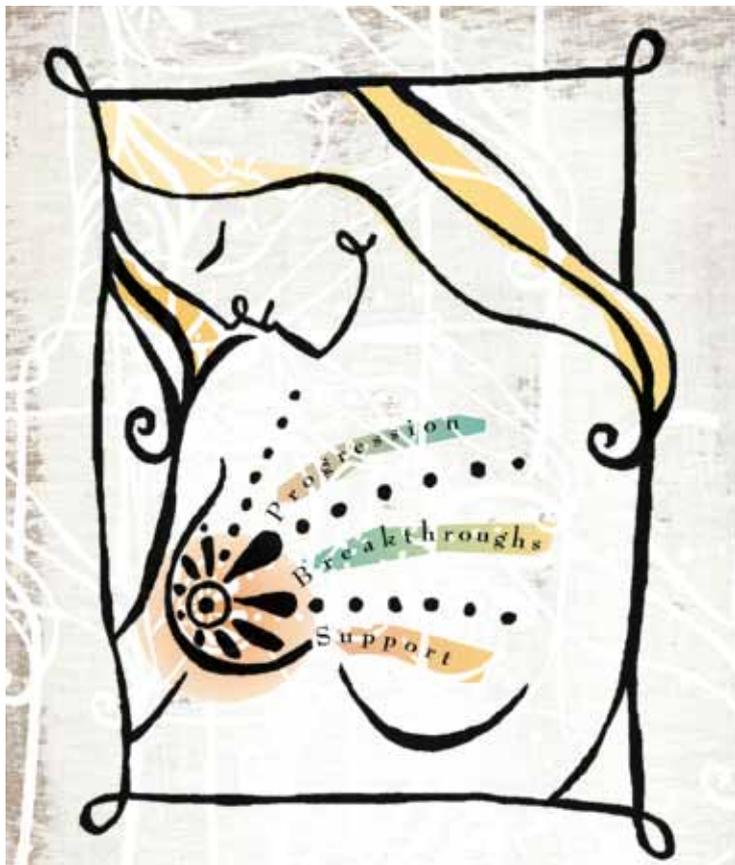


# A Patient's Guide to **Metastatic Breast Cancer**



**Detection & Diagnosis** ■ **Treatment Options** ■ **Coping with Symptoms**  
**& Side Effects** ■ **Living with Metastatic Breast Cancer** ■  
**Patient Perspective** ■ **Questions** ■ **Resources**

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# A Patient's Guide to Metastatic Breast Cancer

**ABOUT 230,000 WOMEN IN THE U.S. WILL LEARN THIS YEAR THAT THEY HAVE INVASIVE BREAST CANCER.** Some 25 percent of those will later develop advanced or metastatic breast cancer, which occurs when cancer originating in the breast spreads, or metastasizes, to other parts of the body, most often the lungs, liver, bones, soft tissue (lymph nodes) and brain.

**LESS THAN 1 percent of breast cancer occurs in males, where it tends to be diagnosed at a later stage than in women.**

While metastatic disease in both women and men is considered incurable, a subset of patients can live longer term (about 15 percent are alive at five years and some can live much longer) with the help of treatment options that have continued to expand. This guide provides an overview of metastatic breast cancer not only to educate those who want to know more about the disease for themselves and their families, but also to help patients with advanced breast cancer make informed decisions about treatments, including therapies recently approved or in late-phase trials.

## **BREAST CANCER AND METASTASES**

With a few exceptions, breast cancer starts in the cells that line either the ducts or the lobules (lobules contain glands that can make milk; ducts transport milk to the nipples). When confined to the ducts or lobules, breast cancer is called *in situ*. When it penetrates the membrane that lines the ducts and lobules, breast cancer is

considered “invasive” and can spread. Breast cancer becomes metastatic when cancer cells from the initial tumor travel out of the breast by way of the lymphatic system or the bloodstream to other parts of the body. No matter what other body part it invades, such as liver or bone, it is still called breast cancer and behaves as such. In some instances, breast cancer can recur in the breast or on the chest wall, which is considered a *local* recurrence and may be curable. This guide focuses on *distant* metastasis only.

Metastatic disease usually develops after initial diagnosis and treatment, but about 5 to 10 percent of patients have metastatic disease at diagnosis. The process by which breast cancer becomes metastatic is complex. Not only must tumor cells move through barriers imposed by the microenvironment surrounding the cells, they also must migrate and thrive in a new environment, despite some restrictions. For example, they may be able to thrive in bone yet not in brain tissue, or vice versa. Fortunately, most cells that leave a primary tumor never make it, dying before they cause further problems. Some cancer

researchers refer to this as the “seed and soil hypothesis” of metastasis: the metastatic seeds of cancer may spread, but they only take root and grow in ideal microenvironments.

### RISK FACTORS

So why do people get breast cancer, and why does it metastasize? In most cases, science can't provide definitive answers. But researchers have uncovered risk factors that help define the likelihood that a person will develop breast cancer, and in some instances, the likelihood that the cancer will metastasize.

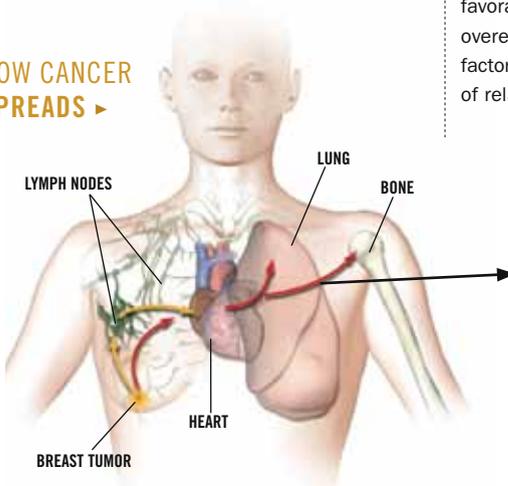
Prolonged exposure of the breast tissue to female hormones is perhaps the most influential risk factor for developing breast cancer, which is why it's more common in women. Also, women who had their first menstrual cycle at an early age, were older

at the time of their first pregnancy, never had children or were older at menopause have a higher risk of developing the disease. Age is another factor: Only about 5 percent of women diagnosed with breast cancer are under age 40; most receive a diagnosis at age 60 or older.

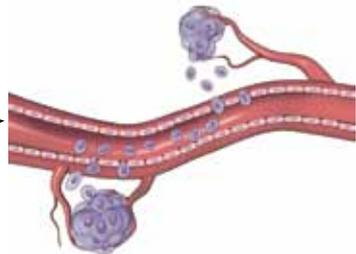
Other risks include having a strong family history of developing breast cancer at a younger age, with a group of those patients harboring a BRCA1 or BRCA2 gene mutation. Smoking, excess weight and alcohol use have also been implicated, but with a weaker association, while pregnancy under age 30, exercise and weight loss may reduce risk.

Predicting the risk of metastasis involves many considerations. A smaller tumor size and lower grade (degree of aggressiveness), a lack of lymph node involvement and the presence of surface receptors for estrogen and/or progesterone are considered more favorable factors. The opposite traits or the overexpression of human epidermal growth factor receptor 2 (HER2) predict a higher risk of relapse.

### 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.



## Detection & Diagnosis

**METASTATIC DISEASE is often discovered when a patient experiences symptoms, which can arise months to years after initial therapy. Imaging studies, serum tumor marker tests (blood tests that may determine the presence of tumor cells in the bloodstream) or liver function tests may be conducted to determine whether the cancer has spread. Symptoms of metastatic breast cancer can be mild to severe, depending on the size and location of the metastases.**

### COMMON SYMPTOMS BY LOCATION

- > **General:** Loss of appetite, weight loss, fatigue, loss of overall sense of health.
- > **Bone:** Bone pain that worsens, or 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 vision.
- > **Skin or lymph nodes:** Visible or palpable new nodules or lumps.

### FINDING METASTASES

Patients who have already dealt with breast cancer may be familiar with many of the scans and tests used to find and identify metastases. They include:

- > **X-ray:** Involves the use of electromagnetic radiation to penetrate the body and cast a shadow of the internal structures. X-rays may show changes in bone architecture associated with metastases to bone.
- > **Computed tomography (CT) scan:** Employs a series of X-rays to generate two- and three-dimensional images of structures inside the body. CT scans can reveal

metastases in the lymph nodes, bones, lungs, liver and brain.

- > **Magnetic resonance imaging (MRI)**

**scan:** Involves using a magnetic field to make two- and three-dimensional images of internal body structures. MRI scans have an enhanced ability to differentiate between various soft tissues in the body.

- > **Positron emission tomography (PET) scan:**

Helps identify areas of increased metabolism (such as tumors or inflammation). 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 precision.

- > **Blood test:** Can reveal possible liver problems; excess calcium (associated with bone metastases); and elevated tumor markers (which may indicate a cancer is growing).

- > **Tap:** Involves extracting a sample of fluid from the spine or between the two layers of the envelope covering the lung to test for the presence of cancer cells.

- > **Biopsy:** Refers to the removal of tissue for examination with a microscope. Lymph node biopsy refers to the fine needle aspiration or surgical removal of one or more nodes, to assess a cancer’s spread. Because breast fluid drains into lymph nodes, breast cancer cells inclined to spread are often first detected in lymph nodes. Other tissues, such as those of liver, lung or bone, can be similarly tested to detect distant spread. For patients with new metastases, a biopsy is recommended if it can be safely done since estrogen and HER2 receptor status can change from the original tumor in up to 20 percent of cases, which may affect treatment options.



## Treatment Options

**BREAST CANCER is such a diverse group of diseases that one-size-fits-all treatment approaches are seldom relevant. Attacking the metastatic cells that have escaped the primary tumor site may involve chemotherapy, hormone therapy, antibody (or targeted) therapy, radiation therapy or (rarely) surgery, or a combination. All of this depends on where the cancer has spread, the extent of metastases, its subtype and the patient's health and philosophy. The survival time for metastatic breast cancer has been improving for several decades due to new treatments and combinations, as well as improved imaging techniques.**

### TARGETING THE ESTROGEN RECEPTOR

If the cancer is estrogen and/or progesterone receptor-positive, treatment may involve hormone therapy, such as aromatase inhibitors (AIs) or tamoxifen. Estrogen fuels growth in estrogen-positive tumors; hormone therapies, also called endocrine therapies, are designed to prevent cancer cells from having access to estrogen.

Many hormone therapies are available for treatment of metastatic breast cancer—a doctor's recommendations will likely depend on whether the patient has been through menopause and has had prior exposure to hormone therapy. Tamoxifen may be used in pre- or postmenopausal women, while the AIs—including anastrozole, letrozole and exemestane—are exclusively used in postmenopausal women and are somewhat more effective than tamoxifen. For premenopausal women, surgical or chemical shutdown of the ovaries may also be an option, after which they are considered postmenopausal and may become candidates for AIs.

Hormone therapy with AIs may produce certain side effects, such as joint pain, particularly in the small joints of hands, bone loss/osteoporosis and vaginal dryness, while hot flashes are experienced with most hormone therapies. Tamoxifen also causes a slight increase in the risk of forming clots and of developing uterine cancer. These risks are considered minimal enough that tamoxifen has been approved for use as a preventive agent in healthy women who are at an increased risk of developing breast cancer.

Recently, the Food & Drug Administration (FDA) approved Afinitor (everolimus), a drug that targets the mammalian target of rapamycin (mTOR) growth pathway inside the cancer cell. It has shown promise in estrogen receptor (ER)-positive metastatic breast cancer. When used with the AI exemestane, Afinitor improved progression-free survival in patients whose cancers had progressed while on hormone therapy. The drug may also decrease the likelihood of resistance to the antibody Herceptin (trastuzumab) in HER2-positive cancers.

### TARGETING THE HER2 RECEPTOR

If the cancer tests positive for the overexpression (or gene amplification) of HER2, as about one in four to five breast cancers do, the patient may be prescribed Herceptin with a chemotherapy drug, typically paclitaxel, docetaxel, Xeloda (capecitabine) or vinorelbine. Recently, docetaxel and Herceptin, along with a newly approved antibody called Perjeta (pertuzumab), was approved as a triple combination; it was superior to docetaxel and Herceptin. Both antibodies are referred to as “targeted” therapies because they silence the cancer-

growth signaling through the HER2 pathway.

Herceptin, used alone or with other drugs, including Perjeta, may increase overall survival in women with metastatic HER2-positive breast cancers. Herceptin cannot penetrate the brain, which may explain why, over time, metastases to the brain are more common in HER2-positive compared with HER2-negative breast cancer.

But another HER2-targeted drug that may cross that barrier is Tykerb (lapatinib), which also blocks the signaling in HER2-positive tumor cells by working inside the cells as opposed to the antibodies that work outside the cells on surface receptors. Tykerb is used with Xeloda in patients whose tumors progress on Herceptin-containing therapy. Another strategy is to continue Herceptin, but change the chemotherapy drug. A recent study also found that women on Tykerb and Herceptin had a better overall survival rate than those on Tykerb alone.

Side effects of anti-HER2 antibodies include flu-like symptoms, diarrhea, rash and, rarely, cardiotoxicity and lung problems. Tykerb can cause diarrhea, rash, as well as other rare but serious side effects (liver damage).

Breast cancer doesn't always retain its original HER2 or hormone status: An estrogen-positive cancer can turn estrogen-negative; HER2-negative cancers can switch to positive. A patient's doctor may suggest another biopsy to determine the subtype of metastases to better tailor treatment.

## CHEMOTHERAPY

Many chemotherapy agents show action against breast cancer metastases, shrinking them or preventing growth, and chemotherapy is often a first treatment for

people with hormone receptor-negative cancers. Chemotherapy drugs are "cytotoxic," meaning they are poisonous to cells and attack rapidly dividing cells. Rapid division is a feature common to most cancer cells, but is also a trait shared by many normal tissues of the body, such as hair roots, digestive tract lining and bone marrow. This causes hair loss, nausea, mouth sores and a drop in blood counts, which can result in anemia and infection.

Chemotherapy currently remains the only treatment option for "triple-negative" breast cancer, which means the cancer is negative for the overexpression of estrogen, progesterone and HER2 receptors. It is also used when hormone therapy is no longer working in hormone-positive cases. It is also commonly used with Herceptin for HER2-positive cases.

Patients with metastatic breast cancer may switch chemotherapy drugs or combinations many times over the course of their treatment, usually because metastases develop drug resistance. Fortunately, there are many different chemotherapy drugs available that work in advanced breast cancer, and many of them can be combined with each other when necessary. They include (in alphabetical order):

- > 5-FU (fluorouracil)
- > Abraxane (albumin-bound paclitaxel)
- > carboplatin
- > cisplatin
- > cyclophosphamide
- > docetaxel
- > Doxil (liposomal doxorubicin)
- > doxorubicin
- > epirubicin
- > gemcitabine
- > Halaven (eribulin)
- > Ixempra (ixabepilone)
- > methotrexate
- > mitomycin
- > mitoxantrone
- > paclitaxel
- > vinblastine
- > vinorelbine
- > Xeloda (capecitabine)

Some patients respond better to certain drugs. In general, many newer drugs have the same or better response rates with fewer side effects compared with older drugs.

Doctors may also suggest combinations of chemotherapy drugs or may combine chemotherapy with other treatments, including targeted therapies. Among the combinations used in metastatic disease is CMF: cyclophosphamide, methotrexate and 5-FU. Other combinations include Xeloda and docetaxel or gemcitabine and paclitaxel. However, these combinations cause more side effects and are used in rapidly growing or extensive tumors. If possible, a single chemotherapy approach is preferred.

## RADIATION

Radiation can help shrink symptomatic metastases, improve bone or nerve pain, or help with difficulty breathing. Radiation is directed “locally” to specific spots of cancer, including those in the brain. Radiation therapy may rarely include use of a radioactive chemical to treat scattered bone metastases that don’t respond to chemotherapy and can’t be easily treated with radiation.

## SURGERY

While mostly reserved for treating early breast cancer, surgery may control symptoms in advanced disease, particularly in patients with painful breast lesions, spinal cord compression or disease-related fractures, or to remove fluid buildup around lungs or in the abdomen. A single brain metastasis may also be removed surgically. There is debate as to whether lumpectomy or mastectomy improves survival for those who have the primary tumor still in the breast.

## INVESTIGATIONAL THERAPIES

> **T-DM1:** This “conjugate” drug combines two cancer-fighting strategies: a target-seeking antibody and a chemotherapy agent fused to deliver cell-killing chemicals to cancer, reducing collateral damage to healthy cells and side effects. The drug includes Herceptin, which targets HER2-positive cancer cells, and a chemotherapy agent called emtansine. A large phase 3 trial showed patients on T-DM1 lived longer without disease progression than those on a more conventional treatment.

> **Poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors:** PARP is an enzyme that helps repair normal damage to a cell’s genetic material. These drugs stop the repair process in damaged cancer cells, which could lead to cell death. PARP inhibitors have had mixed success in clinical trials for metastatic breast cancer, specifically triple-negative disease, and in patients with BRCA mutations. Research is ongoing to determine whether this class of drugs benefits certain subtypes of disease.

> **Antiangiogenic drugs:** Nexavar (sorafenib) and Avastin (bevacizumab) are antiangiogenic drugs—medicines that target the blood vessels that feed a tumor. The FDA pulled approval for Avastin’s use in metastatic breast cancer in November 2011 because, while it delayed progression, it did not improve survival, and there were rare but sometimes serious side effects. Research into identifying a certain subset of patients who respond to the drug is ongoing, but the drug is currently not recommended for metastatic breast cancer. A phase 3 trial involving Nexavar and Xeloda is ongoing after an earlier clinical trial found the combination increased progression-free survival.



## Coping with Symptoms & Side Effects

**WHILE METASTATIC BREAST CANCER is considered incurable, it is treatable, and many patients now live with it as a chronic condition for many years. Several treatment options as well as supportive care can enable a patient to maintain quality of life.**

The symptoms of the disease itself and side effects of treatment can be severe, however, and coping with these symptoms remains a challenge. When one symptom improves, another may appear. For example, a drug may reduce pain but cause constipation.

Chemotherapy may cause nausea and vomiting, neuropathy and anemia; hormone therapy may cause weight gain; while both, along with radiation, may cause fatigue. Many medications, from anti-nausea drugs to anti-depressants, can lessen these side effects.

Following are suggestions for managing symptoms of metastatic breast cancer and easing side effects. These do not apply to everyone. Patients should always keep their doctors informed about symptoms, side effects and remedies they may have tried.

- > **Exercise:** Moderate exercise may lessen fatigue and stress, combat depression, and improve muscle strength and balance. Patients whose breast cancer has metastasized to bone and have an increased risk of fracture might consider swimming or other low- or no-impact exercises less likely to require balance. Patients should always discuss exercise plans with their healthcare providers.
- > **Healthy eating:** Some metastatic breast cancer patients lose their appetites and weight; others, including those on hormone therapy, may gain weight. Balanced diets rich in fruits and vegetables and plenty of fluids are important to maintaining a healthy weight

and helping the body deal with the stress of the disease and its treatment. For nausea or weight loss, patients should consider taking liquid supplements and eating frequent, small meals. Because nausea can be triggered by smell, it may help to avoid foods with strong odors. Appetite stimulants, such as megestrol acetate, may also help.

- > **Bone care:** Bone strengthening medications, such as Aredia (pamidronate), Zometa (zoledronic acid) and Xgeva (denosumab), can lower the risk of fractures and reduce the pain of bone metastases. Some of these medications, however, may increase the risk of developing osteonecrosis of the jaw (ONJ), a rare but serious side effect.
- > **Anemia:** Chemotherapy may trigger anemia, a drop in red blood cells that can cause fatigue. Blood transfusions can improve this for some patients. Certain drugs can also help, but because they can increase the risk of stroke and blood clots, they should be discontinued after chemotherapy ends, and the risks/benefits should be discussed.
- > **Pain and palliative care:** Pain and palliative care experts may be brought in early to manage symptoms that can impact quality of life. Patients should ask their doctor about options for managing pain and other symptoms before these debilitating effects take over. Options may include non-opioid analgesics, opioids, antidepressants, anticonvulsant drugs and nerve blocks, or even stopping a treatment if its side effects outweigh the benefits.
- > **Stress management:** Patients experiencing emotional and physical stress should consider yoga or meditation, or seek relief in writing, art or support groups. Because some therapies can trigger anxiety, a doctor may prescribe an antidepressant.



# Living with Metastatic Breast Cancer

**HOW LONG PATIENTS with metastatic breast cancer can expect to live is impossible to determine. The natural history of this disease is variable, and new treatments keep becoming available. Patients may find it helpful to consider their advanced cancer a chronic condition—one that will require vigilance, but one that is also compatible with a relatively normal quality of life.**

One common treatment strategy is something referred to as “hitchhiking,” which is the process of sticking with one life-sustaining treatment for as long as it is effective, and then moving on to another. Most patients with advanced breast cancer switch treatments many times during the course of illness. Because quality of life is the prime consideration, treatment goals often shift away from aggressive therapy.

Some patients will also take what is referred to as a “chemo holiday,” which is a short break from chemotherapy to give them time to build up energy or find some calm. Patients should always discuss such “breaks” with their doctor, as they are sometimes not advised.

More than likely, patients with advanced cancer will want to consider participating in a clinical trial, which is a research study to explore the effectiveness of a new drug, surgery technique, radiation therapy, combination of treatments or protocol for dealing with side effects. Many of today’s treatments are available because of clinical trials held years ago. Search for an open trial at these websites:

- > [clinicaltrials.gov](http://clinicaltrials.gov)
- > [cancer.gov/clinicaltrials](http://cancer.gov/clinicaltrials)
- > [breastcancertrials.org](http://breastcancertrials.org)

Support is important when dealing with metastatic disease, yet each patient’s needs are unique. Some may need emotional, spiritual or financial support—or all of the above. They might reach out to their spiritual community, friends and family, or search for others in support groups who are going through similar experiences. Some may seek counseling. Healthcare providers may be able to suggest social workers, counselors and palliative care experts.

Finding a role model can also help. Many patients with metastatic breast cancer live long, full lives. Some find joy in doing meaningful work and helping others. Patients might find survivor stories that inspire them.

Finally, regardless of where they are in their disease, patients with advanced breast cancer should tend to their financial and legal affairs. That includes creating an advance directive and a living will. An advance directive is a written set of instructions to guide healthcare when a person is no longer able to make those decisions. Authorizing a healthcare proxy can serve a similar purpose.

Patients might also consider frank discussions with their doctor and family about palliative care, which can be instituted even when patients are still receiving anti-cancer therapy. However, when patients experience significant decline in their health, the harms of many cancer treatments may start to outweigh the benefits, and a discussion about addressing cancer symptoms as opposed to cancer treatments should be held with physicians and family. Many find these discussions difficult to initiate, but making plans relieves some burden of worry, enabling patients to focus on living.



## Patient Perspective

By Rochelle Shoretz

**AS FOUNDER of Sharsheret, an organization for young Jewish women facing breast cancer, as well as a mother living with metastatic breast cancer, Rochelle Shoretz shares her experience of talking to her children about her advanced disease.**

I received my first diagnosis of stage 2 breast cancer at age 28. Seven years later, I received a diagnosis of stage 4 breast cancer. It's taken me two and a half years to really accept that I could live with this for a long time, and it's been a learning process not just for me, but for my children, as well.

When they receive a new diagnosis, some women are open with their children and others are protective. I don't think there's a right way or a wrong way—it's your family's way. When I received my stage 4 diagnosis, I explained to my sons, now 14 and 16, that the type of cancer I have is not curable at this time, but that I can live a long time with treatment. I also acknowledged that I may die younger than an average person would.

I took my sons to meet my doctor at the hospital where I was being treated. I called it a team meeting. It was me, my ex-husband, his new wife, my oncologist and the head of social work. I wanted the boys to see that there was a team of people taking care of me, and I wanted them to feel like they were part of that team. In some ways, I felt that this was really empowering to them.

**Editor's Note:** Sharsheret's Embrace program offers support for women facing advanced breast cancer. Learn more at [sharsheret.org/about/programs-and-services](http://sharsheret.org/about/programs-and-services). Watch an interview with Rochelle Shoretz at [curetoday.com/Rochelle\\_Shoretz\\_video](http://curetoday.com/Rochelle_Shoretz_video)



## Questions to Ask the Doctor

- What are the treatment options for my specific tumor type?
- What are the costs and side effects 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?
- Will this treatment help me live longer or will it relieve symptoms, or both?
- Do I qualify for a clinical trial?
- What symptoms of metastatic breast cancer should I be monitored for?
- Will I be able to continue with my normal daily activities?

## Resources

**AdvancedBC.org**

**American Cancer Society**  
[cancer.org](http://cancer.org); 800-227-2345

**BCMets.org**

**BrainMetsBC.org**

**Breastcancer.org**

**The MetaCancer Foundation**  
[metacancer.org](http://metacancer.org)

**Metastatic Breast Cancer Network**  
[mbcn.org](http://mbcn.org); 888-500-0370

**National Cancer Institute**  
[cancer.gov](http://cancer.gov); 800-4-CANCER (800-422-6237)

**National Comprehensive Cancer Network**  
[nccn.com](http://nccn.com)

**Sharsheret**  
[sharsheret.org](http://sharsheret.org); 866-474-2774

**Susan G. Komen for the Cure**  
[komen.org](http://komen.org); 877-GO-KOMEN (877-465-6636)

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