NCCN GUIDELINES FOR PATIENTS®

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Breast Cancer
Metastatic

STAGE IV

Presented with support from:

NCCN FOUNDATION®
Guiding Treatment, Changing Lives.

Rockin for the Cure©

Available online at NCCN.org/patients

LEARNING that you have cancer can be overwhelming.

While many people know about breast cancer, most patient information focuses on early-stage breast cancers. It is a challenge to find good information on metastatic breast cancer. The goal of this book is to help people with metastatic breast cancer get the best cancer treatment. It explains which cancer tests and treatments are recommended by experts in breast cancer.

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 27 of the world's leading cancer centers. Experts from NCCN have written treatment guidelines for doctors who treat breast cancer. These treatment guidelines suggest what the best practice is for cancer care. The information in this patient book is based on the guidelines written for doctors.

This book focuses on the treatment of metastatic breast cancer. Key points of the book are summarized in the NCCN Quick Guide™. NCCN also offers patient resources on early-stage breast cancer, locally advanced breast cancer, ovarian cancer, and other cancer types. Visit NCCN.org/patients for the for the full library of patient books, summaries, and other resources.

About

National Comprehensive Cancer Network®

These patient guides for cancer care are produced by the National Comprehensive Cancer Network® (NCCN®).

The mission of NCCN is to improve cancer care so people can live better lives. At the core of NCCN are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). NCCN Guidelines® contain information to help health care workers plan the best cancer care. They list options for cancer care that are most likely to have the best results. The NCCN Guidelines for Patients® present the information from the NCCN Guidelines in an easy-to-learn format.

Panels of experts create the NCCN Guidelines. Most of the experts are from NCCN Member Institutions. Their areas of expertise are diverse. Many panels also include a patient advocate. Recommendations in the NCCN Guidelines are based on clinical trials and the experience of the panelists. The NCCN Guidelines are updated at least once a year. When funded, the patient books are updated to reflect the most recent version of the NCCN Guidelines for doctors.

For more information about the NCCN Guidelines, visit NCCN.org/clinical.asp.

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NCCN FOUNDATION®
Guiding Treatment, Changing Lives.

NCCN Foundation was founded by NCCN to raise funds for patient education based on the NCCN Guidelines. NCCN Foundation offers guidance to people with cancer and their caregivers at every step of their cancer journey. This is done by sharing key information from the world's leading cancer experts. This information can be found in a library of NCCN Guidelines for Patients® and other patient education resources. NCCN Foundation is also committed to advancing cancer treatment by funding the nation's promising doctors at the center of cancer research, education, and progress of cancer therapies.

For more information about NCCN Foundation, visit NCCNFoundation.org.

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Endorsed by

BREAST CANCER ALLIANCE
Receiving a cancer diagnosis can be overwhelming, both for the patient and their family. We support the NCCN guidelines for breast cancer with the knowledge that these tools will help to equip patients with many of the educational resources, and answers to questions, they may seek. breastcanceralliance.org

FORCE: FACING OUR RISK OF CANCER EMPOWERED
As the nation's leading organization serving the hereditary breast and ovarian cancer community, FORCE is pleased to endorse the NCCN Guidelines for Patients with breast cancer. This guide provides valuable, evidence-based, expert-reviewed information on the standard of care, empowering patients to make informed decisions about their treatment. facingourrisk.org

LIVING BEYOND BREAST CANCER
Receiving a diagnosis of breast cancer is overwhelming. Having trusted information is essential to help understand one's particular diagnosis and treatment options. The information found in the NCCN Guidelines for Patients: Breast Cancer is accessible, accurate, and will help every step of the way—from the moment of diagnosis through treatment. People can use the NCCN Guidelines for Patients: Breast Cancer to become an informed partner in their own care. lbbc.org

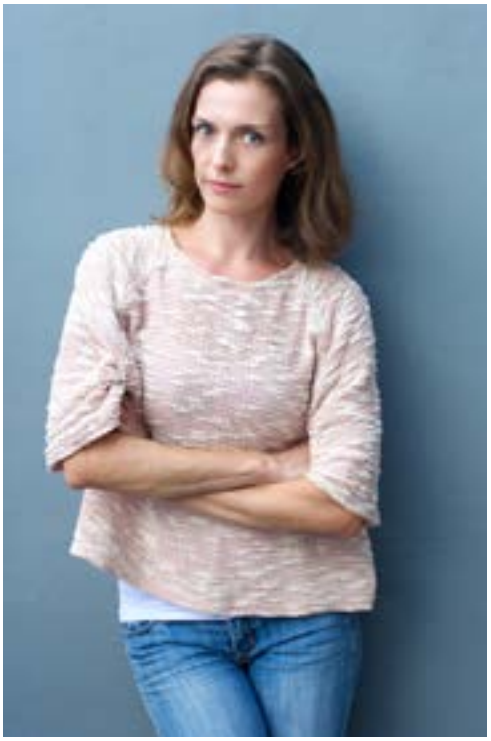
SHARSHERET
Sharsheret is proud to endorse this important resource, the NCCN Guidelines for Patients: Breast Cancer. With this critical tool in hand, women nationwide have the knowledge they need to partner with their healthcare team to navigate the often complicated world of breast cancer care and make informed treatment decisions. sharsheret.org

SISTERS NETWORK, INC.
Sisters Network Inc., a non-profit African-American breast cancer survivors' organization, strongly supports the NCCN Guidelines for breast cancer. This important patient resource provides clear, explanatory language that patients, their families and the general public can understand. sistersnetwork.org

YOUNG SURVIVAL COALITION (YSC)
Young Survival Coalition (YSC) is pleased to endorse the NCCN Guidelines for Patients: Breast Cancer as an invaluable resource for young women diagnosed with breast cancer and their co-survivors. This in-depth, illustrated series clearly explains what breast cancer is, how it is treated and what patients can expect on the journey ahead. youngsurvival.org

Special thank you to

ROCKIN' FOR THE CURE©
NCCN Foundation would like to thank Rockin' for the Cure for providing much needed support for the NCCN Guidelines for Patients! Rockin' For The Cure 2017 was a giant success and we are incredibly grateful to the Rockin' For The Cure team for their hard work and passion to promote cancer awareness. We look forward to 2018. rockinforthecure.net



Contents

How to use this book

Who should read this book?

This book is about treatment for metastatic breast cancer. Almost all breast cancers occur in women. As such, most of this book is written with women in mind. However, men are treated just like women except where noted.

Patients and those who support them—caregivers, family, and friends—may find this book helpful. It is a good starting point to learn what your treatment options may be.

Are the book chapters in a certain order?

The book chapters follow a common treatment pathway. Starting with **Part 1** may be helpful. It explains what breast cancer is.

Part 2 lists what health care is needed before treatment. Cancer tests are used to plan the best treatment for you.

Not all women get the same treatment. In **Part 3**, treatment options based on cancer features are listed. Tips for talking and deciding treatment with your doctor are presented in **Part 4**.

Does this book include all options?

This book includes information for many people. Your treatment team can point out what applies to you. They can also give you more information. While reading, make a list of questions to ask your doctors.

The treatment options are based on science and the experience of NCCN experts. However, their recommendations may not be right for you. Your doctors may suggest other options based on your health and other factors. If other options are given, ask your treatment team questions.

Help! What do the words mean?

In this book, many medical words are included. These are words that your treatment team may say to you. Most of these words may be new to you. It may be a lot to learn.

Don't be discouraged as you read. Keep reading and review the information. Ask your treatment team to explain a word or phrase that you do not understand.

Words that you may not know are defined in the text or in the *Dictionary*. Acronyms are also defined when first used and in the *Glossary*. Acronyms are short words formed from the first letters of several words. One example is DNA for **d**eoxyribo**n**ucleic **a**cid.

1
Breast cancer basics

You've learned that you have breast cancer. It's common to feel shocked and confused. Part 1 reviews some basics that may help you learn about breast cancer.

Women's breasts

Before learning about breast cancer, it is helpful to know about breasts. The ring of darker skin on the outside of the breast is called the areola. The raised tip in the middle of the areola is called the nipple. In young girls, there are small ducts under the nipple that branch into fatty tissue called stroma.

Increases in female hormones during puberty among girls cause their breasts to change. The stroma increases, the ducts grow and branch out like tree limbs, and lobules form at the end of the ducts. Lobules are small sacs that make breast milk after a baby is born. Breast milk drains from the millions of lobules into the ducts that connect to the nipple. See **Figure 1** for a look inside women's breasts.

Lymph is a clear fluid that gives cells water and food. It also helps to fight germs. Lymph drains from breast tissue into lymph vessels within the stroma. **See Figure 2.** Then, it travels to the breast's lymph nodes, most of which are in your armpit. Lymph nodes are small structures that filter and remove germs from lymph. Nodes near the armpit are called axillary lymph nodes.

Figure 1
Inside of breasts

Inside of women's breasts are millions of lobules that form breast milk after a baby is born. Breast milk drains from the lobules into ducts that carry the milk to the nipple. Around the lobules and ducts is soft tissue called stroma.

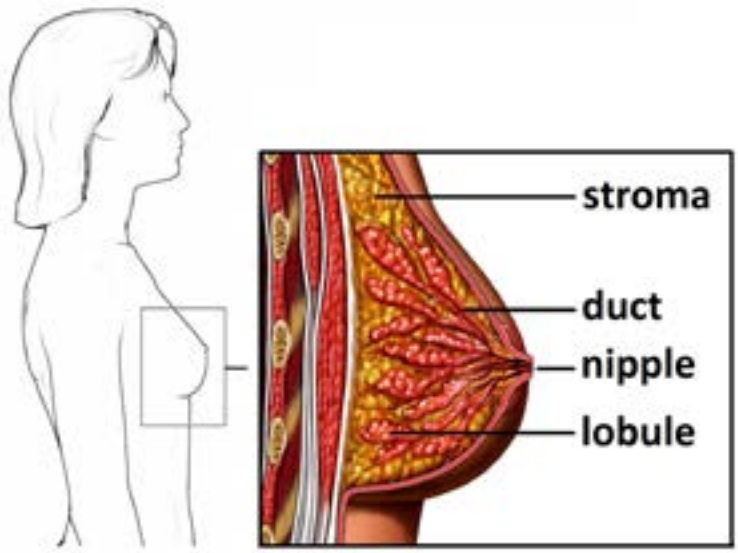
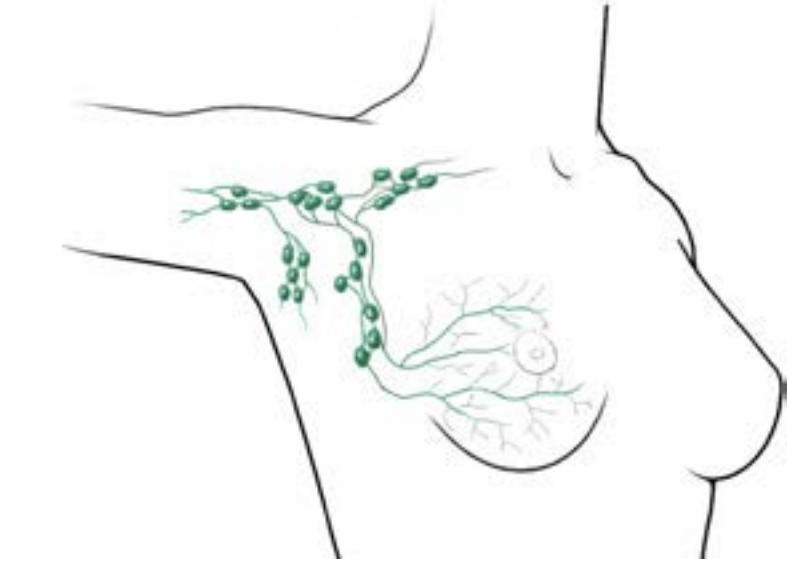


Figure 2
Breast lymph vessels and nodes

Lymph is a clear fluid that gives cells water and food and helps to fight germs. It drains from breast tissue into lymph vessels within the stroma. It then travels to the breast's lymph nodes, most of which are in the armpit. Nodes near the armpit are called axillary lymph nodes.



A disease of cells

Your body is made of trillions of cells. Cancer is a disease of cells. Each type of cancer is named after the cell from which it derived. Breast cancer is a cancer of breast cells.

Almost all breast cancers are carcinomas. Carcinomas are cancers of cells that make up the skin and the tissue that lines or covers organs. In the breast, carcinomas are cancers of cells that line either the ducts or lobules. Most breast cancers start in ductal cells.

Cells have a control center called the nucleus. The nucleus contains chromosomes, which are long strands of DNA (**d**eoxyribo**n**ucleic **a**cid) tightly wrapped around proteins. **See Figure 3.** Within DNA are coded instructions for building new cells and controlling how cells behave. These instructions are called genes.

There can be abnormal changes in genes called mutations. Some types of mutations that are linked to cancer are present in all cells. Other mutations are present only in cancer cells. Mutations cause cancer cells to not behave like normal cells and sometimes look very different from normal cells.

Cancer's threat

Cancer cells don't behave like normal cells in three key ways. First, cancer cells grow more quickly and live longer than normal cells. Normal cells grow and then divide to form new cells when needed. They also die when old or damaged as shown in **Figure 4**. In contrast, cancer cells make new cells that aren't needed and don't die quickly when old or damaged. Over time, cancer cells form a mass called the primary tumor.

The second way cancer cells differ from normal cells is that they can grow into surrounding tissues. If not treated, the primary tumor can grow from a duct or lobule into the stroma. Breast cancers that have grown into the stroma are called "invasive."

Third, unlike normal cells, cancer cells can leave the breast. This process is called metastasis. In this process, cancer cells break away from the tumor and merge with blood or lymph. Then, the cancer cells travel in blood or lymph through vessels to other sites. Once at other sites, cancer cells may form secondary tumors and cause major health problems.

Figure 3
Genetic material in cells

Most human cells contain the "blueprint of life"—the plan by which our bodies are made and work. The plan is found inside of chromosomes, which are long strands of DNA that are tightly wrapped around proteins. Genes are small pieces of DNA that contain instructions for building new cells and controlling how cells behave. Humans have an estimated 20,000 to 25,000 genes.

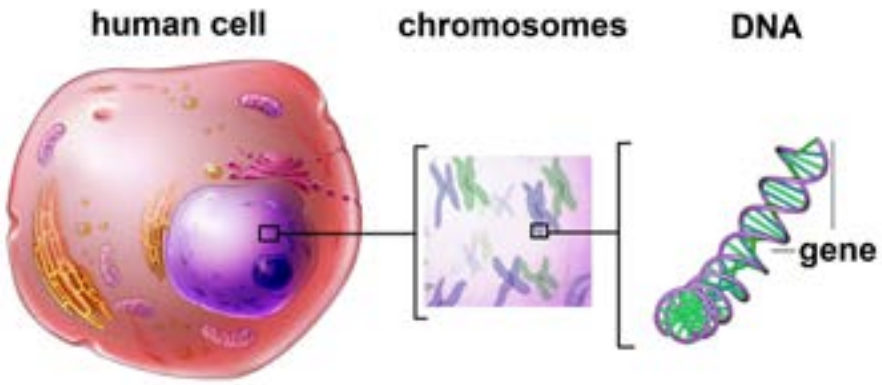
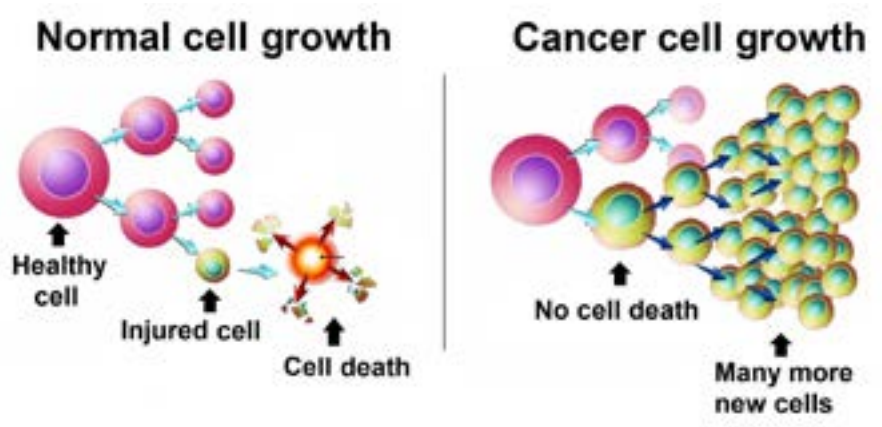


Figure 4
Normal cell growth vs. cancer cell growth

Normal cells increase in number when they are needed and die when old or damaged. In contrast, cancer cells quickly make new cells and live longer because of abnormal changes in genes.



Cancer stage

A cancer stage is a rating by your doctors of the extent of the cancer. It is used to plan which tests may be needed and which treatments are best for you. The AJCC (**A**merican **J**oint **C**ommittee on **C**ancer) staging system is used to stage breast cancer.

Breast cancer is described as stage 0, 1 (I), 2 (II), 3 (III), or 4 (IV). Breast cancers confined within the nipple, ducts, or lobules are rated stage 0. Breast cancers that are stage I or II have grown into the stroma but not into the breast skin or chest wall. Some stage II cancers have also spread to the axillary lymph nodes but not elsewhere. Stage III breast cancers are larger or have spread farther than stage I or II breast cancers. However, stage III cancers haven't spread to distant sites.

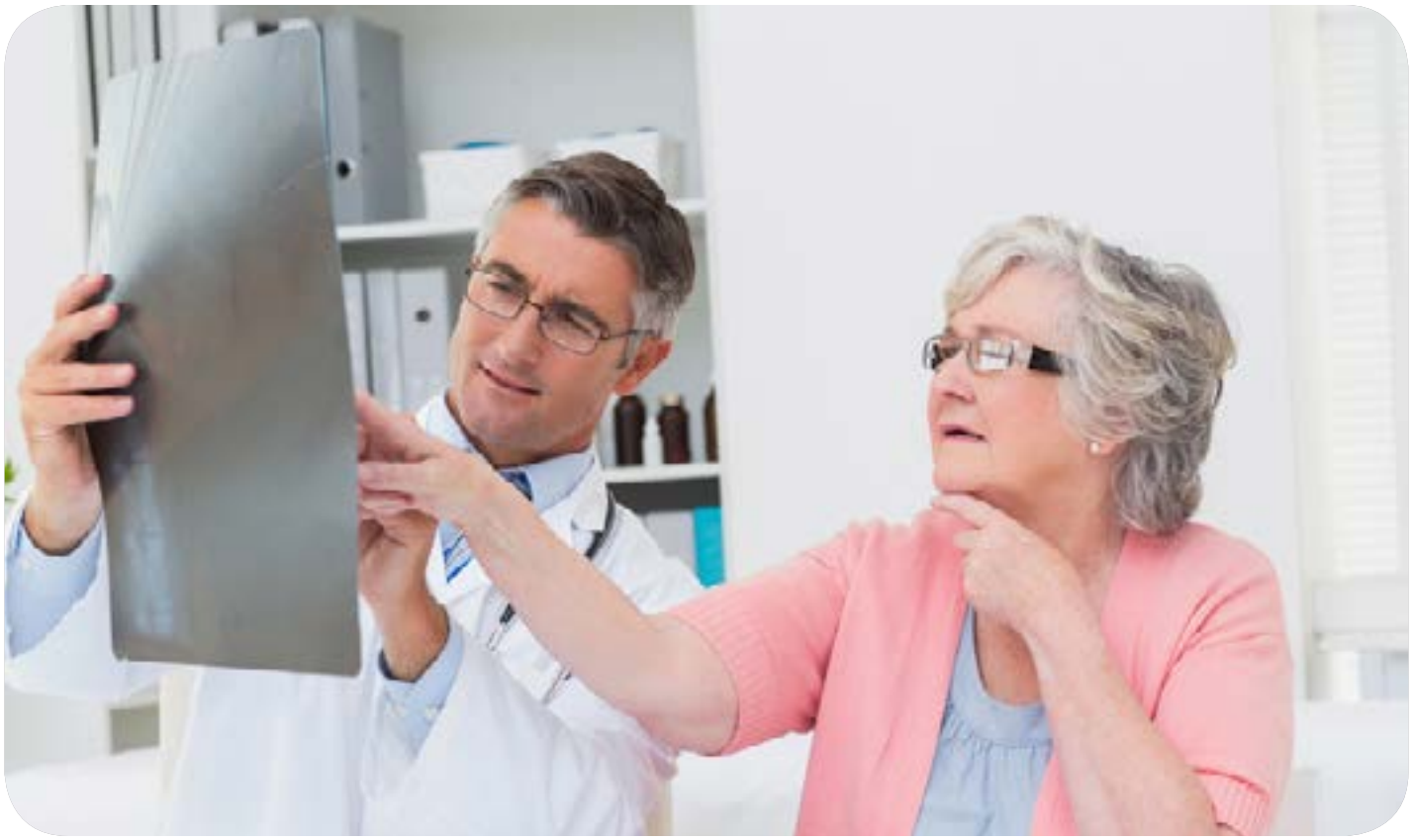
Metastatic breast cancer

Metastatic breast cancers have spread to distant sites outside the breast. Common distant sites include the bones, lungs, brain, and liver. Breast cancer in distant sites is still breast cancer. It's not lung cancer, for example. Stage IV breast cancer is metastatic cancer that was present when the cancer was first found (diagnosis). Sometimes, other stages of breast cancer spread more and become metastatic breast cancer.

Review

- Inside of women's breasts are lobules, ducts, and stroma. Lobules are structures that make breast milk. Ducts carry breast milk from the lobules to the nipple. Stroma is a soft tissue that surrounds the lobules and ducts.
- Breast cancer often starts in the milk ducts or lobules and then spreads into the stroma.
- Breast cancer can spread outside the breast through lymph or blood.
- Metastatic breast cancer has spread to distant sites outside the breast. Stage IV breast cancer is metastatic cancer that was found at diagnosis.

2
Treatment planning



Not all metastatic breast cancers are the same. Your cancer doctor will want to learn all about the cancer you have. Part 2 describes the tests used to learn about breast cancer. Based on the test results, your treatment can be tailored to you. This is called personalized medicine.

Medical history

Your medical history includes any health events and medicines you've taken in your life. Your cancer doctor will want to know about illnesses, breast biopsies, prior treatment with radiation, and if you are pregnant. It may help to make a list of old and new medications while at home to bring to your doctor's office.

Breast cancer and other health conditions can run in families. Thus, your cancer doctor will ask about the medical history of your relatives. Hereditary breast cancers are due to abnormal genes that were passed down from a parent to a child. They are not common. About 1 out of 10 breast cancers are hereditary. Read the section called *Genetic counseling* to learn more.

A medical history is needed for treatment planning. See Guide 1 for a complete list of care that is advised prior to treatment. Some women do not need every test or service listed.

Physical exam

Doctors often perform a physical exam along with taking a medical history. A physical exam is a study of your body for signs of disease. To start, your basic body functions will be measured. These functions include your temperature, blood pressure, and pulse and breathing (respiration) rate. Your weight will also be checked.

During an exam, your doctor will listen to your lungs, heart, and gut. He or she will also look at and feel parts of your body. This is done to see if organs are of normal size, are soft or hard, or cause pain when touched.

Your doctor will touch your breasts and nearby lymph nodes. This is called a clinical breast exam. Your breasts may be felt while you sit or stand up as well as when you lie back. Some women feel uneasy having their breasts touched by their doctor. Keep in mind that this exam provides important information and is quick.

Blood tests

Doctors test blood to look for signs of disease. For a blood test, a needle will be inserted into your vein to remove a sample of blood. The needle may bruise your skin and you may feel dizzy from the blood draw. Your blood sample will then be sent to a lab where a pathologist will test it.

Complete blood count

A CBC (**c**omplete **b**lood **c**ount) measures the number of blood cells in a blood sample. It includes numbers of white blood cells, red blood cells, and platelets. Cancer and other health problems can cause low or high counts.

Comprehensive metabolic panel

Chemicals in your blood come from your liver, bone, and other organs. A comprehensive metabolic panel often includes tests for up to 14 chemicals. The tests show if the level of chemicals is too low or high. Abnormal levels can be caused by cancer or other health problems. Your doctor will use this test to check how well your organs are working before and during treatment.

Guide 1. Health care before cancer treatment

Tests and services	Who should get this care?
Medical history	Everyone
Physical exam	Everyone
CBC	Everyone
Comprehensive metabolic panel	Everyone
Chest diagnostic CT scan with contrast	Everyone
Abdomen ± pelvis diagnostic scans (CT or MRI with contrast)	Everyone
Spine MRI with contrast	Women with certain symptoms
Brain MRI with contrast	Women with certain symptoms
Bone scan or sodium fluoride PET/CT	Everyone
FDG PET/CT	It's an option
X-rays	Women with certain symptoms or signs
Biopsy	Everyone
Hormone receptor test	Everyone
HER2 test	Everyone
Genetic counseling	Women who may have hereditary breast cancer

Imaging tests

Imaging tests make pictures (images) of the insides of your body. They can show which sites have cancer. This information helps your doctors stage the cancer. Certain imaging tests also reveal some features of a tumor and its cells.

A radiologist is a doctor who's an expert in reading images. Your radiologist will convey the imaging results to your cancer doctor. This information helps your doctor decide what the next steps of care should be.

Your treatment team will tell you how to prepare for these tests. You may need to stop taking some medicines and stop eating and drinking for a few hours before the scan. Tell your team if you get nervous when in small spaces. You may be given a medicine called a sedative to help you relax.

Some imaging tests use contrast. Contrast is a dye that will be injected into your bloodstream. It makes the pictures clearer. Some people have an allergic reaction to the dye. Tell your doctor if you've had problems with contrast in the past.

Chest diagnostic CT scan

CT (**c**omputed **t**omography) with contrast of your chest is advised. This scan takes many pictures of a body part from different angles using x-rays. A computer combines the x-ray images to make a detailed picture. During the scan, you will need to lie face up on a table that moves through the machine. **See Figure 5.**

Abdomen ± pelvis diagnostic scans

A scan of your abdomen is advised. Your doctor may also want a scan of your pelvis. Either diagnostic CT or MRI (**m**agnetic **r**esonance **i**maging) with contrast may be used.

MRI is an imaging test that uses a magnetic field and radio waves to make pictures. Before the scan, you

Figure 5. CT machine

Pictures of the insides of your body can be made with an imaging test. During the scan, you will lie on a table that will move into the tunnel of the imaging machine. The pictures will be viewed by a doctor who will look for signs of cancer.

may be fitted with coil devices that emit radio waves. Straps may be used to help you stay in place.

During MRI, you will be inside the machine. An open MRI scanner may be an option at some health centers. The machine makes loud noises but you can wear earplugs. The part of your body that was scanned may feel a bit warm afterward. You will be able to resume your activities right away unless you took a sedative.

Spine and brain MRI

Breast cancer can spread to your spine or brain. Cancer spread to the brain is much less common than to the spine. MRI is very useful for viewing these sites. MRI is advised if your symptoms suggest cancer is present. Contrast will be used. For a brain MRI, a device will be placed around your head that sends and receives radio waves. For spinal MRI, no device is worn.

Bone scan

A bone scan may be used to see if the cancer has spread to your bones. For this scan, a radiotracer will be injected into your bloodstream. The most common radiotracer used for bone scans is technetium. You will need to wait about 3 hours for the radiotracer to enter your bones.

A special camera will be used to take pictures while you lie still on a table. It takes 45 to 60 minutes to complete the pictures. Areas of bone damage use more radiotracer than healthy bone and thus appear as bright spots in the pictures. Bone damage can be caused by cancer as well as by other health problems.

PET/CT

Sometimes CT is combined with PET (**p**ositron **e**mission **t**omography). When used to together, they are called a PET/CT scan. Some cancer centers have one machine that does both scans. At other centers, the scans are done with two machines.

For PET, a radiotracer will first be injected into your body. The radiotracer is detected with a special camera during the scan. Cancer cells appear brighter than normal cells because they use the radiotracer more quickly. PET can show even small amounts of cancer.

Sodium fluoride PET/CT. Instead of a bone scan, images of bones can be made with PET/CT. The radiotracer used to image bones is sodium fluoride. This scan is costly. However, it shows sites of bone damage and repair better than a bone scan. It also has a shorter waiting time of 40 to 60 minutes for the radiotracer to be seen and a shorter scanning time of 15 to 20 minutes.

FDG PET/CT. This scan also detects cancer. FDG (**f**luoro**d**eoxy**g**lucose) is a radiotracer that is made of fluoride and a simple form of sugar called glucose. For this test, you must fast for 4 hours or more.

FDG PET/CT can be done at the same time as diagnostic CT. If the scan detects cancer spread to the bone, a bone scan or sodium fluoride PET/CT may not be needed. FDG PET/CT is most helpful when other imaging tests are unclear. It may help find breast cancer that has spread to nearby lymph nodes or distant sites.

Bone x-rays

X-rays of bones that hurt are advised. Long and weight-bearing bones that aren't normal on bone scan or PET/CT should also be x-rayed. During an x-ray, you must lie still on a table while the x-ray machine sends small amounts of radiation into your body. Images made from the x-rays are seen on a screen.

Biopsy

A biopsy is a procedure that removes tissue or fluid samples for testing. The methods used to remove samples will depend on where the cancer has spread. A biopsy is advised to confirm if the distant site has cancer. If your doctor does not suggest a biopsy, ask why.

If you were treated for earlier stages of breast cancer, tissue from the breast tumor was likely tested. Expect a biopsy of the distant site. In a small number of cases, the biology of the tumor changes. Such changes can greatly impact how the cancer responds to treatments and your treatment options.

Cancer lab tests

Tissue samples from the biopsy will be sent to a pathologist. A pathologist is a doctor who's an expert in testing cells to find disease. He or she will examine the samples using a microscope.

Pathology report

All lab results are recorded in a pathology report. A report will be written each time tissue is removed from your body and tested for cancer. These reports are vital to planning treatment.

Review your pathology report(s) with your doctor. Ask questions if you don't understand. This information can be complex. It's also a good idea to get a copy of your pathology report(s) and take notes.

Histologic typing

If cancer is present, the pathologist will study the parts of the cancer cells to classify the disease. This is called histologic typing. The pathology report will state if the cancer started in the breast or elsewhere.

If breast cancer is found, the subtype will be noted in the report. The most common subtype is ductal breast cancer. Out of every 100 breast cancers, about 85 to 90 are ductal cancers. These cancers started in the breast ducts. Breast cancer can also start in the lobules. These cancers are called lobular breast cancer.

Receptor testing

Not all breast cancer cells are alike. They can differ by the type of receptors they have. A receptor is a protein found in the membrane of cells or inside of cells. Substances bind to the receptors and cause changes within the cell.

Hormone receptor test. Estrogen and progesterone are hormones that are present in all women. Among some women with breast cancer, the cancer cells have receptors to which these hormones attach. After hormones attach, the receptors enter the nucleus and cause cells to grow in number. **See Figure 6.** However, the growth of cancer cells with hormone receptors is usually slower than cancer cells without these receptors.

Testing for hormone receptors is important. There are drugs that can be used to stop hormones from causing cancer growth. IHC (**i**mmuno**h**isto**c**hemistry) is the lab test used by pathologists for hormone receptors.

IHC involves applying a stain to cells then looking at them with a microscope. The stain shows how many cells have hormone receptors and the amount of hormone receptors in the cells. If at least 1 out of every 100 cancer cells stains positive, the cancer is called hormone receptor–positive. If fewer cancer cells stain positive for hormone receptors, the cancer is called hormone receptor–negative.

HER2 test. HER2 (**h**uman **e**pidermal growth factor **r**eceptor **2**) is a receptor within the membrane of breast cells. As shown in **Figure 6**, it extends from within the cell through the membrane to outside of the cell. When activated, it causes breast cancer cells to grow and divide.

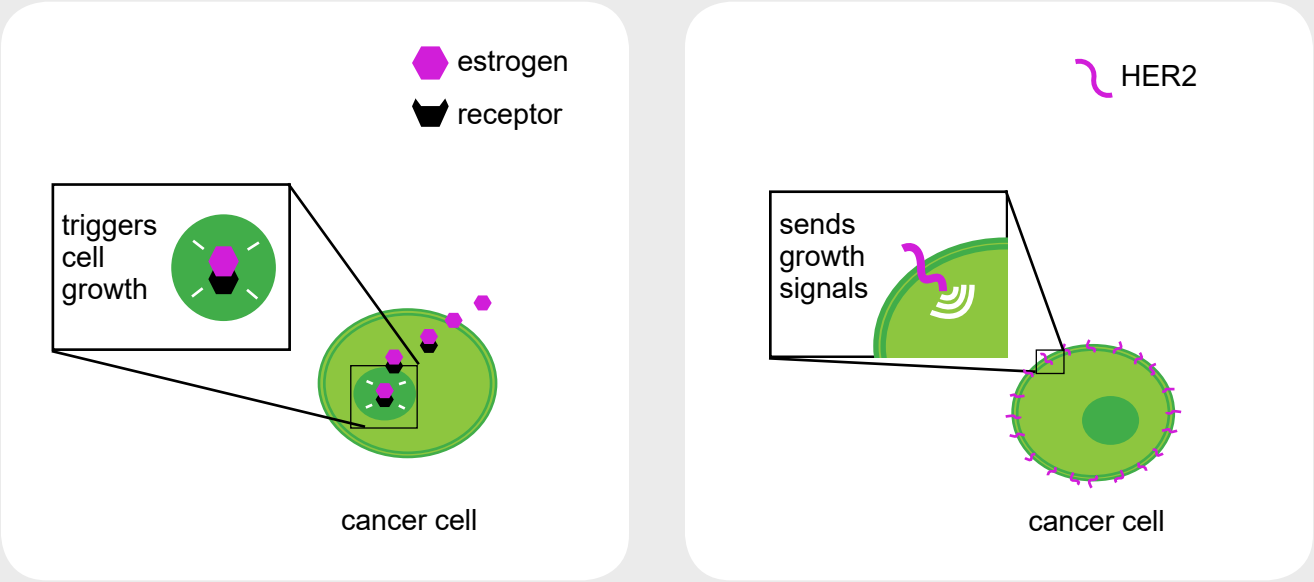
Normal breast cells have two copies of the gene that makes HER2. In contrast, some breast cancers have cells with more than two copies. This causes too many HER2 receptors to be made. Other breast cancers have cells with only two HER2 gene copies but still too many HER2 receptors are made.

With too many HER2 receptors, breast cancer cells grow and divide fast. However, there are drugs to stop these cancer cells from growing. Due to high costs and the side effects of these drugs, it is very important to have tests that correctly show HER2 status.

IHC is used to learn the amount of HER2 receptors. An IHC score of 3+ means that the cancer cells have many HER2 receptors. Another test of HER2 is ISH (**i**n **s**itu **h**ybridization). ISH counts the number of copies of the *HER2* gene. If the cancer cells have too many *HER2* genes or receptors, the cancer is called HER2 positive.

Figure 6. Key receptors in breast cancer

Hormone and HER2 receptors help breast cancer grow. Some women have a high amount of one or both types of receptors. It is important to test for these cell receptors so that the best cancer treatment is received.



Genetic counseling

If you may have hereditary breast cancer, your doctor will refer you for genetic counseling. Most breast cancers are not hereditary. A genetic counselor is an expert in gene mutations that are related to disease. The counselor can tell you more about your chances of having hereditary breast cancer. He or she may suggest that you undergo genetic testing. Genetic testing assesses for gene mutations that increase the chances of getting breast cancer.

Hereditary breast cancer is most often caused by mutations in the *BRCA1* and *BRCA2* genes. Normal *BRCA* genes help to prevent tumor growth by fixing damaged cells and helping cells grow normally. Genetic testing can tell if you have a BRCA or another mutation. Your test results may be used to guide treatment planning.

Some mutations, called VUS (**v**ariants of **u**nknown **s**ignificance), are not fully understood by doctors. Your doctors may know of research that aims to learn more. If interested, ask your doctors about taking part in such research.

Review

- A medical history is a report of all health events in your lifetime. It will include questions about your family's health to help assess if you have hereditary breast cancer.
- Your doctor will examine your body for signs of disease. He or she will touch parts of your body, including your breasts, to see if anything feels abnormal.
- Blood tests may be done to look for signs of cancer outside of your breast.
- Imaging tests make pictures of the insides of your body. Your doctor will be able see inside your body without cutting into it.
- During a biopsy, tissue or fluid samples are removed for testing. Samples are needed to confirm the presence of cancer and to perform cancer cell tests.
- Some breast cancers consist of cells with too many hormone receptors, HER2s, or both. These features are used to plan treatment.
- Genetic counseling may help you decide whether to be tested for hereditary breast cancer.

Waiting for results is often the hardest part of this journey. I am an overachiever when it comes to thinking about worse case scenarios when I don't have all the information.
–Deb

3
Treatment guide

Part 3 is a guide to treatment for metastatic breast cancer. Cancer treatments are briefly described, and treatment options based on cancer features are listed. Part 3 also includes a guide to checking treatment results.

Overview

Treatment of metastatic breast cancer includes treatment of the cancer and support for you. Read this section to learn how metastatic breast cancer is treated. Some details about clinical trials are provided. This section also describes supportive care.

Systemic therapy

Metastatic breast cancer is unlikely to be cured. However, long-term cancer control is often achieved with systemic therapy. Systemic therapy affects all cancer in the body. Medical oncologists are cancer doctors trained to use systemic therapy.

Systemic therapy consists of many types. Endocrine therapy stops cancer growth caused by hormones. Targeted therapy affects other molecules that are key to cancer growth. It differs from classic chemotherapy, which affects a wider range of cells. Chemotherapy, or "chemo," includes drugs that disrupt the life cycle of cancer cells. Keep reading this chapter to learn more about these treatments.

Surgery and radiation therapy are local treatments. They treat cancer in one spot. These treatments may be an option for symptom relief. It is unknown if surgery helps to prolong life. There is ongoing research on how surgery can help treat stage IV cancers. The best time to conduct surgery is also being studied.

The treatment approach for metastatic cancer is to use one treatment after another. A treatment change occurs if the treatment stops working or there are too many side effects. This approach is followed until there are no more options or you become too sick. This allows long-term cancer control for many women.

Your doctor will plan your treatment based on many factors. One key factor is the hormone receptor status of the cancer. As explained on page 18, breast cancers may be either hormone receptor–positive or negative. Treatment options grouped by hormone-receptor status are listed later in this chapter.

"

I could focus on the lifetime of treatments or I could focus on my life in-between treatments. That's my struggle.
–Rosalie

Clinical trials

One of your treatment choices may be to join a clinical trial. Joining a clinical trial is strongly supported. NCCN believes that you will receive the best management in a clinical trial.

New tests and treatments aren't offered to the public as soon as they're made. They first need to be studied. A clinical trial is a type of research that studies a test or treatment in people.

Clinical trials study how safe and helpful tests and treatments are for people. When found to be safe and helpful, they may become tomorrow's standard of care. Because of clinical trials, the tests and treatments in this book are now widely used to help people with breast cancer. Future tests and treatments that may have better results than today's treatments will depend on clinical trials.

New tests and treatments go through a series of clinical trials. These trials aim to ensure they're safe and work. Without clinical trials, there is no way to know if a test or treatment is safe or helpful. Clinical trials have four phases. Some examples of the four phases for treatment are:

- Phase I trials aim to find the safest and best dose of a new drug. Another aim is to find the best way to give the drug with the fewest side effects. These trials often involve about 20 people.
- Phase II trials assess if a drug works for a specific type of cancer.
- Phase III trials compare a new drug to a standard treatment. These trials often involve hundreds or thousands of people.
- Phase IV trials test drugs approved by the U.S. FDA (**F**ood and **D**rug **A**dministration) to learn more about side effects with long-term use.

Joining a clinical trial has benefits. First, you'll have access to the most current cancer care. However, please note that it is unknown how well new treatments work if at all. Second, you will receive the best management of care. Third, the results of your treatment—both good and bad—will be carefully tracked. Fourth, you may help other people who will have cancer in the future.

Clinical trials have risks, too. Like any test or treatment, there may be side effects. Also, new tests or treatments may or may not improve your health. In fact, your health may worsen during a trial. Other downsides may include more hospital trips, paperwork, and extra costs for you.

To join a clinical trial, you must meet the conditions of the study. Patients in a clinical trial are often alike in terms of their cancer and general health. Thus, if patients improve, it's because of the treatment and not because of differences between them.

To join, you'll need to review and sign a paper called an informed consent form. This form describes the study in detail. The study's risks and benefits should be described and may include others than those described above.

Ask your treatment team if there is an open clinical trial that you can join. There may be clinical trials where you're getting treatment or at other treatment centers nearby. You can also find clinical trials through the websites listed in Part 4.

Supportive care

This book focuses on cancer treatment. However, supportive care is important, too. Supportive care doesn't aim to treat cancer but aims to improve quality of life. It can address many needs.

One example of supportive care is treatment for physical and emotional symptoms. Read the next section, *Breast cancer in bone*, for an example. Supportive care can also help with treatment decisions as you may have more than one option. It can also help with coordination of care between health providers. Talk with your treatment team to plan the best supportive care for you.

Breast cancer in bone

A bone metastasis is the spread of cancer to the bone. It is not the same as bone cancer, which starts in bone. Your bones are at risk for injury and disease when cancer spreads to them. Such health problems include bone fractures, bone pain, and squeezing (compression) of the spinal cord. High levels of calcium in the blood, called hypercalcemia, may also occur.

There is supportive care to prevent bone problems caused by bone metastases. Your doctor may prescribe denosumab (Xgeva™), zoledronic acid (Zometa®), or pamidronate (Aredia®). Your treatment team may advise you to take these drugs with calcium and vitamin D.

Denosumab, zoledronic acid, or pamidronate may damage your jawbone. This condition is called osteonecrosis of the jaw. Your chances for osteonecrosis of the jaw are higher if taking certain medications such as chemotherapy. Poor dental health and dental work during cancer treatment will increase your chances, too. Get a dental exam and treatment for any dental problems before starting cancer treatment.

Hormone receptor–positive cancers

Most breast cancers are hormone receptor–positive. Female hormones help hormone receptor–positive cancers grow. Endocrine therapy is a standard treatment for these cancers. It can work just as well as chemotherapy and its side effects are less severe. For some women, targeted therapy with endocrine therapy may be an option.

Endocrine therapy

Some people refer to endocrine therapy as hormone therapy. However, hormone therapy can then be confused with hormone replacement therapy. The former treats breast cancer whereas the latter treats menopausal symptoms.

Endocrine therapy affects female hormones by one of two methods. Some therapies block hormones from working. Others lower hormone levels in the body. The main types of endocrine therapy are described next. The section, *Treatment options*, lists which ones may be an option for you.

Aromatase inhibitors lower estrogen levels in the body. These drugs block a protein that changes a hormone (androgen) into estrogen. They do not affect estrogen made in the ovaries. See Guide 2 for a complete list of drugs for hormone-related growth.

Antiestrogens stop the effect of estrogen on cell growth. SERMs (**s**elective **e**strogen **r**eceptor **m**odulators) attach to estrogen receptors and block estrogen from attaching. SERDs (**s**elective **e**strogen **r**eceptor **d**egraders) block and destroy estrogen receptors. **See Figure 7.**

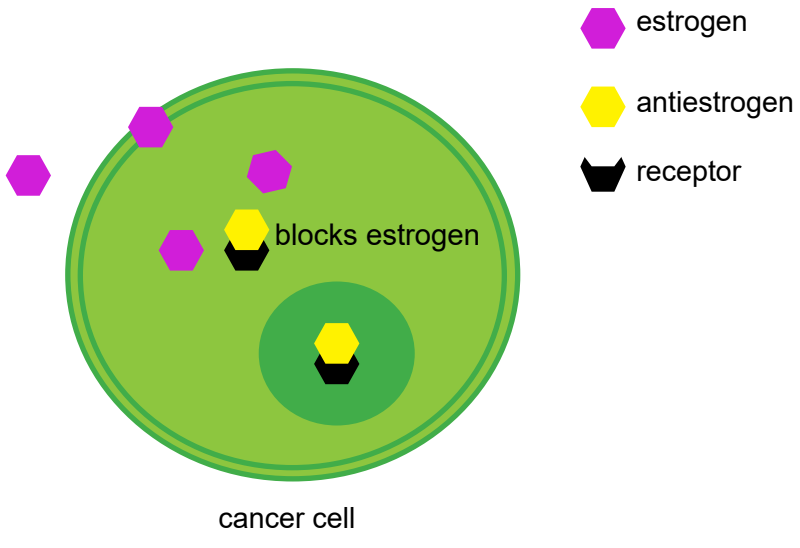
Hormones may treat breast cancer when taken in high doses. It is not known how hormones stop breast cancer cells with hormone receptors from growing. Hormones are not often used for treatment.

Guide 2. Cancer drugs for hormone-related growth

Type	Subtype	Generic name	Brand name	How they work
Antiestrogens	SERD	Fulvestrant	Faslodex®	Prevent key signals for cancer cell growth
	SERM	Tamoxifen citrate	–	
		Toremifene citrate	Fareston®	
Aromatase inhibitors	Non-steroid	Anastrozole	Arimidex®	Lower estrogen levels
		Letrozole	Femara®	
	Steroid	Exemestane	Aromasin®	
Hormones	Estrogen	Ethinyl estradiol	–	Unknown
	Androgen	Fluoxymesterone	Androxy™, Halotestin®	
	Progesterone	Megestrol acetate	Megace®	
Kinase inhibitors	CDK inhibitor	Palbociclib	Ibrance®	Stop key signals for cancer cell growth
		Ribociclib	Kisqali®	
	mTOR inhibitor	Everolimus	Afinitor®	
Ovarian suppression	LHRH agonist	Goserelin acetate	Zoladex®	Lower estrogen levels
		Leuprolide acetate	Lupron Depot®	

Figure 7
Antiestrogens

Antiestrogens are drugs that stop the effect of estrogen on cancer cell growth. There are two types—SERMs and SERDs. Both block estrogen from attaching to its receptor and starting cell growth. SERDs also help to destroy the receptor.



Ovarian ablation permanently stops the ovaries from making hormones. Most often, both ovaries are removed from the body. This surgery is called a bilateral oophorectomy. Radiation to the ovaries also stops the making of hormones, but isn't used often.

Ovarian suppression temporarily stops the ovaries from making hormones. It is achieved with drugs called LHRH (**l**uteinizing **h**ormone-**r**eleasing **h**ormone) agonists. LHRH is a hormone in the brain that helps control the making of estrogen by the ovaries. LHRH agonists stop LHRH from being made, which stops the ovaries from making more hormones.

What to expect. Some endocrine therapies greatly differ by how they are given and what's required of you. An example is one day of surgery versus a few days of radiation therapy. Some drugs are given as monthly injections while others are pills that are taken every day. Your treatment team will give you more information. Questions to ask about treatment are listed in Part 4.

For many women, endocrine therapy causes symptoms of menopause. Menopausal symptoms include hot flashes, vaginal discharge or dryness, sleep problems, weight gain, hair thinning, fatigue, bone loss, and changes in mood. You may have different symptoms from other women.

Tamoxifen also has two rare but more serious side effects: 1) cancer of the uterus; and 2) blood clots. For most women with breast cancer, the benefits of taking tamoxifen far outweigh the risks. Aromatase inhibitors don't cause cancer and very rarely cause blood clots.

Not all the side effects of endocrine therapy are listed here. Please ask your treatment team for a list of all common and rare side effects. If a side effect bothers you, tell your treatment team. There may be ways to help you feel better.

Targeted therapy

Many targeted therapies stop the signals that tell a cell to grow. Within signal pathways are protein kinases. Protein kinases are molecules that move chemicals, called phosphates, from one molecule to another. **See Figure 8.** The phosphate "turns on" the next molecule in the signal pathway.

Targeted therapy for hormone receptor–positive cancers blocks protein kinases. This type of targeted therapy is called kinase inhibitors. **See Figure 9.**

CDK inhibitors stop the action of CDK (**c**yclin-**d**ependent **k**inase). CDK is a protein kinase within the cell nucleus. CDK4 and CDK6 promote cancer growth in hormone receptor–positive cancers. CDK inhibitors attach to CDK and stop growth signals.

Palbociclib and ribociclib are made in pill form. They are taken in a 4-week cycle. You will be on treatment for the first 3 weeks and off treatment for 1 week.

Common side effects include tiredness, nausea, vomiting, diarrhea, constipation, headache, and hair loss. Your white blood cell counts may drop. This may lead to serious infections. Palbociclib can also cause serious blood clots, and ribociclib, liver and heart problems.

mTOR inhibitors stop the action of mTOR (**m**ammalian **t**arget **o**f **r**apamycin). mTOR is a protein kinase within a cell's gel-like substance. Sometimes, endocrine therapy stops working because mTOR is turned on. mTOR inhibitors attach to mTOR and stop growth signals.

Everolimus is a pill that is taken around the same time every day. Common side effects include diarrhea, tiredness, mouth sores, skin rash, cough, and low blood counts. Serious side effects include other cancers, lung problems, infections, and kidney failure.

Figure 8
Protein kinases

Pathways of chemical signals start cell growth. Within the pathways are protein kinases. They move phosphates from one molecule to another. The phosphate "turns on" the next molecule in the pathway.

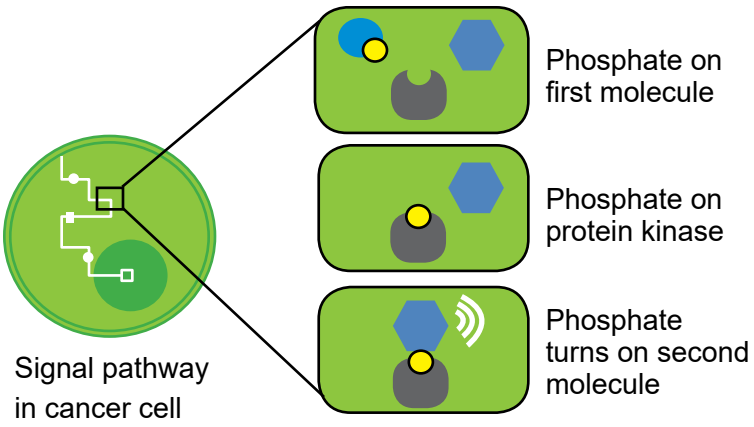
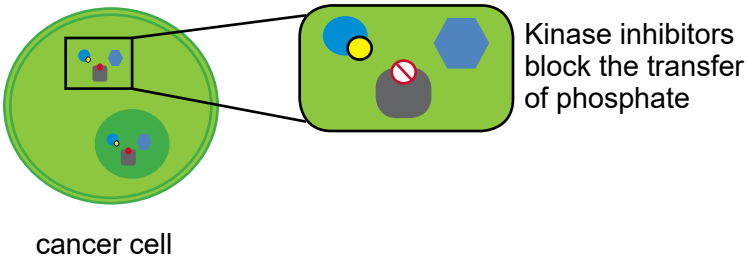


Figure 9
Kinase inhibitors

Kinase inhibitors block the transfer of phosphase and in turn stop growth signals. CDK inhibitors stop signals with the nucleus. mTOR inhibitors stop signals with the cell's gel-like substance.



Guide 3. Treatment options for hormone-related growth

Prior endocrine therapy	What are the options?
None in past year →	• For fast-spreading cancers, maybe chemotherapy first • If in premenopause: ◦ Ovarian ablation or suppression + one therapy listed for postmenopause ◦ SERM alone (tamoxifen or toremifene) • If in postmenopause: ◦ Aromatase inhibitor (anastrozole, letrozole, or exemestane) ◦ Antiestrogen (tamoxifen, toremifene, or fulvestrant) ◦ Palbociclib + letrozole if HER2 negative ◦ Ribociclib + letrozole if HER2 negative
Took in past year →	• For fast-spreading cancers, maybe chemotherapy first • If in premenopause: ◦ Ovarian ablation or suppression + one therapy listed for postmenopause • If in postmenopause: ◦ Aromatase inhibitor (anastrozole, letrozole, or exemestane) ◦ Antiestrogen (tamoxifen, toremifene, or fulvestrant) ◦ Palbociclib + letrozole if HER2 negative ◦ Exemestane + everolimus ◦ Palbociclib + fulvestrant if HER2 negative ◦ Hormones (ethinyl estradiol, fluoxymesterone, or megestrol acetate)

Treatment options

Guide 3 lists the treatment options for hormone receptor–positive breast cancer. Options are based on if you received endocrine therapy in the past year or not. They are also based on menopausal status.

Menopause is the point in time when you won't have another menstrual period again. When a woman hasn't had a period in one or more years, she's often considered in postmenopause. If you get menstrual periods, you are in premenopause.

If you don't get periods, blood tests may be needed to confirm your menopausal status. The amount of estrogen or FSH (**f**ollicle-**s**timulating **h**ormone) in your blood will be measured. Sometimes, these blood tests can't be done until you've been off certain medicines for some time.

Chemotherapy first. Sometimes, breast cancer can spread quickly within internal organs. Your internal organs include your liver and lungs. In this case, you may first receive chemotherapy to quickly control the cancer growth. Chemotherapy works faster than

endocrine therapy. After chemotherapy, you may receive endocrine therapy, which is often less toxic.

Premenopause. Your ovaries are the main source of estrogen and progesterone. To lower hormone levels, ovarian ablation or suppression is advised. You should also receive endocrine therapy for women in postmenopause. These treatments stop the effect of estrogen made from sources other than the ovaries. If you haven't had endocrine therapy in the past year, a second option is to take a SERM.

Postmenopause. In your body, estrogen is made in small amounts by the adrenal glands, liver, and body fat. To reduce estrogen levels, an aromatase inhibitor may be used. It is often the first treatment received if you've had no endocrine therapy in the past year. Other options are an antiestrogen and for HER2-negative cancers, palbociclib or ribociclib with letrozole.

If you took endocrine therapy in the past year, your options depend on multiple factors. They depend on what treatment you had before. They also depend on if the metastatic cancer is being treated for the first time or not. If the cancer progressed during treatment, your options may include exemestane with everolimus, palbociclib with fulvestrant if HER2-negative cancer, and high-dose hormones.

Stopping endocrine therapy. Endocrine therapy is advised until one of two events occurs. Stop taking endocrine therapy if there are no benefits during 3 back-to-back regimens. Stop if there's cancer in your internal organs that is causing symptoms. At this point, chemotherapy may be given. Read *Hormone receptor–negative cancers* to learn more about chemotherapy.

Men with breast cancer

One out of every 100 breast cancers occurs in men. Men with breast cancer are treated much like women. One important difference is treatment with endocrine therapy. Your options are the same as for women in postmenopause. However, aromatase inhibitors should be taken with a treatment that stops the making of testosterone by your testes. Aromatase inhibitors alone won't stop hormone-related cancer growth.

Hormone receptor–negative cancers

These cancers lack hormone receptors that trigger cell growth. Thus, in general, endocrine therapy does not help. Thus, chemotherapy and targeted therapy are used to treat hormone receptor–negative cancers.

The information in this section also applies to endocrine refractory cancers. These cancers didn't improve during 3 back-to-back endocrine regimens. Chemotherapy is the next option.

Chemotherapy

The types of chemotherapy differ in the way they treat cancer. Some kill cancer cells by damaging their DNA or by disrupting the making of DNA. Others interfere with cell parts that are needed for making new cells. Thus, no new cells are made to replace dying cells. The four types of chemotherapy used to treat metastatic breast cancer are listed in Guide 4.

Some chemotherapies work when cells are in an active growth phase. **See Figure 10.** During the active growth phase, cells grow and divide to form a new cell. Chemotherapy drugs that disrupt the growth phase work well for cancer cells that are growing and dividing quickly. Other chemotherapy drugs work in any growth or resting phase.

What to expect. Before starting chemotherapy, your doctor may ask you to stop taking some of your medicines, vitamins, or both. Some of these treatments can cause chemotherapy to not work as well or may cause health problems while on chemotherapy. You may also have to change what you drink and eat. If you smoke, it's important that you stop.

Most chemotherapy for metastatic breast cancers are liquids that are injected into a vein. Some are made as pills to be swallowed. The injection may be one fast shot of drugs into a vein or may be a slow drip called an infusion. Chemotherapy can also be given through a needle surgically placed in the chest or the arm.

Chemotherapy is given in cycles of treatment days followed by days of rest. The cycles vary in length depending on which drugs are used. Giving chemotherapy in cycles gives your body a chance to recover after receiving chemotherapy.

You will need to go to a chemotherapy center to receive the drugs. How long your visit will be depends on which drugs you will get. It can take a few minutes or a few hours to finish a dose of chemotherapy. You may be given drugs to fight nausea and vomiting. To learn more, read the NCCN Guidelines for Patients®: Nausea and Vomiting. You may also get a shot of (peg-)filgrastim under your skin. This medicine increases the number of white blood cells to normal levels.

The reactions to chemotherapy differ among women. Some women have many side effects. Other women have few. Some side effects can be very serious while others can be unpleasant but not serious.

Side effects of chemotherapy depend on the drug type, amount taken, length of treatment, and the person. In general, side effects are caused by the death of fast-growing cells. These cells are found in the hair follicles, gut, mouth, and blood. Thus, common side effects of chemotherapy include low blood cell counts, not feeling hungry, nausea, vomiting, diarrhea, hair loss, and mouth sores.

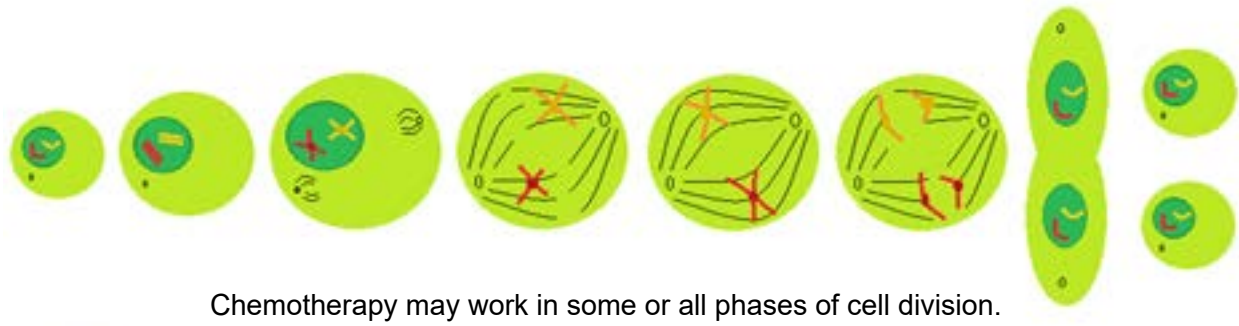
Other side effects of chemotherapy may include anxiety, fatigue, and peripheral neuropathy. Peripheral neuropathy is numbness or tingling of nerves in the hands and feet. Some types of chemotherapy, such as anthracyclines, can cause damage to the heart.

Guide 4. Chemotherapy types

Type	Generic name	Brand name	How they work
Alkylating agents	Carboplatin	–	Damage DNA by adding a chemical to it
	Cisplatin	Platinol®	
	Cyclophosphamide	–	
Anthracyclines	Doxorubicin	–	Damage and disrupt the making of DNA
	Doxorubicin liposomal injection	Doxil®	
	Epirubicin	Ellence®	
Antimetabolites	Capecitabine	Xeloda®	Prevent the "building blocks" of DNA from being used
	Fluorouracil	–	
	Gemcitabine	Gemzar®	
	Methotrexate	–	
Microtubule inhibitors	Docetaxel	Taxotere®	Stop a cell from dividing into two cells
	Eribulin	Halaven™	
	Ixabepilone	Ixempra® Kit	
	Paclitaxel	Taxol®, Abraxane®	
	Vinorelbine	Navelbine®	

Figure 10. Chemotherapy and the cell cycle

A cell goes through many changes to divide into two cells. Science has grouped these changes into 7 main phases. There may be another phase of rest, too. Some chemotherapy drugs work in any phase. Other chemotherapy drugs work in one or two growth phases.



Chemotherapy may work in some or all phases of cell division.

If you're still premenopausal, chemotherapy may cause menopause. However, don't depend on chemotherapy for birth control. You may become pregnant while on chemotherapy, which can cause birth defects. If you had menstrual periods before chemotherapy, use birth control but not birth control with hormones (eg, "the pill").

Not all the side effects of chemotherapy are listed here. Please ask your treatment team for a complete list. If a side effect bothers you, tell your treatment team. There may be ways to help you feel better.

Targeted therapy

There are five targeted therapies for hormone receptor–negative breast cancer. All but one involves HER2. As explained on page 19, some breast cancers have many HER2s. HER2 targeted therapy uses the HER2s to treat HER2-positive cancer.

Cancer cells need the food and oxygen in blood to grow. Cancer cells get blood from blood vessels that have grown into the tumor. VEGF (**v**ascular **e**ndothelial **g**rowth **f**actor) is one of the molecules that triggers the growth of these blood vessels. Targeted therapies involving HER2 or VEGF are listed in Guide 5.

HER2 antibodies stop the action of HER2. Antibodies work outside of the cell. HER2 antibodies attach to HER2 and prevent growth signals from starting. **See Figure 11.**

Trastuzumab and pertuzumab are given by infusion. It takes about 90 minutes to get the first dose of trastuzumab and about 30 minutes for later doses. For pertuzumab, it takes about 60 minutes to get the first dose and about 30 to 60 minutes for later doses.

You may have a mild flu-like response to the first dose of trastuzumab that includes fever, chills, headache, muscle aches, and nausea. This response is less common with the second and third doses.

Other side effects may include damage to the heart and rarely to the lungs.

Common side effects of pertuzumab are diarrhea, nausea, and feeling tired and weak. Less common side effects include skin rash, low white blood cell counts, and mouth sores. It is not yet clear if pertuzumab damages the heart, although trastuzumab may do so.

HER2 conjugates deliver cell-specific chemotherapy. As a targeted therapy, HER2 conjugates attach to HER2s then enter the cell. Once inside, chemotherapy is released.

Ado-trastuzumab emtansine is given by infusion. It takes about 90 minutes to get the first dose and 30 minutes for later doses. It is given every three weeks. Common side effects include headache, nausea, tiredness, diarrhea or constipation, nosebleeds, and pain in your muscles, joints, or bones. Other side effects may include damage to the heart, liver, or lungs.

HER2 inhibitors stop the action of HER2. Inhibitors work inside the cell. HER2 inhibitors attach to HER2 and stop growth signals. **See Figure 11.**

Lapatinib is made as a pill that is taken every day one hour before or after a meal. Common side effects include diarrhea and skin rash. Your hands and feet may become red, swollen, numb, and painful. Less common side effects include fatigue, vomiting, headaches, shortness of breath, and heartburn. Other side effects include heart, liver, and lung problems.

VEGF antibodies stop the action of VEGF. For breast cancer, VEGF inhibitors attach to VEGF. Once attached, VEGF cannot attach to endothelial cells and start growth signals.

Guide 5. Targeted therapy

Type	Generic name	Brand name	How they work
HER2 antibodies	Pertuzumab	Perjeta®	Prevent the start of key signals for cancer cell growth
	Trastuzumab	Herceptin®	
HER2 conjugates	Ado-trastuzumab emtansine	Kadcyla®	Deliver cell-specific chemotherapy
HER2 inhibitors	Lapatinib ditosylate	Tykerb®	Stop key signals for cancer cell growth
VEGF antibodies	Bevacizumab	Avastin®	Prevent the start of key signals for endothelial cell growth

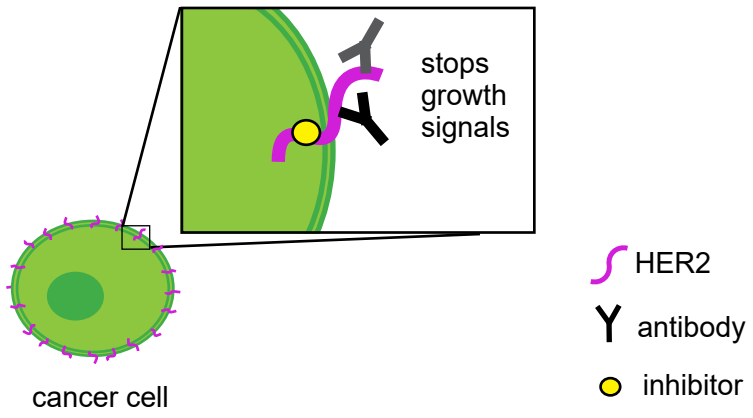
Bevacizumab is not used often to treat breast cancer. It doesn't extend life or improve quality of life. It may help to slow down cancer growth.

Bevacizumab is given by infusion. It takes about 90 minutes to get the first dose and 30 minutes for later doses. Bevacizumab is given every two weeks followed by a two-week rest period.

Common side effects of bevacizumab are high blood pressure, diarrhea, and feeling tired and weak. You might also have nosebleeds, shortness of breath, nausea, and vomiting. Rare but serious effects include stroke, heart attack, kidney damage, holes in the intestine, and bleeding within the body.

Figure 11
HER2 antibodies and inhibitors

Antibodies are Y-shaped proteins that are made by your body to help fight illness. HER2 antibodies are human-made antibodies. They attach to the HER2 on the outside of the cell, which prevents growth signals from starting. HER2 inhibitors attach to HER2 inside the cell and stop growth signals.



Treatment options

Chemotherapy is an option for all hormone receptor–negative cancers. Very rarely, endocrine therapy is received. It may be tried for cancer that has spread to the bones only, soft tissue only, or internal organs without causing symptoms. Examples of soft tissue include muscle, fat, and lymph nodes. Examples of internal organs include the liver, brain, and lungs.

Chemotherapy and targeted therapy options depend on HER2 status. Guide 6 lists the treatment options for HER2-negative cancers. These cancers are also called triple-negative cancers because they also lack hormone receptors. Single agents are grouped into preferred and other agents. These groups are based on how well the drug works, side effects, and treatment schedules. Combination regimens are also listed. They are not better than single agents and have worse side effects.

Guide 7 lists the treatment options for HER2-positive cancers. There are two preferred options for treating metastatic cancer for the first time. They consist of both HER2 antibodies (trastuzumab and

Guide 6. Options for HER2-negative cancers

Preferred single agents	Length of a cycle	Other single agents	Length of a cycle
Doxorubicin	21 days	Cyclophosphamide	28 days
Pegylated liposomal doxorubicin	28 days	Carboplatin	21 to 28 days
Paclitaxel	21 days	Docetaxel	21 or 56 days
Capecitabine	21 days	Albumin-bound paclitaxel	21 or 28 days
Gemcitabine	28 days	Cisplatin	21 days
Vinorelbine	7 days	Epirubicin	21 days
Eribulin	21 days	Ixabepilone	21 days

Combination regimens	Length of a cycle
CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)	21 (FAC) or 28 (CAF) days
FEC (fluorouracil/epirubicin/cyclophosphamide)	28 days
AC (doxorubicin/cyclophosphamide)	21 days
EC (epirubicin/cyclophosphamide)	21 days
CMF (cyclophosphamide/methotrexate/fluorouracil)	28 days
Docetaxel/capecitabine	21 days
GT (gemcitabine/paclitaxel)	21 days
Gemcitabine/carboplatin	21 days
Paclitaxel/bevacizumab	28 days

Guide 7. Options for HER2-positive cancers

Preferred first-line agents	Length of a cycle
Trastuzumab + pertuzumab + docetaxel	21 days
Paclitaxel	21 days
with trastuzumab	7 or 21 days
and pertuzumab	7 or 21 days

Other agents	Length of a cycle
Ado-trastuzumab emtansine	21 days
Weekly paclitaxel and carboplatin	28 days
with trastuzumab	7 or 21 days
Paclitaxel and carboplatin	21 days
with trastuzumab	7 or 21 days
Weekly paclitaxel	7 days
with trastuzumab	7 or 21 days
Paclitaxel	21 days
with trastuzumab	7 or 21 days
Weekly docetaxel	7 days
with trastuzumab	7 or 21 days
Docetaxel	21 days
with trastuzumab	7 or 21 days
Vinorelbine	21 days
with trastuzumab	7 or 21 days
Capecitabine	21 days
with trastuzumab	7 or 21 days

Regimens after trastuzumab use	Length of a cycle
Lapatinib	Daily (not given in cycles)
with capecitabine	21 days
Capecitabine	21 days
with trastuzumab	7 or 21 days
Lapatinib	Daily (not given in cycles)
with trastuzumab	7 or 21 days
Trastuzumab + other agents	Depends on agents

pertuzumab) with either docetaxel or paclitaxel. These options extend life the most. If neither is an option, ado-trastuzumab emtansine may be used first to treat metastatic cancer. Other options are listed in Guide 7.

The cancer may worsen during treatment with trastuzumab. In this case, keep taking a HER2 signal–blocking treatment. Research has shown HER2 treatment still helps. Options are listed in Guide 7.

Stopping chemotherapy. Chemotherapy may not be helpful in two situations. It may not help if there were no benefits during 3 back-to-back regimens. It may do more harm than good if you get too sick. At this point, think about stopping chemotherapy. Supportive care alone may be received.

Checking treatment results

Your doctor will want to know how well treatment is working. The cancer might improve (response). It may stay the same (stable disease). It could also worsen (progression).

Cancer progression occurs because treatment doesn't work. Drug treatment may not work when first given. For some people, drug treatment works at first but then stops working. This is called drug resistance. Resistance to endocrine therapy occurs often.

Different types of tests are used to check treatment results. Some assess the status of cancer. Others assess for side effects of treatment. Guide 8 lists the types and frequency of tests that are advised by NCCN experts. How often these tests are given may differ based on how well treatment is working.

Your doctor will ask you about any new or worse symptoms. He or she will also perform a physical exam and measure your body weight. Your state of general health will be rated using a performance status scale. The two scales commonly used are the ECOG (**E**astern **C**ooperative **O**ncology **G**roup) Performance Scale and the KPS (**K**arnofsky **P**erformance **S**tatus). For either scale, your doctor will choose a score that best represents your health.

Blood samples will need to be drawn to perform three tests. CBC is used to assess the extent of cancer growth within bones. Liver function tests are used to assess the extent of cancer growth within the liver and other organs.

Your blood may also be tested for proteins that can indicate whether treatment is working. These proteins are called tumor markers. Examples of tumor markers include CEA (**c**arcino**e**mbryonic **a**ntigen), CA 15-3 (**c**ancer **a**ntigen 15-3), and CA 27.29 (**c**ancer **a**ntigen 27.29).

One increase in tumor markers doesn't always mean that the cancer has progressed. Your doctor will look for rising levels across a series of tests. Tumor markers may be more helpful than imaging tests when metastases are mainly in bone. Changes in bone lesions are hard to assess on imaging tests.

Three imaging tests may be used to check treatment results. CT with contrast of your chest, abdomen, and pelvis and a bone scan are advised. PET/CT is an option. These scans can show larger or new areas of cancer.

Guide 8. Testing schedule

	Before new treatment	During endocrine therapy	During chemotherapy	Signs of cancer progression
Symptoms	Yes	Every 1–3 months	Before each cycle	Yes
Physical exam	Yes	Every 1–3 months	Before each cycle	Yes
Weight	Yes	Every 1–3 months	Before each cycle	Yes
Performance status	Yes	Every 1–3 months	Before each cycle	Yes
CBC	Yes	Every 1–3 months	Before each cycle	Yes
Liver function tests	Yes	Every 1–3 months	Before each cycle	Yes
CT scan	Yes	Every 2–6 months	Every 2–4 cycles	Yes
Bone scan	Yes	Every 4–6 months	Every 4 cycles	Yes
PET/CT scan	It's an option	It's an option	It's an option	It's an option
Tumor markers	It's an option	It's an option	It's an option	It's an option

Review

- The treatment approach for metastatic breast cancer is to use a whole-body treatment until it doesn't work then use another. This allows long-term cancer control for many women.
- Clinical trials give people access to new tests and treatments that they otherwise can't receive. If proven to work well, they may be approved in time by the FDA.
- Endocrine therapy works well for hormone receptor–positive cancers. These cancers may also be treated with targeted therapy. Which treatment you will receive is based on your prior treatment and menopausal status.
- Chemotherapy and targeted therapy are used to treat hormone receptor–negative cancers. These treatments are also used to treat hormone receptor–positive cancers that haven't improved on 3 back-to-back endocrine therapies. Which treatment you will receive depends on your prior treatment and the HER2 status of the cancer.
- Testing during treatment should occur on a regular basis to check if treatment is working and not causing serious side effects.

"

Side effects from treatment can be difficult to manage. I sometimes wish that treatment wasn't such a bully… except when it comes to fighting the cancer.
–Lynn

4
Making treatment decisions

Having cancer is very stressful. While absorbing the fact that you have cancer, you have to learn about tests and treatments. In addition, the time you have to accept a treatment plan feels short. Parts 1 through 3 described the cancer and treatment options. Part 4 aims to help you make decisions that are in line with your beliefs, wishes, and values.

It's your choice

The role patients want in choosing their treatment differs. You may feel uneasy about making treatment decisions. This may be due to a high level of stress. It may be hard to hear or know what others are saying. Stress, pain, and drugs can limit your ability to make good decisions. You may feel uneasy because you don't know much about cancer. You've never heard the words used to describe cancer, tests, or treatments. Likewise, you may think that your judgment isn't any better than your doctors'.

Letting others decide which option is best may make you feel more at ease. But, whom do you want to make the decisions? You may rely on your doctors alone to make the right decisions. However, your doctors may not tell you which to choose if you have multiple good options. You can also have loved ones help. They can gather information, speak on your behalf, and share in decision-making with your doctors. Even if others decide which treatment you will receive, you still have to agree by signing a consent form.

On the other hand, you may want to take the lead or share in decision-making. Most patients do. In shared decision-making, you and your doctors share information, weigh the options, and agree on a treatment plan. Your doctors know the science behind your plan but you know your concerns and goals. By working together, you are likely to get a higher quality of care and be more satisfied. You'll likely get the treatment you want, at the place you want, and by the doctors you want.

"

It's a fine line between advocating for myself with my treatment team and wanting to be viewed as a good patient.
–Eileen

Questions to ask your doctors

You may meet with experts from different fields of medicine. Strive to have helpful talks with each person. Prepare questions before your visit and ask questions if the person isn't clear. You can also record your talks and get copies of your medical records. It may be helpful to have your spouse, partner, or a friend with you at these visits. A patient advocate or navigator might also be able to come. They can help to ask questions and remember what was said. Suggested questions to ask include:

What's my diagnosis and prognosis?

It's important to know that there are different types of cancer. Cancer can greatly differ even when people have a tumor in the same organ. Based on your test results, your doctors can tell you which type of cancer you have. He or she can also give a prognosis. A prognosis is a prediction of the pattern and outcome of a disease. Knowing the prognosis may affect what you decide about treatment.

1. Where did the cancer start? In what type of cell? Is this cancer common?
2. Is this a fast- or slow-growing breast cancer?
3. What tests do you recommend for me?
4. My first breast cancer was years ago. Should I get a biopsy of my metastatic disease? If no, why not?
5. Where will the tests take place? How long will the tests take and will any test hurt?
6. What if I am pregnant?
7. How do I prepare for testing?
8. Should I bring a list of my medications?
9. Should I bring someone with me?
10. How often are these tests wrong?
11. Would you give me a copy of the pathology report and other test results?
12. Who will talk with me about the next steps? When?

What are my options?

There is no single treatment practice that is best for all patients. There is often more than one treatment option along with clinical trial options. Your doctor will review your test results and recommend treatment options.

1. What will happen if I do nothing?
2. Can I just carefully monitor the cancer?
3. Do you consult NCCN recommendations when considering options?
4. Are you suggesting options other than what NCCN recommends? If yes, why?
5. Do your suggested options include clinical trials? Please explain why.
6. How do my age, health, and other factors affect my options? What if I am pregnant?
7. Which option is proven to work best?
8. Which options lack scientific proof?
9. What are the benefits of each option? Does any option offer a cure or long-term cancer control? Are my chances any better for one option than another? Less time-consuming? Less expensive?
10. What are the risks of each option? What are possible complications? What are the rare and common side effects? Short-lived and long-lasting side effects? Serious or mild side effects? Other risks?
11. How do you know if treatment is working? Should testing for tumor markers be done?
12. What are my options if my treatment stops working?
13. What can be done to prevent or relieve the side effects of treatment?

What does each option require of me?

Many patients consider how each option will practically affect their lives. This information may be important because you have family, jobs, and other duties to take care of. You also may be concerned about getting the help you need. If you have more than one option, choosing the option that is the least taxing may be important to you:

1. Will I have to go to the hospital or elsewhere? How often? How long is each visit?
2. What do I need to think about if I will travel for treatment?
3. Do I have a choice of when to begin treatment? Can I choose the days and times of treatment?
4. How do I prepare for treatment? Do I have to stop taking any of my medicines? Are there foods I will have to avoid?
5. Should I bring someone with me when I get treated?
6. Will the treatment hurt?
7. How much will the treatment cost me? What does my insurance cover?
8. Will I miss work or school? Will I be able to drive?
9. Is home care after treatment needed? If yes, what type?
10. How soon will I be able to manage my own health?
11. When will I be able to return to my normal activities?

What is your experience?

More and more research is finding that patients treated by more experienced doctors have better results. It is important to learn if a doctor is an expert in the cancer treatment he or she is offering.

1. Are you board certified? If yes, in what area?
2. How many patients like me have you treated?
3. How many procedures like the one you're suggesting have you done?
4. Is this treatment a major part of your practice?
5. How many of your patients have had complications?

Deciding between options

Deciding which option is best can be hard. Doctors from different fields of medicine may have different opinions on which option is best for you. This can be very confusing. Your spouse or partner may disagree with which option you want. This can be stressful. In some cases, one option hasn't been shown to work better than another, so science isn't helpful. Some ways to decide on treatment are discussed next.

2nd opinion

The time around deciding a treatment is very stressful. People with cancer often want to get treated as soon as possible. They want to make their cancer go away before it spreads farther. While cancer can't be ignored, usually there is time to think about and choose which option is best for you.

You may wish to have another doctor review your test results and suggest a treatment plan. This is called getting a 2nd opinion. You may completely trust your doctor, but a 2nd opinion about which option is best can help.

Copies of the pathology report, a DVD of the imaging tests, and other test results need to be sent to the doctor giving the 2nd opinion. Some people feel uneasy asking for copies from their doctors. However, a 2nd opinion is a normal part of cancer care.

When doctors have cancer, most will talk with more than one doctor before choosing their treatment. What's more, some health plans require a 2nd opinion. If your health plan doesn't cover the cost of a 2nd opinion, you have the choice of paying for it yourself.

If the two opinions are the same, you may feel more at peace about the treatment you accept to have. If the two opinions differ, think about getting a 3rd opinion. A 3rd opinion may help you decide between your options. Choosing your cancer treatment is a very important decision. It can affect your length and quality of life.

Support groups

Besides talking to health experts, it may help to talk to other people who have walked in your shoes. At support groups, you can ask questions and hear about the experiences of other people with breast cancer. Find a support group at the websites listed on page 45.

Compare benefits and downsides

Every option has benefits and downsides. Consider these when deciding which option is best for you. Talking to others can help identify benefits and downsides you haven't thought of. Scoring each factor from 0 to 10 can also help since some factors may be more important to you than others.

Websites

American Cancer Society
cancer.org/cancer/breast-cancer.html

Breast Cancer Alliance
breastcanceralliance.org

Breastcancer.org
breastcancer.org

Cancer Support Community
cancersupportcommunity.org

Facing Our Risk of Cancer Empowered (FORCE)
facingourrisk.org

Living Beyond Breast Cancer (LBBC)
lbbc.org

Metastatic Breast Cancer Network (MBCN)
mbcn.org

National Cancer Institute (NCI)
cancer.gov/types/breast

National Coalition for Cancer Survivorship
canceradvocacy.org/toolbox

NCCN
nccn.org/patients

Rockin for the Cure©
rockinforthecure.net

Sharsheret
sharsheret.org

Sisters Network, Inc.
sistersnetworkinc.org

Young Survival Coalition (YSC)
youngsurvival.org

Review

- Shared decision-making is a process in which you and your doctors plan treatment together.
- Asking your doctors questions is vital to getting the information you need to make informed decisions.
- Getting a 2nd opinion, attending support groups, and comparing benefits and downsides may help you decide which treatment is best for you.

Glossary

Dictionary

abdomen
The belly area between the chest and pelvis.

adrenal gland
A small organ on top of each kidney that makes hormones.

alkylating agent
A cancer drug that damages coded instructions in cells by adding a chemical to it.

allergic reaction
Symptoms caused when the body is trying to rid itself of invaders.

anthracycline
A cancer drug that damages and disrupts the making of DNA.

antiestrogen
A drug that stops estrogen from attaching to cells.

antimetabolite
A cancer drug that prevents the “building blocks” of DNA from being used.

areola
A darker, circular area of skin on the breast surrounding the nipple.

aromatase inhibitor
A drug that lowers the level of estrogen in the body.

axillary lymph node
A small group of special disease-fighting cells located near the armpit.

bilateral oophorectomy
Surgical removal of both ovaries.

biopsy
Removal of small amounts of tissue or fluid to be tested for disease.

bone mineral density
A test that measures the strength of bones.

bone scan
A test that uses radioactive material to assess for bone damage.

***BRCA1* or *BRCA2* genes**
Coded information within cells that helps to prevent tumor growth by fixing damaged cells and helping cells grow normally. Abnormal changes within these genes increases the chances of developing breast and ovarian cancer.

cancer stage
Rating of the growth and spread of tumors.

carcinoma
Cancer that starts in cells that form the lining of organs and structures in the body.

chemotherapy
Drugs that stop the life cycle of cells so they don’t increase in number.

chest wall
The layer of muscle, bone, and tissue on the outer part of the chest.

clinical breast exam
A physical exam of the breasts by a health professional to feel for disease.

clinical trial
Research on a test or treatment to assess its safety or how well it works.

complete blood count (CBC)
A test of the number of blood cells.

computed tomography (CT)
A test that uses x-rays from many angles to make a picture of the inside of the body.

contrast
A dye put into your body to make clearer pictures during imaging tests.

deoxyribonucleic acid (DNA)
A very thin and long molecule that contains genetic code. Also called the “blueprint of life.”

duct
A tube in the breast that drains breast milk.

ductal carcinoma
A breast cancer that starts in a cell that lines the ducts of the breast.

endocrine therapy
Treatment that stops the making or action of hormones in the body. Also called hormone therapy.

estrogen
A hormone that develops female body traits.

follicle-stimulating hormone (FSH)
A hormone made by the ovaries.

gene
Coded instructions in cells for making new cells and controlling how cells behave.

genetic counseling
Discussion with a health expert about the risk for a disease caused by changes in genes.

hereditary breast cancer
Breast cancer caused by faulty, coded information in cells that was passed down from parent to child.

hormone
Chemical in the body that activates cells or organs.

hormone receptor–negative cancer
Cancer cells that don't use hormones to grow.

hormone receptor–positive cancer
Cancer cells that use hormones to grow.

hot flashes
A health condition of intense body heat and sweat for short periods.

human epidermal growth factor receptor 2 (HER2)
A protein on the edge of a cell that send signals for the cell to grow.

human epidermal growth factor receptor 2 (HER2) inhibitor
A cancer drug that stops the effect of a cell protein called HER2.

human epidermal growth factor receptor 2 (HER2)-negative
Cancer cells with normal numbers of HER2 receptors.

human epidermal growth factor receptor 2 (HER2)-positive
Cancer cells with too many HER2 receptors.

hypercalcemia
High levels of calcium in the blood.

imaging test
A test that makes pictures of the insides of the body.

immunohistochemistry (IHC)
A lab test of cancer cells to find specific cell traits involved in abnormal cell growth.

infusion
A method of giving drugs slowly through a needle into a vein.

in situ hybridization (ISH)
A lab test of that counts the number of copies of a gene.

invasive breast cancer
Cancer cells have grown into the supporting tissue of the breast.

kinase inhibitor
A cancer drug that blocks the transfer of phosphase.

liver function test
A test that measures chemicals made or processed by the liver.

lobular carcinoma
A breast cancer that started in cells that line the breast lobules.

lobule
A gland in the breast that makes breast milk.

luteinizing hormone-releasing hormone (LHRH)
A hormone in the brain that helps control the making of estrogen by the ovaries.

lymph
A clear fluid containing white blood cells.

lymph node
Small groups of special disease-fighting cells located throughout the body.

magnetic resonance imaging (MRI)
A test that uses a magnetic field and radio waves to make pictures of the insides of the body.

medical history
All health events and medications taken to date.

medical oncologist
A doctor who's an expert in cancer drugs.

menopause
The point in time when menstrual periods end.

metastasis
The spread of cancer beyond the breast and nearby lymph nodes to distant sites like bone, lung, liver, or brain.

microtubule inhibitors
Cancer drugs that stop a cell from dividing into two cells.

mutation
An abnormal change in the instructions within cells for making and controlling cells.

osteonecrosis
Death of bone tissue.

ovarian ablation
Methods used to stop the ovaries from making hormones.

ovarian suppression
Methods used to lower the amount of hormones made by the ovaries.

pathologist
A doctor who's an expert in testing cells and tissue to find disease.

pelvis
The area between the hip bones.

performance status
A rating of general health.

periodontal disease
A disease of the gums in the mouth.

physical exam
A review of the body by a health expert for signs of disease.

positron emission tomography (PET)
Use of radioactive material to see the shape and function of body parts.

postmenopause
The state of the end of menstrual periods.

premenopause
The state of having regular menstrual periods.

primary tumor
The first mass of cancer cells in the body.

progesterone
A hormone in women that is involved in sexual development, periods, and pregnancy.

prognosis
The expected pattern and outcome of a disease based on tests.

protein kinase
A molecule that moves chemicals, called phosphates, from one molecule to another.

puberty
The time when teens sexually develop.

radiation therapy
The use of high-energy rays to destroy cancer cells.

receptor
A protein within cells to which substances can attach.

regression
Decreases in the tumor size or spread of cancer.

selective estrogen receptor down-regulator (SERD)
Cancer drug that blocks the effect of estrogen.

selective estrogen receptor modulators (SERM)
Cancer drug that blocks the effect of estrogen.

side effect
An unplanned physical or emotional response to treatment.

stroma
Supportive tissue in the breast.

supportive care
Treatment for the symptoms or health conditions caused by cancer or cancer treatment.

systemic therapy
Treatment of cancer throughout the body.

triple-negative breast cancer
Breast cancer that is not hormone-positive or HER2-positive.

tumor markers
Proteins in the blood that are measured to assess if cancer treatment is working.

vascular endothelial growth factor (VEGF)
A molecule that binds to cells that form blood vessels.

Acronyms

AJCC
American Joint Committee on Cancer

CA
cancer antigen

CBC
complete blood count

CDK
cyclin-dependent kinase

CEA
carcinoembryonic antigen

CT
computed tomography

DNA
deoxyribonucleic acid

ECOG
Eastern Cooperative Oncology Group

FDA
Food and Drug Administration

FDG
fluorodeoxyglucose

FSH
follicle-stimulating hormone

HER2
human epidermal growth factor receptor 2

IHC
immunohistochemistry

ISH
in situ hybridization

LHRH
luteinizing hormone-releasing hormone

KPS
Karnofsky Performance Status

mTOR
mammalian target of rapamycin

NCCN®
National Comprehensive Cancer Network®

MRI
magnetic resonance imaging

PET
positron emission tomography

PET/CT
positron emission tomography/ computed tomography

SERD
selective estrogen receptor degrader

SERM
selective estrogen receptor modulator

VEGF
vascular endothelial growth factor

VUS
variants of unknown significance

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NCCN Member Institutions

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Omaha, Nebraska
800.999.5465
nebraskamed.com/cancer

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Cleveland, Ohio
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216.844.8797 • Case CCC
case.edu/cancer

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Los Angeles, California
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dfbwcc.org
massgeneral.org/cancer

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888.275.3853
dukecancerinstitute.org

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888.369.2427
foxchase.org

Huntsman Cancer Institute
at the University of Utah
Salt Lake City, Utah
877.585.0303
huntsmancancer.org

Fred Hutchinson Cancer
Research Center/
Seattle Cancer Care Alliance
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hopkinskimmelcancercenter.org

Robert H. Lurie Comprehensive Cancer
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Chicago, Illinois
866.587.4322
cancer.northwestern.edu

Mayo Clinic Cancer Center
Phoenix/Scottsdale, Arizona
Jacksonville, Florida
Rochester, Minnesota
800.446.2279 • Arizona
904.953.0853 • Florida
507.538.3270 • Minnesota
mayoclinic.org/departments-centers/mayo-clinic-cancer-center

Memorial Sloan Kettering
Cancer Center
New York, New York
800.525.2225
mskcc.org

Moffitt Cancer Center
Tampa, Florida
800.456.3434
moffitt.org

The Ohio State University
Comprehensive Cancer Center -
James Cancer Hospital and
Solove Research Institute
Columbus, Ohio
800.293.5066
cancer.osu.edu

Roswell Park Cancer Institute
Buffalo, New York
877.275.7724
roswellpark.org

Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine
St. Louis, Missouri
800.600.3606
siteman.wustl.edu

St. Jude Children's Research Hospital
The University of Tennessee
Health Science Center
Memphis, Tennessee
888.226.4343 • stjude.org
901.683.0055 • westclinic.com

Stanford Cancer Institute
Stanford, California
877.668.7535
cancer.stanford.edu

University of Alabama at Birmingham
Comprehensive Cancer Center
Birmingham, Alabama
800.822.0933
www3.ccc.uab.edu

UC San Diego Moores Cancer Center
La Jolla, California
858.657.7000
cancer.ucsd.edu

UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, California
800.689.8273
cancer.ucsf.edu

University of Colorado Cancer Center
Aurora, Colorado
720.848.0300
coloradocancercenter.org

University of Michigan
Comprehensive Cancer Center
Ann Arbor, Michigan
800.865.1125
mcancer.org

The University of Texas
MD Anderson Cancer Center
Houston, Texas
800.392.1611
mdanderson.org

Vanderbilt-Ingram Cancer Center
Nashville, Tennessee
800.811.8480
vicc.org

University of Wisconsin
Carbone Cancer Center
Madison, Wisconsin
608.265.1700
uwhealth.org/cancer

Yale Cancer Center/
Smilow Cancer Hospital
New Haven, Connecticut
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yalecancercenter.org

Notes

Index

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Breast Cancer
Metastatic

Version 2.2017

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