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HER2- ADVANCED BREAST CANCER

and HER2-Low

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HER2- ADVANCED BREAST CANCER

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Knowledge empowers you when making treatment decisions

Being told you have advanced or metastatic breast cancer has likely come as a shock. Start with learning about the type of breast cancer you have. Understanding more about it will help you begin to make a plan for moving forward alongside your multidisciplinary health care team. Although a cure is not yet available for metastatic breast cancer, research advances are making it possible for more people with this diagnosis to live longer, higher-quality lives.

ADVANCED VS. METASTATIC

Advanced breast cancer is a diagnosis that applies to locally advanced and/or metastatic disease. It may be detected upon diagnosis (referred to as de novo). It may also be found in a follow-up exam after treatment for early-stage breast cancer or because of new symptoms.

- **Locally advanced** describes breast cancer that is in the breast and/or axilla (underarm) that can be seen on imaging. This is typically Stage III disease and, if no obvious or overt metastatic disease is detected on body imaging such as CT, PET or bone scans, it is treated with curative intent.
- **Metastatic** breast cancer describes malignant (cancerous) cells that began in breast tissue but have broken away and traveled through the bloodstream or lymph vessels to one or more distant sites in the body, and the disease involvement in other organs is visible on body imaging such as CT, PET or bone scans. When this occurs, the cancer is staged as or upgraded to Stage IV.

Multiple subtypes of breast cancer have been identified, and researchers continue to find differences in the ways these breast cancers grow and respond to treatment. These are some of the types of breast cancer that have the potential for metastasizing:

- Invasive ductal carcinoma, the most common, starts in the lining of the milk ducts in the breast when abnormal cells grow out of control, forming a mass that spreads from the ducts to normal breast tissue.
- Invasive lobular carcinoma, the second most common, starts in the lobules (glands that make milk) and spreads to surrounding normal tissue.
- Inflammatory breast cancer (IBC) is a rare, very aggressive form that grows rapidly and is automatically classified as Stage III or Stage IV, depending on whether it has spread. IBC tends to spread quickly, making it challenging to treat. Most cases are invasive ductal carcinomas in which cancer cells block the lymph vessels, causing the lymph fluid to build up. This results in breast tenderness, swelling, redness and pain. Breast skin can thicken and appear pitted like an orange peel.

Your experience with a metastatic diagnosis will be different than before if you were previously diagnosed at an earlier stage when there was an end date to active treatment. The goal of treating metastatic breast cancer is to slow the cancer's growth, or stop its progression, for as long as possible while keeping side effects manageable.

STAGING AND CLASSIFICATION

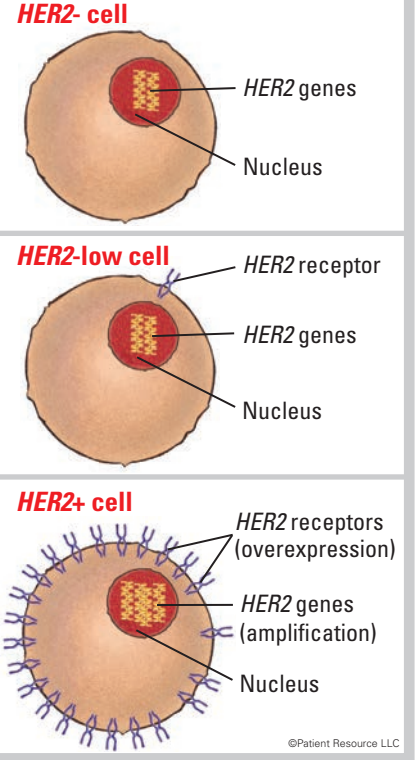
The tumor, node and metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) is used to stage and classify breast cancer (see Tables 1 and 2). The system includes the tumor (T) size, cancer cells found in nearby lymph nodes (N) and cancer that has metastasized (M), or spread, to other parts of the body, such as the bones, brain, liver or lungs.

Patients with advanced breast cancer generally need a biopsy of the metastatic site(s) to confirm the diagnosis as breast cancer and not as a second different type of cancer, and

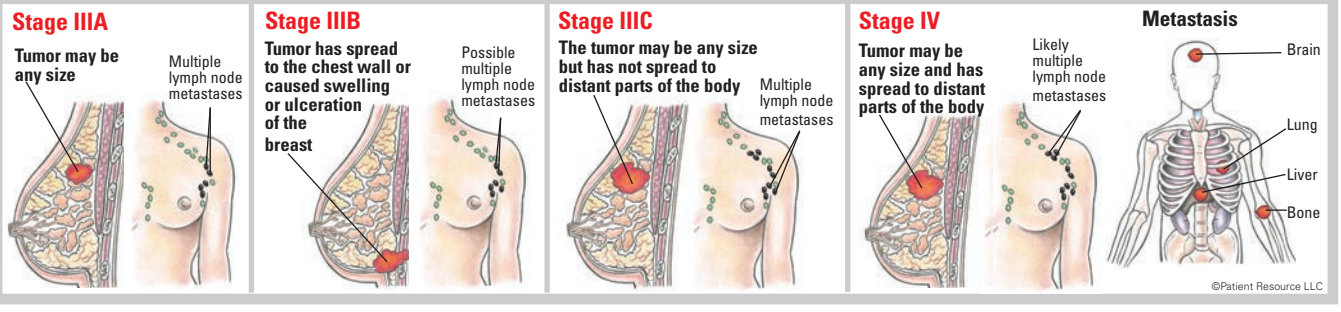
FIGURE 1

HER2 BREAST CELLS

If a breast cell has no or very few *HER2* receptors, it is considered *HER2-* or *HER2-low*. When a breast cell has more than two copies of the *HER2* gene or more receptors than normal, it is considered *HER2+*.



ILLUSTRATED STAGES OF ADVANCED BREAST CANCER



to assess biomarkers on the breast cancer that has spread to distant sites. A second primary breast cancer is not metastatic breast cancer and usually represents a new breast cancer requiring repeat diagnostic work-up (including biomarker testing) followed by treatment.

UNDERSTANDING BIOMARKERS

Determining your biomarker status is a key part of diagnosing breast cancer. Biomarkers are substances such as genes or molecules that can be measured in the blood, plasma, urine, cerebrospinal fluid or other body fluids or tissues with genomic testing. They are produced by cancer cells or other cells of the body in response to cancer. Genomic testing is a laboratory test used to detect biomarkers on the initial tumor biopsy material.

The most common biomarkers in breast cancer are the hormone receptors estrogen (*ER*) and progesterone (*PR*), as well as the genes and receptors for human epidermal growth factor receptor-2 (*HER2*). Every person has *ER, PR* and *HER2* receptors, but the levels of each can change on the cancer cells. Each can be positive (*ER+*, *PR+* and *HER2+*) or negative (*ER-*, *PR-* and *HER2-*), or they may occur in various combinations. These biomarkers are tested for during the initial diagnostic process on a biopsy sample.

Hormone receptor positive (*HR+*) breast cancers indicate that both estrogen and progesterone are supporting the cancer's growth. If it is hormone receptor negative (*HR-*), these hormones are not driving the cancer. It is also possible that the cancer is being driven by only one of the hormones, such as *ER+/PR-* or *ER-/PR+*.

Normal breast cells contain two copies of the *HER2* gene, which makes *HER2* proteins that are receptors on the surface of a cell. The *HER2* genes and protein receptors help manage how a breast cell grows, divides and repairs itself. When a breast cell has more than two copies of the *HER2* gene or more receptors than normal, it is considered *HER2* positive (*HER2+*) breast cancer (flip this guide over to read more about *HER2+* breast cancer). If the breast cell has no or very few *HER2* receptors, it is considered *HER2* negative (*HER2-*) or *HER2*-low.

To determine the cancer's *HER2* status, a tissue biopsy sample will be examined in a laboratory. The two tests that may be used are immunohistochemistry (IHC), which looks for biomarkers, and in situ hybridization (ISH), which looks at genes or chromosomes in a cell.

IHC is typically performed first. It measures the amount of *HER2* proteins on the surface of breast cancer cells. A score is given to determine the *HER2* status, which is measured with a scale of 0 to 3+.

- A score of 0 or 1+ means the cancer is *HER2-*.
- A score of 1+ or 2+ without *HER2* gene amplification is considered borderline

TABLE 1

STAGES OF ADVANCED BREAST CANCER

Stage	TNM classification
IIIA	T0-T3, N2, M0 // T3, N1, M0
IIIB	T4, N0-N2, M0
IIIC	Any T, N3, M0
IV	Any T, Any N, M1

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science+Business Media.

TABLE 2

AJCC TNM SYSTEM FOR CLASSIFYING BREAST CANCER

Classification	Definition
Tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis (DCIS)	Ductal carcinoma in situ.
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma (tissue).
T1 **T1mi** **T1a** **T1b** **T1c**	Tumor ≤ (not more than) 20 mm in greatest dimension. Tumor ≤ (not more than) 1 mm in greatest dimension. Tumor > (more than) 1 mm but ≤ (not more than) 5 mm in greatest dimension. Tumor > (more than) 5 mm but ≤ (not more than) 10 mm in greatest dimension. Tumor > (more than) 10 mm but ≤ (not more than) 20 mm in greatest dimension.
T2	Tumor > (more than) 20 mm but ≤ (not more than) 50 mm in greatest dimension.
T3	Tumor > (more than) 50 mm in greatest dimension.
T4 **T4a** **T4b** **T4c** **T4d**	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules). Extension to the chest wall. Ulceration and/or ipsilateral (on the same side) macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma. Both T4a and T4b are present. Inflammatory carcinoma.
Node (N)	
pNX	Regional lymph nodes cannot be assessed.
pN0 **pN0(i+)** **pN0(mol+)**	No regional lymph node metastasis identified or ITCs (isolated tumor cells) only. ITCs (isolated tumor cells) only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s). Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs (isolated tumor cells) detected.
pN1 **pN1mi** **pN1a** **pN1b** **pN1c**	Micrometastases; or metastases in 1-3 axillary (armpit) lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy. Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm). Metastases in 1-3 axillary (armpit) lymph nodes, at least one metastasis larger than 2.0 mm. Metastases in ipsilateral (on the same side) internal mammary sentinel nodes, excluding ITCs (isolated tumor cells). pN1a and pN1b combined.
pN2 **pN2a** **pN2b**	Metastases in 4-9 axillary (armpit) lymph nodes; or positive ipsilateral (on the same side) internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases. Metastases in 4-9 axillary (armpit) lymph nodes (at least one tumor deposit larger than 2.0 mm). Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary (armpit) nodes.
pN3 **pN3a** **pN3b** **pN3c**	Metastases in 10 or more axillary (armpit) lymph nodes; *or* in infraclavicular (below the clavicle) (Level III axillary) lymph nodes; *or* positive ipsilateral (on the same side) internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes; *or* in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; *or* in ipsilateral supraclavicular (above the clavicle) lymph nodes. Metastases in 10 or more axillary (armpit) lymph nodes (at least one tumor deposit larger than 2.0 mm); *or* metastases to the infraclavicular (below the clavicle) (Level III axillary) lymph nodes. pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b. Metastases in ipsilateral (on the same side) supraclavicular (above the clavicle) lymph nodes.
Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with N0 further resection of nodes.	
Metastasis (M)	
M0 **cM0(i+)**	No clinical or radiographic evidence of distant metastases. No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases.
cM1	Distant metastases detected by clinical and radiographic means.
pM1	Any histologically proven metastases in distant organs; or if in nonregional nodes, metastases greater than 0.2 mm.

and ISH testing may be performed, which counts the number of copies of the *HER2* gene, or you may send your results to another cancer center for a second opinion. If the ISH test is negative, the cancer is considered to be *HER2*-low.

- A score of 3+ means the cancer is *HER2*+.

This guide focuses on advanced and metastatic *HER2*-, *HER2*-low and triple negative breast cancer (TNBC).

UNDERSTANDING *HER2*-, *HER2*-LOW AND TNBC

As you begin learning about the type of breast cancer you have, it may help to understand the differences between *HER2*-, the new *HER2*-low designation and TNBC, which is *ER*-, *PR*- and *HER2*-, meaning none of these are fueling the cancer's growth and none are detectable on the cancer cell. All of these breast cancers may be diagnosed at any stage.

Hormone receptor (*HR*) status for people with *HER2*- or *HER2*-low may be either *HR*+ or *HR*-. Hormone (endocrine) therapy is only used to treat cancers with either estrogen or progesterone receptor expression regardless of *HER2* status.

***HER2*- breast cancer** occurs when the cancer cells do not have *HER2* protein receptors on their surface, which is indicated by an IHC score of 0 or 1+ (see Figure 1, page 4). This indicates that the cancer is not being driven by *HER2* and the receptors are not detected or are only minutely present. If the IHC test is definitive, ISH testing may not be necessary.

Cancer cells that are *HER2*- may grow more slowly and are less likely to recur (return) or spread to other parts of the body than cancer cells with a large amount of *HER2* receptors on their surface (*HER2*+). This subtype does not respond to anti-*HER2* therapy but may be treated with other drug therapies.

***HER2*-low breast cancer** is a new classification of breast cancer. It may have an IHC score of 1+ or 2+ without *HER2* gene amplification. A score of 1+ or 2+ means there is a low level of *HER2* receptors on the surface of the cancer cells, but not enough to be considered *HER2*+. Because the score falls between *HER2*- and *HER2*+, additional testing is required to confirm this type. As a result, your biopsy sample will also have ISH testing.

This new classification is important because patients who are *HER2*- traditionally have not benefitted from anti-*HER2* targeted therapies, which are used to treat *HER2*+ breast cancers. New research, however, has shown that if a breast cancer cell has even a few *HER2* receptors on its surface, the patient may benefit from some anti-*HER2* therapies.

With this *HER2*-low classification, many people who previously did not have access to the therapies that target *HER2* may now qualify for them and benefit in the metastatic setting.

TNBC is diagnosed when the tumor cells do not have estrogen receptors (*ER*-), progesterone receptors (*PR*-) or large amounts of *HER2* protein receptors (*HER2*-) on their surface. This means that the cancer is not being driven by hormones or *HER2*. This type will have an IHC score of 0 to 1+.

Because TNBC is not driven by hormones or *HER2*, it has fewer treatment options. As a result, chemotherapy is often used and may be combined with other drug therapies, including immunotherapies. TNBC diagnoses that were *HER2*- may be retested to determine whether they are actually *HER2*-low, which could make targeted therapy an option. Your biopsy sample may also be tested for the PD-L1 protein to determine whether you are a good candidate for immunotherapy.

Clinical trials are ongoing and continue to look for new ways to treat TNBC. Ask your doctor if you should consider joining a clinical trial.

ONGOING MONITORING

Ongoing testing will become a very important part of your life when you have advanced or metastatic breast cancer. Your doctors will watch you closely to learn about any symptoms you have, detect new signs of cancer growth, check for treatment resistance (when cancer no longer responds to a certain treatment) and identify other changes in your health.

Periodically, your doctor may order a biopsy to determine whether the biomarkers in the cancer have changed (mutated), which may alter future treatment options. This will include retesting for any changes in your *ER*, *PR* and *HER2* status. In some cases, a *HER2*+ diagnosis can turn into *HER2*-, which would change your treatment plan.

Circulating tumor cells (CTCs), which are cells from the tumor that have broken off and are moving throughout the bloodstream, may also be measured to monitor whether the cancer is growing or has become resistant to any therapies in your treatment. Higher numbers of CTCs may indicate the cancer is growing.

To manage the anxiety that accompanies continual follow-up visits and testing, find out when to expect results, how you will receive them, and who will deliver them to you. ■

Questions to ask your doctor

1. **What is the difference between *HER2*-, *HER2*-low and TNBC?**
2. **What treatments are available for my type of breast cancer?**
3. **Could I be *HER2*-low?**
4. **How confident are you in the test results, or is additional testing needed?**
5. **If I was *HER2*- at diagnosis, could I be retested to determine whether I might be *HER2*-low?**
6. **Are *HR* and *HER2* the same thing?**

Timing has been everything for Annie Bond. It took longer than it should to get a Stage IV breast cancer diagnosis. Then, it took time to find the right oncologist, treatment plan and resources. Once she went into remission – an uncommon term with advanced breast cancer but one her doctor encourages her to use – it took time to be comfortable talking about it. But now she does in a big way, sharing messages of hope to other people facing cancer.

Stage IV survivor uses social media to spread real awareness and hope

Self-breast exams weren't on my radar. I was 25 with no family history of breast cancer. Even so, when my boyfriend found a lump in my left breast, I wasted no time getting it checked out. Twice I was told not to worry because I had dense breasts and was "too young" to have breast cancer. Nine months later, the doctor at my annual gynecology appointment finally paid attention. By then, the lump had grown and spread into my lymph nodes and liver. I had Stage IV *ER*+, *PR*+, *HER2*- breast cancer.

I met with an oncologist who gave me a grim prognosis of 2 to 5 years. He wanted to start treatment right away and listed the options I was to choose from: chemo, surgery, radiation, medications with complicated sounding names and terrifying side effects. I thought, "How could I or anyone in my family possibly be qualified to make important decisions about cancer? We aren't doctors."

I needed more information. What were my fertility preservation options? (This doctor had strong feelings about me not doing it.) Were there any financial resources that could help? (The medical office said they had a program but wouldn't give me the information.) Would my insurance cover treatment? (I had just turned 26 so I was dropped from my parents' policy, and this oncologist was out of network on my new policy.)

Although I quickly identified that this oncologist was not a good match for me, I credit him with helping me realize I needed to advocate for myself. Once I sought out more opinions on my treatment, I discovered how skilled and compassionate other cancer centers could be. This inspired me to educate myself and, eventually, others.

Before I even saw my current oncologist, I was set up with a social worker, mental health resources and program assistance. I froze my eggs (which insurance refused to cover) and filled out my first Advance Directive (a very strange experience for a 26-year-old).

We discovered that my cancer is considered Luminal B, which is slow-growing and unusual for someone my age. But this meant I had more treatment options and a better chance of survival.

My boyfriend and my mom were wonderful caregivers through my two years of active treatment, which included hormone therapy, a lumpectomy, removal of 18 lymph nodes, radiation therapy, a liver resection, an oophorectomy and countless tests and scans. I eventually started a new targeted therapy that had just been approved, and I'm still on it today.

During treatment, I adopted two cats and a dog for emotional support. This led me to start a dog walking/pet care business. My career as a stand-up comedian had gone south when late night audiences didn't find my cancer jokes as funny as I did. Some people say laughter is the best medicine. I say medicine is the best medicine, but finding humor and joy in my cancer journey really helps.

I went to group therapy and learned about the power of community and telling my story. Everyone else was saying out loud all the words that were in my brain. We were all young with different cancer diagnoses, but mentally we were playing the same game and dealing with the same struggles. It was so powerful. Once my doctor told me I was considered in remission, I knew I wanted to make a difference.

I started by posting silly videos on TikTok (@AnnieBond). My followers grew and I shared more. I quickly saw solidarity on a much larger scale among people of all ages. It is still so healing for me to get my thoughts out there. My goal is to spread real awareness about the struggles facing survivors and the need for more funding for advanced breast cancer. Just because it's Stage IV doesn't mean it's hopeless. We deserve more. ■

▶ ***Whether it's with me or someone else, find your support.*** *I won't be the person to give you great financial advice (I love going to Scotland on a credit card), but I will remind you of these important things.*

1. ***It's easy to be miserable, and happiness takes work. Find the little things that bring you joy, like dogs and ice cream.***
2. ***Always treat your mental health with the same importance as your physical health. Therapy helps a lot.***
3. ***Like love, we can't see or touch hope, but we know it's real. You are allowed to have hope, even if you have Stage IV cancer. Your story is about you, it's not a generalization of what the world or Google thinks Stage IV means.***
4. ***Take it day by day. There will be good days and bad days. Just keep going.***

Know your goals, your role and your options

When breast cancer is or becomes metastatic, the treatment plan shifts from cure to management, which means preventing or slowing the spread of the cancer and relieving any pain or discomfort. Do not, however, let that distress you. New treatment strategies and ongoing research are offering many people more hope for longer, fuller lives. The goal of reaching "no evidence of disease" may be a very real possibility.

Discuss your goals of treatment. A key part of that is how you hope your daily life will look. Start with questions like these:

- Where will I get my treatments? Are any of them oral so I can take them at home?
- What side effects should I expect, and what is the plan for preventing or managing them?
- When should I begin palliative care?
- Can we adjust treatment times around my work schedule?
- If my cancer becomes resistant, will I have other options? This is also a good time to have an honest conversation about when and why to make the difficult decision of whether to stop treatment.

DRUG THERAPY

Many drug therapies, including targeted therapy, hormone therapy, chemotherapy and immunotherapy, have been developed to treat different combinations of *ER, PR* and *HER2* receptor expression (see Table 1). Often these drugs are used in combination, and it is common for more than one therapy to be included in your treatment plan. These treatments are systemic because they travel throughout the body. You may receive them through an IV into a vein, through a port in your body, as an injection (shot) or orally as a pill or liquid (see Figure 1, page 9).

Targeted therapy uses drugs or other substances to identify, attack and destroy specific types of cancer cells or to slow disease progression. Some interfere with the cancer cells' internal functions; others attack specific receptors on the cancer cells' surfaces; and some target the blood vessels that supply the tumor. More recently, targeted therapy was approved to be used alone to treat metastatic *HER2*-low breast cancers, which may include some diagnoses of triple negative breast cancer (TNBC). Other targeted therapy drugs are sometimes used in combination with hormone therapy to treat *ER*+ or *PR*+ breast cancers or *HER2*- breast cancer with the BReast CAncer 1 or 2 (*BRCA1* or *BRCA2*) gene mutations.

These types of targeted therapy may be used:

- Anti-*HER2* antibody drugs are laboratory-made proteins that can bind to cancer cells and target the *HER2* receptor. They can be used alone or to carry drugs, toxins or radioactive substances directly to cancer cells. This type may be used for *HER2*-low breast cancer.
- Monoclonal antibodies (mAbs) are commonly used. Laboratory-made mAbs that are combined with a toxin such as a chemotherapy drug are known as antibody drug conjugates. Recently approved to treat the newly designated *HER2*-low breast cancer subtype, a mAb attaches to the *HER2* receptor on a cancer cell, gets swallowed by the tumor cell and breaks down inside the cell, releasing the chemotherapy drug, preventing growth signals from *HER2* receptors and causing cell death (see Figure 2, page 9).
- Kinase inhibitors target cancer cells' ability to grow and survive by targeting kinases, which are enzymes that speed up chemical reactions in the body. These inhibitors can be designed to attack enzymes within a cell, proteins or enzymes needed for a cell's growth, or receptors on the cell's surface. Therapies targeting the *NTRK* gene fusion may also be used. This fusion occurs when a piece of the chromosome containing a gene called *NTRK* breaks off and joins with a gene on another chromosome.
- A *PIK3CA* inhibitor prevents the growth of cells by blocking the *PIK3CA* gene, which is frequently mutated in breast cancer.
- Poly (ADP-ribose) polymerase (PARP) inhibitors prevent cancer cells from repairing themselves and lead to tumor cell destruction.
- Tumor-agnostic treatment targets specific genetic mutations to prevent growth regardless of cancer type or where it is.

Hormone therapy, also called endocrine therapy, is primarily used to treat cancer that is estrogen- and/or progesterone-receptor positive (*ER*+/*PR*+). It is actually an anti-hormone because it reduces or blocks the stimulating effect of the hormones on tumor cells. When tumor cells test positive for one or both hormone receptors (*ER*+ and/or *PR*+), it means hormones are fueling the cancer's growth. Blocking hormone receptors or blocking production of hormones by the body can be highly effective in slowing cancer growth or stopping progression.

Hormone therapy is not effective for cancer that is *ER*-/*PR*- because the growth is not driven by hormones. In some cases, biopsied tumor cells may test negative for all three biomarkers (*ER*-, *PR*-, *HER2*-), which is referred to as TNBC.

Depending on your past and current treatments, the length of time before recurrence, how far the cancer has spread, gender and menopausal status (for women), your treatment plan may include any of the following:

TABLE 1

RECEPTOR AND TREATMENT RESPONSE

Receptors	Likely Treatment Response
ER+ **and/or** ***PR+, HER2+*** (triple positive)	Typically responds to anti-estrogen drugs (hormone therapy) and anti-*HER2* drugs (targeted therapy)
ER- **and** ***PR-, HER2+***	Typically responds to anti-*HER2* drugs (targeted therapy) and to chemotherapy but not to anti-estrogen drugs (hormone therapy)
ER+ **and/or** ***PR+, HER2-***	Typically responds to anti-estrogen drugs (hormone therapy), but not likely to respond to anti-*HER2* drugs
ER+ **and/or** ***PR+, HER2-low***	Typically responds to anti-estrogen drugs and anti-*HER2* drugs
ER- **and** ***PR-, HER2-*** (triple negative)	Typically treated with chemotherapy and immunotherapy; not likely to respond to anti-estrogen drugs (hormone therapy) or anti-*HER2* drugs
ER- **and** ***PR-, HER2-low***	Typically treated with chemotherapy, may be treated with anti-*HER2* drugs (targeted therapy) and immunotherapy; not likely to respond to anti-estrogen drugs (hormone therapy)

- Anti-estrogens are substances that keep cells from making or using estrogen. They may stop some cancer cells from growing or even destroy them.
- Aromatase inhibitors are drugs that prevent the production of estrogen, a female hormone, by interfering with an aromatase enzyme. They may benefit postmenopausal women with hormone-dependent breast cancer or younger women whose ovarian function is blocked by drugs or who have had their ovaries removed. Aromatase inhibitors cannot be used in premenopausal women with functioning ovaries.
- Very high doses of hormones may be used to stop cancer growth.
- Ovarian ablation uses surgery, radiation or extreme heat or cold to permanently stop the ovaries from making hormones.
- Ovarian suppression can stop the ovaries from making hormones that promote cancer growth in *ER+/PR+* cancers. Drugs called luteinizing hormone releasing hormone (LHRH) agonists are typically used instead. For premenopausal women, these drugs provide an equivalent alternative to removing the ovaries. Selective estrogen receptor downregulators (SERDs) are also a form of ovarian suppression that block estrogen from attaching to the hormone receptors on the tumor.
- Bilateral oophorectomy is surgery to remove both ovaries. It may be an ablation option for some premenopausal women.

FIGURE 1

SYSTEMIC DRUG THERAPY

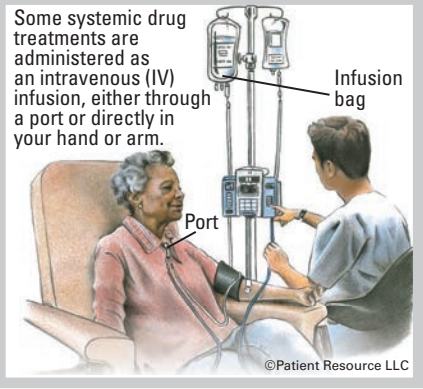
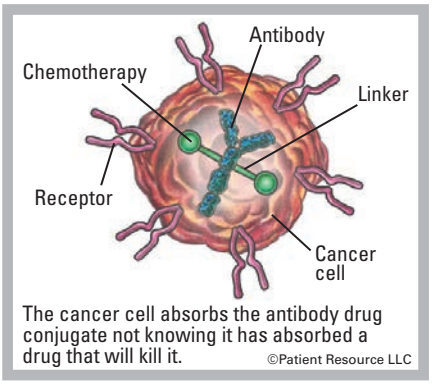


FIGURE 2

ANTIBODY DRUG CONJUGATE



Immunotherapy harnesses the potential of the body's own immune system to recognize and destroy cancer cells. Various types of immunotherapy are approved for advanced and metastatic breast cancer.

- Immune checkpoint inhibitors prevent the immune system from slowing down, allowing it to keep up its fight against the cancer. These drugs do this by targeting and blocking PD-1 or PD-L1.
- Tumor-agnostic treatment, when used as immunotherapy, is approved to treat any type of cancer that has molecular alterations known as microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR) or tumor mutational burden-high (TMB-H).

Chemotherapy kills rapidly multiplying cells throughout the body. It can be given as a single drug or usually is combined with other chemotherapy drugs or other types of treatment. It is most often used to treat *ER-/PR-* cancers or *ER+/PR+* cancers that no longer respond to hormone therapy.

It may be used for metastatic TNBC that does not express PD-L1 and for metastatic *ER+*, *PR+*, *HER2-* or *HER2*-low breast cancer when hormonal therapy is not effective.

Bone-strengthening drugs or bone-modifying agents may be used in addition to systemic treatment or radiation therapy to prevent or delay bone fractures when breast cancer has spread to the bones.

RADIATION THERAPY

This therapy uses high-energy X-rays to kill cancer cells or keep them from growing. Sometimes it is given to control symptoms caused by breast cancer that has spread to specific organs, such as the bones or the brain. It may be used for pain management or to reduce the size of tumors causing discomfort.

SURGERY

Though not a primary treatment, surgery may be an option to alleviate pain related to large tumors or metastases in the brain, spine or lungs, or to help support or stabilize weakened or broken bones.

COMMON DRUG THERAPIES FOR ADVANCED BREAST CANCER

These therapies may be used alone or in combination. For some combination therapies your doctor might suggest, go to www.PatientResource.com/HER2-Advanced_Treatment

TARGETED THERAPY

- abemaciclib (Verzenio)
- alpelisib (Piqray)
- entrectinib (Rozlytrek)
- everolimus (Afinitor, Afinitor Disperz)
- fam-trastuzumab deruxtecan-nxki (Enhertu)
- larotrectinib (Vitrakvi)
- olaparib (Lynparza)
- palbociclib (Ibrance)
- ribociclib (Kisqali)
- ribociclib and letrozole (Kisqali Femara Co-Pack)
- sacituzumab govitecan-hziy (Trodelvy)
- talazoparib (Talzenna)

HORMONE THERAPY

- anastrozole (Arimidex)
- elacestrant (Orserdu)
- ethinyl estradiol
- exemestane (Aromasin)
- fluoxymesterone
- fulvestrant (Faslodex)
- goserelin acetate (Zoladex)
- letrozole (Femara)
- leuprolide acetate (Eligard, Lupron, Lupron Depot)
- megestrol acetate (Megace)
- tamoxifen
- toremifene (Fareston)

IMMUNOTHERAPY

- dostarlimab-gxly (Jemperli)
- pembrolizumab (Keytruda)

CHEMOTHERAPY

- capecitabine (Xeloda)
- carboplatin (Paraplatin)
- cisplatin
- cyclophosphamide
- docetaxel (Taxotere)
- doxorubicin (Adriamycin)
- epirubicin (Ellence)
- eribulin (Halaven)
- fluorouracil (5-FU)
- gemcitabine (Gemzar)
- ixabepilone (Ixempra)
- liposomal doxorubicin (Doxil)
- paclitaxel (Taxol)
- protein-bound paclitaxel (Abraxane)
- vinorelbine (Navelbine)

As of 9/27/23

CLINICAL TRIALS

These medical research studies, which offer access to therapies not yet widely available, may become part of your treatment plan. The advances from clinical trials, including the new *HER2*-low distinction and treatment with an antibody drug conjugate, are offering more hope for the breast cancer community.

ONGOING MONITORING & COMMUNICATION

Your doctor will monitor you closely with tests and imaging so that your treatment plan can be adapted as needed, making it important to stay on schedule with follow-up appointments. ■

ASCO® answers

Nausea and Vomiting

What are nausea and vomiting?

Nausea and vomiting are common side effects of cancer and its treatment. Nausea is feeling like you are going to vomit. Vomiting, or throwing up, is when the contents of your stomach come out of your mouth. Nausea and vomiting may happen before treatment, within 24 hours after treatment, or 2 or more days after treatment. Retching, also called dry heaving, is when your body tries to vomit but nothing comes up.

What causes nausea and vomiting?

Many types of chemotherapy can cause mild to severe nausea and vomiting. Having a history of motion sickness, anxiety, or being younger than 50 (especially for women) may increase your risk of having nausea and vomiting. Radiation therapy, especially to the brain, spinal cord, abdomen, and pelvis, may also cause nausea and vomiting. People who receive total body radiation therapy have the highest risk. Other causes may include cancer that has spread to the brain; a blocked intestine, also called gastrointestinal obstruction; electrolyte imbalance, which is the loss of minerals such as potassium and sodium; an infection or bleeding in the stomach and intestines; heart disease; and other medications. Ask your doctor if you are at risk of nausea and vomiting and what can be done to avoid or manage these symptoms.

What are the risks of nausea and vomiting?

Mild nausea and vomiting can be uncomfortable. Usually it does not cause serious problems. Vomiting a lot and often is a problem. It can cause dehydration, electrolyte imbalance, weight loss, and depression. Severe vomiting can reopen surgical wounds, break bones, or create tears in the esophagus. This is the tube through which food passes from the throat to the stomach. This may lead some people to stop cancer treatment. It is important to tell your health care team if you are concerned about or experience nausea or vomiting so they can help you prevent or manage it. It's best to treat nausea and vomiting as early as possible to try to stop it from getting worse.

How are nausea and vomiting prevented and treated?

It is normal to be concerned about nausea and vomiting, but it may be helpful to know that there are several ways to prevent or relieve these side effects of cancer treatment. Nausea and vomiting can be prevented with medication for most people who are receiving cancer treatment. However, some people may still have nausea even if they are not vomiting. Medications to prevent nausea and vomiting should be taken as prescribed, even after treatment, because the risk of vomiting can continue for several days after treatment. It is important to take these medications to prevent nausea and vomiting from becoming severe. If this happens, it can be more difficult to manage severe nausea and vomiting. If you have nausea and vomiting, even if you are taking your medication as prescribed, tell your health care team. They can recommend other medications. Other options may help, such as distraction, relaxation, positive imagery, and acupuncture. Some herbal products, like ginger, may help with nausea. However, you should talk with your health care team before starting any of these other options. Also, if you feel very worried or anxious about your upcoming cancer treatment, be sure to let your health care providers know that, too.

What if nausea and vomiting don't stop or get worse?

If your nausea and vomiting does not stop or gets worse, talk with your health care team. The cause may need to be identified. If you cannot keep food or water in your body because of severe nausea and vomiting, it can lead to serious dehydration and electrolyte imbalance. Dehydration can lead to other health problems. It is important to talk to your health care team if your symptoms get worse.

ASCO ANSWERS is a collection of oncologist-approved patient education materials developed by the American Society of Clinical Oncology (ASCO) for people with cancer and their caregivers.
For more information, visit **cancer.net/sideeffects**.

Cancer.Net®
ASCO | KNOWLEDGE CONQUERS CANCER

Preserve quality of life with side effect management

Preventing, minimizing and managing the side effects of the cancer and its treatment is a primary focus of your multidisciplinary health care team. They will work together to make you more comfortable and enhance your quality of life. Knowing the side effects that may occur – and setting expectations for how to manage them if they do – will help you feel more prepared for treatment.

People facing cancer today have access to services that are designed to help improve their overall well-being before, during and after treatment. These services are known as supportive care or palliative care.

Palliative care is often confused with hospice care, but they are not the same. Palliative care can begin immediately after diagnosis and last throughout the cancer care continuum. Hospice care is more often used toward the end of life; however, it also has a key component of comfort care included in the services and programs that are offered.

You will work closely with palliative care specialists or other members of your health care team who are trained in side effect and symptom management. These services may be offered at a hospital, cancer center or medical clinic and can be adjusted as your needs change throughout treatment. Your family members, caregivers and others close to you can also benefit from this support. Palliative care specialists should be viewed as quality-of-life coaches who strive to preserve or restore your quality of life, which needs to be the priority for care.

Side effects can vary in intensity. While some are simply an inconvenience, others can disrupt your quality of life. Examples include nausea and vomiting or severe diarrhea that keeps you homebound or mouth sores that prevent you from eating and getting the nutrition your body needs, especially during cancer treatment. Still others may be serious or even life-threatening, making it critical that you know what to do if a potentially serious side effect occurs.

PREPARE FOR SIDE EFFECTS

Your health care team will rely on you to communicate openly about how you feel. Ask about the symptoms to watch for and what you should do if they happen. Some may require alerting the health care team immediately because treatment may help prevent more serious complications. Download a side effect tracker at PatientResource.com/Tracker.

Potentially severe side effects, also known as adverse effects, are uncommon but can occur with certain treatments. Ask your doctor whether you are at risk from the therapies in your treatment plan, how to identify the symptoms and when to seek emergency care. Report symptoms immediately so they can be treated right away. Prompt treatment can be life-saving.

Common physical side effects occur with many types of cancer treatment. Know that every person's reaction is unique, even when the diagnosis and treatment are similar. Also, keep in mind that you likely will not experience all of the possible side effects. To see a list of common side effects, flip this guide over and see Table 1, page 10.

Some of the most common physical side effects of *HER2*- advanced breast cancer treatment are nausea, vomiting, diarrhea, constipation, fatigue, hair loss and anemia. For an in-depth look at prevention and management of nausea and vomiting, see *ASCO Answers: Nausea & Vomiting*, page 10.

Late effects are side effects that develop weeks, months or years after treatment ends. If possible, talk with your doctor before you start a treatment about the symptoms to be prepared for and most concerned about.

ADDITIONAL SUPPORTIVE CARE

Supportive care offers much more than physical relief. It is also designed to ensure your whole person is cared for, and that includes help with the emotional, practical, spiritual, financial and family-related challenges you may have. If you need help in an area not listed here, talk with a member of the team:

- Dietary support may be needed if you have challenges eating or with your appetite.
- Emotional support is available in many forms, both in person and online. Many organizations offer one-on-one buddy programs that pair you with another person who also has *HER2*- advanced breast cancer.
- Fertility support immediately following diagnosis may be necessary if you plan to have children in the future. Your fertility can be affected after a single treatment, and your preservation options will likely become much more limited as treatment goes on.
- Financial counseling is accessible from a social worker, nurse navigator or financial counselor.
- Spiritual or religious guidance may be available from a chaplain or spiritual care advisor at the hospital or in your religious community. Spiritual support is available to you even if you do not consider yourself a religious person.
- Transportation support is available for getting to and from cancer-related appointments. Support may be available from non-profit organizations, community transportation service programs, faith-based organizations and Medicaid.

Ask a member of your health care team for more information. ■

FROM THE ADVISORY BOARD

"You are by no means alone — hundreds of thousands of people are living with advanced breast cancer today. Ask your nurse navigator about support groups and educational programs, and check them out to find the one that serves you best."

~ Lillie Shockney,
RN, BS, MAS, ONN-CG, Patient Resource Advisory Board Member and Breast Cancer Survivor

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