TREATMENT UPDATE:

Metastatic Breast Cancer

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Treatment Update: Metastatic Breast Cancer

TABLE OF CONTENTS

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There are an increasing number of options for the treatment of metastatic breast cancer.

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

Men and women can both be diagnosed with breast cancer, with men representing about 1 percent of all breast cancer cases. Most clinical trials that track the impact of hormone treatments are associated with female biology and treatment updates often refer only to women patients, but there are risks across other populations, including trans women undergoing hormone treatment. This booklet is for anyone facing a breast cancer diagnosis. Your health care team will tailor a treatment plan that best fits your situation.

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 four main subtypes of breast cancer, based on the presence or absence of specific receptors:

- **Hormone receptor (HR) positive.** Cancers that have receptors for estrogen (ER-positive) and/or progesterone (PR-positive) are considered hormone-positive. Nearly two-thirds of ER-positive cancers are also PR-positive.

- **HER2-positive.** This type of breast cancer contains an overabundance of a protein called human epidermal growth factor receptor 2 (HER2). About half of HER2-positive cancers are also HR-positive.
- **HER2-negative/HER2-low.** Breast cancers that do not contain an overabundance of the HER2 protein.
- **Triple-negative.** Breast cancers that do not have receptors for estrogen or progesterone and do not contain an overabundance of the HER2 protein.

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

As an example, mutations in the estrogen receptor gene (ESR1) can cause breast cancer to become resistant to some forms of hormone treatment, with longer exposure to treatment increasing the chance of developing these ESR1 mutations. Testing for ESR1 mutations at each progression can show if the mutation has occurred. Testing by blood (with liquid biopsy) is more sensitive in detecting ESR1 mutations and is currently preferred.

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, also called endocrine therapy, is typically the first treatment approach for HR-positive metastatic breast cancer.

In premenopausal patients, therapy generally begins with ovarian suppression. This prevents the production of estrogen, which 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 estrogen.

Hormone therapy begins along with ovarian suppression therapy, typically with one of the following drugs:

- **Tamoxifen (Soltamox, Nolvadex)** is an estrogen-blocking treatment given to both pre- and postmenopausal patients. Designed to stop the growth of the cancer and shrink the tumor, tamoxifen is often the first treatment approach for younger patients with metastatic breast cancer who have not received any prior hormonal therapy, and is given until ovarian suppression is achieved.

- **Aromatase inhibitors** (AIs) block the action of the enzyme aromatase. This results in lower levels of 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 receive ovarian suppression therapy.
- **Fulvestrant (Faslodex)**, an estrogen-blocking drug, attaches to estrogen receptors and changes their shape. This prevents the receptors from working properly, which slows the growth of breast cancer cells. Fulvestrant is approved by the FDA for postmenopausal women with metastatic breast cancer whose tumors have not responded well to other hormone treatments, such as tamoxifen and an AI. In certain situations, fulvestrant can also be used in the treatment of HR-positive metastatic breast cancer in premenopausal women.
- **Elacestrant (Orserdu),** a Selective Estrogen Receptor Degrader (SERD), is approved for the treatment of ER-positive, HER2-negative ESR1-mutated advanced or metastatic breast cancer following disease progression on at least one line of endocrine therapy. SERDs, also known as estrogen receptor antagonists (ERAs), stop estrogen from helping hormone receptor-positive breast cancer cells to grow.

Tamoxifen, elacestrant and AIs are given in tablet form. Fulvestrant is given by injection.

Targeted Therapy

Targeted therapies 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 therapies are meant to spare healthy tissues and cause fewer and less severe side effects than chemotherapy.

Targeted therapy approaches for HER2-negative/HER2-low metastatic breast cancer include:

- **CDK4/6 inhibitors.** CDK4/6 inhibitors interrupt enzymes that promote the growth of cancer cells. The CDK4/6 inhibitors used in treating ER-positive, HER2-negative/HER2-low 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 letrozole or fulvestrant. Abemaciclib can also be used alone for the treatment of ER-positive, HER2-negative/HER2-low metastatic breast cancer. Abemaciclib, palbociclib and ribociclib are all given in tablet form.
- **mTOR (mammalian target of rapamycin) inhibitors.** mTOR inhibitors are a type of targeted therapy that may increase the effectiveness of hormone therapy. The mTOR inhibitor everolimus (Afinitor) is used in combination with exemestane for the treatment of postmenopausal women with HR-positive, HER2-negative/HER2-low metastatic breast cancer. Everolimus is given in tablet form.

- **PARP inhibitors.** PARP is a type of enzyme that helps repair DNA. In cancer treatment, PARP inhibitors are used to prevent cancer cells from repairing their damaged DNA. This prevention can cause the cancer cells to die, especially those with defective DNA repair pathways, such as BRCA1/2-associated breast cancers. Talazoparib (Talzenna) is approved for the treatment of BRCA-positive, HER2-negative/HER2-low metastatic breast cancer. Olaparib (Lynparza) is approved for the treatment of BRCA-positive, HER2-negative/HER2-low metastatic breast cancer that was previously treated with chemotherapy. Both PARP inhibitors can be used in HR positive or HR negative breast cancer that is not HER2 positive.
- **PIK3CA inhibitor.** Alpelisib (Piqray), in combination with the endocrine therapy fulvestrant, is approved to treat HR-positive, HER2-negative/HER2-low PIK3CA-mutated metastatic breast cancer following treatment with an endocrine-based therapy.
- **AKT/PTEN/PIK3CA inhibitor.** Capivasertib (Truqap), approved by the FDA in November 2023, is used to treat HR-positive, HER2-negative locally advanced or metastatic breast cancers that test positive for certain gene mutations. Capivasertib targets the AKT protein, which helps regulate cell growth and division.

HER2-positive metastatic breast cancer is treated with medications that target aspects of the HER2 protein that is over-expressed on the cancer cells. Treatment approaches for HER2-positive metastatic breast cancer 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 other HER2-directed medications.
- **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 that has already been treated with chemotherapy and trastuzumab. It is sometimes combined with hormone therapy or chemotherapy.
- **Margetuximab-cmkb (Margenza).** Margetuximab-cmkb, in combination with chemotherapy, is used for the treatment of HER2-positive metastatic breast cancer that was previously treated with at least two anti-HER2 regimens.
- **Tucatinib (Tukysa).** Tucatinib is used in combination with trastuzumab and the chemotherapy capecitabine as a therapy for HER2-positive metastatic breast cancer that was previously treated with one or more anti-HER2 regimens.

- **Fam-trastuzumab deruxtecan-nxki (Enhertu)** is used for previously-treated HER2-positive metastatic breast cancer that recurred within 6 months of completing therapy, or that progressed on chemotherapy plus trastuzumab and pertuzumab.
  - **Related note:** In August 2022, the FDA approved fam-trastuzumab deruxtecan-nxki for the treatment of unresectable or metastatic HER2-low breast cancer previously treated with chemotherapy in the metastatic setting or which has recurred during or within six months of completing adjuvant chemotherapy.

All of the above drugs except lapatinib and tucatnib are given intravenously (into a vein). Lapatinib and tucatinib are given in tablet form.

Chemotherapy

Chemotherapy is typically the first approach for treating triple-negative metastatic breast cancer. The most common chemotherapies used include:

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

- **Antibody-drug conjugates** work by combining (linking) a chemotherapy with an antibody that seeks out cancer cells. Sacituzumab govitecan-hziy (Trodelvy) is approved for the treatment of metastatic triple-negative breast cancer that has been treated with at least two prior therapies. Fam-trastuzumab deruxtecan (Enhertu) is approved for triple negative metastatic breast cancer that is also HER2 low.

Chemotherapy can be given as a single drug or as a combination of drugs. Multiple courses of treatment are often given, with breaks between each course. If one treatment approach does not work or stops working, a different chemotherapy (or combination of chemotherapies) is often used. The chemotherapies used for the treatment of metastatic breast cancer are generally given intravenously.

In combination with chemotherapy, the immunotherapy pembrolizumab (Keytruda) is approved by the FDA for the treatment of triple-negative metastatic breast cancer that expresses PD-L1. Pembrolizumab targets PD-L1, a protein that can prevent the body's immune system from attacking tumors.

Notes about chemotherapy in the treatment of metastatic breast cancer

- In addition to treating triple-negative metastatic breast cancer, chemotherapy can be given for hormone-positive metastatic breast cancer that is no longer responding to hormone therapy and for HER2-positive metastatic breast cancer (in combination with anti-HER2 treatments).

- In February 2023, the approval of sacituzumab govitecan-hziy was expanded to include the treatment of locally advanced or metastatic hormone-positive and HER2-negative/HER2-low breast cancer that was previously treated with hormone-based therapy and at least two additional systemic therapies in the metastatic setting.

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 individuals 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.
- Most clinical trials are designed to test a new treatment against, or in combination with, a standard treatment to find out whether the new treatment has any added benefit.
- 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.

There are certain side effects that may occur across different treatment approaches. Following are tips and guidance for managing these side effects.

Managing Digestive Tract Symptoms

Nausea and vomiting

- Avoid food with strong odors as well as overly sweet, greasy, fried, or highly seasoned food.
- Eat meals that are chilled, 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 that provide electrolytes. 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, contact a member of your health care team.
- The BRAT diet (bananas, rice, applesauce, toast) and soluble fiber such as oats, bran and barley can help with diarrhea. Foods high in insoluble fiber, such as leafy greens and most fruits should be avoided as they can worsen diarrhea. Oily foods should also be avoided.
- Avoid foods high in refined sugar and those sweetened with sugar alcohols such as sorbitol and mannitol.

Loss of appetite

- Eating small meals throughout the day is an easy way to take in more protein and calories, which will help maintain your weight. Try to include protein in every meal.
- To keep from feeling full early, avoid liquids with meals or take only small sips (unless you need liquids to help swallow). Drink most of your liquids between meals.
- 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.

Managing Fatigue

Fatigue (extreme tiredness not helped by sleep) is one of the most common side effects of many cancer treatments. If you are receiving a cancer-directed 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:

- To be able to sleep well at night, avoid excessive sleep during the day.
- Take 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.

There are also prescription medications that may help, such as modafinil. Your health care team can provide guidance on whether medication is the right approach for your individual circumstances.

Managing 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 it is safe and to make sure it will not interfere with your treatment. 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. Consult with a member of your health care team before beginning any of these activities.

Treatment-Specific Side Effects

Chemotherapy

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

- Fatigue
- Nausea or vomiting
- Hair loss
- Increased risk of infection (from having too few white blood cells)
- Easy bruising or bleeding (from having a low platelet count)
- Changes in memory or thinking
- Peripheral neuropathy (numbness or tingling in hands and feet)

Hormone Therapy and Targeted Therapy

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

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

Side effects of certain targeted therapies can include diarrhea, liver problems (such as hepatitis and elevated liver enzymes), peripheral neuropathy, problems with blood clotting and wound healing, high blood pressure, mouth sores, high blood sugar and reduced white blood cell count.

Communicating With Your Health Care Team

As you manage your breast 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, nurses, nurse practitioners, physician assistants, 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 (either on paper or in a digital format) 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.

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

Bring someone with you to your appointments or have them be present during telehealth sessions. 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 you bring 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. You can also ask the person who accompanies you to take notes for you, either in your journal or on a tablet or smartphone.

Record your visit if your doctor allows it. Recording the conversation with your doctor gives you a chance to hear specific information again or share it with family members or friends.

Incorporate other health care professionals into your team. Your medical oncologist is an essential member of your health care team, but there are other health care professionals who can help you manage your diagnosis and treatment:

- Your primary care physician should be kept updated about your cancer treatment and any test results.
- Your local pharmacist is a great source of knowledge about the medications you are taking. Have all of your prescriptions filled at the same pharmacy to avoid the possibility of harmful drug interactions.
- Make sure your oncologist knows of any other medical conditions you have or any pain you are experiencing so that they can consult with your primary care physician or your specialist as needed.

Cancer*Care*'s Free Support Services and Programs

It can be very difficult to receive a diagnosis of breast 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 offer 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 composed 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, or ask a friend who's a good listener to come over for a chat.

Frequently Asked Questions

Q: Is radiation a treatment approach for metastatic breast cancer?

A: 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 improve quality of life, as it can:

- Lessen pain from tumors that have spread to the bone or the spine
- Remove pressure from a pinched nerve to reduce pain, numbness, or weakness.
- Decrease bleeding.
- Improve 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 being given for the cancer.

Q: I have been diagnosed with metastatic breast cancer and will be treated with chemotherapy. I want to preserve my fertility. What are my options?

A: Chemotherapy can induce a temporary or permanent menopause in younger women. Before treatment begins, consider consulting with a specialist in reproductive medicine about options that might be right for you. Ask about newer options for preserving fertility, such as oocyte cryopreservation, also known as egg freezing. In this process, the woman's eggs are removed, frozen and stored for later use. Another option involves the freezing of fertilized eggs.

Q: Am I at higher risk of osteoporosis while being treated for metastatic breast cancer?

A: Hormone therapies and chemotherapy can cause bone loss, which increases the risk of osteoporosis (a condition in which bones become weak and brittle). Talk with your health care team about how exercise and changes in your diet may help keep your bones healthy, and about the medications available for bone health:

- Bisphosphonates such as zoledronic acid (Zometa and others) slow the process that causes bone to wear away and break down. These medications belong to a class of drugs called osteoclast inhibitors, which can be used to prevent bone loss and to maintain bone strength if breast cancer has spread to the bones.
- The RANK ligand inhibitor denosumab (Xgeva, Prolia) blocks a factor in bone development known as RANK ligand, which stimulates cells that break bone down. By blocking RANK ligand, these drugs increase bone density and strength. Like bisphosphonates, RANK ligand inhibitors are a type of osteoclast inhibitor.

Q: What is a tumor marker?

A: Tumor markers are proteins manufactured by tumors and shed into the blood. The presence or absence of tumor markers, which is measured by a blood test, can help monitor the effect of current treatment for metastatic breast cancer. Treatment should not be changed based solely on an increase in tumor markers, but updated imaging such a CT scan or PET/CT scan may be ordered if an increase in tumor markers is seen.

Resources

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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

Living Beyond Breast Cancer
855-807-6386
www.lbbc.org

Susan G. Komen
877-465-6636
www.komen.org

Triple Negative Breast Cancer Foundation
877-880-8622
www.tnbcfoundation.org

Medicine Assistance Tool
www.medicineassistancetool.org

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