IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

HORMONE THERAPY USED IN CANCER

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Abstract

Hormonal therapy is mandatory for all patients with hormonereceptor- positive breast neoplasms. It is active both in adjuvant and metastatic disease. The only active adjuvant hormonal therapy in pre- and postmenopause is Tamoxifen. The adjuvant treatment duration influences disease-free survival, the risk of a contralateral breast cancer apparition and overall survival. The aromatase inhibitors: Anastrozol, Letrozol, Exemestan are only used in postmenopause. Fulvestrant is used in recurrent disease after or during treatment with Tamoxifen. LHRH analogues are used in premenopausal patients in adjuvantcy and sometimes in case of recurrences. Around 50% of hormonereceptor- positive breast neoplasms are or become resistant to hormone therapy.

Keywords: Aromatase inhibitors, breast cancer, estrogen receptor antagonist tamoxifen, fulvestrant,

❖ Overview

- Hormone therapy for breast cancer is a treatment for breast cancers that are sensitive to hormones. The most common forms of hormone therapy for breast cancer work by blocking hormones from attaching to receptors on cancer cells or by decreasing the body's production of hormones.

- Hormone therapy is only used for breast cancers that are found to have receptors for the naturally Occurring hormones estrogen or progesterone.

- Hormone therapy for breast cancer is often used after surgery to reduce the risk that the cancer will return. Hormone therapy for breast cancer may also be used to shrink a tumor before surgery, making it more likely the cancer will be removed completely.
  If your cancer has spread to other parts of your body, hormone therapy
  For breast cancer may help control it.

❖ Why it's done

- Hormone therapy for breast cancer is only used to treat cancers that are hormone sensitive (hormone receptor positive breast cancers).

- Doctors refer to these cancers as estrogen receptor positive (ER positive) or progesterone Receptor positive (PR positive).This means that these breast cancers are fueled by the natural hormones estrogen or progesterone.

- A doctor who specializes in analyzing blood and body tissue (pathologist) determines if your cancer is ER positive or PR positive by analyzing a sample of your cancer cells to see if they have receptors for estrogen or progesterone.

❖ **Hormone therapy for breast cancer can help to:**

- Prevent cancer from coming back
- Decrease the risk of cancer developing in other breast tissue
- Slow or stop the growth of cancer that has spread
- Reduce the size of a tumor prior to surgery

❖ **Risk :**

Side effects of hormone therapy for breast cancer include

- Hot flashes
- Vaginal dryness or irritation
- Fatigue
- Nausea
- Joint and muscle pain
- Impotence in men with breast cancer
- Vaginal discharge

❖ **side effect:**

- Blood clots in veins
- Endometrial cancer or uterine cancer
- Cataracts
- Stroke
- Osteoporosis

Breast cancer:

- Some types of breast cancer are affected by hormones, like estrogen and progesterone.
- The breast cancer cells have receptors (proteins) that attach to estrogen and
- Progesterone, which helps them grow.
- Treatments that stop these hormones from attaching to these receptors are called **hormone or endocrine therapy.**
- Hormone therapy can reach cancer cells almost anywhere in the body and not just in the breast. It's recommended for women with tumors that are hormone receptor-positive.
- It does not help women whose tumors don't have hormone receptors.
- Hormone therapy is often used after surgery (as adjuvant therapy) to help reduce the risk of the cancer coming back. Sometimes it is started before surgery (as neo adjuvant therapy). It is usually taken for at least 5 to 10 years.

- Hormone therapy can also be used to treat cancer that has come back after treatment or that has spread to other parts of the body.

❖ How does hormone therapy work?

- About 2 out of 3 breast cancers are hormone receptor-positive. Their cells have receptors (proteins) for the hormones estrogen (ER-positive cancers) and/or progesterone (PR-positive cancers) which help the cancer cells grow and spread.

- There are several types of hormone therapy for breast cancer. Most types of hormone therapy either lower estrogen levels or stop estrogen from acting on breast cancer cells.

❖ What types of hormone therapy are used for breast cancer?

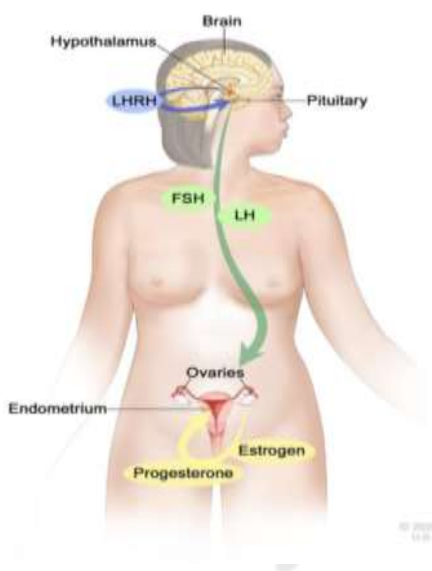
Several strategies are used to treat hormone-sensitive breast cancer:

Blocking ovarian function:

Because the ovaries are the main source of estrogen in premenopausal women, estrogen levels in these women can be reduced by eliminating or suppressing ovarian function. Blocking ovarian function is called ovarian ablation.

Ovarian ablation can be done surgically in an operation to remove the ovaries (called oophorectomy) or by treatment with radiation. This type of ovarian ablation is usually permanent.

Alternatively, ovarian function can be suppressed temporarily by treatment with drugs called gonadotropinreleasing hormone (GnRH) agonists, which are also known as luteinizing hormone-releasing hormone (LHRH) agonists. By mimicking GnRH, these medicines interfere with signals that stimulate the ovaries to produce estrogen.



Examples of ovarian suppression drugs that have been approved by the U.S. Food and Drug Administration (FDA) are goserelin (Zoladex) and leuprolide (Lupron).

Blocking estrogen production: Drugs called aromatase inhibitors are used to block the activity of an enzyme called aromatase, which the body uses to make estrogen in the ovaries and in other tissues. Aromatase inhibitors are used primarily in postmenopausal women because the ovaries in premenopausal women produce too much aromatase for the inhibitors to block effectively. However, these drugs can be used in premenopausal women if they are given together with a drug that suppresses ovarian function.

Examples of aromatase inhibitors approved by the FDA are anastrozole (Arimidex) and letrozole (Femara), both of which temporarily inactivate aromatase, and exemestane (Aromasin), which permanently inactivates aromatase.

Blocking estrogen's effects: Several types of drugs interfere with estrogen's ability to stimulate the growth of breast cancer cells:

Selective estrogen receptor modulators (SERMs) bind to estrogen receptors, preventing estrogen from binding. Examples of SERMs approved by the FDA for treatment of breast cancer are tamoxifen (Nolvadex) and toremifene (Fareston).

Because they bind to estrogen receptors, SERMs can potentially not only block estrogen activity (by preventing estrogen from binding to its receptor) but also mimic the effects of estrogen, depending on where they are expressed in the body. For example, tamoxifen blocks the effects of estrogen in breast tissue but acts like estrogen in the uterus and bone.

Other antiestrogen drugs, such as fulvestrant (Faslodex), work in a somewhat different way to block estrogen's effects. Like SERMs, fulvestrant binds to the estrogen receptor and functions as an estrogen blocker. However, unlike SERMs, fulvestrant does not mimic estrogen. For this reason, it is called a pure antiestrogen. In addition, when fulvestrant binds to the estrogen receptor, the receptor is targeted for destruction.

❖ **Hormone therapy after surgery for breast cancer**

After surgery, hormone therapy can be given to reduce the risk of the cancer coming back. Taking an AI, either alone or after tamoxifen, has been shown to work better than taking just tamoxifen for 5 years.

These hormone therapy schedules are known to be helpful for women who are **postmenopausal when diagnosed:**

- Tamoxifen for 2 to 3 years, followed by an AI for 2 to 3 years (5 years total of treatment)
- Tamoxifen for 2 to 3 years, followed by an AI for 5 years (7 to 8 years of treatment)

- Tamoxifen for 4½ to 6 years, followed by an AI for 5 years (9½ to 11 years of treatment)
- Tamoxifen for 5 to 10 years
- An AI for 5 to 10 years

- An AI for 2 to 3 years, followed by tamoxifen for 2 to 3 years (5 years total of treatment)
- For women who are unable to take an AI, tamoxifen for 5 to 10 years is an option

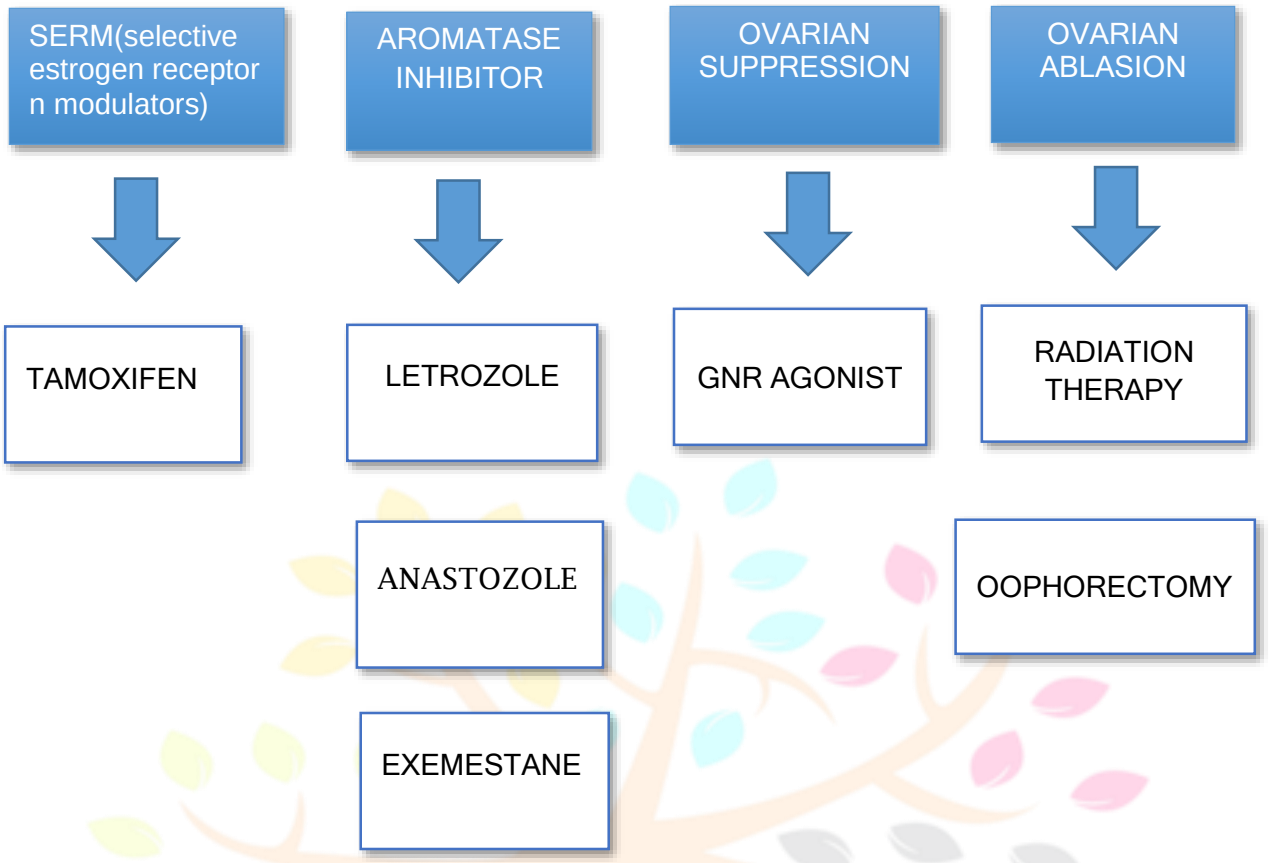
For most post-menopausal women whose cancers are hormone receptor-positive, most doctors recommend taking an AI at some point during adjuvant (after surgery) therapy. Standard treatment is to take these drugs for about 5 years, or to take in sequence with tamoxifen for 5 to 10 years. For women at a higher risk of recurrence, hormone treatment for longer than 5 years may be recommended. Tamoxifen is an option for some women who cannot take an AI. Taking tamoxifen for 10 years is considered more effective than taking it for 5 years, but you and your doctor will decide the best schedule of treatment for you.

These therapy schedules are known to be helpful forwomen who **are pre-menopausal when diagnosed:**

- Tamoxifen (with or without ovarian suppression) for 5 to 10 years.
- Tamoxifen (with or without ovarian suppression) for 5 years followed by an AI for 5 years if you have gone through menopause.
- AI plus some sort of ovarian suppression (see above) for 5 to 10 years.

If you have early-stage breast cancer and had not gone through menopause when you were first diagnosed, your doctor might recommend taking tamoxifen first, and then taking an AI later if you go through menopause during treatment. Another option is ovarian suppression by getting a drug called a luteinizing hormone-releasing hormone (LHRH) agonist, which turns off the ovaries, along with an AI**. Pre-menopausal women should not take an AI alone for breast cancer treatment because it is unsafe and can increase hormone levels.**

Treatment options



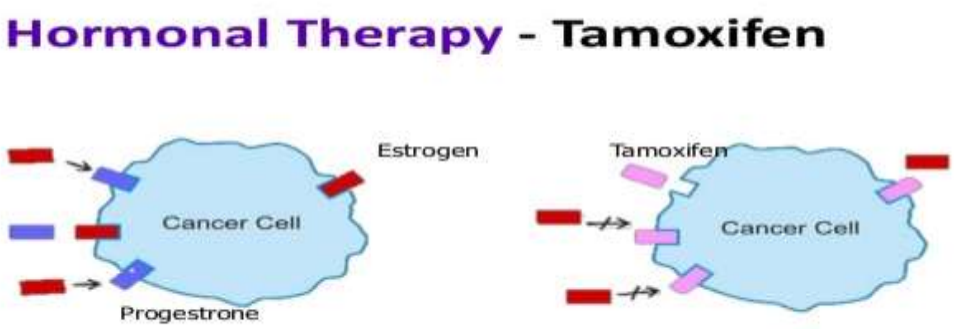
❖ TAMOXIFEN

Pharmacodynamics:

- Tamoxifen is a selective estrogen receptor modulator that inhibits growth and promotes apoptosis in estrogen receptor positive tumors.
- It has a long duration of action as the active metabolite N-desmethyltamoxifen has a half-life of approximately 2 weeks.
- It has a narrow therapeutic index as higher doses can lead to breathing difficulty or convulsions.
- Tamoxifen administration is also associated with an increased incidence of uterine malignancies.

❖ Mechanism of action:

- Tamoxifen competitively inhibits estrogen binding to its receptor, which is critical for its activity in breast cancer cells. Tamoxifen leads to a decrease in tumor growth factor α and insulin-like growth factor and an increase in sex hormone binding globulin. The increase in sex hormone binding globulin limits the amount of freely available estradiol. These changes reduce levels of factors that stimulate tumor growth.



- Tamoxifen has also been shown to induce apoptosis in estrogen receptor positive cells. This action is thought to be the result of inhibition of protein kinase C, which prevents DNA synthesis. Alternate theories for the apoptotic effect of tamoxifen comes from the approximately 3 fold increase in intracellular and mitochondrial calcium ion levels after administration or the induction of tumor growth factor β.

- Tamoxifen has a complex mechanism of action owing to its molecular structure.
- It is chemically very similar to estrogen/estradiol however estradiol is a small carbon- rich steroid and tamoxifen has an extra chain which is important for its antagonistic action.

- Tamoxifen itself is a pro-drug with a relatively low affinity for the estrogen receptor.
- It is metabolized by the cytochrome P450 family to active metabolites such as endoxifen.
- This metabolite has been shown to bind the estrogen receptor (ER) with an almost100-fold greater affinity than tamoxifen.

- Tamoxifen's pro- and anti-estrogenic actions are mediated by its competitive binding to the estrogen receptors (ERα and/or β) which then undergo a conformational change.
- For example, the prolonged binding of tamoxifen to specific genes can lead to a block in the proliferative actions of endogenous estrogen on mammary epithelium by reducing DNA polymerase activity, blocking estradiol uptake and eventually dampening the estrogen response.
- Such changes occur because the estrogen receptors function as ligand-activated transcription factors which can bind their cognate DNA sequences known as estrogen- responsive elements, and activate the transcription of factors that can either stimulate estrogen-like actions or oppose estrogen actions in estrogen target tissues.

Marketed research:

Global Tamoxifen Market Size, Market Share, Application Analysis, Regional Outlook, Growth Trends, Key Players, Competitive Strategies and Forecasts, 2017 - 2025"

The tamoxifen market was valued at USD 676.6 Mn in 2017, and is expected to reach USD 683.6 Mn by 2025, expanding at a CAGR of 0.07% from 2017 - 2025.

This report analyzes the geographical distribution of tamoxifen market in North America, Europe, Asia-Pacific and Rest of the World markets. Currently, North America is the largest market for tamoxifen drugs and it is anticipated that the lead of this region will continue through 2022. Large pool of breast cancer patients, high awareness for breast cancer screening and prevention, well-structured reimbursement scenario and large pool of breast cancer patients.

Asia-Pacific and Rest of the World markets will experience the fastest CAGR during 2016-2022. Improving awareness in Middle East and Africa, high incidence of late stage breast cancer in these regions and rapid development of healthcare infrastructure are the prime drivers of Rest of the World market.

The global tamoxifen market is moderately competitive with AstraZaneca, Teva Pharmaceutical Industries, Allergan, Mylan, Apotex and Midatech the known players. Anticipated merger of Teva with Allergan is expected to bring a shift in market competitive

Contraindications:

- Pregnant women
- no planning to get pregnant
- Men or women who've had blood clots or a stroke.

Common side effects:

- Vaginal dryness or itching
- Irregular periods
- Headache
- Nausea and vomiting
- Skin rash

- Fatigue
- Water retention and weight gain

Major side effects:

- If a woman has gone through menopause, SERMs can increase her risk of developing endometrial cancer3 and uterine sarcoma4. Tell your doctor right away about any unusual vaginal bleeding (a common symptom of this cancer). Most uterine bleeding is not from cancer, but this symptom always needs quick attention.
- Blood clots are another uncommon, but serious side effect. They usually form in the legs (called deep vein thrombosis or DVT), but sometimes a piece of clot in the leg may break off and end up blocking an artery in the lungs (pulmonary embolism or PE). Call your doctor or nurse right away if you develop pain, redness, or swelling in your lower leg (calf), shortness of breath, or chest pain, because these can be symptoms of a DVT or PE. Rarely, tamoxifen has been associated with strokes in postmenopausal women, so tell your doctor if you have severe headaches, confusion, or trouble speaking or moving.
- Eye problems, such as cataracts, are sometimes seen when taking tamoxifen. It is important to tell your doctor right away if you are having any new trouble with your eyesight.
- Bones can be affected. Depending on a woman's menopausal status, tamoxifen can have different effects on the bones. In pre-menopausal women, tamoxifen can cause some bone thinning, but in post-menopausal women it often strengthens bones to some degree. The benefits of taking these drugs outweigh the risks for almost all women with hormone receptor-positive breast cancer.

❖ Medications that stop the body from making estrogen after menopause

Aromatase inhibitors are a class of medicines that reduce the amount of estrogen in your body, depriving breast cancer cells of the hormones they need to grow.

Aromatase inhibitors are only used in women who have undergone menopause. They cannot be used unless your body is in natural menopause or in menopause induced by medications or removal of the ovaries.

Estradiol, the most potent endogenous estrogen, is biosynthesized from androgens by the cytochrome P450 enzyme complex called aromatase.

Aromatase is present in breast tissue, and intratumoral aromatase is the source of local estrogen production in breast cancer tissues. Inhibition of aromatase is an important approach for reducing growth-stimulatory effects of estrogens in estrogen-dependent breast cancer.

Steroidal inhibitors that have been developed to date build upon the basic androstenedione nucleus and incorporate chemical substituents at varying positions on the steroid.

Nonsteroidal aromatase inhibitors can be divided into three classes: aminoglutethimide-like molecules, imidazole/triazole derivatives, and flavonoid analogs. Mechanism-based aromatase inhibitors are steroidal inhibitors that mimic the substrate, are converted by the enzyme to a reactive intermediate, and result in the inactivation of aromatase. Both steroidal and nonsteroidal aromatase inhibitors have shown clinical efficacy in the treatment of breast cancer.

The potent and selective third-generation aromatase inhibitors, anastrozole, letrozole, and exemestane, were introduced into the market as endocrine therapy in postmenopausal patients failing antiestrogen therapy alone or multiple hormonal therapies.

These agents are currently approved as first-line therapy for the treatment of postmenopausal women with metastatic estrogen-dependent breast cancer. Several clinical studies of aromatase inhibitors are currently focusing on the use of these agents in the adjuvant setting for the treatment of early breast cancer. Use of an aromatase inhibitor as initial therapy or after treatment with tamoxifen is now recommended as adjuvant hormonal therapy for a postmenopausal woman with hormone-dependent breast cancer.

Aromatase inhibitors used to treat breast cancer include:

Anastrozole (Arimidex):

Anastrozole is used to reduce the risk of cancer recurrence in women who have been treated for early-stage breast cancer. It can also be used to treat advanced breast cancer.

Exemestane (Aromasin):

Exemestane is used to reduce the risk of cancer recurrence in women who have been treated for early-stage breast cancer. It's sometimes used after taking tamoxifen for two or three years. It can also be used to treat advanced breast cancer in women for whom tamoxifen is no longer working.

Letrozole (Femara):

Letrozole is used to reduce the risk of cancer recurrence in women who have been treated for early-stage breast cancer. It can be used alone or given after completing tamoxifen treatment. Letrozole is also used to treat advanced breast cancer.

Aromatase inhibitors are given as pills you take once a day. All three aromatase inhibitors work the same and reduce the production of estrogen in your body.

How long you continue aromatase inhibitors depends on your specific situation. Current research suggests that the standard approach would be to take these medications for up to 10 years, but every person is different and you and your doctor should carefully assess how long you should take them.

Aromatase Inhibitor Trials

Trial	Treatment Regimens	Subjects	Endpoints	Findings
ATAC, 2005[19]	5 years of 1-mg anastrozole vs 20-mg tamoxifen vs combination therapy	9,366	DFS, safety, incidence of contralateral breast cancer, time to distant recurrence, and OS	After a median follow-up of 68 months, anastrozole significantly prolonged DFS (575 events vs 651 events; HR 0.87; P=0.01)
BIG 1-98, 2006[21]	5 years of 20-mg tamoxifen vs 5 years of 2.5-mg letrozole vs 2 years of 20-mg tamoxifen followed by 3 years of 2.5-mg letrozole vs 2 years of 2.5-mg letrozole followed by 3 years of 20-mg tamoxifen	8,010	DFS, OS, systemic DFS, and time to distant recurrence	Letrozole increased DFS (84.0% vs 81.4%), reduced distant recurrences, and prolonged time to distant metastasis
FACE, 2017[24]	5 years of 2.5-mg letrozole vs 5 years of 1-mg anastrozole	4,136	Safety and efficacy	5-year DFS rate was 84.9% for letrozole vs 82.9% for anastrozole (HR 0.93; 95% CI 0.80-1.07; P=0.3150)
EBCTCG, 2015[25]	5 years of an AI (group 1) vs 5 years of tamoxifen (group 2) vs 2-3 years of tamoxifen followed by an AI to year 5 (group 3) vs 2-3 years of an AI followed by tamoxifen to year 5 (group 4)[a]	31,920	Recurrence, breast cancer mortality, death without recurrence, and all-cause mortality	AIs reduced recurrence rates by nearly 30% compared to tamoxifen

AI, aromatase inhibitor; ATAC, Arimidex, Tamoxifen Alone or in Combination; BIG, Breast International Group; DFS, disease-free survival; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; FACE, Femara Versus Anastrozole Clinical Evaluation; HR, hazard ratio; OS, overall survival.

❖ Treatments to stop ovarian function in premenopausal women:

Women who haven't undergone menopause — either naturally or as a result of cancer treatment — may opt to undergo treatment to stop their ovaries from producing hormones.
Options may include:

- Surgery to remove the ovaries (oophorectomy)
- Radiation therapy aimed at the ovaries
- Medications, such as goserelin (Zoladex)

Treatments to stop ovarian function may allow premenopausal women to take medications only available to postmenopausal women.

❖ Combining targeted therapy with hormone therapies:

Hormone therapy for cancer that spreads to other parts of the body (metastatic breast cancer) sometimes combines hormone therapies with targeted therapy. Targeted therapy drugs attack specific weaknesses in cancer cells. The combination can make hormone therapy more effective.

Medications used in this way include:

- Abemaciclib (Verzenio)
- Palbociclib (Ibrance)
- Ribociclib (Kisqali)
- Everolimus (Afinitor)

Fulvestrant (Faslodex):

- Fulvestrant is a drug that attaches to and breaks down estrogen receptors. It is not a SERM. It is known as a selective estrogen receptor degrader (SERD). It acts like an anti-estrogen throughout the body. When given to pre-menopausal women it must be combined with a luteinizing-hormone releasing hormone (LHRH) agonist to turn off the ovaries (see Ovarian suppression below).

Fulvestrant can be given:

- Alone to treat advanced breast cancer that has not been treated with other hormone therapy.
- Alone to treat advanced breast cancer after other hormone drugs (like tamoxifen and often an aromatase inhibitor) have stopped working.
- In combination with a CDK 4/6 inhibitor or PI3K inhibitor to treat metastatic breast cancer as initial hormone therapy or after other hormone treatments have been tried.

It is given by 2 injections into the buttocks (bottom). For the first month, the 2 shots are given 2 weeks apart. After that, they are given once a month.

Side effects of fulvestrant

- Hot flashes and/or night sweats
- Headache
- Mild nausea

Results:

Endocrine therapies such as tamoxifen have revolutionized the treatment of breast cancer, resulting insignificant decreases in cancer-related mortality. Aromatase inhibitors such as anastrozole and letrozolehave further improved breast cancer survival.

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2.*https://www.mayoclinic.org/tests-procedures/hormone-therapy-for-breast-cancer/about/pac-2038494*

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