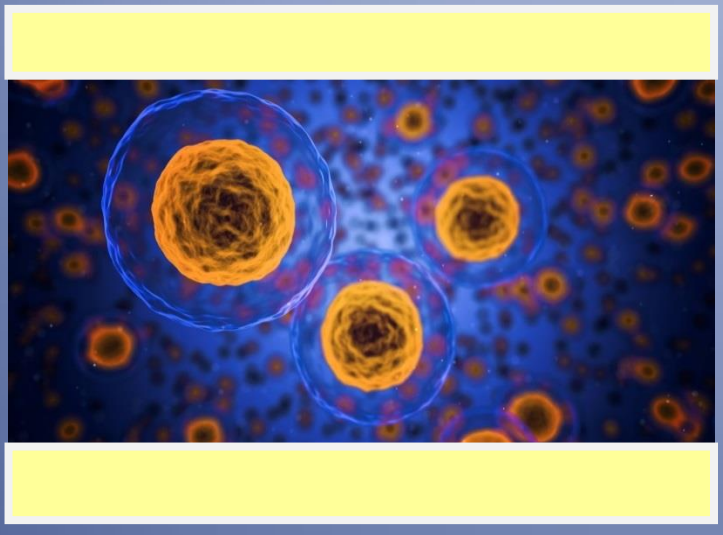


THE INSIDER'S GUIDE TO METASTATIC BREAST CANCER

A Summary of the Disease and its Treatments

by Anne Loeser

TABLE OF CONTENTS

Dedication

This book is dedicated to:

* *My friends who lost their lives to metastatic breast cancer, and to their loved ones and caregivers*

* *Each person whose life has been touched by this disease including patients, their families, friends, and caregivers*

* *The large and valuable group of metastatic breast cancer patients who have provided helpful information captured in this book*

* *My husband Steve, parrot Pumpkin, my friends, and my outstanding integrative health care team*

1. Disclaimer

The material herein has been gleaned from books, Internet sources and other metastatic breast cancer (MBC) patients. It is not a substitute for professional medical diagnosis, treatment, or direction.

Readers are instructed to discuss potential therapies or remedies with their medical teams before taking action.

The author, a metastatic breast cancer patient, is a layperson with no medical training. She does not advocate any specific treatment(s) or type(s) of therapies listed herein.

Although every effort has been made to offer comprehensive, precise, and fact-based information, the author makes no warranties regarding its accuracy, completeness, timeliness, comparative or controversial nature, or usefulness. Since health-related data changes frequently, some material may be outdated, incomplete, or incorrect.

The author does not, and will not, accept any responsibility or liability for any decisions, actions, and/or treatments undertaken or avoided by the reader as the result of perusing this document. Those who do not agree to these terms must close this book and read no further. Those who proceed with reading agree to accept and abide by these terms and conditions without contest.

2. Introduction

The adage that "knowledge is power" is particularly compelling when dealing with issues affecting survival and quality of life.

This book was created with a single purpose: to help metastatic breast cancer (MBC) patients and their loved ones cope with a complex and difficult disease. It provides a wealth of information about approved therapies in the U.S., Canada, Europe, and Australia, scientific studies, cutting edge research, symptom mitigation, clinical trials, palliative care, and more. Readers are encouraged to print and discuss relevant portions with their medical teams in order to jointly assess and decide upon optimal therapeutic approaches.

Viewers preferring an eBook or hardcopy version are welcome to visit ***https://www.amazon.com/Insiders-Guide-Metastatic-Breast-Cancer-ebook-dp-B07NJ8GZ7M/dp/B07NJ8GZ7M/ref=mt_kindle?_encoding=UTF8&me=&qid=1550081148***

Patients wishing to read about heartwarming experiences with MBC, humorous anecdotes, or remarkable recoveries are encouraged to look elsewhere, as *The Insider's Guide to Metastatic Breast Cancer* is none of these. Instead, it is a comprehensive, current, science-based handbook that readers will leverage throughout every step of their experience.

As one reader stated, *"It is a true guide for us, all trying to cope with this terrible disease. It also provides hope, as understanding more about the disease, subtypes and where to look for further information and clinical trials is so useful. I have been trying to collect and document material for 2 years now, but this is nothing compared to the extent of your Guide. Thank you so much for your research, compilation and efforts in sharing this masterpiece of work."*

3. About the Author

Anne Loeser is a layperson with decades' worth of firsthand experience with breast cancer. Her initial encounter with the disease occurred at age 35 when she found a lump during a breast self-examination that subsequently failed to appear on a mammogram and an ultrasound, and was dismissed by her medical team as inconsequential. Four years later in 1993 after Anne's doctor finally agreed to perform a breast biopsy, the results revealed ER+/PR+ breast cancer (HER2 status was not tested at the time). Following a double mastectomy accompanied by lymph node removal, Anne underwent 6 rounds of chemotherapy, 5 years of Tamoxifen, and 7 years of an experimental T/Tn antigen immunotherapy vaccine which unfortunately is no longer available.

Fourteen years after her Stage 2 breast cancer diagnosis, Anne developed a dry hacking cough which was misdiagnosed by multiple physicians over the course of four years as post nasal drip and asthma. Throughout this period Anne continued to work as a software development project manager, returning home nightly with intensifying fatigue and weight loss. Annual appointments with her Medical Oncologist indicated that Anne's Tumor Markers and other routine follow up tests were completely normal, so the possibility of recurrent breast cancer as the cause of her symptoms never crossed either her or her doctor's minds.

A few months after retiring in 2011, Anne became hoarse and visited a medical specialist who determined that one of her vocal cords was paralyzed. A CT scan revealed the presence of multiple lung nodules, one of which was pressing against a laryngeal nerve that in turn was causing vocal cord paralysis. By then, disease-related nerve damage had precipitated a condition called Horner's Syndrome which caused a droopy eyelid, decreased pupil size, and the absence of sweating on the left side of her face. Further tests revealed the presence of malignant pleural and pericardial effusion, and her pathology report revealed MBC that was hormone receptor positive and HER2 negative.

Anne's Medical Oncologist suggested that she enroll in a clinical trial consisting of chemotherapy drugs in an unproven combination (the trial subsequently failed). Instead, at her friends' suggestion, she sought a second opinion from an oncologist who proposed that she try hormonal therapy in the form of an Aromatase Inhibitor. Seeking a second medical opinion spared Anne the toxic side effects of chemotherapy, taught her the importance of seeking multiple expert opinions, and emphasized the value of undertaking research when making treatment decisions. Over time, Anne added a Naturopathic Oncologist to her medical team with the purpose of integrating conventional and complementary therapies into her medical care.

Despite being a layperson with no medical background or scientific training, Anne conducted extensive research regarding MBC and its treatments. The result is this Guide.

An individual member of the Metastatic Breast Cancer Alliance, Anne is a published writer who has co-authored a peer-reviewed ***article*** regarding Atypical Patient Responses that was printed in *Nature Partner Journal Breast Cancer* **[1, PMID:28649647]**.

It is Anne's hope that this book will provide knowledge that will enable you or a loved one to attain the best possible outcome and quality of life.

4. Overview and Suggestions

As previously stated, the purpose of this book is to serve as a reference regarding metastatic breast cancer (MBC) and related therapies. An important consideration is that certain supplements and therapies may interfere with drugs or treatments undertaken by patients. Therefore, when considering new potential therapeutic options, readers should consult with their physician before starting any new therapy or supplement. And whenever possible, the reader is encouraged to obtain a second (or even a third) medical opinion about treatment, especially upon initial MBC diagnosis and when the disease progresses.

Where possible, ***website information*** regarding statistics and studies has been provided. Therefore, patients who find something of interest are encouraged to print the appropriate section of this book along with the corresponding reference information to discuss with their physician.

Whenever extensive information has been provided within a section, a bulleted summary is provided at the beginning in order to provide an "at a glance" overview of the material to follow.

The author has deliberately avoided two topics: cannabis and specific diets. The reason for excluding cannabis is that there are multiple methods of preparing and ingesting it. Due to these variations and inconsistencies - as well as legality issues - this topic has been excluded. With respect to diet, there are nearly as many perspectives and opinions as there are MBC patients! Those who may be interested in diet-related information are encouraged to read an excellent book by Dr. David Servain-Schreiber entitled, *Anti-Cancer: A New Way of Life*. Dr. David Servain-Schreiber was a physician who lived for nearly 20 years with a malignant brain tumor by following the principles in his book as well as conventional treatment.

Although there are many relevant chapters in this book, readers may find the following to be of particular interest:

Helpful Hints and Facts

Types of Breast Cancer – especially the subsection entitled, *Testing for Hormonal and HER2 Status*

Oligometastases (limited tumor spread that may be highly treatable or in some instances, curable)

Tests for Breast Cancer Spread

Personalized Medicine

Clinical Trials Overview

Tumor Biopsy for New Metastatic Sites

Palliative Care

Based upon your cancer's profile:

Hormone Receptor Positive MBC, Hormonal Therapies, and Resistance

HER2 Positive MBC and Related Therapies

Triple Negative MBC and Related Therapies

Hormone Receptor Positive, HER2 Positive MBC and Therapies

5. Helpful Hints and Facts

This section was initiated by a patient named Timarie of the Inspire Advanced Breast Cancer forum. It is reprinted below (with some additions) as per Timarie's consent and the author's gratitude.

1. Keep copies of all your medical records and test results for ease of reference. These include blood tests, pathology reports, clinic summaries, scans and radiology reports, etc. The reports may contain key information that your doctor might not have noticed or mentioned. Furthermore, retaining your own copies will make it easier if you eventually transfer to a different medical network.

2. Whenever possible, select a trusted friend and/or family member to serve as your advocate, and ask them to accompany you to doctors' visits and treatment sessions. Your advocate can take notes and help you later recall important points that were discussed.

3. Seek a second – or even a third – professional opinion before starting any new treatment. A second or third opinion may potentially provide a critical difference in direction and outcome.

4. If you are experiencing difficulty breathing, acute pain, or significant swelling, proceed immediately to the Emergency Room and notify your doctor because these symptoms may be related to a serious medical issue.

5. Bring a list of questions to discuss with your health provider(s) during appointments. A knowledgeable and confident doctor should fully and clearly respond to your questions and concerns. If your doctor is impatient or refuses to answer your questions, consider finding a different physician who will work with you in a considerate manner. Hopefully you'll have a long relationship with your physician, so it's essential that you partner together well!

6. Before beginning a new therapy, consult with your doctor about taking "baseline" tests such as blood work, scans, and DEXA (bone density tests) which can be used for future comparison.

7. Ask your doctor if there are any foods, supplements, or medications that must be avoided while on your treatment. Also make sure your doctor is aware of all medications and supplements that you are taking. Since physicians are not always aware of all possible contraindications, you can look up the drug on this website to personally verify this information: ***https://www.drugs.com/drug_interactions.php***

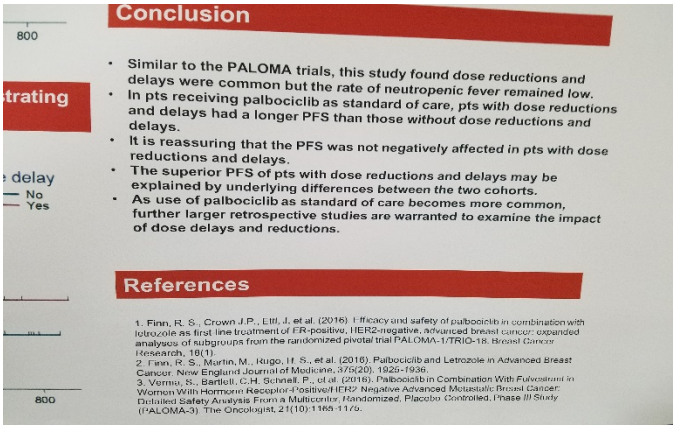
8. Similarly, before embarking on a new treatment, ask your doctor about potential side effects and how to mitigate them if they arise.

9. If you are experiencing pain, discomfort, or other problems, inform your medical team accordingly. If the initial remedy is ineffective, request another (or stronger) option. Continue this process until the prescribed medication or therapy successfully works, or until it works well enough that you are able to live with it. Quality of life issues are all-to-often underreported and/or overlooked. Therefore, it is extremely important that anyone living with MBC strive to obtain the best possible degree of comfort. (The chapter about *Palliative Care* may be especially helpful in this regard).

10. If you are taking a generic drug and are having problematic side effects from it, consider switching to a different drug manufacturer. If that doesn't help, try taking the brand name medication if possible. Many of the ingredients in a drug are not the "active" ingredient; rather, they are included for purposes of holding the pill together, coating it, and controlling the way that the active drug is delivered into the body. Individuals can have varying sensitivities to these inactive ingredients (often referred to as "fillers), and moving from one drug manufacturer to another may therefore help alleviate side effects.

11. If you're having difficulty with side effects from treatment or are concerned about potential side effects, speak with your medical team about reducing the drug's dosage and/or frequency. Too often, the FDA-approved dosages are unnecessarily toxic, and a lower dose may be equally effective. Dr. Tatiana Prowell of the FDA indicated that patients do not have to use the FDA-approved dose of the drug if there is reason for using a smaller, less toxic dose. She stated that, "Dose is something that we are increasingly recognizing as a common error that is probably the easiest to avoid. In oncology, specifically, drug developers tend to move forward with the maximum tolerated dose even though it is not clear it is necessary or appropriate for targeted drugs. This happens even when they have data suggesting that a targeted therapy maximally inhibits or stimulates its target at a much lower dose. It results in a lot of unnecessary toxicity." **From[2, PMID:24875091]:** ***http://cdn2.hubspot.net/hub/1670/file-983271054-pdf/Tatiana_Prowell_(1).pdf?t=1449608504236***

    Data supporting the equal (and in some cases, superior) efficacy of reduced drug doses is becoming increasingly available, as per the following Poster presented at 2017 SABCS.



12. Patients may ask questions and receive a free professional response from Johns Hopkins regarding a potential therapy or other issues at this site**:** ***http://www.hopkinsbreastcenter.org/services/ask_expert/metastatic_breast_cancer/***

13. Consider discussing complementary therapies with your medical team in order to help relieve symptoms and side effects. In a landmark statement made on June 12, 2018, the American Society of Clinical Oncology (ASCO) published its endorsement of integrative therapy guidelines recently established by the Society for Integrative Oncology (SIO). The SIO guidelines were reviewed by an ASCO expert panel and recommend that:

    Music therapy, meditation, stress management, and yoga are used for anxiety/stress reduction.

    Meditation, relaxation, yoga, massage, and music therapy are used for depression/mood disorders.

    Meditation and yoga are practiced in order to improve quality of life.

    Acupressure and acupuncture (in addition to anti-nausea medications) be leveraged for reducing chemotherapy-induced nausea and vomiting. **From[3, PMID:29889605]:** ***https://www.sciencedaily.com/releases/2018/06/180612092128.htm***

14. Explore additional palliative care with your doctor. Palliative care is meant to help anyone living with a serious illness by maximizing their comfort level as much as possible. It differs from hospice care in that you do not need to be near end of life, and you can continue to receive standard treatment. You can request palliative care at any age and any stage of your illness (even upon diagnosis). Studies suggest that when outpatient specialty palliative care is delivered together with routine oncologic care,

symptom management, pain control, and quality of life are significantly improved as a result. (Read more about this helpful option in the *Palliative Care* section of this document).

15. If you are interested in enrolling in a clinical trial, consider calling 1.800.4.CANCER (1.800.422.6237). A knowledgeable representative will conduct a free customized search based upon your cancer's pathology (i.e. ER, PR and HER2 status) as well as your particular interests such as immunotherapy, chemotherapy, hormonal therapy, targeted therapy, etc.

16. If you're seriously considering entering a Phase 2 or a Phase 3 clinical trial, you might want to investigate the efficacy and toxicity results of the experimental drug from a prior clinical trial phase(s). This additional information may prove extremely helpful when deciding whether or not to enroll.

17. If you routinely have trouble scheduling appointments, ask to speak to the scheduler's manager and also notify your physician. Generally, the scheduling staff is managed separately from the physician, so your doctor may be unaware of the effort involved in making an appointment.

18. There is no way to determine in advance what treatments will work for you, although research is making strides in tailoring treatments based upon individual patient characteristics. Other patients with the same hormone receptor and HER2 status as yours may fare differently than you do, so what works well for you might not work well for another patient (or vice versa).

19. If a treatment works well, there is no way to predict how long it will continue to work. It may be effective for months or even years. Regular tests and follow-up visits are needed in order to determine whether your protocol remains effective, or if a change in treatment may be warranted.

20. There is no way to predict what side effects you might experience on a treatment. One person may feel well on a particular protocol whereas another may not. Furthermore, a lack of side effects does not mean that the therapy is not working!

21. If the cancer has spread from one place in your body to another, it is helpful to obtain a biopsy of the tumor(s) in the new area to determine whether the cancer cells have a different hormonal and/or HER2 profile from that those in the original area. An example is cancer changing from HER2- to HER2+, or from ER-to ER+. If the cancer's profile has shifted, it can change your recommended treatment.

22. Blood Tumor Markers (TMs) may be an excellent indicator of how cancer is behaving for some people, whereas they may be completely worthless for others. And in some instances, TMs may start off being accurate and then stop being accurate. Therefore, TMs should never be used in isolation when determining whether to undergo a treatment change.

23. If progression of your cancer is detected, you may want to ask your doctor about delaying a treatment change until a subsequent test (possibly a month or two thereafter) confirms the continuance of progression. The possibility of deferring a change in treatment should only be considered if: 1) the progression is not life-threatening, 2) it is not causing symptoms or complications, and 3) it is not considered by the doctor to be significant enough to warrant immediate change. (One patient taking Ibrance and Faslodex noted that her cancer remained stable for 5 cycles (about 4 months), at which point her CT results showed progression in the liver. The patient's oncologist felt that the treatment should be changed, but due to an unforeseen delay, her treatment was not altered. Two months thereafter, a follow up CT showed stable disease, so she has remained on this treatment for 11 cycles (about 11 months) and her tests continue to show stable disease).

24. At some point you may potentially be a candidate for hormonal therapy irrespective of your cancer's hormone receptivity status, provided that your cancer is in the bones, soft tissue (muscle, fat or nerves), or internal organs and is not causing symptoms. This is because sometimes the metastasis is indeed hormone receptor positive and the test results are incorrect, and also due to the fact that breast cancer can be heterogeneous (for example, some cells may be hormone receptor negative and others may be hormone receptor positive). (More about this is in the section entitled, *Types of Breast Cancer.)*

25. Hormonal therapy is not a less aggressive or a weaker treatment than chemotherapy ("chemo") when prescribed appropriately. Hormonal therapy may have fewer and more tolerable side effects than chemo and can be more effective in certain patients. If your cancer is Estrogen Receptor (ER) and/or Progesterone Receptor (PR) positive (meaning that it is Hormone Receptor [HR] positive), or if your cancer's hormone receptor status is unknown, hormonal therapy is usually a good first choice – provided that you are not experiencing acute symptoms from the disease.

26. Some patients whose breast cancer is considered Hormone Receptor negative and/or HER2 negative may have been misclassified based upon their test results. Additional information about this is provided in section entitled, *Types of Breast Cancer* under *Testing for Hormonal and HER2 Status.*

27. Because it doesn't show up as a solid tumor and looks more like a spider web, Lobular metastatic breast cancer may difficult to diagnose and track. It also tends to migrate to the abdominal area, so if you are diagnosed with Lobular MBC, be especially proactive in reporting abdominal pain and/or swelling to your doctor.

28. If you will be taking the chemo drugs Xeloda or 5-FU, speak with your doctor about getting tested for specific mutations in the DPD (dihydropyrimidine dehydrogenase) gene that could cause severely toxic or potentially life-threatening reactions to these drugs. Approximately 3% to 5% of the population has some degree of DPD deficiency that can put them at risk if they take these drugs.

29. Since chemotherapy and various targeted therapies such as Herceptin (Trastuzumab) can potentially cause damage to the heart, liver, lungs, and/or kidneys, ensure that your medical team is fully aware of any existing medical issues you have regarding these areas, and that you are monitored while taking these drugs.

30. If you receive injections of any kind (including but not limited to Faslodex or Xgeva) request that the vaccine be warmed first and then injected slowly. This will help minimize pain immediately following the injection.

31. If you receive steroids as part of your treatment, you may be more susceptible to getting cataracts. Therefore, be especially diligent about reporting ocular (eye) changes and getting routine eye exams.

32. If you're a "de novo" patient who was diagnosed with MBC without previously having early stage breast cancer, recent research indicates that surgery to remove the primary tumor may help extend survival. **From[4, PMID:29777404]:** ***http://www.eurekalert.org/pub_releases/2016-06/uops-itc060116.php***

33. MBC patients who live in the US should be aware that they may qualify for Social Security Disability Insurance (SSDI) if they have spent sufficient time in the workforce and paid sufficient Social Security taxes. For those who are accepted, there is normally a 5-month waiting period before the first check is issued. Two years after acceptance, patients will be able to go on Medicare. Additional information about SSDI may be found at: ***http://www.ssa.gov/disability/***

34. Remember that many people with MBC can live with the disease for years…possibly longer than statistics might lead one to believe. By the time they are published, survival statistics may be outdated due to the introduction of newer and more effective drugs. How long a particular MBC patient lives seems to be mostly dependent on how well their cancer responds to various treatments. Some people also believe that lifestyle may also play a helpful role in survival. Many patients who were initially given only months to live by their doctors are still alive years later, and for reasons that are being investigated, a very small proportion of patients may proceed to live a normal life span.

6. Types of Breast Cancer and Related Tests

If breast cancer is suspected, a biopsy (removal of tissue) will be done to check to determine what, if any, type of breast cancer is present.

Patients who are already aware of the type of breast cancer they have - such as Invasive Ductal Carcinoma - may prefer to skip a few pages to read about *Tests for Hormonal Status.*

Patients who may not know what type of breast cancer they have are encouraged to review the following section and ask their doctor which type of breast cancer they were diagnosed with. This is important because some types of breast cancer, such as Invasive Lobular Carcinoma, tend to metastasize to parts of the body that other types of breast cancers generally avoid. Therefore, patients with this form of breast cancer need to be especially vigilant in identifying and reporting related symptoms to their doctor.

TYPES OF BREAST CANCER

On a very general level, once breast cancer is found, it is categorized as either **Non-Invasive** or **Invasive:**

- **Non-Invasive Breast Cancer** (also known as Carcinoma In Situ) is when cancer is found inside the milk ducts or lobules, but it appears not to have spread to nearby tissue or beyond. This may also be referred to as "pre-invasive breast carcinoma. In situ breast cancer can subsequently develop into invasive breast cancer. On occasion, people diagnosed with in situ breast cancer have subsequently been found to have breast cancer elsewhere in the body.

  There are Two Common Types of Non-Invasive Breast Cancer (Carcinoma In Situ):

  Ductal Carcinoma In Situ (DCIS) is the most common type of non-invasive breast cancer. "Ductal" means that the cancer starts inside the milk ducts, and "in situ" means that the abnormal growth remains inside milk duct and appears not to have spread to surrounding tissues. Having DCIS can increase the risk of developing an invasive breast cancer later on. Most recurrences happen within the 5 to 10 years after initial diagnosis, and the chance of a recurrence is under 30%.

  Lobular Carcinoma in Situ (LCIS) is an area(s) of abnormal cell growth that increases a person's risk of subsequently developing invasive breast cancer. "Lobular" means that the abnormal cells start growing in the lobules, which are the milk-producing glands at the end of breast ducts. As previously mentioned, "in situ" means that the abnormal growth remains inside milk duct and appears not to have spread to surrounding tissues. People diagnosed with LCIS may tend to have more than one lobule affected. LCIS does not cause symptoms and usually does not show up on a mammogram, so it tends to be diagnosed as a result of a biopsy performed for some other reason.

- **Invasive Breast Cancer** refers to when abnormal cells break out of the lobules or milk ducts and move into nearby breast tissue and/or lymph nodes. Cancer cells can travel from the breast to other parts or organs of the body ("metastasize") through the blood stream or the lymphatic system. Cancer cells may travel early when the tumor is small, or later when the tumor is large.

  There are many types of Invasive Breast Cancer, as described below.

  Invasive Ductal Carcinoma: About 70% to 80% of all breast cancers are Invasive (or Infiltrative) Ductal Carcinoma (**IDC**), where the abnormal cancer cells that began in the milk ducts have spread into other parts of the breast tissue and possibly beyond. **From**: ***http://www.nationalbreastcancer.org/invasive-ductal-carcinoma***

  Specific sub-types of Invasive Ductal Carcinoma (IDC) include:

Invasive Carcinoma of No Special Type (NST) or Not Otherwise Specified (NOS), which is the most common form of invasive breast cancer. It accounts for 55% of breast cancer incidence upon diagnosis. Sometimes this type of cancer is simply referred to as Infiltrating Ductal Carcinoma.

Invasive Cribriform Carcinoma is a type of breast cancer in which the cancer cells invade the stroma (connective tissues of the breast) in nest-like formations between the ducts and lobules. Within the tumor, there are distinctive holes in between the cancer cells, making the tumor resemble Swiss cheese. Invasive cribriform carcinoma is usually low grade. In about 5%-6% of invasive breast cancers, some portion of the tumor can be considered cribriform. Usually, some DCIS of the cribriform type is also present.

Invasive Papillary Carcinomas of the Breast accounts for less than 1-2% of invasive breast cancers. Invasive papillary carcinoma usually has a well-defined border and is made up of small, finger-like projections. In most cases of invasive papillary carcinoma, ductal carcinoma in situ (DCIS) is also present.

Medullary Carcinoma of the Breast represents about 3-5% of all breast cancers. It is called "medullary" because the tumor is a soft, fleshy mass that resembles a part of the brain called the "medulla." It's more common in women who have a BRCA1 mutation. The cells are usually high-grade in their appearance and low-grade in their behavior. So, whereas they look like aggressive abnormal cancer cells, they don't usually act like them. Medullary carcinoma may typically be easier to treat than other types of breast cancer.

Mucinous Carcinoma of the Breast — sometimes called "colloid" carcinoma — is a rare form of invasive ductal carcinoma. In this cancer, the tumor is made up of abnormal cells that "float" in pools of mucin, a key ingredient in the slippery substance known as mucus. In mucinous carcinoma, the mucin becomes part of the tumor and surrounds the breast cancer cells. Under a microscope, it looks like the cancer cells are scattered throughout pools of mucus. Only about 2-3% of invasive breast cancers are "pure" mucinous carcinomas; about 5% of invasive breast cancers appear to have a mucinous component within them, along with other types of cancer cells present. Overall, it is a less aggressive type that responds well to treatment.

Tubular Carcinoma of the Breast is usually small and made up of tube-shaped structures called "tubules." These tumors tend to be low-grade and slow-growing. Studies suggest that tubular carcinomas may account for anywhere from just under 8% to 27% of breast cancers. It tends to be less aggressive and responds well to treatment.

Other categories of Invasive Breast Cancers include:

Inflammatory Breast Cancer (IBC) is a rare and aggressive form of breast cancer. Only about 1% to 5% of all breast cancer cases in the US are inflammatory breast cancers. IBC usually starts with the reddening and swelling of the breast instead of a lump. It tends to grow and spread quickly, with symptoms worsening within days or even hours. It is important to recognize these symptoms and seek prompt medical treatment.

Invasive Lobular Carcinoma (ILC) starts in the breast lobules (the areas of the breast that produce milk). ILC is the second most common type of breast cancer, occurring in 10% of all breast cancer cases. It is usually estrogen and progesterone positive and HER2 receptor negative (although it may harbor a HER2 and/or HER3 mutation) and appears to derive particular benefit from treatment with aromatase inhibitors compared with tamoxifen. **From[5, PMID:27022119]: *http://jco.ascopubs.org/content/early/2016/03/23/JCO.2015.66.3872***

ILC may appear more like a spider web or filmy "sheets" than a solid tumor, and therefore it is frequently difficult to diagnose and track because it does not always appear on scans. This type of cancer may often spread to the ovary, abdomen/stomach, peritoneum (the tissue that lines the abdominal wall and covers organs in the abdomen), and omentum (a membranous double layer of fatty tissue that covers the intestines and organs in the lower abdomen). Sometimes the function of the ureters and bile ducts can also be impacted. On occasion, excess fluid called "ascites" may build up in the abdominal area. Because ILC

does not look like a solid tumor, one cannot completely rule it out - even despite negative scans and test results - especially when Tumor Markers (TMs) are unreliable and the patient is experiencing symptoms. Some people with ILC experience significant issues such as fatigue, weight loss, nausea, abdominal pain or extension ("looking pregnant"), diarrhea, loss of appetite, and /or a feeling of premature fullness while eating. One woman with lobular metastatic cancer and ascites wrote, *"Only when I had a Colonoscopy and EsophaGogastroDuodenoscopy (EGD) with a biopsy did the biopsies reveal the cancer."* So, if ILC is suspected, an EGD, colonoscopy, and other tests may be helpful in diagnosing and tracking it.

Due to the fact that ILC often spreads to the abdominal area, it may cause significant problems with digestion and even create a bowel obstruction. For ILC patients with digestive and/or bowel issues, serial abdominal examinations are essential for identifying the causative issue(s). Imaging studies such as an abdominal series and/or a CT scan of the abdomen and pelvis are helpful to determine whether: 1) a bowel obstruction exists, 2) there may be a perforation, 3) ascites are present, and/or 4) peritonitis is presented (peritonitis is an inflammation of the peritoneum, the tissue that lines the inner wall of the abdomen and covers and supports the abdominal organs). Bowel obstructions can occur at any point in the gastrointestinal tract from the stomach to the rectum, and the initial management of a patient with a bowel obstruction may include administering fluids (possibly intravenously) for dehydration. Some patients with bowel obstructions may need a stent and/or surgery to have the obstruction removed. If ascites is present, they may be drained (either periodically or via an indwelling catheter). Detailed information about peritoneal carcinomatosis (cancer in the peritoneal area that originated in the breast, ovaries, or other organs) and its therapies may be found at **[6, PMID:25940594]:** ***http://onlinelibrary.wiley.com/doi/10.3322/caac.21277/full***

An uncommon subtype of ILC is called **Pleomorphic Lobular Carcinoma**. The term "Pleomorphic" refers to a wide variability in the size, shape and staining of cells and/or their nuclei. Pleomorphic ILC accounts for about 1% of all Invasive Lobular Carcinomas, predominantly affects postmenopausal women between the ages of 60 to 80 and tends to be more aggressive. Pleomorphic lobular carcinoma can exhibit molecular aberrations associated with classical lobular carcinoma and even IDC, such as p53 positivity, overexpression of HER2/neu, changes in E-cadherin protein function, and c-myc (which is a growth regulating gene). The aggressive biology of pleomorphic lobular carcinoma relates to the acquisition of these genetic alterations. **From[7, PMID:24168512]:** ***http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2012-0603-RS?code=coap-site***

In general, ILC breast cancers are hormone receptor positive, HER2 negative, and are characterized by a loss of E-cadherin (Epithelial cadherin). E-cadherin is an important determinant of tumor progression, serving as a suppressor of invasion and metastasis in many contexts. Interestingly, as per the BIG1-98 study, patient with ILC appear to respond better to aromatase inhibitors than to Tamoxifen, and it has been stated that ILC generally tends not to respond favorably to chemotherapy. A notable subset of ILC cancers contain a FGFR mutation for which targeted drugs are being tested in the clinical trial setting as of August 2018. **From[8, PMID:23270564]:** ***https://jeccr.biomedcentral.com/articles/10.1186/1756-9966-31-103***

Loss of function of NF1 "(neurofibromatosis type `1"), a tumor suppressor gene product, is a marker of acquired resistance to endocrine therapy in lobular patients. **From[9, PMID:30423024]:** ***https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdy497/5181087***

Patients with ILC may be interested in visiting the newly-formed Lobular Breast Cancer Alliance at ***https://lobularbreastcancer.org/***

Paget's Disease of the Nipple is a rare form of invasive breast cancer in which cancer cells collect in or around the nipple. The cancer usually affects the ducts of the nipple first and then spreads to the nipple surface and the areola (the dark circle of skin around the nipple). The nipple and areola often become scaly, red, itchy, and irritated. Paget's disease of the nipple accounts for less than 5% of breast cancer. Being aware symptoms is important, given that more than 97% of people with Paget's disease also have cancer, either DCIS or invasive, somewhere else in the breast.

Phyllodes Tumors of the Breast are rare, accounting for less than 1% of all breast tumors. The name "phyllodes" means "leaf like," and refers to the fact that the tumor cells grow in a leaf like pattern. Phyllodes tumors tend to grow quickly, but they rarely spread outside the breast. Although most phyllodes tumors are benign, some are malignant, and others are considered borderline. Phyllodes tumors tend to grow quickly, and they require surgery to reduce the risk of a phyllodes tumor coming back in the breast (local recurrence).

Most above information above is **From:** ***http://www.breastcancer.org/symptoms/types/idc/tests/diagnosing***

TESTING FOR HORMONAL AND HER2 STATUS

When breast cancer cells are found and categorized as described above, the additional tests listed below will be undertaken in order to determine hormonal receptivity (specifically, Estrogen Receptivity [ER] and Progesterone Receptivity [PR]), along with HER2/neu receptivity. The outcome will help to determine the type of treatment(s) the patient will receive:

Hormone Receptivity (HR) Tests: A hormone receptor is a specialized protein located on the surface of or within a cell. The hormone receptor binds to the female hormones Estrogen (ER) and/or Progesterone (PR), which flow through the blood. Once bound, the hormone signals the cell to start growing and multiplying. Most testing labs use a special staining process that makes the hormone receptors show up in a sample of breast cancer tissue. The test is called an ImmunoHistoChemical (IHC) staining assay. When hormone receptors are present, estrogen and/or progesterone can fuel the growth of breast cancer. If either or both the ER and/or PR receptor is found to be positive, the breast cancer is classified as hormone receptor positive. (In the rare instances hormonal test results are inconclusive, the patient should nevertheless be initially treated with hormonal therapy). Hormone receptors are present in the majority of both early- and late-stage breast cancers, with expression found in approximately 65% to 70% of metastatic tumors.

How a patient's hormone receptivity test results appear in their pathology report may vary. Not all labs use the same method for analyzing the results of the test, nor do they have to report the results in exactly the same way.

Generally, hormonal testing results are provided in one of the four ways listed below:

Allred Score Between 0 and 8: The lab may use an "Allred" score between 0 and 8. This technique looks at the percentage of cells that test positive for hormone receptors, as well as how well the receptors show up after staining (this is called "intensity"). The percentage and intensity factors are combined to give a score between 0 and 8. The higher the score, the more receptors were found and the easier they were to see in the sample.

Number Between 0 and 3: "0" means that no ER and or PR receptors are present. "1" indicates that a small number are present. "2" means that a moderate number are present, and "3" represents a large number are present.

Percentage: The results may appear as a percentage that indicates how many cells out of 100 stain positive for hormone receptors. The lab will provide a number between 0% (no cells have receptors) and 100% (all cells have receptors).

Positive or Negative: The lab may simply state the hormone receptor status is "Positive" or "Negative."

If the lab result is reported as just the word "positive" or "negative," patients should ask their doctor for a more definite percentage. Different labs have different cutoff points for calling the cancer either hormone-receptor-positive or hormone-receptor-negative. For example, if between 1% and 9% of the cells stain positive (a category called "borderline" into which 6% of all breast cancers fall), one lab might call this a positive result whereas another lab may declare it a negative result. That said, overall, the most comprehensive breast cancer studies have consistently shown that levels as low as 1% positive-staining carcinoma cells are associated with significant clinical response. **From[10, PMID:21037871]:** ***http://www.archivesofpathology.org/doi/pdf/10.1043/1543-2165-134.6.907***

Some research studies (such as the one immediately below) have shown that ANY positive results, no matter how low (even in the "borderline" 1% to 9% positive category), mean that the patient might be a candidate for hormonal therapy. A score of "0%" would be needed to completely rule out hormonal therapy as a potential treatment (and even then, there may be exceptions as per the third bullet). **From[10, PMID:21037871]:** ***http://www.breastcancer.org/symptoms/testing/types/ihc*** and pages 911 and 913 of ***http://www.archivesofpathology.org/doi/pdf/10.1043/1543-2165-134.6.907***

In a study of 465 people with MBC, 6 (or 24%) of the 25 patients who were placed in the 1% to 9% ("borderline") Estrogen Receptor (ER) positive category based upon their IHC test, ended up being classified as ER positive when tested by ESR1 mRNA expression (which is consistent with ER positive status).

In the same study, 4 (or 67%) of the 6 patients in "exactly" the 10% ER positive category had ER-associated gene signature scores that were consistent with ER-positive status.

Finally, in 16 (or 9%) of the 183 patients whose tumors had tested at absolute 0% for ER receptivity, the study found a gene signature that was consistent with ER positive status. **From[11, PMID:22291085]:** ***http://jco.ascopubs.org/content/30/7/729.long***

Testing for Whether Breast Cancer is HER2 Positive or Negative:

Similar to the hormone receptor test described above, the HER2/neu test looks for a specific kind of protein that is found with certain types of cancer cells, along with the gene that produces that protein. The formal name of that gene is the "human epidermal growth factor receptor 2," which makes HER2 proteins that are receptors on breast cells. Healthy HER2 receptors are the proteins that help manage how a breast cell grows, divides, and repairs itself. But in about 25% of all breast cancer patients, the HER2 gene isn't functioning properly. Instead, it makes too many copies of itself in a process known as "HER2 gene amplification," which results in too many HER2 receptors. (This is sometimes referred to as "HER2 protein overexpression)." The result is that these breast cells grow and divide in an uncontrolled fashion, and the patient's cancer is considered HER2+ (positive).

How the HER2 test results appear in a patient's pathology report will depend on what specific HER2 test is done. <u>There are four possible tests for HER2</u>:

1. **FISH** (**F**luorescence **I**n **S**itu **H**ybridization) **Test:** The Fluorescence In Situ Hybridization test finds out if there are too many copies of the HER2 gene in the cancer cells. The results of the FISH test can be positive (HER2 gene amplification) or negative (no HER2 gene amplification).

2. **IHC test** (**I**mmuno**H**isto**C**hemistry): The ImmunoHistoChemistry test finds out if there is too much HER2 protein in the cancer cells. The results of the IHC test can be: 0 (negative), 1+ (also negative), 2+ (borderline), or 3+ (positive — HER2 protein overexpression).

3. **Inform HER2 Dual ISH Test** (**Inform Dual I**n **S**itu **H**ybridization): The Inform HER2 Dual ISH test finds out if there are too many copies of the HER2 gene in the cancer cells. The results of the Inform HER2 Dual ISH test can be positive (HER2 gene amplification) or negative (no HER2 gene amplification).

4. **SPoT-Light HER2 CISH Test** (**S**ubtraction **P**robe **T**echnology **C**hromogenic **I**n **S**itu **H**ybridization): The SPoT-Light test finds out if there are too many copies of the HER2 gene in the cancer cells. The results of the SPoT-Light test can be positive (HER2 gene amplification) or negative (no HER2 gene amplification).

ASCO HER2 Testing Guidelines advise clinicians to use a bright-field ISH (the latter two test types). This technique also evaluates for amplification of the HER2 gene and uses a regular light microscope rather than a fluorescent microscope**.**
From[12, PMID:29436914; 13, PMID:29939838]: ***https://www.asco.org/about-asco/press-center/news-releases/asco-and-cap-release-updated-guideline-her2-testing-breast***

ASCO guidelines specifically define HER2-positive status as occurring when (on observing within an area of tumor that amounts to >10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (HER2 copy number or HER2/CEP17 ratio by ISH based on counting at least 20 cells within the area). If results are equivocal (uncertain), reflex testing should be performed using an alternative assay (IHC or ISH). Repeat testing should be considered if results seem discordant with other histopathologic findings. **From[12, PMID:29436914; 14, PMID:24101045]:** ***http://jco.ascopubs.org/content/31/31/3997.abstract?ijkey=69fc153977e84d4b3e0333953a9d7fa0a62d119f&keytype2=tf_ipsecsha***

It is important for patients to know which HER2 status test is done on their tumor. Generally, only cancers that test IHC 3+, FISH positive, SPoT-Light HER2 CISH positive, or Inform HER2 Dual ISH positive respond to the medicines that target HER2-positive breast cancers.

An IHC 2+ test result is called borderline. If a patient has an IHC 2+ result, s/he may be wise to have the tissue retested with a more precise HER2 test such as the FISH test, SPoT-Light HER2 CISH test, or the Inform HER2 Dual ISH test. **From:** ***http://www.breastcancer.org/symptoms/diagnosis/her2***

IMPORTANT NOTE: According to the College of American Pathology (CAP), "Laboratory assays for HER2, Estrogen Receptor and Progesterone Receptor are essential in selecting patients for anti-HER2 and hormonal therapy, yet inaccuracies in testing pose a significant problem in ensuring that patients are treated appropriately." **From[14, PMID:24101045]:** ***http://www.cap.org/apps/docs/committees/immunohistochemistry/her2_faqs.pdf***

Before having surgery to obtain a biopsy, patients – both in the US and internationally - should work with their doctors to send the tumor sample to a laboratory that is College of American Pathology (CAP) Certified if at all possible, since CAP is the "gold standard" for laboratory accreditation. Patients and their doctors may search for a list of CAP-Certified Laboratories at: ***http://webapps.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=accrlabsearch_page&hideNavFrame=Y***

Whenever possible, patients should schedule their biopsy on a morning early in the week to minimize the potential for specimen mishandling. (Additional details about the pitfalls besetting tumor testing are provided in the section entitled, *Tumor Biopsy for New Metastatic Sites*).

Patients whose breast cancer cells have neither hormone receptors nor HER2 protein amplification, have what is called "Triple Negative Breast Cancer" (**TNBC**) or "**Basal Like**" breast cancer. TNBC accounts for about 10% to 20% of all breast cancer, and usually the most challenging to treat. That said, patients initially classified as TNBC are encouraged to double-check their Hormone Receptor and HER2 pathology tests to determine whether these tests need to be re-taken in order to obtain more specificity. For example, it is possible that some patients initially classified as hormone receptor negative may fall into the" borderline" hormone receptive positive group and therefore be potential candidates for hormonal therapy.

THE 4 CATEGORIES OF BREAST CANCER

Once a patient's breast cancer has been tested for hormone and HER2 receptors, it is categorized into one of the following four groups:

1. **Luminal A:** This group includes tumors that are both ER and PR positive, but negative for HER2. Luminal A breast cancers are likely to benefit from hormone therapy and they may also benefit from chemotherapy and some targeted therapy. Detailed information for Luminal A breast cancer patients is provided in the section entitled, *Hormone Receptor Positive MBC, Hormonal Therapies, and Resistance.*

2. **Luminal B:** This type includes tumors that are ER positive and/or PR positive, and either HER2 positive or HER2 negative with a high Ki67 score (Ki67 is an antigen [or protein] that sits on the surface of a cell and stimulates the production of an antibody.

The best Ki67 index cut point to distinguish luminal B from luminal A tumors was 13.25%. **From[15, PMID:19436038]: *http://jnci.oxfordjournals.org/content/101/10/736.full***

Luminal B breast cancers may benefit from hormone therapy, chemotherapy and /or targeted therapy. Detailed information for Luminal B breast cancer patients who are ER and/or PR positive and HER2 negative is provided in the section entitled, *Hormone Receptor Positive MBC, Hormonal Therapies, and Resistance.* Information for Luminal B breast cancer patients who are ER and/or PR positive and HER2 positive is provided in the section entitled, *Hormone Receptor Positive, HER2 Positive MBC and Related Therapies.*

3. **HER2 Positive:** This type of breast cancer is comprised of tumors that are ER negative and PR negative, and HER2 positive. HER2 + breast cancers are likely to benefit from treatment that is specifically targeted to HER2, along with chemotherapy. Detailed information for patients with this type of breast cancer is provided in the section entitled, *HER2 Positive MBC and Related Therapies.*

4. **Basal Like (Triple Negative Breast Cancer, or "TNBC"):** This type of breast cancer includes tumors that are ER negative, PR negative and HER2 negative. Basal-like breast cancers are likely to benefit from chemotherapy and potentially some targeted therapy. Additional information for patients with this type of breast cancer is provided in the section entitled, *Triple Negative MBC and Related Therapies.* **From: *http://www.mayoclinic.org/diseases-conditions/breast-cancer/in-depth/breast-cancer/art-20045654?pg=2***

Some researchers are continuing to identify additional sub-categories of breast cancer with the objective of determining which sub-categories might respond best to specific treatments.

7. Hormone Receptor Positive MBC, Hormonal Therapies, and Resistance

Hormone receptors are present in the majority late-stage breast cancers, with expression found in approximately 65% to 70% of metastatic tumors.

Breast cancers that are Estrogen Receptor (ER) positive and/or Progesterone Receptor (PR) positive are considered Hormone Receptor (HR) positive (unless their cancer is also HER2 positive - for which distinct treatment guidelines exist as described in the section entitled, *Hormone Receptor Positive, HER2 Positive MBC and Related Therapies).*

Patients with the type of breast cancer described in this chapter usually are classified as having "Luminal A" MBC, although some "Luminal B" patients may fit this profile. These Luminal B patients are ER positive and/or PR positive, and HER2 negative (but with a high Ki67 score, unlike Luminal A breast cancer).

In many cases, patients with hormone receptor positive breast cancer respond well to hormonal therapies. The concept behind hormonal ("endocrine") therapy is to starve the cancer cells of the estrogen hormone they need in order to thrive. **Except for the caveats below, hormonal therapies (with or without CDK4/6 inhibitors) are normally the first-line therapy for both premenopausal and postmenopausal patients, even when there is visceral disease** (i.e. disease in the soft internal organs such as the lung or liver). In general, if first-line therapy is endocrine therapy instead of chemotherapy, patients will have a better quality of life (QOL). Although randomized studies have been few and far between, the ones that have been done suggest that survival is the same, and some data show that survival is better. From a QOL standpoint, it is felt that endocrine therapy is the best initial treatment for most patients. Even though hormonal therapy may take a little longer to work than chemotherapy, it can be as – or more – effective in some populations. Most hormonal therapies are given in pill form, although Faslodex is administered as an injection.

Caveats: Patients experiencing considerable symptoms or life-threatening disease, who have major liver involvement, Central Nervous System (CNS) involvement, multiple tumors in the lung's lymphatic system, who have had early failure on hormone therapy (less than 6 months) or have been off adjuvant hormonal therapy for less than a year should consider chemotherapy and/or other therapies (possibly with hormonal therapy) instead of hormonal therapy alone. When determining a patient's therapy, doctors also need to consider where the patient's cancer has spread because there are often additional therapies that may be warranted (for example, patients with bone metastasis should also be given a bone-directed therapy such as Xgeva [Denosumab] or Zometa [Zoledronic Acid]). Patients who start out on chemotherapy and achieve a response can subsequently be converted to hormonal therapy. **From[16, PMID:25185096]:** ***http://www.ascopost.com/issues/october-15-2014/asco-clinical-practice-guideline-chemotherapy-and-targeted-therapy-in-advanced-her2-negative-or-her2-status-unknown-breast-cancer/*** and ***https://breastcancer-news.com/bone-directed-therapy/*** and ***https://www.onclive.com/web-exclusives/tripathy-discusses-developments-in-hr-breast-cancer***

According to ASCO 2016 guidelines, genomic or expression profiling should not be used to select initial treatments for metastatic hormone receptor positive breast cancer. **From[17, PMID:27217461]:** ***http://www.medscape.com/viewarticle/864032?src=wnl_edit_tpal&uac=68373MK***

Hormonal therapy for premenopausal women and postmenopausal patients differs somewhat as described below, and the use of a specific agent can be repeated if recurrence happens more than 12 months after the last treatment. **From[17, PMID:27217461]:** ***http://www.medscape.com/viewarticle/864032?src=wnl_edit_tpal&uac=68373MK***

Note: It is recommended that women who do not get their monthly periods request a blood test to determine their true menopausal status. The amount of estrogen and/or FSH (Follicle Stimulating Hormone) in the blood will be helpful in determining menopausal status. In some cases, patients will need to refrain from taking specific medications prior to undergoing testing and should therefore discuss preparations with their doctors.

When to Stop Hormonal Therapy: Guidelines indicate that hormonal therapy should be stopped if there are no benefits from three back-to-back hormonal regimens, and/or the patient has disease in their internal organs that is causing considerable symptoms. At this point, other options such as chemotherapy (and potentially clinical trials) should be considered.

Readers are highly encouraged to review the sections on Hormonal Therapy and Targeted Therapy for detailed and important information.

HORMONAL THERAPIES FOR PREMENOPAUSAL PATIENTS

Much of the information in this section has been provided by Dr. Debu Tripathy, professor and chairman, Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center in an OncLive interview located at: ***https://www.onclive.com/web-exclusives/tripathy-discusses-developments-in-hr-breast-cancer***

Hormonal Therapy Drugs for Premenopausal Patients

Premenopausal women with hormone receptor positive MBC should ideally have either ovarian suppression (through drugs that suppress ovarian function) or ovarian ablation (surgical removal of the ovaries, called "oophorectomy") to put them into menopause, and then they can be treated as if they are postmenopausal.

A list of hormonal therapy drugs for premenopausal patients appears below, and additional detail is located in the section entitled *Hormonal Therapy*.

- **Zoladex (Goserelin), Lupron (Leuprolide)**, or **Trelstar (Triptorelin)** for ovarian suppression

- **Tamoxifen (Nolvadex)** and **Toremifene (Fareston),** which are Selective Estrogen Receptor Modulators, or "SERMs". SERMs work by sitting in the estrogen receptors in breast cells. If a SERM is sitting in the estrogen receptor, there is no room for estrogen and it can't attach to the cell. If estrogen isn't attached to a breast cell, the cell doesn't receive estrogen's signals to grow and multiply. Tamoxifen is more widely used than Fareston in the US, although for premenopausal patients with flaws in their CYP2D6 genetic pathway, Fareston is a better choice than Tamoxifen because it does not rely on this pathway to be effective (more about Tamoxifen and CYP2D6 under *Possible Causes for Hormonal Therapy Resistanc*e in this chapter). Note that in premenopausal patients, medical suppression of the ovaries with gonadotropin-releasing hormone analogues was found to be better when added to tamoxifen than tamoxifen alone. For most premenopausal patients, it therefore became customary to use either surgical or medical ovarian suppression.

- A combination of **Kisqali (Ribociclib)** which is a CDK4/6 inhibitor, along with an Aromatase Inhibitor (AI) such as **Femara (Letrozole), Arimidex (Anastrozole),** or **Exemestane (Aromasin),** received FDA approval in July 2018 as initial endocrine-based therapy for pre- and perimenopausal women with MBC. Patients should be warned that Kisqali has been known to cause QT Interval Prolongation (accelerated heart rate that can lead to loss of consciousness, cardiac arrest, or even death) as well as Hepatobiliary Toxicity (toxicity to the liver, gallbladder, bile ducts, and/or bile).

- When CDK4/6 therapies (or mTOR inhibitors such as Afinitor) are combined with endocrine therapy (i.e. Aromatase Inhibitors or Fulvestrant Faslodex) in premenopausal patients, it is customary to use ovarian suppression.

Hormonal Therapy Sequence for Premenopausal Patients

In general, the sequence of providing hormonal therapy for premenopausal women in the US is as follows. Patients outside the US are urged to discuss these and other potential treatments with their doctor.

- Upon diagnosis, a Luteinizing Hormone-Releasing Hormone (LHRH) agonist such as **Zoladex**, **Lupron** or **Trelstar** is recommended along with a hormonal therapy for postmenopausal patients. (LHRH agonists work by telling the pituitary gland located in the brain to stop producing luteinizing hormone, which in women stimulates the ovaries to release estrogen. The drug does not have a direct effect on breast cancer, only on the ovaries. The resulting lack of estrogen interferes with stimulating cell growth in estrogen-dependent cancer cells. For female MBC patients, ovarian ablation (removal of the ovaries, called "oophorectomy") may be substituted for an LHRH agonist, in which case the patient becomes fully postmenopausal and should follow the hormonal therapy guidelines for postmenopausal patients.

- **Tamoxifen (Fareston)** may be given alone as a first line therapy for premenopausal patients, although it is more common for it to be paired along with an LHRH agonist. Combining ovarian suppression and tamoxifen improves survival over either treatment alone. **From:** ***https://ww5.komen.org/BreastCancer/RecommendedTreatmentsforMetastaticBreastCancer.html***

- A combination of **Kisqali (Ribociclib)** which is a CDK4/6 inhibitor, with an Aromatase Inhibitor (AI) such as **Femara (Letrozole), Arimidex (Anastrozole),** or **Exemestane (Aromasin)**, received FDA approval in July 2018 as initial endocrine-based therapy for pre- and perimenopausal women with MBC.

- After progression (when the cancer has begun to grow again despite treatment), if a female MBC patient still has her ovaries, **ovarian ablation** (removal of the ovaries, called "oophorectomy") may appropriate as second-line therapy because it removes a substantial source of estrogen from being produced by the body. At that point, the woman is considered postmenopausal and should follow the hormonal therapy guidelines for postmenopausal patients.

HORMONAL THERAPIES FOR POSTMENOPAUSAL PATIENTS

Hormonal Therapy Drugs for Postmenopausal Patients:

A description of hormonal therapy drugs for postmenopausal women (and for men) follows. Additional details are located in the section entitled *Hormonal Therapy.*

- **Aromatase Inhibitors (AIs)** such as **Femara (Letrozole), Arimidex (Anastrozole),** or **Exemestane (Aromasin)**. AI's work by blocking the enzyme "aromatase," which converts the hormone androgen into small amounts of estrogen in the body. This means that less estrogen is available to stimulate the growth of hormone-receptor-positive breast cancer cells. Although postmenopausal women do not have ovarian function for producing estrogen, they still produce some estrogen in their adrenal glands and elsewhere, so AIs can be quite effective for this population. Letrozole appears to be a more potent suppressor of total-body aromatization and plasma estrogen levels compared with Arimidex, so this should be taken into consideration when beginning hormonal treatment with an AI. **From[18, PMID:14556923; 19, PMID:11821457; 20, PMID:12775735]:** ***http://www.medscape.org/viewarticle/434229***

  AIs may be prescribed alone as a "monotherapy", or specifically paired with targeted drugs called Cyclin-Dependent Kinases (CDKs). Targeted drugs act upon genes, proteins or other substances that contribute in some way to the growth and development of cancer cells. **Ibrance (Palbociclib), Kisqali (Ribociclib) and Verzenio (Abemaciclib) are FDA-approved CDK4/6 inhibitors.** Patients should be warned that, unlike Ibrance and Verzenio, Kisqali has been known to cause QT Interval Prolongation (accelerated heart rate that can lead to loss of consciousness, cardiac arrest, or even death) as well as Hepatobiliary Toxicity (toxicity to the liver, gallbladder, bile ducts, and/or bile).

It should be noted that **Aromasin** may also specifically be paired with the targeted drug **Afinitor**, but only in the second-line setting.

- **Fulvestrant (Faslodex)** is a Selective Estrogen Downregulator (SERD) which breaks down estrogen receptors on cancer cells. Fulvestrant (Faslodex) may be given alone or paired with **Ibrance, Kisqali, or Verzenio.** The results of a randomized Phase 3 trial indicated that the combination of Faslodex and Ibrance provided a progression-free survival (PFS) of 9.2 months compared with 3.8 months in the group taking Faslodex alone. The Ibrance/Faslodex regimen also extended median Overall Survival (OS) by an absolute difference of 6.9 months (34.9 months on the combination arm vs. 28 months on the Faslodex-only arm). **From[21, PMID:30345905]:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bcd3e8a02-e13e-4ad4-a2d2-1be2a182b4f7%7D/addition-of-palbociclib-to-fulvestrant-extends-os-among-certain-women-with-advanced-breast-cancer***

  The results of the Monarch Phase 2 trial of Faslodex and Verzenio indicated that patients taking both drugs had a PFS of 16.4 months versus 9.3 months in the Faslodex-only group. And finally, a trial of 726 patients found that patients taking Faslodex and Kisqali had a PFS of 20.5 months compared with 12.8 months for patients taking Faslodex alone. **From[22, PMID:26030518; 23, PMID:28533223; 24, PMID:28580882]:** ***http://www.medpagetoday.com/MeetingCoverage/ASCO/51855*** and ***https://seekingalpha.com/article/4110584-eli-lilly-strives-counteract-rivals*** and ***https://www.ajmc.com/newsroom/fda-expands-use-of-ribociclib-in-breast-cancer***

- **Tamoxifen (Nolvadex) or Toremifene (Fareston)**, which are Selective Estrogen Receptor Modulators, or "SERMS." Of these, Tamoxifen is the most commonly used for MBC in the US. SERMs work by sitting in the estrogen receptors in breast cells. If a SERM is in the estrogen receptor, there is no room for estrogen and it can't attach to the cell. If estrogen isn't attached to a breast cell, the cell doesn't receive estrogen's signals to grow and multiply. Tamoxifen is far more widely used in the US, although for postmenopausal patients with flaws in their CYP2D6 genetic pathway, Fareston is a better choice than Tamoxifen because it does not rely on this pathway to be effective (more about Tamoxifen and CYP2D6 under *Possible Causes for Hormonal Therapy Resistance* in this chapter).

  A subset of individuals with metastatic breast cancer may experience a "flare" of their breast cancer within two days to three weeks after starting tamoxifen. This may cause an increase in bone pain, a high blood calcium level, and in individuals with breast cancer involving the skin, an increase in the size and/or number of these skin nodules, or skin redness. These flares usually subside within four to six weeks. In the meantime, the symptoms can be treated with measures that reduce pain and lower blood levels of calcium. **From:** ***http://www.uptodate.com/contents/treatment-of-metastatic-breast-cancer-beyond-the-basics***

- **Estrogen (Ethinyl Estradiol)** may be used to re-sensitize breast cancer to hormonal therapy, and it is an FDA-approved MBC therapy in and of itself, counter-intuitive as it may seem. It has worked for some patients – especially those have been devoid of estrogen exposure for a considerable amount of time because they have been postmenopausal for at least five years or due to long term anti-estrogen treatment. (More about this in the *Hormonal Therapy* section of this document).

- **Megace (Megestrol Acetate)** is a synthetic progesterone (Progestin), which may counteract some of the effects of estrogen. It has an approximate response rate of 25% and a median duration of response of 15 months. **From[25, PMID:10458219; 26, PMID:2141491]:** ***https://www.uptodate.com/contents/treatment-approach-to-metastatic-hormone-receptor-positive-her2-negative-breast-cancer-endocrine-therapy-and-targeted-agents***

- **Halotestin (Fluoxymesterone)** is an Androgen drug. Androgens are male hormones. For MBC patients, androgen drugs are used to block the ability of the pituitary gland to control estrogen production. The most common androgen drug used is Fluoxymesterone (Halotestin), which is given orally as a pill. Typically, Halotestin is inferior to high-dose estrogen and is rarely used to treat metastatic breast cancer. Although it has a response rate of 10% - 20% in pretreated patients, side effects include virilization (masculinization), edema, and jaundice. **From[27, PMID:7459893; 28, PMID:7296499; 29, PMID:1590276]:** ***https://www.ncbi.nlm.nih.gov/pubmed?term=1590276*** and ***https://www.ncbi.nlm.nih.gov/pubmed?term=7296499*** and ***https://www.ncbi.nlm.nih.gov/pubmed?term=7459893***

Hormonal Therapy Sequence for Postmenopausal Patients

The sequence of providing hormonal (endocrine) therapy for postmenopausal patients will vary, as much of it depends upon what - if any - hormonal therapy drugs the patient has previously taken and how recently they were administered. The sequence will also depend upon the country in which the patient resides.

Generally, there is a choice of providing single drugs or a combination of drugs, with combination drugs generally causing more side effects. A physician at the European Society for Medical Oncology (ESMO) 2017 Congress stated that, "*Now, for the first time, we have insights suggesting that patients with certain clinical characteristics may benefit differently from treatment with a CDK 4/6 inhibitor, including the possibility that some patients with a good prognosis may be able to start on endocrine therapy alone. In such patients, CDK 4/6 inhibitors could potentially be reserved as a next line of treatment for metastatic disease. This idea warrants further study given our data.*" Summarizing the data, it was noted that endocrine therapy–naive patients and those with non-visceral, low-volume disease may be more likely to do better on aromatase inhibitors alone initially, although the absolute benefit from CDK 4/6 inhibitor therapy is likely to be higher for these patients.

However, in the PALOMA-2 study which randomized postmenopausal HR+/HER2- patients with no prior systemic therapy to either Letrozole plus Ibrance, or Letrozole plus placebo, the median Progression Free Survival (PFS) for patients on Letrozole plus Ibrance was 36.2 months vs. 27.6 months for patients on Letrozole plus placebo. It should be noted that patients with low disease burden and bone-only disease fared particularly well.

Patients are urged to discuss the various options with their doctor and to verify insurance coverage, since it is possible that some of the combination drug regimens listed below may not be covered by insurance or may be expensive. **From[30, PMID:28968163; 31, PMID:30632023]:** ***http://www.esmo.org/Conferences/Past-Conferences/ESMO-2017-Congress/Press-Media/Press-Releases/Abemaciclib-Initial-Therapy-Improves-Outcome-in-Endocrine-sensitive-Advanced-Breast-Cancer*** and ***https://www.practiceupdate.com/content/sabcsnbsp2017-long-term-follow-up-data-of-paloma-2-confirm-that-palbociclib-letrozole-should-be-a-first-line-option-in-hr-her2-advanced-breast-cancer/61489***

The author has done her best to summarize the recommended hormonal therapy sequence postmenopausal patients in the US, Canada, and Europe, although patients are encouraged to review this list with their doctor since these guidelines may vary.

SEQUENCE OF THERAPIES FOR POSTMENOPAUSAL HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE MBC PATIENTS IN THE US

FDA-Approved First Line Hormonal Treatment Options in the US (depending upon what, if any, recent treatments the patient may have had in the adjuvant setting):

- **Letrozole** alone
- **Arimidex** alone
- **Aromasin** alone
- **Faslodex** alone
- **Faslodex and Kisqali**
- **Letrozole and Verzenio**
- **Letrozole and Ibrance**
- **Letrozole and Kisqali**
- **Arimidex and Verzenio**
- **Arimidex and Ibrance**
- **Arimidex and Kisqali**

- **Aromasin and Verzenio**
- **Aromasin and Ibrance**
- **Aromasin and Kisqali**
- **Tamoxifen or Fareston** (rarely used as a first-line therapy)

FDA-Approved Second Line Hormonal Treatment Options in the US (depending upon prior treatment):

- **Letrozole** alone
- **Arimidex** alone
- **Aromasin** alone
- **Aromasin and Afinitor**
- **Faslodex** alone
- **Faslodex and Verzenio**
- **Faslodex and Kisqali**
- **Faslodex and Ibrance**
- **Tamoxifen or Fareston** (rarely used as a second-line therapy)
- **Verzenio alone** if the patient already underwent endocrine therapy AND chemotherapy that failed. (*Although Verzenio is a CDK4/6 inhibitor and not specifically a hormonal therapy, it is listed here for ease of reference*).

FDA-Approved Third Line Hormonal Treatment Options in the US (depending upon prior treatments):

- **Possibly any of the above therapies** (although not all combinations are widely used in a third-line setting)
- **Tamoxifen or Fareston**

FDA-Approved Fourth Line Hormonal Treatment Options in the US (depending upon prior treatments):

- **Possibly any of the above therapies** (although not all combinations are widely used in a fourth-line setting)
- **Either Estradiol, Megestrol Acetate (Megace), or Halotestin (Fluoxymesterone)**

SEQUENCE OF THERAPIES FOR POSTMENOPAUSAL HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE MBC PATIENTS IN CANADA

First Line Hormonal Treatment Options in Canada (depending upon what, if any, recent treatments the patient may have had in the adjuvant setting):

- **Letrozole** alone
- **Arimidex** alone
- **Aromasin** alone
- **Faslodex** alone
- **Letrozole and Ibrance**
- **Tamoxifen or Fareston** (rarely used as a first-line therapy)

Second Line Hormonal Treatment Options in Canada (depending upon prior treatment):

- **Letrozole** alone
- **Arimidex** alone
- **Aromasin** alone
- **Faslodex** alone

- **Faslodex and Ibrance**
- **Aromasin and Afinitor**
- **Tamoxifen or Fareston** alone

The author was unable to locate specific information about approved third and fourth line therapies for Canadian patients.

SEQUENCE OF THERAPIES FOR POSTMENOPAUSAL HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE MBC PATIENTS IN EUROPE

First Line Hormonal Treatment Options in Europe (depending upon what, if any, recent treatments the patient may have had in the adjuvant setting and their country of residence):

- **Letrozole** alone
- **Arimidex** alone
- **Aromasin alone**
- **Faslodex** alone (Except possibly in the UK, where NICE Guidelines have provisionally rejected it)
- **Faslodex and Verzenio**
- **Tamoxifen or Fareston** alone
- **Letrozole and Ibrance**
- **Letrozole and Kisqali**
- **Letrozole and Verzenio**
- **Arimidex and Ibrance**
- **Arimidex and Kisqali**
- **Arimidex and Verzenio**
- **Aromasin and Ibrance**
- **Aromasin and Kisqali**
- **Aromasin and Verzenio**

Second Line Hormonal Treatment Options in Europe (depending upon prior treatment and country):

- **Letrozole** alone
- **Arimidex** alone
- **Aromasin** alone
- **Faslodex** alone (Except possibly in the UK, where NICE Guidelines had provisionally rejected it)
- **Faslodex and Ibrance** (as above)
- **Faslodex and Verzenio**
- **Letrozole and Afinitor**
- **Letrozole and Verzenio**
- **Arimidex and Afinitor**
- **Arimidex and Verzenio**
- **Aromasin and Afinitor**
- **Aromasin and Verzenio**
- **Tamoxifen and Afinitor**

For MBC patients in the UK: NICE Guidelines indicate that patients with Estrogen Receptor positive MBC are eligible for Ibrance (Palbociclib) in combination with an aromatase inhibitor as first-line therapy, or in combination with Faslodex as second-line therapy.

Kisqali in combination with an aromatase inhibitor has been approved for ER positive MBC patients, and it has also been approved in combination with Faslodex for postmenopausal ER positive patients.

For MBC patients in Scotland: The Scottish Medicines Consortium (SMC) indicated that Ibrance or Kisqali in combination with an aromatase inhibitor is acceptable as first-line treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer.

The author was unable to locate specific information about approved third and fourth line therapies for European patients, although it is possible that the above protocols, if not previously taken, would be candidates.

SEQUENCE OF THERAPIES FOR POSTMENOPAUSAL HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE MBC PATIENTS IN AUSTRALIA

The author offers apologies because it was not possible to locate viable websites regarding specific hormonal therapy sequence for Australian patients.

That said, MBC patients in Australia have reported that Letrozole, Arimidex, Aromasin and Tamoxifen (as well as a similar drug called Fareston [Toremifene]) may be used alone in the first or second line setting. Additionally, after failure of Letrozole or Arimidex, Afinitor may be paired with Aromasin in the second line setting. Alternatively Ribociclib (Kisqali) can be paired with an Aromatase Inhibitor in an approved setting. Notably, each of these drugs is listed on the Pharmaceutical Benefits Scheme (PBS), which means that patients who could benefit from the drug can purchase it for the cost of a relatively reasonable PBS prescription fee.

Although the Therapeutic Goods Administration (TGA) approved the sale of Ibrance (Palbociclib) in 2017, this drug is not listed on the PBS as of Aug. 2018. Therefore, as with any available drug that is not listed on the PBS, Ibrance would need to be paid for by the patient at a considerable price - possibly thousands of dollars a month although there is now a program that caps the per-patient amount at $40,000 as per ***AU Capped Access***. However, as previously noted, Ribociclib (Kisqali), a sister drug to Ibrance, is on the PBS.

Interestingly, although one website indicated that Faslodex (Fulvestrant) is an option for patients who have received prior treatment with Tamoxifen, Faslodex (Fulvestrant) is not listed on the PBS as of Aug. 2018. For those wanting further information, a PBS search by drug name is available at: ***http://www.pbs.gov.au/browse/medicine-listing?initi***

Due to the relative paucity of available information, MBC patients in Australia are encouraged to discuss possible therapies and their associated costs with their physicians.

Making a Decision Regarding Single Agent vs. Combination Hormonal Therapy:
Experts are not in complete agreement regarding which MBC patients should be given single agent vs. combination hormonal therapy after diagnosis. One school of thought is to start endocrine therapy alone in newly diagnosed patients who had a long disease-free interval, low-volume disease, and/or bone-only disease, as they may have a long progression-free interval with endocrine therapy alone. While it is possible that they would do even better with the addition of a CDK4/6 inhibitor, patients should be counseled regarding the treatment schedule for the agents being considered, the need for laboratory and other monitoring, and safety profiles. These are patients who may be more likely to retain endocrine-responsive disease and could have a robust response to endocrine therapy alone; therefore, the use of a CDK4/CDK6 inhibitor might be reserved to those that may not or do not show benefit from single agent therapy. Some physicians feel that endocrine therapy alone is a good strategy for patients wanting to preserve their quality of life, do not want to come in for frequent blood tests (necessary because of the possibility of myelosuppression [a decrease in certain blood cells produced by the bone marrow], and want to avoid other side effects associated with Ibrance, Kisqali or Verzenio in first line therapy. That said, other doctors feel that in order to produce the maximum benefit in metastatic hormone receptor positive breast cancer, a combination of drugs with a CDK4/6 inhibitor such as Ibrance, Kisqali, or Verzenio should be the first choice. **From[32,**

PMID:27959613]: ***http://www.cancernetwork.com/breast-cancer/cdk46-inhibitors-game-changers-management-hormone-receptorpositive-advanced-breast-cancer/page/0/1***

Additional side effects caused by adding targeted therapies to hormonal therapies were discussed at the 2017 Advanced Breast Cancer Conference (ABC) in Lisbon, Portugal. Based on studies of more than 8,000 patients, researchers concluded that the addition of targeted agents to hormonal therapy is associated with a significantly higher risk of grade 3 or 4 adverse side effects overall, irrespective of the specific type of side effect. They noted that the use of anti-HER2 agents, CDK4/6 and PI3K inhibitors significantly increased the risk of grade 3 or 4 fatigue, but mTOR inhibitors (such as Afinitor) did not. Conversely, the use of anti-HER2 agents, PI3K and mTOR inhibitors significantly increased the risk of grade 3 or 4 diarrhea, but CDK4/6 inhibitors did not.

Specifically, CDK4/6 inhibitors increased the risk of grade 3 or 4 adverse side effects almost three-fold; PI3K inhibitors doubled the risk; mTOR inhibitors nearly doubled the risk; and anti-HER2 agents increased the risk 2.5-fold.

Grade 3 or 4 side effects with the highest risk by class of drug were neutropenia (low white blood cell counts) for CDK4/6 inhibitors, stomatitis (sore and inflamed mouth) for mTOR inhibitors, hyperglycemia (high blood sugar levels) for PI3K inhibitors and diarrhea for anti-HER2 agents. **From[33, PMID:29108713]:** ***https://www.eurekalert.org/pub_releases/2017-11/esoo-cti103117.php***

(By way of explanation, Grade 1 toxicity is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is considered life-threatening).

Potential Impact of Being on Afinitor (Everolimus) before Moving on to Ibrance: Very little research has been undertaken to determine which specific treatments render a patient less likely to respond to a future treatment. One small study attempted to address this issue in patients who had previously taken Everolimus (Afinitor) and then went on a regimen with the CDK4/6 inhibitor Ibrance (Palbociclib). In the small population in the study (23 patients), the median Progression Free Survival (PFS) was 2.9 months for patients who had previously taken Afinitor and then moved on to an Ibrance regimen, versus 9.5 months for patients on Ibrance who had not previously been on Afinitor; the clinical benefit rates were 17.4% vs. 66.5% respectively. Since this was a small study, more efforts are needed to determine whether the use of Afinitor before Ibrance (or other CDK4/6 inhibitors) is definitively associated with a low response & clinical benefit rate. **From[34, PMID:29778787]:** ***http://abstracts.asco.org/199/AbstView_199_183542.html***

Side Effects of Hormonal Therapy: Within the first several weeks of hormone therapy, patients may experience some bone/joint pain, hot flashes, dizziness, and other side effects. If a patient feels that that the side effects are becoming too challenging to cope with, they should speak with their doctor about switching to the non-generic form of the drug or possibly switching to another drug. These patients may also wish to refer to the section entitled, *Therapies for Pain and Neuropathy*.

Tips when Taking Faslodex (Fulvestrant): Faslodex shots are administered in the buttocks and can be quite uncomfortable both during and after the injections are given, which is due in part to the thickness of the vaccine. Patients have provided the following tips to mitigate discomfort: Warm the syringes under your armpits for several minutes until the vaccine reaches body temperature, which makes the shots easier to administer. Ask the nurse to gently massage the injection sites before and after the injections. Ensure that there is no weight on the area being injected by standing with your weight on the opposite foot or lying down on your stomach and pointing your toes inward (most patients prefer this method). Have the nurse put numbing spray on the area before injecting the vaccine, and ensure the nurse injects it very slowly (several minutes per site). After the injection, apply ice packs or heat pads to the area (some patients drive home with the car seat heater turned on), drink lots of water, walk as much as possible, and avoid sitting for long periods of time.

Bone Density Loss: Aromatase Inhibitors may cause a loss of bone density, which leads to higher rates of osteoporosis and bone fractures compared to Tamoxifen. Patients who will begin taking AIs should initially have a Bone Density (DEXA) test as a "baseline." and repeat the DEXA test every year or two so that they and their doctor can monitor any loss in bone density and decide how to treat it. Some medications may help prevent or slow down osteoporosis, so physicians may prescribe drugs called bisphosphonates or the drug Xgeva to help preserve bone density. In turn, bisphosphonates and Xgeva may cause bone, joint and/or muscle pain, so patients with these symptoms should report them to their doctor immediately. In rare cases, a serious jawbone disorder called OsteoNecrosis

of the Jaw (ONJ) may occur. If possible, patients should have a dental exam (and inform their dentist about their drug plan) before using a bisphosphonate or Xgeva, and have their teeth cleaned every four months while on the drug. Regular exercise can help strengthen and protect the bones, as can getting enough calcium, Vitamin K2 and Vitamin D. **From[35, PMID:16030366]:** ***http://ww5.komen.org/BreastCancer/AromataseInhibitors.html*** and ***http://www.medscape.com/viewarticle/509074_7***

Changes in Hormone Receptor Status: Breast cancers that are initially ER positive and/or PR positive may become hormone receptor negative over time. Likewise, hormone receptor negative breast cancers can later become hormone receptor positive. (These same principles may also hold true for HER2). Additionally, if the breast cancer comes back elsewhere in the body, the doctor should order another biopsy and retest the tissue's hormonal and HER2 status, because a tumor in one area of the body may have a different hormonal and/or HER2 profile from a tumor elsewhere.

Re-trying ("Recycling Through") Hormonal Therapies: Patients who have developed endocrine resistance and have been on chemotherapy may find this of particular interest. At the 2013 San Antonio Breast Cancer Symposium, one expert from Dana Farber stated that physicians should make for possible for patients with initially hormone sensitive MBC who have had multiple lines of chemotherapy to revisit the endocrine therapies, even in late stage disease. And he added that this methodology is probably not being done with the frequency it deserves.

Possible Causes for Hormonal Therapy Resistance:

Tamoxifen Resistance: For patients whose doctors recommend that they start taking Tamoxifen, and for patients who are currently taking Tamoxifen and not responding, a "CYP2D6" test may be recommended. This is because some people simply will not respond to Tamoxifen due to a flaw in their CYP2D6 genetic pathway. Therefore, patients may want to request a CYP2D6 test (using healthy tissue instead of tumor tissue because it appears that test results with healthy tissue are more accurate). If after taking the CYP2D6 test the patient is found to have a CYP2D6 flaw, then Fareston, which is a Selective Estrogen Receptor Modulator (SERM) similar to Tamoxifen, may be a worthwhile choice for postmenopausal (not premenopausal) women. **From[36, PMID:17882159]:** ***http:/www.fareston.com/hcp/about/continue.html***

Mutations in ESR1 (also known as ER, a gene that encodes an estrogen receptor protein), have been shown to be indicative of resistance to aromatase inhibitors. ESR1 mutations occur rarely in primary breast cancer but have a high prevalence in advanced breast cancers previously treated with aromatase inhibitors, implying evolution through selective treatment pressure. (ESR1 mutations can be identified through blood tests designed to analyze circulating tumor DNA "ctDNA"). Faslodex is the preferred endocrine treatment over Aromatase Inhibitors for patients with ESR mutations. **From:** ***https://www.onclive.com/insights/mbc-endocrine-partner/next-generation-sequencing-in-hr-positive-metastatic-breast-cancer***

Similar to ESR1 mutations, **HER-2 mutations** appear to be associated with resistance to hormone therapy among women with ER-positive MBC, despite the fact that HER2 is not over-expressed on the surface of their cancer cells and they are still considered to be HER2 negative in terms of treatment options.

In lobular MBC patients, loss of function of NF1 ("neurofibromatosis type 1"), a tumor suppressor gene product, is a marker of acquired resistance to endocrine therapy. **From[9, PMID:30423024]:** ***https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdy497/5181087***

Researchers are still exploring the mechanisms by which breast cancer becomes resistant overall to hormonal therapy. "Upregulation" (an increase in the number of receptors on the surface of target cells, making the cells more sensitive to a hormone or another agent) of HER2 by either acquisition of gene amplification or overexpression has been shown to occur in some tumors, so HER2 may play a driving role in tumor progression by serving as an alternative survival pathway or by reducing the level of ER, thus rendering the tumor less responsive to estrogen. Preclinical and clinical data suggest the possibility that tumors can alternate between ER and HER2 as the dominant pathway, with targeted therapy against one pathway causing reactivation of the other. PR, on the other hand, is lost

more frequently than ER with hormonal therapy. With the loss of PR, the tumor becomes more aggressive and patients have a worse survival outcome than patients who maintain PR expression after resistance to one endocrine therapy. PR loss might be associated with increased growth factor signaling and upregulation of the PI3K pathway, which decreases PR and ER expression. **From[37, PMID:20887199]: *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656649/***

In some instances, a patient's hormone receptor positive breast cancer may have been resistant to hormonal therapy from the very beginning. These patients may be placed on chemotherapy and/or targeted therapy, and/or explore other therapies listed herein. In other cases, patients with hormone receptor positive breast cancer will initially respond to hormonal therapy and then become resistant to it over time (this is referred to as "endocrine resistance" or progression). These patients may then try another hormonal therapy as described above, and then yet another, until their cancer is considered completely hormone therapy resistant. When that happens, these patients may be placed on targeted therapy, chemotherapy, and/or explore other therapies in the bulleted sections below.

Although the above information is based upon the overexpression of Estrogen and/or Progesterone, the good news is that many hormone receptor positive breast cancers may also have other types of targets for treatment.

For HER2 negative MBC patients with BRCA germline mutations, Talazoparib and Olaparib have been approved. (Information about these targeted drugs is located under *Research and Potential Therapies Solely for Patients with BRCA1 and/or BRCA2 Mutations*).

In addition, 88% of hormone receptor positive breast cancers are positive for Androgen Receptors (AR), which may be treated (in clinical trials) with targeted drugs in much the same way that hormone receptor positive breast cancers are treated with hormonal drugs. Furthermore, up to 23% of hormone receptor positive patients have an amplification of FGFR1 and/or chromosome 11q. This is significant because therapies are being developed which specifically target these factors. Additional information about Androgen Receptors and FGFR1/11q is located in the section entitled *Research and Potentially Helpful Therapies (*the last of the bullets mentioned below).

For additional information, suggested sections include:

Personalized Medicine

Hormonal Therapy

Chemotherapy

Targeted Therapy

Research and Potentially Helpful Therapies

8. HER2 Positive MBC and Related Therapies

This section applies to patients whose MBC is HER2 receptor positive, and both Estrogen Receptor (ER) and Progesterone Receptor (PR) negative.

HER2 (human epidermal growth factor receptor 2) is a gene that can play a role in the development of breast cancer. Each patient's pathology report should include information about HER2 status, which tells the patient whether or not HER2 is playing a role in the cancer.

The HER2 gene makes HER2 proteins. HER2 proteins are receptors on breast cells. Normally, HER2 receptors help control how a healthy breast cell grows, divides, and repairs itself. In about 25% of breast cancers, the HER2 gene doesn't work correctly and makes too many copies of itself (known as HER2 gene amplification or being HER2 positive).

HER2-positive breast cancers tend to grow faster and are more likely to spread and come back compared to HER2-negative breast cancers. But there are currently many medicines specifically targeting HER2-positive breast cancers, and as a result it is not unusual for patients with HER2+ to have a better prognosis than those with other breast cancer profiles.

Some breast cancers that are initially HER2 positive can become HER2 negative over time. And if the patient's breast cancer comes back elsewhere in the body, his or her doctor should order another biopsy and retest the tissue's hormonal and HER2 status, because a tumor in one area of the body may have a different hormonal and/or HER2 profile from a tumor elsewhere.

When determining a HER2+ patient's therapy, doctors also need to take into account where the patient's cancer has spread because there are often additional therapies that may be warranted.

Specific HER2 + breast cancer treatments, which are often used in conjunction with cytotoxic chemotherapy drugs, are:

- **Herceptin** (Trastuzumab**)** or an approved biosimilar (as per the *Biosimilars* section)
- **Kadcyla** (also known as **TDM-1** or Trastuzumab Emtansine).
- **Perjeta** (Pertuzumab)
- **Tykerb** (Lapatinib)

GUIDELINES FOR HER2 POSITIVE MBC THERAPIES

The following drug guidelines for HER2 positive, hormone receptor negative MBC patients were established by ASCO in 2018.

First-Line Treatment for HER2 Positive MBC:

A combination of Trastuzumab (Herceptin) or an approved biosimilar, Pertuzumab (Perjeta), and a Taxane is recommended for first-line treatment, except for those with clinical congestive heart failure or significantly compromised left ventricular ejection fraction, who should be evaluated on a case-by-case basis. **From[12, PMID:29436914; 13, PMID:29939838; 38, PMID:22149875; 39, PMID:25693012]:** ***https://www.journalofclinicalpathways.com/news/asco-updates-systemic-therapy-guideline-advanced-her2-positive-breast-cancer*** Since Herceptin can cause congestive heart failure in some instances, all breast cancer patients who are candidates for treatment with Herceptin should undergo cardiac testing prior to therapy and thereafter be monitored for heart damage regardless of age. **From[40, PMID:27091709]:** ***http://www.eurekalert.org/pub_releases/2016-04/uhn-bcp041916.php***

It should be noted that the above first-line therapy may be effective even for patients who were pre-treated with Herceptin. Furthermore, the 2018 ASCO guidelines specifically state that patients who have finished trastuzumab-based adjuvant treatment more than 12 months before recurrence should follow first-line HER2-targeted therapy–based treatment recommendations.

From[12, PMID:29436914]: ***https://academic.oup.com/annonc/article/25/suppl_4/iv131/2241144*** and ***https://www.journalofclinicalpathways.com/news/asco-updates-systemic-therapy-guideline-advanced-her2-positive-breast-cancer***

Optimal duration of chemotherapy is at least 4 to 6 months or until maximum response, depending on toxicity and in the absence of progression. HER2-targeted therapy can continue until time of progression or unacceptable toxicities.
From[13, PMID:29939838; 41, PMID:24799487]: ***http://www.ascopost.com/issues/june-25-2014/asco-clinical-practice-guideline-systemic-therapy-for-patients-with-advanced-her2-positive-breast-cancer/***

As per the Oct. 2016 edition of CURE Magazine, patients who have hypertension, are age 50 years or older, have low baseline left ventricular ejection, and/or have been previously treated with an anthracycline chemotherapy may be more susceptible to cardiac issues while on Herceptin, and should ensure that their oncologist works with a cardiologist to determine whether they should receive prophylactic (preventive) ACE inhibitors or beta blockers to prevent or lower the risk of cardiotoxicity.

To prevent the heart damage caused by chemotherapy, a cardiologist teamed up with a medical oncologist and identified a handful of studies that reported success using a beta blocker called Carvedilol. (Beta blockers slow down the heart and lower blood pressure). They tried Carvedilol on about 50 patients during their chemotherapy treatments. The drug's side effects were minimal and it's an affordable, generic medication. In three years, none of the patients had any signs of cardiac damage, whereas normally a small percentage of patients would have already developed heart failure. Another oncologist stated that Coenzyme Q10 (CoQ10) may also afford some protection for women undergoing chemotherapies that compromise heart function. It is believed that CoQ10 helps to maintain a healthy cardiovascular system, and there is evidence of CoQ10 deficiency in heart failure. **From:** ***http://www.thebreastcaresite.com/chemotherapy/take-heart-smart-treatment-understanding-managing-chemo-brain/***

Second Line Treatment for HER2 Positive MBC:

Second-line therapy should be **Kadcyla (TDM-1**). Kadcyla can confer an Overall Survival (OS) of 29.9 months when used as a second-line therapy, which is superior to Lapatinib (Tykerb) plus Xeloda (Capecitabine) which provided an OS of 25.9 months. (Kadcyla can also be a viable first-line therapy in patients for whom Herceptin, Perjeta and a Taxane might be too toxic). **From[42, PMID:26656517]:** ***http://www.jnccn.org/content/13/12/1475.full*** and ***https://www.kadcyla.com/*** and ***https://www.journalofclinicalpathways.com/news/asco-updates-systemic-therapy-guideline-advanced-her2-positive-breast-cancer***

Third-Line Treatment for HER2 Positive MBC:

Third-line treatment depends on what patients received as first- and second-line therapies. If a patient's HER2-positive advanced breast cancer has progressed during or after second-line (or greater) HER2-targeted therapy and the patient has not received T-DM1, then T-DM1 should be given. **From[12, PMID:29436914; 13, PMID:29939838]:** ***https://www.journalofclinicalpathways.com/news/asco-updates-systemic-therapy-guideline-advanced-her2-positive-breast-cancer***

Other third-line options include: chemotherapy with Herceptin or a biosimilar and in some cases with Tykerb (Lapatinib), the combination of Herceptin and Tykerb, or a Perjeta-based regimen if the patient has not received Perjeta beforehand. **From[12, PMID:29436914; 13, PMID:29939838]:** ***http://www.ascopost.com/issues/june-25-2014/asco-clinical-practice-guideline-systemic-therapy-for-patients-with-advanced-her2-positive-breast-cancer/***

The rationale for adding Perjeta to Herceptin is that a study found that HER2+ MBC patients who were given Perjeta on top of Herceptin and chemotherapy lived 15.7 months longer than those on Herceptin and chemotherapy alone. That is the longest extension to survival ever seen for a drug studied in metastatic breast cancer! The median Overall Survival (OS) was 56.5 months for those given Perjeta, Herceptin and chemotherapy against the already impressive 40.8 months for patients taking only the older drugs. Looking at the study results a different way, the risk of dying was reduced by 32% for patients who received the Perjeta/Herceptin/Chemotherapy regimen compared to those who got Herceptin and chemotherapy.

While both Perjeta and Herceptin have side effects, including rash, diarrhea and a potentially adverse impact on heart function, using the two drugs together did not make these issues any worse. **From:** ***http://www.reuters.com/article/2014/09/28/us-health-cancer-roche-idUSKCN0HN06R20140928***

At SABCS 2018, the following additional combinations were also mentioned: Tykerb plus Xeloda, Herceptin plus Xeloda, or Herceptin plus chemotherapy.

Optimal duration of chemotherapy is at least 4 to 6 months or until maximum response, depending on toxicity and in the absence of progression.

For HER2+ patients who have received multiple previous lines of therapy, Kadcyla (TDM1) can still be of major benefit. In the Phase 3 TH3RESA clinical trial, 602 HER2+ pretreated MBC patients were randomly assigned 3.6 milligrams of T-DM1 per kilogram of body weight every three weeks, or treatment of physician's choice. After a median follow-up of 30.5 months, the median overall survival was significantly longer among the 404 patients assigned T-DM1 compared with the 198 patients assigned treatment of physician's choice: 22.7 months compared with 15.8 months. The overall survival benefit was seen regardless of patient age, hormone-receptor status, visceral involvement, and number of prior treatment regimens. **From[43, PMID:24793816]:** ***http://www.sciencedaily.com/releases/2015/12/151211124307.htm***

The addition Afinitor to Herceptin and Paclitaxel failed to extend Progression Free Survival (PFS) in women with HER2+ advanced breast cancer, according to results of a randomized Phase 3 study presented at the San Antonio Breast Cancer Symposium. **From[44, PMID:26092818]:** ***http://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bec80ffa4-afb3-47bf-a84b-94439242bcf3%7D/everolimus-did-not-extend-pfs-in-HER2positive-breast-cancer***

Caution Regarding CNS Metastasis: Patients with HER2 positive MBC should be especially vigilant about unusual symptoms that may be related to Central Nervous System (CNS) issues such as headache, numbness, speech and/or cognitive difficulties, blurred vision, etc. because there is an increased risk for brain metastasis in patients receiving Herceptin. **From[45, PMID:23463626]:** ***http://www.medscape.com/viewarticle/780802*** Additionally, HER2+ MBC patients may have an increased overall risk of CNS metastasis compared with patients who are HER2 negative and/or who have not received a Taxane. **From[46, PMID:16846533]:** ***https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr1516***

Although the above information is based upon the overexpression of HER2, the good news is that many HER2+ breast cancers also have other types of targets for treatment. For example, 50% of HER2+ breast cancers are positive for Androgen Receptors (AR), which can be treated with targeted drugs in much the same way that ER+ breast cancers are treated with ER-suppressing drugs. **From**: ***http://www.coloradocancerblogs.org/new-target-new-drug-in-breast-cancer-enzalutamide-therapeutic-against-androgen/***

In addition to potentially having Androgen Receptors, up to 27% of HER2+ patients may have an amplification of FGFR1 and/or chromosome 11q. This is significant because therapies are being developed which target these factors.

For additional information, suggested sections include:

Personalized Medicine

Chemotherapy

Targeted Therapy

Research and Potentially Helpful Therapies

As a final tip, a useful patient's guide to HER2+ breast cancer is located at ***http://media.curetoday.com/downloads/documents/HER2_pocketguide.pdf***

9. Triple Negative MBC and Related Therapies

Patients whose breast cancer has neither hormone receptors nor HER2 protein amplification, have what is called "Triple Negative Breast Cancer" (**TNBC**) or **Basal-Like** breast cancer, which is generally treated with chemotherapy drugs. TNBC accounts for about 10% to 20% of all breast cancer, and usually the most challenging to treat. That said, patients initially classified as TNBC are encouraged to double-check their Hormone Receptor and their HER2 pathology tests to determine whether these tests need to be re-done in order to obtain more specificity. For example, it is possible that some patients initially classified as hormone receptor negative may fall into the" borderline" hormone receptive positive group, and therefore be potential candidates for hormonal therapy as described in the section entitled *Types of Breast Cancer*. **From[47, PMID:21147047; 48, PMID:23733761; 49, PMID:27816190]: *http://www.ascopost.com/issues/december-15-2012/current-perspectives-on-triple-negative-breast-cancers.aspx***

Some breast cancers that are initially TNBC can change their hormonal and/or HER2 status over time, so if possible, patients should have their tumors re-tested periodically because the outcome may impact their treatment options. Furthermore, if breast cancer comes back elsewhere in the body, doctors should order another biopsy and retest the tissue's hormonal and HER2 status, because a tumor in one area of the body may have a different hormonal and/or HER2 profile than a tumor elsewhere.

When determining a TNBC patient's therapy, doctors also need to consider where the patient's cancer has spread because there are often additional therapies that may be warranted.

Sequence of Therapy for TNBC MBC:

Currently there are no definitive guidelines regarding the sequence of therapy for TNBC patients with MBC. However, as per material provided at 2018 SABCS, there are two potential clinical pathways for treating TNBC MBC:

> *If the patient's tumor has immune cells on or near it that are PDL-1 positive*, then the patient should ideally receive **Atezolizumab with Abraxane** because on the IMPassion130 trial, the median Overall Survival on the combination was 25 months vs. 15.5 months on Abraxane alone. However, this combination has not yet been FDA-approved as of Dec. 2018.
>
> *If the patient's tumor-related immune cells are PDL negative, or the patient cannot obtain the aforementioned drug combination if their tumor-related immune cells are PDL-1 positive*, then **sequential single agent chemotherapy** is recommended. It was advised that combination chemotherapy should only be given in the event of visceral crisis (severe organ dysfunction).

For HER2 negative MBC patients with BRCA germline mutations, Talazoparib and Olaparib have been approved. (Information about these targeted drugs is located under *Research and Potential Therapies Solely for Patients with BRCA1 and/or BRCA2 Mutations*).

Furthermore, patients should be tested for additional mutations or biomarkers that may render them eligible for other therapies, and clinical trial participation is a viable consideration as per the *Research* section of this document.

Halaven Chemotherapy for TNBC: Relative to existing FDA-approved chemotherapy, in a Phase 3 multicenter study, women with metastatic TNBC had a more significant response to treatment with Halaven (Eribulin) versus Xeloda. Additional Phase 3 trials substantiated the effectiveness of Halaven over standard treatment. The two studies showed an overall improvement in survival of 5 months for metastatic breast cancer patients with TNBC. **From[50, PMID:25381136]: *http://www.sciencedaily.com/releases/2014/11/141102212054.htm***

Platinum Chemotherapy (such as Carboplatin and Cisplatin) for TNBC: Many people with TNBC may respond well to platinum chemotherapy drugs. TNBC patients with Homologous Recombination–Deficient (HRD) tumors, which have lost the ability to repair double-stranded DNA breaks, may possibly have a more favorable response to DNA-damaging drugs such as platinum agents and PARP (poly ADP-ribose polymerase) inhibitors. Furthermore, the presence of tumor infiltrating lymphocytes (TILs), a type of white

blood cell, ahead of treatment may help predict a favorable response to platinum-based chemotherapy (and possibly other therapies, such as immunotherapy) in women with triple-negative breast cancer.
From and **[51, PMID:23012302; 52, PMID:25476537; 53, PMID:29275435]:** ***http://www.medicalnewstoday.com/releases/270261.php*** and ***http://www.medicalnewstoday.com/releases/276870.php*** and ***http://www.ascopost.com/issues/january-25-2016/homologous-recombination-deficiency-score-correlated-with-response-to-platinum-in-breast-cancer/***

Platinum Chemotherapy and Abraxane (nab Paclitaxel): In the Phase 2 tenacity study, the combination of Carboplatin and Abraxane reduced the risk of progression or death by 40% compared with another chemotherapy combination as a frontline therapy for patients with TNBC MBC. The median progression-free survival (PFS) was 7.4 months with carboplatin and Abraxane compared with 5.4 months for Gemzar plus Abraxane, and the median overall survival (OS) was 16.4 months vs. 12.1 months respectively. **From[54, PMID:30347025; 55, PMID:29878040]:** ***http://www.onclive.com/web-exclusives/nab-paclitaxel-carboplatin-doublet-superior-in-phase-ii-tnacity-trial***

PARP Inhibitors as Potential Treatment for TNBC: PARP (Poly ADP-Ribose Polymerase) enzyme fixes DNA damage in cells, including DNA damage caused by chemotherapy medicines. Scientists developed PARP inhibitors based on the idea that a medicine that interferes with or inhibits the PARP enzyme might make it harder for cancer cells to fix damaged DNA, which could make chemotherapy more effective. In one early study, 123 women with TNBC MBC already had received one or two previous treatments that had stopped working. Half the women got a PARP Inhibitor called Iniparib with Gemzar and Carboplatin. The other women got only Gemzar and Carboplatin. Median survival for women treated with Iniparib and chemotherapy was 4.6 months longer than for women treated only with chemotherapy. **From[56, PMID:21208101]:** ***https://www.medscape.org/viewarticle/711369*** However, a subsequent larger Phase 3 study of Iniparib had disappointing results. Despite these results, some researchers feel that Iniparib could still provide a benefit to women whose cancer has progressed (worsened) on other treatments. **From[56, PMID:21208101; 57, PMID:25349301]:** ***http://news.cancerconnect.com/phase-iii-trial-fails-to-find-benefit-of-parp-inhibitor-for-triple-negative-breast-cancer/***

Patients with TNBC may want to watch for a potential new drug called IMMU-132 (Sacituzumab Govitecan). This is an SN-38 Antibody-Drug Conjugate (ADC) that targets the "TROP-2" antigen, which in 2014 received considerable publicity for its effectiveness against TNBC. This drug has received FDA "*Breakthrough Therapy*" Designation (*Breakthrough Therapy* Designation is a form of *Fast Track* Designation, which is meant to facilitate the development and review of new drugs intended to treat serious conditions). Additional information is provided in the section entitled, *Research and Potential Therapies for TNBC.*

There may be even more good news on the horizon for MBC patients with TNBC. Research has shown that up to 25% of TNBC tumors express the Androgen Receptor (AR) in much the same way that hormone receptor positive breast cancer expresses the Estrogen Receptor (ER). Clinical trials are underway with drugs to inhibit the Androgen Receptor in much the same way that estrogen suppression therapy inhibits the estrogen receptor in estrogen-receptor-positive breast cancers. Furthermore, a study in the journal Molecular Cancer Therapeutics shows that only about 1 percent of triple-negative breast cancer cells in a tumor must be "androgen-receptor-positive" to show benefit from anti-androgen therapies. There is additional information about Androgen Receptors in the section entitled, *Research and Potential Therapies for All Categories of Breast Cancer.*
From[58, PMID:26201402]:***http://www.oncologynurseadvisor.com/anti-androgen-therapy-may-benefit-wider-spectrum-of-patients-with-triple-negative-breast-cancer/article/359593/*** and ***http://medicalxpress.com/news/2015-02-low-androgen-triple-negative-breast-cancer-anti-androgen.html***

In addition to potentially having Androgen Receptors, up to 7% of TNBC patients may have an amplification of FGFR1 and/or chromosome 11q. This is significant because therapies are in clinical trials which target these factors. Additional information can be found in the section entitled, *Research and Potential Therapies for All Categories of Breast Cancer.*

Other targeted agents for TNBC (and breast cancer in general) are being developed, including mammalian target of rapamycin (mTOR) and NOTCH inhibitors.

Patients with TNBC are at heightened risk for Central Nervous System (CNS) metastasis (brain metastasis and leptomeningeal metastasis are the two types of CNS metastasis). Therefore, TNBC patients should be especially vigilant about CNS-related symptoms such as headaches, dizziness, numbness, speech problems, cognitive issues, and/or blurred vision and report them to their doctor. **From[59, PMID:25144278]:** ***http://www.cancernetwork.com/oncology-journal/management-breast-cancer-brain-metastases-moving-forward-new-options-are-still-needed***

When to Stop Chemotherapy: Guidelines generally indicate that chemotherapy should be stopped if there were no benefits from three back-to-back regimens, and/or when it is determined or felt that these regimens are doing more harm than good. At that point, clinical trials and supportive care should be considered.

For additional information, suggested sections include:

Personalized Medicine

Chemotherapy

Research and Potentially Helpful Therapies

10. Hormone Receptor Positive, HER2 Positive MBC and Therapies

About half of HER2 positive breast cancers are also ER positive and/or PR positive (i.e. Hormone Receptor [HR] Positive). Whereas one might imagine that this type of MBC would respond readily to endocrine and HER2 directed therapy, this is not necessarily the case. Cancers which are both HR+ and HER2+ can behave differently than would be expected based on HER2 or estrogen receptor positivity alone, and may be affected by the relationship between these receptors. This interaction between the receptors is referred to by researchers as "crosstalk."

The crosstalk between HER2 and ER may work to signal hormonal resistance. In other words, communication between the receptors (HER2 and ER) may result in anti-estrogen therapy being less effective in HR+/HER2+ tumors. In a similar fashion, activation of estrogen receptor signaling (related to being ER+) may result in resistance to HER2-targeted therapies. Some Luminal B breast cancers fall into this category. **From[60, PMID:25493235]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4259959/*** and ***https://www.verywellhealth.com/triple-positive-breast-cancer-4151805***

When determining a HR+/HER2+ patient's therapy, doctors also need to consider where the patient's cancer has spread because there are often additional therapies that may be warranted

GUIDELINES FOR HORMONE RECEPTOR POSITIVE, HER2 POSITIVE MBC THERAPY

The following open-ended guidelines for HR+/HER2+ MBC therapies are continually being reassessed.

First-line Therapy for HR+/HER2+ MBC Patients:

First line therapy for HR positive, HER2 positive MBC patients remains controversial.

ASCO 2018 guidelines for HR+/HER2+ MBC patients indicate that endocrine therapy may be used alone as first line therapy, although a qualifying statement said that, "*Although clinicians may discuss using endocrine therapy with or without HER2-targeted therapy, the majority of patients will still receive chemotherapy plus HER2-targeted therapy*." Hence these same guidelines also state that first line treatment might consist of a combination of HER2 targeted therapy (such as Herceptin) and chemotherapy. **From[12, PMID:29436914; 13, PMID:29939838]:** ***https://www.journalofclinicalpathways.com/news/asco-updates-systemic-therapy-guideline-advanced-her2-positive-breast-cancer***

According to information delivered at 2017 SABCS, first line therapy should consist of Herceptin, Perjeta, and hormonal therapy. More recently at 2018 SABCS, first line therapy was suggested to be Letrozole with or without Lapatinib (Tykerb), or an Aromatase Inhibitor (or Tamoxifen) either with or without Herceptin. (For patients with indolent disease, it was disclosed that there is no Overall Survival advantage to combining hormonal therapy with anti-HER2 therapy).

Yet another source indicates that the degree of hormonal expression may help to predict treatment outcomes: according to a 2017 Cure Today magazine article, HR+/HER2+ MBC patients with Estrogen Receptor (ER) expression in *more than 30%* of cancer cells significantly predicted a lower probability of response to chemotherapy plus Herceptin.

For a select group of patients, such as those with contraindications and/or slow growing hormone receptor-positive cancer, hormonal therapy administered with either Herceptin or Tykerb (Lapatinib) may be substituted for a chemotherapy-based HER2-targeted regimen because it may have fewer side effects.

Second-line Therapy for HR+/HER2+ MBC Patients:

Second-line therapy for HR+/HER2+ MBC patients should be **Kadcyla (TDM-1)** or, according to Dr. Roisin Connolly's lecture at 2018 SABCS, **hormonal therapy guidelines may be followed**. Kadcyla is an Antibody Drug Conjugate (ADC) that has generated considerable excitement regarding this class of drugs. ADC's are an emerging novel class of anticancer treatment agents that combines the selectivity of targeted treatment with the cytotoxic potency of chemotherapy drugs.

Third-line Therapy for HR+/HER2+ MBC Patients:

Third-line therapy and beyond may vary. Treatment will depend on what the patient has received in the first- and second-lines. Options may include Kadcyla (TDM1), hormonal therapy or chemotherapy with Herceptin and in some cases with Tykerb, the combination of Herceptin and Tykerb, or a Perjeta-based regimen if the patient had not previously received Perjeta. **From[12, PMID:29436914; 13, PMID:29939838; 41, PMID:24799487; 61, PMID:28327998]:** ***https://www.asco.org/about-asco/press-center/news-releases/asco-issues-two-new-guidelines-treating-patients-advanced-her2*** and ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw544***

Note about Herceptin: In the US and Europe, biosimilar drugs which are comparable to Herceptin have been approved (as per the *Biosimilars* chapter).

New research is underway for HR+/HER2+ patients. According to the PERTAIN Phase 2 study of postmenopausal, locally advanced and MBC patients with hormone receptor positive, HER2 positive breast cancer who had not received chemotherapy for their disease, the addition of an Aromatase Inhibitor (AI) to Pertuzumab (Perjeta) and Trastuzumab (Herceptin) improved Progression Free Survival (PFS) by 3-months. Based on investigator's discretion, induction chemotherapy could be given for 18 to 24-weeks prior to starting endocrine therapy. **From[62, PMID:30106636]:** ***https://www.researchgate.net/publication/314138683_Abstract_S3-04_Primary_analysis_of_PERTAIN_A_randomized_two-arm_open-label_multicenter_phase_II_trial_assessing_the_efficacy_and_safety_of_pertuzumab_given_in_combination_with_trastuzumab_plus_an_arom***

For patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost. Stopping anti-HER2 therapy after several years of sustained complete remission may be considered in some patients, particularly if additional treatments are available in case of progression.
From[61, PMID:28327998]: ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw544***

Some breast cancers can change their hormonal and/or HER2 status over time. Additionally, if the breast cancer comes back elsewhere in the body, the doctor should order another biopsy and retest the tissue's hormonal and HER2 status, because a tumor in one area of the body may have a different hormonal and/or HER2 profile than a tumor elsewhere in the body.

Although the above information is based upon the overexpression of Estrogen and/or Progesterone along with HER2, the good news is that many breast cancers may also have other types of targets for treatment. For example, 88% of hormone receptor positive breast cancers and 50% of HER2 positive breast cancers are positive for Androgen Receptors (AR), which can be treated with targeted drugs in much the same way that hormone receptor positive breast cancers are currently treated with hormonal drugs. Furthermore, up to 23% of hormone receptor positive patients and 27% of HER2 positive breast cancers have an amplification of FGFR1 and/or chromosome 11q. This is significant because therapies are being developed which specifically target these factors.

For additional information, suggested sections include:

Personalized Medicine for tumor testing and other options

Hormone Receptor Positive MBC, Hormonal Therapies, and Resistance

HER2 Positive MBC and Related Therapies

Chemotherapy

Hormonal Therapy

Targeted Therapy

Research and Potentially Helpful Therapies

11. Male MBC

Although uncommon, breast cancer may occur in men. Men at any age may develop breast cancer, but it is usually detected in men between 60 and 70 years old. Recently an inordinate number of men who were exposed to the toxic environment of 9/11 have been diagnosed with male breast cancer, and it is therefore hypothesized that environmental factors may play a role. Male breast cancer comprises less than 1% of all cases of breast cancer, and most – but not all - cases are Invasive (Infiltrating) Ductal Carcinomas (IDC) that is ER+/PR+ (Hormone Receptor+ [HR+]).

Risk factors for breast cancer in men include the following:

Mutations in the BRCA2 gene (these represent the strongest risk for male breast cancer).

Being exposed to radiation and/or environmental toxins.

Having a disease linked to high estrogen levels in the body, such as cirrhosis (liver disease) or Klinefelter syndrome (a genetic disorder).

Having several female relatives who have had breast cancer, especially relatives who have an alteration of the BRCA2 gene.

Information is admittedly sparse regarding male breast cancer, metastatic or otherwise. Therefore, men with MBC are encouraged to read the sections pertaining to their specific type of breast cancer and conduct their own research. Currently, treatment for male breast cancer is similar to that for female breast cancer, although lumpectomy is rare due to the small size of the male breast. Survival for men with breast cancer is similar to survival for women with breast cancer.
From: ***http://www.cancer.gov/cancertopics/pdq/treatment/malebreast/Patient/page1***

Hormonal therapy, chemotherapy, or a combination thereof have been used with some success in male HR+/HER2- MBC. Initially, hormonal therapy is recommended if the cancer is hormone receptor positive. Hormonal therapies may be used sequentially. Chemotherapy can be administered after hormonal agents fail.

According to the largest real-life study yet to investigate treatment and outcomes in men, there is growing evidence that drugs approved for the treatment of breast cancer in women are also effective and well tolerated in men. Researchers analyzed clinical data between January 2008 and December 2014 in the Epidemiological Strategy and Medical Economics Metastatic Breast Cancer (ESME MBC) platform, which collects real-life data from 18 French Comprehensive Cancer Centers for all patients newly diagnosed with MBC starting at least one treatment. They found 149 men from the total of 16,701 patients (0.89%).

Just over three-quarters of the 149 men (105, or 78.4%) had HR+/HER2- MBC, which was a slightly higher proportion than in women.

Results showed that HR+/HER2- men received similar treatments as women with MBC:

Just under half of men with HR+/HER2-negative breast cancer received frontline hormonal therapy with either tamoxifen (20/45), an aromatase inhibitor + luteinizing hormone releasing hormone (LHRH) analogue (18/45), or others (7/45). Their median Progression Free Survival (PFS) in this group was 9.8 months, which was similar to that seen in a matched group of women. Overall survival for the whole population of men included in the database was also similar to that for women (41.8 months).

A smaller number (one in four) of men with HR+/HER2- breast cancer had been treated with front-line chemotherapy. Their median PFS was also similar to a matched group of women receiving chemotherapy (6.9 months), which was nearly 3 months less than the above group who received hormonal therapy.

In terms of clinical implications for HR+/HER2- men with MBC, hormonal therapy should be given in the absence of visceral crisis, and if aromatase inhibitors are prescribed, they should be accompanied with LHRH analogues such as such as Zoladex, Lupron, or Trelstar.

With regard to the use of CDK4/6 inhibitors in men, the international CompLEEment-1 trial included 20 men and many women with HR+, HER2- advanced breast cancer who had not received any prior systemic hormonal therapy for MBC, and no more than one prior regimen of chemotherapy. The men were given Kisqali plus letrozole plus Zoladex, and the women received Kisqali plus letrozole (and Zoladex if they were premenopausal). Overall, the study concluded that the men who received Kisqali plus letrozole plus Zoladex had comparable safety and tolerability as that seen in the women in the trial. **From:** ***https://medicalxpress.com/news/2018-10-drugs-breast-cancer-women-effective.amp***

The above notwithstanding, men with MBC are encouraged to review the sections that are relevant for their type of breast cancer, as well as the sub-section entitled *Testing for Hormonal and HER2 Status* in the *Types of Breast Cancer* chapter because some breast cancer categorized as Hormone Receptor (HR) negative and/or HER2 negative may have been misclassified.

Overall, hormonal therapies for men with HR+/HER2- MBC may include:

- **Tamoxifen** for estrogen receptor–positive patients (usually the first-line treatment for hormone receptor positive male MBC)
- **Aromatase Inhibitors (Letrozole, Arimidex, and Aromasin)** for estrogen receptor–positive patients, possibly accompanied by **Ibrance, Kisqali, or** Verzenio (which are CDK4/CDK6 inhibitors) and a luteinizing hormone-releasing hormone agonist
- **Luteinizing hormone-releasing hormone agonist (such as Lupron, Zoladex or Trelstar) with or without total androgen blockage** ("anti-androgens") for hormone receptor positive patients.
- **Orchiectomy** (surgical removal of one or both testicles)
- **Progesterone**

Guidelines for male HR+/HER2- MBC may suggest that Aromatase Inhibitors (possibly with a CDK4/6 inhibitor) should be taken along with a treatment that stops the making of testosterone by the testes, so male MBC patients are highly encouraged to discuss these additional drugs with their medical oncologists. **From:** ***http://www.cancer.gov/cancertopics/pdq/treatment/malebreast/HealthProfessional/page2***

There have been several small, older studies about therapies for male HR+/HER2- MBC, including:

- **Buserelin and Flutamide** (these drugs may not be fully approved for breast cancer)
- **Faslodex**
- **Femara**
- **Orchiectomy (surgical removal of one or both testicles)**

- **Buserelin and Flutamide** (these drugs may not be fully approved for breast cancer). In an old study, ten men with advanced breast cancer were evaluated for response to treatment with the luteinizing hormone-releasing hormone (LH-RH) analogue, buserelin, alone or in combination with the antiandrogen, flutamide. One of five patients receiving buserelin as a single agent had a partial remission lasting 12 months, and with the addition of flutamide, this lasted over 24 additional months. Three patients had stable disease with a median duration of 6 months (range, two to fourteen). One patient had progressive disease. Of five patients receiving the combination of buserelin and flutamide from the beginning of therapy, four patients (80%) had a partial remission with a median duration of over 15-months (range, over five to sixteen). One patient's disease remained stable for 12-months. **From[63, PMID:2933617]:** ***http://www.uptodate.com/contents/breast-cancer-in-men/abstract/109?utdPopup=true***

- **Faslodex:** There is little data available on treatments (such as Aromatase Inhibitors [AIs]) for Tamoxifen-resistant disease in men. Faslodex (Fulvestrant) has been under-studied in this population. One small study evaluated Faslodex in 5 five men with

progressive visceral metastatic breast cancer. ("Visceral" refers to the internal organs of the body such as the chest/lungs or abdomen/liver). Faslodex was injected at a loading dose of 500mg on day 1 followed by 250mg injected monthly thereafter, until disease progression. A Partial Response (PR) lasting 12-months was obtained in one heavily pretreated patient; while another patient with HER2-positive MBC had Stable Disease (SD) lasting 22-months. Another patient with HER2 positive disease had SD lasting 6-months after early Progressive Disease (PD) on first- and second-line treatments with Aromatase Inhibitors. Of two cases progressing on Faslodex, one had low hormone receptor positivity (ER+ 20% and PR+ 30%), which might explain the lack of response. No side-effects to fulvestrant were reported by all patients.

Another case of successful use of Faslodex after Tamoxifen was reported in a 64-year-old man with hormone receptor positive, HER2-negative MBC. Beyond that, researchers were only able to find one other report on using Faslodex in two men with hormone receptor positive, HER2 negative MBC. After being given Faslodex as primary first-line endocrine therapy, one man had a Partial Response and the other had Stable Disease.

A key reason for trying Faslodex on men is that AIs do not have a clear role in metastatic male breast cancer. AIs inhibit aromatase, the enzyme that produces estrogens by peripheral aromatization of circulating androgens. In men and in postmenopausal women, estrogens are produced almost exclusively through peripheral aromatization of androgens. In men, however, testicular production of estrogens is independent of aromatase, and accounts for about 20% of circulating estrogens. It has also been found that testosterone levels increase after Arimidex treatment in men. It is possible that the hypothalamic–pituitary feedback loop is responsible for this increased testosterone, thereby rendering total estrogen suppression impossible. This may explain why treatment with AIs may be less effective in males than in females. To conclude, the study indicates that Faslodex may be an effective and safe treatment of hormone receptor-positive pretreated metastatic male breast cancer, including cases that overexpress HER2. **From[64, PMID:21447621]:** ***http://annonc.oxfordjournals.org/content/22/4/985.full***

- **Femara (letrozole) combined with a Gonadotropin-Releasing Hormone analog (GnRH) and possibly with a CDK4/6 inhibitor** as a first- or second-line therapy for metastatic male breast cancer patients. In a study of 19 men, 2 patients (10.5%) had complete response, 7 patients (36.8%) experienced a partial response, 7 patients (36. %) had stable disease lasting over 6-months, and 3 patients (15.8%) had progressive disease. Overall, the disease control rate was 84.2%. Median progression-free survival was 12.5-months and median Overall Survival was 35.8-months. The study concluded that the combination of letrozole and gonadotropin-releasing hormone analog is effective and safe in hormone-receptor positive, metastatic male breast cancer patients. **From[65, PMID:23982884]:** ***http://link.springer.com/article/10.1007%2Fs10549-013-2675-y***

- **Orchiectomy (surgical removal of one or both testicles):** In one very old study from 1983, 41 men with MBC were treated with 70 trials of hormone therapy. These included 25 orchiectomies and 45 additive hormonal treatments. The overall response rate was 31%. The response rate was 32% to orchiectomy, 17% to estrogens, 43% to steroids, 25% to Tamoxifen citrate, and 60% to Androgens. The response to additive hormonal therapy was 31% and was not affected by prior orchiectomy (33% v 30%). Median overall response duration was 12-months (17.5-months following orchiectomy, 8.5-months following additive hormonal therapy, 5-months following estrogens, 11-months following steroids, and 8-months following Androgens). Median survival from first metastasis was significantly prolonged in patients responding to orchiectomy and additive hormonal therapy. Patients with a Disease-Free Interval (DFI) longer than 12-months had a 59% response rate to hormonal therapy compared with 9% of those with a DFI no more than 12-months. Interestingly, the response to one form of hormonal therapy did not predict later hormonal response. The study concluded that ablative and additive hormonal therapy offered effective palliation to one third of male breast cancer patients, produced little toxic effects and morbidity, and improved survival duration after metastasis in responders. **From[66, PMID:6824391]:** ***http://www.ncbi.nlm.nih.gov/pubmed/6824391***

The use of **Herceptin and Perjeta** with a taxane should be explored for men with HER2 positive disease, and if a man's metastasis is in the **bones**, he should discuss with his doctor the possibility of receiving **Zometa or Xgeva** in addition to his other systemic therapy.

In addition to the above therapies, Androgen Receptor (AR) therapies may be promising, and clinical trials are underway to test the efficacy of AR targeting drugs. Research indicates that 88% of estrogen-positive breast cancers, 50% of HER2+ breast cancers, and 25% of triple-negative breast cancers (TNBC) are Androgen-Receptor (AR) positive, making Androgen Receptors a possible target for many breast cancers. Furthermore, most male breast cancers are positive for AR. **From[67, PMID:28062545]: *http://erc.endocrinology-journals.org/content/24/3/R27.full***

More information about AR therapies can be found in the section entitled, *Research and Potentially Helpful Therapies.*

Similar to potentially targeting Androgen Receptors, FGFR1 and/or 11q amplifications have been found in all subtypes of MBC, making them targets for emerging therapies. Research has found that 23% of estrogen-positive breast cancers, 27% of HER2+ breast cancers, and 7% of triple-negative breast cancers (TNBC) test positive for these factors. More information about potential therapies for these targets can be found in the section entitled, *Research and Potentially Helpful Therapies*.

Men with MBC may also wish to investigate the possibility of enrolling in a clinical trial, and may wish to refer to the section entitled, *Clinical Trials Overview.* As of August 2018, there are several clinical trials that are recruiting men as well as women.

12. Approved Therapies for Patients with BRCA Mutations

Patients with germline (inherited) BRCA1 or BRCA2 MBC that is HER2 negative have been granted two FDA-approved therapeutic options (**Olaparib and Talzenna**) in addition to therapies based on their cancer subtype as described in previous chapters.

Olaparib (Lynparza) is an oral polymerase (PARP) inhibitor that has promising antitumor activity in patients with metastatic breast cancer and a germline BRCA mutation. In a randomized Phase 3 study of 302 HER2 negative MBC patients with germline BRCA mutations who had received no more than 2 prior chemotherapy regimens, olaparib was compared with a single-agent therapy of the physician's choice. Median PFS (progression-free survival) was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months); and the response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group. **From[68, PMID:28578601]:** ***https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm592357.htm*** and ***https://www.nejm.org/doi/10.1056/NEJMoa1706450?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov&***

Talzenna (Talazoparib) is an oral PARP inhibitor that is used to treat patients with deleterious or suspected deleterious germline BRCA-mutant, HER2-negative locally advanced or metastatic breast cancer. The approval is based on the Phase 3 EMBRACA trial of 431 patients with HER2-negative, germline BRCA-mutant locally advanced or metastatic breast cancer. The patients were randomized to receive either Talzenna or physician's choice of chemotherapy – capecitabine, eribulin, gemcitabine or vinorelbine. The PFS in the Talzenna arm was 8.6 months compared to 5.6 months in the chemotherapy arm, and patients on Talzenna had a better quality of life. The FDA also noted that patient selection for treatment with Talzenna must be based on an FDA-approved companion diagnostic, BRACAnalysis CDx test, which was also granted approval. **From[69, PMID:30124753; 70, PMID:30110579]:** ***https://www.curetoday.com/articles/fda-approves-talzenna-for-breast-cancer-treatment***

13. Approved Therapies Based Upon Tumor Characteristics

Most cancer treatments are developed to treat cancer that has originated in a specific organ or tissue, such as breast cancer or lung cancer. A "tumor (or tissue) agnostic" treatment is meant to treat any type of cancer, provided that the cancer has the specific characteristics targeted by the drug. Studies related to tumor genomics and other attributes are increasingly leading to additional drug approvals, regardless of where the tumor originated.

Keytruda (Pembrolizumab)*:* Keytruda is a PD-1 inhibitor targeted therapy that has been approved for patients with metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. The FDA based the approval in part on data from five uncontrolled, multicohort, multicenter, single-arm clinical trials designed to evaluate Keytruda in 149 patients — including 90 patients with colorectal cancer and 59 patients diagnosed with one of 14 other malignancies. Researchers reported an objective response rate of 39.6% (95% CI, 31.7-47.9) — including 11 complete responses and 48 partial responses — which appeared similar irrespective of malignancy (colorectal cancer, 36%; other cancer type, 46%). Seventy-eight percent of responding patients had responses that lasted for 6 months or longer. **From[71, PMID:29764494]:** ***https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm***

Larotrectinib (Vitrakvi): In Nov. 2018, the FDA granted an accelerated approval to Larotrectinib (Vitrakvi) for the treatment of adult and pediatric patients with solid tumors that have a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic, or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment. The approval is based on findings from patients with TRK-positive tumors enrolled across 3 clinical trials. In results published in the New England Journal of Medicine (NEJM), Larotrectinib induced an objective response rate (ORR) of 75% - 80% in 55 evaluable patients. Per the independent assessment, there were 7 (13%) complete responses, 34 (62%) partial responses, and 7 (13%) patients with stable disease (SD).

At 1 year, 71% of responses were ongoing, with more than half (55%) of patients remaining progression-free at 1 year. The median duration of response had not been reached after a median follow-up of 8.3 months. The same was true for median progression-free survival after a median follow-up of 9.9 months. **From[72, PMID:30333516]:** ***https://www.onclive.com/web-exclusives/fda-approves-larotrectinib-for-ntrk-cancers***

14. Biosimilars

The rapid increase in health care costs—most notably in cancer care and the price of cancer drugs in the United States—has prompted increasing consideration of options for containing the cost of cancer care. One recent strategy is the development of "biosimilars." Unlike generic medications, a biosimilar is a product that is highly similar but not identical to an approved therapy with any differences in efficacy, safety, or purity between the biosimilar and the reference product — except for minor differences in clinically inactive components.

The process by which biosimilars are approved makes it less likely that large Phase 3 comparative clinical trials will be conducted. Therefore, preclinical and limited clinical data will need to be used to extrapolate the indications for which the original therapy was approved, and clinicians must decide on the appropriate incorporation of biosimilars.

Available data from Europe have not suggested that switching an approved therapy to a corresponding biosimilar lead to any safety or efficacy concerns.

Recently, biosimilar drugs have been FDA-approved for specific cancers in the US, as well as in the European Union (EU). The implications for pricing, prescribing, and providing insurance coverage are not entirely clear.

In the US:

- On Dec. 1, 2017, the FDA approved **Ogivri** (Trastuzumab-Dkst) as a biosimilar to Herceptin (trastuzumab) for the treatment of patients with metastatic breast or metastatic stomach cancer whose tumors overexpress the HER2 gene (HER2+). Ogivri is the first biosimilar approved in the U.S. for the treatment of breast cancer or stomach cancer and the second biosimilar approved in the U.S. for the treatment of cancer. **From:** ***https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587378.htm***

- In Dec. 2018, the FDA approved **Herzuma** (trastuzumab-pkrb) as a biosimilar to Herceptin for patients with HER2-overexpressing mbc, either in combination with paclitaxel for first-line treatment or as a single agent in patients who have received one or more chemotherapy regimens for metastatic disease. **From:** ***https://www.businesswire.com/news/home/20181214005566/en/Celltrion-Teva-Announce-FDA-Approval-HERZUMA%C2%AE-trastuzumab-pkrb***

- In Jan. 2019, the FDA approved **SB3** (Ontruzant; trastuzumab-dttb), a biosimilar to Herceptin, for the treatment of patients with HER2-overexpressing breast cancer (including MBC) or metastatic gastric or gastroesophageal junction adenocarcinoma. **From[73, PMID:29373094]:** ***https://www.targetedonc.com/news/third-trastuzumab-biosimilar-gains-fda-approval***

In Europe:

- In Aug. 2018, the European Union approved PF-05280014 (**Trazimera**), a biosimilar to Herceptin, to treat patients with HER2 overexpressing metastatic breast cancer. This approval was based upon the REFLECTIONS B327-02 study (NCT01989676), which was presented at the 2017 ESMO Congress. At 1 year, progression-free survival (PFS) and overall survival (OS) were similar between the treatment groups. **From[74, PMID:30002437; 75, PMID:30568294]:** ***https://www.targetedonc.com/news/trastuzumab-biosimilar-receives-approval-in-europe-for-breast-and-gastric-cancers***

In 2015, ASCO (the American Society of Clinical Oncology) issued a policy brief on biosimilars to provide guidance to its members and to policymakers on the evolving regulatory landscape of biosimilars. The policy brief articulated the following principles, among others:

Biosimilar clinical trials should demonstrate efficacy and safety, including lack of immunogenicity

The FDA should establish a transparent regulatory pathway for approval of biosimilars

Physician choice between biologic products in the best interest of patients should not be restricted

Approved biosimilars should be subject to careful post-market safety surveillance

Interchangeability should be established by clinical trials that are adequately designed and performed to support substitution

Congress should ensure adequate FDA funding to meet new demands

However, the field of biosimilars is still in its infancy within the US, and more information about these products is expected to be revealed over time. **From: *http://am.asco.org/biosimilars-changing-cancer-care-landscape***

15. Oligometastases

Oligometastases (OM) in breast cancer is usually characterized by a solitary lesion (tumor) or a few detectable lesions. These lesions are generally limited to a single organ, in which local therapy (possibly along with systemic therapy) with curative intent could impact survival in a positive manner. This population of "potentially curable" MBC patients is estimated to represent 1% to-10% of newly diagnosed patients with MBC.

A multimodal approach is endorsed for this group. Patients with OM disease can be divided into 3 subtypes:

Those who initially present with Oligometastases

Those with residual Oligometastases after Systemic Therapy (ST)

Those with relapsed Oligometastases after curative locoregional therapy

In another analysis, OM was identified as having one or 2 organs involved with metastatic lesions (excluding the primary lesion resectable by surgery), fewer than 5 lesions per metastasized organ, and lesion diameter less than 5cm. Patients were generally treated with systemic chemotherapy first, and those who achieved Complete Response (CR) or Partial Response (PR) were further treated, if applicable, with local therapy (surgical or radiation therapy) and/or with additional systemic therapy to maintain CR or to induce No Evidence of Disease (NED) with additional systemic therapy.

One interesting study involved patients with a single organ or 2 organs were involved. In those cases where effects of systemic therapy, possibly in combination with other treatments, were evaluated, a Complete Response (CR) or Partial Response (PR) was achieved in 48.5% or 47.1% of cases respectively, with an outstanding overall response rate of 95.6%. Medians estimated were: Overall Survival (OS) of 185.0-months, and relapse-free interval (RFI) of 48.0-months. Three cases (4%) survived for their lifetime without relapse after achieving NED, the definition of clinical cure. This study indicates that OM is a distinct group of patients with long-term prognosis superior to MBC, with reasonable provability for clinical cure. **From[76, PMID:22532161]: *http://www.ncbi.nlm.nih.gov/pubmed/22532161***. A current OM study (NCT02364557) is underway to determine whether surgery (or stereotactic body radiation) combined with systemic treatment is superior to systemic treatment alone. One doctor stated, *"With this strategy, I've had young women with metastatic disease who are living without evidence of disease even 10 years out from diagnosis.*" **From: *https://medicalxpress.com/news/2015-12-clinical-trial-explores-treatment-metastases.html***

In the first randomized Phase 2 clinical trial of its kind, researchers have shown that an aggressive form of high-precision radiation therapy can greatly increase how long oligometastatic patients live, and that it doubles how long they may live without cancer. In this recent study, 99 patients with various types of metastatic cancer were either treated with palliative standard of care radiation therapy, or with stereotactic ablative radiotherapy (also known as stereotactic body radiation therapy [SBRT] - a form of high-precision cancer therapy that delivers substantially higher doses of radiation to the tumor site in just one or a few treatment sessions). Patients who received SBRT treatments lived considerably longer than those who did not. Median overall survival (OS) was 41 months (upper limit not yet reached) for patients given stereotactic radiation, compared to 28 months in the standard treatment arm.

Furthermore, *nearly half (46%) of the patients treated with stereotactic radiation were still alive after five years,* compared to 24% in the control group. Stereotactic radiation also doubled the time patients lived without cancer growth. Progression-free survival (PFS) was 12 months in the SBRT arm, compared to 6 months for those who received standard radiation therapy. **From[77, PMID:22823994]: *https://www.eurekalert.org/pub_releases/2018-10/asfr-hrt101618.php***

16. Conditional Survival

A diagnosis of breast cancer – especially metastatic breast cancer – can be highly discouraging and challenging to deal with. But it must be remembered that more therapies are becoming available regularly, as are new clinical trials. Maintaining optimal health under the circumstances is important not just for well-being, but for surviving long enough to take advantage of potential new and effective treatments. And the good news is that the longer a person lives with metastatic breast cancer, the longer he or she is likely to live! This concept, called "Conditional Survival," is based upon a 2010 statistical analysis of huge numbers of patients in the SEER database. The following percentages are probabilities of five years of relative survival (taking into account breast cancer-specific survival and setting aside other causes of death) for different time periods following a diagnosis with metastatic breast cancer.

At 0 years (i.e. when first diagnosed with MBC), the probability of five MORE years of relative survival is 25.3%

At 1 year already survived MBC, the probability of five MORE years of relative survival is 32.4%

At 2 years already survived MBC, the probability of five MORE years of relative survival is 39.1%

At 3 years already survived MBC, the probability of five MORE years of relative survival is 45.5%

At 4 years already survived MBC, the probability of five MORE years of relative survival is 52.0%

At 5 years already survived MBC, the probability of five MORE years of relative survival is 56.9%

From[78, PMID:20647391]: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228022/table/T2/*** (Look under "Distant" and "Breast Cancer").

A more recent study of conditional survival in breast cancer data from SEER examined cases that were diagnosed during 2000-2008 and followed up through 2013. Specific to distant breast cancer disease, the analysis indicated that five-year relative survival was 30%, and that the improvement in 5-year relative survival from diagnosis to five years already survived for distant disease was 91.4%. **From[79, PMID:29063648]:** ***https://www.omicsonline.org/conference-proceedings/2161-1165-C1-016-001.pdf***

However, the SEER database only records "de novo" MBC patients (those who present with metastatic breast cancer at initial diagnosis) as opposed to patients who initially had early stage breast cancer and later recurred. For example, a patient who initially had Stage 1 breast cancer is recorded as a Stage 1 breast cancer patient in SEER, but if s/he recurs, SEER is not updated to reflect the patient's MBC status. Hence the logical question with respect to Conditional Survival is whether the SEER statistics above apply to recurrent MBC patients. Although the author cannot definitively provide an answer, one particular study of 815 patients studied from 2007 – 2009 in eight hospitals in the Netherlands provides some interesting data regarding this question. In the study, patients were subdivided into 3 groups: de novo, patients who recurred in < 24 months, and patients who recurred in > 24 months. The study concluded that patients with de novo metastatic breast cancer had a significantly better outcome when compared with patients who recurred in < 24 months, but when they were compared with patients who recurred in > 24 months, the outcomes were similar. **From[80, PMID:25880008]:** ***https://www.ncbi.nlm.nih.gov/pubmed/25880008***

17. Tests for Breast Cancer Spread (Metastasis and Progression)

Although breast cancer may be initially found by breast self-examination, mammograms, ultrasounds, and other techniques, there are specific diagnostic tests to determine whether breast cancer has spread (metastasized) elsewhere in the body beyond the breast and immediate lymph nodes. Shortness of breath, chronic cough, weight loss, pain, nausea, abdominal swelling, premature fullness while eating, headache, dizziness, changes in vision, diarrhea, and other issues may be symptoms of breast cancer metastasis, although some people have no symptoms whatsoever.

Although some patients are diagnosed with MBC when their cancer is initially found (these are referred to as "Stage IV" or "de novo" patients, which account for 6% to 10% of patients with MBC), up to 30% of breast cancer patients whose disease was initially confined to the breast and/or the immediate surrounding lymph nodes (i.e. "early stage" breast cancer) will eventually develop MBC. **From[81, PMID:17993229]: *http://www.ncbi.nlm.nih.gov/pubmed/17993229***

Often the two terms – "Stage IV" and "metastatic" – are used interchangeably to refer to breast cancer patients whose cancer has spread beyond the breast and immediate lymph nodes to the bones or other internal organs such as the liver, lungs, and brain.

In addition to initially identifying breast cancer that has spread outside the breast and/or immediate lymph nodes, the tests below may also be given on a regular follow up basis after a patient has been confirmed to have MBC in order to determine whether their treatment is working, or whether there is progression of their disease.

Disease monitoring for progression can be stressful on MBC patients, since it frequently causes anxiety (often referred to as "scanxiety"). According to Dr. Accordino, Assistant Professor of Medicine, Columbia University Irving Medical Center, there are data showing that finding progression immediately when it occurs is not associated with better patient outcomes. Furthermore, doctors may order tumor marker tests and then not do anything with the results - they still order scans on the same schedule they would otherwise have used. So the question is why the physician is putting the patient (if the patient is asymptomatic) through all these tests and giving them scanxiety if the physician is not going to change anything based on the information. **From: *https://www.onclive.com/web-exclusives/study-addresses-breast-cancer-monitoring-burden-on-metastatic-patients?p=1***
Depending upon the type (if any) of medical coverage, tests can be expensive for the patient. Furthermore, certain types of scans expose the patient to radiation, and they can be detrimental to specific organs. Two examples are Contrast Induced Nephropathy (CIN) which is a kidney disorder that occurs in about 2% of patients who undergo CT scans or angiograms that use contrast dyes, and Nephrogenic Systemic Fibrosis (NSF) which is a rare but serious disease affecting skin and other organs that has been found in some patients with advanced chronic kidney disease after exposure to gadolinium-containing contrast dyes that are used in magnetic resonance imaging (MRI).

When the author solicited patients' opinions about the above, one person responded that although she had been asymptomatic, she underwent regular scans, one of which revealed a few new spots of metastasis in her bones which were subsequently radiated. She stated that even if the measures did not stop further progression, the radiation may have averted deterioration in the bone and possibly prevented bone pain. She also raised the possibility that the new spots may have been comprised of newly-mutated cancer that the radiation prevented from spreading any further. Another patient responded that her friend's doctor scanned her every three months and would change her treatment every time a scan showed the slightest progression. As a result, she has run through almost every option in a very short time and now regrets it.

Patients eloquently provided key considerations for establishing a scanning schedule, which may need to be re-addressed over time:

Does the patient's cancer show well on scans? For example, metastatic lobular breast cancer can be difficult to identify via scans.

Is the patient newly diagnosed or has s/he recently changed treatments (in which case more frequent scanning may be preferred).

Is the patient symptomatic?

Does the patient's cancer tend to progress slowly or quickly?

Where are patient's metastases located? (For example, if the patient has brain metastases, failing to locate and treat a new brain met could ultimately cause significant physical and cognitive issues).

How accurate are tumor markers for this patient?

Do the patient's blood tests, such as those for liver function, accurately reflect issues or are they in normal range even when there is a problem?

Is this patient at higher than average risk of harm from contrast agents or radiation?

What causes this particular patient more anxiety, scanning or not scanning?

Given the above, patients should carefully discuss with their medical teams the types of scans they should undergo and the frequency with which they should occur - while weighing the pros and cons of various options. These decisions will need to be revisited if and when the patient's status changes.

TESTS TO IDENTIFY AND TRACK MBC

- **Blood Tests:**
  - *Complete Blood Count (CBC) Test*
  - *Liquid Biopsy*
  - *Liver Function Tests*
  - *Tumor Marker Tests*
- **Bone Scan**
- **Circulating Tumor Cell (CTC) Test**
- **Colonoscopy (with biopsy)**
- **Computed Tomography (CT or CAT) Scan**
- **DEXA or DXA (Bone Density) Test**
- **EsophaGogastroDuodenoscopy (EGD) (with biopsy)**
- **Lumbar Puncture (Spinal Tap)**
- **Magnetic Resonance Imaging (MRI**
- **Positron Emission Tomography (PET) Scan**
- **Ultrasound**
- **X-rays**

- **Blood Tests** can check for the spread of cancer to the liver or bones. They usually include checks for anemia, calcium levels, and liver enzymes. Since the normal range for blood test results may range somewhat from laboratory to laboratory, patients should check their particular lab test results to verify the laboratory's normal range.

  - **Complete Blood Count (CBC) Test, which includes checks for:**

Hematocrit counts, which for women the normal range is 34.9% - 44.5% , and for men the normal range is 38.8% – 50%

Hemoglobin counts, which for women the normal range is 12.0– 15.5 grams/dL , and for men the normal range is 13.5 – 17.5 grams/dL

Platelet counts, which for both men and women the normal range is 150 – 450 billion cells/L. A platelet count that's lower than normal (thrombocytopenia) or higher than normal (thrombocytosis) is often a sign of an underlying medical condition, or it may be a side effect of medication.

Red Blood Cell (RBC) counts, which for women the normal range is 3.9 to 5.03 trillion cells/L, and for men the normal range is 4.32 – 5.72 trillion cells/L

White Blood Cell (WBC) counts, where for both men and women the normal range is 3.5-10.5 billion cells/L. A low white blood cell count (leukopenia) may be caused by a medical condition, such as an autoimmune disorder that destroys white blood cells, bone marrow problems, or cancer. Certain medications also can cause white blood cell counts to drop. A high white blood cell count may indicate an infection or inflammation, or it could indicate the presence of an immune system disorder or bone marrow disease. A high white blood cell count can also be a reaction to medication.

The results of one's hematocrit, hemoglobin and red blood cell count are related because they each measure aspects of the red blood cells. If the measures in these three areas are lower than normal, the patient has anemia. A higher than normal result (erythrocytosis) could point to an underlying medical condition such as heart disease. This information is **From:** ***http://www.mayoclinic.org/tests-procedures/complete-blood-count/basics/results/prc-20014088***

- **Liquid Biopsy:** Liquid biopsies are a relatively new form of cancer-related tests. They use cancer patients' blood samples to analyze trace amounts of free-floating tumor DNA in the blood. This minimally invasive test to identify genetic targets does not require any surgery. Liquid biopsies may provide a more accurate picture of cancer tumor DNA (ctDNA)in the body, as genetic sequencing of free-floating tumor DNA may more accurately capture the diversity of genetic alterations found in cancer cells in different parts of the body versus the small piece of tumor used in conventional biopsies. It is theorized that this type of testing might help identify the population of patients who may benefit most from targeted drugs or combinations. **From[82, PMID:27532364]:** ***http://www.eurekalert.org/pub_releases/2015-12/mskc-msh121115.php***

- **Liver Function Tests** check for liver enzymes (proteins made by the liver that are measured in the blood), and related liver conditions. These tests specifically check the following:

  Alanine aminotransferase (ALT), formerly known as serum glutamic pyruvic transaminase (SGPT). Normal ALT levels are 5 – 50 U/L

  Alkaline phosphatase (ALP, AP, or Alk Phos) Normal levels are 20-120U/L

  Aspartate aminotransferase (AST), formerly known as serum glutamic oxaloacetic transaminase (SGOT). Normal levels are 7 – 40 UL

  Bilirubin, a chemical that is released into the blood, which results from the breakdown of red blood cells. Bilirubin is used by the liver to make bile. Normal levels are 0.2 to 1.2mg/dL

  Lactate dehydrogenase (LDH) Normal levels are 100-220 U/L

  This information is **From:** ***http://chemocare.com/chemotherapy/side-effects/liver-problems-liver-dysfunction.aspx***

- **Tumor Marker ("TM") Tests,** which check for elevated TM levels in the blood. In some people TM tests are accurate, whereas in others they are not. In addition, tumor marker levels may initially rise after effective treatment when cancer cells die rapidly and release the marker into the bloodstream; hence the temporary increase may not necessarily mean treatment failure**. From:** ***http://www.aboutcancer.com/tumor_markers.htm***. However, a consistent increase in tumor marker levels, coupled with lack of clinical improvement, may indicate treatment failure (in patients whose tumor markers are reliable). **From:** ***http://www.patient.co.uk/doctor/Tumour-Markers.htm***

  When TMs rise yet scans do not show progression, patients can feel significant anxiety. The author has yet to find a study indicating that changing treatment based upon TMs alone provides a superior outcome. In fact, patients may want to share this statement with their doctor: *"CEA, CA 15-3, and CA 27.29 tests may be used to add to the information your doctor already has about the cancer. These results may help contribute to decisions about your treatment. However, these biomarkers generally should not be used alone to guide treatment or for monitoring how well treatment is working."* **From[83, PMID:26195705]:** ***http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/biomarkers-guide-treatment-metastatic-breast-cancer***

  Tumor Marker Tests encompass the following: *(Note that ranges may vary somewhat among laboratories):*

  CA 15-3, a protein that is a normal product of breast tissue which does not cause breast cancer. If a cancerous tumor is present, levels of CA 15-3 may increase. The normal range of serum CA 15-3 is less than 30 U/mL. CA15-3 is elevated in more than 70% of metastatic breast cancer patients.

  CA 27-29, which is the only blood test specifically for breast cancer. CA 27-29 is a mucus-containing protein that is produced by the MUC-1 gene. Breast cancer cells will shed copies of the CA 27.29 protein in to the bloodstream. Normal levels are < 38 U/ml. Generally, levels > 100 U/ml signify cancer, but since 30% of patients have elevated CA 27.29 for 30-90 days after treatment, it's best to wait 2 to 3 months after starting new treatment to be checked. CA27-29 is elevated in more than 70% of metastatic breast cancer patients.

  CEA, The CarcinoEmbryonic Antigen is a protein that shows up in the blood and is normally found in the tissue of a developing fetus. After birth, the mother's blood levels of CEA should disappear. Smoking produces higher than normal levels of CEA, so patients should abstain from smoking for several days prior to taking the test. Normal values are less than 3 ng/ml in non-smokers, and less than 5 ng/ml in smokers. CEA is elevated in 55% of MBC patients.

- **Bone Scan** is a test for cancer spread to the bone. During a bone scan, a small amount of a mildly radioactive material is injected into a vein (usually in the arm). The radioactive material travels around the body in the bloodstream, and the bones take it up since more radioactivity is absorbed by abnormal bone than by normal bone. A special scanner is then used to show abnormal areas of bone. These are sometimes called "hot spots." It is important to know that hot spots do not necessarily mean cancer and may just be areas of damaged bone. Some other conditions, such as arthritis, may also show up as hot spots.

- **Circulating Tumor Cell (CTC)** is a blood test that checks for the relative volume of cancer cells in the blood. Some people feel that this test may help doctors to assess patients with MBC to determine whether their treatment is working. The CellSearch test is the only FDA-approved test for CTC assessment, and to the author's knowledge it is not routinely used for monitoring patients. **From[84, PMID:15317891]:** ***http://www.mayomedicallaboratories.com/articles/features/ctc/***

- **Colonoscopy (with biopsy)** is a test that allows the doctor to look at the inner lining of the large intestine (rectum and colon). A thin, flexible tube called a colonoscope is used to look at the colon. A colonoscopy helps find ulcers, colon polyps, tumors, and

areas of inflammation or bleeding. This test may be of particular value when diagnosing and tracking Lobular metastatic breast cancer.

- **Computed Tomography (CT or CAT) Scan** to test for spread to the chest, abdomen, pelvis, and sometimes the brain. The CT scan is an X-ray technique that gives doctors information about the body's internal organs in 2-dimensional slices, or cross-sections. During a CT scan, the patient lies on a moving table and pass through a doughnut-shaped machine that takes X-rays of the body from many different angles. A computer correlates the X-rays to create detailed pictures of the inside of the body. Before the test, the patient may need to have a contrast solution (dye) injected into the arm through an intravenous (IV) line, and/or they may also drink a special solution. Because the dye can affect the kidneys, doctors should perform kidney function tests before administering the contrast solution. CT scans give off radiation, so they should be used only as needed.

- **DEXA (or DXA) Bone Density Test**: This test is not designed to find or track cancer. Instead, it is used to assess bone density, which is especially important for cancer patients because their treatment can lead to bone density loss. DEXA is easy to undergo, takes only 10 to 20 minutes, and the amount of radiation exposure is low. The test results provide both a T-score and a Z-score. The T-score compares the patient's bone density with what is normally expected in a healthy young adult of the same sex and reflects the number of units — called Standard Deviations (SDs) — that the patient's bone density is above or below the average. The Z-score is the number of SDs above or below what's normally expected for someone of the same age, sex, weight, and ethnic or racial origin as the patient. The results are interpreted as follows:

  A T-score above -1 SD is normal

  A T-score between -1 and -2.5 SD is a sign of osteopenia, a condition in which bone density is below normal and may lead to osteoporosis

  A T-score below -2.5 SD indicates osteoporosis

  A Z-score of -2 or lower may suggest that something other than aging is causing abnormal bone loss

- **EsophaGogastroDuodenoscopy (EGD) (with biopsy),** also known as upper endoscopy, is a procedure usually performed by a Gastroenterologist (GI or Gastro Intestinal Doctor). This test involves passing an endoscope (a long, flexible black tube with a light and video camera on one end), through the mouth to examine the esophagus, stomach, and the first part of the small intestine called the duodenum. This test may be of particular value when diagnosing and tracking lobular breast cancer.

- **Lumbar Puncture (Spinal Tap):** This involves withdrawing spinal fluid with a needle and examining it for breast cancer cells. This procedure is used in particular to check for Leptomeningeal Metastasis.

- **Magnetic Resonance Imaging (MRI),** which is a scan to check the brain and/or bones, and possibly other areas of the body such as the meninges. It uses magnetism to create cross section pictures of the body. MRIs can show up soft tissues very clearly, and a single scan can produce many pictures from angles all around the body. The MRI is painless but noisy.

- **Positron Emission Tomography (PET) Scan:** Since cancerous cells multiply more rapidly than normal cells, they are more active. A PET scan creates images of cell activity, using Standardized Uptake Value (SUV) as a measurement. "SUV" describes the level of activity in a particular spot compared to activity elsewhere in the body. An SUV reading of 1 represents baseline (normal) cellular activity. An SUV of 2.5 or greater can indicate metastatic cancer activity. With a PET scan, the patient receives an injection of a small amount of a radioactive drug (tracer) which only stays in the body for a few hours. Depending on which drug is given, the radioactive drug will travel to particular parts of the body. The most common drug is fluorine 18, a radioactive version of glucose. When FDG-18 is injected, it travels to places where glucose is used for energy. It reveals cancers because

they process glucose in a different manner from normal tissue. Occasionally, it can show up areas of infection or inflammation that are not cancerous.

- **Ultrasound** may show secondary cancer in the liver and possibly elsewhere. Ultrasound imaging, also called Ultrasound Scanning or Sonography, uses a small transducer (probe) and ultrasound gel placed directly on the skin. High-frequency sound waves are transmitted from the probe through the gel into the body. The sounds are sent to a computer which uses them to create an image, and there is no radiation exposure to the patient. Because ultrasound images are captured in real-time, they can show the structure and movement of the body's internal organs as well as blood flowing through blood vessels.

- **X-rays** can be used to check the bones and/or lungs for abnormalities.

The majority of the above information is **From:** ***http://www.cancerresearchuk.org/about-cancer/type/breast-cancer/secondary/diagnosis/advanced-breast-cancer-tests*** and ***http://www.cancerresearchuk.org/about-cancer/cancers-in-general/tests/ct-scan***

18. The Microenvironment

Over the past decades, considerable research has been done on the nature of cancerous tumors. Chemotherapy and other types of drugs have been designed to attack the tumor in order to kill malignant cells. Recently, another focus is beginning to emerge regarding the "microenvironment," the area surrounding the tumor itself.

The tumor microenvironment is the collection of normal cells, molecules and blood vessels that surround and feed a tumor cell. According to the American Association for Cancer Research, the communication between the tumor cells and the microenvironment helps drive the process of tumor progression.

Mina J. Bissell, Ph.D., who received an award for outstanding scientific research, showed that the microenvironment provides cancer-driving genes with instructions. Furthermore, breast cancer cells harboring tumor-driving mutations can be influenced to behave normally if their microenvironment is restored to normal. Whether this is true in humans is now being explored. **From:** ***http://www.ascopost.com/issues/june-3-2017-narratives-special-issue/aacr-honors-mina-j-bissell-phd-faacr-with-award-for-lifetime-achievement-in-cancer-research/***

Many people have heard of the term "chemotherapy (chemo) resistance," and in fact there is a section dedicated to it. Cancer cells contain mutations that cause instability, and therefore they can change when something happens to them. So, if a drug is given to a cancer cell, the cell can change its genetic makeup and become resistant to the drug over time. Chemo resistance can also be caused by damage to the surrounding normal cells. In the journal Nature Medicine, Dr. Nelson and his team indicates that certain chemotherapy and radiation therapy cause DNA damage in the normal cells within the tumor microenvironment. In a prostate cancer study, these treatment-induced alterations caused these noncancerous cells to excrete a diverse set of growth factors which promoted therapy resistance and subsequent tumor progression. **From[85, PMID:22863786]:** ***https://www.nature.com/articles/nm.2890***

William Li, President of the Boston-based Angiogenesis Foundation, compared a lone tumor cell to a "bad kid" living in a good neighborhood. Even an aspiring juvenile delinquent won't be able to cause much trouble if he's surrounded by watchful parents! Exercise helps improve the neighborhood, keeping cancers in check, Li said. Failing to exercise — and putting on a lot of weight — damages the neighborhood, making it easier for cancer cells to wreak havoc. In particular, exercise helps to prevent chronic inflammation, a process that can fuel cancers by changing the microenvironment. Li indicated that tumors use the growth signals created during inflammation to feed themselves. Subsequently, tumor cells emit more inflammatory signals, helping them to grow even larger. Exercise may help lower levels of both insulin and estrogen, and exercise also helps to relieve psychological stress - which may further reduce inflammation. Conversely, smoking, heavy drinking, being obese, and eating processed foods may increase inflammation.

In addition to the above, exercise has been broadly known as an effective and safe therapy for breast cancer patients in reducing fatigue, depression and improving overall quality of life, but in a new meta-analysis of 15 clinical studies, involving 1,447 women with breast cancer, it was found that exercise also had a suppressive effect on tumor growth.

A longitudinal study from the Moores Cancer Center at the University of California, San Diego indicates that if a breast cancer patient eats at least five servings of vegetables and fruits a day and walks briskly for 30 minutes, six days a week, her risk of death from her disease is reduced by 50%. Although the study was done on 1,490 patients with early stage breast cancer (not MBC), it may still be noteworthy for advanced breast cancer patients.

Insulin may also play a role regarding cell death. According to researcher Robert Weinberg of the Whitehead Institute for Biomedical Research, insulin and a related protein called Insulin-like Growth Factor (IGF) can interfere with a cancer cell's efforts to commit suicide. A cell's internal security system often goes on alert when cancer genes become active, ordering the cell to self-destruct.

Insulin, however, can bind to the cancer cell and silence those suicide instructions. In this way, high circulating insulin levels can rescue tumor cells that would otherwise die or be near-death.

The above information is **From[86, PMID:17557947; 87, PMID:26167483]:** ***https://www.ncbi.nlm.nih.gov/pubmed/17557947*** and ***http://usatoday30.usatoday.com/news/health/medical/health/medical/breastcancer/story/2011-10-02/Targeting-cells-microenvironment-to-fight-breast-cancer/50638558/1*** and ***http://www.medicalnewstoday.com/releases/286501.php***

19. Personalized Medicine

The US Food and Drug Administration (FDA) defines "personalized medicine" as providing *"the right patient with the right drug at the right dose at the right time."* More broadly, personalized medicine may be thought of as the tailoring of treatment to the individual characteristics, needs, and preferences of a patient and their disease.

From: ***https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/precisionmedicine-medicaldevices/default.htm***

Therefore, some people with MBC may want to explore whether they carry a genetic mutation. In addition to determining whether their daughter(s) should be tested for the mutation, people who test positive for the BRCA1 or BRCA2 mutation may respond more favorably to treatments such as PARP inhibitors and platinum-based chemotherapies. People with the BRCA1 or BRCA2 gene may be more likely to develop breast cancer, and hence may want to undergo more frequent or thorough screening.

BRCA1 and BRCA2 mutations are not the only mutations that can help to drive breast cancer. Many other mutations related to breast cancer are being discovered. Currently, clinical trials are underway to determine which mutation-based therapies may work for a given mutation.

APPROACHES TO PERSONALIZED MEDICINE

Aside from testing for BRCA1 and BRCA2 mutations and testing hormone receptivity and HER2-neu status, other methods that help customize treatments are discussed below.

- **Cytometric Profiling (also known as Chemo Sensitivity Testing)**
- **Molecular Testing (Gene Testing or Molecular Profiling)**
- **Integrative Care**

- **Cytometric Profiling ("Chemo Sensitivity Testing")** uses tens of thousands of whole, living cancer cells and surrounding (microenvironment) tissues which are obtained from the patient. In this process, sections of cancerous tissue (or malignant liquid, called ascites or effusion) are separately exposed to many different candidate chemotherapy drugs so that the cell killing ability of each drug can be observed and measured.
  In cytometric profiling, the tumor or malignant ascites or effusion are tested against different chemotherapy drugs and combinations thereof to see what the cancer cells may be susceptible to and what they may be resistant to. This is still considered controversial and many doctors are not convinced of its value. Furthermore, the test may not be covered by insurance. However, several people have indicated that it has helped them and feel that it was superior to the hit-or-miss approach to chemotherapy that is used today.

  This is a link to a meta-analysis study that concluded that there is a two-fold overall tumor response for a chemo assay-guided therapy versus standard of care therapy. Additionally, patients who received assay-guided therapy compared to those who received standard of care or physician's choice had a significantly higher 1-year survival rate. **From[88]:** ***http://meetinglibrary.asco.org/content/118466-132***

  Two viable organizations that conduct chemo sensitivity testing are **Rational Therapeutics (RT)** at ***http://www.rationaltherapeutics.com/*** and the **Weisenthal Cancer Group** at ***http://www.weisenthalcancer.com/*** Dr. Weisenthal mentored Dr. Nagourney, who leads RT, so Dr. Weisenthal has even more experience although both doctors are highly regarded in their field.

- **Molecular Testing** (also known as "Genetic Testing" or" Molecular Profiling") attempts to link expression of certain genes within a cancer cell to a "theoretical potential" for drug activity. In molecular testing, no chemotherapy or other drugs are actually tested against the cancer, and other biological mechanisms of the cancer cell are ignored. Instead, molecular testing provides a genomic profile of genetic mutations that may help doctors make treatment decisions for patients with cancer by identifying the molecular growth drivers of their cancers and matching them with relevant targeted therapies. However, even though a mutation may be identified, there may or may not be a therapy to target it. Furthermore, even when there may be a therapy that allegedly targets the mutation, it may not work for reasons which are not yet understood. One recent example is the PALOMA-1 clinical trial. In PALOMA-1, patients with targeted mutations fared no better than patients without them. "PALOMA-1 was split into two parts, wherein the first part included 66 patients with ER-positive, HER2-negative advanced breast cancer. The second part examined 99 patients with ER-positive, HER2-negative disease and specific biomarkers, including cyclin D1 amplification, p16 loss, or both. Although preclinical data had suggested that ER-positive patients with cyclin D1 amplification and p16 loss might be best responders, this didn't bear out in in the clinical trial." **From [89, PMID:25524798]:** ***https://www.genomeweb.com/clinical-genomics/pfizers-palbociclib-doubles-pfs-her2-negative-breast-cancer-falls-short-overall***

In addition, although hospitals and companies are beginning to sequence patients' tumors in an attempt to personalize therapy, many are not sequencing each person's normal tissue to filter out noncancerous-related changes and to really understand what is occurring in the tumor. Personalized therapies designed to target the unique genetic changes that drive a person's tumor depend on accurate assessment of a tumor genome, but not all genetic changes in a cancer are directly related to the cancer. Some are "germline" changes, which are inherited changes in genes that are in normal tissues and differ from person to person. Only by comparing the genetic sequence of an individual's tumor with his/her own normal cells can clinicians begin to surmise which changes are more likely to be cancer-related and which treatments are likely to work. **From[90, PMID:25877891]:** ***http://medicalxpress.com/news/2015-04-tumor-only-genetic-sequencing-misguide-cancer.html***

Researchers are beginning to learn that, at least in some cases, targeting genetic mutations through drugs can occasionally backfire. In one study that targeted the PI3K mutation, it was determined that monotherapy (single drug) treatment may actually worsen a patient's cancer by causing more aggressive tumor cell behavior and increasing the likelihood of metastasis to other organs. In the study, PI3K inhibition caused mitochondria (the portion of the cell responsible for energy production) to migrate to the peripheral cytoskeleton of the tumor cells, whereas the mitochondria of untreated cells were seen clustered around the cell nucleus. The net result of this was that PI3K inhibition diverted the mitochondria to specialized regions of the cell membrane that are implicated in cell motility, and the cells could move spontaneously, which permitted invasion. **From[91, PMID:26124089]:** ***http://www.targetedonc.com/articles/pi3k-inhibition-may-fuel-cancer-rather-than-fight-it***

In a presentation at the 2015 San Antonio Breast Cancer Symposium (SABCS), Gordon B. Mills, PhD at MD Anderson, discussed the "unexpected high rate of failure of targeted therapeutics." He indicated that, *"For most of our patients with a biomarker, only a sub-population of patients benefit, and that's usually short-term."* The reasons for resistance include genetics, the therapy selected, and tumor adaptive resistance. Specifically, regarding tumor adaptive resistance, he stated that, *"Tumor cells adapt to the targeted therapeutic in a way that allows them to bypass that stress. And that adaptation is almost always mediated at an RNA or protein level rather than a genomic level and cannot be ascertained by solely studying the DNA level."*

Additional caution regarding the clinical relevance of genetic testing was provided by Dr. Francisco J. Esteva, MD, PhD, who spoke about the subject at the 16th Annual International Congress on the Future of Breast Cancer® (East); *"There are many companies now where you can send tissue or plasma, and they can look for mutations in the tissue or mutations in circulating-free DNA in the plasma. The question is, 'What do you do with that information to be able to personalize these therapies?' That goes into the area of clinical utilities. Technology is ahead of the clinical utility of personalized medicine. We can identify mutations in tumors or in the plasma, but what we do with that information is not clear. That is why it is important to continue to use clinical trials… Over the last 15 years or so, we have been focused on protein coding genes. We even tend to focus on larger genomic testing, but each human cell has 20,000 genes—making it a large and complex system. There are thousands more*

noncoding genes, which we don't know much about, and that is another area where we are trained to focus on if they are expressed, what they regulate, and what they do."

"*Additionally, we have the microenvironment, which relates to the immune system and many other things that are not directly in the cancer cell. We need to be able to understand all of this to truly develop personalized medicine in the future."* **From: *http://www.onclive.com/web-exclusives/esteva-explains-state-of-genomic-testing-in-breast-cancer?p=1***

As per Dr. Nikhil Wagle, a cancer specialist at Boston's Dana-Farber Cancer Institute who helped develop precision-medicine tests, *"There are very few instances in which we can look at a genomic test and pick a drug off the shelf and say, 'That will work.' That's our goal in the long run, but in 2018 we're not there yet. Even when drugs are a good match for a specific mutation, they are not consistently viable. A targeted therapy that works in melanoma, for example, doesn't help people with colorectal cancer—even when patients have the exact same mutation,"* said Dr. Wagle.

Targeted therapies may be even less successful in patients who have exhausted all standard treatments. In a large study published in 2017 in Cancer Discovery, precision medicine failed to help 93% of the 1,000 patients who signed up for the study. At ASCO 2018 —the largest cancer meeting in the world—researchers presented the results of 4 specific precision-medicine studies. Two were total failures and the other two weren't much better - failing to shrink tumors 92% and 95% of the time. Interestingly, these studies received almost no news coverage. **From[92, PMID:28365644]: *https://medicalxpress.com/news/2018-09-analysis-precision-medicine-cancer-precisely.html***

Patients who are interested in Molecular Testing should be aware that on Dec. 1, 2017 the FDA approved the FoundationOne CDX ("F1CDx") by Foundation Medicine Inc. The test is designed to provide information about several genetic mutations that may help guide treatment of patients with cancer. Test results show that F1CDx can identify patients with any of five tumor types - including, breast cancer - who may derive benefit from any of 15 FDA-approved targeted treatments**.** **From: *https://www.healio.com/hematology-oncology/lung-cancer/news/online/%7B0edc9a0d-7f33-4d5c-a62c-b181db32b016%7D/fda-approves-foundationone-cdx-to-detect-cancer-biomarkers?nc=1***

Another option is a Liquid Biopsy, which use cancer patients' blood samples to analyze trace amounts of free-floating tumor DNA in the blood. It may provide a more accurate picture of cancer DNA in the body because genetic sequencing of free-floating tumor DNA may more accurately capture the diversity of genetic alterations found in cancer cells in different parts of the body versus the small piece of tumor used in conventional biopsies.

However, patients should be made aware that two of the most widely used genetic sequencing tests — FoundationOne and Guardant360 — showed "widely discordant" results in the same patients, according to a small online study published in JAMA Oncology. The FoundationOne test sequences clinical tumor samples to characterize the exons of 315 cancer-associated genes and introns from 28 genes involved in rearrangements. The Guardant360 test uses cell-free circulating DNA from blood to sequence 70 genes.

The study evaluated nine patients with breast cancer, pancreatic cancer, thymic carcinoma, lung cancer and salivary gland cancer (n = 1 for each). The results of this study were quite revealing. One patient had no identified genetic alteration using either sequencing test. But among the remaining eight patients harbored 45 alterations, only 10 (22%) of which were concordant (in agreement) between FoundationOne and Guardant360 platforms.

In two (25%) of the other eight patients, there was absolutely no concordance among the described alterations. And although total of 36 drugs were recommended for the eight patients, only nine (24%) of these drugs were recommended for the same patients by both platforms. Notably, in five patients (more than 50%), there was no overlap whatsoever between the drugs recommended by the FoundationOne test and those recommended by the Guardant360 test.

The researchers concluded that the output from genetic testing can differ markedly depending on which genetic test is applied. Furthermore, they stated that these findings are clinically relevant because both the FoundationOne and the Guardant360 tests are performed on thousands of cancer patients each year. **From:** ***http://www.healio.com/hematology-oncology/breast-cancer/news/in-the-journals/%7B7ad8fdf6-0661-4d67-a0b2-773251903520%7D/genetic-sequencing-tests-show-widely-discordant-results***

That said, one exciting aspect of molecular testing and related therapies relates to finding additional receptors or biomarkers which may be excellent targets for emerging therapies. Promising research is underway as per the *Research and Potentially Helpful Therapies* section of this book.

- **Integrative Care:** The above section described molecular testing. However, people are certainly "more" than the sum of their genes and tissue. Therefore, many cancer centers such as MD Anderson and Dana Farber have incorporated "Integrative Cancer Care" to treat patients. Recognizing that cancer and its treatments may have major effects on patients and those who are close to them, the intention of integrative care is to incorporate conventional and supplemental therapies meant to improve health, quality of life, and clinical outcomes. Supplemental integrative therapies may include acupuncture, exercise, massage, meditation, nutritional counseling, and others.

  Some practitioners such as Naturopathic Oncologists (NOs) take integrative care one step further. Naturopathic Oncologists typically recommend a protocol consisting of supplements, dietary recommendations, and/or other therapies that may help to enhance the patient's health, reduce treatment and cancer-related side effects, and hopefully help suppress their cancer. The patient's integrative protocol is also designed to work with their mainstream cancer therapy. Among Naturopathic Oncologists, those who carry the title "FABNO" (Fellow by the American Board of Naturopathic Oncology) have passed stringent examinations in order to meet the highest standard of the profession.

  That said, not all FABNOs are alike, any more than all Medical Oncologists (MOs) are alike. The best FABNOs customize their protocol to address the specific patient's overall situation instead of recommending a "one size fits all" regimen. A thorough FABNO will review the patient's medical records and related test results and will order special laboratory tests that Medical Oncologists typically do not. These additional lab tests may assess the status of biological factors regarding the formation of blood vessels (such as vascular endothelial growth factor [VEGF]) and inflammation markers (such as C-Reactive Protein), that may be indicative of the status of the patient's cancer. Based upon the results of these lab tests and the patient's conventional tests, the Naturopathic Oncologist will design a protocol to address any areas of concern as well as optimize the patient's health and will periodically re-test (and make protocol adjustments if necessary) to ensure the regimen is working.

  It may be possible to work remotely via phone, email and Skype with a Naturopathic Oncologist who lives in a different location than the patient. A list of Naturopathic Physicians can be found at: ***https://oncanp.org/directory/***

  Decades ago, integrative cancer care was nearly unheard of, but it is now becoming more widely available. It is the author's hope that in the future it will become the norm instead of the exception. Both conventional and integrative therapies are referred to throughout this book.

20. MBC Conventional Therapies Overview

There is an outstanding overview about the various therapies (chemotherapy, hormonal, targeted and immunotherapy at ***http://www.patientresource.com/Metastatic_Breast_Treatment.aspx*** **and** ***http://www.uptodate.com/contents/systemic-treatment-of-metastatic-breast-cancer-in-women-chemotherapy***

THERAPIES FOR METASTATIC BREAST CANCER

- **Chemotherapy**
- **Hormonal Therapy**
- **Targeted Therapy**

Chemotherapy

Chemotherapy is the treatment of disease using chemical substances, especially the treatment of cancer by cytotoxic drugs (drugs that kill living cells). Chemotherapy drugs tend not to be selective regarding the cells they target, and both cancer cells and normal cells are killed by chemotherapy.

Chemotherapy is certainly an option to treat MBC, especially if the cancer is HER2+, TNBC, if the cancer has progressed during hormone therapy, or if the patient is experiencing considerable symptoms or a life-threatening situation from their cancer. Chemotherapy is sometimes given as a single drug and sometimes as a combination of up to two or three drugs, either together sequentially. The doctor should explain the advantages and disadvantages of these drugs so that the patient and physician can jointly decide together which treatment course is .best.

Potential heart damage

Because chemotherapy drugs can potentially cause heart damage, all patients who are candidates for chemotherapy should have prior careful clinic evaluation and assessment of cardiovascular risk factors or comorbidities. **From[93, PMID:20555097]:** ***http://annonc.oxfordjournals.org/content/21/suppl_5/v277.full***

Additionally, patients who have hypertension, are age 50 years or older, have low baseline left ventricular ejection, and/or have been previously treated with an anthracycline chemotherapy may be more susceptible to cardiac issues while on chemotherapy, and should ensure that their oncologist works with a cardiologist to determine whether they should receive prophylactic (preventive) ACE inhibitors or beta blockers to prevent or lower the risk of cardiotoxicity. In one study, a cardiologist teamed up with a medical oncologist and identified a handful of studies that reported success using a beta blocker called Carvedilol. (Beta blockers slow down the heart and lower blood pressure). They tried Carvedilol on about 50 patients during their chemotherapy treatments. The drug's side effects were minimal and it's an affordable, generic medication. In three years, none of the patients has any signs of cardiac damage, whereas normally a small percentage of patients would have already developed heart failure. Another oncologist stated that Coenzyme Q10 (CoQ10) may also afford some protection for women undergoing chemotherapies that compromise heart function. It is believed that CoQ10 helps to maintain a healthy cardiovascular system, and there is evidence of CoQ10 deficiency in heart failure. **From:** ***http://www.thebreastcaresite.com/chemotherapy/take-heart-smart-treatment-understanding-managing-chemo-brain/***

Potential damage to liver, lungs, and/or kidneys: In addition to potentially precipitating cardiac damage, chemotherapy drugs have been known to cause damage to the liver, lungs, and kidneys**.** Therefore, patients should be carefully pre-checked to ensure these organs are functioning properly, and they should be carefully and continually monitored while on chemo. **From:**

http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/cancer-drugs/side-effects/your-kidneys-liver-heart-and-lungs-and-cancer-drugs

Neuropathy: Not all chemotherapy drugs cause neuropathy, but up to 60% percent of people with breast cancer and other solid tumors who receive taxanes, vinca alkaloids, and platinum-based chemotherapies will experience neuropathy. According to the October 2016 edition of CURE magazine, wearing frozen gloves and socks can help prevent or mitigate this side effect. Additionally, patients are encouraged to discuss exercise with their doctor because a recent study comparing neuropathy symptoms in exercisers (those who undertook walking and gentle resistance-band workouts) vs. non-exercisers concluded that exercise decreases neuropathy symptoms, as does neurofeedback, which is a conditioning procedure that re-trains the brain in its response to pain and discomfort. **From[94, PMID:28398846]:** ***http://www.eurekalert.org/pub_releases/2016-06/uorm-cae060316.php*** and CURE Magazine, October 2016.

Other side effects: Before taking any chemotherapy drug, patients should first discuss potential side effects with their doctor as well as the reason(s) why their doctor is recommending the drug(s). This conversation should also include specific examples of when patients should notify their doctor immediately or go to the Emergency Room (such as if the patient is experiencing difficulty breathing). Patients are also encouraged to visit the drug's website to learn more about the drug(s) and potential side effects, and to ask their doctor about other therapies if they are concerned about taking a particular drug(s).

Pre-testing to avoid potentially toxic or fatal reactions to specific drugs: Some conditions can render a drug toxic or useless to a patient, such as DPD (dihydropyrimidine dehydrogenase) deficiency relative to Xeloda and 5FU. Therefore, patients about to be put on a chemotherapy regimen should discuss any relevant pre-testing before starting a new drug.

Pre-testing prior to Xeloda (Capecitabine) or 5FU: Patients about to go on the chemo drugs Xeloda or 5-FU should first speak with their doctor about getting tested for specific mutations in the DPD (dihydropyrimidine dehydrogenase) gene that could cause severely toxic or potentially life-threatening reactions to these drugs. Approximately 3% to 5% of the population has some degree of DPD deficiency that can put them at risk if they take these drugs. Risks include acute early-onset toxicity and potentially severe, life-threatening, or even fatal adverse reactions, so pre-testing is crucial. **From[95, PMID:18846242]:** ***https://www.sciencedirect.com/topics/medicine-and-dentistry/dihydropyrimidine-dehydrogenase-deficiency***

One person wrote, "*I started on intensive-dose AMF (Adriamycin, methotrexate, 5-Fu) after my early stage bc diagnosis. I nearly died more than once from complications of the treatment. I experienced grades 3-4 leukopenia, neutropenia, anemia, febrile neutropenia, hand-foot syndrome, fatigue, etc. My oncologist was frightened by my response to the chemo, thinking it would kill me before the cancer ever had a chance to. Flash forward nearly 17 years to my diagnosis with MBC. My (new) oncologist wanted to put me on Xeloda. I researched a bit and requested the DPD testing. It turns out I am at risk for severe toxicity from these drugs. We picked another combo that worked well without nearly the risks for me!*"

Review of other medicines and supplements: Before taking any new drug, patients must make sure to tell their doctor about their medical history, other medications and supplements they are taking because some of these may impact the drug's effectiveness.

Reducing dosage and/or frequency: If a patient will be starting chemotherapy (or is on chemotherapy and experiencing significant side effects), they should consider asking their doctor about the possibility of decreasing the dosage and/or reducing the frequency that it is given. Sometimes a reduced or less frequent dosage may make a world of difference in comfort and pain issues without compromising the drug's effectiveness. An example was a small study of low-dose Doxorubicin (Adriamycin), which was evaluated in 19 heavily pretreated MBC patients. They received 8-12 mg/m2 doxorubicin/week for a treatment period of up to 7 months until a progression of the disease occurred. In 2 of 17 evaluable patients, an objective response with a duration of 3+ and 5 months respectively was achieved. In 9 patients, a stabilization of the disease was observed, whereas the disease progressed in 6. The tolerance for this regimen was remarkable, with neither serious acute toxicity nor any signs of congestive cardiomyopathy even in those patients who were treated beyond a cumulative dose of 450 mg/m2. The conclusion was that weekly low dose doxorubicin monotherapy showed modest activity and was devoid of severe toxicity in heavily pretreated MBC patients. **From[96, PMID:4052636]:** ***https://www.ncbi.nlm.nih.gov/pubmed/4052636***

Chemotherapy for elderly MBC patients: Due to their age and other risk factors, elderly MBC patients are at increased risk of adverse reactions to chemotherapy. Therefore, it may be best to start with a drug that is generally less toxic, and whose dosage can readily be decreased if a significant side effect arises. For such patients, Xeloda might be a viable option. In a study of 78 elderly MBC patients comparing Doxil (pegylated liposomal doxorubicin or "PLD") with Xeloda (capecitabine), median progression-free survival was 5.6 months for the Doxil group versus 7.7 months for the Xeloda group. Median overall survival was 13.8 months for patients on Doxil and 16.8 months for those on Xeloda**. From[97, PMID:24504445]:** ***http://www.ncbi.nlm.nih.gov/pubmed/24504445***

A helpful questionnaire to predict the degree of chemotherapy toxicity in elderly patients is located at **[98, PMID:27185838]:** ***http://www.healio.com/hematology-oncology/geriatric-oncology/news/online/%7Bab834d88-a949-4a28-a7cd-a96a0cbf2696%7D/assessment-tool-may-identify-older-patients-at-risk-for-chemotherapy-toxicity***

Bone density loss: Chemotherapy drugs may cause a loss of bone density, which can lead to osteoporosis and/or bone fractures. Therefore, patients who will begin taking chemotherapy should initially have a Bone Density (DEXA) test as a "baseline" and repeat the test every year or two so that they and their doctor can monitor any loss in bone density and decide how to best address it. Some medications may help prevent or slow down osteoporosis, so physicians may prescribe drugs called bisphosphonates or the drug Xgeva to help preserve bone density. In turn, bisphosphonates and Xgeva may cause bone, joint and/or muscle pain, so patients with these symptoms should report them to their doctor immediately. In rare cases, a serious jawbone disorder called OsteoNecrosis of the Jaw (ONJ) may occur. Therefore, it's important for patients to undergo a dental exam (and inform their dentist about their drug plan) before using a bisphosphonate or Xgeva if at all possible. Regular exercise can help strengthen and protect the bones, as can getting enough calcium, Vitamin K2, and Vitamin D.

Premature Menopause: Chemotherapy can cause premenopausal women to go into menopause, but if they are using birth control, it would still be wise to continue doing so because undergoing chemotherapy when pregnant may cause birth defects, and on rare occasions women who appear to be menopausal can still become pregnant. Women whose birth control contains hormones should speak with their doctors about switching to a form of birth control that is hormone-free.

Hair loss (alopecia): Although not all chemotherapy drugs cause hair loss (alopecia), many of these drugs induce significant hair loss or baldness. In Dec. 2015 the FDA approved the use of "cold caps" which help reduce or prevent hair loss in patients receiving chemotherapy. Cold caps circulate cooled liquid to the scalp during chemotherapy treatment. As a result of the cooling system, blood vessels in the scalp constrict, resulting in decreased hair follicle activity which helps reduce hair loss. **From:** ***https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm565599.htm***

When to Stop Chemotherapy: Many MBC patients sequentially undergo one type of chemotherapy after another. Typically, when one type of chemo fails, their doctor puts them on another chemo drug, then another, ad infinitum. Since chemo drugs can cause considerable side effects, their cumulative effect upon the patient needs to be carefully considered. Although there is no hard and fast rule regarding when to stop chemotherapy (and possibly [re-] try a different type of therapy such as hormonal, targeted, or immunotherapy, or cease treatment altogether), the author located the following studies:

A retrospective review of randomized studies compared shorter versus longer chemotherapy. These studies have generally shown that prolonged treatment is associated with extended Time to Progression but has little effect on Overall Survival. The impact of prolonged therapy may be drug dependent, as some agents (e.g. capecitabine) can be continued for longer periods than others (e.g. anthracyclines and taxanes). A recent systematic review of eight randomized trials including 1,942 patients demonstrated no significant reduction in the risk of death with prolonged therapy. **From[99, PMID:19608616]:** ***http://annonc.oxfordjournals.org/content/20/11/1771.long***

In many cases, people with end-stage metastatic cancer are offered chemotherapy to ease pain and improve their quality of life. When chemotherapy is given for these reasons, it is called palliative chemotherapy. Not much research has looked at whether palliative chemotherapy for end-stage disease actually succeeds in improving quality of life. One study that was published online on July 23, 2015 by JAMA Oncology, followed 312 people diagnosed with end-stage metastatic cancer of various types between 2002 and 2008

who were told they had 6 months or less to live. The people in the study were followed until they died. At the beginning of the study, the researchers asked the people in the study about their quality of life as well as their level of well-being, both physically and psychologically. The researchers also asked the caregiver most familiar with the person's well-being to do the same assessment. After a person died, the researchers asked the caregiver to rate the person's quality of life in the last week of life. The caregivers' assessments were considered accurate because their assessments matched the people's self-assessments when the study started.

For patients who were the sickest and had a lower quality of life when the study started, the caregiver rating of their last week of life was about the same, whether or not the people had received palliative chemotherapy. So, the end-of-life chemotherapy didn't seem to improve quality of life for these people. And for people who were in relatively good health and had better quality of life when the study started, more than half (56%) had worse quality of life in their final week of life after receiving palliative chemotherapy. There was no difference in survival between the people who received palliative chemotherapy and those who didn't.

In general, guidelines generally indicate that chemotherapy should be stopped if there were no benefits from three back-to-back regimens, and/or when it is determined or felt that these regimens are doing more harm than good. At that point, clinical trials and supportive care should be considered.

That said, treatment decisions for end-stage cancer are extremely personal and individualized and need to be discussed in detail with one's medical team. What is right for one person may be completely wrong for another person. It's important for patients to speak with their doctors, family, and other loved ones. There are no hard and fast rules. Some people prefer to receive treatment up until the last day of their lives, while others will stop and prefer to spend the last weeks or months of their lives with their families, with their pain and other symptoms controlled without chemotherapy. **From[100, PMID:26203912]:** ***http://www.breastcancer.org/research-news/end-stage-chemo-for-quality-of-life***

FOUR CLASSES OF CHEMOTHERAPY DRUGS

The following 4 classes of chemotherapy drugs are used in treating MBC:

1. **Alkylating Agents** such as Carboplatin, Cisplatin, and Cyclophosphamide damage DNA by adding a chemical to it

2. **Anthracyclines** such as Doxorubicin and Epirubicin damage and disrupt the creation of DNA

3. **Antimetabolites** such as Capecitabine, Fluorouracil, Gemcitabine and Methotrexate prevent the "building blocks" of DNA from being used.

4. **Microtubule Inhibitors** such as Docetaxel, Eribulin, Ixempra, Paclitaxel and Navelbine stop cells from dividing into two cells.

No single chemotherapy agent has demonstrated superiority in MBC. Treatment should be based on previous therapy, differential toxicity, other medical conditions, and patient preferences. Drugs for which clinical resistance has already been shown should not be reused. **From[16, PMID:25185096]:** ***http://www.ascopost.com/issues/october-15-2014/asco-clinical-practice-guideline-chemotherapy-and-targeted-therapy-in-advanced-her2-negative-or-her2-status-unknown-breast-cancer/***

Methods of chemotherapy delivery: Chemotherapy may be taken in pill or capsule form. Other chemo drugs can be injected or administered by an IntraVenous (IV) line. Patients undergoing IV chemotherapy may require a catheter to be implanted through which the chemotherapy will be administered, instead of having an IV needle inserted into the veins (which can damage the skin if the chemotherapy spills out of the vein).

TYPES OF CHEMOTHERAPY ACCESS DEVICES

Chemotherapy access devices include:

Implanted Ports: An implanted port is a small vascular (blood vessel or vein) access device about the size of a quarter with a hollow space inside that is sealed by a soft top. It is used to carry medications into the bloodstream and is placed in patients who need intermittent to long term IV therapy. The port is connected to a small flexible tube called a catheter. In a minor surgical procedure, the port is implanted, which means it is placed completely beneath the skin, and the catheter is inserted inside a blood vessel. The port allows the doctor or nurse to deliver medications and fluids or withdraw blood samples without having to stick the patient's vein with a needle. People who tend to form blood clots, have a body size that will not allow for proper port placement or access, or have had radiation to the site where the port is intended to be placed may reconsider having a port.

PICC line: This peripherally inserted central catheter, or PICC line, is a central venous catheter inserted into a vein in the arm rather than a vein in the neck or chest.

Tunneled Catheters: This type of catheter is surgically inserted into a vein in the neck or chest and passed under the skin. One end of the catheter remains outside the skin.

A detailed list of access devices is located at: ***http://www.academia.edu/8460728/Chemotherapy_Principles_An_In-depth_Discussion_of_the_Techniques_and_Its_Role_in_Cancer_Treatment***

CHEMOTHERAPY DRUGS FOR MBC

The Table below of FDA-approved MBC Chemotherapy Drugs is from:
http://www.patientresource.com/Metastatic_Breast_Treatment.aspx

Chemotherapy agent or combination	
Generic Name	**Brand Name**
Doxorubicin (see Caution #1 below)	**Adriamycin**
Epirubicin (see Caution #1 below)	**Ellence**
Liposomal Doxorubicin (see Caution #1 below)	**Doxil**
Paclitaxel	**Taxol**
Docetaxel	**Taxotere**
Protein-Bound Paclitaxel (nab-paclitaxel)	**Abraxane**
Capecitabine	**Xeloda**
Gemcitabine	**Gemzar**
Vinorelbine	**Navelbine**
Eribulin	**Halaven**
Cyclophosphamide	**Cytoxan**
Mitoxantrone (see Caution #1 below)	**Novantrone**
Cisplatin	**(various)**
Carboplatin	**(various)**
Etoposide	**VePesid**
Vinblastine	**Velban**
Fluorouracil (5-FU)	**Adrucil**
Methotrexate	**(various)**

Ixabepilone	**Ixempra**
Often-used combinations:	
Cyclophosphamide, Doxorubicin, Fluorouracil (see Caution #1 below)	(CAF/FAC)
Fluorouracil, Epirubicin, Cyclophosphamide (see Caution #1 below)	(FEC)
Doxorubicin, Cyclophosphamide (see Caution #1 below)	**(AC)**
Epirubicin, Cyclophosphamide (see Caution #1 below)	**(EC)**
Doxorubicin and Docetaxel or Paclitaxel (see Caution #1 below)	**(AT)**
Cyclophosphamide, Methotrexate (Folex), Fluorouracil	**(CMF)**
Docetaxel and Capecitabine	
Gemcitabine, Paclitaxel	**(GT)**
Ixabepilone and Capecitabine	

Certain foods and supplements may interfere with chemotherapy, so patients should speak with their doctor about what foods and supplements to avoid.

A <u>single</u> chemotherapy agent is often recommended before a combination is given. This is because the patient may receive significant benefits with fewer side effects with just one drug.

Taxanes, which include the three drugs **Taxol (Paclitaxel), Taxotere (Docetaxel),** and **Abraxane (Nab-Paclitaxel; Protein-Bound Paclitaxel),** are common chemotherapy drugs for treating MBC.

Below is information about pre-testing tumor cells prior to administering taxane treatment, along with a comparison of the three taxane drugs.

Pre-Testing a Tumor before Taxane Treatment: Testing a tumor for RNF5 (an enzyme that in humans is encoded by the RNF5 gene), and glutamine carrier protein levels such as SLC1A5, may to help predict a patient's response to taxane-based therapy. Therefore, patients considering a taxane-based regimen may wish to discuss the following research with their doctor.
Researchers at Sanford-Burnham Medical Research Institute have discovered a mechanism that explains why some breast cancer tumors respond to specific chemotherapies and others do not. The findings highlight the level of glutamine, an essential nutrient for cancer development, as a determinant of breast cancer response to select anticancer therapies such as taxanes. Although researchers have been aware that many tumor cell types are dependent on glutamine for growth and survival, they did not know how glutamine uptake was regulated. The findings also suggest that testing tumors for RNF5 and glutamine carrier protein levels, such as SLC1A5, may be used to identify patients best suited to taxanes-based therapy.

"Our study indicates that a protein called RNF5 determines breast cancer response to paclitaxel, one of the most common chemotherapy drugs," said Ze'ev Ronai, Ph.D., scientific director of Sanford-Burnham's La Jolla campus. *"Paclitaxel belongs to*

a class of drugs called taxanes that work by triggering a stress response in cells that in turn promotes an interaction between RNF5 and glutamine uptake proteins. We found that this interaction causes degradation of the glutamine carrier proteins, leading to an insufficient supply of glutamine and the sensitization of breast cancer tumors to death. In more than 500 breast cancer patient samples, it was found that only 30% of tumors exhibit high levels of RNF5 and low levels of glutamine carrier proteins—the optimal profile for response to paclitaxel."

Furthermore, the aforementioned patient tumors were used to test the predictive value of measuring levels of glutamine carrier proteins as a prognostic marker, and the results indicate that these proteins are an outstanding marker of patient outcome, as good as currently used markers.

Significantly, the Sanford-Burnham Medical Research Institute has begun screening for inhibitors of glutamine carrier proteins as a potential new target for breast cancer treatment. **From[101, PMID:25759021]:** ***http://medicalxpress.com/news/2015-03-mechanism-glutamine-uptake-breast-cancer.html***

Comparing the Three Taxane Drugs (Taxotere, Taxol, and Abraxane):

Taxotere (Docetaxel) **vs. Taxol** (Paclitaxel): Taxotere produced a 32% anti-cancer response compared with Taxol's 25% response, and patients taking Taxotere had a 5.7 month Progression Free Survival (PFS) as opposed to those on Taxol who had a 3.6 month PFS. Patients taking Taxotere had a 15.4 month Overall Survival (OS) as opposed to those on Taxol who experienced a 12.7 month OS. However, there is a small risk of permanent hair loss resulting from the use of Taxotere. **From[102, PMID:23133315]:** ***http://www.coloradolaw.net/html/taxotere-chemo.html***

Abraxane (Nab-Paclitaxel; Protein-Bound Paclitaxel) **vs. Taxol** (Paclitaxel): Abraxane produced a 33% anti-cancer response compared with Taxol's 19% response *(the 19% response rate to Taxol differed in this study from the 25% response rate in the above study).* Patients taking Abraxane had a 5.8-month PFS as opposed to those on Taxol who had a 4.2-month PFS, and patients taking Abraxane had a 16.3-month OS as opposed to those on Taxol who experienced a 13.9-month OS. Only 9% of patients on Abraxane experienced neutropenia (an abnormally low count of neutrophils which area type of white blood cell that helps fight off infections), whereas 22% of patients taking Taxol had neutropenia. Whereas Taxol is administered with a toxic chemical solvent (liquid solution) in addition to the drug, Abraxane uses nanoparticle albumin-bound ("nab") technology. This technique uses albumin, the most abundant protein in the body, to deliver the drug directly to cancer cells. With Abraxane, 50% more of the drug can be administered, more of the active drug is transported into the cancer cells, and patients generally experience fewer side effects. **From[102, PMID:23133315]:** ***http://kahlertregionalcancer.org/tools-resources/types-of-cancer/breast-cancer/stage-iv-breast-cancer/***

Caution Regarding Taxanes: Central Nervous System (**CNS**) relapses such as brain metastasis and/or leptomeningeal metastasis are more common among breast cancer patients who are treated with a Taxane-based chemotherapy regimen. Taxane drugs include **Taxol (Paclitaxel), Taxotere (Docetaxel),** and **Abraxane (Nab-Paclitaxel; Protein-Bound Paclitaxel).** Therefore, patients who have taken, or are taking, a Taxane drug should be especially vigilant about reporting symptoms such as headaches, blurred vision, speech or cognitive difficulties, numbness, and/or dizziness to their physician. **From[46, PMID:16846533]:** ***https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr1516***

Xeloda (Capecitabine): Xeloda is a commonly used oral chemotherapy drug which is often used before other chemotherapy drugs are prescribed for MBC. Xeloda may cause "Hand Foot Syndrome," which is evidenced by peeling and/or blistering of skin on the hands and feet. (The section entitled *Therapies for Hand Foot Syndrome* contains more information about this syndrome and related therapies).

Xeloda/5FU and DPD Deficiency: *Before taking Xeloda or 5-FU/fluorouracil (from which Xeloda is derived) patients should consider getting tested for "DPD Deficiency."* DPD stands for dihydropyrimidine dehydrogenase, which is an enzyme the body makes that helps to process thymine and uracil, which make up part of the structure of our genes. DPD also helps to break down Xeloda and 5-FU. If a patient has low levels (a deficiency) of DPD, they will be more likely to have severe side effects from these chemotherapy drugs because with low or no DPD, the chemotherapy drug builds up in the body and cause severe to fatal side effects. Testing for DPD deficiency usually is done via genetic testing, which should be discussed with one's Medical Oncologist since approximately 3% - 6% of the population has at least a partial DPD deficiency. **From[103, PMID:26551538]:** ***http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/dpd-deficiency-and-fluorouracil***

Xeloda/5FU Dose Reduction: Due to considerable side effects from Xeloda, studies have been done on decreasing the drug's recommended dose and frequency. The current standard dose of Xeloda as monotherapy is 1250 mg/m2 twice daily orally for 2 weeks followed by a one-week rest period in 3-week cycles, although this dosage may be adjusted depending upon the patient's body surface area. **From:** ***https://www.drugs.com/dosage/xeloda.html***
For those suffering significant side effects, a dose of 1,000 mg/m2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m2 total daily dose) for 2 weeks with 1 week of rest may be appropriate. Data presented in a retrospective review demonstrate that the dose of Xeloda can be reduced, either when used alone or in combination with docetaxel, to minimize adverse events without compromising efficacy in terms of Time to Progression or Overall Survival. **From [104, PMID:21856245]:** ***http://mbcn.org/images/uploads/DoseAdjustingCapecitabine.pdf***

Etoposide VePesid): The reasons for highlighting this relatively old chemotherapy drug are that it is taken orally, and that it appears to provide some benefit for a subset of heavily pre-treated patients. In one study, 32 patients who had at least 2 prior chemo regimens received a median of 6 cycles of the drug. Eight patients (25%) had partial response (PR) and 14 patients achieved stable disease (SD). The most common side effects were anemia (43.8%), neutropenia (38.5%), nausea/vomiting (75.0%) and hair loss (62.5%). **From[105, PMID:22490573]:** ***http://www.ncbi.nlm.nih.gov/pubmed/22490573***

Caution Regarding Anthracyclines: Adriamycin (Doxorubicin), Liposomal Doxorubicin (Doxil), Mitoxantrone (Novantrone), and Epirubicin (Ellence) belong to a class of drugs called Anthracyclines, which *may cause serious or life-threatening heart problems* during treatment or months to years after treatment has ended. Patients should ensure that their doctors order tests before and during treatment to check whether their heart is working well enough to safely receive these drugs. These tests may include an ElectroCardioGram (ECG) test that records the electrical activity of the heart, and an echocardiogram test that uses sound waves to measure the heart's ability to pump blood. If there is an abnormal heart rate, or if the tests show the heart's ability to pump blood is in jeopardy, then another drug may be substituted. **From:** ***http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682221.html***

Hormonal Therapy

In general, hormonal therapy drugs have fewer and less severe side effects than chemotherapy drugs, and they may take a little longer to work. The use of a specific agent can be repeated if recurrence happens more than 12 months after the last treatment. **From:** ***http://www.medscape.com/viewarticle/864032?src=wnl_edit_tpal&uac=68373MK***

Before taking any new drug, patients should first discuss potential side effects with their doctor as well as the reason(s) why their doctor is recommending the drug(s). This conversation should also include specific examples as to when patients should notify their doctor immediately or go to the Emergency Room (such as if the patient is experiencing difficulty breathing). Patients are also encouraged to visit the drug's website to learn more about the drug(s) and potential side effects, and to ask their doctor about other

therapies if they are concerned about taking a particular drug(s). And as always, before taking any new drug, patients must make sure to tell their doctor about their medical history, other medications and supplements they are taking, and any concerns they may have. **From:** ***http://ww5.komen.org/BreastCancer/RecommendedTreatmentsforMetastaticBreastCancer.html***

Patients taking certain hormonal therapies such as Aromatase Inhibitors (AIs) may run a higher risk of CardioVascular Disease (CVD) and therefore should ensure that their heart function is periodically monitored by a physician. A retrospective analysis of 13,273 postmenopausal women with hormone receptor-positive breast cancer without prior cardiac issues compared CVD incidence across endocrine therapy categories. The study concluded that, whereas Aromatase Inhibitor (AI)-only patients had a similar risk of stroke and cardiac ischemia (myocardial infarction and angina) as tamoxifen-only users, patients on Aromatase Inhibitors had an increased risk of other CVD issues such as dysrhythmia (abnormal heartbeat), valvular dysfunction (failure of one or more heart valves to function normally), and/or pericarditis (inflammation of the lining of the heart). **From [106, PMID:27100398]:** ***https://www.ncbi.nlm.nih.gov/pubmed/27100398***

When to Stop Hormonal Therapy: Guidelines generally indicate that hormonal therapy should be stopped if there are no benefits from three back-to-back hormonal regimens, and/or the patient has disease in their internal organs that is causing significant symptoms. At this point, other options such as chemotherapy (and potentially clinical trials) should be considered.

The Table below of FDA-approved hormonal drugs below has been subdivided into Premenopausal and Postmenopausal status, because the therapies differ somewhat. In some cases, a listed drug can be combined with another drug as described in the *Hormone Receptor Positive Breast Cancer* section of this Guide.

HORMONAL THERAPY DRUGS BY MENOPAUSAL STATUS FOR HORMONE RECEPTOR POSITIVE MBC

From: *https://www.patientresource.com/Metastatic_Breast_Treatment.aspx*

Menopausal status	Hormonal therapy options
Premenopausal	**Luteinizing Hormone Receptor Hormones (LHRH) Agonists:** Also known as Gonadotropin-Releasing Hormones (GnRHs), these drugs lower the level of estrogen. An LHRH Agonist should always be paired with a hormonal therapy for postmenopausal patients. **Goserelin** (Zoladex) **Leuprolide** (Lupron) **Triptorelin (Trelstar)** **Selective Estrogen-Receptor Modulators (SERMs) with or without an LHRH:** These work like ERDs and block estrogen from attaching to breast cells. But because they are "selective," they allow estrogen to communicate with other cells (such as bone, liver and uterine cells) that also have estrogen receptors. **Tamoxifen** (Nolvadex) **Toremifene** (Fareston) **Kisqali (Ribociclib)** which is a CDK4/6 inhibitor, in combination with an Aromatase Inhibitor (AI) such as **Femara (Letrozole), Arimidex (Anastrozole),** or **Exemestane (Aromasin)** as initial endocrine-based therapy.
Postmenopausal	**Aromatase Inhibitors (AI's),** which lower estrogen levels by keeping one enzyme (called aromatase) from changing other hormones into estrogen. (Aromatase Inhibitors may be given alone, or paired with Ibrance, Kisqali, or Verzenio) **Anastrozole** (Arimidex), **Letrozole** (Femara), **Exemestane** (Aromasin, a steroidal AI) **Selective Estrogen Receptor Downregulators (SERDs):** which break down hormone receptors on cells to prevent estrogen from attaching to the cancer cells. This keeps the cells from receiving the signal from estrogen to multiply. Fulvestrant may be given alone or paired with Ibrance, Kisqali, or Verzenio in specific circumstances. **Fulvestrant** (Faslodex) **Selective Estrogen-Receptor Modulators (SERMs):** These work like ERDs and block estrogen from attaching to breast cells. But because they are "selective," they allow estrogen to communicate with other cells (such as bone, liver and uterine cells) that also have estrogen receptors. **Tamoxifen** (Nolvadex), **Toremifene** (Fareston) **High Dose Estrogen** to Re-sensitize AI-Resistant Breast Cancer to Hormonal Therapy (this is sometimes an effective therapy in and of itself): **Estrogen** (Ethinyl Estradiol) **Synthetic Progesterone (Progestin),** which may counteract some of the effects of estrogen: **Progestin Megestrol Acetate** (Megace)

	Other Hormonal Therapies: **Fluoxymesterone** (Halotestin)

Estrogen:

Counterintuitive as it may appear, estrogen can be administered once hormonal therapy resistance has developed in postmenopausal, hormone receptor positive patients. The "estrogen paradox" refers to the fact that on the one hand estrogens are known to stimulate the growth of breast cancer, whereas on the other hand high doses of estrogens are an effective treatment for this disease. The "gap hypothesis" refers to the fact that High Dose Estrogens (HDEs) are only significantly effective when the breast cancer has been devoid of estrogen exposure for a considerable amount of time, either because the patient is postmenopausal for at least five years or due to long term anti-estrogen treatment.

When estrogen-lowering drugs no longer control metastatic breast cancer, the opposite strategy might work. An excellent summary of multiple studies using various forms of estradiol on Aromatase Inhibitor-resistant MBC patients (with favorable results varying from 26% to 56%) can be found on the last three rows of a Table located at **[107, PMID:27889048]:** ***http://www.sciencedirect.com/science/article/pii/S0378512216302833***

The above link cites a small 2015 study in which 19 postmenopausal ER-positive, AI-resistant MBC patients were treated with low dose estrogen - 2 mg estradiol valerate (E2 V). Clinical benefit was observed in 5 patients (26%), and all five of these patients had stable disease ≥6 months. Four of the five patients were "re-challenged" with the same AI as on which the cancer had progressed and three of these patients (75%) showed evidence of re-sensitization, achieving clinical benefit for a second time. (My note: It should be noted that there are toxicities relative to estrogen treatment).

According to a 2009 study of 66 MBC patients whose hormonal therapy failed and who were facing chemotherapy, raising estrogen levels benefited 30% of these women. Not only did estrogen treatment often stop disease progression, in some patients' metastatic tumors became "re-sensitized" and again responded to anti-estrogen treatment. Another study compared a high 30mg daily dose of estrogen to a low 6mg daily dose, and 30% of patients both groups experienced a clinical benefit: their tumors either shrank or stopped growing. Researchers demonstrated that they could predict fairly accurately which patients would have this positive response. They conducted PET scans before estrogen treatment and 24 hours later. If metastatic tumors flared, or glowed more brightly, in the PET scans after estrogen was started, they were much more likely to be affected by estrogen therapy. **From[108, PMID:PMC3460383]**: ***http://news.wustl.edu/news/Pages/14457.aspx***

Some patients responding and then progressing on high dose estrogen therapy may then respond again to estrogen withdrawal. Occasionally MBC can be controlled for many years by initiating and then sequencing high dose estrogen with estrogen withdrawal over time. One MBC patient with bone metastasis had their disease controlled for over 8 years by alternating cycles of high-dose estrogen with estrogen withdrawal 3 separate times. **From[37, PMID:20887199]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656649***

Fareston:

Some people do not respond to Tamoxifen due to a flaw in their CYP2D6 genetic pathway (as described under *Tamoxifen* below). Patients who do not respond to Tamoxifen may want to request a "CYP2D6" test (using healthy tissue instead of tumor tissue because it appears that test results with healthy tissue are more accurate). If after taking the CYP2D6 test the patient is found to

have a CYP2D6 flaw, then Fareston, which is a Selective Estrogen Receptor Modulator (SERM) like Tamoxifen, may be a viable choice for postmenopausal (not premenopausal) patients. **From:** ***http://www.fareston.com/hcp/about/continue.html***

Faslodex (Fulvestrant):

Faslodex is a widely-used hormonal therapy drug for hormonally sensitive postmenopausal patients after an Aromatase Inhibitor (AI) has failed. Faslodex is classified as a Selective Estrogen Receptor Downregulator (SERD) which works by blocking or breaking down the estrogen receptors on cells.

Faslodex was approved in 2017 as a first-line therapy for MBC patients in the US and Europe. One study indicated that Faslodex improved Overall Survival (OS) by 5.7 months compared with Arimidex as a frontline treatment for postmenopausal women with HR-positive MBC who had not received prior treatment. In the clinical trial, treatment with 500-mg Faslodex reduced the risk of death by 30% compared with Arimidex. The median Overall Survival was 54.1 months with Faslodex compared with 48.4 months with Arimidex. Furthermore, using Faslodex as a first-line therapy for this population also improved time to progression, which was 23.4 months for Faslodex and 13.1 months for Arimidex. **From[109, PMID:14535531; 110, PMID:24317176; 111, PMID:26371134]:*http://www.researchgate.net/publication/9057460_Sequential_hormonal_therapy_for_metastatic_breast_cancer_after_adjuvant_Tamoxifen_or_anastrozole*** and ***http://www.cancernetwork.com/sabcs-2014/fulvestrant-improved-survival-first-line-advanced-breast-cancer*** and ***http://www.lbbc.org/news-opinion/study-finds-higher-dose-fulvestrant-reduces-risk-death***

Faslodex in combination with Kisqali (Ribociclib) has also been FDA-approved for a subset of MBC patients based upon the results of the MONALEESA-3 Trial of 726 MBC patients in which it was demonstrated that Kisqali in combination with fulvestrant (Faslodex) showed an improvement in progression-free survival (PFS). The benefit was seen both in patients who had no prior treatment and in patients who had received 1 prior line of neoadjuvant therapy (in this context, neoadjuvant therapy refers to systemic treatment administered prior to breast surgery). Median Progression Free Survival (PFS) at the time of data cut-off was 20.5 months in patients randomized to receive Kisqali and Faslodex, compared with 12.8 months in those randomized to receive Faslodex alone. **From[112, PMID:29860922]:** ***http://www.targetedonc.com/conference/asco-2018/both-frontlinesecondline-benefit-with-ribociclibfulvestrant-in-hrher2-breast-cancer-across-frontline-and-secondline***
Faslodex, which is injected in the butt, can be a bit painful. For intramuscular injections such as those for Faslodex, it may be helpful to turn one's toe/foot inward, as turning the toe inward makes it impossible to tighten the gluteal muscles. Also, patients should request a localized freeze spray before getting the shot, and the solution should be at body temperature and administered slowly. It is also suggested to walk for at least 30 minutes afterwards to minimize after-effects.

Megace (Megestrol Acetate):

Most breast cancer patients are unaware of an older hormonal therapy drug called Megace. Megace acts in a similar way to the hormone progesterone, which can be an effective treatment for advanced breast cancer. Megace is given either as a pill or a liquid and can also improve appetite in people with poor appetites due to cancer. **From:** ***http://chemocare.com/chemotherapy/drug-info/Megace.aspx***

Tamoxifen (Nolvadex):

Tamoxifen is a commonly prescribed Selective Estrogen Receptor Modulator (SERM) which blocks the effects of estrogen in the breast tissue. SERMs work by sitting in the estrogen receptors in breast cells. If a SERM is in the estrogen receptor, there is no room for estrogen and it can't attach to the cell. If estrogen isn't attached to a breast cell, the cell doesn't receive estrogen's signals to grow and multiply.

Some patients do not respond to Tamoxifen, and there is a "CYP2D6 Test" that can potentially identify these patients. However, there has been reluctance to routinely use this test due to inconsistency of the data supporting it, and two recent analyses of large clinical trial data concluded that CYP2D6 testing did not predict Tamoxifen effectiveness. But *a new study (done on early stage breast cancer patients) suggests that CYP2D6 pre-testing might indeed predict ineffectiveness.* The results show that after 5 years of taking Tamoxifen, breast cancer patients with genetic alterations of CYP2D6 who are considered to be poor metabolizers of Tamoxifen experienced disease recurrence or died at a rate that was 2.5 times higher than women with normal CYP2D6 enzyme activity. In addition, women with intermediate levels of the CYP2D6 enzyme had rates of recurrence or death that were 1.7 times higher than those with normal CYP2D6 activity. However, these genetic alterations in CYP2D6 did not affect the likelihood of recurrence or death in patients who switched to Arimidex following 2 years of Tamoxifen therapy. In fact, for the women who switched to Arimidex, there was a tendency towards a reduction in the odds of reduction for a recurrence. **From[113, PMID:23213055]:** ***http://www.medscape.com/viewarticle/776933***

That said, another article indicates that CYP2D6 testing may be flawed overall when tumor tissue (instead of healthy tissue) is used for sampling: Two large clinical trials found no link between the CYP2D6 genotype and Tamoxifen effectiveness, prompting recommendations against testing. But in a Mayo Clinic study, researchers found that previous studies which had used tumor tissue instead of healthy tissue to determine the CYP2D6 genotype, could lead to a distortion of the patient's CYP2D6 genotype. These researchers showed that there was perfect agreement between CYP2D6 genotypes derived from healthy tissue. In contrast, 20% of the CYP2D6 genotypes were misclassified when tumor (not healthy) tissue was used. **From[114, PMID:25490892]:** ***http://www.medicalnewstoday.com/releases/286786.php***

Patients with hormone receptor positive Invasive Lobular breast cancer (ILC) may derive more benefit from Aromatase Inhibitors than from Tamoxifen. **From[5, PMID:27022119]:** ***http://jco.ascopubs.org/content/early/2016/03/23/JCO.2015.66.3872***

In a study of rats with human breast tumors, exposure to dim light at night made their tumors resistant to Tamoxifen, according to data published in Cancer Research. The negative effects of dim light exposure on Tamoxifen treatment were overcome by giving rats a melatonin supplement during the night. The data suggested that nighttime exposure to light, even dim light, could cause breast tumors to become resistant to Tamoxifen by suppressing melatonin production. Although melatonin supplements are readily available over the counter at most drug and health-food stores, research is not at a point where a general recommendation can be made that breast cancer patients taking Tamoxifen should take melatonin (which can sometimes cause diarrhea and/or stomach issues), although it may be advisable for them to sleep in total darkness when possible. **From[115, PMID:25062775]:** ***https://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=569#.W3RxlaOWyYY***

A subset of individuals with metastatic breast cancer may experience a "flare" of their breast cancer within two days to three weeks after starting tamoxifen. This may cause an increase in bone pain, a high blood calcium level, and in individuals with breast cancer involving the skin, an increase in the size and/or number of these skin nodules, or skin redness. These flares usually subside within four to six weeks. In the meantime, the symptoms can be treated with measures that reduce pain and lower blood levels of calcium. **From:** ***http://www.uptodate.com/contents/treatment-of-metastatic-breast-cancer-beyond-the-basics***

And lastly, patients with hormone receptor positive Invasive Lobular breast cancer (ILC) may derive more benefit from Aromatase Inhibitors than from Tamoxifen. **From[5, PMID:27022119]:** ***http://jco.ascopubs.org/content/early/2016/03/23/JCO.2015.66.3872***

Targeted Therapy

Targeted therapy refers to treatment directed at genes, proteins or other substances that contribute in some way to the growth and development of cancer cells. These agents may possibly slow the progression of metastatic disease by blocking signals from various proteins that stimulate the growth of new cells. Blocking these signals can potentially slow any new growth of cancer cells. Generally, targeted therapies have fewer side effects compared with standard chemotherapy. **From[41, PMID:24799487]:** ***https://www.asco.org/about-asco/press-center/news-releases/asco-issues-two-new-guidelines-treating-patients-advanced-her2***

In breast cancer, mutation of the TP53 gene is the most commonly identified genetic defect, followed by the PI3K mutation. **From[116, PMID:24074787; 117, PMID:25979484; 118, PMID:25199759]:** ***https://www.ncbi.nlm.nih.gov/pubmed/24074787*** and ***http://www.ascopost.com/issues/february-1,-2014/common-mutations-may-impact-neoadjuvant-treatment-outcomes-in-breast-cancer.aspx*** PI3K inhibitor drugs (such as Afinitor) function by impeding one or more of the PI3K enzymes of the PI3K/AKT/mTOR pathway—an important signaling pathway for many cellular functions such as growth control, metabolism, survival, and proliferation. This pathway contains numerous components, the inhibition of which may result in tumor suppression. Therefore, PI3K has been thought of as a "master switch" by many cancer researchers and has become the focus of extensive research on therapies aimed at targeting every aspect of the pathway.

Currently, a targeted therapy drug called Afinitor ("Everolimus") can be used together with Aromasin for postmenopausal Hormone Receptor + HER2- women whose MBC has become resistant to hormone therapy. Afinitor belongs to the class of drugs known as mTOR (mammalian target of rapamycin) inhibitors mentioned above. Data suggest that mTOR inhibitors currently in use, such as Afinitor, will be ineffective against cancers that have a mutation in either KRAS or BRAF gene. **From[119, PMID:20664174]:** ***http://www.pubfacts.com/detail/20664174/PIK3CA-and-KRAS-mutations-predict-for-response-to-everolimus-therapy:-now-thats-RAD001***

Because some targeted therapy drugs can potentially cause **heart damage**, patients who are candidates for targeted therapy should discuss the risks of cardiac toxicity with their doctor and potentially undergo tests to determine cardiac health.

To prevent the heart damage caused by chemotherapy, a cardiologist teamed up with a medical oncologist and identified a handful of studies that reported success using a beta blocker called Carvedilol. (Beta blockers slow down the heart and lower blood pressure). They tried Carvedilol on about 50 patients during their chemotherapy treatments. The drug's side effects were minimal and it's an affordable, generic medication. In three years, none of the patients has any signs of cardiac damage, whereas normally a small percentage of patients would have already developed heart failure. Another oncologist stated that Coenzyme Q10 (CoQ10) may also afford some protection for women undergoing chemotherapies that compromise heart function. It is believed that CoQ10 helps to maintain a healthy cardiovascular system, and there is evidence of CoQ10 deficiency in heart failure. **From:** ***http://www.thebreastcaresite.com/chemotherapy/take-heart-smart-treatment-understanding-managing-chemo-brain/***

Before taking any Targeted Therapy drug, patients should first discuss potential side effects with their doctor as well as the reason(s) why their doctor is recommending the drug(s). They may also wish to share the above Wistar study with their oncologist to obtain their opinion. When discussing targeted therapy treatment, the conversation should also include specific examples as to when patients should notify their doctor immediately or go to the Emergency Room (such as if the patient is experiencing difficulty breathing). Patients are also encouraged to visit the drug's website to learn more about the drug(s) and potential side effects, and to ask their doctor about other therapies if they are concerned about taking a particular drug(s). And last but not least, before taking any new drug, patients must make sure to tell their doctor about their medical history, other medications and supplements they are taking, and any concerns they may have.

Targeted therapy may be administered as an injection, via an IntraVenous (IV) line, or as a pill in the cases of Everolimus (Afinitor), Lapatinib (Tykerb), Ibrance, Kisqali, and Verzenio.

In the case of IV targeted therapy, patients may require a catheter to be implanted through which the drug will be administered, instead of having an IV needle inserted into the veins (which can damage the skin if the medication spills out of the vein). Types of access devices are listed in the section entitled, *Chemotherapy*.

TARGETED THERAPY DRUGS FOR MBC

The Table below of FDA-approved targeted drugs is from:
https://www.patientresource.com/Metastatic_Breast_Treatment.aspx

Targeted therapy agent	Type of MBC	Approved/ recommended treatment	Notes
Trastuzumab (Herceptin) * **Ogivri** (trastuzumab-dkst), **Herzuma** (trastuzumab-pkrb) and **SB3** (Ontruzant; trastuzumab-dttb are FDA-approved biosimilar drugs to Herceptin * **Trazimera** is a biosimilar drug to Herceptin that was approved by the EU in 8/18	HER2+	**Ogivri** and **Herzuma** are approved in combination with paclitaxel (Taxol) for first-line treatment or as a single agent after failure of one or more chemotherapy regimens	Trastuzumab was approved by the FDA for use in 1998
Lapatinib (Tykerb)	HER2+	In combination with capecitabine (Xeloda) after failure of anthracyclines, Taxanes (paclitaxel [Taxol] or docetaxel [Taxotere]) and Trastuzumab (Herceptin)	Approved for use in 2007
	HER2+ and hormone receptor positive	In combination with letrozole (Femara)	Approved for use in 2010
Pertuzumab (Perjeta)	HER2+	In combination with Trastuzumab (Herceptin) and docetaxel (Taxotere)	Approved for use in 2012
Ado-Trastuzumab Emtansine (Kadcyla or TDM-1)	HER2+	As a single agent after failure of Trastuzumab (Herceptin) and Taxanes	Approved for use in 2013
Pembrolizumab (Keytruda)	N/A (See Approved/recommended treatment verbiage to the right):	Metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and for which there is no viable standard therapy	Approved for subset of patients in 2017
Everolimus (Afinitor)	Hormone receptor positive, HER2-Postmenopausal	In combination with Exemestane (Aromasin)	Approved for use in 2012

Ibrance (Palbociclib)	Hormone receptor positive, HER2- Postmenopausal	In combination with Letrozole (Femara), Arimidex (Anastrozole), Aromasin (Exemestane), or Fulvestrant (Faslodex)	Approved in 2/2015 and expanded in 4/2017
Kisqali (Ribociclib)	Hormone receptor positive, HER2- Postmenopausal (previously untreated).	In combination with Letrozole (Femara), Arimidex (Anastrozole), Aromasin (Exemestane), or Fulvestrant (Faslodex)	Approved for use in 3/2017
Targeted therapy agent (Cont'd)	**Type of MBC**	**Approved/recommended treatment**	**Notes**
Verzenio (Abemaciclib)	Hormone receptor positive, HER2- Postmenopausal	In combination with Letrozole (Femara), Arimidex (Anastrozole), Aromasin (Exemestane), Faslodex (Fulvestrant), or alone	Approved for use in 9/2017 and 2/2018
Talazoparib (Talzenna)	HER2- patients with germline BRCA mutations	As monotherapy for HER2- patients with germline BRCA mutations. Notably, the FDA has also approved the BRACAnalysis CDx blood test to identify patients with breast cancer with deleterious or suspected deleterious germline BRCA-mutated disease who are eligible for Talazoparib. Patients must be selected for Talazoparib based on this FDA-approved companion diagnostic.	Approved 10/2018
Olaparib (Lynparza)	HER2- patients with germline BRCA mutations	As monotherapy for HER2- MBC patients who had been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting	Approved 1/2018

Herceptin, Tykerb, Perjeta, and Kadcyla may cause heart problems. Patients should ensure that their doctor orders heart tests before and during treatment to check whether their heart is working well enough to safely receive these drugs. These tests may include an ElectroCardioGram (ECG) test that records the electrical activity of the heart, and an echocardiogram test that uses sound waves to measure the heart's ability to pump blood.

Tykerb and Kadcyla might cause liver problems, so doctors should check the patient's liver function before starting the drug, and then every 4 to 6 weeks during treatment.

Kisqali: Unlike Ibrance or Verzenio, Kisqali has been known to cause QT Interval Prolongation (accelerated heart rate that can lead to loss of consciousness, cardiac arrest, or even death) and Hepatobiliary Toxicity (toxicity to the liver, gallbladder, bile ducts, and/or bile).

Afinitor (Everolimus):

Afinitor is generally used in conjunction with Aromasin (Exemestane) for postmenopausal hormone receptor positive patients after they develop resistance to hormonal therapies (AIs, Faslodex, and/or Tamoxifen).

Patients taking Afinitor may develop lung, breathing problems, or pneumonia, which in some cases may be life-threatening. Patients who experience severe symptoms should immediately go to the Emergency Room and notify their doctor. In some instances, Afinitor may cause kidney failure, so the patient's kidney function should be checked both prior to and while they are on the drug. Additionally, if a patient has any type of liver disease (including hepatitis), they may experience reduced liver function as a result of more of the drug staying in the body than expected, which could lead to unwanted side effects. Afinitor may also increase blood sugar and/or lipid levels, so they should be regularly monitored as well. Therefore, patients taking Afinitor should be monitored closely during treatment for these conditions.

In a trial for advanced breast cancer, 63% of those taking Afinitor had to cut the dose of the drug or temporarily stop treatment, and nearly one in five developed a potentially fatal lung condition known as pneumonitis.

Since 2009, the year the drug was first introduced on the market, there have been nearly 9,000 reports of serious adverse reactions among Afinitor users, including more than 2,700 deaths and more than 3,100 hospitalizations. **From:** ***http://www.jsonline.com/watchdog/watchdogreports/fda-repeatedly-approved-cancer-drug-afinitor-without-proof-it-extended-life-b99628814z1-361607291.html***

A less severe but very common side effect of Afinitor is painful mouth sores, and some patients have discovered that tucking the pill into a small marshmallow and then swallowing it helps reduce the extent of the sores. Other patients recommend first coating the mouth with Cool Whip and then tucking the pill inside additional Cool Whip before swallowing it. Some patients purchase empty gel caps and place the Afinitor pill inside before swallowing it. (The section entitled *Therapies for Mouth Sores* may be helpful for these patients).

Patients who are experiencing significant side effects on the standard 10mg dose of Afinitor are encouraged to speak with their doctor about going on a reduced dose of 5mg, or even 2.5mg.

Several people on various MBC online forums have reported developing metastasis to the liver or lung after taking Afinitor, but as of January 2016, no studies were located which corroborated this phenomenon. Therefore, the possibility that Afinitor may in some way precipitate liver and/or lung metastasis remains anecdotal, yet it is something to be aware of.

21. Chemotherapy Resistance

Chemotherapy resistance occurs when cancer that has been responding to a chemotherapy drug suddenly begins to grow. In other words, the cancer cells are resisting the effects of the chemotherapy. When this occurs, the patient's therapy will need to be changed.

Below is a brief list of possible reasons for chemotherapy resistance:

Some of the cells that are not killed by the chemotherapy may mutate (change) and become resistant to the drug. Once they multiply, there may be more resistant cells than cells that are sensitive to the chemotherapy.

Cancer cells may pump the drug out of the cell as fast as it is going in by using a molecule called p-glycoprotein.

Cancer cells may stop taking in the drugs because the protein that transports the drug across the cell wall stops working.

The cancer cells may learn how to repair the DNA breaks caused by some anti-cancer drugs.

Cancer cells may develop a mechanism that inactivates the drug.

From: ***http://chemocare.com/chemotherapy/what-is-chemotherapy/what-is-drug-resistance.aspx***

In addition to the above reasons for chemoresistance, one mouse study found that not all cancer cells are equal, and only some cancer cells are responsible for keeping the cancer growing. Within a small subset of cancer cells, some kept the cancer growing for long time periods (up to 500 days of repeated tumor transplantation), while others were transient and stopped growing within 100 days. They also discovered a class of cancer cells that could lie dormant before being activated. Importantly, the mutated cancer genes were identical for all of these different cell behaviors.

When chemotherapy was given to mice in which the human tumors were growing, the team found that the long-term growing cells were generally sensitive to treatment. However, the dormant cells were not killed by drug treatment and became activated, causing the tumor to grow again. The cancer cells that survived therapy had the same mutations as the sensitive cancer cells, proving that cellular factors not linked to genetic mutation can be responsible for therapy failure.

This research may challenge conventional wisdom that cancer cells' variable growth properties and resistance to therapy are solely based on the spectrum of genetic mutations within a tumor. Instead, the study found a developmental view of cancer growth where other biological factors and cell functions outside genetic mutations may be important in sustaining disease and contributing to therapy failure. **From[120, PMID:23239622]:** ***http://www.sciencedaily.com/releases/2012/12/121213142309.htm***

Resistance to chemotherapy may appear as the patient receives more and more chemotherapy treatments. A 2010 study of 980 MBC patients treated with chemotherapy suggests that it may be possible to identify subsets of people who are less likely to respond to subsequent chemotherapy treatments. The researchers found that the median Overall Survival became progressively smaller for each successive chemotherapy regimen that the patients were given. The time to treatment failure also shortened as each new regimen was tried, from a median of 9.2 months for first-line therapy, to 7.8 and 6.4 months for the second and third-line chemotherapy drugs. Beyond the third line, there was no significant decrease in the medial time to treatment failure for each successive therapy.

Researchers found that only one factor they analyzed affected a patient's Overall Survival time. That factor was the time to treatment failure for each line of chemotherapy. In summary, the more benefit one type of chemotherapy gave to a patient, the more benefit the

subsequent therapy was likely to provide. This implication may help doctors and patients decide whether to undergo a third- or successive chemotherapy line, if and when other treatment options may be available **From[121, PMID:24179488]: *http://www.sciencedaily.com/releases/2010/10/101009082823.htm***

Patients whose MBC is chemo-resistant are encouraged to view the section(s) under *Personalized Medicine* and *Research and Potentially Helpful Therapies* regarding additional possibilities to consider.

22. Clinical Trials Overview

In addition to the therapies described in the previous section, patients may be candidates for therapies that are currently in a clinical trial. Clinical trials are research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans. These studies may also show which medical approaches work best for certain illnesses or groups of people.

Before a new treatment can be given to patients, the underlying research hypothesis (the explanation for how the new treatment works) must be proven in a laboratory. This stage is called **preclinical research**, and it often takes years to turn this knowledge into a new treatment. If the laboratory research suggests that the treatment might be an effective cancer therapy, the sponsor of the clinical trial files an Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA) asking permission to study the treatment in people. If the IND application is approved, researchers can move on to the next step of research, which includes studies to find out more about the treatment on humans.

Clinical trials usually have patient "eligibility" criteria (for example, a particular hormonal status) and "exclusion" criteria (for example, patients who had a specific previous therapy[ies] may not qualify), so not all patients will viable candidates for a particular clinical trial.

There are three categories of clinical trials or studies:

1. Traditional Clinical Trials

2. Clinical Trials Based Upon Genetic Mutation(s):

Basket Trials

Umbrella Trials

3. Observational Studies (not really a classic "clinical trial" in that they do not provide any drugs to patients)

1. Traditional Clinical Trials:

These studies test the effectiveness of drugs to treat a specific cancer type, such as breast cancer. Hence in a traditional clinical trial environment, a breast cancer patient who is enrolled in a study will be grouped solely with other breast cancer patients. Since Traditional clinical trials have been around for decades and are far more common than the new Basket clinical trials, they are described in detail immediately below (followed by information about the newer Basket clinical trials).

There are normally three phases of traditional clinical trials, and sometimes these phases may overlap. Depending upon the requirements of the specific trial, *patients who enroll may first need to undergo a "washout period" whereby they must stop taking any therapy for their disease for a period of time* before beginning the trial, and it is important for patients to inquire about this and consider the risks involved with foregoing treatment for a period of time.

Phase 1 Traditional Clinical Trials:

The goal of a Phase 1 traditional clinical trial is to show that a new drug or treatment, which has proven to be safe for use in animals, may also be given safely to people. Professionals collect data on the dose, timing, and safety of the treatment. People who participate in Phase 1 traditional clinical trials are often the first to receive a new therapy or combination of therapies.

In Phase 1 traditional clinical trials, the dose of the drug being studied is gradually increased to find the dose that works best without causing severe side effects. This process is called "dose escalation." The first participants are given a small dose of the drug. If there are no or few side effects, the next participants are given higher amounts of the drug until doctors find the highest dose with the fewest side effects. Sometimes, doctors need to find out the best way to give the new treatment, such as by mouth or through a vein. In addition, data is collected regarding how the drug is absorbed and processed throughout the body, along with its side effects.

Phase 1 traditional clinical trials generally last several months to a year, and most often involve a small number of people, usually no more than 10 to 20. Patients whose cancers are no longer responding to standard treatments are often offered treatment in Phase 1 traditional clinical trials. Although Phase 1 traditional clinical trials are not primarily designed to test how well a treatment or combination of treatments may work, an investigational treatment in this Phase may help to slow or stop the growth of a person's cancer.

Phase 2 Traditional Clinical Trials:

Phase 2 studies begin if the Phase 1 traditional clinical trial didn't reveal unacceptable toxicity. While the emphasis in Phase 1 is on safety, the focus in Phase 2 is on effectiveness. Phase 2 traditional clinical trials provide more detailed information about the safety of the treatment in addition to evaluating how well it works. These clinical trials focus on finding out whether the new treatment works for a specific cancer. Effectiveness may be measured by a decrease in tumor size, Progression Free Survival (PFS), and/or Overall Survival (OS). These studies take about two years to complete and usually involve about 20 to 40 people. Sometimes Phase 2 traditional clinical trials will assign patients to one of several possible treatments. This is known as a "randomized" Phase 2 trial, which may include up to several hundred patients. The new treatment needs to show it is likely to work and is safe when compared to the standard treatment in order for it to be tested in Phase 3 traditional clinical trials. At the end of a Phase 2 traditional clinical trial, the FDA and the therapy sponsors try to come to an agreement on how large-scale studies in Phase 3 should be undertaken.

Sometimes Phase 1 and Phase 2 traditional clinical trials may be combined. A **Phase 1/II clinical trial** is a study that tests the safety, side effects, and best dose of a new treatment. Phase 1/II clinical trials also test how well patients respond to a new treatment. In the Phase 2 part of the clinical trial, patients usually receive the highest dose of treatment that did not cause harmful side effects in the Phase 1 part of the clinical trial. Combining Phases I and II may allow research questions to be answered more quickly or with fewer patients.

Phase 3 Traditional Clinical Trials:

Phase 3 studies begin if evidence of effectiveness is shown in Phase 2. The goal of Phase 3 traditional clinical trials is to take a new treatment that has shown promising results when used for a small number of patients with a particular disease in a Phase 2 traditional clinical trial and compare it with the current standard of care for that specific disease. In this Phase, data is gathered from large numbers of patients to determine whether the new treatment is better, and possibly has fewer side effects, than the current standard treatment. As in some Phase 2 clinical trials, Phase 3 clinical trials are usually randomized, meaning that patients receive either the investigational treatment or the standard treatment in a non-ordered way. In Phase 3 studies, at least two and possibly more treatments are compared. The number of people enrolled in a Phase 3 traditional clinical trial may range from the hundreds to the thousands, and these clinical trials take many years to complete.

Once a drug has been shown to work well to treat a specific cancer in a Phase 3 traditional clinical trial, researchers can apply for FDA approval. If data from the traditional clinical trials meet the FDA's standards, the treatment is approved for a specific use. However, doctors sometimes prescribe a drug for a use not specified by the FDA, but rather based upon studies published in peer-reviewed journals showing that the treatment works for other diseases, conditions, or symptoms. This is called "off-label" use. **From**: ***http://www.cancer.net/navigating-cancer-care/how-cancer-treated/clinical-trials/phases-clinical-trials***

2. Clinical Trials Based Upon Genetic Mutations:

These studies attempt to match patients with a specific mutation with a drug that targets that specific mutation. Currently there are two subsets of this type of study:

Basket Trials:

Basket Trials provide the patient with a specific targeted drug(s) based upon the type of mutations that the patient's tumor has, irrespective of the patient's type of cancer. For example, breast cancer patients with a particular genetic mutation may end up in the same Basket clinical trial as patients sharing the same mutation who have lung, pancreatic, or other types of cancer. The drugs included in Basket clinical trials have either already been approved by the U.S. Food and Drug Administration (FDA) for another type of cancer or are still being tested in other studies but have shown some effectiveness against tumors with a particular genetic mutation (placebos are not used in Basket clinical trials). Furthermore, instead of "starting small" with very few patients as is done in traditional clinical trials, numerous drugs will be tested among thousands of patients, each in a different arm of the Basket clinical trials. Two examples of Basket Trials are:

* NCI-Match at: ***https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match***

* TAPUR The TAPUR trial differs from NCI-Match in that is it is studying off-label use of approved targeted therapies. Its advantage is that enrolled patients can obtain the therapy through the trial and thus overcome insurance barriers. More information about this trial is located at: ***http://www.tapur.org/***

Umbrella Trials:

Umbrella trials are similar to Basket Trials in that they provide the patient with a specific targeted drug(s) based upon the type of mutations that the patient's tumor has. However, all enrolled patients must be diagnosed with the same type of cancer.

3. Observational Studies:

The intent of Observational Studies is to monitor participants on their current treatment plan and track health results. These studies do not intervene with a patient's current protocol; they simply strive to better understand the various factors that contribute to patient outcomes. One interesting Observational Study regarding MBC patients is called The MBC Project, and additional information can be found at: ***https://www.mbcproject.org/***

Finding Clinical Trials

Patients may request a **free** professional traditional clinical trial search by calling 1.800.4.CANCER (1.800.422.6237). A trained National Cancer Institute (NCI) professional will obtain specific criteria and forward a list of potential clinical trials that the patient may qualify for. For example, a patient with HER2+ MBC may inquire about Phase 2 or III clinical trials that use immunotherapy vaccines.

Other options include the National Institute of Health at ***https://www.clinicaltrials.gov/*** and the National Cancer Institute at ***http://www.cancer.gov/clinicaltrials/search*** When searching the former, it may be helpful to use the "Advanced Search" feature. Also, in addition to searching for Breast Cancer, searches can be done for "Advanced Malignancies" or "Solid Tumors" because sometimes promising and applicable clinical trials can be located via those search terms.

Currently, not all traditional clinical trials that receive NIH funding are registered on ClinicalTrials.gov, nor are study results consistently provided. Therefore, an initiative by the NIH is underway to ensure that every clinical trial that receives NIH funding is registered on ClinicalTrials.gov and that its results are submitted and posted in a timely manner. The outcome of this initiative will enable patients and their doctors to ultimately view accurate, up to date traditional clinical trial information that will assist them in making related decisions.

For readers in the UK, this is a link for UK-based traditional clinical trials: ***http://www.cancerresearchuk.org/about-cancer/trials/***

For readers in Europe, this is a link for EU-based clinical trials: ***https://www.clinicaltrialsregister.eu/ctr-search/search***

For readers in Australia, this is a link for Australian-based clinical trials: ***https://www.australianclinicaltrials.gov.au/***

Costs: Since enrolling in clinical trials might require patients to travel at considerable expense for airfare and/or lodging, there are several options to help patients reduce or avoid costs. *Hope Lodge* is a program that provides free lodging by the American Cancer Society (ACS). To determine whether free accommodations exist in a clinical trial's geographic area, visit the ACS site: ***https://www.cancer.org/treatment/support-programs-and-services/patient-lodging/hope-lodge.html***

Organizations that provide assistance with flights for cancer patients traveling for treatment purposes are listed on: ***https://www.verywellhealth.com/free-flights-for-cancer-treatment-514502***

Tips: In general, patients who may have a relatively good chance of success with standard treatments should initially try FDA-approved therapy(ies) for their type of cancer instead of a clinical trial. Thereafter, just prior to depleting all possible standard lines of treatment after multiple treatment failures, patients should consider a clinical trial in the absence of immediately life-threatening disease. **From[16, PMID:25185096]:** ***http://www.ascopost.com/issues/october-15-2014/asco-clinical-practice-guideline-chemotherapy-and-targeted-therapy-in-advanced-her2-negative-or-her2-status-unknown-breast-cancer/***

If a patient is interested in a Phase 2 or Phase 3 clinical trial, it might be very helpful to investigate the results of the earlier stage trial(s) of the study drug in order to gain information about its potential efficacy.

23. Access to Unapproved Medications in the US

In addition to clinical trials and obtaining FDA-approved drugs for one's specific type of breast cancer, cancer patients in the US have other methods of gaining access to medication that they hope will help against their disease. Three of these additional options are via:

Off-Label Use: "Off-label" means the medication is being used in a manner not specified in the FDA's approved packaging label or insert. Every prescription drug marketed in the U.S. carries an individual, FDA-approved label, which is a written report that provides detailed instructions regarding the approved uses and doses that are based on the results of clinical studies that the drug maker submitted to the FDA. Many people may be surprised to know that the FDA regulates drug approval, not drug prescribing, and doctors are free to prescribe a drug for any reason they think is medically appropriate**.**

Compassionate (Special) Use Program: Patients who do not meet the eligibility criteria for a clinical trial of an investigational drug may be eligible to receive the drug under a protocol known as a Special Exception or a Compassionate Exemption (Use) to the policy of administering investigational drugs only in a clinical trial. The patient's doctor must contact the sponsor of the investigational drug and provide the patient's medical information and treatment history. The sponsor (the Drug Company or NCI) evaluates the requests on a case-by-case basis. There should be reasonable expectation that the drug will prolong survival or improve quality of life for the patient. In some cases, even patients who qualify on a compassionate basis for treatment with an investigational drug might not be able to obtain the drug if the supply is limited and the demand is high.

Expanded (or Managed) Access: The purpose of this type of program is to make investigational drugs that have significant activity against specific cancers available to patients before the FDA approval process has been completed. Expanded Access protocols allow a larger group of people to be treated with the drug. The sponsor (such as the Pharmaceutical Company or National Cancer Institute [NCI]) must apply to the FDA to make the drug available through an Expanded Access protocol. There must be enough evidence from studies already completed to show that the drug is likely to be effective against a specific type of cancer and that it does not have unreasonable risks. The FDA generally approves Expanded Access only if there are no other satisfactory treatments available for the disease. There are instances where a patient has a serious or life-threatening disease or condition, for which all currently available treatment options have been exhausted and enrollment into a clinical trial is not possible.

Considerations: Investigational drugs given under Compassionate Use or Expanded Access must meet the following three criteria:

There must be substantial clinical evidence that the drug may benefit persons with particular types of cancer

The drug must be able to be given safely outside a clinical trial

The drug must be in sufficient supply for ongoing and planned clinical trials

Patient Eligibility Criteria: In order to be considered for treatment with an investigational drug outside a clinical trial, patients usually must meet the following criteria:

Have undergone standard treatment that has not been successful

Be ineligible for any ongoing clinical trials of this drug

Have no acceptable treatment alternatives

Have a cancer diagnosis for which the investigational drug has demonstrated activity

Be likely to experience benefits that outweigh the risks involved

Costs: In some cases, the drug is provided free of charge, but there may be many exceptions. Before beginning treatment, patients should check with their physician, the sponsor, and their insurer about covering these costs.

Considerations: It is not known whether an investigational drug is better than standard therapy for treating a disease, it's possible that a patient may not receive any benefit. Side effects (both long-term and short-term) from the drug may not be fully understood, especially if the drug is in early phase of testing. Sometimes, obtaining approval for an investigational drug through these protocols can require quite a bit of time. And finally, a patient's health insurance company may not pay expenses associated with receiving the investigational drug.

Patients may find out more about a specific drug by contacting the Drug Company that is developing the drug. Information may also be available from NCI's Cancer Information Service at 1.800.4.CANCER (1.800.422.6237). **From: *http://www.cancer.gov/cancertopics/factsheet/Therapy/investigational-drug-access***

"Right to Try" Laws: In 2018, President Donald Trump signed S.204, the Trickett Wendler, Frank Mongiello, Jordan McLinn and Matthew Bellina Right to Try Act, which allows terminally ill patients to access experimental drugs that have passed Phase 1 clinical trials, but which are not yet approved by the FDA for their condition.

To initiate a potential treatment under the "Right to Try" Law, the patient and their physician should thoroughly discuss the patient's treatment options. If the doctor believes that a therapy that has passed a Phase 1 clinical trial is the patient's best hope, then the patient and physician can jointly initiate contact with that drug manufacturer's Compassionate Use program director to discuss options for access. A sample letter for this is provided below:

Current Date

Drug Company Name
Drug Company Address
Drug Company City, State Zip code

Dear *Name of Compassionate Use/Expanded Access Director*,

My name is *Patient Name*, and I am a metastatic breast cancer patient. During my current course of treatment, I have tried all FDA-approved protocols and my disease is progressing. My physician, *Doctor's Name*, in *Doctor's State*, is a specialist who has made me aware of the current clinical trial of your investigational new drug, *Drug Name*.

My doctor has reviewed published data on this drug. After due consideration, my physician has recommended that I attempt to procure *Drug Name*, as it is my last option to treat my disease. My disease progression, combined with other physical ailments/issues, precluded me a clinical trial participant.

As a result, I am writing to you together with *Doctor's Name*, to request access to *Drug Name* outside of clinical trials. In 2018, President Donald Trump signed S.204, the Trickett Wendler, Frank Mongiello, Jordan McLinn and Matthew Bellina Right to Try Act, which provides patients like me the opportunity to directly request medications from manufacturers like *Drug Company Name* with the approval and recommendation of their treating physician. My physician has co-signed this letter requesting access and will attest to the fact that your IND *Drug Name*, is currently my best course of medical treatment and the best hope to extend my life.

It is my understanding that the law protects your company from any liability for providing the drug and provides your company the appropriate constitutional protection allowing you to provide direct access to *Drug Name*.

Both my doctor and I are more than willing to sign any informed consent materials and waivers you require. Please respond to our request as soon as possible as time is of the essence in my case.

Thank you in advance for your prompt attention to this matter.

Sincerely,

Patient's Name	*Doctor's. Name*
Patient's Address	*Doctor's Address*
Patient's Phone	*Doctor's Phone*

Sponsors of Right to Try Laws claim that the delays stemming from the current lengthy review (application by the patient's physician, FDA review and approval of the request, and potentially other reviews) are unacceptable for terminally ill patients.

Critics of Right to Try Laws charge that they're "feel-good" measures that don't address some of the real reasons that patients don't receive experimental treatments in the first place. They mention that even if the FDA approves a request for an experimental drug or device, the patient might not get it. Drug makers and device companies aren't obligated to provide a therapy to patients who request it, and Right to Try laws are no different. Without any assurance of access to an experimental drug or device, and with no financial support to help patients cover the costs, Right to Try laws give patients false hope, say critics of the laws. **From:** ***http://www.npr.org/blogs/health/2014/11/18/364935413/more-states-adopt-laws-to-ease-access-to-experimental-treatments***

24. Tumor Biopsy for New Metastatic Sites

When breast cancer spreads to the liver or elsewhere in the body – especially when a new organ becomes involved - it is recommended that the tumor(s) be biopsied to re-check the cancer's ER, PR and HER2 profile. The rationale for this suggestion is based upon a retrospective analysis of 1,250 ultrasound-guided liver biopsies carried out at the European Institute of Oncology from August 1999 to March 2009.

The analysis studied ER, PR and HER2 status in 255 patients with matched primary and liver tissue samples.

Changes in ER status were observed in 37 (14.5%) of 255 patients

Changes in PR status were observed in 124 (48.6%) of 255 patients

Changes in HER2 status were observed in 24 (13.9%) of 172 evaluable patients

The study observed a difference in receptor status (ER, PR, and HER2) between primary tumor and liver metastasis, which led to change in therapy for 31 (12.1%) of 255 of patients. **From[122, PMID:21343379]:** ***http://www.ncbi.nlm.nih.gov/pubmed/21343379***

A different study evaluated the characteristics of Circulating Tumor Cells (CTCs) in patients diagnosed with HER2-negative metastatic breast cancer. At least one HER2-positive CTC was found in 18.8% of the HER2-negative MBC patients who had CTCs, indicating frequent discordance between primary tumor and CTCs with regard to HER2 status. The presence of HER2-positive CTCs tended to be associated with hormone-positive primary tumors; in other words, patients with TNBC were less likely to have HER2-positive CTCs than patients with HER2-negative but hormone receptor positive tumors. **From[123, PMID:28586395]:** ***http://ascopubs.org/doi/full/10.1200/PO.17.00023***

A reader of this Guide provided a heads-up indicating that the type of tissue used for biopsy, along with how the biopsied material is handled, can affect the outcome of ER, PR and/or HER2 testing. Whenever possible, it is preferable to have a biopsy done on specimens removed from soft tissue instead of bone (or bone marrow). This is because biopsies done on bones (or bone marrow) can be more prone to error due to the need for a process called "decalcification." Decalcification involves the removal of calcium ions from the bone (usually via acids) in order to make it more flexible and primed for pathological investigation.

Before having surgery to obtain a biopsy, patients should work with their doctors to send the upcoming tumor sample to a laboratory that is College of American Pathology (CAP) Certified if at all possible, since CAP appears to be the "gold standard" for laboratory accreditation. Patients and their doctors may search for a list of CAP-Certified Laboratories at: ***https://www.cap.org/laboratory-improvement/accreditation/accredited-laboratory-and-biorepository-directory***

Additionally, whenever possible, patients should schedule their biopsy on a morning early in the week to minimize the potential for specimen mishandling.

Below is detailed information about factors that can affect biopsy results, along with links to the relevant sources:

Decalcification: Decalcification procedures may destroy estrogen receptor results. If medical staffs are dealing with bone or bone marrow biopsies where there is a question of metastatic breast disease, technicians should consider establishing an alternative protocol so that there is some tissue associated with the bone marrow that hasn't gone through decalcification. It might involve setting aside a small piece of marrow or some clot tissue. This is because the acidification of bone specimens may result in decreased antigenicity of the tumor cells, altering the biomarker status of the metastatic breast cancer. In one small study comparing pathology results from decalcified tissue versus regularly processed tumor, the mean drop for decalcified tissue regarding ER status was 21%, for PR the decrease was 9.8%, and for HER2 the decrease was 1.

Time that Tissue is Left Unattended: The time that a breast cancer sits in the operating room or on the laboratory bench can affect the results of estrogen receptor testing. Estrogen receptor degrades in unfixed tissue. Tissue sitting at room temperature for four to five hours loses a significant amount of estrogen receptor. So, it is very important to get the tissue from the patient to the pathology laboratory and from the grossing bench into fixative as soon as possible. If a patient is scheduled for a biopsy in the evening, on a holiday, or a weekend, arrangements should be in place to make sure the tissue is attended to, gets into fixative, and doesn't sit overnight degrading.

Size of Tumor and the Specific Portion Taken for Biopsy: If a tumor is over two centimeters in size, the center of the tumor will be relatively estrogen receptor negative compared with the edges, because the middle of the tumor is relatively ischemic (i.e. has less blood supply) and will have less reactivity. Another advantage for taking the edge of the tumor for estrogen receptor testing is that the tissue section will often include some benign tissue that may act as an internal control.

Width of Tumor Slice: Another that affects estrogen receptor determination is how the breast tumor tissue is prepared. It does little good to put breast tissue in fixative if it is not sliced thinly enough to expose all the tissue to the fixative in less than three hours. A lot of breast cancer tissue submitted for microscopy is too thick and too big for the tissue cassettes. With too much tissue in a cassette, the result is poorly processed tissue, and poorly processed tissue has poor ER reactivity.

Fixative: The type of fixative as well as the fixation time that the tissue is exposed to the tumor may also impact the results, if the proper guidelines are not followed. **From[124, PMID:21999708]:** ***http://www.readcube.com/articles/10.1111%2Fj.1524-4741.2011.01168.x?r3_referer=wol&tracking_action=preview_click&show_checkout=1***

25. Bone Metastasis

When breast cancer spreads, bone is the most common site of breast cancer metastasis.

Symptoms of bone metastasis include bone pain, fractures, and/or spinal cord compression, although many patients have no symptoms at all.

Bone metastasis can appear in the spine, pelvis, ribs, skull, or other bony locations. Bone metastasis may be detected by X-rays, bone scans, CTs and/or MRIs before or after symptoms arise. In some instances, infections, arthritis, and old fractures may be difficult to distinguish from cancer on these tests. MRIs can be useful when examining nerve roots suspected of being compressed by a tumor, or bone fragments due to tumor destruction and in the setting of spinal cord compromise.

There are no specific blood tests that specifically diagnose bone metastasis. There are, however, several blood tests that a provider can obtain that may suggest the presence of bone lesions, but the diagnosis requires the combination of radiographic evidence, clinical picture, and natural history of the malignancy. For example, elevated levels of calcium or an enzyme called alkaline phosphatase can be related to bone metastasis, but these lab tests alone are insufficient to prove their presence.

Bones are not static. Old bone is constantly being broken down and replaced by new bone. Two types of bone cells are involved in this bone-building process: osteoclasts and osteoblasts. The osteoclasts trigger bone resorption, which means "to lose substance" - they are the cells that break down existing bone to make way for new bone. After the osteoclasts do their work, the osteoblasts trigger the bone building that is necessary to replace the bone that has been resorbed. When tumor cells are in the bone, the breakdown of bone is accelerated, but the buildup of bone is not. As a result, patients with bone metastasis often have thinner bone, and consequently they may have pain and fractures where metastasis occurs. These patients may also develop hypercalcemia—a condition in which too much calcium is released from the bones into the blood.

Patients with bone metastasis who are experiencing severe pain may actually have bone fractures that have gone unnoticed. It is advised that, whenever possible, patients with painful bone metastases consult with an orthopedic oncologist since these physicians specialize in the diagnoses and treatment of primary benign and malignant tumors of the bones and perform surgery.

TREATMENTS FOR BONE METASTASIS

Once bone metastasis has been diagnosed, treatment may include **chemotherapy, hormonal therapy, and/or targeted therapy** based upon the cancer's profile. The following interventions may also be used. (Since in some cases the treatment which targets the cancer also causes pain relief, the procedures listed below also appear in the section entitled, *Therapies for Pain and Neuropathy*).

- **Bisphosphonates/Xgeva**
- **Bone Cement**
- **MRIgFU Ablation Therapy (ExAblate)**
- **Other Current Non-Surgical Ablation Techniques**
  - *Cryoablation*
  - *RadioFrequency Ablation*
  - *Radiopharmaceuticals*
  - *Stereotactic Body Radiation Therapy (SBRT)*
  - *Stereotactic Radiosurgery (SRS), such as Cyberknife and Gamma Knife*
  - *Other techniques*
- **Strontium 89**
- **Surgery**
- **Systemic Therapy**

These therapies are described below:

- **Bisphosphonates and Xgeva:**
  A common treatment for bone metastasis, Bisphosphonates are a class of drugs that retards (slows) bone resorption. Two common drugs to help the bones are **Zometa** (**Zoledronic Acid)** and **Xgeva (Denosumab)**. Xgeva is not a Bisphosphonate; instead it targets a receptor called Receptor Activator of Nuclear Factor Kappa B Ligand ("RANKL"), which is able to block osteoclast formation. In a study of women with bone metastasis from breast cancer, Xgeva delayed bone complications for five months longer than Zometa, although Overall Survival was similar. **From**: ***http://news.cancerconnect.com/xgeva-delays-bone-complications-in-women-with-metastatic-breast-cancer/***

  Patients with renal (kidney) impairment may not be viable candidates for bisphosphonate therapy. The effects on vascular calcifications need further study since bone turnover might exacerbate vascular calcifications in patients with Chronic Kidney Disease (CKD). Even if Bisphosphonates prove safe, their efficacy in this population is uncertain. **From**: ***https://www.uspharmacist.com/article/bisphosphonate-nephrotoxicity-risks-and-use-in-ckd-patients***

  Warning About Bisphosphonates and Xgeva: These drugs may cause bone, joint, and/or muscle pain, so patients with such symptoms should report them to their doctor immediately. In rare cases, a serious jawbone disorder called OsteoNecrosis of the Jaw (ONJ) may occur. Prior to beginning therapy with a bisphosphonate or Xgeva, patients are encouraged to visit their dentist. At that time, the dentist may need to perform preventive dentistry (preemptive extraction of unsalvageable teeth and/or optimization of periodontal health) in order to avoid potential complications later on. Once a patient has begun taking bisphosphonates or Xgeva, they should undertake daily flossing, regular brushing, and use an antibacterial oral rinse to help prevent ONJ. Furthermore, the patient should speak with their dentist about their drug regimen before undertaking any dental procedure.

  Regular exercise can help strengthen and protect the bones, as can getting enough calcium, Vitamin K2, and vitamin D. **From:** ***https://www.hsph.harvard.edu/nutritionsource/what-should-you-eat/calcium-and-milk/calcium-full-story/#growing***

  Frequency of Bisphosphonates: Potentially the risk of ONJ may be reduced as the result of receiving a less frequent dosage after the first year of Bisphosphonate therapy. Patients with MBC to the bone may be able to receive Bisphosphonates less often after the first year of monthly administration. With that practice change, patients may also reduce their risk of serious side effects, according to a study led by researchers at The University of Texas MD Anderson Cancer Center. The research found that receiving Zoledronic Acid every 12 weeks after one year of monthly administration was as effective as continuing to receive it monthly. **From[125, PMID:28125763]:** ***http://www.sciencedaily.com/releases/2014/05/140530142414.htm***

  Side effects from Zometa: Some patients report feeling unwell for several days after receiving a Zometa infusion to mitigate and possibly avoid side effects, the following steps are recommended: 1) Hydrate well the day before the infusion, the day of the infusion, and the day after; 2) Take Tylenol or Advil the day of and the day after the infusion; 3) Ask the nurse ahead of time to set the infusion time for 45 minutes, as faster infusions can cause more side effects; 4) Ask the nurse to provide IV fluids before the infusion.

  Supplementation While Taking Bisphosphonates/Xgeva: Patients on these drugs should speak with their doctor about supplementation with Vitamin D, Calcium, and Vitamin K2 (which acts synergistically with calcium and Vitamin D to make them more effective). The European Society of Medical Oncology (ESM) stated that when a bone modifying agent is given, supplements of calcium and vitamin D are considered mandatory, except in the presence of contra-indications. **From[61, PMID:28327998]:** ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw544***

- **Bone Cement:** One option to strengthen and stabilize a bone is to use injections of quick-setting bone cement or glue called PolyMethyl MethAcrylate (PMMA). When PMMA is injected into a spinal bone it's called "Vertebroplasty" or "Kyphoplasty." This treatment helps to stabilize the bone and relieve pain in most people. When bone cement is injected to strengthen bones

other than the spine, it's called "Cementoplasty." Sometimes, it is used along with surgery, radiation, radiofrequency ablation, or other treatments, depending on the person's medical situation. A person with spinal cord compression, an infection, or in poor health might not do well with this treatment. **From[126, PMID:25363262]:** ***http://www.cancer.org/treatment/understandingyourdiagnosis/bonemetastasis/bone-metastasis-local-treatments***

- **MRIgFU Ablation Therapy (ExAblate).** This type of therapy significantly reduced pain in 67% of patients who received the treatment. The device uses numerous small ultrasound beams designed to target a tumor within the bone, heat it and destroy it. ExAblate was approved by the U.S. Food and Drug Administration as second-line therapy for palliation (relief) of painful metastatic bone tumors. The first-line therapy is typically radiotherapy. The response to ExAblate appears to be as good as radiotherapy, which was notable because it is very unusual to see a second-line treatment with a response rate that is as high as first-line therapy. **From:[127, PMID:24760791]** ***https://www.sciencedaily.com/releases/2013/06/130602144337.htm*** and ***https://www.insightec.com/clinical/oncology***

- **Non-surgical Ablation Techniques:** The term "**a**blation" usually refers to the removal of harmful substances from the body. In this context, placing a needle or probe right into a tumor and using heat, cold, or a chemical to destroy it is called ablation. Ablation may be used if only 1 or 2 bone tumors are causing problems.

  Current non-surgical Ablation Techniques include:

  - *Cryoablation***,** which entails using a very cold probe that is put into the tumor to freeze it, thus killing the cancer cells.

  - *RadioFrequency Ablation (RFA),* which uses a needle that carries an electric current. The electric current that is delivered through the needle heats the tumor to destroy it. RFA is usually done while the patient is under general anesthesia.

  - *Radiopharmaceuticals:* Substances called radiopharmaceuticals are given through a vein, and they use low levels of radioactive material that has a strong attraction to bones. Once in the body, the particles travel to the areas of bone metastasis and release their radiation. This treatment doesn't require a hospital stay, and the patient will not be radioactive after treatment. **From:** ***http://www.mayoclinic.org/diseases-conditions/bone-metastasis/basics/treatment/con-20035450***

  - *Stereotactic Body RadioTherapy (SBRT):* This treatment is similar to central nervous system (CNS) stereotactic radiosurgery (SRS), except that it deals with tumors outside of the CNS. A stereotactic radiation treatment for the body means that a specially designed coordinate-system is used for the exact localization of the tumor in the body in order to treat it with limited but highly precise treatment fields. SBRT involves the delivery of a single high dose radiation treatment or a few fractionated radiation treatments (usually up to 5 treatments). In some particular clinical settings, such as oligometastatic patients and/or those with a long life expectancy, spinal SBRT could be considered a valid therapeutic option to obtain long-lasting palliation. **From:** ***http://radonc.ucla.edu/sbrt***

  - *Stereotactic Radiosurgery (SRS):* Stereotactic Radiosurgery (SRS) uses many precisely focused radiation beams to treat tumors and other problems in the brain, neck and other parts of the body. It is not surgery in the traditional sense because there's no incision. Instead, SRS uses 3-D (three-dimensional) imaging to target high doses of radiation to the affected area with minimal impact on the surrounding healthy tissue. Cyberknife and Gamma Knife are forms of SRS.

  - *Other techniques* utilize alcohol to kill the cells, or leverage other ways to heat the tumor (such as Laser-Induced Interstitial Thermotherapy). After the cancer tissue is destroyed, the space left behind may be filled with bone cement.

- **Strontium 89** (under the brand name **Metastron**) is an older therapy that has been used to treat painful bone metastasis accompanying metastatic breast cancer. **From[128, PMID:9732212]**: ***http://www.cancernetwork.com/oncology-journal/use-strontium-89-metastatic-cancer-us-and-uk-experience***

- **Surgery:** Surgery to remove a primary bone tumor (one that started in the bone) is often done to try and cure the cancer. But often the purpose of surgically treating a bone metastasis is to relieve symptoms and/or stabilize the bone to prevent fractures. Bone metastasis can weaken bones, leading to fractures that tend to heal poorly. An operation can be done to place screws, rods, pins, plates, cages or other devices to make the bone more stable the bone and help prevent fractures. If the bone is already broken, surgery can often relieve pain quickly and help the patient return to their usual activities. If the doctor cannot surgically reinforce a bone that has metastasis, a cast or splint may help stabilize it to reduce pain, so the person can move around.

- **Systemic Therapy:** Depending upon the cancer's hormonal and HER2 status, appropriate systemic therapy (such as hormonal and/or chemotherapy and/or targeted therapy) will usually be administered. Hormone receptor positive patients with extensive bony disease may be at risk for the development of symptomatic hypercalcemia (elevated levels of calcium in the blood) early in the course of hormone therapy, so these levels need to be closely monitored throughout treatment.

For additional information about radiation and bone pain, please refer to the section entitled, *Therapies for Pain and Neuropathy*.

Diet and Bones: Some people now feel that phytates, which are present in certain foods, may prevent adequate absorption of minerals essential to bone health. Caffeine, alcohol and sugars may also be associated with weakening bones. Therefore, patients may want to discuss potential dietary changes with their doctor or nutritionist. **From[129, PMID:22523525; 130, PMID:1609631]:** ***https://americanbonehealth.org/blog-post/how-do-phytates-impact-calcium-absorption/*** and ***https://www.mayoclinic.org/diseases-conditions/osteoporosis/in-depth/osteoporosis/art-20304601***

26. Bone Marrow Metastasis

In rare cases, breast cancer may invade the bone marrow (the hollow part of the bone where blood cells are made). This may cause immature blood cells to be released into the bloodstream, resulting in problems such as anemia (lack of red blood cells). Symptoms may include tiredness, weakness, and/or breathlessness, although some patients experience no symptoms at all. Blood tests and/or a bone marrow biopsy are needed to make a diagnosis of metastasis to the marrow.

The author was unable to find much viable information specifically about the treatment of bone marrow metastasis, which can sometimes cause anemia. Anemia can be treated with regular blood transfusions in the hospital, and readers with bone marrow metastasis may want to view the section entitled, *Therapies to Increase Bone Marrow Production and Blood Counts.*

Systemic therapy such as **chemotherapy, hormonal therapy, and/or targeted therapy** (based upon the patient's hormonal and HER2 status) may be used for bone marrow metastasis, although a delicate balance must be struck with chemotherapy drugs to control bone marrow metastasis that also depress the bone marrow.

27. Liver Metastasis

Symptoms of liver metastasis include loss of appetite, jaundice (a yellowish color of the skin or whites of the eyes), pain in the liver and/or abdominal area, pain in the right shoulder or upper abdomen, dark urine, loss of appetite and/or weight loss. Patients should notify their doctor if they notice any of these signs and go directly to the Emergency Room if they have jaundice. However, some patients with liver metastasis have no symptoms at all.

Whenever breast cancer moves to a new organ, the tumor should be biopsied if possible to re-check its ER, PR and HER2 status (as per the section entitled, *Tumor Biopsy for New Metastatic Sites*).

Liver metastasis may be treated with **chemotherapy and/or hormonal therapy and/or targeted therapy** based upon the cancer's profile, and additional **localized liver-directed** treatment may be available as well. An excellent source of information about directed therapy options is located at: ***http://beatlivertumors.org/directed-therapy.html***

TREATMENTS FOR LIVER METASTASIS

- **Ablative Therapies**
  - *Cryotherapy*
  - *NanoKnife*
  - *RadioFrequency Ablation (RFA)*
- **DEBDOX**
- **HAI Chemotherapy**
- **NKTR-102 (Etirinotecan Pegol)** *(Not Yet FDA-Approved for MBC Patients)*
- **Radioembolization or SIRT/Yttrium 90 Microspheres (Theraspheres)**
- **Transarterial Chemoembolization (TACE)**

These procedures are described below:

- **Ablative Therapies:** Ablative therapies can be performed percutaneously (through the skin) or as an open surgical procedure by a surgeon who specializes in oncology. A special probe is used to access the tumor, and the specific method of treatment as described below is delivered by the probe. Ablation is generally safe and well tolerated. It may be an effective treatment for patients with inoperable metastatic tumors, but this treatment is limited by the size and number of tumors present. Ablative therapies include:

  - *Cryotherapy:* Cryotherapy, also called cryosurgery, cryoablation, or targeted cryoablation therapy, uses the application of extreme cold to destroy the liver tumor.

  - *NanoKnife:* NanoKnife works by applying electrical energy directly into tumors and opening cell walls of the tumor. The cancer cells die; and the healthy tissue remains unharmed.

  - *Radio Frequency Ablation (RFA):* Radiofrequency ablation, also known as RFA, is a technique of heating up liver cancers with probes inserted into the tumors.

- **DEBDOX:** This is a treatment whereby the chemotherapy drug Doxorubicin (in special "beads") is administered directly to the liver. In a study of about 40 patients with MBC to the liver, 75 image-guided procedures with hepatic arterial drug-eluting beads loaded with doxorubicin (DEBDOX) were administered. Treatment was well tolerated with a total of eight patients sustaining 13 adverse events within the 30 days of each treatment session. All adverse events were either a grade I or grade II in toxicity. After a median follow-up of 12 months in all patients, the hepatic progression-free survival was a median of 26 months and overall

survival was a median of 47 months. The treatment of hepatic metastasis from MBC using DEBDOX was therefore deemed to be an effective local therapy with very high response rates and a very safe toxicity profile. **From[131, PMID:22200868]:*https://www.researchgate.net/publication/51895105_Optimal_outcomes_for_liver-dominant_metastatic_breast_cancer_with_transarterial_chemoembolization_with_drug-eluting_beads_loaded_with_doxorubicin***

- **HAI Chemotherapy:** Hepatic Arterial Infusion (HAI) involves a drug delivery system that is implanted under the skin. A catheter from the pump is connected to the gastroduodenal artery, which joins the hepatic (liver) arteries, allowing the pump to infuse only the liver with chemotherapy. One study reviewed the treatment histories and outcomes of nine patients with heavily treated breast cancer liver metastasis who received hepatic arterial infusion (HAI) of floxuridine (FUDR)/dexamethasone (Dex) and systemic chemotherapy. Patients received a median of five HAI treatments, and there were seven (78%) objective responses. Four patients had grade 3 elevations in liver enzymes attributable to HAI. There were no treatment-related deaths. Median survival after starting HAI was 17 months and median Overall Survival from the original breast cancer diagnosis was 110 months. Furthermore, one patient is alive with stable disease on systemic therapy alone. Therefore, HAI and systemic chemotherapy are feasible and can benefit selected patients who have progressed on prior therapies. Patients undergoing the procedure require close monitoring for treatment-limiting toxicities. **From[132, PMID:23173748]: *http://www.ncbi.nlm.nih.gov/pubmed/23173748***

- **NKTR-102 (Etirinotecan Pegol)** – (*Not Yet FDA-Approved for MBC patients):* In a clinical trial called BEACON, 852 patients with advanced breast cancer who had any type of ER/HER-2 status were enrolled. Patients were randomly assigned to receive either NKTR-102 or a physician's choice of standard chemotherapy. The study found that NKTR-102 increased Overall Survival in patients with liver metastasis when compared to the physician's choice chemotherapy. Furthermore, NKTR-102 was less toxic than standard chemotherapy. As of August 2018, there is one recruiting clinical trial underway for MBC patients with metastatic disease with stable brain metastasis. **From[133, PMID:28360015]: *http://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bf8e52d75-2273-432b-9473-b50f936c0765%7D/novel-chemotherapy-drug-demonstrates-activity-in-advanced-breast-cancer*** and ***https://www.clinicaltrials.gov/ct2/show/NCT01991678?term=nktr102&rank=4***

- **Radioembolization, SIRT / Yttrium 90 Microspheres (Theraspheres):** This is a relatively new treatment suitable for use even in patients with extensive liver involvement. Radioactive spheres (very tiny radioactive "seeds") are injected into an artery in the liver. After they are injected through the liver artery, the seeds travel into smaller arteries that feed the tumor. Once they reach the tumor, they give off radiation for about three days. The radioactivity causes damage to cancer cells with little damage to the healthy liver tissue. Radioembolization was safe and provided disease stabilization in 98.5% of the patients' treated liver tumors in a recent study. **From[134, PMID:25156827]*: http://www.sciencedaily.com/releases/2014/03/140324133234.htm***

  That said, the author has read several patient accounts commenting that the procedure was not successful for them, and many patients disclosed that they were greatly fatigued afterwards. Therefore, anyone considering this procedure should gather as much information as possible about the success rate and after-effects experienced by prior patients at the clinic that offers this procedure.

  One person whose liver metastases were allegedly too large for the procedure wrote this valuable tip: "*I had trouble finding a doctor who would do it given the size of my tumors as well as some insurance coverage issues - and I got 3 'no's' from different doctors until I contacted the company who makes the radioactive beads, SIRTEX. Their sales representative hooked me up with a highly skilled interventional radiologist named Ryan Majoria who eventually accepted me. SIRTEX has great customer service and can also provide the name of one of their representatives in the patient's geographic area who will call and talk to the patient personally about their product and whether or not the patient might be a good candidate (of course they are not doctors, but these reps know EVERYTHING from my experience including who the most experienced doctors are who perform the procedure.) SIRTEX's telephone number is: 1-888-474-7839. Patients should ask for the representative in their area to call them. My Y90 procedure went well, and my main side effect is fatigue.*"

  For those are interested, an excellent video about Radioembolization is located at: ***https://www.youtube.com/watch?v=3WwSfGPQq9g***

- **Transarterial Chemoembolization (TACE):** In this technique an interventional radiologist injects a chemotherapeutic agent directly into the arteries supplying the tumors within the liver. Embolization therapies such as TACE have been used for the last two decades by interventional radiologists to treat liver tumors.

Liver metastasis may cause **ascites** in some patients. "Ascites" is a gastroenterological term that refers to an accumulation of fluid in the abdominal (peritoneal) cavity. The ascites can arise from tumors' expression of epithelial cell-adhesion molecule (EpCAM). Additionally, vascular endothelial growth factor (VEGF) has been cited as an important factor affecting vascular permeability, a key factor in ascites production. Ascites are generally evidenced by a distended stomach, shortness of breath, bloating, and/or other discomfort. Patients who believe they may have ascites should notify their doctors immediately. **From[135, PMID:20531969]: *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880345/***

On occasion, liver metastases can obstruct blood flow through the liver, and the obstruction may result in portal hypertension (high blood pressure in the veins surrounding the liver). The high blood pressure can lead to swollen veins in the belly and esophagus and may also cause ascites.

In patients with cancer-related ascites, diet restrictions and/or diuretics might not be effective, although there have been some exceptions. Paracentesis (a procedure whereby fluid is taken out using a long, thin needle put through the belly) may be the first-line ascites treatment. If needed, a catheter (either indwelling or a peritoneovenous shunt) may be left in place to drain so that fluid can be removed in such a manner that the patient does not need to undergo repeated procedures**.** Some patients have reported that draining the ascites daily instead of every few days provides them with superior relief. **From: *http://www.emedicinehealth.com/ascites/page7_em.htm***

Treatment options for draining abdominal ascites often entail the use of an indwelling catheter, paracentesis, or peritoneovenous shunting.

Indwelling (Pleurx or Aspira) Catheter: This is the surgical insertion, under general anesthesia, of a small tube placed temporarily into the abdominal space that allows the patient or his/her family member to drain the fluid into a bottle as needed. Patients with an indwelling catheter are fully mobile and are not "attached" to the draining bottle except when draining the fluid. If there is no more drainage at all, the catheter is removed either in the doctor's office or an outpatient procedure. The Pleurx catheter works via suction, and the newer gentler model is the Aspira catheter, which may be a bit less uncomfortable because uses gravity instead of suction for draining.

Paracentesis: Under sterile conditions, a needle is placed into the peritoneal space and fluid is withdrawn. Paracentesis may be a viable first step if the ascites accumulates quickly and the abdominal distension causes pain or shortness of breath. Because the peritoneal fluid contains albumin, if large amounts of fluid (more than 5 liters) are withdrawn, an albumin transfusion may be needed. If warranted, the catheter maybe left in place to drain, so that fluid can be periodically removed, and the patient does not need to undergo repeated procedures. Paracentesis may be done more than once, but if it becomes a frequent necessity for symptom control, other options may be considered.

Peritoneovenous shunting: This is a surgical operation that may on occasion be used in patients who are not candidates for, or who have failed treatment with, paracentesis or indwelling catheters. Peritoneovenous shunting entails the use of a tube for draining fluid back into the veins, instead of draining fluid externally as is done with indwelling catheters.

A patient who has been living with abdominal ascites for a year provided the following tips that have helped her relieve some of the discomfort caused by ascites and draining:

Letting the Alcohol Dry Thoroughly: If you have the type of drain that requires wiping with an alcohol wipe, ensure that the alcohol is completely dry by waiting at least 30 seconds after wiping before attaching the valve. The evaporative process, more

than the effects of the alcohol, help to kill the bacteria. Also, do not blow on the drying spot to speed the process, as this can cause contamination. (Also remember to first wash your hands before starting the draining process).

After Draining: Stand up slowly after draining and watch your blood pressure - mine drops very low, while heart rate races. Don't fall down.

Fluids: Drink plenty of fluids, especially around draining times. Replenish with liquids that contain electrolytes like coconut water & broth.

Clothing: Do not wear any tight clothing or belts. Instead, wear drawstring hip hugger pants or elastic waist pants and skirts. Wear tops that skim your belly, rather than bind it.

Meals: Eat small meals and wait at least 4 hours after eating before bedtime. Avoid foods that can lead to reflux such as citrus fruits and juices. coffee, tea, alcohol, chocolate, and spicy food. If possible, do not eat after 4PM or 5PM to avoid discomfort during sleep.

Exercise: Gentle walking, yoga and stretching may help. Anything that compresses the belly like the yoga poses of forward bends and child's pose may not help, nor does vigorous exercise that jostles the belly.

Gentle Rubbing: I hold my belly with my hands and rub gently in the direction my colon runs - lower left up to liver area, across upper belly to upper right and then down right side.

Oral Hygiene: The dry mouth after many months of draining can be difficult - so drink water frequently, rinse with glycerin and marshmallow tea if possible. Biotene may help some people in mitigating dry mouth. Holding a bit of coconut oil in the mouth can help.

Sleep and Rest: Sleep or rest on the back or the side, not on the belly.

Drugs that may help alleviate ascites and/or related discomfort:

Avastin (Bevacizumab): In one study, nine patients with refractory malignant ascites were given Avastin. Three patients had breast cancer, three had colon cancer, 2 had uterine cancer and one had ovarian cancer. Prior therapy included systemic chemotherapy and large volume paracentesis. All patients had rapid re-accumulation within 2 weeks of paracentesis before treatment. Patients were given intraperitoneal bevacizumab at 5 mg/kg monthly. Malignant ascites resolved without reaccumulating or repeat paracentesis in all nine patients after a single intraperitoneal dose of bevacizumab over a median observation period of over two months. **From[136, PMID:22927770]:** ***http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.9043***

Catumaxomab (Removab): Although the author was not able to locate studies with breast cancer patients, a study on ovarian cancer patients was reported. Catumaximab was evaluated as part of a Phase 1/II dose-escalating study for intraperitoneal (IP) application in 23 patients with ovarian cancer who had ascites with EpCAM-positive tumor cells. The patients were treated with 4–5 intraperitoneal infusions of catumaxomab in doses of 10 to 200 micrograms within 9–13 days with loading doses of 5–10 µg. The maximum tolerated dose was defined at 10, 20, 50, 200, and 200 µg for the first through fifth doses. Treatment with catumaxomab resulted in significant and sustained reduction of ascites flow rate. A total of 22 of 23 patients did not require paracentesis between the last infusion and the end of study one month later, and tumor cell monitoring revealed a reduction of EpCAM-positive malignant cells in the ascites**. From[135, PMID:20531969]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880345/***

A separate study of 26 cancer patients who received at least three of four IP instillations of catumaxomab led to a median interval of 15 days before a patient required an intraperitoneal puncture. Median overall survival was 92.5 days, but five patients remained

alive and free of puncture for as long as 876 days. It was concluded that IP catumaxomab can be administered in relatively frail outpatients, achieving good ascites control. A survival benefit was seen in fit patients who received complete IP catumaxomab treatment and were able to undergo subsequent systemic therapy. **From[137, PMID:26417039]:** ***http://www.medpagetoday.com/MeetingCoverage/SGO/44939***

Iscador (Mistletoe extract): Iscador is a nontoxic therapy widely used in Europe that is made from the extract of fresh sap of the plant known as mistletoe. It must be prescribed by a doctor. A Phase 2 study was undertaken of 23 patients with various types of cancer who had ascites which required repeated peritoneal punctures for draining. The time-interval between the first two punctures was measured and defined as the baseline. Following each subsequent puncture, Iscador M® 10 mg was injected intraperitoneally. The intervals between later punctures were compared to previous intervals. Following the first injection, the median time-interval between draining increased from 7 to 12 days, reaching 13 days after the second injection, nearly double the initial draining interval. One patient with ovarian cancer had a clinical objective response represented by a reduction in CA-125 levels from 800 U/ml to 102 U/ml, and improvement in ascites accumulation and in performance status; this regression lasted for 12 months. No toxicity was observed in any of the patients. **From[138, PMID:16739342]:** ***http://ar.iiarjournals.org/content/26/1B/709.full.pdf*** Once prescribed, Iscador may be difficult to procure. A viable source may be H & F Apothecary, Ltd., Chestnut Ridge, NY.Telephone: 1.845.352.6165

Octreotide (Sandostatin LAR®): Thirty-three patients were enrolled in a two-arm study, with 16 patients assigned to the octreotide arm and 17 to the control arm. The median time to next paracentesis was 28 and 14 days in the octreotide and placebo arm, respectively. After adjustment for extracted ascites volume and abdominal girth change, no statistically significant difference between the groups was observed, although octreotide-treated patients described less of abdominal bloating, abdominal discomfort, and shortness of breath at one month. As prescribed in this trial, octreotide did not seem effective in prolonging the time to next paracentesis, although symptoms had improved. **From[139, PMID:22572824]:** ***http://www.ncbi.nlm.nih.gov/pubmed/22572824***

In some cases, ascites may lead to **bowel obstruction**, which can cause nausea and vomiting. In addition to draining the fluid as described above, other therapies may be of help in cases of bowel obstruction:

Octreotide (Sandostatin LAR®): Some physicians report success with some patients by using the oral medication Octreotide (described above) in cases of malignant bowel obstruction, as well as in instances of trapped "loops" of bowel that are non-operable. Octreotide is a hormone secreted in the pancreas and pituitary gland that inhibits gastric secretion, thereby reducing gastric and pancreatic juices and relieving fluid-induced pressure.

Surgery: If the patient can withstand surgery, then they may benefit from surgery if they are in good physical condition with only one site of obstruction, if there is no resolution of the bowel obstruction after 48 to 72 hours of conservative management.

Other Medical Management: When the patient's situation is not favorable for undergoing surgery (or possibly stenting), medical management should be the mainstay of care, the aim being symptom relief. Pain caused by tumors can be relieved by strong opioids given subcutaneously or transdermally to ensure proper absorption that the oral route cannot provide. Cramp-related pain, if present, can be treated subcutaneously with anticholinergic (nerve blocking) drugs such as Hyoscine Butylbromide or Scopolamine (for which a transdermal patch is also available). Nausea can be reduced with regular administration of antiemetic drugs, Haloperidol being a commonly used medication. Prokinetic medications such as Metoclopramide, which are used to help control acid reflux, should be avoided. **From[140, PMID:22859627]:** ***http://www.cfp.ca/content/58/6/648.full***

28. Lung Metastasis

Although many patients with lung metastasis have no symptoms, those who do may experience coughing, hoarseness, and/or shortness of breath. Occasionally there may be pain in the chest, ribs, or upper back. As is generally the case whenever breast cancer moves to a new organ, the tumor should be biopsied whenever possible to re-check its ER, PR and HER2 status (as per the section entitled, "*Tumor Biopsy for New Metastatic Sites*.")

TREATMENTS FOR LUNG METASTASIS

Lungs are quite delicate, since they need to remain flexible in order to expand and contract properly during breathing. Furthermore, they are highly vascular, as they contain many blood vessels. Therefore, interventional therapies such as surgery and radiation, which may cause damage to the lung, have not been done very frequently when MBC spreads to the lung. That said, surgery and radiation have recently begun to be used in cases of Oligometastases with encouraging results as described below.

Overall, therapies to treat breast cancer metastasis to the lung include:

- **Radiofrequency Ablation (RFA),** in some cases
- **Surgery,** in specific instances
- **Systemic Therapy** (most commonly used)

- **Radiofrequency Ablation:** Radiofrequency Ablation uses a needle that carries an electric current which is delivered through the needle to heat the tumor to destroy it. Researchers from Europe, the United States, and Australia conducted a clinical trial, referred to as the "RAPTURE" study, to further evaluate the use of RFA in lung tumors among 106 patients. These patients had either NSCLC (a type of lung cancer) or lung metastasis from various other types of cancers. In these patients, the site of cancer within the lung was 3.5 centimeters in diameter or smaller. All patients were considered ineligible for treatment with chemotherapy or radiation therapy.

  Of the patients who underwent RFA, two years later:

  88% of patients achieved a complete disappearance of cancer at the site of RFA, which lasted for at least one year.

  Overall Survival at one year was 92% for patients with metastasis from sites other than the colon

  Overall Survival at two years was 64% metastasis from sites other than the colon

  From[141, PMID:24574771]: ***http://news.cancerconnect.com/radiofrequency-ablation-effective-for-primary-lung-tumors-and-lung-metastases-from-breast-cancer/***

- **Surgery:** There is also some promising evidence that **surgical removal** of limited lung metastasis might in certain cases confer a considerable benefit. In one study, investigators enrolled 81 women with lung metastasis from April 1982 to May 2007 into a surgical study. The median Overall Survival of all participants whose lung metastasis were surgically removed was 82.4 months (almost 7 years).

  Of the 81 women who had surgery for metastatic breast cancer to the lung:

  81.5% had complete surgical removal of the metastasis and a survival rate of 104.3 months (an estimated 9 years)

  7.4% had some tumor cells still visible via microscope and a survival rate of 23.6 months (an estimated 2 years)

11% had cancers that were visible to the naked eye, and a survival rate of 20.2 months (a little under 2 years)

Investigators found that survival improved significantly if the cancer was ER and/or PR positive. The number and size of metastasis were also factors that influenced survival. Women with a single metastasis lived longer than those who had two or more, and women with metastasis smaller than three centimeters survived longer than those with metastasis larger than three centimeters.

Seven women in the study also had metastasis in the *mediastinal* (between the lungs) and hilar (the airways of the lungs) lymph nodes. Women with no cancer in their mediastinal or hilar lymph nodes experienced prolonged median survival rates compared with those with who had metastasis in these lymph nodes (103.4 months [about 8.6 years] and 32.1 months [about 2.7 years], respectively). **From[142, PMID:23391172]:** ***http://www.lbbc.org/news-opinion/study-suggests-surgery-women-lung-metastases-may-improve-survival***

- **Systemic Therapy:** Lung metastasis is most commonly treated with systemic therapy such as **chemotherapy, hormonal therapy and//or targeted therapy** based upon the cancer's profile. In many cases, patients have "diffuse" disease (tumors spread over a wide area) which may possibly make them ineligible for the therapies listed above. In many instances, systemic therapy may be quite effective in reducing lung metastasis and providing relief to symptomatic patients.

Pleural effusion, which may accompany lung metastasis, is a buildup of fluid between the layers of tissue that line the lungs and chest cavity. Often the fluid contains cancer cells. Pathology testing should whether the pleural effusion is "exudative" (the fluid has excess protein, blood, or evidence of inflammation or infection) or "transudative" (characterized by a low cell and protein content), based on the chemistry of the fluid. If the fluid transudative it's very unlikely to be malignant, and if it's exudative, malignancy is still a possibility even if malignant cells don't show up when the fluid is tested, so re-testing should be done as warranted, along with any other recommended tests. If the effusion turns out to have malignant cells, testing should be done for ER, PR, and HER2 receptivity, since it is possible that the cancer cells in the effusion may have a different profile than metastasis elsewhere in the body.

For patients who have pleural effusion, there are three methods of draining the fluid to provide relief:

Indwelling (Pleurx or Aspira) Catheter: This is the surgical insertion, under general anesthesia, of a small tube placed temporarily into the pleural space that allows the patient or his/her family member to drain the fluid into a bottle as needed. Patients with an indwelling catheter are fully mobile and are not "attached" to the draining bottle except when draining the fluid. Once there is no more drainage at all, the catheter is removed either in the doctor's office or an outpatient procedure. Overall, indwelling catheters seem to help prevent the fluid from building up again, provided that the patient's systemic treatment is working. The Pleurx catheter works via suction, and the newer gentler model is the Aspira catheter, which is a bit less uncomfortable because uses gravity instead of suction for draining.

Pleurodesis (sometimes referred to as a "talc procedure") is a process in which substances, such as talc, are used to try to get the edge of the lung to stick to the chest wall to decrease the chance of the fluid returning. Although this procedure seems to help prevent the fluid from building up again (provided that systemic treatment is working) it can be painful and usually requires a brief hospital stay. Some patients have reported discomfort months and even years after the procedure. In rare cases, the procedure may fail altogether, rendering it impossible to drain the fluid thereafter because it becomes trapped in a honeycomb of many small pockets (called "loculations"). Of all options for draining malignant pleural effusion, this appears to be the most risk-prone.

Thoracentesis (sometimes referred to as "tapping") is an outpatient procedure that involves placing one needle per required side into the pleural space. Although local anesthesia is administered, this procedure can be uncomfortable and may cause scarring if repeated over time. The procedure also does not hinder fluid buildup again. These tips may make the procedure less uncomfortable: 1) Request a numbing agent before the needle is inserted to feel more comfortable after the procedure. 2) Request that the fluid to be withdrawn slowly in order to avoid low blood pressure or a "fainting" feeling afterwards. 3) Lean forward with a soft pillow supporting your head and upper torso while the draining is underway via your back.

Warning: If a patient is experiencing shortness of breath but the doctor cannot find anything in the lungs that is causing it, the patient should be checked carefully for blood clots as well as for cardiac issues. Either of these issues may cause symptoms that appear to be lung related problems, when in fact they are not. Additionally, a condition called "pneumonitis" (inflammation of the lung), can cause shortness of breath and coughing. Since pneumonitis can be caused by cancer treatments such as chemotherapy and radiation, MBC patients may be particularly susceptible.

29. Brain Metastasis

Symptoms of brain metastasis include headaches, clumsiness, lethargy, loss of memory, difficulty concentrating, change in physical sensation such as numbness or pain/tingling, speech difficulties, vision changes, vomiting (with or without nausea) weakness in a body area, fever, and/or personality changes. Some patients with brain metastasis have no symptoms at all.

An estimated 10% to 30% of all breast cancer patients will eventually develop Breast Cancer Brain Metastasis (BCBM). BCBM and Leptomeningeal Metastasis (LM) are the two types of Central Nervous System (CNS) metastasis. Brain metastases may have characteristics that differ from mbc tumors elsewhere in the body.

CNS metastasis is more common in the following MBC patient populations than in other MBC patients, so these patients should be especially vigilant about reporting any symptoms described above to their doctor.

- **HER2+**
- **TNBC**
- **Patients with CK-19 mRNA-positive Circulating Tumor Cells** (CTCs)

From: ***http://www.cancernetwork.com/oncology-journal/management-breast-cancer-brain-metastases-moving-forward-new-options-are-still-needed*** and ***https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr1516***

A unique hurdle in the development of therapies for BCBM is the presence of the blood-brain barrier (BBB), a tight layer of endothelial cells that acts as a selective barrier to the diffusion of systemic therapies such as chemotherapy. **From[143, PMID:25144276]:** ***http://www.cancernetwork.com/oncology-journal/updates-management-breast-cancer-brain-metastases***

Despite the presence of the BBB, there is considerable information about the use of drugs for people with brain metastasis in this section.

In May 2014, ASCO issued the following treatment guidelines for HER2 positive MBC patients with brain metastasis (the author was unable to find similar guidelines for HER2 negative MBC):

> For patients with favorable prognosis for survival, surgery and/or radiotherapy are recommended, depending on the size and number of metastasis, resectability, and symptoms. *(Note: No specific mention was made here for targeted and/or chemotherapy, so it might be worth discussing the pros and cons of systemic with one's doctor).*
>
> For patients with a poor prognosis for survival, options include surgery, Whole Brain Radiation (WBR) therapy, and systemic therapies with some evidence of activity in the setting of brain metastasis such as Tykerb and Xeloda.
>
> Additional options include best supportive care, enrollment in a clinical trial, and/or palliative care. **From[41, PMID:24799487]:** ***https://www.asco.org/about-asco/press-center/news-releases/asco-issues-two-new-guidelines-treating-patients-advanced-her2***

Brain metastasis may be treated through non-drug techniques, medications, or both.

NON-DRUG TREATMENTS FOR BRAIN METASTASIS

- **Brain Surgery**
- **Proton Therapy**

- **Radiosurgery** such as:
  - *CyberKnife*
  - *Gamma Knife*
- **Whole Brain Radiation Therapy (WBR or WBRT)**

These procedures are described below:

- **Brain surgery** may be used for one or two large metastasis that need to be removed immediately because of potential brain damage, or when the metastasis is too big for radiosurgery. **From**: ***https://www.brainmetsbc.org/en/content/current-treatments-brain-metastases***

- **Proton (Pencil Beam) Therapy:** Traditional radiation therapy affects everything in its path, so doctors have to limit the dose delivered to the tumor in order to minimize damage to surrounding healthy tissue. In proton therapy, protons enter the body with a low dose of radiation which increases when the beam slows down within the tumor, and then the protons stop without going any further to harm further tissue. Compared to an X-ray beam, a proton beam has a low "entrance dose" (the dose delivered from the surface of the skin to the front of the tumor), a high dose designed to cover the entire tumor, and no "exit dose" beyond the tumor. The combined effect is claimed to provide greater precision in targeting the tumor with a more potent dose of radiation. The accuracy of proton therapy for treatment delivery is within approximately one millimeter. MD Anderson is currently using pencil beam scanning to treat cancers of the prostate, brain, base of the skull and eye, and this therapy may be worth inquiring about for MBC patients with brain metastasis. **From:** ***https://www.mdanderson.org/patients-family/diagnosis-treatment/care-centers-clinics/proton-therapy-center.html***

- **Radiosurgery (SRS): Radiosurgery, also called Stereotactic RadioSurgery or SRS:** The term "radiosurgery" is misleading because the procedure does not involve surgery. Radiation is given from the outside the head without having to cut into the skull. This is a procedure that aims very high doses of radiation (higher than WBRT) directly at brain metastasis. Because the beams of radiation converge from many different directions, the rest of the brain is spared these high doses. Unlike WBRT, only the metastasis is targeted, not the entire brain, which minimizes toxicities. It can be used to treat metastasis deep within the brain (such as in the brainstem), where regular surgery cannot be done safely. It is considered to be at least as effective as surgical resection, although that has not been completely proven.

  Radiosurgery is generally not used for more than three metastases at a time, or for metastasis that are larger than approximately 3 centimeters. However, more and more patients and their doctors are going outside these guidelines, treating more than three metastasis as well as metastasis larger than 3 centimeters. In fact, the efficacy of SRS without WBRT has been demonstrated in a multi-institutional prospective observational trial that found that overall survival in patients with 5 – 10 brain metastases was non-inferior to the same therapy in patients with only 2 – 4 lesions. **From[144, PMID:24621620]:** ***http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470204514700610.pdf***

  Severe side effects occur in only 1-2% of those treated with radiosurgery. These include seizures, edema, hemorrhage, and radionecrosis (dead tumor tissue). Radionecrosis from radiosurgery can be hard to distinguish from recurring brain metastasis. Usually radionecrosis is treated with a corticosteroid, so sometimes surgery is necessary to biopsy the lesion to determine if it is, in fact, radionecrosis or recurring metastasis.

  Radiosurgery can be repeated if new brain metastasis appears, and it can also be used after regular surgery or WBRT as a "boost" to prevent brain metastasis from recurring in the same location. **From[145, PMID:24281220]:** ***http://www.brainmetsbc.org/en/content/current-treatments-brain-metastases***

  Forms of Radiosurgery include:

- *Cyberknife*, which is a form of SRS. It is a non-invasive alternative to surgery for the treatment of both cancerous and non-cancerous tumors anywhere in the body, including the head. The treatment – which delivers beams of high dose radiation to tumors with extreme accuracy – offers new hope to patients worldwide. The Cyberknife treatment involves no cutting and claims to be the world's first and only robotic radiosurgery system designed to treat tumors throughout the body non-invasively. It provides a pain-free, non-surgical option for patients who have inoperable or surgically complex tumors, or who may be looking for an alternative to surgery. **From:** ***http://www.cyberknife.com/*** The CyberKnife differs from the Gamma Knife (below) by employing real-time X-ray images to guide treatment; and as a result, has expanded SRS to sites outside the brain. It does not require a head frame screwed into the skull for immobilization, thus avoiding the pain, headache, nausea and risk of infection seen at times with stereotactic frames. Instead, a non-invasive thermoplastic head mask and image guidance allows stereotactic immobilization. **From:** ***http://csn.cancer.org/node/189965***

- *Gamma Knife*, which is also a form of SRS. It is a blade-free radiosurgical treatment that delivers a dose of gamma radiation to the target with surgical precision. Gamma Knife radiosurgery delivers more than 200 precise radiation beams that converge deep within the brain to shrink or even destroy diseased or damaged tissue. Alone, each of the beams contains harmless doses of radiation so surrounding tissue remains unaffected, protecting the important functions of the brain. **From:** ***http://www.pennmedicine.org/neurosurgery/patient-care/clinical-programs/gamma-knife/***

- **Whole Brain Radiation Therapy (WBR or WBRT)**: Whole brain radiation therapy is used for the treatment of multiple and larger brain metastasis. It is also used for those patients with rapidly progressing metastatic disease outside of the brain and for what is known as "poor performance status" (ability to take care of oneself). As its name indicates, radiation is delivered to the entire brain. WBR has been shown in research studies to extend life and improve the quality of life for patients whose brain metastasis are causing symptoms. 30% to 40% of patients will achieve a complete reversal of symptoms, while 75% to 85% of patients will experience some improvement or stabilization of their symptoms, especially headache and seizure. **From[146, PMID:27330360]:** ***http://www.brainmetsbc.org/en/content/current-treatments-brain-metastases***

  There is a type of WBR that is a "**hippocampus sparing procedure**" which may help to preserve a degree of memory that might otherwise be lost because of the procedure. In a study of 113 patients, at four months after undergoing the hippocampus sparing procedure, the decline in recall (as compared to baseline) was 7%, significantly better than the 30% cognitive decline in the historical control group that received WBR without the hippocampus sparing procedure**. From[147, PMID:25349290]**: ***http://jco.ascopubs.org/content/early/2014/10/21/JCO.2014.57.2909***

  A retrospective study reviewed the status of 253 breast cancer patients with brain metastasis who were treated with WBR. The results were consistent with mounting evidence that histone deacetylase **(HDAC) inhibitors such as Valproic Acid (VPA) synergize with radiation to improve patient outcomes**. VPA and its derivative, divalproex, are oral drugs that are currently used for the treatment of convulsions, migraines and bipolar disorder. The study found that breast cancer patients who received VPA with WBR had a 6-month longer Overall Survival than those who did not receive VPA. **From[148, PMID:26482599]:** ***http://www.sciencedirect.com/science/article/pii/S0167814015005514***

  Herceptin can also be combined with Whole Brain Radiation for HER2+ patients, as per the results of a study of 31 patients presenting HER2+ metastatic breast cancer in the brain and treated with Whole Brain Radiation and trastuzumab. After Whole Brain Radiation therapy was completed, radiologic responses were observed in 23 patients (74.2%), including 6 patients (19.4%) who had with a complete radiologic response and 17 patients (54.8%) with a partial radiologic response. **From[149, PMID:28177431]**: ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw532***

DRUG TREATMENTS FOR BRAIN METASTASIS

Despite the presence of the Blood Brain Barrier (BBB), some drugs appear helpful in treating brain metastasis and/or side effects from treatment include:

- **Ang1005** – *(Not Yet FDA-Approved for MBC Patients)*
- **Avastin (Bevacizumab) and Irinotecan (CPT-11 or Camptosar)** *(Not Yet FDA-Approved for MBC Patients)*
- **Boswellia Serrata**
- **Chemotherapy Drugs**
- **Dexamethasone (Decadron)**
- **Emend (Apripitant)**
- **Herceptin (Trastuzumab) given Intrathecally**
- **Hormonal Therapies**
- **Kadcyla (TDM-1)**
- **Lapatinib (Tykerb) and Xeloda (Capecitabine)**
- **Mannitol**
- **Namenda**
- **Neratinib (NERLYNX) and Xeloda (Capecitabine) or Taxol (Paclitaxel)** (*Neratinib is Not Yet FDA-Approved for MBC Patients)*
- **NKTR-102 (Etirinotecan Pegol)** *(Not Yet FDA-Approved for MBC Patients)*
- **Temodar** *(Not Yet FDA-Approved for MBC Patients)*
- **Tucatinib (ONT-380)** *(Not Yet FDA-Approved for MBC Patients)*
- **Verzenio (Abemaciclib)**

- **ANG1005:** This Taxol-like drug, which is being studied as of August 2018 in a clinical trial for MBC patients with brain metastasis, is providing encouraging results in this population. In a Phase 2 study of 10 patients with a total of 32 metastatic brain lesions, 15 of the 32 lesions showed a 20% or greater reduction within a specified timeframe. Among patients who went on to additional cycles of ANG1005, two of the 10 patients had confirmed partial responses and seven patients had stable disease. In another study of 130 MBC patients who had received a median of 6 prior therapies (most of which included a prior taxane treatment), ANG1005 showed a promising degree of success in those with brain metastasis or leptomeningeal metastasis. Overall, the best intracranial response in included ten women with partial responses and 31 with stable disease. This included a 21% partial response rate in women with HER–2-positive disease, 13% in women with HER–2-negative disease and 17% with triple-negative disease. Among 34 patients evaluable for extracranial tumor responses, one (3%) achieved a complete response, two (6%) achieved a partial response and 27 (79%) demonstrated stable disease. These data equated to a clinical benefit rate of 88%. 93% of patients with HER2-positive disease achieved stable disease. Among patients with leptomeningeal metastasis, the rate of 6-month Overall Survival was 63.6 %. **From [150, PMID:30258901]** ***http://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bace6ced1-4050-412c-80c3-fb59bbab7a12%7D/novel-agent-crosses-blood-brain-barrier-to-treat-cns-metastasis-from-breast-cancer***

- **Avastin (Bevacizumab) and Irinotecan (CPT-11 or Camptosar)** – *Not Yet FDA-Approved.* A very small study of four women with HER2 positive brain metastasis who had failed other treatments and received Avastin and Irinotecan indicated that 100% of the patients had clinical response to treatment and their median Overall Survival was 5 months longer than expected. **From[151, PMID:26634139]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4664841/***

- **Boswellia Serrata (BS)** is not a treatment. Instead, it is used to help relieve edema (swelling): Patients irradiated for brain tumors often suffer from cerebral edema and are usually treated with Dexamethasone, a steroid which has various side effects *and can promote tumor growth*. In one study, 44 patients with primary or secondary malignant cerebral tumors were randomly assigned to radiotherapy plus either BS or placebo. Blood samples were taken to analyze the serum concentration of boswellic acids (AKBA and KBA). Compared with baseline, a reduction of cerebral edema of more than 75% was found in 60% of patients receiving BS, and in only 26% of patients receiving placebo. These findings may be based on an additional antitumor effect. There were no severe adverse events in either group. BS did not have a significant impact on quality of life or cognitive function. Therefore, Boswellia Serrata could potentially be steroid-sparing for patients receiving brain irradiation. **From[152, PMID:21287538]:** ***http://www.ncbi.nlm.nih.gov/pubmed/21287538***

One patient wrote that the Dexamethasone initially helped her enormously, but she subsequently began reacting badly to it the longer she was on it. She weaned off it in less than two weeks by taking Boswellia Serreta and found that 1,800 mg was comparable to half a dose of Dexamethasone. So, she boosted her Boswellia intake to two caplets 4 times a day during radiation no longer needed to take any steroids. (Note: Patients interested in taking Boswellia should confer with their doctor about dosage and frequency).

- **Chemotherapy Drugs:** Some studies have suggested that **Xeloda** (Capecitabine), high-dose **Methotrexate,** the Platinum drugs **Carboplatin** and **Cisplatin**, and **Adriamycin** (Doxorubicin) can be effective in shrinking brain metastasis. **From:** ***http://www.brainmetsbc.org/index.php?q=content/current-treatments-brain-metastases#HT***

- **Dexamethasone (Decadron):** Although not a cancer treatment in and of itself, a steroid called Dexamethasone is given to patients with brain metastasis (often at the time of diagnosis) to reduce cerebral edema (swelling). That said, Dexamethasone may bind to a segment of DNA that may activate genes associated with drug resistance and poor patient outcomes, so alternative anti-inflammatories should be considered. **From[153, PMID:26374485]:** ***http://www.eurekalert.org/pub_releases/2015-10/osuw-ssn100615.php***

- **Emend (Apripitant)**: This is an anti-nausea drug that may help combat brain metastasis in addition to reducing nausea. In the laboratory (not human) setting, Emend was associated with a reduction in brain tumor growth, and it also caused cell death in the tumor cells. This drug may offer further opportunities to study possible brain tumor treatments over the coming years. **From[154, PMID:24818961]:** ***http://www.sciencedaily.com/releases/2013/03/130319124221.htm***

- **Herceptin (Trastuzumab) given Intrathecally (in the spinal canal)***:* Studies have shown that HER2+ patients treated with IV Herceptin have significantly lower concentrations of the drug in their Cerebral Spinal Fluid (CSF) than elsewhere in their bodies. This could explain the subsequent development of CNS metastasis when non-CNS metastasis are under control. Researchers hypothesized that the lack of efficacy of IV Herceptin with respect to brain metastasis in HER2-overexpressing breast cancers may result from a deficient Blood Brain Barrier (BBB) passage, and that Intrathecal Herceptin administration might overcome this deficiency. A study of one HER2+ patient who had liver metastasis for 6 years and brain metastasis for 2.5 years, showed that after 6 months with an efficacious Intrathecal Herceptin concentration, she was still alive without treatment toxicity, and the progression of her brain and epidural metastasis had halted. **From[155, PMID:25547506]:** ***http://jco.ascopubs.org/content/early/2014/12/29/JCO.2012.44.8894.full***

  Herceptin can also be combined with Whole Brain Radiation, as per the results of a study of 31 patients presenting HER2+ metastatic breast cancer in the brain and treated with Whole Brain Radiation and trastuzumab.. After Whole Brain Radiation therapy was completed, radiologic responses were observed in 23 patients (74.2%), including 6 patients (19.4%) who had with a complete radiologic response and 17 patients (54.8%) with a partial radiologic response. **From[149, PMID:28177431]**: ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw532***

- **Hormonal Therapies:** Hormonal therapies such as Tamoxifen, Letrozole, and Megace have been shown to be effective in treating breast cancer brain metastasis in some women with ER-positive tumors. **From[156, PMID:24367181]:** ***https://www.brainmetsbc.org/index.php?q=content/current-treatments-brain-metastases#HT***

- **Kadcyla (TDM-1) for pre-treated Asymptomatic HER2+ MBC:** One study indicated that patients with HER2 positive MBC with pre-treated CNS metastasis and no symptoms who took Kadcyla experienced significantly longer Overall Survival (OS) than those assigned Xeloda plus Tykerb. **From[157, PMID:25355722]:** ***http://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B6433cb8b-e23f-4134-b2e9-ed9fe37a6005%7D/ado-trastuzumab-emtansine-significantly-extended-os-in-HER2positive-breast-cancer-with-cns-metastasis***

- **Lapatinib (Tykerb) and Xeloda (Capecitabine):** The studies that have explored the combination of Lapatinib and are generally small in size, ranging from 13 to 138 patients. In nearly all studies, 85–100% of patients received prior Herceptin and Whole Brain Radiation. CNS response ranged from 20 to 30%, which appears to be an improvement over responses observed with Lapatinib alone. One study addressed the role of the Lapatinib and Xeloda combination prior to WBRT. In this study, 45 patients with newly diagnosed Brain Metastasis (BM) were enrolled, of which 36 (80%) patients had two or more BM and 42 (93%) patients received prior Herceptin. This study showed an impressive (67%) CNS response rate, defined as 50% volumetric reduction of CNS lesions. Median time to progression was 5.5-months and median time to whole-brain irradiation was 8.3 months. Lapatinib may also be used in combination with Temodar in HER2+ MBC patients, as per the results of a small Phase 1 study in which sixteen patients with HER2+, progressive brain metastasis was enrolled. Fourteen of these patients had previously been treated with Whole Brain Radiation. For the 15 assessable patients, stable disease was achieved from the combination of lapatinib and Temodar in 10 patients (67%) and progression of disease in five patients (33%). **From[149, PMID:28177431; 158, PMID:22335578]:** ***http://www.medscape.com/viewarticle/759026_5*** and ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw532***

- **Mannitol** (a diuretic) is not a cancer treatment. Instead, it helps remove fluid from the brain (and reduce swelling). **From[159, PMID:7976640]:** ***https://www.ncbi.nlm.nih.gov/pubmed/7976640***

- **Namenda (Memantine HCL)** is an Alzheimer's drug that may help preserve cognitive skills after Whole Brain Radiation (WBR). In one study, patients treated with memantine had better cognitive function over time. Specifically, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBR. **From[160, PMID:23956241]**: ***https://www.ncbi.nlm.nih.gov/pubmed/23956241***

- **Neratinib (NERLYNX) and Xeloda (Capecitabine) or Taxol (Paclitaxel)** – *Not Yet FDA-Approved:* Neratinib is an orally-ingested drug that crosses the blood brain barrier (BBB). In a clinical trial of 39 HER2+ pre-treated MBC patients with brain metastasis, the combination of Neratinib and Xeloda patients and expected to reach a total of 60, all patients received once-daily, oral Neratinib who had not received prior therapy with Tykerb, 49% of the patients exhibited an objective response. Of the 39 patients in the study, 30% had undergone surgery, 65% had received prior whole brain radiotherapy (WBR), and 35% had undergone stereotactic radiosurgery to the brain. In the study, patients had a median time to CNS progression of 5.5 months, and median overall survival was 13.5 months, but survival data are still immature, the researchers said. The combo therapy was well-tolerated, with the most common treatment-related adverse event being treatable diarrhea. **From[161, PMID:26834058]:** ***https://breastcancer-news.com/2017/06/08/pb272-capecitabine-shows-promise-for-breast-cancer-brain-metastasis/***

  As of April 2018, Neratinib has been included as a recommended treatment option in the latest National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Central Nervous System Cancers for Breast Cancer patients with brain metastasis. The NCCN designated Neratinib in combination with capecitabine as a category 2A treatment option, and Neratinib in combination with paclitaxel as a category 2B treatment option. (A Category 2A option means that based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate, and a Category 2B: option indicates that based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate). **From:** ***http://markets.businessinsider.com/news/stocks/nccn-guidelines-for-central-nervous-system-cancers-include-nerlynx-neratinib-in-combination-with-capecitabine-or-paclitaxel-as-treatment-options-for-patients-with-breast-cancer-brain-metastases-1020244431***

- **NKTR-102 (Etirinotecan Pegol)** – *Not Yet FDA-Approved:* In a clinical trial called BEACON, 852 patients with advanced breast cancer who had any type of ER/HER-2 status were enrolled. Patients were randomly assigned to receive either NKTR-102 or a physician's choice of standard chemotherapy. The study found that NKTR-102 doubled Overall Survival in patients with brain metastasis when compared to the physician's choice chemotherapy. Furthermore, NKTR-102 was less toxic than standard chemotherapy. As of August 2018, there is a recruiting clinical trial (NCT02915744) for this drug, and MBC patients with brain metastasis may be eligible. **From[162, PMID:26482278]:** ***http://www.healio.com/hematology-oncology/breast-***

cancer/news/online/%7Bf8e52d75-2273-432b-9473-b50f936c0765%7D/novel-chemotherapy-drug-demonstrates-activity-in-advanced-breast-cancer

- **Temodar (Temozolomide)** *(Not Yet FDA-Approved for MBC Patients)* has recently been used as a single agent to treat brain metastasis from breast cancer in clinical trials. In one study, complete remission was achieved in 36% of patients, and an additional 58% had a partial response. **From:** ***http://emedicine.medscape.com/article/1157902-treatment*** As previously mentioned, Temodar may also be used in combination with lapatinib in HER2+ MBC patients, as per the results of a small Phase 1 study in which sixteen patients with HER2+, progressive brain metastasis were enrolled. Fourteen of these patients had previously been treated with Whole Brain Radiation. For the 15 assessable patients, stable disease was achieved from the combination of lapatinib and Temodar in 10 patients (67%) and progression of disease in five patients (33%). **From[149, PMID:28177431]:** ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw532***

- **Tucatinib (ONT-380)** *(Not Yet FDA-Approved for MBC Patients):* Tucatinib (ONT-380) is a small molecule inhibitor of the HER2 growth factor receptor. The drug works by targeting the HER2 "tyrosine kinase" - a link in the chain of communication that allows HER2 receptors to signal the growth of the cell. The fact that it is a small molecule means the drug is able to pass through the blood-brain barrier to act against brain metastasis of the disease.

  In the first study of Tucatinib with TDM-1, all 8 evaluable patients with brain metastasis experienced more than 50% reduction in primary brain tumor size. In another study of 33 evaluable patients with metastatic HER2+ breast cancer (with and without brain metastasis), 19 (58 percent) showed clinical benefit, with 16 achieving at least "stable disease" (i.e. no tumor progression while on trial), 11 patients experienced "partial response" (i.e. tumor shrinkage of more than 30%). Of 8 patients with brain metastasis, 5 achieved at least stable disease, with 2 partial responses and one complete response in which existing brain metastasis were undetectable after treatment. **From[163; 164]**: ***https://www.eurekalert.org/pub_releases/2015-05/uocd-ohs052915.php*** and ***http://www.eurekalert.org/pub_releases/2015-12/uoca-spp120915.php***

- **Verzenio (Abemaciclib**): Verzenio is a CDK4/6 inhibitor similar to the already FDA-approved drugs Ibrance and Kisqali. In Sept. 2017, it was approved as a second-line therapy in combination with Faslodex for hormone receptor positive, HER2 negative postmenopausal patients whose first line endocrine therapy failed. In Feb. 2018, Verzenio was approved in combination with an Aromatase Inhibitor (AI) as first line therapy for hormone receptor positive, HER2 negative postmenopausal MBC patients. Verzenio is also approved alone (as a monotherapy) for hormone receptor positive, HER2 negative postmenopausal patients whose first line endocrine therapy failed and who also received prior chemotherapy that failed. A unique characteristic of Verzenio is its potential ability to cross the blood-brain barrier, making it a potentially attractive treatment option for brain metastasis. **From[165, PMID:29910656]:** ***http://www.onclive.com/publications/contemporary-oncology/2014/november-2014/targeting-cell-cycle-progression-cdk46-inhibition-in-breast-cancer/3#sthash.wCkkuV7J.dpuf*** and ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B48de16f7-6e3e-4440-b680-fce9166abf7c%7D/fda-expands-verzenio-approval-for-breast-cancer***

Clinical Trials: A list of Clinical Trials solely for brain metastasis is located at: ***http://brainmetsbc.org/en/content/available-clinical-trials-links***

A clinical trial for patients receiving WBR entails the use of an additional experimental drug called RRx-001, which appears to sensitize (or re-sensitize) tumors to treatment. In a study of 25 patients with advanced malignant incurable tumors that were rapidly progressing, disease control was evident in 71% of patients, with stable disease for more than 4 months in 28% of patients. **From[166, PMID:26296952]:** ***http://www.targetedonc.com/news/epigentic-targeted-agent-may-combat-resistance-in-many-cancers***

In this clinical trial specifically for patients undergoing WBR, the rationale for using RRx-001 is that RRx-001 releases a gas called nitric oxide, which widens the diameter of blood vessels and allows the delivery of more oxygen to tumors. The presence of oxygen in tumors is critical for the effectiveness of radiation therapy, since cancer cells are about two to three times more vulnerable to

radiation when oxygen is present. Hence it is hoped that WBR will be more effective when combined with this experimental drug. **From:** ***https://www.clinicaltrials.gov/ct2/show/NCT02215512?term=rrx-001&rank=1***

An excellent online support forum for those whose MBC has metastasized to the brain is: ***https://community.breastcancer.org/forum/8/topic/777599?page=1***

30. Leptomeningeal Metastasis

Breast Cancer Brain Metastasis (BCBM) and Leptomeningeal Metastasis (LM), also known as Carcinomatous Meningitis, are the two types of Central Nervous System (CNS) metastasis.

LM occurs when breast cancer spreads to the meninges, which are layers of tissue that cover the brain and the spinal cord. Metastasis can spread to the meninges through the blood or they can travel from brain metastasis via the cerebrospinal fluid that flows through the meninges. About 2% to 5% of patients with metastatic breast cancer experience LM. Symptoms of LM may include headache, backache, loss of sensation in the face (especially the chin), loss of bladder or bowel control, constipation, dizziness, extreme fatigue, confusion, weakness or loss of sensation in the legs and inner thighs, vision problems and/or hearing difficulties. Elevated CerebroSpinal Fluid (CSF) pressure, white blood count, and protein levels, and lowered glucose levels can also be signs of LM. Some patients with LM have no symptoms at all.

CNS metastasis is more common in the following MBC patient populations than in other MBC patients, so these patients should be especially vigilant about reporting any symptoms described above to their doctor:

- **HER2+**
- **TNBC**
- **Patients with CK-19 mRNA-positive Circulating Tumor Cells** (CTCs)

From[59, PMID:25144278; 167, PMID:19228746; 168, PMID:28021379; 169, PMID:27220421]: *http://www.ascopost.com/issues/march-15,-2014/how-to-approach-the-problem-of-cns-metastasis-in-her2-positive-patients.aspx*

Although LM usually occurs at a later stage in the course of metastatic breast cancer, in very rare instances, it can occur as a first metastasis. LM is difficult to treat because many drugs are not able to penetrate from the bloodstream through the meninges into the cerebrospinal fluid. Often brain metastasis and LM occur at the same time. For that reason, women diagnosed with LM should also have an MRI of the brain. **From: *https://www.brainmetsbc.org/en/content/leptomeningeal-metastases-1***

LM can be difficult to diagnose. The most common method is by withdrawing spinal fluid with a needle and examining it for breast cancer cells. This procedure is called a spinal tap or lumbar puncture. If the first lumbar puncture comes out negative, it must be repeated two more times to assure a 90% chance of an accurate diagnosis. Doing one puncture only assures 45% accuracy. It is important that the lumbar puncture be close to the site of the suspected area of leptomeningeal metastasis. An MRI with gadolinium (a contrast agent) of the entire brain and spine can also be used to diagnosis LM and may be better than a CT scan. An MRI with a radioactive tracer can also be used to locate obstructions in the spinal fluid or blood flow caused by LM. However, on an MRI, inflammatory disease or local infection can sometimes be mistaken for LM. **From: *https://www.brainmetsbc.org/en/content/leptomeningeal-metastases-1***

Once LM is diagnosed, it is important to check:

*The patient's **ER, PR and HER2 status**, as this will help to determine potential therapies.*

Whether the disease is bulky or diffuse:

- *Bulky Disease:* Radiation therapy is only given to relieve symptoms in areas of bulky disease because chemotherapeutic agents do not appear to penetrate tumors or nodules (smaller tumors) in the meninges**.**

- *Diffuse Disease:* Chemotherapy is given for diffuse disease and may extend life for several months, or sometimes for a longer time.

Whether IntraCranial Pressure (ICP) is elevated. If intracranial pressure is elevated, radiation may be a way to relieve CerebroSpinal Fluid (CSF) obstruction if needed. Relief of CSF outflow obstruction has been shown to improve functional status and is likely to prolong survival in these cases. A VentriculoPeritoneal Shunt (VPS) placement procedure can be used, which carries a small risk of hemorrhage, infection, or shunt malfunction. However, placement of a VPS is a definitive treatment for elevated ICP and may be combined with a reversible on/off valve to facilitate administration of IntraThecal (IT) chemotherapy. For those in whom a surgical procedure is not desired or tolerable, palliative Radiation Therapy is also effective in relieving CSF outflow obstruction, although the duration of benefit is variable. **From[170, PMID:23593536]: *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3623833/***

The information below focuses on medications to treat LM. In addition to drugs, **palliative radiotherapy** can be used with Intrathecal or intravenous chemotherapy.

Unfortunately, there currently is no agreed-upon standard treatment LM. Sometimes the benefits of treatment are offset by treatment side effects. Especially if there is uncontrollable disease in other organs, treating symptoms of the disease but not the disease itself may be the best option.

DRUG DELIVERY OPTIONS FOR LEPTOMENINGEAL METASTASIS

Depending on the therapy, drug delivery may be provided as follows:

- **IntraThecally (IT)** directly into the cerebrospinal fluid, usually via an Ommaya reservoir
- **Orally**
- **Through an IV port**

- **Intrathecally delivered drugs** are usually administered directly into the cerebrospinal fluid through an Ommaya reservoir, which is a device inserted in the head, under the scalp. The hair where the reservoir will be inserted is shaved and the patient is put to sleep or made very drowsy while the device is put in place. There may be a small raised area where the Ommaya reservoir is located. Like a port, the device remains in place during the course of treatment. Intrathecal therapy is generally reserved for patients whose systemic disease is under reasonable control and who are in good physical condition. It is important to have cerebrospinal flow studies done before intrathecal chemotherapy is undertaken to make sure there are no blockages. Occasionally, doctors will use radiation to relieve flow blockages.
  Interestingly, one MBC patient indicated that because her doctor had worked at a Children's Hospital, he was versed in using children's' ports and provided her with a pediatric Ommaya port, which she said is more comfortable than the adult version.

  There is no direct evidence that IntraThecal (IT) chemotherapy, which is introduced directly into the cerebrospinal fluid, is better than intravenous chemotherapy, which is given through the veins.

- **Orally** administered medications are usually taken in pill, capsule, or liquid form.

- **IV (Intravenous) Ports**: The types of chemotherapy "port" devices are listed in the section entitled, *Chemotherapy.*

TREATMENTS FOR LEPTOMENINGEAL METASTASIS

LM drug options are varied and may include the following drugs. Typically, Cytarabine, Herceptin, Methotrexate and Thiotepa are the most commonly used.

- **ANG1005** *(Not Yet FDA- Approved for MBC Patients)*
- **CranioSpinal Irradiation (CSI)**
- **Cytarabine (DepoCyt)**
- **Gemzar (Gemcitabine)**
- **Herceptin, with or without Tykerb**
- **Hormonal Therapies**
- **Leucovorin**
- **Methotrexate**
- **Thiotepa (Thioplex)** *(Not Yet FDA-Approved for MBC Patients)*
- **Whole Brain Radiation (WBR)**
- **Xeloda (Capecitabine)**

- **ANG1005** *(Not Yet FDA-Approved for MBC Patients)*: This is a Taxol-like drug being studied to treat brain metastasis and Leptomeningeal Metastasis (LM). Interim Phase 2 study results demonstrate that breast cancer patients with brain metastasis treated with ANG1005, including a subset of patients with LM, achieved encouraging responses. Of the 21 heavily pre-treated patients with LM, 5 patients (24%) achieved a partial response and 11 patients (52%) had stable disease. Estimates of survival in patients with LM treated with ANG1005 predict a median survival of 38.4 weeks as compared to 4-6 weeks if left untreated, or 12-24 weeks with conventional chemotherapy. In addition, ANG1005 demonstrated intracranial and extracranial antitumor activity in patients with various other subtypes of breast cancer including patients previously treated with paclitaxel. ANG1005 was shown to be generally safe and well-tolerated and demonstrated an adverse event profile consistent with conventional taxane therapy. As of August 2018, there is a recruiting ANG1005 clinical trial for LM patients. **From[171, PMID:PMC4638625]:** ***http://www.businesswire.com/news/home/20151120005128/en/Angiochem-Reports-Positive-Clinical-Data-ANG1005-Breast***

- **CranioSpinal Irradiation (CSI):** Full CranioSpinal Irradiation to the skull and/or spine may lead to complete or partial response in approximately half of breast cancer patients with leptomeningeal disease, though it is not curative, and reports are limited. This therapy can cause significant side effects, so other treatments may be preferable. **From[172, PMID:23593093]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625760/***

- **Cytarabine** also known as **DepoCyt, Cytosar-U, Ara-C,** or **Cytosine Arabinoside** belongs to a group of drugs called anti-metabolites which interfere with cells' ability to make DNA and RNA, which stops the growth of cancer cells.

- **Gemzar (Gemcitabine):** This is a commonly used chemotherapy drug for MBC which may be helpful in cases of LM. **From[173, PMID:26279806]:** ***http://emedicine.medscape.com/article/1156338-treatment***

- **Herceptin**: For women with HER2 positive LM there is increasing and seemingly successful use of intrathecal Herceptin both with chemotherapy and alone. Many of these successes have been reported as case studies, although one small trial was done in Spain with promising results. Several trials are now underway to verify these results in larger numbers of patients. In these case studies, low dose (15mg-40mg weekly) and high dose (100mg-150mg weekly) Herceptin have been used. High doses appear not to be toxic and the brain swelling that it causes can be controlled by gradually increasing the dose of Herceptin and using steroids. Intrathecal Herceptin can also be delivered by lumbar puncture to the spine. One woman survived 27 months after LM diagnosis. A complete leptomeningeal response, with no evidence LM at necropsy, was achieved after receiving 67 weekly administrations of intrathecal Herceptin with marked clinical improvement and no adverse events. In some cases, Herceptin may be combined with Tykerb. . **From[174, PMID:21369716]:** ***http://www.ncbi.nlm.nih.gov/pubmed/21369716***

- **Hormonal Therapies:** There have been reports of remissions with **Arimidex, Aromasin, Letrozole, Megace** and **Tamoxifen.** Sometimes the drug may be administered IntraThecally. **From[172, PMID:23593093; 175, PMID:15813508]:** ***http://www.brainmetsbc.org/en/content/leptomeningeal-metastases-1*** and ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625760/***

- **Leucovorin** can be used as a rescue after dose-intense Methotrexate therapy to lessen the effects of Methotrexate **From:** ***http://www.aboutcancer.com/meningeal_review_utd.htm***

- **Methotrexate** is one of the most commonly used chemotherapy agents for LM. It appears as though IV chemotherapy with high-dose Methotrexate may confer increased survival over radiation therapy alone.
  From[170, PMID:23593536]: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3623833/***

- **Thiotepa (Thioplex**) is another commonly used agent. This drug is cleared from CerebroSpinal Fluid within minutes and has survival curves similar to those of Methotrexate with less neurologic toxicity **From[173, PMID:26279806]:** ***http://emedicine.medscape.com/article/1156338-treatment***

- **Whole Brain Radiation (WBR)**: As its name indicates, in this therapy, radiation is delivered to the entire brain. One study reported a series of patients with leptomeningeal spread of cancer, of which 46 patients had breast cancer, and 43 underwent WBR. Among the breast cancer patients, there was a 61% "crude" rate of stabilization or improvement of symptoms with WBR.
  From[172, PMID:23593093]: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625760/***

  Preservation of Memory with WBR: There is a type of WBR that is a "hippocampus sparing procedure" which may help to preserve a degree of memory that might otherwise be lost as a result of the procedure. In a study of 113 patients, at four months after undergoing the hippocampus sparing procedure, the decline in recall (as compared to baseline) was 7%, significantly better than the 30% cognitive decline in the historical control group that received WBR without the hippocampus sparing procedure.
  From[147, PMID:25349290]: ***http://jco.ascopubs.org/content/early/2014/10/21/JCO.2014.57.2909***

- **Xeloda (Capecitabine):** There have been some reports of remission with this drug. **From:** ***http://www.brainmetsbc.org/en/content/leptomeningeal-metastases-1***

One person wrote that his mother, who has HER2 negative LM, was given Intrathecal Methotrexate via lumbar puncture twice a week for one month and weekly the next month. Afterwards, she received it every 3 weeks. Xeloda was added after the 6th dose at a concentration of 1500 mg in the morning and 1500mg in the evening daily, and she is now in remission.

Although somewhat dated, detailed information about potential therapies for LM can be found at **[176, PMID:9782234]:** ***http://bcwatchdigest-brain.evidencewatch.com/***

For some patients, a **clinical trial** may be appropriate. For a free professional clinical trial search, call 1.800.4.CANCER (1.800.422.6237). A trained National Cancer Institute (NCI) professional will obtain the patient's specific criteria and forward a list of potential clinical trials. Please see the *Clinical Trials Overview* section for further information.

Although LM can be difficult to treat, below are some wonderfully encouraging messages by members of online MBC forums:

Here is a husband's account of a completely successful treatment for his HER2+ wife who was diagnosed with LM, brain, and spinal metastasis:

"We were able to get the neuro-oncologist to agree to administer IntraThecal (IT) Herceptin at 0.6 mg/kg of weight versus the usual (lower) 10 mg starting dose. My wife's dose was boosted to the target of 80 mg after four initial treatments. She remained at this level for the remainder of the treatment. While patients treated at the higher dose do not appear to have negative effects than the lower dose patients, the initial dose appears to have significant potential for nausea and vomiting 24 to 72 hours after the first treatment. This may be due to cancer cells being killed and releasing their toxins into the brain cavity. Improvements in MRI scans, CFS protein and glucose, and tumor markers are seen within four weeks at this higher dosage.

Magic happened! The first dose of 40 mg of Intrathecal Herceptin was given to my wife on January 12, 2012. When she showed no ill effects, three additional weekly treatments were done. An MRI on February 2, 2012 showed that progression of the disease had stopped. It was determined that 0.400 mg of Topotecan would be added to the intrathecal treatment as well, with a twice per week regimen. This treatment is a syringe addition of solution into the reservoir via a topical needle. Total treatment time for both medications is less than ten minutes.

Two weeks later additional systemic Herceptin and Navelbine were added to reduce the risk of the tumors spreading to other parts of her body. Abnormal cells had been seen in the blood, and tumor markers had become elevated. The IT treatments occurred on Mondays and Thursdays with the intravenous treatments the following day, on Fridays. The intravenous treatment was initiated with a 225 mg per week dose of Herceptin and 42 mg of Navelbine. After four weeks, the IV Herceptin was reduced to 125 mg. The combined IT and IV treatments led to a significant reduction in MRI contrast agent uptake for both the spine and brain. In addition, no abnormal cells were found in the fluid removed from the spinal tap or Ommaya, and none were seen in a blood sample. This news was outstanding. The decision was made to reduce the Topotecan to once per week, and the Navelbine was reduced to three weeks on and one week off. After the reduced treatment was initiated, her white blood cell count showed a drop, so Neupogen was added to the regimen on day 1 and 2 after the Navelbine IV treatment.

Evaluation of the MRI was performed after four weeks for the spine and brain. A PET scan was done on June 1, 2012. The results of these scans showed only background levels that were consistent with normal tissue. There was no longer any evidence of the cancer. The IT Herceptin and Navelbine have been reduced to once every two weeks, with the IV Herceptin and Navelbine scheduled to be reduced to once every two weeks. The goal is to have a once per month treatment of IT Herceptin and IV Herceptin to allow my wife a near normal life.

We are hopeful that a full scale clinical trial of high-dose intrathecal Herceptin will be conducted, with multiple sites, to allow more women to be given a chance to live. This treatment was novel due to the higher dose of Herceptin than had been previously thought to be needed. The need for a higher effective dose might be due to the significantly higher turnover of the cerebral spinal fluid versus the blood supply. It is well documented that Herceptin cannot pass through the blood-brain barrier, and Xeloda/Tykerb are not effective in the long term for brain or leptomeningeal involvement of HER2-positive tumors.

My wife's treatment inspired another husband in Europe to have the same treatment done for his wife who was in similar straits. His wife's results were as amazing as my wife's were." **From:** ***http://www.brainmetsbc.org/en/content/magic-happened-husband-tells-story-his-wife-s-success-treatment-her2-leptomeningeal-and-brai***

Another person wrote this about a patient: "The wonderful doctors at UCLA gave her a spinal injection of methotrexate. She didn't like that so off she went to surgery where they installed an Ommaya reservoir and ever since has been getting Herceptin through it every 3 weeks. In addition, she takes Tykerb. And here is the miracle part...no further sign of LM and she is doing very well today."

Another individual wrote, "I confronted my oncologist a couple of weeks ago to tell him that I am feeling quite anxious about the statistics concerning LM and he gave me more faith by telling me that he had a couple of patients who are still going after 4 and 5 years!!!!!"

One patient shared the following: "I was diagnosed with LM about 26 months ago. I have an Ommaya port and had depocyte injected for about 4 months. I also had Decadron which made my legs so weak. I started with almost blacking out if I sat to long and then got up. That was fluid buildup in brain. Finally, the doctor decided to put a shunt in to drain fluid. I cannot use Ommaya port anymore and I am now on Gemzar. So far so good - feeling good! When I was diagnosed with LM over 2 years ago my doctor told me to get things in order. Once I got off the steroids my legs got stronger. I look like a new person, now and feel like a new person."

One lady wrote that instead of having the Ommaya port, she opted to have radiation on an area of her spine where there was a cluster of tumor cells. She was then put on Xeloda, an oral chemo, and Avastin (which now has been dis-approved for treating breast cancer). She is now doing well.

Another person had two treatments of Methotrexate through a spinal tap (intrathecal) and then began Xeloda. Her symptoms were headaches and nausea and indicated that she is doing much better a few months later.

Patients also reported that the Ommaya port was not painful and that there were no side effects from Cytarabine,-just the steroids.

A patient who conducts extensive research has experienced regressing LM and brain metastasis on the following protocol consisting of conventional and supplemental therapies. She also follows a low-carbohydrate, modified ketogenic diet. The reason that her therapy has been provided herein is because both brain metastasis and LM can be considerably challenging to treat. (As with any potential therapy, patients are highly advised to confer with their oncologist when considering a particular therapeutic regimen).

IT Topotecan, weekly

IT Herceptin, 100 mg weekly

IV Avastin, every two weeks

IV Kadcyla, every three weeks

Hyperbaric oxygen (HBOT), 1-2 times a week

IV Artesunate (an anti-malaria drug)

IV DCA (Dichloroacetate sodium)

IV Poly-MVA (an antioxidant)

IV Vitamin C, 75 grams (dosage may vary based upon body mass)

31. Abdominal, Peritoneal, Omentum, and Ovarian Metastasis

Patients with metastatic lobular breast cancer are more likely than are other types of metastatic breast cancer patients to have their cancer spread to the abdominal (gastric) area, the ovary, and/or the peritoneum (which is the membrane that lines the abdominal cavity and covers most of the abdominal organ).

- **Gastric (abdominal) metastasis** from breast cancer mimics a primary gastric tumor, as symptoms can be nonspecific and include anorexia, abdominal pain, early satiety (fullness), nausea and vomiting, and bleeding. Radiological and endoscopic findings can also be like those of a primary gastrointestinal tumor. The differential diagnosis between the two types of cancer is very important to treat the patients properly and to avoid unnecessary surgery. Breast cancer cells that have spread to this area should be examined for hormonal and HER2 status, as that may influence the course of treatment.
  Breast cancer metastasis to the stomach represents evidence of systemic disease and therefore systemic therapy, such as chemotherapy and/or hormonal therapy (rather than surgical resection) is indicated. In most cases, surgical resection is not possible due to local invasion. Some experts feel that surgical treatment should be reserved only for patients who develop complications such as obstruction or bleeding. However, one study showed that patients with metastasis only to the gastrointestinal tract who underwent palliative surgical resection tended to have a more prolonged median survival (44 vs. 9 months). The decision-making process for surgical intervention should be based on the clinical presentation and symptoms, the availability of chemotherapeutic options, and a quality of life discussion. **From[177, PMID:20032432]:** ***http://ar.iiarjournals.org/content/29/11/4759.full***

- **Peritoneal metastasis** (metastasis to the thin tissue lining the abdomen) is a bit difficult to treat, but recently a new procedure called Hyperthermic IntraPeritoneal Chemotherapy (**HIPEC**) has been developed and appears promising. This is a highly concentrated, heated chemotherapy treatment that is delivered directly to the abdomen during surgery. Of five patients treated in one study, one patient died of disease at 56 months, and 4 are alive and disease-free at 13, 45, 74 and 128 months. These encouraging outcomes suggest that cytoreduction (surgical removal of visible tumors) and HIPEC may be a viable approach to offer to highly selected patients with peritoneal carcinomatosis from breast cancer. **From[178, PMID:23523180]:** ***http://www.ncbi.nlm.nih.gov/pubmed/23523180***

- The **omentum** is a large fatty structure that hangs off the colon and drapes over the intestines inside the abdomen, and breast cancer may occasionally metastasize there. No specific therapy regarding treatment for cancer that has spread to this site could be found.

- For those with **ovarian metastasis**, one study found that survival may be improved significantly when optimal debulking surgery (a procedure whereby a surgically incurable malignant tumor is partially removed without curative intent) is performed. **From[179, PMID:20041486]:** ***http://www.ncbi.nlm.nih.gov/pubmed/20041486***

- **Other Areas:** Sometimes breast cancer metastasis may impact or block the function of the **ureters (**tubes made of smooth muscle fibers that propel urine from the kidneys to the urinary bladder) and/or **bile ducts** (which carry bile from the liver and gallbladder through the pancreas to the small intestine and/or the **duodenum** (the first and shortest section of the small intestine). Patients will need to be individually assessed regarding appropriate treatment when this occurs.

It is possible that the doctor will recommend systemic therapy based upon the patient's hormonal and HER2 profile after cancer metastasizes to the above site(s).

Ascites (excess fluid): "Ascites" is a gastroenterological term that refers to an accumulation of fluid in the abdominal (peritoneal) cavity. The ascites can arise from tumors' expression of epithelial cell-adhesion molecule (EpCAM). Additionally, vascular

endothelial growth factor (VEGF) has been cited as an important factor affecting vascular permeability, a key factor in ascites production. **From[135, PMID:20531969]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880345/***

Ascites are generally evidenced by a distended stomach, shortness of breath, bloating, and/or other discomfort. Patients who believe they may have ascites should notify their doctors immediately.

In patients with cancer-related ascites, diet restrictions and/or diuretics will generally not be effective, although there have been some exceptions. Paracentesis (a procedure whereby fluid is taken out using a long, thin needle put through the belly) may be the first-line ascites treatment. If needed, a catheter (either indwelling or a peritoneovenous shunt) may be left in place to drain so that fluid can be removed in such a manner that the patient does not need to undergo repeated procedures**.** Some patients have reported that draining the ascites daily instead of every few days provides them with superior relief. **From[180, PMID:21427184]:** ***http://www.emedicinehealth.com/ascites/page7_em.htm***

Catheters: Treatment options for draining abdominal ascites often entail the use of an indwelling catheter, paracentesis, or peritoneovenous shunting.

Indwelling (Pleurx, Aspira, or Tenckhoff) Catheter: This is the surgical insertion, under general anesthesia, of a small tube placed temporarily into the abdominal space that allows the patient or his/her family member to drain the fluid into a bottle as needed. Patients with an indwelling catheter are fully mobile and are not "attached" to the draining bottle except when draining the fluid. If there is no more drainage at all, the catheter is removed either in the doctor's office or an outpatient procedure. The Pleurx catheter works via suction, and the newer gentler model is the Aspira catheter, which may be a bit less uncomfortable because uses gravity instead of suction for draining.

Paracentesis: Under sterile conditions, a needle is placed into the peritoneal space and fluid is withdrawn. Paracentesis may be a viable first step if the ascites accumulates quickly and the abdominal distension causes pain or shortness of breath. Because the peritoneal fluid contains albumin, if large amounts of fluid (more than 5 liters) are withdrawn, an albumin transfusion may be needed. If warranted, the catheter maybe left in place to drain, so that fluid can be periodically removed, and the patient does not need to undergo repeated procedures. Paracentesis may be done more than once, but if it becomes a frequent necessity for symptom control, other options may be considered.

Peritoneovenous shunting: This is a surgical operation that may on occasion be used in patients who are not candidates for, or who have failed treatment with, paracentesis or indwelling catheters. Peritoneovenous shunting entails the use of a tube for draining fluid back into the veins, instead of draining fluid externally as is done with indwelling catheters.

A patient who has been living with abdominal ascites for a year kindly provided the following **tips** that have helped her to alleviate some of the discomfort caused by ascites and draining:

After Draining: Stand up slowly after draining and watch your blood pressure - mine drops very low, while heart rate races. Don't fall.

Fluids: Drink plenty of fluids, especially around draining times. Replenish with liquids that contain electrolytes like coconut water & broth.

Clothing: Do not wear any tight clothing or belts. Instead, wear drawstring hip hugger pants or elastic waist pants and skirts. Wear tops that skim your belly, rather than bind it.

Meals: Eat small meals and wait at least 4 hours after eating before bedtime. Avoid foods that can lead to reflux such as citrus fruits and juices, coffee, tea, alcohol, chocolate, and spicy food. If possible, do not eat after 4PM or 5PM to avoid discomfort during sleep.

Exercise: Gentle walking, yoga and stretching may help. Anything that compresses the belly like the yoga poses of forward bends and child's pose may not help, nor does vigorous exercise that jostles the belly.

Gentle Rubbing: I hold my belly with my hands and rub gently in the direction my colon runs - lower left up to liver area, across upper belly to upper right and then down right side.

Oral Hygiene: The dry mouth after many months of draining can be difficult - so drink water frequently, rinse with glycerin and marshmallow tea if possible. Biotene may help some people in mitigating dry mouth. Holding a bit of coconut oil in the mouth can help.

Sleep and Rest: Sleep or rest on the back or the side, not on the belly

Drugs that may help alleviate ascites and/or related discomfort:

Avastin (Bevacizumab) *(Not Yet FDA-Approved for MBC Patients)***:** In one study, nine patients with refractory malignant ascites were given Avastin. Three patients had breast cancer, three had colon cancer, 2 had uterine cancer and one had ovarian cancer. Prior therapy included systemic chemotherapy and large volume paracentesis. All patients had rapid re-accumulation within 2 weeks of paracentesis before treatment. Patients were given intraperitoneal bevacizumab at 5 mg/kg monthly. Malignant ascites resolved without reaccumulating or repeat paracentesis in all nine patients after a single intraperitoneal dose of bevacizumab over a median observation period of over two months. **From[181]:** ***http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.9043***

Catumaxomab (Removab) *(Not Yet FDA-Approved for MBC Patients)***:** Although the author was not able to locate studies with breast cancer patients, a study on ovarian cancer patients was reported. Catumaximab was evaluated as part of a Phase 1/II dose-escalating study for intraperitoneal (IP) application in 23 patients with ovarian cancer who had ascites with EpCAM-positive tumor cells. The patients were treated with 4–5 intraperitoneal infusions of catumaxomab in doses of 10 to 200 micrograms within 9–13 days with loading doses of 5–10 µg. The maximum tolerated dose was defined at 10, 20, 50, 200, and 200 µg for the first through fifth doses. Treatment with catumaxomab resulted in significant and sustained reduction of ascites flow rate. A total of 22 of 23 patients did not require paracentesis between the last infusion and the end of study one month later, and tumor cell monitoring revealed a reduction of EpCAM-positive malignant cells in the ascites**. From[135, PMID:20531969]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880345/***

A separate study of 26 cancer patients who received at least three of four IP instillations of catumaxomab led to a median interval of 15 days before a patient required an intraperitoneal puncture. Median overall survival was 92.5 days, but five patients remained alive and free of puncture for as long as 876 days. It was concluded that IP catumaxomab can be administered in relatively frail outpatients, achieving good ascites control. A survival benefit was seen in fit patients who received complete IP catumaxomab treatment and were able to undergo subsequent systemic therapy. **From:** ***http://www.medpagetoday.com/MeetingCoverage/SGO/44939***

Iscador (Mistletoe extract) *(Not Yet FDA-Approved for MBC Patients)***:** Iscador is a nontoxic therapy widely used in Europe that is made from the extract of fresh sap of the plant known as mistletoe. It must be prescribed by a doctor. A Phase 2 study was undertaken of 23 patients with various types of cancer who had ascites which required repeated peritoneal punctures for draining. The time-interval between the first two punctures was measured and defined as the baseline. Following each subsequent puncture, Iscador M® 10 mg was injected intraperitoneally. The intervals between later punctures were compared to previous intervals. Following the first injection, the median time-interval between draining increased from 7 to 12 days, reaching 13 days after the second injection, nearly double the initial draining interval. One patient with ovarian cancer had a clinical objective response represented by a reduction in CA-125 levels from 800 U/ml to 102 U/ml, and improvement in ascites accumulation and in performance status; this regression lasted for 12 months. No toxicity was observed in any of the patients. **From[138, PMID:16739342]:** ***http://ar.iiarjournals.org/content/26/1B/709.full.pdf*** Once prescribed, Iscador may be difficult to procure. One reputable source is H & F Apothecary, Ltd., Chestnut Ridge, NY. Telephone: 1.845.352.6165

Octreotide (Sandostatin LAR®: Thirty-three patients were enrolled in a two-arm study, with 16 patients assigned to the octreotide arm and 17 to the control arm. The median time to next paracentesis was 28 and 14 days in the octreotide and placebo arm, respectively. After adjustment for extracted ascites volume and abdominal girth change, no statistically significant difference between the groups was observed, although octreotide-treated patients described less of abdominal bloating, abdominal discomfort, and shortness of breath at one month. As prescribed in this trial, octreotide did not seem effective in prolonging the time to next paracentesis, although symptoms had improved. **From[139, PMID:22572824]:** ***http://www.ncbi.nlm.nih.gov/pubmed/22572824***

In some cases, ascites may lead to **bowel obstruction**, which can precipitate nausea and vomiting. In addition to draining the fluid as described above, these therapies may be of help in cases of bowel obstruction.

Octreotide (Sandostatin LAR®): Some physicians report success with some patients by using the oral medication Octreotide (described above) in cases of malignant bowel obstruction, as well as in instances of trapped "loops" of bowel that are non-operable. Octreotide is a hormone secreted in the pancreas and pituitary gland that inhibits gastric secretion, thereby reducing gastric and pancreatic juices and relieving fluid-induced pressure.

Surgery: If the patient can withstand surgery, then they may benefit from surgery if they are in good physical condition with only one site of obstruction, if there is no resolution of the bowel obstruction after 48 to 72 hours of conservative management.

Other Medical Management: When the patient's situation is not favorable for undergoing surgery (or possibly stenting), medical management should be the mainstay of care, the aim being symptom relief. Pain caused by tumors can be relieved by strong opioids given subcutaneously or transdermally to ensure proper absorption that the oral route cannot provide. Cramp-related pain, if present, can be treated subcutaneously with anticholinergic (nerve blocking) drugs such as Hyoscine Butylbromide or Scopolamine (for which a transdermal patch is also available). Nausea can be reduced with regular administration of antiemetic drugs, Haloperidol being a commonly used medication. Prokinetic medications such as Metoclopramide, which are used to help control acid reflux, should be avoided. **From[140, PMID:22859627]:** ***http://www.cfp.ca/content/58/6/648.full***

32. Ocular Metastasis

Breast cancer metastasis to the eye can be difficult to diagnose because there may be no symptoms, although patients sometimes have blurred vision or see flashing lights. If cancer is suspected, the patient should be referred to an ophthalmologist rather than an optometrist for an examination of the eye itself. If cancer is found, treatment should be coordinated among the patient's medic al Oncologist, Radiation Oncologist (as warranted), and ophthalmologist.

Because of the high association between intraocular disease and metastatic disease in the brain and central nervous system, when there is a diagnosis suggestive of intraocular (eye) metastasis, it is suggested to get imaging of the brain and central nervous system to make sure there is no involvement of those areas. **From[182, PMID:23222564]: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3574252/***

TREATMENTS FOR OCULAR METASTASIS

Therapies for ocular metastasis may include:

- **PhotoDynamic Therapy (PDT)**
- **Plaque Brachytherapy**
- **Proton or Charged Particle Radiotherapy**
- **Radiation Therapy or Laser Surgery**
- **Systemic Therapy**

- **PhotoDynamic Therapy (PDT) is** a treatment that uses special drugs, called "photosensitizing agents," along with light to kill cancer cells. The drugs only work after they have been activated or "turned on" by certain kinds of light. In one study, 9 metastasis in 8 eyes were treated with PDT. After PDT, complete control with resolution of sub retinal fluid was achieved in 7 tumors (78%), with mean tumor thickness reduction of 39%. Two tumors failed to respond to PDT, both requiring plaque radiotherapy.

- **Plaque Brachytherapy** is a form of radiation therapy that delivers a highly concentrated radiation dose to the tumor with relatively less radiation to surrounding healthy tissues and takes only two days to complete, compared with daily radiation for four weeks with external beam radiation. Plaque radiotherapy has proven effective in cases of solitary metastasis and those that failed to respond favorably to external beam radiation. Most patients treated with radiation maintain good vision. One doctor reported having a patient with very advanced MBC and 15 tumors in her eyes. She was able to preserve 20/20 vision for the next 3 or 4 years.

- **Proton or Charged Particle (Pencil Beam) Therapy:** Traditional radiation therapy affects everything in its path, so doctors have to limit the dose delivered to the tumor in order to minimize damage to surrounding healthy tissue. In proton therapy, protons enter the body with a low dose of radiation which increases when the beam slows down within the tumor, and then the protons stop without going any further to harm further tissue. Compared to an X-ray beam, a proton beam has a low "entrance dose" (the dose delivered from the surface of the skin to the front of the tumor), a high dose designed to cover the entire tumor, and no "exit dose" beyond the tumor. The combined effect is claimed to provide greater precision in targeting the tumor with a more potent dose of radiation.

- **Radiation Therapy or Laser Surgery:** Treatment for metastasis to the eye may include radiation therapy, although laser surgery may be used in some cases. **External-beam radiation** is a common treatment option, especially if there is multifocal involvement, but occasionally plaque brachytherapy (described above) is used if there is one tumor.

- **Systemic Therapy** such as chemotherapy (especially a Taxane [Taxol, Taxotere, or Abraxane]), hormonal and/or targeted therapy may sometimes be helpful against ocular metastasis.

From[182, PMID:23222564; 183, PMID:22386261]: ***http://www.ncbi.nlm.nih.gov/pubmed/22386261*** and ***http://www.eyecancer.com/conditions-and-treatments/treatments/6/eye-and-vision-sparing-radiation-therapy-for-intraocular-tumors*** and ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3574252/***

33. Skin (Cutaneous) Metastasis and Ulcerating Breast Tumors

Skin metastasis from breast cancer may appear similar to other skin maladies such as cellulitis, lymphedema, or a rash. Therefore, a biopsy is warranted in order to determine whether the symptom is indeed metastatic breast cancer. There is relatively little literature written about the treatment of skin metastasis from breast cancer, although several interesting therapies appear below.

On occasion, breast cancer tumor(s) themselves can break through the skin, resulting in wounds to the skin. As the cancer grows, it blocks and damages tiny blood vessels, which can starve the area of oxygen. This causes the skin and underlying tissue to die (necrosis). There may also be infection, and areas of the wound may become ulcerated. These ulcerating (also called "fungating") cancer wounds are relatively rare, and most people who have cancer will never have one. The symptoms they may cause include leakage, an unpleasant smell, pain, bleeding and itching. Treatment for ulcerating breast tumors is similar to that for skin metastasis.

TREATMENTS FOR SKIN (CUTANEOUS) METASTASIS AND ULCERATING BREAST TUMORS

As described below, therapies for skin metastasis may include:

- **Cryotherapy**
- **ElectroChemoTherapy (ECT)**
- **Imiquimod Cream**
- **Medihoney**
- **Miltex (Miltefosine)**
- **Other:**
  - *Laser Ablation*
  - *Radiofrequency Ablation*
  - *Radiotherapy*
  - *Systemic therapy*
  - *Surgery*
- **REM-001 Therapy**
- **Silvasorb Gel**
- **Tucatinib (ONT-380)** *(Not yet FDA-approved for MBC Patients)*

- **Cryotherapy,** which refers to a treatment in which surface skin lesions are frozen, often by using liquid nitrogen, may sometimes be used to destroy skin lesions. **From:** ***http://dermnetnz.org/lesions/metastasis.html***

- A new treatment **called ElectroChemoTherapy (ECT)** has been proposed as a complementary therapeutic technique for controlling cutaneous and subcutaneous metastasis. ECT is a non-thermal tumor ablation therapy providing electric currents (electric pulses) to cancer cells. The procedure increases cell membrane permeability and enhances the penetration of drugs into the cancer cells. Bleomycin, an "antitumor antibiotic" and cisplatin may be the most suitable candidates for the combined use with ECT. In one small observational study, 12 breast cancer patients with skin metastasis were given Bleomycin followed by the application of brief electric pulses to the tumor area. There was a Complete Response of 75.3%, a Partial Response in 17%, and no change in 7.7%. No serious ECT-related adverse events were reported. **From[184, PMID:PMC3499246]:** ***http://www.biomedcentral.com/1471-2482/12/S1/S6*** For those with ulcerating breast tumors, electrochemotherapy may help control bleeding, pain and discharge, and the treatment can be repeated if needed.

- One small study indicated that **Imiquimod Cream** applied topically may be helpful against skin metastasis in about 20% of patients: **From[185, PMID:22767669]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3580198/***

- **Medihoney**: At the 2010 Symposium on Advanced Wound Care (SAWC) and the Wound Healing Society (WHS), an international conference drawing clinicians from all over the globe, a clinician presented a series of cases illustrating the benefits

of MEDIHONEY® dressings not only in the treatment of fungating tumor wounds but in eliminating their odor and the stigma that goes with it. MEDIHONEY® dressings are a unique line of products whose active ingredient is medical-grade active Leptospermum honey (ALH) that can succeed in alleviating wounds when other treatments have failed. **From:** ***http://www.news-medical.net/news/20100417/Honey-beneficial-for-treatment-of-fungating-tumor-wounds.aspx***

- A topical therapy called **Miltex** (**Miltefosine**) may be helpful if it is available. In a small study, 25 patients were treated, most of whom had been heavily pre-treated. A response was seen in 9 patients with skin lesions from metastatic breast cancer (1 complete response, 2 partial responses, 6 minor responses) giving a total response rate of 36%, with stable disease in 11 patients (44%) and progressive disease in 5 (20%). **From[186, PMID:10602908]:** ***http://link.springer.com/article/10.1007%2Fs002800051114?LI=true*** and ***http://dermnetnz.org/lesions/metastasis.html***

- In some cases, the literature about treating skin metastasis indicates that *surgical excision*, which might be followed by radiotherapy and/or *systemic treatment*, may be viable. And when surgical excision is not possible, there may be several therapeutic options such as *laser ablation*, *radiofrequency ablation* (which uses a needle that carries an electric current to heat the tumor to destroy it)**,** *or radiotherapy*.

- **REM-001 Therapy:** This therapy may also be referred to as a photodynamic therapy because it includes light. There are three parts to REM-001 Therapy: a laser light source, a light delivery system, and the drug REM-001. The first step in the treatment is injecting REM-001 into a patient's bloodstream, which can convey it to the tumor. Then, a physician uses a fiber-optic wand to illuminate the tumor. Because the drug is photosensitive, it is activated only at the tumor site, reducing the possibility of severe side effects. In four Phase 2/3 clinical trials of REM-001 among 148 patients for whom prior radiation therapy failed, the complete response rate was 80 percent. **From:** ***https://breastcancer-news.com/2017/04/12/rem-001-benefits-most-women-with-skin-cancer-that-arises-from-breast-cancer/***

- **Silvasorb Gel:** SilvaSorb Gel creates an antimicrobial barrier and is used for use on pressure ulcers, partial- and full-thickness wounds, leg ulcers, diabetic foot ulcers, graft wounds, first- and second-degree burns, and surgical wounds. One MBC patient with skin metastases indicated that she believed it helped her fungating skin met to heal. She gently flushed the area with a mild saline solution, applied the Silvasorb, and covered with a loose bandage. Admittedly, she is not sure whether to credit the product, her chemo, or a combination of both, but she is grateful that her wound is almost completely healed.

- **Tucatinib (ONT-380)** *(Not Yet FDA-Approved for MBC Patients).* In a very small study of 8 heavily pre-treated women with HER2 positive skin metastasis, Tucatinib was combined with Xeloda and/or Herceptin. One patient had a complete response, defined as a disappearance of all skin lesions. Three patients had partial responses, defined as a greater than 30% reduction in the sum of diameters of all target skin lesions from baseline. The remaining four patients had stable disease. As of August 2018, there is one recruiting clinical trial in the US for this drug (NCT02614794). **From[187, PMID:29804905]:** ***http://www.medicalnewstoday.com/articles/313476.php***

ADDITIONAL TIPS FOR THOSE WITH ULCERATING ("FUNGATING") BREAST WOUNDS:

Leakage or discharges, along with an unpleasant smell, are probably the most common symptoms of a breast wound. These issues often arise due to infection. Therefore, patients may want to consider applying dressings that are very absorbent and which have been specially treated. Some wound dressings can be left in place for several days, but this depends on the amount of fluid leaking from the wound and where the wound is located.

To help against leakage and odor, patients may wish to consider the following:

- **Antibacterial Essential Oils**
- **Antibiotics**
- **Barrier film or cream**

- **Changing the dressings regularly**
- **Dressings containing:**
  Charcoal
  Medical Grade Honey
  Silver

- **Antibacterial Essential Oils:** A study of 30 patients with head and neck cancer who had malodorous wounds found that rinsing ulcers with an antibacterial essential oil mixture (mainly based on Eucalyptus oil) twice a day caused the patients to experience complete resolution of the foul smell by only the third or fourth day of therapy. As a secondary effect, the oils had anti-inflammatory an in some patients' ulcers started to heal and achieved complete normalization. (A related source indicated the mixture was eucalyptus, melaleuca, lemongrass, lemon, clove leaf, and thyme in a 40% ethanol base). **From[188, PMID:16785038]:** ***https://www.researchgate.net/publication/6998989_Antibacterial_essential_oils_in_malodorous_cancer_patients_Clinical_observations_in_30_patients***

- **Antibiotics** can help control any infection that may be present in the wound, which can help to reduce the smell. Applying antibiotic gels directly on the wound can also help.

- **Barrier Film or Cream:** Because the discharge or leakage from a wound can make the healthy skin around it sore and red, it's often helpful to apply a barrier film or cream, such as **Cavilon**, to the skin around the wound to protect it.

- **Changing the dressings regularly** can help stop the discharge from building up. Sometimes, only the top layer of the dressing needs to be changed. Substances in the dressings that may promote healing include:

Dressings containing charcoal can help to mitigate smell.

Dressings containing medical grade honey such as Activon can also help to prevent bacteria growth. **From[189, PMID:PMC5098468]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5098468/***

Dressings containing silver can reduce the number of bacteria in the wound and help to control the odor. **From[190, PMID:24832784]:** ***http://www.cochrane.org/CD003948/WOUNDS_topical-agents-and-dressings-for-fungating-wounds-ulcers-caused-by-cancer***

34. Research and Potentially Helpful Therapies

For ease of reference, this section has been subdivided into the sub-sections below.

Before trying a new therapy, herb, or supplement, patients should consult with their physician to ensure that it is safe and will not interfere with their current therapy.

Important Note:

By now, most MBC patients are aware that many breast cancer cells "over-express" various receptors for Estrogen, Progesterone, and/or HER2/neu (sometimes referred to as ERBB2) , and that there are currently therapies that target receptors.

The good news is that more types of breast cancer cell receptors and growth factors are continually being discovered across all MBC subtypes, such as Androgen and FGFR1 (which may signify resistance to hormonal therapy). There is also a target of the zinc transporter "LIV-1" (SLC39A6), which is expressed in most MBC patients, including TNBC.

As of August 2018, drugs targeting AR, FGFR1, and LIV1 are being tested in clinical trials.

Research indicates that 88% of estrogen-positive breast cancers, 50% of HER2+ breast cancers, and 25% of triple-negative breast cancers (TNBC) are Androgen-Receptor (AR) positive. An ImmunoHistoChemistry (IHC) can be used to identify AR positive breast cancers in a similar manner to identifying ER+ and/or PR+ breast cancers.

Testing for FGFR1 overexpression is undertaken via the FISH (Fluorescence In Situ Hybridization) Test.

For ease of reference, research and potentially helpful therapy information has been subdivided into the sections listed below. All patients are encouraged to read the section entitled, *Research and Potential Therapies for All Categories of Breast Cancer* before proceeding to the next most applicable section for their cancer.

Research and Potential Therapies for All Categories of Breast Cancer

Research and Potential Therapies for Hormone Receptor Positive MBC

Research and Potential Therapies for HER2 Positive MBC

Research and Potential Therapies for HER2 Negative MBC (Including TNBC)

Research and Potential Therapies for Solely for TNBC

Research and Potential Therapies for Hormone Receptor Positive, HER2 Positive MBC

Research and Potential Therapies Solely for Patients with BRCA1 and/or BRCA2 Mutations

Research and Potential Therapies for Patients with Other Tumor Mutations and Biomarkers

Research and Potential Therapies for All Categories of Breast Cancer

Topics in this section include the following:

- **Antibiotics** (this is a hypothesis which warrants further study)
- **Aspirin (low-dose)**
- **Bezielle (BZL101)** *(Not Yet FDA-Approved for MBC Patients)*
- **Bisphosphonate Comparison of Zometa (Zoledronic Acid) vs. Xgeva (Denosumab)** *(Both FDA-approved)*
- **Curcumin**
- **Diet and Exercise**
- **Enzalutamide (Xtandi or MDV3100):** an Androgen Receptor Blocking Therapy *(Not Yet FDA-Approved for MBC Patients)*
- **Fasting During Chemotherapy**
- **FGFR1 and 11q Targeted Therapy (Lucitanib and Dovitinib)** *(Not Yet FDA-Approved for MBC Patients)*
- **Green Tea**
- **hTERT Immunotherapy Vaccine** *(Not Yet FDA-Approved for MBC Patients)*
- **Iscador (Mistletoe Extract)** *(Not Yet FDA-Approved for MBC Patients)*
- **Melatonin**
- **Metformin**
- **Metronomic Chemotherapy**
- **Reolysin (Pelareorep)** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Fast Track status)*
- **Saline-Based Adjuvant in Vaccines Increases Their Success**
- **Tetrathiomolybdate (TM), A Copper Reducing Drug** *(Not Yet FDA-Approved for MBC Patients)*
- **Vitamin D Levels and Survival**
- **Zytiga (Abiraterone Acetate)** an Androgen Receptor Blocking Therapy *(Not Yet FDA-Approved for MBC Patients)*

- **Antibiotics** (hypothesized): The concept behind using antibiotics in cancer therapy is that cellular mutations are thought to accumulate in tissue stem cells, which in may turn drive the formation of Cancer Stem Cells (CSCs). Based on this premise, a new study in Italy will target a common attribute of CSCs across multiple tumor types – namely mitochondrial biogenesis (replication) for the survival of CSCs.

  Because mitochondria evolved from bacteria, many FDA-approved antibiotics target mitochondria as a mild side-effect which is well-tolerated in most patients. In a preclinical study, it was found that 4-to-5 different classes of FDA-approved antibiotics which inhibit mitochondrial biogenesis could be used to eradicate CSCs in at least 12 different cancer cell lines across 8 different tumor types, including breast cancer. The antibiotic "Doxycycline" may be especially attractive as a new anti-cancer agent because it has a long half-life and has been used successfully for the long-term treatment of patients with various infections.

  Recent clinical trials with the antibiotics Doxycycline and Azithromycin show positive therapeutic effects in cancer patients, although their selective effects on eradicating cancer stem cells are not yet known. These trials were performed on advanced or treatment-resistant patients with B-cell lymphoma or lung cancer. In lung cancers, Azithromycin significantly increased 1-year patient survival from 45% to 75%, a 1.7-fold increase. And even lymphoma patients who were "bacteria-free" benefited from only a 3-week course of doxycycline therapy, and some showed complete remission of the disease. Future clinical trials for testing the efficacy of mitochondrially-targeted antibiotics in multiple cancer types are now clearly clinically warranted. **From the PDF version of [191, PMID:25625193]:** ***http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&op=view&page=article&path%5B%5D=3174***

- **Aspirin (low-dose):** According to a study reported in the July 2014 edition of the British Journal of Cancer, 4,627 women diagnosed with breast cancer were followed for an average of 5.7 years. 14.7% of these patients took aspirin regularly prior to diagnosis, and 22.4% took aspirin following their diagnosis, for an average of 2.4 years. Patients who used aspirin after diagnosis tended to be older, have fewer metastasis, and smaller tumors. They were less likely to have been treated with chemotherapy, radiation or surgery, and were more likely to have used endocrine (hormonal) therapy. The study concluded that taking aspirin after a breast cancer diagnosis reduced the risk of all-cause mortality by 47% and specifically reduced the risk of dying from

breast-cancer by 58%. Conversely taking aspirin before diagnosis increased overall mortality risk by 62% and doubled the risk of dying from breast cancer after contracting the disease.

One potential explanation for how aspirin may help reduce cancer mortality was undertaken by researchers who made a biological breakthrough to help explain how lymphatic vessels – key to the transmission of tumors throughout the body – respond to cancer. Molecules like the aspirin could effectively work by reducing the dilation of these major vessels and reduce the capacity of tumors to spread to distant sites. By studying the lymphatic vessels, the researchers found that a particular gene changed its expression in cancers which spread, but not in cancers which didn't spread. (The gene is a link between a tumor's growth and a cellular pathway that can cause inflammation and vessel dilation). Once these lymphatic vessels widen, they can act as "supply lines" to tumors as their conduits. But aspirin acts to shut down the dilation of the vessels.
From[192, PMID:24945997; 193, PMID:22340592]: ***https://medivizor.com/view_article/112440?utm_campaign=website&utm_source=sendgrid.com&utm_medium=email*** and ***http://www.nydailynews.com/life-style/health/aspirin-found-stop-spread-cancer-article-1.1023017***

Note 1: The study did not state the dosage taken by those who were using aspirin before cancer diagnosis. Based upon a Medivizor follow up comment, 99% of the post-diagnosis aspirin prescriptions were for 75 mg dosage.

Note 2: Before adding aspirin or any other supplement to their cancer regimens, patients should first consult with their doctor because aspirins may thin the blood, which can be harmful to some patients.

- **Bezielle (BZL101)** *(Not Yet FDA-Approved for MBC Patients)* by Bionovo, Inc. is an oral drug designed for the treatment of advanced breast cancer that targets diseased cells while leaving normal cells intact. Some research indicates that normal cells depend primarily on the citric acid cycle (>85%) and very little on glycolysis (<7%) for energy production, whereas cancer cells depend largely on glycolysis (>85%) for energy production. Bezielle induces greater production of reactive oxygen species in cancer cells. This results in high levels of DNA damage and the hyperactivation of PARP. Of the evaluable sixteen MBC patients in an early study, five (31%) were stable on Bezielle for greater than 90 days, and two (13%) were stable on Bezielle for greater than 180 days. Three patients (19%) on Bezielle had objective tumor regression. Four patients discontinued from the study with stable disease. A patient who discontinued Bezielle treatment with stable disease continues to be stable for 832 days and has not started any new anticancer treatment. **From[194, PMID:17111207]:** ***http://www.medicalnewstoday.com/releases/159803.php*** and ***http://www.drugs.com/clinical_trials/bionovo-presents-positive-results-phase-1b-trial-bezielle-metastatic-breast-cancer-7867.html***

  As of August 2018, the author was unable to locate any active recruiting clinical trials in the US for BZL101 and suggests that interested readers contact Bionovo, the drug's manufacturer, for more information.

- **Bisphosphonate Comparison of Zometa (Zoledronic Acid) vs. Xgeva (Denosumab):** In a Phase 3 study of MBC patients with bone metastasis, Xgeva was shown to be superior to Zometa in preventing Skeletal Related Events (SREs) such as fractures or the need for radiotherapy. Xgeva prolonged the time to first radiation to bone by 26%, and also prolonged the time to first SRE, or hypercalcemia of malignancy, by 18%. Furthermore, 10% or more patients had a clinically meaningful improvement in Health-Related Quality of Life with Xgeva as compared to Zometa. **From[195, PMID:22893628]:** ***http://clincancerres.aacrjournals.org/content/early/2012/08/01/1078-0432.CCR-11-3310.abstract***

- **Curcumin:** This in is a naturally occurring chemical compound that is found in the turmeric spice. Curcumin and turmeric are sometimes used interchangeably, but the technical difference between the two is that turmeric is the yellowish powder used to flavor foods, while curcumin is a chemical contained within turmeric. Curcumin inhibits metastasis to the lungs of mice with breast cancer, report researchers at The University of Texas MD Anderson Cancer Center. The study reports that curcumin appears to shut down a protein active in the spread of breast cancer to a major target for metastasis. Though the study results are early, researchers found that the nontoxic natural substance not only repelled progression of the disease to the lungs, but also appeared to reverse the effects of Taxol that may trigger spread of the disease with use over a long period of time.

One interesting laboratory study on cell lines indicates that curcumin may act in a similar manner to a class of drugs known as mTOR (mammalian target of rapamycin) inhibitors, which blocks a type of protein that helps all cells – both healthy and cancerous – get the energy they need. When these proteins don't act normally, they can help certain breast cancers grow. mTOR inhibitors help to block specific proteins, resulting in cell death. Afinitor (Everolimus) is an mTOR inhibitor, and this study implies that curcumin may work in a somewhat similar manner. **From[196, PMID:19176385]:** ***http://www.ncbi.nlm.nih.gov/pubmed/19176385***

Curcumin may also help to suppress an unwanted result of taking Taxol. Because Taxol is so toxic, it activates a protein that produces an inflammatory response that induces metastasis. Curcumin appears to suppress this response, making it less possible for the cancer to spread. In fact, researchers found that adding curcumin to Taxol actually enhances its effect. Curcumin appears to break down the dose, making the therapy less toxic and just as powerful while delivering the same level of efficacy. **From[197, PMID:PMC5386596]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5386596/***

Warning: Patients undergoing Doxorubicin (Adriamycin) or Cyclophosphamide (Cytoxan) chemotherapy should refrain from taking curcumin while on this therapy, since it can interfere with the effectiveness of these drugs. **From[198, PMID:12097302]:** ***http://www.ncbi.nlm.nih.gov/pubmed/12097302***

- **Diet and Exercise:** Breast cancer survivors who eat a healthy diet and exercise moderately can reduce their risk of dying from breast cancer by half (50%), regardless of their weight, suggests a new longitudinal study from the Moores Cancer Center at the University of California. Previous studies have looked at the impact of diet or physical activity on breast cancer survival, with mixed results. This study, published in the *Journal of Clinical Oncology*, is the first to look at a combination of both diet and exercise in breast cancer. The study looked at 1,490 women with early stage breast cancer (not MBC) who had completed their primary therapy prior to enrollment and were then followed for between five and 11 years. Women who were both physically active and had a healthy diet were much more likely to survive through the follow-up period than the rest of the study group. The mortality rate was 7%, approximately half of that seen for the rest of the study population.
  The study concluded that even if a woman is overweight, if she eats at least five servings of vegetables and fruits a day and walks briskly for 30 minutes, six days a week, her risk of death from her disease is reduced by 50%, provided the patient follows both the diet and exercise programs. Although the study was done on early stage breast cancer (not MBC) patients, it may still be noteworthy for those with MBC. **From[86, PMID:17557947]:** ***http://health.ucsd.edu/news/2007/Pages/6-8-breastcancer-obesity.aspx***

- **Enzalutamide (Xtandi or MDV3100), an Androgen Receptor (AR) Blocker** *(Not Yet FDA-Approved for MBC Patients):* Just as a large amount of breast cancers are ER positive, a majority of breast cancers are Androgen Receptor (AR) positive. In a study of 2,171 invasive breast cancers 77% overall were positive for AR by immunohistochemistry. **Among breast cancer subtypes, 88% of ER+, 59% of HER2+, and 32% of TNBC were positive for AR expression** by immunohistochemistry. Similar to ER and PR, AR expression is associated with a well-differentiated state and with more indolent breast cancers. **From [199, PMID:24451109]:** ***http://breast-cancer-research.com/content/16/1/R7***

  Therefore, it may make sense to therapeutically target Androgen Receptors in AR+ MBC in a similar manner as ER receptors are targeted in breast cancer. One AR blocking drug is Enzalutamide, and as of August 2018, there are actively recruiting Enzalutamide clinical trials.

- **Fasting During Chemotherapy:** A study on mice found that fasting prior to chemotherapy often led to more tumor shrinkage than chemotherapy alone. And in some cases, the combination apparently eliminated certain kinds of cancer. The researchers hypothesized that this fasting–chemo combo might possibly promote the survival of advanced stage cancer patients by both retarding tumor progression and reducing side effects.
  Mice that had metastasized cancer and were put on the fasting-chemo plan showed a 40% greater reduction in their metastasis than those that had been fed before receiving chemotherapy. They also seemed to live longer after getting this treatment. Fasting

appeared to protect normal cells from chemotherapy's toxic effects by rerouting energy from growing and reproducing to internal maintenance. But cancer cells do not undergo this switch to self-repair and appear to remain susceptible to drug-induced damage.

The problem is that fasting for two to three days in mice would be the equivalent of fasting for four to five days in humans, which could have multiple impacts upon the body. The other concern is that people with cancer—and especially those already undergoing treatment—have often already lost a substantial amount of weight. Therefore, prescribing days without food could be dangerous. It was concluded that fasting should not be something patients attempt independently. So, although this is an interesting approach, it remains controversial. **From [200, PMID:22323820]:** ***http://www.scientificamerican.com/article/fasting-might-boost-chemo/***

- **FGFR1 and 11q Targeted Therapy** *(Not Yet FDA-Approved for MBC Patients):* Similar to the HER2 protein, Fibroblast Growth Factor Receptor 1 (FGFR1) is a protein that sits on the surface of cells. On breast and other cancer cells, the FGFR1 protein receives signals that can encourage the cancer cells to grow and spread. Currently doctors don't routinely test to see if a breast cancer is FGFR1-positive or FGFR1-negative. Breast cancers that are FGFR1-positive tend to be more resistant to treatments, including hormonal therapy if the cancer also is hormone-receptor-positive.
  11q Amplification: Some breast cancers have amplification of the chromosome region 11q amplicon (a piece of DNA or RNA that is the source and/or product of natural or artificial amplification or replication events). 11q contains genes that code for FGF3, FGF4, and FGF19 proteins. These genetic amplification events have been associated with resistance to targeted and endocrine therapies.

  FGFR1 and/or 11q amplification have been found in all subtypes of MBC: 23% of ER+, 27% of HER2+, and 7% of TNBC contain these amplifications.

  As of August 2018, there is one recruiting clinical trial (NCT03238196) for MBC patients whose MBC is hormone receptor positive, HER2 negative, and FGFR amplified. The experimental drug is called Erdafitinib, which is an orally bioavailable, pan fibroblast growth factor receptor (FGFR) inhibitor with potential antineoplastic activity. Upon oral administration, Erdafitinib binds to and inhibits FGFR.

- **Green Tea:** Green tea may possess attributes that could be helpful in both ER positive and ER negative breast cancers, as well as in HER2 positive breast cancer. According to an article in the Oct. 2014 "Pharmacology" Journal, green tea has been found to block certain steps in carcinogenesis (cancer formation) and induce apoptosis (cell death) in cancer cells. These abilities are attributed, at least in part, to EGCG (EpiGalloCatechin Gallate) which are catechins (anti-oxidants) that are found in green tea.

  The article cites green tea's applications to the following:

  HER2 positive breast cancer: Green tea may inhibit HER-2/neu signaling in breast cancer cells.

  ER negative breast cancer Re-sensitization to Estrogen: One study observed that the treatment of ER negative breast cancer cells with green tea micronutrients led to the reactivation of ER-alpha expression.

  Synergy with Selective Estrogen Receptor Modulators (SERMS): Another review suggests that green tea catechins exhibit a synergistic interaction with SERMS such as Tamoxifen in the treatment of ER-positive and ER-negative breast cancers.

  Overcoming Tamoxifen/SERM Resistance: Even in cases of Tamoxifen resistant breast cancer, administering green tea catechins with Tamoxifen have been reported to reverse Tamoxifen resistance.

  Mitigating Resistance to Chemotherapy: Finally, it has been shown that green tea micronutrients may be helpful in reducing resistance to chemotherapy.

(As an aside, there has been no evidence of interaction between green tea catechins and Aromatase Inhibitors). **From[201, PMID:25471334]:** ***https://www.ncbi.nlm.nih.gov/pubmed/25471334***

- **hTERT Immunotherapy Vaccine by Inovio Pharmaceuticals** *(Not Yet FDA-Approved for MBC Patients):* An unusual enzyme called "telomerase" acts on parts of chromosomes known as telomeres. Telomeres, which are lengths of DNA at the the end of a chromosome, are specialized structures that are involved in cell replication and stability. The telomerase enzyme has recently been found in many human tumors, and the presence of telomerase in various human cancers (and its absence in many normal cells) implies that the enzyme might be a good target for anticancer drugs. In theory, a lack of telomerase may slow the growth of tumors by causing continually dividing cells to lose their telomeres and to die before they did much damage. A cancer vaccine - directed against human telomerase reverse transcriptase (hTERT) - may elicit a cytotoxic T cell response against telomerase-expressing tumor cells, which may result in tumor cell death as described below.

  A University of Pennsylvania study used hTERT to vaccinate 19 women with MBC. At the start of the study, the women had no measurable T-cell response to hTERT. After up to eight vaccinations with the hTERT peptide, however, 13 of the 19 women made T-cells that reacted to the peptide, and those responded lived significantly longer. People who responded lived 32 months versus a median of 17 (for those who did not respond). Three of the women who were responders have lived more than three years. (As of August 2018, the author was unable to locate a recruiting hTERT clinical trial for MBC patients). **From:** ***http://www.cancer.gov/drugdictionary?cdrid=615723*** and ***http://health.usnews.com/health-news/family-health/articles/2008/06/26/breast-cancer-vaccines-look-promising*** and ***http://www.scientificamerican.com/article/telomeres-telomerase-and/***

- **Iscador (Mistletoe Extract)** *(Not Yet FDA-Approved for MBC Patients):* Iscador is a nontoxic therapy widely used in Europe that is made from the lacto-fermented extract of fresh sap of the plant known as mistletoe. It must be prescribed by a doctor and is injected just under the skin according to a specific schedule. Although Iscador has been used as a cancer therapy for many years, there are not many robust studies about it. The good news is that this is beginning to change. One study that appears credible involves 1,442 non-metastatic breast cancer patients (710 tests and 732 controls) who were analyzed regarding efficacy and safety. At baseline, the test group (the one that took Iscador) had a more advanced disease and worse prognostic factors profile. After a median duration of 52 months on mistletoe therapy, significantly fewer test group patients (16.2%) than control patients (54.0%) developed Adverse Drug Reactions (ADRs) attributed to their conventional therapy. In the test group, the majority of the symptoms disappeared more frequently, and overall mortality hazard was significantly lower than in the control group. **From[202, PMID:15353899]:** ***http://www.ncbi.nlm.nih.gov/pubmed/15353899?dopt=Abstract*** Additional Iscador study information can be found at: ***https://www.cancer.gov/about-cancer/treatment/cam/hp/mistletoe-pdq***

  Note: Once prescribed, Iscador may be difficult to procure. One reputable source is H & F Apothecary, Ltd., Chestnut Ridge, NY. Telephone: 1.845.352.6165

- **Melatonin:** Melatonin is a hormone produced in the brain by the pineal gland from the amino acid tryptophan. The pineal gland's production and release of melatonin is stimulated by (and remain high in) darkness and decreased by light. There has been research on melatonin and breast cancer models, and several potential mechanisms have been suggested such as melatonin acting as an anti-estrogen and possibly down-regulating the expression of estrogen receptors. Furthermore, several clinical trials have suggested the potential of melatonin in the management of breast cancer. (Note that in some patients, melatonin has been known to cause stomach issues and/or diarrhea).

  In a study of 150 "solid tumor" patients (including breast cancer patients), the 1-year survival rate and the objective tumor regression rate were significantly higher in patients concomitantly treated with melatonin and chemotherapy than in those who received chemotherapy alone. In addition, the simultaneous administration of melatonin was found to significantly reduce the frequency of low platelet counts, neurotoxicity, heart damage, sores, and fatigue. Therefore, this study suggested that melatonin may enhance the efficacy of chemotherapy and reduce its toxicity, at least in advanced cancer patients of poor clinical status. The

positive cancer prevention capabilities of melatonin are believed to be at their strongest when taken at night. Thus, it may be beneficial for chemotherapeutic drugs to be given at night along with melatonin, thereby maximizing the effect of both types of drugs. **From [203, PMID:10674014]:** ***http://www.ncbi.nlm.nih.gov/pubmed/10674014***

In another study, 14 MBC ER+ patients who were unresponsive to Tamoxifen alone were given 20 mg melatonin daily in the evening along with Tamoxifen. A response was achieved in 28% of these patients. **From[204, PMID:PMC2033724]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2033724/***

- **Metformin:** The diabetes drug Metformin belongs to a class of drugs known as Biguanides. These drugs work by preventing the production of glucose in the liver, improving the body's sensitivity towards insulin and reducing the amount of sugar absorbed by the intestines. Recently, metformin has emerged as a potential anticancer agent. Epidemiological, preclinical, and clinical evidence supports the use of metformin as a cancer therapy. The ability of metformin to lower circulating insulin may be particularly important for the treatment of cancers that are associated with higher-than-normal insulin, such as those of the breast and colon. Moreover, metformin may exhibit direct inhibitory effects on cancer cells by inhibiting mammalian target of rapamycin (mTOR) signalling and protein synthesis. **From[205, PMID:21470407]:** ***http://www.biomedcentral.com/1741-7015/9/33***

  In a human study that analyzed the effect of metformin on survival rates for breast cancer patients, researchers examined clinical outcomes for 1,215 patients who were diagnosed and underwent surgical treatment for breast cancer between 1997 and 2013. Ninety-seven patients reported using metformin before their diagnosis, and 97 reported use of the drug after diagnosis. Results of the study showed that the patients who used metformin before being diagnosed with breast cancer were more than twice as likely to die as patients who never used the drug, while patients who began using metformin after their cancer diagnosis were almost 50% more likely to survive than non-users. This analysis concludes that use and efficacy of Metformin is time-dependent (i.e. whether it is taken before vs. after diagnosis). **From[206]:** ***http://medicalxpress.com/news/2016-06-diabetes-drug-metformin-cancer-treatment.html***

- **Metronomic Chemotherapy:** This refers to low-dose chemotherapy that is continually administered on a daily schedule (known as "metronomic" because it is regular like the beat of a metronome). The theory behind Metronomic Chemotherapy is that it promotes the continual death of endothelial cells that are attempting to form new blood vessels (blood vessels are required for tumors to survive). This may be referred to as "disrupting the angiogenesis process." Pre-clinical and clinical evidence supports metronomic chemotherapy as an efficient tool to fight certain types of cancer. However, the development of metronomic chemotherapy faces terra incognita. It seems very unlikely that a single metronomic regimen will have universal efficacy and the optimal combination regimens of metronomic chemotherapy remain to be determined for any given tumor type. Future preclinical and clinical studies will need to define the best agents to use according to tumor type, the number of agents to be incorporated, the doses of each agent to be used alone or in combination, and the timing of drug administration. Treatment duration and the best way to cease therapy also need to be optimized. **From:** ***https://www.medscape.com/viewarticle/726912_10***
  One study focused on Time To Treatment Failure (TTF) as a parameter that predicts patient survival. The study retrospectively compared clinical outcomes of patients with MBC who showed TTF of 12 months or more (26 patients) and less than 12 months (29 patients). Of note, the proportion of patients who received metronomic regimens was significantly higher in patients with TTF greater than 12 months compared to those with TTF less than12 months. Median TTP and Overall Survival were significantly longer in the metronomic compared to the non-metronomic group (TTP was 30 vs. 4 months; OS was 68 vs. 28 months). The results suggested that metronomic chemotherapy is useful for palliative care and also improved clinical outcomes as a regimen for which long-term administration may be expected. **From [207, PMID:24649151]:** ***http://www.pubfacts.com/detail/24649151/Metronomic-chemotherapy-for-metastatic-breast-cancer-to-prolong-time-to-treatment-failure-to-12-mont***

- **Reolysin (Pelareorep)** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Fast Track status):* A combination of the immunotherapy drug called Reolysin (Pelareorep) and the chemotherapy Taxol (paclitaxel) increased the overall survival rate of patients with advanced or metastatic breast cancer by 67%, compared with Taxol alone, according to a Phase 2 clinical trial. The median survival rate of the breast cancer patients was 17.4 months with combo therapy, versus 10.4 months with Taxol by

itself, the study showed. In May 2017, Reolysin was conferred *Fast Track* designation for MBC by the FDA. *Fast Track* is a process designed to facilitate the development and review of drugs to treat serious conditions and fill an unmet medical need. Its overall purpose is to get important new drugs to the patient earlier. **From:** ***https://immuno-oncologynews.com/2017/04/17/reolysin-combo-therapy-significantly-increases-breast-cancer-survival-rate/***

- **Saline-Based Adjuvant (Solution) in Vaccines Increases Their Success** as per MD Anderson: A common substance used in many cancer vaccines to boost immune attack betrays the cause by facilitating a buildup of T cells at the vaccination site, which then summon more T cells to help with the perceived threat. Researchers found that only a few T-Cells get to the tumor while many more are stuck at - or double back to - the vaccination site. The team found that a major culprit in this failure is incomplete Freund's adjuvant (IFA), which is a mineral oil-based adjuvant included in many vaccines to stoke the immune response. Switching to a saline-based adjuvant in a melanoma vaccine reversed the T cell effect in mice. When scientists tested a vaccine based on a saline solution instead of IFA, they found that antigens cleared more quickly but did not spark the desired T cell response. A combination of three stimulatory molecules (Covax) was added to the saline/peptide vaccine, which produced a strong T cell response.

  A comparison of saline/peptide/covax vs. IFA/peptide/Covax showed the saline version caused T cells to successfully target the tumors and destroy them, whereas the IFA version focused T cells at the vaccination site, killing normal tissue and inducing chemokines that killed T cells**. From [208, PMID:23455713]:** ***http://www.mdanderson.org/newsroom/news-releases/2013/cancer-vaccines-channel-immune-attack-to-injection-site.html***

- **Tetrathiomolybdate (TM), a Copper Reducing Drug***(Not Yet FDA-Approved for MBC Patients):* In a study of 29 patients with either stage 3 or stage 4 breast cancer who were NED (No Evidence of Disease) and who took the copper-reducing drug tetrathiomolybdate (TM), the progression-free survival rate has been 85% to date. Additionally, in a very small study of 11 women with TNBC MBC (which is the most difficult MBC to treat), only two of 11 study participants relapsed within 10 months after using the anti-copper drug. According to the researchers, copper is essential to the metastatic process. Copper is a key component of enzymes that help turn on angiogenesis (the formation of new blood vessels, which is essential for tumors to grow) in the tumor microenvironment. Copper also appears to play a role in directing cancer cell migration and invasion. TM is a copper chelation compound (chelation involves the removal of heavy metals) that has been used to treat Wilson's disease, a hereditary copper metabolism disorder. **From[209, PMID:23406736]:** ***https://news.weill.cornell.edu/news/2013/02/copper-depletion-therapy-keeps-high-risk-triple-negative-breast-cancer-at-bay***

  Note: In a small Phase 1 study of 18 metastatic patients (but not necessarily MBC – there were several cancer types) on this therapy. Fourteen patients achieved the target copper deficiency before disease progression or other disease complications. Of these, eight patients either progressed within 30 days of achieving copper deficiency or have had stable disease for <90 days. It is unlikely that most of these tumors experienced an antiangiogenic environment long enough to evaluate clinical response to this type of therapy. In all patients removed from the protocol, much more rapid rates of progression of disease were noted clinically after discontinuation of TM therapy. (So, this is a caution regarding potential rebounding effects after TM discontinuation). **From[210, PMID:10656425]:** ***http://clincancerres.aacrjournals.org/content/6/1/1.full***

- **Vitamin D, 25-Hydroxy:** New research suggests that breast cancer patients with high levels of Vitamin D in their blood are twice as likely to survive the disease as patients with low levels. The study included a total of 4,443 patients with breast cancer, all of whom were followed for an average of 9 years. Patients were divided into groups dependent on the levels of 25-hydroxyvitamin D in their blood. Women in the "high" group had an average of 30 nanograms per milliliter (ng/ml) of 25-hydroxyvitamin D in their blood, while women in the "low" group had an average of 17 ng/ml in their blood.

  The team found that women who had high levels of 25-hydroxyvitamin D in their blood had a 50% lower fatality rate, compared with women who had low levels of 25-hydroxyvitamin D in their blood. The theory behind Vitamin D's success against breast

cancer is that Vitamin D metabolites increase communication between cells by activating a protein that halts aggressive cell division. As long as vitamin D receptors are present, tumor growth is prevented and kept from expanding its blood supply. And the good news is that Vitamin D receptors are not lost until a tumor is very advanced. **From [211, PMID:24922127]: *http://www.medicalnewstoday.com/articles/273728.php***

Researchers found that about three-quarters of estrogen-dependent tumors and two-thirds of estrogen-independent tumors expressed hormone receptors for vitamin D and testosterone (androgen). They revealed that treatment of breast cancer cells with hormones that activate vitamin D and testosterone receptors reduced the growth of cancer cells. In addition, these hormones increased the efficacy of standard chemotherapy. **From [212, PMID:24463450]: *http://med.miami.edu/news/researchers-discover-new-hormone-receptors-to-target-when-treating-breast-c***

- **Zytiga (Abiraterone Acetate) an Androgen Receptor Blocking Therapy***(Not Yet FDA-Approved for MBC Patients):* Just as a large amount of breast cancers are ER positive, a majority of breast cancers are Androgen Receptor (AR) positive. In a study of 2,171 invasive breast cancers, 77% overall were positive for AR by immunohistochemistry. Among breast cancer subtypes, 88% of ER+, 59% of HER2+, and 32% of TNBC were positive for AR expression by immunohistochemistry. Zytiga works by interrupting the androgen-making process at three sources: the testes (in men), the adrenal glands, and the tumor itself. In a Phase 1 clinical trial of Zytiga, 6 MBC patients had been heavily pretreated with chemotherapy and hormonal therapy, so any response would be deemed remarkable. Of these patients, there was one response to Zytiga with an Overall Survival of 14 months. This is an important result and shows that Zytiga can continue to work when other therapies such as chemotherapy have failed. As of August 2018, there are several clinical trials underway for AR+ MBC patients. **From[213, PMID:21552212]: *http://abiraterone.blogspot.com/2012/09/advanced-breast-cancer-responds-to.html***

Research and Potential Therapies for Hormone Receptor Positive MBC

Topics in this section include the following:

- **Alisertib (MLN8237)** *(Not Yet FDA-Approved for MBC Patients)*
- **Arimidex and Faslodex** *(This Combination is Not Yet FDA-Approved for MBC Patients)*
- **Bazedoxifene,** a European anti-osteoporosis drug *(Not Yet FDA-Approved for MBC Patients)*
- **Bortezomib (Velcade)** *(Not Yet FDA-Approved for MBC Patients)* **and Fulvestrant (Faslodex)** for MBC That's Resistant to AIs
- **Buparlisib (BKM120) and Fulvestrant**
- **CDK4/CDK6 Inhibitors** *(The following three CDK4/6 inhibitors have been FDA-approved for MBC patients):*
  - *Ibrance(Palbociclib*
  - *Kisqali (Ribociclib)*
  - *Verzenio (Abemaciclib)*
- **Endoxifen (or Z-Endoxifen) for ER+ MBC**, Including Hormone Therapy Resistant Breast Cancer *(Not Yet FDA-Approved for MBC Patients)*
- **Entinostat (SNDX-275 or MS-275)** for Hormone Therapy Resistant Breast Cancer *(Not Yet FDA-Approved for MBC Patients, but which has been accorded Breakthrough Therapy status)*
- **GTX-024 (Enobosarm)** *(Not Yet FDA-Approved for MBC Patients)*
- **HER2 Targeted Therapy for HER2 Negative Patients** *(Not Yet FDA-Approved for MBC Patients)*
- **HydroxyChloroQuine** for Resistance to Tamoxifen and Faslodex *(Not Yet FDA-Approved for MBC Patients)*
- **Mammaglobin-A Vaccine Clinical Trial** *(Not Yet FDA-Approved for MBC Patients)*
- **Pictilisib (GDC-0941),** a PI3K Inhibitor *(Not Yet FDA-Approved for MBC Patients)*
- **RAD1901 (Elacestrant)** *(Not Yet FDA-Approved for MBC Patients, but has received Fast Track Designation)*

- **Re-Trying Hormonal Therapies**
- **Resveratrol**
- **SERCAs (Selective Estrogen Receptor Covalent Antagonists)** *(Not Yet FDA-Approved for MBC Patients)*
- **Tamoxifen Resistance and Fareston**
- **Testosterone Propionate Study**
- **Venetoclax (ABT-199)** *(Not Yet FDA-Approved for MBC Patients)*

- **Alisertib (MLN0237)** *(Not Yet FDA-Approved for MBC Patients):* This is an oral drug under investigation for its potential to overcome endocrine therapy resistance in advanced breast cancer patients. In a study of 45 response-evaluable patients, 6 (13%) had a Partial Response and 26 (58%) had stable disease. Median duration of stable disease was 68 days, of which 2 patients (4%) had stable disease longer than 6 months. **From [214]: *http://cancerres.aacrjournals.org/content/72/24_Supplement/P6-10-02.short***

- **Arimidex and Faslodex** (*This combination is not Yet FDA-Approved for MBC Patients):* In a study presented at 2017 SABCS, it was reported that for hormone receptor positive, HER2 negative MBC patients on the combination arm, there was a median Overall Survival (OS) of 49.8 months, which is the longest ever reported for this type of patient. The combination appeared to be of special benefit to patients with no prior endocrine therapy, and/or who recurred after 10 years following a diagnosis of early stage disease. However, as of August 2018, the author was unable to locate a recruiting study for this combination.

- **Bazedoxifene, a European anti-osteoporosis drug** *(Not Yet FDA-Approved for MBC Patients):* For readers in Europe, a drug called Bazedoxifene, which is approved in Europe to treat osteoporosis, has been shown to stop the growth of breast cancer cells - even in cancers that have become resistant to current targeted therapies. A Duke Cancer Institute study indicates that Bazedoxifene packs a powerful tow-way punch that not only prevents estrogen from fueling breast cancer cell growth, but also flags the estrogen receptor for destruction. Researchers found that Bazedoxifene binds to the estrogen receptor and interferes with its activity, but the surprising thing was that it also "degrades" the estrogen receptor (gets rid of it). In animal and cell culture studies, the drug inhibited growth both in estrogen-dependent breast cancer cells and in cells that had developed resistance to Tamoxifen and/or to Aromatase Inhibitors. As of August 2018, this drug is not available for MBC use (even in clinical trials) in the USA. **From [215, PMID:23536434]: *http://www.sciencedaily.com/releases/2013/06/130615152341.htm***

- **Bortezomib (Velcade)** *(Not Yet FDA-Approved for MBC Patients)* **and Fulvestrant (Faslodex) for MBC that is Resistant to AIs:** A new combination of cancer drugs delayed disease progression for patients with hormone-receptor-positive MBC, according to a multi-center Phase 2 trial. The study enrolled 118 post-menopausal women with metastatic hormone-receptor-positive breast cancer whose cancer continued to progress after being treated with an Aromatase Inhibitor. The result was that the combination of the drugs Bortezomib and Faslodex — versus Faslodex alone — doubled the rate of survival at 12 months and doubled the number of patients whose cancer had not progressed after one year from 14% to 28%. Bortezomib is a "proteasome inhibitor" that prevents cancer cells from clearing toxic material. Faslodex causes clumping of the estrogen-receptor protein. When Bortezomib blocks the ability of the cell to clear these protein clumps, they grow larger and become toxic to the cancer cells. This, in turn, amplifies the effectiveness of Faslodex. The study results also suggest that the drug combination can delay or overcome resistance to Faslodex. **From [216, PMID:28721390]: *http://medicine.yale.edu/news/article.aspx?id=8462***

- **Buparlisib (BKM120)** ***(Not Yet FDA-Approved for MBC Patients)*** **and Faslodex (Fulvestrant):** Buparlisib is a PI3K inhibitor which may be effective in modestly delaying progression, especially in a subset of MBC patients in whom liquid biopsy identifies a PI3K mutation. In the Phase 3 BELLE-2 clinical trial, 1,147 women were randomly assigned to receive either a combination of Buparlisib and Faslodex or Faslodex plus placebo. The study showed a statistically significant 22% reduction in risk for progression with the addition of Buparlisib to Faslodex, yielding a small Progression Free Survival (PFS) of 6.9 months, versus

5 months in the Faslodex-only arm. But among 200 patients in whom the PI3KCA mutation was detected by liquid biopsy, there was a 44% reduction in the risk for progression for those treated with Buparlisib and Faslodex instead of Faslodex alone. Overall Survival (OS) figures from this study are not yet available. It should be noted that Buparlisib may cause substantial side effects such as elevated liver enzymes, nausea, diarrhea, and depression**. From[217, PMID:28576675]:** ***http://www.medscape.com/viewarticle/855908#vp_1***

- **CDK4/CDK6 Inhibitors (Ibrance, Kisqali, and Verzenio** *(FDA-Approved):* Cell growth and division in normal breast cells is normally tightly regulated. Some of the main proteins involved in cell regulation are the Cyclin D Kinase proteins (CDK) 4 and 6. These proteins interact with other proteins to instruct a cell when to grow and when not to grow. Researchers are evaluating investigational drugs that block CDK-4/6 function using the hypothesis that by inhibiting this function in cancer cells, they can restrict the cancer cells' growth.

  There are currently three CDK4/CDK6 inhibitor drugs available for ER Positive HER2 negative MBC:

  - *Ibrance (Palbociclib):* This oral drug has been FDA approved in conjunction with Letrozole, Arimidex, or Aromasin as first line treatment, or with Faslodex as second line treatment (as per the PALOMA-III clinical trial below) for postmenopausal MBC patients who are hormone receptor positive and HER2 negative. FDA approval of Ibrance in combination with Aromatase Inhibitors was based upon the PALOMA-II Trial, which as a randomized, placebo-controlled, Phase 3 trial consisting of 666 postmenopausal hormone receptor positive, HER2 negative MBC patients who had not received prior systemic therapy. Median Progression Free Survival (PFS) was 24.8 months for the Ibrance (Palbociclib) + letrozole group vs 14.5 months for the letrozole-only group. Common adverse events among patients taking Ibrance +letrozole were neutropenia – (low levels of neutrophils which are a type of white blood cell) (79.5%), fatigue (37.4%), nausea (35.1%), joint pain (33.3%), and hair thinning/loss (32.9%). Permanent discontinuation due to adverse effects was 9.7% among patients taking both Ibrance and Letrozole, vs. 5.9% among patients taking letrozole alone. (It has since been determined that patients taking Ibrance may also be at increased risk for blood clots). Subsequent information regarding Overall Survival (OS) showed a modest benefit for patients in the Ibrance plus Letrozole arm (37.5 months) vs. those taking Letrozole alone (34.5 months). **From[218, PMID:30515674]:** ***http://meetinglibrary.asco.org/content/165131-176*** and ***https://www.Ibrance.com/side-effects***

    A different clinical trial called PALOMA-III paired Ibrance with Faslodex (fulvestrant) instead of with Letrozole. In this larger study, 521 pre-/peri- and postmenopausal patients with hormone receptor positive and human epidermal growth factor receptor-negative (HR+/HER2-) advanced disease were enrolled. These women had typically already relapsed on hormone therapy and were not candidates for the HER2-blocking therapy Herceptin. The patients were randomized to treatment and control arms at a 2:1 ratio (with 345 treated and 172 receiving placebo). The treatment arm received Ibrance together with Faslodex, and the placebo arm received Faslodex plus placebo. The study was stopped after only 10 months because it met the primary endpoint of improving Progression-Free Survival (time to cancer relapse). Patients taking Ibrance plus Faslodex showed a median Progression-Free Survival of 9.2 months compared to 3.8 months on Faslodex with placebo. Progression of cancer occurred in only 25% the patients who took Ibrance plus Faslodex, vs. 50% of patients treated with Faslodex plus placebo. **From [22, PMID:26030518]:** ***https://www.targetedonc.com/news/os-endpoint-not-met-with-palbociclib-in-paloma3-breast-cancer-study*** and ***http://medicalxpress.com/news/2015-06-practice-changing-option-tough-breast-cancer.html***

    Furthermore, the above PALOMAIII study revealed that the combination of Ibrance and Faslodex resulted in a clinically meaningful improvement in Overall Survival (not just Progression Free Survival) among women with hormone receptor-positive, HER2-negative breast cancer whose disease relapsed or progressed on hormonal therapy. The Ibrance/Faslodex regimen extended median Overall Survival (OS) by an absolute difference of 6.9 months (34.9 months on the combination arm vs. 28 months on the Faslodex-only arm). Researchers observed even greater OS benefits among women with endocrine-sensitive disease (median, 39.7 months on the combination arm vs. 29.7 months on the Faslodex-only arm) and those with non-visceral disease (median, 46.9 months on the combination arm vs. 35.4 months on the Faslodex-only arm). **From:**

https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bcd3e8a02-e13e-4ad4-a2d2-1be2a182b4f7%7D/addition-of-palbociclib-to-fulvestrant-extends-os-among-certain-women-with-advanced-breast-cancer

- *Kisqali (Ribociclib):* This oral drug has been FDA approved in conjunction with Letrozole, Arimidex, Aromasin, or Faslodex as a first-line therapy for postmenopausal MBC patients who are hormone receptor positive and HER2 negative. It has also been approved for this population as second-line combination therapy with Faslodex after initial failure with endocrine therapy. Kisqali has also been approved in combination with an Aromatase Inhibitor (AI) such as Letrozole, Arimidex, or Aromasin, for premenopausal, hormone receptor positive, HER2 negative MBC patients.
  It should be noted that Kisqali is accompanied by warnings and precautions about QT interval prolongation (which can lead to a type of cardiac arrhythmia that is a risk factor for death) and hepatobiliary toxicity (having to do with the liver plus the gallbladder, bile ducts, or bile). **From:** ***http://www.medscape.com/viewarticle/877177***

  In the MONALEESA-3 Trial of 726 MBC patients, Kisqali in combination with fulvestrant (Faslodex) showed an improvement in PFS in postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer. The benefit was seen both in patients who had no prior treatment and in patients who had received 1 prior line of neoadjuvant therapy (in this context, neoadjuvant therapy refers to systemic treatment administered prior to breast surgery). PFS at the time of data cut-off was 20.5 months in patients randomized to Kisqali and Faslodex compared with 12.8 months in those randomized to Faslodex alone. **From[112, PMID:29860922]:** ***http://www.targetedonc.com/conference/asco-2018/both-frontlinesecondline-benefit-with-ribociclibfulvestrant-in-hrher2-breast-cancer-across-frontline-and-secondline***

  It is noteworthy that Kisqali plus endocrine therapy appears to be highly effective for MBC patients with HR+/HER2- visceral disease. Nearly 60% of patients enrolled in the MONALEESA trials had visceral metastases such as lung and/or liver, and all benefited from treatment with Kisqali in combination with endocrine therapy. In patients with visceral metastases, Kisqali plus endocrine therapy yielded a median PFS of 24.4 months compared with a median PFS of 11.9 months for patients with visceral disease on endocrine therapy alone. Furthermore, the ORR of patients with visceral disease on the combination therapy closely resembled the ORR of patients with bone-only disease who were on the combination. **From:** ***https://www.pharmacypracticenews.com/Clinical/Article/12-18/Kisqali-Improves-Outcomes-and-Survival-Rates-in-Women-With-Metastatic-Breast-Cancer-/53612***

  A poster presented at SABCS 2018 revealed that a study of patients experiencing adverse effects in the MONALEESA program of Kisqali indicated that dose reductions from the prescribed 600mg daily to 400mg daily and even 200mg daily did not compromise response to treatment, and most patients needed only one dose reduction to relieve their symptoms.

- *Verzenio (Abemaciclib):* This oral drug was FDA-approved for MBC patients in September 2017. It appears have strong single-agent activity, meaning that it may be used alone (as well as in combination with other drugs).

  One study of Verzenio included 47 patients with MBC who received a median of seven prior therapies. The majority had two or more metastatic sites and 74% had visceral (internal organ) metastasis. Among Hormone Receptor positive patients, 9 (25%) had confirmed partial responses and 20 (56%) had stable disease, including 2 with unconfirmed partial responses. The clinical benefit rate was 61%, and disease control rate was 81%.
  Even though Verzenio is highly effective when given alone, it has also been studied in combination with endocrine therapy. A Phase 1b trial of 73 patients evaluated the drug with a variety of endocrine agents and reported an impressive overall disease control rate of 67% among 36 patients treated with Verzenio and a nonsteroidal AI such as Letrozole or Arimidex, and when the drug was paired with Tamoxifen, the disease control rate was and 75% among 16 patients. Another double-blind, placebo-controlled, randomized Phase 3 trial of 493 postmenopausal patients with hormone receptor-positive, HER-2-negative MBC who had received no prior systemic treatment for advanced disease found that the combination of Verzenio

plus either Letrozole or Arimidex increased progression Free Survival (PFS) to 28.2 months in the combination arm vs. 14.8 months in the Letrozole-only or Arimidex-only arm. **From:** ***https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm598404.htm***

Data from the Phase 3 MONARCH 2 trial of HR+/HER2- MBC patients who progressed on prior endocrine therapy and were then treated with Verzenio and fulvestrant (Faslodex) indicate a 45% decreased risk for progression. In the trial, patients were randomly assigned in a 2:1 ratio to receive Verzenio + fulvestrant (446 patients) or placebo with fulvestrant (223 patients). Median progression-free survival (PFS) was 16.4 months for patients on Verzenio with fulvestrant and 9.3 months for those on placebo with fulvestrant. The median duration of response was not reached for patients on Verzenio with fulvestrant and was 25.6 months for those on placebo with fulvestrant. The Objective Response Rate (ORR) was 35.2% for the Verzenio combination vs 16.1% for patients on fulvestrant alone. **From[24, PMID:28580882]:** ***http://www.cancertherapyadvisor.com/asco-2017/abemaciclib-fulvestrant-breast-cancer-endocrine-effective treatment/article/666229/***

The combination of Verzenio and Keytruda (Pembrolizumab) showed preliminary signs of activity without additive toxicity in 28 HR+, HER2- patients who had ≥3 sites of metastatic disease and had received a median of 3 prior therapies for metastatic disease. At a 4-month analysis, the objective response rate (ORR) with the combination was 14.3%, which was less than the 19.7% response rate seen with single-agent Verzenio in the MONARCH-1 trial. However, the trial investigators noted **that *the median time to response for Verzenio has historically been 3.7 months***, suggesting the efficacy is likely to improve with longer follow-up. The rationale for this combination of drugs came from preclinical data showing that Verzenio may induce intra-tumor immune inflammation with synergy and enhanced efficacy seen when combined with PD-L1 blockade in the setting of anti–PD-L1 refractory disease. **From[23, PMID:28533223]:** ***http://www.onclive.com/web-exclusives/abemaciclib-pembrolizumab-shows-early-promise-for-hrher2-breast-cancer***

A unique characteristic of Verzenio is its ability to cross the blood-brain barrier, making it a potentially attractive treatment option for brain metastasis. **From:** ***http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.1019***

The most common side effects of Verzenio were diarrhea, fatigue, nausea, vomiting, leukopenia (low white blood cell count), and neutropenia (an abnormally low count of neutrophils, a type of white blood cell that helps fight off infections). Side effects were tolerable, and no patient discontinued study due to drug-related toxicity. **From[219; 220]:** ***http://www.ascopost.com/issues/may-1,-2014/ly2835219-shows-strong-single-agent-activity-in-preliminary-study-in-metastatic-breast-cancer.aspx***

- **Endoxifen (or Z-Endoxifen) for ER+ MBC, Including Hormonal Therapy Resistant Breast Cancer** *(Not Yet FDA-Approved for MBC Patients):* A Phase 1 trial of Endoxifen, an active metabolite of Tamoxifen, indicates that the experimental drug is safe, with early evidence for anti-tumor activity. The findings indicate that Z-endoxifen, co-developed by Mayo Clinic Cancer Center and the National Cancer Institute (NCI), may provide a new and better treatment for some women with ER+ breast cancer and, in particular, for those women who do not respond to Tamoxifen and Aromatase Inhibitors. There was up to 60-fold higher levels of Endoxifen compared to Endoxifen levels achieved with the standard dose of Tamoxifen, says Matthew Goetz, M.D., a Mayo Clinic oncologist. Additionally, there is evidence for tumor regression in patients who had failed standard hormonal therapies including Aromatase Inhibitors, Faslodex and Tamoxifen. This drug is also effective for patients with CYP2D6 metabolism issues who are not able to benefit from Tamoxifen. **From[221, PMID:PMC5648176]:** ***https://www.sciencedaily.com/releases/2013/12/131212185835.htm*** and ***https://www.sciencedaily.com/releases/2017/08/170830202125.htm***

- **Entinostat (SNDX-275 or MS-275)** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Breakthrough Therapy status):* This drug belongs to a class of drugs called HDAC (Histone DeACetylase) Inhibitors. Mutations of genes that encode HDACs have been linked to tumor development, and HDACs may be promising therapeutic targets for cancer treatment. The FDA has designated Entinostat as a "*Breakthrough Therapy*" for the treatment of locally recurrent or metastatic Estrogen Receptor (ER)-positive breast cancer when added to Aromasin in postmenopausal women whose disease has progressed following nonsteroidal Aromatase Inhibitor therapy. (*Breakthrough Therapy* Designation is a form of *Fast Track* Designation, which is meant to facilitate the development and review of new drugs intended to treat serious conditions). In an earlier Phase 2 study called ENCORE 301, (a randomized, placebo-controlled Phase 2 study of Aromasin with and without Entinostat) there was improvement in Overall Survival for patients treated with Aromasin plus Entinostat. At a median follow up of 25 months, treatment with the combination resulted in an 8.3-month improvement in Overall Survival, corresponding to a 41% reduction in the risk of dying. As of August 2018, there are several recruiting clinical trials for this drug. **From[222, PMID:27037751; 223, PMID:23650416]:** ***http://www.empr.com/phase-2-trial-update-of-entinostat-for-metastatic-breast-cancer/article/243134/*** and ***http://www.ascopost.com/ViewNews.aspx?nid=8525***

- **GTX-024 (Enobosarm)** *(Not Yet FDA-Approved for MBC Patients):* This anti-androgen drug was tested in a study of 22 heavily pretreated ER positive, Androgen Receptor (AR) positive MBC patients. On average, these patients had 4 prior hormonal therapies for the treatment of their breast cancer and 91% had also received prior chemotherapy. Nine of these patients achieved Clinical Benefit Response, which was defined as either a complete response (CR), partial response (PR) or stable disease (SD). **From:** ***https://www.businesswire.com/news/home/20161208005320/en/GTx-Reports-Results-Ongoing-Enobosarm-Phase-2***

- **HER2 Targeted Therapy for HER2 Negative Patients** *(Not Yet FDA-Approved for MBC Patients):* In a presentation at the 2015 San Antonio Breast Cancer Symposium, the results of a German study providing HER2 therapy to HER2 negative MBC patients were discussed. In this study, 25 heavily pretreated HER2 negative MBC patients who had failed anywhere from 2 to 16 prior therapies received Herceptin plus Lapatinib or Herceptin plus Pertuzumab. HER2-targeting therapy was given either alone or with endocrine therapy, chemotherapy, or targeted drugs. 10 patients had a Partial Response and another 10 patients had Stable Disease, with Median Overall Survival of 63 weeks. **From[224]:** ***http://annonc.oxfordjournals.org/content/26/suppl_3/iii8.2.full.pdf+html***

- **HydroxyChloroQuine (HCQ) for Resistance to Tamoxifen and Faslodex** *(Combination is Not Yet FDA-Approved***:** HCQ may reverse resistance to Tamoxifen and possibly Faslodex, according to one study in mice. In the journal Clinical Cancer Research, investigators felt that adding HCQ to Tamoxifen could provide a new treatment option for some women with advanced, postmenopausal (ER+) breast cancer. While many of these women are treated with Tamoxifen, which blocks estrogen from fueling the tumor, 50% of these cancers will either not respond or will become resistant to Tamoxifen over time. HCQ was developed to treat malaria, and is now being used to treat rheumatoid arthritis and lupus. This study was the first to test HCQ's ability to restore breast cancer cell sensitivity to Tamoxifen or to Faslodex. Previous research found that Tamoxifen resistance occurs because a pro-survival pathway is switched on in breast cancer cells. HCQ functions by turning off that very same molecular pathway, according to researchers. It was found that the combination of Tamoxifen and HCQ was more effective than Faslodex and HCQ due to activities within the tumor's microenvironment. (As of August 2018, there is no recruiting clinical trial underway for this drug for MBC patients.) **From[225, PMID:24928945]:** ***http://gumc.georgetown.edu/news/Tamoxifen-Resistant-Breast-Cancer-Reversed-When-Drug-Paired-with-Anti-malaria-Agent***

- **Mammaglobin-A Vaccine Clinical Trial** *(Not Yet FDA-Approved for MBC Patients):* This vaccine primes a type of white blood cell to seek out and destroy cells with the mammaglobin-A protein. In the smaller proportion of breast cancer patients whose tumors do not produce mammaglobin-A, this vaccine would not be effective. In a new study, 14 patients with MBC that expressed mammaglobin-A were vaccinated. Patients experienced few side effects including rash, tenderness at the

vaccination site and mild flu-like symptoms. Although the trial was designed to test vaccine safety, preliminary evidence indicated the vaccine slowed the cancer's progression, even in patients who tended to have weaker immune systems because of their advanced disease and exposure to chemotherapy. Of the 14 patients who received the vaccine, about 50% showed no progression of their cancer one year after receiving the vaccine. Unfortunately for those with metastatic disease, the researchers plan further studies solely on early stage breast cancer patients. **From[226, PMID:25451106]: *https://source.wustl.edu/2014/12/breast-cancer-vaccine-shows-promise-in-small-clinical-trial/***

- **Pictilisib (GDC-0941), a PI3K Inhibitor Plus Faslodex** *(Not Yet FDA-Approved for MBC Patients):* Data from the Phase 2 FERGI trial presented at the 2014 San Antonio Breast Cancer Symposium showed no improvement overall from using a Pictilisib/Faslodex combination to treat women with Aromatase Inhibitor (AI)-resistant advanced hormone receptor-positive breast cancers ***unless their tumors were positive for both ER and PR.*** Patients in this subgroup were 56 % less likely to have their disease progress if they had received Pictilisib instead of a placebo, along with Faslodex. The median progression-free survival was 7.4 months for those who received Pictilisib and Faslodex, which is an improvement over the 3.7 months median progression-free survival for those who received Faslodex plus a placebo. One surprising study result was that having breast cancer with a mutation in the PIK3CA gene, a central component of the PI3K signaling pathway, was not predictive of benefit from Pictilisib. As of August 2018, there is no recruiting clinical trial of this drug for MBC patients. **From[227, PMID:25810580]: *https://blog.aacr.org/sabcs-2014-trial-testing-pictilisib-fulvestrant-combo-generates-mixed-results/***

- **RAD1901 (Elacestrant)** *(Not Yet FDA-Approved for MBC Patients, but has Fast Track Designation):* RAD1901 is an oral selective estrogen receptor degrader (SERD) which is being evaluated for potential use as an oral non-steroidal treatment for estrogen receptor positive breast cancer at high doses. In a study of 40 heavily pre-treated ER+, HER2-negative advanced breast cancer patients taking RAD1901, the objective response rate (ORR) was 23%, the median Progression Free Survival (PFS) was 4.5 months, and clinical benefit rate at 24 weeks was 42%. Notably, 38% of these patients previously received Faslodex (which is another SERD), 40% received Ibrance (palbociclib) or another CDK inhibitor, and 50% had an ESR1 mutation which may be indicative of hormone therapy resistance. It should be noted that 15 of the 40 patients remained on treatment as of the cut-off date. In October 2017, RAD1901 was granted *Fast Track* Designation by the FDA, which is a process designed to facilitate the development and review of drugs to treat serious conditions and fill an unmet medical need. Its overall purpose is to get important new drugs to the patient earlier **From: *https://www.zacks.com/stock/news/263042/radius-rdus-announces-positive-data-on-breast-cancer-drug***

- **Retrying ("Recycling Through") Hormonal Therapies:** Patients who have developed endocrine resistance and have been on chemotherapy may find this of particular interest. At the 2013 San Antonio Breast Cancer Symposium, one expert from Dana Farber stated that one of the most common suggestions that physicians should make for patients with initially hormone sensitive MBC who have had multiple lines of chemotherapy is to revisit the endocrine therapies, even in late stage disease. And he added that this methodology is probably not being done with the frequency it deserves.

- **Resveratrol:** New research shows that resveratrol, the "healthy" ingredient in red grapes, red wine, and other foods may stop breast cancer cells from growing by blocking the growth effects of estrogen. This discovery suggests for the first time that resveratrol may be able to counteract malignant progression since it inhibits the proliferation of hormone resistant breast cancer cells. This may have important implications for treating women with breast cancer whose tumors develop resistance to hormonal therapy. To make this discovery, researchers used several breast cancer cell lines expressing the estrogen receptor to test the effects of resveratrol. Researchers then treated the different cells with resveratrol and compared their growth with cells left untreated. They found an important reduction in cell growth in cells treated by resveratrol, while no changes were seen in untreated cells. Additional experiments revealed that this effect was related to a drastic reduction of estrogen receptor levels caused by resveratrol itself. Whereas these results are exciting, they do not imply that people go out and start using red wine or resveratrol supplements as a treatment for breast cancer. But it does infer that further investigation is warranted. **From[228, PMID:21737614]: *http://www.sciencedaily.com/releases/2011/09/110929103222.htm***

- **SERCAs (Selective Estrogen Receptor Covalent Antagonists)** *(Not Yet FDA-Approved for MBC Patients:* SERCAs are novel series of compounds with a unique mode of inhibition that potently targets both wild-type and mutant ERα, which are indicative of hormonal therapy resistance). They inactivate the estrogen receptor by targeting a cysteine (amino acid) that is not present in other nuclear hormone receptors, leading to a unique biological and activity profile that differs from Selective Estrogen Receptor Modulators (SERMs) and Selective Estrogen Receptor Degraders (SERDs). SERCAs such as H3B-6545 have begun being tested in clinical trials for HR+/HER2- mbc patients who have progressed on prior therapy.

- **Tamoxifen Resistance and Fareston: Fareston:** For patients whose doctors recommend that they start taking Tamoxifen, and for patients who are not responding well to Tamoxifen, a "CYP2D6" test may be recommended. This is because some people simply will not respond to Tamoxifen due to a flaw in their CYP2D6 genetic pathway. Therefore, patients may want to request a CYP2D6 test (using healthy tissue instead of tumor tissue because it appears that test results with healthy tissue are more accurate). If after taking the CYP2D6 test the patient is found to have a CYP2D6 flaw, then Fareston, which is a Selective Estrogen Receptor Modulator (SERM) similar to Tamoxifen, may be a worthwhile choice for postmenopausal (not premenopausal) patients**. From:** ***http://www.fareston.com/hcp/about/continue.html***

- **Testosterone Propionate for Hormone Sensitive MBC** *(Not Yet FDA-Approved for MBC Patients):* Testosterone is a steroid hormone that stimulates development of male secondary sexual characteristics. It is produced in the adrenal cortex, testes (in men) and ovaries (in women). In the past, testosterone was the most common line of hormonal therapy for MBC, but its use has been almost completely abandoned in the past 40 years. However, because of earlier reports on favorable therapeutic results, testosterone was re-evaluated for treatment of hormone-responsive patients who have become refractory (resistant) to other lines of hormonal therapy. In the study, 53 hormone receptor positive MBC patients who had become resistant to hormonal treatment and whose disease was progressing, were treated with testosterone propionate, 250 mg once every two weeks, twice, and then once every four weeks until disease progression, drug toxicity, or death. Regression of disease was seen in 17% of patients, and stabilization of disease was seen in 41.5%. The study concluded that testosterone showed significant therapeutic activity in previously hormone-treated patients with MBC who were no longer responding to such treatment and whose disease was progressing. **From[229, PMID:24596374]:** ***http://www.ncbi.nlm.nih.gov/pubmed/24596374***

- **Venetoclax (ABT-199)** (*Not Yet FDA-Approved for MBC Patients):* Venetoclax is a BCL-2 inhibitor that is currently approved for Chronic Lymphocytic Leukemia. In a study of 33 evaluable Hormone Receptor (HR) positive, BCL-2 positive patients who received the combination of Venetoclax and tamoxifen, the median PFS was 36 weeks overall. Based upon dosages, the median PFS was 23 weeks in those who received doses of Venetoclax at less than 800 mg., versus 51 weeks in those who received 800 mg of Venetoclax (the maximum dose in the study). In the 24 patients who received the maximum dosage, the ORR was 54% and the CBR was 75%, with 1 Complete Response (4%) and 12 Partial Responses (50%). The median DOR was 42 weeks, and 8 patients from the 800-mg cohort remain on study treatment. **From[230, PMID:30518523]:** ***https://www.onclive.com/conference-coverage/sabcs-2018/venetoclax-has-impressive-activity-in-er-and-bcl2-breast-cancer***

Research and Potential Therapies for HER2 Positive MBC

Topics in this section include the following:

- **Alisertib (MLN0237)** *(Not Yet FDA-Approved for MBC Patients)*
- **Bisphosphonates**
- **CDK4/6 Inhibitors** *(FDA-approved for MBC Patients)*
- **DS-8201** *(Not Yet FDA-Approved for MBC Patients, bit has been accorded Breakthrough Therapy status)*

- **Entinostat** (**SNDX-275 o**r **MS-275)** for Her2+ MBC Patients for whom Herceptin has Failed *(Not Yet FDA-Approved for MBC Patients, but has been accorded Breakthrough Therapy status)*
- **HER2 Targeted Therapy Plus "Soft" Chemo** *(for older patients)*
- **Ibrance (Palbociclib) and Herceptin (Trastuzumab)**
- **Keytruda (Pembrolizumab)** *(FDA-approved for patients with metastatic, microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options)*
- **Margetuximab** *(Not Yet FDA-Approved for MBC Patients)*
- **MCLA-128** *(Not Yet FDA-Approved for MBC Patients)*
- **Neratinib** *(Not Yet FDA-Approved for MBC Patients)*
- **Poziotinib** *(Not Yet FDA-Approved for MBC Patients)*
- **Tucatinib (ONT-380)** *(Not Yet FDA-Approved for MBC Patients)*

- **Alisertib (MLN0237)** *(Not Yet FDA-Approved for MBC Patients):* This is an oral drug under investigation for its potential to overcome endocrine therapy resistance in advanced breast cancer patients, which even had a positive impact on a HER2+ patient. In a study of 45 response-evaluable patients, 6 (13%) had a Partial Response and 26 (58%) had stable disease. Median duration of stable disease was 68 days, of which 2 patients (4%) had stable disease longer than 6 months. One HER2+ patient with 2 prior lines of therapy had a Partial Response of 6 months. **From[214]:** ***http://cancerres.aacrjournals.org/content/72/24_Supplement/P6-10-02.short***

- **Bisphosphonates: Potential Anti-Cancer Activity (especially HER2):** One study indicates that Bisphosphonates (a medication for osteoporosis) may bind to the enzymes related to HER proteins, preventing the passing on of growth signals. The study results revolved around four types of protein-related receptors: HER1, HER2, HER3, and HER4. These "HER" family members occur on the surfaces of many cell types and regulate cell division and proliferation. By binding to the HER proteins, Bisphosphonates may help to prevent the passing on of growth signals. **From[231, PMID:25453081]:** ***http://www.eurekalert.org/pub_releases/2014-12/tmsh-wuo120114.php***

- **CDK4/6 Inhibitors:** CDKs are Cyclin-Dependent Kinase, which are targeted drugs act upon genes, proteins or other substances that contribute in some way to the growth and development of cancer cells. Ibrance (Palbociclib), Kisqali (Ribociclib) and Verzenio (Abemaciclib) are FDA-approved CDK4/6 inhibitors for hormone receptor positive, HER2 negative MBC patients. As of August 2018, there are clinical trials underway to test CDK4/6 inhibitor efficacy (given together with other drugs) on HER2 positive MBC patients.

- **DS-8201** *(Not Yet FDA-Approved for MBC Patients but has been accorded Breakthrough Therapy status):* The investigational HER2-targeting antibody-drug conjugate DS-8201 received an FDA "*Breakthrough Therapy*" Designation for the treatment of patients with HER2-positive, locally advanced, or metastatic breast cancer who have been treated with trastuzumab (Herceptin) and pertuzumab (Perjeta) and have disease progression after ado-trastuzumab emtansine (T-DM1; Kadcyla). (*Breakthrough Therapy Designation* is a form of *Fast Track* Designation, which is meant to facilitate the development and review of new drugs intended to treat serious conditions). The FDA awarded the breakthrough designation based on an ongoing, dose escalation/expansion Phase 1 study that had 2 parts. In part 1 of the study, investigators used a modified continuous reassessment method to identify the expansion dose in patients with breast or gastric cancer. Part 2 of the study was designed to evaluate the safety and efficacy in 4 expansion cohorts, including patients HER2-positive breast cancer previously treated with T-DM1. The metastatic breast patients in Part 2 of the study had an overall response rate (ORR) of 42.2% and a disease control rate of 97.8%. Among patients with prior T-DM1, the ORR was 45.7% and the Disease Control Rate (DCR) was 100%. (The Disease Control Rate [DCR] is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention in clinical trials of anticancer agents). For those with prior T-DM1 plus pertuzumab, the corresponding rates were 46.7% and 100%, respectively. The median progression-free survival for patients with metastatic breast cancer was 45.4 weeks. As of August 2018, there are recruiting clinical trials for DS-8201.

From[232, PMID:29037983]: ***http://www.onclive.com/web-exclusives/fda-grants-ds8201-breakthrough-designation-for-her2-breast-cancer***

- **Entinostat (SNDX-275 or MS-275)** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Breakthrough Therapy status):* This drug belongs to a class of drugs called HDAC (Histone DeACetylase) Inhibitors. Mutations of genes that encode HDACs have been linked to tumor development, and HDACs may be promising therapeutic targets for cancer treatment. The FDA has designated Entinostat as a *Breakthrough Therapy* for the treatment of locally recurrent or metastatic Estrogen Receptor (ER)-positive breast cancer when added to Aromasin in postmenopausal women whose disease has progressed following nonsteroidal Aromatase Inhibitor therapy. (As previously mentioned, *Breakthrough Therapy* Designation is a form of *Fast Track* Designation, which is meant to facilitate the development and review of new drugs intended to treat serious conditions). In an earlier Phase 2 study called ENCORE 301, (a randomized, placebo-controlled Phase 2 study of Aromasin with and without Entinostat), there was improvement in Overall Survival for patients treated with Aromasin plus Entinostat. At a median follow up of 25 months, treatment with the combination resulted in an 8.3 months improvement in Overall Survival, corresponding to a 41% reduction in the risk of dying. **From[222, PMID:27037751; 223, PMID:23650416]:** ***http://www.empr.com/phase-2-trial-update-of-entinostat-for-metastatic-breast-cancer/article/243134/*** and ***http://www.ascopost.com/ViewNews.aspx?nid=8525***

- **HER2 Targeted Therapy Plus "Soft" Chemo** (for older patients): While docetaxel combined with trastuzumab and pertuzumab has been shown to be effective in younger patients with HER2 positive MBC, it can be significantly toxic and affect quality of life, particularly in older patients. In a randomized, Phase 2 trial, 80 patients were randomly assigned to receive trastuzumab and pertuzumab (TP) or TP plus metronomic oral cyclophosphamide (TPM). The patients were 70 years of age or older, or 60 years or older if they presented with certain functional limitations. The use of trastuzumab and pertuzumab with the "softer" chemotherapy of "metronomic" (continuous or frequent administration) oral cyclophosphamide provided patients with seven months longer progression-free survival compared to patients who were treated with trastuzumab and pertuzumab alone. At a median follow-up of 20.7 months, the median progression-free survival was 5.6 months in the TP group versus 12.7 months in the TPM group. **From[233, PMID:29433963]:** ***https://www.medpagetoday.com/hematologyoncology/breastcancer/71076***

- **Ibrance (Palbociclib) and Herceptin (Trastuzumab):** In the PATRICIA Phase 2 study, the combination of palbociclib and Herceptin demonstrated safety and efficacy in pre-treated patients with advanced HER2+ breast cancer. Investigators enrolled patients who had received 2 to 4 prior lines of therapy into 3 cohorts: 1 cohort contained patients with Hormone Receptor (HR) negative/HER2+ disease, and the other 2 cohorts included patients with ER+/HER2+ disease.

  Patients with HR negative/HER2+ breast cancer received Ibrance + Herceptin. At 6 months, 5 of 15 the patients in the HR-/HER2+ cohort attained Progression Free Survival (PFS). Of the HR+/HER2+ group, 6 of 15 patients who received Ibrance and Herceptin without letrozole achieved PFS, and 8 of 15 patients who received Ibrance and Herceptin with letrozole were also progression-free. **From:** ***https://www.onclive.com/conference-coverage/sabcs-2018/palbociclib-combo-active-in-her2-breast-cancer***

- **Keytruda (Pembrolizumab),** a PD-1 Inhibitor Immunotherapy Drug: *(FDA-approved for patients with metastatic, microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options):*

  An early clinical trial was undertaken with 27 evaluable TNBC MBC patients who had been heavily pre-treated (i.e. half of whom had received three or more lines of therapy in the advanced cancer setting). Of the patients who received Keytruda, five responded to treatment, including one Complete Response, and four Partial Responses. Additionally, seven patients had stable disease at a median follow-up of 9.9 months. The overall clinical benefit rate with Keytruda was 44%.

  For patients with HER2 positive, PDL-1 positive MBC that is resistant to Herceptin (trastuzumab) or TDM-1 treatment, the results of the PANACEA clinical trial may be intriguing. The results of this trial indicated that the combination of Keytruda and Herceptin reached an objective response rate (ORR) of 15.2% in patients with trastuzumab or TDM-1 resistant, PD-L1–positive,

HER2-positive MBC with an average disease control duration of 11.1 months. Higher levels of sTILs (stromal Tumor Infiltrating Lymphocytes) were associated with improved response and disease control in the PDL-1 positive group. Among PD-L1+ patients with sTILs ≥5%, the disease control rate was 47%, versus 5% in patients with sTILs <5%. Notably, patients with PDL-1 negative disease did not respond whatsoever to this treatment. Keytruda has been FDA-approved for patients with metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. **From[234, PMID:19917869; 235, PMID:30765258; 236, PMID:23341518]**: ***http://www.onclive.com/conference-coverage/SABCS-2014/Pembrolizumab-Elicits-Antitumor-Responses-in-TNBC*** and ***https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm*** and ***http://www.onclive.com/conference-coverage/sabcs-2017/pembrolizumabtrastuzumab-active-in-her2positive-breast-cancer***

- **Margetuximab** *(Not Yet FDA-Approved for MBC Patients):* Patients with heavily pretreated metastatic HER2-positive breast cancer who took margetuximab and chemotherapy experienced a 24% reduction in the risk of disease progression or death compared with patients taking Herceptin (trastuzumab) and chemotherapy, as per the results of the Phase 3 SOPHIA study. Approximately 85% of the 536 participants were CD16A (FcγRIIIa) 158F allele carriers (i.e. they carried a variant form of the gene), which was previously linked with diminished clinical response to Herceptin and other antibodies. There was a 32% reduction in the risk of disease progression or death for this subgroup of patients in the margetuximab arm versus the Herceptin arm of the study. These results are especially encouraging because the patients had previously received ≥2 prior lines of HER2-directed therapy. **From[237]:** ***https://www.targetedonc.com/news/margetuximab-demonstrates-positive-pfs-findings-in-metastatic-her2-breast-cancer***

- **MCLA-128** *(Not Yet FDA-Approved for MBC Patients):* MCLA-128 is a bi-specific antibody that targets both the HER2 and HER3 proteins associated with breast cancer. In a small Phase 1/2 clinical trial of 11 HER2-positive metastatic breast cancer patients who failed several prior lines of HER2 inhibitor therapy, one of the 11 patients achieved a partial response to the treatment that lasted more than eight months and seven patients' disease became stable (in four of the seven it was stable more than five months). The clinical benefit rate of the treatment was 64 percent, meaning that 64 percent of patients either responded to treatment or achieved a stable disease for at least 12 weeks. As of August 2018, there is at least one recruiting clinical trial (NCT02912949) for MCLA-128 for HER2 positive MBC patients**: From[238]:** ***https://breastcancer-news.com/2017/05/23/initial-trial-results-show-mcla-128-benefits-metastastic-breast-cancer-patients/***

- **Neratinib** *(Not Yet FDA-Approved for MBC Patients):* In a small Phase 1b dose-escalation study evaluating trastuzumab emtansine (T-DM-1) with Neratinib in 16 pre-treated women with metastatic HER2-positive breast cancer, it was found that the objective response (CR/PR) rate was 56%. More specifically, the efficacy results from the trial demonstrated that 3 patients had a complete response (CR) lasting 17.1 months, 11.9 months and 12+ months; 6 patients had a partial response (PR); 3 patients had stable disease (SD); and 4 patients had progressive disease (PD). As of August 2018, there is at least one actively recruiting MBC clinical trial for this drug for HER2 positive MBC patients. **From[239]:** ***http://www.pumabiotechnology.com/pr20170402_03.html***

- **Poziotinib** *(Not Yet FDA-Approved for MBC Patients):* This is an oral, HER-2 directed therapy directed at HER2+ MBC patients for whom at least two prior HER2 therapies and a taxane failed. In a study described at the 2015 San Antonio Breast Cancer Symposium, Poziotinib provided an overall response rate of 60%, a clinical benefit rate of 80%, and a medial Progression Free Survival of 28 weeks. As of August 2018, there are several recruiting clinical trials underway for Poziotinib. **From[240]:** ***https://www.abstracts2view.com/sabcs15/view.php?nu=SABCS15L_1313&terms=***

- **Tucatinib (ONT-380)** *(Not Yet FDA-Approved for MBC Patients):* Tucatinib (ONT-380) is a well-tolerated oral drug that is a small molecule inhibitor of the HER2 growth factor receptor. The drug works by targeting the HER2 "tyrosine kinase" - a link in the chain of communication that allows HER2 receptors to signal the growth of the cell. In a study of 50 women with HER2+ MBC who had progressed despite a median 5 previous treatment regimens, 27% of these heavily pretreated patients saw clinical benefit from the drug, with at least stable disease at 24 or more weeks after the start of treatment. These data led to two subsequent Phase 1b studies, resulting in Tucatinib earning FDA Fast-Track Status. The drug might also be somewhat protective against brain

metastasis, according to a presentation at 2017 SABCS. **From[241, PMID:28053022]:** ***https://www.sciencedaily.com/releases/2017/01/170111091449.htm***

Promising antitumor activity was seen in in a Phase 1b study of heavily pretreated HER2+ MBC patients, some of whom had brain metastasis, with the use of Tucatinib in combination with capecitabine (Xeloda), trastuzumab (Herceptin), or both agents. The results showed that 83% (5/6) of patients with measurable disease treated with Tucatinib/capecitabine had an objective response, as did 40% (6/15) of patients receiving Tucatinib/trastuzumab. 61% (14/23) of patients treated with the combination of all 3 drugs had an objective response. The median duration of response was 8.9 months in the Tucatinib/trastuzumab arm, 5.2 months in the Tucatinib/capecitabine arm, and 11.0 months with all three drugs. **From[242, PMID:29955792; 243, PMID:29804900]:** ***http://www.targetedonc.com/news/tucatinib-demonstrates-activity-in-heavily-pretreated-her2-breast-cancer***

Another Phase 1b study paired Tucatinib with T-DM1 in heavily pretreated HER2-positive breast cancer. Of the 57 patients treated, 48 % responded to the combination, with cancer control of median 8.2 months. Importantly, Tucatinib acted against brain metastasis stemming from HER2+ breast cancer, a major cause of mortality from the disease. As of August 2018, there are two recruiting clinical trials (NCT02614794 and NCT03054363) of Tucatinib for HER2+ MBC patients. **From[242, PMID:29955792]:** ***https://medicalxpress.com/news/2018-07-clinical-trial-results-tucatinib-t-dm1.html***

Research and Potential Therapies for HER2 Negative MBC (Including TNBC)

As of August 2018, the drug Herceptin is FDA-approved solely for breast cancer patients whose cancer is HER2 positive. Interestingly, researchers from the University of Michigan report that Herceptin may help women with HER2 negative tumors as well. The revelation emerged from a study in which 174 women without HER2 receptors were miscategorized as having tumors with the protein and were treated with Herceptin. Surprisingly, the treatment worked for them too. These women essentially given Herceptin for a year by mistake! The surprising thing was when the data were analyzed, those women actually benefited more from the Herceptin than the women whose tumors were HER2 positive. Their reduction in recurrence was 50%, even though their tumors were classified as HER2 negative.

The research team believes the results are driven by a small group of cancer stem cells that represent 1% to 5% of the cells in a tumor but are largely responsible for spreading cancer to other tissues and locations. These cancer stem cells in many HER2 negative breast cancers may still make HER2, but not in enough quantities to register the cancer as HER2 positive. But because they are the cells responsible for metastasis, blocking their growth with Herceptin may lead to fewer recurrences for patients. One researcher hypothesized that cancer stem cells are like the "seeds of the cancer" because they can cause metastasis and have the unlimited potential to reproduce, whereas the other 90% to 95% of the cancer cells are essentially dead-end cells (so even though they form the bulk of the tumor, they don't cause the spread).

To further test their theory, the researchers bred mice with HER2 negative breast cancer and showed that HER2 positive (not negative) stem cells in these animals spread to the bone, in the same way it does in humans. They also confirmed that Herceptin effectively knocked out these stem cells.

Another research team at the UC Davis Department of Radiation Oncology examined breast tumors previously thought to be HER2 negative. To their surprise, the researchers located small groups of aggressive, treatment-resistant HER2-positive Breast Cancer Stem Cells (BCSCs) in the tumors. The team found that HER2 and CD44 positive BCSCs were found in 57.1% of primary tumors and 84.6% of recurrent tumors.

In addition to identifying this previously hidden group of HER2-positive stem cells, further examination provided new insights into how these BCSCs maintain their resistance to treatment. A complex network of proteins, including HER2, modulates metastasis, programmed cell death, and other functions. As a result, these cells survive the gamut of traditional anti-cancer therapies.

"We feel this research will have a major scientific, as well as clinical, impact," says Li. *"We now have a better understanding of how BCSCs resist radiation and other treatments."*

While recent research has shown that patients with HER2-negative breast cancer can indeed benefit from HER2 treatments, prior to this study, no one truly understood the mechanisms. This research provides detailed confirmation that HER2 treatment can potentially improve outcomes in HER2-negative breast cancers. **From[244, PMID:23442322; 245, PMID:PMC3593096]:** ***http://healthland.time.com/2013/02/27/herceptin-may-benefit-wider-group-of-breast-cancer-patients/*** and ***http://www.ucdmc.ucdavis.edu/publish/news/newsroom/7282***

Balixafortide (POL6326) (*Not yet FDA approved):* Balixafortide is a potent and highly selective blocker of CXCR4, a "G-protein coupled receptor (GPCR)" that regulates the trafficking of cancer cells and cells of the patient's immune system. CXCR4 also plays a critical role in tumor growth, survival, angiogenesis and metastasis. High CXCR4 levels have been detected in almost all human tumor types, including breast cancer, and high CXCR4 expression is known to correlate with aggressive metastatic behavior of cancer cells. The anti-cancer effects of Balixafortide are thought to include direct suppression of metastatic spread, sensitization of tumor cells to chemotherapy, and activation of the immune system.

A Phase 1 clinical trial combining Balixafortide with Halaven (Eribulin) enrolled 25 patients who had histologically confirmed HER2-negative MBC (including TNBC MBC) and were in the second to fourth line of chemotherapy in the metastatic setting and had evidence of CXCR4 expression. Most patients had metastatic sites most commonly in the liver (76%) and bone (60%), followed by the lung (36%) and lymph nodes (20%). Among the 24 patients included in the efficacy data calculation, the objective response rate was 38%. Zero patients had a complete response, 9 patients (38%) achieved a partial response, and 7 patients (29%) had meaningful stable disease of 6 months. The clinical benefit rate was 67%. Fourteen of the 24 patients remained on treatment for 8 cycles or longer. Balixafortide has been granted "*Fast Track*" designation by the FDA in April 2018. **From[246, PMID:29706375]:** ***http://www.targetedonc.com/news/fda-grants-balixafortide-fast-track-designation-for-treatment-of-metastatic-breast-cancer-subset***

Research and Potential Therapies Solely for TNBC

Topics in this section include the following:

- **Abraxane (nab-paclitaxel) and Carboplatin combination**
- **ABT-888 (Veliparib)** *(Not Yet FDA-Approved for MBC Patients)*
- **Atezolizumab (Tecentriq or MPDL3280A)** *(Not Yet FDA-Approved for MBC Patients)*
- **Bicalutamide (Casodex)** *(Not Yet FDA-Approved for MBC Patients)*
- **Enzalutamide (Xtandi or MDV3100),** an Androgen Receptor Blocking Therapy *(Not Yet FDA-Approved for MBC Patients)*
- **IMMU-132 (Sacituzumab Govitecan):** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Breakthrough Therapy status)*
  - **Keytruda ((Pembrolizumab),** a PD-1 Inhibitor Immunotherapy Drug *(Approved in a Limited MBC Setting)*
- **Melatonin**
- **Neratinib,** a HER2 Targeted Drug being studied in TNBC *(Not Yet FDA-Approved for MBC Patients)*
- **Rose Hip Extract**

- **SGN-LIV1A** *(Not Yet FDA-Approved for MBC Patients)*
  - **Tetrathiomolybdate** (**TM**), a Copper Reduction Drug *(Not Yet FDA-Approved for MBC Patients)*
- **Vantictumab** *(Not Yet FDA-Approved for MBC Patients)*
- **Zejula (Niraparib) and Keytruda (Pembrolizumab)** *(Zejula is Not Yet FDA-Approved for MBC Patients)*

- **Abraxane (nab-paclitaxel) and Carboplatin combination:** In the Phase 2 TnAcity clinical trial, frontline nab-paclitaxel (Abraxane) plus carboplatin lowered the risk of progression compared with 2 other chemotherapy regimens in patients with metastatic TNBC. The nab-paclitaxel/carboplatin doublet arm had a median progression-free survival (PFS) of 7.4 months versus 5.4 months with nab-paclitaxel/gemcitabine (Gemzar), and 6.0 months with gemcitabine/carboplatin. Moreover, the 12-month PFS rates were 27%, 13%, and 11%, respectively; hence the 12-month PFS for Abraxane and Carboplatin was more than double than the other combination regimens**. From[55, PMID:29878040; 247, PMID:26673577]:** ***http://www.onclive.com/web-exclusives/yardley-discusses-evolving-role-of-nabpaclitaxel-in-tnbc***

- **ABT-888 (Veliparib)** *(Not Yet FDA-Approved for MBC Patients):* This is an oral, potent PARP Inhibitor which inhibits the enzyme poly ADP ribose polymerase (PARP). PARP Inhibitors are developed for multiple indications; the most important is the treatment of cancer. Some forms of cancer are more dependent on PARP than regular cells, making PARP an attractive target for these types of cancers. In one human study, Veliparib was combined with Carboplatin and Taxol. The objective response rate in TNBC was 52%. Among the 21 evaluable TNBC pts, response was 60% in BRCA1/2+ patients, 67% in non-BRCA1/2 patients, and 29% in patients with unknown BRCA1/2 status. **From[163]:** ***http://abstracts.asco.org/156/AbstView_156_152623.html***

- **Atezolizumab (Tecentriq or MPDL3280A)** *(Not Yet FDA-Approved for MBC Patients):* This is an immunogenic drug that works in combination with chemotherapy. In a Phase 1b study, Atezolizumab plus nab-paclitaxel (Abraxane) was explored across several lines of treatment regardless of PD-L1 status for patients with metastatic TNBC. In the second-line setting, the confirmed overall response rate (ORR) was 25% and in the third-line and beyond the ORR was 28.6%. Across the full trial, the ORR was 41.7%. **From:** ***https://www.cancercommons.org/news/Atezolizumabnab-paclitaxel-combo-shows-high-response-rates-in-tnbc/***

  In another Phase 1 trial testing MPDL3280A, 12 TNBC patients whose tumors had the PD-L1 protein were studied. Most had already undergone at least two prior therapies. Patients received intravenous injections of MPDL3280A every three weeks for up to one year. Of the nine patients who could be evaluated, one patient had a Complete Response, two had a Partial Response and one patient had Stable Disease. All of these responses occurred within six weeks of receiving the first dose of the drug. Outcomes appear to indicate that MPDL3280A, when paired with Abraxane in metastatic TNBC patients, had a confirmed overall response rate of 42% which outperformed another PD-L1 inhibitor called Avelumab. As of August 2018, clinical trials using MPDL3280A against solid tumors are underway. **From:** ***http://www.medpagetoday.com/MeetingCoverage/SABCS/55236***

  A different study included 112 patients evaluable for response, and of those, 11 responded to treatment (complete and partial responses). Both 1- and 2-year overall survival (OS) rates for these 11 responders was 100%; for non-responders, the OS rates were 33% and 11% respectively. In general, higher response was associated with higher Tumor Infiltrating Lymphocytes (TILs), with higher CD8 T cells, and to a lesser degree with higher PD-L1 on immune cells, but these markers weren't certain in a way that could warrant patient selection, and therefore additional biomarker-related research is warranted.
  From[248]: ***http://www.targetedonc.com/news/Atezolizumab-demonstrates-longterm-responses-in-subset-of-tnbc***

  The Phase 3 IMPassion130 in which 902 patients with previously untreated metastatic TNBC received either Abraxane alone, or a combination of Abraxane plus Atezolizumab (Tecentriq), revealed that patients receiving the combination had an improved median Progression Free Survival (7.2 months vs. 5.5 months). Importantly, an interim Overall Survival (OS) analysis showed median survival of 21.3 months with the Atezolizumab/Abraxane regimen vs. 17.6 months with Abraxane alone. Notably, the Atezolizumab/Abraxane regimen conferred a considerable OS benefit to patients with PD-L1-positive disease (median 25 months on the combination arm vs. 15.5 months on Abraxane alone). At SABCS 2018, Doctor Leisha A. Emens, co-leader of the Hillman Cancer Immunology and Immunotherapy Program, disclosed that the best responders were patients whose immune cells on or

near the tumor expressed PDL-1, stating, *"PD-L1 immune cell expression was the best predictor of clinical benefit."* In Nov. 2018, the FDA granted priority review regarding approval for Atezolizumab in combination with Abraxane for first-line treatment of unresectable metastatic PD-L1-positive, triple-negative breast cancer. **From[249, PMID:30345906]:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B9942e58b-6f48-45cb-837f-444cf53d4063%7D/Atezolizumab-combination-extends-survival-for-some-patients-with-metastatic-triple-negative-breast-cancer*** and ***http://hillman.upmc.com/find/providers/leisha-emens-177665***

- **Bicalutamide** *(Not Yet FDA-Approved for MBC Patients):* Bicalutamide is sold under the brand name Casodex among others, is an antiandrogen medication that is primarily used to treat prostate cancer and is not yet FDA-approved for MBC. In a Phase 2 study called "TBCRC011" which included 26 patients who were estrogen receptor–negative, progesterone receptor–negative, and androgen receptor–positive (immunohistochemistry > 10%), treatment with bicalutamide (150 mg/d) led to a clinical benefit rate of 19%, and in the 7 patients who achieved stable disease, 5 lasted more than 6 months. Median progression-free survival was 12 weeks. One researcher observed, *"What was striking was that some patients responded for a very long time; in fact, some were on androgen receptor–targeted therapy for years."* As of August 2018, there is a study (NCT03055312) of Bicalutamide for AR+ TNBC MBC patients. **From[250, PMID:23965901]:** ***http://www.ascopost.com/issues/june-10-2017/targeting-the-androgen-receptor-in-breast-cancer/***

- **Enzalutamide (Xtandi or MDV3100), an Androgen Receptor (AR) Blocker** *(Not Yet FDA-Approved for MBC Patients):* Just as a large amount of breast cancers are ER positive, a majority of breast cancers are Androgen Receptor (AR) positive. In a study of 2,171 invasive breast cancers 77% overall were positive for AR by immunohistochemistry. Among breast cancer subtypes, 88% of ER+, 59% of HER2+, and **32% of TNBC were positive for AR expression** by immunohistochemistry. Similar to ER and PR, AR expression is associated with a well-differentiated state and with more indolent breast cancers. **From[199, PMID:24451109]:** ***http://breast-cancer-research.com/content/16/1/R7***

  In a Phase 2 trial, enzalutamide was tested in 118 patients with androgen receptor–positive advanced TNBC patients with any number of prior treatments whose androgen receptor positivity was any expression (> 0%) by immunohistochemistry, and this definition was applied to the intent-to-treat population. An additional 75 patients had androgen receptor levels ≥ 10%, and this definition was applied to the evaluable population.

  In the intent-to-treat population of 118 patients, the clinical benefit rates were 25% at 16 weeks (the primary endpoint) and 20% at 24 weeks. In the evaluable population of 75 patients, the clinical benefit rates were 35% at 16 weeks and 29% at 24 weeks, respectively. Median progression-free survival was 12.6 weeks in the intent-to-treat group and 14.7 weeks in the evaluable subset.

  The researchers then applied an androgen-driven genomic signature (PREDICT androgen receptor, now known as Dx), classifying patients as Dx-positive or Dx-negative, and found that biomarker-positive patients had a doubling in progression-free survival. In the subset of patients who had only one prior therapy, Dx-positive patients had a median progression-free survival of 9.3 months, vs 2.0 months for biomarker-negative patients. Overall survival was also doubled in the biomarker-positive group.

  (Note: A less promising Androgen drug is Zytiga (Abiraterone acetate), which was studied in a small group of triple-negative patients (38% with androgen receptor expression ≥ 10%). It resulted in a 24-week clinical benefit rate of 20% at 24 weeks with a median progression-free survival of less than 3 months)**. From:** ***http://www.ascopost.com/issues/june-10-2017/targeting-the-androgen-receptor-in-breast-cancer/***

- **IMMU-132 (Sacituzumab Govitecan)** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Breakthrough Therapy status):* IMMU-132 is an SN-38 Antibody-Drug Conjugate (ADC) that targets a special antigen called "TROP-2" expressed on many cancers. (ADCs are an emerging novel class of anticancer treatment agents that combines the selectivity of targeted treatment with the cytotoxic potency of chemotherapy drugs). IMMU-132 has received FDA "*Breakthrough Therapy*" Designation (*Breakthrough Therapy* Designation is a form of *Fast Track* Designation, which is meant to facilitate the development

and review of new drugs intended to treat serious conditions). IMMU-132 has been, and continues to be, intensively studied in clinical trials and it is hoped that it will be FDA-approved soon.

In 2014 IMMU-132 received much publicity for its effectiveness against TNBC. IMMU-132 has been reported to produce a Partial Response Rate of 30% and a 70% Clinical Benefit Rate (stable disease), in patients with metastatic TNBC who had been heavily pretreated.

In a different study reported in the ASCO 2015 conference, of 49 MBC patients with TNBC who took IMMU-132, 15 patients (31%), showed a reduction in tumor size of 30% or more. Two of these patients had a complete response. Adding the 22 patients with responses between less than 30% tumor shrinkage and less than 20% tumor increase, the disease control rate was 76%**.** IMMU-132 also produced significant duration of response in these responding patients. The median Progression Free Survival (PFS) was 6 months for the 48 patients who received the optimal doses of 8 or 10 mg/kg. Importantly, 63% of patients (22 of 35) had a time-to-progression *longer than their last therapy*, and disease progression has not yet happened in 56% of patients at the time of analysis.

At the 2015 SABCS conference, a study reported that among the 60 intent-to-treat TNBC MBC patients who had received a median of 5 prior lines of therapy, the interim median progression-free survival was 6.0 months, with 58% of patients having experienced a progression-free survival event. There is a significant positive correlation between progression-free survival and maximal tumor shrinkage relative to baseline for the 31 patients whose cancer had progressed after reporting stable disease, partial, or complete response as their best response. Median overall survival data were too early to report, with 83% of patients still alive. **From[250, PMID:23965901; 251, PMID:25779953; 252, PMID:25847936]:** ***http://www.streetinsider.com/Corporate+News/Immunomedics+(IMMU)+Announces+Positive+Complete+Response+Data+from+Sacituzumab+Govitecan+Study+in+TNBC/10610385.html***

At the 2017 SABCS conference, it was disclosed that a blinded, independent review by an adjudication team of radiologists determined an Overall Response Rate (ORR) of 31%, including six Complete Responses (CRs) and 28 Partial Responses (PRs), in 110 patients with metastatic TNBC after receiving treatment. The median duration of response was 9.1 months. Notably, 9 responders were progression-free for more than one year from start of treatment, 4 of which were longer than two years. As of data cutoff on June 30, 2017, 12 responding patients were still receiving the drug. *Overall, patients benefited from IMMU-132 treatment irrespective of age, onset of metastatic disease, or number of prior regimens.* **From:** ***https://globenewswire.com/news-release/2017/12/06/1234225/0/en/Immunomedics-Announces-Updated-Results-With-Sacituzumab-Govitecan-IMMU-132-In-Patients-With-Relapsed-Or-Refractory-Metastatic-Triple-Negative-Breast-Cancer-mTNBC.html***

The most common toxicity reported has been neutropenia (abnormally low count of neutrophils, a type of white blood cell that helps fight off infections), although it has appeared manageable with dose reductions or administration of myeloid growth factors. As of August 2018, there is one recruiting IMMU-132 clinical trial (NCT02574455) for TNBC MBC patients.

- **Keytruda (Pembrolizumab/MK-3475), a PD-1 Inhibitor Immunotherapy Drug** *(Approved in a Limited MBC Setting):* Pembrolizumab is known as a PD-1 inhibitor drug. The PD-1 protein and a related molecule called PD-L1, play a key role in the ability of tumor cells to evade the host's immune system. Interactions between PD-1 and PD-L1 were found in preclinical studies to enhance immune function and help promote antitumor activity.

  Keytruda has already been FDA-approved for any cancer patient who has metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Based upon recent research,-Keytruda has been found to be effective in MBC patients with TNBC, according to an international clinical trial led by NYU. The trial investigated Keytruda in two separate cohorts (groups) of patients: Cohort A, which included 170 heavily pre-treated MBC TNBC patients regardless of PD-L1 expression, and Cohort B, which included 52 MBC patients with PD-L1-positive tumors who received it as first-line therapy.

In Cohort A, Keytruda shrunk tumors by more than 30% in eight (5%) of 170 pre-treated patients and stabilized the disease in 35 (21%) of pre-treated patients. Of the eight who experienced tumor reduction, all of them lived at least another year. The remaining patients in this cohort had a lower chance of survival. In Cohort B--those who received Keytruda as first-line therapy and had PD-L1 positive tumors, 12 (23%) of 52 patients saw tumors shrink by more than 30%, while the disease was stabilized in nine (17%) of them. Interestingly, based upon these results, PDL-1 expression did not impact patients' outcomes for MBC patients with TNBC who took Keytruda. (As of August 2018, there are several actively recruiting Keytruda trials for MBC patients). **From:** ***https://www.eurekalert.org/pub_releases/2017-06/nlmc-ide060117.php***

- **Melatonin as a Possibility for TNBC:** An early stage study shows melatonin - a hormone that regulates the body's sleep and wake cycles - may have the potential to help slow the growth of certain breast cancer tumors, according to researchers from Henry Ford Hospital in Detroit. The study found that melatonin may inhibit tumor growth and cell production, as well as block the formation of new blood vessels in ER-negative breast cancer models. These early stage research results with melatonin in TNBC animal models achieved a lab result that has not been seen anywhere else, researchers claim. However, the study's researchers cautioned that this research is still in its very early stages and results are not yet ready to be translated for patient use. **From[253, PMID:24416386]:** ***http://www.scienceworldreport.com/articles/12478/20140128/melatonin-slow-tumor-growths-breast-cancer.htm***

- **Neratinib** *(Not Yet FDA-Approved for MBC Patients):* Preliminary activity of Pembrolizumab + Neratinib is encouraging in metastatic triple-negative breast cancer. Durable responses have been observed irrespective of BRCA1/2 or PD-L1 status or prior platinum exposure, and as of August 2018 there are recruiting clinical trials underway for this drug. **From:** ***https://www.practiceupdate.com/content/asco-2018-preliminary-activity-of-pembrolizumab-neratinib-is-encouraging-in-metastatic-triple-negative-breast-cancer/69208***

- **Rose Hip Extract:** In a test tube study, the scientists treated tissue cultures of triple negative breast cancer cells with several concentrations of rosehip extract. Exposure to the highest concentration decreased triple negative breast cancer cell proliferation by 50 percent. The effect was reduced with decreasing concentrations. The extract also enhanced the ability of the commonly used breast cancer chemotherapy drug Doxorubicin (Adriamycin) to decrease cell proliferation and migration in the tissue cultures, suggesting rosehip extract might be a beneficial addition to the overall treatment regimen for patients with triple negative breast cancer. (Note: The optimal dosage for human supplementation was not mentioned in the study). **From:** ***http://www.sciencedaily.com/releases/2015/03/150329141007.htm***

- **SGN-LIV1A:** *(Not Yet FDA-Approved for MBC Patients):* The LIV-1 protein is expressed by most metastatic breast cancers, including TNBC. SGN–LIV1A, an Antibody Drug Conjugate (ADC), is an experimental drug that targets the zinc transporter LIV-1 for the treatment of metastatic breast cancer. In a Phase 1 study, data were reported from 53 patients (35 with TNBC) with LIV-1-expressing MBC who were treated with SGN-LIV1A monotherapy administered every three weeks. Patients had received a median of four prior systemic therapies for metastatic disease. Among evaluable TNBC patients, 37% achieved a partial response (PR). The disease control rate (DCR), defined as patients achieving a complete response (CR), PR or stable disease (SD), was 67% and the clinical benefit rate (CBR), defined as patients achieving CR or PR of any duration plus patients achieving SD lasting at least 24 weeks, was 47%. At the time of an interim data analysis, the estimated median progression-free survival for metastatic triple-negative breast cancer patients was 12 weeks with seven patients remaining on treatment. As of August 2018, there are two clinical trials (NCT03310957 and NCT03424005) underway for TNBC MBC patients. **From:** ***https://adcreview.com/news/sgn-liv1a-monotherapy-data-show-37-orr-heavily-pretreated-triple-negative-metastatic-breast-cancer/***

- **Tetrathiomolybdate (TM), A Copper Reduction Drug** *(Not Yet FDA-Approved for MBC Patients):* In a very small study of 11 women with TNBC MBC, only two of 11 study participants relapsed within 10 months after using the anti-copper drug. According to the researchers, copper is essential to the metastatic process. Copper is a key component of enzymes that help turn on angiogenesis (the formation of new blood vessels, which is essential for tumors to grow) in the tumor microenvironment. Copper

also appears to play a role in directing cancer cell migration and invasion. TM is a copper chelation compound (chelation involves the removal of heavy metals) that has been used to treat Wilson's disease, a hereditary copper metabolism disorder.

TM can be procured via a doctor's prescription, and patients must be followed closely by a doctor when undertaking TM copper reduction. Patients' copper levels must be by the doctor both for copper levels and for anemia. There are several compounding pharmacies that make TM, but it is an involved process which is a bit complicated.

Note: In a small Phase 1 study of 18 metastatic patients (but not necessarily MBC – there were several cancer types) on this therapy. Fourteen patients achieved the target copper deficiency before disease progression or other disease complications. Of these, eight patients either progressed within 30 days of achieving copper deficiency or have had stable disease for <90 days. The remaining six patients experienced stable disease (five of six patients) or progression of disease at only one site, with stable disease elsewhere (one of six patients). In all patients removed from the protocol, much more rapid rates of progression of disease were noted clinically after discontinuation of TM therapy. So, this is a caution regarding potential rebounding effects after TM discontinuation. **From[210, PMID:10656425]:** ***http://clincancerres.aacrjournals.org/content/6/1/1.full***

- **Vantictumab** *(Not yet FDA-approved for MBC patients):* This is a drug that seeks cell-surface proteins, namely the proteins of something called the "frizzled" receptor. The "frizzled" receptor is an essential link in the "Wnt" signaling pathway, which transmits growth and survival signals to breast cancer stem cells. Instead of bringing a poison such as a chemotherapy drug to kill TNBC cells marked with frizzled receptors, vantictumab simply attaches to these receptors, plugging their ability to catch other molecules, and thus impeding signals that these frizzled receptors could otherwise have transmitted inside the cell to encourage growth and replication. Of 21 TNBC patients treated in a Phase 1b trial of vantictumab, 33% percent achieved at least a partial response. **From:** ***http://www.coloradocancerblogs.org/asco-finally-targeted-therapy-triple-negative-breast-cancer/***

- **Zejula (Niraparib) and Keytruda (Pembrolizumab):** *(Not yet FDA-approved for MBC patients):* A combination of Keytruda (Pembrolizumab) and Zejula (Niraparib), which is a PARP inhibitor, has shown promising and durable response rates in pre-treated TNBC MBC patients, regardless of their BRCA mutational status according to the Phase 1/2 trial called TOPACIO in which 46 TNBC patients were assessed. Among them, 15 had BRCA mutations, and 5 had genetic alterations in other DNA repair genes. Three patients had complete responses, 10 had partial tumor reductions, and 10 had their disease stabilized with the treatment. This represents an overall response rate of 28% and a disease control rate of 50%. As expected, patients with BRCA mutations had the best response rates at 60%, followed by those with mutations in other DNA repair genes at 55%, and those who were positive for the PD-L1 protein — a biomarker that predicts response to Keytruda — at 36%. Overall, the 15 patients with BRCA mutations lived for a median of 8.3 months without their disease progressing, which is superior to the three to five months seen with standard chemotherapy, or the rates seen with either agent alone. **From:** ***https://breastcancer-news.com/2018/06/18/zejula-keytruda-promising-response-rates-phase-1-2-trial-breast-cancer/?amp***

Research and Potential Therapies for Hormone Receptor Positive, HER2 Positive MBC

- **Aromatase Inhibitor, Herceptin (Trastuzumab) and Pertuzumab (Perjeta)**
- **Aromatase Inhibitor, Herceptin (Trastuzumab) and Lapatinib (Tykerb)**
- **Ibrance (Palbociclib) and Herceptin (Trastuzumab), with or without Letrozole**

- **Aromatase Inhibitor + Herceptin (Trastuzumab) + Pertuzumab (Perjeta):** The Phase 2 PERTAIN study enrolled 258 women with HER2-positive, HR positive locally advanced or MBC who were not previously treated with systemic non-hormonal therapy in the advanced-disease setting. Patients received either Herceptin (with or without a taxane for 18–24 weeks) plus an aromatase inhibitor (Arimidex or Letrozole), or else they received Herceptin (with or without a taxane for 18–24 weeks) plus Perjeta plus an aromatase inhibitor. The triplet combination of Herceptin (with or without a taxane), plus Perjeta and an aromatase inhibitor resulted in a median PFS of 18.9 months, compared to 15.8 months for Herceptin (with or without a taxane) plus an aromatase

inhibitor. Furthermore, the DOR was significantly longer with the triplet (27.1 vs 15.1 months). **From:** ***http://www.ascopost.com/issues/january-25-2017/pertuzumab-trastuzumab-plus-aromatase-inhibitor-beneficial-in-metastatic-breast-cancer/***

- **Aromatase Inhibitor, Herceptin (Trastuzumab) and Lapatinib (Tykerb):** The "triplet" therapy combination of lapatinib (Tykerb), trastuzumab (Herceptin), and an aromatase inhibitor (AI) reduced the risk for death or progression by 38% in women with HER2+/HR+ metastatic breast cancer (MBC) compared with those treated with a targeted agent plus AI, according to findings published in the Journal of Clinical Oncology from the Phase 3 ALTERNATIVE study of 355 patients. Prior treatment with endocrine therapy in the neoadjuvant, adjuvant, and/or first-line metastatic settings was allowed, as was Herceptin plus chemotherapy in similar settings The median PFS was 11 months for the triplet therapy combination versus 5.7 months for women assigned to Herceptin plus AI, and the median PFS also favored the triplet compared to Herceptin plus AI (8.3 months vs 5.7 months). Although OS data were immature at the time of this analysis, they trended in favor of the triplet therapy versus trastuzumab plus AI (median OS, 46.0 vs 40.0 months). The researchers concluded that the PFS benefit obtained with lapatinib plus Herceptin plus AI in patients with HER2-positive, HR-positive MBC who had been previously treated is clinically meaningful and robust, and that the triplet combination can potentially offer an effective and well-tolerated, chemotherapy-sparing alternative treatment regimen for patients for whom chemotherapy is not intended. **From[254, PMID:29244528]:** ***http://www.onclive.com/web-exclusives/dual-her2-blockade-superior-for-pfs-in-her2hr-metastatic-breast-cancer***

- **Ibrance and Herceptin, with or without Letrozole:** In the PATRICIA Phase 2 study, the combination of palbociclib (Ibrance) and trastuzumab (Herceptin) demonstrated safety and efficacy in pre-treated patients with advanced HER2+ breast cancer, some of whom were also hormone receptor positive. Investigators enrolled patients who had received 2 to 4 prior lines of therapy into 3 cohorts: 2 cohorts contained patients with ER+/HER2+ disease, and 1 cohort contained patients with ER-/HER2+ disease.

  Patients with ER+/HER2+ breast cancer were randomized to receive Ibrance + Herceptin with or without letrozole. Overall, 19 of 45 patients in the 3 cohorts remained progression free at 6 months with the combination. At 6 months, 6 (40%) of 15 patients with ER+HER2+ mbc who received Ibrance and Herceptin without letrozole achieved PFS, and 8 (53%) of 15 ER+/HER2+ mbc patients who received Ibrance and Herceptin with letrozole were also progression-free. (5 (33%) of 15 the patients in the ER-/HER2+ cohort attained Progression Free Survival at 6 months with Ibrance and Herceptin). **From[255]:** ***https://www.onclive.com/conference-coverage/sabcs-2018/palbociclib-combo-active-in-her2-breast-cancer***

Research and Potential Therapies Solely for Patients with BRCA1 and/or BRCA2 Mutations

Patients harboring BRCA1 or BRCA2 (BRCA1/2) gene mutations account for approximately 5% of all breast cancers and approximately 15–20% of hereditary breast cancers. The prevalence of BRCA1/2 germline (inherited) mutations is considerably higher among certain ethnic groups (e.g., Ashkenazi Jews) and in certain geographic areas. According to recent estimates, 55–65% of women who inherit a BRCA1 mutation and around 45% of women who inherit a BRCA2 mutation will develop breast cancer by the age of 70, and an increasing number of specific therapies (such as PARP inhibitors described below and platinum chemotherapies) are being studied in this subset of patients.

A substance that blocks an enzyme in cells called "PARP." PARP helps repair DNA when it becomes damaged. DNA damage may be caused by many things, including exposure to UV light, radiation, certain anticancer drugs, or other substances in the environment. In cancer treatment, blocking PARP may help keep cancer cells from repairing their damaged DNA, causing them to die. Overall, PARP inhibitors are a type of targeted therapy increasingly being evaluated in certain groups of cancer patients.
Topics in this section include the following:

FDA Approved Therapies for BRCA- Positive HER2 Negative MBC Patients:

- **Olaparib (Lynparza)** ***(FDA-Approved as a monotherapy)***
- **Talazoparib (Talzenna)** ***(FDA-approved as a monotherapy)***

- **Olaparib (Lynparza)** is an oral polymerase (PARP) inhibitor that was FDA-approved as a monotherapy in Jan. 2018 for MBC patients with germline BRCA mutations whose cancer is HER2 negative and who had been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting. The approval was based on a randomized Phase 3 study of 302 HER2 negative MBC patients with germline BRCA mutations who had received no more than 2 prior chemotherapy regimens in which olaparib was compared with a single-agent therapy of the physician's choice. Median Progression-Free Survival (PFS) was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months); and the response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group. The Overall Survival (OS) was 2.2 months longer for olaparib (19.3 months with olaparib vs 17.1 months with standard chemotherapy). Significantly, olaparib is better tolerated than chemotherapy. **From:** ***https://www.medscape.com/viewarticle/895337***

- **Talazoparib (Talzenna)***:* Talazoparib is an oral polymerase (PARP) inhibitor that was FDA-approved in Oct. 2018 for MBC patients with germline (inherited) BRCA mutations whose cancer is HER2 negative. Notably, the FDA approved the BRACAnalysis CDx blood test developed by Myriad Genetic Laboratories, Inc. to identify patients with breast cancer with deleterious or suspected deleterious germline BRCA-mutated disease who are eligible for Talazoparib. Patients must be selected for Talazoparib based on this FDA-approved companion diagnostic.

  In terms of the potency of PARP inhibition, Talazoparib surpasses Veliparib, Olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula). In addition, the FDA approved the BRACAnalysis CDx test, developed by Myriad Genetic Laboratories, Inc., to identify patients with breast cancer with deleterious or suspected deleterious germline BRCA-mutated disease who are eligible for talazoparib. Patients must be selected for talazoparib based on this FDA-approved companion diagnostic.

  The Phase 3 EMBRACA trial for patients with germline (inherited) BRCA1/2-positive locally advanced and/or metastatic breast cancer (MBC) demonstrated superior progression-free survival (PFS) in people treated with Talazoparib, compared to patients who received physician's choice standard of care chemotherapy. The median PFS was 8.6 months for patients treated with Talazoparib vs. 5.6 months for those treated with chemotherapy. This represents a 46% reduction in the risk of disease progression. In addition, the proportion of patients achieving a complete or partial response (objective response rate) in the Talazoparib group was more than twice that of the control arm (62.6% for the Talazoparib group vs. 27.2% for the chemotherapy group). The study concluded that Talazoparib demonstrated superior clinical benefit in all subsets of patients, regardless of receptor subtype (hormone receptor–positive or triple-negative breast cancer), number of prior lines of chemotherapy, BRCA mutation type, and central nervous system metastasis **From:** ***https://www.businesswire.com/news/home/20171208005117/en/Talazoparib-Significantly-Extends-Progression-Free-Survival-Phase-3***

Studies for BRCA- Positive HER2 Negative MBC Patients:

- **Carboplatin vs. Docetaxel (Taxotere)**
- **Lurbinectedin (PM01183)** *(Not Yet FDA-Approved for MBC Patients)*
- **Olaparib and Durvalumab** *(Durvalumab is Not Yet FDA-Approved for MBC Patients)*
- **Veliparib with and Without Carboplatin** *(Combination Not Yet FDA-Approved for MBC Patients)*

- **Carboplatin vs Docetaxel (Taxotere):** According to one study, patients with BRCA1 and/or BRCA2 mutations with any ER, PR, and HER2 status experienced significantly greater response and progression-free survival with carboplatin than with docetaxel. In one study, the median Progression Free Survival (PFS) for patients with BRCA1/2 mutations in the carboplatin group was 6.8 months versus 3.1 months for BRCA1/2 mutation-negative patients in the carboplatin group; the PFS was 4.8 months for patients with BRCA1/2 mutations in the docetaxel group vs. 4.6 months for BRCA1/2 mutation-negative docetaxel

group. **From:** ***http://www.cancertherapyadvisor.com/sabcs-2014/carboplatin-better-outcomes-docetaxel-advanced-breast-cancer/article/387941/***

- **Lurbinectedin (PM01183)** *(Not Yet FDA-Approved for MBC Patients):* According to one study, Lurbinectedin shows promising clinical benefit in pretreated patients with metastatic breast cancer and BRCA1 or BRCA2 mutations, including patients previously treated with platinum. Of the 54 patients with evaluable data (61% of whom had two or more metastatic sites), the Overall Response Rate (ORR) was 39% in patients receiving the fixed 7 mg/m2 dose, and 44% in patients dosed at 3.5 mg/m2, with an ORR of 40.7%. The best overall response included a complete response in one (2%) patient, partial response in 21 (39%) patients, and stable disease in 23 (43%) patients. Just 9 (17%) patients with advanced metastatic breast cancer experienced progressive disease. The median duration of response was 6.7 months and progression-free survival was 4.1+ months. Notably, platinum pre-treated patients demonstrated an ORR of 26%. **From[256]:** ***http://www.esmo.org/Conferences/Past-Conferences/ESMO-2016-Congress/News-Articles/Antitumour-Activity-Demonstrated-With-Lurbinectedin-in-Patients-With-Metastatic-Breast-Cancer-and-BRCA-Mutations***

- **Olaparib in combination with Durvalumab *("Imfinzi")*** *(Combination Not Yet FDA-Approved for MBC Patients):* Durvalumab is a PD-L1 inhibitor being studied in HER2 negative MBC patients with BRCA1 or BRCA2 germline mutations. The Mediola study consists of 25 pretreated MBC patients who had BRCA germline mutations and HER2 negative MBC. Twelve of these patients had HR positive tumors and 13 had TNBC. The combination of Olaparib and Durvalumab demonstrated a Disease Control Rate (DCR) of 80%, and a 52% Overall Response Rate (ORR) which consisted entirely of partial responses. Responses were seen regardless of hormone receptor status, BRCA mutation type, or receipt of prior platinum-based chemotherapy. The longest response was ongoing at 308+ days, and the median DOR was not yet reached at the time of the analysis. Although medians have not yet been attained, the Kaplan-Meier curves indicated that approximately 70% of patients remained progression free, and most patients remained alive at the time of the analysis. **From[257, PMID:28792849; 258, PMID:30220927]:** ***http://www.onclive.com/web-exclusives/olaparibdurvalumab-combo-effective-for-brcamutant-breast-cancer***

- **Veliparib with and without Carboplatin** *(Combination Not Yet FDA-Approved for MBC Patients):* In a dual study of MBC patients with BRCA mutations, Phase 1 patients received carboplatin and Veliparib, which is a PARP inhibitor. In a companion Phase 2 trial, patients received single-agent Veliparib, and upon progression, received the combination of carboplatin and Veliparib. In the Phase 1 trial of the carboplatin and Veliparib combination, the progression-free survival (PFS) was 8.7 months, and the overall survival (OS) was18.8 months, with three patients remaining complete response (CR) beyond 3 years. In the Phase 2 trial of Veliparib alone, the PFS was 5.2 months and the OS were 14.5 months. (Only one of 30 patients responded to the combination therapy after progression on Veliparib alone). **From[259, PMID:28356425]:** ***https://www.ncbi.nlm.nih.gov/pubmed/28356425***

Research and Potential Therapies for Patients with Other Tumor Mutations and Biomarkers

As genetic mutations in tumors are increasingly being studied, specific therapies are being developed and tested to treat patients whose cancers exhibit these anomalies or who have specific biomarkers. For example, clinical trials are underway for MBC patients whose tumors have been found to have PIK3, P53, and other mutations, some of which have encouraging results.

PIK3CA Mutations in pre-treated Hormone Receptor+/HER2- Patients: In the SOLAR-1 Phase 3 clinical trial which compared Faslodex plus the targeted therapy Alpelisib (BLY719) versus Faslodex and placebo, postmenopausal patients with PIK3CA mutations (found via liquid or tumor biopsy) in the Faslodex/Alpelisib arm fared substantially better (median PFS 11.0 months) than similar patients in the Faslodex plus placebo arm (median PFS 5.7 months). Patients in this trial had received 1 or more lines of prior hormonal therapy but no chemotherapy. The ORR in the PIK3CA-mutant cohort was 26.6% in the Faslodex/Alpelisib arm compared with 12.8% in the Faslodex/placebo arm. These results, assessed after a median follow-up of 20 months, translated into a 35% reduction in

the risk of progression or death in favor of Faslodex/Alpelisib arm. There was no advantage to providing Alpelisib in patients without a PIK3CA mutation.

Due to the encouraging results of this trial, a new "Managed Access Program" (NCT03706573) has been established to allow access to Alpelisib for eligible patients diagnosed with HR+ MBC who have a PI3KCA mutation. **From:** ***https://www.targetedonc.com/conference/esmo-2018/solar1-trial-results-demonstrate-a-benefit-for-genomic-testing-in-breast-cancer*** and ***https://clinicaltrials.gov/ct2/show/NCT03706573***

P53 Mutations: Another interesting clinical trial included MBC patients with p53 mutated tumors. The study showed that the 30 patients who were treated with REOLYSIN (an immuno- oncology viral agent) in combination with Taxol had a median Overall Survival of 20.9-months versus 10.4-months for the 31 patients treated only with Taxol. **From:** ***https://www.oncolyticsbiotech.com/press-releases/detail/33/oncolytics-biotech-inc-s-reolysin-more-than-doubles***

HER2 or HER3 Mutations in Hormone Receptor Positive Patients: The SUMMIT Phase 2 trial sought to evaluate the safety and efficacy of Neratinib (Nerlynx) in Hormone Receptor (HR) positive patients who have solid tumors with activating HER2 or HER3 mutations. In the HER2-mutant, HR+ positive breast cancer cohort, 47 patients received Neratinib in combination with Faslodex (fulvestrant). In this group, 43 patients (92%) had HER2 negative disease, and the patients had received a median of 3 prior lines of therapy in the metastatic setting (range 0-11 prior regimens). All patients had been previously treated with hormonal therapy prior to entering the study, including 25 patients (53%) who had received prior Faslodex. 20 patients (43%) had received prior cyclin-dependent kinase 4/6 (CDK4/6)-inhibitor therapy. Overall, 14 patients (30%) experienced an objective response, which included 4 patients with a complete response and 10 patients with partial responses, and 22 patients (47%) experienced clinical benefit (*clinical benefit is defined as confirmed complete response or partial response or stable disease for at least 24 weeks*). The median DOR was 9.2 months and the median PFS was 5.4 months. Patients who had received prior Faslodex or CDK4/6 inhibitor targeted therapy prior to entering the trial also benefited from the combination treatment. Of note, 6 patients (30%) with prior CDK4/6-inhibitor exposure demonstrated confirmed responses, with the duration of responses ranging from 4.5 - 14.8 months. Four patients were still on treatment at the time of data reporting. **From[260, PMID:28274957; 261, PMID:29420467]:** ***https://markets.on.nytimes.com/research/stocks/news/press_release.asp?docTag=201812060800BIZWIRE_USPRX____BW5252&feedID=600&press_symbol=44478224***

Study of HER3 Overexpressed MBC Patients: U3-1402, an investigational antibody-drug conjugate (ADC) targeting HER3, induced objective response in more than 40% of 42 heavily pretreated patients with HER3-expressing breast cancer, according to results presented at the 2018 San Antonio Breast Cancer Symposium. The ORR was 42.9% (18/42), the median PFS was 8.3 months, and the overall disease control rate (DCR) was 90.5% (38/42). Most responses proved to be durable, as the median duration of response (DOR) was not yet reached (range, 2.8-13.8 months) after a median follow-up of 10.5 months. Twenty-one patients remained on treatment as of the November 6, 2018 data cutoff. **From[262]:** ***https://www.onclive.com/conference-coverage/sabcs-2018/her3targeting-antibodydrug-conjugate-shows-encouraging-activity-in-advanced-breast-cancer***

Since there are numerous clinical trials underway that target various mutations in tumors, patients whose tumors have known mutations may wish to search for clinical trials using the mutation names (such as PIK3, p53, ESR1, etc.) as keywords in their clinical trial search terms. Additional tips for finding clinical trials are provided in the *Clinical Trials Overview* section of this document.

35. Therapies for Pain and Neuropathy

Pain and neuropathy are frequent and highly distressing symptoms experienced by cancer patients. In some instances, they may be caused by the cancer itself, and/or in other cases they may be caused by treatment. Neuropathy (sometimes referred to as peripheral neuropathy) is a result of damage to the peripheral nerves. Neuropathy may cause weakness, numbness and pain, usually in the hands and feet. If a patient experiences significant pain and/or neuropathy, they should contact their doctor. And if subsequent intervention fails to help to relieve these symptoms and the patient remains in considerable discomfort, the patient might consider arranging for palliative care as per the *Palliative Care* section of this Guide.

Unfortunately, cancer pain is often undertreated, causing unnecessary misery for the patient.

Under-treatment is due to many factors, including:

Professional and public pressure to avoid opioid abuse and overdose. In response to the increasing hesitancy to adequately medicate cancer patients for pain, the American Society of Clinical Oncology (ASCO) issued the *"ASCO Policy Statement on Opioid Therapy: Protecting Access to Treatment for Cancer-Related Pain,"* in May 2016. The statement provides principles to balance public health concerns regarding the abuse and misuse of prescription opioids with the need to ensure access to appropriate pain management for cancer patients and survivors. The policy states, ***"Cancer patients are a special population - ASCO believes that cancer patients should be largely exempt from regulations restricting access to or limiting doses of prescription opioids*** *in recognition of the unique nature of their disease, its treatment, and potentially life-long adverse health effects from having had cancer."* **From:** ***https://www.asco.org/advocacy-policy/asco-in-action/asco-releases-principles-balancing-appropriate-patient-access?etcid=37861275&etrid=1396253832&linkid=ASCO+Releases+Policy+Statement+on+Opioid+Therapy%3a+Protecting+Access+to+Treatment+for+Cancer-Related+Pain_btn***

Patients' reluctance to speak up about their pain. Some patients don't want to "bother" their doctors about pain or other symptoms because they do not want to be viewed as a complainer, or they may fear that the pain means that their cancer is getting worse and therefore they prefer to ignore it. If a patient fails to bring their pain to a doctor's attention, they may be causing themselves unnecessary suffering because they and their doctor would otherwise be able to develop a plan to reduce their pain.

Doctors' reluctance to ask patients about their pain levels. People living with cancer should be asked by their doctors, nurses and other medical staff if they are having any pain. If the patient is in pain, then a plan should be developed between the patient and their medical team to reduce the pain. And if the remedy fails to work, consultations and therapies should be provided until the patient's pain becomes manageable.

Fear of addiction. Some people are afraid of becoming addicted to pain medications. This is something that typically doesn't happen when taking pain medications under a doctor's care.

Fear of side effects. Patients may have concerns about being sleepy, being unable to communicate with family and friends or acting strangely while on pain medication. In fact, although strong pain medications can initially cause drowsiness, that side effect usually goes away with steady dosing.

In many instances, the less potent pain medications (which are purchased Over The Counter, or "OTC") may have more side effects. For instance, common OTC pain relievers might damage the kidneys, cause ulcers, or raise the patient's blood pressure. Aspirin can cause gastrointestinal bleeding, and acetaminophen (such as Tylenol) can cause liver damage if too much of the drug is taken.

Recent evidence suggests that good control of symptoms, including pain, actually helps people to live longer!

There are several options for treating cancer pain. One method is to remove the source of the pain, if possible, through surgery, chemotherapy, radiation and/or some other form of treatment. If that cannot be done, pain medications can usually control the pain. These medications are listed immediately below.

OVERVIEW OF PAIN MEDICATIONS

Pain medications may include one or more of the following. Patients may occasionally need to try one medication after the other (with their doctor's approval) until they find optimal relief. Physicians prescribing drugs for pain relief must also be made fully aware of all other medications the patient is taking. *Before purchasing pain relievers, it is advisable to first check the ingredients to see whether the product contains Benzocaine. The FDA has issued a warning about the use of benzocaine, the main ingredient in some over-the-counter liquids and gels. Benzocaine is associated with a rare but serious condition called methemoglobinemia, which greatly reduces the amount of oxygen carried through the bloodstream. In the most severe cases, the condition can be life-threatening*.

- **Antidepressants**
- **Anti-seizure Medication**
- **Muscle Relaxers**
- **Nerve Blocks (including Epidurals)**
- **Over the Counter Drugs (OTC)**
- **Pain Pump**
- **Strong Opioids**
- **Weak Opioids**

- **Antidepressants.** Certain medications called "tricyclic antidepressants" have been found to help relieve pain by interfering with chemical processes in the brain and spinal cord that causes a person to feel pain. Examples include **Amitriptyline, Doxepin** and **Nortriptyline (Pamelor).** Additionally, some people experienced a significant decrease in neuropathy-induced pain when they took a prescription antidepressant drug called **Cymbalta (Duloxetine).**
  From[263, PMID:26141332]: ***http://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/basics/treatment/con-20019948***

- **Anti-seizure Medications.** Certain medications such as **Gabapentin (Gralise, Neurontin)** and **Pregabalin (Lyrica**), which were developed to treat epilepsy, may relieve nerve pain**. From[263, PMID:26141332]:** ***http://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/basics/treatment/con-20019948***

- **Muscle Relaxers**: Muscle Relaxers such as Flexeril (Cyclobenzaprine) can help to alleviate painful muscle spasms. Potassium and magnesium supplements can also be helpful in relieving muscle cramps, as can Epsom salt baths.

- **Nerve Blocks (including Epidurals)**: Specialized treatment involving the injection of a nerve-numbing substance may be used. This may help prevent pain messages traveling along that nerve pathway from reaching the brain.

- **Over-The-Counter (OTC)** and prescription-strength pain relievers include Aspirin, Acetaminophen (Tylenol) and Ibuprofen (Advil, Motrin).

- **Pain Pump:** A pain pump may be a viable consideration when oral and IV pain medications fail to control pain adequately. The pain pump is an implanted drug infusion system that releases prescribed amounts of pain medication directly to the pain receptors (nerves) near the spine. The entire system consists of a pump and a catheter. The pump, whose purpose is to store and deliver pain medication, is surgically placed in the abdomen. The catheter is inserted into the intrathecal (spinal canal) space surrounding the spinal cord. The catheter is then connected to the drug pump. The doctor fills the pump with pain medication using a needle. The pump sends the medication through the catheter directly to the spinal area where pain receptors are located. Patients return

to their doctor for more medicine when the pump needs to be refilled. Before having the pump implanted, an epidural screening test provides a temporary evaluation period so that patients can determine whether the targeted drug delivery truly relieves the pain. It is worthy to note that the system can be turned off, or surgically removed, if eventually desired.

One person with bone metastases broke several ribs due to severe coughing and decided to have a pain pump inserted. She was also allergic to several pain medications and has had no allergic reaction to the four the medications in the pump. After three years of living with the pump, she claims not to have experienced side effects such as drowsiness or constipation because the drugs bypass the digestive system, and the dosage is a fraction of the norm (since the drugs are delivered directly to the pain receptors). She has the pump refilled every two months and can administer an extra injection if necessary. In summary, she claims to be much more comfortable than she had been before she used the pump. More information about pain pumps is located at **[264, PMID:17387357]:** ***http://www.medtronic.com/us-en/patients/treatments-therapies/drug-pump-chronic-pain.html***

- **Strong Opioids** medications include **Morphine (Avinza, Ms Contin**, others), **Oxycodone (OxyContin, Roxicodone**, others), **hydromorphone (Dilaudid, Exalgo**), **Fentanyl (Actiq, Fentora**, **Subsys** [an under-the-tongue spray] and others), **Methadone (Dolophine, Methadose**), and **Tapentadol (Nucynta). Tramadol (Ultram)** is a painkiller similar to opioids. Some other painkillers are:

    - *Hysingla ER* is another strong opioid, which has the same active ingredient (hydrocodone) as Zohydro ER, the only other approved extended-release hydrocodone product. There are important differences between the two drugs. Hysingla ER has approved abuse-deterrent labeling, while Zohydro ER does not. Also, Hysingla ER is taken every 24 hours, whereas Zohydro ER is taken every 12 hours, and therefore comes in lower dosage strengths. **From:** ***https://www.pharmacist.com/article/fda-approves-hysingla-abuse-deterrent-properties***

    - *Targiniq ER*, which was FDA-approved in 2014, is a new opioid that is an extended-release/long-acting opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Targiniq ER has properties that are expected to deter, but not totally prevent, abuse of the drug by snorting and injection. In addition, the Naloxone in Targiniq ER blocks the euphoric effects of oxycodone and helps circumvent the constipation that usually accompanies the ingestion of opioids.

    - *Zohydro ER* is a new extended-release, oral opioid indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment.

- **Weak Opioids** (derived from a drug called Opium) such as codeine

Many of the above medications are taken orally, so they are easy to use. Medications may come in tablet form, or they may be made to dissolve quickly in the mouth. However, if a patient is unable to take medications orally, they may also be taken intravenously, rectally or through the skin using a patch.
Other therapies such as **Acupuncture, Acupressure, Massage, Meditation, Physical Therapy, Yoga,** and other relaxation techniques may also help to alleviate pain.

Pain Therapies for one category of pain (such as Bone Pain) may potentially overlap with therapies that are used in another pain category (such as Aromatase Inhibitor-induced pain). Therefore, patients experiencing *any* type of pain are encouraged to read this entire section. And as a reminder, patients should consult with their physician before taking any new therapy, medication, herb or supplement.

Pain and Neuropathy Therapies have been divided into the following sub-categories:

- **Therapies for Bone Pain**

- **Therapies for Aromatase Inhibitor-induced Pain** (also known as "Arthralgia")
- **Therapies for Peripheral Neuropathy Pain**
- **Therapies for Stomach Pain**

THERAPIES FOR BONE PAIN

Tumors in the bone release specific factors that cause pain. These microscopic messengers tell the bone to destroy itself. And as the bone erodes or becomes more fragile, further pain may occur. Unfortunately, bone pain from bone metastasis is very common, and therefore this particular section about bone pain is the first one addressed in this section. Many of the therapies used to relieve bone pain are the same as those to treat the actual bone metastasis itself.

Patients with bone metastasis who are experiencing severe pain may have bone fractures that have gone unnoticed. It is advised that, whenever possible, patients with painful bone metastases consult with an orthopedic oncologist, since these physicians specialize in the diagnoses and treatment of primary benign and malignant tumors of the bones and perform surgery.

Non-Medication therapies for bone pain relief include the following, and patients with bone pain may also want to review the section below entitled *Therapies for Aromatase Inhibitor-Induced Pain* (*Arthralgia):*

- **Bone Cement**
- **Calmare Scrambler Therapy**
- **Claritin**
- **Infrared Heating Pad**
- **MRIgFU Ablation Therapy (ExAblate)**
- **Other Current Non-Surgical Ablation Techniques**
  - *Cryoablation*
  - *External beam radiation*
  - *RadioFrequency Ablation*
  - *Radiopharmaceuticals*
  - *Stereotactic Body RadioTherapy (SBRT)*
  - *Stereotactic RadioSurgery (SRS)*
  - *Other techniques*
  - *Samarium Sm 153 lexidronam (Quadramet)*
- **Strontium 89**
- **Surgery**
- **Vertebroplasty**

- **Bone Cement:** One option to strengthen and stabilize a bone is to use injections of quick-setting bone cement or glue called PolyMethyl MethAcrylate (PMMA). When PMMA is injected into a spinal bone it's called "Vertebroplasty" or "Kyphoplasty." This treatment helps to stabilize the bone and relieve pain in most people. When bone cement is injected to strengthen bones other than the spine, it's called "Cementoplasty." Sometimes, it is used along with surgery, radiation, radiofrequency ablation, or other treatments, depending on the person's medical situation. A person with spinal cord compression, an infection, or in poor health might not do well with this treatment. **From[265, PMID:20981329]:** ***http://www.cancer.org/treatment/understandingyourdiagnosis/bonemetastasis/bone-metastasis-local-treatments***

- **Calmare Scrambler Therapy:** Scrambler therapy is a pain management approach that uses a machine to block the transmission of pain signals by providing non-pain information to nerve fibers that have been receiving pain messages. Scrambler therapy has been shown to be effective at reducing pain symptoms in patients with severe, drug-resistant pain from terminal cancer. Although

people may think of it as being similar to transcutaneous electrical nerve stimulation (TENS) therapy, scrambler therapy is felt to work through a different mechanism. TENS is thought to work through the gateway theory of pain relief, whereby normal touch sensations blocks pain sensations. Scrambler therapy, on the other hand, is proposed to provide normal-self, non-pain electrical information via nerves that have been transmitting chronic pain information. Through a process termed plasticity, this is able to retrain the brain so that it does not ascribe pain to the chronic pain area. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B39fb0977-4c06-4d72-8c04-841b6e172bba%7D/mayo-clinic-researchers-test-scrambler-therapy-for-pain***

- **Claritin:** Nearly a third of people given Neulasta injections to increase white blood cell counts experience bone pain. Recently it was found that the antihistamine Claritin (loratidine) decreased the risk of adverse Neulasta side effects, and many mbc patients who are taking Neulasta reported that Claritin has helped relieve pain.

- **Infrared Heating Pad,** which uses infrared technology that can penetrate several inches deep into the body for pain relief and relaxation. One woman wrote that she tried using the Infrared Heating Pad on her back for intense pain from bone metastases and her back pain almost completely subsided.

- **MRIgFU Ablation Therapy (ExAblate**). This type of therapy significantly reduced pain in 67% of patients who received the treatment. The device uses numerous small ultrasound beams designed to target a tumor within the bone, heat it and destroy it. ExAblate was approved by the U.S. Food and Drug Administration as second-line therapy for palliation (relief) of painful metastatic bone tumors. The first-line therapy is typically radiotherapy. The response to ExAblate appears to be as good as radiotherapy, which was notable because it is very unusual to see a second-line treatment with a response rate that is as high as first-line therapy **From:** ***http://www.sciencedaily.com/releases/2013/06/130602144337.htm*** and ***https://www.insightec.com/clinical/oncology***

- **Non-surgical Ablation Techniques:** The term "ablation" usually refers to the removal of harmful substances from the body. In this context, placing a needle or probe right into a tumor and using heat, cold, or a chemical to destroy it is called ablation. Ablation may be used if only 1 or 2 bone tumors are causing problems.

  Current non-surgical ablation techniques include:

  - *Cryoablation***,** which entails using a very cold probe that is put into the tumor to freeze it, thus killing the cancer cells.

  - *External Beam Radiation,* which is a very common ablation technique.

  - *RadioFrequency Ablation (RFA):* Radiofrequency Ablation uses a needle that carries an electric current. The electric current is delivered through the needle to heat the tumor to destroy it. RFA is usually done while the patient is under general anesthesia. Studies indicate that RFA for spinal metastasis results in clinically significant pain relief for 90% of patients. It can also be repeated, if necessary, although most patients do not need a repeat procedure. **From:** ***http://vitalsigns.uclahealth.org/spring2017/files/7.html***

  - *Radiopharmaceuticals:* Substances called radiopharmaceuticals are given through a vein, and they use low levels of radioactive material that has a strong attraction to bones. Once in the body, the particles travel to the areas of bone metastasis and release their radiation. This treatment doesn't require a hospital stay, and the patient will not be radioactive after treatment. **From:** ***http://www.mayoclinic.org/diseases-conditions/bone-metastasis/basics/treatment/con-20035450***

  - *Stereotactic Body RadioTherapy (SBRT):* This treatment is similar to central nervous system (CNS) stereotactic radiosurgery (SRS), except that it deals with tumors outside of the CNS. A stereotactic radiation treatment for the body means that a specially designed coordinate-system is used for the exact localization of the tumor in the body in order to treat it with limited but highly precise treatment fields. SBRT involves the delivery of a single high dose radiation treatment or a few fractionated radiation treatments (usually up to 5 treatments). In some particular clinical settings, such as oligometastatic patients and/or

those with a long life expectancy, spinal SBRT could be considered a valid therapeutic option to obtain long-lasting palliation. **From:** ***http://radonc.ucla.edu/sbrt***

- *Stereotactic Radiosurgery (SRS)* is a form of radiation therapy that focuses high-power energy on a small area of the body such as. tumors and other problems in the brain, spine, and neck. It is not surgery in the traditional sense because there's no incision. Instead, SRS uses 3-D (three-dimensional) imaging to target high doses of radiation to the affected area with minimal impact on the surrounding healthy tissue. Gamma Knife and Cyberknife are forms of SRS. **From[266, PMID:PMC3291699]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3291699/***

  - *Other techniques* utilize **alcohol** to kill the cells, or other ways to **heat** the tumor (such as **Laser-Induced Interstitial Thermotherapy).** After the cancer tissue is destroyed, the space left behind may be filled with bone cement.

    - *Samarium Sm 153 lexidronam (Quadramet):* This is a radiopharmaceutical (a group of drugs which have radioactivity) which is used to help relieve the bone pain that may occur with certain kinds of cancer. The radioactive samarium is taken up in the bone cancer area and gives off radiation that helps provide relief of pain, and several clinical trials point to its success in this regard. One of these was a multicenter trial conducted in China in which patients with painful bone metastasis from a variety of primary tumors were treated with this compound. Pain was assessed using a composite of pain scores and analgesic consumption. Overall, 73% of patients, independent of dose level, experienced effective pain palliation. Analgesic use was reduced significantly or completely in 82% of those responding. **From[267, PMID:PMC1472939]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1472939/***

- **Strontium 89** (under the brand name **Metastron**) is an older therapy that has been used to treat painful bone metastasis accompanying metastatic breast cancer. **From**: ***http://www.cancernetwork.com/oncology-journal/use-strontium-89-metastatic-cancer-us-and-uk-experience***

- **Surgery:** Surgery to remove a primary bone tumor (one that started in the bone) is often done to try and cure the cancer. But often the purpose of surgically treating a bone metastasis is to relieve symptoms and/or stabilize the bone to prevent fractures. Bone metastasis can weaken bones, leading to fractures that tend to heal poorly. An operation can be done to place screws, rods, pins, plates, cages or other devices to make the bone more stable the bone and help prevent fractures. If the bone is already broken, surgery can often relieve pain quickly and help the patient return to their usual activities. If the doctor cannot surgically reinforce a bone that has metastasis, a cast or splint may help stabilize it to reduce pain, so the person can move around.

- **Vertebroplasty:** This is a special type of surgery intended to stabilize spinal fracture(s) and to stop the resulting pain. Vertebroplasty is considered a minimally invasive surgical procedure because it is done through a small puncture in the patient's skin (as opposed to an open incision). One patient indicated that she had a vertebroplasty under twilight sedation followed by radiotherapy and has felt much better in the 5 years since.

Robaxin as a Medication for Bone-Specific Pain: In addition to the items listed under *Pain Medications* in the beginning of this section, a drug called Robaxin (Methocarbamol) was praised by one patient with bone pain. Robaxin is a central muscle relaxant used to treat skeletal muscle spasms. She wrote, *"Someone recommended an unlikely drug to me which has had excellent effect on my bone pain and general aches and pains. It's called Robaxin, which may be worth asking to try because it has helped me a lot. I can't take the Oxy's and Percocet and Vicodin. They make me vomit and become dizzy. Robaxin has helped me a lot."*

THERAPIES FOR AROMATASE INHIBITOR-INDUCED PAIN ("ARTHRALGIA")

Up to half of women on Aromatase Inhibitor (AI) therapy experience joint pain. Several specific therapies other than drugs for pain resulting from taking AIs (which is referred to as "arthralgia") include:

- **Acupuncture and Electroacupuncture**

- **Amla-Plex**
- **Calmare Scrambler Therapy**
- **Celebrex**
- **Curcumin**
- **Cymbalta**
- **Exercise**
- **Glucosamine HCI 1500 mg with Chondroitin Sulfate 1200 before bedtime**
- **Infrared Heating Pad**
- **Massage**
- **Reiki**
- **"Stop Pain Spray"**
- **Switching to the "Brand Name" of the Drug or Another Generic Manufacturer**
- **Walgreens Extra Strength Muscle Rub**

- **Acupuncture and Electroacupuncture** may often helpful in relieving pain of varying origination. Acupuncture involves inserting thin sterile needles into different points on the body by a skilled practitioner. Acupuncture has been used for centuries for pain relief and other purposes. An international research team pooled the results of 29 studies involving nearly 18,000 participants. Some had acupuncture, some had "sham" acupuncture, and some didn't have acupuncture at all. Overall, acupuncture relieved pain by about 50%. **Electroacupuncture,** a form of acupuncture in which a small electric current is passed between pairs of acupuncture needles, appears to relieve symptoms associated with AIs in breast cancer patients. In study participants with AI-associated joint pain, electroacupuncture produced significant and "clinically relevant improvements" compared with usual care. **From[268, PMID:22965186; 269, PMID:24210070]:** ***http://www.health.harvard.edu/blog/acupuncture-is-worth-a-try-for-chronic-pain-201304016042*** and ***http://www.medscape.org/viewarticle/832348***

- **Amla-Plex** (by Ayush Herbs): This is an Ayurvedic herbal "paste" that is purported to enhance the immune system. (Ayurvedic medicine is a system that originated in northern India over 5,000 years ago). The author stumbled upon its efficacy for joint pain when she began taking it at her Naturopathic Oncologist's suggestion in order to bolster her immune system. Coincidentally, she was suffering from a painful episode of bursitis at the time and noticed that by the evening of the first dose her bursitis felt less acute. Each day thereafter the pain decreased, and one week later it had disappeared. Surprised and pleased, she researched the mixture and found it is purported to have anti-inflammatory properties, which evidently worked in her situation.

- **Calmare Scrambler Therapy:** Scrambler therapy is a pain management approach that uses a machine to block the transmission of pain signals by providing non-pain information to nerve fibers that have been receiving pain messages. Scrambler therapy has been shown to be effective at reducing pain symptoms in patients with severe, drug-resistant pain from terminal cancer. Although people may think of it as being similar to transcutaneous electrical nerve stimulation (TENS) therapy, scrambler therapy is felt to work through a different mechanism. TENS is thought to work through the gateway theory of pain relief, whereby normal touch sensations blocks pain sensations. Scrambler therapy, on the other hand, is proposed to provide normal-self, non-pain electrical information via nerves that have been transmitting chronic pain information. Through a process termed plasticity, this is able to retrain the brain so that it does not ascribe pain to the chronic pain area. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B39fb0977-4c06-4d72-8c04-841b6e172bba%7D/mayo-clinic-researchers-test-scrambler-therapy-for-pain***

- **Celebrex:** One person reported pain relief with a daily dose of 200 mg of **Celebrex,** a nonsteroidal anti-inflammatory drug used to treat pain or inflammation

- **Curcumin/Turmeric:** Curcumin, which has powerful antioxidant and anti-inflammatory properties, is the most active constituent of turmeric**.** Some studies show that turmeric may help fight infections and some cancers. Since inflammation may be associated with joint pain, adding turmeric (mixed with freshly ground black pepper and olive oil for bioavailability) to foods or taking

supplements may help relieve symptoms. **From[270, PMID:23847105]:** ***https://www.webmd.com/vitamins/ai/ingredientmono-662/turmeric***
Warning: Patients undergoing Doxorubicin (Adriamycin) or Cyclophosphamide (Cytoxan) chemotherapy should refrain from taking curcumin while on this therapy, since it can interfere with the effectiveness of these drugs. **From[198, PMID:12097302]:** ***http://www.ncbi.nlm.nih.gov/pubmed/12097302***

- **Cymbalta:** Several patients who experienced joint pain from AIs reported a significant decrease within days after beginning to take a prescription antidepressant drug called Cymbalta (Duloxetine), even on a reduced dose as low as 20mg.

- **Exercise** may help relieve AI-related pain, according to research published in the Journal of Clinical Oncology. Exercise consisted of 150 minutes per week of aerobic exercise, and twice-weekly supervised strength training. The researchers found that, at 12 months, the worst joint pain scores decreased by 29% in the exercise group. **From[271, PMID:25452437]:** ***http://medicalxpress.com/news/2014-12-eases-arthralgia-aromatase-inhibitors.html***

- **Glucosamine HCI 1500 mg with Chondroitin Sulfate 1200 mg** taken in a single capsule before bedtime may provide relief. Some people swear that over-the-counter dietary supplements called glucosamine and chondroitin ease arthritis pain, reduce stiffness, and protect joints from further damage, although others say they didn't help as much as they'd hoped.

    - **Infrared Heating Pad**, which uses infrared technology that can penetrate several inches deep into the body for pain relief and relaxation.

    - **Massage:** Clinical studies show that massage can alleviate symptoms such as pain, stress/anxiety, nausea, insomnia, fatigue, and depression. **From[272, PMID:15336336]:** ***http://www.mskcc.org/cancer-care/herb/massage-therapy***

- **Reiki:** Reiki is based on the belief that spiritual energy can be channeled through a Reiki practitioner to heal the patient's spirit. This is thought to help release the body's natural healing powers. Reiki is most often given as a hands-on treatment. There are many individual reports about Reiki's power to increase feelings of well-being and refresh the spirit. One small controlled pilot study found that Reiki was linked with reduced pain in patients with advanced cancer. **From [273, PMID:20664124]** ***https://www.uclahealth.org/rehab/workfiles/Urban%20Zen/Clinical_Perspective_Reiki_for_Mind.pdf***

- **"Stop Pain Spray:"** One person wrote that she uses this spray on her lumbar region and achy joint areas, and it took about 30 minutes to work.

- **Switching to the "Brand Name" of the Drug:** Interestingly, generic forms of a specific drug (i.e. Letrozole) may have some different ingredients - called "fillers" - than the name brand of the drug (i.e. Femara). So, switching to the name brand name drug or to another generic form of it may sometimes help (one lady indicated that switched from Anastrozole to brand-name Arimidex and experienced profound relief). If switching to the brand-name drug is not possible due to insurance related issues, then trying a different manufacturer of the generic drug may help.

- **Walgreens Extra Strength Muscle Rub:** One person wrote that when the pain in her hands gets very bad, she applies Walgreens Extra Strength Muscle Rub and wears a cotton glove over it (this would also work well on the feet, when covered with cotton socks).

THERAPIES FOR PERIPHERAL NEUROPATHY

Remedies other than pain medications for peripheral neuropathy-induced pain include:

- **Acupuncture**
- **Alpha-Lipoic Acid (ALA)**
- **Amino Acids**
- **Calmare Scrambler Therapy**
- **Capsaicin Cream**
- **Exercise**
- **Herbs**
- **Infrared Heating Pad**
- **Lidoderm Patches**
- **Massage**
- **Milkweed Balm**
- **Nerve Repair Optimizer**
- **Neuropathy Support Formula**
- **Physical Therapy**
- **Reiki**
- **Shoes that are Comfortable**
- **Topricin Pain Cream**
- **Transcutaneous Electrical Nerve Stimulation (TENS) unit**

- **Acupuncture:** According to one study, acupuncture both alleviated symptoms of peripheral neuropathy and increased nerve conduction. In the study, 21 patients received acupuncture therapy according to classical Chinese Medicine while 26 patients received the best medical care but no specific neuropathy treatment. Sixteen patients (76%) in the acupuncture group improved symptomatically and objectively, while only four patients in the control group (15%) did so. **From[274, PMID:17355547]:** ***http://www.ncbi.nlm.nih.gov/pubmed/17355547***

- **Alpha-Lipoic Acid (ALA)**: This antioxidant has been used as a treatment for peripheral neuropathy in Europe for years to relieve pain. In a study of neuropathic pain caused by diabetes, it was concluded that alpha lipoic acid leads to a significant and clinically relevant reduction in neuropathic pain. **From[275, PMID:20421656]:** ***http://www.ncbi.nlm.nih.gov/pubmed/20421656***

- **Amino acids** such as **acetyl-L-carnitine** may help improve peripheral neuropathy in people who have undergone chemotherapy. **From:** ***http://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/basics/alternative-medicine/con-20019948***

- **Calmare Scrambler Therapy:** Scrambler therapy is a pain management approach that uses a machine to block the transmission of pain signals by providing non-pain information to nerve fibers that have been receiving pain messages. Scrambler therapy has been shown to be effective at reducing pain symptoms in patients with severe, drug-resistant pain from terminal cancer. Although people may think of it as being similar to transcutaneous electrical nerve stimulation (TENS) therapy, scrambler therapy is felt to work through a different mechanism. TENS is thought to work through the gateway theory of pain relief, whereby normal touch sensations blocks pain sensations. Scrambler therapy, on the other hand, is proposed to provide normal-self, non-pain electrical information via nerves that have been transmitting chronic pain information. Through a process termed plasticity, this is able to retrain the brain so that it does not ascribe pain to the chronic pain area. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B39fb0977-4c06-4d72-8c04-841b6e172bba%7D/mayo-clinic-researchers-test-scrambler-therapy-for-pain***

- **Capsaicin Cream** containing an ingredient found naturally in hot peppers which can cause modest improvements in peripheral neuropathy. Doctors may suggest using this cream with other treatments. Skin burning and irritation may occur, but usually lessens over time. However, some people may not be able to tolerate it.

- **Exercise:** Up to 60% percent of people with breast cancer and other solid tumors who receive taxanes, vinca alkaloids, and platinum-based chemotherapies will experience neuropathy. To reduce this side effect, patients are encouraged to discuss exercise with their doctor because a recent study comparing neuropathy symptoms in exercisers (those who undertook walking and gentle resistance-band workouts) vs. non-exercisers concluded that exercise decreases neuropathy symptoms. **From:** ***http://www.eurekalert.org/pub_releases/2016-06/uorm-cae060316.php***

- **Herbs** such as evening primrose oil may speed recovery from neuropathy. **From:** ***http://www.drugs.com/npp/evening-primrose-oil.html***

- **Infrared Heating Pad,** which uses infrared technology that can penetrate several inches deep into the body for pain relief and relaxation. One woman wrote that she started experiencing extreme pain in her liver, sometimes crying when a Percocet wore off. Initially, she tried it on her back for intense pain from bone metastases and reported that her back pain almost completely subsided.

- **Lidoderm patches** (especially for disc problems in the back), such as **Voltaren gel,** and/or **Arnica cream** may be helpful.

- **Massage:** Clinical studies show that massage and touch therapy can alleviate symptoms such as pain, fatigue, stress/anxiety, nausea, insomnia, and depression. **From:** ***http://www.mskcc.org/cancer-care/herb/massage-therapy***

- **Milkweed Balm**: One woman wrote, *"I found this in a Cancer Magazine and decided to order 2 ounces of it. I am not into this kind of stuff, but I have to say it has helped my neuropathy and other aches and pain. I slather on my feet at night with socks and AM with socks. Also, on my 62-year-old aches and pains. It is working well for me. I have been getting weekly Taxol since July and now finally have some relief."*

- **Nerve Repair Optimizer (which contains Alpha Lipoic Acid):** Several patients have claimed to have good result using this, and some use it in conjunction with Neuropathy Support Formula (immediately below).

- **Neuropathy Support Formula:** Several patients have claimed to have good result using this, potentially in conjunction with Nerve Repair Optimizer (above).

- **Physical Therapy** may in some instances help alleviate neuropathy-induced pain.

- **Reiki:** Reiki is based on the belief that spiritual energy can be channeled through a Reiki practitioner to heal the patient's spirit. This is thought to help release the body's natural healing powers. Reiki is most often given as a hands-on treatment. There are many individual reports about Reiki's power to increase feelings of well-being and refresh the spirit. Some patients who were getting cancer treatment have reported an increased sense of well-being after Reiki sessions. One small controlled pilot study found that Reiki was linked with reduced pain in patients with advanced cancer. **From:** ***http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/manualhealingandphysicaltouch/reiki***
- **Shoes that are comfortable**, such as Dansko, Sketchers with memory foam, and Birkenstocks can help relieve pain while walking.

- **Topricin Topical Pain Relief Cream** has been claimed to be very helpful according several people with painful neuropathy.

- **Transcutaneous Electrical Nerve Stimulation (TENS) unit,** where adhesive electrodes are placed on the skin to deliver a gentle electric current at varying frequencies. TENS may be applied for 30 minutes daily for about a month. **From[263, PMID:26141332]:** ***http://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/basics/treatment/con-20019948***
One person swore by an ultrasound unit called MPO US Pro 2000 Ultrasound Unit, which she used to help mitigate back pain:

THERAPIES FOR STOMACH PAIN

Antispasmodic medications may be of help for stomach pain: One lady reported terrible pain at night in her abdominal area. She wrote that she learned it is called "intestinal neuropathy" and is a rare, but very real side effect of Navelbine. The solution which worked is antispasmodic.

Note: Stomach (abdominal) pain may be caused by many different reasons, so it is very important for patients with abdominal pain to contact their doctor.

36. Therapies to Ease Depression and Anxiety

Often accompanying the unwelcome effects of MBC and its treatments are feelings of anxiety and/or depression. The terms "anxiety" and "depression" are frequently used interchangeably, yet they are a bit different:

People suffering from anxiety have a sense of doubt and vulnerability about future events. The attention of anxious people is focused on their prospects, along with fear that those future prospects will be bad. Patients suffering from depression may think they already **know** what will happen and believe it will be bad. Some key symptoms include:

Feeling sad and/or hopeless

Lack of interest and enjoyment in activities that used to be fun and interesting

A feeling of psychological "numbness"

Physical aches and pains without apparent cause

Lack of energy

Restlessness and/or irritability

Difficulty concentrating, remembering, and/or making decisions

Changes in appetite and weight

Unwelcome changes in usual sleep patterns

Social withdrawal

In extreme cases, thoughts of death and suicide

Patients with anxiety and/or depression are encouraged to consult with their doctor about possible ways to decrease these unwelcome feelings.

THERAPIES OTHER THAN DRUGS TO TREAT ANXIETY AND DEPRESSION

- **Acupuncture and Electroacupuncture**
- **Cognitive-Behavioral Therapy (CBT)**
- **Enjoyment**
- **Individual Psychotherapy**
- **Massage**
- **Mindfulness**
- **Pet(s)**
- **Reiki**
- **Support Groups**
- **Tai Chi**

- **Acupuncture or Electroacupuncture:** Acupuncture involves inserting thin sterile needles into different points on the body by a skilled practitioner and has been used for centuries. . One study found that **Electroacupuncture**—in which a mild electric current is transmitted through tiny needles inserted into the skin —was just as effective as Prozac in reducing symptoms of depression. **From[276, PMID:23647408]:** ***http://www.scientificamerican.com/article/can-acupuncture-treat-depression/***

- **Cognitive-Behavioral Therapy (CBT),** which can help patients identify and restructure negative thoughts and increase positive behaviors. In one study, 124 patients with MBC who received 8 weekly sessions of group CBT reported reduced depression and mood disturbance, and improved self-esteem compared with a no-therapy control group.

- **Doing something enjoyable** such as watching a funny movie or reading a good book may help ease anxiety or depression.

- **Individual Psychotherapy** may be of enormous benefit to some patients.

- **Massage:** Clinical studies show that massage can alleviate symptoms such as depression and anxiety, stress, nausea, insomnia, pain, and fatigue. **From[272, PMID:15336336]:** ***http://www.mskcc.org/cancer-care/herb/massage-therapy***

- **Mindfulness:** Mindfulness techniques including (but not limited to) meditation and yoga may be highly effective in reducing depression. A study of 35 cancer patients examined the effectiveness of Mindfulness-Based Stress Reduction (MBSR) on depression and other symptoms. The MBSR group received training in mindfulness meditation, yoga, and self-regulatory responses to stress. Compared to control groups, the MBSR group reported large improvements regarding depression, fatigue, energy, and sleep disturbance. Results were maintained or strengthened at 1-month follow-up, and improvements in all outcomes were maintained 6 months after completing the course. **From[277, PMID:25132206]:** ***http://www.ncbi.nlm.nih.gov/pubmed/25132206***

- **Pet(s):** Often, having a pet may enable a depressed or anxious person to relax and feel much calmer. MBC patients may not always want – or be able to care for – some types of animals (such as a very energetic puppy). Even is relatively simple companion such as a goldfish may provide patients with relaxation and enjoyment.

- **Reiki:** Reiki is based on the belief that spiritual energy can be channeled through a Reiki practitioner to heal the patient's spirit. This is thought to help release the body's natural healing powers. Reiki is most often given as a hands-on treatment. There are many individual reports about Reiki's power to increase feelings of well-being and refresh the spirit. Some patients who were getting cancer treatment have reported an increased sense of well-being after Reiki sessions.
  From:
  http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/manualhealingandphysicaltouch/reiki

- **Support Groups,** whether face-to-face, telephone, or over the Internet, may help to enable people suffering from depression to feel less alone. For patients desiring **Telephone Support**, a list may be found at: ***http://www.mbcn.org/telephone-support-groups/***

- **Tai Chi:** This form of slow-moving meditation, is just as effective as Cognitive Behavioral Therapy (formerly the sole "gold standard" for insomnia treatment), with both showing enduring benefits over one year. Because tai chi promotes robust improvements in sleep health in breast cancer survivors with insomnia, it offers the additional benefits of improving depressive symptoms and fatigue. **From**: ***https://www.eurekalert.org/pub_releases/2017-05/uoc--tcr050917.php***

Before reading further, it may be helpful to know that there are three main chemical messengers, referred to as "neurotransmitters," that are involved in depression (as follows). While their effect on mood is not completely clear, doctors recognize that modulating

these brain chemicals may help with depression. Physicians prescribing antidepressants must also be made fully aware of all other medications the patient is taking (see Warning about Tamoxifen Interactions below).

The three main chemical messengers (neurotransmitters) involved in depression are:

1. Dopamine
2. Norepinephrine
3. Serotonin

DRUGS FOR TREATING ANXIETY AND DEPRESSION

Warning about Tamoxifen Interactions: Some antidepressant drugs can interfere with the body's ability to process Tamoxifen effectively. *Patients taking Tamoxifen should preferably **not** be given the following drugs or supplements* for depression unless a viable reason is provided by their doctor.

Paxil (paroxetine)

Prozac (fluoxetine)

Cymbalta (duloxetine)

Wellbutrin (bupropion)

Zoloft (sertraline)

Saint John's Wort (hypericum)

The following drugs are of lower risk, or have not been well-studied:

Celexa (citalopram) – Slight risk of interaction with Tamoxifen

Lexapro (escitalopram) – Slight risk of interaction with Tamoxifen

Pristiq (desvenlafaxine) – There may be a slight risk of interaction with Tamoxifen, although it has not been well-studied.

Remeron (mirtazapine) – There may be a slight risk of interaction with Tamoxifen, although it has not been well-studied.

From[278, PMID:20141708]: ***https://www.verywell.com/antidepressants-that-interact-with-tamoxifen-430175***

Categories of Antidepressants are:

- **Atypical Antidepressants**
- **Benzodiazepines**
- **BuSpar**
- **Monoamine Oxidase Inhibitors (MAOIs). MAOIs**
- **Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs).**
- **Selective Serotonin Reuptake Inhibitors (SSRIs)**
- **Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)**

- **Tricyclic Antidepressants**

- **Atypical Antidepressants**. These medications don't fit neatly into any of the other antidepressant categories listed below. They include Trazodone **(Oleptro), Mirtazapine (Remeron)** and **Vortioxetine (Brintellix).** They are sedating and usually taken in the evening. A newer medication called **Vilazodone (Viibryd**) is thought to have a low risk of sexual side effects.

- **Benzodiazepines:** This class of drugs is frequently used for short-term management of anxiety. Benzodiazepines such as **Xanax (Alprazolam), Clonazepam, (Klonopin) Valium (Diazepam)**, and **Ativan (Lorazepam)** can be effective in promoting relaxation and reducing physical symptoms of anxiety.

- **BuSpar:** Also known as Buspirone, BuSpar is an antianxiety agent that is not related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs. Instead, it belongs to a group of anti-anxiety drugs called anxiolytics, but it seems to work somewhat differently than other drugs in that class. Though researchers don't know exactly how BuSpar reduces anxiety, they believe it competes with serotonin and dopamine, chemical brain messengers involved with causing anxiety symptoms. Doctors prescribe it for anxiety disorders and short-term relief of anxiety symptoms

- **Monoamine Oxidase Inhibitors (MAOIs). MAOIs**: This class of drugs, which includes such as medications as **Tranylcypromine (Parnate), Phenelzine (Nardil)** and **Isocarboxazid (Marplan)** may be prescribed after other medications haven't worked, because these can have serious side effects. Using an MAOI requires a strict diet due to dangerous (or even deadly) interactions with foods such as cheeses, pickles and wines and some medications, including birth control pills, decongestants and certain herbal supplements. **Selegiline (Emsam),** a newer MAOI that is applied on the skin as a patch, may cause fewer side effects than other MAOIs. .

- **Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs):** These drugs act as a reuptake inhibitor for the neurotransmitters norepinephrine and dopamine by blocking the action of the norepinephrine transporter (NET) and the dopamine transporter (DAT), respectively. **Bupropion (Wellbutrin, Aplenzin, Forfivo XL**) falls into this category, and it's one of the few antidepressants that are not frequently associated with sexual side effects.

- **Selective Serotonin Reuptake Inhibitors (SSRIs):** SSRIs, which are the most commonly prescribed anti-depressant drugs, ease depression by blocking the reabsorption (reuptake) of serotonin in the brain. Changing the balance of serotonin seems to help brain cells send and receive chemical messages, which in turn boosts mood.

- **Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):** Like NDRIs and SSRIs, these drugs work by affecting chemical messengers (neurotransmitters) used to communicate between brain cells. SNRIs affect both serotonin and norepinephrine, which are two of the three neurotransmitters. Therefore, medications in this group of antidepressants are sometimes called "dual-action" antidepressants. **Duloxetine (Cymbalta) and Desvenlafaxine (Pristiq)** are commonly-prescribed SNRIs.

- **Tricyclic Antidepressants.** These drugs, such as **Imipramine (Tofranil), Nortriptyline (Pamelor), Amitriptyline, Doxepin, Trimipramine (Surmontil), Desipramine (Norpramin)** and **Protriptyline (Vivactil)** — tend to cause more side effects than newer antidepressants. Therefore, tricyclic antidepressants generally aren't prescribed unless the patient has tried other antidepressants without improvement. **From[279; 280, PMID:20041476; 281, PMID:12551730]:** ***http://www.currentpsychiatry.com/index.php?id=22661&tx_ttnews[tt_news]=175454*** and ***http://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20044970*** and ***http://www.mayoclinic.org/diseases-conditions/depression/in-depth/ssris/art-20044825*** and ***http://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20046273***

One patient who suffered from depression wrote about a combination of drugs that successfully helped to treat her condition: "*I have had very good results (18 months) from pairing 150 mg Effexor, an antidepressant, with 15 mg Dextroamphetamine, a stimulant. I*

noticed how much the stimulant had enhanced the effect of the antidepressant when I allowed the prescription to run out. I let it go for a few weeks, and was really stunned by the comparative achiness, deep fatigue and loss of pleasure I felt. I got back on the Dextroamphetamine stimulant and felt increased well-being, much less fatigue, and a normal level of interest in life. The combination has done more for me than I ever expected. I don't know if others have noticed the enhancement of an antidepressant in quite the same way, but it sure is interesting!"

37. Therapies to Reduce Fatigue and Insomnia

Cancer Related Fatigue (CRF) is the most common physical issue faced by cancer patients. It's more than simply being tired – physically, mentally, and emotionally. For many people living with cancer, everyday activities – talking on the phone, shopping for groceries, even lifting a fork to eat – can be overwhelming tasks. Additionally, many patients also experience insomnia, which is the inability to fall asleep within a reasonable amount of time and to remain asleep adequately through the night. Understandably, patients with insomnia may feel fatigued during the day. Both issues can be caused by cancer treatment, stress, pain, anxiety and/or depression, and even perhaps by the cancer itself.

For people undergoing chemotherapy in cycles, fatigue often becomes worse for the first few days and then gets better until the next treatment, when the pattern begins again. For those getting radiation, fatigue usually gets worse as the treatment goes on. Treatment and the cancer itself may directly or indirectly (i.e. through lowering blood counts) cause the patient to feel exhausted. Left untreated, cancer-related fatigue can upset the patient's quality of life by adversely affecting daily routines, self-care, recreation, relationships, and general well-being.

Many breast cancer patients may not be aware that fatigue may be a by-product of infections such as Urinary Tract Infections (UTIs), although no other symptoms may be present. Thinning of the tissues of the vagina, bladder and urethra, as well as change in the vaginal environment after menopause, may make these areas less resistant to bacteria and cause more frequent urinary tract infections. Additionally, low estrogen levels have been linked to recurrent UTIs. Therefore, patients who experience fatigue for no apparent reason may wish to consider obtaining a urine test to determine whether they may be suffering from a UTI, for which the most common treatment is antibiotics.

People with MBC should not assume that their fatigue and/or insomnia are acceptable problems that cannot be treated. Patients are encouraged to speak with their doctor about these concerns, and to discuss Palliative Care (please refer to the *Palliative Care* section for additional information).

Patients who are currently working may also wish to discuss potential Short-Term Disability (STD) and Long-Term Disability (LTD) benefits with their employer.

NON-DRUG THERAPIES TO REDUCE FATIGUE

There are several therapies other than drugs that patients may wish to try in order to reduce fatigue:

- **Acupuncture**
- **Adequate water and food intake**
- **Exercise**
- **Korean Ginseng**
- **Massage**
- **Mindfulness**
- **Music Therapy**
- **Reiki**
- **Tai Chi**

- **Acupuncture:** Acupuncture may be a powerful tool for improving fatigue. It involves inserting thin sterile needles into different points on the body by a skilled practitioner. Based upon a study of 246 patients with breast cancer, acupuncture improved their general fatigue, physical fatigue, mental fatigue, anxiety and depression, and quality of life. **From[282, PMID:23109700]:** ***http://www.ncbi.nlm.nih.gov/pubmed/23109700***

- **Adequate fluid intake** during the day (not before bed) and **good nutritional consumption** - especially protein – may be helpful in enabling patients to feel more alert.

- **Exercise** can be regarded as beneficial for individuals with cancer-related fatigue during and post-cancer therapy, specifically those with solid tumors. **From[283, PMID:23152233]:** ***http://www.ncbi.nlm.nih.gov/pubmed/23152233***

- **Korean Ginseng**: One lady wrote that her Medical Oncologist suggests Korean Ginseng to help his patients combat fatigue. She takes one 650mg capsule of Sona Korean Ginseng daily with breakfast, with two months on and one month off, and has experienced a profound difference in energy.

- **Massage:** Clinical studies show that massage can alleviate symptoms such as fatigue, stress/anxiety, nausea, insomnia, pain, and depression. **From[272, PMID:15336336]:** ***http://www.mskcc.org/cancer-care/herb/massage-therapy***

- **Mindfulness:** Mindfulness techniques including (but not limited to) meditation and yoga may be highly effective in reducing fatigue and boosting energy. A study of 35 cancer patients examined the effectiveness of Mindfulness-Based Stress Reduction (MBSR) for Cancer Related Fatigue and related symptoms. The MBSR group received training in mindfulness meditation, yoga, and self-regulatory responses to stress. Compared to control groups, the MBSR group reported large improvements regarding fatigue, energy, depression, and sleep disturbance. Results were maintained or strengthened at 1-month follow-up, and improvements in all outcomes were maintained 6 months after completing the course. **From[277, PMID:25132206]:** ***http://www.ncbi.nlm.nih.gov/pubmed/25132206***

- **Music Therapy:** Music therapy includes singing, listening to music, learning a musical instrument, and performing music. One study found that music therapy daily greatly increased relaxation sensations and significantly decreased fatigue sensation in treated cancer survivors. **From[284, PMID:21056846]:** ***http://www.ncbi.nlm.nih.gov/pubmed/21056846***

- **Reiki:** Reiki is based on the belief that spiritual energy can be channeled through a Reiki practitioner to heal the patient's spirit. This is thought to help release the body's natural healing powers. Reiki is most often given as a hands-on treatment. There are many individual reports about Reiki's power to increase feelings of well-being and refresh the spirit. Some patients who were getting cancer treatment have reported an increased sense of well-being, with less pain, nausea, and vomiting after Reiki sessions. One small controlled pilot study found that Reiki was linked with reduced pain in patients with advanced cancer. **From:** ***http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/manualhealingandphysicaltouch/reiki***

- **Tai Chi:** This form of slow-moving meditation, is just as effective as Cognitive Behavioral Therapy (formerly the sole "gold standard" for insomnia treatment), with both showing enduring benefits over one year. Because tai chi promotes robust improvements in sleep health in breast cancer survivors with insomnia, it offers the additional benefits of improving depressive symptoms and fatigue. **From:** ***https://www.eurekalert.org/pub_releases/2017-05/uoc--tcr050917.php***

DRUGS THAT MAY REDUCE FATIGUE

Prescription medications for cancer-related fatigue include but are not limited to:

- **Aranesp,** which has been found to be superior to placebo for treating cancer-related fatigue in anemic patients.
  Warning: Before a patient can begin taking Aranesp, they must sign an acknowledgment indicating that they understand the risks, which include the possibility that their tumor may grow faster and that they may die sooner.
  From: ***http://www.fda.gov/downloads/Drugs/DrugSafety/ucm085918.pdf***

- **Provigil and Ritalin:** Research has indicated that stimulants of the Central Nervous System (CNS), such as **Provigil** and **Ritalin**, may alleviate cancer-related fatigue **From[285, PMID:18053430; 286, PMID:18695134]:** ***http://news.cancerconnect.com/ritalin-and-epoetins-may-alleviate-cancer-related-fatigue/*** and ***http://www.jnccn.org/content/5/10/1081.abstract***

NON-DRUG THERAPIES TO IMPROVE SLEEP

There are many things that patients may try in order to obtain a good night's sleep, including but not limited to:

- **Acupuncture**
- **Avoiding caffeine and stimulating activities**
- **Avoiding long afternoon naps**
- **Cognitive Behavioral Therapy (CBT)**
- **Cortisol Manager** (a supplement)
- **Establishing a relaxing pre-sleep routine**
- **Exercise**
- **Going to bed only when sleepy**
- **Mindfulness**
- **Reading Before Bed**
- **Reducing blue Light at Night**
- **Setting a consistent time to lie down and get up**
- **Silicone earplugs**
- **Sleep Clinic Assessment**
- **Wearing Blue Light Glasses**

- **Acupuncture** involves inserting thin sterile needles into different points on the body by a skilled practitioner. Acupuncture has been used for centuries for pain relief and other purposes and is commonly used to treat insomnia in China. Clinical studies have shown that acupuncture may have a beneficial effect on insomnia compared with Western medication. **From[287, PMID:19922248]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3156618/***

- **Avoiding caffeine and stimulating activities** (such as avoiding exercising) in the evening may help make patients feel more relaxed at bedtime.

- **Avoiding long afternoon naps** may enable people to feel sleepier at bedtime.

- **Cognitive Behavioral Therapy (CBT):** CBT is considered the standard of care for insomnia in the general population and has also shown great promise for cancer patients. CBT has been shown to help 70%–80% of patients in the general population who receive it and to reduce by half the need for sleep medications taken by cancer patients. CBT has multiple components—stimulus control, sleep hygiene, relaxation, and others—that can be tailored to a patient's needs. People with insomnia often respond well to stimulus control therapy, which reconditions them to associate their bedrooms only with sleep. As patients learn healthy sleep hygiene (for instance, developing a relaxing bedtime ritual; getting up if sleep is difficult and only returning to bed when sleepy; and controlling environmental factors such as light, temperature, and noise), sleep comes to them more easily. Progressive muscle relaxation and guided imagery are often also very effective. Depending on the severity of the insomnia, patients can work individually with a psychologist or sleep specialist, participate in group therapy administered by a trained nurse or counselor, or self-administer cognitive behavioral therapy. **From[288, PMID:PMC4069142]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4069142/***

- **Cortisol Manager** (a supplement): This supplement was suggested by the author's Naturopathic Oncologist to reduce stress and enhance her quality of sleep, and it has accomplished both beautifully. (As previously mentioned, before taking any new supplement, patients should first speak with their doctor).

- **Establishing a relaxing pre-sleep routine** and using it consistently may help to condition patients to sleep much better.

- **Exercise** may help relieve insomnia, but it may take a little while before the patient experiences good results. **From[289, PMID:PMC3370319]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3370319/***

- **Going to bed only when sleepy and using the bedroom only for sleep and sexual activities** can help patients to sleep better.

- **Mindfulness:** Mindfulness techniques including (but not limited to) meditation and yoga may be highly effective in reducing sleep disturbance. A study of 35 cancer patients examined the effectiveness of Mindfulness-Based Stress Reduction (MBSR) on depression and other symptoms. The MBSR group received training in mindfulness meditation, yoga, and self-regulatory responses to stress. Compared to control groups, the MBSR group reported large improvements regarding sleep disturbance, depression, fatigue, and energy. Results were maintained or strengthened at 1-month follow-up, and improvements in all outcomes were maintained 6 months after completing the course. **From[277, PMID:25132206]:** ***http://www.ncbi.nlm.nih.gov/pubmed/25132206***

- **Reading before bed** may help some people to relax.

- **Reducing Blue Light at Night**: A key contributor to sleep problems may be the use of artificial lighting and electronics at night. Electronic devices such as PCs, TVs, and even overhead lights emit light of a blue wavelength, which tricks the brain into thinking that it is daytime. Some studies suggest that blue light in the evening disrupts the brain's natural sleep-wake cycles, which are crucial for optimal function of the body. One way to avoid blue light in the evening is to wear special amber-colored glasses which block all blue light so that the brain doesn't get the signal that it is supposed to stay awake. Another popular way to avoid blue light in the evening is to install a program called "Flux" on one's computer. This program automatically adjusts the color and brightness of the computer screen based on the patient's time zone. **From[290, PMID:16842544]:** ***http://authoritynutrition.com/block-blue-light-to-sleep-better***

- **Setting a consistent time to lie down and get up** may help to develop good sleeping habits.

- **Silicone earplugs** may help people to sleep better if noise is keeping them up at night.

- **Sleep Clinic Assessment:** Some patients with insomnia who have visited a Sleep Clinic have obtained relief through various means, so it may be worth speaking with one's doctor about a referral. Sleep clinics may teach patients the Cognitive Behavior Therapies mentioned above and may on occasion work with the patient's doctor regarding medication.

- **Wearing Blue Light Glasses:** A key contributor to sleep problems may be the use of artificial lighting and electronics at night. Electronic devices such as PCs, TVs, and even overhead lights emit light of a blue wavelength, which tricks the brain into thinking that it is daytime. Some studies suggest that blue light in the evening disrupts the brain's natural sleep-wake cycles, which are crucial for optimal function of the body. One way to avoid blue light in the evening is to wear special amber-colored glasses which block all blue light so that the brain doesn't get the signal that it is supposed to stay awake. Another popular way to avoid blue light in the evening is to install a program called "Flux" on one's computer. This program automatically adjusts the color and brightness of the computer screen based on the patient's time zone. **From:** ***http://authoritynutrition.com/block-blue-light-to-sleep-better***

DRUGS TO IMPROVE SLEEP

Occasionally, doctors may prescribe sedative medications for sleep problems, and patients taking them must be closely monitored. It is possible to become dependent upon these medications, meaning that patients who stop taking them may experience withdrawal symptoms when stopping the medication. It is also possible to become tolerant to these medications, with the effects wearing off as time goes on. Additionally, sleep medications can last a long time in in the body, causing people taking them to feel tired during the day. Therefore, patients who are considering taking a sleep medication should discuss the "pros" and "cons" with their doctor. Physicians prescribing sleep medications, many of which are listed below, must also be made *fully aware* of all other medications the patient is taking.

Alprazolam (Xanax)

Chlordiazepoxide (Librium)

Clonazepam (KlonopinTM)

Clorazepate (Tranxene)

Diazepam (Valium)

Estazolam (Prosom)

Flurazepam (Dalmane)

Intermezzo (Zolpidem Tartrate)

Lorazepam (Ativan)

Lunesta (Eszopiclone)

Oxazepam (Serax)

Prazepam (Centrax)

Quazepam (Doral)

Sonata (Zaleplon)

Temazepam (Restoril)

Triazolam (Halcion)

Zolpidem Tartrate (Ambien)

Much of the above information is **From[291, PMID:19581220; 292, PMID:24733803; 293, PMID:15014609]:** ***http://my.clevelandclinic.org/health/diseases_conditions/hic_Cancer_Overview/hic_Cancer-Related_Fatigue*** and ***http://www.cancer.net/navigating-cancer-care/side-effects/fatigue*** and ***http://chemocare.com/chemotherapy/side-effects/sleep-problems.aspx***

38. Therapies to Reduce Nausea

Many cancer patients undergoing chemotherapy, radiation, and other cancer treatments may experience nausea or queasiness, which may or may not be accompanied by vomiting. This is a particularly distressing side effect which can sometimes lead to dehydration and loss of appetite. Certain classes of drugs, such as Serotonin (5-HT3) Antagonists, are given prior to (and shortly after) chemotherapy to avoid or minimize potential nausea, and – like pain – it is best to try to avoid nausea to begin with than to play "catch up" to try reducing it later.

That said, many additional drugs can be provided if the patient feels nauseous. In the case of acute nausea, some physicians believe that combining a 5-HT3 receptor antagonist, an NK1 receptor antagonist, and a corticosteroid such as prednisone can eliminate nausea in most patients. From: CURE Today Magazine Summer 2016 issue, page 24.

It is advised to call the doctor if the patient:

Might have inhaled vomited material

Vomits more than 3 times an hour for 3 or more hours

Vomits blood or material that looks like coffee grounds

Cannot take in more than 4 cups of liquid or ice chips in a day or can't eat for more than 2 days

Cannot take medicines

Becomes weak, dizzy, or confused

Loses 2 or more pounds in 1 to 2 days (this means they are losing too much water and might be dehydrated)

Develops dark yellow urine and doesn't have to urinate as much

THERAPIES OTHER THAN DRUGS TO REDUCE NAUSEA

Below are several anti-nausea **remedies other than drugs**:

- **Acupressure**
- **Acupuncture**
- **Chewing Gum**
- **Ginger**
- **Massage**
- **Queasy Pops**
- **Sea Bands**

- **Acupressure:** Acupressure is an ancient healing art that is based on the traditional Chinese medicine practice of acupuncture. Finger pressure is used to stimulate trigger points on the body (called acupoints). Pressing these points can help release muscle tension and promote blood circulation. Research suggests that it can also relieve many common side effects of chemotherapy. A "how to" video on how patients can reduce chemo-induced nausea by using acupressure is located **at:** ***https://www.mskcc.org/cancer-care/patient-education/acupressure-nausea-and-vomiting***

- **Acupuncture:** Acupuncture involves the insertion of sterile, hair-thin needles by a skilled practitioner into specific points on the skin, called "acupuncture points," after which they are gently removed. In a study at Duke University, the use of acupuncture was compared to the use of Zofran (chemical name: ondansetron), an anti-nausea medication, before breast cancer surgery to reduce the nausea that can occur after surgery. The acupuncture treatment was found to work better than Zofran at controlling nausea. **From:** ***http://www.breastcancer.org/treatment/comp_med/types/acupuncture***

- **Chewing Gum (especially mint)** can help to ease feelings of nausea.

- **Ginger:** Adding a quarter to a half teaspoon of ground ginger to hot water or food may help ease nausea. Additionally, ginger capsules are sold in grocery stores are pharmacies, and taking them as suggested on the label may help. Some people have reported that drinking ginger ale also helps, and others have found relief from eating candied ginger.

- **Massage:** Clinical studies show that massage can alleviate symptoms such as nausea, stress/anxiety, insomnia, pain, fatigue, and depression. **From[272, PMID:15336336]:** ***http://www.mskcc.org/cancer-care/herb/massage-therapy***

- **Queasy Pops** are lollipops especially manufactured to combat nausea and are popular with some cancer patients.

- **Sea Bands,** which are elastic bands worn on the wrist that apply pressure to specific acupressure points for nausea. According to their website, Sea-Bands have been clinically proven to relieve motion sickness and morning sickness in addition to helping with post-operative and chemotherapy-induced nausea.

DRUGS THAT REDUCE NAUSEA

Patients may need to try several different medications before they find one that works well for them. Some of the most common anti-nausea/vomiting medicines (grouped by drug type) are listed below.

- **Antacids**
- **Anti-Anxiety Drugs**
- **Cannabinoids (including the newly-approved drug Dronabinol)**
- **Dopamine Antagonists**
- **Neurokinin 1 (NK1) Receptor Antagonists**
- **Olanzapine**
- **Serotonin 5-HT(3) Antagonists**
- **Steroids**
- **Varubi IV**

- **Antacids (H2 Blockers or proton pump inhibitors)** may help. Common antacids include **Prilosec** and **Tagament.** These drugs decrease stomach acid and may help against queasiness.

- **Anti-anxiety drugs** such as **Lorazepam** (**Ativan**) and Alprazolam (**Xanax**) may alleviate nausea.

- **Cannabinoids such as Dronabinol** (**Marinol**) and **Nabilone** (**Cesamet**) which contain the active ingredient in marijuana, have helped some patients. They may be used to treat nausea and vomiting from chemotherapy when the usual anti-nausea drugs do not work and may also be used to stimulate appetite.

- **Dopamine Antagonists** include **Prochlorperazine (Compazine), Droperidol (Inapsine), Haloperidol (Haldol), Metoclopramide (Reglan),** and **Promethazine (Phenergan).** These drugs are often used "as needed" to prevent nausea and

vomiting. The patient will take the medicine at the first sign of nausea to keep it from getting worse. These drugs can also cause unplanned movements called *extrapyramidal effects* such as restlessness, tremors, sticking out the tongue, muscle tightness, and involuntary muscle contractions or spasms. Patients should let their doctor know right away if this happens. These side effects can usually be stopped with other medicines such as diphenhydramine (Benadryl). In some cases, it may be necessary to stop the drug and try another one.

- **Neurokinin 1 (NK1) Antagonists** such as oral **Emend (Aprepitant), Fosaprepitant** (the IV form of Emend), **Varubi (Rolapitant)** and **Akynzeo (NEPA or Netupitant).** Emend is especially good for treating delayed nausea and vomiting. When given intravenously as Fosaprepitant, one dose covers the next 3 days. When taken by mouth, the drug may be repeated for a total of 3 days. Varubi is an oral drug that was FSA-approved in 2015. Akynzeo is a "combination" drug comprised of the 5-HT(3) receptor antagonist Aloxi plus an NK1 antagonist.

- **Olanzapine:** This is an antipsychotic drug with relatively few side effects. It can be used "off label" to control nausea after other medications have failed to do so.

- **Serotonin (5-HT3) Antagonists such as Ondansetron (Zofran), Palonosetron (Aloxi), Dolasetron (Anzemet)** and **Granisetron (Kytril or Sancuso)** are given before chemotherapy to help prevent or minimize nausea, and then often are recommended a few days afterward. Palonosetron is usually given once before starting a 3-day cycle of chemotherapy; and its effects last longer than the other drugs in this group. This also makes Palonosetron a good drug to prevent delayed nausea and vomiting. These drugs are often given along with a steroid (below).

- **Steroids** include **Dexamethasone (Decadron)** and **Methylprednisolone (Solumedrol** or **Medrol).** These drugs may already be part of a patient's chemotherapy plan and are often given the day of chemo and possibly for a few days afterwards. That said, *Dexamethasone may bind to a segment of DNA that may activate genes associated with drug resistance and poor patient outcomes,* so alternative anti-inflammatories should be considered. **From[153, PMID:26374485]:** ***http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/nauseaandvomiting/nauseaandvomiting/nausea-and-vomiting-drugs*** and ***http://www.eurekalert.org/pub_releases/2015-10/osuw-ssn100615.php***

- **Varubi IV:** The FDA approved Varubi IV in October 2017 to prevent chemotherapy-induced nausea and vomiting. Whereas the majority of anti-nausea drugs for chemotherapy are administered intravenously, Varubi IV is a tablet taken orally.

39. Therapies to Increase Appetite

For many reasons, people with cancer may experience a decrease in appetite. In some instances, chemotherapy, radiation and other therapies may affect one's sense of taste, and as a result these patients may lose interest in food. If a specific cancer patient has another clear reason for weight loss, such as bowel obstruction or severe depression, prescribing an appetite stimulant in the absence of treating the underlying cause is unlikely to help

Generally, there are several options that may stimulate appetite, but if a patient continues to lose weight they should notify their doctor.

THERAPIES OTHER THAN DRUGS TO STIMULATE APPETITE

- MBC patients have reported that **exercising, drinking protein shakes**, and **consuming as much protein as possible** (such as nuts and almond butter) were helpful.

- One person stated that **OncoQOL** appeared to be helping her. OncoQOL is a product line consisting of nutritional supplements formulated to support the unique nutritional needs of patients undergoing cancer treatment.

DRUGS THAT MAY STIMULATE APPETITE

- **Cannabinoids such as Dronabinol** (**Marinol**) and **Nabilone** (**Cesamet**) which contain the active ingredient in marijuana, have helped some patients. They may be used to treat nausea and vomiting from chemotherapy when the usual anti-nausea drugs do not work and may also be used to stimulate appetite. In one study of patients undergoing chemotherapy reported by the University of New Mexico, Marinole improved appetite by 38%. **From[294, PMID:12618922]:** ***http://www.livestrong.com/article/274979-list-of-appetite-stimulants/***

- **Mirtazapine** and **Gherlin** are two relatively new drugs that are being studied to determine their impact on cancer-related appetite loss.

- A class of drugs called **Progestational Agents**, which includes **Megace (Megestrol Acetate**) and **Medroxyprogesterone** have been associated with appetite stimulation and weight gain. Studies suggest improved effectiveness in patients with better digestive function. Therefore, therefore, targeted nutritional strategies such as digestive enzymes or elemental diets may also be useful.

A Note about Cachexia: In severe cases, advanced cancer patients exhibit a syndrome called "cachexia," which is evidenced by dramatic weight loss and reduction in muscle mass. In two European studies called ROMANA 1 and ROMANA 2, advanced lung cancer patients with cachexia who took the experimental drug **Anamorelin** gained over 2 pounds over the course of 12 weeks, instead of losing additional weight (as did those in the group that didn't take the drugs). However, the status of this experimental drug in the USA is still unknown.

40. Therapies to Increase Bone Marrow Production and Blood Counts

Bone marrow tissue inside the bones produces blood cells. Strong, healthy bone marrow requires foods rich in vitamins and minerals. There are two types of bone marrow: red marrow which consists mainly of blood-forming tissue, and yellow marrow which is mainly made up of fat cells. Red blood cells, platelets, and most white blood cells arise in red marrow. Both types of bone marrow contain numerous blood vessels and capillaries.

When the bone marrow is damaged by radiation, chemotherapeutic drugs, or disease, a decrease in blood cell production can compromise the immune system and lead to infections. **From[295, PMID:22654110]:** ***http://www.tpims.org/news/168-researchers-discover-mechanism-that-helps-control-blood-cell-production-in-bone-marrow***

Much of the non-drug information below about how to enhance the bone marrow (and blood counts in general) is **From**: ***http://www.livestrong.com/article/480567-foods-that-strengthen-bone-marrow/***

This section has been divided into the following sub-sections:

- **Therapies to Support the Bone Marrow**
- **Therapies for Low Platelet Counts (Thrombocytopenia)**
- **Therapies for Low Red Blood Cell Counts**
- **Therapies for Low White Blood Cell Counts (Neutropenia)**

THERAPIES TO SUPPORT THE BONE MARROW

- **Blood Transfusions**
- **Iron** *(please be careful with this, as described below)*
- **Folic Acid/Folate/Vitamin B9** (*also be careful with this, as described below)*
- **Protein**
- **Vitamin A**
- **Vitamin B6 (Pyridoxine)**
- **Vitamin B12**

- **Blood Transfusion:** In some instances, oncologists may recommend one or more blood transfusions if a patient's blood counts remain very low.

- **Iron**: Foods rich in iron can help bone marrow function more effectively. Some iron is stored in the bone marrow, spleen or liver. Most of the iron absorbed is used by the bone marrow for erythropoiesis, a process producing new red blood cells. Iron-rich foods include red meats, shellfish, cabbage, lima beans and iron-fortified cereals and bread. Consuming foods high in vitamin C may aid in the absorption of iron, and vitamin C sources include citrus fruits like oranges, grapefruit and tangerines.
  Although the evidence is limited and mixed, it appears that iron deficiency might promote breast cancer in young women whereas excess iron might promote it in postmenopausal and older women. It is also possible that iron has a more important role in breast cancer metastasis than in its initial development. **From[296, PMID:23800380]:** ***http://foodforbreastcancer.com/news/iron-deficiency-is-linked-to-metastasis-in-mouse-model-of-premenopausal-breast-cancer***

- **Folate or Vitamin B9**: This is a B vitamin that aids in platelet functioning and DNA synthesis, which is a vital step in cell reproduction and is needed for the bone marrow to produce red blood cells. A deficiency of this nutrient can lead to "megaloblastic anemia," in which the bone marrow produces large and abnormally developed red blood cells. A deficiency may also result in fewer red blood cells, depriving the body's cells of adequate oxygen and nutrients. Folate rich foods include as brown rice, broccoli, brussels sprouts, spinach, chickpeas and fortified cereals, liver, egg yolk, beans, almonds, sweet potato, wholegrain bread, spinach, cabbage, oranges and peaches.
  However, folic acid (a synthetic form of folate found in some supplements and processed foods) has been linked to the growth of mammary tumors in rats according to at least one study, so patients should be careful about taking it due to potential risk. **From[297, PMID:24465421]**: ***http://www.ncbi.nlm.nih.gov/pubmed/24465421***

- **Protein:** Protein-rich foods are broken down into amino acids, the building material for every cell in the body. Adults generally require an average of 46 to 56 grams of protein every day to help sustain healthy bone marrow and other tissue. Good sources include meat, poultry, fish, dairy foods, legumes and vegetables.

- **Vitamin A** Foods rich in vitamin A help regulate proteins generated in one's cells, which aids in cellular development. Vitamin A is particularly known to promote stem cell maturation in the bone marrow. Vitamin A-rich foods include carrots, sweet potatoes, cantaloupe, pumpkin, cod liver oil and eggs.

- **Vitamin B6 (Pyridoxine)** helps to form hemoglobin, the substance inside red blood cells that binds to oxygen. Like other B vitamins, it also plays a role in producing energy to sustain every cell in the body, including the bone marrow. Normally, people should have about 1.2 to 1.4 milligrams of this vitamin from their diet every day. Good sources include poultry, fish, eggs, whole grains, milk, potatoes and fortified cereals.

- **Vitamin B12** is essential for the production of healthy bone marrow. Folic acid and vitamin B12 work together during hematopoiesis, the manufacturing of bone marrow blood cells. Vitamin B12 is available only in animal foods (meat and dairy products) or yeast extracts (such as brewer's yeast) and can also be administered by injection. **From[298, PMID:23301732]:** ***http://www.drugs.com/health-guide/vitamin-b12-deficiency.html***

THERAPIES FOR LOW PLATELET COUNTS ("THROMBOCYTOPENIA")

- **Neumega:** This is a blood cell growth factor approved by the FDA for the prevention of low platelet counts. Clinical studies have shown that Neumega prevents thrombocytopenia and decreases the need for platelet transfusions in patients at high risk for developing a low platelet count. **From[299, PMID:20620439]:** ***http://www.texasoncology.com/cancer-treatment/chemotherapy/understanding-and-monitoring-your-blood-counts/***

- **Papaya Leaf may help boost platelet counts.** One person on an online MBC forum wrote that she brewed dried papaya leaf to make a strong tea and drank a quart a day for a few weeks. Her platelet counts rose dramatically, and she was able to avoid the blood transfusion that her doctors were ordering. After this success, the lady repeated this advice to several others who were experiencing the same problems, and each time the platelets came up significantly. When the author told a friend with low platelets about the papaya leaf therapy, this was her response: "*When I got your message about papaya leaves, I called my friend who grows papaya trees. She gave me fresh leaves, and I was grinding them with juice and that I drank twice a day. Five days later I went to my oncologist for chemotherapy. My platelets almost doubled (they went from 35K to 59K) and four days later I was able to get chemo. I can't thank you enough! My oncologist asked me what helped, and I told him about papaya leaves.*"

  Those interested in fresh papaya leaves can purchase them at: ***http://www.bananaplants.net/frcutpaleand.html*** There are also many places that sell dried papaya leaves, which can be brewed as tea. Dried organic papaya leaves are sold by Amazon at: ***http://www.amazon.com/100-Organic-Papaya-Leaves-Sifted/dp/B004VYXU12***

If fresh papaya leaves are purchased, the recipe is as follows: Wash and partly dry several medium-size papaya leaves. Cut them up like cabbage and place them in a saucepan with 2 quarts of water. Bring the water and leaves to the boil and simmer without a lid until the water is reduced by half. Strain the liquid and bottle in glass containers. The concentrate will keep in the refrigerator for three to four days. If it becomes cloudy, it should be discarded. Although the recommended dosage in the original recipe is 3 Tablespoons three times a day, patients may want to start with less just to be safe.

One patient reported taking organic papaya leaf extract at a dose of 10-20 drops/day. Her platelets started at 88, the next week she took 20-30 drops daily and her platelets increased to 460. After she stopped taking the extract, her platelets fell back to 89. Once she added the papaya extract back and remained on it, her platelets remained in normal range.

In addition to boosting platelets, papaya leaf extract boosts the production of key signaling molecules called Th1-type cytokines. This regulation of the immune system, in addition to papaya's direct anti-tumor effect on various cancers, suggests possible therapeutic strategies that use the immune system to fight cancers. In fact, when scientists exposed 10 different types of cancer cell cultures to four strengths of papaya leaf extract and measured the effect of the extract after 24 hours, the papaya had slowed the growth of tumors in all the cultures. **From[300, PMID:19961915]:** ***https://www.naturalnews.com/028472_papaya_breast_cancer.html***

- **Sharks Liver Oil and Chlorophyll Tablets**: The husband of an MBC patient indicated that shark's liver oil and chlorophyll tablets successfully helped to maintain his wife's platelet counts.

- **Steak, Pineapple, and Exercise:** One person wrote that eating two organic steaks (she was vegetarian prior) and two pineapples per week boosted her platelets considerably. Additionally, exercising before taking a blood test may help to increase platelet counts.

- **Wheatgrass, Pumpkin and Spinach** can also be helpful as per ***http://www.top10homeremedies.com/how-to/increase-low-platelet-count.html***

THERAPIES FOR LOW RED BLOOD CELL COUNTS

Sharks Liver Oil and Chlorophyll Tablets: The husband of an MBC patient indicated that shark's liver oil and chlorophyll tablets successfully helped to maintain his wife's red blood cell counts.

Erythropoietin is a blood cell growth factor that selectively increases production of red blood cells. There are two commercially available forms of erythropoietin for use in patients, namely, **Epoetin Alfa** (**Epogen** or **Procrit)** and **Darbepoetin Alfa** (**Aranesp**). Aranesp is a unique, longer-acting form of erythropoietin and is more convenient because it allows patients to receive fewer injections than with Epogen/Procrit. **From[299, PMID:20620439]:** ***http://www.texasoncology.com/cancer-treatment/chemotherapy/understanding-and-monitoring-your-blood-counts/***

Warning: Before a patient can begin taking the above medications, they must sign an acknowledgment indicating that they understand the risks, which include the possibility that their tumor may grow faster and that they may die sooner. **From:** ***http://www.fda.gov/downloads/Drugs/Drugsafety/ucm088988.pdf*** and ***http://www.fda.gov/downloads/Drugs/DrugSafety/ucm085918.pdf***

THERAPIES FOR LOW WHITE BLOOD CELL COUNTS ("NEUTROPENIA")

- **Astragalus** has been known to increase white blood cell counts.

- **Guava and red pepper may help increase white blood cell counts.** One person advised blending 6 small guava fruits (or 2 large ones) with one organic red bell pepper and a cup of water. The juice should be consumed three times daily and re-made as needed.

- **Olive Leaf Extract** has been reported by some patients as being helpful in raising white blood cell counts.

- **Colony Stimulating Factors** (**CSFs**) **and Growth Factors:** Specific drugs called Colony Stimulating Factors can increase white blood cell counts and help prevent infection during chemotherapy. CSFs include **Neupogen** (filgrastim), and **Neulasta** (pegfilgrastim). Another CSF is **Srgramostim** (**Leukine** or **Prokine**). These medications are usually given as shots 24 hours after a chemotherapy treatment. In two clinical trials, a single dose of Neulasta was proven to be as effective as an average of 11 daily injections of Neupogen for the management of low white blood counts. **From:** ***http://www.choosingwisely.org/doctor-patient-lists/drugs-to-boost-white-blood-cells-for-cancer-patients-on-chemotherapy/***

41. Therapies for Constipation

Sometimes cancer treatment may cause constipation, which is abnormally delayed or infrequent passage of usually dry, hardened feces (stool or bowel movement). Although constipation is normally not something to be highly concerned about, patients should contact their doctor if they experience any of the following:

Pain in the stomach

Fever

Inability to pass gas.

Nausea, and/or vomiting along with constipation

If the patient has not had a bowel movement in three days despite following the recommendations of their doctor

If the stomach looks swollen and/or feels hard to the touch

THERAPIES OTHER THAN DRUGS TO RELIEVE CONSTIPATION

- **Drinking lots of purified water** throughout the day
- **Eating high-fiber foods** such as prunes, prune juice, consuming All-Bran cereal, and adding 1 to 2 Tbsp. of freshly ground flaxseeds to a meal.
- **"The Bomb" Recipe:** Combine 1 cup high fiber bran cereal, once cup applesauce, and ½ cup prune juice. Add cinnamon to taste. *(After consuming, do not venture too far from the bathroom!)*

The following may also help to relieve constipation:

Aloelax Tablets (recommended by a patient on a constipating chemotherapy drug)

Bisacodyl (Dulcolax)

Docusate sodium (Colace)

Glycerin suppository

Lactulose (Chronulac)

Linzess (a prescription medication)

Miralax

Psyllium (Metamucil)

Magnesium citrate

Magnesium hydroxide (Milk of Magnesia)

Senna (Senokot)

Sorbitol and sodium phosphate (Fleet's enema)

Stool softeners

Note: Some patients who are on opioid drugs for pain experience severe constipation called Opioid Induced Constipation (**OIC**) that cannot easily be alleviated. For these patients, **Methylnaltrexone (Relistor)** injections may be considered, although •It is not known if RELISTOR is safe and effective if used for longer than 4 months in people with advanced illness. There is evidence that Relistor may also provide a survival benefit for certain cancer patients. In a retrospective survival analysis of 229 late-stage cancer patients enrolled in two clinical trials for relief of constipation, 117 patients received Relistor for opioid-induced constipation and 112 were given a placebo. Fifty-seven percent of the patients who received Relistor experienced relief from constipation; 43 percent did not. Patients who received and responded to Relistor lived, on average, twice as long as those who did not respond or were given the placebo. These patients also had significantly fewer reports of tumor progression (7.6%) compared to those who did not respond (22%) or who took the placebo (25.4%).

The above is **From[301, PMID:25135384; 302, PMID:27857691; 303, PMID:27573565]:** ***http://chemocare.com/chemotherapy/side-effects/constipation-and-chemotherapy.aspx#.VLbqAkYtFdq*** and ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4108020/*** and ***http://www.hopkinsbreastcenter.org/artemis/201511/6.html***

42. Therapies for Diarrhea

Diarrhea typically causes stomach cramps and loose, watery stools. Mostly it is an inconvenience, but if symptoms persist or become worse, it could be a sign of something more serious. Diarrhea can also lead to other problems such as severe dehydration.

Patients who experience any of the following should notify their doctor:

Six or more loose bowel movements a day for more than two days

Blood in the stool

Inability to urinate for 12 hours or more

Inability to drink liquids

Weight loss due to diarrhea

Diarrhea after several days of constipation

Severe abdominal pain

Fever of 101 F (38.3 C) or higher

Shaking chills

REMEDIES FOR DIARRHEA

- **Avoid foods that can irritate the digestive tract**. These foods include dairy products, spicy foods, alcohol, foods and beverages that contain caffeine, and foods that are high in fiber and fat.
- **Drinking Clear Liquids:** As soon as diarrhea starts, patients should switch to a temporary diet of clear liquids such as water, apple juice, clear broth, and avoid milk products.
- **Imodium** is a medication that can help alleviate diarrhea.
- **Kaopectate** is another medication that can help against diarrhea.
- A prescription drug called **Lomotil,** which is a combination of diphenoxylate and atropine, can be very helpful against diarrhea.
- There is also **Paregoric,** which is a weak camphorated tincture of opium. In some states it used to be over the counter and in others it must be prescribed.
- Eat **low-fiber foods:** As the diarrhea starts to improve, patients may add foods low in fiber to the diet, such as Bananas, Rice, Applesauce and Toast (called the "**BRAT" diet).**
- Eat **foods that are high in potassium** such as bananas, potatoes and apricots. Potassium is an important mineral that can be lost through diarrhea. Patients with kidney problems should first consult with their doctor before eating foods that are high in potassium.

- **Rice with extra water:** One person highly recommends cooking white (not brown) rice with extra water or broth and overcooking it. Chicken or other light solid foods can be added for taste and nutrition.

- Eat **small, frequent meals** throughout the day for energy and nutrients.

A large part of the above information is **From**: ***http://www.mayoclinic.org/diseases-conditions/cancer/in-depth/diarrhea/art-20044799***

43. Therapies for Hand Foot Syndrome

Hand-Foot Syndrome (HFS), also called Palmar-Plantar Erythrodysesthesia, is a side effect of some chemotherapy drugs – especially Xeloda (Capecitabine) and Taxanes. HFS occurs when drugs used to treat the cancer affect the growth of skin cells or capillaries (small blood vessels) in the hands and feet. Once the drug is out of the blood vessels, it damages the surrounding tissues. HFS causes redness, swelling, and /or pain on the palms of the hands and/or the soles of the feet. Sometimes blisters may appear. Although less common, hand-foot syndrome sometimes occurs on other areas of the skin such as the knees and the elbows.

Patients who take drugs that may cause HFS should request a list of tips to avoid or mitigate HFS from their doctor. It is also recommended that patients discuss with their doctor the possibility of reducing the dosage and/or frequency of the drug as described below:

Due to considerable side effects from Xeloda, studies have been done on decreasing the drug's recommended dose and frequency. The current standard dose of Xeloda as monotherapy is 1250 mg/m2 twice daily orally for 2 weeks followed by a one-week rest period in 3-week cycles, although this dosage may be adjusted depending upon the patient's body surface area. **From: *https://www.drugs.com/dosage/xeloda.html***

For those suffering significant side effects, a dose of 1,000 mg/m2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m2 total daily dose) for 2 weeks with 1 week of rest may be appropriate. Data presented in a retrospective review demonstrate that the dose of Xeloda can be reduced, either when used alone or in combination with docetaxel, to minimize adverse events without compromising efficacy in terms of Time To Progression or Overall Survival. **From[104, PMID:21856245]: *http://mbcn.org/images/uploads/DoseAdjustingCapecitabine.pdf***

Non-drug remedies for Hand Foot Syndrome that some MBC patients have reported to be helpful are listed below. Patients should first consult with their doctor before taking any new supplement or beginning a new therapy.

NON-DRUG HAND FOOT REMEDIES

- **Activ-Flex Bandages**
- **Aloe Vera**
- **Biafine Cream**
- **Coconut Oil and Water Soak**
- **Emollients**
- **Emu Oil**
- **Gloves or socks on the area**
- **Henna Paste**
- **Ice Packs during Chemotherapy**
- **Liquid Bandages**
- **MEBO Cream (Moist Exposed Burn Ointment)**
- **Milkweed Balm**
- **Urea Cream (10%)**
- **Vitamin B6**
- **Vitamin E**
- **Shoes that are Very Comfortable!**

- **Activ Flex Bandages**: One person reported that she tried the Activ Flex and they did wonders for her sores. According to their website, Activ Flex bandages are clinically proven to heal wounds faster. A white gel develops under the bandage and helps

healing, in addition to forming a waterproof and dirt-proof seal. She mentioned that after a day or two of applying the bandage, the cracks are much better.

- **Aloe Vera:** Many people have reported excellent results applying Aloe Vera gel to peeling and .cracking skin. Some use the actual plant by opening a leaf and applying the gel to the skin, and others say there is no difference between using the plant vs. using 100% Aloe Vera gel purchased at the store.

- **Biafine Cream,** a topical non-steroidal medication, can ease discomfort.

- **Coconut Oil and Water Soak:** One person indicated that they soak their hands and feet in tepid filtered water and liquefied coconut oil, and immediately after she uses use lotion, socks and gloves.

- **Emollients:** Emollients are special moisturizers that soothe dry, cracked, and irritated skin. Most doctors recommend emollient products such as **Aquaphor, Aveeno with lanolin, Bag Balm, Lubriderm, Nubian Indian Hemp and Haitian Vetiver Lotion,** and **Udder Cream.** Patients should lightly apply emollients several times a day but should not rub the skin. Wearing socks and/or gloves after application will help to retain moisture. One patient wrote, "*Nubian Indian Hemp and Haitian Vetiver Lotion was the only remedy that worked for me. I've tried most of the remedies and that's the only thing that helped the burning. It can be purchased at Whole Foods, at most organic stores, and on Amazon. I suggest that people lather it on before bed, in the morning, and during the day. Let it sit for a few minutes before putting on socks. It may tingle when first applied."*

- **Pure Emu Oil** (which can be purchased online) may help to provide a degree of relief.

- **Gloves:** Wearing household gloves when washing dishes or doing other chores will help to protect the skin, as will socks – especially if the area has been rubbed with an emollient.

- **Henna Paste:** Some people have claimed relief by using "henna paste" as per the following recipe: *Mix1/4 cup water, 1/8 cup henna powder, and a squirt of lemon juice (only if the skin is not already cracked). Bring the water to a boil and turn off the heat. Add the henna slowly and stir until it is like cream of tomato soup. Let it cool. Paint a thin layer on the affected areas (some people recommend a foam paint brush). Let everything dry, which takes up to 15 minutes.* Some people cover it up (for example, with socks on their feet) until their next shower. Henna can be purchased at an Indian grocery store or online.

- **Ice packs under the hands and feet during the infusion of certain chemotherapies (Paclitaxel, Taxotere, Abraxane,** and **Doxorubicin [Adriamycin]**) may help prevent Hand-Foot Syndrome.

- **Liquid Bandages**: One person wrote that liquid bandages, which adhere to and help heal the skin, have worked beautifully for her.

- **MEBO Cream (Moist Exposed Burn Ointment):** One reader wrote about her positive experience using this cream for radiation burns and subsequently for Hand Foot Syndrome, *"I first used this for severe radiation burns on my breast; it actually helped regenerate the tissue, and this was an open 3-inch wound. My surgeon was shocked as I refused skin transplants because he said they would most likely fail because underlying blood supply was dead. I read the literature about healing burn wounds and came up with MEBO. I also recently used it for hand and foot syndrome due to Xeloda and now can confirm it helped a lot. I sometimes have to order it from China or Chinatown and have also found sellers on Amazon."*

- **Milkweed Balm:** One person reported excellent results with Milkweed Balm, stating *"It actually is the best moisturizer I have ever found and is very healing. I am not into quick fixes but, for me, applying it 3 times a day on the rough areas has really helped. I have no cracks in my skin and I used to all the time."* According to their website, Milkweed Balm is a rare combination of

Omega 7s, which is found in the skin's sebum and diminishes as we age, full of antioxidants, anti-inflammatory agents, phosphorous, magnesium, calcium and zinc.

- **Urea Creams (10%):** According to a study in the Journal of Clinical Oncology, researchers have found that 10% urea cream (there are various brands on the market) is superior at preventing hand-foot syndrome during the first 6 weeks of treatment with capecitabine (Xeloda). One patient mentioned that it has been helpful in treating her Hand Foot Syndrome after it developed. **From[304, PMID:26124485]:** ***http://www.oncologynurseadvisor.com/headlines/urea-cream-ointment-hand-foot-syndrome-treatment/article/423603/***

- **Vitamin B6:** Vitamin B6 may be recommended for people who are likely to develop HFS or already suffer from it. **From[305, PMID:18235127]:** ***https://www.oncolink.org/cancer-treatment/chemotherapy/side-effects/hand-foot-syndrome***

- **Vitamin E:** In a retrospective study, 15 of 32 patients with HFS improved after taking 100mg of Vitamin E daily**. From[306, PMID:21494409]**: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3076356/***

- **Shoes that are Comfortable:** Comfortable shoes such as Dansko, Sketchers with memory foam, and Birkenstocks may help to protect skin on the feet from rubbing.

DRUGS TO RELIEVE HAND FOOT SYNDROME

- **Pain relievers**
- **Topical Anesthetics**
- **Topical Creams**

- **Pain relievers** may help, such as **Ibuprofen** (multiple brand names), **Naproxen** (multiple brand names such as **Aleve**), and **Celebrex**. *Before purchasing pain relievers, it is advisable to first check the ingredients to see whether the product contains Benzocaine. The FDA has issued a warning about the use of benzocaine, the main ingredient in some over-the-counter liquids and gels. Benzocaine is associated with a rare but serious condition called methemoglobinemia, which greatly reduces the amount of oxygen carried through the bloodstream. In the most severe cases, the condition can be life-threatening.*

- **Topical anesthetics**, such **as Lidocaine (Lidothesin, Lidoderm, Xylocaine, Xylocitin),** may be used as a cream or a patch over painful areas in the palms and soles.

- **Topical moisturizing exfoliant creams** are available, either over the counter or through prescription, such as those containing urea, salicylic acid, or ammonium lactate.

The above medication information is **From:** ***http://www.cancer.net/navigating-cancer-care/side-effects/hand-foot-syndrome-or-palmar-plantar-erythrodysesthesia***

44. Therapies for Leg or Foot Cramps

Leg cramps – especially at night – can be exceptionally painful and sleep disruptive. If a patient suffers from leg cramps, the following may be helpful:

THERAPIES TO RELIEVE LEG CRAMPS

- A **calcium, magnesium, and/or potassium deficiency** could be causing the cramps, so it is advisable for patients to have their doctor check their blood for levels of these minerals.
- A healthy **diet with plenty of fresh fruits and vegetables** may help to decrease the frequency of leg cramps
- **Magnesium Glycinate** can be helpful in easing muscles and preventing cramping.
- If there is no deficiency in magnesium and/or potassium, a surprising but often-effective remedy is to place a **brand-new bar of soap** between the mattress and sheet on the patient's side of the foot of the bed. The theory behind this is that special ingredients in the bar of soap may help to alleviate the cramps. Although it sounds like an unlikely remedy, many people swear by it. Once a cramp is felt, rubbing a dry bar of soap on the affected area can ease the cramp (the author has success with this every time!).
- Many people find that **wearing shoes that have cushioned foot beds and arch supports** helps to prevent or decrease leg cramps.
- Applying **warm compresses** to the affected area(s) may help.
- **Drinking a sufficient amount of water** is essential, since cramps are often caused by dehydration.

45. Therapies for Liver Support

Over time, chemotherapy, other cancer treatments, and breast cancer itself may take a toll on the liver. As a result, the liver may become enlarged and/or the patient's liver enzymes may increase above normal range. Patients should refrain from alcohol, aspirin, and Tylenol if they have liver damage.

Patients should contact their doctor if they experience any of the following:

Jaundice, which is a yellowing of the skin and/or whites of the eyes. (Patients with jaundice should go directly to the Emergency Room and ensure that doctors run tests for tumors that may be obstructing the flow of bile, as well as running other tests).

Bowel movements that are lighter in color than normal or clay-colored

Pain in the liver (the liver is in the right upper quadrant of the abdomen and also extends across the midline toward the left upper quadrant of the abdomen)

NON-DRUG LIVER SUPPORT THERAPIES

A few **non-drug liver remedies** that may help to bolster the liver are listed below. As with any new supplement, patients should first consult with their doctor before taking it.

- **Drink an Apple Cider Vinegar** mixture (consisting of 1 to 2 tsp. of Apple Cider Vinegar with one 8-oz. glass of water) an hour before each meal. **From:** ***http://www.livestrong.com/article/95855-use-vinegar-detoxify-liver/***

- **Avocados:** avocados are rich sources of Vitamin C, Vitamin E, and Vitamin K, which are antioxidants that neutralize free radicals and may help reduce inflammation. Neutralizing or deactivating harmful free radicals in the liver may be instrumental in protecting liver cells from damage.

- **Castor Oil Packs** placed externally over the liver may help to relieve discomfort**.**

- **Milk Thistle (Silybin Phytosome)** which should not be taken if the patient is on an Aromatase Inhibitor, as it may interfere with the drug's effectiveness. Otherwise, milk thistle extract may generally be used to maintain liver health and to protect the liver from the effects of toxins such as alcohol, a polluted environment or workplace, and a host of liver related diseases.

DRUGS TO SUPPORT THE LIVER

Drugs that may be prescribed by the doctor for liver dysfunction include**:**

- **Diuretics:** These drugs are also known as "water pills" because they work to prevent or treat fluid accumulation by making the patient urinate out extra fluid. Some examples of this medication may include furosemide (**Lasix)** and **Hydrochlorothiazide**.

  However, **in patients with cancer-related ascites** (accumulation of fluid in the abdomen due to cancer-related damage to the liver), **diet restrictions and diuretics are not effective**. For additional information, please refer to the section entitled, *Liver Metastasis*.

- **Pain Medicines:** The patient's physician may order medication for pain, if there is any. Many of these medications are processed through the liver, but in certain dosages they are safe. For ease of reference, a list of pain medications is provided in the section entitled, *Therapies for Pain and Neuropathy.* Patients may also wish to seek palliative care (please refer to the *Palliative Care* section for more information).

Most of the above information is **From[307, PMID:16473644]:** ***http://chemocare.com/chemotherapy/side-effects/liver-problems-liver-dysfunction.aspx*** and ***http://www.emedicinehealth.com/ascites/page7_em.htm*** and ***http://www.liversupport.com/wordpress/2013/03/liver-health-eats-the-almighty-avocado/***

46. Therapies for Mouth Sores

Patients taking Afinitor (Everolimus) and/or other cancer drugs may experience mouth sores which are painful and that can interfere with their ability to eat comfortably. Mouth sores are the result of "oral mucositis," which occurs when cancer treatments break down the rapidly divided epithelial cells lining the gastro-intestinal tract (which goes from the mouth to the anus).

REMEDIES FOR MOUTH SORES

Below are some therapies which may be helpful in preventing and treating mouth sores. As with any supplement, patients should first check with their doctor.

- **Acidophilus**
- **Aloe Vera Juice**
- **Biotene Mouth Rinse and Toothpaste**
- **Canker Cover**
- **Canker Rid**
- **Debacterol**
- **Dexamethasone Oral Rinse**
- **Difflam Oral Rinse**
- **Gelclair**
- **Licorice Root (DGL) Wafers**
- **Lysine**
- **Miscellaneous Over the Counter Therapies**
- **Mugard**
- **Organic Honey**
- **Salt/Baking Soda/Water rinse**
- **Triamcinolone Topical Cream**

- **Acidophilus:** This is a probiotic, which is a live bacteria and yeasts that are good for health, especially for the digestive system. Acidophilus is found in yogurt, or it can be taken in pill form

- **Aloe Vera Juice** applied to the sore. The juice has antibacterial and antifungal properties.

- **Biotene Mouth Rinse** and Biotene Toothpaste have been recommended by some patients.

- **Canker Cover** by Quantum Health, which is a tablet-like patch made from edible ingredients, has been known to help. It sticks to any canker sore or mouth ulcer within seconds, and then forms a patch that lasts from 8 to 12 hours.

- **Canker-Rid** by Durham's Bee Farm, Inc. has received significant praise from several patients for relieving mouth sores.

- **Debacterol** was recommended by a patient because it is a liquid topical agent that is used in the treatment of ulcerating oral mucosal lesions such as canker sores. Patients interested in Debacterol are encouraged to identify a Dental or Medical Practitioner in their area who offers Debacterol treatment of canker sores to their patients.

- **Dexamethasone Oral Rinse:** A study of women treated with a combination of Aromasin and Afinitor for MBC found that daily use of a steroid-based mouthwash markedly decreased the incidence and severity of stomatitis (an inflammation of - or sores in -

the mouth and lips), and researchers recommend that this preventive regimen become standard of care in this setting. In a clinical trial called "SWISH" it was determined that after 8 weeks of using the mouthwash 4 times daily, incidence of grade ≥2 stomatitis was 2.4%, and stomatitis of all grades was 21.2%, compared with 33% and 67% of patients, respectively). **From[308, PMID:28314691]:** ***http://www.oncnursingnews.com/web-exclusives/steroid-mouthwash-reduces-rate-and-severity-of-mtor-inhibitorassociated-stomatitis***

- **Difflam Oral Rinse:** This spray reduces inflammation and was highly praised by one patient in eliminating her mouth sores.

- **Gelclair** is a prescription oral rinse gel that relieves pain by lightly coating the surface of the mouth, soothing oral lesions. One patient with mouth sores wrote that it is the only thing that she's tried that has worked for her.

- **Licorice Root (DGL) Wafers** are popular with some patients.

- **Lysine** is used for preventing and treating cold sores (caused by the virus called herpes simplex labialis). It is taken by mouth or applied directly to the skin for this use. One patient mentioned that her oncologist recommended Lysine at a dose of 1,000 mg per day, and after only 3 weeks, her mouth sores were vastly reduced.

- **Miscellaneous Over the Counter Therapies** include: **Anbesol** or **Orabase** to coat the mouth sores before eating. And to help ease pain, patients may try **Amosan, Anbesol, Gly-Oxide, Orabase,** or **Zilactin**.

- **Mugard** is a rinse especially developed for mouth sores. Patients may need to obtain a prescription for this from their doctor.

- **Organic Honey:** The honey can be applied on its own, or 1 teaspoon of honey may be mixed with 1/4 teaspoon of turmeric, and then be applied to the sore(s). The turmeric may burn a little at first.

- **Salt/Baking Soda/Water rinse**: This may be swished in the mouth 4 or more times daily**.** Also, **a paste** can be made from **baking soda and water** and applied directly to the canker sore.

- **Triamcinolone Topical Cream** can be obtained through a doctor's prescription. One patient says she applies it to the sore before bedtime, and by morning the sores are virtually healed.

Helpful Hint: If a patient will begin taking Afinitor or another drug that may cause mouth sores, they might first consider first coating the mouth with Cool Whip before taking the pill (if the drug is taken orally), and then put the pill inside the Cool Whip (or inside a marshmallow) before swallowing it. Marshmallows are reported to be particularly helpful by patients taking medications that cause mouth sores.

47. Therapies for Osteonecrosis of the Jaw (ONJ)

Bisphosphonate therapy (or therapy with Xgeva) is an important aspect of treatment for patients with bone metastasis. Osteonecrosis of the jaw (ONJ) is a complication related to bisphosphonate or Xgeva therapy and has been reported in 3% to 7% of patients with metastatic breast cancer who undergo these therapies. Symptoms include jaw pain, bone infection and/or inflammation ("osteomyelitis" and/or "osteitis"), bone erosion, tooth or periodontal infection, toothache, and gum or soft tissue ("gingival") ulceration and/or erosion.

The more potent bisphosphonates carry significantly higher risk of producing ONJ than oral bisphosphonates, and there is no appreciable difference in the risk of ONJ between Zometa and Xgeva. The duration of bisphosphonate therapy is also associated with the development of ONJ, with longer duration of treatment contributing to greater risk.

Prior to beginning therapy with a bisphosphonate or Xgeva, patients are encouraged to visit their dentist. At that time, the dentist may need to undergo preventive dentistry (preemptive extraction of unsalvageable teeth and/or optimization of periodontal health) to avoid potential complications later on. Patients on bisphosphonates may be encouraged gently brush their teeth after each meal, rinse their mouth with salt water, and visit their dentist regularly for careful cleanings. These patients should speak with their dentist about their drug regimen before undertaking any new dental procedure. Finally, patients with ONJ who are taking bisphosphonates and who later require considerable dental work should ask their medical doctor about delaying their bisphosphonate therapy before and/or after the procedure, and also discuss taking prophylactic antibiotics before and/or after the procedure.

Treatment objectives for patients with an established diagnosis of ONJ aim to eliminate pain, prevent or control infection of the soft tissue and bone, and minimize the progression or occurrence of bone necrosis (bone death).

People who have been diagnosed with ONJ should seek the care of a Maxillofacial Surgeon (a physician who combines dental, medical, and surgical skills and who specializes in the face, jaws, and soft tissues). A list of Maxillofacial Surgeons by State is located at: ***http://www.healthgrades.com/oral-surgery-maxillofacial-surgery-directory***

Treatment for ONJ varies by Stage as follows.

STAGES AND CORRESPONDING TREATMENT OF ONJ:

Stage 1: The disease is characterized by exposed necrotic (dead) bone which is asymptomatic without any evidence of soft tissue inflammation or infection. Patients with Stage 1 disease should use oral antimicrobial rinses with 0.12% chlorhexidine daily and have regular clinical follow-up with a dentist or oral surgeon.

Stage 2: The disease is characterized by exposed necrotic bone associated with pain and soft tissue inflammation or infection. Patients with this stage of disease should use of antimicrobial therapy along with analgesics and daily oral antimicrobial rinses and may be prescribed antibiotics.

Stage 3: The disease is characterized by exposed necrotic bone associated with pain, soft tissue inflammation or infection, fracture, and other bone and/or soft tissue abnormalities. Stage 3 disease represents the most difficult group to treat as they may be resistant to antibiotic therapy. These patients usually require surgical removal of the dead bone and/or tissue ("debridement") in addition to analgesics and oral antimicrobial rinses.

From[309, PMID:22923892; 310, PMID:19021059; 311, PMID:27114946]: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424936/*** and ***http://www.uptodate.com/contents/medication-related-osteonecrosis-of-the-jaw-in-patients-with-cancer*** and ***http://www.ncbi.nlm.nih.gov/pubmed/19021059***

48. Therapies for Radiated Skin

When patients undergo radiation therapy, they may experience damage to the skin in the irradiated area. Therefore, patients who are about to undergo (or who have undertaken) radiation should request a list of helpful tips to help minimize side effects. Many people have reported some success with the following remedies.

THERAPIES FOR RADIATED SKIN

- **Aloe Plant Juice or Gel**
- **Biafine Cream**
- **Boswellia**
- **Calendula**
- **Emollients**
- **Emu Oil**
- **Loose, Cotton Clothing**
- **MEBO Cream (Moist Exposed Burn Ointment)**
- **Miaderm**
- **Silvadene and/or Domeboro**
- **Warm** (not hot) **Water**

- One person gently rubbed the juice from a leaf of the **Aloe plant** over the affected area and reported good results. (Some patients have used 100% aloe gel purchased from a health food store instead of using the plant itself).

- **Biafine Cream,** which is a topical non-steroidal medication, can ease discomfort. One person wrote, *"It was wonderful and almost immediately effective."*

- **Boswellia:** A study was undertaken to determine whether a cream containing boswellic acids (in this case, it was a cream called Bosexil) would help to prevent and relieve radiation-induced adverse effects in breast cancer patients. The results indicated that the use of a boswellia-based cream was effective in reducing radiation-induced erythema (skin irritation) and was well tolerated by patients. **From[312, PMID:25967706]: *http://www.ncbi.nlm.nih.gov/pubmed/25967706***

- **Calendula,** derived from the marigold flower, has alleged anti-inflammatory properties and is often used for wound healing. A recent trial found that calendula was significantly better than Biafine cream in preventing mild-to-severe acute radiation dermatitis in breast cancer patients, as well as in providing pain relief. Patients applied calendula to irradiated skin at least twice a day at the onset of radiation therapy and continued this until completion of treatment.

- **Emollients:** Emollients are special moisturizers that soothe dry, cracked, and irritated skin. Physicians may recommend specific emollients that are especially helpful for relieving radiation-induced discomfort.

- One person indicated that she applied pure **Emu Oil** (which can be purchased online) and obtained immediate relief.

- Wearing **loose, cotton clothing** around the affected area instead of tight synthetic clothing may be cooler and more comfortable.

- **MEBO Cream (Moist Exposed Burn Ointment):** One reader wrote about her positive experience using this cream for radiation burns and subsequently for Hand Foot Syndrome, *"I first used this for severe radiation burns on my breast; it actually helped regenerate the tissue, and this was an open 3 inch wound. My surgeon was shocked as I refused skin transplants because he said they would most likely fail because underlying blood supply was dead. I read the literature about healing burn wounds and came*

up with MEBO. I also recently used it for hand and foot syndrome due to Xeloda and now can confirm it helped a lot. I sometimes have to order it from China or Chinatown and have also found sellers on Amazon."

- **Miaderm Radiation Relief Cream** can be purchased over the counter at a local pharmacy. The formula was developed by a Radiation Oncologist to help prevent radiation dermatitis, as well as soothe and restore irradiated skin.

- **Silvadene** (**Silver Sulfadiazine) and Domeboro** (which is an Over the Counter drug): One person wrote that she mixed Domeboro according to directions and kept it in a jar in the refrigerator. She soaked sterile gauze pads in the Domeboro solution and placed them on the affected area, leaving them on for 15 to 30 minutes. Then she dried the area with a blow dryer on a cool setting. Afterwards she applied Silvadene (Silver Sulfadiazine) with a sterile Q-Tip. Finally, she covered it with several layers of Telfa, a non-adherent dressing that her radiation oncologist gave her. She reported that the results were very good!

- Using **warm (not hot) water** while bathing will help prevent the skin from feeling more irritated.

49. Palliative Care

Palliative care is meant to help anyone with a serious illness by maximizing their comfort level as much as possible. It differs from hospice care in that the patient does not need to be near end of life, and they can continue to receive standard treatment while on palliative care. Patients can request it at any age and any stage of an illness (even upon diagnosis), and it can be used along with curative treatment. Palliative care is not dependent on prognosis. With palliative care, patients can expect to have more control over their care, along with a comfortable and supportive atmosphere that reduces anxiety and stress. The patient's condition and situation are reviewed regularly by their palliative care team, and they are discussed with the patient to make sure that the patient's needs and wishes are being met and that treatments are in line with the patient's goals.

Palliative care can reduce symptoms such as pain, shortness of breath, fatigue, constipation, nausea, loss of appetite and difficulty sleeping. It addresses the whole person and helps them to carry on with daily life. It can improve one's ability to go through medical treatments and help the patient to better understand their condition and choices for medical care. In short, it enhances the patient's Quality Of Life (QOL).

Therefore, patients may wish to start palliative care early for best results, and they should request it from their doctor instead of waiting for their medical team to bring it up.

Most insurance plans, including Medicare and Medicaid, cover all or part of palliative care treatment. Palliative care is generally available in a number of places including hospitals, outpatient clinics, long-term-care facilities, hospices, or home. Usually a team of specialists, including palliative care doctors, nurses and social workers, provide this type of care in conjunction with the patient's doctor. Massage therapists, pharmacists, nutritionists and others might also be part of the team. To obtain palliative care in order to manage cancer or treatment side effects, the patient should speak with her or his doctor or nurse. Alternatively, patients can look up Palliative Care providers in their area at: ***http://getpalliativecare.org/providers/***

From: ***https://getpalliativecare.org/whatis/faq/*** and ***http://www.choosingwisely.org/wp-content/uploads/2014/09/Palliative-Care-Support-at-any-time-during-a-serious-illness.pdf***

50. Hospice Care

Hospice is an important benefit that provides special care for terminally ill patients who may have only months to live. Unlike those in palliative care, people who receive hospice are also no longer receiving curative treatment for their underlying disease. Once enrolled through a referral from the primary care physician, a patient's hospice care program - which is overseen by a team of hospice professionals - is usually administered in the home, although it can be elsewhere such as a hospital or hospice facility. Hospice often relies upon the family caregiver, as well as a visiting hospice nurse.

Most hospice programs concentrate on providing comfort to the patient rather than curing or reducing their disease. By electing to forego extensive life-prolonging treatment, hospice patients can concentrate on getting the most out of the time they have left, without some of the negative side-effects that life prolonging treatments can have. Many hospice patients achieve a level of comfort that allows them to address the emotional and practical issues of dying.

Before considering hospice, it is important to check one's insurance policy limits for payment. While hospice can be considered an all-inclusive treatment in terms of payment, insurance coverage for hospice may vary. Some hospice programs offer subsidized care for the economically disadvantaged or for patients not covered under their own insurance. Many hospice programs are covered under Medicare.

Before the actual need for Hospice Care arises, patients and/or their loved ones may wish to consider locating Hospice providers in their community by visiting ***https://hospicefoundation.org/Hospice-Directory*** or ***http://www.nhpco.org/find-hospice***

In addition to obvious items (regarding Medicare Certification, Licensure, Accreditation, Insurance Coverage, and Quality Assurance), the following points should also be considered when evaluating potential Hospices:

Do the care providers hold certification in Hospice and Palliative Care? (Certification in Hospice and Palliative Care is not required in order to practice, but it does indicate specialized study and expertise in the field).

Precisely what services does the Hospice provide? In addition to "standard" services that all Hospices offer, some Hospices deliver extra services that may be of benefit such as "pre-Hospice" care for those who are not yet medically ready for actual Hospice. It is also helpful to ascertain how the patient's current professional services align with the services the Hospice provides, especially if there is something that is currently being supplied that the Hospice would not be able to offer.

How does the Hospice handle admissions? Can the admissions process be completed during non-standard business hours? And how quickly can the Hospice begin providing services?

How will the Hospice address specific concerns? Part of this discussion should include mentioning specific concerns or issues and inquiring about how the Hospice staff would address them.

How does the Hospice handle in-home support if a crisis arises? Some Hospices are prepared to send a member of their team to one's home at any time, even during non-standard business hours. Others provide support over the telephone but might not dispatch staff to the home. It is also helpful to inquire whether all members of the Hospice team are available to provide support in a crisis situation that occurs at night or on a weekend, or if only some team members are available. Finally, it is helpful to ask about the average response time.

How does the Hospice handle in-patient care? Even if the patient is primarily receiving care at home, it may become necessary for them to enter an in-patient facility for the management of complicated symptoms, or for periods of respite. To that end, it is

helpful to ascertain which facilities in the community the Hospice organization partners with, as well as to visit these facilities to make sure that the patient would be comfortable receiving care there if the need arises.

What are the Hospice's expectations regarding the family's involvement in caregiving? It is very important to ensure that the Hospice's expectations are aligned with the care that family members are willing and able to provide.

What services do volunteers offer? It is also helpful to find out how quickly a volunteer is able to come if requested, and how the Hospice screens and trains volunteers.

From: ***http://www.caregiverslibrary.org/caregivers-resources/grp-end-of-life-issues/hsgrp-hospice/hospice-vs-palliative-care-article.aspx*** and ***http://www.alsa.org/als-care/resources/fyi/hospice.html***

51. Other References

Excellent resources for metastatic breast cancer patients, including legal assistance and financial aid, are located at: ***http://MBCN.org/support-resources/category/resources*** and ***http://www.patientadvocate.org/***

Low-income patients needing financial assistance for medical treatment may want to ascertain from their State Dept. of Health whether their state participates in the Breast and Cervical Cancer Treatment Program.

Complementary therapy-related links: The author does not necessarily endorse any (or any one) of the following, and they are listed for informational purposes only.

Annie Appleseed Project, which provides information, education and advocacy for people with cancer, their family and friends: ***http://www.annieappleseedproject.org***

The Block Center for Integrative Cancer Treatment, which empowers patients to help them become nutritionally, physically and psychologically fit to better fight cancer ***http://www.blockmd.com/***

Bruckner Oncology, whose mission is to provide a more effective, less toxic , tailored treatment approach for patients with cancer ***http://www.bruckneroncology.com/page.cfm?page=18***

Dr. Ralph Moss "Cancer Decisions" Reports and Newsletters about conventional and alternative therapies: ***http://www.cancerdecisions.com/***

Dr. Daniel Rubin, Naturopathic Oncologist: ***http://listenandcare.com/***

Jeanne Wallace, Oncology-based Nutritionist: ***http://www.nutritional-solutions.net***

A different perspective regarding complementary treatment is located at: *http://www.quackwatch.com*

Online metastatic breast cancer support forums:

Inspire Advanced Breast Cancer Community: ***https://www.inspire.com/groups/advanced-breast-cancer/***

Breast Cancer Discussion Board for Stage IV and Metastatic Breast Cancer ***https://community.breastcancer.org/forum/8***

Recommended Reading:

Anti-Cancer: A New Way of Life by Dr. David Servain-Schreiber. This book, written by an MD, describes his treatment of and remission from brain cancer. It contains excellent science-based information about nutrition and offers integrative approaches to healing.

Life Over Cancer by Dr. Keith Block. As medical director of the Block Center for Integrative Cancer Treatment in Evanston, Illinois, Dr. Block distilled almost thirty years of experience into a book that describes integrative treatment for cancer, describing standard therapies, nutrition, and other approaches that aim to maximize wellness.

The Metastatic Breast Cancer Alliance's "Landscape Analysis" is a report about the issues confronting people with MBC The report summary is located at: ***https://www.mbcalliance.org/wp-content/uploads/Executive-Summary_Dec2014_published.pdf***

52. Wrap-Up: The Beetle in My Bathtub
(A True Story)

This morning after I rubbed my eyes and trotted to the bathroom, I noticed a little black beetle lying motionless in my bathtub. The world is full of these types of beetles and there was nothing exceptional about this one except for his lack of motion. He lay inert on the cold, damp surface of my tub and remained completely still as I gingerly nudged him. So I gently picked him up with a bit of tissue and rather unceremoniously dropped him into the toilet. Thereafter I went about my business attending to my morning ablutions.

After I while I noticed a startling motion in the toilet: the beetle paddling madly for his life. From the beetle's perspective, things must have looked pretty bleak: a seemingly endless ocean of cold water (after lying cold and wet in the tub all night) and absolutely no way of climbing up the toilet's smooth porcelain rim to dry out and warm up. I immediately dipped a cloth into the toilet and brought the exhausted beetle safely to the surface of my sink's counter, where he dried up and slowly began stretching his limbs. After a while he was "good to go," and my husband gently took him outside to sit on a leaf of our favorite magnolia tree.

All day I thought about this beetle. His seemingly inevitable demise and his astonishing recovery.

Now we'll switch gears. A few years ago I'd gone tubing on a beautiful river with a friend. I found myself on the side of the riverbank where a man-made tunnel with a horizontal bar at the end (that could literally decapitate a person) had incongruously been constructed. It was only after I began the journey that I was warned of this hazard; if I'd known beforehand I would have shunned the adventure completely. Despite paddling furiously against the strong currents, in the end I could not circumvent the tunnel and entered it at warp speed. Thankfully, I managed to duck at the last minute and emerged on the other side with head and torso intact. After gratefully catching my breath, I recognized that there was absolutely nothing more I could have done to avoid the situation despite every effort.

So back to this morning's beetle. For him or her, things could not have appeared bleaker. A cold, damp night followed by a furious paddle in a (thankfully clean) toilet. Followed by an unexpected dramatic rescue.

The beetle and I have a lot in common.

And I like to think that, for us - through the most difficult of circumstances - there may be hope.

With appreciation and best wishes,

Anne

53. Glossary

Although not all the terms below have been used in this document, they are commonly found when researching MBC and other diseases.

Adjuvant therapy: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back.

Advanced cancer: A term used to describe cancer that is unlikely to be cured. It may be primary cancer in which the cancer is confined to an organ or tissue, or secondary cancer which is cancer that has metastasized (spread) to another area of the body.

Adverse Event (AE): An undesirable experience associated with the use of a medical product (such as a drug) in a patient. Adverse events are often categorized into the following "Grades:" Grade 0 – None, or within normal limits, Grade 1 - Mild, Grade 2 – Moderate, Grade 3 – Severe, Grade 4 – Life-threatening, Grade 5 - Death

Agonist: A chemical that binds to a receptor and activates the receptor to produce a biological response. Whereas an agonist causes an action, an "antagonist" blocks the action of the agonist.

Akt: Protein kinase B (PKB), also known as Akt, is a protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration.

ALK: A protein called anaplastic lymphoma kinase (ALK), which may be involved in cell growth. Mutated (changed) forms of the ALK gene and protein have been found in some types of cancer.

Anemia: A condition that develops when the blood lacks enough healthy red blood cells or hemoglobin. Hemoglobin is a main part of red blood cells and binds oxygen. If there are too few or abnormal red blood cells (rbc's), or the hemoglobin is abnormal or low, the cells in the body will not get enough oxygen. Causes of anemia may include but are not limited to: iron deficiency, Vitamin B-12 deficiency, disease in the bone marrow, to chronic disease such as cancer and HIV/AIDS, and other conditions.

Angiogenesis: A process through which new blood vessels form from pre-existing vessels. Tumors require nutrients and oxygen to grow and spread, and these are available in the blood. Tumors send chemical signals that stimulate blood vessel growth, and therefore anti-angiogenesis drugs are being studied relative to treating cancer.

Antagonist: A substance that acts against and blocks an action.

Antibodies: Large proteins found in the body. They are recruited by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody has a unique target known as an antigen present on the invading organism.

Antibody Drug Conjugate (ADC): An emerging novel class of anticancer treatment agents that combines the selectivity of targeted treatment with the cytotoxic potency of chemotherapy drugs. Kadcyla (TDM-1) is an example of an ADC.

Antigens: Molecules capable of inducing an immune response (to produce an antibody) in the host organism. Antigens are "targeted" by antibodies. Examples of antigens include microorganisms (bacteria, fungi, parasites, and viruses) and chemicals.

Apoptosis: Cell death.

Aromatase Inhibitors (AIs): A class of drugs used in the treatment of breast cancer in postmenopausal women. Aromatase inhibitors work by blocking the enzyme aromatase, which converts androgen hormones (testosterone and androstenedione) into small amounts of estrogen (specifically estradiol and estrone) in the body. This means that less estrogen is available to stimulate the growth of

hormone-receptor-positive breast cancer cells. The Aromatase Inhibitors used in the US are Femara (letrozole), Arimidex (Anastrozole), and Aromasin (exemestane), all of which are taken orally.

Arthralgia: Joint pain which is a result of injury, infection, illnesses (in particular arthritis) or a reaction to medication. Patients taking Aromatase Inhibitors may experience arthralgia.

ASCO (American Society of Clinical Oncology): A leading professional organization that seeks to provide the highest-quality resources in education, policy, the pioneering of clinical research, and advancing the care for patients with cancer.

Ascites: Abnormal accumulation fluid in the abdominal (peritoneal) cavity. Ascites may result when breast cancer metastasizes to the liver or peritoneum.

Assay: A measurement performed on a biological sample.

Asymptomatic: Presenting no outward signs or symptoms of disease.

Basket trial: A clinical trial in which researchers test the effect of a single drug on a specific mutation in a variety of cancer types.

BCL-2: BCL-2 is a cell survival protein best known for its roles in inhibiting apoptosis (cell death) and promoting oncogenesis (the formation of a cancer whereby normal cells are transformed into cancer cells). The majority of breast cancer is BCL-2 positive.

Biological products: Products that are regulated by the Food and Drug Administration (FDA) and are used to diagnose, prevent, treat, and cure diseases and medical conditions. Biological products are a diverse category of products and are generally large, complex molecules. They may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs.

Biomarker: A quantifiable biological molecule such as a protein, DNA, RNA, or biological compound that is measured in a biological sample (blood, DNA, a tumor, etc.) and that acts as an indicator for a specific biological state or condition. In the context of personalized cancer therapy, biomarkers are used to determine patient prognosis and predict which patients will have the highest likelihood of responding to selected therapies or have adverse side effects with particular therapies. Biomarker tests are currently being used to predict the likelihood of benefit, which integrates both sensitivity and resistance to targeted therapies.

Biosimilar Drugs: Biological products that are highly similar to and have no clinically meaningful differences from an existing FDA-approved reference product. Biosimilars and generic drugs are versions of brand name drugs and may offer more affordable treatment options to patients. Biosimilars and generics are each approved through different abbreviated pathways that avoid duplicating costly clinical trials. But biosimilars are not generics, and there are important differences between biosimilars and generic drugs. For example, the active ingredients of generic drugs are the same as those of brand name drugs. In addition, the manufacturer of a generic drug must demonstrate that the generic is bioequivalent to the brand name drug. By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product except for minor differences in clinically inactive components. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness.

Bisphosphonates: A group of medicines that slow down or prevent bone loss, strengthening bones. Bisphosphonates inhibit osteoclasts which are responsible for breaking down and reabsorbing minerals such as calcium from bone (the process is known as bone resorption). Bisphosphonates allow osteoblasts (bone-building cells) to work more effectively, improving bone mass. People taking bisphosphonates (or Xgeva, which is a targeted bone-directed therapy but not a bisphosphonate) are at increased risk for Osteonecrosis of the Jaw (ONJ), whereby the jaw bone becomes exposed and begins to starve from a lack of blood.

Biopsy: The removal of a sample of tissue taken from the body to examine it more closely for abnormalities. A pathology report is subsequently issued to describe the findings of examining tissue removed during a biopsy.

Blood Brain Barrier (BBB): A network of blood vessels and tissue that is made up of closely spaced cells and helps keep harmful substances from reaching the brain. The blood-brain barrier lets some substances, such as water, oxygen, carbon dioxide, and general anesthetics, pass into the brain. It also keeps out bacteria and other substances, such as many anticancer drugs.

Bone Scan: An imaging test that can often problems (such as cancer) in the bone earlier than a regular X-ray test. During a bone scan, a radioactive substance called a tracer is injected into a vein in the arm. The tracer travels through the bloodstream and into the bones, and a special camera takes pictures of the tracer in the bones.

BRCA: A gene that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA1/2 gene has a higher risk of getting breast, ovarian, prostate, and other types of .cancer.

Breakthrough Therapy Designation: A "breakthrough therapy" is a drug intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease or condition and whereby preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies. If a drug is "designated" as a breakthrough therapy, FDA will expedite its development and review.

Cachexia: A condition that causes extreme weight loss as well as muscle wasting. Cachexia is a result or side effect of chronic conditions, such as cancer, type 1 diabetes, HIV, and multiple sclerosis.

Cancer (Malignancy): A group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. These contrast with benign tumors, which do not spread to other parts of the body.

Case control study: An observational study of people with a disease such as breast cancer compared with a similar control group without the disease. It could retrospectively examine, for example, women with breast cancer and their level of physical activity compared to that of matched women without breast cancer.

CDKs: CDKs are Cyclin-Dependent Kinases, which are targeted drugs act upon genes, proteins or other substances that contribute in some way to the growth and development of cancer cells. Ibrance (Palbociclib), Kisqali (Ribociclib) and Verzenio (Abemaciclib) are FDA-approved CDK4/6 inhibitors for hormone receptor positive, HER2 negative MBC patients. There are currently clinical trials underway to test CDK4/6 inhibitor efficacy on HER2 positive MBC patients.

Central Nervous System (CNS): CNS is the part of the nervous system consisting of the brain and spinal cord to which sensory impulses are transmitted and from which motor impulses pass out, and which coordinates the activity of the entire nervous system.

Checkpoint Inhibitors: Drugs which are usually made of antibodies that unleash an immune system attack on cancer cells. Checkpoint inhibitors work by enabling immune cells to recognize and attack tumors.

This therapy is sometimes called immune checkpoint blockade because the molecule that acts as a brake on immune cells — the checkpoint — is blocked by the drug.

Chemokines: Cytokines that attract cells to a site of infection or inflammation.

Chemoresistance: Low or no response to a drug that is generally considered effective in many tumors.

Chemosensitivity: High response to a drug in which tumor cells die more quickly or at a much lower drug concentration compared to many other tumors.

Chemotherapy ("chemo"): A type of treatment that includes a medication or combination of medications to treat cancer with the goal of stopping the growth of cancer cells. It is considered a systemic therapy in that it may affect the patient's entire body. Depending upon the drug, it can be given orally, intravenously, or as an injection.

Circulating Tumor Cells (CTCs): Cancer cells that detach from a malignant tumor and travel through the bloodstream or lymphatic system to other parts of the body. In cancer patients, no or low levels of CTCs is considered to be a favorable prognostic indicator.

Circulating Tumor DNA (ctDNA): Fragmented DNA found in the bloodstream that comes from cancerous cells. Low ctDNA is favorably prognostic because it signifies low tumor turnover and/or smaller tumor burden.

Clinical Benefit Rate (CBR): The percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention in clinical trials of anticancer agents (same as Disease Control Rate).

Clinical Trials: Research investigations in which people voluntarily test new experimental treatments (or new ways of diagnosing, detecting, and/or managing diseases or medical conditions). Some clinical trials use a placebo in a "control group" against which people undergoing the experimental treatment are compared. Typically, clinical trials are divided into three sequential phases: Phase 1, where increasing doses of the drug are given to determine the toxicity levels and side effects of the investigational therapy, Phase 2 which tests the therapy's efficacy, and Phase 3 which compares the investigational therapy's efficacy and safety with the current standard of care.

Co-morbidity: Other diseases or conditions the patient may have.

Cohort study: A study of a group of patients with certain similarities, such as a particular disease or treatment at a particular hospital or institute who are followed up over a period of time. In contrast to many clinical trials, cohort studies are observational, meaning that patients in a cohort receive standard of care as determined by their physicians rather than novel treatments such as in a clinical trial; researchers observe a cohort and intervene in a clinical trial. In addition, unlike many clinical trials, cohort studies can be carried out over many years or decades and can thus be used to obtain much longer-term data than typical clinical trials. Cohort studies can be retrospective, meaning that data for a group of patients are examined after the patients have been treated, or prospective, meaning that researchers will enroll patients in their cohort with selected characteristics (for example, all patients with a certain disease treated at a certain institute who underwent a particular imaging technique or received a certain treatment). Carefully defined cohort studies can establish a cause between two events.

Compassionate Use/Expanded Access: The use of an investigational, unapproved drug to treat a terminally ill patient (outside of a clinical trial) when no other approved treatments are available.

Complete Response (CR): Disappearance of all indications of a disease (such as cancer) following a treatment.

Conditional Survival: The probability of surviving a further amount of years, given that a patient has already survived a specific number of years after the diagnosis of a chronic disease.

Confidence interval: A range used to calculate the possible degree of error between the population studied and the wider population it is expected to represent. It is based on the concept that if a study were repeated in a different set of participants, the results would vary slightly. It is usually expressed in a range referred to as the 95% confidence interval (CI), meaning that the findings are true 95% of the time, allowing for a 5% error.

Confounding factor: A variable that is not being measured in a study, but that may influence the results. In a study measuring the effect of alcohol consumption on breast cancer risk, obesity may be a confounding factor because it may influence a woman's risk of the disease regardless of whether she is drinks alcohol.

CT (Computerized tomography) Scan: A CT scan combines a series of X-ray images taken from different angles and uses computer processing to create cross-sectional images, or "slices," of the bones, blood vessels and soft tissues inside the body. CT scan images provide more detailed information than plain X-rays. Sometimes CT scans are accompanied by a special dye ("contrast") in order to help highlight in greater detail the areas of you're the body that are being examined. As is the case with PET scans and MRIs, CT scans can be quite useful in detecting cancer, ascertaining whether cancer has spread, and checking whether a cancer treatment is working.

CyberKnife: A painless, non-invasive form of Stereotactic RadioSurgey (SRS) r treatment that delivers high doses of precisely targeted radiation to destroy tumors or lesions within the body. It uses a robotic arm to deliver highly focused beams of radiation. CyberKnife can treat cancer anywhere on the body in one to five radiation treatments. Whereas Gamma Knife radiosurgery is dedicated exclusively to applications involving the upper neck and head, CyberKnife is more diverse in that it may be used for any location in the body that might benefit from surgical alternatives.

Cyclin-Dependent Kinases (CDKs): A family of proteins that play a role in cell cycle regulation. Ibrance (Palbociclib), Kisqali (Ribociclib), and Verzenio (Abemaciclib) are CDKs (specifically, CDK4/CDK6 inhibitors) that are classified as targeted therapies that have been approved for use in combination with Aromatase Inhibitors and/or Faslodex in specific instances, and Verzenio may be prescribed alone after prior endocrine and chemotherapy failure.

Cytochrome: Proteins that carry iron and that function in metabolism.

Cytokines: A group of small molecules released by immune cells that affect the nearby cells.

Cytoskeleton: The scaffold of proteins located inside cells that determines the shape of the cells and that helps cells move.

De-identified data: Information about a patient's medical condition that is anonymous due to removal of personal information such as name, social security number, date of birth, etc. De-identification allows data from an individual patient to be shared among researchers for analysis without compromising the patient's privacy.

de novo - In cancer, the first occurrence of cancer in the body. People who are diagnosed with de novo Stage IV breast cancer were never previously diagnosed with early stage breast cancer. It is estimated that 6% - 10% of all MBC cases are diagnosed as de novo.

DEXA Scan (Dual X-ray Absorptiometry): A test that measures bone density (a measurement of how strong the bones are) that uses X-ray beams to determine whether a person has osteopenia (bone density that is lower than normal peak density but not low enough to be classified as osteoporosis) or osteoporosis (a condition of fragile bone with an increased susceptibility to fracture). Unlike some other types of tests such as MRIs, PET, and CT scans, the patient lies on an open X-ray table instead of a closed tunnel when taking a DEXA Scan.

Disease Control Rate (DCR): The percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and/or stable disease to a therapeutic intervention in clinical trials of anticancer agents. DCR is the sum of the complete, partial and stable disease rates. (Same as Clinical Benefit rate).

DNA (Deoxyribonucleic Acid): A molecule that carries the genetic instructions used in the growth, development, functioning and reproduction of all known living organisms and many viruses. Both DNA and ribonucleic acid (RNA) are nucleic acids (small biomolecules that are essential to all known forms of life).

Downregulated: Decreased.

Duration of Response (DOR): Time from confirmation of a partial response (PR), complete response (CR) or stable disease (SD), until the disease has been shown to progress following treatment (progressive disease or PD).

Early Stage Breast Cancer: Cancer that originated in the breast that has not metastasized (spread) to distant organs. Early stage breast cancer includes Stage 0 (DCIS/Ductal Carcinoma in Situ), Stage I, Stage II, and Stage IIIA breast cancer.

EGFR (Epithelial Growth Factor Receptor): The EGFR gene provides instructions for making a receptor protein called the epidermal growth factor receptor, which spans the cell membrane so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning allows the receptor to attach (bind) to other proteins, called ligands, outside the cell and to receive signals that help the cell respond to its environment.

Endocrine (Hormonal) Therapy: In the context of MBC, endocrine therapy is a type of treatment specifically for patients with hormone receptor-positive breast cancer. The purpose of endocrine therapy is to prevent breast cancer cells in these patients from being nourished by estrogen. There are various types of hormonal therapies, such as Aromatase Inhibitors, Selective Estrogen Receptor Modulators (SERMs), Selective Estrogen Degraders or Downregulators (SERDs), and Luteinizing Hormone-Releasing Hormone Agonists (the latter for premenopausal women).

Endoscopy/EGD (Esophagogastroduodenoscopy): A test that examines the lining of the esophagus, stomach, and duodenum (the upper part of the small intestine). An endoscope is a small camera on a tube, and the EGD test involves passing an endoscope down the throat and along the length of your esophagus. A biopsy may be taken of the tissue to test for abnormalities. EGDs can be especially useful for those diagnosed with lobular MBC, which tends to gravitate to the abdominal area and tends not to show up on other types of scans due to the fact that it more closely resembles a spider web that solid tissue and hence is harder to detect.

Epigenics: Modifications to the expression of genes which do not involve changes to the genetic code itself.

ESR1 Mutations: Mutations in the estrogen-receptor-alpha (ESR1) gene that generally signify resistance to endocrine therapy. Such mutations may be acquired during therapy with Aromatase Inhibitors (AIs), and can appear as much as 6 months prior to clinical progression. Common ESR1 mutations are Y537S and D538G.

Estrogen Receptor (ER) positive breast cancer: A breast cancer subtype in which there are estrogen receptors on the surface of the cells that bind to estrogen. Patients with ER+ (positive) breast cancer are classified as Hormone Receptor (HR) positive.

Event-Free Survival (EFS): Time from randomization to disease progression, death, or discontinuation of treatment for any reason (e.g., toxicity, patient preference, or initiation, of a new treatment without documented progression).

Expanded Access/Compassionate Use: The use of an investigational, unapproved drug to treat a terminally ill patient (outside of a clinical trial) when no other approved treatments are available.

External Beam Radiation (EBRT): External beam radiation therapy (EBRT) directs a beam of radiation from outside the body at cancerous tissues inside the body. It is a cancer treatment option that uses doses of radiation to destroy cancerous cells and shrink tumors. Examples of EBRT include 3D conformal radiation therapy, IMRT, IGRT, TomoTherapy and Stereotactic Radiosurgery (SRS).

Extracellular matrix: Proteins located outside of cells that provide physical support to cells.

Ex vivo: Tissue or cells removed from a person or animal.

Fast Track Designation: An FDA designation of an investigational drug for expedited review to facilitate development of drugs which treat a serious or life-threatening condition and which fill an unmet medical need. (*Fast Track* designation must be requested by the drug company).

FDA (Food and Drug Administration, or USFDA): A US federal agency that is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs/medications, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics, animal foods & feed, and veterinary products.

FISH (Fluorescence in situ Hybridization) Test. A test done on breast cancer tissue removed during a biopsy that looks for specific genes or portions of genes. It is commonly used to check whether there are extra copies of the HER2 gene.

Fungating wound: Ulcerating cancer wounds that develop when cancer that is growing under the skin breaks through the skin. Symptoms, which are highly distressing, include leakage, an unpleasant smell, pain, bleeding and itching.

Gamma Knife: A non-invasive Stereotactic RadioSurgery (SRS) instrument that involves no scalpel or incision. Gamma Knife differs from CyberKnife (also a form of SRS) in that it is dedicated exclusively to applications involving the upper neck and head. Gamma Knife can target brain or cervical spine cancer with a single treatment of high-dose radiation. Patients typically are in and out of the hospital in a day's time – and back to their normal routines soon after treatment. Gamma Knife radiosurgery may be used in place of or in addition to traditional surgery or whole brain radiation, depending on the patient's diagnosis.

Generic Drugs: Copies of brand-name drugs that have exactly the same dosage, intended use, effects, side effects, route of administration, risks, safety, and strength as the original drug. Their pharmacological effects are exactly the same as those of their brand-name counterparts. (Note: In some cases, patients have reported different side effects when using a generic drug vs. the corresponding brand name drug).

Genotype: The genes carried by an individual that determine the characteristics of proteins, cells, organs, or the entire individual.

Germline: Genetic material contained in cellular lineage which can be passed to the next generation.

Germline-derived polymorphism: DNA changes that are inheritable (found in egg and sperm cells and thus passed down to offspring). The variants may or may not influence cancer etiology, progression, or metastasis, and are more likely to influence a response to therapy.

Hand Foot Syndrome: Hand-foot syndrome is also called palmar-plantar Erythrodysesthesia. It is a side effect of some cancer treatments, such as Xeloda (Capecitabine). Symptoms include redness, swelling, and pain on the palms of the hands and/or the soles of the feet, sometimes accompanied with blisters. It may sometimes appear elsewhere on the skin, such as the knees or elbows, although this is less common.

Hazard ratio: A term commonly found in clinical trial results which compares the likelihood of an event (such as death) occurring in one population compared to another population (for example, a treated group and a placebo group) over time and is generally shown as a number close to 1.0. A hazard ratio higher than 1.0 means an increased likelihood of an event occurring. For example, a hazard ratio of 2.0 means that the event is twice as likely to occur in one population compared to another population. A hazard ratio less than 1.0 means the event is less likely to occur in one population compared to the other, and a hazard ratio of 1.0 means that the event is equally likely to occur in the two populations.

HDAC Inhibitors: HDAC (Histone Deacetylases) inhibitors cause changes in the status of specific proteins, resulting in changes in gene expression, induction of apoptosis (cell death), cell cycle arrest, and inhibition of metastasis. HDAC inhibitors are a subgroup of targeted therapies currently being studied in clinical trials.

Hemoglobin: A red pigment that imparts the familiar red color to red blood cells and to blood. Functionally, hemoglobin is the key chemical compound that combines with oxygen from the lungs and carries the oxygen from the lungs to cells throughout the body.

HER2-positive breast cancer: A subtype of breast cancer that tests positive for a protein called Human Epidermal Growth Factor Receptor 2 (HER2), which promotes the growth of cancer cells. In about 1 of every 5 breast cancers, the cancer cells have a gene mutation that makes an excess of the HER2 protein. Targeted therapy with Herceptin (Trastuzumab) and other drugs has revolutionized treatment for this breast cancer subtype.

Heterogeneous: Different or mixed. A heterogeneous population of patients has many different characteristics. A heterogeneous tumor has cells with different properties.

Hormonal (or Endocrine) Therapy: In the context of MBC, hormonal therapy is a type of treatment specifically for patients with hormone receptor-positive breast cancer. The purpose of hormonal therapy is to prevent breast cancer cells in these patients from being nourished by estrogen. There are various types of hormonal therapies, such as Aromatase Inhibitors, Selective Estrogen Receptor Modulators (SERMs), Selective Estrogen Degraders or Downregulators (SERDs), and Luteinizing Hormone-Releasing Hormone Agonists (the latter for premenopausal women).

Hormone Receptive (HR) Positive Breast Cancer: Some breast cancer cells need estrogen and/or progesterone hormones to grow. These cancer cells have special proteins inside, called hormone receptors. When the body's hormones attach to the cells' hormone receptors, the cancer cells grow. Hormone receptor- positive breast cancers have Estrogen Receptors (ER) and possibly Progesterone Receptors (PR) that, when stimulated by hormones, cause the cancer cells to grow.

Hospice Care: Considered to be the model for quality, compassionate care for people facing a life-limiting illness or injury, hospice care involves a team-oriented approach to expert medical care, pain management, and emotional and spiritual support customized to the patient's needs and wishes if they have 6 months or less to live. When medical professionals and patients agree that chemotherapy and other active treatments are not working and there is no prospect of remission, hospice care can take over. It can be provided in the patient's home or in a facility, and its focus is on pain management and the patient's general comfort.

IHC (ImmunoHistoChemistry) Test: A special staining process performed on fresh or frozen breast cancer tissue removed during biopsy. IHC is used to show whether or not the cancer cells have HER2 receptors and/or hormone receptors on their surface.

Immunosuppression: A reduction of the activation or efficacy of the immune system that can result from illness or drugs.

Immunotherapy: Immunotherapy, also called biologic therapy, is a type of cancer treatment that boosts the body's natural defenses to fight the cancer. It uses substances made by the body or in a laboratory to improve or restore immune system function.

Incidence: Incidence is the number of newly diagnosed cases of a disease that occur over a defined period of time within a specified population.

In vitro: In a test tube or culture plate.

In vivo: In a person's or animal's body.

Interaction: A drug interaction is a situation in which a substance (usually another drug, a food or beverage, or a supplement) affects the activity of a drug when both are administered together. ... The interaction of the two substances may also increase the risk that side effects will occur and/or impact the effectiveness of the drug.

Intraperitoneal: within or through the membrane that lines the walls of the abdominal cavity.

Intravenous (IV): Into a vein. IV medications are a solutions administered directly into the venous circulation via a syringe, port, or intravenous catheter (tube).

Kaplan-Meier Curve: The Kaplan-Meier estimate ("curve") is the simplest way of computing survival over time, while taking into account complexities associated with multiple subjects or situations.

Ki-67 Index: A measure of how rapidly tumor cells are dividing. Results of <10% indicate a low division rate, 10-20% are borderline, and >20% is considered a high division rate.

Kinase: A key regulator of cell function that constitutes one of the largest and most functionally diverse gene families. ... Kinases are particularly prominent in co-ordination of complex functions such as the cell cycle.

Leptomeningeal Metastasis (LM), Leptomeningeal Carcinomatosis [LC], or Carcinomatous Meningitis: A difficult-to-treat condition that occurs when cancer spreads to the meninges, which are layers of tissue that cover the brain and the spinal cord.

Ligand: A substance that forms a complex with a biomolecule to serve a biological purpose. Ligands and receptors fit together like keys into locks. The binding of a ligand to receptor allows the receptor to attach to a nearby receptor protein. As a result, signaling pathways within the cell are triggered that promote cell growth and division (proliferation) and cell survival.

Liquid Biopsy: A test done on a sample of blood (or in rarer instances, the urine or Cerebral Spinal Fluid) to look for cancer cells from a tumor, and/or for pieces of DNA from tumor cells.

Local (or localized) therapy: Treatment that is directed to a specific organ or limited area of the body, such as the breast or an abnormal growth on the skin.

Lumbar puncture (spinal tap): A procedure to collect and look at the fluid (cerebrospinal fluid, or CSF) surrounding the brain and spinal cord. During a lumbar puncture, a needle is carefully inserted into the spinal canal low in the back (lumbar area). Samples of CSF are collected and later examined to determine whether any abnormalities exist. Among other purposes, lumbar punctures are used to determine whether a patient may have Leptomeningeal Metastasis (LM).

Luteinizing Hormone-Releasing Hormone Agonists: Luteinizing hormone releasing hormone (LHRH) agonists such as Zoladex are an established therapy for hormone-dependent metastatic pre-menopausal breast cancer. Their mechanism of action in this disease is the suppression of ovarian estrogen production. In premenopausal MBC patients, it is a method used to render the patient postmenopausal and thus eligible to receive hormonal therapies available to postmenopausal women.

Lymphocytes: A type of white blood cell (wbc) that is part of the immune system. There are two main types of lymphocytes: B cells and t cells. B cells produce antibodies that are used to attack invading bacteria, viruses, and toxins. T cells destroy cells in the body that have been taken over by viruses or cancer.

Median survival: The length of time from diagnosis until half of the patients are still alive. In a clinical trial, measuring the median survival is a method of determining how effective a treatment is.

Medical Oncologist (MO): A doctor who has special training in diagnosing and treating cancer in adults using chemotherapy, hormonal therapy, biological therapy, and targeted therapy. A medical oncologist often is the main health care provider for a patient who has cancer.

Meninges: The three membranes (the dura mater, arachnoid, and pia mater) that line the skull and vertebral canal and enclose the brain and spinal cord.

Menopause: Menopause is defined as the time when a woman has not had a menstrual period for 12 consecutive months. Women in menopause are referred to as being postmenopausal. In cases when a woman's ovaries are surgically removed (called oophorectomy"), she becomes postmenopausal irrespective of her age.

Meta-analysis: A systematic process in which similar data collected from multiple studies are re-analyzed to increase statistical power.

Metabolize: To metabolize is to break down. For example, enzymes in the liver break down or metabolize drugs and other foreign substances so that they can be excreted from the body. Metabolism can activate an inactive drug or inactivate an active drug.

Metastasis: The medical term for cancer that spreads to a different part of the body from where it started.

Metastatic Breast Cancer (MBC) or Stage IV Breast Cancer or Advanced Breast Cancer: Cancer that originated in the breast and metastasized (spread) beyond the breast and surrounding lymph nodes to distant organs. The most common distant organs in which MBC is found are the liver, lungs, bones, and brain.

Metronomic Therapy: This refers to the continuous or frequent administration of low-doses of anti-cancer drugs, often with other forms of therapy.

Microenvironment: The environment in which a tumor is located. The microenvironment consists of a variety of molecules, cells, and blood vessels, all of which may affect the survival of tumor cells and the response to therapy.

microRNA: RNA that is transcribed (i.e., the RNA code is used to make a certain protein) from DNA in the cell's nucleus but that does not encode a protein. microRNAs bind to other RNA molecules called messenger RNA or mRNA that encode proteins and regulate the translation of mRNA into protein.

Molecular Breast Cancer Sub-typing: Researchers are studying how molecular subtypes of breast cancer may be useful in planning treatment and developing new therapies. The profile of each subtype is determined using molecular and genetic information from tumor cells, and most studies divide breast cancer into 4 major molecular subtypes: 1) Luminal A (ER+, HER2-, low Ki-67 Index)). 2) Luminal B (ER+, either HER2+ or HER2-, high Ki-67 Index), 3) TNBC/basal-like which is ER-, PR-, and HER2-, and 4) HER2 Enriched which is ER-, PR-, and HER2+.

mRNA (messenger RNA): A subtype of RNA. An mRNA molecule carries a portion of the DNA code to other parts of the cell for processing. mRNA is created during transcription.

Mitochondria: The part of the cell responsible for energy production.

Modality: A regimen; a series of practices.

Molecular aberrations: Abnormal variations present in DNA that include:

Amplifications and duplications: more copies of a gene or multi-gene region than are normally present

Copy number variation: a different number of copies of a gene

Deletion: removal of DNA from a sequence

Insertion: addition of extra DNA to a sequence

Multi-gene fusion: joining of two genes or parts of genes that are not normally found together

Mutation: a change in the DNA sequence

Rearrangement: a section of DNA that is moved to another location

Translocation: swapping the location of genes, often between two different chromosomes

Truncation: shortening of a gene

Molecular pathways: The stepwise process by which different proteins in one or more cells send a message that changes the status or function of another cell.

Molecular testing: The analysis of DNA, RNA, and/or protein from a biological sample such as blood or a tumor.

Molecule: An electrically neutral group of two or more atoms held together by chemical bonds. In humans, body composition may be analyzed in terms of "molecular type" such as water, protein, connective tissue, fats (or lipids), hydroxylapatite (a mineral in bones), carbohydrates (such as glycogen and glucose) and DNA.

Monotherapy: Treatment with a single drug instead of using a combination of drugs.

Mortality The number of people who die from a disease during a specified period of time within a specific population. It is expressed as a rate per 100,000 population and is usually age-adjusted.

MRI (Magnetic Resonance Imaging): A test that uses powerful magnets, radio waves, and a computer to make detailed pictures inside the body. to diagnose you or to see how well you've responded to treatment. Unlike X-rays and CT scans, an MRI doesn't use radiation. . As is the case with PET and CT scans, MRIs can be quite useful in detecting cancer, ascertaining whether cancer has spread, and checking whether a cancer treatment is working, and MRIs are typically used for examining the brain and spinal cord.

mTOR: The mammalian target of rapamycin (mTOR) signaling pathway senses and integrates a variety of environmental cues to regulate organismal growth and homeostasis. The pathway regulates many major cellular processes and is implicated in an increasing number of pathological conditions, including cancer. The drug Afinitor (Everolimus) inhibits mTOR and in some patients can reduce cell growth.

NEAD (No Evidence of Active Disease): A term that is used when examinations and tests can find no active cancer in a person who has been treated for cancer. The terms NEAD and NED are sometimes used interchangeably.

NED (No Evidence of Disease): A term that is used when examinations and tests can find no cancer in a person who has been treated for cancer.

Neuropathy: A condition where one or more parts of the nervous system are not working properly. Neuropathy generally involves "peripheral" nerves, which are those outside the brain and spinal cord. Symptoms of neuropathy include pain, numbness, and weakness.

Neutropenia: An abnormally low level of neutrophils. Neutrophils are a common type of white blood cell important to fighting off infections - particularly those caused by bacteria.

Objective Response Rate (ORR): Percentage of patients whose disease decreased (Partial Response – PR) and/or disappears (Complete Response – CR) after treatment.

Off Label Use: Using an FDA-approved drug for an unapproved use to treat the patient's disease or medical condition. An example is Prazosin, which is approved for the use of hypertension, but it is used "off label" to treat nightmares related to post-traumatic stress disorder (PTSD).

Oligometastatic disease: Characterized by solitary or few detectable metastatic lesions that are usually limited to a single organ. Some studies indicate that in such cases, a combination of localized and systemic treatment can potentially be curative in some cases.

Ommaya Port (or reservoir): A device consisting of a small port (about the size of a quarter) that is placed underneath the skin on the head, which is attached to a catheter (tube) that is threaded into a ventricle (open space) in the brain. Cerebrospinal Fluid (CSF) is

produced in the ventricles and an Ommaya Port gains direct access to the CSF. Patients can feel the port that sits under the skin, which will be elevated in that area. The purpose of an Ommaya Port is to deliver drugs (such as those for brain or leptomeningeal metastasis) to the CSF that would normally not be able to reach it due to the blood brain barrier.

Oncogene: Genetic material that carries the ability to induce cancer.

Oncogenesis: The formation of a cancer whereby normal cells are transformed into cancer cells.

Oncology: The study of cancer.

Oophorectomy: Surgical removal of the ovaries. In premenopausal MBC patients, it is a method used to render the patient postmenopausal and thus eligible to receive hormonal therapies available to postmenopausal women.

Osteonecrosis of the Jaw (ONJ): Osteonecrosis of the jaw occurs when the jaw bone is exposed and begins to starve from a lack of blood. In MBC patients, taking bone-directed medications such as Xgeva or Zometa increase the risk of ONJ.

Overall Response Rate (ORR): The proportion of patients with reduction in disease burden of a predefined amount.

Overall Survival (OS): Time from clinical trial randomization until death from any cause. (Not all trials are randomized. In nonrandomized trials, time from study enrollment is commonly used).

Overexpression: This refers to levels (often of a protein or mRNA) that are higher than normal.

P-Value: P-values are used to express statistical significance and represent the probability that the effect observed in a study could be the result of chance alone. Generally, a P-value ≤ 0.05 is considered statistically significant. If the P-value is > 0.05, then chance cannot be excluded as an explanation for the findings.

Palliative Care: A multidisciplinary approach to specialized medical and nursing care for people with life-limiting illnesses. It focuses on providing patients with relief from the symptoms, pain, physical stress, and mental stress of the terminal diagnosis. Palliative Care differs from Hospice Care in that the patient can continue with therapy for their disease while on Palliative Care.

PARP (Poly ADP-Ribose Polymerase) Inhibitor: PARP is an enzyme that repairs DNA damage in cells, including DNA damage caused by chemotherapy medicines. Scientists developed PARP inhibitors based on the idea that a medicine that interferes with or inhibits the PARP enzyme might make it harder for cancer cells to fix their damaged DNA.

Partial Response (PR): In cancer, a reduction of at least 30% in a tumor following a treatment, but not a complete disappearance.

Pathology Report: A document that contains the diagnosis determined by examining cells and tissues under a microscope.

PD-1: Programmed Death 1 (PD-1) is an immune inhibitory receptor expressed on several immune cells, particularly cytotoxic T cells. PD-1 acts as a type of "off switch" that helps prevent T cells from attacking other cells in the body. PD-1 attaches to PDL-1, a protein found on some normal cells and some cancer cells. This interaction tells the T cells to leave the other cells alone and not attack them. Some cancer cells contain large amounts of PDL-1, which helps them hide from attack by immune cells. The PD-1/PD-L1 pathway has shown some promising clinical success as a cancer immunotherapy target. Keytruda (Pembrolizumab) is an example of a drug that works as an anti-PD-1 immunotherapy which has been FDA-approved for any cancer patient who has metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Pericardium: The membrane enclosing the heart. On rare occasions, breast cancer metastasis may cause pericardial effusion.

Perimenopause: Menopause is defined as the time when a woman has not had a menstrual period for 12 consecutive months, and the time that precedes preceding menopause has been referred to as the perimenopause, although there is no strict medical definition for this. Perimenopause usually begins for women in their 40s but may start as early as the late 30s. Perimenopausal women will have had one or more periods within 12 months, And typically begin experiencing menopausal symptoms such as mood swings, irregular periods, and/or hot flashes.

Peritoneum: The membrane that forms the lining of the abdominal cavity. Metastatic lobular breast cancer tends to gravitate to the peritoneum.

PET (Positron Emission Tomography) Scan: A PET scan is an imaging test that helps reveal how the body's tissues and organs are functioning. A PET scan uses a radioactive drug ("tracer") to show this activity. Cancer cells show up as bright spots on PET scans because they have a higher metabolic rate and therefore absorb the tracer faster than do normal cells. As is the case with CT scans and MRIs, PET scans can be quite useful in detecting cancer, ascertaining whether cancer has spread, and checking whether a cancer treatment is working.

Pharmacogenomics: The study of how genes affect a person's response to drugs.

Pharmacokinetics: The body's processing of drugs.

Phenotype: The characteristics of a protein, cell, organ, or organism as determined by its genes.

PI3K: Also called Phosphatidylinositol-3 kinase and PI3 kinase. An enzyme that transmits signals in cells and that helps control .cell growth.

Placebo: Placebo is an inactive form of a treatment drug being investigated. The placebo arm of a clinical trial is used as a control to compare how effective or safe the actual treatment drug is.

Pleural Effusion: A condition in which excess fluid builds around the lung. Among other causes, it can result from breast cancer metastasizing to the lung.

Pneumonitis: Inflammation in the lungs that is non-infectious. Pneumonitis can cause difficulty breathing and/or coughing, and may be caused by certain treatments for MBC.

Port: A small disc made of plastic or metal about the size of a quarter that sits just under the skin. The port is attached to a catheter (tube) that is threaded into a vein or specific area for purposes of extracting blood or delivering a drug(s) to a patient.

Postmenopausal women: Women who have not had a menstrual period for 12 consecutive months. In cases when a woman's ovaries are surgically removed (called oophorectomy"), the woman immediately becomes postmenopausal irrespective of her age.

Progesterone Receptor-positive (PR+): Describes cells that have a protein to which the hormone progesterone will bind.

Polymorphisms: Different forms of a gene, which are called "variant alleles."

Precision medicine/personalized medicine: Using an individual's genes and other characteristics to select treatments for a disease or to determine a prognosis.

Premenopausal women: Women who have had one or more periods within a 12-month calendar year and who have not yet begun experiencing menopausal symptoms such as mood swings, irregular periods, and/or hot flashes.

Prevalence: Prevalence refers to the number of existing cases of a disease in a population at a given point in time.

Progression-Free Survival (PFS): Time from randomization until disease progression or death.

Progesterone Receptor (PR) positive breast cancer: A breast cancer subtype in which there are progesterone receptors on the surface of the cells that bind to estrogen. Patients with PR+ (positive) breast cancer are classified as Hormone Receptor (HR) positive.

Proliferation (as in cell proliferation): Cell proliferation is the process that results in an increase of the number of cells and is defined by the balance between cell divisions versus cell loss through cell death or differentiation. Cell proliferation is increased in tumors.

Progressive Disease (PD): Patients or proportion of patients with a greater than or equal to 25% increase in size of disease since previous measurement.

Promoter methylation: The promoter is a section of a gene that regulates expression of the gene (i.e., if the gene is switched "on" or "off"). Methylation is addition of a chemical group called a methyl group. Addition or removal of a methyl group from a promoter is a common way for cells to temporarily turn genes on or off.

Prospective: A term used to describe a trial or data in which the information will be collected in the future according to a specified plan.

Proton Beam Therapy: A type of radiation treatment that uses protons to treat cancer. A proton is a positively charged particle. At high energy, protons can destroy cancer cells. Proton therapy is a type of external-beam radiation therapy which painlessly delivers radiation through the skin from a machine outside the body. With proton therapy, radiation does not go beyond the tumor. In contrast, with photon-based external-beam radiation therapy, x-rays continue depositing radiation as they exit the body, which can damage healthy tissue.

PubMed®: A freely accessible database of journal citations and abstracts created by the US National Library of Medicine. PubMed draws a large component of its content from the US National Library of Medicine's MEDLINE® database.

Quality of life (QOL): A person's well-being and satisfaction with life that includes the person's ability or desire to participate in social, physical, employment, education, religious, etc. activities.

Radiation Oncologist (RO): A doctor who specializes in the use of radiation techniques to treat cancer.

Randomized control studies: Randomized controlled studies are considered the gold standard for clinical research and testing new treatments, particularly when they are double-blind, placebo-controlled trials. The participants are assigned a treatment by chance ("randomization"). In double-blind trials, both the trial participants and the research team are unaware of which treatment has been assigned to whom. Placebo-controlled trials test a treatment or intervention against a placebo (the same in appearance as the study drug but with no treatment effects). However, in cancer trials new treatments are tested against the standard treatment, and placebo would be given as part of a treatment combination.

Receptor: A protein molecule that receives chemical signals from outside a cell. When such chemical signals bind to a receptor, they cause some form of cellular/tissue response such as a change in the activity of a cell.

Recurrence: Cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected.

Reference product: A biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved based on, among other things, a full complement of safety and effectiveness data.

Retrospective: When used to describe a trial or data, retrospective means that the information already exists, such as in electronic medical records or banked tumor samples and will be collected and analyzed as is.

Right to Try Laws: US state laws that were created to let terminally ill patients try experimental therapies (drugs, biologics, devices) that have completed Phase 1 testing but have not been fully approved by the FDA.

Risk Ratio: A term used when comparing the risk of a disease or outcome in one group in contrast to another group. The risk ratio is measured as relative risk (RR), i.e., the likelihood of developing an outcome/disease in the exposed group relative to those not exposed, such as the, risk of developing breast cancer in women who undertook regular physical activity and those who did not. These are measured against the absolute risk, which is the probability of a specified outcome/disease occurring in a specified population (e.g., breast cancer in all women living in the US).

RNA (Ribonucleic acid): A specific type of molecule that is essential in various biological roles in coding, decoding, regulation, and expression of genes. Both RNA and DNA (Deoxyribonucleic Acid): are nucleic acids (small biomolecules that are essential to all known forms of life).

SABCS (San Antonio Breast Cancer Symposium): An annual conference (usually in December) designed to provide state-of-the-art information on the experimental biology, etiology, prevention, diagnosis, and therapy of breast cancer and premalignant breast disease, to an international audience of academic and private physicians and researchers as well as patient advocates.

"Scanxiety": A term referring to the anxiety a patient feels when preparing for tests that will reveal the status of their disease, undergoing these tests, and waiting for the results.

SERCA (Selective Estrogen Receptor Covalent Antagonist): A novel series of compounds with a unique mode of inhibition that potently targets both wild-type and mutant ERα, which are indicative of hormonal therapy resistance). They inactivate the estrogen receptor by targeting a cysteine (amino acid) that is not present in other nuclear hormone receptors, leading to a unique biological and activity profile that differs from Selective Estrogen Receptor Modulators (SERMs) and Selective Estrogen Receptor Degraders (SERDs). SERCAs (such as H3B-6545) have begun being tested in clinical trials for HR+/HER2- mbc patients who progressed on prior therapy.

SERD (Selective Estrogen Receptor Degrader or Downregulator): A type of drug which binds to the estrogen receptor (ER) and, in the process of doing so, causes the ER to be degraded and thus downregulated (decreased). SERDs are used to treat hormone receptor positive postmenopausal women with metastatic breast cancer. The only FDA-approved SERD is Fulvestrant (Faslodex), although others are being developed and studied in clinical trials. Fulvestrant comes as a solution (liquid) to be injected slowly over 1 to 2 minutes into a muscle in the buttocks. Fulvestrant is administered by a doctor or nurse in a medical office and is usually given once every 2 weeks for the first 3 doses (days 1, 15, and 29) and then once a month thereafter.

SERM (Selective Estrogen Receptor Modulator): A type of drug that blocks the effects of estrogen in the breast tissue. SERMs work by sitting in the estrogen receptors in breast cells. If a SERM is in the estrogen receptor, there is no room for estrogen and it can't attach to the cell. If estrogen isn't attached to a breast cell, the cell doesn't receive estrogen's signals to grow and multiply. SERMs used in the US are Tamoxifen in pill form (also called Tamoxifen Citrate or Nolvadex); Tamoxifen in liquid form (brand name: Soltamox), Fareston (Toremifene) and Evista (Raloxifene). Tamoxifen is the oldest, most well-known, and most-prescribed SERM. All SERMs are taken orally.

Single nucleotide polymorphism (SNP): A small, single change in the DNA sequence.

Somatic mutations: Changes in DNA that originate in the tumor and are thus not inheritable (not passed down to offspring because they are not present in eggs and sperm). Such changes impact cancer progression and acquired resistance to therapy.

Stable Disease (SD): Between a 30% reduction or less than a 25% increase in the size of all detectable disease.

Stem cells: "Undifferentiated" biological cells that can differentiate into specialized cells and can divide to produce more stem cells. (Cell differentiation refers to a process in which a less specialized cell becomes a more specialized cell type. The classic example is the process by which a zygote [a fertilized egg] develops from a single cell into a multicellular embryo that further develops into a more complex fetus).

Stereotactic Radiosurgery (SRS): Stereotactic radiosurgery (SRS) uses many precisely focused radiation beams to treat tumors and other problems in the brain, neck and other parts of the body. It is not surgery in the traditional sense because there's no incision. Instead, SRS uses 3-D (three-dimensional) imaging to target high doses of radiation to the affected area with minimal impact on the surrounding healthy tissue. Common forms of SRS are Gamma Knife and CyberKnife.

Stomatitis: An inflammation of (or sores in) the mouth and lips. The drug Afinitor (Everolimus) often causes stomatitis in patients.

Stroma: The supportive framework of an organ (or gland or other structure), usually composed of connective tissue.

Subcutaneous: Under the skin. A subcutaneous injection is a method of administering medication. In this type of injection, a short needle is used to inject a drug into the tissue layer between the skin and the muscle. For example, the drug Fulvestrant (Faslodex) is administered subcutaneously into the buttocks.

Subtype: A term describing the smaller groups that a type of cancer can be divided into based on certain characteristics of the cancer cells. Examples are as hormone receptor positive or negative (referring to an excess of Estrogen and Progesterone Receptors), HER2 positive or negative, and Triple Negative Breast Cancer "TNBC," which is neither hormone receptor positive nor HER2 receptor positive.

Surgical Oncologist: General surgeons who have completed an additional three years of fellowship training in all cancers in order to diagnose, biopsy, and surgically treat cancer.

Surveillance, Epidemiology, and End Results (SEER): A program of the National Cancer Institute that acts as a repository for cancer statistics concerning incidence and survival in the US.

Systematic review: An overview of primary studies, such as randomized controlled trials in cases of therapy or treatment, or prospective cohort studies for prognosis-related factors that used explicit and reproducible methods. A systematic review is done by searching for published studies that measured the same variables and outcomes in the same way.

Systemic therapy: Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body.

Targeted deep sequencing: "Deep" sequencing refers to sequencing the same region of DNA multiple times (hundreds of times). This is required if the tissue sample contains a mixture of cell types as in a biopsy sample or if a mutation is rare. "Targeted" refers to sequencing a selected DNA region of interest.

Targeted therapy: In cancer, a treatment that is aimed at a specific characteristic of a tumor.

Telomere: The tip of a chromosome that functions to prevent deterioration of the chromosome.

Thrombocytopenia: A condition characterized by abnormally low levels of thrombocytes, also known as platelets, in the blood.

Time to Progression (TTP): Time from randomization until objective tumor progression; does not include deaths.

Time to Next Treatment (TTNT): Time from end of primary treatment to institution of next therapy.

Time to Treatment Failure (TTF): Time from clinical trial randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

Toxicity: The degree to which a chemical substance or a particular mixture of substances can damage an organism. Sometimes, as with Adverse Events, "Grades" are used to describe toxicity levels: Grade 0 – None, or within normal limits, Grade 1 - Mild, Grade 2 – Moderate, Grade 3 – Severe, Grade 4 – Life-threatening, Grade 5 - Death

Transcription: Transcription is the first step of gene expression, in which a particular segment of DNA is copied into RNA (especially mRNA) by the enzyme RNA polymerase.

Translational Research/Medicine: Translational research is the process of applying knowledge from basic biology and clinical trials to approved techniques and tools that address critical medical needs and improve health outcomes.

Triple-Negative Breast Cancer (TNBC): Breast cancer cells that do not have estrogen receptors, progesterone receptors, or large amounts of the HER2/neu protein. TNBC is the most challenging breast cancer subtype to treat because hormonal therapy and HER2-directed therapy usually does not work on patients with TNBC.

Triple-Positive breast cancer: An often-overlooked subtype of breast cancer in which the cells have estrogen receptors and/or progesterone receptors, as well as large amounts of the HER2/neu protein.

Tumor (or Tissue) Agnostic Therapies: Therapies that are based upon specific molecular signatures of the cancer, as opposed to where the cancer originated.

Tumor Infiltrating Lymphocytes (TILs): These are white blood cells that have left the bloodstream and migrated into a tumor. They are mononuclear immune cells, a mix of different types of cells (i.e., T cells, B cells, NK cells, macrophages) in variable proportions, with T cells being the most abundant.

Tumor Markers (TMs): TM tests check for elevated biomarker levels (namely CEA, CA15-3, and CA 27.29) in the blood. In some people TM test results are accurate, whereas in others they are not. In addition, tumor marker levels may initially rise after effective treatment when cancer cells die rapidly and release the marker into the bloodstream; hence the temporary increase may not necessarily mean treatment failure. However, a consistent increase in tumor marker levels, coupled with lack of clinical improvement, may potentially indicate treatment failure, at which point scans are advisable before considering changing the patient's treatment.

Umbrella trials: Clinical trials that test the impact of different drugs on various mutations in a single type of cancer.

Unresectable: Unable to be removed through surgery.

Vasculature: The arrangement or distribution of blood vessels in an area of the body.

Visceral disease: Disease that is found in the viscera, which are the soft internal organs of the body including the lungs, heart, and the organs of the digestive, excretory, reproductive, and circulatory systems. The term "visceral crisis" refers to severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Whole Brain Radiation (WBR): A type of external radiation therapy used to treat patients who have cancer in the brain. It is often used to treat patients whose cancer has spread to the brain, and the radiation is given to the whole brain over a period of many weeks. For patients with a limited number of brain metastasis, WBR should be avoided in favor of other options (such as Gamma Knife) because WBR does not prolong survival, reduces quality of life, and causes cognitive decline. (Regarding cognitive decline, a newer method of delivering WBR called Hippocampal Sparing WBR is now being used in some locations in an effort to preserve cognitive function).

Whole exome sequencing: Sequencing of all regions of DNA that encode proteins.

Whole genome sequencing: Sequencing all DNA of an organism or tissue sample.

Wild Type: A strain, gene, or characteristic that prevails among individuals in natural conditions, as distinct from an atypical mutant type.

Xenograft: Transplanted tissue from one type of organism (such as a human) into another type of organism (such as a mouse) for research or transplantation purposes.

Y-90 Radioembolization: Radioembolization is a minimally invasive procedure that combines embolization (a procedure which prevents blood flow to a tissue or organ) and radiation therapy to treat cancer in the liver. Tiny glass or resin beads filled with the radioactive isotope yttrium Y-90 are placed inside the blood vessels that feed a tumor. This blocks the supply of blood to the cancer cells and delivers a high dose of radiation to the tumor while sparing normal tissue. Radioembolization allows for internal delivery of radiation through the arteries supplying the cancer, thereby allowing concentration of high doses of radiation in the cancer with minimal effect on the surrounding healthy tissues. Y-90 Radioembolization may also be referred to as SIRT (Selective Internal Radiation Therapy) when beads called SIR-Spheres® are used.

54. Bibliography

1. De La Torre, K., et al., *Moonshots and metastatic disease: the need for a multi-faceted approach when studying atypical responses.* NPJ Breast Cancer, 2017. **3**: p. 7.
2. Prowell, T., *An audience with Tatiana Prowell. Interviewed by Asher Mullard.* Nat Rev Drug Discov, 2014. **13**(6): p. 410-1.
3. Lyman, G.H., et al., *Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline.* Journal of Clinical Oncology, 2018. **36**(25): p. 2647-2655.
4. Soran, A., et al., *Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01.* Ann Surg Oncol, 2018. **25**(11): p. 3141-3149.
5. Gatza, M.L. and L.A. Carey, *Another Breast Cancer Entity Confirmed: Genomics of Invasive Lobular Breast Cancer.* J Clin Oncol, 2016. **34**(16): p. 1838-9.
6. Lambert, L.A., *Looking up: Recent advances in understanding and treating peritoneal carcinomatosis.* CA Cancer J Clin, 2015. **65**(4): p. 284-98.
7. Butler, D. and M. Rosa, *Pleomorphic lobular carcinoma of the breast: a morphologically and clinically distinct variant of lobular carcinoma.* Arch Pathol Lab Med, 2013. **137**(11): p. 1688-92.
8. Brunello, E., et al., *FGFR-1 amplification in metastatic lymph-nodal and haematogenous lobular breast carcinoma.* J Exp Clin Cancer Res, 2012. **31**: p. 103.
9. Sokol, E.S., et al., *Loss of function of NF1 is a mechanism of acquired resistance to endocrine therapy in lobular breast cancer.* Ann Oncol, 2019. **30**(1): p. 115-123.
10. Hammond, M.E., et al., *American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer.* J Oncol Pract, 2010. **6**(4): p. 195-7.
11. Iwamoto, T., et al., *Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry.* J Clin Oncol, 2012. **30**(7): p. 729-34.
12. *Guideline Summary: American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor HER2 Testing in Breast Cancer.* Journal of Oncology Practice, 2007. **3**(1): p. 48-50.
13. Giordano, S.H., et al., *Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Clinical Practice Guideline Update.* Journal of Clinical Oncology, 2018. **36**(26): p. 2736-2740.
14. Wolff, A.C., et al., *Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.* J Clin Oncol, 2013. **31**(31): p. 3997-4013.
15. Cheang, M.C., et al., *Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer.* J Natl Cancer Inst, 2009. **101**(10): p. 736-50.
16. Partridge, A.H., et al., *Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol, 2014. **32**(29): p. 3307-29.
17. Rugo, H.S., et al., *Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline.* Journal of Clinical Oncology, 2016. **34**(25): p. 3069-3103.
18. Rose, C., et al., *An open randomised trial of second-line endocrine therapy in advanced breast cancer. comparison of the aromatase inhibitors letrozole and anastrozole.* Eur J Cancer, 2003. **39**(16): p. 2318-27.

19. Geisler, J., et al., *Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study.* J Clin Oncol, 2002. **20**(3): p. 751-7.
20. Mouridsen, H., et al., *Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group.* J Clin Oncol, 2003. **21**(11): p. 2101-9.
21. Turner, N.C., et al., *Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer.* N Engl J Med, 2018. **379**(20): p. 1926-1936.
22. Turner, N.C., et al., *Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.* N Engl J Med, 2015. **373**(3): p. 209-19.
23. Dickler, M.N., et al., *MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer.* Clin Cancer Res, 2017. **23**(17): p. 5218-5224.
24. Sledge, G.W., Jr., et al., *MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.* J Clin Oncol, 2017. **35**(25): p. 2875-2884.
25. Abrams, J., et al., *Dose-response trial of megestrol acetate in advanced breast cancer: cancer and leukemia group B phase III study 8741.* J Clin Oncol, 1999. **17**(1): p. 64-73.
26. Willemse, P.H., et al., *A randomized comparison of megestrol acetate (MA) and medroxyprogesterone acetate (MPA) in patients with advanced breast cancer.* Eur J Cancer, 1990. **26**(3): p. 337-43.
27. Coombes, R.C., et al., *Danazol treatment of advanced breast cancer.* Cancer Treat Rep, 1980. **64**(10-11): p. 1073-6.
28. Manni, A., B.M. Arafah, and O.H. Pearson, *Androgen-induced remissions after antiestrogen and hypophysectomy in stage IV breast cancer.* Cancer, 1981. **48**(11): p. 2507-9.
29. Schifeling, D.J., et al., *Fluoxymesterone as third line endocrine therapy for advanced breast cancer. A phase II trial of the Piedmont Oncology Association.* Am J Clin Oncol, 1992. **15**(3): p. 233-5.
30. Goetz, M.P., et al., *MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer.* J Clin Oncol, 2017. **35**(32): p. 3638-3646.
31. Rugo, H.S., et al., *Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up.* Breast Cancer Res Treat, 2019.
32. Finn, R.S., et al., *Palbociclib and Letrozole in Advanced Breast Cancer.* N Engl J Med, 2016. **375**(20): p. 1925-1936.
33. Martel, S., et al., *Risk of adverse events with the addition of targeted agents to endocrine therapy in patients with hormone receptor-positive metastatic breast cancer: A systematic review and meta-analysis.* Cancer Treat Rev, 2018. **62**: p. 123-132.
34. Dhakal, A., et al., *Efficacy of Palbociclib Combinations in Hormone Receptor-Positive Metastatic Breast Cancer Patients After Prior Everolimus Treatment.* Clin Breast Cancer, 2018. **18**(6): p. e1401-e1405.
35. Adams, J. and J. Pepping, *Vitamin K in the treatment and prevention of osteoporosis and arterial calcification.* American Journal of Health-System Pharmacy, 2005. **62**(15): p. 1574-1581.
36. Goetz, M.P., A. Kamal, and M.M. Ames, *Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response.* Clinical pharmacology and therapeutics, 2008. **83**(1): p. 160-166.
37. Osborne, C.K. and R. Schiff, *MECHANISMS OF ENDOCRINE RESISTANCE IN BREAST CANCER.* Annual review of medicine, 2011. **62**: p. 233-247.

38. Baselga, J., et al., *Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.* N Engl J Med, 2012. **366**(2): p. 109-19.
39. Swain, S.M., et al., *Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer.* N Engl J Med, 2015. **372**(8): p. 724-34.
40. Thavendiranathan, P., et al., *Breast Cancer Therapy-Related Cardiac Dysfunction in Adult Women Treated in Routine Clinical Practice: A Population-Based Cohort Study.* J Clin Oncol, 2016. **34**(19): p. 2239-46.
41. Ramakrishna, N., et al., *Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline.* J Clin Oncol, 2014. **32**(19): p. 2100-8.
42. Gradishar, W.J., et al., *NCCN Guidelines Insights Breast Cancer, Version 1.2016.* J Natl Compr Canc Netw, 2015. **13**(12): p. 1475-85.
43. Krop, I.E., et al., *Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial.* The Lancet Oncology, 2014. **15**(7): p. 689-699.
44. Hurvitz, S.A., et al., *Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial.* Lancet Oncol, 2015. **16**(7): p. 816-29.
45. Olson, E.M., et al., *Incidence and risk of central nervous system metastases as site of first recurrence in patients with HER2-positive breast cancer treated with adjuvant trastuzumab.* Ann Oncol, 2013. **24**(6): p. 1526-33.
46. Souglakos, J., et al., *Central nervous system relapse in patients with breast cancer is associated with advanced stages, with the presence of circulating occult tumor cells and with the HER2/neu status.* Breast Cancer Res, 2006. **8**(4): p. R36.
47. Prat, A. and C.M. Perou, *Deconstructing the molecular portraits of breast cancer.* Mol Oncol, 2011. **5**(1): p. 5-23.
48. Baselga, J., et al., *Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer.* J Clin Oncol, 2013. **31**(20): p. 2586-92.
49. Gucalp, A. and T.A. Traina, *Targeting the androgen receptor in triple-negative breast cancer.* Current problems in cancer, 2016. **40**(2-4): p. 141-150.
50. Twelves, C., et al., *Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies.* Breast cancer research and treatment, 2014. **148**(3): p. 553-561.
51. Andre, F. and C.C. Zielinski, *Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents.* Ann Oncol, 2012. **23 Suppl 6**: p. vi46-51.
52. Connolly, R.M., et al., *TBCRC 008: early change in 18F-FDG uptake on PET predicts response to preoperative systemic therapy in human epidermal growth factor receptor 2-negative primary operable breast cancer.* J Nucl Med, 2015. **56**(1): p. 31-7.
53. Telli, M.L., et al., *Homologous recombination deficiency (HRD) status predicts response to standard neoadjuvant chemotherapy in patients with triple-negative or BRCA1/2 mutation-associated breast cancer.* Breast Cancer Res Treat, 2018. **168**(3): p. 625-630.
54. Adams, S., et al., *Atezolizumab Plus nab-Paclitaxel in the Treatment of Metastatic Triple-Negative Breast Cancer With 2-Year Survival Follow-up: A Phase 1b Clinical Trial.* JAMA Oncol, 2018.
55. Yardley, D.A., et al., *nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial.* Ann Oncol, 2018. **29**(8): p. 1763-1770.

56. O'Shaughnessy, J., et al., *Iniparib plus chemotherapy in metastatic triple-negative breast cancer.* N Engl J Med, 2011. **364**(3): p. 205-14.
57. O'Shaughnessy, J., et al., *Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer.* J Clin Oncol, 2014. **32**(34): p. 3840-7.
58. Barton, V.N., et al., *Androgen Receptor Biology in Triple Negative Breast Cancer: a Case for Classification as AR+ or Quadruple Negative Disease.* Horm Cancer, 2015. **6**(5-6): p. 206-13.
59. Pahuja, S. and S. Puhalla, *Management of breast cancer brain metastases is moving forward, but new options are still needed.* Oncology (Williston Park), 2014. **28**(7): p. 585, 590-2.
60. Milani, A., et al., *Overcoming endocrine resistance in metastatic breast cancer: Current evidence and future directions.* World J Clin Oncol, 2014. **5**(5): p. 990-1001.
61. Cardoso, F., et al., *3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3).* Annals of Oncology, 2017. **28**(1): p. 16-33.
62. Rimawi, M., et al., *First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial.* J Clin Oncol, 2018. **36**(28): p. 2826-2835.
63. Lopez, M., et al., *Hormonal treatment of disseminated male breast cancer.* Oncology, 1985. **42**(6): p. 345-9.
64. Masci, G., et al., *Fulvestrant for advanced male breast cancer patients: a case series.* Ann Oncol, 2011. **22**(4): p. 985.
65. Di Lauro, L., et al., *Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer.* Breast Cancer Res Treat, 2013. **141**(1): p. 119-23.
66. Kantarjian, H., et al., *Hormonal therapy for metastatic male breast cancer.* Arch Intern Med, 1983. **143**(2): p. 237-40.
67. Severson, T.M. and W. Zwart, *A review of estrogen receptor/androgen receptor genomics in male breast cancer.* Endocr Relat Cancer, 2017. **24**(3): p. R27-R34.
68. Robson, M., et al., *Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.* N Engl J Med, 2017. **377**(6): p. 523-533.
69. Ettl, J., et al., *Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial.* Ann Oncol, 2018. **29**(9): p. 1939-1947.
70. Litton, J.K., et al., *Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation.* N Engl J Med, 2018. **379**(8): p. 753-763.
71. Yan, L. and W. Zhang, *Precision medicine becomes reality-tumor type-agnostic therapy.* Cancer communications (London, England), 2018. **38**(1): p. 6-6.
72. Cocco, E., M. Scaltriti, and A. Drilon, *NTRK fusion-positive cancers and TRK inhibitor therapy.* Nat Rev Clin Oncol, 2018. **15**(12): p. 731-747.
73. Pivot, X., et al., *Phase III, Randomized, Double-Blind Study Comparing the Efficacy, Safety, and Immunogenicity of SB3 (Trastuzumab Biosimilar) and Reference Trastuzumab in Patients Treated With Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer.* J Clin Oncol, 2018. **36**(10): p. 968-974.
74. Lammers, P.E., et al., *Neoadjuvant PF-05280014 (a potential trastuzumab biosimilar) versus trastuzumab for operable HER2+ breast cancer.* Br J Cancer, 2018. **119**(3): p. 266-273.

75. Pegram, M.D., et al., *PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study.* Br J Cancer, 2019. **120**(2): p. 172-182.
76. Kobayashi, T., et al., *Possible clinical cure of metastatic breast cancer: lessons from our 30-year experience with oligometastatic breast cancer patients and literature review.* Breast Cancer, 2012. **19**(3): p. 218-37.
77. Palma, D.A., et al., *Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial.* BMC Cancer, 2012. **12**: p. 305.
78. Merrill, R.M. and B.D. Hunter, *Conditional survival among cancer patients in the United States.* Oncologist, 2010. **15**(8): p. 873-82.
79. Merrill, R.M., *Conditional relative survival among female breast cancer patients in the United States.* Breast J, 2018. **24**(3): p. 435-437.
80. Lobbezoo, D.J., et al., *Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer?* Br J Cancer, 2015. **112**(9): p. 1445-51.
81. Gonzalez-Angulo, A.M., F. Morales-Vasquez, and G.N. Hortobagyi, *Overview of resistance to systemic therapy in patients with breast cancer.* Adv Exp Med Biol, 2007. **608**: p. 1-22.
82. Chandarlapaty, S., et al., *Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial.* JAMA Oncol, 2016. **2**(10): p. 1310-1315.
83. Van Poznak, C., et al., *Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol, 2015. **33**(24): p. 2695-704.
84. Cristofanilli, M., et al., *Circulating tumor cells, disease progression, and survival in metastatic breast cancer.* N Engl J Med, 2004. **351**(8): p. 781-91.
85. Sun, Y., et al., *Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B.* Nature Medicine, 2012. **18**: p. 1359.
86. Pierce, J.P., et al., *Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity.* J Clin Oncol, 2007. **25**(17): p. 2345-51.
87. Meneses-Echavez, J.F., E. Gonzalez-Jimenez, and R. Ramirez-Velez, *Effects of Supervised Multimodal Exercise Interventions on Cancer-Related Fatigue: Systematic Review and Meta-Analysis of Randomized Controlled Trials.* Biomed Res Int, 2015. **2015**: p. 328636.
88. Apfel, C., et al., *Accuracy and clinical utility of in vitro cytometric profiling to personalize chemotherapy: Preliminary findings of a systematic review and meta-analysis.* Journal of Clinical Oncology, 2013. **31**(15_suppl): p. e22188-e22188.
89. Finn, R.S., et al., *The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.* Lancet Oncol, 2015. **16**(1): p. 25-35.
90. Jones, S., et al., *Personalized genomic analyses for cancer mutation discovery and interpretation.* Sci Transl Med, 2015. **7**(283): p. 283ra53.
91. Caino, M.C., et al., *PI3K therapy reprograms mitochondrial trafficking to fuel tumor cell invasion.* Proc Natl Acad Sci U S A, 2015. **112**(28): p. 8638-43.
92. Massard, C., et al., *High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial.* Cancer Discov, 2017. **7**(6): p. 586-595.
93. Bovelli, D., et al., *Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines.* Ann Oncol, 2010. **21 Suppl 5**: p. v277-82.

94. Blum, J.L., et al., *Anthracyclines in Early Breast Cancer: The ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology).* J Clin Oncol, 2017. **35**(23): p. 2647-2655.
95. Saif, M.W., et al., *DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY (DPD) IN GI MALIGNANCIES: EXPERIENCE OF 4-YEARS.* Pakistan journal of medical sciences, 2007. **23**(6): p. 832-839.
96. Scheithauer, W., C. Zielinksi, and H. Ludwig, *Weekly low dose doxorubicin monotherapy in metastatic breast cancer resistant to previous hormonal and cytostatic treatment.* Breast Cancer Res Treat, 1985. **6**(1): p. 89-93.
97. Smorenburg, C.H., et al., *A randomized phase III study comparing pegylated liposomal doxorubicin with capecitabine as first-line chemotherapy in elderly patients with metastatic breast cancer: results of the OMEGA study of the Dutch Breast Cancer Research Group BOOG.* Ann Oncol, 2014. **25**(3): p. 599-605.
98. Hurria, A., et al., *Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer.* J Clin Oncol, 2016. **34**(20): p. 2366-71.
99. Beslija, S., et al., *Third consensus on medical treatment of metastatic breast cancer.* Ann Oncol, 2009. **20**(11): p. 1771-85.
100. Prigerson, H.G., et al., *Chemotherapy Use, Performance Status, and Quality of Life at the End of Life.* JAMA Oncol, 2015. **1**(6): p. 778-84.
101. Jeon, Y.J., et al., *Regulation of glutamine carrier proteins by RNF5 determines breast cancer response to ER stress-inducing chemotherapies.* Cancer Cell, 2015. **27**(3): p. 354-69.
102. Gradishar, W.J., *Taxanes for the treatment of metastatic breast cancer.* Breast cancer : basic and clinical research, 2012. **6**: p. 159-171.
103. van Staveren, M.C., et al., *Evaluation of an oral uracil loading test to identify DPD-deficient patients using a limited sampling strategy.* British journal of clinical pharmacology, 2016. **81**(3): p. 553-561.
104. Leonard, R., et al., *Dose-adjusting capecitabine minimizes adverse effects while maintaining efficacy: a retrospective review of capecitabine for metastatic breast cancer.* Clin Breast Cancer, 2011. **11**(6): p. 349-56.
105. Yuan, P., et al., *Oral etoposide monotherapy is effective for metastatic breast cancer with heavy prior therapy.* Chin Med J (Engl), 2012. **125**(5): p. 775-9.
106. Haque, R., et al., *Cardiovascular Disease After Aromatase Inhibitor Use.* JAMA Oncol, 2016. **2**(12): p. 1590-1597.
107. Coelingh Bennink, H.J.T., et al., *The use of high-dose estrogens for the treatment of breast cancer.* Maturitas, 2017. **95**: p. 11-23.
108. Ellis, M.J., et al., *Lower-dose (6 mg Daily) versus High-dose (30 mg Daily) Oral Estradiol Therapy of Hormone-receptor-positive, Aromatase-inhibitor-resistant Advanced Breast Cancer: A Randomized Phase 2 Study.* JAMA : the journal of the American Medical Association, 2009. **302**(7): p. 774-780.
109. Carlson, R.W. and I.C. Henderson, *Sequential hormonal therapy for metastatic breast cancer after adjuvant tamoxifen or anastrozole.* Breast Cancer Res Treat, 2003. **80 Suppl 1**: p. S19-26; discussion S27-8.
110. Di Leo, A., et al., *Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial.* J Natl Cancer Inst, 2014. **106**(1): p. djt337.
111. Ellis, M.J., et al., *Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study.* J Clin Oncol, 2015. **33**(32): p. 3781-7.
112. Slamon, D.J., et al., *Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3.* J Clin Oncol, 2018. **36**(24): p. 2465-2472.
113. Goetz, M.P., et al., *CYP2D6 metabolism and patient outcome in the Austrian Breast and Colorectal Cancer Study Group trial (ABCSG) 8.* Clin Cancer Res, 2013. **19**(2): p. 500-7.

114. Goetz, M.P., et al., *Loss of heterozygosity at the CYP2D6 locus in breast cancer: implications for germline pharmacogenetic studies.* J Natl Cancer Inst, 2014. **107**(2).
115. Dauchy, R.T., et al., *Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer.* Cancer Res, 2014. **74**(15): p. 4099-110.
116. Bertheau, P., et al., *p53 in breast cancer subtypes and new insights into response to chemotherapy.* Breast, 2013. **22 Suppl 2**: p. S27-9.
117. Yuan, H., et al., *Association of PIK3CA Mutation Status before and after Neoadjuvant Chemotherapy with Response to Chemotherapy in Women with Breast Cancer.* Clin Cancer Res, 2015. **21**(19): p. 4365-72.
118. Loibl, S., et al., *PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer.* J Clin Oncol, 2014. **32**(29): p. 3212-20.
119. Mohseni, M. and B.H. Park, *PIK3CA and KRAS mutations predict for response to everolimus therapy: now that's RAD001.* J Clin Invest, 2010. **120**(8): p. 2655-8.
120. Kreso, A., et al., *Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer.* Science, 2013. **339**(6119): p. 543-8.
121. Palumbo, R., et al., *Which patients with metastatic breast cancer benefit from subsequent lines of treatment? An update for clinicians.* Therapeutic advances in medical oncology, 2013. **5**(6): p. 334-350.
122. Curigliano, G., et al., *Should liver metastases of breast cancer be biopsied to improve treatment choice?* Ann Oncol, 2011. **22**(10): p. 2227-33.
123. Jaeger, B.A.S., et al., *The HER2 phenotype of circulating tumor cells in HER2-positive early breast cancer: A translational research project of a prospective randomized phase III trial.* PloS one, 2017. **12**(6): p. e0173593-e0173593.
124. Darvishian, F., et al., *Impact of decalcification on receptor status in breast cancer.* Breast J, 2011. **17**(6): p. 689-91.
125. Hortobagyi, G.N., et al., *Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial.* JAMA oncology, 2017. **3**(7): p. 906-912.
126. Barragán-Campos, H.M., et al., *Percutaneous vertebroplasty in vertebral metastases from breast cancer: interest in terms of pain relief and quality of life.* Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences, 2014. **20**(5): p. 591-602.
127. Hurwitz, M.D., et al., *Magnetic resonance-guided focused ultrasound for patients with painful bone metastases: phase III trial results.* J Natl Cancer Inst, 2014. **106**(5).
128. Baziotis, N., et al., *Strontium-89 chloride in the treatment of bone metastases from breast cancer.* Oncology, 1998. **55**(5): p. 377-81.
129. Price, C.T., J.R. Langford, and F.A. Liporace, *Essential Nutrients for Bone Health and a Review of their Availability in the Average North American Diet.* The open orthopaedics journal, 2012. **6**: p. 143-149.
130. Cooper, C., et al., *Is caffeine consumption a risk factor for osteoporosis?* J Bone Miner Res, 1992. **7**(4): p. 465-71.
131. Martin, R.C., et al., *Optimal outcomes for liver-dominant metastatic breast cancer with transarterial chemoembolization with drug-eluting beads loaded with doxorubicin.* Breast Cancer Res Treat, 2012. **132**(2): p. 753-63.
132. Ang, C., et al., *Hepatic arterial infusion and systemic chemotherapy for breast cancer liver metastases.* Breast J, 2013. **19**(1): p. 96-9.

133. Twelves, C., et al., *Health-related quality of life in patients with locally recurrent or metastatic breast cancer treated with etirinotecan pegol versus treatment of physician's choice: Results from the randomised phase III BEACON trial.* Eur J Cancer, 2017. **76**: p. 205-215.
134. Gordon, A.C., et al., *Yttrium-90 radioembolization stops progression of targeted breast cancer liver metastases after failed chemotherapy.* Journal of vascular and interventional radiology : JVIR, 2014. **25**(10): p. 1523-1532.e15322.
135. Ammouri, L. and E.E. Prommer, *Palliative treatment of malignant ascites: profile of catumaxomab.* Biologics, 2010. **4**: p. 103-10.
136. Eskander, R.N. and K.S. Tewari, *Emerging treatment options for management of malignant ascites in patients with ovarian cancer.* International journal of women's health, 2012. **4**: p. 395-404.
137. Kurbacher, C.M., et al., *Outpatient Intraperitoneal Catumaxomab Therapy for Malignant Ascites Related to Advanced Gynecologic Neoplasms.* The oncologist, 2015. **20**(11): p. 1333-1341.
138. Bar-Sela, G., et al., *Reducing malignant ascites accumulation by repeated intraperitoneal administrations of a Viscum album extract.* Anticancer Res, 2006. **26**(1B): p. 709-13.
139. Jatoi, A., et al., *A pilot study of long-acting octreotide for symptomatic malignant ascites.* Oncology, 2012. **82**(6): p. 315-20.
140. Tradounsky, G., *Palliation of gastrointestinal obstruction.* Can Fam Physician, 2012. **58**(6): p. 648-52, e317-21.
141. Hiraki, T., et al., *Radiofrequency ablation as treatment for pulmonary metastasis of colorectal cancer.* World journal of gastroenterology, 2014. **20**(4): p. 988-996.
142. Meimarakis, G., et al., *Prolonged Overall Survival After Pulmonary Metastasectomy in Patients With Breast Cancer.* The Annals of Thoracic Surgery, 2013. **95**(4): p. 1170-1180.
143. Lim, E. and N.U. Lin, *Updates on the management of breast cancer brain metastases.* Oncology (Williston Park), 2014. **28**(7): p. 572-8.
144. Yamamoto, M., et al., *Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study.* The Lancet Oncology, 2014. **15**(4): p. 387-395.
145. Chi, A. and R. Komaki, *Treatment of brain metastasis from lung cancer.* Cancers, 2010. **2**(4): p. 2100-2137.
146. Rodin, D., et al., *The Brain Metastases Symptom Checklist as a novel tool for symptom measurement in patients with brain metastases undergoing whole-brain radiotherapy.* Current oncology (Toronto, Ont.), 2016. **23**(3): p. e239-e247.
147. Gondi, V., et al., *Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial.* J Clin Oncol, 2014. **32**(34): p. 3810-6.
148. Reddy, J.P., et al., *Antiepileptic drug use improves overall survival in breast cancer patients with brain metastases in the setting of whole brain radiotherapy.* Radiother Oncol, 2015. **117**(2): p. 308-14.
149. Costa, R., et al., *Developmental therapeutics for patients with breast cancer and central nervous system metastasis: current landscape and future perspectives.* Annals of Oncology, 2017. **28**(1): p. 44-56.
150. Li, F. and S.-C. Tang, *Targeting metastatic breast cancer with ANG1005, a novel peptide-paclitaxel conjugate that crosses the blood-brain-barrier (BBB).* Genes & diseases, 2017. **4**(1): p. 1-3.
151. Sengupta, S., et al., *CPT-11/bevacizumab for the treatment of refractory brain metastases in patients with HER2–neu-positive breast cancer.* Oxford Medical Case Reports, 2015. **2015**(4): p. 254-257.
152. Kirste, S., et al., *Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial.* Cancer, 2011. **117**(16): p. 3788-95.

153. Chen, Z., et al., *Ligand-dependent genomic function of glucocorticoid receptor in triple-negative breast cancer.* Nat Commun, 2015. **6**: p. 8323.
154. Harford-Wright, E., et al., *Treatment with the NK1 antagonist emend reduces blood brain barrier dysfunction and edema formation in an experimental model of brain tumors.* PLoS One, 2014. **9**(5): p. e97002.
155. Bousquet, G., et al., *Intrathecal Trastuzumab Halts Progression of CNS Metastases in Breast Cancer.* J Clin Oncol, 2016. **34**(16): p. e151-5.
156. Schneider, R., et al., *Aromatase inhibitors in the treatment of breast cancer in post-menopausal female patients: an update.* Breast cancer (Dove Medical Press), 2011. **3**: p. 113-125.
157. Krop, I.E., et al., *Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA.* Ann Oncol, 2015. **26**(1): p. 113-9.
158. Azim, H.A. and H.A. Azim, Jr., *Systemic treatment of brain metastases in HER2-positive breast cancer: current status and future directions.* Future Oncol, 2012. **8**(2): p. 135-44.
159. von Berenberg, P., et al., *Treatment of traumatic brain edema by multiple doses of mannitol.* Acta Neurochir Suppl (Wien), 1994. **60**: p. 531-3.
160. Brown, P.D., et al., *Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial.* Neuro Oncol, 2013. **15**(10): p. 1429-37.
161. Freedman, R.A., et al., *Translational Breast Cancer Research Consortium (TBCRC) 022: A Phase II Trial of Neratinib for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases.* J Clin Oncol, 2016. **34**(9): p. 945-52.
162. Perez, E.A., et al., *Etirinotecan pegol (NKTR-102) versus treatment of physician's choice in women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine (BEACON): a randomised, open-label, multicentre, phase 3 trial.* Lancet Oncol, 2015. **16**(15): p. 1556-68.
163. Pahuja, S., et al., *A phase I study of veliparib (ABT-888) in combination with weekly carboplatin and paclitaxel in advanced solid malignancies and enriched for triple-negative breast cancer (TNBC).* Journal of Clinical Oncology, 2015. **33**(15_suppl): p. 1015-1015.
164. Anders, C.K., et al., *A randomized, double-blinded, controlled study of tucatinib (ONT-380) vs. placebo in combination with capecitabine (C) and trastuzumab (Tz) in patients with pretreated HER2+ unresectable locally advanced or metastatic breast carcinoma (mBC) (HER2CLIMB).* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. TPS1107-TPS1107.
165. Matutino, A., et al., *Hormone receptor-positive, HER2-negative metastatic breast cancer: redrawing the lines.* Current oncology (Toronto, Ont.), 2018. **25**(Suppl 1): p. S131-S141.
166. Reid, T., et al., *Safety and activity of RRx-001 in patients with advanced cancer: a first-in-human, open-label, dose-escalation phase 1 study.* Lancet Oncol, 2015. **16**(9): p. 1133-1142.
167. Lin, N.U., et al., *Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer.* Clin Cancer Res, 2009. **15**(4): p. 1452-9.
168. Bachelot, T.D., et al., *LANDSCAPE: An FNCLCC phase II study with lapatinib (L) and capecitabine (C) in patients with brain metastases (BM) from HER2-positive (+) metastatic breast cancer (MBC) before whole-brain radiotherapy (WBR).* Journal of Clinical Oncology, 2011. **29**(15_suppl): p. 509-509.
169. Peiris-Pages, M., et al., *Cancer stem cell metabolism.* Breast Cancer Res, 2016. **18**(1): p. 55.
170. Scott, B.J. and S. Kesari, *Leptomeningeal metastases in breast cancer.* Am J Cancer Res, 2013. **3**(2): p. 117-26.
171. Kumthekar, P., et al., *BMET-23: ANG1005, A NOVEL BRAIN-PENETRANT PEPTIDE-TAXANE CONJUGATE, FOR THE TREATMENT OF CNS METASTASES FROM BREAST CANCER.* Neuro-Oncology, 2015. **17**(Suppl 5): p. v50-v50.

172. Vincent, A., et al., *Prolonged regression of metastatic leptomeningeal breast cancer that has failed conventional therapy: a case report and review of the literature.* J Breast Cancer, 2013. **16**(1): p. 122-6.
173. Gwak, H.S., et al., *Recent Advancements of Treatment for Leptomeningeal Carcinomatosis.* J Korean Neurosurg Soc, 2015. **58**(1): p. 1-8.
174. Oliveira, M., et al., *Complete response in HER2+ leptomeningeal carcinomatosis from breast cancer with intrathecal trastuzumab.* Breast Cancer Res Treat, 2011. **127**(3): p. 841-4.
175. DeAngelis, L.M. and D. Boutros, *Leptomeningeal metastasis.* Cancer Invest, 2005. **23**(2): p. 145-54.
176. Yang, C.C., et al., *Dose volume histogram analysis of the gamma knife radiosurgery treating twenty-five metastatic intracranial tumors.* Stereotact Funct Neurosurg, 1998. **70 Suppl 1**: p. 41-9.
177. Pectasides, D., et al., *Gastric metastases originating from breast cancer: report of 8 cases and review of the literature.* Anticancer Res, 2009. **29**(11): p. 4759-63.
178. Cardi, M., et al., *Treatment of peritoneal carcinomatosis from breast cancer by maximal cytoreduction and HIPEC: a preliminary report on 5 cases.* Breast, 2013. **22**(5): p. 845-9.
179. Bigorie, V., et al., *Ovarian metastases from breast cancer: report of 29 cases.* Cancer, 2010. **116**(4): p. 799-804.
180. Tapping, C.R., L. Ling, and A. Razack, *PleurX drain use in the management of malignant ascites: safety, complications, long-term patency and factors predictive of success.* The British journal of radiology, 2012. **85**(1013): p. 623-628.
181. El-Shami, K., A. Elsaid, and Y. El-Kerm, *Open-label safety and efficacy pilot trial of intraperitoneal bevacizumab as palliative treatment in refractory malignant ascites.* Journal of Clinical Oncology, 2007. **25**(18_suppl): p. 9043-9043.
182. Cohen, V.M., *Ocular metastases.* Eye (Lond), 2013. **27**(2): p. 137-41.
183. Kaliki, S., et al., *Photodynamic therapy for choroidal metastasis in 8 cases.* Ophthalmology, 2012. **119**(6): p. 1218-22.
184. Benevento, R., et al., *Electrochemotherapy of cutaneous metastasis from breast cancer in elderly patients: a preliminary report.* BMC Surgery, 2012. **12**(1): p. S6.
185. Adams, S., et al., *Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer.* Clin Cancer Res, 2012. **18**(24): p. 6748-57.
186. Clive, S., J. Gardiner, and R.C. Leonard, *Miltefosine as a topical treatment for cutaneous metastases in breast carcinoma.* Cancer Chemother Pharmacol, 1999. **44 Suppl**: p. S29-30.
187. Murthy, R., et al., *Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study.* Lancet Oncol, 2018. **19**(7): p. 880-888.
188. Warnke, P.H., et al., *Antibacterial essential oils in malodorous cancer patients: clinical observations in 30 patients.* Phytomedicine, 2006. **13**(7): p. 463-7.
189. Akhmetova, A., et al., *A Comprehensive Review of Topical Odor-Controlling Treatment Options for Chronic Wounds.* Journal of Wound, Ostomy, and Continence Nursing, 2016. **43**(6): p. 598-609.
190. Adderley, U.J. and I.G. Holt, *Topical agents and dressings for fungating wounds.* Cochrane Database Syst Rev, 2014(5): p. CD003948.
191. Lamb, R., et al., *Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: treating cancer like an infectious disease.* Oncotarget, 2015. **6**(7): p. 4569-84.
192. Fraser, D.M., et al., *Aspirin use and survival after the diagnosis of breast cancer: a population-based cohort study.* Br J Cancer, 2014. **111**(3): p. 623-7.

193. Karnezis, T., et al., *VEGF-D promotes tumor metastasis by regulating prostaglandins produced by the collecting lymphatic endothelium.* Cancer Cell, 2012. **21**(2): p. 181-95.
194. Rugo, H., et al., *Phase I trial and antitumor effects of BZL101 for patients with advanced breast cancer.* Breast Cancer Res Treat, 2007. **105**(1): p. 17-28.
195. Martin, M., et al., *Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid.* Clin Cancer Res, 2012. **18**(17): p. 4841-9.
196. Beevers, C.S., et al., *Curcumin disrupts the Mammalian target of rapamycin-raptor complex.* Cancer Res, 2009. **69**(3): p. 1000-8.
197. Panda, A.K., et al., *New insights into therapeutic activity and anticancer properties of curcumin.* Journal of Experimental Pharmacology, 2017. **9**: p. 31-45.
198. Somasundaram, S., et al., *Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer.* Cancer Res, 2002. **62**(13): p. 3868-75.
199. Cochrane, D.R., et al., *Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide.* Breast Cancer Res, 2014. **16**(1): p. R7.
200. Lee, C., et al., *Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy.* Sci Transl Med, 2012. **4**(124): p. 124ra27.
201. Yiannakopoulou, E.C., *Interaction of green tea catechins with breast cancer endocrine treatment: a systematic review.* Pharmacology, 2014. **94**(5-6): p. 245-8.
202. Bock, P.R., et al., *Retrolective, comparative, epidemiological cohort study with parallel groups design for evaluation of efficacy and safety of drugs with "well-established use".* Forsch Komplementarmed Klass Naturheilkd, 2004. **11 Suppl 1**: p. 23-9.
203. Lissoni, P., et al., *Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status.* Eur J Cancer, 1999. **35**(12): p. 1688-92.
204. Lissoni, P., et al., *Modulation of cancer endocrine therapy by melatonin: a phase II study of tamoxifen plus melatonin in metastatic breast cancer patients progressing under tamoxifen alone.* British Journal of Cancer, 1995. **71**(4): p. 854-856.
205. Dowling, R.J., P.J. Goodwin, and V. Stambolic, *Understanding the benefit of metformin use in cancer treatment.* BMC Med, 2011. **9**: p. 33.
206. Li, Y.R., et al., *The impact of long-standing metformin use on survival in breast cancer patients.* Journal of Clinical Oncology, 2016. **34**(15_suppl): p. 1569-1569.
207. Kontani, K., et al., *Metronomic chemotherapy for metastatic breast cancer to prolong time to treatment failure to 12 months or more.* Mol Clin Oncol, 2013. **1**(2): p. 225-230.
208. Hailemichael, Y., et al., *Persistent antigen at vaccination sites induces tumor-specific CD8(+) T cell sequestration, dysfunction and deletion.* Nat Med, 2013. **19**(4): p. 465-72.
209. Jain, S., et al., *Tetrathiomolybdate-associated copper depletion decreases circulating endothelial progenitor cells in women with breast cancer at high risk of relapse.* Ann Oncol, 2013. **24**(6): p. 1491-8.
210. Brewer, G.J., et al., *Treatment of Metastatic Cancer with Tetrathiomolybdate, an Anticopper, Antiangiogenic Agent: Phase I Study.* Clinical Cancer Research, 2000. **6**(1): p. 1-10.
211. Garland, C.F., et al., *Meta-analysis of all-cause mortality according to serum 25-hydroxyvitamin D.* Am J Public Health, 2014. **104**(8): p. e43-50.
212. Santagata, S., et al., *Taxonomy of breast cancer based on normal cell phenotype predicts outcome.* J Clin Invest, 2014. **124**(2): p. 859-70.

213. Collins, L.C., et al., *Androgen receptor expression in breast cancer in relation to molecular phenotype: results from the Nurses' Health Study.* Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc, 2011. **24**(7): p. 924-931.
214. Alvarez, R.H., et al., *Abstract P6-10-02: MLN8237 (alisertib), an investigational Aurora A Kinase inhibitor, in patients with breast cancer: Emerging phase 2 results.* Cancer Research, 2014. **72**(24 Supplement): p. P6-10-02-P6-10-02.
215. Wardell, S.E., et al., *Bazedoxifene exhibits antiestrogenic activity in animal models of tamoxifen-resistant breast cancer: implications for treatment of advanced disease.* Clin Cancer Res, 2013. **19**(9): p. 2420-31.
216. Adelson, K., et al., *Randomized phase II trial of fulvestrant alone or in combination with bortezomib in hormone receptor-positive metastatic breast cancer resistant to aromatase inhibitors: a New York Cancer Consortium trial.* NPJ Breast Cancer, 2016. **2**: p. 16037.
217. Baselga, J., et al., *Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet Oncol, 2017. **18**(7): p. 904-916.
218. Mukai, H., et al., *Palbociclib in combination with letrozole in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: PALOMA-2 subgroup analysis of Japanese patients.* Int J Clin Oncol, 2018.
219. Finn, R.S., et al., *Abstract CT101: Final results of a randomized Phase II study of PD 0332991, a cyclin-dependent kinase (CDK)-4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (PALOMA-1; TRIO-18).* Cancer Research, 2014. **74**(19 Supplement): p. CT101.
220. Patnaik, A., et al., *Abstract CT232: Clinical activity of LY2835219, a novel cell cycle inhibitor selective for CDK4 and CDK6, in patients with metastatic breast cancer.* Cancer Research, 2014. **74**(19 Supplement): p. CT232.
221. Goetz, M.P., et al., *First-in-Human Phase I Study of the Tamoxifen Metabolite Z-Endoxifen in Women With Endocrine-Refractory Metastatic Breast Cancer.* Journal of Clinical Oncology, 2017. **35**(30): p. 3391-3400.
222. Zahnow, C.A., et al., *Inhibitors of DNA Methylation, Histone Deacetylation, and Histone Demethylation: A Perfect Combination for Cancer Therapy.* Adv Cancer Res, 2016. **130**: p. 55-111.
223. Yardley, D.A., et al., *Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor.* J Clin Oncol, 2013. **31**(17): p. 2128-35.
224. Kurbacher, C.M., et al., *20PTargeting HER2 in patients with HER2-negative metastatic breast cancer with elevated serum levels of the HER2 extracellular domain and/or HER2-positive circulating tumor cells in the clinical routine.* Annals of Oncology, 2015. **26**(suppl_3): p. iii8-iii8.
225. Cook, K.L., et al., *Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer.* Clin Cancer Res, 2014. **20**(12): p. 3222-32.
226. Tiriveedhi, V., et al., *Safety and preliminary evidence of biologic efficacy of a mammaglobin-a DNA vaccine in patients with stable metastatic breast cancer.* Clin Cancer Res, 2014. **20**(23): p. 5964-75.
227. Dawood, S., *Updates from the 2014 San antonio breast cancer symposium.* Indian J Med Paediatr Oncol, 2015. **36**(1): p. 66-70.
228. De Amicis, F., et al., *Resveratrol, through NF-Y/p53/Sin3/HDAC1 complex phosphorylation, inhibits estrogen receptor alpha gene expression via p38MAPK/CK2 signaling in human breast cancer cells.* FASEB J, 2011. **25**(10): p. 3695-707.

229. Boni, C., et al., *Therapeutic activity of testosterone in metastatic breast cancer.* Anticancer Res, 2014. **34**(3): p. 1287-90.
230. Lok, S.W., et al., *A Phase Ib Dose-Escalation and Expansion Study of the BCL2 Inhibitor Venetoclax Combined with Tamoxifen in ER and BCL2-Positive Metastatic Breast Cancer.* Cancer Discov, 2019. **9**(3): p. 354-369.
231. Yuen, T., et al., *Bisphosphonates inactivate human EGFRs to exert antitumor actions.* Proc Natl Acad Sci U S A, 2014. **111**(50): p. 17989-94.
232. Doi, T., et al., *Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study.* Lancet Oncol, 2017. **18**(11): p. 1512-1522.
233. Wildiers, H., et al., *Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group.* Lancet Oncol, 2018. **19**(3): p. 323-336.
234. Denkert, C., et al., *Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer.* J Clin Oncol, 2010. **28**(1): p. 105-13.
235. Loi, S., et al., *Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial.* Lancet Oncol, 2019.
236. Loi, S., et al., *Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98.* J Clin Oncol, 2013. **31**(7): p. 860-7.
237. Rugo, H.S., et al., *SOPHIA: A phase 3, randomized study of margetuximab (M) plus chemotherapy (CTX) vs trastuzumab (T) plus CTX in the treatment of patients with HER2+ metastatic breast cancer (MBC).* Journal of Clinical Oncology, 2016. **34**(15_suppl): p. TPS630-TPS630.
238. Alsina, M., et al., *First-in-human phase 1/2 study of MCLA-128, a full length IgG1 bispecific antibody targeting HER2 and HER3: Final phase 1 data and preliminary activity in HER2+ metastatic breast cancer (MBC).* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 2522-2522.
239. Abraham, J., et al., *NSABP FB-10: Phase Ib dose-escalation trial evaluating trastuzumab emtansine (T-DM1) with neratinib (N) in women with metastatic HER2+ breast cancer (MBC).* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 1027-1027.
240. Im, S.A., et al., *Abstract P4-13-19: Poziotinib, an oral, irreversible pan-HER inhibitor, demonstrates promising clinical activity in metastatic HER2 positive breast cancer patients.* Cancer Research, 2016. **76**(4 Supplement): p. P4-13-19.
241. Moulder, S.L., et al., *Phase I Study of ONT-380, a HER2 Inhibitor, in Patients with HER2(+)-Advanced Solid Tumors, with an Expansion Cohort in HER2(+) Metastatic Breast Cancer (MBC).* Clin Cancer Res, 2017. **23**(14): p. 3529-3536.
242. Borges, V.F., et al., *Tucatinib Combined With Ado-Trastuzumab Emtansine in Advanced ERBB2/HER2-Positive Metastatic Breast Cancer: A Phase 1b Clinical Trial.* JAMA Oncol, 2018. **4**(9): p. 1214-1220.
243. Gianni, L., *Is there room for another HER2-targeting drug?* Lancet Oncol, 2018. **19**(7): p. 847-849.
244. Ithimakin, S., et al., *HER2 Drives Luminal Breast Cancer Stem Cells in the Absence of HER2 Amplification: Implications for Efficacy of Adjuvant Trastuzumab.* Cancer Research, 2013. **73**(5): p. 1635-1646.
245. Duru, N., et al., *HER2-Associated Radioresistance of Breast Cancer Stem Cells Isolated from HER2-Negative Breast Cancer Cells.* Clinical Cancer Research, 2012. **18**(24): p. 6634-6647.
246. Pernas, S., et al., *Balixafortide plus eribulin in HER2-negative metastatic breast cancer: a phase 1, single-arm, dose-escalation trial.* Lancet Oncol, 2018. **19**(6): p. 812-824.

247. Yardley, D.A., et al., *Phase II/III weekly nab-paclitaxel plus gemcitabine or carboplatin versus gemcitabine/carboplatin as first-line treatment of patients with metastatic triple-negative breast cancer (the tnAcity study): study protocol for a randomized controlled trial.* Trials, 2015. **16**: p. 575.
248. Schmid, P., et al., *Abstract 2986: Atezolizumab in metastatic TNBC (mTNBC): Long-term clinical outcomes and biomarker analyses.* Cancer Research, 2017. **77**(13 Supplement): p. 2986.
249. Schmid, P., et al., *Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer.* N Engl J Med, 2018. **379**(22): p. 2108-2121.
250. Gucalp, A., et al., *Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer.* Clin Cancer Res, 2013. **19**(19): p. 5505-12.
251. Forero-Torres, A., et al., *TBCRC 019: A Phase II Trial of Nanoparticle Albumin-Bound Paclitaxel with or without the Anti-Death Receptor 5 Monoclonal Antibody Tigatuzumab in Patients with Triple-Negative Breast Cancer.* Clin Cancer Res, 2015. **21**(12): p. 2722-9.
252. Isakoff, S.J., et al., *TBCRC009: A Multicenter Phase II Clinical Trial of Platinum Monotherapy With Biomarker Assessment in Metastatic Triple-Negative Breast Cancer.* J Clin Oncol, 2015. **33**(17): p. 1902-9.
253. Jardim-Perassi, B.V., et al., *Effect of melatonin on tumor growth and angiogenesis in xenograft model of breast cancer.* PLoS One, 2014. **9**(1): p. e85311.
254. Johnston, S.R.D., et al., *Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade With Lapatinib Plus Trastuzumab in Combination With an Aromatase Inhibitor in Postmenopausal Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: ALTERNATIVE.* J Clin Oncol, 2018. **36**(8): p. 741-748.
255. Villagrasa, P., et al., *SOLTI-1303 PATRICIA: A phase II study of palbociclib and trastuzumab (HR+ with or without letrozole) in trastuzumab-pretreated, postmenopausal patients with HER2-positive metastatic breast cancer.* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. TPS1101-TPS1101.
256. Balmaña, J., et al., *Anti-tumor activity of PM01183 (lurbinectedin) in BRCA1/2-associated metastatic breast cancer patients: results of a single-agent phase II trial.* Annals of Oncology, 2016. **27**(suppl_6): p. 223O-223O.
257. *Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation.* N Engl J Med, 2017. **377**(17): p. 1700.
258. Bartsch, R. and E. Bergen, *SABCS 2017: update on chemotherapy, targeted therapy, and immunotherapy.* Memo, 2018. **11**(3): p. 204-207.
259. Somlo, G., et al., *Efficacy of the PARP Inhibitor Veliparib with Carboplatin or as a Single Agent in Patients with Germline BRCA1- or BRCA2-Associated Metastatic Breast Cancer: California Cancer Consortium Trial NCT01149083.* Clin Cancer Res, 2017. **23**(15): p. 4066-4076.
260. Hanker, A.B., et al., *An Acquired HER2(T798I) Gatekeeper Mutation Induces Resistance to Neratinib in a Patient with HER2 Mutant-Driven Breast Cancer.* Cancer Discov, 2017. **7**(6): p. 575-585.
261. Hyman, D.M., et al., *HER kinase inhibition in patients with HER2- and HER3-mutant cancers.* Nature, 2018. **554**(7691): p. 189-194.
262. Kogawa, T., et al., *Single agent activity of U3-1402, a HER3-targeting antibody-drug conjugate, in breast cancer patients: Phase 1 dose escalation study.* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 2512-2512.
263. Watson, J.C. and P.J.B. Dyck, *Peripheral Neuropathy: A Practical Approach to Diagnosis and Symptom Management.* Mayo Clinic Proceedings. **90**(7): p. 940-951.
264. Ruan, X., *Drug-related side effects of long-term intrathecal morphine therapy.* Pain Physician, 2007. **10**(2): p. 357-66.

265. Luo, J., M.A. Adams, and P. Dolan, *Vertebroplasty and Kyphoplasty Can Restore Normal Spine Mechanics following Osteoporotic Vertebral Fracture.* Journal of osteoporosis, 2010. **2010**: p. 729257-729257.
266. Sohn, S. and C.K. Chung, *The Role of Stereotactic Radiosurgery in Metastasis to the Spine.* Journal of Korean Neurosurgical Society, 2012. **51**(1): p. 1-7.
267. Sartor, O., *Overview of Samarium Sm 153 Lexidronam in the Treatment of Painful Metastatic Bone Disease.* Reviews in Urology, 2004. **6**(Suppl 10): p. S3-S12.
268. Vickers, A.J., et al., *Acupuncture for chronic pain: individual patient data meta-analysis.* Arch Intern Med, 2012. **172**(19): p. 1444-53.
269. Mao, J.J., et al., *A randomised trial of electro-acupuncture for arthralgia related to aromatase inhibitor use.* Eur J Cancer, 2014. **50**(2): p. 267-76.
270. Aggarwal, B.B., et al., *Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric.* Mol Nutr Food Res, 2013. **57**(9): p. 1529-42.
271. Irwin, M.L., et al., *Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors.* J Clin Oncol, 2015. **33**(10): p. 1104-11.
272. Cassileth, B.R. and A.J. Vickers, *Massage therapy for symptom control: outcome study at a major cancer center.* J Pain Symptom Manage, 2004. **28**(3): p. 244-9.
273. Miles, P., *Reiki for mind, body, and spirit support of cancer patients.* Adv Mind Body Med, 2007. **22**(2): p. 20-6.
274. Schroder, S., et al., *Acupuncture treatment improves nerve conduction in peripheral neuropathy.* Eur J Neurol, 2007. **14**(3): p. 276-81.
275. Mijnhout, G.S., et al., *Alpha lipoic acid: a new treatment for neuropathic pain in patients with diabetes?* Neth J Med, 2010. **68**(4): p. 158-62.
276. Sun, H., et al., *Effects of electroacupuncture on depression and the production of glial cell line-derived neurotrophic factor compared with fluoxetine: a randomized controlled pilot study.* J Altern Complement Med, 2013. **19**(9): p. 733-9.
277. Johns, S.A., et al., *Randomized controlled pilot study of mindfulness-based stress reduction for persistently fatigued cancer survivors.* Psychooncology, 2015. **24**(8): p. 885-93.
278. Desmarais, J.E. and K.J. Looper, *Interactions between tamoxifen and antidepressants via cytochrome P450 2D6.* J Clin Psychiatry, 2009. **70**(12): p. 1688-97.
279. Riba, P.A.M.B., *Tailoring depression treatment for women with breast cancer.* Current Psychiatry, 2010. **9**(11): p. 39-49.
280. Dell'Osso, B., et al., *Serotonin norepinephrine reuptake inhibitors (SNRIs) in anxiety disorders: a comprehensive review of their clinical efficacy.* Hum Psychopharmacol, 2010. **25**(1): p. 17-29.
281. Vaswani, M., F.K. Linda, and S. Ramesh, *Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review.* Prog Neuropsychopharmacol Biol Psychiatry, 2003. **27**(1): p. 85-102.
282. Molassiotis, A., et al., *Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial.* J Clin Oncol, 2012. **30**(36): p. 4470-6.
283. Cramp, F. and J. Byron-Daniel, *Exercise for the management of cancer-related fatigue in adults.* Cochrane Database Syst Rev, 2012. **11**: p. CD006145.
284. Chuang, C.Y., et al., *Effects of music therapy on subjective sensations and heart rate variability in treated cancer survivors: a pilot study.* Complement Ther Med, 2010. **18**(5): p. 224-6.
285. Breitbart, W. and Y. Alici-Evcimen, *Update on psychotropic medications for cancer-related fatigue.* J Natl Compr Canc Netw, 2007. **5**(10): p. 1081-91.

286. Minton, O., et al., *A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue.* J Natl Cancer Inst, 2008. **100**(16): p. 1155-66.
287. Cao, H., et al., *Acupuncture for treatment of insomnia: a systematic review of randomized controlled trials.* J Altern Complement Med, 2009. **15**(11): p. 1171-86.
288. Garland, S.N., et al., *Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients.* Neuropsychiatric Disease and Treatment, 2014. **10**: p. 1113-1124.
289. Passos, G.S., et al., *Is exercise an alternative treatment for chronic insomnia?* Clinics, 2012. **67**(6): p. 653-659.
290. Sasseville, A., et al., *Blue blocker glasses impede the capacity of bright light to suppress melatonin production.* J Pineal Res, 2006. **41**(1): p. 73-8.
291. Berger, A.M., *Update on the state of the science: sleep-wake disturbances in adult patients with cancer.* Oncol Nurs Forum, 2009. **36**(4): p. E165-77.
292. Bower, J.E., et al., *Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation.* J Clin Oncol, 2014. **32**(17): p. 1840-50.
293. Pagel, J.F. and B.L. Parnes, *Medications for the Treatment of Sleep Disorders: An Overview.* Prim Care Companion J Clin Psychiatry, 2001. **3**(3): p. 118-125.
294. Walsh, D., K.A. Nelson, and F.A. Mahmoud, *Established and potential therapeutic applications of cannabinoids in oncology.* Support Care Cancer, 2003. **11**(3): p. 137-43.
295. Goncharova, V., et al., *Hyaluronan expressed by the hematopoietic microenvironment is required for bone marrow hematopoiesis.* J Biol Chem, 2012. **287**(30): p. 25419-33.
296. Jian, J., et al., *A link between premenopausal iron deficiency and breast cancer malignancy.* BMC Cancer, 2013. **13**: p. 307.
297. Deghan Manshadi, S., et al., *Folic acid supplementation promotes mammary tumor progression in a rat model.* PLoS One, 2014. **9**(1): p. e84635.
298. Stabler, S.P., *Clinical practice. Vitamin B12 deficiency.* N Engl J Med, 2013. **368**(2): p. 149-60.
299. Bryan, J., et al., *Thrombocytopenia in patients with myelodysplastic syndromes.* Semin Hematol, 2010. **47**(3): p. 274-80.
300. Otsuki, N., et al., *Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects.* J Ethnopharmacol, 2010. **127**(3): p. 760-7.
301. DePriest, A.Z. and K. Miller, *Oxycodone/Naloxone: role in chronic pain management, opioid-induced constipation, and abuse deterrence.* Pain Ther, 2014. **3**(1): p. 1-15.
302. McQuade, R.M., et al., *Chemotherapy-Induced Constipation and Diarrhea: Pathophysiology, Current and Emerging Treatments.* Front Pharmacol, 2016. **7**: p. 414.
303. Janku, F., et al., *Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer.* Ann Oncol, 2016. **27**(11): p. 2032-2038.
304. Hofheinz, R.-D., et al., *Mapisal Versus Urea Cream as Prophylaxis for Capecitabine-Associated Hand-Foot Syndrome: A Randomized Phase III Trial of the AIO Quality of Life Working Group.* Journal of Clinical Oncology, 2015. **33**(22): p. 2444-2449.
305. Velicer, C.M. and C.M. Ulrich, *Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review.* J Clin Oncol, 2008. **26**(4): p. 665-73.
306. Yamamoto, D., et al., *Efficacy of Vitamin E Treatment for Hand-Foot Syndrome in Patients Receiving Capecitabine.* Breast Care (Basel), 2010. **5**(6): p. 415-416.
307. Floyd, J., et al., *Hepatotoxicity of chemotherapy.* Semin Oncol, 2006. **33**(1): p. 50-67.

308. Rugo, H.S., et al., *Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial.* Lancet Oncol, 2017. **18**(5): p. 654-662.
309. Varun, B., et al., *Bisphosphonate induced osteonecrosis of jaw in breast cancer patients: A systematic review.* J Oral Maxillofac Pathol, 2012. **16**(2): p. 210-4.
310. Montefusco, V., et al., *Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates.* Leuk Lymphoma, 2008. **49**(11): p. 2156-62.
311. Rosella, D., et al., *Medication-related osteonecrosis of the jaw: Clinical and practical guidelines.* J Int Soc Prev Community Dent, 2016. **6**(2): p. 97-104.
312. Togni, S., et al., *Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial.* Eur Rev Med Pharmacol Sci, 2015. **19**(8): p. 1338-44.