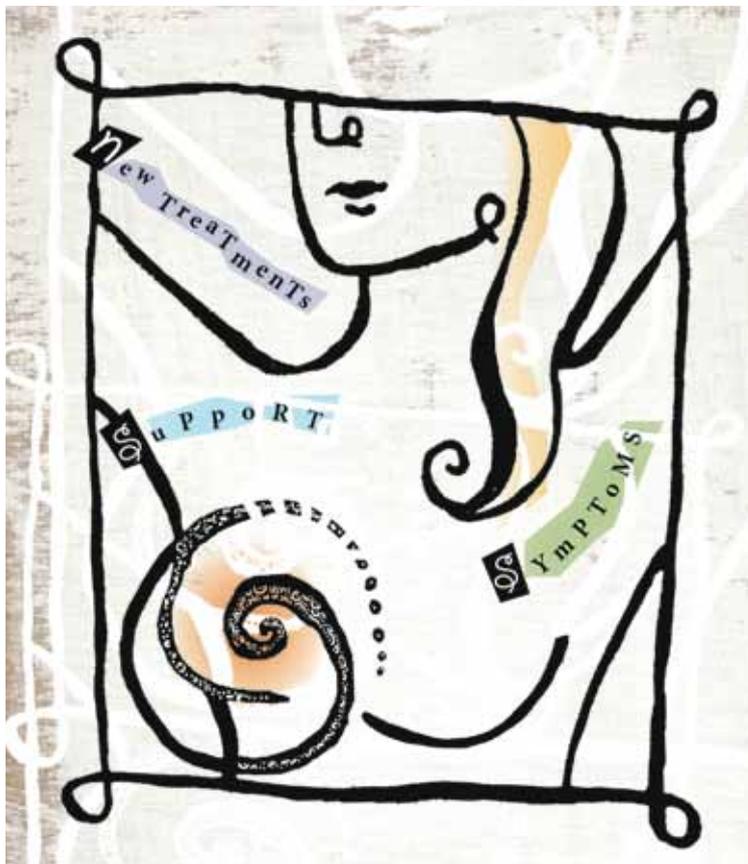


# A Patient's Guide to **Metastatic Breast Cancer**



**Detection and Diagnosis** ■ **Treatment Options**  
**Symptoms and Side Effects** ■ **Living with Metastatic Disease**  
**A Patient's Story** ■ **Questions to Ask the Doctor** ■ **Resources**

[ SECOND EDITION ]

**cure**

CANCER UPDATES, RESEARCH & EDUCATION

Combining science with humanity,  
**CURE** makes cancer understandable.

I have metastatic breast cancer.

I want to get more from my hormone therapy.

Because I'm still here in the moment.

And this is my **MORE**

Persons shown are not actual patients.

Currently available data have not shown an increase in overall survival. Additional data will be available in the future.



I think of **AFINITOR** as hormone therapy **PLUS**—combined with exemestane, it gives me **MORE**.

**MORE** out of my hormone treatment.

**MORE** time before progression.

**MORE** in the moment.

AFINITOR® (everolimus) Tablets is a prescription medicine used to treat advanced hormone receptor-positive, HER2-negative breast cancer, along with the medicine exemestane, in postmenopausal women who have already received certain other medicines for their cancer.

If you're a postmenopausal woman with advanced hormone receptor-positive, HER2-negative breast cancer, you now have a treatment choice that offers you MORE than hormone therapy alone: AFINITOR combined with exemestane tablets. AFINITOR is the first treatment in 10 years to be specifically approved for HR+, HER2- metastatic breast cancer patients. Adding AFINITOR to the hormone therapy exemestane is proven to extend the hormone therapy's benefits, more than doubling the time before cancer progression compared to exemestane alone.

The median progression-free period was 7.8 months with AFINITOR plus exemestane vs 3.2 months with exemestane alone. AFINITOR is offered in a once-daily dose.

Learn **MORE**. Ask your doctor about **AFINITOR**.

#### Important Safety Information

Patients should not take AFINITOR if they are allergic to AFINITOR or to any of its ingredients. Patients should tell their healthcare provider before taking AFINITOR if they are allergic to sirolimus (Rapamune®) or temsirolimus (Torisel®).

Learn more at [NETWORKMBC.net](http://NETWORKMBC.net)

**AFINITOR**<sup>®</sup>  
(everolimus) tablets  
2.5mg 5mg 7.5mg 10mg

Hormone therapy **PLUS.**

Exemestane is available in the US under the brand name Aromasin® from Pfizer. It is also available in generic form.

## IMPORTANT SAFETY INFORMATION

Patients should not take AFINITOR if they are allergic to AFINITOR or to any of its ingredients. Patients should tell their healthcare provider before taking AFINITOR if they are allergic to sirolimus (Rapamune®) or temsirolimus (Torisel®).

AFINITOR can cause serious side effects, which can even lead to death. If patients experience these side effects, they may need to stop taking AFINITOR for a while or use a lower dose. Patients should follow their healthcare provider's instructions. Serious side effects include:

**Lung or Breathing Problems:** In some patients, lung or breathing problems may be severe and can even lead to death. Patients should tell their healthcare provider right away if they have any of these symptoms: new or worsening cough, shortness of breath, chest pain, difficulty breathing, or wheezing.

**Infections:** AFINITOR may make patients more likely to develop an infection, such as pneumonia, or a bacterial, fungal, or viral infection. Viral infections may include reactivation of hepatitis B in people who have had hepatitis B in the past. In some people these infections may be severe and can even lead to death. Patients may need to be treated as soon as possible. Patients should tell their healthcare provider right away if they have a temperature of 100.5°F or above, chills, or do not feel well. Symptoms of hepatitis B or infection may include the following: fever, chills, skin rash, joint pain and inflammation, tiredness, loss of appetite, nausea, pale stools or dark urine, yellowing of the skin, or pain in the upper right side of the stomach.

**Kidney Failure:** Patients taking AFINITOR may develop kidney failure. In some people this may be severe and can even lead to death. Patients should have tests to check their kidney function before and during their treatment with AFINITOR.

Before taking AFINITOR, tell your healthcare provider about all your medical conditions, including if you:

- Have or have had kidney problems
- Have or have had liver problems
- Have diabetes or high blood sugar
- Have high blood cholesterol levels
- Have any infections
- Previously had hepatitis B
- Are scheduled to receive any vaccinations. You should not receive a live vaccine or be around people who have recently received a live vaccine during your treatment with AFINITOR. If you are not sure about the type of vaccine, ask your healthcare provider
- Have other medical conditions
- Are pregnant or could become pregnant. AFINITOR can cause harm to your unborn baby. You should use effective birth control while using AFINITOR and for 8 weeks after stopping treatment
- Are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take AFINITOR or breastfeed. You should not do both

Tell your healthcare provider about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Using AFINITOR with certain other medicines can cause serious side effects. Keep a list of medicines you take and show it to your healthcare provider when you get a new medicine. Especially tell your healthcare provider if you take St. John's wort (*Hypericum perforatum*), medicines that weaken your immune system (your body's ability to fight infections and other problems), or medicines for:

- Fungal infections
- Bacterial infections
- Tuberculosis
- Seizures
- HIV-AIDS
- Heart conditions or high blood pressure

If you are taking any medicines for the conditions previously listed, your healthcare provider might need to prescribe a different medicine or your dose of AFINITOR may need to be changed. Tell your healthcare provider before you start taking any new medicine.

**Common Side Effects:** Common side effects include mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or gel that does not contain alcohol, peroxide, iodine, or thyme.

Other common side effects include:

- Infections
- Feeling weak or tired
- Cough, shortness of breath
- Diarrhea and constipation
- Rash, dry skin, and itching
- Nausea and vomiting
- Fever
- Loss of appetite, weight loss
- Swelling of arms, hands, feet, ankles, face, or other parts of the body
- Abnormal taste
- Dry mouth
- Inflammation of the lining of the digestive system
- Headache
- Nose bleeds
- Pain in arms and legs, mouth and throat, back or joints
- High blood glucose
- High blood pressure
- Difficulty sleeping
- Hair loss
- Muscle spasms
- Feeling dizzy
- Nail disorders

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of AFINITOR.

For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

**Please see Brief Summary of Prescribing Information on adjacent pages.**

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## **Brief Summary of Important Risk Information. This information does not take the place of talking with your doctor about your medical condition or treatment.**

### AFINITOR<sup>®</sup> (everolimus) Tablets

#### **What is AFINITOR?**

AFINITOR<sup>®</sup> (everolimus) Tablets is a prescription medicine used to treat advanced hormone receptor-positive, HER2-negative breast cancer, along with the medicine exemestane, in postmenopausal women who have already received certain other medicines for their cancer.

#### **What is the most important information I should know about AFINITOR?**

**AFINITOR can cause serious side effects. These serious side effects include:**

#### **1. You may develop lung or breathing problems.**

In some people lung or breathing problems may be severe and can even lead to death. Tell your healthcare provider right away if you have any of these symptoms:

- New or worsening cough
- Shortness of breath
- Chest pain
- Difficulty breathing
- Wheezing

#### **2. You may be more likely to develop an infection, such as pneumonia, or a bacterial, fungal, or viral infection.**

Viral infections may include active hepatitis B in people who have had hepatitis B in the past (reactivation). In some people these infections may be severe and can even lead to death. You may need to be treated as soon as possible. Tell your healthcare provider right away if you have a temperature of 100.5°F or above, chills, or do not feel well.

Symptoms of hepatitis B or infection may include the following:

- Fever
- Chills
- Skin rash
- Joint pain and inflammation
- Tiredness
- Loss of appetite
- Nausea
- Pale stools or dark urine
- Yellowing of the skin
- Pain in the upper right side of the stomach

#### **3. You may develop kidney failure.**

In some people this may be severe and can even lead to death. Your healthcare provider should do tests to check your kidney function before and during your treatment with AFINITOR.

**If you have any of the serious side effects listed above, you may need to stop taking AFINITOR for a while or use a lower dose. Follow your healthcare provider's instructions.**

### Who should not take AFINITOR?

Do not take AFINITOR if you are allergic to everolimus or to any of the ingredients in AFINITOR. See full Prescribing Information for a complete list of ingredients in AFINITOR.

Talk to your healthcare provider before taking this medicine if you are allergic to:

- sirolimus (Rapamune®)
- temsirolimus (Torisel®)

Ask your healthcare provider if you do not know.

### What should I tell my healthcare provider before taking AFINITOR?

Tell your healthcare provider about all of your medical conditions, including if you (check all that apply):

- |   |   |
|---|---|
| <input type="checkbox"/> Have or have had kidney problems   | <input type="checkbox"/> Have other medical conditions  |
| <input type="checkbox"/> Have or have had liver problems  | <input type="checkbox"/> Are pregnant, or could become pregnant. AFINITOR can cause harm to your unborn baby. You should use effective birth control while using AFINITOR and for 8 weeks after stopping treatment.                         |
| <input type="checkbox"/> Have diabetes or high blood sugar  | <input type="checkbox"/> Are breastfeeding or plan to breastfeed. It is not known if AFINITOR passes into your breast milk. You and your healthcare provider should decide if you will take AFINITOR or breastfeed. You should not do both. |
| <input type="checkbox"/> Have high blood cholesterol levels   |   |
| <input type="checkbox"/> Have any infections  |   |
| <input type="checkbox"/> Previously had hepatitis B   |   |
| <input type="checkbox"/> Are scheduled to receive any vaccinations. You should not receive a live vaccine or be around people who have recently received a live vaccine during your treatment with AFINITOR. If you are not sure about the type of immunization or vaccine, ask your healthcare provider. |   |

**If you have checked any of the boxes above, be sure to discuss with your doctor before taking AFINITOR.**

**Tell your healthcare provider about all of the medicines you take**, including prescription and nonprescription medicines, vitamins, and herbal supplements. AFINITOR may affect the way other medicines work, and other medicines can affect how AFINITOR works. Using AFINITOR with other medicines can cause serious side effects. Know the medicines you take. Keep a list of them, and show it to your healthcare provider and pharmacist when you get a new medicine. Especially tell your healthcare provider if you take:

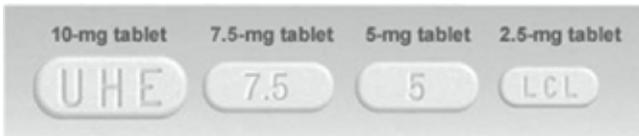
- |  |   |   |
|--|---|---|
| • St. John's Wort<br>( <i>Hypericum perforatum</i> ) | • Medicine for:<br>– Fungal infections<br>– Bacterial infections<br>– Tuberculosis<br>– Seizures<br>– HIV-AIDS<br>– Heart conditions or high blood pressure | • Medicines that weaken your immune system (your body's ability to fight infections and other problems) |
|--|---|---|

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one of those taken for the conditions listed above. If you are taking any medicines for the conditions listed above, your healthcare provider might need to prescribe a different medicine or your dose of AFINITOR may need to be changed. You should also tell your healthcare provider before you start taking any new medicine.

**How should I take AFINITOR?**

Your healthcare provider will prescribe the dose of AFINITOR that is right for you. Take AFINITOR exactly as your healthcare provider tells you to. Your healthcare provider may change your dose of AFINITOR if needed.

- Use scissors to open the blister pack
- Swallow AFINITOR tablets whole with a glass of water. Do not take any tablet that is broken or crushed
- Take AFINITOR 1 time each day at about the same time
- Take AFINITOR the same way each time, either with food or without food
- If you take too much AFINITOR contact your healthcare provider or go to the nearest hospital emergency department right away. Take the pack of AFINITOR with you
- If you miss a dose of AFINITOR, you may still take it up to 6 hours after the time you normally take it. If it is more than 6 hours after you normally take your AFINITOR, skip the dose for that day. The next day, take AFINITOR at your usual time. Do not take 2 doses to make up for the 1 that you missed. If you are not sure about what to do, call your healthcare provider
- You should have blood tests before you start AFINITOR and as needed during your treatment. These will include tests to check your blood cell count, kidney and liver function, cholesterol, and blood sugar levels

**What should I avoid while taking AFINITOR?**

You should not drink grapefruit juice or eat grapefruit during your treatment with AFINITOR. It may make the amount of AFINITOR in your blood increase to a harmful level.

**What are the possible side effects of AFINITOR?**

AFINITOR can cause serious side effects. See “What is the most important information I should know about AFINITOR?” for more information.

Common side effects of AFINITOR in people with advanced hormone receptor-positive, HER2-negative breast cancer include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol, peroxide, iodine, or thyme
- Infections
- Feeling weak or tired
- Cough, shortness of breath
- Diarrhea and constipation
- Rash, dry skin, and itching
- Nausea and vomiting
- Fever
- Loss of appetite, weight loss
- Swelling of arms, hands, feet, ankles, face or other parts of the body
- Abnormal taste
- Dry mouth
- Inflammation of lining of the digestive system
- Headache
- Nose bleeds
- Pain in arms and legs, mouth and throat, back or joints
- High blood glucose
- High blood pressure
- Difficulty sleeping
- Hair loss
- Muscle spasms
- Feeling dizzy
- Nail disorders

**Tell your healthcare provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of AFINITOR. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.**

**Keep AFINITOR and all medicines out of the reach of children.**

#### **General information about AFINITOR**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AFINITOR for a condition for which it was not prescribed. Do not give AFINITOR to other people, even if they have the same symptoms or condition you have. It may harm them.

This leaflet summarizes the most important information about AFINITOR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information written for healthcare professionals. For more information call 1-888-423-4648 or go to [www.AFINITOR.com](http://www.AFINITOR.com).

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# A Patient's Guide to Metastatic Breast Cancer

**ABOUT 232,000 WOMEN AND MORE THAN 2,000 MEN WILL RECEIVE A DIAGNOSIS OF INVASIVE BREAST CANCER THIS YEAR.** The disease is a diverse one, showing up in different parts of the breast, at different degrees of development and in various forms. The risk that breast cancer will spread to other parts of the body depends on many factors. Breast cancer that spreads outside the breast to other parts of the body is called metastatic breast cancer. Most breast cancer is diagnosed at an early stage—that is, without any spread—and most patients will never experience metastatic disease.

**METASTATIC BREAST CANCER (also referred to as “advanced” or “late-stage”) is often treated as a chronic disease, and one that is incurable.** But some patients survive for many years: 15 percent are alive five years after a stage 4 diagnosis, and treatment options for metastatic breast cancer continue to expand.

## WHEN BREAST CANCER SPREADS

Breast cancer usually starts in cells that line the breast's lobules or ducts (lobules contain glands that can make milk; ducts

transport milk to the nipples). “In situ” breast cancer remains confined to the ducts or lobules. When it penetrates the membrane that lines the ducts and lobules, it's termed “invasive.”

In the case of invasive cancer, cells move through the lymphatic system or the bloodstream to other parts of the body from the primary site. When breast cancer metastasizes, it turns up most often in the bones, brain, liver or lungs. Regardless of its location, it is still called breast cancer and it

is treated as such.

The process of metastasis is complex—most metastatic cells that escape a primary tumor die off. Tumor cells must manage to survive the very different microenvironments they encounter, and they must thrive and divide in one of those new locations. Some may be able to survive in bone but not lung tissue; others might grow in brain tissue, but die in bone.

Breast cancer can also recur in or invade the breast or chest wall. In this situation, the cancer is considered a “local recurrence” and might be curable. This guide, however, focuses only on cancer that metastasizes away from the original site.

### **RISK FACTORS FOR BREAST CANCER**

With breast cancer, certain risk factors cannot be changed, such as gender, genetic mutations and family history or age.

One of the most significant risk factors for breast cancer is prolonged uninterrupted exposure of breast tissue to female hormones—this is the primary reason the disease is far more common in women. For the same reason, women who had their first menstrual cycle at an early age, were older at first pregnancy, never had children or were older at menopause have a greater risk of developing invasive breast cancer, as do those who take postmenopausal estrogen and progesterone replacement therapy.

Another factor is age: 95 percent of women who receive a breast cancer diagnosis are older than 40, and half are older than 60.

Family history, especially when family members developed breast cancer at a young age, is another uncontrollable factor,

as is having a BRCA1 or BRCA2 gene mutation.

Some risk factors that can be controlled include weight, age at first pregnancy, breast feeding, physical inactivity and smoking.

### **RISK FACTORS FOR DEVELOPING METASTATIC DISEASE**

Risk factors for developing metastases are determined by evaluating large populations. Because of this, it can be difficult to ascertain specific factors leading to an individual’s diagnosis. In general, however, smaller tumors and lower grades (tumors that grow less aggressively) confer lower risk of metastasis. If the cancer has not spread to lymph nodes, or cancer cells have receptors for estrogen and progesterone (estrogen-positive and progesterone-positive tumors), the prognosis is generally more positive. HER2-positive tumors (which have an overexpression of human epidermal growth factor receptor 2), even small tumors, carry a higher risk of relapse and metastasis—but there are also targeted treatments for this type of cancer that can lower the chance of spread.

This guide provides an overview of metastatic breast cancer for those seeking to understand more about the disease, treatment options, clinical trials and new therapies.



# Detection and Diagnosis

**MOST CASES of metastatic breast cancer in the U.S. are documented after initial diagnosis and treatment of early-stage cancer. Only about 5 to 10 percent of women have metastatic disease at first diagnosis. Recent research has turned up a slight increase in the risk of advanced breast cancer for women between the ages 25 and 39.**

Metastatic disease is usually discovered when a patient begins experiencing symptoms, months to several years after an initial cancer diagnosis and treatment. These symptoms may be general—loss of appetite, feeling under the weather, fatigue—or specific to the location of the tumor (for example, bone pain in cases of bone metastases). Symptoms can be mild to severe, depending on the size and location of the tumor. Various tests—imaging studies, blood tests or liver function tests, for example—can determine whether cancer has spread.

## COMMON SYMPTOMS BY LOCATION

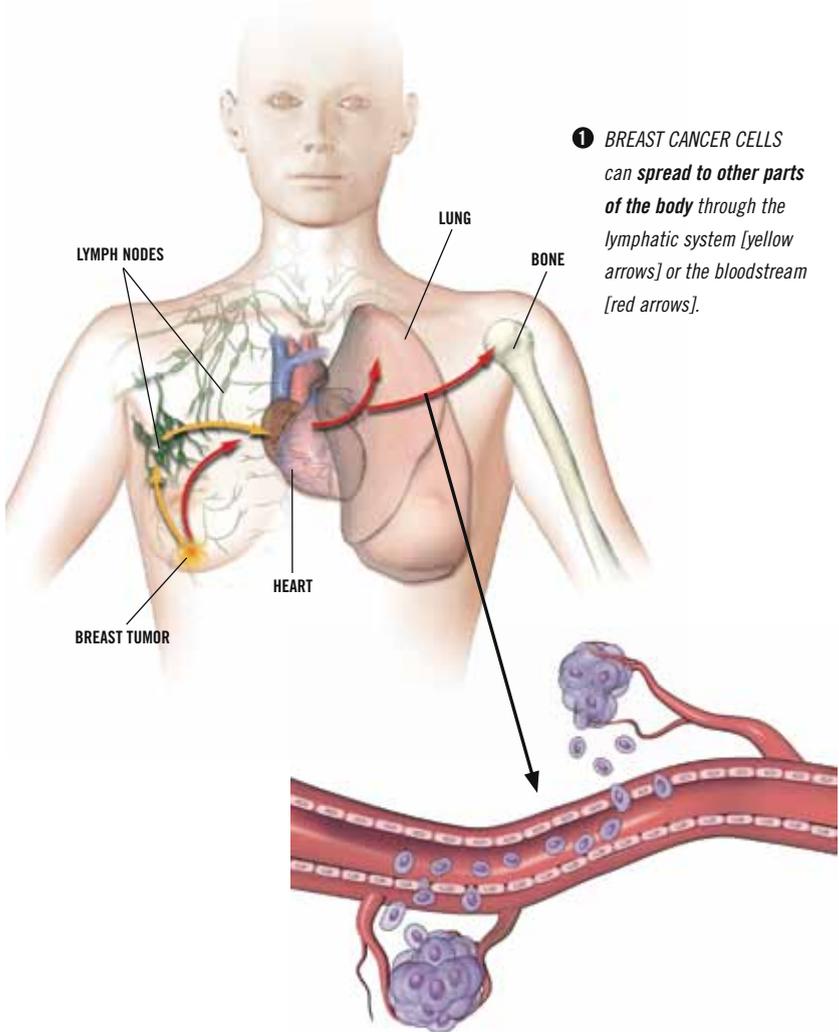
- > **General:** Loss of appetite, weight loss, fatigue, feelings of poor health.
- > **Bone:** Bone pain that worsens, a fracture with minimal or no trauma.
- > **Lungs:** Shortness of breath, persistent coughing, chest pain.
- > **Liver:** Skin yellowing (jaundice) with dark urine, abdominal pain and swelling, bloating.
- > **Brain:** Headaches, seizures, unsteadiness, confusion, nausea, changes in or loss of vision.
- > **Skin:** Rash, itchiness.
- > **Lymph nodes:** Visible or palpable new nodules or lumps.

## FINDING METASTASES

Techniques used to detect metastatic breast cancer are similar to those used to search for, identify and stage initial breast cancers. Detection tools include:

- > **X-ray:** Involves the use of electromagnetic radiation to penetrate the body and cast a shadow of internal structures (structures with different composition and density let more or fewer X-rays through). Mammography is a form of X-ray, and other types of X-rays may show changes in bone architecture associated with metastases to bones.
- > **Computed tomography (CT) scan:** Uses a series of X-rays to generate two- and three-dimensional images of structures inside the body. CT scans can reveal metastases in the bones, brain, liver, lungs and lymph nodes.
- > **Magnetic resonance imaging (MRI) scan:** Involves using radio waves and a strong magnetic field to make two- and three-dimensional images of internal body structures based on their water content. MRI scans are particularly useful for differentiating tissue layers, imaging joints and detecting metastases in bones, brain and liver.
- > **Positron emission tomography (PET) scan:** Identifies areas of increased metabolism, which can include tumors or inflammation and repair. A sugar solution “tagged” with radioactivity is injected before the scan. Dividing cells use more glucose, so they show up as “hot spots” when scanned. PET scans may be combined with CT scans for greater accuracy.
- > **Blood test:** Can reveal probable metastases. Some tests look for evidence of circulating tumor cells, others detect a drop in blood counts that could mean infiltration of bone marrow or excess calcium that is associated

## HOW CANCER SPREADS



- ❶ BREAST CANCER CELLS can **spread to other parts of the body** through the lymphatic system [yellow arrows] or the bloodstream [red arrows].

- ❷ WHEN CANCER SPREADS through the blood, cancer cells detach from the primary tumor and **squeeze through the blood vessel wall** to enter the bloodstream. The cancer cells must again travel from inside the blood vessel and into distant body tissues.

with cancer growth or bone metastases. Still others detect problems in liver function associated with liver metastases. Tumor markers, such as CA 15-3 or CA 27.29, are proteins that can also be followed over time to assess response to therapy along with scans.

➤ **Tap:** Involves extracting a sample of fluid from the spine, the membranes covering the lungs or the abdominal organs to test for the presence of cancer cells.

➤ **Biopsy:** Refers to removing a piece of tissue so it can be examined with a microscope and tested for certain characteristics. Doctors may biopsy lymph nodes with fine needles (aspiration) or with surgical removal of one or more nodes to evaluate a cancer's spread. Because breast fluid drains into lymph nodes, breast cancer cells inclined to spread are often detected first in lymph nodes. Bone, liver or lung tissues can be similarly tested to detect distant spread. For patients with new metastases, a biopsy can help determine characteristics of the metastasis, such as hormone and HER2 receptor status. Such status can change from the original tumor, and may affect treatment options.

## DIAGNOSING METASTATIC DISEASE

A metastatic breast cancer diagnosis will take into account a tumor's size and growth patterns, hormone receptor and HER2 receptor status, and gene expression. Oncologists will consider these tumor-related factors when determining possible therapies. Once a diagnosis is made, treatment will depend on many variables, such as the patient's overall health, values, preferences and lifestyle. Many treatments will be familiar to patients who received a primary cancer diagnosis months or years before a

metastatic diagnosis.

Tumor-related factors an oncologist might consider when discussing possible therapies include:

- **Size and growth patterns.** Large versus small tumors and the tumors' growth pattern could influence treatment options.
- **Hormone (estrogen and progesterone) status.** Breast cancer metastases testing positive for hormone receptors can be treated with different therapies than metastases involving hormone-negative tumors. Metastases do not always maintain the same hormone status as primary cancers—these “conversions” can occur 10 to 40 percent of the time, with progesterone status more likely to change than the estrogen status.
- **HER2 status.** Primary and metastatic breast cancers that test positive for HER2 receptors tend to be more aggressive than HER2-negative cancers. HER2 status can also shift when a cancer metastasizes. It is now believed to be better for the patient to have HER2-positive cancer because of the availability of several anti-HER2 therapies.
- **Gene expression.** Genetic profiling tests, such as Oncotype Dx and MammaPrint, can help determine the chances of cancer metastasizing, and in the case of Oncotype Dx, to predict the benefit of postoperative chemotherapy. Gene expression tests are often used in research settings. MammaPrint is another commercial assay, and there are several others as well, all of which are used primarily for early stage breast cancer. Newer gene sequencing and protein panel tests are entering the clinical arena to help with treatment choices, including experimental targeted therapies, but such tests are still not considered routine.



# Treatment Options

**THERE IS no one-size-fits-all treatment protocol for metastatic breast cancer. The disease itself is too diverse: Tumors with hormone receptors or that overexpress HER2 receptors respond to drugs differently than those without. Cancer can also shift character as it metastasizes, so metastases may demand different approaches than primary cancers. And patients are diverse, too: Some opt for more aggressive treatment than others, depending on the balance between side effects and the chances and length of response to treatment.**

Since the 1990s, new treatments and effective combinations and successions of treatments have been improving the survival time for people with metastatic breast cancer. Recent research has led to testing of new monitoring tools, including blood tests for tumor genetics, to assess whether a treatment is working or if it's time to try a new strategy.

To attack the metastatic cells that escape a primary tumor and set up shop elsewhere, oncologists might suggest a variety of treatment options, including a combination or succession of chemotherapy, hormone therapy, antibody or “targeted” therapy, radiation therapy or, in rare cases, surgery.

Treatment options depend not only on the tumor subtype but also on location of the metastases—bone versus liver, for example—and on a patient's health and preferences. Categories of cancer and treatment possibilities include the following:

## TARGETING HORMONE-POSITIVE CANCERS

Hormones can fuel the growth of tumors

that have receptors for estrogen and/ or progesterone, so hormonal therapy treatments are tailored to lower or block the effects of hormones on cancer cells. A class of drugs called aromatase inhibitors (AIs) work effectively in this way and are used only in post-menopausal women. AIs include anastrozole, letrozole and exemestane. Tamoxifen and toremifene are hormone therapies used for women who are pre- or post-menopausal, with tamoxifen used often as a first treatment for men with hormone-positive breast cancer.

For premenopausal women, surgical or chemical shutdown of the ovaries may also be an option. Zoladex (goserelin) and leuprolide are hormone therapies used for such “ovarian blockades.” After ovarian shutdown, women are considered postmenopausal and become candidates for AIs.

Afinitor (everolimus), a biologic drug, is also used to treat estrogen-positive, metastatic breast cancer. It targets a growth pathway inside cancer cells and is used in combination with the AI exemestane for patients whose cancer progresses or recurs after using letrozole or anastrozole.

Faslodex (fulvestrant) is another type of estrogen receptor-blocking drug. It is injected into the muscle monthly to treat metastatic breast cancer in post-menopausal women, usually after tamoxifen or AIs are no longer effective.

## TREATING HER2-POSITIVE CANCERS

About 20 percent of breast cancers test positive for the overexpression of a protein called HER2, which is involved in cancer growth. Although HER2-positive cancers are often aggressive, several drugs are

available to specifically target these cancer cells. Herceptin (trastuzumab) and Perjeta (pertuzumab) are monoclonal antibodies that target the HER2 pathway. Herceptin can be used alone or with hormone therapy in some cases, but is more commonly used with chemotherapy (often with paclitaxel, docetaxel or vinorelbine). More recently, the addition of Perjeta to Herceptin plus docetaxel has been shown to improve median overall survival. One antibody-drug conjugate, Kadcyła (ado-trastuzumab emtansine), includes Herceptin chemically linked to the chemotherapy agent emtansine, and is effective if cancer progresses on Herceptin.

Tykerb (lapatinib), an oral agent, also targets the HER2 pathway in tumor cells and is typically given with the oral chemotherapy Xeloda (capecitabine) to patients with tumors that no longer respond to Herceptin. It may cross the so-called blood-brain barrier more easily than Herceptin and could be effective in treating brain metastases. Tykerb is sometimes combined with letrozole. A recent randomized trial established the superiority of Kadcyła over the combination of Tykerb and Xeloda after prior Herceptin, leading to Kadcyła's FDA approval.

Recent research has shown improved progression-free survival among women taking Tykerb and Herceptin in combination rather than Tykerb alone, without adversely affecting quality of life.

Afinitor might reverse Herceptin resistance and has been shown to modestly delay disease progression when added to second-line Herceptin and chemotherapy. Afinitor, however, remains investigational.

It is common to transition through many

sequential regimens, depending on response and progression of the disease. Researchers are developing biomarkers that can predict the benefit of specific drugs to help further personalize therapy.

## CHEMOTHERAPY

Many chemotherapy agents can be effective at treating breast cancer metastases, shrinking them or preventing their growth. Chemotherapy is often a first treatment for people with cancers that lack hormone receptors. Chemotherapy drugs are "cytotoxic," meaning they are poisonous to cells and preferentially attack rapidly dividing cells. Many healthy body tissues also contain cells that divide rapidly, including hair roots, the lining of the digestive tract and bone marrow. As such, though chemotherapy attacks cancer cells, it can also lead to side effects, including hair loss, nausea, mouth sores and a drop in blood counts, which can result in anemia and infection.

For triple-negative breast cancer, chemotherapy is the only treatment option, though other medicines are under investigation. Triple-negative breast cancer lacks receptors for estrogen and progesterone, and does not overexpress HER2.

Chemotherapy is commonly used in hormone receptor-positive cancers when hormone therapies become ineffective. It can also be used with Herceptin in HER2-positive cancers.

Patients with metastatic breast cancer might switch chemotherapy drugs or combinations many times over the course of their treatment, usually because metastases develop drug resistance. Fortunately, there are many chemotherapy drugs available

that work in advanced breast cancer, and many of them can be combined with each other, and with other types of therapies. Chemotherapy agents include 5-FU (fluorouracil), cisplatin, doxorubicin, gemcitabine, Halaven (eribulin), Ixempria (ixabepilone) and vinorelbine. Combinations used in metastatic disease can include CMF (cyclophosphamide, methotrexate and 5-FU); Xeloda with docetaxel; and gemcitabine with paclitaxel. Combinations of chemotherapy agents can cause powerful side effects, so single chemotherapy approaches might be preferred, unless tumors are particularly aggressive or extensive.

### BONE METASTASES

- > **Radiation:** Oncologists use radiation to shrink metastases in the bones, brain or lungs that cause pain or other symptoms. Radiation therapy can be delivered conventionally or with focused beams. Rarely, radiopharmaceuticals are used, which allow radioactive chemicals to treat scattered bone metastases.
- > **Surgery:** Surgery can be used to control the symptoms of advanced breast cancer, including occasionally relieving spinal cord compression, repairing a fractured bone, or removing fluid buildup around the lungs or abdomen. Surgery may also be used to remove single brain, liver or lung metastases.

### UNDER INVESTIGATION

- > **PARP inhibitors:** PARP refers to the repair enzyme poly (ADP-ribose) polymerase. PARP inhibitors stop the normal process that cancer cells use to repair DNA damage, including damage caused by certain chemotherapeutic agents, such as

platinum-based drugs. Without such repairs, cancer cells would die. In clinical trials for metastatic breast cancer, including triple-negative disease, PARP inhibitors have had mixed success, with better activity noted in BRCA-related cancers. Research is ongoing to determine which subtypes might respond to this class of drugs.

- > **Antiangiogenic drugs:** This class of drugs targets the blood vessels that feed tumors—Nexavar (sorafenib) and Avastin (bevacizumab) are examples, though neither has yet to be approved for use in metastatic breast cancer. The FDA revoked approval for Avastin's use in metastatic breast cancer in 2011 because the drug delayed tumor progression but did not improve survival or quality of life. Additionally, Avastin caused rare but potentially life-threatening side effects. Avastin and other antiangiogenic drugs are used to treat other types of cancer and are being tested in clinical trials to evaluate their effectiveness in a subset of patients with metastatic breast cancer.
- > **Palbociclib:** In the spring of 2013, the FDA designated palbociclib as a “breakthrough therapy,” meaning it will receive expedited review for use in breast cancer. This drug disrupts the cancer cell cycle, and early clinical trials of the drug with hormone therapy involving women with estrogen-positive, HER2-negative cancers showed promise.

Numerous other biologic and chemotherapeutic agents are in testing alone and in combination, and increasingly, there is an effort to identify biomarkers (molecules in the body that may signal how effectively a person will respond to a particular therapy) to better individualize treatment.



## Symptoms and Side Effects

**ALTHOUGH METASTATIC BREAST CANCER is considered incurable, it is treatable, and many people live with it as a chronic condition for years. Supportive care and careful consideration of treatment options can help patients maintain quality of life. Still, the symptoms of the disease itself and the side effects of treatments can be severe, and coping with them can be an ongoing challenge.**

A drug that effectively reduces pain, for example, could cause severe constipation. Chemotherapy may trigger nausea, hair changes, anemia or severe fatigue. Tumors and their metastases can produce substances that trigger symptoms, including fatigue, poor appetite and weight loss. The direct effects of tumorous growth and invasion can result in pain, fractures, bleeding and obstruction of hollow organs, depending on where the cancer spreads. Anxiety and depression can result from the awareness of the diagnosis itself.

Many treatments are available to lessen some of these symptoms and side effects, including anti-nausea drugs, bone boosters (to prevent painful fractures), moderate exercise and antidepressants. Patients should keep their doctors informed about all symptoms, side effects and remedies they have tried. There is evidence that some integrative therapies, including music therapy, hypnosis, relaxation and acupuncture, can alleviate some symptoms. But some herbal products could cause harm by interacting with other treatments. Following are some symptoms of metastatic breast cancer and side effects of treatment, as well as suggestions for managing these situations:

- > **Fatigue, muscle weakness and imbalance:** Moderate exercise might reduce many symptoms of metastatic cancer, including fatigue, muscle weakness and imbalance. All patients should discuss exercise plans with their healthcare providers. This is especially important for patients whose breast cancer has metastasized to their bones, which increases the risk of fracture.
- > **Bone issues:** Bone-strengthening medications, such as zoledronic acid, Aredia (pamidronate) and Xgeva (denosumab), can lower the complications of bone metastases, such as fracture and pain. In rare cases, these medications can cause bone pain soon after their administration and increase the risk of developing osteonecrosis of the jaw (meaning the jawbone dies).
- > **Pain:** Pain is one of the most common and difficult symptoms of metastatic cancer, and palliative care experts can help manage symptoms to improve quality of life. Interventions are often more effective early on, so patients should ask about options before symptoms become debilitating. Pain management may include non-opioid analgesics, opioids, antidepressants, anticonvulsant drugs and nerve blocks. In some cases it may be worth discontinuing a treatment if painful side effects outweigh the benefits.
- > **Anemia:** Chemotherapy can trigger anemia, a fatigue-inducing drop in red blood cells. For some patients, blood transfusions help; for others, medicines may be necessary. Some anemia drugs can reduce the need for transfusion, but carry increased risk of sometimes fatal stroke and blood clots. These drugs are usually stopped when chemotherapy ends, but can be discussed



## Living with Metastatic Disease

later, in terms of risks and benefits. Factors other than anemia may also contribute to fatigue. Balancing moderate activity and rest with healthy eating can help. Short walks, brief naps and at least eight hours of sleep at night may also help counter fatigue.

- **Hot flashes and other hormone effects:** Anti-estrogen or estrogen-blocking therapy can bring on symptoms of menopause, but there are treatments to lessen their side effects. Arthralgia (joint pain) could require pain management, physical therapy or change of drug. Other side effects of hormone therapy that might necessitate intervention include bone loss, gastrointestinal distress, rash, vaginal symptoms and, in the case of tamoxifen, risk of blood clots.
- **Stress, depression and anxiety:** Research has shown that patients who manage stress in positive ways (relaxation techniques, yoga, meditation or exercise) suffer less depression and anxiety, experience fewer symptoms and report a better quality of life. Stress management can include anti-anxiety drugs to counter the anxiety that may come with certain cancer treatments, or antidepressants to treat depression.
- **Nausea:** In addition to anti-nausea medications, patients might want to take liquid dietary supplements and eat frequent, small meals to reduce nausea. It's also helpful to avoid foods with strong odors, to eat cold foods or to try an appetite stimulant.

**ALTHOUGH METASTATIC BREAST CANCER is often treated as a chronic disease, it's important to remember that, in many ways, patients can still lead a normal life.**

The course of metastatic breast cancer is variable, and while survival statistics are helpful, they don't reflect every patient's situation. More drugs are under evaluation than ever before, underscoring the importance of reviewing treatment options, including participating in clinical trials. Ideas for maximizing quality of life and obtaining effective treatment include:

- **Hitchhiking:** Metastatic cancer may not be curable, but it might be controlled by a succession of treatments. This strategy is sometimes referred to as "hitchhiking." When one therapy is no longer effective, a patient catches the next "ride," switching to another life-sustaining therapy. Most patients with advanced breast cancer switch treatments many times.
- **Less-aggressive therapy:** Sometimes, quality of life will be more important than aggressive treatment, because the side effects of chemotherapy, radiation, surgery or other treatments can be severe. Some patients will be given the option for "a "chemo holiday" by their doctor. This is a short break for re-building energy or finding calm.
- **Clinical trials:** Clinical trials are research studies exploring the effectiveness of new drugs, surgical techniques, radiation therapy, combinations of therapies and treatments for side effects. Many of today's treatments are available because patients participated in trials that took place years ago. Patients can perform customized searches for trials at [clinicaltrials.gov](http://clinicaltrials.gov), [breastcancertrials.org](http://breastcancertrials.org) or



## A Patient's Story

[cancer.gov/clinicaltrials](http://cancer.gov/clinicaltrials).

> **Support:** Emotional, spiritual and financial support is essential when dealing with metastatic disease. Some patients might find solace reaching out to members of a spiritual community, a support group of people going through similar experiences, or friends and family. Healthcare providers can suggest social workers, counselors and experts in palliative care (symptom management).

> **Role models:** Patients with metastatic disease can, in some cases, live long, full lives. Finding a role model whose life is inspirational can help. Some patients can become role models themselves by helping others, doing meaningful work, or spending quality time with friends and family.

> **Planning:** Patients with advanced breast cancer should tend to financial and legal affairs, regardless of where they are on the continuum of care. This includes creating an advance directive or living will (a written set of instructions to guide health care if and when the patient is no longer able to make those decisions). Authorizing a healthcare proxy serves a similar purpose, but laws vary by state. Patients might also consider discussing palliative care with their doctors and family. Palliative care is important both early in disease progression to prevent debilitating side effects and later on if quality of life begins to decline. When patients experience significant decline in their health, the side effects of cancer treatments might start to outweigh the benefits. It can be difficult to initiate such discussions with physicians and family, but many patients find that talking frankly can relieve some emotional burden, enabling them to focus on surviving with a better quality of life.

**WHEN CJ CORNELIUSSEN-JAMES learned in 2006 that her breast cancer had metastasized, she began the complicated and seemingly endless series of medical appointments and treatment decisions that are all too familiar to patients with metastatic disease.**

Should she have surgery or not? What type of therapeutic regimen? Should she participate in a clinical trial? And, for CJ, how should she respond to the oncologist who advised her only to “pray.”

“I told him, ‘If I wanted that kind of advice, I’d go to a pastor,’” CJ says. She changed oncologists.

Today, at 62, CJ has had no evidence of disease for six years. She co-founded METAvivor, a national research and support nonprofit for metastatic breast cancer, and serves as its director of advocacy. She’s also helping her husband deal with lymphoma. CJ takes the hormone therapy drug Faslodex (fulvestrant), which can block or slow the growth of some cancers. When her doctor gave her a choice to stop or continue the drug, CJ chose to continue.

“It’s a bit of a security blanket,” she says. “Living with a metastasis, you know you have dormant cells in your body. They may not do anything for 25 years; they may activate tomorrow. Nobody knows for sure.”

Her metastatic cancer is part of every decision she makes, she says, “because it’s simply part of me.” She considers it when planning a trip, a house project or a pricey club membership. “What if I relapse? What if my treatment schedule changes?”

Recently, CJ purchased a two-year magazine subscription. “I used to never do that,” she says in a moment of optimism.



## Questions to Ask the Doctor

- What is metastatic breast cancer?
- Where in my body has the cancer spread?
- How rapidly is the cancer growing?
- What are the treatment options?
- What are the side effects associated with those treatments?
- What are the costs associated with those treatments?
- How and why did you suggest this treatment option for me?
- What are the chances my cancer will respond to the treatment and for how long?
- When will I be tested to see if the treatment is working?
- Will this treatment help me live longer, will it relieve symptoms, or both?
- Do I qualify for a clinical trial?
- What symptoms of metastatic breast cancer should I be monitored for?
- How will I be monitored?
- What are tumor markers?
- What diagnostic tests can be done to reveal biomarkers and potential therapies?
- Are there any complementary or integrative therapies that would help me?
- Will I be able to continue with my normal daily activities?
- What do I tell my family and friends?
- Where can I find support or a palliative or pain specialist, if needed?
- What is palliative care and how is it different from hospice care?
- How will you keep me informed?



## Resources

### **AdvancedBC.org**

**American Cancer Society**  
cancer.org  
800-227-2345

**American Pain Foundation**  
painfoundation.org  
888-615-7246

### **BCMets.org**

### **BrainMetsBC.org**

### **Breastcancer.org**

**Cancer Legal Resource Center**  
cancerlegalresourcecenter.org  
866-843-2572

**Clinical Trials Help**  
cancertrialshelp.org  
877-227-8451

**The MetaCancer Foundation**  
metacancer.org

**Metastatic Breast Cancer Network**  
mbcn.org  
888-500-0370

**METAvivor Research and Support**  
metavivor.org  
410-491-5760

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

**National Comprehensive Cancer Network**  
nccn.com

**Partnership for Prescription Assistance**  
pparx.org  
888-477-2669

**Sharsheret**  
sharsheret.org  
866-474-2774

**Susan G. Komen for the Cure**  
komen.org  
877-465-6636

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