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#Reference From NCCN Guidelines

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# 1

## Breast cancer basics

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**Metastatic breast cancer is breast cancer that has spread to other parts of the body. Metastatic breast cancer is also called advanced breast cancer.**

Breast tissue contains glands that can make milk. These milk glands are called lobules. Lobules look like tiny clusters of grapes. Small tubes called ducts connect the lobules to the nipple.

The ring of darker breast skin is called the areola. The raised tip within the areola is called the nipple. The nipple-areola complex (NAC) is a term that refers to both parts.

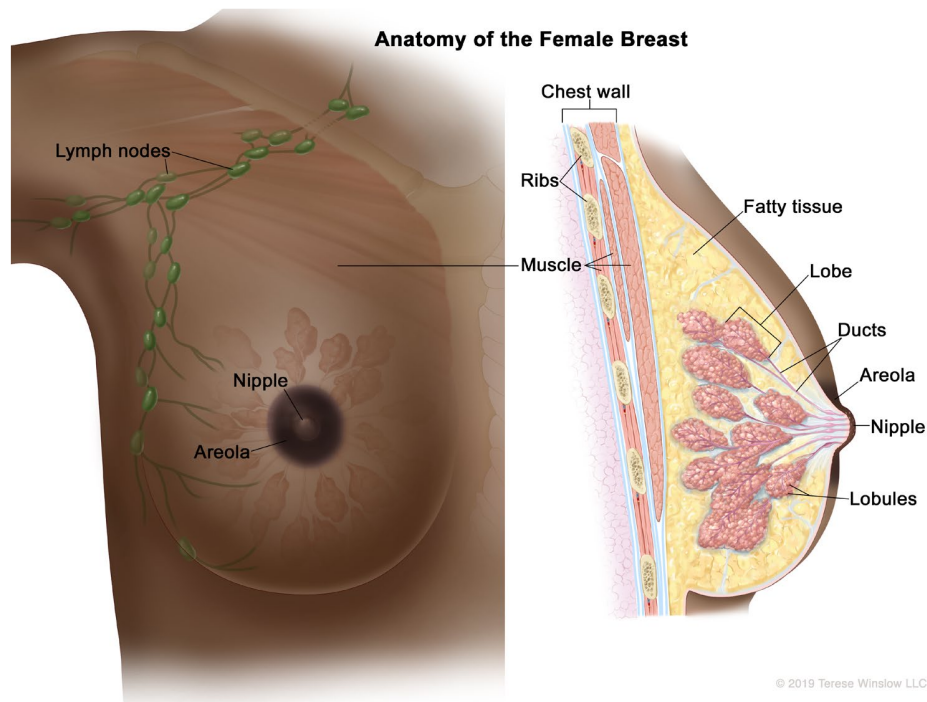
## The breast

The breast is an organ and a gland found on the chest. The breast is made of milk ducts and lobules, fat, nerves, lymph and blood vessels, ligaments, and other connective tissue. Behind the breast is the pectoral (chest) muscle and ribs. Muscle and ligaments help hold the breast in place.

Lymph drains from breast tissue into lymph vessels and travels to lymph nodes near your armpit (axilla). Lymph is a clear fluid that gives cells water and food. It also helps to fight germs. Nodes near the armpit are called axillary lymph nodes (ALNs).

### The breast

**The breast is a glandular organ made up of milk ducts, fat, nerves, blood and lymph vessels, ligaments, and other connective tissue.**



## Breast cancer

Breast cancer starts in the cells of the breast. Almost all breast cancers are a subtype called carcinomas. Carcinomas are cancers that start in the cells that line the inner or outer surfaces of the body. There are different types of breast carcinoma, most of which arise in cells that make up the lining (epithelial cells) in the terminal duct lobular units (TDLUs) of the breast. The most common types are either ductal or lobular.

Anyone can develop breast cancer, including those assigned male at birth. Although there are some differences between those assigned male and those assigned female at birth, treatment is very similar for all genders.

## How breast cancer spreads

Cancer cells don't behave like normal cells. Cancer cells differ from normal cells in the following ways.

### Primary tumor

Over time, cancer cells form a mass called a primary tumor.

### Invasive

Cancer cells can grow into surrounding tissues. Invasive breast cancer is breast cancer that has spread from the milk ducts or milk glands (lobules) into the surrounding breast tissue or nearby lymph nodes.

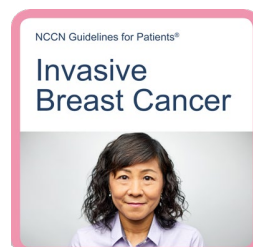
### Metastasis

Unlike normal cells, cancer cells can spread and form tumors in other parts of the body called metastases. In this process, cancer cells break away from the first (primary) tumor and travel through blood or lymph vessels to distant sites. Once in other sites, cancer cells may form secondary tumors. Since cancer cells can spread through the blood, it is still possible to develop metastases even when the axillary lymph nodes are negative for cancer.

- Cancer that has spread to a nearby body part such as the axillary lymph nodes is called a local metastasis. It might be referred to as locoregional disease or locally advanced.
- Cancer that has spread to a body part far from the primary tumor is called a distant metastasis.

Breast cancer can metastasize almost anywhere but most commonly spreads to the bone (including spine), lungs, liver, brain, or distant lymph nodes. Breast cancer that has metastasized to other parts of the body is still called breast cancer.

More information on invasive breast cancer is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



## Key points

- Anyone can develop breast cancer, but breast cancer occurs more frequently in persons assigned female at birth.
- Inside breasts are lobules, ducts, fat, blood and lymph vessels, ligaments, and connective tissue. Lobules are structures that make breast milk. Ducts carry breast milk from the lobules to the nipple.
- Breast cancer arises from epithelial cells (cells that make up the lining) in the terminal duct lobular units (TDLUs) of the breast and then spreads into surrounding tissue.
- Invasive breast cancer has grown outside the ducts or lobules into surrounding tissue. Once outside the ducts or lobules, breast cancer can spread through lymph or blood to lymph nodes or other parts of the body.
- Metastatic breast cancer (MBC) has spread outside the breast and lymph nodes. It is possible to have MBC when axillary lymph nodes do not have cancer.



### **Let us know what you think!**

**Please take a moment to complete an online survey about the NCCN Guidelines for Patients.**

[NCCN.org/patients/response](https://www.nccn.org/patients/response)

# 2

## Testing for MBC

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**Not all breast cancers are the same. Treatment planning starts with testing. Your care team will gather information about the cancer you have. This chapter presents an overview of the tests you might receive and what to expect.**

### Test results

Results from imaging studies and biopsy will be used to determine your treatment plan. The biopsy sample will be tested for estrogen and progesterone hormone receptors and human epidermal growth factor receptor 2 (HER2) receptors. Treatment will be based on these findings.

It is important you understand what these tests mean. Ask questions about your test results.

Keep these things in mind:

- Choose a friend, family member, or peer who can drive you to appointments, provide meals, or offer emotional support during diagnosis and treatment. This can be different people for different tasks or change over time.
- Bring someone with you to doctor visits, if possible, or have someone on the phone or join you for telehealth visits.
- Write down questions and take notes during appointments. Don't be afraid to

ask your care team questions. Get to know your care team and help them get to know you.

- Get copies of blood tests, imaging results, and reports about the specific type of cancer you have. Your test results and visit notes are likely available through a patient portal. Signing up for this portal can be one way to review those results and notes, too.
- Organize your papers. Create files for insurance forms, medical records, and test results. You can do the same on your computer, phone, or other electronic device.
- Keep a list of contact information for everyone on your care team. Add it to your phone. Hang the list on your refrigerator or keep it in a place where someone can access it in an emergency. Keep your primary care physician (PCP) informed of changes to this list. You are encouraged to keep your PCP in the loop. They are great partners in your care.
- In your contact list, include information on the exact type of cancer you have, as well as any treatments you've received and the date each treatment started.
- Set up a MyChart or health record account if it's available, which can help you track your appointments and communicate with your care team. Remember that in many places the MyChart or portal messages are not immediately seen by a nurse or physician, so urgent concerns are best called to the triage phone number. Ask your care team to learn more about how best to communicate with them.



For possible tests, **see Guide 1.**

## General health tests

### Medical history

A medical history is a record of all health issues and treatments you have had in your life. Be prepared to list any illness or injury and when it happened. Bring a list of old and new medicines and any over-the-counter (OTC) medicines, herbals, or supplements you take. Some supplements interact and affect medicines that your care team may prescribe. Tell your care team about any symptoms you have. A medical history, sometimes called a health history, will help determine which treatment is best for you.

### Family history

Some cancers and other diseases can run in families. Your care team will ask about the health history of family members who are blood relatives. This information is called a family history. Ask all family members about their health issues like heart disease, cancer, and diabetes, and at what age they were diagnosed. It's important to know the specific type of cancer, or where the cancer started, if it is in multiple locations, and if they had genetic testing.

#### Guide 1 Possible tests

Medical history and physical exam

Imaging tests as needed

Biopsy with pathology review

Determine tumor status including:

- Estrogen receptor (ER) and progesterone receptor (PR) status
- HER2 status

Genetic counseling and testing if at risk for hereditary breast cancer or has triple-negative breast cancer (TNBC)

Address fertility and sexual health concerns

Pregnancy test in those of childbearing potential

Assess for distress

### Physical exam

During a physical exam, your health care provider may:

- Check your temperature, blood pressure, pulse, and breathing rate
- Check your height and weight
- Listen to your lungs and heart
- Look in your eyes, ears, nose, and throat
- Feel and apply pressure to parts of your body to see if organs are of normal size, are soft or hard, or cause pain when touched
- Examine your breasts to look for lumps, nipple discharge or bleeding, or skin changes
- Feel for enlarged lymph nodes in your neck, underarm, and groin
- Examine your spine and back

### Clinical breast exam

Clinical breast exam (CBE) is a physical exam of the bare breast performed by a health care provider to check for lumps or other changes. It is done while you are seated and/or lying down. Your provider should take time to palpate (feel) the entire breast, including the armpit. A nurse or assistant might also be in the room during the exam.



### Create a medical binder

A medical binder or notebook is a great way to organize all of your records in one place.

- ✓ Make copies of blood tests, imaging results, and reports about your specific type of cancer. It will be helpful when getting a second opinion.
- ✓ Choose a binder that meets your needs. Consider a zipper pocket to include a pen, small calendar, and insurance cards.
- ✓ Create folders for insurance forms, test types (blood, imaging, pathology, radiology, genetics), treatments, and procedures. Organize items in the folder by date.
- ✓ Use online patient portals to view your test results and other records. Download or print the records to add to your binder.
- ✓ Add a section for questions and to take notes.

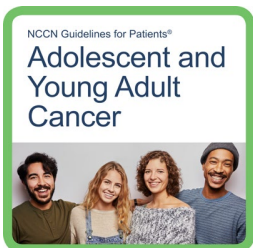
Bring your medical binder to appointments. You never know when you might need it!

## Fertility (all genders)

Treatment such as chemotherapy can affect your fertility, the ability to have children. If you think you want children in the future, ask your care team how cancer and cancer treatment might change your fertility. To preserve your fertility, you may need to take action before starting cancer treatment. Those who want to have children in the future should be referred to a fertility specialist to discuss the options before starting treatment.

Fertility preservation is all about keeping your options open, whether you know you want to have children later in life or aren't sure at the moment. Fertility and reproductive specialists can help you sort through what may be best for your situation.

More information on fertility preservation in adolescents and young adults is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



### Changes in fertility

Treatment might cause your fertility to be temporarily or permanently impaired or interrupted. This loss of fertility is related to your age at time of diagnosis, treatment type(s), treatment dose, and treatment length. Talk to your care team about your concerns and if you are planning a pregnancy.

### Preventing pregnancy during treatment

Cancer and cancer treatment can affect the ovaries and damage sperm. If you become pregnant during chemotherapy, radiation therapy, or other types of systemic therapy, serious birth defects can occur. Speak with your care team about preventing pregnancy while being treated for cancer. Hormonal birth control may or may not be recommended, so ask your doctor about options such as intrauterine devices (IUDs) and barrier methods. Types of barrier methods include condoms, diaphragms, cervical caps, and the contraceptive sponge.

### Those with ovaries

Those who can become pregnant will have a pregnancy test before starting treatment. Cancer treatment can hurt the developing baby if you are or become pregnant during treatment. Therefore, birth control to prevent pregnancy during and after treatment is recommended. If you are pregnant or breastfeeding at the time of your cancer diagnosis, certain treatments will need to be avoided.

Menstruation, menses, menstrual flow, or your period may stop during treatment, but often returns within 2 years after treatment. It is still possible to become pregnant even though you might not have a period. Therefore, birth control is recommended during and after treatment. Consult your doctor for the best time to plan a pregnancy.

### Those with testicles

Cancer and cancer treatment can damage sperm. Therefore, use contraception (birth control) such as condoms to prevent pregnancy during and immediately after cancer treatment.

**Testing takes time. It might take days or weeks for all test results to come in.**

## Blood tests

Blood tests check for signs of disease and how well organs are working. They require a sample of your blood, which is removed through a needle placed into your vein.

### Alkaline phosphatase

Alkaline phosphatase (ALP) is an enzyme found in the blood. High levels of ALP can be a sign cancer has spread to the bone or liver. A bone scan might be performed if you have high levels of ALP.

### Liver function tests

Liver function tests (LFTs) look at the health of your liver by measuring chemicals that are made or processed by the liver. Levels that are too high or low signal that the liver is not working well or that cancer has spread to the liver.

### Pregnancy test

Those who can become pregnant will be given a pregnancy test before treatment begins.

### Complete blood count

A complete blood count (CBC) measures the levels of red blood cells (RBCs), white blood cells (WBCs), and platelets (PLTs) in your blood. Red blood cells carry oxygen throughout your body, white blood cells fight infection, and platelets control bleeding.

### Comprehensive metabolic panel

A comprehensive metabolic panel (CMP) measures 14 different substances in your blood. It is usually done on the plasma part of your blood. A CMP provides important information about how well your kidneys and liver are working, among other things.

### Imaging tests

Imaging tests take pictures of the inside of your body. Imaging tests show the primary tumor, or where the cancer started, and look for cancer in other parts of the body. Tests are based on if metastatic disease is suspected and any symptoms you might have. You will not have all these tests listed in this section.

A radiologist, an expert in interpreting imaging tests, will write a report and send this report to your health care provider (HCP). It is likely that the report will be sent directly to you through your patient portal or patient access system. You should discuss these results with your HCP.

#### Bone scan

A bone scan uses a radiotracer. A radiotracer is a substance that releases small amounts of radiation. Before the pictures are taken, the tracer will be injected into your vein. It can take a few hours for the tracer to enter your bones.

A special camera will take pictures of the tracer in your bones as it moves over your body. Areas of bone damage take up more radiotracer than healthy bone and show up as bright spots on the pictures. Bone damage can be caused by cancer, cancer treatment, previous injuries, or other health issues.

#### Bone x-ray

An x-ray uses low-dose radiation to take one picture at a time. A tumor changes the way radiation is absorbed and will show up on the x-ray. X-rays are also good at showing bone issues. Your care team may order x-rays if

your bones hurt or were abnormal on a bone scan.

#### Contrast material

Contrast materials are not dyes, but substances that help make the pictures of the inside of the body clearer. The contrast is not permanent and will leave the body in your urine after the test. There is more than one type of contrast and it differs depending on the test. Tell your care team if you have had allergic reactions to contrast in the past. This is important. You might be given medicines to avoid the effects of those allergies.

#### CT scan

A computed tomography (CT or CAT) scan uses x-rays and computer technology to take pictures of the inside of the body. It takes many x-rays of the same body part from different angles. All the images are combined to make one detailed picture. A CT scan of your chest, abdomen, and/or pelvis might be one of the tests used to look for cancer. Intravenous (IV) contrast is often used.

#### MRI scan

A magnetic resonance imaging (MRI) scan uses radio waves and powerful magnets to take pictures of the inside of the body. It does not use x-rays. Because of the very strong magnets used in the MRI machine, tell the technologist if you have any metal in your body. During the test, you will likely be asked to hold your breath for 10 to 20 seconds as the technician collects the images. Contrast is often used.

A closed MRI has a capsule-like design where the magnet surrounds you. An open MRI has a magnetic top and bottom, which allows for an opening on each end. Closed MRIs are more common than open MRIs, so if you have claustrophobia (a dread or fear of enclosed spaces), be sure to talk to your care team about it.

- **A breast MRI** might be used in addition to a mammogram. Contrast should be used. You will be positioned face down in the machine with your arms above your head.
- **A spine or brain MRI** can be used to detect breast cancer that has spread (metastasized) to your spine or brain. For a brain MRI, a device is placed around your head. For a spine MRI, no device is worn. Contrast should be used in an MRI.

### PET scan

A positron emission tomography (PET) scan uses a radioactive drug called a tracer. A tracer is a substance injected into a vein to see where cancer cells are in the body and if they are using sugar produced by your body to grow. Cancer cells show up as bright spots on PET scans. However, not all tumors will appear on a PET scan. Also, not all bright spots are cancer. It is normal for the brain, heart, kidneys, and bladder to be bright on PET. Inflammation or infection can also show up as a bright spot. When a PET scan is combined with CT, it is called a PET/CT scan.

Types of PET/CT scans include:

- **An FDG-PET/CT** uses a radiotracer called fluorodeoxyglucose (FDG). It is made of fluoride and a simple form of sugar called glucose. You cannot eat or drink for at least 4 hours before the scan. This scan is most helpful when other imaging results are unclear. It may help find cancer in lymph nodes and distant sites. If it clearly shows cancer in the bone, a bone scan and sodium fluoride PET/CT may not be needed.
- **An FES-PET/CT** might be used instead of FDG-PET/CT when cancer is estrogen receptor-positive (ER+). FES is a radioactive form of the hormone estrogen.
- **A sodium fluoride PET/CT** might be used instead of a bone scan. In this test, the radiotracer is made of sodium fluoride.

### Ultrasound

An ultrasound (US) uses high-energy sound waves to form pictures of the inside of the body. This is similar to the sonogram used for pregnancy. A wand-like probe (transducer) will be held and moved on your bare breast using gel. It may also be placed below your armpit. Ultrasound does not use x-rays. It is good at showing small areas of cancer that are near the skin. Sometimes, a breast ultrasound or MRI is used to guide a biopsy.

# Biopsy

A biopsy is a procedure that removes a sample of tissue or fluid. The sample is sent to a lab for testing. A pathologist will examine the biopsy for cancer and write a report called a pathology report. Ask questions about your biopsy results and what it means for your treatment.

There are different types of biopsies. Some biopsies are guided using imaging, such as ultrasound or MRI. If metastatic disease is suspected, one or more tumors will be biopsied to confirm disease and help guide treatment. You may have tissue removed from the breast, lymph nodes, or other areas of the body affected by cancer.

Types of possible biopsies include:

- **Fine-needle aspiration (FNA)** or core biopsy (CB) uses needles of different sizes to remove a sample of tissue or fluid. In a vacuum-assisted core biopsy (VACB), suction is used to remove the sample with a special vacuum device.
- **Incisional biopsy** removes a small amount of tissue through a small cut in the skin or body.
- **Excisional biopsy** removes the entire abnormal area. This is not the preferred type of biopsy but may be necessary if other methods are not possible or when the biopsy results don't match the expected findings.

Before biopsies are performed, the area is usually injected with numbing medicine. A core needle biopsy (CNB) removes more than one tissue sample, but usually through the same area on the breast. The samples are small.

**Since your type of breast cancer may change over time, a repeat biopsy may be needed to guide treatment.**

The needle is often guided into the tumor with imaging. When mammography is used during a biopsy, it is called a stereotactic needle biopsy.

There are both physical and emotional experiences in having biopsies. You may need to rest and place an ice pack on the biopsy area after the procedure. If you are working or have other commitments, you may want to take the day off to rest.

## Biopsy of metastasis

Metastasis is the spread of cancer to an area of the body such as the bones, lungs, or liver. A biopsy of the metastasis is typically needed to confirm the presence of cancer. If there is more than one metastasis, more than one site may be biopsied. The type of biopsy used depends on the location of the suspected metastases and other factors. These biopsies are usually guided by imaging tests like ultrasound (US) or CT.

## Biopsy results

Histology is the study of the anatomy (structure) of cells, tissues, and organs under a microscope. It is used to make treatment decisions. Your pathology report will contain information about histology, such as invasive ductal carcinoma or invasive lobular carcinoma.

### Hormone receptor status

Your blood carries hormones throughout your body. A hormone is a substance made by a gland in your body. A receptor is a protein found inside or on the surface of a cell. When hormones attach (bind) to specific receptors, it causes changes within the cell.

When hormones attach to receptors inside breast cancer cells, they can cause cancer to grow. If found, these receptors may be targeted using endocrine therapy.

There are 2 types of hormone receptors:

- **Estrogen** – plays a role in breast development
- **Progesterone** – plays a role in menstrual cycle and pregnancy

Hormone receptor (HR) testing should be done on any new tumors. A biopsy sample will be used.

### Immunohistochemistry

Immunohistochemistry (IHC) is a special staining process that involves adding a chemical marker to cells. These cells are then studied using a microscope. IHC can find estrogen, progesterone, and HER2 receptors in breast cancer cells. A pathologist will measure how many cells have estrogen and/or progesterone receptors and the number of receptors inside each cell.

### Estrogen receptor-positive (ER+) breast cancer cells

- ✓ In ER+ breast cancer, testing finds estrogen hormone receptors in at least 1 out of every 100 cancer cells.
- ✓ In ER-low–positive invasive breast cancer, testing finds estrogen hormone receptors in 1 to 10 out of every 100 cancer cells.
- ✓ Endocrine therapy might not be recommended for ER-low–positive invasive breast cancer.

### Hormone receptor-positive

In hormone receptor-positive (HR+) breast cancer, IHC finds estrogen and/or progesterone hormone receptors. Most breast cancers are HR+.

- **Estrogen receptor (ER)** is stimulated by estrogen and provides survival and proliferation (rapid growth) signals. Cancer cells deprived of estrogen or that have their ER signal blocked with treatment may stop growing or die.
- **Progesterone receptor (PR)** binds progesterone and provides survival and proliferation signals. It is thought that PR expression also suggests the tumor is estrogen dependent.

HR+ breast cancer is treated with endocrine therapy, which blocks estrogen receptor signaling or decreases estrogen production.



### Hormone receptor-negative

Hormone receptor-negative (HR-) breast cancer cells do not have estrogen or progesterone hormone receptors. These cancers are sometimes simply called hormone negative. HR- cancers often grow faster than HR+ cancers. Both the estrogen and progesterone receptors need to be negative for breast cancer to be considered HR-.

### HER2 status

Human epidermal growth factor receptor 2 (HER2) is a protein involved in normal cell growth. It is found on the surface of all cells. When amounts are high, it causes cells to grow and divide. Some breast cancers have too many HER2 genes or receptors. Too many HER2s is called HER2-positive (HER2+). You might hear it called HER2 overexpression or amplification.

There are 2 tests for HER2:

- **Immunohistochemistry (IHC)** measures receptors. If the IHC score is 3+, the cancer is HER2+. If the score is 0 or 1, it is considered HER2-. If the score is 2+, further testing is needed.
- **In situ hybridization (ISH)** counts the number of copies of the HER2 gene. This test is done mainly when the IHC score is unclear.

HER2 testing should be done on all new tumors. A tumor biopsy sample will be used. You might have more than one HER2 test. Newer drugs that target HER2 have recently been shown to be effective in some people with metastatic breast cancer with lower levels

of HER2 expression (1+ and 2+ by IHC) called HER2-low.

### FISH/ISH

Fluorescence in situ hybridization (FISH) or other ISH methods like dual ISH are testing methods that involve special dyes called probes that attach to pieces of DNA, the genetic material in a person's cells.

### Biomarker testing

A sample from a biopsy of your tumor may be tested to look for specific DNA (deoxyribonucleic acid) mutations/alterations, protein levels, or other molecular features. This information is used to choose the best treatment for you. It is sometimes called molecular testing or tumor profiling, tumor sequencing, gene expression profiling, or genomic testing.

Biomarker testing includes tests of genes or their products (proteins). It identifies the presence or absence of mutations and certain proteins that might suggest treatment. Proteins are written like this: BRCA. Genes are written with italics like this: *BRCA*. HER2 and hormone receptor status are part of biomarker testing. Your treatment team will recommend the best types of biomarker testing that are important for you.

### Tumor mutation testing

Tumor mutation testing or tumor genomic aberration testing uses a sample of your tumor or blood to see if the cancer cells have any specific DNA mutations. This is a different type of DNA testing than the genetic testing for

mutations you may have inherited from your parents. In tumor mutation testing, only the tumor is tested and not the rest of your body.

Testing is done using a variety of methods such as FISH, ISH, IHC, next-generation sequencing (NGS), and/or polymerase chain reaction (PCR). These methods are used to identify the presence of gene mutations, alterations, rearrangements, or fusions.

- Certain mutations such as *PIK3CA*, *AKT1*, *PTEN*, *ESR1*, *NTRK*, and *RET* can be targeted with specific therapies. Testing for *ESR1* and *RET* mutations is done on hormone receptor-positive tumors.
- Germline *BRCA1/2* testing is recommended for all patients with metastatic breast cancer, unless it has already been done (more recently than 2014).

### PD-1 and PD-L1 testing

Programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) are immune proteins. If either protein is expressed on the surface of cancer cells, it can cause your immune cells to ignore the cancer and suppress the anti-tumor immune response. If your cancer expresses either protein, you might have treatment that combines chemotherapy and a checkpoint inhibitor therapy. This is designed to activate your immune system to better fight off the cancer cells. Usually this test is done when hormone receptors and HER2 testing are negative (like in triple-negative tumors).

### MSI-H/dMMR mutation

Microsatellites are short, repeated strings of DNA. When errors or defects occur, they are fixed by mismatch repair (MMR) proteins. Some cancers have DNA mutations or changes that prevent these errors from being fixed. This is called microsatellite instability (MSI) or deficient mismatch repair (dMMR). When cancer cells have more than a normal number of microsatellites, it is called MSI-H (microsatellite instability-high). This is often due to dMMR genes.

### Tumor mutational burden

When there are 10 or more mutations per million base pairs of tumor DNA, it is called tumor mutational burden-high (TMB-H). TMB-H can be used to help predict response to cancer treatment using immune checkpoint inhibitors that target the proteins PD-1 and PD-L1.

### Next-generation sequencing

Next-generation sequencing (NGS) is a high-throughput method used to determine the DNA sequence or gene changes of cancer cells in your tumor. This method would only be used if enough tumor tissue remains after other biomarker testing has been completed.

### PCR

A polymerase chain reaction (PCR) is a lab process that can make millions or billions of copies of your DNA (genetic information). PCR is very sensitive. It can find 1 abnormal cell among more than 100,000 normal cells. These copies called PCR product might be used for NGS.

### ***NTRK* gene fusions**

In a tumor with an *NTRK* gene fusion, a piece of the *NTRK* gene and a piece of another gene fuse or join. This activates the *NTRK* gene in a way that causes uncontrolled cell growth. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek) might be used to target advanced or metastatic HR+/HER2- cancer that is *NTRK* gene fusion-positive. *NTRK* gene fusions are rare.

### ***RET* gene fusions**

A *RET* gene mutation is related to cell growth (proliferation). Selpercatinib (Retevmo) might be used to target advanced or metastatic HR+ with HER2- tumors with a *RET* fusion.

### **Tumor markers**

Your blood or biopsy tissue may be tested for proteins called tumor markers. Knowing this information can help plan treatment. Examples of some tumor markers in breast cancer include carcinoembryonic antigen (CEA), CA 15-3, and CA 27.29. An increase in the level of certain tumor markers could mean that the cancer has grown or spread (progressed). However, not everyone has elevated levels of these markers and tumor markers alone are not a reliable method of detecting breast cancer.

### **Liquid biopsy**

Some abnormal changes (mutations) can be found by testing circulating tumor DNA (ctDNA) in the blood. In a liquid biopsy, a sample of blood is taken to look for cancer cells or for pieces of DNA from tumor cells. Sometimes, testing can quickly use up a tumor sample and a liquid biopsy might be an option in this case.

## **What is your family health history?**

Some cancers and other diseases run in families—those who are related to you through genes passed down from biological parent to child. This information is called a family health history. Ask blood relatives about their health issues like heart disease, cancer, and diabetes, and at what age they were diagnosed. For relatives who were diagnosed with cancer, ask them (or other relatives if they are no longer living) what type of cancer they had, if they died from the cancer, and at what age the cancer was diagnosed.

Start by asking your parents, siblings, and children. Next, talk to half-siblings, aunts and uncles, nieces and nephews, grandparents, and grandchildren.

Write down what you learn about your family history and share this information with your health care provider.

Some of the questions to ask include:

- ✓ How old were you when each of these diseases and health conditions was diagnosed?
- ✓ What is our family's ancestry—from what countries did our ancestors originate?

## Genetic cancer risk testing

About 1 out of 10 breast cancers are hereditary. Depending on your family history or other features of your cancer, your health care provider might refer you for hereditary genetic testing to learn more about your cancer. A genetic counselor or trained provider will speak to you about the results. Test results may be used to guide treatment planning.

Genetic testing is done using blood or saliva from spitting into a cup or a cheek swab. The goal is to look for gene mutations inherited from your biological parents called germline mutations. Some mutations can put you at risk for more than one type of cancer. You can pass these genes on to your children. Also, other blood relatives might carry these mutations. Tell your care team if there is a family history of cancer.

### **BRCA tests**

Everyone has *BRCA* genes. Normal *BRCA* genes help to prevent tumor growth. They help fix damaged cells and help cells grow normally. *BRCA* mutations put you at risk for more than one type of cancer. Mutations in *BRCA1* or *BRCA2* increase the risk of breast, ovarian, prostate, pancreatic, and melanoma skin cancers. Mutated *BRCA* genes can also affect how well some treatments work. These tests might be repeated if you were tested over 10 years ago (technology has changed since 2014).

### **Other genes**

Other genes such as *PALB2*, *p53*, *CHEK2*, and *ATM* might be tested. For example, *PALB2* normally helps prevent cancer. When *PALB2*

mutates, it no longer works correctly. Those with a *PALB2* mutation have a higher risk of developing breast cancer.

## Distress screening

It is normal to have strong feelings about being diagnosed with cancer and your feelings can also change from day to day and week to week. Talk to your care team and those whom you feel most comfortable about how you are feeling. There are services and people who can help you. Support and counseling are available. Many treatment teams include mind and body therapists who can help.

Dealing with a cancer diagnosis can be stressful and may cause further distress. Distress is an unpleasant experience of a mental, physical, social, or spiritual nature. It can affect how you feel, think, and act. Distress might include feelings of sadness, fear, helplessness, worry, anger, and guilt. You may also experience depression, anxiety, and sleep issues. Your treatment team will screen your level of distress. This is part of your cancer care.

Your cancer diagnosis may affect your family or loved ones. They may feel some degree of anxiety or depression. They can talk to a social worker and seek help, too.

More information on distress is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.

## Performance status

Performance status (PS) is a person's general level of fitness and ability to perform daily tasks. Your state of general health will be rated using a PS scale called Eastern Cooperative Oncology Group (ECOG). PS is one factor taken into consideration when choosing a treatment plan. Your preferences about treatment are always important.

The ECOG PS scores range from 0 to 5.

- **PS 0** means the person is fully active.
- **PS 1** means the person is still able to perform light to moderate activity, but with some limitations.
- **PS 2** means the person is limited to the chair or bed less than half of the time and still able to care for self.
- **PS 3** means the person is limited to the chair or bed more than half of the time.
- **PS 4** means the person is totally confined to the bed or chair and completely disabled.
- **PS 5** means the person is not alive.

Good PS is usually PS 0 or PS 1.

## Key points

- Tests are used to find cancer, plan treatment, and check how well treatment is working.
- You will have a physical exam, including a breast exam, to see if anything feels or looks abnormal.
- Treatment can affect your fertility, the ability to have children.
- 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.
- A sample from a biopsy of your tumor will be tested for estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, grade, and histology. This provides information about the behavior of your cancer, as well as treatments to which your cancer may respond.
- About 1 out of 10 breast cancers are hereditary. Depending on your family history or other features of your cancer, you might be referred for genetic testing, to speak with a genetic counselor, and possibly to have genetic testing.

# 3

## Breast cancer staging

- 24 How breast cancer is staged
- 25 TNM scores
- 28 Key points

**Cancer staging is used to reflect prognosis and to guide treatment decisions. It describes the size and location of the tumor and if cancer has spread to lymph nodes, organs, or other parts of the body. It also takes into account hormone receptor (HR) and HER2 status.**

## How breast cancer is staged

A cancer stage is a way to describe the extent of the cancer at the time you are first diagnosed. The American Joint Committee on Cancer (AJCC) created a staging system to determine how much cancer is in your body, where it is located, and what subtype you have. This is called staging.

Based on testing, your cancer will be assigned a stage. Staging helps to predict prognosis and is needed to make treatment decisions. A prognosis is the course your cancer will likely take. AJCC is just one type of staging system.

Information gathered during staging:

- **The extent (size) of the tumor (T):** How large is the cancer? Has it grown into nearby areas?
- **The spread to nearby lymph nodes (N):** Has the cancer spread to nearby lymph nodes? If so, how many? Where?
- **The spread (metastasis) to distant sites (M):** Has the cancer spread to distant organs such as the lungs or liver?
- **Estrogen receptor (ER) status:** Does the cancer have the protein called an estrogen receptor?
- **Progesterone receptor (PR) status:** Does the cancer have the protein called a progesterone receptor?
- **Human epidermal growth factor receptor 2 (HER2) status:** Does the cancer make too much of a protein called HER2?
- **Grade of the cancer (G):** How much do the cancer cells look like normal cells?
- **Biomarker testing:** Does the cancer have any genes, proteins, markers, or mutations that might suggest treatment?

Staging is based on a combination of information to reach a final numbered stage. It takes into account what can be felt during a physical exam, what can be seen on imaging tests, and what is found during a biopsy or surgery. Often, not all information is available at the initial evaluation. More information can be gathered as treatment begins.

Staging includes:

- **Anatomic** – based on extent of cancer as defined by tumor size (T), lymph node status (N), and distant metastasis (M).
- **Prognostic** – includes anatomic TNM plus tumor grade and the status of the biomarkers such as HER2, ER, and PR. Prognostic stage also includes the assumption that you are treated with the standard-of-care approaches.

## TNM scores

The tumor, node, metastasis (TNM) system is used to stage breast cancer. In this system, the letters T, N, and M describe different areas of cancer growth. Based on cancer test results, a score or number is assigned to each letter. The higher the number, the larger the tumor or the more the cancer has spread. These scores will be combined to assign the cancer a stage. A TNM example might look like this: T2N1M0 or T2, N1, M0.

- **T (tumor)** – Depth and spread of the main (primary) tumor(s) in one or both breasts
- **N (node)** – If cancer has spread to nearby (regional) lymph nodes
- **M (metastasis)** – If cancer has spread to distant parts of the body or metastasized

## Treatment options by cell receptor type

There are many treatments for metastatic breast cancer. Which ones are right for you are based on many factors. Two important factors are the hormone receptor (HR) and HER2 status of any tumors.

Hormone receptors include estrogen and progesterone. A tumor is considered hormone receptor-positive (HR+) if an increased number of estrogen receptors, progesterone receptors, or both are found.

HER2 is a protein involved in normal cell growth. There might be higher amounts of HER2 in your breast cancer. If this is the case, it is called HER2-positive (HER2+) breast cancer.

- ✓ **Endocrine therapy** stops cancer growth caused by hormones. It is a standard treatment for hormone receptor-positive (HR+) cancers. HR+ cancer can be estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+).
- ✓ **HER2-targeted therapy** is a standard treatment for HER2+ cancers.
- ✓ **Chemotherapy** is often the first treatment for hormone receptor-negative (HR-) cancers.

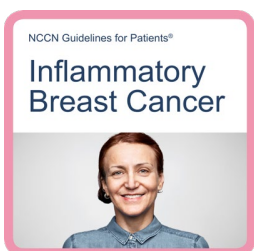


#### T = Tumor

The primary tumor size can be measured in centimeters (cm) or millimeters (mm). One inch is equal to 2.54 cm. A large pea is 1 cm (10 mm). A golf ball is 4 cm (40 mm). A tumor micrometastasis is a very small collection of cancerous cells smaller than 1 mm. It might be written as T1mi. Ipsilateral means on the same side of the body.

- **T1** Tumor is 2 cm (20 mm) or less
  - **T1mi** Tumor is micrometastasis of 1 mm or less
  - **T1a** Tumor is 1.1 mm to 5 mm
  - **T1b** Tumor is 5.1 mm to 10 mm
  - **T1c** Tumor is 10.1 mm to 20 mm
  - **T2** Tumor is 2.1 cm to 5 cm
- **T3** Tumor is more than 5 cm
- **T4** Tumor is of any size and has invaded nearby structures such as the chest wall and skin of the breast
- **T4d** Tumor is inflammatory carcinoma (inflammatory breast cancer)

More information on inflammatory breast cancer is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



#### N = Regional lymph node

Lymph, a clear fluid containing cells that help fight infections and other diseases, drains through channels into lymphatic vessels. From here, lymph drains into lymph nodes. Lymph nodes work as filters to help fight infection.

Regional lymph nodes are those located near the breast in the armpit (axilla). If breast cancer spreads, it often goes first to nearby lymph nodes under the arm. It can also sometimes spread to lymph nodes near the collarbone or near the breastbone. However, it is possible for cancerous cells to travel through lymph and blood to other parts of the body without having gone to the lymph nodes first. Knowing if the cancer has spread to your lymph nodes helps doctors find the best way to treat your cancer.

- **N0** means no cancer is in the regional lymph nodes. Isolated tumor cells (ITCs) may be present. These are malignant cell clusters no larger than 0.2 mm.
- **N1mi** means micrometastases (approximately 200 cells, larger than 0.2 mm, but not larger than 2.0 mm) are found in lymph nodes.
- **N1, N2, N3** means regional lymph node metastases are found. The higher the number, the more lymph nodes that have metastases.

### M = Metastasis

Cancer that has spread to distant parts of the body is shown as M1. This is metastatic breast cancer (MBC). The most common sites for metastasis are bone and lung.

- **M0** means no evidence of distant metastasis.
- **M1** means distant metastasis is found. This is metastatic breast cancer.

### Grade

Grade describes how abnormal the tumor cells look under a microscope (called histology). Higher-grade cancers tend to grow and spread faster than lower-grade cancers. GX means the grade can't be determined, followed by G1, G2, and G3. G3 is the highest grade for breast cancers.

- **GX** – Grade cannot be determined
- **G1** – Low
- **G2** – Intermediate
- **G3** – High

### Numbered stages

Numbered stages are based on TNM scores and receptor (hormone and HER2) status. Stages range from stage 0 to stage 4, with 4 being the most advanced. They might be written as stage 0, stage I, stage II, stage III, and stage IV.

- **Stage 0 is noninvasive** – Noninvasive breast cancer is rated stage 0. Ductal carcinoma in situ (DCIS) is found only in the ducts (Tis). It has not spread to the surrounding breast tissue, lymph nodes (N0), or distant sites (M0).
- **Stages 1, 2, and 3 are invasive** – Invasive breast cancer is rated stage 1, 2, or 3. It has grown outside the ducts, lobules, or breast skin. Cancer might be in the axillary lymph nodes.
- **Stage 4 is metastatic** – In stage 4 breast cancer, cancer has spread to distant sites at the time of diagnosis. Metastatic disease more commonly develops from earlier stages. Sometimes, the first diagnosis is stage 4 metastatic breast cancer (called de novo).

## Key points

- Staging helps to predict prognosis and is needed to make treatment decisions. A prognosis is the course your cancer will likely take.
- The tumor, node, metastasis (TNM) system is used to stage breast cancer.
- Clinical stage (c) is the rating given before any treatment. It is written as cTNM.
- Pathologic stage (p) or surgical stage is determined by examining tissue removed during surgery. It is written as pTNM.
- Grade describes how abnormal the tumor cells look under a microscope (called histology).
- Regional lymph nodes are found near the breast.

# 4

## Treating breast cancer

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**Systemic therapy is the main or primary treatment for metastatic breast cancer. The goal of treatment is to prevent or slow the spread of cancer. Together, you and your care team will choose a treatment plan that is best for you.**

### Care team

Treating breast cancer takes a team approach. Treatment decisions should involve a multidisciplinary team (MDT). An MDT is a team of health care and psychosocial care professionals from different professional backgrounds who have knowledge (expertise) and experience in your type of cancer. This team is united in the planning and implementing of your treatment. Ask who will coordinate your care.

Some members of your care team will be with you throughout cancer treatment, while others will only be there for parts of it. Get to know your care team and help them get to know you.

Depending on your diagnosis, the care team might include the following specialists:

- **Oncologists** specialize in diagnosing and treating cancer. Types of oncologists include medical, radiation, and surgical oncologists.
- **Oncology nurses and advanced practice providers (APPs)** provide your hands-on care, like giving systemic therapy, managing your care, answering questions, and helping you cope with side effects.
- **Oncology pharmacists** are experts in knowing how to use medicines to treat cancer and to manage symptoms and side effects.
- **Palliative care specialists** concentrate on preventing and alleviating suffering and improving quality of life.
- **Nutritionists and dietitians** can provide guidance on what foods are most suitable for your condition.
- **An occupational therapist** helps people with the tasks of daily living.
- **A physical therapist** helps people move with greater comfort and ease.
- **A certified lymphedema therapist** gives a type of massage called manual lymph drainage.
- **Psychologists and psychiatrists** are mental health experts who can help manage issues such as depression, anxiety, or other mental health conditions that can affect how you think and feel.

- **Social workers** help people solve and cope with problems in their everyday lives. Clinical social workers also diagnose and treat mental, behavioral, and emotional issues. The anxiety a person feels when diagnosed with cancer might be managed by a social worker in some cancer centers. They, or other designated professionals, can help navigate the complexities of financial and insurance stresses.
- **Spiritual care specialists** identify and support those with spiritual distress or unmet spiritual needs.
- **Smoking cessation specialists** can provide medication and counseling for those who would like to stop using tobacco or nicotine products.
- **A research team** helps to collect research data and coordinate care if you are in a clinical trial. Clinical trials help bring new therapies to patients and advance the treatment for everyone. Consider asking your care team about access to clinical trials.



### Warnings about supplements and drug interactions

You might be asked to stop taking or avoid certain herbal supplements when on a systemic therapy. Some supplements can affect the ability of a drug to do its job. This is called a drug interaction.

**It is critical to speak with your care team about any supplements you may be taking. Some examples include:**

- Turmeric
- Ginkgo biloba
- Green tea extract
- St. John's Wort
- Antioxidants

Certain medicines can also affect the ability of a drug to do its job. Antacids, heart or blood pressure medicine, and antidepressants are just some of the medicines that might interact with a systemic therapy or supportive care medicines given during systemic therapy. Therefore, it is very important to tell your care team about any medicines, vitamins, over-the-counter (OTC) drugs, herbals, or supplements you are taking.

**Bring a list with you to every visit.**

## Systemic therapy

Systemic therapy is the main or primary treatment for metastatic breast cancer. The goal of treatment is to prevent or slow the spread of cancer.

System therapy works throughout the body and includes:

- Chemotherapy
- HER2-targeted therapy
- Other targeted therapies
- Immunotherapy
- Endocrine therapy

Treatment is a combination of therapies that are often given in a specific order (sequential). There are many treatment options. Many factors play a role in how the cancer will respond to treatment. It is important to have regular talks with your care team about your goals for treatment and your treatment plan.

For systemic therapy examples, **see Guide 2.**

## Chemotherapy

Chemotherapy kills fast-dividing cells throughout the body, including cancer cells and some normal cells. More than one chemotherapy may be used to treat invasive breast cancer. When only one drug is used, it's called a single agent. A combination or multi-agent regimen is the use of two or more chemotherapy drugs.

Some chemotherapy drugs are liquids that are infused into a vein or injected under the skin with a needle. Other chemotherapy drugs may be given as a pill that is swallowed.

Some examples of chemotherapy drugs include the following:

- **Anthracyclines** include doxorubicin and epirubicin.
- **Taxanes** include docetaxel, paclitaxel, and albumin-bound paclitaxel.
- **Antimetabolites** include capecitabine, fluorouracil, gemcitabine, and methotrexate.

Most chemotherapy is given in cycles of treatment days followed by days of rest. This allows the body to recover before the next cycle. Cycles vary in length depending on which drugs are used. The number of treatment days per cycle and the total number of cycles given also vary.

## Guide 2

## Systemic therapy examples

|   |   |  |
|---|---|--|
| <b>Chemotherapy examples</b>  | <ul style="list-style-type: none"> <li>• Capecitabine (Xeloda)</li> <li>• Carboplatin</li> <li>• Cisplatin</li> <li>• Cyclophosphamide</li> <li>• Docetaxel (Taxotere)</li> <li>• Doxorubicin (Adriamycin)</li> <li>• Epirubicin (Ellence)</li> </ul>   | <ul style="list-style-type: none"> <li>• Eribulin (Halaven)</li> <li>• Fluorouracil</li> <li>• Gemcitabine</li> <li>• Methotrexate</li> <li>• Paclitaxel</li> <li>• Vinorelbine</li> </ul>   |
| <b>Targeted therapy examples</b>  | Antibody drug conjugate   | <ul style="list-style-type: none"> <li>• Sacituzumab govitecan-hziy (Trodelvy)</li> </ul>  |
|   | CDK4/6 inhibitors   | <ul style="list-style-type: none"> <li>• Abemaciclib (Verzenio)</li> <li>• Palbociclib (Ibrance)</li> <li>• Ribociclib (Kisqali)</li> </ul>  |
|   | PARP inhibitors   | <ul style="list-style-type: none"> <li>• Olaparib (Lynparza)</li> <li>• Talazoparib (Talzenna)</li> </ul>  |
| <b>HER2-targeting therapy (antibody, inhibitor, and conjugate) examples</b> | PIK3CA, AKT1, PTEN, and mTOR inhibitors   | <ul style="list-style-type: none"> <li>• Alpelisib (Piqray)</li> <li>• Capivasertib (Truqap)</li> <li>• Everolimus (Afinitor)</li> </ul>   |
|   | <ul style="list-style-type: none"> <li>• Pertuzumab (Perjeta)</li> <li>• Trastuzumab (Herceptin) or trastuzumab substitutes (biosimilars) such as Kanjinti, Ogivri, Herzuma, Ontruzant, and Trazimera</li> <li>• Ado-trastuzumab emtansine (T-DM1) (Kadcyla)</li> <li>• Fam-trastuzumab deruxtecan-nxki (Enhertu, T-DXd)</li> </ul> | <ul style="list-style-type: none"> <li>• Lapatinib (Tykerb)</li> <li>• Margetuximab-cmkb (Margenza)</li> <li>• Neratinib (Nerlynx)</li> <li>• Tucatinib (Tukysa)</li> <li>• Phesgo as a substitute for combination therapy of trastuzumab with pertuzumab</li> </ul> |
| <b>Immunotherapy</b>  | <ul style="list-style-type: none"> <li>• Pembrolizumab (Keytruda)</li> <li>• Dostarlimab-gxly (Jemperli)</li> </ul>   |  |
| <b>Endocrine therapy</b>  | • Endocrine therapy can be found in Guide 3.  |  |



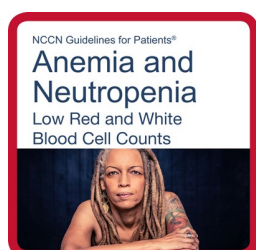
## Antibody drug conjugate

An antibody drug conjugate (ADC) delivers cell-specific chemotherapy. It attaches to a protein found on the outside of the cancer cell, then enters the cell. Once inside the cell, chemotherapy is released. Ado-trastuzumab emtansine (Kadcyla) and fam-trastuzumab deruxtecan-nxki (Enhertu, T-DXd) attach to HER2. Sacituzumab govitecan-hziy (Trodelvy) attaches to Trop-2. ADCs are given in cycles.

## Myeloid growth factors

Certain chemotherapies and antibody drug conjugates can reduce the cells that fight infection. Treatments with myeloid growth factors (MGFs) can help increase the number of white blood cells and prevent infections.

More information on MGFs can be found in the *NCCN Guidelines for Patients: Anemia and Neutropenia*, at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



## HER2-targeted therapy

HER2 is a protein involved in normal cell growth. There might be higher amounts of HER2 in your breast cancer. If this is the case, it is called HER2-positive (HER2+) breast cancer. HER2-targeted therapy is drug therapy that treats HER2+ breast cancer. Some HER2-targeted therapy is given with chemotherapy. However, it might be used alone or in combination with endocrine therapy.

HER2-targeted therapies include:

- **HER2 antibodies** prevent HER2 growth signals from outside the cell. They also increase the attack of immune cells on cancer cells.
- **HER2 inhibitors** stop HER2 growth signals from within the cell.
- **HER2 conjugates or HER2 antibody drug conjugates (ADCs)** deliver cell-specific chemotherapy. They attach directly to HER2s then enter the cell. Once inside, chemotherapy is released.

Your heart will be monitored before and during treatment with HER2-targeted therapy. Tests will measure the left ventricular ejection fraction (LVEF), the amount of blood pumping from the left side of the heart.

## Other targeted therapies

This section is for inhibitors that are different from inhibitors used in HER2-targeted therapy.

### CDK4/6 inhibitors

Cyclin-dependent kinase (CDK) is a cell protein that helps cells grow and divide. For hormone receptor-positive (HR+), HER2-negative cancer, taking a CDK4/6 inhibitor with endocrine therapy may help control cancer longer and improve survival. With all CDK4/6 regimens, those who are premenopausal must also receive ovarian ablation or suppression. CDK4/6 inhibitors include abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali).

### PARP inhibitors

Cancer cells often become damaged. PARP is a cell protein that repairs cancer cells and allows them to survive. Blocking PARP can cause cancer cells to die. Olaparib (Lynparza) and talazoparib (Talzenna) are examples of a PARP inhibitor (PARPi).

### PIK3CA, PTEN, and AKT1 inhibitors

The *PIK3CA* gene is one of the most frequently mutated genes in breast cancers. *PTEN* and *AKT* are also part of this important pathway in cancer cells and can be altered less commonly in breast cancers. A mutation or alteration in these genes can lead to increased growth of cancer cells and resistance to various treatments. Alpelisib (Piqray) is an example of a PIK3CA inhibitor and capivasertib (Truqap) is an AKT1 inhibitor.

### mTOR inhibitors

mTOR is a cell protein that helps cells grow and divide. Endocrine therapy may stop working if mTOR becomes overactive. mTOR inhibitors are used to get endocrine therapy working again.

Everolimus (Afinitor) is an mTOR inhibitor. Most often, it is taken with exemestane. For some, it may be taken with fulvestrant or tamoxifen.

## Immunotherapy

Immunotherapy is a type of systemic treatment that tries to reactivate the immune system against tumor cells. The immune system has many on and off switches. Tumors take advantage of off switches. Two leading off switches are PD-1 and CTLA4. Immunotherapy can block these off switches, which helps the immune system turn on. Immunotherapy can be given alone or with other types of treatment. Pembrolizumab (Keytruda) and dostarlimab-gxly (Jemperli) are immunotherapy examples.

## Endocrine therapy

Endocrine therapy blocks estrogen or progesterone to treat hormone receptor-positive (HR+) breast cancer. The endocrine system is made up of organs and tissues that produce hormones. Hormones are natural chemicals released into the bloodstream.

There are 4 hormones that might be targeted in endocrine therapy:

- **Estrogen** is made mainly by the ovaries, but is also made by other tissues in the body such as fat tissue.
- **Progesterone** is made mainly by the ovaries.
- **Luteinizing hormone-releasing hormone (LHRH)** is made by a part of the brain called the hypothalamus. It tells the ovaries to make estrogen and progesterone and testicles to make testosterone. LHRH is also called gonadotropin-releasing hormone (GnRH).
- **Androgen** is made by the adrenal glands, testicles, and ovaries.

Hormones may cause breast cancer to grow. Endocrine therapy will stop your body from making hormones or it will block what hormones do in the body. This can slow tumor growth or shrink the tumor for a period of time.

Endocrine therapy is sometimes called hormone therapy or anti-estrogen. It is not the same as hormone replacement therapy (HRT) used for menopause. **See Guide 3.**

There is one type of surgical endocrine therapy:

- **Bilateral oophorectomy** is surgery to remove both ovaries.

Other main types of endocrine therapy that might be used for breast cancer:

- **Ovarian ablation** uses radiation to permanently stop the ovaries from making hormones.
- **Ovarian suppression** uses drugs to temporarily stop the ovaries from making hormones. It is achieved with drugs called LHRH agonists. These drugs stop LHRH from being made, which stops the ovaries from making hormones. LHRH agonists include goserelin (Zoladex) and leuprolide (Lupron Depot). These are injected every 4 or 12 weeks.
- **Aromatase inhibitors (AIs)** stop a type of hormone called androgen from changing into estrogen by interfering with an enzyme called aromatase. They do not affect estrogen made by the ovaries. Non-steroidal aromatase inhibitors include anastrozole (Arimidex) and letrozole (Femara). Exemestane (Aromasin) is a steroidal aromatase inhibitor.
- **Estrogen receptor (ER) modulators** or anti-estrogens prevent hormones from binding to receptors.
- **Selective estrogen receptor modulators (SERMs)** block estrogen from attaching to hormone receptors. They include tamoxifen and toremifene (Fareston).
- **Selective estrogen receptor degraders (SERDs)** block and

destroy estrogen receptors. Fulvestrant (Faslodex) and elacestrant (Orserdu) are SERDs.

- **Gonadotropin-releasing hormone (GnRH) agonists** might be used to suppress ovarian hormone or testosterone production.

### Testosterone

For those assigned male at birth whose bodies continue to make testosterone, endocrine therapy includes tamoxifen or an aromatase inhibitor with a testosterone-suppressing therapy.

Endocrine therapy will suppress the production of hormones and affect one's ability to become pregnant during treatment. Those who want to have children in the future should be referred to a fertility specialist before starting endocrine therapy.

### Guide 3 Endocrine therapy types

|  |  |
|--|--|
| <b>Bilateral oophorectomy</b>              | Surgery to remove both ovaries.  |
| <b>Ovarian ablation</b>                    | Radiation to permanently stop the ovaries from making hormones.  |
| <b>Ovarian or testosterone suppression</b> | Drugs to temporarily stop the ovaries or testicles from making hormones such as LHRH and GnRH.   |
| <b>Aromatase inhibitors (AIs)</b>          | Drugs to stop a type of hormone called androgen from changing into estrogen by interfering with an enzyme called aromatase. Non-steroidal AIs include anastrozole (Arimidex) and letrozole (Femara). Exemestane (Aromasin) is a steroidal AI.  |
| <b>Estrogen receptor (ER) modulators</b>   | <ul style="list-style-type: none"> <li>• <b>Selective estrogen receptor modulators (SERMs)</b> block estrogen from attaching to hormone receptors. Tamoxifen and toremifene (Fareston) are SERMs.</li> <li>• <b>Selective estrogen receptor degraders (SERDs)</b> block and destroy estrogen receptors. Fulvestrant (Faslodex) and elacestrant (Orserdu) are SERDs.</li> </ul> |
| <b>Hormones</b>                            | Hormone examples include ethinyl estradiol, fluoxymesterone, and megestrol acetate (Megace).   |

## Premenopause

If you have menstrual periods, you are in premenopause. In premenopause, the ovaries are the main source of estrogen and progesterone.

GnRH agonists may be used to temporarily induce menopause for those in premenopause. A combination of GnRH agonists and tamoxifen or aromatase inhibitors may be considered as endocrine therapy for those in premenopause. Ovarian suppression or ablation can be considered for hormone receptor-positive (HR+) metastatic breast cancer.

## Menopause

In menopause, the ovaries permanently stop producing hormones and menstrual periods stop. Estrogen and progesterone levels are low, but the adrenal glands, liver, and body fat continue to make small amounts of estrogen. If you don't have periods, a test using a blood sample may be used to confirm your status.

Cancer treatment can cause a temporary menopause. If you stopped having periods due to removal of your uterus (hysterectomy) but you still have your ovaries, then you should have your menopausal status confirmed with a blood test. If both ovaries have been removed (with or without your uterus), you are in menopause.

**Standard of care is the best-known way to treat a particular disease based on past clinical trials. There may be more than one treatment regimen that is considered standard of care. Ask your care team what treatment options are available and if a clinical trial might be right for you.**



### Bone-strengthening therapy

Medicines that target the bones may be given to help relieve bone pain or reduce the risk of bone-related problems. Some medicines work by slowing or stopping bone breakdown, while others help increase bone thickness.

When breast cancer spreads to distant sites, it may metastasize in your bones. This puts your bones at risk for injury and disease. Such problems include fractures, bone pain, high calcium levels in the blood, and squeezing (compression) of the spinal cord. Some treatments for breast cancer, like aromatase inhibitors or GnRH agonists, can cause bone loss (osteoporosis), which put you at an increased risk for fractures.

Drugs used to prevent bone loss and fractures:

- Oral bisphosphonates
- Zoledronic acid (Zometa)
- Pamidronate (Aredia)
- Denosumab (Prolia)

Drugs used to treat bone metastases:

- Zoledronic acid (Zometa)
- Pamidronate (Aredia)
- Denosumab (Xgeva) or substitute (biosimilar)

You may be screened for bone weakness (osteoporosis) using a bone mineral density test. This measures how much calcium and other minerals are in your bones. It is also called a dual-energy x-ray absorptiometry (DEXA) scan and is painless. Bone mineral

density tests look for osteoporosis and help predict your risk for bone fractures.

### **Zoledronic acid, pamidronate, and denosumab**

Zoledronic acid, pamidronate, and denosumab are used to prevent bone loss (osteoporosis) and fractures caused by endocrine therapy. Zoledronic acid and denosumab are also used in those with metastatic breast cancer who have bone metastases to help reduce the likelihood of fractures, pain, or other complications arising from cancer in bone. You might have blood tests to monitor kidney function, calcium levels, and magnesium levels. A calcium and vitamin D supplement will likely be recommended by your doctor.

Let your dentist know if you are taking any of these medicines. Also, ask your care team how these medicines might affect your teeth and jaw. Osteonecrosis, or bone tissue death of the jaw, is a rare but serious side effect. Tell your care team about any planned trips to the dentist and surgeries or dental procedures that might also affect the jawbone. It will be important to take care of your teeth and to see a dentist before starting treatment with any of these drugs.

## Clinical trials

A clinical trial is a type of medical research study. After being developed and tested in a laboratory, potential new ways of treating cancer need to be studied in people. If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

### Phases

Most cancer clinical trials focus on treatment. Treatment trials are done in phases.

- **Phase 1 trials** study the dose, safety, and side effects of an investigational drug or treatment approach. They also look for early signs that the drug or approach is helpful.
- **Phase 2 trials** study how well the drug or approach works against a specific type of cancer.
- **Phase 3 trials** test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase 4 trials** study the long-term safety and benefit of an FDA-approved treatment.



## Finding a clinical trial

### In the United States

**NCCN Cancer Centers**

[NCCN.org/cancercenters](https://www.nccn.org/cancercenters)

**The National Cancer Institute (NCI)**

[cancer.gov/about-cancer/treatment/clinical-trials/search](https://www.cancer.gov/about-cancer/treatment/clinical-trials/search)

### Worldwide

**The U.S. National Library of Medicine (NLM)**

[clinicaltrials.gov](https://clinicaltrials.gov)

### Need help finding a clinical trial?

**NCI's Cancer Information Service (CIS)**

1.800.4.CANCER (1.800.422.6237)

[cancer.gov/contact](https://www.cancer.gov/contact)

### Who can enroll?

Every clinical trial has rules for joining, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. These requirements ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

### Informed consent

Clinical trials are managed by a group of experts called a research team. The research team will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss with family, friends, or others whom you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

### Start the conversation

Don't wait for your doctor to bring up clinical trials. Start the conversation and learn about all of your treatment options. If you find a study that you may be eligible for, ask your treatment team if you meet the requirements. If you have already started standard treatment you may not be eligible for certain clinical trials. Try not to be discouraged if you cannot join. New clinical trials are always becoming available.

### Frequently asked questions

There are many myths and misconceptions surrounding clinical trials. The possible benefits and risks are not well understood by many with cancer.

#### Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in cancer clinical trials. It is common to receive either a placebo with a standard treatment, or a new drug with a standard treatment. You will be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll.

#### Do I have to pay to be in a clinical trial?

Rarely. It depends on the study, your health insurance, and the state in which you live. Your treatment team and the research team can help determine if you are responsible for any costs.



## Supportive care

Supportive care will be specific to your needs. Supportive care is health care given to prevent, reduce, and relieve suffering, and to improve quality of life. Supportive care might include pain relief, palliative care, emotional or spiritual support, financial aid, or family counseling. Tell your care team how you are feeling and about any side effects so they can be managed. Supportive care, best supportive care, and palliative care often mean the same thing.

It is very important to take care of yourself by eating well, drinking plenty of fluids, exercising, and doing things that make you feel energized.

### Side effects

All cancer treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person. Some side effects may be harmful to your health. Others may just be unpleasant. Treatment can cause several side effects. Some are very serious.

Ask for a complete list of side effects of your treatments. Also, tell your treatment team about any new or worsening symptoms. There may be ways to help you feel better. There are also ways to prevent some side effects.

### Blood clots

Cancer or cancer treatment can cause blood clots to form. This can block blood flow and oxygen in the body. Blood clots can break loose and travel to other parts of the body causing lung problems (pulmonary embolism

**It is important to tell your care team about all side effects so they can be managed.**

or PE), stroke or other health issues. Venous thromboembolism (VTE) refers to blood clots in the veins.

### Bone health

Breast cancer may spread to your bones. Some breast cancer treatments may also weaken your bones. Both can put your bones at increased risk for injury and disease. Such 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.

Medicine may be given to help relieve bone pain and reduce the risk of other bone problems. Some medicines work by slowing or stopping bone breakdown, while others help increase bone thickness. It is usually recommended that you take calcium and vitamin D with these bone health medicines. Talk to your care team first.

### Diarrhea or constipation

Diarrhea is frequent and watery bowel movements. Your care team will tell you how to manage diarrhea. It is important to drink lots of fluids. Constipation is also common, especially if taking certain pain medicines. Drinking fluids, staying active, and taking medicines for constipation are often recommended.

### Difficulty eating and loss of appetite

Sometimes side effects from surgery, cancer, or other treatments might cause you to feel not hungry or sick to your stomach (nauseated). Healthy eating is important during treatment. It includes eating a balanced diet, eating the right amount of food, and drinking enough fluids. A registered dietitian who is an expert in nutrition and food can help. Speak to your care team if you have trouble eating or maintaining your weight.

### Distress

Depression, anxiety, and sleeping issues are common and are a normal part of cancer diagnosis. Talk to your care team and with those whom you feel most comfortable about how you are feeling. There are services, people, and medicine that can help you. Support and counseling services are available.

### Fatigue

Fatigue is extreme tiredness and inability to function due to lack of energy. Fatigue may be caused by cancer or it may be a side effect of treatment. Let your care team know how you are feeling and if fatigue is getting in the way of doing the things you enjoy. Eating a balanced diet, exercise, yoga, acupuncture, and massage therapy can help. You might be referred to a nutritionist or dietitian to help with fatigue.

### Hair loss

Chemotherapy may cause hair loss (alopecia) all over your body—not just on your scalp. Some chemotherapy drugs are more likely than others to cause hair loss. Dosage might also affect the amount of hair loss. Most of the time, hair loss from chemotherapy is temporary. Hair often regrows 3 to 6 months after treatment ends. Your hair may be a different shade or texture. Scalp cooling (or scalp hypothermia) might help lessen hair loss in those receiving certain types of chemotherapy.

### Low blood cell counts

Some cancer treatments can cause low blood cell counts.

- **Anemia** is a condition where your body does not have enough healthy blood cells, resulting in less oxygen being carried to your cells. You might tire easily if you are anemic.
- **Neutropenia** is a decrease in neutrophils, a type of white blood cell. This puts you at risk for infection.
- **Thrombocytopenia** is a condition where there are not enough platelets found in the blood. This puts you at risk for bleeding.

### Lymphedema

Lymphedema is a condition in which lymph fluid builds up in tissues and causes swelling. It may be caused when part of the lymph system is damaged or blocked, such as during surgery to remove lymph nodes, or by radiation therapy. Cancers that block lymph vessels can also cause lymphedema. Swelling usually develops slowly over time. It may develop during treatment, or it may start years after treatment. If you have lymphedema, you may be referred to an expert in lymphedema management. The swelling may be reduced by exercise, massage, compression devices, and other means.

### Nausea and vomiting

Nausea and vomiting are common side effects of treatment. You will be given medicine to prevent nausea and vomiting or treat it if you start to notice symptoms.

### Neurocognitive or neuropsychological effects

Some treatments can damage the nervous system (neurotoxicity) causing problems with concentration, memory, and thinking. Survivors are at risk for neurotoxicity and might be recommended for neuropsychological testing. Neuropsychology looks at how the health of your brain affects your thinking and behavior. Neuropsychological testing can identify your limits and a health care professional can create a plan to help with these limits.

### Neuropathy

Neuropathy is a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse over time. Neuropathy may be caused by cancer or cancer treatment. Most of the time, neuropathy goes away after treatment.

### Organ issues

Treatment might cause your kidneys, liver, heart, and pancreas to not work as well as they should.

### Pain

Tell your care team about any pain or discomfort. You might meet with a palliative care specialist or with a pain specialist to manage pain.

### QOL

Cancer and its treatment can affect your overall well-being or quality of life (QOL). For more information on quality of life, see *NCCN Guidelines for Patients: Palliative Care* at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



## Survivorship

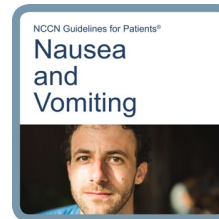
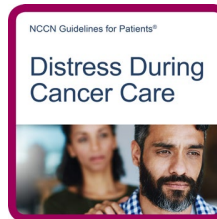
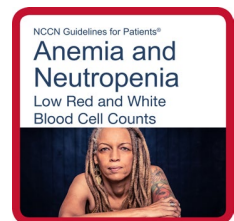
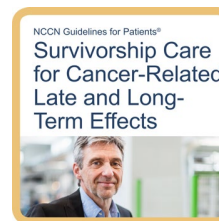
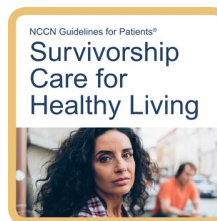
A person is a cancer survivor from the time of diagnosis until the end of life. It is important to keep any follow-up doctor visits and imaging test appointments. Seek good routine medical care.

Tell your care team about any symptoms such as headaches, menstrual spotting between periods or new onset of spotting after menopause (if prior tamoxifen), shortness of breath that you notice with walking, or bone pain. Side effects can be managed. Continue to take all medicine such as endocrine therapy exactly as prescribed and do not miss or skip doses.

For more information on survivorship, see [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.

### Supportive care resources

More information on supportive care is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



## Key points

- Systemic therapy works throughout the body and is the main treatment for metastatic breast cancer. The goal of treatment is to prevent or slow the spread of cancer.
- HER2-targeted therapy is drug therapy that treats HER2+ breast cancer.
- Treatment is a combination of systemic therapies that are often given in a specific order (sequential).
- Endocrine therapy blocks estrogen or progesterone to treat hormone receptor-positive (HR+) breast cancer.
- A clinical trial is a type of research that studies a treatment to see how safe it is and how well it works.
- Supportive care is health care that relieves symptoms caused by treatment and improves quality of life. Supportive care is always given.
- All cancer treatments can cause unwanted health issues called side effects. It is important for you to tell your care team about all your side effects so they can be managed.

### Keep a pain diary

A pain diary is a written record that helps you keep track of when you have pain, how bad it is, what causes it, and what makes it better or worse. Use a pain diary to discuss your pain with your care team. You might be referred to a specialist for pain management.

Include in your pain diary:

- ✓ The time and dose of all medicines
- ✓ When pain starts and ends or lessens
- ✓ Where you feel pain
- ✓ A description of your pain. Is it throbbing, sharp, tingling, shooting, or burning? Is it constant, or does it come and go?
- ✓ Does the pain change at different times of day? When?
- ✓ Does the pain get worse before or after meals? Does certain food or drink make it better?
- ✓ Does the pain get better or worse with activity? What kind of activity?
- ✓ Does the pain keep you from falling asleep at night? Does pain wake you up in the night?
- ✓ A rating of your pain from 0 (no pain) to 10 (worst pain you have ever felt)
- ✓ Does pain get in the way of you doing the things you enjoy?

# 5

## Your treatment options

- 48 HR+ and HER2-
- 50 HER2+
- 51 TNBC
- 52 Monitoring
- 52 Disease progression
- 53 Key points

**Treatment is based on the cancer's hormone receptor (HR) and HER2 status, and any mutations that might be found. Together, you and your care team will choose a treatment plan that is best for you.**

next treatment will depend on your tumor's response to the initial treatment, the types of mutations that are specific to your cancer, and if your situation or health has changed.

Treatment is based on if:

- You are in visceral crisis (organs aren't working as well as they should)
- You had endocrine therapy and if yes, then how long ago and what type

## HR+ and HER2-

In hormone receptor-positive (HR+) breast cancer, estrogen (ER+) and/or progesterone receptors (PR+) are found. When no HER2 receptors are found, then it is HER2-. Initial treatment for ER+ and/or PR+ with HER2- is endocrine therapy plus a CDK4/6 inhibitor (abemaciclib, ribociclib, or palbociclib). The

### Visceral crisis

When cancer within internal organs causes severe symptoms or causes organs to stop working as they should, it is called a visceral crisis. If you are in visceral crisis, the goal is to get you stable. This may be accomplished by using chemotherapy. Other systemic therapies might also be used.

**Your preferences about treatment are always important. Talk to your care team and make your wishes known.**



**No visceral crisis**

If you are not in visceral crisis, then endocrine therapy often combined with CDK4/6 inhibitors is usually given. Later on, systemic therapy specific to HER2- breast cancer will be given. Those who are premenopausal might have ovarian suppression or ablation in addition to endocrine therapy. Systemic therapy options (including endocrine therapy) can be found in **Guide 4**.

Sometimes, HR+ cancer does not respond or stops responding to endocrine therapy called endocrine refractory. If this happens, chemotherapy or antibody drug conjugates (ADCs) will be given. If an ER+ tumor is resistant to endocrine therapy, then TNBC systemic therapy options found on page 53 will be considered.

| <b>Guide 4</b><br><b>Systemic therapy options: HR+ and HER2- without visceral crisis</b> |   |
|--|---|
| <b>Preferred first-line options</b>  | <ul style="list-style-type: none"> <li>• Aromatase inhibitor with CDK4/6 inhibitor</li> <li>• Fulvestrant with CDK4/6 inhibitor</li> <li>• For germline <i>BRCA1</i> or <i>BRCA2</i> mutations, olaparib or talazoparib</li> </ul>  |
| <b>Preferred second-line and next-line options</b>                                       | <ul style="list-style-type: none"> <li>• Fulvestrant with CDK4/6 inhibitor if CDK4/6 inhibitor not used before</li> <li>• For <i>PIK3CA</i>, <i>AKT1</i>, or <i>PTEN</i> mutation, alpelisib with fulvestrant or capivasertib with fulvestrant</li> <li>• Everolimus with endocrine therapy (exemestane, fulvestrant, or tamoxifen)</li> <li>• For germline <i>BRCA1</i> or <i>BRCA2</i> mutations, olaparib or talazoparib if not used before</li> </ul> |
| <b>Other recommended</b>   | <ul style="list-style-type: none"> <li>• Selective ER down-regulator (fulvestrant). For an <i>ESR1</i> mutation, elacestrant.</li> <li>• Selective ER down-regulator with a non-steroidal aromatase inhibitor</li> <li>• Non-steroidal aromatase inhibitor (anastrozole or letrozole)</li> <li>• Selective ER modulator (tamoxifen)</li> <li>• Steroidal aromatase inactivator (exemestane)</li> </ul>  |
| <b>Used in some cases</b>  | <ul style="list-style-type: none"> <li>• Megestrol acetate</li> <li>• Ethinyl estradiol</li> <li>• Abemaciclib</li> <li>• For <i>NTRK</i> fusion, larotrectinib or entrectinib</li> <li>• For MSI-H/dMMR, pembrolizumab or dostarlimab-gxly</li> <li>• For TMB-H, pembrolizumab</li> <li>• For <i>RET</i> fusion, selpercatinib</li> </ul>  |
| <b>Notes</b>   | <ul style="list-style-type: none"> <li>• Those who are in premenopause or perimenopause might have ovarian suppression or ablation in addition to endocrine therapy.</li> </ul>   |



## HER2+

When HER2 receptors are found (amplified or overexpressed), the cancer is HER2-positive (HER2+). It is treated with HER2-targeted therapy and other systemic therapies as found in **Guide 5**.

Those with HER2+ and HR+ disease may also benefit from treatment with endocrine therapy. These can include aromatase inhibitors (AIs), tamoxifen, or fulvestrant. Those who are premenopausal might have ovarian suppression or ablation in addition to endocrine therapy.

### Guide 5 HER2-targeted therapy options

|                            |  |
|----------------------------|--|
| <b>First-line options</b>  | <ul style="list-style-type: none"> <li>• Pertuzumab, trastuzumab, and docetaxel (preferred)</li> <li>• Pertuzumab, trastuzumab, and paclitaxel (preferred)</li> </ul>  |
| <b>Second-line options</b> | <ul style="list-style-type: none"> <li>• Fam-trastuzumab deruxtecan-nxki (T-DXd) (preferred)</li> </ul>  |
| <b>Third-line options</b>  | <ul style="list-style-type: none"> <li>• Tucatinib, trastuzumab, and capecitabine (preferred)</li> <li>• Ado-trastuzumab emtansine (T-DM1)</li> </ul>  |
| <b>Next-line options</b>   | <ul style="list-style-type: none"> <li>• Trastuzumab and docetaxel or vinorelbine</li> <li>• Trastuzumab and paclitaxel with or without carboplatin</li> <li>• Capecitabine with trastuzumab or lapatinib</li> <li>• Trastuzumab and lapatinib (without cytotoxic therapy)</li> <li>• Trastuzumab with other chemotherapy agents</li> <li>• Neratinib and capecitabine</li> <li>• Margetuximab-cmkb with chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)</li> <li>• Targeted therapy might be used if specific mutations are found</li> </ul> |
| <b>Notes</b>               | <ul style="list-style-type: none"> <li>• An FDA-approved biosimilar or substitute might be used for trastuzumab</li> </ul>   |

## TNBC

Triple-negative breast cancer (TNBC) is estrogen receptor-negative (ER-), progesterone receptor-negative (PR-), and HER2-negative (HER2-).

There are many variations within TNBC. It is a group of diseases that we are learning more about all the time. Treatment is usually chemotherapy, and sometimes immunotherapy or targeted therapy.

TNBC systemic therapy options are found in **Guide 6**.

### Guide 6

#### Systemic therapy options: TNBC

|                                  |  |
|----------------------------------|--|
| <p><b>Preferred options</b></p>  | <ul style="list-style-type: none"> <li>• Anthracyclines such as doxorubicin or liposomal doxorubicin</li> <li>• Taxanes such as paclitaxel</li> <li>• Antimetabolites such as capecitabine or gemcitabine</li> <li>• Microtubule inhibitors such as vinorelbine or eribulin</li> <li>• For PD-L1–positive with a combined positive score (CPS) of 10 or more, pembrolizumab with chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine with carboplatin)</li> <li>• For germline <i>BRCA1</i> or <i>BRCA2</i> mutations, olaparib, talazoparib, cisplatin, or carboplatin</li> <li>• Sacituzumab govitecan-hziy</li> <li>• Fam-trastuzumab deruxtecan-nxki (T-DXd)</li> </ul> |
| <p><b>Other recommended</b></p>  | <ul style="list-style-type: none"> <li>• Cyclophosphamide</li> <li>• Docetaxel</li> <li>• Albumin-bound paclitaxel</li> <li>• Epirubicin</li> <li>• Ixabepilone</li> </ul>   |
| <p><b>Used in some cases</b></p> | <ul style="list-style-type: none"> <li>• Doxorubicin and cyclophosphamide (AC)</li> <li>• Epirubicin and cyclophosphamide (EC)</li> <li>• Cyclophosphamide, methotrexate, and fluorouracil (CMF)</li> <li>• Docetaxel and capecitabine</li> <li>• Gemcitabine and paclitaxel (GT)</li> <li>• Gemcitabine and carboplatin</li> <li>• Carboplatin and paclitaxel or albumin-bound paclitaxel</li> </ul>  |
| <p><b>Notes</b></p>              | <ul style="list-style-type: none"> <li>• Alternative taxanes (such as docetaxel, paclitaxel, albumin-bound paclitaxel) might be substituted in some cases</li> <li>• Targeted therapy might be used if specific mutations are found</li> </ul>   |

## Monitoring

You will be monitored throughout treatment. Monitoring includes physical exams, blood tests, imaging scans, and tumor testing (if needed). Monitoring is used to see if your cancer is responding to treatment, is stable, or is progressing.

Monitoring is important. You will be monitored for symptoms caused by cancer, such as pain from bone metastases. The goal of monitoring is to determine if treatment provides benefit. Benefit includes keeping cancer stable.

It is important to keep follow-up visits and imaging test appointments. Seek good routine medical care. Continue to take all medicines as prescribed.

## Disease progression

Disease progression is defined by the growth or spread of cancer as shown on imaging tests or physical exam of the tumor.

Most people will be able to have many rounds (lines) of systemic therapy. After multiple lines of systemic therapy, it might be time to consider ending systemic therapy and focus on supportive care. Supportive care is sometimes called palliative care. Systemic therapy has side effects that may impact your quality of life. If you and your care team decide to stop systemic therapy, supportive care will continue.

Your preferences and goals of treatment are always important. The goals of treatment can be thought of as curative or palliative. This means that treatment aims to cure or in

the case of palliative care, treatment aims to preserve function and/or maintain comfort. Goals of treatment may change over time. Talk with your care team and make your wishes known.

### **Progression or toxicity on endocrine therapy**

First-line therapy is the first treatment given. If cancer progresses while on first-line endocrine therapy, then you will likely switch to a different endocrine therapy. Targeted therapy might be added. Sometimes, your cancer becomes resistant to endocrine therapy. If this happens, endocrine therapy will be stopped and a systemic therapy will be used.

### **Cancer progresses on systemic therapy with HER2-targeted therapy**

If cancer progresses while you are on HER2-targeted therapy, then another line of therapy is an option. In this case, a different HER2-targeted therapy will be given.

## Key points

- In hormone receptor-positive (HR+) cancer, hormone receptors for estrogen (ER+) and/or progesterone (PR+) are found. In HER2-positive (HER2+) cancer, HER2 receptors are found (amplified or overexpressed).
- Initial treatment for ER+ and/or PR+ with HER2- is endocrine therapy plus a CDK4/6 inhibitor. Later on, systemic therapy specific to HER2- breast cancer will be given.
- HER2+ cancer is treated with HER2-targeted therapy and other systemic therapies.
- Those with HER2+ and HR+ disease may also benefit from treatment with endocrine therapy.
- In triple-negative breast cancer (TNBC), receptors for estrogen, progesterone, and HER2 are not found. TNBC is usually treated with chemotherapy and sometimes immunotherapy or targeted therapy.
- Before each new line of therapy, you and your care team will discuss the risks and benefits of treatment, your overall health, and your goals for treatment.

# 6

## Making treatment decisions

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- 55 Questions to ask
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**It's important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your care team.**

## It's your choice

In shared decision-making, you and your team share information, discuss the options, and agree on a treatment plan. It starts with an open and honest conversation between you and your care team.

Treatment decisions are very personal. What is important to you may not be important to someone else. Some things that may play a role in your decision-making:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments
- Your feelings about pain or side effects
- Cost of treatment, travel to treatment centers, and time away from school or work
- Quality of life and length of life
- How active you are and the activities that are important to you

Think about what you want from treatment. Discuss openly the risks and benefits of specific treatments and procedures. Weigh options and share concerns with your

care team. If you take the time to build a relationship with your care team, it will help you feel supported when considering options and making treatment decisions.

## Second opinion

It is normal to want to start treatment as soon as possible. While cancer can't be ignored, there is time to have another doctor review your test results and suggest a treatment plan. This is called getting a second opinion, and it's a normal part of cancer care. Even doctors get second opinions!

Things you can do to prepare:

- Check with your insurance company about its rules on second opinions. There may be out-of-pocket costs to see doctors who are not part of your insurance plan.
- Make plans to have copies of all your records sent to the doctor you will see for your second opinion.

## Support groups

Many people diagnosed with cancer find support groups to be helpful. Support groups often include people at different stages of treatment. Some people may be newly diagnosed, while others may be finished with treatment. If your hospital or community doesn't have support groups for people with cancer, check out the websites listed in this book.

## Questions to ask

Possible questions to ask your care team are listed on the following pages. Feel free to use these questions or come up with your own.

















## Resources

**Bag It**

[BagItCancer.org](http://BagItCancer.org)

**Breast Cancer Alliance**

[Breastcanceralliance.org](http://Breastcanceralliance.org)

**Breastcancer.org**

[Breastcancer.org](http://Breastcancer.org)

**CanCare**

[Cancare.org](http://Cancare.org)

**CancerCare**

[Cancercare.org](http://Cancercare.org)

**Cancer Hope Network**

[cancerhopenetwork.org](http://cancerhopenetwork.org)

**DiepC Foundation**

[diepcfoundation.org](http://diepcfoundation.org)

**FORCE: Facing Our Risk of Cancer  
Empowered**

[facingourrisk.org](http://facingourrisk.org)

**GPAC Global Patient Advocacy Coalition**

[GPACunited.org](http://GPACunited.org)

**Inflammatory Breast Cancer Research  
Foundation**

[ibcresearch.org](http://ibcresearch.org)

**Lobular Breast Cancer Alliance**

[lobularbreastcancer.org](http://lobularbreastcancer.org)

**National Coalition for Cancer Survivorship**

[canceradvocacy.org](http://canceradvocacy.org)

**Sharsheret**

[sharsheret.org](http://sharsheret.org)

**Triage Cancer**

[Triagecancer.org](http://Triagecancer.org)

**Unite for HER**

[uniteforher.org](http://uniteforher.org)

**Young Survival Coalition**

[youngsurvival.org](http://youngsurvival.org)



## Words to know

### **anti-estrogen**

A drug that stops estrogen from attaching to cells.

### **aromatase inhibitor (AI)**

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

### **axillary lymph node (ALN)**

A small disease-fighting structure that is near the armpit (axilla).

### **bilateral oophorectomy**

An operation that removes both ovaries.

### **biopsy**

A procedure that removes fluid or tissue samples to be tested for a disease.

### **bone mineral density**

A test that measures the strength of bones.

### **bone scan**

A test that makes pictures of bones to assess for health problems.

### **cancer stage**

A rating of the outlook of a cancer based on its growth and spread.

### **carcinoma**

A cancer of cells that line the inner or outer surfaces of the body.

### **chest wall**

The layer of muscle, bone, and fat that protects the vital organs.

### **clinical breast exam (CBE)**

Touching of a breast by a health expert to feel for diseases.

### **clinical trial**

A type of research that assesses health tests or treatments.

### **contrast**

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

### **core needle biopsy (CNB)**

A procedure that removes tissue samples with a hollow needle. Also called core biopsy.

### **deoxyribonucleic acid (DNA)**

A chain of chemicals in cells that contains coded instructions for making and controlling cells.

### **duct**

A tube-shaped structure through which milk travels to the nipple.

### **ductal carcinoma**

A cancer derived from cells that line small tube-shaped vessels.

### **endocrine therapy**

A cancer treatment that stops the making or action of estrogen. Also called hormone therapy.

### **estrogen**

A hormone that plays a role in breast development.

### **estrogen receptor (ER)**

A protein inside cells that binds to estrogen.

### **estrogen receptor-negative (ER-)**

A type of breast cancer that doesn't use estrogen to grow.



## Words to know

### **estrogen receptor-positive (ER+)**

A type of breast cancer that uses estrogen to grow.

### **fine-needle aspiration (FNA)**

A procedure that removes tissue samples with a very thin needle.

### **gene**

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

### **genetic counseling**

Expert guidance on the chance for a disease that is passed down in families.

### **hereditary breast cancer**

Breast cancer likely caused by abnormal genes passed down from biological parent to child.

### **histology**

The structure of cells, tissue, and organs as viewed under a microscope.

### **hormone**

A chemical in the body that triggers a response from cells or organs.

### **hormone receptor-negative cancer (HR-)**

Cancer cells that don't use hormones to grow.

### **hormone receptor-positive cancer (HR+)**

Cancer cells that use hormones to grow.

### **human epidermal growth factor receptor 2 (HER2)**

A protein on the surface of a cell that sends signals for the cell to grow.

### **imaging test**

A test that makes pictures (images) of the insides of the body.

### **immunohistochemistry (IHC)**

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

### **infraclavicular**

The area right below the collarbone.

### **in situ hybridization (ISH)**

A lab test of the number of a gene.

### **internal mammary**

The area along the breastbone.

### **invasive breast cancer**

The growth of breast cancer into the breast's supporting tissue (stroma).

### **lobular carcinoma**

A breast cancer that started in cells that line the breast glands (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.

### **lymphadenopathy**

Lymph nodes that are abnormal in size or consistency.

### **lymphedema**

Swelling in the body caused by a buildup of fluid called lymph.

### **lymph node**

A small, bean-shaped disease-fighting structure.

### **magnetic resonance imaging (MRI)**

A test that uses radio waves and powerful magnets to make pictures of the insides of the body.

### **mammogram**

A picture of the insides of the breast that is made using x-rays.

## Words to know

### **medical oncologist**

A doctor who is an expert in cancer drugs.

### **menopause**

12 months after the last menstrual period.

### **mutation**

An abnormal change in DNA.

### **nipple-areola complex (NAC)**

The ring of darker breast skin is called the areola. The raised tip within the areola is called the nipple.

### **palpable adenopathy**

Lymph nodes that feel abnormal in size or consistency.

### **pathologist**

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

### **perimenopause**

Refers to the time during which your body makes the natural transition to menopause.

### **positron emission tomography (PET)**

A test that uses radioactive material to see the shape and function of body parts.

### **postmenopause**

The state of having no more menstrual periods.

### **premenopause**

The state of having menstrual periods.

### **primary tumor**

The first mass of cancer cells.

### **progesterone**

A hormone involved in sexual development, periods, and pregnancy.

### **prognosis**

The likely course and outcome of a disease based on tests.

### **selective estrogen receptor degrader (SERD)**

A drug that blocks and destroys estrogen receptors.

### **selective estrogen receptor modulator (SERM)**

A drug that blocks the effect of estrogen inside cells.

### **side effect**

An unhealthy or unpleasant physical or emotional response to treatment.

### **standard of care**

The best-known way to treat a particular disease based on past clinical trials. There may be more than one treatment regimen that is considered standard of care.

### **supportive care**

Health care that includes symptom relief but not cancer treatment. Also called palliative care or best supportive care.

### **supraclavicular**

The area right above the collarbone.

### **systemic therapy**

Drug treatment that works throughout the body.

### **triple-negative breast cancer (TNBC)**

A breast cancer that does not use hormones or the HER2 protein to grow.

### **ultrasound**

A test that uses sound waves to take pictures of the inside of the body.

### **visceral crisis**

When organs aren't working as well as they should.

# NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Version 2.2024. It was adapted, reviewed, and published with help from the following people:

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# NCCN Cancer Centers

**Abramson Cancer Center**  
at the University of Pennsylvania  
Philadelphia, Pennsylvania  
800.789.7366 • [pennmedicine.org/cancer](http://pennmedicine.org/cancer)

**Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer Center and  
Cleveland Clinic Taussig Cancer Institute**  
Cleveland, Ohio  
UH Seidman Cancer Center  
800.641.2422 • [uhhospitals.org/services/cancer-services](http://uhhospitals.org/services/cancer-services)  
CC Taussig Cancer Institute  
866.223.8100 • [my.clevelandclinic.org/departments/cancer](http://my.clevelandclinic.org/departments/cancer)  
Case CCC  
216.844.8797 • [case.edu/cancer](http://case.edu/cancer)

**City of Hope National Medical Center**  
Duarte, California  
800.826.4673 • [cityofhope.org](http://cityofhope.org)

**Dana-Farber/Brigham and Women's Cancer Center |  
Mass General Cancer Center**  
Boston, Massachusetts  
877.442.3324 • [youhaveus.org](http://youhaveus.org)  
617.726.5130 • [massgeneral.org/cancer-center](http://massgeneral.org/cancer-center)

**Duke Cancer Institute**  
Durham, North Carolina  
888.275.3853 • [dukecancerinstitute.org](http://dukecancerinstitute.org)

**Fox Chase Cancer Center**  
Philadelphia, Pennsylvania  
888.369.2427 • [foxchase.org](http://foxchase.org)

**Fred & Pamela Buffett Cancer Center**  
Omaha, Nebraska  
402.559.5600 • [unmc.edu/cancercenter](http://unmc.edu/cancercenter)

**Fred Hutchinson Cancer Center**  
Seattle, Washington  
206.667.5000 • [fredhutch.org](http://fredhutch.org)

**Huntsman Cancer Institute at the University of Utah**  
Salt Lake City, Utah  
800.824.2073 • [healthcare.utah.edu/huntsmancancerinstitute](http://healthcare.utah.edu/huntsmancancerinstitute)

**Indiana University Melvin and Bren Simon  
Comprehensive Cancer Center**  
Indianapolis, Indiana  
888.600.4822 • [www.cancer.iu.edu](http://www.cancer.iu.edu)

**Mayo Clinic Comprehensive Cancer Center**  
Phoenix/Scottsdale, Arizona  
Jacksonville, Florida  
Rochester, Minnesota  
480.301.8000 • Arizona  
904.953.0853 • Florida  
507.538.3270 • Minnesota  
[mayoclinic.org/cancercenter](http://mayoclinic.org/cancercenter)

**Memorial Sloan Kettering Cancer Center**  
New York, New York  
800.525.2225 • [mskcc.org](http://mskcc.org)

**Moffitt Cancer Center**  
Tampa, Florida  
888.663.3488 • [moffitt.org](http://moffitt.org)

**O'Neal Comprehensive Cancer Center at UAB**  
Birmingham, Alabama  
800.822.0933 • [uab.edu/onealcancercenter](http://uab.edu/onealcancercenter)

**Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University**  
Chicago, Illinois  
866.587.4322 • [cancer.northwestern.edu](http://cancer.northwestern.edu)

**Roswell Park Comprehensive Cancer Center**  
Buffalo, New York  
877.275.7724 • [roswellpark.org](http://roswellpark.org)

**Siteman Cancer Center at Barnes-Jewish Hospital  
and Washington University School of Medicine**  
St. Louis, Missouri  
800.600.3606 • [siteman.wustl.edu](http://siteman.wustl.edu)

**St. Jude Children's Research Hospital/  
The University of Tennessee Health Science Center**  
Memphis, Tennessee  
866.278.5833 • [stjude.org](http://stjude.org)  
901.448.5500 • [uthsc.edu](http://uthsc.edu)

**Stanford Cancer Institute**  
Stanford, California  
877.668.7535 • [cancer.stanford.edu](http://cancer.stanford.edu)

**The Ohio State University Comprehensive Cancer Center -  
James Cancer Hospital and Solove Research Institute**  
Columbus, Ohio  
800.293.5066 • [cancer.osu.edu](http://cancer.osu.edu)

**The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins**  
Baltimore, Maryland  
410.955.8964  
[www.hopkinskimmelcancercenter.org](http://www.hopkinskimmelcancercenter.org)

**The UChicago Medicine Comprehensive Cancer Center**  
Chicago, Illinois  
773.702.1000 • [uchicagomedicine.org/cancer](http://uchicagomedicine.org/cancer)

**The University of Texas MD Anderson Cancer Center**  
Houston, Texas  
844.269.5922 • [mdanderson.org](http://mdanderson.org)

**UC Davis Comprehensive Cancer Center**  
Sacramento, California  
916.734.5959 • 800.770.9261  
[health.ucdavis.edu/cancer](http://health.ucdavis.edu/cancer)

**UC San Diego Moores Cancer Center**  
La Jolla, California  
858.822.6100 • [cancer.ucsd.edu](http://cancer.ucsd.edu)

**UCLA Jonsson Comprehensive Cancer Center**  
Los Angeles, California  
310.825.5268 • [uclahealth.org/cancer](http://uclahealth.org/cancer)

UCSF Helen Diller Family  
Comprehensive Cancer Center  
San Francisco, California  
800.689.8273 • [cancer.ucsf.edu](http://cancer.ucsf.edu)

University of Colorado Cancer Center  
Aurora, Colorado  
720.848.0300 • [coloradocancercenter.org](http://coloradocancercenter.org)

University of Michigan Rogel Cancer Center  
Ann Arbor, Michigan  
800.865.1125 • [rogelcancercenter.org](http://rogelcancercenter.org)

University of Wisconsin Carbone Cancer Center  
Madison, Wisconsin  
608.265.1700 • [uwhealth.org/cancer](http://uwhealth.org/cancer)

UT Southwestern Simmons  
Comprehensive Cancer Center  
Dallas, Texas  
214.648.3111 • [utsouthwestern.edu/simmons](http://utsouthwestern.edu/simmons)

Vanderbilt-Ingram Cancer Center  
Nashville, Tennessee  
877.936.8422 • [vicc.org](http://vicc.org)

Yale Cancer Center/Smilow Cancer Hospital  
New Haven, Connecticut  
855.4.SMILOW • [yalecancercenter.org](http://yalecancercenter.org)



### **We want your feedback!**

**Our goal is to provide helpful and  
easy-to-understand information  
on cancer.**

**Take our survey to let us know  
what we got right and what we  
could do better.**

**[NCCN.org/patients/feedback](http://NCCN.org/patients/feedback)**



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**BSES MG Hospital (Andheri):**

**9 am to 10 am (Monday to Friday)**

**Nanavati Max Hospital (Vile Parle):**

**10 am to 12 pm (Monday to Saturday)**

**S. L. Raheja Hospital (Mahim):**

**12 pm to 4 pm (Monday to Saturday)**

**Suvarna Hospital (Borivali):**

**5 pm to 6 pm (Monday and Friday)**

**Sushrut Hospital (Chembur):**

**By appointment**

**Hinduja Hospital (Khar): By**

**appointment**

**Galaxy Healthcare (Borivali): By**

**appointment**



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