Potential for Early Intervention in 1L HR+/HER2− aBC

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1L SoC for HR+/HER2– aBC is AI + CDK4/6i; however, existing evidence demonstrates the need to improve outcomes



Patient experience on AI may be challenging due to **tolerability**[1–3]



Efficacy declines from the 1L to 2L treatment setting[2–11]



Quality of life declines from 1L to 2L and there are no differences between regimens in the 2L setting[12,13]



Poor **quality of life** is associated with worse **survival outcomes**[14]



Attrition occurs between **1L and 2L**; **1 in 5** patients do not receive 2L therapy[15]



Exposure to AI drives the emergence of ***ESR1*m** which are associated with **risk of disease progression**, **increased tumor complexity** and **poor efficacy outcomes**[16–23]

1L=first-line; 2L=second-line; aBC=advanced breast cancer; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; *ESR1m*=estrogen receptor one gene mutation; HER2= human epidermal growth factor receptor 2; HR=hormone receptor; SoC=standard of care.

1. Finn RS, et al. *N Engl J Med*. 2016;375:1925–1936; 2. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541–1547; 3. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5; 4. Kalinsky K, et al. *J Clin Oncol*. 2025;43:1101–1112; 5. Jhaveri KL, et al. *N Engl J Med*. 2025;392:1189–1202; 6. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070 (Supplementary Appendix); 7. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256; 8. Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174:719–729; 9. Mayer EL, et al. Presented at SABCS 2022, 6–10 December. San Antonio, TX. Abstract #GS3-06; 10. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004–4013; 11. Rugo HS, et al. *Lancet Oncol*. 2024;25:e629–e638; 12. Sonke GS, et al. *Nature*. 2024;636:474–480; 13. Marschner N, et al. *JAMA Netw Open*. 2020;3:e200643 (and Supplementary Materials); 14. Huang RS, et al. *JAMA Oncol*. 2025;11:1303–1312; 15. Hartkopf A, et al. *Geburtshilfe Frauenheilkd*. 2024;84:459–469; 16. Bidard FC, et al. Presented at ASCO 2020, May 29–June 02. Virtual. Abstract #1010; 17. Lloyd MR, et al. *Ther Adv Med Oncol*. 2022;14:17588359221113694; 18. Patel R, et al. *NPJ Breast Cancer*. 2023;9:20; 19. Dustin D, et al. *Cancer*. 2019;125:3714–3728; 20. Clatot F, et al. *Breast Cancer Res*. 2020;22:56; 21. Lloyd MR, et al. *Clin Cancer Res*. 2022;28:821–830; 22. Meisel JL, et al. Presented at SABCS 2025, 9–12 December. San Antonio, TX. Poster PS2-02-04; 23. Lloyd MR, et al. *NEJM Evid*. 2024;3:EVIDoa2300231.

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Patients taking an AI may have mixed experiences regarding adverse reactions, tolerability and QoL[1–3]



AI-induced musculoskeletal syndrome is well documented, causing symptoms such as:[4]

Arthralgia	Myalgia	Arthritis	Stiffness

Potentially leading to discontinuation of aromatase inhibitors[3]



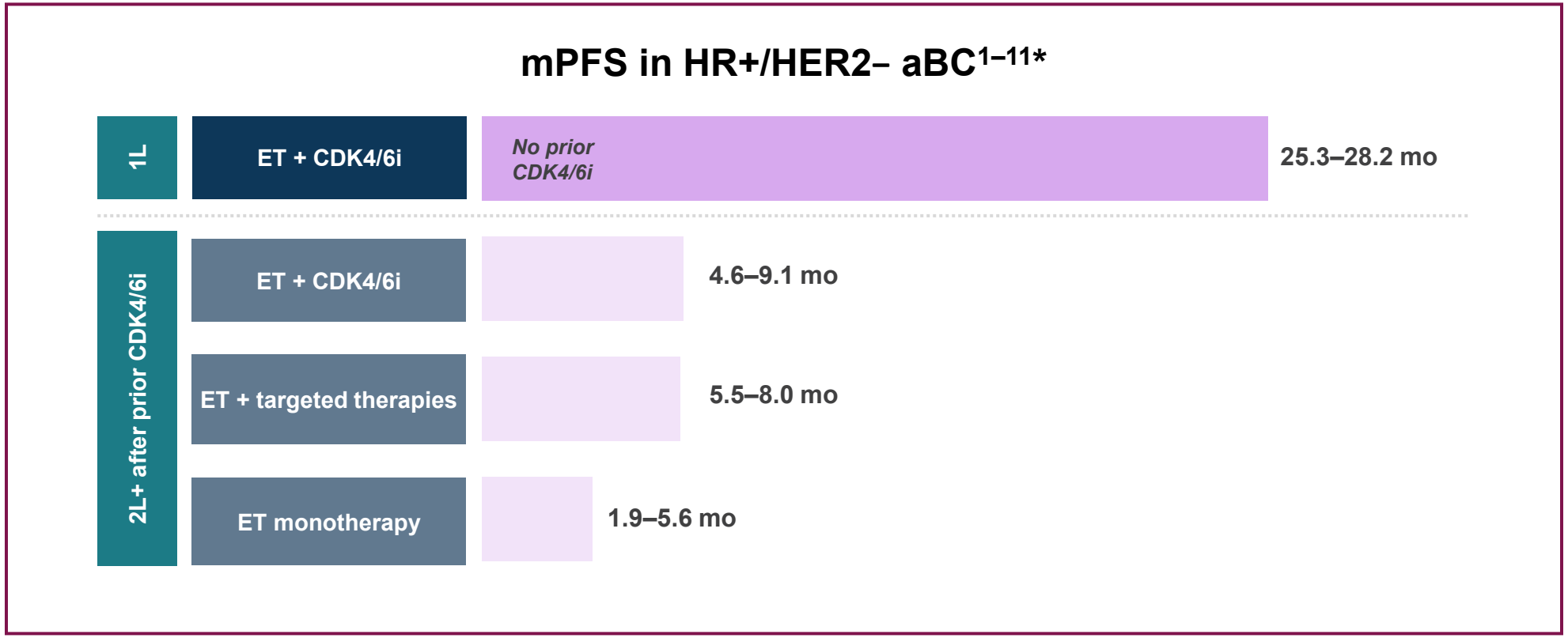
Research is being completed to see if innovation of ET combinations might be an effective strategy to improve patient outcomes and experiences before their first clinical progression[5,6]

AI=aromatase inhibitor; ET=endocrine therapy; QoL=quality of life.

1. Marschner N, et al. *JAMA Netw Open*. 2020;3:e200643; 2. Gelmon K, et al. *Breast*. 2025;84:104603; 3. Henry NL, et al. *J Clin Oncol*. 2012;30:936–942; 4. Andrikopoulou A, et al. *Cancers (Basel)*. 2021;13:465; 5. Turner N, et al. *Future Oncol*. 2023;19:559–573; 6. Bidard FC, et al. *Lancet Oncol*. 2022;23:1367–1377.

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1L AI + CDK4/6i may yield 25–28 months mPFS; however, patients will experience disease progression and efficacy outcomes decline in the 2L setting



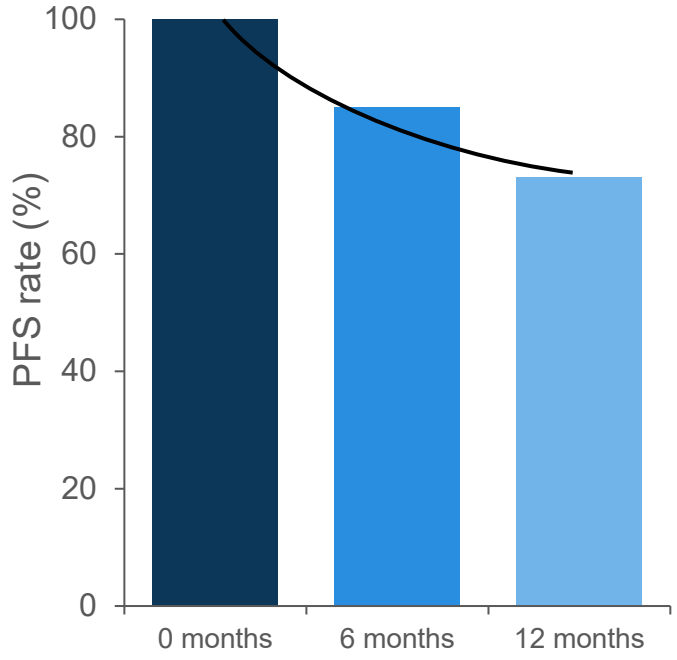
*Cross-trial comparisons do not constitute substantial evidence, as varying study designs, methodology and patient populations limit the ability to draw conclusions of comparative efficacy and safety.
1L=first-line; 2L=second-line; aBC=advanced breast cancer; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mo=month; mPFS=median progression-free survival.

1. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541–1547; 2. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5; 3. Kalinsky K, et al. *J Clin Oncol*. 2025;43:1101–1112; 4. Jhaveri KL, et al. *N Engl J Med*. 2025;392:1189–1202; 5. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070 (Supplementary Appendix); 6. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256; 7. Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174:719–729; 8. Mayer EL, et al. Presented at SABCS 2022, 6–10 December. San Antonio, TX. Abstract #GS3-06; 9. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004–4013; 10. Rugo HS, et al. *Lancet Oncol*. 2024;25:e629–e638; 11. Campone, M et al. *N Engl J Med.* 2025;393:556–568.

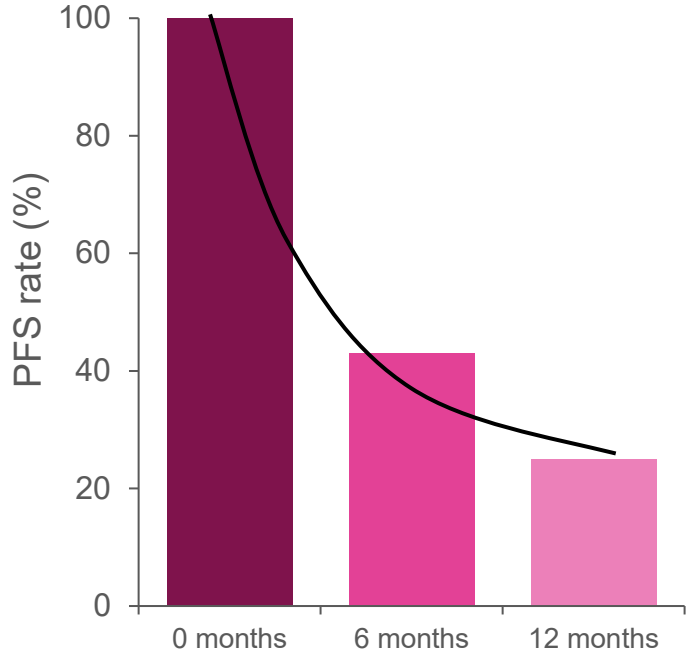
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After 6 months of 1L treatment, ~85% of women with HR+ aBC remain progression free; however, in 2L, with FDA-approved novel ET monotherapies, this decreases to ~43% after 6 months

PFS rates at 6 and 12 months with 1L AI + CDK4/6i in HR+/HER2− aBC[1–3*†]



PFS rates at 6 and 12 months with 2L novel ET mono in HR+/HER2− aBC[4–6*‡]



This steep decline in the 2L setting highlights the importance of maximizing time on treatment before the first clinical progression, before the disease becomes more challenging to treat[1–6]

*Cross-trial comparisons do not constitute substantial evidence, as varying study designs, methodology and patient populations limit the ability to draw conclusions of comparative efficacy and safety; †For 1L AI + CDK4/6i, estimated PFS rates at 6 and 12 months were extrapolated from the Kaplan–Meier PFS curves from MONALEESA-2, MONARCH-3, and PALOMA-2. Mean values across the three trials are shown for each time point; ‡For 2L novel ET monotherapy, PFS rates use published values in the *ESR1*m-altered population in EMBER-3 and EMERALD (6 and 12 months) and VERITAC-2 (6 months). The 12-month PFS rate in VERITAC-2 was extrapolated from the Kaplan–Meier curve. Mean values across the three trials are shown for each time point.

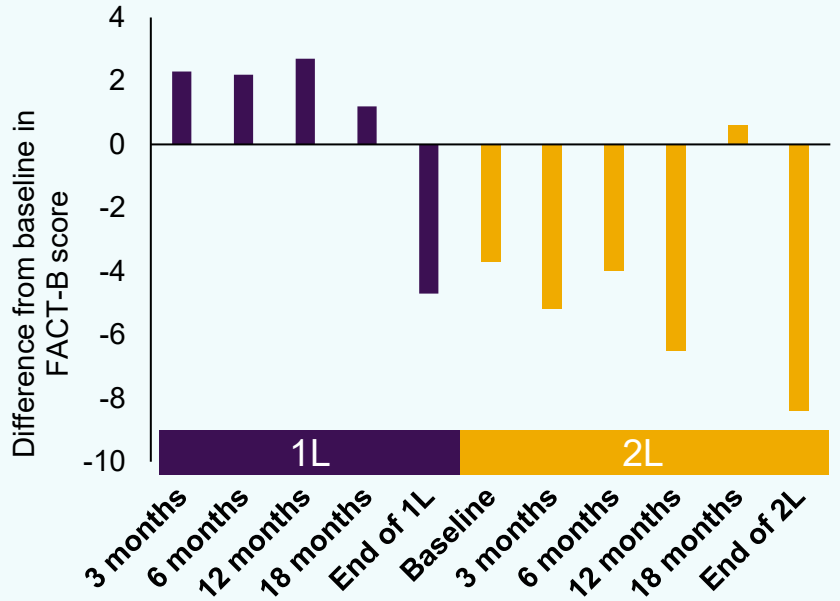
1L=first-line; 2L=second-line; aBC=advanced breast cancer; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ET=endocrine therapy; FDA=Food and Drug Administration; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mono=monotherapy; PFS=progression-free survival.

1. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541–1547; 2. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5; 3. Rugo HS, et al. *Breast Cancer Res Treat*. 2019;174:719–729; 4. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256; 5. Jhaveri K, et al, *N Engl J Med*. 2025;392:1189–1202; 6. Campone, M et al. *N Engl J Med*. 2025;393:556–568.

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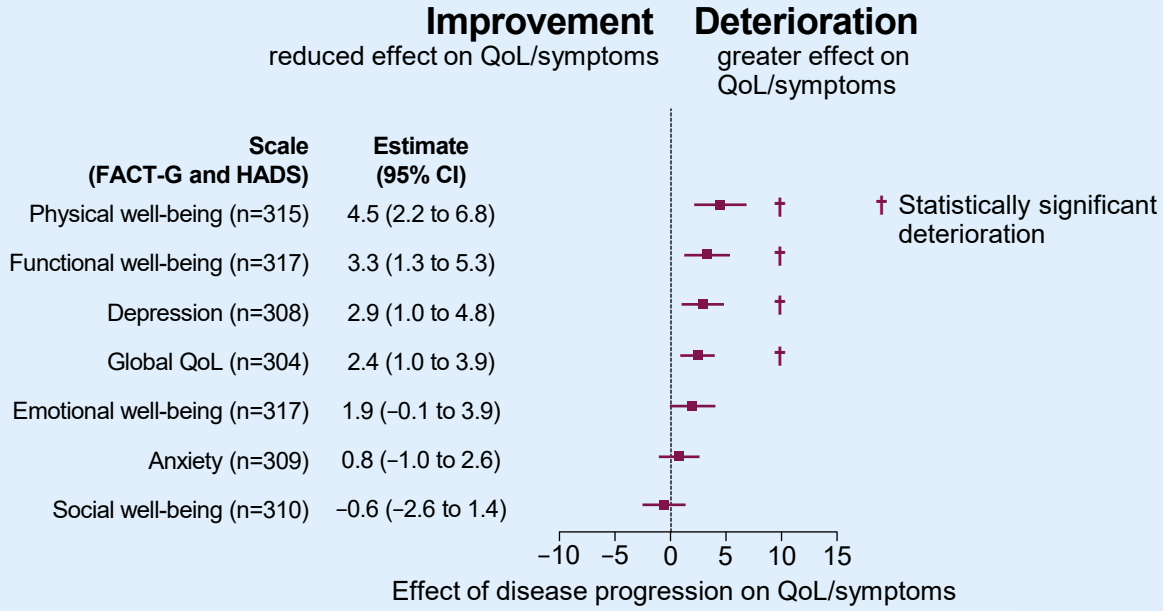
With 1L SoC there is generally an adequate QoL for patients; however, QoL may also worsen after patients progress to 2L therapy

HRQoL in 1L and 2L HR+/HER2− aBC[1]*



Adapted from Sonke GS, et al. 2024

Linear mixed model for association of first disease progression with QoL and symptoms[2]*



Adapted from Marschner N, et al. 2020

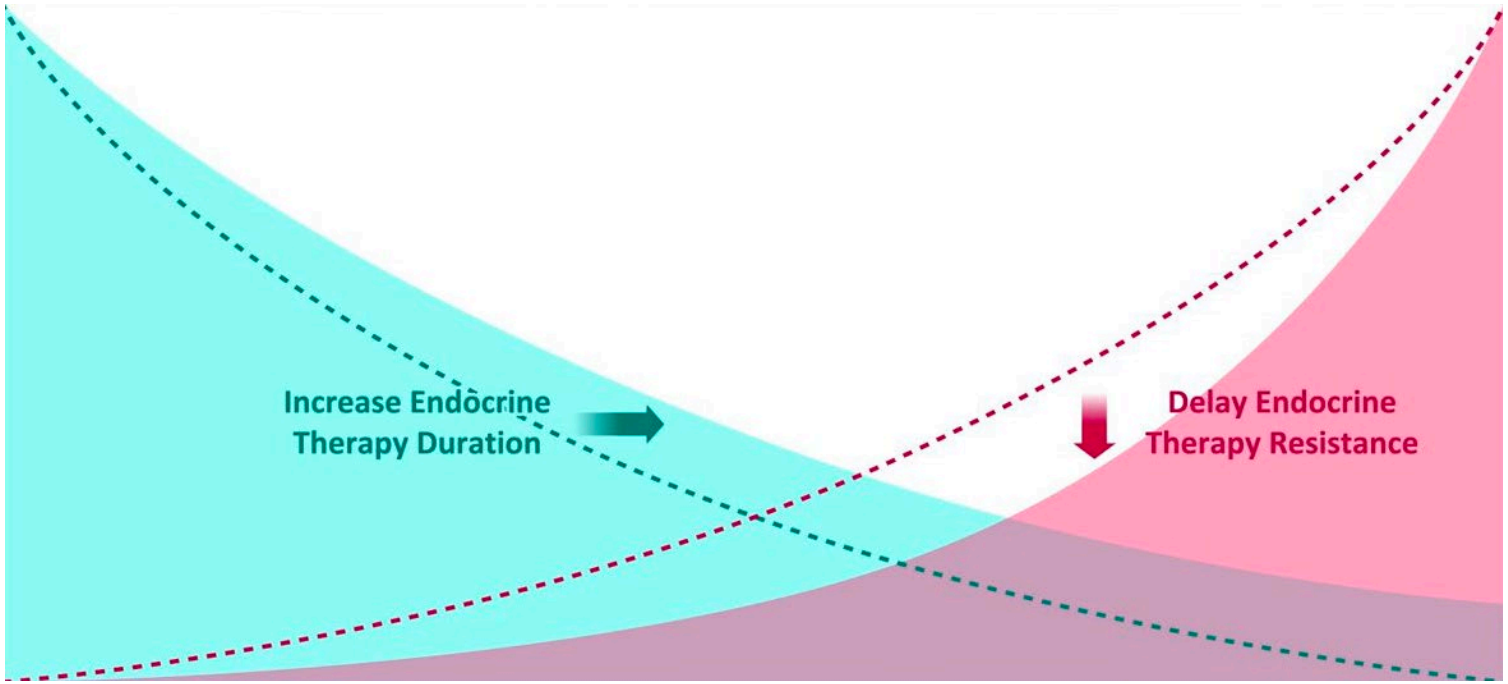
Such deterioration can involve **increased depression**, as well as **declines in functional and physical well-being[2]**

*The bar chart and forest plot are from different studies and are not meant to be interpreted together. The domains on the forest plot are not causing the results depicted in the bar chart.
1L=first-line; 2L=second-line; aBC=advanced breast cancer; CI=confidence interval; FACT-B=Functional Assessment of Cancer Therapy–Breast; FACT-G=Functional Assessment of Cancer Therapy–General; HADS=Hospital Anxiety and Depression Scale; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; HRQoL=health-related quality of life; QoL=quality of life; SoC=standard of care.

1. Sonke GS, et al. *Nature*. 2024;636:474-480; 2. Marschner N, et al. *JAMA Netw Open*. 2020;3:e200643 (and Supplementary Materials).

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Extending the duration and benefit of 1L treatment while delaying resistance is crucial for the well-being of patients[1–3]



Adapted from Bidard FC, et al. 2022; Turner N, et al. 2023; Barrios C, et al, 2023.

†In theory, based on the study designs of PADA-1 and SERENA-6 which used an investigational testing approach.[1–3]
1L=first-line; 2L=second-line; AI=aromatase inhibitor; ET=endocrine therapy; PRO=patient-reported outcome; QoL=quality of life; SERD=selective estrogen receptor degrader.

1. Turner N, et al. *Future Oncol*. 2023;19:559–573; 2. Bidard FC, et al. *Lancet Oncol*. 2022;23:1367–1377; 3. Barrios C, et al. *Treatment post-CDK4/6 inhibitors: single agent endocrine therapy.* Presented at SABCS 2023, 5–9 December. San Antonio, TX.

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There is an interplay between QoL and survival outcomes: Patients with higher scores in GHS and QoL are associated with improved survival outcomes vs. patients with lower scores



Systematic review of ~44,000 patients with solid tumors with 31 RCTs (44.9%) included in a meta-analysis[1]*

Higher GHS and QoL were associated with **improved OS** (hazard ratio 0.99; 95% CI, 0.98–0.99)†

Physical functioning (hazard ratio 0.94; 95% CI, 0.92–0.96)† and **role functioning** (hazard ratio 0.96; 95% CI, 0.94–0.98)† were associated with **improved OS**

These **QoL measures** also offered independent **prognostic information** for OS across cancer types

Pooled analysis of EORTC QLQ-C30 data in BC (N=8544):‡
In the advanced disease cohort (77% HR+/HER2−), each additional clinically important baseline PRO domain was associated with worse OS (hazard ratio 1.05; 95% CI 1.03–1.07)[2]

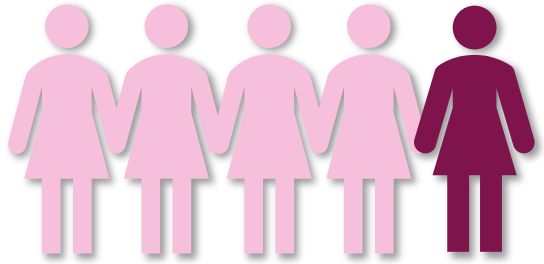
*In total, 69 RCTs comprising 44,030 patients were included in the systematic review with 31 RCTs (44.9%) meeting inclusion criteria for the meta-analysis.[1] †Because PROs are modeled as continuous 0–100 scales, hazard ratios near one are expected and may still indicate meaningful prognostic association when applied across larger score differences.[1,2] ‡The full cohort pooled eight BC trials (N=8,544), including early-stage (n=5,893) and advanced-stage (n=2,651) disease; associations between baseline clinically important EORTC QLQ-C30 domains and survival/adverse events were evaluated using adjusted Cox regression.[2]
(a)BC=(advanced) breast cancer; CI=confidence interval; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; GHS=global health status; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; OS=overall survival; PRO=patient-reported outcome; QoL=quality of life; RCT=randomized controlled trial.

1. Huang RS, et al. *JAMA Oncol*. 2025;11:1303–1312; 2. Menz A, et al. *Breast Cancer Res Treat*. 2025;210:565–578.

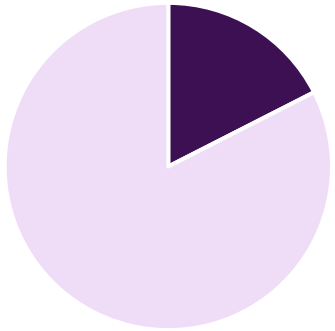
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One approach to maximizing treatment outcomes is to use the most effective treatments as early as possible as not all patients receive subsequent lines of therapy

~1 in 5 patients with HR+/HER2− aBC treated in 1L, **do not receive 2L therapy*[1–3]**

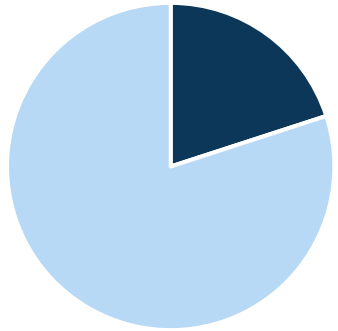


US: 20% of women did not receive 2L treatment[1*†]



Based on medical records from 199 women with HR+/HER2− aBC across three cancer centers in the US

Europe: 17%‡–18% of women did not receive 2L treatment[2,3]



Two studies including >3,400 women with HR+/HER2− aBC in Europe

To understand attrition rates and to aid in clinical decision-making, larger multicenter studies need to be completed across the US

***Attrition rates described are based on a small set of studies and interpretation of these data are limited by small patient and center numbers.[1–3]**
†Attrition was due to death, disease progression, adverse reactions or even financial reasons;[1] ‡For patients receiving 1L ET + CDK4/6i.
1L=first-line; 2L=second-line; aBC=advanced breast cancer; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.
1. Tan CJ, et al. Presented at Miami Breast Cancer Annual Conference 2025, 6–9 March. Miami, FL. Poster 97; 2. Hartkopf AD, et al. *Geburtshilfe Frauenheilkd*. 2024;84:459–469;
3. Basile D, et al. *Breast*. 2021;57:104–112.

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US: 20% of women did not receive 2L treatment[1*†]

Based on medical records from 150 women with HR+/HER2− aBC across three cancer centers in the US

Europe: 17%‡–18% of women did not receive 2L treatment[2,3]

Two studies including >3,400 women with HR+/HER2− aBC in Europe

Additionally, patients with **visceral crises** or **rapidly progressing disease** may only have **chemotherapy** as their next treatment option instead of ET

To understand attrition rates and to aid in clinical decision-making, larger multicenter studies need to be completed across the US

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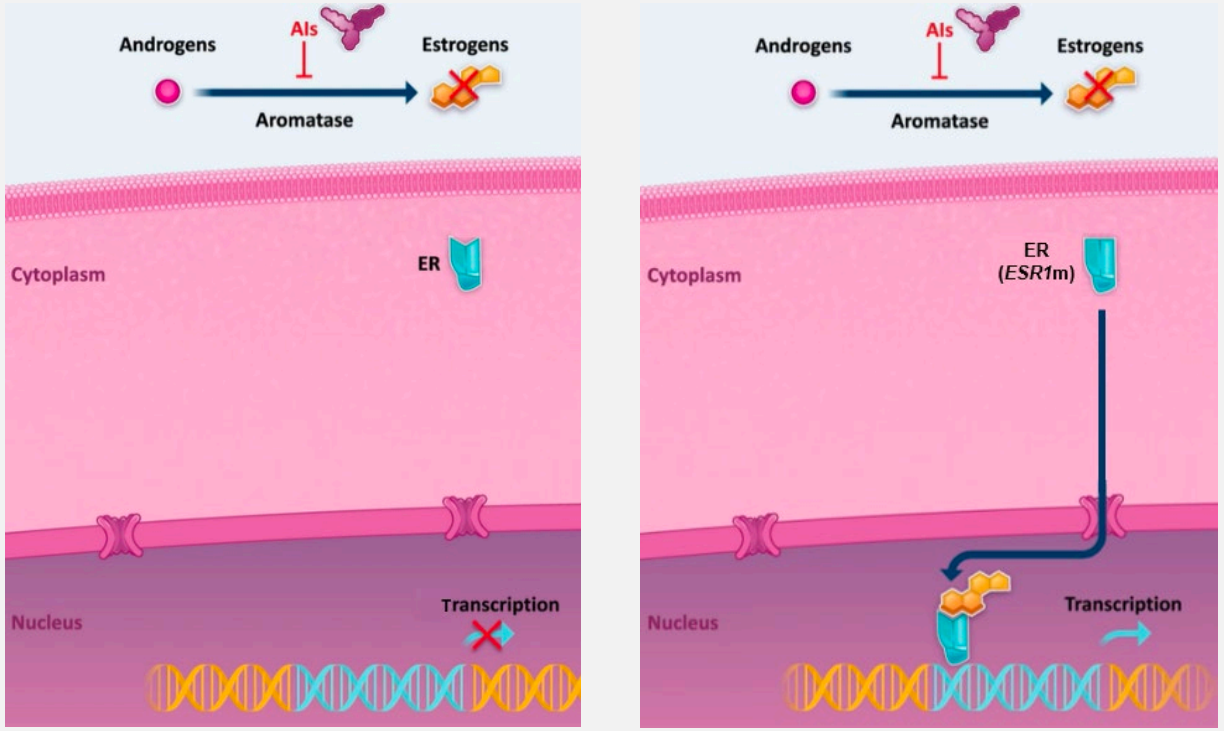
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As AIs have no direct effect on the estrogen receptor, *ESR1*m may emerge that make the estrogen receptor active, even in the absence of estrogen[1,2]



*ESR1*m is a well characterized and widely accepted resistance mechanism

AI=aromatase inhibitor; ER=estrogen receptor; *ESR1*m=estrogen receptor one gene mutation.

1. Turner N, et al. *Future Oncol*. 2023;19:559–573; 2. Lloyd MR, et al. *Ther Adv Med Oncol*. 2022;14:17588359221113694.

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As exposure to AI increases, the rate of *ESR1*m also increases in the aBC setting, which signals that the cancer is at risk of progression

*ESR1*m emergence across 1L treatment

<5%
of patients with HR+ aBC have detectable *ESR1*m at the start of 1L treatment[1,2]

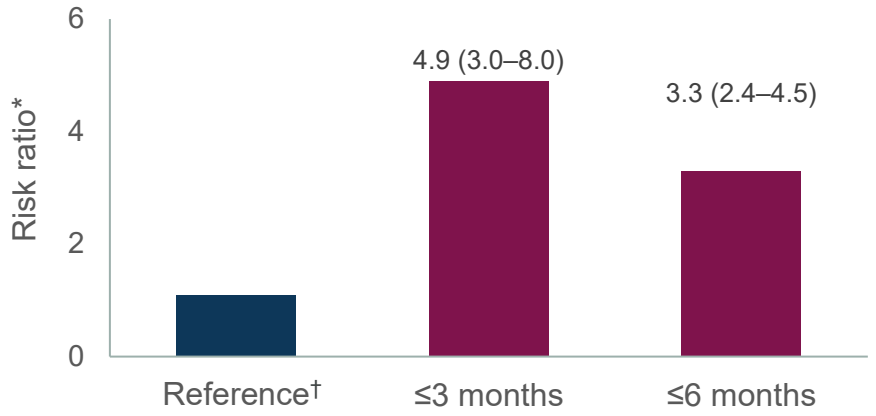
~30–50%
of patients have detectable *ESR1*m by the end of 1L treatment[3–6]



Start of 1L treatment for aBC (*de novo* or after adjuvant AI)

*ESR1*m are the most common mechanism of ET resistance associated with AI treatment[2,7,8]

Risk ratio of progression, according to timing of *ESR1*m detection (n=18)[9]*



***ESR1*m detection** in 18/103 women with HR+/HER2− aBC was **associated with a 3-fold increase in the risk of disease progression** within 6 months vs. those with no *ESR1*m detected[9]

In addition, the emergence of *ESR1*m is associated with increased genetic complexity, including a high rate of polyclonal *ESR1*m and potentially other mutations[10]

***These data are based on small patient numbers and should be interpreted with caution**.[9] †Patients with tumors in which *ESR1*m were not detected.[9]
1L=first-line; aBC=advanced breast cancer; AI=aromatase inhibitor; *ESR1*m=estrogen receptor one gene mutation; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.

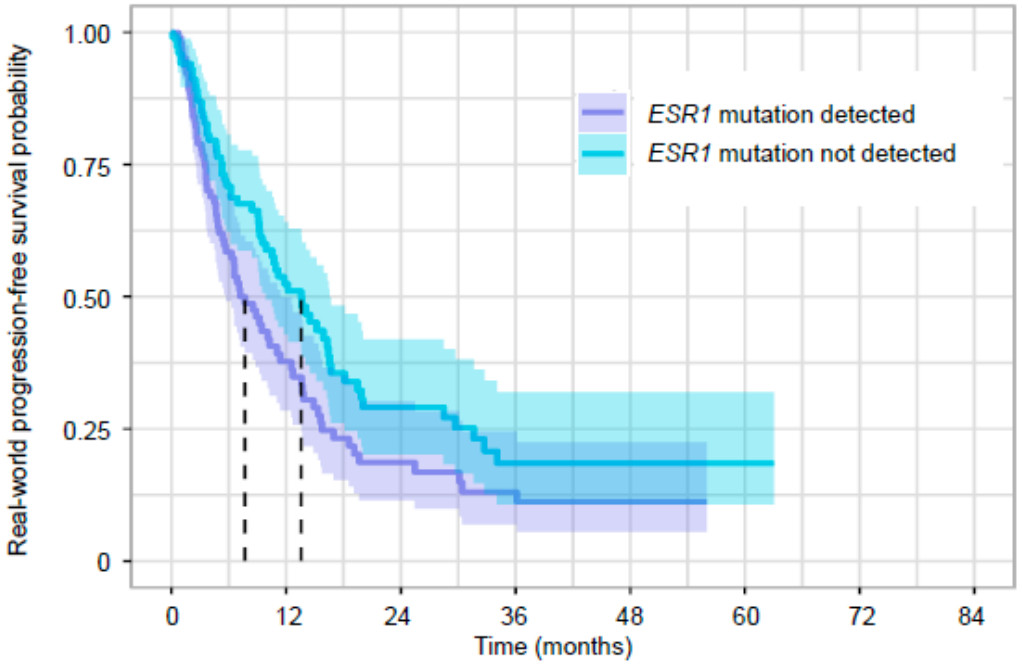
1. Bidard, FC et al. Presented at ASCO 2020, May 29–June 02. Virtual. Abstract #1010; 2. Lloyd MR, et al. *Ther Adv Med Oncol*. 2022;14:17588359221113694; 3. Bidard FC, et al. *J Clin Oncol* 2022;40:3246–56; 4. Bhave MA, et al. *Breast Cancer Res Treat* 2024;207:599–609; 5. Chaudhary N, et al. *NPJ Breast Cancer* 2024;10:15; 6. Fribbens C, et al. *Ann Oncol*. 2018;29:145–153; 7. Patel R, et al. *NPJ Breast Cancer*. 2023;9:20; 8. Dustin D, et al. *Cancer*. 2019;125:3714–3728; 9. Clatot F, et al. *Breast Cancer Res*. 2020;22:56; 10. Pejerrey S, et al. *Horm Cancer*. 2018;9:215–228.

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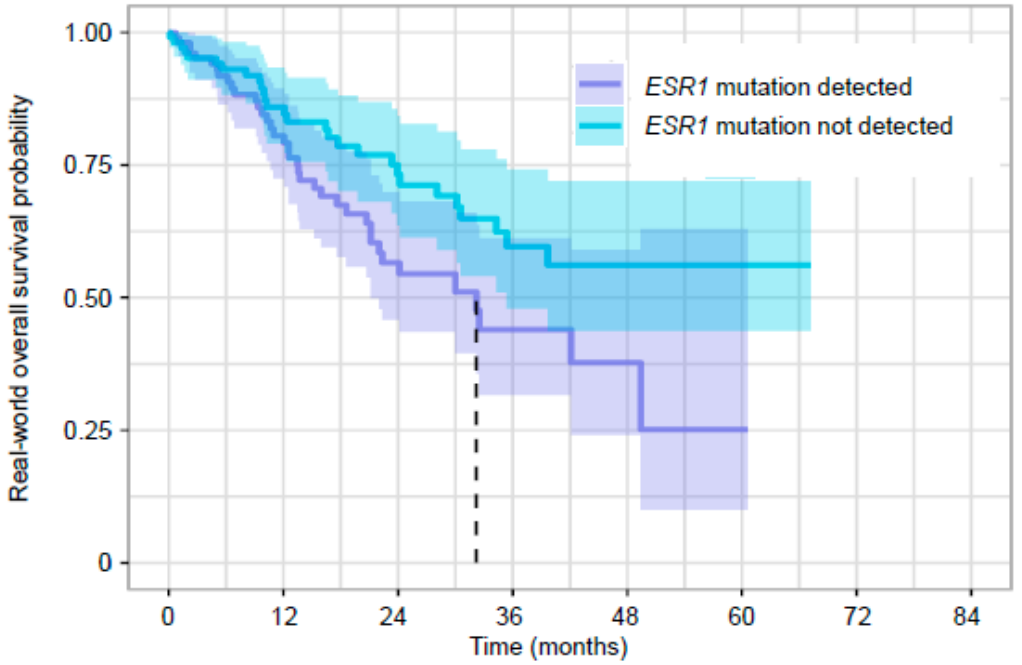
Patients with *ESR1*m have shorter PFS and OS than those without *ESR1*m detected during 1L treatment[1,2]

RW results when patients with *ESR1*m are compared to the patients without *ESR1*m detected[2]

PFS after the first *ESR1*m test during 1L*



OS after the first *ESR1*m test during 1L*



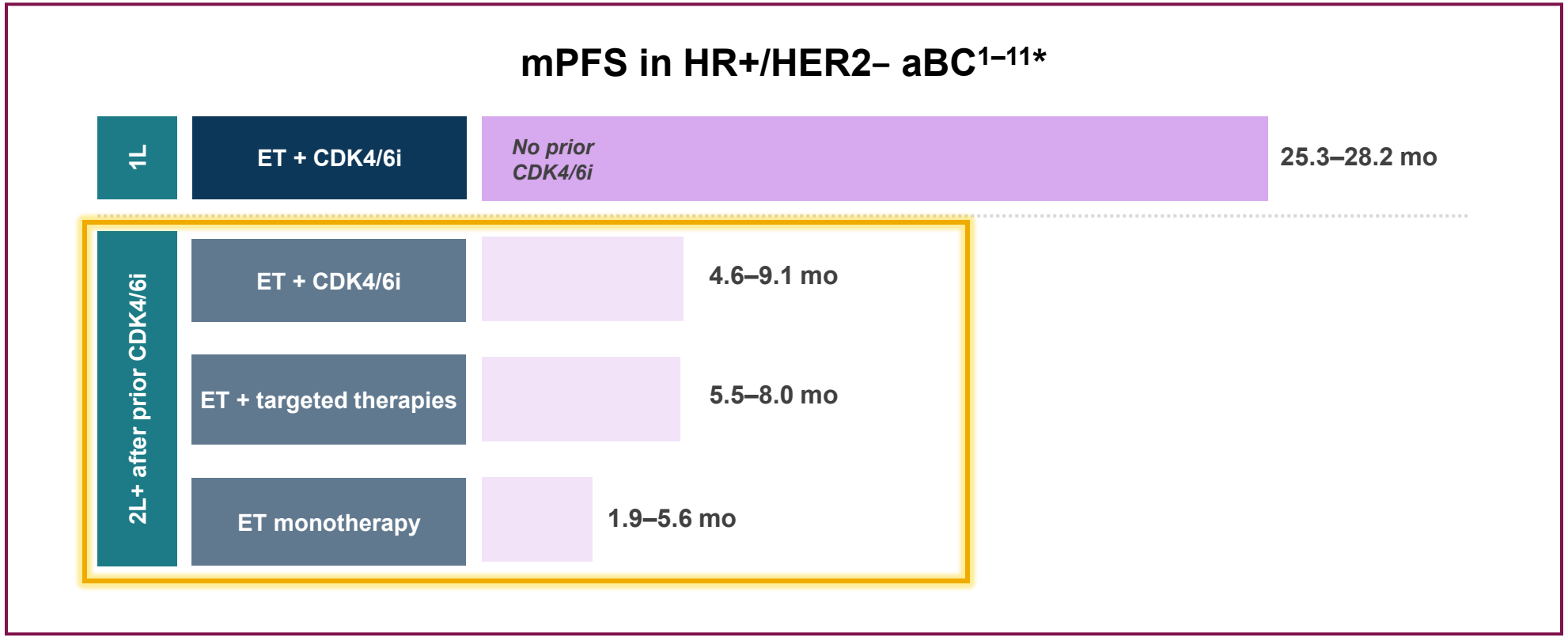
*Propensity score matching was carried out.

1L=first line; *ESR1*(m)=estrogen receptor one gene (mutation); OS=overall survival; PFS=progression-free survival; RW=real world.

1. Lloyd MR, et al. *NEJM Evid*. 2024;3:EVIDoa2300231; 2. Meisel JL, et al. Presented at SABCS 2025, 9–12 December. San Antonio, TX. Poster PS2-02-04.

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These increases in tumor and mutational burden over time may be responsible for some of the limitations of current 2L therapies



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1L=first-line; 2L=second-line; aBC=advanced breast cancer; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mo=month; mPFS=median progression-free survival.

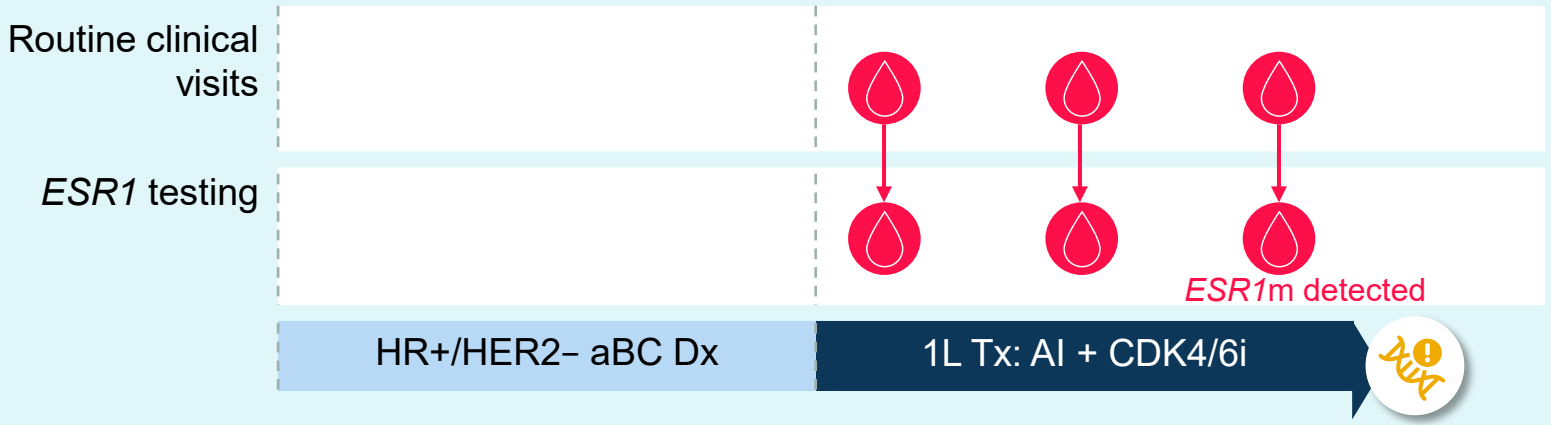
1. Hortobagyi GN, et al. *Ann Oncol*. 2018;29:1541–1547; 2. Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5; 3. Kalinsky K, et al. *J Clin Oncol*. 2025;43:1101–1112; 4. Jhaveri KL, et al. *N Engl J Med*. 2025;392:1189–1202; 5. Turner NC, et al. *N Engl J Med*. 2023;388:2058–2070 (Supplementary Appendix); 6. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246–3256; 7. Rugo H, et al. *Breast Cancer Res Treat*. 2019;174:719–729; 8. Mayer EL, et al. Presented at SABCS 2022, 6–10 December. San Antonio, TX. Abstract #GS3-06; 9. Kalinsky K, et al. *J Clin Oncol*. 2023;41:4004–4013; 10. Rugo HS, et al. *Lancet Oncol*. 2024;25:e629–e638; 11. Campone, M et al. *N Engl J Med.* 2025;393:556–568.

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To help patients have the best chance of extending the benefit of 1L AI + CDK4/6i, it may be critical to detect emerging endocrine resistance as early as possible

One potential approach would be to **integrate ctDNA monitoring for *ESR1*m** with **routine bloodwork**

Investigational *ESR1*m monitoring during 1L treatment[1–5]



Adapted from Bidard FC, et al. 2022; Living Beyond Breast Cancer. Metastatic breast cancer to the bones; Living Beyond Breast Cancer. Testing and precision medicine.

Then to follow up with patients during their routine clinical visits

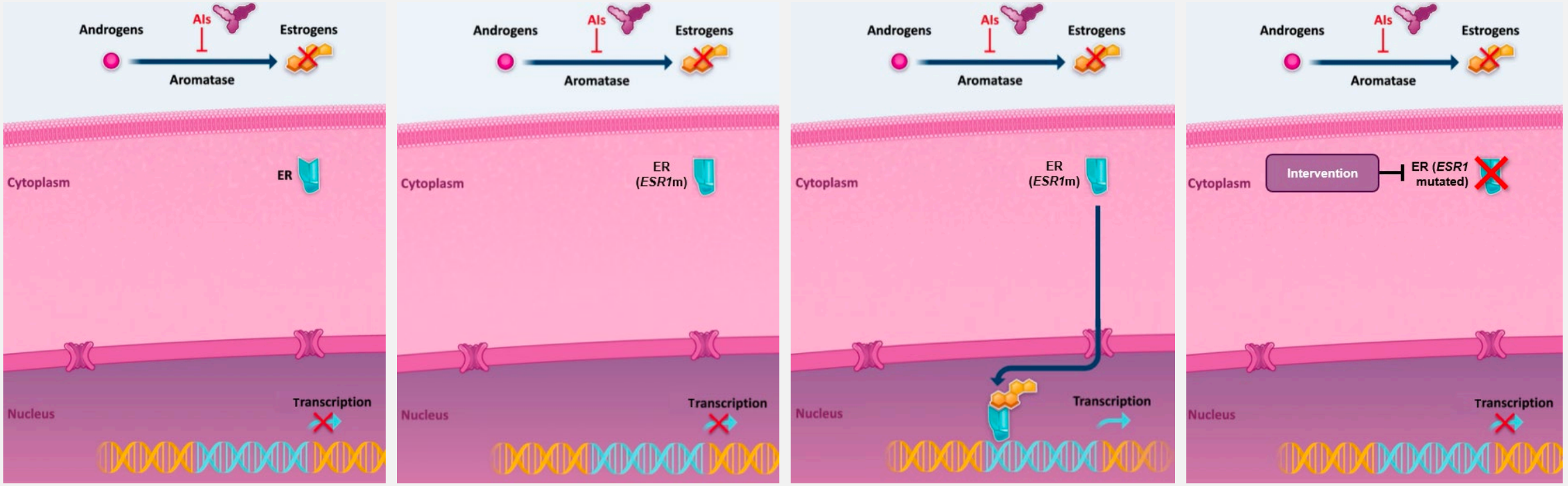
An approach like this hopes to lead to personalized treatment-decisions with improved patient outcomes, by using the **right intervention** for the **right patient**, at the **right time**[1,4]

1L=first-line; aBC=advanced breast cancer; AI=aromatase inhibitor; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ctDNA=circulating tumor DNA; Dx=diagnosis; *ESR1*m=estrogen receptor one gene mutation; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; Tx=treatment.

1. Bidard FC, et al. *Lancet Oncol*. 2022;23:1367–1377; 2. Living Beyond Breast Cancer. Metastatic breast cancer to the bones. Available at: https://www.lbbc.org/about-breast-cancer/types-breast-cancer/metastatic-breast-cancer/bone-metastases (Accessed April 2026); 3. Living Beyond Breast Cancer. Testing and precision medicine. Available at: https://www.lbbc.org/about-breast-cancer/testing (Accessed April 2026); 4. Turner N, et al. *Future Oncol*. 2023;19:559–573; 5. Bidard FC, et al. *N Engl J Med*. 2025;393:569–580.

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For HR+/HER2– aBC, proactive intervention at the earliest emergence of *ESR1*m during 1L ET may help address endocrine resistance, before the cancer becomes harder to treat[1–6]



Adapted from Turner N, et al. 2023

1L=first-line; aBC=advanced breast cancer; AI=aromatase inhibitor; ER=estrogen receptor; *ESR1*(m)=estrogen receptor one gene (mutation); ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.

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