TREATMENT UPDATE:

Metastatic Breast Cancer

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Treatment Update: Metastatic Breast Cancer

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For women coping with metastatic breast cancer, the number of treatment options continues to grow.

In metastatic breast cancer, the cancer has spread beyond the breast to other parts of the body, such as the lymph nodes, skin, bone, liver, or lungs. In most cases, metastatic breast cancer is a recurrence (return) of previously-treated breast cancer.

There are several types of breast cancer, each with its own unique characteristics, and treatment approaches are tailored to the specific type.

Types of Breast Cancer

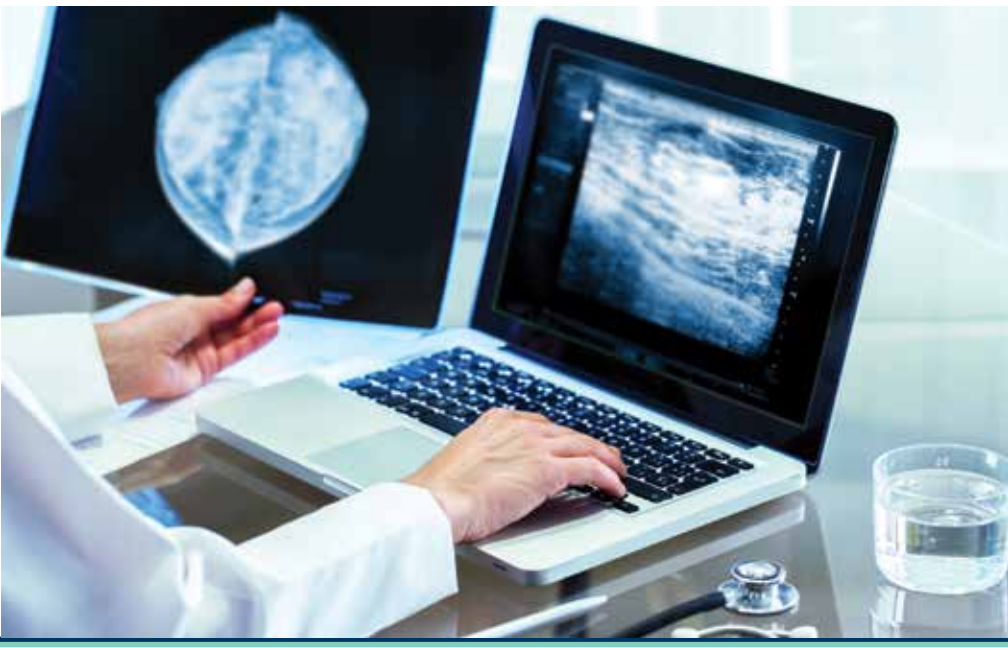
Hormones and other chemical messengers in the bloodstream can attach to specialized proteins (called receptors) and fuel the growth of cancer cells. These receptors may lie within or on the surface of cancer cells.

There are three main types of breast cancer, each with its own set of subtypes.

- **Hormone-positive.** Cancers that have receptors for the female hormone estrogen (are ER-positive) and/or progesterone (are PR-positive) are considered hormone-sensitive. ER-positive cancers account for about 65 percent of breast cancers. Nearly two thirds of ER-positive cancers also have receptors for progesterone (are PR-positive as well as ER-positive).

- **HER2-positive.** Cancers that are positive for the "human epidermal growth factor receptor 2" (HER2) have an abundance of HER2 receptor cells on their surface. HER2-positive cancers are less common than ER-positive cancers, accounting for about 20 to 25 percent of cases. Some HER2-positive cancers are also are hormone-sensitive.
- **Triple-negative.** Approximately 15 percent of women with breast cancer have a type called triple-negative. These tumors do not have receptors for estrogen or progesterone and do not have excess HER2 receptors on their surface.

When breast cancer recurs and metastasizes (spreads), it can have the same characteristics (be the same type) as the original breast cancer, or it can have different characteristics. Because tumors can change their biological characteristics over time, it is advisable that a biopsy (testing of the tumor tissue) be performed on any recurrence of the cancer. The results of the biopsy will guide treatment recommendations.



Treatment Options

Treatment approaches for metastatic breast cancer are individualized, taking into consideration its specific type, the parts of the body where it has spread, and the preferences of the patient.

Hormone Therapy

Hormone therapy is commonly the first treatment approach for hormone-positive metastatic breast cancer.

If the woman being treated is premenopausal, hormone therapy generally begins with "suppression" of the ovaries, preventing the production of estrogen that can fuel cancer growth. Ovarian suppression can involve the surgical removal of the ovaries (oophorectomy), but it is more common to use drugs, such as leuprolide (Lupron) or goserelin (Zoladex) to temporarily stop the ovaries from producing hormones.

After ovarian suppression, hormone therapy typically takes a defined path:

- **Tamoxifen** (Soltamox, Nolvadex) is an estrogen-blocking treatment given to both pre- and postmenopausal women. Designed to stop the growth of the cancer and shrink the tumor, tamoxifen is often the first treatment approach for young women with metastatic breast cancer who have not received any prior hormonal therapy.
- **Aromatase inhibitors** (AIs) block the action of the enzyme aromatase. This results in lower levels of circulating estrogen and has the effect of slowing the growth of hormone-sensitive tumors. Three types of AIs are approved by the U. S. Food and Drug Administration (FDA): anastrozole (Arimidex and others), letrozole (Femara and others) and exemestane (Aromasin and

others). AIs are a treatment option for postmenopausal women and for premenopausal women who received ovarian suppression therapy, and are given in pill form.

- **Fulvestrant (Faslodex)**, an estrogen-blocking drug, attaches to estrogen receptors and changes their shape, preventing the receptors from working properly, which slows the growth of breast cancer cells. Fulvestrant is FDA-approved only for postmenopausal women with metastatic breast cancer whose tumors have not responded well to other hormone treatments, such as tamoxifen and an AI. Fulvestrant is given by an injection.

Chemotherapy

Chemotherapy is typically the first approach for triple-negative metastatic breast cancer, as hormone therapy is not effective in treating this type of cancer. Chemotherapy can also be used for the treatment of hormone-positive metastatic breast cancer that is no longer responding to hormone therapy, and for the treatment of HER2-positive metastatic breast cancer, in combination with anti-HER2 treatments (see next section: Targeted Treatments).

Chemotherapy drugs that treat metastatic breast cancer often differ from those used at the time of initial treatment. The most common chemotherapy drugs used to treat metastatic breast cancer are:

- **Anthracyclines,** such as doxorubicin (Adriamycin), pegylated liposomal doxorubicin (Doxil, Caelyx), and epirubicin (Ellence).
- **Antimetabolites,** such as capecitabine (Xeloda) and gemcitabine (Gemzar).
- **Antimicrotubule agents,** such as ixabepilone (Ixempra), eribulin (Halaven), and vinorelbine (Navelbine).
- **Antitumor antibiotics,** such as mitoxantrone (Novantrone).

- **Platinum agents,** such as platinol (Cisplatin) and carboplatin (Paraplatin).
- **Taxanes,** such as paclitaxel (Taxol), docetaxel (Taxotere), and albumin-bound paclitaxel (Abraxane).

Women being treated with chemotherapy for metastatic breast cancer often receive multiple courses of treatment, with breaks between each course. If one chemotherapy drug (or combination of drugs) does not work or stops working, a different type of chemotherapy can be used.

Targeted Treatments

Targeted treatments focus on specific molecules and cell mechanisms thought to be important for cancer cell survival and growth, taking advantage of what researchers have learned in recent years about how cancer cells grow. Targeted treatments are meant to spare healthy tissues and cause fewer and less severe side effects than chemotherapy.

HER2-positive metastatic breast cancer

Targeted treatments are the primary therapy approach for HER2-positive metastatic breast cancer. The drugs commonly used include:

- **Trastuzumab (Herceptin).** Trastuzumab targets HER2-positive cancer cells, slowing or stopping their growth. Trastuzumab can be used alone, in combination with chemotherapy, or with chemotherapy plus pertuzumab.
- **Trastuzumab emtansine (Kadcyla).** Trastuzumab emtansine, also called T-DMI, is the combination of trastuzumab and a chemotherapy called DMI. Combining these drugs allows for the targeted delivery of chemotherapy to HER2-positive cancer cells.

- **Pertuzumab (Perjeta).** Like trastuzumab, pertuzumab targets HER2-postive cancer cells. Pertuzumab is often given in combination with trastuzumab and chemotherapy.
- **Lapatinib (Tykerb).** Lapatinib blocks certain enzymes, inhibiting the growth of cancer cells. Lapatinib is used for the treatment of HER2-positive metastatic breast cancer in women who have already been treated with chemotherapy and trastuzumab. It is sometimes combined with hormone therapy or chemotherapy.

Trastuzumab, trastuzumab emtansine, and pertuzumab are all given intravenously (into a vein). Lapatinib is given in pill form.

Hormone-positive, HER2-negative metastatic breast cancer
There are targeted treatments specifically designed for the treatment of ER-positive, HER2-negative metastatic breast cancer:

- **CDK4/6 inhibitors.** CDK4/6 inhibitors are designed to interrupt enzymes that promote the growth of cancer cells. The CDK4/6 inhibitors used in treating ER-positive, HER2-negative metastatic breast cancer are abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali). Each of these drugs can be given in combination with hormone therapy, such as the aromatase inhibitor letrozole or the hormone therapy fulvestrant. Abemaciclib can also be used alone for the treatment of these types of cancers. Abemaciclib, palbociclib, and ribociclib are all given in pill form.
- **mTOR (mammalian target of rapamycin) inhibitors.** mTOR inhibitors are a type of targeted treatment drug that may increase the effectiveness of hormone therapy. The mTOR inhibitor everolimus (Afinitor) is used in combination with

the aromatase inhibitor exemestane for postmenopausal women with hormone-positive, HER2-negtative metastatic breast cancer. Everolimus is given in pill form.

Radiation

Radiation is not a primary treatment approach for metastatic breast cancer, but it can be used in conjunction with other treatments to shrink tumors and to improve quality of life by:

- Lessening pain from tumors that have spread to the bone or the spine.
- Removing pressure from a pinched nerve to reduce pain, numbness, or weakness.
- Decreasing bleeding.
- Improving breathing by opening a blocked airway.

If radiation treatments are given, the dose and schedule is based on a number of factors, including the severity of the pain or loss of function, and the type and schedule of other treatments begin given for the cancer.

The Importance of Clinical Trials

Clinical trials are the standard by which we measure the worth of new treatments and the quality of life of patients as they receive those treatments. For this reason, doctors and researchers urge people with cancer to take part in clinical trials.

Your doctor can guide you in making a decision about whether a clinical trial is right for you. Here are a few things that you should know:

- Often, people who take part in clinical trials gain access to and benefit from new treatments.
- Before you participate in a clinical trial, you will be fully informed as to the risks and benefits of the trial, including any possible side effects.
- Many clinical trials are designed to test a new treatment against a standard treatment to find out whether the new treatment has any added benefit.
- Participation is voluntary and does not affect your access to treatment in other settings. You can stop taking part in a clinical trial at any time for any reason.

Treatment Side Effects

All cancer treatments can cause side effects. It's important that you report any side effects that you experience to your health care team so they can help you manage them. Report them right away—don't wait for your next appointment. Doing so will improve your quality of life and allow you to stick with your treatment plan. It's important to remember that not all patients experience all side effects, and patients may experience side effects not listed here.

Side Effects of Chemotherapy

The side effects of chemotherapy depend on the type and dose of drugs given and the length of time they are used, and can include:

- Infections
- Headaches
- Reduction in blood cell counts, with need for transfusions of red blood cells or platelets
- Fatigue
- Bruising or bleeding
- Abnormal taste of food; loss of appetite
- Nausea
- Rashes
- Hair loss
- Hearing loss
- Diarrhea
- Mouth sores or painful swallowing
- Changes in the skin (dryness, rashes, darkening, or lines on the fingernails)
- Pain, tingling, and numbness, especially in hands and feet (neuropathy)

Side Effects of Targeted Treatments and Hormone Therapy

Targeted treatment drugs and hormone therapy don't have the same effect on the body as do chemotherapy drugs, but they can still cause side effects.

Side effects of certain targeted therapies can include diarrhea, liver problems (such as hepatitis and elevated liver enzymes), nerve damage, problems with blood clotting and wound healing, and high blood pressure.

The side effects of hormone therapy are dependent on the type of therapy and include hot flashes (seen more with tamoxifen) and joint pain (seen more with aromatase inhibitors).

Side Effects of Radiation Therapy

Changes to the skin are the most common side effects of radiation therapy; those changes can include dryness, swelling, peeling, redness, and blistering. It's especially important to contact your health care team if there is any open skin or painful areas, as this could indicate an infection.

General Side Effects

Some side effects may occur across treatment approaches. This section provides tips and guidance on how to manage these side effects should they occur.

Digestive Tract Symptoms

Nausea and vomiting

- Avoid food with strong odors, as well as overly sweet, greasy, fried, or highly seasoned food.
- Eat meals cold or at room temperature, which often makes food more easily tolerated.
- Nibble on dry crackers or toast. These bland foods are easy on the stomach.
- Having something in your stomach when you take medication may help ease nausea.

Diarrhea

- Drink plenty of water. Ask your doctor about using drinks such as Gatorade which provide electrolytes as well as liquid. Electrolytes are body salts that must stay in balance for cells to work properly.
- Over-the-counter medicines such as loperamide (Imodium A-D and others) and prescription drugs are available for diarrhea but should be used only if necessary. If the diarrhea is bad enough that you need medicine, discuss it with your doctor or nurse.
- Choose foods that contain soluble fiber—for example beans, oat cereals, oranges, and flaxseeds. High-pectin foods such as peaches, apples, oranges, grapefruit, bananas, and apricots can also help to avoid diarrhea.

- Low fat food choices are less likely to cause diarrhea than fatty, greasy, or fried foods. The fats you eat should come from healthy sources, such as olive oil, canola oil, avocado, olives, nuts, and seeds.

Loss of appetite

- To help maintain your weight, eat small meals throughout the day. That's an easy way to take in more protein and calories. Try to include protein in every meal.
- Be as physically active as you can. Sometimes, taking a short walk an hour or so before meals can help you feel hungry.
- Keep high-calorie, high-protein snacks on hand such as hard-boiled eggs, peanut butter, cheese, ice cream, granola bars, liquid nutritional supplements, puddings, nuts, canned tuna, or trail mix.
- If you are struggling to maintain your appetite, talk to your health care team about whether appetite-building medication could be right for you.

Fatigue

Fatigue (extreme tiredness not helped by sleep) is one of the most common side effects of many cancer treatments. If you are taking a medication, your doctor may lower the dose of the drug, as long as it does not make the treatment less effective. If you are experiencing fatigue, talk to your doctor about whether taking a smaller dose is right for you.

There are a number of other tips for reducing fatigue:

- Take several short naps or breaks.
- Take short walks or do some light exercise, if possible.
- Try easier or shorter versions of the activities you enjoy.
- Ask your family or friends to help you with tasks you find difficult or tiring.

Fatigue can be a symptom of other illnesses, such as anemia, diabetes, thyroid problems, heart disease, rheumatoid arthritis, and depression. So be sure to ask your doctor if he or she thinks any of these conditions may be contributing to your fatigue.

Pain

There are a number of options for pain relief, including prescription and over-the-counter medications. It's important to talk to a member of your health care team before taking any over-the-counter medication, to determine if they are safe and will not interfere with your treatments. Many pain medications can lead to constipation, which may make your pain worse. Your doctor can prescribe medications that help to avoid constipation.

Physical therapy, acupuncture, and massage may also be of help in managing your pain. Other techniques, such as mindfulness meditation, deep breathing exercises, and yoga may also be

helpful. Consult with a member of your health care team before beginning any of these activities.

Bone Loss

Hormone therapies and chemotherapy can cause bone loss, which increases a woman's risk for osteoporosis (a condition in which bones become weak and brittle, leading to a higher risk of fracture). Talk with your health care team about how exercise and changes in your diet may help keep your bones healthy.

It's also important to talk to your doctor about the medications available for bone health:

- **Bisphosphonates** such as zoledronic acid (Zometa and others) slow the process by which bone wears away and breaks down. These medications belong to a class of drugs called osteoclast inhibitors.
- **RANK ligand inhibitors** block a factor in bone development known as RANK ligand, which stimulates cells that break down bone. By blocking RANK ligand, these drugs increase bone density and strength. So far, the only drug approved in this class is denosumab (Xgeva, Prolia). Like bisphosphonates, RANK ligand inhibitors are a type of osteoclast inhibitor.

Communicating with Your Health Care Team

As you manage your cancer, it's important to remember that you are a consumer of health care. The best way to make decisions about health care is to educate yourself about your diagnosis and get to know the members of your health care team, including doctors, nurse practitioners, physician assistants, nurses, dietitians, social workers and patient navigators.

Here are some tips for improving communication with your health care team:

Start a health care journal. Having a health care journal or notebook will allow you to keep all of your health information in one place. You may want to write down the names and contact information of the members of your health care team, as well as any questions for your doctor. Keep a diary of your daily experiences with symptoms related to your illness or treatment. You can separate your journal or notebook into different sections to help keep it organized.

Prepare a list of questions. Before your next medical appointment, write down your questions and concerns. Because your doctor may have limited time, you should ask your most important questions first, and be as specific and brief as possible.

Bring someone with you to your appointments. Even if you have a journal and a prepared list of questions or concerns, it's always helpful to have support when you go to your appointments. The person who accompanies you can serve as a second set of ears.

He or she may also think of questions to ask your doctor or remember details about your symptoms or treatment that you may have forgotten.

Write down your doctor's answers. Taking notes will help you remember your doctor's responses, advice, and instructions. If you cannot write down the answers, ask the person who accompanies you to do that for you. If you have a mobile device, ask if you can use it to take notes or record the conversation. Taking notes will help you review the information later.

Cancer*Care*'s Free Support Services and Programs

It is very difficult to receive a diagnosis of cancer, and adjusting to the necessary changes in your life can be challenging.

Cancer*Care* can help. We are a national nonprofit organization providing free, professional services to anyone affected by cancer. Our licensed oncology social workers can provide support and education, help in navigating the complicated health care system, and provide information on support groups and other resources.

To learn more about how Cancer*Care* helps, call us at 800-813-HOPE (4673) or visit www.cancercare.org.

You will likely also build your own personal support network, comprised of family and friends. In doing so, it's best to take some time to think about the people in your life and how they are best suited to help. Match the task to their strengths—ask a family member who loves to shop to pick up something for you at the store; ask a friend who's a good listener to come over for a chat.

Frequently Asked Questions

Q: What are PARP inhibitors? Do they have a role in the treatment of metastatic breast cancer?

A: PARP is a type of enzyme that helps repair DNA. PARP inhibitors are designed to prevent cancer cells from repairing their damaged DNA; this prevention can cause the cancer cells to die. In clinical trials, PARP inhibitors have shown promise in patients with BRCA-positive or triple-negative metastatic breast cancer. The PARP inhibitor olaparib is currently approved by the FDA for the treatment of BRCA-related ovarian cancer.

Q: Are there any drugs available for the treatment of lymphedema?

A: Lymphedema, a painful swelling of the arms or legs caused by a buildup of lymphatic fluid, affects many women being treated for breast cancer. It is an area of ongoing research and concern. There are no medications for lymphedema currently approved by the FDA, but there is hope for progress, and there is a clinical trial underway for a gene therapy designed to repair damage to the lymphatic system. If you are experiencing lymphedema, talk to your health care team immediately and discuss steps you can take to manage your symptoms. Read Cancer*Care*'s fact sheet "Lymphedema: Finding Resources and Support" for more information.

Q: What is a tumor marker?

A: Tumor markers are proteins manufactured by tumors and shed into the blood. They can be measured through a blood test, and some oncologists find the measurements useful in assessing the success of treatment in women with metastatic breast cancer. In those women, the presence or absence of tumor markers may help guide treatment options.

Q: I've heard about hand-foot syndrome. What is it and what can I do to prevent it?

A: Hand-foot syndrome (HFS) is a side effect of some types of chemotherapy and other medicines used in the treatment of breast cancer. Symptoms can include numbness, tingling, burning, itching, redness, swelling, and discomfort. In severe cases, there can be cracked or peeling skin, blisters or sores, and intense pain.

The risk of HFS can be lessened by following these tips during the week after each chemotherapy treatment:

- Avoid prolonged heat exposure on hands and feet.
- Avoid using hand tools and kitchen knives. The squeezing or chopping motions can cause excessive pressure and increase symptoms.
- Stay off your feet as much as possible if you are starting to notice symptoms; this may require taking a break from exercising.
- Talk to your health care team about using a 10% urea cream; a study has found that it may be helpful in preventing HFS.

Resources

CancerCare®
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American Cancer Society
800-227-2345
www.cancer.org

Cancer.Net
Patient information from the American Society of Clinical Oncology
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www.cancer.net

National Cancer Institute
800-422-6237
www.cancer.gov

Cancer Support Community
888-793-9355
www.cancersupportcommunity.org

National Coalition for Cancer Survivorship
877-622-7937
www.canceradvocacy.org

BreastCancer.org
610-642-6550
www.breastcancer.org

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www.lbbc.org

Metastatic Breast Cancer Network
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Susan G. Komen
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www.komen.org

Triple Negative Breast Cancer Foundation
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