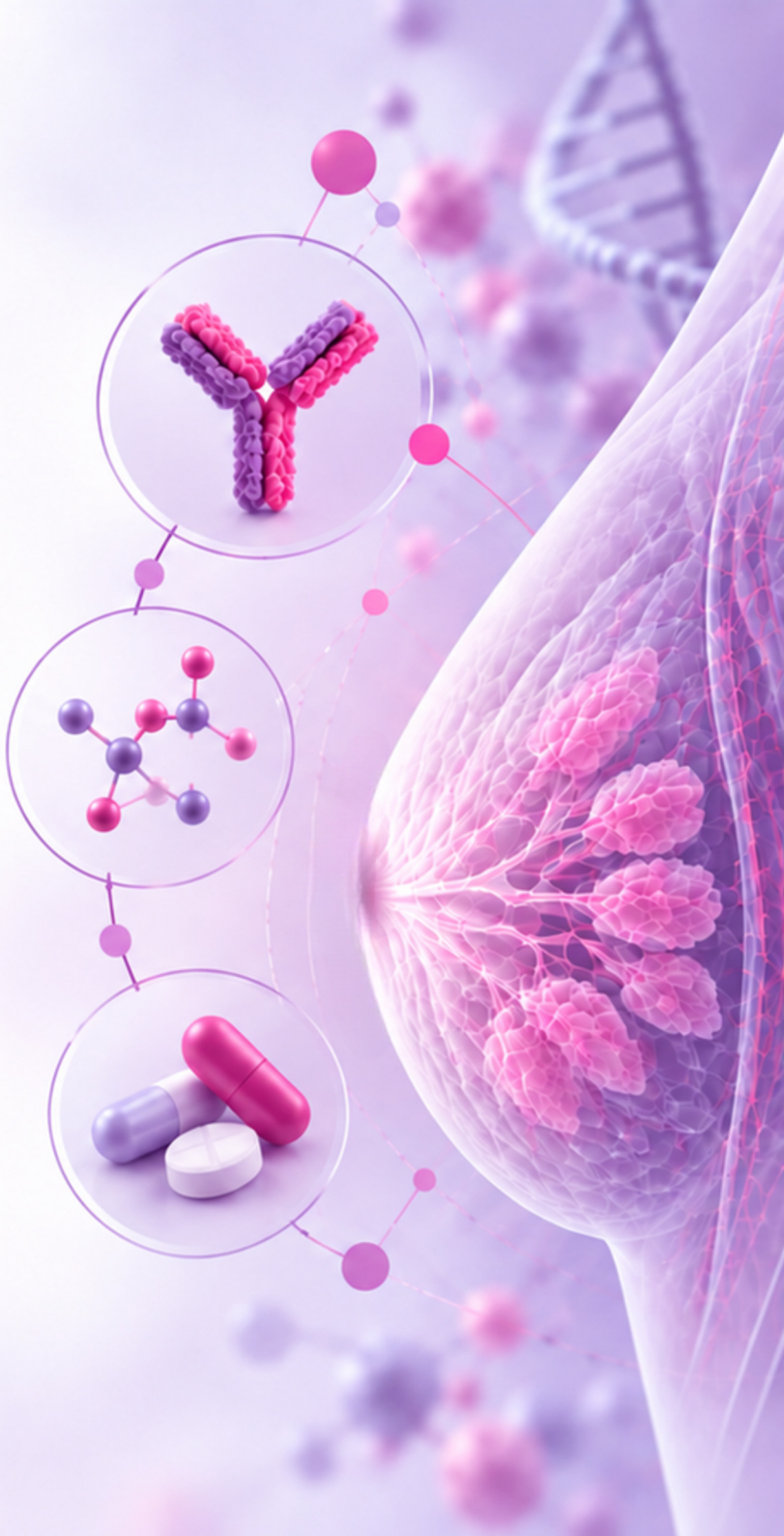
YOUNG WOMEN'S BREAST CANCER RESEARCH INSTITUTE

EMERGING ADVANCES IN BREAST CANCER TREATMENT FOR YOUNG WOMEN

A 2026 Evidence Digest on Breast Cancer in Young Women

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THE INSTITUTE

The **Young Women's Breast Cancer Research Institute (YWBCRI)** is an international, collaborative research organization focused on the early biological factors that influence breast cancer risk, development, and progression in young women. The Institute is advancing understanding of breast cancer in young women by moving research upstream—from established disease toward the biological changes that precede and shape its development.

YWBCRI brings together investigators and collaborators across international sites to study the early biology, detection, interception, and prevention of breast cancer in young women. Its scientific programs focus on early, quantifiable, and potentially reversible biological states shaped by metabolism, mitochondrial activity, immune response, hormonal influences, developmental timing, environmental exposures, and the tissue microenvironment.

Through human-centered, systems-level research, the Institute aims to generate new insights that may support risk prediction, earlier detection, biological interception, and prevention. Its research is organized into three interconnected scientific programs.

Earlier Biology. Earlier Detection. Earlier Interruption. Earlier Prevention.

YWBCRI is a scientific research initiative of the Breast Cancer in Young Women Foundation.

ABOUT THIS EDUCATIONAL SERIES

Emerging Advances in Breast Cancer Treatment for Young Women is an educational evidence series featuring recent studies with particular relevance to the treatment of breast cancer in younger and premenopausal women.

The **2025–2026 *Evidence Digest*** brings together **14 completed studies** spanning endocrine therapy, CDK4/6 inhibition, genomic treatment guidance, ovarian function and suppression, fertility preservation, pregnancy, and emerging molecular approaches to treatment resistance. A final section highlights ongoing NCI-listed clinical trials that may help inform future treatment.

The studies differ in their focus on young women. Some directly examine young or premenopausal populations, while others provide broader evidence with relevance to these groups. The Digest identifies this distinction to avoid extending conclusions beyond the populations actually studied.

Together, the series depicts an evolving treatment landscape in which care for young women with breast cancer increasingly integrates tumor biology, age, menopausal and ovarian function, genomic risk, reproductive priorities, and molecular changes during therapy.

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MITOCHONDRIAL FIELD EFFECT



MICROINVASIVE DCIS BIOLOGY



SYSTEMIC SIGNAL DETECTION

Treating Breast Cancer in Young Women: Beyond Age to Biology and Personalized Care

Breast cancer in a young woman is not simply breast cancer diagnosed earlier in life. Treatment advances have transformed breast cancer care, but an important question remains: does evidence drawn largely from broad adult populations—now beginning to change—reflect the therapeutic realities of a woman diagnosed at 25, 30, or 35? For younger women, active ovarian function, endocrine physiology, fertility and pregnancy plans, treatment-induced ovarian injury, and longer-term recurrence risks shape treatment choices and consequences. Thus, age is more than a demographic factor; it directly affects care.

Recent evidence is clarifying when this distinction matters. Long-term endocrine studies highlight the importance of ovarian suppression and treatment intensity, while newer data suggest that prescribed ovarian suppression may not always achieve complete biological suppression. Genomic assays can help refine treatment decisions, but the benefit of chemotherapy in premenopausal women raises questions about how much stems from direct cytotoxicity versus ovarian suppression.

A second shift is emerging at the intersection of treatment and reproductive biology. Ovarian reserve can now be monitored with increasingly sensitive measures, while fertility-preservation strategies are being evaluated not only for reproductive success but also for oncologic safety and for their effects on the tumor. Temporarily interrupting endocrine therapy to pursue pregnancy further blurs the traditional boundary between cancer treatment and reproductive planning.

Perhaps the most forward-looking change is the shift from treating disease based on what is visible to responding to biological change. Serial circulating tumor DNA can reveal emerging endocrine resistance before it appears on imaging, potentially allowing therapy to change while the disease remains clinically controlled. This marks a move away from treatment guided primarily by established disease state toward molecularly informed therapeutic interception.

LOOKING AHEAD

The challenge ahead is not only to make increasingly effective treatments accessible to younger women but also to generate evidence that reflects the biology and therapeutic context of breast cancer at younger ages. Treatment must increasingly account for the tumor, the young host, and how both evolve over time.

— Editors

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SELECTED HIGHLIGHTS
01–07

01 15-Year SOFT/TEXT — Endocrine Therapy



- Long-term follow-up confirms the benefits of suppressing ovarian function with endocrine therapy, especially for women at greater risk of recurrence.
- **BCYW:** Supporting evidence in premenopausal women; treatment intensity may matter especially at younger ages.

02 NATALEE — Adjuvant Ribociclib



- Adding ribociclib to endocrine therapy for 3 years improved invasive disease-free survival among patients with HR+/HER2– early breast cancer.
- **BCYW:** Premenopausal women received ovarian suppression, allowing CDK4/6 inhibition to be extended into curative treatment.

03 Pembrolizumab and Ovarian Reserve



- AMH declined markedly during chemotherapy in young women with TNBC, but the study found no statistically significant additional decline associated with pembrolizumab.
- **BCYW:** Emphasizes the significant impact of systemic therapy on ovarian function and the need for prospective data on reproductive toxicity.

04 Young-PEARL — CDK4/6 Therapy



- For premenopausal patients with HR+/HER2– metastatic disease, palbociclib combined with endocrine therapy and ovarian suppression offered an effective treatment strategy that avoided chemotherapy.
- **BCYW:** One of the few randomized treatment trials conducted specifically in premenopausal women.

05 POSITIVE — Pregnancy After Endocrine Therapy Interruption



- Temporarily interrupting adjuvant endocrine therapy to attempt pregnancy was not associated with a higher short-term recurrence risk than in the external control cohort.
- **BCYW:** Addresses a key treatment–reproduction decision facing young women with HR+ breast cancer.

06 Oncotype DX ≤25 — Premenopausal, Node+



- Real-world evidence indicates that chemotherapy may improve overall survival in some premenopausal women with node-positive HR+/HER2– disease, even when recurrence scores are ≤25.
- **BCYW:** Raises the unresolved question of whether direct chemotherapy offers a benefit over chemotherapy-induced ovarian suppression.

07 RSClinN+ — Integrating Genomic and Clinical Risk



- Combining recurrence scores with clinical and pathologic factors provides more individualized estimates of recurrence risk and chemotherapy benefit in node-positive HR+/HER2– disease.
- **BCYW:** Among premenopausal women, the recurrence score alone did not identify a group that clearly received no benefit from chemotherapy.

SELECTED HIGHLIGHTS
08–14

08



Extended Endocrine Therapy Beyond Five Years

- Among women aged 40 or younger with node-positive HR+ disease, extending endocrine therapy beyond five years was linked to improved breast cancer-free and distant recurrence-free survival.
- **BCYW:** Provides age-specific evidence about treatment duration—a question of particular relevance to young women who face a prolonged risk of recurrence.

09



Ultra-Sensitive AMH During Chemotherapy

- Highly sensitive AMH measurements tracked profound changes in ovarian reserve during chemotherapy and showed potential for identifying women at risk of premature ovarian insufficiency.
- **BCYW:** May assess treatment-related ovarian injury more precisely than menstrual status alone.

10



Ovarian Suppression — Is Suppression Always Complete?

- Some women receiving GnRH-agonist ovarian suppression did not achieve adequate biological suppression during endocrine therapy.
- **BCYW:** Highlights the need to monitor estradiol, particularly when ovarian suppression is paired with an aromatase inhibitor.

11



Fertility Preservation Before Treatment

- Among women with ER+ breast cancer, preoperative controlled ovarian stimulation for fertility preservation was not associated with poorer observed oncologic outcomes.
- **BCYW:** Supports considering fertility preservation before systemic therapy, while acknowledging that the evidence is observational.

12



Breast Tumor During Ovarian Stimulation

- Paired tumor analyses assessed whether short-term ovarian stimulation with letrozole changes breast-tumor biology before treatment.
- **BCYW:** Addresses a key biological concern in fertility preservation for young women with hormone-sensitive disease.

13



Pregnancy After Fertility Preservation

- Long-term follow-up found that pregnancies occurred after breast cancer treatment; many were conceived naturally, while a smaller proportion used previously cryopreserved material.
- **BCYW:** Fertility preservation should be considered as part of the broader reproductive journey after treatment, not solely by the number of oocytes or embryos stored.

14



SERENA-6 — Treating Resistance Before Progression

- Detecting an emerging ESR1 mutation in ctDNA enabled an endocrine-therapy switch before radiographic progression, extending progression-free survival.
- **BCYW:** Not specific to age, but it introduces a treatment model that may intercept molecular resistance while the disease remains clinically controlled.

KEY MESSAGE

Breast cancer treatment for young women is moving beyond age alone to consider tumor biology, ovarian function, genomic risk, reproductive priorities, and how molecular features change over time.

01

15-Year SOFT/TEXT:
How Much Endocrine Treatment Does a Young Woman Need?

Final 15-Year Outcomes Clarify Who Benefits Most From Ovarian Function Suppression

STUDY

Francis PA, Pagani O, et al. Final outcomes of the SOFT and TEXT phase III trials in premenopausal hormone receptor-positive early breast cancer. Ann Oncol. 2026;37(10):1367–1385.

THE EVIDENCE GAP

For premenopausal women with HR-positive early breast cancer, the long-term benefit of adding ovarian function suppression (OFS)—and which young women benefit most—has remained uncertain.

POPULATION & DESIGN

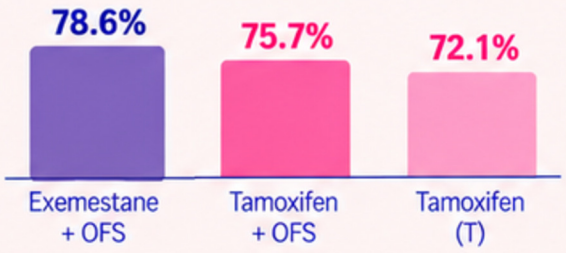
- Phase III randomized trials (SOFT and TEXT; international).
- Premenopausal women ≤50 years with HR-positive early breast cancer.
- SOFT: n = 3,047, randomized to 5 years tamoxifen (T) alone, T + OFS, or exemestane + OFS (E+OFS).
- TEXT: n = 2,660, randomized to 5 years tamoxifen + OFS (T+OFS) or exemestane + OFS (E+OFS).
- Final outcomes reported at 15 years.

BCYW RELEVANCE

- Provides the longest follow-up on endocrine therapy with or without OFS in premenopausal women.
- Clarifies which young women benefit most.
- Supports individualized treatment based on recurrence risk and tolerability.
- Important for shared decision-making regarding treatment duration and OFS use in young women.

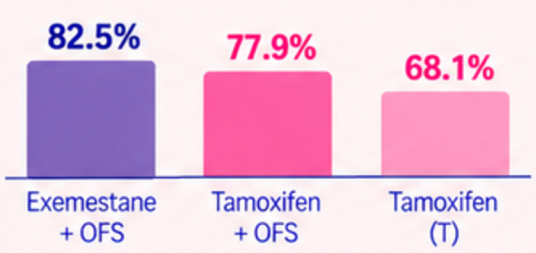
KEY RESULTS

15-Year Breast Cancer–Free Interval (BCFI)
SOFT trial



T + OFS vs T:
HR 0.82 (95% CI 0.69–0.98); *P* = 0.03.

15-Year Overall Survival in Women <35 Years, HER2-Negative
(subgroup n = 241)



COMBINED SOFT/TEXT RESULT

In HER2-negative disease (n = 4,035), **exemestane + OFS vs tamoxifen + OFS reduced distant recurrence:**

HR 0.75
(95% CI 0.63–0.90).

STUDY & POPULATION

- Long-term benefit is not uniform across all premenopausal women.
- Absolute survival benefit was largest in higher-risk groups, particularly very young women and those with high-grade tumors.
- In women <35 with HER2-negative disease, the 15-year survival separation was clinically substantial.
- Treatment choice should balance recurrence risk, endocrine benefit, toxicity, quality of life, fertility, and patient priorities.

THE BOTTOM LINE

At 15 years, ovarian suppression—particularly exemestane + OFS—provides the greatest long-term benefit in higher-risk premenopausal women. The strongest survival separation was seen in very young women with HER2-negative disease.

02

ADJUVANT RIBOCICLIB:
Extending CDK4/6 Inhibition Into Curative Treatment

Five-Year Results from NATALEE Show Significant Survival Benefit for High-Risk HR+/HER2– Early Breast Cancer—Including Premenopausal Women

STUDY

Crown J, et al. Adjuvant ribociclib plus nonsteroidal aromatase inhibitor therapy in patients with HR-positive/HER2-negative early breast cancer: 5-year follow-up of NATALEE efficacy outcomes and updated overall survival. ESMO Open. 2025;10(11):105858.

THE EVIDENCE GAP

While CDK4/6 inhibitors have transformed metastatic HR+ breast cancer care, their role in early-stage disease was unknown. Could adding ribociclib to endocrine therapy in the adjuvant setting prevent recurrences and improve survival in high-risk patients—including premenopausal women?

STUDY & POPULATION

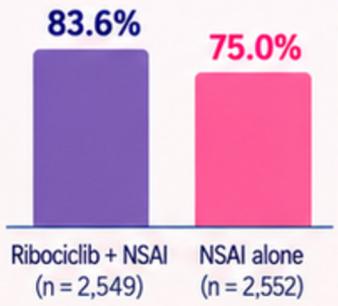
- Phase III NATALEE trial (global, randomized).
- HR-positive, HER2-negative early breast cancer.
- Stage II–III or stage I with high-risk features.
- N = 5,101.
- Included premenopausal women (~46%); OFS allowed per guidelines.
- Randomized 1:1:
  - Ribociclib 400 mg (days 1–21, every 28 days) + nonsteroidal aromatase inhibitor (NSAI) for up to 3 years.
  - NSAI alone.
- Median follow-up: 5 years.

BCYW RELEVANCE

- Meaningful improvement in survival and distant recurrence prevention in high-risk HR+/HER2– early breast cancer.
- Includes premenopausal women, many of whom require OFS.
- Reduces risk during the years when recurrence can have the greatest impact on long life ahead.
- Supports aggressive, contemporary treatment for young women with high-risk disease.

KEY 5-YEAR RESULTS

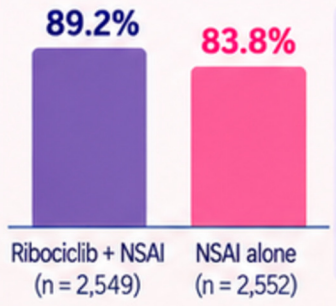
Invasive Disease–Free Survival (IDFS)



HR 0.71 (95% CI 0.63–0.79)

Δ 8.6% absolute improvement

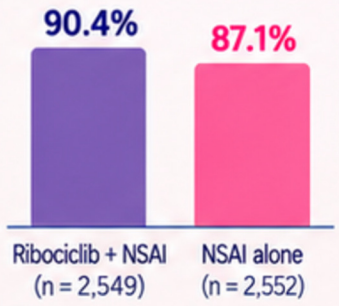
Distant Recurrence–Free Survival (DRFS)



HR 0.72 (95% CI 0.60–0.86)

Δ 5.4% absolute improvement

Overall Survival (OS)



HR 0.72 (95% CI 0.57–0.92)

Δ 3.3% absolute improvement

WHAT THIS MEANS

- First CDK4/6 inhibitor to show significant overall survival benefit in early breast cancer.
- Benefits were seen early and sustained through 5 years for IDFS, DRFS, and OS.
- Includes young, premenopausal women—an important group with higher baseline risk.
- Safety profile consistent with prior CDK4/6 inhibitor experience; manageable toxicities.

THE BOTTOM LINE

At 5 years, adjuvant ribociclib plus a nonsteroidal aromatase inhibitor significantly improves invasive disease–free survival, distant recurrence–free survival, and overall survival compared with endocrine therapy alone in high-risk HR+/HER2– early breast cancer.

03

Pembrolizumab in Young TNBC:
Survival Gain— and What Happens to Ovarian Reserve?

A 2025 Study Evaluates the Impact on Ovarian Reserve in Young Women

STUDY

Perdrix A, et al. Impact of pembrolizumab on ovarian function in young triple-negative breast cancer patients treated with chemo-immunotherapy. *Breast Cancer Res Treat.* 2025;212(1):79–86.

THE EVIDENCE GAP

Does adding pembrolizumab to standard chemotherapy cause additional damage to ovarian reserve in young women with triple-negative breast cancer (TNBC)?

STUDY DESIGN & POPULATION

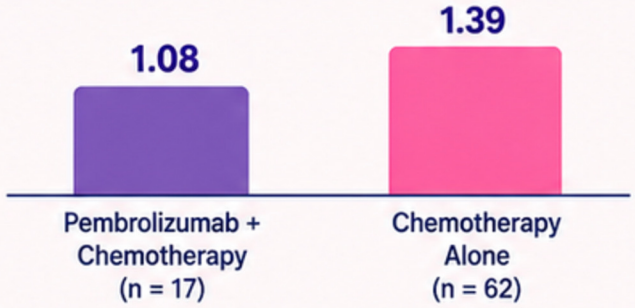
- Retrospective study of young women with TNBC (age <43 years).
- Ovarian markers measured before treatment and 1 year after starting treatment.
- Pembrolizumab + chemotherapy: n = 17.
- Chemotherapy without pembrolizumab: n = 62.

BCYW RELEVANCE

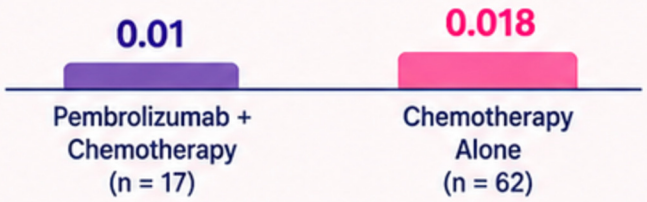
- Pembrolizumab improved outcomes in early TNBC without additional decline in ovarian reserve beyond chemotherapy alone.
- Ovarian impact remained substantial in both groups.
- Important information for young women considering chemo-immunotherapy.

KEY RESULTS

AMH Levels Before Treatment
(Median, ng/mL)



AMH Levels at 1 Year
(Median, ng/mL)



No statistically significant additional decline in AMH with pembrolizumab vs chemotherapy alone (P = 0.25).

IMPACT ON OVARIAN RESERVE



of women receiving pembrolizumab + chemotherapy had undetectable AMH levels at 1 year.

Profound ovarian impact observed in both groups, driven by chemotherapy.

THE BOTTOM LINE

In young women with TNBC, pembrolizumab added to chemotherapy did not show additional short-term harm to ovarian reserve beyond chemotherapy alone, though ovarian impact remained substantial.

04

Young-PEARL:

Palbociclib + Endocrine Therapy vs. Capecitabine in Premenopausal Women with HR+/HER2– Metastatic Breast Cancer

Overall Survival Analysis from a Randomized Phase 2 Study

STUDY

Ahn H, et al. Palbociclib plus endocrine therapy versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (Young-PEARL): overall survival analysis of a randomised, open-label, phase 2 study. *Lancet Oncol.* 2025;26(3):343–354.

THE EVIDENCE GAP

In premenopausal women with HR+/HER2– metastatic breast cancer, it was uncertain whether palbociclib plus endocrine therapy with ovarian suppression (OFS) provides a durable survival benefit compared with capecitabine.

STUDY DESIGN & POPULATION

- Multicentre, randomized, open-label, phase 2 study in South Korea.
- Premenopausal women with HR-positive, HER2-negative metastatic breast cancer.
- Total randomized: n = 184.
- Modified intention-to-treat analysis: n = 174.
  - Palbociclib + exemestane + leuprorelin (OFS): n = 90.
  - Capecitabine: n = 84.
- Median follow-up: 54.0 months.

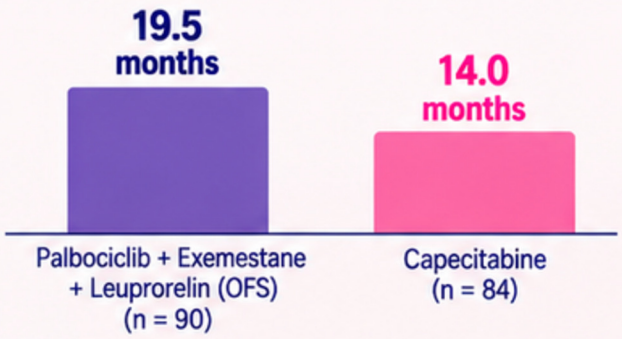
BCYW RELEVANCE

- Provides direct randomized evidence specifically in premenopausal women with HR+/HER2– metastatic disease.
- Significant PFS benefit supports CDK4/6 inhibitor + endocrine therapy/OFS as an upfront treatment option.
- Final analysis did not show improved OS compared with capecitabine.
- Treatment choice should reflect efficacy, toxicity, access, and patient priorities.

KEY RESULTS

Median Progression-Free Survival (PFS)

(Months)



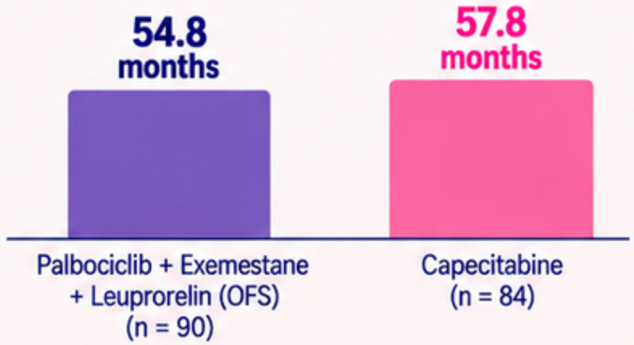
HR 0.74
(90% CI 0.57–0.98)

One-sided
P = 0.036

SIGNIFICANT PFS BENEFIT

Median Overall Survival (OS)

(Months)



HR 1.02
(95% CI 0.69–1.51)

P = 0.92

NO SIGNIFICANT OS DIFFERENCE

THE BOTTOM LINE

With extended follow-up, palbociclib + exemestane + ovarian suppression maintained a significant progression-free survival benefit over capecitabine, but did not improve overall survival.

05

POSITIVE 2026:
Can Young Women Temporarily Interrupt Endocrine Therapy for Pregnancy?

First Prospective Trial Showing That Young Women Can Pause Endocrine Therapy to Attempt Pregnancy Without Compromising Short-Term Outcomes

STUDY

Pagani O, et al. Updated results of the POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial. *Ann Oncol.* 2026 Sep;37(9):1230–1241.

THE EVIDENCE GAP

Standard endocrine therapy for HR+ breast cancer lasts 5–10 years, overlapping with peak reproductive years. Until now, there was no prospective evidence on whether temporarily interrupting therapy to try for a pregnancy was safe.

STUDY DESIGN & POPULATION

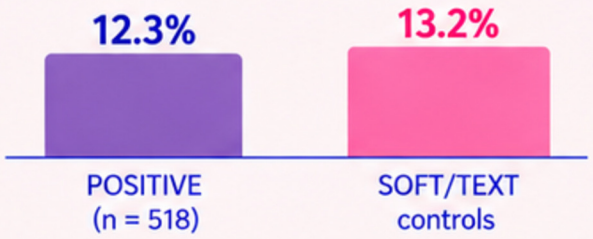
- Single-arm, prospective POSITIVE trial (international).
- 518 women ≤42 years with HR-positive, stage I–III breast cancer.
- Received 18–30 months of endocrine therapy.
- Therapy was temporarily interrupted for up to 2 years to attempt pregnancy.
- Outcomes compared with matched external controls from SOFT/TEXT trials.
- Median follow-up: 71 months.

BCYW RELEVANCE

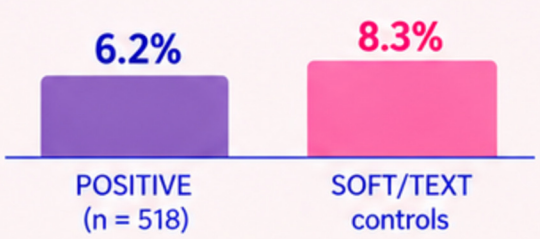
- Provides the first prospective evidence to guide shared decisions for young women with HR+ breast cancer who wish to become mothers.
- Treatments can be planned around life goals.
- Temporary interruption did not increase short-term recurrence risk.
- Longer follow-up is essential, as HR+ breast cancer can recur late.

KEY RESULTS (5-YEAR)

Breast Cancer–Free Interval Events



Distant Recurrence Events



Pregnancy Outcomes
(among 497 women evaluable)

76% had at least one pregnancy

69% had at least one live birth

These results demonstrate that many young survivors can achieve pregnancy and build their families after a cancer diagnosis.

THE BOTTOM LINE

Among women ≤42 years with HR-positive early breast cancer, temporarily interrupting endocrine therapy after 18–30 months to attempt pregnancy did not increase short-term recurrence risk and allowed most women to achieve pregnancy and live birth.

06

Chemotherapy Benefit in Premenopausal Node-Positive HR+ Disease With Oncotype DX ≤25

Real-World Evidence in Young Women

STUDY

Kumar PA, et al. The impact of adjuvant chemotherapy on overall survival in premenopausal (age ≤50 years) hormone and node positive breast cancer patients with an Oncotype Dx score of 25 or less: A NCDB analysis. *Breast Cancer Res Treat*. 2026;215(1):32.

THE EVIDENCE GAP

In premenopausal women with hormone receptor-positive, node-positive breast cancer and low Oncotype DX scores (≤25), it remains uncertain whether adjuvant chemotherapy is necessary, as most trial data are from mixed-age populations with limited representation of younger women.

POPULATION & DESIGN

- National Cancer Database (NCDB) analysis.
- Premenopausal women (age ≤50 years) with hormone receptor-positive, node-positive early breast cancer and Oncotype DX ≤25.
- Compared overall survival between those who received adjuvant chemotherapy and those who did not.
- Adjusted for relevant clinical and pathological factors using multivariable analysis.

BCYW RELEVANCE

- Provides real-world evidence on the benefit of chemotherapy in young, premenopausal women with low genomic risk.
- Helps inform shared decision-making and avoid potential overtreatment.
- Addresses a clinically relevant group often underrepresented in trial data.
- Supports use of genomic assays to guide treatment in younger women.

KEY RESULTS

Chemotherapy Group (n = 1,197)

5-Year Overall Survival	10-Year Overall Survival	5-Year Breast Cancer–Specific Survival	10-Year Breast Cancer–Specific Survival
96.2% (95% CI, 94.8–97.3)	89.3% (95% CI, 87.2–91.1)	98.7% (95% CI, 97.6–99.5)	96.5% (95% CI, 94.9–97.8)

No Chemotherapy Group (n = 2,664)

5-Year Overall Survival	10-Year Overall Survival	5-Year Breast Cancer–Specific Survival	10-Year Breast Cancer–Specific Survival
94.5% (95% CI, 93.4–95.5)	86.6% (95% CI, 85.0–88.0)	98.1% (95% CI, 97.4–98.8)	95.7% (95% CI, 94.6–96.8)

Adjusted Hazard Ratios (Chemotherapy vs No Chemotherapy)

Outcome	HR (95% CI)	P value
Overall survival	0.68 (0.58–0.80)	<0.001
Breast cancer–specific survival	0.62 (0.50–0.76)	<0.001

THE BOTTOM LINE

In premenopausal women (≤50 years) with hormone receptor-positive, node-positive breast cancer and an Oncotype DX score ≤25, adjuvant chemotherapy was associated with significantly improved overall and breast cancer–specific survival in this real-world analysis.

07

Does Low Genomic Risk Mean Premenopausal Women Can Avoid Chemotherapy?

The new RSClinN+ tool combines genomic and clinical factors to better estimate prognosis and chemotherapy benefit in node-positive HR+ breast cancer.

STUDY

Pusztai L, et al. Development and Validation of the RSClinN+ Tool to Predict Prognosis and Chemotherapy Benefit for Hormone Receptor-Positive, Node-Positive Breast Cancer. *J Clin Oncol.* 2025;43(8):919–928.

THE EVIDENCE GAP

In premenopausal women with node-positive HR+ breast cancer, a low Oncotype DX recurrence score (RS ≤25) does not consistently identify those who gain no benefit from chemotherapy. An integrated model is needed to personalize treatment decisions beyond RS alone.

STUDY & POPULATION

- Pooled patient-level data from RxPONDER (S1007) and S8814 trials.
- Development cohort: 5,283 patients; external validation cohort: 592 patients.
- HR-positive, HER2-negative, node-positive early breast cancer.
- Included both premenopausal and postmenopausal women.
- Assessed 21-gene RS and key clinical-pathologic factors.

Primary outcomes:
Invasive disease-free survival (IDFS) and chemotherapy benefit.

WHAT IS RSClinN+?

A validated prognostic and predictive tool that integrates:

- 21-Gene Recurrence Score (RS)
- Age at diagnosis
- Tumor size
- Tumor grade
- Nodal involvement (number of positive nodes)

Provides individualized 10-year prognosis and chemotherapy benefit by menopausal status.

KEY FINDINGS

BETTER RISK PREDICTION
RSClinN+ outperformed RS alone and clinicopathologic factors for IDFS in both development and validation cohorts.

CHEMOTHERAPY BENEFIT
In premenopausal women with RS ≤25, there was no significant interaction between RS and chemotherapy benefit—RS alone could not identify a subgroup with no benefit.

EXTERNAL VALIDATION
RSClinN+ estimates of 10-year IDFS closely matched observed outcomes across risk groups.

RSClinN+ refines treatment decisions by combining tumor biology with patient characteristics.

THE BOTTOM LINE

RSClinN+ is a validated tool that integrates the 21-gene Recurrence Score with age, tumor size, grade, and nodal burden to better predict prognosis and chemotherapy benefit in HR-positive, node-positive breast cancer.

In premenopausal women with RS ≤25, chemotherapy benefit cannot be ruled out by RS alone.

YW 08

After 5 Years: Should Endocrine Therapy Continue in Young Premenopausal Women?

Extended Treatment Associated With Lower Recurrence Risk

STUDY

Valenza C, et al. Extended endocrine therapy following 5 years of adjuvant LHRH agonist in premenopausal patients with node-positive, HR-positive breast cancer: a cohort study. *J Clin Oncol.* 2026;44(6):486–496. doi:10.1200/JCO-25-01660. PMID: 41538747.

THE EVIDENCE GAP

Young women with HR-positive breast cancer face a prolonged risk of recurrence, yet evidence guiding endocrine treatment beyond the first 5 years is limited for premenopausal women. It remains uncertain whether extended endocrine therapy after 5 years of ovarian suppression meaningfully reduces recurrence in this specifically young, higher-risk population.

POPULATION & DESIGN

- 501 women diagnosed at age ≤40 years with node-positive, HR-positive early breast cancer.
- All remained premenopausal and recurrence-free after completing 5 years of LHRH agonist–based endocrine therapy.
- 287 (57%) received extended endocrine therapy (median 3.7 years); 214 stopped.
- Among those continuing: 48% tamoxifen alone and 52% LHRHa + tamoxifen or aromatase inhibitor.
- Median follow-up from year 5: 7.3 years (IQR 2.3–5.0).

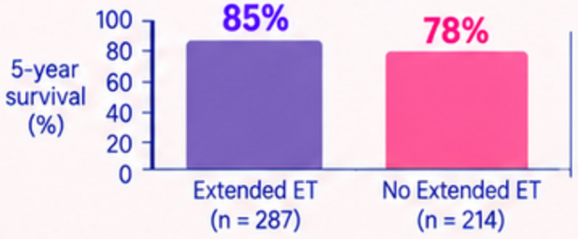
BCYW RELEVANCE

- Specifically addresses women diagnosed at ≤40 years who remain premenopausal at year 5—an under-studied, higher-risk group.
- Extended endocrine therapy may further reduce recurrence risk beyond 5 years, especially in young women with node-positive disease.
- The findings support individualized decision-making regarding continuation of endocrine therapy in young women.
- Prospective trials are needed to confirm the optimal duration and type of extended therapy in this population.

KEY RESULTS

5-Year PS-Weighted IBCFS (from Year 5)

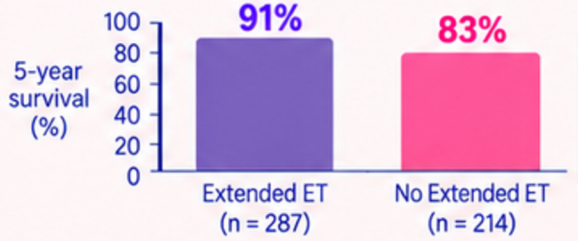
Invasive breast cancer–free survival



HR 0.63 (95% CI, 0.44–0.89) *P* = 0.0135

5-Year PS-Weighted DRFS (from Year 5)

Distant recurrence–free survival



HR 0.49 (95% CI, 0.31–0.79) *P* < 0.0001

Major cardiovascular events and fractures were reported in ~1% of women in each group.

THE BOTTOM LINE

For young women who remain premenopausal at year 5, continued endocrine therapy was associated with lower recurrence risk, but prospective confirmation is still needed.

09

Can We Predict Ovarian Failure While Chemotherapy Is Still Underway?

Ultra-Sensitive AMH Assay Predicts Premature Ovarian Insufficiency

STUDY

Kuang X, Ji M, Tang Y, et al.
Monitoring ovarian reserve dynamics via a high-sensitivity anti-Müllerian hormone assay in premenopausal breast cancer patients undergoing chemotherapy.
Hum Reprod. 2026, *published online* Aug 28, 2026. doi:10.1093/humrep/deag136. PMID: 42664366.

THE EVIDENCE GAP

Chemotherapy can substantially damage ovarian reserve in young women with breast cancer, but conventional AMH assays often become undetectable after chemotherapy, making it difficult to distinguish very low residual ovarian reserve from complete loss of function. Can a more sensitive AMH assay track ovarian damage during treatment and predict premature ovarian insufficiency (POI)?

POPULATION & DESIGN

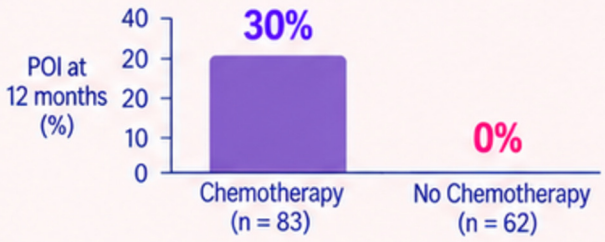
- Prospective cohort study of 145 premenopausal women aged 18–46 years with newly diagnosed breast cancer.
- 83 scheduled for chemotherapy; 62 did not receive chemotherapy.
- Serum AMH measured before treatment, after each chemotherapy cycle, at the end of chemotherapy, and at 3, 6, and 12 months afterward.
- Ultra-sensitive AMH assay with a detection limit of 0.13 pg/mL (approximately 100-fold more sensitive than conventional assays).
- Premature ovarian insufficiency (POI) defined as oligo/amenorrhea with FSH >25 mIU/mL.

BCYW RELEVANCE

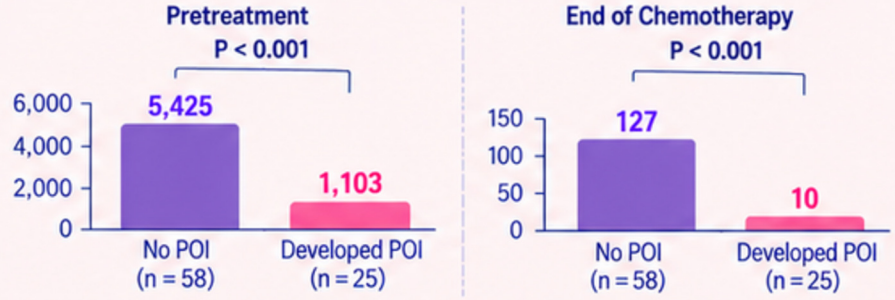
- Ultra-sensitive AMH assay quantified very low residual ovarian reserve during chemotherapy, including levels that conventional assays may miss.
- Low AMH levels before and at the end of chemotherapy predicted 12-month POI.
- May support earlier, individualized fertility counseling and reproductive planning for young women with breast cancer.
- Single-center study with attrition and 12 months of follow-up; long-term fertility outcomes (e.g., pregnancy, live birth) are unknown.

KEY RESULTS

At 12 months, 30% of the breast-cancer cohort exhibited POI.



AMH Levels (Median, pg/mL)



Prediction of Premature Ovarian Insufficiency (POI)

Pretreatment AMH
AUC 0.86
67% sensitivity
95% specificity

End of Chemotherapy AMH
AUC 0.89
81% sensitivity
93% specificity

THE BOTTOM LINE

An ultra-sensitive AMH assay detected very low residual ovarian reserve during chemotherapy and predicted 12-month POI, potentially enabling earlier identification of young women at high risk.

10

Ovarian Suppression: Is Suppression Always Complete?

About 1 in 10 Premenopausal Women Experience Inadequate Suppression

STUDY

Nardin S, et al. Comparison of suboptimal versus adequate ovarian function suppression in premenopausal women with early breast cancer treated with adjuvant endocrine therapy: an exploratory analysis of two prospective studies. *Eur J Cancer. 2026;236:116266.*

THE EVIDENCE GAP

Ovarian function suppression (OFS) with a GnRH agonist, combined with tamoxifen or an aromatase inhibitor, is a key treatment for premenopausal women with HR-positive breast cancer. However, receiving OFS does not always mean that ovarian estrogen production is completely suppressed. The frequency and predictors of inadequate suppression in routine treatment remain insufficiently defined.

POPULATION & DESIGN

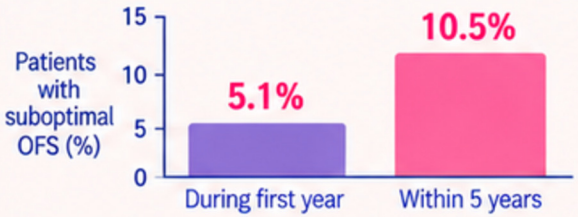
- Exploratory analysis of two prospective Italian observational studies (PREFER and GIM 23-POSTER).
- 343 premenopausal women with early breast cancer receiving adjuvant endocrine therapy with ovarian function suppression.
- 315 had adequate ovarian suppression; 28 experienced suboptimal suppression.
- Median follow-up: 44.4 months.
- Suboptimal OFS defined as estradiol >25.1 ng/L or resumption of menstruation during GnRH agonist treatment.

BCYW RELEVANCE

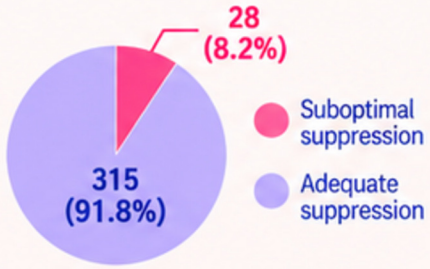
- Prescribing ovarian suppression and achieving ovarian suppression are not the same.
- About 1 in 10 premenopausal women had suboptimal suppression within 5 years.
- Inadequate suppression was strongly associated with concurrent aromatase inhibitor use.
- Regular monitoring of estradiol levels during OFS, especially with aromatase inhibitors, may be important to ensure effective treatment.

KEY RESULTS

Frequency of Suboptimal Ovarian Suppression

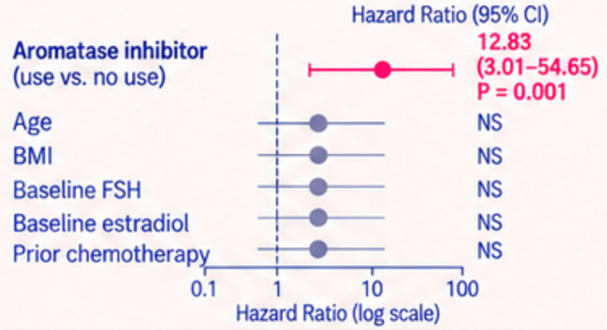


Adequate vs. Suboptimal Suppression



Total: 343 premenopausal women

Factors Associated with Suboptimal OFS



Median Follow-up

44.4 months



THE BOTTOM LINE

About 1 in 10 premenopausal women receiving GnRH agonist ovarian suppression experienced suboptimal suppression within five years—highlighting that ovarian suppression may need to be verified, not simply assumed.

11

Fertility Preservation Before Treatment: Is Preoperative Ovarian Stimulation Oncologically Safe?

Reassuring 5-Year Outcomes in ER-Positive Breast Cancer

STUDY

Chen JH, et al. Oncologic Safety of Preoperative Controlled Ovarian Stimulation for Fertility Preservation Among Women with Estrogen Receptor Positive Breast Cancer. *Ann Surg Oncol. 2026; published online July 5, 2026.*

THE EVIDENCE GAP

Controlled ovarian stimulation (COS) allows oocyte/embryo cryopreservation before gonadotoxic treatment, but in ER-positive breast cancer there is concern about stimulating the ovaries while a hormone-responsive primary tumor remains in situ. The key question is whether preoperative COS delays treatment or compromises oncologic outcomes.

POPULATION & DESIGN

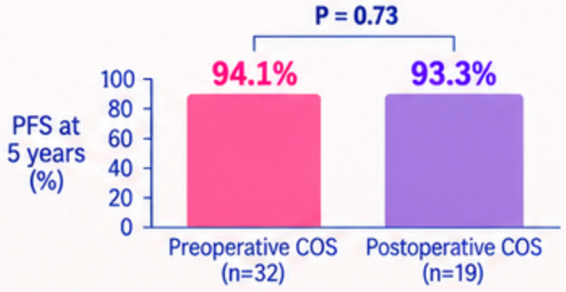
- Single-institution retrospective cohort, 2014–2024. 51 women with ER-positive breast cancer underwent COS: 32 preoperative and 19 postoperative.
- Median follow-up: 5.5 years.
- Primary endpoint: progression-free survival (PFS).
- Among women receiving neoadjuvant systemic therapy, 30 who underwent preoperative COS were propensity-score matched 1:1 to controls who did not undergo COS, matched by age, HER2 status, and clinical stage.

BCYW RELEVANCE

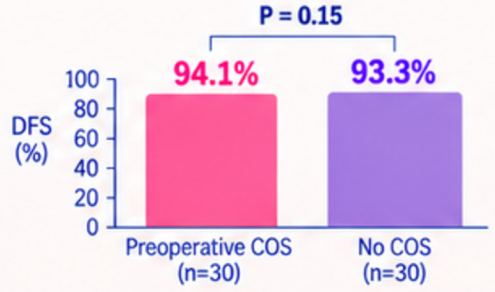
- Directly addresses a major fertility-preservation concern for young/reproductive-age women with ER-positive breast cancer.
- Preoperative COS was not associated with increased progression or death in this cohort.
- COS was associated with a longer interval before neoadjuvant therapy, so multidisciplinary coordination remains important.
- Small, retrospective, single-center study; findings are reassuring but not definitive.

KEY RESULTS

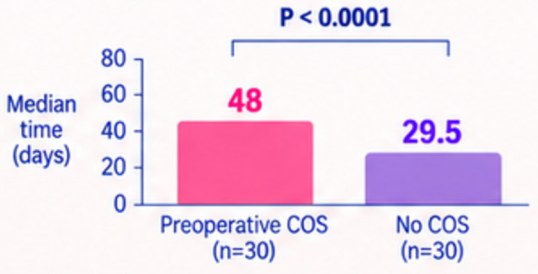
5-Year Progression-Free Survival (Preoperative vs Postoperative COS)



Disease-Free Survival in Neoadjuvant Matched Comparison



Median Time from Diagnosis to Neoadjuvant Systemic Therapy



Events During Neoadjuvant Period (Preoperative COS)

0

No disease-progression events during the neoadjuvant period among women undergoing preoperative fertility preservation (n=30).

THE BOTTOM LINE

Preoperative ovarian stimulation for fertility preservation was not associated with worse oncologic outcomes in this ER-positive breast cancer cohort—providing reassuring, though not definitive, evidence for young women who need fertility preservation before gonadotoxic treatment.

12

What Happens to the Breast Tumor During Ovarian Stimulation?

Paired-Biopsy Analysis Shows No Meaningful Molecular Changes

STUDY

Barral El Gaoui Y, et al. Molecular effects of ovarian stimulation for fertility preservation in breast cancer: a paired-biopsy analysis. *ESMO Open*. 2026;11(7):108281.

THE EVIDENCE GAP

Controlled ovarian stimulation (COS) for fertility preservation transiently increases hormone levels, raising concern that it may stimulate the breast tumor, particularly in hormone receptor–positive disease. While clinical outcomes are reassuring, direct biological evidence is needed to determine whether COS alters tumor characteristics during this short period before cancer treatment.

POPULATION & DESIGN

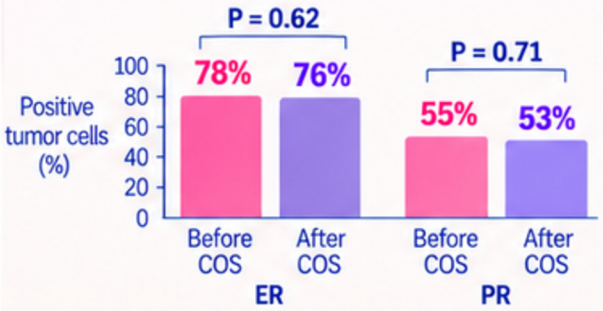
- Prospective paired-biopsy study.
- Women with early breast cancer undergoing COS for fertility preservation, with letrozole co-treatment.
- Matched tumor core biopsies obtained before and after COS from the same patients.
- Tumors evaluated for ER, PR, Ki-67, tumor-infiltrating lymphocytes (TILs), and molecular features including PAM50 subtype and risk-of-recurrence (ROR) score.
- Each patient served as her own control, minimizing interpatient variability.

BCYW RELEVANCE

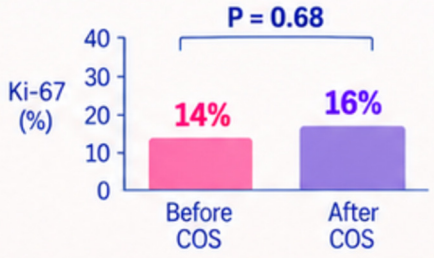
- Provides direct molecular evidence that COS does not induce short-term biological activation of the breast tumor when letrozole is used.
- Reinforces the oncologic safety of fertility preservation from a tumor biology perspective.
- Supports counseling of young women with ER-positive breast cancer who are considering COS before treatment.
- Findings should be interpreted in light of the responder-based, long-term follow-up design.

KEY RESULTS

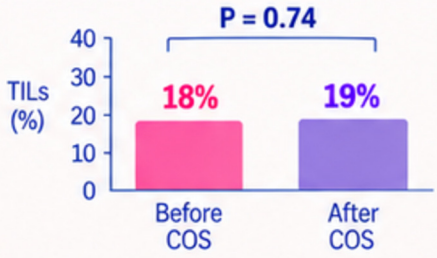
Hormone Receptor Expression (No Significant Change)



Ki-67 Proliferation Index (No Significant Change)



Tumor-Infiltrating Lymphocytes (No Significant Change)

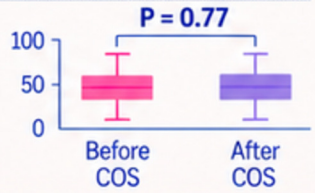


Molecular Subtype and Recurrence Risk (Stable During COS)

PAM50 subtype
No significant change in distribution



Risk-of-recurrence (ROR) score
No significant change (median values)



THE BOTTOM LINE

Paired tumor biopsies showed no significant changes in ER, PR, Ki-67, TILs, PAM50 molecular subtype, or risk-of-recurrence score during letrozole-based ovarian stimulation—providing direct biological reassurance for fertility preservation in young women with breast cancer.

YW 13

After Fertility Preservation:
Do Young Women Actually Achieve Pregnancy?
Long-Term Reproductive Outcomes After Ovarian Stimulation

STUDY

Paans BF, et al. Reproductive outcomes after fertility preservation using tamoxifen or letrozole in women with breast cancer: a long-term follow-up. *F&S Reports*. 2026;7(2):125–133.

THE EVIDENCE GAP

Ovarian stimulation can preserve oocytes/embryos before breast-cancer treatment, but young women ultimately need long-term evidence about whether pregnancy occurs after treatment, whether conception is natural or requires assisted reproduction, and whether adding tamoxifen or letrozole during stimulation affects later pregnancy or live-birth outcomes.

POPULATION & DESIGN

- Follow-up of the multicentre randomized open-label STIM-RCT plus STIM-cohort.
- Women aged 18–43 years with breast cancer who chose fertility preservation through ovarian stimulation.
- 216 surviving women invited to follow-up (141 STIM-RCT, 75 STIM-cohort).
- 95 STIM-RCT responders: mean follow-up: 7 years.
- Among the 95 responders: 36 received tamoxifen, 32 letrozole, and 27 no addition.

BCYW RELEVANCE

- Directly addresses long-term reproductive outcomes important to young women after breast-cancer treatment.
- Most observed pregnancies were conceived naturally.
- No evidence of different pregnancy or live-birth rates when tamoxifen or letrozole was added versus standard stimulation.
- Findings should be interpreted in light of the responder-based, long-term follow-up design.

KEY RESULTS

STIM-RCT Responders (n = 95)

Women became pregnant (at least once)	Total pregnancies	Conceived naturally (unassisted)	Used cryopreserved oocytes/embryos
44 of 95 responders	**63** pregnancies	**76%** 48 of 63 pregnancies	**7%** 7 of 95 responders

STIM-Cohort (n = 75)

Women became pregnant (at least once)	Total pregnancies	Conceived naturally (unassisted)	Used cryopreserved oocytes/embryos
20 of 75 women	**30** pregnancies	**90%** of pregnancies	**1** woman used cryopreserved embryos

Comparison of Pregnancy and Live-Birth Rates (Tamoxifen or Letrozole vs Standard Stimulation)

Outcome	Tamoxifen vs Standard RR (95% CI)	Letrozole vs Standard RR (95% CI)
Pregnancy rate	**0.92** (0.54–1.58)	**0.84** (0.48–1.50)
Live-birth rate	**0.81** (0.54–1.22)	**0.82** (0.53–1.26)

THE BOTTOM LINE

After about 7 years of follow-up, pregnancy was achievable after breast-cancer treatment, and most observed pregnancies occurred naturally; adding tamoxifen or letrozole during ovarian stimulation was not associated with different pregnancy or live-birth rates.

14

Can We Treat Endocrine Resistance Before the Cancer Progresses?

SERENA-6: ctDNA-Guided Switching at Emerging ESR1 Mutation

STUDY

Bidard FC, et al. First-Line Camizestrant for Emerging ESR1-Mutated Advanced Breast Cancer. *N Engl J Med.* 2025;393:569–580.

THE EVIDENCE GAP

ESR1 mutations are a common acquired mechanism of resistance to aromatase inhibitor plus CDK4/6 inhibitor therapy in ER-positive breast cancer. Standard treatment changes usually follow clinical or radiographic progression. SERENA-6 tested whether serial ctDNA monitoring could detect emerging ESR1 resistance and guide an endocrine treatment switch before radiographic progression.

POPULATION & DESIGN

- Randomized, phase 3 SERENA-6 trial. Patients with ER-positive/HER2-negative advanced breast cancer.
- 3,256 patients underwent serial ctDNA *ESR1* testing every 2–3 months while receiving first-line aromatase inhibitor plus CDK4/6 inhibitor.
- 315 patients with newly detected ESR1 mutation and no radiographic progression were randomized: 157 switched aromatase inhibitor to camizestrant 75 mg daily (continued same CDK4/6 inhibitor), 158 continued the same aromatase inhibitor plus CDK4/6 inhibitor.
- Interim median follow-up: 12.6 months.

BCYW RELEVANCE

NOT BCYW-SPECIFIC. Conducted in patients with advanced breast cancer.

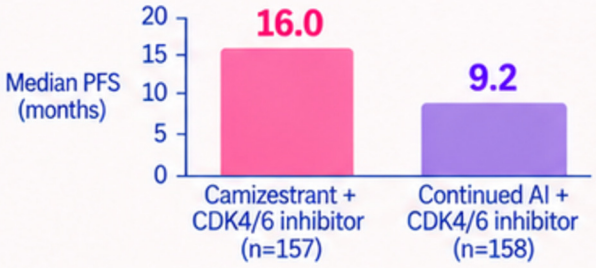
Premenopausal/perimenopausal women were represented; the subgroup combining pre/perimenopausal women and men showed a directionally consistent benefit (HR 0.39; 95% CI 0.19–0.79), but this was a subgroup, not a dedicated young-women analysis.

Provides proof of concept for molecular interception—treating ESR1 resistance before radiographic progression.

May be relevant to younger women with HR-positive advanced breast cancer, for whom durable endocrine control is a key goal.

KEY RESULTS

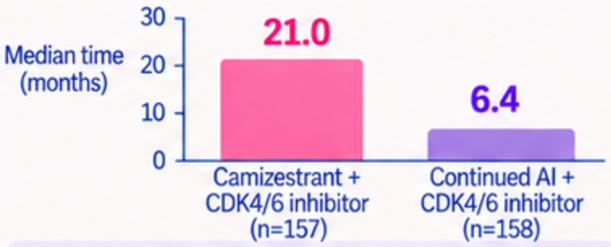
Median Progression-Free Survival (PFS)



HR 0.44
(95% CI 0.31–0.60)
P < 0.0001

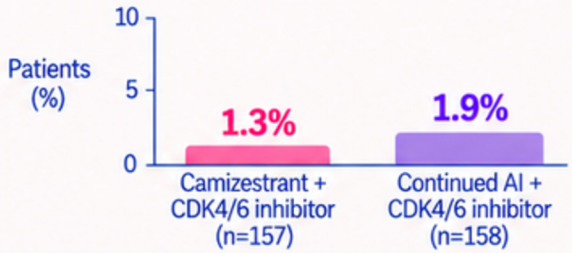
↓ 56%
lower risk of progression or death

Median Time to Deterioration in Global Health Status (QOL)



HR 0.54 (95% CI 0.34–0.84)

Treatment Discontinuation Due to Adverse Events



THE BOTTOM LINE

SERENA-6 shows that emerging *ESR1* resistance can be detected in blood and acted on before radiographic progression—introducing a molecular-interception strategy for endocrine-resistant HR+/HER2– advanced breast cancer.

WHAT'S NEXT IN BCYW TREATMENT?

5 Ongoing Trials Designed Around Premenopausal and Young Women

01 | OFSET
NCT05879926

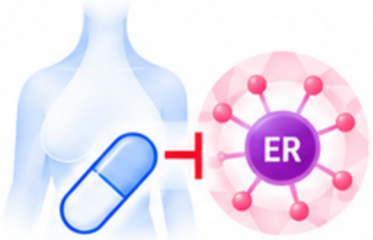


AGE: PREMENOPAUSAL WOMEN

Population:
Premenopausal women with HR+/HER2– early breast cancer and defined 21-gene Recurrence Scores.

Question:
Does chemotherapy provide benefit beyond optimal ovarian function suppression + endocrine therapy?

02 | preEMBER
NCT07287098

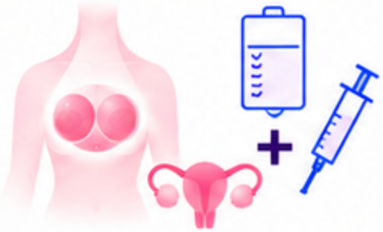


AGE: PREMENOPAUSAL WOMEN

Population:
Premenopausal women with ER+/HER2– early breast cancer.

Question:
Can the oral SERD imlunestrant effectively suppress ER signaling, including investigation of treatment with versus without ovarian suppression?

03 | NCT06225284
GnRH Agonist + Neoadjuvant Chemotherapy in TNBC



AGE: PREMENOPAUSAL WOMEN

Population:
Premenopausal women with early triple-negative breast cancer.

Question:
Does adding a GnRH agonist during neoadjuvant chemotherapy influence treatment response and outcomes in premenopausal TNBC?

04 | RENAISSANCE
NCT06184750



AGE: 18–55 (PREMENOPAUSAL WOMEN)

Population:
Premenopausal women at increased breast cancer risk.

Question:
Can low-dose tamoxifen be individualized according to biological response, creating a more tolerable approach to pharmacologic prevention?

05 | Acolbifene vs Low-Dose Tamoxifen
NCT05941520



AGE: PREMENOPAUSAL WOMEN

Population:
Premenopausal women at increased breast cancer risk.

Question:
Can acolbifene or low-dose tamoxifen favorably modify breast-tissue, imaging and circulating risk biomarkers while providing a better prevention strategy?

THE BOTTOM LINE

The next generation of BCYW trials is beginning to ask questions specifically around **premenopausal biology** — not simply enrolling young women into trials designed for all ages. From optimizing ovarian suppression and potentially avoiding chemotherapy to next-generation endocrine therapy and pharmacologic prevention, these studies could help make treatment increasingly specific to younger women.

Learn more about these and other clinical trials at: **https://www.cancer.gov/about-cancer/treatment/clinical-trials**

EVIDENCE GAPS

Examples of Unresolved Issues Facing Young Women

01 | Age-Specific Biology and Treatment Evidence

Young women remain underrepresented in many pivotal treatment trials. Premenopausal patients are often grouped together, even though they differ in age, ovarian function, tumor biology, and reproductive priorities.

02 | Chemotherapy Benefit Versus Ovarian Suppression

In premenopausal women with HR-positive breast cancer, the relative contributions of chemotherapy's direct effects and ovarian suppression are still unclear. Prospective trials are needed to determine whether optimized ovarian suppression and endocrine therapy can replace chemotherapy for selected patients.

03 | Optimizing Ovarian Suppression and Hormone Therapy

The optimal intensity and duration of endocrine treatment for very young women remain unclear. More evidence is needed to determine when ovarian suppression is inadequate, how to monitor it, and which patients benefit from extended treatment.

04 | Genomic Risk and Treatment Selection

Genomic assays improve recurrence-risk estimates but remain limited in identifying premenopausal women who can safely avoid chemotherapy. Models that combine genomic risk, clinical characteristics, ovarian function, and age-specific biology still need further validation.

05 | Ovarian Toxicity and Reproductive Outcomes

Long-term evidence linking treatment-related changes in ovarian reserve to subsequent ovarian recovery, fertility, pregnancy, and live birth remains limited. More prospective studies are needed to distinguish temporary ovarian dysfunction from irreversible damage.

06 | Fertility Preservation and Oncologic Safety

Early studies provide reassuring evidence that ovarian stimulation before treatment may be safe, even for people with hormone-sensitive breast cancer. However, larger prospective studies with longer follow-up are needed to confirm oncologic safety and evaluate reproductive outcomes.

07 | Molecular Resistance and Therapeutic Interception

Circulating tumor DNA may help identify emerging resistance before it appears on imaging. Whether treatment changes guided by molecular findings improve long-term survival, and how well these approaches work specifically in younger women, remains to be established.

08 | Long-Term Outcomes and Young-Women-Specific Trials

Treatment strategies should be evaluated not only for early recurrence and progression-free survival, but also for their long-term effects. Trials focused specifically on young women are needed to assess long-term survival, treatment toxicity, ovarian function, reproductive outcomes, and quality of life.

THE BOTTOM LINE

The key evidence gap is not just whether effective treatments exist, but whether age-specific biologic evidence can show which treatment is best for young women with breast cancer, at what intensity and duration, and what the long-term consequences may be.

IMPLICATIONS FOR BCYW TREATMENT

Where Treatment Is Going

The evidence assembled in this Digest points to a broader shift in how breast cancer treatment for young women is understood. The field is moving beyond simply applying standard breast cancer therapies at a younger age. Increasingly, treatment must account for the interplay among tumor biology, ovarian function, endocrine state, genomic risk, reproductive goals, and molecular evolution over time.

From Age To Biological Context

Chronological age alone does not fully define the therapeutic context of breast cancer in young women. Premenopausal endocrine physiology and ovarian function can affect treatment selection, therapeutic effects, toxicity, and reproductive outcomes. The emerging framework therefore considers disease in younger women within its biological and physiological context, rather than treating age as an isolated variable.

From Treatment Selection to Treatment Calibration

The question is increasingly not just which treatment to use, but also how much to give, to whom, and for how long. Evidence from endocrine therapy, ovarian suppression, chemotherapy, CDK4/6 inhibition, and genomic risk assessment points toward better tailoring treatment intensity and duration to recurrence risk, endocrine state, and individual tumor characteristics.

From Reproductive Preservation to Treatment Integration

Ovarian function is at once a therapeutic target, a potential mediator of treatment effects, and a consequence of treatment. Fertility preservation, ovarian reserve, pregnancy, and interruptions to endocrine therapy are therefore being incorporated into therapeutic decision-making, rather than considered only after cancer treatment.

From Static to Evolving Disease

Treatment has traditionally been guided by characteristics measured at diagnosis or at clinical progression. Serial molecular monitoring offers a different paradigm: it detects biological changes during therapy and may enable action against emerging resistance before clinical or radiographic progression. This moves treatment toward a more dynamic, biology-informed approach over the course of disease.

THE BOTTOM LINE

Breast cancer treatment for young women is moving toward a more biologically informed, personalized approach that brings together tumor biology, premenopausal physiology, genomic risk, reproductive priorities, and molecular changes during treatment.

REFERENCES FOR THE HIGHLIGHTED STUDIES

01 | 15-Year SOFT/TEXT: How Much Endocrine Treatment Does a Young Woman Need?

Francis PA, et al.; SOFT and TEXT Investigators. Final outcomes of the SOFT and TEXT phase III trials in premenopausal hormone receptor-positive early breast cancer. *Ann Oncol*. 2026;37(10):1367–1385.

02 | Adjuvant Ribociclib: Extending CDK4/6 Inhibition Into Curative Treatment

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