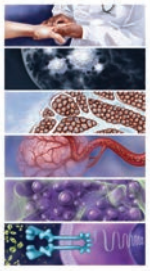
A Supplement to JADPRO
Journal of the Advanced Practitioner in Oncology

Contents

VOL 7 | SUPPL 2 | NOV/DEC 2016



Cover illustration: Artist's depiction of the many aspects of HER2-positive breast cancer. Artwork by Alexandra and David Baker, ©2016, DNA Illustrations, Inc., Asheville, North Carolina.

CE Information 2
Narrative 5

Meet the Team

In this supplement to JADPRO, we review the collaborative practice model in the treatment and management of patients with HER2-positive breast cancer. To highlight how collaborative practice works in the real world, we have included comments and discussion with three individuals bringing different perspectives on the breast cancer experience: Angela DeMichele, MD, MSCE, Jennie Greco Lattimer, MSN, BSN, CRNP, and Rachel F., their patient.

Angela DeMichele, MD, MSCE, is a medical oncologist at the Rena Rowan Breast Center in the Abramson Cancer Center, Perelman Center for Advanced Medicine, University of Pennsylvania. She is a professor of medicine and epidemiology at the University of Pennsylvania School of Medicine in Philadelphia.

Jennie Greco Lattimer, MSN, BSN, CRNP, is a nurse practitioner at the Rena Rowan Breast Center in the Abramson Cancer Center, Perelman Center for Advanced Medicine, University of Pennsylvania. She specializes in medical oncology, and is board certified as an adult nurse practitioner and an oncology certified nurse.

Rachel F., a mother of two, was diagnosed in 2015, at age 38, with stage IV HER2-positive breast cancer. She received treatment under the care of Dr. DeMichele and Ms. Lattimer and is currently embracing life and navigating the course of this challenging disease under the supervision of the team.

.75 This supplement provides **.75 CREDIT/CONTACT HOUR**

HOW TO EARN CREDIT

To access the learning assessment and evaluation form online, visit http://meded.hbrsd.com/
Statement of Credit: Participants who successfully complete this activity (including scoring a minimum of 70% on the learning assessment and completing and submitting the evaluation form with an E-mail address) will be able to download a statement of credit.

Supported by an educational grant from Genentech

A CONTINUING EDUCATION ACTIVITY

MENISCUS EDUCATIONAL INSTITUTE
JADPRO Journal of the Advanced Practitioner in Oncology

Managing the Care of Patients With HER2-Positive Breast Cancer: A Collaborative Practice Model

A continuing education article for physicians, PAs, doctors of nursing practice, nurse practitioners, advanced practice nurses including clinical nurse specialists, and other advanced degree nurses.

Release date: November 17, 2016
Expiration date: November 17, 2017

Estimated time to complete activity: 0.75 hour

Meniscus Educational Institute
3131 Princeton Pike, Building 1, Suite 205A
Lawrenceville, NJ 08648
Voice: 609-246-5000
Fax: 609-449-7969
E-mail: lrubin@meniscusedu.com

Journal of the Advanced Practitioner in Oncology
94 North Woodhull Road
Huntington, NY 11743
Voice: 631-692-0800
Fax: 631-692-0805
E-mail: claudine@harborsidepress.com

This supplement is supported by an educational grant from Genentech.

Faculty

Angela DeMichele, MD, MSCE, Alan and Jill Miller Endowed Chair in Breast Cancer Excellence and Professor of Medicine and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Jennie Greco Lattimer, MSN, BSN, CRNP, Oncology Nurse Practitioner, University of Pennsylvania Perelman Center for Advanced Medicine, Philadelphia, PA

Activity Rationale and Purpose

Providers use many frequently prescribed drugs across disease states without a clear understanding of their mechanisms: which targets they hit, what processes they alter, which of these actions are the key to therapeutic efficacy, and which are responsible for toxicity. Breast cancer expert faculty identified a lack of understanding of HER2 testing that is now standard practice for women with breast cancer, although it is not always clear which test to use and how test results impact selection of therapy.

Neoadjuvant therapy for patients with HER2-positive breast cancer can enhance resectability and reduce tumor burden prior to surgery and/or radiation therapy and may enhance outcomes.

Oncology nurses and other advanced practitioners need to understand the potential benefits of neoadjuvant therapy for HER2-positive breast cancer, the scientific basis for new HER2-targeted treatments that could improve neoadjuvant responses and/or tumor resectability, and in many cases educate patients and support them in the decision process.

Intended Audience

The activity's target audience will consist of physicians, PAs, doctors of nursing practice, nurse practitioners, advanced practice nurses including clinical nurse specialists, and other advanced degree nurses.

Learning Objectives

After completing this educational activity, participants should be able to:

1. Describe scientific updates and key practice changes in the management of locally advanced and metastatic HER2-positive breast cancer
2. Review HER2 testing guidelines for patients with breast cancer
3. Discuss best sequencing of FDA approved targeted agents, mechanism of action and toxicities
4. Explain the role of neoadjuvant chemotherapy in HER2-positive breast cancer, including use of HER2-targeted agents
5. Describe collaboration between various members of the healthcare team (including but not limited to physician, nurse practitioner, PA, and pharmacist) in management strategies for patients with locally advanced and metastatic HER2-positive breast cancer

Continuing Education

Statement of Credit—Participants who successfully complete this activity (including the submission of the post-test and evaluation form) will receive a statement of credit.

Physicians. This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Meniscus Educational Institute and the Advanced Practitioner Society for Hematology and Oncology (APSHO). The Meniscus Educational Institute is accredited by the ACCME to provide continuing medical education for physicians.

The Meniscus Educational Institute designates this journal article for a maximum of 0.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses. This activity for 0.75 contact hour is provided by the Meniscus Educational Institute.

The Meniscus Educational Institute is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Provider approved by the California Board of Registered Nursing, Provider No. 13164, for 0.75 contact hour.

Financial Disclosures

All individuals in positions to control the content of this program (eg, planners, faculty, content reviewers) are expected to disclose all financial relationships with commercial interests that may have a direct bearing on the subject matter of this continuing education activity. Meniscus Educational Institute has identified and resolved all conflicts of interest in accordance with the MEI policies and procedures. Participants have the responsibility to assess the impact (if any) of the disclosed information on the educational value of the activity.

FACULTY

Angela DeMichele, MD, MSCE, has served as a consultant for Novartis and Pfizer, and has received grants from Calithera Biosciences, Genentech, Novartis, and Pfizer.

Jennie Greco Lattimer, MSN, BSN, CRNP, has served on a speakers bureau for Genentech.

LEAD NURSE PLANNER

Wendy J. Smith, ACNP, AOCN®, has nothing to disclose.

PLANNERS

Alana Brody has nothing to disclose.
Chris Cherry has nothing to disclose.
Jeannine Coronna has nothing to disclose.
Claudine Kiffer has nothing to disclose.
Patti McLafferty has nothing to disclose.
Lynn Rubin has nothing to disclose.
Christine Wilson has nothing to disclose.
Annie Yueh has nothing to disclose.

CONTENT REVIEWERS

Karen Abbas, MS, RN, AOCN®, has nothing to disclose.
Moshe Ornstein, MD, MA, has nothing to disclose.

Disclaimer

This activity has been designed to provide continuing education that is focused on specific objectives. In selecting educational activities, clinicians should pay special attention to the relevance of those objectives and the application to their particular needs. The intent of all Meniscus Educational Institute educational opportunities is to provide learning that will improve patient care. Clinicians are encouraged to reflect on this activity and its applicability to their own patient population.

The opinions expressed in this activity are those of the faculty and reviewers and do not represent an endorsement by Meniscus Educational Institute of any specific therapeutics or approaches to diagnosis or patient management.

Product Disclosure

This educational activity may contain discussion of published as well as investigational uses of agents that are not approved by the US Food and Drug Administration. For additional information about approved uses, including approved indications, contraindications, and warnings, please refer to the prescribing information for each product.

How to Earn Credit

To access the learning assessment and evaluation form online, visit http://meded.hbrsd.com/
Statement of Credit: Participants who successfully complete this activity (including scoring a minimum of 70% on the learning assessment and completing and submitting the evaluation form with an E-mail address) will be able to download a statement of credit.

Managing the Care of Patients With HER2-Positive Breast Cancer: A Collaborative Practice Model

INTERVIEWS AND REPORTING BY CHRISTINE WILSON

Contributors' disclosures of potential conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2016.7.7.11

In this special supplement to the *Journal of the Advanced Practitioner in Oncology*, or JADPRO, we review the treatment and management of patients with HER2-positive breast cancer and discuss a treatment model in which the physician and nurse practitioner work together to efficiently care for the patient. To add depth and perspective, we have included comments and discussion from people involved in different parts of the breast cancer experience: Angela DeMichele, MD, a breast cancer specialist at the Abramson Cancer Center of the University of Pennsylvania; Jennie Greco Lattimer, NP, who has worked closely with Dr. DeMichele for 15 years; and Rachel F., a patient who was diagnosed with metastatic HER2-positive breast cancer at age 38 in July 2015. To view video interviews with the three participants and gain additional perspectives, access a special enhanced digital version of this supplement at **advancedpractitioner.com/narratives/her2.**

Breast cancer is a complex group of diseases. New understanding of its biology and genetics has shown that breast cancer is characterized by multiple subtypes, which all have significant impact on treatment decisions and prognosis.

Human epidermal growth factor receptor 2 (HER2)–positive breast cancer has been recognized as a distinct subtype since the early 1980s when researchers discovered a link between high levels of HER2 and the ability of cancer cells to grow rapidly (Kumar & Badve, 2008). HER2 receptors can signal to the nucleus when bound to their ligand or heregulin, or simply through homodimerization (due to the high density of receptors on the cell surface) or heterodimerization between HER2 and its partners, HER1, HER3, and HER4. This discovery led to the development of trastuzumab (Herceptin)—a monoclonal antibody that targets HER2 overamplification—and has transformed HER2-positive breast cancer from a disease with a poor prognosis to one that can be treated effectively, especially in its early stages (National Cancer Institute [NCI], 2016a).

However, both de novo and acquired resistance to trastuzumab exists. Activity of members of the HER family, including HER1, 3, and rarely, 4,

Jennie Greco Lattimer, NP
Today, it is so important that nurse practitioners and our advanced practice colleagues understand the science of treating breast cancers. The treatments are really based on understanding the biology of the tumor. Many patients want to know how the drugs work. It's complex and it's critical that I am able to explain the treatment to my patients in a language they can understand.

Rachel F.
I had never heard of HER2 before my diagnosis. I did a lot of research on my own, but it made a difference to have both my doctor and the nurse practitioner explain the treatment. I told them there was no such thing as too much information for me. I wanted to know everything.

coexist with HER2 overexpression, often heterodimerizing with HER2, which can be an escape mechanism when HER2 homodimerization is blocked. The HER3 mutation may play a particularly important role in tumor resistance to HER2 blockades (NCI, 2016b; Harbeck et al., 2013).

Today, receptor profiling of breast cancer is standard and essential to determining optimal therapy. Approximately 25% of breast cancer patients test positive for HER2 overexpression or amplification (Breastcancer.org, 2016). Patients with stage I–III HER2-positive disease typically undergo either adjuvant or neoadjuvant treatment in addition to surgery and radiation therapy. This approach produces high rates of complete response to neoadjuvant therapy as well as long-term survival (Glaberman, Dayao, & Royce, 2014).

> **The HER family of** genes and proteins are very similar in structure and function. If we shut down HER2, it is not uncommon for HER2 to bind to HER3 and activate that pathway. HER2 may also engage in what we call 'crosstalk' with hormonal pathways. These are the primary modes of resistance for these tumors. We are actively engaged in deepening our understanding of how these pathways work and interact with each other, and conducting trials to develop new or modified combinations of agents that shut down or inhibit these signaling cascades and block crosstalk.
>
> —Angela DeMichele, MD

Patients diagnosed with metastatic (i.e., stage IV) HER2-positive breast cancer or whose disease recurs following primary treatment have a number of treatment options, including several targeted therapies and chemotherapeutic agents, often given in combination. Although these treatments have significantly prolonged overall survival and quality of life for patients with HER2-positive advanced disease, the vast majority of these patients still die of their breast cancer (Cancer.Net, 2014). This results from the ability of HER2-positive tumors to become resistant to therapy as well as from their heterogeneity. For this reason, additional HER2-directed therapies have been developed that can circumvent resistance and/or take advantage of the ability of HER2 to bind ligand.

Four targeted therapies have been approved for treating HER2-positive breast cancer, as well as a number of chemotherapeutic agents with known activity in treating this type of breast cancer. In addition, research has shown that HER2

mutations, as well as others in the HER family, play a significant role in the growth of a number of other cancers, including gastric and potentially lung and pancreatic tumors (Subbiah & Gonzalez-Angulo, 2014).

Pertuzumab, another monoclonal antibody, binds HER2, but at a different extracellular residue, which can block HER2/HER3 heterodimerization, and appears to synergize with trastuzumab. Ado-trastuzumab emtansine (T-DM1) is a drug/antibody conjugate that uses the trastuzumab to bind HER2 for delivery of the chemotherapeutic payload, emtansine. And small-molecule inhibitors, such as lapatinib and neratinib, bind the interacellular component of HER2, blocking signaling pathways.

Additional research now focuses not only on developing new HER2-targeted therapies but also on how to optimally use these existing agents. There is also a real need to identify biomarkers to assess which patients are at high risk for recurrence and who will respond to specific treatment approaches.

The side effects that patients on HER2-positive therapy experience depend largely on the agents used. Trastuzumab and other targeted therapies often have relatively few side effects and are well tolerated, with chronic diarrhea, rashes, and fatigue among the most commonly reported problems. Approximately 10% to 12% of patients on trastuzumab develop heart failure or decreased left ventricular ejection fraction that often requires discontinuation of the therapy, although this effect can be reversible with treatment cessation and managed with medical therapy. One current goal of treatment for HER2-positive breast cancer is to obtain optimal outcomes with minimal toxicity by minimizing, where possible, the use of chemotherapy (Morgan, 2016).

The best treatment for patients with HER2-positive breast cancer is team based, with the advanced practitioner playing a key role in managing the disease and providing comprehensive care for the patient. This article describes a model in which the physician has primary responsibility for developing and overseeing the treatment plan, while the nurse practitioner provides the majority of ongoing care, treatment monitoring, and survivorship planning for patients.

In many ways, the treatment of HER2-positive breast cancer exemplifies the extraordinary progress that has been made in understanding and treating cancer in the past 3 decades. These advances have resulted from a deepening knowledge of the biology of cancer cells and the development of therapies targeted to the differences between normal and malignant cells. There is both great promise for the future and a great need for additional research to ensure that every patient benefits from available therapies. For patients, the challenges of living with a diagnosis of HER2-positive breast cancer, at every stage, are significant and require a comprehensive care plan implemented by both a physician and an advanced practitioner.

Angela DeMichele, MD
At the University of Pennsylvania, we have a true partnership: The physician develops the treatment plan throughout the course of the disease, and the NP sees each patient on a regular basis to monitor and manage side effects. The NP answers questions and communicates directly with other members of the care team.

Jennie Greco Lattimer, NP
Patients ask me questions they might not ask their doctor. When someone is first diagnosed, I explain HER2-positive disease and how the treatments work. Patients often have a lot of concerns about being able to work, how they'll care for their children during treatment, and side effects. If a patient has an adverse reaction to treatment, the infusion room nurses call me first. I'm also very involved in guiding survivorship planning and follow-up.

Rachel F.
I wasn't sure at first how I felt about seeing the nurse practitioner. I really liked and trusted my doctor and felt a strong bond with her. I thought I only wanted to see my doctor—but now I am fine with the team. When I have a problem, Jennie is there and can fix it quickly. That accessibility and quick response is really valuable. I can trust her and rely on her daily, yet I know that Dr. DeMichele is there too.

WHAT IS HER2?

The History

In the early 1980s, cancer researchers first discovered that a mutated gene could stimulate the growth of cancer cells. Additional laboratory research identified that gene as the human epidermal growth factor receptor 2, or the HER2 gene. Led by Dennis Slamon, MD, and his colleagues at the University of California, Los Angeles, medical researchers recognized the potential importance of this mutation and worked to understand the links between HER2 and various types of cancer. The researchers found very high levels of HER2 in about 25% of breast cancers and that this was associated with rapidly increased rates of cancer cell growth. Other investigators determined that the presence of HER2 in breast cancer cells also correlated with a higher risk of recurrence, metastasis, and lower overall survival rates. HER2-positive breast cancer, as it came to be known, was identified as a specific subtype of the disease, noted for its aggressive behavior and poor prognosis (NCI, 2016a).

Gene amplification means that there are too many copies of a normal appearing gene and that there is an overabundance of the protein that the gene produces. A normal cell has two copies of the HER2 gene. HER2-positive cancer cells have multiple copies.

—Angela DeMichele, MD

Slamon and his group collaborated with researchers from the University of Texas and others to develop an agent that could block the activity of the HER2 gene and thus slow the growth of the cancer. This was among the first efforts to target a known difference between normal and cancer cells as a therapy. In 1998, following a series of clinical trials, the US Food and Drug Administration (FDA) approved the HER2-specific monoclonal antibody trastuzumab for use in treating patients with metastatic HER2-positive breast cancer. A phase III trial comparing trastuzumab and chemotherapy with chemotherapy alone demonstrated significant improvements in time to disease progression (7.6 vs. 4.6 months). More impressively, twice as many patients on the combined therapy were disease-free 12 months after beginning therapy compared with those just on chemotherapy (28% vs. 14%, respectively). Additional trials demonstrated a clear advantage of trastuzumab-based therapy for HER2-positive breast cancer in the adjuvant setting. The introduction of trastuzumab transformed HER2-positive breast cancer from a disease with a poor prognosis to one that can be treated effectively and often cured when it is

Before we knew about HER2 as an important factor in breast cancer, and didn't have these drugs, HER2-positive breast cancer was considered the most dangerous kind of breast cancer because it can be so aggressive. But having these very effective therapies has really changed the natural history of the disease.

—Angela DeMichele, MD

diagnosed early. Patients with advanced disease benefit from treatment in terms of both longer survival and better quality of life (Baselga et al., 1996).

Although trastuzumab represented a major step forward, it was not the end of the story. In the past decade, three additional targeted agents have been approved to treat HER2-positive breast cancer: pertuzumab (Perjeta), lapatinib (Tykerb), and ado-trastuzumab emtansine (Kadcyla). These drugs all have different mechanisms for targeting HER overamplification, and they are often used in combination with chemotherapy.

The Science

The HER2 gene, located on chromosome 17q21, is found on the cell's outer surface and codes for a protein of the same name: HER2. Normal cells have two copies of the HER2 gene, which encodes a receptor protein that receives signals from the external environment that trigger cell growth and help cells survive. The problem arises when errors in DNA replication create too many copies of the gene and overexpress the HER2 protein (Ruben & Yarden, 2001; see Figure).

This uncontrolled cell growth is the reason that HER2-positive breast cancer was regarded as one of the most aggressive subtypes with a generally poor prognosis. But HER2 turned out to be a "driver mutation," or "proto-oncogene," for these cancers, meaning that if the signaling is blocked, the protein is not produced and the growth stops. One mechanism for achieving that goal is to use monoclonal antibodies designed to attach to a specific protein and inhibit its growth. Trastuzumab is a HER2-specific monoclonal antibody that is effective in blocking HER2 signaling in both the adjuvant/neoadjuvant and metastatic settings. The monoclonal antibody, in effect, removes or clears the HER2 protein from the surface of the cells.

As with many effective cancer therapies, resistance poses a significant problem. It can either occur de novo, meaning

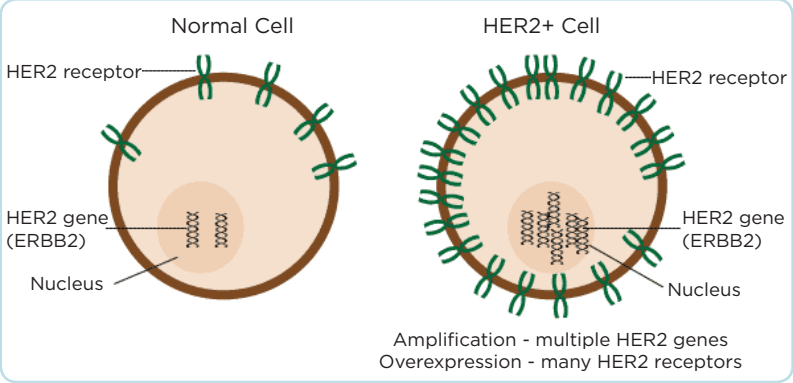


Figure. Overexpression/amplifcation of HER2 genes in HER2-positive breast cancer.

Dr. DeMichele very clearly sat down with my husband and me at the beginning and explained the different types of cancer receptor cells and what that meant for my treatment options. She told me that even though I was stage IV, we could manage it together so I could hold on to my normal life.

—Rachel F.

that there is no response to targeted therapy, or after a positive response. Most patients with metastatic disease treated with trastuzumab relapse within 1 year of beginning therapy. Research has shown that the HER2 gene is one of a family of genes—HER1 (also known as epidermal growth factor receptor), HER3, and HER4—that all contribute to cell growth–signaling pathways. HER1, 2, and 3 are known to be involved in the growth of cancer cells, while HER4 is unusual and not believed to be oncogenic. In some instances, HER2 binds to HER3, a phenomenon known as heterodimerization, or to other signaling pathways (Rubin & Yarden, 2001). This cross-talk, as it is called, allows the signaling pathways to reactivate and the cancer cells to begin growing again (Harbeck et al., 2013).

The utilization of a variety of agents with different mechanisms in targeting the HER family signaling pathways is critical to optimizing outcomes for patients with advanced HER2-positive breast cancer:

- **Pertuzumab** is a monoclonal antibody used in combination with trastuzumab to block both HER2 and HER3 heterodimerization. The CLEOPATRA study provided strong evidence of the value of combining trastuzumab and pertuzumab with docetaxel in patients with metastatic HER2-positive breast cancer in the neoadjuvant setting.
- **Lapatinib** is a tyrosine kinase inhibitor (TKI) that interrupts the HER2 and HER3 signaling pathways on the part of the receptor that is inside the cell. It is used with aromatase inhibitors in hormone-positive patients or with capecitabine for patients with metastatic HER2-positive breast cancer. Several other TKIs are under investigation for treating HER2-positive breast cancer, including neratinib and afatinib.
- **Ado-trastuzumab emtansine**, also known as T-DM1, is an antibody-drug conjugate consisting of trastuzumab and a cytotoxic agent, emtansine. T-DM1 enters cells and binds to tubulin—proteins important to the function and structure of the cells—preventing dimerization of the receptor and shutting down the signaling pathways. By conjugating emtansine to trastuzumab, the effects of emtansine are limited largely to cancer cells, sparing normal cells the extremely toxic effects of emtansine, and making the drug tolerable and effective. The EMILIA trial demonstrated that T-DM1 can extend survival in patients who have already been treated with trastuzumab alone and have progressed. Trials are now underway to determine the role of T-DM1 in adjuvant/neoadjuvant patients (Drakaki & Hurvitz, 2015).

The science of cancer is very interesting now. It's so important to be able to explain it all in the way each patient needs to hear it. It's an art, really. I've learned a lot from the way Dr. DeMichele explains things to patients, but I've been able to put my own spin on it too. It's a wonderful field to be in as far as science and innovation leading to better lives for our patients.

—Jennie Greco Lattimer, NP

DIAGNOSING HER2-POSITIVE BREAST CANCER

Establishing the histologic and biologic subtype is critical for every patient diagnosed with invasive breast cancer. For patients with stage I–III disease, testing is done at the time of initial surgical biopsy. Patients diagnosed with stage IV breast cancer or who have recurrent disease should have HER2 testing done at the sites of metastasis, if possible.

The FDA has approved four methods of testing for HER2 status:

- **Immunohistochemistry (IHC)** measures how much of the HER2 protein is present on the cancer cell surface. Results are rated on a scale of 0-1+ (negative), 2+ (borderline), and 3+ (positive).
- **Fluorescence in situ hybridization (FISH)** measures the numbers of HER2 gene copies inside each cell. Results are either positive, negative, or indeterminate.
- **Subtraction probe technology chromogenic in situ hybridization (SPoT-Light HER2 CISH)** measures the number of HER2 gene copies in cancer cells. The results are either positive, negative, or indeterminate.
- **INFORM HER2 dual in situ hybridization (ISH)** also measures the number of HER2 gene copies in cancer cells. The results are either positive, negative, or indeterminate.

HER2 testing can yield clearly positive or negative results or results that are borderline or unclear. Borderline IHC 2+ results should be retested with the more sensitive FISH test, SPoT-Light HER2 CISH test, or INFORM HER2 Dual ISH test to provide more precise information. By the same token, borderline FISH results should be retested with IHC. Evidence suggests there may be benefit in treating patients with low positive HER2 levels, making sensitive, accurate testing crucial to determining treatment. Studies are underway to evaluate the impact of using trastuzumab or T-DM1 with patients who have IHC 1+ and 2+ and FISH– scores.

HER2 status can change over the course of the disease. A tumor that is initially diagnosed as positive for HER2 can potentially become negative if it metastasizes, or conversely, a HER2- tumor can convert to positive when it spreads. For this reason, it is critical to retest tissue from metastatic sites even in patients who have previously been treated with HER2-targeted therapies to confirm HER2 status.

HER2-positive breast cancers are also assessed for hormone receptor status (estrogen receptor [ER]/progesterone receptor [PR]). Approximately 50% of patients with HER2-positive disease are also hormone receptor positive, and this influences treatment decisions.

Angela DeMichele, MD
We do the protein expression (IHC) test first, and if that is borderline or unclear, then we do the gene copy test (FISH) to confirm the HER2 status.

Rachel F.
My orthopedic surgeon found my mass while he was investigating my back pain. The biopsy was done at the same time as the surgery to relieve that pain. When he got the results, he called me and said, "Your oncologist is going to be happy. Your tumor is ER/PR-positive and HER2-positive. That means there are a lot of good options for you."

Jennie Greco Lattimer, NP
My patients are often confused by the difference between genetic testing to determine who is at high risk of developing cancer and genetic testing to help make treatment decisions. They may have heard of BRCA1 and 2 and be worried about that for themselves and their families, but most are not aware of HER2 status before their diagnosis.

Breast cancer is a multiclonal disease. It's possible that you can do a great job at killing the cells that are targeted—but another clone can arise, escape, and reach other sites or organs. We see this on a regular basis and it demonstrates the importance of biopsying metastases whenever possible before making treatment decisions.

—Angela DeMichele, MD

EARLY-STAGE HER2-POSITIVE BREAST CANCER

Treatment Options for Early-Stage HER2-Positive Breast Cancer

Every patient with a confirmed diagnosis of HER2-positive breast cancer needs treatment with HER2-targeted agents in combination with chemotherapy or endocrine therapy. Currently, this is true regardless of the size of the tumor and node status. Prior to the introduction of trastuzumab, the majority of women diagnosed with even early-stage HER2-positive breast cancer had higher rates of relapse, recurrence, and metastasis. Today, the disease-free survival (DFS) rate for patients with early-stage HER2-positive breast cancer is over 90% for patients with hormone receptor–positive disease and 84% for those with hormone receptor–negative disease. Overall 5-year survival for both groups is more than 95%. For patients with stage I–III disease, initial treatment includes surgery, radiation therapy where necessary, and either neoadjuvant or adjuvant therapy (Glaberman, Dayao, & Royce, 2014).

The current standard of care for a patient with stage I–III HER2-positive breast cancer is adjuvant chemotherapy (i.e., taxane with or without an anthracycline or a non-anthracycline regimen that includes carboplatin) plus trastuzumab for 12 months. There are a number of chemotherapy regimens that have been shown to be effective. And although all adjuvant and neoadjuvant therapy for HER2-positive breast cancer involves trastuzumab, the choice of chemotherapy depends on the patient's tumor status, overall health, and choice, as well as physician preference.

Taxanes include docetaxel and paclitaxel. Patients who are hormone receptor positive may also receive endocrine therapy typically after the completion of chemotherapy. Anthracyclines have been associated with irreversible cardiac toxicity and may be used less frequently in older patients or those who have preexisting cardiac conditions or risk factors. Research is increasingly focusing on developing a range of therapeutic approaches matched to the individual tumor and situation.

The most commonly used adjuvant regimens for early-stage HER2-positive breast cancer are:

- Trastuzumab with doxorubicin, cyclophosphamide, and either docetaxel or paclitaxel (AC-TH)
- Trastuzumab with docetaxel and carboplatin (TCH)
- Trastuzumab as a single agent after other therapies, including anthracyclines (Sparano, 2016)

Traditionally, neoadjuvant therapy has been used to shrink locally advanced and large tumors prior to surgery either to improve outcomes or allow for breast-conserving surgery. Researchers are

Is Trastuzumab Immunotherapy?

Many researchers believe that one of the primary mechanisms of trastuzumab is to stimulate the immune system, specifically to promote adaptive immunity, or the body's ability to recognize and react to an abnormality. Others assert that trastuzumab works primarily by blocking the signaling pathways. Researchers have established that HER2-positive breast cancer is immunogenic. There is, however, evidence that patients whose tumors have high numbers of tumor-infiltrating lymphocytes—a marker for immune response—do not benefit from adding trastuzumab to chemotherapy. The question remains open, with strong opinions on both sides, and much more work is needed to understand the relationship between breast cancer and the immune system, as well as the exact mechanisms by which targeted agents work.

studying this approach for patients with earlier disease as well. Neoadjuvant therapy now frequently includes pertuzumab. The FDA has approved pertuzumab for neoadjuvant therapy but not for adjuvant treatment of HER2-positive breast cancer. Adding pertuzumab does not significantly increase toxicity in a regimen that includes docetaxel, and it appears to have the greatest benefit in patients with stage IIb– III disease and in those who are hormone receptor negative (Sparano, 2016).

Today, the outcomes of treatment for most patients with early-stage HER2-positive disease are positive. "The bar for new drugs is very high right now," says Dr. DeMichele. "Our goals now are to identify the subset of patients who are at greater risk for recurrence, as well as to refine our approaches so that we are getting the best outcome for every patient with the least amount of toxicity."

Managing the Care of Patients With Early-Stage HER2-Positive Breast Cancer

Patients with all stages of HER2-positive breast cancer face a multitude of physical and emotional challenges. Optimal care is best delivered by a team capable of providing a full spectrum of both treatment options and supportive care. The advanced practitioner can play a key role in helping patients understand their diagnosis and treatment, manage side effects, and engage with resources to address issues such as distress, anxiety, nutrition, and exercise.

Side Effects of Treatment for Early-Stage HER2-Positive Breast Cancer

The nature and severity of side effects for patients receiving adjuvant or neoadjuvant therapy for early-stage HER2-

PERSPECTIVES

Angela DeMichele, MD
I am a huge fan of neoadjuvant therapy. It has the obvious advantage of making it easier to do surgery, but there are other advantages too. We know that patients who receive adjuvant therapy have excellent outcomes, but for those who achieve a complete pathologic response with neoadjuvant therapy, the results are even better. These patients have an excellent prognosis. We can tell them that they are very unlikely to relapse. With adjuvant therapy, it's a waiting game. In addition, the FDA granted accelerated approval for the use of pertuzumab for neoadjuvant therapy for HER2-positive disease. That means we can add an extra drug up front that gives us the dual blockade we know is effective.

Jennie Greco Lattimer, NP
When we first propose neoadjuvant therapy, our patients often feel worried about leaving the cancer in place for an extended period of time. It's natural for them to feel that way. We explain that this is active treatment for both the breast tumor and any microscopic cells that may have escaped the breast, and that we can monitor their responses very carefully. There is more uncertainty with adjuvant therapy because we can't see what's happening. Once patients understand that, they really get on board with the neoadjuvant approach.

Rachel F.
I had terrible side effects from the adjuvant chemo. I was sick all the time and had no energy or appetite. But the day the chemo ended, I was more anxious than relieved. It was like those drugs were fighting the cancer, and I felt like maybe we should just keep doing it.

Jennie Greco Lattimer, NP
Patients on HER2-positive treatment often experience diarrhea and muscle aches. If they are on chemo, they also have nausea and fatigue. The diarrhea can be very debilitating and take people away from their normal lives. They end up hurting and just staying home. That's an important issue to address. When I see patients every week or every 3 weeks, I can notice little things that are indications of problems they are having or changes in their disease status.

positive breast cancer depend largely on the chemotherapy agents that are used and their doses. Targeted therapies, while they do involve some toxicity, are often well tolerated, with some patients reporting mild or no adverse effects. More chemotherapy usually means more side effects of the kind usually associated with cytotoxic drugs. This includes alopecia, which continues to be a major issue for many women being treated for breast cancer.

Cardiac Damage: The most serious potential toxicity from targeted agents, including trastuzumab, pertuzumab, and T-DM1, is congestive heart failure or reduced cardiac function, resulting from heart muscle damage. The overall risk to patients taking trastuzumab is low (2% to 4%), but it is higher in older patients, those who have preexisting heart conditions or hypertension, and those taking anthracyclines. It is essential to monitor ejection fraction with echocardiograms and multigated acquisition (MUGA) scans in any patient taking these agents, usually every 3 months. A decrease in the left ventricular ejection fraction may require taking that patient off the therapy. Although heart damage from anthracyclines is considered permanent, evidence shows that damage from targeted therapies is reversible in most patients. In addition to a treatment break, medication can also be helpful in preserving ejection fraction, even in the short term while recovery occurs. Patients should be reevaluated after being off therapy for a period of 6 months (Volkova & Russell, 2011).

> **Hair loss is huge for** our patients. It is much more than just the impact on physical appearance to many women. Targeted therapies don't cause hair loss, and we can often choose chemotherapy agents that minimize that risk.
>
> —Jennie Greco Lattimer, NP

Infusion Reactions: Some patients experience symptoms following infusion of trastuzumab, including nausea, chills, fever, headache, dizziness, and weakness. These symptoms should usually subside within 24 hours of the infusion. Treatment for an infusion reaction may include stopping the infusion, administering corticosteroids, anti-histamine or anti-adrenergic therapies, and, in rare instances, instituting prolonged monitoring to assure full resolution of symptoms. Treatment for minor reactions can typically be resumed with a decreased infusion rate and corticosteroid pretreatment.

Diarrhea: Chronic diarrhea is the most common side effect in patients who take HER blockers, occurring in as many as 95% of patients. The prevalence and physical impact of

having diarrhea is one factor that has led to the recommendation that trastuzumab treatment be discontinued after 1 year. Studies have demonstrated no significant increased benefit from continuing treatment for longer periods, but they have found that shorter treatment spans do compromise outcomes (Bhardwaj, 2014).

Distress Screening and Psychosocial Support

Research has shown that a high percentage of patients with cancer experience some level of distress or anxiety and that those levels are often highest during the period from diagnosis through the first year of treatment. Advanced practitioners can play a key role in assessing these emotional and social issues and assuring that patients have access to appropriate resources. The availability of nurse practitioners and other advanced practitioners to answer questions, listen, and help patients and caregivers find resources is critical in managing these important issues (NCI, 2015).

Survivorship Planning

For many patients, with all types of cancer, the end of active treatment is a difficult time. One key issue is assuring that patients receive high-level medical and psychosocial support as they make the transition and beyond. Every treatment center needs to decide whether to keep patients in the system or refer them back to their primary care doctors.

Chemo brain, or cognitive impairment, is a real problem for some of our patients. It isn't listed as a side effect, but it is a reality for patients receiving chemotherapy, and one that we need to acknowledge and help them work through.
—Jennie Greco Lattimer, NP

At the University of Pennsylvania, the survivorship program works to provide each patient with a sense of continuity while not consuming physician time with follow-up visits. They do this by shifting the locus of treatment to the survivorship clinic and to a relationship with nurse practitioners. In addition to follow-up care for the cancer and management of any long-term effects, the survivorship clinic emphasizes preventative care and overall health management.

Cardiac toxicity is a major side effect with HER2 targeted therapy, so we watch a patient's ejection fraction. If it drops below a certain number, we'll need to stop therapy because we know that it can cause more toxicity.
—Jennie Greco Lattimer, NP

RECURRENT AND METASTATIC HER2-POSITIVE BREAST CANCER

Living With Metastatic HER2-Positive Breast Cancer: A Patient Profile

In April 2015, 38-year-old Rachel F. developed severe back pain. At the time, she was healthy and the mother of an 8-year-

Rachel F.
I was so relieved when I first met Dr. DeMichele. I wanted someone to take charge and say "I'm managing this and you don't have to be the only one working so hard." It was also very important to feel like I had a connection with the doctor.

Angela DeMichele, MD
When I see a patient diagnosed with advanced disease, my goal is to communicate that we are going to approach this as a chronic disease. I tell them we have treatments that will work for a while and then stop working, and then we will try something else—and that there are new things being developed right now that may be available down the line.

Rachel F.
When I first was diagnosed, I was in crisis mode. I assumed that I had very little time left. I kept thinking of things I would never do again, things for myself, for my kids that would never happen. I would never go on vacation again. I had letters to write, Christmas ornaments to make. I thought I had no time.

Jennie Greco Lattimer, NP
The first question many patients with metastatic disease ask is "How many months do I have?" We don't put a number on it. We talk about living with their disease. We encourage them to live their lives as much as possible. Many of our patients are actively involved in working or taking care of their children.

old son and 10-year-old daughter. She was also a successful professional with a demanding career in fundraising and business development for a major nonprofit organization. For 4 months, her pain levels increased until she was unable to walk without support. A magnetic resonance imaging (MRI) scan revealed a compression fracture at the L3 level, and she was referred to an orthopedic surgeon for a procedure to relieve her pain.

The workup revealed extensive bone lesions consistent with metastatic cancer, as well as a breast mass that proved to be the primary tumor. Rachel was referred to the University of Pennsylvania and diagnosed with HER2+/ER+/PR+ stage IV breast cancer with extensive bony metastases but no organ involvement. She was started on first-line therapy with trastuzumab, pertuzumab, and docetaxel, and she experienced significant nausea and fatigue during her six cycles of chemotherapy as well as diarrhea related to the pertuzumab. One year after her diagnosis, she continues on trastuzumab and pertuzumab with only mild side effects. She also takes tamoxifen and leuprolide.

Rachel's clinical response to treatment has been excellent. Her focus is now on "making her children's lives as normal as possible." She has stopped working outside the home in order to spend more time with them and to deal with the demands of her treatment schedule. She looks and feels good but is very aware of the uncertainty of her future. "If I have 2 years to live," she says, "then I want to spend it with my family, but if it's 10, I guess I should get a job. You just don't know though. Even in my most normal moments, I am aware that my future is limited. I am out of the crisis mode and into living with a chronic disease, but it's still really hard, every day."

Approximately 70% of advanced HER2-positive breast cancer is diagnosed as recurrent disease, with 30% being de novo. The former number has decreased and continues to fall with the use of more effective primary treatment. Although metastatic (stage IV) HER2-positive breast cancer is not considered curable, a number of available treatment options have been shown to extend survival with good quality of life. A small percentage of patients experience long-term responses lasting years or more.

As noted previously, it is important to attempt to biopsy metastatic sites in order to confirm the HER2 status of the disease. HER2-positive tumors can become HER2 negative, and in some cases, the opposite can occur. Knowing the HER2 status is critical to making appropriate treatment decisions.

The most common sites of metastasis for HER2-positive breast cancer are bone, liver, lungs, and brain. Brain metastases are common in HER2-positive disease and require an altered approach to treatment, as most agents do not cross the blood–brain barrier. Patients are typically not screened regularly for brain metastases, but any patient who exhibits symp-

toms such as headaches, confusion, memory loss, weakness, or numbness should be evaluated. Treatment includes radiation and, in cases of limited (i.e., one to four) metastases, surgery to remove the tumors. Those patients with metastatic disease in other sites should continue to receive anti-HER2 therapy (Kennecke et al., 2010).

Treatment Options for Metastatic and Recurrent HER2-Positive Breast Cancer

Clinical trials have played a critical role in establishing the current arsenal of therapies available to treat both early-stage and metastatic HER2-positive breast cancer. There is still a strong focus on developing new agents, including those that block multiple pathways, TKI inhibitors, and immunotherapy. Many trials aim to uncover the optimal use of therapies both to improve outcomes and minimize toxicity.

First-Line Treatment

- For patients who have not previously received anti-HER2 therapy, the first-line treatment is trastuzumab, pertuzumab, and chemotherapy, often with docetaxel or paclitaxel.
- Hormone receptor–positive patients receive tamoxifen and an aromatase inhibitor plus either trastuzumab or lapatinib.
- Patients who have previously been treated with trastuzumab receive additional trastuzumab, pertuzumab, and chemotherapy, typically either docetaxel or paclitaxel.

Note that the CLEOPATRA study established the benefit of adding pertuzumab to the then standard first-line regimen of trastuzumab and docetaxel. The benefit was seen in overall survival (56.5 vs. 40.8 months) with little difference in the toxicity profile, and there was no increase in cardiac toxicity in the pertuzumab arm (Swain et al., 2013). As pertuzumab provides a dual blockade of HER2, it is now considered standard in first-line therapy—as well as neoadjuvant therapy in many patients. Figuring out how to shut off cancer cells' ability to utilize alternatively signaling pathways is a crucial step forward in the effort to prevent or delay treatment resistance.

Even patients who have relapsed or recurred after receiving trastuzumab can still benefit from it in the metastatic setting when it is combined with pertuzumab or chemotherapy. In first-line therapy for HER2-positive metastatic breast cancer, the chemotherapy is usually given for 4 to 6 months, while the anti-HER2 therapy and endocrine therapy continue indefinitely, when appropriate.

Resistance continues to be a major issue in treating metastatic HER2-positive breast cancer. Most metastatic patients

Angela DeMichele, MD
We continue the anti-HER2 drugs indefinitely. They do have side effects, but they are generally tolerable. The chemo causes both short- and long-term effects, and the evidence is strong that there is no benefit in giving more than six cycles. That can be difficult for patients to understand, but we are looking for the best outcomes with the best quality of life.

Rachel F.
Now I'm trying to make my life and my family's life as normal as possible. It's still hard though. It's been a very different year than I expected, but really, most days look like they did before my diagnosis.

Rachel F.
It's always there, knowing that the next scan will show progression, that we'll run out of treatments. Sometimes I think I'm doing well emotionally, and then I'll spend a whole day crying. It's not that I don't dream anymore of what can be, but it's so much more fine, more limited.

Angela DeMichele, MD
Every person living with metastatic HER2-positive breast cancer lives with that uncertainty. The clinical course is going to be different for each person. We are providing the best treatment available, but we also have to support a patient's other needs as well. That can mean managing the long-term effects of treatment, dealing with issues related to sexuality and intimacy, scheduling nutritional consults, or just understanding that as much progress as we have made, our patients inhabit a strange and difficult world.

will relapse, often after 18-24 months on first-line treatment (NCI, 2016b).

Second-Line Treatment

Ado-trastuzumab emtansine: The most promising agent currently available for treating patients with HER2-positive breast cancer who progress on first-line therapy is ado-trastuzumab emtansine (T-DM1). This antibody-drug conjugate incorporates the HER2-targeted antitumor properties of trastuzumab with the cytotoxic agent emtansine (DM1). The combination is a mechanism for delivering the drug intracellularly, potentially improving the response rates and benefits to patients while minimizing damage to normal tissue.

Several studies have established the benefit of T-DM1 as second-line therapy for HER2-positive breast cancer. T-DM1 is usually given as a single agent and has a favorable toxicity profile when compared with regimens that include chemotherapy or lapatinib. The most common adverse effect is thrombocytopenia, while diarrhea, a side effect of other treatments, is less common. A large study, MARIANNE, demonstrated that T-DM1 either as a single agent or in combination with pertuzumab did not yield better results than the current standard, trastuzumab/taxane, for first-line therapy in previously untreated metastatic HER2-positive patients.

Lapatinib: Lapatinib is a TKI that is often used in combination with chemotherapy or an aromatase inhibitor in hormone receptor–positive patients who have relapsed on anti-HER2 targeted therapies. Capecitabine is the most common chemotherapy agent combined with lapatinib. The most common side effects of lapatinib are rash and diarrhea.

Chemotherapy: Several drugs have activity against metastatic breast cancer. They include anthracyclines, taxanes, alkylating agents, platinums, antimetabolites, vinca alkaloids, and other drugs such as gemcitabine. Anthracyclines are associated with cardiac toxicity, a risk that is increased when they are used with anti-HER2 agents. As a result, many physicians now prefer to use nonanthracyclines whenever possible in treating HER2-positive breast cancer.

There is little evidence to support giving combination chemotherapy to patients who have progressed on first- and second-line therapies for their advanced disease. Although response rates tend to be higher with the combinations, overall survival does not. The physician and patient together should choose which agents to use in what order and for what duration based on the rate of disease progression, the patient's health status, and life preferences.

Trials are currently underway to reduce the incidence of cardiotoxicity in patients receiving anthracyclines. These include using a cardio protective drug, dexrazoxane, and altering the method of administration for doxorubicin. Patient selection

is also important in minimizing cardiotoxicity. Patients who are older and have a history of chest wall irradiation, previous exposure to anthracyclines, hypertension, and underlying heart disease or diabetes are all at increased risk of developing treatment-limiting or life-threatening heart issues (NCI, 2016b).

A number of new HER2-targeted agents are currently in clinical trials, as are new approaches to the treatment of HER2-positive brain metastases. It is important to consider clinical trials as a way to extend treatment options for patients.

Clinician Roles in Managing the Care of Patients With Metastatic and Recurrent HER2-Positive Breast Cancer

Regardless of whether it is de novo or a recurrence, the diagnosis of metastatic breast cancer is a life-altering event. A person moves from being a healthy person to a patient with an incurable disease, finding her worst anxieties confirmed. Many patients are not aware of the meaning of metastatic breast cancer until they learn they have it. For the HER2-positive metastatic population, physicians and advanced practitioners need to:

- Educate patients about the available treatment options
- Educate patients about the potential chronic nature of the disease
- Provide care and support for side effects, especially those resulting from chemotherapy
- Provide social and emotional support to help patients deal with uncertainty, anxiety, and depression
- Help patients align treatment decisions with their values and life goals

FUTURE IMPLICATIONS

In 3 decades, HER2-positive breast cancer has been transformed from a disease noted for its aggressive clinical course and poor prognosis to one that is often curable when detected early and treatable in its advanced stages. Through collaborative practice, clinicians will be able to best support their patients as they journey through this life-altering experience.

Acknowledgments

Grateful thanks to Dr. DeMichele and Ms. Lattimer for sharing their time, expertise, and unique perspectives. Special appreciation goes to Rachel F. for sharing her candid comments, and her unique perspective on this life-altering experience.

Disclosure

Dr. DeMichele has been a consultant for Novartis and Pfizer, and has received grants from Calithera Biosciences, Genentech, Novartis, and Pfizer. Ms. Lattimer has served on a speakers bureau for Genentech.

PERSPECTIVES

Angela DeMichele, MD
The current paradigm for advanced HER2-positive breast cancer is HER2 therapy indefinitely. We have a number of options that we can use depending on the previous treatment history, hormone receptor status, and the patient's overall health status and goals.

Rachel F.
People ask me all the time when I will finish my treatment. They don't understand that the answer is never. I look healthy and I feel good, and it is very hard for people to grasp that I have a chronic disease that could threaten my life at any time.

References

American Cancer Society. (2016). How is breast cancer classified? Retrieved from cancer.org/cancer/breastcancer/detailedguide/breast-cancer-classifying

Baselga, J., Tripathy, D., Mendelsohn, J., Baughman, S., Benz, C. C., Dantis, L.,...Norton, L. (1996). Phase II study of weekly intravenous recombinant humanized anti-P185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *J Clin Oncol, 14*(3), 737–744.

Bhardwaj, A. S., & Tiersten, A. D. (2014). Common adverse effects of anti-HER2 therapies and practical management recommendations. Retrieved from www.onclive.com/publications/contemporary-oncology/2014/february-2014/common-adverse-effects-of-anti-HER2-therapies-and-practical-management-recommendations

Breastcancer.org. (2016). HER2 status. Retrieved from http://www.breastcancer.org/symptoms/diagnosis/her2

Cancer.Net. (2014). Treatment of metastatic HER2-positive breast cancer. Retrieved from http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-her2-positive-breast-cancer

Drakaki, A., & Hurvitz, S. (2015). HER2-positive breast cancer: Update on new and emerging agents. *American Journal of Hematology/Oncology, 11*, 17–23.

Glaberman, U.-B., Dayao, Z., & Royce, M. (2014). HER2-targeted therapy for early-stage breast cancer: A comprehensive review. *Oncology (Williston Park), 28*(4), 281–289.

Harbeck, N., Beckmann, M. W., Rody, A., Schneeweiss, A., Müller, V., Fehm, T.,...Jacisch, C. (2013). HER2 dimerization inhibitor pertuzumab: Mode of action and clinical data in breast cancer. *Breast Care (Basel), 8*(1), 49–55. http://dx.doi.org/10.1159/000346837

Kennecke, H., Rinat, Y., Woods, R., Cheang, M. C., Voduc, D., Speers, C. H.,...Gelmon, K. (2010). Metastatic behavior of breast cancer subtypes. *Journal of Clinical Oncology, 28*(20), 3271–3277. http://dx.doi.org/10.1200/JCO.2009.25.9820

Kumar, G. L., & Badve, S. S. (2008.) Milestones in the discovery of HER2 proto-oncogene and trastuzumab (Herceptin). Retrieved from http://www.dako.com/index/knowledge-center/kc_publications/kc_publications_connection/kc_publications_connection12.htm/28827_2008_conn12_milestones_discovery_her2_proto-oncogene_and_trastuzumab_kumar_and_badve.pdf

Morgan, J. P. (2016). Cardiotoxicity of trastuzumab and other HER2-targeted agents. Retrieved from http://www.uptodate.com/contents/cardiotoxicity-of-trastuzumab-and-other-her2-targeted-agents

National Cancer Institute. (2015). Adjustment to Cancer: Anxiety and Distress (PDQ)–Health Professional Version. Retrieved from http://www.cancer.gov/about-cancer/coping/feelings/anxiety-distress-hp-pdq

National Cancer Institute. (2016a). A story of discovery: HER2's genetic link to breast cancer spurs development of new treatments. Retrieved from www.cancer.gov/research/progress/discovery/HER2

National Cancer Institute. (2016b). Breast Cancer Treatment (PDQ)–Health Professional Version: Metastatic Breast Cancer. Retrieved from http://www.cancer.gov/types/breast/hp/breast-treatment-pdq

Rubin, I., & Yarden, Y. (2001). The basic biology of HER2. *Annals of Oncology, 12*(suppl 1), S3–S8.

Sparano, J. A. (2016). Breast cancer treatment protocols. Retrieved from http://emedicine.medscape.com/article/2006464-overview

Subbiah, I. M., & Gonzalez-Angulo, A. M. (2014). Advances and future directions in the targeting of HER2-positive breast cancer: Implications for the future. *Current Treatment Options in Oncology, 15*(1), 41–54. http://dx.doi.org/10.1007/s11864-013-0262-4

Swain, S. M., Kim, S. B., Cortes, J., Ro, J., Semiglazov V., Campone, M.,...Baselga, J. (2013). Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA stupd): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncology, 14*(6), 461–471.

Volkova, M., & Russell, R. 3rd. (2011). Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Current Cardiology Reviews, 7*(4), 214–220.