Adjuvant hormone therapy in breast cancer

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premenopausal women

postmenopausal women

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- **Fewer than one-third of women with newly diagnosed breast cancer are premenopausal**

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HIGH-RISK, HORMONE RECEPTOR-POSITIVE CANCERS

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The addition of (OFS)/ablation to either an aromatase inhibitor (AI) or tamoxifen for some patients results in a clinically significant reduction in the risk of recurrence but does increase toxicity.

- **For those at the highest risk for recurrence, we suggest OFS with an AI (or OFS with tamoxifen, as an alternative), given that this subset of patients has the highest likelihood of experiencing benefit.**

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Trial (SOFT)

(TEXT)

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- Formal criteria to define high risk are not present.
- Patients in whom chemotherapy is indicated, such as patients with the presence of pathologically involved lymph nodes, large tumor size, high risk of recurrence based on a genomic assay, or other high-risk features for which the patient received chemotherapy. In addition, we also consider women at a younger age (ie, ≤35 years)

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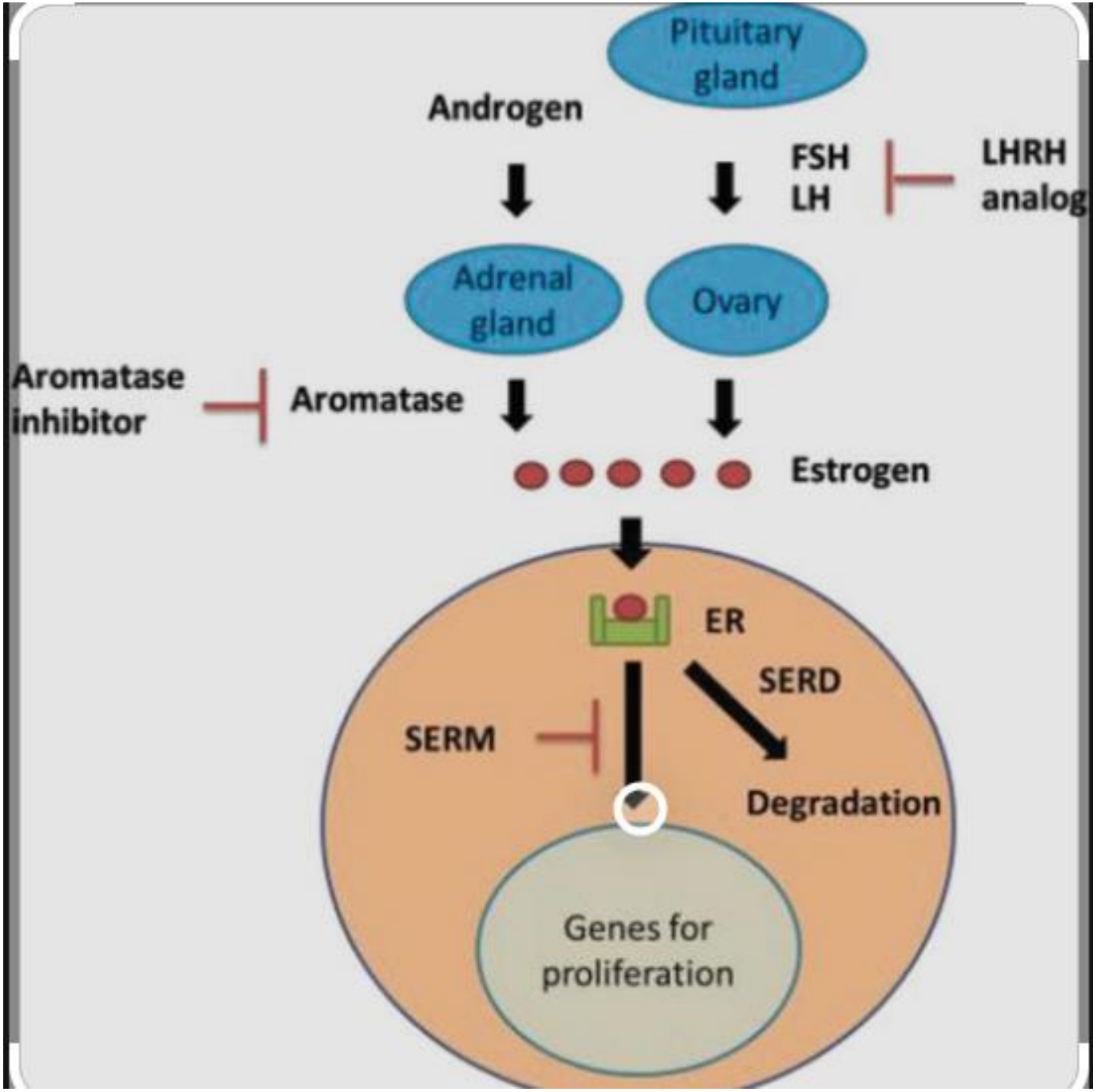
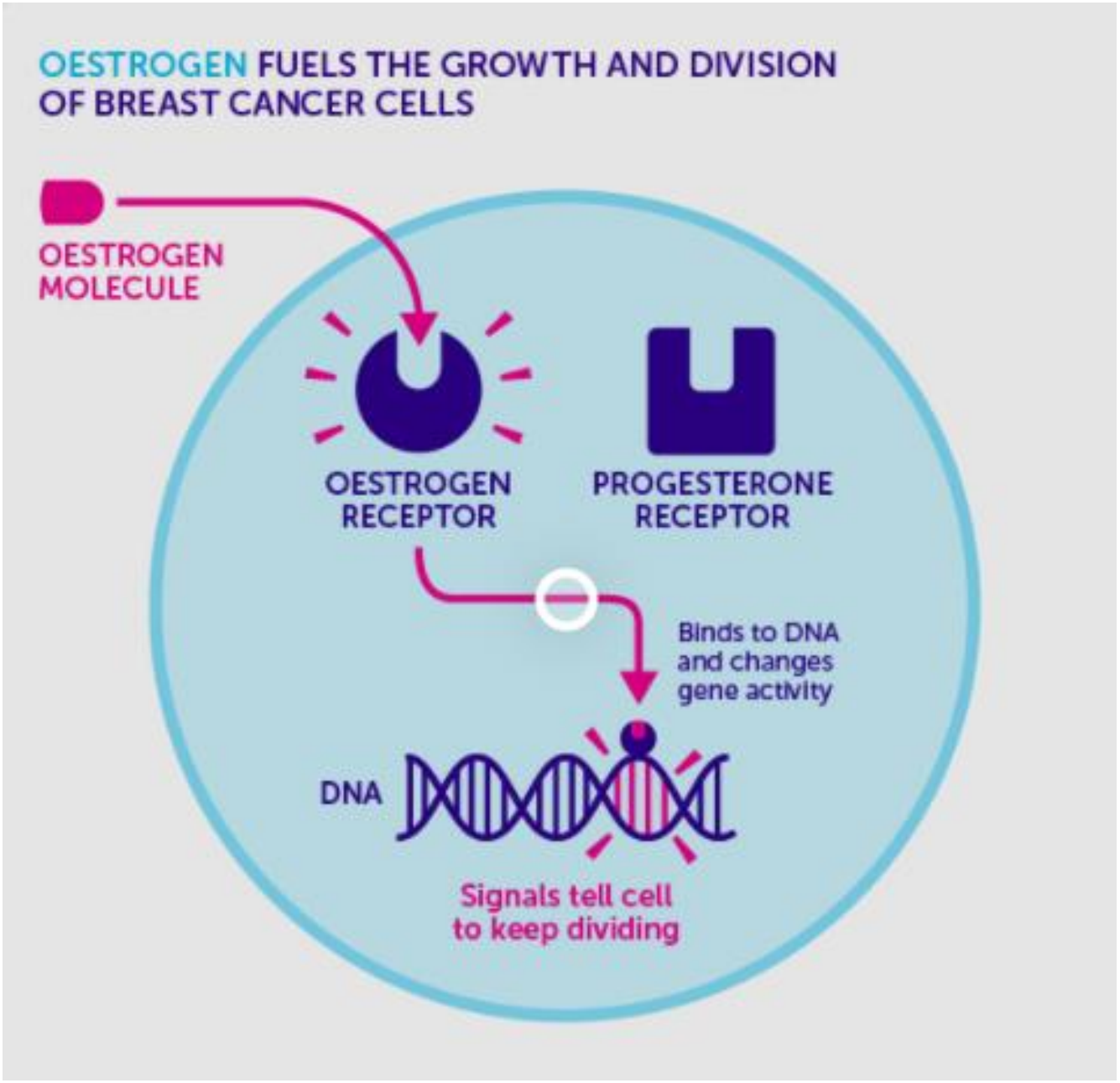
Ovarian suppression plus endocrine therapy

- **Ovarian function can be suppressed with GnRHa or by permanent methods, such as oophorectomy or, rarely, irradiation.**


Pituitary gland
Androgen
FSH
LH
LHRH analog
Adrenal gland
Ovary
Aromatase inhibitor
Aromatase
Estrogen
ER
SERD
SERM
Degradation
Genes for proliferation


OESTROGEN FUELS THE GROWTH AND DIVISION OF BREAST CANCER CELLS
OESTROGEN MOLECULE
OESTROGEN RECEPTOR
PROGESTERONE RECEPTOR
Binds to DNA and changes gene activity
DNA
Signals tell cell to keep dividing

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Suppression of Ovarian Function Trial (SOFT), over 3000 such women were randomly assigned to one of three arms:

- **tamoxifen alone,**
- **tamoxifen plus OFS, or**
- **exemestane plus OFS.**

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In the Tamoxifen and Exemestane Trial (TEXT), over 2600 premenopausal women were randomly assigned to receive tamoxifen plus OFS or exemestane plus OFS after surgery.

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- **Results of SOFT in the overall population, at median follow-up of eight years:**

  - Compared with tamoxifen alone, tamoxifen plus OFS improved eight-year disease-free survival (DFS) rate (83 versus 79 percent; hazard ratio [HR] 0.76, 95% CI 0.62-0.93), as did exemestane plus OFS (86 versus 79 percent; HR 0.65, 95% CI 0.53-0.81).
  - Tamoxifen plus OFS also modestly improved survival

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- However, freedom from distant recurrence at eight years was similar between patients receiving tamoxifen plus OFS versus tamoxifen alone (89 versus 88 percent; HR 0.86, 95% CI 0.66-1.13), and it was only modestly improved for those receiving exemestane plus OFS (91 percent; HR versus tamoxifen 0.73, 95% CI 0.55-0.96).

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These data suggest a possible modest DFS benefit with the addition of OFS to either tamoxifen or AI over tamoxifen alone for patients with hormone receptor positive breast cancer.

But may not justify the more intensive side effects for many average-risk patients.

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Exploratory and subgroup analyses suggest that patients with a higher risk of relapse may derive a benefit with OFS plus either AI or tamoxifen versus tamoxifen alone.

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Toxicity

The side effect profile of OFS or ablation mimics symptoms of estrogen deprivation, as with menopause.

Across both SOFT and TEXT, toxicities were greater among those receiving OFS relative to single-agent tamoxifen.

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Investigational approach

monarchE trial

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

REVIEW

CDK4/6 inhibitors as adjuvant treatment for hormone receptor-positive, HER2-negative early breast cancer: a systematic review and meta-analysis

E. Agostinetto[1,2,3*], L. Vian[4], R. Caparica[1], M. Bruzzone[5], M. Ceppi[5], M. Lambertini[6,7], N. Pondé[4] & E. de Azambuja[1]

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The administration of adjuvant CDK4/6 inh to patients with HRþ/HER2 EBC showed a trend for an IDFS benefit and an increase in the risk of toxicities and treatment discontinuation. The role of adjuvant CDK4/6 inh remains controversial and a longer follow-up of these randomized controlled trials is needed before supporting a straightforward change in clinical practice.

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Clinical Trial > J Clin Oncol. 2020 Dec 1;38(34):3987-3998. doi: 10.1200/JCO.20.02514. Epub 2020 Sep 20.

Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE)

Stephen R D Johnston [1], Nadia Harbeck [2], Roberto Hegg [3], Masakazu Toi [4], Miguel Martin [5], Zhi Min Shao [6], Qing Yuan Zhang [7], Jorge Luis Martinez Rodriguez [8], Mario Campone [9],

Conclusion: Abemaciclib when combined with ET is the first CDK4/6 inhibitor to demonstrate a significant improvement in IDFS in patients with HR+, HER2- node-positive EBC at high risk of early recurrence.

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oncology PRO
Educational Portal for Oncologists

Proffered Paper - Breast cancer, early stage

LBA12 - PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer

Conclusions

Within the PALLAS trial, at IA2, two years of adjuvant palbociclib with ET did not improve iDFS compared to ET alone. Ongoing long-term follow-up and additional clinical and translational analyses will explore the effect of P in this patient population.

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LOW-TO-AVERAGE-RISK, HORMONE RECEPTOR-POSITIVE CANCERS

For most women who appear not to be at high risk of recurrence, and who are over the age of 35 years, we initiate tamoxifen as single-agent therapy.

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Some women at average risk of relapse, particularly those who have residual breast tissue and are therefore at risk for a new breast primary, may reasonably choose to pursue ovarian function suppression (OFS) in addition an aromatase inhibitor (AI).

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For many women who initiate single-agent tamoxifen, we transition to an AI later in the course of therapy if the patient remains amenorrheic and has follicle-stimulating hormone (FSH) and serum estradiol levels that are in the postmenopausal range.

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LOW-TO-AVERAGE-RISK, HORMONE RECEPTOR-POSITIVE CANCERS

- Tamoxifen **versus OFS plus endocrine therapy**

Thus, although the relative risk reduction is similar across patient subgroups, the absolute benefits are lower for those at those at average and low risk.

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LOW-TO-AVERAGE-RISK, HORMONE RECEPTOR-POSITIVE CANCERS

Therefore, tamoxifen alone is suggested in these patients, given increased toxicities associated with OFS plus endocrine therapy

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Risk of ovarian function reactivation on an AI

- The risk of recovering ovarian function with AI treatment alone appears to be age related, although it has been observed even in women in their early 50s.

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In a prospective substudy of SOFT, the SOFT Estrogen Suppression Study (SOFT-EST), estradiol levels were measured in a central laboratory at several time points during the first year of therapy with triptorelin, and, at each time point, 17 percent of the women receiving OFS and exemestane were found to have levels above those that have been reported in postmenopausal women on AIs.

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DURATION OF ENDOCRINE THERAPY

The **minimum duration** of treatment with endocrine therapy **is 5 years**, although extended treatment to 10 years is appropriate in women with higher-risk disease.

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For women with smaller, node-negative tumors, such as those who are candidates for tamoxifen alone, it is not clear that there is a suficiently high risk of late recurrence to justify the side effects and risks of extended endocrine therapy, and a decision should be made based on individual preferences.

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In general, women who have been treated with tamoxifen only may have a higher likelihood of benefit with extended endocrine therapy.

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for premenopausal women receiving ovarian function suppression (OFS) with a GnRHa, we continue it for the duration of endocrine therapy or offer oophorectomy, if OFS is well tolerated.

One trial has evaluated a shorter course of OFS (two years) , with promising results, but two versus five years have not been compared in a head-to-head fashion, and we would therefore stop at two years only for those not tolerating treatment.

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Patients who became amenorrheic during chemotherapy

- **Amenorrhea is not a reliable indicator of menstrual status.**
- **There are no tests that can reliably predict whether or when ovarian function might occur (though chemotherapy-induced menopause is more likely to be permanent in patients in their mid-40s and above).**

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For that reason, premenopausal women with chemotherapy-induced amenorrhea should be treated as premenopausal. For such women, if an aromatase inhibitor (AI) is being considered after completion of chemotherapy, it should only be used in conjunction with either gonadotropin-releasing hormone agonist (GnRHa) therapy or following oophorectomy.

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Importance of contraception

Women who are of childbearing potential can remain fertile on tamoxifen and should be advised to use an effective means of contraception while on tamoxifen treatment (we consider ovarian function suppression adequate for contraception, for those who are additionally receiving this therapy and are compliant)

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Following completion of tamoxifen treatment, a waiting period of two months from drug discontinuation prior to attempting pregnancy is suggested to ensure that it has been cleared from the body.

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For women who become pregnant while taking tamoxifen, tamoxifen should be discontinued because its use during pregnancy is associated with congenital anomalies.

- **The baseline rate of congenital malformations is 3 to 4 percent.**

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OVARIAN HORMONE PRESERVATION

- **Medical therapy to protect ovarian hormone function may benefit younger women receiving gonadotoxic drugs**

Role of GnRH agonist

- **GnRH agonists suppress ovarian function and, therefore, have been theorized to protect the ovary**

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Role of GnRH agonist

However, the ovarian follicles are still exposed to these DNA-damaging agents even though the ovarian hormone production is suppressed.

As primordial follicles do not express gonadotropin receptors, it is unclear how GnRH agonist therapy would enhance survival of these cells, if at all.

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Role of GnRH agonist

The efficacy of GnRH therapy for preservation of fertility and/or ovarian function is difficult to assess because:

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Role of GnRH agonist

The complexity of study data is demonstrated by a 2015 trial done to determine if treatment with the GnRH agonist goserelin preserved ovarian function in women receiving chemotherapy for breast cancer. This trial assigned 218 premenopausal women with operable, receptor-negative breast cancer to receive either standard chemotherapy or standard chemotherapy with goserelin treatment.

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Role of GnRH agonist

Gonadotropin levels are not completely suppressed with the medication dose used in this study or when such therapy is initiated one week prior to chemotherapy, as was done in this trial

In addition, primordial follicle oocytes, which make up the ovarian reserve, do not have FSH or GnRH agonist receptors.

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Role of GnRH agonist

In an animal study, the authors demonstrated that GnRH agonist coadministration did not prevent chemotherapyinduced primordial follicle DNA damage and apoptotic death.

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Role of GnRH agonist

As above, we do not offer GnRH analog co-treatment to breast cancer patients or other cancer patients undergoing cytotoxic treatment to preserve fertility or ovarian function because the results are unproven and data conflict.

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DEFINITION OF MENOPAUSE

- **Women 60 years and older are postmenopausal**
- **Women less than 60 years are postmenopausal if one of the following conditions is met:**
  - They previously underwent a bilateral oophorectomy.
  - They have not had any menstrual periods for 12 months or more in the absence of tamoxifen, chemotherapy, or ovarian suppression, and the serum estradiol is in the postmenopausal range.
  - They are amenorrheic on tamoxifen, and follicle-stimulating hormone (FSH) and serum estradiol are in the postmenopausal range.

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- **Nearly all postmenopausal women who are candidates for endocrine therapy should be offered treatment, regardless of age**

- **patients at risk for treatment-related toxicities due to adjuvant endocrine therapy should be managed appropriately, with care coordinated between their oncology team and primary care clinician.**

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AIs as preferred therapy

- **AIs have consistently been shown to improve outcomes for postmenopausal women with hormone receptor-positive breast cancer compared with tamoxifen, both during and after treatment.**
- **Although tamoxifen is an acceptable alternative for women who are intolerant of AIs.**

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AIs as preferred therapy

- Anastrozole (1 mg daily)
- Letrozole (2.5 mg daily)
- Exemestane (25 mg daily)

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- **The highest risk for recurrence is within the first few years after initial diagnosis, and that the more effective treatment strategy, aromatase inhibition, is preferable to tamoxifen during that time.**

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- **However, once patients have remained disease free for a few years, switching to tamoxifen is similarly effective to continuation of AI treatment, and there may be a longer carry-over effect with tamoxifen than an AI in terms of protection against contralateral breast cancer.**

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Comparison between AIs

- **Evidence suggests similar clinical outcomes and tolerability between the aromatase inhibitors (AIs)**

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Side effects

- **AIs may also reactivate ovarian function in premenopausal women**
- **Musculoskeletal pains and stiffness(**AIMSS)
- **Sexual dysfunction**
- **cognitive problems ??**
- **hair thinning**
- **Osteoporosis, fractures, cardiovascular disease, diabetes, hypercholesterolemia**

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DURATION OF ENDOCRINE TREATMENT

Women treated with adjuvant endocrine therapy are treated for a minimum duration of five years, with extended therapy offered to some with higher-risk features. Observational data suggest that the risk of distant recurrence after five years of adjuvant endocrine treatment continues steadily for at least the subsequent 15 years.

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Selection of patients for extended therapy

Some data suggest that longer durations of endocrine therapy improve disease-free survival (DFS), if not overall survival (OS).

- **For women with larger tumors or node-positive disease, we suggest extended endocrine treatment.**

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TIMING OF ENDOCRINE THERAPY

For women with hormone receptor-positive breast cancer who are not recommended to receive other adjuvant therapy (eg, chemotherapy and/or radiotherapy), endocrine therapy is usually initiated four to six weeks after surgery.

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TIMING OF ENDOCRINE THERAPY

For patients receiving adjuvant chemotherapy, the initiation of endocrine therapy is commonly begun after chemotherapy has completed (ie, sequentially)

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TIMING OF ENDOCRINE THERAPY

For women receiving adjuvant radiation therapy (RT) for breast cancer, some experts at UpToDate initiate endocrine therapy concurrently with RT, while other experts initiate endocrine therapy sequentially.

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ADDITIONAL CONSIDERATIONS FOR HER2-POSITIVE DISEASE

- **Initiate endocrine therapy once chemotherapy has been completed (during maintenance trastuzumab)**

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INVESTIGATIONAL APPROACH

Adjuvant CDK 4/6 inhibitor with endocrine therapy

Addition of abemaciclib did not reach statistical significance among postmenopausal women (IDFS HR 0.82, 95% CI 0.62-1.08; distant recurrence-free survival HR 0.76, 95% CI 0.56-1.04), they were statistically significant in the premenopausal subset.

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INVESTIGATIONAL APPROACH

Adjuvant CDK 4/6 inhibitor with endocrine therapy

- Taken together, these data suggest that the **role of adjuvant CDK 4/6 inhibition is still unclear.**