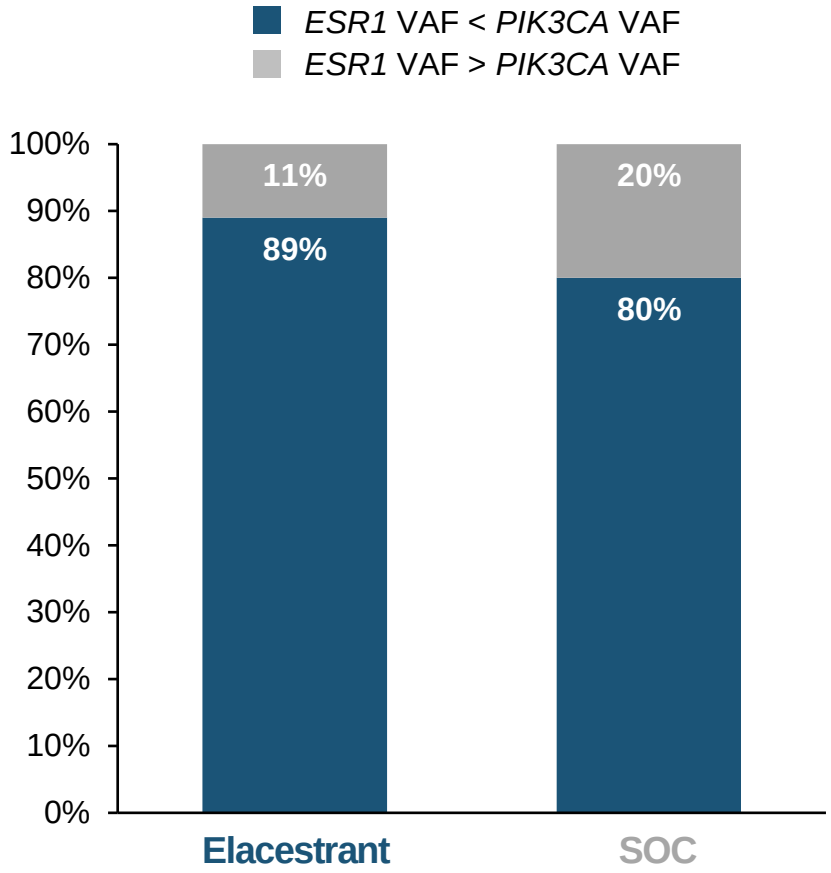
# Elacestrant was associated with a longer PFS compared with SOC even though 89% of *ESR1* mutations were characterized by having a lower VAF compared to *PIK3CA* VAF[1,2]

## Post-hoc analysis: Prior ET + CDK4/6i ≥12 months with the coexistence of *ESR1*-mut and *PIK3CA*-mut tumors




| | Elacestrant (n=27) | SOC (n=35) |
|---|---|---|
| **mPFS, months** [95% CI] | **5.5** [2.1-10.8] | **1.9** [1.8-3.9] |
| **HR** [95% CI] | **0.42** [0.18-0.94] | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Elacestrant** | 27 | 13 | 7 | 6 | 6 | 5 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 |
| **SOC** | 35 | 10 | 6 | 5 | 5 | 3 | 1 | 0 | | | | | | |




**This was an exploratory analysis. Post-hoc analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.**

[a]Includes E545K, H1047R, E542K, and others.

CDK4/6, cyclin dependent kinase 4/6; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; mPFS, median progression-free survival; mut, mutation; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; SOC, standard of care.

1. Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309; 2. Bardia et al SABCS 2024. P1-01-25.

# EMERALD: Safety[1]

*Most common adverse events ≥ 10% in either arm in the overall population[1]*

| | Elacestrant (n=237) | | SOC (n=230) | |
|---|---|---|---|---|
| **Adverse events[1,a]** | **All grades (%)** | **Grade ≥3 (%)** | **All grades (%)** | **Grade ≥3 (%)** |
| Nausea | 35 | 2.5 | 19 | 0.9 |
| Vomiting[b] | 19 | 0.8 | 9 | 0 |
| Diarrhea | 13 | 0 | 10 | 1 |
| Constipation | 12 | 0 | 6 | 0 |
| Abdominal pain[b] | 11 | 1 | 10 | 0.9 |
| Dyspepsia | 10 | 0 | 2.6 | 0 |
| Fatigue[b] | 26 | 2 | 27 | 1 |
| Decreased appetite | 15 | 0.8 | 10 | 0.4 |
| Headache | 12 | 2 | 12 | 0 |
| Hot flush | 11 | 0 | 8 | 0 |

| **Nausea summary[1]** | **Elacestrant (n=237)** | **SOC (n=230)** |
|---|---|---|
| Grade 3 nausea, % | 2.5 | 0.9 |
| Dose-reduction rate due to nausea, % | 1.3 | NA |
| Discontinuation rate due to nausea, % | 1.3 | 0 |
| Antiemetic use*, % | 8.0 | 10.3 (AI)<br>3.7 (fulvestrant) |

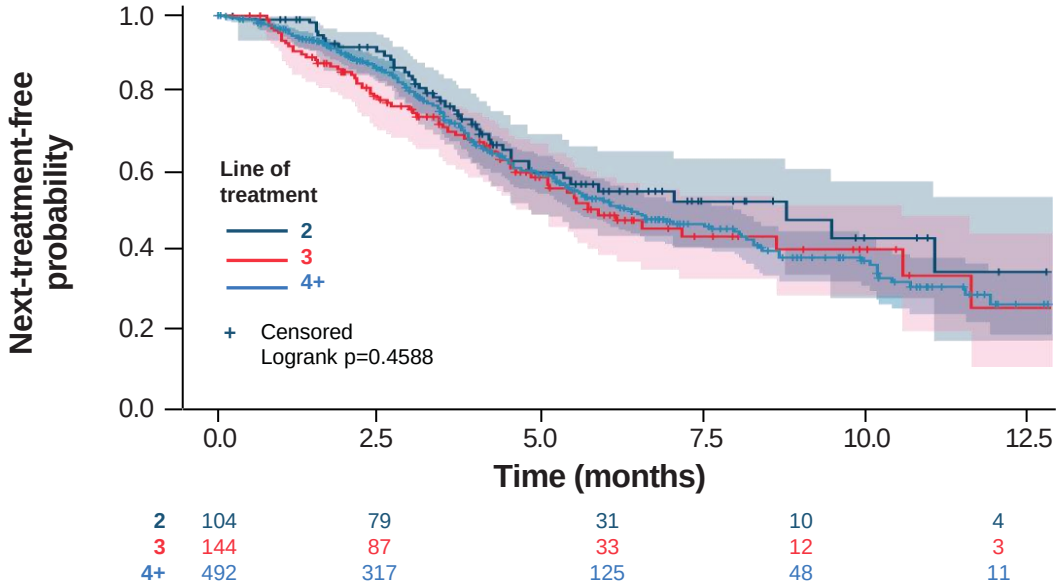
Nausea was generally reported early, with a median time to first onset of 14 days.[2]
*Patients may have been on antiemetics prior to enrollment.[1]

- No grade 4 treatment-related AEs were reported[1]
- Treatment-related AEs leading to discontinuation were 3.4% and 0.9% in the elacestrant and SOC arms, respectively[1]
- No hematologic safety signal was observed, and none of the patients in either treatment arm had sinus bradycardia[1]

[a]Adverse events were graded using NCI CTCAE version 5.0; [b]Includes other related terms.
AI, aromatase inhibitor; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SOC, standard of care (fulvestrant or aromatase inhibitor).
1. Bardia A, et al. *Clin Cancer Res.* 2024;30(19):4299–4309; 2. Stemline. ORSERDU (elacestrant) SmPC. 2024.

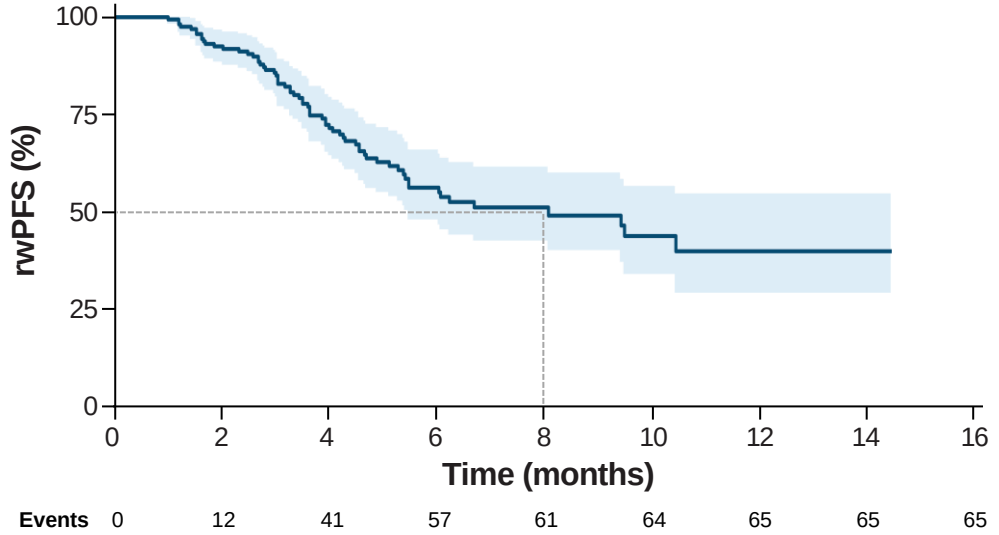
# RWE elacestrant data shows consistent rwTTNT and rwPFS benefit among clinically relevant subgroups

**Lloyd et al. GUARDANT INFORM (n=742)**
**rwTTNT:1–2 prior lines of ET[1]**




| | 2L (n=104) | 3L (n=144) |
|---|---|---|
| Event | 42 | 62 |
| Median rwTTNT, mo [95% CI] | **8.8** [4.8-NR] | **5.9** [4.6-10.6] |

**Swallow et al. KRD US Claims (n=276)**
**rwPFS: 1–2 prior lines of ET[2]**




| | 2/3L (n=166) |
|---|---|
| Events, n (%) | 65 |
| Median rwPFS, mo [95% CI] | **8.0** [5.5-NR] |

**This was an exploratory analysis. RWE analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.**
2/3L,second/third line; CI, confidence interval; ET, endocrine therapy; NR, not reached; RWE, real world evidence; rwPFS, real world progression-free survival; rwTTNT, real world time to next treatment.
1. Adapted from Lloyd M, et al. SABCS 2024. Abstract PS7-05; 2. Swallow et al. SABCS 2024. Abstract P3 10-08.

# RWE elacestrant data shows consistent ~8-9 months benefit in line with the 8.6 months in patients with longer prior CDK4/6i (>12 mo) from the EMERALD subgroup analysis

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***

| | Bardia et al, EMERALD CCR (n=78)[1] | Lloyd et al, Guardant Inform (n=742)[2] | Swallow et al, Komodo Claims (n=276)[3] |
|---|---|---|---|
| **Baseline Characteristics** | | | |
| Prior CDK4/6i in mBC | 100% | 83% | 90% |
| Prior CDK4/6i for >12 mo | 100% | - | 88% |
| Prior fulvestrant in mBC | 23% | 53% | 61% |
| Prior chemo in mBC | 20% | 41% | 33% |
| **Efficacy** | *mPFS (months)* | *mTTNT (months)* | *rwPFS (months)* |
| **2L** | **–** | **8.8** | **–** |
| **2-3L** | **8.6** | **–** | **8.0** |

**This was an exploratory analysis. RWE analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.**

2L, second line; 3L, third line; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; mBC; metastatic breast cancer; mPFS, median progression-free survival; mo, months; RWE, real world evidence; rwPFS, real world progression-free survival; mTTNT, median time to next treatment.

1. Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309; 2. Lloyd M, et al. SABCS 2024. Abstract PS7-05; 3. Swallow E, et al. SABCS 2024. Abstract P3 10-08.

# RWE elacestrant monotherapy shows consistent data with AKT/PI3K inhibitors in patients with both *ESR1* and *PIK3CA* co-existing mutations

***Comparisons of efficacy and safety should not be drawn or inferred in the absence of head-to-head studies***

| | Bardia et al, EMERALD CCR (n=27)[1] *mPFS (months)* | Lloyd et al, Guardant Inform (n=234)[2] *mTTNT (months)* | Rugo et al, BYLieve (n=27)[3] *mPFS (months)* | Turner et al, CAPItello-291 (n=113)[4] *mPFS (months)* |
|---|---|---|---|---|
| **Prior CDK4/6i Only AKT/*PIK3CA*-mut** | N/A | N/A | **8.1** | **5.5** |
| **Prior CDK4/6i *PIK3CA*-mut *AND* *ESR1*-mut** | **5.5** | **5.2** | **5.6** | N/A |

**This was an exploratory analysis. RWE analysis results are observational in nature. There was no prespecified statistical procedure controlling for type 1 error.**

AKT, protein kinase B; *ESR1,* estrogen receptor 1; mPFS, median progression-free survival; mTTNT, median real-world time to next treatment; mut, mutation; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RWE, real-world evidence.

1. Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309; 2. Lloyd M, et al. SABCS 2024. Abstract PS7-05; 3. Rugo H, et al. *Lancet Oncol*. 2021;22:489-498; 4. Turner NC, et al. *N Engl J Med.* 2023;388:2058-2070.

# Key takeaways

**Second-line treatment** choices are defined by the **eligibility to receive endocrine therapy** and a driven by **biomarker status**. For patients with retained endocrine-sensitivity guidelines recommend exhausting sequential ET-based regimens in 2L+ settings[1]

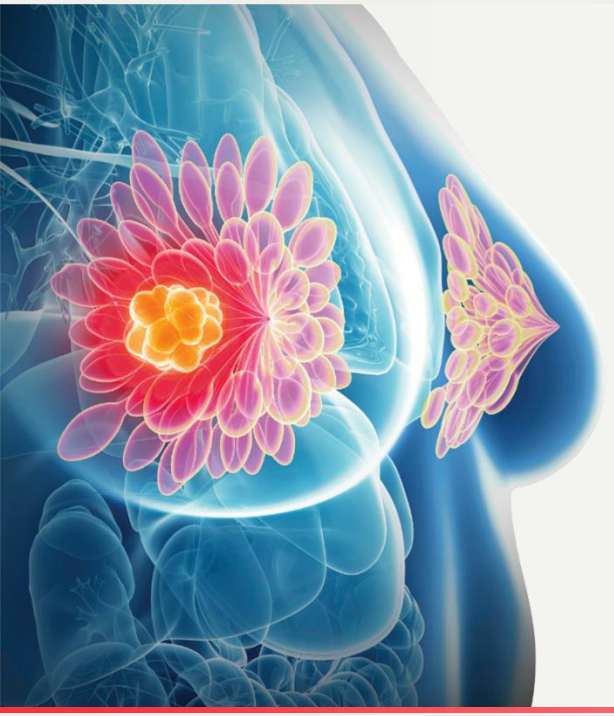
**CDK4/6 inhibitor rechallenge** shows **clinical benefit mainly after palbociclib** prior exposure. **Outcomes across studies are heterogeneous**[2-6]

**Real world evidence of single agent elacestrant** shows **improved results versus EMERALD** study, reflecting its **use in the endocrine sensitive population**[7-10]

**In tumors retaining endocrine-sensitivity and coexisting *PIK3CA* and *ESR1* mutations**, **elacestrant monotherapy** can be a good option before PI3K/AKT inhibitors as **data shows similar efficacy with a manageable safety profile**[8]

2L, second line; AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1,* estrogen receptor 1 gene; ET, endocrine therapy; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RWE, real-world evidence.

1. Gennari A, et al. *Ann Oncol.* 2021;32: 1475-1495; 2. Kalinsky K, et al. *J Clin Oncol.* 2023;41:4004-4013; 3. Mayer EL, et al. *J Clin Oncol*. 2024;42:2050-2060; 4. Llombart-Cussac A, et al. *J Clin Oncol*. 2023;41:S1001–S1001 (oral presentation); 5. Kalinsky K, et al. *J Clin Oncol.* 2024;42. Abstract LBA1001; 6. Jhaveri KL, et al. *N Engl J Med*. 2025;392:1189-1202; 7. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246-3256; 8. Bardia A, et al. *Clin Cancer Res*. 2024;30:4299-4309; 9. Lloyd M, et al. SABCS 2024. Abstract PS7-05; 10. Swallow E, et al. SABCS 2024. Abstract P3 10-08.



# Emerging Biomarkers in Metastatic BC

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Institut Jules Bordet, Hôpital Universitaire de Bruxelles

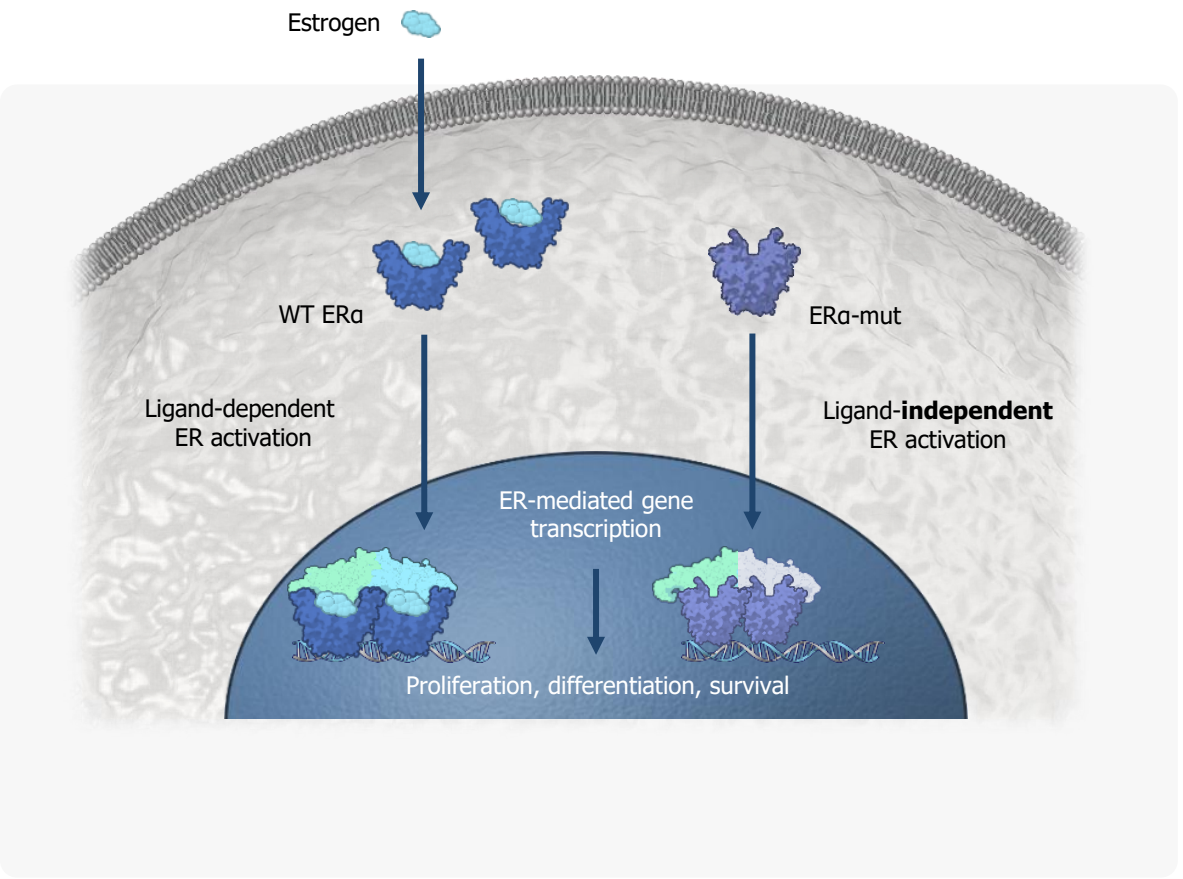
BC, breast cancer.

MENARINI group

Stemline® A Menarini Group Company

# *ESR1* mutations: A mechanism of acquired endocrine resistance

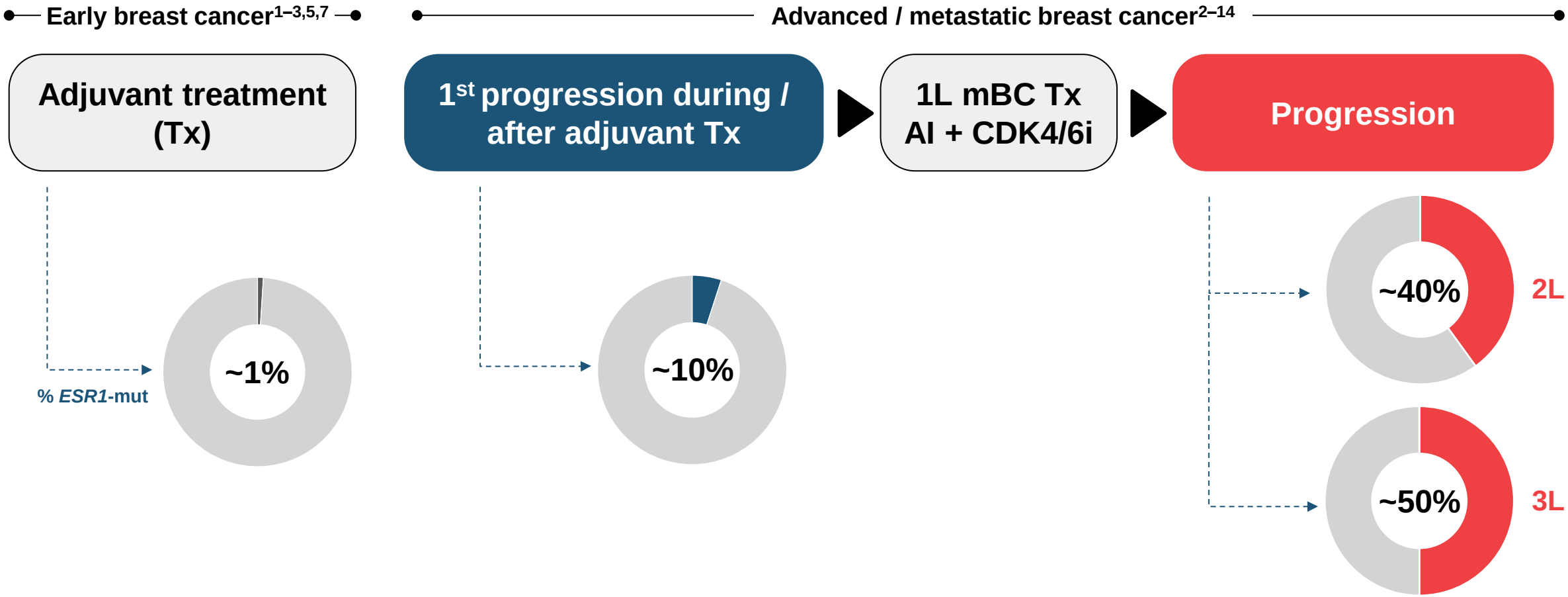
- *ESR1*-mut are:[1-8]
  - Acquired under the selective pressure of endocrine therapy (ET), particularly aromatase inhibitors, and are rarely detected in the primary tumor
  - Subclonal and heterogeneous within the tumor
  - Commonly affecting the ligand-binding domain of ERα, resulting in ligand-independent ERα activation and constitutive signaling.
  - One of the main mechanisms of endocrine resistance and a key driver of disease progression
- Other mutations may be present in ET-naïve breast cancer (e.g., *PIK3CA* and *BRCA* mutations)[5,9]




BRCA, breast cancer gene; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; mut, mutation/mutated; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; wt , wild type.

1.Clatot F, et al. *Breast Cancer Res*. 2020;22(1):56; 2. Chandarlapaty S, et al. *JAMA Oncol*. 2016;2(10):1310-1315; 3. Turner NC, et al. *Clin Cancer Res*. 2020;26(19):5172-5177; 4. Zundelevich A, et al. *Breast Cancer Res*. 2020;22(1):16; 5. Schiavon G, et al. *Sci Transl Med.* 2015;7(313):313ra182; 6. Tarabichi M, et al. *Nat Methods*. 2021;18(2):144-155; 7. Dustin D, et al. *Cancer.* 2019;125(21):3714-3728; 8. Brett JO, et al. *Breast Cancer Res*. 2021;23(1):85; 9. Lei JT, et al. *Breast*. 2019;48 Suppl 1(Suppl 1):S26-S30.

# Longer exposure to ET in mBC increases the chance of developing *ESR1* mutation during treatment[1-10]

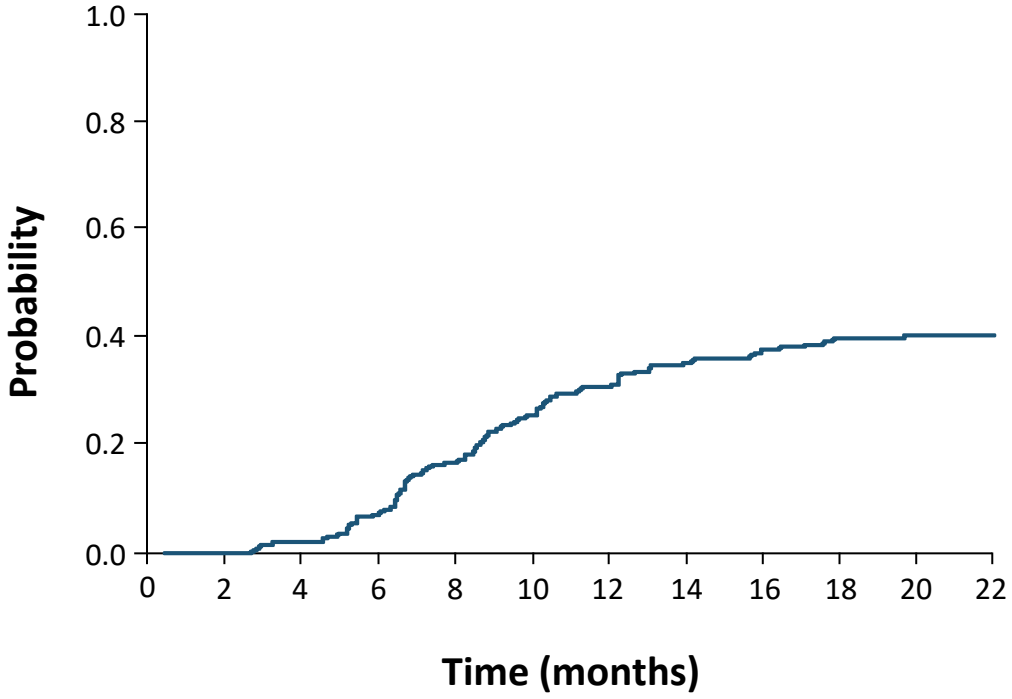



1/2/3L, first/second/third line; AI, aromatase inhibitor; AKT, protein kinase B; *BRCA1/2*, breast cancer gene 1/2; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; mBC, metastatic breast cancer; *mut*, mutation.

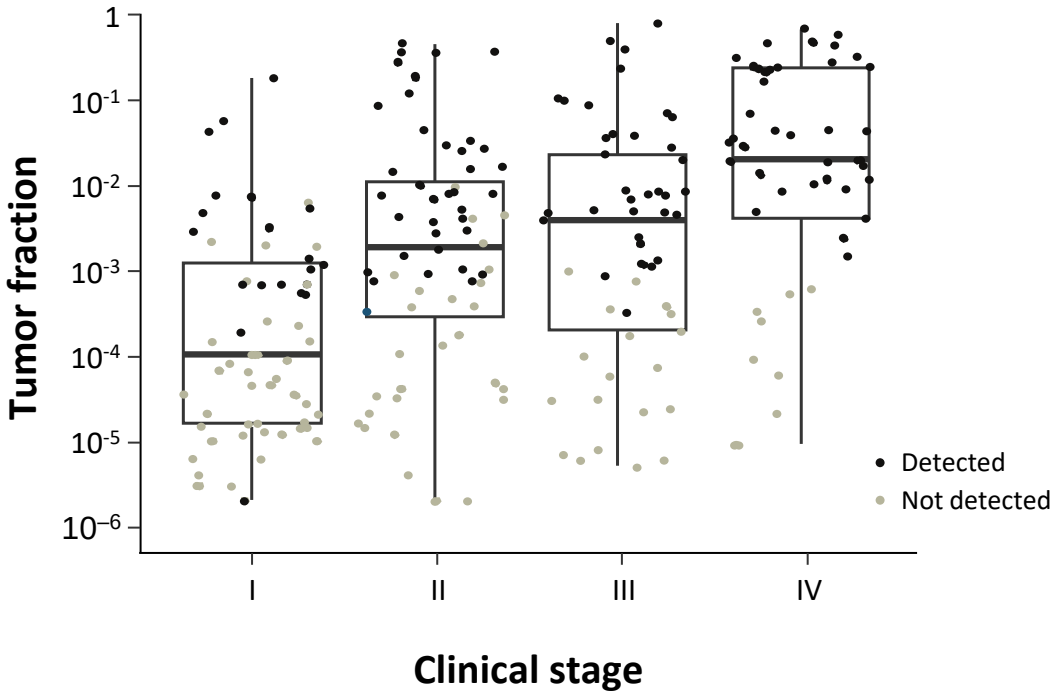
1.Jeselsohn R, et al. *Clin. Cancer Res.* 2014;20:1757–1767; 2.Allouchery V, et al. *Breast Cancer Res.* 2018;20:40; 3.Schiavon G, et al. *Sci. Transl. Med.* 2015;7(313):313ra182; 4.Brett JO, et al. *Breast Cancer Res.* 2021;23(1):85; 5.Toy W, et al. *Nat. Genet.* 2013;45(12):1439–1445; 6.Bidard FC, et al. *J. Clin. Oncol.* 2022;40:3246–3256; 7.Jhaveri K, et al. *Ann. Oncol.* 2023;34(suppl_2):S334–S390; 8.Lin N, et al. *Ann. Oncol.* 2023;34(suppl_2):S334–S390; 9.Bhave MA, et al. *Breast Cancer Res. Treat.* 2024; 10.Lee N, et al. *Int. J. Mol. Sci.* 2020;21(22):8807; 11.Kalinsky K, et al. *J Clin Oncol*. 2024;42: Abstract LBA1001; 12. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189-1202; 13. Miguel M. *J Clin Oncol.* 2024;42(18):2149-2160; 14. Tolaney SM, et al. *J Clin Oncol*. 2023;41(24):4014-4024.

# *ESR1* mutation can be identified in ctDNA at progression[1] ctDNA tumor fraction is associated with cancer aggressiveness[2]

## *ESR1*-mut cumulative incidence during 1L ET + CDK4/6i[3]




## ctDNA tumor fraction by cancer clinical stage[2]

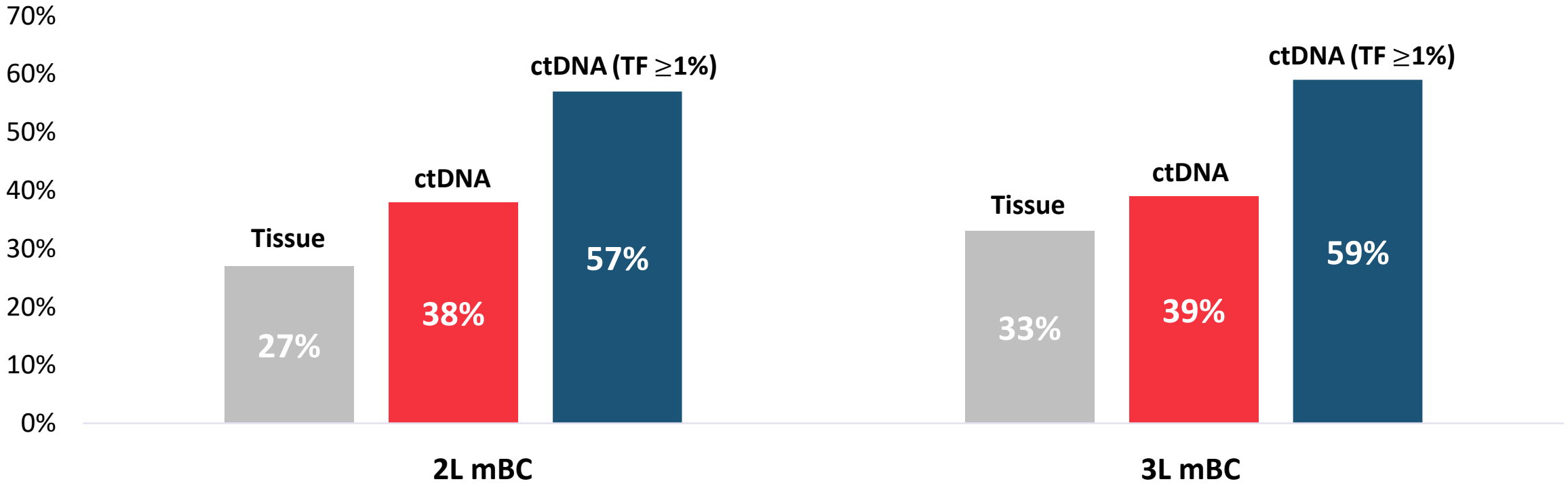



1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circular tumor DNA; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; mut, mutation.

1. Schiavon G, et al. Sci *Transl Med*. 2015;7:313ra182; 2. Bredno J, et al. *Am J Pathol*. 2022;192:1368–1378; 3. Adapted from Bidard F-C, ESMO 2019; Poster 307PD.

# *ESR1* mutations are subclonal and heterogenous within the tumor[1,2]

## *ESR1*-mut prevalence rate in mBC by line in tissue and liquid biopsies[3]




2/3L, second/third line; ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1 gene; mBC, metastatic breast cancer; mut, mutation; TF, tumor fraction.

1. Dustin D, et al. *Cancer*. 2019.1;125(21):3714-3728; 2. Burstein HJ, et al. *J Clin Oncol.* 2023;41(18):3423-3425; 3. Adapted from: Bhave MA, et al. *Breast Cancer Res Treat*. 2024;207:599-609.

# *ESR1* mutation testing: Tissue vs liquid biopsy

**Tissue Biopsy**[1-5]

- Low sensitivity for *ESR1*-mut
- Invasive
- Long turnaround time
- Given the subclonal and heterogeneous nature of *ESR1*-mut within the tumor, all mutations may not be detected
- Primary archival tissue should not be used, as *ESR1*-mut are typically acquired during the metastatic breast cancer treatment

**Liquid Biopsy**[1-3,6-8]

- High sensitivity for *ESR1*-mut
- Minimally invasive
- Fast sample acquisition
- Reveals tumor heterogeneity, including presence of subclonal *ESR1*-mut from all metastatic disease sites

**Available *ESR1*-mut detection methods include**[9,a]**:**

- NGS (may be part of a solid tumor panel)
- Digital PCR assays

[a]Physicians should use discretion to determine the appropriate test. Refer to diagnostic manufacturers' technical information to ensure ESR1 gene coverage.
*ESR1*, estrogen receptor 1 gene; mut, mutation.

1. Lone SN, et al. *Mol Cancer.* 2022;21(1):79; 2. Pascual J, et al. *Ann Onco*l. 2022;33(8):750-768; 3. Spoerke JM, et al. *Nat Commun.* 2016;7:11579; 4. Franken A, et al. *J Mol Dia*gn. 2020;22(1):111-121; 5. Gradishar WJ, et al. *J Natl Compr Canc Netw*. 2023;21(6):594-608; 6. Tarabichi M, et al. *Nat Methods*. 2021;18(2):144-155; 7. Dustin D, et al. *Cancer.* 2019;125(21):3714-3728; 8. Burstein HJ, et al. *J Clin Oncol*. 2023;41(18):3423-3425; 9. Lee N, et al. *Int J Mol Sci.* 2020;21(22):8807.

# When to test

**Patients should get tested for *ESR1*-mut at each progression on their metastatic treatment, if not detected previously.[1-5]**

ESMO

**European Society of Medical Oncology (ESMO)[1,2]**

- NGS of plasma or tissue biopsy should be carried out after resistance to ET in order to optimize the likelihood of **detecting *ESR1*-mut**

NCCN[3]

**National Comprehensive Cancer Network® (NCCN®)[3,4]**

- **Detection of *ESR1*-mut:** NGS or PCR (**ctDNA preferred**)
- Given the acquired nature of *ESR1*-mut during metastatic breast cancer treatment, **primary archived breast cancer tissue should NOT be used** as a source of tumor tissue for *ESR1*-mut testing

ASCO

**American Society of Clinical Oncology (ASCO)[5]**

- **Detection of *ESR1*-mut:** Blood-based **ctDNA is preferred** owing to greater sensitivity
- *ESR1*-mut develop in response to selection pressure during ET and are typically undetectable in the primary tumor
- Patients whose tumor or ctDNA tests remain *ESR1*-wt may warrant re-testing at subsequent progression(s) to determine if an *ESR1*-mut has arisen

ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; mBC, metastatic breast cancer; mut, mutation; NGS, next generation sequencing; PCR, polymerase chain reaction; wt, wild-type.

1. Mosele MF, et al. *Ann Oncol*. 2024;35(7):588-606; 2. Pascual J, et al. *Ann Oncol.* 2022;33(8):750-768; 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2025. © *National Comprehensive Cancer Network*, Inc. 2024. All rights reserved. Accessed March 18, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 4. Gradishar WJ, et al. *J Natl Compr Canc Netw*. 2023;21(6):594-608; 5. Burstein HJ, et al. *J Clin Oncol.* 2023;41(18):3423-3425.

# Key takeaways

Intrinsic alterations like ***BRCA* and *PIK3CA* mutations can be detected at the moment of disease diagnosis in tissue** samples[1,2]

***ESR1* mutations are found in up to 50% patients upon testing at progression on prior endocrine therapy in the metastatic setting**[3-12]

**Testing for *ESR1* mutations should occur at each progression on ET** if not detected previously, due to increasing chances of finding it[13-16]

***ESR1* mutations are subclonal and heterogenous** therefore, **not always detected with tissue biopsy. Blood-based ctDNA is considered the preferred testing methodology** for *ESR1* mutations[16-18]

**Archival tissue from primary tumor should NOT be used to identify *ESR1* mutations**, as *ESR1* mutations develop mainly during metastatic treatment[18]

ctDNA, circulating tumor DNA; *ESR1*, estrogen receptor 1; ET, endocrine therapy; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

1. Mosele MF, et al. *Ann Oncol*. 2024;35:588-606. 2. National Comprehensive Cancer Network. Breast Cancer (Version 4.2024); 3.Kalinsky K, et al. *J Clin Oncol*. 2024;42: Abstract LBA1001; 4. Jhaveri KL, et al. *N Engl J Med.* 2025;392(12):1189-1202; 5. Miguel M. J Clin Oncol. 2024;42(18):2149-2160; 6. Tolaney SM, et al. *J Clin Oncol*. 2023;41(24):4014-4024; 7. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246–3256. 8. Brett JO, et al. *Breast Cancer Res*. 2021;23:85; 9. Bidard et al. *Lancet Oncol*. 2022;23:1367–1377; 10. Santiago Novello RG, et al. *ESMO Open*. 2023;8(suppl 4):104409. Abstract 220P; 11. Lin et al. *Annals of Oncology.* 2023;34 (suppl_2): S334–S390; 12. Bhave MA, et al. *Breast Cancer Res Treat*. Published online: 14 June 2024; 13. Jeselsohn R, et al. *Clin Cancer Res*. 2014;20:1757–1767; 14. Jeselsohn R, et al. *Cancer Cell*. 2018;33:173–186; 15. Allouchery V et al. *Breast Cancer Res*. 2018;20:40. 16. Burstein HJ, et al *J Clin Oncol*. 2023;41:3423–3425; 17. Turner NC, et al. *Lancet Oncol*. 2020;21:1296–1308; 18. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2025. © *National Comprehensive Cancer Network*, Inc. 2024. All rights reserved. Accessed March 18, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

# Discussion and Q&A

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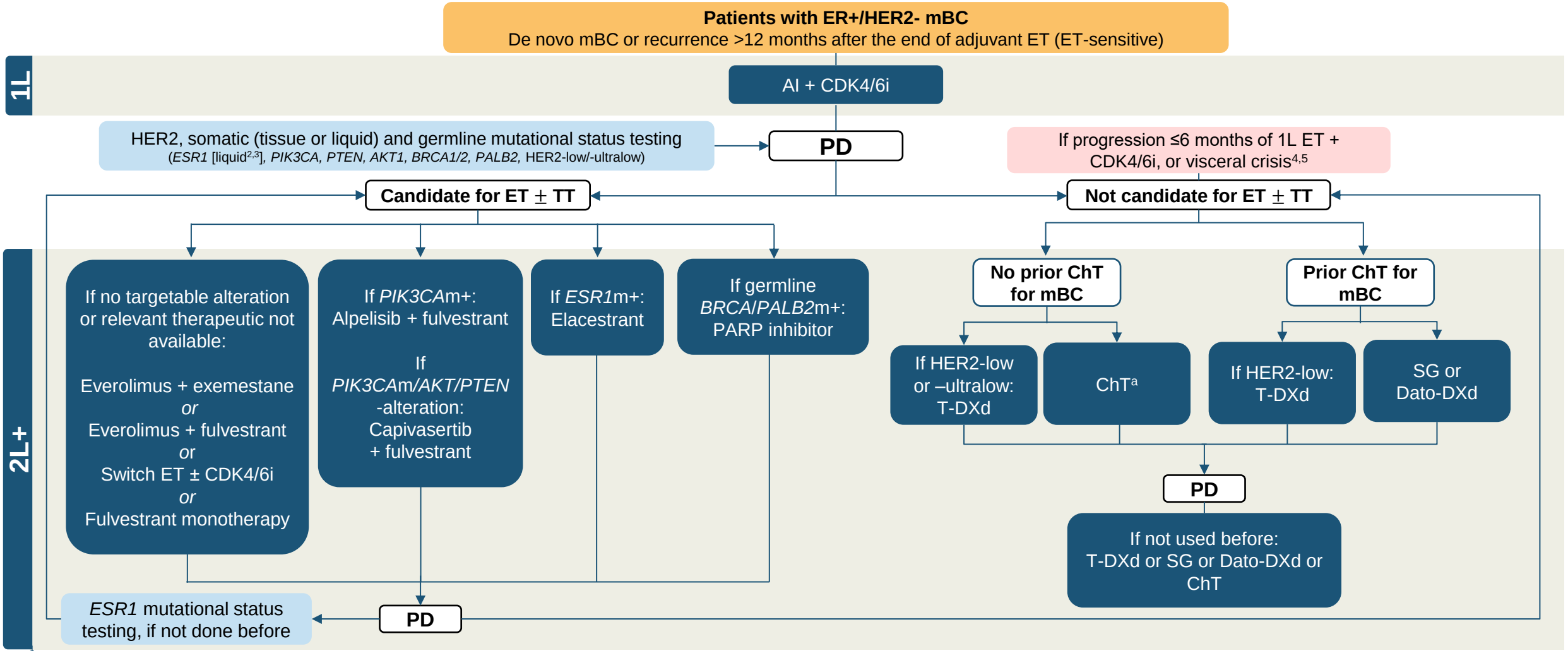
# Second-line treatment choice is defined by the eligibility to receive endocrine therapy and driven by biomarker status. Patients should be tested at progression for genomic alterations[1,2]




[a]Taxane–bevacizumab or capecitabine–bevacizumab. 1/2L , first/second line; AI, aromatase inhibitor; *BRCA*, BReast CAncer gene; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ChT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ER, estrogen receptor; *ESR1*, estrogen receptor 1 gene; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; mBC, metastatic breast cancer; *PALB2*, partner and localizer of BRCA2; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase; SG, sacituzumab govitecan; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

Adapted from: 1. Gennari A, et al. *Ann Oncol* 2021;32(12): 1475-1495. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025 (Accessed April 2025); 2. Burstein HJ, et al. J Clin Oncol. 2023;41(18):3423-3425; 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2025. © *National Comprehensive Cancer Network*, Inc. 2024. All rights reserved. Accessed March 18, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way; 4. Bardia A, et al. *N Engl J Med*. 2024;391(22):2110-2122; 5. Cardoso F, et al. *Breast*. 2024:76:103756.